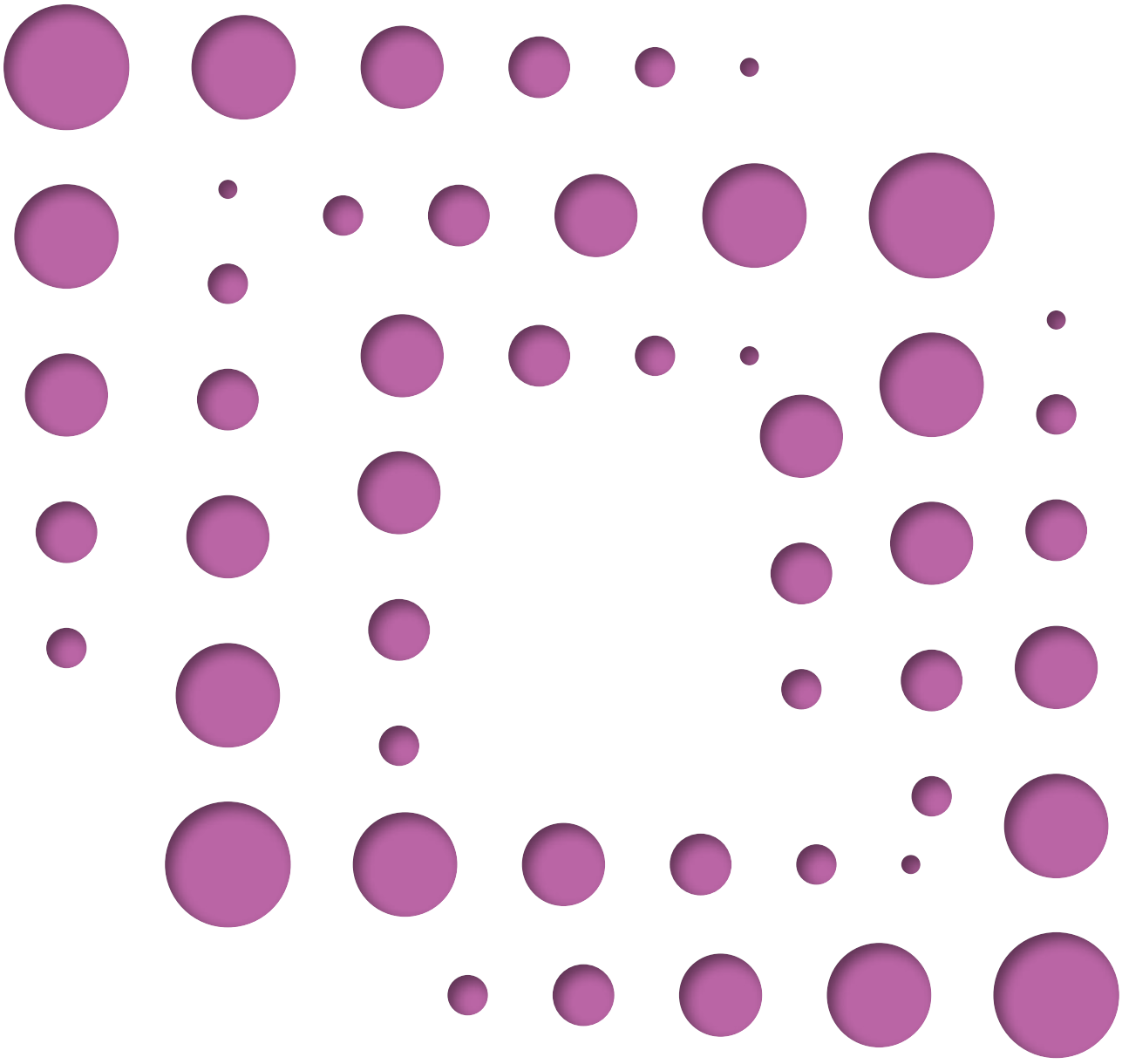

Scientific Annual Report 2021

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Contents

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Scientific Annual Report 2021

Director of Research
René Medema

Introduction

During the COVID pandemic, we have experienced the power of fundamental science and profited from years of immunological research. In our daily lives, we have learned to adapt and be even more flexible and creative than before. However, the harsh truth is that 2021 has also been yet another challenging year, which has been particularly tough on our young researchers, who have come from many countries in the world to work in the NKI as a PhD student or a Postdoc. Normally, this means getting a great amount of work done, but also having a great time, spent with a large group of people from different backgrounds both scientifically and culturally. During the past two years, such stimulating interactions have been under great pressure, and a survey held amongst our PhD students revealed that they have experienced substantial stress. This merits our closest attention.

In 2021, the Netherlands Cancer Institute welcomed two new members of our Board of Directors. In June, medical oncologist Jacqueline Stouthard was appointed Medical Director, succeeding Maas Jan Heineman, who temporarily filled this position after Emile Voest stepped down at the start of the year. We also welcomed Ymke Fokma, who succeeded Marien van der Meer as Director of Operations and Management. I want to thank Emile, Marien, and Maas Jan for their wonderful work, and I am looking forward to continue working with Jacqueline and Ymke. In 2021, we also welcomed Martijn Stuiver as associate group leader in the Survivorship group, to develop a research group focusing on functional recovery of cancer. His appointment underscores the importance of evidence-based supportive care to cancer treatment.

In our Strategy 2030, entitled 'a cure for every cancer and excellent care for every patient', diagnostics, and specifically early diagnostics, is a focus area. In 2021, we worked hard to get our Center for Early Diagnostics ready for opening its doors on 4 January 2022. Early detection will lead to less invasive treatment, better survival, and a higher quality of life. Other innovative focus areas are digital oncology and artificial intelligence. Not because patients are data rather than persons, but because we need huge amounts of data to be able to better personalize cancer treatment.

Responsible research has always been high on the NKI agenda, and a crucial aspect of responsible research is building and safeguarding a safe, inclusive, and inspiring work environment, which allows all our colleagues to flourish. This is why, in 2021, we launched a dedicated Culture & Behavior program, aimed at creating a work environment in which we can correct one another, are open to different ideas, learn from mistakes, and trust each other. Another important aspect of responsible research is building a culture of transparency. In 2021, our Board of Directors formally embarked on a policy of transparency about our animal research, which means listening well to society as well as explaining why tackling a complex disease such as cancer is not yet possible without - responsible - animal research, next to developing complementary research models. Along with 14 other organizations, we signed the Dutch Transparency Agreement on Animal Testing.

In 2021, we also made new discoveries, published new findings, and implemented new knowledge into the clinic and the health system at large. For instance, our researchers managed to improve the screening test for colorectal cancer, after years of research into the biology of how high-risk precursors of colorectal cancer develop into actual tumours. Other researchers showed that patient-derived tumor fragments can predict response to immunotherapy. I am also proud and grateful that funders and donors once again put their trust into our researchers and our institute, enabling us to start new exciting and impactful projects.

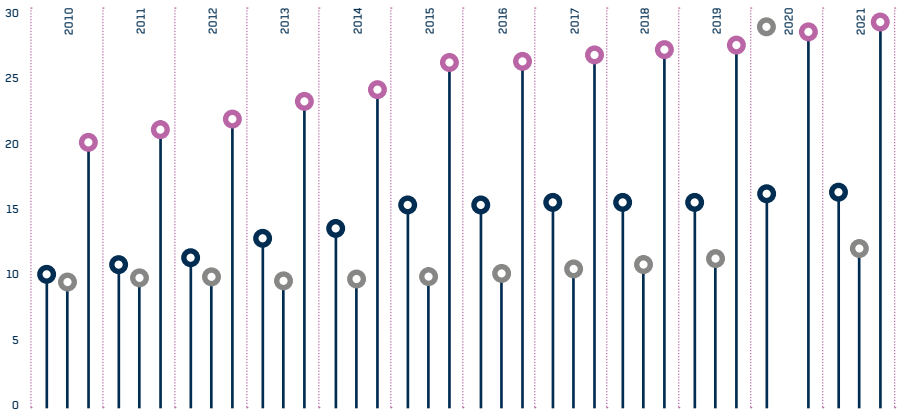
Collaboration has also been flourishing, despite the pandemic, within EU-Life, Cancer Core Europe, Oncode, and in many other settings. To name just two: With our EU-Life partners, we launched the EMERALD program, a new PhD program that provides medical doctors with state-of-the-art biomedicine training and helps bridge the gap between laboratory research and clinical practice. In addition, supported by the Dutch Cancer Foundation, all academic producers of cellular therapy in the Netherlands started working together to accelerate the development of cellular therapy and its implementation in the clinic.

I want to end by thanking all our employees for all their work and stamina, despite work pressure and COVID restrictions, and everyone else who supported us and collaborated with us, including the Dutch Cancer Society for their institutional support and the Ministry of Health, Welfare and Sport for their core funding.
Most of all, I want to thank all our patients and donors for their trust in our hospital and our research.

René Medema
Director of Research

FIGURE 1

CORE RESEARCH FUNDING THE NETHERLANDS CANCER INSTITUTE - ANTONI VAN LEEUWENHOEK HOSPITAL BY THE DUTCH CANCER SOCIETY AND THE MINISTRY OF HEALTH, WELFARE AND SPORT IN THE PERIOD 2010-2021 IN MILLION EUROS.



- **DUTCH CANCER SOCIETY**
- **MINISTRY OF HEALTH, WELFARE & SPORT***
- **TOTAL**

* EXCLUDED ARE THE REIMBURSEMENTS FOR INTEREST AND DEPRECIATION OF BUILDINGS

A SELECTION OF HONOURS AND APPOINTMENTS

- Immunologist Ton Schumacher received the Louis-Jeantet Prize for translational medicine, together with Jerome Galon of the Institut National de la Santé et de la Recherche Médicale in Paris, for their innovative work in cancer immunology.

- Joris van de Haar, who defended his PhD thesis cum laude in 2021, has won the Antoni van Leeuwenhoek Award 2021 for his extraordinary research in the field of bioinformatics and precision oncology. The NKI awards the Antoni van Leeuwenhoek award every year to its most talented young researcher.

- The Patient Impact Award, the NKI's annual prize for the most impactful clinical innovation, was awarded to the Neoadjuvant Immunotherapy team, headed by medical oncologist and research leader Christian Blank.

- PhD student Josephine Lopes Cardozo has been awarded a Special Merit Awards by the ASCO Conquer Cancer Foundation for her abstract about predicting ultralow risk patients with the 70-gene signature (Mammaprint) in the MINDACT trial.

- Lung cancer research led by Egbert Smit was selected by the American Society of Clinical Oncology for inclusion in the *Clinical Cancer Advances 2021*, which highlights the most impactful research advances of the past year.

- Benjamin Rowland, leader of the chromosome biology group, has been awarded a Vici Grant by the Dutch Research Council (NWO), for research into why chromosomes are neatly positioned next to each other in the cell nucleus.

- Medical oncologist and research group leader Marleen Kok has been awarded a Vidi grant by the Dutch Research Council, as well as a Dutch Cancer Society grant for improving immunotherapy in triple-negative breast cancer.

- Karin de Visser, group leader in the department of Tumor Biology and Immunology, has been elected as a member of EMBO, the prestigious international organization of leading researchers in the life sciences.

- Medical Oncologist and Personalized Oncology group leader Winette van der Graaf has been elected EORTC President-Elect.

- Ton Schumacher, leader of the Cancer Immunology, has been elected as 2021 Fellow of the American Association for Cancer Research Academy, as well as a member of the Royal Netherlands Academy of Arts and Sciences.

- Lotje Zuur, head & neck surgeon and group leader, has been appointed professor of otorhinolaryngology at the Leiden University Medical Center.

- Urologist Henk van der Poel has been appointed professor of image-guided surgical oncology at the Amsterdam UMC.

- Medical oncologist and Medical Cluster Head Jacqueline Stouthard was appointed Medical Director of the Netherlands Cancer Institute as from 1 June 2021. She succeeded Maas Jan Heineman, who has temporarily filled this position after Medical Director Emile Voest stepped down on 1 January 2021.

- Ymke Fokma, member of the Board of Directors of the Dijklander hospital, has been appointed Director of Organization and Business Operations of the Netherlands Cancer Institute as from 1 November 2021.

- In 2021, The Dutch Cancer Society has awarded grants to seventeen research teams at the Netherlands Cancer Institute.

RESEARCH HIGHLIGHTS

In all five of our research themes, and very often in multidisciplinary settings, our researchers and clinicians have again made progress in understanding cancer and bringing new knowledge to the clinic. Here, we present some of our 2021 research highlights.

FUNDAMENTAL RESEARCH

Genome organization from mosquitoes to humans

With the aid of zoos from all over the world, an international group of scientists, led by the Chromosome Biology group of Benjamin Rowland, managed to unravel the way in which chromosomes organize themselves in the cell nucleus. The researchers noticed that organisms often have either one type of chromosome folding (separate nests, as seen in humans) or another type (centromeres clustered together, as seen in mosquitoes). The Rowland group showed that a protein complex called condensin II plays a crucial role in this great folding divide. When they turned off condensin II in human cells, the chromosomes suddenly folded in a way that is normally seen in other organisms such as the mosquito or the mushroom. Thankfully, we don't yet know how to change people into mosquitoes or mushrooms or vice versa, but as far as the type of folding of the chromosomes is concerned, we do.

Claire Hoenkamp et al., *Science,* 28 May 2021

Sloppy cancer cells reveal their secrets

Haste makes waste, our grandmothers told us. Cancer cells, in their rush to multiply, don't heed these wise words at all. And they pay the price, as researchers from the Reuven Agami Oncogenomics group discovered. In 2020, this group already showed that cancer cells produce extremely sloppy proteins, by skipping an important step in reading the RNA sequence in times of food deprivation. However, due to their weirdness, these proteins make themselves visible to the immune system. In 2021, the Agami group discovered that this sloppiness in cancer cells can be caused by a mutation in the KRAS oncogene, meaning that it is inherent to many cancer types. Drugs that suppress this oncogene also prevent sloppiness, they saw, thereby also rendering the cells less visible to the immune system. However, sloppy protein production returns once the cancer cell becomes resistant to the drug. Hopefully, new types of immunotherapy will be able to take care of these resistant, but outstanding cancer cells.

Julien Champagne et al., *Molecular Cell,* 24 September 2021

Exploring the role of non-coding DNA in cancer

Most studies of DNA mutations related to cancer have focused on the protein-coding parts of the genome. However, the human genome consists of only 3% of coding DNA. Thanks to a donation from the Saxum Volutum Foundation, an interdisciplinary team including group leaders Bas van Steensel, Wilbert Zwart and Emile Voest will be able to systematically identify functionally relevant non-coding mutations in cancer genomes on an unprecedented scale in the coming five years. The team intends to develop computer algorithms that automatically recognize the most important non-coding mutations in the DNA of an individual patient in order to ultimately develop new tools for better diagnosis and treatment of patients.

Intestinal cancer cells take advantage of healthy cells

New research led by Saskia Suijkerbuijk from Jacco van Rheenen's Intravital Microscopy of Cancer group showed that intestinal cancer cells use competitive signals to kill surrounding healthy intestinal cells and grow faster themselves. The team showed that in organoids wild-type intestine cells are actively eliminated by cancer cells, that cell competition boosts proliferation of intestinal cancer cells and that the remaining healthy cells adopt a fetal-like state. Their study confirms that surrounding tissue also plays a crucial role in tumor growth and that we need to study this closely.

Ana Krotenberg Garcia et al., *Cell Reports,* 6 July 2021

PRECISION ONCOLOGY

New stool test can further improve colorectal cancer screening

The Dutch colorectal cancer screening program, using the fecal immunochemical test (FIT), is a highly successful program. The FIT stool test has a high sensitivity (80%) for cancer. However, its sensitivity to high-risk cancer precursors (advanced adenomas) is less than 30%. The Gerrit Meijer group (Translational Gastrointestinal Oncology), together with researchers from Amsterdam UMC and Erasmus MC, now identified two additional biomarker proteins for detecting advanced adenomas. The researchers validated the new test (mFIT) for clinical use, and a prospective trial including 13,300 participants of the Dutch national bowel-screening program will be launched in the spring of 2022. The new biomarker panel is estimated to have a 35% higher sensitivity for detection of advanced adenomas relative to the current FIT, without increasing the percentage of false positive test results.

Willemijn de Klaver et al., *Annals of Internal Medicine*, 20 July 2021

Smart combination therapy for liver cancer tackles drug resistance

In order to prevent new precision drugs from needlessly failing during clinical development, pharmaceutical companies should move towards an approach involving smart combinations of drugs from the start, according to Rene Bernards, leader of the Functional Cancer Genetics group. In 2012, in a seminal *Nature* paper, he introduced his first rational combination therapy, which is now standard of care for colorectal cancer. In 2021, a team of researchers from the NKI and the Jiao Tong University in Shanghai led by Bernards discovered a comparable combination therapy for liver cancer, which is one of the most common cancer types worldwide. Unfortunately, one of the few targeted drugs on the market for liver cancer (lenvatinib), shows no effect in 75 percent of patients. By blocking all possible cellular pathways one by one, the team discovered why this is the case and how this insensitivity to lenvatinib can be overcome by combining this with another drug. The researchers ran a first-in-human clinical study in patients at the Eastern Hepatobiliary Surgery Hospital in Shanghai, who showed resistance to levatinib from the start, with 4 out 10 patients responding to the combination treatment.

Haojie Jin et al., *Nature*, 21 July 2021, and Jeff Settleman, João Fernandes Neto and Rene Bernards, *Cancer Discovery*, May 2021

TABLE 1

SHORT TERM CITATIONS AND IMPACT OF SCIENTIFIC ARTICLES PUBLISHED BY THE NETHERLANDS CANCER INSTITUTE RESEARCH STAFF 2007-2021

PUBLICATION YEAR	PUBLICATIONS*	CITATIONS	CITATIONS/ PUBLICATIONS	IMPACT
2007	430	5605	13,0	2969
2008	442	5657	12,8	2590
2009	511	7904	15,5	3074
2010	481	8788	18,3	2841
2011	459	8651	18,8	3110
2012	573	9268	16,2	3333
2013	512	8989	17,6	3228
2014	596	9599	16,1	3935
2015	659	19618	29,8	5234
2016	793	15087	19,0	5344
2017	727	18371	25,3	5891
2018	795	20712	26,0	6143
2019	899	24650	27,4	7142
2020	892			6103
2021	990**			8784**

* SINCE 2014 A NEW STANDARD WAS USED TO PERFORM THE CITATION AND IMPACT FACTOR ANALYSES. CONSEQUENTLY THE NUMBERS CAN DIFFER FROM THE PREVIOUS YEARS.

** ANALYSIS WAS PERFORMED IN FEBRUARY 2022. DATA CAN BE SUBJECT TO CHANGE.

Actionable metastatic cancer genome is remarkably stable over time

By sequencing a patient's entire tumor genome, all DNA errors are made visible in one go. However, there has been uncertainty about how often this procedure should be repeated, as it is known that tumors continuously change their DNA to adapt to given treatments. Researchers from the groups of Emile Voest and Lodewyk Wessels now discovered that actionable DNA errors remain remarkably stable over time, despite treatment with drugs. This means that one test will almost always be sufficient. Also in view of the costs of a Whole Genome Sequencing test, this is important new knowledge.

Joris van de Haar et al., *Nature Medicine*, 9 August 2021

IMAGE-GUIDED THERAPY

Radiation boost lowers risk of prostate cancer recurrence

An additional external-beam radiation dose delivered directly to the tumor can benefit the prospects of men with non-metastatic prostate cancer, without causing additional side effects. The risk of relapse within five years for these men is smaller than for men who did not receive this boost, as shown by a large-scale study (the FLAME-trial), initiated by the UMC Utrecht in collaboration with the NKI, UZ Leuven and Radboudumc, and led by NKI group leader Uulke van de Heide (Imaging Technology in Radiotherapy). Physicians deliver radiation to the entire prostate, as cancer cells often occur in several areas throughout the prostate. Only the main tumor is visible on a scan. If the cancer returns, it often recurs right where the visible tumor was located. Delivering an additional dose to this specific area appears to be very effective.

Linda Kerkmeijer et al., *Journal of Clinical Oncology*, 20 January 2021

New collaboration in AI for precision radiotherapy

The Netherlands Cancer Institute, University of Amsterdam (UvA), and Elekta agreed to collaborate on developing new AI strategies for the further improvement of precision radiotherapy. This concerns the personalization of treatment by improving the quality of imaging used during treatment, predicting and accounting for changes in the patient's anatomy over time, and automatically adapting radiation delivery each time a patient is treated. The collaborating parties have been awarded a grant of the Rijksdienst voor Ondernemend Nederland (RVO), making the Partnership for Online Personalized AI-driven Adaptive RT (POP-AART) lab a reality.

New research: Detecting breast cancer with MRI

Radiologist Ritse Mann is developing a 'smart MRI scan' for faster breast cancer diagnostics. In his research project, which was funded by the Dutch Cancer Society in March 2021, he is working on the development of an algorithm that can detect breast abnormalities quickly during the MRI scan. If no abnormalities are detected, the MRI procedure can end. This means that the average examination time for women will be a maximum of 3 minutes instead of the current 20 minutes; the scan will only take this long for a select group of women. This saves a lot of time and opens up the possibility of examining larger patient groups, making MRI a potential method for breast cancer screening.

IMMUNOTHERAPY

'Tumor avatars' can predict a patient's response to immunotherapy

Junior group leader Daniela Thommen (Precision Cancer Immunotherapy) has taken a major hurdle in the quest for the most powerful tumor model system. Together with researchers from the Schumacher group as well as many clinicians, Thommen's group succeeded in showing that her innovative platform of patient-derived tumor fragments called 'tumor avatars' can indeed predict whether the corresponding real-life patients will benefit from immunotherapy. The team treated these tumor avatars outside the patient with different therapies, analyzed the reaction of the tumor avatars in the lab to immunotherapy called PD-1 blockade, and linked this information to treatment responses from 38 patients with various cancer types. They also found a number of new

biomarkers for response or resistance to immunotherapy.

Paula Voabil et al., *Nature Medicine*, 8 July 2021

Rapid immune response predicts excellent prognosis

The risk of recurrence for patients with melanomas is much smaller if the immune system starts cleaning up the tumor cells rapidly following neoadjuvant immunotherapy, according to two studies by the International Neoadjuvant Melanoma Consortium (INMC). Even a *partial* pathological response to immunotherapy proved to have a highly beneficial long-term effect. Medical oncologist and group leader Christian Blank was involved in both publications, one of which concerned his group's own research (the 2-4 years follow-up of the OPACIN-neo and OPACIN study, respectively). These findings provided the rationale for the international phase 3 NADINA study, in which neoadjuvant immunotherapy is compared with standard adjuvant therapy in macroscopic stage III melanoma.

Lisette Rozeman et al., *Nature Medicine*, 8 February 2021 and Alexander Menzies et al, *Nature Medicine*, 8 February 2021

Neo-adjuvant immunotherapy also effective in mouth and throat cancer

Immunotherapy before surgery for late-stage mouth and throat cancer to prevent recurrence of the condition is safe and effective, according to the results of the IMCISION trial conducted at the Netherlands Cancer Institute, led by head and neck surgeon and group leader Lotje Zuur.

Joris Vos et al., *Nature Communications*, 22 December 2021

New national collaboration to accelerate development of cellular therapy

The Netherlands Cancer Institute is part of a new national platform for the development of cellular therapy for cancer, funded by the Dutch Cancer Society. In the new platform, called DARE-NL, the NKI, eight University Medical Centers, Sanquin and the Princess Maxima Center for Pediatric Oncology joined forces to accelerate the development of cellular therapy and its implementation into the clinic.

Cancer researchers shed light on COVID immunity

Researchers from the Pia Kvistborg group (Checkpoint Targeting and T cells) have identified new viral targets that can potentially help develop new SARS-CoV-2 vaccines. Currently, all vaccines are focused on the spike, but the NKI researchers explored a broad landscape of viral protein parts that human immune cells can recognize. Surprisingly, the most important protein part they found is not on the spike but is part of the so-called open-reading frame 1ab. In line with other studies, their data suggest that it may be important to consider other parts of the virus to elicit strong immune responses in the next generation COVID vaccines. In 2020, the researchers had temporarily stopped their cancer research to study how the immune system recognizes SARS-CoV-2.

Anastasia Gangaev et al., *Nature Communications*, 10 May 2021

COVID-19 vaccine safe and effective for cancer patients

Most patients with tumors in an organ or tissue who are receiving treatment with immuno-therapy and/or chemotherapy respond well to the COVID-19 vaccine. A study conducted by UMC Groningen, Erasmus MC in Rotterdam, and the NKI, together with the RIVM and the Netherlands Comprehensive Cancer Organization (IKNL), shows that it is safe and usually effective to vaccinate these patients. The results of this study (the VOICE study) were presented on September 20 at the European Society of Medical Oncology congress.

SURVIVORSHIP

New group leader Martijn Stuiver will focus on functional recovery from cancer

Clinical epidemiologist and physical therapist Martijn Stuiver has been appointed associate group leader to team up with Lonneke van de Poll and her Cancer Survivorship group, and develop his own Functional Recovery from Cancer group. The goal of his research is to understand how functional impairments caused by cancer and cancer treatment impact peoples' functioning in daily life, how these impairments can be prevented or mitigated by targeted and timely offered rehabilitation interventions - exercise in particular; and to support implementation of successful interventions into usual care.

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M van der Meer
Till July 2021

Y Fokma
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HL Ploegh
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C Swanton
Professor in Cancer, Chief Clinician Cancer Research UK, Francis Crick Institute, United Kingdom


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A

Reuven Agami

Division head, group leader Division Oncogenomics

Reuven Agami PhD Group leader
Daniela Annibali PhD Post-doc
Julien Champagne PhD Post-doc
Yuval Malka PhD Post-doc
Abhijeet Pataskar PhD Post-doc
Sebastian Dieter MD PhD student
Adva Kochavi PhD student
Pierre-René Körner PhD student
Domenica Lovecchio PhD student
Kelly Mordente PhD student
Miha Sovrovic PhD student
Demi Wernaart PhD student
Naomi Blommaert Technical staff
Remco Nagel PhD Technical staff

Key publications

Bartok O, Pataskar A, Nagel R, Laos M, Goldfarb E, Hayoun D, Levy R, Körner PR, Kreuger IZM, Champagne J, Zaal EA, Bleijerveld OB, Huang X, Kenski J, Wargo J, Brandis A, Levin Y, Mizrahi O, Alon M, Lebon S, Yang W, Nielsen MM, Stern-Ginossar N, Altelaar M, Berkers CR, Geiger T, Peeper DS, Olweus J, Samuels Y, Agami R. Anti-tumour immunity induces aberrant peptide presentation in melanoma. Nature. 2021;590(7845):332-337

Champagne J, Pataskar A, Blommaert N, Nagel R, Wernaart D, Ramalho S, Kenski J, Bleijerveld OB, Zaal EA, Berkers, CR, Altelaar M, Peeper DS, Faller WJ, Agami R. Oncogene-dependent sloppiness in mRNA translation. Mol Cell. 2021;81(22):4709-4721.e9

Pataskar A, Champagne J, Nagel R, et al., and Agami R. Tryptophan depletion results in tryptophan to phenylalanine subtitutants Nature (in press)

Uncovering novel vulnerabilities of cancer

Our main research objective is to identify novel cellular vulnerabilities that can be exploited for cancer therapies. For this purpose, we are developing innovative genomic and genetic tools. Currently we focus on the impact amino acid shortages have on protein production. Tissue expansion is restricted by physical, oxidative, nutritional, and immunological stresses that control the rate by which proteins are synthesized. To ascertain uncontrolled proliferation and aggressive behaviour, oncogenic aberrations enhance protein production by deregulating mRNA translation. This action, we find, comes at the expense of the quality by which proteins are produced, a phenomenon we coined "Sloppiness". The outcome of sloppiness is the production of aberrant proteins, and the presentation of aberrant (neo)epitopes at the cell surface of tumor cells. By characterizing aberrant epitopes in cancer cells we aim to develop novel immunological tools to boost tumour-cell killing.

Oncogene-dependent *Sloppiness* in mRNA translation

Extensive tumour inflammation, which is reflected by high levels of infiltrating T cells and interferon-γ (IFNγ) signalling, improves the response of patients to checkpoint immunotherapy. Many tumours, however, escape by activating cellular pathways that lead to immunosuppression. One such mechanism is the production of kynurenine from tryptophan by the enzyme IDO1, which is induced by IFNγ. However, clinical trials using IDO1 inhibitors in combination with immunotherapy in patients with melanoma failed to improve the efficacy of treatment. The role of IDO1 and the consequent degradation of tryptophan in mRNA translation and cancer progression therefore remains unclear. We showed that IFNγ-induced tryptophan depletion provokes ribosomal frameshifting events allowing ribosomes to bypass tryptophan codons in the absence of tryptophan. This results in the production of aberrant proteins that are processed and presented as aberrant peptides at the cell surface. Interestingly, priming of naive T cells from healthy donors with aberrant peptides induces peptide-specific T cell reactivity.

Next, we investigated the extent and the underlying mechanisms related to tryptophan shortage-mediated aberrant protein expression, and show that it is a widespread phenomenon in cancer. We termed this event ***Sloppiness*** and strikingly observed its association with oncogenic MAPK pathway hyperactivation. While oncogenes empower cancer progression and aggressiveness, they also expose a vulnerability by provoking the production of aberrant peptides through sloppiness.

Lastly, we also show that despite tryptophan depletion, in-frame protein synthesis bypassing tryptophan codons continues. Using mass spectrometry, we identified tryptophan to phenylalanine (W>F) codon reassignment as the major event that facilitates in-frame protein synthesis in IFNg-treated and tryptophan-depleted cancer cells. W>F substitutions were enriched in tumours compared with adjacent normal tissues, and their appearance was associated with IDO1 expression and T-cell and oncogenic signalling activities. We further show that W>F substitutions are presented on HLA molecules at the cell surface and activate T cell responses, indicating their potential impact on the repertoire of neo-peptides presented by cancer cells.

A comprehensive enhancer screen for YAP oncogenesis

Frequent activation of the co-transcriptional factor YAP is observed in a large number of solid tumors. Activated-YAP binds genomic enhancer loci and stimulates cancer aggressiveness. Although thousands of YAP binding-sites were annotated, their functional importance is mostly unknown. We therefore explored a functional genetic enhancer screening approach to identify regulatory enhancer elements that are required for YAP function. We identified the enhancer of TRAM2, and showed its importance for YAP-induced cell proliferation, migration and invasion phenotypes. TRAM2 correlation with poor patient survival pinpointed its significance for human health. Thus, TRAM2 is a key novel mediator of YAP-induced oncogenic proliferation and cellular invasiveness.

Leila Akkari

Group leader
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Daniel Taranto MSc PhD student
Marnix de Groot MSc Technical staff
Shanna Handgraaf MSc Technical staff
Lotte van Mil MSc Technical staff
Efi Tsouri MSc Technical staff

Key publications

Jin H, Shi Y, Lv Y, Yuan S, Ramirez CFA, Lieftink C, Wang L, Wang S, Wang C, Dias MH, Jochems F, Yang Y, Bosma A, Hijmans EM, de Groot MHP, Vegna S, Cui D, Zhou Y, Ling J, Wang H, Guo Y, Zheng X, Isima N, Wu H, Sun C, Beijersbergen RL, Akkari L, Zhou W, Zhai B, Qin W, Bernards R. EGFR activation limits the response of liver cancer to Lenvatinib. Nature 2021;595(7869):730-734

Li MO, Wolf N, Raulet DH, Akkari L, Pittet MJ, Rodriguez PC, Kaplan RN, Munitz A, Zhang Z, Cheng S, Bhardwaj N. Innate immune cells in the tumor microenvironement. Cancer Cell 2021;39(6):725-729

Taranto D, Ramirez CFA, Vegna S, de Groot MHP, de Wit N, Van Baalen M, Klarenbeek S, Akkari L. Multiparametric analyses of hepatocellular carcinoma somatic mouse models and their associated tumor microenvironment. Curr Protoc. 2021;1(6):e147

Macrophage dynamics in cancer progression and response to treatment

The overall goal of our research group is to determine the mechanisms utilized by tumors to shape myeloid cell subset content and education to their advantage, and how the evolution of these cells' programming influences response to therapy. Through mechanistic understanding of the crosstalk between macrophage subpopulations and cancer cells, we aim to contribute to the design of novel innate cell centric immunomodulatory strategies that can potentiate anti-cancer therapy response.

Uncovering macrophage subsets' diversity and education in the course of GBM malignancy

In murine and human glioblastoma (GBM), the dominant non-cancerous cell populations are the innate immune tumor-associated macrophages (TAMs). However, the relative abundance and contribution of each macrophage subsets, namely the brain resident microglia (MG) and tumor-recruited monocyte derived macrophages (MDMs) in GBM progression and response to radiotherapy was previously unknown. In light of the ontogenical differences between these two subset of TAMs, we identified radiation-specific, stage-dependent MG and MDM phenotype in murine gliomas, and confirmed these findings in human tumors. At the single cell level, we resolved the diversity of the different subset of these TAMs, and identified that metabolic demands in the cancer cells shape their pro-tumorigenic features. Therapeutically, hindering the adapted education that these cells acquire post-radiotherapy delayed the emergence of GBM recurrence. Our findings revealed the dynamics and plasticity of distinct macrophage subsets, which has translational relevance for enhancing the efficacy of combination therapy in GBM.

Understanding and resolving GBM resistance to T-cell centric immunotherapy

Incorporating anti-PD1 T-cell immunotherapy (IT) to the current standard of care treatment in GBM has failed to provide therapeutic results. In collaboration with Dr Gerben Borst, we are investigating the molecular mechanisms specific to the brain tumor microenvironment (TME) that underlie the lack of efficacy of IT in GBM, particularly when combined with radiotherapy. Using pre-clinical murine models of the disease response to IT, we identified that the TME composition, abundant in myeloid cells and poorly immunogenic, is dominantly responsible for the limited efficacy of aPD1 treatment, rather than the tumor mutational burden of cancer cells. We found that the numbers of regulatory T cells acutely increased in irradiated GBM treated with immunotherapy, and that therapeutic depletion of these cells in combination treatment led to unleash the efficacy of T cell centric aPD1 treatment. These findings support the concept of a timely combination of IT with complementary immunomodulation approaches to enforce anti-tumor immunity in radiotherapy-treated GBM.

Unraveling the cancer cell genetics' regulation of the HCC immune tumor microenvironment

We have developed multiple hepatocellular carcinoma (HCC) murine models using the relevant oncogenic drivers of this disease, by taking advantage of hydrodynamic gene delivery and the Sleeping Beauty-mediated somatic integration in mouse hepatocytes *in vivo*. We found that different oncogenic drivers distinctively shape the HCC tumor microenvironment. We generated aggressive or slow-growing HCC which contained different amounts of myeloid cells, including tissue-resident or infiltrating macrophages. Our results support the hypothesis that the GM-CSF pathway activity correlates with chronic inflammation and tumor growth through increased infiltration of suppressive myeloid cells in myeloid-dominant HCC and that the underlying genetic background of liver cancer cells regulates the responsiveness of this pathway activity.

B

Regina Beets-Tan

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Oncologic imaging research

The research brings together physicians, computer scientists, engineers to work in synergy on the development of imaging technologies to improve personalised treatment.

Imaging for Organ preservation

The group has a longstanding record of accomplishment in MRI for organ preserving treatment of rectal cancer. This rectal cancer imaging research is expanded with an EU funded study aiming at developing AI models to predict outcome using data from MRI, endoscopy and biopsy. A nationwide study funded by the Dutch Cancer Soc generates real life evidence using imaging and clinical data from over 10 Dutch medical centers. The organ-preservation research is extended to oesophageal, breast and urogenital cancer. Establishment of a multimodal stratification tool using endoscopy and MRI empowered by AI is a focus of this research. A spin-off research is the creation of a digital infrastructure aiming to exchange data for implementation studies and training.

Multiparametric imaging

In colorectal cancer multicenter studies aim to build models linking multiple MR and CT parameters to clinical data to predict treatment response and outcome. This is also the focus in Head and Neck cancer research. In prostate cancer we aim to develop MR- based risk models that can accurately stratify patients for individualized treatment. Breast MRI research focuses on establishing the value of MRI for prediction of response to neoadjuvant treatment. Research in peritoneal carcinomatosis investigates whether whole body MRI can be used to select colorectal and ovarian cancer patients for cytoreductive surgery. In all research lines AI based solutions are developed and validated.

Interventional Oncology

Research focuses on evaluating the efficacy and safety of new treatment methods such as ablation, radioembolization, vertebroplasty etc and on imaging methods, incl AI, to accurately detect local recurrence after treatment. Real-time ultrasound/ ^{18}FDG-PET-CT fusion guided fine-needle aspiration for nodal staging of Head and Neck cancer investigates the value of multimodality imaging to guide interventional procedures.

Artificial Intelligence in Immunotherapy and Radiogenomics

AI research leverages AI methodologies to develop non-invasive AI-biomarkers and bring clinically-usable algorithms into the clinic. The research focuses on exploring predictive AI signatures of response to immunotherapy in several cancer types. A main research line is a fully-automated AI approach (PAM) to monitor serial/longitudinal images of immunotherapy.
The radio-genomics research aims to link radiomics signatures with clinically relevant genetic mutations using imaging and genomic data from ~2000 patients, creating the largest Pancancer radiogenomics cohort in literature. Within the context of the new Cancer of Unknown Primary clinic, the imaging group is exploring the role of AI as a tool for diagnosis in this patient cohort. Alongside the research development of new AI tools, our team has begun developing a workflow for translation of these algorithms into an experimental clinical workflow. An important step towards this goal is studying the human-machine interaction (HMI), a running project that our department is collaborating with the HMI team at the Universiteit Twente.

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Haak HE, Beets GL, Peeters K, Nelemans PJ, Valentini V, Rödel C, Kuo L, Calvo FA, Garcia-Aguilar J, Glynne-Jones R, Pucciarelli S, Suarez J, Theodoropoulos G, Biondo S, Lambregts DMJ, Beets-Tan RGH, Maas M. Prevalence of nodal involvement in rectal cancer after chemoradiotherapy. Br J Surg. 2021;108(10):1251-1258

Trebeschi S, Bodalal Z, Boellaard TN, Tareco Bucho TM, Drago SG, Kurilova I, Calin-Vainak AM, Delli Pizzi A, Muller M, Hummelink K, Hartemink KJ, Nguyen-Kim TDL, Smit EF, Aerts HJWL, Beets-Tan RGH. Prognostic value of deep learning-mediated treatment monitoring in lung cancer patients receiving immunotherapy. Front Oncol 2021;11:609054

Cancer specific dependencies

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Jin H, Shi Y, Lv Y, Yuan S, Ramirez CFA, Lieftink C, Wang L, Wang S, Wang C, Dias MH, Jochems F, Yang Y, Bosma A, Hijmans EM, de Groot MHP, Vegna S, Cui D, Zhou Y, Ling J, Wang H, Guo Y, Zheng X, Isima N, Wu H, Sun C, Beijersbergen RL, Akkari L, Zhou W, Zhai B, Qin W, Bernards R. EGFR activation limits the response of liver cancer to lenvatinib. Nature. 2021;595(7869):730-734

Paes Dias M, Tripathi V, van der Heijden I, Cong K, Manolika EM, Bhin J, Gogola E, Galanos P, Annunziato S, Lieftink C, Andújar-Sánchez M, Chakrabarty S, Smith GCM, van de Ven M, Beijersbergen RL, Bartkova J, Rottenberg S, Cantor S, Bartek J, Ray Chaudhuri A, Jonkers J. Loss of nuclear DNA ligase III reverts PARP inhibitor resistance in BRCA1/53BP1 double-deficient cells by exposing ssDNA gaps. Mol Cell. 2021;81(22):4692-4708

Our research continues to evolve around the development and use of functional genomic screening technologies for the discovery of regulators of crucial pathways deregulated in cancer, genotype specific dependencies and synthetic lethal interactions that can be explored as drug targets in precision therapy. In 2021, we continued to apply our pooled screening platforms in combination with specific screening models to identify tumor type specific targets, identify potential effective drug combinations and to understand the mechanisms of drug resistance.

Functional genomic screens based on cell proliferation and survival are key for the identification of genes that determine drug response and treatment resistance. However, many biological phenotypes are better captured by cellular phenotypes or transcriptional changes. We have further optimized our single well CRISPR screening platform using transfection of synthetic sgRNAs in cell lines expressing CAS9. This is followed by automated high-throughput microscopy or by generation of indexed RNA seq libraries using methods like plate-seq in combination with DNA capture. With this latter pipeline, we study the role of subsets of genes, for example epigenetic modifiers, in the control of the (low) expression of specific gene sets.

In 2021, the KWF sponsored the ScreeninC national infrastructure, consisting of three research sites (LACDR Leiden, ERIBA Groningen and NKI Amsterdam). It gained momentum with a number of collaborative projects with groups from different universities in the Netherlands. These projects involve the development of novel screening models based on CRISPR genome editing, the application of pooled CRISPR screens with custom sgRNA libraries and the optimization of single well CRISPR screens with microscopy-based dynamic read-outs. We provided expertise and reagents for the screens and performed data analysis, data integration and interpretation of the screening results. We will continue to provide these services and support for research groups in the Netherlands and expand on our technology platform to further increase the output of screening projects.

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Severson TM, Zhu Y, De Marzo AM, Jones T, Simons JW, Nelson WG, Yegnasubramanian S, Freedman ML, Wessels L, Bergman AM, Haffner MC, Zwart W. Androgen receptor epigenetic analysis reveals constrained transcriptional heterogeneity among clonal prostate cancer metastases. Mol Oncol. 2021;15:1942-1955

Siefert JC, Cioni B, Muraro MJ, Alshalalfa M, Vivié J, Van der Poel HG, Schoots IG, Bekers E, Feng FY, Wessels L, Zwart W, Bergman AM. The prognostic potential of human prostate cancer-associated macrophage subtypes as revealed by single-cell transcriptomics. Mol Cancer Res, 2021 (in print)

Interactions between prostate cancer and its microenvironment

The prostate cancer microenvironment consists of resident and recruted stromal and immune cells. Our lab has an interest in the interaction between normal prostate cells and prostate cancer. There is abundant evidence that these cells play a crucial role in the initiation and progression of prostate cancer. In contrast to the tumor cells, the stroma and infiltratred immune cells in the tumor microenvironment consist of normally regulated cells and might hold promise for clinical valuable biomarkers and drug targets.

Identification of genes critically involved in macrophage mediated cell-kill evasion

To identify critical factors for cytotoxic macrophages mediated cell-kill (CMPKill), we performed a genome-wide CRISPR knock-out screen in LNCaP prostate cancer cells in coculture with cytotoxic macrophages (figure A). LNCaP cells were transduced with the Brunello library and cultured in testosterone proficient conditions. Five gene knock-outs with a significant survival advantage were identified; AR, PRKCD (Protein Kinase C δ) and three genes that are components of the I*k*B kinase (IKK) complex (CHUK, IKBKB and IKBKG), which is essential for activation of members of the nuclear factor-*k*B (NF*k*B) family of transcription factors (figure B). These hits were validated in single knock-outs for the genes of interest, in coculture of with cytotoxic macrophages. We currently study the interactions between the three pathways and the exact mechanism of prostate cancer cell CMPKill evasion.

Prostate cancer cells with an acquired resistance to macrophage mediated cell kill

The mechanism of resistance to CMPKill was also assessed through a second independent approach. LNCaP cells were rendered resistant to CMPKill by repetitive exposure of LNCaP cells to cytotoxic macrophages. Gene set enrichment analysis suggests a decreased AR signaling in CMPKill resistant LNCaP cells. Moreover, resistant cells showed an increased hedgehog and KRAS signaling. Phospho-proteomics studies showed that CMPKill resistant LNCaP cells had enriched phosphorylation of MAPK and decreased PRKCD phosphorylation. Current studies concentrate on phenotypic alterations of the CMPKill resistant LNCaP cells and efficacy of drugs targeting the increased signaling pathways in reverting the CMPKill resistance.

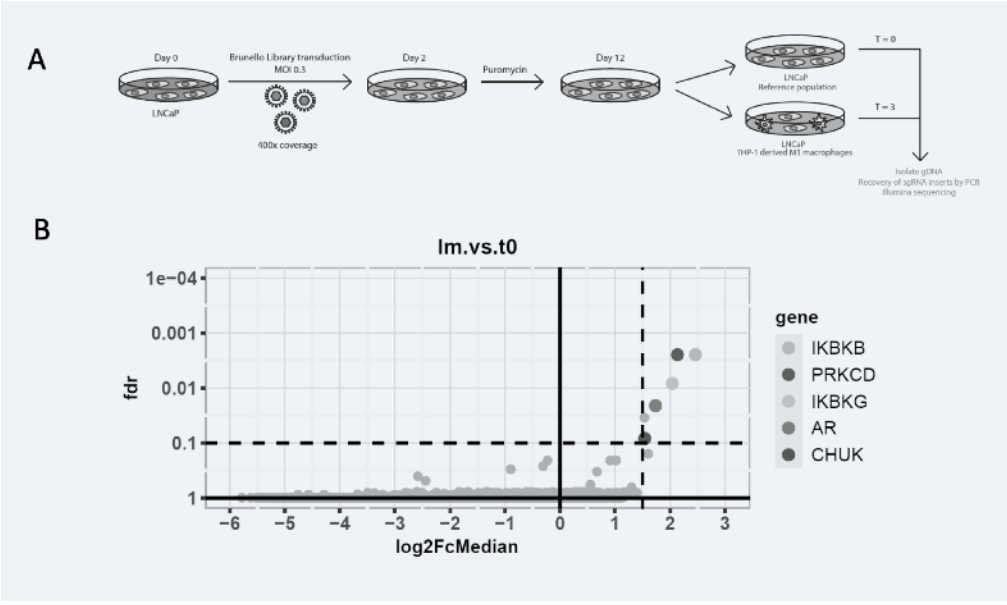

Figure A. Genome wide CRISPR knock-out screen in human prostate cancer LNCaP cells in co-culture with THP-1 derived cytotoxic macrophages
Figure B. Results of the screen. Cells with a knock-out for AR, PRKCD and NF*k*B signaling were resistant to cytotoxic macrophages mediated cell-kill

Rene Bernards

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Functional genomics

My group uses genome-scale functional genetic approaches to identify powerful drug combinations, new drug targets and mechanisms of drug resistance.

Vulnerabilities of senescent cancer cells

Therapeutic induction of senescence followed by a treatment that selectively kills senescent cancer cells (senolysis) is a promising new strategy for the treatment of cancer. Using an inducible CRISPR library in senescent cells, we found that activation of death receptor signaling has powerful senolytic activity in a broad range of senescent cancer cells. Our data also indicate that senescent cells have a "bystander" effect on non-senescent cells in that activation of death receptor 5 by agonistic antibody in proliferating cancer cells is enhanced by the presence of senescent cancer cells.

Vulnerabilities of Drug Tolerant Persister cells

Recent data indicate that cancer therapy leads to the selective survival of a small sub-population of cancer cells that cycle slowly and have non-genetic adaptations enabling escape from therapy. Such so-called Drug Tolerant Persister cells (DTPs) can re-enter the cell cycle after drug withdrawal, making their eradication critical to successful cancer therapy. We have initiated a program to find vulnerabilities of DTPs using the approach described above for senescent cancer cells. Early results indicate that DTPs have different vulnerabilities as compared to senescent cells.

Paradoxical activation of mitogenic signaling pathways

We have recently postulated that further activation of mitogenic signaling pathways that are already activated by oncogenic mutations can lead to cell death, especially when combined with drugs that suppress the stress response pathways that allow cancer cells to deal with hyper-activated mitogenic signaling. To test this model, we employed LB-100, a compound that inhibits protein phosphatase 2A. Treatment of KRAS mutant colon cancer cells with LB-100 leads to hyperactivated MAPK signaling and provokes considerable mitotic and DNA damage stress. We have systematically suppressed the major stress response pathways to find the most lethal combination of mitogenic activation by LB-100 and suppression of stress responses. Our data indicate that LB-100 is strongly synthetic lethal with inhibition of the WEE1 mitotic kinase. This suggests a novel strategy to treat cancer that we have dubbed "paradoxical intervention" because of the counter-intuitive activation of oncogenic signaling as the basis for a cancer therapy.

Targeting the MAP kinase pathway

We have published in 2018 that loss of the MAPK component MAP2K4 sensitizes cancer cells to inhibition by the MEK kinase. In collaboration with Heparegenix in Germany, we have obtained access to a small molecule inhibitor of MAP2K4: HRX-233. Our data indicate that HRX-233 is synthetic lethal with MEK inhibition in a range of KRAS mutant colon cancer cell lines, as the two drugs synergistically inhibit ERK activation. We aim to start testing this combination in the clinic in the near future.

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Jochems F, Thijssen B, De Conti G, Jansen R, Pogacar Z, Groot K, Wang L, Schepers A, Wang C, Jin H, Beijersbergen RL, Leite de Oliveira R, Wessels L, Bernards, R. The cancer SENESCopedia – a delineation of cancer cell senescence. Cell Rep. 2021;36:109441

Settleman J, Fernandes Neto JM, Bernards R. Thinking differently about cancer treatment regimens. Cancer Discov. 2021;11:1016-23

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Menzies AM, Amaria RN, Rozeman EA, Huang AC, Tetzlaff MT, van de Wiel BA, Lo S, Tarhini AA, Burton EM, Scolyer RA, Wargo JA, Blank CU, Long GV. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med. 2021;27(2):301-309

Rozeman EA, Hoefsmit EP, Reijers ILM, Saw RPM, Versluis JM, Krijgsman O, Dimitriadis P, Sikorska K, van de Wiel BA, Eriksson H, Gonzalez M, Cornelissen S, Broeks A, Klop WMC, Zuur CL, van Houdt WJ, Peeper DS, Spillane AJ, van Akkooi ACJ, Scolyer RA, Schumacher TNM, Menzies AM, Long GV, Blank CU. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med. 2021;27(2):256-263

Versluis JM, Reijers ILM, Rozeman EA, Menzies AM, van Akkooi ACJ, Wouters MW, Ch'ng S, Saw RPM, Scolyer RA, van de Wiel BA, Schilling B, Long GV, Blank CU. Neoadjuvant ipilimumab plus nivolumab in synchronous clinical stage III melanoma. Eur J Cancer. 2021;148:51-57

Personalizing immunotherapy

We aim to improve the outcome of patients by personalizing immunotherapy. The major vehicle for this is neoadjuvant immunotherapy. For example, in melanoma, baseline tumor mutational burden (TMB) and the interferon-gamma signature (IFN-signature) can be used as strong predictors of pathologic response and event-free survival (figure 1).

Biomarker identification for personalized immunotherapy

Our IFN-signature algorithm was applied in the first personalized neoadjuvant immunotherapy trial escalating the therapy for unfavorable tumors and de-escalating in favorable tumors, with excellent results (pathologic response of 90% in IFN sign high patients treated with a-PD-1 monotherapy only, DONIMI trial, Table 1).
Additional signature analyses have identified another cell type/cytokine. We have also identified soluble markers, that are associated with impaired response upon neoadjuvant therapy. This fine-tuning of the neoadjuvant therapies will allow further personalization of the therapy.
Finally, we achieved to start an international investigator initiated multicenter phase 3 trial testing neoadjuvant versus adjuvant immunotherapy in stage III melanoma. We hope to establish with this trial neoadjuvant immunotherapy in some years.

Targeting regulatory T cell (Treg) induction within the tumor microenvironment

The tumor microenvironment is characterized by low glucose and high lactic acid. We found that the combination of these two unfavorable factors hampers effector T cells. Currently, we are testing novel approaches in interfering into the induction of Treg, while supporting the T effector functions.

Improving anti-tumor immune responses by early activation

Signature analyses indicate that patients not responding to neoadjuvant combination of checkpoint inhibition have insufficient early immune activation and antigen presentation. By developing unspecific immune stimulation by performing a high-throughput drug-screen we identified molecules that possibly reverse this impairment in these patients.

Improving the quality of life of patients cured after neoadjuvant immunotherapy

With the high event-free survival, the long-term adverse events become more relevant. PRADO was the first trial personalizing surgery according to pathologic response, showing that in 60% of patients extensive surgery could be omitted, improving their quality of life significantly. Using app-based patient reported outcomes we plan to personalize also the follow-up and identify QoL challenges much earlier.

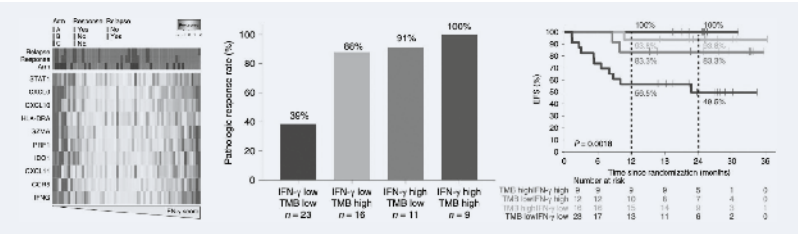

Figure 1 Rozeman et al. Nat Med 2021

PATHOLOGICAL RESPONSE	A: IFN-γ high NIVO (N=10)	B: IFN-γ high NIVO + DOM BID (N=10)	C: IFN-γ low NIVO + DOM BID (N=10)	D: IFN-γ low IPI + NIVO + DOM QD (N=10)
pRR	9 (90%)	8 (80%)	3 (30%)	4 (40%)
pCR	7 (70%)	5 (50%)	1 (10%)	3 (30%)
near-pCR	1 (10%)	1 (10%)	- -	1 (10%)
pPR	1 (10%)	2 (20%)	2 (20%)	- -
pNR	1 (10%)	2 (20%)	7 (70%)	6 (60%)

Figure 2 Reijers et al, LBA ESMO 2021

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Starreveld DEJ, Habers GEA, Valdimarsdottir HB, Kessels R, Daniëls LA, Leeuwen FE van, Bleiker EMA. Cancer-related fatigue in relation to chronotype and sleep quality in (non-)Hodgkin lymphoma survivors. J Biol Rhythms 2021;36(1):71-83

Ter Stege JA, Oldenburg HSA, Woerdeman LAE, Witkamp AJ, Kieffer JM, van Huizum MA, van Duijnhoven FH, Hahn DEE, Gerritsma MA, Kuenen MA, Kimmings AN, Ruhé PQ, Krabbe-Timmerman IS, van 't Riet M, Corten EML, Sherman KA, Bleiker EMA. Decisional conflict in breast cancer patients considering immediate breast reconstruction. Breast 2021;55:91-97

Psychosocial oncology in clinical genetics and survivorship care

This psychosocial oncology group is concentrating on survivorship and quality of life in individuals with cancer, and those at high risk because of an inherited gene mutation. The overall aim of the research is to improve the quality of life and quality of care. The study designs vary from observational (uptake and impact studies) and prospective (long-term surveillance studies) to randomized controlled trials (psychosocial intervention studies to support shared decision making and improve quality of life and quality of care). Examples of ongoing studies on the two main themes of this group (clinical genetics and survivorship) are described.

Clinical genetics

Development of a decisional support tool for hereditary gastric cancer

With financial support of the *Maag Lever Darm Stichting* we developed online information, including decision aids for carriers of a pathological variant in the *CDH1* or a *CTNNA1* gene. Carriers of these mutations have a high risk to develop gastric cancer before the age of 40. In addition, female carriers have an increased risk to develop breast cancer. As gastric surveillance is not reliable, prophylactic surgery including the removal of the stomach is recommended. Living without a stomach has many challenges. In 2021, we completed the needs assessment (semi-structured interviews) among 17 *CDH1*- or *CTNNA1*-mutation carriers and 17 healthcare professionals. Subsequently, we developed a website with information and three decision aids that focus on the decision whether or not to do DNA-testing, and the pros and cons of surveillance versus preventive surgery (stomach and breast). This online tool is being tested and will be launched in February 2022.

Survivorship and supportive care

Supporting women in making a well-informed decision about breast reconstruction: the development and evaluation of an online decision aid (TANGO-project)

The goal of the TANGO-project (funded by Alpe d'HuZes/KWF) is to develop, evaluate and implement an online patient decision aid (pDA) for breast cancer patients who consider immediate breast reconstruction after mastectomy. First, the pDA was developed in line with the information needs of patients and professionals by a multidisciplinary team. Subsequently, we performed a multicenter RCT to study the impact of the pDA on the decision-making process and the decision quality. In total, 250 patients were recruited. Patients were allocated to an intervention group (online pDA) or control group (KWF leaflet). Decisional conflict decreased over time in both groups, with no difference between both groups over time. However, patients in the intervention group felt better prepared for decision-making than patients in the control group (p=.002). Currently, the pDA is being used in five hospitals in the Netherlands.

Improving sleep quality, psychosocial functioning, and cancer related fatigue with light therapy (SPARKLE-study)

The SPARKLE-study (financially supported by the KWF) is a multi-center RCT to investigate the efficacy and working mechanisms of light therapy as a treatment for cancer-related fatigue in (non-)Hodgkin survivors. We randomly assigned 166 survivors of (non-)Hodgkin lymphoma presenting with chronic cancer-related fatigue (mean survival 13 years) to a bright white light intervention (BWL) or dim white light comparison (DWL) group. There were no significant differences between BWL and DWL in the reduction in fatigue over time. Both BWL and DWL significantly ($p < 0.001$) improved fatigue levels during the intervention followed by a slight reduction in this effect during nine moths follow-up. Similar results were found for depression, sleep quality, and some aspects of quality of life. Light therapy had no effect on circadian rhythms. We concluded that BWL was not superior in reducing fatigue compared to DWL in HL and DLBCL survivors. Remarkably, the total sample showed clinically relevant and persistent improvements on fatigue not commonly seen in longitudinal observational studies in these survivors.

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Sarbanes SL, Blomen VA, Lam E, Heissel S, Luna JM, Brummelkamp TR, Falck-Pedersen E, Hoffmann HH, Rice CM. E3 ubiquitin ligase Mindbomb 1 facilitates nuclear delivery of adenovirus genomes. Proc Natl Acad Sci U S A. 2021;118(1):e2015794118

Experimental biomedical genetics

Following a classical genetic approach, we mutate the genome and study the consequences. To apply this with high precision and throughput to disease-relevant processes we use a sequencing-based approach in haploid human cells to link millions of mutations in parallel to quantitative cellular phenotypes. Using this method, we study how genes collaborate to affect phenotypes, link new genes to human disease and address outstanding mysteries in cell biology.

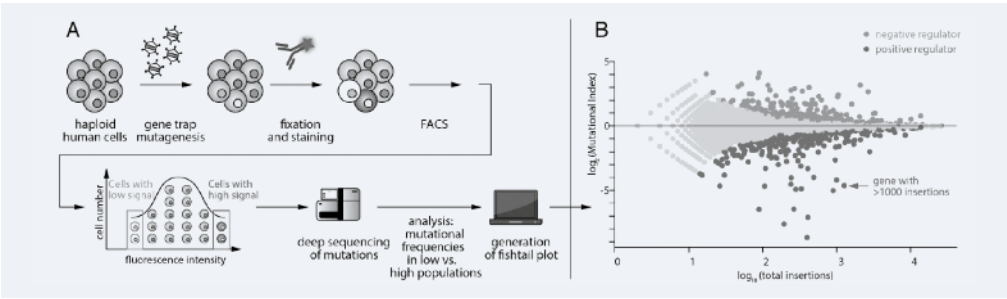
Regulators of Molecular Phenotypes

Human cells produce thousands of complex molecules, in particular proteins. Each protein contributes to a biological function and needs to be produced in the right amount, modified, repaired, replaced, inhibited, activated or brought to a location or complex when needed. These processes are orchestrated by the products of human genes. Whereas comprehensive charts are available depicting biochemical pathways, comparable maps do not exist for genetic tuning of the proteins in our cells.

Over the last few years, my group has extended our haploid genetic system to link genotypes to quantitative molecular phenotypes based on cellular protein readouts (Brockmann et al, Nature, 2017, see figure). This method identified new regulators of signaling pathways, a new component of the PD1-PD-L1 pathway (Mezzadra et al, Nature, 2017), an enzymatic modifier of the CD47 pathway (Logtenberg et al, Nature medicine, 2018), a new component of the mammalian cholesterol sensing pathway (Loregger et al, Nat Comm 2020), as well as the first enzymes that are able to catalyze tubulin detyrosination (Nieuwenhuis et al, Science, 2017).

Whereas interesting findings can be derived from an individual experiment our laboratory has assigned regulators to >100 quantitative phenotypes enabling comparative analysis. These comparisons point out specific regulators that affect only a limited number of traits and broad genetic regulators affecting many traits and can be used to cluster genes with similar phenotypic output. Finally, comparisons can reveal the emergence of new biological networks that only become critical in a mutant state.

During the last year we have used this platform to identify a long-sought factor required for the synthesis of mature actin (one of the most abundant and well-studied proteins in the cytosol), the final missing component of the tubulin tyrosination-detyrosination cycle impacting on our cytoskeleton and a new tightly-regulated pathway involved in lipid homeostasis.



The use of haploid human cells to identify genes that affect protein modifications or abundance.
Figure A. haploid human cells are mutagenized using a gene-trap virus and subsequently fixed, permeabilized and stained using an antibody of interest. Cells are sorted using fluorescence-associated cell sorting (FACS) to isolate distinct phenotypic populations with the highest or lowest level of the stained molecule. DNA is extracted and mutations are sequenced and assigned to genes.
Figure B. Example of a fishtail graph displaying genes that cause increased protein signal upon mutation (yellow dots) or decreased (blue dots). The relative mutation frequency in the high vs low channel is indicated on the y-axis and the number of mutations identified per gene on the x-axis. Each gene is represented by a single dot.

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Key publications

Duits DEM, de Visser KE. Impact of cancer cell-intrinsic features on neutrophil behavior. Semin Immunol. 2021 (in press)

Kos K, de Visser KE. Neutrophils create a fertile soil for metastasis. Cancer Cell 2021;39(3):301-303

Kos K, de Visser KE. The multifaceted role of regulatory T cells in breast cancer. Annu Rev Cancer Biol. 2021;5:291-310

Impact of the immune system on metastatic breast cancer and therapy response

Metastasis formation and unresponsiveness to conventional therapies are the challenges in cancer patient care that urgently need solutions. We study how the immune system influences breast cancer metastasis and therapy responsiveness. Through mechanistic understanding of the crosstalk between the immune system and cancer cells, we aim to contribute to the design of novel immunomodulatory strategies to fight metastatic breast cancer.

Understanding the crosstalk between breast cancer and the immune system

For successful dissemination and metastasis, cancer cells must evade detection and destruction by the immune system. In this longstanding research line in the lab, we study how mammary tumors shape both the intratumoral and the systemic immune landscape and how this contributes to immune escape. We observed that regulatory T cells (Tregs) systemically expand and undergo tissue-specific phenotypic alterations during primary mammary tumorigenesis. This tissue-specific rewiring of Tregs has functional significance, as tumor-educated Tregs promote lymph node metastasis, but not lung metastasis in our preclinical metastasis model (Kos *et al.* under review). Another immune cell type that expands systemically during mammary tumorigenesis are neutrophils. Together with Dr. Elzo de Wit, we have observed that tumor-education of neutrophils begins during haematopoiesis with tissue specification adding an additional layer of complexity to pro-metastatic neutrophil evolution (Garner *et al.* in preparation). How mammary tumors shape the immune system is influenced by their genetic makeup (Wellenstein *et al.* Nature 2019; Duits & De Visser. Semin Immunol 2021). We discovered that the immune landscape of tumors differs substantially between mammary tumors with different hotspot p53 mutations (Wellenstein, Duits *et al.* under revision) or with different oncogenic mutations in *PIK3CA* (van Weverwijk, in preparation). These insights will set the stage for tailoring immunomodulatory therapies to the DNA code of tumors of individual patients.

Dissecting the impact of the immune system on the efficacy of anti-cancer therapies

The immune system influences the success of cancer therapies, however, the exact underlying mechanisms are largely unknown. Together with medical oncologist and researcher Marleen Kok (NKI/AVL) we have established an extensive immunomonitoring program to comprehensively profile the peripheral immune landscape of breast cancer patients treated with immune checkpoint inhibitors, with the aim to identify immune-parameters associated with immunotherapy response and to gain a deeper understanding of the complex cancer-immune crosstalk in breast cancer patients. By combining this translational research with fundamental research, we have discovered an unanticipated causal role for eosinophils in the therapeutic benefit provided by immune checkpoint blockade (ICB) in combination with chemotherapy (Blomberg, Garner, Spagnuolo, Voorwerk *et al.* in preparation). In parallel, our preclinical studies show that depletion of neutrophils or regulatory T cells improves ICB response of breast cancer (Spagnuolo, Blomberg, Kos et al. in preparation). By gaining mechanistic insights into how the immune system impacts the therapeutic benefit of anti-cancer therapies, we aim to contribute to the rational design of effective immunomodulatory strategies to fight breast cancer.

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Liu NQ, Magnitov M, Schijns M, van Schaik, T, van der Weide RH, Teunissen H, van Steensel B, de Wit E. Rapid depletion of CTCF and cohesin proteins reveals dynamic features of chromosome architecture. bioRxiv 2021.08.27.457977

Liu NQ, Maresca M, van den Brand T, Braccioli L, Schijns MMGA, Teunissen H, Bruneau BG, Nora EP, de Wit E. WAPL maintains a cohesin loading cycle to preserve cell-type-specific distal gene regulation. Nat Genet. 2021;53(1):100-109

Van der Weide RH, van den Brand T, Haarhuis JHI, Teunissen H, Rowland BD, de Wit E. Hi-C analyses with GENOVA: a case study with cohesin variants. NAR Genom Bioinform. 2021;3(2):lqab040

Genome function and dynamics

Our research centers around the question: how are genes regulated within the context of the three-dimensional (3D) genome? We use a combination of genetic and acute perturbation experiments in combination with genomics tools to understand how distal regulatory elements (e.g. enhancers) contribute to the regulation of genes. In addition to implementing and developing genomics methods we also develop software for the analysis of chromosome conformation capture data.

Genomics changes at high temporal resolution

Gene regulation is a highly dynamic process and can be dependent on so-called distal enhancers located hundreds of kilobases away from their target promoter. We have shown that regulation by distal enhancers is dependent on a dynamic process called loop extrusion. Loop extrusion is mediated by the cohesin complex and is also important for shaping the 3D genome. To assess functional regulatory relationships between enhancers, promoter, regulators and the 3D genome we perform loss-of-function analysis of the crucial regulators of loop extrusion. To properly assess cause-and-effect relationships on a genome-wide scale we need acute loss of the proteins combined with genomics measurements at high temporal resolution, enabling the separation of primary from secondary effects.

We have invested in setting up acute protein depletion tools in mouse embryonic stem cells which allow us to functionally knock-out proteins within one hour by the addition of a small molecule. We have used this to perform loss-of-function analysis of transcription factors, cohesin and cohesin regulators (Liu et al 2021, Nature Genetics). This has enabled us to elucidate the role of these proteins in organizing the 3D genome and gene regulation.

Synthetic embryo models for studying gene regulatory control of cell fate transitions

The study of early development in mammals is hampered by the fact that embryos develop *in utero*. We have set up a synthetic *in vitro* differentiation system which enables development of embryo-like structures from mouse embryonic stem cells called gastruloids. We have determined the changes in the regulatory landscape of gastruloids at single cell resolution. This has enabled us to define regulatory trajectories and cell fate transitions with unprecedented temporal resolution. By performing gastruloid differentiation in cells in which key regulatory factors such as CDX2 were ablated we can assess the contribution of these factors to *in vitro* differentiation.

By combining the gastruloid differentiation protocol with acute depletion of regulators of the 3D genome we can study the role of these factors in the differentiation process. Many of the regulators of the 3D genome are highly essential in development, but loss of these factors in cell lines often has only limited effects on gene expression. In gastruloids, we find that disruption of the 3D genome can severely affect the morphology of gastruloids. However, loss of the regulators is not intrinsically lethal to the cells or their differentiation potential. We want to use these models to elucidate how these factors contribute to acurate spatiotemporal gene expression and thereby guide proper early development.

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Alkan F, Silva J, Barberà EP, Faller WJ. Ribo-ODDR: Oligo design pipeline for experiment-specific rRNA depletion in ribo-seq. Bioinformatics. 2021;37(17):2659-67

Champagne J, Pataskar A, Blommaert N, Nagel R, Wernaart D, Ramalho S, Kenski J, Bleijerveld OB, Zaal EA, Berkers CR, Altelaar M, Peeper DS, Faller WJ, Agami R. Oncogene-dependent sloppiness in mRNA translation. Mol Cell. 2021;81(22):4709-4721.e9

Minnee E, Faller WJ. Translation initiation and its relevance in colorectal cancer. FEBS J. 2021;288(23):6635-6651

RNA translation in health and disease

The main interest of our lab is in the role that RNA translation plays in normal and cancer cells. Understanding this mechanism of gene regulation, and how it is hijacked in cancer, will allow us to uncover proteins and pathways involved in cancer phenotypes.

RNA translation in intestinal stem cells

In particular we are focused on the stem cell populations in the intestine, and cancers of the same organ. We study this using genetically modified mouse models (GEMMS), and 3d organoid culture, which allow us to maintain the complexity of the organ, while still providing tractable systems to study.

Stem cells are the drivers of colorectal cancer development, and also mediate resistance to therapy. Previous studies have suggested that there are global changes in protein synthesis in stem cells compared to differentiated cells. Using *in vivo* and *in vitro* tools, we have shown that collisions between ribosomes cause dramatic changes in intestinal stem cells. These collisions happen under conditions of nutrient deprivation or inhibition of mTOR.

These collisions cause the activation of a kinase called Zakα, which results in the appearance of fetal-like stem cells, which have distinct characteristics, including a switch in the metabolic pathways used by the cell. We are now studying this stem cell population to understand its function in the normal intestine and cancer, and trying to understand whether it is a process that can be targeted with therapy.

Ribosomal heterogeneity in normal and cancer tissue

In the last number of years, we have come to realize that not all ribosomes are the same. Differences in their composition and modification result in distinct populations, which can have major ramifications on the specific mRNAs that are being translated. This has proven difficult to study however, as we lack techniques to identify it.

We have developed a novel method to detect these different ribosome populations in the cell. We do this by combining ribosome profiling data with the known 3d structure of the ribosome, allowing us to predict the changes in the composition of the ribosome in different contexts. We have developed a pipeline called ARF (Analysis of rRNA Fragments) to automate this analysis, and have applied it to several biological situations. For example, we have shown that during development, one ribosomal protein changes consistently across all tested organs, and that this results in changes what mRNAs are being translated most efficiently.

Using this approach, we are now beginning to understand what ribosome populations are present in different cell types, and how oncogenic mutations can change them.

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Key publications

Bakker NAM, Rotman J, van Beurden M, Zijlmans HJM, van Ruiten M, [...], van den Berg JH, van Trommel NE. HPV-16 E6/E7 DNA tattoo vaccination using genetically optimized vaccines elicit clinical and immunological responses in patients with usual vulvar intraepithelial neoplasia (uVIN): a phase I/II clinical trial. J Immunother Cancer. 2021;9(8):e002547

Matas-Rico E, Frijlink E, van der Haar Àvila I, Menegakis A, van Zon M, [...], Perrakis A, Verbrugge I, van den Berg JH, Borst J, Moolenaar WH. Autotaxin impedes anti-tumor immunity by suppressing chemotaxis and tumor infiltration of CD8+ T cells. Cell Rep. 2021;37(7):110013

Van den Berg JH, Heemskerk B, van Rooij N, Gomez-Eerland R, [...], van Buuren MM, Kvistborg P, Spits H, Schotte R, Mallo H, Karger M, van der Hage JA, Wouters MWJM, Pronk LM, Geukes Foppen MH, Blank CU, Beijnen JH, Nuijen B, Schumacher TN, Haanen JBAG. Tumor infiltrating lymphocytes (TIL) therapy in metastatic melanoma: boosting of neoantigen-specific T cell reactivity and long-term follow-up. J Immunother Cancer. 2020;8(2):e000848

Immunotherapy, immunomonitoring and production facility

This research line is aimed at developing novel T cell-directed or based immunotherapies that can be applied in cancer patients. The focus is on patients with solid tumors, including melanoma, NSCLC, renal cell carcinoma, ovarian cancer and HPV-associated cancers. These immunotherapies comprise DNA-based vaccines and T cell products, including Tumor infiltrating Lymphocytes (TILs) and genetically modified peripheral blood T cells. GMP production of these advanced therapeutic medicinal products (ATMPs) takes place in the Biotherapeutics Unit (BTU), situated in the hospital pharmacy.

A second objective concerns immunomonitoring, primarily to evaluate the effects of (novel) immunotherapies. These studies are conducted together with the Schumacher, Kvistborg, Thommen and Blank labs at the NKI-AVL and with national and international collaborators.

Highlights 2021

In collaboration with Sanquin and one European cancer center in Copenhagen, Denmark, we are continuing our international, randomized controlled phase III trial in stage IV melanoma patients, comparing Tumor Infiltrating Lymphocytes (TIL) with standard of care for second line treatment. Enrollment of patients started in October 2014. Up to date 161 patients have been randomized. Materials (liquid and tumor biopsies) are being collected for immunomonitoring and additional translational research. We have established additional funding through a Dutch Cancer Society Grant to set-up a potency assay, required for EMA registration.

In addition, in close collaboration with a commercial partner, we have developed a novel T cell-based therapy based on autologous peripheral blood T cells directed against patient-specific neo-antigens. After having set-up and validated the GMP production process the phase Ib/II clinical trial for patients with refractory melanoma, has been opened in November 2020. Up to date, three patients have been infused successfully.

In 2019, we obtained a large translational ZonMW grant to develop a fully personalized TCR gene therapy. In a Proof-of-Concept study in melanoma patients, patient-specific neoantigen-specific TCRs will be identified using technology developed by Ton Schumacher and Wouter Scheper, and transferred to patient T cells using CRISPR/Cas9 technology.

In close collaboration with another commercial partner we are further developing an alternative strategy for isolation of neoantigen-specific TCRs for clinical application. The aim is to file the clinical trial package for this study to the Dutch regulatory authority end of 2021.

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Van Bockstal MR, Cooks M, Nederlof I, [...], Horlings H, van Deurzen CHM. Interobserver agreement of PD-L1/SP142 immunohistochemistry and Tumor-Infiltrating Lymphocytes (TILs) in distant metastases of triple-negative breast cancer: A proof-of-concept study. A report on behalf of the International Immuno-Oncology Biomarker Working Group. Cancers (Basel). 2021;13(19):4910

Panteli A, Teuwen J, Horlings H, Gavves E. Sparse-shot Learning with Exclusive Cross-Entropy for Extremely Many Localisations. *Proceedings of the IEEE/CVF International Conference on Computer Vision (ICCV)* pp. 2813-2823, (2021).

Our team focuses on the development of "Computational Pathology" approaches that combines clinical, pathology, and genomics data with image analysis of solid tumors to identity biomarkers for prediction of treatment response. We train powerful computers to recognize the tumor and its microenvironment by annotating pathology samples from the clinic. Combining these image-based quantitative results with genetic analysis of the cancer-immune interactions can be complementary or offer completely new observations to empower precision oncology. Last year our highlights have been the following:

Deep learning Ki67-Algorithm

Window studies are gaining traction to assess (molecular) changes in short timeframes. Decreased tumor cell positivity for the proliferation marker Ki67 is often used as a proxy for treatment response. We compared pathologist assessed and an automated deep learning algorithm to detect IHC-based Ki67 expression in samples from pre- and postmenopausal women in a neo-adjuvant, endocrine therapy focused trial (NCT00738777), randomized between tamoxifen, anastrozole, or fulvestrant.

We developed a deep learning Ki67 algorithm, by means of a convolutional neural network (CNN). The algorithm was trained and validated on a dataset containing whole slide images of KI67 stained tumor tissue of 4,599 breast cancer patients treated at the Antoni van Leeuwenhoek. In short, Ki67 staining positivity in tumor cells is determined by the colour and brightness of the staining area within each nucleus contour (Fig. 1). This resulted in an algorithm with ≥92% performance compared to the detection of positive/negative Ki-67 nuclei by a pathologists. After establishing the performance of the AI algorithm, we next set out to apply the algorithm on all samples included in the trial. Based on the algorithm results, and in agreement with the pathologist' observations, the magnitude of Ki67 change differed between pre- and postmenopausal patients (p-value = 0.033) who received tamoxifen. Upon tamoxifen, IHC-based Ki67 levels were decreased in both pre- and postmenopausal breast cancer patients. The magnitude of decrease of Ki67 IHC was smaller in pre- versus postmenopausal women. We found a direct relationship between post-treatment estradiol levels and the magnitude of the Ki67 decrease in tumors. These data suggest that an automated deep learning IHC-based Ki67 may be an appropriate biomarker for tamoxifen response in premenopausal breast cancer patients, but anti-proliferative effect size depends on estradiol levels.

PD-L1 and Tumor infiltrating lymphocytes

Patients with advanced triple-negative breast cancer (TNBC) benefit from treatment with atezolizumab, provided that the tumor contains ≥1% of PD-L1/SP142-positive immune cells. Numbers of tumor-infiltrating lymphocytes (TILs) vary strongly according to the anatomic localization of TNBC metastases. We investigated inter-pathologist agreement in the assessment of PD-L1/SP142 immunohistochemistry and TILs. Ten pathologists evaluated PD-L1/SP142 expression in a proficiency test comprising 28 primary TNBCs, as well as PD-L1/SP142 expression and levels of TILs in 49 distant TNBC metastases with various localizations. Interobserver agreement for PD-L1 status (positive vs. negative) was high in the proficiency test: the corresponding scores as percentages showed good agreement with the consensus diagnosis. In TNBC metastases, there was substantial variability in PD-L1 status at the individual patient level. For one in five patients, the chance of treatment was essentially random, with half of the pathologists designating them as positive and half negative. Assessment of PD-L1/SP142 and TILs as percentages in TNBC metastases showed poor and moderate agreement, respectively. Additional training for metastatic TNBC is required to enhance interobserver agreement. Such training, focusing on metastatic specimens, seems worthwhile, since the same pathologists obtained high percentages of concordance (ranging from 93% to 100%) on the PD-L1 status of primary TNBCs. In the coming year we will develop and test if an artificial intelligence-based method can assess PDL1 and Tils and enhance interobserver agreement between pathologists.

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Kwesi-Maliepaard EM, Jacobs H, van Leeuwen F. Signals for antigen-independent differentiation of memory CD8+ T cells. Cell Mol Life Sci. 2021;78(19-20):6395-6408

Will Castro LSEP, Pieters W, Alemdehy MF, Aslam MA, Buoninfante OA, Raaijmakers JA, Pilzecker B, van den Berk PCM, Te Riele H, Medema RH, Pedrosa RC, Jacobs H. The Widely Used Antihelmintic Drug Albendazole is a Potent Inducer of Loss of Heterozygosity. Front Pharmacol. 2021;18;12:596535

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Molecular programming of differentiation and mutagenesis in lymphocytes

To generate the enormous diversity of antigen receptors, lymphocytes and their precursors activate specific mutation pathways to remodel antigen-receptor genes. Besides studying the role of DNA damage response (DDR) and DNA damage tolerance (DDT) components in shaping the antigen-receptor repertoire our model systems provide novel insights into genome maintenance and tissue homeostasis. Our research mainly focuses on two subjects: (1) DDT in physiology and cancer treatment, (2) Molecular regulation of normal and malignant lymphocyte development and differentiation.

Histone methyltransferase DOT1L controls state-specific identity during B cell differentiation

We identified a critical role for the histone H3K79 methyltransferase DOT1L in B-cell differentiation. Mouse B cells lacking Dot1L fail to establish germinal centers (GC) and normal humoral immune responses *in vivo*. *In vitro*, activated B cells in which Dot1L was deleted or inhibited show aberrant differentiation and prematurely acquired plasma cell characteristics. Epigenomics and transcriptomics analysis revealed that DOT1L promotes expression of a pro-proliferative, pro-GC program. DOT1L indirectly supports the repression of an anti-proliferative plasma cell differentiation program by maintaining the repression of Polycomb Repressor Complex 2 (PRC2) targets. Our findings identify DOT1L as a key in establishing an epigenetic barrier that warrants B-cell naivety and GC B-cell differentiation.

Signals for antigen-independent differentiation of memory CD8 $^{+}$ T cells

A substantial fraction of $CD8^{+}$ T cells acquires memory features independently of antigen exposure. These antigen-inexperienced memory T cells (T_{AIM}) exhibit characteristics of conventional or true memory cells, including antigen-specific responses. In addition, they show responsiveness to innate stimuli and have been suggested to provide additional levels of protection toward infections and cancer. We reviewed the current understanding of T_{AIM} cells, focusing on extrinsic and intrinsic molecular conditions that underlie their development, molecular definitions and immunological properties, as well as transcriptional and epigenetic regulation.

