A Multi-Arm, Multi-Stage Platform Trial For Relapsed Neuroblastoma

Version: 2.0

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SIGNATURE PAGE

BEACON2 Trial Protocol v2.0 (11-Jun-2024)

This protocol has been approved by:

Name: Dr Lucas Moreno **Trial Role:** Chief Investigator

Signature [redacted] **Date:** 11 / JUN 2024

This protocol describes the BEACON2 trial and provides information about procedures for participants taking part in the BEACON2 trial. The protocol should not be used as a guide for treatment of participants not taking part in the BEACON2 trial.

Sponsor Statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the Integrated Research Application System (IRAS) Form by the sponsor will serve as confirmation of approval of this protocol.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

CONTENTS

TRIAL SYNOPSIS

Title

BEACON2: A multi-arm multi-stage platform trial for relapsed neuroblastoma.

Trial Design

BEACON2 is a platform multi-arm multi-stage (MAMS) randomised phase I/phase II, open-label, international trial.

The trial will comprise two tiers: Tier 1 will be the main randomisation, starting with the randomisation of Arms A vs B. Participants will be randomised at trial entry to receive one of the regimens. Tier 2 will include a dose expansion/confirmation cohort (Arm C and future arms), before the new arm is introduced to Tier 1. Using the rolling MAMS design will allow the introduction of novel agents or regimens as new arms, if appropriate. The introduction of new arms will take place pending approval of a substantial amendment by each relevant Competent Authority.

Aims

- To improve survival for patients with relapsed neuroblastoma by developing novel combinations that are ready for clinical implementation
- To establish a platform trial to evaluate novel combinations in relapsed neuroblastoma, within a seamless phase 1-2 trial that can lead to regulatory approvals and impact clinical practice; allowing dose confirmation cohorts for novel combinations
- To evaluate safety, activity, efficacy and quality of life for these novel combinations in relapsed neuroblastoma participants
- To improve our understanding of relapsed neuroblastoma biology, tumour clonal evolution, tumour microenvironment and develop biomarkers of response and resistance to direct the development targeted therapies by conducting a comprehensive biomarker sample collection.

Objectives

Primary

- To test novel treatments against current best available treatment in relapsed neuroblastoma

Secondary

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

Tertiary

- To evaluate of the role of circulating biomarkers and tumour molecular profiles in blood and tumour as prognostic and predictive biomarkers in relapsed neuroblastoma, including neuroblastoma mRNAs, circulating DNA, biomarkers of immune response and the tumour microenvironment and analysis of genomic aberrations in relapsed tumours

Outcome Measures

Primary Endpoint

- Progression-Free Survival time (as per INRC 2017) – for Tier 1 (randomised comparison)
- Definition of a safe and tolerable combination regimen – for Tier 2 (dose expansion-confirmation cohorts)

Secondary Endpoints

- Best objective response (complete and partial response) as per INRC 2017 during trial treatment (12 cycles)
- Clinical benefit (complete, partial and minor response and stable disease) as per INRC 2017.
- Time response to progression (for responders)
- Overall Survival time
- Quality of life measured by Peds-QL questionnaires
- Incidence and Severity of AEs

Exploratory Endpoints

- Quality of life of caregivers measured by Peds-QL questionnaires
- Correlation between objective response using INRC 2017 and PFS/OS
- Changes in circulating biomarkers and tumour molecular profiles in tumour and blood, including mRNA levels, analysis of immune response and tumour microenvironment, analyses of genomic aberrations in relapsed neuroblastoma (e.g. MYCN, ALK, RAS/MAPK pathway, ATRX) and development of novel biomarkers.

Participant Population

Participants aged ≥1 with relapsed neuroblastoma.

Sample Size

This is a multi-arm multi-stage phase 1-2 trial, hence modifications with the addition of new arms during the conduct of the trial are expected.

For each arm in Tier 1, 75 patients will be recruited to complete phase 2 investigation. For each arm in Tier 2, 10 patients will be recruited to complete phase 1 investigation.

Approximately 160 participants are initially planned, 75 in each arm of Tier 1 and 10 participants for one dose-confirmation cohort in Tier 2. Expansion of recruitment may be considered after adding novel arms.

Main Inclusion and Exclusion Criteria

Inclusion Criteria (Common to Tier 1 and Tier 2)

Disease specific

- Histologically proven neuroblastoma as per International Neuroblastoma Staging System (INSS)[1] definition
- 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)
- Measurable disease by cross sectional imaging or evaluable disease (uptake on MIBG scan with or without bone marrow histology), as per INRC [2, 3]. Participants with only bone marrow detectable disease (bone marrow aspirate or trephine) are NOT eligible for the study

General

- Age ≥1 year
- Signed informed consent from participant, parent or guardian

Performance and organ function

- 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)
- Life expectancy of ≥12 weeks
- Bone marrow function (within 72 hours prior to randomisation):
  - Platelets ≥ 50 x 10^9/L (unsupported for 72 hours)
  - ANC ≥ 0.50 x 10^9/L (no G-CSF support for 72 hours)
  - Haemoglobin > 8 g/dL (transfusions allowed)
- Renal function (within 72 hours prior to randomisation):
  - 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
  - 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 m^2
- Liver function (within 72 hours prior to randomisation):
  - 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.
- Coagulation:
  - Participants must not have an active uncontrolled coagulopathy.
  - 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.
- 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

- More than one relapse event or ineligible for Tier 1.

NB- 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):

- bevacizumab,
- any anti-GD2 antibody given with chemotherapy ('chemo-immunotherapy')
- previous treatment with temozolomide with irinotecan

Exclusion Criteria (Common to Tier 1 and Tier 2)

- Known contraindication or hypersensitivity to:
  - Any study drug or component of the formulation
  - Chinese hamster ovary products or other recombinant human or humanised antibodies.
  - 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.
- 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
- Prior severe arterial thrombo-embolic events (e.g. cardiac ischemia, cerebral vascular accident, peripheral arterial thrombosis) or any ongoing arterial thrombo-embolic events
- A history of (noninfectious) pneumonitis requiring steroids, or current pneumonitis.
- Patients that are allergic to all therapies for Pnemocystis jirovecii pneumonia and can thus not receive prophylaxis for PJP
- Uncontrolled infection
- Inadequate recovery from prior surgery with ongoing ≥ Grade 3 surgical complications. Grade ≥ 2 wound dehiscence.
- 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:
  - Core biopsies within previous 24hr
  - Open excisional biopsies within previous 48hr
  - Major surgery within previous 2 weeks
  - Bone marrow aspirates/trephines, within previous 48hr
  - Tunnelled central line insertion within previous 48hr
- Washout from prior treatments (at start of trial treatment):
  - Chemotherapy within previous 2 weeks (1 week for oral metronomic chemotherapy regimens)
  - Any anti-GD2 therapy within previous 2 weeks
  - Craniospinal radiotherapy or MIBG therapy within previous 6 weeks
  - Radiotherapy to the tumour bed within previous 2 weeks (no washout for palliative radiotherapy)
  - Myeloablative therapy with haematopoietic stem cell rescue (autologous stem cell transplant) within previous 8 weeks
  - Allogeneic stem cell transplant within previous 12 weeks (with absence of active ≥ G2 acute GVHD)
  - 14 days or 5 half-lives (whichever occurs later) from last administration of an IMP in an IMP-trial
- 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
- Use of enzyme inducing anticonvulsants within 72hr of start of trial treatment
- Conditions that increase the risk of bevacizumab-related toxicities:
  - History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
  - History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or active gastrointestinal bleeding within 6 months prior to study enrolment
  - Current chronic intestinal inflammatory disease/bowel obstruction
- Intolerance to galactose and fructose, lactase deficiency, and/or defect of absorption of galactose and fructose

- Males or females of reproductive potential may not participate unless they agree to use a highly effective 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.
- Pregnant or lactating participant
- Live or live-attenuated vaccines given within previous 28 days prior to study enrolment
- Any uncontrolled medical condition that poses an additional risk to the participant

Tier 1 Specific Exclusion Criteria

- More than one relapse/progression event after the start of high risk neuroblastoma therapy
- Previous treatments that are not allowed
    - Bevacizumab for *relapsed* neuroblastoma. Patients who have received BIT for *refractory* disease are not excluded, providing no progression of disease during this treatment occurred
    - 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.

Trial Treatment

Tier 1:

Arm A: dbIT

Dinutuximab beta 10 mg/m^2/day iv days 1-7, Irinotecan 50 mg/m^2 iv days 1-5, Temozolomide 100 mg/m^2 po days 1-5
3 weekly x12 cycles

Arm B: BIT

Bevacizumab 15 mg/kg iv day 1, Irinotecan 50 mg/m^2 iv days 1-5, Temozolomide 100 mg/m^2 po days 1-5
3 weekly x12 cycles

Tier 2:

Arm C: dbBIT

Bevacizumab 15 mg/kg/day iv day 1, Dinutuximab beta 10 mg/m^2/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

Sub Studies

Translational Sub Study

Primary Tumour Tissue

Samples of tumour tissue collected at the time of diagnosis, during frontline therapy and/or at the time of relapse (where possible) will be collected for genome and expression profile of DNA and RNA. **This**

sample is mandatory for study entry; if no tumour or subsequent molecular profiling is available this will be discussed with the Coordinating Sponsor and the Chief Investigator/clinical coordinator before study entry.

Liquid Biopsy Samples

Blood samples for the analysis of circulating biomarkers and immunological studies should be collected from all patients at the same time points as those required for standard clinical care:

- Baseline
- Pre cycles 2, 4, 6, 9
- Pre Cycle 12 or End of Treatment

Constitutional DNA taken once at any time will be required for pharmacogenetic studies and is *optional*.

Bone marrow aspirate taken at baseline will be required for circulating biomarker analysis and is *optional*.

Trial Duration

Initially, trial duration is 3 years of participant recruitment; which can be extended due to the incorporation of new arms through a substantial amendment, plus 5 years of participant follow up.

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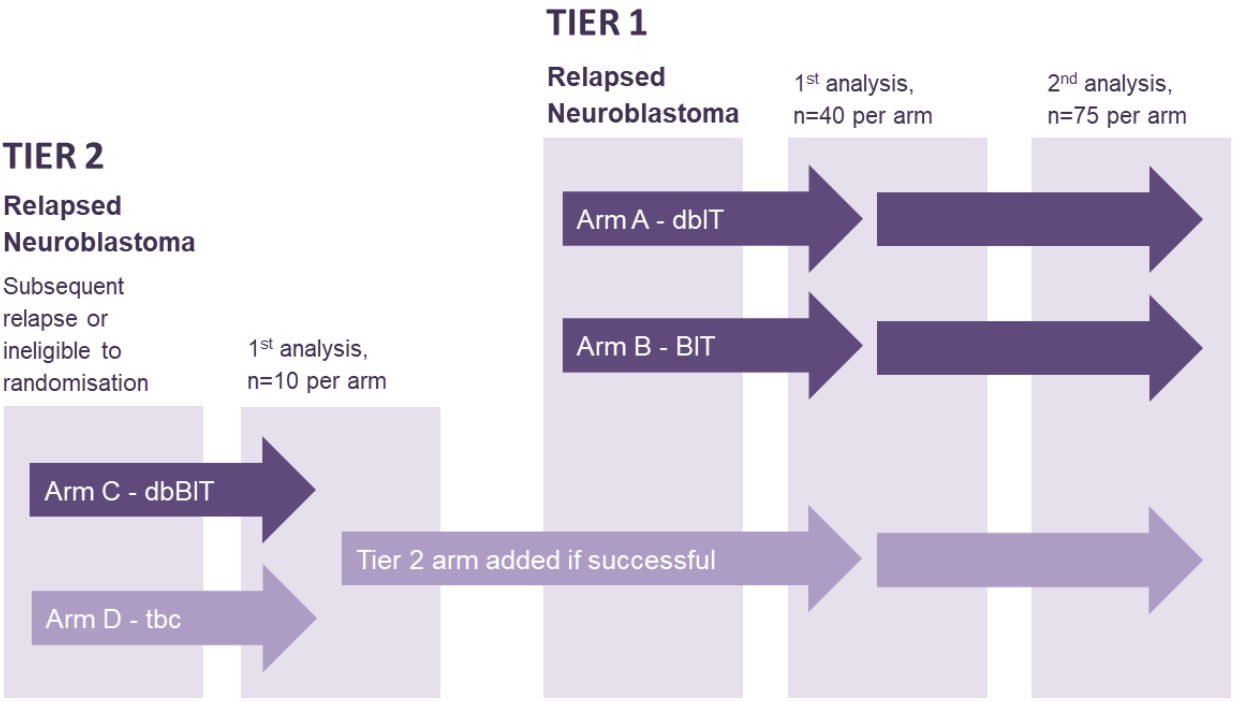
Trial Schema



SCHEDULE OF EVENTS

Refer to Section 9 Assessments and Section 10 Sample Collection for details.

Table 1 - Schedule of Events

Protocol Activity	Screening / Baseline	Pre Dosing (All Cycles)	Post Cycles 2, 4, 6, 9	Post Cycle 12 & End of Treatment	Follow Up – 3-24 months[10]	Follow Up – 3-5 years[10]
Window (days)	28 [11]	-3	Within 7 days of starting next cycle	21 days after last Cycle 12 dose or last dose[13]	+/-28	+/-60
Informed Consent / Assent	X					
Medical History	X					
Physical Examination and Performance status[1]	X	X		X	X	
Weight and Height[2]	X	X		X	X	X
Health-related quality of life (HRQoL)[3]	X		X	X		
Laboratory Tests						
Haematology[4]	X	X		X		
Blood Chemistry[4]	X	X		X		
Clotting[4]	X	**Repeat if clinically indicated**				
Urinalysis[5]	X	X *For participants receiving bevacizumab only*		X		
Pregnancy Test[6]	X	X		X		
Estimated Glomerular Filtration Rate (GFR)[7]	X					
Tumour Assessment[8]						
MRI (preferred) or CT scan of brain	X		**Repeat if clinically indicated**			
MRI (preferred) or CT scan of tumour	X		X	X	X	
I^{123}-mIBG (^{18}FDG PET/CT scan if mIBG negative)	X		X	X	X[12]	
Bilateral Bone Marrow Aspirate and Trephine	X	**Repeat if positive or clinically suspected**				
Sample Collection[9]						
Tumour Tissue	X					
Blood samples	X		X	X		
Bone marrow aspirate	X					
Miscellaneous						
Adverse Events	**X** (assess throughout study)					
Concomitant Medications	**X** (assess throughout study)					

1. Performance status will be reported using the Lansky scale for 1-12 year olds and using the Karnofsky scale for older participants. Performance status and physical examina ion (including blood pressure, heart rate, temperature, oxygen saturation, weight and height will be performed at screening and within 24hr prior to each cycle in all treatment arms. In pa ients where bevacizumab infusions become not synchronised with chemotherapy administration, physical examination will also be performed prior to each injection of bevacizumab. Menstrual status (regularity of menstruation) in females of childbearing potential should be assessed at screening, end of treatment and during follow up. A clinical assessment of pupil responses should be conducted before starting each cycle. If there are any concerns about vision or pupil responses during treatment or follow up, a referral to an ophthalmologist should be considered.
2. Patient's weight will be measured at screening, on day 1 of each cycle prior to dosing and at he end of treatment. Body height will be measured at screening, on day 1 of each cycle prior to dosing and at the end of treatment. After end of treatment, weight and height will be performed at each follow up visit.
3. HRQoL: HRQoL assessment using PedsQL for patients and parent/guardian, and PedsQL Family Impact Module for parent/guardian will be performed at baseline (in 1 week prior to study entry), Post Cycles 2, 4, 6, and at the End of treatment visit. It is highly recommended that all questionnaires will be collected on the visits prior to subject's drug administration or any other interaction with site staff.
4. Haematology, biochemistry and clotting blood tests must be done at screening and within 72hr prior to cycle 1 dosing. Unless required by the investigator, safety tests will not be repeated at cycle 1, day 1 prior to dosing. Beginning in cycle 2 and continuing for all subsequent cycles, pre-dose activities can be done within 72hr pre-dose. It is recommended that blood counts are monitored weekly for all patients. Additional safety assessments may be done according to institutional standard of care. Laboratory tests and clinical visits as part of standard care can be performed at the par icipant's local hospital, provided they are conducted on time and the local hospital and trial site have a procedure to receive and review them timely. Patients should be visited in between cycles as per routine practice. These tests must also be performed at end of treatment. Haematology includes - haemoglobin (Hb), white blood cells (WBC) with differential count, neutrophils, lymphocytes and platelets. Biochemistry includes - sodium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALT or AST. If both ALT and AST are not measured at screening, the same measurement must consistently be performed throughout the trial duration. Clotting includes INR and APTT and should only be performed at baseline and when clinically indicated.
5. Urinalysis: A Urinalysis test (early morning urine dipstick and/or protein/creatinine ratio) will be performed at screening and within 24hr prior to each bevacizumab injection and the start of each cycle of treatment. This will also be repeated at the end of treatment. If there are signs of proteinuria, a sample must be sent for determination of albumin/protein and creatinine in urine, and the albumin or protein/creatinine ratio must be calculated.
6. For girls who are post-menarchal, a urine (preferred) or serum pregnancy test will be done at screening (within 72hr of dosing), prior to each cycle and at end of treatment. Additional tests may be performed as required by institutional policy or local regulations. If the results are inconclusive, a repeat test must be performed using a serum sample to definitively determine pregnancy status. In addition, a pregnancy test will be done whenever one menstrual cycle is missing during treatment or a potential pregnancy is suspected. Females who become pregnant while on study will be discontinued immediately and the outcome of the pregnancy will be followed.
7. Estimated GFR should be carried out at screening up to 7 days prior to eligibility assessment in patients with a level of serum creatinine $\geq$ 1.5 ULN for age.
8. Tumour assessments: The minimum requirement is a cross sectional image of site of measurable disease by MRI (preferred) or CT, performed wi hin 6 weeks prior to receiving the first dose of trial treatment. A scan including the brain (either CT or MRI) must also be performed at screening to assess participant's eligibility with regard to the presence of bleeding brain metastases. At baseline, MIBG scans (or ^{18}-FDG PET/CT scan for patients with MIBG negative disease) and bilateral bone marrow aspirates and trephine are to be done within 6 weeks prior to receiving the first dose of trial treatment. Additional investigations of possible metastatic sites should be done upon presentation of signs and symptoms. Bone marrow assessments will only be repeated after 2, 4, 6, 9 and 12 courses if positive at screening or clinically indicated (until they become negative). To ensure comparability, the same scanner, equipment, method and technique used during baseline should be consistently used throughout the study. Tumour lesions previously irradiated will be considered measurable only if progressing. Scans should be completed up to 7 days prior to cycles 3, 5, 7, 10 and at end of treatment. Response assessment will be performed with the same modalities used at screening. Tumour assessments do not have to be repeated where the following cycle is delayed due to toxicity.
9. **Please refer to the BEACON2 Laboratory Manual before taking samples.** Tumour molecular profiling: Samples of tumour tissue collected at the time of diagnosis or during frontline therapy and/or at he time of relapse will be collected. **This sample is mandatory for study entry, if no tumour or subsequent molecular profiling is available this will be discussed with the Coordinating Sponsor and the Chief Investigator before study entry.** For patients participating in other sequencing programs, it is acceptable to share DNA or sequencing data extracted from the tumour samples. Archival tumour tissue either as paraffin embedded or frozen material will be collected. Blood samples will be obtained at baseline, post cycles 2, 4, 6, 9 and 12 for the biomarker analysis. Samples for constitutional DNA analyses are optional (samples can be collected the same day as starting he next cycle, but have to be collected before study drug administration). Bone marrow aspirate at baseline for circulating biomarkers and circulating tumour cells may be taken at baseline and is optional. Samples will be taken from all patients.
10. Follow up assessments will be scheduled 3 monthly for 2 years after end of treatment, and then annually at 3, 4 and 5 years after the registration date, unless the patient withdraws consent. Patients that progress or develop relapse will still have survival, disease status and treatment received data collected for them at the time points for follow up visits. Additional follow up visits will be scheduled as needed to monitor any sustained unresolved, treatment emergent adverse events.
11. Screening period window: (Assessments performed outside of these windows should be repeated for screening)
    - Medical History – Within 4 weeks prior to trial entry
    - Physical examination and Performance status – Within 24h prior to trial entry
    - Health-related quality of life (HRQoL) – Within 1 week prior to trial entry
    - Haematology – Within 72 hours prior to trial entry
    - Biochemistry - Within 72 hours prior to trial entry
    - Clotting – Wi hin 72 hours prior to trial entry
    - Urinalysis – Within 72hours prior to trial entry
    - Pregnancy tes ing – Within 72 hours prior to trial entry
    - GFR - Within 7 days prior to trial entry
    - Tumour Assessment - Within 6 weeks prior to trial entry
12. I123-mIBG scans are highly encouraged during the first 2 years after end of treatment but are not considered mandatory.
13. Assessments performed post cycle 12 or at the end of treatment should be performed 21 days after the last cycle 12 dose or last dose if patient discontinued treatment early. However, the assessments can be performed before 21 days if a new treatment is planned to commence within that timeframe if the patient has progressed.

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Overview of high risk neuroblastoma

Neuroblastoma is the most common extracranial solid tumour in childhood and the principal cause of death due to cancer in infancy. More than 1200 cases/year are diagnosed in USA and Europe. Half of those cases are considered high-risk disease (metastatic >18 months of age or harbouring *MYCN* amplification) [4]. Despite intensive multi-modal therapies, over 50% of patients with high-risk neuroblastoma experience relapse or have disease which is refractory to front-line chemotherapy. Outcome for patients with relapsed or refractory neuroblastoma is dismal, with less than 10% long-term survival [5-9]. There is an unmet need to develop new therapeutic strategies and test new agents in children with neuroblastoma.

1.1.2 Results of Phase 2 trials in relapsed neuroblastoma

A number of second-line strategies have been tested in patients with relapsed or refractory neuroblastoma over the last 30 years, including chemotherapy, immunotherapy or targeted radionuclide therapy. The majority of these are single-arm phase 2 trials and show a wide range of response rates (0 to 64%) [5, 10, 11] and provide limited data about survival outcomes. Heterogenous inclusion criteria and study designs make any comparison between studies very difficult and randomised studies have been lacking. Results of studies conducted internationally are summarised below [12-15]:

Table 2 – Results of Phase 2 trials in relapsed neuroblastoma

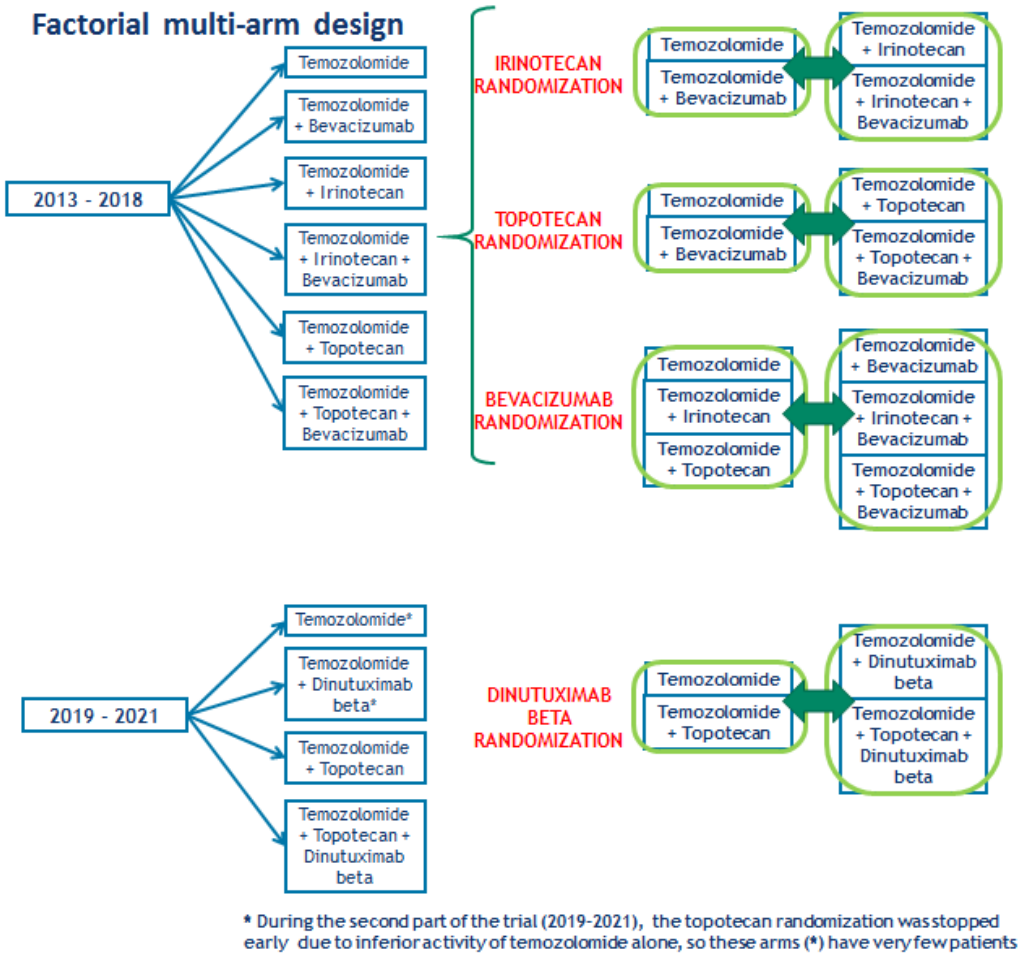
Regimen (reference)	N	Objective Response Rate	1-year PFS
Irinotecan-temozolomide: Bagatell JCO 2011	55	Bagatell: 15% [in BEACON: 17%]	Bagatell: Not reported [in BEACON: 35%]
Topotecan-temozolomide: Di Giannatale Eur J Cancer 2013	38	Di Giannatale: 24% [in BEACON: 28%]	Di Giannatale: 45% [in BEACON: 42%]
Bevacizumab-irino-tem: Moreno, J Clin Oncol 2024[79]	30	23%	67%
DIT: Dinutuximab-GM-CSF-Irino-tem: Mody JCO 2021	53	42%	67%
Topo-tem-dinutiximab beta: Gray ASCO 2022	42	35%	49%
HITS: Naxitamab-GM-CSF-Irino-tem: Mora ASCO 2022	46	39%	Not reported
Hu14.18K322A-GM-CSF-IL2-Chemotherapy: Federico, Clin Cancer Res 2017	13	61%	Median time to progression 274 days
RIST ([17] rapamycin, irinotecan, dasatinib, temozolomide): Corbacioglu ASCO 2023	62		Median PFS 11 months

1.1.3 Results of BEACON-Neuroblastoma trial

The BEACON Neuroblastoma trial was a pan-European ITCC and SIOPEN collaboration in partnership with an ITCC-accredited academic sponsor; Birmingham's Cancer Research UK Clinical Trials Unit. The trial recruited 225

participants from 10 European countries from 2013-2021. It evaluated three chemotherapy regimens: temozolomide, irinotecan-temozolomide and topotecan-temozolomide, and two novel agents (bevacizumab and dinutuximab beta) added to chemotherapy. It is the largest randomised study conducted in patients with relapsed / refractory neuroblastoma. The trial used a factorial 3x2 design which grouped participants on different arms according to the randomisation (see figure 1 below) e.g. for the bevacizumab randomisation, all participants receiving chemotherapy plus bevacizumab were compared to all participants receiving chemotherapy without bevacizumab, a design that allows multiple questions in a small sample size when no interactions between the different arms are present.

