NORTH STUDY:
A Phase II Study of Panobinostat in Paediatric, Adolescent and Young Adult Patients with Solid Tumours Including Osteosarcoma, Malignant Rhabdoid Tumour/Atypical Teratoid Rhabdoid Tumours and Neuroblastoma

Statistical Analysis Plan

V1.0
December2024

Protocol: ACCT008/ASSG35
ClinicalTrials.gov ID: NCT04897880
Novartis Ref: CLBH589XAU13T
Based on protocol Version 5, dated 18Sept2020

Alannah Rudkin.
Clinical Epidemiology & Biostatistics
Murdoch Children's Research Institute
The Royal Children's Hospital, 50 Flemington Road
Parkville, Victoria 3052 Australia

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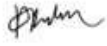
List of Abbreviations

AE	Adverse Event
ATRT	Atypical Teratoid Rhabdoid Tumour
CBR	Clinical Benefit Rate
CR	Complete Response
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CT	Computed tomography scan
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
FDG-PET	fluorodeoxyglucose positron emission tomography
GCP	Good Clinical Practice
INRC	International Neuroblastoma Response Criteria
ITT	Intent-To-Treat
MRT	Malignant Rhabdoid Tumour MRI
Magnetic resonance imaging	
OS	Overall survival
PR	Partial Response
PMNC	Peripheral Mononuclear Cells
PD	Progressive Disease
RT	Radiotherapy
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SSI	Significant Safety Issue
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTP	Time to progression

1. ADMINISTRATIVE INFORMATION

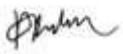
Protocol: ACCT008/ASSG35; Version 5; 18Sep2020
Novartis Ref: CLBH589XAU13T
ClinicalTrials.gov Identifier: NCT04897880

1.1 Document Version History

Version Date	Version	Author	Signature	Change Description	Reason/Comment
December 2024	1.0	AR		Initial release.	Not applicable.

1.2 Approvals

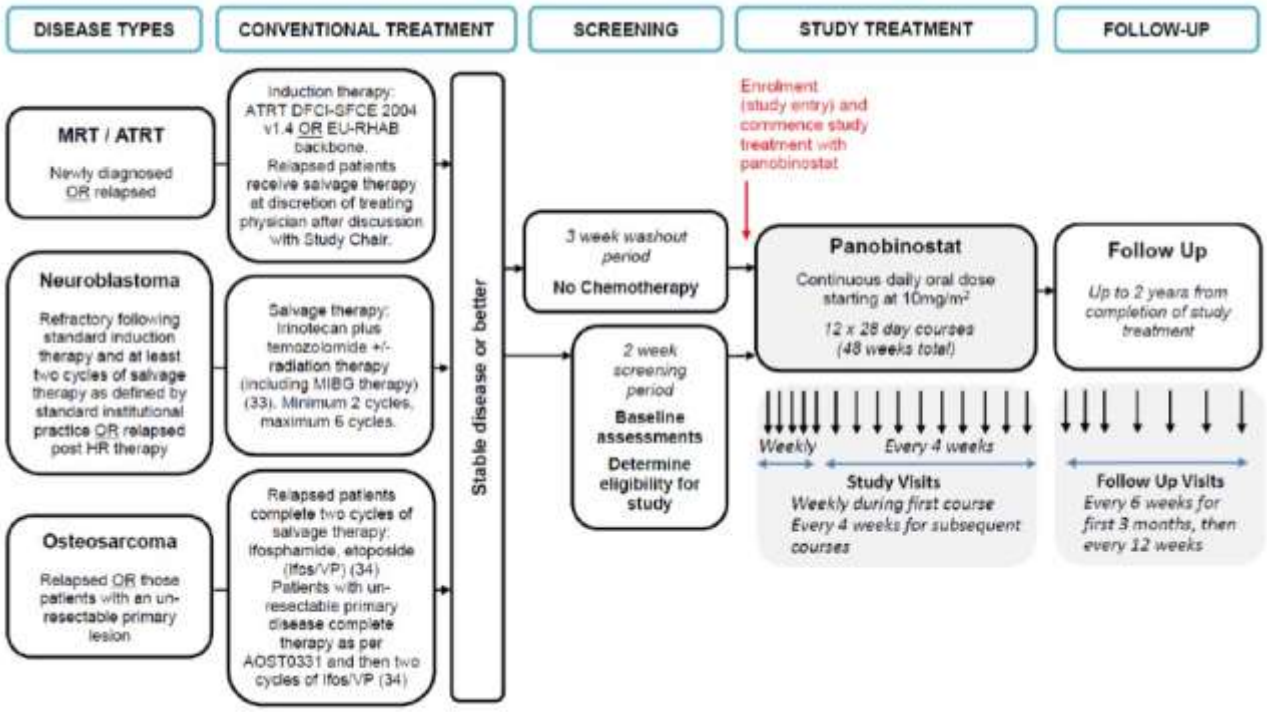
The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

Name	Role on Study	Affiliation	Signature	Date
Prof David Ashley	Study Chair	The Preston Robert Tisch Brain Tumor Centre Duke University Medical Centre		21Aug2024 (draft reviewed, unable to review December 2024 version)
A/Prof Jayesh Desai	Study Chair	Drug Development Group Peter MacCallum Cancer Centre	[redacted]	06/01/25
Dr Paul Wood	Study Chair	Children's Cancer Centre, Monash Children's Hospital, Monash Health		16Dec2024
Alannah Rudkin	Statistician	Murdoch Children's Research Institute		09Dec2024

2. STUDY SYNOPSIS

This is a multi-centre, open-label, single-arm Phase 2 study in participants < 40 years old with refractory solid and CNS tumours. Participants were stratified by tumour type: osteosarcoma, neuroblastoma, and malignant rhabdoid tumour or atypical teratoid rhabdoid tumours (ATRT/MRT). Eligible participants included those with refractory or relapsed osteosarcoma, neuroblastoma and MRT/ATRT, or newly diagnosed MRT/ATRT that were stable after completion of standard therapy. Participants must have had histologic verification of the diagnosis of malignancy at either the time of initial diagnosis or at relapse. A maximum of 60 participants (20 per strata) were planned to be treated with panobinostat as a continuous oral dose starting at 10 mg/m^2 per day. Study treatment was planned to continue until disease progression, intolerable toxicity, or participant decision for a maximum of one year (12 treatment courses of 28 days duration each). Patients will be followed for up to 2 years from completion of study therapy.