Albendazole is a potent inducer of loss of heterozygosity

The antihelminthic drug albendazole (ABZ) acts as potent tubulin polymerization inhibitor. Applying UV-Vis spectrometry, we here also demonstrate ABZ as a DNA intercalator. This insight led us to determine the primary mode of ABZ action in mammalian cells. As revealed by RNA sequencing, ABZ did neither grossly affect replication as analyzed by survival and replication stress signaling, nor the transcriptome. Actually, unbiased transcriptome analysis revealed a marked cell cycle signature in ABZ exposed cells. Short-term exposure to ABZ arrested mammalian cells in G2/M cell cycle stages associated with frequent gains and losses of chromatin. Cellular analyses revealed ABZ as a potent mammalian spindle poison, explaining the serious chromosome segregation defects. Since chromosomal aberrations promote both cancer development and cell death, we determined if besides its general cytotoxicity, ABZ could predispose to tumor development. As measured by loss of heterozygosity (LOH) *in vitro* and *in vivo* ABZ was found as a potent inducer of LOH and accelerator of chromosomal missegregation.

Telomere and genome integrity

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De Krijger I, Boersma V, Jacobs JJL. REV7: Jack of many trades. Trends Cell Biol. 2021;31(8):686-701

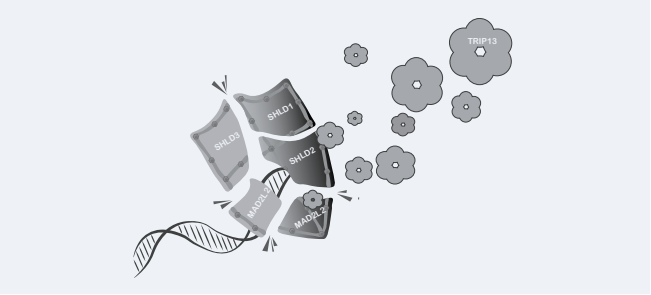
Appropriate responses to DNA damage are critical for maintaining genome integrity and preventing pathology such as cancer. In addition, how normal cells and cancer cells respond to DNA damage not only affects the efficacy and specificity of DNA damaging cancer therapies, but is also an important factor in development of therapy resistance. Therefore, to increase our understanding of cancer development and improve DNA damaging cancer therapies we study the molecular mechanisms of DNA damage response (DDR) and DNA repair activities at telomeres and at DNA double-strand breaks (DSBs), as these are only partially understood.

DNA repair pathway choice

The main mechanisms to repair DSBs, non-homologous end joining (NHEJ) and homologous recombination (HR), are activated by 53BP1 and BRCA1, respectively. The appropriate use of these pathways is critical for genome stability and is regulated at the level of resection of the exposed DNA end. In earlier work, we found the HORMA-domain protein MAD2L2 (or REV7) to promote NHEJ and inhibit HR at uncapped telomeres and DSBs by counteracting 5' DNA end-resection downstream of 53BP1. Thereby MAD2L2 contributes to DNA repair pathway choice and to the synthetic lethality of BRCA1-deficient cancer cells treated with PARP inhibitors. We subsequently found three uncharacterized factors, SHLD1, SHLD2 and SHLD3, to act with MAD2L2 in a complex called shieldin. Shieldin protects DNA ends against excessive resection, thereby promoting NHEJ and inhibiting HR, by potentially blocking nucleases and recruiting CST to promote fill-in DNA synthesis.

Recently, we investigated the requirements for shieldin assembly and activity. We found that appropriate function of MAD2L2 in DNA repair requires it to dimerize, and we showed how this is mediated by, and affects, interaction with the other shieldin components. In absence of MAD2L2 dimerization, shieldin can not assemble into a functional complex and DNA repair by NHEJ is impaired in multiple settings, including at uncapped telomeres and during immunoglobulin class-switch recombination. Moreover, MAD2L2 dimerization, along with the presence of SHLD3, allows shieldin to interact with the ATPase TRIP13. TRIP13 can drive a topological switch that involves the conversion of a "closed" to "open" conformation of the "safety-belt", a structurally mobile element within HORMA-domain proteins that entraps a peptide of an interacting protein when it is in its closed conformation, and that releases the peptide upon switching to its open conformation. Besides mediating the interaction of MAD2L2 with multiple different proteins, the safety belt of MAD2L2 also mediates its interaction with SHLD3.

Indeed, we found the (dis)assembly of shieldin at DSBs and shieldin-controlled DNA repair to be sensitive to the presence and activity of TRIP13. While our findings are largely in line with TRIP13 driving disassembly and inactivation of shieldin, we also obtained seemingly opposing results in several conditions when inactivating TRIP13. These results suggest that TRIP13 is important for appropriate dynamic engagement of MAD2L2 in different protein complexes, by enabling MAD2L2 to shuttle between different protein complexes or promoting disassembly of MAD2L2 protein complexes at the right place and time. Together, our data provide important insights in shieldin function and the potential of TRIP13 inhibition for modulating DNA repair.



At DNA double-strand breaks and uncapped telomeres the shieldin complex, composed of MAD2L2, SHLD1, SHLD2 and SHLD3, acts as a shield against excessive DNA end-resection activities. Dimerization of MAD2L2 is critical to both the assembly of shieldin from its individual components and the disassembly of shieldin by the TRIP13 ATPase.

J

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Publication

Harkes R, Kukk O, Mukherjee S, Klarenbeek J, van den Broek B, Jalink K. Dynamic FRET-FLIM based screening of signal transduction pathways. Sci Rep 2021;11(1):20711

Biophysics of cell signaling

We use biophysical techniques, including FRET and FLIM microscopy, electrophysiology, and mechanical manipulations of cells to study cell signaling events and cytoskeletal dynamics with high spatial and temporal resolution. Advanced microscopy, especially 'functional imaging', is at the heart of all research projects in our lab. Functional imaging microscopy aims at understanding the function (rather than just the localization or concentration) of the biomolecules that constitute our cells. We develop novel methodologies, including hard- and software for various advanced microscopy applications, FRET and FLIM sensors, and methods to combine these techniques with (genetic) screening technology. These techniques are used in research projects in our group as well as in collaborations within and outside our institute.

Towards pooled genetic microscopy screens

In collaboration with the Beijersbergen lab, we have been implementing a new microscopy-based pooled genetic screening concept, which should enable genetic screens for basically any phenotype that can be assessed by light microscopy in either fixed or living cells. Pooled microscopy screening is an emerging powerful technique that is poised to eventually replace large, costly and time-consuming multi-well genetic screens. Cells expressing a photo-activatable red fluorescent protein are infected with a mixed viral library of CRISPR/Cas guide RNAs. Cells are imaged at high resolution and desired phenotypes are then detected automatically by computer image analysis, including deep-learning methods. Subsequently, interesting phenotypes ('hits') are marked semi-permanently by e.g. photoconversion of photo-activatable RFP with a brief flash of light. The activated RFP tags, present in just a few cells among the (up to) millions of imaged cells, can then be isolated from the population by FACS sorting, or by direct cell picking using micromanipulation. Alternative methods for hit selection will be tested too. In the last two years, similar though much more laborious pooled imaging screens have appeared in the high-impact literature and we believe that it is essential that the NKI stays at the forefront of these developments. A main advantage over more conventional pooled screens is that it allows picking up any knockdown-induced changes in the individual cells, be it in their morphology, differentiation status, duration of mitotic phases, kinetic properties of cell signaling as detected by FRET or any other phenotype, as long as it can be detected by automated image analysis.

FRET/FLIM microscopy finally fast enough to do screens

Pooled screens should be particularly powerful in identifying novel constituents of signal transduction pathways. The outcome of signaling events commonly depends not only on the strength of signaling events, but also on their time course and subcellular location. Thus, time-lapse microscopy of living cells is pivotal, using indicators such as small-molecule probes and in particular FRET sensors. However, in a multiwell format a genome-wide screen of just one-hour time lapses would take years to complete. Challenges such as medium evaporation and aging, variability of results due to differences in cell confluency, et cetera have hampered efforts in this direction. Pooled screens do not suffer from such challenges, but on the other hand require instrumentation to detect FRET that must be both extremely vast and very quantitative. Fluorescence lifetime microscopy (FLIM) is the most quantitative method to detect FRET. FLIM records the fluorescence lifetime of a fluorophore, i.e. the average time that a fluorophore remains in the excited state following excitation and is an intrinsically quantitative method to detect molecular interactions in living cells. FLIM has traditionally been much to slow and also is a photon-hungry technique. We have therefore collaborated with industrial partners to develop extremely fast, flexible and highly sensitive FRET/FLIM detection on both confocal and widefield microscopes. Using these developments, we have now moved forward and implemented the first FRET/FLIM screens for dynamic signaling events.

Mouse models of breast cancer

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Key publications

Paes Dias M, et al. Loss of nuclear DNA ligase III reverts PARP inhibitor resistance in BRCA1/53BP1 double-deficient cells by exposing ssDNA gaps. Mol Cell. 2021;81(22):4692-4708

Pulver EM, et al. A BRCA1 coiled-coil domain variant disrupting PALB2 interaction promotes the development of mammary tumors and confers a targetable defect in homologous recombination repair. Cancer Res. 2021;81(24):6171-6182

We study breast cancer biology in mouse models. We use genetically engineered and patient-derived tumor xenograft (PDX) models to (1) study cancer cell-intrinsic and -extrinsic mechanisms of tumor development and progression; (2) develop novel therapeutic strategies for tumor prevention and treatment; (3) study mechanisms of therapy resistance.

Immune evasion in triple-negative breast cancer

Although many triple-negative breast cancers (TNBCs) are genomically unstable, they show poor response to immunotherapy. Using mouse models of BRCA1-proficient and -deficient TNBC, we found that MYC overexpression suppresses inflammatory signaling induced by BRCA1 loss. ChIP-sequencing revealed that MYC directly binds promoters of multiple interferon-signaling genes, which were downregulated upon MYC overexpression. Our data reveal that MYC suppresses innate immunity and facilitates immune escape, explaining the poor immunogenicity of MYC-overexpressing TNBCs.

Combatting PARPi resistance in BRCA1-deficient breast cancer

Although BRCA1-deficient cancers are highly sensitive to poly(ADP-ribose) polymerase inhibitors (PARPi), they ultimately acquire resistance. Functional genetic screens in BRCA1-deficient cells that acquired PARPi resistance via loss of 53BP1, identified nuclear LIG3 as a suppressor of PARPi toxicity. LIG3 depletion in BRCA1-deficient cells results in increased replication fork asymmetry and ssDNA gaps behind the forks, resulting in accumulation of chromosomal abnormalities. Our results highlight LIG3 as a candidate therapeutic target for enhancing PARPi sensitivity.

Identification of truncated FGFR2 as a clinically actionable oncogene

By combining transposon-based screening and tumor modelling in mice with analysis of human oncogenomics datasets, we found that truncation of exon 18 (E18) is central to the oncogenicity of FGFR2. Genomic alterations that generate stable E18-truncated FGFR2 are also actionable therapeutic targets, as shown in preclinical tumor models and in a clinical trial. Thus, we uncovered a novel paradigm in oncogenic FGFR2 signaling and propose that cancers harboring any FGFR2 variant that truncates E18 should be considered for FGFR-targeted therapies.

Role of CAFs in ILC

Invasive lobular carcinoma (ILC), the second most common breast cancer subtype, is characterized by a large infiltrate of cancer-associated fibroblasts (CAFs). By performing various transplantation techniques using clinically relevant ILC mouse models, we found that all CAFs originate from tissue-resident normal fibroblasts. Single-cell transcriptomics revealed two populations of normal mammary fibroblasts giving rise to three CAF populations that possess distinct functions. Furthermore, transcriptomics analysis of tumor-CAF interactions revealed an intricate network of ECM-receptor based crosstalk. Genetic perturbations in this network inhibited ILC development in mice.

In vivo models of DCIS

The advent of breast screening has resulted in increased detection of Ductal Carcinoma In Situ (DCIS) as well as overtreatment since most DCIS lesions will not progress into invasive breast cancer. To gain better insight into the biology of DCIS, we have developed somatically engineered rat models and intraductal PDX models of DCIS. We are using these models to (i) validate candidate DCIS driver genes, (ii) identify factors that distinguish indolent DCIS from potentially hazardous lesions, (iii) study response of DCIS to targeted therapeutics.

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Key publications

Hammerl D, Martens J, Timmermans M, Smid M, Trapman-Jansen A, Foekens R, Isaeva O, Voorwerk L, Balcioglu H, Wijers R, Nederlof I, Horlings H, Salgado R, Kok M*, Debets R*. Spatial immunophenotypes predict response to anti-PD1 treatment and capture distinct paths of T-cell evasion in triple negative breast cancer. Nat Commun, 2021;12(1):5668

McGrail D, Pilié P, Dai H, Nguyen T, Lam A, Liang Y, Voorwerk L, Kok M, Zhang X, Rosen J, Heimberger A, Peterson C, Jonasch E & Lin S. Replication stress response defects are associated with response to immune checkpoint blockade in non-hypermutated cancers. Sci Transl Med, 2021;13(617)

Voorwerk L, Kok M. 'IMpassionate conflicts' in immunotherapy trials for metastatic triple-negative breast cancer. Ann Oncol 2021;32(8):947-949

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Improving breast cancer immunotherapy

Cancer immunotherapy, especially PD1-blockade, has resulted in durable anti-tumor responses in a subgroup of breast cancer patients. However, the overall response rates are still modest. Using innovative clinical trial approaches as well as applying state-of-the-art knowledge from basic cancer immunology, we work on i) the identification of those breast cancer patients that will benefit from immunotherapy, and ii) a better understanding of the interactions between breast cancer and tumor-associated as well as circulating immune cells in order to develop novel immunomodulatory strategies.

Modulation of the tumor microenvironment to improve response to PD-1 blockade

The response rate of triple negative breast cancer (TNBC) patients to PD-1 blockade is low, highlighting an urgent clinical need for strategies that render the TNBC tumor microenvironment (TME) more sensitive to PD-1 blockade. Immunomodulatory mechanisms have been proposed for both chemotherapy and irradiation, but it has not been established whether these therapies can favorably change the TME. In the currently ongoing TONIC trial (NCT04159818), patients with metastatic TNBC are randomized to anti-PD1 without induction or to one of two induction treatments, consisting of a two-week low-dose regimen of cisplatin or doxorubicin, all followed by anti-PD-1. These arms are expansion cohort of TONIC stage I in which most clinical responses were observed on anti-PD1 in the cisplatin and doxorubicin induction cohorts. After doxorubicin and cisplatin induction, we detected an upregulation of immune-related genes, involved in PD-1/PD-L1, and T-cell cytotoxicity pathways. This was supported by enrichment among upregulated genes related to inflammation, JAK-STAT and TNFα-signaling after doxorubicin. (Voorwerk et al. Nature Medicine 2019). Results of these expansion cohorts are expected in 2022. Together with the Erasmus MC we discovered that spatial CD8- immunophenotypes are associated with outcome after anti-PD1. These excluded, ignored and inflamed phenotypes can be captured by a gene classifier that predicts prognosis of various cancers as well as anti-PD1 response in our TONIC trial.

For invasive lobular breast cancer, which is considered a classical 'cold' tumor. The GELATO (NCT03147040) study is a multicenter phase 2 trial initiated for ILC patients with metastatic disease. Based on the preclinical data we hypothesize synergy between platinum and immune checkpoint blockade in a subgroup of immune-related ILC. This year at ESMO Breast Cancer we presented the first clinical results. With an objective response rate of 19% the first stage of the trial (n=21) has met its primary endpoint. Interestingly, most responses were seen in triple negative ILC patients.

Releasing CD8 and NK cells in HER2-positive metastatic breast cancer

In 2020, the phase II MIMOSA (NCT04307329) study has started in which the novel generation checkpoint inhibitor monalizumab is tested in combination with trastuzumab in HER2-positive metastatic breast cancer.

Neoadjuvant immunotherapy for immunogenic breast tumors

So far research has focused on the addition of PD1-blockade to standard neoadjuvant chemotherapy. Knowledge on which early breast tumors could be effectively treated with immune checkpoint blockade without chemotherapy is lacking. The BELLINI study (NCT03815890) has started in 2019 and evaluates the value of PD1-blockade and anti-CTLA4 in HER2-negative breast tumors with high levels of tumor-infiltrating lymphocytes (sTILs).

Systemic immune characteristics in breast cancer patients

There is substantial evidence that suppressive immune cells and soluble immune mediators can blunt the anti-cancer T cells response. Right now the question is whether this immunosuppressive phenomenon is present in BC patients. In collaboration with the group of prof Karin de Visser we have set-up a pipeline for analyses of these systemic immunosuppressive components using flow cytometry combined with functional assays on fresh material from BC patients who receive various combinations of chemo-immunotherapy in our clinical trials.

T cells in cancer

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Key publications

Gangaev A, Ketelaars SLC, Isaeva OI, Patiwael S, Dopler A, Hoefakker K, De Biasi S, Gibellini L, Mussini C, Guaraldi G, Girardis M, Ormeno CMPT, Hekking PJM, Lardy NM, Toebes M, Balderas R, Schumacher TN, Ovaa H, Cossarizza A, Kvistborg P. Identification and characterization of a SARS-CoV-2 specific CD8 T cell response with immunodominant features. Nat Commun 2021;12(1)2593

Gangaev A, Rozeman EA, Rohaan MW, Isaeva OI, Philips D, Patiwael S, van den Berg JH, Ribas A, Schadendorf D, Schilling B, Schumacher TN, Blank CU, Haanen JBAG, Kvistborg P. Differential effects of PD-1 and CTLA-4 blockade on the melanoma-reactive CD8 T cell response. Proc Natl Acad Sci UAS 2021;118(43) doi

Nagler A, Kalaora S, Barbolin C, Gangaev A, Ketelaars SLC, Alon M, Pai J Benedek G, Yahalom-Ronen Y, Erez N, Greenberg P, Yagel G, Peri A, Levin Y, Satpathy AT, Bar-Haim E, Paran N, Kvistborg P, Sanuals Y. Identification of presented SARS-CoV-2 HLA class I and HLA class II peptides using peptidomics. Cell Rep. 2021;35(13)

Even though ICB has significantly improved survival of cancer patients, there is still a large proportion of patients not responding, despite of the presence of tumor-infiltrating CD8 T cells. Our ambition is to focus on research with clear impact for patients, and we strongly believe that a better understanding of the tumor-specific T-cell response is key to this. Our research is divided into two pillars, with the tumor-specific T-cell response as the unifying element:

1. Dissecting the states of the tumor-specific T cells.

We aim to understand the T-cell properties that result in T cells being reinvigorated by ICB. Over the last year, we have initiated work studying the tumor-specific T cells in cancers with low ICB responsiveness, such as mesothelioma, ovarian cancer, bladder cancer and triple negative breast cancer. By focusing our analyses on tumor-specific T cells rather than bulk T cells, this work will help understand which T-cell states are reprogrammable and therefore important for clinical response to ICB.

2. Investigating the role of ribosomal heterogeneity in tumor cell sensitivity to T-cell response.

This is a novel research field which has emerged over the last years with the recognition that ribosomes are not a single population, but rather a heterogenous population with differing roles. This is a fundamental mechanism of gene regulation that is relevant in all aspects of biology. We are working to understand the role of ribosome populations on tumor cell sensitivity to T-cell attack. Our initial work has provided proof of principle that heterogeneity of ribosomal proteins can play a role in T-cell response to melanoma.

In silico analysis reveals a significant conservation of T-cell epitopes across SARS-CoV-2 variants

In addition to our core research lines, we have contributed to the understanding of the immune response to SARS-CoV-2 over the last two years. Selective immune pressure can select for virus variants harboring mutations leading to immune escape. For viruses causing acute infections such as SARS-CoV-2, such pressure is expected primarily from the antibody responses induced through natural infection and vaccinations. In contrast, selective pressure by T cells in primarily relevant for chronic infections due to the high level of MHC polymorphism. In line with these expectations, computational analysis of the consequence of mutations defining SARS-CoV-2 variants of concern and interest on T-cell recognized epitopes revealed a highly limited effect. Only a limited number of T-cell epitopes were changed in terms of either predicted binding affinity to MHC or predicted immunogenicity. The observed changes in the peptide characteristics were bi-directional indicating a stochastic effect of gained mutations. This suggests a lack of T-cell pressure in the evolutionary development of the virus. However, as the current vaccine design is limited to the spike protein and there is an accumulation of mutations in this protein induced by a selective pressure by antibody responses, there is also a higher effect on the T-cell epitopes encoded by the spike protein. This observation argues for an update of the vaccine design to include other parts of the virus encoding numerous T-cell epitopes to ensure T cells can still protect against severe COVID-19 even if variants can escape antibody responses and the protection against infection is limited.

L

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Publications

Gowthaman U, Ivanov M, Schwarz I, Patel HP, Müller NA, García-Pichardo D, Lenstra TL, Marquardt S. The Hda1 histone deacetylase limits divergent non-coding transcription and restricts transcription initiation frequency. EMBO J. 2021;40(23):e108903

Patel HP, Brouwer I, Lenstra TL. Optimized protocol for single-molecule RNA FISH to visualize gene expression in S. cerevisiae. STAR Protoc. 2021;2(3):100647

Transcription dynamics in single cells

Gene expression is tightly regulated to ensure that genes are transcribed in the right cell at the right time. Single-cell studies have shown that individual cells in a population can show considerable variability in gene expression, arising from the random collision of molecules. This stochastic gene expression variation can influence important cell fate decisions and can also contribute to heterogeneity in tumors. We use cutting-edge single-molecule imaging approaches to visualize transcription in living cells, in order to understand the mechanisms and regulation of transcription dynamics in single cells.

Understanding how chromatin regulates transcriptional bursting

Previous studies on transcription dynamics have shown that genes are often not transcribed in a continuous fashion, but show transcriptional bursting, with periods of gene activity followed by periods of inactivity. Bursting has been linked to the stochastic positioning of nucleosomes. However, how bursting is regulated by remodeling of promoter nucleosomes is unknown. In this study, we use single-molecule live-cell imaging of *GAL10* transcription in budding yeast to measure how transcriptional bursting changes upon single and double perturbations of chromatin remodeling factors, the transcription factor Gal4 and preinitiation complex (PIC) components. Using dynamic epistasis analysis, we reveal how remodeling of different nucleosomes regulates individual transcriptional bursting parameters (figure 1). At the nucleosome covering the Gal4 binding sites, RSC acts synergistically with Gal4 binding to facilitate each burst. Conversely, nucleosome remodeling at the TATA box controls only the first burst upon galactose induction. In the absence of remodelers, nucleosomes at canonical TATA boxes are displaced by TBP binding to allow for transcription activation. Overall, our results reveal how promoter nucleosome remodeling, together with transcription factor and PIC binding regulates the kinetics of transcriptional bursting.

Transcription dynamics of neighboring genes

During transcription, RNA polymerase generates under- and overwound DNA, called DNA supercoiling. Transcription and DNA supercoiling are interdependent, since the torsional tension generated by transcription can accumulate and influence transcription dynamics itself. In bacteria, buildup and release of supercoils are thought to cause transcriptional bursting, but the regulatory impact of transcription-induced supercoiling in eukaryotes is unexplored. In addition, supercoils can propagate along the chromatin, but whether supercoils influence transcription of closely spaced neighboring genes is still unclear. Using single-molecule dual-color transcription imaging at the *GAL* locus in budding yeast, we found that in wildtype, the divergent and tandem *GAL* gene pairs exhibit temporally correlated initiation. Supercoiling accumulation reduces the correlation of both gene pairs, and introduces a refractory period and periodic transcription. Negative supercoils generated from the transcription of *GAL7* inhibit transcription of the upstream *GAL10* gene, a mechanism that is also observed at tandem genes genome-wide. Unlike in bacteria, supercoiling accumulation is not the main driver of transcriptional bursting in eukaryotes, but limits coordinated expression of closely positioned genes.

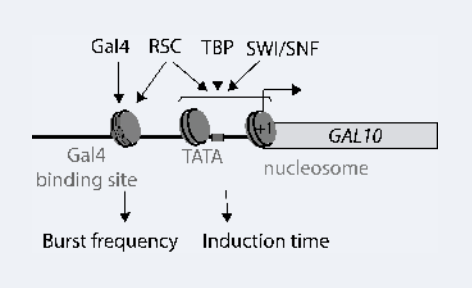

Figure 1. Remodeling at different promoter nucleosomes by the indicated factors has specialized effects on transcriptional bursting, regulating either burst frequency or induction time.

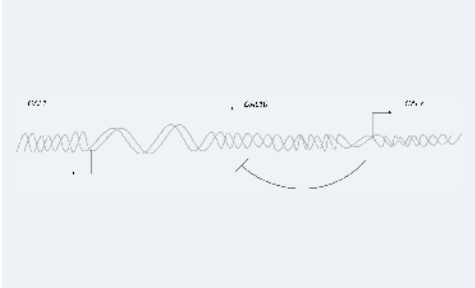

Figure 2. Upon supercoiling accumulation, negative supercoils generated from the transcription of *GAL7* inhibit transcription of the upstream *GAL10* gene at the *GAL* locus.

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Development of cancer biomarker tests with clinical utility

Mission statement: The Linn lab's commitment is to define the best treatment for each (breast) cancer patient preferring simple solutions to minimize harm to the planet and people.

In the clinic, we mainly use anticancer drugs based on outcomes of clinical trials that have identified the best treatment for the average breast cancer patient, not considering differential patient and tumor characteristics that define the case mixes studied. Hence, this approach serves only those patients whose outcome improves substantially with 'the best treatment' identified, while harming patients that do not derive benefit.

The focus of our research line is to unravel underlying tumor and host mechanisms that ultimately define treatment efficacy and develop tests that will guide individualized treatment decisions in the clinic and eventually improve survival. For this purpose, we use several genome-wide approaches and molecular techniques, in order to dissect the mechanisms that divide clinically well-defined cohorts of breast cancer patients into resistant and sensitive to a particular treatment. We have a close collaboration with the groups of Jos Jonkers and Jacco van Rheenen, who use genetically engineered mouse models for breast cancer, to study differential drug sensitivity in a controlled fashion. In addition, we collaborate with the group of Wilbert Zwart, focusing on molecular mechanisms underlying endocrine therapy resistance.
A second research line focuses on prognostic molecular classifiers for adjuvant systemic treatment advice in breast cancer in collaboration with the groups of Marjanka Schmidt, Marleen Kok, and Renée de Menezes.

Stromal tumor-infiltrating lymphocytes (TILs) are prognostic and predictive

To develop prognostic tests, we make use of a population-based cohort of ± 2,300 young, node-negative breast cancer patients (age <40 yrs), diagnosed in 1989-2000 in the Netherlands (PARADIGM cohort). In that era, node-negativity was judged as a favorable prognostic marker and hence, none of these patients had received adjuvant systemic therapy. In collaboration with the International TIL Working Group, we showed that patients with triple negative breast cancer and ≥75% TILs have an excellent 15-years overall survival of ±94%, paving the way for de-escalation studies.
In the MATADOR trial that compared adjuvant dose-dense doxorubicin-cyclophosphamide (AC) with docetaxel-AC (TAC) in HER2-negative, mainly node-positive breast cancer patients, TILs appeared a predictive marker for taxane benefit in the triple-negative subgroup. In collaboration with the van Rheenen groep further clinical and preclinical supporting evidence has been generated for this finding.

Molecular mechanisms underlying sensitivity to alkylating agents

Our institute previously described characteristic DNA copy number aberrations of *BRCA1*- and *BRCA2*-mutated breast cancers. We called these profiles BRCA-like profiles. In posthoc analyses of several randomized controlled trials we have demonstrated that BRCA1-like breast cancer patients derive significant benefit from intensified alkylating agents and PARP inhibition in the (neo)adjuvant setting. In a prospective, randomized trial for BRCA1-like, triple-negative breast cancer patients we have shown that stage II patients do not require intensified alkylating chemotherapy with autologous stem cell transplant (NCT01057069). In this group, standard alkylating chemotherapy including carboplatin is as efficacious. However, for stage III patients a significant and substantial benefit for the intensified regimen was observed in a secondary analysis that requires confirmation.
Recently, we set out to develop ovarian cancer-specific BRCA1/2-like classifiers. In collaboration with Rita Schmutzler (Cologne, Germany) we demonstrated that the novel ovarian specific BRCA1/2-like classifiers could identify ±50% of all ovarian cancers as homologous recombination deficient (HRD). Three-quarters of these HRD ovarian cancers had an (epi)genetic event in a homologous recombination repair gene.

Key publications

Dackus GM, Jóźwiak K, Sonke GS, van der Wall E, van Diest PJ, Siesling S, Hauptmann M, Linn SC. Adjuvant aromatase inhibitors or tamoxifen following chemotherapy for perimenopausal breast cancer patients. J Natl Cancer Inst 2021;113: 1506-1514

Joosten SEP, Wellenstein M, Koornstra R, van Rossum A, Sanders J, van der Noort V, Ferrandez MC, Harkes R, Mandjes IAM, Rosing H, Huitema A, Beijnen JH, Wesseling J, van Diest PJ, Horlings HM, Linn SC, Zwart W. IHC-based Ki67 as response biomarker to tamoxifen in breast cancer window trials enrolling premenopausal women. NPJ Breast Cancer 2021;7:138

Schouten PC, Richters L, Vis DJ, Kommoss S, van Dijk E, Ernst C, Kluin RJC, Marmé F, Lips EH, Schmidt S, Scheerman E, Prieske K, van Deurzen CHM, Burges A, Ewing-Graham PC, Dietrich D, Jager A, de Gregorio N, Hauke J, du Bois A, Nederlof PM, Wessels LF, Hahnen E, Harter P, Linn SC, Schmutzler RK. Ovarian cancer-specific BRCA-like copy-number aberration classifiers detect mutations associated with homologous recombination deficiency in the AGO-TR1 Trial. Clin Cancer Res 2021;27:6559-6569

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Key publications

García-Santisteban I, Llopis A, Krenning L, Vallejo-Rodríguez J, van den Broek B, Zubiaga AM, Medema RH. Sustained CHK2 activity, but not ATM activity, is critical to maintain a G1 arrest after DNA damage in untransformed cells. BMC Biol. 2021;19:35

Hornsveld M, Feringa FM, Krenning L, van den Berg J, Smits LMM, Nguyen NBT, Rodríguez-Colman MJ, Dansen TB, Medema RH, Burgering BMT. A FOXO-dependent replication checkpoint restricts proliferation of damaged cells. Cell Rep. 2021;34:108675

Manjón AG, Linder S, Teunissen H, Friskes A, Zwart W, de Wit E, Medema RH. Unexpected gene activation following CRISPR-Cas9-mediated genome editing. EMBO 2021

Cell cycle checkpoints and chromosome segregation

We strive to understand how cells maintain genome stability. We study the cellular responses to genome imbalances caused by chromosome segregation errors and the response to DNA double strand breaks.

The cellular response to DNA damage

Our aim is to identify vulnerabilities of cells that are exposed to commonly used genotoxic therapies that induce DNA double strand breaks (DSBs). We discovered that the G1 arrest imposed by DNA damage can be overridden only if ATM is inhibited prior to DNA damage in G1 phase. Once the DDR is engaged, its downstream target Chk2 can sustain its own activity, implying that the checkpoint is maintained even if the lesion is repaired (Garcia-Santisteban et al., BMC Biol. 19:35). We also discovered that hypoxia protects cells from IR-induced DNA lesions by causing cells to enter a quiescent state in which they are relatively refractory to damage. This phenomenon acts in parallel to the well described "oxygen effect"; which refers to less efficient induction of DSBs by IR in low oxygen. Importantly, we could show that the "quiescence effect" is lost in HPV-positive tumors (Menegakis et al., Cells 10:610).

We managed to complete our inventory of the mechanisms by which DNA lesions induce a permanent cell cycle exit by showing that replication stress triggers a FoxO-dependent exit in S/G2 (Hornsveld et al., Cell Rep. 34:108675). Finally, in an effort to study possible effects of DSBs on epigenetic stability we made use of CRISPR/Cas9-induced DSBs. We investigated if DSBs could produce epigenetic scars that result in gene activation associated with acquired drug resistance. We did find evidence that this is the case, but also identified an unexpected mode of gene activation that can occur when using lentiviral sgRNA-delivery. We showed that this can result in integration of the sgRNA-vector, causing "artificial" gene activation (Gonzalez-Manjon EMBO Rep. doi: 10.15252/embr.202153902). Thus, for studies like these it is important to induce DSBs using non-integrative systems, such as transfection of RNP-complexes.

Aneuploidy and segregation errors

Aneuploidy and chromosomal instability (CIN) are both acknowledged hallmarks of cancer. It has been hypothesized that aneuploidy *per se* can be sufficient to drive CIN. However, it has remained controversial if and which aspects of aneuploidy can drive CIN. We systematically tested the impact of different types of aneuploidies on the induction of CIN. We observed increased segregation errors in cells harboring trisomies and we found that the level of instability strongly correlated to the number of gained genes. Strikingly, we found that monosomies did not trigger CIN. We hypothesized that excess protein production associated with chromosomal gains generates a burden on protein production, folding and turnover machineries and thereby results in CIN. Indeed, inhibiting protein degradation or interfering with protein folding was sufficient to induce CIN in otherwise chromosomally stable cells (Hintzen et al, 2021, bioRxiv 2021.08.31.458318). Finally, we are further expanding on our latest research interest that focuses on the tolerance to extrachromosomal circular DNA (ecDNA), another unique karyotypic feature of cancer cells. We developed ecDNA-containing cell lines in which ecDNA structures can be visualized by live cell microscopy and that allow for the identification of factors that are essential for the maintenance and/or tolerance to these extrachromosomal structures.

Translational gastrointestinal oncology

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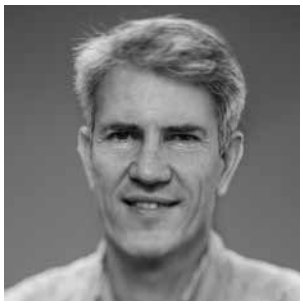

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Translational Gastrointestinal Oncology

Translating disease biology into new diagnostic applications holds great promise for improving outcome for patients. We characterize gastrointestinal pre-malignant and malignant lesions at DNA, RNA, and protein level by tumor profiling using multiple-omics techniques for biomarker development, to improve colorectal cancer screening as well as to stratify patient groups and arrive at individually tailored therapies. Disease biology is studied using pre-clinical model systems such as organoid cultures. Clinical validation is performed by making use of large series of patient sample collections derived from screening programs and multi-center clinical trials. To facilitate the logistics that are needed for these validation studies, we are involved in several (inter)national research infrastructure programs.

Early detection of colorectal cancer

Colorectal cancer screening programs using the fecal immunochemical test have a high sensitivity for cancer (80%) but <30% for advanced adenomas (i.e. precursors). We aim to improve on this by unravelling the biology of adenoma to carcinoma progression, and identifying and clinically validating novel biomarkers. This includes improved stratification of patients in groups at low- or high-risk of developing CRC.

A protein biomarker panel for *colorectal cancer screening* was identified and validated for clinical utility. This biomarker panel is estimated to have a 35% higher sensitivity for detection of advanced adenomas relative to the current FIT (i.e. 37.8% versus 28.1%, respectively). A prospective trial including 13,300 participants of the Dutch national bowel screening program is being prepared. The trial is planned to be launched in the beginning of 2022.

The MOCCAS (MOlecular stool testing for Colorectal CAncer Surveillance) study (n=3830) has shown that stool molecular testing can be used safely to reduce the number of colonoscopies in CRC surveillance (manuscript in preparation).

Our understanding of the natural history of colorectal adenoma to cancer progression still is incomplete. Previously, we observed specific DNA copy number alterations to be associated with this critical step. In the IntEnd study we aim to further substantiate this observation by evaluating these features in a large retrospective series (n=700) of adenoma patients with detailed follow-up, and model alternative surveillance strategies. Within the same study we are also evaluating POFUT1, which we identified as a biomarker for risk of progression.

Adenoma to carcinoma progression is also studied at the functional level. To this end we have established a library of ~50 human high-risk and low-risk adenoma organoids, based on their pattern of DNA copy number alterations. Current studies involve detailed phosphoproteomics analysis in collaboration with Connie Jimenez (AmsterdamUMC) as well as longitudinal analysis of chromosomal instability (CIN) by means of single-cell Karyo-sequencing and cell imaging, in collaboration with Geert Kops (Hubrecht Institute). Moreover, in collaboration with Victor Velculescu (Johns Hopkins, Baltimore, USA) we are investigating in these same adenoma organoids, DNA fragmentation patterns, in comparison to normal colon epithelium and cancer organoids, and relate these patterns with DNA copy number alterations associated with adenoma-to-carcinoma progression and with CIN.

Patient stratification

With DNA-, RNA-, and protein-profiling we aim to stratify patients to optimize treatment outcomes. Whole Genome Sequencing (WGS) captures an accurate, unbiased and complete view of genomic characteristics of a tumor in one single test on a relatively low amount of tumor material. WGS can identify 'clinically actionable' targets in more patients than regular diagnostics, allowing a match with a registered and approved therapy. In the WIDE (WGS Implementation in standard cancer

Key publications

Bolhuis K, van 't Erve I, Mijnals C, Delis-Van Diemen PM, Huiskens J, Komurcu A, Lopez-Yurda M, van den Broek D, Swijnenburg RJ, Meijer GA, Punt CJA, Fijneman RJA. Postoperative circulating tumour DNA is associated with pathologic response and recurrence-free survival after resection of colorectal cancer liver metastases. EBioMedicine. 2021;70:103498

De Klaver W, Wisse PHA, van Wifferen F, Bosch LJW, Jimenez CR, van der Hulst RWM, Fijneman RJA, Kuipers EJ, Greuter MJE, Carvalho B, Spaander MCW, Dekker E, Coupé VMH, de Wit M, Meijer GA. Clinical validation of a multitarget fecal immunochemical test for colorectal cancer screening: A diagnostic test accuracy study. Ann Intern Med. 2021;174(9):1224-1231

Den Uil SH, de Wit M, Slebos RJC, Delis-van Diemen PM, Sanders J, Piersma SR, Pham TV, Coupé VMH, Bril H, Stockmann HBAC, Jimenez CR, Meijer GA, Fijneman RJA. Quantitative analysis of CDX2 protein expression improves its clinical utility as a prognostic biomarker in stage II and III colon cancer. Eur J Cancer. 2021;144:91-100

Mathios D, Johansen JS, Cristiano S, Medina JE, Phallen J, [...], Carvalho B, de Wit M, Carey J, Dracopoli NC, [...], Fijneman RJA, Nielsen HJ, Meijer GA, Andersen CL, Mellemgaard A, Bojesen SE, Scharpf RB, Velculescu VE. Detection and characterization of lung cancer using cell-free DNA fragmentomes. Nat Commun. 2021;12(1):5060

Van 't Erve I, Rovers KP, Constantinides A, Bolhuis K, Wassenaar EC, Lurvink RJ, Huysentruyt CJ, Snaebjornsson P, Boerma D, van den Broek D, Buffart TE, Lahaye MJ, Aalbers AG, Kok NF, Meijer GA, Punt CJ, Kranenburg O, de Hingh IH, Fijneman RJ. Detection of tumor-derived cell-free DNA from colorectal cancer peritoneal metastases in plasma and peritoneal fluid. J Pathol Clin Res. 2021;7(3):203-208

Van 't Erve I, Wesdorp NJ, Medina JE, Ferreira L, Leal A, Huiskens J, Bolhuis K, van Waesberghe J-HTM, Swijnenburg R-J, van den Broek D, Velculescu VE, Kazemier G, Punt CJA, Meijer GA, Fijneman RJA. KRAS A146 mutations are associated with distinct clinical behavior in patients with colorectal liver metastases. JCO Precis Oncol 2021;5:PO.21.00223

Diagnostics for Every cancer patient) project we have investigated together with Hartwig Medical Foundation and UMCU the (i) feasibility and (ii) impact of WGS-based diagnostics in patients with metastatic disease in routine clinical practice. In immediate follow up to the successful WIDE study, as one of the first institutes worldwide we now have implemented WGS in routine patient care. We make use of these extensive WGS tumor-profiling efforts to gain insight in the prevalence of chromosomal rearrangement structural variants (SVs), a type of DNA alterations that has not been studied extensively so far. We examine the biological impact of SVs on tumor progression and its prognostic value in localized (non-metastatic) CRC.

Liquid biopsies (i.e. blood samples) contain minute amounts of tumor material, can be obtained longitudinally and are less burdensome than tissue biopsies. We investigate whether analysis of liquid biopsy circulating tumor DNA (ctDNA) can be applied as biomarkers to better determine who to treat, how to treat, and when to treat patients. Detection of ctDNA after surgery of stage II or III CRC patients is highly prognostic for disease recurrence and may therefore guide decisions who (not) to treat with adjuvant chemotherapy (ACT). For observational studies we collect and analyze blood samples longitudinally from stage II (MEDOCC study) and stage III (PROVENC3 study) CRC patients, making use of the infrastructure of the Prospective Dutch CRC cohort (PLCRC). Moreover, the MEDOCC-CrEATE ctDNA biomarker-driven interventional clinical trial is ongoing, which aims to examine the willingness of stage II colon cancer patients with detectable ctDNA after surgery to accept ACT and whether ACT reduces the risk of disease recurrence in these patients. In the metastatic setting, levels of ctDNA in patients with peritoneal metastases were much lower compared to patients with liver metastases, indicating biological variation in ctDNA detectability due to the metastatic site. Among patients with liver metastases, presence of a KRAS mutation in codon A146 was associated with unexpectedly high levels of ctDNA due to high tumor burden, revealing distinct clinical behavior for this particular subset of patients.

To pave the path for implementation of ctDNA applications, the multicenter-multistakeholder project COIN (ctDNA on the way to Implementation in the Netherlands) is establishing a clinical validation framework for efficiently investigating the clinical utility of ctDNA towards clinical implementation.

Translational research infrastructure

Successfully developing biomarkers to clinical implementation is critically dependent on dedicated infrastructure for facilitating study logistics and FAIR data stewardship. TGO acts as a leading clinical domain expert group (https://www.health-ri.nl) in co-developing this infrastructure, both locally as well as in the context of the Dutch national health data infrastructure for research and innovation, Health-RI, that received EUR 69M National Growth Fund funding. This user input is of critical importance to make sure that the needs of end users are met by the solutions built. These solutions comprise a series of applications to accommodate the different types of research generated. For visualizing, querying and exploring translational research data cBioPortal is used as the main data integration platform, while there is a close collaboration with the cBioPortal development team at MSKCC, including a shared PhD project. Internationally, we align our activities with initiatives such as Cancer Core Europe and AACR GENIE.

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Key publications

Boshuizen J, Pencheva N, Krijgsman O, Altimari DD, Castro PG, de Bruijn B, Ligtenberg MA, Gresnigt-Van den Heuvel E, Vredevoogd DW, Song JY, Visser N, Apriamashvili G, Janmaat ML, Plantinga TS, Franken P, Houtkamp M, Lingnau A, Jure-Kunkel M, Peeper DS. Cooperative targeting of immunotherapy-resistant Melanoma and lung cancer by an AXL-targeting antibody–drug conjugate and immune checkpoint blockade. Cancer Res. 2021;81(7):1775-1787

Krijgsman O, Kemper K, Boshuizen J, […], Adams DJ, Blank CU, Peeper DS. Predictive immune-checkpoint blockade classifiers identify tumors responding to inhibition of PD-1 and/or CTLA-4. Clin Cancer Res. 2021

Functional genomics for rational tumor and immune cell combination therapy

Introduction

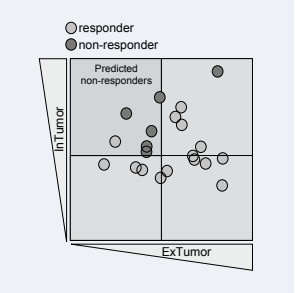
We use function-based, genome-wide experimental strategies to develop rational cancer treatment combinations, targeting both tumor and immune cells. By screening for novel therapeutic targets and predictive biomarkers, we aim to achieve more durable clinical responses for patients. On the one hand, we are increasing our understanding of how cancer cells rewire their signaling networks, to expose and exploit new pharmacologically tractable tumor susceptibilities, also in the context of immunotherapy. On the other, we are manipulating various cell types from the patient's own immune system to boost their specific cytotoxicity towards tumor cells. With these function-based approaches, we develop new rational therapy combinations, which simultaneously eliminate the patient's tumor and harness the immune system.

Predictive Immune-Checkpoint Blockade classifiers

Combining anti-PD-1 + anti-CTLA-4 immune checkpoint blockade (ICB) shows improved patient benefit, but is associated with severe immune-related adverse events and exceedingly high cost. Therefore, there is a dire need to predict which patients respond to monotherapy and which require combination ICB treatment. Using our XenofilteR deconvolution algorithm we developed a purely tumor cell-intrinsic signature ("InTumor") and a signature comprising tumor cell-extrinsic RNA reads ("ExTumor"). Whereas the InTumor signature predicts response to anti-PD-1, the ExTumor predicts anti-CTLA-4 benefit. When used in conjunction, the InTumor and ExTumor signatures identify not only patients who have a substantially higher chance of responding to combination treatment than to either monotherapy, but also those who are likely to benefit little from anti-CTLA-4 on top of anti-PD-1. We suggest that these signatures may be exploited to distinguish melanoma patients who need combination ICB blockade from those who likely benefit from either monotherapy.

Targeting immunotherapy-resistant melanoma and lung cancer by an AXL-targeting Antibody–Drug Conjugate and ICB

The receptor tyrosine kinase AXL is commonly implicated in therapy resistance and may serve as a marker for therapy-refractory tumors, for example in melanoma, as we previously demonstrated. We established for several melanoma and lung cancer models that enapotamab vedotin (EnaV), an antibody–drug conjugate targeting AXL, effectively targets tumors displaying insensitivity to immunotherapy or tumor-specific T cells. EnaV treatment induced an inflammatory response and immunogenic cell death in tumor cells and promoted induction of a memory-like phenotype in cytotoxic T cells. Combining EnaV with tumor-specific T cells proved superior to either treatment alone and induced ICB benefit. These findings indicate that targeting AXL-expressing, immunotherapyresistant tumors with EnaV causes an immune-stimulating tumor microenvironment and enhances sensitivity to ICB, warranting further investigation of this treatment combination.



Joint InTumor and ExTumor signatures predict response to ICB combination therapy.

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Ida de Vries PhD student
Danique Ammerlaan Technical staff
Maarten Hekkelman Software engineer
Hans Wienk Project manager
Ren Xie Research assistant

Key publications

Borza R, Salgado-Polo F, Moolenaar WH, Perrakis A. Structure and function of the Ecto-Nucleotide Pyrophosphatase-Phosphodiesterase (ENPP) family: tidying up diversity. J Biol Chem. 2021:101526

Deng X, Salgado-Polo F, Shao T, Xiao Z, Van R, Chen J, Rong J, Haider A, Shao Y, Josephson L, Perrakis A, Liang SH. Imaging Autotaxin in vivo with ^{18}F-labeled positron emission tomography ligands. J Med Chem. 2021;64(20):15053-15068

De Vries I, Kwakman T, Lu XJ, Hekkelman ML, Deshpande M, Velankar S, Perrakis A, Joosten RP. New restraints and validation approaches for nucleic acid structures in PDB-REDO. Acta Crystallogr D Struct Biol. 2021;77(Pt 9):1127-1141

Structural biology

We aim to provide molecular insight to macromolecular interactions and structures, understanding how they regulate specific biological activities in space and in time. In parallel we develop concepts, algorithms, and software for improving methods for such work. Our work enables the development of new specific drugs and biologics.

Understanding signaling cascades related to Autotaxin

Autotaxin (ATX) produces the signaling phospholipid LPA; LPA and ATX are involved in cancer metastasis and other pathogenic situations. We have extended our active interest on inhibitors that affect ATX action, to a collaboration that delivered the first PET probe for looking at Autotaxin activity *in vivo*. Our focus remains in understanding how different inhibitors, targeting catalytic and non-catalytic activities of ATX, can have different clinical results in specific pathologies and how ATX itself is crucial not only for making LPA, but also specifically delivering it to specific subset of the cell surface LPA receptors. A developing interest is the role of ATX in modulating the immune response in the tumor microenvironment.

Structural studies of microtubule interacting proteins

Our long-standing interest in designing new molecules to inhibit the protein-protein interactions that interfere with the kinetochore NDC80 complex and the Mps1 kinase or microtubules, is ongoing. We also study the dynein adaptor Spindly that drives kinetochore expansion in a dynein-independent manner, promoting initial microtubule capture and subsequent correct maturation of attachments. Finally, we have an active interest on two related mitotic kinases: the Bub1 kinase, for which we are evaluating its structure with new inhibitors from the collaborating group of Mario van der Stelt at Leiden University; and the BubR1 pseudokinase, combining experimental and computation approaches (AlphaFold) to understand how specific mutants related to hereditary disease.
We also study tubulin detyrosination enzymes, together with the group of Thijn Brummelkamp. We previously characterized the structure of the VASH1:SVBP complex, explaining how SVBP acts as a unique structural chaperone of the VASH1 catalytic subunit, and deciphering the specificity determinants for the C-terminal tyrosine of the α-tubulin tail. The discovery of MATCAP, a new tubulin detyrosination enzyme by the same collaborators, led us to the structure determination of MATCAP, its detailed biochemical characterization and the determination of the structure of MATCAP bound to microtubules by cryo-EM.

Methods for X-ray crystallography

PDB-REDO is a project we lead together with Robbie Joosten. We strive to make better crystallographic structure models by improving published structures and making them available through the PDB_REDO data bank and providing a web-server that allows practicing crystallographers to take full advantage of the PDB_REDO procedure. A focus of this year has been to deploy PDB-REDO in the Cloud and increase the FAIRness of data (in collaboration with EOSC-Life) and in validating and improving complexes of protein with nucleic acids – DNA and RNA.

The advent of AlphaFold, making available hundreds of thousands of predicted protein models to all scientists, already conveys a transforming effect in structural biology. In AlphaFill, we are bringing together the accuracy of experimental crystallographic models in describing complexes of proteins with small molecule ligands – such as existing or future drugs – with the power of predicted structure models. We "fuse" the PDB-REDO and the AlphaFold databases, in the AlphaFill database, that has "transplanted" ligands in predicted models that are similar to experimentally determined complex structures. That is a first step towards training an artificial intelligence algorithm to find binding pockets for common ligands in predicted protein structures.

Health technology assessment

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Key publications

Byng, D, Retèl VP, Engelhardt EG, Groothuis CGM, Van Til JA, Schmitz RSJM, van Duijnhoven F, Wesseling J, Bleiker E, van Harten WH. Preferences of treatment strategies among women with low-risk DCIS and oncologists. Cancers 2021;13 (16):3962

Simons MJHG, Retèl VP, Ramaekers BLT, Butter R, Mankor JM, Paats MS, Aerts JGJV, Mfumbilwa ZA, Roepman P, Coupé VMH, Uyl-de Groot CA, van Harten WH, Joore MA. Early cost effectiveness of whole-genome sequencing as a clinical diagnostic test for patients with inoperable stage IIIB,C/IV Non-squamous Non-small-Cell Lung Cancer. Pharmacoeconomics. 2021;39(12):1429-1442

Van Ommen-Nijhof A, Retèl VP, van den Heuvel M, Jager A, van Harten WH & Sonke GS. A revolving fund to study efficient use of expensive drugs: big wheels keep on turning. Annals Oncol. 2021;32(10):1212-1215

Early Health Technology Assessment

In the landscape of oncology, many high-tech technology and drug pipelines are being developed with impressive results for patients. However, with many of these new technologies having exorbitant prices and growing numbers of new patients and survivors, the financial pressure is increasing; thus the chance of successful implementation and coverage of new technologies decreases. Instruments such as Health Technology Assessment (HTA) are used to increase the chances of innovations reaching the patient and reduce wasting R&D funding.
The role of HTA is supportive alongside the total translational research pathway. In early development stages, our team informs R&D of new health technologies by means of e.g. prioritization, early cost-effectiveness analyses, budget impact analyses, scenario drafting and patient preferences research. In later stages (e.g. alongside phase III clinical trials), the aim of HTA is to inform reimbursement decisions. For very promising new technologies, we coordinate Coverage with Evidence Development (CED) programs, where (early) HTA plays an important role towards the final coverage decision.

HTA in molecular diagnostics in personalized oncology

In the Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO) study, we have worked on providing evidence for the implementation of Whole Genome Sequencing (WGS) in the Netherlands, together with 8 academic centers. There were 6 work packages, in which we worked together on 1) the validation of WGS compared to NGS, 2) a WGS-based biomarker to select patients who would not respond to immunotherapy, 3) real world data-based analysis of the potential effect of NGS-based targeted therapies, 4) the potential cost-effectiveness of WGS compared to standard molecular diagnostics, 5) the intended and unintended consequences of nation-wide implementation of WGS, and 6) the Ethical and legal implications of WGS implementation for oncology patients. We drafted several future scenario's regarding the implementation of WGS, in collaboration with experts. In an early cost-effectiveness analysis we demonstrated the criteria for WGS to become cost-effective. With an agent-based dynamic simulation model, we showed the capacity for WGS in the Netherlands. And finally, we proposed a guideline for clinicians for whether or not to re-contact patients in case of secondary findings based on WGS. In the ctDNA on the way to implementation in the Netherlands (COIN) study, our group is working on a framework for HTA in several indications for ctDNA, which should be supportive in future HTA studies in ctDNA.

HTA for treatment de-escalation

In the PRECISION consortium, a large CRUK program where we would like to distinguish between lethal cancers that need treating, and non-lethal cancers that do not, Danalyn Byng has been working on early HTA topics. First she showed that, based on real world data from the SEER registry, women with primary DCIS and low-risk features demonstrate minimal differences by treatment strategy in experiencing subsequent breast events. Furthermore, she performed a discrete choice experiment amongst patients and health care provided regarding treatment preferences for low-grade DCIS.

Pricing mechanisms for oncology drugs

Together with group of Wim van Harten, Nora Franzen has performed a laboratory gaming experiment on transparency of oncology drug prices. Based on the work of Nora Franzen, the European Fair Pricing Network (EFPN) has been initiated in 2019, which is a collaboration between the European Cancer Leagues and the Organization of European Cancer Institutes. Within this network, further research will be conducted e.g. on the topics of access to drugs, transparency, and simulation modeling of pricing mechanisms.

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Key publications

Hoencamp C, Dudchenko O, Elbatsh AMO, Brahmachari S, Raaijmakers JA, van Schaik T, Sedeño Cacciatore Á, Contessoto VG, van Heesbeen RGHP, van den Broek B, Mhaskar AN, Teunissen H, St Hilaire BG, Weisz D, Omer AD, Pham M, Colaric Z, Yang Z, Rao SSP, [...], Kornberg RD, Warren WC, Cary G, Gómez-Skarmeta JL, Hinman V, Lindblad-Toh K, Di Palma F, Maeshima K, Multani AS, Pathak S, Nel-Themaat L, Behringer RR, Kaur P, Medema RH, van Steensel B, de Wit E, Onuchic JN, Di Pierro M, Lieberman Aiden E, Rowland BD. 3D genomics across the tree of life reveals condensin II as a determinant of architecture type. Science, 2021;372:984-989

Van der Weide RH, van den Brand T, Haarhuis JHI, Teunissen H, Rowland BD, de Wit E. Hi-C analyses with GENOVA: a case study with cohesin variants. NAR Genom Bioinform, 2021;3:lqab040

Van Ruiten MS, Rowland BD. On the choreography of genome folding: a grand pas de deux of cohesin and CTCF. Curr Opin Cell Biol, 2021;70:84-90

Chromosome Biology

Human chromosomes are centimetres in length, but are folded such that they fit into a cell of micrometre-scale dimensions. Within this confined setting, chromosomes allow for tightly controlled cellular processes such as mitosis and transcription. These processes are made possible by two conserved protein complexes known as cohesin and condensin. Both cohesin and condensin are so-called SMC complexes that by building DNA loops, and by holding together DNA elements, provide structure to chromosomes.

Research in our lab centres on the mode of action of cohesin and condensin. How do these complexes form DNA loops and shape the genome in 3D? How do these complexes entrap and release DNA? How does cohesin stably lock together the sister chromatids? How does condensin drive mitotic chromosome condensation? And how does the action of these complexes affect nuclear organization, gene expression, and genomic stability? We are addressing these questions using a multi-disciplinary approach that covers genetics, genomics, biochemistry and imaging.

DNA folding by cohesin and CTCF

The cohesin complex is essential for the formation of chromatin loops across the genome. We found that the cohesin release factor WAPL limits the degree by which loops can be enlarged. The interphase genome turns out to be structured through a continuous cycle of formation, enlargement, loss and re-formation of loops by cohesin (Haarhuis et al., Cell 2017). Cohesin builds loops that connect CTCF sites along chromosomes. With the laboratory of Daniel Panne, we found that the interaction between a segment of the CTCF N-terminus and the SA2-SCC1 subunits of cohesin stabilizes cohesin on chromatin. This interaction turns out to be essential for CTCF-anchored loops. We suggest that the mode by which CTCF controls cohesin is shared by multiple other key chromosomal regulators (Li et al., Nature, 2020).

Chromosome organization by condensin

As cells enter mitosis, condensin complexes convert the genome into compact and rigid chromosomes. Condensin drives chromosome condensation through the formation of loops along the DNA. This vital process ensures that chromosomes are shortened enough to allow the splitting in half of the cell during cytokinesis without DNA getting caught in the middle. We discovered a functional asymmetry within condensin's ABC-like ATPase machinery (Elbatsh et al., Mol Cell, 2019). Asymmetric ATPases with distinct roles for each ATPase site are likely to reflect a universal principle for SMC complexes that enables these ancient molecular machines to intricately control chromosome architecture.

This year, in a large-scale collaboration with the labs of Erez Lieberman Aiden, Michele di Pierro, José Onuchic, and multiple NKI-based labs, we revealed that the condensin II complex plays a major role in shaping the genome at macro-scale. Cells deficient for condensin II display a completely different kind of genome organization that more resembles the kind of genome folding often found in fungi or insects. In this state, the centromeres of all chromosomes cluster together at the nucleolus. Our data supports the model that condensin II acts in mitosis, or in the early stages of nuclear organization, to establish nuclear organization at macro-scale (Hoencamp et al., Science, 2021).

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Marianne Kuenen Research assistant

Cognitive function in cancer patients

The projects constituting our lines of research center around the characterization of the incidence, pattern and course of cognitive problems associated with cancer and cancer therapies, the risk factors for cognitive problems and the mechanisms that underlie cognitive problems in patients with tumours either inside or outside the CNS. Our research is also directed to develop, evaluate and implement interventions to minimize and manage cognitive problems.

Does exercise improve cognitive function in breast cancer patients receiving chemotherapy?

Breast cancer patients treated with chemotherapy are frequently confronted with cognitive problems. We investigated whether exercise improves cognition in chemotherapy-exposed breast cancer patients 2-4 years after diagnosis.
Chemotherapy-exposed breast cancer patients with self-reported cognitive problems reflected on neuropsychological tests were randomized to an exercise or control group. The 6-month exercise intervention consisted of supervised aerobic and strength training (2 hrs/week), and Nordic/power walking (2 hrs/week). Our primary outcome was memory functioning (Hopkins Verbal Learning Test-Revised; HVLT-R). Secondary outcomes included online neuropsychological tests (ACS), self-reported cognition, physical fitness (VO_{2peak}), fatigue, QoL, depression and anxiety.
We randomized 181 patients to the exercise (*n=91*) or control group (*n=90*). Two-third of the patients attended ≥80% of the exercise sessions and physical fitness significantly improved compared to control patients. No difference in favor of the intervention group was seen on the primary outcome. Significant beneficial intervention effects were found for self-reported cognitive functioning, fatigue, QoL, and depression. A hypothesis-driven analysis in highly fatigued patients, showed positive exercise effects on tested cognitive functioning.
We conclude that a 6-month exercise intervention improved self-reported cognitive functioning and physical fitness, fatigue, QoL, and depression in chemotherapy-exposed breast cancer patients with cognitive problems. Tested cognitive functioning was not affected. However, subgroup analysis indicated a positive effect of exercise on tested cognitive functioning in highly fatigued patients.

Trajectories of cognitive symptoms and associated factors in cancer survivors after return to work: An 18-month longitudinal cohort study

Cognitive symptoms affect cancer survivors' functioning at work. To date, cognitive symptoms trajectories in working cancer survivors and the factors associated with these trajectories have not been examined.
Data from a heterogeneous group of working cancer survivors (n = 379) of the longitudinal 'Work-Life-after-Cancer' study, linked with Netherlands Cancer Registry data, were used. The Cognitive Symptom Checklist-Work was administered at baseline (within the first three months after return to work), 6, 12, and 18 months follow-up to measure self-perceived memory and executive function symptoms. Group-Based Trajectory Modeling was used to identify trajectories of cognitive function symptoms and factors associated with these trajectories.
Four trajectories were identified. All memory symptoms trajectories were found to be stable and were labeled as "stable-high" (15.3% of the sample), "stable-moderately high" (39.6%), "stable-moderately low" (32.0%), and "stable-low" (13.0%). Executive function symptoms trajectories changed over time and were labeled as: "increasing-high" (10.1%), "stable-moderately high" (32.0%), "decreasing-moderately low" (35.5%), and "stable-low" (22.4%). Higher symptoms trajectories were associated with older age, longer time from diagnosis to return to work, more quantitative work demands, and higher levels of depressive symptoms at baseline.
In cancer survivors who returned to work, four cognitive symptoms trajectory subgroups were identified, representing different but relatively stable severity levels of cognitive symptoms. Clinicians and occupational physicians should assess cognitive symptoms at baseline after return to work to identify patients with higher symptoms trajectories. In case of cognitive symptoms, it is important to also screen for psychological factors to provide appropriate guidance.

Key publications

De Ruiter MB, Reneman L, Kieffer JM, Oldenburg HSA, Schagen SB. Brain white matter microstructure as a risk factor for cognitive decline after chemotherapy for breast cancer. J Clin Oncol. 2021;10;39:3908-3917

Lee Meeuw Kjoe PR, van der Wall E, Schagen SB. Endocrine Therapy With or Without CDK4/6 Inhibitors in women with hormone-receptor positive breast cancer: What do we know about the effects on cognition? Clin Breast Cancer. 2021;14:S1526-8209(21)00239-1

Van der Willik KD, Jóźwiak K, Hauptmann M, van de Velde EED, Compter A, Ruiter R, Stricker BH, Ikram MA, Schagen SB. Change in cognition before and after non-central nervous system cancer diagnosis: A population-based cohort study. Psychooncology. 2021;30(10):1699-1710

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Key publications

Li W, Sparidans RW, Lebre MC, Beijnen JH, Schinkel AH. ABCB1 and ABCG2 control brain accumulation and intestinal disposition of the novel ROS1/TRK/ALK inhibitor repotrectinib, while OATP1A/1B, ABCG2, and CYP3A limit its oral availability. Pharmaceutics. 2021;13:1761

Martins MLF, Wilthagen EA, Oviedo-Joekes E, Beijnen JH, de Grave N, Uchtenhagen A, Beck T, Van den Brink W, Schinkel AH. The suitability of oral diacetylmorphine in treatment-refractory patients with heroin dependence: A scoping review. Drug Alcohol Depend. 2021;227:108984

Wang Y, Sparidans RW, Potters S, Lebre MC, Beijnen JH, Schinkel AH. ABCB1 and ABCG2, but not CYP3A4 limit oral availability and brain accumulation of the RET inhibitor pralsetinib. Pharmacol Res. 2021;172:105850

Genes and proteins involved in anticancer drug resistance and pharmacokinetics

We study genes and proteins that affect drug resistance in tumors, or influence the pharmacological and toxicological behavior of (anticancer) drugs and toxins, including carcinogens. Of special interest are multispecific drug efflux and uptake transporters, as well as drug-metabolizing enzymes. Insight into these systems may: i) improve pharmacotherapy approaches for cancer and other diseases; ii) increase insights into factors determining susceptibility to toxins and carcinogens, and; iii) allow elucidation of physiological functions. To understand the roles of these proteins we generate and analyze knockout or transgenic mice lacking or overexpressing the relevant genes. Below we describe a few recent studies illustrating our approach.

ABCB1 and ABCG2 control brain accumulation of the ROS1/TRK/ALK inhibitor repotrectinib, while OATP1A/1B, ABCG2, and CYP3A limit its oral availability

Repotrectinib shows high activity against ROS1/TRK/ALK fusion-positive cancers in preclinical studies. We explored the roles of the multidrug efflux transporters ABCB1 and ABCG2, the OATP1A/1B uptake transporter(s), and the CYP3A complex in the pharmacokinetics of repotrectinib in genetically modified mouse models. *In vitro*, human ABCB1 and ABCG2, and mouse Abcg2 efficiently transported repotrectinib. Oral repotrectinib showed higher plasma exposure in Abcg2-deficient mouse strains. Brain-to-plasma ratios were 14.2-fold increased in *Abcb1a/1b;Abcg2*$^{-/-}$ mice, but not in single *Abcg2*$^{-/-}$ mice. Small intestinal content recovery of repotrectinib was 13.6-fold decreased in *Abcb1a/1b;Abcg2*$^{-/-}$ mice. *Abcb1a/1b;Abcg2*$^{-/-}$ mice displayed transient, mild, likely CNS-localized toxicity. Oatp1a/1b deficiency caused a 2.3-fold increased oral availability and corresponding decrease in liver distribution of repotrectinib. In *Cyp3a*$^{-/-}$ mice, repotrectinib plasma $AUC_{0\text{-}8h}$ was 2.3-fold increased, and subsequently reduced 2.0-fold in humanized CYP3A4 transgenic mice. Thus, all the tested transporters and CYPA markedly affect repotrectinib pharmacokinetics. These insights may help to optimize the therapeutic application of repotrectinib.

ABCB1 and ABCG2, but not CYP3A4 limit oral availability and brain accumulation of the RET inhibitor pralsetinib

Pralsetinib is approved for treatment of rearranged during transfection (RET) proto-oncogene fusion-positive non-small cell lung cancer. We investigated whether the efflux transporters ABCB1 and ABCG2, the SLCO1A/1B uptake transporters and the drug-metabolizing enzyme CYP3A influence pralsetinib pharmacokinetics. *In vitro*, pralsetinib was efficiently transported by human ABCB1 and mouse Abcg2, but not human ABCG2. *In vivo*, Abcb1a/1b markedly and Abcg2 slightly limited pralsetinib brain penetration. *Abcb1a/1b;Abcg2*$^{-/-}$ mice showed 1.5-fold higher plasma exposure, 23-fold increased brain penetration, and 4-fold reduced recovery of pralsetinib in the small intestinal content. Slco1a/1b deficiency did not affect pralsetinib oral availability or tissue exposure. Oral coadministration of the ABCB1/ABCG2 inhibitor elacridar boosted pralsetinib plasma exposure (1.3-fold) and brain penetration (19.6-fold) in wild-type mice. Additionally, pralsetinib was a modest substrate of mouse Cyp3a, but not of human CYP3A4, which did not noticeably restrict the oral availability of pralsetinib. Thus, mainly the ABC transporters affected pralsetinib pharmacokinetics. The obtained insights may be useful in the further clinical development of pralsetinib.

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Key publications

Escala-Garcia M, et al. Germline variants and breast cancer survival in patients with distant metastases at primary breast cancer diagnosis. Sci Rep. 2021;11(1):19787.

Lakeman IMM, et al. The predictive ability of the 313 variant-based polygenic risk score for contralateral breast cancer risk prediction in women of European ancestry with a heterozygous BRCA1 or BRCA2 pathogenic variant. Genet Med. 2021;23(9):1726-1737

Morra A, et al. Breast Cancer Risk Factors and Survival by Tumor Subtype: Pooled Analyses from the Breast Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev. 2021;30(4):623-642

Molecular breast cancer epidemiology

Our work spans the themes of precision oncology (prevention) and survivorship. We investigate germline genetic variants for their impact on breast cancer subtype development and outcome. We strive to translate and implement our findings in models and tools to support clinicians and patients in shared decision-making and to ultimately prevent breast cancer and recurrence of cancer, to reduce overtreatment, and to improve outcome. We also investigate, develop, and implement Ethical, Legal, and Societal (ESLI) practices for the use of human data and materials in scientific research.

Understanding and predicting risk of contralateral breast cancer

We have proven that a polygenic risk score (PRS) of 313 common genetic variants is an important risk factor for the development of contralateral breast cancer in the general population and to a lesser extent in *BRCA1/2* mutation carriers. Using data of the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), we found that the estrogen receptor (ER)-negative PRS-313 was most strongly associated with contralateral breast cancer risk (HR per SD:1.12; 95%CI:1.06-1.18) and the ER-positive PRS313 (HR:1.15; 95%CI:1.07-1.25) in *BRCA1* and *BRCA2* germline mutation carriers, respectively (Lakeman, et al). The next step planned is implementation research to introduce the PRS in clinical genetics.

Genetic etiology of breast cancer subtypes and outcome

Discovery studies on germline variants and survival have been lagging behind the breast cancer risk studies mainly due to limited power. However, within the given limitations, we have been leading at the forefront of this field. Using data of the Breast Cancer Association Consortium (BCAC), we have conducted several GWAS for breast cancer survival in clinically relevant subgroups (e.g. Escala-Garcia et al). We concluded that there is no evidence that common germline variants have large impact on breast cancer prognosis. However, this may be different for specific gene treatment interactions and for the role or rare variants. While several reviews have been published specifically on survival in *BRCA1/2* mutation carriers, seeing yet another review being published, we wrote a critical letter in an attempt to keep up epidemiological standards, including also an overview of the seven reviews published (Wang, et al. Breast Cancer Res Treat. 2021).

Prognostication and treatment decisions remain challenging, given the heterogeneity of breast cancer, and we eventually need all pieces of the puzzle to best advice women in choices of treatment, follow-up and (changes in) lifestyle. A relevant question is therefore whether and how non-genetic breast cancer risk factors affect breast cancer survival, and in particular whether there are differential associations between subtypes. While we confirmed associations between modifiable lifestyle factors (e.g. high BMI, smoking, lack of physical activity) and 10-year all-cause mortality; there was no strong evidence that associations differed by ER status or intrinsic-like subtype.

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Key publications

Sahillioglu AC, et al. CRASH-IT Switch Enables Reversible and Dose-Dependent Control of TCR and CAR T-cell Function. Cancer Immunol Res. 202;9:999-1007

Van der Leun AM, et al. Single-cell analysis of regions of interest (SCARI) using a photosensitive tag. Nat Chem Biol. 2021;11:1139-1147

Voabil P, et al. An ex vivo tumor fragment platform to dissect response to PD-1 blockade in cancer. Nat Med. 2021;7:1250-1261

Dissecting and manipulating tumor-specific immunity

The aim of our research is simple 1). To design novel technologies to examine and modify immune responses 2). To subsequently use these technologies to unravel and manipulate immune recognition of human cancer. Some of the highlights of the past year have been the following:

Dissecting immune recognition in human cancer

There is now widespread evidence for the clinical value of T cell-based immunotherapies in a number of human cancers. However, our ability to carry out mechanistic studies on the immune infiltrates in human tumors has historically been limited. To overcome this limitation, we have developed an ex vivo human tumor fragment culture system that allows one to measure the effect of pathway blockade using either biotherapeutics or small molecule inhibitors. Using this platform, we have asked the question to what extent PD-1 blockade can boost the activity of resident intratumoral T cells, and whether such immune reactivation can be predicted by the composition of the tumor microenvironment. Key findings of this work, carried out in collaboration with the group of Daniela Thommen, have been that ex vivo PD-1 blockade can rekindle intratumoral immune function in part of human tumors, and that such reactivation strongly predicts clinical response to PD-1 blockade. Furthermore, reactivation of intratumoral T cells by PD-1 blockade was shown to boost the production of T cell attracting cytokines, such as CXCL9 and 10, thereby providing a potential mechanistic explanation for the subsequent influx of novel T cell pools, as shown in clinical studies. Notably, the capacity of tumors to respond to PD-1 blockade was predicted well by a number of parameters that report on the presence of tertiary lymphoid structures, and it will be of interest to understand to what extent immune reactivation is biased towards such structures. In addition, it will be of value to exploit the patient-derived tumor fragment platform to dissect whether the immunological effects of biotherapeutics that either block PD-1 or its ligands PD-L1 and PD-L2 are comparable.

External control over T cell activity

Over the past years, a series of CAR- and TCR-based technologies has been developed that allow one to redirect T and NK cell activity towards tumor-associated antigens of interest, and in particular the clinical activity of CAR T cells in hematological malignancies has been substantial. However, on-target off-tumor toxicity forms a substantial limitation of gene-modified T cell therapies, and efforts that allow reversible control of T cell activity are therefore of major interest. To achieve such external control over the activity of infused cell products, we have developed a modular switch, called CRASH-IT, that brings an inhibitory domain to activated ITAM receptors, thereby allowing their silencing. Furthermore, the presence of a small molecule regulated degron in this switch allows external control over the extent of inhibition. In work over the past year, we have identified inhibitory domains of SIGLEC receptors as particularly powerful silencers of ITAM receptor activity, yielding switch systems with a very high dynamic range. In addition, we have shown that this technology allows the regulation of the activity of both CAR- and TCR-modified cells using an approved small molecule, and based on these data, a series of applications is currently envisioned.

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Baas R, van der Wal FJ, Bleijerveld OB, van Attikum H, Sixma TK. Proteomic analysis identifies novel binding partners of BAP1. PLoS One. 2021;16(9):e0257688

Dharadhar S, Dijk WJ, Scheffers S, Fish A, Sixma TK. Insert L1 is a central hub for allosteric regulation of USP1 activity. EMBO Rep. 2021;1-14

Perrakis A, Sixma TK. AI revolutions in biology. EMBO Rep. 2021;1-6

Development of cancer is generally due to errors that occur in cellular pathways. Understanding the mechanisms of underlying processes will help to determine where the errors occur and how they can be treated. We combine biochemical and biophysical methods, including X-ray crystallography and cryo-EM (electron microscopy) to study protein function. Since the appearance of alphafold, we also make use of structural information from artificial intelligence (AI) [3]. This leads to insights in molecular mechanisms that we validate in cells. In addition, our structures provide targets for drug design studies. In this work we focus primarily on proteins involved in mismatch repair and ubiquitin conjugation, particularly in stress response and DNA repair pathways.

DNA mismatch repair

DNA mismatch repair (MMR) plays a crucial role in maintaining genome stability. Defects in the mismatch repair proteins in humans predispose to Lynch syndrome (or hereditary non-polyposis colorectal cancer) and are associated with a variety of sporadic cancers. DNA mismatch repair is initiated by recognition of a mismatch or an unpaired base by MutS (in Escherichia coli) or its MSH homologs (in humans). Initial recognition of the mismatch is followed by an ATP-dependent conformational change of MutS into a sliding clamp state that is recognized specifically by the next protein in the mismatch repair cascade, MutL.
We are interested in the activation mechanism of the repair cascade and the response to DNA binding. In collaboration with Peter Friedhoff in Giessen and Joyce Lebbink in Rotterdam we study the activated state of MutL and its effect on UvrD. We also use cryo-EM to study the DNA interaction of MutSα and correlate this to Lynch syndrome mutations, in a collaboration with the group of Hein te Riele.

Ubiquitin conjugation

Ubiquitin conjugation is an important signal in cellular pathways, changing the fate of a target protein, by degradation, relocalisation or complex formation. Deregulation of ubiquitin-dependent processes often leads to cancer. Ubiquitin signals are balanced by deubiquitinating enzymes (DUBs), which antagonize ubiquitination of specific protein substrates. Because ubiquitination pathways are critically important, we focus on mechanisms of ubiquitin (de)conjugation to aid the process of drug design.
We are interested in the process of H2A and PCNA ubiquitination. In both cases mono-ubiquitination gives critical signals in DNA repair. Recently we were able to reconstitute nucleosome complexes with E3 ligases or DUBs and obtain initial cryo-EM data. Several enzyme substrate complexes are now being studied in more detail. We are especially interested how the relevant substrate affects the reaction.
We studied the enzymatic activity of USP1, a DUB that regulates PCNA ubiquitination, a mark that is important for recruitment of translesion polymerases when replications forks are stalled by DNA damage. USP1 activity depends on an allosteric activator, UAF1 and this is tightly controlled. This DUB has three defined inserts relative to paralogs USP12 and USP46, while these also have a second WDR20-mediated activation step. We found that USP1 by itself is auto-inhibited by its inserts L1 and L3 together. This auto-inhibition can be relieved by UAF1 to a state that is equivalent to WDR20 and UAF1 mediated activity. The insert L1 is also important for substrate-dependent increase of USP1 activity, by both DNA and PCNA interactions, and this process is independent of UAF1-mediated activation. All in all we found that insert L1 acts as a regulatory hub for substrate-mediated activity enhancement and for allosteric activation upon UAF1 binding [2]. As USP1 inhibitors are entering clinical trials good understanding of its regulation can be important for the interpretation of the results.
BAP1 is a tumor-suppressor that is frequently deleted in a number of tumors including uveal melanoma and mesothelioma. It forms complexes with an established set of proteins, identified through IP mass spectrometry. Here we extended on these studies by by expressing GFP-tagged BAP1 in an endogenous BAP1 deficient cell line and identified novel interactors in the cytosol. These included Histone acetyltransferase 1 (HAT1) and all subunits of the heptameric coat protein complex I (COPI) that is involved in vesicle formation and protein cargo binding and sorting. We were able to validate the interactions of BAP1 with HAT1 and the COPI complex at endogenous levels [1].

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Key publications

Beekman C, Schaake E, Sonke JJ, Remeijer P. Deformation trajectory prediction using a neural network trained on finite element data-application to library of CTVs creation for cervical cancer. Phys Med Biol. 2021;66(21)

La Fontaine MD, Bruin NM, van Kranen S, Knegjens JL, van de Kamer JB, Vogel WV, Sonke JJ. The dynamics and prognostic value of FDG PET-metrics in weekly monitoring of (chemo)radiotherapy for NSCLC. Radiother Oncol. 2021;160:107-114

Stankovic U, Ploeger LS, Sonke JJ. Improving linac integrated cone beam computed tomography image quality using tube current modulation, Med Phys. 2021;48(4):1739-1749

Adaptive radiation therapy

Introduction

Geometrical uncertainties such as setup error, posture change, organ motion, deformations and treatment response limit the precision and accuracy of radiation therapy (RT). Consequently, the actually delivered dose typically deviates from the planned dose. To minimize the deleterious effects of geometrical uncertainties, adaptive radiation therapy (ART) aims to characterize the patient's specific variation through an image feedback loop and adapt the patients' treatment plan accordingly. Adaptive radiation therapy research therefore includes 1) improving in room imaging, 2) patient variability characterization, 3) treatment plan modification and 4) outcome modeling.

Tube Current Modulation in Cone Beam Computed Tomography

Linac integrated cone beam computed tomography (CBCT), typically employs a constant fluence per projection image. As human anatomy is not circle symmetric, such acquisition scheme leads to suboptimal image quality. The purpose of this work was to implement tube current modulation (TCM) and evaluate its impact on image quality under varying scatter conditions. TCM was successfully implemented by varying the X-ray pulse width per projection inversely proportional to the square root of the attenuation through the isocenter region estimated from the planning CT. TCM led to 30-78% reduction of the angular anisotropicity of the noise power spectrum. The amount of reduction depended on the scatter conditions, with lower values corresponding to higher scatter conditions. The same was true for the contrast to noise that was improved by about 12% (high scatter) to 30% (low scatter). In conclusion, TCM can improve CBCT image quality, but this depends on the amount of detected x-ray scatter.

Deformation trajectory prediction for library of CTVs creation for cervical cancer radiotherapy

Library of plans allow for daily adaption of the treatment plan to the anatomy of the day. Library of plan creation requires fast prediction of realistic, time-parametrized deformations between pairs of input segmentations. To that end, we trained a 3D convolutional neural network (CNN) to predict a stationary velocity field given the distance maps of the cervix CTV in empty and full bladder anatomy. Diffeomorphic deformation trajectories between the two states were obtained by time integration. The network was trained on cervix CTV deformations of 20 patients generated by finite element modeling (FEM). Validation was performed on an independent dataset. The median Dice score over the validation subjects between the predicted and FEM libraries was >0.95 throughout the deformation, with a median 90 percentile surface distance of <3 mm. Clinical evaluation showed improved library properties over the method currently used in clinic.

The prognostic value of weekly FDG PET in for non-small cell lung cancer chemo-radiotherapy

Response assessment early in the course of chemo-radiotherapy may enable individualized treatment strategies. The purpose of this study was therefore to investigate if the relative change in FDG-PET SUVmax over the course of treatment was associated with disease progression and overall survival. To that end, 28 patients received two pre-treatment FDG-PET scans and four during-treatment scans at weekly intervals. SUVmax was normalized to the start of treatment and analyzed using linear regression. Linear regression coefficients of other first order PET-metrics were grouped according to dissimilarity. Associations to patient outcome were analyzed using Cox hazard ratio. All investigated FDG PET metrics linearly decreased during treatment. Relative change in SUVmax was not associated to patient outcome while several other first order PET-metrics such as changes in total lesion glycolysis were related to patient outcome. A single optimal imaging time-point could not be identified.

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Receptors for matrix adhesion

Our main aim is to understand the molecular mechanisms that regulate the interaction of cells with components of the extracellular matrix and to establish the role of cell adhesion receptors in health and disease. A major class of cell adhesion receptors are formed by members of the integrin family. We would like to understand how integrins interact with their ligands and assemble multiprotein complexes at the cell-substratum site in normal and pathological conditions, define the interplay among different integrins and understand the underlying molecular mechanisms.