Figure 1 – BEACON-Neuroblastoma Trial Design



Chemotherapy backbone:

International cooperative groups have developed several temozolomide based chemotherapy regimens such as temozolomide, irinotecan-temozolomide or topotecan-temozolomide [18-20] which have been tested in patients with relapsed/refractory neuroblastoma regimens; the BEACON-Neuroblastoma trial compared these, testing the addition of irinotecan, and then topotecan, to a temozolomide backbone. The addition of irinotecan or topotecan to temozolomide did not achieve higher response rates. However, more patients seem to achieve disease stabilisation and hence, PFS is prolonged. Toxicity profiles are consistent with what had been previously reported, confirming

that the addition of irinotecan is associated with more diarrhoea and other gastrointestinal symptoms, which can be severe and debilitating in a proportion of patients, whereas the addition of topotecan is associated with increased myelotoxicity. On the basis of this it was concluded that there is benefit in adding either irinotecan or topotecan to temozolomide, but there is insufficient evidence to choose one of these as superior to the other.

Addition of bevacizumab to a temozolomide based chemotherapy backbone:

The testing of the addition of an anti-angiogenetic agent (bevacizumab) to the chemotherapy backbone in BEACON-Neuroblastoma was based on strong preclinical rationale of therapeutic benefit of antiangiogenic agents in neuroblastoma [21-26], particularly in combination with irinotecan-temozolomide-based chemotherapy [27]. Bevacizumab is among the most established of antiangiogenic drugs and has gained approval in many adult indications at the beginning of the era of targeted therapies. In the BEACON-Neuroblastoma trial, objective responses were seen in 21/80 patients (Objective Response Rate [ORR]=26%, [95% CI 17% - 37%]) in the bevacizumab arms, and in 14/80 patients (ORR=18%, [95% CI 10% - 28%]) in the non-bevacizumab arms; risk ratio (RR) was 1.52, [95% CI 0.83 – 2.77], p=0.17. HR for PFS was 0.89 [95% CI 0.63-1.27]. One-year PFS in the bevacizumab arms was 0.46 [95% CI 0.34 – 0.56] compared with 0.38 [95% CI 0.27 – 0.49] in the non-bevacizumab arms. The pre-defined success criterion for PFS (improvement of 15% in PFS at 1p=0.15) was met. HR for OS was 1.01 [95% CI 0.70-1.45]. One-year OS was 0.69 [95% CI 0.57 – 0.77] for bevacizumab arms compared with 0.58 [95% CI 0.47 – 0.68] for non-bevacizumab arms.

Thus the success criteria were met for response and PFS; within the limitations of evidence generated within a randomised phase 2 trial. The addition of bevacizumab also increased toxicity, mainly related to increased myelotoxicity. Consistently with other large trials in the paediatric population, bevacizumab-specific toxicities seen in adults were rare, although proteinuria occurred in 13% of patients, being grade 3-4 in 5% [28, 29] . Hence, within the recognised burden of toxicities related to chemotherapy administration in relapsed/refractory neuroblastoma, the toxicity profile of the addition of bevacizumab was acceptable.

Of note, 1 and 2-year PFS estimates for patients in the bevacizumab-irinotecan-temozolomide arm were particularly promising 0.67 [95% CI 0.47 – 0.80] and 0.50 [95% CI 0.31 – 0.66] respectively. One and 2-year OS estimates for bevacizumab-irinotecan-temozolomide were 0.77 [95% CI 0.57 – 0.88] and 0.73 [95% CI 0.54 – 0.86], respectively. While the trial had a factorial design, assuming no interaction between bevacizumab and the different chemotherapy regimens, heterogeneity testing for PFS showed some evidence of a potential interaction between irinotecan and bevacizumab; showing that the BIT combination could be synergistic in this patient population. Notwithstanding the challenges of interpretation of factorial trials in small populations, the promising outcomes from the BIT arm warrant further evaluation.

Addition of dinutuximab beta to the chemotherapy backbone:

Anti-GD2 antibody, given alone, or with cytokines, has been demonstrated to improve outcome when given as maintenance therapy to patients with high-risk neuroblastoma [30, 31]. More recently, a number of studies have reported impressive response rates, in both relapse/refractory and upfront settings, when anti-GD2 is given in conjunction with chemotherapy [32-34]. The BEACON-Immuno trial investigated the addition of dinutuximab beta to chemotherapy (temozolomide or temozolomide/topotecan). Significant improvements were demonstrated in both objective response rate (ORR) and progression free survival when the anti-GD2 antibody was given with chemotherapy. ORR was approximately twice as high in patients receiving concurrent dinutuximab beta (34.8% vs 18.2%), with an adjusted risk ratio for response of 2.19 (80% CI 1.15-4.15) and one-side p-values of significant difference of 0.12. This met the pre-defined success criteria for the trial (one-sided $p < 0.23$ for response), and represented a substantial and clinically significant benefit for patients. This also translated into a significant improvement in PFS with chemo-immunotherapy, with 1-year PFS of 53% compared to 27% for patients receiving chemotherapy alone (adjusted HR of 0.67 (95% CI 0.35 – 1.328) (p=0.23)). These results are in line with previously reported smaller and/or non-randomised trials in this setting. The US Children's Oncology Group (COG) ANBL1221 study reported ORR 52.9% (9/17) of an initial randomised cohort and 13/36 (36.1%) of a non-randomised expansion

cohort of patients administered dinutuximab with irinotecan, temozolomide and GM-CSF [33]. Importantly, dinutuximab beta given with TTo was adequately tolerated by the majority of patients. The incidence of adverse events, with the exception of neurological toxicities, was similar to patients receiving chemotherapy alone, with no increase in myelosuppression or infection. Neurological toxicities were more common in patients receiving dBT/dBTTo. The majority of these were mild (≤ Grade 2) other than one case of Grade 3 myelitis, which improved but did not fully resolve within the follow up period. This requires further monitoring in future studies, but the overall toxicity burden of this chemoimmunotherapy in this population of heavily pre-treated patients appears acceptable. This therefore provides very encouraging phase 2 evidence supporting the efficacy of dinutuximab beta based chemoimmunotherapy in patients with relapsed and refractory neuroblastoma. Further clinical trials are required to provide definitive evidence of efficacy, and also to evaluate in comparison with other combinational therapies.

1.1.4 New targets and novel combinational therapies in relapsed neuroblastoma

In the current landscape of multimodal therapy for high risk neuroblastoma, chemo-immunotherapy and ALK targeted therapy (for participants with ALK aberrations) will be tested in the frontline setting by both the COG and SIOPEN regimens. The top priority for the relapsed setting is to develop combinations of chemotherapy with other immunotherapeutic or molecularly targeted agents [35]. Several novel immunotherapy combinations have shown potent therapeutic effects in pre-clinical neuroblastoma models. Prioritising which of these should be identified for inclusion in clinical trial is challenging, given that there is no agreed ‘standard’ immunocompetent murine model and models vary considerably in their immunogenicity and aggressiveness, such that it is hard to compare efficacy of therapies tested in different models. To overcome this challenge, our group will work with clinicians and scientists across the globe to accelerate preclinical testing. Novel arms will be validated by SIOPEN and ITCC collaborators. A further challenge is the lack of clinical paediatric safety and preliminary activity data on the specific combinations. The ‘Tier 2’ aspect of this trial will facilitate rapid clinical translation of such novel combinations of agents to generate initial data in small cohorts that can then be taken forward into the main trial randomisation (named Tier 1).

Future arms in combination with existing arms will be incorporated after data on ongoing phase 1/1b paediatric trials of targeted and immunotherapy agents currently ongoing internationally is available; and could include anti-CD47 monoclonal antibodies, Aurora kinase inhibitors, GSK3β inhibitors, or even novel CAR-T cell based therapies.

1.2 Trial Rationale

1.2.1 Justification for participant population

Despite advances with the introduction of anti-GD2 immunotherapy, there is a major unmet need to develop new drugs for treatment of high risk neuroblastoma. Around half of participants relapse despite intensive therapies, and outcome following relapse is dismal (<10% long term survival) [9, 36]. Combining chemotherapy with anti-GD2 therapy has been the most significant advance in relapsed therapy but implementing this into clinical practice faces numerous challenges and is still largely unavailable across Europe [37].

The BEACON trial established a pan-European platform to compare different relapse regimens and identified two promising regimens (combining chemotherapy with either anti-GD2 or anti-VEGF) in the phase 2 setting. Additional evidence is required to establish the future first relapse regimen to build on novel combinations, and to obtain regulatory and health care provider approval for these novel therapies to become standard of care. Still, further innovation is required to cure the majority of children who still die from disease.

A recent participant advocate-led editorial in the topic highlights key challenges [38]: 1) improve access to innovation through clinical trials, 2) ensure appropriate options for participants after trial closure and 3) forward planning for positive results. Indeed, the multi-stakeholder platform ACCELERATE recently initiated a working group on

"Innovation after a first paediatric regulatory approval", a situation where the barriers to implement chemo-immunotherapy combinations are paradigmatic.

European neuroblastoma experts from ITCC and SIOPEN and patient advocacy groups strongly support the need to develop a new platform trial focused on relapsed neuroblastoma. Building on the results of BEACON, the trial will confirm which combination should be taken forward and identify novel combinations that further improve survival in this participant group.

Based on our experience, the BEACON platform will be modified to focus on relapse participants, retaining the ability to compare multiple arms, but avoiding factorial design, and will have two tiers (Tier 1, a first relapse randomisation and Tier 2, to facilitate smaller dose confirmation expansion cohorts of novel regimens) to be most efficient. The network of sites will be significantly enlarged to facilitate rapid recruitment and widen access to novel drugs globally.

Refractory patients will not be included in this trial. The analyses of results from BEACON and BEACON Immuno trials and other studies conducted internationally show that relapse and refractory patients represent different patient populations that cannot be merged for a common analysis. While both have a major unmet need to develop new therapies, patients with refractory disease need therapies that achieve a rapid and robust antitumour response, in order to proceed rapidly to consolidation and maintenance strategies (e.g. tandem high dose chemotherapy and maintenance anti-GD2 therapy). Hence, the SIOPEN group is currently including refractory patients within the frontline high risk neuroblastoma strategy.

Eligibility criteria in terms of organ function have been adapted to the needs of the population with relapsed neuroblastoma, that often suffers from bone marrow metastases or is heavily pretreated. Given the experience of the BEACON trial where grade 3-4 haematological and non-haematological events were reversible and manageable, the required platelet or neutrophil count, or ALT/AST have been adapted.

Median age for children recruited in the BEACON trial was 5 (range 1-21 years). Relapsed high risk neuroblastoma is exceptional in children younger than 1 year of age, given that 1) infants <18 months of age are mostly considered intermediate risk and 2) even some patients diagnosed as infants, by the time a relapse occurs, these have become >1 year of age. For these reasons, and given the lack of data on bevacizumab therapy and chemo-immunotherapy in this very young population, lower age at trial entry will be one year of age. Neuroblastoma can occur in older adolescents and young adults, hence no upper age limit has been included.

The trial will include patients with first relapsed neuroblastoma with adequate organ function; and be open across multiple sites in 15+ countries, thus providing wide access to the trial across all the countries where it opens. The trial population will be highly representative of the whole population of children with first relapsed neuroblastoma.

1.2.2 Justification for design

The BEACON2 trial will be a platform trial that will comprise one main randomisation (Tier 1) and a dose confirmation element (Tier 2). The main randomisation (Tier 1) will have a multi-arm randomised phase 2 design. Following this design, each arm will have two stages for completion of phase 2.. The multi-stage nature of the trial will greatly maximise the efficiency of the trial allowing the possible completion of both phase 1, 2 and potentially 3 within the same trial depending on the results seen at each interim assessment. Regarding its multi-arm nature, the trial will start with two arms, based on the most promising regimens identified from previous trials conducted by SIOPEN and others across the globe. However, the design will allow flexibility to incorporate more arms as the trial evolves if the evidence supports it. For pragmatic reasons, no more than 3 arms will be open in Tier 1 at a time. The rEECur trial for relapsed Ewing sarcoma (NCT02727387) has used a similar multi-arm multi-stage trial proving highly efficient addressing multiple treatments over time [39]. Despite multiple novel anticancer drugs becoming increasingly available for paediatric use, most of phase 1 data is as single agent and the data on combinations with standard of care therapies is still very limited. For this reason, Tier 2 of the trial will allow rapid confirmation of novel

combination schedules. Regimens with no expected overlapping toxicities will be included, and testing within the Tier 2 will provide confirmation that the doses and schedules are safe. Patients will only be eligible for Tier 2 when not eligible for Tier 1 (e.g. Tier 2 will not compete for recruitment of Tier 1). More than one treatment arm may be available in Tier 2 at any given time.

The majority of tests and procedures performed during screening (see section 7.1 and section 8.1) and the scans performed throughout (see section 9.1), are routinely considered as standard of care in relapsed neuroblastoma and would likely be performed whether the participant was entered into the trial or not. Furthermore, the assessments undertaken during treatment, after treatment and during follow up (see section 9) are also very similar to standard of care. Additional biopsies, procedures and surgeries for the collection of tumour or bone marrow, will not be required as a consequence of trial participation. This is because samples will be collected from procedures performed as part of standard of care, provided informed consent has been obtained. Throughout the participant's treatment additional blood samples, equivalent to around 40 ml of blood, will be collected. The participant will also have the option of consenting to the collection, storage, and DNA analysis of an additional blood sample to be analysed for use in research associated with this trial. When possible, the blood will be drawn from the long line, Hickman or Port-a-cath at the same time as blood being taken for routine blood tests. Therefore, the characteristics of the BEACON2 trial intervention are considered as being comparable to normal clinical practice. Combinations of chemotherapy with both anti-GD2 therapy and bevacizumab are currently widely used across Europe and North America in children with relapsed neuroblastoma.

1.2.3 Justification for dosage of IMP's

All of the IMPs used within this clinical trial have marketing authorisation issued by the European Medicines Agency (EMA) but are being used outside of their licenced indication for the purposes of this trial, with the exception of temozolomide oral suspension which is not yet licensed. Further information can be found in the Pharmacy Manual. There is a need for temozolomide as an oral suspension as it offers a solution for infants and young children who may not be able to swallow capsules, thus not excluding this patient population.

1.2.4 Benefit Risk Assessment

As discussed in section 1.2.1 Justification for participant population and section 1.2.2 Justification for design, there are numerous benefits associated with the proposed study regime. Please see the following information relating to known and expected risks associated to the proposed study regime, as well as measures taken in accordance to the risk profile of the medicinal product.

1.2.4.1 Trial Treatment

All IMPs within the trial regimens have been widely used (within trials and/or as part of standard of care) in this indication in paediatrics and the safety profiles of the IMPs used in Tier 1 on this trial are well characterised. However, new combinations may give increased risk of toxicity, and the combinations are not fully established practice.

The study involves a phase 1 dose finding trial (Tier 2, arm C) in which dinutuximab beta is added to t bevacizumab-irinotecan-temozolomide (BIT) to create a new regimen, dbBIT. The benefits of adding dinutuximab beta to an antiangiogenic and chemotherapy based regimen have not yet been explored in patients with relapsed neuroblastoma. The protocol has therefore been designed to first establish a safe dose of dinutuximab beta in combination with BIT, and then if established to take this safe dose forward into Phase II testing of activity (Tier 1).

In the randomised component of this trial (Tier 1), there is a risk that patients may not be assigned to the treatment group that they or their parents would prefer. The treatment that participants receive cannot be selected by choice.

If a patient does not wish to have their treatment allocated by chance i.e. by randomisation, then they cannot be part of this study and will receive alternative treatment as recommended by their doctor.

As the efficacy of the BIT, dbIT and dbBIT drug combinations have not been fully established in a paediatric population, the patient group includes patients for whom no treatment of greater curative potential is available and the alternative management, including best supportive care/palliation will be explained to the patient and/or family, to enable an informed decision regarding trial participation.

As with all clinical trial studies the drug treatments may involve risks that are already known, as well as risks that are currently unknown. Patients will be closely monitored for side effects throughout the course of the treatment and during follow up.

1.2.4.2 Pregnancy

There is a risk that if a patient (or their partner) becomes pregnant while receiving trial treatment or immediately after, that the unborn baby could be affected. For this reason, sites will ensure that all females of childbearing potential undergo a urine pregnancy test prior to receiving trial medications, prior to each treatment cycle and at the end of treatment. We will also educate all patients of childbearing potential regarding the need for adequate contraception whilst they are receiving trial drugs and for 6 months afterwards. Should a patient or their partner become pregnant between the time of commencing study treatment and up to six months after completion, treatment should be discontinued immediately, trial participation will be terminated for safety reasons and the pregnancy outcome will be monitored. If a patient's partner becomes pregnant during this period, we would also like to collect details of the outcome of the pregnancy with their permission.

1.2.4.3 Collection and use of Samples

During the trial, patients will have blood samples taken for trial related purposes. The risks of having blood taken from a vein include pain, bruising or infection at the site where the blood was taken, and fainting. Where possible blood will be taken from a patient's Hickman line or Portacath rather than directly from a vein, there is a still a small risk of infection associated with doing this. Where possible blood samples taken for research purposes will be taken at the same time as routine blood sampling to minimise distress to patients. Guidance from the European Medicines Agency and Medicines for Children Research Network will be adhered to regarding the maximum volumes of blood collected for research purposes.

During this study, optional samples of bone marrow will be taken so that we can see if any neuroblastoma has spread to this area. Risks of bone marrow sampling include pain, bleeding and infection at the sampling site. If a patient is allocated to receive bevacizumab there is an additional risk of poor wound healing after having this test. For this reason, patients who have no neuroblastoma in their bone marrow at the beginning of the study will not have bone marrow samples repeated again during the study. Patients will likely be given either a general anaesthetic or sedative to make them drowsy whilst the test is performed. Sedatives are usually well tolerated but there is a small chance patients may experience an allergic reaction to this, feel sick or develop an irregular heartbeat.

During the informed consent process, participants or their parents (if aged under 16 years) will be given the option of the patient contributing a blood sample for genetic germline DNA analysis. It is possible in rare cases that the analysis of this sample could uncover findings that may have direct implications on the patients clinical care (e.g. a rare genetic abnormality). Participants/parents are fully informed that should they agree to having this sample taken and this situation arises, their study doctor will be informed and will take the necessary steps to refer the patient for the relevant clinical care.

1.2.4.4 Scans

By participating in this trial patients may have up to 14 CT, MRI or nuclear medicine (MIBG) scans depending on the location of their tumour. Radiation may cause cell damage which can, after many years or decades, become cancerous.

In order for some scans to be performed, “contrast agents” are given through the patient’s central line or cannula. Whilst these contrast agents allow doctors to gain a clear picture of what is happening inside the body they also carry a small risk themselves. A small number of people have an allergic reaction to them which, while usually mild and easily treatable, can be life threatening. For this reason, we ask that all patients/parents tell their doctor if they have experienced a previous reaction to contrast agents.

1.2.5 Choice of treatment arms for BEACON2 – Tier 1

The BEACON-Neuroblastoma trial has identified two arms which require further evaluation:

Dinutuximab beta-irinotecan-temozolomide

The combination of chemotherapy with anti-GD2 immunotherapy has achieved improved results compared to chemotherapy alone. ORR was approximately twice as high in patients receiving concurrent dinutuximab beta (34.8% vs 18.2%), with an adjusted risk ratio for response of 2.19 (80% CI 1.15-4.15) and one-side p-values of 0.12. There was also a significant improvement in PFS with the chemo-immunotherapy, with 1-year PFS 53% compared to 27% for patients receiving chemotherapy alone (adjusted HR of 0.67 (95% CI 0.35 – 1.328) (p=0.23)). This data is in line with that of the ANBL1221 trial conducted by the COG with dinutuximab-GM-CSF-irinotecan-temozolomide, which showed an ORR of 42% (95% CI, 28.2% to 54.8%) and 1-year PFS of 67.9% (95% CI, 55.4% to 80.5%) for children with RR-NB [32, 33] and other studies with chemo-immunotherapy conducted internationally using several anti-GD2 antibodies and chemotherapy regimens (see Table 2).

The BEACON trial has provided sufficient evidence showing that chemotherapy alone (e.g. irinotecan-temozolomide or topotecan-temozolomide) have inferior outcomes compared to the combinations with bevacizumab or dinutuximab beta. Hence, there is strong agreement in the scientific and patient advocacy communities that it is not acceptable to include chemotherapy alone arms in the BEACON2 trial.

Chemo-immunotherapy trials conducted in North America have also included GM-CSF, which is not available in Europe. While no comparative data is available, given the promising results shown in BEACON Immuno with chemo-immunotherapy without GM-CSF, the BEACON2 trial will also not include GM-CSF.

The dose of dinutuximab beta-irinotecan-temozolomide has now been aligned with the regimen used by the Children’s Oncology Group, with dinutuximab beta (10mg/m2/day) now given for 7 days every 3 weeks coupled with irinotecan-temozolomide chemotherapy. This dose is equivalent to the current use of dinutuximab beta approved for maintenance of high risk neuroblastoma (10mg/m2/day for 10 days every 5 weeks).

Bevacizumab-irinotecan-temozolomide

Bevacizumab-irinotecan-temozolomide (BIT) arm demonstrated very promising 1 year PFS and OS (0.67 and 0.77 respectively). The toxicity and tolerability of the regimen has been demonstrated to be acceptable.

To date, there has been no direct comparison between the BIT regimen and anti-GD2 chemoimmunotherapy based. The first objective of the BEACON2 study will be therefore to directly compare these regimens to identify the regimen with the best efficacy. Irinotecan will be used in both regimens to allow direct comparison of the effects of the additional bevacizumab/dinutuximab beta. Although the BEACON Immuno trial used topotecan rather than irinotecan, other international trials have shown similar results with irinotecan containing anti-GD2 chemo-immunotherapy [33, 40].

1.2.6 Choice of treatment arms for BEACON2 – Tier 2 (Testing novel combinational arms)

It is likely that improvements in outcome for patients with relapsed neuroblastoma will only be achieved by combinational therapies. Our focus will be on testing regimens which build on current established combinational therapies (e.g. BIT, anti-GD2/chemotherapy) based on solid scientific rationale and/or pre-clinical data.

Dinutuximab beta-Bevacizumab-Irinotecan-Temozolomide

As discussed above, the addition of each of bevacizumab and dinutuximab beta both met their phase 2 success criteria for improving PFS in BEACON. Although the exact mechanism of action accounting for the therapeutic benefits of adding these respective agents to a chemotherapy backbone is not clear, it is likely they are different, given that bevacizumab is an anti-angiogenic agent, and anti-GD2 is an immunotherapy. Therefore, there is potential for there to be additive benefit of giving both agents with the chemotherapy backbone. In addition, as well as 'normalising' the tumour vasculature, enhancing delivery of chemotherapy + immunotherapy, bevacizumab may also favourably modify the immune microenvironment, including promotion of tumour infiltrating lymphocytes and suppression in the number and function of inhibitory populations, including myeloid derived suppressor cells, regulatory T cells and M2 macrophages [41-43]. In pre-clinical neuroblastoma models, it has been reported to augment infiltration and efficacy of anti-GD2 CAR T cells [44] and there are a number of clinical studies in adult tumours, indicating benefit in combining bevacizumab with checkpoint blockade [45-47]. There is therefore rationale beyond just potential additive effects, for combining bevacizumab with anti-GD2 plus chemotherapy, with the aim of favourably modifying the tumour immune and vascular microenvironment to improve the efficacy of chemo-immunotherapy.

Given the different mechanisms of action and toxicity profiles of dinutuximab beta and bevacizumab, it is anticipated that the addition of both agents together to a chemotherapy backbone would also be acceptable in terms of toxicity and tolerability.

Other novel combinations for testing in Tier 2

There are a number of potential combinational regimens which show promise, but that are not yet ready for clinical testing. Our group has formed a network of international collaborators to accelerate preclinical testing and on-going discussions within SIOPEN and ITCC consortia, will prioritise and validate these for inclusion in Tier 2, as new data becomes available.

1.2.7 Rationale for biological studies and future data sharing

Biomarkers have been defined as biological characteristics that can be objectively measured and evaluated as an indicator of normal biological, pathological processes, or pharmacological responses to a therapeutic intervention [48].

In regards to anticancer drug development, three main types of biomarkers have been defined [49]:

- Prognostic biomarkers, give information on prognostic features helping to distinguish between cases with good or poor outcome, independent of treatment.
- Predictive biomarkers assess the probability that a patient will benefit from a particular treatment.
- Pharmacological/Pharmacodynamic (PD) biomarkers, measure effects of the drug on the tumour. PD biomarkers are of major value in making "go-no-go" decisions and assess performance of new drugs.

The use of biomarkers will accelerate and improve drug development [50-52]. In this study, a comprehensive biomarker evaluation has been developed taking into account all considerations for research in the paediatric population. Details on when to collect specific samples and how to process them are described in the BEACON2

Laboratory manual. Samples and images will only be collected for research when required as per standard of care for the patients, and volumes of blood will comply with local, national and international policies.

Importantly, the status of molecular genetic alterations known to be clinically decision making should be known upon study entry, including tumour MYCN amplification status, and ALK amplification/mutation status.

