Stichting Kinderoncologie Nederland
SKION

# EVOLUTIE

SKION DAG 14 APRIL 2022

## -SYLLABUS-

## HEMATO-ONCOLOGIE

## 2022

# Inhoud

# 1. Voorwoord

Het is het 20e jaar dat de SKION-dagen worden georganiseerd. Een mijlpaal! De waardering voor dit samenzijn is onverminderd hoog: veel inschrijvingen, groot enthousiasme om mee te denken over de inhoud van de dag.
De bal ligt bij de hemato-oncologie, met de uitdaging om voor een breder publiek een leerzaam en aantrekkelijk aanbod te presenteren. Eigenlijk is één dag te weinig om recht te doen aan alles wat er gebeurt in deze grote afdeling. Zie het daarom vooral als een steekproef, van verschillende disciplines en initiatieven.

Natuurlijk is er een update van de relevante M4C groepen: lymfatische leukemie, myeloïde maligniteiten, beenmergfalen en myelodysplastisch syndroom, lymfomen en cross cutting: immuuntherapie en stamceltransplantatie. Alleen al daarmee is een dag te vullen, maar we hebben die tijd helaas niet. We hebben de voorzitters van deze groepen gevraagd om met een update te komen die interessant is voor een breder publiek. We horen graag uw evaluatie.

In workshops gaan we nader in op zaken die alle professionals in het Máxima aangaan: hoe communiceer je adequaat in de hectische weken dat een gezin plotseling aangewezen is op onze kennis en kunde? En hoe kijkt een ouder daarop terug?
CAR T: eigen afweercellen die tumoren herkennen? Het is al werkelijkheid voor sommige vormen van leukemie en we hebben veel grotere ambities: een eigen laboratorium waar we ze op maat kunnen gaan maken ligt op de tekentafel. Wat betekent dat voor de kanker-behandeling van morgen, ook op andere terreinen zoals hersentumoren of neuroblastoom?
Regelmatig komt er, bijvoorbeeld ’s avonds laat, een patiënt binnen met een bedreigde luchtweg door een tumor in de borstkas. Wat is dan het plan van aanpak en wie wordt de kapitein op dit schip in stormachtig weer?

Aan het einde van de dag is er een eminente gastspreker: sir Mel Greaves, vanuit het Verenigd Koninkrijk. Het verhaal van een leven lang creatief en succesvol baanbrekend onderzoek naar de oorsprong van kinderkanker. Inspirerend, daar kunt u op rekenen!

SKION heeft een EVOLUTIE zo niet een transitie doorgemaakt, van een landelijke spin in het web naar een kritische vriend van het Máxima:

- Van toegevoegde waarde in het opstellen van evalueerbare richtlijnen in de zorg,
- Betrokken bij de evaluatie van richtlijnen, tijdens bijvoorbeeld de SKION-dagen;
- HET netwerk van professionals in de kinderoncologie in Nederland.

Die netwerkfunctie is ook heel praktisch in te vullen: met een drankje en een hapje. Gelukkig kan het nu ook weer. We sluiten de dag dus daarom af met een borrel, op loopafstand, in the Basket.

We wensen jullie een inspirerende SKION-dag toe!

**Namens de SKION-dagen commissie,**
Marc Bierings, Hans Merks en Marc Vincent

**Namens de afdeling hemato-oncologie**
Josef Vormoor

# 2. Programma

*Donderdag 14 april 2022 (Prinses Máxima Centrum & online)*

| | |
|---|---|
| **08.00 - 08.30 uur** | **Ontvangst met koffie/thee in de Foyer** |
| **08.30 - 08.45 uur** | **Welkom en opening**<br>*Marc Vincent, MHA & prof. dr Josef Vormoor* |

| 8.45-12.10 uur | Trialupdates & bijdragen van de verschillende M4C's |
|---|---|
| **8.45-9.45 uur** | **Evolutie M4C ALL**<br>*dr. Judith Boer, prof. dr. Monique den Boer, prof. dr. Rob Pieters, dr. Inge van der Sluis en dr. Janine Stutterheim* |
| **9.45-10.15 uur** | **Update van de M4C groep lymfomen**<br>*dr. Ruben van Boxtel, dr. Melanie Hagleitner, dr. Jan Loeffen, dr. Friederike Meyer-Wentrup en dr. Margreet Veening* |
| 10.15-10.35 uur | Koffie/thee en postersessie in de Foyer |
| **10.35-11.05 uur** | **Evolutie: van stamcel naar myelodysplasie**<br>*dr. Katja Heitink-Pollé* |
| **11.05-11.35 uur** | **Update klinische studies myeloïde maligniteiten**<br>dr. Bianca Goemans en dr. Alice van Velzen |
| 11.35-11.40 uur | Korte break |
| **11.40-12.10 uur** | **M4C HCT en immunotherapie**<br>*Annelisa Cornel MSc, dr. Caroline Lindemans en dr. Stefan Nierkens* |

| | |
|---|---|
| 12.10 - 12.55 uur | Lunch & Postersessie in de Foyer<br>Posters worden gepresenteerd door: Aeltsje Brinksma, Brenda Hansen, Agnes van den Hoogen, Martine Mol, Ida Ophorst, Lineke Rehorst-Klein Lugtenbelt, Anne van Rooijen, Tirza Schuerhoff, Julia Simon en Hanneke Stuart |

| 12.55-15.00 uur | Parallel programma – Workshops in het Auditorium |
|---|---|
| **12.55-13.55 uur** | **Workshop 'Een tumor in de borstkas: wat doe je (niet)?!'**<br>*drs. Natasja Dors, dr. Melanie Hagleitner, dr. Caroline Hulsker, dr. Kim van Loon, dr. Esther van Mastrigt, Alexandra Neuenfeldt, Suzanne van Roekel* |
| 13.55-14.00 uur | Zaalwissel |
| **14.00-15.00 uur** | **Workshop CAR T**<br>*dr. Friso Calkoen, dr Miranda Dierselhuis, dr. Jasper van der Lugt en Marieke van der Vlugt* |

| 12.55-15.00 uur | Parallel programma – Workshops in de Kleine Zaal |
|---|---|
| **12.55-13.55 uur** | **Workshop 'De eerste weken, wat komt er allemaal aan informatie op je af...'**<br>*Lisa Bakker-Provoost, drs. Esther van den Bergh, Stephanie de Heer, Conradien Hormann-Jansen, Dionne Mooij-Kiebert, dr. Leonie Naeije en Merel de Zeeuw* |
| 13.55-14.00 uur | Zaalwissel |
| **14.00-15.00 uur** | **Workshop 'Geïntegreerde top- diagnostiek in de kinderoncologie'**<br>*Dr. Valérie de Haas & dr. Marijn Vermeulen* |

| | |
|---|---|
| 15.00-15.15 uur | Koffie/thee en postersessie in de Foyer |
| **15.15 – 16.15 uur** | **Childhood Acute Lymphoblastic Leukaemia: an evolutionary portrait**<br>*Prof. Sir. Mel Greaves* |
| **16.15-16.45 uur** | **Afsluiting**<br>*Marc Vincent, MHA & prof. dr. Josef Vormoor* |
| **Vanaf 16.45 uur** | **Borrel**<br>*The Basket (Genevelaan 8, te Utrecht)* |

*De syllabus kan tijdens de SKION dag op tablet, telefoon of laptop worden ingezien*

# 3. Abstract lezing - Childhood Acute Lymphoblastic Leukaemia: an evolutionary portrait

*Prof. Sir Mel Greaves – Hoogleraar celbiologie (Centre for Evolution and Cancer. Institute of Cancer Research, Londen)*
Tijd: 15.15-16.15 uur
Locatie: Auditorium

ALL is the most common paediatric malignancy in the developed world and provides a paradigm for cancer research and treatment in terms of re-iterated clinical trials of combinatorial chemotherapy, biology and genomics.

A major variant (~65%) of ALL has ETV6-RUNX1 gene fusion or hyperdiploidy as alternative founder lesions coupled with secondary, highly recurrent copy number gene alterations (CNA). The latter, mostly deletions, arise via intrinsic recombinase (RAG1/2) mutagenesis. This obviates the need for genome wide instability and, in combination with the rarity of strong oncogenes and lack of TP53 mutations, may underpin the high (>90%) curability of this subset of ALL. We employed a number of strategies to uncover the timing, sequence and clonal architecture of these key genetic events and generate a natural history profile for ALL.

As an evolutionary process , cancer development is driven by intrinsic properties of 'target' cells and adaptive responses of those cells to both environmental and micro- environmental ,selective pressures. This provides a perspective for placing the biology of ALL in the context of causation . Inherited genetic variation contributes to risk in ALL, probably impacting co-operatively with acquired mutations in the cancer cells. Epidemiological data endorse the idea that critical and potentially modifiable risk factors are surrogates for acquisition of the infant gut microbiome and immune network priming in infancy. ALL incidence is linked , geographically and over time, to development and affluence . Paradoxically , 'development', whilst eradicating lethal infectious diseases , has resulted in an evolutionary mismatch between the historically programmed requirements of the immune system for microbial priming and contemporary life style variables that reduce provision of those beneficial microbes in early life. These variables include C- section birth, abbreviated breast feeding and fewer social contacts. In the absence of adequate immune priming , later , otherwise innocuous and common infections can result in chronic inflammation that promotes or triggers overt ALL in susceptible individuals who carry silent, pre malignant clones .

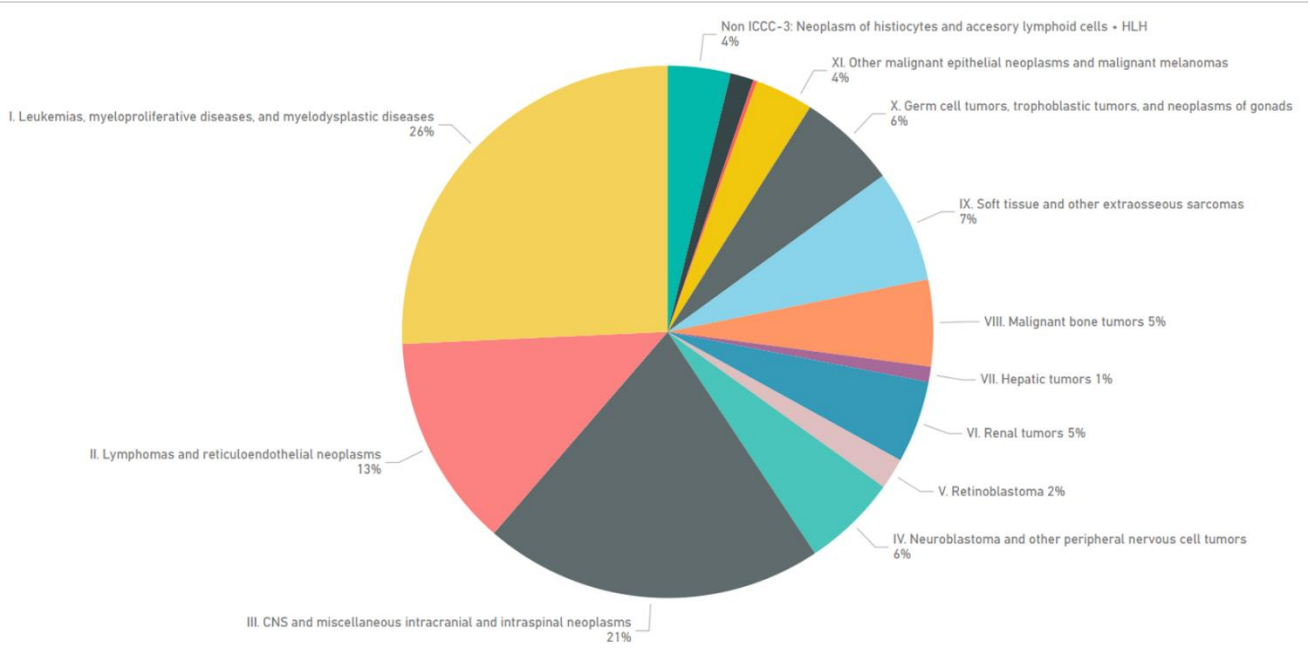
This causal scenario is being modelled in mice and, if correct , childhood ALL may be preventable by prophylactic boosting of the gut microbiome in infancy.

# 4. Basisregistratie en Zorgactiviteit

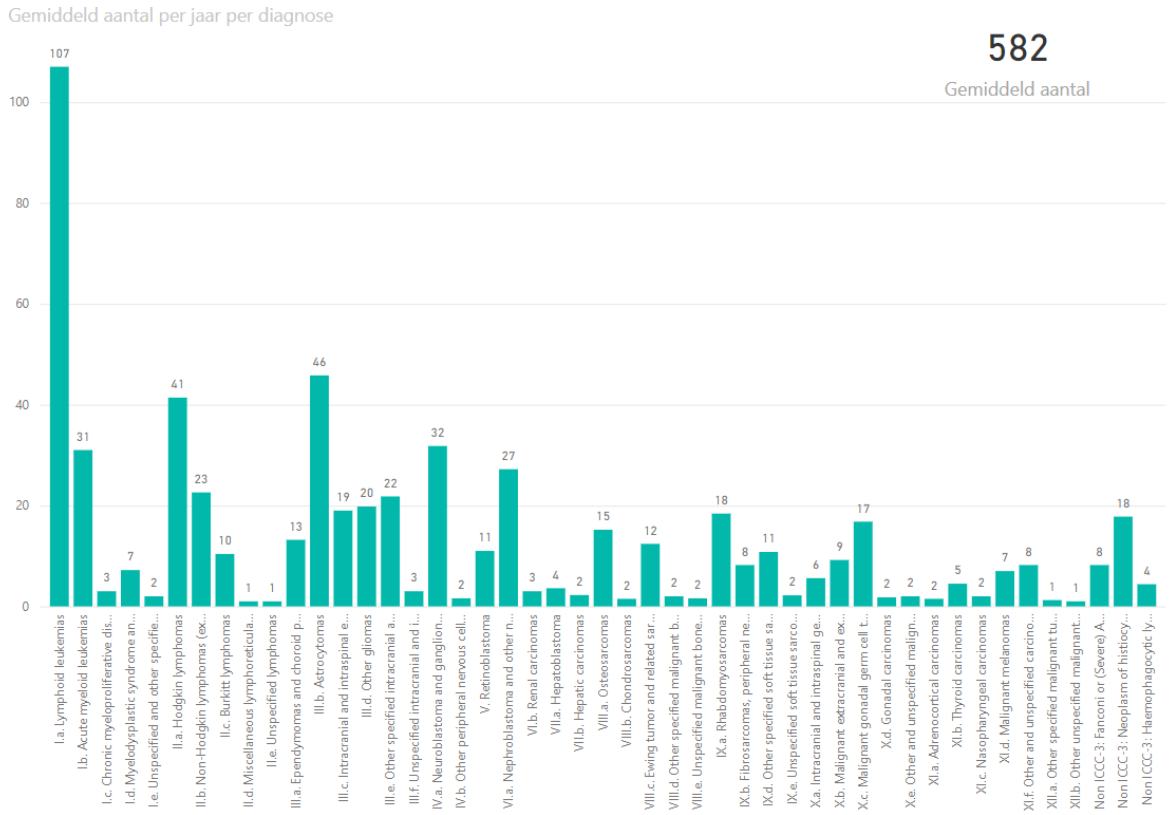
## 4.1. Basisregistratie

In de Basisregistratie worden sinds 2003 alle kinderen, tussen de 0 en 18 jaar, met een (pre-)maligne aandoening geregistreerd. Tussen 2016 en 2020 zijn er gemiddeld 582 nieuwe diagnoses geregistreerd. In 2020, het meest recente volledige jaar, zijn 590 nieuwe diagnoses geregistreerd.