Assembly of different integrin-based adhesion structures

Integrins are obligate heterodimers composed of α and β subunits. In mammals 18 α and 8 β subunits have been characterized. We are investigating three integrins that are clustered in different adhesion structures and associate with distinct cytoskeletal elements. These are laminin-binding α3β1 and α6β4, and αVβ5, a receptor for vitronectin. While the integrins α3β1 and αVβ5 are connected to the actin cytoskeleton in focal adhesions, α6β4 associates with the intermediate filament system in hemidesmosomes. Additionally, integrins α3β1 and αVβ5 can localize to adhesion structures that are seemingly not connected with the actin cytoskeleton; αVβ5 can be found in flat clathrin lattices and α3β1, when in complex with CD151, resides in tetraspanin webs. In the past year, we investigated the mechanisms that regulates the subcellular distribution of β5 and show that β5 has approximately a 7-fold higher affinity for the clathrin adaptor ARH than for talin, and a 5-fold higher affinity for Numb; all proteins that bind to the membrane-proximal NPxY motif of the β5 cytoplasmic domain. Furthermore, we show that phosphomimetic substitutions at two serines in the β5 cytoplasmic domain diminishes the clustering of β5 in flat clathrin lattice and that the activity of myosin II and the resulting tension is an important factor in determining the localization of β5 at focal adhesions versus flat clathrin lattice. Adhesion structures that can diminish focal adhesion assembly and cellular tension, such as the α6β4-containing hemidesmosomes promote the localization of integrin αVβ5 in flat clathrin lattices.

Role of integrins in health and disease

Integrin α3β1, which mediates the adhesion of epithelial cells to laminin-332 and -511 in the basement membrane and plays a role in the maintenance of cell-cell contacts, has been implicated both as a promoter and suppressor of tumorigenesis and metastasis in different types of tumors. Among others, we observed such dual role in cancer in a model of chemically induced skin tumorigenesis (DMBA/TPA treatment) in mice, where α3β1 is required for the initiation and development of the disease. Recently, we showed that α3β1 together with its tetraspanin partner CD151 controls the activation of several pro-tumorigenic signaling pathways, including FAK-Src, Akt, STAT3 and Smad signaling pathways. Remarkably, α3β1 and CD151 can support Akt and STAT 3 activity independently of α3β1 ligation by laminin-332 and as such control the essential survival signals required for suprabasal keratin-10 expression during keratinocyte differentiation.

The integrin adhesome in colorectal adenoma-to-carcinoma progression

Besides binding to their extracellular matrix ligands, integrins form adhesion complexes by interacting with multiple intracellular proteins, which subsequently bind to other scaffold and cytoskeletal linker proteins to establish linkages between the extracellular matrix and the intracellular cytoskeleton. Collectively, this assembly of proteins is known as the 'integrin adhesome'. In order to get a better understanding of the molecular composition of the integrin adhesome, we have conducted proximity biotinylation assays using different integrin subunits as bait. From these studies, we identified components of the integrin α5β1 and αVβ3 adhesome that were also found to be differentially phosphorylated in colorectal adenoma versus carcinoma tissues in a phospho-proteomics analysis performed by the research group of Beatriz Carvalho and Gerrit Meijer (NKI, Diagnostic Oncology department). Our research groups have joined forces to set up several *in vitro* and *in vivo* models to study if and how the integrin adhesome contributes to the colorectal adenoma-to-carcinoma progression.

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Publications

Ramovs V, Krotenberg Garcia A, Kreft M, Sonnenberg A. Integrin α3β1 is a key regulator of several protumorigenic pathways during skin carcinogenesis. J Invest Dermatol. 2021;141(4):732-741.e6

Te Molder L, de Pereda JM, Sonnenberg A. Regulation of hemidesmosome dynamics and cell signaling by integrin α6β4. Cell Sci. 2021;134(18):jcs259004

Te Molder L, Kreft M, Heemskerk N, Schuring J, de Pereda JM, Wilhelmsen K, Sonnenberg A. EGFR-dependent tyrosine phosphorylation of integrin β4 is not required for downstream signaling events in cancer cell lines. Sci Rep. 2021;11(1):8675

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Key publications

Benedict B. Vulnerabilities of cancer cells suffering from DNA replication stress. Thesis VU University Amsterdam 2021

Will Castro LSEP, Pieters W, Alemdehy MF, Aslam MA, Buoninfante OA, Raaijmakers JA, Pilzecker B, van den Berk PCM, Te Riele H, Medema RH, Pedrosa RC, Jacobs H. The Widely Used Antihelmintic Drug Albendazole is a Potent Inducer of Loss of Heterozygosity. Front Pharmacol 2021;12:596535

Genomic instability and carcinogenesis

How does genomic instability develop and affect initiation and progression of cancer? We focus on two causes of genomic instability: *(1)* loss of DNA mismatch repair (MMR) and *(2)* defective G_1/S control causing unscheduled S-phase entry and replication stress.

Impact of the gut microbiota on tumor development

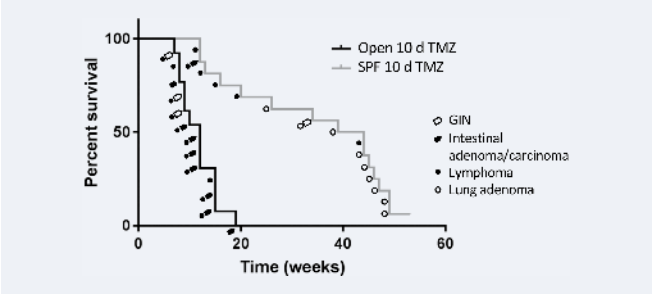
Inherited defects in DNA MMR genes cause the cancer predisposition Lynch syndrome (LS). We modelled this condition in *Msh2-Lynch* mice (Wojciechowicz et al., Gastroenterology 2014). However, intestinal tumorigenesis was virtually lost when animals were transferred from an open animal facility to a specific pathogen-free (SPF) environment (see figure). By 16S rRNA gene sequencing, we detected large differences in gut microbiota composition in the two facilities. Transplantation of preserved feces from open-housed animals into SPF animals strongly impacted the immune landscape, enhanced epithelial proliferation and migration, and increased microsatellite instability in untransformed MSH2-deficient crypts. Pro-proliferative and pro-mutagenic gut microbes may therefore be strong but actionable risk factors for tumor development in LS patients.

Unclassified variants of MMR genes

While deleterious MMR gene variants (deletions, stop codons) are clearly causative for LS, single nucleotide variants are often difficult to interpret. We developed a functional test to phenotype such 'Variants of uncertain significance' (VUS): "oligonucleotide-directed mutation screening" (ODMS) (Houlleberghs et al., PNAS 2016; **PLoS Genet** 2017; J Med Genet 2020). Briefly, the VUS is introduced into ±0.01% of cells that are hemizygous for a MMR gene, by oligonucleotide-directed gene editing (Van Ravesteyn et al., PNAS 2016; Plos Genet 2020); when the VUS is deleterious, colonies appear in 6-thioguanine (6TG)- or MNNG-containing medium, while the absence of colonies indicates wild-type activity. ODMS in human cells allows us to also address extra-exonic variants (promoter, intron). To implement ODMS in clinical diagnostics, we founded the nationwide KWF-sponsored consortium IN*VUS*E (*"investigating variants of uncertain significance for use in clinical practice"*). By combining ODMS with a biochemical assay and clinical data, IN*VUS*E is classifying all Dutch MMR variants, aiding the identification of LS families and instalment of proper surveillance.

Replication stress

Unscheduled S-phase entry of G_1/S checkpoint defective, mitogen-starved cells causes replication stress, revealed by slow fork progression, low origin firing, DNA breaks and proliferative arrest. Strikingly, disruption of the *Tp53/p21*^{CIP1} axis allowed mitogen-independent proliferation, not only by attenuated DNA damage response, but rather by restored origin firing and reduced DNA breakage, although replication speed remained low (Benedict et al., Elife 2018). Genetic screens divulged pathways critical for this proliferation: the helicase RECQL prevents MRE11-dependent replication fork collapse (Benedict et al., Life Sci All 2020), while the cohesion antagonist WAPL is critical for rapid RAD51-dependent repair of broken forks (Benedict et al., Dev Cell 2020). At the same time, cohesion loaders are needed to prevent excessive lethal sister chromatid cohesion loss. In many cancer cell lines, sister chromatid cohesion removal is necessary to handle oncogene-induced DNA replication stress. Other critical pathways are currently under investigation.



Intestinal tumorigenesis induced by temozolomide (TMZ) treatment of *Msh2-Lynch* mice is strongly reduced when mice are transferred from an open to an SPF facility.

AI for oncology

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Key publications

Garrett Fernandes M, Bussink J, Stam B, Wijsman R, Schinagl D, Monshouwer R, and Teuwen J. Deep learning model for automatic contouring of cardiovascular substructures on radiotherapy planning CT images: Dosimetric validation and reader study based clinical acceptability testing. Radiother Oncol. 2021;165:52-59

Panteli A, Teuwen J, Horlings H, and Gavves E. Sparse-Shot Learning with Exclusive Cross-Entropy for Extremely Many Localisations. Proceedings of the IEEE/CVF International Conference on Computer Vision (ICCV) 2021:2813-2823

Teuwen J, Moriakov N, Fedon C, Caballo M, Reiser I, Bakic P, García E, Diaz O, Michielsen K, and Sechopoulos I. Deep learning reconstruction of digital breast tomosynthesis images for accurate breast density and patient-specific radiation dose estimation. Med Image Anal. 2021;71:102061

Our main aim is to develop artificial intelligence (AI) innovations to improve the diagnosis and therapy of cancer. AI has surpassed human performance in many tasks, and we intend to bring that power to cancer research. Nonetheless, our intention is not to replace humans but to create enabling technology to improve cancer diagnosis and therapy. To do this, we deploy many AI algorithms and research ways to improve these algorithms; applying AI to an oncological problem brings a unique set of challenges. To do this, last year we focussed our research on three research lines: (1) predicting immunotherapy response, (2) reducing breast cancer overtreatment, (3) image reconstruction.

Immunotherapy outcome prediction

In the last decade, cancer immunotherapy has been revolutionizing cancer care. Immunotherapy is a systemic cancer treatment that exploits the power of the body's immune system to fight cancer cells by boosting the immune response. Despite the success of immunotherapy in treating specific cancer types, the overall response rate is low. Because of potential side effects and the high cost of immunotherapy, it is crucial to identify which patients would benefit from this therapy. To help improve therapy selection, we have developed algorithms that can predict microsatellite instability and provide an accurate tumor-infiltrating lymphocyte assessment based on hematoxylin & eosin (H&E) stained tissue.

Reducing breast cancer overtreatment

Breast cancer is one of the leading causes of cancer death among women worldwide. An accurate risk assessment of breast cancers or their precursors is paramount to deciding the appropriate treatment regime. Several studies have shown that it is possible to avoid neoadjuvant therapy in more cases of early-stage breast cancers than the current recurrence risk assessment models suggest. We have developed an algorithm for an accurate risk assessment of ductal carcinoma in situ (DCIS), a potential precursor of breast cancer. As current risk models do not provide enough information to predict whether a DCIS lesion will progress into invasive breast cancer, building a better model will lead to less overtreatment of breast cancer patients and a better quality of life.

Image reconstruction

Medical imaging is the cornerstone of modern medicine. An important problem to solve in medical imaging is how to relate the measured machine data to the actual patient anatomy, which we want to visualize. This process is called reconstruction. We developed deep learning-based reconstruction algorithms to enable new treatment paradigms in radiation oncology in both Cone Beam CT (CBCT)-guided therapies and MRI-guided therapies.

Ideally, a CBCT scan could be used to adapt the treatment plan to the current patient anatomy and tumor response. However, this is limited because of the poor contrast and non-calibrated intensity values required to compute the accumulated dose to the tumor and healthy tissue. We develop algorithms that can accurately predict the tissue attenuation values to be used for daily replanning of radiotherapy.

On the other hand, in MRI-guided radiotherapy, an image can be acquired during radiation delivery. This allows the opportunity to adapt the treatment to the constantly changing patient. This requires a very fast reconstruction of a highly accelerated image. For this purpose, we have also developed algorithms and an open source toolkit called direct.

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Key publications

Koelzer VH, Herzig P, Zlobec I, Heinzelmann V, Lardinois D, Walseng E, Rader C, Mertz KD, Zippelius A, Thommen DS. Integrated functional and spatial profiling of tumour immune responses induced by immunotherapy: the iPROFILER platform. Immuno-Oncology and Technology. 2021;10:1-14

Pelly VS, Moeini A, Roelofsen LM, Bonavita E, Bell CR, Hutton C, Blanco-Gomez A, Banyard A, Bromley CP, Flanagan E, Chiang SC, Jørgensen C, Schumacher TN, Thommen DS, Zelenay S. Anti-inflammatory drugs remodel the tumor immune environment to enhance Immune checkpoint blockade efficacy. Cancer Discov. 2021;11(10):2602-2619

Voabil P, de Bruijn M, Roelofsen LM, Hendriks SH, Brokamp S, van den Braber M, Broeks A, Sanders J, Herzig P, Zippelius A, Blank CU, Hartemink KJ, Monkhorst K, Haanen JBAG, Schumacher TN, Thommen DS. An ex vivo tumor fragment platform to dissect response to PD-1 blockade in cancer. Nat Med. 2021;27(7):1250-1261

Dissecting and modulating reactive anti-tumor immunity using patient-derived tumor models

The overall aim of our research is to develop and use patient-derived tumor models to (1) understand the diversity in immune cell activity in human cancers, (2) determine how tumoricidal immune responses in human cancer lesions can be induced or reinvigorated by therapy, and (3) use the resulting information to develop novel therapeutic strategies and biomarkers for patient stratification.

Immunological response of human cancers to PD-1 blockade

While the clinical activity of immune checkpoint blocking (ICB) antibodies, i.e. inhibiting the PD-1/PD-L1 axis, is well established, the immunological changes that occur in human cancer tissue upon ICB are still poorly understood. Importantly, technical approaches that allow to perform mechanistic studies on immune infiltrates in human cancer tissue are lacking. To overcome this limitation, we have developed and used a patient-derived tumor fragment (PDTF) platform to profile the early immunological response of five different cancer types to ex vivo PD-1 blockade. A key finding of this work has been that immune reactivation in PDTFs upon anti-PD-1 was highly predictive for clinical response. In collaboration with the Schumacher lab, we are now extending this work to understand how distinct intratumoral immune cells are reactivated by ICB at single cell level.

A second important observation was that immune reactivation occurred in only some of the tumor fragments of individual patients, but those responding fragments showed a highly consistent pattern of response, suggesting spatial heterogeneity. Our current work focuses on elucidating the role of such spatial immune organization for anti-tumor immunity. To this end, we developed technology to integrate functional and spatial profiling of human cancers. By combining PDTF cultures with an IHC-based digital imaging platform, we were able to capture spatially restricted immune activation patterns upon stimulation by a bispecific antibody in lung and ovarian cancer PDTFs. As a next step, we aim to expand this platform with high-dimensional imaging technologies to dissect the spatial organization of immune activity upon ICB.

Modulating pro-tumorigenic inflammation in human tumor tissue

The balance of pro- and anti-tumorigenic inflammatory mediators in the tumor microenvironment plays a pivotal role in determining tumor progression and ICB treatment outcome. Manipulating the flavor of tumor inflammation thus represents an attractive strategy to improve ICB efficacy. To address this question, we collaborated with the group of Santiago Zelenay from the CRUK Manchester Institute, who previously demonstrated that cancer cell expression of COX2 and production of PGE2 play a dominant role in tumor evasion by directly inhibiting adaptive immune responses, in favor of tumor-promoting inflammation. Therefore, we tested whether the anti-inflammatory drug celecoxib (CXB), a selective COX2 inhibitor, can be repurposed to modulate intratumoral inflammation. Exposure of PDTFs to CXB significantly inhibited PGE2 release and induced a shift in cytokine and chemokine profile of $PGE2^{high}$ compared to $PGE2^{low}$ tumors, leading to a significant increase in the levels of CXCL9 and CXCL10, and concomitant dampening of immunosuppressive factors, in line with data obtained from CXB treatment of tumor bearing mice by the Zelenay group. Importantly, CXB treatment in addition to anti-CD3 stimulation also enhanced T cell activation and effector function. Altogether, our findings suggest that inhibition of the COX2/PGE2 axis rapidly shifts the tumor inflammatory landscape towards one more favorable to ICB efficacy.

Cancer survivorship

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Our research objective is to *measure* and *understand* the impact of cancer and treatment and *improve* patient (reported) outcomes by developing supportive care strategies.

Measuring: International development of quality of life questionnaires and core outcome sets

In 2021, we completed the international validation study of the disease-specific EORTC QoL questionnaires for patients with (non) Hodgkin lymphoma or chronic lymphoblastic leukemia. In addition, we conducted a systematic review for the development of an EORTC QoL questionnaire for patients with advanced melanoma. In the framework of the Health Outcomes Observatory project (EU H2020), we held expert meetings and conducted two Delphi studies to develop a core outcome set for metastatic breast cancer and lung cancer.

Understanding: Patient Reported Outcome Measures (PROMs) in clinical practice and randomized trials

In 2020, we started implementing and evaluating PROMs in daily clinical practice in the AVL clinic. In the past year, >300 melanoma and >500 breast cancer patients completed PROMs before and after their treatment. Meanwhile, other tumor working groups have also started to measure PROMs routinely. These data will give us insight into the impact of new cancer treatments on physical and psychosocial functioning and provide clues for improvements in supportive care. In addition, we are also evaluating the impact of (neo-)adjuvant immunotherapies on the QoL of patients participating in several clinical trials.
Furthermore, we used the population-based PROFILES registry that I set up in 2009, to study the physical and psychosocial impact of cancer and its treatment. Today, we have evaluated patient-reported outcomes of more than 40,000 cancer survivors in 80 hospitals in the Netherlands, resulting in >150 scientific publications. In 2021, we wrote 24 papers including research on sex-differences in symptoms and functioning. We also applied network analyses to improve our understanding of the underlying mechanisms that affect survivors' symptom burden.

Improving: Randomized Trials to evaluate impact of health care interventions

In 2020, we were active with four randomized trials on healthcare interventions: 1) For the ENSURE (ENdometrial cancer SURvivors' follow-up carE) trial, the 3-year follow-up has been completed. We are currently analysing data of 300 women with early stage endometrial cancer who were randomised to 4 or 10-13 follow-up visits in 3 years; 2) In the PROSPEC (PROstate cancer follow-up care in Secondary and Primary hEalth Care) trial, the last patients have been included in 2021, but we can only start analysing the data in 2023 when 2 years of follow-up will be completed; 3) We continued to collect data for the pragmatic cluster randomized GERSOC (GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma) and the 4) SYMPRO-Lung (SYMptom monitoring with patient-reported outcomes among lung cancer patients in the Netherlands) trial.

FUNCTIONAL RECOVERY FROM CANCER AND ITS TREATMENT

Our research objective is to *measure* and *understand* the impact of cancer and treatment, and of supportive care interventions that aim to *improve* functional recovery for patients living with or beyond cancer. We do this by developing supportive care strategies, with a focus on allied health professions and the role of exercise. We also strive to actively support implementation of research findings into clinical practice.

Measuring: functional assessment protocols

In 2021, we completed several studies in the field of functional assessment, including exercise

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Key publications

Groen WG, Naaktgeboren WR, van Harten WH, van Vulpen JK, Kool N, Sonke GS, van der Wall E, Velthuis MJ, Aaronson NK, May AM, Stuiver MM. Physical fitness and chemotherapy tolerance in patients with early stage breast cancer. MSSE. 2021 (in press)

Groen WG, Ten Tusscher MR, Verbeek R, Geleijn E, Sonke GS, Konings IR, Van der Vorst MJ, van Zweeden AA, Schrama JG, Vrijaldenhoven S, Bakker SD, Aaronson NK, Stuiver MM. Feasibility and outcomes of a goal-directed physical therapy program for patients with metastatic breast cancer. Support Care Cancer. 2021;29(6):3287-3298

Karsten RT, Hilgers FJM, van der Molen L, van Sluis K, Smeele LE, Stuiver MM. The Timed Swallowing Proficiency for Eating and Drinking (SPEAD) test: Development and initial validation of an instrument to objectify (impaired) swallowing capacity in head and neck cancer patients. Dysphagia. 2021;36(6):1072-1087

Oerlemans S, Arts LPJ, Kieffer JM, Prins J, Hoogendoorn M, van der Poel M, Koster A, Lensen C, Stevens WBC, Issa D, Pruijt JFM, Oosterveld M, van der Griend R, Nijziel M, Tick L, Posthuma EFM, van de Poll-Franse LV. Web-based return of individual patient-reported outcome results among patients with lymphoma: Randomized controlled trial. J Med Internet Res. 2021;23(12):e27886

Oerlemans S, Schagen SB, van den Hurk CJ, Husson O, Schoormans D, van de Poll-Franse LV. Self-perceived cognitive functioning and quality of life among cancer survivors: results from the PROFILES registry. J Cancer Surviv. 2021

Oertelt-Prigione S, de Rooij BH, Mols F, Oerlemans S, Husson O, Schoormans D, Haanen JB, van de Poll-Franse LV. Sex-differences in symptoms and functioning in >5000 cancer survivors: Results from the PROFILES registry. Eur J Cancer. 2021;156:24-34

testing for cancer rehabilitation; development and validation of a novel instrument for assessment of swallowing capacity; and development and testing of a novel protocol for lymphedema assessment in the head and neck area using tissue-dielectric constant measurements.

Understanding: preferences for physical exercise of people with metastasized breast cancer, physical fitness and chemotherapy completion, functional outcomes after head and neck cancer treatment, and non-response to physical activity intervention studies,

As work package leader of PERSPECTIVE, the social sciences sub-study of the EU-funded PREFERABLE project, we collected survey data and conducted focus groups in five European countries, to investigate views about and preferences for supervised exercise of people with metastasized breast cancer. In a joint project with the UMCU, we pooled data from previously conducted exercise trials, and showed that low baseline physical fitness is associated with a higher risk of premature chemotherapy cessation in breast cancer patients. In a follow-up study to assess the outcomes of current routine clinical care for people treated with radiotherapy for head and neck cancer (HNC), we found that mouth opening, swallowing and speech are still impaired at 12 months post-treatment, and that patients with HPV-related tumors and those with sarcopenia are at risk for poorer outcomes. These insights will help us further improve the rehabilitation protocols in HNC care. Using data from non-responders to the randomized controlled PABLO trial, we established that survivors of breast and prostate cancer successfully self-select for participation in an online/blended care intervention to improve physical activity levels.

Improving: Randomized Trials to evaluate impact of health care interventions, innovative care programs, and translating evidence into clinical practice

We analysed and published the results of the randomized controlled PABLO trial (see above), and of the evaluation of a newly developed physiotherapy program for people with metastasized breast cancer. We continued recruitment in the PREFERABLE EFFECT RCT, which evaluates cost-effectiveness of a supervised exercise program for people with metastasized breast cancer. We started preparations for a multi-centre randomized controlled trial on multimodal prehabilitation for bladder cancer surgery. We started an innovative care program to support people with breast cancer in weight management during and after treatment. With regard to implementation, we developed a guideline for physical therapist led exercise for people with cancer, commissioned by the Royal Dutch Society of Physical Therapy. Also, we developed evidence-based treatment protocols to be used by physical therapists and exercise professionals for supervising exercise programs for people with prostate cancer (NEXT PRO); these were published in the public domain and will be implemented in Onconet (www.onconet.nu).

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Personalized Oncology in sarcoma and adolescent and young adult (AYA) cancer patients

Summary research

The personalized oncology group is currently concentrating on two principal research lines: (1) the short-, long-term and late consequences of cancer at adolescent and young adult age; (2) diagnosis, treatment, outcome and health-related quality of life issues of people with sarcoma.

Adolescents and Young Adults

Adolescent and Young Adult (AYA) cancer patients, diagnosed with cancer between the age of 18-39 years old, suffer from delay in diagnosis, lack of centralization of care, age-adjusted expertise and follow-up care. This group presents with a unique spectrum of cancers, distinctive tumor biology, cancer risk factors, developmental challenges and treatment regimens that are different compared to children. There will be a burden of medical and psychosocial problems, which could result in compromised health-related quality of life and reduced life expectancy. Findings derived from childhood cancer survivors cannot be extrapolated to AYA. It is imperative for advances in the field of AYA oncology to pool data sources (patient-reported outcomes, clinical, genetic and biological data) across institutions and create large cohorts that include the full range of AYA ages and diagnoses to be able to address the many pressing questions that remain unanswered in this vulnerable population. We are currently running the SURVAYA study to examine the long-term consequences of cancer at AYA age among people who were diagnosed 5-20 years ago. Additionally, we are working on a unique nationwide infrastructure (COMPRAYA) for research into the prevalence, predictive and prognostic markers (risk factors) and underlying mechanisms of (age-specific) medical and psychosocial outcomes, and to facilitate the development and testing of (early) intervention strategies to improve these outcomes for patients (at risk). We will establish a prospective observational cohort of 1-year AYA cancer survivors followed prospectively for 20+ years or until death. Within COMPRAYA we will pay special attention to AYA cancer patients living with life-limiting cancer: how does this diagnosis impacts normal (daily) life and what are the challenges they face within the health care system?

Sarcoma

Health-related quality Of Life In patients with advanced Soft TIssue sarcomas treated with Chemotherapy: the HOLISTIC study

Chemotherapy is the mainstay of treatment for patients with metastatic soft tissue sarcomas (STS). Treatment intent is usually palliative, aiming to improve symptoms, stabilize or reduce tumour-burden and extend life. Clinical trials for advanced STS have traditionally used radiological response, time to progression and survival as measures of treatment efficacy. Treatment decisions are often challenging due to modest response rates and potential adverse side-effects. Health-related quality of life (HRQoL) is at least equally- or more important than survival for many patients with advanced cancer. Systematically collecting HRQoL data during chemotherapy can provide greater insight into treatment efficacy from the patient perspective. The primary aims of this study are to evaluate HRQoL in patients with advanced STS treated with chemotherapy over time, explore the decision-making process and patient reflections post-treatment.

QUality *of life and Experiences of Sarcoma Trajectories: the QUEST study*

The prognosis of patients with rare cancers in general and sarcomas in particular suffers from delay in diagnosis. Routes to diagnosis have neither been studied in detail in larger numbers before, nor in a direct comparison between two countries with different health systems. Comprehensive assessment of diagnostic delays and its determinants, including demographic, clinical, psychosocial and health care system factors, is necessary to improve referral pathways and come to best practice and patient reported outcomes for sarcoma patients. This study aims to quantify diagnostic delay (including patient, general practitioner and system delay) and evaluates routes to diagnosis and referral to sarcoma expert centers in the Netherlands and England; to comprehensively evaluate risk factors of diagnostic delay; determine the association between diagnostic delay and outcomes (HRQoL, quality adjusted life years, patient satisfaction, TNM classification, time to local/distant relapse and overall survival); and to assess differences between both countries.

Key publications

Burgers VWG, van der Graaf WTA, van der Meer DJ, McCabe MG, Rijneveld AW, van den Bent MJ, Husson O. Adolescents and Young Adults living with an uncertain or poor cancer prognosis: The "New" lost tribe. J Natl Compr Canc Netw. 2021;19(3):240-246

Den Hollander D, Fiore M, Martin-Broto J, Kasper B, Casado Herraez A, Kulis D, Nixon I, Sodergren SC, Eichler M, van Houdt WJ, Desar IME, Ray-Coquard I, Piccinin C, Kosela-Paterczyk H, Miah A, Hentschel L, Singer S, Wilson R, van der Graaf WTA, Husson O. Incorporating the patient voice in sarcoma research: How can we assess health-related quality of life in this heterogeneous group of patients? A study protocol. Cancers (Basel). 2020;13(1):1

Drabbe C, Grünhagen DJ, Van Houdt WJ, Braam PM, Soomers VLMN, Van der Hage JA, De Haan JJ, Keymeulen KBMI, Husson O, Van der Graaf WTA. Diagnosed with a rare cancer: experiences of adult sarcoma survivors with the healthcare system-results from the SURVSARC study. Cancers (Basel). 2021;13(4):679

Husson O, Ligtenberg MJL, van de Poll-Franse LV, Prins JB, van den Bent MJ, van Eenbergen MC, Fles R, Manten-Horst E, Gietema JA, van der Graaf WTA. COMPRehensive assessment of incidence, risk factors and mechanisms of impaired medical and psychosocial health outcomes among Adolescents and Young Adults with cancer: the prospective observational COMPRAYA cohort study. Cancers (Basel). 2021;13(10):2348

Husson O, Reeve BB, Darlington A, Cheung C Sodergren S, van der Graaf WTA, Salsman J. Next Step for global Adolescent and Young Adult oncology: A core patient-centered outcome set. J Natl Cancer Inst. 2021

Younger E, Jones RL, den Hollander D, Soomers VLMN, Desar IME, Benson C, Young RJ, Oosten AW, de Haan JJ, Miah A, Zaidi S, Gelderblom H, Steeghs N, Husson O, van der Graaf WTA. Priorities and preferences of advanced soft tissue sarcoma patients starting palliative chemotherapy: baseline results from the HOLISTIC study. ESMO Open. 2021;6(5):100258

Incorporating the patient voice in sarcoma research: how can we assess health-related quality of life in this heterogeneous group of patients

There is limited high-quality HRQoL data in sarcoma. Previous studies have predominantly used generic HRQoL instruments, which cover some relevant issues but do not capture all the unique experiences of patients with sarcoma, and thus lack content validity. A sarcoma-specific questionnaire or validated items should be able to detect, with more sensitivity, side-effects, symptoms and problems with function that are particularly relevant to patients with different presentations and subtypes of sarcomas. Given the heterogeneity of the disease in terms of subtype, location, age and treatment, the development of a single sarcoma questionnaire is impossible. Therefore, we have started a study to develop standards of HRQoL measurement in the broad spectrum of patients with sarcoma. This is a collaborative project between the EORTC Quality of Life Group (QLG) and the EORTC Soft Tissue and Bone Sarcoma Group (STBSG).

Sarcoma Priority Setting Partnership Study

Research in sarcoma has historically been the domain of scientists and clinicians attempting to understand the disease in an effort to develop effective treatments. There is growing recognition of the importance of integrating patient perspectives (e.g., preferences, expectations, and expanded definitions of what constitutes "successful" outcomes) into clinical research. This evolution is reflected in the growth of patient-centered organizations and patient advocacy groups that seek to meaningfully integrate patients into the process of prioritizing research needs and creating alliances wherein patients and researchers can partner together to accomplish research goals. The group leaders are leading a project together with the patient advocacy group SPAEN aiming to identify the unanswered questions about sarcoma from patient, carer and clinical perspectives and then prioritise those that patients, carers and clinicians agree are the most important for research to address.

Imaging technology in radiation oncology

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Key publications

Keesman R, van der Bijl E, Janssen TM, Vijlbrief T, Pos FJ, van der heide UA. Clinical workflow for treating patients with a metallic hip prosthesis using magnetic resonance imaging-guided radiotherapy. Phys Imaging Radiat Oncol. 2020;15:85-90

Kerkmeijer LGW, Groen VH, Pos FJ, Haustermans K, Monninkhof EM, Smeenk RJ, Kunze-Busch M, de Boer JCJ, van der Voort van Zijp J, van Vulpen M, Draulans C, van den Bergh L, Isebaert S, van der heide UA. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: Results from the FLAME randomized phase III trial. J Clin Oncol. 2021;39(7):787-796

van Houdt PJ, Saeed H, Thorwarth D, Fuller CD, Hall WA, McDonald BA, Shukla-Dave A, Kooreman ES, Philippens MEP, van Lier ALHMW, Keesman R, Mahmood F, Coolens C, Stanescu T, Wang J, Tyagi N, Wetscherek A, van der Heide UA. Eur J Integration of quantitative imaging biomarkers in clinical trials for MR-guided radiotherapy: Conceptual guidance for multicentre studies from the MR-Linac Consortium Imaging Biomarker Working Group. Cancer. 2021;153:64-71

Dose painting for prostate cancer

The FLAME trial is a multi-center phase III randomized trial of dose escalation in prostate cancer using external-beam radiotherapy. In this study, an isotoxic focal boost to the visible tumor inside the prostate up to a dose of 95 Gy was given and compared to the standard treatment of 77 Gy to the gland (see figure). In total 571 patients have been randomized. We demonstrated that isotoxic focal boosting in patients with intermediate and high-risk prostate cancer improves 5-year biochemical disease-free survival from 85% in the standard arm to 92% in the focal boost arm ($p<0.001$). The positive effect of focal boosting appears even more striking in the dose effect relations. Patients with ISUP grade ≥ 2 disease, have failure rates dropping from over 25% at 77 Gy to below 10% at a higher dose.

Isotoxic boosting was chosen deliberately to avoid additional toxicity as long as the benefit of focal boosting was unproven. We strictly adhered to pre-specified dose constraints to organs at risk, compromising the focal boost dose if necessary. This approach was effective as no significantly increased toxicity was observed compared to the standard arm.

Quantitative MRI for radiotherapy

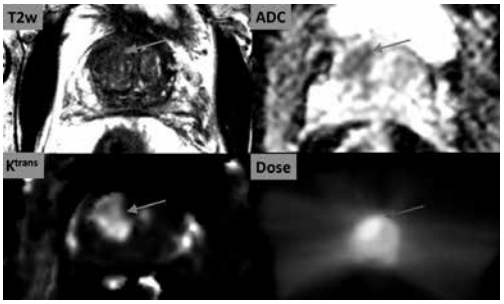
While many imaging biomarker studies have been conducted to establish their prognostic value after radiotherapy, the vast majority of studies is small and the methodology between studies varies widely. We earlier designed a QA framework for quantitative MRI protocols and demonstrated that measurement of consistent T2 and apparent diffusion coefficient values is feasible in a multi-center setting on diagnostic MRI scanners as well as on the Unity MR-linac.

To facilitate systematic investigations of the prognostic and predictive value of (changes in) quantitative MRI biomarkers within the MR-linac consortium, we developed a study design that integrates technical and clinical validation of MRI biomarkers for response prediction in multi-center interventional clinical studies.

On the Unity MR-linac system patients receive an MRI as part of each treatment fraction. We measured diffusion and perfusion characteristics of the tissue on a daily basis using intra-voxel incoherent motion MRI, avoiding the need to administer contrast agent. In a cohort of 43 patients with prostate cancer, who received 20 fractions of radiotherapy on an MR-linac in three centers, we showed changes in diffusion and perfusion parameters during treatment.

MRI-guided radiotherapy

The department of Radiation Oncology has now treated close to 400 patients on the Unity MR-linac. The pre-RADAR study, aimed at finding the safe boost dose for tumors in the irradiation of rectal cancer, started recently. The Umbrella-II trial allows us to investigate the feasibility of multiple techniques and software for MR-guided adaptive radiation therapy on the system. We recently received approval for a new umbrella protocol allowing test-retest measurements of quantitative MRI, for further development of new MRI techniques.



Example of patient included in the FLAME trial, with multiparametric MRI (T2w, ADC and K^{trans}) and dose distribution with focal boost. The red arrow indicates the location of the tumor, the blue arrow the location of the focal boost.

V

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Key publications

Bellmunt J, Hussain M, Gschwend JE, Albers P, Oudard S, Castellano D, Daneshmand S, Nishiyama H, Majchrowicz M, Degaonkar V, Shi Y, Mariathasan S, Grivas P, Drakaki A, O'Donnell PH, Rosenberg JE, Geynisman DM, Petrylak DP, Hoffman-Censits J, Bedke J, Kalebasty AR, Zakharia Y, van der Heijden MS, Sternberg CN, Davarpanah NN, Powles T, Group IMS. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(4):525-37

Palit SAL, van Dorp J, Vis D, Lieftink C, Linder S, Beijersbergen R, Bergman AM, Zwart W, van der Heijden MS. A kinome-centered CRISPR-Cas9 screen identifies activated BRAF to modulate enzalutamide resistance with potential therapeutic implications in BRAF-mutated prostate cancer. Sci Rep. 2021;11(1):13683

Van Dijk N, Gil-Jimenez A, Silina K, Van Montfoort ML, Einerhand S, Jonkman L, Voskuilen CS, Peters D, Sanders J, Lubeck Y, Broeks A, Hooijberg E, Vis DJ, Van den Broek M, Wessels LFA, Van Rhijn BWG, Van der Heijden MS. The tumor immune landscape and architecture of tertiary lymphoid structures in urothelial cancer. Frontiers Immunology 2021 (in press)

Personalized treatment of urological cancers

Individualized therapy in bladder cancer: biomarkers and the tumor-immune microenvironment

Bladder cancer is a common cancer, with a worldwide prevalence of 2.7 million patients. Although bladder cancer is often superficial at diagnosis, 30-40% of patients present with more advanced disease or progress to more aggressive disease. For patients with locally advanced or metastatic bladder cancer, platinum-based chemotherapy is the mainstay of treatment. Most patients will eventually die of their disease. In recent years, immunotherapy has shown to be active in bladder cancer. Impressive responses are seen, however only a minority of patients benefits from these treatments and it is unclear which patients respond. We aim to advance the development of a personalized approach to bladder cancer by exploring and targeting the tumor-immune microenvironment and finding biomarkers that can guide systemic therapy. Our key focus is on the neoadjuvant setting, as we believe the highest gains in cure rates can be achieved here. Through the large number of bladder cancer patients, excellent multidisciplinary collaboration and broad availability of clinical trials with novel therapeutics at the NKI-AVL, discoveries can rapidly be translated into clinical trials.

Neoadjuvant treatment with combination immunotherapy

In 2020, the first cohort of the NABUCCO study was published. In this study, we investigate the feasibility of pre-operative ipilimumab/nivolumab in locoregionally advanced bladder cancer. 24 patients were enrolled, of whom 23 (96%) had resection <12 weeks from 1st cycle, meeting the primary endpoint. Grade 3/4 irAEs occurred in 54% of pts; 42% when excluding clinically insignificant lab deviations. 11/24 patients (46%) achieved a pCR. 3 additional pts (12%) had a small focus of noninvasive cancer at resection. Pathological response were not associated with pre-existing T-cell immunity, suggesting that anti-CTLA4/PD1 combination therapy may be able to induce immune responses in "cold" tumors. A follow-up cohort of 30 patients, testing ipilimumab 3 mg/kg vs 1 mg/kg in combination with nivolumab showed a higher pathological complete response in ipi 3/nivo 1 (43%) compared to ipi 1/nivo 3 (7%). Translational work is ongoing. Further clinical studies in this setting include the addition of domatinostat (TURANDOT) and a study to test if induction with ipilimumab + nivolumab enables a bladder-sparing treatment (INDI-BLADE).

Genetic mechanisms of resistance to androgen receptor inhibitors

Novel androgen receptor (AR) inhibitors have clinical benefit in castration-resistant prostate cancer patients. Still, cancer cells eventually develop resistance to these therapies. We are investigating genetic resistance to these drugs through several means.

In a CRISPR-Cas9 genetic screen using prostate cancer cells, loss of BRAF conferred increased sensitivity to the AR antagonist enzalutamide. Additionally, MAPK inhibitors were synergistic with enzalutamide. Two *BRAF*-mutated CRPC patients were found to respond poorly to AR inhibition, suggesting that co-targeting AR and the MAPK pathway could be a viable strategy in *BRAF* mutated CRPC.

In another component of this project, clinical samples are being collected through the CPCT network and sequenced using WGS. In addition, plasma is collected to analyze development of genetic resistance throughout treatment.

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Key publications

Vande Wiel H, Stuiver MM, May AM, van Grinsven S, Aaronson NK, Oldenburg SA, van de Poel HG, Retel VP, van Harten WH & Groen W. Effects of- and lessons learned from an internet based physical activity support program on physical activity levels of breast and prostate cancer survivors: The PABLO randomized controlled trial. Cancers 2021;13 (15):3665

Kehrloesser S, Oberst S, […], Van Harten W. Analysing the attributes of Comprehensive Cancer Centres and Cancer Centres across Europe to identify key hallmarks. Molec. Oncol. 2021;15(5):1277-1288

Van Ommen-Nijhof A, Retèl VP, van den Heuvel M, Jager A, van Harten WH & Sonke GS. A revolving fund to study efficient use of expensive drugs: big wheels keep on turning. Annals Oncol. 2021;32(10):1212-1215

Early stage technology assessment, oncology services and cancer rehabilitation

Early Stage Technology Assessment

As healthcare costs are continuously increasing, sustainability of future oncology services is an important issue. Increasingly we expect Health Technology Assessment (HTA) to be involved in policy and coverage decisions, but also in earlier stages in the translational research process.
In 2015 an early HTA of TIL-adoptive cell technology in advanced melanoma started in a Coverage with Evidence Development program, as well as in 2017 for gastric HIPEC and high dose chemotherapy for stage III breast cancer (SUBITO trial), and in 2020, HIPEC for Ovarian cancer was started. The CED programs are coordinated by Valesca Retèl, and for all programs, early stage HTA publications are available. Joost Verbeek conducts a PhD project on the early stage HTA in the ongoing CED programs. Valesca Retèl works as Senior Scientist with the NKI and in the Health Technology and Services Research group at the University of Twente; in 2021 she started to build on her own group. She is principal investigator of the TANGO project in the Personalized Medicine program of ZonMw (HTA coordinator: Wim van Harten) on early HTA models regarding implementation of Whole Genome Sequencing. In TANGO the work package on ethics and legal aspects, produced a comment in Nature Reviews Genetics and a series of papers on cost effectiveness of WGS in lung carcinoma and melanoma treatment.
Danalyn Bing is active in the field of HTA in de- escalating treatment for early stage breast cancer and DCIS in the PRECISION consortium: because of access to large US databases we have established a cooperation with Duke's University, North Carolina. Nora Franzen is investigating alternatives for the present system of patents and pricing in expensive cancer drugs and exciting data from our cooperation with the Economics group of Theo Offerman from the University of Amsterdam provide evidence on certain forms of Transparency in negotiating drug prices. This work will be published in 2022. The European Fair Pricing Network, hosted by the NKI and launched in 2019, started with projects such as an in depth study in differences in access to innovative cancer drugs form an institutional viewpoint. Further, a large study on Socio Economic Consequences (SEC) of cancer and its treatment was initiated in 10 EU countries. This was also supported by a grant from the Organization of European Cancer Institutes (OECI). Results will be available in the course of the second quarter of 2022. For the EFPN, Julie Vancoppenolle is contributing as PhD student, and Simone Koole was succeeded by Nora Franzen as a post-doc.

Improving Oncology Services

Benchmarking is a powerful tool to inform management on improvement options and patients on the quality of services. In 2020 we concluded a sequel to the EU-subsidized project BENCH-CAN to validate a European benchmarking system on Comprehensive Cancer Care focusing on pathway benchmarking, including value-based health care principles (with Anke Wind as PostDoc). Involvement in the European Accreditation and Designation system from the OECI, leads to a series of papers on quality and characteristics of Cancer Centers.

Rehabilitation, Physical Activity and Cancer

Laura Kooij performed research into e-health interventions and survivorship care and chronic disease. She defended her thesis in Dec. 2021. Charlotte IJsbrandy worked at IQ-Healthcare in Nijmegen on the structured implementation of physical activity interventions for cancer survivors in ten Dutch hospitals and defended her PhD early 2021.
The PABLO RCT has been finished in 2021, which involves a web-based and blended intervention on physical activity in breast and prostate cancer survivors. PhD student Hester van de Wiel focuses on aspects that influence effectiveness from both physical as psychological perspective. Willeke Naaktgeboren performs a KWF-funded PhD project on cardiovascular status and late effects after physical exercise interventions during chemotherapy in the PACT-PACES-HEART study. Further a major KWF funded study for an RCT on prehabilitation in surgery for patients with muscle invasive bladder cancer (ENHANCE) started Sept 2021 with Emine Akdemir as PhD student and Maike Swegers as PostDoc. Martijn Stuiver took over as PI (from Wim Groen) and we work in close cooperation with Prof. Dr. Anne May from UMCU.

Cancer epidemiology

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The cancer epidemiology group is currently concentrating on two principal research lines: (1) the long-term health consequences of cancer treatment, particularly in terms of the risk of developing second malignancies or cardiovascular disease; and (2) the etiology of hormone related cancers, with a focus on breast and ovarian cancer. Special interest is in cancer etiology in BRCA1/2 families and late effects of ovarian stimulation for in Vitro Fertilization.

Late effects of cancer treatment

Now that curative treatment is available for a substantial group of cancer patients, it is increasingly important to evaluate how the occurrence of late complications of treatment affects their long-term survival. We aim to evaluate the risk of second malignant neoplasms (SMNs) and cardiovascular disease (CVD) after radiotherapy (RT), chemotherapy (CT) and immunotherapy for Hodgkin lymphoma (HL, n=8,500), non-Hodgkin lymphoma (n=3,200), testicular cancer (n=7,100) and breast cancer (n~23,000) over a period of up to 40 years after primary treatment.

In 2021, we developed and validated prediction models for absolute risk of treatment-related cardiovascular diseases, specifically risk of coronary heart disease (CHD) and heart failure (HF) for survivors of adolescent/adult Hodgkin lymphoma (HL). Published prediction models for cardiovascular disease risk in cancer survivors focused on risk in childhood cancer survivors. We now used a multicenter cohort including 1,433 5-year HL survivors treated between 1965-2000 and aged 18-50 years at HL diagnosis, with complete data on administered chemotherapy regimens, radiotherapy volumes and doses and cardiovascular follow-up. External validation for the CHD model was performed using a Canadian cohort of 708 HL survivors treated in 1988-2004 at ages of 18-50 years.

After a median follow-up time of 24 years, 341 survivors had developed CHD and 102 HF. We were able to predict CHD and HF risk at 20 and 30 years after treatment with moderate to good overall calibration and moderate discrimination (Area Under the Curve (AUC): 0.69-0.74), which was confirmed by external validation for the CHD model (AUCs: 0.73-0.74). Our model, which included prescribed mediastinal radiation dose, sex, age, smoking status at HL treatment and anthracycline treatment resulted in 30-year risks ranging from 4-53% for CHD and 2-27% for HF, depending on risk factors. We concluded that these models are useful to identify HL survivors who may benefit from targeted screening for CVD and early treatment for CVD risk factors.

Contralateral testicular cancer (CTC) is the most frequent subsequent cancer in testicular cancer survivors. Although some studies suggest that prior treatment with platinum-based chemotherapy affects CTC risk, a relationship between CTC risk and platinum dose has not been assessed previously. In a large, multicenter cohort including 4,755 patients treated for testicular cancer before the age of 50 years and between 1989 and 2007, we analyzed the association between the number of platinum-based chemotherapy cycles and CTC risk. CTC was diagnosed in 136 patients, resulting in a cumulative incidence of 3.4% after 20 years of follow up. The risk of developing a CTC decreased with age, was lower after non-seminomatous testicular cancer (Hazard ratio 0.58) and decreased with every additional cycle of platinum-containing chemotherapy (Hazard ratio per cycle 0.74).. Our study shows that approximately one in every 30 testicular cancer survivor will develop a CTC, with CTC incidence increasing up to 20 years after primary testicular cancer. Our study is the first to show that treatment with platinum-based chemotherapy shows a dose-dependent inverse association with CTC risk.

Etiology of hormone-related cancers

In our nationwide cohort study among families tested for a BRCA1/2 mutation (HEBON study; 48,757 relatives, including 42,539 women (6,293 BRCA1/2 mutation carriers) and 6,508 men (including 1,821 BRCA1/2 mutation carriers), we are studying whether 1) hormonal/life-style factors modify cancer risk in BRCA1/2 families, and 2) common genetic alterations are associated with the risk of breast cancer among BRCA1/2 carriers.

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Publications

Blok JM, Groot HJ, Huele EH, de Wit R, Horenblas S, Nuver J, Groenewegen G, [...], Vanneste BGL, Smilde TJ, Aarts MJB, Gietema JA, Meijer RP, Schaapveld M. Dose-dependent effect of platinum-based chemotherapy on the risk of Metachronous Contralateral Testicular Cancer. J Clin Oncol. 2021;39(4):319-327

De Vries S, Schaapveld M, Janus CPM, [...], Plattel WJ, van Spronsen DJ, van Imhoff GW, de Boer JP, Aleman BMP, van Leeuwen FE. Long-term cause-specific mortality in hodgkin lymphoma patients. J Natl Cancer Inst. 2021;113(6):760-769

Moskowitz CS, Ronckers CM, Chou JF, [...], Armstrong GT, Robison LL, van Leeuwen FE, Oeffinger KC. Development and validation of a breast cancer risk prediction model for childhood cancer survivors treated with chest radiation: A report from the Childhood Cancer Survivor Study and the Dutch Hodgkin late effects and LATER Cohorts. J Clin Oncol, 2021

Roberti S, van Leeuwen FE, Hauptmann M, Pfeiffer RM. Bias correction for estimates from linear excess relative risk models in small case-control studies. Stat Med, 2021

Schrijver LH, Antoniou AC, Olsson H, [...], van Leeuwen FE, Easton DF, Andrieu N, Rookus MA; Epidemiological Study of Familial Breast Cancer, Gene Etude Prospective Sein Ovaire Sein, Hereditary Breast and Ovarian Cancer Research Group Netherlands, and International BRCA1/2 Carrier Cohort Study. Oral contraceptive use and ovarian cancer risk for BRCA1/2 mutation carriers: an international cohort study. Am J Obstet Gynecol. 2021;225(1):51.e1-51.e17

Spaan M, van den Belt-Dusebout AW, Lambalk CB, van Boven HH, Schats R, Kortman M, Broekmans FJM, Laven JSE, van Santbrink EJP, Braat DDM, van der Westerlaken LAJ, Cohlen BJ, Cantineau AEP, Smeenk JMJ, van Rumste MM, Goddijn M, van Golde RJT, Meeuwissen PAM, Hamilton CJCM, Ouwens GM, Gerritsma MA, Schaapveld M, Burger CW, van Leeuwen FE. Long-term risk of ovarian cancer and borderline tumors after assisted reproductive technology. JNCI J Natl Cancer Inst, 2021

In 2021, we examined the effect of oral contraceptives (OCs) on the risk of ovarian cancer in BRCA1/2 carriers. In the general population, OCs strongly reduce ovarian cancer risk and therefore OC use has been suggested as chemoprevention in BRCA1/2 mutation carriers. However, previous studies in carriers were small and did not examine various characteristics of OCP use such as duration of use and timing of use. We conducted an international cohort study on ovarian cancer risk in 3,989 *BRCA1* and 2,445 *BRCA2* mutation carriers. Age-dependent weighted Cox regression analyses were stratified by study and birth cohort. Overall, 56% versus 86% of ovarian cancer cases versus unaffected carriers ever used OCs, with a median duration of use of 7 years. In *BRCA1* mutation carriers multivariable analyses including duration of use, age at first use and time since last use, only duration of use was associated with ovarian cancer risk, with significantly lower risks with longer durations of use (<5 years reference, 5-9 years hazard ratio (HR) =0.67, 10+ years HR=0.37; p_{trend}=0.008). The decreased risk after long durations of use persisted for at least 15 years since last OC use. Long-term OC use also reduced ovarian cancer risk in BRCA2 carriers, but there was no power for subgroup analyses.

The aim of the Nightingale Study, a cohort of 59,947 nurses, is to assess the association between shift work and risk of breast cancer. The first prospective analyses are ongoing using 626 incident cases of breast cancer identified through a recent linkage with the Netherlands Cancer Registry.

The aim of the nationwide OMEGA study is to assess risk of hormone-related cancers after fertility treatment in a nationwide cohort of 30,625 women who received ovarian stimulation for assisted reproductive technology (ART) in 1983-2000 and 9,988 subfertile women not treated with ART. In 2021, we investigated the long-term risk of endometrial cancer. After a median follow-up duration of 24 years, 137 endometrial cancers were diagnosed. Endometrial cancer risk after ART was not significantly increased compared with the general population (standardized incidence ratio =1.11) nor compared with the non-ART group (multivariably adjusted HR =1.11). Risk did not increase with longer follow-up or with more ART cycles. Risk of endometrial cancer within the cohort did not vary by cause of subfertility. Histologically proven endometriosis was associated with an increased risk of endometrial cancer (HR=1.69). Irrespective of ART exposure, risk significantly decreased with an increasing number of births (≥2 births HR=0.34) and longer duration of OC use (≥6 years HR=0.30). Obese women (BMI ≥30) were at significantly increased risk compared to women with a normal BMI (HR=4.04).
In conclusion, in the first three decades after ART, there does not appear to be an increased risk of endometrial cancer after ART.
Analyses are ongoing on the effect of IVF treatment on childhood cancer in a large cohort of 30,000 children conceived by intracytoplasmic sperm injection or IVF compared with 13,761 children that were naturally conceived.

Thirty-year cumulative incidence of coronary heart disease in 5-year male and female Hodgkin lymphoma survivors

		Men		Women	
		Non-smoker at HL diagnosis	Smoker at HL diagnosis	Non-smoker at HL diagnosis	Smoker at HL diagnosis
Age at HL 18-24 years	No medRT	9.3 (6.2-12.6)	12.1 (9.2-15.9)	4.2 (2.8-5.9)	5.6 (6.8-7.7)
	≤35 Gy	17.0 (12.7-21.9)	21.9 (17.3-26.5)	7.9 (5.9-10.1)	10.4 (7.9-13.2)
	>35 Gy	29.9 (23.0-36.8)	37.1 (30.4-44.0)	14.7 (11.2-18.6)	19.1 (14.9-23.6)
Age at HL 25-34 years	No medRT	13.9 (10.1-18.0)	17.7 (13.7-22.1)	6.5 (4.5-8.7)	8.5 (5.9-11.6)
	≤35 Gy	24.5 (19.9 (29.2)	30.2 (26.1-34.4)	12.0 (9.4-5.1)	15.5 (12.2-19.2)
	>35 Gy	40.2 (33.6-47.2)	47.4 (41.4-53.4)	21.6 (17.2-26.3)	27.0 (21.8-32.7)
Age at HL 35-50 years	No medRT	19.3 (14.3-24.6)	23.6 (18.0-30.0)	9.6 (6.7-13.2)	12.2 (8.6-16.9)
	≤35 Gy	32.0 (25.9-38.6)	37.4 (31.6-43.6)	17.2 (13.2-21.5)	21.3 (16.3-27.0)
	>35 Gy	48.1 (39.4-56.5)	53.1 (46.2-60.1)	29.1 (23.4-35.9)	34.7 (27.3-42.3)

30-year CHD CumInc
<10%
10-19%
20-29%
30%

HL=Hodgkin lymphoma, medRT=mediastinal RT

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Key publications

Aslam MA, Alemdehy MF, Kwesi-Maliepaard EM, Muhaimin FI, Caganova M, Pardieck IN, van den Brand T, van Welsem T, de Rink I, Song J-Y, de Wit E, Arens R, Jacobs H, van Leeuwen F. Histone methyltransferase DOT1L controls state-specific identity during B cell differentiation. EMBO Rep. 2021;22:e51184

Kwesi-Maliepaard EM, Jacobs H, van Leeuwen F. Signals for antigen-independent differentiation of memory CD8(+) T cells. Cell Mol Life Sci. 2021;78:6395-408

Van Breugel M, van Leeuwen F. Epi-Decoder: Decoding the local proteome of a genomic locus by massive parallel chromatin immunoprecipitation combined with DNA barcoding. Methods Mol Biol. 2021 (in press)

Chromatin Dynamics

Switching genes on or off and keeping them in that state involves packaging of the genome by wrapping it around histone proteins. Histones carry different chemical modifications that affect the packaging of DNA by so-called epigenetic mechanisms. The Van Leeuwen lab studies mechanisms and principles of epigenetic regulation using innovative proteomic, genetic, and (epi)genomics approaches. Our general strategy is to develop new tools and technologies, most recently two DNA-barcoding approaches to discover epigenetic regulators and to decode proteomes of specific genomic loci. These innovations enable us to explore new areas of chromatin biology and to dissect specific chromatin processes in high molecular detail. We take advantage of yeast as a powerful model system. In parallel, we are developing tools in mice and cultured human cells using CRISPR-Cas9 to translate our findings to mammals. We use mouse and human cell models to unravel the role of chromatin-based mechanisms in T- and B-cell development and cancer.

Function and regulation of histone methylation

We previously discovered the histone methyltransferase Dot1, which methylates lysine 79 of histone H3 (H3K79). This modification influences gene regulation and oncogenic transformation in mammals. Using yeast screens, we discovered a conserved regulatory mechanism of Dot1 in yeast and DOT1L in mouse T cells with relevance for lymphomagenesis. Recently, we uncovered a role for DOT1L as an epigenetic barrier in T- and B-cell differentiation (figure 1). These findings are relevant for the use of DOT1L inhibitors in the treatment of leukemia and lymphoma and for potential strategies for immunomodulation.

Decoding chromatin proteomes by DNA sequencing

Gene regulation involves interactions of specific genomic loci with many different proteins. How these interactions are orchestrated at any given location is largely unknown because systematically measuring protein-DNA interactions at a specific locus in the genome is challenging. To address this problem, we developed DNA barcode-based Epigenetics technologies in yeast. Epi-Decoder, a method orthogonal to proteomics, enables decoding of local chromatin proteomes, uncovering hundreds of chromatin-interacting proteins at actively transcribed barcoded loci (Fig. 2). Epi-ID, which is aimed at identifying regulators of known chromatin marks or chromatin-binding proteins, recently led to the discovery that H3K79 methylation in yeast and mice is regulated by a histone deacetylase.

Together, the aim of our studies is to provide a deep molecular understanding of the dynamics and inheritance of protein-based epigenetic information in dividing cells and the impact of chromatin-based information on gene regulation in normal development and disease.

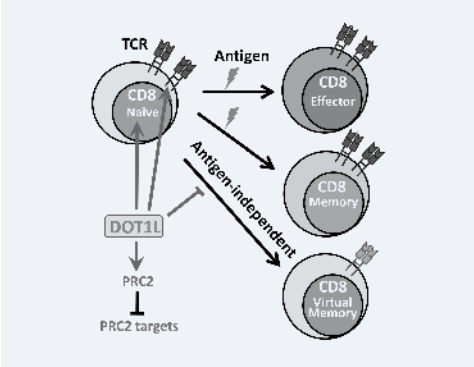

Figure 1. DOT1L affects CD8$^+$ T cell differentiation by preventing antigen-independent differentiation of naïve cells towards virtual memory cells, by supporting T-cell receptor (TCR) levels and signaling, and by indirectly promoting repression of targets of the PRC2 repressor complex.

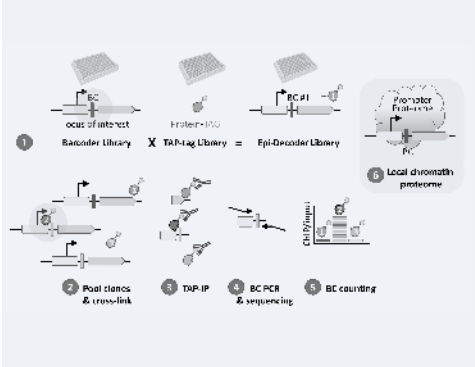

Figure 2. Epi-Decoder defines the local proteome around a barcoded (BC) locus of interest. It involves combining a yeast library with a barcoded locus (BC) and a library of tagged proteins. Using library pools, the amount of co-immunoprecipitation (TAP-IP) of each barcode reports on the abundance of each protein at the locus.

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Van den Berk P, Lancini C, Company C, Serresi M, Sanchez-Bailon MP, Hulsman D, Pritchard C, Song JY, Schmitt MJ, Tanger E, Popp O, Mertins P, Huijbers IJ, Jacobs H, van Lohuizen M, Gargiulo G, Citterio E. USP15 deubiquitinase safeguards hematopoiesis and genome integrity in hematopoietic stem cells and leukemia cells. Cell Rep. 2020;33(13):108533

Mbefo M, Berger A, Schouwey K, Gérard X, Kostic C, Beryozkin A, Sharon D, Dolfuss H, Munier F, Tran HV, van Lohuizen M, Beltran WA, Arsenijevic Y.Int J Mol Sci. Enhancer of Zeste Homolog 2 (EZH2) contributes to Rod Photoreceptor Death Process in several forms of retinal degeneration and its activity can serve as a biomarker for therapy efficacy. 2021;22(17):9331

Role of polycomb-group genes in transcriptional repression, stem cell fate and tumorigenesis

We study transcriptional repression by Polycomb-group (PcG) protein complexes, and the effects of deregulation of PcG genes on development, cell cycle control, cancer and stem cell maintenance. For this a range of conditional polycomb transgenic and knockout mouse models are used in combination with specific cancer-predisposing mutations mimicking closely cognate human cancers. Recent focus is on using CISPR screens and drug screens in selected polycomb-dependent tumor models to uncover new synthetic lethal interactions and vulnerabilities.

Context-dependent roles of PRC2 in tumorigenesis

We recently demonstrated an oncogenic role for *Ezh2* (histone methyltransferase and catalytic subunit of Polycomb repressive complex 2 (PRC2) in *Kras* driven non-small cell lung cancer. However, prolonged inactivation of PRC2 in aggressive *Kras;P53* mutant NSCLC uncovered a profound tumor suppressive function for PRC2 loss resulting in tumor cell identity change, driven by inflammatory responses and EMT. This resulted in new vulnerabilities that can be exploited using combined inhibition of PRC2 and inflammatory responses. Ezh2 is overexpressed in glioblastoma multiforme (GBM) suggesting a oncogenic role. In a mouse model for GBM we demonstrated using inducible Ezh2 shRNAs and specific Ezh2 inhibitors that short-term inhibition indeed slowed tumor growth and prolonged survival. However, prolonged Ezh2 inhibition caused a switch in cell fate, resulting in enhanced proliferation and invasion, enhanced DNA repair and activation of a stem cell network, resulting in therapy-resistant aggressive GBM. This illustrates that dosing of Ezh2 inhibition is critical, and Ezh2 inhibitors need to be used with caution. We are using these GBM models with CRISPR screens to find more effective combination therapies.

Modeling and investigating BAP1-deficient malignant mesothelioma

Besides PRC2, also a variety of PRC1 complexes contribute to dynamic polycomb repression. These PRC1 complexes differ in subunit constitution but all harbor a critical E3 ubiquitin ligase monoubiquitylates H2A at K119. This mark can be removed by the de-ubiquitylase BAP1. Interestingly, BAP1 is a prominent tumor suppressor that is frequently mutated in malignant mesothelioma (MM), uveal melanoma and clear cell renal cancers. Together with the Berns lab we have generated a conditional mouse model that closely mimics BAP1-deficient human MM. Interestingly, BAP1 deficient MM shows increased polycomb repression and recruitment and dependency on PRC2 and Ezh2. We are using this model and tumor cell lines to screen for the underlying cancer relevant polycomb targets and pathways. This model is also used to screen for new vulnerabilities and targeted combination therapies., which yielded new targetable metabolic and epigenetic dependencies.

Genome wide Chromatin profiling using a transposon-reporter system

In collaboration with the Wessels and van Steensel labs we have developed high-throughput chromatin profiling by using Thousands of PiggyBac transposon-based Reporters In Parallel (TRIP). The power of TRIP lies in combining different (inducible) transcriptional reporters in transposons with random barcoding and high throughput sequencing to study position effects and influences of local chromatin and epigenetic states on reporter expression. As an example, we recently used TRIP to test the genome-wide influence of epigenomic context on CRISPR-Cas9 activity.

V

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Key publications

Bornes L, Belthier G, van Rheenen J. Epithelial-to-Mesenchymal Transition in the Light of Plasticity and Hybrid E/M States. J Clin Med. 2021;10(11):2403

Kester L, Seinstra D, van Rossum AGJ, Vennin C, Hoogstraat M, van der Velden D, Opdam M, [...], van Oudenaarden A, Linn SC, van Rheenen J. Differential survival and therapy benefit of patients with breast cancer are characterized by distinct epithelial and immune cell micro-environments. Clin Cancer Res. 2021

Krotenberg Garcia A, Fumagalli A, Le HQ, Jackstadt R, Lannagan TRM, Sansom OJ, van Rheenen J, Suijkerbuijk SJE. Active elimination of intestinal cells drives oncogenic growth in organoids. Cell Rep. 2021;36(1):109307

Intravital microscopy of cancer plasticity

Our laboratory studies the identity, behavior, and fate of cells that drive tumor initiation, progression, metastasis and the development of therapy resistance. These populations of cells are difficult to study since they are rare, and their behavior (e.g. migration) and traits (e.g. stemness) change over time. To be able to study these dangerous cells, we have developed intravital microscopy techniques to visualize individual cells in real-time in living animals, often referred to as intravital microscopy. In order to trace specific cell types (e.g. stem cells, EMT cells, proliferative cells) within the primary tumor and at distant organs for several weeks, we combine genetic mouse models for breast and colorectal cancer with fluorescent mouse models in which identity, behavior or lineage is labeled by fluorescent colors.

Active elimination of intestinal cells drives oncogenic growth

Competitive cell interactions play a crucial role in quality control during development and homeostasis. We showed that cancer cells use such interactions to actively eliminate wild-type intestine cells in enteroid monolayers and organoids (Krotenberg et al, Cell Rep 2021). This apoptosis-dependent process boosts proliferation of intestinal cancer cells. The remaining wild-type population activates markers of primitive epithelia and transits to a fetal-like state. Prevention of this cell-state transition avoids elimination of wild-type cells and, importantly, limits the proliferation of cancer cells. Jun N-terminal kinase (JNK) signaling is activated in competing cells and is required for cell-state change and elimination of wild-type cells. Thus, cell competition drives growth of cancer cells by active out-competition of wild-type cells through forced cell death and cell-state change in a JNK-dependent manner.

Tumor initiation and progression revealed at the single cell level

Adult stem cells (SCs) are long-lived, able to self-renew and differentiate into specialized cells to drive tissue homeostasis and tissue repair, and in addition are considered crucial for the initiation of tumors. We study the behavior and fate of SCs, and in particular when they acquire oncogenic mutations, in intestinal and mammary tissues. We identified the mechanisms that drive the elimination of most of the oncogenic mutant cells. Although these mechanisms may be protective of tumorigenesis, we found that this also comes at a cost. It drives the spread of surviving oncogenic mutant cells over larger areas, thereby priming tissues for tumorigenesis. We think this is of particularly important for the progression of benign breast lesions (DCIS) towards malignant lesions (IDC).

Cellular mechanisms that drive therapy resistance

The cellular composition of tumors is highly heterogeneous, and can have a large influence on how tumors respond to therapy. We have related the cellular composition of tumors in breast cancer patients to their response to different therapies and showed that the cellular composition can be used to select the optimal treatment. In mouse models, we are currently dissectioning the cellular and molecular explanation for these observations, and hope to identify new biomarkers for personalized medicine.

The menstrual cycle determines chemo sensitivity in breast cancer

Through intravital microscopy, we showed that the estrous cycle drives cycles of proliferation in mammary ducts and tumors. Our studies indicate that distinct phases of proliferation are accompanied by different chemo sensitivities in mice and patients. For breast cancer patients from multiple subtypes we found striking differences in tumor responses and overall survival when the treatment started at luteal or follicular phase of the menstrual cycle. Collectively, our studies revealed that the menstrual rhythm determines chemo sensitivity, which suggests that optimal timing of treatment can be exploited to further improve the benefit of chemotherapy. This work resulted in two submitted stories.

Chromatin genomics

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Schep R, Brinkman EK, Leemans C, Vergara X, van der Weide RH, Morris B, van Schaik T, Manzo SG, Peric-Hupkes D, van den Berg J, Beijersbergen RL, Medema RH, van Steensel B. Impact of chromatin context on Cas9-induced DNA double-strand break repair pathway balance. Mol Cell 2021;81(10):2216-2230.e10

Wang Y, Zhang Y, Zhang R, van Schaik T, Zhang L, Sasaki T, Peric-Hupkes D, Chen Y, Gilbert DM, van Steensel B, Belmont AS, Ma J. SPIN reveals genome-wide landscape of nuclear compartmentalization. Genome Biol. 2021;22(1):36

Gene expression is controlled by promoters and enhancers, and by packaging of DNA into chromatin inside the nucleus. We develop and apply new genomics techniques to reveal the interplay of chromatin and regulatory elements, to study the architecture of chromosomes inside the nucleus, and to investigate how broken DNA is repaired in the context of chromatin.

Genomics tools to study regulatory elements

How enhancers 'choose' their target promoter(s) is still poorly understood. We have begun to dissect this logic by testing thousands of enhancer – promoter pairs in a multiplexed reporter assay. The data indicate that more than 50% of enhancers are selective for certain promoters. In addition, we are developing strategies to relocate regulatory elements to hundreds of alternative positions in a genomic locus; to probe the activities of many transcription factors in parallel; and to construct computational models to identify key sequences in regulatory elements. These approaches provide insights into fundamental principles of gene regulation.

Non-coding mutations in cancer

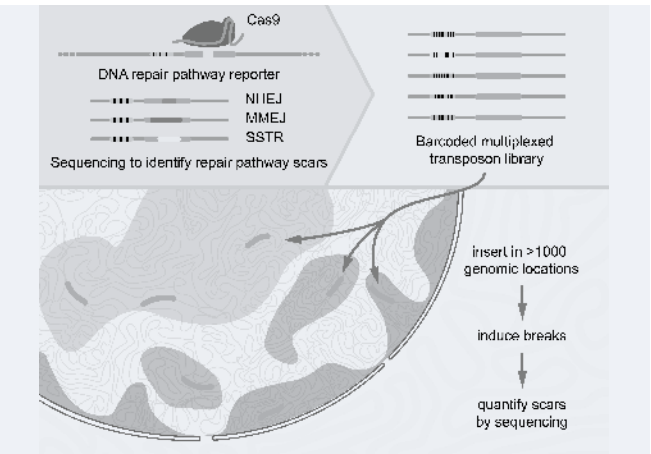
Together with six other laboratories in the Netherlands, we have started a large interdisciplinary project to systematically search for non-coding mutations in cancer genomes that alter the activity of critical genes. We will use powerful genomics, genetics, proteomics and computational approaches for this purpose.

Nuclear compartments and gene regulation

Transcriptionally inactive genes are often positioned at the nuclear lamina, as part of large lamina-associated domains (LADs). As member of the international 4DNucleome consortium we have generated systematic maps of lamina interactions, which were used to construct computational models of the compartmentalization of the genome inside the nucleus. We have also begun to map association of the genome with nucleoli, and discovered a role for the protein Ki-67 in the control of heterochromatin positioning in the nucleus. Together with the Rowland lab, we found that condensin II partially controls genome – lamina interactions. These results extend our understanding of the dynamic spatial architecture of chromosomes in relation to gene regulation.

Chromatin effects on DNA double strand break repair

DNA double-strand break (DSB) repair is mediated by multiple pathways. Using a newly developed multiplexed reporter assay in combination with Cas9 cutting, we systematically measured the relative activities of three DSB repair pathways as a function of chromatin context in >1,000 genomic locations. This revealed that repair pathway choice is modulated by the local chromatin context.



A multiplexed reporter assay to probe several DSB repair pathways. When a particular DNA sequence is cut with Cas9, it can be repaired by different repair pathways that each leave a distinct "scar" (mutation) in the DNA. We inserted this sequence, together with a DNA "barcode" into >1,000 genomic locations, and measured how the balance between the pathways was affected by the local chromatin context.

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Key publications

De Gooijer MC, Kemper EM, Buil LCM, Çitirikkaya CH, Buckle T, Beijnen JH, van Tellingen O. ATP-binding cassette transporters restrict drug delivery and efficacy against brain tumors even when blood-brain barrier integrity is lost. Cell Rep Med, 2021;2(1):100184

Li W, Sparidans RW, Martins MLF, El-Lari M, Lebre MC, van Tellingen O, Beijnen JH, Schinkel AH. ABCB1 and ABCG2 Restrict Brain and Testis Accumulation and, Alongside CYP3A, Limit Oral Availability of the Novel TRK Inhibitor Selitrectinib. Mol Cancer Ther. 2021;20(6):1173-1182

Van Winden LJ, Lanfermeijer M, Heijboer AC, van Tellingen O, Bergman AM, van der Poel HG, Jonker N, van Rossum HH. Retrospective analysis of serum testosterone levels by LC-MS/MS in chemically castrated prostate cancer patients: Biological variation and analytical performance specifications. Clin Chim Acta. 2021;521:70-75

Glioblastomas and the quest for better therapies

General introduction

Glioblastoma (GBM) is a uniformly fatal brain tumor. The location and invasive nature of GBM renders complete surgical resection impossible. Side effects prohibit the delivery of curative doses of radiotherapy (RT) and the blood-brain barrier (BBB) hinders the adequate delivery of drugs. Our mission is to develop more effective pharmacotherapies for this disease by conducting *in vitro* and *in vivo* studies using experimental brain tumor models.

Beating the Barrier to improve drug delivery

The ABC transporters ABCG2 and ABCB1 expressed at the BBB reduce the brain penetration of many drugs. Although this barrier is leakier in brain tumors, we have shown that ABC transporters are expressed and functional in brain tumor vasculature. They can restrict drug efficacy even when tumor vessels are leaky both in primary as well as in secondary (metastatic) brain tumors. Elacridar is a potent inhibitor of both ABCB1 and ABCG2 and is developed in the 1990s. The bioavailability of the conventional oral formulation was very low. We have improved this by selective deuteration and changing the formulation and achieved sustained plasma levels above 1–2 µM in rats and dogs. Next, we have shown that these levels are sufficient to inhibit ABCB1 at the BBB, however, increasing the brain distribution of Abcg2 substrate drugs is more difficult or for some drugs even impossible. Tariquidar is a structurally similar compound and a clinical grade parenteral drug formulation is available providing plasma levels of 2 µM. Consequently, tariquidar has been tested more often in human studies attempting to enhance the brain distribution of ABC-substrate drugs. However, only with moderate success. We have benchmarked tariquidar with elacridar and found that tariquidar is much less potent. This is most likely because tariquidar is such a poor ABCG2 inhibitor that it cannot prevent its own elimination from the brain by ABCG2. Thus, elacridar clearly outperforms tariquidar as a pharmaco-enhancer for brain penetration of ABC-transporter substrate drugs.

Multi-Targeted Combination Therapy (MTCT) for GBM

We found that targeting PI3K, MEK and CDK4/6 simultaneously has great potential for treating GBM. We are currently testing several PI3K, MEK and CDK4/6 inhibitors in vitro and in vivo to select candidates with good brain penetration and find the most effective combination. Notably, MTCT not only shuts down proliferation but also causes permanent growth inhibition by the induction of senescence and the secretion of a senescence-associated secretory phenotype (SASP). MTCT-senescent cells have increased mitochondrial reactive oxygen species (mtROS). However, despite the mutagenic nature of ROS, they do not acquire nuclear DNA damage. Excitingly, we find that MTCT-senescence is dependent on functional mitochondria and their ability to produce mtROS.

Tumor Treating Fields combination treatments

Tumor Treating Fields (TTFields); a novel treatment modality for GBM. We found a striking synergy when TTFields was combined with Wee1 or Chk1 inhibitors in vitro. By using live cell imaging, we found that TTFields extends the time in S and G2, indicating replication stress. This was further substantiated by experimental evidence on other replication stress markers. In vivo intervention studies with TTFields and a Wee1 inhibitor are ongoing.

Mitotic enrichment as an efficient radiosensitization strategy

We have built this strategy on the knowledge that cells are more vulnerable to radiation in mitosis than in other phases of the cell cycle. We discovered that ABT-751 is a potentially ideal candidate drug. It is an orally bioavailable and brain penetrable tubulin disrupting agent that can readily be implemented in the standard-of-care chemo-radiation treatment of GBM. Together with impact-investors we are in the process of setting up academic-pharma sponsored clinical study. In parallel, we are expanding our pipeline to other primary and secondary brain tumors

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Key publications

Van de Haar J, Hoes L, Roepman P, Lolkema M, Verheul H, Gelderblom H, de Langen A, Smit E, Cuppen E, Wessels L, Voest E. Limited evolution of the actionable metastatic cancer genome under therapeutic pressure. Nat. Med. 2021;27(9):1553-1563

Van der Wijngaart H, Hoes L, van Berge Henegouwen J, van der Velden D, Zeverijn L, Roepman P, Van Werkhoven E, de Leng W, Jansen A, Mehra N, Robbrecht D, Labots M, de Groot D, Hoeben A, Hamberg P, Gelderblom H, Voest E, Verheul H. The importance of bi-allelic inactivation of BRCA1/2 in patient selection for olaparib - a Drug Rediscovery Protocol (DRUP) cohort. Clin Cancer Res 2021

Veninga V, Voest E. Tumor organoids: Opportunities and challenges to guide precision medicine. Cancer Cell, 2021;39(9):1190-1201

Understanding vulnerabilities in tumors by employing co-culture models and genomics

Emile Voest is professor of Medical Oncology, group leader at the NKI, senior scientist of the Oncode Institute, medical oncologist, and translational scientist. He is the current director of Cancer Core Europe. His laboratory group is devoted to bringing precision medicine to patients and is focused on mechanistic studies of tumor biology and applying computational science and genomics to better understand how tumors respond to a certain treatment. The results from these studies are subsequently tested for their value in patients.

Genomics, immunotherapy and organoid co-culture models

Genomic guided personalized medicine

In 2021, we completed an important project. One of the outstanding questions in large scale genomic testing was how often a patient should be tested, given the genomic instability of cancer and impact of intermittent treatment. In the largest series of paired biopsies with whole genome sequencing (WGS) and clinical follow up reported we showed that the conservation of actionable targets (experimental and standard of care) is high, ranging from 92 (experimental) to 99% (standard of care). This has clinical consequences because it means that with a single biopsy for WGS all treatment opportunities become visible which helps in preparing the best treatment plan. The NKI has now started implementing WGS in daily clinical practice and the results of 1200 patients will be published in 2022. The Drug Rediscovery Protocol, in short, the DRUP study is now a brand name for defined off label use of approved drugs. In this multi-pharma (13 companies to date), multi-drug (37 drugs to date), multi-center (37 centers) study we now have created a platform through which patients can get access to approved medication based on a genomic profile coupled to a tumor type. At the closure of 2021, we have received and reviewed >2000 patient submissions of which almost 1000 patients have received treatment with targeted agents. We have now completed several molecularly defined cohorts of patients treated with a particular drug. The clinical benefit rate remains at 30% in this population of patients who exhausted all other treatment options. DRUP studies are now initiated all over Europe and in Canada and data sharing is mandatory.

To further expand real life data collection, we initiated the DRUG Access Protocol (DAP) which focuses on creating access for patients with on label drugs. Drugs with conditional approval, named patient programs, compassionate use programs all are part of the comprehensive protocol. In 2021, more than 70 patients have been included.

Immunotherapy and tumor-organoid co-cultures

By using our large-scale genomics efforts, we have identified several interesting leads to better understand and potentially use the immune system to combat cancer. This has resulted in broadening our co-culture models to other immune cells than T cells. We have now incorporated several other immune cells, including gammadelta T cells, NK cells and monocytes/macrophages and hope to dissect very specific interactions between cancer cells, immune components and the microbiome.

In summary, my group is strongly committed to develop a better understanding of individual tumors and their responsiveness to immunotherapy and targeted therapy. By a combination of biologists, computational scientists, chemist, and clinicians we are uniquely positioned to address these questions.

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Key publications

Almekinders MMM, [...], Wesseling J. Breast adipocyte size associates with ipsilateral invasive breast cancer risk after ductal carcinoma in situ. npj Breast Cancer. 2021;7(1):31

Van Seijen M, [...], Lips EH, Wesseling J. Variability in grading of ductal carcinoma in situ among an international group of pathologists. J Pathol Clin Res. 2021;7(3):233-42

Van Seijen M, Lips EH, Fu L, [...], Wesseling J, Schaapveld M. Long-term risk of subsequent ipsilateral lesions after surgery with or without radiotherapy for ductal carcinoma in situ of the breast. Br J Cancer. 2021

Conquer overtreatment of ductal carcinoma in situ

Our DCIS research is embedded in the Grand Challenge PRECISION Initiative for which Wesseling is the Lead Principal Investigator. Below some of the 2021 highlights of his group are listed.

Positive margings and lesion relate to subsequent IBC risk after DCIS

To identify the risk factors of DCIS for subsequent invasive breast cancer (IBC), 4 large PRECISION cohorts were pooled from the UK, US and the Netherlands comprising 48,575 women with primary DCIS (median follow-up time of 7.6 years). Margin status and lesion size were independent predictors of subsequent invasive breast cancer risk. This well annotated dataset enables us to identify clinico-pathological risk factors for subsequent events after DCIS. The results of this study will be an important step towards a DCIS risk prediction model.

One out of five subsequent IBC is not related to the initial DCIS

We challenged the dogma that DCIS is the precursor of subsequent IBC, as we identified both clonally related recurrences as well as a smaller but substantial proportion (20%) of invasive recurrences in patients with a prior DCIS diagnosis that are likely new primaries. So, DCIS could also be a risk lesion for IBC later on in life.

Expression signatures from progressive DCIS are different from the non-progressive ones

To distinguish harmless from potentially progressive DCIS, we explored differences in copy number variations, mutations, and RNA expression signatures between harmless and progressive DCIS, we are completing comprehensive genomic profiling. First, we completed the transcriptomic sequencing of 693 primary DCIS samples and are exploring the development of novel gene expression classifiers to distinguish indolent from aggressive DCIS. Building a predictor for the DCIS hazard we achieved a significant predictive power within the NKI cohort, which we could validate in the UK cohort for early recurrences (within 5 years). The predictor was enriched for cell cycle hallmarks. We plan to integrate expression and copy number data available from our case-control cohort (n=465).

