Stichting Kinderoncologie Nederland
SKION

Beleef het Brein

SKION-DAG 3 NOVEMBER 2022

-SYLLABUS-

NEURO-ONCOLOGIE

2022

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1. Voorwoord

Het is het 20e jaar dat de SKION-dagen worden georganiseerd! Een mijlpaal, en de waardering voor dit samenzijn is onverminderd hoog: veel inschrijvingen, groot enthousiasme om mee te denken over de inhoud van de dag.

SKION heeft sinds vorig jaar een evolutie zoniet een transitie doorgemaakt: van de landelijke spin in het web van de kinderoncologie naar de kritische vriend van het Prinses Máxima Centrum. Vanuit deze rol blijft het SKION van grote waarde in het autoriseren van evalueerbare richtlijnen in de kinderoncologische zorg, betrokken bij de evaluatie daarvan, en relevant in het bieden van een netwerk voor de professionals in de kinderoncologie in Nederland.
Tijdens deze SKION-dag presenteert bureau SKION de resultaten van haar activiteiten met betrekking tot de methodiek van vaststellen en evalueren van richtlijnen. We zullen ook onze ambitie voor de komende drie jaren met jullie delen.

Tijdens iedere SKION-dag ligt de focus op één van de afdelingen van het Prinses Máxima Centrum voor kinderoncologie, te weten: hemato-oncologie (inclusief stamceltransplantatie), solide tumoren, neuro-oncologie en quality of life. De syllabus wordt dan ook gevuld met gegevens van de betreffende afdeling/expertisegebied. Op 3 november heeft de afdeling neuro-oncologie het genoegen deze dag te mogen organiseren, met de uitdaging om voor een breder publiek, een leerzaam en aantrekkelijk aanbod te presenteren. Eén dag is krap om recht te doen aan alles wat er gebeurt op dit gebied. Zie het daarom vooral als een keuze uit een kleurrijk palet uitgevoerd door professionals uit verschillende disciplines.

Allereerst wordt een overzicht gepresenteerd van studies en richtlijnen voor neuro-oncologische aandoeningen. De aandacht zal hierbij gericht zijn op de nieuwe ontwikkelingen in een vertaling voor een breder publiek. We horen graag uw evaluatie.

In workshops gaan we nader in op zaken die relevant zijn voor alle professionals in het Máxima, in de Shared Care Centra of daarbuiten. Dit keer hebben wij 2 onderwerpen gekozen. De eerste workshop heeft als titel: ‘een hersentumor is meer dan alleen hoofdpijn’. In de tweede workshop getiteld: hoofdpijn bij de professional’ gaan we in op ethische vraagstukken binnen de kinderoncologie. Het hoogtepunt van deze dag is de lezing van Prof. dr. Victor Lamme, hoogleraar en hersenonderzoeker aan de Universiteit van Amsterdam. Professor Lamme zal nieuwe perspectieven schetsen over aspecten die ons allen raken, zowel bij de interactie met de patiënt als ook persoonlijk.

Wij verwachten U hiermee een zeer gevarieerd en boeiend programma te kunnen bieden met veel ruimte voor Uw actieve participatie, U bent allen van harte uitgenodigd op 3 november. Graag zullen wij U dan welkom heten,

Namens de SKION-commissie en bureau SKION,
Marc Bierings en Marc Vincent

Namens de afdeling neuro-oncologie,
Eelco Hoving, Kim Boshuisen en Sabine Plasschaert

2. Programma

Donderdag 3 november 2022 (Prinses Máxima Centrum & online)

"Beleef het Brein"

Plenair ochtendprogramma in het Auditorium

Voorzitter: *dr. Rick Brandsma (kinderneuroloog UMCU/WKZ, Prinses Máxima Centrum)*

Vicevoorzitter: *dr. Michael Meister (postdoc, Prinses Máxima Centrum)*

08.30 - 09.00 uur Ontvangst met koffie/thee in de Foyer

09.00 - 09.15 uur **Welkom en opening**
Prof. dr. Eelco Hoving (neurochirurg en clinical director afdeling neuro-oncologie, Prinses Máxima Centrum)
Marc Vincent, MHA (directeur, SKION)

9.15 - 10.15 uur **Standaard zorg in richtlijnen, hoe staat het ervoor?**
Dr. Marc Bierings (kinderoncoloog en voorzitter Centrale Raad, Prinses Máxima Centrum & SKION)
Marilyn Diks, MSc (beleidsmedewerker, SKION)
Marc Vincent, MHA (directeur, SKION)

10.15 - 10.45 uur Koffie/thee in de Foyer

10.45 - 11.30 uur **Trialportfolio neuro-oncologie**
Fase III studies - dr. Sabine Plasschaert (kinderoncoloog, Prinses Máxima Centrum)
Fase I/II studies - dr. Evelien de Vos (kinderoncoloog, Prinses Máxima Centrum)

11.30 - 12.00 uur **In & rondom de Tumor: Bloed Hersen Barrière & Micro-omgeving**
Dr. Dannis van Vuurden (kinderoncoloog, Prinses Máxima Centrum)

12.00 - 12.15 uur **Innovaties in de neurochirurgie**
Prof. dr. Eelco Hoving (neurochirurg en clinical director, Prinses Máxima Centrum)

12.15 - 13.30 uur Lunchen en netwerken in de Foyer
Poster walk in de Foyer

Workshops in het Auditorium

Vicevoorzitter: *Armanda Markesteijn – van Leeuwen, MSc (verpleegkundig specialist, Prinses Máxima Centrum)*

13.30 - 14.25 uur **Een hersentumor is meer dan alleen hoofdpijn**
Dr. Janneke van den Bergen (kinderneuroloog, UMCU/WKZ, Prinses Máxima Centrum)
Dr. Jeanine Voorman (revalidatiearts, UMCU/WKZ, Prinses Máxima Centrum)
Voorzitter: *dr. Kim Boshuisen (kinderneuroloog, UMCU/WKZ, Prinses Máxima Centrum)*

14.35 - 15.30 uur **Hoofdpijn bij de professional**
Dr. Netteke Schouten (kinderoncoloog, Prinses Máxima Centrum)
Drs. Rianne Maillé (psycholoog en consulent professionele steun, Maillé voor medici, Prinses Máxima Centrum)
Voorzitter: dr. *Sabine Plasschaert (kinderoncoloog, Prinses Máxima Centrum)*

Workshops in de Kleine Zaal

Vicevoorzitter: *Renske Karens – van Vliet (teamleider zorg, Prinses Máxima Centrum)*

13.30 - 14.25 uur **Hoofdpijn bij de professional**
Dr. Netteke Schouten (kinderoncoloog, Prinses Máxima Centrum)
Drs. Rianne Maillé (psycholoog en consulent professionele steun, Maillé voor medici, Prinses Máxima Centrum)
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Voorzitter: *dr. Kim Boshuisen (kinderneuroloog, UMCU/WKZ, Prinses Máxima Centrum)*

15.30 - 16.00 uur Koffie/thee in de Foyer

Plenair programma in het Auditorium “Trigger je brein”

Voorzitter: *prof. dr. Eelco Hoving (neurochirurg en clinical director, Prinses Máxima Centrum)*
Vicevoorzitter: *dr. Astrid v/d Heide (kinderneuroloog, UMCU/WKZ, Prinses Máxima Centrum)*

16.00 - 17.00 uur **Gastlezing - Hebben arts en patiënt wel vrije wil?**
Prof. dr. Victor Lamme (hoogleraar en hersenonderzoeker, Universiteit van Amsterdam)

17.00 - 17.15 uur **Afsluiting**
Prof. dr. Eelco Hoving (neurochirurg en clinical director, Prinses Máxima Centrum)
Marc Vincent, MHA (directeur, SKION)

17.15 - 18.00 uur Borrel in de Foyer

3. Abstract gastlezing – Hebben arts en patiënt wel vrije wil?

Prof. dr. Victor A.F. Lamme, Hoogleraar en hersenonderzoeker (Universiteit van Amsterdam, afd. Psychologie)

Tijd: 16.00-17.00 uur
Locatie: Auditorium

Vrije keuze voor behandeling en shared decision making staan centraal in de moderne gezondheidszorg. Maar hoe vrij zijn de keuzes die wij maken? Victor Lamme laat in een verhaal vol interactie, opmerkelijke filmpjes en sprekende voorbeelden zien hoe ons brein werkt en zonder dat we het weten voor ons de beslissingen neemt. Hoe worden keuzes beïnvloed door onbewuste emoties, wat we horen en zien, media, internet of de omgeving? En waarom hebben voorlichting en bewustwording vaak geen zin? Maar leer ook op welke 'knoppen' in het brein je kunt drukken om de patiënt wel degelijk de juiste keuze te laten maken. En lach daarbij ook een beetje om jezelf!

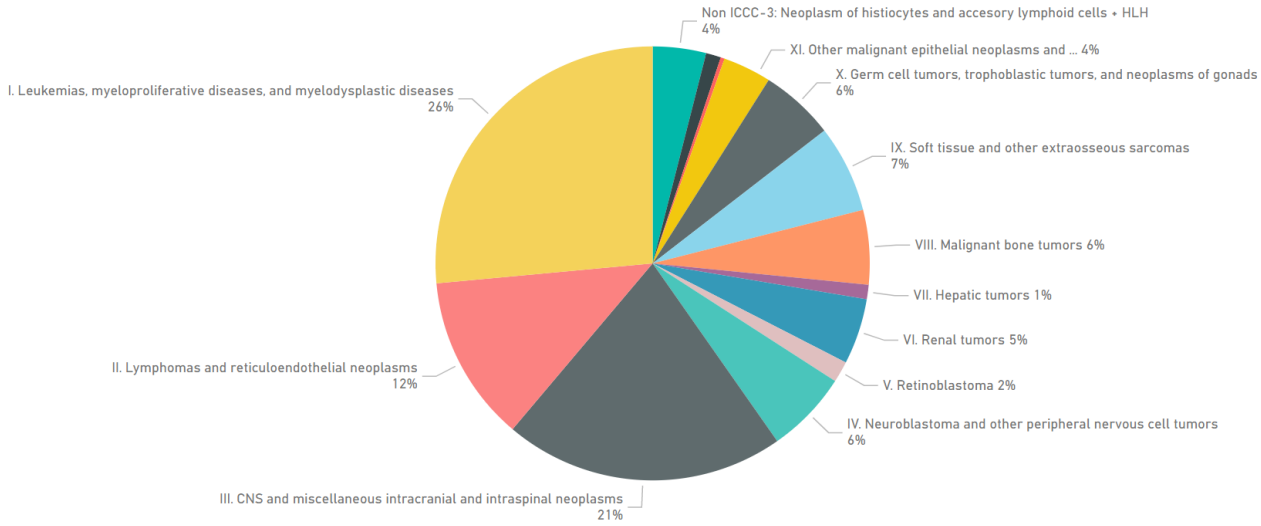
Victor Lamme is hoogleraar en hersenonderzoeker aan de Universiteit van Amsterdam. Hij publiceerde in tijdschriften als *Nature* en *Science,* maar schreef met evenveel plezier populaire bestsellers als 'De Vrije Wil Bestaat Niet' en 'Waarom?'. Hij weet als geen ander zijn kennis over het brein te vertalen naar de praktijk en is daarom een veelgevraagd gast op podia, in kranten en op radio en TV. Zijn lezingen zitten tjokvol verrassende inzichten en eye-openers voor iedereen die menselijk gedrag effectief wil beïnvloeden.

4. Basisregistratie en Zorgactiviteit

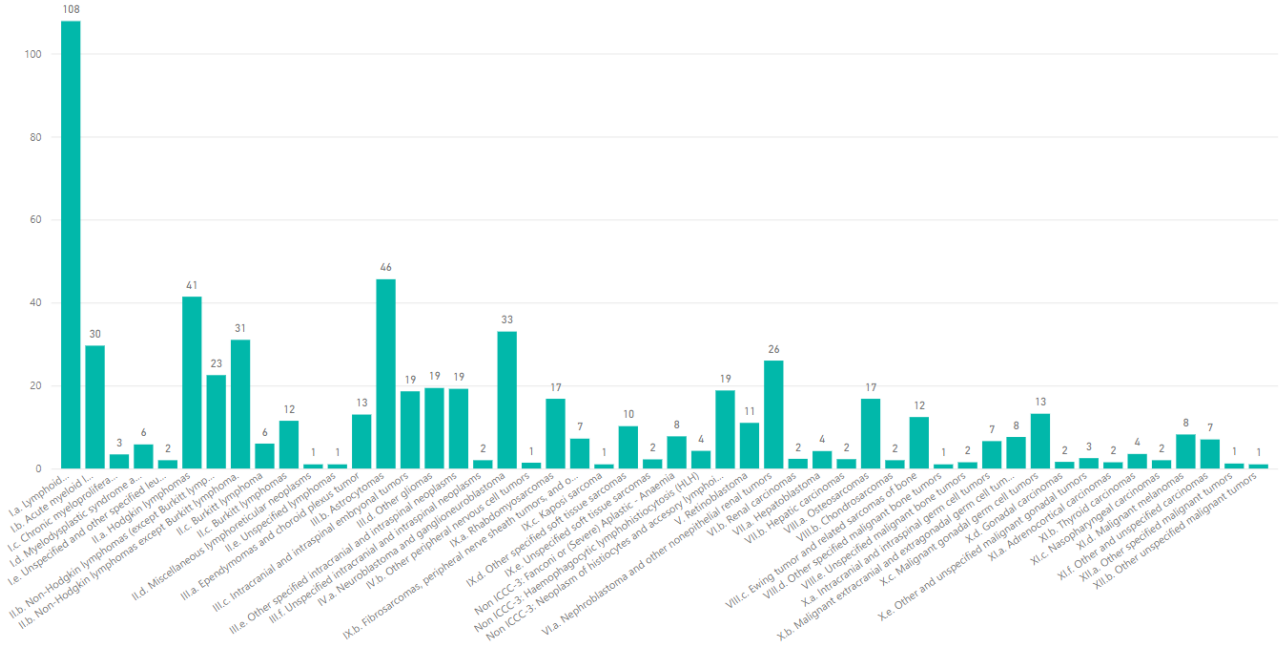
4.1 Basisregistratie

In de Basisregistratie worden sinds 2003 alle kinderen, tussen de 0 en 18 jaar, met een (pre-)maligne aandoening geregistreerd. Tussen 2017 en 2021 zijn er gemiddeld 567 nieuwe diagnoses geregistreerd. In 2021, het meest recente volledige jaar, zijn 516 nieuwe diagnoses geregistreerd.

