princess máxima center
pediatric oncology

Care & Research
Annual Report 2019

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Preface
Chief Medical Officer & Chief Scientific Officer

Prof. dr. Rob Pieters & prof. dr. Alexander Eggermont

April, 2020

In 2019 we completed the transition phase. While we continue to optimize, there is already a Princess Máxima Center today that is future-proof. Ready to do what we have been created for: provide a cure for every child with cancer while maintaining an optimal quality of life. 2019 was the first full year of our center in which we treated all children diagnosed with cancer in the Netherlands. During this year, we have taken important steps in the context of our mission. For example, the development of CAR T-cell therapies has become a new standard of treatment, both in the Netherlands and in pediatric oncology. The layout of our care departments has been further developed; the integration of care and research evolved, and our treatments and services were optimally tailored to the wishes of children and their parents.

Also important was the founding of a new, fourth, care department named Quality of Life. In this new department, seven already existing teams were bundled to give an extra boost to the quality of life for children with cancer. Within this department we started our own Anesthesiology, Sedation & Pain team, which focuses on stress-free and pain-free care. Also we founded the Children's Comfort Team Utrecht, together with the Wilhelmina Children's Hospital (WKZ), specializing in pediatric palliative care.

The Diagnostics laboratory, the Pharmacy, and the Trial and Data Center experienced substantial growth in 2019, both quantitatively and qualitatively. They evolved into well-functioning departments that make an indispensable contribution to both care and research. In addition, the collaboration with the twenty Shared Care Centers was further optimized while maintaining high professional standards. This collaboration is important, since it offers our children the opportunity to have less complex parts of their treatment done close to home.

Our research department continued to grow in 2019. We started the year with 26 research groups and ended with 32, ranging from basic through translational to clinical research. In order to create space, we invested in furnishing the fourth floor.

Thanks to the Children Cancer-Free Foundation (KiKa), this floor now offers fully equipped laboratories and office spaces. In total, the Princess Máxima Center is involved in approximately hundred clinical studies and we had 375 Princess Máxima Center affiliated articles published in 2019. In the past year we also took significant steps in collaborating internationally with regards to our research. Highlights include the award of two ERC grants for a total of 3.5 million euros, and the award of several research prizes, such as the Keio Medical Science Price, won by former Chief Scientific Officer (CSO) Hans Clevers for his groundbreaking work on stem cells and organoids. Shortly after this Hans Clevers passed the CSO baton on to Alexander Eggermont, but he remains closely involved in the Princess Máxima Center as a principal investigator.

In 2019 we also welcomed two new professors. Martha Grootenhuis was appointed Professor of pediatric psycho-oncology at Utrecht University and Wim Tissing as Professor supportive care in pediatric oncology at the University of Groningen.

For the coming years the overarching ambition of the Princess Máxima Center is to develop and implement innovations in care and (clinical) research. The center wants to be a research hospital where patient care and research go hand–in-hand. We want to optimally integrate scientific research into our clinical programs and foster innovation. The structure within which we do this is the 'Máxima Comprehensive Childhood Cancer Center' (M4C). Implementing the M4C is a core part of our new multiannual strategy (Focused and promising), which will start in 2020.

The education and training of our employees are also indispensable elements in achieving our mission. For this we need the best professionals. In 2019, the Academy trained many pediatric oncology professionals by providing numerous (refresher) courses, internships for both care professionals and researchers.

All these important and positive developments would never have been possible without the support of our many partners, among others, the Parents, Children, and Cancer association (VOKK); the Dutch Childhood Oncology group (SKION); the Princess Máxima Center Foundation and its partners; and the UMC Utrecht / WKZ. Special thanks also go to KiKa, the main sponsor of scientific research at the Princess Máxima Center for many years now. In 2019, the Princess Máxima Center also concluded a new agreement with the Ministry of Health for the Academic Care Availability Contribution (BBAZ). As of 2020, we will receive an annual contribution from the Ministry for the infrastructure of our scientific research. This agreement confirms the academic position of the Princess Máxima Center in the Dutch healthcare landscape.

'For the coming years the overarching ambition of the Princess Máxima Center is to develop and implement innovations in care and (clinical) research'

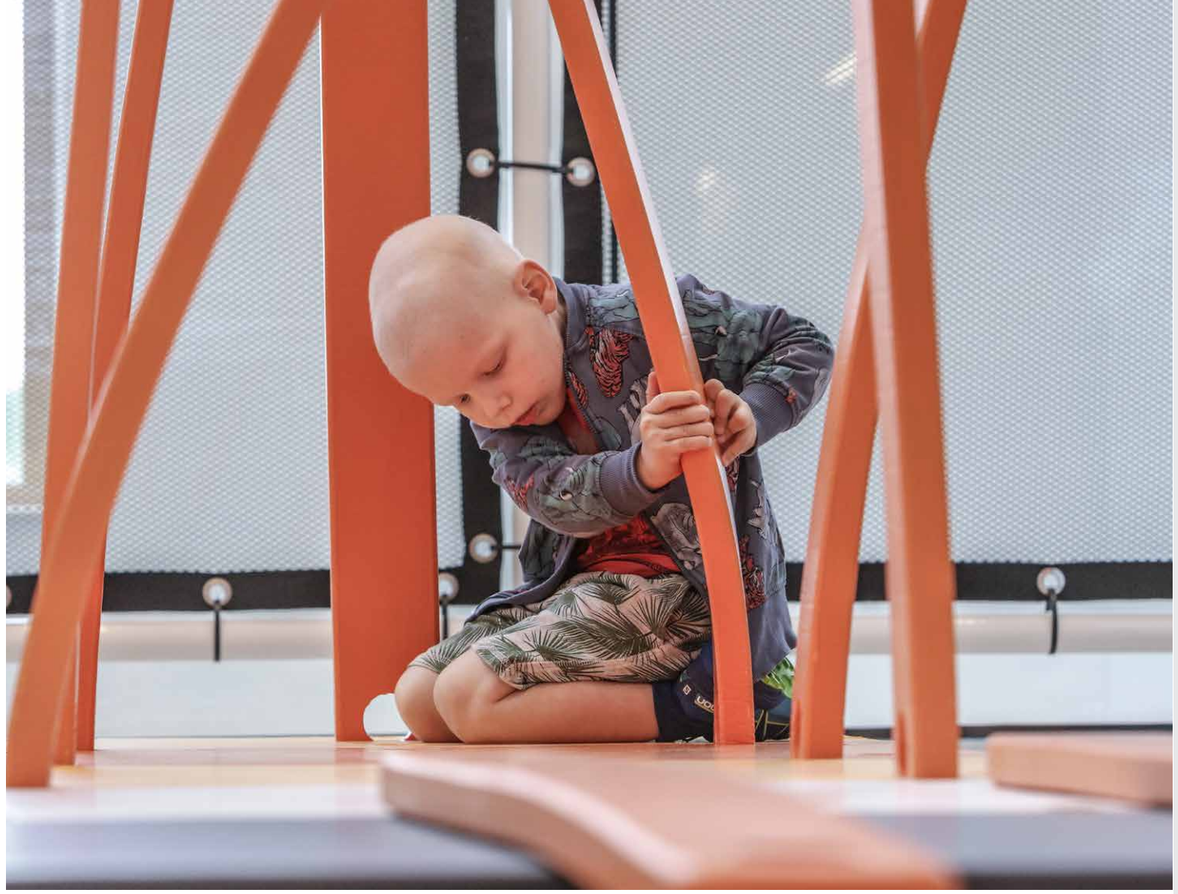
Furthermore, the representative advisory bodies made an important contribution to the growth and development of our center. Moreover we welcomed two new boards; the Medical Advisory Council (MAR) and the Nursing Advisory Council (VAR). Both boards advise the board of directors from respectively a medical perspective, and a nursing & paramedical point of view. Most welcome additions!

In addition to giving our children and parents a vote in what we do, we also find it important to provide them with proper information. In 2019, therefore, a very successful series of information evenings were held during which our professionals talked about specific elements of treatment or research. Given the enthusiasm we will certainly continue these information evenings.

This annual care & research report provides an insight into how we performed as a center in 2019. It shows that we have developed strongly again, that there are of course still plenty of challenges left, but above all it gives us the confidence that we are on the right track!

Preface
Chair, Scientific Advisory Board
Princess Máxima Center

Prof. William E. Evans, MD, PhD



April, 2020

The Princess Máxima Center for pediatric oncology is accelerating its work to provide treatment and discover new cures for children with cancer, even amidst the COVID-19 pandemic. For children with cancer and their families, this unprecedented pandemic presents a second major challenge to their health, on top of their battle with cancer. The pandemic should soon end, but childhood cancer will remain a challenge.

The past year, 2019, was a time of continued growth at the Princess Máxima Center, with the addition of six new faculty research leaders (Principal Investigators) and dozens of new staff investigators to expand the scope of research programs. The Princess Máxima Center's early success has facilitated the recruitment of these world-class scientists from top research institutions around the world, including Stanford University and St. Jude Children's Research Hospital in the US, Heidelberg University in Germany, and the Hubrecht Institute and Radboud Institute in The Netherlands. The Princess Máxima Center is now approaching capacity of its research space, which presents a new challenge for continuing to advance science on campus.

Following an international search, the Princess Máxima Center was fortunate to also recruit prof. dr. Alexander Eggermont, MD, PhD, to become its new Chief Scientific Officer, taking over for prof. Hans Clevers, MD, PhD, who led the launch of research at the Princess Máxima Center. Prof. dr. Eggermont comes to the Princess Máxima Center from Gustave Roussy Cancer Institute in Paris, where he served as the General Director for the past nine years. We cannot thank prof. dr. Clevers enough for his enormous contributions to the successful establishment of science at the Princess Máxima Center and we wish him continued success as he returns full time to his pioneering research in cancer and stem cell biology. We are delighted that he will continue his research program at the Princess Máxima Center.

We welcome prof. dr. Eggermont to his new leadership role at the Princess Máxima Center, which he assumed after having served on the Princess Máxima Center's Scientific Advisory Board (SAB) from its inception. Therefore, prof. dr. Eggermont was able to 'hit the ground running', having deep knowledge of the Princess Máxima Center programs from his work as an SAB member. He has taken the baton from professor Clevers at full speed, joining professor Rob Pieters, MD, PhD, the Princess Máxima Center Chief Medical Officer, in drafting an ambitious strategic plan for the Princess Máxima Center to grow its research programs in the coming years.

Members of the Scientific Advisory Board have been involved in offering initial feedback on the draft Strategic Plan, and the entire SAB will be meeting at the Princess Máxima Center in October 2020 to assist the leadership team in shaping these plans and establishing priorities for initiating new programs to complement the strong scientific foundation already in place at the Princess Máxima Center.

These are extraordinary times in science and medicine, with technology and computational sciences advancing at a rapid pace, fueling new avenues of research that will lead to a deeper understanding of what causes childhood cancers, and how better to treat them. It is critically important that children benefit from these technological and scientific advances, because cancer remains the leading cause of death by disease in children in The Netherlands and other developed countries. The Princess Máxima Center has quickly become an international leader in the fight against childhood cancer, and its strong leadership team has assembled a world-class team of clinicians and scientists who are now collaborating to discover new treatment options to improve cure rates for children with cancer. The Scientific Advisory Board remains enthusiastic about the future of the Princess Máxima Center and strongly committed to assisting the leadership team moving forward.

'The Princess Máxima Center is rapidly becoming an international leader in finding cures for children with cancer'

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General introduction

Princess Máxima Center

Around 600 children in the Netherlands get cancer every year, and one in four children who are diagnosed with cancer dies from this illness. More than ten years ago, a group of parents and healthcare professionals started working toward one national children's cancer center that could accelerate advances in treatment. Those efforts led to the creation of the Princess Máxima Center for pediatric oncology: a unique center that brings together all the highly complex care and research for children with cancer in the Netherlands. This concentration and integration of specialized pediatric oncology reflects our mission:

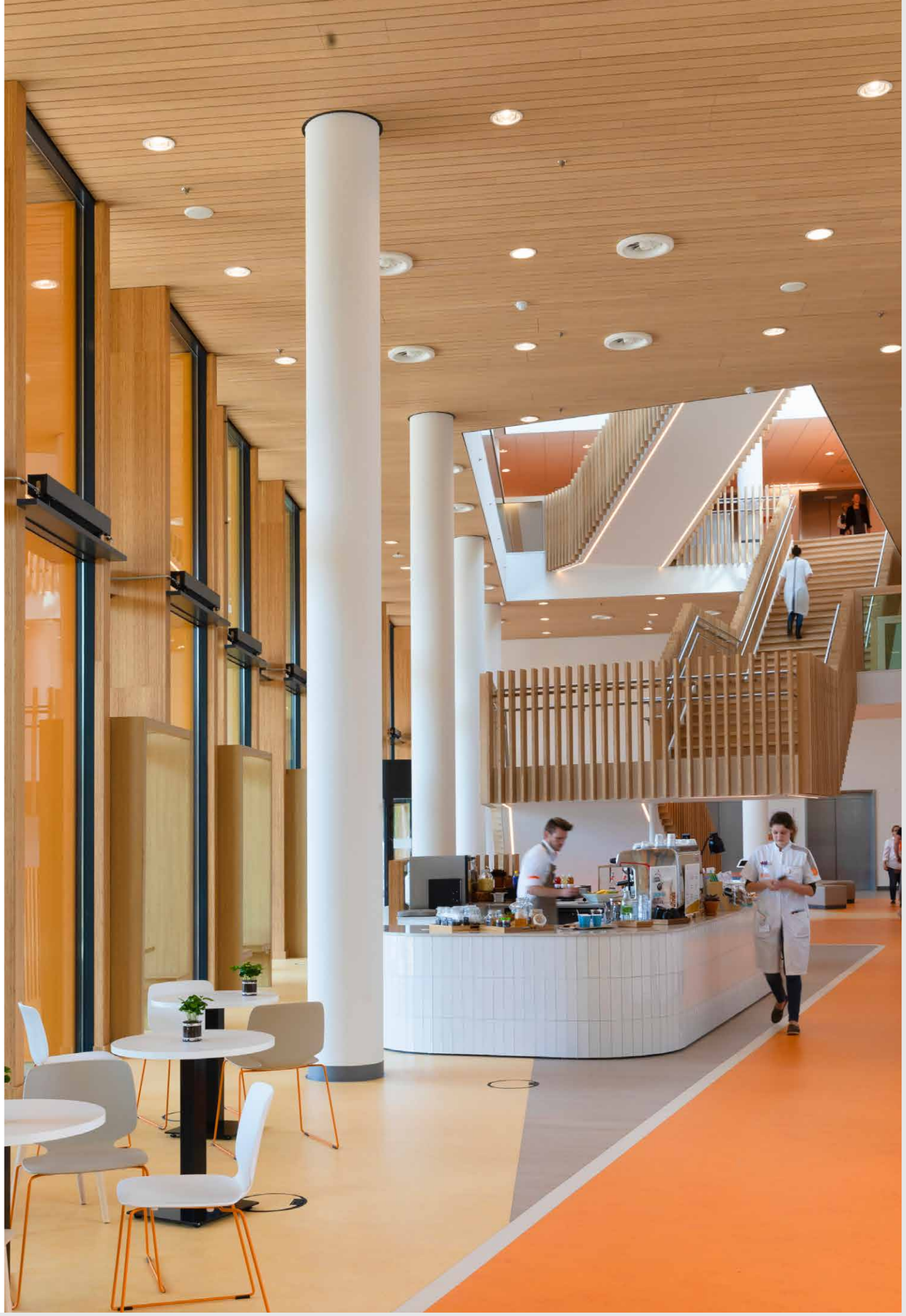
'To provide a cure for every child with cancer while maintaining an optimal quality of life'

Mission

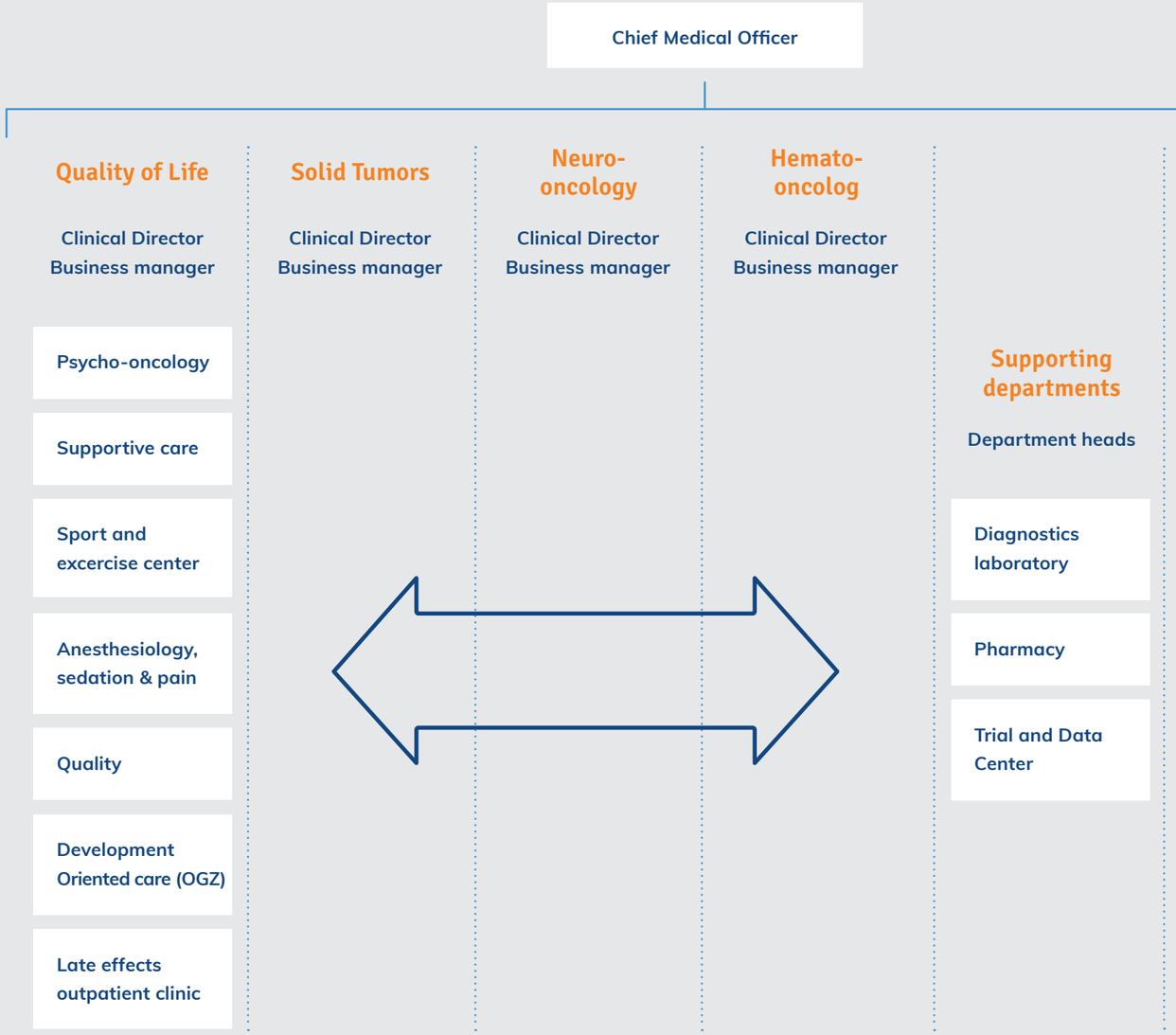
From the moment a child gets diagnosed with cancer, the Princess Máxima Center is fully focused on the welfare of that child, and her or his parents and family. We are completely committed to curing every child we encounter: free of disease, with as little pain and stress, as few side effects and complications, and as little long-term harm as possible. All this is done with the minimum possible disturbance to the child's development. A crucial element in constantly improving our care and quality of survival/life is our investment in scientific research. The research goals range from finding a cure, and optimizing psychosocial development, to improving surgeries, and understanding why children get cancer. These insights are used to optimize treatments and diagnosis.

Our mission emerges from the commitment of parents, survivors, care professionals and scientists in pediatric oncology. They have joined forces to achieve quicker and greater progress in the understanding and treatment of childhood cancer. Crucial to this is attracting and training the best professionals. We are certain that we can realize our mission, given the results of recent years in pediatric oncology, and the prospects that new scientific insights, therapies and technologies offer us. The representatives of parents and children are a reliable compass in this regard.

After the successful transition to our brand new building in 2018, 2019 was the first real full year for the Princess Máxima Center, and was used to significantly optimize our processes. Also, the integration of care and research was further shaped by the initiation of the Máxima Comprehensive Childhood Cancer Center (M4C). This joint healthcare and research annual report provides insight into how our departments and professionals contributed to our mission in 2019. In doing so, we base ourselves on the outcomes of the past year, and provide insight into the steps we took in 2019 based on figures, research results, publications and other developments.



Organization chart Care & Academy



Our organization chart

Care
In the Princess Máxima Center there are four clinical care departments, namely Solid tumors (SO), Neuro-oncology (NO), Hematology-oncology (HO), and Quality of Life (QoL). The Quality of Life department was newly formed in 2019 and brings together all professionals involved in quality of life, including the Late effects outpatient clinic. Every clinical department is led by a clinical director and a business manager. Together they are responsible for the realization of the goals and ambitions of the department concerned, and report directly to the chief medical officer, who is a member of the board of directors. Alongside the clinical care departments there are the care support departments: the Diagnostic laboratory, the Pharmacy, and the Trial and Data Center. The Diagnostic laboratory and Pharmacy each have their own department head who is integrally responsible and reports directly to the chief medical officer. Because of the nature of its activities, the Trial and Data Center is placed under both care and research.

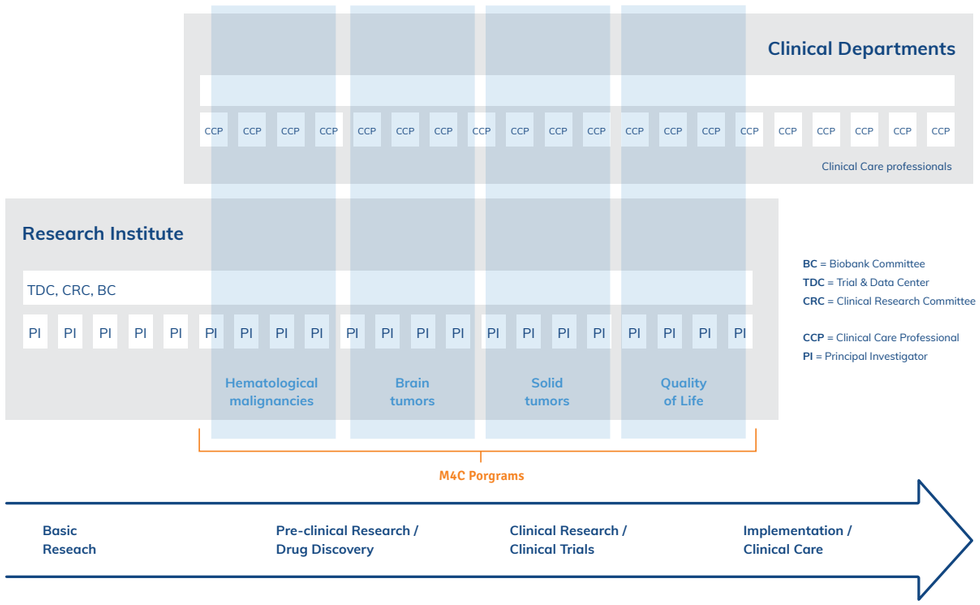
Academy
The Princess Máxima Center's Academy is a separate pillar within our organization and led by a management board. This board also reports directly to the chief medical officer.

Organization chart Research

Research
The research department consists of 32 research groups. Each research group is led by a principal investigator (PI), whose expertise directs the focus of the research. Some of these groups are strengthened with a co-PI (often a clinician), whose expertise complements the PI. The department is led by the scientific director and a managing director, who are supported by the research staff. The research department has a flat organization in which all PIs, whether junior or senior, report directly to the chief scientific officer (CSO). From the central support staff teams, dedicated members are assigned to the research department.

The Máxima Comprehensive Childhood Cancer Center (M4C)
To optimally integrate scientific research into our clinical programs and to foster innovation, the Máxima Comprehensive Childhood Cancer Center (M4C) structure was developed in 2019. The M4C forms the biotope for clinical scientists, pediatric oncologists and other clinical specialists who are engaged in research. It aims to simplify and accelerate the translation of fundamental, preclinical and clinical research, carried out by ourselves and by others, to clinical practice. At the same time, the research generates ideas from patient care.

Máxima Comprehensive Childhood Cancer Center (M4C)



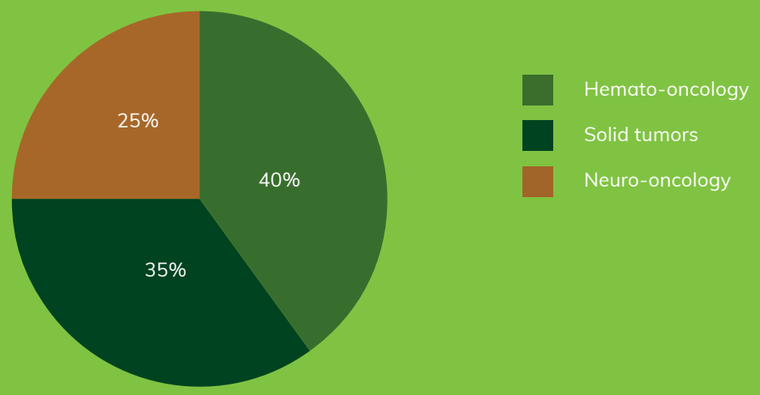
Facts & figures

Patient numbers 2019

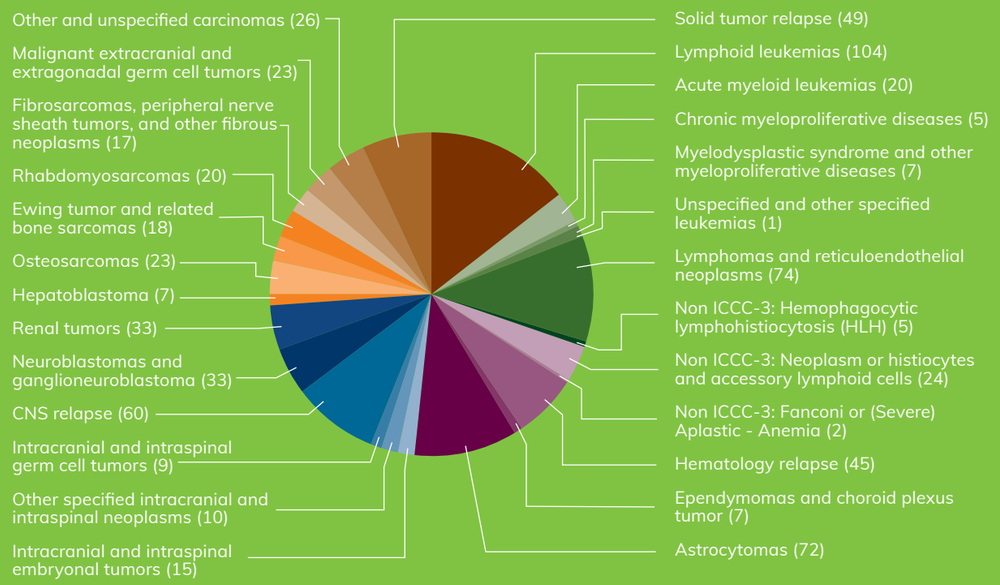
In 2019, a total of 878 patients with a suspected malignant tumor were seen in the Princess Máxima Center, of whom 709 patients were actually diagnosed with malignant tumors (555 new and 154 relapses). The patients had many different types of cancer: 40 percent were treated in Hematology-oncology, 35 percent in Solid tumors and 25 percent in Neuro-oncology. The pie chart below shows the patient distribution based on the diagnosis date for all of 2019. More information on 2019 is presented in the following figures.

Percentages of diagnosed children in 2019

(per clinical department)

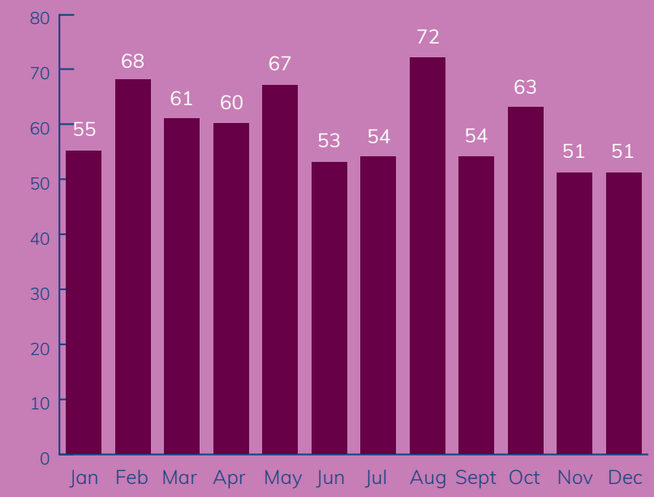


Spread of new patients in 2019, according to ICCC-3 classification



Number of patients with malignant diagnoses in 2019

(per month, based on SKION diagnosis data)



Late effects outpatient clinic

The Princess Máxima Center has a Late effects outpatient clinic for former patients who have been cured of cancer. Here, we focus on investigating, diagnosing and treating late effects of cancer treatment.

Unique Late effects patients	2019
Children	763
Adults	1320
Total	**2083**

Our staff as of December 2019

Care staff members, almost 800 in total

- ~ 100 medical specialists and doctors (85 FTE)
- > 270 nurses (225 FTE)
- ~ 250 healthcare support professionals (186 FTE)

Academy staff

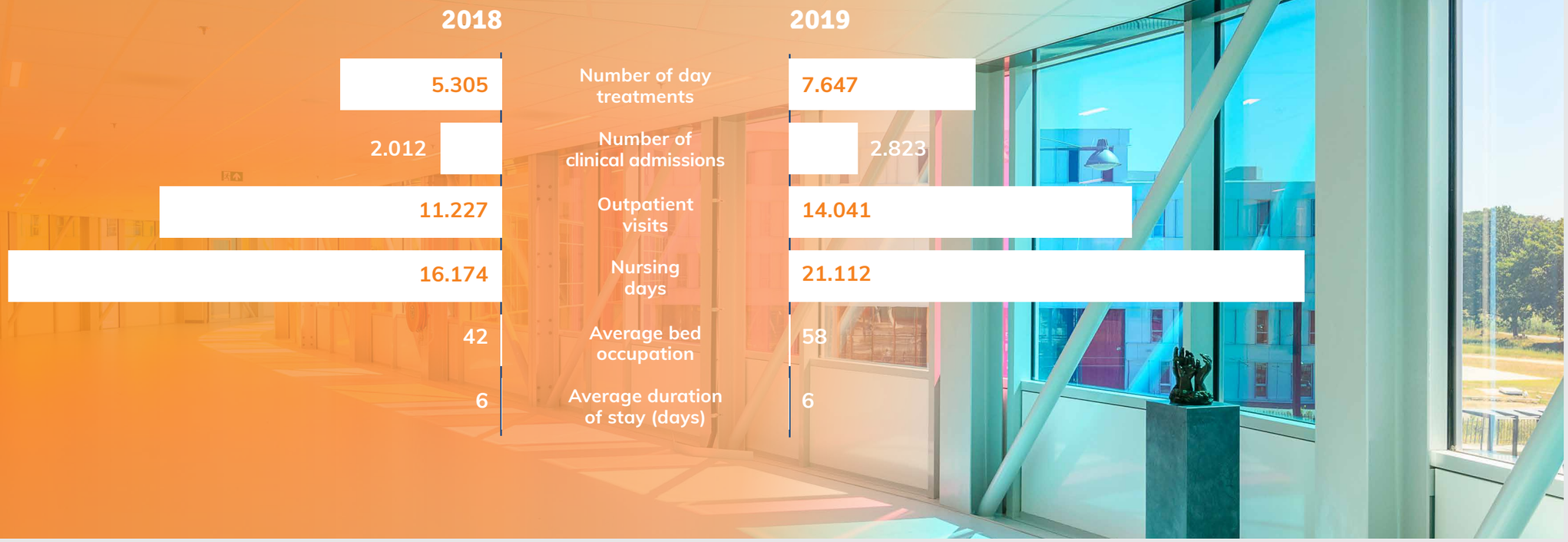
- 22 employees (18 FTE)

Research staff

- 436 employees (371 FTE)
- 112 PhD students
- 17 percent international staff, with a total of 28 nationalities

General care figures 2019*

*) The new Princess Máxima Center opened its doors on May 18th, 2018, thus concentrating pediatric oncological care and research in the Netherlands in one place. This explains why the figures in 2019 are higher than in 2018.



Overview of major events

January

Anne Rios, Jarno Drost and Ruben van Boxtel join Oncode as Junior investigators
Oncode Institute is committed to curing cancer by facilitating and funding scientific research. Its committee selected dr. Rios, dr. Drost and dr. Van Boxtel to join Oncode. Dr. Rios uses advanced imaging techniques to visualize organs and tumors in their entirety, as well as tissue in 3D, up to the cellular level. Dr. Drost investigates the development of kidney and rhabdoid tumors in children, and dr. Van Boxtel investigates the damage of childhood cancer and therapy-related second cancers.

Commissioning of RIVA Robots by the pharmacy
From January 2019, the RIVA robots, 'the Rolls Royces of pharmaceutical robots', have been used for various medication preparations in the cleanroom of the pharmacy. A first in Europe. With these robots, hundreds of sterile products can be prepared every day, fully customized and even safer than before.

Start of Anesthesia, Sedation and Pain team
The Princess Máxima Center started its own Anesthesia, Sedation and Pain team, to increase the capacity and quality of anesthesia and sedation for patients. Anesthesia and sedation are being developed and embedded in both of the center's MRIs, as well as in Nuclear Medicine and the sedation chambers.

Launch of Avicenna leadership courses
The Princess Máxima Center launched its leadership program 'Towards Excellence', developed by the Avicenna Academy for Leadership. The program, which is of great importance for the development of our organization, was spread over five meetings, and covered the following subjects: innovation, team development, change management, the organization of excellent services, and the creation of shared leadership.

February

International Childhood Cancer Day
On International Childhood Cancer Day, children with cancer receive the attention they deserve. In 2002, the Parents, Children and Cancer Association / *Vereniging Ouders, Kinderen & Kanker* (VOKK) initiated the first International Childhood Cancer Day, a worldwide collaboration of parent organizations in the field of pediatric oncology. The VOKK made an appeal to wear its '*Kanjers met LEF*' wristband. The proceeds will support projects for children with cancer in developing countries.

March

Inaugural lecture by Eelco Hoving
On March 5, 2019, prof. dr. Eelco Hoving delivered his inaugural lecture entitled 'The child is the priority' in the Academy building, following his appointment as Professor of Oncological Neurosurgery in Children at Utrecht University. Prof. dr. Frank Miedema, former dean of the Faculty of Medicine, praised him as 'an asset to Utrecht'.

April

Scientific Retreat
In 2019, 271 researchers from the Princess Máxima Center took part in an annual retreat. During this two-day retreat, the researchers presented their work to each other, took part in various team-building activities, and enjoyed an extensive social program. Ex-government minister and former professor of molecular genetics Ronald Plasterk delivered a keynote lecture.

May

Start of VAR and MAR
In 2019, the Nursing Advisory Council / *Verpleegkundige Adviesraad* (VAR) and the Medical Advisory Council / *Medische Adviesraad* (MAR) were established at the Princess Máxima Center. The VAR is an internal representative advisory body that advises the Board of Directors and relevant stakeholders on the professional activities of nurses and paramedics in our center. The MAR is also a representative advisory body and represents academic specialists in healthcare.

June

Maarten van der Weijden swims Eleven Cities Tour
Maarten van der Weijden swam the '*11stedenzwemtocht*', a swimming tour which passes through eleven Frysian cities from 21 to 24 June 2019, raising over 6 million euros for the Dutch Cancer Society (KWF) and the Children Cancer-free Foundation (KiKa). Part of the proceeds were going to the Princess Máxima Center. Dr. Jarno Drost and prof. dr. Eelco Hoving's research on rare, aggressive, rhabdoid tumors was one of the 11 charities he swam for.

Reward for care / research project
At the Princess Máxima Center, care and research for pediatric oncology are centralized. The strengths of this are the pooling of knowledge, and the emergence of more and more collaborations between healthcare and science, as the directors of the Princess Máxima Center can concur. To further stimulate this, prof. dr. Hans Clevers, former Chief Scientific Officer (CSO) of the Princess Máxima Center, established the one-off Princess Máxima Reward to fund a research project led by a preclinical and a clinical researcher.

July

'Heroes of the Princess Máxima Center' Documentary
In three episodes, the AVROTROS TV series 'Heroes of the Princess Máxima Center' ('*Helden van het Máxima*') provided a unique look behind the scenes of the Princess Máxima Center. Day and night, staff members work tirelessly to treat children with cancer, making the difference between life and death. A number of our staff members were followed in this series.

September

Establishment of the Quality of Life department, with Clinical director dr. Wouter Kollen
Quality of Life (QoL) was established as the fourth clinical department of the Princess Máxima Center, with Wouter Kollen appointed as Clinical director. QoL consists of teams for psycho-oncology, supportive care, anesthesia, sedation & pain (ASAP), a sports and exercise center, development-oriented care (OGZ), quality and the Late effects outpatient clinic. The professionals within these teams are focused on quality of life and function right across the other three care departments. This new department will better position the tasks of the teams involved, and make the organizational structure within healthcare more transparent.

Establishment of the Children's Comfort Team Utrecht
The Children's Comfort Team Utrecht (KCTU) was established in September. This multidisciplinary team consists of professionals with medical, nursing, pedagogical, psychosocial and spiritual expertise. The comfort team supports families and organizes (palliative) care throughout the care chain from the Princess Máxima Center and the Wilhelmina Children's Hospital (WKZ). In the Netherlands, seven Children's Comfort Teams have been established.

ERC awards € 1.5 million to dr. Jarno Drost
The European Research Council (ERC) awarded a start-up grant to dr. Jarno Drost. Drost leads a research group at the Princess Máxima Center and specializes in research into rhabdoid tumors, aggressive tumors in the brain, kidneys and soft tissues. With this grant he has started a research project to uncover the nature of these tumors.

October

Weekend of Science
During the Weekend of Science, the Princess Máxima Center gave a glimpse behind the scenes of its scientific work. Research opened its doors and through short presentations, interactive demonstrations and experiments, young and old were introduced to cancer research.

Alexander Eggermont new CSO in the Princess Máxima Center
On October 1, 2019, prof. dr. Alexander Eggermont was appointed Chief Scientific Officer (CSO) of the Princess Máxima Center. He succeeded prof. dr. Hans Clevers, who stepped down in June. For the past 9 years, Eggermont has been the Director of the Institute Gustave Roussy, the renowned oncology care and research institute in France.

November

Opening of the Auditorium
In November 2019, the Auditorium was opened on the top floor of the Princess Máxima Center, as a place of innovation and inspiration. For care, the Auditorium provides space for discussions with specialists around the world. Research can organize presentations, lectures and meetings. For Academy, it is a place for internal and external education, and the Foundation can hold network meetings, presentations and business meetings there.

December

Queen Máxima at the Princess Máxima Center
On December 3, 2019, Queen Máxima paid a working visit to the Princess Máxima Center. First she visited the day treatment unit where she had short encounters with children and parents, before being informed about how care professionals and researchers work together.

New agreement between the Ministry of VWS and the Princess Máxima Center
On December 10, Diana Monissen, CEO of the Princess Máxima Center, and Bas van den Dungen, Director-general Curative Care of the Ministry of Health, Welfare and Sport (VWS), signed an agreement for the Availability Contribution Academic Care (BBAZ). Thanks to this agreement, the Princess Máxima Center will receive a fixed annual contribution to the center's research infrastructure from 2020 onward. The contribution for 2020 is €10 million.

ERC awards two million euros to dr. Ruben van Boxtel
The European Research Council (ERC) awarded a Consolidator grant to dr. Ruben van Boxtel. Van Boxtel leads a research group at the Princess Máxima Center and seeks an answer to the question of why children get cancer. With this grant, Late effects, in particular the development of second cancers, can be assessed in children treated with chemotherapy.

Presentation of new multiannual strategy, 'Focused and promising'
After intensive preparations, in close collaboration between many stakeholders in the organization, the new multiannual strategy for 2020-2024 was finalized. It provides the guidelines for making meaningful progress in the coming years in order to realize our mission.

Public involvement

In the Princess Máxima Center, all activity strives to better the prognoses for children with cancer. Every employee works toward the mission to cure every child with cancer with an optimal quality of life. The societal impact of our work is therefore undeniable.

It is important to share the developments in care, our research projects and visions; not only within the healthcare and academic worlds, but also with the children, parents and general public.

The Princess Máxima Center therefore invests in activities to disseminate our results. This includes media appearances, events and non-academic presentations.

Parents and children

In 2019, a series of information evenings were organized in which professionals were invited to present their work to parents and former patients. These evenings had an interactive character, with ample opportunity for questions and the chance to continue the conversation afterwards. Each evening was hosted by a pediatric oncologist, who could help interpret and clarify the translation from bench to bedside. The table below lists the topics of the various evenings. This format, which was set up in consultation with the VOKK and Client Council, and in collaboration with the Academy, turned out to be a great success and will be continued in 2020.

General public

In addition to the information evenings for parents, there were two national events in which information on research was delivered to the public: 'Expedition Next' in May 2019, and the 'Weekend of Science' ('*Weekend van de Wetenschap*') in October 2019. With small experiments and flash talks we introduced different aspects of pediatric oncological research to society.

Our professionals regularly appear in a broad variety of media, including on TV (e.g. Jinek, RTV Utrecht), in newspapers (e.g. Financieel Dagblad) and in magazines (e.g. Elsevier Weekblad, LINDA). The documentary 'Heroes of the Princess Máxima Center' ('*Helden van het Máxima*'), featuring a number of our professionals including chief medical officer Rob Pieters, PI Jan Molenaar, PhD student Lianne Wellens, nurses Arno Deege and Kim Kamphuis and pharmacist Karima Aamri-Bouzbib, was broadcast on national television in July. The documentary series 'Top doctors' ('*Topdokters*') has closely followed one of our oncologists and PIs, Dannis van Vuurden, during his work in the clinic and research. This series will be broadcast in 2020.

Information evenings 2019

Date	Theme	Title	Chair	Presentations
Mar 21	Science	Why do children get cancer?	Wouter Kollen	Patrick Kemmeren How do aberrations in the DNA originate?
				Ruben van Boxtel Can we prevent childhood cancer?
				Roland Kuiper Is childhood cancer heritable
Jun 13	Care	Pain and stress reduction	Marianne van de Wetering	Laura Beek & Tom Joosten Anxiety and stress management
				Maarten Mensink Pain reduction
				Alexandra Roessingh Activities and distractions
Jun 27	Science	Will there be new treatments?	Wouter Kollen	Dannis van Vuurden How do we get the medicine to the tumor site?
				Jan Molenaar Every child it's own treatment; can we give targeted therapy?
				Natasha van Eijkelenburg When is it safe to give new medication to children?
Sept 5	Science	What kind of research is done with the children?	Peter Hoogerbrugge	Bastiaan Tops What is the Biobank?
				Marc van de Wetering What do we do with patient-derived tumor tissue?
				Wim Tissing How can we limit the side effects?
Oct 1	Care	Dexamethasone	Jennifer van Dijk	Valerie de Haas Mechanism of effects and side effects
				Jennifer van Dijk & Conradien Hormann Symptoms of side effects and practical tips
Nov 21	Science	Having cancer is more than the disease alone	Wouter Kollen	Martha Grootenhuis What is the effect of having cancer on your psychosocial health?
				Raphaële van Litsenburg How do childhood cancer and sleep affect each other?
				Wilbert Vermeij What effect may nutrition have on cancer and curing?