1.2.8 Exploratory biomarker assays performed in blood, blood-derived plasma, bone marrow aspirates and tumour samples

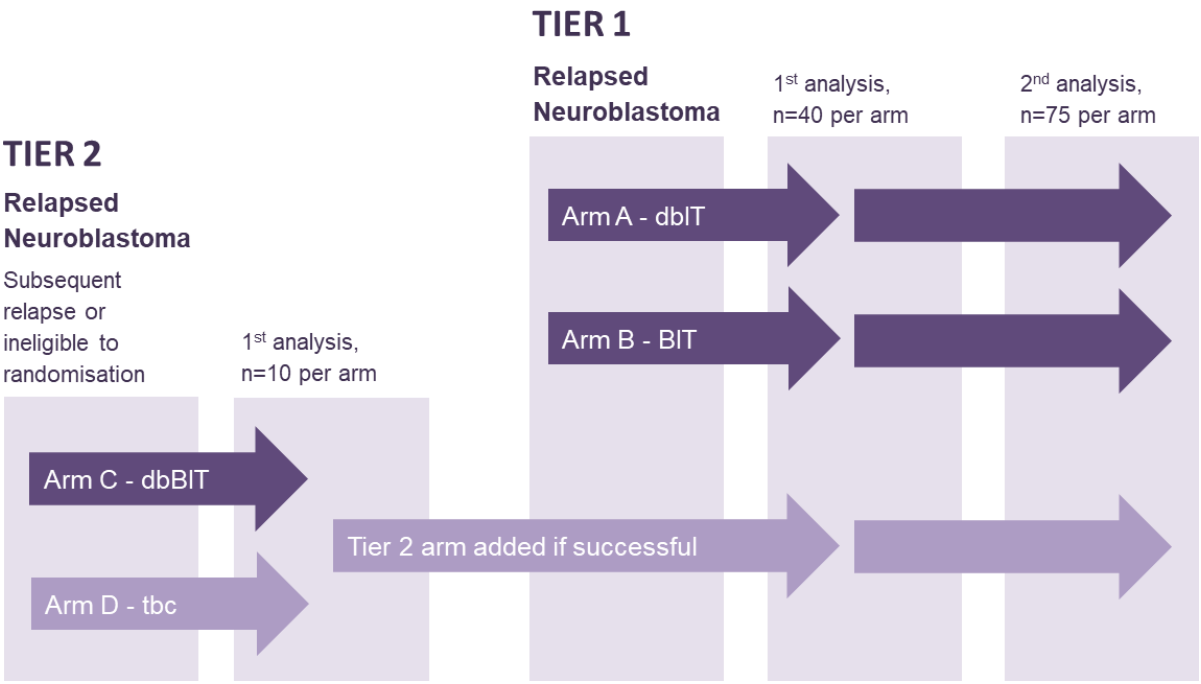
Blood and plasma samples will be taken at study entry, during and at the end of treatment for exploratory biomarker studies; see BEACON2 Laboratory manual. Bone marrow aspirates at study entry may be collected for exploratory molecular studies of circulating biomarkers, neuroblastoma cells and the bone marrow microenvironment. Biological studies include, but are not limited to:

- Tumour molecular profiling. Tumour and blood-derived plasma DNA will be sequenced and tumour gene expression profiling performed to explore possible associations between the tumour molecular profile, candidate molecular predictors and clinical outcome. This will be performed in tumour samples collected at baseline study entry (for clinical purposes) or at the time of diagnosis. Existing genomic and biomarker data collected from patients prior to entry into BEACON2 will be sought to provide a complete genomic and biomarker profile of patients.
- Circulating tumour DNA and RNA will be assessed at study entry, during and at the end of treatment as potential surrogate markers of tumour burden, response of patients to treatment or development of resistance mechanisms.
- Biomarker analyses on blood samples will include identifying potential markers of prognosis or response to new therapies, and the biology of neuroblastoma.
- Optional exploratory studies in bone marrow aspirates at study entry will investigate the molecular genotype and phenotype of neuroblastoma cells in the bone marrow and the bone marrow microenvironment.

2. TRIAL DESIGN

BEACON2 is a platform multi-arm multi-stage (MAMS) randomised phase 1/phase 2, open-label, international trial. The trial will comprise two tiers: Tier 1 will be the main randomisation, starting with the randomisation of Arms A vs B. Participants will be randomised at trial entry to receive one of the regimens. Tier 2 will include a dose expansion/confirmation cohort (Arm C and future arms), before this is introduced to Tier 1. Using the rolling MAMS design will allow the introduction of novel agents or regimens as new arms, if appropriate. The introduction of new arms will take place pending approval of a substantial amendment by each relevant Competent Authority.

Figure 2 – Trial Scheme



2.1 TIER 1 (Main Randomisation)

Arm A: dinutuximab beta, irinotecan and temozolomide (dbIT)

Arm B: bevacizumab, irinotecan and temozolomide (BIT)

40 participants will be recruited to each arm in the first stage. A further 35 (total n=75 per arm) will be recruited following an interim analysis.

Stratification variables used in this trial include:

- Measurable (disease can be measured in cross-sectional imaging as per RECIST v1.1, e.g. soft tissue disease measures >1cm longest diameter) vs evaluable disease (e.g. disease that is non-measurable per RECIST 1.1 or only detectable by MIBG or PET/CT scan)[53]
- MYCN amplification / no amplification / unknown

- Prior Chemo-Immunotherapy (e.g. chemotherapy with anti-GD2 therapy)
- Prior Bevacizumab, Irinotecan and Temozolomide (BIT) treatment

2.2 TIER 2 (Dose Expansion Cohort)

Arm C: dinutuximab beta, bevacizumab, irinotecan and temozolomide (dbBIT).

A safety run-in cohort of 10 participants will be recruited from selected sites. The sites selected to participate in Tier 2 will be decided by the TMG, whose decision will be based on whether they are ITCC Phase 1 centres, have experience in early phase trials, their historical site data return and capacity of their NCC to provide the monitoring required. The primary endpoint of this cohort will be the occurrence of dose-limiting toxicities (DLTs) defined using standard definitions [54].

A DLT is defined as a trial IMP-related adverse event occurring during the DLT assessment period (first cycle, i.e. 3 weeks) that meets 1 of the following criteria:

- Recurrent Grade 3 bronchospasm
- Grade 4 anaphylaxis or allergic reaction
- Grade ≥3 serum sickness
- Grade ≥3 neurological or vision toxicity (as defined in section 11.1)
- Severe, unrelenting neuropathic pain not controlled by maximal analgesia
- Recurrent Grade ≥3 capillary leak syndrome
- Grade 4 hyponatremia (<120 mmol/L) lasting >24 hours despite appropriate fluid management
- Grade 4 skin toxicity
- Grade ≥3 cardiac toxicity
- Any Grade 4 toxicity (laboratory abnormality or non-hematological toxicity) that leads to change of management defined as: chemotherapy dose reduction or delay of next cycle more than >14 days
- Any grade ≥4 toxicity leading to any intensive care unit hospitalization for mechanical ventilation/ionotropic support/hemofiltration
- Any toxic death (Grade 5 toxicity)
- Persistent (>72h) Grade 3 nausea, vomiting or diarrhea despite optimal therapy
- Grade 3 total bilirubin lasting >72h
- ≥ Grade 3 ALT/AST unless resolves in ≤7 days
- Any laboratory abnormality that meets the definition of drug-induced liver injury (DILI) as defined per Hy's law
- Grade 4 anemia
- Grade 4 febrile neutropenia
- Grade 4 thrombocytopenia requiring transfusions for more than 7 days
- Grade 3 thrombocytopenia with Grade ≥3 bleeding
- Specific for treatment with Bevacizumab:
- Grade ≥3 hypertension not controlled by antihypertensive therapy
- Grade >3 proteinuria
- All other haematological toxicities will be not be considered DLTs

Patients will only be assessable for DLT evaluation provided they have received at least 75% of the planned drug dosing a DLT was the reason not to complete dosing and they have not received any other anti-cancer treatment that is not allowed in the protocol These patients not contributing to the DLT assessment will be replaced.

All DLTs will be evaluated by the trial CI/Clinical coordinator as well as by the Trial Management Group (TMG) and DMC.

The investigator will fill in the DLT form as soon as a DLT occurs and/or at the end of the DLT period. At the latest, the form has to be sent to Sponsor within two working days after end of DLT period. All DLTs require continued monitoring and follow-up reporting until they resolve to grade 1 or less, until the patient begins another treatment regimen or until the toxicity is determined to be unresolvable or stabilized.

Recruitment to Tier 2:

Before a patient can be registered to Tier 2, the local team must contact the Coordinating Sponsor to confirm a slot is available.

For the first 6 patients, no more than 3 patients will be undergoing the 1st cycle of treatment at any one time, i.e:

- First 3 patients are recruited without any time restrictions
- 4th patient can only be recruited once one patient has completed 1 full cycle of treatment
- 5th patient can only be recruited once 2 patients have completed 1 full cycle of treatment
- 6th -10th patients can only be recruited once 3 patients have completed 1 full cycle of treatment

If 1-2 patients experience ≥1 DLTs, recruit further 3 patients (total 6) to achieve 3 patients completing 1 full cycle.

If 3 patients experience ≥1 DLTs then reduce dose of any or all of the agents by 25%, dependant on the specific DLTs seen and continue recruitment.

Inclusion of Tier 2 treatment in Tier 1:

The decision to move an arm from Tier 2 to the main randomisation (Tier 1) will be taken by the TMG based on preclinical rationale, mechanism of action, early signs of activity, low proportion of DLTs, lack of overlapping toxicities and feasibility of the combination.

2.3 Treatment Duration

Participants will receive treatment for 12 courses, lasting approximately 36 weeks.

For patients pursuing other consolidation-type therapies, it is acceptable to withdraw from BEACON2 trial treatment after 6 cycles. Data about subsequent therapies received before and after subsequent progression/relapse will be collected in the Case Report Form (CRF).

3. AIMS, OBJECTIVES AND OUTCOME MEASURES

3.1 Aims

- To improve survival for patients with relapsed neuroblastoma by developing novel combinations that are ready for clinical implementation
- To establish a platform trial to evaluate novel combinations in relapsed neuroblastoma, within a seamless phase 1-2 trial that can lead to regulatory approvals and impact clinical practice; allowing dose confirmation cohorts for novel combinations
- To evaluate safety, activity, efficacy and quality of life for these novel combinations in relapsed neuroblastoma participants
- To improve our understanding of relapsed neuroblastoma biology, tumour clonal evolution, tumour microenvironment and develop biomarkers of response and resistance to direct the development targeted therapies by conducting a comprehensive biomarker sample collection.

3.2 Objectives

3.2.1 Primary

- To test novel treatments against current best available treatment in relapsed neuroblastoma

3.2.2 Secondary

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

3.2.3 Tertiary

- To evaluate the role of circulating biomarkers and tumour molecular profiles in blood and tumour as prognostic and predictive biomarkers in relapsed neuroblastoma, including neuroblastoma mRNAs, circulating DNA, biomarkers of immune response and the tumour microenvironment and analysis of genomic aberrations in relapsed tumours.

3.3 Outcome Measures

3.3.1 Primary Endpoint

- Progression-Free Survival time (as per INRC 2017 [2]) – for Tier 1 (randomised comparison)
- Definition of a safe and tolerable combination regimen – for Tier 2 (dose expansion-confirmation cohorts)

3.3.2 Secondary Endpoints

- Best objective response (complete and partial response) as per INRC 2017 during trial treatment (12 cycles)
- Clinical benefit (complete, partial and minor response and stable disease) per the INRC 2017.
- Time response to progression/duration of response (for responders)
- Overall Survival time
- Quality of life measured by Peds-QL questionnaires
- Incidence and Severity of AEs

3.3.3 Exploratory/Tertiary Endpoints

- Quality of life of caregivers measured by Peds-QL questionnaires
- Correlation between objective response using INRC 2017 and PFS/OS
- Changes in circulating biomarkers and tumour molecular profiles in blood and tumour, including mRNAs, analysis of immune response and tumour microenvironment, analyses of genomic aberrations in relapsed neuroblastoma (e.g. MYCN, ALK, RAS/MAPK pathway, ATRX) and development of novel biomarkers.

4. ELIGIBILTY

4.1 Tier 1 Eligibility

Participants meeting the criteria below are eligible to participate in Tier 1 trial treatment. Eligibility must be confirmed by an Investigator (defined as the individual who has the responsibility for the medical care of the participant i.e., typically a consultant level doctor), named on the trial delegation log.

4.1.1 Tier 1 Inclusion Criteria

Disease specific

- Histologically proven neuroblastoma as per International Neuroblastoma Staging System (INSS)[1] definition
- 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)
- Measurable disease by cross sectional imaging or evaluable disease (uptake on MIBG scan with or without bone marrow histology), as per INRC [2, 3]. Participants with only bone marrow detectable disease (bone marrow aspirate or trephine) are NOT eligible for the study

General

- Age ≥1 year
- Signed informed consent from participant, parent or guardian

Performance and organ function

- 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)
- Life expectancy of ≥ 12 weeks
- Bone marrow function (within 72 hours prior to randomisation):
  - Platelets ≥ 50 x 10^9/L (unsupported for 72 hours)
  - ANC ≥ 0.50 x 10^9/L (no G-CSF support for 72 hours)
  - Haemoglobin > 8 g/dL (transfusions allowed)
- Renal function (within 72 hours prior to randomisation):
  - 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
  - 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 m^2
- Liver function (within 72 hours prior to randomisation):
  - 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.
- Coagulation:
  - Participants must not have an active uncontrolled coagulopathy.
  - 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.
- 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.

4.1.2 Tier 1 Exclusion Criteria

- Known contraindication or hypersensitivity to:
  - Any study drug or component of the formulation
  - Chinese hamster ovary products or other recombinant human or humanised antibodies.
  - 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.
- 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
- Prior severe arterial thrombo-embolic events (e.g. cardiac ischemia, cerebral vascular accident, peripheral arterial thrombosis) or any ongoing arterial thrombo-embolic events
- A history of (noninfectious) pneumonitis requiring steroids, or current pneumonitis.
- Patients that are allergic to all therapies for Pnemocystis jirovecii pneumonia and can thus not receive prophylaxis for PJP
- Uncontrolled infection
- Inadequate recovery from prior surgery with ongoing ≥ Grade 3 surgical complications. Grade ≥ 2 wound dehiscence.

- 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:
  - Core biopsies within previous 24hr
  - Open excisional biopsies within previous 48hr
  - Major surgery within previous 2 weeks.
  - Bone marrow aspirates/trephines, within previous 48hr
  - Tunnelled central line insertion within previous 48hr
- Washout from prior treatments (at start of trial treatment):
  - Chemotherapy within previous 2 weeks (1 week for oral metronomic chemotherapy regimens)
  - Any anti-GD2 therapy within previous 2 weeks
  - Craniospinal radiotherapy or MIBG therapy within previous 6 weeks
  - Radiotherapy to the tumour bed within previous 2 weeks (no washout for palliative radiotherapy)
  - Myeloablative therapy with haematopoietic stem cell rescue (autologous stem cell transplant) within previous 8 weeks
  - Allogeneic stem cell transplant within previous 12 weeks (with absence of active ≥G2 acute GVHD)
  - 14 days or 5 half-lives (whichever occurs later) from last administration of an IMP in an IMP-trial
- 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
- Use of enzyme inducing anticonvulsants within 72hr of randomisation
- Conditions that increase the risk of bevacizumab-related toxicities:
  - History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
  - History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or active gastrointestinal bleeding within 6 months prior to study enrolment
  - Current chronic intestinal inflammatory disease/bowel obstruction
- Intolerance to galactose and fructose, lactase deficiency, and/or defect of absorption of galactose and fructose
- Males or females of reproductive potential may not participate unless they agree to use a highly effective 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.
- Pregnant or lactating participant
- Live or live-attenuated vaccines given within previous 28 days prior to study enrolment
- Any uncontrolled medical condition that poses an additional risk to the participant

Tier 1 Specific Exclusion Criteria

- More than one relapse event after the start of high risk neuroblastoma therapy
- Previous treatments that are not allowed
  - Bevacizumab for *relapsed* neuroblastoma (patients who have received BIT for *refractory* disease are not excluded, providing no progression of disease during this treatment occurred
  - 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.

4.2 Tier 2 Eligibility

Participants must have been previously pre-screened or screened for Tier 1 and found to be ineligible, before being assessed for Tier 2 eligibility. A reason for the ineligibility for Tier 1 must be provided on the Tier 2 Registration form.

Before offering participation on Tier 2, the local team must confirm with the Coordinating Sponsor that a slot is available for treatment in Tier 2.

Participants meeting the criteria below are eligible to participate in Tier 2 of the trial. Eligibility must be confirmed by an Investigator (defined as the individual who has the responsibility for the medical care of the participant i.e., typically a consultant level doctor), named on the trial delegation log.

4.2.1 Tier 2 Inclusion Criteria

Disease specific

- Histologically proven neuroblastoma as per International Neuroblastoma Staging System (INSS) [1] definition
- 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)
- Measurable disease by cross sectional imaging or evaluable disease (uptake on MIBG scan with or without bone marrow histology), as per INRC [2, 3]. Participants with only bone marrow detectable disease (bone marrow aspirate or trephine) are NOT eligible for the study

General

- Age ≥1
- Signed informed consent from participant, parent or guardian

Performance and organ function

- 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)
- Life expectancy of ≥12 weeks
- Bone marrow function (within 72hr prior to registration):
  - Platelets ≥ 50 x 10^9/L (unsupported for 72hr)
  - ANC ≥ 0.50 x 10^9/L (no G-CSF support for 72hr)
  - Haemoglobin > 8 g/dL (transfusions allowed)
- Renal function (within 72 hours prior to registration):
  - 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
  - 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 m^2
- Liver function (within 72 hours prior to registration):

- 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.

- Coagulation:
  - Participants must not have an active uncontrolled coagulopathy
  - 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.
- 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

- More than one relapse event

NB- 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):
  - bevacizumab,
  - any anti-GD2 antibody given with chemotherapy ('chemo-immunotherapy')
  - previous treatment with temozolomide with irinotecan

4.2.2 Tier 2 Exclusion Criteria

- Known contraindication or hypersensitivity to:
  - Any study drug or component of the formulation
  - Chinese hamster ovary products or other recombinant human or humanised antibodies.
  - Participants with mild previous hypersensitivity reactions to anti-GD2 antibodies may be included, but those with severe (or G4) hypersensitivity reactions to antiGD2 antibodies will be excluded.
- 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
- Prior severe arterial thrombo-embolic events (e.g. cardiac ischemia, cerebral vascular accident, peripheral arterial thrombosis) or any ongoing arterial thrombo-embolic events
- A history of (noninfectious) pneumonitis requiring steroids, or current pneumonitis.
- Patients that are allergic to all therapies for Pnemocystis jirovecii pneumonia and can thus not receive prophylaxis for PJP
- Uncontrolled infection
- Inadequate recovery from prior surgery with ongoing ≥Grade 3 surgical complications. Grade ≥2 wound dehiscence.
- Recent surgical procedures (at start of trial treatment). Patient can be registered up to 48h prior to these periods being completed provided that trial treatment only starts after complying with all of them:
  - Core biopsies within previous 24hr
  - Open excisional biopsies within previous 48hr
  - Major surgery within previous 2 weeks.
  - Bone marrow aspirates/trephines, within previous 48hr
  - Tunnelled central line insertion within previous 48hr

- Wash out from prior treatment (at start of trial treatment):
  - Chemotherapy within previous 2 weeks (1 week for oral metronomic chemotherapy regimens)
  - Any anti-GD2 therapy within previous 2 weeks
  - Craniospinal radiotherapy or MIBG therapy within previous 6 weeks
  - Radiotherapy to the tumour bed within previous 2 weeks (no washout for palliative radiotherapy)
  - Myeloablative therapy with haematopoietic stem cell rescue (autologous stem cell transplant) within previous 8 weeks
  - Allogeneic stem cell transplant within previous 12 weeks (with absence of active ≥G2 acute GVHD)
  - 14 days or 5 half-lives (whichever occurs later) from last administration of an IMP in an IMP-trial
- 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
- Use of enzyme inducing anticonvulsants within 72 hours of start of treatment
- Conditions that increase the risk of bevacizumab-related toxicities:
  - History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
  - History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or active gastrointestinal bleeding within 6 months prior to study enrolment
  - Current chronic intestinal inflammatory disease/bowel obstruction
- Intolerance to galactose and fructose, lactase deficiency, and/or defect of absorption of galactose and fructose
- Males or females of reproductive potential may not participate unless they agree to use a highly effective 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.
- Pregnant or lactating participant
- Live or live-attenuated vaccines given within previous 28 days prior to study enrolment
- Any uncontrolled medical condition that poses an additional risk to the participant

5. SCREENING AND CONSENT

5.1 Participant Identification

Participants will be identified by clinicians as per local practice, e.g. in multi-disciplinary teams meetings. Participants may be referred to trial participating sites by local hospitals for eligibility assessment by Investigators.

5.2 Screening

The majority of the screening tests defined in this protocol are standard practice and can be commenced prior to obtaining consent. However, where tests do not form part of standard medical practice for this group of participants, at a specific site, consent (see section 5.3) should be obtained prior to these tests being performed.

Investigators are expected to maintain a Screening/Enrolment Log of all potential participants considered for the trial. This Log will include limited information about the potential participant (e.g. date of diagnosis and gender) and

the date and outcome of the screening process (e.g. enrolled into trial, reason for ineligibility or refused to participate).

For participants who appear to meet the criteria for participation in the trial, the Investigator will provide the potential participant with the current approved Participant Information Sheet to allow them to make an informed decision regarding their participation. If informed consent is given (see Section 5.3), the Investigator will conduct a full screening evaluation to ensure that the participant satisfies all inclusion and exclusion criteria (note, participants must meet the all the eligibility criteria at the time they are entered into the trial, see sections 4.1 and 4.2). This evaluation should be documented in the medical records. A participant who gives written informed consent and who satisfies all the inclusion and exclusion criteria may be entered into the trial (see section 6). Note that assessments conducted as standard of care do not require trial specific informed consent and may be provided as screening data if conducted within the stipulated time period prior to trial entry. Assessments required at screening are listed in the flowchart of assessments and detailed in sections 7.2 and 8.2.

5.3 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent for each participant prior to performing any trial related procedure. A Participant/Parent Information Sheet (PIS) is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. The Investigator should also stress that the participant is completely free to refuse to take part or withdraw from the trial at any time. The participant should be given ample time (e.g. 24 hours) to read the PIS and to discuss their participation with others outside of the site research team. The participant must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the participant to refuse to participate in the trial without giving a reason must be respected.

Specific PIS and Informed Consent Forms (ICF's) are provided for Tier 1 and Tier 2. Country specific PIS are provided.

If the participant, parent or legal guardian expresses an interest in [their child] participating in the trial they should be asked to sign and date one copy of the latest approved version of the ICF. The Investigator must then sign and date the form. For children under the age of 16, a parent or legal guardian will sign the ICF. Written assent can also be obtained from patients under the age of 16 years where possible, using the relevant section on the ICF.

A copy of the ICF should be given to the participant, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial the participant's trial number should be entered on the ICF maintained in the ISF. In addition, if the participant has given explicit consent a copy of the signed ICF must be sent in the post to the Trials Office for review.

Details of the informed consent discussions should be recorded in the participant's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the PIS and ICF. Throughout the trial the participant should have the opportunity to ask questions about the trial and any new information that may be relevant to the participant's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the participant in which case the process above should be followed and the participant's right to withdraw from the trial respected.

Electronic copies of the approved country-specific PIS and ICF are available and should be printed or photocopied onto the headed paper of the local institution.

Details of all participants approached about the trial should be recorded on the Participant Screening/Enrolment Log. Where appropriate and with the participant's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

6. TRIAL ENTRY

6.1 Time Frame for Trial Entry

Participants should be entered into the trial as soon as possible and within a maximum of 4 weeks from commencement of screening assessments. Trial treatment should ideally start within one week of trial entry.

6.2 Trial Entry Process

Participants can be entered into the trial once the applicable National Coordinating Centre (NCC) has confirmed that all regulatory requirements have been met by the trial site and the site has been activated by the UK Coordinating Centre.

It will be proposed to the participant and/or participant's parent/guardian to participate in the BEACON2 trial by signing the **ICF** (for either **Tier 1** or **Tier 2**). Once informed consent has been obtained, participants are assessed for either Tier 1 participation using Tier 1 screening assessments (see Tier 1 Screening section 8.1) for further details) or Tier 2 participation using Tier 2 screening assessments (see Tier 2 Screening section 8.2) for further details), depending on the number of relapses of neuroblastoma. Tier 1 is only for first relapse neuroblastoma participants and Tier 2 is only for second (and subsequent) relapsed neuroblastoma participants.

The eligibility of a participant for Tier 1 may be able to be assessed without screening assessments (i.e. based on previous treatment and disease history). If the participant is not eligible for Tier 1 (e.g. prior relapse treated with chemo-immunotherapy or BIT, or has had more than one relapse), it may be proposed to the participant and/or participant's parent/guardian to participate in the BEACON2 (Tier 2) trial directly.

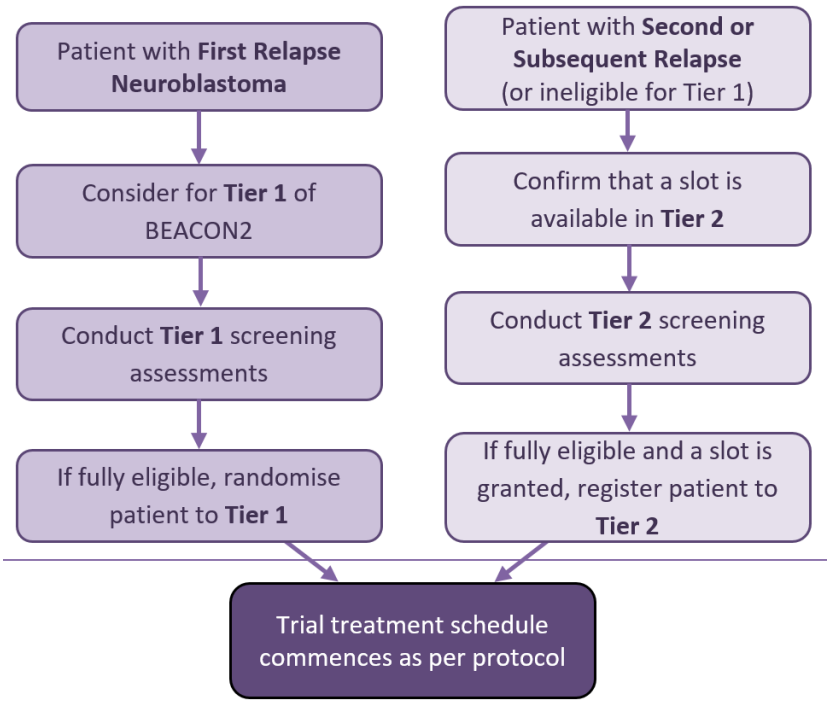
The randomisation to Tier 1 or registration to Tier 2 must be performed prior to the commencement of any trial treatment. This procedure is outlined in the diagram (

Figure 3 – Trial Entry Process) below.