In Figuur 1 zijn de in de Basisregistratie gemiddeld geregistreerde diagnoses over de jaren 2016 – 2020 uitgesplitst naar ICCC-3 hoofdklasse. In Figuur 2 zijn de gemiddelde in de Basisregistratie geregistreerde diagnoses over de jaren 2016- 2020 uitgesplitst naar ICCC-3 subklasse. Zoals bekend is leukemie de meest voorkomende vorm van kanker bij kinderen, gevolgd door de hersentumoren. Dit wordt bevestigd door de aantallen in de Basisregistratie.




**Figuur 1:** Verdeling diagnoses in Basisregistratie 2016-2020 uitgesplitst naar ICCC-3 klasse (SKION, 2022)




**Figuur 2:** Gemiddeld aantal geregistreerde ziektegevallen per jaar in Basisregistratie 2016-2020 uitgesplitst naar ICCC-3 subklasse (SKION, 2022).

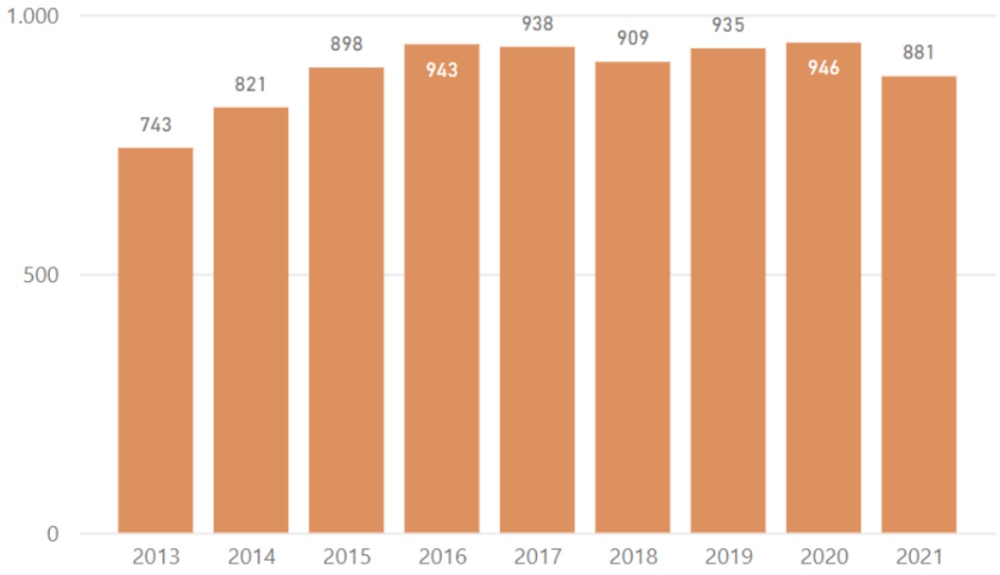
## Meer cijfers?

http://tiny.cc/SKION_BR_Visual

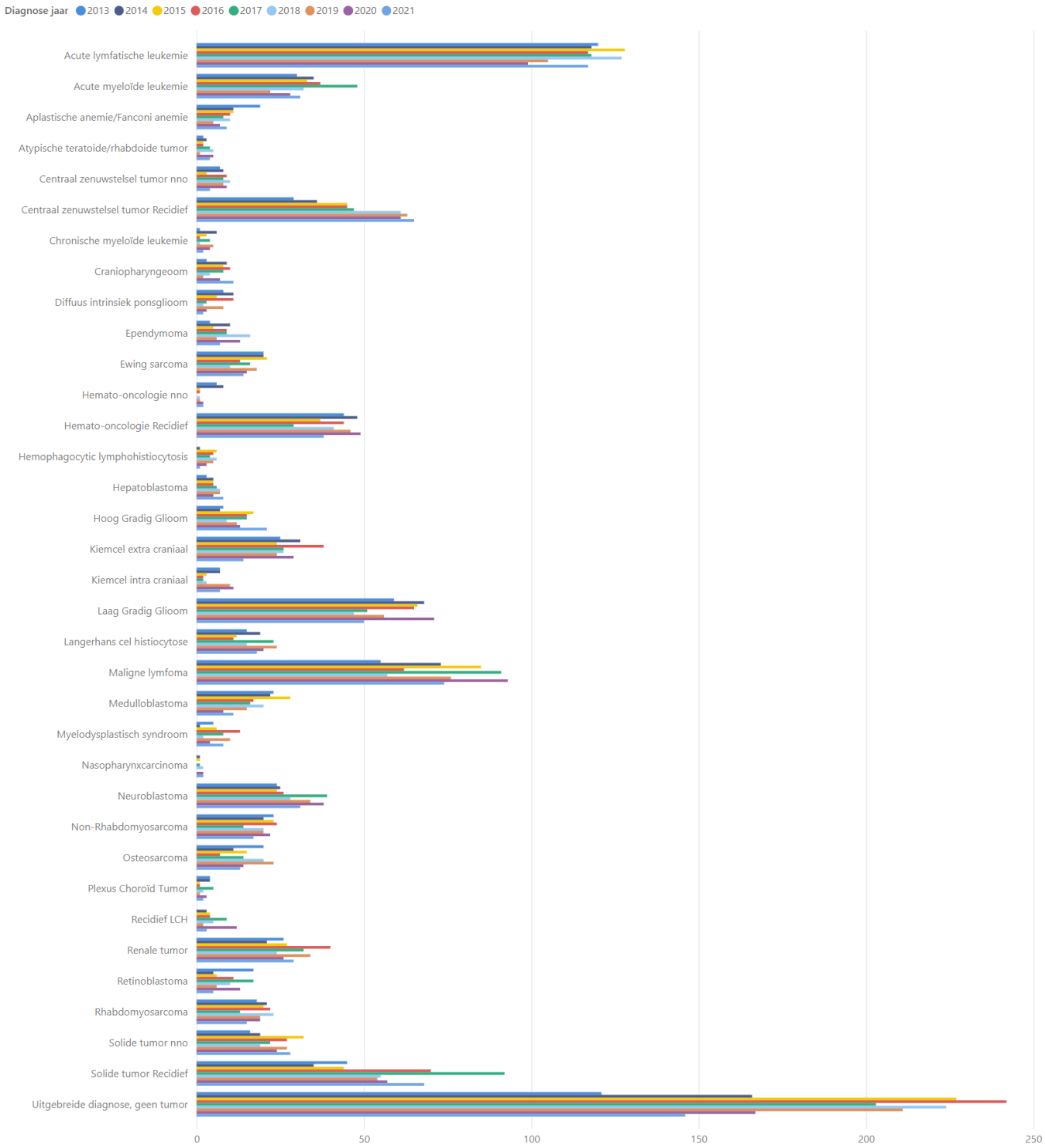
## 4.2. Zorgactiviteit

Op 1 januari 2013 is in Nederland de SKION Zorgactiviteit registratieprocedure van start gegaan t.b.v. de financiële declaraties van zorgproducten door de kinderoncologische centra in Nederland. Dit vond plaats in het kader van de DOT (DBC Onderweg naar Transparantie) declaraties. Voor elke melding van een kinderoncologische diagnose door een kinderoncologische centrum wordt een Zorgactiviteit (ZA) uitgegeven. Deze ZA wordt gebaseerd op onder andere de histologie en het stadium van de aandoening. Op basis hiervan en de aard van de aandoening wordt vervolgens de zorgzwaarte toegekend. In 2012 heeft het Centraal bureau van SKION (Laboratorium en Trial en Data Centrum) in samenwerking met o.a. de voorzitters van de Protocol- en Ziektecommissies een indeling systematiek en formulier logistiek opgezet.

In Figuur 3 is een overizcht weergegeven van het totaal aantal Zorgactiviteit aanmeldingen per diagnosejaar. Figuur 4 toont de aangemelde zorgactiviteiten per ziektebeeld per jaar (2013-2021).




**Figuur 3**: Totaal aantal Zorgactiviteit aanmeldingen per diagnosejaar (SKION, 2022).




**Figuur 4:** Aantal Zorgactiviteit aanmeldingen per ziektebeeld (SKION, 2022).

## 4.3. Wijziging verantwoordelijkheden

Tot 1 januari 2021 was SKION verantwoordelijk voor het bijhouden van de Basisregistratie en voor de uitgifte van de Zorgactiviteit. Sinds de inbedding van het SKION Laboratorium en Trial en Data Centrum in het Diagnostisch Lab en het Trial en Data Centrum van het Prinses Máxima Centrum, is het Prinses Máxima Centrum hier primair verantwoordelijk voor.

SKION focust zich vanaf 2021 op het vaststellen en het monitoren van landelijke behandelrichtlijnen binnen de kinderoncologie. Hiertoe is in 2019 de Centrale Raad opgericht. De Centrale Raad is een multidisciplinair orgaan dat verantwoordelijk is voor het beoordelen van behandelrichtlijnen en het adviseren van de Raad van Bestuur en Raad van Toezicht van SKION over de authorisatie van richtlijnen.
Een overzicht van de behandelrichtlijnen (en studies) op het gebied van hemato-oncologie is weergeven in Hoofdstuk 5.

***Meer info over de Centrale Raad? En SKION-richtlijnen?***
Skion - Centrale Raad (CR)
Skion - Voor professionals

# 5. Overzicht behandelrichtlijnen en studies hemato-oncologie

## 5.1. Behandelrichtlijnen en studies M4C ALL

| Aandoening | Initieel, recidief, refractair | Protocol | Type | Status per 01-04-2022 | Fase |
|---|---|---|---|---|---|
| ALL | Initieel | ALLtogether | Studie | Open | Fase III |
| ALL <1 jr zonder MLL-r | Initieel | ALLtogether | Studie | Open | Fase III |
| ALL < 1 jr met MLL-r | Initieel | Interfant06 | Studie | Open | Fase III |
| ALL < 1 jr met MLL-r | Initieel | Blinatumomab in infant ALL | Studie | Open | Fase I/II |
| ALL Ph+ | Initieel | EsPhALL2017/COGAALL1631 | Studie | Open | Fase III |
| HR B-ALL, MRD + bij einde consolidatie | Initieel | CASSIOPEIA | Studie | Open | Fase II |
| CD19+ BCP-ALL | Initieel | Blinatumomab therapy | Richtlijn | - | - |
| ALL SCT | Initieel | ALL SCTped 2012 FORUM | Studie | Open | Fase II/III |
| HR ALL | 1e recidief | IntReALL HR 2010 | Studie | Open | Fase II |
| ALL Ph+ | Recidief; refractair | Ponatinib 2018 | Studie | Open | Fase I/II |
| ALL Ph+ of MPAL | Recidief; refractair; Intolerant BCR-ALBL1-targeted TKI; BCR-ABL1 T315I mutatie | Pontanib-1501 | Studie | Open | Fase I/II |
| CD22+ BCP-ALL | 1e recidief VHR; 1e recidief na SCT; ≥ 2e recidief; refractair | Inotuzumab ITCC 059 | Studie | Open | Fase I/II |
| CD19+ BCP-ALL | Recidief na SCT; ≥ 2e recidief; refractair | Tisagenlecleucel | Richtlijn | - | - |
| CD19+ BCP-ALL | 1e recidief na SCT; ≥ 2e recidief | Blinatumomab therapy | Richtlijn | - | - |
| CD19+ BCP-ALL | 1e recidief na SCT; ≥ 2e recidief | Clofarabine based therapy | Richtlijn | - | - |
| CD19+ BCP-ALL | 1e of 2e recidief; refractair | ZUMA-4 | Studie | Open | Fase I/II |
| CD19+ BCP-ALL | ≥ 1 recidief; recidief na SCT; refractair | JCAR017 | Studie | Open | Fase I/II |
| CD38+ T- ALL | ≥ 2e recidief; refractair | Daratumumab ALL2005 | Studie | Open | Fase II |

| Aandoening | Initieel, recidief, refractair | Protocol | Type | Status per 01-04-2022 | Fase |
|---|---|---|---|---|---|
| T-ALL | 1e recidief na SCT; ≥ 2e recidief | Nelarabine based therapy | Richtlijn | - | - |
| B- ALL<br>T-ALL | 1$^{e}$ of 2$^{e}$ recidief; refractair | Isatuximab ACT15378 | Studie | Open | Fase I/II |
| MLL-r infant ALL | 1e recidief na SCT; > 2e recidief; refractair | Irinotecan in infants met MLL-r R/R ALL | Richtlijn | - | - |
| MLL-r infant ALL | ≥ 1 recidief; recidief na SCT; refractair | Tisagenlecleucel | Richtlijn | - | - |
| MLL-r infant ALL | Recidief na SCT; recidief/ refractair | JCAR017 | Richtlijn | - | - |
| ALL | ≥ 2e recidief | Clofarabine based therapy | Richtlijn | - | - |
| ALL | ≥ 2e recidief; refractair | M13-833 Venetoclax | Studie | Open | Fase I |
| ALL met RAS-pad activatie | ≥ 2e recidief; refractair | Seludex 2016 | Studie | Open | Fase I/II |

## 5.2. Behandelrichtlijnen en studies M4C myeloïde maligniteiten

| Aandoening | Initieel recidief, refractair | Protocol | Type | Status studie per 01-04-2022 | Fase |
|---|---|---|---|---|---|
| AML | Initieel | NOPHO-DBH AML2012 | Studie | Open | Fase III |
| AML Down | Initieel | ML DS 2018 | Studie | Open | Fase III |
| TMD Down | Initieel | TMD bij Down syndroom | Richtlijn | - | - |
| AML | Recidief | Behandeladvies recidief AML | Richtlijn | - | - |
| AML CD38+ | Recidief | Isatuximab ACT15378 | Studie | Open | Fase I/II |
| AML met FLT3 ITD | Recidief; refractair | AC220-A-U202 (Quizartinib) | Studie | Open | Fase I/II |
| AML met KMT2A rearrangement | Recidief | SNDX studie | Studie | Nog niet open | Fase I/II |
| AML, vroeg recidief (<12 mnd) | Recidief | Vyxeos | Studie | Open | Fase Ib |
| AML of cardiotoxiciteit | 2e recidief | PedAL venetoclax | Studie | Open | Fase I |
| AML | ≥ 2e recidief; refractair | PARC studie | Studie | Gesloten | Fase I/II |
| AML | Moleculair recidief | AMoRe 2017 | Studie | Open | Fase II |
| | | | | | |
| APL | Initieel | ICC APL Study 02 | Richtlijn | - | - |
| APL | Recidief | ICC APL Study 02 | Richtlijn | - | - |
| | | | | | |
| CML, ph+ | Initieel | I-CML-Ped Study | Studie | Open | - |
| CML, ph+ | Initieel | BJH Guideline: Managing children with CML | Richtlijn | - | - |
| Chronische fase CML | Initieel | Bosutinib ITCC-054 | Studie | Open | Fase I/II |
| CML of intolerant voor eerdere TKI | Refractair | Bosutinib ITCC-054 | Studie | Open | Fase I/II |
| CML | Recidief; refractair | Ponatinib 2018 | Studie | Open | Fase I/II |
| | | | | | |
| LCH | Initieel | LCH IV | Studie | Open | - |
| LCH | Recidief | LCH IV | Studie | Open | - |