In Figuur 1 zijn de in de Basisregistratie gemiddeld geregistreerde diagnoses over de jaren 2017 – 2021 uitgesplitst naar ICCC-3 hoofdklasse. In Figuur 2 zijn de gemiddelde in de Basisregistratie geregistreerde diagnoses over de jaren 2017- 2021 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 2017-2021 uitgesplitst naar ICCC-3 klasse (SKION, 2022)



Figuur 2: Gemiddeld aantal geregistreerde ziektegevallen per jaar in Basisregistratie 2017-2021 uitgesplitst naar ICCC-3 subklasse (SKION, 2022).

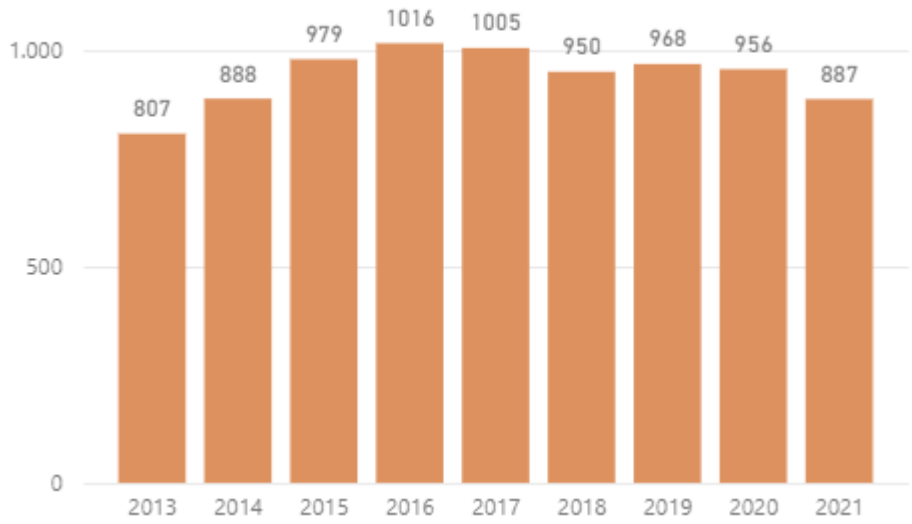
Meer cijfers?

http://tiny.cc/SKION_BR_Visual

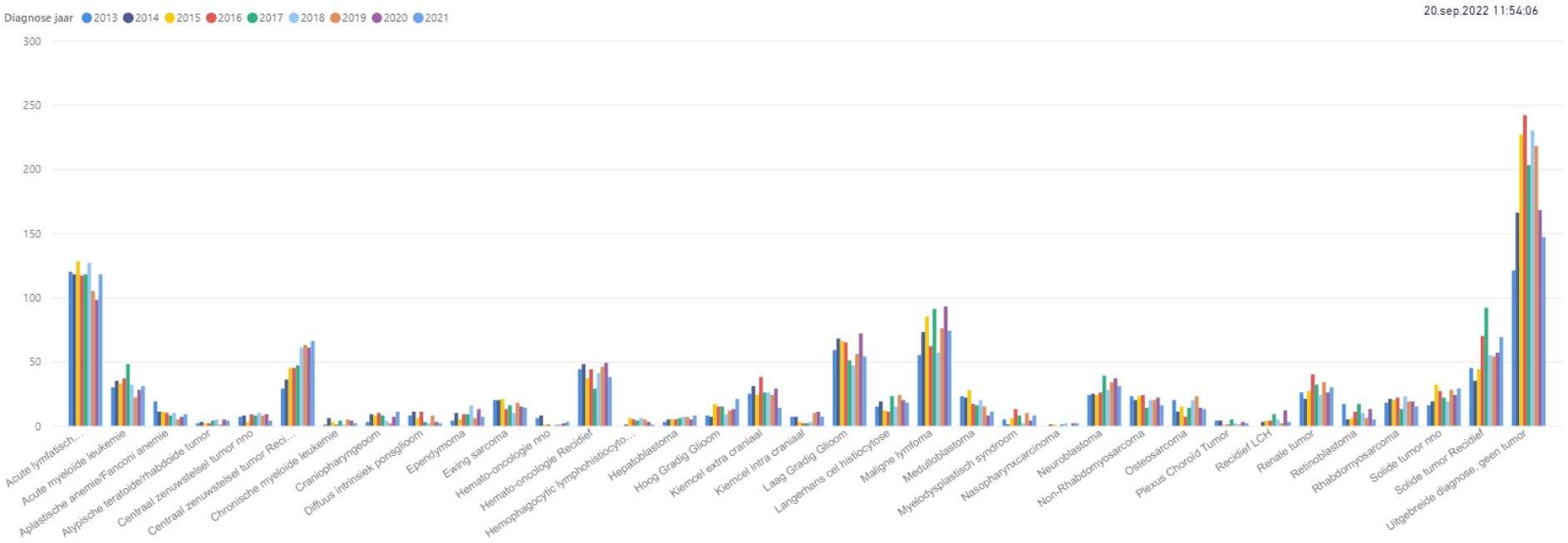
4.2 Zorgactiviteit

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 evalueren van landelijke (behandel)richtlijnen 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 richtlijnen en het adviseren van de Raad van Bestuur en Raad van Toezicht van SKION over de authorisatie van deze richtlijnen.
Een overzicht van de richtlijnen (en studies) op het gebied van neuro-oncologie is weergeven in Hoofdstuk 5.

Meer info over de Centrale Raad? En SKION-richtlijnen?

Skion - Centrale Raad (CR)
Skion - Voor professionals

4 Overzicht richtlijnen en studies neuro-oncologie

4.1 Richtlijnen en studies eerstelijnsbehandeling

Ziektebeeld	Protocol	Type	Opmerking
Atypische teratoide rhabdoide tumor	ATRT-01 (SIOP)	Studie	Phase III studie Open Q4 2022
CNS Germ Cell Tumor	SIOP II CNS GCT	Richtlijn	
Choroid Plexus tumor	CPT SIOP 2000	Richtlijn	
DIPG/DMG	PNOC-022 (PNOC)	Studie	Phase II open Q4 2022
Ependymoom	Ependymoma II (SIOP)	Studie	Phase III
Laaggradig glioom **Bij NF-1**	LGG-2004 Vinblastine	Richtlijn Richtlijn	In 2023 wordt nieuwe studie geopend (FIREFLY II)
Hooggradig glioom	ACNS0126/0423	Richtlijn	In 2023 gaat studie open HIT-HGG-2013
Glioom BRAFV600 gemuteerd	Dabrafinib/trametinib (CDRB436G2201, Novartis)	Studie	Phase II studie. Dicht voor nieuwe inclusies
Medulloblastoom <4 jaar	HIT-MED Guidance	Richtlijn	
Medulloblastoom >3 jaar standard risk	PNET-5	Studie/richtlijn	Studie, inclusie gesloten
Medulloblastoom >3 jaar High risk	HR-MB (SIOP)	Studie	Phase III studie

4.2 Studies recidief patiënten

Studie	Indicatie	Volledige naam studie
INFORM2	Alle hooggradige hersentumoren vanaf de leeftijd van 6 jaar	INFORM2 exploratory multinational phase I/II combination study of Nivolumab and Entinostat in children and adolescents with refractory high-risk malignancies
PNOC-022	Diffuus Midline Gliomen	Combination Therapy Trial using an Adaptive Platform Design for Children and Young Adults with Diffuse Midline Gliomas (DMGs) including Diffuse Intrinsic Pontine Gliomas (DIPGs) at Initial Diagnosis, Post-Radiation Therapy and at Time of Progression
Firefly I	Laaggradig gliomen	Phase 2, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of the Oral Pan-RAF Inhibitor DAY101 in Pediatric Patients with RAFBRAF Altered, Recurrent or Progressive Low-Grade Glioma
Ponatinib	PDGFRA positieve hersentumoren	An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Ponatinib for the Treatment of Recurrent or Refractory Leukemias or Solid Tumors in Pediatric Participants

5 Studie informatie

5.1 Atypisch teratoïde rhabdoïde tumoren – ATRT01

Protocol:	An international prospective umbrella trial for children with atypical teratoid/rhabdoid tumours (ATRT) Including: A randomized phase III study evaluating the non-inferiority of three courses of high-dose chemotherapy (HDCT) compared to focal radiotherapy as consolidation therapy
National coordinator:	Dr. Niels Franke
Contact person TDC:	Debbie Hendrickx

GENERAL DETAILS	
Sponsor:	German Paediatric Oncology Group, GPOH gGmbH
Coordinating Investigator:	Professor Dr. med. Michael C. Frühwald PhD
Sites in The Netherlands, PI:	Prinses Máxima Center, Dr. Niels Franke UMCG, dr. John Maduro
Study Status:	Study is approved, but not yet open

STUDY DESIGN	
Study Design:	Prospective, open label multicentre, international, umbrella trial including a randomized phase III study evaluating the non-inferiority of 3 courses of high-dose chemotherapy compared to focal radiotherapy plus standard chemotherapy as a consolidation measure following conventional chemotherapy in children with ATRT ranging from 12 – 35 months at the time of consolidation (RT vs. HDCT).
Primary objective:	**Part A**: To test the non-inferiority, as evaluated by 2-year overall survival (OS), of three courses of HDCT compared to focal RT plus conventional chemotherapy as consolidation therapy following conventional chemotherapy in children with ATRT aged 12 – 35 months at consolidation therapy.

Part B:
To assess the efficacy, as evaluated by OS, of three courses of HDCT as a consolidation measure following conventional-type chemotherapy in children with ATRT aged <12 months or with contraindications to RT at the time of HDCT and not eligible for randomization within Part A of this protocol, compared to historical controls.

Part C:
To assess the efficacy, as evaluated by overall survival, of RT as a consolidation measure combined with conventional-type chemotherapy in children aged ≥36 months with ATRT or contraindications to HDCT and ineligibility for Part A, compared to historical controls.

Study population:	Patients with ATRT of any site and any stage.

STUDY OVERVIEW

This study includes three parts:

1) Part A (Randomized trial):

This is an international, prospective, open, randomized, multicentre phase III clinical trial.
Patients with ATRT, who have received three courses of induction chemotherapy and approach the potential start of RT, who are in SD or better, who are 12-35 months of age, who have no sign of metastases at most recent evaluation and have no synchronous tumours.

This trial evaluates the non-inferiority of
a) three courses of HDCT employing carboplatin and thiotepa followed by SCR
compared to
b) a total of 12 courses of conventional dose chemotherapy with high conformal RT to the involved field.

The trial will assess the OS in both arms and as a secondary endpoint, the neurocognitive outcome in both arms.