The study design schematic is presented in Figure 2.1-1



Schedule of Analyses:
The dose evaluation and study expansion analyses in each strata were evaluated separately to this SAP. They are described below.

Dose Evaluation
The biological activity of panobinostat at a given dose level was determined by the real-time acetylation status (as defined by acetylated H4 on Peripheral Mononuclear Cells (PMNC)s) at day eight compared with pre-treatment. This analysis was performed for a minimum of 2 patients in each strata at the required dose levels. Once biological activity was confirmed via the acetylation status of H4 on PMNC at any dosing level in any strata, it did not need to be repeated and dosing adjustments could be made on dose limiting toxicities (DLTs) and adverse events (AEs) alone.

i) If significant increase in acetylation, and therefore biological activity, was demonstrated at the starting dose of 10 mg/m^2 then no dosing adjustment took place unless DLTs/AEs were observed. ii) In the case of drug toxicity and irrespective of biological activity, intra-patient dose reductions in 2 mg/m^2 increments were applied, and the dose level for the strata reviewed. iii) In the case of inadequate biological activity, with no toxicity, intra-patient dose escalations of 2 mg/m^2 were recommended.

The final dose per strata was the level where continuous dosing was maintained for a 4-week period with acceptable toxicity and biological effect. The final Panobinostat doses were 6mg/m2 per day for the ATRT/MRT cohort, 8mg/m2 per day for the neuroblastoma cohort, and 4mg/m2 per day for the osteosarcoma cohort.

Study Expansion

The study employed a Simon two-stage minimax design (1). At trial design stage an initial efficacy analysis was planned when a minimum of 9 patients in each strata were enrolled. The regimen would be considered worthy of further study if disease stability at 4 months was observed in 3 or more of the first 9 patients in a stratum and less than 30% of patients experience a DLT at the final dose level. If this was achieved, recruitment would proceed to a total of 20 patients in each strata.

However, due to uncertainty of panobinostat supply, a decision was made to permanently close the osteosarcoma and neuroblastoma arms prior to the initial efficacy analysis when 9 and 2 had been enrolled in the osteosarcoma and neuroblastoma arms, respectively. At that time, it was decided to continue recruitment into the ATRT/MRT cohort who had met the initial efficacy criteria for 3/9 participants with disease stability and <30% experiencing a DLT at the final dose level. The ATRT/MRT arm closed in December 2021 due to termination of the study supply agreement, at that time 14 participants had been enrolled in the ATRT/MRT arm.

2.1 OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

The primary aims of this study are as follows:

a) To define the anti-tumour activity of low dose continuous panobinostat.

b) To define and describe the toxicities of panobinostat for patients on a continuous dosing schedule.

2.1.2 SECONDARY OBJECTIVES

The secondary aims are:

a) To define the anti-tumour activity of low dose continuous panobinostat using functional imaging techniques.

b) To assess the biologic activity of low dose panobinostat by measuring histone acetylation status in peripheral mononuclear cells (PMNC), bone marrow and fresh tumour tissue specimens in all patients (when available).

2.2 ENDPOINTS

2.2.1 PRIMARY ENDPOINTS

a) Estimated 2-year Event free survival (EFS). EFS is calculated as the time from study enrolment to first documented disease progression, relapse or second malignancy, or death from any cause

b) Estimated 2-year Overall Survival (OS). OS is calculated as the time from study enrolment to death from any cause.

c) Safety, as assessed by incidence of adverse events graded according to the NCI-CTCAE, version 4.0 [Time Frame: 1 week to 12 months after intervention commencement]

2.2.2 SECONDARY ENDPOINTS

a) Efficacy as measured by Clinical Benefit Rate (percentage of patients with stable disease or better using MRI/CT imaging) at 6 and 12 months after intervention commencement. Stable disease is defined as MRT/ATRT/Osteosarcoma with complete response (CR), partial response (PR), minor response (MR), stable disease (SD) overall response. Neuroblastoma with CR/PR/SD or Non-CR/Non-PD overall response.

2.2.3 EXPLORATORY ENDPOINTS

a) Comparing overall and event free survival for ATRT patients to historical data. Comparison of EFS and OS up to 2 years post enrolment.

2.3 STUDY POPULATION

Inclusion criteria:

- Patients must be < 40 years of age.
- Patients with refractory or relapsed osteosarcoma, neuroblastoma and MRT/ATRT or newly diagnosed MRT/ATRT. Patients must have had histological verification of the diagnosis of malignancy at time of diagnosis or relapse.
- Patient's disease is considered refractory, according to their treating hospital standard practice guidelines, to conventional therapy except for newly diagnosed ATRT/MRT. This includes relapsed patients who may be off treatment. Patients must have stable disease (SD) or better.
- Karnofsky ≥ 60% for patients ≥ 16 years of age, OR Lansky ≥ 60% for patients < 16 years of age.
- Life expectancy of greater than 8 weeks.
- Fully recovered from acute toxic effects of all prior chemotherapy, immunotherapy or radiotherapy prior to entering study.
- Patients with CNS tumours who are receiving dexamethasone must be on a stable or decreasing dose for at least 1 week.
- Adequate BM function – peripheral ANC ≥ 750/µl (0.75 x 10^9/L); platelet count ≥ 75,000/µl (75 x 10^9/L); haemoglobin ≥ 8g/dL (80 g/L).
- Adequate renal function – age-adjusted normal serum creatinine or GFR > 70ml/min/1.73m^2.
- Adequate liver function – total bilirubin ≤ 1.5 x IULN for age, ALT ≤ 5 x IULN for age, and albumin ≥ 2g/dL (20g/L).
- Adequate cardiac function – shortening fraction of ≥ 27% OR ejection fraction of ≥ 50% by echocardiogram.
- Adequate respiratory function defined as no evidence of dyspnoea at rest, no exercise intolerance and pulse oximetry (SaO_2) > 94% in room air.
- Adequate CNS function – seizure free for 2 months.