Fat cell size and DCIS COX-2 levels relate strongly to subsequent IBC risk

In evaluating whether the adipocytes are relevant to the risk of progression to IBC, we found that large breast adipocyte size combined with high COX-2 expression in DCIS is associated with a higher risk of subsequent iIBC, while smaller adipocytes and low COX-2 expression related to a risk comparable to IBC risk in the general population (3). In comprehensive microenvironment multiplexed profiling in a large well-annotated case-control series, the immune cell density was strongly associated with DCIS-intrinsic properties, but not with risk of progression to IBC.

Aritificial Intelligence distinguishes high from low risk DCIS

Using AI on primary DCIS H&E tissue slides, we have built a deep-learning based classifier with an AUC of 0.93. This is highly promising, as no current biomarker shows such a good performance. Currently, we are validating these results.

Women with screen-detected low-risk DCIS are willing to test safety of active surveillance

For low-risk DCIS, we run the LORD-trial in which women with screen-detected DCIS can opt for annual mammography. This trials captures approximately 40% of women in the Netherlands with such a DCIS lesion. About about 2 out of 3 opt for active surveillance, indicating many of these women and their doctors feel safe to de-escalate treatment for low-risk DCIS.

Computational cancer biology

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Key publications

Mourragui SMC, et al. Predicting patient response with models trained on cell lines and patient-derived xenografts by nonlinear transfer learning. Proc Natl Acad Sci U S A. 2021;118(49):e2106682118

Van Dijk et al. Preoperative ipilimumab plus nivolumab in locoregionally advanced urothelial cancer: the NABUCCO trial. Nat Med. 2020;26(12):1839-1844

Van de Haar J, et al. Limited evolution of the actionable metastatic cancer genome under therapeutic pressure. Nat Med. 2021

We aim to further our basic understanding of cancer with a specific emphasis on therapy response. To this end we focus on three themes. In **Theme 1: Identification of cancer genes and their interactions**, we develop data-driven, statistical approaches to identify cancer genes and model their molecular interactions. In **Theme 2: Understanding and predicting drug response we** employ data-driven and semi-mechanistic approaches to understand and predict drug response. **Theme 3: Immunology**, deals with computational challenges in understanding the immune systems and how we can better predict response to checkpoint blockade. Below we present some exemplary projects from these themes.

Limited evolution of the actionable metastatic cancer genome under therapeutic pressure

Genomic profiling is critical for the identification of treatment options for metastatic cancer, but it is unclear how frequently this procedure should be repeated. We analyzed whole-genome sequencing (WGS) data of 250 biopsy pairs, longitudinally collected over the treatment course of 231 adult patients with a variety of metastatic solid malignancies. Within the biopsy interval (median, 6.4 months), patients received one or multiple lines of standard-of-care (SOC) treatments. SOC biomarkers and biomarkers for clinical trial enrollment could be identified in 23% and 72% of biopsies, respectively. For SOC genomic biomarkers, we observed full concordance between the first and the second biopsy in 99% of pairs. Of the 219 identified biomarkers for clinical trial enrollment from the first biopsies, we recovered 94% in the follow-up biopsies, while the no additional biomarkers for clinical trial enrollment were identified in 91% of patients. More-frequent genomic evolution was observed when considering specific genes targeted by small-molecule inhibitors or hormonal therapies. This demonstrates that a single WGS analysis of a metastatic biopsy is generally sufficient to identify SOC genomic biomarkers and to identify investigational treatment opportunities.

Identifying selective multi-drug combinations using Comparative Network Reconstruction

Inhibition of aberrant signaling with targeting inhibitors is an important treatment strategy in cancer. Unfortunately, response is often short-lived. Multi-drug combinations have the potential to mitigate compensatory mechanisms, but must be selective and administered at low dose. To identify optimal combination treatments, we developed a combined experimental and computational pipeline. For the experimental component, we perform, for a given isogenic cell line pair, a limited set of drug perturbations and record pre- and post-treatment signaling states and longer-term viability. In the computational component we employ these to reconstruct cell line specific signaling networks and map signaling output to cell viability. We employ these models to prioritize selective low-dose, multi-drug combinations. As proof of principle, we applied this approach to a breast cell line and an isogenic clone with an activating PI3K mutation. We showed that combinations selective for the mutant line can not be identified, while multiple anti-selective multi-drug combinations (reducing the viability of the parental cells and not the PI3K mutant cells) were identified. Remarkably, we were able to experimentally validate 25 of the 30 anti-selective combinations. This pipeline will allow for the identification of biomarker-specific combination treatment regimens.

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Duinkerken C, De Weger V, Dreschler W, Van der Molen L, Pluim, Rosing, Nuijen B, Hauptmann M, Beijnen J, Balm A, De Boer JP, Burgers S, Marchetti S, Schellens J, Zuur C. Transtympanic sodium thiosulfate for prevention of cisplatin-induced ototoxicity: A randomized clinical trial. Otol Neurotol. 2021;42(5):678-685

Vos J, Elbers J, Krijgsman O, Traets J, Qiao X, Van der Leun A, Lubeck Y, Seignette I, Smit L, Willems S, Van den Brekel M, Dirven R, Karakullukcu M, Karssemakers L, Klop W, Lohuis P, Schreuder W, Smeele L, Van der Velden L, Tan I, Onderwater S, Jasperse B, Vogel W, Al-Mamgani A, Keijser A, Van der Noort V, Broeks A, Hooijberg E, Peeper D, Schumacher T, Blank C, De Boer JP, Haanen J, Zuur C. Neoadjuvant immunotherapy with nivolumab and ipilimumab induces major pathological responses in patients with head and neck squamous cell carcinoma. Nature Comm. 2021

Vos J*, Zuur C*, Smit L, De Boer JP, Al-Mamgani A, Van den Brekel M, Haanen J, Vogel W. [18F]FDG-PET accurately identifes pathological response early upon neoadjuvant immune checkpoint blockade in head and neck squamous cell carcinoma. EJNMMI, 2021

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Improving treatment responses in head and neck cancer

Novel treatments to improve clinical outcome in head and neck cancer

Head and neck cancer can be categorized by two distinct aetiologies: tobacco and/or alcohol use in combination with genetic predisposition, or infection and activity of viral oncogenes. Despite intensive treatment regimens of extensive and mutilating surgery w/wo adjuvant (chemo-) radiotherapy, the prognosis in our patients remains relatively poor. In addition, HPV-negative HNSCC patients are elderly and relatively co-morbid patients that may suffer premature non-cancer-related or treatment-related death.

To improve clinical outcome in HNSCC patients, we have performed the phase Ib/II "IMCISION" trial (EudraCT 2016_002366_31) employing neoadjuvant nivolumab (NIVO) w/wo ipilimumab (IPI) immunotherapy prior to standard of care surgery in patients with advanced head and neck cancer. In IMCISION, we found significant cancer reduction, defined as $<10\%$ remaining viable cancer cells at the primary tumor site, in 35% of our patients after only two immunotherapy courses (in 4 weeks) at time of surgery (in week 5). This promising observation raises the question whether immunotherapy by itself could lead to durable complete remissions of cancer in patients and whether extensive surgery in these cases is still necessary for (an improved) 2- and 5-year cancer-free survival. We are currently designing the IMCISION2 trial to test this hypothesis with the aim to observe durable complete responses at the primary tumor site after immunotherapy while adding time and withholding extensive surgery in these patients. If so, we believe that the intended IMCISION2 trial will be practise changing and will significantly impact clinical outcome of our patients in terms of overall survival and quality of life.

In 2020 we have also started another phase II trial employing 'Neo-adjuvant nivolumab or nivolumab with ipilimumab prior to surgery in advanced cutaneous squamous cell carcinoma patients; the MATISSE trial' EudraCT: 2020-001074-30.

In the N12MTG phase 1 trial we have administered an oto-protective drug (STS) in the middle ear of cancer patients, ultimately to prevent ciplatinum-related permanent hearing loss. Drug application was safe and to our great enthusiasm, clinically relevant protection against hearing loss was observed in several patients. Thereafter, we filed two patents, 1: for the drug formulation, application and indication, and 2: for a novel middle ear injection device and kit. We are currently organizing a national multi-center phase III trial aiming to prove a systematic efficacy of middle ear STS injections to prevent platinum-related irreversible hearing loss in cancer patients.

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Key publications

Joosten SEP, Wellenstein M, [...], Wesseling J, van Diest PJ, Horlings HM, Linn SC, Zwart W. IHC-based Ki67 as response biomarker to tamoxifen in breast cancer window trials enrolling premenopausal women. NPJ Breast Cancer. 2021;7(1):138

Prekovic S, Schuurman K, [...], de Visser KE, Faller W, Beijersbergen R, Altelaar M, de Wit E, Medema R, Zwart W. Glucocorticoid receptor triggers a reversible drug-tolerant dormancy state with acquired therapeutic vulnerabilities in lung cancer. Nat Commun. 2021;12(1):4360

Severson TM, Zhu Y, De Marzo AM, [...], Wessels L, Bergman AM, Haffner MC, Zwart W. Epigenetic and transcriptional analysis reveals a core transcriptional program conserved in clonal prostate cancer metastases. Mol Oncol. 2021;15(7):1942-55

Hormones in cancer

We study functional genomics of hormone receptor action in cancer. Steroid hormone receptors are evolutionary highly conserved transcription factors, and critical drivers in the development and progression of multiple cancer types. Where we stand today, hormonal therapies represent the first and most successful targeted therapies in the treatment of breast cancer and prostate cancer patients, yet resistance is commonly observed.
We mainly focus on prostate cancer and breast cancer, but also explore function of hormone receptors in endometrial cancer and lung cancer. Strong parallels and shared biological features exist between hormone-regulated cancers, presenting a unique opportunity for synergism of projects in the lab. Our ultimate goal is to better understand hormonal signaling and elucidate the mechanisms of therapy resistance, ultimately contributing to personalized treatment, identification of novel therapeutic options and limiting over-treatment.

Androgen Receptor enhancer plasticity in prostate cancer

AR binds the genome at thousands of regions in prostate cancer. In comparing different disease states, we found AR to be highly plastic and altered in tumor development (Mazrooei et al. 2019) and progression (Stelloo et al. 2015) with limited intra-patient heterogeneity between clonal metastases (Severson et al. 2021).

We currently focus on perturbation effects, to address the question: What impact does treatment have on enhancer plasticity, and what is the consequence thereof on tumor progression and therapy resistance? With Henk van der Poel and Andre Bergman, a single-arm open label phase 2 neoadjuvant trial was initiated, enrolling 55 high-risk prostate cancer patients (Dynamics of Androgen Receptor Genomics and Transcriptomics After Neoadjuvant Androgen Ablation (DARANA); NCT03297385) for 3 months of pre-operative AR-targeting Enzalutamide. We observed a genomic relocation of pioneer factor FOXA1 after treatment, regulating newly acquired active enhancers to drive genes critical for prostate cancer proliferation. While AR bound at these regions, no AR activity was observed at these sites, but activated instead by classical circadian regulator ARNTL. This study pioneers in positioning the circadian rhythm machinery as driver for endocrine therapy resistance, and ongoing experiments are aimed to confirm these observations in xenograft models (Linder et al., 2021 MedRxiv, in revision for Cancer Discovery).

Ki67 as response biomarker in premenopausal breast cancer patients

Ki67 is used to determine response to neoadjuvant hormonal therapy in breast cancer, but has not yet been tested for performance in pre-menopausal patients. Together with Sabine Linn and Hugo Horlings, we assessed IHC-based Ki67 in samples from pre- and postmenopausal women in a neo-adjuvant, endocrine therapy focused trial (NCT00738777), randomized between tamoxifen, anastrozole, or fulvestrant (Joosten et al., 2021). Upon tamoxifen, IHC-based Ki67 levels were decreased in both pre- and postmenopausal breast cancer patients, which was confirmed using mRNA-based cell proliferation markers. The magnitude of decrease of Ki67 IHC was smaller in pre- versus postmenopausal women. We found a direct relationship between post-treatment estradiol levels and the magnitude of the Ki67 decrease in tumors. These data suggest IHC-based Ki67 may be an appropriate biomarker for tamoxifen response in premenopausal breast cancer patients, but anti-proliferative effect size depends on estradiol levels.


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Division of Diagnostic Translational Oncology

INTRODUCTION

The division of Diagnostic Translational Oncology (DTO), headed by prof dr Gerrit Meijer, integrates the research efforts at all departments of the cluster of Diagnostic Oncology (DOD) headed by dr Marcel Stokkel. The overarching mission of DTO research is to develop the best diagnostics for the best possible treatment of cancer. The DTO Research Committee is an important instrument for stimulating cross talk between participating departments, and focuses on developing the concept of integrated diagnostics. Research efforts are directed towards addressing important unmet clinical needs ranging from early detection to precision oncology diagnostics. In order to achieve this goal, we put much effort into bringing together at the individual patient level data from multiple diagnostic modalities and integrate these with patient outcome data (i.e. the DTO Data Platform that acts as a crystallisation point for the Digital Oncology program). This platform will facilitate discovery and clinical validation of imaging and laboratory biomarkers as well as artificial intelligence applications.

DEPARTMENT OF CLINICAL CHEMISTRY AND LABORATORY CHEMISTRY

The department of Clinical Chemistry and Laboratory Medicine is responsible for the routine analysis of laboratory diagnostics for patient care. The department has the aim to bridge basal biomarker research and routine clinical application of meaningful biomarkers. Furthermore, the institutional biobank for blood- and fluid-based samples is hosted from this department.

Liquid Biopsies

Liquid biopsies are increasingly used in clinical care, with our department involved in biobank initiatives and numerous studies exploring this biomarker both technically and from an implementation perspective. The department is project leader for the COIN project (ctDNA on the road to implementation in the Netherlands), a multidisciplinary consortium in the Netherlands to come to evidence-based implementation of ctDNA. Research in 2021 was published on the benefit of NGS of ctDNA both in lung and colorectal cancer, implementation, detection and technical analysis of circulating tumor DNA.

Clinical and diagnostic validation of biomarkers

For monitoring of cancer, tumor biomarkers are often used. Unfortunately for many of these markers used in daily practice objective insights in what consecutive obtained results clinically mean, is lacking. A platform called Re-marker was developed to support clinical studies validating the diagnostic performance of

longitudinal tumour biomarkers. Investigations focus amongst others on early detection of immunotherapy non-responsiveness in melanoma and non-small cell lung cancer. In addition, research in 2021 further explored the impact of HE4 and cyfra21.1.

State-of-the-art steroid analysis for breast and prostate cancer

In (advanced) breast and prostate cancer, steroid hormones are important drivers of tumour growth. Most systematic treatments are therefore aimed at interfering with these signaling pathways. At the department of Clinical Chemistry and Laboratory Medicine new state-of-the-art, LC-MS/MS based assays for amongst others testosterone and estrogens have been developed for routine clinical diagnostics. These offer superior analytical performance and enable studying the relevance of these steroid concentrations as prognostic and predictive markers.

DEPARTMENT OF MEDICAL PHYSICS AND TECHNOLOGY

Our department actively participates in several hospital-wide research lines. We introduce new techniques, facilitate their implementation, and advise on regulatory issues. A mechanical workshop is part of our department, where we build, adapt, and design devices used in several clinical and pre-clinical research projects.

Our expertise and skills:

- MR physics: develop, implement, and evaluate new MRI sequences for biomarkers and image-guided therapy applications.
- Medical imaging: develop segmentation, registration, and visualization algorithms for image-guided therapy applications. PACS interface to facilitate large-scale imaging studies (in collaboration with the Radiomics group).
- Pharmacokinetic modeling and radiation dose calculations.
- Optical and physiological measurement techniques: development, implementation, and evaluation.
- We are member of the medical ethics committee to evaluate studies involving medical devices.

THE NETHERLANDS CANCER INSTITUTE FAMILY CANCER CLINIC

For many of the 1500 patients (families) visiting the Family Cancer Clinic the indication for referral is a possible genetic predisposition for breast and/or ovarian cancer. Other indications include suspected Lynch syndrome, colorectal polyposis syndromes, Li-Fraumeni syndrome and a possible genetic predisposition for stomach cancer, renal cancer, melanoma and pancreatic cancer.
Increasingly, results of DNA-analysis have implications for the treatment of cancer. This development results in more referrals and, sometimes, a different way of genetic counselling.

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Key publications

KEY PUBLICATIONS DEPARTMENT OF CLINICAL CHEMISTRY AND LABORATORY CHEMISTRY

Muller M, Hoogendoorn R, Moritz RJG, van der Noort V, Lanfermeijer M, Korse CM, van den Broek D, ten Hoeve JJ, Baas P, van Rossum HH, van den Heuvel MM. Validation of a clinical blood-based decision aid to guide immunotherapy treatment in patients with non-small cell lung cancer. Tumour Biol. 2021;43(1):115-27

Schouten RD, Vessies DCL, Bosch LJW, Barlo NP, van Lindert ASR, Cillessen SAGM, van den Broek D, van den Heuvel MM, Monkhorst K. Clinical utility of plasma-based comprehensive molecular profiling in advanced non-small cell lung cancer. JCO Precis Oncol. 2021;5:1112-21

Vessies DCL, Linders TC, Lanfermeijer M, Ramkisoensing KL, van der Noort V, Schouten RD, Meijer GA, van den Heuvel MM, Monkhorst K, van den Broek D. An automated correction algorithm (ALPACA) for ddPCR data using adaptive limit of blank and correction of false positive events improves specificity of mutation detection. Clin Chem. 2021;67(7):959-67

KEY PUBLICATIONS DEPARTMENT OF MEDICAL PHYSICS AND TECHNOLOGY

De Vries-Huizing DMV, Versleijen MWJ, Sinaasappel M, Walraven I, Geluk-Jonker MM, Tesselaar MET, Hendrikx JJMA, de Wit-van der Veen BJ, Stokkel MPM. Haematotoxicity during peptide receptor radionuclide therapy: Baseline parameters differences and effect on patient's therapy course. PLoS One. 2021;16(11):e0260073

Karsten RT, Ter Beek LC, Jasperse B, van Alphen MJA, Peeters JM, van der Molen L, Hilgers FJM, Stuiver MM, Smeele LE.Dysphagia. MRI assessment of swallow muscle activation with the swallow exercise aid and with conventional exercises in healthy volunteers: an explorative biomechanical study. 2021;36(1):41-53

Vollenbrock SE, Voncken FEM, Lambregts DMJ, Maas M, Donswijk ML, Vegt E, Ter Beek LC, van Dieren JM, van Sandick JW, Aleman BMP, Beets-Tan RGH, Bartels-Rutten A. Clinical response assessment on DW-MRI compared with FDG-PET/CT after neoadjuvant chemoradiotherapy in patients with oesophageal cancer. Eur J Nucl Med Mol Imaging. 2021;48(1):176-185

KEY PUBLICATIONS THE NETHERLANDS CANCER INSTITUTE FAMILY CANCER CLINIC

Coignard J, Lush M, Beesley J, Hogervorst FBL, HEBON Investigators; Schmidt MK, […] Easton DF, Andrieu N, Antoniou AC. A case-only study to identify genetic modifiers of breast cancer risk for BRCA1/BRCA2 mutation carriers. Nat Commun. 2021;12(1):1078

Terra L, Hooning MJ, Heemskerk-Gerritsen BAM, van Beurden M, Roeters van Lennep JE, van Doorn HC, de Hullu JA, Mom C, van Dorst EBL, Mourits MJE, Slangen BFM, Gaarenstroom KN, Zillikens MC, Leiner T, van der Kolk L, Collee M, Wevers M, Ausems MGEM, van Engelen K, Berger LP, van Asperen CJ, Gomez-Garcia EB, van de Beek I, Rookus MA, Hauptmann M, Bleiker EM, Schagen SB, Aaronson NK, Maas AHEM, van Leeuwen FE. Long-term morbidity and health after early menopause due to oophorectomy in women at increased risk of ovarian cancer: Protocol for a nationwide cross-sectional study with prospective follow-up (HARMOny Study). JMIR Res Protoc. 2021;10(1):e24414

The DNA-diagnostic laboratory of the Family Cancer Clinic

The implementation of Next Generation Sequencing (NGS) made it possible to offer a wide range of test panels for our diagnostic routine testing. For HBOC we test 8 high to moderate risk genes using germline and somatic DNA, isolated from blood cells and more importantly FFPE fixed tumor or normal tissue cells. For hereditary colon cancer, we test 5 MMR genes. In the last quarter of 2021, we have implemented a novel NGS test approach, which replaces and expand our current NGS panels for germline DNA. A similar approach is pursued for FFPE isolated DNA and with a focus on HBOC and colorectal cancer and familial polyps. A larger panel of 50 genes for hereditary cancers is on the way. In September we started with Tumor First, testing of DNA isolated from ovarian cancer and prostate cancer to test for mutations in treatment actionable genes, which are also involved in hereditary cancer such as BRCA1 and BRCA2. A different approach is the DISCOVER study which aims to test germline DNA first from the same set of genes in patients with metastatic prostate cancer. In both approaches, gynecologist and urologist resp. are ordering the test. Clinical Genetics are monitoring the logistics and the outcome. During the past year, we have discussed with several stake holders the possibility to implement Whole Genome Sequencing in a germline setting. For this purpose we make use of WGS data (both somatic and germline) generated by the Hartwig Medical Foundation. This is a kind of secondary use of their data in search for biomarkers and novel treatment options for metastatic tumors (a prolongation on the WIDE study and a collaboration between our Pathology department, clinical genetics and HMF.

Research projects

We contribute to national (HEBON) and international (BCAC, CIMBA) efforts to understand the etiology, risk and outcome of breast cancer. We are involved in international efforts to establish polygenic risk scores for breast cancer and we are looking for opportunities for implementation studies in the clinic, in collaboration with group Schmidt. In 2017 a unique prospective breast cancer study was granted by Pink Ribbon/KWF (in close cooperation with M.J. Hooning and A. Hollestelle, ErasmusMC, M.K. Schmidt, and M.A. Adank, AVL-NKI) to assess all aspects of breast cancer in women from families with a CHEK2 c.1100delC mutation. For this study, women are currently invited to participate. In addition, we participate in the Paradigm study to investigate whether mutation/HRD status is correlated with outcome in young triple negative breast cancer patients (M. Schmidt (Department of Molecular Pathology), E. Rosenberg).

TP53-mutation carriers from Li-Fraumeni syndrome families nation-wide are screened by total body MRI in the NKI. Data on the MRI-results and on the psychosocial impact of this screening tool (M. Ruijs, E. Bleiker, G. Sonke (Division of Medical Oncology) and C. Loo (Division of Radiology)) are continuously collected. In close cooperation between the PSOE (E. Bleiker) and the Family Cancer Clinic (F. Menko, L. v.d. Kolk) new methods for informing family members are developed and evaluated aimed at improving the communication of cancer risk and better use of preventive measures.

Furthermore, we participate in ongoing collaborations (inter) nationally to elucidate the clinical role of DNA variants found by the DNA diagnostic laboratory such as INVUSE (MMR VUS), the national consortium CRAFT that focuses on BRCA1/2, PALB2 and CHEK2 VUSses and in ENIGMA. In addition we participate in a NWO TTW project "Phenotypic assessment of intra- and extra-exonic variants of disease-related genes present in the human population" (E.H. Rosenberg, F. Bleeker, F. Menko, L. v.d. Kolk). Our department is also interested in the ethical, legal and social aspects of unsolicited genomic findings, particularly in the context of tumor (WGS) testing and clinical genetic testing and counseling (L. v.d. Kolk is a member of the core team of the ELSI Service desk and of the WGS board).

DEPARTMENT OF NUCLEAR MEDICINE

The research lines initiated by the department of nuclear medicine (NM) are organized around four main topics; 1. personalized radionuclide therapy, 2. early diagnosis and response prediction, 3. imaging of tumour microenvironment to guide (immuno)therapy and 4. radioguided surgery. Targeted treatments with ^{177}Lu-Dotatate (advanced neuroendocrine tumours) and ^{177}Lu-PSMA (advanced prostate cancer) have been developed and implemented at the AVL. This has enabled the department to advance as one of the key players for radionuclide therapy in the Netherlands. To optimize patient outcome of these therapies, our research focusses on personalized therapy and response prediction. Maximizing absorbed dose in lesions while minimizing the harmful effects of radiation to normal tissues remains a challenge, as is the lacking international consensus on optimal dose-levels and response assessment techniques. The development of physiologically and population-based pharmacokinetic models, in collaboration with the Pharmacy, allows to simulate peptide and dose distributions. These predictions can be used to identify crucial factors that influence tumour and normal tissue uptake, and are the basis for future clinical studies.

Nuclear imaging is imbedded in a broad spectrum of oncological workflows to localize tumour lesions, identify (early) response and predict treatment outcome. The introduction of PSMA-based imaging has had a major impact on the workflow for both primary and advanced prostate cancer. Based on previous research, this technique is now used to predict therapy outcome for intermediate and high-risk patients, localize residual tumor after surgery or evaluate the extent of disease recurrence. Due to the highly-tumor specific nature of these peptides they were used in several studies for real-time image guidance during prostatectomy or identification of tumor-positive lymph nodes during resection. Furthermore, it was shown that PSMA-based PET holds potential for quantifying salivary gland toxicity during radiation therapy. The fact that salivary tissue shows PSMA-mediated accumulation has led to the identification of unknown bilateral macroscopic salivary glands, which is indicated as a potential new organ at risk for radiation therapy.

The development of radiopharmaceuticals for radionuclide therapy or specific imaging of the tumor microenvironment is one of the major advances in the field. Collaborations with

Ykema BLM, Adan F, Crijns MB, Bleeker FE, Dekker E, Bekkenk MW, Snaebjornsson P, van Leerdam ME. Cutaneous squamous cell carcinoma is associated with Lynch syndrome: widening the spectrum of Lynch syndrome-associated tumours. Br J Dermatol. 2021;185(2):462-463

KEY PUBLICATIONS DEPARTMENT OF NUCLEAR MEDICINE

Meijer D, van Leeuwen PJ, Roberts MJ, Siriwardana AR, Morton A, Yaxley JW, Samaratunga H, Emmett L, van de Ven PM, van der Poel HG, Donswijk ML, Boellaard TN, Schoots IG, Oprea-Lager DE, Coughlin GD, Vis AN. External Validation and Addition of Prostate-specific Membrane Antigen Positron Emission Tomography to the Most Frequently Used Nomograms for the Prediction of Pelvic Lymph-node Metastases: an International Multicenter Study. Eur Urol. 2021;80(2):234-242

Olde Heuvel J, de Wit-van der Veen BJ, van der Poel HG, van Leeuwen PJ, Bekers EM, Grootendorst MR, Vyas KN, Slump CH, Stokkel MPM. Cerenkov Luminescence Imaging in prostate cancer: not the only light that shines. J Nucl Med. 2021:jnumed.120.260034

Van Andel L, Aalbersberg EA, Geluk-Jonker MM, Stokkel MPM, Beijnen JH, Hendrikx JJMA. The development and validation of a high performance liquid chromatography method to determine the radiochemical purity of [^{177}Lu] Lu-HA-DOTA-TATE in pharmaceutical preparations. J Chromatogr B Analyt Technol Biomed Life Sci. 2021;1171:122605

KEY PUBLICATIONS DEPARTMENT OF PATHOLOGY

Koemans WJ, van Dieren JM, van den Berg JG, Meijer GA, Snaebjornsson P, Chalabi M, Lecot F, Riedl R, Krijgsman O, Hofland I, Broeks A, Voncken FEM, Peppelenbosch MP, Sosef MN, van Sandick JW, & Kodach LL. High CD8(+) tumour-infiltrating lymphocyte density associates with unfavourable prognosis in oesophageal adenocarcinoma following poor response to neoadjuvant chemoradiotherapy. Histopathology. 2021;79:238-51

Rawson RV, Adhikari C, Bierman C, Lo SN, Shklovskaya E, Rozeman EA, Menzies AM, van Akkooi ACJ, Shannon KF, Gonzalez M, Guminski AD, Tetzlaff MT, Stretch JR, Eriksson H, van Thienen JV, Wouters MW, Haanen J, Klop WMC, Zuur CL, van Houdt WJ, Nieweg OE, Ch'ng S, Rizos H, Saw RPM, Spillane AJ, Wilmott JS, Blank CU, Long GV, van de Wiel BA, & Scolyer RA. Pathological response and tumour bed histopathological features correlate with survival following neoadjuvant immunotherapy in stage III melanoma. Ann Oncol. 2021;32:766-77

Schouten RD, Vessies DCL, Bosch LJW, Barlo NP, van Lindert ASR, Cillessen S, van den Broek D, van den Heuvel MM, & Monkhorst K. Clinical utility of plasma-based comprehensive molecular profiling in advanced non-small-cell lung cancer. JCO Precis Oncol. 2021;5

KEY PUBLICATIONS DEPARTMENT OF RADIOLOGY

De Koekkoek-Doll PK, Roberti S, van den Brekel MW, Maas M, Smit L, Beets-Tan R, Castelijns J. Value of assessing peripheral vascularisation with micro-flow imaging, resistive index and absent hilum sign as predictor for malignancy in lymph nodes in head and neck squamous cell carcinoma. Cancers (Basel). 2021;13(20):5071

Engbersen MP, Rijsemus CJV, Nederend J, Aalbers AGJ, de Hingh IHJT, Retel V, Lambregts DMJ, Van der Hoeven EJRJ, Boerma D, Wiezer MJ, De Vries M, Madsen EVE, Brandt-Kerkhof ARM, Van Koeverden S, De Reuver PR, Beets-Tan RGH, Kok NFM, Lahaye MJ. Dedicated MRI staging versus surgical staging of peritoneal metastases in colorectal cancer patients considered for CRS-HIPEC; the DISCO randomised multicenter trial. BMC Cancer. 2021;21(1):464

Trebeschi S, Bodalal Z, Boellaard TN, Tareco Bucho TM, Drago SG, Kurilova I, Calin-Vainak AM, Delli Pizzi A, Muller M, Hummelink K, Hartemink KJ, Nguyen-Kim TDL, Smit EF, Aerts HJWL, Beets-Tan RGH. Prognostic value of deep learning-mediated treatment monitoring in lung cancer patients receiving immunotherapy. Front Oncol. 2021;11:609054

the lung and melanoma groups of the AVL, AMC-Vu and UMCG have led to the publication of three first-in-human studies with novel PD-1 and PD-L1 tracers. These imaging biomarkers are intended as non-invasive tools to select patient or assess clinical response to guide immunotherapy. Though the predictive value of these imaging biomarkers needs to be verified in larger clinical studies, they can provide a crucial insight into the biochemical immune response at a lesion basis.

DEPARTMENT OF PATHOLOGY

Pathology is all about diagnosing the nature of disease processes, to guide clinical decision-making and optimize personalized and precision treatment of cancer patients. Our challenge is to generate as much relevant information from tissue, cell and DNA samples aimed at the best personalized treatment for patients today and in the future. Important questions to be answered relate to finding, validating, and implementing prognostic and predictive biomarkers, combined with solving tumor classification challenges. Substantial parts of pathology related research is conducted within independent NKI research groups like the Translational Gastrointestinal Oncology group (Gerrit Meijer, Remond Fijneman, and Beatriz Carvalho), prediction of outcome of DCIS and breast cancer (Jelle Wesseling) and computational pathology (Hugo Horlings). The description and progression of this research can be found in the first part of this annual report, including key references. The research progress of the Laboratory of Familiar Tumors is incorporated in the chapter of the Department of Clinical Genetics.

Translational Research for improved diagnostics

In precision oncology treatment, choices are guided by changes in tumor DNA, or in mRNA or protein expression. In 2021 at the department of pathology, in collaboration with several clinical departments, a number of precision diagnostics studies based on tumor mRNA, or (circulating) tumor DNA have been conducted. The department of pathology's Molecular Diagnostics team and the CFMPB, have conducted prospective nanoString profiling for stratifying patients over the respective arms of the DONIMI clinical trial. In this trial, we offer stage III melanoma patients personalized combinations of neoadjuvant immune therapy based on their interferon (IFN) -gamma RNA expression signature. The interim results were presented in an oral presentation at the ESMO 2021.

In close collaboration with the department of Clinical Chemistry (Daan van de Broek), and in the context of the Dutch national COIN (ctDNA on the way to implementation in the Netherlands) consortium, pathology researchers (Remond Fijneman, Kim Monkhorst, Linda Bosch and Gerrit Meijer) perform translational studies using cell-free circulating tumor DNA as prognostic and predictive biomarkers for colorectal cancer and lung cancer. The use of tumor tissue-guided plasma circulating tumor DNA sequencing is now performed for stage II colon cancer patients within the framework of MEDOCC-CrEATE. In this ctDNA driven interventions study we offer patients with detectable ctDNA after surgery adjuvant chemotherapy to improve clinical benefit.

The number of biomarkers in precision oncology and the patient populations that may benefit, continue to increase rapidly. This causes a continuous demand for new assays being validated and implemented, putting a substantial strain on molecular diagnostics laboratories. An alternative approach is using the most comprehensive test, i.e. whole genome sequencing (WGS), instead. Adapting to any new DNA based biomarker in the WGS approach only requires adapting bioinformatics pipelines, while all of the wet lab technology is already in place. Against this background, the WIDE study has been conducted at our department, aiming to evaluate the feasibility, clinical validation, cost-effectiveness and added value of WGS in routine diagnostics in 1200 patients with (suspected) metastatic cancer. By the end of 2020, and within 20 months after the start of the project, all 1200 patients have been included. Preliminary analyses show that WGS can be successfully completed in routine diagnostics (feasibility 70% at sample level). In addition, WGS has proven to be a clinically valid test (clinical validation of 99.2%) in comparison to standard of care molecular diagnostics. Actionable biomarkers (for which a study is available in the Netherlands) were found in 71% of patients with successful WGS analysis. WGS also showed added value in differential diagnostics. In about 71% of the biopsies where a definitive diagnosis could not be made with regular diagnostics, WGS appeared to facilitate a conclusive diagnosis, thereby preventing possible under or over-treatment. Furthermore, it also appears that WGS provides strong indications for a definitive diagnosis in 68% of patients with cancer or unknown primary (CUP). WGS also allows the integration of germline diagnostics into cancer diagnostics. An estimated 10% of the patients in the WIDE study have a hereditary predisposition for which a clinical genetic treatment plan exists. These patients and their families can now be adequately advised and included in screening programs. The cost-effectiveness of the WGS workflow versus the regular diagnostics is currently being studied.

A further spin-off of WIDE has been the use of WGS for resolving the tumor of origin in patients with cancers of unknown primary (CUP), which has led to implementing a dedicated CUP clinic at NKI, with Petur Snaebjornsson involved as pathology lead.

Translational Research Core

In addition to the major lines of research, the department of Pathology is facilitating translational research at NKI through its contribution to the Translational Research Core (TRC). The TRC provides research services for basic, translational and clinical researchers to accelerate laboratory discoveries into patient care. The TRC offers state of the art expertise from pathologists, molecular biologists, biomedical scientists and bioinformaticians. The TRC also offers data services related to pathology. An important asset to this is the Core Facility Molecular Pathology (CFMPB, headed by Annegien Broeks) which is key to tissue biobanking as well as laboratory support for translational studies. CFMPB has developed automated staining protocols for multiplex fluorescent marker panels. Details about the CFMPB are reported elsewhere in this annual report, including key references. The clinical studies unit of the TRC supports the logistics of the pathology part of clinical studies, sample handling and shipping of tissues. In the context of the TRC and in close collaboration with CFMPB, multi spectral imaging, employing Vectra-Polaris hardware (Akoya) and HALO

image analysis software (Indica Labs), is further developed (coordinated by Erik Hooijberg). Ten HALO license seats are available for on-site and remote use. A second module for artificial intelligence has been added recently. In 2021, the outdated Vectra-3 has been replaced by the innovative high-throughput multiplex imaging device Vectra-POLARIS (Akoya). Multiple options for high dimensional protein marker discovery have been explored. Miltenyi's Macsima has been tested at the vendors laboratory site. The CODEX (Akoya) machine has been tested at NKI in a collaborative effort with end users and will be installed in 2022 allowing in depth analysis of tens of protein markers found in the tumor-microenvironment of human as well as animal, FFPE fixed, tissues.

Two dedicated research pathologists aid in reviewing and scoring human tissues after single, triple or multiplex (IF) staining employing Slidescore or HALO software for a large number of research projects. Most staff members are actively involved in multidisciplinary research activities in the field of thoracic oncology, urology, gastrointestinal oncology, melanoma, ovarian cancer, head and neck cancer and immunotherapy.

DEPARTMENT OF RADIOLOGY

Imaging Research at the Department of Radiology is multidisciplinary and brings together physicians, computer scientists, and engineers to work in synergy to develop imaging technologies to improve personalised treatment. It focuses on Imaging for Organ Preservation, Multi-parametric Imaging, Interventional oncology, developing and implementing AI techniques with focus on AI in Immunotherapy and Radiogenomics. The research team consists of 28 PhD students, 7 post-doc scientists and 41 academic staff radiologists. The group has a longstanding collaborative research line in MRI for organ preservation in rectal cancer with surgical, radiotherapy, and gastroenterology research teams worldwide. In 2021, we completed a nationwide study investigating the role of multi-parametric imaging for organ preservation in rectal cancer using clinical data from over 10 Dutch medical centres. The rectal research is expanded with an EU funded study aiming to develop AI models to predict outcomes using MRI, endoscopy, and biopsy data. Research in imaging for organ preservation extends to various other tumour types, including breast, urogenital and oesophagal cancer. Together with Erasmus MC, we investigated the value of a multimodal stratification tool in oesophagal cancer using endoscopy and MRI, which resulted in a thesis. Ongoing multi-modality imaging projects, together with the Department of Nuclear Medicine, investigate the value of combining whole-body MRI with PET with a thesis completed in 2021. Research in peritoneal metastases has shown that whole-body MRI can select colorectal and ovarian cancer patients for cytoreductive surgery. Two ongoing multicenter trials funded by the Dutch Organization of Science investigate whether MRI can reduce the number of futile surgeries by providing accurate information on the extent of disease. In colon cancer, multicenter research link CT parameters and AI models with the aim to establish imaging biomarkers that can select patients who will benefit from neoadjuvant chemotherapy. The research team is involved as a lead in national and international trials that are running for this purpose. Research in Head and Neck cancer assesses the value of parametric MRI for predicting and monitoring treatment outcomes, including developments of AI prediction models. Another HN project shows that real-time ultrasound fusion with ^{18}FDG-PET-CT for the guidance of fine-needle aspiration in nodal staging significantly increases the accuracy of detecting malignant nodes. In prostate cancer, our studies aim to develop MR- based risk models that can accurately stratify patients for individualised treatment, including active surveillance. MR measures of anatomical pelvic structures are being validated to predict urinary continence after radical prostate resection. Breast imaging research revolves around specific core themes, including the value of breast MRI for screening, the prediction of response to neoadjuvant systemic treatment, the development and validation of artificial intelligence solutions for various breast imaging modalities and the de-escalation of therapy aggressiveness through optimal use of imaging and minimally invasive procedures.

Interventional Oncology Research focuses on evaluating the efficacy and safety of new techniques. A thesis project investigated the effectiveness of intra-hepatic Mitomycin-C (combined with Y90 radioembolisation) in breast cancer liver metastases and kidney MWA. A registration trial for interventional treatment of complex, painful bone metastases non-responsive to conventional therapies is ongoing.

Artificial Intelligence in Immunotherapy and Radiogenomics AI research leverages AI methodologies to develop non-invasive AI-biomarkers and bring clinically-usable algorithms into the clinic. The research explores predictive AI signatures of response to immunotherapy in several cancer types. In the light of last year's AI in Immunotherapy doctoral thesis, a novel research line has started to take shape around a fully-automated AI approach (PAM) to monitoring serial/longitudinal images of immunotherapy patients. One of the critical projects for the coming year for this line will be the validation of PAM in a large-scale *pancancer* setting. The Radiogenomics research line has also begun to harness its extensive imaging database for clinical goals. An AI algorithm developed within this line has been shown to differentiate primary tumours from metastases. Within the context of the new AvL CUP/PTO clinic, the radiogenomics line is exploring the role of radiological AI as a valuable tool for diagnosis in this patient cohort. Alongside the research development of imaging AI tools, our team has begun developing a workflow for translation of these algorithms into an experimental clinical workflow. An important step towards this goal is studying the human-machine interaction (HMI), a running project that our department is collaborating with the HMI team at the Universiteit Twente.

Gabe Sonke

Head Division of Medical Oncology

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Division of Medical Oncology

The Division of Medical Oncology includes the Departments of Gastroenterology, Internal Medicine, Neurology, Pharmacology, Psychiatry, and Pulmonology. The Division has a maximum capacity of 60 in-patient beds, a day clinic hosting 54 beds for chemotherapy, a large outpatient clinic, and a GCP certified Clinical Research Unit (CRU) for the conduct of phase I-IV clinical trials with 16 beds. The Division treats about 13,000 patients per year, accommodates a staff of 59 medical specialists, and offers a training program for residents in gastroenterology, medical oncology, neurology, and pulmonology.

Research at the Division of Medical Oncology

The translational research in the Division follows the five main research themes of the NKI-AVL. The Division aims to combine high quality care with cutting edge research. These ambitions are matched by a strong focus on clinical and translational research and close collaborations between clinical and research staff within the institute. A selection of clinicians serves as group leaders of laboratory-based research and spend 25-50% of their time on laboratory research. The NKI funds part of their salary and research staff. In addition, the Division actively stimulates other clinicians to initiate clinical research.

Translational research in Medical Oncology requires laboratory space and expertise, which is provided by the research sections (NKI), such as Divisions of Experimental Therapy, Immunology, Molecular Biology, Molecular Carcinogenesis, and Molecular Genetics. There is also strong interaction with the Departments of Pathology and Molecular Pathology.

Around 65 PhD students currently employed, and all participate in the oncology graduate school of Amsterdam (OOA) accredited by the Royal Netherlands Academy of Sciences (KNAW). Approximately 130 clinical trials are actively recruiting patients. All new clinical trials are reviewed by an internal committee on clinical and translational research (CKTO). This committee is composed of research oriented medical specialists from the Division and selects potential studies based on alignment with the Institute's research themes, study methodology, translational research opportunities, competing studies, and financial and logistical arrangements. Despite the ongoing COVID-19 pandemic, inclusion in most clinical trials continued as planned.

BREAST AND OVARIAN CANCER

Background and objectives

The objective of this research program is to develop and improve systemic therapy for patients with early breast cancer and to improve treatment options in (oligo-) metastatic breast cancer. Our studies are in close collaboration with the Dutch Breast Cancer Research Group (BOOG), the EORTC Breast Cancer Group, the Breast International Group (BIG), the International TIL Working Group, and Cancer Core Europe. In 2021, we included 154 patients in 18 clinical studies. The team is also involved in optimizing the treatment of ovarian cancer.

(Neo)adjuvant systemic treatment

The neoadjuvant chemotherapy program is the core of a multidisciplinary research effort to optimize systemic treatment and response prediction. It currently comprises studies for ER+/HER2- tumors (NEOLBC, BELLINI), triple negative tumors (SUBITO, BELLINI) and HER2+ tumors (TRAIN-3). Building on the N4+ study results, the SUBITO study evaluates high-dose chemotherapy with stem cell transplant in women with high-risk HER2-negative breast cancer harboring homologous recombination deficiency. The BELLINI study started in 2019 and evaluates PD1-blockade and anti-CTLA4 in HER2-negative breast tumors with high levels of tumor-infiltrating lymphocytes (sTILs). In HER2-positive disease, we published three-year follow-up data of the TRAIN-2 study in JAMA Oncology, establishing anthracycline-free regimens in this setting. The TRAIN-3 study on image-guided de-escalation of pre-operative chemotherapy completed its accrual of 440 patients in 2021. The TRAIN-4 study will begin accrual in 2022 and evaluates safety and initial activity of chemotherapy-free treatment with trastuzumab, pertuzumab and tucatinib.

Metastatic breast cancer

The OLIGO study and TRIPLE-B-study investigate the treatment of patients whose tumors harbor DNA repair defects as interrogated with the BRCA-like test. The triple B-study evaluates the addition of anti-PDL1 (atezolizumab) to a backbone of paclitaxel or platinum-based chemotherapy as first line treatment for metastatic TNBC. The international NKI led phase Ib/II POSEIDON study investigated the optimal use of isoform selective PI3K inhibition with tamoxifen in ER+HER2- MBC and met its primary endpoint, which was presented at ESMO 2021. In addition, the nationwide SEQUEL-BREAST and SONIA studies investigate the optimal use of PI3K inhibition and CDK4/6 inhibition. SONIA has recently completed its accrual of 1050 patients. In 2019, we published in Nature Medicine the first data of the TONIC trial showing that induction with doxorubicin or cisplatin can result in a more favorable tumor microenvironment and more responses on nivolumab in metastatic TNBC. Together with the Erasmus MC we discovered that spatial CD8-immunephenotypes are associated with outcome after anti-PD1 (Nature Communications). Currently we are validating these results in the TONIC-2 trial. The GELATO study is a multicenter phase 2 trial evaluating anti-PDL1 with carboplatin as immune induction treatment for patients with advanced invasive lobular breast cancer (ILC). The clinical data of stage I of the GELATO trial have been presented at ESMO Breast Cancer 2021. In 2020, the phase II MIMOSA-study has started in which the novel generation checkpoint inhibitor monalizumab is tested in combination with trastuzumab in HER2-positive metastatic breast cancer.

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Key publications

KEY PUBLICATIONS BREAST AND OVARIAN CANCER

Dackus GM, Jóźwiak K, Sonke GS, van der Wall E, van Diest PJ, Siesling S, Hauptmann M, Linn SC. Adjuvant aromatase inhibitors or tamoxifen following chemotherapy for perimenopausal breast cancer patients. J Natl Cancer Inst 2021;113:1506-1514

Hammerl D, Martens J, Timmermans M, Smid M, Trapman-Jansen A, Foekens R, Isaeva O, Voorwerk L, Balcioglu H, Wijers R, Nederlof I, Horlings H, Salgado R, Kok M, Debets R. Spatial immunophenotypes predict response to anti-PD1 treatment and capture distinct paths of T-cell evasion in triple negative breast cancer. Nat Commun 2021;12:5668

Van der Voort A, van Ramshorst MS, van Werkhoven ED, Mandjes IA, Kemper I, Vulink AJ, Oving IM, Honkoop AH, Tick LW, van de Wouw AJ, Mandigers CM, van Warmerdam LJ, Wesseling J, Vrancken Peeters MT, Linn SC, Sonke GS. Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual ERBB2 blockade in patients with ERBB2-positive breast cancer: a secondary analysis of the TRAIN-2 randomized, phase 3 trial. JAMA Oncol 2021; 7: 978-984

KEY PUBLICATIONS CLINICAL IMMUNOTHERAPY

Menzies AM, Amaria RN, Rozeman EA, Huang AC, Tetzlaff MT, van de Wiel BA, Lo S, Tarhini AA, Burton EM, Pennington TE, Saw RP, Xu X, Karakousis GC, Ascierto PA, Spillane AJ, van Akkooi AC, Davies MA, Mitchell TC, Tawbi HA, Scolyer RA, Wargo JA, Blank CU, Long GV. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med 2021;27:301-309

Rozeman EA, Hoefsmit EP, Reijers IL, Saw RP, Versluis JM, Krijgsman O, Dimitriadis P, Sikorska K, van de Wiel BA, Eriksson H, Gonzalez M, Torres Acosta A, Grijpink-Ongering LG, Shannon K, Haanen JB, Stretch J, Ch'ng S, Nieweg OE, Mallo HA, Adriaansz S, Kerkhoven RM, Cornelissen S, Broeks A, Klop WM, Zuur CL, van Houdt WJ, Peeper DS, Spillane AJ, van Akkooi AC, Scolyer RA, Schumacher TN, Menzies AM, Long GV, Blank CU. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med 2021;27:256-263

Van der Veldt AA, Oosting SF, Dingemans AC, Fehrmann RS, Geurts van Kessel C, Jalving M, Rimmelzwaan GF, Kvistborg P, Blank CU, Smit EF, Lemmens VE, Hiltermann TJ, Koopmans MP, Huckriede AL, Rots NY, van Els CA, van Baarle D, Haanen JB, de Vries EG. COVID-19 vaccination: the VOICE for patients with cancer. Nat Med 2021;27:568-569

KEY PUBLICATIONS GASTROENTEROLOGY

Breekveldt EC, Lansdorp-Vogelaar I, Toes-Zoutendijk E, Spaander MC, van Vuuren AJ, van Kemenade FJ, Ramakers CR, Dekker E, Nagtegaal ID, Krul MF, Kok NF, Kuhlmann KF, Vink GR, van Leerdam ME, Elferink MA; Dutch National Colorectal Cancer Screening Working Group. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study. Lancet Gastroenterol Hepatol 2021 (in press)

De Steur WO, van Amelsfoort RM, Hartgrink HH, Putter H, Meershoek-Klein Kranenbarg E, van Grieken NC, van Sandick JW, Claassen YH, Braak JP, Jansen EP, Sikorska K, van Tinteren H, Walraven I, Lind P, Nordsmark M, van Berge Henegouwen MI, van Laarhoven HW, Cats A, Verheij M, van de Velde CJ; CRITICS investigators. Adjuvant chemotherapy is superior to chemoradiation after D2 surgery for gastric cancer in the per-protocol analysis of the randomized CRITICS trial. Ann Oncol 2021;32:360-367

Van de Haar J, Hoes LR, Roepman P, Lolkema MP, Verheul HM, Gelderblom H, de Langen AJ, Smit EF, Cuppen E, Wessels LF, Voest EE. Limited evolution of the actionable metastatic cancer genome under therapeutic pressure. Nat Med 2021;27:1553-1563

KEY PUBLICATIONS PHASE I & CLINICAL PHARMACOLOGY

Molenaar-Kuijsten L, Braal CL, Groenland SL, de Vries N, Rosing H, Beijnen JH, Koolen SL, Vulink AJ, van Dongen MG, Mathijssen RH, Huitema AD, Steeghs N; Dutch Pharmacology Oncology Group (DPOG). Effects of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib: a randomized cross-over trial in patients with breast cancer. Clin Pharmacol Ther 2021 (in press)

Van Brummelen EM, Huijberts S, van Herpen C, Desar I, Opdam F, van Geel R, Marchetti S, Steeghs N, Monkhorst K, Thijssen B, Rosing H, Huitema A, Beijnen J, Bernards R, Schellens J. Phase I study of Afatinib and Selumetinib in patients with KRAS-mutated colorectal, non-small cell lung, and pancreatic Cancer. Oncologist 2021;26:290-e545

Groenland SL, Verheijen RB, Joerger M, Mathijssen RH, Sparreboom A, Beijnen JH, Beumer JH, Huitema AD, Steeghs N. Precision dosing of targeted therapies is ready for prime time. Clin Cancer Res 2021 (in press)

KEY PUBLICATIONS SARCOMA AND ADOLESCENT AND YOUNG ADULT (AYA)

Drabbe C, Grünhagen DJ, van Houdt WJ, Braam PM, Soomers VL, van der Hage JA, de Haan JJ, Keymeulen KB, Husson O, van der Graaf WT. Diagnosed with a rare cancer: experiences of adult sarcoma survivors with the healthcare system-results from the SURVSARC study. Cancers (Basel) 2021;13:679

Husson O, Ligtenberg MJ, van de Poll-Franse LV, Prins JB, van den Bent MJ, van Eenbergen MC, Fles R, Manten-Horst E, Gietema JA, van der Graaf WT. Comprehensive assessment of incidence, risk factors and mechanisms of impaired medical and psychosocial health outcomes among adolescents and young adults with cancer: the prospective observational COMPRAYA cohort study. Cancers (Basel) 2021;13:2348

Younger E, Jones RL, den Hollander D, Soomers VL, Desar IM, Benson C, Young RJ, Oosten AW, de Haan JJ, Miah A, Zaidi S, Gelderblom H, Steeghs N, van der Graaf WT, Husson O. Priorities and preferences of advanced soft tissue sarcoma patients starting palliative chemotherapy: baseline results from the HOLISTIC study. ESMO Open 2021;6:100258

Ovarian cancer

Following our 2019 publication in the New England Journal of Medicine on hyperthermic intraperitoneal chemotherapy (HIPEC) during interval debulking surgery, we set up the OVHIPEC-2 study, which evaluates HIPEC added to primary surgery. This study is now open for accrual in the Netherlands, France, Italy and the United States. We also continue our investigator-initiated study on neo-adjuvant chemo-immunotherapy in stage IV ovarian cancer.

CLINICAL IMMUNOTHERAPY

Background and objectives

Our group is primarily involved in the treatment of melanoma and renal cell carcinoma patients. Research focuses on neo-adjuvant targeted and immunotherapies, dissection of immunological changes upon immune checkpoint inhibition plus targeted agents, combination with local therapy, and to a large extent on adoptive cellular therapies.

Clinical adoptive T cell transfer program

There is an unmet medical need for patients with stage IV melanoma who have failed anti-PD-1 treatment. Based on promising data from ours and other institutes, we initiated the first phase 3 TIL trial worldwide, which compares efficacy of TIL therapy versus ipilimumab as first or second line treatment in stage IV melanoma. Collaborating with Herlev Hospital in Denmark and Sanquin, 161 patients have been randomized so far. We received financial support from the Dutch Cancer Society to set-up a potency assay required for EMA registration, if the trial is positive. Together with BioNTech we have developed a strategy to induce and augment neoantigen-specific T cell populations from peripheral blood of metastatic melanoma patients for adoptive transfer. A proof-of-concept phase Ib trial has started and three patients have been successfully infused.

Neoadjuvant immune checkpoint inhibition in melanoma
Anti-PD-1 (nivolumab, pembrolizumab) with or without anti-CTLA4 (ipilimumab) has become standard therapy for metastatic melanoma. Nivolumab and pembrolizumab are also used as adjuvant therapy in stage III melanoma, improving recurrence-free survival of many patients. We have pioneered in developing neoadjuvant checkpoint inhibition studies, with the idea of inducing broader immune responses with checkpoint when the primary tumor is in situ. The four-year update of the initial OpACIN trial was published this year and confirmed long-term relapse free survival in patients achieving a pathologic response. The OpACIN-neo trial established high efficacy with a combination regimen that has reduced toxicity and therefore allows broad application. The subsequent PRADO extension cohort closed inclusion in 2019 and first data were presented at ASCO 2020 showing that response-driven extent of surgery and either giving or withholding adjuvant therapy is feasible and lead to improved quality of live. However, the relapse-free survival data are pending and are mature beginning 2022. Based on all these data, a phase 3 investigator initiated international registration trial (NADINA study), comparing neoadjuvant versus standard adjuvant checkpoint inhibition, has been initiated this year by our group.

Novel combinations, like HDACi + PD-1-blockade +/- CTLA-4 blockade (DONIMI) or oncolytic virus therapy (T-VEC) + PD-1 blockade (NIVEC), are currently tested as investigator-initiated trials with the aim to develop alternatives for patients not responding to neoadjuvant ipilimumab + nivolumab. In the DONIMI trial we prospectively tested the IFN-gamma signature algorithm, that was developed at our institute. Early data indicate, that this signature will help the physician to advice the patient to be treated by neoadjuvant anti-PD-1 monotherapy versus combinations. Such approaches will eventually lead to personalized neoadjuvant immunotherapy.

In addition, we are testing in a pilot, electronic patient reported outcomes (ePROs) coupled with urgency algorithms improve the early symptom detection, the communication with the healthcare providers, and allow early interventions. This will improve the quality of life of long-term survivors further and personalize in the future the extent of follow-up. Together with MD Anderson Houston and Melanoma Institute Australia (MIA), the NKI has set-up the International Neoadjuvant Melanoma Consortium (INMC). Together, we published this year a large pooled analysis on neoadjuvant targeted and immunotherapy, which aims to convince regulators to use early response markers as surrogate outcome for long-term relapse free survival. This would allow an earlier access to neoadjuvant therapies for patients.

Renal cell cancer

In kidney cancer, we have developed neoadjuvant studies for high risk clear cell RCC. The Neoavax trial completed its accrual of 40. In this study, avelumab + axitinib were given for 12 weeks prior to surgery. A second study, NESCIO, has just opened. In this randomized controlled phase Ib/II study, high risk clear cell RCC patients will receive either nivolumab, or nivolumab plus ipilimumab, or nivolumab plus relatlimab (anti-LAG-3) for six weeks prior to surgery. Extensive translational research is part of both studies.

KEY PUBLICATIONS THORACIC ONCOLOGY

Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, Mansfield AS, Popat S, Jahan T, Antonia S, Oulkhouir Y, Bautista Y, Cornelissen R, Greillier L, Grossi F, Kowalski D, Rodríguez-Cid J, Aanur P, Oukessou A, Baudelet C, Zalcman G. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021;397:375-386

De Gooijer CJ, van der Noort V, Stigt JA, Baas P, Biesma B, Cornelissen R, van Walree N, van Heemst RC, Soud MY, Groen HJ, den Brekel AJ, Buikhuisen WA, Bootsma GP, Dammeijer F, van Tinteren H, Lalezari F, Aerts JG, Burgers JA; NVALT19 study group. Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma (NVALT19): an investigator-initiated, randomised, open-label, phase 2 trial. Lancet Respir Med 2021;9:585-592

Smit J, Borm FJ, Niemeijer AN, Huisman MC, Hoekstra OS, Boellaard R, Oprea-Lager DE, Vugts DJ, van Dongen GA, de Wit-van der Veen BJ, Thunnissen E, Smit EF, de Langen AJ. PD-L1 PET/CT imaging with radiolabeled durvalumab in patients with advanced stage non-small cell lung cancer. J Nucl Med 2021 [Online ahead of print]

KEY PUBLICATIONS UROLOGIC ONCOLOGY

Badrising SK, Louhanepessy RD, van der Noort V, Kieffer J, Coenen JL, Hamberg P, Beeker A, Wagenaar N, Lam M, Celik F, Loosveld OJL, Oostdijk A, Zuetenhorst H, de Feijter JM, Dezentjé VO, Ras-van Spijk S, Vegt E, Haanen JB, van de Poll-Franse LV, Zwart W, Bergman AM. Integrated analysis of pain, health-related quality of life, and analgesic use in patients with metastatic castration-resistant prostate cancer treated with Radium-223. Prostate Cancer Prostatic Dis 2021 (in press)

Blok JM, van der Poel HG, Kerst JM, Bex A, Brouwer OR, Bosch JL, Horenblas S, Meijer RP. Clinical outcome of robot-assisted residual mass resection in metastatic nonseminomatous germ cell tumor. World J Urol 2021;39:1969-1976

Van der Heijden MS, Loriot Y, Durán I, Ravaud A, Retz M, Vogelzang NJ, Nelson B, Wang J, Shen X, Powles T. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma: a long-term overall survival and safety update from the phase 3 IMvigor211 clinical trial. Eur Urol 2021;80:7-11

GASTROENTEROLOGY

Background and objectives

The Department of Gastroenterology is involved in early detection and prevention of and innovative multimodality treatments for gastrointestinal cancers including neuro-endocrine tumors (NET) and hereditary GI-cancer syndromes.

Upper GI cancer

For esophageal cancer, MRI imaging and PET-CT studies are being performed. We started a neo-adjuvant pilot study with immunotherapy combined with chemotherapy for GI-junction and gastric cancer, results are expected in 2022. Furthermore, we are evaluating a watch-and-wait policy for esophageal cancer. In the randomized, phase III CRITICS study we showed that adjuvant chemotherapy was superior in terms of overall survival compared to chemoradiotherapy in the per protocol analyses. Several biomarker studies are in progress.

Lower GI cancer

We lead the evaluation of the Dutch population-based CRC screening program (www.rivm.nlwww.rivm.nl) in collaboration with the Erasmus MC in Rotterdam. We published data on yield of the first five years of this Dutch program. Furthermore, we are expert center for hereditary GI cancer syndromes and run several research projects in patients with hereditary CRC syndromes and second primary CRCs. The Department also has made significant impact on the level of translational research specifically focusing on interaction between the immune system and tumors. Using tumor organoids, we have established a unique protocol to study why some GI tumors respond differently to checkpoint inhibition than others. Other studies focus on DPD activity. Genotype-guided dosing resulted in adequate systemic drug exposure and improved safety. Prospective studies are ongoing. We are involved in translational and multicenter clinical studies with targeted and immunotherapy for CRC in all stages. All patients are included in the neo-adjuvant Immunotherapy study for CRC and are now analyzed. The preliminary data have been published in Nature Medicine, showing (near) complete responses in MMR deficient CRCs.

Neuro-endocrine tumors (NET)

In close collaboration with UMCU Utrecht, we are an ENET center of excellence and a Dutch NFU GEP-NET expertise center. Following the start of PRRT in March 2016, we have all techniques to diagnose and treat patients with a GEP-NET. Several research projects are going including exploring new blood biomarkers in patients with metastatic NET as well as GEP-NEC.

PHASE I & CLINICAL PHARMACOLOGY

Background and objectives

The Clinical Pharmacology Unit of the Division of Medical Oncology works closely together with the Department of Pharmacy & Pharmacology and the division of Pharmacology. Jointly, we perform 46 phase I/II, pharmacological and proof of concept studies. We are referral center for phase I studies in the Netherlands. We annually screen over 350 and recruit over 200 new patients in early phase industry sponsored and investigator initiated clinical trials.

Drug-drug interaction studies

We demonstrated proof-of-concept evidence that doses of CYP3A4 metabolized oral anticancer drugs can be decreased when combined with moderate CYP3A4 inhibitors to prevent side effects and to diminish costs. One study investigated boosting of the EGFR inhibitor erlotinib with the strong CYP3A4 inhibitor ritonavir. We demonstrated that we can half the costs of these expensive drugs by co-administration with ritonavir. The second study investigated the effects of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of Palbociclib.

Phenotyping in oncology

From PK analyses, it has been observed that the CYP3A4 is an important factor in the pharmacokinetics of many (anticancer) drugs, including taxanes. Recently, PK of intravenous docetaxel was shown to different in patients with castration resistant prostate cancer, as compared to patients with other types of solid tumors. We initiated a CYP3A phenotyping study with midazolam to further investigate phenotype differences between cancer types.

Personalized dosing of oral anti-cancer drugs

Oral targeted anti-cancer agents have a narrow therapeutic index, and a marked pharmacokinetic interpatient variability. The number of patients that are either over- or underdosed is alarming. We conduct a study in over 1000 Dutch patients and further implement personalized dosing also integrating pharmacogenomics (e.g. CYP3A4*22). A new investigator initiated Phase I/Ib study with the combination of RMC-4630 (SHP2 inhibitor) and LY-3214996 (ERK inhibitor) in metastatic KRAS mutant colon, pancreas and lung cancer – The SHERPA-trial – was approved this year.

Early clinical First in Human pilot studies

In the Basket of Basket trial within the Cancer Core Europe Consortium, we treat patients according to molecular targets. In the first module, we included patients with a signature in the tumor who benefit from the ant-PDL1 agent atezolizumab. A second module targeting FGFR rearrangements was opened. Patients are discussed weekly in an international tumor board. The CCE consortium was granted an EU subsidy (DART-WP12) to integrate online tools in patients participating in the Basket of Basket study assessing side effects and quality of life.

SARCOMA AND ADOLESCENT AND YOUNG ADULT (AYA)

Summary research

The personalized oncology group is currently concentrating on two principal research lines: (1) the short-, long-term and late consequences of cancer at adolescent and young adult age; (2) diagnosis, treatment, outcome and health-related quality of life issues of people with sarcoma.

Adolescents and Young Adults

We are currently running the SURVAYA study to examine the long-term consequences of cancer at AYA age among people who were diagnosed 5-20 years ago. Additionally, we are working on a unique nationwide infrastructure (COMPRAYA) for research into the prevalence, predictive and prognostic markers (risk factors) and underlying mechanisms of (age-specific) medical and psychosocial outcomes, and to facilitate the development and testing of (early) intervention strategies to improve these outcomes for patients (at risk). We will establish a prospective observational cohort of 1-year AYA cancer survivors followed prospectively for 20+ years or until death. Within COMPRAYA we will pay special attention to AYA cancer patients living with life-limiting cancer: how does this diagnosis impacts normal (daily) life and what are the challenges they face within the health care system?

Sarcoma

We designed the HOLISTIC study (Health-related quality Of Life In patients with advanced Soft TIssue sarcomas treated with Chemotherapy). The aims of this study are to evaluate HRQoL in patients with advanced STS treated with chemotherapy over time, explore the decision-making process and patient reflections post-treatment. The Quest study (Quality of life and Experiences of Sarcoma Trajectories) aims to quantify diagnostic delay (including patient, general practitioner and system delay) and evaluates routes to diagnosis and referral to sarcoma expert centers in the Netherlands and England. In addition, the study will comprehensively evaluate risk factors of diagnostic delay, determine the association between diagnostic delay and outcomes (HRQoL, quality adjusted life years, patient satisfaction, TNM classification, time to local/distant relapse and overall survival) and assess differences between both countries. We also started a study to develop standards of HRQoL measurement in the broad spectrum of patients with sarcoma. This project aims to incorporate the patient voice in sarcoma research and is a collaborative project between the EORTC Quality of Life Group (QLG) and the EORTC Soft Tissue and Bone Sarcoma Group (STBSG). Similarly, we are leading a project together with the patient advocacy group SPAEN aiming to identify and prioritize the unanswered questions about sarcoma from patient, caregiver and clinical perspectives.

THORACIC ONCOLOGY

Background and objectives

The Department of Thoracic Oncology stands for optimizing patient care, performing translation research, and introducing new therapies. Despite the detrimental impact of COVID-19, we have been able to continue to treat and include patients in studies with non-small cell lung cancer and mesothelioma.

Immune checkpoint inhibition

Recent trials have led to the implementation of IO treatment with or without chemotherapy as the standard treatment of advanced NSCLC. However, only a subset of patients benefits from checkpoint inhibition and better predictive biomarkers are needed. Therefore, in multiple clinical trials, we are evaluating positron emission tomography (PET) with PD-(L)1 directed tracers for their predictive power. Since IO has an established role in the first line treatment setting, we now focus on how to treat disease recurrence. In collaboration with the Thommen and Peeper groups we investigate potential mechanisms of IO resistance. Emphasis is on clinical studies after failure of first line IO with or without chemotherapy with T cell therapies and other novel IO agents or combinations. Also, neoadjuvant studies investigate the effect of IO in patients with locally advanced disease.

Malignant pleural mesothelioma (MPM)

Our Department has contributed significantly to the first line Checkmate 743 study of nivolumab-ipilimumab in first line setting, and we authored the primary publication in Lancet. The Pemmela study in recurrent MPM investigates the combination of lenvatinib with pembrolizumab and opened for accrual in March 2021. We succeeded to complete the inclusion of 36 patients within 9 months. Clinical follow up and analysis of all tumor and plasma samples is ongoing.

Neuro endocrine tumors (ENETS center of excellence)

We continue to focus on the diagnosis and treatment of patients with neuro endocrine tumors. The Phase 3 study with Lanreotide versus placebo has now been completed. Genetic analysis of the spectrum of neuroendocrine tumours using WGS and NGS is underway. Using molecular subtypes the ability to predict response to systemic treatment in metastatic carcinoids will be examined in a retrospective analysis. The development of organoids will be continued.

Targeted agents

AvL is the largest referral center in the Netherlands for patients with oncogenic driven non-small-cell lung cancer. Our molecular tumor board (MTB) is open for participating centers and as a consultant we participate in other MTB's. Over 15 dedicated phase I-III studies are open for specific oncogenic mutations and in several clinical trials we are top recruiter. Whole genome sequencing has been implemented as standard of care to identify genomic markers that sensitizes tumors for targeted treatment. The results of whole genome analysis during (targeted) treatment were published in Nature Medicine. Three PhD's are working on primary and secondary resistance to tyrosine kinase inhibitors. Preliminary results were presented at ESMO 2021 and WCLC 2021.

UROLOGIC ONCOLOGY

Background and objectives

The group focuses on the treatment of prostate, bladder, testicular, penile and rare urological cancers. We aim to contribute to international trials and to play a leading role in initiation of national trials and translational research.

Prostate cancer

in 2019, multiple investigator-initiated and industry-sponsored trials in metastatic castration resistant prostate cancer (mCRPC) were open for recruitment. Investigator initiated trials included the national OSTRICh study, which randomized patients between cabazitaxel and abiraterone or enzalutamide as second line treatment. Biomarker studies include serum levels of cytokines involved in neutrophil homeostasis and analysis of cfDNA. In the PRESTO study, biopsies of metastatic sites are taken prior to enzalutamide treatment. In the biopsies, chromatin accessibility and binding profiles of transcription factors to the chromatin are assessed, which may hold biomarker properties as a predictor of response to enzalutamide. The ROTOR registry aims to assess activity of radium-223 in contemporary patients and the course of pain in a non-study population treated with radium-223. Multiple biomarker studies are connected to this study.

Bladder cancer

In 2021, we completed the second cohort of the NABUCCO study, investigating the feasibility of pre-operative ipilimumab/nivolumab (ipi/nivo) in locoregionally advanced bladder cancer. In cohort 1, treatment was shown to be feasible, and 11/24 patients (46%) achieved a pCR. In cohort 2, high vs low-dose ipi was investigated. We observed a pCR in 6/14 (43%) evaluable pts treated with ipi 3 + nivo 1 (arm A). In contrast, a pCR was observed only in 1/14 (7%) evaluable pts treated with ipi 1 + nivo 3 (arm B). We are currently conducting a follow-up study investigating the addition of an HDAC-inhibitor (TURANDOT) and induction immunotherapy followed by bladder preservation (INDI-BLADE). Another investigator-initiated trial ICRA, is investigating paclitaxel in combination with anti-CTLA4 (tremelimumab) for urothelial cancer progressing to chemotherapy and checkpoint blockade.

Testicular cancer

The AvL multidisciplinary testicular cancer group (*Expert Centre for rare urological diseases*) has an ongoing focus on patient treatment, including salvage chemotherapy and robotic laparoscopic retroperitoneal surgery. Moreover, the group has a specific interest in long-term effects of platinum-containing therapy, including hearing loss, fatigue, cardio-vascular risks and second tumors.

Penile cancer

The PERICLES study investigated treatment with atezolizumab (anti-PDL1) in advanced penile cancer patients. Patients withg locoregional lymph node metastases also received radiotherapy. The study completed enrolment in 2021.

Theo Ruers

Division Head
Division Surgical Oncology

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Division of Surgical Oncology

IMAGE GUIDED SURGERY

This research line aims to optimize surgical procedures by better surgical guidance during operative procedures. To this end new imaging technologies are developed and tested to improve tumor mapping and staging pre and intra-operatively. These imaging and surgical guidance procedures should lead to more radical resections while sparing normal tissue and organ function. The research line is a strong collaboration between the NKI-AVL, Technical University Twente and industrial partners. For the moment 3 project lines are running. In the first project we are developing tools for optical guidance during surgery by means of spectroscopy. We showed that the accuracy to detect malignancies by optical tissue measurements for various cancers varied from 90-95%. We are currently testing this technology in the clinical workflow of breast cancer surgery. Furthermore, the technology is evaluated in a STW project in combination with ultrasound, while in a EU project optical tissue measurement are used for response monitoring within needle devices. In a second project line we aim to improve the balance between radical surgery and tissue sparing, by bringing innovative navigation technology to the OR. We introduced the first in world electromagnetic navigation system for abdominal, pelvic and liver surgery. Over 200 patients have been operated and surgeons decided to use navigation as standard technology for complex colorectal pelvic surgery. The project team was able to obtain funding from the KWF/Alp d'HuZes, KWF and the Vriendenloterij. In the beginning of 2021, the NKI started a spin-off company (Bcon-medical) to bring this technology to the market. A third project line concentrates on the introduction of hyperspectral imaging for cancer surgery. This project is funded by the European project Astonish and received a grants from the Dutch Cancer Society (KWF), TKI and recently also from STW/KWF. We aim that in the near future all tumor resection samples can be analysed almost real time within the OR which should prevent secondary surgeries because of inadequate tumor resections. In 2021 two KWF projects were granted, one on navigation technology another one on smart surgical devices for breast cancer treatment.

SURGICAL ONCOLOGY

In the Department of Surgical Oncology patient care and clinical research is organized in subunits who work in multidisciplinary teams: breast, melanoma/sarcoma, chest/upper GI and liver/lower gi/colorectal peritoneal metastases. In 2021 five of the nineteen staff surgeons had an academic affiliation as Professor at UVA, Twente University, Leiden University and Maastricht University. All staff surgeons are actively involved in surgical oncology research. In 2021 there were 25 full time researchers associated with the department, and 14 part time researchers

and students. These research efforts resulted in 218 peer reviewed English language full publications, 3 PhD theses, several research grants and regular media coverage.
The goal of the research of the Department is twofold: to improve the survival of patients with more advanced disease and to improve the quality of life of all patients by minimizing the side-effects and impact of surgical treatment. A first common theme is to explore better combinations of systemic therapy, radiotherapy and surgery, and to incorporate the recent advances in immunotherapy. These therapies are increasingly applied in a neoadjuvant setting and with a good assessment of the response it becomes possible to individually tailor the extent of surgery to the type of response, or even omit surgery altogether. Some very advanced unresectable tumours may become resectable after neoadjuvant therapy. A second common theme is the technical development and clinical use of intra-operative imaging and tissue differentiation techniques to allow a more precise identification of tumour tissue leading to a better complete removal of the tumour and sparing of non-involved tissues. A third theme is to gain more knowledge on treatment and outcome through the use of large national and international registries generating real life data. This provides not only new information, but also has the potential to improve the outcome through feedback of results to surgeons and health care systems. As a consequence surgeons of the department are very much involved in national and international initiatives and networks.

HEAD AND NECK ONCOLOGY AND SURGERY

In 2021 research lines were restructured around three themes: Image Guided Treatment (led by MJA van Alphen), Quality of Life (led by L van der Molen) and Immunotherapy (led by CL Zuur). Several grants were applied for, and one grant, on radiogenomics (Hanarth foundation) was obtained so far. A large European grant (Horizon Pathfinder), on developing a digital twin for counseling, scored 4.5/5, but was rejected. Clinical research remains an important part of our research efforts.

Highlights

Lotje Zuur has been appointed as Professor at the University of Leiden, LUMC. She will focus on immunotherapy and translational research. The IMCISION trial paper was accepted in Nature Communications. The neoadjuvant IT trial in advanced stage cutaneous SCC is running.
Image guided treatment: the 3D and image guided group was very active in digitizing facial prostheses, developing a personalized mandibular prosthesis (with Mobius Industries) and many other projects. An innovative project on planning, intraoperative surveillance and postoperative assessment using 3D imaging was started. A universal navigated cutting device is tested in patients.
Quality of Life: A redesigned Swallowing Exercise Aid, with patents from the NKI is being produced by Atos Medical. We participate in an international trial using this device and will start a study on swallowing and speech after laryngectomy, using this device and out new high resolution manometer.

In 2021, 52 peer reviewed articles were published and 6 PhD theses were defended.

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Key publications

Abu-Ghanem Y, van Thienen JV, Blank C, Aarts MJB, Jewett M, de Jong IJ, Lattouf JB, van Melick HHE, Wood L, Mulders P, Rottey S, Wagstaff J, Zondervan P, Powles T, Neven A, Collette L, Tombal B, Haanen J, Bex A. Cytoreductive nephrectomy and exposure to sunitinib - a post hoc analysis of the Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) trial. BJU Int. 2021

Bakker NAM, Rotman J, van Beurden M, Zijlmans HJM, van Ruiten M, Samuels S, Nuijen B, Beijnen J, De Visser K, Haanen J, Schumacher T, de Gruijl TD, Jordanova ES, Kenter GG, van den Berg JH, van Trommel NE. HPV-16 E6/E7 DNA tattoo vaccination using genetically optimized vaccines elicit clinical and immunological responses in patients with usual vulvar intraepithelial neoplasia (uVIN): a phase I/II clinical trial. J Immunother Cancer. 2021

Berger DMS, van den Berg NS, van der Noort V, van der Hiel B, Valdés Olmos RA, Buckle TA, KleinJan GH, Brouwer OR, Vermeeren L, Karakullukçu B, van den Brekel MWM, van de Wiel BA, Nieweg OE, Balm AJM, van Leeuwen FWB, Klop WMC. Technologic (r)evolution leads to detection of more sentinel nodes in patients with melanoma in the head and neck region. J Nucl Med. 2021;62:1357-62

Betz-Stablein B, D'Alessandro B, Koh U, Plasmeijer E, Janda M, Menzies SW, Hofmann-Wellenhof R, Green AC, Soyer HP. Reproducible Naevus Counts Using 3D Total Body Photography and Convolutional Neural Networks. Dermatology. 2021:1-8

Brouwer de Koning SG, Geldof F, van Veen RLP, van Alphen MJA, Karssemakers LHE, Nijkamp J, Schreuder WH, Ruers TJM, Karakullukcu MB. Electromagnetic surgical navigation in patients undergoing mandibular surgery. Sci Rep. 2021;11:465

Elshot YS, Zupan-Kajcovski B, Klop WMC, Bekkenk MW, Crijns MB, de Rie MA, Balm AJM. Handheld reflectance confocal microscopy: Personalized and accurate presurgical delineation of Lentigo maligna (melanoma) Head Neck. 2021;43(3): 895-902

Fokas E, Appelt A, Glynne-Jones R, Beets G, Perez R, Garcia-Aguilar J, Rullier E, Joshua Smith J, Marijnen C, Peters FP, van der Valk M, Beets-Tan R, Myint AS, Gerard JP, Bach SP, Ghadimi M, Hofheinz RD, Bujko K, Gani C, Haustermans K, Minsky BD, Ludmir E, West NP, Gambacorta MA, Valentini V, Buyse M, Renehan AG, Gilbert A, Sebag-Montefiore D, Rodel C. International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer. Nat Rev Clin Oncol. 2021

Houwink API, Šrámek M, Hulshoff L, Haanen JBAG. Perioperatieve zorg rondom oncologische patiënten met toxiciteit na immunotherapie. A&I, praktijkgerichte nascholing over peroperatieve geneeskunde. 2021

Kooijman MML, Hage JJ, Oldenburg HSA, Stouthard JM, Woerdeman LAE. Surgical complications of skin-sparing mastectomy and immediate implant-based breast reconstruction in women concurrently treated with adjuvant chemotherapy for breast cancer. Ann Plast Surg. 2021;86:146-50

Lange M, Hage JJ, Hartveld L, Zijlmans HJMAA, van Beurden M. Reconstruction of the meatus urethrae after oncologic vulvectomy: Outcome of 42 vaginal flap advancements in 41 women. Ann Plast Surg. 2021

Leemans M, Muller SH, van Alphen MJA, Vallenduuk W, Dirven R, van den Brekel MWM. Adjustable breathing resistance for laryngectomized patients: proof of principle in a novel heat and moisture exchanger cassette. Head Neck. 2021;43:1073-8

UROLOGY

Inauguration

Prof. dr. H.G. van der Poel, Beeldgeleide urologie, 1-10-2021 Amsterdam UMC

Promotions

Sarah Ottenhof, Immunology, Imaging and Treatment of Advanced Penile Carcinoma
Judith Bosschieter, Diagnosis and Treatment of Urothelial Carcinoma of the Bladder

Research report

In 2021 the urologists group differentiated the onco-urological care and research in focus groups in the field of renal, bladder, prostate, penile, and testis cancer. All members were both clinically as well as scientifically active, participating in mainly online meetings and several PhD programs at the department. Collaboration in several national and international consortia was performed.

Highlights 2021

Of 143 publications from the department the selected highlights in 2021 were:

Renal cancer: A post-hoc analysis was published on the randomized SURTIME trial on the role of cytoreductive nephrectomy. Starting with sunitinib rather than nephrectomy in metastasized disease lead to earlier and more profound disease controle.

Abu-Ghanem Y et al. Cytoreductive nephrectomy and exposure to sunitinib - a post hoc analysis of the Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) trial. BJU Int. 2021

Bladder cancer: In a retrospective comparison the WHO1973 grading system was found to outperform the WHO2004/2016 grading system for prediction of tumor progression in non-muscle invasive bladder cancer.

Van Rhijn BWG et al. Multi-center EAU Non-Muscle-Invasive Bladder Cancer Guidelines Panel Study Consortium on the WHO1973 WHO 2004 2016 Classification Systems for Grade. Prognostic Value of the WHO1973 and WHO2004/2016 Classification Systems for Grade in Primary Ta/T1 Non-muscle-invasive Bladder Cancer: A Multicenter European Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel Study. Eur Urol Oncol. 2021;4(2):182-191

Penile cancer: The risk of death was decreased with an increased number of myeloid cells in the intratumoral stroma.

Rafael TS et al. Distinct Patterns of Myeloid Cell Infiltration in Patients With hrHPV-Positive and hrHPV-Negative Penile Squamous Cell Carcinoma: The Importance of Assessing Myeloid Cell Densities Within the Spatial Context of the Tumor. Front Immunol. 2021;12:682030

GYNAECOLOGY

Ovarian carcinoma

In 2021 our project on early detection of ovarian carcinoma with biomarkers was initiated in 3 participating centers. A consensus process was completed of executing HIPEC during interval cytoreduction as part of the implementation study funded by KWF. The OVHIPEC 2 study, which evaluates the value of HIPEC during primary cytoreduction continues to accrue well and an additional international 11 sites were opened for accrual in 2021.