2) Part B (HDCT):

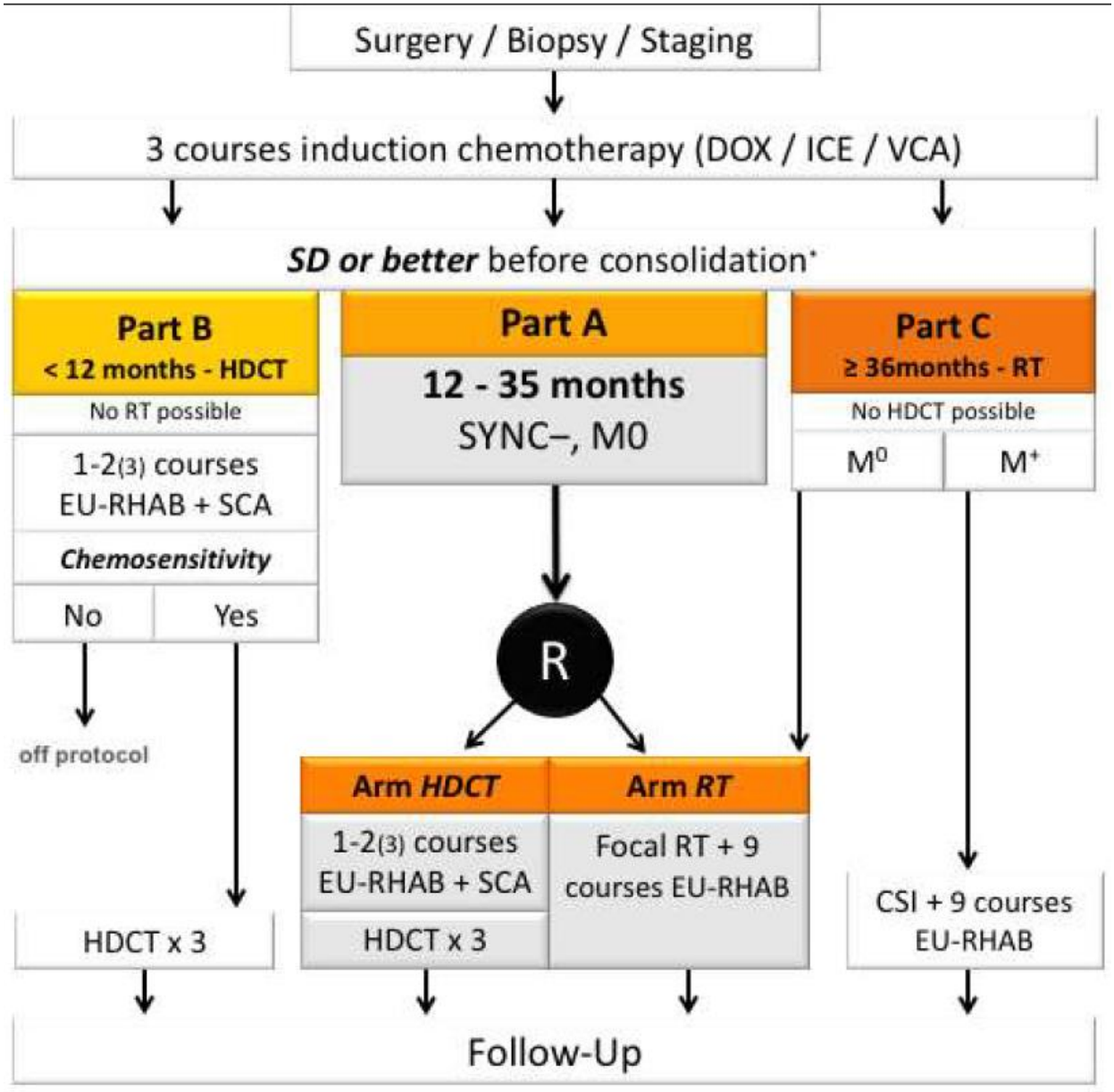
Radiotherapy of the developing brain is considered to be contraindicated in children below 12 months of age due to the potential for severe neurological and neuro-endocrine side effects. Part B of SIOPE ATRT01 seeks to collect data from this particular group of patients in the frame of a phase III single-arm prospective study and includes patients with ATRT under the age of 12 months, who are not eligible for randomization according to Part A. In case of local progression on therapy we consider patient off protocol and suggest to contact the trial centre for further individual advice. This may consist of salvage measures such as re-resection, but also in referral to Phase I/II approaches.
Under exceptional circumstances, due to contraindications for RT in a child 12-36 months or even older and at the same time presence of exclusion criteria for Part A, it may be advisable to treat patients in Part B. Those individual cases will be discussed with the trial coordination committee.

3) Part C (RT):

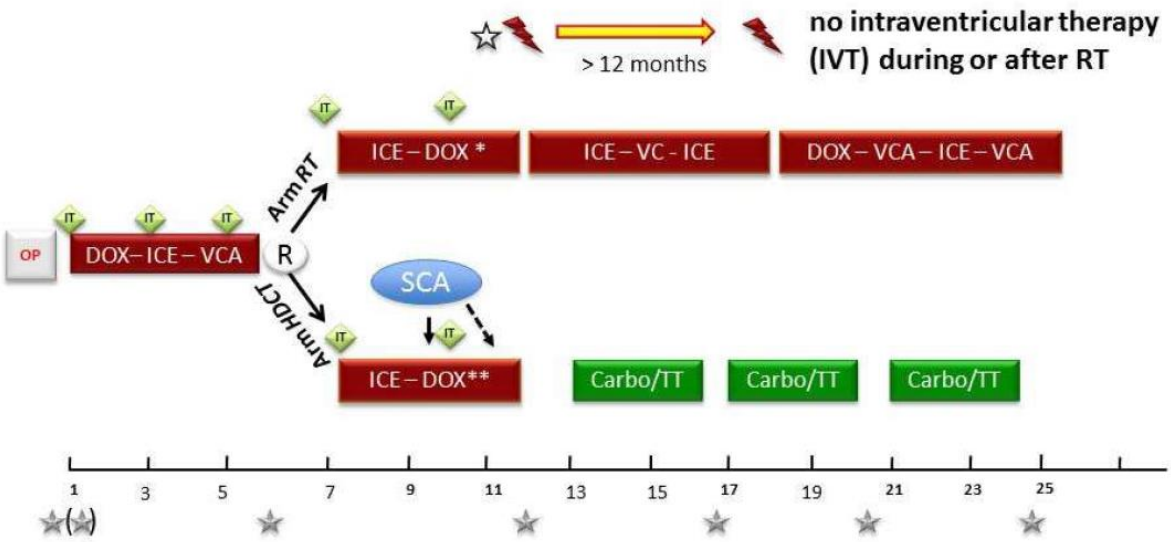
Patients above the age of 3 years (≥36 months) will in general tolerate RT. It is considered standard to perform RT in these children. Part C of SIOPE ATRT01 is a phase III study of conventional chemotherapy with radiotherapy in children with ATRT, aged at least 36 months and older, who are not eligible for randomization in Part A and who do not demonstrate contraindications for RT. They will be treated with conventional induction chemotherapy followed by focal (localized disease) or craniospinal (metastatic disease) RT combined with up to a total of 12 courses of conventional dose chemotherapy. The sequence of chemotherapy courses may be changed if in conflict with local therapy (e.g. no DOX with RT, timing of SCA etc..).

RT to the primary tumour bed will be administered as early as possible after induction (e.g. 4th course) and reassessment (at least 12 months of age at RT, clinical condition of the patient).

Under exceptional circumstances (no HDCT possible in a child 12-36 months e.g. due to a lack of stem cells or other exclusion criteria for Part A) it may be advisable to treat patients in Part C regardless of an age of 12-36 months. Those individual cases will be discussed with the trial coordination committee.



Flow of randomized Part A



* Sequence of chemotherapy may be changed if in conflict with local therapy (e.g. no DOX with RT, timing of SCA etc)
** If insufficient stem cell harvest after ICE, replace DOX by VCA
Response assessment (MRI, CSF evaluation)
(Response assessment) Repeat response assessment (MRI, CSF evaluation) if chemotherapy is started more than 14 days after surgery
Consider complete staging before planning of radiotherapy
Radiotherapy as early as possible after induction (e.g. 4th course) and reassessment (at least 12 months of age)
SCA Stem cell apheresis

PLANNING and RECRUITMENT	*Cut off date:* 27SEP2022

Planning:

Start international recruitment:	01JUN2021
Start national recruitment:	Q4 2022
Expected date end of recruitment:	31MAY2026
Expected date last patient out:	31MAY2029

International recruitment:

Recruitment target protocol:	152 patients (76 in each arm) shall be randomized.
Actual number of patients included:	Arm A_HDCT: 2 Arm A_RT: 0 Arm B: 1 patient Arm C: 2 patients

National recruitment:

Recruitment target national:	10 patients
Actual number of patients included:	Study not yet open for recruitment

5.2 Diffuus intrinsiek ponsglioom/diffuse midline gliomas – PNOC-022 (PNOC)

Protocol:	PNOC022: A Combination Therapy Trial using an Adaptive Platform Design for Children and Young Adults with Diffuse Midline Gliomas (DMGs) including Diffuse Intrinsic Pontine Gliomas (DIPGs) at Initial Diagnosis, Post-Radiation Therapy and at Time of Progression
National coordinator:	Dr. Jasper van der Lugt
Contact person TDC:	Raoull Hoogendijk and Debbie Hendrickx

GENERAL DETAILS

Sponsor:	University of California, San Francisco
Coordinating Investigator:	Dr. Sabine Mueller
Sites in The Netherlands, PI:	Prinses Máxima Center, Dr. Jasper van der Lugt
Study Status:	Study is submitted. SIV scheduled for mid Oct 2022

STUDY DESIGN

Study Design:	This is a multi-arm, multi-cohort trial using a Bayesian drug combination platform design for children and young adults with DMGs. This trial will randomize participants at study entry who are at different stages of disease (newly diagnosed (Cohort 1), post-radiation therapy but with no evidence of progression (Cohort 2), and at time of progression (Cohort 3) to different combination therapies. Given the very favorable safety profile of ONC201 and anticipated known side effects of novel agents to be used in this trial, no specific phase 1 evaluations of the combination therapy will be conducted within the confines of this trial but, toxicity will be carefully monitored throughout the trial and stopping rules will be implemented. ONC201 will be used as a backbone and will be combined with novel agents that have been shown in preclinical studies to be additive or synergistic in combination. At this moment, study arms 2, 4 and 6 are open, which include paxalisib as novel agent.
Primary objective:	**<u>Cohorts 1 and 2</u>** **Maintenance Combinations:** - To assess efficacy of combination therapy with ONC201 and novel agent in participants with DMG based on median progression-free survival at 6 months (PFS6)

Cohort 3
- To assess efficacy of combination therapy with ONC201 and novel agent in participants with recurrent DMG based on overall survival at 7 months (OS7)

Study population:

This study will enroll children and young adults (2-39 years of age) with diffuse midline gliomas (DMGs; excluding Grade 2, H3K27M negative tumors) at different stages of their disease.

Cohort 1: Will include participants with newly diagnosed DMGs.

Cohort 2: Will include participants with DMGs who have completed focal radiation therapy and are within 4-14 weeks from completion of radiation therapy without evidence of progression.

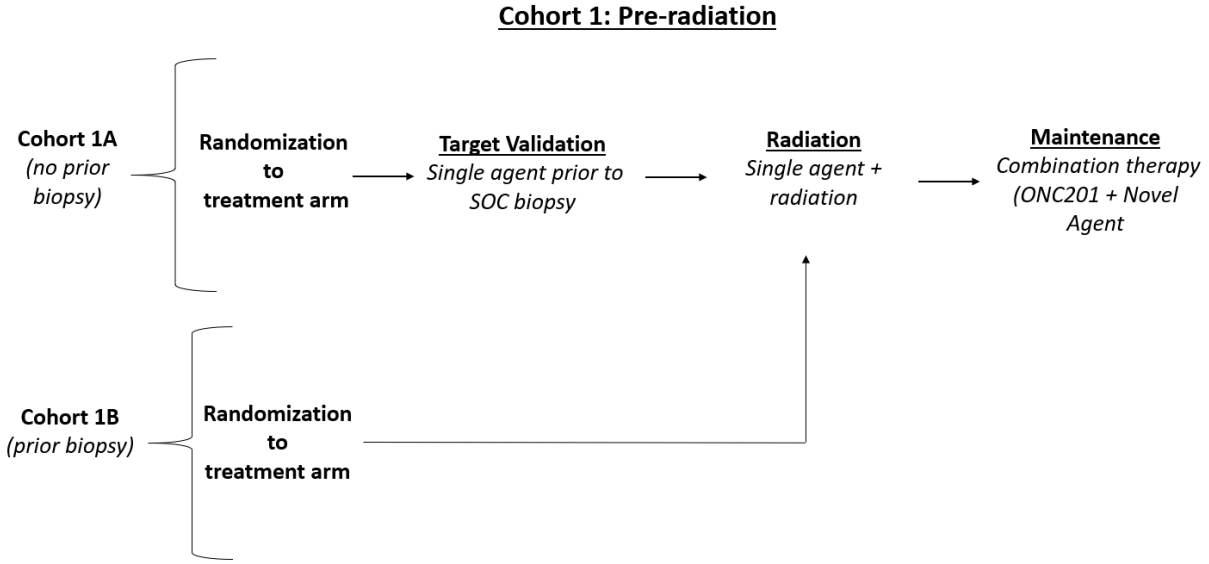
Cohort 3: Will include participants with DMGs who have evidence of progression but have not been treated for this progression and have not previously undergone re-irradiation therapy.

