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A trial looking at different treatments for neuroblastoma which has come back after initial therapy

Submission date 01/05/2024	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 26/06/2024	**Overall study status** Ongoing	
Last Edited 05/06/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Neuroblastoma is one of the most common solid childhood tumours, and a major cause of cancer-related death in children. More than 1200 children/young adults a year are diagnosed in USA and Europe. Around 600 of these cases are considered high-risk, which means the cancer is more difficult to treat successfully. Despite improvements in survival over recent decades, a significant proportion of patients with high-risk neuroblastoma have disease that does not respond to standard treatments (refractory neuroblastoma) or comes back after completion of standard frontline treatment (relapsed neuroblastoma). Therefore, there is a need to develop new treatment strategies and test new drugs to improve outcomes for children with neuroblastoma.

Aims of the BEACON2 trial:
• To improve survival for patients with relapsed neuroblastoma by developing new treatment combinations
• To evaluate new treatment combinations in relapsed neuroblastoma, within a phase I/II trial that can impact clinical practice, while also allowing dose confirmation for new promising combinations
• To evaluate the safety, activity, efficacy and impact on quality of life of these new treatment combinations in relapsed neuroblastoma patients
• To improve our understanding of relapsed neuroblastoma biology and advance the development of targeted therapies using biomarkers, by conducting a comprehensive biomarker sample collection.

Who can participate?
Patients aged 1 year or older with neuroblastoma will be recruited from hospitals throughout the UK, Europe and Australasia.

What does the study involve?
BEACON2 is a randomised phase I/phase II, open label, international trial. The trial will have two tiers: Tier 1 will be the main randomisation for two treatment arms initially. Participants will be

randomised at trial entry to receive one of the available regimens, treatment A or treatment B. Tier 2 will include smaller dose expansion/confirmation cohorts for more novel experimental treatment combinations (Arm C and future arms), with the potential for them to be moved to Tier 1.

Current Tier 1 (Randomisation Tier) Treatment Arms in the BEACON2 Trial:
Arm A: dbIT Treatment with dinutuximab beta, irinotecan, and temozolomide, 3 weekly x12 cycles
Arm B: BIT Treatment with bevacizumab, irinotecan, and temozolomide, 3 weekly x12 cycles

Current Tier 2 (Registration Only Tier) Treatment Arms in the BEACON2 Trial:
Arm C: dbIT Treatment with dinutuximab beta, bevacizumab, irinotecan, and temozolomide, 3 weekly x12 cycles

What are the possible benefits and risks of participating?
The treatment you receive in this trial may help treat your neuroblastoma. We cannot promise to what extent the trial will help you but the information we get from this trial will help improve the treatment of people with neuroblastoma in the future.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
April 2024 to December 2030

Who is funding the study?
The study is funded by the international charity Fight Kids Cancer.

Who is the main contact?
BEACON2 Trial Team, beacon2@trials.bham.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-treatment-children-young-people-neuroblastoma-come-back-after-treatment-beacon2

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Public, Scientific

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Additional identifiers

EudraCT/CTIS number
2022-003816-10

IRAS number
1006346

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
RG_22-136, IRAS 1006346, CPMS 59016

Study information

Scientific Title
BEACON2 - a multi-arm, multi-stage platform trial for relapsed neuroblastoma

Acronym
BEACON2

Study objectives
Primary objective:
To test novel treatments against current best available treatment in relapsed neuroblastoma

Secondary objective:
To evaluate the safety of the regimens, anti-tumour response, longer term outcome and quality of life

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 19/06/2024, London - City & East Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8124; cityandeast.rec@hra.nhs.uk), ref: 24/LO/0412

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Relapsed Neuroblastoma

Interventions
Tier 1 Treatment Details:
Arm A: dbIT Dinutuximab beta 10 mg/m2/day iv days 1-7, Irinotecan 50 mg/m² iv days 1-5, Temozolomide 100 mg/m² po days 1-5.
3 weekly x12 cycles
Arm B: BIT Bevacizumab 15 mg/kg iv day 1, Irinotecan 50 mg/m² iv days 1-5, Temozolomide 100 mg/m² po days 1-5.
3 weekly x12 cycles

Tier 2 Treatment Details:
Arm C: dbBIT Bevacizumab 15 mg/kg/day iv day 1, Dinutuximab beta 10 mg/m²/day iv days 1-7, Irinotecan 50 mg/m² iv days 1-5, Temozolomide 100 mg/m² po days 1-5.
3 weekly x12 cycles

Follow-up:
After 12 cycles of treatment, participants will be followed up for a minimum of 5 years from the date of registration/randomisation, or until death if sooner.