- Adequate serum calcium, magnesium, and potassium concentrations – all must be ≥ ILLN for age, with or without supplementation.
- If female and post-menarcheal, pregnancy test must be negative.
- If of reproductive potential, have agreed to use effective contraceptive method.
- If female and lactating, have agreed not to breastfeed.
- Patient and/or their legal representative have signed a written informed consent form.

Exclusion criteria:

- Patients who have received myelosuppressive chemotherapy and/or biologic therapy within 3 weeks (4 weeks if prior nitrosourea).
- Patient has received local palliative radiotherapy within 2 weeks.
- Patient has received craniospinal radiotherapy within 3 weeks.
- Patient has received ≥ 50% radiation of pelvis within 6 weeks.
- Patient has received other substantial BM radiation within 6 weeks.
- Have received growth factor(s) within 1 week.
- Are receiving enzyme inducing anticonvulsant therapy. In order to be eligible, patients must be transferred to and stabilised on an eligible anticonvulsant as listed in Appendix II as per local institutional practice. (See Appendix II for a list of enzyme inducing and nonenzyme inducing anticonvulsants).
- Are on medications associated with prolongation of QTc interval as listed in Appendix III.
- Are receiving hydrochlorothiazide.
- Are receiving metronidazole and/or disulfiram. This is due to the increased risk of metabolic acidosis when patients are concomitantly on panobinostat and metronidazole and/or disulfiram.
- Patients with uncontrolled sepsis.
- Patients who have previously received panobinostat.
- Patients with symptoms of congestive heart failure, uncontrolled cardiac rhythm disturbance, or a QTc (Fridericia's formula) that is > 450 msec.

2.4 INTERVENTION

A three-week washout period was required after conventional myelosuppressive chemotherapy and/or biologic therapy to start Panobinostat therapy.

Panobinostat was supplied in capsule form and administered orally. Each course consisted of 4 weeks (28 days). Treatment will continue for up to 12 months consisting of 12 treatment courses, each of 4 weeks (28 days) duration.

Intra-patient dose adjustments of 2 mg/m2 were made to a starting dose of 10 mg/m^2 based on DLTs/AEs and biological activity, and dose level for that stratum reviewed. For full criteria for dose escalation and reduction see protocol version 5.0 18Sep2020. The final dose per strata was the level where continuous dosing is maintained for a 4-week period with acceptable toxicity and biological effect.

Protocol therapy could be terminated for the following reasons: a)
Progressive disease (radiographic or clinical)

b) Irreversible or unacceptable dose-limiting toxicity
c) Other adverse event
d) Refusal of further protocol therapy by patient or parent/guardian
e) Physician determines it is not in the patient's best interest
f) Pregnancy
g) Termination or suspension of clinical trial

The investigator's clinical judgment was used to determine whether a subject should be removed from treatment or from the study due to progressive disease, AE or DLT, or another reason.

2.5 RANDOMISATION AND BLINDING

This a single arm open label study.

2.6 SAMPLE SIZE

The study employed a Simon two-stage minimax design (1). A 30% gain in Clinical Benefit Rate (CBR) was considered as the minimum gain required to warrant further study of this regimen. In this case the clinical benefit to be observed is stability of disease. 70% stability at 4 months would be indicative of clinical utility, whereas a rate of 40% would be the lower limit of interest, with α = .15 and β = .10. The minimal accrual number required in each strata was 14 patients. This was increased to 20 patients in each strata, over 3 years, for a total of 60 patients.

The biological activity analysis was performed for a minimum of 2 patients in each strata at the required dose levels.

2.7 STUDY PROCEDURES

All entry requirements had to be completed during the four-week screening period before study enrolment.

Studies to be Obtained	**Pre-salvage therapy [a]**	**Screening prior to enrolment (Baseline)**	**Weeks 1-4 (first 28 day course)**	**Subsequent Months (28 day courses)**	**Follow-up [b]**
History (including AEs/DLTs)		X	Weekly	X	X
Physical Exam (height, weight, BSA)		X	Weekly	X	X
Performance Status Refer to Appendix I		X	Weekly	X	X
Full Blood Evaluation (FBE) with Differential & Blood Film		X	Weekly	X	X
Urinalysis [c]		X	Weekly	X	
Urea & Electrolytes Calcium, Magnesium & Potassium		X	Weekly	X	X
Renal Function/GFR/Creatinine		X	Weekly	X	X
Liver Function Tests including Total Protein & Serum Albumin		X	Weekly	X	X

Thyroid Function Tests (TFTs including TSH, T3, T4)		X		End of therapy	
CT/MRI of Primary Tumour [d]	X	X		2 monthly	X [e]
MRI Spine (ATRT only) **Refer to Section** Error! Reference source not found.	X	X		2 monthly [f]	X [e,f]
FDG-PET/DOTATATE [g]	X	X		2 monthly	X [e]
MIBG (Neuroblastoma only)	X	X		2 monthly	X [e]
CXR (ATRT only)	X	X [h]		End of therapy	
Abdominal Ultrasound (ATRT only)	X	X [h]		End of therapy	
MRI Brain (MRT only, not primary site)	X	X [h]		End of therapy	
CT Chest / CXR (Osteosarcoma only, non-lung primary)	X	X (CT and CXR)		2 monthly (CXR, CT and CXR at end of therapy)	X (CT or CXR)
Blood Samples – HDACi [Not applicable to United States]		Pretreatment	7 days after first dose		
Bone Marrow Evaluation (only if clinically indicated) including HDACi studies [Not applicable to United States]		X	End of Course	If positive at baseline or as clinically indicated	
Pregnancy Test [i]		X			
ECG		X	End of Course	X	
Echocardiogram		X		6 monthly	

a If applicable and where available, these will be the last set of imaging investigations performed as part of routine patient care prior to salvage therapy.

b Up to 2 years from completion of therapy. c Not mandated at every time point, urinalysis performed per institutional practice.

d Use the same imaging modality throughout the course of the study e Follow-up imaging studies are not required if there is documented evidence of overt clinical progression. Follow-up imaging is 3 monthly or per routine follow-up.

f Repeat Spine MRI only if initially positive

g Use FDG-PET in non-CNS MRT.