## 5.3. Behandelrichtlijnen en studies M4C maligne lymfomen

| Aandoening | Initieel, recidief, refractair | Protocol | Type | Status studie per 01-04-2022 | Fase |
|---|---|---|---|---|---|
| ALCL | Initieel | ALCL99 | Richtlijn | - | - |
| ALCL | Recidief; refractair | CRISP | Studie | Open | Fase 1b |
| | | | | | |
| B-NHL | Initieel | B-NHL2008 | Richtlijn | - | - |
| B-NHL | Initieel | Inter-B-NHL-Ritux 2010 | Richtlijn | - | - |
| Burkitt | Recidief | R-ICE/R-VICI | Richtlijn | - | - |
| Burkitt | Recidief | Zuma-4 | Studie | Open | Fase I/II |
| DLBCL; andere rijpe B-NHL | Recidief | R-ICE/HD-BEAM +/- allo-SCT | Richtlijn | - | - |
| PMBCL | Initieel | Inter-B-NHL-Ritux 2010 | Richtlijn | - | - |
| | | | | | |
| Hodgkin | Initieel | Pembrolizumab 2017-001123-53 | Studie | Open | Fase II |
| Hodgkin | Initieel | EuroNet-PHL-C2 | Richtlijn | - | - |
| Hodgkin | Recidief | Nivolumab /Brentuximab | Richtlijn | - | - |
| Hodgkin | Recidief | IGEV | Richtlijn | - | - |
| LPHL stadium 1/2 | Initieel | EuroNet-PHL-LP1 | Richtlijn | - | - |
| LPHL stadium 3 | Initieel | R-CVP | Richtlijn | - | - |
| LPHL stadium 4 | Initieel | EuroNet-PHL-C2 | Richtlijn | - | - |
| | | | | | |
| LBL | Initieel | LBL-2018 | Studie | Open | Fase III |
| LBL | Recidief | InterReALL + allo | Richtlijn | - | - |
| LBL | Recidief | Daratumumab (T-LBL)<br>Zoals bij ALL | Studie | Open | Fase II |

## 5.4. Behandelrichtlijnen en studies M4C beenmergfalen en myelodysplastisch syndroom

| Aandoening | Initieel, recidief, refractair | Protocol | Type | Status studie per 01-04-2022 | Fase |
|---|---|---|---|---|---|
| BMF | Initieel | Diagnostiek beenmergfalen | Richtlijn | - | - |
| | | | | | |
| AA | Initieel | Aplastische anemie | Richtlijn | - | - |
| | | | | | |
| FA | Initieel | Fanconi anemie | Richtlijn | - | - |
| | | | | | |
| MDS | Initieel | EWOG/MDS 2006 | Richtlijn | - | - |

## 5.5. Behandelrichtlijnen en studies hematopoietische stamceltransplantatie en immunotherapie

| Aandoening | Protocol | Type | Status studie per 01-04-2022 | Fase |
|---|---|---|---|---|
| ALL SCT | ALL SCTped 2012 FORUM | Studie | Open | Fase II/III |
| Acute GvHD | Behandelrichtlijn acute GvHD bij pediatrische patiënten | Richtlijn | - | - |
| Chronische GvHD | Ibrutinib GvHD 2017 | Studie | Open | Fase I/II |

## 5.6. Tumorspecifieke, supportive care en overige studies

| Studie | Indicatie | Volledige titel |
|---|---|---|
| | | **Tumorspecifiek** |
| **MRI-Ciproxin study** | Skeletcomplicaties Ciprofloxacin ALL | Skeletal Complications of Prophylactic Ciprofloxacin in the Treatment of Pediatric ALL |
| **Pro-Teico study** | Infectie profylaxe AML | Teicoplanin as Infection Prophylaxis in Pediatric Acute MyeloidLeukemia (Pro-Teico study). An open-label, randomized clinical trial on teicoplanin infection prophylaxis in pediatric patients with acute myeloid leukemia |
| | | **Supportive care** |
| **DuLamp** | Mucositis | Divergent Low Level Laser Therapy as novel treatment for oral mucositis in pediatric cancer patients |
| | | **Overig** |
| **ITHER** | HR, recidiverende en refractaire maligniteiten | Clinical implementation of a pediatric cancer precision medicine program, enforced with personalized models. Individualized Therapies for Children with Very High Risk, Relapsed or Refractory Malignancies. |
| **PAVO** | CAR T | Long Term Follow-Up of Patients Exposed to Lentiviral-Based CAR T-Cell Therapy |
| **PIKACHU-study** | GvHD na HCT | PK/PD of corticosteroids in graft-versus-host disease after hematopoietic cell transplantation in children |

# 6. Studie informatie

## 6.1. Acute lymfatische leukemie - ALLtogether

| | |
|---|---|
| **Protocol:** | ALLTogether1 – A Treatment study protocol of the ALLTogether Consortium for children and young adults (0-45 years of age) with newly diagnosed acute lymphoblastic leukaemia (ALL) |
| **National coordinator:** | dr. I.M. van der Sluis |
| **Contact person TDC:** | F. Verwer |

**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | Karolinska University Hospital |
| **Coordinating Investigator:** | M. Heyman |
| **Sites in The Netherlands, PI:** | Princess Máxima Center, dr. I.M. van der Sluis<br>UMC Utrecht, dr. L.E. van der Wagen (not opened yet) |
| **Study Status:** | Open |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | The treatment protocol is an international multi-centre prospective, open label study arranged as a master protocol with additional non-randomised and randomized interventions. The randomised interventions are phase III and one of the non-randomised interventions is a phase II trial. |
| Primary objective: | The Primary Objective is to improve survival and quality of survival in children and young adults with acute lymphoblastic leukaemia (ALL) by testing a number of randomised and non-randomised interventions.<br>Since failure of the current treatment of ALL in children and young adults are due to both under- and overtreatment, both under- and over-treatment related adverse outcomes are targeted.<br>Thus, these interventions are designed to either:<br>– decrease the risk of serious side-effects and therapy-failure by treatment-related death for patients at low risk of relapse.<br>– decrease the risk of relapse for patients at high risk of relapse and therapy-failure by death from disease.<br>– decrease the risk of relapse and reduce toxic side-effects for patients with genetic lesions targetable by Tyrosine-kinase inhibition by the addition of Imatinib to standard chemotherapy.<br>– decrease the risk of serious side-effects for patients with high-risk B-cell precursor ALL by making them available for experimental immunotherapy. |

| | |
|---|---|
| Study population: | Patients with newly diagnosed T-lymphoblastic (T-cell) or B-lymphoblastic precursor (BCP) leukaemia (ALL), age 0- < 46 years, with the exception of infants with KMT2A-rearranged (KMT2A-r) BCP ALL.<br>In the Netherlands patients with age 0 - ≤ 25 years will be included. |

## STUDY OVERVIEW

Treatment in the ALLTogether protocol is based on risk-adapted stratification. Risk-factors that are used to identify patients with higher or lower risk of relapse include:

- Clinical criteria such as age, WBC count, genetic alterations
- MRD Response to (induction) therapy

Patients will be divided into five treatment strata:

- Standard Risk (SR)
- Intermediate Risk-low (IR-low)
- Intermediate Risk-high (IR-high)
- High-Risk (HR)-chemo
- HR-HSCT

The therapy consists of well-known therapy-elements:

- Induction
- Consolidation 1
- Consolidation 2
- Consolidation 3
- Delayed intensification
- Maintenance

HR patients are treated with HR blocks, and for Down patients an Interim Maintenance phase or a Capizzi-element is inserted replacing the standard CNS-consolidation.
A small selection of patients will have allogeneic stem-cell transplant (allo-SCT) as proposed standard of care and some of those patients may also qualify for experimental CAR-T therapy (conducted in separate studies).

**DESCRIPTION OF STUDY INTERVENTIONS:**

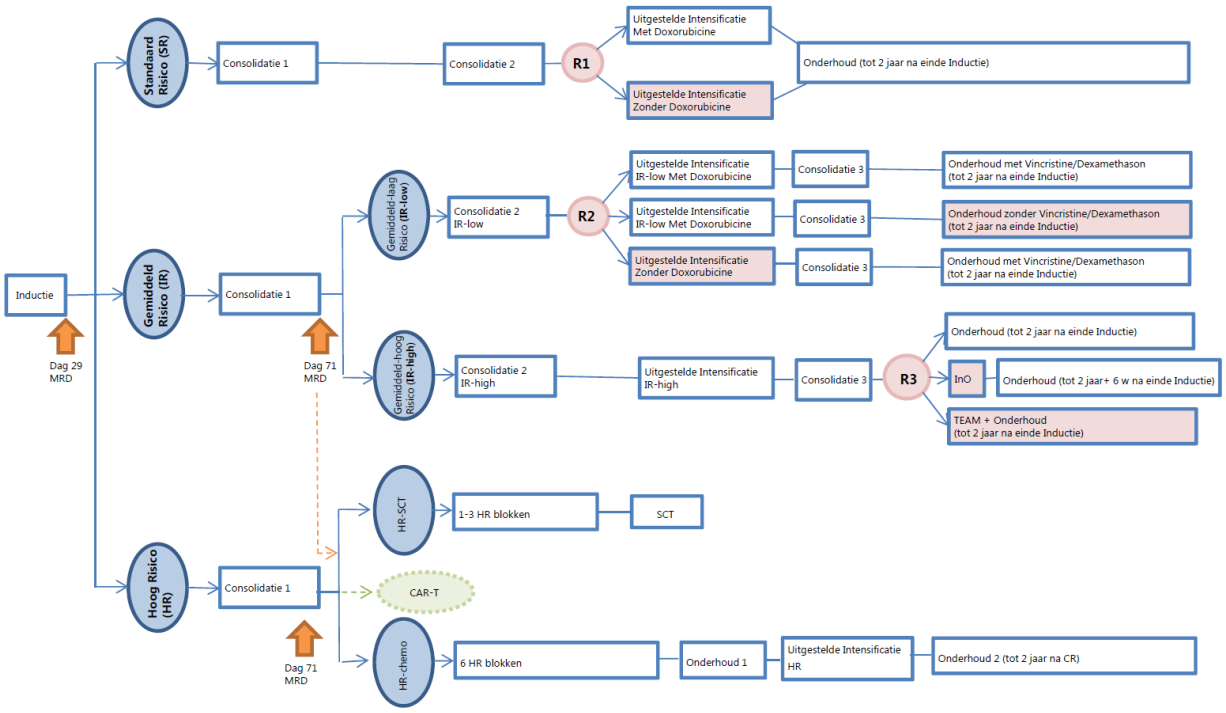
1. **Randomisation 1:** For SR patients it is tested if therapy can be safely reduced by the randomised omission of Doxorubicin in the Delayed Intensification phase.
2. **Randomisation 2:** IR-Low patients it is tested if the therapy may be safely reduced by the randomised omission of either Doxorubicin in the Delayed Intensification phase or the omission of Vincristine(VCR)/ Dexamethasone(Dexa) pulses in the Maintenance phase.
3. **Randomisation 3:**
   For IR-high patients it is tested if the relapse-risk can be reduced (and thereby the disease-free survival increased) by:
   a) the randomised introduction of two cycles of a new agent (Inotuzumab) before the Maintenance phase, or

b) the randomised introduction of low dose 6TG as and addition to the standard 6MP/MTX-based maintenance therapy.

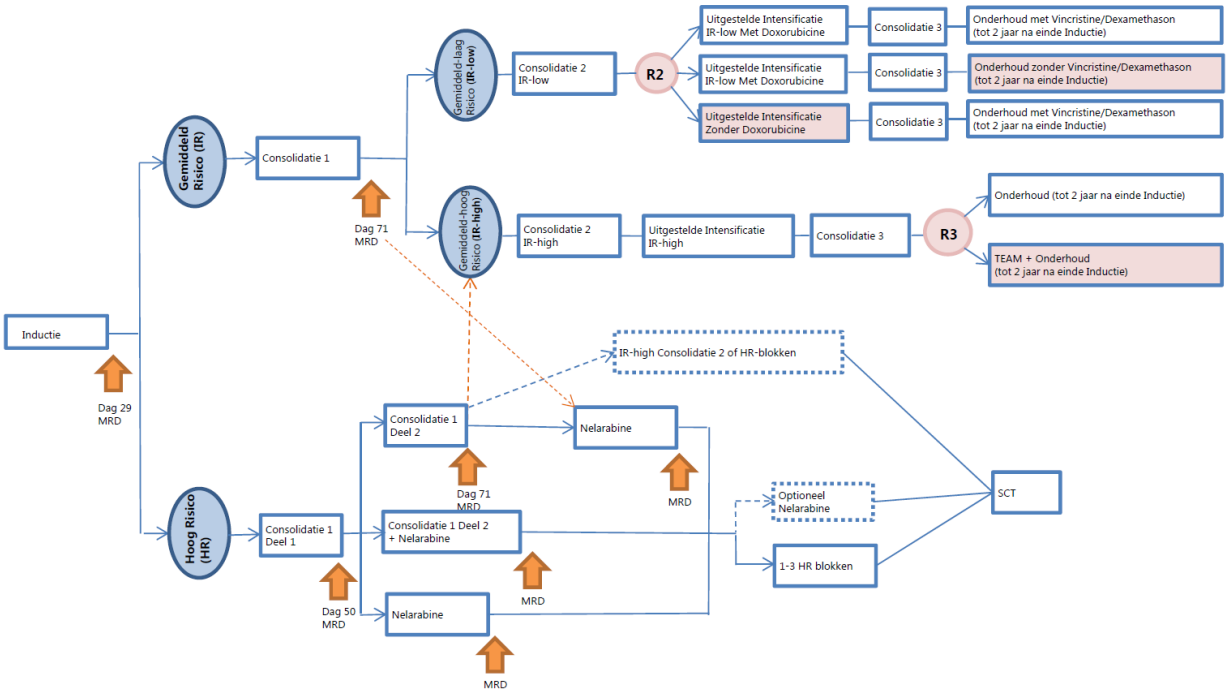
4) **TKI intervention:** For patients with ABL-class fusion genes in their leukaemic clone the TKI Imatinib will be introduced from day 15 of induction (<25 years) or day 30 (≥25 years).
5) HR BCP patients, for whom intensive HR chemotherapy or allo-HSCT is considered standard of care, are allowed to be enrolled in **separate CAR-T cell trials,** to improve the chance of cure while avoiding many of the toxic side-effects of allo-SCT.
   The remaining patients with HR-characteristics will be treated according to the protocol HR-arm.
6) **Blinatumomab intervention in Down Syndrome patients** with CD19 positive ALL. Down Syndrome-ALL patients who have end of Induction MRD detectable with MRD < 25 % will have 2 consolidation blocks replaced with two blocks of Blinatumomab. Outcomes will be compared with historical controls.