Fields of interest

Quality of life

Interview with Clinical Director

Dr. Wouter Kollen

Alongside curing patients, one of the main focuses for the Princess Máxima Center is promoting quality of life. It is with good reason that the mission is: to provide a cure for every child with cancer while maintaining an optimal quality of life. The Quality of Life department was set up in 2019 to connect and strengthen all the teams in the Princess Máxima Center that were already working on the issue. Quality of Life became the fourth care department in the Princess Máxima Center. Its staff works closely with the other three care departments, as well as the Princess Máxima Center's research and other departments. Furthermore, the Quality of Life department is responsible for the organization of shared care and for the connection between the Princess Máxima Center, the Children's Advisory Board and the parents' organizations: the Client Council / Cliëntenraad (CR), and the Parents, Children and Cancer Association / Vereniging Ouders, Kinderen & Kanker (VOKK).

Development domains

Quality of Life focuses on the child in development, with attention for the physical, social, emotional, cognitive and spiritual domains during all phases of life – not only during treatment, but also in follow-up and in the later years after treatment. The central question is how the professionals of the Princess Máxima Center relate to the needs of children, parents and families. The department strives to continually improve care in terms of quality of life, with the participation of parents and children.

Collaboration

The department works together intensively with the other care departments. Quality of Life has a matrix structure so that the professionals are also part of the other care departments. This means that there is a whole new way of implementing certain quality themes in care. For instance, in cooperation with the Academy, the Quality team has set up an e-learning and an escape room in which care professionals are trained in an almost playful way on subjects that in the past were often difficult to tackle.

Pain app

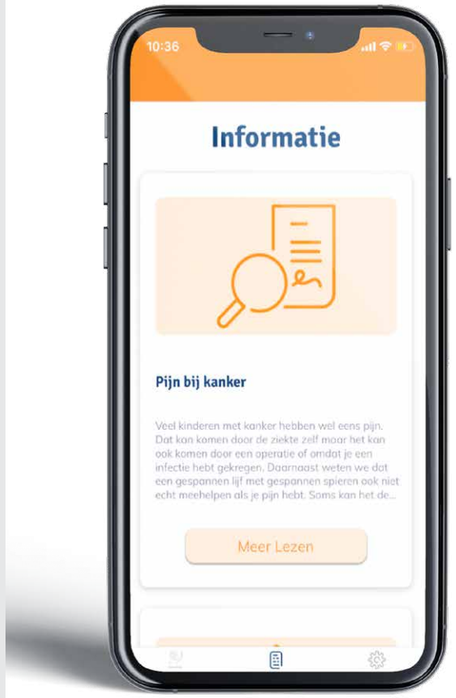
Alongside this clinically oriented collaboration, there is also very close partnership in the field of patient-related research. A nice example of the integral collaboration between care and research is the development of a special pain app, which children can use at home to indicate if they are in pain. Professionals from supportive care work very closely with professionals from the pain team on the app. An initial study has shown that parents rate this app very highly.

Synergy

The synergy that has emerged by uniting all elements in a single Quality of Life department in 2019 has delivered important results too. In recent years, Psycho-oncology has developed medical hypnotherapy and specific language use to reduce children's fear and stress. Collaboration with the anesthesiology, sedation and pain team is therefore essential. Within Quality of Life, teams and professionals can find each other more easily and therefore work better together on similar pathways. Furthermore, the expertise of Psycho-oncology can now be better integrated into the Late effects outpatient clinic.

Support

The Quality of Life department delivers extra support to the Development-oriented care / Ontwikkelingsgerichte zorg (OGZ) across the whole organization. Among other things, this has resulted in the start of traditional classroom lessons in the Princess Máxima Center, and classes coming to the Princess Máxima Center to visit their sick classmate. In 2019, the Sport and exercise center set up a tailored exercise program for every age group that helps with recovery, provides a distraction and raises awareness among children and parents of the importance of exercise, both now and in the future.



Máxima Childhood Comprehensive Cancer Center (M4C)

The four principal investigators (PIs) of Psycho-oncology, Neuro-psychology, Supportive care and Late effects participate directly in the Quality of Life department, and this contributes to shaping the Máxima Childhood Comprehensive Cancer Center (M4C). This integral combination of research expertise within the Quality of Life care department works as a catalyst for various forms of scientific research. The department also initiates research in the field of nursing care. For instance, a nursing care researcher from supportive care has started work on further improving and unifying guidelines on various aspects of nursing care. The Trial and Data Center, which is essential for clinical research into medicines and types of tumors, will also provide specific support to clinical research from the Quality of Life department in 2020.

Extra focus

In practice, parents and children are already experiencing the extra focus on quality of life from the new Quality of Life department and are reacting enthusiastically to it. They feel increasingly supported in all of the main aspects that determine quality of life. Parents say that the Princess Máxima Center has made huge progress over the course of a year, in terms of being more hospitable to parents, parents feeling 'seen', the pain app, lessons in the center's classrooms and visits by classmates. There is specific attention for brothers and sisters, and a special focus on teenagers. The Quality of Life department is proud of what it has already achieved in a short time, and the staff is full of energy and ideas to further improve the quality of life of patients, survivors, parents and families in the coming years.

Looking ahead

In the Princess Máxima Center's multiannual strategy, Quality of Life was named as one of the key strategic objectives for the coming years. Three main themes are central to quality of life. First and foremost, there is the standardization and monitoring of outcomes to identify the best practices at an international level. The second theme is about implementing those best practices that emphasize anxiety and stress reduction, improving cultural sensitivity and communicating with people from different cultural backgrounds. It also involves prioritizing the continued development of individual care plans, so that not only parents and children but also staff gets better insight into what a family needs. The third theme is about empowering children and families, by giving patients and their parents more control over the elements of care for which they can truly take the lead. In addition, a specific program will be developed for the neuro-psychological follow-up of children with a brain tumor.

General

Alongside the work done by the seven teams, the Quality of Life department is working on a number of other things. For instance, in 2019 our professional support counselor started, in order to improve the quality of life of our employees. She helps professionals in the Princess Máxima Center deal with the mental strain that comes from working with children with cancer on a daily basis. Structural consultation with parents and children from the Children's Advisory Board, Client Council and VOKK takes place in the department regularly. Furthermore, Quality of Life focuses on improving information and communication around all aspects of pediatric cancer and treatment. The alignment with shared care is an equally important task, and in 2019 a lot of work was put into improving IDT so that Shared Care centers can work optimally with the Princess Máxima Center's systems. Last year, two members of staff with a research background started working in the department, and are now further developing clinically within care. This is also contributing to the further integration of care and research. Moreover, there is intensive partnership with colleagues from UMCU and WKZ on various themes that have a direct impact on quality of life.

'Parents and children are already experiencing the extra focus on quality of life with the opening of the new Quality of Life department'

Dr. Wouter Kollen, Clinical Director

The seven Quality of Life teams

The Quality of Life department consists of the following teams:

- Psycho-oncology
- Anesthesiology, sedation & pain (ASAP)
- Supportive care
- Sport and exercise center
- Development-oriented care (OGZ)
- Quality
- Late effects outpatient clinic

Psycho-oncology

Prof. dr. Martha Grootenhuis, Head

The Psycho-oncology staff is responsible for providing psychosocial support to parents and children. Accessible care is available to children and parents as soon as they enter the Princess Máxima Center. Through the introduction of weekend services, care is now available seven days a week. Continuity of care has been strengthened through systematic screening of family stress and risk factors using the KLIK portal. ‘On Course’ is offered online to give support when dealing with illness and treatment. Furthermore, in the pain, fear and stress reduction program, over 110 employees have attended training on medical hypnosis and suitable language. On the multidisciplinary level there has been a contribution to the supportive care guidelines, semen preservation, fear and pain reduction, fertility, memorial services, cultural sensitivity and medical ethics. The team has also delivered contributions to the Nurse Advisory Board / Verpleegkundige Adviesraad (VAR), Medical Advisory Board / Medische Adviesraad (MAR) and the children’s comfort team for the Utrecht region.

Furthermore, contributions have been made to the ‘Maximaal op Maat’ (Maximum Personalization) program for the induction of new nursing staff. Among other things, lessons have covered medical traumatic stress and development psychology. Education has also been delivered for Outreach. More than ten PhD candidates are researching (neuro-)psychological outcomes, interventions, and sleep. Together with a new Neuropsychology PI, care and research for children with a brain tumor has been improved.

Anesthesiology, sedation & pain (ASAP)

Drs. Maarten Mensink, Head

Since January 1, 2019, the Princess Máxima Center has had its own Anesthesiology, sedation and pain team, aiming to make an optimal contribution to stress-free and pain-free care. In 2019 the focus was on embedding anesthesiology care and sedation, including preoperative screening. The main objectives were to ensure that as many diagnostic interventions or a combination of scans as possible are done when a patient is under a single anesthetic, and to make it possible to conduct extra procedures in the MRI environment, while a patient is under anesthetic.

Furthermore, within the team, pain physicians and pain consultants have further shaped pain care by attracting and recruiting nursing pain consultants and pain physicians. This expansion means that pain care is guaranteed 24 hours a day, and pain consultants are also present at weekends. Therefore, comprehensive pain care can be delivered to children – not only complex oncological pain care, but also perioperative pain care and pain care in the IC. To ensure continuity, recruitment of student pain consultants, who will work part-time at the Princess Máxima Center and follow a part-time pain consultancy course at HAN University of Applied Sciences, has started.

In terms of research, the ASAP team has been involved in the development of new tools, such as the KLIK pain monitor, and fundoscopy under sedation for brain tumor diagnosis. Additionally, the team has initiated pharmacological research, including on the use of gabapentin as an anti-neuropathic with ALL patients.

Supportive care

Prof. dr. Wim Tissing, Head

Supportive care focuses on the treatment and prevention of side effects resulting from pediatric cancer treatment. In 2019, the collaboration with sub-specialists in the WKZ was further optimized, so that there is now a fully-fledged partnership in supportive care, including in the domains of pediatric infectiology, pediatric nephrology and pediatric endocrinology. Collaboration with VOKK has also been optimized, so they are now fully part of the team. All guidelines and protocols from the old pediatric oncology centers have been transformed into a single set of supportive care guidelines for the Princess Máxima Center. Dietetics has been strengthened in 2019. The dieticians team has been expanded and is now firmly imbedded in the Supportive care team of the Quality of Life department.

2019 marked the start of the implementation of the Child Comfort Team. This team, which focuses on pediatric palliative care, began with three pediatric oncologists and five nurses and has since been expanded to include a spiritual counselor, a psychologist, medical social workers, pedagogical care, the care mediation service (BZU) and the pain team. The team is available 24 hours a day for questions about pediatric palliative care. Furthermore, a start has been made with providing additional pediatric palliative care training for care professionals.

In 2019, full-fledged research began in the domain of supportive care. Here, collaboration with the WKZ has been crucial. At the moment, studies are being conducted into pediatric infectiology, nutrition/nutritional condition, development guidelines, pediatric endocrinology, pediatric IC, pediatric palliative care, line infections, and nausea and vomiting.

Sport and exercise center

Patrick van der Torre, Head

The Sport and exercise center offers specialized physical therapy care for children with cancer, and contributes to their health and quality of life. Currently the team consists of seven pediatric physical therapists, one oncology physical therapist and an exercise therapist, all of whom have specific focal areas. The physical therapists all work at the Late effects outpatient clinic, where they study survivors and deliver advice.

Multidisciplinary consulting hours for children with a hypothalamus dysfunction, Chemo Induced Pregnancy clinic and children with an hourglass neuroblastoma started in 2019. The partnership between different professionals delivers combined knowledge and expertise, and ensures better alignment with, and advice for, children and their parents.

Alongside this specialized care, through the '*Maximaal Bewegen*' (Maximum Exercise) program the center offers sport and exercise activities to children of all ages, every weekday – from baby gym to sport for adolescents. Children who are unable to attend group activities can get individual support in their own rooms. Exercise programs are delivered by four students from the Sport and exercise program from Hilversum and the CIOS in Goes, under the supervision of a pediatric physical therapist.

In 2019, a lot of training was given to other care professionals on the integration of exercise in the regular oncology therapy program, as well. Discussions were held with nurses, doctors and facility management teams about how they can contribution to this. With the help of the Foundation, two new gardens were set up for sport and exercise, so that children can enjoy exercising outside, together with their parents.

Development-oriented care (OGZ)

Dr. Hanneke de Ridder–Sluiter

The central focus in Development-oriented care / Ontwikkelingsgerichte Zorg (OGZ) is the development of children and their families. The OGZ staff participates in organization-wide projects and working groups in order to realize the vision of development-oriented care. Alongside this, the various teams also have a specific focus.

The KLIK system systematically monitors the quality of life of children and, based on the data, interventions are offered. In 2019, 72 percent of children and parents filled in the KLIK system. The Educational provision / Educatieve Voorziening (EV) team, together with children, parents and the children's regular schools, ensure that schooling can continue. The children receive lessons in their rooms, in the day treatment and, since fall 2019, in classrooms too. Since 2019, it has been possible for children to invite their classmates to visit the Princess Máxima Center. In the Science and Discovery Center, children can explain their diagnosis and treatment to their classmates. This means that classmates get more insight and understanding of the situation, and the children can share their own experiences. Also in 2019, together with various partners and volunteers, daily activities and events were organized for children of different age groups, together with their brothers and sisters. These activities are a distraction for the children, help them to relax, and stimulate wider development.

Thanks to the teenagers' project, what are known as 'communication cards' have been introduced. Children and parents can hang these cards outside their rooms to indicate what their wishes and needs are, e.g. 'no visits for the moment please'. This means they have more privacy and control. Moreover, a Teenagers e-learning module for care professionals has been developed, and the youth website has been updated.

At the end of 2019, a life questions consultant began to provide support to parents, children and staff around life questions. She is also involved in the remembrance gatherings for families who have lost a child, at home or in the Princess Máxima Center. Four such gatherings were held in 2019.

Quality

Josje van Inzen-van IJsseldijk, Head

In 2019, the Quality team made a big contribution to making care even safer and of a higher quality. A new document management system (iMáxima) was introduced which means greater uniformity between the working methods of the Princess Máxima Center and the Shared Care centers. Furthermore, a new system was developed for the safe reporting of incidents. With this system it is much easier to conduct analyses and to flag up noteworthy or unusual things. This supports the monitoring that is carried out by the Quality professionals themselves, and delivers additional input for improvements in care and care processes.

Moreover, in 2019 improvements were made in terms of access to quality indicators that need to be provided to the Health and Youth Care Inspectorate / Inspectie Gezondheidszorg en Jeugd (IGJ). Importantly, there have been developments in what are known as pediatric early warning signs (PEWS). By regularly monitoring a number of factors, a good picture can be built up of a child's physical condition. PEWS comprises frequent measurement of, among other things, a child's heartbeat, breathing, blood pressure and temperature. Systematic monitoring of these data allows healthcare professionals to intervene before a serious incident occurs. For example, an IC doctor can be called in before a child experiences an acute, unexpected deterioration. PEWS ensures an improvement in the quality and safety of care for a child, and means care professionals have more control and therefore peace of mind.

The Princess Máxima Center strives to continually improve, on the basis of indications and feedback from parents and children. That is why, on the initiative of the Client Council, a special team of councilors has been set up. The so called 'ombudsvrouwen' converse with parents who have a question or want to give feedback. They provide support to the parents and, where necessary, facilitate discussions between parents and care professionals, or help with complaint procedures.

Since its foundation, the Princess Máxima Center has met various national and international accreditation standards. The IGJ paid a number of visits to the Princess Máxima Center in 2019, and for each one the final assessment was positive. Moreover, the Quality team carried out 18 internal audits using specially trained auditors.

All the findings from the instruments introduced by Quality finally come together in the purpose-built quality system. This is used to gather and coordinate results and points for improvement.

Late effects outpatient clinic

Magda Verhoeven-van Korlaar, Head

In the Late effects outpatient clinic, Late effects of treatment can be detected in good time. Late effects can emerge years after treatment. The Late effect outpatient clinic coordinates care for survivors. In 2019, a lot of time and energy was invested in transferring the necessary medical data from the academic hospitals to the Princess Máxima Center. Data management has now been integrated in the Trial and Data Center. Further improvements have been made to the invitation policy and the planning process, and the first steps toward standardization have been made (handbook, order sets). Tariffs have also been reviewed. Additionally, attention has been paid to internal and external communication (weekly memo, consultation structures, information folder). In the coming year, the emphasis will be on the optimization of processes and production, as well as the establishment and strengthening of partnership agreements. For further improvement of care in the Late effects outpatient clinic, the participation of the VOX survivors is crucial. This interest group, which is part of VOKK, will be intensively involved in the further development of the Late effects outpatient clinic in the years to come.

Clinical research

Psycho-oncology/neuropsychology: SUSPECT study

In the SUSPECT study prospective research is done into the impact of sleep and stress problems on the cognition and brain development of children who have recently been diagnosed with a brain tumor. This information will help with the development of interventions for this group of vulnerable patients.

Psycho-oncology: MICADO study

The MICADO study explores sleep and quality of life for children after cancer. We investigate the effectiveness of Cognitive Behavioral Therapy for Insomnia (CBT-i), an online sleep treatment 'i-Sleep' for young people (13-24 years old) who have trouble sleeping after cancer (treatment).

Supportive care: ALL-11 & infection prevention

Previously, no prophylaxis against fungal infections was administered in the first four weeks of treatment for Acute Lymphoblastic Leukemia (ALL), as it could not be used at the same time as chemotherapy. The alternative was daily intravenous medication. We have developed and evaluated a dosing method that reduces the need for intravenous medication to twice a week instead of every day.

Supportive care: Sensory study

Although changes in smell and taste are a common complaint in children with cancer, they have never been studied. We have developed and evaluated a method that enables us to study this, meaning we will soon be able to start research into how smell and taste change, and deliver tailored advice on the basis of this data.

Preclinical research

In the lab, researchers are working from a molecular and cell-biological perspective to optimize the quality of life of children with cancer. The effects of exercise and diet on the ageing of cells are studied. The toxicity of treatment on DNA is analyzed on cells that have been grown in the lab. Relapses and the emergence of second cancers through treatment are also studied.

Alyodawi *et al.*, J Cachexia Sarcopenia Muscle, 2019

This study shows that muscle growth in mouse models slows cell ageing. If the DNA can be damaged through pediatric oncology treatment, it is beneficial to slow ageing down as much as possible.

In the spotlight | Principal Investigator

Dr. Marita Partanen

Coming over from across the Atlantic to start a research group from scratch isn't easy for a young clinical researcher. But the opportunity was too good, and the challenge too exciting to turn down, says the Canadian neuropsychologist dr. Marita Partanen. 'Cancer treatments can have a serious impact on a child's development. I'm convinced we can improve the quality of our patients' lives, now and in their future.'

Cognitive skills may decline in children with cancer, explains Partanen. Treatment can cause a drop in IQ or other neurocognitive skills, which may reduce the quality of life during and after treatment. Cognitive decline can be caused by various factors, but it is possible to detect these early in treatment. Partanen's group focuses on the early identification and intervention of neurocognitive impairments using a combination of neuropsychological and neuroimaging measures. These studies will ultimately help to prevent further neuropsychological difficulties in patients and survivors of child cancer.

Longitudinal screening program

'Before I came to the Princess Máxima Center in September 2019, I worked at St. Jude Children's Research Hospital in the US, where I did research and clinical assessments with children with various cancers and blood disorders. Usually, as neuropsychologists, we do 5- to 6-hour assessments with these children in order to identify their possible impairments. However, we need something 'shorter' as a test, in order to reach more patients and to monitor their cognitive development over time. The usual assessments are just a one-point test, but growing up means changing. It's important for pediatric oncology to have something similar to the growth charts pediatricians use to monitor whether a child is following his or her normal trajectory.'

Developing such a longitudinal neuropsychological screening program is one of the aims of Partanen's group. If doctors and neuropsychologists can start following children close to diagnosis, it will enable them to differentiate risk factors more precisely, and intervene if necessary.

Changing brain structures

The other main focus of the group is developing brain-imaging techniques. Partanen: 'Using modern MRI scanners with high resolution, we try to find abnormalities in the brain that point towards specific cognitive problems. It is crucial to target intervention early on and limit cognitive decline.' These declines have been associated with white matter impairments in the brain, for example. Other subtle changes can be detected with neuroimaging, which can provide further insight into the neurobiological substrates of and interventions for cognitive deficits in pediatric oncology, says Partanen.

Treatment that fits best

Research can help determine whether vascular, structural, or functional changes in the brain are associated with neurocognitive functioning in children with cancer. Partanen: 'With imaging we try to identify the structures in the brain that might change because of the disease, treatment, or other factors. This insight is important in order to choose the treatment that fits best for an individual patient. You can have two kids of the same age and diagnosis, but they can show a completely different outcome. Until now it's often hard to tell why. MRI imaging can help us understand the underlying mechanisms.'

Close link to clinical practice

For Partanen, collaboration of research and healthcare is crucial. 'We work closely together across all disciplines involved. I started my work here with meeting many different departments and groups that I would be encountering in my research. Our type of research cannot be done without a very close link to clinical practice. This is how we get our research questions. But it's a two-way street. The things we discover are only useful if we implement them successfully in the clinic.' Partanen sees parents as important partners as well. They have to give their consent, but usually that's not a problem at all. 'Every parent wants the best possible treatment for their child. Moreover, most parents are keen on collaborating since good research will also help other children in the future. People really want to support us in our efforts to accomplish the mission of the Princess Máxima Center.'

Better starting position

It has been an intense first half-year for Partanen. Her personal aim is to learn Dutch as quickly as possible, in order to be able to communicate with parents and children. She sees a very clear commitment to research as crucial to where the Princess Máxima Center is heading. 'Our studies in the field of neuropsychology answer a need that is felt by every person involved. Everybody can see the devastating effects treatment of child cancer can have on daily life, school and work. I strongly believe our research will help children to get a better starting position for the rest of their lives.'

'Identifying neuropsychological problems early is the key to preventing them'

Dr. Marita Partanen, Principal Investigator

Hemato-oncology

Hemato-oncology covers the treatment of children and young people with the whole spectrum of different types of leukemia, lymphoma, histiocytosis and bone marrow failure syndrome. Our state-of-the-art diagnostic facilities include morphology/ histology, flow cytometry as well as all current molecular sequencing techniques (RNAseq, WES). The treatment modalities in our portfolio are chemotherapy, cellular therapies (such as allogeneic stem cell transplantation and CAR T-cell therapy), targeted therapies with small molecules and occasionally radiotherapy. The stem cell transplantation unit is a partnership between the Princess Máxima Center and the Wilhelmina Children's Hospital (WKZ). Children with benign disorders, e.g. metabolic disorders, are also treated on this unit. We invest in preclinical and clinical research in line with our mission to provide a cure for every child with cancer while maintaining an optimal quality of life. Immunotherapy (with antibodies and CAR T-cells) plays an important role in improving outcomes, both by reducing toxicity and by offering treatment opportunities for patients who previously had no chance of a cure.

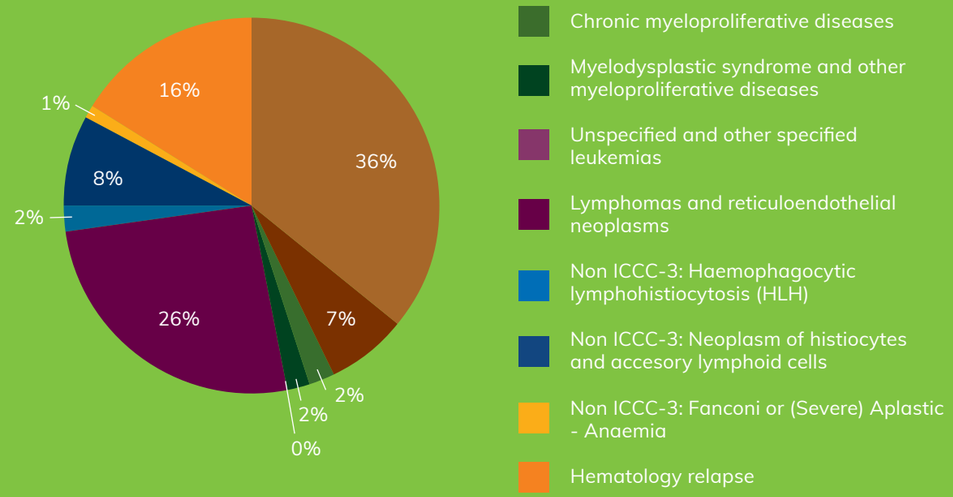
Patient numbers

The following tables en charts show the hemato-oncology patient numbers in 2019.

Hemato-oncology

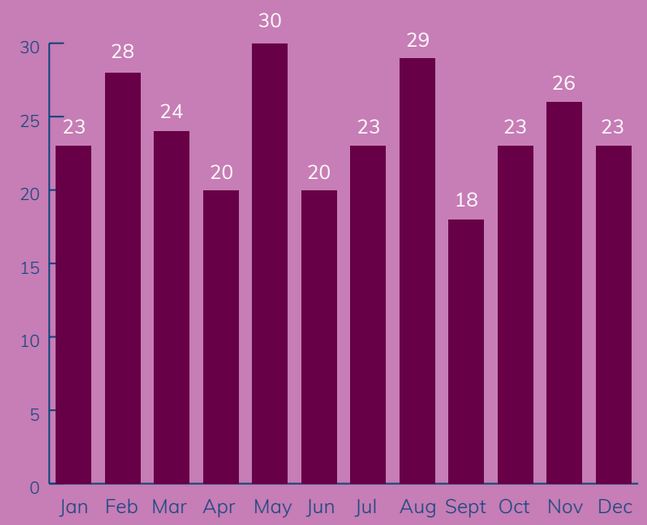
ICCC-3	Disease	Patient numbers
I.a	Lymphoid leukemias	104
I.b	Acute myeloid leukemias	20
I.c	Chronic myeloproliferative diseases	5
I.d	Myelodysplastic syndrome and other myeloproliferative diseases	7
I.e	Unspecified and other specified leukemias	1
II	Lymphomas and reticuloendothelial neoplasms	74
	Non ICCC-3: Haemophagocytic lymphohistiocytosis (HLH)	5
	Non ICCC-3: Neoplasm of histiocytes and accesory lymphoid cells	24
	Non ICCC-3: Fanconi or (Severe) Aplastic - Anaemia	2
	Hematology relapse	24
	Total	**287**

Hemato-oncology patients in 2019
According to ICCC-3 classification



Hemato-oncology patient numbers per month

Based on SKION diagnosis data



Cellular therapy			N
Allogeneic Stem cell transplants	10 benign	39 malign	49
Umbilical cord blood unit transplants used			22
CAR T-cell therapies			12

Research in hemato-oncology

Pediatric hemato-oncology revolves around cancer of the blood. Acute leukemia is the most prevalent type of cancer in children and the result of uncontrolled growth of immature white blood cells. When affecting the lymphoid lineage it is known as Acute Lymphoblastic Leukemia (ALL), and when myeloid cells are involved it is called Acute Myeloid Leukemia (AML). To date about 90 percent of ALL and 70 percent of AML patients are successfully treated. However, a significant number of children still relapse, and then have a much lower chance of being cured. Childhood lymphoma is cancer of the lymph node and also includes different types, such as Hodgkin's lymphoma, Burkitt's lymphoma, T-cell lymphoblastic lymphoma, anaplastic large cell lymphoma and other rarer forms of lymphoma. The most common types of childhood lymphoma have a cure rate of almost 90 percent.

The Máxima Comprehensive Childhood Cancer Center (M4C)

To closely link the research institute with the hospital, and to embed research and innovation well within the clinical program, the Máxima Comprehensive Childhood Cancer Center (M4C)

was developed and implementation started in 2019. The M4C facilitates the future development of novel therapies and accelerates the translation of research into clinical practice.

The development of novel therapies can either be focused around specific diseases or around specific treatment modalities. Within Hemato-oncology there are four Máxima Comprehensive Childhood Cancer Center (M4C) groups, and we offer a large portfolio of clinical trials to our patients. The M4C groups within Hemato-oncology cover the following disease/treatment modalities:

- Acute lymphoblastic leukemia
- Lymphoma
- Myeloid malignancies
- Myelodysplastic syndromes/Bone marrow failure syndromes
- Cellular therapies/hematopoietic stem cell transplantation

Adolescents and Young Adults

Together with the adult hematologists from UMC Utrecht, the Hemato-oncology department at the Princess Máxima Center is engaged in developing better care for adolescents and young adults (AYA) with leukemia and lymphoma. Cancer does not respect age boundaries, and certain types of cancer that are more common in children also occur in young adults, and vice versa. Combining the expertise for the different types of cancer provides opportunities to improve outcomes in this often-neglected age group, and chances to develop common clinical pathways. A specific focus on this collaboration is around the development of novel cellular immunotherapies for children and young adults with leukemia and lymphoma.

Preclinical research

Since the opening of the Princess Máxima Center in 2018, nine research teams with a broad portfolio of expertise have been working together with clinicians within the Máxima Comprehensive Childhood Cancer Center to improve cure rates and quality of life for children and young people with hemato-oncological malignancies. The different teams study how the genetic makeup of the leukemia impacts response to therapy, and ultimately outcomes, taking into account the unique interactions between the leukemia and the bone marrow microenvironment. Using state-of-the-art technology, CRISPR-Cas9 based methods are applied to model genomic abnormalities in ALL, define mechanisms of therapy resistance and identify molecular targets that can overcome therapy resistance; and single-cell DNA sequencing is used to uncover how AML evolves from a single mutational event in bone marrow stem cells to a full-blown leukemia. Some groups focus on specific types of leukemia, e.g., T-cell leukemia or leukemia driven by a specific oncogene (the MLL gene). Others focus on the role of genetic predisposition in pediatric cancers, including ALL, and how the ALL genome is affected in response to treatment.

A good example of this basic research and how it may be translated into the clinic is the following project: in collaboration with researchers at St. Jude Children's Research Hospital, a detailed study comparing ALL at diagnosis and relapse identified a novel subset of ALL with increased number of changes in the DNA (hypermutated ALL). Following up from this initial observation, new research aimed at providing insights into the molecular mechanism driving hypermutation in ALL, and the effects of therapy, was initiated in 2019. Insight into the molecular mechanisms that drive this type of ALL opens new lines of investigation into novel therapies, potentially including immunotherapy with checkpoint inhibitors – an approach that has been successful in other types of tumors with a high mutational burden.

Important output

- **Agraz-Doblas *et al.*, Haematologica, 2019**
  A detailed genomic/transcriptomic analysis identified a small population of primitive leukemic progenitors in MLL-rearranged B-cell ALL, resembling immature human fetal liver hematopoietic stem and progenitor cells. The same study revealed that in about 45 percent of MLL-AF4 rearranged leukemias (the most prevalent MLL-fusion protein in infants), expression of the reciprocal AF4-MLL fusion is observed. Patients expressing this reciprocal fusion mRNA showed a significantly better event-free and overall survival.

- **Assi SA *et al.*, Nat Genet., 2019**
  This study, which was led by researchers from University of Birmingham, in collaboration with researchers from University of Newcastle, provides a comprehensive description of AML subtypes and their transcriptional networks, and identifies with AP-1, which is a central and shared component of these networks that is amenable to therapeutic targeting.

- **Belver *et al.*, Cancer Discovery, 2019**
  In a large collaborative study with Adolfo Ferrando, Columbia University, New York, a paper was published describing how aberrant regulation of chromatin accessibility to oncogenic enhancers drives leukemic transformation in T-ALL.

- **Polak R *et al.*, Haematologica, 2019**
  A collaborative study with researchers from Erasmus MC in Rotterdam demonstrates the significance of autophagy for pediatric t(12;21) ALL, and shows that targeting this cellular process with a well-tolerated and repurposed drug impairs leukemic propagation. It thus provides evidence for the therapeutic value of targeting autophagy in ALL.

Clinical research

Through personalizing therapies we work hard to improve outcomes for our young patients with leukemia and lymphoma and, at the same time, to reduce toxicity and Late effects of current treatments.

An important step toward a higher cure rate for children with high risk and relapsed acute lymphoblastic leukemia has been the development of CAR T-cell therapies. The patients' own T-cells are modified so that they can now detect and destroy the leukemic cells. At the beginning of 2019, the Princess Máxima Center treated its first patient with his own CAR T-cells. Very quickly this program has expanded and the Princess Máxima Center is now one of Europe's largest centers offering cellular and other forms of immunotherapy for children with leukemia and lymphoma.

Together with the adult hematologists and the cell therapy facility (CTF) at UMC Utrecht we are in the process of developing our own capability to produce CAR T-cells. This will reduce the time that is necessary to make CAR T-cells (important for patients with a rapidly progressive disease), and will enable us to develop new CAR -based cellular therapies.

Highlights from our clinical studies include:

- **Inotuzumab Ozogamicin (InO)**
  Inotuzumab is an antibody conjugated with a toxin. It recognizes a surface marker on the leukemic blasts and thus carries the toxin ozogamicin to the leukemic cells, causing

cell death. Results of the phase I study of Inotuzumab Ozogamicin (InO) in children with relapsed/refractory ALL, presented by Brivio, Zwaan et *al.* at the annual meeting of the American Society of Hematology in Orlando in 2019, determined a safe dose of InO, and showed a remarkable overall response rate of 80 percent, with 79 percent of patients with relapsed or refractory disease reaching an MRD negative complete remission. Currently the Phase 2 of the study is ongoing, and an additional patient cohort is planned to test the combination of InO with chemotherapy. This effective and well-tolerated immunologically targeted delivery of chemotherapy to leukemic cells will be part of the future standard therapy for relapsed ALL patients and also be studied in newly diagnosed ALL patients in the All Together protocol.

- **Blinatumomab**
  Blinatumomab is a bi-specific antibody that binds both leukemic blasts and T-cells, making the leukemic cells visible for T-cells so that the former can be destroyed. In the IntReALL study for children with relapsed ALL expressing CD19, therapy with Blinatumomab was compared with chemotherapy as one of the treatment modules to prepare children for hematopoietic stem cell transplantation. In 2019, the randomization between Blinatumomab and chemotherapy was prematurely stopped because patients treated with Blinatumomab showed a better survival rate. Similar data were reported from the U.S. Children's Oncology Group, documenting better survival rates and less toxicity in children with relapsed ALL treated with Blinatumomab. This is an important step in improving therapy for children with relapsed CD19-positive ALL.

- **FORUM study**
  In 2019 the FORUM study in children with ALL undergoing allogeneic stem cell transplantation was prematurely stopped, as it became apparent that significantly more relapses occurred in the group conditioned with chemotherapy than the group treated with radiotherapy. Hence all children > 4 years with ALL that need a hematopoietic stem cell transplantation are now receiving radiotherapy. This was an unexpected result and has led to a change in clinical practice.

Interview with Clinical Director

Prof. dr. Josef Vormoor

The Hemato-oncology department at the Princess Máxima Center is the national treatment center for children and teenagers with leukemia and lymphoma.

Immunotherapy

In 2019 we got new tools to treat children and young people with relapsed and refractory B-lineage ALL. As outlined in this annual report, studies with new antibodies targeting toxins (Inotuzumab Ozogamicin) or T-cells (Blinatumomab) to the leukemic cells showed fantastic response rates in children with relapsed and refractory ALL. Moreover, CAR T-cells became available within the regular care for patients with relapsed or refractory B-lineage ALL. We now have a whole set of new therapies in our armory, and we need to study how best to use and combine them with traditional chemotherapy and stem cell transplantation. Immunotherapy is no magic wand; however, it clearly provides a chance to cure patients that were previously on a palliative trajectory. Though not without significant side effects, the antibodies and CAR cells currently in use seem to have a much better profile of acute and long-term toxicity as compared with intensive high-dose chemotherapy and stem cell transplantation. Immunotherapy may therefore not only be of relevance for improving the survival rates of our patients, but also for improving the quality of life of long-term survivors.

Innovation

The impact of these new treatments is huge – at this moment primarily for children with relapsed or refractory B-lineage ALL. However, as part of large international clinical studies, we are now going to test how to best introduce immunotherapy in the treatment of patients with newly diagnosed ALL. The fundamental questions are: can we further reduce relapses for children with high risk ALL? And can we avoid stem cell transplantation in very high-risk patients who until now had no realistic chance of cure without a transplant? In the long-term, I expect that we will also explore immunotherapy as a tool to reduce chemotherapy and chemotherapy-related side effects in standard risk ALL.

Clinical program

2019 was important to further lay down and develop the structure of our department. Our outpatient clinics, our day treatment unit and our clinical wards are now running smoothly and we have managed to establish well-integrated multidisciplinary teams in all the different units. The integration of research within our clinical program has made big steps forward in 2019 and, as described, novel therapies have successfully been introduced in our clinical program. In addition to further developing and implementing the Máxima Comprehensive Childhood Cancer Center (M4C) within our department, we will work closely with our patients, parents and survivors to further improve our clinical program.

'2019 was an important year in which new immunotherapies became available to us, providing new chances to cure children with relapsed ALL'

Prof dr. Josef Vormoor, Clinical Director

Interview with
Clinical lead, Stem Cell Transplantation

Dr. Marc Bierings

The Stem Cell Transplantation (SCT) center offers stem cell transplantation as therapy for children with malignant disease (under treatment at the Princess Máxima Center) and certain non-malignant diseases (under treatment at the Wilhelmina Children's Hospital (WKZ)). Our transplant unit is a combined program from both hospitals (Princess Máxima Center and WKZ), and it is one of the largest transplant programs solely dedicated to the treatment of children in Europe.

Team development

In 2019, our unit evolved into a stable, multidisciplinary team of highly qualified, dedicated and passionate professionals. Highly specialized physicians, nurses and other professionals work closely together to provide an outstanding service.

Collaborations

Being a combined program, we naturally have a close collaboration with benign hematology, immunology and metabolic disorders at the WKZ. There is a national coordination for the transplantation for children with non-malignant disease with the SCT team for children in Leiden. Another important partner for our unit is the adult SCT team at UMC Utrecht, including its different laboratories (e.g., HLA typing, cell therapy facility). Our SCT team also has close links with the Solid Tumors department at the Princess Máxima Center for autologous stem cell transplantations. These transplantations of the patients' own stem cells are done under my responsibility as clinical lead of the SCT program.

Expertise in immunomonitoring

Within our department a lot of expertise has been built up in recent years in the monitoring of immunotherapies. How does the body react to a stem cell transplantation? How does the new immune system and anti-tumor immunity develop? This research includes both clinical and laboratory studies. Immunotherapy is one of the focus areas in the strategic plan of the Princess Máxima Center and our team is well positioned both clinically and in research, to study the effectiveness of immunotherapy in the whole range of malignancies. Because of our expertise with cellular therapies, CAR T-cell therapy was started on our unit and, in 2019, the first 12 children received CAR T-cells on our ward.

'With our expertise in stem cell transplantation, both in clinical care and research, we can bring immunotherapy to the next level'

Dr. Marc Bierings, Clinical lead, Stem Cell Transplantation

In the spotlight | Principal Investigator

Dr. Ruben van Boxtel

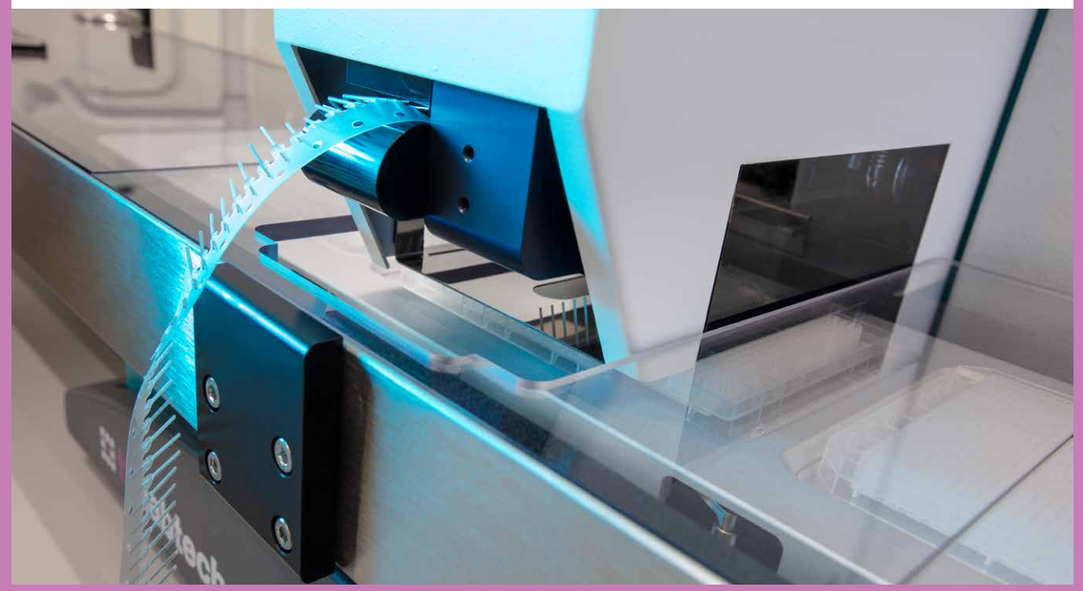
Dr. Ruben van Boxtel focuses on researching the causes of childhood cancer and better understanding of the disease. He researches how the DNA of normal cells gets damaged, and uses this knowledge to find answers around the occurrence of childhood cancer and Late effects as a result of treatments.

Unique

Van Boxtel is enthusiastic about the integral collaboration between research and care. 'I conduct basic research and I meet a lot with clinicians to discuss questions that they have and we can possibly answer by using our techniques and knowledge. That is really unique', he says. According to Van Boxtel, the reason behind this is not only the combination of care and research in the Princess Máxima Center. 'It is also the passion that we all have here and the single mission that drives us.' Though the Princess Máxima Center is the largest pediatric oncology center in Europe, Van Boxtel says it is precisely the right size to achieve integral collaboration in an optimal way.

M4C AML working group

Van Boxtel and his group are closely involved in the stem cell transplantation center and Hemato-oncology department. They research the effects of stem cell transplantations and the occurrence of AML in children and therapy-related AML. The integral



collaboration of his group with care strengthened in 2019. For example, a special M4C AML working group was set up, comprising clinicians and researchers. ‘Clinicians bring us questions and we present our research and findings, so the exchange goes both ways’, explains Van Boxtel. His group now includes two clinicians who conduct research. ‘They provide a lot of knowledge about certain patient pathologies, while those who do basic research in the group deliver technical and biological expertise. By working together we strengthen each other’, says Van Boxtel.

Research

In 2019, Van Boxtel and his group carried out important research, the majority of which will be published in 2020. Research was done into why children with Down syndrome are more prone to getting leukemia. Together with prof. dr. Hans Clevers, research was carried out into precisely how bacteria can cause cancer. Other important studies include research on the effects of stem cell transplantation, and an investigation into the ageing of stem cells, led by stem cell transplantation doctor Mirjam Belderbos. According to Van Boxtel, this latter study is a good example of collaboration between a basic researcher and a clinician. His group also did research into the occurrence of AML in children, and studied the effects of ALL treatment on the normal cells in children’s bone marrow.

Identify the most damaging components

In the long term, the basic research from Van Boxtel’s group will contribute to better survival rates and better quality of life for survivors. As an example he cites a study to identify the most damaging components of chemotherapy. ‘We are also going to connect this study with the emergence of a second cancer, a therapy-related tumor, which we got a European Research Council (ERC) grant for’, he says. ‘If you know which components are the most damaging, you can make adjustments to the therapy. Patients will directly benefit from this.’ Parents also benefit from basic research. ‘A parent once asked me why a child gets cancer’, continues Van Boxtel, ‘and I then realized that having more knowledge about this, and being able to provide a good explanation, is also really important for parents.’

Understanding

Van Boxtel says that on an international level there is more understanding of the importance of research into how normal cells accumulate DNA mutations and can become malignant. ‘Until recently it was believed that cancer was mainly caused by an unfortunate combination of faulty DNA mutations’, he explains. ‘It is important to better investigate the role of normal cells in their natural context. More understanding about how cancer occurs can help us to better fight the disease and maybe even prevent it.’ Until now, research into how normal cells accumulate DNA mutations and can transform into cancer cells happens in just two places in the world: at the Princess Máxima Center, and at The Wellcome Sanger Institute in the United Kingdom. ‘Such research has only been possible in the last few years, thanks to the recent development of new techniques, in which we have also played a part.’