Participants that experience progression/relapse on Tier 1 may be considered for participation into Tier 2 arms, if they have received at least 3 cycles of Tier 1 treatment.

In case several arms in Tier 2 become available, study participants might be recruited to one specific arm by clinician's choice with approval of the trial CI or clinical coordinator; based on prior therapies or highest expected benefit.

Figure 3 – Trial Entry Process



7. TIER 1 (MAIN RANDOMISATION)

7.1 Tier 1 Screening

No trial specific procedure should be carried out prior to signing the Tier 1 Trial Entry consent form for this study (see section 5.3). All participants who have been consented as part of screening must undergo the following assessments/procedures within 28 days prior to randomisation and as indicated below.

7.2 Tier 1 Screening Assessments (Assessment Timepoint A)

- Imaging of measurable or evaluable disease (MRI (preferred) or CT including the brain, MIBG scan (or ^{18}FDG PET/CT scans if MIBG negative disease) and bilateral bone marrow aspirates and trephines (assessed by local morphology)) must have been performed within 4 weeks prior to trial entry and within 6 weeks prior to starting trial treatment. Screening tumour assessment should be recorded on the Tumour Assessment CRF, recording disease as per INRC 2017 (target and non-target lesions), with cross-sectional imaging (primary tumour and metastatic soft tissue) mIBG according to the SIOPEN score and bone marrow assessment (report of bilateral aspirates and trephines).
- Complete medical history (including past medical history, concurrent medical events and dates of all previous anticancer treatment) within 4 weeks prior to trial entry.
- Health-related quality of life (HRQoL) assessment will be performed within 1 week prior to trial entry.
- Full clinical examination (including physical exam, blood pressure, heart rate, temperature, oxygen saturation, weight and height) and performance status at screening and within 24hr prior to trial entry.
- Haematology [includes Haemoglobin (Hb), white blood cells (WBC), neutrophil count, lymphocytes and platelets] at screening and within 72hr prior to dosing. If more than 72hr elapse from screening to initiation of trial therapy, they should be repeated
- Biochemistry (includes sodium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, and ALT or AST) must be done at screening and within 72hr prior to dosing
- An estimated GFR must be carried out in participants with serum creatinine $\geq$ 1.5 ULN for age within 7 days of randomisation
- A urine (preferred) or serum pregnancy test will be done on females who are post-menarche within 72hr prior to cycle 1 dosing. Results of the tests are needed to determine participant eligibility and testing may need to be repeated so that result from the pregnancy test are available for within 72hr before cycle 1 dosing
- Sampling:
    - A blood sample for the molecular monitoring analysis of mRNA (as per BEACON2 Laboratory Manual)
    - A whole blood sample taken for DNA constitutional analyses at baseline (optional to participant/parent)
    - A blood sample for exploratory biomarkers should be collected before study drug administration
    - Available tumour sample to be identified prior to starting study medications. If a sample is not available, the local physician must agree the potential study entry with the Coordinating Sponsor and the CI always before starting trial medication. The tumour sample will be shipped on a regular basis as arranged with the Sponsor. It is acceptable to share DNA that has already been extracted or raw data for those patients that have already been undergone sequencing studies. Where feasible, samples from diagnosis and at the time of relapse will be collected. Please see BEACON2 Laboratory Manual for further details

- Any ongoing adverse events from previous treatment and concomitant medications must be documented and continued to be assessed throughout the study. Records of ongoing concomitant medication will not be collected on the CRF, but should be available for reporting when an SAE occurs

7.3 Tier 1 Randomisation

Randomisation for Tier 1 of the trial should be performed by sites using the online electronic remote data capture system (eRDC). Informed consent should be obtained prior to any trial-related procedures. Once a paper Tier 1 Eligibility Checklist has been completed, in order to randomise a participant, the online Tier 1 Randomisation Form must be completed. All of the required information, including stratification factors, must be available at the time of randomisation.

The following information about minimisation factors will be necessary to randomise a patient:

- Measurable vs evaluable disease
- MYCN amplification / no amplification / unknown
- Prior Immuno-Chemotherapy
- Prior Bevacizumab, Irinotecan and Temozolomide (BIT) treatment

Randomisation of participants can be achieved by logging on to:

https://www.cancertrials.bham.ac.uk/CRCTUPortal

This program will confirm eligibility and allocate treatment via a computerised minimisation algorithm, developed by the CRCTU.

A copy of the Randomisation Confirmation Report and the participant's Trial number (TNO) should be printed and retained in the Investigator Site File (ISF) and participant's notes. The TNO should be written on the Informed Consent Form filed in the ISF and used on all serious adverse event (SAE) forms and correspondence relating to that participant. In addition, where possible a copy of the participant's Informed Consent Form must be sent in the post to the National Coordinating Centre Trial Office.

7.4 Tier 1 Emergency Randomisation

In case of any problems with online randomisation, a paper Eligibility Checklist and paper Randomisation Form should be completed. These details can be phoned through to the BEACON2- Trial Office at the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, UK, using the number below:

STUDY ENTRY/ RANDOMISATION

(09:00 to 17:00 GMT / BST, Monday to Friday)

☎ +44 (0)121 414 3799/ (0)121 414 5345

7.5 Tier 1 Treatment Details

7.5.1 Tier 1 Investigational Medicinal Products

The following drugs are IMPs in Tier 1:

NB- Topotecan is included as an IMP in instances of severe irinotecan-related toxicity. Please refer to Section 11.3 Chemotherapy Dose modifications.

Table 3 - IMPs in Tier 1

IMP	Formulation
Dinutuximab beta	Infusion
Bevacizumab	Infusion
Irinotecan	Infusion
Topotecan	Infusion
Temozolomide	Capsule
Temozolomide	Oral Suspension

7.5.2 Tier 1 Treatment Schedule

Arm A: dbIT

Dinutuximab beta 10 mg/m^2/day iv days 1-7, Irinotecan 50 mg/m^2 iv days 1-5, Temozolomide 100 mg/m^2 po days 1-5
3 weekly x12 cycles

Arm B: BIT

Bevacizumab 15 mg/kg iv day 1, Irinotecan 50 mg/m^2 iv days 1-5, Temozolomide 100 mg/m^2 po days 1-5.
3 weekly x12 cycles

Refer to the BEACON2 Pharmacy Manual for further details.

Table 4 - Tier 1 Treatment Schedule

	Day 1	Day 2-5	Day 6-7	Day 22
Treatment duration: 12 cycles = 36 weeks, response assessed every 3 cycles				
Arm A: dbIT	Dinutuximab beta 10mg/m^2/day iv Irinotecan 50mg/m^2 iv* Temozolomide 100mg/m^2 po	Dinutuximab beta 10mg/m^2/day iv Irinotecan 50mg/m^2 iv* Temozolomide 100mg/m^2 po	Dinutuximab beta 10mg/m^2/day iv	Day 1 of next cycle starts

Arm B: BIT	Bevacizumab 15mg/kg iv Irinotecan 50mg/m^2 iv* Temozolomide 100mg/m^2 po	Irinotecan 50mg/m^2 iv* Temozolomide 100mg/m^2 po		Day 1 of next cycle starts

- *NB- in extreme cases of toxicity, irinotecan may be replaced with topotecan. Refer to 7.5.3 below.

After six cycles of treatment, local control including surgery and radiotherapy may be used in parallel to trial treatment. Trial treatment can be interrupted temporarily to allow for local control. This information will be collected in the CRF.

For patients pursuing other consolidation-type therapies (such as stem cell transplantation), it is acceptable to withdraw from BEACON2 trial treatment after 6 cycles. Data about subsequent therapies received before and after subsequent progression/relapse will be collected in the CRF.

Participants should remain admitted as in-patients during the first course. For subsequent courses, institutional practice can be applied, and participants can be discharged on ambulatory pumps if clinically well.

After 12 cycles of treatment, patients will continue to be followed up as specified in protocol section 16. Treatments received after trial treatment (before or after developing progressive disease) can follow SIOPEN guidelines and the data will be collected in the CRF.

7.5.3 Tier 1 IMP Administration

Dinutuximab beta

The dose of dinutuximab beta will be 10 mg/m^2/day given through a 24-hour infusion for 7 days (days 1-7). In order to administer dinutuximab beta in combination with chemotherapy without interruptions of dinutuximab beta infusions, it is necessary to have a double access as per routine practice for the administration of chemo-immunotherapy.

Bevacizumab

If allocated to Arm B (BIT) the dose of bevacizumab will be 15 mg/kg given intravenously. Bevacizumab should be administered prior to chemotherapy as per local practice. The total dose will be rounded to the nearest 5mg.

- Bevacizumab **MUST not** be administered within 48 hours of any minor surgical procedure (e.g. bone marrow exam or insertion of central venous access device [CVAD]) or within 2 weeks of major surgery. In all cases, the investigator should verify that there are no wound healing complications before the administration of bevacizumab.
- In case of severe toxicity related to bevacizumab, the drug **MUST** be stopped and not dose reduced. See Section 11.2 for criteria. In case of a prolonged dose interruption, the local physician will discuss with the Coordinating Sponsor and the medical team the appropriateness of re-starting treatment with bevacizumab, given that 4 to 6 weeks will be needed to achieve steady-state concentrations again and there is risk of subsequent toxicity related to bevacizumab. For those participants that are near completion of the treatment course it will be advisable to stop bevacizumab permanently. **In case of chemotherapy-related toxicities**

require that cycles of chemotherapy are delayed, **the administration of bevacizumab should be kept to schedule** (e.g. 3-weekly) even if discoordinated with administration of chemotherapy.

Irinotecan

The dose of irinotecan will be 50 mg/m²/day. Irinotecan will be given intravenously over 1 hour on days 1-5, one hour following the administration of temozolomide. The total administered dose of chemotherapy may be rounded up or down to the nearest dose that can be accurately measured. Irinotecan will be administered as per local practice. ***Topotecan - In instances of severe irinotecan-related toxicity***

The dose of topotecan will be 0.75 mg/m²/day. Topotecan will be given intravenously over 30mins on Days 1-5, at least one hour following the administration of temozolomide. The administered dose of chemotherapy may be rounded up or down to the nearest dose that can be accurately measured.

Temozolomide

The dose of temozolomide will be 100 mg/m²/day orally. Where possible, doses will be rounded to the nearest 5mg as per the table in Appendix 5 – Temozolomide Dosing. Temozolomide will be administered as per local practice.

7.5.4 Tier 1 – Important Administration Information

The participant's height and weight (BW) must be measured prior to each cycle of treatment, and BSA should be calculated using local institutional procedures. It is important that the same procedure is used throughout the trial.

Bevacizumab is prescribed per kg. Temozolomide, irinotecan, topotecan and dinutuximab beta are prescribed per body surface area (BSA).

It is recommended that the same dose is given to the participant every cycle, using the doses calculated using the screening or Cycle 1 BW and BSA, UNLESS the calculated dose(s) have changed by ≥10% from the values obtained at screening/cycle 1.

If a participant's BW exceeds that for the 98th centile for their age:

- Bevacizumab doses should be calculated with the weight for the 98th centile
- Irinotecan, temozolomide and dinutuximab beta doses should be calculated using the BSA, using the BW for the 98th centile and the participant's actual height.
- In all cases, the dosing of overweight participants should be discussed and agreed with the Coordinating Sponsor before the administration of any IMP.

For patients with a body weight of ≤10kg, the temozolomide dose will be reduced to 3.3 mg/kg/day, irinotecan to 1.7 mg/kg/day and topotecan to 0.025 mg/kg/day. There is no planned dose reduction of dinutuximab beta for patients that are ≤10 kg.

7.6 Tier 1 Treatment Verification

Verification of dosing is recorded by local practice, i.e. in pharmacy records and/or in participant's notes.

7.7 Tier 1 Treatment Breaks and Compensation

NOTE: The toxicity profiles of dinutuximab beta, bevacizumab, irinotecan, topotecan and temozolomide are different. They should be considered separately and any necessary treatment modification to one element of the study treatment should not cause a change or delay to the other element. This is particularly important with respect to bevacizumab which takes 4 – 6 weeks to achieve steady state levels. Any treatment delay will require steady state levels to be re-established. Bevacizumab infusions should be kept at 3 weekly intervals and do not necessarily need to be synchronised with irinotecan and temozolomide. Dinutuximab beta infusions should be aligned with the start of irinotecan-temozolomide treatment cycles.

The maximum delay to the administration of chemotherapy due to adverse events is 36 days. The delay may be extended over 36 days only if the participant is showing a good response to the treatment and agreement is obtained from the Sponsor.

Refer to Section 11 Dose Modifications for more details.

8. TIER 2 (DOSE EXPANSION COHORT)

8.1 Tier 2 Screening

No trial specific procedure should be carried out prior to signing the Tier 2 Trial Entry consent form for this study, (see section 5.3). All participants who have been consented as part of screening must undergo the following assessments/procedures within 28 days prior to registration and as indicated below.

8.2 Tier 2 Screening Assessments (Assessment Timepoint A)

- Imaging of measurable or evaluable disease (MRI (preferred) or CT including the brain, MIBG scan (or ^{18}-FDG PET/CT scans if MIBG negative disease) and bilateral bone marrow aspirates and trephines (assessed by local morphology)) must have been performed within 4 weeks prior to trial entry and within 6 weeks prior to starting trial treatment. Screening tumour assessment should be recorded on the Tumour Assessment CRF, recording disease as per INRC 2017 (target and non-target lesions), with cross-sectional imaging (primary tumour and metastatic soft tissue), mIBG (or PET/CT if MIBG scan is negative) according to the SIOPEN score and bone marrow assessment (report of bilateral aspirates and trephines).
- Complete medical history (including past medical history, concurrent medical events and dates of all previous anticancer treatment) within 4 weeks prior to trial entry.
- Full clinical examination (including physical exam, blood pressure, heart rate, temperature, oxygen saturation, weight and height) and performance status at screening and within 24hr prior to trial entry.
- Haematology [includes haemoglobin (Hb), white blood cells (WBC), neutrophil count, lymphocytes and platelets] at screening and within 72hr prior to dosing. If more than 72hr elapse from screening to initiation of trial therapy, they should be repeated
- Biochemistry (includes sodium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, and ALT or AST) must be done at screening and within 72 hours prior to dosing
- An estimated GFR must be carried out in participants with serum creatinine $\geq$ 1.5 ULN for age within 7 days of registration

- A urine (preferred) or serum pregnancy test will be done on girls who are post-menarche within 72hr prior to cycle 1 dosing. Results of the tests are needed to determine participant eligibility and testing may need to be repeated so that result from the pregnancy test are available for within 72hr before cycle 1 dosing
- Sampling:
  - A blood sample for the molecular monitoring analysis of mRNA (as per BEACON2 Laboratory Manual)
  - A whole blood sample taken for DNA constitutional analyses at baseline (optional to participant/parent)
  - A blood sample for exploratory biomarkers should be collected before study drug administration
  - Available tumour sample to be identified prior to starting study medications. If a sample is not available, the local physician must agree the potential study entry with the Coordinating Sponsor and the CI always before starting trial medication. The tumour sample will be shipped on a regular basis as arranged with the Sponsor. It is acceptable to share DNA that has already been extracted or raw data for those patients that have already been undergone sequencing studies. Where feasible, samples from diagnosis and at the time of relapse will be collected. Please see BEACON2 Laboratory Manual for further details.
- Any ongoing adverse events from previous treatment and concomitant medications must be documented and continued to be assessed throughout the study. Records of ongoing concomitant medication will not be collected on the CRF, but should be available for reporting when an SAE occurs

8.3 Tier 2 Registration

Before offering participation on Tier 2, the local team must confirm with the Coordinating Sponsor that a slot is available. Refer to Section 2.2 TIER 2 (Dose Expansion Cohort).

Registration for Tier 2 treatment should be performed by sites using the online electronic remote data capture system (eRDC). Informed consent should be obtained prior to any trial-related procedures. Once a paper Tier 2 Eligibility Checklist has been completed, in order to register a participant, the online Tier 2 Registration Form must be completed. All of the required information, including stratification factors, must be available at the time of registration.

Registration of participants can be achieved by logging on to:

https://www.cancertrials.bham.ac.uk/CRCTUPortal

A copy of the Registration Confirmation Report and the participant's Trial Number (TNO) should be printed and retained in the Investigator Site File (ISF) and participant's notes. The TNO should be written on the Informed Consent Form filed in the ISF and used on all serious adverse event (SAE) forms and correspondence relating to that participant. In addition, where possible a copy of the participant's Informed Consent Form must be sent in the post to the National Coordinating Centre Trial Office.

8.4 Emergency Registration

In case of any problems with online registration, a paper Eligibility Checklist and paper Registration Form should be completed. These details can be phoned through to the BEACON2 Trial Office at the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, UK using the numbers below:

STUDY ENTRY/ REGISTRATION

(09:00 to 17:00 GMT / BST, Monday to Friday)

☎ +44 (0)121 414 3799/ (0)121 414 45345

8.5 Tier 2 Treatment Details

8.5.1 Tier 2 Investigational Medicinal Products

The following drugs are IMPs in Tier 2:

NB – Topotecan is included as an IMP in instances of severe irinotecan-related toxicity. Please refer to Section 11.3 Chemotherapy Dose modifications.

Table 5 - IMPs in Tier 2

IMP	Formulation
Dinutuximab beta	Infusion
Bevacizumab	Infusion
Irinotecan	Infusion
Topotecan	Infusion
Temozolomide	Capsule
Temozolomide	Oral Suspension

8.5.2 Tier 2 Treatment Schedule

Arm C: dbBIT

Bevacizumab 15 mg/kg/day iv day 1, Dinutuximab beta 10 mg/m^2/day iv days 1-7, Irinotecan 50 mg/m^2 iv days 1-5, Temozolomide 100 mg/m^2 po days 1-5
3 weekly x12 cycles

Refer to the BEACON2 Pharmacy manual for further details.

Table 6 – Tier 2 Treatment Schedule

	Day 1	Day 2-5	Day 6-7	Day 22
Treatment duration: 12 cycles = 36 weeks, response assessed every 3 cycles				
Arm C: dbBIT	Dinutuximab beta 10mg/m^2 iv Bevacizumab 15mg/kg iv Irinotecan 50mg/m^2 iv*	Dinutuximab beta 10mg/m^2/day iv Irinotecan 50mg/m^2/day iv*	Dinutuximab beta 10mg/m^2/day iv	Day 1 of next cycle starts

	Temozolomide 100mg/m^2 po	Temozolomide 100mg/m^2/day po		

- *NB- in extreme cases of toxicity, irinotecan may be replaced with topotecan. Refer to 8.5.3 below.

After six cycles of treatment, local control including surgery and radiotherapy may be used in parallel to trial treatment. Trial treatment can be interrupted temporarily to allow for local control. This information will be collected in the CRF.

For patients pursuing other consolidation-type therapies, it is acceptable to withdraw from BEACON2 trial treatment after 6 cycles (4 months). Data about subsequent therapies received before and after subsequent progression/relapse will be collected in the CRF.

Participants should remain admitted as in-patients during the first course. For subsequent courses, institutional practice can be applied, and participants can be discharged on ambulatory pumps if clinically well.

After 12 cycles of treatment, patients will continue to be followed up as specified in protocol section 16. Treatments received after trial treatment (before or after developing progressive disease) can follow SIOPEN guidelines and will be collected.

In order to administer dB in combination with chemotherapy without interruptions of dB infusions, it is necessary to have a double central access. This can be achieved through a double lumen central line (Hickman or Port-a-Cath) or two single lumen central lines (e.g. one Port-a-cath and a PICC line).

8.5.3 Tier 2 Administration

Dinutuximab beta

The dose of dinutuximab beta will be 10 mg/m^2/day given through a 24-hour infusion for 7 days (days 1-7).

For administration of dbBIT, on day 1 patients should first receive iv bevacizumab first, then followed by the start of infusion of dinutuximab beta, and then irinotecan and temozolomide. On the following days (2-7), patients will receive a continuous infusion of dinutuximab beta. Irinotecan will be given through a different line without interrupting the dinutuximab beta infusion.

Bevacizumab:

The dose of bevacizumab will be 15 mg/kg given intravenously. Bevacizumab should be administered prior to chemotherapy and as per local practice. The total dose will be rounded to the nearest 5mg.

- Bevacizumab **MUST not** be administered within 48hr of any minor surgical procedure (e.g. bone marrow exam or insertion of central venous access device [CVAD]) or within 2 weeks of major surgery. In all cases, the investigator should verify that there are no wound healing complications before the administration of bevacizumab.
- In case of severe toxicity related to bevacizumab, the drug **MUST** be stopped and not dose reduced. See section 11.2 for criteria. In case of a prolonged dose interruption, the local physician will discuss with the Coordinating Sponsor and the medical team the appropriateness of re-starting treatment with bevacizumab, given that 4 to 6 weeks will be needed to achieve steady-state concentrations again and there is risk of subsequent toxicity related to bevacizumab. For those participants that are near completion of the treatment

course it will be advisable to stop bevacizumab permanently. **In case of chemotherapy-related toxicities** require that cycles of chemotherapy are delayed, **the administration of bevacizumab should be kept to schedule** (e.g. 3-weekly) even if discoordinated with administration of chemotherapy.

Irinotecan

The dose of irinotecan will be 50 mg/m²/day. Irinotecan will be given intravenously over 1 hour on days 1-5, one hour following the administration of temozolomide. The total administered dose of chemotherapy may be rounded up or down to the nearest dose that can be accurately measured. Irinotecan will be administered as per local practice.

Topotecan - In instances of severe irinotecan-related toxicity

The dose of topotecan will be 0.75 mg/m^2/day. Topotecan will be given intravenously over 30mins on days 1-5, at least one hour following the administration of temozolomide. The administered dose of chemotherapy may be rounded up or down to the nearest dose that can be accurately measured.

Temozolomide

The dose of temozolomide will be 100 mg/m^2/day orally. Where possible, doses will be rounded to the nearest 5mg as per the table in Appendix 5 – Temozolomide Dosing. Temozolomide will be administered as per local practice.

8.5.4 Tier 2 Important Administration Information

The participant's height and weight (BW) must be measured prior to each cycle of treatment, and BSA should be calculated using local institutional procedures. It is important that the same procedure is used throughout the trial.

Bevacizumab is prescribed per kg. Dinutuximab beta, irinotecan, topotecan, and temozolomide are prescribed per body surface area (BSA).

It is recommended that the same dose is given to the participant every cycle, using the doses calculated using the screening or Cycle 1 BW and BSA, UNLESS the calculated dose(s) have changed by ≥10% from the values obtained at screening/cycle 1.

If a participant's BW exceeds that for the 98th centile for their age:

- Bevacizumab doses should be calculated with the weight for the 98th centile
- Irinotecan, temozolomide and dinutuximab beta doses should be calculated using the BSA, using the BW for the 98th centile and the participant's actual height.
- In all cases, the dosing of overweight participants should be discussed and agreed with the Coordinating Sponsor before the administration of any IMP.

For patients with a body weight of ≤10kg, the temozolomide dose will be reduced to 3.3 mg/kg/day, irinotecan to 1.7 mg/kg/day and topotecan to 0.025 mg/kg/day. There is no planned dose reduction of dinutuximab beta for patients that are ≤10 kg.

8.6 Tier 2 Treatment Verification

Verification of dosing is recorded by local practice, i.e. in pharmacy records and/or in participant's notes.

8.7 Tier 2 Treatment Breaks and Compensation

NOTE: The toxicity profiles of dinutuximab beta, bevacizumab, irinotecan, topotecan, and temozolomide are different. They should be considered separately and any necessary treatment modification to one element of the study treatment should not cause a change or delay to the other element. This is particularly important with respect to bevacizumab which takes 4 – 6 weeks to achieve steady state levels. Any treatment delay will require steady state levels to be re-established. Bevacizumab infusions should be kept at 3 weekly intervals and do not necessarily need to be synchronised with dinutuximab beta, irinotecan and temozolomide. Dinutuximab beta infusions should be aligned with the start of irinotecan-temozolomide treatment cycles.

The maximum delay to the administration of chemotherapy due to adverse events is 36 days. The delay may be extended over 36 days only if the participant is showing a good response to the treatment and agreement is obtained from the Sponsor.

Refer to section 11 Dose Modifications for more details.

9. ASSESSMENTS

All participants receiving a single dose or more of study medications will be considered evaluable for toxicity. Safety endpoints include adverse events, clinical examination (including blood pressure, heart rate, temperature, oxygen saturation, weight and height) and laboratory tests (haematology, chemistry).

All study related procedures must be performed at the study site or at accredited centres/laboratories to which the study site refers participants for laboratory tests or imaging if these cannot be routinely performed at the study site.

Laboratory tests and safety assessments as part of standard care can be performed at the participant's local hospital in between cycles, provided they are conducted on time and the local hospital has a procedure to receive and review them in a timely manner.

In the case of laboratory tests, safety assessments and additional investigations not as part of study related procedures being performed at the participant's local hospital, it is the Investigator's responsibility to ensure he/she receives and reviews the results. The results must be recorded on the CRF as required, and the reports from the other hospitals must be available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used. It is the Principal Investigator's responsibility at each site to obtain these.

9.1 Tumour Assessment

As per INRC2017, the minimum requirement is a cross sectional image of site of measurable disease by MRI (preferred) or CT, performed within 6 weeks prior to receiving the first dose of trial treatment. A scan including the brain (either CT or MRI) must also be performed at screening to assess participant's eligibility with regard to the presence of bleeding brain metastases. At baseline, MIBG scans (or ^{18}-FDG PET/CT scan for patients with MIBG

negative disease) and bilateral bone marrow aspirates and trephines are to be done within 6 weeks prior to receiving the first dose of trial treatment. Additional investigations of possible metastatic sites should be done upon presentation of signs and symptoms. Tumour lesions previously irradiated will be considered measurable only if progressing. Scans should be completed up to 7 days prior to cycles 3, 5, 7 and 10, following cycle 12; and at end of treatment if the participant discontinues treatment early. A brain CT/MRI must be repeated following cycles 2, 4, 6, 9 and 12 only if clinically indicated. Tumour assessments do not have to be repeated where the following cycle is delayed due to toxicity. Response assessment will be performed with the same modalities used at screening (MRI/CT/MIBG/bone marrow histology as appropriate). To ensure comparability, the same scanner, equipment, method and technique used during baseline should be consistently used throughout the study.