**Treatment overviews:**

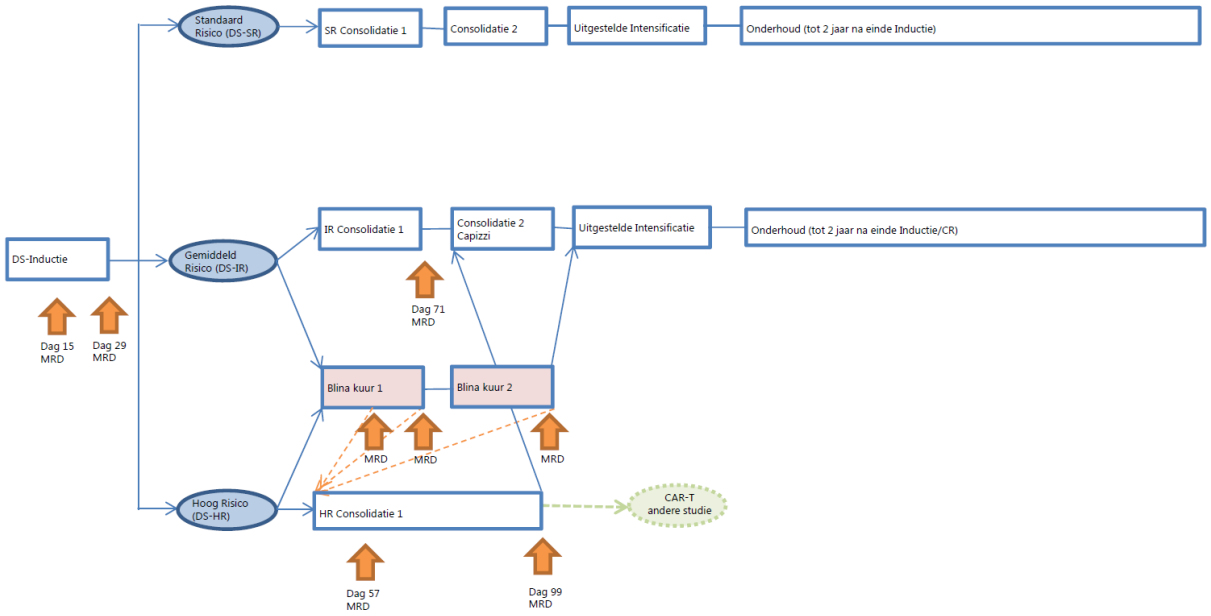
**BCP ALL:**



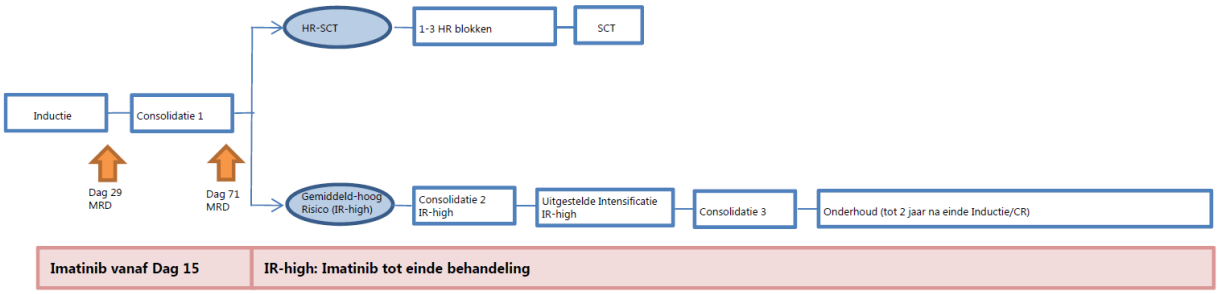
**T-ALL:**




**DS-ALL:**



**ABL-class ALL:**




| **PLANNING and RECRUITMENT** | *Cut off date: 29-MAR-2022* |
|---|---|

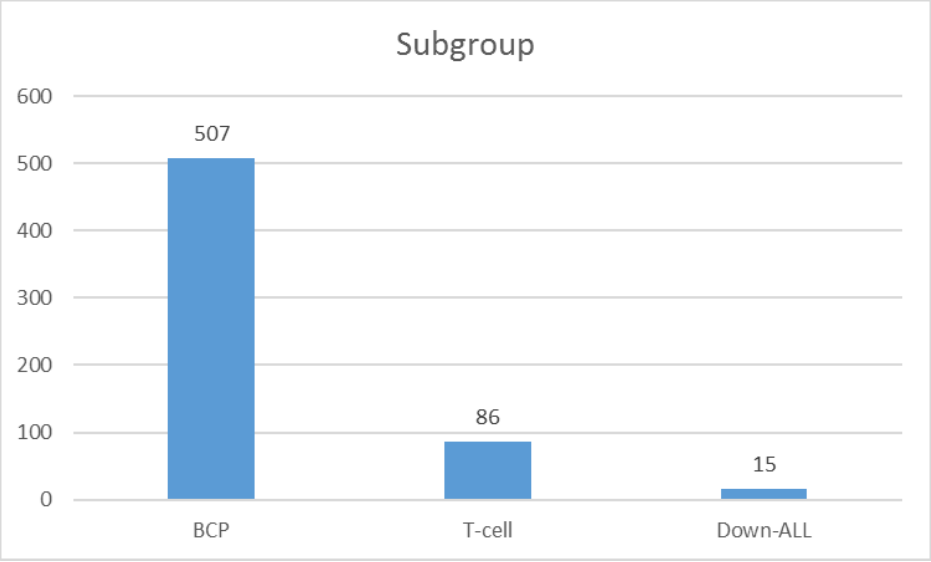
***Planning:***

| | |
|---|---|
| Start international recruitment: | 13-JUL-2020 |
| Start national recruitment: | 13-JUL-2020 |
| Expected date end of recruitment: | JUL-2025 |
| Expected date last patient out: | JUL-2030 |

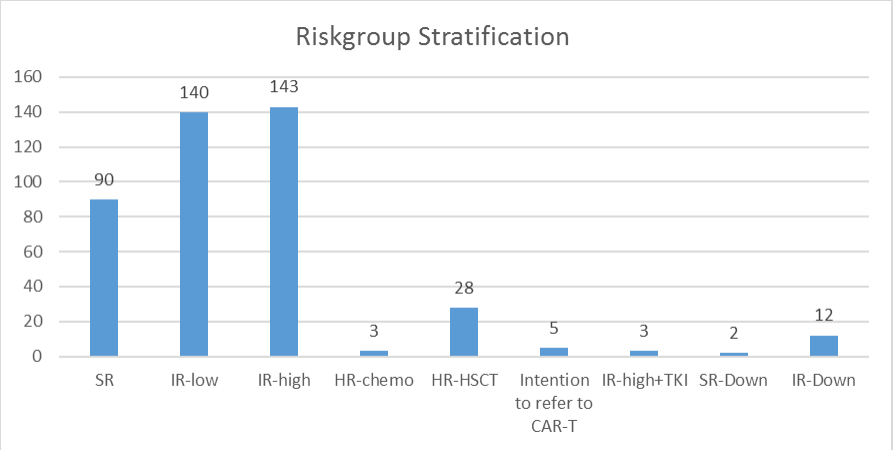
***International recruitment:***

| | |
|---|---|
| Recruitment target protocol: | 6430 patients |
| Actual number of patients included: | 608 patients |

No. of patients included per subgroup:



Riskgroup stratification: 426 patients have final riskgroup stratification reported:




Patients randomised / enrolled into the interventions:

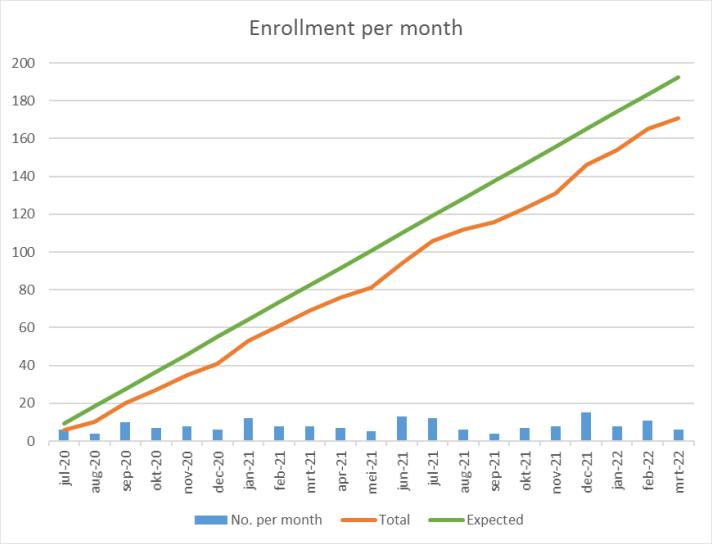
| Intervention | No. of patients |
|---|---|
| Randomisation 1 | 68 |
| Randomisation 2 | 101 |
| Randomisation 3 | 58 |
| TKI for ABL-class fusion | 6 |
| DS-Blina | 10 |

***National recruitment:***

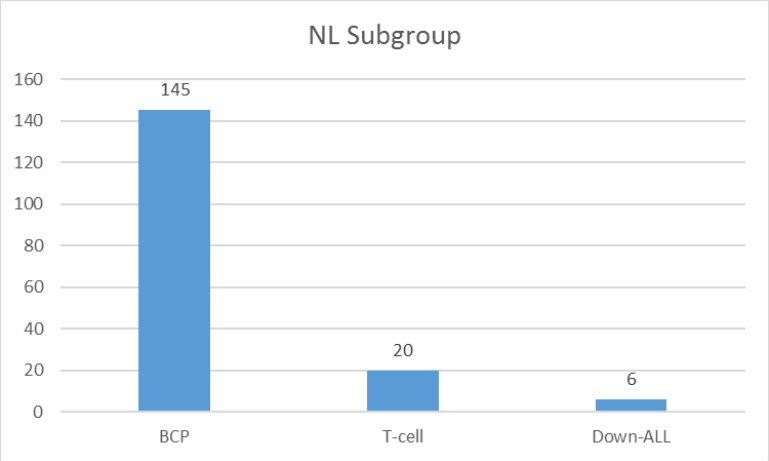
Recruitment target national: 565 patients

Actual number of patients included: 171 patients

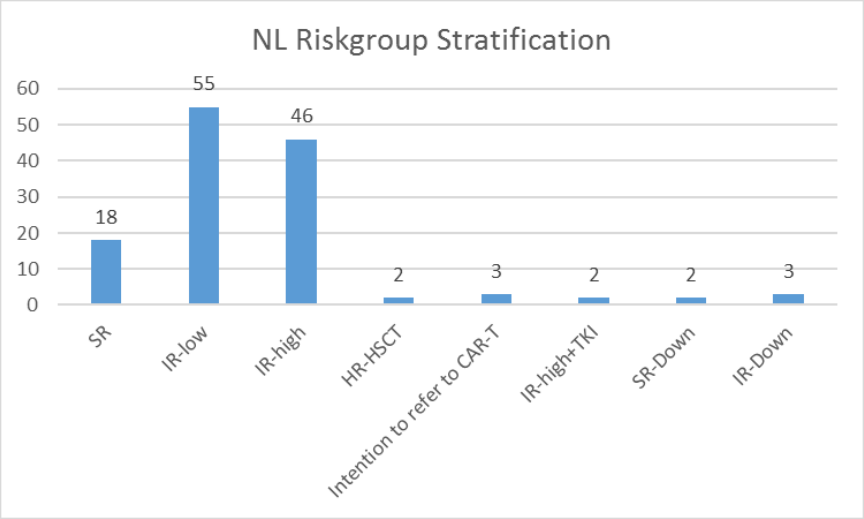
***Recruitment graphs:***



No. of patients included per subgroup:




Riskgroup stratification: 131 patients have final riskgroup stratification reported:




Patients randomised / enrolled into the interventions:

| Intervention | No. of patients |
|---|---|
| Randomisation 1 | 13 |
| Randomisation 2 | 38 |
| Randomisation 3 | 18 |
| TKI for ABL-class fusion | 2 |
| DS-Blina | 3 |

**ABSTRACTS / PUBLICATIONS**

*None yet*

## 6.2. Acute lymfatische leukemie - Interfant06

| | |
|---|---|
| **Protocol:** | International collaborative treatment protocol for infants under one year with acute lymphoblastic or biphenotypic leukemia |
| **National coordinator:** | Prof. dr. R. Pieters |
| **Contact person TDC:** | F. Verwer |

**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | AIEOP |
| **Coordinating Investigator:** | Prof. Dr. R. Pieters |
| **Sites in The Netherlands, PI:** | Princess Máxima Center, R. Pieters |
| **Study Status:** | Open |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | Multicenter randomized phase III study (randomization closed since 01-AUG-2016) |
| Primary objective: | To assess the role of an early intensification of two "AML" induction blocks versus protocol Ib directly after induction, in a randomized way in MR and HR patients. Randomisation stopped for patients diagnosed after the 1st of August 2016 |
| Study population: | Children aged 365 days or less with newly diagnosed acute lymphoblastic leukemia (ALL) or biphenotypic leukemia according to EGIL criteria. |

**Further details**

See https://prinsesmaxima.iprova.nl/QC/84-DJ-85

## 6.3. Acute lymfatische leukemie - Blinatumomab in infant ALL

| | |
|---|---|
| **Protocol:** | 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. A collaborative study of the Interfant network. |
| **National coordinator:** | I.M. van der Sluis |
| **Contact person TDC:** | P.E. Scholte-van Houtem |

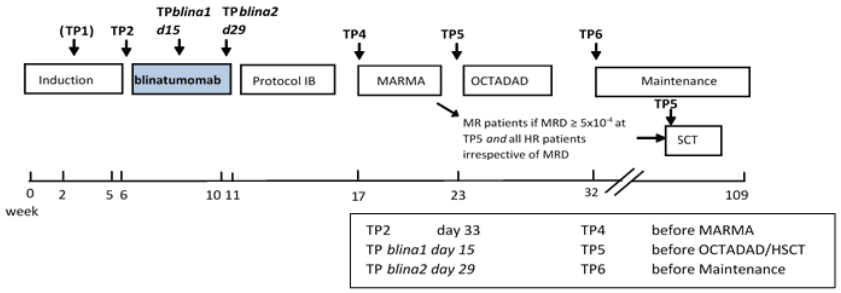
**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | Princess Máxima Center |
| **Coordinating Investigator:** | I.M. van der Sluis |
| **Sites in The Netherlands, PI:** | Princess Máxima Center, R. Pieters |
| **Study Status:** | Closed for new patient inclusions. Follow-up continues until February 2024. |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | Prospective, single-arm, international multi-center study. |
| Primary objective: | To assess the safety of 1 course of blinatumomab added to the Interfant-06 backbone in infants with newly diagnosed ALL. |
| Study population: | Newly diagnosed infants with ALL, who are treated according to the Interfant-06 protocol, stratified into the medium or high risk group, and have M1 or M2 marrow at the end of induction. |

**STUDY OVERVIEW**




Blinatumomab is added to the standard arm of the Interfant-06 backbone (IA-IB-MARMA-OCTADAD-maintenance). After induction therapy (IA) patients will receive 1 course of blinatumomab 15 µg/m2/day as a 4 week continuous infusion before protocol IB. After this blinatumomab course the patients continue with the regular Interfant-06 protocol.