Successful year

In all respects, 2019 was a successful year for Van Boxtel. He was appointed a member of the Oncode Institute. With his group he was awarded various grants, including a prestigious grant from the ERC. Van Boxtel is very proud of his research group. ‘Every single member of the team is a passionate researcher with his or her own specialism’, he says. ‘It is a very diverse team including a bioinformatician, stem cell biologists, immunologists and even a plant geneticist who works with information technology. What is nice is that everyone helps and complements each other, meaning we are continually reaching higher levels’, concludes Van Boxtel.

‘I conduct basic research and get to talk to clinicians every day. That is really unique’

Dr. Ruben van Boxtel, Principal Investigator

Solid tumors

The Solid Tumors department is a specialized unit for children and young adults with malignant tumors in solid organs, soft tissues and bone. The care for children with solid tumors is organized on a multidisciplinary level with pediatric oncologists, surgical specialists, radiologists and nuclear physicians, radiotherapists, pathologists, nurse specialists, a psychosocial team and paramedics. The care is centered around multidisciplinary meetings and a prominent role for the patient's personal oncologist. There are a number of therapy 'specialties' implemented for solid tumors, such as AMORE Brachytherapy for the localized treatment of head & neck tumors, bladder & prostate tumors, and MRI-guided photon radiotherapy. We set up orthopedic surgical care for bone tumors on site and in collaboration with the national bone centers. We offer proton radiotherapy, and liver surgery, both in partnership with the University Medical Center Groningen (UMCG).

Solid tumors are almost always developmental tumors of organs. During the normal embryonal development of organs, small defects in DNA or development lead to the development of cancer. Many of these tumors appear in children under the age of 10. These so-called blastomas typically emerge in the liver, adrenal gland, kidney or lungs, but also occur elsewhere. Furthermore, there is a large group of patients with soft tissue and bone tumors, or sarcomas. These tumors are mostly seen in adolescents and young adults. The causes are not well understood, but possibly the accelerated growth during puberty plays a role. Cure rates for children with blastomas and sarcomas are variable, ranging from 30 percent to 95 percent, with an average of 70 percent. The state-of-the-art treatment is tailored for each individual, and the research is focused on better treatments and drugs for high-risk patients, better understanding of the origin of blastomas and sarcomas, and better quality of life for our children.

Patient numbers

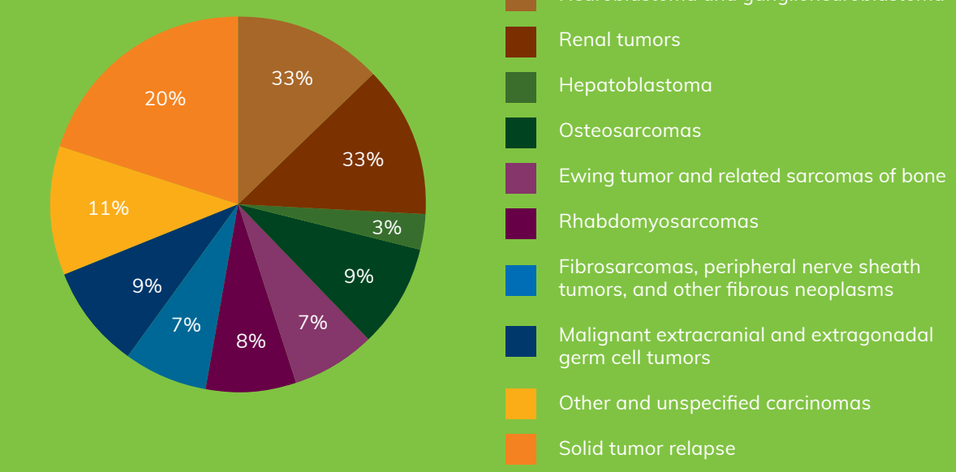
The following tables en charts show the solid tumors patient numbers in 2019.

Solid tumors

ICCC-3	Disease	Patient numbers
IV.a	Neuroblastoma and ganglioneuroblastoma	33
VI	Renal tumors	33
VII.a	Hepatoblastoma	7
VIII.a	Osteosarcomas	23
VIII.c	Ewing tumor and related sarcomas of bone	18
IX.a	Rhabdomyosarcomas	20
IX.b	Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms	17
X.b	Malignant extracranial and extragonadal germ cell tumors	23
XI.f	Other and unspecified carcinomas	26
	Solid tumor relapse	49
Total		**249**

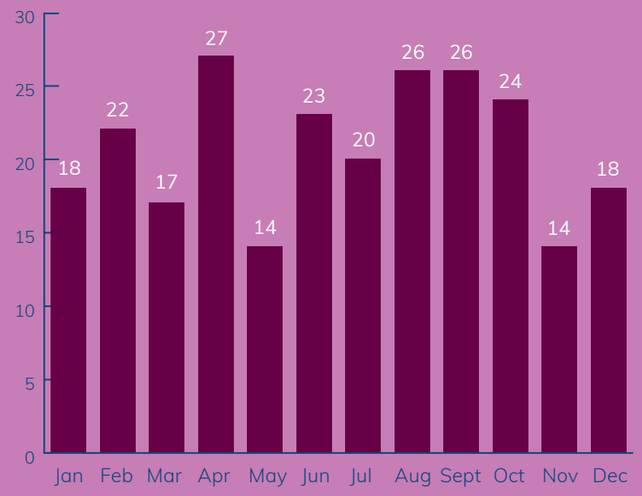
Solid tumors patients in 2019

According to ICCC-3 classification



Solid tumors patient numbers per month

Based on SKION diagnosis data



Autologous stem cell transplantations	N
Number of autologous aphereses (CD34 + stem cells)	35
Number of autologous reinfusions (CD34 + stem cells)	47

Research in solid tumors

In recent years, we have seen major improvements in the treatment of solid tumors in children. Outcome of treatment is dependent upon tumor type, disease stage and tumor genetics. The problems we face in improving care for children with cancer are large and complex. Our extensive team of scientists and physicians is experienced in many fields of science, ranging from fundamental biology, and advanced diagnostics, to early clinical trials. Our aim is to improve outcome and long-term quality of life after treatment.

Preclinical research

Several researchers are focused on specific disease types. An important part of the research for patients with neuroblastomas is focused on improved ‘personalized medicine’ and involves structural molecular analyses of each individual tumor and testing drugs on the patient’s tumor tissue. Normal bone formation is studied in relation to the molecular mechanisms driving osteosarcoma, a disease mostly affecting adolescents and young adults. Survival rates for osteosarcoma have not improved much over the past decades, and studies are focused on understanding key pathways driving normal bone development such as BMP, Wnt and Notch signaling, with the aim of developing novel targets for therapy. The pathobiology of human germ cell tumors is studied using a developmental biology-based approach to improve the outcome and

quality of life for children. A new research line into the biology of pediatric liver cancers was started in 2019.

Other research groups drive the development and implementation of novel technologies such as bioinformatics, molecular profiling, organoid development and single cell sequencing. In addition, the development of liquid biopsies in solid tumors is being explored to improve diagnostics and disease monitoring.

Important output

- **Herold *et al.*, Nature, 2019**
  This collaborative study, led by researchers from the University of Würzburg, Würzburg, Germany, describes a mechanism by which the MYCN gene, an oncogene frequently activated in neuroblastomas, alters global gene expression.

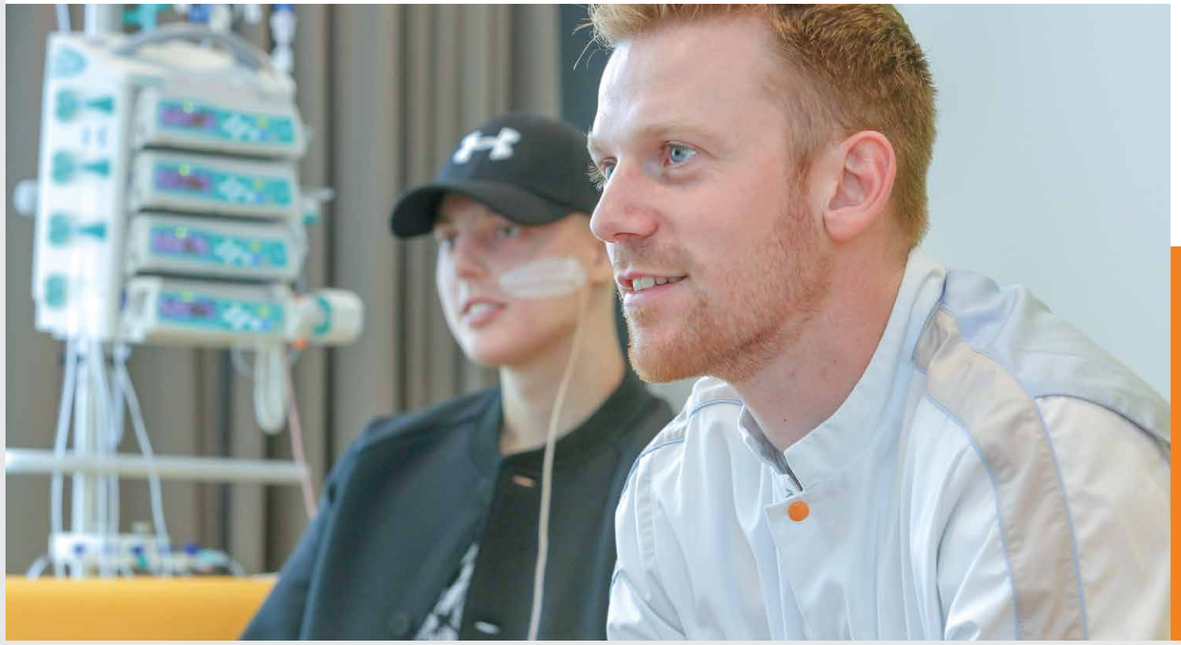
- **de Kanter *et al.*, Nucleic Acids Research, 2019**
  A new algorithm with the acronym CHEETAH (CHaracterization of cEll Types Aided by Hierarchical classification) was developed to provide a hierarchical cell type identification, including the identification of intermediate or unassigned categories.

- **Oosterhuis and Looijenga, Nature Reviews, 2019**
  This authoritative review emphasizes the developmental nature of germ cell tumors, and presents recent molecular insights into the pathogenesis of this disease.

- **Tuveson and Clevers, Science, 2019**
  By combining organoids with (tumor-associated) fibroblasts and immune cells, the tumor microenvironment was demonstrated to be more faithfully mimicked, providing new testing opportunities for immune-oncology applications.

Clinical research

Most children successfully undergo one single treatment with a standard therapy, which in most cases is a trial protocol as well. Close to 80 percent of the children are included in such phase III trials. Data is collected for the remaining 20 percent as a standard procedure, as well as for care evaluation purposes. Furthermore, the department has invested in oncologists who are trained to conduct early phase I/II drug trials. These oncologists are active participants in the international Innovative Therapies for Children with Cancer (ITCC) consortium.



Interview with Clinical Director

Dr. Max van Noesel

The Solid Tumors department is responsible for the diagnosis and treatment of children with solid tumors.

In 2019, the Solid Tumors department took important steps in research for the benefit of children with cancer within the framework of the Máxima Comprehensive Childhood Cancer Center (M4C). A great improvement has been made in the sequencing of all tumors to know precisely which DNA aberrations are involved in a patient's tumor. This individual knowledge makes it possible to deliver tumor-specific treatments to patients with a low chance of cure. In the past year, 5-10 new clinical phase I-II studies (early clinical trials) have been started in our department, including the European ESMART study that gives access to various new medicines for children with specific DNA aberrations in the tumor cells.

Theranostics

For children with solid tumors, a multi-year plan has been started for theranostics, which is a combination of nuclear therapy and diagnostics. This is a relatively new technique that already has proven results in adult medicine, and is also used to some extent in pediatric medicine. In theranostics, a radioactive label is coupled to a tumor-specific protein on the cancer cells, in order to perform a PET scan to detect all tumor sites in the body. Therapeutically, by using a heavier radioactive label it enables irradiation of tumor cells from within. In the coming years, the Solid Tumor department will further develop this technique, in particular for children with metastases with an insufficient response to chemotherapy.

Organoids

In 2019, in close collaboration with the research department, many insights were gained into the genesis and biology of, primarily, kidney tumors. Generally, organoids can be derived from all

What are organoids?

After a tumor biopsy or resection, tissue is primarily used for diagnosis. However, excess tissue is used to grow into mini-tumors. They are called organoids, since they are exact copies of the organ or tissue of origin, at a molecular and cellular level. In a laboratory, these organoids are used as a model system to study the characteristics of a tumor and to test medicines. In the Princess Máxima Center, the organoid technology facility focuses on optimizing this technique for growing organoids from various pediatric tumors, which was first described by prof. dr. Hans Clevers.

tumors, but so far it is most successful for kidney tumors and neuroblastomas. Organoids represent a new tumor model for the study of solid tumors in children. By 2019, we were able to develop organoids for all types of pediatric renal tumors. This is a big leap forward because these organoids – 'mini-organs' cultured from the patient's own tumor cells – provide great insight into the genesis and biology of tumors. Ultimately, these insights will contribute to the development of new treatments. Organoids are an enormous source of knowledge in the coming years.

Clinical care

Clinical care further developed in 2019 to create an optimally organized clinic with a very professional team that delivers many services for and focuses on the needs of children and parents. In 2019, two important specialties were further developed. The apherisis process for autologous stem cell transplantation was made highly efficient, and thereby less burdensome to patients. Previously, the isolation and collection of stem cells using a cell dialysis machine usually took two days. Last year, under the guidance of a nurse specialist, the Solid Tumors department was able to transform this process into a one-day treatment.

Immunotherapy

In recent years, the Solid Tumors department has implemented anti-GD2 based immunotherapy for neuroblastomas. Many new insights and changes, both national and international, have optimized this therapy. Toward 2020, the department started a new protocol to deliver immunotherapy on an outpatient clinic basis. This method is not only safer and more efficient, but also much less toxic for children. Just like the improved apheresis processes, the more efficient immunotherapy is the result of the concentration of all cancer patients and the pooling of all expertise inside the Princess Máxima Center, for the benefit of patients. In many of these improvements, nurse specialists have played a crucial role.

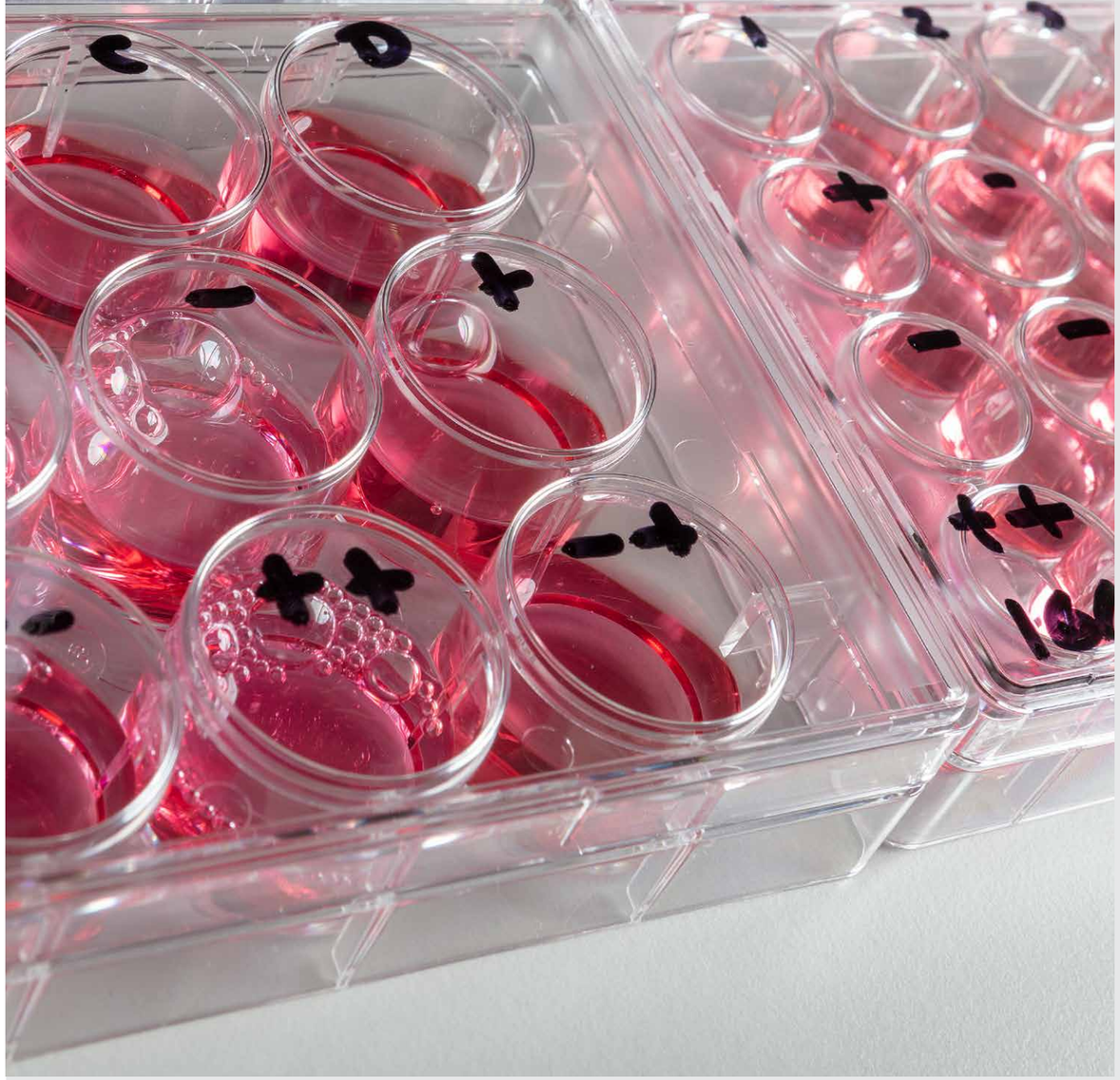
Collaboration

The collaboration with the research department has been very fruitful in 2019. Through the integration of care and research, a growing focus on important issues has emerged. Development of tumor targets for new medicines, theranostics and immunotherapy are important issues to work on in the next years. The Solid Tumors department is collaborating with many internal research groups and the Imaging & Oncology division of UMC Utrecht. The focus in immunology and immunotherapy is on unraveling the microenvironment of a tumor to acquire fundamental knowledge on tumor-involved immune cells. This is done in conjunction with pathologists and immunologists.

Culturing organoids and generating insight into development biology is achieved by collaboration with many internal research groups. Such insight is very important for solid tumors in particular, as these are tumors that develop in internal organs. Many pediatric oncologists and researchers from the Princess Máxima Center are part of international partnerships for clinical therapy development and research, in order to deliver optimal care for children with cancer in the Netherlands.

Conclusion

All in all, important steps forward have been taken in 2019. Clinical care has been further optimized with a focus on quality of care, efficiency of care processes and the development of clinical studies for new medicines. Important results have been achieved through an intensive partnership between the Solid Tumor department and research department. The new Máxima Comprehensive Childhood Cancer Center (M4C) offers a solid foundation for further advances in treatments and innovations to be made in the coming years, such as the development of theranostics, immunology and immunotherapy, the development of organoids and related research into the developmental biology of various tumors. At the same time, existing international partnerships will be strengthened.



'The development of organoids for all types of kidney tumors is a big leap forward. It is an enormous source of knowledge for the coming years'

Dr. Max van Noesel, Clinical Director

In the spotlight
Dr. Anne Rios, Principal Investigator

‘We visualize the unexpected’

Dr. Anne Rios, originally from Marseille, France, has headed the Princess Máxima Imaging Center and an independent research group since 2017. She started her career doing research into breast cancer, using 3D imaging technology to identify how stem cells reorganize the tissue during normal development and cancer progression. At the Princess Máxima Center, Rios is refining this kind of technology for childhood cancer so that cancer processes will become literally visible in developing organs.

Dynamic imaging, molecular engineering, confocal, multiphoton and lightsheet microscopy technologies have all been Rios’ passion for years now. It is very hard to explain what this is all about technically, but for a quick glimpse one only needs to watch the fascinating video on the Princess Máxima Center’s website. In a ten-second clip you see a 3D kidney spinning around, leaving you flabbergasted with all the colors and details. Rios: ‘It’s no coincidence that we show this image, since one of the group’s focuses is on Wilms tumor, a renal cancer that typically occurs in children. With our imaging technology, in combination with machine-learning computing techniques, we try to comprehend the progression of the tumor in the kidney. We look closely at the cellular organization, including the interaction with the neighboring microenvironment.’

Improving diagnosis and treatment

‘This type of innovation can improve the diagnosis and treatment of children with cancer’, says Rios. ‘We work very closely together with Ronald de Krijger from the pathology department. We hope to introduce our technology into the diagnosis pipeline soon. Our combined aim is clear: finding out what makes the difference between patients. We are trying to determine the correlation between what imaging shows us and clinical outcome. Why is it that a treatment works well in patient A while patient B is confronted with a relapse or gets new metastases? Why do cancer cells in patient B seem to be more aggressive? If we combine pathological data with our images the answers will be much more precise.’

Decipher the mechanisms

The Wilms tumor program is an example of very promising imaging techniques being used to visualize intact organs and tumors in 3D, encompassing the entire tissue, down to a sub-cellular resolution. Rios: ‘We aim to advance imaging technologies for cancer biology. We are now implementing this 3D methodology and other advanced imaging techniques such as intravital, super resolution, and multiplex imaging to decipher the cellular and molecular mechanisms governing the initiation and progression of childhood cancer in a developing organ. Apart from kidney cancer we have set up research lines for high-grade glioma and neuroblastoma, for example.’

Light up the tumor

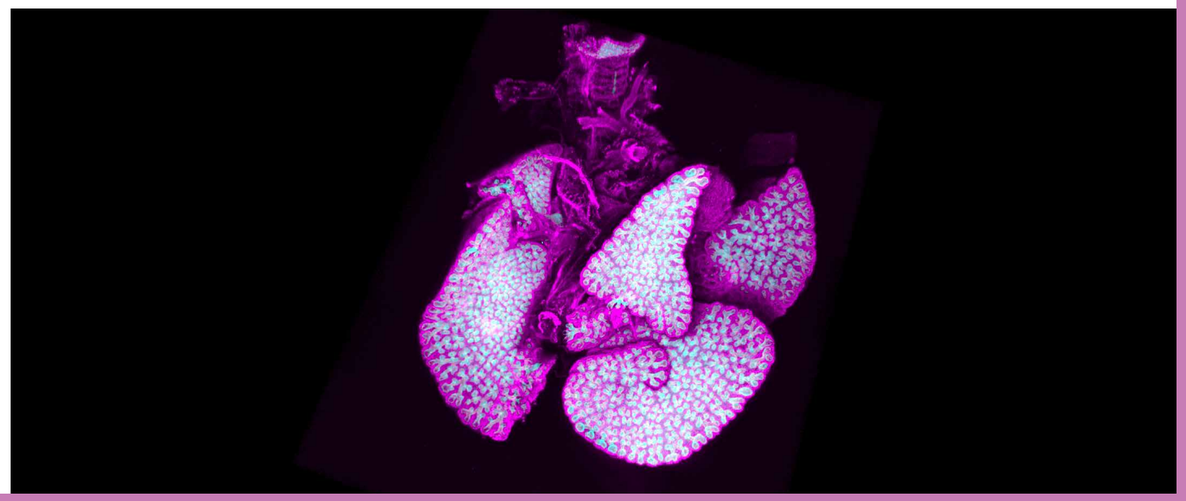
The imaging technology can also be useful in surgery. Therefore another important partner is prof. dr. Marc Wijnen, head of the surgical specialties at the Princess Máxima Center. Rios: ‘Imaging technology can be used to light up the tumor you want to remove. And fluorescence visualization can help a surgeon to better perform an operation. Two of our PhD students are currently working on this. It’s a technique that is gaining momentum in adult oncology, but in pediatric oncology it’s still at a pioneering stage. I’m happy we can contribute to this for the patients of the Princess Máxima Center.’

Happiness program

Although 2019 was a challenging year for Rios in different aspects, it was also very successful. For personal reasons Rios had to leave her team for a longer period in 2019. She found this very hard, but the team came together, supporting each other and managing well. ‘Fortunately we just did a so-called happiness program with the entire group, with team building, increasing work satisfaction and improving our combined efficiency as a team. I’m very positive about the results. It really made everybody in the team feel like being a member of a family, in which everybody can express what he or she thinks and feels. In my opinion this is very important in any sort of close collaboration.’
Despite the challenges, last year was very fruitful. Rios is very proud of the Innovation Award from the St. Baldrick’s Foundation that the team received in 2019. Moreover, Rios was selected as a member of Oncode, and was awarded a starting grant from the European Research Council (ERC). This will supply the group with funding to, amongst other things, develop dynamic imaging for cellular immunotherapy. Rios: ‘We want to understand the behavioral patterns of both cancer cells and the immune cells that attack them. We literally want to capture the cellular behavior in a movie, so that we are able to look at the molecular mechanisms behind the movement of all cells involved.’

Communicating science

Apart from the relatively hard time Rios encountered personally, she still is very positive about the past year. Two papers are being prepared for publication in 2020. And the efforts of her group don’t stop at the walls of the Princess Máxima Center, she adds. The team also uses 3D technology to inform others about ‘how cancer works’. Rios: ‘We developed a 3D stereo display that uses 3D glasses to immerse the public in virtual entire organs and associated cancers. This type of visualization is a strong asset to engage the community in the fight against cancer. It can create a new trend in communicating science.
If we reach the larger scientific community and the public, I’m convinced we will accomplish our mission even sooner.’



Neuro-oncology

In 2019 further consolidation of centralized neuro-oncology care in children has been achieved. Thanks to the enormous efforts of the nursing staff in our Neuro-oncology ward, a dedicated neuro-oncological nursing team has been created. Dedicated teams have also been set up in day treatment, the outpatient clinic and supporting staff.

Our multidisciplinary medical staff has learned to work together in a complementary fashion in order to provide optimal care for our patients. A lot of effort has been put into defining state of the art treatment protocols for the various tumor entities manifesting in our patients. In addition, we have prepared for participation in important international clinical trials.

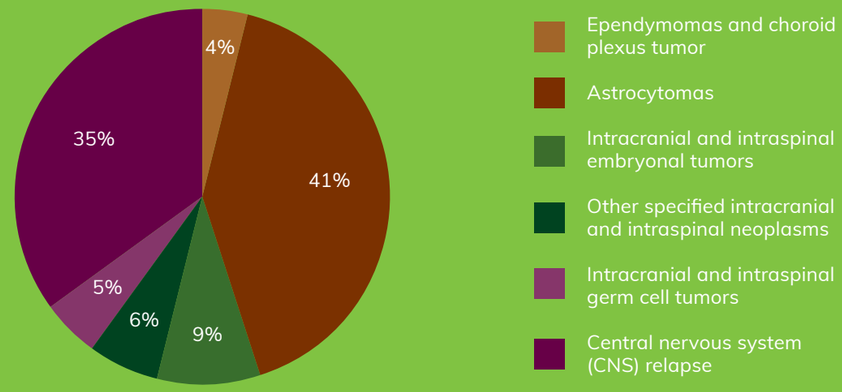
Neuro-oncology research has been strengthened by the assignment of Marcel Kool as Principal Investigator (PI), with special expertise and focus on basic and translational research in embryonal tumors. Together with the other neuro-oncology related research groups we face the challenge to realize further integration of care and research.

Patient numbers

The following tables en charts show the neuro-oncology patient numbers in 2019.

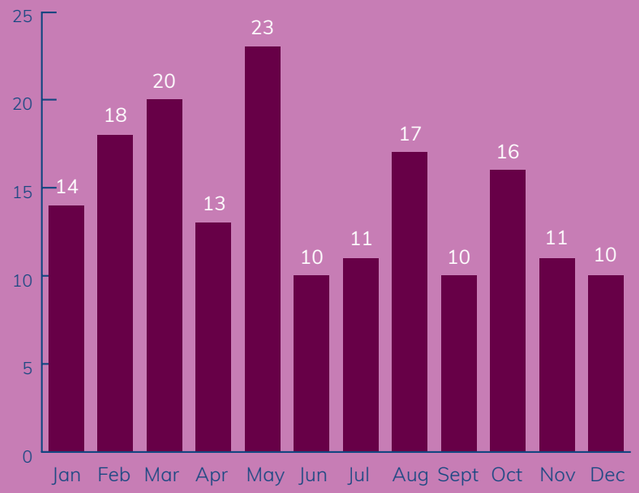
ICCC-3	Disease	Number
III.a	**Ependymomas and choroid plexus tumor**	**7**
	Ependymoma	6
	Choroid Plexus Tumor	1
III.b	**Astrocytomas**	**72**
	Diffuse intrinsic pontine glioma	8
	High-grade glioma	12
	Low-grade glioma	52
III.c	**Intracranial and intraspinal embryonal tumors**	**15**
	Atypical teratoid/rhabdoid tumor	1
	Medulloblastoma	14
III.e	**Other specified intracranial and intraspinal neoplasms**	**10**
	Central nervous system (CNS) tumor, not otherwise specified (NOS)	8
	Craniopharyngioma	2
X.a	**Intracranial and intraspinal germ cell tumors**	**9**
	CNS relapse	60
	Total	**173**

Neuro-oncology patients in 2019
According to ICCC-3 classification



Neuro-oncology patient numbers per month

Based on SKION diagnosis data



Neurosurgical procedures in the Princess Máxima Center	N
Tumor resections	83
Tumor biopsies	26
Total	**109***

* 80 percent of all neurosurgical procedures in children with central nervous system (CNS) tumors in the Netherlands

Research in neuro-oncology

The outlook for children with brain tumors is generally less favorable than for other pediatric cancers, although the success of treatment is strongly dependent on the stage, location and tissue type (cell and origin). Some brain tumors, such as diffuse intrinsic pontine glioma (DIPG), are universally fatal, while low-grade tumors such as pilocytic astrocytoma show an excellent prognosis. Survival rates for medulloblastoma, the most common brain tumor in children under the age of 16, are between 60 percent and 80 percent, depending on subtype and stage of the disease.

Preclinical research

A number of PIs from different areas of research have joined the Princess Máxima Center to further improve outcome and quality of life for children with brain tumors. Complementary approaches range from (epi)genomics, single cell sequencing, and functional biological studies, to advanced imaging, and more translational studies. The latter include the development of methods aimed at improving delivery of drugs across the blood-brain barrier (BBB), and novel methods for *in vivo* imaging to improve localization of tumors during surgery. Similar to solid tumors, organoid models and so-called patient-derived xenograft (PDX) models – in which primary tumor samples are transplanted into immunocompromised mice – are generated at a high pace, to allow preclinical testing of new (targeted) compounds. An area under development is the potential use of immune modulators or other immune-based therapies in the treatment of high-grade brain tumors.

An important collaboration between the Hopp Children's Cancer Center (KiTZ) in Heidelberg, Germany and the Princess Máxima Center has been established by recruiting Marcel Kool, who divides his time between the two centers. While the Heidelberg group continues the genomic and epigenomic analysis of brain tumors, the Princess Máxima Center group will direct its attention to disease modeling using organoid technology. Combining results, expertise and clinical data from both centers is expected to accelerate brain research in the Princess Máxima Center in the years to come.

Important output

- **Dekkers et *al.*, Nature protocols, 2019**
  A novel method for 3D imaging of organoids by combining fluorescence-based reporters and immune-based labeling techniques with a new clearing method was described.

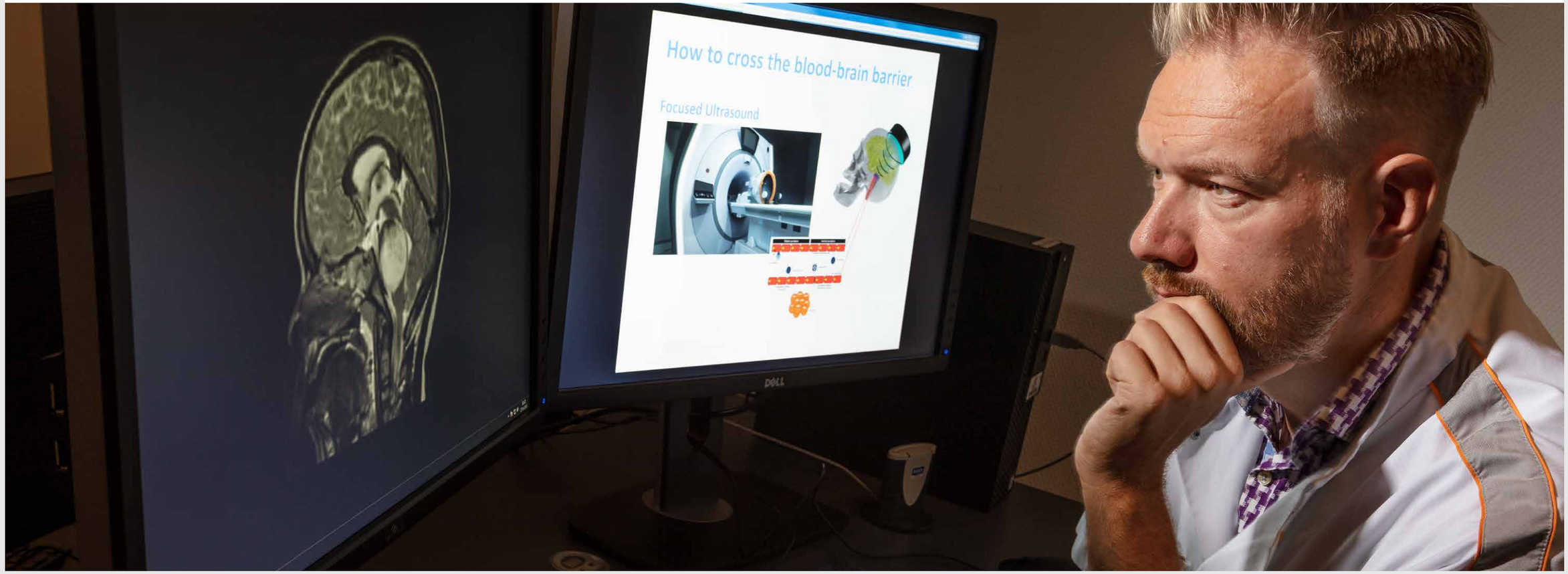
- **Metselaar et *al.*, EBioMedicine, 2019**
  This study shows that celastrol, a compound that passes the BBB, synergizes with carboplatin *in vivo*, a mechanism involving FANCD2, a key regulator of the DNA damage response.

- **Lambo et *al.*, Nature 2019**
  This paper, written in collaboration with the KiTZ and other institutes, describes the molecular landscape of Embryonal Tumors with Multilayered Rosettes (ETMRs), a rare embryonal brain tumor with a dismal outcome.

Clinical research

Participation and initiation of early phase studies in neuro-oncology will be taken to the next stage by Jasper van der Lugt. International collaboration in Innovative Therapies for Children with Cancer (ITCC)-brain and participation in international consortiums will be explored.

Several relevant phase III clinical studies covering important Central Nervous System (CNS) tumors have been prepared to start in 2020: the Primitive Neuroectodermal Tumor (PNET) V study for medulloblastomas (Sabine Plasschaert), the High-risk Medulloblastomas study (Corry Gidding), the Ependymoma II study (Jasper van der Lugt), and the Low-grade Astrocytomas (LOGGIC) study (Netteke Schouten).



Interview with Clinical Director

Prof. dr. Eelco Hoving

Neuro-oncology

The mortality rate of children diagnosed with a central nervous system tumor is around 30 percent, the highest of all childhood cancers. The Neuro-oncology department is committed to increasing the chances of cure for this group. Neuro-oncology is one of the focus topics in the new multiannual strategy of the Princess Máxima Center, which gives an extra impulse to research and improving treatments.

Phase III Studies

In 2019, the Neuro-oncology department made extensive preparations to participate in key clinical studies: the PNET 5 study on medulloblastomas, the most common malignant brain tumor in children, and studies on high-risk medulloblastomas, ependymomas and low-grade astrocytomas. These studies cover the vast majority of neuro-oncological tumors. In 2019, all treatment protocols were further evaluated by the neuro-oncologists, and standardized and refined where necessary.

Quality of life

The Neuro-oncology department, in close collaboration with the Quality of Life department, maps the neuropsychological consequences during the different moments of treatment in all children with a brain tumor. This can provide insight into which neuropsychological damage occurs when, and how it can best be treated and guided. The foundation for this method was laid in 2019. In addition, psychosocial care is a fundamental part of the care for all children in the Neuro-oncology department.

Surgery and Expertise

In 2019, more than 80 percent of all neurosurgical procedures in the Netherlands on children with tumors in the central nervous system were performed in the Princess Máxima Center. These neurosurgical procedures are an integral part of the treatment strategy. The treatment strategy for all children with these tumors was discussed and established by the national tumor board for neuro-oncology in the Princess Máxima Center. This tumor board meets twice a week, bringing together all specialists involved and representatives from Research. In addition, all diagnostics, complex chemotherapy and study treatments are performed in the Princess Máxima Center. All this, in combination with the concentration of all the patients, has led to a rapid increase in the expertise of the team.

Phase I / II studies and Biobank

In 2019, the necessary infrastructure was built to participate in Phase I / II studies. Tissue material of all tumors is available for molecular diagnostics, and almost all patients consent to having their tumor tissue added to the Biobank. This enables the department to investigate individual tumors optimally and in-depth, in order to achieve the most appropriate treatment for new tumors, as well as for recurrent tumors.

Cooperation

Neuro-oncology is an eminently multidisciplinary discipline, in which pediatric neuro-oncologists work closely with radiotherapists, pediatric neurosurgeons, pediatric neurologists, pediatric endocrinologists, and pediatric rehabilitation doctors, as well as neuroradiologists and neuropathologists. Furthermore, neuropsychologists from the Quality of Life department play an important role, as the quality of survival with brain tumors is strongly influenced by the tumor and the various treatments. In addition, Neuro-oncology cooperates in the development of cross-departmental treatments such as immunotherapy.

The integration of neuro-oncological care and research will take shape through collaboration in the Máxima Comprehensive Childhood Cancer Center (M4C). This structure is now being built up from three umbrella tumor workgroups:

- Glial tumors:
  - High grade
  - Low grade
- Embryonic tumors:
  - Medulloblastomas
  - Atypical Teratoid Rhabdoid Tumors (ATRT)
- Craniopharyngeomas

Research

The Neuro-oncology department works intensively together with various PI groups. In 2019, the Kool group started with a focus on embryonic and rare brain tumors. There is collaboration with the Drost group in the field of ATRT, and with the Hulleman group in the field of high-grade gliomas. The group of pediatric neuro-oncologist and researcher Van Vuurden focuses on brain stem cancer (DIPG), and the administration of medicines across the blood-brain barrier. Marc van de Wetering of the Clevers group focuses on cultivating organoids, which is very complex work. Within the Partanen group, the neuropsychological research is further developed, and with the Wijnen group research is carried out into perioperative imaging and holography of brain tumors.

Conclusion

In 2019, the Neuro-oncology department laid a solid foundation to progress in the coming years toward greater cure rates with an optimal quality of life. Our protocols have been updated and active participation in clinical studies will be completed for the major tumor types. This also applies to the neuro-oncological research programs within the research department, which will increasingly be integrated with neuro-oncological care within the structure of the M4C.

As neuro-oncology is a focus topic in the Princess Máxima Center's new multiannual strategy, neuro-oncological care and research will receive an additional impulse in the next few years.

‘The concentration of both patients and experts has led to a rapid increase in expertise’

Prof. dr. Eelco Hoving, Clinical Director

In the spotlight | Principal Investigator

Dr. Marcel Kool

Dr. Marcel Kool has been active in the field of brain tumors for more than twenty years, the last nine of which as leader of a research group at the KiTZ in Heidelberg. Since September 2019, he has also been a principal investigator at the Princess Máxima Center. In particular, the immediate availability of patient material and the knowledge of organoids in the Princess Máxima Center means that, for Kool's research into brain tumors in children, working in two places offers a great deal of added value. 'By working together, we connect the best of both worlds.'

In his research at both the KiTZ and at the Princess Máxima Center, Kool focuses on pediatric brain tumors, in particular embryonic brain tumors and ependymomas. 'Many international collaborations already exist from Heidelberg, so a lot of patient material is available that has been extensively researched in recent years, and which has led to many new discoveries. In the Princess Máxima Center, due to the concentration of patients, research material is immediately available, which is a great advantage for experiments that require fresh tumor material', explains Kool.

Testing

'In terms of content, the focus is on integrating research from the KiTZ and the Princess Máxima Center', continues Kool. 'We have sequenced a lot of brain tumors in the past five to ten years, so we know what the most important genes and drivers are.' Now it is important to accelerate and transform these insights into new treatments', Kool states. The expertise in the Princess Máxima Center in the field of organoids is of great importance. 'If you want to realize new treatments in the clinical practice, you must first test them extensively in the lab with the right models', says Kool. 'Of course we do that in Heidelberg, but testing with organoids as well brings a lot of added value. Cultivating brain tumors in organoids is still difficult, but accelerating new clinical trials is our focus in the coming years.'

Scaling up

To transfer knowledge from the lab to the clinic more quickly, preclinical tests also need to be scaled up. 'We must find new ways of carrying out large-scale testing', says Kool. Therefore, the KiTZ and the Princess Máxima Center are part of a large European consortium that strives to generate at least 400 PDX models of the most aggressive forms of childhood tumors in mice. When it comes to organoids, the researchers are also looking for ways to scale up, for example by investigating whether they can be grown on microchips. 'Upscaling is a challenge, but we are definitely taking steps forward', according to Kool.

International

By moving into clinical trials more quickly, patients can ultimately be treated earlier with an innovative therapy. Cooperation between the KiTZ and the Princess Máxima Center facilitates this. Kool believes it is possible that other major centers such as the St. Jude Children's Research Hospital in the US and the Curie Institute and Gustave Roussy in France will also collaborate to accelerate clinical trials. 'We are seeing more and more different types of tumors. Brain tumors are rare in themselves, and the more we divide them into specific types, the rarer they become. This means that clinical trials can only be achieved through international cooperation.'

Immunotherapy

In the coming years, the application of immunotherapy will also be a focal point for Kool and his group at the Princess Máxima Center. 'Indeed, in some forms of brain tumors, a lot of immune cells can be detected, so we should be able to really achieve results with immunotherapy', explains Kool. In this regard, he emphasizes the importance of detailed molecular classification. 'In recent years, molecular classification has improved tremendously in the world; we are now able to classify tumors much better, and that is very important to determine exactly which therapy can be used for a certain type of tumor.' The knowledge that Kool brings in this area is crucial for starting to use immunotherapy in the treatment of children with brain tumors. This is a good example of the integral collaboration between care and research. 'You can no longer separate care and research from each other', notes Kool.

New treatment

When asked about one of his most important studies, Kool describes an investigation into a rare and very aggressive brain tumor for which there is no cure yet. He collected material from 200 patients from across the globe, and the research gave more insight into the biology of this tumor type, called ETMR. The results have recently been published in Nature. 'We ended up with a drug that has been used for decades but not for patients with this type of tumor', explains Kool. He is now working hard with testing and setting up the clinical trial worldwide. 'I'm hopeful that we will devise a new treatment for these children in the coming years', he adds.

Building bridges

Kool not only integrates his research into brain tumors, but also makes connections between the KiTZ and the Princess Máxima Center when it comes to other subjects and forms of childhood cancer. 'That is definitely the intention', he concludes. 'We want to collaborate more in both research and healthcare. In that sense I am a kind of bridge builder who makes the broader connection between the two institutes. That also has real added value for research and for care, and therefore for the objective we all have: to provide a cure for more children, with fewer Late effects.'