Endometrial cancer

We contributed to the submission of the EUGENIE trial, an international study on staging of endometrial cancer based on the new molecular classification, to Kom op tegen kanker in Belgium. We underscored the importance of this trial during a Highlight session at the ESGO conference (October 2021) and in a *Commentary* in the IJGC.

Cervical cancer

We started a multicenter international study (CONTESSA/ NEOCON-F) to explore the potential to use neo-adjuvant chemotherapy for young women with cervical cancer who aim to preserve their fertility. We continue to improve the current procedure to screening for cervical cancer and we are planning a trial to incorporate our molecular markers into the nationwide screening for cervical cancer.

Vulvar cancer

We continue to explore the value of paclitaxel-carboplatin in vulvar cancer. VULCANize I and CRAVAT studies currently explore this in a phase II setting in our unit. In 2021 we elaborated a KWF grant application for VULCANize II where we aim to use neoadjuvant chemotherapy for locally advanced vulvar cancer in a randomized setting.

Cancer and pregnancy

In May 2021 we launched the Advisory Board on Cancer, Infertility and Pregnancy (ABCIP). In *The Lancet Oncology* we changed the definition of pregnancy associated breast cancer and elaborated a review of immunotherapy during pregnancy.

Gestational Trophoblastic Disease

In 2021 the Amsterdam Trophoblastic Team received accreditation with the NFU. Dr van Trommel became secretary of the International Society for the Studies in Trophoblastic Disease (ISSTD) and dr Lok became the president of the European Organisation for the Treatment of Trophoblastic disease (EOTTD). We actively participated to the international tumor board.

Lopes Cardozo JMN, Byng D, Drukker CA, Schmidt MK, Binuya MA, van 't Veer LJ, Cardoso F, Piccart M, Smorenburg CH, Poncet C, Rutgers EJT. Outcome without any adjuvant systemic treatment in stage I ER+/HER2- breast cancer patients included in the MINDACT trial. Ann Oncol. 2021

Rafael TS, de Vries HM, Ottenhof SR, Hofland I, Broeks A, de Jong J, Bekers E, Horenblas S, de Menezes RX, Jordanova ES, Brouwer OR. Distinct Patterns of Myeloid Cell Infiltration in Patients With hrHPV-Positive and hrHPV-Negative Penile Squamous Cell Carcinoma: The Importance of Assessing Myeloid Cell Densities Within the Spatial Context of the Tumor. Front Immunol. 2021;14;12:682030

Rozeman EA, Hoefsmit EP, Reijers ILM, Saw RPM, Versluis JM, Krijgsman O, Dimitriadis P, Sikorska K, van de Wiel BA, Eriksson H, Gonzalez M, Torres Acosta A, Grijpink-Ongering LG, Shannon K, Haanen J, Stretch J, Ch'ng S, Nieweg OE, Mallo HA, Adriaansz S, Kerkhoven RM, Cornelissen S, Broeks A, Klop WMC, Zuur CL, van Houdt WJ, Peeper DS, Spillane AJ, van Akkooi ACJ, Scolyer RA, Schumacher TNM, Menzies AM, Long GV, Blank CU. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med. Feb 2021;27(2):256-263

Van Gerwen M, Maggen C, Cardonick E, Verwaaijen EJ, van den Heuvel-Eibrink M, Shmakov RG, Boere I, Gziri MM, Ottevanger PB, Lok CAR, Halaska M, Shao LT, Struys I, van Dijk-Lokkart EM, Van Calsteren K, Fruscio R, Zola P, Scarfone G, Amant F. Association of Chemotherapy Timing in Pregnancy With Congenital Malformation.International Network on Cancer, Infertility and Pregnancy. JAMA Netw Open. 2021

Van Huizum MA, Hage JJ, Russell NS, Rutgers EJ, Woerdeman LAE. Combined skin-sparing mastectomy and immediate implant-based breast reconstruction: Outcome following mantle field irradiation versus outcome following whole-breast irradiation. J Plast Reconstr Aesthet Surg. 2021

Van Rhijn BWG, Hentschel AE, Bründl J, Compérat EM, Hernández V, Čapoun O, Bruins HM, Cohen D, Rouprêt M, Shariat SF, Mostafid AH, Zigeuner R, Dominguez-Escrig JL, Burger M, Soukup V, Gontero P, Palou J, van der Kwast TH, Babjuk M, Sylvester RJ; Multi-center EAU Non-Muscle-Invasive Bladder Cancer Guidelines Panel Study Consortium on the WHO1973 WHO 2004 2016 Classification Systems for Grade. Prognostic Value of the WHO1973 and WHO2004/2016 Classification Systems for Grade in Primary Ta/T1 Non-muscle-invasive Bladder Cancer: A Multicenter European Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel Study. Eur Urol Oncol. 2021;4(2):182-191

Veerman H, Houwink API, Schutte PFE, Nieuwenhuijzen JA, Roeleveld TA, Wit E, Mazel JW, van der Sluis TM, Vis AN, van Leeuwen PJ, van der Poel HG. Intraoperative Strategies to Reduce Catheter-Related Bladder Discomfort in the Early Postoperative Period after Robot-Assisted Radical Prostatectomy. J Urol. 2021;205(6):1671-1680

Vos LMC, Aronson SL, van Driel WJ, Huitema ADR, Schagen van Leeuwen JH, Lok CAR, Sonke GS. Translational and pharmacological principles of hyperthermic intraperitoneal chemotherapy for ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 2021

Ykema BLM, Adan F, Crijns MB, Bleeker FE, Dekker E, Bekkenk MW, Snaebjornsson P, van Leerdam ME. Cutaneous squamous cell carcinoma is associated with Lynch syndrome; widening the spectrum of Lynch syndrome associated tumours. Br J Dermatol 2021:185(2):462-463

PLASTIC AND RECONSTRUCTIVE SURGERY

Our research is focused on innovations of reconstructive techniques after ablative surgery by other specialists. As such, we introduced a 'limited' (n = 17) and an 'extended' (n =25) technique of anterior vaginal wall advancement to reconstruct the meatus urethrae after vulvectomy. We observed one neomeatal stenosis and one case of partial vaginal wall flap necrosis as major complications following the 'limited' technique and one circumferential neomeatal dehiscence and occlusion as major complication after the 'extended' technique. Both cases were felt to have been preventable and not caused by a flaw of design of the advancement technique. Consequently, we advised applying these techniques to prevent circular inset of the neo-meatus. The 'extended' technique offers a solution in cases where the peri-urethral vulvar defect cannot be closed by transpositioning of labial skin.

Likewise, we evaluated the use of glabrous split skin grafts (n = 19) to close excisional defects on the weight-bearing plantar surface of the foot to prevent more extensive and eventful flap surgery. We observed 100% graft take and 2 wound infections that could be treated conservatively. Postoperatively, partial weight bearing was possible after a median of 4 weeks, and full weight bearing after 10 weeks. Sixteen patients (0.84) returned to full mobility (including sports) without orthotics. This made us conclude that this is a simpler, safe and effective technique that provides durable plantar cover and minimal donor site morbidity.

DERMATOLOGY

Systemic 'targeted' therapy with Hedgehog pathway inhibitors for locally advanced and metastasized basal cell carcinoma

Basal cell carcinoma (BCC) is the most frequent skin cancer worldwide, with one in five inhabitants of the Netherlands affected at least once in their lifetime. Most BCC can be either excised or treated with destructive- or radiotherapy. However, in rare cases this is not possible due to either a large size of the BCC or local invasion in certain structures like the orbita, nose or ear canal. In addition very rarely BCC metastasize to either lymph nodes or visceral organs.

Since 2013 the hedgehog signaling pathway inhibitor vismodegib (Erivedge®) is registered in the Netherlands for systemic treatment of locally advanced or metastasized BCC. Since June 2021 sonidegib (Odomzo®) is registered for the treatment of locally advanced BCC.
Hedgehog inhibitors work by inhibiting the hedgehog signaling pathway, of which patched 1 (PTCH1) and smoothened (SMO) are the part that play an important role in the development of BCC. By inhibiting the pathway cell proliferation is inhibited. Current research shows that in most cases tumour size reduced and sometimes completely disappear. For an optimal effect Hedgehog inhibitors have to be taken lifelong but due to resistance of the tumour or side effects the treatment is often paused or stopped. There is still a need for other therapies, of which PD1-inhibition with cemiplimab seems the most promising.

The number of patients on hedgehog inhibitors is small and was therefore traditionally only prescribed in academic hospitals in the Netherlands. Since January 2021 hedgehog inhibitors are also prescribed at the Dermatology department in AVL and we have currently eight patients on vismodegib, making us one of the largest centers in the Netherlands. We collaborate with the department of Oncology and Head and Neck to give excellent care to patients with locally advanced or metastasized BCC. In collaboration with the other prescribing centers in the Netherlands we are about to take part in a prospective as well as retrospective registry for patients on hedgehog inhibitors. Additionally we are analyzing the institute's experience with locally advanced BCC's before the start of hedgehog inhibitor treatment.

ANESTHESIOLOGY, INTENSIVE CARE MEDICINE AND PAIN MEDICINE

Research of the department of anesthesiology consists of participation in national and international multi-center trials. We seek collaboration with other academic hospitals in the Netherlands and in Europe through the European Society of Anesthesiology and Intensive Care. Priority is given to research projects that impact oncological populations.

Additionally, address research questions that are relevant to us locally. One of the highlights of 2021 has been the start of an RCT, comparing the effects of the erector spinae plane block to the paravertebral block on postoperative pain and opioid use in breast cancer patients.

Recently we have been awarded funding by the Stichting Patiëntenzorg Antoni van Leeuwenhoek that will enable a research project that assess the effects of non-pharmacological stress-reducing interventions in the PACU on postoperative pain and use of opioids and we hope to develop this project in 2022.

Corrie Marijnen

Head Division of Radiation Oncology

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Alice Couwenberg MD PhD Post-doc, clinical resident
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Celia Juan de la Cruz PhD student
Chavelli Kensen PhD student
Ernst Kooreman PhD student
Anneliz de Leeuw PhD student
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Roque Rodriguez Outeiral PhD student
Lukas Schröder PhD student
Astrid Slagter PhD student
Paul Slangen PhD student
Tania Sluckin MD PhD student
Uros Stankovic PhD student
Max Tanaka MD PhD student
Evalien Veldhuijzen PhD student
George Yiasemis PhD student

Division of Radiation Oncology

INTRODUCTION

Following the change of leadership, the division of Radiation Oncology has redefined its research ambitions for the coming ten years. In 2030, we will be a leading example for large international centers because we are pushing the boundaries in our search for the best possible options for our patients. To achieve that, we are frontrunner in the area of personalized medicine, through continuous adaptation of the treatment according to the characteristics of the tumor and the patients' preferences. These ambitions can be summarized in the following:

Mission 2030

Through the **comprehensive approach** of clinical care and research, the department offers the most progressive treatment worldwide.

Vision 2030

We will **continuously** take **all relevant factors** into account to ensure a **personal and tailored** treatment for **every patient**.

Based on this 2030 vision, the ongoing and future research addresses 1) optimization of the therapeutic window by increasing efficacy and decreasing toxicity, 2) better patient selection for better individualized treatment management, and 3) acquisition of information for shared decision making.
The research activities within the division of Radiation Oncology are mostly clustered within four of the five institutionwide themes: personalized treatment, immunotherapy, image guided treatment and survivorship. Most research projects have a multi-disciplinary character, combining clinical, physics, biological and/or epidemiology efforts, with a strong focus on translational research and innovation.

HIGHLIGHTS

- 2 KWF proposals have been awarded
- 3 randomized controlled trials published
- 1 practice changing phase II trial published
- Discovery of a new salivary gland

PERSONALIZED RADIOTHERAPY

Personalized radiotherapy aims to individualize treatment through the use of genetic profiling and biology-driven imaging for patient selection and treatment modification/adaptation and the use of targeted agents during radiotherapy. The ongoing and future research addresses 1) novel insights in the irradiation response of tumors, 2) optimal patient selection for better individualized treatment management, and 3) optimization of combined-modality-targeted therapeutics to increase the therapeutic window. Our research follows the bench to bedside approach with the focus on the clinical needs and opportunities in our daily clinical practice. Importantly, we initiated new and promising collaborations with other research groups to use state-of-the-art pre-clinical tools and to enable innovative translational studies contributing to the personalized radiotherapy treatment approach.

Translational research

Modulation of targeted agents to optimize the radiotherapy outcome

To improve the success of radiotherapy, we develop novel strategies that enhance the local response using targeted agents. Besides the underlying mechanism of radiosensitization, the timing of administration of targeted agents during radiotherapy is crucial.

For different radiosensitization strategies we have observed that the timing of administration relative to the RT is critical; 1) In collaboration with the Akkari group we observed different outcomes of the combination of RT and immunotherapy dependent on the timing of the two modalities. We are currently exploiting why this is, and the optimal sequence of this combination treatment. 2) Also for the radiosensitization strategy of increasing the number of mitotic cells during RT (mitotic enrichment strategy) we observed both *in vitro* and *in vivo* a very promising outcome in which the timing of the agents relative to the RT was critical (and explains the failures of previous historical attempts). This work is done in collaboration with the van Tellingen group and we are working to move this strategy into clinical trials.

Identification and exploitation of DNA repair defects

DNA damage response and repair processes play a role in tumorigenesis and cellular resistance to cancer treatments. We previously identified DNA crosslink repair defects in HNSCC that can be exploited by PARP and other DNA repair inhibitors. This prompted the development of predictive models to identify such defects in tumor specimen of advanced HPV-negative HNSCC patients prior to chemoradiotherapy. We find that such repair defects are associated with poor prognosis and an increased risk for metastasis. These patients however benefit most from high cumulative cisplatin doses, revealing relevance in treatment outcome. Enabled by a multicentric study with 197 HNSCC samples, we further evaluated individual biological determinants of patient outcomes in a multifactorial context and demonstrate a differential role in distant metastasis risk or locoregional control.

Key publications

Al-Mamgani A, Kessels R, Navran A, Hamming-Vrieze O, Zuur CL, Paul de Boer J, Jonker MCJ, Janssen T, Sonke JJ, Marijnen CAM. Reduction of GTV to high-risk CTV radiation margin in head and neck squamous cell carcinoma significantly reduced acute and late radiation-related toxicity with comparable outcomes. Radiother Oncol. 2021;162:170-7

Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, Roodvoets AGH, Nagtegaal ID, Beets-Tan RGH, Blomqvist LK, Fokstuen T, Ten Tije AJ, Capdevila J, Hendriks MP, Edhemovic I, Cervantes A, Nilsson PJ, Glimelius B, van de Velde CJH, Hospers GAP; RAPIDO collaborative investigators. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22:29-42

Beekman C, Schaake E, Sonke JJ, Remeijer P. Deformation trajectory prediction using a neural network trained on finite element data-application to library of CTVs creation for cervical cancer. Phys Med Biol. 2021;66

Belderbos JSA, De Ruysscher DKM, De Jaeger K, Koppe F, Lambrecht MLF, Lievens YN, et al. Phase 3 randomized trial of prophylactic cranial irradiation with or without hippocampus avoidance in SCLC (NCT01780675). J Thorac Oncol. 2021;16:840-9

Bonvalot S, Gronchi A, Le Péchoux C, Baldini EH, Haas RL. STRASS: Positive results in a negative trial. Lancet Oncol 2021;22:e4

Couwenberg A, van der Heide U, Janssen T, van Triest B, Remeijer P, Marijnen C, Sonke JJ, Nowee M. Master protocol trial design for technical feasibility of MR-guided radiotherapy. Radiother Oncol. 2021;166:33-36

De Haan R, van den Heuvel MM, van Diessen J, Peulen HMU, van Werkhoven E, de Langen AJ, Lalezari F, Pluim D, Verwijs-Janssen M, Vens C, Schellens JHM, Steeghs N, Verheij M, van Triest B. Phase I and Pharmacologic study of Olaparib in combination with high-dose radiotherapy with and without concurrent Cisplatin for non-small cell lung cancer. Clin Cancer Res. 2021;27:1256-66

Fokas E, Appelt A, Glynne-Jones R, Beets G, Perez R, Garcia-Aguilar J, Rullier E, Joshua Smith J, Marijnen CAM, Peters FP, van der Valk M, Beets-Tan R, Myint AS, Gerard JP, Bach SP, Ghadimi M, Hofheinz RD, Bujko K, Gani C, Haustermans K, Minsky BD, Ludmir E, West NP, Gambacorta MA, Valentini V, Buyse M, Renehan AG, Gilbert A, Sebag-Montefiore D, Rödel C. International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer. Nat Rev Clin Oncol. 2021;18:805-16

Kerkmeijer LGW, Groen VH, Pos FJ, Haustermans K, Monninkhof EM, Smeenk RJ, Kunze-Busch M, de Boer JCJ, van der Voort van Zijp J, van Vulpen M, Draulans C, van den Bergh L, Isebaert S, van der Heide UA. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: Results from the FLAME randomized phase III trial. J Clin Oncol. 2021;39:787-96

La Fontaine MD, Bruin NM, van Kranen S, Knegjens JL, van de Kamer JB, Vogel WV, Sonke JJ. The dynamics and prognostic value of FDG PET-metrics in weekly monitoring of (chemo)radiotherapy for NSCLC. Radiother Oncol. 2021;160:107-14

Lansu J, Bovée JVMG, Braam P, van Boven H, Flucke U, Bonenkamp JJ, Miah AB, Zaidi SH, Thway K, Bruland ØS, Baldini EH, Jebsen NL, Scholten AN, van den Ende PLA, Krol ADG, Ubbels JF, van der Hage JA, van Werkhoven E, Klomp HM, van der Graaf WTA, van Coevorden F, Schrage Y, van Houdt WJ, Haas RL. Dose reduction of preoperative radiotherapy in Myxoid Liposarcoma: A nonrandomized controlled trial. JAMA Oncol. 2021;7:e20586

Poortmans PM, Struikmans H, De Brouwer P, Weltens C, Fortpied C, Kirkove C, Budach V, Peignaux-Casasnovas K, van der Leij F, Vonk E, Valli M, vanTienhoven G, Weidner N, Noel G, Guckenberger M, Koiter E, vanLimbergen E, Engelen A, Fourquet A, Bartelink H; EORTC Radiation Oncology and Breast Cancer Groups. Side effects 15 years after lymph node irradiation in breast cancer: Randomized EORTC trial 22922/10925. J Natl Cancer Inst. 2021;113:1360-8

Rodríguez Outeiral R, Bos P, Al-Mamgani A, Jasperse B, Simões R, van der Heide UA. Oropharyngeal primary tumor segmentation for radiotherapy planning on magnetic resonance imaging using deep learning. Phys Imaging Radiat Oncol. 2021;19:39-44

Slagter AE, Vollebergh MA, Caspers IA, van Sandick JW, Sikorska K, Lind P, Nordsmark M, Putter H, Braak JPBM, Meershoek-Klein Kranenbarg E, van de Velde CJH, Jansen EPM, Cats A, van Laarhoven HWM, van Grieken NCT, Verheij M. Prognostic value of tumor markers and ctDNA in patients with resectable gastric cancer receiving perioperative treatment: results from the CRITICS trial. Gastric Cancer. 2021 (in press)

Valstar MH, de Bakker BS, Steenbakkers RJHM, de Jong KH, Smit LA, Klein Nulent TJW, van Es RJJ, Hofland I, de Keizer B, Jasperse B, Balm AJM, van der Schaaf A, Langendijk JA, Smeele LE, Vogel WV. The tubarial salivary glands: A potential new organ at risk for radiotherapy. Radiother Oncol. 2021;154:292-8

Van Houdt PJ, Saeed H, Thorwarth D, Fuller CD, Hall WA, McDonald BA, Shukla-Dave A, Kooreman ES, Philippens MEP, van Lier ALHMW, Keesman R, Mahmood F, Coolens C, Stanescu T, Wang J, Tyagi N, Wetscherek A, van der Heide UA. Integration of quantitative imaging biomarkers in clinical trials for MR-guided radiotherapy: Conceptual guidance for multicentre studies from the MR-Linac Consortium Imaging Biomarker Working Group. Eur J Cancer. 2021;153:64-71

Van Houdt PJ, Yang Y, van der Heide UA. Quantitative magnetic resonance imaging for biological image-guided adaptive radiotherapy. Front Oncol. 2021;10:615643

Yiasemis G, Zhang C, Sánchez CI, Sonke JJ, Teuwen J. Deep MRI reconstruction with radial subsampling. arXiv 2021

Clinical research

Interaction study

High dose radiotherapy is often indicated for patients on systemic targeted agents (including immunotherapy). However, the combination of radiotherapy with a potential radiosensitizer could easily lead to normal tissue damage, while discontinuation of the drug during radiotherapy could lead to rapid disease progression. We currently face a lack of consensus about the optimal strategy in this situation. Although case reports and several phase I/II studies exist, mostly evidence based data are missing to easily write the urgently needed guideline. Therefore, we developed a draft guideline based on an extensive literature search, combined with all available clinical, pharmacological and radiobiological knowledge. We started an international collaboration to publish an ESTRO-ESMO consensus guideline, based on our draft. This will be followed by a national observational study based on this guideline.

Individualizing preoperative radiation for sarcoma patients

From a radiation-oncology perspective, sarcomas can be subdivided into subtypes that are radiation sensitive and those being more resistant. For the radiosensitive myxoid liposarcoma dose de-escalation has been proven safe and effective and will be further evaluated in a global registry. In more radioresistant sarcomas, increasing the radiation dose in patients that still have to undergo definitive surgery is probably not clinically feasible. Therefore, investigations into radiation sensitizers are warranted. For this purpose phase I and II trials with angiogenesis inhibitors have been initiated. Further investigations, combining novel targeted drugs (e.g. interfering with the DNA Damage Response pathways) with preoperative radiotherapy are being designed and will start to accrue patients. In these trials, pathology will be correlated with bio-imaging (e.g. perfusion and diffusion weighted MRI imaging) for early response prediction.
Because these modifications to the standard 50 Gy preoperative RT will all, at least to a certain extent, have impact on the quality of life, the sarcoma working group initiated projects documenting both health-related quality of life domains as well as patient reported outcomes.

Individualizing radiotherapy indication for breast cancer: shared decision making.

The BRASA study, a national multicenter pre and post intervention study has been completed. This study investigated the implementation and effects of an on-line patient decision aid on shared decision making for 4 situations where the administration of (extra) radiotherapy is a preference sensitive decision. A total of 214 patients were included in the trial of which 189 had exposure to the decision aid. Patients using the PtDA did not improve scores on decisional conflict or on perceived SDM but had better knowledge about their treatment options and choose for less intensive treatments, without increasing consultation time.

Immunotherapy

Radio-immunotherapy

We are setting up a new research line into the effect of radiotherapy on the immune system in lung cancer. Immune checkpoint inhibitors alone have shown survival benefit in

stage III and IV NSCLC patients. However, median progression free survival in stage IV is currently 9 months. Although we have indications to believe radiotherapy can (re)invigorate the response to immune checkpoint inhibitors, it is currently unclear which dose/schedule/type of radiotherapy is optimal. We are collaborating with the department of pulmonology and several other institutes on this topic. Currently we are performing a multicenter phase II study (MAASTRO initiative) combining radiotherapy (with or without aPD-L1) and L19-IL2. New studies and collaborations are being set up.

SURVIVORSHIP

In the last decades, cancer treatments have improved significantly, leading to improved cure rates. Consequently, increasing numbers of cancer survivors are at risk of developing (late) adverse effects, which in turn may affect quality of life (QOL) and long-term survival. Therefore, treatment individualization and optimization to decrease adverse event risk, as well as early detection and monitoring strategies of adverse events are warranted. To be able to do so, accurate documentation of acute and long-term side effects is needed.

Assessment of increased risk of cardiac disease

In 2021 we continued our work on increased risk of cardiac disease after treatment for breast cancer. In an international collaboration, the impact of uncertainties in cardiac dose reconstruction on dose-response relationship for radiation related heart disease was studied. For all five reconstruction methods the relationship between reconstructed and CT-planning-based doses was linear. The results increase confidence in the published dose–response relationships for the risk of radiation related heart disease in cancer survivors. This may encourage doctors to use these dose-response relationships when estimating individualized risks for patients and selection of patients for proton therapy will be facilitated by these models.

Treatment optimization to reduce side effects after prophylactic cranial irradiation (PCI)

In collaboration with the PSOE department we conducted the multicenter phase III trial to investigate neuro-cognitive functioning and safety of PCI with or without hippocampus avoidance in Small Cell Lung Cancer (SCLC). This trial did not show lower probability of cognitive decline in SCLC patients receiving hippocampus avoidance PCI compared to conventional PCI. Clearly our understanding of the relationship between dose to the hippocampus and cognitive function is still incomplete. Analysis of QoL as well as the hippocampal volumes on follow-up MRI scans and correlate the results with neurocognitive tests is currently ongoing.

Reducing side effects in breast cancer: PAPBI study

Partial breast irradiation (PBI) instead of whole breast irradiation is a safe alternative for women with low risk breast cancer and has been shown to give less toxicity and better cosmesis. However, with standard postoperative PBI still large volumes are irradiated. When radiotherapy is given preoperatively, more accurate tumor delineation can be performed, resulting in smaller radiotherapy volumes. The results of our phase II PAPBI trial, in which all patients received preoperative PBI are very promising; low complication rates, limited fibrosis/induration in a small volume and good-excellent cosmetic results. The aim of PAPBI-2, an international, multicenter randomized phase III trial, is to confirm the hypothesis that preoperative PBI leads to significantly and clinically relevant less toxicity and better cosmesis compared to postoperative PBI. A KWF grant has been awarded for this trial.

Accurate monitoring and modeling of adverse event development

The Patient Reported Outcomes Version of the Common Terminology Criteria of Adverse Events (PRO-CTCAE) item library covers a wide range of symptoms. In collaboration with the NCI, we translated and linguistically validated the PRO-CTCAE item library in Dutch and developed a subset relevant for patients with lung cancer. This PRO-CTCAE subset is a feasible choice for weekly monitoring during a longer period and is currently being tested in the SYMPRO lung trial. In parallel, implementation of a PRO-CTCAE subset for rectal cancer is developed.

Organ preservation in rectal cancer

In collaboration with the groups of Beets and Beets-Tan, a continuous program to improve organ-preserving strategies in rectal cancer has been started. For this purpose, neoadjuvant (chemo)radiotherapy is applied to patients indicating a wish for organ sparing strategies. The safety and optimal treatment strategy in organ preservation is currently being investigated in the TESAR and STAR-TreC trials, both multicenter, international phase III trials for early rectal cancer patients. Our department is the lead of the radiotherapy for both trials, facilitating a good quality assurance system and accumulation of toxicity data. Collaborations have been established to correlate toxicity data and dose distributions of organs at risk. In parallel, several strategies are developed to increase the efficacy of the (chemo) radiotherapy. In the nearby future, boost doses will be delivered with either contact therapy, brachytherapy or the MR-Linac.

IMAGE GUIDED RADIOTHERAPY

Inter- and intra-tumor variability challenge optimal treatment selection and delivery. Imaging allows to quantify such variability non-invasively. Image guided radiotherapy is the process of image acquisition, image processing and treatment modification for optimal treatment selection and delivery. Our image guided research activities span a broad range of disease sites and all major imaging modalities.

Adaptive Radiotherapy

Day-to-day shape variation of the target in Cervix cancer radiotherapy results in considerable geometric uncertainties. A library of plan strategy, designed bases on a full and empty bladder CT scan has previously been proposed to mitigate these uncertainties. Accurate inter- and extrapolation of unseen anatomical bladder filling anatomical states, however, remains a challenge. Therefore, biomechanical modeling was used to generate a series of physiologically plausible cervix CTVs. The model preserved CTV volumes throughout the deformation.

Moreover, regional residual errors between repeat and library CTV reduced by up to 3 mm when averaged over the group of large movers. For individual cases, this regional error reduction could be as large as 8 mm.

Biologically adaptive radiotherapy was explored in a prospective clinical trial through the use of serial FDG-PET-CT to determine the boost dose and to guide boost segmentation in head and neck cancer. FDG-PET/CT scans were made at baseline and for redelineation and replanning at the end of weeks 2 and 4 of radiation therapy. The metabolically active part of the primary tumor received a 2 Gy/week boost on top of the 70 Gy baseline dose per partial metabolic response. One patient received 70 Gy after complete metabolic response in week 2, seven patients received 74 Gy and 12 patients received 78 Gy, In total, 85% of adaptations were completed correctly and no patient experienced grade ≥4 toxicity rendering the study feasible.

To improve the precision of dose delivery in the clinic, the department develops MRI-guided radiotherapy with the Elekta Unity system. The department participates in the MR-linac consortium to further develop the methodology and conduct joint clinical trials. The NKI leads the consortium tumor site groups on rectal cancer and oligo-metastases.
So far, about 200 patients have been treated on the MR-linac at NKI, delivering a total of about 2000 treatment fractions. About half of the patients were treated for prostate cancer. Thirty-four patients were treated with stereotactic radiotherapy for liver metastases. Compared to radiotherapy on a standard linear accelerator, this treatment has the advantage that no fiducial markers need to be inserted for accurate positioning. For this reason, MRI-guided radiotherapy is now considered the standard treatment for liver metastases at the department. Other patient groups that are treated on the MR-linac are rectal cancer and lymph node metastases.
Ninety percent of these patients participate in a clinical trial. Up to now, the majority of studies involved the testing of feasibility of a specific treatment technique in the Umbrella-2 trial and studies to investigate the potential of quantitative MRI for response monitoring. 4D MRI-guided radiotherapy was developed for liver metastases and now is the standard treatment. For oligometastases in the upper abdomen and primary kidney tumors, the feasibility of 4D MRI guidance is tested. Interventional trials for escalating the tumor dose are in preparation for prostate and rectal cancer.

Epid dosimetry is used for quality assurance of radiotherapy treatment delivery in the clinic. For MRI-guided treatments on the MR-linac, 3D dosimetric verification of the online adaptive workflows is essential, as their complexity is unprecedented in radiation oncology. We have demonstrated the feasibility and accuracy of back-projection portal dosimetry for verification of Unity MR-linac treatments and introduced this in our routine clinical practice.

Quantitative MRI for radiotherapy

To realize our vision of daily adaptive treatments, the development of imaging biomarkers is necessary to track changes in relevant characteristics of the cancer and healthy tissue. The work on quantitative MRI techniques has been expanded to the MR-linac, demonstrating that daily acquisition of quantitative MRI sequences is feasible without prolonging the treatment time. A consensus recommendation on the acquisition of diffusion-weighted MRI on the Unity system has been established and published. We routinely acquire quantitative MRI sequences such as diffusion-weighted MRI to study the treatment response in prostate, rectum, liver and oligometastases.

Individualizing irradiation treatment for Head and Neck patients

The overall theme for the Head and Neck research is reducing toxicity with similar oncological outcome. The SUSPECT II study will investigate in 90 patients whether the contralateral draining lymph node harbor malignancy by performing sentinel node procedure in patients with contralateral hot spot on the SPECT/CT, aiming to reduce the treated volume to the ipsilateral neck only.
In the prospective PECAN study we evaluate the role of ctDNA as a predictor of the presence of residual disease and for the early detection of tumor recurrence in 70 patients with HNSCC treated with (chemo)radiation. Furthermore, we are working on a proof-of-concept study of neo-adjuvant immunotherapy combined with low-dose radiotherapy followed by the standard of care (chemo)radiation in locally-advanced HNSCC, aiming to investigate the role of this strategy in identifying the complete responders for future de-escalation studies.

Dose painting for prostate cancer

The FLAME trial, a multi-center phase III randomized trial of dose escalation in prostate cancer using external-beam radiotherapy, has reached its primary endpoint of 5y biochemical failure free survival in 2020.
In this study, a focal boost to the visible tumor inside the prostate to a dose of 95 Gy was given and compared to the standard treatment of 77 Gy to the gland. In total 571 patients have been randomized.

To prepare for more widespread application of focal boosting in prostate cancer, we developed and validated an anatomy-based model to identify the highest possible dose to the tumor given its location relative to organs at risk.
There is a trend in modern radiotherapy of prostate cancer to reduce the number of treatment fractions. For high-risk prostate cancer irradiation in 20 fractions is now used, but for low-intermediate risk extreme hypofractionation in 5 fractions is now standard. For patients with high-risk cancer, we started the hypoFLAME-2 trial in collaboration with the FLAME consortium to investigate the toxicity focal boosting in combination with extreme hypofractionation.

Improved efficacy in locally advanced and recurrent rectal cancer

Despite improvements in local control for rectal cancer, the results for advanced rectal cancer are still suboptimal. Our department is the radiotherapy lead in several strategies to improve outcome for this group. The RAPIDO trial, an international phase III study, demonstrates the superiority of neoadjuvant chemotherapy preceded by short course radiotherapy both in disease related treatment failures as well as in increased pCR rates indicates. Further investigations towards better patient selection based on risk factors is ongoing.

For patients with involved lateral lymph nodes, the likelihood of a local recurrence is unacceptably high. Therefore, a national trial on the treatment of these nodes is initiated and awarded with a KWF grant.
In collaboration with the Catharina Hospital Eindhoven, a KWF grant has been received for the improvement of radiotherapy quality in recurrent rectal cancers in the setting of a multicenter randomized trial, investigating the beneficial effect of adding neoadjuvant chemotherapy for this particular group of patients.

Artificial intelligence

Artificial intelligence in general and deep learning specifically is a rapidly developing field that is likely to affect many aspects of the radiotherapy chain. Therefore we are expanding our AI related research where currently 15 postdocs, PhD students and master students are focusing on AI related projects. AI related projects range from image reconstruction and image analysis to outcome prediction.
More specifically, deep learning based reconstruction of (4D) MRI and CBCT are being trained. U-net based network designs are being optimized for auto-segmentation of both organs at risk and target volumes as well as for deformable image registration. Machine learning is also developed for quality assurance of manual or automatically contoured structures. Deep learning is also being explored for dose prediction. Finally, deep learning is being explored to predict treatment outcome based on multi-modality imaging.

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Division of Pharmacy & Pharmacology and Biometrics

The division of Pharmacy & Pharmacology and Biometrics was founded in 2016. Research programs in *Pharmacy & Pharmacology* focus on drug manufacturing including cellular immunotherapies, bioanalysis and pharmacokinetics-pharmacodynamics (PK-PD) of (anticancer) drugs for both preclinical and clinical projects and in *Biometrics* we focus on collection and analyzing of clinical data and interpretation.

After a large-scale move in 2020 for both the Pharmacy & Pharmacology department and the Biometrics department to a new building the year 2021 was all about to settle down, to get used and to enjoy the brand new work environment. Despite all the COVID-19 related restrictions imposed on us, the new housing is a great and inspiring experience. The pharmacy houses modern, state-of-the-art facilities for drug storage, dispensing, manufacturing, laboratory and supportive services. This enables us to continue our work and to provide daily pharmaceutical patient care and research in accordance with the highest international standards. Related with that, in 2021 our GLP (Good Laboratory Practice) and GMP (Good Manufacturing Practice) licenses have been extended. The Biometrics department is now housed on the top, sixth floor of Building-I with offices and meeting rooms that fulfill all modern needs to make it a very pleasant, "feel good", efficient working space. Now the Pharmacy & Pharmacology and Biometrics departments are physically housed in the same building we see an increase in mutual interactions between the departments. Nevertheless and unfortunately, as with others in the Institute, the COVID-19 pandemic has seriously influenced our work in 2021 and it is foreseen to do so in the next year.

PHARMACY & PHARMACOLOGY

Drug manufacturing

The hospital pharmacy holds a manufacturing license for the production and quality control of Investigational Medicinal Products (IMPs), including Advanced Therapy Medicinal Products (ATMPs) and five licensed pharmaceutical products. Early 2021, because of COVID-19, a "distant" (digital) GMP inspection by the Dutch Health Inspectorate (IGJ) was completed successfully. In 2022, IGJ will return "live" to finalize the site clearance of the new production facility in the I-building comprising three dedicated cleanrooms for the manufacture of ATMPs for clinical use.
In the past year, the biotech facility of the hospital pharmacy (named BioTherapeutics Unit, BTU) continued the production of Tumor Infiltrating Lymphocytes (TIL) infusions for metastatic melanoma patients treated in the first multi-center phase III trial with TIL therapy in the world. For this unique and fully academic trial, six TIL products were manufactured in-house

in 2021; productions were supported by the neighboring blood bank Sanquin. The trial is scheduled to be finalized Q1 2022, after which a challenging phase towards EMA registration is entered. Also in 2021, a first TIL product was manufactured in an "ultimum refugium" setting for a non-small cell lung carcinoma (NSCLC) patient, preceding a multi-TIL clinical trial in which TIL therapy for other malignancies is investigated, initially for NSCLC. The close collaboration with two US biotech companies was continued in 2021. The first project involves the manufacture of a novel T cell therapy directed against patient specific neo-antigens. This cell therapy product consists of patient unique, neo-antigen directed T cells, cultured from autologous peripheral blood by several rounds of peptide stimulation. In 2021, five clinical productions were completed successfully. For the second project, also involving a personalized TCR engineered T cell therapy, a production process was developed and concluded by three successful engineering runs. By the end of 2021, a clinical trial submission including the Investigational Medicinal Product Dossier (IMPD) will be done at the Central Committee on Research Involving Human subjects (CCMO). In addition to the collaborations the BTU is working on the manufacturing process of an in-house developed personalized T cell receptor (TCR) engineered T cell therapy using CRISPR/Cas 9 technology, making use of an automated cell culture system. All work in the BTU is performed in close collaboration with the Haanen group and the division of Molecular Oncology and Immunology.

Apart from the continued manufacture of licensed product, in 2021 four small-molecule formulation projects were initiated for both internal and external partners. One project concerns the development of an oral pediatric formulation of an alkylating agent. Two projects concern the reviving and/or repurposing of known anticancer agents to be formulated and manufactured for early phase clinical trials as an oral capsule and a lyophilized powder for solution for intravenous infusion, respectively. The fourth project concerns the in-house manufacture of oral tablets of an investigational tyrosine kinase inhibitor discontinued by pharma. In 2021, over 20 mono- and (international) multi-center clinical trials were supported with packaging and distribution activities.

Bioanalytical method development + implementation in pharmacokinetic studies

Our Therapeutic Drug Monitoring (TDM) service for the optimization of drug treatment has been extended in 2021 with the oral oncolytic drugs alpelisib, binimetinib, cabozantinib, encorafenib, and tepotinib. This year we have received more than 5,000 samples from treated patients for TDM analysis. A bioanalytical method for the determination of the anti-cancer monoclonal antibodies (MAbs) nivolumab, pembrolizumab and ipilimumab has been developed and validated in human serum and this method has been used to support a Phase 1B Study to assess safety and efficacy of Neo-Adjuvant Bladder Urothelial Carcinoma COmbination-immunotherapy (NABUCCO). In this clinical trial, the effects of short-term preoperative treatment combinations with ipilimumab and nivolumab in patients with high-risk stage III resectable urothelial cancer are examined. Nivolumab is a human mAb that inhibits the binding of PD-L1 and ipilimumab is a mAb which binds to the cytotoxic T-lymphocyte associated protein 4 (CTLA-4). Analysis are

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Key publications

KEY PUBLICATIONS OF DIVISION OF PHARMACOLOGY

Bakker NAM, Rotman J, van Beurden M, Zijlmans HJM, van Ruiten M, Samuels S, Nuijen B, Beijnen J, De Visser K, Haanen J, Schumacher T, de Gruijl TD, Jordanova ES, Kenter GG, van den Berg JH, van Trommel NE. HPV-16 E6/E7 DNA tattoo vaccination using genetically optimized vaccines elicit clinical and immunological responses in patients with usual vulvar intraepithelial neoplasia (uVIN): a phase I/II clinical trial. J Immunother Cancer. 2021;9:e002547

Damoiseaux D, Li W, Beijnen JH, Schinkel AH, Huitema ADR, Dorlo TPC. Population Pharmacokinetic Modelling to Support the Evaluation of Preclinical Pharmacokinetic Experiments with Lorlatinib. J Pharm Sci. 2021;S0022-3549(21)00498-6

De Jong KAM, Rosing H, Vermunt M, Huitema ADR, Beijnen JH. Quantification of anti-SARS-CoV-2 antibodies in human serum with LC-QTOF-MS. J Pharm Biomed Anal. 2021;205:114319

Siebinga H, de Wit-van der Veen BJ, Beijnen JH, Stokkel MPM, Dorlo TPC, Huitema ADR, Hendrikx JJMA. A physiologically based pharmacokinetic (PBPK) model to describe organ distribution of ^{68}Ga-DOTATATE in patients without neuroendocrine tumors. EJNMMI Res. 2021;11:73.

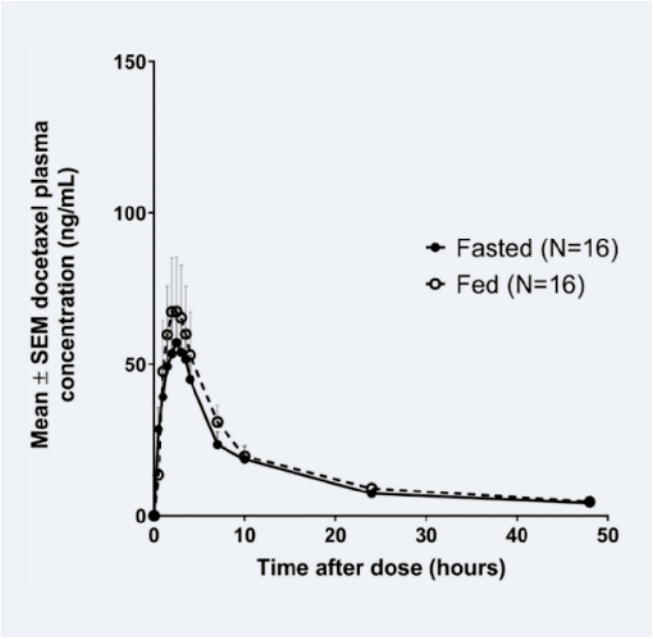

Figure 1. Mean plasma concentration (+ standard error of the mean (SEM)) versus time curves of docetaxel after administration of ModraDoc006/r in fasted and fed conditions (Vermunt *et al.* Drugs R D. 2021;21:103-111).

ongoing and PK-PD evaluations will be performed upon completion of the study.
Two studies on taxanes were published in 2021 for which our laboratory analyzed blood samples. ModraDoc006 is a novel docetaxel tablet formulation that is co-administrated with the cytochrome P450 3A4 and P-glycoprotein inhibitor ritonavir(r). A study was conducted to evaluate the effect of food consumed prior to administration of ModraDoc006/r on the pharmacokinetics of docetaxel and ritonavir. In total, 16 patients completed the food-effect study. Blood samples were analyzed using liquid chromatography with triple quadrupole mass spectrometric (LC-MS/MS) detection. A high-fat meal prior to administration of ModraDoc006/r resulted in a slightly higher docetaxel exposure and lower ritonavir C_{max}. Since this was a small effect, it was concluded that the intake of a light meal did not affect the systemic exposure to docetaxel. Furthermore, an open-label phase 1 trial clinical study with ModraPac001 and ModraPac005, novel oral paclitaxel formulations, was supported. In this study, 37 patients were treated with up to twice-daily 30-mg paclitaxel combined with twice-daily 100-mg ritonavir (ModraPac005/r 30-30/100-100) in 9 dose levels. At the MTD/RP2D of ModraPac005/r 20-20/100-100, the maximum paclitaxel plasma concentration and area under the plasma concentration-time curve until 24 hours (AUC_{0-24h}) were 34.6 ng/mL (coefficient of variation, 79%) and 255 ng • h/mL (coefficient of variation, 62%), respectively. Stable disease was observed in 15 of 31 evaluable patients.

Palbociclib, an oral inhibitor of cyclin-dependent kinases 4 and 6, is used in the treatment of locally advanced and metastatic breast cancer, and is extensively metabolized by cytochrome P450 enzyme 3A4 (CYP3A4). The effects of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib was investigated. A randomized crossover trial comparing the pharmacokinetics of palbociclib monotherapy 125 mg once daily (q.d.) with palbociclib 125 mg q.d. plus oral erythromycin 500 mg three times daily for seven days. Eleven evaluable patients were enrolled. Concomitant intake of palbociclib with the moderate CYP3A4 inhibitor erythromycin resulted in an increase in palbociclib AUC_{0-24h} and C_{max} of both 43%. Therefore, a dose reduction of palbociclib to 75 mg q.d. is rational, when palbociclib and moderate CYP3A4 inhibitors are used concomitantly.

The dihydropyrimidine dehydrogenase (DPD) substrate uracil in serum was analyzed weekly for a multicenter study to prevent the increased risk of developing severe fluoropyrimidine-related toxicity in patients treated with capecitabine or 5-FU and DPD deficiency. Paclitaxel, cyclophosphamide, doxorubicin, and platinum, originating from carboplatin and cisplatin, were determined in maternal milk samples to investigate whether lactation is safe during and after cancer treatment of the mother. Binimetinib, lapatinib and vinorelbine were quantified in plasma, tumor tissue and skin in a dose escalating phase 1 / 2 study with RAS mutated metastatic colorectal cancer.

We continued to support pre-clinical pharmaceutical research in collaboration with the Schinkel group. We studied the pharmacokinetic interactions of several drugs with multidrug efflux transporters and the multidrug metabolizing enzymes in *in vitro* transport assays and knockout and transgenic mouse models. Plasma pharmacokinetics and tissue distribution of abamaciclib (and its metabolites M2, M18 and M20), milciclib, cabazitaxel, niraparib, and di-acetylmorphine were investigated.

Pharmacokinetics and Pharmacodynamics (PK/PD) modelling and simulation

The PK/PD modelling and simulation group of the department maintains two high performance computational servers, part of the NKI Research HPC facility, dedicated to PK/PD modelling and simulation purposes. The group develops pharmacometric modelling methodologies, combining mathematical and statistical models, to relate drug exposure to diverse measures of treatment outcome for both toxicity and efficacy. PK/PD modelling and simulation has been applied to optimize therapy of approved anticancer agents and novel agents used in clinical trials and is increasingly also being implemented in clinical trial design, to optimize dose regimens and study procedures. In 2021, the group further consolidated its activities in clinical trials in pediatric oncology in collaboration with the Princess Máxima Center (PMC) for pediatric oncology.

Since 2010 a large-scale Therapeutic Drug Monitoring program is operational for precision dosing of oral anticancer agents. Most kinase inhibitors have a narrow therapeutic index, however, the currently approved dosing paradigm is a “one-size-fits-all” approach. We implemented TDM for these drugs in clinical practice, where plasma concentrations are routinely measured and reported to the treating physician together with a clinical pharmacological review and dosing advice. In 2021, we further developed guidance on the feasibility and use of TDM for individualized precision dosing of various oral targeted anticancer agents and its implementation in the clinic.

New scientific and methodological areas of interest that were initiated by the PK/PD modelling and simulation group in 2021 include the development and application of whole-body physiologically-based pharmacokinetic models (PBPK). These bottom-up mathematical models were used for animal-to-human translation of drug exposure and effects but also to identify and better understand mechanistic aspects of drug distribution, *e.g.* in relation to organ and tumor distribution of radioactive agents. Notably, continued activities in the area of treatment optimization for special patient populations, led to various studies to characterize drug exposure and drug exposure-response relationships and optimized precision dosing in pregnant women and children. In 2021, the PK/PD modelling and simulation group led or was involved in >50 publications in international peer-reviewed journals.

Our program on treatment optimization of the repurposed anticancer PI3K/Akt inhibitor miltefosine for the neglected tropical parasitic disease leishmaniasis has been largely extended with various clinical PK/PD studies conducted in 2021 in India, Bangladesh, Sudan, Ethiopia and Kenya, funded through H2020. Related to this, the group is currently involved in the preparation of clinical trials to optimize cancer therapies for malnourished children in low-income countries in Africa, in collaboration with the Princess Máxima Center (Utrecht).

BIOMETRICS

The Biometrics Department serves as the medical data center of the institute and provides the infrastructure for clinical research through biostatistical support, centralized patient data collection and documentation, data processing and coordinated administration and monitoring of clinical trials. We collaborate in clinical research projects both within the institute and in national and international multicenter studies. Working procedures follow Good Clinical Practice (GCP) and reporting and data sharing follow National and International laws and guidelines.

Tumor Registries

The tumor registry group maintains three important types of registries. Traditionally since 1955 using paper registration and since 1977 electronically, the group collects data from dossiers of patients visiting the hospital with benign, pre-malignant, and malignant tumors. Depending on the clinical involvement at the hospital with respect to the diagnosis and therapy of the tumor, the number of items collected ranges from minimal to very extensive. The registry allows querying medical information for indicators, research projects and policy matters. In December 2020 the department celebrated its 65th anniversary.

Between July 2020 and June 2021 we see a 10% decrease in total amount of registries (9650) compared to the same period the year before. Impact from COVID-19 is suspected as we saw a decline in diagnoses during the lockdown period in certain types of cancer (Mamma, Lung, GE).

A selection of cases of about 3700 tumors, who have been diagnosed and/or treated primarily in the Netherlands Cancer Institute, is sent to the National Cancer Registry at regular

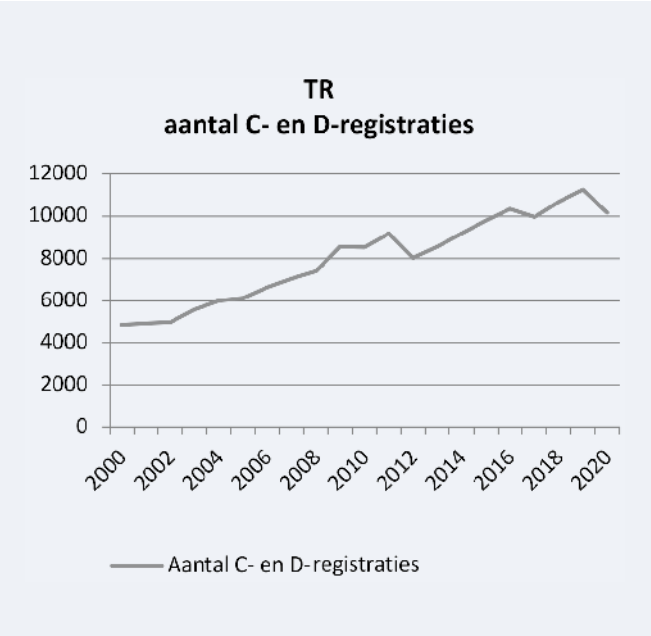

Figure 2. Number of C- and D-registrations

KEY PUBLICATIONS OF DIVISION OF BIOMETRICS

Al-Mamgani A, Kessels R, Navran A, Hamming-Vrieze O, Zuur CL, de Boer JP, Jonker MCJ, Janssen T, Sonke JJ, Marijnen CAM. Reduction of GTV to high-risk CTV radiation margin in head and neck squamous cell carcinoma significantly reduced acute and late radiation-related toxicity with comparable outcomes. Radiother Oncol. 2021;162:170-177

Caspers IA, Sikorska K, Slagter AE, van Amelsfoort RM, Meershoek-Klein Kranenbarg E, van de Velde C, Lind P, Nordsmark M, Jansen E, Verheij M, van Sandick JW, Cats A, van Grieken N. Risk factors for metachronous isolated peritoneal metastasis after preoperative chemotherapy and potentially curative gastric cancer resection: Results from the CRITICS trial. Cancers (Basel) 2021;13(18):4626

De Gooijer CJ, van der Noort V, Stigt JA, Baas P, Biesma B, Cornelissen R, van Walree N, van Heemst RC, Soud MY, Groen H, den Brekel A, Buikhuisen WA, Bootsma GP, Dammeijer F, van Tinteren H, Lalezari F, Aerts JG, Burgers JA, NVALT19 study group. Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma (NVALT19): an investigator-initiated, randomised, open-label, phase 2 trial. Lancet Respir Med 2021;9(6):585-592

Kersten MJ, Driessen J, Zijlstra JM, Plattel WJ, Morschhauser F, Lugtenburg PJ, Brice P, Hutchings M, Gastinne T, Liu R, Burggraaff CN, Nijland M, Tonino SH, Arens A, Valkema R, van Tinteren H, Lopez-Yurda, M., Diepstra A, De Jong D, Hagenbeek A. Combining brentuximab vedotin with dexamethasone, high-dose cytarabine and cisplatin as salvage treatment in relapsed or refractory Hodgkin lymphoma: the phase II HOVON/LLPC Transplant BRaVE study. Haematologica 2021;106(4):1129-1137

Rozeman EA, Hoefsmit EP, Reijers I, Saw R, Versluis JM, Krijgsman O, Dimitriadis P, Sikorska K, van de Wiel BA, Eriksson H, Gonzalez M, Torres Acosta A, Grijpink-Ongering LG, Shannon K, Haanen J, Stretch J, Ch'ng S, Nieweg OE, Mallo HA, Adriaansz S, […] Blank CU. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med 2021;27(2):256-263

Vessies D, Linders TC, Lanfermeijer M, Ramkisoensing KL, van der Noort V, Schouten RD, Meijer GA, van den Heuvel MM, Monkhorst K, van den Broek D. An Automated Correction Algorithm (ALPACA) for ddPCR Data Using Adaptive Limit of Blank and Correction of False Positive Events Improves Specificity of Mutation Detection. Clin Chem 2021;67(7):959-967

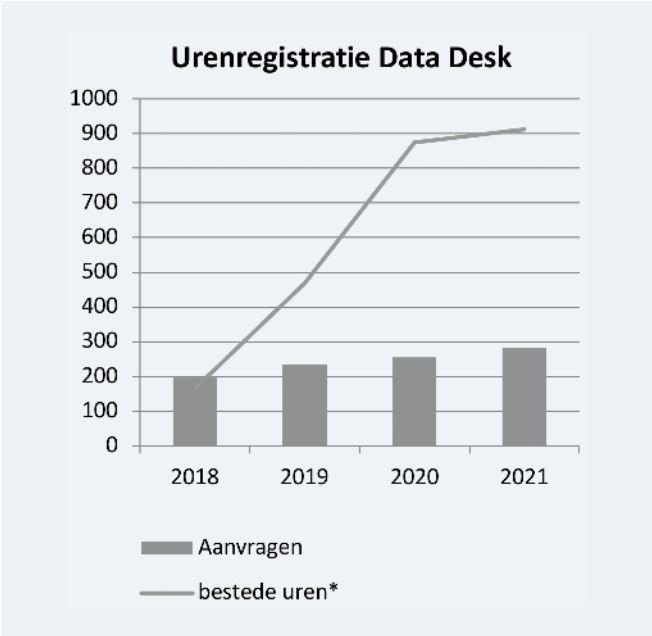

Figure 3. Data Desk Requests

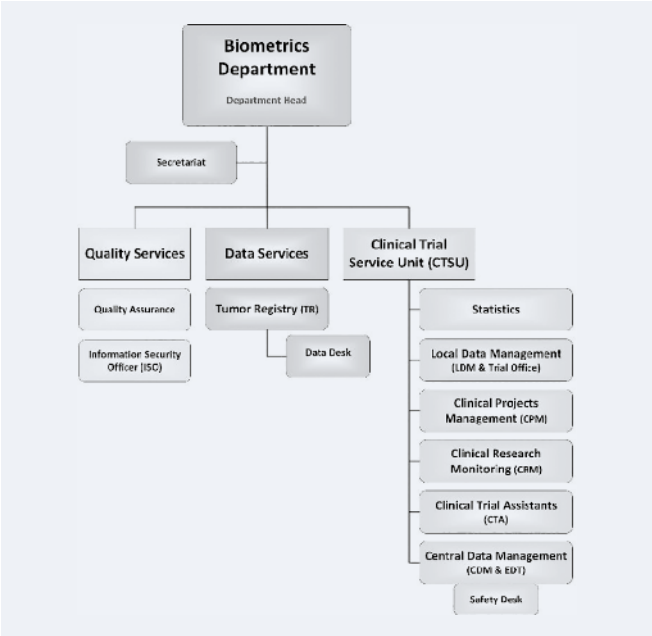

Figure 4. CTSU composition

intervals. In the last two decades, the number of registrations have more than doubled (figure 2).

A second series of registries belongs to the category of quality registers. The Dutch Institute for Clinical Auditing (DICA) develops most of these registries. DICA aims at creating valid monitoring systems for quality in healthcare by collecting a fixed set of items of interest per area over time. The system is set up to continuously audit quality of care through online benchmarking, taking patient- and disease characteristics into account. Between July 2020 and June 2021, we also saw a 10% decrease of registrations; approximately 3700 patients (~4100 the year before) were registered in 12 different specialized cancer registries, i.e. breast (NBCA), colorectal (DCRA), upper gastro-intestinal (DUCA), lung surgery (DLCA-S) and lung radiotherapy (DLCA-R), melanoma (DMTR), gynecologic (DGOA) and gynecologic radiotherapy, liver (DHBA) and head and neck cancer (DHNA). An implant registry (DBIR) is generated directly from the electronic sources and last year a bladder cancer registry (BlaZib) was continued, organized by the IKNL. A substantial amount of data in the registries is recorded in an unstructured way. In collaboration with information specialists from the department I&A, efforts are made to complete the registries more efficiently by connecting various electronic sources and writing sophisticated queries.

A third registry, starting from July 2015, is the Landelijke Basisregistratie Ziekenhuiszorg (LBZ). This is a registry of medical, administrative and financial data of patients at the outpatient clinic, the daycare department or who have been hospitalized. Key aspects are the use of ICD-10, an international coding system for diagnosis, and a standardized list of medical activities. In 2020 approximately 13.200 hospital admittances were registered in the AvL and provided to the LBZ. Data up to Aug 2021 show 9056 admittances so far.

Data Desk

In 2018, the DataDesk was introduced in the institute. The DataDesk is a virtual desk for data- and information requests from anywhere in the institute: e.g. scientific research, business and management questions and clinical questions in general (quality-, diagnostics-, treatment related). The idea is to facilitate researchers, clinicians and staff by providing one single point of access for all questions, which can be asked by completing in a web-form. Questions and answers are recorded, stored and are thus retrievable. A team is available to answer questions either directly, by using the tumor registry or other sources from the data warehouse (DWH), or to relay the questions to the relevant subdesks, i.e. experts in particular areas with access to specific sources of data. Before answering, a request will be checked for the necessary approval, which is, in case of individual personal data permission of the Institutional Review Board (IRB) or the Medical Research Ethics Committee (MREC).

The department plays a central role in this process and now has six data desk specialists (1.6 FTE) to process the requests coming from the institute. Even though the number of requests remain stable, we do see a significant increase in the complexity of the requests and hence the number of hours spent on each request. This gives rise to an increased need to invest in Data Science solutions (fig. 3).

Clinical Trial Service Unit

The Biometrics Department (fig. 3) provides logistic support for clinical trials performed in and by the institute. For a full investigator-initiated trial there is a line-up of people involved: Clinical Project Managers facilitate the development of protocols and submission to Medical Research-Ethics Committee (MREC) and coordinate the projects; local data managers facilitate the initiation of studies and perform the registration of pre-screening, screening and entry of patients into clinical trials. They perform drug resupplies and are the source of information with regard to clinical trials in general. Central data management designs the Case Record Forms and takes care of the quality of the central databases of investigator-initiated

studies and monitors these to ensure that the clinical trials are conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirement(s). All processes follow a Quality Management System which was formally introduced in 2018 and is based on ICH-GCP(R2) and published on the internal document management system.

In the beginning of 2021, an organizational change happened where the Contracting team was moved to the NKI as part of the new Knowledge Transfer & Contracting department. The relationship with the contract managers remains very close as they still support the creation of all clinical trial agreements and other agreements needed to perform the clinical trials with external parties.

The number of studies approved according to the Medical Research Involving Human Subjects Act (WMO) – open for patient inclusion over the past 5 years is ranging between 230 and 320, while the number of patients registered still increases. In 2021, almost 2600 patients were registered centrally in one of the WMO approved studies. We did see an increase in percentage for Investigator-Initiated Studies (IIS) compared to pharma-initiated studies. In 2021, approximately 96% of all new WMO studies were IIS and in 84% of those the NKI-AVL was the sponsor of the IIS study.


ASTEDT

Koen Verhoef

Head Knowledge Transfer & Contracting

Koen Verhoef Manager
Marije Marsman Senior business developer
Tim Moser Senior business developer
Anje Raven Business developer, clinical contract manager
Toni Danilovski Senior clinical contract manager
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Patricia Plasier-Carpentier Clinical contract manager
Suzan Stijger Clinical contract manager
Jan-Willem van Wees Clinical contract manager
Hylke Galama Senior legal counsel
Marin Hubertus Legal counsel
Stephanie de Meza Legal counsel
Danique Koning Legal counsel
Sanne Genee Legal counsel

Knowledge Transfer & Contracting

2021 started with the formalization of the merger of the former Technology Transfer Office (TTO) with the WA clinical contracts team into a new support team for both pre-clinical and clinical research. The resulting team was renamed to Knowledge Transfer & Contracting (KT&C for short) and serves as a single point of contact for researchers and physicians within NKI-AVL regarding all research contract and Intellectual Property matters, as well as a single point of contact for other academic research organizations as well as for companies.

KT&C helps researchers and clinicians to conclude research-related contracts, both with other academic research institutions as well as with industry. In addition, KT&C is charged with maximizing the chances that the Institute's research results find application in healthcare.
One of the major aims of the Netherlands Cancer Institute is to see its scientific breakthroughs being turned into novel products and services that benefit cancer patients. KT&C manages the patent portfolio and other intellectual property assets of the institute and actively engages with life science and healthcare companies and biotech investors who have the commitment and resources to bring our innovations to the market. In addition, KT&C also handles all consultancy agreements for the institute and has a sizeable portfolio of research materials which it licenses to industry.

SELECTED HIGHLIGHTS

Spin-off CRCbioscreen

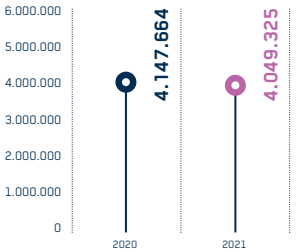
CRCbioscreen BV launched in Q1 of 2021 as a spin-off company of NKI-AVL, developing a next-generation population screening test for the presence of (precursors lesions of) colorectal cancer. The launch was made possible among others by investments from several private investors that are affiliated with NKI-AVL through the AVL Donation Investment Fund that was set up in 2020. Additional investments in the company were made by The Mark Foundation for Cancer Research and impact fund HumanPlus, and the private investments were leveraged by a successful grant application under a national funding programme for public-private collaborative research operated by Health~Holland.
The available capital allows the company to conduct a prospective study into the performance of the next-gen test in a head-to-head comparison with the test that is currently in use in population screening in the Netherlands and other countries. NKI-AVL has licensed a portfolio of several patent families to CRCbioscreen and continues to support the company as a shareholder.

Spin-off Bcon Medical

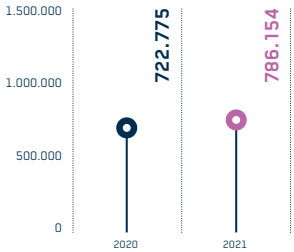
In more than 20% of operated cancer patients, surgery is inadequate, either because of incomplete removal of the tumor or because too much healthy tissue is removed or damaged. Tumor positive resection margins are a strong predictor for tumor recurrence, while damage to healthy tissue can result in long lasting complications such as urinary incontinence or sexual dysfunction. A surgeon therefore has to work in a sometimes tiny window in which the tumor can be completely removed while simultaneously sparing healthy tissue. A surgical navigation system can help surgeons to find that window much more easily than is possible by the surgeon's own touch and sight.

At NKI, a first such system that was developed in-house by the team of Prof. Dr. Theo Ruers is now routinely and successfully used for some particularly difficult surgical procedures within our hospital. As this 'home-brew' system can, for regulatory reasons, not be produced and installed at scale in other hospitals, it requires development into a commercial product. Having established the business case and with the help of experienced Med Tech entrepreneur Dr Nijs van der Vaart, who has previously led large development teams at Philips, the business plan for spin-off company Bcon Medical was pitched to private investors affiliated with the AVL Donation Investment Fund and a total of 1.4M€ was raised. HumanPlus also participated in this financing round.
As with CRCbioscreen, the money invested was leveraged through a public-private R&D grant that allows the company to simultaneously work on the productization of the existing system and to develop new technology for the next generation navigation systems that are envisaged. NKI-AVL has licensed several patent families in the field of surgical navigation to Bcon Medical. The company is focused on making electromagnetic navigation solutions available and affordable for all surgical oncology hospitals.

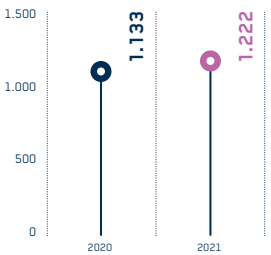
TECHNOLOGY TRANSFER OFFICE 2020



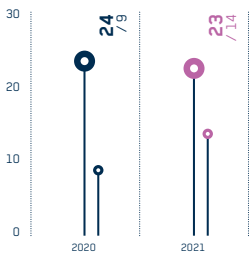
License income: € 4.049.325



Freely disposable income from contract research and consulting: € 786.154



In total, 1.222 research- and commercial contracts were negotiated and executed



KT&C received 23 invention disclosures and filed 14 priority patent applications, part of which were managed by Oncode Institute

Research facilities

Modern day biomedical research depends on expensive equipment and extensive experience with very specialized techniques. Individual researchers need to use a wide range of techniques for their work. It is impossible for anyone to master them all or to receive the budget to buy all the equipment they are likely to need. The NKI has resolved this problem, and used its funding in the most efficient way, by creating dedicated, centralized technology (core) facilities that serve the whole institute. These research facilities play an essential role in almost all research performed at the NKI. All NKI scientists have direct access to these facilities. Involvement of user committees and periodic review of the facilities ensure that they maintain a high standard and cater to the needs of the researchers.

The facilities of the NKI are offered free of charge to NKI-researchers. In some cases, the costs of consumables are charged to the budget of the research group. In principle, there is no restriction on the amount of time one can utilize a facility. When extensive support from a facility is required, this is discussed beforehand and in some cases a group leader transfers some budget to the facility in order to finance extra support (e.g. for recruitment of extra staff).

Most facilities of the NKI are supervised by a user committee. The Research Council installs these user committees, which consist of faculty members and postdocs, PhD students and/or technicians. The user committees meet at least once a year and they see to the quality of the service provided by the facility and make sure that the facility caters to the need of the researchers. They also review requests for new equipment for the facility and discuss implementing new technologies. The head of the facility and the director of operations are invited to the user committee meetings.

In 2021, the research groups and the facilities had to deal with the restrictions due to the corona pandemic. The staff members of the facilities have shown great and exceptional flexibility and commitment to maintain the service of the facilities at a very high level under difficult circumstances.

The research facilities of the NKI are presented on the next pages. In addition, the institute has a biometrics facility and clinical trial unit that both support clinical research (see Division of Pharmacology & Biometrics and Division of Medical Oncology) and a Pharmacy which is licensed to manufacture drugs and cell therapies for use in humans (see Division of Pharmacology & Biometrics). In addition to these facilities, we also provide the researchers with the following facilities:

- the Data Desk provides access to the fast amount of data collected in our institute over the years: data about diagnosis, treatment, treatment outcome, patient characteristics, etc. All these data are collected via different systems (the electronic patient records (HiX), pathology databases, clinical laboratory systems, etc.). These systems are mined via a data warehouse that brings the data from a patient or tumor from the different applications together. Researchers can ask for a dataset to be retrieved via the data warehouse through the Data Desk. First, they fill out a brief request form and then a data steward will discuss what they precisely need. This leads to retrieval of the actual information needed to answer their research question and also supports data-minimalization (a requirement of the General Data Protection Regulation). The dataset is handed out, (pseudo-)anonymized if possible, after being registered and after a check has been performed on consent of the patients for use of their data (General Data Protection Regulation requirements). Afterwards, enriched data can be fed into the data warehouse for later use;

- in 2019 the NKI got its own Electron Microscope (EM) again. We now have a 200 kV JEOL F200 EM mounted with a refurbished K2 high-resolution camera and software for doing cryoEM on protein complexes. We also have access to EM's at the Amsterdam University Medical Center for morphology in plastic embedded material and quality checking of cryoEM grids that needed to be imaged at NECEN (Leiden) on the 300 kV Titans;
- IT support for the development of software and databases and access to high-performance computing facilities. This support is provided through the general IT department of the institute and also through a dedicated group of IT specialists;
- library with dedicated support for data management and literature searches and providing access to a large collection of electronic journals and books;
- cryogenic storage of cells and tissues in a centralized liquid nitrogen storage facility;
- culture labs at different containment levels;
- dedicated labs for working with radionuclides;
- technical workshop that can make modifications to existing equipment or develop new tools;
- glassware cleaning.

Furthermore, researchers are supported by the finance, IT, HR, communication, training and general services departments.

Proteomics Facility

Maarten Altelaar

Head Proteomics Facility

The NKI Proteomics Facility supports users from all over the institute to address proteomics questions within their research projects. The facility provides advice, performs proteomics sample preparation, runs the LC-MS/MS systems and performs data analysis. The facility is involved in many research projects and reports on these subjects in scientific publications with NKI investigators.

Equipment and Workflow

Aided by funding from the NKI and the NWO X-Omics Initiative, we were happy to upgrade part of our fleet in 2021. Our facility still operates a Thermo Orbitrap Fusion hybrid mass spectrometer equipped with a Proxeon nLC1200 nano-LC system for LC-MS/MS-based peptide/protein identification and quantification, but this year we replaced our Thermo Q Exactive HF-X hybrid Quadrupole-Orbitrap mass spectrometer with a state-of-the-art Thermo Orbitrap Exploris 480 mass spectrometer equipped with FAIMS, also coupled to a Proxeon nLC1200 nano-LC system. Due to the upgrade, instrument downtime decreased, leading to shorter sample queues.

Researchers contact our facility with their proteomics question(s) and we discuss the optimal experimental design with them. Samples are then typically delivered as either gel (bands), immunoprecipitation beads, cell pellets or lysates. In all cases, the facility then performs sample preparation which involves enzymatic digestion of proteins to peptides for bottom-up proteomics. Depending on sample complexity or the specific research question, samples are pre-fractionated at the protein level by SDS-PAGE, or at the peptide level using a dedicated offline High-pH HPLC fractionation system (Agilent 1200) in order to increase depth of proteome coverage. Peptide samples are run on one of the LC-MS/MS systems, after which data analysis is performed using dedicated software. Finally, data sheets containing identified and/or quantified proteins, protein modification sites, identified protein interactors, regulated proteins/modification sites or pathways are communicated with the researcher.

Close to 90 experiments

Projects to which the facility has provided their services include immunoprecipitation experiments aimed at unraveling protein-protein interactions, global proteome profiling of cell lines and post-translational modification-focused profiling such as protein phosphorylation and ubiquitination. Despite the ongoing pandemic, 2021 brought an increased workload to our facility, with close to 90 experiments performed for researchers from about 20 research groups within the institute. We saw a continuing increase in the number of larger-scale discovery projects involving both whole proteome and phosphoproteome profiling and we expect this trend to continue.

Maarten Altelaar PhD Head
Onno Bleijerveld PhD Senior post-doc
Liesbeth Hoekman BSc Technical staff

Key publications

Champagne J, Pataskar A, Blommaert N, Nagel R, Wernaart D, Ramalho S, Kenski J, Bleijerveld OB, Zaal EA, Berkers CR, Altelaar M, Peeper DS, Faller WJ, Agami R. Oncogene-dependent sloppiness in mRNA translation. Mol Cell. 2021;81(22):4709-4721.e9

De Krijger I, Föhr B, Pérez SH, Vincendeau E, Serrat J, Thouin AM, Susvirkar V, Lescale C, Paniagua I, Hoekman L, Kaur S, Altelaar M, Deriano L, Faesen AC, Jacobs JJL. MAD2L2 dimerization and TRIP13 control shieldin activity in DNA repair. Nat Commun. 2021:12(1):5421

Prekovic S, Schuurman K, Mayayo-Peralta I, Manjón AG, Buijs M, Yavuz S, Wellenstein MD, Barrera A, Monkhorst K, Huber A, Morris B, Lieftink C, Chalkiadakis T, Alkan F, Silva J, Győrffy B, Hoekman L, van den Broek B, Teunissen H, Debets DO, Severson T, Jonkers J, Reddy T, de Visser KE, Faller W, Beijersbergen R, Altelaar M, de Wit E, Medema R, Zwart W. Glucocorticoid receptor triggers a reversible drug-tolerant dormancy state with acquired therapeutic vulnerabilities in lung cancer. Nat Commun. 2021;12(1):4360

The NKI Robotics and Screening Center

Roderick Beijersbergen

Roderick Beijersbergen PhD Head
Cor Lieftink MSc Bioinformatician
Ben Morris Technical staff

Key publications

Mayayo-Peralta I, Faggion B, Hoekman L, Morris B, Lieftink C, Goldsbrough I, Buluwela L, Siefert JC, Post H, Altelaar M, Beijersbergen R, Ali S, Zwart W, Prekovic S. Ribociclib induces broad chemotherapy resistance and EGFR dependency in ESR1 wildtype and mutant breast cancer. Cancers (Basel). 2021;13(24):6314

Prekovic S, Schuurman K, Mayayo-Peralta I, Manjón AG, Buijs M, Yavuz S, Wellenstein MD, Barrera A, Monkhorst K, Huber A, Morris B, Lieftink C, Chalkiadakis T, Alkan F, Silva J, Győrffy B, Hoekman L, van den Broek B, Teunissen H, Debets DO, Severson T, Jonkers J, Reddy T, de Visser KE, Faller W, Beijersbergen R, Altelaar M, de Wit E, Medema R, Zwart W. Glucocorticoid receptor triggers a reversible drug-tolerant dormancy state with acquired therapeutic vulnerabilities in lung cancer. Nat Commun. 2021;12(1):4360

Schep R, Brinkman EK, Leemans C, Vergara X, van der Weide RH, Morris B, van Schaik T, Manzo SG, Peric-Hupkes D, van den Berg J, Beijersbergen RL, Medema RH, van Steensel B. Impact of chromatin context on Cas9-induced DNA double-strand break repair pathway balance. Mol Cell. 2021;81(10):2216-2230

The NKI Robotics and Screening Center (NRSC) accelerates research by providing integrated services ranging from functional genomic screening, small-molecule screening, high-throughput methods to data analysis and integration. The NRSC supports the functional investigation of the mammalian genome for the unraveling of molecular pathways and mechanisms and how these can be explored as targets for treatment of disease. Access to our diverse compound collections and drug screening platforms further supports clinical translation of these findings. The NRSC provides expert guidance on the design, execution and analysis of genetic and compound screens. In addition to providing access to our screening infrastructure and technologies, the NRSC also works to improve technologies to perturb gene function and to implement new screening technologies and platforms.

Since the generation of the first NKI human shRNA library in 2002, we have extended our RNAi platform with several large (genome-wide) collections for human and mouse. These collections are available as individual reagents and can be used to generate smaller sub-collections for specific screening projects. We have generated several sub-collections representing gene-sets of interest. In addition to our RNAi platforms we also provide access to CRISPR/CAS9 technologies including CRISPR based transcriptional repression (CRISPRi) and activation (CRISPRa) screening. We continued the generation of custom libraries for subsets of genes for specific applications using custom vector designs.

The NRSC has a close collaboration with the ScreeninC national infrastructure, supported by the Dutch Cancer Foundation (KWF), which started at the end of 2020. The NRSC provide expertise, tools and infrastructure to ScreeninC to allow for the application of functional genomic technologies from advanced model generation to large-scale screening. ScreeninC gives clinical and basic research groups in the Netherlands access to unique research tools allowing them to expand their ongoing research programs and to initiate new research projects.

In 2021, we have assisted more than 30 researchers with their screening projects. The majority of these projects involved our pooled CRISPR screening platforms and support was given in the design of the screens, providing screening regents and protocols, the generation of custom sgRNA libraries and data-analysis and interpretation of the screening results. We have also provided individual reagents for validation and follow-up.

There is a continued interest in the use of our compound collections for cell-based screening. The majority of compound screening projects made use of our NKI compound screening library of ~2500 compounds representing different collections including the LOPAC collection (1,250 pharmacological active compounds), the NCI diversity and oncology sets, the John Hopkins FDA and foreign approved drugs and bioactive compounds (1,450 compounds) and several enzyme specific collections including kinase, apoptosis, epigenetic modifiers and a collection of protease inhibitors. The NRSC has also offers the Oncode drug repurposing collection of more than 5500 compounds for cell-based screening. NRSC supported the development and optimization of different screening models, performed the screen and provided data analysis for hit selection. In 2021, the NRSC has performed five drug-repurposing screens and provided screen data analysis, data integration and screen interpretation for several others.

We continued to offer two-way and three-way synergy analysis using our digital dispenser and provide different synergy calculations to support the identification of rational drug combinations for more effective cancer treatments.

Laboratory Animal Center

Els Hermans

Head Laboratory Animal Center

Els Hermans DVM MSc PhD Head
Jurriaan Bagmeijer Team leader
Leo Ennen BSc Team leader
Jan Kleinsma Team leader
Hafid Kharmich Team leader
Sin-ming Sit BSc Information manager
Doreen Ram DVM Veterinarian
Mahdi Hamidi DVM PhD Veterinarian
Mijke de Vreij-Kruidenier DVM Veterinarian
Sander Morrien System administrator
Animal caretakers: 25
Logistics employees: 4

NKI aims to make a significant contribution to solving the cancer problem by conducting excellent research of which preclinical in-vivo experiments are an essential part. Thanks to the unique knowledge and expertise, the state-of-the-art facilities and the development and implementation of innovations, the NKI Laboratory Animal Center (LAC) plays an (inter)national leading role in preclinical cancer research with laboratory animals.

Activities

The LAC is a state-of-the-art animal facility housed in a high-tech 8,000 m^2 building fully operational since 2016 with a maximum capacity of 21,000 individually ventilated cages (IVCs) for housing wild-type and genetically engineered rodents. All animals are housed in disposable IVC systems, minimizing the risk of cross-infection, improving ergonomics and obviating the need for a robotics infrastructure for cage-washing. Ultimately, the LAC provides state-of-the-art services to approximately 200 NKI researchers working with rodent models of human cancer as well as a growing number of academic and industrial parties in the Netherlands and abroad.

The LAC consists of five independent microbiological units:

- The T3 breeding unit is dedicated to nucleus- and production breeding of transgenic unique mice strains under specific and opportunistic pathogen free (SOPF) conditions. This unit is only accessible for authorized staff of the animal facility to guarantee a clean and stable health status of the colonies. All mouse lines that are re-derived via caesarian section or embryo transfer, or recovered from frozen sperm or embryos, are imported into this unit.

- The T3 BSL2 unit is a negative barrier area for biosafety-level (BSL) 2 experiments and infection studies. Depending on the infectious agent, mice are housed in IVCs or isolators.

- The T2 unit is a combined experimental and breeding unit where mice are kept under specific pathogen free (SPF) conditions. T2 supports the Animal Model Facility that creates custom-made genetically engineered mouse strains for researchers and performs cryopreservation of mouse strains by freezing sperm or embryos.

- The T1 unit is a negative barrier area that houses the Mouse Cancer Clinic for preclinical imaging and intervention studies. This unit is equipped with small-animal systems for image-guided radiation therapy (IGRT), bioluminescence and fluorescence imaging, MRI, PET-CT, SPECT-CT, and intra-vital imaging.

- The T0 quarantine and sanitation unit is dedicated to importing mice from non-approved vendors or other research facilities. All mice are sanitized either via embryo transfer or caesarian section within a short time frame. Also small-scale ‘dirty’ experiments can be performed here.

A team of 25 animal caretakers and 3 team leaders are responsible for colony management, day-to-day housing and husbandry of the animals including welfare and biotechnical support on T0, T2 and T3. All procedures are designed to minimize a potential import of pathogenic organisms aiming to guarantee the microbiological health status of the different strains in the facility. A dedicated logistics team and two office managers provide general support. An information manager and system administrator are responsible for various laboratory animal-related IT systems and its output towards end users. Three veterinarians supervise the health and welfare of the laboratory animals. They also support the researchers by contributing to the responsible design and implementation of animal experiments and by proposing possible alternatives.

BioImaging Facility

Marjolijn Mertz

Facility manager

Marjolijn Mertz MSc Facility manager
Lenny Brocks PhD Imaging scientist
Bram van den Broek PhD Imaging scientist, BioImaging analyst
Amalie Dick PhD Imaging scientist
Rolf Harkes PhD Imaging scientist, BioImaging analyst

Key publications

Almekinders MMM, Schaapveld M, Thijssen B, et al. Breast adipocyte size associates with ipsilateral invasive breast cancer risk after ductal carcinoma in situ. NPJ Breast Cancer. 2021;7(1):31

Menegakis A, et al. Resistance of hypoxic cells to ionizing radiation Is mediated in part via hypoxia-induced quiescence. Cells. 2021;10(3):610

Hoencamp C, et al. 3D genomics across the tree of life reveals condensin II as a determinant of architecture type. Science. 2021;372(6545):984-989

The BioImaging Facility contributes to state-of-the-art research by providing infrastructure, knowledge and training for image acquisition and analysis using advanced microscopy and software tools. We provide access to a diverse collection of high-end imaging systems from macroscopes to super-resolution microscopes. Our experienced staff with specialized expertise in all stages of the workflow, from experimental design to computational analysis, offers advice and guidance for every step in a bioimaging project.

Rolf Harkes joined our team in August. He works in close collaboration with other scientists on the design and implementation of new workflows. His work covers various aspects of bioimage analysis such as machine learning and deep learning. One key aspect of analysis pipelines is the usability and integration into our data infrastructure.

This year, we added one confocal microscope to the facility: a Leica SP8 from Kees Jalink's group, which is equipped for live cell imaging and Fluorescence Lifetime Imaging (FLIM).
Additionally, we upgraded our fluorescence imaging macroscope with a motorized stage, which now allows multiposition experiments, tile scan overviews and 3D imaging.

The BioImaging Facility is part of the van Leeuwenhoek Centre for Advanced Microscopy, Amsterdam (LCAM), a formal collaboration between three innovative light microscopy centers, located at the University of Amsterdam (UvA), the Academic Medical Centre (AMC) and the Netherlands Cancer Institute (NKI). The BioImaging Facility, together with the Jalink lab and Van Rheenen lab constitute the NKI part of LCAM.

Equipment list

Confocal microscopes	Zeiss 980 Airyscan2
	Leica TCS SP8
	Leica TCS SP8 WLL with FLIM-FCS (live cell)
	Andor Dragonfly Spinning Disk Confocal with TIRF (live cell)
	2x Leica TCS SP5 (1x live cell)
Widefield microscopes	3x Zeiss Observer Z1 (2x live cell)
	Zeiss AxioVert 200M with color camera
	Zeiss Axio ScanZ1 Slidescanner
Macroscope	Zeiss AxioZoom V16 Stereo microscope
Three high-end workstations with image processing & analysis software (Huygens, Imaris, Matlab, Leica LASX en Zeiss Zen)	
HIVE: High Speed Centralized Data Repository	

Annegien Broeks

Head Core Facility Molecular Pathology & Biobanking

Annegien Broeks PhD Head
Maartje Alkemade Technical staff
Linde Braaf Technical staff
Sten Cornelissen Technical staff
Robert Elens Technical staff
Hans Halfwerk Technical staff
Willem Hoefakker Technical staff
Ingrid Hofland Technical staff
Donne Majoor Technical staff
Michiel de Maaker Technical staff
Dennis Peters Technical staff
Joyce Sanders Technical staff
Iris Seignette Technical staff
Shiva Vonk Technical staff
Rens van der Waal Technical staff
Wouter Kievit IT staff
Yush Lam IT staff
Sharon Hinrich Logistics staff
Esther Holman Logistics staff
Jose Overwater Logistics staff

Key publications

Almekinders MMM, Schaapveld M, [...]; Grand Challenge PRECISION Consortium, Desmedt C, Wesseling J. Breast adipocyte size associates with ipsilateral invasive breast cancer risk after ductal carcinoma in situ. NPJ Breast Cancer. 2021;7(1):31

Rozeman EA, Hoefsmit EP, Reijers ILM, [...], Spillane AJ, van Akkooi ACJ, Scolyer RA, Schumacher TNM, Menzies AM, Long GV, Blank CU. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med. 2021;27(2):256-263

Voabil P, de Bruijn M, Roelofsen LM, Hendriks SH, Brokamp S, [...], Haanen JBAG, Schumacher TN, Thommen DS. An ex vivo tumor fragment platform to dissect response to PD-1 blockade in cancer. Nat Med. 2021;27(7):1250-1261

Core Facility Molecular Pathology & Biobanking

The Core Facility Molecular Pathology & Biobanking (CFMPB, founded in 2010) is established to ensure that human biospecimens are used properly and efficiently. The facility provides professional expertise and support regarding medical-ethical and legal issues. The CFMPB coordinates, assists and facilitates all kind of research involving human biospecimens (e.g. serum, blood, ctDNA, FFPE and FF biopsies, DNA & RNA) upon IRB aproval. All CFMPB activities are supported by our web application 'the Application and Request Tool' ART. ART is the online tool for the Institutional Review Board (IRB); study registration (IRBm*aterial*, IRBd*ata* and IRBb*iobank)* and review. Subsequently, ART is the CFMPB LIMS; sample requests, labwork logistics, consent check, track and trace of biospecimens and cost recovery (https://irb.nki.nl/). All the user activities (histology & digital pathology, immunohistochemistry, molecular genetics) are stored in the ART database and by doing so, information about the applications, biospecimen identifiers, succeeding actions and derivatives accumulates and this enriches the data already available.

The CFMPB:

1. Provides full service of FFPE sectioning, frozen sectioning, histochemical stains (HE's), micro/macro dissection of tissue, design and construction of Tissue Micro Arrays (TMA) and slide digitization.

2. Provides a fully equipped and dedicated immunohistochemistry (IHC) lab. All routine IHC is performed using the BenchMark Ultra (Ventana, Roche) automated stainers, in close collaboration with the human diagnostic pathology department (480 antibody protocols available in total of which 370 are in research setting only). Additionally we have 2 Discovery Ultra (Ventana, Roche) automated stainers with a broad array of tissue testing capabilities for developing new IHC protocols, multiplexing (brightfield brown, yellow, purple red and green and fluorescent), RNA scope and FISH.

3. Provides digital pathology; all IHC slides are scanned (P1000 3DHistech) and scored digitally by a pathologist using the Slidescore tool. All data is uploaded in the ART database. The Vectra Polaris scanner (Akoya) is used for multi spectral IF imaging and HALO software (Indica labs) is used for digital image analysis.

4. Provides high quality molecular standards; all DNA and RNA isolations from human (biobank) samples (FFPE, FF, serum, blood etc.) are performed by, or under supervision of, the CFMPB technicians (and in the clinical chemistry department). All samples are handled and stored in our dedicated lab (pre-PCR, QC conditions) under supervision of the coordinating technicians according to standard protocols modified and adapted to the specific requirements per project. A variety of molecular analysis techniques are offered, in close collaboration with the molecular diagnostic department (Sequenom Mass array, PCR, (digital) MLPA, Archer, HPV typing, NGS, Nanostring. Ampliseq, etc.).

In 2020, 73 new material studies started and 621 studies with human biopsecimens were active.

Protein Facility

Patrick Celie

Head Protein Facility

The genes within the DNA encode all the proteins that cells require to stay vital and function properly within a living organism. Proteins are essential molecules involved in almost all biological processes. DNA damage - as occurs in cancer - may cause mutations within genes and hence can lead to generations of dysfunctional proteins. These mutated proteins could become inactive or even hyperactive and cause deregulation of cellular function and growth. To understand the (dys) function of proteins, recombinant proteins can be designed, produced, purified and subsequently be characterized by a variety of functional and structural methods *in vitro*. The Protein Facility provides dedicated equipment, knowledge and experienced personnel to support all these experiments. We offer access to both internal and external academic researchers.

Patrick Celie PhD Head
Alexander Fish PhD Research associate
Danique Ammerlaan Technical staff
Justina Kazokaite PhD Technical staff
John de Widt Technical staff

Key publications

Ahmad MUD, Fish A, Molenaar J, Sreeramulu S, Richter C, Altincekic N, Schwalbe H, Wienk H, Perrakis A. Nano-Differential Scanning Fluorimetry for Screening in Fragment-based Lead Discovery. J Vis Exp. 2021;171: e62469

López-Méndez B, Baron B, Brautigam CA, Jowitt TA, Knauer SH, Uebel S, Williams MA, Sedivy A, Abian O, Abreu C, Adamczyk M, Bal W, Berger S, Buell AK, Carolis C, Daviter T, Fish A, Garcia-Alai M, Guenther C, Hamacek J, Holková J, Houser J, Johnson C, Kelly S, Leech A, Mas C, Matulis D, McLaughlin SH, Montserret R, Nasreddine R, Nehmé R, Nguyen Q, Ortega-Alarcón D, Perez K, Pirc K, Piszczek G, Podobnik M, Rodrigo N, Rokov-Plavec J, Schaefer S, Sharpe T, Southall J, Staunton D, Tavares P, Vanek O, Weyand M, Wu D. Reproducibility and accuracy of microscale thermophoresis in the NanoTemper Monolith: a multi laboratory benchmark study. Eur Biophys J. 2021;50:411-427

Equipment

The facility houses multiple shakers and incubators for protein expression in E. coli, Sf9 insect cells and mammalian cells. Automated chromatography systems are available for purification of proteins at analytical- or preparative scale. Purified proteins can be characterized in terms of purity, stability (Prometheus nanoDSF, Nanotemper), stoichiometry and composition of protein complexes (SEC-MALLS, Wyatt). The facility is equipped with a broad selection of instruments for protein interaction studies including a Biacore T200 SPR (GE Healthcare), VP-ITC (Microcal), Monolith NT.115 MST (Nanotemper), Stopped-Flow system (TgK Scientific), PHERAstar and CLARIOstar (BMG Labtech) plate readers for fluorescent experiments. The facility also supports high throughput protein crystallization screening and optimization using a CyBi-SELMA (CyBio) liquid dispenser, a Mosquito (SPT Labtech) nanoliter drop setter, a Formulator (Formulatrix) for liquid preparation and two RockImager systems (Formulatrix) for storage and automated imaging of crystallization trials at 4 °C and 20 °C.

Projects

The Protein facility has contributed to multiple projects filed by more than 15 research groups within the NKI-AVL. Together these projects covered all facets of the facility, including protein- and antibody production, biophysical characterization and crystallization. At the end of 2020, the facility has become available to the Oncode institute as Proteins4Oncode. This allows research teams to access the facility under the same terms and conditions as for NKI research groups. Several research groups have already made use of this opportunity and some projects are still in progress. About 20% of annual facility time has been spent on external projects, either initiated through direct collaboration or via access through Instruct-ERIC (https://instruct-eric.eu/), a European infrastructure in structural biology which provides access to high-end technology, and through iNEXT-Discovery (Infrastructure for NMR, EM and X-rays for Translational Research; https://inext-discovery.eu/network/inext-d/home), funded by the Horizon-2020 framework program. Due to the COVID-19 restrictions, most of these projects have been executed via remote access, i.e. for external researchers who were not able to visit on-site, projects were exclusively performed by Facility staff.

EU Networks

In addition to the participation in Instruct-ERIC and iNEXT-Discovery networks, the Protein facility is also a member of the P4EU consortium of protein expression facilities in Europe (https://p4eu.org/). This network is crucial to keep up-to-date with the latest developments in protein research and is of great value for the implementation of new methods and technologies. This year, the annual meeting organized in December was again virtual.

Animal Model Facility

Paul Krimpenfort

Head Animal Model Facility

Paul Krimpenfort PhD Head of facility
Fina van de Ahé Technical staff
Rahmen Bin Ali BSc Technical staff
Jolijn ten Hacken Technical staff
Linda Henneman PhD Technical staff
Lona Kroese MSc Technical staff
Colin Pritchard MSc Technical staff
Tanya Vermeeren-Braumuller BSc Technical staff

Key publications

Pulver EM, Mukherjee C, van de Kamp G, Roobol SJ, Rother MB, van der Gulden H, de Bruijn R, Lattanzio MV, van der Burg E, Drenth AP, Verkaik NS, Hahn K, Klarenbeek S, de Korte-Grimmerink R, van de Ven M, Pritchard CEJ, Huijbers IJ, Xia B, van Gent DC, Essers J, van Attikum H, Ray Chaudhuri A, Bouwman P, Jonkers J. A BRCA1 Coiled-Coil Domain Variant Disrupting PALB2 Interaction Promotes the Development of Mammary Tumors and Confers a Targetable Defect in Homologous Recombination Repair. Cancer Res. 2021;81(24):6171-6182

Trabjerg MS, Andersen DC, Huntjens P, Oklinski KE, Bolther L, Hald JL, Baisgaard AE, Mørk K, Warming N, Kullab UB, Kroese LJ, Pritchard CEJ, Huijbers IJ, Nieland JDV. Downregulating carnitine palmitoyl transferase 1 affects disease progression in the SOD1 G93A mouse model of ALS. Commun Biol. 2021;4(1):509

Van den Berk P, Lancini C, Company C, Serresi M, Sanchez-Bailon MP, Hulsman D, Pritchard C, Song JY, Schmitt MJ, Tanger E, Popp O, Mertins P, Huijbers IJ, Jacobs H, van Lohuizen M, Gargiulo G, Citterio E. USP15 Deubiquitinase Safeguards Hematopoiesis and Genome Integrity in Hematopoietic Stem Cells and Leukemia Cells. Cell Rep. 2020;33(13):108533

General services

From 2020 on the Animal Modeling Facility (AMF) operated in the new organizational structure of the Animal Facility. It continued two main activities: 1) the generation of genetically engineered model (GEM) strains and 2) technical support to the cryopreservation and sanitation/revitalization service of the Animal Facility. Despite some initial concerns related to the formality of responsibilities, in practice both activities are being performed smoothly in close collaboration and prioritizing consultation with the teams on T2 and T3.

In 2021, the AMF finished 17 GEM strains and was developing 22 projects also including ES cell derivation and modification and virus production. As in 2020 most GEM strategies were based on CRISPR/Cas technology but now aiming at increasingly more complex modifications.
Due to the implementation of the NKI policy related to the reduction of animals 'bred but not used' the number of strains subjected to cryopreservation and consequently revitalization has significantly increased. In total, the AMF and the T2/T3 units performed 5 embryo freezing, 45 sperm cryopreservation (including quality control) and 10 sanitation/revitalization sessions.

Recent developments

The success rate of CRISPR/Cas strategies using zygotes is quite unpredictable meaning that the generation of many GEM strains is carried out on a trial and error 'basis' requiring many animals and expenses. To prevent this, the actual generation of modified animals is now often proceeded by validating the modification strategy by initial genotyping of blastocysts derived from CRISPR/Cas manipulated zygotes especially in case of background strains less efficient in embryo transfer procedures.
The application of cancer models carrying multiple mutant alleles based on germline modification will remain time and mice consuming as this requires multiple breeding steps. In contrast, somatic modelling technologies enables the swift and direct set up of experimental cohorts of any preferred background (GEMs, immune compromised, etc.) These technologies include the use of lentiviral transduction and 'in vivo' tissue electroporation, both enabling somatic CRISPR/Cas mediated gene modification and tissue specific transgene expression. The AMF has set up a pipeline for the generation and production of lentiviral vector systems to support these strategies. Also, the first somatic electroporation procedures are being set up for various tissues with a priority on abdominal tissues.
A new item in the service package of the AMF is the derivation and subsequent modification of ES cell cultures for initial 'in vitro' studies and possible subsequent GEM model generation.
An important and challenging aim of the AMF is the extension of generating GEMs to the rat. For many research questions the rat is a better animal model than the mouse, e.g. for physiological, metabolic and neurological studies and for the development of bio-imaging technologies. The AMF is now setting up the necessary genetic modification and embryological procedures for the rat.

Logistics

To improve the logistics of the AMF's production line the quality of commercially available frozen embryos have been tested in several experimental conditions. The commercial source would be an excellent alternative, especially in the case of the rat. So far however, commercially obtained embryos did not fulfil the requirements needed for efficient GEM model generation. For generating GEMs in the rat, the AMF is now concentrating first on testing genetic modification strategies on rat embryos obtained in house by similar procedures as for the mouse.
Two technological improvements have been introduced in the running operational procedures: 1) Electroporation of zygotes both 'in vitro' and directly 'in vivo' (oviductal) is being applied to introduce subtle gene modifications, either inactivating INDELs or small insertions. 2) The efficiency IVF can be significantly improved or by treating isolated oocytes by zona permeabilization procedures, especially ultra-sound targeted drilling.

Research High-Performance Computing facility

Robbie Joosten

Head Structural Biology

Daniel Vis

Head Computational Biology

Robbie Joosten PhD Head
Daniel Vis PhD Head
Ismail Koraichi BSc Systems engineer
Torben Wriedt MSc Systems engineer
Anastassis Perrakis PhD Scientific supervisor
Lodewyk Wessels PhD Scientific supervisor

The Research High-Performance Computing (RHPC) facility deploys, maintains a secure High-Performance Computing solution for research groups and facilities within the NKI. The RHPC facility takes care of the technical details so that the research groups can focus on the science.

In 2021, we upgraded the operating system of all our computational cancer biology and bioinformatics branch servers. We purchased and installed several new CPU servers for research groups. We also increased the available network storage space for individual groups and backups.

To meet the growing compute and storage requirements of our structural biology and GPU computing users, we installed a new cluster management and job scheduling system for our cryo-EM and Oncode GPU servers and upgraded the internal storage of existing machines. We also acquired and installed a new storage server to capture the data generated with the NKI's electron microscope.
We also welcomed Jonas Teuwen, leading the new Artificial Intelligence (AI) research group, for whom we installed servers with new GPUs models as well as attached network storage.

Further upgrades at the RHPC facility include:
- We implemented a lot of new web content (for example, ShinyApp server, HiGlass, websites supporting publications).
- We facilitated the purchase of a new server for the Protein facility and deployed it.
- We extended the local disk capacity for several group-owned servers.
- We have onboarded a new set of users to Google Cloud Platform (GCP) to work with data from the national sequencing initiative run by the Hartwig Medical Foundation (HMF).

We ensure the facility's security by adhering to best practices and undergo external security audits in active collaboration with our Institute's information security officers (ISOs). Due to the increasingly complex security and privacy requirements, we have regular risk assessment meetings with the ISOs next to the existing schedule of security management meetings.
The facility now has 262 active users on 65 servers with around 1384 CPUs, 9.5 TB of RAM, and 3.143 PB of storage. The GPU-branch consists of more than 72 GPUs, 32 of which are available to Oncode users, while another few are dedicated to cryo-electron microscopy.
A selection of the scientific output by the facility's users as papers is highlighted here. In addition, RHPC hosts scientific output and data repositories, for instance, the AlphaFill.eu databank of AlphaFold structures annotated with their co-factors, ions, and ligands.

Key publications

De Vries I, et al. New restraints and validation approaches for nucleic acid structures in PDB-REDO. Acta Crystallogr D Struct Biol. 2021;77(Pt 9):1127-1141

Mourragui MC, et al. Predicting patient response with models trained on cell lines and patient derived xenografts by non-linear transfer learning. PNAS 2021;118(49):e2106682118

Schep R, et al. Impact of chromatin context on Cas9-induced DNA double-strand break repair pathway balance. Mol Cell. 2021;81(10):2216-2230.e10

Genomics Core Facility

Roderick Beijersbergen

Head Genomics Core Facility (from 1-10-2021)

Ron Kerkhoven

Head Genomics Core Facility (until 1-10-2021)

Roderick Beijersbergen PhD Head (from 1-10-2021)
Ron Kerkhoven PhD Head (until 1-10-2021)
Marja Nieuwland MSc Wet-lab team leader
Arno Velds MSc Bioinformatic team leader
Roel Kluin MSc Bioinformatic staff
Iris de Rink MSc Bioinformatic staff
Shan Baban MSc Technical staff
Wim Brugman MSc Technical staff
Charlaine van Steenis MSc Technical staff
Jessica Sieljes MSc Technical staff
Sacha Schepers Technical staff

The Genomics Core Facility (GCF) provides services, expertise and analysis for genomics research. The GCF runs high-end, up-to-date sequencing platforms including a MiSeq, a NextSeq550Dx, a NovaSeq6000 and the Oxford Nanopore system. In 2021, we continued to expand on our capabilities to perform single cell sequencing using our Chromium10x platform and gained experience with the Visium Spatial gene expression platform. The facility continued to be involved in the development and implementation of new technologies and innovative sequencing applications through collaboration with research groups within the institute. We have expanded our bioinformatics platforms including capacity for analysis of 10x chromium data.

In 2021, we handled 380 projects for more than a hundred individual researchers. Despite the challenges with the ongoing Covid pandemic, we succeeded to maintain our throughput to a level similar to 2019 and 2020. The work performed by the GCF in 2021 included workflows for RNAseq, CHIPseq, CNVseq, Exome sequencing, single cell 3' and 5' RNA seq and TCR seq. These projects included almost 4000 samples with the majority for Poly A+ RNA sequencing and copy number variation analysis. We handled almost 180 samples on our 10x Chromium single cell analysis platform. Around 50% of our projects consist of ready to sequence libraries generated by the individual research groups. For these projects, we perform QC and quantification for optimal flow-cell density. All 2021 projects resulted in a total of 225 runs on our different sequencing platforms, including 40 runs on our new NovaSeq6000 system. In 2021 we already observed a strong decrease in the use of the HiSeq2500 system as result of the replacement of this system by the NovaSeq6000 from January 2022 onwards.

The know-how and expertise of the GCF contributes to the development and improvement of sequencing methods and strategies including know-how on multiplexing strategies including the use of "dark cycles", multiple sequence primers, incorporation of barcodes or custom indices. We have experience in working with poor quality DNA, RNA and small amounts of input material (1-10 ng RNA), using e.g. Smart-seq2. In the coming year we will continue to expand our capabilities on single cell sequencing, spatial transcriptomics, plate-seq, massive parallel sequencing using combinatorial indexing (SCI-seq) and ImmunoSEQ technology.

Data generated by our sequencing machines is stored centrally and secured at the NKI-IT department in the GCF database. Users receive links to primary data files (FASTQ) and have the choice to perform data analysis on their own or to collaborate with the bioinformatics staff of the GCF for more in-depth analysis.

Experimental Animal Pathology

Sjoerd Klarenbeek

Head Experimental Animal Pathology

Sjoerd Klarenbeek Pathologist
Ji-Ying Song Pathologist
Lex de Vrije Technical staff
Ela Razavi Technical staff
Ellen Riem Technical staff
Jelrik van der Meer Technical staff
Chayenne van Duijn Technical staff

The Experimental Animal Pathology facility provides broad pathology support for research projects involving the use of animals. Our technicians process and embed tissues, organoids and cells, make sections (including cryosections), and perform a wide range of techniques such as routine histology staining, histochemistry, and immunohistochemistry. This year, many new protocols have been developed and optimized for immunohistochemistry, which we added to our long list of antibodies available for immunohistochemistry for epitopes of mouse, rat, or human origin. In addition, we provide a new service to researchers: upon request, we scan the slides for digital pathology analysis and image sharing and archiving.

Our pathologists collaborate with many scientists and play an active role in their projects, train and educate personnel, help to perform dissections, and provide detailed microscopic analysis of pathologic changes not only in tumor tissue but also in all organs. The pathologists perform histopathology phenotyping of new mouse models of diseases, therapeutic evaluation of translational medicine, as well as diagnostic pathology of sick animals. We contribute content for presentations and publications, and pathologic findings can play a pivotal role in scientific projects, discovering and validating important aspects of the pathogenesis and dynamics of disease.

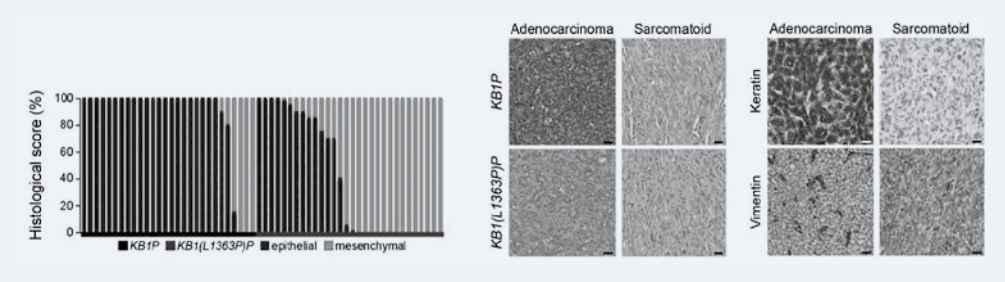
As an example, we studied the effects of a genetic variant of uncertain clinical significance (VUS) of the tumor suppressor BRCA1, with a mutation in the coiled-coil domain (*L1363P*). We found that this VUS disrupted interaction with PALB2 and led to embryonic lethality. *Keratin14-Cre*-driven tissue-specific mutation in the mammary gland contributed to tumor formation, but with a different histopathologic profile compared with BRCA1 loss, leading to more sarcomatoid features indicative of epithelial-to-mesenchymal transition (EMT, see illustration below) and a more stable DNA copy number profile, while the tumors were deficient in homologous recombination repair (HRR) and responsive to cisplatin and PARP inhibition.

Key publications

Aslam MA, Alemdehy MF, Kwesi-Maliepaard EM, Muhaimin FI, Caganova M, Pardieck IN, van den Brand T, van Welsem T, de Rink I, Song JY, de Wit E, Arens R, Jacobs H, van Leeuwen F. Histone methyltransferase DOT1L controls state-specific identity during B cell differentiation. EMBO Rep. 2021;22(2):e51184

Pulver EM, Mukherjee C, van de Kamp G, Roobol SJ, Rother MB, van der Gulden H, de Bruijn R, Lattanzio MV, van der Burg E, Drenth AP, Verkaik NS, Hahn K, Klarenbeek S, de Korte-Grimmerink R, van de Ven M, Pritchard CEJ, Huijbers IJ, Xia B, van Gent DC, Essers J, van Attikum H, Ray Chaudhuri A, Bouwman P, Jonkers J. A BRCA1 coiled-coil domain variant disrupting PALB2 interaction promotes the development of mammary tumors and confers a targetable defect in homologous recombination repair. Cancer Res. 2021;canres.1415.2021

Van den Berk P, Lancini C, Company C, Serresi M, Sanchez-Bailon MP, Hulsman D, Pritchard C, Song JY, Schmitt MJ, Tanger E, Popp O, Mertins P, Huijbers IJ, Jacobs H, van Lohuizen M, Gargiulo G, Citterio E. USP15 Deubiquitinase Safeguards Hematopoiesis and Genome Integrity in Hematopoietic Stem Cells and Leukemia Cells. Cell Rep. 2020;33(13):108533



Histopathological characterization of mammary tumors. Hematoxylin and eosin stains reveal morphologic differences with higher occurrence of sarcomatoid/mesenchymal-like tumor morphology, confirmed with low expression of keratin and high expression of vimentin. (For the complete publication and color images see Pulver *et al.* Cancer Research, 2021)

Flow Cytometry Facility

Martijn van Baalen

Head Flow Cytometry Facility

The Flow Cytometry Facility provides access to high-end conventional and full spectrum flow cytometers and state-of-the-art cell-sorting equipment. We actively support researchers of the NKI with tailored advice and practical assistance in all phases of their experiments with regard to analytical flow cytometry and cell sorting.

The Flow Cytometry Facility maintains seven analytical flow cytometers for basic and high-parameter interrogation of biological samples on a single cell level, and five high-end cell sorters for isolation of the cells of interest. All instruments are housed in BSL 2 lab environment. We are responsible for interactions with instrument manufacturers to schedule routine maintenance and unexpected repairs. Furthermore, Quality Assurance and Quality Control are routinely performed to ensure consistent and robust performance. The available equipment provides flexibility and allows for tailored approaches to address a wide range of scientific problems and biological questions.

Our full cell sorting service by expert sort operators allows for bulk isolation and (indexed) single cell sorting of specific cell subsets from heterogeneous samples, based on scatter parameters up to complex immunological panels with 18 fluorescent labels, for a wide range of post-isolation applications. Some examples of post bulk sorting applications are: *in vitro* expansion and functional assays; *in vivo* transplantation; protein, DNA and RNA extraction for applications such as mass spectrometry, sequencing for genetic screens and mRNA expression respectively. Common post-sort single cell applications include: cloning; DamID assays; qPCR; and sequencing.

We strive to meet the researcher's specific needs by providing tailored assistance with experimental design, sample preparation, data acquisition and analysis, enabling the highest possible resolution, data quality and reproducibility. We provide introductory courses to allow independent use of the available analytical instruments and to ensure a high level of theoretical knowledge, optimal instrument use, and data quality. Additionally, we provide introductory and advanced training sessions on theoretical and technical topics related to flow cytometry, and independent operation of cell sorting instruments. We also organize specialized workshops and seminars on topics such as tumor dissociation and other sample preparation methods, optimizing protocols for staining of intracellular targets, and data analysis methods.

Finally, we are actively involved in (inter)national and virtual cytometry networks and instrument user groups to exchange knowledge with colleagues from the wider community, and allow investigators of the NKI to benefit from the latest developments and insights in the field of cytometry.

Martijn van Baalen Head
Frank van Diepen Operator
Anita Pfauth Operator
Guido de Roo Operator

Key publications

Bhowmick D, van Diepen F, Pfauth A, Tissier R, Ratliff ML. A gain and dynamic range independent index to quantify spillover spread to aid panel design in flow cytometry. Sci Rep. 2021;11(1):20553

Lei X, Palomero J, de Rink I, de Wit T, van Baalen M, Xiao Y, Borst J. Flagellin/TLR5 stimulate myeloid progenitors to enter lung tissue and to locally differentiate into macrophages. Front Immunol. 2021;12:621665

Van der Leun AM, Hoekstra ME, Reinalda L, Scheele CLGJ, Toebes M, van de Graaff MJ, Chen LYY, Li H, Bercovich A, Lubling Y, David E, Thommen DS, Tanay A, van Rheenen J, Amit I, van Kasteren SI, Schumacher TN. Single-cell analysis of regions of interest (SCARI) using a photosensitive tag. Nat Chem Biol. 2021;17(11):1139-1147

Mouse Cancer Clinic / Animal Facility T1

Marieke van de Ven

Head Mouse Cancer Clinic / Animal Facility T1

Marieke van de Ven PhD Head T1
Olaf van Tellingen Head of Pharmacology Facility
Ben van de Graaff Team leader Animal Facility T1
Natalie Proost BSc Project coordinator
Niels de Wit BSc Project coordinator
Milo van Batenburg Technical staff
Manon Boeije BSc Technical staff
Artur Burylo Technical staff
Nadia Florijn BSc Technical staff
Ashley Pascual BSc Technical staff
Marloes Nulle BSc Technical staff
Bjørn Siteur Technical staff
Justin Sprengers BSc Technical staff
Ien Verheij BSc Technical staff
Seven animal caretakers

Key publications

Calandrini C, et al. Organoid-based drug screening reveals neddylation as therapeutic target for malignant rhabdoid tumors Cell Rep 2021;36(8):109568

Chakrabarty S, et al. Microfluidic cancer-on-chip platform for prediction of drug response using organotypic tumor slice culture. Cancer Res. 2021

Dias MP, Tripathi V,van der Heijden I, Cong K, Manolika E-M, Bhin J, Gogola E, Galanos P, Annunziato S, Lieftink C, Andújar-Sánchez M, Chakrabarty S, Smith GCM, van de Ven M, Beijersbergen RL, Bartkova J, Rottenberg S, Cantor S, Bartek J, Chaudhuri AR, Jonkers J. Loss of Nuclear DNA Ligase III Reverts PARP Inhibitor Resistance in BRCA1/53BP1 Double-deficient Cells by Exposing ssDNA Gaps. Mol Cell. 2021;81(22):4692-4708

Activities

The Mouse Cancer Clinic / T1 is a facility where advanced mouse models are used as surrogate for cancer patients to identify and validate targets that can be exploited by anti-cancer therapy. The Mouse Cancer Clinic is composed of an intervention unit, a preclinical imaging facility and a Bio-Pharmacy Unit working together in close collaboration with research groups at the NKI, other academic partners and pharmaceutical companies. The main objective is to find and test novel anti-cancer treatments, using the advanced cancer models, such as transgenic (spontaneous) mouse models, orthotopic transplantation models, human xenograft models that have been developed/established at the NKI.

The knowledge of the molecular pathology of cancer cells is rapidly expanding and this now helps to design interventions that specifically interfere in the critical steps that drive cancer cells. This holds the promise of generating more efficacious therapies with fewer side effects. In order to more accurately translate preclinical studies to clinical outcome, it is essential to use cancer models that faithfully recapitulate the human disease. Moreover, when the treatment involves testing of new agents, it is necessary to consider the pharmacokinetic behavior of the experimental drugs in relation to their pharmacodynamics effects (target inhibition), especially since species-differences in pharmacokinetics of drugs is a potentially confounding factor. Obviously, it is not very useful when a drug demonstrates pre-clinical efficacy only at a dose level that results in plasma concentrations that cannot be achieved in patients. Therefore, we include the collection of data on plasma exposure (C_{max} and AUC, half-life) of test compounds in these intervention studies.

With the knowledge on pharmacokinetic behavior being established, an intervention study using one of our advanced mouse models can be designed guided by novel insights from basic research and clinical demands. Various approaches to treat cancer with classical chemotherapy, molecularly targeted agents, immuno-modulators, radiotherapy or combinations thereof are currently ongoing. In addition to systemically administered agents, we are also investigating loco-regional applications of drugs, surgery and radiation. The pre-clinical Intervention Unit can take care of the whole trajectory of preclinical trial design and execution, including support in the design/setup of the study, design suitable drug formulations, planning and execution of treatments, follow-up of tumor growth and/or metastasis formation, assessment of therapy response, collection of tissues and reporting of data. The longitudinal follow-up of tumors is greatly facilitated by dedicated state-of-the-art small animal imaging systems, including SPECT/CT, PET/CT and 7T MRI. Local and precise radiation beams can be delivered using the new image-guided radiation therapy system for small animals. The lab of the bio-pharmacy unit is equipped with analytical instruments (LC-MS/MS, LC-UV/PDA, LC-FD and GFAAS) to execute bioanalytical assays.

This year the Mouse Cancer Clinic carried out around 135 projects for more than 10 groups inside the NKI. 27 of the projects were for external academic customers and 24 for small pharmaceutical companies.

Next to that the Imaging Facility made approximately 4.000 scans in 2021. Approximately 45% of these scans were made by the personnel of the Imaging Unit in 2020, the remaining 55% was made by technicians or researchers themselves provided with support from the Imaging Unit. Also the first MRI scans on rats and the first F19 MRI images of phantoms were made. Last but not least, 2021 was the year a new irradiator was installed on T1 that has a smart planning software to make even more accurate radiation therapy possible.

Biostatistics Centre

Renee Menezes

Head Biostatistics Centre

At the Biostatistics Centre, 2021 has been a very busy year. After our new group was completed in the Autumn of 2020, the focus during much of 2021 has been on putting together a flexible and transparent way of working, as well as increasing the centre's visibility to other researchers.

With remote working, doing reproducible research has become even more important. Researchers welcomed the use of dynamic reports for making analyses much more transparent, even during online meetings. All analyses can be easily rerun, by us or by others, so studies with similar questions and data can easily benefit from previous work.

The two courses we organize, Introduction to R and Medical Statistics with R, were in high demand. In these courses, we also teach principles of reproducible research, including how to produce dynamic reports. Due to restrictions in group sizes, we have offered them twice in 2021. Having taken care of the long waiting list of interested participants, we are looking forward to a less intensive course schedule in 2022.

To help us stay in touch, a group in TEAMS of NKI R users has been set up. Members can ask, and help each other with, simple questions about statistics or R. There are channels dedicated to the HPC, to working on the MDW and to Tutorials. Via the latter, we disseminate knowledge about tools and analyses. We have short presentations about making R packages and about the principles of reproducible research. This group is for all in the institute to use. Here we have also placed the guidelines for making colour-blind friendly figures. This virtual meeting point has come to stay, as a repository and a way of communicating within our large institute, regardless of what the new way of working becomes.

Renee X Menezes PhD Head
Leyla Azarang PhD Biostatistician
Renaud Tissier PhD Biostatistician

Key publications

Azarang L and Giorgi R. Estimation of covariate effects on net survivals in the relative survival progressive illness-death model. Statistical Methods in Medical Research. 2021; 30:1538-53

Khelil M, Griffin H, Bleeker MCG, Steenbergen RDM, Zheng K, Saunders-Wood T, Samuels S, Rotman J, Vos W, van den Akker BE, Menezes RX, Kenter GG, Doorbar J, Jordanova ES. Delta-like ligand-Notch1 signalling is selectively modulated by HPV16 E6 to promote squamous cell proliferation and correlates with cervical cancer prognosis. Cancer Res. 2021;81:1909-21

Rafael TS, de Vries HM, Ottenhof SR, Hofland I, Broeks A, de Jong J, Bekers E, Horenblas S, Menezes RX, Jordanoa ES and Brouwer OR. Distinct patterns of myeloid cell infiltration in patients with hrHPV-positive and hrHPV-negative penile squamous cell carcinoma: The importance of assessing myeloid cell densities within the spatial context of the tumor. Front Immunol. 2021;12:682030

Education in oncology

The Netherlands Cancer Institute offers a variety of opportunities for practical and theoretical training to (trainee) technicians, University Master students, PhD students and Post-doctoral Fellows. Research and clinical staff and their group members are involved in theoretical and practical training. Many staff members have joint appointments as professors at Dutch universities and even more contribute to the regular curriculum at various universities. The research divisions attract students from universities throughout the Netherlands. The NKI has a formal affiliation with the Science Faculty of the University of Amsterdam (UvA) and is committed to make a contribution to Master student teaching. The institute participates in the Oncology Graduate School Amsterdam, together with the medical faculties of the Amsterdam UMC. All educational activities are supervised by the Teaching Committee, which consists of Roderick Beijersbergen (chair and dean Master students), Hein te Riele (general affairs and dean PhD students), Fred van Leeuwen (dean Post-docs), Wilbert Zwart (HLO students).

MASTER STUDENTS

The program in Experimental Oncology attracts Master students of national and international universities. Students generally have a background in (Medical) Biology, Health Sciences, Chemistry, Pharmacology, Medicine, or Psychology. The program offers combined practical and theoretical training in various aspects of experimental oncology. Practical training includes participation in ongoing research projects for a minimum of 4 months.

In 2021, 63 Dutch university Master students completed a placement of 6-10 months at the biomedical research divisions. The students came primarily from the Amsterdam UMC (35), but also from other universities inside (25) and outside The Netherlands (3). The institute also provides practical training opportunities for Bachelor students of the HLO (Universities of Applied Science, 12), who stay for similar periods of time as the university students and like these, often make significant contributions to research progress of the PhD students and Postfdocs who supervise them.
The core element of theoretical training is the master course Experimental Oncology (Table 1). This master course is a compulsory course for Amsterdam UMC Master students in Biomedical Sciences, track Oncology. It is also offered as an elective to master students who do an internship at the NKI or follow a master program in a biomedical area at a Dutch university. Other interested parties such as PhD students are welcome to attend the lectures as listener upon enrollment as attendee. The master course has an interactive program consisting of tutorials, student assignments, presentations, and discussions. Assignments included a study on the history of the development, potential biomarkers, adverse effects, mechanisms of resistance and drug improvements of a targeted therapy currently in clinical use, a study of an outstanding question in oncology covering latest developments and technologies and the design and writing of a research proposal. Assignments were concluded with a written assay, a presentation or a pitch talk.

TABLE 1
COURSE IN EXPERIMENTAL ONCOLOGY

LECTURES	
Epidemiology	F van Leeuwen
Radiotherapy	M de Jong
Clinical trials	M Sousan
Next generation sequencing	R Beijersbergen, A Velds
Early diagnostics	B Carvalho, R Fijneman
Hormone regulated cancers	W Zwart, A Bergman, H Horlings
DNA damage and repair	J Jansen (LUMC), M Tijsterman (LUMC)
Aneuploidy and cancer	J Raaijmakers
DNA damage and repair radiotherapy	C Vens
Telomerase and cancer	J Jacobs
Chromosome morphogenesis	B Rowland
Epigenetics in cancer	E de Wit, Fr van Leeuwen
Cancer genomics	L Wessels
Targeted Therapy	R Beijersbergen
Functional genomics	T Brummelkamp
Novel strategies in targeted therapy	R Bernards
Mouse models of cancer	J Jonkers
Non-coding landscape and cancer	R Agami
RNA translation and the ribosome	W Faller
Protein structure and design	T Sixma
Tumor microenvironment	K de Visser
Macrophages in the microenvironment	L Akkari
T cell function and dysfunction in tumor control	D Thommen
TCR and neoantigens	W Scheper
CAR-T-therapy	M Themeli (AUMC)
Targeted therapy in melanoma	D Peeper

PHD STUDENTS

PhD students at the NKI-AVL participate in the Oncology Graduate School Amsterdam (OOA), an alliance of the oncology research divisions of the NKI-AVL and the Amsterdam UMC. The number of PhD students has been rising rapidly in the past years. In 2021, the institute had 416 PhD students registered at the OOA; 39 NKI-AVL students defended a PhD thesis at a Dutch university.

In 2021, we have introduced a new format of the OOA Training and Supervision program that helps students to select courses and activities and keep track of their progress to achieve 30 ECTS. The OOA course program includes in-depth courses on different topics in cancer research, but also technical courses such as English writing, biostatistics and -informatics, microscopy and animal handling. Students with an insufficient background in cancer research can attend the course Experimental Oncology for Master students or the course Basic Oncology for PhD students. Besides joining interdepartmental work discussions, the students have the opportunity to attend meet-the-expert lunch sessions with international experts invited at the Friday morning seminar program. Twice during their PhD trajectory, students participate in the annual retreat (Table 2).

Once a year, each PhD student meets with their advisory committee to evaluate the progress of research. Each committee has independent members from within and outside the division. The committee discusses progress with the supervisor and the student jointly and separately. At the more elaborate midterm review after 2 years, the likelihood of achieving a PhD within a reasonable time frame is discussed. This meeting can be used to redefine goals if necessary.

TABLE 2.

OOA COURSE PROGRAM 2021

36 educational activities throughout 2021

765 course participants

4.1 average evaluation rate (1-5 point scale)

COURSE	ECTS	STUDENTS	COURSE LEADERS	RATING
Basic Microscopy (2x)	1.5	34	J Belien, L Brocks, A Dick, M Mertz, E Reits, N van der Wel (AUMC/NKI)	4.2
Basic Oncology	3.0	70	M Bijlsma, N van Grieken, R van de Ven (AUMC)	3.8
BioBusiness	3.0	14	J van Beijnum, A Griffioen, E Huijbers (AUMC)	4.5
CRISPR genome editing	2.5	40	R Beijersbergen, R Leite de Olivera, R Wolthuis (AUMC/NKI)	4.1
Ethics and Integrity – NKI edition (13x)	2.0	236	P Borst, M Schmidt, B van Steensel (NKI)	3.6
Ethics and Integrity – Amsterdam UMC edition (4x)	2.0	72	A Griffioen, M Spaargaren, E Ruhé (AUMC)	3.9
Genetic engineering in model organisms	1.5	18	L Daxinger, P Hohenstein, H te Riele, E Robanus Maandag (LUMC/NKI)	4.3
Histopathology human tumors	0.6	42	N Donner (AUMC)	4.2
ImageJ/Fiji (2x)	0.6	43	B van der Broek, M Mertz (NKI)	4.3
Indesign Thesis Printing	0.1	43	N Nijhuis (Gildeprint)	3.4
2x Introduction to R (2x)	1.2	30	L Azarang, R de Menezes, R Tissier (NKI)	4.3
Medical Statistics with R (2x)	1.5	30	L Azarang, R de Menezes, R Tissier (NKI)	4.3
Mouse morphology, Genetics & Function	1.5	20	J Seppen, V Christoffels (AUMC)	4.1
Writing a scientific article (4x)	1.0	80	A Griffioen, H te Riele, E Ruhé (AUMC/NKI)	4.1

Unfortunately, due to COVID-19 measures, also in 2021 our annual PhD student retreat had to be cancelled. Normally, the retreat provides an excellent opportunity for PhD students to train their presentation and interaction skills as it is entirely focused on the research of the graduate students themselves, presented and discussed in poster sessions and oral presentations. Importantly, students are in charge of chairing sessions, monitoring discussions and selecting prizewinners for the best posters and presentations. By mixing basic and clinical research, we hope to stimulate translational interactions, bottom-up research and collaborations between the Amsterdam oncology centers.

Senior PhD students can participate in a joint retreat with other cancer institutes in Europe, including:
- The CRUK Institutes (Cambridge, Glasgow, London, Manchester and Oxford)
- The Institute of Cancer Research (ICR)
- German Cancer Research Center (DKFZ)
- The Max Delbruck Center for Molecular Medicine (MDC)
- The Netherlands Cancer Institute (NKI)
- The European School of Molecular Medicine (SEMM: IFOM-IEO)

This retreat gives students the opportunity to become acquainted with oncology centers of excellence throughout Europe. Unfortunately, also this event had to be cancelled in 2021.

The NKI-AVL has a highly active PhD student council composed of representatives of each research division. In 2021 the council has installed task forces focusing on mental health support for PhD students and the organization of an alternative OOA retreat.

Based on the outcome of a mental health survey among PhD students, a support structure for PhD students was developed that will include the installment of intervision groups, with or without professional guidance. To help new students to find their way, the council has composed a comprehensive "Starter Package" containing a wealth of useful information. As an alternative for the traditional 3-day OOA retreat, the council organized a 1-day event at the Cobra museum Amstelveen. Due to surging COVID-19 cases at the end of the year, this event had to be postponed and will now take place in May 2022.

POSTDOCS

In 2021, the NKI-AVL hosted approximately 173 Postdocs & 27 senior Postdoctoral Fellows, almost half of which are from abroad and with equal gender representation. The Postdocs at the NKI are represented by a very active postdoc committee (postdocs@nki). They organize workshops and special events such as (alumni) career development seminars and workshops about intellectual property and entrepreneurship. In addition, they regularly bring issues that matter to Postdocs and others to the attention of NKI management.

The postdoc committee is also actively involved in the NKI Postdoc Career Development Program that is offered by the NKI to all its Postdocs. This program has been developed together with AVL Academy and the postdoc dean. The goals of the program are to provide Postdocs with the tools to take charge of their professional and personal development at the NKI, to promote maximum achievement of Postdocs at the NKI, and to prepare them for the next steps in their careers.

The Basic Postdoc Program includes lively interactions among the participants, and informal chats with one of the PIs and René Medema.

The program, which is tailored to NKI Postdocs, consists of special workshops of ~ 12 participants given by professional trainers but with input and active participation of NKI group leaders. The trainers all have a background in science and are fluent in English. The program is flexible and adjusted every year based on the evaluations of the workshops and suggestions from the Postdocs. Due to the COVID-19 pandemic several workshops in 2021 were held online and for meetings in person the number of participants per group was reduced.

During their first year at the NKI, Postdocs participate in a basic program, which consists of three one-day workshops. The basic program is mandatory for new NKI Postdocs. In 2021, 40 Postdocs participated in the basic program (3 groups).

NKI Basic Postdoc Career Development Program 2021

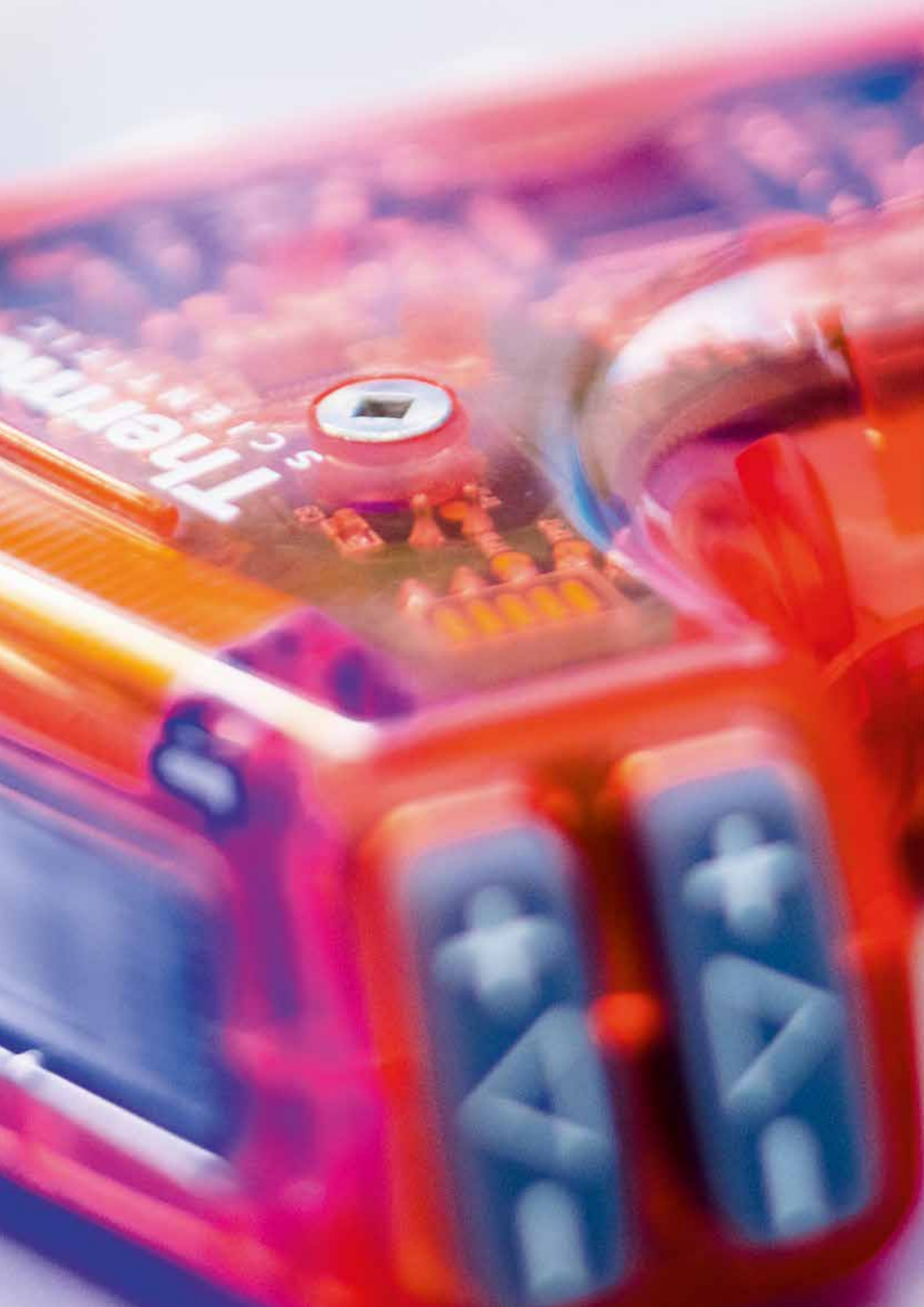
Day 1. Personal effectiveness: time and project management
Day 2. Communication & cooperation
Day 3. Creating your future, take ownership

The Basic Postdoc Program includes lively interactions among the participants, and informal chats with one of the PIs and The Director of Research.

All Postdocs that have completed the basic program are invited in subsequent years to follow one of the one-day workshops as part of the Advanced Postdoc Career Development Program. In 2021, 56 Postdocs participated in a workshop of the advanced program.

NKI Advanced Postdoc Career Development Program 2021

- Energy and balance as powerful tools to increase your impact at work – Evaluation: 9,4
- Grant Writing – Evaluation: 9,3
- Influencing group dynamics – Evaluation: 8
- Packaging your research into an elevator pitch for successful interviews, grant applications, and publications – Evaluation: 9
- Giving effective presentations – Evaluation: 9



Clinical trials

ALL SITES

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
B09BIO (biobank)	NKI-AVL biobank - patienten	Daan van den Broek	Biobank	22/1/2010
B18NCI (N-CIA)	The Netherlands facility for Cancer-Immune Analysis (N-CIA) 25-2-2019: studying the immune landscape of tumors.	John Haanen	Biobank	22/5/2019
B21PBL	Onderzoek van het afweersysteem en kanker met bloed	John Haanen	Biobank	27/07/2021
B21QAS	Quantification of anti-SARS-CoV-2 antibodies in human serum with LC-QTOF-MS	Alwin Huitema	other	27/07/2021
C19CDP	post trial access programma M14CDP	Neeltje Steeghs	other	08/01/2020
C19FAP	post trial access programma M15FAP (FAP IL-2v)	Neeltje Steeghs	other	08/01/2020
C19LOX (LIBRETTO-201)	Expanded Access Program LOXO-292	Sjaak Burgers	other	4/6/2019 (20/12/2021)
C20ERD	patient access program voor erdafitinib	Michiel van der Heijden	other	13/02/2020
C20LAR	Early Access Program (EAP) Larotrectinib (CBG goedgekeurd CUP programma) voor patiënten met solide tumoren die een neurotrofe tyosinereceptorkinase (NTRK) genfusie vertonen.	André Bergman	other	16/07/2020
C20PAZ	Free of Charge program pazopanib	Winette van der Graaf	other	14/8/2020 (17/12/2021)
E1620	Development of a module to supplement the EORTC Core instrument for the assessment of Health Related Quality of Life in Adolescents and Young Adults (AYAs) aged 14-39 years with cancer	Olga Husson	other	15/06/2021
M09NIB	The NIB-Cohort study, therapeutic drug monitoring of tyrosine kinase inhibitors	Neeltje Steeghs	other	09/06/2009
M11PCT (CPCT-02)	Development of a platform for next-generation DNA sequencing based personalized treatment for cancer patients : protocol to obtain biopsies from patients with metastatic cancer (CPCT-02 biopsy protocol)	Neeltje Steeghs	other	24/01/2012
M12SEN (senior)	observational study to evaluate pharmacokinetics and pharmacodynamics of docetaxel,paclitaxel, doxorubicine, gemcitabine, vinorelbine and capecitabine in elderly patients	Neeltje Steeghs	other	13/09/2012
M14CIP (CIP-study)	Cancer in Pregnancy (CIP-study)	Christianne Lok	other	17/02/2015
M14MCL	A Phase I Study of MCLA-128, a Human IgG1 Bispecific Antibody Targeting HER2 and HER3, in Patients with Solid Tumours	Frans Opdam	Phase I/II	11/03/2015
M15DRU (DRUP)	A National Study to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile; The Drug Rediscovery Protocol (DRUP trial)	Emile Voest	Phase I	25/07/2016
M15FAP (BP29842)	An open-label, multicenter, dose-escalation, Phase I study to evaluate safety, pharmacokinetics, and therapeutic activity of RO6874281, an immunocytokine consisting of interleukin 2 variant (IL-2v) targeting fibroblast activation protein-α (FAP), in patients with advanced and/or metastatic solid tumors	Neeltje Steeghs	Phase I	18/12/2015 (13/1/2021)
M15KEY (KEYNOTE 158)	A clinical trial of Pembrolizumab (MK-3475) evaluating predictive biomarkers in subjects with advanced solid tumors (KEYNOTE 158)	Marloes van Dongen	Phase II	29/02/2016

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M15PRM (PRMT5i)	A phase I, open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3326595 in subjects with solid tumors and non-Hodgkin's lymphoma.	Frans Opdam	Phase I	27/10/2016
M16BAN	A Phase 1/2a Study of BMS-986179 Administered in Combination with Nivolumab (BMS-936558, anti-PD-1 Monoclonal Antibody) in Advanced Solid Tumors	Neeltje Steeghs	Phase I/II	2/9/2016 (4/1/2022)
M16GAC (Induce-1)	A Phase I Open Label study of GSK3359609 administered alone and in combination with anticancer agents in subjects with selected advanced solid tumors <font color = RED> (only COHORT 1B open)	Frans Opdam	Phase I	30/05/2017
M16LAG	A phase 1/2a dose escalation and cohort expansion study of the safety, tolerability, and efficacy of anti-LAG-3 monoclonal antibody (BMS-986016) administered alone and in combination with anti-PD-1 monoclonal antibody (Nivolumab, BMS-936558) in advanced solid tumors	Sofie Wilgenhof	Phase I/II	6/12/2016 (1/8/2021)
M16MOL (MEDIOLA)	A phase I/II study of MEDI4736 (anti-PD-L1 Antibody) in combination with Olaparib (PARP inhibitor) in patients with advanced solid tumors	Neeltje Steeghs	Phase I/II	01/09/2016
M16NFC	Multicenter study evaluating the hybrid approach using a novel fluorescence camera – Identifying the value of intraoperative fluorescence imaging during sentinel node biopsy procedures	Simon Horenblas	Phase II	09/11/2017
M16STT (STARTRK-2)	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROS1 or ALK gene rearrangements. (STARTRK-2) <font color = RED> (arm 'NSCLC ROS1 Basket' is closed. 'NTRK1/2/3 (evaluable basket only: NSCLC, MCRC, small solid tumors)' and 'ROS1 (evaluable basket only: MCRC, small solid tumors' are open)'	Egbert Smit	Phase II	24/08/2016
M17CAR (CAR-B)	Cognitieve Outcome after WBRT or SRS in Patients with Brain Metastases	Terry Wiersma	Phase III	11/03/2020
M17CIP	INCIP fertility substudy	Christianne Lok	other	25/04/2019
M17LET	An open-label, multi-center, roll-over study to assess long term safety of lenvatinib monotherapy or lenvatinib combination regimen or comparator treatment arm to cancer patients in Eisai sponsored lenvatinib trials	Marloes van Dongen	Phase II	15/08/2018
M17MPE	A Phase 1 Study of MK-5890 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors	Marloes van Dongen	Phase I	15/05/2018
M17PCV	A phase Ia/Ib open-label, dose-escalation study of the safety and pharmacokinetics of RO7198457 as a single agent and in Ccombination with Atezolizumab in patients with locally advanced or metastatic tumors	Neeltje Steeghs	Phase I	4/10/2018 (3/8/2021)
M17TDM	Therapeutic drug monitoring for oral anti-cancer drugs	Neeltje Steeghs	other	09/08/2017
M18AXL	First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (HuMax®-AXL-ADC) in patients with solid tumors	Christian Blank	Phase I	21/1/2019 (17/12/2021)
M18BOB	Basket of Baskets: A modular, open-label, phase II, multicentre study to evaluate targeted agents in molecularly selected populations with advanced solid tumours	Frans Opdam	Phase II	08/02/2019
M18BRM	A phase I drug-drug interactions study between Brigatinib and the CYP3A substrate Midazolam in patients with ALK-postive or ROS1-postive solid tumors	Egbert Smit	Phase I	13/6/2019 (7/9/2021)
M18FLH (FLUYT-Prevent)	Fluid Hydration to prevent: Post-ERCP Pancreatitis: FLUYT-Prevent. A randomized, superiority multicenter trial	Thomas Wijkerslooth	Phase III	04/02/2019
M18GSK	A Phase I First Time in Human Open Label Study of GSK3745417 administered with and without Anticancer Agents in Participants with Selected Advanced Solid Tumors	Neeltje Steeghs	Phase I	31/10/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18IWO (i-WORC)	internet-based Work-related cognitive Rehabilitation for Cancer survivors: a randomised controlled trial (i-WORC studie)	Sanne Schagen	Phase III	08/03/2019
M18SPX (SPHINX)	Endoscopic sphincterotomy before fully covered self-expandable metal stent placement for malignant extrahepatic biliary obstruction to prevent pancreatitis: a randomised controlled trial (Sphinx)	Thomas Wijkerslooth	other	28/02/2019
M18TMB (CheckMate 848)	A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H) (CheckMate 848: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 848)	Neeltje Steeghs	Phase II	14/1/2019 (21/1/2021)
M18TNO	An open-label, multi-center, phase I, dose finding study of oral TNO155 in adult patients with advanced solid tumors	Neeltje Steeghs	Phase I	13/02/2019
M19ALP (Alpe2U)	Improving the safety of fluoropyrimidine-based chemotherapy by combined DPYD genotype-guided and DPD phenotype-guided dose-individualization.	Annemieke Cats	other	14/08/2019
M19CPE (CICILIA)	A first-in-human, open-label, dose escaltion followed by dose expansion phase I/IIa trial to evaluate the safety, prelimenary efficacy and pharmacokinetics of intratumoral CyPep-1 in patients with advanced solid tumors.	Frans Opdam	Phase I/II	28/01/2020
M19EBP	A sequential 2-arm, Open-label Phase 1 Study to evaluate the effects of Encorafenib in combination with Binimetinib on the Pharmacokinetics of Losartan, Midazolam, Caffeine, Omeprazole, and Dextromethorphan administered in a cocktail approach and on the Pharmacokinetics of Rosuvastatin in patients with BRAF V600-mutant unresectable or metastatic Melanoma or other advanced solid tumors	Frans Opdam	Phase I	23/06/2020
M19ING (Actuate 1801)	Actuate 1801: Phase 1/2 study of 9-ING-41, a glycogen synthase kinase-3 beta (GSK-3β) inhibitor, as a single agent and combined with chemotherapy, in patients with refractory hematologic malignancies or solid tumors.	Neeltje Steeghs	Phase I/II	16/06/2020
M19INT	Phase I/Ib open-label, multiple ascending dose, First-in-Human Study, to investigate the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of INT-1B3 in Patients with Advanced Solid Tumors.	Frans Opdam	Phase I	12/01/2021
M19MCL	A phase I, open-label, Dose-Escalation, Safety, tolerability, and preliminary Efficacy study of MCL-145 in participants with advanced or metastatic malignancies	Marloes van Dongen	Phase I	03/05/2021
M19MOM (MOMENTUM)	The MOMENTUM study – The Multiple Outcome Evaluation of Radiation Therapy using the MR-Linac.	Marlies Nowee	other	27/03/2019
M19OVC (OnVaCT)	Realizing better doctor-patient dialogue about choices in palliative care and early phase clinical trial participation.	Neeltje Steeghs	other	10/07/2019
M19PCC (PROSPECT)	HOPE FOR THE BEST, PREPARE FOR THE WORST: Towards a better understanding of unawareness of prognosis in advanced cancer patients	Sjaak Burgers	other	23/7/2019 (11/5/2021)
M19PSC (PERISCOPE)	Klinische waarde van perfusie MRI bij gliomen en hersenuitzaaiingen: PERISCOPE project	Dieta Brandsma	other	09/11/2020
M19RET	A phase I/II study with Highly-selective RET inhibitor, BLU-667, in patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and other advanced solid tumors <font color=RED> (only cohort 5 open)	Joop de Langen	Phase I/II	21/1/2020 (11/1/2022)
M19SFV	Phase I/II pharmacokinetic multi-tumor study of subcutaneous formulation of nivolumab monotherapy	Marloes van Dongen	Phase I/II	01/05/2019
M19STR (STAR22)	CYP3A4*22 genotype-guided dosing of TKI's in cancer patients: a new way of personalized therapy (STAR22 / STER22 / STAR 22 / STER 22).	Neeltje Steeghs	Phase IV	07/06/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M19TCF	Long Term Follow-Up of Participants Exposed to GSK3377794 (NY-ESO-1c259 T), a Genetically Engineered NY-ESO-1 Specific T Cell Receptor	John Haanen	other	27/08/2020
M19TCS (IGNYTE-ESO)	Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered NY-ESO-1-Specific (c259) T Cells, alone or in combination withother agents, in HLA-A2+ Participants with NY-ESO-1 and/or LAGE-1a Positive Solid Tumors (IGNYTE-ESO)	John Haanen	other	22/07/2020
M19TRI	A phase 1/2, open-label, multi-center, first-in-human-study of the safety, tolerability,pharmacokinetics, and anti-tumor activity of TPX-0005 in patients with advancedsolid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements (TRIDENT-1)	Joop de Langen	Phase I/II	29/04/2020
M19VAY (SURVAYA)	Health-related quality of life and late effects among SURVivors of cancer in Adolescence and Young Adulthood: The SURVAYA study'	Winette van der Graaf	other	8/1/2020 (17/12/2021)
M19WVE (WAVE)	An open-label, multi-center, global study to evaluate long term safety and efficacy in patients who are receiving or who previously received Durvalumab in other protocols (WAVE)	Paul Baas	Phase IV	06/04/2020
M20CBT (POTENTIA)	A Phase 1 Open-Label, Dose Escalation and Expansion Trial to Investigate the Safety, Pharmacokinetics and Pharmacodynamics of CB307, a Trispecific Humabody® T-cell Enhancer, in Patients with PSMA+ Advanced and/or Metastatic Solid Tumours. (POTENTIA)	Frans Opdam	Phase I	24/12/2021
M20CLD	Phase 1/2a, first-in-human, open-label, dose escalation trial with expansion cohorts to evaluate safety and preliminary efficacy of CLDN6 CAR-T with or without CLDN6 RNA-LPX in patients with CLDN6-positive relapsed or refractory advanced solid tumors	John Haanen	Phase I/II	16/09/2020
M20COM (COMPRAYA)	COMPRehensive assessment of prevalence, risk factors and mechanisms of impaired medical and psychosocial health outcomes among Adolescents and Young Adults with cancer: the COMPRAYA study	Winette van der Graaf	other	17/11/2020
M20DRA (Drug Access)	A Dutch National Study to Facilitate Patient Access to Novel Anti-cancer Drugs Awaiting regulatory approval or reimbursement – The DRUG access Protocol	Emile Voest	Phase II	10/09/2020
M20EUR (EURO RELAX)	The impact of deep versus standard muscle relaxation on intra-operative safety during laparoscopic surgery: a multicenter strategy study – EURO RELAX STUDY	Suzanne Broens	other	28/09/2020
M20FCO	AN OPEN-LABEL, MULTICENTER, PHASE IB STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY ANTI-TUMOR ACTIVITY OF RO7122290, A FIBROBLAST ACTIVATION PROTEIN-A (FAP) TARGETED 4-1BB LIGAND (CD137L), IN COMBINATION WITH CIBISATAMAB WITH OBINUTUZUMAB PRE-TREATMENT, IN PARTICIPANTS WITH PREVIOUSLY TREATED, METASTATIC, MICROSATELLITESTABLE COLORECTAL ADENOCARCINOMA WITH HIGH CEACAMCEACA5 EXPRESSION	Marloes van Dongen	Phase I	20/04/2021
M20FUT	A phase 2 study of Futibatinib in patients with specific FGFR aberrations (TAS-120)	Frans Opdam	Phase II	15/12/2020
M20IVY (INVAYA)	Adolescents and Young Adults (AYA) living with life-limiting cancer: The INVAYA study	Winette van der Graaf	other	09/09/2020
M20JDQ	A phase Ib/II open-label, multi-center dose escalation study of JDQ443 in patients with advanced solid tumors harboring the KRAS G12C mutation.	Neeltje Steeghs	Phase I/II	29/04/2021
M20MAA	Phase 1/2a Study of Monoclonal Antibody BMS-986218 Monotherapy and in Combination With Nivolumab in Patients With Advanced Solid Tumors	Marloes van Dongen	Phase I/II	24/02/2021
M20MED (MEDI5752)	A Phase 1, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability Pharmacokinetics Immunogenicity, and Antitumor Activity of MEDI5752 in Subjects with Advanced Solid Tumors	Marloes van Dongen	Phase I	09/09/2020

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M20NOW (DPYD-NOW)	A prospective, multicenter, observational study to identify novel deleterious variants in the DPYD gene in patients of non-Western descent: The DPYD-NOW study	Annemieke Cats	other	24/08/2020
M20PMB	A multicenter, open label, phase III extension trial to study the long-term safety and efficacy in participants with advanced tumors who are currently on treatment or in follow up in a Pembrolizumab trial	Paul Baas	Phase III	10/08/2020
M20QSU (QLQ-SURV100)	Phase 3B Research ProtocolL: a Delphi study and pretesting to finalize the provisional survivorship core questionnaire (QLQ-SURV100)	Lonneke van de Poll-Franse	Phase III	5/8/2020 (27/12/2021)
M20RCA	An open label, multicenter, dose escalation and extension, phase 1A/1B study to evaluate safety, pharmacokinetics, and therapeutic activity of RO7284775, a PD-1 targeted IL-2 variant (IL-2V) immunocytokine, alone or in combination with atezolizumab in participants with advanced and/or metastatic solid tumors	Neeltje Steeghs	Phase I	18/05/2020
M20TAB	A Phase 1 First-in-Human Study with ABBV-155 Alone and in Combination with Taxane Therapy in Adults with Relapsed and/or Refractory Solid Tumors	Egbert Smit	Phase I	26/01/2021
M20TDX (DESTINY-PanTumor02)	A Phase II, multicenter, open-label study to evaluate the efficacy and safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the treatment of selected HER2 Expressing Tumors.(DESTINY-PanTumor02)	Neeltje Steeghs	Phase II	14/04/2021
M20VOI (VOICE)	Vaccination against cOvid In CancEr (VOICE)	John Haanen	other	19/02/2021
M20XMA	A PHASE Ia/Ib, OPEN-LABEL, MULTICENTER, GLOBAL, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF XmAb24306 AS A SINGLE AGENT AND IN COMBINATION WITH ATEZOLIZUMAB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS	Neeltje Steeghs	Phase I	12/05/2021
M21AET	Master Protocol to Assess the Safety and Recommended Phase 2 Dose of Next Generations of Autologous Enhanced NY-ESO-1/ LAGE-1a TCR Engineered Tcells, alone or in combination with other agents, in Participants with Advanced Tumors.	John Haanen	other	15/11/2021
M21BIM	An open label, Phase I dose escalation trial, with dose confirmation and expansion, of BI 1810631 as monotherapy in patients with advanced or metastatic solid tumors with HER2 aberrations.	Frans Opdam	Phase I	11/08/2021
M21BTR	A phase 1a/b, open-label, dose-escalation study of the safety and pharmacokinetics of BTRC4017A administered intravenously as a single agent and in combination with Trastuzumab in patients with locally advanced or metastatic HER2-expressing cancers	Marloes van Dongen	Phase I	13/12/2021
M21GDC	A phase I dose-escalation and dose-expansion study evaluating the safety, pharmcokinetics, and activity of GDC-6036 in patients with advanced or metastatic solid tumors with a KRAS G12C mutation.	Marloes van Dongen	Phase I	14/09/2021
M21MPA	A phase 1, first-in-human, multicenter, open-label, dose-escalation study to characterize the safety and tolerability of MP0317 in patients with relapsed/ refractory advanced solid tumors	Neeltje Steeghs	Phase I	14/12/2021
M21SAR	Open-label, multi-cohort, Phase 2 trial, evaluating the efficacy and safety of SAR408701 in patients with CEACAM5-positive advanced solid tumors	Marloes van Dongen	Phase II	04/08/2021
M21SCC (SEC)	Socio-economic consequences of cancer care, a patient perspective (SEC trial)	Wim van Harten	other	28/04/2021
M21STP (STEPS)	SusTained Employability in cancer Patients and their partnerS (STEPS)	Iris van der Ploeg	other	15/10/2021

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M21VIP	multicenter, open-label, phase 2 basket study of MK-7684A, a co-formation of Vibostolimab (MK-7684) with Pembrolizumab (MK-3475), with or without other anticancer therapies in participants with selected solid tumors	Marloes van Dongen	Phase II	06/12/2021
N14CCT	Phase I pharmacological study of continuous and intermittent chronomodulated capecitabine therapy	Serena Marchetti	Phase I	18/06/2014
N15LDC	The effect of prehydration on the pharmacokinetics of low-dose Cisplatin	Wouter Vogel	Phase IV	06/11/2015
N16LND (TALENT)	Targeted Abdominal Lymph nodE dissections randomized for surgical NavigaTion (TALENT)	Theo Ruers	other	25/01/2017
N16PDA	Validation of Pharmacokinetic Assays for determination of Nivolumab and Pembrolizumab concentrations in serum	Serena Marchetti	other	16/01/2017
N16UMB (UMBRELLA-I)	MR-sequence optimization and Workflow development for treatment guidance, using the integrated MR scanner of the MR Linac system. Towards MR guided Adaptive Radiation Therapy. (UMBRELLA)	Marlies Nowee	other	26/04/2017
N17SAN	studie naar immunotherapie voor de behandeling van kankerpatienten	Koen Hartemink	other	16/01/2019
N18BREL (UMBRELLA -2)	The MR-Linac Technical Feasibility Protocol For Development of MR-guided Adaptive Radiation Therapy	Marlies Nowee	other	26/09/2018
N18MRC	Development of MRCAT: electron density maps for radiotherapy dose calculations from MR images as alternative for planning CT scans	Abrahim Al-Mamgani	other	21/03/2018
N18POR	Comparison of preoperative and intraoperative image registration using an ultrasound-based navigation system during liver surgery.	Theo Ruers	other	28/06/2019
N18TIME	Idle time scanning on the MR-linac	Marlies Nowee	other	07/03/2019
N18ULN	Ultrasound-based navigation during liver surgery	Theo Ruers	Phase I	10/08/2018
N18WGS (WIDE)	WGS implementation in standard care Diagnostics for Each cancer patient (WIDE)	Gerrit Meijer	other	10/4/2019 (19/1/2021)
N19PPG	Photo plethysmography for in vivo perfusion imaging	Theo Ruers	other	21/01/2020
N20ADC	Pharmacokinetics of (Fos)Aprepitant, Dexamethasone and their Interaction in Patients with Chemotherapy Induced Nausea and Vomiting: A Pilot Study	Neeltje Steeghs	other	10/03/2021
N20COV	Onderzoek naar de invloed van het coronavirus op de (na)zorg en het welbevinden van kankerpatiënten	Lonneke van de Poll-Franse	other	16/4/2020 (27/12/2021)
N20CYM	Phenotyping study of the CYP3A4 activity in patients with prostate cancer versus patients with other types of solid tumours with oral midazolam	Frans Opdam	other	10/02/2021
N20STE (STEP-IN)	STart Exercising, keeP exercisINg	Martijn Stuiver	other	09/02/2021
N20TUS	Tracked ultrasound for patient registration in surgical navigation during abdominal cancer surgery	Theo Ruers	Pilot	28/05/2020
N21LND	Image-guided navigation during robotic lymph node removal	Theo Ruers	other	10/11/2021
N21VUR	Intra-operative pelvic vessel acquisition, towards ultrasound registration for surgical navigation	Theo Ruers	other	29/11/2021

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
BIOBANK				
B15CTD	Circulating tumor DNA in cancer patients: development of a clinical diagnostic tests and establishment of a biobank	Winan van Houdt	Biobank	07/10/2015
B15HHC	Analyse van weefsel van patienten met een tumor in het hoofd-halsgebied.	Lotje Zuur	Biobank	03/09/2015
B15IMM	Longitudinal tumor and blood sampling in patients with advanced stage urothelial cancer of the bladder for the analysis of mechanisms of response to immunotherapy.	Michiel van der Heijden	Biobank	07/10/2015
B15OES (Together)	Tissue sampling of oesophagogastric cancer to enable tailored therapies (TOGETHER study)	Johanna van Sandick	Biobank	17/06/2015
B16BBC	Melanoma transcriptome protocol; Blood collection NETest	Margot Tesselaar	Biobank	14/4/2016 (30/8/2021)
B16BHW	Blood sampling of healthy women and early stage breast cancer patients	Jelle Wesseling	Biobank	11/07/2016
B16CLM	Determining the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients with suspicion of leptomenigual matastases	Dieta Brandsma	Biobank	19/09/2017
B16IMM	Biobank Immunotherapy baseline samples	Huub van Rossum	Biobank	03/10/2016
B16MEL	Understanding tumor immune escape in patients with stage III melanoma	Alex van Akkooi	Biobank	28/08/2017
B16NBC	Tissue and blood sampling to find predictive markers for neoadjuvant chemotherapy benefit in breast cancer – Neoadjuvant Therapy Breast Cancer Biobank	Gabe Sonke	Biobank	27/06/2016
B16PON	Paired healthy & tumor organoid Biobank (adenomas)	Emile Voest	Biobank	14/07/2016
B16TGT	Translational Gastrointestinal Oncology – tissue	Gerrit Meijer	Biobank	14/07/2016
B17PRE (PRECISION)	Prevent Ductal Carcinoma In Situ Invasive Overtreatment Now	Jelle Wesseling	Biobank	28/11/2017
B18UBC	Longitudinal tumor, urine and blood sampling in patients with urinary tract cancer treated with chemotherapy	Michiel van der Heijden	Biobank	15/10/2018
B20ARC (ARCHIPELAGO)	Archipelago of Ovarian Cancer Research	Christianne Lok	other	21/09/2020
B20CDH	Biobank of gastric tissue and organoids from patients with a germline CDH-1 mutation.	Jolanda van Dieren	Biobank	21/06/2021
BRAIN / CNS				
M19IPA (IPAX-1)	A multi-centre, open label, single arm, dose-finding phase I/II study to evaluate safety, tolerability, dosing schedule, and preliminary efficacy of carrier-added 4-L-[131I]iodo-phenylalanine ([131I]I-IPA), administered as a single or repetitive injections in patients with recurrent glioblastoma multiforme (GBM), concomitantly to 2nd line external radiation therapy (XRT) – IPAX-1	Wouter Vogel	Phase I/II	15/7/2019 (9/7/2021)
M19PSC (PERISCOPE)	Klinische waarde van perfusie MRI bij gliomen en hersenuitzaaiingen: PERISCOPE project	Dieta Brandsma	other	09/11/2020

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
BREAST				
B21BCB	Blood and tissue sampling to find biomarkers for early diagnosis and individualizing treatment in breast cancer	Gabe Sonke	Biobank	02/12/2021
C18OLA	Compassionate use programma olaparib CAPSULES. (Betreft N=1 free of charge programma voor patiënten die reeds zijn ingesteld op CAPSULES)	Frans Opdam	other	25/03/2020
C19OLA	Compassionate use Olaparib (N=1 programma)	Carolien Smorenburg	other	10/12/2019 (4/1/2022)
C20ALP	CBG goedgekeurd CU programma alpelisib	Carolien Smorenburg	other	20/07/2020
C20NIR	Compassionate use Niraparib (Free of charge programma).	Serena Marchetti	other	05/03/2020
C21TDX	Trastuzumab deruxtecan in Her2+ metastasized breast cancer patients after one or more anti-HER 2 treatment schedules	Gabe Sonke	other	27/07/2021
C21TUC	Tucatinib combined with trastuzumab and capecitabine in patients with HER-2 positive, locally advanced or metastasized breast cancer who have had at least 2 previous anti HER-2 treatment schedules.	Gabe Sonke	other	27/07/2021
E155O (MINDACTRelapses)	Dissecting the pathways of endocrine and chemotherapy resistance in breast cancer:A translational research project of the EORTC 10041/BIG 3-04 MINDACT clinical trial.	Emiel Rutgers	other	12/05/2021
E1617	Follow-up in early and locally advanced breast cancer patients	Frederieke van Duijnhoven	other	10/06/2020
M05BRI (BRIGHT)	Long term risk of breast cancer following treatment of Hodgkin's disease	Nicola Russell	other	5/1/2006 (27/12/2021)
M12DEN (DENSE)	Early detection of breast cancer in women with dense breasts (DENSE study)	Claudette Loo	other	19/9/2012 (16/12/2021)
M12SSU (TESTBREAST)	Detectie van onstekingsgeassocieerde eiwitprofielen in het serum, speeksel en urine van patienten met mammatumoren	Emiel Rutgers	other	17/4/2012 (22/12/2021)
M13TNB (TRIPLE-B)	Biomarker discovery randomized phase IIb trial with Carboplatin-Cyclophosphamide versus Paclitaxel with or without Atezolizumab as first-line treatment in advanced triple negative breast cancer	Sabine Linn	Phase II	09/07/2013
M14ABC (ABC)	A feasibility study of niraparib for advanced, BRCA1-like, HER2-negative breast cancer patients: the ABC study	Sabine Linn	Phase II	15/1/2018 (20/1/2021)
M14CNB (BOOG 2013-08)	Clinically node negative breast cancer patients undergoing breast conserving therapy: Sentinel lymph node procedure versus follow-up. A Dutch randomized controlled multicentre trial.	Frederieke van Duijnhoven	Phase III	14/9/2016 (10/1/2022)
M14HAR (HARBOR)	Identifying subgroups with high cardiovascular risk in breast cancer survivors (HARBOR)	Floor van Leeuwen	other	13/04/2015
M14POS (POSEIDON)	Phase I/prospective randomized phase II trial Of the Safety and Efficacy of tamoxifen in combination with the Isoform selective Pi3K inhibitor GDC-0032 compared with tamoxifen alONe in hormone receptor positive, HER2 negative, metastatic breast cancer patients with prior exposure to endocrine treatment (POSEIDON trial)	Sabine Linn	Phase I/II	31/10/2014
M15PAP (PAPBI-2)	Pre- versus Postoperative Accelerated Partial Breast Irradiation in early stage breast cancer patients, A randomized phase III trial (PAPBI-2)	Astrid Scholten	Phase III	17/08/2016