## PLANNING and RECRUITMENT

*Cut off date: 01/04/2022*

***Planning:***

| | |
|---|---|
| Start international recruitment: | 31-JUL-2018 (actual date) |
| Start national recruitment: | 29-NOV-2018 (actual date) |
| Expected date end of recruitment: | 05-JUL-2021 (actual date) |
| Expected date last patient out: | 31-JAN-2024 |

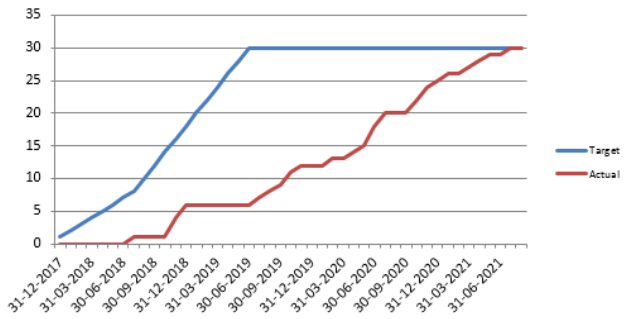
***International recruitment:***

| | |
|---|---|
| Recruitment target protocol: | 30 patients |
| Actual number of patients included: | 30 patients |

***National recruitment:***

| | |
|---|---|
| Recruitment target national: | 8 patients |
| Actual number of patients included: | 9 patients |

**Recruitment graph:**




## ABSTRACTS / PUBLICATIONS

IM van Der Sluis, P De Lorenzo, R Kotecha t al. A Phase 2 Study to Test the Feasibility, Safety and Efficacy of the Addition of Blinatumomab to the Interfant06 Backbone in Infants with Newly Diagnosed *KMT2A*-Rearranged Acute Lymphoblastic Leukemia. a Collaborative Study of the Interfant Network. *Blood* 2021; 138 (Supplement 1): 361. doi: https://doi.org/10.1182/blood-2021-144843

## 6.4. Acute lymfatische leukemie - EsPhALL2017/COGAALL1631

| | |
|---|---|
| **Protocol:** | EsPhALL2017/COGAALL1631 – International phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones |
| **National coordinator:** | Prof. Dr. R. Pieters |
| **Contact person TDC:** | F. Verwer |

**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | University of Milano-Bicocca |
| **Coordinating Investigator:** | Prof. Andrea Biondi |
| **Sites in The Netherlands, PI:** | Princess Máxima Center, dr. I.M. van der Sluis |
| **Study Status:** | Open |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | EsPhALL 2017/COG AALL1631 is an international collaborative protocol conducted by COG and EsPhALL with the primary objective of reducing treatment-related morbidity and mortality without adversely impacting DFS in Ph+ and ABL-class fusion positive ALL patients classified as Standard Risk (SR) based on low minimal residual disease (MRD) at week 10-12 of therapy. |
| Primary objective: | To compare disease-free survival (DFS) of Standard Risk (SR) pediatric Ph+ ALL treated with continuous imatinib combined with either a high-risk COG ALL chemotherapy backbone or the more intensive EsPhALL chemotherapy backbone. |
| Study population: | Patiënts with BCR-ABL1 fusion genes: newly diagnosed ALL (B-ALL or T-ALL) or mixed phenotypic acute leukemia (MPAL meeting 2016 WHO definition) with definitive evidence of BCR-ABL1 fusion by karyotype, FISH and/or RT-PCR. Age > 1 year and < 21 years at ALL diagnosis. |

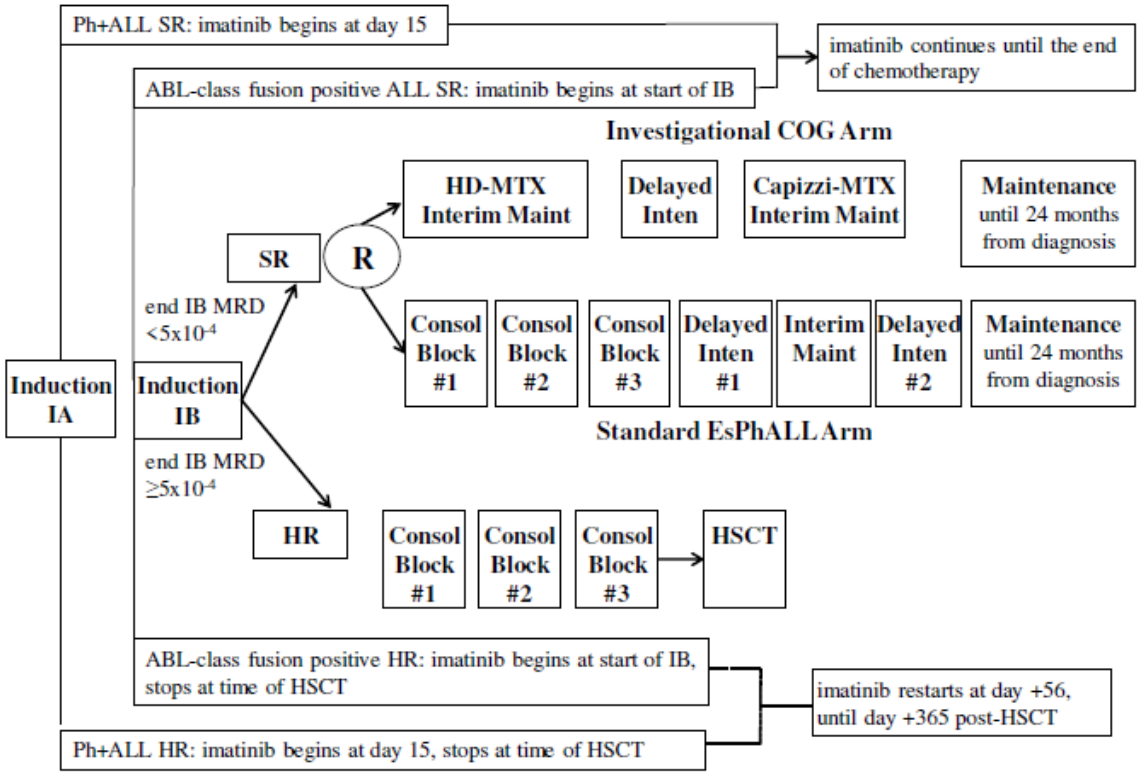
## STUDY OVERVIEW

All patients will begin Induction IA according to the institutional standard of care.
Patients will begin imatinib once daily at the time of trial enrollment or earlier, but no more than 14-days before enrollment.
After study entry, patients should receive at least 14 days of imatinib along with the rest of Induction IA therapy.
Two weeks after the end of Induction IB, a bone marrow aspirate will be performed.
Imatinib alone will be administered until end Induction IB MRD results are available and the final risk group is assigned.
End of Induction IB MRD results will be used to risk-stratify patients as follows:
**Standard risk (SR):** MRD < 5 x $10^{-4}$
**High risk (HR):** MRD ≥ 5 x $10^{-4}$

After risk group assignment, SR patients will be randomized to 1 of 2 regimens:

- **Arm A (EsPhALL Arm):** Current EsPhALL chemotherapy backbone + imatinib
- **Arm B (Investigational COG Arm):** COG HR chemotherapy backbone + imatinib

HR patients will be directly assigned to HR treatment arm (standard EsPhALL backbone) and allocated to HSCT in CR1. HSCT should occur as soon as feasible after recovery from Consolidation Block #3. Imatinib will be administered to all HR patients from Day +56 until Day +365 post-HSCT.



| **PLANNING and RECRUITMENT** | *Cut off date: 07-AUG-2021* |
|---|---|

***Planning:***

| | |
|---|---|
| Start international recruitment: | 08-AUG-2017 |
| Start national recruitment: | 09-NOV-2018 |
| Expected date end of recruitment: | AUG-2023 |
| Expected date last patient out: | DEC-2026 |

***International recruitment:***

| | |
|---|---|
| Recruitment target protocol: | 700 patients |
| Actual number of patients included: | 325 patients (226 SR patients in randomized study) |

***National recruitment:***

| | |
|---|---|
| Recruitment target national: | 28 patients |
| Actual number of patients included: | 8 patients (all SR patients, included in randomized study) |

**ABSTRACTS / PUBLICATIONS**

*None yet*

## 6.5. Acute lymfatische leukemie - CASSIOPEIA

**Protocol:** 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.

**GENERAL DETAILS**

**Sponsor:** *Novartis*

**Sites in The Netherlands, PI:** *Prinses Máxima Centrum, prof. dr. R. Pieters*

**Study Status:** Open

**STUDY DESIGN**

**Study Design:** This is a single arm, open-label, multi-center, phase II study

**Primary objective:** To evaluate the efficacy of tisagenlecleucel therapy as measured by the 5 year disease-free survival (DFS) by investigator assessment

**Study population:** The target population consists of pediatric and young adult subjects aged 1 to 25 years with de novo National Cancer Institute (NCI) HR BALL who are in CR1 after first-line treatment and are MRD ≥ 0.01% at EOC by central laboratory assessment

**Further details**

See https://prinsesmaxima.iprova.nl/QC/KF-57-68

## 6.6. Acute lymfatische leukemie - ALL SCTped 2012 FORUM

| | |
|---|---|
| **Protocol:** | ALL SCTped 2012 FORUM - Allogeneic Stem Cell Transplantation in Children and Adolescents with Acute Lymphoblastic Leukaemia |
| **National coordinator:** | Dr. M.B. Bierings |
| **Contact person TDC:** | J. Mur |

**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | St. Anna Kinderkrebsforschung GmbH, Wenen |
| **Coordinating Investigator:** | Prof. Dr. Christina Peters |
| **Sites in The Netherlands, PI:** | Princess Máxima Center, dr. M.B. Bierings<br>Leiden University Medical Center, Prof. Dr. A. Lankester (closed)<br>Wilhelmina's Children Hospital, dr. M.B. Bierins (site closed) |
| **Study Status:** | Open for recruitment, protocol randomisation closed |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | The ALL SCTped 2012 FORUM is a multinational, multi-centre, randomized, controlled, prospective phase III study for the therapy and therapy optimisation for children and adolescents with ALL in complete remission. The randomization is closed since December 2018, the study continued as registration. |
| Primary objective: | **Stratum 1 – randomisation related question was closed in December 2018; patients are in active follow-up**: To show that a non total body irradiation (TBI) containing conditioning (Flu/Thio/ivBu or Flu/Thio/Treo) results in a non-inferior survival as compared to conditioning with TBI/Etoposide in children older than 4 years after HSCT from a Human leucocyte antigen (HLA) identical sibling donor (MSD) or a HLA matched donor (MD).<br><br>**Stratum 1 – MSD/MD:** To explore the impact of risk factors on the incidence of adverse events of special interest (AESIs) and on overall survival and event free survival in the entire MSD/MD cohort (question 3 and 5).<br><br>**Stratum 2 - MMD:** To explore event free survival (EFS) after HSCT from HLA mismatched donors using mismatched unrelated donors (MMD), mismatched cord blood or HLA haplo-identical family members. |

| | |
|---|---|
| Study population: | Children and adolescents less than 21 years old with the diagnosis ALL in first or any following remission with high risk (HR) or very HR of recurrence of ALL. |

## PLANNING and RECRUITMENT

*Cut off date: 01/01/2022*

***Planning:***

| | |
|---|---|
| Start international recruitment: | 13-APR-2013 |
| Start national recruitment: | 01-JAN-2015 |
| Expected date end of recruitment: | 01-MAY-2023 |
| Expected date last patient out: | 01-MAY-2028 |

***International recruitment:***

| | |
|---|---|
| Recruitment target protocol: | >1000 patients |
| Actual number of patients included: | 1491 patients |

***National recruitment:***

| | |
|---|---|
| Recruitment target national: | 15 patients |
| Actual number of patients included: | 20 patients |

## ABSTRACTS / PUBLICATIONS

***'Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study'***, Peters et. al.
DOI: 10.1200/JCO.20.02529, Journal of Clinical Oncology 39, no. 4 (February 01, 2021) 295-307

## 6.7. Acute myeloide leukemie - NOPHO-DBH AML2012

**Protocol:** NOPHO-DBH AML 2012 Protocol: Research study for treatment of children and adolescents with acute myeloid leukaemia 0-18 years

**National coordinator:** Prof. Dr. G.J.L. Kaspers

**Contact person TDC:** F. Verwer

**GENERAL DETAILS**

**Sponsor:** Västra Götaland Regionen

**Coordinating Investigator:** J. Abrahamsson

**Sites in The Netherlands, PI:** Princess Máxima Center, Prof. dr. G.J.L. Kaspers

**Sites closed for recruitment:** Academisch Medisch Centrum, dr. F.C.H. Abbink
UMC Groningen, dr. W.J.E. Tissing
Erasmus MC, Prof. dr. C.M. Zwaan
VU medisch centrum, Prof. Dr. G.J.L. Kaspers
Radboud UMC, dr. M. Hagleitner
UMC Utrecht, dr. M.B. Bierings

**Study Status:** Open

**STUDY DESIGN**

Study Design: The NOPHO-DBH AML2012 study is a treatment and research protocol which contains two randomised studies. The first compares the efficacy of mitoxantrone vs. liposomal daunorubicin in the first induction course (DNX study) and the second compares the efficacy of ADxE vs. FLADx as the second induction course (FLADx study).

Primary objective: The AML 2012 study is a treatment and research protocol with the overall aim of improving prognosis for children and adolescents with AML.
The specific aims of the randomised studies are:
1) To investigate if either DaunoXome or Mitoxantrone, when given in course 1, is more effective in reducing the MRD level to < 0.1% as measured on day 22.
2) To investigate if either of the courses ADxE or FLADx is more effective in reducing the MRD level to < 0.1% after the second induction course.

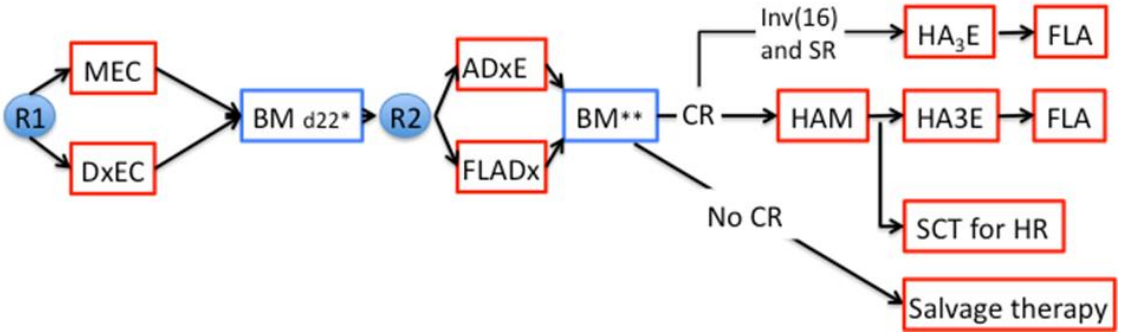
Study population: Patients with newly diagnosed Acute Myeloid Leukemia (AML), excluding patients with MDS-AML, myeloid leukemia of Down syndrome and acute promyelocytic leukemia, age <19 years at time of diagnosis.

## STUDY OVERVIEW

To improve outcome, an intensified induction regimen will be given, and a response guided risk-group stratification using flow cytometric MRD measurements to evaluate therapy response will be used. Patients with a poor response to the two induction courses will be assigned to the high-risk group and receive consolidation therapy including stem cell transplantation whereas those with a good response will be given three chemotherapy courses as consolidation therapy. An exception are patients with good response and inv(16), who will not be given HAM and thus receive two consolidation courses only. The only other cytogenetic feature that will affect risk stratification is the presence of an FLT3-ITD mutation which, when not associated with concomitant nucleophosmin (NPM1) mutation, will stratify patients to the high-risk group.

AML 2012 includes two randomised studies that both address the efficacy of induction therapy.
The first study compares the efficacy of mitoxantrone and DaunoXome in the first treatment course.
The second study compares ADxE (low-dose cytarabine, DaunoXome and etoposide) with FLADx (fludarabine, high-dose cytarabine and DaunoXome) as the second induction course.
DaunoXome can be replaced by Daunorubicine, in case DaunoXome is not available.

**Treatment overview:**




Per 13-12-2018 the 1st randomisation is closed, and all patients will receive MEC as 1st induction course.
Per 09-08-2021 the 2nd randomisation is also closed. All patients will receive standard AD(x)E as 2nd induction course.