Use FDG-PET in all osteosarcoma and neuroblastoma (if not MIGB avid).

Could be DOTATATE scans in neuroblastoma patients, when available, following discussion with Study Chair.

h Scans performed outside the four-week screening period as standard of care, are acceptable.

i Females of child-bearing age required a negative pregnancy test prior to entering study.

j Follow-up for participants remaining on study was every 6 weeks for the first 3 months, then every 3 months for up to 2 years from completion of therapy. Patients may needed to be seen more frequently than these defined intervals based on their medical needs.

In instances where participants discontinued study drug before completion of therapy, they were encouraged to continue with study follow-up visits as long as such procedures did not pose a risk to the well-being of the patient.

Measurement of effect

Survival Measure

At each study visit (every 28 days) while on treatment, patient study status will be collected. If a patient terminates treatment early, the reason and date will be collected. This includes progressive disease, toxicity or adverse event, and death.

Follow-up for participants remaining on study will be every 6 weeks for the first 3 months, then every 3 months for up to 2 years from completion of therapy.
After treatment completion, patient death or lost to follow up will be collected at follow up visits.

Event Measure

Radiographic progressive disease will be captured in the overall response at each disease assessment as per section 9 of protocol. Clinical progression will be documented during study visits as described above.

Full details of the background to the trial and its design are presented in the protocol.

3. GENERAL STATISTICAL METHODOLOGY

3.1. SCOPE

The biological activity analysis was performed during the trial to determine dosing levels (real time acetylation data). This analysis and its results are not in the scope of this analysis. See section 4.3 of protocol for more information.

3.2. ANALYSIS SOFTWARE

All analyses will be performed using Stata Release 18 or later.

3.3. DATA VERIFICATION

All variables included in analysis will be assessed for validity. Range checks will be performed on all continuous variables. Categorical variables will be assessed for consistency with the protocol and relevant data dictionary. Any data verification queries will be raised with the study team.

3.4. DEFINITION OF BASELINE

Baseline will be defined period between consent date and date of enrolment.

Date of enrolment (day 0) will be the eligibility visit date in the database, *visdat*.

Baseline values used to define changes in measurements over time for each participant are defined as the closest to and including day 0 within the preceding 28 days. Where more than one measurement is available within this window the closest to enrolment will be used.

Patients were enrolled on the study once all eligibility requirements for the study were met. The National Coordinating Centre, in conjunction with the Study Chair, reviewed the submitted eligibility information and supporting source documentation.

Start of treatment is defined as (Week 1 Day 1 *visdat*) from the study status database.

3.5. ASSESSMENT OF RESPONSE

The revised Response Evaluation Criteria in Solid Tumours (RECIST), Version 1.1, will be used to evaluate tumour response for non-CNS solid tumours. The Response Assessment in NeuroOncology Working Group's updated response assessment criteria (RANO) will be used to evaluate tumour response for CNS solid tumours. The revised International Neuroblastoma Response Criteria will be used to evaluate tumour response for neuroblastoma. For further details of these definitions please refer to the protocol.
The study investigator's evaluation of overall response will be used in analysis.

3.6. ADVERSE EVENTS

Adverse events will be coded according to the Common Terminology Criteria for Adverse Events V4.0 (CTCAE V4.0).

3.7. YEAR, MONTH AND DURATION

The following conversion factors will be used to convert days to months or years: 1 month =30.4375 days, 1 year = 365.25 days. Duration will be calculated as (end date – start date + 1).

4. DESCRIPTIVE STATISTICS

Analysis will be completed by disease strata;
MRT/ATRT (strata 1), osteosarcoma (strata 2), or neuroblastoma (strata 3).

4.1. RECRUITMENT AND FOLLOW-UP

A CONSORT flowchart of patient enrolment and follow up will be provided.
The number of patients and the proportions who were consented, screen failed, enrolled, completed treatment, and completed follow-up will be summarised by disease strata.

4.2. BASELINE CHARACTERISTICS

Patient and disease characteristics at baseline will be summarised by disease strata. Continuous variables will be reported with mean with range and categorical variables will be reported with frequencies and proportions. For neuroblastoma, results for the two individual patients will be reported. A listing of all characteristics for each patient will be provided.

This will include number with study indication (MRT/ATRT, osteosarcoma, neuroblastoma), disease event (newly diagnosed, relapsed, refractory, un-resectable lesion), number of relapse if applicable, disease status (stable disease, remission), central nervous system (CNS) disease, best response to prior treatment, prior surgery, prior chemotherapy, prior radiotherapy (RT) and location, RT total dose (Gy) if applicable, and other prior treatment.
Patient demographics summarised will include age, sex, ethnicity, indigenous status, and baseline performance score (Karnofsky ≥ 16 years old, Lansky < 16 years old).

4.3. PROTOCOL DEVIATIONS

Protocol deviations will be listed and summarised by disease strata.

4.4. COMPLIANCE

Mean (range) number of treatment courses completed (28 days per cycle) and time in follow up (weeks) will be summarised by disease strata. The number of patients who completed each course (full 28 days) will be listed for each disease strata, with reasons for early treatment termination listed.
Panobinostat dose (mg/m^2) days compliant, and total days of treatment will be summarised by mean and range by disease strata. A summary of dose received by treatment course will also be listed.

4.5. CONCOMITANT THERAPIES

All medications and significant non-drug therapies will be recorded throughout the study period. This includes medications commenced from 14 days before until 28 days after the study drug is administered. Medications include both prescribed and over the counter (OTC) medications including herbal and vitamin treatments.

A listing of concomitant medications will include medication name and reason sorted by disease strata.