Follow up visits until progression or relapse occurs will include:

Three-monthly visits up to 2 years from the end of treatment will include the following assessments:
• Tumour assessment (a minimum of a cross sectional image of site of measurable disease by MRI (preferred) or CT and MIBG scans)
• Vital signs and physical exam
• Survival status (including progression)
• Treatments received (if any)
• Additional assessments as per local practice may be included

Beyond 2 years from end of treatment, follow-up visits will be carried out annually at 3, 4 and 5 years after the registration date and will include the following assessments only:
• Survival status
• Treatments received
• Additional assessments as per local practice
• AEs and late effects

Follow up visits after progression or relapse occurs:

Follow up visits will be done annually for at least 5 years from the date of registration and will include the following assessments only:
• Survival status
• AEs and late effects (including the occurrence of second malignant neoplasms (SMN))
• Treatments received
• Additional assessments as per local practice may be included.

Randomisation/Registration Process:
Randomisation for Tier 1 and registration for Tier 2 should be performed by sites using the online electronic remote data capture system (eRDC).

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacogenetic, Therapy

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Temodal (temozolomide capsule), Campto (irinotecan), Avastin (bevacizumab), Hycamtin (topotecan), Quaziba (dinutuximab beta), KIZFIZO (temozolomide oral suspension)

Primary outcome measure
Tier 1 (randomised comparison): Progression-Free Survival time (per the INRC 2017). In Tier 1, interim analyses will be conducted for each arm when 40 patients (stage 1) and 75 patients (stage 2) have been recruited and reached six months after randomisation.
Tier 2 (dose expansion-confirmation cohorts): Definition of a safe and tolerable combination regimen. For Tier 2, an assessment will be made after recruitment of 10 patients of whether the toxicity is acceptable for the intervention to be incorporated into the main Tier 1 randomisation.

Secondary outcome measures
1. Best objective response (complete and partial response) per the INRC 2017 during trial treatment (12 cycles)
2. Clinical benefit (complete, partial and minor response and stable disease) per the INRC 2017, at treatment cycle 2, 4, 6, 9 and 12/end of treatment.
3. Time response to progression/Duration of Response for responders (the time from randomisation to progression).
4. Overall Survival time (the time from randomisation to death).

5. Quality of life of patients measured by Peds-QL questionnaires, at baseline and after treatment cycle 2, 4, 6, 9 and 12/end of treatment.
6. Incidence and Severity of AEs throughout the trial.

The final analysis will be conducted when all patients have been followed up for at least 5 years.

Overall study start date
29/04/2024

Completion date
31/12/2030

Eligibility

Key inclusion criteria
Disease specific
1. Histologically proven neuroblastoma as per International Neuroblastoma Staging System (INSS) definition
2. High risk relapsed neuroblastoma (relapsed or progressed after being defined as High Risk at any time following diagnosis or progressed/relapsed as high-risk neuroblastoma)
3. Measurable disease by cross sectional imaging or evaluable disease (uptake on MIBG scan with or without bone marrow histology), as per INRC. Participants with only bone marrow detectable disease (bone marrow aspirate or trephine) are NOT eligible for the study

General
1. Age ≥1 year
2. Signed informed consent from participant, parent or guardian

Performance and organ function
1. Performance Status: Lansky (for patients ≤12 years of age) or Karnofsky (for those >12) ≥ 50%,

(Participants 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 prior to randomisation):
3.1. Platelets ≥ 50 x 10^9/L (unsupported for 72 hours)
3.2. ANC ≥ 0.50 x 10^9/L (no G-CSF support for 72 hours)
3.3. Haemoglobin > 8 g/dL (transfusions allowed)
4. Renal function (within 72 hours prior to randomisation):
4.1. Absence of clinically significant proteinuria (either early morning urine dipstick ≤2+) or if dipstick urinalysis shows > 2+ proteinuria, 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 measured GFR (radioisotope or 24 hour urine calculated creatinine clearance) must be ≥ 60 ml/min/1.73 m²
5. Liver function (within 72 hours prior to randomisation):
5.1. Absence of clinically significant signs of liver dysfunction. AST or ALT ≤3.0 ULN and total bilirubin ≤1.5 ULN. In patients with liver metastases, AST or ALT ≤5 ULN and total bilirubin ≤2.5 ULN is allowed.
6. Coagulation:
6.1. Participants must not have an active uncontrolled coagulopathy.