## PLANNING and RECRUITMENT

*Cut off date: 07-MAR-2022*

***Planning:***

| | |
|---|---|
| Start international recruitment: | 01-MAR-2013 |
| Start national recruitment: | 11-JAN-2014 |
| Expected date end of recruitment: | JAN-2023 |
| Expected date last patient out: | JAN-2028 |

***International recruitment:***

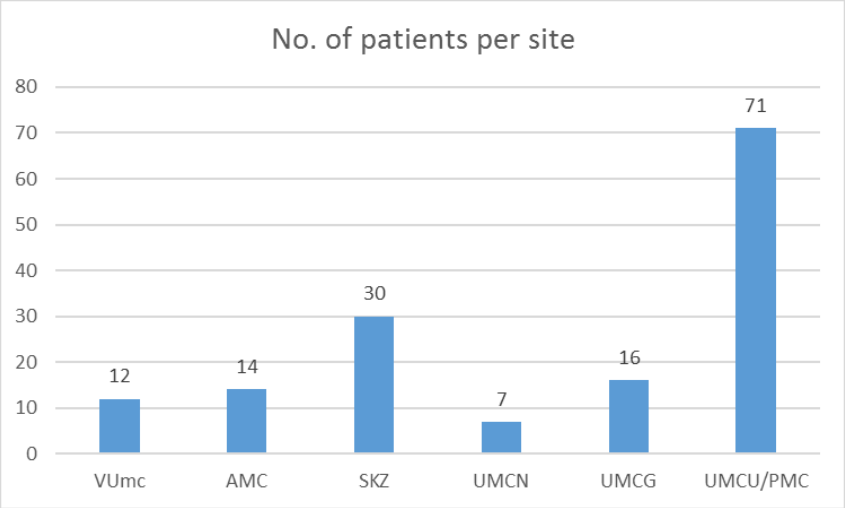
| | |
|---|---|
| Recruitment target protocol: | 750 patients |
| Actual number of patients included: | 770 patients |

***National recruitment:***

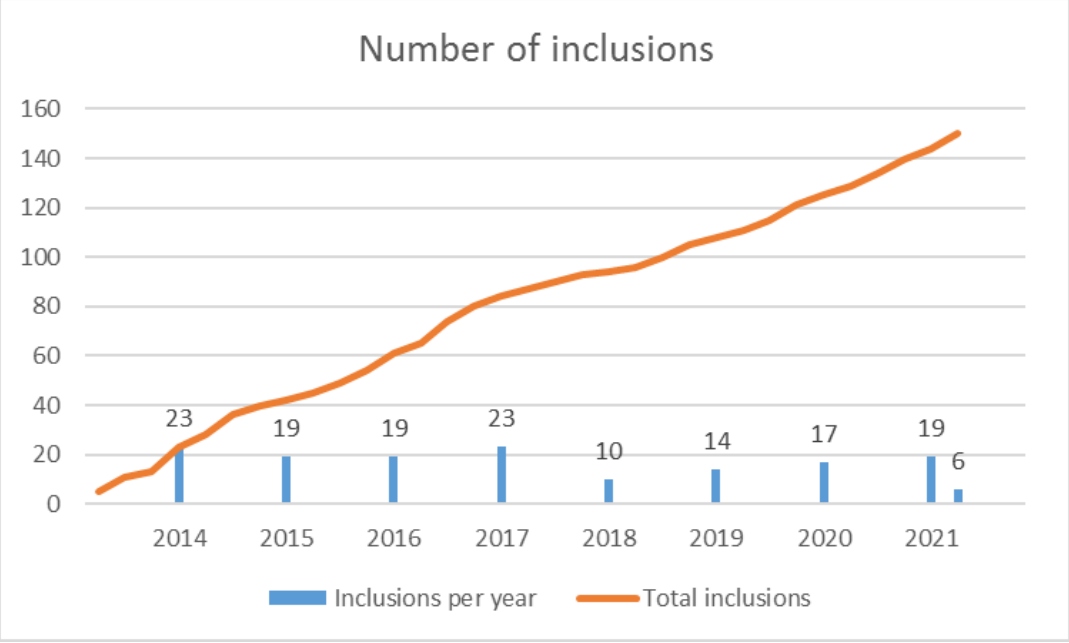
Recruitment target national: 150 patients

Actual number of patients included: 150 patients

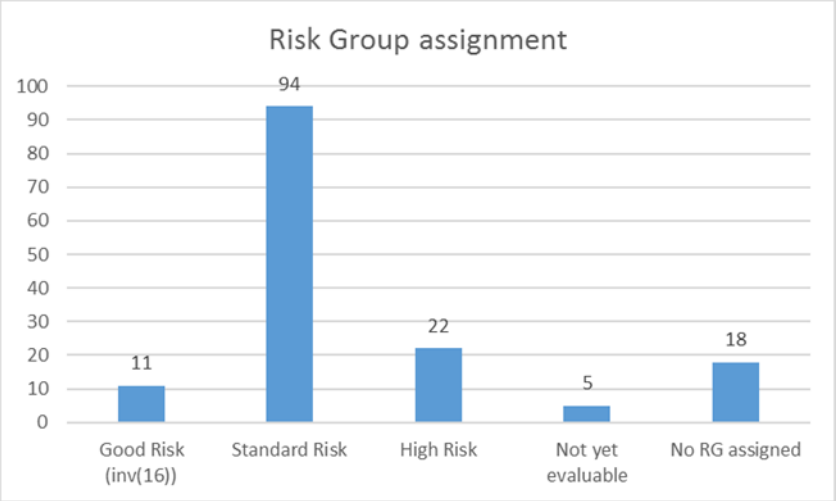
Number of patients included per site:




***Recruitment graphs:***



**Riskgroup assignment:**




**ABSTRACTS / PUBLICATIONS**

*None yet*

## 6.8. Acute myeloide leukemie - ML DS 2018

| | |
|---|---|
| **Protocol:** | Phase III Clinical Trial for CPX-351 in Myeloid Leukemia in Children with Down Syndrome 2018 |
| **National coordinator:** | Dr. B.F. Goemans |
| **Contact person TDC:** | J. Mur |

**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | German Pediatric Oncology Group (GPOH) |
| **Coordinating Investigator:** | Prof. Dr. Jan-Henning Klusmann |
| **Sites in The Netherlands, PI:** | Princess Máxima Center, dr. B.F. Goemans |
| **Study Status:** | Open |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | ML-DS 2018 is a prospective, non-randomized, open-label, historically-controlled, international and multicenter phase III trial for children with ML-DS. The single-arm non-inferiority trial will be compared against the historical control (ML-DS 2006 trial) with event free survival as the primary endpoint. |
| Primary objective: | Achieving an event-free survival, which is not inferior to the ML-DS 2006 trial. |
| Study population: | Children with myeloid leukemia associated with Down syndrome (ML-DS). |

**PLANNING and RECRUITMENT** *Cut off date: 01/04/2022*

***Planning:***

| | |
|---|---|
| Start international recruitment: | 01-NOV-2021 |
| Start national recruitment: | 23-FEB-2022 |
| Expected date end of recruitment: | 01-APR-2028 |
| Expected date last patient out: | 01-APR-2030 |

***International recruitment:***

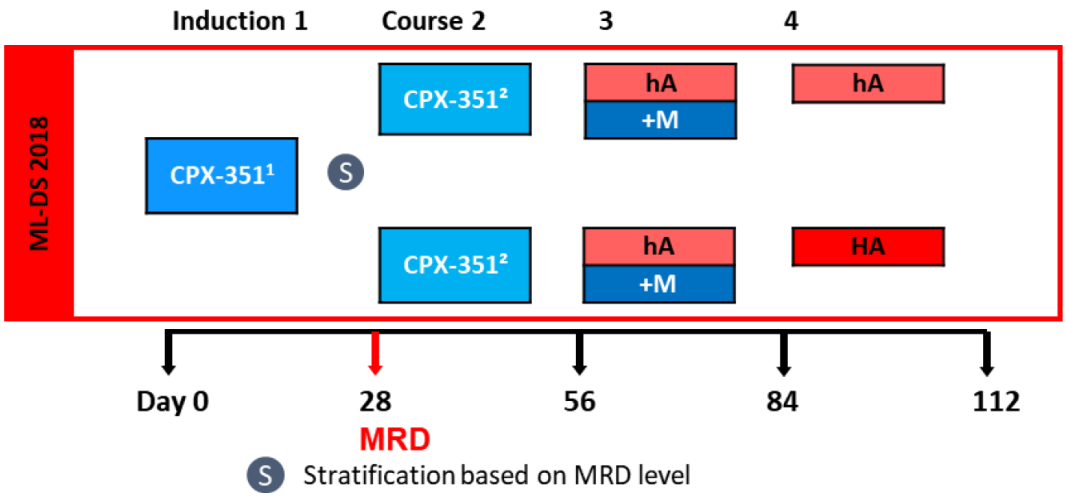
| | |
|---|---|
| Recruitment target protocol: | 150 patients |
| Actual number of patients included: | unknown, about 1 to 5 patients included |

***National recruitment:***

Recruitment target national: 10 patients

Actual number of patients included: 0 patients

**STUDY OVERVIEW**



## 6.9. Chronische myeloïde leukemie - I-CML-Ped Study

| | |
|---|---|
| **Protocol:** | INTERNATIONAL STUDY of chronic myeloid leukemia (CML) Treatment and Outcomes in Children and Adolescents (I-CML-Ped Study) |
| **National coordinator:** | dr. A.B. Versluys |
| **Contact person TDC:** | Femke Verwer |

**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | Centre Hospitalier Universitaire de Poitiers |
| **Coordinating Investigator:** | dr. F Millot |
| **Sites in The Netherlands, PI:** | Princess Máxima Center, Dr. A.B. Versluys |
| **Study Status:** | Open |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | Observational study |
| Primary objective: | 1) To describe the characteristics of CML in a large cohort of patients less than 18 years of age;<br>2) To describe the treatment policies;<br>3) To identify prognostic factors in this age-group;<br>4) To determine prognostic scoring systems in this population in order to optimize individual treatment choices;<br>5) To determine side effects and long term effects of treatments, mainly the tyrosine kinase inhibitor effect, on growth and development of a pediatric population. |
| Study population: | All patients less than 18 years of age with newly diagnosed Philadelphia positive and/or bcr-abl positive CML are eligible whatever the phase of the disease, the type of treatment and the enrollment or not in a clinical study. |

**Further details**

See https://prinsesmaxima.iprova.nl/QC/CX-NK-74

## 6.10. Chronische myeloïde leukemie - Bosutinib ITCC-054

| | |
|---|---|
| **Protocol:** | 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 |
| **National coordinator:** | NVT |
| **Contact person TDC:** | Marieke Willemse |

**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | Erasmus MC (EU, Switzerland, Israel) in collaboration with COG (Sponsor for the USA sites) |
| **Coordinating Investigator:** | Prof. Dr. C.M. Zwaan |
| **Sites in The Netherlands, PI:** | Erasmus MC/Sophia, Dr. C.M. Zwaan<br>Princess Máxima Center, Dr .I.M van der Sluis |
| **Study Status:** | Open |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | Phase 1-2, multicenter, international, single-arm, open-label study designed to identify a recommended dose of bosutinib administered orally once daily in pediatric patients with newly diagnosed chronic phase Ph+ CML (ND CML) and pediatric patients with Ph+CML who have received at least one prior TKI therapy (R/I CML), to preliminary estimate the safety and tolerability and efficacy, and to evaluate the PK of bosutinib in this patient population. |
| Primary objective: | **Phase 1:**<br>To determine the Recommended Phase 2 Dose (RP2D) of bosutinib for R/I ($RP2D_{R/I}$) and ND chronic phase ($RP2D_{ND}$) pediatric patients with CML, based on the pharmacokinetic, safety and tolerability profile of bosutinib observed at various dose levels in pediatric patients with CML who are resistant or intolerant to prior TKI therapy.<br><br>**Phase 2:**<br>To assess the PK of bosutinib at the $RP2D_{ND}$ and $RP2D_{R/I}$ in pediatric patients with ND or R/I Ph + CML and to assess the population PK of bosutinib. |
| Study population: | Pediatric patients (Age ≥1 and <18 years ) with newly diagnosed chronic phase or resistant/intolerant Ph + Chronic Myeloid Leukemia |

## STUDY OVERVIEW

The ITCC-054/AAML1921 study is conducted in Europe (including Switzerland and Israel,) and in the USA. COG acts as Sponsor for the USA sites. It is an intent-to-file study in collaboration with the pharmaceutical company.

| ***Sites:*** | |
|---|---|
| Number of Sites opened **EU** | **21**/23 open |
| Number of Sites opened **USA** | **41**/45 open |
| ***Phase 1 – Open for R/I patients*** | |
| # patients treated on DL1 (300mg/m2) | 6 – (No DLTs, escalation to DL2A) |
| # patients treated on DL2A (350mg/m2) | 11 – (1 DLT, escalation to DL2B) |
| # patients treated on DL2B (400mg/m2) | 10 – (1 DLT, slot increase to 10)<br>1 subject (39-88) not evaluable (treatment <21 days), slot replaced<br>1 subject (44-81) did not start treatment due to low ANC, slot replaced |
| Slots available: | **1** slot currently available on **DL2B** |
| In screening | 0 |
| ***Phase 2 – open for ND patients only*** | |
| # ND patients treated (300mg/m2) | **16** |
| In screening | 0 |
| ***Total numbers:*** | |
| Total number of patients screened | **45** |
| Total number of Screen Failures | 1 (subject 40-45 (ND), uncontrolled infection) |

## PLANNING and RECRUITMENT *Cutoff date: 04/APR/2022*

***Planning:***

Start international recruitment: 12-JUL-2017

Start national recruitment: 02-SEP-2016

Expected date end of recruitment: 01-FEB-2023

Expected date last patient out: 01-FEB- 2032

***International recruitment:***

Recruitment target protocol: 60 patients

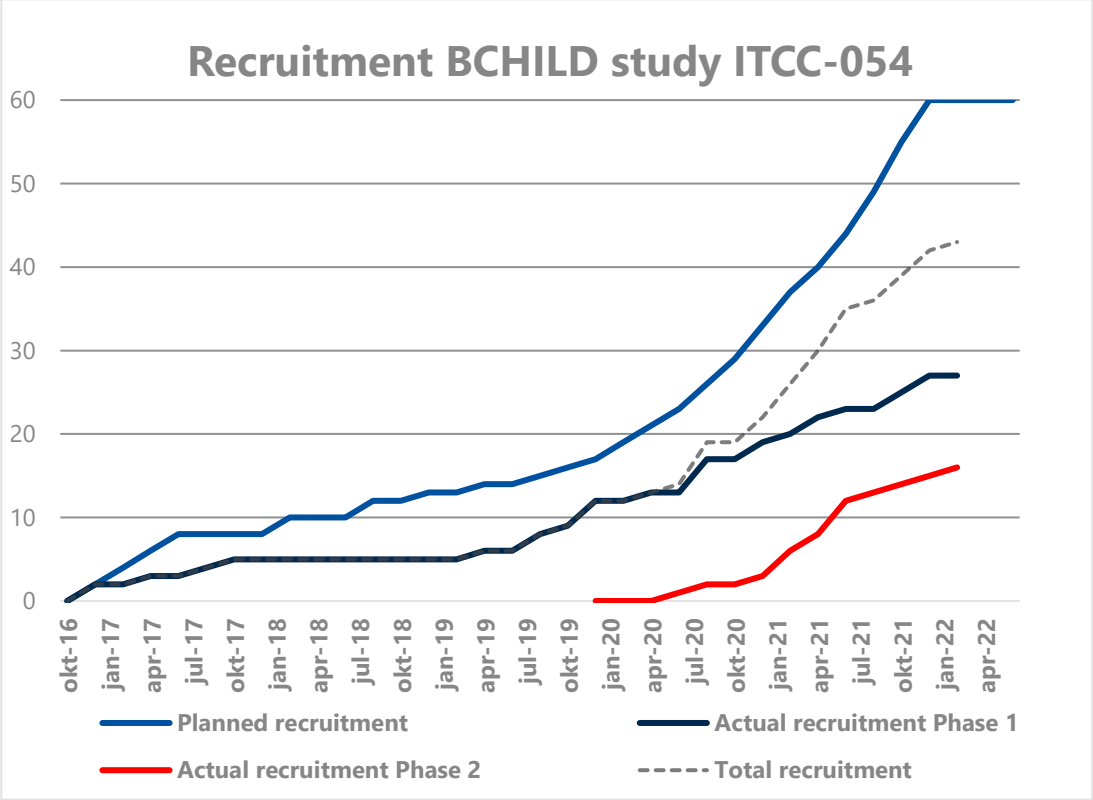
Actual number of patients included: 43 patients - 27 R/I patients, 16 ND patients

