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

Submission date 22/02/2013	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 24/04/2013	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 08/03/2024	**Condition category** Cancer	[_] Individual participant data [_] 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/crctu/trials/beacon/index.aspx

Contact information

Type(s)
Scientific

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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 Commitee 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 dBTTo
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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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
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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

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 ≥ 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)
2. Life expectancy of ≥12 weeks
3. Bone marrow function (within 72 hours of eligibility assessment):
No bone marrow disease:
1. Platelets ≥ 75 x 109/L (unsupported for 72 hours)
2. ANC ≥ 0.75 x 109/L (no G-CSF support for 72 hours)
3. Haemoglobin > 7.5 g/dL (transfusions allowed)
Bone marrow disease:
1. Platelets ≥ 50 x109/L (unsupported for 72 hours)
2. ANC ≥0.5 x 109/L (no G-CSF for 72 hours)
3. Haemoglobin > 7.5 g/dL (transfusions allowed)
4. Renal function (within 72 hours of eligibility assessment):
4.1. Absence of clinically significant proteinuria (early morning urine dipstick ≤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 < 0.5g
4.2. Serum creatinine ≤1.5 ULN for age, if higher, a calculated GFR (radioisotope) must be ≥ 60 ml /min/1.73 m2
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 ≥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 haematopoeitic 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, Cancer Research UK (CRUK), 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