'There is a lot of research knowledge available to make immunotherapy in brain tumors a success in the coming years'

Dr. Marcel Kool, Principal Investigator

Supporting departments

Pharmacy

Short interview with dr. Lidwien Hanff

‘I am continuously impressed by the pharmacy team’s commitment and willingness to continuously improve’

What have been the pharmacy’s main goals in the past year?

‘In 2019, the pharmacy had a number of goals. Firstly, we continued to transfer the preparation of parenteral drugs from the ward to the pharmacy, resulting in the centralized preparation of more than 90 percent of all parenteral administrations. The process of timely and safe delivery of cytostatics has been further optimized, with the aim of minimizing waiting time for day treatment and outpatient care. Thirdly, collaboration between the clinical wards and the pharmacy resulted in improvements on various medication-related processes, including the facilities and range of drugs stored at the ward and improvement of medication verification-processes. Fourthly, we have started providing specialist care at home, including the administration of cytostatics. We are also demonstrably doing well in terms of quality, with the Harmonization of Quality Assessment in the Dutch Healthcare Sector/ Harmonisatie Kwaliteitsbeoordeling in de Zorgsector (HKZ) certification for the outpatient pharmaceutical care and the successful Good Manufacturing Practice in Hospital Pharmacies (GMP-Z) audit by an independent external party. Finally, we organized team-building activities aimed at increasing job satisfaction and improving teamwork, and we held peer-to-peer sessions focused on dealing with emotions.’

What new developments have taken place?

‘An important milestone was the full operationalization of our IV robots, the first in Europe. Another development was the implementation of the European Falsified Medicines Directive, to verify every drug package on authenticity. In addition, the support in processing follow-up prescription requests by pharmacy technicians has considerably reduced the workload for the nurse specialists.’

How do you look back on the performance in 2019? And what are you most proud of?

‘Things have become more settled in the past year. Special achievements include the increasingly smooth process of clinical and outpatient drug delivery, including chemotherapy at home, and the production of more than 600 patient preparations per day. The most important factor, however, is the team, which is very committed and is getting better and better at working together.’

Which developments form the basis for 2020?

‘The multiannual strategy and the pharmacy’s wish to further deepen its knowledge, develop an independent pharmacological research line and establish a drug research laboratory.In addition, we are aiming for two quality milestones in 2020. First, we aim to obtain a formal manufacturer’s license to label and randomize study medication for clinical drug research in accordance with GCP guidelines. Secondly, we want to carry out an audit to determine whether we meet the Dutch Professional Standard for Pharmacies in Hospitals / Beroepsstandaard Apotheken in Ziekenhuizen (BAZ). Improving the sub-optimal IDT systems and retaining sufficiently trained personnel also remain important points for attention.’

What progress has been made in the area of the integration of care and research (M4C), and how important is this?

‘The trial pharmacy is developing into a full-fledged part of the pharmacy. It functions independently of the UMC Utrecht and offers professional support to researchers for clinical studies. In addition, the pharmacy aims to have an independent research line and a bioanalytics research laboratory to embed pharmacology in M4C.’

Key facts & figures 2019

Description	2019
Clinical prescriptions	62,936 orders
Practocol-based treatment	13,945 treatments
Individual Chemotherapeutic parenteral preparations	46,860 preparations
Non chemotherapeutic parenteral preparations (incl. batch preparations)	179,070 preparations
Admission and discharge verification	4,371 verifications
Outpatient prescriptions	28,456 prescriptions
Drug Research trials	50 trials
Individual programs with non-registered medicines	20 drug-programs

Diagnostic laboratory

Short interview with dr. Bastiaan Tops

‘The foundation is there, so let’s start building!’

What have been the diagnostic lab’s main goals in the past year?

‘In the past year, we have mainly focused on optimizing work processes within the diagnostic laboratory, as well as coordinating processes between the lab and Care, and between the lab and Research. The latter includes the way in which tissue is processed for and stored in the Biobank. With Care, we have intensified contacts and have prepared for a number of major projects for 2020, including the facilitation of a number of large, labor-intensive studies (e.g., AL2G and iTHER), the introduction of a new IT system, and the laboratory’s quality accreditation.’

What new developments have taken place?

‘Several developments have taken place in 2019. For example, we introduced the ‘CD34 assay’ through flow cytometry within the lab. We use this assay to quickly determine the right moment for the collection of stem cells (so-called stem cell apheresis). Furthermore, a lot of hard work has gone into setting up tests to determine ‘minimal residual disease’ in ALL. Validation of these tests is almost complete. Lastly, we introduced ‘RNA sequencing’ in conjunction with the pathology and genetics departments of the UMCU, and are currently writing a scientific publication on this.’

How do you look back on the performance in 2019? And what are you most proud of?

‘I’m very proud of the whole team. It’s not easy to optimize basic processes and at the same time implement all kinds of innovations, but the people in the lab have made it happen. In addition, we now provide rapid diagnostics and have short lines of communication with Care, partly due to the participation of pathologists (and other staff members) on the tumor boards, so that results can also be discussed and explained in detail.’

Which developments form the basis for 2020?

‘In recent years, in collaboration with the research department, enormous efforts have been made on the bio-informatic infrastructure. Now that we have this foundation, we can develop and implement algorithms in the coming period to get more information from our molecular tests. As a result, we really hope to take diagnostics to a higher level. In addition, we will start using a new IT system for tissue diagnostics, so that we can better support our diagnostics, but also our Biobank processes.’

What progress has been made in the area of the integration of care and research (M4C), and how important is this?

‘Staff members from the diagnostic lab are involved in various tumor groups, but in 2019 this was still based on individual initiatives. The ambition is to achieve more structural and overarching cooperation in the near future, together with Care and Research. This is the only way we will achieve our objective. The M4C structure will be of great added value in this regard.’

Key facts & figures 2019

In 2019, the diagnostic laboratory has:

performed

7000

regular diagnostic analyzes

processed

29.581

samples and stored these in the Biobank

facilitated

440

clinical studies, for which

1512

samples were processed and stored

Trial and Data Center

Short interview with prof. dr. Michel Zwaan

‘Clinical research is of great importance to continuously improve the quality of treatments, but also the quality of life. In this respect, collaboration is indispensable’

What have been the Trial and Data Center’s main goals in the past year?

‘In 2019, after the concentration of pediatric oncological care, we continued our transition to get the basics of the Trial and Data Center in order. For example, all studies are now internally assessed by a scientific committee. A team of researchers examines the protocols, the scientific quality and the feasibility of the proposed research. It was also very important to properly set up the informed consent procedure for the Biobank, because this material enables our preclinical researchers to conduct their research in the laboratory.’

What new developments have taken place?

‘Important partnerships are emerging with researchers from the UMC Utrecht. Furthermore, several international consortia have asked the Princess Máxima Center to be the international cooperation partner to conduct research in Europe. That’s something I’m proud of because it shows our clout, and because our patients can benefit from such collaborations. As the largest pediatric oncology center in Europe, we must also play a leading role in implementing research, not for the accolades, but because we can make a difference with our size and ambitions, and - not unimportantly - with the resources we have at our disposal. I’d really like to pay tribute to everyone who has contributed to our success by, for example, fundraising or being a donor.’

How do you look back on the performance in 2019? And what are you most proud of?

‘That in such a short time we have brought together a group of people who work well together, and whose objective is to carry out good research and thus help to improve the prognosis for children with cancer. You really notice that everyone wants to contribute to this.’

Which developments form the basis for 2020?

‘In 2020 we want to begin a number of studies with new medicines. The results of these studies will be used to ensure that the medicines are registered for pediatric oncology. That sounds a bit theoretical, but it is an important process to ensure that these medicines are also available in regular care, and are reimbursed by health insurers. We will therefore continue to focus on this kind of ‘intent-to-file’ research. This requires a higher level of specialization and training, which in turn contributes to the very purpose for which the Princess Máxima Center was established.’

What progress has been made in the area of the integration of care and research (M4C), and how important is this?

‘In pediatric oncology, we have the unique situation that care and research go hand in hand. This is also the basis for the enormous progress in pediatric oncology since the foundation of the Dutch Childhood Oncology Group (previously Dutch Childhood Leukemia Study Group / Stichting Nederlandse Werkgroep Leukemie bij Kinderen) in 1972. All children receive treatment based on a protocol in which both standard treatment is determined and scientific questions are answered. So integration of care and research already existed in this way.’ (For more about research in the Trial and Data Center, see chapter ‘Research’.)

‘Additionally, we aim to create a better connection with preclinical research. Clinicians find themselves confronted with questions in the clinic. Questions, which we try to answer with experiments in the lab. On the other hand, we need to translate the knowledge we gain in the lab into clinical studies.’

Key facts & figures 2019

~ 100

studies

~ 80

people

46

Total number of phase I/II studies

34

Total number of phase III studies

69

Total number of studies approved by the Clinical Research Committee

Nursing care

In the spotlight

Pauline van Tilburg, Jacqueline Zoon & Yvette van Beuningen

The nursing staff of the Princess Máxima Center plays an important role in realizing the mission: to provide a cure for every child with cancer while maintaining an optimal quality of life. How do they look back at 2019? Pauline van Tilburg, pediatric oncology nurse and care coordinator in the Solid Tumors department, Jacqueline Zoon, Day treatment unit and Outpatient clinics team leader, and Yvette van Beuningen, pediatric oncology nurse and care coordinator in the Hemato-oncology department, discuss their year.

What were your most important achievements in 2019?

Pauline: ‘We’ve become more professionalized. For example, we have set up focus groups for a variety of focus areas. We have also introduced innovations. For instance, we now nurse children with trachea cannulas in the Solid Tumors and Neuro-oncology departments. Alongside this we’re going to start

Nurses working at the Princess Máxima Center

>270

Fte nurses

~225

with home immunotherapy in spring 2020. We've improved the training, now work in fixed teams and also focus on teambuilding.'

Yvette: 'Well, there's really too much to mention everything, but for me the most important thing has been that we've built up the teams, as this has improved patient care.'

Jacqueline: 'Various improvements have been made in the Day treatment unit so that appointments and treatments run more smoothly for parents and children. We've developed combination appointments in the outpatient clinics and fixed contact points for parents and children. In the Day treatment we now also work in fixed teams, so children and their parents see familiar faces every time.'

What has this meant for patients?

Yvette: 'We put children and parents at the center of everything we do. In our department, a number of oncologists and a team leader regularly carry out interviews with parents and share points for improvements with the team. For example, parents have fed back that they sometimes lacked a daily overview. In response, the psychosocial team, doctors and nurses have made a dedicated space on the whiteboards in the rooms to provide parents with a better overview of the day.'

Pauline: 'Thanks to the fixed teams and the focus groups there are increasing knowledge levels among the nursing staff, which is of course beneficial for children and parents.'

Which results are you most proud of in 2019?

Jacqueline: 'For me, it's all the staff members who roll up their sleeves and make a difference, day in, day out. I also think it's really fantastic that children can move freely through the whole of the Princess Máxima Center, even while connected to a drip, so they can continue to develop by going to school while they are undergoing treatment, visiting the physio room and so on.'

Pauline: 'I'm really proud of the collaborative spirit and the drive of our employees around achieving our mission.'

This is what **Yvette** recognizes as well: 'You can really see the groundbreaking and passionate spirit in all of us. I'm proud of how the team is working, how well collaboration is going, and how we take on things in order to make improvements.'

Yvette and Pauline, you are part of the Nursing Advisory Board (VAR) that was set up in 2019. What is the aim of the VAR?

Pauline: 'The VAR is an advisory board comprising the nursing staff and paramedics. The board focuses on 'the care of tomorrow' and provides recommendations to the Board of Directors. We have started with a number of themes: talent development among staff, taking pride in your profession and research and development-oriented care.'

Yvette: 'The VAR gives nurses and paramedics a powerful voice, and we can support the development of the nursing and paramedic professions, provide recommendations in this regard, and even initiate developments ourselves. In 2019, we organized a lunch meeting for the nursing staff and paramedics to brainstorm and discuss ideas, and it was very well attended.'

Also in 2019, more nurses were needed. What has been the impact of this on the wards?

Yvette: 'For now, the primary focus is still on training, while there is also a big group of pediatric oncology nurses that would like to develop themselves and have certain ambitions. The challenge now is to ensure that they can develop further. The 'fascinate and connect' program addresses this issue.'

Pauline: 'A lot is being asked of our current nursing staff. Firstly, they are sometimes working extra shifts, and secondly they are spending a lot of time training new colleagues.'

The concentration of all pediatric oncology patients in the Princess Máxima Center means the work is sometimes very tough. How do you deal with this, and what support do you get?

Pauline: 'As we now work in fixed teams there is more attention for each other. Furthermore, a lot of use is made of the Princess Máxima Center's professional support counselor. Also in the Solid Tumors and Neuro-oncology departments we've started with intervision (peer coaching) among nurses, so we can discuss a case in small groups if one of us has had a difficult experience. And in our everyday work we do regular evaluations with each other.'

Yvette: 'Yes, working in fixed teams really helps, as you know each other better. And in the Hemato-oncology department we also use the professional support counselor. Furthermore, we've set up multidisciplinary 'communication hours' in which cases are discussed.'

Jacqueline: 'Also as team leaders we pay a lot of attention to the impact of the work, by evaluating cases in the departments concerned.'

'The VAR gives nurses and paramedics a powerful voice, and we can support the development of the nursing and paramedic professions, provide recommendations in this regard, and even initiate developments ourselves'

Yvette van Beuningen

Collaborations

The Princess Máxima Center strongly believes in the power of collaboration. Only by sharing knowledge and expertise internally, as well as with external national and international partners, can we accomplish our mission. Internal collaborations, between specialists, researchers and care professionals are encouraged, as are partnerships with both nearby institutes in Utrecht Science Park, and institutes further away, not only in the rest of the Netherlands but across the globe.

Shared Care

The Princess Máxima Center works together closely with twenty hospitals in the Netherlands, the so-called Shared Care centers, based on the principle: central treatment if necessary, close to home if possible. This means that children can have less complex parts of their treatment done in their own region.

In 2019, further development of the collaboration between the Princess Máxima Center and the Shared Care centers was a focal point. The conditions for this collaboration and continuous information exchange were further realized. The Shared Care centers were granted access to the iMáxima document management system and Practocol Planner to view chemotherapy treatment plans. In addition, more employees within the Shared Care centers were given access to the HiX patient file database with a simplified application procedure. As a result, continuity of care has been guaranteed.

The development of cooperation between the Princess Máxima Center and the Shared Care centers is assured by the National Shared Care Committee. This committee met several times in 2019, which led to a couple of significant milestones: the standardization of work agreements, and the drafting of the assessment framework for the care chain of pediatric oncology.

The regional representatives and the Shared Care organization, led by the Clinical Director of Quality of Life, paid several visits to the Shared Care centers. During these visits, the cooperation and opportunities for education were focus points. In addition to this, the Shared Care centers were also given access to the Online Learning Portal of the Princess Máxima Center to promote the exchange of knowledge.

The Shared Care organization is committed to further consolidating this collaboration.

National Shared Care Committee
met four times

Shared Care day
took place twice
(March 20 and Sept 18,
Themes: Neuro-oncology
and Supportive care),
250 healthcare professionals
attended

Newsletter
published three times

Number of shared care visits
thirteen

Realized / simplified access to the following systems
HiX, iMáxima, Practocol Planner, Online Learning Portal

Shared Care centers

Flevo hospital
Almere
Amsterdam UMC
Amsterdam
Amphia hospital
Breda
Reinier de Graaf hospital / Haga
Delft
Deventer hospital
Deventer
Hospital Gelderse Vallei
Ede
Catharina hospital
Eindhoven
Medisch Spectrum Twente
Enschede
Admiraal de Ruijter hospital
Goes
Academic Medical Center Groningen
Groningen
Dijklander hospital
Hoorn
Medical Center Leeuwarden
Leeuwarden
Maastricht Academic Medical Center
Maastricht
St. Antonius hospital
Nieuwegein
Radboud Academic Medical Center / Amalia Children's hospital
Nijmegen
Maasstad hospital
Rotterdam
Erasmus Medical Center / Sophia Children's hospital
Rotterdam
Jeroen Bosch hospital
's Hertogenbosch
VieCuri
Venlo
Isala Clinics
Zwolle

UMC Utrecht

Collaboration in specialized care and research

The Princess Máxima Center provides highly specialized care for which it collaborates intensively with the UMC Utrecht. This collaboration was further intensified and professionalized in 2019. Specialized pediatricians of the UMC Utrecht work with us every day to help cure children with cancer: infectious diseases specialists, cardiologists, nephrologists, lung specialists, endocrinologists, intensivists, neurologists, and radiotherapists. These professionals are of great value to the functioning of the Princess Máxima Center, as they give us access to general pediatric knowledge and skills.

The Princess Máxima Center also uses the intensive care ward and the operating rooms of the Wilhelmina Children's Hospital (WKZ). We have also close collaboration in neurosurgery, the surgical specialties and the clinical chemical laboratory. Radio diagnostic lab technicians and radiologists of the UMC Utrecht work in the Princess Máxima Center's radiology department. Furthermore, transfer nurses of the UMC Utrecht work in the Princess Máxima Center to support children and their parents in terms of quality of life and home networks.

As mentioned in chapter 'Fields of interest', another important partnership between the Princess Máxima Center and UMC Utrecht is the stem cell transplantation unit in the Princess Máxima Center. Children with both benign and malignant disorders are treated on this unit.

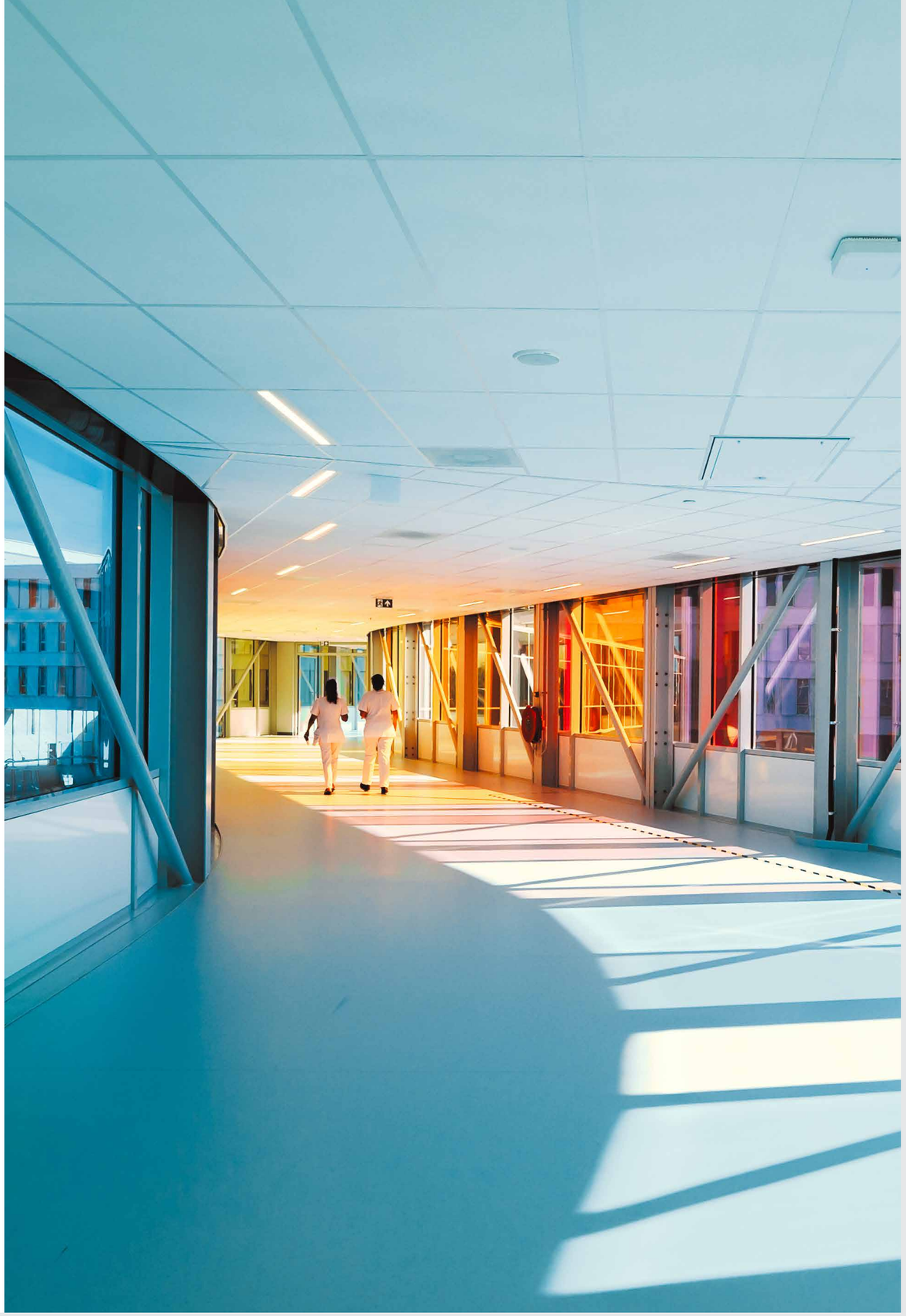
The research department of the Princess Máxima Center and the UMC Utrecht also closely work together on several projects. For the focus areas Child Health and Cancer our professionals come together with the UMC Utrecht to improve both research and care. In addition, in 2019 we established the Medical Ethics Committee (METC) Utrecht (https://www.metcutrecht.nl/), in close cooperation with the UMC Utrecht. Staff from both the Princess Máxima Center and the UMC Utrecht sit on the METC. We have worked very hard to set up an assessment process that is as diligent and independent as possible.

Strategic partnership

The UMC Utrecht is also an important strategic partner of the Princess Máxima Center. Close cooperation with the UMC Utrecht offers outstanding possibilities for sharing expertise around pediatric specialisms, which further improves the quality of both pediatric oncology and care at the UMC Utrecht. And by utilizing the knowledge and quality of the UMC Utrecht, we can effectively integrate care and research.

Furthermore, this partnership offers us more opportunities to develop innovative diagnostics and treatment. The first steps have already been taken in the fields of radiology, nuclear medicine, immunotherapy, and radiotherapy to facilitate new analyses and therapies for patients in our center. This set an example and provides a driving force for further innovative diagnostics and treatment in the future. Another major collaborative theme is our contribution to improving the treatment of specific patient groups, such as Adolescents and Young Adults (AYAs).

Under the supervision of a steering committee, three joint research projects have been initiated between UMC Utrecht and the Princess Máxima Center. These projects focus on common priorities: Immuno-oncology, theranostics, and High-Intensity Focused Ultrasound (HIFU).



National and international collaborations

Besides the shared care centers and the UMC Utrecht, the Princess Máxima Center has close ties with other national institutes. For multiple research projects, collaboration with our neighbors in the Hubrecht Institute has been very fruitful. Furthermore, six Principal Investigators (PIs) in the Princess Máxima Center are members of the Oncode Institute, which aims to cure cancer by facilitating and funding scientific research. Agreements around legal services and animal experiments with, among others, the Netherlands Cancer Institute (NKI) have been very valuable. These and other collaborations have proven to be successful in 2019 and prior to that, and will continue to be powerful in the future.

Utrecht University's Graduate School of Life Sciences PhD programs Cell, Stem Cell and Development (CS&D) and Clinical and Translation Oncology (CTO) are open to our PhD students as well as PhD students from the UMC Utrecht, Hubrecht Institute and Utrecht University. Several professionals at the Princess Máxima Center have a professorship at Utrecht University. In 2019, Martha Grootenhuis was appointed Professor of Pediatric Psycho-oncology at Utrecht University's Faculty of Medicine.

Also internationally, the Princess Máxima Center has strong connections. Princess Máxima Center researchers and clinicians collaborate in multiple European consortiums, and are well represented at conferences such as that of the International Society of Paediatric Oncology (SIOP). With Alexander Eggermont as Chief Scientific Officer (CSO), the ties with Gustav Roussy in Paris and KiTZ in Heidelberg will be strengthened. Many of our researchers and pediatric oncologists collaborate with colleagues from St. Jude Children's Research Hospital in Memphis (Tennessee, USA). In April 2019, a delegation from the Princess Máxima Center visited St. Jude to learn more about their approach, focus and strategy.

Education

Academy

Together with the professionals of the Princess Máxima Center, the Academy provides education and training for healthcare personnel, but also for researchers and other staff members. The Academy grew to 18 FTE employees in 2019, allowing us to concentrate on various focus areas.

Recognitions and Accreditations

In 2019, the Dutch Pediatric Association (NVK) extended the recognition for the pediatric oncology subspecialism in the Princess Máxima Center, confirming that the hospital is specialized in training pediatricians to diagnose and treat children with cancer. The Princess Máxima Center is also recognized for the training of healthcare psychologists. Various courses are accredited by the professional associations NVK, Nursing Specialist Register, Quality Register Nursing and Care Providers, the Dutch Institute for Psychologists, and the Royal Dutch Society of Physical Therapy. The Master's Course Pediatric Oncology was also accredited by the European Accreditation Council for Continuing Medical Education in 2019.

Learning & development

In 2019, the Princess Máxima Center's first Basic Course Regulatory and Organization for Clinical Researchers (BROK) took place. This course, consisting of an e-learning module, a national exam and a center-specific module is a legal requirement for all clinical researchers. Patient service courses for doctor's assistants have taken place in order to realize an unambiguous way of working and to enable them to deal with busy and difficult moments.

The one-year nursing training in pediatric oncology started twice in 2019 for students of the Princess Máxima Center and the shared care centers. In addition, 30 pediatric oncology nurses and 28 pediatric nurses were successfully trained and licensed in 2019. There was a total of 500 participants in skills training sessions, learning to use (new) equipment and procedures. There were another 3,000 participants who followed various courses.

In 2019, a total of 13 fellows underwent the training to switch from pediatrician to pediatric oncologist, of which ten are still being trained, while the other three have completed their training. This two-and-a-half-year program mainly consists of learning on the job, but includes a structured educational program as well. Also, eight pediatric oncology nurses participated in a two-year program to become nurse specialists. In 2019, a total of € 3.0 million was approved by several organizations, mainly government-based, for various educational activities.

The Academy organizes various internships inside the Princess Máxima Center, for its own employees and for employees of the shared care centers, as well as colleagues from abroad. In 2019 the Academy facilitated over 600 internships for people from outside the Princess Máxima Center.

In addition to care and research, education and training is the third key activity of the Princess Máxima Center and essential in getting the best out of every professional

The organization of conferences and symposiums also expanded in 2019, partly due to the opening of the auditorium. The Academy organized five (inter-)national conferences in 2019 in collaboration with care and research. The first and second modules of the second Master's Course Pediatric Oncology were conducted as well. More than thirty participants from over ten countries followed that program. For our partners, including the shared care centers, five meetings were organized in 2019 with a total of 320 participants.

Academy numbers

Learning & development	Figures
Classical training sessions taken	3,000
Online training sessions completed	3,400
Signed-off sections of the Quality Passport	2,250

Conferences & training	Events	Participants
Internal training	95	1554
External training	5	320
Masters Course (2 modules)	2	90
National symposium / conference	1	80
International symposium / conference	4	140
Information evenings for parents	7	285
Internal inspiration sessions	4	150

Internships and PhD students	Figures
Co-assistants	24 interns
Residents	19 interns
Fellowships	10 interns
Clinical scientific internships	18 interns
Research Internships	37 interns
Shared Care traineeships	35 interns
Pediatric oncology nursing internships	40 interns
Physiotherapy, 'Maximaal bewegen', Pharmacy and non-clinical staff internships	22 interns
Child Life specialist care and extramural internships (internal and 5 months external)	28 interns
Other	54 interns
Total number of interns	287
Total number of internships	>600
Total number of PhD students	112

Research meetings and seminars

Sharing knowledge is a key component of research. Therefore, the Princess Máxima Center provides a platform for PhD students and postdocs to share their projects and results with their peers. Both researchers and clinicians are encouraged to join these Máxima Research Meetings to keep up-to-date with the center's ongoing projects.

Additionally, the Princess Máxima Center organizes weekly research seminars, to which experts are invited to present their work. Hosting seminars with nationally and internationally renowned speakers provides opportunities to expand the network and initiate or strengthen collaborations. (Overview of seminars on next page.)

Thanks to the new auditorium, which opened in November 2019, the dissemination of knowledge will be even better in the coming years.

Internal speakers
13

External speakers
21

Research seminars 2019

Date	Speaker	Affiliation	Title of seminar
Jan 30	Prof. Eduardo Eyras, PhD	Pompeu Fabra University of Barcelona, Spain	Functional and immunogenic impacts of RNA processing alterations in cancer
Feb 6	Prof. Anthony V Moorman, PhD	Wolfson Childhood Cancer Research Centre, Northern Institute for Cancer Research, Newcastle, UK	New approaches to risk stratification in childhood leukaemia
Feb 13	Benedetta Artegiani, PhD	Hubrecht Instituut, Utrecht, Netherlands	Adult stem cells in homeostasis and cancer
Feb 20	Will Mifsud, MD, PhD	Sidra Medicine, Doha, Qatar	Evolutionary trajectories in pediatric kidney cancer: biological and clinical implications
Feb 25	Peng Weng Chuan, PhD	Stanford University School of Medicine, CA, USA	Exploiting tissue regenerative signals for the culture of primary hepatocytes
Feb 28	Prof. Chris Garcia, PhD	Stanford University School of Medicine, CA, USA and Howard Hughes Medical Institute, MD, USA	Exploiting immune receptor structural principles to open new therapeutic doors
Mar 20	Marcel Kool, PhD	DKFZ & KiTZ, Heidelberg, Germany	Molecular classification and characterization of pediatric brain tumors – new insights in ependymoma and ETMR
Mar 27	Astrid van Halteren, PhD	Willem-Alexander Children's Hospital/LUMC, Leiden, Netherlands	Challenges in understanding presentation & outcome of Langerhans Cell Histiocytosis
May 13	Machi Scaradavou, MD PhD	New York Blood Center, New York, USA	Cord blood banking and cord blood cell therapies
May 29	Rupert Handgretinger, MD	Department of Hematology/ Oncology and General Pediatrics Children's University Hospital, University of Tübingen, Germany	Immunotherapeutic approaches for pediatric cancer: current status and future outlooks
June 14	Prof. John Anderson, PhD	UCL Great Ormond Street Hospital, London, UK	T cell engineering for childhood solid cancers
July 4	William Weiss, MD, PhD	UCSF Brain Tumor Center, San Francisco, CA, USA	New models and vulnerabilities for pediatric neural tumors
Sep 11	Erik Rozemuller, PhD	GenDx, Utrecht, Netherlands	Genetic diversity, a blessing and the curse
Sep 18	Prof. Huib Caron, MD, PhD	Roche, Basel, Switzerland	Science-driven development of the Roche oncology pipeline for children with cancer
Oct 2	Prof. Constanze Bonifer, PhD	University of Birmingham, Birmingham, UK	Understanding acute myeloid leukemia: From data collection to molecular mechanism
Oct 9	Prof. Peter Ehrlich, PhD	Ann Arbor, Michigan University, MI, USA	The challenge of Stage V pediatric renal tumors, and the benefit of integrating biology, based on the COG experience
Oct 30	Sebastiaan van Heesch, PhD	Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany	Translational regulation and novel small proteins in human tissue
Oct 30	Prof. Gareth Veal, PhD	Newcastle Cancer Centre Pharmacology Group, Newcastle University, UK	Utilisation of Clinical Pharmacology Studies to Support the Treatment of Childhood Cancer Patients - a UK Experience
Nov 1	Prof. W. Hamish Wallace, PhD	University of Edinburgh & Royal Hospital for Sick Children, Edinburgh, UK	Fertility preservation for young people with cancer
Nov 6	Thomas Mercher, PhD	INSERM & Gustave Roussy institute, Paris, France	Pediatric myeloid leukemia: fusion oncogenes & specificities
Nov 13	Jim Geller, PhD	Cincinnati Children's Hospital Medical Center, OH, USA	Novel Therapy for Pediatric, Adolescent and Young Adult Kidney Cancers: Trials and Tribulations
Nov 20	Laura H. Heitman, PhD	Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, Netherlands	G protein-coupled receptors and novel drug discovery concepts – and their importance for cancer research

Outreach

‘We are proud to contribute to the well-being of children with cancer here and in less-privileged countries’

Prof. dr. Gertjan Kaspers,
Pediatric oncologist and
Director of the Academy and Outreach

In 2019 the Outreach Program of the Princess Máxima Center consisted of four twinning programs, which were strong and formal collaborations with hospitals in Blantyre (Malawi), Eldoret (Kenya), Pristina (Kosovo) and Yogyakarta (Indonesia). We provide our knowledge and skills for better treatment of individual patients and for improved diagnostics and psychosocial care.

The Princess Máxima Center allows personnel to visit these partner hospitals twice a year. Financial support from the World Child Cancer NL foundation covers travel costs, enabling mainly pediatricians to visit our center and to join the Masters Course Pediatric Oncology, and the foundation also funds research projects with an international impact. In Sub-Saharan Africa, an international network of six hospitals is successfully involved in projects on the Wilms tumor, and around supportive care. Hundreds of doctors, nurses and other healthcare professionals have already been trained in these low- and middle-income countries. Furthermore, information to parents has been improved, and treatment protocols and guidelines for supportive care have been updated and implemented.

Research

Expansion of Research

Extra research floor

In 2019, the previously unfinished fourth floor of the new building was transformed into an additional complete and functional floor for research, to complement the two existing research levels with extra labs and offices. As a result it is now possible to attract more national and international talent in order to both expand and deepen the focus areas. The rapid growth of research in the Princess Máxima Center meant that, in 2019, offices and labs were full. Although the opening of the fourth floor has created more space, the growth curve predicts that in spring 2020 we will need to rearrange our workspace again to make room for new employees and groups of researchers.

Expansion of research groups

The Princess Máxima Center is an attractive employer for national and international scientific talent. The number of research groups has grown from 26 in 2018 to 32 at the end of 2019. The 473 researchers in the Princess Máxima Center have 28 different nationalities, with the majority being Dutch (~83 percent). After the appointments of Eelco Hoving, Martha Grootenhuis and Wim Tissing, and the arrival of Alexander Eggermont, 19 professors are now affiliated with the Princess Máxima Center.

Prof. dr. Eelco Hoving held his inaugural speech in honor of his appointment as professor. Martha Grootenhuis was appointed as Professor of Pediatric Psycho-oncology at the Medical Faculty of Utrecht University. Wim Tissing was appointed as Professor of Supportive care in pediatric oncology at the University of Groningen (RUG).

New focus areas

Principal Investigator	Date	Focus area	Origin
Prof. dr. Henk Stunnenberg	March 2019	(Epi)genomics and transcripto-mics	Radboud UMC, Nijmegen
Dr. Hans Merks	May 2019	Rhabdomyosarcoma	Princess Máxima Center for pediatric oncology
Dr. Marita Partanen	September 2019	Neuropsychology	St. Jude Children's Research Hospital, Memphis, TN, VS
Dr. Marcel Kool	September 2019	Brain tumors	DFKZ, Heidelberg, Germany
Dr. Weng Peng	December 2019	Hepatoblastoma	Stanford University, San Fran-cisco, CA, VS
Dr. Benedetta Artigiani	December 2019	Brain organoids	Hubrecht Institute, Utrecht

Co-principal investigators

Next to the PIs, who are leading the research groups, co-principal investigators are appointed as to specific research groups. With this system, where fundamental scientists are coupled to clinicians and/or senior scientists that are working within the same area of interest, the quality of research as well as the level of collaboration is even further increased.

Co-PI	PI	Topic
Ronald de Krijger	Jarno Drost	Tumor pathology
Eelco Hoving	Jarno Drost	Rhabdoid tumors
Marjolijn Jongmans	Roland Kuiper	Cancer genetics
Gert-Jan Kaspers	Ronald Stam	Clinical AML
Max van Noesel	Jan Molenaar	Neuroblastoma
Bastiaan Tops	Frank Holstege	Cancer genomics
Josef Vormoor	Olaf Heidenreich	Fusion genes

Research funding

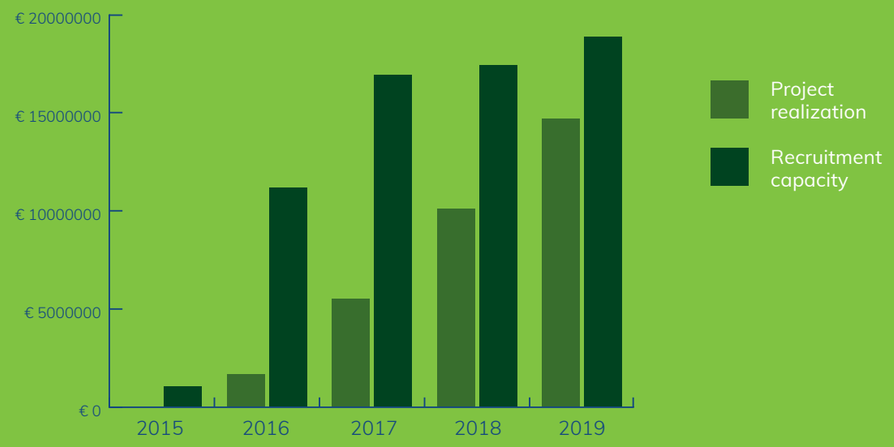
The research of the Princess Máxima Center is dependent on external funding, which consists of core funding and project funding.

Core funding

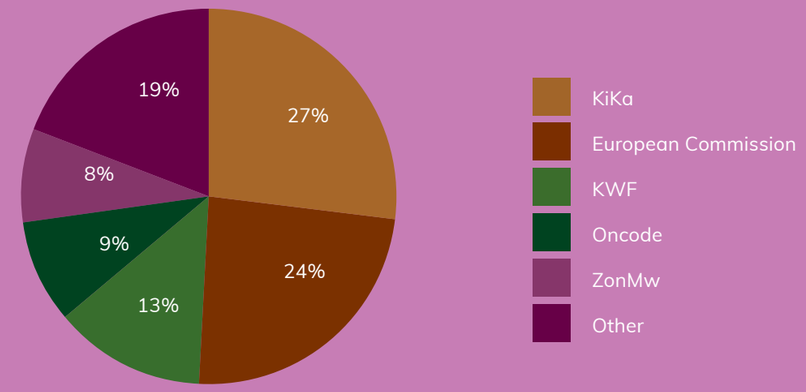
The Children Cancer-Free Foundation (KiKa) is the main sponsor of scientific research at the Princess Máxima Center. The core funding that KiKa has provided since the start of the Princess Máxima Center provides the financial basis for each research group and core facility. The Ministry of Health (VWS) has added to the core funding on a yearly basis from 2017 to 2019.

In December 2019, an agreement for a structural contribution from the Ministry of Health was signed. The Academic Care Availability Contribution/ *Beschikbaarheidbijdrage Academische Zorg* (BBAZ) is allocated to care centers with an academic component. In 2020 this will amount to €10 million for the Princess Máxima Center. For 2021 and 2022 this will be increased to €11 million and €12 million, respectively.

Project funding



Source of external funding 2019



Project funding

In addition, our researchers have been very successful in obtaining project funding from various sources. Project funding allows research groups to expand in terms of research projects, group members and equipment. The total recruiting capacity was €18.8 million in 2019. Total project realization in 2019 was €14.6 million. Chart 'Project funding' shows the Total project funding and realization over the years 2015-2019 for the Princess Máxima Center's research groups.

In a highly competitive scientific environment, the total of €18.8 million of project funding testifies to the high quality of project proposals, relevance to society and expertise of the researchers in the Princess Máxima Center. The chart above shows the distribution of the project funding of 2019 allocated by the various funds.

Major funds in 2019 came from KiKa, the European Commission, the Dutch Cancer Society (KWF), Oncode and ZonMW. KiKa funded fourteen project proposals from Princess Máxima Center researchers in 2019. A project led by dr. Olaf Heidenreich on direct and indirect targeting of leukemic fusion genes was awarded €1.4 million by KiKa.

Also major funds were awarded to the Princess Máxima Center by the European Commission. Two projects funded by European Research Council (ERC) Starting Grants were initiated in 2019. A study led by dr. Anne Rios aimed at deciphering the invasive nature of diffuse intrinsic pontine glioma, and a project led by dr. Jarno Drost on malignant rhabdoid tumors, each received €1.5 million from the European Commission.

In 2019, six projects from the Princess Máxima Center were selected by the Dutch Cancer Society (KWF) for funding, and ZonMW gave funding to three Princess Máxima Center projects. Three researchers were welcomed by Oncode Institute as junior members, resulting in an additional €600,000 in project funding for their research groups.

Core facilities

The research of the Princess Máxima Center is dependent on external funding, which consists of core funding and project funding.

Biobank

The Princess Máxima Center Biobank stores excess human biological materials and derivatives thereof (like DNA) for future research purposes, provided that patients and/or parents have given their consent. All patient materials and associated clinical and biological data are collected and registered in a pseudonymized way. The Diagnostic Laboratory safeguards the quality of these samples and ensures they are processed and stored in the most optimal way.

In 2019 the commitment of patients to participate in the Biobank was very high. From all patients that completed the consent form, 96 percent gave permission for body materials and data to be stored. The total number of patients that gave their consent steadily increased over the year to almost 1000 (from 353 to 946).

The initial backlog in retrieving the consent forms, dating back to the start of the Princess Máxima Center, has almost been resolved due to process optimization. This is also evident from the current inclusion numbers.

The purpose of the Biobank is to enable investigators to use the collection to find improved treatment options for future patients. Access to this valuable material is only granted after the Biobank and Data Access Committee (BDAC) have approved the submitted research proposals. So far, 90 percent of the current research groups have submitted one or more Biobank requests.

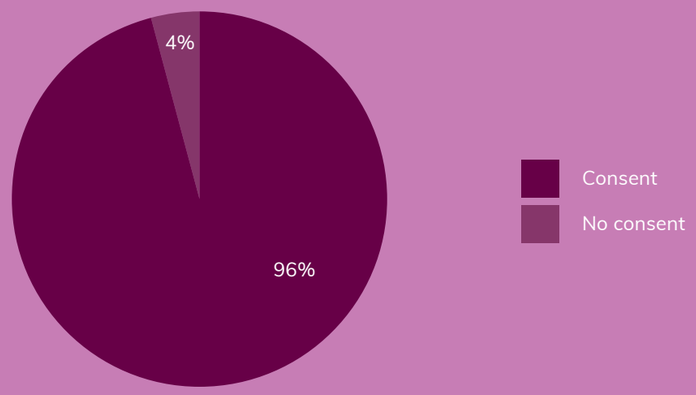
A total of 56 requests were approved in 2019, of which almost a third was related to a hemato-oncologic topic. The objectives of the other requests were related, in equal numbers, to the neuro-oncology, solid tumors and quality of life programs in the Princess Máxima Center. This is also a reflection of the Biobank's composition: a large part comprises the cohort of blood and bone marrow samples collected by the Dutch Childhood Oncology Group (DCOG) in the past. More detailed information about this cohort can be found in the annual report 2019 of the DCOG (SKION).

New developments such as Whole Genome Sequencing have enabled the BDAC to store these data too and make them available to investigators. The increased collaboration between PIs from different research groups and clinicians in submitting proposals to the BDAC is also noteworthy. In almost a quarter of the requests, the applicants originated from different research groups.

In the last quarter of 2019, Marion Persoon started as the Biobank coordinator, to further optimize and implement the procedures. Inventories are being prepared to enable the diagnostic laboratory to store the most optimal set of materials for each tumor type in the Biobank.

A single central system to review the storage and issue of material and data would be a next step in the Biobank's optimization.

2019 Consent for Biobank inclusion



Trial and Data Center

The Trial and Data Center (TDC) is the group within the research department that conducts and supports all clinical trials within the Princess Máxima Center. For some trials the employees of the TDC act on behalf of the international or national sponsor of the trial; for other trials, the Princess Máxima Center is a participating site only.

There is a wide range of clinical studies, from pharmaceutical research in Phase I/II, to studies carried out by Princess Máxima Center researchers and international colleagues. In total the Princess Máxima Center is involved in about hundred studies, which are very diverse. An overview over the open clinical studies can be found in Appendix 1. The TDC has expanded a lot in 2019 to fulfill the ambitions of the Princess Máxima Center, with the number of employees growing to 80.

In order to get reliable results, patient groups have to be sufficiently large. Therefore, collaborations with other countries in Europe, as well as the United States and Canada, are essential. The TDC supports studies in all departments: Hemato-oncology, Neuro-oncology, Solid tumors and also Quality of Life.

FACs and flow cytometry

Distinguishing between different cell types has always been a pivotal issue for cancer research. The recent surge in single cell genomics throughout the life sciences, and the interest in immunotherapy, has raised the importance and demand for cell population selection and characterization by cytometry and by fluorescence activated cell sorting (FACS) even further.

In 2019, this general increase in demand at the Princess Máxima Center was further boosted by the growth in the number of researchers at the center. This past year was the first year of complete operations in the Flow Cytometry and FACS facility. While at the end of 2018, 50 users from 12 different groups were using the facility, these numbers have now risen to more than 100 scientists from 15 research groups. Although a high-end FACS machine needs to be operated by a specialized operator, an important strategy for the Princess Máxima Center – one rarely implemented in other research institutes – is to train researchers to do their own sorting. The capacity to do this was greatly increased in 2019 through acquisition of a second user-operated FACS machine. Two

such machines are now available, each placed at a different biological hazard level. Training users to operate these FACS machines themselves (90 additional users were trained in 2019) has resulted in a huge capacity for these types of analyses, especially given that the entire management, maintenance, training and high-end operation is carried out by a single, highly dedicated facility manager. The entire current equipment of the facility encompasses four FACS machines and five cytometers. There is excellent collaboration with diagnostics and increasing interest from partners outside the Princess Máxima Center. 2019 also saw the first scientific publications that involved facility work (Schutgens et *al.*, 2019).

Single-Cell Genomics Facility

Besides the diseased cancer cells, tumors also consist of cells that support tumor growth, as well as immune cells that influence them. By determining all the different cell populations and their interplay, pediatric cancers can be better understood. This can be achieved by applying single-cell approaches including single-cell RNA sequencing (scRNAseq). In collaboration with many research groups, the single-cell genomics facility is involved in all aspects of such projects, from planning and execution to developing analysis pipelines and training researchers. The facility is led by dr. Thanasis Margaritis and is involved in projects from the Clevers, Den Boer, Drost, Janda, Heidenreich, Holstege, Hulleman, Looijenga, Meijerink, Merks, Molenaar, Peng, Rios, Stam, Stunnenberg, Tytgat and Van Boxtel groups, thereby encompassing a broad group of pediatric cancers.

The standard platform is a modified SORT-Seq protocol. It involves making scRNAseq libraries of cells, FACS-sorted into 384-well plates. scRNAseq data require extensive processing and computational resources. This is accomplished by Sharq, a facility-developed data-processing and analysis pipeline that runs on the Utrecht High Performance Computing (HPC) environment. A second platform, the 10xGenomics Chromium Single Cell Controller, was added in 2019. This is the leading microfluidics platform. Comparison by the facility shows that the two platforms have different strengths and are complementary. The facility can provide integration of data from these platforms. Labchip GX Touch HT was also acquired this year to enable QC of scRNAseq libraries.

In 2019, the facility also started training wet-lab researchers and bioinformaticians in scRNAseq data analyses. Two graduate students developed procedures for cell type classification and copy number variation detection using scRNAseq data, leading to publication of one of the methods (de Kanter et *al.*, 2019). Further highlights included the addition of dr. Lindy Visser to the team, as well as the first scientific publications from the Princess Máxima Center that make use of the work (Schutgens et *al.*, 2019).

High throughput screening

The High-Throughput Screening (HTS) facility offers fully automated, large-scale, efficient, flexible, accurate, reproducible and cost-effective drug testing. The aim is to facilitate the accelerated identification and validation of improved treatment strategies and disease-associated genes and proteins by supporting the development, performance and analysis of high-throughput perturbation assays.

In 2019, the HTS facility, which is embedded in the Molenaar group, was installed at the Princess Máxima Center. This new facility includes state-of-the-art robotic systems and a collection of compound libraries. The implementation of the HTS involved the installation of equipment, software, training, customization and an extensive Site Acceptance Test (SAT). Furthermore, the working plates of the compound library of 200 compounds specific for pediatric cancer were prepared.

Since December 2019, fully automatic single drug screens have been performed at the HTS facility on classical cell lines, organoids and isogenic systems. In the next phase, the facility can be

Equipment in the HTS facility

Beckman Coulter Biomek i7 Hybrid automated workstation with HEPA filter	Liquid handling workstation with deck positions for assay and compound plates, robot grippers and flexible arms, shuttles to move the plates, 96w and 384w pipette heads, heating and cooling modules, shakers, capper and decapper, centrifuge, and a barcode tracker
Cytomat 10C incubator	Fully automated incubator and storage module for high-capacity cell growth and assay incubation
Cytomat 9 hotel	Storage hotel for tip boxes and compound microplates
Echo 550 liquid handler	Acoustic liquid handling for precise nL transfer volumes of drug solutions
Thermo Multidrop Combi reagent dispenser	Provides precise dispensing of solutions, ensuring reproducible assay data
Spectramax i3x	Microplate reader for absorbance, luminescence and fluorescence detection

upgraded and expanded with new techniques and equipment. So far, 12 research groups within and outside the Princess Máxima Center have used or are planning to use the HTS facility for research purposes, or to explore the opportunities for a drug screen-based treatment advice.

Microscopy and Imaging Center

The Princess Máxima Imaging Center, founded by dr. Anne Rios in 2017 and managed by dr. Frank Bos, provides access to and training in advanced widefield, confocal, multiphoton and light sheet microscopy technologies. Applications include single-cell resolution 3D imaging of organoids, intact tumors and their surrounding tissue, live cell imaging and intravital imaging. These technologies are made available for research into all pediatric cancers.

In 2019, 51 new users have been trained from five additional research groups, bringing the total number to 93 users from 19 different groups. In addition, new systems have been added to the facility, to ensure they stay up to speed with the latest developments. The center obtained a Quest Imaging System for pre-clinical research into fluorescent-guided surgery, and identification and evaluation of probes to specifically light up tumor tissue. In addition, an IVIS Spectrum µCT Imaging System for 3D bioluminescence detection *in vivo* was acquired, which allows monitoring of tumor growth over time in animal models.

An important achievement of 2019 was the development of a novel sample preparation protocol for volumetric imaging of organoids. Since these stem cell cultures self-organize into ex vivo 'mini-organ' or tumoroid three-dimensional structures, 3D imaging provides an essential tool for probing their complexity. Our 3D imaging protocol was used to characterize several novel organoid biobanks developed by research groups of the Princess Máxima Center (Schutgens et *al.*, 2019; Sachs et *al.*, 2019). In addition, a new pipeline of dynamic imaging and data mining of cell behavior was implemented, which has provided novel insight into the tumor-targeting potential and strategies of cellular immunotherapy (manuscript submitted).

Because of the wide applicability of the technologies provided, the Princess Máxima Imaging Center attracts a large number of external collaborators and is currently looking to expand the capacity to fulfill these requests.

Organoid facility

Since October 2018, the organoid facility has supported organoid-based projects by facilitating quality-tested conditioned media, growth factors and know-how. Every research group can contact the facility with their needs regarding their organoid projects. By the end of 2018 the facility was used by nine different research groups. This number increased to thirteen research groups in 2019, thereby encompassing a broad group of pediatric cancers.

To study different types of pediatric tumors, model systems are essential. Organoids provide such model systems. Organoids are derived from patient material and resemble tumors that grow in children. This enables analysis of a tumor cell's genetic, metabolic and communicative characteristics. Moreover, it provides an efficient and safe manner to test large sets of therapies. The growth of tumor cells outside of the body requires precision and detailed know-how. This know-how and expertise is offered by the organoid facility. At this point, fourteen different reagents are provided to accommodate the cultivation of various types of organoids.

By providing reagents and know-how, the organoid facility contributes to the research of almost half of the research groups embedded in Princess Máxima Center (covering neurologic, solid as well as hematologic malignancies). Moreover, organoid technology is starting to be implemented in individualized medicine programs (Ither 2.0) and is therefore supported by this facility.

In 2019, we have also initiated several collaborations with external parties, including Cambridge University (UK), University of Würzburg (Germany) and the VU University Amsterdam (Netherlands).

Research groups

Research group dr. Benedetta Artegiani

Started in December 2019

In 2019, research of dr. Benedetta Artegiani has been focused on optimizing and exploiting the use of human liver organoids for both cancer biology and to study normal liver physiology.

Members of the Artegiani Group

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External Funding

-

Research Lines

Artegiani generated for the first time CRISPR/Cas9 genome edited human liver organoids. She used this system to understand the function of a gene often mutated in liver tumors, but whose function was not clearly identified yet, BAP1. Artegiani could link an unbalance epigenetic regulation in BAP1 mutant organoids, due to the lack of BAP1-mediated deubiquitination of H2ALys119, with the appearance of specific malignant features, which led to generation of tumors upon xenotransplantation of the BAP1 deficient organoids. This study, in addition to elucidating the function of a critical gene in the development of a deadly liver cancer, represents the first example of the potential of conjugating the organoid technology and CRISPR/Cas9 for mechanistic studies of tumorigenesis. Additionally, she described a new approach, CRISPR–HOT (CRISPR– Cas9-mediated homology-independent organoid transgenesis), which enables the efficient generation of knock-in human organoids representing different tissues. CRISPR–HOT was used to fluorescently tag and visualize subcellular structural molecules and to generate several human liver reporter lines in organoids. Combining tubulin tagging with TP53 knock-out revealed that TP53 is involved in controlling hepatocyte ploidy and mitotic spindle fidelity.

By fostering our understanding of human liver cancers and optimizing tools necessary to improve the use of organoids to study cancer biology and human physiology, Artegiani envisage important translational applications for diagnostic, prognostic and therapeutic purposes, which could be relevant to the society.

Total external publications 2019: 2

Research group prof. dr. Monique den Boer

Started in June 2018

Members of the den Boer Group

PhD student
Hormann, F.M. (Femke)
Kordek, A.K. (Aleksandra)
Michels, N. (Naomi)
Montecchini, O. (Oksana)
Outersterp, I. van (Inge)
Sandt, I. van de (Iris)
Smeets, M.W.E. (Mandy)

Postdoc
Dingjan, I. (Ilse)
Ven, C. van de (Cesca)
Boer, J.M. (Judith)

Bio-informatician
Hoogkamer, A.Q. (Alex)

Technician
Jurriëns, C.M. (Chérise)
Kleef - Boeree, A. van (Aurélie)
Meijers, F. (Femke)
Orsel, S.J. (Jan)
Vermeeren, M.M.P. (Myrthe)

Graduate student
Bouma, R.G. (Rianne)
Lugt, R.P. van der (Ruben)
Mooij, E.J. (Eva)
Kloppenburg, L. (Lotte)

The overall research aim of the Den Boer group is to find new molecular markers that point to more efficacious ways to treat children with B-cell precursor acute lymphoblastic leukemia (BCP-ALL). The strength is that the program bridges research and clinics, which is illustrated by several inventions that have been implemented in clinics, and was awarded by the Dutch Childhood Oncology Group (DCOG) with the ODAS award in 2019.

Main topics of research are:

- dissecting genetic lesions with prognostic and/or therapeutic potential
- elucidating the leukemic bone marrow niche and how to interfere with this protective niche
- studying the interaction between healthy immune cells and leukemia, including efficacy of immune therapeutics
- exploring targeted drugs and drug combinations (*ex vivo*, *in vivo*)
- valorization of molecular profiling and assessment of new precision medicines in early clinical trial settings (in collaboration with prof. Michel Zwaan)

Research lines and results of importance

In short, Den Boer's BCP-ALL program consists of two research lines:

- oncogenomics
- leukemic niche

In the **oncogenomics research line**, the team focuses on the role of genetic abnormalities and deregulated (phospho)proteins in the pathobiology of pediatric BCP-ALL in order to find new prognostic biomarkers and drugs with high efficacy and specificity.
In the recent past, Den Boer discovered a new high-risk type of pediatric ALL, i.e. BCR-ABL1-like ALL, by means of genomic studies (Den Boer *et al.*, 2009). This new type of BCP-ALL is characterized by a high frequency of deletions in the *IKAROS* (IKZF1) gene and abnormalities affecting ABL class genes, which both affect further normal B-cell development. Following this discovery, the IKZF1 deletion was implemented as stratification marker in the new treatment protocol for newly diagnosed ALL (DCOG ALL-11 study). In meantime, BCR-ABL-like cases were further genomically characterized in an international setting. This resulted in the discovery of ABL-class fusion genes and an official WHO classification in 2016. In 2020, the ALLtogether study will start, in which these ABL-class cases will be treated with tyrosine kinase inhibitors as part of their upfront therapy. Den Boer will be PI for the molecular response studies of this group of patients. In addition, we identified new lesions in other types of BCP-ALL, e.g. NUTM1 fusion genes in infants (Hormann *et al.*, 2019) and epigenetic lesions in children with Down syndrome ALL (Michels *et al.*, submitted).

In the **leukemic niche research line**, the Den Boer group addresses the interaction between leukemic cells and the bone marrow microenvironment. They discovered a pro-survival communication mechanism induced by tunneling nanotubes, which increased the viability of leukemic cells and reduced the sensitivity of leukemic cells to chemotherapeutic drugs (Polak *et al.*, 2015; NWO's Vici grant). The team discovered that autophagosomes are transported via these nanotubes and contribute to this survival benefit (Dingjan et al). In addition, they discovered that leukemic cells manipulate mesenchymal stromal cells to produce proteins beneficial to the leukemia, a.o. cytokines (Smeets *et al.*). These results has prompted us to develop new models in which immune modulation can be studied, including 3D models (*ex vivo*; Montecchini *et al.*) and scaffold models (*in vivo*; Van de Ven *et al.*)

Top 3 publications

- Hormann, F. M., Hoogkamer, A. Q., Beverloo, H. B., Boeree, A., Dingjan, I., Wattel, M. M., . . . Boer, J. M. (2019). NUTM1 is a recurrent fusion gene partner in B-cell precursor acute lymphoblastic leukemia associated with increased expression of genes on chromosome band 10p12.31-12.2. *Haematologica*. PMID: 30872366

- Hamadeh, L., Enshaei, A., Schwab, C., Alonso, C. N., Attarbaschi, A., Barbany, G., . . . International, B. F. M. S. G. (2019). Validation of the United Kingdom copy-number alteration classifier in 3239 children with B-cell precursor ALL. *Blood advances*. PMID: 30651283

- Polak, R., Bierings, M. B., van der Leije, C. S., Sanders, M. A., Roovers, O., Marchante, J. R. M., . . . Buitenhuis, M. (2019). Autophagy inhibition as a potential future targeted therapy for ETV6-RUNX1-driven B-cell precursor acute lymphoblastic leukemia. *Haematologica*. PMID: 30381299

Total Princess Máxima Center affiliated publications 2019: 6

External Funding

Children Cancer-free Foundation (KiKa)
A humanized bone marrow micro-environment mouse model for acute lymphoblastic leukaemia.
€100.549

Awards

ODAS prize pediatric oncology
Monique den Boer

NWO ZonMW Open Science Award
Monique den Boer

Research group dr. Ruben van Boxtel

Started in September 2017

Members of the van Boxtel Group

Co-PI
Belderbos, M.E. (Mirjam)

PhD student
Hasaart, K.A.L. (Karlijn)
Gorter de Vries, S.L.I. (Sophie)
Groenen, N.M. (Niels)
Manders, F.M. (Freek)
Peci, F. (Flavia)
Rosendahl Huber, A.K.M. (Axel)

Postdoc
Brandsma, A.M. (Arianne)
Middelkamp, S.H.A. (Sjors)

Bioinformatician
Oka, R. (Rurika)
Roosmalen, M.J. van (Mark)

Technician
Verheul, M. (Mark)

Graduate student
Dinter, J.T. van (Jip)
Lancee, A.M. (Melissa)
Leeuwen, A.J.C.N. van (Anaïs)
Leij, S. van der (Sophie)
Plugge, S.F. (Susanna)
Tjoonk, N.H. (Niels)
Tropa Martins, M.M.V. (Madalena)

In addition Van Boxtel supervises a PhD student, shared with other Máxima research groups.

Why do children get cancer? The overall aim of our research is to determine the mechanisms and rate-limiting steps underlying the genesis of childhood cancers.

Research Lines

The Van Boxtel group focuses on three main topics:

Topic 1: Study the etiology of childhood cancers. Although aging is the biggest risk factor for cancer, the incidence of some cancers, such as leukemia, is higher in children compared to young adolescents. We aim to clarify this paradox and, by doing so, obtain insight into the molecular and cellular mechanism underlying cancer initiation.

Topic 2: Explore how cancer treatment causes second malignancies in cancer survivors. Therapy-related malignancies are a major cause of long-term mortality among childhood cancer survivors. However, it is unclear how exposure to chemo- and/or radiotherapy early in life induces carcinogenesis. Van Boxtel aims to determine the genotoxic effects of cancer treatment on normal tissues and study how this contributes to the development of second malignancies in cancer survivors.

Topic 3: Dissect the etiology of cancer-associated mutational signatures. Specific patterns in cancer genomes reflect activity of mutational processes and can have diagnostic value. However, for many of these signatures the underlying mechanism is unclear. The Van Boxtel group aims to identify the processes causing specific mutational signatures in cancer and examine their predictive value.

For this, the team uses **DNA as an historical archive to reconstruct a cell's life history**. DNA mutations occur naturally during each cell division, and reflect the combined activity of DNA mutagenic and repair activity. Our multidisciplinary group combines *in vitro* stem cell culture systems with genome-wide sequencing technology and in-depth mutational analyses to characterize mutation accumulation in human cells and tissues. By studying mutation profiles, selection dynamics and clonal composition during normal ageing and in pediatric malignancies, we aim to pinpoint the origin of childhood cancer and of therapy-related neoplasms, and to identify causative processes.

Top 3 publications

- Driehuis, E., Kolders, S., Spelier, S., Lõhmussaar, K., Willems, S. M., Devriese, L. A., . . . Clevers, H. (2019). Oral Mucosal Organoids as a Potential Platform for Personalized Cancer Therapy. *Cancer discovery*. PMID: 31053628

- Huber, A. R., Manders, F., Oka, R., & van Boxtel, R. (2019). Characterizing Mutational Load and Clonal Composition of Human Blood. *Journal of visualized experiments : JoVE*. PMID: 31355782

- Kuijk, E., Blokzijl, F., Jager, M., Besselink, N., Boymans, S., Chuva de Sousa Lopes, S. M., . . . Cuppen, E. (2019). Early divergence of mutational processes in human fetal tissues. *Science advances*. PMID: 31149636

Total Princess Máxima Center affiliated publications 2019: 3
Total external publications 2019: 2

External Funding

Dutch Cancer Society (KWF)
Defining mutational footprints predicting genetic predisposition and therapy sensitivity in cancer
KWF 12090
Together with Roland Kuiper and Jarno Drost
€732.626

Oncode
Junior investigator programme
€600.000

EBMT Research Fellowship Grant
Cord versus marrow: Are young stem cells superior for transplantation?
Tracing the clonal dynamics of single HSCs in human hematopoietic stem cell recipients
Project leader Mirjam Belderbos
€30.000

Awards

Junior Investigator Programme
Ruben van Boxtel

ERC consolidator grant
Ruben van Boxtel

EBMT Research Fellowship Grant
Mirjam Belderbos

Research group prof. dr. Hans Clevers

Started in 2015

Members of the Clevers Group

PhD student
Bleijs, M.W. (Margit)
Hanemaaijer, E.S. (Evelyn)

Postdoc
Hendriks, D.F.G. (Delilah)
Roerink, S.F. (Sophie)
Wetering, M.L. van de (Marc)

Technician
Ringnalda, F.C.A.S. (Femke)

Researcher
Sanders, K. (Karin)

Graduate student
Engels, S.A.G. (Sem)
Verweij, L.H.G. (Laurens)

The Clevers group is a pioneer in the field of Wnt signaling, organoid technology and adult stem cells in health and disease. Upon establishing a research group in the Princess Máxima Center, this knowledge and experience was used to initiate a research line aiming to establish organoid technology for pediatric cancers. The Clevers group and others have shown that patient derived organoids retain the characteristics of the tissue of origin and as such can be regarded as patients' avatars. This allows the use of organoids to predict drug sensitivity and guide the oncologist to choose the best therapy for the individual patient.

Research Lines

Pediatric cancer in particular will benefit from the development of organoid models. Given the wide range of pediatric cancer entities, most pediatric cancer types are rare, which severely hampers research. The Clevers group aims to fill this gap by developing organoid technology for pediatric cancers. Clevers envisions that pediatric cancer organoids will accelerate research and, as patients' avatars, guide therapy.

Originally focusing on neuroblastoma, medulloblastoma and Ewing sarcoma, the group now has broadened their scope and included rare pediatric cancers which are hardly studied because of their rareness. The team has successfully generated cancer organoids from rare pediatric cancers such as Pleuropulmonary blastoma, NUT-midline carcinoma, Desmoplastic Small Round Cell Tumor and several pediatric liver malignancies. These cancer organoids will be used in drug screening projects to identify drugs that may cure these otherwise deadly cancer entities. Next to direct processing of the tissues, we viably freeze all brain and rare tumor samples, creating a biobank of live material to be used for single cell sequencing, organoid derivation and patient-derived xenograft (PDX) establishment.

Research group of Hans Clevers. The Clevers group started in 2016 in the Princess Máxima Center. Clevers is also PI at the Hubrecht Institute for Developmental Biology and Stem Cell research. From 2015 - June 2019 he has been CSO of the Princess Máxima Center.

Top 3 publications

- Gehart, H., van Es, J. H., Hamer, K., Beumer, J., Kretzschmar, K., Dekkers, J. F., . . . Clevers, H. (2019). Identification of Enteroendocrine Regulators by Real-Time Single-Cell Differentiation Mapping. *Cell*. PMID: 30712869

- Kopper, O., de Witte, C. J., Lõhmussaar, K., Valle-Inclan, J. E., Hami, N., Kester, L., . . . Clevers, H. (2019). An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity. *Nature medicine*. PMID: 31011202

- Artegiani B, van Voorthuijsen L, Lindeboom RGH, Seinstra D, Heo I, Tapia P, López-Iglesias C, Postrach D, Dayton T, Oka R, Hu H, van Boxtel R, van Es JH, Offerhaus J, Peters PJ, van Rheenen J, Vermeulen M, Clevers H. (2019) Probing the Tumor Suppressor Function of BAP1 in CRISPR-Engineered Human Liver Organoids. *Cell Stem Cell* PMID: 31130514

Total Princess Máxima Center affiliated publications 2019: 28
Total external publications 2019: 17

External PhD thesis defenses

- Else Driehuis, October 2019, Hubrecht Institute
  Organoïden als model voor fundamenteel en translationeel oncologisch onderzoek. Promotores: Prof. dr. J.C. Clevers and prof. dr. P.J. van Diest, co-promotor: dr. S. Willems

External Funding

No grants

Awards

Keio Medical Science Prize of the Keio University (Japan)
Hans Clevers

Citation Laureate, Web of Science Group
Hans Clevers

Research group dr. Jarno Drost

Started in November 2016

Members of the Drost Group

Co-PI
De Krijger, R. (Ronald)

PhD student
Custers, L.M.C. (Lars)
Calandrini, C. (Camilla)
Paassen, I.E.K. (Irene)

MD/PhD student
Ooms, A.H.A.G. (Ariadne)

Postdoc
Buhl, J. (Juliane)
Fumagalli, A. (Arianna)
Morales-Rodriguez, F. (Francisco)

Technician
Haan, S. de (Sanne)
Derakhshan, S. (Sepideh)

Graduate students
Morsink, C.D. (Chloé)
Mathijsen, L. M. (Luka)
Wezel, M.D. van (Marloes)

In addition Drost supervises one PhD student, shared with other Máxima research groups.

The Drost group studies the molecular mechanisms underlying the development of childhood kidney and rhabdoid tumors. They aim to understand how these tumors develop during embryonic development and to find new, less toxic, therapeutic opportunities. Drost and his team combine innovative pre-clinical models (such as organoids) with state-of-the-art (single-cell) genomics and transcriptomics, barcode lineage tracing, and high-throughput drug screens to study fundamental processes driving tumor growth and therapy resistance.

Research Lines

Research lines include (but are not limited to):

- Establishment of organoid models from kidney and rhabdoid (renal, extrarenal and brain) tumors. At the time of writing, the Drost group established organoids from >100 patients (Calandrini et *al.*, *Nature Communications*, accepted for publication).

- Organoids as a platform for high-throughput drug screens. We identified several drugs that inhibit rhabdoid tumor growth *in vitro* and *in vivo*. Mechanistic studies are currently ongoing. Moreover, Drost aims to develop cell-based (immuno)therapies (with Janda group).

- The Drost group uses organoids in combination with genome-editing tools (e.g. CRISPR screens) to study the signaling pathways underlying high-risk cases.

- Genetic tracing to find genetic heterogeneity within Wilms tumors. Drost uses clonally-expanded organoids grown from different regions of a Wilms tumor and matching healthy kidney tissue for genome sequencing to reveal phylogenetic relations.

- Identify cellular origin of renal and rhabdoid tumors. Using genetic tracing and single-cell transcriptomics on healthy and tumor tissues (with Holstege group), Drost aims to identify healthy counterparts for several renal tumor subtypes (manuscript in revision & manuscript in preparation).

- Metabolic profiling of renal and rhabdoid tumors to identify metabolic vulnerabilities.

- Identification of mutational signatures predicting genetic predisposition and therapy sensitivity in cancer (with Van Boxtel and Kuiper groups).

The organoid facility is embedded in the Drost group, which involves supporting organoid-based projects by facilitating quality-tested conditioned media, growth factors and know-how.

Top 3 Publications 2019

- Coorens, T.H.H., Treger, T.D., Al-Saadi, R., Moore, L., Tran, M.G.B., Mitchell, T.J., Tugnait, S., Thevanesan, C., Young, M.D., Oliver, T.R.W., Oostveen, M., Collord, G., Tarpey, P.S., Cagan, A., Hooks, Y., Brougham, M., Reynolds, B.C., Barone, G., Anderson, J., Jorgensen, M., Burke, G.A.A., Visser, J., Nicholson, J.C., Smeulders, N., Mushtaq, I., Stewart, G.D., Campbell, P.J., Wedge, D.C., Martincorena, I., Rampling, D., Hook, L., Warren, A.Y., Coleman, N., Chowdhury, T., Sebire, N., Drost, J., Saeb-Parsy, K., Stratton, M.R., Straathof, K., Pritchard-Jones, K., Behjati, S. Embryonal precursors of Wilms tumor. *Science* 2019 Dec 6;366(6470):1247-1251. doi: 10.1126/science.aax1323. PMID: 31806814; PMCID: PMC6914378.

- Bleijs, M., van de Wetering, M., Clevers, H., Drost, J.#. Xenograft and organoid model systems in cancer research. *EMBO Journal* 2019;38(15):e101654. doi:10.15252/embj.2019101654

- Schutgens, F., Rookmaaker, M.B., Margaritis, T., Rios, A., Ammerlaan, C., Jansen, J., Gijzen, L., Vormann, M., Vonk, A., Viveen, M., Yengej, F.Y., Derakhshan, S., de Winter-de Groot, K.M., Artegiani, B., van Boxtel, R., Cuppen, E., Hendrickx, A.P.A., van den Heuvel-Eibrink, M.M., Heitzer, E., Lanz, H., Beekman, J., Murk, J.L., Masereeuw, R., Holstege, F., Drost, J., Verhaar, M.C., Clevers, H. Tubuloids derived from human adult kidney and urine for personalized disease modeling. *Nature Biotechnology* 2019 Mar, 37 (3): 303 – 313.

Total Princess Máxima Center affiliated publications 2019: 3

External Funding

Dutch Cancer Society (KWF)
Defining mutational footprints predicting genetic predisposition and therapy sensitivity in cancer
KWF 12090
Together with Ruben van Boxtel and Roland Kuiper
€732.626

Oncode
Junior investigator programme
€600.000

European Commission
Deciphering the cellular origin and evolution of malignant rhabdoid tumors
ERC starting grant
€1.500.000

Children Cancer-free Foundation (KiKa)
Feasibility study for organoid-directed treatment of relapsed Wilms tumors
KiKa 360
€125.000

Nikai4Life
Searching for combination therapy against rhabdoid tumors
€120.000

Awards

Junior Investigator Programme
Jarno Drost

ERC starting grant
Jarno Drost

Research group prof. dr. Martha Grootenhuis

Started in September 2015

Members of the Grootenhuis Group

PhD student
Joosten, M.M.H. (Mala)
Erp, L.M.E. van (Loes)
Peersmann, S.H.M. (Shosha)
Engels-van Bindsbergen, K.L.A. (Kelly)
Hooft van Huijsduijnen, E.A.B. (Eva)
Kooten, J.A.M.C. van (Jojanneke)

MD/PhD student
Bon, S.B.B. (Sebastian)
Rensen, N. (Niki)
Steur, L.M.H. (Lindsay)

Postdoc
Schepers, S.A. (Sasja)
Litsenburg, R.R.L. van (Raphaële)
Maurice-Stam, h. (Heleen)
Wouters, R.H.P. (Roel)

Researcher
Huizinga, G.A. (Gea)

Research nurse
Legemaat, M. (Monique)

In addition Grootenhuis supervises eleven PhD students, shared with other Máxima research groups or external partners.

The research of prof. dr. Martha Grootenhuis focuses on the psychosocial consequences (outcome) of childhood cancer. By this emotional consequences of both children with cancer as well as their family members is meant. It includes stress due to medical treatment (medical traumatic stress), emotional-behavioral outcomes (e.g. anxiety and depression), but also quality of life and sleep. We are not only examining these effects during treatment, but also afterwards, until the adult age. How vulnerable children, adolescents and (young) adults, parents and siblings are, depends on risk and protective factors. We study 1) the (neuro)psychosocial outcomes and quality of life; 2) risk and protective factors and 3) the development, feasibility, effectiveness and implementation of psychosocial interventions.

Research Lines

Relevance to society

We know children with cancer face challenges during their development into adulthood on all quality of life (QoL) domains that is physical, emotional, social and cognitive functioning. Systematic attention for these domains was lacking in clinical practice. A solution could be to fill in questionnaires about QoL and discuss this during a visit with the doctor. With the development of the KLIK portal this has become possible. Research has even shown that when doctors discuss QoL, children and parents are more satisfied and the feel their voices are heard, and they feel more in control. The research team of Grootenhuis has been responsible for the development and implementation in pediatric oncology care.

KLIK fits in with the development of value-driven care, joint decision-making and patient-centered care, making it an effective intervention to improve care for children with cancer and their parents. The KLIK portal is proven to be an effective and implementable way to catch up with PROMs in the consultation room and with that, the communication between practitioner and child and parents. With the mission of the Princess Máxima Center, curing children with a good Quality of Life, this portal is the proven standard to work with.

Top 3 publications

- Bult, M. K., van Bindsbergen, K. L. A., Schepers, S. A., de Ridder-Sluiter, H. G., Verhaak, C. M., van Litsenburg, R. R. L., . . . Grootenhuis, M. A. (2019). Health-Related Quality of Life of Adolescents with Cancer During the First Year of Treatment. *Journal of adolescent and young adult oncology*. PMID: 31268387

- Rensen, N., Steur, L. M. H., Schepers, S. A., Merks, J. H. M., Moll, A. C., Grootenhuis, M. A., . . . van Litsenburg, R. R. L. (2019). Concurrence of sleep problems and distress: prevalence and determinants in parents of children with cancer. *European journal of psychotraumatology*. PMID: 31448065

- Steur, L. M. H., Kaspers, G. J. L., Van Someren, E. J. W., Van Eijkelenburg, N. K. A., Van der Sluis, I. M., Dors, N., . . . Van Litsenburg, R. R. L. (2019). Sleep-wake rhythm disruption is associated with cancer-related fatigue in pediatric acute lymphoblastic leukemia. *Sleep*. PMID: 31889198

Total Princess Máxima Center affiliated publications 2019: 25

External PhD thesis defenses

- Hedy van Oers, September 2019, University of Amsterdam
  Parent Reported Outcomes. Measure development and implementation in pediatric clinical practice. Promotor: Prof. dr. M.A. Grootenhuis, co-promotor: Dr. L. Haverman

- Bas Vaarwerk, November 2019, University of Amsterdam
  Optimizing rhabdomyosarcoma treatment. Assessing the role of imaging and local treatment in pediatric rhabdomyosarcoma. Promotores: Prof. dr. H.N. Caron and prof. dr. R.R.R. van Rijn, co-promotores: Dr. J.H.M. Merks and prof. dr. M.A. Grootenhuis

- Els van Meijel, November 2019, University of Amsterdam
  Invisible injuries. Posttraumatic stress in children, adolescents and their parents following accidents. Promotores: Prof. dr. R.J.L. Lindauer and prof. dr. M.A. Grootenhuis, co-promotor: Prof. dr. F. Boer

External Funding

Children Cancer-free Foundation (KiKa)
Parent's understanding, views and experiences concerning genomic sequencing in a pediatric renal cancer research setting
KiKa 339
€91.854

Children Cancer-free Foundation (KiKa)
Risk and protective factors of long-term psychosocial Late effects in adult survivors of childhood: the DCOG LATER Psycho-oncology study
KiKa 361
€279.557

Princess Máxima Center Foundation
Brussen in Beeld
€15.000

Awards

Avi Sadeh Memorial Travel Award
Lindsay Steur – supervised by Raphaële van Litsenburg

KNAW Ter Meulen fonds
Niki Rensen - supervised by Raphaële van Litsenburg

Research group prof. dr. Olaf Heidenreich

Started in September 2018

Members of the Heidenreich Group

Co-PI
Vormoor, H.J. (Josef)
Halteren, A.G.S. van (Astrid)

PhD student
Cameron, R.L. (Rachel)
Derevianko, P.K. (Polina)
Rasouli, M. (Milad)
Swart, L.E. (Laura)

Postdoc
Barneh, F. (Farnaz)
Krippner - Heidenreich, A. (Anja)

Technician
Nelson, R.N. (Ryan)
Oort, A.T. van (Anita)

Graduate student
Benthem, F. B. (Floor)
Smink, J.S. (Job)

The general vision of prof. dr. Olaf Heidenreich is to translate novel insights into molecular mechanisms of leukemic fusion genes into innovative therapeutic concepts with the ultimate aim to improve both cure rates and quality of patient life.

Research Lines

Functional dissection of leukemic transcriptional networks
In depth analysis of RNA-seq data upon RUNX1/ETO perturbation experiments showed that this transcription factor controls the composition of a variety of mRNAs via regulating the choice of transcriptional start sites and alternative splicing of transcripts leading to the expression of protein isoforms. Ongoing experiments investigate the underlying molecular mechanisms by which RUNX1/ETO controls alternative splicing and how protein isoforms contribute to leukaemic maintenance.

Therapeutic targeting of fusion genes by siRNA delivery
Heidenreich and his team have developed a liposomal siRNA delivery approach to target leukemic fusion transcripts in both leukaemic cell lines and patient-derived primary AML cells both in tissue culture and *in vivo*. They are further optimizing our liposomal formulations for improved association, *in vivo* retention and uptake by leukemic cells and tissues. Furthermore, they are exploring possible combinations of liposomal siRNA formulations with drugs in patient-derived material both in tissue culture and in immunodeficient mice.

An *ex vivo* platform for determining patient-specific treatment responses
Unlike leukemic cell lines, patient-derived leukemic cells still represent the clonal heterogeneity present in a patient. However, the major bottleneck for a more general application of patient-derived cells in drug testing is their low viability in tissue culture. Heidenreich has addressed this challenge by establishing a human bone marrow-derived MSC platform. To that end, he established several MSC-derived iPSC lines that can be differentiated into different niche components including MSC-associated lineages and endothelial cells. His group is currently employing these platforms for establishing novel drug combinations in PDX in tissue culture, to rapidly validate patient-specific drug sensitivities and to investigate the communication between AML cells and bone marrow stroma.

Publications 2019

- Assi, S. A., Imperato, M. R., Coleman, D. J. L., Pickin, A., Potluri, S., Ptasinska, A., . . . Bonifer, C. (2019). Subtype-specific regulatory network rewiring in acute myeloid leukemia. *Nature genetics*. PMID: 30420649

- Schoenherr C, Wohlan K, Dallmann I, Pich A, Hegermann J, Ganser A, Hilfiker-Kleiner D, Heidenreich O, Scherr M, Eder M. (2019) Stable depletion of RUNX1-ETO in Kasumi-1 cells induces expression and enhanced proteolytic activity of Cathepsin G and Neutrophil Elastase. *PLoS One*. PMID: 31826021

Total Princess Máxima Center affiliated publications 2019: 2
Total external publications 2019: 4

External PhD thesis defenses

- Shalini Sankar, September 2019, Newcastle University
  The Mechanistic Role of the Splicing Factors PHF5A and SF3B1 in Leukaemia Propagation and Self-Renewal. Promotor: Prof. dr. Olaf Heidenreich, co-promoter: Prof. dr. Josef Vormoor

- Milene Dalmina, August 2019, Newcastle University
  Development of New Nanocarriers for the Delivery of siRNA against RUNX1/ETO gene for the Treatment of Acute Myeloid Leukaemia. Promoter: Dr. David Fulton, co-promoter: Prof. dr. Olaf Heidenreich

- Asmida Isa, May 2019, Newcastle University
  Functional Characterisation of SLC2A3 and PFKP in t(8;21)-positive Acute Myeloid Leukaemia. Promoter: Prof. dr. Olaf Heidenreich.

- Yuzhe Shi, October 2019, Newcastle University
  T-cell checkpoint pathways modulate cell cycle and steroid response in T-cell Acute Lymphoblastic Leukaemia. Promoter: Dr. Frederik van Delft, co-promoter: Prof. dr. Olaf Heidenreich

External Funding

Children Cancer-free Foundation (KiKa)
Killing the culprit: direct and indirect therapeutic targeting of a leukaemic fusion gene
KiKa 329
€1.447.818

Research group prof. dr. Marry van den Heuvel-Eibrink

Started January 2015

Members of the van den Heuvel Group

PhD student
Groenendijk, A. (Alissa)
Kooi, A.L.F. van der (Anne-Lotte)
Meijer, A.J.M. (Annelot)
Raymakers - Janssen, P.A.M.A. (Paulien)
Velde, M.E. van de (Mirjam)
Verwaaijen, E.J. (Emma
Wood, A.M.L. (Amber)
MD/PhD student
Atteveld, J.E. van (Jenneke)
Beek, J.N. van der (Justine)
Bertrums, E.J.M. (Eline)
Diepstraten, F.A. (Robin)
Hol, J.A. (Janna)
Hulst, A.M. van (Annelienke)
Mul, J. (Joeri)
Oosterom, N. (Natanja)
Perk, M.E.M. van der (Madeleine)
Pluimakers, V.G. (Vincent)
Researcher
Bos, A.M.E. (Anna)
Postdoc
Hartman, J.E.M. (Annelies)
Psychologist
Gerwen, M.M.A. van (Mathilde)
Project employee
Peer, S.E. van (Sophie)
Graduate student
Holtbach, F.C.E.D. (Fréderique)
Jonkeren, E.A.B. (Els)
Winter, D.T.C. de (Demi)

In addition Van den Heuvel-Eibrink supervises nine group members, shared with other Máxima research groups or external partners.

Prof. dr. Van den Heuvel-Eibrink is appointed as Professor Translational pediatric oncology at Utrecht University. Her translational research is pursued in strong collaboration with the Drost group.

The program comprises two research lines

Renal tumors: Translational Research (biology, survival and toxicity) outcome determinants research, diagnostic innovation (radiology, diagnostic discriminating molecular biomarker identification), oncogenetic characterization research (genotype-phenotype correlation and identification of renal tumor-susceptibility), molecular research (NGS, organoids, and target identification, compound screens), innovative treatment development, in Wilms tumors, as well as rare non-Wilms tumors. Van den Heuvel-Eibrink is the international co-chair of the SIOP-RTSG group that is currently initiating optimal treatment and research development in more than 50 countries (four continents) through the UMBRELLA protocol, and chairs the SIOP-RTSG office that is located in the Princess Máxima Center (embedded in the TDC), that is connected to the trial center in the NKI, Amsterdam. The SIOP-RTSG group strongly collaborates the COG- RTSG, through the HARMONICA initiative (Chairs: prof. dr. Geller (USA) and prof. dr. Van den Heuvel-Eibrink (SIOP-other continents)).
Renal tumor research

- **Implementation of innovative diagnostics** (DWI-MRI, and immunotherapy, artificial intelligence in radiology and pathology, and evidence-based guidance of genetic counseling) in clinical practice for children with renal tumors
- **Identification of predisposed children and prevention of renal tumors and the impact of NGS on families**
- **Target identification and implementation of novel treatment strategies** in clinical practice to enhance outcome and to avoid toxicity, translational PDO-projects with compound screens, immunotherapy, innovative radiotherapy (IMRT), support of innovative surgery (3D modelling and IF) development of first phase clinical trials with novel targeted drugs (including immunotherapy) for rare adverse prognostic subgroups, including relapsed renal tumors in conjunction with the international field.

Quality of cure and toxicity research: This research line is directed to the identification of (genetic) determinants of early and late toxicity of childhood cancer, with a special focus on renal- and ototoxicity, and including endocrine toxicity, and trials to enhance quality of care and survival. This program includes international surveillance guideline development, creation of prediction models and intervention studies.

- To prove **feasibility** of standard surveillance programs for **toxicity** on a national level of childhood cancer patients and survivors.
- To identify genetic, life style and clinical (treatment related) risk factors and to **create prediction models** for treatment related ototoxicity, gonadal function, kidney function and endocrine impairment, to optimize surveillance strategies.
- To create and implement successful strategies for **prevention** and early (during treatment) **intervention** of dexamethasone related neurocognitive impairment, renal toxicity, ototoxicity, metabolic syndrome, female gonadal fertility (OTC), and bone toxicity, supported by clinical studies and preclinical (mouse) models.
- Follow-up of children from mothers with Cancer in Pregnancy (CIP)

Top 3 publications

- Clemens et *al.*, (2019). Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. *Lancet Oncol*. PMID: 30614474
- Schutgens et *al.*, (2019). Tubuloids derived from human adult kidney and urine for personalized disease modeling. *Nat Biotechnol*. PMID: 30833775
- van Atteveld et *al.*, (2019). Prediction of Low and Very Low Bone Mineral Density Among Adult Survivors of Childhood Cancer. *J Clin Oncol*. PMID: 31169453

Total Princess Máxima Center affiliated publications 2019: 48

Successfully Defended Theses

Princess Máxima Center / Utrecht University

- Eva Clemens, March 2019
  Clinical and genetic determinants of ototoxicity during and after childhood cancer. Promotor: Prof. dr. M.M. van den Heuvel-Eibrink, co-promotores: dr. M. van Grotel and dr. A. de Vries
- Natanja van Oosterom, October 2019
  (Epigenetic) and biological determinats of methotrexate induce mucositis in children with ALL. Promotores: Prof.dr. M.M. van den Heuvel-Eibrink and prof. dr. R. Pieters, co-promotor: Dr. S.Heil
- Ariadne Ooms, November 2019
  Wilms Tumor Molecular Unraveling. Promotor: Prof. dr. M.M. van den Heuvel-Eibrink, co-promoteres: Dr. J. Drost and dr. R de Krijger

External PhD defenses

- A.L. van der Kooi, October 2019, Erasmus University Rotterdam
  Gonadal Late effects during and after childhood cancer. Promotores: Prof. dr. J.Laven and prof. dr. M.M. van den Heuvel-Eibrink

External Funding

Princess Máxima Center Foundation
PAREL – Preserving ovARian function through cryoprEservation and informing girLs with cancer about infertility due to gonadotoxic treatment
€75.790

Awards

SIOP young investigator award October 2019
Jenneke Atteveld

Research group prof. dr. Jan Hoeijmakers

Started in October 2017

Members of the Hoeijmakers Group

PhD student
Birkisdottir, M.B. (Maria Bjork)
Boogaard, W.M.C. van den (Winnie)
Tang, Z. (Ziqin)

Postdoc
Vermeij, W.P. (Wilbert)
Vonk, W.I.M. (Willianne)

Bio-informatician
Ozinga, R.A. (Rutger)

Technician
Rijksen - Kamp, Y.M.A. (Yvonne)
Smit, K. (Kimberly)

Graduate student
Duizer, L. (Lisanne)
Gilhuis, C.N. (Niek)
Heijmink, L. (Lisanne)
Koevorden, J. W. van (Willemijn)
Schneemann, S.S. (Sara)
Siebrand, C.J. (Cynthia)

Research Lines

The Hoeijmakers group studies genomic instability and its consequences for cancer and aging, two aspects highly relevant for treatment and Quality of Life of children with cancer. Massive DNA damage, the main cause of genome instability, occurs continuously in every cell and has two main consequences. First, it can lead to mutations and chromosomal aberrations that facilitate carcinogenesis including evolution to malignancy and eventually therapy resistance, frustrating effective cure. Hence, DNA damage is of utmost importance for all aspects of cancer and cancer treatment. Secondly, DNA damage triggers cellular death, senescence and overall functional decline. Indeed, the Hoeijmakers group discovered that DNA damage is a main (if not the) driver of aging in mammals. Importantly, in cancer therapy, DNA damage is used to kill tumor cells by most common anti-cancer treatment modalities. Based on the link with aging, we predicted that DNA-damaging chemo- and radiotherapy would accelerate aging. This expectation was confirmed in long-term cancer survivors (e.g. LATER study).