Response after 2, 4, 6, 9 and 12 cycles of treatment will be determined for participants with evaluable disease (only MIBG avid disease) using a semi-quantitative score (see Appendix 3 - SIOPEN scoring methods for neuroblastoma) and the International Neuroblastoma Response Criteria Appendix 2 - Tumour Staging - INRC Classification [2] Participants with MIBG negative scans but lesions on ^{18}FDG-PET/CT scans will be evaluated with ^{18}FDG-PET/CT. For these patients the number of FDG-avid bone lesions will be recorded and be used as score to calculate the % reduction or increase in comparison with baseline.

Participants who fail treatment (i.e. develop PD) early, prior to response evaluation, will be considered to be non-responders.

Response will be categorised as Complete Response (CR), Partial Response (PR), Minor Response (MR), Stable Disease (SD), Progressive Disease (PD – including the appearance of new lesions) or Non Evaluable (NE) as per INRC 2017.

For evaluation of bone marrow involvement, bilateral iliac crest bone marrow aspirates and trephines will be performed at screening and only be repeated after 2, 4, 6, 9 and 12 courses if positive at screening or clinically indicated (until they become negative). CR in BM will be defined when 2 aspirates and 2 trephines are negative in a previously involved BM. PD will be defined as per [55], as either bone marrow without tumour infiltration that becomes >5% tumour infiltration on reassessment, or bone marrow with tumour infiltration that increases by >2-fold and is >20% tumour infiltration on reassessment. The published international guidelines to evaluate response in the bone marrow component will be used at the time of the analysis [55].

9.2 Urinalysis

A Urinalysis test (early morning urine dipstick and/or protein/creatinine ratio) will be performed at screening. For participants receiving bevacizumab, this will be repeated within 24 hours prior to each bevacizumab injection and the start of each cycle of treatment. This will also be repeated at the end of treatment. If there are signs of proteinuria, a sample must be sent for determination of albumin/protein and creatinine in urine, and the albumin or protein/creatinine ratio must be calculated.

9.3 GFR

Estimated GFR should be carried out at screening up to 7 days prior to eligibility assessment in participants with a level of serum creatinine $\geq$ 1.5 ULN for age.

9.4 Haematology and Blood chemistry

Haematology, biochemistry and clotting blood tests must be done at screening and within 72hr prior to cycle 1 dosing. Unless required by the investigator, safety tests will not be repeated at cycle 1, day 1 prior to dosing. Beginning in cycle 2 and continuing for all subsequent cycles, pre-dose activities can be done within 72hr pre-dose. It is recommended that blood counts are monitored weekly for all participants. Additional safety assessments may be done according to institutional standard of care. Laboratory tests and clinical visits as part of standard care can be performed at the participant's local hospital, provided they are conducted on time and the local hospital and trial site have a procedure to receive and review them timely. Patients should be visited in between cycles as per routine practice. These tests must also be performed at end of treatment.

Haematology includes - haemoglobin (Hb), white blood cells (WBC) with differential count, neutrophils, lymphocytes and platelets. Biochemistry includes - sodium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, and ALT or AST. Clotting includes INR and APTT and should only be performed at baseline and when clinically indicated.

9.5 Physical examination / symptom assessment

Performance status will be reported using the Lansky scale for 1-12 year olds and using the Karnofsky scale for older participants. Performance status and physical examination (including blood pressure (BP), heart rate (HR), temperature, oxygen saturation, weight and height) will be performed at screening/baseline and within 24 hours prior to each cycle in all treatment arms. Both examinations will also be performed at the end of treatment visit, and at each follow up visit for 2 years. In patients where bevacizumab infusions become not synchronised with chemotherapy administration, physical examination will also be performed prior to each injection of bevacizumab. A clinical assessment of pupil responses should be conducted before starting each cycle. If there are any concerns about vision or pupil responses during treatment or follow up, a referral to an ophthalmologist should be considered. Patient's weight will be measured at screening, on day 1 of each cycle prior to dosing and at the end of treatment. Body height will be measured at screening, on day 1 of each cycle prior to dosing and at the end of treatment. After end of treatment, weight, and height will be performed at each follow up visit.

Menstrual status (regularity of menstruation) in females of childbearing potential should be assessed at screening, end of treatment and during follow up. For females who are post-menarchal, a urine (preferred) or serum pregnancy test will be done at screening (within 72hr of dosing), prior to each treatment cycle and at end of treatment. If the results are inconclusive, a repeat test must be performed using a urine sample. In addition, a pregnancy test will be done whenever one menstrual cycle is missing during treatment or a potential pregnancy is suspected. Females who become pregnant while on study will be discontinued immediately and the outcome of the pregnancy will be followed. Pregnancy tests may be repeated during study if required by hospital regulations and/or Research Ethics Committees (RECs).

10. SAMPLE COLLECTION

10.1 Tumour tissue

Refer to Section 21 Translational Sub-Study. The evaluation of neuroblastoma related biomarkers will be performed on samples of tumour tissue collected at the time of diagnosis or during frontline therapy and/or at the time of

relapse will be collected. Archival tumour tissue either as paraffin embedded (FFPE), unstained slides or frozen material will be collected.

Where molecular profiling has already been performed, available genomic data on study participants will be imported. For patients participating in other sequencing programs, it is acceptable to share DNA or sequencing data extracted from the tumour samples.

Molecular profiling of tumour is mandatory for study entry; if no tumour or molecular profiling is available this should be discussed with the Coordinating Sponsor and the Chief Investigator/Clinical coordinator **before** study entry.

Participants or their parents will be asked to give consent to retrieve any analyses already performed, any previously stored tumour sample (which could be at different hospitals) and any future samples collected during the course of the study treatment or follow up. Tumour tissue obtained at the time of relapse is especially valuable and should be obtained if ethically and clinically indicated. If a biopsy was performed fresh frozen tissue should be sent for analyses. If this is not possible FFPE tumour tissue blocks or unstained sections of these tumours must be sent for analyses instead. After completion of biomarker studies, any tumour blocks not utilised will be returned to sites where requested. Surplus material, extracted DNA and RNA will be stored at the SIOPEN reference laboratories. Please refer to the BEACON2 Laboratory Manual for further details.

Links to the SIOPEN BioPortal will be established and instrumental to retrieving biological data acquired for a given patient at different time points.

10.2 Blood Samples

Blood samples will be obtained at baseline, pre cycles 2, 4, 6, 9, 12 and EOT for the molecular monitoring analysis. Blood samples for constitutional DNA analyses and bone marrow samples are optional. Samples (excepting those for constitutional DNA analyses) will be taken from all patients.

Table 7 – Sample collection time-points

Sample	Time point			
	Diagnosis	**Relapse**	**Screening**	**Pre cycle 2, 4, 6,9, 12 & EOT**
Tumour Tissue*	X	X		
Blood		X	X	X**
Bone marrow aspirate			X	

*Where no previous sequencing exists

**Pre treatment

11. DOSE MODIFICATIONS

Participants should be carefully monitored for toxicity. All toxicities will be graded according to version 5.0 of the NCI CTCAE. Doses are to be modified based on the most severe toxicity that the participant experiences, related or possibly related to the study treatment between each cycle of treatment. Dose adjustments, delays and discontinuation should be managed according to local guidelines and at the clinician's discretion.

Participants should be assessed for the development of IMP related adverse events prior to **each** administration. The same criteria used at study entry for haematology renal and liver function should be used to start subsequent cycles. Day 1 of the next cycle may be delayed for up to 14 days of toxicity.

Adverse events should be classified according to whether, in the physician's judgement, these are likely to be related to bevacizumab, dinutuximab beta or chemotherapy (irinotecan/topotecan ± temozolomide) toxicity. These should be managed separately.

NOTE: The toxicity profiles of the IMPs are different. They should be considered separately and any necessary treatment modification to one element of the study treatment may not need an adjustment or delay to the other element.

The maximum delay to the administration of chemotherapy due to adverse events is 36 days. The delay may be extended over 36 days only if the participant is showing a good response to the treatment and agreement is obtained from the Coordinating Sponsor.

11.1 Dose modifications for dinutuximab beta

Institutional practice should be followed to manage the specific toxicities.

Table 8 – dose modifications for dinutuximab beta

Adverse Event	Severity/Intensity (CTCAE grade)	Action
Anaphylaxis	≤ Grade 2	Maximise anti-histamines and supportive care; consider reducing to 50% rate if worsening symptoms
	Grade 3	Interrupt infusion and give supportive measures. Resume at 50% rate when resolves to ≤ Grade 2
	Recurrent Grade 3 or any Grade 4	Permanently discontinue dinutuximab beta
Capillary leak syndrome	≤ Grade 2	Decrease infusion to 50%. Resume to 100% if resolves with supportive measures
	Grade 3	Interrupt infusion and give supportive measures. Resume at 50% rate when resolves to ≤ Grade 2
	Recurrent Grade 3 or any Grade 4	Permanently discontinue dinutuximab beta
Fever	If persistently 40ºC despite maximal supportive measures	Pause dinutuximab beta infusion and resume once toxicity has resolved to ≤ Grade 2 fever
Hypotension	≤ Grade 2	Slow infusion to 50% rate. Resume 100% rate once resolves
	≥ Grade 3	If hypotension not responsive to 20 ml/kg fluid challenge then discontinue dinutuximab beta infusion, support blood pressure with IV fluids, and vaso-pressors if necessary. Dinutuximab beta infusion may be restarted at 50% once participant stable without blood pressure support, and then increased to 100% rate if tolerated.
	If participant requires ventilator support	Participant should permanently discontinue dinutuximab beta
Neuropathy	Grade 1	Continue infusion and close observation

	Grade 2	Pause dinutuximab beta. Restart at 50% if resolves to Grade 1 or less. If not resolved within 48 hrs then omit from current cycle. If not resolved to Grade 1 by time next cycle due then permanently discontinue
	≥Grade 3	Permanently discontinue dinutuximab beta Consider high dose systemic steroids / IVIG (Discuss with the coordinating sponsor and CI)
Pain	≥ Grade 3 despite analgesia	Pause dinutuximab beta infusion, resume at 50% rate once pain controlled. Increase to 100% rate as tolerated
Visual acuity or ocular toxicity	Dilated pupils with sluggish responses	Interrupt infusion. Resume at 50% rate once resolves Impaired visual accommodation, correctable with eye glasses does NOT need dose modification, provided that these toxicities are judged to be tolerable by the responsible clinician, as well as the participant and family Accommodation disorders and ophthalmoplegia have been described as common Adverse Events and do not require any dose modifications
	≥ Grade 3	Permanently discontinue dinutuximab beta
Hyponatraemia	≤ Grade 2	Supportive measures. Continue 100% infusion rate
	Grade 3	Continue dinutuximab beta at 100% rate unless symptomatic hyponatraemia in which sodium < 125 mmol/L for more than 48 hours despite corrective measures
	Grade 4 (< 120 mmol/l despite appropriate corrective measures)	Permanently discontinue dinutuximab beta
Dyspnoea	≤ Grade 2: Oxygen supplementation needed to maintain oxygen saturations > 90%	Regular salbutamol +/- epinephrine nebulisers if bronchospasm or stridor. If saturations not maintained then stop dinutuximab beta infusion; restart at 50% rate if symptoms resolve (saturations > 90% in air) and then increased to 100% if tolerated.
	Grade 3	Stop dinutuximab infusion. If symptoms resolve with supportive measures as above, and saturations > 90% in air, then restart dinutuximab beta at 50% and then increase to 100% as tolerated
	Grade 4	Permanently discontinue dinutuximab beta
Cardiac toxicity (including tachycardia, cardiac failure, left ventricular dysfunction	≥ Grade 3	Permanently discontinue dinutuximab beta

and pericardial effusion)		
GI symptoms (diarrhoea / vomiting)	Grade 4	Pause dinutuximab beta infusion, restart infusion when symptoms settle
Infection	In the case of any ≥ Grade 3 infection occurring during dinutuximab beta infusion	Dinutuximab beta should be omitted until infection is controlled. In the case of uncomplicated bacteraemia or febrile neutropenia in clinically stable children it may then be restarted, but for any other ≥ Grade 3 infections it should be aborted until the next cycle. Temperature alone, in the absence of other signs of infection, should not be considered a reason to stop dinutuximab beta

11.2 Dose modifications for bevacizumab

Bevacizumab takes 4 – 6 weeks to achieve steady state levels. Any treatment delay will require steady state levels to be re-established. Bevacizumab administration should be delayed if any of the side effects, outlined below, has been observed. Once a participant has met the re-treatment criteria (refer to section 7.5 and section 8.5), bevacizumab administration should recommence. Regardless of the reason for the delay in bevacizumab, participants must discontinue bevacizumab when the administration of bevacizumab had to be interrupted for more than 6 weeks.

Table 9 - Toxicities requiring bevacizumab dose delay

Adverse Event	Severity/Intensity (CTCAE grade)	Bevucizumab Action
Infusion-related Reaction/Infusional Site Extravasation	Grade ≤4	Infusion and allergic reactions should be managed by local standards. Bevacizumab must be delayed or discontinued in the case of any reactions of Grade 4
Hypertension	Grade 2-3	Guidelines to age-specific percentiles of blood pressure can be accessed at http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf Delay bevacizumab administration Initiate anti-hypertensive therapy Resume bevacizumab once systolic and/or diastolic BP for age and sex is below the 95th percentile

	Grade 4	Discontinue bevacizumab
Wound healing complications	Any grade	**Delay bevacizumab** until the wound has satisfactorily healed
Proteinuria	Grade 2-3	**Delay bevacizumab** until recovery to grade 1
	Grade 4	Discontinue bevacizumab
Venous thrombosis/embolism (including vascular access device)	Grade 3	Delay bevacizumab Bevacizumab may be resumed once the participant has been fully anticoagulated and if the participant has not experienced a Grade 3 or 4 haemorrhagic event Low-molecular-weight heparin should be prescribed and the treatment monitored in compliance with the approved product labelling or according to local clinical practice guidelines Similarly, for participants on a coumarin derivative or unfractionated heparin, the INR and APPT, respectively, should be within therapeutic range. **Permanently discontinue bevacizumab** if the VTE worsens or recurs after resuming therapy
Any other clinically significant (CTCAE Grade 3/4) AEs that, according to the physician's discretion, are not clearly associated with chemotherapy and could be related to Bevacizumab	Grade 3 or 4	**Delay bevacizumab** until recovery to grade 1 or resolution

Permanently discontinue bevacizumab for any of the following toxicities:

Left ventricular systolic dysfunction	Grade 3 or 4
Heart failure	Any grade
Gastrointestinal (GI) perforation	Any grade
Tracheo-oesophageal fistula	Any grade
Any non−tracheo-oesophageal fistula	Grade 4
Recto-vaginal fistulae	Grade 3-5
Proctalgia	Grade 3-4
Haemorrhage: Non-pulmonary or non-CNS	Grade 3-4

Haemorrhage: Pulmonary or CNS	Grade 2/3/4
Posterior reversible encephalopathy syndrome (PRES)	Any grade
Venous thrombosis/embolism	Grade 4
Any arterial thrombosis/embolism	Any grade
Myocardial infarction	Any grade
Cerebrovascular ischemia	Transient ischaemic attacks (TIAs), Cerebrovascular accidents (stroke)
Osteonecrosis	Any grade
Eye disorders	Grade 4
Necrotising fasciitis	Any grade
Weight decrease	Grade 3

11.3 Chemotherapy dose modifications

The following dose modifications are provided as recommendations. In case an alternative management strategy is thought to be beneficial for the participant, the case will be discussed with the Coordinating Sponsor.

Note: All platelets cut-off values require no platelet transfusions within 72 hours of starting the cycle. For those participants with known bone marrow involvement, the cut-off values required are ANC ≥0.5 x10^9/L and platelets ≥50 x10^9/L.

Table 10 – Dose levels for dose adjustments

Drug	Starting dose	Reduction 20% Dose level – 1	Reduction 40% Dose level – 2
Temozolomide	100mg/m^2/d for 5 days every 3 weeks	80 mg/m^2/d for 5 days every 3 weeks	60 mg/m^2/d for 5 days every 3 weeks

Irinotecan	50mg/m^2/d for 5 days every 3 weeks	40 mg/m^2/d for 5 days every 3 weeks	30 mg/m^2/d for 5 days every 3 weeks

*If not recovered 15 days after expected date of start (i.e. day 36 after start of cycle), refer to Coordinating Sponsor to discuss individual case

Table 11 – Dose modifications for toxicity

	Bevacizumab	Dinutuximab beta	Irinotecan	Temozolomide
ANC < 0.5 x 10^9/L or Platelet count < 50 x10^9/L But recovered on day 21 after the start of a cycle	No dose reduction	No dose reduction	No dose reduction	No dose reduction
ANC < 0.5 x 10^9/L or Platelet count < 50 x10^9/L But recovered between day 22 to 28 after the start of a cycle	No dose reduction	No dose reduction	No dose reduction	2nd occurrence: Decrease to dose level -1
ANC < 0.5 x 10^9/L or Platelet count < 50 x10^9/L But recovered between day 29 to 35 after the start of a cycle	No dose reduction	No dose reduction	1st occurrence: Decrease to dose level -1 2nd occurrence: Decrease to dose level -2	1st occurrence: Decrease to dose level -1 2nd occurrence: Decrease to dose level -2
ANC < 0.5 x 10^9/L or Platelet count < 50 x10^9/L On day 36 after the start of the cycle	No dose reduction	No dose reduction	Consider discontinuation of study treatment*	Consider discontinuation of study treatment*
Elevated ALT, AST, ALP, Bilirubin Grade 2	No dose reduction	No dose modification	No dose modification	No dose modification

Elevated ALT, AST, ALP, Bilirubin Grade 3 that recovers to grade ≤2 before day 35	No dose reduction	No dose modification	No dose modification	No dose modification
Elevated ALT, AST, ALP, Bilirubin Grade 3 not recovered to grade ≤2 before day 35	No dose reduction	No dose modification	2nd occurrence: Discontinue study treatment	1st occurrence: Decrease to dose level -1 2nd occurrence: Discontinue study treatment
Elevated ALT, AST, ALP, GGT, Bilirubin Grade 4	No dose reduction	Reduce to 50% for cycle; can be increased to 100% for subsequent cycles providing improved to Grade 2	2nd occurrence: Discontinue study treatment	1st occurrence: Decrease to dose level -1 2nd occurrence: Discontinue study treatment
Diarrhoea > 3 days despite maximum Loperamide therapy Grade 3 or 4	No dose reduction	For Grade 3 no reduction; For Grade 4, pause Dinutuximab beta infusion, restart infusion when symptoms settle.	1st occurrence: Decrease to dose level -1. 2nd occurrence: Contact Coordinating Sponsor and consider switch to Topotecan.	No dose reduction

11.3.1 Topotecan

In instances of severe irinotecan-related toxicity, topotecan may be substituted for irinotecan.

The dose of topotecan will be 0.75mg/m^2/day. Topotecan will be given intravenously over 30mins on Days 1-5, at least one hour following the administration of temozolomide. The administered dose of chemotherapy may be rounded up or down to the nearest dose that can be accurately measured.

Table 12 – Treatment Administration Summary per arm using Topotecan as a Substitute for Irinotecan

	Day 1	Day 2-5	Day 6-7	Day 22
Treatment duration: 12 cycles = 36 weeks, response assessed every 3 cycles				
Arm A: dbToT	Dinutuximab beta 10mg/m^2/day iv Topotecan 0.75mg/m^2 iv Temozolomide 100mg/m^2 po	Dinutuximab beta 10mg/m^2/day iv Topotecan 0.75mg/m^2 iv Temozolomide 100mg/m^2 po	Dinutuximab beta 10mg/m^2/day iv	Day 1 of next cycle starts
Arm B: BToT	Bevacizumab 15mg/kg iv Topotecan 0.75mg/m^2 iv Temozolomide 100mg/m^2 po	Topotecan 0.75mg/m^2 iv Temozolomide 100mg/m^2 po		Day 1 of next cycle starts
Arm C: dbBToT	Dinutuximab beta 10mg/m^2/day iv Bevacizumab 15mg/kg iv Topotecan 0.75mg/m^2 iv Temozolomide 100mg/m^2 po	Dinutuximab beta 10mg/m^2/day iv Topotecan 0.75mg/m^2 iv Temozolomide 100mg/m^2 po	Dinutuximab beta 10mg/m/day iv	Day 1 of next cycle starts

12. SUPPORTIVE TREATMENT

12.1 Supportive Care

Supportive care should be given according to local institutional guidelines. The below guidance is recommended.

12.1.1 Irinotecan-related diarrhoea

Irinotecan-related diarrhoea should be managed as per local guidelines. The use of cefixime (in the absence of any contraindications), atropine (for early onset) or loperamide (for delayed onset diarrhoea) are highly recommended.

12.1.2 Nausea and Vomiting

Anti-emetics may be used, at the investigator's discretion, for the prevention and/or treatment of nausea and vomiting. Local anti-emetic policies for chemotherapy should be followed, when necessary.

12.1.3 Growth Factors

Prophylactic and therapeutic usage of G-CSF should be at the discretion of the treating physician on an individual case basis. For patients in Tier 2, prophylactic use of G-CSF is not allowed during cycle 1.

12.1.4 Fever and neutropenia

Antibiotics should be administered on the basis of institutional policy.

12.1.5 Blood products

Therapeutic use of blood products will be permitted. A platelet count of 50 is required to start each cycle of chemotherapy, therefore platelet infusion can occur where clinically indicated.

12.1.6 Pneumocystis jirovecii pneumonia (PJP) prophylaxis

PJP prophylaxis is highly recommended for participants receiving temozolomide. Drugs and schedules for PJP prophylaxis should be according to institutional policies.

12.2 Pain management

It is anticipated that patients receiving dinutuximab beta by the continuous infusion schedule will be able to be managed largely on an outpatient patient basis, with oral opioid or non-opioid medication providing adequate pain control. However, since neuropathic pain is an anticipated side effect even in a prolonged continuous infusion setting, all patients should receive premedication with gabapentin from at least 3 days prior to the start of the dinutuximab beta, as well as intravenous morphine prior to and during antibody infusions as required.

Concomitant standard pain management should be established with or without IV opioid analgesia and should follow standard WHO guidelines including medications as follows:

12.2.1 Gabapentin

- Prior to receiving dinutuximab beta, the patient should be primed with oral gabapentin, starting 3 days prior to the start of the dinutuximab beta infusion.
- The recommended oral dose of gabapentin is 10 mg/kg/dose once daily on day 1, increasing to 10 mg/kg/dose twice daily on day 2 and 10 mg/kg three times a day thereafter.
- Gabapentin may either be stopped at the end of each continuous antibody infusion (and restarted 3 days prior to subsequent cycle) or continued throughout cycles and stopped after the end of the last infusion, according to local guidelines.
- Maximum single dose for Gabapentin as per institutional guidelines.

12.2.2 Intravenous morphine

- An intravenous opioid (e.g. morphine infusion 0.03 mg/kg/hr or equivalent) should be commenced 1-2 hour prior to starting the first dinutuximab beta infusion (Cycle 1). Thereafter, it is recommended to administer a continuous morphine (or alternative intravenous opioid at equivalent dose) infusion rate of up to 0.03 mg/kg/hour on the first day, with additional boluses as required (in accordance with local guidelines).
- Ideally intravenous morphine can be weaned off on a daily basis over the first 5 days (e.g. to 0.02 mg/kg/hour to 0.01 mg/kg/h to 0.005 mg/kg/hour).
- Boluses can then be given as required either self-administered or nurse administered at 0.02 mg/kg/dose. If continuous opioid is required for more than 5 days then the dose should be weaned at the end of treatment by 20% each day. It is expected that the IV opioid can be rapidly tapered off, depending on the individual patient's pain tolerance.
- Subsequent cycles may be started with intravenous morphine as above, depending on the amount of opioid required in the previous cycle, until a safe and well tolerated out-patient pain management regime is in place for the individual patient.

12.2.3 Oral and transdermal opioids: e.g. oral morphine

- Can be administered at a dose of 0.2 - 0.4 mg/kg every 4-6 hours. It is not advised to use long acting morphine in this situation as it takes 48 hours to stabilise the dose and probably is not useful. Oral tramadol may be considered once oral morphine is sufficient at lower doses to control pain satisfactorily. Alternatively transdermal application of fentanyl patches may be used in centres where fentanyl patches are regularly used for pain control. The equivalent transdermal fentanyl dose rate in µg/hr will be calculated from the current use of IV morphine according to the manufacturer's guidelines. This allows for pain management during continuous infusion of dinutuximab beta in an outpatient setting.

12.2.4 Non-steroidal anti-inflammatory drugs (NSAIDs)

- Used as per local guidelines, dosing and availability as a fixed regimen during antibody treatment.
- Paracetamol
  - Recommended dosages as per institutional guidelines.
- Ibuprofen
  - This is the most widely used NSAID in paediatrics. It is approved from age 6 months onwards and has a longer duration of action (6-8 hours). Recommended dosages as per institutional guidelines. Ibuprofen should be used according to local clinical practice. Caution must be taken if platelet count < 50 x 10^9/L due to increased risk of bleeding.
- Metamizole
  - Because of its spasmolytic properties metamizole is particularly suitable for visceral pain or colicky pain. More useful than repeated short infusions, is a long-term infusion with a dosage of 2.5 to 3.0 mg/kg/h, always with close monitoring of blood pressure values. Metamizole is approved for use from the age of three months onwards. A risk assessment for agranulocytosis in children receiving metamizole therapy is not possible at present.
  - Recommended dosage of Metamizole: 10 mg/kg PO every 6 hours as needed or long-term infusion with a dosage of 2.5 to 3.0 mg/kg/h. However, in some European countries, the use of Metamizole is not permitted in paediatric patients and this national guidance needs to be respected.
- Other NSAIDs, e.g. Indomethacin or Ketoralac
  - May be used as per institutional guidelines, as an alternative to ibuprofen if fever not controlled.

12.2.5 Hyoscine-butyl-bromide or hyoscyamine

- May be used for children for abdominal pain not responding to morphine, as per institutional guidelines.

13. CONCOMITANT MEDICATION

Participants must be instructed not to take any additional medications, including over-the-counter (OTC) products and herbal remedies, during the study without prior consultation with their doctor (local PI).

No chemotherapy, hormonal anticancer therapy, or experimental anticancer medications other than those that are study-related will be permitted while the participant is receiving study treatment.

Caution must be taken for participants receiving bevacizumab if intravenous bisphosphonates are given simultaneously or sequentially.

Due to their immunosuppressive activity, concomitant treatment with corticosteroids is not recommended within 2 weeks prior to the first treatment course until 1 week after the last treatment course with dinutuximab beta, except for life-threatening conditions.