***National recruitment:***

Recruitment target national: 10 patients

Actual number of patients included: 7 patients – 4 Erasmus MC/Sophia, 3 Princess Máxima Center

***Recruitment graphs:***




**ABSTRACTS / PUBLICATIONS**

Paper: A Phase I/II Study of Bosutinib in Pediatric Patients with Resistant/Intolerant or Newly Diagnosed Philadelphia Chromosome-Positive Chronic Myeloid Leukemia, Study ITCC (Innovative Therapies for Children with Cancer European Consortium) 054 and COG (Children's Oncology Group Consortium) AAML1921: Results from the Phase I Trial in Resistant/Intolerant Patients (confex.com)

## 6.11. Langerhans Cel Histiocytose - LCH IV

**Protocol:** LCH-IV: International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis

**National coordinator:** Dr. C. van den Bos

**Contact person TDC:** F. Verwer

**GENERAL DETAILS**

**Sponsor:** St. Anna Kinderkrebsforschung

**Coordinating Investigator:** M. Minkov

**Sites in The Netherlands, PI:** Princess Máxima Center, dr. C. van den Bos

**Sites closed for recruitment:** Academisch Medisch Centrum, dr. F.C.H. Abbink
UMC Groningen, dr. W.J.E. Tissing
Erasmus MC, dr. A.C.H. de Vries
VU medisch centrum, dr. F.C.H. Abbink

**Study Status:** Open

**STUDY DESIGN**

Study Design: The LCH-IV is an international, multicenter, prospective clinical study for pediatric LCH (age < 18 years).

Primary objective:

- To investigate whether mortality in MS-LCH can be further decreased by an early switch of patients with risk organ involvement who do not respond to front-line therapy to more intensive salvage treatment (Stratum III or Stratum IV).
- To investigate in a randomized fashion whether further prolongation (12 vs. 24 months) and intensification (± mercaptopurine) of continuation therapy will reduce the reactivation rate and permanent consequences in MS-LCH.
- To investigate in a randomized fashion whether prolongation of continuation therapy (6 vs. 12 months) will reduce the reactivation rate and permanent consequences in SS-LCH patients with isolated “CNS-Risk” lesion or multifocal bone lesions.
- To investigate whether second-line therapy with PRED/ARA-C/VCR for 24 weeks, followed by 24 months of continuation therapy (indometacin vs. 6-MP/MTX) can help achieve disease resolution, prevent further reactivations and permanent consequences in patients with non-risk LCH (MS-LCH without risk organ involvement, isolated “CNS-Risk” lesion, or multifocal bone lesions), who are non-responders to first-line therapy, or experience disease progression/ reactivation in non-risk organs on or off first-line therapy.
- To study the value of 2-CdA in patients with isolated tumorous CNS-LCH

- To study whether systemic therapy with intravenous immunoglobulin (IVIG) or low dose cytarabine for patients with clinically manifest neurodegenerative CNS-LCH can achieve improvement of the neuro-psychological symptoms.
- To study the spectrum and incidence of permanent consequences in systemically treated patients, identify possible risk factors, and assess the role of systemic treatment in their prevention
- To prospectively study the natural course of SS-LCH in patients who initially are not candidates for systemic therapy, with respect to disease progression, reactivations, need for medical interventions, as well as permanent consequences, at any time after diagnosis.

Study population:

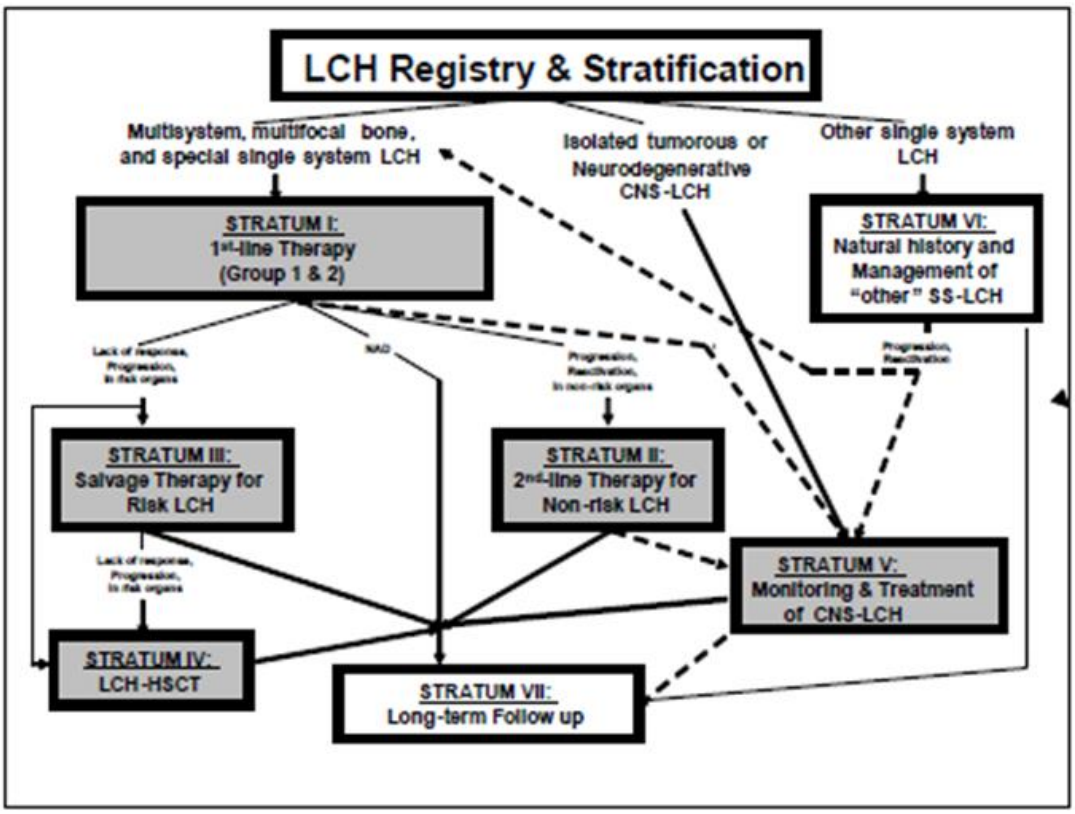
Patients < 18 years with definitive diagnosis of Langerhans cell histiocytosis.
**Stratum I Group 1:** Multisystem LCH:
Two or more organs/systems involved, with or without involvement of "Risk Organs" (e.g. hematopoietic system, liver, or spleen)
**Stratum I Group 2:** Single-system LCH:
- isolated "CNS-risk" lesion
- multifocal bone lesions (MFB)

**Stratum II:** Second-line treatment for non-risk LCH:
Patients of Stratum I who have:
- Progressive disease (AD worse) in non-risk organs after 6 weeks
- AD intermediate or worse in non-risk organs or AD better in risk organs after 12 weeks
- Disease progression (AD worse) in non-risk organs at any time during continuation treatment, AD intermediate or worse in risk-organs, who do not meet organ dysfunction eligibility criteria at any time of Stratum I treatment
- Active disease at the end of Stratum I treatment
- Disease reactivation in non-risk organs at any time after completion of Stratum I treatment
- Disease reactivation in risk-organs, who do not meet organ dysfunction criteriaat any time or after completion of Stratum I treatment

## STUDY OVERVIEW

**OVERALL TREATMENT CONCEPT:**
Depending on stratification and indication for treatment at the next step the patients will be assigned to the following Strata:

- **STRATUM I:** First-line therapy for patients with MS-LCH (Group 1) and patients with SS-LCH (isolated CNS-risk or multifocal bone lesions) (Group 2). Treatment includes randomized comparisons in both Groups
- **STRATUM II:** Second-line treatment for non-risk LCH. Treatment includes randomized comparison of two continuation treatment regimens.
- **STRATUM III:** Salvage treatment for risk LCH (patients with dysfunction of risk organs who fail first-line therapy)
- **STRATUM IV:** Stem Cell transplant for risk LCH (patients with dysfunction of risk organs who fail first-line therapy)
- **STRATUM V:** Monitoring and Treatment of isolated tumorous and neurodegenerative CNS-LCH
- **STRATUM VI:** Natural history and management of "other" SS-LCH not eligible for stratum I group 2
- **STRATUM VII:** Long-term follow-up




Patients may need to be enrolled in multiple strata sequentially as dictated by the course of their disease.

| **PLANNING and RECRUITMENT** | *Cut off date: 05-APR-2022* |
|---|---|

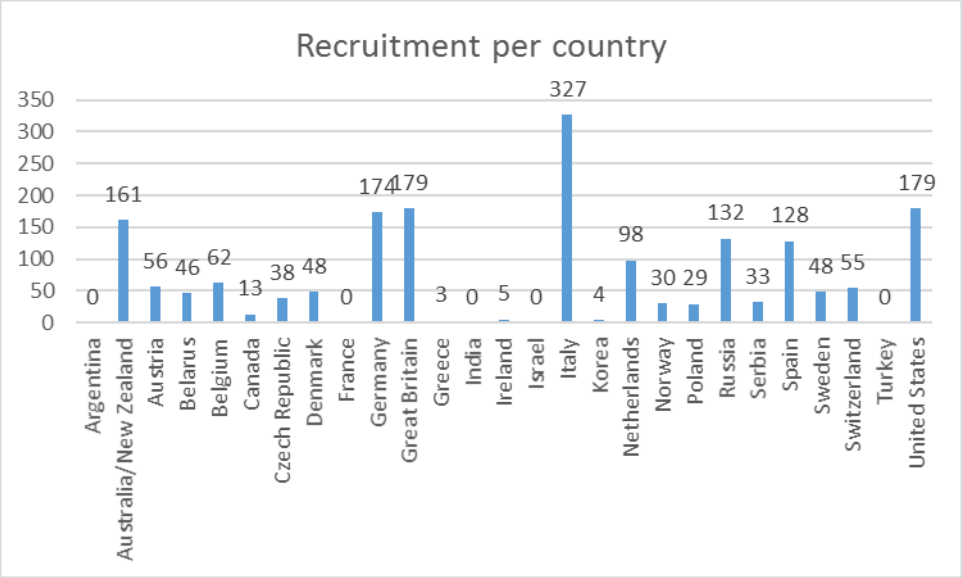
***Planning:***

| | |
|---|---|
| Start international recruitment: | 01-DEC-2011 |
| Start national recruitment: | 15-JAN-2014 |
| Expected date end of recruitment: | JAN-2023 |
| Expected date last patient out: | JAN-2028 |

***International recruitment:***

| | |
|---|---|
| Recruitment target protocol: | 1400 patients in Stratum I |
| Actual number of patients included: | 1848 patients total |

***Recruitment graphs:***




Inclusions per stratum:

| Stratum | No. of patients |
|---|---|
| Stratum I-Group 1 | 431 |
| Stratum I-Group 2 | 561 |
| Stratum II | 167 |
| Stratum III | 19 |
| Stratum IV | 0 |
| Stratum V | 20 |
| StratumVI | 782 |
| Stratum VII | 850 |
| No Stratum | 94 |

***National recruitment:***

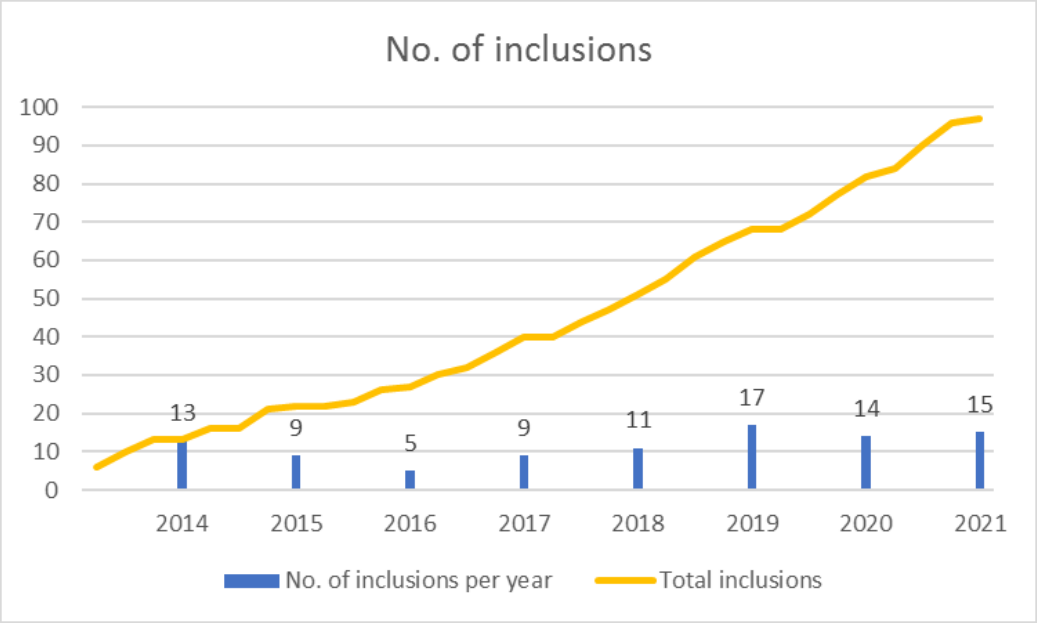
Recruitment target national: 85 patients

Actual number of patients included: 98 patients

Number of patients included per site:

| Site | No. of inclusions: |
|---|---|
| AMC | 25 |
| ErasmusMC | 6 |
| Prinses Máxima Centrum | 62 |
| UMCG | 4 |
| VUmc | 1 |

***Recruitment graphs:***




Inclusions per stratum:

| Stratum | 1st line therapy | 2nd line therapy | Salvage therapy |
|---|---|---|---|
| Stratum I group 1 | 16 | 1 | |
| Stratum I group 2 | 30 | | |
| Stratum II | | 12 | |
| Stratum III | | | 0 |
| Stratum IV | | 0 | 0 |
| Stratum V | 0 | | |
| Stratum VI | 52 | | |
| Stratum VII | | 6 | |
| **Total** | **98** | **18** | **0** |

**ABSTRACTS / PUBLICATIONS**

*None yet*

## 6.12. Hodgkin Lymfoom - Pembrolizumab 2017-001123-53

| | |
|---|---|
| **Protocol:** | An Open-label, Uncontrolled, Multicenter Phase II Trial of MK-3475 (Pembrolizumab) in Children and Young Adults with Newly Diagnosed Classical Hodgkin Lymphoma with Inadequate (Slow Early) Response to Frontline Chemotherapy (KEYNOTE 667). |