Recently, in mice and cell systems we found that dietary restriction (DR) and short-term fasting induce a surprisingly powerful, protective 'survival response', which suppresses growth and prioritizes resilience mechanisms (e.g. anti-oxidant systems). This response is also constitutively activated in our DNA repair deficient, progeroid mouse mutants and most likely serves to delay accelerated aging. Importantly, the team discovered that DR reduces DNA damage and thereby delays aging. Additionally, preconditioning by DR or short-term fasting strongly protect from ischemia reperfusion injury, caused by massive oxygen radicals upon blood supply after long ischemia in surgery.

Using the mouse models for human DNA repair syndromes the Hoeijmakers team intends to obtain full understanding of the intriguing 'survival response' and derive rational-based nutritional and pharmacological strategies, that promote healthy aging, postpone dementias and reduce the severe, short- and long-term side effects of chemo- and radiotherapy and thereby improve quality of life particularly in children with cancer. Although the approach involves overall health, the group pays specific attention to cognitive and other features of neurodegeneration as they found neurofunctioning to benefit disproportionally from nutritional interventions.

Top 3 publications

- Alyodawi K*, Vermeij WP*, Omairi S, Kretz O, Hopkinson M, Solagna F, Joch B, Brandt RMC, Barnhoorn S, van Vliet N, Ridwan Y, Essers J, Mitchell R, Morash T, Pasternack A, Ritvos O, Matsakas A, Collins-Hooper H, Huber TB, Hoeijmakers JHJ, Patel K. (2019). Compression of morbidity in a progeroid mouse model through the attenuation of myostatin/activin signalling. *Journal of cachexia, sarcopenia and muscle*. PMID: 30916493

- Milanese C, Bombardieri CR, Sepe S, Barnhoorn S, Payán-Goméz C, Caruso D, Audano M, Pedretti S, Vermeij WP, Brandt RMC, Gyenis A, Wamelink MM, de Wit AS, Janssens RC, Leen R, van Kuilenburg ABP, Mitro N, Hoeijmakers JHJ, Mastroberardino PG. (2019). DNA damage and transcription stress cause ATP-mediated redesign of metabolism and potentiation of anti-oxidant buffering. *Nature communications*. PMID: 31653834

- Lans H, Hoeijmakers JHJ, Vermeulen W, Marteijn JA. (2019). The DNA damage response to transcription stress. Nature reviews. *Molecular cell biology*. PMID: 31558824

Total Princess Máxima Center affiliated publications 2019: 7
Total external publications 2019: 1

External PhD defences

- Maria Vougioukalaki, February 2019, Erasmus MC
  Impact of Endogenous Damage on Adult Stem Cells and Tissue Homeostasis. Promotor: Prof. dr. J.H.J. Hoeijmakers, co-promotor: Dr. Joris Pothof

- Marjolein Baar. June 2019, Erasmus MC
  Promotor: Prof.dr. J.H.J. Hoeijmakers, co-promotores: Dr. Joris Pothof, dr. Peter L.J. de Keizer

External Funding

Oncode
Measuring functional metabolism in pediatric oncology
€100.000

Campagneteam Huntington
Understanding the pathogenicity of mutant Huntingtin conformations and their modulation by the chaperonin TRiC/CCT
€250.000

Research group prof. dr. Frank Holstege

Started in January 2016

Members of the Holstege Group

PhD student
Demartino, J.R. (Jeff)
Jonge, W.J. de (Wim)
Meister, M.T. (Michael)

Postdoc
Margaritis, A. (Thanasis)

Bioinformatician
Candelli, T. (Tito)
Visser, L.L. (Lindy)
Lijnzaad, P. (Philip)

Technician
Bodewes, E.C.R. (Eduard)
Frazer, E.A. (Ewa)
Poplonski, T.M. (Tomasz)
Groot Koerkamp, M.J.A. (Marian)

Labmanager/technician
Brok, M.O. (Mariel)

Graduate student
Boulogne, F. (Floranne)

Research Lines

Genomics, gene expression and soft tissue sarcoma organoids for pediatric cancer

In 2019 the main focus of the Holstege group has been further establishing its two main lines of research: studies of the cellular heterogeneity of pediatric tumors (in collaboration with many groups) and studying soft tissue sarcomas with tumor organoid models (with Max van Noesel, Hans Merks, Rutger Knops, Uta Flucke and Sheila Terwisscha van Scheltinga). Highlights include the development of a method to automatically identify cell type in single cell data, aquisition of an additional single cell RNA sequencing platform and expansion of this team to deal with the many projects that have been started. Initial drug screens (with Jan Molenaar) on a panel of soft tissue sarcoma tumoroids that the Holstege group has generated, has also proven successful and they are pleased to have shown that these new cancer models can be used to generate clinically relevant results. In addition to organoids derived from embryonal and alveolar rhabdomyosarcomas the panel now also includes tumor organoids derived from even rarer types of soft tissue sarcomas.

Besides these research lines, Holstege and his group are also heavily involved in research infrastructure. Besides the single cell genomics facility (leader Thanasis Margaritis), this includes the flow cytometry and FACS facility (leader Tomasz Poplonski), coordination of genomic data generation for research and precision medicine (with Patrick Kemmeren and Bastiaan Tops) and further establishment of the Princess Máxima Center biobank (Holstege is chair of the project team). Although characterized as infrastructure, these projects are yielding important results in their own right. A great example includes the almost 50 percent increase in clinically relevant fusion transcripts being detected in the first cohort of patients now routinely being analyzed by RNAseq in the diagnostic lab: an early sign that the investments in institute-broad, multi-disciplinary approaches are starting to pay off.

Top 3 publications 2019

- Aristizabal, M. J., Dever, K., Negri, G. L., Shen, M., Hawe, N., Benschop, J. J., . . . Kobor, M. S. (2019). Regulation of Skn7-dependent, oxidative stress-induced genes by the RNA polymerase II-CTD phosphatase, Fcp1, and Mediator kinase subunit, Cdk8, in yeast. The Journal of biological chemistry. PMID: 31506296

- de Kanter, J. K., Lijnzaad, P., Candelli, T., Margaritis, T., & Holstege, F. C. P. (2019). CHETAH: a selective, hierarchical cell type identification method for single-cell RNA sequencing. Nucleic acids research. PMID: 31226206

- Schutgens, F., Rookmaaker, M. B., Margaritis, T., Rios, A., Ammerlaan, C., Jansen, J., . . . Clevers, H. (2019). Tubuloids derived from human adult kidney and urine for personalized disease modeling. Nature biotechnology. PMID: 30833775

Total Princess Máxima Center affiliated publications 2019: 4

External Funding

-

Research group dr. Esther Hulleman

Started in 2018

Members of the Hulleman Group

PhD student
Das, A.I. (Arvid)
Haumann, R. (Rianne)
Mackelenbergh, M.G. van (Madelaine)
Meel, H. (Hans)
Metselaar, D.S. (Dennis)

Postdoc
Bianco, J.I. (John)

Technician
Goulding, J.R. (Joshua)
Waranecki, P.M. (Piotr)

Graduate student
Huizen, G.V. ter (Giovanna)

Research in the Hulleman laboratory focuses on highly aggressive brain tumors, such as pediatric high-grade glioma, diffuse midline glioma (DMG), ependymoma, and atypical teratoid rhabdoid tumors (ATRT). The Hulleman laboratory performs translational research, which comprises the development of novel treatment modalities, the establishment of primary tumor models, drug screens, liquid biopsies, and the histological and molecular characterization of tumor material for the identification of novel drug targets.

Research Lines

In the past year, the Hulleman group has focused on the design of combinational therapies that may be implemented in the clinic. By using compounds that cross the blood-brain-barrier (BBB) at concentrations that are achievable in blood plasma, the team aims to facilitate pre-clinical findings to the patient. The presence of an intact BBB often is a major hurdle in the treatment of malignant brain tumors, hampering the delivery of chemotherapy to the tumor. One example of BBB-penetrable compounds that they found to act synergistically is the combination of the natural compound celastrol with the classic chemotherapeutic carboplatin. Celastrol inhibits the repair of DNA damage that is induced by carboplatin in pediatric high-grade glioma, thus leading to tumor cell death (Metselaar *et al.*, 2019). Other examples include a combinational treatment for ATRTs (Meel *et al.*, 2019) and DMG. For the latter, the group combined the AXL inhibitor bemcentinib with panobinostat, an inhibitor of histone deacetylases (HDACs). This combination reverses the intrinsic therapy resistance of histone mutated DMG cells, and may therefore be used as a backbone for multiple treatment modalities, sensitizing tumor cells to other forms of therapy. As both bemcentinib and panobinostat cross the BBB, this combination may also target diffusely growing/migrating tumor cells that are often difficult to reach. Since the results seem very promising, Hulleman and her team are currently investigating the possibilities to use this combination in a clinical trial for the treatment of histone mutated DMG.

Top 3 publications

- Meel, M. H., Guillén Navarro, M., de Gooijer, M. C., Metselaar, D. S., Waranecki, P., Breur, M., . . . Hulleman, E. (2019). MEK/MELK inhibition and blood-brain barrier-deficiencies in atypical teratoid/rhabdoid tumors. *Neuro-oncology*. PMID: 31504799

- Meel, M. H., Kaspers, G. J. L., & Hulleman, E. (2019). Preclinical therapeutic targets in diffuse midline glioma. *Drug resistance updates: reviews and commentaries in antimicrobial and anticancer chemotherapy*. PMID: 31202081

- Metselaar, D. S., Meel, M. H., Benedict, B., Waranecki, P., Koster, J., Kaspers, G. J. L., & Hulleman, E. (2019). Celastrol-induced degradation of FANCD2 sensitizes pediatric high-grade gliomas to the DNA-crosslinking agent carboplatin. *EBioMedicine*. PMID: 31735550

Total Princess Máxima Center affiliated publications 2019: 3
Total external publications 2019: 2

External Funding

Children Cancer-free Foundation (KiKa)
Enabling preclinical immunotherapeutic studies for pediatric diffuse midline glioma
KiKa 358
€512.131

Stichting Semmy
Identification of therapeutic targets for diffuse midline glioma by functional genetic screening
€670.000

Research group dr. Claudia Janda

Started in September 2018

Members of the Janda Group

PhD Student
Gosselink, I.F. (Irene)
Koelewijn, J. (Jannet)

Technician
Jansen, L. (Lisa)

Graduate Student
Bonnink, M.Y.S. (Shira)
Rijt, F.L.H. van (Fenna)

Osteosarcoma (OS) is the most malignant bone tumor in children and young adults, accounting for around 3 percent of all childhood cancers. It is an aggressive tumor that frequently develops metastases in lung and other tissues. Current standard treatment consists of pre- and post-operative chemotherapy and surgical resection, which however is ineffective in some patient subgroups, in particular in patients with metastatic disease.

Research Lines

Despite extensive efforts to enhance current or identify new OS therapies, treatment and survival rates have remained unchanged over the past decades. Major bottlenecks for the development of better therapies are 1) the limited understanding of the molecular mechanisms underlying normal bone development and OS evolution, and 2) the lack of representative OS models that can be utilized for mechanistic studies, drug target identification and drug development. In collaboration with Profs. Frank Holstege and Hans Merks, the Janda laboratory has initiated some core projects to address these limitations:

- The Janda group characterizes OS tumor cells and the tumor (immune) micro-environment of diagnostic biopsies, resections and metastases by single-cell RNA sequencing and imaging approaches, and establish organoid cultures, forming the basis of mechanistic studies, small molecule drug screens and experiments to identify new targets for antibody and cell-based therapies.

- Janda and her team establish protein and antibody-related technologies at the Princess Máxima Center to facilitate the identification of cancer associated cell surface antigens as new targets for antibody and cell-based therapies and the development of target-specific antibodies. In collaboration with the laboratories of prof. dr. Frank Holstege, prof. dr. Monique den Boer and dr. Jarno Drost, Janda focuses on projects related to bone and soft tissue sarcoma, leukemia and kidney tumors.

- The team characterizes normal bone development and regeneration throughout the entire life-span of mice by single-cell RNA sequencing and imaging approaches, forming a conceptual framework for OS evolution and interrogating adverse effects of pediatric cancer treatments on bone development.

Publications 2019

- Dang, L. T., Miao, Y., Ha, A., Yuki, K., Park, K., Janda, C. Y., . . . Baker, D. (2019). Receptor subtype discrimination using extensive shape complementary designed interfaces. *Nature structural & molecular biology*. PMID: 31086346

Total Princess Máxima Center affiliated publications 2019: 1

External Funding

Stichting Loeka
Wetenschappelijk onderzoek naar osteosacroom
€76.000

Research group dr. Patrick Kemmeren

Started in January 2016

The Kemmeren group is a computational biology group that uses a combination of bioinformatics and systems biology to understand pediatric cancer. They have developed a unique combination of expertise in bioinformatics, gene expression profiling and molecular-genetic interactions.

Research Lines

Since joining the institute, the Kemmeren group has developed several research lines including investigating mechanisms of genetic interactions in pediatric cancer, classification of tumor subtypes using DNA methylation data and improving structural variation detection in pediatric cancer. Through collaborations with St. Jude Children's research hospital, Memphis, Tenessee, and DKFZ in Heidelberg, Germany, Kemmeren and his team have been able to generate a comprehensive map of genetic interactions in pediatric cancer and are validating the computational predictions in collaboration with research groups in the Princess Máxima Center. They also have extensive experience in setting up and coordinating bioinformatics infrastructures such as high-performance computing, workflow management systems as well as data sharing and collaboration facilities. Within the institute, Kemmeren coordinates a number of institute-wide activities centered around the use of big data for research and diagnostic purposes. These include the bioinformatics expertise core, translational bioinformatics, biobank bioinformatics and research data integration platform. The Kemmeren group has setup a unique platform shared between diagnostics and research that allows us to quickly transform key findings and technological improvements in research to diagnostic applications. Through the involvement in both basic research projects as well as in translational projects, they are committed to improving our understanding of pediatric cancer biology, while at the same time also directly benefiting patient care by implementing computational analyses in routine diagnostics.

Members of the Kemmeren Group

PhD student
Belzen, I.A.E.M. van (Ianthe)

Postdoc
Daub, J.T. (Josephine)
Hehir - Kwa, J.Y. (Jayne)
Kerstens, H.H.D. (Hinri)

Bioinformatician
Geer - de Jong, E. van de (Ellen)
Kersjes, D.J.E. (Denise)
Picandet, L.P. (Laurène)
Run, C.P.A. van (Chris)
Willemsen, A.M. (Marcel)

Technician
Verhagen, K. (Kim)

Graduate student
Bon, C.A.W.M. (Chantal)

Top 3 publications

- Amini, S., Jacobsen, A., Ivanova, O., Lijnzaad, P., Heringa, J., Holstege, F. C. P., . . . Kemmeren, P. (2019). The ability of transcription factors to differentially regulate gene expression is a crucial component of the mechanism underlying inversion, a frequently observed genetic interaction pattern. *PLoS computational biology*. PMID: 31083661

- Jacobsen, A., Ivanova, O., Amini, S., Heringa, J., Kemmeren, P., & Feenstra, K. A. (2019). A framework for exhaustive modelling of genetic interaction pattern using Petri nets. *Bioinformatics* (Oxford, England). PMID: 31845959

- Weidema, M. E., van de Geer, E., Koelsche, C., Desar, I. M. E., Kemmeren, P., Hillebrandt-Roeffen, M. H. S., . . . Group, P. (2020). DNA Methylation Profiling Identifies Distinct Clusters in Angiosarcomas. *Clinical cancer research : an official journal of the American Association for Cancer Research*. PMID: 31562204

Total Princess Máxima Center affiliated publications 2019: 5

External Funding

Princess Máxima Center Foundation
Biobank IT project
€100.000

NWO-ENW
Organization BioSB2020
€10.000

Research group dr. Marcel Kool

Started in September 2019

Members of the Kool Group

PhD student
Odé, Z. (Zelda)
Roosen, M.M. (Mieke)

The research program of dr. Marcel Kool is focused on pediatric brain tumors. Kool is a world-leading expert in especially ependymoma and embryonal brain tumors, which include medulloblastomas (MB), atypical / teratoid rhabdoid tumors (ATRTs), embryonal tumors with multilayered rosettes (ETMRs), and other previously called primitive neuroectodermal tumors of the central nervous system (CNS-PNETs), and has published several landmark papers for each of these different entities. Kool has been working at the Hopp Children's Cancer Center (KiTZ) in Heidelberg, Germany, since April 2011 and since September 2019 he is also working at the Princess Máxima Center. While his group in Heidelberg continues to work on the genomic and epigenomic analyses of these different entities and how to translate (epi)genomic findings to the clinic, his new group at the Princess Máxima Center is focused on modeling pediatric brain tumors using organoids. Working at these two centers has the advantage that expertise, data and other knowledge can be integrated quickly in order to move even faster.

Research Lines

Over the years Kool and others have shown with multi-omic analyses of large series of many different brain tumor entities that each of these different brain tumor entities contain multiple distinct molecular subtypes that not only differ genetically and epigenetically, but also demographically and clinically. Identification of all these distinct molecular subtypes has led to a better insight what is driving these tumors and revealed that some distinct subtypes respond well to current therapies while others do much worse. However, even when treatments are effective, they often come with a cost as patients may suffer long-term from serious side effects caused by the intensive treatments. In order to develop better, less toxic, and more subtype specific treatments, many new and well-characterized preclinical models representing all the different molecular subtypes are needed to test new therapeutic strategies. Many different preclinical models exist, including cell lines, organoids, and xenograft models, and each have their advantages and disadvantages. In Heidelberg the Kool group has established already a large repertoire of xenograft models for *in vivo* testing, but they do not represent (yet) all the different molecular subtypes as some do not grow (that well) in mice.

The focus of the Kool group in Utrecht will be to set up a biobank of molecularly well-characterized brain tumor organoid models representing all the different molecular subtypes of embryonal tumors and ependymomas, using all the knowledge and expertise on organoids that exists at the Princess Máxima Center. Tumor organoids will be either derived directly from tumor material, or by manipulating normal brain (cerebral and cerebellar) organoids generated from different lines of iPSCs made from patient derived blood cells. These different brain tumor organoid models will be used in drug screens to find new ways how to treat these tumors and they will be used to study the development of the brain tumors in more detail using single cell genomic analyses.

Publications 2019

- Dyberg, C., Andonova, T., Olsen, T. K., Brodin, B., Kool, M., Kogner, P., . . . Wickstrom, M. (2019). Inhibition of Rho-Associated Kinase Suppresses Medulloblastoma Growth. *Cancers*. PMID: 31888022

- Korshunov, A., Okonechnikov, K., Sahm, F., Ryzhova, M., Stichel, D., Schrimpf, D., . . . von Deimling, A. (2019). Transcriptional profiling of medulloblastoma with extensive nodularity (MBEN) reveals two clinically relevant tumor subsets with VSNL1 as potent prognostic marker. *Acta neuropathologica*. PMID: 31781912

Total Princess Máxima Center affiliated publications 2019: 2
Total external publications 2019: 38

External PhD thesis defenses

- Jens-Martin Hübner, June 2019, Hopp *Childrens Cancer Center (KiTZ) Heidelberg*. Promotor: Prof. Stefan Pfister, co-promotor: dr. Marcel Kool

- Sander Lambo, October 2019, Hopp Childrens Cancer Center (KiTZ) Heidelberg. Promotor: Prof. Stefan Pfister, co-promotor: dr. Marcel Kool

External Funding

-

Research group prof. dr. Leontien Kremer

Started in February 2017

External Funding

European Commission
PanCare Follow Up
€711.875

Children Cancer-free Foundation (KiKa)
The EARLY pilot study: Early detection of cARdiovascuLar toxicitY in children with cancer
KiKa 365
Together with Annelies Mavinkurve-Groothuis
€124.981

European Commission
Harmonic
Together with Cécile Ronckers
€10.000

Children Cancer-free Foundation (KiKa)
Risk and protective factors of long-term psychosocial Late effects in adult survivors of childhood: the DCOG LATER Psycho-oncology study
KiKa 361
Together with Martha Grootenhuis
€279.557

Research Lines

(Epidemiological) Survivorship LATER research
The Kremer group is focusing on getting more insight in risk factors (including genetic and environmental), optimal diagnostic tests, and (preventive) treatment for health problems in survivors of childhood cancer. Prof. dr. Leontien Kremer and het team are experts in research on subsequent tumors, overall burden of diseases, cardiac diseases, aging, lifestyle and radiation-associated health problems after treatment of childhood cancer. Research is embedded in local, national, and international networks. Furthermore, the group focuses on innovations in survivorship care. Kremer is the project leader of the Dutch LATER cohort study including 6000 survivors and is the coordinator of the international PanCareFollowUp Study on follow-up care.

Evidence-Based pediatric oncology
Systematic reviews and guidelines combine knowledge and recommendations for patient care. The Kremer group hosts the editorial base of Cochrane Childhood Cancer (www.childhoodcancer.cochrane.org) for Cochrane systematic reviews on childhood cancer (internet journal IF 7,755). The group is providing knowledge to develop guidelines in pediatric oncology, on surveillance of childhood cancer survivors (www.IGHG.org), on fertility preservation, palliative care and other areas in pediatric oncology.

Outcome research
A new focus of the Kremer group will be on the development of outcome indicators of care. This will be done in collaboration with parents, children, health care professionals, insurance companies, and policy makers. These outcome indicators can be used to evaluate care based on the concepts of Value-Based Medicine nationally and internationally.

Examples of relevance for society are:
- Collaboration with survivors: an example is the yearly LATER for LATER symposium.
- International leadership in systematic reviews and survivorship guidelines. Guidelines include a balance between benefits and harms. Specials efforts are made to include the costs in the decision-making process.
- The group is leading a PanEuropean grant (PanCareFollowUp) focusing on implementation of optimal survivorship care in Europe, including an evaluation of the cost-effectiveness of survivorship care in Europe, and promotion of a healthy lifestyle using ehealth.

Top 3 publications

- Feijen, E. A. M., Leisenring, W. M., Stratton, K. L., Ness, K. K., van der Pal, H. J. H., van Dalen, E. C., . . . Kremer, L.C, Chow, E. J. (2019). Derivation of Anthracycline and Anthraquinone Equivalence Ratios to Doxorubicin for Late-Onset Cardiotoxicity. *JAMA oncology*. PMID: 30703192

- Kok, J. L., Teepen, J. C., van der Pal, H. J., van Leeuwen, F. E., Tissing, W. J. E., Neggers, S. J. C. M. M., . . . Group, D.-L. S. (2019). Incidence of and Risk Factors for Histologically Confirmed Solid Benign Tumors Among Long-term Survivors of Childhood Cancer. *JAMA oncology*. PMID: 30920605

- Teepen, J. C., Kok, J. L., Kremer, L. C., Tissing, W. J. E., van den Heuvel-Eibrink, M. M., Loonen, J. J., . . . Group, D.-L. S. (2019). Long-Term Risk of Skin Cancer Among Childhood Cancer Survivors: A DCOG-LATER Cohort Study. *Journal of the National Cancer Institute*. PMID: 30802904

Total Princess Máxima Center affiliated publications: 27

External PhD thesis defences

- Erik Loeffen, 3 april 2019, UMCG
  Perfect pitstops: Towards evidence-based supportive care in children with cancer. Promotores: Dr. W Tissing and prof. dr. L. Kremer, co-promotor: Dr. Marianne van de Wetering

- Judith Kok, 2 oktober 2019, Amsterdam UMC locatie AMC
  Radiation exposure assessment and risk of subsequent tumors in childhood cancer survivors. Promotores: Prof. dr. L. Kremer and prof. dr. F. van Leeuwen, co-promotor: Dr. C. Ronckers

Members of the Kremer group

Co-PI
Ronckers, C.M. (Cécile)
Pluijm, S. (Saskia)
PhD student
Hazewinkel-Beijer, J.G.M. (Josien)
Kok, J.L. (Judith)
Leerink, J.M. (Jan)
Merkx, R. (Remy)
Reedijk, A.M.J. (Ardine)
Streefkerk, N. (Nina)
Teunenbroek, K.C. van (Kim)
Verbruggen, L.C. (Lisanne)
Wang, Y. (Yuehan)
MD/PhD student
Baat, E.C. de (Esmee)
Kalsbeek, R.J. van (Rebecca)
Postdoc
Feijen, E.A.M. (Lieke)
Teepen, J.C. (Jop)
Datamanager
Geelhoed, J.C. (Jolande)
Heus-Colijn, G.C.G. de (Gerda)
Linden, F. van der (Felice)
Mantici, A. (Aslihan)
Schippers, M.C.J. (Monique)
Medical researcher
van Dalen, E.C. (Elvira)
Mulder, R.L. (Renée)
Research nurse
Beilen - Wisselink, I.R.A. van (Inge)
Project employee
Noorman, J.K. (Jos)
Graduate student
Baysinger, M.A. (Madeline)
Donker, C (Casper)
Dungen, L.D.W. van den (Lauren)
Steensma, P.C. (Philippa)
Tap, S.C. (Stephan)
Thomas, M (Mirre)
Van Rijn D.G.M. (Daphne)
Werner, E.E. (Eefje)

In addition Kremer supervises eight PhD students, shared with other Máxima research groups or external partners.

Research group dr. Roland Kuiper

Started in November 2016

Members of the Kuiper Group

Co-PI
Jongmans, M.C.J. (Marjolijn)

PhD student
Antic, Z. (Zeljko)
Bakhuizen, J.J. (Jette)
Engelen, N. van (Nienke)
Weijers, D.D. (Dilys)
Yu, J. (Jiangyan)

Postdoc
Lelieveld, S.H. (Stefan)
Sabatella, M. (Mariangela)

Bioinformatician
Bhaskaran, R.B. (Rajith)
Dijk, F. van (Freerk)
Morgado, L. (Lionel)

Technician
Reijmersdal, S.V. van (Simon)
Bladergroen, R.S. (Reno)

Graduate student
Bosbeek, C.M. van (Charlotte)
Wilke, Y.F.A.B. (Yano)

Research Lines

Childhood Cancer Genetics and Predisposition
In an estimated 8-10 percent of children with cancer, heredity has played a decisive role. Recognition of cancer susceptibility in children with cancer is of high clinical significance, as it may lead to modifications in treatment protocols, cancer surveillance for early detection of second primary malignancies, and information of cancer risks and cancer surveillance for family members. Our group studies the genetics of childhood cancer from molecular (Kuiper, PI) to clinical (Jongmans, co-PI) perspective, in order to improve recognition of cancer predisposition, reveal its prevalence and identify novel genes and mechanisms that play a role. Kuiper's research group focuses on rare individual cases of cancer in children with a suspected but unexplained underlying genetic cause, as well as on unselected cohorts of cancer subtypes, like renal cancer. In a recently started a KWF-funded project (collaboration with PIs Van Boxtel and Drost) we aim to define the typical mutational consequences in childhood cancer patients with underlying DNA repair syndromes with the aim to improve recognition of these patients based on tumor sequence data and evaluate risks and opportunities for treatment in these children. With this translational research they aim to increase the knowledge and awareness of hereditary cancer and thereby improve the care for children with hereditary forms of cancer.

Mutational mechanisms in pediatric ALL
Pediatric ALL typically has a low mutational load, but Kuiper and his team recently found that a substantial proportion of relapses shows a hypermutation phenotype, caused different mutational mechanisms. They hypothesize that these active mutational mechanisms may drive (relapsed) ALL, and could have consequences for treatment. The team currently studies this phenomenon further in a large series of relapses, including second relapses, in order to explore the causative mechanisms, and investigate the causes and consequences of leukemia therapy regimens on hypermutation phenotypes.

Top 3 publications

- Diets, I. J., Hoyer, J., Ekici, A. B., Popp, B., Hoogerbrugge, N., van Reijmersdal, S. V., . . . Metzler, M. (2019). TRIM28 haploinsufficiency predisposes to Wilms tumor. *International journal of cancer*. PMID: 30694527

- Diets, I. J., van der Donk, R., Baltrunaite, K., Waanders, E., Reijnders, M. R. F., Dingemans, A. J. M., . . . Jongmans, M. C. J. (2019). De Novo and Inherited Pathogenic Variants in KDM3B Cause Intellectual Disability, Short Stature, and Facial Dysmorphism. *American journal of human genetics*. PMID: 30929739

- Grolleman J.E., de Voer R.M., Elsayed F.A., Nielsen M., Weren R.D.A., Palles C., ..., Kuiper R.P. (2019) Mutational Signature Analysis Reveals NTHL1 Deficiency to Cause a Multi-tumor Phenotype. *Cancer Cell*. 35:256-266. PMID: 30753826

Total Princess Máxima Center affiliated publications 2019: 8

External Funding

Children Cancer-free Foundation (KiKa)
The contribution of genetic predisposition to pediatric cancer: a study integrating extensive phenotyping and state of the art genotyping
KiKa 355
Together with Hans Merks
€595.935

Dutch Cancer Society (KWF)
Defining mutational footprints predicting genetic predisposition and therapy sensitivity in cancer
KWF 12090
Together with Ruben van Boxtel and Jarno Drost
€732.626

Dutch Cancer Society (KWF)
Mechanisms of hypermutation in relapsed acute lymphoblastic leukemia in children and implication for treatment
KWF 12482
€550.403

Research group dr. Frank van Leeuwen

Started in June 2018

BCP-ALL is the most common pediatric cancer. Although cure rates are approaching 90 percent, (relapsed) ALL remains one of the leading causes of cancer related death in children. Moreover, current treatment protocols are associated with serious toxicities, particularly in high risk or relapsed ALL patients.

Members of the van Leeuwen Group

PhD student
Butler, M. (Miriam)
Cox, W.P.J. (Willem)
Tee, T.M. (Trisha)
Vervoort, B.M.T. (Britt)

Postdoc
Lahri, M.R.S. (Rachita)
Meer, L.T. van der (Laurens)

Technician
Dahaoui, A. (Ahmed)
Ingen Schenau, D.S. van (Dorette)
Jongeneel, C.H. (Lieneke)

Graduate student
Jansen, S.S. (Shelby)
Ruiter, T.J.J. (Titine)

Research Lines

Improving Asparaginase therapy response by targeting Bruton Tyrosine Kinase (BTK)
Asparaginase (ASNase) is a key component in the treatment of acute lymphoblastic leukemia (ALL). A poor response to ASNase is associated with increased relapse risk. Using a CRISPR/Cas9 based kinome screen, we discovered that the targeted agent Ibrutinib, strongly sensitizes leukemic cells to ASNase induced apoptosis both *in vitro* and in pre-clinical models using patient-derived xenografts. Our ultimate aim is to introduce ASNase/ibrutininb combination therapies in the clinic.

This is a project funded by the Dutch Cancer Foundation (KWF).

Defining specific vulnerabilities in relapsed TP53 mutated acute lymphoblastic leukemia
Deletions or mutations affecting tumor suppressor TP53 predict a very poor response to therapy in relapsed ALL. We study the effects of targeted TP53 mutations or deletions in well defined ALL cell line models to determine how these affect gene expression and response to different treatments. This project involves a collaboration with prof.dr. Peter Hoogerbrugge (pediatric oncologist) and members of IntReALL, a pan European study group aimed at improving the treatment and outcome of relapsed ALL.

Improving therapy response in *IKZF1* deleted leukemia
Aberrations affecting the B-lymphoid transcription factor *IKZF1* occur in about 15 percent of pediatric ALL patients and are associated with increased relapse risk. By genetic modeling in ALL cell lines we found that (single copy) *IKZF1* loss confers resistance to glucocorticoids as well as to the antimetabolite cytarabine (AraC). Similarly, in patient-derived xenografts, *IKZF1* loss was strongly associated with resistance to these drugs. The aim of this project is to use reverse genetic sceens to identify drugs that can overcome therapy resistance in *IKZF1* deleted ALL. We expect that these experiments will allow us to optimize treatment of *IKZF1*-deleted ALL by enhancing the therapeutic efficacy glucocorticoids or antimetabolites.

This is a project funded by the Dutch Cancer Society (KWF) and Children Cancer-free Foundation (KiKa).

Publications 2019

- Vrenken, K. S., Vervoort, B. M. T., van Ingen Schenau, D. S., Derks, Y. H. W., van Emst, L., Grytsenko, P. G., . . . van Leeuwen, F. N. (2019). The transcriptional repressor SNAI2 impairs neuroblastoma differentiation and inhibits response to retinoic acid therapy. *Biochimica et biophysica acta. Molecular basis of disease*. PMID: 31862304

Total Princess Máxima Center affiliated publications 2019: 1
Total external publications 2019: 1

External PhD thesis defenses

- Rene Marke, August 2019, Radboud UMC
  Role of tumor suppressor IKZF1 in leukemia development and therapy resistance. Promotor: Prof. dr. P. Hoogerbrugge, co-promotor: Dr. F. van Leeuwen and dr. B. Scheijen

External Funding

Dutch Cancer Society (KWF)
Mechanisms of hypermutation in relapsed acute lymphoblastic leukemia in children and implication for treatment
KWF 12482
Together with Roland Kuiper
€550.403

Awards

Tom Voûte Award
Kirsten Vrenken

Research group prof. dr. Leendert Looijenga

Started in October 2018

Members of the Looijenga Group

PhD student
Lobo, J.L. (João)
Sriram, S.S. (Sruthi)
Timmerman, D.M. (Dennis)

Postdoc
Lahri, M.R.S. (Rachita)

Visiting fellow
Spiller C. (Cassy)

Technician
Gillis, A.J.M. (Ad)

Graduate student
Berg, A.I.S. van den (Annette)
Remmers, T.L. (Tessa)
Veenstra, J.C. (Charlotte)

Germ cell tumors (GCTs) have been considered a highly heterogeneous group of neoplasms. Prof. dr. Leendert Looijenga and his team developed an updated classification system, encompassing all variants of GCTs, included into seven defined types. Application of this system will secure proper diagnosis, facilitating optimal clinical care as well as performance of effective scientific studies. However, there are still a number of clinical challenges.

Research Lines

The challenges relate to optimal (first) diagnosis and subsequent follow-up. The first is linked to identification of risk factors, while the latter requires informative tools preventing over- and undertreatment, with minimal side effects. Therefore, improved risk assessment per patient will be highly beneficial. Defined informative biomarkers have been actively applied in a clinical setting, both for histological evaluation as well as liquid biopsy analyses. These include AFP, hCG (and LDH), although significant limitations exist, both regarding sensitivity and specificity. As such, identification of more informative biomarkers is of utmost importance (both during under surveillance and systemic treatment). The Looijenga group actively contributed to this field, and demonstrated that other molecular biomarkers are of additional value. These include a defined set of microRNAs (i.e., miR-371-3 family), as well as XIST expression and its promoter demethylation. Of specific interest is that these are both informative for GCT diagnosis and follow-up, as well as evaluation of the presence of spermatogenesis (i.e. alternative read-out of Johnsen score). This supports the close similarities between normal (embryonic) development and GCTs, based on which we classify GCTs as developmental cancers. The expression profile of miR-371-3 and miR-885-5p, both interestingly counteractively regulating the TP53 pathway (suppression vs activation), is found to determine formation of (mature) teratoma. This is of clinical impact for optimal decision making during clinical follow-up (patent application filed). Activities are in line with goals of patient support groups (https://dsdnederland.nl/ & https://zaadbalkanker.nl/), and embedded in the Master and PhD programs UMCU.

Top 3 publications

- Lobo, J., Gillis, A. J. M., van den Berg, A., Dorssers, L. C. J., Belge, G., Dieckmann, K.-P., . . . Looijenga, L. H. J. (2019). Identification and Validation Model for Informative Liquid Biopsy-Based microRNA Biomarkers: Insights from Germ Cell Tumor In Vitro, *In vivo* and Patient-Derived Data. Cells. PMID: 31847394

- Lobo, J., Nunes, S. P., Gillis, A. J. M., Barros-Silva, D., Miranda-Gonçalves, V., Berg, A. v. d., . . . Looijenga, L. H. J. (2019). XIST-Promoter Demethylation as Tissue Biomarker for Testicular Germ Cell Tumors and Spermatogenesis Quality. Cancers. PMID: 31533343

- Oosterhuis, J. W., & Looijenga, L. H. J. (2019). Human germ cell tumours from a developmental perspective. Nature Reviews Cancer. PMID: 31413324

Total Princess Máxima Center affiliated publications 2019: 10
Total external publications 2019: 15

External Funding

Bergh in het Zadel
Treatment resistance of Germ Cell Tumors
€56 000

Patents 2019

Patent: Methods of typing germ cell tumors

Awards

2nd price best presentation ECP 2019
João Lobo

Tom Voûte award 2019
João Lobo

Research group dr. Jules Meijerink

Started in September 2016

Members of the Meijerink Group

PhD student
Cordo, V. (Valentina)
Kroeze, E. (Emma)
Poort, V.M. (Vera)
Zwet, J.C.G. van der (Jordy)

Postdoc
Canté, K. (Kirsten)
Vroegindeweij, E.M. (Eric)

Technician
Buijs - Gladdines, J.G.C.A.M. (Jessica)
Hagelaar, R. (Rico)
Nulle, M.E. (Marloes)
Smits, W.K. (Wilco)

Graduate student
Gill, I. (Iris)
Graus, L.T.M. (Laura)
Kasliwal, S. (Saumya)
Wijenberg, L. (Laura)

The overall goal of the Meijerink group is to understand the intrinsic and extrinsic pathogenic mechanisms that underlie T-cell malignancies in children. In this research line, the focus is on T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), that both represent diseases of deranged thymocyte development. The generated knowledge aims to develop novel therapeutic strategies for these diseases specifically, but is focused on broader applicability of findings towards other diseases in children and adults.

Research Lines

The Meijerink group has three projects that focus on genetic findings in relation to elucidating pathogenic mechanisms for T-ALL and T-LBL:

- KiKa-295 (Kirsten Canté-Barrett, senior postdoc): This project is focused on the modes of action of the ETP-ALL oncogene MEF2C that we identified before.
- KiKa-244 (Eric Vroegindeweij, former postdoc): In this project the experiments are currently being completed and results are being written down for publication.
- Máxima-2019 (Emma Kroeze, PhD student, started in 2019): The goal of this project is genetic deciphering of T-LBL (co-PI Jan Loeffen)

Two other projects are focused on the mechanisms by IL7 signal transduction mutations that result into steroid resistance, and identification of targeted strategies to restore therapeutic efficacy.

- KiKa-219 (Jordy van der Zwet, PhD student, started in 2016): This project focuses on IL7 signaling mutation in relation to steroid resistance.
- KWF-2016-10355 (Valentina Cordo, PhD student, started in 2017): Phospho-proteomics as prediction tool for treatment using targeted compounds is being investigated.

One project is focused on the role of stromal safe haven niches in therapy resistance, disease dissemination, and relapse in T-ALL and T-LBL.

- KiKa-335 (Vera Poort, PhD student, started in 2019): This project aims at elucidating the thymus niche for T-ALL

Top 3 publications

- Van Der Zwet, J.C.G., Cordo', V., Canté-Barrett, K., Meijerink, J.P.P. Multi-omic approaches to improve outcome for T-cell acute lymphoblastic leukemia patients. *Adv Biol Regul*. 2019 Aug 26:100647. doi: 10.1016/j.jbior.2019.100647.

- Belver, L., Yang, A.Y., Albero, R., Herranz, D., Brundu, F.G., Quinn, S.A., Perez-Duran, P., Alvarez, S., Gianni, F., Rashkovan, M., Gurung, D., Rocha, P.P., Raviram, R., Reglero, C., Cortes, J.R., Cooke, A.J., Wendorff, A.A., Cordo', V., Meijerink, J.P.P., Rabadan, R., Ferrando, A.A. Gata3-controlled nucleosome eviction drives Myc enhancer activity in T-cell development and leukemia. *Cancer Discov*. 2019 Sep 13. pii: CD-19-0471. doi: 10.1158/2159-8290.CD-19-0471.

- De Smedt, R., Peirs, S., Morscio, J., Matthijssens, F., Roels, J., Reunes, L., Lintermans, B., Goossens, S., Lammens, T., Van Roy, N., Touzart, A., Jenni, S., Tsai, Y.C., Lovisa, F., Mussolin, L., Serafin, V., Van Nieuwerburgh, F., Deforce, D., Uyttebroeck, A., Tousseyn, T., Burkhardt, B., Klapper, W., De Moerloose, B., Benoit, Y., Macintyre, E., Bourquin, J.P., Basso, G., Accordi, B., Bornhauser, B. Meijerink, J.P.P, Vandenberghe, P., Van Vlierberghe, P. Pre-clinical evaluation of second generation PIM inhibitors for the treatment of T-cell acute lymphoblastic leukemia and lymphoma. *Haematologica*. 2019 Jan;104(1):e17-e20. doi: 10.3324/haematol.2018.199257. Epub 2018 Aug 3.

Total Princess Máxima Center affiliated publications 2019: 5

External Funding

Children Cancer-free Foundation (KiKa)
Exploring thymus safe haven niches for T-cell acute lymphoblastic leukemia that drives therapy failure and relapse
€102.702

Princess Máxima Center Foundation
T-ALL conference 2020
€60.000

Awards

Fullbright award
Saumya Kasliwal

Research group dr. Hans Merks

Started in May 2019

Members of the Merks Group

PhD student
Hol, M.L.F. (Marinka)
Ewijk, van R. (Roelof)
Morfouace, M. (Michele)
Postema, F.A.M. (Floor)
Tigelaar, L. (Leonie)
Vaarwerk, B. (Bas)

Postdoc
Haveman, L. (Lianne)
Schoot, R. (Reineke)

In addition Merks supervises four PhD students, shared with other Máxima research groups or external partners.

Intr The focus of the Merks group is to answer key clinical questions in pediatric sarcoma treatment with the aim to improve cure and quality of life. As Chair of the European pediatric Soft tissue sarcoma Study Group (EpSSG) and Vice-Chair of the Executive Board of the EuroEwing Consortium (EEC) Merks' aim is to coordinate, design and implement international prospective clinical trials, including translational research, focused on sarcoma across the pediatric and young adult age range. Research in pediatric sarcoma pre-eminently is a multidisciplinary collaboration including a diversity of basic, translational and clinical research partners.

Research Lines

- **The Pediatric Sarcoma Imaging Group aims to design and implement innovative imaging studies to identify early biomarkers that predict outcome in clinical trials and individual patient care, and optimize staging**. This entails a close collaboration with the PROVIDI lab of Alexander Leemans (Imaging Sciences Institute UMCU), Simone ter Horst and Bart de Keizer (Radiology UMCU) and prof. dr. Rick van Rijn (AUMC)

- **Individualized prediction of treatment-induced facial deformities and functional impairments for children with head and neck rhabdomyosarcoma (HN RMS)**. This international (US, Fr, UK) multicenter multidisciplinary project aims to develop a decision support model that enables well-informed shared multimodal treatment decision making based on Adverse Event prediction for individual HN RMS patients.

- **Functional outcome and quality of life after local therapy for bone sarcoma in children.** This multidisciplinary project aims to describe functional outcome and quality of life in bone sarcoma survivors with the ultimate goal to generate a prediction model for local therapy related adverse effects and functional outcome.

- **Recognition of cancer predisposition syndromes (CPS).** The aim is to develop strategies to guarantee recognition of established CPS in childhood cancer patients and identify potential new CPS in collaboration with the Kuiper group and Raoul Hennekam (AUMC).

Top 3 publications

- Bisogno, G., De Salvo, G. L., Bergeron, C., Gallego Melcón, S., Merks, J. H., Kelsey, A., . . . European paediatric Soft tissue sarcoma Study, G. (2019). Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial. The Lancet. *Oncology*. PMID: 31562043

- Vaarwerk, B., Bisogno, G., McHugh, K., Brisse, H. J., Morosi, C., Corradini, N., . . . Merks, J.H.M. (2019). Indeterminate Pulmonary Nodules at Diagnosis in Rhabdomyosarcoma: Are They Clinically Significant? A Report From the European Paediatric Soft Tissue Sarcoma Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. PMID: 30702969

- Vaarwerk, B., Mallebranche, C., Affinita, M. C., van der Lee, J. H., Ferrari, A., Chisholm, J. C., . . . Merks, J. H. M. (2019). Is surveillance imaging in pediatric patients treated for localized rhabdomyosarcoma useful? The European experience. *Cancer*. PMID: 31750944

Total Princess Máxima Center affiliated publications 2019: 15
Total external publications 2019: 5

External PhD thesis defenses

- Bas Vaarwerk, November 2019, University of Amsterdam
  Optimizing rhabdomyosarcoma treatment. Assessing the role of imaging and local treatment in pediatric rhabdomyosarcoma.
  Promotores: Prof. dr. H.N. Caron and prof. dr. R.R.R. van Rijn, co-promotores: Dr. J.H.M. Merks and prof. dr. M.A. Grootenhuis

External Funding

Children Cancer-free Foundation (KiKa)
Diffusion Weighted Imaging; urgent need for surrogate endpoints in pediatric rhabdomyosarcoma.
KiKa 357
€599.872

Children Cancer-free Foundation (KiKa)
The contribution of genetic predisposition to pediatric cancer: a study integrating extensive phenotyping and state of the art genotyping
KiKa 355
Together with Roland Kuiper
€595.935

Research group dr. Jan Molenaar

Started in January 2016

External Funding

Dutch Cancer Society (KWF)
BRCAddict? Harnessing BRCAness as a therapeutic target in high-risk pediatrie solid tumors
€317.415

European Commission
individualizedPaediatricCure: Cloud-based virtualpatient models for precision paediatric oncology
€629.110

ZonMw
Research projects on personalized medicine – smart combination of pre-clinical and clinical research with data and IDT solutions
€150.928

Awards

ODAS prize pediatric oncology
Jan Molenaar

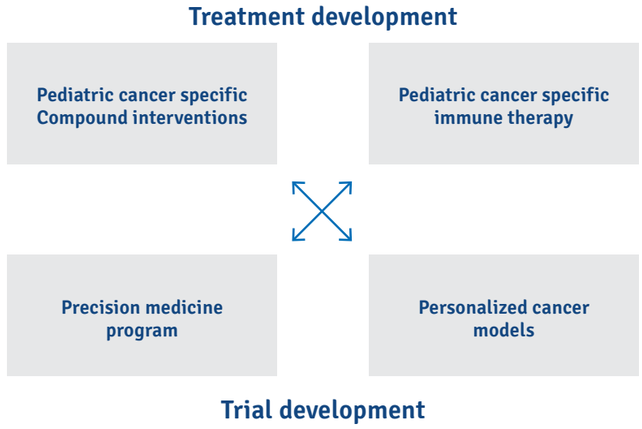
The Molenaar group is specialized in translational research in pediatric solid tumors with a focus on Neuroblastoma. As nine out of ten clinical trials fail, there is a strong need for the development of new targeted drugs that are less toxic and more effective. The Molenaar group aims to 1) identify and validate specific interventions for neuroblastoma and other solid tumors; 2) generate a platform to perform evidence based, targeted compound, combination trials in biomarker positive patients.

Research Lines

For this purpose, the team has developed an experimental pipeline which starts with basic molecular biologic research and ends with implementation of new treatment options for pediatric cancer patients. Crucial in this pipeline is the use of high throughput analysis including WES, WGS, RNAseq, Array profiling, scRNAseq and compound screening. The group is studying ATRX, aberrations in the G1 checkpoint, BCL-2, MDM2, CHK1 as potential interventions. The first steps have been made in the field of immunological interventions by established co-culture systems and single cell RNAseq analysis of the tumor microenvironment.

Molenaar and his team have established a fully automated compound screening facility in the Princess Máxima Center. Other research groups within and outside the Princess Máxima Center can use this facility to identify and validate novel tumor-specific biomarker-drug response associations, identify safe drug combinations, translate large-scale drug screens in tumor organoids into personalized treatment options and identify novel potential target genes by high-throughput perturbation studies using CRISPR/Cas9. To support implementation of targeted therapeutic options our groups has initiated the iTHER precision medicine program for pediatric cancer, which has included 172 patients.

With a close (international) collaboration between pediatric oncologist, surgeons, pathologist, researchers, patients and parents, the Molenaar group strives to make a difference in neuroblastoma patients and use this as a blueprint for other pediatric cancer types.



Top 3 publications

- Herold, S., Kalb, J., Büchel, G., Ade, C. P., Baluapuri, A., Xu, J., . . . Eilers, M. (2019). Recruitment of BRCA1 limits MYCN-driven accumulation of stalled RNA polymerase. *Nature*. PMID: 30894746

- Jones, D. T. W., Banito, A., Grünewald, T. G. P., Haber, M., Jäger, N., Kool, M., . . . Pfister, S. M. (2019). Molecular characteristics and therapeutic vulnerabilities across paediatric solid tumours. Nature reviews. *Cancer*. PMID: 31300807

- Tas, M. L., Nagtegaal, M., Kraal, K. C. J. M., Tytgat, G. A. M., Abeling, N. G. G. M., Koster, J., . . . van Noesel, M. M. (2019). Neuroblastoma stage 4S: Tumor regression rate and risk factors of progressive disease. *Pediatric blood & cancer*. PMID: 31736229

Total Princess Máxima Center affiliated publications 2019: 4

Members of the Molenaar Group

PhD student
Eleveld, T.F. (Thomas)
Gerven, M.R. van (Michael)
Hassan, W.M.K. (Waleed)
Keller, K.M. (Kaylee)
Schubert, N.A. (Nil)
Vernooij, L. (Lindy)

MD/PhD student
Langenberg, K.P.S. (Karin)

Postdoc
Boogaard, T.L. van den (Marlinde)
Dolman, M.E.M. (Emmy)
Szanto, C.L. (Celina)

Bio-informatician
Hooff, S.R. van (Sander)

Technician
Alles, L.K. (Lindy)
Arkel, J. van (Jennemiek)
Essing, A.H.W. (Anke)
Koopmans, B. (Bianca)
Ober, K. (Kimberley)
Schild, G.G. (Linda)

Lab manager
Serbanescu - Ebus, M.E.G. (Marli)

Graduate student
Broeils, L.A. (Luuk)
Handel, K. van den (Kim)
Hoek, J.J.F. van der (Jessica)
Hortensius, M. (Marjolein)
Lankhorst, L.H. (Lina)
Meijs, L.A.M. (Loes)
Pleijte, C.J.H. (Corine)
Strijker, J. G. M. (Josephine)
Vries, I. de (Iris)

Visiting fellow
Chatsisvili, A. (Anna)

Research group dr. Marita Partanen

Started in September 2019

Members of the Partanen Group

Graduate student
Böing, S. (Sanne)

External Funding

-

Children who experience cancer may develop neurocognitive impairments after treatment. Dr. Marita Partanen focuses on the early identification and intervention of these impairments using a combination of neuropsychological and neuroimaging measures. These studies will ultimately lead to potential intervention targets to prevent further neuropsychological difficulties in patients and survivors of cancer.

Research Lines

- **Screening of neuropsychological impairments**
  Cognitive skills may be impacted after treatment for cancer. A change in overall IQ or related domains may impact a child's quality of life during and after treatment. These cognitive deficits may be caused by various factors, but it is possible to detect these deficits early in treatment or survivorship. One aim of our research is to identify neuropsychological impairments in patients aged 2-18 years old using a longitudinal screening battery.

- **Neurobiological bases of neuropsychological impairments**
  Declines in cognitive performance have been associated with white matter impairments in the brain. Other subtle changes can be detected with neuroimaging, which can provide further insight into the neurobiological substrates of and interventions for cognitive deficits. One aim of our research is to determine whether vascular or structural changes in the brain are associated with neurocognitive functioning.

Total external publications 2019: 3

Research group dr. Weng Chuan Peng

Started in December 2019

Members of the Peng Group

-

External Funding

-

Dr. Weng Chuan Peng joined Princess Máxima Center in December 2019 and his group will be focusing on pediatric liver cancer, which is a rare cancer that affects approximately 1 in a million children. In the Netherlands, about 8 – 10 children are diagnosed with liver cancer every year. The most common malignant liver tumors in children are hepatoblastoma (HB) and hepatocelullar carcinoma (HCC). Due to the limited number of patients and biopsy samples, childhood liver cancer has been relatively understudied.

Research Lines

Peng will investigate the biology underlying the various subtypes of HB and HCC, using techniques such as single cell gene expression profiling, spatially-resolved transcriptomics, advanced imaging techniques, tumor organoids and mouse models. For example, he would like to understand why some tumor subtypes are more aggresive than others and respond poorly to chemotherapy. One of the immediate goals is to establish a liver organoid biobank for all patients treated here. These 'tumoroids' will be used for genomic analysis, high throughout screening, antibody screening, and for predicting responses to chemotherapy, among others.

In addition to pediatric liver cancer, Peng's team will study the postnatal development and regeneration of the healthy liver, which can help us better understand how liver tumors arise in children. Having recently demonstrated that murine hepatocyte organoid can be propagated indefinitely and could engraft efficiently in the injured livers of mice (Peng *et al.*, Cell, 2018), he will continue to work towards enabling cell transplantation using *in vitro* expanded human hepatocytes, which may one day replace the need for organ transplant.

At the Princess Máxima Center, Peng's group will be working closely together with clinicians (e.g., Jozsef Zsiros, pediatric oncologist; Ronald de Krijger, pathologist). Through the understanding of tumor pathology, novel treatments for hard-to-cure liver tumor subtypes may be found, which may expose fewer children to chemotherapy, and ultimately cure more children without compromising their quality of life.

Research group prof. dr. Rob Pieters

Started in 2014

Members of the Pieters Group

MD/PhD student
Brigitha, L.J. (Leiah)
Kloos, R. (Robin)
Dekker, L. (Linde)

Pediatric oncologist
Sluis, I.M. van der (Inge)

Graduate student
Averesch, L. (Lysanne)
Binsbergen, A. van (Annelien)
Koning, J. de (Joyce)
Roest, M. (Merel)
Steinhauer, F. (Freya)

The focus of the Pieters group is the development of new, more personalized therapies for childhood acute lymphoblastic leukemia (ALL). Data from preclinical, translational and clinical studies on (epi) genetic abnormalities, from monitoring of early therapy responses by minimal residual disease (MRD) and from therapeutic drug monitoring are implemented and studied in national and international clinical study protocols in childhood ALL.

Research Lines

The goals are:

- to implement cellular therapy, especially CAR-T cells, in the treatment protocols for frontline and relapsed ALL
- to implement monoclonal antibodies in ALL treatment schedules
- to reduce therapy and thereby improving the quality of life for low risk patients selected by genetic features and MRD
- to (further) develop specific therapies for molecular genetic subclasses of ALL
- develop more rational use of chemotherapeutic agents such as asparaginase

The development of improved treatment protocols contributes directly to the mission of the Princess Máxima Center, i.e. a higher cure rate and better quality of life for children with cancer. In 2019, the Pieters groups has started using CD19 directed CAR-T cells in ALL and treated 14 patients with this. International guidelines on the diagnostic work-up of acute leukemia in children were published. For MLL rearranged infant ALL, the team reported the outcome of our large international study, our phase I/II study with a FLT3 inhibitor and published international guidelines how to treat this high risk type of ALL. Also, outcome of international studies on other specific genetic subtypes of ALL in which Pieters and colleagues participated were reported, such as BCR-ABL rearranged ALL and hypodiploid ALL. Therapy for children with ALL with an ABL1 class rearrangement therapy was changed by adding a specific tyrosine kinase inhibitor. Several studies on how to use therapeutic drug monitoring of asparaginases were published leading to a better use of this class of drugs and showing the cost-effectiveness of this approach. In collaboration with preclinical investigators from our institute and from other countries Pieters and his team showed the predictive value of several molecular genetic abnormalities and MRD which led to a new and improved stratification scheme for patients to receive less or more intensive chemotherapy. Finally, in collaboration with several groups studying supportive care and side effects we showed which genetic and clinical parameters influenced the occurrence of side effects such as mucositis, thrombo-embolism, infections and treatment-related mortality.

Top 3 publications

- de Haas, V., Ismaila, N., Advani, A., Arber, D. A., Dabney, R. S., Patel-Donelly, D., . . . Zhang, L. (2019). Initial Diagnostic Work-Up of Acute Leukemia: ASCO Clinical Practice Guideline Endorsement of the College of American Pathologists and American Society of Hematology Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. PMID: 30523709

- Kloos, R., van der Sluis, I. M., Mastrobattista, E., Hennink, W., Pieters, R., & Verhoef, J.-J. (2019). Acute lymphoblastic leukaemia patients treated with PEGasparaginase develop antibodies to PEG and the succinate linker. *British journal of haematology*. PMID: 31883112

- Pieters, R., De Lorenzo, P., Ancliffe, P., Aversa, L. A., Brethon, B., Biondi, A., . . . Valsecchi, M. G. (2019). Outcome of Infants Younger Than 1 Year With Acute Lymphoblastic Leukemia Treated With the Interfant-06 Protocol: Results From an International Phase III Randomized Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. PMID: 312834077

Total Princess Máxima Center affiliated publications 2019: 24

External Funding

-

Research group dr. Anne Rios

Started in March 2017

Members of the Rios Group

PhD student
Beßler, N.B. (Nils)
Ineveld, R.L. van (Ravian)
Vliet, E.J. van (Esmée)
MD/PhD Student
Wellens, L.M.
Postdoc
Alieva Krashennikova, M. (Maria)
Bos, F.L. (Frank)
Dekkers, J.F. (Florijn)
Researcher
Kleinnijenhuis, M. (Michiel)
Technician
Ariese, H.C.R. (Rijndert)
Buchholz, M.B. (Maj-Britt)
Rebel, H.G. (Heggert)
Wezenaar, A.K.L. (Amber)
Lab manager
Johnson, H.R. (Hannah)
Grant writer
Wehrens, E.J.M. (Ellen)
Graduate student
Barrera Román, M. (Mario)
Blank, S. de (Sam)
De la Jara Ortiz, F. (Fàtima)
Ineveld, V.R. van (Victor)
Hoek, M.H. van den (Marjet)
Kooiman, B.A.P. (Berend)
Llibre I Palomar, G. (Gerard)
Martinez Mir, C. (Clara)

The Rios group implements 3D imaging strategies to investigate tumor cell dynamics underlying pediatric cancer progression, as well as the tumor-targeting behavior of cellular immunotherapies. On behalf of the Princess Máxima Imaging Center, the Rios group ensures that the imaging expertise gained will be applied towards understanding and potentially treating all subtypes of childhood cancer. In addition, they develop unique ways to visualize and display their 3D imaging data to inspire the future generation of scientists and engage the public into the fight against cancer.

Research Lines

Dr. Anne Rios and colleagues have further advanced their large-scale single-cell 3D imaging technology, among others for application on both fixed and live organoids. They published their method of fixed organoid imaging in *Nature Protocols* and have successfully contributed this protocol to multiple high impact publications, among others *Cell* 2019. Importantly, using their newest imaging platforms, Rios has gained progress in unravelling the cellular heterogeneity of Wilm's tumors and identified previously unrecognized tumor cell populations (*manuscript in preparation*). By combining 3D imaging with lineage tracing technology, she revealed profound clonal restriction in breast cancer and similar technologies will be applied in a newly developed model of Diffuse Intrinsic Pontine Glioma (DIPG) to characterize tumor cell invasion (*Cancer Cell* 2019).

To better comprehend the extensive and complex information retrieved from single-cell 3D imaging datasets, Rios implemented novel machine-learning-based data mining approaches. These predictive algorithms provide comprehensive, unbiased and in-depth analysis of cell behavior. The team not only applies it to tumor cells, e.g. to characterize and understand tumor cell invasive behavior in the DIPG model, but also to immune cells. Here, they apply 3D imaging and data mining to profile, understand and potentially improve the tumor-targeting behavior of cellular immunotherapies. In doing, so they demonstrated broad potential of an emerging metabolic targeting T cell product for breast cancer and identified specific behavioral patterns related to efficient targeting (*manuscript in preparation*). Rios envisions that the generation of complex 3D imaging data and the right tools to comprehend these large datasets will help to gain fundamental knowledge on cancer, identify new targets for therapeutic intervention and predict effectiveness of cellular therapies in a patient specific manner.

Top 3 publications

- Dekkers, J. F., Alieva, M., Wellens, L. M., Ariese, H. C. R., Jamieson, P. R., Vonk, A. M., . . . Rios, A. C. (2019). High-resolution 3D imaging of fixed and cleared organoids. *Nature protocols*. PMID: 31053799

- Gehart, H., van Es, J. H., Hamer, K., Beumer, J., Kretzschmar, K., Dekkers, J. F., . . . Clevers, H. (2019). Identification of Enteroendocrine Regulators by Real-Time Single-Cell Differentiation Mapping. *Cell*. PMID: 30712869

- Rios, A. C., Capaldo, B. D., Vaillant, F., Pal, B., van Ineveld, R., Dawson, C. A., . . . Visvader, J. E. (2019). Intraclonal Plasticity in Mammary Tumors Revealed through Large-Scale Single-Cell Resolution 3D Imaging. *Cancer cell*. PMID: 30930118

Total Princess Máxima Center affiliated publications 2019: 7

External Funding

European Commission
Deciphering and targeting the invasive nature of Diffuse Intrinsic Pontine Glioma — CANCER INVASION
ERC starting grant
€1.500.000

Oncode
Female Junior Investigator programme
€600.00

St. Baldrick's Foundation
3D imaging innovation: a fresh eye on paediatric cancer
€673.975

Awards

St. Baldrick's Robert J. Arceci International innovation award
Anne Rios

KNAW Faces of Science Award
Lianne Wellens

Research group dr. Ronald Stam

Started in September 2016

Members of the Stam Group

PhD student
Adriaanse F.R.S. (Fabienne)
Schneider, P. (Pauline)
Wander, P. (Priscilla)
Verbeek, T.C.A.I. (Tamara)

Postdoc
Garrido Castro, P. (Patricia)
Jones, L.A. (Luke)
Vrenken, K.S. (Kirsten)

Technician
Rockx - Brouwer, D. (Dedeke)
Arentsen - Peters, T.C.J.M. (Susan)

Although the prognosis for childhood leukemia in general has steadily and progressively been improved over the last decades, there still remain various subtypes of patients that are at high-risk of therapy failure. The 5-year event free survival chances of patients diagnosed with MLL-rearranged acute lymphoblastic and myeloid leukemia, or *NUP98* translocated acute myeloid leukemia, to date remain <40 percent. Hence, current therapeutic regimens clearly are not suitable for these specific patient groups, emphasizing the urgent need for more adequate treatment options for these children.

Research Lines

Using various high-throughput screening approaches, including elaborate drug library screens, drug synergy screens, RNA and whole genome sequencing, CRISPR/Cas9 library screens, single-cell sequencing, microarray and protein array analyses, dr. Ronald Stam and his team are continuously searching for novel therapeutic targets and innovative treatment strategies. In 2019 all of these efforts have resulted in the identification of multiple innovative treatment rationales and potential therapeutics directed against newly recognized vulnerabilities in high-risk types of leukemia such as *MLL*-rearranged ALL and AML. With the majority of the *in vitro* work completed in 2019, Stam is currently setting up refined and comprehensive *in vivo* mouse models in order to validate the potential of identified therapeutic options, striving to provide sufficient preclinical evidence that allows the application of these newly found treatment opportunities in a clinical setting in the near future.

Taken together, Stam strongly believes that this work is of high clinical relevance with great social value. With the current research strategies and ongoing research lines he envisions that, in the next 5 years, they will further strengthen the social and clinical impact of the work by providing full preclinical evidence for multiple treatment options for various high-risk types of pediatric acute leukemia.

Top 3 publications

- Agraz-Doblas, A., Bueno, C., Bashford-Rogers, R., Roy, A., Schneider, P., Bardini, M., . . . Stam, R. W. (2019). Unraveling the cellular origin and clinical prognostic markers of infant B-cell acute lymphoblastic leukemia using genome-wide analysis. *Haematologica*. PMID: 30679323

- Hyrenius-Wittsten, A., Pilheden, M., Falqués-Costa, A., Eriksson, M., Sturesson, H., Schneider, P., . . . Hagström-Andersson, A. K. (2019). FLT3(N676K) drives acute myeloid leukemia in a xenograft model of KMT2A-MLLT3 leukemogenesis. *Leukemia*. PMID: 30953031

- Zwaan, C. M., Söderhäll, S., Brethon, B., Luciani, M., Rizzari, C., Stam, R. W., . . . Pieters, R. (2019). A phase 1/2, open-label, dose-escalation study of midostaurin in children with relapsed or refractory acute leukaemia. *British journal of haematology*. PMID: 30203832

Total Princess Máxima Center affiliated publications 2019: 5

External PhD thesis defenses

- Mark Kerstjens, September 2019, Erasmus Medical Center
  Identification of novel therapeutic strategies against MLL-rearranged acute lymphoblastic leukemia in infants.
  Promotor: Prof. dr. R. Pieters, co-promotor: Dr. R.W. Stam

- Emma Driessen, October 2019, Erasmus Medical Center
  Determinants of clinical outcome in MLL-rearranged infant acute lymphoblastic leukemia. Promotor: Prof. dr. R. Pieters, co-promotor: Dr. R.W. Stam

External Funding

Dutch Cancer Society (KWF)
Identifying novel treatment strategies for infant MLL-rearranged acute lymphoblastic leukemia using comprehensive preclinical modelling
KWF 11863
Together with Frank van Leeuwen
€514.757

Children Cancer-free Foundation (KiKa)
Modelling induction therapy and relapse in high-risk pediatric AMLs using patient-derived xenografts
KiKa 336
€101.888

Research group prof. dr. Henk Stunnenberg

Started in 2019

Members of the Stunnenberg Group

PhD student
Keramati, F. (Farid)
Safadeh E. (Elham)
Yu , Z. (Zhijun)
Zhai, Y.Z. (Yanan)

MD/PhD student
Ruiz Moreno, C.C. (Cristian)

Postdoc
Bos-Spruijt, C.G. (Nelleke)
Brázda, P.B. (Peter)

Bioinformatician
Megchelenbrink, W.L. (Wout)
Singh, P. (Prashant)

Technician
Dirks, R. (Robin)

The basis of the current research of the Stunnenberg group is the genome wide and multi-omics expertise to unveil the (dys)regulation in health and disease. In previous work, Stunnenberg and his team have generated highly detailed profiles of the transcriptomic and epigenomic differences between cell states and how the interplay between distinct regulatory layers shapes the cellular function. The studies on innate immune cells challenged the view that only adaptive immune cells can build an immunological memory. The implications of the findings have ramification for targeting (innate) immune cells in cancer treatment. Tumors are infiltrated by macrophages that are key regulators of the immune system. Tumor-associated macrophages (TAMs) are often turned into tumor supporters instead of tumor adversaries by the tumor. Our knowledge of the factors and mechanisms of this reprogramming is still limited. The expertise in epigenome/transcriptome analysis of cancer and immune cell puts the Stunnenberg group in an ideal position to study the interplay between immune and cancer cells.

The group is applying single cell approaches to generate tens of thousands of single cell RNA transcriptome profiles, targeted single cell mutational analysis and single cell epigenomic profiles. The analysis pipelines and toolboxes at Máxima have successfully been established. The team has further implemented single cell nuclei transcriptome and epigenome protocols with which they can analyze snap frozen tissue that is readily available biobanks. The integrated approach promises to identify rare cell-types such as tumor initiating cells, dissect clonal heterogeneity, define the tumor micro environment (TME) and ultimately the spatial organization of and communication between tumors and tissues.

The caveat of single cell profiling is that cells are taken out of their cellular/tissue context losing information of their location and cell patterns. Stunnenberg has therefore started a collaboration with the Rios group to resolve the spatial resolution to unveil interaction/communication through cell-cell contacts that can lead to reprogramming of immune cells such as macrophages. Rapidly evolving imaging-based technologies, laser capture microdissection and targeted in situ RNA sequencing amongst others are becoming essential tools to determine the communication between (tumor) tissue and their microenvironment to overcome immune suppression.

Brain tumors under scrutiny
Despite the progress made in understanding the molecular underpinnings of DIPG in children, there are many questions that remain unsolved such as the influence of the epigenome in the pathogenesis and the intricate and complex regulatory processes in cancer cells and their interaction with the tumor micro-environment. The Stunnenberg group has successfully generated single nuclei RNA and ATAC profiles from snap frozen tissue. They expect to unveil a genome-wide panorama of the interactions between DNA regulatory elements and gene expression changes that might influence brain tumor progression, maintenance and response to therapy. Stunneberg collaborates with Nilsson (SciLifeLab, Sweden) applying spatial transcriptomic approaches (in situ sequencing) taken the differential expressed, cell type specific genes as the basis to assess the cellular location and the interaction of cancer cells with their stromal and immune cell environment.

AML cohort study
One major limitation for research in childhood AML is the limited availability of comprehensive sequence information from sufficiently sized cohorts. In collaboration with the Zwaan and Heidenreich groups, the Stunnenberg group has started to generate global transcriptome and exome sequencing and bulk RNA-seq data of several hundred samples. This database will constitute an enabling resource for functional studies in childhood AML. It will be steadily amended by whole exome sequencing (WES) and RNA-seq data of new AML patients generated by the Pathology unit of the Princess Máxima Center.

To obtain detailed insights into the composition of the bone marrow prior, during and after treatment, the team performs longitudinal single cell RNA-seq of 70-80 patients at diagnosis, at the end of treatment and, if occurring, at relapse. These experiments will provide novel insights into the treatment response at single cell level and significantly extend our understanding of clonal evolution and treatment-related changes in the composition of the leukemic immune-environment. The analysis of these data will provide an invaluable basis for novel treatment strategies combining chemo-, targeted and immunotherapeutic components.

Publications 2019

- Benedetti, R., Dell'Aversana, C., De Marchi, T., Rotili, D., Liu, N. Q., Novakovic, B., . . . Altucci, L. (2019). Inhibition of Histone Demethylases LSD1 and UTX Regulates ERα Signaling in Breast Cancer. *Cancers*. PMID: 31888209

- Hoeijmakers, W. A. M., Miao, J., Schmidt, S., Toenhake, C. G., Shrestha, S., Venhuizen, J., . . . Bártfai, R. (2019). Epigenetic reader complexes of the human malaria parasite, Plasmodium falciparum. *Nucleic acids research*. PMID: 31728527

Total Princess Máxima Center affiliated publications 2019: 2
Total external publications 2019: 10

External Funding

European Commission
An Integrated Platform for Developing Brain Cancer Diagnostic Techniques
€200.624

The Paradifference Foundation
SDHB-Related Metastatic Pheochromocytomas and Paraganglioma's: Creating the Essentials for Targeted Therapy
€165.617

ZonMw
Epigenetic targeting for prevention of sepsis-induced macrophage tolerance in humans
€800.499
Children Cancer-free Foundation
KiKa Fast track
€621.779

Princess Máxima Center
AML sequencing
€995.000

Research group prof. dr. Wim Tissing

Started in June 2018

Members of the Tissing Group

PhD student
Kok, N.T.M. (Natascha)
Mijnster, R.J.M. (Ruben)
Simon, J.D.H.P. (Julia)
Stavleu, D.C. (Debbie)
Stoutjesdijk, F.S. (Francis)

MD/PhD student
Bury, D. (Didi)
Kooijmans, E.C.M. (Esmee)
Soeteman, M. (Marijn)

Postdoc
IJpma, I. (Irene)
Loeffen, E.A.H. (Erik)

Researcher
Brink, M. van den (Mirjam)
Brüggemann, R.J.M. (Roger)
Santen, H.M. van (Hanneke)

Research student
Havermans, R.C. (Remco)
Kruimer, D.M. (Demi)

The translational supportive care research group started in 2018 and gets its research questions from the multidisciplinary clinical supportive care group, in which pediatric oncologists and many other sub specialists collaborate to optimize supportive care. The goal of the supportive care research group is to do research to improve morbidity and mortality, and also to improve the quality of life of the patients.

Research Lines

Several lines of research have been established so far: infectiology, nutrition, nausea & vomiting and palliative care. Moreover, the Tissing group has been working to get new knowledge as quickly and optimal as possible to the professionals involved in patient care, by developing clinical guidelines, and also by developing ways to evaluate whether the care is of optimal quality.
By developing a research group on the whole spectrum of supportive care, the Princess Máxima Center has a unique position internationally, where in other large centers in the world only specific topics are studied, not in an integrated research group.

The survival of childhood cancer has improved substantially over the last 30 years. This has been reached by more intensive treatment regimens, with the downside that it comes with more side effects. The mission of the Princess Máxima Center is to reach 100 percent survival. This can only be obtained by improving prevention and treatment of treatment-related side effects, since for example in hematological malignancies 50 percent of the mortality is treatment related.
Moreover, when more than 75 percent of the patients survive, it is increasingly important how these patients survive, and what the quality of their lives is during and after treatment. In 2019 we started a new research line on endocrinological side effects of anti-cancer treatment (Dr H. van Santen).
Examples of Tissing's research aiming at improved quality of life are 1. looking for ways to get children home when unnecessarily admitted for febrile neutropenia, 2. looking for better pain management at home, and 3. looking for new ways to treat oral mucositis.
Lastly, the number of papers covering the field of supportive care in pediatric oncology has increased dramatically, making it impossible for all clinicians to read and remember them. Therefore the Tissing group aims to develop clinical practice guidelines, guiding clinicians in there work based on extensive searches of the literature.

Top 3 publications

- Loeffen, E. A. H., Knops, R. R. G., Boerhof, J., Feijen, E. A. M. L., Merks, J. H. M., Reedijk, A. M. J., . . . Tissing, W. J. E. (2019). Treatment-related mortality in children with cancer: Prevalence and risk factors. *European journal of cancer (Oxford, England : 1990)*. PMID: 31569066

- Wardill, H. R., Tissing, W. J. E., Kissow, H., & Stringer, A. M. (2019). Animal models of mucositis: critical tools for advancing pathobiological understanding and identifying therapeutic targets. *Current opinion in supportive and palliative care*. PMID: 30925531

- Ten Berg, S., Loeffen, E. A. H., van de Wetering, M. D., Martens, D. H. J., van Ede, C. M., Kremer, L. C. M., & Tissing, W. J. E. (2019). Development of pediatric oncology supportive care indicators: Evaluation of febrile neutropenia care in the north of the Netherlands. *Pediatric blood & cancer*. PMID: 30318786

Total Princess Máxima Center affiliated publications 2019: 18
Total external publications 2019: 6

External Funding

Children Cancer-free Foundation (KiKa)
The THYRO-Dynamics study: Is the dynamics of thyroid hormones durecng cancer treatment in children adaptive or disruptive? – a prospective evaluation
KiKa 340
€293.097

Research group dr. Lieve Tytgat

Started in September 2016

The research performed by the Tytgat group is translational with focus on pediatric solid tumors. The ultimate aim is to translate basic scientific findings into clinical practice. The Tytgat group has two main focuses; liquid biopsies in pediatric solid tumors and translational studies in neuroblastoma.

Members of the Tytgat Group

PhD student
Hochheuser, C.H. (Caroline)

MD/PhD student
Barneveld, A. van (Astrid)
Blom, A.J. (Thomas)
Lak, N.S.M. (Nathalie)
Verly, I.R.N. (Iedan)
Zogchel, L.M.J. van (Lieke)

Postdoc
Stutterheim, J. (Janine)
Timmerman, I. (Ilse)

Graduate student
Heijerman, L.S.A. (Lotte)
Lurvink, R.C.M. (Roosmarijn)

In addition Tytgat supervises two PhD students, shared with other Máxima research groups.

Research Lines

- **Liquid Biopsies**: dr. Tytgat has formed the **Princess Máxima Center liquid biopsy consortium**, uniting all groups studying (or aiming to study) liquid biopsies, to accelerate clinical implementation of liquid biopsies. Liquid biopsies are easy to obtain, can be sampled sequentially and are not as invasive as primary tumor biopsies. Liquid biopsies van be used to detect circulating tumor derived DNA and RNA (from primary tumor and metastases) for mutation analysis, copy number aberrations (CNA's), gene expression etc. In our center whole exome sequencing (WES) of the primary tumor, RNA sequencing and methylomic analysis are being performed at diagnosis on primary tumor biopsies. The Tytgat group will study these analyses in liquid biopsies in paired samples derived from patients with pediatric solid tumors. First, time of sampling and sampling procedures will be organized and ethical approval will be pursued (PhD A van Barneveld). Next, new (joint) projects will be identified with members of the liquid biopsy consortium.

- Currently **liquid biopsies** are being studied in **rhabdomyosarcoma, neuroblastoma and renal tumors.**

- **Neuroblastoma**: Studies on 123I-MIBG imaging (PhD T Blom), urinary catecholamines (PhD I Verly), liquid biopsies (PhD L van Zogchel), mesenchymal stroma cells (MSCs) and metastasizing neuroblastoma cells (PhD C Hoghheuser, post-doc I Timmerman), surgery in high-risk neuroblastoma (PhD M Jans, co-PI M Wijnen). Clinical aspects of neuroblastoma, (PhD M Tas, PI Van Noesel, co-PI Tytgat).

- **Rhabdomyosarcoma** : Liquid biopsies in rhabdomyosarcoma(PhD N Lak, Post-doc J Stutterheim).

- By collaboration (our center) and international (chair Neuroblastoma liquid biopsy consortium), TRANSSCAN-2 project, and a ITCC/KickCancer project, dr Tytgat accelerates the clinical implementation of liquid biopsies.

Top 3 publications

- Zogchel LMJ*, van Wijk J, Timmerman I, Vo NK, Zappeij-Kannegieter L, deCarolis B, Simon T, van Noesel MM, Molenaar JJ, van Groningen T, Versteeg R, Caron HN, van der Schoot CE, Koster J*, van Nes J*, Tytgat GAM*. (2019) Mesenchymal neuroblastoma cells are undetected by current mRNA marker panels: the development of a specific neuroblastoma mesenchymal MRD panel. *JCO Precision Oncology*

- Kraal, K. C. J. M., Timmerman, I., Kansen, H. M., van den Bos, C., Zsiros, J., van den Berg, H., . . . Tytgat, G. A. M. (2019). Peripheral Stem Cell Apheresis is Feasible Post (131)Iodine-Metaiodobenzylguanidine-Therapy in High-Risk Neuroblastoma, but Results in Delayed Platelet Reconstitution. *Clinical cancer research : an official journal of the American Association for Cancer Research*. PMID: 30314967

- Verly, I. R. N., Leen, R., Meinsma, J. R., Hooijer, G. K. J., Savci-Heijink, C. D., van Nes, J., . . . Tytgat, G. A. M. (2019). Catecholamine excretion profiles identify clinical subgroups of neuroblastoma patients. *European journal of cancer (Oxford, England : 1990)*. PMID: 30798085

Total Princess Máxima Center affiliated publications 2019: 8
Total external publications 2019: 1

External PhD defenses

- Iedan Verly, December 2019, University of Amsterdam
Catecholamine metabolites in neuroblastoma patients.
Promotores: Prof. dr. R. Pieters, prof. dr. R. Wanders,
co-promotores: Dr. G.A.M. Tytgat, dr. A. van Kuilenburg

External Funding

Dutch Cancer Society (KWF)
Advancing Liquid Biopsies for Monitoring and Personalized Treatment of Children with Neuroblastomas (LIOUIDHOPE)
KWF 8352
€277.663

Children Cancer-free Foundation (KiKa)
Improving diagnostic accuracy and patient comfort of neuroblastoma patient imaging by using 18F-mFBG PET-CT instead of 123I-mIBG imaging
KiKa 327
€99.655

Research group dr. Dannis van Vuurden

Started in June 2018

Members of the van Vuurden Group

PhD student
Baugh, J. (Josh)
El-Khouly, F.E. (Fatma)
Hart, E. ‘t (Elvin)
Hoogendijk, R. (Raoull)
Kebede, M.S. (Milen)
Nuijts, M.A. (Myrthe)

Postdoc
Derieppe, M.P.P. (Marc)
Veldhuijzen van Zanten, S.E.M. (Sophie)

Researcher
Ries, M.R. (Mario)

Technician
Besse, H.C. (Helen)
Su, Y. (Yan)

Graduate student
Akkerman, I.R. (Ilse)
Broek, T.J.M. van den (Thijs)

In addition Van Vuurden supervises a PhD student, shared with an external partner.

The focus of the Van Vuurden group, both in preclinical/ translational as in clinical research, is on pediatric high-grade brain tumors, with an emphasis on (1) the development of therapies that cross the *blood-brain barrier* (BBB)and (2) studies on datasets from high-grade brain tumors, such as the European DIPG Registry and national databases.

Research Lines

As the BBB seems to be a major hurdle in the treatment of children (and adults) with brain tumors, research in the group focuses on new possibilities to circumvent or better cross this barrier, using (I) focused ultrasound-mediated (FUS) BBB disruption (collaboration with the department of Imaging Sciences of UMC Utrecht), (II) nanomedicinal solutions and (III) convection-enhanced delivery. Combining these strategies with novel immunotherapeutic approaches, targeting the innate and adaptive immune system, will be investigated to ultimately translate the findings into clinical trials.

Clinical drug delivery studies using convection-enhanced delivery in DIPG are expected to start shortly and for FUS-mediated BBB disruption, the Princess Máxima Center and UMCU have embarked on the acquisition of a clinical system for FUS therapy in patients with brain tumors. Clinical trials using FUS are expected to be initiated soon after this infrastructure is in place, in collaboration with colleagues from the department of neurology/neurosurgery of the UMCU and national and international partners.

Studies using national (IKNL collaboration) and international (SIOPE DIPG Registry) datasets have been initiated to study clinical, radiological and biology data of high-grade brain tumor and DIPG patients respectively, for prediction modelling as well as to detect potential effective therapeutic strategies. With regard to the DIPG registry, research how the processing of legal and organizational requirements, consent and medical necessity-based access-to-data can be automatized, including issues as variability, ownership, data protection and privacy, is ongoing.

Publications

- El-Khouly, F. E., Veldhuijzen van Zanten, S. E. M., Santa-Maria Lopez, V., Hendrikse, N. H., Kaspers, G. J. L., Loizos, G., . . . van Vuurden, D. G. (2019). Diagnostics and treatment of diffuse intrinsic pontine glioma: where do we stand? Journal of neuro-oncology. PMID: 31522324

- van Kooten, J. A. M. C., Maurice-Stam, H., Schouten, A. Y. N., van Vuurden, D. G., Granzen, B., Gidding, C., . . . Grootenhuis, M. A. (2019). High occurrence of sleep problems in survivors of a childhood brain tumor with neurocognitive complaints: The association with psychosocial and behavioral executive functioning. Pediatric blood & cancer. PMID: 31418996

Total Princess Máxima Center affiliated publications 2019: 2
Total external publications 2019: 1

External Funding

-

Research group prof. dr. Marc Wijnen

Started in 2016

Members of the Wijnen Group

PhD Student
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Fitski, M. (Matthijs)
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Lee, Y.T. (York Tien)
Jacovides, M. (Mike)

Graduate student
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Brasz, M.F. (Mechteld)
Brugge, A.H. ter (Annemiek)
El Mansori, I. (Issam)
Prinsse, K. (Kyra)

The surgical research of prof. dr. Wijnen is aimed at reducing morbidity in oncological surgery while at the same time remove tumor tissue more precisely. By improving and implementing imaging techniques to optimize pre- and per-operative visualization of solid tumors in children his team aims to clinically prove these concepts. They also emphasize the role of strict documentation of results to improve surgical care.

Research Lines

- 3D Imaging techniques, 3D printing and augmented reality techniques will present the surgeon with more 3D knowledge before and during the operation, this technique is being developed in conjunction with the Technical University Twente and the RadboudUMC.

- Using fluorescence guided surgery in pediatric oncology is a new field but will be applicable to many types of tumor and surgery. It will help discern healthy from tumor tissue and in this way prevent tumor spill and removal of too much healthy tissue. For this not only general fluorophores will be used, also the development of patient specific fluorophore labelled antibodies are being tested. Wijnen and his team are working on this topic with LUMC.

- Implementing tools for prospective complication registration in solid tumor surgery and access surgery.

- Germ cell tumor surgery results in the Netherlands and the implication of centralization.

- Local and loco regional control in extremity rhabdomyosarcoma.

Top 3 publication 2019

- van den Bosch, C. H., van der Bruggen, J. T., Frakking, F. N. J., Terwisscha van Scheltinga, C. E. J., van de Ven, C. P., van Grotel, M., . . . Wijnen, M. H. W. A. (2019). Incidence, severity and outcome of central line related complications in pediatric oncology patients; A single center study. *Journal of pediatric surgery*. PMID: 30415957

- van Poll, D., Wilde, J., van de Ven, K., Asimakidou, M., Heij, H., & Wijnen, M. (2019). Higher incidence of surgery-related complications in Wilms tumor nephrectomy from clinical records analysis compared with central database registration. *Pediatric blood & cancer*. PMID: 30393993

- Wellens, L. M., Meulstee, J., van de Ven, C. P., Terwisscha van Scheltinga, C. E. J., Littooij, A. S., van den Heuvel-Eibrink, M. M., . . . Wijnen, M. H. W. A. (2019). Comparison of 3-Dimensional and Augmented Reality Kidney Models With Conventional Imaging Data in the Preoperative Assessment of Children With Wilms Tumors. *JAMA network open*. PMID: 31002326

Total Princess Máxima Center affiliated publications 2019: 4

External Funding

-

Research group prof. dr. Michel Zwaan

Started in 2016

Members of the Zwaan Group

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Bertrums, E. (Eline)
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Lindemans, C. (Caroline) MD
Lugt van der, J. (Jasper) MD
Sluis van der, I.M. (Inge) MD
Vormoor, B. (Britta) MD

The Zwaan group focusses on drug development/early clinical trials, with a specific interest in acute myeloid leukemias (AML) and Down syndrome related leukemias, and Zwaan supervises several clinical research fellows and PhD students, together with PIs in the research institute. Zwaan is also also heading the Trial and Data Center (TDC).

Research Lines

1. Early phase and other clinical trials:
The early clinical trial program includes clinical studies of novel agents for children with cancer. Moreover, the group focuses on therapeutic drug monitoring, bioequivalence of pediatric-friendly formulations, and pediatric pharmacokinetics/dynamics. As international coordinating PI, Zwaan leads several academic phase 1-2 'intent to file' studies (e.g inotuzumab ozogamicin and bosutinib). Other investigator-led studies concern blinatumomab for infant ALL (Vd Sluis), crizotinib for ALK-rearranged malignancies (Vd Lugt) and a dendritic vaccination study in AML (Nierkens/Boelens/Lindemans). Population PK of various chemotherapeutic agents, and the PK interaction between aprepitant & steroids in children, is studied together with Nijstad/Huitema/De Vos. In pediatric AML major efforts will go to the PEDAL initiative, which is a relapsed AML master protocol with multiple phase 1-2 arms. Kaspers will lead an upfront study with quizartinib in the NOPHO-DBH consortium. This is in line with the discussions at the AML FORUM meeting which Zwaan hosted in the Netherlands in 2019, where the landscape for pediatric AML early drug development was discussed with all stakeholders including the EMA and FDA. Taken together this will provide the Princess Máxima Center with a European leadership position in the field of clinical research.

2. Acute Myeloid Leukemia (AML):
Pediatric AML is a relatively rare malignancy characterized by significant heterogeneity in genetic aberrations. Despite intensive treatment with chemotherapy and stem cell therapy (SCT) outcome plateaus at ~70 percent overall survival. The main focus of the Zwaan group is on elucidating the genetic background and improving the risk group stratification of pediatric AML.

Zwaan and his team are currently setting up a Máxima Comprehensive Childhood Cancer Center AML group, in which we will embed the currently ongoing preclinical AML efforts, generated by Van Boxtel, Heidenreich, Stam and Stunnenberg, with clinical participation from Vormoor, Goemans, Kaspers and myself. All newly diagnosed AML samples undergo standard sequencing and RNA-seq to detect the relevant molecular abnormalities for appropriate risk-group classification (Tops). MRD tools need further refinement especially for RQ-PCR of fusion genes, next to improvements in flow-cytometry (Sonneveld). The collaboration involves for example investigating the complexity of treatment response by single cell sequencing, studying the role of the immune environment, and targeting fusion genes with novel methods of drug delivery, but also clinical research in ped AML developing immunotherapy, in close collaboration with COG and the Leukemia and Lymphoma Society (PEDAL initiative). Taken together these approaches should lead to better treatment outcome for this disease.

Top 3 publications

- Geoerger, B., Zwaan, C. M., Marshall, L. V., Michon, J., Bourdeaut, F., Casanova, M., . . . Trippett, T. (2019). Atezolizumab for children and young adults with previously treated solid tumours, non-Hodgkin lymphoma, and Hodgkin lymphoma (iMATRIX): a multicentre phase 1-2 study. The Lancet. *Oncology*. PMID: 31780255

- Hijiya, N., Maschan, A., Rizzari, C., Shimada, H., Dufour, C., Goto, H., . . . Sosothikul, D. (2019). Phase 2 study of nilotinib in pediatric patients with Philadelphia chromosome-positive chronic myeloid leukemia. *Blood*. PMID: 31511239

- Sassen, S. D. T., Mathôt, R. A. A., Pieters, R., van Westreenen, M., de Haas, V., Kaspers, G. J. L., . . . Zwaan, C. M. (2019). Population Pharmacokinetics and -Dynamics of Ciprofloxacin Prophylaxis in Pediatric ALL Patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. PMID: 31790556

Total Princess Máxima Center affiliated publications 2019: 12
Total external publications 2019: 8

TDC staff

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Kloes, A.M.J. van der (Marjanka)
Mangert, D. (Dominique)
Marcelis, M. (Maartje)
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Overveld, A.P.J.A. van (Merian)
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Groot de- Kruseman, H. (Hester)
DCOG Data entry
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DCOG Trialmanagement
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Mur, J. (Jaap)
Verwer, F. (Femke)
Vreijling, J. (Jacqueline)
Wiessen, E. (Evelyn)

Appendix

Appendix 1

Clinical Studies
Phase I/II

Open Investigator-sponsored studies
Hemato-oncology

Study	Work title	Setting	Role DCOG-ECTC	Date of opening NL	Status
A Phase I/II study of Azacitidine (Vidaza®) in pediatric patients with newly diagnosed or relapsed high-grade pediatric MDS or JMML: A collaborative EWOG-MDS and ITCC	Vidaza	European	Erasmus MC sponsor	Approved 07-03-2012 First pt. 19-09-2013	Inclusion closed (12-02-2020)
A Phase I/II study of Bosutinib in pediatric patients with newly diagnosed chronic phase or resistant/intolerant Ph+ Chronic Myeloid Leukemia, study ITCC-054/COG AAML1921	Bosutinib (BCHILD)	International	Erasmus MC sponsor	Approved 13-06-2016 First pt. 25-11-2016	Open
A phase I/II study of Inotuzumab Ozogamicin as a single agent and in combination with chemotherapy for pediatric CD22-positive relapsed/ refractory Acute Lymphoblastic Leukemia - Study ITCC-059	Inotuzumab	International	Erasmus MC sponsor	Approved 02-09-2016 First pt. 23-01-2017	Open
A pilot study to test the feasibility, safety and efficacy of the addition of the BiTE antibody Blinatumomab to the Interfant-06 backbone in infants with MLL-rearranged acute lymphoblastic leukemia	Blinatumomab Infant	International	Princess Máxima Center sponsor	Approved 17-10-2017 First pt. 31-07-2018	Open
Identification of pediatric Hodgkin lymphoma biomarkers and novel therapeutic targets	Hodgkin Biomarker	European	Erasmus MC sponsor	Approved 21-07-2016 First pt. 16-11-2016	Open
International multicenter open-label, phase II study to treat molecular relapse of pediatric acute myeloid leukemia with azacitidine	AMoRe2017	European	GPOH sponsor	Approved 06-02-2019	Open
Skeletal complications of profylactic Ciproxin in the treatment of pediatric ALL	MRI-study	National	Erasmus MC sponsor (monocenter)	Approved 16-05-2013 First pt. 09-09-2014	Open

Open Company-sponsored studies
Hemato-oncology

Study	Worktitle	Date of approval in 1st site in NL (Princess Máxima Center)	Status
A Phase II Study of Dasatinib Therapy in Children and Adolescents with Ph+ Leukemia with Resistance or Intolerance to Imatinib (CA180226).	CA180-226	17-09-2009 (27-08-2018)	Open in Princess Máxima Center
A phase II, open-label, non-controlled, intra-patient doseescalation study to characterize the pharmacokinetics after oral administration of eltrombopag in pediatric patients with refractory, relapsed or treatment naïve severe aplastic anemia or recurrent aplastic anemia	CETB Revolade	14-11-2018	Open in Princess Máxima Center
A Randomized, Open-label, Controlled Phase III Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects with High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)	Blinatumomab 20120215	28-09-2015 (10-08-2018)	Inclusion closed (16-09-2019)
A Randomized, Open-label, Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Patients With Relapsed or Refractory Mature B-cell non-Hodgkin Lymphoma	Ibrutinib Sparkle	24-04-2017	Open in Princess Máxima Center
CA209-744 -Risk-based, response-adapted, Phase II open-label trial of nivolumab + brentuximab vedotin (N + Bv) for children, adolescents, and young adults with relapsed/ refractory (R/R) CD30 + classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by brentuximab + bendamustine (Bv + B) for participants with a suboptimal response (CheckMate 744)	CA209-744	28-08-2017	Open in Erasmus MC and Princess Máxima Center
Open-label, Multicenter, Phase II Study Evaluating the Efficacy and Safety of Daratumumab in Pediatric and Young Adult Subjects ≥1 and ≤30 Years of Age With Relapsed/Refractory Precursor B-cell or T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma	Daratumumab ALL2005	21-08-2018	Open in Princess Máxima Center
Open-label, Single-arm Trial to Evaluate Antitumor Activity, Safety, and Pharmacokinetics of Isatuximab Used in Combination With Chemotherapy in Pediatric Patients From 28 Days to Less Than 18 Years of Age With Relapsed/ Refractory B or T Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia In First or Second Relapse	Isatuximab	12-09-2019	Open in Princess Máxima Center
Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced SolidTumors and Hematological Malignancies	Durvalumab **	17-09-2019	Open in Princess Máxima Center
An Open-Label, Single-Arm, Phase I/II Study Evaluating the Safety and Efficacy of Ponatinib for the Treatment of Recurrent or Refractory Leukemias or Solid Tumors in Pediatric Participants	Ponatinib **	22-01-2020	Open in Princess Máxima Center
Phase I/II, multi-center, dose-escalating study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of quizartinib administered in combination with re-induction chemotherapy, and as a single-agent maintenance therapy, in pediatric relapsed/refractory AML subjects aged 1 month to < 18 years (and young adults aged up to 21 years) with FLT-3-ITD mutations	Quizartinib	31-01-2019	Open in Princess Máxima Center

** Study includes both Hematologic Malignancies as Solid Tumors

Open Investigator-sponsored studies

Neuro-oncology

Study	Work title	Setting	Role DCOG-ECTC	Date of opening NL	Status
Biological Medicine for Diffuse Intrinsic Pontine Glioma (DIPG) Eradication	BIOMEDE	European	IGR sponsor Erasmus MC national cosponsor	Approved 13-02-2018 First pt. 19-02-2019	Open
Phase I/II Study of Vinblastine in combination with Nilotinib in Children, Adolescents, and young adults with refractory or recurrent low-grade glioma	Vinilo	European	IGR sponsor Erasmus MC national cosponsor	Approved 03-02-2014 First pt. 10-07-2013	Inclusion closed (17-05-2019)

Open Company-sponsored studies

Neuro-oncology

Study	Worktitle	Date of approval in 1st site in NL (Princess Máxima Center)	Status
Clinical Protocol CA209-908 Phase Ib /II Clinical Trial of Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Pediatric Subjects with High Grade Primary CNS Malignancies	CA209-908	27-10-2017	Inclusion closed (07-03-2019)
INTELLANCE 2: ABT-414 alone or ABT-414 plus temozolomide versus lomustine or temozolomide for recurrent glioblastoma: a randomized phase II study of the EORTC Brain Tumor Group	M14-483	23-06-2015 (31-07-2018)	Study closed (25-09-2019)
Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive relapsed or refractory High Grade Glioma (HGG).	Dabrafenib TADPOLE-G	14-02-2018 (22-08-2018)	Open in Princess Máxima Center

Open Investigator-sponsored studies

Solid tumors

Study	Work title	Setting	Role DCOG-ECTC	Date of opening NL	Status
A randomised phase IIb trial of BEvACizumab added to Temozolomide ± IrinOtecan for children with refractory/ relapsed Neuroblastoma	Beacon	European	Birmingham sponsor Erasmus MC national cosponsor	Approved 16-02-2015 First pt. 14-10-2015	Open
An international multicenter phase II randomised trial evaluating and comparing two intensification treatment strategies for metastatic neuroblastoma patients with a poor response to induction chemotherapy A SIOPEN Study	VERITAS	International	IGR sponsor SKION NCC	27-09-2019 First pt. 20-02-2020	Open
International Randomized Phase II trial of the combination of Vincristine and Irinotecan with or without temozolomide (VI or VIT) in children and adults with refractory or relapsed rhabdomyosarcoma	VIT	European	Oscar Lambret (Lille) sponsor AMC national cosponsor	Approved 31-10-2011 First pt. 09-10-2012	Closed for inclusion (04- 2018)
Phase II trial of the addition of Gemcitabine to 131I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma.	MIBG-GEM	International	AMC sponsor	Approved 16-07-2009 First pt. 15-03-2011	Closed for inclusion (18-02- 2018)

Open Company-sponsored studies

Solid tumors

Study	Worktitle	Date of approval in 1st site in NL (Princess Máxima Center)	Status
An early phase, multicenter, open-label study of the safety and pharmacokinetics of atezolizumab (MPDL3280A) in pediatric and young adult patients with previously treated solid tumors.	Anti PDL-1	11-12-2015 (01-11-2018)	Study closed (05-09-2019)
An Open-Label, Single-Arm, Phase I/II Study Evaluating the Safety and Efficacy of Ponatinib for the Treatment of Recurrent or Refractory Leukemias or Solid Tumors in Pediatric Participants	Ponatinib **	22-01-2020	Open in Princess Máxima Center
An open-label, two stage adapative design study of bevacizumab with standard chemotherapy in minors with metastatic rhabdomyosarcoma, non-rhabdo-myosarcoma soft tissue sarcoma, or high-risk Ewing sarcoma/soft tissue PNET. Protocol nr. BO20924.	Bernie	21-08-2008 (14-03-2018)	Study closed (05-08-2019)
Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies	Durvalumab **	17-09-2019	Open in Princess Máxima Center

** Study includes both Hematologic Malignancies as Solid Tumors

Open Investigator-sponsored studies

Stem Cell Transplantation

Study	Work title	Setting	Role DCOG-ECTC	Date of opening NL	Status
Prospective Analysis of an Individualized Dosing Regimen of ATG (Thymoglobulin) in Children Undergoing HCT: reducing Toxicity and improving Effectivity (PARACHUTE)	Parachute-ATG	National	UMC Utrecht sponsor (monocenter)	Approved 05-02-2015 First pt. 21-06-2015	Study closed (23-09-2019)

Open Company-sponsored studies

Stem Cell Transplantation (including Phase III studies)

Study	Worktitle	Date of approval in 1st site in NL (Princess Máxima Center)	Status
A Multicenter, Randomized, Phase III Registration Trial of Transplantation of NiCord®, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies	NiCord-III	20-07-2017 (04-06-2018)	Inclusion closed (24-12-2019)
A Phase III Study of Lenti-D Drug Product After Myeloablative Conditioning Using Busulfan and Fludarabine in Subjects ≤ 17 Years of Age With Cerebral Adrenoleukodystrophy (CALD)	ALD-104	24-06-2019	Study on hold
A phase II trial of tisagenlecleucel in first-line high-risk (HR) pediatric and young adult patients with B-cell acute lymphoblastic leukemia (B-ALL) who are minimal residual disease (MRD) positive at the end of consolidation (EOC) therapy	CASSIOPEIA	14-06-2019	Open in Princess Máxima Center
A Phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in pediatric patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL) (BIANCA)	BIANCA	25-06-2019	Open in Princess Máxima Center
A phase III randomized open-label multi-center study of ruxolitinib versus best available therapy in patients with corticosteroid-refractory acute graft vs. host disease after allogeneic stem cell transplantation	REACH 2	17-01-2018 (12-04-2018)	Study closed (09-05-2019)
A phase III randomized open-label multi-center study of ruxolitinib vs. best available therapy in patients with corticosteroid-refractory chronic graft vs host disease after allogeneic stem cell transplantation (REACH 3)	REACH 3	02-11-2017 (30-07-2018)	Inclusion closed (06-11-2019)
A Prospective and Retrospective Data Collection Study to Evaluate Outcomes in Males ≤17 Years of Age Undergoing Allogeneic Hematopoietic Stem Cell Transplantation for the Treatment of Cerebral Adrenoleukodystrophy	ALD-103	12-09-2018	Study closed (28-02-2020)
An Open-label, Randomized, Multi-center, Parallel Group, Two-arm Study to Assess the Safety, Overall Tolerability, and Antiviral Activity of Brincidofovir versus Standard of Care for Treatment of Adenovirus Infections in High-risk Pediatric Allogeneic Hematopoietic Cell Transplant Recipients	Chimerix AdAPT	21-12-2018	Study closed (10-05-2019)
A Phase I/II Multi-Center Study Evaluating the Safety and Efficacy of KTE C19 in Pediatric and Adolescent Subjects with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-4)	ZUMA-4	27-09-2017	Open in Princess Máxima Center
Phase I/II Dose Finding, Safety and Efficacy Study of Ibrutinib in Pediatric Subjects with Chronic Graft Versus Host Disease (cGVHD)	PCYC1146-IM	20-11-2019	Open in Princess Máxima Center

Open Investigator-sponsored studies

Other Indications

Study	Work title	Setting	Role DCOG-ECTC	Date of opening NL	Status
A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies - Study ITCC 053	CRISP	European	Erasmus MC sponsor	Approved 03-11-2016 First pt. 22-05-2018	Open
European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in children	E-SMART	European	IGR sponsor Erasmus MC national cosponsor	Approved 23-02-2018 First pt. 14-05-2018	Open
INFORM2 exploratory multinational phase I/II combination study of Nivolumab and Entinostat in children and adolescents with refractory high-risk malignancies	INFORM2 NivEnt	European	Heidelberg sponsor Erasmus MC national cosponsor	Approved 27-06-2019	Open
Towards Individualized Therapies for Children with Relapsed/Refractory Malignancies using Molecular Profiling	iTHER	National	SKION sponsor	Approved 09-01-2017 First pt. 18-04-2017	Open

Open Company-sponsored studies

Other Indications

Study	Worktitle	Date of approval in 1st site in NL (Princess Máxima Center)	Status
A Phase I Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma	Epizyme EZH-102	21-02-2017 (27-06-2018)	Open in Princess Máxima Center
A Phase I Study of the Safety and pharmacokinetics of Venetoclax in Pediatric and Young Adult Patients with Relapsed or Refractory Malignancies	M13-833	19-12-2017	Open in Princess Máxima Center
A Phase I/II Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors	LOXO	25-09-2018	Open in Princess Máxima Center
A phase IV, open-label, single arm study to evaluate the safety and tolerability of a three-day fosaprepitant regimen administered for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric participants receiving emetogenic chemotherapy	Fosaprepitant MK0517-045	24-10-2019	Open in Princess Máxima Center
A Phase I, open-label, dose escalation study of LDK378 in pediatric patients with malignancies that have a genetic alternation in anaplastic lymphoma kinase (ALK)	CLDK	06-08-2013 (13-08-2018)	Study closed (22-07-2019)
Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged ≥1 year to <18 years with recurrent/refractory neuroectodermal tumours,rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology.	Afatinib	25-07-2016 (09-07-2018)	Inclusion closed (19-12-2019)

Other Investigator-initiated studies

Other indications

Study	Date of opening Princess Máxima Center	Status
Cancer in Pregnancy (CIP)	06-06-2018	Open
Clinical validation of a dried blood spot (DBS) method for the analysis of immunosuppressive and antifungal drugs in pediatric patients (Protect)	01-09-2018	Open
Divergent Low Level Laser Therapy as novel treatment for oral mucositis in pediatric cancer patients (DuLamp)	(Not applicable)	On hold in Princess Máxima Center
Double blind placebo controlled randomized intervention study to validate the beneficial effect of hydrocortisone on dexamethasone induced neurobehavioral side effects in pediatric acute lymphoblastic leukemia (Dexadagen2)	10-04-2018	Open
Identifying the critically ill pediatric cancer patient (SO-PEWS)	14-09-2016	Open
Managing Insomnia after Childhood Cancer in Adolescents (Micado-1)	01-11-2018	Open
Managing Insomnia after Childhood Cancer in Adolescents (Micado-2)	29-08-2018	Open
Patient-Reported Outcomes in children and Adolescents with Chronic/life-threatening diseases and Tailored Interventions in a digital Environment (ProActive)	01-03-2017	Open
Pharmacokinetics of (Fos)aprepitant, Dexamethasone and their interaction in children with chemotherapy induced nausea and vomiting: a pilot study (Aprepitant Pilot)	15-02-2019	Open
PINOCCHIO-study: Pharmacokinetics of chemotherapeutic agents in children's oncology (PINOCCHIO)	26-06-2018	Open
Reducing Pain in Pediatric Oncology Patients at Home A Feasibility Study of the KLIK Pijnmonitor (RELIEF-1)	22-10-2019	Closed for inclusion (16-12-2019)
Smell and Taste (Dys)function in Children with Cancer - a Feasibility Study - (SENSORY)	29-03-2019	Closed for inclusion (06-11-2019)
The impact of genetic predisposition in pediatric renal cancer: genotypic and phenotypic characterization (WES-KidTs)	Initiation Visit 14-05-2018 First pt. 07-06-2018	Open
The search for frequency, determinants, the predictive value of mycobiome, and the role of innovative diagnostics in Invasive Fungal infections in pediatric oncology patients (MiFi)	15-11-2017	Closed for inclusion (09-07-2019)
Validatie van een klinisch screeningsinstrument voor tumor predispositiesyndromen bij kinderen met kanker (TuPS)	12-07-2016	Closed for inclusion (01-04-2019)
Vincristine-Induced Neuropathy in Children with Cancer (VINCA)	Dec 2016 First inclusion March 2017	Closed for inclusion Only follow-up

Appendix 1

Clinical studies
Phase III

Hematology-oncology

Study	Work title	Status Protocol	Date protocol open in NL
A registry for hemophagocytic lymphohistiocytosis (HLH)	HLH registry	Open	24-11-2016
Acquired aplastic anemia: a best available treatment guideline for Dutch Childhood Oncology Group centers.	Aplastische Anemie (SAA 2010)	Open	14-06-2010
An open-label study to evaluate the safety and efficacy of IMATINIB with chemotherapy in pediatric patients with Ph+/ BCR-ABL+ acute lymphoblastic leukemia (Ph+ALL)	EsPhALL	Inclusion closed, only FU	01-09-2004
Diagnostiek, behandeling en follow-up van patiënten met Fanconi anemie	Fanconi Anemie	Open	01-11-2007
First international Inter-Group Study for nodular lymphocyte-predominant Hodgkin's Lymphoma in Children and Adolescents	EuroNet-PHL-LP1	Inclusion closed, only FU	30-03-2011
Intergroup trial for children or adolescents with B-Cell NHL or B-AL: Evaluation of Rituximab efficacy and safety in high risk patients	Inter-B-NHL ritux 2010	Inclusion closed (13-06-2017)	24-04-2013
International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis	LCH-IV	Open	06-01-2014
International collaborative treatment protocol for infants under one year with acute lymphoblastic or biphenotypic leukemia	Interfant 06	Open, registration only	01-01-2006
International phase III trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones	EsPhALL2017/ COGAALL1631	Open	18-07-2018
International Study for Treatment of Standard Risk Childhood Relapsed ALL 2010: A randomized Phase III Study Conducted by the Resistant Disease Committee of the International BFM Study Group	IntReALL SR 2010	Open	26-04-2016
International study of chronic myeloid leukemia (CML) Treatment and Outcomes in Children and Adolescents	I-CML-Ped Study	Open	11-08-2011

Allogeneic Stem Cell Transplantation in Children and Adolescents with Acute Lymphoblastic Leukaemia	ALL SCTped FORUM	Open, randomization closed	10-09-2014
National treatment protocol for B-cell Non-Hodgkin lymphoma or B-ALL children and adolescents	SKION B-NHL/B-ALL 2008	Open	03-12-2009
NOPHO-DBH AML 2012 Protocol: Research study for treatment of children and adolescents with acute myeloid leukaemia 0-18 years	NOPHO DBH AML 2012	Open	01-01-2014
Prospective non–randomized multi-center study for epidemiology and characterization of Myelodysplastic Syndromes (MDS) and Juvenile Myelomonocytic Leukemia (JMML) in childhood	EWOG MDS 2006	Open	01-01-2007
Second International Inter-Group Study for Classical Hodgkin's Lymphoma in Children and Adolescents	EuroNet-PHL-C2	Open	09-09-2016
Treatment study for patients with acute promyelocytic leukemia under 21 years of age	ICC APL Study 01	Open	14-9-2010
Treatment study protocol of the Dutch Childhood Oncology Group for children and adolescents (1-19 year) with newly diagnosed acute lymphoblastic leukemia	ALL-11	Open	01-04-2012

Neuro-oncology

Study	Work title	Status Protocol	Date protocol open in NL
A SIOPE Registry for Diffuse Intrinsic Pontine Glioma (DIPG)	SIOPE DIPG Registry	Open	01-01-2017
An international prospective trial on medulloblastoma (MB) in children older than 3 to 5 years with WNT biological profile (PNET 5 MB – LR and PNET 5 MB - WNT – HR), average-risk biological profile (PNET 5 MB – SR), or TP53 mutation, and registry for MB occurring in the context of genetic predisposition	SIOP PNET5	Open	17-02-2020
Cooperative multicenter Study for Children and Adolescents with Low Grade Glioma	SIOP LGG 2004	Registration closed	17-12-2007

Solid tumors

Study	Work title	Status Protocol	Date protocol open in NL
EpSSG - NRSTS 2005: a protocol for Localized Non-Rhabdomyosarcoma Soft Tissue Sarcomas	EpSSG NRSTS 2005	Study closed (02-03-2020)	01-09-2006
EWING08, clinical trial for the treatment of EWING sarcoma	EWING2008	Study closed (30-06-2019)	03-10-2011
Nephroblastoma clinical trial and study SIOP 2001	SIOP 2001 Wilms'	Study closed (06-06-2019)	01-01-2001
Neuroblastoma national database 2000-2015	NBL Registry	Open	01-06-2018
Paediatric Hepatic International Tumour Trial	PHITT	Open	07-03-2019
Prospective study registry of peripheral neuroblastic tumours presenting with spinal canal involvement (SCI)	NB with SCI	Open	04-11-2014
RMS 2005: a protocol for non metastatic rhabdomyosarcoma	EpSSG RMS 2005	Study closed (09-12-2019)	10-08-2006
UMBRELLA PROTOCOL SIOP-RTSG 2016 Integrated research and guidelines for standardized diagnostics and therapy for paediatric renal tumours	Umbrella	Open	25-02-2019

Appendix 1

Late effects studies

Studies with a visit to the Late effects ('LATER') outpatient clinic on Late effects after childhood cancer

Study	Work title	Status Protocol	Date protocol open in NL
LATER Study: Thyroid function, in children and adults, after treatment for childhood cancer (THYR)	LATER THYR	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Adult growth hormone deficiency in childhood cancer survivors (EGHA)	LATER EGHA	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Metabolic syndrome parameters in adult survivors of childhood cancer (METS)	LATER METS	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Reproductive potential in male survivors of childhood cancer (FRTM)	LATER FRTM	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Bone mineral density and body composition in survivors of childhood cancer (BONE)	LATER BONE	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Sexual function and psychosexual development in long-term childhood cancer survivors (SEXP)	LATER SEXP	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Late cadiovascular toxicity in long-term childhood cancer survivors (CARD)	LATER CARD	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Long-term renal effects in Dutch survivors of childhood cancer (RENA)	LATER RENA	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Is pulmonary dysfunction a late effect of cyclophosphamide treatment	LATER PULM	Study closed in 2019	25-4-2016
LATER Study: Fatigue in childhood cancer survivors (FATI)	LATER FATI	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Long-term psychosocial consequences of childhood cancer (PSYS)	LATER PSYS	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Impaired splenic function in long-term survivors of childhood cancer; diagnostic and therapeutic strategies (SPLE)	LATER SPLE	Inclusion closed (01-03-2020)	25-4-2016
LATER Study: Hyposalivation in long-term survivors of pediatric cancers following different treatment regiments (SALI)	LATER SALI	Inclusion closed (01-03-2020)	25-4-2016

Appendix 1

CRC Approved studies

Approved studies Clinical Research Committee Princess Máxima Center

Nr.	Study	Work title	PI	Date approval
2018-002	Phase II trial of nivolumab for pediatric and adult relapsing/ refractory ALK+ anaplastic large cell lymphoma, for evaluation of response in patients with progressive disease (Cohort 1) or as consolidative immunotherapy in patients in complete remission after relapse (Cohort 2)	Nivolumab ALCL	Dr. Beishuizen	15-01-2019
2018-004	Visual impairment in children with a brain tumor in the Netherlands: a prospective nationwide study using standard visual testing and optical coherence tomography	KIZZ	Dr. Schouten-van Meeteren	12-02-2019
2018-011	An international multicenter phase II randomised trial evaluating and comparing two intensification treatment strategies for metastatic neuroblastoma patients with a poor response to induction chemotherapy. A SIOPEN STUDY	VERITAS	Dr. Kraal	12-02-2019
2018-014	Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies	Durvalumab / Tremelimumab	Prof. dr. Zwaan	04-06-2019
2018-018	A phase II trial of tisagenlecleucel in first-line high-risk (HR) pediatric and young adult patients with B-cell acute lymphoblastic leukemia (B-ALL) who are minimal residual disease (MRD) positive at the end of consolidation (EOC) therapy	CASSIOPEIA	Prof. dr. Pieters	12-02-2019
2018-020	MICADO-2: Managing insomnia after childhood cancer in adolescents. Randomized controlled trial to evaluate the effect of online cognitive behavioral therapy for insomnia on sleep-efficiency and quality of life in adolescents and young adults after childhood cancer	MICADO-2	Dr. van Litsenburg	12-02-2019
2018-024	Pharmacokinetics of aprepitant, dexamethasone and their interaction in children with chemotherapy induced nausea and vomiting: a pilot study	Aprepitant pilot	Dr. de Vos-Kerkhof	12-02-2019
2018-026	Early detection of acute and early-onset cardiovascular toxicity in children with cancer using a multiparametric approach	EARLY	Prof. dr. Kremer	27-08-2019
2018-028	Phase I/II Dose Finding, Safety and Efficacy Study of Ibrutinib in Pediatric Subjects with Chronic Graft Versus Host Disease (cGVHD)	Ibrutinib cGvHD	Dr. Lindemans	12-02-2019

2018-030	Improving diagnostic accuracy and patient comfort of neuroblastoma patient imaging by using 18F-mFBG PET-CT instead of 123I-mIBG imaging	F-mFBG PET NBL imaging	Dr. Tytgat	05-11-2019
2018-031	A phase I/II, multi-center, dose-escalating study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of Quizartinib administered in combination with the-induction chemotherapy, and as a single-agent maintenance therapy, in pediatric relapsed/refractory AML subjects aged 1 month to <18 years (and young adults aged up to 21 years) with FLT3-ITD mutations	AC220-A-U202 Quizartinib	Prof. dr. Zwaan	12-02-2019
2018-032	The efficacy of a lock solution containing taurolidine, citrate and heparin for the prevention of tunneled central line-associated bloodstream infections in pediatric oncology patients, a randomized controlled, mono-centre trial	CATERPILLAR	Prof. dr. Wijnen	26-02-2019
2018-033	Smell and Taste Dysfunction in Children with Cancer - a Feasibility Study	SENSORY	Dr. Tissing	12-02-2019
2018-039	Implementing Pediatric Advance Care Planning Toolkit	IMPACT	Dr. Michiels	26-02-2019
2019-001	International Registry for Relapsed Pediatric APL: A collaboration between Children's Oncology Group (COG) and International BFM Study Group (I-BFM-SG)	Relapsed APL registry	Prof. dr. Kaspers	04-06-2019
2019-002	Preserving ovarian function through cryopreservation and informing girls with cancer about infertility due to gonadotoxic treatment	PAREL	Prof. dr. van den Heuvel-Eibrink	13-08-2019
2019-005	A comprehensive and targeted therapy approach in pediatric malignant pontine gliomas	VUmc-DIPG01	Dr. van Vuurden	18-06-2019
2019-006	Open-label, Single-arm Trial to Evaluate Antitumor Activity, Safety, and Pharmacokinetics of Isatuximab Used in Combination With Chemotherapy in Pediatric Patients From 28 Days to Less Than 18 Years of Age With Relapsed/ Refractory B or T Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia in First or Second Relapse	Isatuximab	Dr. B.J. Vormoor	09-04-2019
2019-007	The THYRO-Dynamics study: Is the dynamics of thyroid hormones during cancer treatment in children adaptive or disruptive? - a propspective evaluation	THYRO-Dynamics	Prof. dr. van den Heuvel-Eibrink	18-07-2019
2019-008	Single-cell tracing of genomic mutations in human hematopoietic stem cell transplantation recipients	Tracing stem cells	Dr. Belderbos	20-03-2019
2019-009	Evaluation of prophylactic micafungin treatment for invasive fungal diseases in children with ALL	OPTIMA	Dr. Tissing	21-05-2019
2019-010	Body composition of patients with neuroblastoma	BODY	Dr. Tissing	12-03-2019
2019-012	Granulosa Cell Tumours: a step towards targeted therapy	Granulosa study	Dr. Mavinlkurve-Groothuis	27-08-2019
2019-013	Pilotstudy of the application ‘Mijn Máxima Plan’	Mijn Máxima Plan	Prof. dr. Grootenhuis	23-04-2019
2019-014	A retrospective study on compassionate use of Inotuzumab Ozogamicin in infants and younger children with relapsed or refractory acute lymphoblastic leukemia (ALL)	InO compassionate use	Prof. dr. Zwaan	26-02-2019

2019-015	CAMPFIRE: Children's and Young Adult Master Protocol for Innovatibe Pediatric Research AD1: A Randomized, Open-Label Phase II Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumor AD2: A Randomized, Open-Label Phase 2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Synovial Sarcoma	CAMPFIRE	Dr. van Eijkelenburg	17-12-2019
2019-016	Dabrafenib amendments 2 and 3: Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)	Dabrafenib AM2 and AM3	Dr. van der Lugt	04-06-2019
2019-017	BEACON amendment 11: A randomised phase IIb trial of BEvACizumab added to Temozolomide ± IrinOtecan for children with refractory/relapsed Neuroblastoma. BEACON amendment 11 for protocol version 6.0	BEACON AM11	Dr. van Eijkelenburg	09-04-2019
2019-018	Non-invasive characterization of paediatric brain tumours using metabolic imaging at high magnetic field	7T MRI brain	Dr. Plasschaert	10-09-2019
2019-021	Parent’s understanding, views and experiences concerning genomic sequencing in a paediatric renal cancer research setting	WES-KidTs parent interviews	Prof. dr. van den Heuvel-Eibrink	18-06-2019
2019-022	International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma	rEECur	Dr. Merks	18-06-2019
2019-023	Een zorgethische studie naar de geleefde ervaring van kinderverpleegkundigen ten aanzien van second victimhood	Kundig en kwetsbaar	Anja Portengen	07-05-2019
2019-024	Resting energy expenditure in children with cancer	ENERGICE	Dr. Tissing	09-04-2019
2019-026	Children treated with vincristine: A trial regarding pharmacokinetics, DNA and toxicity of targeted therapy in pediatric oncology patients.	CHAPATI (Outreach)	Prof. dr. Kaspers	10-09-2019
2019-027	A Phase IV, Open-label, Single Arm Study to Evaluate the Safety and Tolerability of a Three-day Fosaprepitant Regimen Administered for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Participants Receiving Emetogenic Chemotherapy	Fosaprepitant MK0517-045	Prof. dr. Zwaan	13-08-2019
2019-028	UMBRELLA: Integrated research and guidelines for standardized diagnostics and therapy	UMBRELLA	Prof. dr. van den Heuvel-Eibrink	26-03-2019
2019-029	The Cerebellar Mutism Syndrome (CMS): description of Neuropsychological characteristics and Neuroradiological trajectories and assessment of risk factors in children treated for posterior fossa Brain Tumors	CMS study	Prof. dr. Grootenhuis	09-04-2019
2019-030	High-Risk Neuroblastoma Study 2 of SIOP-Europa-Neuroblastoma (SIOPEN)	HR-NBL2/ SIOPEN	Dr. Tytgat	16-07-2019
2019-031	Paediatric Hepatic International Tumour Trial	PHITT	Dr. Zsiros	18-06-2019
2019-032	Treatment study for children and adolescents with Acute Promyelocytic Leukemia	ICC APL Study 02	Prof. dr. Kaspers	22-10-2019

2019-034	FaR-RMS - An overarching study of Children and adults with Frontline and Relapsed Rhabdomyosarcoma	FaR-RMS	Dr. Merks	10-09-2019
2019-035	An International Prospective Trial on Medulloblastoma (MB) in Children Older Than 3 to 5 Years With WNT Biological Profile (PNET 5 MB - LR and PNET 5 MB - WNT-HR), Average-risk Biological Profile (PNET 5 MB-SR), Or TP35 Mutation, and Registry For MB Occurring in the Context of Genetic Predisposition	PNET5	Dr. Plasschaert	18-06-2019
2019-036	A Phase I/II, Multicenter, Open Label, Multi Arm Study Evaluating The Safety, Tolerability, Pharmacokinetics, and Preliminary Activity of Idasanutlin In Combination With Either Chemotherapy Or Venetoclax In The Treatment Of Pediatric And Young Adult Patients With Relapsed/Refractory Acute Leukemias Or Solid Tumors	GO40871 - Idasanutlin	Prof. dr. Zwaan	02-07-2019
2019-038	National Rhabdomyosarcoma Registry	National Rhabdomyo-sarcoma Registry	Dr. Merks	04-06-2019
2019-039	A Phase I Trial of the CD123 X CD3 Dual Affinity Re-targeting Antibody Flotetuzumab (NSC#808294) in Children, Adolescents And Young Adults With Relapsed or Refractory Acute Myeloid Leukemia	Flotetuzumab - ADVL1812	Prof. dr. Zwaan	16-07-2019
2019-040	iTHER 2.0: Clinical implementation of a pediatric cancer precision medicine program, enforced with personalized models	iTHER 2.0	Prof. dr. Zwaan	24-12-2019
2019-042	A phase I/II post-cord blood HCT dendritic cell vaccination trial directed against WT1 for pediatric and young adult acute myeloid leukemia: the U-DANCE-anti-AML trial	U-DANCE	Dr. Lindemans	17-12-2019
2019-043	An Open-Label, Single-Arm, Phase I/II Study Evaluating the Safety and Efficacy of Ponatinib for the Treatment of Recurrent or Refractory Leukemias or Solid Tumors in Pediatric Participants	Ponatinib - INCB 84344-102	Prof. dr. Zwaan	02-07-2019
2019-044	The Holland Sleep Disorder Questionnaire (HSDQ) in adolescents without a pediatric cancer diagnosis	HSDQ validation	Prof. dr. Grootenhuis	22-07-2019
2019-045	International Study for Treatment of High Risk Childhood Relapsed ALL 2010 - A randomized Phase II Study Conducted by the Resistant Disease Committee of the International BFM Study Group	IntReALL HR 2010	Prof. dr. Hoogerbrugge	27-08-2019
2019-047	A prospective study on determinants of ototoxicity during treatment of childhood cancer (the SOUND study)	SOUND	Prof. dr. van den Heuvel-Eibrink	24-06-2019
2019-048	The Dutch Childhood Craniopharyngioma Cohort study	Craniopharyn-gioma Cohort study	Prof. dr. Tissing	18-06-2019
2019-050	A Phase Ib study of Vyxeos® (liposomal daunorubicin and cytarabine) in combination with Clofarabine in children with relapsed/refractory AML	Vyxeos	Prof. dr. Zwaan	17-12-2019
2019-051	Reducing Pain in Pediatric Oncology Patients at Home. A Feasibility Study of the KLIK painmonitor (RELIEF-1)	RELIEF-1	Prof. dr. Tissing	27-08-2019

2019-053	International Multi-center, Open-label, Phase 2 Study to Treat Molecular Relapse of Pediatric Acute Myeloid Leukemia with Azacitidine	AMoRe 2017	Prof. dr. Zwaan	30-07-2019
2019-054	Ervaringen van zorgprofessionals met verlies- en rouwzorg aan ouders rondom het levenseinde van hun kind	EMBRACE	Prof. dr. Grootenhuis	16-07-2019
2019-057	SeluDex: an international phase I/II expansion trial of the MEK inhibitor selumetinib in combination with dexamethasone for the treatment of relapsed/refractory RAS-pathway mutated paediatric and adult Acute Lymphoblastic Leukaemia (ALL)	SeluDex	Dr. B.J. Vormoor	10-09-2019
2019-058	An international Clinical Program for the diagnosis and treatment of children, adolcescents and young adults with ependymoma	Ependymoma II	Dr. van der Lugt	22-10-2019
2019-059	ALLTogether1 - A Treatment study protocol of the ALLTogether Consortium for children and young adults (1-45 years of age) with newly diagnosed acute lymphoblastic leukaemie (ALL)	ALLTogether-1	Dr. van der Sluis	27-08-2019
2019-060	Teicoplanin as Infection Prophylaxis in Pediatric Acute Myeloid Leukemia (Pro-Teico): An open-label, randomized clinical trial on teicoplanin infection prophylaxis in pediatric patients with acute myeloid leukemia	Pro-Teico	Prof. dr. Kaspers	17-12-2019
2019-062	International concerted action to refer children with relapsed and refractory leukemia/lymphoma to the right precision medicines trials: A platform for rational treatment choice based on molecular profiling and drug sensitivity testing.	Haem-Precision (grant)	Prof. dr. Zwaan	13-08-2019
2019-065	Improving care for children with a brain tumor. The SuSPeCT study: getting insight into stress, sleep and cognitive functioning.	SuSPeCT	Prof. dr. Grootenhuis	22-10-2019
2019-067	Long Term Follow-up of Patients Exposed to Lentiviral-Based CD19 directed CAR T-CELL Therapy	PAVO	Prof. dr. Zwaan	08-10-2019
2019-068	A social robot to support children with cancer during treatment: A survey about the opinions of health care providers in pediatric oncology	Social robots	Prof. dr. Grootenhuis	22-10-2019
2019-070	Smell and Taste changes in Childhood Cancer Patients (SENSORY-2)	SENSORY-2	Prof. dr. Tissing	03-12-2019
2019-073	A phase I/II study evaluating the safety and activity of Pegylated recombinant human Arginase (BCT-100) in Relapsed/refractory cancers of Children and young adults	PARC	Dr. van Eijkelenburg	03-12-2019
2019-075	A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)	OLIE	Dr. van Eijkelenburg	17-12-2019
2019-076	Evaluating the feasibility and outcomes of implementing PanCareFollowUp Care as usual care in four European countries: a prospective cohort-study	PanCare FollowUp	Prof. dr. Kremer	17-12-2019
2019-077	Facilitators and barriers in childhood cancer survivors for adopting healthy lifestyle behaviours: a qualitative study	PCFU Facilitators and barriers healthy lifestyle	Prof. dr. Kremer	17-12-2019

Appendix 2

Princess Máxima Center publications

- Aden, K., Bartsch, K., Dahl, J., Reijns, M. A. M., Esser, D., Sheibani-Tezerji, R., . . . Rosenstiel, P. (2019). Epithelial RNase H2 Maintains Genome Integrity and Prevents Intestinal Tumorigenesis in Mice. *Gastroenterology*. PMID: 30273559

- Admiraal, R., & Boelens, J. J. (2019). Pharmacotherapy in Pediatric Hematopoietic Cell Transplantation. *Handbook of experimental pharmacology*. PMID: 31375921

- Admiraal, R., de Witte, M. A., Huitema, A., & Nierkens, S. (2019). Pharmacological Considerations in Antithymocyte Globulin Exposure Calculation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. PMID: 30928628

- Admiraal, R., Jol-van der Zijde, C. M., Furtado Silva, J. M., Knibbe, C. A. J., Lankester, A. C., Boelens, J. J., . . . Bredius, R. G. M. (2019). Population Pharmacokinetics of Alemtuzumab (Campath) in Pediatric Hematopoietic Cell Transplantation: Towards Individualized Dosing to Improve Outcome. *Clinical pharmacokinetics*. PMID: 31131436

- Agraz-Doblas, A., Bueno, C., Bashford-Rogers, R., Roy, A., Schneider, P., Bardini, M., . . . Stam, R. W. (2019). Unraveling the cellular origin and clinical prognostic markers of infant B-cell acute lymphoblastic leukemia using genome-wide analysis. *Haematologica*. PMID: 30679323

- Albersen, M., Bökenkamp, A., Schotman, H., & Smetsers, S. (2019a). Hyperphosphatemia in an 11-year-old girl with acute myeloid leukemia: Answers. *Pediatric nephrology (Berlin, Germany)*. PMID: 30291428

- Albersen, M., Bökenkamp, A., Schotman, H., & Smetsers, S. (2019b). Hyperphosphatemia in an 11-year-old girl with acute myeloid leukemia: Questions. *Pediatric nephrology (Berlin, Germany)*. PMID: 30291427

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