Concomitant use of intravenous immunoglobulins is not recommended as they may interfere with dinutuximab beta-dependent cellular cytotoxicity.

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, apalutamide) of CYP3A4 may alter the metabolism of irinotecan and should be avoided.

Treatment-related adverse events related to concomitant medication should be treated according to local practice.

Palliative radiotherapy to non-target lesions present at trial entry, or symptomatic target lesions in participants that have other target lesions that allow evaluation of response will be permitted.

Immunisation with live vaccine will not be permitted. All vaccinations (including influenza and covid-19) should be avoided during administration of dinutuximab beta until 10 weeks after the last treatment course, due to immune stimulation through dinutuximab beta and possible risk for rare neurological toxicities. Live vaccines, in addition to prohibition during conduct of the study, must be prohibited for three months after the last dose of chemotherapy.

14. CONTRACEPTION

Females of childbearing potential who are sexually active with a non-sterilised male partner and non-sterilised male participants with a partner of childbearing potential must use at least one highly effective method of contraception (see Table 13) for 6 months after the last dose of Investigational Medicinal Product plus a barrier method of contraception, e.g. condom. Not engaging in sexual activity for the total duration of the drug treatment is acceptable; however, periodic abstinence, the rhythm method and the withdrawal method are not acceptable.

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

It is advised that sperm or egg preservation should be offered prior to treatment with temozolomide and bevacizumab respectively as per standard practice to patients at risk of irreversible infertility, where appropriate.

Male participants should refrain from sperm donation for 6 months after receiving the last dose of study treatment.

Table 13 – Highly Effective Methods of Contraception* (<1% Failure Rate)

Highly Effective Contraception Methods*	Contraceptive measures Not Considered Highly Effective
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]	Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
Progestogen-only hormonal contraception associated with inhibition of ovulation[1]	Male or female condom with or without spermicide[5]
Intrauterine device[2]	Cap, diaphragm, or sponge with spermicide[5]
Intrauterine hormone-releasing system[2]	
Bilateral tubal occlusion[2]	
Vasectomised partner[2,3]	
Sexual abstinence[4]	

* Highly effective methods of contraception, is defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

1. Hormonal contraception may be susceptible to interaction with the Investigational Medicinal Product, which may reduce the efficacy of the contraception method.

2. Contraception methods that in the context of this guidance are considered to have low user dependency.

3. Vasectomised partner is a highly effective birth control method, provided that the partner is the sole sexual partner of the woman considered to be of childbearing potential and that the vasectomised partner has received medical assessment of the surgical success.

4. In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

5. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are not considered acceptable birth control methods in this clinical trial.

15. TREATMENT COMPLIANCE

Dinutuximab beta, bevacizumab, irinotecan and topotecan will be administered intravenously and temozolomide will be given orally. Information regarding the dates for all drugs and doses of treatment administered will be recorded in the participant's medical records. Sites should complete the Home Drug Administration Discussion

Checklist, to document the discussion between site and patient/caregiver, regarding the safe and effective administration of oral Temozolomide at home.

Participants and/or parents must be instructed to return any unused capsules or oral suspension of temozolomide if dispensed for home use and the amount of remaining returned IMP will be recorded. Sites should follow their local practice for destruction of unused capsules and oral suspension. For more information regarding accountability procedures for the supply and administration of medicinal products to participants, please refer to the Pharmacy Manual. Copies of master drug accountability logs will be requested by the Trial Office for central monitoring every 6 months.

16. PARTICIPANT FOLLOW UP

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

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.

Laboratory tests and safety assessments as part of standard care can be performed at the participant's local hospital at follow up time-points, provided they are conducted on time and the local hospital has a procedure to

receive and review them in a timely manner. It is the Investigator's responsibility to ensure he/she receives and reviews the results. The results must be recorded on the CRF as required, and the reports from the other hospitals must be available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used. It is the Principal Investigator's responsibility at each site to obtain these.

Additional follow up visits will be scheduled as needed, to monitor any sustained unresolved, treatment emergent adverse events.

In the event of progression/relapse, the type of progression/relapse will be recorded (local/metastatic/combined) as well as all treatment that is started after trial participation.

17. TRIAL TREATMENT DISCONTINUATION AND PARTICIPANT WITHDRAWAL

17.1 Treatment Discontinuation

Participants should discontinue trial treatment in the following circumstances:

- In the event of progression (as per INRC 2017)
- In the event of unacceptable toxicity (see section 11)
- At the request of the participant (see section 17.2 Participant Withdrawal)

In the event of a female participant becoming pregnant (see section 1.2.4.2 and section 18.1.6)A Treatment Discontinuation Form should be completed to document the reason for treatment discontinuation. Follow up visits continue as scheduled, unless the participant withdraws from data collection (see section 17.2).

17.2 Participant Withdrawal

Participants may withdraw from study treatment at any time at their own request or at the request of their parents (if participant under 16 years of age), or they may stop study treatment at any time at the discretion of the treating Investigator or CI for safety, behavioural, or administrative reasons. If a participant does not return for a scheduled visit, every effort should be made to contact the participant. In any circumstance, every effort should be made to document participant outcome where possible.

The Investigator should:

- Enquire about the reason for withdrawal
- Request the participant return for a final visit, if applicable
- Follow up with the participant regarding any unresolved adverse events
- Perform a physical exam on the participant (including height, weight, oxygen saturation and blood pressure/pulse)
- Arrange for a tumour assessment and all safety labs (full blood count and biochemistry) to be collected

Participants who withdraw from trial treatment will continue to be followed up as per the protocol for at least 5 years after registration.

Participants/parents/legal guardians may withdraw consent at any time during the trial. The details of the withdrawal should be clearly documented and communicated to the BEACON2 Trial Office.

There are three types of withdrawal as detailed below:

- Participant or their parent(s)/legal guardian would like to withdraw the participant from the trial, but is willing for the participant to be followed-up according to the trial schedule (follow-up data can be collected and used in the trial analysis)
- Participant or their parent(s)/legal guardian does not wish for the participant to attend trial follow-up visits but is willing for the participant to be followed-up at standard clinic visits (follow-up data can be collected at standard clinic visits and used in the trial analysis)
- Participant or their parent(s)/legal guardian is not willing for the participant to be followed up for trial purposes at any further visits (any data collected prior to the withdrawal of consent will be used in the trial analysis)

The following should be clearly documented in the medical notes:

- The date the participant or their parent(s)/legal guardian withdraw consent
- The reason, if given
- Type of withdrawal

If a participant withdraws from the trial, please complete and return a Treatment Discontinuation Form and a Withdrawal of Consent Form if applicable.

18. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 7. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the participant (this should be documented in the source data) with reference to the Summary of Product Characteristics or Investigator Brochure as appropriate.

18.1 Reporting Requirements

18.1.1 Tier 1 Adverse Events

AEs (see Appendix 7 - Definition of Adverse Events for definition) are commonly encountered in participants receiving adjuvant chemotherapy. As the safety profiles of the Investigational Medicinal Products used in this trial are well characterised, only Grade 3 and Grade 4 (by CTCAE v5.0) AEs experienced during treatment will be reported.

An abnormal laboratory value should only be reported if it:

- Results in participant early discontinuation from the study treatment

- Requires treatment, modification or interruption of dose, or any other therapeutic intervention (including blood product transfusion), or is judged to be of significant clinical importance

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded.

18.1.2 Tier 2 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 7 - Definition of Adverse Events for definition) should be reported. Please note this includes abnormal laboratory findings.

18.1.3 Serious Adverse Advents

Investigators should report AEs that meet the definition of an SAE (see Appendix 7 - Definition of Adverse Events for definition) and are not excluded from the reporting process as described below.

18.1.4 Events That Do Not Require Reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form.

Hospitalisations for:

- Protocol defined treatment
- Pre-planned elective procedures unless the condition worsens
- Treatment for progression of the participant's cancer
- Progression or death as a result of the participant's cancer, as this information is captured elsewhere on the Case Report Form
- Events that do not require expedited (immediate) reporting which will be reported on an Expected Serious Adverse Reaction Form

18.1.5 Expected Serious Adverse Reactions

Participants receiving adjuvant chemotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment. For this reason the following SAEs do not require expedited (immediate) reporting by site and are not regarded as unexpected for the purpose of this trial:

- Admissions to control nausea and vomiting unless the condition is life threatening or proves fatal
- Admissions for supportive treatment (i.e. transfusions or blood products for anaemia/ thrombocytopenia/severe infections, management of diarrhoea, stoma site (line) infections) during an episode of myelosuppression, unless this proves fatal or requires admission to a high dependency or intensive care facility
- Uncomplicated febrile neutropenia
- Admission for transfusion or allergic reaction that resolves within 24h (unless the condition is life threatening or proves fatal)

- Prolongation of inpatient hospitalisation due to fever related to dinutuximab beta (unless the condition is life threatening or proves fatal)

An Expected Serious Adverse Reaction Form can be completed for these specific events instead of a Serious Adverse Event Form. However, if there is any doubt over whether an event meets the relevant definition above, a Serious Adverse Event Form should be completed.

18.1.6 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of participants in order to provide SAE data on congenital anomalies or birth defects.

If a female participant becomes pregnant during the course of the trial, trial treatment should be discontinued immediately.

In the event that a participant or their partner becomes pregnant during the course of the trial and for six months after last dose of study drug, please complete a Pregnancy Notification Form (providing the participant's details) and return to the Trials Office as soon as possible. If it is the participant who is pregnant, provide outcome data on a follow-up Pregnancy Notification Form. Where the participant's partner is pregnant consent must first be obtained and the participant should be given a pregnancy release of information form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy, they should sign the pregnancy release of information form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

18.1.7 Post-trial Suspected Unexpected Serious Adverse Reactions

Serious Adverse Events that are judged to be at least possibly related to the Investigational Medicinal Product and are unexpected must still be reported in an expedited manner irrespective of how long after Investigational Medicinal Product administration the reaction occurred.

18.1.8 Overdose

An overdose is defined as a subject receiving a dose of Investigational Medicinal Product(s) in excess of 20% of the planned trial treatment within the current cycle.

Any overdose with or without associated Adverse Events/Serious Adverse Events, is required to be reported within 24hours of first knowledge of the event to the Trial Office.

If the overdose results in an Adverse Event, this must also be recorded on an Adverse Event Form.

18.1.9 Medication Error

A medication error is an unintended failure or mistake in the treatment of a participant that either causes harm or has the potential to cause harm.

A medication error is a human or process related failure while the drug is under control of the trial site staff or participant.

Examples of events to be reported as medication errors include:

- Dispensing error e.g., medication prepared incorrectly
- Drug not administered or taken as indicated, e.g., wrong site of administration, tablet crushed instead of taken whole
- Wrong participant received the medication
- Wrong drug administered to participant

Examples of events that **do not** require reporting as medication errors include:

- Participant accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as an Adverse Event, but an Adverse Event may occur as a consequence of the medication error.

Any medication error with or without associated Adverse Event/Serious Adverse Event is required to be reported within 24hours of first knowledge of the event to the Trial Office.

If the medication error results in an Adverse Event, this must also be recorded on an Adverse Event Form.

18.2 Reporting period

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last trial treatment.

SAEs that are judged to be at least possibly related to the IMPs must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

18.3 Reporting Procedure

18.3.1 Site

Adverse Events

For more detailed instructions on Adverse Event reporting refer to the Adverse Event Form Completion Guidelines contained in section 6 of the Investigator Site File

Adverse Events (as defined in Appendix 7) should be reported on an Adverse Event Form and where applicable on a Serious Adverse Event Form. Serious adverse events which have been identified in the protocol as not requiring immediate reporting (i.e. events listed in section 18.1.4) should be recorded on the Adverse Event Form instead. An Adverse Event Form should be completed at each cycle. AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (see Appendix 8 - Common Toxicity Criteria Gradings). Any AEs

experienced by the participant but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

Serious Adverse Events

For more detailed instructions on Serious Adverse Event reporting refer to the Serious Adverse Event Form Completion Guidelines contained in section 5 of the Investigator Site File.

Adverse Events defined as serious and that require reporting as a Serious Adverse Event (excluding events listed in section 18.1.4) should be reported on a Serious Adverse Event Form. When completing the form, the Investigator will be asked to define the causality and the severity of the Adverse Event which should be documented using the Common Terminology Criteria for Adverse Events version 5.0.

The form should be emailed to the Trial Office as soon as possible and no later than 24 hours after first becoming aware of the event.

Email Serious Adverse Event Form to:

Reg@trials.bham.ac.uk
CC to beacon2@trials.bham.ac.uk
Include "BEACON2 SAE" in the subject line

On receipt the Trial Office will allocate each Serious Adverse Event a unique reference number. The site will be informed of the Serious Adverse Event reference number in an email acknowledging receipt of the event. If confirmation of receipt is not received within 1 working day please contact the Trial Office. The Serious Adverse Event reference number should be quoted on all correspondence and follow-up reports regarding the Serious Adverse Event. The email from the Trial Office acknowledging receipt should be filed with the Serious Adverse Event Form in the Investigator Site File.

For Serious Adverse Event Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trial Office and a copy kept in the Investigator Site File.

Investigators should also report Serious Adverse Events to their own Trust in accordance with local practice.

Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

18.3.2 BEACON2 Trials Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Summary of Product Characteristics, or Investigator Brochure as applicable) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

18.3.3 Reporting to the Competent Authority and main Research Ethics Committee

Suspected Unexpected Serious Adverse Reactions

Individual events categorised as SUSARs will be reported to the EudraVigilance Clinical Trial Module (EVCTM) and to each non-EU country as required. Events will be reported in accordance within the regulatory specified time frame:

- Fatal or life threatening SUSARs within a maximum of 7 days with a detailed follow-up report within an additional 8 days
- All other SUSARs within a maximum of 15 days

Serious Adverse Reactions

The UK Coordinating Centre will produce a Development Safety Update Report (including Serious Adverse Reactions and Suspected Unexpected Serious Adverse Events) annually from the date of the first Clinical Trial Authorisation received for the trial in any country until the submission of the End of Trial Declaration. The National Coordinating Centres will be provided with a copy of this report and where contractually required to do so, will report to the relevant Competent Authority and Research Ethics Committee.

Adverse Events

Details of all Adverse Events will be reported to the Competent Authority on request.

Other safety issues identified during the course of the trial

The Competent Authority and Research Ethics Committee(s) will be notified immediately if a significant safety issue is identified during the course of the trial.

18.3.4 Investigators

Details of all Suspected Unexpected Serious Adverse Events and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

18.3.5 Data Monitoring Committee

The independent Data Monitoring Committee will review all Serious Adverse Events.

18.3.6 Manufacturer of Investigational Medicinal Product

All Serious Adverse Events will be reported to Recordati Rare Diseases Recordati Group as manufacturer of the dinutuximab beta by the Coordinating Sponsor within 7 days by email.

19. CENTRAL REVIEW PROCESSES

As an additional measure of quality control, at least one independent blinded radiologist and at least one nuclear medicine physician will review all CT, MRI, MIBG and PET/CT scans at baseline and at tumour assessment time-points (Post cycle 2, 4, 6, 9 12 and EOT), for all participants. Further details to be provided by the Trial Office.

20. QUALITY OF LIFE STUDY

20.1 Purpose of Quality of Life

HRQOL is a multi-dimensional concept commonly used to examine the impact of health status on quality of life. There is an increasing recognition in oncology of the importance of improving patients' QOL throughout the disease course *[56, 57]*. Studies conducted with paediatric population suggest that HRQOL in children during cancer therapy is significantly lower than in the healthy population *[58, 59]*. Also, association between intensity of treatment and child-reported HRQOL has been assessed: high-risk children reported poorer QOL than children with a low or moderate risk *[60]*. Therefore, there is a growing acclaim in paediatric cancer research of the importance of improving patients' QOL throughout the new therapies *[61]*. Key aspects of the HRQOL in paediatric oncology include the child's physical (physical functioning, symptoms), psychological (body image, self-esteem, distress, behavioural problems, cognitive functioning), and social health (interpersonal relationships, social functioning, and general health perceptions *[62]*. Parents and patient's family members are also affected by the cancer diagnosis and treatment and may also be instrumental in the management of the disease *[63-65]*. Hence, optimal assessment of how children's health affects their families is of both clinical and research importance.

As most of these aspects are subjective, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recommended the use of patient-reported outcome (PRO) measures to support labelling claims in oncology *[66, 67]*. In addition, paediatric HRQOL measurement instruments must be sensitive to cognitive development and integrate both child self-report and parent/guardian proxy-report to reflect their potentially unique perspectives. With this goal in mind, in this study, HRQOL is evaluated as a secondary objective to determine the impact of each treatment arm in patient's and family's QOL.

20.2 Questionnaires

HRQOL will be assessed with the Pediatric Quality of Life Inventory (PedsQL) 3.0 Cancer Module *[68]* and with the PedsQL Family Impact Module *[69]*.

The PedsQL 3.0 Cancer Module is a modular instrument designed to measure pediatric cancer specific HRQOL in children, adolescents,young people and adults. The PedsQL 3.0 Cancer Module has been translated in over 49 languages according to a standardized translation procedure.

The questionnaires comprise parallel child self-report and parent proxy-report formats. Child self-report includes ages 5–7 years (young child), ages 8–12 years (child), ages 13–18 years (adolescent), ages 18-25 (young people) and 26+ years (adults). Parent proxy-report includes ages 2–4 years (toddler), 5–7 years (young child), 8–12 years

(child), and 13–18 years (adolescent). The parent proxy-report forms are designed to assess the parent's/guardian's perceptions of their child's HRQOL. The items for each of the forms are essentially the same, differing in developmentally proper language, and first or third person tense. The 27-item multidimensional PedsQL 3.0 Cancer Module encompasses 8 scales: 1) pain and hurt (2 items), 2) nausea (5 items), 3) procedural anxiety (3 items), 4) treatment anxiety (3 items), 5) worry (3 items), 6) cognitive problems (5 items), 7) perceived physical appearance (3 items), and 8) communication (3 items).

The instructions ask how much of a problem each item has been during the past 1 month. A 5-point Likert response scale is utilized across child self-report for ages 8–18+ years and parent proxy-report (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). To further increase the ease of use for the young child self-report (ages 5–7 years), the Likert scale is reworded and simplified to a 3-point scale (0 = not at all a problem; 2 = sometimes a problem; 4 = a lot of a problem), with each response choice anchored to a happy to sad faces scale. Parent proxy-report also includes the toddler age range (ages 2–4 years), which does not include a self-report form given developmental limitations on self-report for children younger than 5 years of age and includes only 3 items for the school functioning scale.

Items are reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher PedsQL 3.0 scores indicate better HRQOL. Scale scores are computed as the sum of the items divided by the number of items answered. If more than 50% of the items in the scale are missing, the scale score is not computed.

The PedsQL Family Impact Module *[69]* was designed to measure the impact of pediatric chronic health conditions on parents and the family. Despite it is not specific to evaluate QOL in parents of children and AYA with cancer, the questionnaire has demonstrated reliability and validity in families with children with complex chronic health conditions. Implemented as a complement to the PedsQL Cancer Module, the PedsQL Family Impact Module gives a quantitative indicator of the parent's self-reported HRQOL and family functioning as a result of their child's cancer disease. The PedsQL Family Impact Module has been translated in over 20 languages according to a standardized translation procedure.

The PedsQL Family Impact Module measures parent/guardian self-reported physical, emotional, social, and cognitive functioning, communication, and worry. The 36-item PedsQL Family Impact Module Scales encompass 6 scales measuring parent self-reported functioning: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items), 5) Communication (3 items), 6) Worry (5 items), and 2 scales measuring parent/guardian reported family functioning; 7) Daily Activities (3 items) and 8) Family Relationships (5 items).

The scale has five response options, 'never', 'almost never', 'sometimes', 'often' and 'almost always' (corresponding to scores of 100, 75, 50, 25 and 0). Regarding the interpretation of the scale, higher scores indicate better functioning (less negative impact). The PedsQL Family Impact Module Total Scale Score is calculated as the sum of the 36 item scores divided by the number of items answered. If more than 50% of the items in the scale are missing, the scale score is not computed.

20.3 Target Accrual

HRQOL questionnaires will be performed in all trial participants.

20.4 Time Points and Procedure

Questionnaires will be filled at baseline (within 7 days before treatment initiation), at assessment time-points (cycles 2, 4, 6) and at EOT visit (21 days after cycle 12 dose or last dose given), according to Table 1 - Schedule of Events. HRQOL data must be collected regardless of the participant's progression status and treatment completion.

Sites will be provided with a supply of the HRQOL questionnaires at site initiation. Questionnaires must be filled out on paper at the hospital when patients come for the scheduled visit according to the "PedsQL™ Administration Guidelines" (see Appendix 9 – PedsQL™ Administration Guidelines). The questionnaire will be handed out to the patients by the investigator or a study nurse before seeing the doctor for clinical evaluations. Patients should complete the questionnaires by themselves in their own language during the visit as completely and accurately as possible. It is recommended that a key person at each centre should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

Data will be entered onto the eCRF database.

21. TRANSLATIONAL SUB-STUDY/ BIOLOGICAL STUDIES

21.1 Purpose of Translational Sub-study

In relapsed neuroblastoma, biological studies of the primary tumour, metastatic sites and liquid biopsies for analysis of prognostic and especially predictive biomarkers are of utmost importance. These studies require rigorous sample collections, according to well-defined standard operating procedures (SOPs).

- Genome and expression profile of DNA and RNA isolated from tumour at relapse whenever possible; constitutional DNA will be required for genomic studies.

21.1.1 Primary tumour tissue

Samples of tumour tissue collected at the time of diagnosis, during frontline therapy and/or at the time of relapse (where possible) will be collected for genome and expression profile of DNA and RNA. **This sample is mandatory for study entry; if no tumour or subsequent molecular profiling is available this will be discussed with the Coordinating Sponsor and the Chief Investigator before study entry.**

Whenever possible, analysis of tumour tissue of the primary tumour, or a metastatic site, obtained at relapse, should be performed: following tissue sampling both frozen tumour tissue and formalin fixed paraffin embedded tumour tissue are to be collected at diagnosis according to local SOPs and processes.

In situations where no tumour tissue can be obtained (due to the clinical situation of the patient, or sampling difficulties, or because no primary was identified) the following analyses may be done on a representative metastatic sample (invaded bone marrow, invaded lymph node), possibly following enrichment techniques. If neither a primary tumour nor a metastatic site can be obtained at relapse, a blood sample for analysis of circulating tumour DNA should be obtained at study entry and at all protocol-defined timepoints.

The following investigations will be performed for all patients on tumour tissue:

Genetic analyses:

- MYCN copy number status (clinical decision making at diagnosis)

The following genetic analyses are highly recommended:

- Whole exome or whole genome sequencing (> 100 x) of paired tumour and germline material should be performed for calling of SNVs/mutations, structural variations, and overall copy number profile and indels. RNAseq should be performed for expression profiling. Results should be analysed and reviewed by a molecular biologist, with a report highlighting clinically relevant biological findings. Alternatively, NGS panel sequencing (minimal consensus of 17 genes, including ALK) and Genomic copy number profile (high resolution aCGH and/or SNPa and/or lcWGS) can be applied.
- Telomere maintenance mechanism and ALT status.
- The report of the molecular profile should be recorded as in ongoing precision medicine programs [70]
- It is mandatory to analyse the ALK copy number status (amplified yes/no) and mutation status (mutated yes/no) on a new sample obtained at relapse/progression (primary tumour and/or metastatic site). If no tumour sample can be obtained at relapse/progression, the ALK status may be determined on circulating tumour DNA extracted from blood or bone marrow plasma.

21.1.2 Liquid biopsy samples

Blood samples for the analysis of circulating biomarkers and immunological studies should be collected from all patients at the same time points as those required for standard clinical care:

- Baseline
- Post cycles 2, 4, 6, 9
- Post cycle 12 or End of Treatment

Core studies include analysis of circulating RNAs [71, 72] and DNAs [73-75].

Constitutional DNA taken once at any time will be required for pharmacogenetic studies and is *optional*.

Bone marrow aspirate taken at baseline will be required for circulating biomarker analysis and is *optional*.

21.2 Samples to be Collected

Quality control of samples for diagnostic and research procedures and the collaboration within the SIOPEN network are of high importance.

21.2.1 Tumour tissue

For the Tumour tissue samples, FFPE blocks, unstained slides or frozen samples are required from diagnosis, and from relapse if available. Analysis includes, but is not limited to, MYCN, copy number profile or NGS panel sequencing, telomere maintenance mechanism and/or ALT status. Samples should be sent to a central accredited laboratory identified by the country National Coordinating Centre and Coordinating Sponsor.

As a clinically decision making biomarker, ALK amplification/mutation status on a sample obtained at relapse/progression should be determined.

21.2.2 Blood samples for circulating Biomarker Analysis

Blood for analysis of circulating biomarkers and circulating tumour cells should be collected at time points: Baseline, post cycle 2, 4, 6, 9 and 12, and end of treatment (if not received 12 cycles). Samples should be sent to a central accredited laboratory identified by the country National Coordinating Centre and Coordinating Sponsor. Please see BEACON2 Laboratory manual. The maximum volume of blood (including the routine blood specimen collected for clinical care) will not exceed the maximum according to body weight, as indicated in the Guidelines for Paediatric Blood Volume for Research Purposes/HREC [76] and guidance by the European Medicines Agency (EMA 2008).

The following samples should be collected:

- Blood samples for CTC and circulating biomarker studies

21.2.3 OPTIONAL - Bone marrow samples for circulating Biomarker Analysis

Bone marrow aspirates for analysis of circulating biomarkers and characterisation of circulating tumour cells may be collected at baseline/entry into the study.

The following samples should be collected:

- Bone marrow samples for CTC and circulating biomarker studies
- Bone marrow samples for characterisation of neuroblastoma cells and the tumour microenvironment and preclinical model development

21.2.4 OPTIONAL - Blood plasma for constitutional DNA

Blood plasma should be collected at any time point for constitutional DNA analysis and pharmacogenomics, where patient/parent guardian consent is obtained. Samples should be sent to a central accredited laboratory identified by the country National Coordinating Centre and Coordinating Sponsor.

21.2.5 Where to send the samples

Quality control of samples for diagnostic and research procedures and the collaboration within the SIOPEN network are of high importance. Please refer to the BEACON2 Laboratory Manual for details on sample preparation, sample conservation, shipping and reference laboratories.

21.3 End of Trial Arrangements

Any biological samples remaining at the end of the trial will be transferred to a central tissue bank identified by the country National Coordinating Centre and Coordinating Sponsor or made available to another approved ethical project.

22. DATA HANDLING AND RECORD KEEPING

This trial will use an electronic remote data capture (eRDC) system which will be used for completion of CRFs. Access to the eRDC system will be granted to individuals via the BEACON2 Trial Office.

SAE reporting will be entirely paper-based throughout the course of the trial.

22.1 Data Collection

22.1.1 CRF

The Case Report Form will comprise the following forms:

Table 14 – CRF

Form	Summary of data recorded	Schedule for submission
Eligibility Checklist Tier 1	Confirmation of eligibility and satisfactory staging investigations where necessary	To be completed prior to randomisation
Eligibility Checklist Tier 2	Confirmation of eligibility and satisfactory staging investigations where necessary	To be completed prior to registration
Randomisation Form (Tier 1)	Participant details; details of stratification variables; confirmation of treatment; optional consent issues	As soon as possible after randomisation
Registration Form (Tier 2)	Participant details; details of stratification variables; optional consent issues	As soon as possible after registration
Screening Form	Physical examination details, baseline performance status, baseline laboratory results (Haematology/Biochemistry/Clotting), urinalysis and Glomerular Filtration (GFR) test results, menstrual status, pregnancy testing details.	Within 1 month of registration/ randomisation
Arm A dbIT Treatment Form	Details of dbIT Treatment	Within 1 month of visit
Arm B BIT Treatment Form	Details of BIT Treatment	Within 1 month of visit

Arm C dbBIT Treatment Form	Details of dbBIT Treatment	Within 2 weeks of treatment visit
Adverse Events Form	Details of AEs experienced	To be completed at all treatment cycles, within 1 month of visit
HRQOL Forms (Participant/Parent-Proxy)	Details of participants quality of life responses	To be completed at baseline, Post cycles 2, 4, 6, and EOT
Tumour Assessment Form - Baseline	Details of tumour assessment measured by MRI/CT/MIBG/bone marrow histology	To be completed at baseline within 1 month of visit
Tumour Assessment Form - Response	Details of tumour assessment and response measured by MRI/CT/MIBG/bone marrow histology	To be completed Post cycles 2, 4, 6, 9, 12 and EOT
Follow up Form – 3m-24m	Details follow up visit, disease status, physical examination details, performance status, laboratory results (haematology/biochemistry/clotting if clinically indicated), Urinalysis test results.	To be completed at all follow-up visits up until 2 years post end of treatment date, within 1 month of visit
Follow up Form – 3y-5y	Details follow up visit, disease status, laboratory results (haematology/biochemistry/clotting if clinically indicated), Urinalysis test results.	To be completed at follow-up visits year 3, 4 and 5, within 1 month of visit
Disease and Medical History Form	Details of first diagnosis, details of disease at time of randomisation/registration, details of prior neuroblastoma treatment, none-neuroblastoma medical history.	Within 1 month of registration/ randomisation
End of Treatment Form	Treatment details, physical examination details, performance status, laboratory results (haematology/biochemistry/clotting if clinically indicated), urinalysis test results.	When patient has finished course of protocol defined treatment or as soon as possible if patient discontinues early
Pre Cycle Form	Physical examination details, performance status, laboratory results (haematology/biochemistry/clotting if clinically indicated), urinalysis test results.	To be completed prior to starting cycles 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.

22.1.2 Ad hoc forms

Table 15 – Ad Hoc Forms

Form	Summary of data recorded	Schedule for submission
Death Form	Date and cause of death	Immediately upon notification of participant's death
Deviation Form	Completed in the event of a deviation from the protocol	Immediately upon discovering deviation
Expected SAR Form	Details of expected SAR	Immediately upon discovering an expected SAR
Pregnancy Notification Form	Pregnancy information and outcome	As soon as possible after becoming aware that a participant is pregnant during the reporting period
Relapse/Progression Notification Form	Completed in the event of a relapse. Relapse/progression details, details of further treatment.	Immediately upon discovering that a participant has relapsed
Serious Adverse Event Form	Details of Serious Adverse Event	Immediately upon discovering a Serious Adverse Event
Withdrawal Form	Used to notify the Trials Office of participant withdrawal from the trial	Immediately upon participant withdrawal

This trial will use an electronic Case Report Form system to capture the Case Report Form data, obtained from the participant's medical notes as per the site's standard procedures. Paper Case Report Forms will also be available as a backup. Access to the electronic Case Report Form system will be granted to individuals by the Trial Office.

https://www.cancertrials.bham.ac.uk

The Investigator will ensure all data from all participant visits are promptly entered into the electronic Case Report Form system in accordance with the CRF Completion Guidelines. The Case Report Form must be completed by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log). The exceptions to this are the Eligibility Checklist, Serious Adverse Event Form and Expected SAR Form which can be completed by an authorised member of the site research team but must be co-signed by the Investigator.

For the purposes of this trial Serious Adverse Event Forms and Expected SAR Forms will be captured on paper and entered onto the electronic Case Report Form system by the Trial Office. QoL Booklets will be returned to the Trial Office and will be regarded as source data.

A master copy of the paper Case Report Form is available in the Investigator Site File. If the electronic Case Report Form system is unavailable for any length of time the Trial Office may instruct sites to complete the paper Case Report Form to ensure timely monitoring of participant data. These forms may be entered onto the system by the Trial Office.

For paper SAE and expected SAR Forms, the completed originals should be sent to the Trial Office and a copy filed in the Investigator Site File.

Entries on the paper Case Report Form should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on the Case Report Form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the Investigator to ensure that the Case Report Form has been completed correctly and that the data are accurate.

The Case Report Form may be amended from time to time by the Trial Office throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the Case Report Form must be implemented by participating sites immediately on receipt.

The following data may not be captured in the source data, e.g., Quality of Life which will be recorded directly onto the Case Report Form.

22.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years after the end of the trial or following the processing of all biological material collected for research, whichever is the later. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

23. QUALITY MANAGEMENT

23.1 Site Set-up and Initiation

All sites will be required to sign appropriate contracts with their National Coordinating Centre prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements and registration forms and supply a current CV with evidence of recent GCP training to the Trials Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trials Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and

other documentation required for the conduct of the trial. The Trials Office must be informed immediately of any change in the site research team.

23.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the BEACON2 Quality Management Plan and the National Coordinating Centre Monitoring Plan for each respective country. It is the responsibility of the participating National Coordinating Centre to ensure that the level and process of monitoring described in the National Coordinating Centre Monitoring Plan for that country is in accordance with their national regulations and to inform the Coordinating Sponsor of any issues.

Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the BEACON2 trial staff access to source documents as requested. More information on monitoring will be detailed in the UK Quality Management Plan and the International Monitoring Plan.

23.3 Central Monitoring

Where a participant has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to BEACON2 Trial Management Group, and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main Research Ethics Committee (REC) and the Medicines for Healthcare products Regulatory Agency (MHRA).

23.4 Audit and Inspection

The Investigators and institutions involved in the clinical trial will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are requested to notify the applicable NCC of any inspections by the relevant competent authority. NCC's will notify the UK coordinating centre of any significant audit findings.

23.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Coordinating Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

National Coordinating Centres and sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

24. END OF TRIAL DEFINITION

The trial ends when (a) decision has been taken that no further arms will be added and (b) the last arm reaches an arm-dropping criterion or maximum sample size and (c) on the date of the last patient last follow-up. The National Coordinating Centre will notify the Competent Authority and Research Ethics Committee that the trial has ended and will provide them with a summary of the clinical trial report within 6 months of the end of trial.

The trial results will be included on the clinical trial registry (ISRCTN) and on the Clinical Trials Information System. A lay summary will be included on the UK Health Research Authority website, the Clinical Trials Information System, and the trial website (https://www.birmingham.ac.uk/research/crctu/trials/beacon2/index.aspx) and the Cancer Research UK website.

25. STATISTICAL CONSIDERATIONS

25.1 Definition of Outcome Measures

25.1.1 Primary Outcome

See Section 3.3.1 for details

- Tier 1 (randomised comparison): Progression-Free Survival time (per the INRC 2017 [2])
- Tier 2 (dose expansion-confirmation cohorts): Definition of a safe and tolerable combination regimen

25.1.2 Secondary Outcome

See Section 3.3.2 for details

- Best objective response (complete and partial response) per the INRC 2017 during trial treatment (12 cycles)

- Clinical benefit (complete, partial and minor response and stable disease) per the INRC 2017
- Time response to progression/Duration of Response (for responders)
- Overall Survival time
- Quality of life of patients measured by Peds-QL questionnaires
- Incidence and Severity of AEs

25.1.3 Exploratory/Tertiary Outcome

See Section 3.3.23 for details

- Quality of life of caregivers measured by Peds-QL questionnaires
- Correlation between objective response using INRC 2017 and PFS/OS
- Changes in circulating biomarkers and tumour molecular profiles in tumour and blood, including analysis circulating RNAs and CDNAs, immune response and tumour microenvironment, analyses of genomic aberrations in relapsed neuroblastoma (e.g. MYCN, ALK, RAS/MAPK, ATRX among others) and development of novel biomarkers.

25.2 Trial Design

25.2.1 General Principles

BEACON2 is designed as a two stage, Phase 1/2 multi-arm platform trial, with the possibility of extending recruitment into a Phase 3 evaluation, and additional dose expansion/confirmation cohorts (Tier 2) to be conducted (where necessary) before introduction of new agents to the main randomisation (Tier 1). The trial will aim to recruit a maximum of 75 patients per arm, with an interim analysis at the end of the first stage, when 40 patients have completed six cycles of treatment. At the interim analysis, arms that are clearly inferior can be terminated. When stage 2 is completed (75 patients per arm), recruitment will terminate. The DMC will consider whether there is strong evidence that randomisation should continue, and if there is, we will seek to re-open randomisation, and recruit up to a total of 112 patients per arm.

The design allows the introduction of novel agents or regimens as new trial arms, following approval of a substantial amendment by the relevant Competent Authority (the MHRA in the UK). This trial will use Bayesian statistical methods, largely because they are helpful in interpreting trials in limited populations as they can quantify the probability of benefit.

25.2.2 Sample Size

Because relapsed neuroblastoma is a rare condition, the sample size is necessarily limited. The target sample sizes are therefore partly determined by pragmatic considerations, including the need to maintain clinical engagement, and for the trial to report results within a reasonably short period.

The target sample size for stage 2 is 75 patients per arm. Based on simulations, we expect this sample size to have a reasonable probability of giving a positive result if the true hazard ratio between intervention and comparator is in the region of 0.7, and a low probability of showing benefit if it is in fact ineffective or harmful (Table 16).Because we do not have extensive data on the expected hazard rate in the comparator group, we assumed three plausible scenarios of hazard rate (high, medium and low). With the High hazard rate, approximately 30% of participants

would be event free after 1 year, with the medium rate it would be approximately 55%, and with the low rate, approximately 70% (see Statistical Analysis Plan [SAP] for more details).

The proportion of simulations in which the probability of finding a hazard ratio of less than 1 between the intervention arm and comparator was greater than 0.80 and greater than 0.95 (based on 1000 simulations). We assume a recruitment rate of 45 patients per year.

Table 16 – Sample size and power for analysis at 75 patients per arm.

True Hazard Ratio	Comparator Hazard Rate	P(HR <1) > 0.8	P(HR<1) > 0.95
0.6	High	0.957	0.849
0.7	High	0.866	0.620
0.8	High	0.623	0.317
1.0	High	0.192	0.050
1.1	High	0.077	0.017
1.25	High	0.017	0.002
0.6	Medium	0.921	0.723
0.7	Medium	0.785	0.488
0.8	Medium	0.563	0.262
1,0	Medium	0.209	0.059
1.1	Medium	0.098	0.019
1.25	Medium	0.025	0.004
0.6	Low	0.803	0.543
0.7	Low	0.653	0.345
0.8	Low	0.460	0.191
1,0	Low	0.196	0.060
1.1	Low	0.123	0.025
1.25	Low	0.046	0.014

The trial has a good probability of finding, at the analysis of 75 patients per arm, a convincing probability of benefit, in scenarios where the true hazard ratio is 0.7 or lower, and the comparator event rate is medium or high. Scenarios where the intervention is inactive or harmful (hazard ratio of 1 or higher) are very unlikely to lead to an erroneous conclusively positive result (please see the right hand column, showing the proportion of simulations finding a probability that the hazard ratio is less than 1 of > 0.95).

After completion of stage 2, the DMC may request randomisation to continue (if feasible), up to a total of 112 per arm. Table 17 (below) gives the same operating characteristics for this larger sample size. As expected, the increased sample size would give higher probabilities of correctly concluding effectiveness.

Table 17 – Sample size and power for analysis at 112 patients per arm.

The proportion of simulations in which the probability of finding a hazard ratio of less than 1 between the intervention arm and comparator was greater than 0.80 and greater than 0.95 (based on 1000 simulations).

True Hazard Ratio	Comparator Hazard Rate	P(HR <1) > 0.8	P(HR<1) > 0.95
0.6	High	0.988	0.943
0.7	High	0.925	0.763
0.8	High	0.765	0.453
1.0	High	0.212	0.049
1.1	High	0.061	0.012
1.25	High	0.006	0
0.6	Medium	0.973	0.875
0.7	Medium	0.874	0.625
0.8	Medium	0.674	0.377
1.0	Medium	0.181	0.052
1.1	Medium	0.087	0.015
1.25	Medium	0.019	0.002
0.6	Low	0.926	0.730
0.7	Low	0.770	0.477
0.8	Low	0.549	0.271
1.0	Low	0.188	0.043
1.1	Low	0.097	0.018
1.25	Low	0.015	0.003

25.3 Analyses

25.3.1 Comparisons

BEACON2 is designed as a multi-arm, two stage Phase II trial, evaluating novel treatments and combinations of drugs. There is no defined standard care treatment for this population, so the trial does not contain a standard care arm. Each intervention arm will be compared with a concurrently-recruiting comparator arm (we do not use the terms control or standard care arm in this trial because variation in standard clinical practice exists). Arm A will initially be the comparator arm, as this represents the current best treatment agreed by the clinical community. Hence for the first arms to open (Arm B and Arm C) the primary comparisons will be between these arms and Arm A. In the future, if another arm is found to be superior to Arm A, the comparator arm may be changed.

The randomisation will begin with two arms (A versus B), with later addition of Arm C if Tier 2 for Arm C is completed successfully. No more than three arms (i.e. one comparator and two intervention arms) will be open simultaneously, so that evaluation of novel interventions can be achieved relatively quickly. Randomisation to the comparator arm will remain open until it is replaced as comparator, or the trial ends.

Primary comparisons of the trial will be between each intervention arm and concurrent patients recruited to the comparator arm, hence for Arm C, the primary comparison will be between patients randomised to Arm C and those randomised to Arm A (the comparator) during the period that Arm C was open.

25.3.2 Tier 2

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.

A Tier 2 arm will be considered not tolerable if ≥3/10 DLTs are identified. This would indicate a greater than 90% posterior probability that the true DLT rate was less than 0.5.

The decision to move an arm from Tier 2 to the main randomisation (Tier 1) will be taken by the TMG based on preclinical rationale, mechanism of action, early signs of activity, low proportion of DLTs, lack of overlapping toxicities and feasibility of the combination. For more details, see Section 2 Trial Design.

25.3.3 Stage 1 interim analysis

In Tier 1, an interim analysis will be conducted for each arm when 40 patients have been recruited and reached six cycles after randomisation. The timing is a compromise between the need for early evaluation, and allowing enough time for a reasonable number of events to occur. At this interim analysis, possible decisions are:

- Termination of randomisation to the experimental arm, if it does not meet the statistical threshold for continuation. The criteria will be based on a combination of PFS events, tumour response, and toxicity.
- Continuation of randomisation to both experimental and comparator arms.

To determine whether an arm should be terminated, we will calculate a utility score based on occurrence of PFS events (death or progression), tumour response and toxicity. Arm termination decisions will use a combination of these outcomes, so that unacceptable toxicity or evidence than an intervention is inferior to its comparator in events or tumour response would lead to closure of the arm. Full details and operating characteristics will be presented in the SAP.

Progression to stage 2 is also dependent on there being no external or operational reasons for terminating randomisation to that arm (e.g. unavailability of the drug). Results of the interim analyses will be provided to the DMC, who will make recommendations about progression or termination of trial arms.

25.3.4 Completion of stage 2

After 75 patients have been recruited to an intervention arm, the trial phase 2 question will be completed and recruitment to that arm will be paused. A second interim analysis will be conducted and supplied in confidence to the DMC. Most interventions are expected to be terminated at this point, but the DMC are able to recommend continuation of a comparison in exceptional circumstances that require further randomisation. If the DMC recommend continuation, randomisation to the arm will be re-opened if this is feasible, and recruitment will continue up to a total of 112 patients. The exceptional decision to move to phase 3 will be taken by the TMG, advised by the DMC and TSC, considering the following aspects:

- Compelling evidence that further randomisation is necessary

- Availability of drug supply for intervention and comparator arms
- Potential competition with other arms
- Feasibility in terms of expected completion of the phase 3 evaluation

If an arm remains open to recruit up to 112 patients, the relevant comparator arm will also have to remain open.

25.4 Analysis of Outcome Measures

The main analytical approaches are summarised here. Full details will be specified in a SAP which will be prepared by the trial statisticians and finalised before any analysis is undertaken.

25.4.1 Statistical Methods

The main analysis for each intervention arm will be conducted when recruitment to the arm has closed and all patients have been followed up for at least 2 years. The final analysis will be conducted when all patients have been followed up for at least five years. All analyses will be undertaken on an intention to treat basis, including all patients randomised to each arm, regardless of the intervention actually received. The primary comparisons for each arm will be with concurrently-recruited patients from the comparator arm. Further details are included in the SAP.

The primary comparisons will be with concurrently-recruited patients from the comparator arm, which will be Arm A, unless, during the trial, unequivocal emerging evidence suggests the comparator has to be changed.

Throughout the analyses, we will use a Bayesian statistical approach, so presentation of the results will be based around posterior distributions of the parameters of interest derived from the analysis models.

The primary outcome, progression-free survival time, and overall survival time, are time to event outcomes. They are defined as the time from randomisation the first failure event (progression or death). Patients without an event at the time of analysis will be censored at their date last seen/last available assessment date. These outcomes will be analysed using appropriate survival modelling techniques such as Cox proportional hazards models or parametric survival models. We will estimate the hazard ratio between each intervention arm and the comparator arm, and estimate the proportion event-free at specific time points. Models will incorporate prognostically important covariates, including factors used for minimisation.

Time to event outcomes will be illustrated using Kaplan-Meier plots, and results will be presented as plots of the posterior distributions of the hazard ratio estimated from the models, and summarised with a point estimate and 95% interval.

Analysis of binary response outcomes will use logistic regression models, incorporating relevant covariates, as for the primary outcome. Plots of the posterior distributions of parameters will be presented, with point estimates and 95% intervals.

Trial research staff will check incoming data for compliance with the protocol, data consistency, missing data and timing. Sites will be sent requests for missing data or clarification of inconsistencies or discrepancies. Missing and ambiguous data will be queried. If there are extensive missing data, we will consider applying multiple imputation methods to adjust for the impact of the missing observations. If there are few missing data, no adjustment will be undertaken.

For analysis of quality of life, we expect no clinically important differences between the treatment arms. We will use longitudinal models to analyse the trajectory of quality of life through time in each randomised group. We will estimate the quality of life scores at clinically relevant time points, and the probabilities that differences exceed the clinically important threshold of 10 points.

Change from baseline per timepoint will be reported in a descriptive manner to provide support for the main results. An overall effect of the treatment on the QOL scores will be determined. Differences will only be considered as clinically relevant if they exceed the 10-point threshold. The proportion of patients experiencing a clinically relevant change will be provided as well. For all QOL domains and items, cross-sectional descriptions of the average scores will be presented by treatment arm together with confidence intervals and a graphical display of the patterns of change over time will be provided. Missing data is a potential major source of bias in HRQOL assessment. In case overall compliance is deemed too low (<50%), only a descriptive analysis will be performed instead of the main analysis.

Adverse events will be classified according to CTCAE, and a tabular summary of reported AEs, SAEs and SUSARs will be produced.

25.4.2 Interim Analysis

Analytical methods for the interim analysis will be the same as for the final analysis (see 25.4.1).

25.4.3 Subgroup and Other Analyses

No subgroup analyses of the main outcome variables are planned.

Analysis of laboratory data will be performed as specified in the analysis plan.

26. TRIAL ORGANISATIONAL STRUCTURE

26.1 Sponsor

The University of Birmingham is the Coordinating Sponsor for this study.

26.2 Coordinating Sponsor

The University of Birmingham is the Coordinating Sponsor. The Coordinating Sponsor has delegated the set-up, management, and analysis of the trial to the UK Coordinating Centre. The role of the UK Coordinating Centre is assumed by the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham. The trial will be set-up, managed and analysed in the UK in accordance with CRCTU standard policy and procedures.

26.3 National Coordinating Centres

National Coordinating Centres are responsible for the conduct of the trial within their own country. The UK Coordinating Centre will undertake the responsibilities of National Coordinating Centre in the UK.

Each National Coordinating Centre (see the introductory pages for the list) will manage the trial in accordance with the trial protocol and their standard policy and procedures.

26.4 Trial Management Group

A Trial Management Group will be established, and will include the Chief Investigator, University of Birmingham Lead Investigator, Pharmacist, Clinical Coordinators, Co-investigators, Patient and Public Involvement and Engagement Representatives, the Trial Management Team Leader (or delegate), the Trial Biostatistician, the Trial Coordinator, and the Monitor. Other key trial personnel may be invited to join the Trial Management Group as appropriate to ensure representation from a range of professional groups.

26.5 Trial Steering Committee

An independent Trial Steering Committee will be set up to oversee the conduct of the trial. The Committee will be chaired by an independent Chair. Membership will include independent clinicians and at least one participant advocate. Selected members of the Trial Management Group including the Chief Investigator and Trial Biostatistician will report to the Trial Steering Committee. A secretariat will be provided by the Trial Coordinator.

The Trial Steering Committee will operate in accordance with a trial specific charter based upon the template created by the Damocles Group.

The Trial Steering Committee will meet shortly before commencement of the trial and then annually thereafter (usually be held remotely) after the Data Monitoring Committee meeting.

The Trial Steering Committee will supervise the conduct of the trial, monitoring progress including recruitment, data completeness, losses to follow-up, and deviations from the protocol. They will make recommendations about conduct and continuation of the trial to the Coordinating Sponsor.

26.6 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants.

The Data Monitoring Committee will operate in accordance with a trial specific charter based upon the template created by the Damocles Group.

The Data Monitoring Committee will meet in-person or remotely every 12 months while participants are on treatment. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently. An emergency meeting may also be convened if a safety issue is identified. The Data Monitoring Committee will report to the TMG who will convey the findings of the Data Monitoring Committee to the Trial Steering Committee. The Data Monitoring Committee may consider recommending the

discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

26.7 Participant and Public Involvement

Members of the public will be mainly represented by patient advocates. They will be involved in all steps of the development of the clinical trial:

- Design of the research. A PPI representative will be included on the Trial Management Group and active in design discussions. Protocol design will be presented at international conferences, committees and cooperative groups with PPI involvement (e.g. ITCC, SIOPEN or NCRI)
- Management and conduct of the research. A PPI Representative will be included in the TMG. The TSC will also include PPI representatives.
- Analysis of results: PPI representatives, members of the TMG and TSC will participate to the analysis of the results.
- Dissemination of findings: Results will be presented at PPI forum and national/international meetings.

Patient representatives and patient advocacy organisations have been involved in the trial from its inception by making substantial contributions to the design of the trial, as well as being on the Trial Management Group, Trial Steering Committee and reviewing trial documentation. This will continue throughout the trial. Advocates mainly pushed to avoid having chemotherapy-only arms (all current novel arms within the trial include novel promising combinations), as chemotherapy alone would not be acceptable for parents; and also for the incorporation of the evaluation of QoL for patients and caregivers. Advocates from ITCC and SIOPEN advocate committees have also reviewed and supported BEACON2, and will continue to work throughout the trial to disseminate it and promote recruitment.

26.8 Peer Review

This clinical trial proposal underwent international peer review from the funding organisation (Fight Kids Cancer) as well as scientific bodies (SIOPEN, ITCC & NCRI neuroblastoma subgroup).

27. FINANCE

This is a clinician-initiated and clinician-led trial funded by Fight Kids Cancer.

Dinutuximab beta is provided free of charge by Recordati Industria Chimica E Farmaceutica S.P.A, including labelling and distribution. Bevacizumab, irinotecan and temozolomide will not be provided free of charge by the Coordinating Sponsor and are available commercially.

No individual per participant payment will be made to Investigators or participants.

The BEACON2 trial is a National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio study.

28. ETHICAL AND REGULATORY CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the protocol, Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 2018, Human Tissue Act 2008 and Good Clinical Practice (GCP)) and the applicable European regulations (which include the Clinical Trials Regulation (No 536/2014) and subsequent amendments) in European Countries. This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any participants are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

29. CONFIDENTIALITY AND DATA PROTECTION

Personal data (participants and research staff) recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 or other relevant data protection legislation in each country. The Data Protection Officer will act as the Data Controller for this trial.

Further information about how data is handled by the University of Birmingham and the CRCTU can be found within the CRCTU Privacy Notice (https://www.birmingham.ac.uk/crctu).

With the participant's consent, their participant identifiers e.g. National Health Service (NHS) number, or in Scotland the Community Health Index (CHI), will be collected at trial entry to allow tracing through the Cancer Registries and the NHS Information Centre for Health and Social Care (service formally provided by the Office of National Statistics) and to assist with long-term follow-up via other health care professionals (e.g. participant's GP). Participants will be identified using only their unique trial number on the Case Report Form and correspondence between an NCC and the participating sites in its country. However, if local regulation/guidance permits, participants are asked to give permission for the applicable NCC to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process and may also be forwarded to other health care professionals involved in the treatment of the participant (e.g. participant's GP) if local regulation/guidance permits.

The Investigator must maintain documents not for submission to the applicable NCC (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

The NCCs will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Representatives of the BEACON2 trial team may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

30. INSURANCE AND INDEMNITY

The Coordinating Sponsor will obtain adequate insurance to cover negligent harm arising from the design of the protocol and its liabilities in relation to the trial.

The NCCs are responsible for obtaining insurance to set up and run the trial in their respective countries and for ensuring that sites in their country are adequately covered.

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for participants treated, whether or not the participant is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

31. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the corresponding contracts between Coordinating Sponsor and National Coordinating Centres/sites.

Individual countries will be allowed to publish their efficacy results, however the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the TMG decides otherwise.