5. ANALYSIS OF THE PRIMARY OUTCOME(S)

5.1. MAIN ANALYSIS

5.1.1. Event free survival

Primary Estimand

Population: All patients eligible and enrolled into trial with MRT/ATRT (strata 1), osteosarcoma (strata 2), or neuroblastoma (strata 3).
Treatment: Panobinostat
Outcome: Estimated 2-year Event free survival (EFS). EFS is calculated as the time from study enrolment to first documented disease progression, relapse or second malignancy, or death from any cause up to 2 years after study enrolment. The latest possible time of risk being 2 years after enrolment, or the last date known alive.

Summary measure: The probability of EFS (Kaplan-Meier) at with 95%CI will be estimated each stratum*. Kaplan- Meier curves will be plotted for EFS probability, enrolment date as start of risk period. Median EFS time will be calculated at 2 years post-enrolment.

**only calculated if stratum had adequate sample size (osteosarcoma and ATRT/MRT only).*

Subgroup Analysis:
Descriptive statistics (proportions) by subgroup for each disease strata.

Age at enrolment <36 months (3 years old) vs. ≥36 months
Radiation therapy (RT) vs. no RT
Disease status at trial entry (complete response vs stable disease)

Intercurrent Events
Potential intercurrent events:
Patient comes off study or treatment due to toxicity before an event is observed. Patient comes off study or treatment to receive another treatment.

Strategy for handling intercurrent event:
Treatment policy
EFS will be estimated for patients regardless of early treatment or trial termination. This approach assumes that data collected is reflective of those missing data (patients who withdrew from trial).

Sensitivity Analysis
Composite Strategy
Patients coming off study or protocol treatment due to an irreversible or unacceptable dose limiting toxicity or a Serious adverse event (SAE) before an event is observed, will be handled by the composite strategy. The removal from study/treatment date will be treated as an event.

Patients coming off study or protocol treatment to receive another treatment will also be handled by this strategy in the same analysis.

Primary Estimand Calculation

EFS will be estimated and visualised using the Stata sts list and graph commands.

stset tvar, fail(event) origin(time enrol_date) enter(time consent_date)
sts list, strata(disease type) risk table(6 12 24) sts graph, strata(disease type) risk table(0 6 12 18 24) xlabel(0 6 12 18 24) tmax(24) Median EFS will be estimated using Stata stsum command *stsum, by(disease type)*

Subgroup analysis
The proportion in each group and 95%CI will be estimated using Statas *ci proportions* command.

Sensitivity analysis (as above with alternate event) *stset tvar, fail(event_comp) origin(time enrol_date) enter(time consent_date)*

Where time is in months and patients will be censored at their last known contact alive.

5.1.2. Overall survival

Primary Estimand
Population: All patients eligible and enrolled into trial with MRT/ATRT (strata 1), osteosarcoma (strata 2), or neuroblastoma (strata 3).
Treatment: Panobinostat, dosing as per protocol.
Outcome: Estimated Overall Survival (OS). OS is calculated as the time from study enrolment to death from any cause.
Summary measure: The OS probability (Kaplan-Meier) and 95%CI will be estimated for each stratum* up to 2 years post- enrolment. Kaplan- Meier curves will be plotted for OS probability; enrolment date as start of risk period. The number of deaths and the median OS time will be reported up to 2 years post-enrolment.

**only calculated if stratum had adequate sample size (osteosarcoma and ATRT/MRT only).*

Subgroup Analysis:
As per section 5.1.1

Intercurrent Events
Potential intercurrent events:
Patient comes off study due to toxicity, or to start a new treatment.

Strategy for handling intercurrent event:

Patients coming off study due to a related toxicity or to start a new treatment will be handled with the treatment policy. OS will be analysed for all patients regardless of treatment received until last study visit.

Sensitivity Analysis

Composite Strategy

Patients coming off study due to toxicity or to start a new treatment before death could be observed will be handled by the composite strategy. The removal from study date will be treated as an event/death in sensitivity analysis.

Estimand Calculation

OS will be estimated and visualised using the Stata sts list and graph commands.
stset tvar, fail(death) origin(time enrol_date) enter(time consent_date) sts list, strata(disease type)
sts graph, strata(disease type) tmax(24)
Median OS will be estimated using Stata stsum command *stsum, by(disease type)*

Where time is in months and patients will be censored at their last known contact alive.

5.1.3 -Safety

Adverse events will be summarised by grade and type defined by CTCAE Version 4 from 1 week to 12 months after intervention commencement.

Relationship to study drug (definite, probable, possible) adverse events summarised in a table, with the worst AE grade reported by each participant.

A summary table of Dose Limiting Toxicities will include AE type, grade, and frequency.

6. SECONDARY ENDPOINTS

Measurement of effect

Evaluation of disease will be conducted by the investigator as outlined in the protocol. Stable disease will be confirmed on study entry, and tumour response determined at each imaging assessment time point. Overall response as determined by the investigator will be used for the secondary efficacy outcome analysis.

Response Assessment for Non-CNS Solid Tumours - Osteosarcoma and MRT

The revised Response Evaluation Criteria in Solid Tumours (RECIST), Version 1.1, will be used to evaluate tumour response, as assessed by medical imaging.

Overall Response for Non-CNS Tumours (Measurable Disease)

. **Target lesions**	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	**CR**
CR	Non-CR/non-PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non-CR/non-PD/ Not evaluated	No	**PR**
SD	Non-CR/non-PD/ Not evaluated	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**
Not evaluated	Non-PD	No	**Inevaluable**

Overall Response for Non-CNS Tumours (Non-Measurable Disease)

Non-target lesions	**New lesions**	**Overall response**
CR	No	**CR**
Non-CR/non-PD	No	**Non-CR/nonPD**
Not all evaluated	No	**Inevaluable**
Unequivocal PD	Yes or No	**PD**
Any	Yes	**PD**

Response Assessment for CNS Solid Tumours- ATRT

The Response Assessment in Neuro-Oncology Working Group's (RANO) updated response assessment criteria, will be used to evaluate tumour response. Overall response will be defined by the response of the individual components – contrast enhancing lesions, non-enhancing lesions, new lesions, corticosteroids, and clinical status per the investigator at each imaging timepoint.