6.2. Anticoagulation is permitted as long as the INR or APTT is within therapeutic limits (according to the medical standard of the institution) and the participant has been on a stable dose of anticoagulants for at least two weeks at the time of study enrolment.
7. Blood pressure below 95th centile for age and sex. Participants ≥18 years of age should have a blood pressure ≤150/90 mmHg (within 72 hours prior to randomisation). Use of antihypertensive medication is permitted.

Tier 2 Specific Inclusion Criteria
1. More than one relapse event.
2. The following previous treatments are allowed provided that the principal investigator expects a favourable benefit/risk assessment (e.g. patients could derive potential benefit from the Tier 2 combination):
2.1. bevacizumab,
2.2. any anti-GD2 antibody given with chemotherapy ('chemo-immunotherapy')
2.3. previous treatment with temozolomide with irinotecan

Participant type(s)
Patient

Age group
Mixed

Lower age limit
1 Years

Sex
Both

Target number of participants
160

Key exclusion criteria
Common to Tier 1 and Tier 2:
1. Known contraindication or hypersensitivity to:
1.1. Any study drug or component of the formulation
1.2. Chinese hamster ovary products or other recombinant human or humanised antibodies.
1.3. Participants 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.
2. Clinically significant neurological toxicity, uncontrolled seizures or objective peripheral neuropathy (>grade 2). (Unresolved neurological deficits from previous spinal cord compression or surgeries are acceptable). Participants with previous ≥ Grade 3 motor neurotoxicity secondary to anti-GD2 are excluded, even if recovered
3. Prior severe arterial thrombo-embolic events (e.g. cardiac ischemia, cerebral vascular accident, peripheral arterial thrombosis) or any ongoing arterial thrombo-embolic events
4. A history of (noninfectious) pneumonitis requiring steroids, or current pneumonitis.
5. Patients that are allergic to all therapies for Pnemocystis jirovecii pneumonia and can thus not receive prophylaxis for PJP
6. Uncontrolled infection
7. Inadequate recovery from prior surgery with ongoing ≥Grade 3 surgical complications. Grade ≥2 wound dehiscence.

8. Recent surgical procedures (at start of trial treatment.) Patient can be randomised up to 48hr prior to these periods being completed provided that trial treatment only starts after complying with all of them:
8.1. Core biopsies within previous 24hr
8.2. Open excisional biopsies within previous 48hr
8.3. Major surgery within previous 2 weeks.
8.4. Bone marrow aspirates/trephines, within previous 48hr
8.5. Tunnelled central line insertion within previous 48hr
9. Washout from prior treatments (at start of trial treatment):
9.1. Chemotherapy within previous 2 weeks (1 week for oral metronomic chemotherapy regimens)
9.2. Any anti-GD2 therapy within previous 2 weeks
9.3. Craniospinal radiotherapy or MIBG therapy within previous 6 weeks
9.4. Radiotherapy to the tumour bed within previous 2 weeks (no washout for palliative radiotherapy)
9.5. Myeloablative therapy with haematopoietic stem cell rescue (autologous stem cell transplant) within previous 8 weeks
9.6. Allogeneic stem cell transplant within previous 12 weeks (with absence of active ≥G2 acute GVHD)
9.7. 14 days or 5 half-lives (whichever occurs later) from last administration of an IMP in an IMP-trial
10. Bleeding metastases (participants with CNS metastases can be enrolled as long as the metastases are not bleeding). At least 6 months from any ≥G3 haemoptysis or pulmonary haemorrhage
11. Use of enzyme inducing anticonvulsants within 72hr of randomisation
12. Conditions that increase the risk of bevacizumab-related toxicities:
12.1 History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
12.2 History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or active gastrointestinal bleeding within 6 months prior to study enrolment
12.3 Current chronic intestinal inflammatory disease/bowel obstruction
13. Intolerance to galactose and fructose, lactase deficiency, and/or defect of absorption of galactose and fructose
14. Males or females of reproductive potential may not participate unless they agree to use an adequate method of birth control, i.e. with a failure rate of less than 1% per year, (e.g. implants, injectables, combined oral contraceptives, IUDs, sexual abstinence or vasectomised partner), for the duration of study therapy and for up to 6 months after the last dose of trial drugs. A negative urine or serum pregnancy test must be obtained within 72 hours prior to dosing in females who are post-menarche.
15. Pregnant or lactating participant
16. Live or live-attenuated vaccines given within previous 28 days prior to study enrolment
17. Any uncontrolled medical condition that poses an additional risk to the participant