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M16BRC (SUBITO)	Substantially improving the cure rate of highrisk BRCA1-like breast cancer patients with personalized therapy (SUBITO) an international randomized phase III trial	Sabine Linn	Phase III	13/10/2016
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Neeltje Steeghs	Phase I	1/11/2016 (4/1/2022)
M17GEL (GELATO)	AssessinG Efficacy of carboplatin and ATezOlizumab in metastatic Lobular breast cancer: GELATO-trial	Marleen Kok	Phase I/II	06/10/2017
M17PRP (precise)	Discovery of prognostic molecular markers (PRECiSE)	Gabe Sonke	other	22/08/2017
M17SJA (SONIA)	Endocrine therapy plus CDK 4/6 inhibition in first or second line for hormone receptor positive advanced breast cancer. (SONIA studie)	Gabe Sonke	Phase III	9/11/2017 (9/9/2021)
M17TOP (TOP-1)	Tailored treatment in Older Patients (TOP-1): Omission of radiotherapy in elderly patients with low risk breast cancer	Marie Jeanne Vrancken Peeters	other	28/02/2018
M18BEL (BELLINI)	Pre-operative phase II trial for breast cancer with nivolumab in combination with novel IO (BELLINI trial)	Marleen Kok	Phase II	22/07/2019
M18CYP	Effect of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib	Neeltje Steeghs	Phase IV	13/2/2019 (24/9/2021)
M18HAR (HARMony)	favorable and unfavorable effects of risk-reducing salpingo-oophorectomy (RRSO) in women with a high genetic risk of ovarian cancer" Verkorte titel: HARMOny	Floor van Leeuwen	other	12/09/2018
M18LBC (NEOLBC)	Tailoring Neoadjuvant therapy in hormone receptor positive, HER2 negative, luminal breast cancer (NEOLBC)	Sabine Linn	Phase II	15/11/2018 (26/3/2021)
M18LORD (E1401)	Management of low grade ductal carcinoma in situ (low-grade DCIS): a randomized, multicenter, non-inferiority trial, standard therapy versus active surveillance (voorheen E1401)	Jelle Wesseling	Phase III	02/02/2017
M18TRD (TRAIN-3)	Image-guided de-escalation of systemic neoadjuvant treatment in HER2-positive breast cancer: the TRAIN-3 study	Gabe Sonke	Phase II	15/2/2019 (16/3/2021)
M19CAD	Phase Ib, multicenter, open-label dose escalation and expansion platform study of select immunotherapy combinations in adult patients with triple negative breast cancer	Neeltje Steeghs	Phase I	23/5/2019 (11/5/2021)
M19CON (CONTROL DCIS)	Ipsilateral invasive breast cancer-free rate at 10 years; A prospective non-randomized comparison observational study of screen-detected low-risk DCIS between active surveillance and conventional treatment. CONventional Treatment Or Leave DCIS (CONTROL DCIS)	Jelle Wesseling	other	31/10/2019 (27/12/2021)
M19EFF (EFFECT)	EFFECT, Effects of structured and individualized exercise in patients with metastatic breast cancer on fatigue and quality of life	Martijn Stuiver	other	13/02/2020
M19IMM	Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in subjects with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) who have failed at least two prior chemotherapy regimens	Sabine Linn	Phase III	20/02/2020
M19PER (perspective)	PERSPECTIVEs of patients on exercise interventions after the diagnosis of metastasized breast cancer: the PERSPECTIVE study	Martijn Stuiver	other	12/12/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M20DST (DESTINY-Breast06)	A Phase 3, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting (DESTINY-Breast06).	Vincent Dezentjé	Phase III	16/07/2021
M20HRC (HER2CLIMB-02)	Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer (HER2CLIMB-02)	Gabe Sonke	Phase III	29/09/2021
M20MIM (MINIMAX)	Minimal invasive axillary staging and treatment after neoadjuvant systemic therapy (NST) in node positive breast cancer (MINIMAX): a Dutch multicenter observational study to gain insight in less and more invasive axillary staging and treatment in relation to oncologic safety and quality of life (QoL) to develop evidence-based guideline.	Marie Jeanne Vrancken Peeters	other	14/01/2021
M20NVP	A Randomized, Multicenter, Double-blind, Placebo-controlled Phase 3 Study of Nivolumab Versus Placebo in Combination With Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in Patients With High-risk, Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Primary Breast Cancer.	Marleen Kok	Phase III	06/10/2020
M21AMA (AMAZONE)	Prevention of Persistent Pain after Breast Cancer Treatment by web-based Cognitive Behavioural Therapy	Iris van der Ploeg	other	11/06/2021
M21KNB (KEYNOTE-B49)	A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the Treatment of Chemotherapy-Candidate Hormone Receptor-Positive, Human Epidermal Growth FactoReceptor 2-Negative (HR+/HER2-) Locally Recurrent Inoperable or Metastatic Breast Cancer (KEYNOTE-B49)	Marleen Kok	Phase III	08/12/2021
M21MBM	Development of a module to supplement the EORTC QLQ-C30 in the assessment of Health Related Quality of Life in patients with Metastatic Breast Cancer.	Frederieke van Duijnhoven	Phase I-III	14/09/2021
N08AFT (AFTER)	A randomized prospective trial of 2-6 weeks pre-operative hormonal treatment for hormone receptor positive breast cancer: Anastrozole +/- fulvestrant or tamoxifen exposure - response in molecular profile (AFTER-study)	Sabine Linn	Phase II	04/08/2008
N12OLG (OLIGO)	High-dose alkylating chemotherapy in oligo-metastatic breast cancer harboring homologous recombination deficiency	Gabe Sonke	Phase III	03/07/2012
N16MIC (MICRA)	MICRA study: Minimally Invasive Complete Response Assessment of the breast after neoadjuvant chemotherapy	Marie Jeanne Vrancken Peeters	other	06/04/2016
N18CPB	Ervaren beperkingen ten gevolge chronische pijn na borstkanker: een kwalitatieve studie naar het perspectief van de patiënt	Kirsten Nienhuys	other	25/4/2018 (28/12/2021)
N19ASC (ASICS)	Avoiding Sentinel lymph node biopsyselect clinically node negative breast cancer patients after neoadjuvant systemic therapy	Marie Jeanne Vrancken Peeters	other	22/01/2020
N19BOR (BORSpec19)	Using optical spectroscopy for the detection of positive resection margins for invasive ductal carcinoma and ductal carcinoma in situ during breast conserving surgery (BORSpec19)	Theo Ruers	other	19/08/2020
N19MIM (MIMOSA)	Monalizumab and trastuzumab In Metastatic HER2-pOSitive breAst cancer: MIMOSA-trial	Marleen Kok	Phase II	16/07/2020
N19NEO	Quality of life experience after neoadjuvant chemotherapy in HER2-positive breast cancer patients: a focus group study	Gabe Sonke	other	09/03/2020

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N19TON (TONIC-2)	Immune induction strategies to improve response to immune checkpoint blockade in triple-negative breast cancer (TNBC) patients: the TONIC-2 trial.	Marleen Kok	other	13/02/2020
N20CBC	Interviewing patients and oncology specialists on the design and use of PredictCBC, a contralateral breast cancer risk prediction model	Marjanka Schmidt	other	20/2/2020 (27/12/2021)
N20ESP (ESP)	Ultrasound-guided erector spinae plane block versus paravertebral block in breast cancer patients undergoing mastectomy with immediate reconstruction – a non-inferiority trial. A single-centre randomized controlled non-inferiority trial with a parallel group design. – the ESP study		other	09/06/2021
N21LBB	Evaluation of a liquid biopsy biomarker to predict the response to whole brain radiotherapy (WBRT) in patients with brain metastasis.	Dieta Brandsma	other	30/8/2021 (3/11/2021)
N21MBR (EMBRACE)	WEight Management for BReAst CancEr (EMBRACE)	Martijn Stuiver	other	11/03/2021

GASTRO INTESTINAL

C14GIST	prospectieve registratie GIST patienten	Neeltje Steeghs	other	13/01/2014
C20ENC	Free of Charge program encorafenib	Frans Opdam	other	06/07/2020
C20MSI	Medical Need Program first line MSI-H metastasized colorectal cancer	Myriam Chalabi	other	09/11/2020
C20RIP	EXPANDED ACCESS PROGRAM FOR RIPRETINIB IN PATIENTS WITH LOCALLY ADVANCED UNRESECTABLE OR METASTATIC GIST WHO HAVE RECEIVED TREATMENT WITH PRIOR THERAPIES	Neeltje Steeghs	other	14/12/2020
E1560	EORTC ILOC study: Phase II of immunotherapy plus local tumor ablation (RFA or stereotactic radiotherapy) in patients with colorectal cancer liver metastases	Theo Ruers	Phase II	18/1/2019 (9/3/2021)
M09OCB	A pilot evaluating response to induction chemotherapy with oxaliplatin, capecitabine and bevacizumab in patients with extensive peritoneal carcinomatosis of colorectar origin	Arend Aalbers	Pilot	25/03/2010
M13ORC (ORCHESTRA)	A randomized multicenter clinical trial for patients with multi-organ, colorectal cancer metastases comparing the combination of chemotherapy and maximal tumor debulking versus chemotherapy alone (ORCHESTRA)	Cecile Grootscholten	Phase III	09/06/2015
M14CR5 (CAIRO-5)	Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases - CAIRO5 - a randomised phase 3 study of the Dutch Colorectal Cancer Group (DCCG)	Cecile Grootscholten	Phase III	09/06/2015
M14TUM (TUMOROID)	Tumor organoids: feasibility to predict sensitivity to treatment in cancer patients (TUMOROID trial).	Emile Voest	Pilot	22/7/2014 (22/12/2021)
M15CRI (CRITICS-II)	A multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery vs. neo-adjuvant chemotherapy and chemoradiotherapy followed by surgery vs. neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer (CRITICS-II)	Marcel Verheij	Phase II/III	23/06/2017
M15INN (INNOVATION)	INtegratioN of trastuzumab, with or without pertuzumab, into periOperatiVe chemotherApy of HER-2 posiTIve stOmach caNcer: the INNOVATION-TRIAL	Annemieke Cats	Phase II	9/5/2019 (31/12/2021)
M15MOC (MOCCAS)	Molecular stool test for colorectal cancer surveillance (MOCCAS)	Monique van Leerdam	other	20/01/2016

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M15PEC (PERISCOPE II)	Treatment of peritoneal dissemination in stomach cancer patients with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (Periscope II)	Johanna van Sandick	Phase III	23/08/2017
M16PCP (PACAP-POCOP)	PAncreatic CAncer Project - Prospective Observational Cohort study of Oesophageal-gastric cancer Patients - A prospective observational cohort study - The PACAP-POCOP project	Cecile Grootscholten	other	09/02/2021
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Neeltje Steeghs	Phase I	1/11/2016 (4/1/2022)
M16TSR (TESAR)	Rectal preserving treatment for early rectal cancer. A multi-centred randomised trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer.	Monique van Leerdam	Phase III	17/08/2016
M16VIB (MoTriColor2)	A phase II study of vinorelbine in advanced BRAF-like colon cancer (EORTC1616)	Neeltje Steeghs	Phase II	2/2/2018 (17/8/2021)
M16WAS	Multicentre evaluation of the "wait-and-see" policy for complete responders after chemoradiotherapy for rectal cancer	Geerard Beets	Phase III	24/02/2017
M17CR6 (CAIRO6)	Investigating the benefit of perioperative systemic therapy in patients undergoing cytoreductive surgery with HIPEC for peritoneal metastases of colorectal cancer: the multicentre, phase II-III, prospective, randomised CAIRO6 study.	Arend Aalbers	Phase III	07/09/2017
M17CRC (PLCRC)	Prospective data collection initiative on colorectal cancer - a prospective observational cohort study - (PLCRC)	Geerard Beets	Phase IV	22/08/2017
M18LUT (LUTIA)	Intra-arterial lutetium-177-dotatate for treatment of patients with neuro-endocrine tumor liver metastases: The LUTIA Study	Marcel Stokkel	Phase II	29/1/2019 (25/11/2021)
M18PIE (PRIDE)	Preoperative Image-guided Identification of Response to neoadjuvant chemoradiotherapy in Esophageal cancer (PRIDE trial)	Marcel Verheij	other	31/05/2018
M18PUMP	Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases in patients with a low clinical risk score – a randomized controlled trial	Koert Kuhlmann	Phase III	19/02/2019
M18SAN (SANO)	Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer (SANO trial: "Surgery As Needed for Oesophageal cancer")	Johanna van Sandick	Phase III	25/6/2018 (6/8/2021)
M18SPO	The (ir)relevance of WHO criterion 2 for the diagnosis of Serrated Polyposis Syndrome	Monique van Leerdam	other	29/11/2018 (22/12/2021)
M18STAR (*STAR-LNPCP)	Standardizing TrAining for endoscopic Resection of Large Non-Pedunculated Colorectal Polyps: it is prime-time to change practice (*STAR-LNPCP)	Monique van Leerdam	other	03/04/2019
M19AHW (CheckMate 8HW)	Phase 3b Randomized Clinical Trial of Nivolumab Alone, or in Combination with Ipilimumab in Participants with Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient Metastatic Colorectal Cancer (dMMR). (CheckMate 8HW: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 8HW)	Cecile Grootscholten	Phase III	24/09/2019
M19BIX (BIOPEX 2)	Gluteal turnover flap for closure of the perineal wound after abdominoperineal resection for rectal cancer.	Arend Aalbers	Phase III	26/02/2020
M19CLP (COLOPEC II)	Second and third look laparoscopy in pT4 colon cancer patients for early detection of peritoneal metastases; the COLOPEC II randomized multicentre trial.	Arend Aalbers	Phase III	25/04/2019
M19DSC (DISCO)	Dedicated MR imaging vs surgical staging of peritoneal carcinomatosis in colorectal cancer patients: a randomized multicenter trial	Max Lahaye	other	31/10/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M19FTR	Prospective Registration of endoscopic Full Thickness Resection in the Netherlands	Thomas Wijkerslooth	other	22/11/2019
M19FTRO	Long-term oncological outcomes of endoscopic full-thickness resection after previous (potential) incomplete resection of T1 CRC.(A national prospective cohort study)	Thomas Wijkerslooth	other	22/11/2019
M19IMP (IMPACT - CRC)	Image guided treatment optimalization with cetuximab for patients with metastatic colorectal cancer: IMPACT - CRC As part of the imaging program: Towards patient tailored cancer treatment supported by molecular imaging IMPACT: Imaging Patients for Cancer drug selecTion	Tineke Buffart	Phase II	19/7/2019 (21/5/2021)
M19PIT (PUMP-IT)	Hepatic arterial infusion PUMP chemotherapy combined with systemIc chemoTherapy for potentially resectable colorectal liver metastases	Koert Kuhlmann	Phase II	03/09/2020
M19SUN (SUNRISE-CRC)	A randomized phase II study of pulsatile high-dose sunitinib versus TAS-102 in patients with metastatic colorectal carcinoma (mCRC).	Joeri Douma	Phase II	24/06/2020
M19TGR (TIGER)	Distribution of lymph node metastases in esophageal carcinoma	Johanna van Sandick	other	10/07/2019
M20BCR (Breakwater)	An Open-label, Multicenter, Randomized Phase 3 Study of First-line Encorafenib Plus Cetuximab With or Without Chemotherapy Agents versus Standard of Care Therapy with a Safety Lead-in of Encorafenib and Cetuximab Plus Chemotherapy In Participants with Metastatic BRAF V600E-Mutant Colorectal Cancer. (Breakwater).	Marieke Vollebergh	Phase III	08/04/2021
M20CPC	A phase Ib, multicenter, open-label dose escalation and expansion platform study of select drug combinations in adult patients with advanced or metastatic BRAF V600 colorectal cancer	Marloes van Dongen	Phase I	12/10/2020
M20CTN	Onderzoek naar de risico's op kanker in CTNNA1-families. Establishing cancer risks in CTNNA1 families.	Lizet van der Kolk	other	15/12/2020
M20DES (DESTINY03)	A Phase 1/2b Multicenter, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Antitumor Activity of Trastuzumab Deruxtecan (DS-8201a) monotherapy and combinations in Adult Subjects with HER2 Overexpressing Gastric Cancer.	Neeltje Steeghs	Phase I/II	12/10/2020
M20GIQ	Life with GIST	Winette van der Graaf	other	18/5/2020 (17/12/2021)
M20HBT (HERBERT II)	HERBERT II: external beam radiation therapy (EBRT) followed by high-dose rate endorectal brachytherapy (HDR-BT) in elderly early rectal cancer patients not undergoing surgery: A randomized multicenter phase III study	Femke Peters	Phase III	12/10/2020
M20LYS	The Scent of Lynch Syndrome: VOC-profiles for early detection of colorectal neoplasia.	Monique van Leerdam	other	07/12/2020
M20MTH (MATTERHORN)	A Randomized, Double-blind, Placebo-controlled, Phase III Study of Neoadjuvant-Adjuvant Durvalumab and FLOT Chemotherapy Followed by Adjuvant Durvalumab in Patients with Resectable Gastric and Gastroesophageal Junction Cancer (GC/GEJC) (MATTERHORN)	Myriam Chalabi	Phase III	08/04/2021
M20PAX (OPAXX)	Organ preservation in patients with a good clinical response after neoadjuvant chemoradiation for locally advanced rectal cancer: optimization of treatment strategies and defining the role of additional contact X-ray therapy versus extending the waiting interval and local excision (OPAXX)	Brechtje A. Grotenhuis	Phase II/III	01/04/2021
M20PEX (PelvEx II)	Multicentre, open-label, randomised, controlled, parallel arms clinical trial of induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer.	Arend Aalbers	Phase III	12/11/2020

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M20SAM (SAMURAI)	Needle-knife inciSion therApy coMpared to Usual caRe of recurrent esophagogastric Anastomotlc strictures: a multicenter randomized controlled trial (SAMURAI-study)	Jolanda van Dieren	other	28/01/2021
M20STA (STAR-TREC)	Can we Save the rectum by watchful waiting or TransAnal surgery following (chemo)Radiotherapy versus Total mesorectal excision for early REctal Cancer?	Femke Peters	Phase III	04/03/2021
M20TNT (TENT)	Triage of Elderly Needing Treatment (TENT)	Corrie Marijnen	other	27/01/2021
M20TRS (TRIASSIC)	Multicentre, randomised controlled trial comparing TRansanal minimal InvAsive Surgery (TAMIS) and endoscopic Submucosal dIsseCtion (ESD) for resection of non-pedunculated rectal lesions	Brechtje A. Grotenhuis	other	22/10/2020
M21AIM (AIMS)	Evaluation of methylation marker analysis on anal swabs for the detection of anal cancer	Baukelien van Triest	other	22/03/2021
M21APP (Stoma APPtimize)	Improving quality of life of patients having a stoma by offering personalised and timed guidance in a patient-centred mobile application (Stoma APPtimize)	Brechtje A. Grotenhuis	other	22/04/2021
M21DUP	A personalised surveillance and intervention protocol for duodenal polyposis in patients with familial adenomatous polyposis: an international multi-centre prospective study	Monique van Leerdam	other	27/12/2021
M21FAP	Long term outcomes after (procto)colectomy in patients with familial adenomatous polyposis: an international multi-centre cohort study.	Monique van Leerdam	other	27/12/2021
M21MOS (MOSAIC)	Mosaic mutations in patients with colorectal adenomas and/or cancer	Monique van Leerdam	other	12/11/2021
M21PRR (pre-RADAR)	Towards Response guided ADAptive Radiotherapy for organ preserving treatment of intermediate risk rectal cancer (preRADAR): a phase I dose finding trial	Femke Peters	Phase I	29/07/2021
M21PSI	A personalised surveillance and intervention protocol for patients with familial adenomatous polyposis that have undergone (procto)colectomy: an international multi-centre prospective study	Monique van Leerdam	other	27/12/2021
M21RIG (Right)	Prospective mapping of surgical variations in laparoscopic right hemicolectomy and development of optimized and standardized surgical technique for right-sided colon cancer (Right study)	Brechtje A. Grotenhuis		27/12/2021
M21SCC (SEC)	Socio-economic consequences of cancer care, a patient perspective (SEC trial)	Wim van Harten	other	28/04/2021
M21SN2 (SANO-2)	A prospective cohort study on active surveillance after neoadjuvant chemoradiation for oesophageal cancer: SANO-2 study.	Johanna van Sandick	other	03/06/2021
N12INT	Pilot study to evaluate the tumor-reactiviity of infiltrating T cells in human malignancies	Wouter Scheper	Pilot	05/09/2012
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/2014
N14RCS (ColoSpect)	In vivo identification of rectum and coloncarcinoma during surgery using optical spectroscopy techniques (ColoSpect)	Theo Ruers	other	31/07/2014
N16BTC	Blood Transcript Analysis in colorectal cancer patients	Margot Tesselaar	other	23/08/2016
N16NCI (NICHE)	Nivolumab, Ipilimumab and COX2-inhibition in early stage colon cancer: an unbiased approach for signals of sensitivity. The NICHE TRIAL	Myriam Chalabi	Phase II	20/01/2017
N16OCR	A prospective observational cohort for the clinical evaluation of innovative image guided surgical interventions in rectal cancer.	Theo Ruers	other	13/10/2016

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N17PND (PANDA)	Neoadjuvant capecitabine, oxaliplatin, docetaxel and atezolizumab in non-metastatic, resectable gastric and GE-junction cancer. The PANDA trial	Myriam Chalabi	Phase II	27/2/2018 (14/7/2021)
N18TRZ (TARZAN)	Neoadjuvant treatment in rectal cancer with radiotherapy followed by atezolizumab and bevacizumab (TARZAN)	Myriam Chalabi	Phase I/II	26/09/2019
N18ULN	Ultrasound-based navigation during liver surgery	Theo Ruers	Phase I	10/08/2018
N20PPC	Selecting a Subset of PRO-CTCAE for Rectal Cancer Patients	Femke Peters	other	22/01/2020
N20QUE	Registration of rectal cancer patients treated with contact x-ray brachytherapy – The experience of undergoing contact brachytherapy in older fragile rectal cancer patients unfit for surgery	Baukelien van Triest	other	08/12/2020
N20RPA	Prospective registration study for contact brachytherapy in rectal cancer patients	Baukelien van Triest	other	08/12/2020

GYNAECOLOGICAL

B18NCI (N-CIA)	The Netherlands facility for Cancer-Immune Analysis (N-CIA) 25-2-2019: studying the immune landscape of tumors.	John Haanen	Biobank	22/05/2019
B20NCC (NEOCON-CON)	Cervixcarcinoom Biobank: collecting specimen in NEOCON trial and controls	Nienke van Trommel	Biobank	28/05/2021
C21DOS	Early acces programma van dostarlimab, bij gevorderd of gerecidiveerd MSI-H endometriumcarcinoom.	Frans Opdam	other	03/09/2021
M10MKO	Phase II and pharmacological study with WEE-1 inhibitor MK-1775 combined with carboplatin in patients with p53 mutated epithelial ovarian cancer	Frans Opdam	Phase II	8/7/2010 (2/12/2021)
M14BBB (tripleB)	The Blood-Belly Barrier	Christianne Lok	other	03/05/2016
M16RTE (PORTEC 4a)	Randomised Phase III Trial of molecular profile-based versus standard recommendations for adjuvant radiotherapy for women with early stage endometrial cancer.	Marlies Nowee	Phase III	08/02/2017
M16SOL (SOLUTION)	Biomarker detection in cytology samples of women with gynaecologic cancer: a multicentric study	Nienke van Trommel	Biobank	30/01/2017
M16SON (SONAR-2)	Sentinel node in ovarian cancer (SONAR-2)	Willemien van Driel	Phase I	15/09/2016
M17EBR (EMBRACE-II)	Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive Brachytherapy in locally advanced Cervical cancer (EMBRACE-II)	Eva Schaake	other	04/06/2018
M17GINC (GINA-Cervix)	The state of the (sentinel) lymph node microenvironment in patients with cancer of the cervix	Henry Zijlmans	other	28/02/2018
M17GINV (GINA-Vulva)	The state of the (sentinel) lymph node microenvironment in patients with HPV-positive and HPV-negative cancer of the vulva	Henry Zijlmans	other	28/02/2018
M17GSC (GERSOC)	GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma (GERSOC)	Hans Trum	other	07/06/2018
M17MRO	Clinical impact of dedicated MR staging of ovarian cancer	Max Lahaye	other	17/04/2018

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17OVH (OVHIPEC-2)	Phase III Randomized clinical trial for stage III epithelial ovarian cancer randomizing between primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy: OVHIPEC-2	Willemien van Driel	Phase III	21/06/2019
M17PDV (PADOVA)	Physical Activity and Dietary intervention in OVArian cancer (PADOVA): a RCT evaluating effects on body composition, physical function, and fatigue	Willemien van Driel	other	01/05/2018
M18BAM	An open-label, first-in-human, multi-center study to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of a thorium-227 labeled antibody-chelator conjugate, BAY 2287411 injection, in patients with solid tumors known to express mesothelin	Egbert Smit	Phase I	13/2/2019 (12/1/2021)
M18CRA	Cancer risk assessment in women with vulvar intraepithelial neoplasia. Historic cohort study (part I) + Prospective study (part 2)	Marc van Beurden	other	06/11/2018
M18FUG (FUCHSia)	An open-label, single arm, prospective, multi-center, tandem two stage designed, phase II study to evaluate the efficacy of Fulvestrant in women with recurrent/ metastatic estrogen receptor positive gynecological malignancies	Frederic Amant	Phase II	13/06/2019
M18IQM (IQ-EMBRACE)	Quantitative MR Imaging in Locally Advanced Cervical Cancer -Sub-study under the EMBRACE II protocol (IQ-EMBRACE)	Eva Schaake	other	26/09/2019
M19CVT (CRAVAT)	Treatment of metastatic vulvar carcinoma in a neoadjuvant setting with Carboplatin and Paclitaxel chemotherapy	Henry Zijlmans	Phase II	20/05/2020
M19FCS (FOCUS)	Follow-up among cervical cancer survivors, perspectives from survivors, informal caregivers and health care providers (FOCUS): a cross-sectional population-based study	Nienke van Trommel	other	10/02/2021
M19GRA (GRANULOSA)	Granulosa cell tumors: a step towards targeted therapy	Christianne Lok	other	23/04/2019
M19HRO	Health-state utilities and health-related quality of life in patients with advanced stage ovarian cancer in different states of disease	Willemien van Driel	other	10/01/2020
M19VLC (VULCANIZE)	Treatment of locally advanced vulvar carcinoma in a neoadjuvant setting with Carboplatin and Paclitaxel chemotherapy	Henry Zijlmans	Phase II	11/03/2020
M20IMO	Implementation of a decision aid for advanced stage ovarian cancer patients	Willemien van Driel	other	06/01/2021
M20OVD (OVI-DETECT)	OVI-DETECT; Liquid biopsies for improving the pre-operative diagnosis of ovarian cancer.	Christianne Lok	other	16/06/2021
M20QCV	Survey among Dutch gynaecological oncologists on the use of topical corticosteroids in patients treated for lichen sclerosus-associated vulvar squamous cell carcinoma	Marc van Beurden	other	13/7/2020 (21/12/2021)
M20SFU (SOLFU)	Onderzoek naar de rol van biomarkers na de behandeling van het cervixcarcinoom	Nienke van Trommel	other	07/09/2020
M20SPC (SPARC)	A nurse-led sexual rehabilitation programme for women with gynaecological cancers receiving radiotherapy: a randomized multicentre trial	Marlies Nowee	Phase III	18/3/2021 (31/12/2021)
M20TBW (TUBA-WISP II)	Tubectomy with delayed oophorectomy as alternative for risk-reducing salpingo-oophorectomy in BRCA-women to assess the safety of prevention	Marc van Beurden	other	24/11/2020
M20TES (CoNteSSa-NeoCon)	Figo 2018 stage IB2(>= 2 cm - < 4 cm) Cervical cancer treatment with neoadjuvant chemotherapy followed by fertility sparing surgery (CoNteSSa / Neo-adjuvant chemotherapy and conservative surgery in cervical cancer to preserve fertility (NeoCon-F)	Nienke van Trommel	other	18/03/2021

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M21MAP	De MAPPING-applicatie als een instrument om risicocommunicatie te faciliteren in gedeelde besluitvorming tussen gynaecologen en patiënten met een gynaecologische maligniteit.	Christianne Lok	other	16/09/2021
N12INT	Pilot study to evaluate the tumor-reactiviity of infiltrating T cells in human malignancies	Wouter Scheper	Pilot	05/09/2012
N15TCH	Isolation of T cell receptors from human papilloma virus (HPV)-reactive or other tumor-reactive T cells from patients with oropharyngeal, cervical or vulvar cancer	Lotje Zuur	other	13/07/2016
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/2016
N16OPE	Feasibility study of neo-adjuvant treatment with carboplatin, paclitaxel and pembrolizumab in primary stage IV serous ovarian cancer	Gabe Sonke	Phase I	19/07/2017
N16SIG	Safety, immunogenicity and clinical response of sig-HELP-E6SH/E7SH-kdel, injected in the epidermis by DNA tattoo vaccination, in HPV16-positive vulvar intraepithelial neoplasia: a phase I/II study.	Gemma Kenter	Phase I/II	9/11/2016 (6/7/2021)
N20QCV	Survey on the use of topical corticosteroids among patients surgically treated for lichen sclerosus-associated vulvar squamous cell carcinoma	Marc van Beurden	other	16/4/2020 (21/12/2021)
N20QMG (QUAMIGYNO)	Evaluation of quality of peri-operative care for patients with a non-western migrant background receiving gynaecologic-oncological care (QUAMIGYNO).	Marc van Beurden	other	14/01/2021

HEAD AND NECK

M16OPS	Optical properties of the sinonasal cavity after surgical tumor resection	Baris Karakullukcu	other	1/3/2017 (23/12/2021)
M16SPS	Combination of salvage surgery and adjuvant photodynamic therapy in management of recurrent or residual sinonasal tumors.	Baris Karakullukcu	other	26/01/2017
M17CPI	Validation and psychometric properties of the Dutch version of the Communicative Participation Item Bank (CPIB) short form.	Michiel van de Brekel	other	16/10/2017 (20/12/2021)
M17OSA	Prevalence of Obstructive Sleep Apnea Syndrome (OSAS) after treatment for advanced stage head and neck cancer	Ludi Smeele	other	28/02/2019
M18ISA	A randomized, double-blind, placebo-controlled, phase 2 study of Cemiplimab versus the combination of Cemiplimab with ISA101b in the treatment of subjects with HPV16-positive Platin-resistant oropharyngeal cancer (OPC)	Jan Paul de Boer	Phase II	01/05/2019
M18KOC	Ontwikkeling van een keuzehulp voor patiënten met een orofarynxtumor waarbij curatieve chirurgie een behandeloptie is	Ludi Smeele	other	22/02/2019
M18TUN (TUNE)	Validation of TUNE criteria in patients treated with chemoradiotherapy using cisplatin for head and neck squamous cell carcinoma.	Lotje Zuur	other	15/05/2018
M19ABB	Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: Phase I study of ABBV-368 plus Tilsotolimod and Other Therapy Combinations	Marloes van Dongen	Phase I	7/7/2020 (3/12/2021)
M19IND (INDUCE-3)	A Randomized, Double-blind, Adaptive, Phase II/III Study of GSK3359609 or Placebo in Combination with Pembrolizumab for First-Line Treatment of PD-L1 Positive Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma.	Jan Paul de Boer	Phase II/III	29/6/2020 (10/5/2021)
M19SUS (SUSPECT-2)	Mapping of sentinel lymph node drainage Using Spect/CT to tailor highly selective elective nodal irradiation in node-negative neck of patientens with head and neck cancer	Abrahim Al-Mamgani	Phase II	25/06/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M20FAQ (FACE -Q)	The Dutch FACE-Q Head and Neck Cancer Multicenter validation study.	Ludi Smeele	other	07/07/2020
M20ITL (INTERLINK-1)	A Phase 3 Randomized, Double-blind, Multicenter, Global Study of Monalizumab or Placebo in Combination With Cetuximab in Patients With Recurrent or Metastatic squamous Cell Carcinoma of the Head and Neck Previously Treated With an Immune Checkpoint Inhibitor	Jan Paul de Boer	Phase III	30/11/2020
M20OMM (OROMM)	The gut and oral microbiome and metabolome as potential novel biomarker for disease progression and treatment response in head and neck squamous cell carcinoma (HNSCC); a pilot study (OROMM Study)	Lotje Zuur	Pilot	23/06/2021
M20PMF (PECTORALIS)	Prophylactic pectoralis major flap to compensate for increased risk of pharyngocutaneous fistula in laryngectomy patients with low skeletal muscle mass. (PECTORALIS-study)	Michiel van de Brekel	other	16/11/2020
M20TPS (TAPAS-esr11)	Predicting and synthesizing plausible speech examples after oral cancer treatment.	Michiel van de Brekel	other	09/11/2020
M21ISR (MDTP)	Intensive swallowing Rehabilitation after Head-Neck Cancer (ISR-HNC)	Lisette van der Molen	other	19/05/2021
M21SCC (SEC)	Socio-economic consequences of cancer care, a patient perspective (SEC trial)	Wim van Harten	other	28/04/2021
M21SDH	Shared decision-making in de hoofd-hals chirurgie	Michiel van de Brekel	other	20/04/2021
N12MAC (M&M)	Exploring the contribution of Macrophages in the microenvironment of HPV-induced squamous cell carcinoma of the head and neck	Jan Paul de Boer	other	31/8/2012 (27/12/2021)
N14IMR (IMRAD)	The immunological aspects of conventional therapies for the treatment of head and neck squamous cell carcinoma (HNSCC). An exploratory study to study the mmunological effects of (chemo)radiotherapy in HNSCC patients	Lotje Zuur	other	23/03/2015
N14LMN	Lymphatic mapping of the neck in patients with oral cavity malignancies using ICG-nanocolloid	Martin Klop	other	10/06/2015
N15HTC	Longitudinal analysis of head and neck cancer-specific immunity in patients treated with (salvage) surgery	Lotje Zuur	other	16/12/2015
N15SHA (SHAFE)	Effect of a silicone foam dressing (XtraSorb Foam) and hydrocolloid dressing (XtraSorb HCS) compared to silicone foam dressing (Mepilex) or an alginate (Kaltostat) combined with a semipermeable film (Tegaderm) on the donor site after split-thickness skin graft: a randomized controlled trial (SHAFE-study)	Peter Lohuis	other	31/05/2016
N15TCH	Isolation of T cell receptors from human papilloma virus (HPV)-reactive or other tumor-reactive T cells from patients with oropharyngeal, cervical or vulvar cancer	Lotje Zuur	other	13/07/2016
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/2016
N17DSI	Determining the dose-effect relation of salivary gland irradiation and cell loss with PSMA PET	Wouter Vogel	other	23/5/2017 (12/2/2021)
N17LFO	Effectiveness of lipofilling in patients with oropharyngeal dysfunction (speech and/or swallowing) after treatment for head and neck cancer	Ludi Smeele	Phase II	19/12/2017
N17SPE (SPEAT)	The timed Swallowing Performance EATing and drinking (SPEAT) test to objectify dysphagia in head and neck cancer patients	Ludi Smeele	other	24/4/2018 (1/12/2021)
N17TOT	Tracking of oral cavity carcinomas in head and neck surgery	Baris Karakullukcu	other	18/04/2017

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N18HSP	Are circulating hematopoietic stem and progenitor cells a potential biomarker for therapy response and disease progression in patients with squamous cell carcinoma of the head and neck?	Lotje Zuur	other	06/07/2018
N18PCN (PECAN)	Prospective study Evaluating CtDNA as a biomarker for treatment failure in head and Neck squamous cell carcinoma	Abrahim Al-Mamgani	other	15/5/2018 (25/6/2021)
N18VOQ	Voice quality and voice related quality of life in patients treated with totallaryngectomy; A prospective data collection.	Klaske van Sluis	other	20/02/2018
N19ECD	The effect of clinical documentation at the point of care on documentation time	Richard Dirven	other	27/01/2020
N19IFC (INFLUENCE)	INtra-operative evaluation of a novel FLUorescENt C-mEt tracer in penile and tongue cancer	Baris Karakullukcu	other	13/11/2019
N19IRM (RIfRaM)	Revolutionary implant for reconstruction purposes after mandibular resection, RIfRaM study	Baris Karakullukcu	other	25/11/2021
N19MPA	Feasibility study moldable peristomal adhesive for lung and speech rehabilitation after total laryngectomy	Richard Dirven	other	19/03/2020
N19RTT	Real-time assesment of tongue tumor resection margins using 3D ultrasound	Ludi Smeele	other	28/01/2021
N20EHM	The Influence of the New Energy HME on Physical Activity and Patient Satisfaction in Laryngectomized Patients	Michiel van de Brekel	Pilot	18/11/2020
N20HIT	Vragenlijstonderzoek naar de prevalentie van, en risicofactoren gerelateerd aan, peristomale huidirritatie in totaal gelaryngectomeerde (TLE) patiënten.	Richard Dirven	other	12/11/2020
N20HTM	The effect of Heat and Moisture Exchangers on tracheal mucociliary clearance in laryngectomized individuals.	Michiel van de Brekel	other	13/09/2021
N20LYM	Lymfoedeem na hoofd-hals oncologie	Michiel van de Brekel	other	28/08/2020
N21OGT	Het gebruik van ondersteunende gebaren en het aanpassen van taalgebruik binnen verbale communicatie na een totale laryngectomie	Michiel van de Brekel	other	01/12/2021
N21SMM (SMMnose)	A personalized nasal prosthesis using statistical shape modelling (SSM)	Baris Karakullukcu		02/07/2021
N21VEG	Early clinical feasibility study of a new voice prosthesis: the Provox Vega HP – part 3	Michiel van de Brekel	other	27/12/2021

LUNG

C15MET	compassionate use programma crizotinib voor patienten met een MET mutatie	Michel van den Heuvel	other	28/01/2015
C18CET	Compassionate use cetuximab (free of charge programma) voor off-label indicaties, waarvoor geen andere behandelopties zijn en waarvoor een rationale voor gebruik cetuximab beschikbaar is.	Egbert Smit	other	12/12/2019 (27/12/2021)
C18NIV	Compassionate use Nivolumab (Free of charge programma) bij mesothelioma	Paul Baas	other	6/12/2019 (24/9/2021)
C19BLU	BLU-667 Expanded Access programma	Joop de Langen	other	19/02/2020
C19LOR	Compassionate use Lorlatinib (Free of charge programma) bij ROS+ NSCLC	Joop de Langen	other	03/09/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
C20BRI	NPP (free of charge) Brigatinib	Joop de Langen	other	05/10/2020
C20CAP	Named patient managed access program (NPP MAP) Capmatinib (INC280) voor MET amplificatie of MET mutatie positief NSCLC	Joop de Langen	other	09/06/2020
C20ENT	entrectinib CUP voor patienten met NSCLC stadium IV met EGFR exon 19 deletie, NTRK1 fusie en progressie op osimertinib	Joop de Langen	other	16/12/2020
C20IMA	FOC programma Imatinib	Joop de Langen	other	16/09/2020
C20LUR	compassionate use programma lurbinectidine	Willemijn Theelen	other	12/08/2020
C20OSI	Free of Charge programma (FOC) / Coulance regeling bij lokaal gevorderd of gemetastaseerd EGFR+ NSCLC met een L858SR en/of exon 19 del mutatie - meerdere lijns	Egbert Smit	other	07/07/2020
C21AMI	Compassionate Use Programma Amavantamab	Joop de Langen	other	02/12/2021
C21AMI	Amivantanab bij EGFR exon 20 insertie positief NSCLC	Joop de Langen	other	13/12/2021
C21CAB	Free of Charge single patient programma voor cabozantinib (Cabometyx®)	Willemijn Theelen	other	24/09/2021
C21INI	compassionate use programma ipilimumab en nivolumab	Paul Baas	other	21/05/2021
C21MOB	compassionate use programma voor mobocertinib voor NSCLC patienten met EGFR exon 20 insertie mutatie of HER2 exon 20 insertie mutatie	Gerrina Ruiter	other	24/08/2021
C21REP	repotrectinib voor ROS gemuteerd NSCLC met resistentiemutaties	Joop de Langen	other	17/08/2021
C21SEL	Free of Charge (Om-Niet) programma selpercatinib / LOXO-292 (Retsevmo®).	Joop de Langen	other	26/2/2021 (22/11/2021)
C21SOT	NPP Sotorasib (AMG510)	Paul Baas	other	23/03/2021
E1205	EORTC randomized phase II study of pleurectomy/ decortication (P/D) preceded or followed by chemotherapy in patients with early stage malignant pleural mesothelioma	Paul Baas	Phase II	15/03/2018
E1825	Activity of Lorlatinib based on ALK resistance mutations on blood in ALK positive NSCLC patients previously treated with 2nd generation ALK inhibitor	Joop de Langen	other	14/05/2021
M14TUM (TUMOROID)	Tumor organoids: feasibility to predict sensitivity to treatment in cancer patients (TUMOROID trial).	Emile Voest	Pilot	22/7/2014 (22/12/2021)
M15N22 (NVALT 22)	First line chemotherapy in KRAS mutated non-small cell lung cancer patients: a phase III comparing cisplatin-pemetrexed with carboplatin-paclitaxel-bevacizumab: NVALT22	Egbert Smit	Phase III	5/7/2016 (14/7/2021)
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Neeltje Steeghs	Phase I	1/11/2016 (4/1/2022)
M16STT (STARTRK-2)	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROS1 or ALK gene rearrangements. (STARTRK-2) <font color = RED> (arm 'NSCLC ROS1 Basket' is closed. 'NTRK1/2/3 (evaluable basket only: NSCLC, MCRC, small solid tumors)' and 'ROS1 (evaluable basket only: MCRC, small solid tumors' are open)'	Egbert Smit	Phase II	24/08/2016

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17DNM (DENIM)	A randomized, open-label phase II/III study with dendritic cells loaded with allogenic tumor cell lysate (PheraLys) in subjects with mesothelioma as maintenance treatment (MesoPher) after chemotherapy. (DENIM)	Paul Baas	Phase II/III	15/11/2018 (26/3/2021)
M17FNN	[18]F-PD-L1 PET/CT to predict response to Nivolumab in patients with NSCLC	Joop de Langen	other	26/10/2018
M17IMG	[89]Zr-pembrolizumab-PET imaging in patients with locally advanced or metastatic melanoma or non-small cell lung cancer	John Haanen	Pilot	23/07/2018
M17RLC (RETHO)	Reirradiation for recurrent lung cancer in the thorax: overall survival, local control, and toxicity: a phase 2 trial (RETHO)	Joost Knegjens	Phase II	07/11/2018
M17SAT (SATIN)	Safety of TKI concurrent with cranial radiotherapy in NSCLC patients; the SATIN platform trial <font color = RED> cohort 1(Osi+SRT) = VOL	Egbert Smit	Phase IV	27/05/2019
M18ACX (AFACET)	Phase II study of afatinib in combination with cetuximab in EGFR exon 20 insertion positive non-small-cell lung cancer	Joop de Langen	Phase II	11/12/2018 (22/12/2021)
M18ALE (ALERT-lung)	A single arm phase II trial evaluating the activity of alectinib for the treatment of pretreated RET-rearranged advanced NSCLC (ALERT-lung)	Egbert Smit	Phase II	17/5/2019 (31/3/2021)
M18AMG (AMG 757)	A Phase I study evaluating the safety, tolerability and pharmacokinetics of AMG 757 in subject with small cell lung cancer	Neeltje Steeghs	Phase I	27/02/2019
M18BAM	An open-label, first-in-human, multi-center study to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of a thorium-227 labeled antibody-chelator conjugate, BAY 2287411 injection, in patients with solid tumors known to express mesothelin	Egbert Smit	Phase I	13/2/2019 (12/1/2021)
M18BNI	An Exploratory Study of the Biologic Effects and biomarkers of Nivolumab Combined With Ipilimumab in Subjects With Treatment-Naive Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) (CheckMate 592) - Part I	Joop de Langen	Phase II	23/10/2018
M18BRM	A phase I drug-drug interactions study between Brigatinib and the CYP3A substrate Midazolam in patients with ALK-postive or ROSI-postive solid tumors	Egbert Smit	Phase I	13/6/2019 (7/9/2021)
M18COS	11C-osimertinib-PET/CT to identify T790M positive tumors in patients that are T790M negative in a single tumor biopsy and a circulating tumor DNA sample	Joop de Langen	Phase I/II	10/04/2019
M18IRL (ImmunoSABR)	Phase II study examining the activity of L19-IL2 immunotherapy and stereotactic ablative radiotherapy in metastatic non-small cell lung cancer (ImmunoSABR)	Monique de Jong	Phase II	26/09/2019
M18MPR (IMPROVE)	Individualized pemetrexed dosing in patients with non-small cell lung cancer or mesothelioma based on renal function to improve treatment response <font color=RED>(arm "IMPROVE-III" is closed, IMPROVE-II is closed, IMPROVE-I is open)	Sjaak Burgers	Phase II	23/01/2019
M18OSI (OSIRIS)	OSIRIS: Osimertinib resistance analysis in patients with EGFR mutation positive non-small-cell lung carcinoma that have progressed on osimertinib treatment <font color = RED> (9/11/20: only open for patients with progression on 1st line osimertinib)	Joop de Langen	other	23/07/2019
M18PST (Position-20)	Patients on osimertinib with EGFR mutation exon 20, non-T790M. The position-20 trial.	Joop de Langen	Phase II	21/1/2019 (26/5/2021)
M18SRP	Combining SBRT and immunotherapy in early stage NSCLC patients planned for surgery: exploring safety and immunological proof of principle	Joop de Langen	Phase II	25/05/2018
M18TAT (TATIN)	Track and treat in NSCLC (TATIN) – ctDNA guided treatment of early resistance to targeted treatment in patients with EGFR positive NSCLC <font color = RED> (Cohort 2e lijn osimertinib gesloten, alleen nog 1e lijn osimertinib includeren)	Joop de Langen	Phase II	17/7/2019 (17/12/2021)

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18TEO	Trastuzumab-emtansine and osimertinib combination treatment to target HER2 bypass track resistance in EGFR mutation poitive NSCL	Joop de Langen	Phase II	19/12/2018 (17/5/2021)
M18TEP (VISION)	A phase II single-arm trial to investigate tepotinib in advanced (Stage IIIB/IV) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations or MET amplifications (VISION) <font color=RED>(Cohort A+ B closed)	Egbert Smit	Phase II	3/4/2019 (27/12/2021)
M19BAY	An open-label, multicenter, phase 1/2 study of radium-223 dichloride in combination with pembrolizumab in participant with stage IV non-small-lung cancer	Egbert Smit	Phase I/II	30/11/2020
M19CCR (HALO)	Cardiac changes after radiotherapy with high fraction doses for early stage NSCLC cancer. Per 09/06/2021: Cardiac changes after stereotactic radiotherapy for early stage NSCLC cancer or lung metastasis	José Belderbos	other	04/02/2020
M19CLN	A phase 1/2a open-label, multi-center trial to assess safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of CLN-081 in patients with non-small cell lung cancer harboring EGFR exon 20 insertion.	Egbert Smit	Phase I/II	12/05/2020
M19EBL	a phase 2, open-label study with Encorafenib + Binimetinib in patients with BRAF V600F-mutant non-small cell lung cancer	Egbert Smit	Phase II	27/11/2019
M19LNC	Lorlatinib neurocognitive adverse events: how to improve patient care	Egbert Smit	other	18/12/2019
M19MDM	A phase 1b/2 study of the dual MDMX/MDM2 Inhibitor, ALRN-6924, for the prevention of topetecan-induved Myelosuppression During treatment for Small Cell lung cancer	Egbert Smit	Phase I/II	28/10/2020 (2/4/2021)
M19ORC (ORCHARD)	A biomarker-directed phase 2 platform study in patients with advanced non-small cell lung cancer disease whose disease has progressed on first-line Osimertinib therapy (ORCHARD) <font color = RED> Group A Module 1 CLOSED Module 2,3,5, 6 OPEN Group B Module 3,4 CLOSED Group C Open (ONLY FOR: Sclc transformation, squamous transformation & actionable mutation with potential treatment that is not currently available within ORCHARD	Joop de Langen	Phase II	12/02/2020
M19OSB (OSIBOOST)	Pharmacokinetic boosting of osimertinib in patients with non-small cell lung cancer using cobicistat; the OSIBOOSTpilot study	Egbert Smit	Pilot	20/05/2020
M19PAC (PACIFIC-R)	First real-world data on unresectable stage III NSCLC patients treated with Durvalumab after henoradiotherapy (PACIFIC-Real World)	Paul Baas	other	28/01/2020
M19RET	A phase I/II study with Highly-selective RET inhibitor, BLU-667, in patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and other advanced solid tumors <font color=RED> (only cohort 5 open)	Joop de Langen	Phase I/II	21/1/2020 (11/1/2022)
M19SYM (SYMPRO-Lung)	Symptom monitoring with patient-reported outcomes using a web application among lung cancer patients in the Netherlands (SYMPRO-Lung)	José Belderbos	other	24/09/2019
M19TCL	A Phase 1b/2a Pilot Randomized Study to Evaluate the Safety and Tolerability of Autologous T-Cells Expressing Enhanced TCRs (T-Cell Receptors) Specific for NY-ESO-1/LAGE-1a (GSK3377794) Alone, or in Combination with Pembrolizumab in HLA-A2+ Participants with NY-ESO-1- or LAGE-1a-Positive Advanced or Recurrent Non-Small Cell Lung Cancer	John Haanen	Phase I/II	19/06/2020
M19TPO (INSIGHT 2)	A phase II single-arm study to investigate tepotinib combined with osimertinib in MET amplified, advanced or metastatic non-small cell lung cancer (NSCLC) harboring activating EGFR mutations and having acquired resistance to prior 1st to 3rd generation EGFR-tyrosine kinase inhibitor therapy (INSIGHT 2)	Egbert Smit	Phase II	03/12/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M19UNS	A multicenter, open-label phase I study of U3-1402 in subjects with metastatic or unresectable non-small cell lung cancer	Egbert Smit	Phase I	24/6/2020 (27/12/2021)
M20ACH (ACHILES)	A randomized phase II study comparing atezolizumab after concurrent chemoradiotherapy with chemoradiotherapy alone in limited disease small-cell lung cancer.	Willemijn Theelen	Phase II	28/10/2020
M20CBR (CodeBreak 200)	A phase 3 multicenter, randomized open-label, active-controlled study of AMG 510 versus docetaxel for the treatment of previously treated locally advanced and unresectable or metastatatic NSCLC subject with mutated KRAS p.G12C.	Joop de Langen	Phase III	26/05/2020
M20DEL (DESTINY-lung02)	A phase 2, multicenter, randomized study of Trastuzumab Deruxtecan in subjects with HER2-mutated metastatic non-small cell lung cancer (NSCLC) [DESTINY-Lung02]	Egbert Smit	Phase II	30/11/2021
M20HRT (HERTHENA-Lung01)	HERTHENA-Lung01:A phase 2 randomized open-label study of Patritumab Deruxtecan (U3-1402) in subjects with previously treated metastatic or locally advanced EGFR-mutated non-small cell lung cancer (NSCLC)	Egbert Smit	Phase II	02/06/2021
M20KRY (KRYSTAL-007)	A phase 2 trial of MRTX849 in combination with Pembrolizumab in patients with advanced non-small cell lung cancer with KRAS G12C mutation	Egbert Smit	Phase II	02/07/2021
M20LDS	Phase 2, multicenter, randomised study of DS-1062a in advanced or metastatic non-small cell lung cancer with actionable genomic alterations and previously treated with kinase inhibitor therapy and platinum-based chemotherapy with or without prior immunotherapy	Paul Baas	Phase II	09/07/2021
M20NPN	A phase 3, randomized, double-blind, placebo-controlled, multicenter study comparing Niraparib plus Pembrolizumab versus Placebo plus Pembrolizumab as maintanance therapy in participants whose disease has remained stable or responded to first-line Platinum-based chemotherapy with Pembrolizumab for stge III or IV non-small cell lung cancer	Egbert Smit	Phase III	29/03/2021
M20PRA	A randomized, open-label, phase 3 study of Pralsetinib versus Standard of Care for first line treatment of RET fusion-positive, metastatic Non-Small Cell Lung Cancer	Joop de Langen	Phase III	29/12/2020
M20SAP (SAPPHIRE)	A randomized phase 3 study of Sitravatinib in combination with Nivolumab versus Docetaxel in patients with advanced non-squamous non-small cell lung cancer with disease progression on or after platinum-based chemotherapy and checkpoint inhibitor therapy.(SAPPHIRE)	Egbert Smit	Phase III	31/12/2020
M20TEL	Phase 2, open-label safety and efficacy study of Telisotuzumab Vedotin (ABBV-399) in subjects with previously treated c-Met+ Non-Small Cell Lung Cancer <font color = RED> (update 8JUN21: stage 2 open for non-squamous EGFR WT (both intermediate and high MET expression); non-squamous EGFR mut on hold; squamous closed)	Joop de Langen	Phase II	11/09/2020
M20TRM	Unraveling tumor response and resistance to combined chemotherapy and PD-L1 inhibition with minimal invasive techniques in patients with advanced NSCLC with targetable disease	Joop de Langen	other	03/02/2021
M21ECL	Randomized, open-label, multicenter, phase III study of Entrectinib versus Crizotinib in patients with locally-advanced or metastatic non-small lung cancer harboring ROS1 gene rearrangements with and without central nervous system metastases.	Joop de Langen	Phase III	06/12/2021
M21ILL	A Phase 2 Multicenter Study of Autologous Tumor Infiltrating Lymphocytes (LN-145) in Patients with Metastatic Non-Small-Cell Lung Cancer.	John Haanen	Phase II	01/12/2021
M21PDC (PDC-LUNG-101)	An open-label, dose-escalation, phase I/II study to assess the safety, the tolerability, the immunogenicity and the preliminary clinical activity of the therapeutic cancer vaccine, PDC*lung01, associated or not with anti-PD-1 treatment in patients with non-small-cell lung cancer (NSCLC).	Willemijn Theelen	Phase I/II	03/11/2021

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N12LON	Longitudinal analysis of lung cancer-specific immunity in stage III and IV lung cancer patients	Egbert Smit	other	18/1/2013 (8/3/2021)
N13FPB	Fluid phase biopsy (circulating tumour DNA and serum tumour markers) in patients with non-small cell lung cancer	Sjaak Burgers	other	17/12/2013
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/2014
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/2016
N17DTL (Induction-1)	A Phase Ib, Open-label, Single-center study to assess the safety of cancer-immunotherapy induction with Tremelimumab and Durvalumab prior to Chemoradiotherapy in the treatment of locally advanced NSCLC.	Willemijn Theelen	Phase I	05/10/2018
N18NUA (NUANCE)	NUtritional Assessment in Non-small Cell lung cancer patients (NUANCE)	Martijn Stuiver	other	29/06/2018
N18PET	Novel Ga68-PSMA PET tracer to differentiate between radiation necrosis and tumor progression in stereotactic irradiated brain metastases	Dieta Brandsma	other	14/08/2019
N19ORA (ORA-LM)	Osimertinib resistance analysis of leptomeningeal metastasis in patients with EGFR mutation positive non-small-cell lung carcinoma that have LM progression on osimertinib treatment	Joop de Langen	other	22/07/2020
N19PEM (PEMMELA)	PEMbrolizumab Plus Lenvatinib In Second Line And Third Line Malignant Pleural MEsotheLiomA Patients: A Single Arm Phase II Study (PEMMELA).	Sjaak Burgers	Phase II	06/01/2021
N19RER	A Open-label Single-arm pharmacokinetic Trial, Investigating the Effect of CYP3A4 inhibitor Ritonavir on the Pharmacokinetics of Erlotinib.	Neeltje Steeghs	other	25/4/2019 (2/12/2021)
N21LBB	Evaluation of a liquid biopsy biomarker to predict the response to whole brain radiotherapy (WBRT) in patients with brain metastasis.	Dieta Brandsma	other	30/8/2021 (3/11/2021)
N21PEL (PREM MRL)	Patient-reported experience MR-Linac compared to conventional linac	José Belderbos	other	20/10/2021

LYMPHOMA - HODGKIN'S DISEASE

M19BET (BETER-REFLECT)	BETER-REFLECT Biobank: a REsource For studies on Late Effects of Cancer Treatment	Floor van Leeuwen	other	31/03/2021

LYMPHOMA - NON-HODGKIN'S

M15PRM (PRMT5i)	A phase I, open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3326595 in subjects with solid tumors and non-Hodgkin's lymphoma.	Frans Opdam	Phase I	27/10/2016
M18CNH (CLARITY)	Cardiotoxicity and other Late effects After Radiotherapy and Immuno-chemoTherapy for non-Hodgkin lYmphoma	Floor van Leeuwen	Other	07/10/2019
M19BET (BETER-REFLECT)	BETER-REFLECT Biobank: a REsource For studies on Late Effects of Cancer Treatment	Floor van Leeuwen	other	31/03/2021

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
MELANOMA / SKIN				
B20MCC	Understanding tumor immune escape in patients with Merkel cell carcinoma	Alex van Akkooi	Biobank	13/08/2020
C16DAT	Free of charge programma (FOC) dabrafenib/trametinib bij adjuvante behandeling van melanoom bij volwassen patienten met BRAF mutatie	Aafke Meerveld-Eggink	other	12/10/2020 (23/12/2021)
C18CEM	NPP programma cemiplimab	John Haanen	other	09/11/2018
C19CEM	Free of charge (FOC) programma cemiplimab	John Haanen	other	27/01/2021
C19DAT	Compassionate use Dabrafenib / trametinib (Free of charge programma) bij adjuvante behandeling van melanoom	Aafke Meerveld-Eggink	other	6/12/2019 (27/12/2021)
E1208MG (Minitub)	Minitub: Prospective registry of Sentinel Node (SN) positive melanoma patients with minimal SN tumor burden who undergo Completion Lymph Node Dissection (CLND) or Nodal Observation	Alex van Akkooi	other	23/04/2015
E1612 (EBIN)	Combination of targeted therapy (encorafenib and binimetinib) followed by combination of immunotherapy (ipilimumab and nivolumab) vs immediate combination of immunotherapy in patients with unresectable or metastatic melanoma with BRAF V600 mutation : an EORTC randomized phase II study (EBIN)	Alex van Akkooi	Phase II	27/05/2019
M14TIL	Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma	John Haanen	Phase III	06/08/2014
M16OPN (OpACINneo/ PRADO)	Multicenter Phase 2 Study to Identify of the Optimal neo-Adjuvant Combination Scheme of Ipilimumab and Nivolumab (OpACIN-neo)	Christian Blank	Phase II	1/11/2016 (17/12/2021)
M17IMG	[89]Zr-pembrolizumab-PET imaging in patients with locally advanced or metastatic melanoma or non-small cell lung cancer	John Haanen	Pilot	23/07/2018
M17PTS (POINTING)	POINTING:Towards patient-tailored cancer immunotherapy supported by a multifaceted predictive signature composed of integrative omics and molecular imaging	John Haanen	other	12/11/2018
M18NKN	A Phase 3, Randomized, Open-label Study of NKTR-214 Combined with Nivolumab Versus Nivolumab in Participants with Previously Untreated Unresectable or Metastatic Melanoma	Christian Blank	Phase III	27/5/2019 (24/9/2021)
M19DON (DONIMI)	Multicenter Phase 1b trial testing the Neoadjuvant Combination of Domatinostat, Nivolumab, and Ipilimumab, in IFN-gamma signature -low and IFN-gamma signature-high RECIST 1.1-measurable Stage III Cutaneous or Unknown Primary Melanoma – DONIMI	Christian Blank	Phase I	27/12/2019
M19EBP	A sequential 2-arm, Open-label Phase 1 Study to evaluate the effects of Encorafenib in combination with Binimetinib on the Pharmacokinetics of Losartan, Midazolam, Caffeine, Omeprazole, and Dextromethorphan administered in a cocktail approach and on the Pharmacokinetics of Rosuvastatin in patients with BRAF V600-mutant unresectable or metastatic Melanoma or other advanced solid tumors	Frans Opdam	Phase I	23/06/2020
M19SST (Safe Stop Trial)	Safe Stop Trial: observational study of the STOP & GO strategy of PD-1 blockade in advanced melanoma patients upon achieving a complete or partial response.	John Haanen	Phase II/III	10/05/2019
M20CPG	Prospective Dutch cohort study of a primary melanoma gene-signature (CP-GEP model) to predict sentinel node status. "CP-GEP Implementation"	Alex van Akkooi	other	02/12/2020
M20ITM (Intrim 1)	A Randomized Controlled Phase II Clinical Trial with Intradermal IMO-2125 (Tilsotolimod) in pT3-4 cN0M0 Melanoma (Intrim 1 study)	Alex van Akkooi	Phase II	22/12/2020

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M20MER (MERKLIN 2)	A phase II, open label study to investigate the efficacy and safety of domatinostat in combination with avelumab in patients with advanced unresectable/metastatic Merkel Cell Carcinoma progressing on anti-PD-(L)1 antibody therapy – the MERKLIN 2 study	Margot Tesselaar	Phase II	01/02/2021
M20NIT (NivoILP)	A phase Ib/II randomized double-blind placebo controlled trial evaluating the effect of nivolumab for patients with in-transit melanoma metastases treated with isolated limb perfusion (NIVOILP)	Winan van Houdt	Phase I/II	26/08/2021
M20SMI	A Cross-sectional Survey to Evaluate Patient Knowledge of Safety Messages Included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC® ("Patient Survey")	Alex van Akkooi	other	12/10/2020
M20TVC (MASTERKEY-115)	Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects With Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti-PD-1 Based Therapy.	Alex van Akkooi	Phase II	3/8/2020 (20/12/2021)
M21DER (DERMSTRIP)	DERMSTRIP Pilot study: Non-invasive detection of the cutaneous cytokine profile during adjuvant nivolumab treatment of stage III melanoma patients by skin tape stripping.	Elsemieke Plasmeijer	Pilot	20/09/2021
M21MKN (MERKLIN 1)	A phase II, open label, multicenter study to investigate the efficacy and safety of domatinostat in combination with avelumab in patients with treatment-naïve metastatic Merkel Cell Carcinoma - the MERKLIN 1 Study	Margot Tesselaar	Phase II	11/10/2021
M21NDN (NADINA)	Multicenter phase 3 trial comparing Neoadjuvant Ipilimumab + Nivolumab versus standard adjuvant Nivolumab in macroscopic stage III melanoma – NADINA	Christian Blank	Phase III	02/07/2021
N03LAM	Longitudinal analysis of melanoma-specific immunity in stage III and IV melanoma patients	John Haanen	other	22/08/2003
N16VOM	HDAC inhibitor vorinostat in resistant BRAF V600 mutated advanced melanoma	Sofie Wilgenhof	other	24/06/2016
N17BCC (BCC-COMI)	Noninvasive diagnostics and subtyping of basal cell carcinoma in the head and neck by dermoscopy and handheld reflectance confocal microscopy	Fons Balm	other	19/04/2017
N18PET	Novel Ga68-PSMA PET tracer to differentiate between radiation necrosis and tumor progression in stereotactic irradiated brain metastases	Dieta Brandsma	other	14/08/2019
N19PME (PRIME)	PET/CT Robustness In Melanoma (PRIME)	Marcel Stokkel	other	10/06/2020
N19TVN (NIVEC)	Neo-adjuvant T-VEC + Nivolumab combination therapy for resectable early metastatic (stage IIIB/C/IV M1a) melanoma with injectable disease (NIVEC trial)	Alex van Akkooi	other	08/09/2020
N20MAT (MATISSE)	Neo-adjuvant nivoluMab or nivolumab with ipilimumAb in advanced cuTaneous squamous cell carcinoma patIents prior to Standard of care SurgEry; the MATISSE trial	Lotje Zuur	other	30/07/2020
N20PTC (NEO-PTC)	An open-label, phase I study of NEO-PTC-01 in patients with advanced or metastatic melanoma.	John Haanen	Phase I	16/11/2020
N21LBB	Evaluation of a liquid biopsy biomarker to predict the response to whole brain radiotherapy (WBRT) in patients with brain metastasis.	Dieta Brandsma	other	30/8/2021 (3/11/2021)

MISCELLANEOUS

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
B18HIR	Blood sampling of healthy volunteers for immunological research	Marleen Kok	Biobank	08/02/2019
C19MOL	Compassionate Use for GSK525762 in NUT Midline Carcinoma (Molibresib CU209447)	Neeltje Steeghs	other	29/11/2019
C20EVE	MAP Everolimus for unknown primary NEC	Margot Tesselaar	other	30/11/2020
C20LAN	Post trial access program M17LAN	Wieneke Buikhuisen	other	06/02/2020
C21SEL	Free of Charge (Om-Niet) programma selpercatinib / LOXO-292 (Retsevmo®).	Joop de Langen	other	26/2/2021 (22/11/2021)
E1525 (nivothym)	Single-arm, multicenter, phase II study of nivolumab in patients with type B3 thymoma and thymic carcinoma previously treated with chemotherapy	Sjaak Burgers	Phase II	20/02/2019
M16STT (STARTRK-2)	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROSI or ALK gene rearrangements. (STARTRK-2) <font color = RED> (arm 'NSCLC ROS1 Basket' is closed. 'NTRK1/2/3 (evaluable basket only: NSCLC, MCRC, small solid tumors)' and 'ROS1 (evaluable basket only: MCRC, small solid tumors' are open)'	Egbert Smit	Phase II	24/08/2016
M19CMB (COMBO)	Focus on values to stimulate shared decisions in patients with thyroid cancer: A multifaceted COMmunication BOoster (COMBO)	Jan Paul de Boer	other	26/02/2020
M19MTC (LIBRETTO-531)	A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing LOXO-292 to Physicians Choice of Cabozantinib or Vandetanib in Patients with Progressive, Advanced, Kinase Inhibitor Naïve, RET-Mutant Medullary Thyroid Cancer (LIBRETTO-531.	Jan Paul de Boer	Phase III	02/04/2021
M19RET	A phase I/II study with Highly-selective RET inhibitor, BLU-667, in patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and other advanced solid tumors <font color=RED> (only cohort 5 open)	Joop de Langen	Phase I/II	21/1/2020 (11/1/2022)
M20CPC	A phase Ib, multicenter, open-label dose escalation and expansion platform study of select drug combinations in adult patients with advanced or metastatic BRAF V600 colorectal cancer	Marloes van Dongen	Phase I	12/10/2020
M20OTL	A phase 1a/1b/2 study to assess the safety, tolerability and pharmacokinetics of OTL78, a PSMA-targeted fluorescent agent, for the intraoperative imaging of prostate cancer	Henk van der Poel	Phase I/II	24/6/2020 (25/3/2021)
M20WTC (WaTCh)	Determinants and mediating mechanisms of quality of life and disease-specific symptoms among thyroid cancer patients: the WaTCh study	Jan Paul de Boer	other	08/11/2021
M21ATC (TRAP)	TReatment details of the Anaplastic thyroid cancer Patient in the Netherlands (TRAP)	Jan Paul de Boer	other	26/07/2021
N17MRD	Healthy volunteer imaging techniques development for motion management in MR-guided adaptive radiotherapy	Jan Jakob Sonke	other	09/11/2017
N18ISI	Inhibition of salivary glands to reduce uptake of radioactive Iodine	Wouter Vogel	Pilot	29/1/2019 (2/2/2021)
N20HYN	Feasibility study for visualization of the hypoglossal nerve in healthy individuals using the 3D nerve view MRI sequence	Bas Jasperse	other	17/02/2020
N21OGT	Het gebruik van ondersteunende gebaren en het aanpassen van taalgebruik binnen verbale communicatie na een totale laryngectomie	Michiel van de Brekel	other	01/12/2021
N21VMR	Test-retest quantitative MRI in healthy volunteers	Femke Peters	other	03/11/2021

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
NIET WMO STUDIES				
B19BIO	Blood Biobank healthy volunteers	Daan van den Broek	Biobank	19/08/2019
M18ORG	Modeling neuroendocrine tumors using adult stem cellderived organoids (NET organoids)	Margot Tesselaar	other	23/11/2018
N19USD	Implementatie Utrecht Symptoom Dagboek	Cecile Grootscholten	Pilot	11/3/2020 (22/12/2021)
SOFT TISSUE / OSTEOSARCOMA				
C20BLU	Avapritinib (BLU-285) Compassionate Use Program (CUP)	Neeltje Steeghs	other	08/10/2020
E1749	Incorporating the patient voice in sarcoma research: How can we assess health-related quality of life in this heterogeneous group of patients?	Winette van der Graaf	other	29/01/2020
E1809 (STRASS 2)	A randomized phase III study of neoadjuvant chemotherapy followed by surgery versus surgery alone for patients with High Risk RetroPeritoneal Sarcoma (STRASS 2)	Winan van Houdt	Phase III	10/08/2021
M15GCD (GALLOP)	Gastrointestinal stromal tumors (GIST): assessment of mutation in tumors and in circulating tumor DNA and measurement of TKI plasma exposure to optimize treatment	Neeltje Steeghs	other	12/03/2015
M16ITF (SSG XXII)	Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study	Neeltje Steeghs	Phase III	04/07/2017
M19TCS (IGNYTE-ESO)	Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered NY-ESO-1-Specific (c259) T Cells, alone or in combination withother agents, in HLA-A2+ Participants with NY-ESO-1 and/or LAGE-1a Positive Solid Tumors (IGNYTE-ESO)	John Haanen	other	22/07/2020
M19TDG	Taste disturbances in patients with gastrointestinal stromal tumors treated with tyrosine-kinase inhibitors	Neeltje Steeghs	other	12/12/2019
M20DMY	International prospective registry on local treatment approaches in myxoid liposarcomas.	Rick Haas	other	18/01/2021
M20QDF	The evaluation of health-related quality of life issues experienced by patients with desmoid-type fibromatosis	Winette van der Graaf	other	4/5/2020 (17/12/2021)
M20SCP (SCOPES)	Short Course Of Preoperative Radiotherapy in Head and Neck-, Trunk- and Extremity Soft Tissue Sarcomas; a randomized phase II clinical trial'	Rick Haas	Phase II	11/03/2021
M20SQL	Health-related Quality of Life- and Patient Reported Outcome assessment in soft tissue sarcoma patients	Rick Haas	other	01/10/2020
M21PIM (PIMP)	The value of a risk prediction tool (PERSARC) for effective treatment decisions of soft tissue sarcomas patients. (PIMP study)	Yvonne Schrage	other	04/08/2021
N16STS	Development of a platform of Patient Derived Xenografts (PDX) of Soft Tissue Sarcomas (STS): Protocol to obtain biopsies from patients with non-metastatic STS.	Rick Haas	Biobank	30/01/2017
N19PCA	Neoadjuvant trial on the efficacy of propranolol monotherapy in cutaneous angiosarcoma.	Neeltje Steeghs	other	03/12/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
URO-GENITAL				
C19IPI	Compassionate use Ipilimumab bij RCC, in combinatie met nivolumab (Free of charge programma bij sluisindicatie)	John Haanen	other	10/12/2019
C21AVE	monotherapie avelumab	Sil Kordes	other	08/10/2021
C21EVE	enfortumab vedotin expanded access program ((EV-902))	Michiel van der Heijden	other	28/09/2021
E1407 (TIGER)	A randomised phase III trial comparing conventional-Dose chemotherapy using paclitaxel, ifosfamide, and cisplatin (TIP) with high dose chemotherapy using mobilizing paclitaxel followed by High-dose carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ cell tumours	Martijn Kerst	Phase III	20/10/2016
M10PCM (PCMM)	Prostate cancer molecular medicine (PCMM)	Henk van der Poel	other	17/2/2011 (4/1/2022)
M13PSN	Prospective randomized multicenter comparison of indocyanine green (ICG)-99mTc-nanocolloid vs. 99mTcnanocolloid plus an intraoperative injection of ICG for the detection and surgical resection of the sentinel nodes in patients with prostate cancer	Henk van der Poel	Phase II	17/4/2014 (4/1/2022)
M14HSN	Sentinel node biopsy for bladder cancer using the hybrid tracer	Bas van Rhijn	other	26/02/2015
M14MSU (GO29293)	a phase II, multicenter, single-arm study of MPDL3280A in patients with locally advanced or metastatic urothelial bladder cancer	Michiel van der Heijden	Phase II	26/8/2014 (9/2/2021)
M15RTO (ROTOR)	Registry of Treatment Outcomes in a non-study population of Symptomatic Metastasized Castration Resistant Prostate Cancer (mCRPC) Patients Treated with Radium-223 (ROTOR-registry). WMO-protocol.	André Bergman	other	30/10/2015 (16/8/2021)
M16ARA (ARASENS)	A randomized, double-blind, placebo-controlled Phase III study of ODM-201 versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone-sensitive prostate cancer (ARASENS)	André Bergman	Phase III	10/05/2017
M16FPV (Fingerprint)	Vascular fingerprint to identify patients at risk for arterial cardiovascular events within the first year after start of cisplatin-based chemotherapy for testicular cancer: a validation study	Martijn Kerst	other	07/10/2016
M16OST (OSTRICh)	A randomized, open label, Phase IIB trial of Optimal Sequencing of Treatment Options for Poor Risk Metastasized Castration Resistant Prostate Cancer Previously Treated with Docetaxel (OSTRICh trial)	André Bergman	Phase II	01/06/2017
M17AIR	A Phase 3 Randomized Study Comparing Nivolumab and Ipilimumab Combination vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse	Hans van Thienen	Phase III	21/08/2017
M17MRP (MR PROPER)	MRI of the prostate with prior individual risk asessment (MR PROPER)	Henk van der Poel	other	23/1/2018 (4/1/2022)
M17NIU (CheckMate 901)	A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer	Michiel van der Heijden	Phase III	29/05/2017
M17PRO (PROSPEC)	prostate cancer follow-up care in secondary and primary health care (PROSPEC study)	Lonneke van de Poll-Franse	other	12/04/2018
M17SFC (Sunniforecast)	A Phase 2, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab Versus Sunitinib Monotherapy in Subjects with Previously Untreated and Advanced (unresectable or metastatic) non-clear Cell Renal Cell Carcinoma	John Haanen	Phase II	27/03/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18BMS	A Phase 3, Randomized, Study of Neoadjuvant Chemotherapy alone versus Neoadjuvant Chemotherapy plus Nivolumab or Nivolumab and BMS-986205, Followed by Continued Post-Surgery Therapy with Nivolumab or Nivolumab and BMS-986205 in Participants with Muscle-Invasive Bladder Cancer	Michiel van der Heijden	Phase III	29/01/2020
M18CLR (CLEAR)	E7080-G000-307: "A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR)"	Hans van Thienen	Phase III	23/10/2018
M18ERC (EASE RCC)	European Active Surveillance of Renal Cell Carcinoma study (E.A.S.E. RCC study)	Axel Bex	other	07/08/2018
M18ICR (ICRA)	ICRA (Improve Checkpoint-blockade Response in Advanced urothelial cancer), an adaptive clinical study to determine efficacy of combining weekly paclitaxel with tremelimumab +/- durvalumab (MEDI4736).	Michiel van der Heijden	Phase I/II	25/04/2019
M18NBB	A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined with Intravesical BCG in Participants with BCG-Unresponsive, High-Risk, Non-Muscle Invasive Bladder Cancer	Michiel van der Heijden	Phase II	16/11/2018 (4/1/2022)
M18NIA (NIAGARA)	A phase III, randomized, open-label, multi-center, global study to determine the efficacy and safety of Durvalumab in combination with Gemcitabine+Cisplatin for neoadjuvant treatment followed by Durvalumab alone for adjuvant treatment in patients with muscle-invasive bladder cancer (NIAGARA)	Michiel van der Heijden	Phase III	25/4/2019 (2/8/2021)
M18RAP (CERA-PRO)	Cost-Effectiveness of Robot-Assisted Prostatectomy versus laparoscopic prostatectomy a 5 year mulit institutional study of PROMs from a Dutch perspective: CERA-PRO	Henk van der Poel	other	12/4/2018 (4/1/2022)
M18ZIR (ZIRCON)	A confirmatory, prospective, open-label, multi-centre phase 3 study to evaluate diagnostic performance of 89Zirconium-labelled girentuximab(89Zr-TLX250) to non-invasively detect clear cell renal cell carcinoma (ccRCC) by positron emission tomography/CT (PET/CT) imaging in patients with indeterminate renal masses (ZIRCON study)	Marcel Stokkel	Phase III	12/07/2019
M19CRS (CROSS)	Identifying motivational differences associated with cancer-related fatigue: a cross-sectional study in testicular cancer survivors	Martijn Kerst	other	31/08/2020
M19CTR (CATCHER)	Diagnostic yield of colonoscopy surveillance in testicular cancer survivors treated with platinum-based chemotherapy	Monique van Leerdam	other	27/11/2019
M19HFL (Hypo-Flame 2.0)	Hypofractionated Focal Lesion Ablative Microboost in prostate cancer 2.0	Floris Pos	Phase II	2/11/2020 (2/12/2021)
M19KLK (KEYLYNK-010)	A Phase 3, Randomized Open-label study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) Who are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment with One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010)	André Bergman	Phase III	9/5/2019 (2/7/2021)
M19KNT (KEYNOTE-921)	A Phase 3, Randomized, Double-blind Study of Pembrolizumab (MK-3475) Plus Docetaxel Plus Prednisone versus Placebo Plus Docetaxel Plus Prednisone in Participants with Chemotherapy-naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) who have Progressed on a Next Generation Hormonal Agent (NHA) (KEYNOTE-921)	André Bergman	Phase III	27/06/2019
M19LNG (LONG)	Identifying motivational alterations associated with cancer-related fatigue: a longitudinal study in testicular cancer patients.	Martijn Kerst	other	19/10/2020
M19MAG (MAGNITUDE)	A phase 3 randomized, placebo-controlled, double-blind study of Niraparib in combination with Abiraterone acetate and Prednisone versus Abiraterone acetate and Prednisone for treatment of subjects with metastatic prostate cancer.	André Bergman	Phase III	03/07/2019

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M19NEK (nektar)	A Phase 2, randomized, non-comparative, open-label study of NKTR-214 in combination with nivolumab and of chemotherapy in cisplatin ineligible, locally advanced or metastatic urothelial cancer patients with low PD-L1 expression (Nektar studie)	Michiel van der Heijden	Phase II	12/8/2019 (7/6/2021)
M19NKT	A Phase 3, randomized, study of neoadjuvant and adjuvant nivolumab plus NKTR-214, versus nivolumab alone versus standard of care (SOC) in participants with muscle-invasive bladder cancer who are cisplatin ineligible.	Michiel van der Heijden	Phase III	14/05/2020
M19OTE (PROTEUS)	Randomized, double-blind, placebo-controlled, phase 3 study of Apalutamide in subjects with high-risk, localized or locally advanced prostate cancer who are candidates for radical prostatectomy.	Henk van der Poel	Phase III	28/10/2019
M19PKN	Prostaatkankernetwerk registry	Henk van der Poel	other	18/02/2020
M19PRS (PRIAS)	Prostate cancer Research International: Active Surveillance (PRIAS)	Henk van der Poel	other	12/12/2019
M19TPL	Transperineal Laser Ablation for focal treatment of Prostate Cancer: Safety and Ablative Efficacy evaluation using post-radical Prostatectomy Histological Analysis	Pim van Leeuwen	Pilot	13/08/2020
M19TRA (TRACE)	99mTechnetium based PSMA-Radioguided Assisted surgery for prostate Cancer (TRACE) feasibility Study	Pim van Leeuwen	Pilot	11/03/2020
M20ARV (AARDVARC)	A Phase II, Open-label, Study to Assess the Efficacy, Safety, and Tolerability of AZD4635 in Combination with Durvalumab and in Combination with Cabazitaxel and Durvalumab in Patients Who Have Progressive Metastatic Castrate-Resistant Prostate Cancer (AARDVARC)	André Bergman	Phase II	29/04/2021
M20BIN	A Phase Ib Trial to Evaluate the Efficacy and Safety of Bintrafusp Alfa Monotherapy in Metastatic or Locally Advanced/Unresectable Urothelial Cancer with Disease Progression or Recurrence Following Treatment with a Platinum Agent (keynote-213152)	Michiel van der Heijden	Phase I	06/10/2020
M20CPT (CAPItello-281)	A Phase III Double-Blind, Randomised, Placebo Controlled Study Assessing the Efficacy and Safety of Capivasertib + Abiraterone Versus Placebo + Abiraterone as Treatment for Patients with De Novo Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) Characterised by PTEN deficiency (CAPItello-281)	André Bergman	Phase III	25/11/2020
M20CRP (KEYNOTE-992)	A Phase 3, Randomized, Double-blind, Placebo-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Chemoradiotherapy (CRT) versus CRT Alone in Participants with Muscle-invasive Bladder Cancer (MIBC) (KEYNOTE-992).	Michiel van der Heijden	Phase III	22/07/2020
M20CTX	A Phase 1, Open-Label, Multicenter, Dose Escalation and Cohort Expansion Study of the Safety and Efficacy of Allogeneic CRISPR-Cas9-Engineered T Cells (CTX130) in Adult Subjects with Advanced, Relapsed or Refractory Renal Cell Carcinoma (RCC) with Clear Cell Differentiation.	John Haanen	Phase I	25/02/2021
M20CZR	A Phase II, Multicentre, Open-Label Study of Cabozantinib as 2nd Line Treatment in Subjects with Unresectable, Locally Advanced or Metastatic Renal Cell Carcinoma with Clear-cell Component Who Progressed After 1st Line Treatment with Checkpoint Inhibitors	John Haanen	Phase II	30/07/2020
M20DIS (DISCOVER)	DISCOVER – Prostate Cancer Study: Detecting Increased Susceptibility for Cancer in relatives by Offering genetic Variant Evaluation as Regular health care: prostate cancer	Henk van der Poel	other	04/03/2021

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M20FRM (PROSTAPROGRESS)	A confirmatory, prospective, open-label, single-arm, reader-blinded multi-centre phase 3 study to assess the diagnostic accuracy of Ferumoxtran-10-enhanced Magnetic Resonance Imaging (MRI) and unenhanced MRI in reference to histopathology in newly-diagnosed prostate cancer (PCA) patients, scheduled for radical prostatectomy (RP) with extended pelvic lymph node dissection (ePLND)	Ivo Schoots	Phase III	12/05/2021
M20MKE (KEYNOTE-991)	A phase 3, randomized, double blind trial of Pembrolizumab (MK3475) plus Enzalutamide plus ADT versus placebo plus Enzalutamide plus ADT in participants with metastatic hormone sensitive prostate cancer (mHSPC)	André Bergman	Phase III	18/8/2020 (30/6/2021)
M20MKR	Phase 2 Study of MK-6482 in Participants With Advanced Renal Cell Carcinoma	John Haanen	Phase II	22/10/2020 (5/10/2021)
M20MLC	An open-label, randomized, phase 3 study of MK-6482 in combination with Lenvatinib (MK-7902) vs Cabozantinib for second-line or third-line treatment in participants with advanced renal cell carcinoma who have progressed after prior anti-PD-1/L1 therapy	John Haanen	Phase III	07/05/2021
M20OTL	A phase 1a/1b/2 study to assess the safety, tolerability and pharmacokinetics of OTL78, a PSMA-targeted fluorescent agent, for the intraoperative imaging of prostate cancer	Henk van der Poel	Phase I/II	24/6/2020 (25/3/2021)
M20PPT (PEACH)	PSMA-PET/CT imaging in the EArly detection of Cancer of the prostate with High risk features (PEACH trial)	Pim van Leeuwen	other	02/02/2021
M20PRD (PREDICT)	Prospective Randomized Controlled Trial To Evaluate The Prognostic Role of Lymph Node Dissection In Men With Intermediate Risk Prostate Cancer Treated With Radical Prostatectomy (PREDICT-Study)	Henk van der Poel	other	16/06/2021
M20PRE (PRE-PREVENCYS)	The accuracy of detecting residual disease following neo-adjuvant chemotherapy in patients with muscle-invasive bladder cancer	Bas van Rhijn	other	22/10/2020
M20PRF (PROOF302)	Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Infigratinib for the Adjuvant Treatment of Subjects with Invasive Urothelial Carcinoma with Susceptible FGFR3 Genetic Alterations (PROOF 302)	Jeantine de Feijter	Phase III	09/07/2021
M20SGN	An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab with or without chemotherapy, versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer.	Michiel van der Heijden	Phase III	01/04/2021
M20THR (THOR)	A phase 3 study of Erdafitinib compared with Vinflunine or Docetaxel or Pembrolizumab in subjects with advanced urothelial cancer and selected FGFR gene aberrations.	Jeantine de Feijter	Phase III	31/08/2020
M21JNP	A Phase 1 Study of JNJ-78278343, a T Cell Redirecting Agent Targeting Human Kallikrein-2 (KLK2), for Advanced Prostate Cancer.	Marloes van Dongen	Phase I	06/09/2021
M21MUP	Improving the algorithm and preliminary assessment of the performance of 3D multiparametric ultrasound for the detection, grading and localization of prostate cancer.	Henk van der Poel	other	16/09/2021
M21NSC (NESCIO)	Prospective, randomized, non-comparative, neoadjuvant phase II study with combination immuno-oncology in primary clear cell renal cell cancer at risk for recurrence or distant metastases (NESCIO-trial)	John Haanen	Phase I/II	05/01/2022
M21PQ1 (PROQURE-1)	Tolerability of concurrent External Beam Radiotherapy + Lu-PSMA for node-positive prostate cancer (PROQURE-1)	Wouter Vogel	Phase I	14/12/2021
M21TAR	Phase 2b Clinical Study Evaluating Efficacy and Safety of TAR-200 in Combination with Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in Participants with High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Intravesical Bacillus Calmette-Guerin (BCG) who are Ineligible for or Elected Not to Undergo Radical Cystectomy.	Michiel van der Heijden	Phase II	03/11/2021

Type of cancer Study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M21TUR (TURANDOT)	A Phase 1b Trial in Stage II-III URothelial cANcer to explore pre-operative DOmaTinostat, nivolumab and ipilimumab – TURANDOT	Michiel van der Heijden	Phase I	23/08/2021
N14DAR (DARANA)	Dynamics of Androgen Receptor genomics and transcriptomics after neoadjuvant androgen ablation (DARANA)	Henk van der Poel	Phase II	27/08/2014
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/2014
N15DOP	Weekly ModraDoc006/r in combination with hormonal treatment and high-dose intensity-modulated radiation therapy in patients with high-risk early stage prostate cancer	Baukelien van Triest	Phase I	12/05/2016
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/2016
N17DIP	Clinical pharmacokinetics of intravenous docetaxel in patients with castration-resistant prostate cancer and non-castration-resistant prostate cancer	André Bergman	other	27/12/2017 (24/9/2021)
N17JAV (NEOJAVALIN)	Neoadjuvant AXITINIB plus AVELUMAB for patients with localized RCC and a moderate to high risk of recurrence. A phase II study of the Netherlands Cancer Institute (NEOJAVALIN)	Axel Bex	Phase II	16/05/2018
N17NAB (NABUCCO)	Phase 1B Study to assess safety and efficacy of Neo-Adjuvant Bladder Urothelial Carcinoma COmbination-immunotherapy (NABUCCO/CA209-9Y4))	Michiel van der Heijden	Phase I	04/12/2017
N18CLI (CLIPPS)	A feasibility study on Cerenkov Luminescence Imaging during prostate cancer surgery using Gallium-68 PSMA (CLIPPS)	Marcel Stokkel	other	12/02/2019
N18PER (PERICLES)	PEnile cancer Radio- and Immunotherapy CLinical Exploration Study – a Phase 1B study of atezolizumab with or without radiotherapy in penile cancer.(PERICLES)	Michiel van der Heijden	Phase I	21/9/2018 (2/8/2021)
N18PSM	Variatie in PSMA receptor expressie over de tijd in prostaatkanker	Marcel Stokkel	other	19/12/2018
N19IFC (INFLUENCE)	INtra-operative evaluation of a novel FLUorescENt C-mEt tracer in penile and tongue cancer	Baris Karakullukcu	other	13/11/2019
N20ADT	implementatie onderzoek voorlichting androgeen deprivatie therapie	Esther Wit	other	15/12/2020
N20CYM	Phenotyping study of the CYP3A4 activity in patients with prostate cancer versus patients with other types of solid tumours with oral midazolam	Frans Opdam	other	10/02/2021
N20DPP	Using a drop-in probe to conduct optical measurements during robot assisted laparoscopic prostatectomy.	Theo Ruers	Pilot	29/03/2021
N20PIP (PARTI)	Prostatic Artery Injection vs intravenous injection of 18F-DCFPyL for the evaluation of Prostate Cancer (PARTI)	Henk van der Poel	other	25/02/2021
N20PRO	Selecting a subset of PRO-CTCAE for prostate cancer patients	Floris Pos	other	21/1/2020 (12/1/2021)
N20SSG	Does stimulation of salivary glands by oral intake increase uptake of PSMA-ligands?	Wouter Vogel	Phase II	18/8/2020 (2/2/2021)
N20TOP	Evaluatie patiënt tevredenheid van de operatieve behandeling bij prostaatkanker	Pim van Leeuwen	other	18/5/2020 (27/12/2021)
N20TSE	Current practices and patient perceptions of personalized risk information of treatment side effects	Lonneke van de Poll-Franse	other	16/12/2020
N21IGN	Feasibility of in vivo image-guided navigation during a robot-assisted prostatectomy.	Theo Ruers	other	31/03/2021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Invited speakers

Nicola Aceto
ETH Zurich, Institute of Molecular Health Sciences, Switzerland
Biology and vulnerabilities of circulating tumor cells

Reuven Agami
Netherlands Cancer Institute, Amsterdam, Erasmus MC Rotterdam, Oncode Institute Utrecht, the Netherlands
Sloppiness Inm RNAT ranslationl nC ancer

Matthias Altmeyer
Molecular Mechanisms of Disease (DMMD), University of Zurich, Switzerland
Charting cellular responses to genotoxic stress

Roderick Beijersbergen
Netherlands Cancer Institute, Amsterdam, the Netherlands
Diving deep; Large scale functional genomic screening for complex and dynamic phenotypes

Alistair Boettiger
Stanford University School of Medicine, Stanford, USA
How does structurally flexible chromatin regulate reliable gene expression?