Complete Response (CR)	***Requires <u>all</u> the following criteria to be met:***	
	Contrast enhancing disease	Complete Response: Complete disappearance of all measurable and non-measurable disease
	New lesions	No new lesions
	Non-enhancing lesions	Stable or improved T2/FLAIR lesions
	Corticosteroids	Patient off corticosteroids (or on physiologic replacement doses only)
	Clinical Status	Stable or improved clinically
Partial Response (PR)	***Requires <u>all</u> the following criteria to be met:***	
	Contrast enhancing disease	Partial Response: ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions
		No progression of non-measurable disease
	New lesions	No new lesions
	Non-enhancing lesions	Stable or improved T2/FLAIR lesions on the same or lower dose of corticosteroids compared with baseline scan
	Corticosteroids	Corticosteroid dose at the time of evaluation no greater than the dose at time of baseline scan
	Clinical Status	Stable or improved clinically
Stable Disease (SD)	***Requires <u>all</u> the following criteria to be met:***	
	Contrast enhancing disease	Stable Disease: Does not qualify for complete response, partial response, or progression
	New lesions	No new lesions
	Non-enhancing lesions	Stable T2/FLAIR lesions on the same or lower dose of corticosteroids compared with baseline scan
	Corticosteroids	Corticosteroid dose at the time of evaluation no greater than the dose at time of baseline scan
	Clinical Status	Stable or improved clinically
Progressive Disease (PD)	***Defined by <u>any</u> of the following:***	
	Contrast enhancing disease	Progressive Disease: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumour measurement obtained at baseline (if no decrease) or best response, on stable or increases doses of corticosteroids
		Clear progression of non-measurable disease
	New lesions	Any new lesion
	Non-enhancing lesions	Significant increase in T2/FLAIR lesions on stable or increasing doses of corticosteroids, not caused by comorbid events
	Corticosteroids	N/A *
	Clinical Status	Clear clinical deterioration not attributable to other causes apart from the tumour or changes in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition.

* Increase in corticosteroid alone will not be taken into account in determining PD, in the absence of persistent clinical deterioration

NOTE: Patients with non-measurable disease only cannot have a complete response, the best response possible is stable disease.

Response Assessment for Neuroblastoma

The revised International Neuroblastoma Response Criteria (INRC) will be used to evaluate tumour response. Overall response will be defined by the response of the individual components – soft tissue, bone, and bone marrow disease per the investigator at each imaging timepoint..

Overall Response	Criterion
Complete Response (CR)	All components meet criteria for CR
Partial Response (PR)	PR in at least one component and all other components are either CR, MD (minimal disease, bone marrow), PR (soft tissue or bone), or not involved* (NI); no component with PD
Minor Response (MR)	PR or CR in at least one component but at least one other component with SD; no component with PD
Stable Disease (SD)	SD in one component with no better than SD or not involved* (NI) in any other component; no component with PD
Progressive Disease (PD)	Any component with PD

* Site not involved at study entry and remains uninvolved.

See Appendix VI in protocol for more detail of Tumour Response Assessment Criteria and definitions.

6.1 MAIN ANALYSIS

6.1.1 Clinical Benefit rate

Estimand

Population: All patients eligible and enrolled into trial with MRT/ATRT (strata 1), osteosarcoma (strata 2), or neuroblastoma (strata 3).
Treatment: Panobinostat, dosing as per protocol.
Outcome: Efficacy as measured by Clinical Benefit Rate (CBR)
Summary measure: Clinical benefit rate (CBR) is the proportion of patients with an overall response of stable disease or better at MRI/CT imaging at 6- and 12-months post treatment commencement. CBR proportion (95% CI) and number will be reported for each disease strata.

Stable disease is defined as MRT/ATRT/Osteosarcoma with CR/PR/MR/SD/ overall response. Neuroblastoma with CR/PR/SD or Non-CR/Non-PD overall response.

6- and 12- months post treatment commencement will be the overall response disease assessment closest to 6 or 12 months *(30.437 days × (6 or 12) = XX days*) after the patient first dose (day 1 course 1) or enrolled date if patient didn't start treatment.

Intercurrent Events

Potential intercurrent events:

Patient comes off study or treatment due to toxicity before an event is observed. Patient comes off study or treatment to receive another treatment.

Strategy for handling intercurrent event:

Treatment policy

CBR will be estimated for patients regardless early treatment or trial termination..

Sensitivity Analysis

Composite Strategy

Composite strategy includes early treatment termination as no benefit (not stable disease).

Calculation of Estimand

The CBR and 95%CI will be estimated using Statas *ci proportions* command.

7. EXPLORATORY OUTCOMES

7.1 COMPARISON TO HISTORICAL DATA

Comparison of NORTH ATRT patients to historical control will be outlined in a separate document. This will be attached as an appendix to this SAP once complete.

8. MISSING DATA

The number of patients with missing disease response/imaging at each timepoint will be listed by disease strata and any reasons provided listed.

Last patient contact and timepoint censored will be summarised and listed for patients.

9. LISTINGS, TABLES AND FIGURES

9.1. LIST OF LISTINGS

Listing 1	Listing of patient and disease characteristics at baseline
Listing 2	Listing of protocol deviations by strata
Listing 3	Concomitant Medication

9.2. LIST OF TABLES

Table 1	Patient recruitment and screening
Table 2	Disease Characteristics at Baseline
Table 3	Patient Characteristics at Baseline
Table 4	Summary of treatment courses and follow up completed.
Table 5	Number of patients completed each course by disease strata
Table 6	Panobinostat Dosing by disease strata
Table 7	Panobinostat Compliance by disease strata
Table 8	Primary Outcome: Event free Survival
Table 9	Primary Outcome: Overall Survival
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Table 11	Dose Limiting Toxicities
Table 12	Secondary Outcome: Clinical Benefit Rate
Table 13	Missing data
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9.3. LIST OF FIGURES

Figure 1	CONSORT diagram- NORTH trial
Figure 2	Kaplan-Meier curves of EFS
Figure 3	Kaplan-Meier curves of OS

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APPENDIX A. EXAMPLE TABLES AND FIGURES

Listing 1: Patient and disease characteristics at baseline

1

Table 1- Patient recruitment

	Disease Type

Trial Stage				**MRT/ ATRT**	**Neuroblastoma†**	**Osteosarcoma†**
Consented	*n*	*n*	*n*			
Screen fail	*n*	*n*	*n*			
Enrolled	*n*	*n*	*n*			
Number completed full treatment course (12 cycles)	*n*	*n*	*n*			
Completed full follow-up (2 years post end of treatment)	*n*	*n*	*n*			

†The osteosarcoma and neuroblastoma arms were closed to recruitment prior to the initial efficacy analysis due to Panobinostat supply analysis due to Panobinostat supply

Table 2 – Disease Characteristics at Baseline

Disease	**MRT/ATRT**	Malignant Rhabdoid Tumor (MRT)	Atypical Teratoid Rhabdoid Tumor (ATRT)	**Osteosarcoma**	**Neuroblastoma**

	n	n	n	n	n
Event	Newly Diagnosed n(%)	Newly Diagnosed n(%)	Newly Diagnosed n(%)	Un-resectable lesion n(%)	Refractory n(%)
	Relapsed n(%)	Relapsed n(%)	Relapsed n(%)	Relapsed n(%)	Relapsed n(%)
Relapse no.	1 n(%) 2 n(%) 3 n(%) 4 n(%)	1 n(%) 2 n(%) 3 n(%) 4 n(%)	1 n(%) 2 n(%) 3 n(%) 4 n(%)	1 n(%) 2 n(%) 3 n(%) 4 n(%)	1 n(%) 2 n(%) 3 n(%) 4 n(%)
Status	CR (n%) SD (%)	CR (n%) SD (%)	CR (n%) SD (%)	CR (n%) SD (%)	CR (n%) SD (%)
CNS involvement n(%)		n(%)	n(%)	n(%)	n(%)
Best Response	CR n(%) SD n(%) PR n(%)	CR n(%) SD n(%) PR n(%)	CR n(%) SD n(%) PR n(%)	CR n(%) SD n(%) PR n(%)n(%)	CR n(%) SD n(%) PR n(%)
Surgery n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Chemotherapy n(%)		n(%)	n(%)	n(%)	n(%)
RT	RT n(%) Spine n(%) Chest/thorax n(%) Abdomen n(%) Tibia n(%)	Brain or skull n(%) Spine n(%) Chest/thorax n(%) Abdomen n(%) Tibia n(%)	Brain or skull n(%) Spine n(%) Chest/thorax n(%) Abdomen n(%) Tibia n(%)	Brain or skull n(%) Spine n(%) Chest/thorax n(%) Abdomen n(%) Tibia n(%)	Brain or skull n(%) Spine n(%) Chest/thorax n(%) Abdomen n(%) Tibia n(%)
RT Total Dose (Gy) mean(min-max)		mean(min-max)	mean(min-max)	mean(min-max)	mean(min-max)
	BMT/PBSC n(%)	BMT/PBSC n(%)	BMT/PBSC n(%)	BMT/PBSC n(%)	BMT/PBSC n(%)
Other treatment					
	Other (list) n(%)	Other (list) n(%)	Other (list) n(%)	Other (list) n(%)	Other (list) n(%)

Complete Response (CR),Stable Disease (SD), Central Nervous System (CNS),Radiotherapy (RT), RT Total Dose (mean, range), Bone Marrow Transplant (BMT), Peripheral blood stem cells (PBSC)

Table 3 – Patient Characteristics at Baseline

Disease		Malignant Rhabdoid	Atypical Teratoid Rhabdoid Tumor		
MRT/ATRT	mean (min-max)	mean (min-max)	mean (min-max)	mean (min-max)	X,X
Tumor (MRT) (ATRT) Osteosarcoma Neuroblastoma	Male n(%) Female n(%)	Male n(%) Female n(%)	Male n(%) Female n(%)	Male n(%) Female n(%)	X,X
Age	Asian n(%) Black n(%) Caucasian n(%) Unknown n(%) Other n(%)	Asian n(%) Black n(%) Caucasian n(%) Unknown n(%) Other n(%)	Asian n(%) Black n(%) Caucasian n(%) Unknown n(%) Other n(%)	Asian n(%) Black n(%) Caucasian n(%) Unknown n(%) Other n(%)	X,X
Sex					
Ethnicity	Neither Aboriginal or Torres Strait Islander n(%)	Neither Aboriginal or Torres Strait Islander n(%)	Neither Aboriginal or Torres Strait Islander n(%)	Neither Aboriginal or Torres Strait Islander n(%)	
	Both Aboriginal or Torres Strait Islander n(%)	Both Aboriginal or Torres Strait Islander n(%)	Both Aboriginal or Torres Strait Islander X,X n(%)	Both Aboriginal or Torres Strait Islander n(%)	
	Aboriginal n(%) Torres Strait Islander n(%)	Aboriginal n(%) Torres Strait Islander n(%)	Aboriginal n(%) Torres Strait Islander n(%)	Aboriginal n(%) Torres Strait Islander n(%)	
	Unknown n(%)	Unknown n(%)	Unknown n(%)	n(%)	
Indigenous status	Unknown n(%)		Unknown n(%)		
Performance Score	mean (min-max)	mean (min-max)	mean (min-max)	mean (min-max)	X,X

Performance Score (Karnofsky ≥ 16 years old, Lansky < 16 years old). Neuroblastoma n=2, numbers reported.

Listing 2: List of protocol deviations, by site.

Site	**Deviation**	**Timepoint**	**Date**
x	*x*	*x*	*x*

Table 4 – Summary of treatment courses and follow up completed.

	MRT/ATRT	**Osteosarcoma**	**Neuroblastoma**
Number of completed courses of treatment	*mean(min-max)*	*mean(min-max)*	*X,X*
Time in Follow Up (weeks) Mean and range (min-max)	*mean(min-max)*	*mean(min-max)*	*X,X*

Table 5 – Number of patients completed each course by disease strata.

	Number of Patients who completed Course (28 days)				
				Number of Early	**Early Termination**
MRT/ATRT	*n*	*n*	*n*	*n*	*x*
Osteosarcoma	*n*	*n*	*n*	*n*	*x*
Neuroblastoma	*n*	*n*	*n*	*n*	*x*
Terminations	*n*	*n*	*n*	*n*	*x*
Reason	*n*	*n*	*n*	*n*	*x*
Course 1	*n*	*n*	*n*	*n*	*x*
Course 2	*n*	*n*	*n*	*n*	*x*
Course 3	*n*	*n*	*n*	*n*	*x*
Course 4	*n*	*n*	*n*	*n*	*x*
Course 5	*n*	*n*	*n*	*n*	*x*
Course 6	*n*	*n*	*n*	*n*	*x*
Course 7	*n*	*n*	*n*	*n*	*x*
Course 8	*n*	*n*	*n*	*n*	*x*
Course 9					
Course 10					
Course 11					
Course 12					

Table 6 – Panobinostat Dosing by Course and Disease strata

Patient Dosing (mg/m2)

	MRT/ATRT	Osteosarcoma	Neuroblastoma
Course 1	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 2	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 3	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 4	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 5	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 6	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 7	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 8	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 9	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 10	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 11	*mean(minmax)*	*mean(minmax)*	*X,X*
Course 12	*mean(minmax)*	*mean(minmax)*	*X,X*

Table 7 – Panobinostat Compliance by Course and Disease strata

	Dose (mg/m2)	Days Compliant	Total Days
MRT/ATRT	*mean(min-max)*	*mean(min-max)*	*mean(min-max)*
Osteosarcoma	*mean(min-max)*	*mean(min-max)*	*mean(min-max)*
Neuroblastoma	*X, X*	*X, X)*	*X, X)*

Mean and range (min-max)

Listing 3: Concomitant Medication

Sorted by disease strata.

Disease Strata	Medication Name	Medication Reason
MRT/ATRT	*x*	*x*

MRT/ATRT	*x*	*x*
MRT/ATRT	*x*	*x*
Osteosarcoma	*x*	*x*
Osteosarcoma	*x*	*x*
Osteosarcoma	*x*	*x*
Neuroblastoma	*x*	*x*
Neuroblastoma	*x*	*x*
Neuroblastoma	*x*	*x*

Table 8 - Primary Endpoint: Event Free Survival

Primary Outcome- EFS			
	x(95%CI)	*x(95%CI)*	*X*
	x(min-max)	*x(min-max)*	*NA*
	x(95%CI)	*x(95%CI)*	*X*
	x(min-max)	*x(min-max)*	*NA*
	Proportion (95%CI)		
	Proportion(95%CI)		
	Proportion(95%CI)		
	MRT/ATRT	**Osteosarcoma**	**Neuroblastoma**
Overall EFS (95%CI)			
Median EFS, months (95%CI)			
Sensitivity Analysis - Composite Strategy			
Overall EFS (95%CI)			
Median EFS, months (95%CI)			
Subgroup Analysis			
Age at enrolment (<36 months vs. (≥36 months)			
Radiation therapy (RT vs. no RT)			

Up to 2 years post study enrolment

Table 9: Primary Endpoint: Overall Survival

Primary Outcome- Overall Survival	**MRT/ATRT**	**Osteosarcoma**	**Neuroblastoma**

Disease status			
Overall Survival (95%CI)	*x(95%CI)*	*x(95%CI)*	
Median overall survival, months (95%CI)	*x(95%CI)*	*x(95%CI)*	
Number of deaths	*n*	*n*	*n*
Subgroup Analysis	*Proportion (95%CI)*		
Age at enrolment (<36 months vs. (≥36 months)	*Proportion (95%CI)*		
Radiation therapy (RT vs. no RT)	*Proportion (95%CI)*		
Disease Status			

Up to 2 years post study enrolment

Table 10 - Treatment-Related Adverse Events

Treatment-Related Adverse Events Toxicity (CTCAE v4.0)	Any Grade				
	n(%)	*n*	*n*	*n*	*n*
Grade 4 *event*	*n(%)*	*n*	*n*	*n*	*n*
event *event*	*n(%)*	*n*	*n*	*n*	*n*
event *event*	*n(%)*	*n*	*n*	*n*	*n*

Event Grade 1
Grade 2
Grade 3

Table 11 – Dose Limiting Toxicities

Dose Limiting Toxicity Adverse Events Toxicity (CTCAE v4.0)	
1	*n*
2	*n*
3	*n*
4	*n*

Grade Frequency
event event event event

Table 12- Secondary Outcome: Clinical Benefit Rate

Secondary Outcome- Clinical Benefit Rate			
	x(95%CI)	*x(95%CI)*	*x*
	x(95%CI)	*x(95%CI)*	*x*
	x(95%CI)	*x(95%CI)*	*x*
	x(95%CI)	*x(95%CI)*	*x*
	MRT/ATRT	**Osteosarcoma**	**Neuroblastoma**

CBR at 6 months %(95%CI)
CBR at 12 months %(95%CI)
Sensitivity Analysis - Composite Strategy
CBR at 6 months %(95%CI)
CBR at 12 months %(95%CI)

Table 13 -Missing Data

Missing Outcome Data		
Disease Strata	**Data Missing**	**Reason missing**
MRT/ATRT	*Disease Assessment*	*Scan not performed (n)*
Osteosarcoma	*Lesions not measured on scan (n)*	
Neuroblastoma		*Other reasons (n)*

Table 14 -Censored table

Study ID	Last patient contact (Timepoint)	Censored (Y/N)
1	*Week 6*	*Y*
2	*Follow-up*	*N*

STATISTICAL REPORT

Final Audit Report 2025-01-06

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By:	Alannah Rudkin (alannahrudkin@gmail.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAAW_WVYuYZRonABUXmlJo-ObbJ8Z7yT7TD

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