Tier 1 Specific Exclusion Criteria
1. More than one relapse event after the start of high risk neuroblastoma therapy
2. Previous treatments that are not allowed
2.1. Bevacizumab for relapsed neuroblastoma (patients who have received BIT for refractory disease are not excluded, providing no progression of disease during this treatment occured
2.2. Treatment with any anti-GD2 antibody given with chemotherapy (‘chemo-immunotherapy’) for treatment of relapsed neuroblastoma. Prior treatment with chemo-immunotherapy for refractory disease is allowed, provided no disease progression during this therapy.

Date of first enrolment
22/11/2024

Date of final enrolment
31/12/2025

Locations

Countries of recruitment
Australia

Austria

Belgium

Denmark

England

Finland

France

Germany

Ireland

Israel

Italy

Netherlands

New Zealand

Northern Ireland

Norway

Poland

Scotland

Spain

Sweden

Switzerland

United Kingdom

Wales

Study participating centre
Addenbrookes
Addenbrookes Hospital
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Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Alder Hey Children's NHS Foundation Trust
Alder Hey Hospital
Eaton Road
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Liverpool
United Kingdom
L12 2AP

Study participating centre
Birmingham Childrens Hospital (ladywood)
Ladywood Middleway
Ladywood
Birmingham
United Kingdom
B16 8ET

Study participating centre
Bristol Childrens Hospital
Upper Maudlin Street
Bristol
United Kingdom
BS2 8BJ

Study participating centre
Great North Children's Hospital
Victoria Wing, Royal Victoria Infirmary
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Great Ormond Street Hospital
Great Ormond Street
London
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WC1N 3JH

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Noahs Ark Childrens Hospital for Wales
Cardiff & Vale University Health Bd
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Nottingham Children's Hospital
Queen's Medical Centre
Derby Rd
Nottingham
United Kingdom
NG7 2UH

Study participating centre

Royal Aberdeen Children's Hospital
Aberdeen Royal Infirmary
Westburn Rd
Aberdeen
United Kingdom
AB25 2ZG

Study participating centre
The Royal Belfast Hospital for Sick Children
274 Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre
Royal Hospital for Children and Young People
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Edinburgh
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EH16 4TJ

Study participating centre
Royal Hospital for Children Glasgow
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United Kingdom
G51 4TF

Study participating centre
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M27 4HA

Study participating centre
The Royal Marsden Hospital
Fulham Road

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SW3 6JJ

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Study participating centre
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Sponsor type

University/education

Website
http://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Fight Kids Cancer

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Submission to regulatory authorities

Intention to publish date
30/06/2031

Individual participant data (IPD) sharing plan
It is planned that data will be shared with academic initiatives such as INRG and SIOPEN Bioportal to facilitate academic research in the field; and also it is highly likely that the data may be requested by pharmaceutical companies to support approvals for neuroblastoma.

The CRCTU is committed to responsible and controlled sharing of anonymised clinical trial data with the wider research community to maximise potential patient benefit while protecting the privacy and confidentiality of trial participants. Data anonymised in compliance with the Information Commissioners Office requirements, using a procedure based on guidelines from the Medical Research Council (MRC) Methodology Hubs and Information Commissioners Office, will be available for sharing with researchers outside of the trials team within 6 months of the primary publication.

IPD sharing plan summary
Available on request, Other