A randomised phase IIb trial of bevacizumab added to temozolomide ± irinotecan for children with refractory/relapsed neuroblastoma - BEACON-Neuroblastoma Trial

Published: 19-03-2014
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-518931-12-00 check the CTIS register for the current data. Primary:- To test whether bevacizumab added to a backbone chemotherapy regimen (temozolomide or irinotecan-temozolomide or topotecan-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50504

Source
ToetsingOnline

Brief title
BEACON-Neuroblastoma Trial: Bevacizumab, Temozolomide ± Irinotecan

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Neuroblastoma

Research involving
Human

Sponsors and support

Primary sponsor: The University of Birmingham
Source(s) of monetary or material Support: Ministerie van OC&W,Euasa Pharma UK, zij geven alleen gratis Qarziba, geen financiele ondersteuning,Roche, zij geven alleen gratis Avastin, geen financiele ondersteuning,Stichting Imagine for Margo

Intervention

Keyword: Dinutuximab Beta, Neuroblastoma in children, Temozolomide, Topotecan

Outcome measures

Primary outcome

Primary Endpoint:

- Best response (Complete Response [CR], or Partial Response [PR][1] at any

time during the first 6 cycles of trial treatment

Secondary outcome

Secondary Endpoints:

- Safety of the regimens: Incidence and severity of Adverse Events (AE)s

- Progression-free survival (PFS)

- Event-free survival (EFS)

- Overall survival (OS)

Exploratory/Tertiary Endpoints:

- Changes in magnetic resonance imaging (MRI) derived functional imaging

biomarkers of angiogenesis: this will not take place in the NL due to lack of

financing

- Changes in circulating mRNA levels for TH, PHOX2B and DCX in bone marrow and

blood samples

- Pharmacokinetics of bevacizumab

Study description

Background summary

Neuroblastoma is the most common extracranial solid tumour in childhood and the principal cause of death due to cancer in infancy. It is also, after domestic accident, the second most frequent cause of mortality in children. More than 1200 cases/year are diagnosed in USA and Europe. Half of those cases are considered high-risk disease (metastatic/MYCN amplified). With the use of intensive chemotherapy, surgery, myeloablative chemotherapy with haematopoeitic stem cell rescue, radiotherapy and differentiating therapy with 13-cis-retinoic acid, long-term survival for children with high-risk neuroblastoma has moderately improved over the past 30 years, but in long-term reports, overall survival is still below 50%. The recent introduction of immunotherapy into the multimodal treatment of neuroblastoma has shown promising results with improvements in 2-year event free survival (EFS) of up to 20% after the addition of the anti-GD2 monoclonal antibody ch14.18 with interleukin-2 and GM-CSF, although it remains to be established the long-term benefit of this modality where late relapses have been described.
Up to 60% of children with high risk neuroblastoma will experience relapse with current therapies. In metastatic neuroblastoma, 10-year OS was 2% after relapse and 1.5% after progression according to Italian Registry data. In INRG, a database with outcomes from 8800 children with neuroblastoma treated worldwide, 5-year overall survival (OS) after relapse was 8% for non-infants with relapsed metastatic neuroblastoma and 4% for those with MYCN amplification. There is an unmet need to develop new therapeutic strategies and test new agents in children with neuroblastoma.
In addition to relapsed neuroblastoma, there are some patients that remain refractory to current front-line conventional chemotherapy and also require novel therapies.

Neuroblastoma is a highly vascular tumour. It has been shown that a high level of expression of angiogenesis factors VEGF (Vascular Endothelial Growth Factor) A and B is associated with poor prognosis. Bevacizumab is a recombinant humanised monoclonal antibody against VEGF that blocks the binding of VEGF to its receptors. It has been used in a large number of adult patients during extensive phase III investigations and post-marketing authorisation (see bevacizumab Summary of Product Characteristics [SPC]) as single agent, or in combination, with chemotherapy or radiotherapy. Studies in adults have established the safety profile with manageable toxicity as a single agent and

in combination including experience with irinotecan in high grade glioma. A phase I single agent evaluation of bevacizumab and a phase II study in combination with irinotecan for high grade and diffuse pontine gliomas have been completed in paediatrics while there are currently more than ten trials using bevacizumab in combination in children with solid tumours. To date, frequent toxicities reported in children have been infusion reactions, proteinuria, rash, hypertension or haematological toxicity. Severe grade 3-4 toxicities have been rare, consisting of central nervous system (CNS) events (ischaemia/haemorrhage), hypertension, proteinuria, haematological toxicity and fatigue:
COG conducted a Phase I trial (Study AVF2771s) of bevacizumab in children with refractory extracranial solid tumours. The primary aims included determining the maximum-tolerated dose (MTD) or recommended Phase II (RP2D) dose through use of a restricted dose escalation scheme based on clinically efficacious doses in adults, defining dose limiting toxicities (DLTs) and other toxicities and describing bevacizumab pharmacokinetics (PK) in children. Secondary aims included assessment of bevacizumab anti-tumour activity and exploration of potential biomarkers of anti-angiogenesis. Overall, bevacizumab therapy was well tolerated in these paediatric patients and had an acceptable toxicity profile when administered at doses of 5, 10, or 15 mg/kg every 2 weeks.

A randomised Phase II design is needed to ensure that patients allocated to the experimental treatments are similar to those in the control group, thereby avoiding problems of interpretation to which previous non-randomised studies in this disease area have been subjected. Randomisation controls for selection factors and will allow an unbiased estimate of the differences between arms at the end of the trial.

Topotecan-temozolomide has been shown in a recent non-randomised studyies (TOTEM) [24] to result in positive response rates of 24%, clinical benefit ratio of 79% and 1-year progression free survival of 42% and a favourable toxicity profile. Topotecan has been added to this randomised study to obtain to provide supporting data for the use of topotecan in the treatment of neuroblastoma in children.

Currently there is no standard chemotherapy for children with relapsed/refractory neuroblastoma after first line treatment and both irinotecan-temozolomide and temozolomide alone have been used. Temozolomide and irinotecan-temozolomide are the combinations selected for evaluation as they have shown the most promising results with tolerable side effects and are widely used internationally. The irinotecan-temozolomide combination is widely considered a *standard* treatment for relapsed or refractory neuroblastoma, yet there is no good evidence that this regimen is any better than single agent temozolomide: two studies of irinotecan-temozolomide have reported response rates of 8% and 15%, while a single study of temozolomide has reported a response rate of 20%. Hence, there is no justification for the use of irinotecan-temozolomide as the standard

backbone in this trial and a randomisation between irinotecan-temozolomide and temozolomide has been incorporated in order to obtain unbiased evidence on the role of irinotecan.

The factorial design used in this trial will allow the benefit of a new agent (bevacizumab) to be evaluated as well as evidence on the role of irinotecan and less patients will be enrolled in one single trial than would be required for two different trials. A Phase II trial is needed to obtain initial evidence of activity before proceeding, if appropriate, to a Phase III trial that will evaluate efficacy.
The best backbone chemotherapy regimen will be used to combine with new molecularly targeted agents. Considering the large number of potential molecularly targeted agents, novel clinical trial designs are required to test agents efficiently.

Background for the dinutuximab beta amendment
GD2 is a ganglioside which is an excellent target in neuroblastoma. It is almost universally expressed on neuroblastoma cells, but has a relatively limited distribution (neurons, skin melanocytes and peripheral pain fibres) on normal tissues. After the ANBL0032 study by the US Children*s Oncology Group was reported, immunotherapy with the anti-GD2 monoclonal antibody dinutuximab together with GM-CSF and interleukin-2 (IL-2) was introduced as consolidation treatment after myeloablative chemotherapy in high risk neuroblastoma. Dinutuximab (Unituxin, United Therapeutics) has FDA approval, but is not available in Europe.

Dinutuximab beta (Quarziba, Eusa Pharma) is closely related to dinutuximab. The two antibodies have identical amino acid sequences, but are produced in different cell lines. This results in differing glycosylation patterns, which confer some differences in biological properties. Therefore, although the antibodies have similar specificity for GD2, they should be considered as distinct agents. Dinutuximab beta received marketing authorisation from the EMA in 2017. Dinutuximab beta has been most widely used in Europe, in the context of the trials conducted by the European Neuroblastoma Research Network (SIOPEN) where it has been given as consolidation therapy, with and without adjuvant IL-2. In patients with relapsed or refract

Study objective

This study has been transitioned to CTIS with ID 2024-518931-12-00 check the CTIS register for the current data.

Primary:
- To test whether bevacizumab added to a backbone chemotherapy regimen (temozolomide or irinotecan-temozolomide or topotecan-temozolomide) demonstrates activity in children with relapsed or refractory neuroblastoma
- To test whether the addition of irinotecan to temozolomide increases the

activity of chemotherapy in children with relapsed or refractory neuroblastoma
- To test whether the addition of topotecan to temozolomide increases the activity of chemotherapy in children with relapsed or refractory neuroblastoma
- To test whether Dinutuximab Beta added to a backbone chemotherapy regimen (temozolomide or topotecan-temozolomide) demonstrates activity in children with relapsed or refractory neuroblastoma

Secondary:
- To evaluate the safety of the regimens

Tertiary:
- To undertake preliminary evaluation of the changes in magnetic resonance imaging (MRI) derived functional imaging biomarkers of angiogenesis. This will not take place in the Netherlanda due to lack of financing
- To undertake preliminary evaluation of the role of circulating mRNA levels for tyrosine hydroxylase (TH), paired-like homeobox 2b (PHOX2B) and doublecortin (DCX) as prognostic/predictive biomarkers in this refractory/relapsed setting
- To study the pharmacokinetics of bevacizumab in children with neuroblastoma
- To undertake a preliminary evaluation of the role of tumour molecular profiles including pharmacogenomic profiles as prognostic and predictive biomarkers in children with neuroblastoma
- To perform a preliminary evaluation of the role of circulating angiogenic cytokines as pharmacodynamic, prognostic and predictive biomarkers in children with neuroblastoma
- To undertake a preliminary evaluation of biomarkers of response to anti-GD2-therapy (Fc/KIR polymorphisms, ADCC and ADA(s) and of Dinutuximab Beta pharmacokinetics (PK)
- Pilot descriptive study of neuroblastoma markers that may include: O6-methylguanine-methyltransferase (MGMT) status, immunohistochemistry and immunofluorescence markers on tumour samples (such as microvessel density (MVD), CD31, Ki67, NRP1, VEGFR-1, VEGFR-2, C-KIT), DNA/RNA extraction from tissue sections for tumour mutation screening and tumour expression profiling
- A preliminary correlation of the different biomarkers (Fc/KIR polymorphisms, Antibody Dependent Cellular Toxicity (ADCC) and Anti-drug Antibodies (ADAs) will be made with parameters of anti-tumour activity (response rate, PFS and OS), PK parameters (Dinutuximab Beta trough levels) for this chemo immunotherapy regimen will be described

Study design

This is an international open-label, randomised, multicentre phase II trial of temozolomide ± irinotecan, with or without bevacizumab or Dinutumximab Beta, for the treatment of patients with relapsed or refractory neuroblastoma. The study will evaluate the safety and activity of these combinations.

Patients will receive treatment for 6 courses, lasting 18 or 24 weeks depending

on the arm of the trial that they are randomised to.
Patients with a response (CR, PR) or stable disease (SD) while on the BEACON-Neuroblastoma trial will receive 6 cycles of trial treatment. If the patient has achieved a satisfactory response (i.e. CR, PR or SD) with acceptable toxicity, treatment may be extended beyond 6 cycles (up to 12 cycles) after discussion with the Sponsor and the CI.

Patients will be registered into the trial and randomised at the same time to one of the following four arms (approximately 30 patients per arm):

Schedule 1: Temozolomide: 200 mg/m2/day , D1-5 po, q28d
Schedule 2: Temozolomide: 200 mg/m2/day , D1-5 po + Bevacizumab: 10 mg/kg, D1+D15 iv, q28d
Schedule 3: Temozolomide: 100 mg/m2/day , D1-5 po + Irinotecan: 50 mg/m2/day, D1-5 iv, q21d (closed in June 2018)
Schedule 4: Temozolomide: 100 mg/m2/day , D1-5 po + Irinotecan: 50 mg/m2/day, D1-5 iv + Bevacizumab: 15 mg/kg, D1 iv, q21d (closed in June 2018)
Schedule 5: Temozolomide: 150 mg/m2/day , D1-5 po + Topotecan 0,75 mg/m2/day, D1-5 iv, q28d
Schedule 6: Temozolomide: 150 mg/m2/day , D1-5 po + Topotecan 0,75 mg/m2/day, D1-5 iv + Bevacizumab: 10 mg/kg, D1+D15 iv, q28d

Following completion of the bevacizumab randomization (160 patients) in March 2019 64 additional patients will be registered into the trial and randomized at the same time to one of the following four arms (with a 2:1 ration in the Dinutuximab Beta arms):
Schedule T: Temozolomide: 200 mg/m2/day, D1-5 po, q28d
Schedule dBT: Temozolomide: 200 mg/m2/day, D1-5 po+ Dinutuximab Beta 10 mg/kg/day 24h iv, D1-7, q28d
Schedule TTo: Temozolomide: 150 rng/m2/day, D1-5 po+ Topotecan 0,75 mg/m2/day, D1-5 iv, q28d
Schedule dBTTo: Temozolomide: 150 mg/m2/day , D1-5 po+ Topotecan 0,75 mg/m2/day, D1-5 iv+ Dinutuximab Beta: 10 mg/kg/day 24h iv, D1-7, q28d

On January 28, 2020 the arms T and dBT are closed for inclusion following an Urgent Safety Measure by the sponsor. Following review and discussion of the results of the bevacizumab and irinotecan randomisations for event-free and overall survival in the BEACON-Neuroblastoma trial at the Trial Management Group (TMG), the results show that temozolomide alone is inferior.

Intervention

Study medication as described above depending on the cohort the pt is randomized in.

Study burden and risks

Bevacizumab
Bevacizumab has been used for many years in up to a million of adult patients to treat a variety of adult cancers and has been shown to be safe. Side effects in adults are well known however only a few hundred children have received bevacizumab and so it is possible that some side effects could occur that we have not expected. The main known side effects are:

• High blood pressure during treatment in about 25% of patients - your child*s doctor will check their blood pressure regularly
• Feeling sick in about 60% of patients
• Constipation in about 40% of patients
• Diarrhoea - this can be severe in up to 1 in 3 people treated
• Fatigue (tiredness) during and after treatment
• Pain and weakness affecting the joints, muscles, chest and abdomen
• Numbness or tingling in fingers and toes
• Slow wound healing
• Protein in the urine in about 25% of patients - your child will have their urine tested regularly
• Increased risk of bleeding - your child*s gums may bleed easily and they may have nose bleeds, It is important to tell your child*s doctor if you notice any bleeding
• Poor appetite

A small number of children have had bevacizumab to date and it is not known whether it will have any effect in the growth of the bones. We will monitor your child growth at every visit and we will perform an X-Ray of the left hand and wrist to monitor their bone age. There are other rare side effects of bevacizumab. If you would like a list of these, please ask your child*s doctor.

Irinotecan
The most common side effects of irinotecan are:

• Diarrhoea (see note below)
• Changes to blood liver enzyme levels and bilirubin levels
• Temporary hair loss
• A reduction in the number of blood cells that are produced by the bone marrow which leads to:
o Fewer white blood cells (neutropenia), which can increase the risk of getting an infection, some of which may be life threatening or possibly fatal
o Fewer red blood cells (anaemia) - this can result in shortness of breath, weakness and fatigue. We will monitor your child closely and they may be given a blood transfusion if their red cell levels become too low
o Fewer platelets (thrombocytopenia) - this may cause your child to bruise or bleed more easily. We will monitor your child closely and they may be given a platelet transfusion if their platelet levels become too low

Other possible less common side effects include nausea and vomiting,

constipation, feeling weak, increased creatinine levels in the blood (an indication of abnormal kidney function), dehydration, fever and the development of an *Acute Cholinergic Syndrome* (diarrhoea, flushing, watery eyes, nose and mouth, constricted pupils, visual disturbance and dizziness within 24 hours of last receiving irinotecan).

Special note about diarrhoea:

If your child*s develops diarrhoea that starts more than 24 hours after they last received irinotecan (*delayed diarrhoea*) it may become serious. The diarrhoea should be treated and kept under close supervision. After the first diarrhoea appears it is important to do the following:

1. Give your child any anti-diarrhoeal treatment that their doctor has prescribed
2. Ensure that your child drinks lots of fluids
3. Inform your child*s doctor about their diarrhoea

There are other rare side effects of irinotecan. If you would like a list of these, please ask your child*s doctor.

Temozolomide
Temozolomide is usually very well tolerated, but possible side effects include:

1. Nausea and/or vomiting
2. A reduction in red blood cells, white blood cells and platelets as mentioned above for irinotecan
3. Inflammation of the gums and other membranes and linings
4. Weight loss
5. Hair loss in rare cases

There are other rare side effects of Temozolomide. If you would like a list of these, please ask your child*s doctor.

Topotecan

Topotecan has been used in adults over a number of years and the side effects are well known. Possible side effects include:

• A reduction in red blood cells, white blood cells and platelets as mentioned above for temozolomide, irinotecan and bevacizumab
• Fever
• Loss of appetite
• Vomiting and diarrhoea
• Constipation
• Abdominal pain

• Hair loss
• Itchy skin
• Tiredness

Other important side effects:
There have been some cases of the following side effects in patients receiving topotecan, including some with fatal outcomes:
• bowel inflammation (neutropenic colitis)
• excessive immune reaction (sepsis)
• lung disease

Dinutuximab Beta
The most important side effect of this anti-GD2 drug is severe pain, which can occur temporarily. The pain is controlled with strong pain medication, including morphine per infusion. Other side effects that may occur during the administration of the medicine are fever, cough and severe allergic reactions. Eye problems can also occur, these are usually temporary. Some patients retain fluid; in severe cases this can cause low blood pressure and breathing difficulties.

Other possible side effects are:
* Pain in the head, back, abdomen, intestines, arms, legs, joints or other parts of the body that require pain medication during the infusion
* Accelerated heartbeat
* Lowering of blood pressure
* Nausea and vomiting
* Diarrhea
* Constipation
* Fever
* Retain swelling and moisture
* Skin rash
* Cough
* Infections
* Decrease in the number of white blood cells, red blood cells and platelets. A decrease in the number of white blood cells increases the chance of an infection, possibly with a fever. Treatment with antibiotics is then often necessary. If the number of red blood cells (this is called anemia or anemia) decreases, a feeling of tiredness may arise. Fewer platelets can increase the risk of bleeding and bleeding after an injury, but spontaneous bleeding can also occur. If necessary, platelets or red blood cells should be treated with a transfusion.
* Neurological problems, including loss of function of nerves, which can sometimes be serious or permanent

There are even more rare side effects with Dinutuximab Beta, which can sometimes be serious or life-threatening.

Group allocation

As this is a randomised trial, there is a possibility that your child may not be assigned to the treatment group that you (or they) would prefer. The treatment that your child receives cannot be selected by choice. If you do not wish for your child to have their treatment allocated by chance i.e. by randomisation, then they cannot be part of this study and will receive treatment as recommended by their doctor.

Blood Sampling Risk

If your child takes part in this clinical trial, additional blood samples will be taken. The risks of having blood taken from the vein include pain, bruising or infection at the site where the blood is taken, and fainting. If your child has a Hickman line or Port-a-cath, blood will be taken from there instead of directly from a peripheral vein. In this case there is a slight risk of infection when the device is used, but this is no more than for any other occasion when it is used.

Bone Marrow Sampling Risks

During this study, samples of your child*s bone marrow will be taken so that we can see if neuroblastoma has spread to this area. Additional bone marrow sampling will also be performed at the same time for research purposes as detailed in the Biomarker section of question 6 earlier. Risks of bone marrow sampling include pain, bleeding and infection at the sampling site. If your child is allocated to receive bevacizumab there is an additional risk of poor wound healing after having this test. For this reason, children who are receiving bevacizumab and have no neuroblastoma in their bone marrow at the beginning of the study will not have bone marrow samples taken after receiv

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Disease specific• Histologically proven neuroblastoma as per International Neuroblastoma Staging System (INSS) definition • Relapsed or refractory neuroblastomao Relapsed: any relapsed or progressed high-risk neuroblastoma o Refractory high risk disease: Lack of adequate response to frontline therapy that precludes the patient from proceeding to consolidation therapies (e.g myeloablative chemotherapy)• Measurable disease by cross sectional imaging (RECIST) or evaluable disease (uptake on MIBG scan with or without bone marrow histology). Patients with only bone marrow detectable disease (bone marrow aspirate or trephine) are NOT eligible for the studyGeneral• Age >=1 to <=21 years• Informed consent from patient, parent or guardianPerformance and organ function• Performance Status:o Lansky >= 50%, Karnofsky >= 50% or ECOG <=3 (Patients who are unable to walk because of paralysis, but who are able to sit upright unassisted in a wheelchair, will be considered ambulatory for the purpose of assessing performance score)• Life expectancy of >=12 weeks• Bone marrow function (within 72 hours of randomisation):o No bone marrow disease: * Platelets >= 75 x 10e9/L (unsupported for 72 hours) * ANC >= 0.75 x 10e9/L (no G-CSF support for 72 hours)* Haemoglobin >= 8 g/dL (transfusions allowed)o Bone marrow disease: * Platelets >= 50 x109/L (unsupported for 72 hours) * ANC >=0.5 x 10e9/L (no G-CSF for 72 hours)* Haemaglobin >= 8 g/dL (transfusions allowed) • Renal function (within 7 days of randomisation):o Serum creatinine <=1.5 ULN for age, if higher, a calculated GFR (radioisotope or 24 hour urine calculated creatinine clearance) must be >= 60 ml/min/1.73 m2 • Liver function (within 72 hours of randomisation): AST and ALT <=3 ULN and total bilirubin <=1.5 ULN. In

case of liver metastases, AST and ALT <=5 ULN and total bilirubin <=2.5 ULN• Cardiac function measured by echocardiogram within 4 weeks of randomization or within 12 weeks if the patient has not received anthracyclines or cardiotoxics in between, shortening fraction >=29% on echocardiogram • • Adequate lung function: no dyspnea at rest and pulse oximetry > 94% in room air

• Females of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to initiation of treatment. Sexually active women of childbearing potential must agree to use acceptable and appropriate contraception during the study and for at least 6 months after the last study treatment administration. Sexually active male patients must agree to use condoms during the study for at least 6 months after the last study treatment administration.

• Availability and willingness to place a double central venous access if needed for trial treatment and supportive care in case of treatment with chemo-immunotherapy
(neuronen, perifere pijn vezels, huid) aanwezig is. Dinut

Exclusion criteria

• Previous treatment with temozolomide
• Previous treatment with chemotherapy in combination with anti-GD2 directed therapy (*chemo immunotherapy*) with any anti-GD2 antibody. Prior treatment with anti-GD2 directed therapy alone with/without cytokines is allowed provided a 4 week wash-out period is met
• Known hypersensitivity to:o Any study drug or component of the formulation o Patients with mild previous hypersensitivity reactions to anti-GD2 antibodies may be included, but those with severe (or G4) hypersensitivity reactions to anti-GD2 antibodies will be excluded• Clinically significant neurological deficit, uncontrolled seizures or objective peripheral neuropathy (>grade 2). (Unresolved neurological deficits from spinal cord compression are acceptable)

• Uncontrolled infection

• Inadequate recovery from prior surgery with no ongoing >= grade 3 surgical complications. For core biopsies, no less than 24 hours; for open excisional biopsies, no less than 48 hours; for major surgery , no less than 2 weeks• Patient less than (at point of planned date of randomisation):o Two weeks from prior chemotherapy. One week from prior oral metronomic chemotherapy (i.e. oral etoposide or oral cyclophosphamide)o Six weeks from prior craniospinal radiotherapy or MIBG therapy and two weeks from radiotherapy to the tumour bed. No washout is required for palliative radiotherapyo Eight weeks from prior high dose chemotherapy with autologous haempoietic stem cell rescue o Three months from prior allogeneic stem cell transplant, no ongoing treatment with

immunosuppressive agents and no signs of >=grade 2 acute graft versus host diseaseo 14 days or 5 half-lives (whichever occurs later) from last administration of an IMP in an IMP-trialo 14 days or 5 half-lives (whichever occurs later) from last administration of any other biological/targeted anticancer agent• Bleeding metastases (Patients with CNS metastases can be enrolled as long as the metastases are not bleeding)• Pregnant or lactating patient• Any uncontrolled medical condition that poses an additional risk to the patient • Low probability of treatment compliancet geen anthracyclines of cardi

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-10-2015
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	bevacizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Irinotecan

Generic name:	irinotecan-HCL trihydrate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Qarziba
Generic name:	Dinutuximab Beta
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Temodal
Generic name:	temozolomide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Topotecan
Generic name:	Topotecan hydrochloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-03-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-03-2016
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	24-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-518931-12-00
EudraCT	EUCTR2012-000072-42-NL
ISRCTN	ISRCTN40708286
CCMO	NL46591.078.13