32. DATA AND SAMPLE SHARING

The CRCTU is committed to responsible and controlled sharing of anonymised clinical trial data with the wider research community to maximise potential participant 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.

Data resulting from this trial will be shared with the International Neuroblastoma Risk Group (INRG) to contribute to the Data Commons database to facilitate international, multi-institutional, interdisciplinary research in childhood neuroblastoma. Linked anonymised data (linked using trial, SIOPEN, INRG or another unique identification number) may be provided to other 3rd parties (e.g., pharmaceutical companies or other academic institutions) for research and safety monitoring. These regulatory authorities or research organisations could be within the UK or abroad. This may be to countries outside of Europe where data protection regulations differ. Any such request is carefully considered and will only be granted if the necessary procedures and approvals are in place.

The trial data will participate in the BIOPORTAL study and linkage of data to other SIOPEN studies.

More detailed information on the CRCTU's Data Sharing Policy and the mechanism for obtaining data can be found on the CRCTU website: https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/index.aspx.

33. REFERENCE LIST

1. Brodeur, G.M., et al., *Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment.* J Clin Oncol, 1993. **11**(8): p. 1466-77.
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APPENDIX 1 – ABBREVIATIONS

AE	ADVERSE EVENT
AESI	ADVERSE EVENT OF SPECIAL INTEREST
ALT	ALANINE AMINOTRANSFERASE
ANC	ABSOLUTE NEUTROPHIL COUNT
APTT	ACTIVATED PARTIAL THROMBOPLASTIN TIME
AST	ASPARTATE AMINOTRANSFERASE
AR	ADVERSE REACTION
AYA	ADOLESCENT AND YOUNG ADULT
BIT	BEVACIZUMAB + IRINOTECAN + TEMOZOLOMIDE ARM
BM	BONE MARROW
BP	BLOOD PRESSURE
BSA	BODY SURFACE AREA
CI	CHIEF INVESTIGATOR
COG	CHILDREN'S ONCOLOGY GROUP
CNS	CENTRAL NERVOUS SYSTEM
CR	COMPLETE RESPONSE
CRF	CASE REPORT FORM
CR UK	CANCER RESEARCH UK
CRCTU	CANCER RESEARCH UK CLINICAL TRIALS UNIT (UNIVERSITY OF BIRMINGHAM)
CRN	CLINICAL RESEARCH NETWORK
CSR	CLINICAL STUDY REPORT
CT	COMPUTERISED TOMOGRAPHY
CTC	COMMON TERMINOLOGY CRITERIA
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

dbIT	DINUTUXIMAB BETA + IRINOTECAN + TEMOZOLOMIDE ARM
dbBIT	DINUTUXIMAB BETA + BEVACIZUMAB + IRINOTECAN +TEMOZOLOMIDE ARM
DLT	DOSE LIMITING TOXICITY
DMC	DATA MONITORING COMMITTEE
DNA	DEOXYRIBONUCLEIC ACID
efs	EVENT FREE SURVIVAL
ema	eUROPEAN MEDICINES AGENCY
eRDC	ELECTRONIC REMOTE DATA CAPTURE
EOT	END OF TREATMENT
FDG-PET	FLUORODEOXYGLUCOSE - POSITRON EMISSION TOMOGRAPHY
FFPE	FORMALIN-FIXED PARAFFIN EMBEDDED
GCP	GOOD CLINICAL PRACTICE
G-CSF	GRANULOCYTE COLONY STIMULATING FACTOR
GD2	GANGLIOSIDE EXPRESSED ON THE SURFACE OF THE MAJORITY OF NEUROBLASTOMA TUMOURS
GFR	GLOMERULAR FILTRATION RATE
GM-CSF	GRANULOCYTE-MONOCYTE COLONY STIMULATING FACTOR
GGT	GAMMA-GLUTAMYL TRANSPEPTIDASE
GP	GENERAL PRACTITIONER
HR	HEART RATE
IB	INVESTIGATOR BROCHURE
ICF	INFORMED CONSENT FORM
ICH	INTERNATIONAL CONFERENCE ON HARMONISATION
IMP	INVESTIGATIONAL MEDICINAL PRODUCT
INR	INTERNATIONAL NORMALISED RATIO
INRC	INTERNATIONAL NEUROBLASTOMA RESPONSE CRITERIA

INRG	INTERNATIONAL NEUROBLASTOMA RISK GROUP
INSS	INTERNATIONAL NEUROBLASTOMA STAGING SYSTEM
IRF	INSTITUTIONAL REVIEW BOARD
ISF	INVESTIGATOR SITE FILE
ITCC	INNOVATIVE THERAPIES FOR CHILDREN WITH CANCER
IV	INTRAVENOUS
MIBG	META-IODO-BENZYL-GUANIDINE
MHRA	MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
MRI	MAGNETIC RESONANCE IMAGING
MYCN	MYELOCYTOMATOSIS VIRAL RELATED ONCOGENE
NCI	NATIONAL COORDINATING INVESTIGATORS
NCC	NATIONAL COORDINATOR
NR	NO RESPONSE
OS	OVERALL SURVIVAL
OTC	OVER THE COUNTER
PD	PROGRESSSIVE DISEASE
PFS	PROGRESSION FREE SURVIVAL
PI	PRINCIPAL INVESTIGATOR
PIS	PARTICIPANT INFORMATION SHEET
PJP	PNEUMOCYSTIS JIROVECII PNEUMONIA
PK	PHARMACOKINETICS
PRES	POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME
PO	ORALLY
PR	PARTIAL RESPONSE
REC	RESEARCH ETHICS COMMITTEE
RNA	RIBONUCLEIC ACID

SAE	SERIOUS ADVERSE EVENT
SAR	SERIOUS ADVERSE REACTION
SD	STABLE DISEASE
SIOPEN	INTERNATIONAL SOCIETY PAEDIATRIC ONCOLOGY EUROPEAN NEUROBLASTOMA GROUP
SNP	SINGLE NUCLEOTIDE POLYMORPHISM
SPC	SUMMARY OF PRODUCT CHARACTERISTICS
SUSAR	SUSPECTED UNEXPECTED SEVERE ADVERSE REACTION
TH	TYROSINE HYDROXYLASE
TMG	TRIAL MANAGEMENT GROUP
TSC	TRIAL STEERING COMMITTEE
UAR	UNEXPECTED ADVERSE REACTION
ULN	UPPER LIMIT OF NORMAL
VTE	VENOUS THROMBO-EMBOLISM
VEGF	VASCULAR ENDOTHELIAL GROWTH FACTOR
VGPR	VERY GOOD PARTIAL RESPONSE
WMA	WORLD MEDICAL ASSOCIATION

APPENDIX 2 - TUMOUR STAGING - INRC CLASSIFICATION [2]

Primary Tumor

Response of primary tumor using both RECIST criteria and MIBG (or FDG if tumor is MIBG nonavid) uptake will be used. In patients with bilateral adrenal lesions, response will be based on the sum of the longest dimensions of both sites unless biopsy proves one to be ganglioneuroma. In patients with multifocal nonadrenal disease, the largest tumor will be considered the primary tumor, and additional lesions will be assessed as metastatic sites unless biopsy proven to be ganglioneuroma.

In some patients, it may be difficult to distinguish postoperative changes in soft tissues in the primary tumor bed from true residual neuroblastoma using anatomic imaging alone. This is particularly true when residual soft tissue masses are small (1 cm at longest diameter). For this reason, patients with MIBG-nonavid lesions measuring less than 1 cm in diameter would be considered to have achieved complete response (CR) in the primary site if the tumor was initially MIBG avid. For patients with MIBG-nonavid tumors at the time of diagnosis, small residual tumors must not demonstrate increased metabolic activity by FDG-PET imaging and, if biopsied, must not demonstrate neuroblastoma or ganglioneuroblastoma .

Primary (soft tissue) Tumor Response

Response	Anatomic + MIBG (FDG-PET†) Imaging
CR	< 10 mm residual soft tissue at primary site AND Complete resolution of MIBG or FDG-PET uptake (for MIBG-nonavid tumors) at primary site
PR	≥ 30% decrease in longest diameter of primary site AND MIBG or FDG-PET uptake at primary site stable, improved, or resolved
PD	> 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND Minimum absolute increase of 5 mm in longest dimension‡
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site

Abbreviations: CR, complete response; FDG, [^{18}F]fluorodeoxyglucose; MIBG, metaiodobenzylguanidine; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.
*Not for use in assessment of metastatic sites.
†Used for MIBG-nonavid tumors.
‡Mass that does not meet PD measurement criteria but has fluctuating MIBG avidity will not be considered PD.

Metastatic Soft Tissue and Bone Disease

Tumour Response at Metastatic Soft Tissue and Bone Sites

A combination of anatomic imaging and radionuclide scans will be used to assess response in soft tissue (including lymph node and non–lymph node) and bone metastases MIBG semiquantitative scoring systems have been previously used for response assessment with international consensus developed for use of these scoring systems in disease response.

Although differences exist in the approach to absolute scoring in the various systems, comparisons of the relative scores as defined by the SIOPEN scoring system and the Curie scoring system (used in COG) have yielded consistent designations of response and have validated MIBG relative scoring as prognostic for overall response and patient outcome in patients with newly diagnosed neuroblastoma. The consensus recommendation is to use the MIBG relative score on bone sectors (the absolute score of bone lesions at time of response assessment divided by the absolute score of bone lesions at baseline before therapeutic interventions) for response assessment. The same scoring method (e.g., Curie, SIOPEN) should be used at each time point of response assessment.

MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

Response	Anatomic + MIBG (FDG-PET*) Imaging
CR	Resolution of all sites of disease, defined as: Nonprimary target and nontarget lesions measure < 10 mm AND Lymph nodes identified as target lesions decrease to a short axis < 10 mm AND MIBG uptake or FDG-PET uptake (for MIBG-nonavid tumors) of nonprimary lesions resolves completely
PR	≥ 30% decrease in sum of diameters† of nonprimary target lesions compared with baseline AND all of the following: Nontarget lesions may be stable or smaller in size AND No new lesions AND ≥ 50% reduction in MIBG absolute bone score (relative MIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG-PET–avid bone lesions‡§
PD	Any of the following: Any new soft tissue lesion detected by CT/MRI that is also MIBG avid or FDG-PET avid Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be neuroblastoma or ganglioneuroblastoma Any new bone site that is MIBG avid A new bone site that is FDG-PET avid (for MIBG-nonavid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions Relative MIBG score ≥ 1.2§
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD of nonprimary lesions

Abbreviations: CR, complete response; CT, computed tomography; FDG, [^{18}F] fluorodeoxyglucose; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

*Used for MIBG-nonavid tumors

†Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (ie, cervical, axillary nodes) added to the sum of the longest diameters of non–lymph node soft tissue metastases. Masses of conglomerate nondiscrete lymph nodes will be measured using longest diameter.

‡For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

§Relative MIBG score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at baseline before therapeutic interventions. The same scoring method (eg, Curie or International Society of Pediatric Oncology European Neuroblastoma) must be used at all assessment time points. MIBG single-photon emission computed tomography (SPECT) or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

Bone Marrow Metastases

Bone Marrow Metastasis Response*

Exact quantification of bone marrow involvement at all sites should be reported; the percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine or biopsy (with immunohistochemical staining encouraged) or counting of the number of tumor cells in aspirates by cytology or immunocytology (recommended if available) divided by the number of hematopoietic or mononuclear cells evaluated to obtain a percentage of involvement (methodology described by Burchill et al). The bone marrow sample with the highest percentage of tumor infiltration is used in the response algorithm. Neuroblastoma infiltration in the marrow can be heterogeneously distributed throughout the skeleton. Because the clinical impact of this heterogeneity has not yet been fully evaluated, detection of more than 0% to # 5% tumor infiltration in bone marrow will represent a new category of minimal disease.

Response	Cytology†/Histology‡
CR	Bone marrow with no tumor infiltration on reassessment, independent of baseline tumor involvement
PD	Any of the following: Bone marrow without tumor infiltration that becomes > 5% tumor infiltration on reassessment OR Bone marrow with tumor infiltration that increases by > two-fold and has > 20% tumor infiltration on reassessment
MD	Any of the following: Bone marrow with ≤ 5% tumor infiltration and remains > 0 to ≤ 5% tumor infiltration on reassessment OR Bone marrow with no tumor infiltration that has ≤ 5% tumor infiltration on reassessment OR Bone marrow with > 20% tumor infiltration that has > 0 to ≤ 5% tumor infiltration on reassessment
SD	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration on reassessment but does not meet CR, MD, or PD criteria

NOTE. In the case of discrepant results between aspirations or core biopsies from two or more sites taken at the same time, the highest infiltration result should be reported using the criteria in this table.
Abbreviations: CR, complete response; MD, minimal disease; PD, progressive disease; SD, stable disease.
*Response will be compared with baseline disease evaluations before enrollment in a clinical trial or, for newly diagnosed patients, with baseline at specific times during therapy (ie, at diagnosis and before start of therapy, before specific phases of therapy such as induction, high-dose chemotherapy with stem-cell rescue consolidation, or postconsolidation immunotherapy).
†Accompanied by immunocytology (recommended, not mandatory).
‡Accompanied by immunohistochemistry; specific recommendations included in article by Burchill et al.[19]

Overall Response

Determination of Overall Response

Overall response will be defined by combining response of the individual components (i.e., soft tissue, bone, and bone marrow disease). All components must be evaluated and of sufficient quality to fully assess overall response. An overall CR requires that all involved components have a CR. An overall partial response includes a partial response of all soft tissue and bone sites or noninvolvement in one of these components but allows residual minimal disease in the bone marrow. The prior category of mixed response has been eliminated, and a new category, minor response, has been included. Minor response requires a partial response or CR in at least one component, stable disease for at least one component, and no evidence of progressive disease in any component. Progressive disease in any one component defines overall progressive disease.

Response	Criterion
CR	All components meet criteria for CR
PR	PR in at least one component and all other components are either CR, MD* (bone marrow), PR (soft tissue or bone), or NI†; no component with PD
MR	PR or CR in at least one component but at least one other component with SD; no component with PD
SD	SD in one component with no better than SD or NI† in any other component; no component with PD
PD	Any component with PD

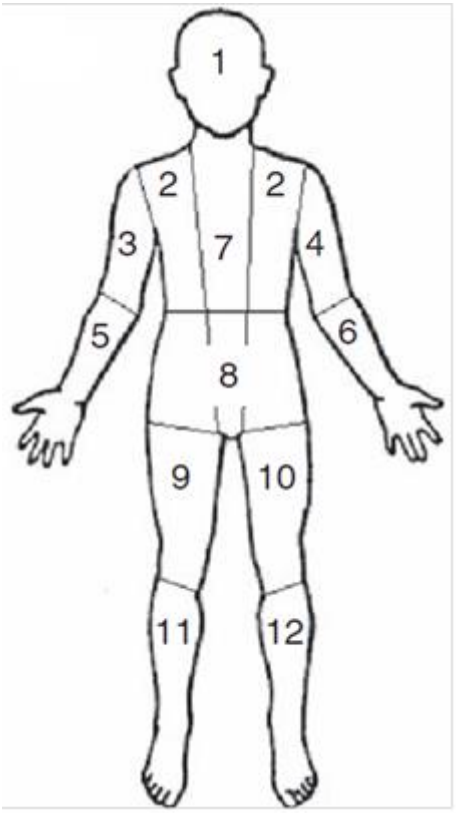
Abbreviations: CR, complete response; MD, minimal disease; MR, minor response; NI, not involved; PD, progressive disease; PR, partial response; SD, stable disease.
*For bone marrow assessment only.
†Site not involved at study entry and remains uninvolved.

Overall Response Criteria

Primary Tumor	Soft Tissue or Bone Metastatic Disease (MIBG or FDG-PET)	Bone Marrow Metastatic Disease (cytology*/histology†)	Overall
CR	CR	CR	CR
	CR for one response component with either CR or NI for other components		CR
CR	CR	MD	PR
CR	PR	CR	PR
CR	PR	MD	PR
CR	PR	NI	PR
CR	NI	MD	PR
PR	CR	CR	PR
PR	CR	NI	PR
PR	CR	MD	PR
PR	PR	CR	PR
PR	PR	NI	PR
PR	PR	MD	PR
PR	NI	CR	PR
PR	NI	NI	PR
PR	NI	MD	PR
NI	CR	MD	PR
NI	PR	CR	PR
NI	PR	MD	PR
CR	CR	SD	MR
CR	PR	SD	MR
CR	SD	CR	MR
CR	SD	MD	MR
CR	SD	SD	MR
CR	SD	NI	MR
CR	NI	SD	MR
PR	CR	SD	MR
PR	PR	SD	MR
PR	SD	CR	MR
PR	SD	MD	MR
PR	SD	SD	MR
PR	SD	NI	MR
PR	NI	SD	MR
SD	CR	CR	MR
SD	CR	MD	MR
SD	CR	SD	MR
SD	CR	NI	MR
SD	PR	CR	MR
SD	PR	MD	MR
SD	PR	SD	MR
SD	PR	NI	MR
SD	SD	CR	MR
SD	NI	CR	MR
NI	CR	SD	MR
NI	PR	SD	MR
NI	SD	CR	MR
SD	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
NI	NI	MD	SD
SD	SD	SD	SD
SD	NI	SD	SD
SD	NI	SD	SD
NI	SD	SD	SD
NI	SD	NI	SD
NI	NI	SD	SD
PD in any one component			PD
Response of not evaluable for any one of the three components that had measurable/evaluable tumor at study enrollment and no PD for any component			Not evaluable
No response evaluation performed for any of the three components			Not done

Abbreviations: CR, complete response; MD, minimal disease; MR, minor response; NI, not involved (site not involved at study entry and remains uninvolved); PD, progressive disease; PR, partial response; SD, stable disease.
*Accompanied by immunocytology (recommended, not mandatory).
†Accompanied by immunohistochemistry; specific recommendations included in article by Burchill et al.[19]

APPENDIX 3 - SIOPEN SCORING METHODS FOR NEUROBLASTOMA



The SIOPEN Method

The SIOPEN method: the skeletal distribution of MIBG is recorded in 12 anatomical body segments as follows: skull, thoracic cage, proximal right upper limb, distal right upper limb, proximal left upper limb, distal left upper limb, spine, pelvis, proximal right lower limb, distal right lower limb, proximal left lower limb and distal left lower limb. The extent and pattern of skeletal MIBG involvement is scored using a 0–6 scale to discriminate between focal discrete lesions and patterns of more diffuse infiltration.

Each segment is scored as 0. no involvement; 1. one discrete lesion; 2. two discrete lesions; 3. three discrete lesions; 4. > 3 discrete foci or a single diffuse lesion involving < 50% of a bone; 5. diffuse involvement of > 50 to 95% of an entire bone; 6, diffuse involvement of the entire bone, with a maximum score of 72. The SIOPEN score is the current method being used in Europe for the prospective phase 3 neuroblastoma trial. [77, 78]

Where the MIBG is negative, FDG-PET/CT is used. The total number of discrete metastatic and bone-avid lesions should be recorded.

APPENDIX 4 – LANKSY AND KARNOFSKY

LANSKY PLAY SCALE

100 %	Fully active, normal
90%	Minor restrictions in strenuous physical activity
80%	Active, but tired more quickly
70%	Greater restriction of play *and* less time spent in play activity
60%	Up and around, but active play minimal; keeps busy by being involved in quieter activities
50%	Lying around much of the day, but gets dressed; no active playing participates in all quiet play and activities
40%	Mainly in bed; participates in quiet activities
30%	Bedbound; needing assistance even for quiet play
20%	Sleeping often; play entirely limited to very passive activities
10 %	Doesn't play; does not get out of bed
0%	Unresponsive

KARNOFSKY AND ECOG SCALES

Karnofsky Index	Description
Able to carry on normal activity; no special care is needed.	
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity, minor symptoms or signs of disease.
80	Normal activity with effort, some signs or symptoms of disease.
Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.	
70	Cares for self, unable to carry on normal activity or to do work.
60	Requires occasional assistance from others, but able to care for most needs
50	Requires considerable assistance from others and frequent medical care.
Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.	
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalisation indicated, death not imminent.
20	Very sick, hospitalisation necessary, active supportive treatment necessary.
10	Moribund, fatal processes progressing rapidly.
0	Dead

APPENDIX 5 – TEMOZOLOMIDE DOSING

These tables are to be followed where possible. In other circumstances, please round to nearest practical dose:

	Temozolomide 100mg/m^2/day	
BSA (m^2)	**Calculated Dose (mg)**	**Administered Dose (mg)**
.20 – .50	3.35 mg/kg/day	3.35 mg/kg/day
.51	51	50
.52 – .53	52 – 53	50
.54 - .56	54 – 56	55
.57 - .58	57 – 58	55
.59 - .61	59 – 61	60
.62 – .63	62 – 63	60
.64 - .66	64 – 66	65
.67 – .68	67 – 68	65
.69 - .71	69 – 71	70
.72 – .73	72 – 73	70
.74 - .76	74 – 76	75
.77 – .78	77 – 78	75
.79 - .81	79 – 81	80
.82 – .83	82 – 83	80
.84 - .86	84 – 86	85
.87 – .88	87 – 88	85
.89 - .91	89 – 91	90
.92 - .93	92 – 93	90
.94 - .96	94 – 96	95
.97 - .99	97 – 99	95

APPENDIX 6 - WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the

48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my participant will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the participant's interest when providing medical care which might have the effect of weakening the physical and mental condition of the participant."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a participant, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with

national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

In any medical study, every participant - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

The refusal of the participant to participate in a study must never interfere with the physician-participant relationship.

If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the participant.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

The subject should be volunteers - either healthy persons or participants for whom the experimental design is not related to the participant's illness.

The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

APPENDIX 7 - DEFINITION OF ADVERSE EVENTS

Adverse Event (AE)

Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered.

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

- Results in death (unrelated to original cancer)
- Is life threatening*
- Requires hospitalisation** or prolongation of existing in-participant hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria.

* Life threatening in the definition of a Serious Adverse Event refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal in participant admission, even if the hospitalisation is a precautionary measure for continued observation. Thus, hospitalisation for protocol treatment (e.g., line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g., respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an Adverse Event is serious in other situations. Important Adverse Events that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction (SAR)

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Serious Adverse Reaction that is unexpected i.e., the nature, or severity of the event is not consistent with the applicable product information.

A Suspected Unexpected Serious Adverse Reaction should meet the definition of an Adverse Reaction, Unexpected Adverse Reaction and Serious Adverse Reaction.

Unexpected Adverse Reaction (UAR)

An Adverse Reaction, the nature or severity of which is not consistent with the Reference Safety Information.

When the outcome of an Adverse Reaction is not consistent with the Reference Safety Information, the Adverse Reaction should be considered unexpected.

Related Event

An event which resulted from the administration of any of the research procedures.

Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

APPENDIX 8 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The full CTCAE document is available on the National Cancer Institute (NCI) website and is provided in the Investigator Site File.

APPENDIX 9 – PEDSQL™ ADMINISTRATION GUIDELINES

The following guidelines are intended for use by individuals trained in the administration of standardized questionnaires. The PedsQL™ administrator is crucial in developing rapport with the respondents, emphasizing the importance of the questionnaire, addressing concerns, and ensuring that the PedsQL™ is completed accurately and confidentially.

General Protocol

Create a procedure for assigning identification numbers that will allow for parent/child comparisons as well as comparisons of baseline/follow-up data.

If feasible, the PedsQL™ should be completed *before* the respondents complete any other health data forms and *before* they see their physician or healthcare provider.

The parent/child should first complete the PedsQL™ Generic Core Scales and then complete any additional PedsQL™ Module.

Parents, Children (8-12) and Teens (13-18) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen. For the Young Child (5-7), the PedsQL™ should be administered by reading the instructions and each item to the young child word for word. At the beginning of each subscale repeat the recall interval instructions (one month or 7 days) to remind the young child to respond only for that specific recall interval. Use the separate page with the three faces response choices to help the young child understand how to answer. When reading items aloud to a child, intonation should be kept neutral to avoid suggesting an answer.

If a child has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the child (e.g., administering the Young Child (5-7) Self-Report version with the three faces response choices to an 8 year old). However, if a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL™ may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent.

The parent and child must complete the questionnaires *independently* of one another. Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires, but that it is important to get both the parent's and the child's *individual* perspectives. If you are administering the questionnaire to the child, the child should be facing away from the parent.

If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what *they think the question means*. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child and/or the parent has the option of not answering a question if they truly do not understand the question.

If a parent/child asks you to interpret the responses, tell her/him that you are not trained to interpret or provide a score for the answers given. If the PedsQL™ is being used for a clinical study, let the parent/child know that their answers will be combined with other participants' answers and analyzed as a group rather than as individual respondents.

Document all reasons for refusals and non-completions of the PedsQL™.

Administering the PedsQL™

The following scripts have been developed as a guide to introduce the PedsQL™ to the child and his/her parent(s). Modify the language to a style that is most appropriate for you and the respondent.

For the child:

The PedsQL™ asks you questions about how you feel and what you think about your health. It is not a test, and there are no right or wrong answers. It takes about 5 minutes to complete. If you have any questions, please let me know.

For the parent:

The PedsQL™ is a questionnaire that assesses health-related quality of life in children and adolescents. It contains questions about your child's physical, emotional, social, and school functioning **in the past one month (**or for the Acute version**, in the past 7 days)**.

The PedsQL™ is brief and typically takes less than 5 minutes to complete. It is not a test, and there are no right or wrong answers. Please be sure to read the instructions carefully and choose the response that is the closest to how you truly feel. Please do not compare your answers with your child's responses. We are interested in your and your child's **individual** perspectives. However, feel free to discuss the questionnaire with your child **after** you have both completed it and returned it to me. If you have any questions, please let me know.

General Protocol

Provide the respondent with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. Remain nearby should questions or concerns arise.

When the parent/child returns the PedsQL™, look it over and check to see that all answers have been completed. Verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, please ask the parent or child to indicate their response.

Ask the participants if they had any difficulties completing the questionnaire or if they have any other comments regarding the questionnaire. Document any important feedback.

Thank the parent and child for taking the time to complete the questionnaire. If the study design involves following up with these respondents, let them know that they may be asked to complete the PedsQL™ again at another time. Indicate when they can expect to be contacted again if known.

BEACON 2
TRIAL OFFICE

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✉ **BEACON2@bham.ac.uk**

Trial Database

https://www.cancertrials.bham.ac.uk

Serious Adverse Event Reporting

Reg@trials.bham.ac.uk
CC beacon2@trials.bham.ac.uk
Include "BEACON2 SAE" in the subject line