Stirling Churchman
Harvard Medical School, Boston, USA
Choreography of gene expression, from the nucleus to mitochondria

Markus Covert
Stanford University, Stanford, USA
The Enemy of My Enemy: New Insights Regarding Bacteriophage-Mammalian Cell Interactions

Alan D'Andrea
Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA
Overcoming PARP Inhibitor Resistance

Bart Deplancke
EPFL, Institute of Bio-engineering & Swiss Institute of Bioinformatics, Lausanne, Switzerland
Dissecting the role of a regulatory variant in cancer (CLL) predisposition and progression

Mikala Egeblad
Cold Spring Harbor Laboratory, Long Island, New York, USA
Heroes and villains - innate immune cells regulating metastasis

Eran Elinav
Weizmann Institute of Science, Rehovot, Israël
Host micro biome interactions in health and disease

Manel Esteller
Josep Carreras Leukaemia Research Institute, Barcelona, Spain
Epigenetics and epitranscriptomics in cancer: From knowledge to applications

Marcia Haigis
Blavatnik Institute, Cell Biology, Harvard Medical School, Boston, USA
Investigating metabolism in the tumor microenvironment

Christine Iacobuzio-Donahue
David M. Rubenstein Center for Pancreatic Cancer Research, MSKCC, New York, USA
New insights into pancreatic cancer biology and genetics

Carl June
Center for Cellular Immunotherapies, Parker Institute for Cancer Immunotherapy, Perelman School of Medicine, Philadelphia, USA
Engineered T cells: all the cells are strong, and their children are all above average

Lee Kraus
UT Southwestern Medical Center, Dallas, USA
Molecular mechanisms of enhancer assembly and function

Arnaud Krebs
Genome Biology, EMBL, Heidelberg, Germany
Cooperativity and antagonism at cis-regulatory elements

Galit Lahav
Novartis Professor and Chair of Systems Biology, Harvard Medical School, Boston, USA
Protein Dynamics and Decision Making in Single Cells

Fred van Leeuwen
Netherlands Cancer Institute, Amsterdam, the Netherlands
Decoding epigenetic mechanisms of gene regulation

David Levens
Center for Cancer Research, NCI, Bethesda, Maryland, USA
The regulation of transcription by DNA conformation, supercoiling and MYC

Núria López-Bigas
ICREA-Research Professor at Institute for Research in Biomedicine (IRB Barcelona), Spain
Computational analysis of cancer genomes

Laura Mackay
Peter Doherty Institute, University of Melbourne, Australia
Regulation of resident memory T cells

Chris Marine
VIB/KU Leuven, Belgium
Nongenetic mechanisms of tumor evolution and therapy resistance

Jurgen Marteijn
Oncode Institute, Erasmus MC, Rotterdam, the Netherlands
Unraveling the cellular responses to DNA damage-induced transcription stress

Pamela Ohashi
Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University of Toronto, Canada
Insights in immune regulation from the tumor microenvironment

Philippe Pasero
Institute of Human Genetics, CNRS and University of Montpellier, France
Cellular responses to replication stress: from stalled forks to inflammation

Alexandros Pertsinidis
Structural Biology Program, Memorial Sloan Kettering Cancer Center, New York, USA
Single-molecule imaging of transcription mechanisms in live cells

Marisol Soengas
Spanish National Cancer Research Centre, Madrid, Spain
Imaging and targeting (pre)metastatic niches in melanoma

Sabine Vogler
Austrian National Public Health Institute (GÖG), Vienna, Austria
Challenges of pricing new cancer medicines

Ashani Weeraratna
Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
Age against the Machine - How aging disrupts the homeostasis of cancer

Britta Weigelt
Memorial Sloan Kettering Cancer Center, New York, USA
Deconstructing the molecular heterogeneity of gynecologic cancer

Pieter Rein ten Wolde
Biochemical Networks, Amolf, Science Park Amsterdam, the Netherlands
The bacterial cell cycle: an adder or a sizer?

Philip Zegerman
Wellcome Trust/Cancer Research UK, Gurdon Institute and Department of Biochemistry, Cambridge, UK
DNA replication initiation control - new beginnings

Research projects supported by the Dutch Cancer Society

Principal investigator	Title	Started	Ended / Ends
Agami, R.	Exploring the role of serine metabolism adaptations in platinum resistant high grade serous ovarian cancer	01/9/18	31/8/22
Agami, R.	Cancer-induced Sloppiness in protein production	01/10/21	30/9/25
Agami, R.	Exploiting proline vulnerability for cancer therapy	01/11/17	31/10/21
Akkari, L.	Investigating the Cancer Cell-Mediated Shaping of the Liver Immune Environment	01/1/19	31/12/22
Akkari, L.	Harnessing the tumor immune microenvironment in the context of pro-senescence therapy: A novel therapeutic approach for liver cancer	01/9/21	31/8/25
Akkari, L.	Improving the effects of standard of care therapy in glioma by modulating tumor-associated macrophages and microglia functions	01/6/17	31/5/22
Amant, F.C.H.	Cancer treatment during pregnancy: addressing the Later concerns of its fetal safety (CRADLE-II)	01/6/21	31/5/25
Amant, F.C.H.	CRADLE: Cancer tReAtment During pregnancy: from fetaL safety to maternal Efficacy	01/5/17	31/1/22
Amant, F.C.H.	Postpartum breast cancer diagnosed during involution: a distinct entity with unique clinicopathological, molecular and immunological features?	01/1/18	30/4/22
Beets, G.L.	Multicenter evaluation of the 'wait-and-see' policy for complete responders after chemo radiotherapy for rectal cancer	01/10/15	30/9/21
Beijersbergen, R.L.	ScreeninC: a national infrastructure for functional genome editing and large scale functional genomic screening	01/10/20	30/9/24
Bleiker, E.M.A.	Choices in breast surgery and reconstruction: implementation and testing of a web-based psycho-educational intervention to facilitate decision making	01/11/15	31/5/21
Bleiker, E.M.A.	The effect of light-therapy on fatigue and psychosocial functioning in long-term survivors of (non-) Hodgkin lymphoma: a randomized controlled trial	01/8/16	31/5/21
Borst, G.R.	New era of radio sensitization by modulating radio sensitizing agents during RT	01/2/18	31/12/23
Borst, J.G.	Achieving synergy between radiotherapy and immunotherapy to increase control of metastatic cancer	01/2/18	31/1/23
Brummelkamp, T.R.	identification and validation of genetic factors that determine sensitivity to Weel inhibition in high-grade ovarian cancer and related cancers	01/10/18	30/9/23
Burgers, J.A.	Switch maintenance treatment with gemcitabine for patients with malignant mesothelioma who do not progress after 1st line therapy with a pemetrexed-platinum combination. A randomized open label phase II study	01/3/13	31/10/22
Driel, van W.J.	Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for stage III ovarian cancer: a randomized phase III trial (OVHIPEC-2)	01/12/19	31/5/26
Driel, van W.J.	Implementation of HIPEC for patients with stage III ovarian carcinoma treated with neoadjuvant chemotherapy and interval debulking in the Netherlands	01/8/19	31/7/22
Faller, W.J.	The role of translation elongation in models of intestinal cancer	01/7/17	30/6/22
Graaf, van der W.T.A.	Dutch nationwide infrastructure for COMPRehensive health outcome and intervention research among Adolescent and Young Adult cancer survivors (COMPRAYA)	01/1/20	31/12/24
Haanen, J.B.A.G.	Deep profiling of T cell reactivity against cancer for improved immunotherapy	01/1/21	31/12/24
Haanen, J.B.A.G.	POINTING: Towards patient-tailored cancer immunotherapy supported by a multifaceted predictive signature composed of integrative omics and molecular imaging	01/9/17	31/8/23
Haanen, J.B.A.G.	Netherlands Facility for Cancer Immune Analysis (N-CIA)	01/5/18	30/4/24

Principal investigator	Title	Started	Ended / Ends
Hartemink, K.J.	A comparison of stereotactic ablative radiotherapy versus minimally invasive lobectomy for early-stage non-small cell lung cancer. ESLUNG	01/3/21	31/8/22
Harten, van W.H.	Does physical exercise during adjuvant cardiotoxic chemotherapy protect against cardiac injury among women with breast cancer? HEART	01/9/17	31/1/22
Hauptmann, M.	Statistical assessment of cancer risks from therapeutic radiation exposure incorporating the spatial distribution of radiation dose in the target organ	01/12/17	31/5/22
Hauptmann, M.	Novel statistical methods for efficient identification of biomarkers for personalized cancer treatment	01/9/17	30/4/23
Heide, van der U.A.	PRocESs study: PRostate cancer - Expansion of surveillance Selection	01/3/21	28/2/25
Heide, van der U.A.	Brachytherapy for rectal cancer: a better balance between tumor control and side effects.	01/11/14	30/4/22
Heide, van der U.A.	Focal escalation of the radiation dose to the tumor in prostate cancer	01/4/17	31/3/21
Heijden, van der M.S.	Phase 2 clinical study to assess efficacy of Induction ipilimumab/nivolumab to spare the bladder in urothelial bladder cancer (IndiBlade)	01/7/21	30/6/25
Heijden, van der M.S.	Genetic causes of resistance to new androgen receptor signaling inhibitors in circulating tumor DNA of metastasized castration resistant prostate cancer patients	01/6/15	31/5/21
Horlings, H.M.	Genetic properties of breast carcinomas associated with cancer-immune interactions	01/11/17	31/10/22
Houdt, van W.J.	Development of a translational ex-vivo model of zD cells and organoids as a predictive tool for soft tissue sarcoma	01/7/20	30/6/24
Husson, O.	Psychosocial and physical problems and needs of adolescents and young adults (AYAs) with cancer: Towards comprehensive patient-centered care	01/10/18	30/6/21
Husson, O.	Psychosocial and physical problems and needs of adolescents and young adults (AYAs) with cancer: Towards comprehensive patient-centered care	01/10/18	30/6/21
Jacobs, H.B.	Targeting epigenetic crosstalk in Diffuse Large B Cell Lymphoma	01/5/20	30/4/24
Jacobs, H.B.	Precision Cancer Therapy: Profiting from Tumor Specific Defects and Synthetic Lethality in the DNA Damage Tolerance System	01/3/17	31/3/22
Jacobs, H.B.	Role of DNA Damage Tolerance Pathways in Genome Maintenance, Tissue Homeostasis, and Cancer Suppression	01/10/17	31/3/22
Jacobs, J.J.L.	Mechanisms to overcome replication challenges at telomeres	01/8/19	31/7/23
Jacobs, J.J.L.	Revealing novel modes of DNA repair control by ubiquitin(-like) reversal	01/10/20	30/9/24
Jacobs, J.J.L.	Mechanisms of DNA repair pathway control at DNA double-strand breaks and telomeres	01/10/17	30/6/22
Jong, de M.C.	INTERACTION of hypofractionated radiotherapy with targeted agents, antibodies and immunotherapy	01/4/20	31/3/24
Jonkers, J.M.M.	Functional validation of somatic variants of unknown significance in clinically actionable kinases.	01/6/21	31/5/25
Jonkers, J.M.M.	Combatting therapy resistance by integrating genomic, transcriptomic and proteomic data from mouse models of invasive lobular breast carcinoma	01/1/17	31/12/21
Kok, M.	Improving immune checkpoint blockade for advanced triple negative breast cancer patients	01/9/21	31/8/25
Krimpenfort, P.J.A.	CustoMICE: a facility for production and distribution of engineered mouse models for cancer research	01/1/18	30/6/21
Kvistborg, P.	How checkpoint blockade alters the quality of tumor specific T cells	01/10/16	31/1/22
Lambregts, D.M.J.	Development and validation of a multiparametric imaging model for pre-treatment response prediction in rectal cancer: the road towards organ-preservation	01/10/17	31/10/21

Principal investigator	Title	Started	Ended / Ends
Leerdam, van M.E.	Evaluation of optimal intervals for colonoscopy surveillance: a randomized trial	01/2/17	31/1/29
Leeuwen, van F.	DOT1L as a druggable epigenetic writer in T cell programming and immunotherapy	01/12/18	31/8/21
Leeuwen, van F.	Targeting epigenetic crosstalk in Diffuse Large B Cell Lymphoma	01/5/20	30/4/24
Leeuwen, van F.E.	Prediction tools for Hodgkin lymphoma patients to weigh benefits and harms of different treatment and survivorship care strategies	01/9/20	31/8/24
Leeuwen, van F.E.	Favorable and unfavorable effects of risk-reducing salpingo-oophorectomy(RRSO) in women at high genetic risk of ovarian cancer	01/7/17	31/10/22
Leeuwen, van F.E.	Cardiotoxicity and second cancer risk after treatment of aggressive B-cell Non-Hodgkin lymphoma	01/1/18	30/9/22
Leeuwen, van F.E.	The BETER-REFLECT biobank: A REsource For studies on Late Effects of Cancer Treatment	01/2/18	31/1/23
Leeuwen, van F.E.	A risk prediction tool for cardiovascular disease in breast cancer patients. PREDICT	01/12/17	01/3/22
Leeuwen, van F.E.	Psychosocial factors and cancer incidence: a pre-planned meta-analysis of the pSychosocial	01/12/17	30/11/21
Linn, S.C.	The substantially improving the cure rate of high-risk BRCAi-like breast cancer patients with personalized therapy (SUBITO) trial; an international randomized phase III trial. SUBITO study.	01/2/16	31/12/22
Lohuizen, van M.M.S.	Identifying and testing new intervention therapies for mesotheliomas.	01/9/18	31/8/22
Lok, C.A.R.	OVI-DETECT; Liquid biopsies for improving the pre-operative diagnosis of ovarian cancer	01/11/20	31/10/24
Mann, R.M.	AI-based adaptive breast MRI to optimize throughput and accuracy	01/9/21	31/8/25
Medema, R.H.	Unbalanced genomes: why do cancer cells not care?	01/11/19	31/10/23
Meijer, G.A.	Towards implementation of liquid biopsy cell-free circulating tumor DNA as prognostic biomarker for stage I II colon cancer patients. PROVENC3	01/7/19	31/12/22
Meijer, G.A.	MOCCAS; Molecular Stool test for postpolypectomie surveillance	01/7/15	30/9/21
Meijer, G.A.	Liquid biopsy analyses of cell-free circulating tumor DNA as predictive and prognostic biomarker for colorectal cancer patients with metastatic disease	01/10/17	31/3/22
Nowee, M.E.	Towards personalized MRI-guided radiotherapy for liver oligometastases	01/8/21	31/7/25
Opdam, F.L.	Identification and validation of genetic factors that determine sensitivity to Weel inhibition in high-grade ovarian cancer and related cancers	01/10/18	30/9/23
Peeper, D.S.	AXL as an anchor to combat therapy-refractory Soft Tissue Sarcoma	01/9/19	31/8/23
Peeper, D.S.	Targeting phenotype switching as a therapy for melanoma	01/9/17	31/8/22
Ploeg, van der I.M.C.	Prevention of Persistent Pain after Breast Cancer Treatment by web-based Cognitive Behavioral Therapy (AMAZONE)	01/7/21	30/6/22
Poll, van de L.V.	A randomized study, PROstate cancer follow-up care in secondary and Primary health care (PROSPEC)	01/9/17	31/8/22
Rheenen, van J.E	Mechanistic insight in the role of cell competition in growth of colorectal cancer liver metastases	01/1/19	31/12/22
Rheenen, van J.E	The intermediate filament network in glioma invasion	01/5/17	31/10/21
Riele, te H.P.J.	INVUSE: Investigation of variants of uncertain clinical significance for use in clinical practice	01/2/18	31/1/22
Riele, te H.P.J.	Targeting replication rescue pathways	01/3/18	28/2/23

Principal investigator	Title	Started	Ended / Ends
Rookus, M.A.	The potential association between circadian disruption and hormone-related cancer risk; prospective cohort study among 59,947 female nurses	01/8/20	31/7/24
Rookus, M.A.	A nationwide prospective cohort study among 59,947 female nurses to elucidate the potential association between shift work and risk of breast cancer	01/2/16	31/1/21
Rowland, B.D.	SWI/SNF-mediated cohesin loading: A dual role in tumorigenesis?	01/7/19	30/6/23
Rowland, B.D.	A universal binding hub on cohesin to control the genome?	01/1/21	31/12/24
Ruers, T.J.M.	Augmented reality for precision surgery in cancer	01/11/20	31/10/24
Ruers, T.J.M.	Towards minimal invasive breast cancer treatment	01/10/21	30/9/25
Ruers, T.J.M.	TomTom voor de OK	01/1/17	31/12/21
Ruers, T.J.M.	Improving the outcome of breast cancer surgery by real time assessment of resection margins using Hyperspectral Imaging	01/1/18	30/6/22
Schagen, S.B.	Monitoring, understanding and managing cognitive problems in cancer patients without central nervous system disease: putting knowledge into practice	01/1/17	30/6/24
Schagen, S.B.	Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer	01/9/16	31/8/21
Schmidt, M.K.	Risk prediction, screening and Therapy of breast cancer in women from CHEK2 c.1100delC families in the Netherlands (in ART).	01/11/17	31/10/21
Schmidt, M.K.	Balancing risks of under- and overtreatment in young breast cancer patients: a focus on the triple negative subtype	01/2/19	31/1/23
Schmidt, M.K.	Nationwide infrastructure integrating research and health care to improve management for Dutch women with familiar breast cancer risk	01/8/20	31/7/25
Scholten, A.N.	Pre-versus postoperative accelerated partial breast irradiation in early stage breast cancer patients (PAPBI-2). A randomized phase III trial. M15PAP	01/1/21	31/12/24
Schoots, I.G.	PROCESS study: PROstate Cancer - Expansion of Surveillance Selection criteria with MR imaging	01/3/21	28/2/25
Schröder, C.P.	"SONImage study: Can molecular imaging predict outcome to first-line endocrine treatment I CDK4,/6 inhibition in advanced ER+ breast cancer?"	01/1/20	31/12/23
Sixma, T.K.	Structural analysis of individual PRC1 complexes to enable selective drug discovery	01/4/21	31/3/25
Sonke, G.S.	High-dose alkylating chemotherapy in oligo-metastatic breast cancer harboring homologous recombination deficiency	01/7/12	01/4/21
Sonke, J.J.	Cardiac changes after radiotherapy with high fraction doses for early stage lung cancer. M19CCR.	01/9/19	28/2/23
Sonke, J.J.	Proton Therapy Research Infrastructure - ProTRAIT	01/2/18	31/10/21
Sonnenberg, A.	Analysis of the role of PEAK1, an integrin-associated pseudokinase, in the initiation and progression of colorectal carcinomas	01/10/19	30/9/23
Steeghs, N.	Treatment of gastrointestinal stromal tumors based on serial mutation analysis of circulating tumor DNA: GALLOP	01/3/18	28/2/22
Stuiver, M.M.	(Cost-)effectiveness of a multimodal prehabilitation program in patients with muscle invasive bladder cancer. The ENHANCE randomized controlled trial	01/9/21	31/8/25
Tellingen, van O.	Multi-target combination therapy (MTCT) targeting PI3K, MAPK and CDK4/6-Rb pathways for treatment of glioblastoma.	01/12/20	30/11/24

Principal investigator	Title	Started	Ended / Ends
Thommen, D.S.	Dysfunctional T cells in predicting and modulating the response to PD-1 blockade in human cancer	01/6/19	31/5/23
Trommel, van N.E.	Neo-Adjuvant Chemotherapy and Less Extensive Surgery in Cervical Cancer to Preserve Fertility (CONTESSA/NEOCON-F - M20TES).	01/2/21	31/1/25
Verheij, M.	Multicentre randomised phase II trial of neo-adjuvant chemotherapy vs. chemotherapy/ chemoradiotherapy vs. chemoradiotherapy followed by surgery in resectable gastric cancer (CRITICS-II)'	01/12/17	30/6/22
Visser, de K.E.	Understanding and exploiting eosinophils to enhance the response of breast cancer to immunotherapy	01/5/21	30/4/25
Visser, de K.E.	Enhancing the success of immunotherapy for metastatic breast cancer by overcoming tumorassociated immunosuppressive mechanisms	01/5/17	31/10/21
Visser, de K.E.	Dissecting how tumor-associated myeloid cells counteract chemotherapy response of breast cancer	01/4/18	31/3/22
Voest, E.E.	Tumor organoids: feasibility to predict sensitivity to treatment in cancer patients (TUMOROID trial M14TUM)	01/7/15	31/12/21
Voest, E.E.	The Drug Rediscovery Protocol (DRUP trial)	01/6/17	31/5/22
Vogel, W.V.	Comprehensive functional salivary gland management to avoid an iatrogenic dry mouth	01/11/17	30/11/21
Wesseling, J.	PROACTING: PRedicting neOAdjuvant Chemotherapy Treatment response with deep learnING	01/7/19	31/12/21
Wesseling, J.	Which current liquid biopsy techniques allow treatment monitoring in the neoadjuvant breast cancer setting?	01/9/20	31/8/22
Wesseling, J.	Combining features from in-depth mammography analysis and pathology to optimize referral of possible invasive breast cancers at screening (IMAGINE).	01/7/19	30/6/23
Wesseling, J.	Management of low risk ductal carcinoma in situ: watchful waiting or not? A randomized, non-inferiority trial. (LORD Trial)	01/2/15	28/2/21
Wesseling, J.	Management of low grade ductal carcinoma in situ: active surveillance or not? A randomized, non-inferiority phase III trial (LORD studie)	01/7/15	30/9/22
Wesseling, J.	Improving breast cancer screening among young high risk women by blood-based methods. E. Lips	01/2/18	31/1/23
Wessels, L.F.A.	From fixed to functional pathology: defining intermediate phenotypes that determine prognosis and therapy response	01/12/18	31/5/21
Wessels, L.F.A.	Phosphoproteomics and integrative analysis to enable precision medicine for anti-EGFR therapy in colorectal cancer	01/1/20	31/12/23
Wessels, L.F.A.	OVI-DETECT; Liquid biopsies for improving the pre-operative diagnosis of ovarian cancer.	01/11/20	31/10/24
Wessels, L.F.A.	Combatting therapy resistance by integrating genomic, transcriptomic and proteomic data from mouse models of invasive lobular breast carcinoma	01/1/17	31/12/21
Wessels, L.F.A.	Genetic causes of resistance to new androgen receptor signaling inhibitors in circulating tumor DNA of metastasized castration resistant prostate cancer patients	01/6/15	31/5/21
Zwart, W.T.	Unraveling DNA repair / Estrogen Receptor interplay in breast cancer	01/6/19	31/5/23
Zwart, W.T.	Exploiting the Glucocorticoid Receptor signaling axis to induce growth arrest in lung cancer	01/11/19	31/10/23
Zwart, W.T.	Biomarker discovery for prognostication and treatment selection in prostate cancer through Androgen Receptor profiling	01/6/17	31/1/22

Research projects supported by other organisations

Principal investigator	Granting agency	Title	Started	Ended / Ends
Agami, R.	AVL Foundation	Ribosome profiling	01/01/20	31/12/23
Agami, R.	AVL Foundation	Immunopeptidomics for the detection of novel cancer-relevant immunogenic peptides	01/02/21	31/01/22
Agami, R.	EMBO	Fellowship A. Pataskar	01/11/20	31/03/21
Agami, R.	European Commission	Breaking borders, Functional genetic screens of structural regulatory DNA elements	01/09/19	31/08/24
Agami, R.	ZonMw	Uncovering cancerous enhancers of prostate and breast cancers	01/03/17	28/02/21
Akkari, L.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/17	31/12/21
Akkari, L.	The Royal Institution for the Advancement of Learning/McGill University	Harnessing the brain tumor immune-microenvironment to enhance therapeutic efficacy	01/01/19	31/12/22
Akkari, L.	ZonMw	Investigating the Consequences of Macrophage Evolution in Brain Tumor Recurrence Post-Radiotherapy	01/11/19	31/10/24
Akkooi, van A.C.J.	Amgen B.V.	the infra structure registry: prospective melanoma stadium III registry	01/07/17	30/06/21
Amant, F.C.H.	AVL Foundation	Is breastfeeding possible for women with a diagnosis of breast cancer during pregnancy or lactation? (GALACTIc).	01/01/21	31/12/22
Amant, F.C.H.	European Commission	CRADLE: Cancer tReAtment During pregnancy: from fetaL safety to maternal Efficacy	01/10/15	31/03/21
Amant, F.C.H.	KU Leuven Research & Development	Co-Culturen sarcoom organoids	01/12/19	30/11/22
Baas, P.	AVL Foundation	E-Nose	01/11/19	31/10/22
Baas, P.	European Commission	DC-based immunotherapy to treat Malignant Mesothelioma	01/01/16	31/12/21
Beets - Tan, R.G.H.	European Commission	Active Monitoring of Cancer As An Alternative To Surgery' – 'CAST'	01/11/19	31/10/23
Beets, G.L.	Covidien AG	The Grant is to support a fellowship for the specialty education of healthcare Professionals in the area of lung surgery.	01/02/21	31/01/22
Beijersbergen, R.L.	Ambagon Therapeutics, Inc.	Stabilization of 14-3-3 protein-protein interactions as potential new therapeutic strategy for cancer	01/02/21	31/01/22
Beijersbergen, R.L./ Peeper, D.S.	Merck Sharp & Dohme Corp.	Identification of chromatin modifiers genes that upon inactivation show a synthetic lethal phenotype with Switch/Sucrose NonFermentable (SWI/SNF) chromatin-remodeling complex mutations in tumor cell lines.	08/09/15	08/09/21
Beijnen, J.H.	European Commission	Afri-KA-DIA: Towards an adapted, safe, effective combination treatment for African visceral leishmaniasis (Kala Azar) and improved diagnostic tools (Horizon 2020 EU funding for Research & Innovation)	01/11/17	30/11/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Beijnen, J.H.	European Commission	Efficacy and Safety of a newly registered Artemisinin-Based Combination (Pyronaridine- Artesunate - PYRAMAX®) for the treatment of uncomplicated malaria in African pregnant women	01/03/19	29/02/24
Belderbos - Candiff, J.S.A.	NVRO	Ontwikkeling en implementatie van PRO-CTCAE-subsets voor longkankerpatiënten.	01/09/19	30/06/22
Belderbos - Candiff, J.S.A.	IKNL	Implementatie van patiënt-gerapporteerde (PRO) monitoring van bijwerkingen en therapietrouw van systemische behandeling	01/08/18	31/07/21
Bergman, A.M.	AVL Foundation	CRISPR screen to identify genes critical for prostate cancer cells faith in a context with macrophages and cancer associated fibroblasts	01/01/19	31/12/24
Bergman, A.M.	Stichting DUOS	Zijn er in prostaatkankermetastasen van eerder op de prostaat bestraalde patiënten mutaties te vinden passend bij ioniserende bestraling?'	01/06/19	31/05/22
Bergman, A.M.	Stichting DUOS	Kan next-generation-sequencing van cfDNA in base-line plasma een response voorspellen op cabazitaxel en abiraterone/enzalutamide in docetaxel behandelde hoog-risico mCRPC patiënten?	01/04/21	31/03/23
Bernards, R.	AVL Foundation	AVL Foundation onderzoek alvleesklierkanker en het KRAS-gen	01/01/20	31/12/22
Bernards, R.	CGC	POC clinical trial voor melanoma atiënten	01/12/15	31/12/21
Bernards, R.	European Commission	SENCAN - Senescence therapy for cancer	01/10/18	30/09/23
Bernards, R.	Health-Holland	Exploiting senescence for the treatment of cancer	01/04/21	30/09/23
Bernards, R.	HepaRegeniX GmbH	Synthetic lethal interactions of MKK4 inhibitors in KRAS mutant cancers	01/10/21	01/02/22
Bernards, R.	Lixte Biotechnology Holdings, INC	Synthetic lethal combinations of LB-100 and stress-targeted drugs	08/10/21	07/10/23
Bernards, R.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/13	31/12/21
Bernards, R.	Stand up to cancer (SU2C)	SU2C - Targeting SHP2 in pancreatic cancer	01/11/18	30/06/23
Bernards, R.	Stichting Oncode Institute	Building a Reproducible Single - Cell Experimental Workflow to Capture Tumour Drug Resistance (PERSIST- SEQ)	01/10/21	30/09/25
Bernards, R.	The Mark Foundation for Cancer Research	Overcoming heterogeneity to kill senescent cancer cells	01/01/20	31/03/21
Beurden, van M.	AVL Foundation	Onderzoek naar vrouwen met LS, die kanker ontwikkelen	01/05/18	31/07/22
Bex, A.	AVL Foundation	Onderzoek heldercellige niercelcarcinoom	22/01/20	21/01/23
Blank, C.U.	AVL Foundation	Impulsplan Immuuntherapie	01/04/18	04/03/21
Blank, C.U.	Bristol Myers Squibb Company USA	3D analyses of melanoma treated with Ipilimumab + Nivolumab neoadjuvant	01/01/19	07/05/22

Principal investigator	Granting agency	Title	Started	Ended / Ends
Blank, C.U.	Bristol Myers Squibb Company USA	Characterization of stage III melanoma nonresponders upon neoadjuvant IPI1 NIVO3 by TMB, RNA-signature analyses.	15/04/21	30/09/22
Blank, C.U.	Bristol Myers Squibb France	A prospective multicenter cohort study of late physical, psychological and social effects in patients treated with IO for advance melanoma (vervolg van M15AMS).	01/07/16	31/12/21
Blank, C.U.	Bristol Myers Squibb USA	Multi-parameter AI analyses of patients treated with neoadjuvant checkpoint inhibition to predict response and toxicity in melanoma and other tumor types	01/01/21	31/12/22
Blank, C.U.	Melanoma Research Alliance	Overcoming upfront resistance to neoadjuvant CTLA-4 plus PD-1 blockade	01/09/20	31/08/23
Bleiker, E.M.A.	EORTC	EORTC kwaliteit van leven data	01/12/15	31/12/21
Bleiker, E.M.A.	MAAG LEVER DARM Stichting	Het ontwikkelen en implementeren van een e-learning met keuzehulpen erfelijke maagkanker (HEDERA)	01/08/20	16/11/21
Bleiker, E.M.A.	Stichting Roparun	Het optimaliseren en implementeren van de online borstreconstructie keuzehulp voor vrouwen met borstkanker.	01/07/19	31/07/21
Borst, J.G.	AVL Foundation	Dendritic Cell project	01/01/18	31/12/22
Brekel, van den M.W.M.	ATOS	Research and new product development	01/01/14	31/12/22
Brekel, van den M.W.M.	AVL Foundation	Head and neck cancer research	01/10/10	31/12/22
Brekel, van den M.W.M.	AVL Foundation	Hoofd-Hals Targeted therapy	01/01/15	31/12/22
Brekel, van den M.W.M.	Brunel	Research project	01/01/14	31/12/22
Brekel, van den M.W.M.	European Commission	Training Network on Automatic Processing of PAthological Speech	01/11/17	31/10/21
Brekel, van den M.W.M.	Patiënten-vereniging Hoofd-Hals	De ontwikkeling van een keuzehulp voor patiënten met een orofarynxcarcinoom waarvoor een chirurgisch curatieve behandeling mogelijk is.	01/07/18	31/03/22
Broek, van den D.	ZonMw	ctDNA on the way to implementation in the Netherlands (COIN)	27/03/19	26/03/23
Brummelkamp, T.R.	CIHR-IRSC / Canadian Institutes of Health Research	Exploiting proline vulnerability for cancer therapy	01/05/19	30/04/21
Brummelkamp, T.R.	European Commission	A global alliance for Zika virus control and prevention – ZIKAlliance	01/10/16	30/09/21
Brummelkamp, T.R.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/13	31/12/21
Brummelkamp, T.R.	NWO Beleids-ontwikkeling & Ondersteuning	Human Genes and Intracellular Phenotypes	01/03/17	28/02/22
Brummelkamp, T.R. / Wessels, L.F.A.	Health-Holland	A genomics compendium to identify therapeutic targets	01/12/19	30/11/23

Principal investigator	Granting agency	Title	Started	Ended / Ends
Chalabi, M.	Bristol Myers Squibb International	Towards deciphering immune escape mechanisms of early colon cancers and developing rationales for future treatment strategies: translational research plan for the NICHE trial	01/10/17	31/07/21
Dorland, B.	IKNL	Dutch Oncology Research Platform (DORP)	01/06/19	31/05/23
Dorland, B.	NVALT	A phase III prospective double blind placebo controlled randomized study of adjuvant MEDI4736 in completely resected non-small cell lung cancer (NVALT 24)	08/02/18	08/08/22
Driel, van W.J.	AVL Foundation	Onderzoek voor ovarium carcinoom	01/10/17	30/09/22
Driel, van W.J.	ZonMw	Phase III Randomized clinical trial for stage III ovarian carcinoma randomizing between primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy	01/01/20	31/12/25
Faller, W.J.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/17	31/12/21
Faller, W.J.	NWO Exacte en Natuurweten-schappen	The identification and functional analysis of translationally regulated mRNAs important for stem cell identity	01/06/20	30/11/23
Faller, W.J.	UMC Utrecht	Effects of translation and ploidy in HCC	01/01/21	31/12/21
Fast, M.F.	NWO	Breathe easy: adapting lung radiotherapy in a heartbeat	01/09/19	31/08/24
Haanen, J.B.A.G.	Asher Biothera-peutics, Inc.	Characterizing immunological responses to novel engineered molecules in TIL-based systems	01/07/21	30/06/22
Haanen, J.B.A.G.	AVL Foundation	ACT with TCR gene modified T-cells	01/01/19	30/06/22
Haanen, J.B.A.G.	AVL Foundation	Immunotherapy	01/01/19	31/12/22
Haanen, J.B.A.G.	AVL Foundation	NIVEC-N19TVN	01/01/20	30/06/24
Haanen, J.B.A.G.	AVL Foundation	Effect van microbioom (darmflora)-transplantatie bij immuuntherapie	01/01/21	31/12/23
Haanen, J.B.A.G.	University Medical Center Groningen (UMCG)	POINTING: Towards patient-tailored cancer immunotherapy supported by a multifaceted predictive signature composed of integrative omics and molecular imaging	01/09/17	31/08/23
Haanen, J.B.A.G.	ZonMw	Randomized controlled trial comparing TIL treatment to ipilimumab for the treatment of advanced stage melanoma	01/07/15	30/06/22
Haanen, J.B.A.G.	ZonMw	Individualized T cell receptor (TCR) gene therapy, from bench to men	01/09/19	31/08/25
Haas, R.L.M.	AVL Foundation	Radiobiology of Sarcomas. Radiotherapy fractionation sensitivity of (myxoid lipo-) sarcomas in vitro and in vivo	01/06/16	31/12/22
Harten, van W.H.	AVL Foundation	Monopolie met maatschappelijk rendement - Verantwoord omgaan met patenten in de oncologie	01/01/17	30/09/21
Harten, van W.H.	Intuitive Surgical Operations Inc.	CERA-PRO: cost-effectiveness of robot-assisted prostatectomy compared to laparoscopic prostatectomy: 6-8 year multi institutional PROM's follow-up study out of a Dutch perspective	01/09/19	31/08/27
Harten, van W.H.	OECI	One-shot project	01/12/20	30/11/21
Harten, van W.H.	ZonMw	Technology Assessrnent of Next Generation Sequencing in Personalized Oncology (TANGO)	31/12/16	28/11/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Heide, van der U.A.	Health-Holland	Magnetic en Momentum	01/06/18	28/02/23
Heide, van der U.A.	Philips Finland	Feasibility of MR-only in Radiation Oncology	13/12/17	28/02/22
Heide, van der U.A.	Rijksdienst voor Ondernemend Nederland	Automation in Radiotherapy Workflow (ARTWORK)	01/01/20	30/01/22
Heijden, van der M.S.	Bristol Myers Squibb Company USA	Modulation of the tumor-immune microenvironment in muscle-invasive bladder cancer by neo-adjuvant systemic therapy	07/05/20	30/04/22
Heijden, van der M.S.	Stichting DUOS	Translationeel onderzoek immunotherapie bij peniskanker	01/06/19	31/05/22
Heijden, van der M.S.	Stichting Zeldzame Ziekten Fonds	subsidieovereenkomst Peniscarcinoom	01/04/21	31/03/23
Hofland, L.	AVL Foundation	Hoofdhuidkoeling	01/11/18	01/03/22
Horenblas, S.	AVL Foundation	Immunological aspects of the microenvironment of primary tumours, tumour-positive and tumour-negative lymph nodes in HPV+ and HPV- penile cancer patients	01/01/17	31/12/22
Horenblas, S.	AVL Foundation	Testis onderzoek	01/01/19	31/12/22
Horenblas, S.	Stichting J.C. van Veen	Onderzoek urologie	01/01/11	31/12/21
Horlings, H.M.	AVL Foundation	Start-up package Horlings	01/09/19	31/08/24
Horlings, H.M.	AVL Foundation	Project Game tegen Kanker	05/08/21	31/10/21
Horlings, H.M.	European Commission	Central Repository for Digital Pathology	01/02/21	31/01/27
Horlings, H.M.	Health-Holland	HISTO-AI: Artificial Intelligence for HISTOpathological images as the next step towards personalised immunotherapy	01/09/20	31/08/24
Houdt, van W.J.	EORTC	Transitional study moving towards logical and personal combination therapies in the treatment of melanoma in-transit metastases and improving understanding of underlying biology	01/05/18	31/12/21
Houdt, van W.J.	Merck B.V.	Aim of this project is to build a database from already existing data from patients treated in routine practice at NKI-AVL since the implementation of new local Merkel Cell Carcinoma (MCC) diagnostic and treatment guidelines in 2017.	01/01/21	31/12/21
Houdt, van W.J.	SkylineDx B.V.	Retrospective validation study of a primary melanoma genesignature to determine its prognostic value for more accurate staging of SN-negative melanoma patients	01/04/21	31/03/23
Houwink, A.P.I.	AVL Foundation	Intensive Care	01/04/21	31/03/26
Huitema, A.D.R.	Merus B.V.	Support of clinical development program of the Merus bispecific monoclonal antibody MCLA-117 with PK/PD modeling and simulation	01/09/16	30/06/21
Huitema, A.D.R.	Radboudumc	Individualized PeMetRexed dOsing in lung cancER and mesothelioma patients to improVE treatment response and allow treatment of patients with impaired renal function – The IMPROVE study	01/12/17	30/11/21
Husson, O.	EORTC	Incorporating the patient voice in sarcoma research: How can we assess health-related quality of life in this heterogeneous group of patients?	01/01/19	30/06/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Husson, O.	NWO Beleids-ontwikkeling & Ondersteuning	Facing the unthinkable in the prime of life: Prevalence, risk factors and mechanisms of impaired medical and psychological health outcomes among adolescents and young adults with cancer	01/12/19	30/11/24
Husson, O.	NWO Beleids-ontwikkeling & Ondersteuning	Aspasia	01/12/19	30/11/24
Husson, O.	Sarcoma Patients EuroNet e.V./ Assoc.	SPAEN sarcoomonderzoek	01/05/19	30/04/21
Jacobs, H.B.	ZonMw	The role of stable immunoglobulin transcripts in establishing allelic exclusion.	01/04/14	31/03/21
Jacobs, H.B./Leeuwen, van F.	ZonMw	Epigenetic control of cytotoxic T cells to modulate immune responses	01/06/19	25/11/21
Jacobs, J.J.L.	EMBO	Small Grant for funding of research materials	01/01/17	31/12/22
Jacobs, J.J.L.	European Commission	Joint Training and Research Program on Chromatin Dynamics and the DNA Damage Response - aDDRess	01/03/19	28/02/23
Jalink, C.	European Commission	Microscopy of living cancer cells at physiological oxygen levels: the MICROX platform	15/09/19	14/09/22
Jong, de M.C.	European Commission	Clinical proof of concept through a randomised phase II study: a combination of immunotherapy and stereotactic ablative radiotherapy as a curative treatment for limited metastatic lung cancer – IMMUNOSABR	01/01/17	30/06/23
Jonkers, J.M.M.	Artios Pharma Ltd.	Research Collaboration Agreement	01/04/19	31/12/21
Jonkers, J.M.M.	European Commission	Generation of the CanPath prototype - a platform for predictive cancer pathway modeling	01/03/16	30/11/21
Jonkers, J.M.M.	NWO	MCCA2.0 Overbruggingskrediet - Models to Combat Cancer and Aging	01/09/21	31/08/23
Jonkers, J.M.M.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/13	31/12/21
Jonkers, J.M.M.	Stichting Oncode Institute	Turning Mutations into Patient Specific Biomarkers to Guide Personalized Treatment of Ovarian Cancer	01/03/20	31/12/21
Jonkers, J.M.M.	Stichting Oncode Institute	Gremlin 1	01/11/21	31/10/22
Jonkers, J.M.M.	University of Copenhagen	Unraveling the genetic background of familial breast cancer"	01/01/18	30/09/22
Jonkers, J.M.M.	ZonMw	Deciphering the contribution of cancer-associated fibroblasts to invasive lobular carcinoma development, progression and tumor microenvironment	01/01/19	31/12/21
Jonkers, J.M.M./ Wesseling, J.	Cancer Prevention	Immunoprevention of BRCA1-associated mammary cancer	01/03/18	28/02/21
Karakullukcu, M.B.	AVL Foundation	3D Lab	01/04/17	31/12/22
Kerkhoven, R.M.	AVL Foundation	NovaSeq6000	01/04/20	31/03/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Kerkhoven, R.M.	AVL Foundation	LabChip GX Touch	01/03/21	28/02/22
Kerkhoven, R.M.	Stichting Oncode Institute	De-coding tumor heterogeneity using single cell sequencing technologies	01/01/18	31/12/22
Kok, M.	AVL Foundation	Start-up package Kok	01/12/18	30/11/23
Kok, M.	AVL Foundation	Hoe omzeilt borstkanker het immuunsysteem?	01/01/19	28/07/21
Kok, M.	AVL Foundation	Verbeteren van immuuntherapie bij borstkanker	01/01/21	31/12/23
Kok, M.	Breast Cancer Research Foundation	Exploiting the Foreign Antigenic Space in Breast Cancer	01/10/17	30/06/21
Krimpenfort, P.J.A.	European Commission	Towards enduring mouse resources and services advancing research into human health and disease	01/01/17	31/12/21
Kuhlmann, K.F.D.	AVL Foundation	PUMP-IT Trial (M19PIT)	01/11/19	31/12/24
Kvistborg, P.	AVL Foundation	Immune competence and toxicity to checkpoint targeting therapy in melanoma	01/01/21	31/12/22
Kvistborg, P.	Merck Sharp & Dohme Corp.	Feasibility study of neo-adjuvant treatment with carboplatin, paclitaxel and pembrolizumab in stage IV epithelial ovarian cancer	01/10/16	31/12/21
Kvistborg, P.	Merck Sharp & Dohme Corp.	To compare the tumor reactivity and antigenic determinants of CD8+ TCR clones in tumor tissue from KN161 participants who respond to pembrolizumab compared to KN161 participants who do not respond to pembrolizumab	02/11/18	31/10/23
Kvistborg, P.	The Mark Foundation for Cancer Research	The role of ribosomal heterogeneity in T cell recognition of tumor cells	01/12/21	31/12/22
Lahaye, M.J.	ZonMw	Clinical impact of dedicated MR staging of ovarian cancer patients M17MRO	01/02/18	31/01/22
Lahaye, M.J.	ZonMw	MR imaging vs surgical staging of peritoneal carcimatosis in colorectal cancer patients; a randomized multicenter trial	01/09/19	31/08/23
Langen, de A.J.	Merus N.V.	Collaboration for identification of NRG1-fusion cases in Lung Cancer	01/03/19	31/12/22
Leerdam, van M.E.	MAAG LEVER DARM Stichting	Diagnostic yield of colonscopy surveillance in testicular cancer survivors treated with platinum-based chemotherapy (M19CTR)	01/09/20	31/08/23
Leeuwen, van F.E.	AVL Foundation	Beter Project	01/06/18	31/05/22
Leeuwen, van F.E.	European Commission	Implications of Medical Low Dose Radiation Exposure	01/06/17	28/02/22
Leeuwen, van F.E.	RIVM	Silicone breast Implant related health COmplaints in the Netherlands (SICON)	01/06/21	31/05/25
Leeuwen, van F.E.	The General Hospital Corporation D b/a Massachussetts General Hospital	LIFT-OMEGA	01/09/17	30/11/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Leeuwen, van F.E.	VIOZ Stichting Vrienden Integrale Oncologische Zorg	Ondersteuning opzet nieuwe BETER-poliklinieken voor nazorg vooroverlevers van lymfklierkanker	01/08/21	31/03/23
Leeuwen, van F.E.	ZonMw	Evaluation of nationwide long-term follow-up care for lymphoma survivors in the Netherlands: does survivorship care at the BETER clinics reduce morbidity and mortality from late effects of lymphoma treatment and associated costs?	01/12/20	31/05/25
Lenstra, T.L.	European Commission	Single-molecule visualization of transcription dynamics to understand regulatory mechanisms of transcriptional bursting and its effects on cellular fitness – BURSTREG	01/01/18	31/12/22
Lenstra, T.L.	NWO	Unravelling how DNA organization is linked to transcriptional dynamics	01/09/18	22/04/22
Lenstra, T.L.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/17	31/12/21
Lenstra, T.L.	Stichting Oncode Institute	3D orbital tracking microscope	01/08/19	31/07/22
Linn, S.C.	A Sister's Hope	PI3K pathway activation in primary and metastatic estrogen receptor alpha (ERa) positive breast cancer and the association with drug response	01/12/12	30/06/22
Linn, S.C.	A Sister's Hope	Mutational analysis and BRCA1-like classification in WSG-ADAPT TN-Trial	01/01/17	30/06/22
Linn, S.C.	Agendia N.V.	Validation of Ultralow threshold MammaPrint in the IKA trial	01/03/19	31/12/23
Linn, S.C.	AVL Foundation	Learning from unexpected cures	01/04/14	30/06/22
Linn, S.C.	AVL Foundation	ADAPT BRCA-like project	01/01/17	30/06/22
Linn, S.C.	AVL Foundation	Breast cancer research aimed at saving lives.	01/11/17	01/11/22
Linn, S.C.	AVL Foundation	Development of a test to assess PI3K and/or MAPK pathway activation based on gene expression data that can predict lack of benefit from adjuvant tamoxifen	01/01/20	30/11/22
Linn, S.C.	AVL Foundation	Naar behandeling op maat bij borstkanker - 'licht als het kan, zwaar als het moet'	01/01/21	30/06/22
Linn, S.C.	AVL Foundation	De-escalating chemo in high-sTILs TNBC	01/11/21	31/10/22
Linn, S.C.	ZonMw	Substantiële verbetering van de overleving van stadium III, BRCA1-like borstkanker patiënten met doelgerichte behandeling. SUBITO	01/01/17	31/12/22
Lohuizen, van M.M.S.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/13	31/12/21
Lohuizen, van M.M.S.	Stichting Oncode Institute	EZH2 + FGFR inhibitor Combination Therapy to Treat BAP1 Deficient Tumors	01/07/19	28/02/21
Luenen, van H.G.A.M.	AVL Foundation	Corona-noodfonds	01/01/21	31/12/22
Luenen, van H.G.A.M.	AVL Foundation	Extra capaciteit flowcytometrie operator	15/03/21	31/12/22
Marijnen, C.A.M.	AVL Foundation	Image Guided Therapy – onderzoek met de Gamma Knife	01/01/17	31/12/22

Principal investigator	Granting agency	Title	Started	Ended / Ends
Marijnen, C.A.M.	AVL Foundation	Prospective study evaluating ctDNA as a biomarker for treatment response in head and neck squamous cell carcinoma	01/05/19	30/04/22
Marijnen, C.A.M.	NVRO	De ontwikkeling van een PRO-bijwerkingensubset voor prostaatkankerpatiënten	01/09/19	31/12/21
Medema, R.H.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/13	31/12/21
Meijer, G.A.	AACR	'The Molecular Early Detection Of Colorectal Cancer (MEDOCC) project'	01/04/15	30/09/22
Meijer, G.A.	AACR	GENIE Project	01/07/16	31/12/23
Meijer, G.A.	AVL Foundation	Darmkanker en biomarkers	01/03/17	30/06/22
Meijer, G.A.	BBMRI-NL	BBMRI 2.0	01/01/15	30/09/21
Meijer, G.A.	BBMRI-NL	X-omics	01/09/18	31/08/23
Meijer, G.A.	EIT Health e.V.	Cancer Core Europe - Virtual Data Center	01/03/19	30/04/23
Meijer, G.A.	Health-Holland	Liquid biopsy-based molecular diagnostics to monitor therapy rspinse in metastatic colorectal cancer: PLCRC-ORCA EXTended beyond RAS	01/01/17	31/05/22
Meijer, G.A.	Health-Holland	Stratification of stage IIand stage III colon cancer patients for treatment with Stratifact	01/09/19	31/08/23
Meijer, G.A.	Health-Holland	Prospective clinical validation of a novel multitarget FIT in the Dutch CRC screening program	01/06/21	31/12/23
Meijer, G.A.	Health-Holland	Targeted detection and functional characterization of chromosomal breakpoint structural variants in colorectal cancer: advancing towards biomarker assay development	01/10/21	30/09/24
Meijer, G.A.	MAAG LEVER DARM Stichting	Using pks+ E. coli status for improving colorectal cancer early detection	01/10/20	30/09/22
Meijer, G.A.	Stichting Sacha Swarttouw-Hijmans	Vrij circulerend tumor DNA (ctDNA) als biomarker voor monitoring van patiënten met rectumkanker	01/05/18	31/10/22
Meijer, G.A.	Stichting Sacha Swarttouw-Hijmans	Securing Blood from Colon Adenoma Patients in the CLIPPER Trial to Enable Development of Biomarkers for Early Detection of High-Risk Colon Adenomas and CRC. The SAMPLE Study	01/05/18	31/10/22
Meijer, G.A.	ZonMw	Molecular adenoma features to predict colorectal cancer risk	10/06/19	10/06/22
Meijer, G.A.	ZonMw	WGS Implementation in standard cancer Diagnostics for Each cancer patient (WIDE)	15/07/19	15/07/22
Nederlof, P.M.	Roche Nederland BV	CGH Array	01/10/12	31/07/22
Nijenhuis, C.M.	Biontech Neon Therapeutics	BioNTech (oud NEON) manufacturing agreement	28/08/19	27/08/22
Nijenhuis, C.M.	Neogene Therapeutics B.V.	Develop TCR and target characterization assays (Safety data)	01/09/20	31/08/22

Principal investigator	Granting agency	Title	Started	Ended / Ends
Nuijen, B.	Modra Pharmaceuticals Holding B.V.	To provide clinical services for Study: Multicenter safety, feasibility and pharmacokinetic phase I-II trial of ModraDoc006/r in patients with metastatic castration-resistant prostate cancer (M17DOC)	25/05/17	30/06/21
Nuijen, B.	Modra Pharmaceuticals Holding B.V.	A multicentre phase IIa study to evaluate the efficacy and tolerability of ModraDoc006/r in patients with recurrent or metastatic HER-2 negative breast cancer, suitable for treatment with a taxane (M18DMB)	01/01/19	31/07/21
Opdam, F.L.	European Commission	Building Data Rich Clinical Trials	01/02/21	31/01/25
Peeper, D.S.	AVL Foundation	Screening novel therapeutic targets for immuno oncology (part II)	01/04/21	31/03/23
Peeper, D.S.	Bristol Myers Squibb Company USA	Defining and tackling immunotherapy resistance in melonoma and lung cancer	01/08/17	31/07/21
Peeper, D.S.	Bristol Myers Squibb Company USA	SERPINB9 as a Potential New IO Target and Predictive Biomarker.	01/06/21	31/05/22
Peeper, D.S.	Health-Holland	Developing and optimizing inhibitors for next-generation immune-oncology.	01/08/20	11/01/23
Peeper, D.S.	Josephine Nefkens Stichting p/a Hembrug b.v.	Identificatie van nieuwe immuuntherapie met Itellicyt Screener PLUS	01/03/18	28/02/22
Peeper, D.S.	Merck Sharp & Dohme Corp.	Identify tumor-intrinsic factors that induce resistance to anti PD-1 antibody treatment in vivo (Keytruda resistome) in the D10 system.	13/11/18	28/11/21
Peeper, D.S.	Stichting Oncode Institute	TDF_TWEAKR	01/09/19	30/06/22
Peeper, D.S.	Stichting Oncode Institute	Establishing AGN192403 as a first-in-class, orally-available PD-1 inhibitor.	25/09/20	30/09/21
Peeper, D.S.	Stichting Oncode Institute	Repurposing BACE1 Alzheimer's inhibitors for immunotherapy.	01/01/21	31/12/21
Perrakis, A.	European Commission	Infrastructure for transnational access and discovery in structural biology	01/02/20	31/01/24
Perrakis, A.	Galapagos NV	Mechanistic differences between ATX inhibitors reflect their in vivo action and success in the clinic	01/03/20	31/01/22
Perrakis, A.	Instruct-ERIC	EOSC-Life: Providing an open collaborative space for digital biology in Europe	19/04/21	31/05/22
Perrakis, A.	Janssen Research & Development	Enhancement of PDB_REDO algorithms and software	01/01/16	31/12/22
Perrakis, A.	STFC Science & Technology Facilities Council C/O UK SBS Ltd	CCP4 Software Derivative Work	01/06/19	31/05/24

Principal investigator	Granting agency	Title	Started	Ended / Ends
Perrakis, A.	Stichting Oncode Institute	A distributed GPU in-frastructure to enable Artificial Intelligence and Deep Learning applications in Cancer Genomics, Proteomics, and Structural Cell Biology	01/03/20	31/08/21
Perrakis, A.	Stichting Oncode Institute	Proteins4Oncode	01/11/20	31/12/22
Poel, van der H.G.	AVL Foundation	Behandeling van lymfeklieruitzaaiingen bij prostaatkanker.	01/10/20	30/09/24
Poel, van der H.G.	AVL Foundation	Verbetering van de diagnostiek van prostaatkanker in Prostaatkankernetwerk Nederland.	01/10/20	30/09/24
Poel, van der H.G.	Intuitive Surgical Operations Inc.	Robot-assisted radioguided surgery using a drop-in gamma probe	01/03/18	31/03/22
Poll, van de L.V.	AVL Foundation	Quality of life research in Melanoma patients treated with immunotherapy.	01/12/20	30/11/22
Poll, van de L.V.	EORTC	Phase II and III development of an EORTC QOL cancer survivorship questionnaire	01/02/17	30/09/21
Poll, van de L.V.	EORTC	Development of a questionnaire module for patients with metastatic malignant melanoma	16/11/20	15/11/24
Poll, van de L.V.	European Commission	Cancer Patients Better Life Experience (CAPABLE)	01/01/20	31/12/23
Poll, van de L.V.	Stichting Roparun	Project CALM	01/10/18	30/09/21
Poll, van de L.V.	University of Toronto Department of Medicine	Teaching principles of managing cancer and living meaningfully (CALM) to oncology nurses: a feasibility study of an intervention to improve professional empathy in oncology nurses	01/06/20	31/05/23
Retel, V.P.	Stichting Oncode Institute	HTA Vorinostat in resistant BRAF V600 mutated advanced Melanoma	15/07/20	14/07/22
Retel, V.P.	Zorginstituut Nederland	TippingPoint	03/12/21	15/07/23
Rheenen, van J.E	CGC	CGC IV	01/10/17	31/12/21
Rheenen, van J.E	Dr. Josef Steiner Krebsstiftung	Cancer Research Award 2017	01/10/17	30/09/21
Rheenen, van J.E	EMBO	Long-Term Fellowship H. Messal	01/08/19	31/07/21
Rheenen, van J.E	Institut de Bioenginyeria de Catalunya (IBEC)	Enabling technologies to map nuclear mechanosensing: from organoids to tumors.	01/12/20	30/11/23
Rheenen, van J.E	NWO Exacte en Natuurweten-schappen	Organoids in time.	16/07/20	15/07/25
Rheenen, van J.E	Stichting Ammodo	Inhibiting inflammation/repair responds to prevent or slow-down recurrence of therapy-resistant cancer.	31/03/20	30/03/25

Principal investigator	Granting agency	Title	Started	Ended / Ends
Rheenen, van J.E	ZonMw	Molecular control of ductal carcinoma progression in the breast	01/08/21	31/07/24
Riele, te H.P.J.	STW	Phenotypic assessment of intra- and extra-exonic variants of disease-related genes present in the human population.	01/01/17	30/06/21
Rosing, H.	AMR AMC Medical Research B.V.	Determination of cisplatin, carboplatin, cyclophosphamide, epirubicin, doxorubicin and paclitaxel in maternal and infant's biomatrices to investigate the pharmacokinetics	01/04/18	31/12/21
Rosing, H.	Biontech Neon Therapeutics	Qualification of an UPLC-MS method for the identity analysis of neo-antigen peptides drug products and the quality control of these products	01/03/18	31/12/21
Rosing, H.	ITCC	Development of an LC-MS/MS method for the quantification of temsirolimus and sirolimis in human K2EDTA	01/10/16	31/12/21
Rosing, H.	ITCC	Determination of carboplatin, cisplatin, cytarabine, actinomycin D, daunorubicin, doxorubicin, etoposide, methotrexate and vinictistine in samples collected from patients entered in the Pinocchio study	01/05/18	31/12/21
Rosing, H.	KIKA Stichting Kinderen Kankervrij	Pharmacokinetics of aprepitant and interaction with Dexamethasone: a pilot study	01/05/18	31/12/21
Rosing, H.	Prinses Maxima Centrum Kinderoncologie	A Phase Ib study of Vyxeos (liposomal daunorubicin and cytarabine) in combination with Clofarabine in children with relapsed/refractory AML	20/07/20	30/06/24
Rosing, H.	Roche Nederland BV	LC-MS/MS determination of cyclophosphamide and 4-hydroxy cyclophosphamide in human plasma samples collected in study NP40126	29/01/18	31/12/21
Rosing, H.	UMC Utrecht	A Dose-Escalating Phase I/II Study in Patients with RAS-Mutated Metastatic Colorectal Cancer to Investigate Safety and Clinical Activity of the Triple Combination of: MEK- inhibitor binimetinib, Pan-EGFR inhibitor lapatinib and the Microtubule Targeting Agent (MTA) vinorelbine	01/07/20	30/06/22
Rosing, H.	VU Medisch Centrum	Development of an LC-MS/MS method for the quantification of vincristine in dried blot spots	01/12/18	31/12/21
Rossum, van H.H.	Health-Holland	Production and validation of home blood collection system for Covid-19 test and other blood-based diagnostics	01/06/20	30/09/21
Rowland, B.D.	European Commission	Cohesin-mediated chromosomal looping: from linear paths to 3D effects	01/04/18	31/03/23
Ruers, T.J.M.	AVL Foundation	Optical guided surgery	01/11/14	31/07/23
Ruers, T.J.M.	AVL Foundation	Pixel analyse voor (vroeg)detectie van dikke darmkanker.	01/01/17	31/12/22
Ruers, T.J.M.	AVL Foundation	Fluorscene Life Time Imaging	01/09/19	31/08/22
Ruers, T.J.M.	European Commission	ICT-03-2018-2019 - Photonics Manufacturing Pilot Lines for Photonic Components and Devices	01/01/20	31/12/23
Ruers, T.J.M.	Health-Holland	TomTom project van Venture Challenge Fall 2016	01/12/16	30/11/21
Ruers, T.J.M.	Health-Holland	Hyperspectral Imaging for Improving Cancer Surgery	01/04/19	31/07/22
Ruers, T.J.M.	Innovation Exchange Amsterdam	MaMaLoc: Magnetische Marker voor Chirurgische Lokalisatie. Amsterdam Science & Innovation Award	01/06/16	30/06/22

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Ruers, T.J.M.	Intuitive Surgical Operations Inc.	Improving robotic surgery of prostate cancer by real time tissue characterrization using Diffuse Reflection Spectroscopy. Development of clinical implementation of existing technology	01/01/20	31/12/21
Ruers, T.J.M.	NWO Beleids-ontwikkeling & Ondersteuning	Smart Laparoscopes for Oncologic Surgery	06/08/20	05/08/24
Ruers, T.J.M.	Philips	Research collaboration	01/04/10	31/12/22
Ruers, T.J.M.	STW	Combining Optics and Acoustics For Realtime Guidance during Cancer Surgery	01/04/18	31/03/22
Sandick, van J.W.	ZonMw	Combinatie behandeling van cytoreductieve chirurgie en hypertherme intraperitoneale chemotherapie (HIPEC) bij patiënten met een maagcarcinoom en synchrone buikvliesmefasfasen en/of tumorpositief buikvocht.	01/10/17	30/09/22
Schmidt, M.K.	European Commission	Breast CAncer STratification: understanding the determinants of risk and prognosis of molecular subtypes – B-CAST	01/09/15	28/02/21
Schmidt, M.K.	European Commission	Beyond 1M Genomes	01/06/20	31/05/23
Schmidt, M.K.	Health – RI	Health-RI ELSI	01/12/21	30/11/23
Schmidt, M.K.	Health-Holland	PREDICT-NL: pathways to smart validation and clinical embedding of prediction tools for oncology and beyond	25/05/20	24/05/23
Schmidt, M.K.	NIH National Institutes of Health, National Cancer Institute	Data management and harmonization services for pathology, treatment and survival data from The Breast Cancer Association Consortium being contributed to the Confluence project	20/08/20	19/08/22
Schmidt, M.K.	NWO	BBMRI.nl National Roadmap for Large-Scale Research Infrastructure Bridge Funding 2020	01/04/21	31/03/23
Schmidt, M.K.	ZonMw	Personalized medicine: servicedesk ethiek en recht	01/09/17	31/08/21
Schmidt, M.K.	ZonMw	Practical help towards responsible use of residual biospecimens and data in medical research in the Netherlands	01/10/19	31/03/21
Schumacher, A.N.M.	European Commission	Sensitivity of human tumors to T cell attack	01/12/17	30/11/22
Schumacher, A.N.M.	Louis-Jeantet Foundation	Research grant	09/02/21	08/02/26
Schumacher, A.N.M.	Merck KGaA	Single cell analysis of the tumour-immune ecosystem in human cancer: Dissecting the dynamics of immune-tumour cross talk following checkpoint blockade.	01/06/17	31/12/21
Schumacher, A.N.M.	NWO Beleids-ontwikkeling & Ondersteuning	Stevinpremie	23/06/20	22/06/25
Schumacher, A.N.M.	Roche Nederland BV	T cell responses and mapping of neo-antigen-specific T cell repertoires in follicular lymphoma patients after local anti-CD20 therapy	01/04/14	31/12/21
Sixma, T.K.	Health-Holland	Development of activity-based probes for metalloDUBs	01/09/19	31/08/21
Sixma, T.K.	NWO	The molecular mechanism of USP48, a BRCA1 antagonist during DNA damage response	01/09/18	31/08/22

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Sixma, T.K.	NWO	The mechanism of USP1 activation	01/05/20	30/04/24
Sixma, T.K.	NWO	The regulation of PCNA ubiquitination	01/12/21	30/11/25
Sixma, T.K.	NWO Beleids-ontwikkeling & Ondersteuning	Structure-function analysis of transcription-associated DNA repair	01/06/18	31/05/24
Sixma, T.K.	NWO Beleids-ontwikkeling & Ondersteuning	A program to enable discovery of catalytic and/or inhibitors of the USP4/11/15 family of deubiquitinating enzymes	01/10/18	08/02/22
Sixma, T.K.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/13	31/12/21
Sixma, T.K.	NWO Chemische Wetenschappen	A movie of DNA mismatch repair: how information is transmitted by conformational change	01/01/17	31/12/22
Sonke, G.S.	AVL Foundation	Long-term survival in HER2+ Breast Cancer	01/01/18	30/06/21
Sonke, G.S.	AVL Foundation	Borstkanker onderzoek	01/01/21	31/12/23
Sonke, G.S.	Maarten van de Weijden Foundation	COntinue the SaMe systemic therapy after local ablative therapy for Oligo progression	01/01/21	31/12/23
Sonke, J.J.	Elekta Ltd	Research Agreement	10/08/10	31/12/22
Sonke, J.J.	Elekta Ltd	Partnership for Online Personalized AI-driven Adaptive RadioTherapy (POP AART)	01/04/21	31/03/26
Sonke, J.J.	European Commission	European medical application and radiation protection concept: strategic research agenda and roadmap interlinking to health and digitisation aspects - EURAMED rocc-n-roll	01/09/20	31/08/23
Steeghs, N.	Glaxo Smith Kline Durham USA	Oncology Clinical and Translational consortium (OCTC)	22/10/13	12/10/22
Steensel, van B.	AVL Foundation	Chromatin Genomics	01/11/14	31/10/24
Steensel, van B.	AVL Foundation	Finding regulatory mutations in the non-coding cancer genome	01/09/21	31/08/26
Steensel, van B.	European Commission	Genomics of Chromosome Architecture and Dynamics in Singel Cells	01/03/17	31/08/22
Steensel, van B.	European Commission	TWISTING THE BOUNDARIES: ROLE OF TOPOISOMERASE 1 AT THE NUCLEAR LAMINA	01/09/20	31/08/22
Steensel, van B.	European Commission	From chromatin fibers to lamina-associated domains: what are the recognition determinants? I.am.a.LAD	01/12/21	30/11/23
Steensel, van B.	University of Illinois	NIH 4DNucleome	28/09/15	31/07/21
Steensel, van B.	ZonMw	Identifying causal genetic variants for a better understanding and diagnosis of neurodevelopmental disorders.	01/12/21	30/11/25
Stuiver, M.M.	Astellas Pharma BV	Next steps towards implementation of exercise programming for individuals with advanced prostate cancer	01/08/20	15/12/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Stuiver, M.M.	European Commission	Project on Exercise for Fatigue Eradication in Advanced Breast cancer to improve quality of life - PREFERABLE - M19EFF	01/01/19	31/12/23
Stuiver, M.M.	Het Nationaal Fonds tegen Kanker	EMBRACE WEight Management for BReaSt CancEr	01/01/21	31/12/23
Stuiver, M.M.	KNGF	Start exercising, keep exercising (STEP-IN): A toolkit for physiotherapists to support exercise maintenance among cancer survivors after supervised exercise interventions.	01/06/20	31/05/22
Stuiver, M.M.	KNGF	Fysio-/oefentherapie Aanpak Stroomlijning kwaliteitsstandaarden: Het FAST project	01/09/20	31/08/21
Stuiver, M.M.	Nutricia Nederland B.V.	Voedingsstatus en het beloop van de behandeling van stadium III longkanker.	01/11/17	31/12/21
Stuiver, M.M.	NWO	Personalized monitoring of health status during cancer treatment using minimally-invasive wearables	01/05/21	30/04/22
Tellingen, van O.	AVL Foundation	Improving chemoradiation therapy of GBM by inhibition of glioma invasion: A Proof-of-Concept study	01/12/17	30/06/22
Tellingen, van O.	AVL Foundation	Multi-Targeted Combination Therapy for treatment of glioblastoma: in vivo proof-of-concept study	01/06/18	30/09/22
Tellingen, van O.	CellProtect Australia PTY Ltd	Combination of S-CP201 and irradiation for treatment of glioblastoma: In vitro and in vivo studies.	01/12/21	30/11/22
Tellingen, van O.	Debiopharm International SA	Efficacy study of Wee1 inhibitor Debio 0123 and radiotherapy against orthotopic intracranial tumor models	01/10/18	31/12/22
Tellingen, van O.	Izumi Biosciences INC	Modulation of the metabolism of elacridar by deuteration	01/10/18	30/09/22
Tellingen, van O.	Numeric Biotech Holding BV	To determine drugability, safety parameters and potential efficacy of the proprietary compound NBT-103	01/04/21	31/03/22
Tellingen, van O.	Stichting Semmy	Therapeutic reversal of the mesenchymal transition in diffuse midline glioma.	01/07/19	30/06/23
Tesselaar, M.E.T.	Merck B.V.	Database of retrospectively and subsequent prospectively gathered data of all MCC patients treated in the Netherlands as platform for a national MCC database.	01/09/18	31/12/22
Thommen, D.S.	Asher Biotherapeutics, Inc.	Ccharacterizing immunological responses to novel engineered molecules in TIL and PDTF settings	15/02/21	14/02/23
Thommen, D.S.	AVL Foundation	DNA gala	01/09/19	31/08/24
Thommen, D.S.	Bristol Myers Squibb Company USA	REsPonses to noveL Immunotherapies in ex vivo Cultured tumor frAgments (REPLICA)	14/02/18	31/12/21
Thommen, D.S.	Bristol Myers Squibb Company USA	Simultaneous versus sequential combination of nivolumab and ipilimumab in human tumor explants.	01/10/19	31/03/24

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Topff, L.P.C.	Gemeente Rotterdam: Programma Kansen voor West II	Project imAgIng EFRO II	01/08/21	31/07/23
Trommel, van N.E.	AVL Foundation	Onderzoek ADP Cervixcarcinoom	01/09/17	31/08/21
Trommel, van N.E.	AVL Foundation	Onderzoek ADP Ovariumcarcinoom	01/09/17	31/08/21
Trum, J.W.	ZonMw	GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma (GERSOC)	15/08/17	15/08/23
Trum, J.W.	ZonMw	Inclusieversneller GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma	15/09/20	15/12/21
Ven, van de H.W.M.	European Commission	EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts	01/02/18	31/01/22
Ven, van de H.W.M.	Stichting Oncode Institute	UCB Mouse clinic	01/11/21	31/10/22
Visser, de K.E.	AIRC	Dissecting how cancer-associated inflammation shapes iNKT cell activity during breast cancer metastatic progression"	01/01/21	31/07/21
Visser, de K.E.	EMBO	Dissecting how cancer-associated inflammation shapes iNKT cell activity during breast cancer metastatic progression	01/08/21	31/07/23
Visser, de K.E.	F. Hoffmann-LaRoche Ltd	Rational identification and in vivo validation of effective immunotherapy opportunities for metastatic breast cancer	12/04/19	12/10/22
Visser, de K.E.	Stichting Oncode Institute	Oncode - Deciphering the Cancer-Immune Landscape; towards personalized immune intervention strategies	01/08/18	31/07/21
Visser, de K.E.	ZonMw	Dissecting cancer cell-intrinsic mechanisms dictating the immune landscape of breast cancer; towards personalized immune intervention strategies	01/09/19	31/08/24
Voest, E.E.	aCBG	Convenant CBG	01/05/17	30/04/22
Voest, E.E.	AVL Foundation	Microbiome	01/07/21	30/06/23
Voest, E.E.	Genome Research Ltd, Wellcome Trust Sanger Inst.	Identification of targets modulating lymphocyte-mediated tumour cell killing	01/08/20	31/07/23
Voest, E.E./Haanen, J.B.A.G.	AVL Foundation	Precision Cell Therapy: the next wave in personalized cancer treatment	01/06/20	31/05/25
Vrancken Peeters, M.J.T.F.D.	AVL Foundation	De-escalatie van behandeling na neoadjuvante systemische behandeling / Optimalisatie van de oncoplastische chirurgie	01/12/21	31/12/24
Vrancken Peeters, M.J.T.F.D.	Innovatiefonds	Towards omitting breast surgery in patients with pathologic complete response after neoadjuvant systemic therapy	01/03/18	30/09/21
Wesseling, J.	AVL Foundation	Het ontwikkelen van een test om te bepalen of DCIS (Ductaal Carcinoom in Situ – mogelijke voorloper van borstkanker) wel of geen borstkanker wordt	01/01/21	31/12/24
Wesseling, J.	Cancer Research UK	Grand Challenge Precision	01/05/17	30/04/23
Wesseling, J.	ZonMw	Breast CAlcification Risk Evaluation Study	01/12/20	30/11/24

Principal investigator	Granting agency	Title	Started	Ended / Ends
Wessels, L.F.A.	CGC	Bioinformatica	01/11/13	31/12/21
Wessels, L.F.A.	NWO Beleids-ontwikkeling & Ondersteuning	Zwaartekracht programma 2012	01/01/13	31/12/21
Wessels, L.F.A.	Vall D'Hebron Institute of Oncology	Basket of Baskets: A modular, open-label, phase II, multicentre study to evaluate targeted agents in molecularly selected populations with advanced solid tumours	01/11/18	31/10/22
Wit, de E.	European Commission	Deconstructing gene regulation through functional dissection of the 3D genome - FuncDis3D	01/09/20	31/08/25
Zuur, C.L.	Stichting Zeldzame Ziekten Fonds	het melanoom van de slijmvliezen (mucosaal melanoom)	01/12/19	30/06/21
Zuur, C.L.	W.M. de Hoopstichting	Aanschaf en opzetten laboratoriummaterialen voor het onderzoeken van bloedaanmaak bij hoofd-hals kankerpatiënten voor en na behandeling.	01/04/18	30/09/21
Zwart, W.T.	A Sister's Hope	Ex-vivo intervention of metastatic breast cancers for novel drug testing and development in endocrine therapy-resistance	01/12/17	31/05/21
Zwart, W.T.	Dana Farber Cancer Institute	Defining and functionally characterizing the epigenome in lethal prostate cancer	30/09/19	29/09/22
Zwart, W.T.	Dana Farber Cancer Institute	Prostate cancer	01/09/21	31/08/24
Zwart, W.T.	Dana Farber Cancer Institute	Leveraging epigenomics to target acquired vulnerabilities in treatment resistant prostate cancer	19/11/21	18/11/23
Zwart, W.T.	European Commission	Training network in drug discovery targeting TRIM Ubiquitin ligases in disease – TRIM-NET	01/01/19	31/12/22
Zwart, W.T.	Fonds National Suisse De La Recherche Scientfique	Identification of ER-mediated 3D genome alterations that drive endocrine resistance in breast cancer	01/02/20	31/01/22
Zwart, W.T.	The Mark Foundation for Cancer Research	Short-term 3D-printing-based cultures of metastatic breast cancer for tailored therapy selection.	01/12/18	06/03/21
Zwart, W.T.	ZonMw	Proteomic and genomic evaluation of metastatic breast cancer to facilitate personalized treatment selection	01/12/16	30/11/21

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