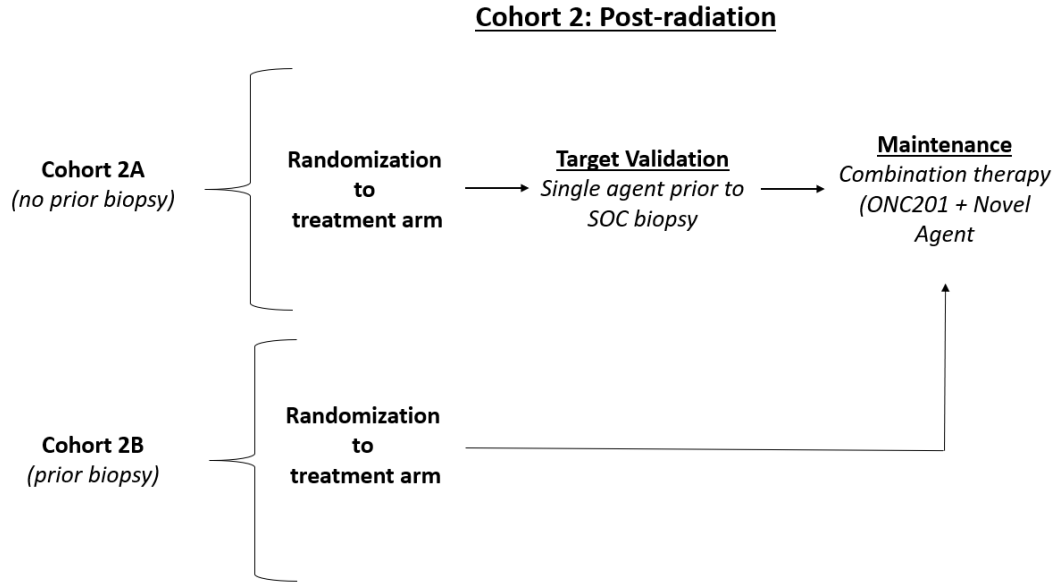
STUDY OVERVIEW

Target Validation Phase:
The key to successful development of novel agents in the treatment of DMGs is confirmation of BBB penetration. Additionally, development and validation of relevant biomarkers of drug penetration and downstream anti-tumor effects are crucial in the development of these novel agents. For most novel agents included in this study, BBB penetration has not been confirmed in participants with DMGs. To address this knowledge gap, we will enroll participants in a Target Validation phase of the study with newly-diagnosed DMGs preradiation (Cohort 1A), post-radiation (Cohort 2A), and at progression (Cohort 3A) to receive single-agent therapy immediately prior to standard-of-care tumor tissue collection. This invaluable data will allow for a) determination of intratumoral drug concentrations and b) development of relevant biomarkers of drug response. Of note, given that it is conceivable that BBB penetration of agents differs in tumors pre- and post-radiation therapy and between newly diagnosed and recurrence, we will assess the drug penetration separately in each cohort.

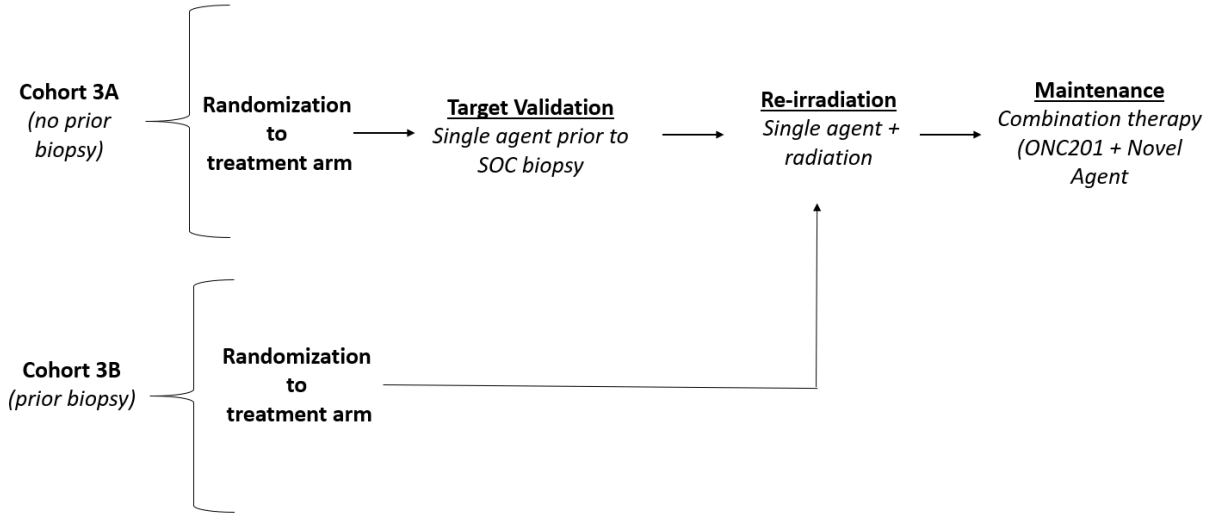
Radiation Therapy Phase:
Participants will receive ONC201 weekly, or a novel agent in combination with standard-of-care focal radiation therapy. ONC201 given concurrently during up-front radiation therapy has been well tolerated on the current phase 1 study. Novel agents will only be incorporated into the Radiation Therapy Phase if they have an appropriate safety profile in adult and pediatric populations.

Maintenance Phase:
DMGs have historically demonstrated minimal response to single agent therapy. It is clear from decades of clinical research that combination therapy is often necessary for improvement in clinical outcomes in children with brain tumors. Given the lack of efficacious standard therapy, aside from focal radiation therapy, in participants with DMGs, we aim to utilize a combination maintenance approach. In the Maintenance Phase, participants will receive a combination therapy with ONC201 and a novel agent.





Cohort 3: Progression



Arm	Single Agent in Target Validation and/or Radiation Phase	Combination Therapy in Maintenance Phase	Arm Status
Arm 2	TV: ONC201 day -1 RT: ONC201 once weekly	ONC201 + paxalisib	Cohort 1: Open Cohort 2: Open Cohort 3: Open
Arm 4	TV: ONC201 day -2, -1 RT: ONC201 once weekly	ONC201 + paxalisib	Cohort 1: Open Cohort 2: Open Cohort 3: Open
Arm 6	Paxalisib	ONC201 + paxalisib	Cohort 1: Open Cohort 2: Open Cohort 3: Open

PLANNING and RECRUITMENT *Cut off date:* 20SEP2022

Planning:

Start international recruitment: 25OCT2021

Start national recruitment: Q4 2022

Expected date end of recruitment: Q3 2025

Expected date last patient out: Q1 2026

International recruitment:

Recruitment target protocol:	Cohort 1: 33 patients Cohort 2: 33 patients Cohort 3: 42 patients
Actual number of patients included:	Cohort 1: 10 patients Cohort 2: 21 patients Cohort 3: 8 patients

National recruitment:

Recruitment target national:	5-10 patients
Actual number of patients included:	Study not yet open for recruitment

ABSTRACTS / PUBLICATIONS

Not available yet

5.3 Diffuus intrinsiek ponsglioom/diffuse midline gliomas – DIPG/DMG Registry

Protocol:	A SIOPE Registry for Diffuse Intrinsic Pontine Glioma (DIPG) and Diffuse Midline Glioma (DMG)
National coordinator:	dr. D.G. van Vuurden
Contact person TDC:	T.C. Godschalk

GENERAL DETAILS

Sponsor:	Executive Committee of the DIPG/DMG Network
Legal Entity:	Princess Máxima Center
Coordinating Investigator:	dr. D.G. van Vuurden
Sites in The Netherlands, PI:	Princess Máxima Center, dr. D.G. van Vuurden
Study Status:	Open

STUDY DESIGN

Study Design:	The DIPG Registry started as a retrospective registry of patients with DIPG from a few European countries. In 2016 the protocol changed to a European prospective observational registry of patients with DIPG. In 2021 preparations started to also include patients with DMG. This amendment is planned to become effective in Q4 2022.
Primary objective:	To provide a comprehensive dataset to allow for international collaborative research in the field of DIPG/DMG. The SIOPE DIPG/DMG Registry was developed based on international agreements, made by a Network of experts studying and treating DIPG/DMG; the SIOPE DIPG/DMG Network.
Study population:	Patients with DIPG aged between 0 and 21 year. After implementation of the amendment, the study population will include patients diagnosed with DIPG and DMG diagnosed from 2016, without an age limitation.

STUDY OVERVIEW

Not applicable

PLANNING and RECRUITMENT *Cut off date: 01-09-2022*

Planning:

Start international recruitment:	03-MAY-2017 (prospective registry)
Start national recruitment:	17-MAY-2019
Expected date end of recruitment:	No recruitment end is set, ungoing registry
Expected date last patient out:	No recruitment end is set, ungoing registry

International recruitment:

Recruitment target protocol:	No recruitment target is set, ungoing registry
Actual number of patients included:	964
Optioneel uitsplitsen in subgroepen	Retrospective cohort DIPG: 634
	Prospectively included DIPG: 330
	DMG: inclusion has not started yet

National recruitment:

Recruitment target national:	10 per year
Actual number of patients included:	15 patients

Recruitment tables:

Retrospective cohort DIPG patients:

Country	#patients
Croatia	7
France	113
Germany	278
Italy	79
Netherlands	114
United Kingdom	43
TOTAL	**634**

Prospectively included DIPG patients:

Country	#patients
Italy	110
Russia	51
Spain	48
Hungary	32
Mexico	18
Netherlands	15
Belgium	13
Turkey	13
Croatia	11
Greece	11
UK	7
France	1
TOTAL	**330**

ABSTRACTS / PUBLICATIONS

1. Veldhuijzen van Zanten SEM et al. “Development of the SIOPE DIPG Network, Registry and Imaging Repository: A collaborative effort to optimize research into a rare and lethal disease.” J. Neurooncology 2017; 132(2):255-66

2. Hoffman LM et al. “Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries.” J Clin Oncol. 2018; Jul 1;36(19):1963-1972

5.4 Ependymoom – Ependymoma II

Protocol:	An international clinical program for the diagnosis and treatment of children, adolescents and young adults with ependymoma
National coordinator:	dr. J. van der Lugt
Contact person TDC:	E. Wiesen

GENERAL DETAILS

Sponsor:	University Medical Centre Léon Bérard
Coordinating Investigator:	dr. P. Leblond
Sites in The Netherlands, PI:	Princess Máxima Center, dr. J. van der Lugt UMCG, dr. J.H. Maduro
Study Status:	Open for new patient inclusions

STUDY DESIGN

Study Design:
The Ependymoma Program is a comprehensive program to improve the accuracy of the primary diagnosis of ependymoma and explore different therapeutic strategies in children, adolescents and young adults, accordingly. This program is opened to all patients diagnosed with ependymoma below the age of 22 years. It will include a centralised review of pre and post-operative imaging to assess the completeness of the resection. It will also include a central review of pathology to confirm the histological diagnosis. The biological markers 1q gain, Tenascin C status, RELA-fusion, YAP fusion, H3.3K27me3 and molecular subgroup by methylation array will be prospectively assessed for prospective evaluation of disease subgroups. Further biological evaluations will be coordinated within the integrated BIOMECA study.
After surgery and central review of imaging and pathology, patients will be offered the opportunity to undergo second look surgery, if possible. Patients will be enrolled in one of 3 different strata according to the outcome of the initial surgical resection (residual disease vs no residual disease), their age or eligibility / suitability to receive radiotherapy. These 3 different strata correspond to 3 therapeutic strategies according to the patient status.

Stratum 1: is designed as a randomised phase III study for patients who have had a complete resection, with no measurable residual disease (as confirmed by centrally reviewed MRI) and are ≥ 12 months and < 22 years at diagnosis. Those patients will be randomised to receive conformal radiotherapy followed by either 16 weeks of chemotherapy with VEC+CDDP, or observation

Stratum 2: is designed as a randomized phase II study for patients who have inoperable measurable residual disease and who are ≥ 12 months and < 22 years at diagnosis. Those patients will be randomized to two different treatment schedules of chemotherapy either with VEC or VEC+ high dose methotrexate (VEC +HD-MTX).

After completion of the frontline chemotherapy, patients will be assessed for response (MRI) and will receive second look surgery when feasible. For those patients who remain unresectable with residual disease despite frontline chemotherapy and for whom second line surgery is not feasible, there will be a study of the safety of a radiotherapy boost of 8 Gy that will be administered to the residual tumour immediately after the completion of the conformal radiotherapy. Patients without evidence of residual disease after the chemotherapy and/or a second look surgery are not eligible for radiotherapy boost. All patients who have not shown progression under chemotherapy will receive, as maintenance therapy, a 16 week course of VEC+CDDP following completion of radiotherapy

Stratum 3: is designed as a randomised phase II chemotherapy study in children <12 months of age or those not eligible to receive radiotherapy. These patients will be randomised to receive a dose dense chemotherapy alternating myelosuppressive and relatively non-myelosuppressive drugs at 2 weekly intervals, with or without, the addition of the histone deacetylase inhibitor, valproate

Observational study: after staging phase, patients that do not fulfil the inclusion criteria of one of the interventional strata will be enrolled and followed up via an observational study which will be analysed descriptively

Primary objective:
Overall program: to determine whether the assessment of residual disease can be improved by a centralized review of post-operative MRI and whether such review increases the rate of complete resection compared to historical controls. Does central neurosurgical and radiological review increase resection rates?

Stratum 1: to test the hypothesis that there will be an improvement in progression-free survival in patients who receive 16 weeks chemotherapy (VEC+CDDP) following surgical resection and conformal radiotherapy when compared to those that undergo surgical resection and radiotherapy alone

Stratum 2: to compare the activity of 2 post-operative chemotherapy schedules, VEC or VEC+HD-MTX in patients who have incompletely resected tumour

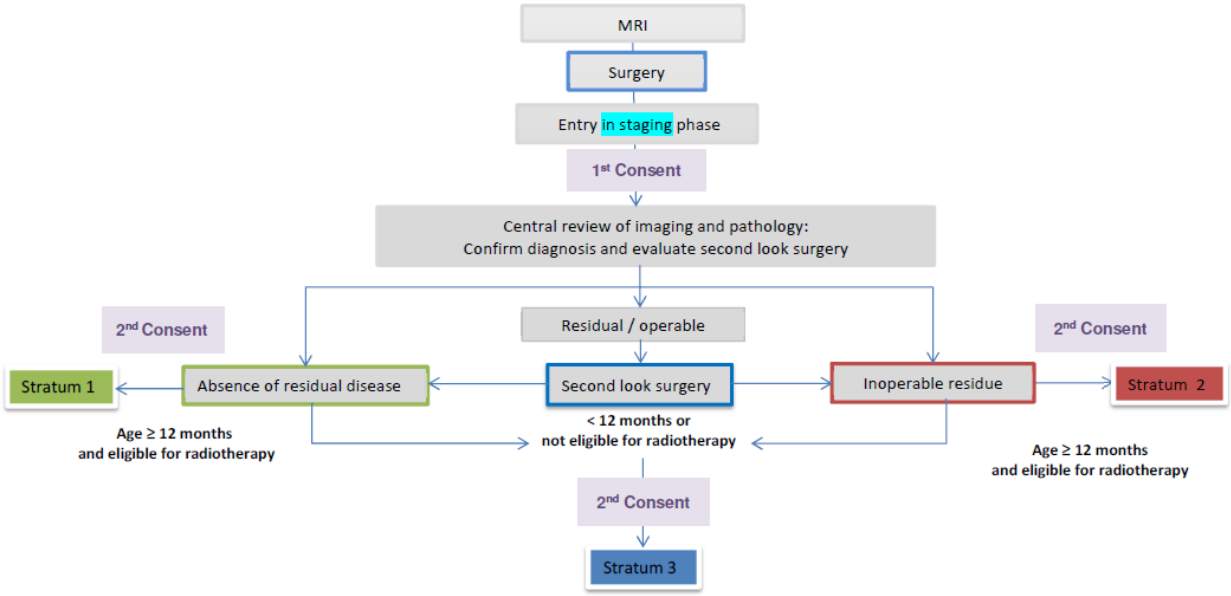
Stratum 3: to evaluate the progression free survival in children unable to receive radiation therapy and who receive valproate, as a histone deacetylase inhibitor in addition to the primary chemotherapy strategy when compared to those that undergo chemotherapy without valproate

Study population:
Stratum 1: patients with no measurable residual disease and ≥12 months of age - phase III

Stratum 2: patients with inoperable measurable residual disease and ≥12 months of age - phase II

Stratum 3: randomized phase II chemotherapy study in children < 12 months of age or those not eligible to receive radiotherapy

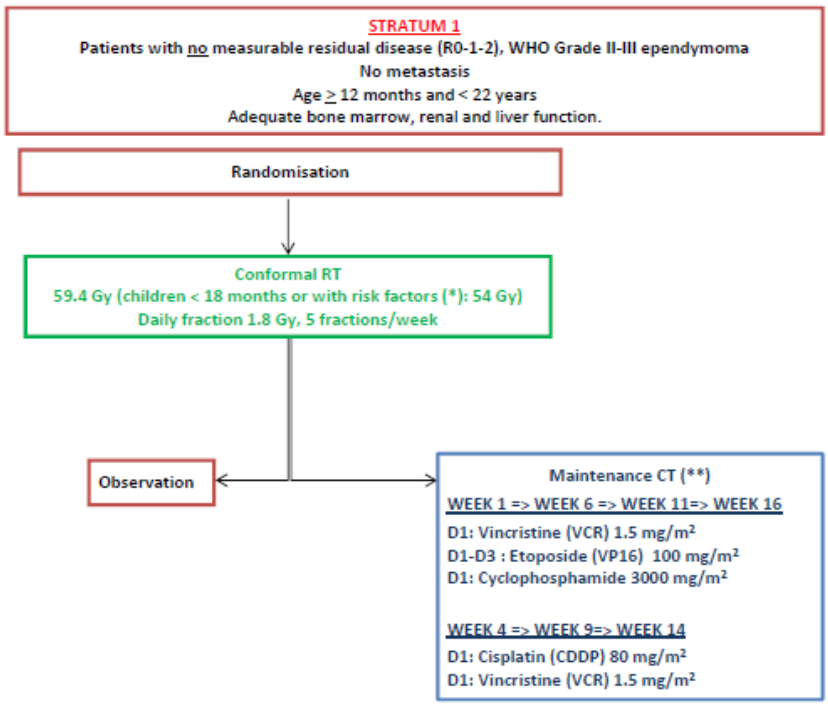
STUDY OVERVIEW



Study overview:

Treatment overviews:

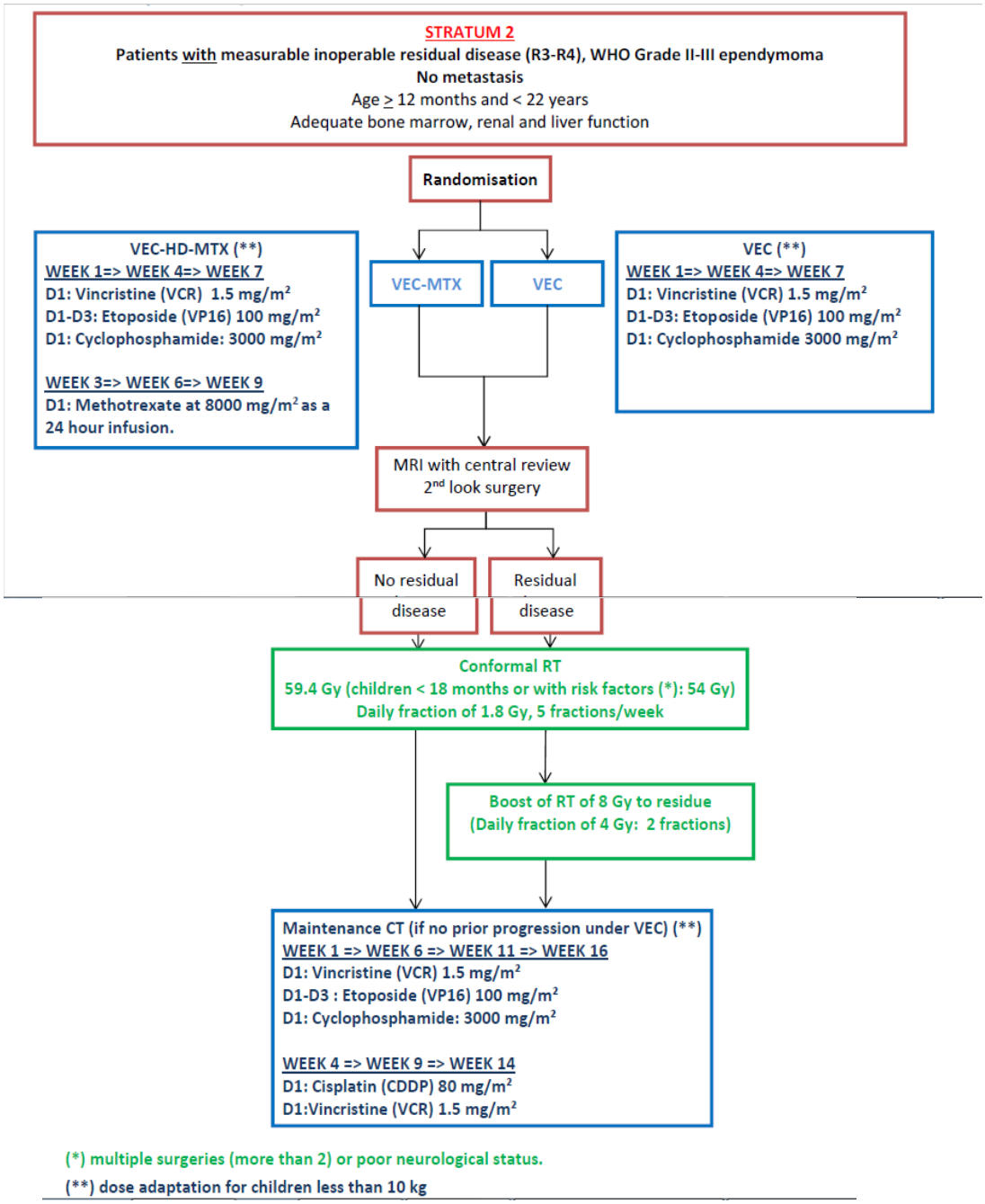
Stratum 1:



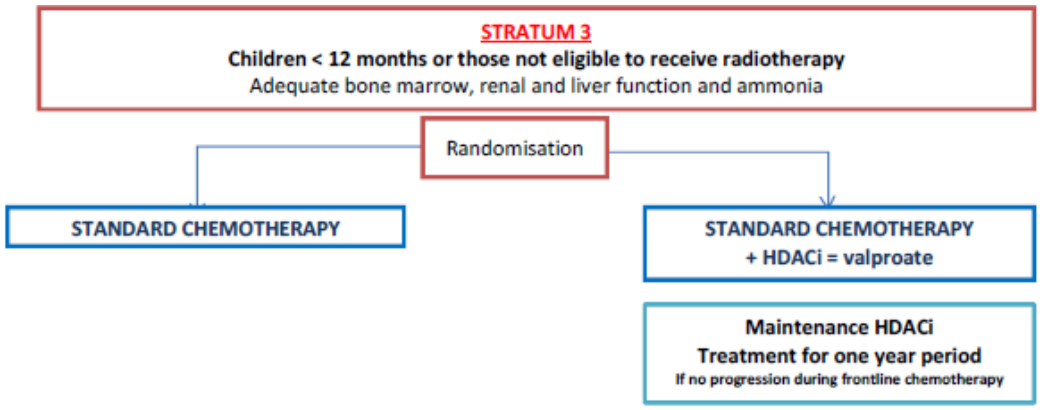
(*) multiple surgeries (more than 2) or poor neurological status.

(**) dose adaptation for children less than 10 kg

Stratum 2:



Stratum 3:



PLANNING and RECRUITMENT

Cut off date: Sep 2022

Planning:

Start international recruitment:	03-Jun-2015
Start national recruitment:	13-Jul-2020
Expected date end of recruitment:	03-Jun-2025
Expected date last patient out:	03-Jun-2030

International recruitment:

Recruitment target protocol:	480 patients
Actual number of patients included:	694 patients
	Stratum 1: 251
	Stratum 2: 42
	Stratum 3: 40

(Staging: 94, Observational: 21, Staging + Observational: 241, Stratum 1 + Observational: 39, Stratum 2 + Observational: 10, Stratum 3 + Observational: 18)

National recruitment:

Recruitment target national:	40 patients
Actual number of patients included:	14 patients

ABSTRACTS / PUBLICATIONS

Not available yet

5.5 LOGGIC Core

Protocol:	LOw Grade Glioma In Children: BioClinical Data Bank
National coordinator:	dr. A.Y. N. Schouten – van Meeteren
Contact person TDC:	T.C. Godschalk

GENERAL DETAILS

Sponsor:	Hopp Children's Cancer Center Heidelberg (KiTZ) German Cancer Research Center (DKFZ)
Coordinating Investigator:	Prof. dr. O. Witt
Sites in The Netherlands, PI:	Princess Máxima Center, dr. A.Y.N. Schouten – van Meeteren
Study Status:	Open

STUDY DESIGN

Study Design:	Non-interventional observational registry including biological and clinical data
Primary objective:	The overall aim of the LOGGIC Core BioClinical Data Bank is to set up a molecular and clinical data bank for pediatric low grade gliomas
Study population:	Children, adolescents and young adults 0 to 21 years old with all subtypes of LGG tumours at primary diagnosis or progression/relapse

STUDY OVERVIEW

Not applicable

PLANNING and RECRUITMENT *Cut off date: 16-08-2022*

Planning:

Start international recruitment:	01-Jan-2019
Start national recruitment:	01-Jun-2022
Expected date end of recruitment:	No end date is expected, ungoing registry
Expected date last patient out:	No end date is expected, ungoing registry

International recruitment:

Recruitment target protocol:	No recruitment target is set
Actual number of patients included:	779 patients

National recruitment:

Recruitment target national:	40 patients per year
Actual number of patients included:	4 patients

ABSTRACTS / PUBLICATIONS

Not available yet

5.6 Glioom BRAFV600 gemuteerd – Dabrafinib/trametinib

Protocol:	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)
National coordinator:	
Contact person TDC:	Start-up coordinator TDC

GENERAL DETAILS

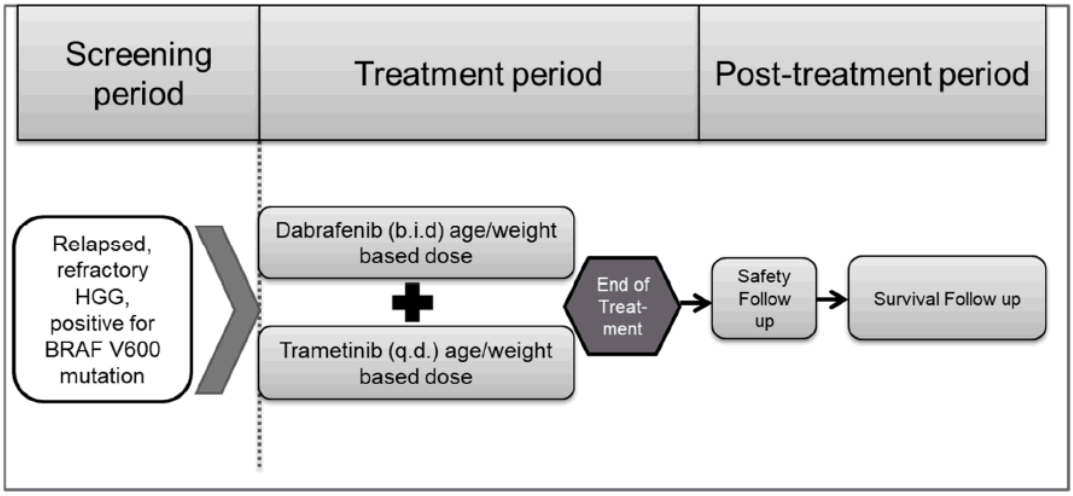
Sponsor:	Novartis
Coordinating Investigator:	
Sites in The Netherlands, PI:	Princess Máxima Center, dr. J. van der Lugt
Study Status:	Closed for inclusion

STUDY DESIGN

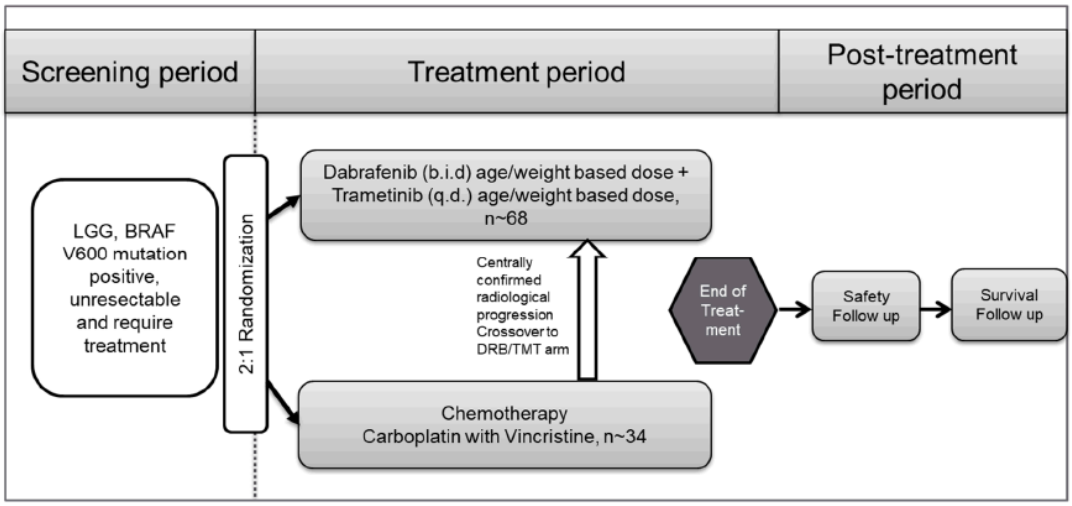
Study Design:	Multi-center, open-label, phase II study
Primary objective:	The primary objective of the High Grade Glioma cohort is to evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria. The primary objective of the Low Grade Glioma cohort is to compare the anti-tumor activity of dabrafenib in combination with trametinib to the combination of carboplatin and vincristine, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria.
Study population:	Children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)

STUDY OVERVIEW

Study design HGG cohort



Study design LGG cohort



PLANNING and RECRUITMENT

Cut off date: 19/10/2022

Planning:

Start international recruitment:

Start national recruitment: 19-SEP-2019

Expected date end of recruitment: 03-DEC-2020

Expected date last patient out: DEC-2022

International recruitment:

Recruitment target protocol:	142
Actual number of patients included:	149

National recruitment:

Recruitment target national:	5
Actual number of patients included:	5

ABSTRACTS / PUBLICATIONS

Primary analysis of a phase II trial of dabrafenib plus trametinib (dab + tram) in BRAF V600–mutant pediatric low-grade glioma (pLGG). | Journal of Clinical Oncology (ascopubs.org)

5.7 Medulloblastoom (>3 jr SR) – PNET5

Protocol:	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 in the context of genetic predisposition
National coordinator:	dr. S.L.A. Plasschaert
Contact person TDC:	T.C. Godschalk

GENERAL DETAILS

Sponsor:	University Medical Centre Hamburg-Eppendorf
Coordinating Investigator:	Prof. dr. S. Rutkowski
Sites in The Netherlands, PI:	Princess Máxima Center, dr. S.L.A. Plasschaert UMCG, dr. J.H. Maduro
Study Status:	Closed for new patient inclusions. Follow-up continues until March 2027.

STUDY DESIGN

Study Design:	LR-arm: This is an international, prospective, Phase-II, open study in patients between the ages of 3 to 5 years and less than 16 years, with 'standard-risk' medulloblastoma and a low-risk biological profile SR-arm: an international, prospective, Phase-III, randomised study in patients between the ages of 3 to 5 years and less than 22 years, with 'standard-risk' medulloblastoma and an average-risk biological profile WNT-HR-arm: an international study in patients older than 3 to 5 years, with a medulloblastoma with low-risk biological profile (WNT-activation) and clinically high-risk features SHH-TP53-arm: an international, prospective phase II study for patients with SHH-activated, *TP53* somatic or germline including mosaicism mutated medulloblastoma Registry: registry of patients with genetic predisposition and MB
Primary objective:	LR-arm: to confirm that the 3-year event-free survival rate in children and adolescents with standard-risk medulloblastoma having a low-risk biological profile remains in excess of 80% when patients are treated with 18.0 Gy neuraxis irradiation plus boost to the primary tumour, and reduced-intensity chemotherapy. SR-arm: to test whether the event-free survival in children and adolescents with standard-risk medulloblastoma having an average-risk biological profile is

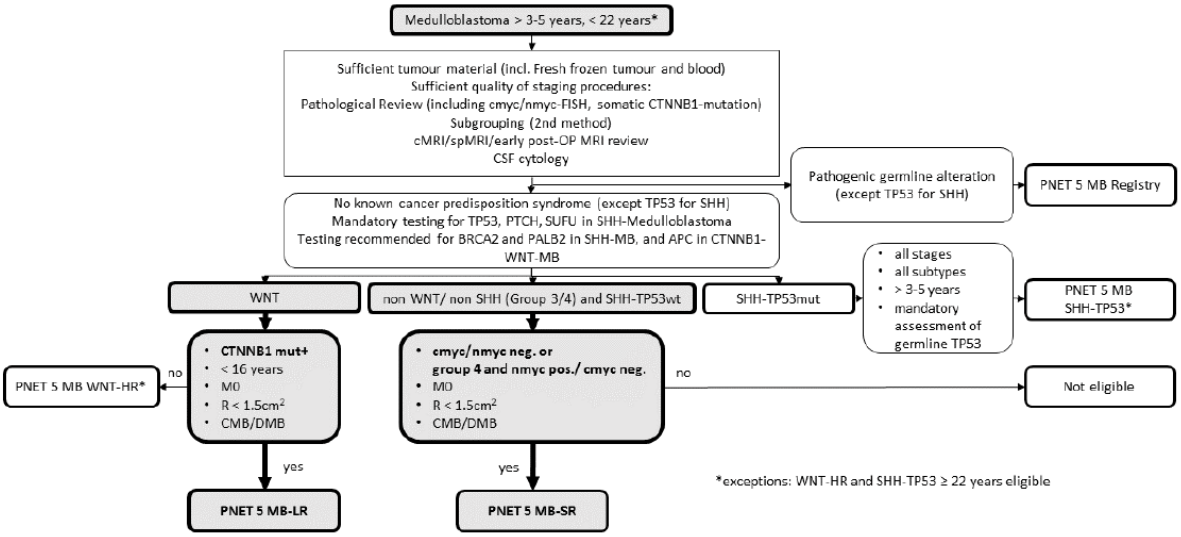
different for patients treated with or without carboplatin concomitantly with radiotherapy (23.4 Gy neuraxis irradiation plus boost to the primary tumour) followed by a modified maintenance chemotherapy.
WNT-HR-arm: to confirm the 3-year event-free survival of rate of 80% in children and adolescents with high-risk medulloblastoma having a low-risk biological profile when patients are treated with 23.4 Gy (35.2 Gy) neuraxis irradiation plus boost to the primary tumour (and metastates, if applicable) and reduced-intensity chemotherapy
SHH-TP53-arm: to determine the superiority of event-free survival in MB SHH-*TP53*-mutant patients receiving treatment adapted to presence of somatic or germline *TP53* mutation in comparison to historic MB SHH *TP53*mut cohort
Registry: data on initial presentation, treatment and outcome can be documented for all medulloblastoma patients with diagnosis of a pathogenic germline alteration or cancer predisposition syndrome, who cannot be included in any prospective trial due to unavailability or due to physician or family decision. The acquired data are intended to generate a prospective data base to inform the clinical decisions on treatment for the next patients and possibly the next trials

Study population:

LR-arm: patients between the ages of 3 to 5 years and less than 16 years, with 'standard-risk' medulloblastoma and a low-risk biological profile.
SR-arm: patients between the ages of 3 to 5 years and less than 22 years, with 'standard-risk' medulloblastoma and an average-risk biological profile.
WNT-HR-arm: patients older than 3 to 5 years, with a medulloblastoma with low-risk biological profile (WNT-activation) and clinically high-risk features
SHH-TP53-arm: patients older than 3 to 5 years, with SHH-activated, *TP53* somatic or germline including mosaicism mutated medulloblastoma
Registry: patients with medulloblastoma not eligible for the other study arms and identified with pathological germline alternation.

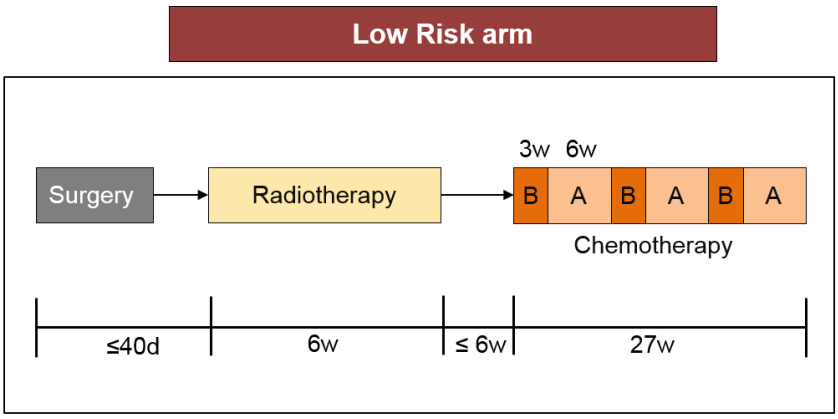
STUDY OVERVIEW

Study overview:



Treatment overviews:

LR-arm:

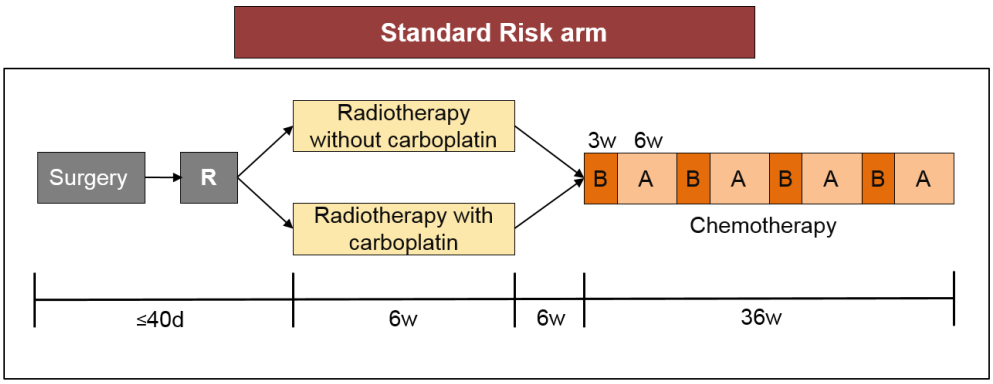


Radiotherapy:
- CSI **18 Gy,** primary tumor 54.0 Gy

Cycle A:
- Cisplatin 70 mg/m^2 (d1)
- Lomustin 75 mg/m^2 (d1)
- Vincristin 1.5 mg/m^2 (d1, 8, 15)

Cycle B:
- Cyclophosphamide 1000 mg/m^2 (d1-2)
- Vincristin 1.5 mg/ m^2 (d1)

SR-arm:

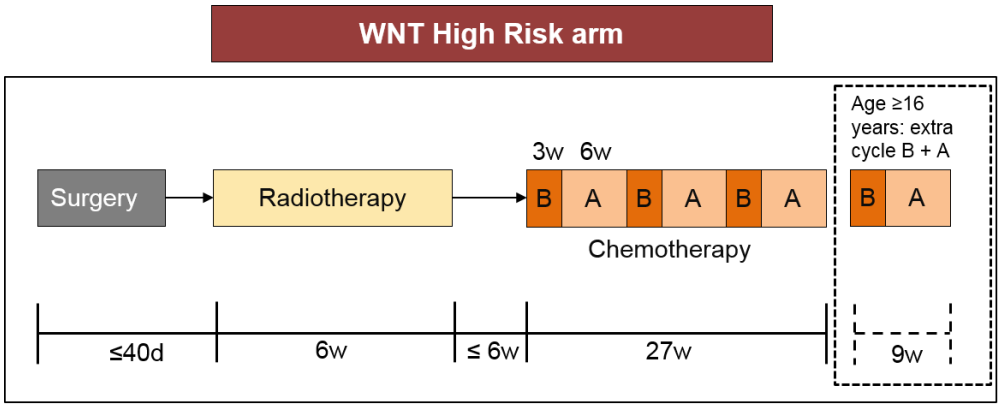


Radiotherapy:
- CSI 23.4 Gy**,** primary tumor 54.0 Gy
- Randomisation for carboplatin
  - Carboplatin: 35 mg/m^2/day for 6w
  - 1-4 hours before RT

Cycle A:
- Cisplatin 70 mg/m^2 (d1)
- Lomustin 75 mg/m^2 (d1)
- Vincristin 1.5 mg/m^2 (d1, 8, 15)

Cycle B:
- Cyclophosphamide 1000 mg/m^2 (d1-2)
- Vincristin 1.5 mg/m^2 (d1)

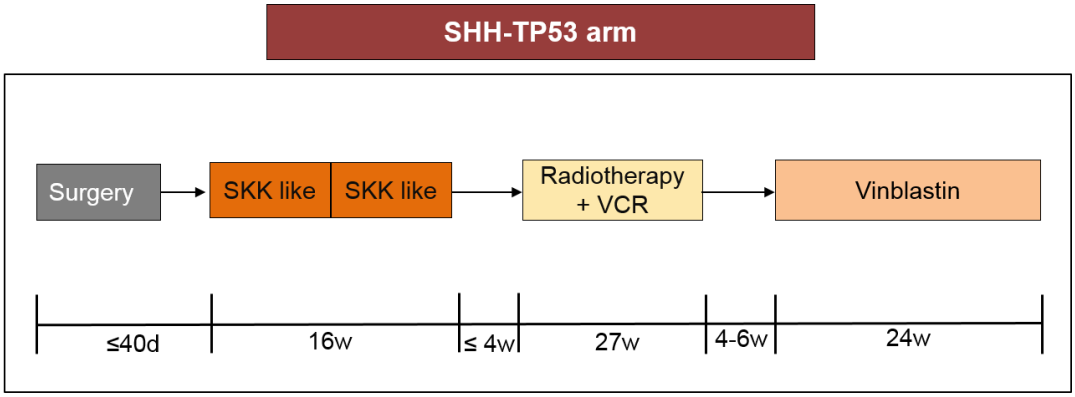
WNT-HR-arm:



Radiotherapy:
- <16y, M0/+; and ≥16y, M0:
  CSI 23.4 Gy, primary tumor 54.0 Gy
- ≥16y, M+:
  CSI 36.0 Gy, primary tumor 54.0 Gy

Chemotherapy:
- <16y: 6 cycles (BAB_ABA)
- ≥16y: 8 cycles (BAB_ABA_BA)
- Cycles A+B similar as LR/SR-arm

SHH-TP53-arm:



Induction chemotherapy (SKK-like):
- Doxorubicin 37.5 mg/m^2 (d1-2)
- Vincristin 1.5 mg/m^2 (d1, 15, 29, 43)
- High dose MTX 5 m/m^2 (d15, 29)
- Carboplatin 200 mg/m^2 (d43-45)
- Intraventricular MTX 2 mg (d1-4, 15-16, 29-30, 43-46)

Maintenaince chemotherapy:
- Vinblastin 5 mg/m^2 (d1), 24 weeks

Radiochemotherapy:
- Weekly vincristin 1.5mg/m^2 (d1)
- Somatic TP53mut:
  CSI 36.0 Gy, tumor 54.0 Gy
- Germline TP53mut, M0: Focal RT
  Safety margin 23.4 Gy, tumor 54.0 Gy
- Germline TP53mut, M+:
  CSI 23.4 Gy, tumor 54.0 Gy

Registry: no specific treatment recommendations; best clinical practice.

Note: In protocol version 13.0, the sequence of the maintenance chemotherapy was changed to Cycle B and A. Earlier protocols had the sequence Cycle A and B.

PLANNING and RECRUITMENT

Cut off date: 05/04/2022

Planning:

Start international recruitment:	25-Jun-2014
Start national recruitment:	27-Nov-2020
Expected date end of recruitment:	05-Apr-2022
Expected date last patient out:	05-Apr-2026

International recruitment:

Recruitment target protocol:	410 patients
Actual number of patients included:	401 patients
	LR-arm: 81
	SR-arm: 300
	WNT-HR-arm: 11
	SHH-TP53-arm: 6
	Registry: 3

National recruitment:

Recruitment target national:	35 patients
Actual number of patients included:	5 patients; all included in the SR-arm

ABSTRACTS / PUBLICATIONS

Not available yet

5.8 Medulloblastoom (>3 jr HR)) – SIOP-HRMB

Protocol: An international prospective trial on clinically high-risk medulloblastoma (HR-MB) in patients older than 3 years

National coordinator: dr. C.E.M. Gidding

Contact person TDC: E. Wiesen

GENERAL DETAILS

Sponsor: University of Birmingham

Coordinating Investigator: prof. S. Bailey

Sites in The Netherlands, PI: Princess Máxima Center, dr. C.E.M. Gidding
UMCG, dr. J.H. Maduro

Study Status: Open for new patient inclusions

STUDY DESIGN

Study Design:
SIOP-HRMB is an international, prospective, phase III randomised trial in patients aged 3 years and older with 'high-risk' medulloblastoma with a high-risk biological profile. Prior to entry into the trial, patients will undergo a screening phase. This will include a clinical and molecular diagnostic assessment. Biological assessments will be carried out centrally in accordance with a national scheme, see section 18. Eligible and consenting patients will be entered into the SIOP-HRMB trial and randomised to R1 after a definitive diagnosis of high risk medulloblastoma, prior to starting induction chemotherapy.

Randomisation 1 (R1) will compare three different treatment arms. Patients will be randomised between:
• Arm A: Conventional radiotherapy (36 Gy CSI) (control arm)
• Arm B: HART radiotherapy (39.2 Gy CSI)
• Arm C: High-dose chemotherapy followed by conventional radiotherapy (36 Gy CSI)

All trial patients will be randomised at trial entry. For the majority of patients taking part in R1, randomisation will take place prior to the commencement of induction chemotherapy. However, in cases of clinical urgency to start induction patients may be treated with one cycle of induction chemotherapy prior to trial entry/randomisation at the discretion of the treating Investigator. Any patients who are found to be ineligible after trial entry e.g. due to SHH P53 germline mutation will be excluded from the analysis of R1 and will be withdrawn from the trial (see section 24).

Enough time should be allowed after randomisation for stem cells to be harvested in patients randomised to the high-dose chemotherapy/conventional RT arm. Both experimental arms (Arms B and C) will be evaluated with an interim analysis with an aim to drop one of the experimental arms, so that the final analysis of R1 is a comparison of one experimental arm vs control. The interim analysis will take a 'pick-a-winner' selection design. One of the R1 treatment arms will be removed from R1 via substantial amendment. In the event that one of the experimental arms becomes unavailable for the trial, R1 will randomize between the remaining available treatment arms.

Randomisation 2 (R2) will compare two different maintenance regimens. Patients will be randomised between:
• Arm D: Maintenance therapy with vincristine (VCR)/CCNU/cisplatin alternating with VCR/cyclophosphamide (control arm)
• Arm E: Temozolomide maintenance therapy

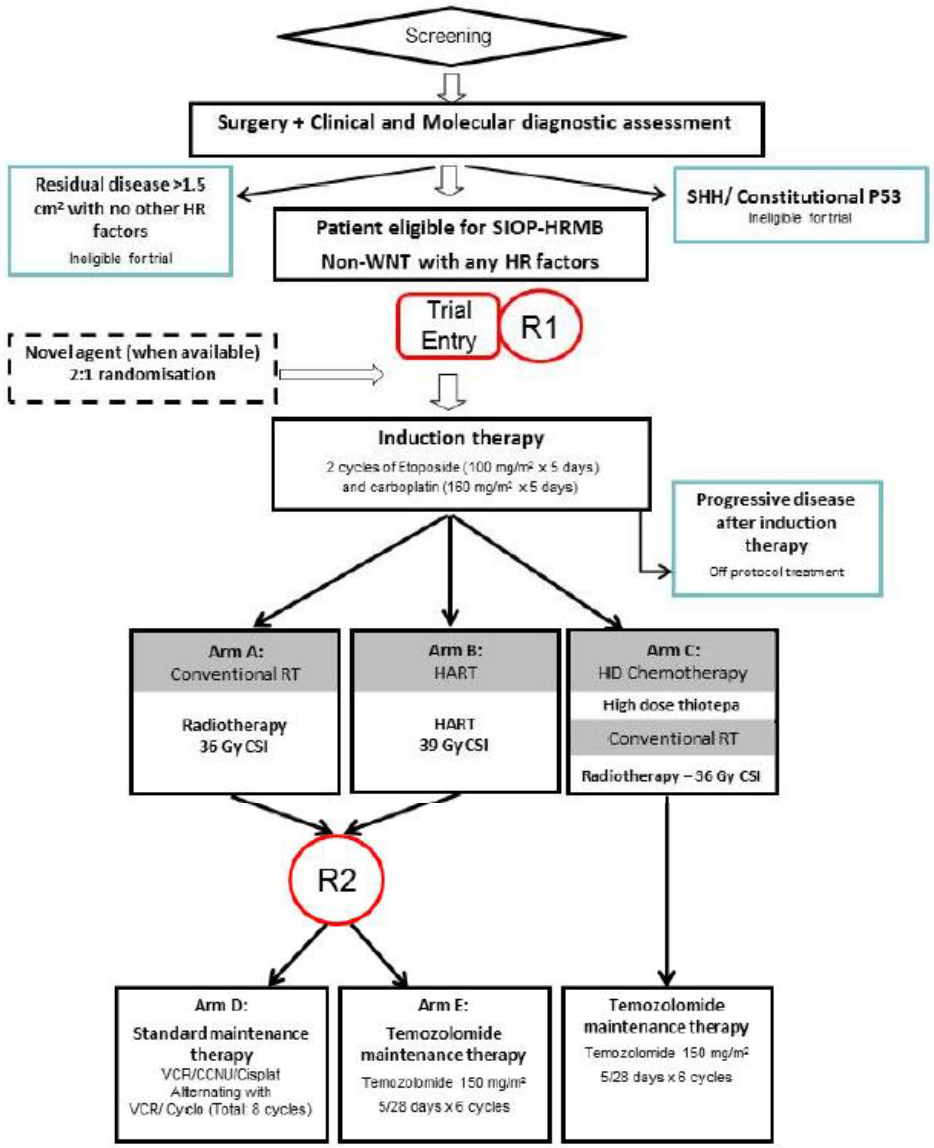
Participation in R2 is not mandatory. Randomisation will take place after completion of radiotherapy and within 7 days prior to the planned start of maintenance therapy. Patients who take part in R1 and are treated in accordance with Arm C (high-dose chemotherapy) will not be eligible to take part in R2, as it is felt that Arm D maintenance therapy will not be tolerated due to bone marrow suppression. This group of patients will be treated with Arm E temozolomide maintenance therapy; however will not contribute to the analysis of R2. Treatment and adverse event data will be collected for this group of patients. Patients who do not take part in R2 and have received either conventional radiotherapy alone or HART radiotherapy will be treated with standard maintenance therapy, as per arm D.

Primary objective:
Overall program:
• To evaluate whether the outcome in children, young people and adults with HR-MB is improved over standard therapy for those treated with: (i) conventional (once a day) radiotherapy (RT) (standard therapy), (ii) hyperfractionated-accelerated radiotherapy (HART), or (iii) high-dose therapy (HDT) with thiotepa followed by conventional RT.
• To evaluate whether the outcome in HR-MB is different for those treated with two different maintenance chemotherapy therapies.

Study population:
Children, teenagers and adults with newly diagnosed high-risk medulloblastoma.

STUDY OVERVIEW

Study overview:

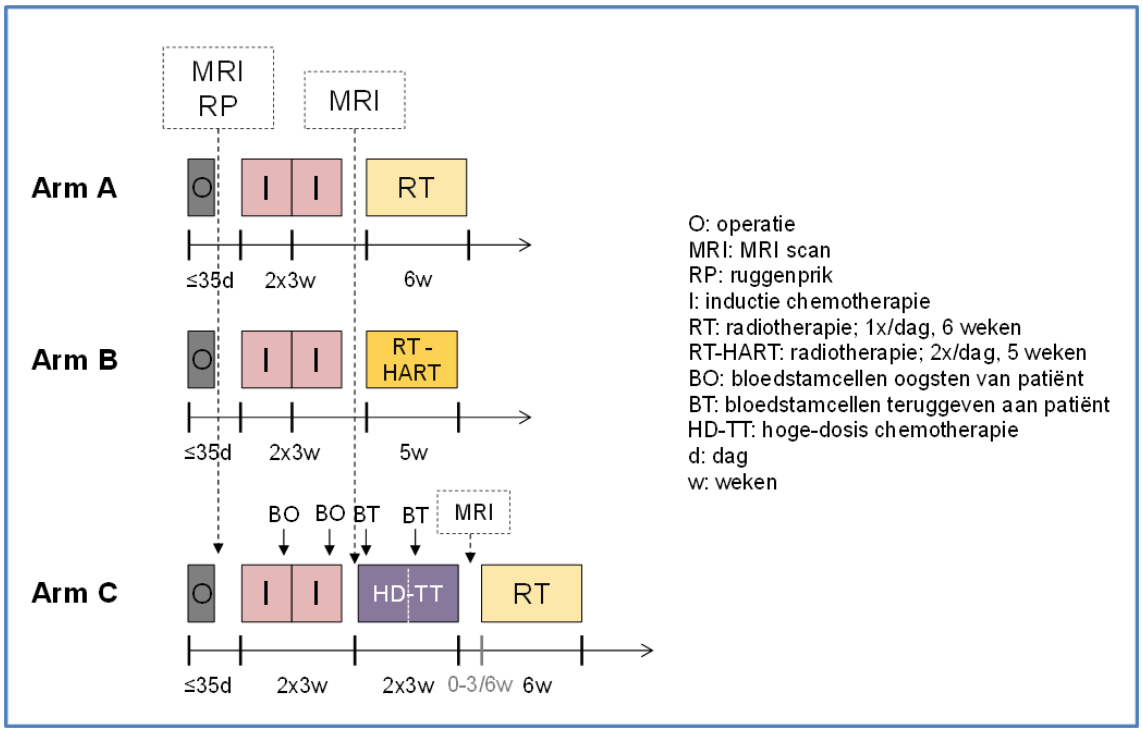


R1: Randomisation 1. To be performed at trial entry after screening.

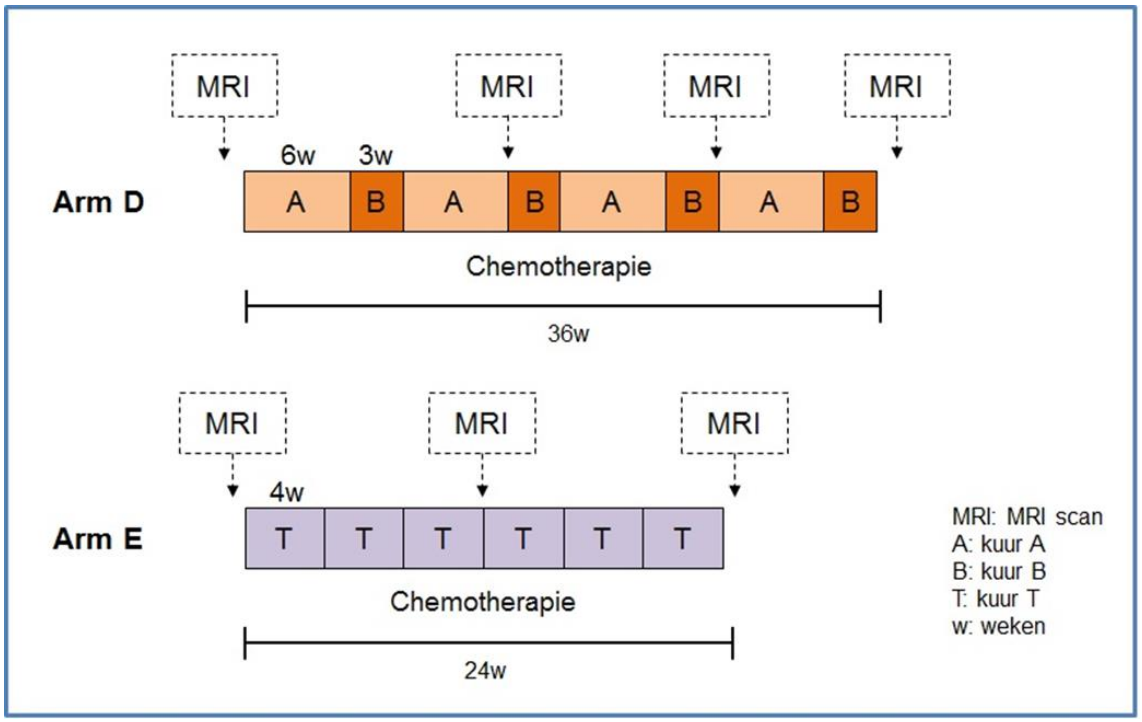
R2: Randomisation 2. To be performed after completion of radiotherapy and within 7 days prior to the planned start of maintenance therapy

Patients who are not eligible for further protocol therapy are advised to be treated in accordance with the current national guidelines.

Treatment arms 1st randomisation:



Treatment arms 2nd randomisation:



PLANNING and RECRUITMENT

Cut off date: Sep 2022

Planning:

Start international recruitment:	30-Jul-2021
Start national recruitment:	first patient to be included
Expected date end of recruitment:	Dec-2028
Expected date last patient out:	Dec-2031

International recruitment:

Recruitment target protocol:	850 patients
Actual number of patients included:	17 patients
	Screened: 17
	Recruited: 9
	Randomised: Arm A - 3, Arm B – 4, Arm C – 2, Arm D – 1, Arm E – 2,

National recruitment:

Recruitment target national:	40 patients
Actual number of patients included:	0 patients

ABSTRACTS / PUBLICATIONS

Not available yet

5.9 Refractaire HR maligniteiten - INFORM2

Protocol:	**INFORM2** exploratory multinational phase I/II combination study of **Niv**olumab and **Ent**inostat in children and adolescents with refractory high-risk malignancies
National coordinator:	Jasper van der Lugt
Contact person TDC:	Yvonne Ruchti

GENERAL DETAILS

Sponsor:	Ruprecht-Karls-University Heidelberg, Medical Faculty represented by Universitätsklinikum Heidelberg and its Commercial Managing Director Mrs. Katrin Erk Im Neuenheimer Feld 672 69120 Heidelberg, Germany
Coordinating Investigator:	Prof. Dr. Olaf Witt, MD
Sites in The Netherlands, PI:	Princess Máxima Center, Jasper van der lugt
Study Status:	Open

STUDY DESIGN

Study Design:
INFORM2 NivEnt is an exploratory nonrandomized, open-label, multinational and multicenter seamless phase I/II trial of nivolumab and entinostat in children and adolescents with relapsed / refractory or progressive high-risk solid tumors and CNS tumors. Two group phase I evaluating safety profile and determination of RP2D of combination treatment. Four group phase II basket trial evaluating activity of the combination treatment.

Primary objective:
Phase I
To determine the recommended phase II dose (RP2D) of the combination treatment with nivolumab and entinostat administered to adolescents 12-21 years with progressive, relapsed, refractory high-risk solid tumors and CNS tumors.
To determine the recommended phase II dose (RP2D) of the combination treatment with nivolumab and entinostat administered to children 6-11 years with progressive, relapsed, refractory high-risk solid tumors and CNS tumors.

Phase II
To evaluate activity and safety of the combination treatment of nivolumab and entinostat in children and adolescents with refractory/relapsed/progressive *high-risk solid tumors and CNS tumors* in four different groups: Group A: a high mutational load (> 100 somatic SNVs/exome), Group B: PD-L1 high mRNA expression (RPKM > 3), Group C: Focal MYC(N) amplification or Group D: Patients with biomarker low tumors according to the definitions of group A-C.

Study population:
Children and adolescents with refractory/relapsed/progressive high-risk solid tumors or CNS tumors with no standard of care treatment available.

STUDY OVERVIEW

Not applicable

PLANNING and RECRUITMENT

Cut off date: 11/10/2022

Planning:

Start international recruitment:	12-nov-2019
Start national recruitment:	12-nov-2019
Expected date end of recruitment:	30-jun-2024
Expected date last patient out:	30-jun-2025

International recruitment:

Recruitment target protocol:	128 patients
Actual number of patients included:	032 patients

National recruitment:

Recruitment target national:	007 patients
Actual number of patients included:	011 patients

ABSTRACTS / PUBLICATIONS

Not available

5.10 Laaggradig glioom – Firefly I

Protocol:	FIREFLY-1: A Phase 2, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of the Oral Pan-RAF Inhibitor DAY101 in Pediatric Patients with RAF Altered, Recurrent or Progressive Low-Grade Glioma and Advanced Solid Tumors
National coordinator:	
Contact person TDC:	Start-up coordinator TDC

GENERAL DETAILS

Sponsor:	DOT Therapeutics-1 Inc. (Day One)
Coordinating Investigator:	
Sites in The Netherlands, PI:	Princess Máxima Center, dr. J. van der Lugt
Study Status:	Open for arm 3, enrollment for Arms 1 and 2 is closed.

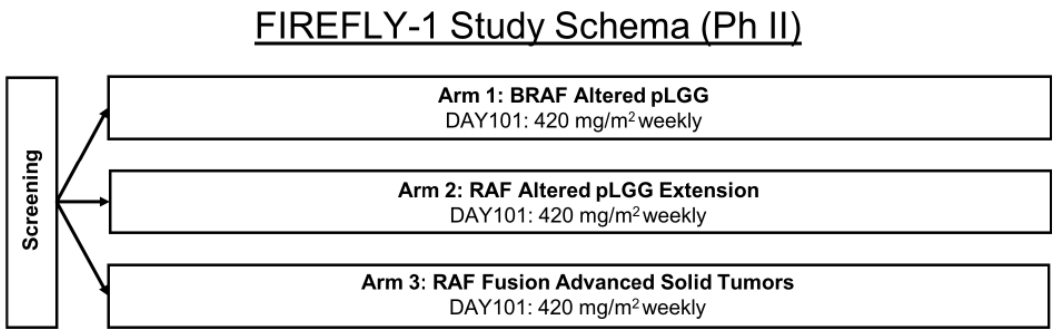
STUDY DESIGN

Study Design:	International, multicenter, Phase 2, prospective study
Primary objective:	The primary objective of Arm 1 (LOW-GRADE GLIOMA) is to evaluate the overall response rate (ORR) as determined by an independent radiology review committee (IRC) and measured by the proportion of patients with best overall confirmed response of complete response (CR) or partial response (PR) by Response Assessment in Neuro-Oncology (RANO) criteria following treatment with DAY101 in pediatric patients aged 6 months to 25 years, inclusive, with a relapsed or progressive low-grade glioma harboring a known activating v-raf murine sarcoma viral oncogene homolog B (BRAF) alteration. The primary objective of Arm 2 (LOW-GRADE GLIOMA EXTENSION) is to assess the safety and tolerability of DAY101 in pediatric patients aged 6 months to 25 years, inclusive, with a relapsed or progressive low-grade glioma harboring a known or expected to be activating RAF alteration. The primary objective of Arm 3 (ADVANCED SOLID TUMOR) is to evaluate the preliminary efficacy of DAY101 as measured by the ORR as determined by an IRC following treatment with DAY101 in pediatric patients aged 6 months to 25 years, inclusive, with a relapsed or progressive advanced solid tumor harboring a known or expected to be activating RAF fusion.

Study population: Pediatric Patients with RAF Altered, Recurrent or Progressive Low-Grade Glioma and Advanced Solid Tumors.

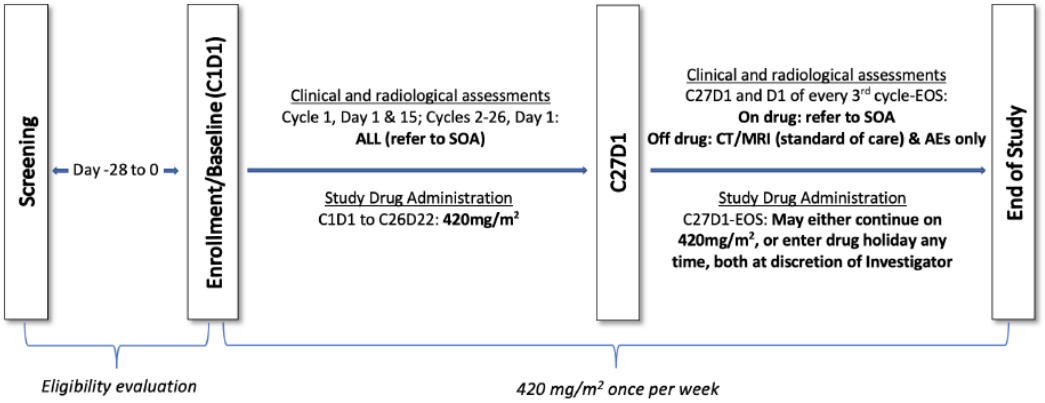
STUDY OVERVIEW

Study design schema



Abbreviations: pLGG, pediatric low-grade glioma.

Treatment schema



Abbreviations: C, cycle; D, day; EOS, end of study; CT, computerized tomography; MRI, magnetic resonance imaging; SOA, schedule of assessments.

PLANNING and RECRUITMENT *Cut off date: 19/10/2022*

Planning:

Start international recruitment:

Start national recruitment: NOV-2021

Expected date end of recruitment: SEP-2022

Expected date last patient out: 01-FEB-2024

International recruitment:

Recruitment target protocol (status):

Arm 1 (Low-Grade Glioma): Approximately 60 patients (reached)
Arm 2 (Low-Grade Glioma Extension): Up to 60 patients (reached)
Arm 3 (Advanced Solid Tumor): Up to 20 patients (still open)

National recruitment:

Recruitment target national:	10
Actual number of patients included:	9

ABSTRACTS / PUBLICATIONS

FIREFLY-1 (PNOC 026): A phase 2 study to evaluate the safety and efficacy of tovorafenib (DAY101) in pediatric patients with RAF-altered recurrent or progressive low-grade glioma or advanced solid tumors. | Journal of Clinical Oncology (ascopubs.org)

6 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: