

A trial of BEvACizumab added to temozolomide +/- irinOtecan for children with refractory /relapsed Neuroblastoma

Submission date 22/02/2013	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 24/04/2013	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 08/03/2024	Condition category Cancer	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-bevacizuamb-and-chemotherapy-for-children-and-young-people-with-neuroblastoma-beacon>

Study website

<https://www.birmingham.ac.uk/research/crcctu/trials/beacon/index.aspx>

Contact information

Type(s)

Scientific

Contact name

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Additional identifiers

EudraCT/CTIS number

2012-000072-42

IRAS number

ClinicalTrials.gov number
NCT02308527

Secondary identifying numbers
RG_11-087

Study information

Scientific Title

A randomised phase IIb trial of BEvACizumab added to temozolomide +/- irinOtecan for children with refractory/relapsed Neuroblastoma

Acronym

BEACON-Neuroblastoma

Study objectives

Current study hypothesis as of 25/03/2019:

Primary objectives:

1. To test whether bevacizumab added to a backbone chemotherapy regimen (temozolomide or irinotecan-temozolomide) demonstrates activity in children with relapsed or refractory neuroblastoma
2. To test whether the addition of irinotecan to temozolomide increases the activity of chemotherapy in children with relapsed or refractory neuroblastoma
3. To test whether the addition of topotecan to temozolomide increases the activity of chemotherapy in children with relapsed or refractory neuroblastoma
4. To test whether dinutuximab beta added to a backbone chemotherapy regimen (temozolomide or temozolomide + topotecan) demonstrates activity in children with relapsed or refractory neuroblastoma.

Secondary objectives:

1. To evaluate the safety of the regimens

Previous study hypothesis:

Primary objectives:

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

Secondary objectives:

1. To evaluate the safety of the regimens

Ethics approval required

Old ethics approval format

Ethics approval(s)

The NRES Committee West Midlands - Coventry & Warwickshire, 06/02/2013, ref: 13/WM/0023

Study design

Interventional phase II randomised open label international multicentre 2x2 factorial trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied

Neuroblastoma in children aged ≥ 1 to ≤ 21 years

Interventions

Current intervention as of 25/03/2019:

Investigational medicinal products: bevacizumab, irinotecan, temozolomide, topotecan, dinutuximab beta, cyclophosphamide

Arm T:

Temozolomide 200 mg/m² per day oral on days 1-5 every 4 weeks

Duration of intervention: 24 weeks

Arm BT:

Temozolomide 200 mg/m² per day oral on days 1-5 every 4 weeks

Bevacizumab 10mg/kg intravenous on days 1 and 15 every 4 weeks

Duration of intervention: 24 weeks

Arm IT:

Temozolomide 100 mg/m² per day oral on days 1-5 every 3 weeks

Irinotecan 50 mg/m² per day intravenous on days 1-5 every 3 weeks

Duration of intervention: 18 weeks

Arm BIT:

Temozolomide 100 mg/m² per day oral on days 1-5 every 3 weeks

Irinotecan 50 mg/m² per day intravenous on days 1-5 every 3 weeks

Bevacizumab 15 mg/kg intravenous on day 1 every 3 weeks

Duration of intervention: 18 weeks

Arm TTo:

Topotecan 0.75 mg/m²/day intravenous on days 1-5 every 4 weeks

Temozolomide 200 mg/m² per day oral on days 1-5 every 4 weeks

Duration of intervention: 24 weeks

Arm BTTo:

Topotecan 0.75 mg/m²/day intravenous on days 1-5 every 4 weeks

Temozolomide 200 mg/m² per day oral on days 1-5 every 4 weeks

Bevacizumab 10mg/kg intravenous on days 1 and 15 every 4 weeks

Duration of intervention: 24 weeks

Arm dBT

Dinutuximab beta 10 mg/m²/day 24-h infusion on days 1-7 every 4 weeks

Temozolomide 200 mg/m²/day oral on days 1-5 every 4 weeks

Duration of intervention: 24 weeks

Arm dBTTTo

Dinutuximab beta 10 mg/m²/day 24-h infusion on days 1-7 every 4 weeks

Temozolomide 200 mg/m²/day oral on days 1-5 every 4 weeks

Topotecan 0.75mg/m²/day intravenous on days 1-5 every 4 weeks

Duration of intervention: 24 weeks

Previous intervention:

Investigational Medicinal Products: Bevacizumab, Irinotecan, Temozolomide

Arm T:

Temozolomide 200 mg/m² per day oral on days 1-5 every 4 weeks

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Duration of intervention: 18 weeks

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Temozolomide 100 mg/m² per day oral on days 1-5 every 3 weeks

Irinotecan 50 mg/m² per day intravenous on days 1-5 every 3 weeks

Bevacizumab 15mg/kg intravenous on day 1 every 3 weeks

Duration of intervention: 18 weeks

Added 28/08/2018:

Arm TTo:

Topotecan 0.75 mg/m²/day intravenous on days 1-5 every 4 weeks

Temozolomide 200 mg/m² per day oral on days 1-5 every 4 weeks

Duration of intervention: 24 weeks

Arm BTTto:

Topotecan 0.75 mg/m²/day intravenous on days 1-5 every 4 weeks

Temozolomide 200 mg/m² per day oral on days 1-5 every 4 weeks

Bevacizumab 10mg/kg intravenous on days 1 and 15 every 4 weeks

Duration of intervention: 24 weeks

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

Bevacizumab, temozolomide, irinotecan, topotecan, dinutuximab beta, cyclophosphamide

Primary outcome measure

Best response (Complete Response [CR], or Partial Response [PR][1] at any time during the first 6 cycles of trial treatment

Secondary outcome measures

1. Safety of the regimens: Incidence and severity of Adverse Events (AEs)
2. Progression-free survival (PFS)
3. Overall survival (OS)

Overall study start date

01/04/2013

Completion date

30/06/2026

Eligibility

Key inclusion criteria

Disease specific

1. Histologically proven neuroblastoma as per International Neuroblastoma Staging System (INSS) [1] definition
2. Relapsed or refractory neuroblastoma
 - 2.1. Relapsed: any relapsed or progressed high-risk neuroblastoma
 - 2.2. Refractory high risk disease: Lack of adequate response to frontline therapy that precludes the patient from proceeding to consolidation therapies (e.g myeloablative chemotherapy)
3. 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 study

General

1. Age ≥ 1 to ≤ 21 years
2. Informed consent from patient, parent or guardian

Performance and organ function

1. Performance Status:

- 1.1. Lansky $\geq 50\%$, Karnofsky $\geq 50\%$ 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)
2. Life expectancy of ≥ 12 weeks
3. Bone marrow function (within 72 hours of eligibility assessment):
No bone marrow disease:
 1. Platelets $\geq 75 \times 10^9/L$ (unsupported for 72 hours)
 2. ANC $\geq 0.75 \times 10^9/L$ (no G-CSF support for 72 hours)
 3. Haemoglobin $> 7.5 \text{ g/dL}$ (transfusions allowed)
 Bone marrow disease:
 1. Platelets $\geq 50 \times 10^9/L$ (unsupported for 72 hours)
 2. ANC $\geq 0.5 \times 10^9/L$ (no G-CSF for 72 hours)
 3. Haemoglobin $> 7.5 \text{ g/dL}$ (transfusions allowed)
4. Renal function (within 72 hours of eligibility assessment):
 - 4.1. Absence of clinically significant proteinuria (early morning urine dipstick $\leq 2+$). When the dipstick urinalysis shows a proteinuria $> 2+$, a protein:creatinine (Pr/Cr) ratio must be < 0.5 or a 24 hour protein excretion must be $< 0.5\text{g}$
 - 4.2. Serum creatinine ≤ 1.5 ULN for age, if higher, a calculated GFR (radioisotope) must be $\geq 60 \text{ ml/min/1.73 m}^2$
5. Liver function (within 72 hours of eligibility assessment): AST and ALT ≤ 2.5 ULN and total bilirubin ≤ 1.5 ULN. In case of liver metastases, AST and ALT ≤ 5 ULN and total bilirubin ≤ 2.5 ULN
6. Cardiac function, shortening fraction $\geq 29\%$ on echocardiogram
7. Coagulation, patients not on anticoagulation must have an INR ≤ 1.5 and APTT ≤ 1.5 ULN for age. Anticoagulation is permitted as long as the INR or APTT is within therapeutic limits (according to the medical standard of the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks at the time of study enrolment. Blood pressure below 95th centile for age and sex. Use of antihypertensive medication is permitted
8. Males or females of reproductive potential may not participate unless they agree to use an effective contraceptive method, for the duration of study therapy and for up to 6 months after the last dose of trial drugs. A negative urine pregnancy test must be obtained within 72 hours prior to dosing in females who are post-menarche

Participant type(s)

Patient

Age group

Child

Lower age limit

1 Years

Upper age limit

21 Years

Sex

Both

Target number of participants

224

Key exclusion criteria

1. Previous treatment with bevacizumab, temozolomide, irinotecan or any combination of these drugs
2. Known hypersensitivity to:
 - 2.1. Any study drug or component of the formulation
 - 2.2. Chinese hamster ovary products or other recombinant human or humanised antibodies
3. Prior severe arterial thrombo-embolic events (e.g. cardiac ischemia, cerebral vascular accident, peripheral arterial thrombosis)
4. Any ongoing arterial thrombo-embolic events
5. Patient less than (at point of eligibility assessment):
 - 5.1. 48 hours post bone marrow aspirate/trephine
 - 5.2. 48 hours post central line insertion
 - 5.3. Four weeks post major surgery
 - 5.4. One week post core biopsy
 - 5.5. Two weeks from prior chemotherapy
 - 5.6. Six weeks from prior craniospinal or MIBG therapy and two weeks from radiotherapy to the tumour bed
 - 5.7. Eight weeks from prior myeloablative therapy with haematopoietic stem cell rescue (autologous stem cell transplant)
 - 5.8. Three months from prior allogeneic stem cell transplant
 - 5.9. Two weeks from last administration of an IMP in an IMP-trial
6. Bleeding metastases (patients with CNS metastases can be enrolled as long as the metastases are not bleeding)
7. Invasion of major blood vessels
8. Use of enzyme inducing anticonvulsants within 72 hours of eligibility assessment
9. History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
10. History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or active gastrointestinal bleeding within 6 months prior to study enrolment
11. Pregnant or lactating patient
12. Any uncontrolled medical condition that poses an additional risk to the patient (i.e. haemoptysis, non-healing, bone fracture, wound/ulcer)
13. Low probability of treatment compliance
14. Planned immunisation with live vaccine

Date of first enrolment

01/04/2013

Date of final enrolment

30/06/2021

Locations

Countries of recruitment

Austria

Belgium

Denmark

England

France

Germany

Ireland

Italy

Netherlands

Spain

Switzerland

United Kingdom

Study participating centre

The Royal Marsden NHS Foundation Trust & Institute of Cancer Research

15 Cotswold Rd

Sutton

Surrey

United Kingdom

SM2 5PT

Sponsor information

Organisation

University of Birmingham

Sponsor details

c/o Dr Birgit Whitman

Edgbaston

Birmingham

England

United Kingdom

B15 2TT

Sponsor type

University/education

Website

<http://www.birmingham.ac.uk>

ROR

<https://ror.org/03angcq70>

Funder(s)

Funder type

Charity

Funder Name

Cancer Research UK (UK) - Clinical Trials Awards & Advisory Committee: C1536/A14426

Alternative Name(s)

CR_UK, Cancer Research UK - London, CRUK

Funding Body Type

Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location

United Kingdom

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal.

Intention to publish date

30/06/2027

Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No