**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | Merck Sharp & Dohme Corp. (MSD) |
| **Sites in The Netherlands, PI:** | *Prinses Máxima Centrum, dr. A.* Beishuizen |
| **Study Status:** | Open |

**STUDY DESIGN**

| | |
|---|---|
| **Study Design:** | Parallel, multisided, uncontrolled trial |
| **Primary objective:** | To evaluate the objective response rate (ORR) by International Working Group (IWG) criteria as assessed by blinded independent central review (BICR) [Cheson, B. D., et al 2007] of pembrolizumab in combination with chemotherapy in slow early responders (SERs) by risk group (low, high). |
| **Study population:** | Children 3 to 17 years of age and young adults 18 to 25 years of age with newly diagnosed cHL |

**Further details**

See https://prinsesmaxima.iprova.nl/QC/58-FT-78

## 6.13. Lymfoblastair lymfoom - LBL-2018

| | |
|---|---|
| **Protocol:** | LBL 2018 - International cooperative treatment protocol for children and adolescents with lymphoblastic lymphoma |
| **National coordinator:** | dr. J.L.C. Loeffen |
| **Contact person TDC:** | D.A.E. Hendrickx PhD and J.J.P. Vreijling |

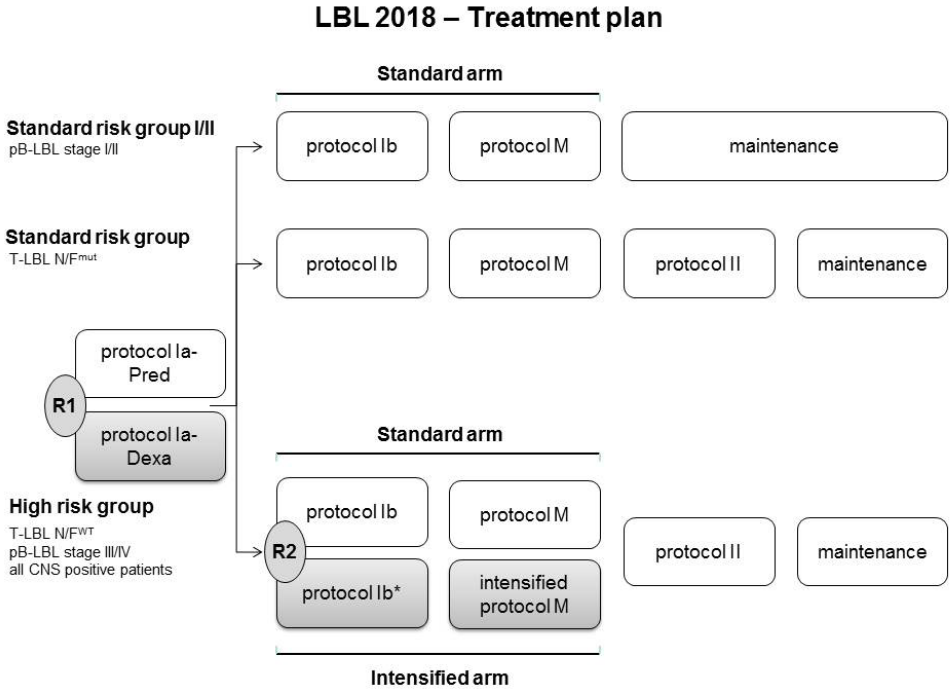
**GENERAL DETAILS**

| | |
|---|---|
| **Sponsor:** | University Hospital Münster |
| **Coordinating Investigator:** | Prof. Dr. B. Burkhardt |
| **Sites in The Netherlands, PI:** | Princess Máxima Center, dr. J.L.C. Loeffen |
| **Study Status:** | Open |

**STUDY DESIGN**

| | |
|---|---|
| Study Design: | International inter-group multi-centre open-label randomized prospective clinical trial |
| Primary objective: | • Randomization R1 Dexamethason vs Prednisolon in induction: Cumulative incidence of relapse with involvement of the CNS (CNS-relapse, pCICR). The time to relapse is the time from randomization to the first relapse or the date of last follow-up. Other events (non-response, progressive disease, relapse, second malignancy or death before and in CR) will be taken into account as competing events.<br>• Randomization R2 in High group (Notch1/FBXW7 wildtype) standard arm vs experimental arm with High risk blocks: Estimated probability of event-free survival (pEFS). The pEFS is the time from randomization to the first event (non-response, progressive disease, relapse, second malignancy or death from any cause) or date of last follow-up. |
| Study population: | Children and adolescents up to 18 years of age with untreated lymphoblastic lymphoma are potentially eligible for the study LBL 2018. |

## STUDY OVERVIEW




## PLANNING and RECRUITMENT

*Cut off date: 01/Apr/2022*

***Planning:***

Start international recruitment: 23-Aug-2019

Start national recruitment: 24-Jun-2021

Expected date end of recruitment: 22-Nov-2024

Expected date last patient out: 22-Nov-2027

***International recruitment (Cut off date 16/Dec/2021):***

Recruitment target protocol: 683 patients

Actual number of patients included: 156 patients

| **Initial treatment for whole core study cohort, incl. randomization R1** | **Patient no.** |
|---|---|
| Standard arm, protocol Ia with prednisolone (SA-Pred), including 13 patients not randomised and hence treated in the standard arm | 86 |
| Experimental arm, protocol Ia with dexamethasone (EA-Dexa) | 69 |
| Not applicable (drop-out) | 1 |
| Total | 156 |

| Risk-group adapted treatment, incl. randomisation 2 for high risk group | Patient no. |
|---|---|
| Standard risk group I/II | 5 |
| Standard risk group | 78 |
| High risk group, standard arm (incl. 10 patients not randomised) | 37 |
| High risk group, experimental arm | 26 |
| Risk group not yet known | 8 |
| Not applicable (drop-out) | 2 |
| Total | 156 |

***National recruitment:***

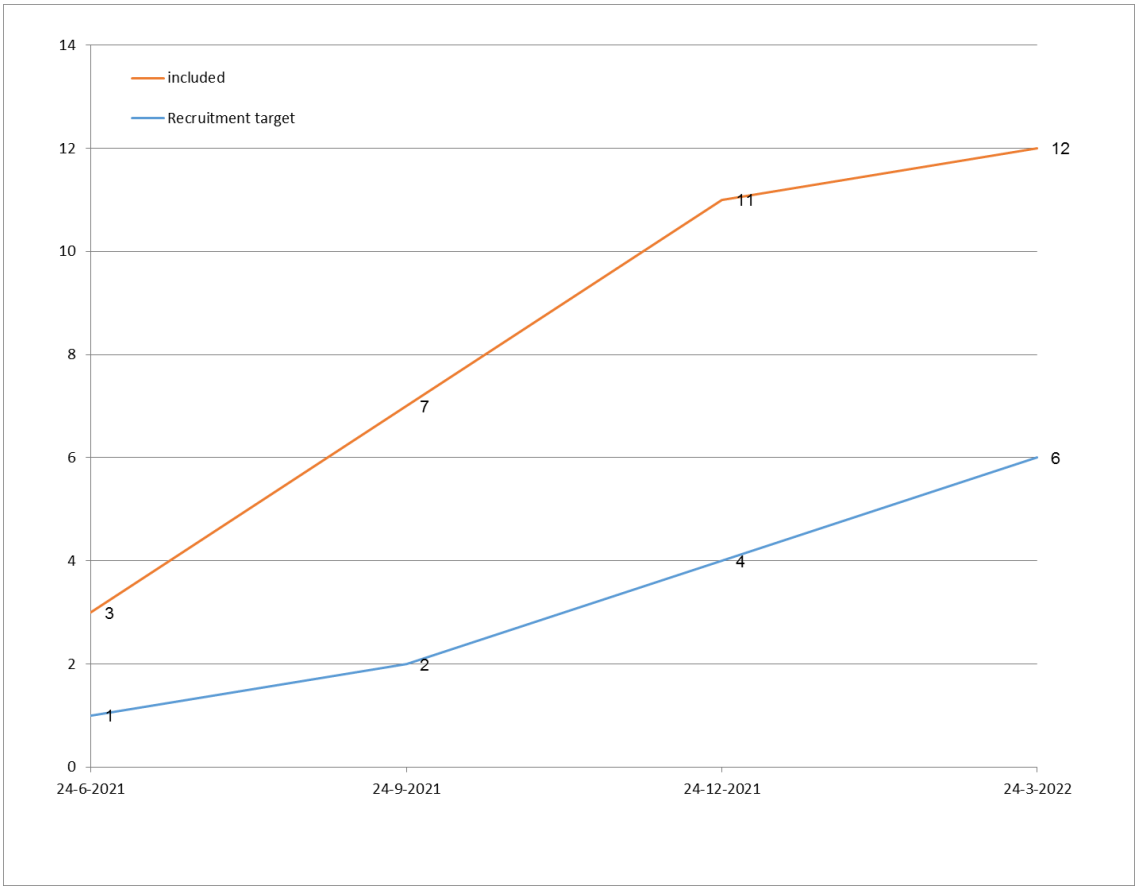
Recruitment target national: 42 patients

Actual number of patients included: 12 patients

| Initial treatment for whole core study cohort, incl. randomization R1 | Patient no. |
|---|---|
| Standard arm, protocol Ia with prednisolone (SA-Pred), including 13 patients not randomised and hence treated in the standard arm | 8 |
| Experimental arm, protocol Ia with dexamethasone (EA-Dexa) | 4 |
| Total | 12 |

| Risk-group adapted treatment, incl. randomisation 2 for high risk group | Patient no. |
|---|---|
| Standard risk group I/II | 0 |
| Standard risk group | 6 |
| High risk group, standard arm (incl. 1 patient not randomised) | 3 |
| High risk group, experimental arm | 0 |
| Risk group not yet known | 3 |
| Total | 12 |

***Recruitment graphs:***




**ABSTRACTS / PUBLICATIONS**

Trinquand, Amélie; Plesa, Adriana; Abdo, Chrystelle; Subtil, Fabien; Aladjidi, Nathalie; Rigaud, Charlotte et al. (2021):
Toward Pediatric T Lymphoblastic Lymphoma Stratification Based on Minimal Disseminated Disease and NOTCH1/FBXW7 Status.
In: HemaSphere 5 (10), e641. DOI: 10.1097/HS9.0000000000000641.

Lovisa, Federica; Gallingani, Ilaria; Varotto, Elena; Pasin, Cristiano; Carraro, Elisa; Michielotto, Barbara et al. (2021):
Prognostic Role of Minimal Disseminated Disease and NOTCH1/FBXW7 Mutational Status in Children with Lymphoblastic Lymphoma: The AIEOP Experience.
In: Diagnostics (Basel, Switzerland) 11 (9). DOI: 10.3390/diagnostics11091594

Burkhardt, Birgit; Taj, Mary; Garnier, Nathalie; Minard-Colin, Veronique; Hazar, Volkan; Mellgren, Karin et al. (2021):
Treatment and Outcome Analysis of 639 Relapsed Non-Hodgkin Lymphomas in Children and Adolescents and Resulting Treatment Recommendations.
In: Cancers 13 (9). DOI: 10.3390/cancers13092075

Kroeze, Emma; Weijers, Dilys D.; Hagleitner, Melanie M.; Groot-Kruseman, Hester A. de; Jongmans, Marjolijn C. J.; Kuiper, Roland P. et al. (2022):

High Prevalence of Constitutional Mismatch Repair Deficiency in a Pediatric T-cell Lymphoblastic Lymphoma Cohort.
In: HemaSphere 6 (1), e668. DOI: 10.1097/HS9.0000000000000668.

Huang, Shuang; Jin, Ling; Yang, Jing; Duan, Yanlong; Zhang, Meng; Zhou, Chunju; Zhang, Yong-Hong (2021):
Characteristics of Central Nervous System (CNS) Involvement in Children With Non-Hodgkin's Lymphoma (NHL) and the Diagnostic Value of CSF Flow Cytometry in CNS Positive Disease.
In: Technology in cancer research & treatment 20, 15330338211016372. DOI: 10.1177/15330338211016372.

Samosir, Sunny Mariana; Utamayasa, I. Ketut Alit; Andarsini, Mia Ratwita; Rahman, Mahrus A.; Ontoseno, Teddy; Hidayat, Taufiq et al. (2021):
Risk Factors of Daunorubicine Induced Early Cardiotoxicity in Childhood Acute Lymphoblastic Leukemia: A Retrospective Study.
In: Asian Pacific journal of cancer prevention : APJCP 22 (5), S. 1407–1412. DOI: 10.31557/APJCP.2021.22.5.1407

## 7. Verpleegkundig onderzoek

## Orale mucositis

De afgelopen twee jaar is de oude SKION richtlijn herzien. Komend jaar zal deze richtlijn geïmplementeerd worden. De studies die hieruit voorkomen zijn:

Nulmeting van prestatie-indicatoren mondzorg voorafgaand aan de implementatie van de nieuwe richtlijn - Ida Bremer-Ophorst, Manon Roozendaal, vpk Máxima & Robin Dwarswaard, student HBO-V.

Haalbaarheid van mucositis meetinstrument Chimes onder verpleegkundigen en ouders - Ida Bremer-Ophorst, vpk Máxima & Florence Lingg, master student VW.

Therapietrouw mondzorg bij adolescenten - Linde Pothoff VS i.o.

## Misselijkheid

Het onderzoek naar misselijkheid spitst zich toe op het vinden van een geschikt meetinstrument voor misselijkheid en het ontwikkelen van niet-medicamenteuze interventies.

Validatie onderzoek van twee meetinstrumenten voor misselijkheid, dit onderzoek is onderdeel van de Davinchy studie - Els Haverkate, vpk Máxima.

Perspectief van verpleegkundigen op de implementaie van een meetinstrument voor misselijkheid - Marlies de Wit, master student VW.

Prevalentie, ernst en risicofactoren voor misselijkheid tijdens het eerste jaar van de behandeling en de impact op kwaliteit van leven, een analyse van KLIK data - Rosanne Been, vpk Máxima.

Niet-medicamenteuze behandeling van misselijkheid - Muriel Bakker VS i.o.

## Onderwerpen masterthesis verpleegkundig specialisten

Acht verpleegkundig specialisten werken aan hun masterthesis, twee onderwerpen zijn hierboven al beschreven. De overige onderwerpen zijn:

Behoeftes van kind en ouders bij het toedienen van HD MTX kuur - Anne Awater VS i.o.

Onderzoek naar factoren die van invloed zijn op hoe kinderen (12-18 jaar), ouders en zorgverleners omgaan met onderzekerheden van de CAR-T therapie - Marieke van der Vlugt VS i.o.

Vermoeidheid bij kinderen met een laaggradig glioom - Sanne Houtepen VS i.o.

Wensen en behoeften van adolescenten (> 16 jaar) op het gebied van privacy tijdens polibezoek en opvattingen van professionals binnen de hematologie over vertrouweljke zorg - Laura Stroo VS i.o.

Deelonderzoek Caterpillar studie - Lieke Walstijn VS i.o.

Complementaire interventies voor het verbeteren van comfort bij de hematologische patiënt - Annette Feenstra VS i.o.

1 Withycombe J Pediatrc Oncol Nursing 2019
2 Basch J Clin Oncol 2016

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## Sponsoren

Deze SKION-dag wordt mede mogelijk gemaakt door: