# Protocol

**A Phase I/II Dose-escalation and Expansion Cohort Trial of Intracerebroventricular Radioimmunotherapy Using $^{177}$Lu-DTPA-omburtamab in Pediatric and Adolescent Patients with Recurrent or Refractory Medulloblastoma**

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## SYNOPSIS

**Title of trial:** A Phase I/II Dose-escalation and Expansion Cohort Trial of Intracerebroventricular Radioimmunotherapy Using $^{177}$Lu-DTPA-omburtamab in Pediatric and Adolescent Patients with Recurrent or Refractory Medulloblastoma

**Indication:** Recurrent or refractory medulloblastoma.

**Number of investigators and trial centers:**
Part 1 will be conducted at approximately 9 sites: 4 sites in North America and 5 in Europe
Part 2 is planned to be conducted at approximately 2 additional sites in North America and Europe

**Development phase:** Phase I/II

**Objectives:**
The primary objective of Part 1 (dose-escalation phase) is to explore the tolerability of up to 2 cycles of intracerebroventricular $^{177}$Lu-DTPA-omburtamab treatment in pediatric and adolescent patients with recurrent or refractory medulloblastoma. The maximum tolerated dose (MTD) and/or the recommended Phase 2 dose for Part 2 (RP2D) will be determined.
The primary objective of Part 2 (cohort-expansion phase) is to establish a safety profile of repeated dosing of $^{177}$Lu-DTPA-omburtamab in pediatric and adolescent patients with recurrent or refractory medulloblastoma.
The secondary objectives of Part 1 are:

- to evaluate the absorbed radiation doses to cerebrospinal fluid (CSF) and blood of $^{177}$Lu-DTPA-omburtamab after intracerebroventricular administration
- to evaluate organ dosimetry of $^{177}$Lu-DTPA-omburtamab
- to evaluate the pharmacokinetic (PK) profile of $^{177}$Lu-DTPA-omburtamab.

The secondary objectives of Part 2 are:

- to evaluate the PK profile of $^{177}$Lu-DTPA-omburtamab
- to evaluate the investigator-assessed response
- to evaluate the investigator-assessed DoR
- to evaluate PFS
- to evaluate overall survival (OS).

**Methodology/trial design:**
This is a Phase I/II, open-label, safety and efficacy trial in pediatric and adolescent patients (3 to 19 years) with recurrent or refractory medulloblastoma.
Part 1 will be a dose-escalation phase with a 3+3 sequential-group design (except for the first dose level, which will consist of a single patient only), in which patients will receive a maximum of two 5-week cycles of treatment with intracerebroventricular $^{177}$Lu-DTPA-omburtamab. A Data Monitoring Committee will review the safety data from previous dose levels and provide recommendations on whether dose escalation should continue. In Part 1, Cycle 1 will comprise a dosimetry dose on Day 1 and a treatment dose on Day 8, while Cycle 2 will comprise a treatment dose on Day 1. Successive dosing groups will receive escalating treatment doses of lutetium-177 conjugated to a fixed mass dose of approximately 1 mg DTPA-omburtamab; the dosimetry dose will be fixed for all patients.
Part 2 will be a cohort-expansion phase in which patients will receive a maximum of 5 cycles of intracerebroventricular $^{177}$Lu-DTPA-omburtamab at the RP2D determined in Part 1. All cycles in Part 2 will comprise a treatment dose on Day 1.
The AEs will be evaluated according to CTCAE version 5.0.

**Number of patients:**
In Part 1, the chosen sample size is customary for dose-escalation studies of this nature and is not based on statistical considerations. It is estimated that up to 25 patients will participate in Part 1. Actual number of patients will depend on the number of dose-limiting toxicities (DLTs) observed.
In Part 2, 24 patients are expected to participate, which will provide at least 90% probability to detect an adverse event (AE) occurring in 10% of exposed patients.
The assumption is that 20 out of the 24 patients in Part 2 are evaluable. With 20 patients evaluable for response and a response rate of 25% (~ to 5 responders out of 20), the lower limit of the 95% confidence interval will be 9%.

**Key criteria for inclusion and exclusion:**
The key inclusion criteria are:

1. Histologically confirmed diagnosis of medulloblastoma.
2. SHH, Group 3, or Group 4 according to World Health Organization 2016 classification.
3. Recurrent or refractory to frontline therapy, defined as:
    a. For Part 1 only: Recurrent (maximum of 2 recurrences) or refractory to frontline therapy. Prior frontline or second-line therapy may involve surgery, craniospinal irradiation, stereotactic radiosurgery, and multi-agent chemotherapy regimens.
    b. For Part 2 only: Recurrent (maximum of 1 recurrence) or refractory to frontline therapy. Patients with recurrent disease must have received second-line chemotherapy for progressive disease. Prior frontline or second-line therapy may involve surgery, craniospinal irradiation, stereotactic radiosurgery, and multi-agent chemotherapy regimens.
4. Have refractory disease, focal or multifocal recurrent disease, or pure leptomeningeal disease. Cytological or radiographic remission is allowed; however, not simultaneously.
5. Performance status score of 50 to 100, both inclusive, on the Lansky [<16 years] or Karnofsky [≥16 years] scales.
6. Aged 3 to 19 years, both inclusive, at the time of the first planned dose of trial treatment.
7. Life expectancy of at least 3 months, as judged by the investigator.
8. Acceptable liver and kidney function and hematological status.
9. Written informed consent from legal guardian(s) and/or child obtained in accordance with local regulations. Pediatric patients must provide assent as required by local regulations.

The key exclusion criteria are:

1. Obstructive or symptomatic communicating hydrocephalus as determined by Ommaya patency/CSF flow assessment.
2. Any tumor lesion measuring >15 mm in the smallest diameter.
3. Ventriculoperitoneal shunts without programmable valves. Ventriculo-atrial or ventriculo-pleural shunts.
4. Grade 4 nervous system disorder. Stable neurological deficits due to brain tumor or surgery and hearing loss are allowed.
5. Uncontrolled life-threatening infection.
6. Received radiation therapy (focal or cranio-spinal irradiation), systemic or intrathecal cytotoxic chemotherapy, or immunotherapy (including monoclonal antibodies; corticosteroids not included) less than 3 weeks prior to the Dosimetry Dose (or until recovery from clinically significant adverse events). Received nitrosoureas less than 6 weeks prior to the Dosimetry Dose.
7. Received any prior anti–B7-H3 treatment.
8. Non-hematologic organ toxicity Grade 3 or above; specifically, any renal, cardiac, hepatic, pulmonary, and gastrointestinal system toxicity.

9. Other significant disease or condition that in the investigator's opinion would exclude the patient from the trial.
10. Females of childbearing potential, who are pregnant, breast feeding, intend to become pregnant, or are not using highly effective contraceptive methods or males who are not using highly effective contraceptive methods.

**Test products, dose, and mode of administration:**

Local safety instructions for storage and handling of radioactive drug products must be strictly followed. Radiation safety precautions may include patient isolation and the use of lead shielding, or designated rooms to ensure that the dose rate in the surrounding areas meets regulatory requirements. $^{177}$Lu-DTPA-omburtamab will be administered via an indwelling intracerebroventricular access device (e.g., Ommaya catheter). The infusion reservoir must be flushed with human serum albumin (HSA) and CSF after each infusion. To avoid an additional procedure and burden to the patient, it can be considered to place the intracerebroventricular access device in connection with any tumor resection procedure that may be performed before entry into the trial. In this case, the informed consent form must be signed before the tumor resection.

In Part 1 only, at the start of the first 5-week treatment cycle, a 5 mCi dosimetry dose will be administered on Day 1. If the dosimetry dose of 5 mCi delivers a too low acquisition of radioactivity count, the dosimetry dose will be increased to 10 mCi for subsequent patients, at the Sponsor's discretion. A treatment dose with a fixed mass dose of approximately 1 mg DTPA-omburtamab will be labelled with increasing radioactivity doses of lutetium-177 and will be administered on Day 8 of Cycle 1. The planned radioactivity dose levels in the escalation phase are:

- Dose Level 1 (1+2 patients): 10 mCi
- Dose Level 2 (3+3 design): 25 mCi
- Dose Level 3 (3+3 design): 50 mCi
- Dose Level 4 (3+3 design): 65 mCi
- Dose Level 5 (3+3 design): 85 mCi.

A maximum of 1 additional intermediate dose level may be added to the trial if warranted based on the findings from previous dose levels. If a patient experiences a Grade 3 or 4 non-hematologic AE or other DLTs after receiving the dosimetry dose, the treatment dose will not be administered, and the patient will be discontinued from trial treatment. Patients who are not discontinued from treatment will be eligible for 1 additional treatment cycle with the same dose as administered in the first cycle. The second treatment cycle of Part 1 will consist of a treatment dose on Day 1.

In Part 2, all treatment cycles will consist of a treatment dose on Day 1; the dose level will be the RP2D determined in Part 1. Patients who are not discontinued from treatment will be eligible for up to 5 treatment cycles in Part 2. Dose reductions due to toxicity are permitted in Part 2 only.

**Reference therapy, dose, dose form, and mode of administration:**

Not applicable.

**Duration of patient participation in trial:**

Planned screening duration: 29 days (longer screening period is allowed (e.g., due to logistics); however, screening period of >60 days with individual patient considerations to be discussed with the sponsor.

Planned treatment duration: Up to two 5-week treatment cycles may be administered in Part 1 and up to five 5-week cycles may be administered in Part 2.

Planned duration of trial participation: 19 weeks (Part 1); 104 weeks (Part 2).

Estimated recruitment period: Q4-2021 to Q3-2023.

**Analysis populations:**

The following analysis sets will be included for this trial:

**Safety Analysis Set:** will consist of all patients who received at least 1 dosimetry or treatment dose.

**DLT Evaluable Analysis Set:** will include patients in the dose escalation who as a minimum is evaluated during the 5 weeks DLT evaluation period, or who has a DLT during the DLT evaluation period. This analysis set is a subset of the Safety Analysis Set.
**Full Analysis Set (FAS):** will consist of all patients in the Safety Analysis Set.
**Dosimetry Analysis Set (Part 1 only):** will consist of all patients who received the dosimetry dose and have evaluable data for absorbed doses to CSF and blood or by whole-body planar scan.
**PK Analysis Set:** will consist of all patients who received at least 1 treatment dose of trial drug and have evaluable pharmacokinetic (PK) data.

**Evaluation: Safety**

Primary Endpoint:

- Part 1: Number of DLTs.
- Part 2: Number and severity of TEAEs.

**Evaluation: Efficacy**

The secondary efficacy endpoints are:

Part 2

- Response, as defined by the RAPNO criteria (as determined from MRI assessments, neurological examination, and CSF cytology).
    - ORR calculated as the proportion of all evaluable patients achieving a response (PR or CR) as best overall response at the time of assessment.
- Investigator-assessed DoR, defined as the time from response (CR or PR) to progression.
- PFS defined as the time from first treatment to date of leptomeningeal progression or death from any cause, whichever comes first.
- OS defined as the time from first treatment to date of death.

**Evaluation: Vital signs and other safety procedures**

Patients will undergo monitoring for AEs; vital sign assessments; neurological assessments and radiographical investigation for evaluation of neurological AEs); and assessment of performance status (Lansky [<16 years] or Karnofsky [≥16 years] scales).

**Evaluation: Dosimetry, imaging, and laboratory evaluations**

Patients will undergo:

- Clinical chemistry and hematology assessments.
- Blood and CSF draws for calculation of absorbed doses (Part 1 only).
- Whole-organ dosimetry measurements based on gamma (and SPECT, if possible) scans (Part 1 only).
- Brain and spine MRI.
- CSF sampling for cytology, total protein, glucose, circulating tumor DNA (ctDNA; if the patient has given informed consent to this analysis), and cell count.
- Blood and CSF draws for PK; and blood and CSF draws for anti-drug antibody (ADA) analysis and for potential culture (in case of elevated body temperature).

**Statistical methods:**
Summary statistics, listings, and statistical analyses will be performed for patients included in the relevant analysis sets. PFS will be censored at last disease evaluation with no evidence of progression. OS will be censored at last date known to be alive.

**Efficacy statistical methods:**
The investigator-assessed response will be assessed in Part 2 according to RAPNO criteria (MRI, neurological examination, and CSF cytology), as well as according to CSF cytology alone. The ORR and its 95% confidence intervals will be calculated using the Clopper-Pearson exact methodology.
The investigator-assessed DoR will be estimated using Kaplan-Meier methods. The median DoR and corresponding 95% confidence interval will be calculated.
PFS time will be estimated using Kaplan-Meier methods. The median PFS time as well as the proportion of patients without PFS events at 1 and 2 years post first dose will be estimated in Part 2, along with their respective 95% confidence intervals.
Estimates of OS at 1 year and 2 years post first dose will be made in Part 2 only using Kaplan-Meier methods.

**Safety statistical methods:**
Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or later. All AEs will be listed. Non–treatment-emergent AEs (Non-TEAEs) will be listed separately. All TEAEs, adverse drug reactions (ADRs), AEs of special interest, serious AEs, and serious ADRs will be summarized by system organ class and preferred terms for each treatment group. In Part 1, the DLTs will be listed.
Changes in vital signs, hematology, and clinical chemistry parameters from baseline to the end of the trial will be examined. Treatment-emergent changes from normal values to abnormal values in key laboratory parameters may be identified. Development of ADA will be examined. Effects on cognitive functions will be assessed by summarizing changes from baseline in performance testing results using descriptive statistics.

**Statistical methods for calculation of absorbed doses to CSF and blood (Part 1 only):**
The radioactivity measurements in CSF and blood will be used for calculation of the mean absorbed radiation dose after administration of the dosimetry and treatment doses. The maximum observed radioactivity count in blood will be determined and the elimination half-life, residence time, and the time-activity curves will be presented. Individual and mean absorbed radiation dose to CSF and blood will be summarized using descriptive statistics for all patients in the Dosimetry Analysis Set and by trial site.

**Dosimetry statistical methods (Part 1 only):**
Spinal cord, brain, and non-target region of interest absorbed radiation doses will be estimated based on whole-body planar gamma camera (and SPECT, if possible) scans, and CSF and blood mean absorbed radiation doses will be calculated on the basis of measurement of scintillation counts in the samples. Individual and mean dosimetry data will be calculated per trial site and will be summarized using descriptive statistics.

**Pharmacokinetic statistical methods:**
The serum and CSF PK parameters of $^{177}$Lu-DTPA-omburtamab following the treatment doses in Cycles 1 and 2 will be calculated using standard noncompartmental methods in both study parts. Standard PK parameters (such as maximum observed drug concentration, area under the concentration-time curve, half-life) will be calculated.

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## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADA | anti-drug antibody |
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| CAR | chelator-to-antibody ratio |
| CD | cluster of differentiation |
| CDR | complementarity-determining regions |
| cGy | centigray |
| Ci | curie |
| $C_{max}$ | maximum observed drug concentration |
| CNS | central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| CR | complete response |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| ctDNA | circulating tumor deoxyribonucleic acid |
| CTA | clinical trial agreement |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | dose-limiting toxicity |
| DMC | Data Monitoring Committee |
| DoR | duration of response |
| DTPA | Used as short for p-SCN-Bn-CHX-A″-DTPA (see this abbreviation) |
| EC | Ethics Committee |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| ELISA | enzyme-linked immunosorbent assay |
| EOT | end of treatment |
| eGFR | estimated glomerular filtration rate |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GM-CSF | granulocyte-macrophage colony-stimulating factor |
| GMP | Good Manufacturing Practices |
| Gy | gray |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| ICV | intracerebroventricular |
| IMP | investigational medicinal product |
| IRB | Institutional Review Board |
| IV | intravenous |
| mCi | millicurie |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| NOAEL | no-observed-adverse-effect level |

| | |
|---|---|
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PR | partial response |
| p-SCN-Bn-CHX-A″-DTPA | [(R)-2-Amino-3-(4-isothiocyanatophenyl)propyl]-trans-(S,S)-cyclohexane-1,2- diamine-pentaacetic acid |
| RAPNO | Response Assessment in Pediatric Neuro-oncology |
| RP2D | recommended Phase II dose |
| SAE | serious adverse event |
| SOC | system organ class (MedDRA classification) |
| SPECT | single-photon emission computed tomography |
| SPR | surface plasmon resonance |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| VP | Ventriculoperitoneal |
| Y-mAbs | Y-mAbs Therapeutics |

# 1. INTRODUCTION

Y-mAbs Therapeutics (Y-mAbs) is developing $^{177}$Lu-DTPA-omburtamab for the treatment of B7-H3-positive tumors, including medulloblastoma. The same monoclonal antibody, omburtamab, radiolabeled with iodine-131 ($^{131}$I-omburtamab) is currently under development for treatment of pediatric patients with recurrent or refractory neuroblastoma with central nervous system (CNS)/leptomeningeal metastasis.

When labeled with a radionuclide, omburtamab targets B7-H3 (also known as cluster of differentiation 276 [CD276]) on the cell membrane and delivers a radioactive payload, including DNA damage and cell death, to B7-H3–expressing tumors without being internalized or activating effector functions[1, 2]. B7-H3 is a transmembrane glycoprotein of the B7/CD28 immunoglobulin superfamily that is minimally expressed in normal tissues and modulates immune functions in tumor surveillance, infections, and autoimmune diseases. B7-H3 is overexpressed on the cell membrane of a broad range of human tumors of neuroectodermal, mesenchymal, and epithelial origin in adult and pediatric patients and its presence is often correlated with negative prognosis and poor clinical outcome. Lutetium-177 and iodine-131 are β-radiation emitters with similar half-lives (approximately 6.7 and 8 days, respectively)[3]. Lutetium-177 has a lower maximum β-emission than iodine-131 (496 keV versus 610 keV), resulting in a shorter penetration distance (mean 0.67 mm) in soft tissue, making this radionuclide ideal for delivering tumoricidal β-radiation to small volumes such as minimal residual disease following surgery, micrometastatic disease, and tumor cells near the surface of cavities, while further reducing the risk of normal tissue toxicity such as neurodegeneration and myelosuppression and negating specific toxicity to the thyroid. In addition, 2 photon energy peaks (208 keV and 113 keV) can be used for gamma imaging, demonstrating its use as a theragnostic agent.

Notably, while the iodogen method of preparation of $^{131}$I-omburtamab is well suited for the limited population with recurrent or refractory neuroblastoma with CNS/leptomeningeal metastasis, there are important manufacturing advantages to the use of lutetium-177 for radioimmunotherapy for indications in larger populations, such as the availability of carrier-free lutetium-177 and reduced radiation exposure during radiopharmaceutical manufacturing and patient administration. $^{177}$Lu-DOTATATE (Lutathera) is approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors and several lutetium-177–radiolabeled pharmaceuticals are actively under study for the treatment of multiple cancer indications such as prostate ($^{177}$Lu-J591[4], $^{177}$Lu-PSMA-617[5]) and non-Hodgkin's lymphoma ($^{177}$Lu-lilotomab[6]).

This will be a first-in-human trial of $^{177}$Lu-DTPA-omburtamab in pediatric and adolescent patients with recurrent or refractory medulloblastoma.

## 1.1. Trial Rationale

Medulloblastoma is the most common pediatric brain tumor, comprising around 20% of all childhood brain tumors, with 25% to 35% diagnosed at <3 years of age and a peak incidence at 5 to 9 years of age[7]. These embryonal tumors of the cerebellum have a propensity to invade and disseminate in the cerebrospinal fluid (CSF), and frequently metastasize throughout the CNS.

Approximately 30% of pediatric cases present with metastases at diagnosis, with the highest incidence in infants.

Standard frontline therapy for medulloblastoma includes surgery, high-dose craniospinal radiation, and chemotherapy. Recurrent/refractory medulloblastoma represents a marked clinical challenge because there is no generally accepted standard of care. Often re-surgery and systemic chemotherapy are pursued, in addition to autologous stem cell transplantation. However, the outcome is dismal and often fatal.

The overall survival (OS) rates for medulloblastoma are 70% to 80% in standard-risk patients[8] and 30% to 60% in high-risk patients[9]. Significant neurocognitive deficits emerge in nearly all survivors and effective treatment regimens associated with less neurocognitive toxicity would provide an improvement over current therapeutic options[10].

Medulloblastoma is one of the many tumor types shown to express increased levels of the transmembrane glycoprotein B7-H3. Recent studies have shown that at least 96% of pediatric medulloblastomas stained positive for B7-H3 expression[11, 12] and in another study in patients with a range of solid tumors, 2 out of 2 medulloblastoma patients exhibited binding of omburtamab[1]. Its broad expression in medulloblastoma, along with limited expression on normal cells and lack of expression on normal brain tissues[1, 2] make B7-H3 an ideal target for an antibody therapy.

In the current trial, Y-mAbs proposes to use the same intracerebroventricular route of administration as for $^{131}$I-omburtamab in neuroblastoma patients with CNS/Leptomeningeal relapse, to evaluate the safety and efficacy of $^{177}$Lu-DTPA-omburtamab radioimmunotherapy in recurrent or refractory medulloblastoma patients. The reasons for developing $^{177}$Lu-DTPA-omburtamab include:

- Lutetium-177 and iodine-131 are both β-emitters with comparable half-lives.
- While iodine-131 is directly labeled to omburtamab via tyrosine residues in both the antigen-binding complementarity-determining regions (CDR) and non-CDR regions, lutetium-177 binds to the chelator, p-SCN-Bn-CHX-A''-DTPA conjugated to omburtamab.
- The lower maximum β-energy of lutetium-177 versus iodine-131 (496 keV versus 610 keV) may curtail myelosuppression observed with $^{131}$I-omburtamab.
- Lutetium-177 is not associated with specific toxicity to the thyroid, the main organ for iodine uptake.
- Lutetium-177 is an ideal radionuclide for delivering tumoricidal β-radiation to small volumes, including minimal residual disease following surgery, micrometastatic disease, and tumor cells near the surface of cavities, while further reducing the risk of normal tissue toxicity.

- Lutetium-177 has 2 photon energy peaks (208 keV and 113 keV) that can be used for imaging with the same therapeutic agent in whole-body planar scintillation camera scanning and most single-photon emission computed tomography (SPECT) scanners available today.

- Manufacturing of $^{177}$Lu-DTPA-omburtamab for a larger population is more practical than manufacturing of $^{131}$I-omburtamab given the availability of commercial, Good Manufacturing Practices (GMP), carrier-free lutetium-177 and the lower operator radiation exposure inherent to its lower maximum β-energy.

This first-in-human trial will primarily evaluate the safety of intracerebroventricular (i.e., administered into the cerebral ventricles of the brain) $^{177}$Lu-DTPA-omburtamab and secondarily, the dosimetry and efficacy in pediatric and adolescent medulloblastoma patients.

## 1.2. Background

### 1.2.1. Summary of Clinical Information for $^{131}$I-omburtamab

$^{131}$I-omburtamab has been studied in clinical trials initiated at Memorial Sloan Kettering Cancer Center over 15 years. In Trial 03-133, intracerebroventricular administration of $^{131}$I-omburtamab is being evaluated in patients with central nervous system/leptomeningeal neoplasms in an open-label, single-dose trial with a dose-escalation part that has been finalized and a cohort-expansion part that is currently ongoing (NCT00089245). The primary objective of trial 03-133 is to define the clinical toxicities of intracerebroventricular $^{131}$I-omburtamab. The trial has patients in follow-up and is closed for enrolment.

In a separate Phase II/III trial, intracerebroventricularly administered $^{131}$I-omburtamab is under evaluation in neuroblastoma patients with CNS relapse as evidenced by CNS/leptomeningeal metastases (Investigational New Drug 009351; NCT03275402; Trial 101).

The overall safety profile of $^{131}$I-omburtamab administered as an intracerebroventricular infusion to in total 133 pediatric patients with neuroblastoma and CNS/LM metastasis is based on data from two clinical trials (Trial 03-133, N = 109; and Trial 101, N = 24). Furthermore, $^{131}$I-omburtamab has been administered to a total of 170 patients in Trial 03-133 and Trial 101 without any indication of acute adverse effects on the major physiological systems (e.g., cardiovascular, respiratory, renal, and central nervous systems).

**Trial 03-133**
As of 30 June 2019, the most common adverse events (AEs) (≥10%) were lymphopenia, platelet count decreased, white blood cell count decreased, neutrophil count decreased, vomiting, hemoglobin decreased, cough, headache, contusion, diarrhea, rhinorrhea, decreased appetite, pyrexia, abdominal pain, and nausea. The most common serious adverse events (≥5%) were platelet count decreased, neutrophil count decreased, and white blood cell count decreased. Less frequent, but clinically significant serious adverse events (<5%) include myelodysplastic syndrome, acute myeloid leukemia, seizure, and depressed level of consciousness. 10% of patients discontinued from treatment with $^{131}$I-omburtamab due to adverse events, including decreased platelet count, chemical meningitis, and immune thrombocytopenic purpura. Serious infusion reactions included chemical meningitis, vomiting, pyrexia, headache, and nausea.

**Trial 101**
As of 01 Jun 2020, the most common AEs (≥10%) were platelet count decreased, white blood cell count decreased, lymphocyte count decreased, neutrophil count decreased, nausea, headache and anemia, vomiting, pain, and pyrexia. The most common serious adverse reaction (≥10%) was platelet count decreased. Less frequent, but clinically significant serious AEs related to $^{131}$I-omburtamab administration were chemical meningitis and intracranial hemorrhage. The most common AE leading to discontinuation of $^{131}$I-omburtamab was platelet count decreased. Serious infusion reactions occurred in one patient (chemical meningitis).

**Selected AEs in Trials 03-133 and 101**
Myelosuppression is caused by radiation-related adverse effects on the bone marrow and may result in severe and prolonged cytopenia. In Trial 03-133 and Trial 101, a total of 81.7% and 87.5%, respectively, had at least one event related to cytopenia. The most commonly reported hematopoietic cytopenia events were lymphopenia, platelet count decreased, and white blood cell count decreased.

Chemical meningitis is an inflammation of the meninges. Symptoms include fever, headache, nausea, and vomiting. Three patients experienced SAEs of chemical meningitis (2/109 and 1/24 in Trial 03-133 and Trial 101, respectively).

**Serious infusion reactions in Trials 03-133 and 101**
$^{131}$I-omburtamab may potentially cause serious infusion reactions. Serious infusion reactions were reported by 4% of patients across Trial 03-133 and Trial 101 (4/109 and 1/24 respectively). These included chemical meningitis, nausea (1/109 in Trial 03-133) and vomiting (1/109 in Trial 03-133). Anaphylactic reactions have not been reported in these clinical trials.

**Recommended Phase II Dose for $^{131}$I-omburtamab**
A recommended Phase II dose (RP2D) of 50 mCi/cycle for up to 2 cycles was established for $^{131}$I-omburtamab for the treatment of B7-H3-positive tumors with CNS/leptomeningeal metastases, including neuroblastoma patients. Patients with other indications were also treated in Trial 03-133, including those with ependymoma, medulloblastoma, and B7-H3-positive solid tumors with CNS/leptomeningeal metastases including malignant melanoma and ovarian cancer.

**Efficacy**
The median survival after treatment with $^{131}$I-omburtamab of the 107 neuroblastoma patients with CNS/leptomeningeal metastases included in the interim analysis of Trial 03-133, was 50 months versus 6 months in various historical cohorts[13-15]. While survival past 3 years for patients with neuroblastoma CNS/leptomeningeal metastases historically is rare (<10%), the estimated 3- and 5-year survival for neuroblastoma patients with CNS/leptomeningeal metastases relapse receiving $^{131}$I-omburtamab are 56% and 43%, respectively. Survivors have been followed for up to 14.1 years, and 57 (53.3%) of the 107 patients treated with $^{131}$I-omburtamab remained alive at their last follow-up. These results have led to Breakthrough Designation by the US Food and Drug Administration.

In the same trial (03-133), 21 patients with recurrent medulloblastoma and 9 patients with ependymoma were treated with $^{131}$I-omburtamab. Although the number of patients was too low to evaluate the efficacy, the therapy was well tolerated in the medulloblastoma cohort.

$^{131}$I-3F8, which targets tumor expressing ganglioside GD2 is another intracerebroventricular β-emitter radioimmunotherapy for the treatment of medulloblastoma, which was evaluated in a clinical trial at Memorial Sloan Kettering Cancer Center. In the Phase II trial (NCT00445965), data from 43 medulloblastoma patients showed superior survival among those receiving $^{131}$I-3F8 as part of second remission consolidation when compared to patients with radiographically measurable disease. The median of the total absorbed dose in CSF was 1,453 cGy (range: 350 to 2,784 cGy). No treatment-related deaths were reported[16].

### 1.2.2. Pharmacology of $^{177}$Lu-DTPA-omburtamab

#### *1.2.2.1. Binding Affinity of Omburtamab for B7-H3*

The B7-H3 receptor is overexpressed on the cell membrane of a broad spectrum of tumor types and is minimally expressed in normal human tissues[1, 17-19]. Omburtamab, a B7-H3 antibody, was used to confirm specific B7-H3 expression in formalin-fixed and paraffin-embedded medulloblastoma tumors in an immunohistochemistry study sponsored by Y-mAbs.

The binding affinity of omburtamab for recombinant B7-H3 antigens from mouse, rat, monkey, and human was determined using surface plasmon resonance (SPR). Omburtamab binds to monkey and human B7-H3 with high affinity and equilibrium dissociation constants of 1.6 and 1.1 pM, respectively, while binding to mouse or rat B7-H3 was not detectable by SPR.

The in vitro binding affinity of omburtamab for recombinant human B7-H3 protein (2Ig and 4Ig isoforms; 4Ig is the dominant isoform) was compared for naked, chelated, and lutetium-175–labeled antibody using SPR. Higher conjugation ratios of CHX-A″-DTPA reduced the affinity of omburtamab and $^{175}$Lu-DTPA-omburtamab to 4Ig-B7-H3. Labeling of the conjugates with cold lutetium-175 did not further change omburtamab binding affinity for B7-H3 protein and labeling with iodine-127 did not affect binding affinity. For a chelator-to-antibody ratio of 3 (CAR 3), binding affinity to 4Ig-B7-H3 is 5- to 7-fold lower than omburtamab or $^{131}$I-omburtamab. A CAR 3 was chosen for development of the clinical product.

Accordingly, an in vitro potency test for the final product, $^{177}$Lu-DTPA-omburtamab, has been developed using biotinylated B7-H3–streptavidin beads. This assay has consistently shown immunoreactivities greater than 70% at end-of-synthesis for $^{177}$Lu-DTPA-omburtamab (CAR 3).

#### *1.2.2.2. Tumor-targeting and Antitumor Activity of Radiolabeled Omburtamab*

Athymic nude mice bearing DAOY (B7-H3–expressing medulloblastoma) xenografts were given a single intravenous (IV) dose of $^{177}$Lu-DTPA-omburtamab (CAR 3) or $^{125}$I-omburtamab for proof-of-concept tumor targeting. SPECT/computed tomography (CT) and *ex vivo* gamma counting of organs showed that over 120 hours, accumulation of $^{177}$Lu-DTPA-omburtamab in the tumor was similar to or greater than that observed with $^{125}$I-omburtamab.

In another study, nonclinical antitumor efficacy was evaluated in male and female nude mice subcutaneously inoculated with DAOY xenografts and given a single IV injection of 522 ± 22 µCi $^{177}$Lu-DTPA-omburtamab (CAR 3) (mass dose of 50 µg), 509 ± 62 µCi $^{131}$I-omburtamab (mass dose of 50 µg), or 50 µg omburtamab. For $^{177}$Lu-DTPA-omburtamab, measurements taken prior to Day 15 post dose suggest lower percent change in tumor volume in animals that received radiolabeled omburtamab compared to unlabeled omburtamab. However, all animals from this group died on study due to non-recovering myelosuppression as measured by hematocrit and hematopoietic cell counts, a known dose-limiting toxicity (DLT) for radioimmunotherapy (euthanasia for weight loss [4/7 animals], found dead [3/7 animals]); see Section 1.2.3. The findings are consistent with mortality seen in female athymic nude mice given a single intraperitoneal injection of approximately 500 µCi $^{177}$Lu-DTPA-omburtamab, $^{131}$I-omburtamab, or $^{131}$I-humanized-omburtamab (CAR3) (50 µg mass dose). By Day 19, all animals in the $^{177}$Lu-DTPA-omburtamab group were found dead or euthanized (2/8 found dead, 5/8 euthanized due to weight loss, 1/8 euthanized due to low hematocrit); 5/6 and 3/7 animals in the $^{131}$I-omburtamab and $^{131}$I-humanized-omburtamab groups, respectively, were euthanized due to weight loss. Hematocrit and red and white blood cell counts were decreased in animals given $^{177}$Lu-DTPA-omburtamab or $^{131}$I-omburtamab. Follow-up evaluations support the conclusion that 500 µCi was sufficient to cause severe, non-recovering myelosuppression due to bone marrow toxicity. The dose-limiting organ for IV injection was the skeleton (i.e., bone marrow) and dosimetry estimates indicated the maximum tolerated dose (MTD) for IV injection in this model are 245 µCi $^{177}$Lu-DTPA-omburtamab and 236 µCi $^{131}$I-omburtamab, levels that were exceeded by nearly double in the efficacy study. Given the nonclinical antitumor activity of $^{131}$I-omburtamab in athymic nude mice bearing HTB82 xenografts[20], the clinical data, the demonstrated binding affinity to recombinant human B7-H3 protein by both SPR and immunohistochemistry, tumor-to-blood ratios, mean residence time, and tissue irradiation range of the 2 radiolabels, it is anticipated that $^{177}$Lu-DTPA-omburtamab antitumor activity will be favorable compared to that of $^{131}$I-omburtamab.

### 1.2.3. Toxicology of $^{177}$Lu-DTPA-omburtamab

In accordance with the guidance[21, 22], no standalone safety pharmacology studies have been conducted with $^{177}$Lu-DTPA-omburtamab.

Safety in the cardiovascular system and CNS was evaluated in a Good Laboratory Practice (GLP) toxicity study in juvenile monkeys (aged 10.5 to 11 months) given a single intracerebroventricular infusion of DTPA-omburtamab (CAR 1). The cynomolgus monkey was the selected species because the intended clinical route of administration is not feasible in rodents. Juvenile monkeys (i.e., aged 10.5 to 11 months) were selected because of the intended clinical use of $^{177}$Lu-DTPA-omburtamab in the pediatric and adolescent patient population. In addition to the intended route of administration, monkeys were the selected species based upon the demonstrated binding of omburtamab with high affinity to the recombinant human and cynomolgus monkey B7-H3. The juvenile monkey provides an assessment of safety for any off-tumor, on-target toxicity not detectable by immunohistochemistry. There was no treatment-related effect on electrocardiogram parameters or the neurological measures of postural/behavioral reactions, cranial nerve functions evaluated via eye position and facial muscle control/symmetry, or pain.

The safety of the radiolabeled monoclonal antibody is limited by radiation-induced toxicity. The main animal model selected to test radiotoxicity was the naïve rat. While omburtamab does not bind to rodent B7-H3, this common testing model is suitable to determine normal organ dosimetry and acute and delayed radiotoxicity from intrathecal administration in statistically relevant numbers. Body weight and clinical pathology were monitored for 6 weeks post dose in male and female rats given a single low (target 200 µCi) or high (target 500 µCi) dose intrathecal injection of $^{177}$Lu-DTPA-omburtamab or $^{131}$I-omburtamab. Animals were sacrificed and histopathology of critical organs showed that all tissues were within normal limits and there was no evidence of radiation damage, in particular to the bone marrow and kidneys in any of the treatment groups. Body weight increases were normal in all groups. Red blood cell concentrations and hematocrit were stable and white blood cell concentrations decreased, although within or slightly above the normal range, in all groups for the duration of the study. Furthermore, to support repeat-dosing schedules in human, the radiotoxicity in Sprague Dawley rats given an intrathecal injection once every 3 weeks for a total of 3 treatments of $^{177}$Lu-DTPA-omburtamab or $^{131}$I-omburtamab has been examined. There were no signs of radiotoxicity as seen by blood biomarkers or bodyweights and there was no histological evidence of radiation damage in any tissue including the bone marrow and the kidney.

As mentioned, several deaths occurred in the $^{177}$Lu-DTPA-omburtamab groups of 2 mouse studies with different objectives than toxicity due to non-recovering myelosuppression between Weeks 2 and 3 on study, evidenced by decreased white and red blood cells and hematocrit. In 1 study, IV injection of $^{177}$Lu-DTPA-omburtamab at approximately 500 µCi (mean 522 µCi) caused the death of all animals in the group while the injection of $^{131}$I-omburtamab at approximately 500 µCi (mean 509 µCi) did not. However, in another study, a dose of approximately 500 µCi of either $^{177}$Lu-DTPA-omburtamab or $^{131}$I-omburtamab resulted in severe reduction of blood counts and required euthanasia due to weight loss or were found dead by Day 19 ($^{131}$I-omburtamab: 5/6 animals; $^{177}$Lu-DTPA-omburtamab: 7/7 animals). *In vivo* imaging data were collected from 1 animal in the $^{177}$Lu-DTPA-omburtamab group in this study, and accumulation of radioactivity in the bone was confirmed. We consider that these studies do not indicate undue risk to the patients in our study due to the following:

- The doses used in the mice were administered IV and greatly exceeded the calculated limit of radiation to the bone marrow in mice (245 µCi) and was accompanied by myelosuppression.

- Furthermore, on a body weight basis, the doses correspond to approximately 200 mCi in a 5-year-old child of 10 kg, and approximately 20× the proposed starting dose of 10 mCi administered intracerebroventricularly.

- Dosimetry estimates for a 5-year-old child from biodistribution studies from intrathecal administration in naïve rats suggest comparable if not lower absorbed doses to the bone marrow for $^{177}$Lu-DTPA-omburtamab than for $^{131}$I-omburtamab (approximately 20 cGy/10 mCi versus 25 cGy/10 mCi). This is consistent with the more favorable β-energy for lutetium-177.

- Data from the $^{131}$I-omburtamab trials indicate that although myelosuppression was the main non-dose-limiting AE, radioimmunotherapy was well tolerated even after treatment with external beam craniospinal radiation and a boost to the primary site, which contribute 28 and 24 Gy, respectively, while $^{131}$I-omburtamab resulted in a mean CSF absorbed dose of 0.60 Gy/mCi (0.17 to 2.07 Gy/mCi)[23]. $^{131}$I-omburtamab therapy corresponds to less than 30% of the total radiation received by these patients. Animal-based dosimetry predicts a dose to the brain of 13.2 and 14.4 cGy/10 mCi for $^{177}$Lu-DTPA-omburtamab and $^{131}$I-omburtamab respectively. The higher absorbed doses reported in patients may be due to the difference in measuring brain versus CSF and reflect the presence of tumor in patients versus naïve animals.

Nevertheless, to confirm our hypothesis, a follow-up study in nude mice evaluating extended (8 weeks) radiotoxicity, and in particular, the threshold and reversibility of myelosuppression after administration of 100 or 200 µCi $^{177}$Lu-DTPA-omburtamab or 100 µCi $^{131}$I-omburtamab has been conducted. These doses correspond to 40 and 80 mCi on a body weight basis for a 10-kg child. At 5 weeks post dose, no adverse findings have been noted as measured by mortality, morbidity, clinical signs, body weights, or clinical chemistries. Results show that lower levels of radioactivity are not associated with significant myelosuppression. There was no significant group differences in body weight. At 1 week post dose, red blood cell counts and hematocrit were decreased in animals given 200 µCi $^{177}$Lu-DTPA-omburtamab, and these changes showed continued recovery at 2 through 5 weeks post dose.

#### *1.2.3.1. Radiotoxicity of Omburtamab Labels Other Than Lutetium-177*

A non-GLP study was conducted to evaluate radiotoxicity of $^{131}$I-omburtamab in 2 male cynomolgus monkeys given multiple doses of 3.62 to 8.3 mCi $^{131}$I-omburtamab via intrathecal injection. One monkey was preimmunized with $^{131}$I-omburtamab by IV administration 210 and 127 days prior to study initiation to evaluate anti-drug antibody (ADA) generation.

$^{131}$I-omburtamab produced detectable spikes of $^{131}$I-omburtamab in the CSF and comparatively lower levels of radiation in the blood. Suppressed levels in the blood of the preimmunized animal were likely due to a monkey anti-mouse antibody response that did not affect levels measured in the CSF. In general, total radioactivity elimination from the CNS was nearly complete by 48 hours post dose. $^{131}$I-omburtamab was tolerable for nontraumatic cisternal puncture. The findings associated with dosing, including changes in laboratory values measured in the CSF and blood, were transient and reversible. Beyond the injection site, no significant gross pathology or histopathological findings were noted in either animal and no long-term toxicities were observed after extended follow-up (i.e., >1200 days after the last dose).

Single-dose studies with the monoclonal antibody have been conducted for biotinylated omburtamab, $^{131}$I-omburtamab, and $^{124}$I-omburtamab in xenografted mice[20, 24], naïve rats[24, 25], or monkeys[25]. The test agents were administered via IV or intratumoral infusions for mice, intraparenchymal infusion or convection-enhanced delivery for rats, and convection-enhanced delivery for monkeys. There was no evidence of neurological toxicity with biotinylated omburtamab. The radiolabeled antibodies were well tolerated in mice, rats, and monkeys at radioactivity doses up to 500 µCi $^{131}$I-omburtamab or 1 mCi $^{124}$I-omburtamab, the highest levels of radioactivity evaluated.

### 1.2.4. Preclinical Pharmacokinetics of $^{177}$Lu-DTPA-omburtamab

Electrochemiluminescence assays were developed and validated to support quantification of DTPA-omburtamab in plasma and CSF from cynomolgus monkey.

No standalone pharmacokinetic (PK) studies have been conducted with $^{177}$Lu-DTPA-omburtamab. Toxicokinetic parameters were determined in juvenile monkeys given a single intracerebroventricular infusion of vehicle or DTPA-omburtamab (CAR 1). The no-observed-adverse-effect level (NOAEL) of 1.5 mg/kg DTPA-omburtamab corresponded to a maximum observed drug concentration ($C_{max}$) of 18,200 ng/mL total omburtamab and a mean area under the concentration-time curve (AUC) from time 0 to 672 hours of 1,350,000 hr·ng/mL and AUC from time 0 to infinity of 1,300,000 hr·ng/mL. There were no sex differences in toxicokinetic parameters. Total omburtamab was detectable in plasma at 1 hour post dose. Maximum plasma concentration and AUC increased with increasing dose in a greater than dose proportional manner. Time to maximum concentration was 12 hours and half-life was 23.9 to 26.1 hours. Mean clearance and volume of distribution of total omburtamab decreased with increasing dose. Total omburtamab was detectable in CSF in all dose groups at 24 hours post dose, and below the limit of quantification on Day 30. Concentrations were dose proportional for 0.1 and 0.75 mg/kg DTPA-omburtamab. There was no further increase in CSF levels at 24 hours post dose for 1.5 mg/kg compared to 0.75 mg/kg.

Biodistribution of $^{177}$Lu-DTPA-omburtamab (CAR 3.6 and 3) was evaluated in 2 studies with Sprague Dawley rats given a single intrathecal injection, and in 1 study with tumor-bearing athymic nude mice given a single IV injection of $^{177}$Lu-DTPA-omburtamab (CAR 3). The compound in these 3 studies was comparable to the clinical formulation (i.e., CAR ≈ 3).

$^{177}$Lu-DTPA-omburtamab concentration was significantly greater than the $^{125}$I-omburtamab concentration in the bone (1, 48, 144, and 192 hours), kidneys (48 and 192 hours), liver (all timepoints), and cervical spine (24, 48, 144, and 192 hours). $^{177}$Lu-DTPA-omburtamab concentration was significantly lower than $^{125}$I-omburtamab concentration in the cervical spine and upper thoracic spine at 1 hour and the lumbar spine at 5 hours. After 24 hours, the only region with $^{177}$Lu-DTPA-omburtamab concentration that was lower than the $^{125}$I-omburtamab concentration was the heart. $^{177}$Lu-DTPA-omburtamab gamma counts at 192 hours were generally increased compared to $^{125}$I-omburtamab. The liver, cervical lymph nodes, and spleen had the highest concentrations of $^{177}$Lu-DTPA-omburtamab at 192 hours. The highest concentrations of $^{125}$I-omburtamab at 192 hours were in the skin, liver, and cervical lymph nodes. Blood uptake for both labeled test articles was greatest at 24 hours.

In a second rat study, rats were given a single intrathecal injection of 174.3 ± 6.4 or 442.8 ± 17.3µCi $^{177}$Lu-DTPA-omburtamab (CAR 3) or 451 ± 37.6 µCi $^{131}$I-omburtamab. Biodistribution was evaluated up to 288 hours post dose. The highest levels of radioactivity were seen with the high dose of $^{177}$Lu-DTPA-omburtamab within the vertebral canal and brain at 1 hour post dose with subsequent clearance of radiopharmaceutical from these regions by 24 hours. At 24 hours and later, the highest radioactivity was in the liver and the deep and superficial cervical lymph nodes. Relatively little radioactivity was observed in the heart, lungs, spleen, kidneys, and humerus. Distribution of radioactivity over time following administration of the low dose was similar to high dose of $^{177}$Lu-DTPA-omburtamab.

Biodistribution was evaluated for up to 120 hours post dose and gamma counting was conducted at 120 hours post dose in male and female athymic nude mice bearing DAOY xenografts. Compared to $^{125}$I-omburtamab, $^{177}$Lu-DTPA-omburtamab accumulated 2-fold more in tumor relative to blood, and 2-fold less relative to liver. *In vivo* concentrations of $^{177}$Lu-DTPA-omburtamab were significantly ($p < 0.05$) higher in tumor, blood, liver, lung, spleen, kidney, bladder, muscle, and bone at 120 hours post dose compared to $^{125}$I-omburtamab. *Ex vivo* concentrations of $^{177}$Lu-DTPA-omburtamab at 120 hours post dose were significantly ($p < 0.05$) higher in the tumor, liver, spleen, kidney, and bone compared to $^{125}$I-omburtamab.

#### *1.2.4.1. Dosimetry*

The biodistribution data extrapolated from the SPECT/CT images were used as the input for dosimetry analysis (i.e., percentage injected dose per gram in key organs of interest over time) to generate estimates for 5-year-old (19 kg) humans. The 3 organs with the highest absorbed doses, the liver, heart wall, and kidneys, were the same for both test agents, albeit with different rank orders, and the effective doses were similar for the 2 test articles. The absorbed doses were higher in the liver and lower in the heart wall and kidneys with $^{177}$Lu-DTPA-omburtamab than $^{125}$I-omburtamab. Estimated absorbed doses for 5-year-olds are shown in Table 1.

## Table 1: Estimated Absorbed Doses for a 5-year-old Human (19 kg)

| | mGy/MBq | | mGy/mCi | | cGy per 25 mCi (1 dose) | | cGy per 10 mCi (1 dose) | | cGy per 10 mCi (2 dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Target Organ** | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** |
| Adrenals | 0.48 | 0.48 | 17.86 | 17.63 | 44.65 | 44.08 | 17.86 | 17.63 | 35.72 | 35.26 |
| Brain | 0.31 | 0.34 | 11.49 | 12.70 | 28.72 | 31.76 | 11.49 | 12.70 | 22.976 | 25.41 |
| Breasts | - | - | - | - | - | - | - | - | - | - |
| Esophagus | 0.44 | 0.44 | 16.41 | 16.38 | 41.02 | 40.95 | 16.41 | 16.38 | 32.82 | 32.76 |
| Eyes | 0.42 | 0.41 | 15.53 | 15.26 | 38.83 | 38.16 | 15.53 | 15.26 | 31.06 | 30.53 |
| Gallbladder Wall | 0.50 | 0.46 | 18.40 | 17.05 | 45.99 | 42.63 | 18.40 | 17.05 | 36.79 | 34.10 |
| Heart Wall | 1.03 | 1.02 | 38.02 | 37.68 | 95.06 | 94.21 | 38.02 | 37.68 | 76.05 | 75.37 |
| Kidneys | 1.20 | 1.20 | 44.40 | 44.40 | 111.00 | 111.00 | 44.40 | 44.40 | 88.80 | 88.80 |
| Left colon | 0.44 | 0.43 | 16.26 | 15.97 | 40.65 | 39.93 | 16.26 | 15.97 | 32.52 | 31.94 |
| Liver | 3.12 | 3.12 | 115.50 | 115.50 | 288.76 | 288.76 | 115.50 | 115.50 | 231.01 | 231.01 |
| Lungs | 0.44 | 0.43 | 16.21 | 16.01 | 40.52 | 40.02 | 16.21 | 16.01 | 32.42 | 32.02 |
| Osteogenic Cells | 1.90 | 1.88 | 70.36 | 69.38 | 175.90 | 173.44 | 70.36 | 69.38 | 140.72 | 138.75 |
| Ovaries | - | 0.43 | - | 15.82 | - | 39.54 | - | 15.82 | - | 31.63 |
| Pancreas | 0.45 | 0.46 | 16.55 | 17.13 | 41.36 | 42.83 | 16.54 | 17.13 | 33.09 | 34.26 |
| Prostate | 0.42 | - | 15.66 | - | 39.16 | - | 15.66 | - | 31.33 | - |
| Rectum | 0.43 | 0.42 | 16.05 | 15.71 | 40.13 | 39.27 | 16.05 | 15.71 | 32.10 | 31.42 |
| Red Marrow | 0.62 | 0.60 | 22.91 | 22.36 | 57.27 | 55.90 | 22.91 | 22.36 | 45.82 | 44.72 |
| Right colon | 0.44 | 0.44 | 16.45 | 16.27 | 41.13 | 40.67 | 16.45 | 16.27 | 32.90 | 32.54 |
| Salivary Glands | 0.43 | 0.42 | 15.77 | 15.53 | 39.44 | 38.82 | 15.78 | 15.53 | 31.55 | 31.06 |
| Small Intestine | 0.44 | 0.43 | 16.21 | 16.01 | 40.52 | 40.04 | 16.21 | 16.02 | 32.42 | 32.03 |
| Spleen | 0.43 | 0.43 | 15.98 | 15.89 | 39.96 | 39.71 | 15.98 | 15.88 | 31.97 | 31.77 |
| Stomach Wall | 0.44 | 0.43 | 16.25 | 16.04 | 40.62 | 40.10 | 16.25 | 16.04 | 32.50 | 32.08 |
| Testes | 0.41 | - | 15.23 | - | 38.08 | - | 15.23 | - | 30.46 | - |
| Thymus | 0.43 | 0.43 | 15.95 | 15.73 | 39.87 | 39.31 | 15.95 | 15.72 | 31.90 | 31.45 |
| Thyroid | 0.42 | 0.42 | 15.69 | 15.66 | 39.22 | 39.16 | 15.69 | 15.66 | 31.38 | 31.33 |
| Urinary Bladder Wall | 0.43 | 0.42 | 15.97 | 15.61 | 39.93 | 39.02 | 15.97 | 15.61 | 31.94 | 31.22 |
| Uterus | - | 0.43 | - | 15.85 | - | 39.62 | - | 15.85 | - | 31.70 |
| Total Body | 0.58 | 0.58 | 21.56 | 21.55 | 53.91 | 53.88 | 21.56 | 21.55 | 43.13 | 43.10 |

## 1.3. Benefit-risk Assessment

Medulloblastoma is a disease associated with significant mortality and morbidity for which there is a large unmet need for effective treatments with less neurocognitive toxicity.

Lutetium-177 radiolabeled pharmaceuticals are currently approved (Lutathera) and being evaluated for treatment of multiple cancer indications, and $^{131}$I-omburtamab has known antitumor activity in animal models and in humans. Given the biodistribution, binding data, tumor uptake, and dosimetry data collected, it is reasonable to predict that $^{177}$Lu-DTPA-omburtamab will have similar therapeutic potential and that 10 mCi is an acceptable starting dose in human (Section 3.3.3). In a rodent model, higher residence times in the brain are associated with greater tumor uptake with $^{177}$Lu-DTPA-omburtamab than with $^{131}$I-omburtamab. However, for every organ, except liver, $^{177}$Lu-DTPA-omburtamab showed lower absorbed doses (estimated by scaling to effective doses of 0.19 versus 0.28 mGy/MBq in females weighing 60 kg) suggesting greater tolerance for higher doses when administered into the CNS compartment. Based on dosimetry, 10 mCi $^{131}$I-omburtamab administered to a 10-kg child would deliver 14.4 cGy to the brain while 10 mCi of $^{177}$Lu-DTPA-omburtamab would deliver 13.2 cGy. For comparison, data published by Kramer et al. 2015[23] indicated that the mean CSF absorbed dose in patients receiving $^{131}$I-omburtamab was 0.60 Gy/mCi (0.17 to 2.07 Gy/mCi) and was well tolerated, even for patients who had received prior external beam craniospinal irradiation (in some cases twice) and a boost to the primary site (i.e., in total up to 28 × 2 and 24 Gy, respectively). The clinical efficacy and safety of direct infusion of $^{131}$I-conjugated antibodies (i.e., anti-B7-H3 and anti-GD2) into the CSF via an indwelling catheter (e.g., Ommaya catheter) has been demonstrated (Section 1.2.1). The conjugation of lutetium-177 with omburtamab allows for selectively targeting B7-H3, shown to be expressed on tumor cells and minimally in normal tissues. Preliminary findings suggest acceptable safety of $^{131}$I-omburtamab against recurrent/relapsed medulloblastoma and of $^{131}$I-3F8 (anti-GD2) against medulloblastoma[16]. Taken together, the information supports the safety of intracerebroventricular administration of $^{177}$Lu-DTPA-omburtamab for the treatment of recurrent or refractory medulloblastoma in pediatric and adolescent patients.

For more detailed information about the known and expected benefits and risks and reasonably expected AEs of $^{177}$Lu-DTPA-omburtamab, please refer to the Investigator's Brochure.

# 2. OBJECTIVES AND ENDPOINTS

## 2.1. Objectives

### 2.1.1. Primary Objectives

The primary objective of Part 1 (dose-escalation phase) of this trial is to explore the tolerability of up to 2 cycles of intracerebroventricular $^{177}$Lu-DTPA-omburtamab treatment in pediatric and adolescent patients with recurrent or refractory medulloblastoma. The MTD and/or the RP2D for Part 2 will be determined.

The primary objective of Part 2 (cohort-expansion phase) of this trial is to establish a safety profile of repeated dosing of $^{177}$Lu-DTPA-omburtamab in pediatric and adolescent patients with recurrent or refractory medulloblastoma.

### 2.1.2. Secondary Objectives

The secondary objectives of Part 1 (dose-escalation phase) are:

- to evaluate the absorbed radiation doses to CSF and blood of $^{177}$Lu-DTPA-omburtamab after intracerebroventricular administration
- to evaluate organ dosimetry of $^{177}$Lu-DTPA-omburtamab
- to evaluate the PK profile of $^{177}$Lu-DTPA-omburtamab

The secondary objectives of Part 2 (cohort-expansion phase) are:

- to evaluate the PK profile of $^{177}$Lu-DTPA-omburtamab
- to evaluate the investigator-assessed response
- to evaluate the investigator-assessed DoR
- to evaluate PFS
- to evaluate OS.

## 2.2. Endpoints

### 2.2.1. Primary Endpoints

The primary endpoint of Part 1 is number of DLTs.

The primary endpoint of Part 2 is number and severity of TEAEs.

### 2.2.2. Secondary Endpoints

#### *2.2.2.1. Part 1*

- Lutetium-177 activity in blood and CSF including derivation of best-fit uptake and/or clearance parameters (maximum count, elimination half-life) of time-activity curves and residence times (i.e., cumulated activity in µCi·h/g).
- Whole-body, organ, blood, and CSF radiation dosimetry.
- PK profile of $^{177}$Lu-DTPA-omburtamab in serum and CSF.

#### *2.2.2.2. Part 2*

- PK profile of $^{177}$Lu-DTPA-omburtamab in blood and CSF.
- Response, as defined by the RAPNO criteria (as determined from MRI assessments, neurological examination, and CSF cytology).
    - ORR, calculated as the proportion of all evaluable patients achieving a response (PR or CR) as best overall response at end of Cycle 1 and Cycle 3, EOT Visit, and at each Follow-up Visit.
- Investigator-assessed DoR, defined as the time from first response (CR or PR) to progression.
- PFS, defined as the time from first treatment to date of leptomeningeal progression or death from any cause, whichever comes first.
- OS defined as the time from first treatment to date of death.

# 3. INVESTIGATION PLAN

## 3.1. Overall Trial Design and Plan Description

This is a Phase I/II, open-label, safety and efficacy trial in pediatric and adolescent patients (3 to 19 years) with recurrent or refractory medulloblastoma. The trial will be conducted in 2 parts:

- Part 1: a dose-escalation phase with a 3+3 sequential-group design (except for the first dose level, which will consist of a single patient only) of five planned dose levels, and in which up to 25 patients will receive a maximum of two 5-week cycles of treatment with intracerebroventricular $^{177}$Lu-DTPA-omburtamab. Patients will receive a dosimetry dose in Week 1. Treatment doses will follow in Week 2 of the first cycle, and on the first day of Cycle 2. Adjustments to the dosing schedule will be accommodated on a patient-by-patient basis depending on the clinical condition of the patient. A Data Monitoring Committee (DMC) will review the safety data from previous dose levels and provide recommendations on whether dose escalation should continue. The MTD and/or RP2D will be determined.

- Part 2: a cohort-expansion phase in which approximately 24 patients with recurrent or refractory medulloblastoma will receive a maximum of five cycles of treatment with intracerebroventricular $^{177}$Lu-DTPA-omburtamab at the RP2D determined in Part 1.

Patients participating in Part 1 are not permitted to participate in Part 2.

$^{177}$Lu-DTPA-omburtamab will be administered via an indwelling intracerebroventricular access device (e.g., Ommaya reservoir). To avoid an additional procedure and burden to the patient, it can be considered to place the intracerebroventricular access device in connection with any tumor resection procedure that may be performed before entry into the trial. In this case, the informed consent form (ICF) must be signed before the tumor resection.

Potential participants will be screened to assess their eligibility to enter the trial within 29 days prior to the first $^{177}$Lu-DTPA-omburtamab dose; however, signing the ICF and placement of the intracerebroventricular access device is allowed earlier than this. Final assessment of the eligibility criteria is done prior to first dose. In Part 1 Cycle 1, the dosimetry and treatment doses should be administered under controlled conditions with inpatient care for at least 24 hours after investigational medicinal product (IMP) administration. As a routine precaution, patients must be monitored during the infusion and with close observation for two hours after the infusion with readily available resuscitation equipment and access to emergency units. Staff should be qualified in resuscitation and the physician must be readily accessible for assistance during the day of the infusion. The infusion reservoir must be flushed with human serum albumin and CSF after each infusion. The patient must be observed regularly, and the patient can be discharged after 24 hours if no safety issues are observed.

In Part 1 Cycle 2 and in Part 2 Cycle 1 to 5, patients can be treated in an outpatient setting or can be admitted as inpatients for infusions; however, all patients should be observed for a minimum of 2 hours after end of each infusion and can be released if no safety issues are observed.

An external DMC will be established to review the data and recommend upon dose escalation (Section 4.4).

Local safety instructions for storage and handling of radioactive drug products must be strictly followed. Radiation safety precautions may include patient isolation and the use of lead shielding, or designated rooms to ensure that the dose rate in the surrounding areas meets regulatory requirements.

A detailed Schedule of Assessments is included in Appendix 3.

### 3.1.1. Part 1 (Dose-escalation Phase)

Part 1 will comprise 1 dose level consisting of a single patient followed by additional dose levels that use a 3+3 design (see Figure 1).

In the first 5-week treatment cycle, a 5 mCi dosimetry dose will be administered on Day 1 and a treatment dose (according to the assigned dose level, as listed below) will be administered on Day 8 (see Figure 1 for a schematic of a treatment cycle in Part 1). However, if a patient experiences a Grade 3 or 4 non-hematologic AE (including an AE considered to be a Grade 3 or 4 nervous system disorder) or other DLT after receiving the dosimetry infusion, the treatment dose will not be administered, and the patient will be discontinued from trial treatment. If the dosimetry dose of 5 mCi turns out to deliver a too low acquisition of radioactivity count (see Section 7.2), the dosimetry dose will be increased to 10 mCi for subsequent patients, at the sponsor's discretion.

A fixed mass dose of approximately 1 mg DTPA-omburtamab will be labelled with increasing radioactivity doses. This mass dose was selected based on the clinical experience with iodine-labelled omburtamab, in which the same mass dose has been shown to be stable and to support clinical use in concentrations up to 100 mCi/ml. The planned radioactivity dose levels are:

- Dose Level 1 (1+2 patients): 10 mCi
- Dose Level 2 (3+3 design): 25 mCi
- Dose Level 3 (3+3 design): 50 mCi
- Dose Level 4 (3+3 design): 65 mCi
- Dose Level 5 (3+3 design): 85 mCi.

A maximum of 1 additional intermediate dose level may be added to the trial if warranted based on the findings from previous dose levels (see Section 3.1.1.1).

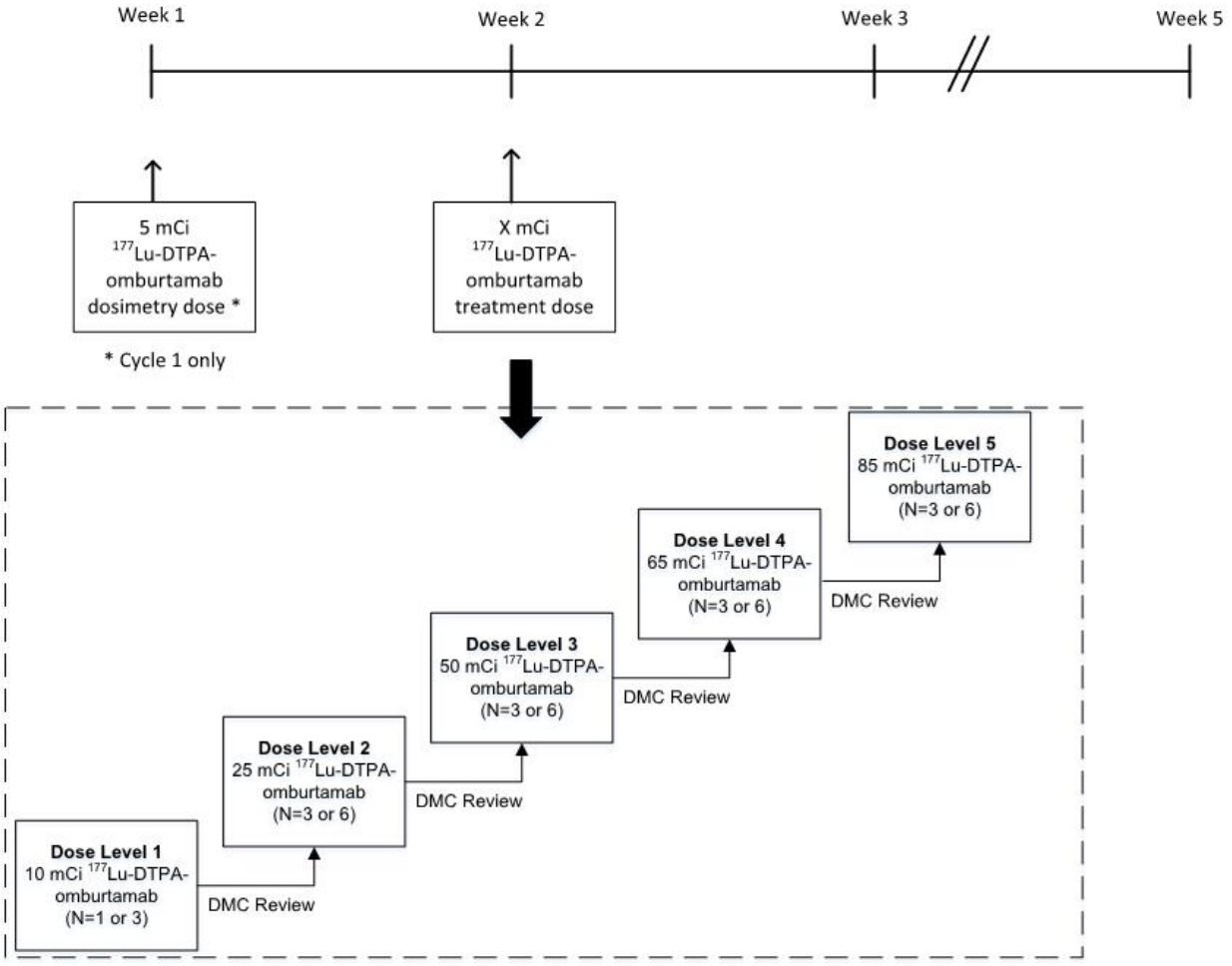
Patients who are not discontinued from treatment (according to the criteria in Section 4.3.2) will be eligible for a second treatment cycle at the same dose administered in the first cycle. The second treatment cycle will not include a dosimetry dose but will instead consist of a treatment dose on Day 1 of the cycle.

In Part 1, the patients will receive a maximum of 2 treatment cycles. Patients who do not experience a DLT will be eligible for Cycle 2 dosing at the same dose administered in Cycle 1. Cycle 2 dosing will not include a dosimetry dose but only a treatment dose on the first day of the cycle.

Patients will undergo monitoring for AEs; routine safety assessments (vital signs, clinical chemistry, hematology); whole-body planar gamma camera (and SPECT, if possible) scans for dosimetry measurements; CSF sampling for total protein, glucose, ctDNA (if the patient has given informed consent to this analysis), and cell count; blood and CSF draws for PK; and blood and CSF draws for ADA analysis and for potential culture (only in case of elevated body temperature); neurological assessments and radiographical investigation for evaluation of neurological AEs; and assessment of performance status (Lansky [<16 years] or Karnofsky [≥ 16 years] scales). Efficacy assessments include brain and spine MRI, CSF sampling for cytology, and neurological examination.

Patients will return for an EOT Visit 5 to 6 weeks after the last dose of $^{177}$Lu-DTPA-omburtamab to assess safety. End of Trial data will be entered to the eCRF. In addition, all patients who are dosed with $^{177}$Lu-DTPA-omburtamab will enter a post-trial monitoring period in which they will be regularly (e.g., yearly) followed up for secondary malignancies (see Section 7.4.5.3) for at least 10 years after end of trial, or until death, if sooner. This post-trial monitoring can be conducted by contacting the patient or the general practitioner, the referral site (if applicable), or by checking medical records or other sources.

**Figure 1: Trial Design – Part 1 Cycle 1**




Abbreviations: DMC = Data Monitoring Committee; N = number of patients.
* If the dosimetry dose of 5 mCi turns out to deliver a too low acquisition of radioactivity count (see Section 7.2), the dosimetry dose will be increased to 10 mCi for subsequent patients, at the sponsor's discretion.
After Cycle 1, the treatment dose will be administered on Day 1 (Week 1) of the cycle.

### *3.1.1.1. Dose Escalation and Stopping Rules*

As detailed in Section 4.4, a DMC will be formed to independently review the safety data from previous dose level(s) and make recommendations on whether dose escalation should continue. Based on the DMC recommendation, following review by the sponsor, the doses may be escalated or reduced and may be lower than the starting dose.

The starting treatment dose of lutetium-177 in Part 1 will be 10 mCi. Planned dose escalations (with a 3+3 design) are 25, 50, 65, and 85 mCi. Up to 1 additional dose level may be recruited to investigate an intermediate dose of investigational medicinal product (IMP), if warranted based on the safety findings from previous dose level(s). The requirement for an additional dose level will be agreed with the sponsor in consultation with the DMC and will be documented in the

Trial Master File. Dosing at any additional dose level will be subject to the same dose-escalation rules as for the planned dose levels, as described below. The maximum planned dose is 85 mCi.

Initially, 1 patient will be allocated to Dose Level 1 and subsequent dose escalations will be conducted using a classic 3+3 design. If no treatment-related Grade 3 or higher AEs are observed in the first patient, escalation from Dose Level 1 to Dose Level 2 will proceed with 3 patients being allocated to Dose Level 2, after DMC evaluation and recommendation. If a Grade 3 or higher treatment-related AE occurs, a further 2 patients will be enrolled at Dose Level 1.

The DMC will receive all SAE on an ongoing basis. The DMC will make the final assessment of whether the event qualifies as a DLT.

The first enrolled patient in each dose level will be observed for a minimum of two weeks after the treatment dose before subsequent patients will be dosed at the same dose. During the two weeks of observation, safety surveillance will focus on DLTs (including myelosuppression). If a DLT is observed in the first patient, a second patient will be included and observed for a minimum of two weeks after the treatment dose before the third patient is included. If no DLT is observed in the first patient, two subsequent patients will receive the treatment dose, but at least two days apart.

Escalation and de-escalation decisions will then be determined by the number of DLTs (as defined in Section 3.1.1.2) observed during Cycle 1 and the number of patients evaluable for DLTs, as follows.

- If no DLT is observed in the initial 3-patients at each dose level, 3 patients will be enrolled into and dosed in the next dose level. Dose escalation will continue in this manner until a DLT is observed or the highest planned dose level has been completed.

- If 1 DLT is observed in the initial 3-patients at each dose level, an additional 3 patients will (if recommended by the DMC) be enrolled at that dose level.

    - If no further DLTs are observed among the 3 additional patients (i.e., the total number of DLTs in the 6-patient dose level is 1), dose escalation will proceed with 3 patients being enrolled into the next dose level.

    - If ≥1 DLT is observed among the 3 additional patients (i.e., the total number of DLTs in the 6-patient dose level is ≥2), dose escalation will be stopped by the sponsor, upon consultation with the DMC.

        - If warranted, dosing may proceed with 3 patients being enrolled into an additional dose level that is intermediate between that of the current and the previous dose level. If dose escalation is stopped, the dose level immediately below that at which the DLTs were observed will be considered the MTD.

- If 2 or 3 DLTs are observed in the initial 3-patients at each dose level, dose escalation will stop. If warranted, dosing may proceed with 3 patients being enrolled into an

additional dose level that is intermediate between that of the current and the previous dose level. Otherwise, the dose level immediately below that at which the DLTs were observed will be considered the MTD. No further patients will be enrolled into the current dose level.

If only 3 patients were treated at the dose level below the intolerable dose 3 more patients will be recruited at that dose level to ensure that no more than 1 DLT occurs out of 6 patients.

Doses will be escalated until:

- The highest planned dose level has been found to be tolerated (i.e., stopping criteria were not met), or
- A toxic dose level has been identified.

When the dose-escalation phase of the trial has stopped due to toxicity, the MTD is identified as the highest non-toxic dose level (see Section 3.1.2).

#### *3.1.1.2. Definition of Dose-limiting Toxicity*

DLTs are defined as AEs (graded according to CTCAE version 5) occurring within 5 weeks after first IMP administration in Cycle 1 of Part 1 and that are considered possibly or probably related to IMP and meet any of the following criteria:

- Grade 4 myelosuppression (i.e., anemia, thrombocytopenia, or neutropenia) lasting more than 1 week, or more than 3 weeks following intervention (e.g., blood transfusion or granulocyte-macrophage colony-stimulating factor [GM-CSF])
- Any other Grade 4 hematological AE
- Grade ≥3 thrombocytopenia associated with bleeding
- Grade ≥3 febrile neutropenia (i.e., fever concurrent with neutropenia) lasting more than 5 days despite use of growth factors and antibiotics
- Grade 4 infusion-related reactions/anaphylaxis
- Grade 3 infusion-related reactions (excluding fever and Grade 3 abnormal laboratory values) that do not resolve to Grade ≤1 within 5 days of onset.
- Any non-hematological Grade ≥3 AE that is not listed in the list of exemptions below

DLTs must be entered onto the clinical AE report form and be reported from site to sponsor within 24 hours of the investigator's first knowledge of the event (see Section 7.4.5.2). If any of the side effects mentioned in the DLT definitions occur during Cycle 2 in Part 1, these will be discussed at the first upcoming preplanned DMC meeting, and the Sponsor Safety Committee will evaluate the DMC recommendations for further dosing.

**Non-hematological Exemptions:**

The following events are expected due to IMP and administration route and, if self-limiting and resolved within a short timeframe, will not constitute DLTs but should be reported as AEs/SAEs according to reporting guidelines:

- Grade 3 laboratory values considered not clinically significant
- Grade 3 fever without neutropenia (lasting less than 5 days)
- Grade 3 headache or vomiting for less than 48 hours (with adequate supportive care).
- Grade 3 nausea and fatigue, persisting for less than 7 days (with adequate supportive care).

### 3.1.2. Maximum Tolerated Dose and Recommended Phase II Dose Definition

The MTD is identified as the highest non-toxic dose level on which 6 patients have been treated, i.e., the dose level immediately below that at which 2 or more DLTs were observed and dose escalation was stopped. If only 3 patients were treated at the immediately lower dose level, 3 additional patients will be recruited at this dose level to ensure that no more than 1 DLT occurs out of 6 patients.

The RP2D will be defined as the highest tolerable dose, MTD, or a lower dose. For example, the RP2D may be lower than the MTD if accumulated toxicity over 2 cycles at the MTD is judged or proved to be non-tolerable.

### 3.1.3. Part 2 (Cohort-expansion Phase)

Part 2 will be conducted in approximately 24 patients with medulloblastoma recurrent or refractory to frontline therapy and, if they have recurrent disease, they must have received second-line chemotherapy for progressive disease (PD). Patients with a maximum of 1 recurrence of disease will be included.

Patients will receive $^{177}$Lu-DTPA-omburtamab at the RP2D determined in Part 1.

$^{177}$Lu-DTPA-omburtamab will be administered via an indwelling intracerebroventricular access device (e.g., Ommaya catheter) on Day 1 of each treatment cycle. Patients who are not discontinued from treatment (according to the criteria in Section 4.3.2) will be eligible for another treatment cycle at the same dose administered in the first cycle, up to a maximum of 5 treatment cycles per patient. The expected cumulated absorbed dose calculated based on the dosimetry data in the escalation part will assist in guiding (by the DMC) the maximum number of cycles feasible in the expansion phase.

Patients can be treated in an outpatient setting or can be admitted as inpatients for infusions; however, all patients should be observed for a minimum of 2 hours after end of each infusion.

Patients will undergo monitoring for AEs; routine safety assessments (vital signs, clinical chemistry, hematology); CSF sampling for total protein, glucose, ctDNA (if the patient has given informed consent to this analysis), and cell count; blood and CSF draws for PK; and blood and CSF draws for potential culture (only in case of elevated body temperature); neurological assessments and radiographical investigation for evaluation of neurological AEs; assessment of performance status (Lansky [<16 years] or Karnofsky [≥16 years] scales). CSF and blood will be drawn for PK and ADA analysis. Efficacy assessments include brain and spine MRI, CSF cytology, and neurological examination.

Patients will return for an EOT Visit 5 to 6 weeks after the last dose and for regular Follow-up Visits up to 104 weeks after the last infusion of $^{177}$Lu-DTPA-omburtamab to assess safety, efficacy, secondary malignancies, and long-term survival. In addition, all patients who are dosed with $^{177}$Lu-DTPA-omburtamab will be regularly monitored for secondary malignancies (see Section 7.4.5.3) for at least 10 years after end of trial, or until death, if sooner. This post-trial monitoring can be conducted by contacting the patient or the general practitioner, the referral site (if applicable), or by checking medical records or other sources.

## 3.2. Discussion of Trial Design

The sequential-group, escalating-dose design of Part 1 will ensure that safety and tolerability are assessed at lower dose levels before progressing to dosing at higher doses. The 3+3 dose-escalation algorithm employed will prevent unnecessary exposure to the trial drug by allowing dose-escalation decisions to be made based on smaller, 3-patient dose levels in the absence of DLTs, while enabling a dose level to be expanded to 6 patients where necessary to provide more information on the incidence of DLTs. The first enrolled patient at each dose level will be observed for a minimum of two weeks after the treatment dose before subsequent patients will be dosed

As there is relevant and substantial clinical experience from the comparable drug $^{131}$I-omburtamab (see Section 1.1 and Section 1.2.1), this enrolment strategy is considered appropriate for this trial.

Patients will be closely monitored for safety and efficacy throughout the treatment periods and up to 6 weeks (Part 1) and 104 weeks (Part 2) after the last dose. Considering the baseline advanced disease, and that most if not all patients have received high-dose cranial spinal irradiation prior to trial inclusion, 104 weeks in Part 2 appears to be a relevant follow-up duration in these advanced cancer patients with limited survival. A DMC will monitor safety data during Part 1 and make recommendations on dose escalation. All patients will be additionally monitored for secondary malignancies throughout the trial and for at least 10 years after end of trial, or until death, if sooner.

The trial will be conducted in 2 parts. The dose-escalation phase (Part 1) of the trial will be conducted prior to starting the cohort-expansion phase (Part 2) so that the safety data from Part 1 may inform the RP2D for Part 2.

For the first treatment dose level at 10 mCi, a single patient will be dosed at an anticipated low first-in-human starting dose level. Given the myelosuppression observed after IV injection in our

mouse studies, a 10 mCi starting dose level is proposed which corresponds to an 8-fold safety margin over the highest no-adverse-events dose administered IV in the mice (200 µCi corresponds to 80 mCi in a 10-kg child). As limited antitumorigenic effect is expected at the 10 mCi dose, only 1 patient is planned to receive this dose level if no Grade 3 or higher AEs are observed in the first patient.

The DMC can recommend to stop the trial based on treatment-emergent safety findings (see Section 4.4.1). In addition, a planned cohort-expansion phase (Part 2) will enable the RP2D to be studied in a larger number of patients.

A maximum of 2 cycles of treatment will be permitted in Part 1, during which the RP2D to be used in Part 2 will be determined based on dose-escalation findings from Part 1, primarily based on the overall safety and tolerability findings across both cycles in Part 1. Once the RP2D has been selected, patients in Part 2 of the trial will be eligible for up to 5 cycles of treatment.

There is no effective salvage treatment for patients with recurrent medulloblastoma, and the prognosis for these patients is poor. With preliminary data suggesting a potential application of omburtamab-based radioimmunotherapy in medulloblastoma patients, an open-label design has been chosen and found to be ethically defendable. Patients with WNT molecular subgroup of medulloblastoma are excluded because Wnt+ recurrent tumors are sensitive to systemic chemotherapy with excellent prognosis[9].

As medulloblastoma is primarily a disease of childhood, only pediatric or adolescent patients (up to 19 years of age) will be recruited. Patients below the age of 3 years will be excluded because standard-of-care therapy for this age group differs from that for older patients. Patients in both parts must be recurrent or refractory to frontline therapy. In Part 2 only, patients who have recurrent disease must have received second-line chemotherapy for progressive disease. Patients with 2 or more recurrences of medulloblastoma are expected to have short OS times, which may compromise the ability to assess the safety of $^{177}$Lu-DTPA-omburtamab for up to five 5-week cycles in the expansion phase; therefore, such patients will not be eligible for Part 2. Whether the patient has adequate CSF flow for intrathecal therapy will be determined by Ommaya patency/CSF flow assessment as outlined in Appendix 7. Patients with obstructive or symptomatic communicating hydrocephalus are not eligible for Part 1 or Part 2.

## 3.3. Selection of Doses in the Trial

### 3.3.1. Selection of DTPA-omburtamab Mass Dose

All patients dosed in this trial will receive lutetium-177 conjugated to a fixed mass dose of approximately 1 mg DTPA-omburtamab. A mass dose of 1 mg omburtamab has been used and found to be safe in a trial with >170 patients treated with $^{131}$I-omburtamab. It is expected that a specific activity of 100 mCi/mg DTPA-omburtamab will be achievable. The final mass will be determined based on the specific activity of the supplied lutetium-177 (mCi/mg), the age and decay of the isotope, and the efficiency of the labeling process.

The monoclonal antibody in $^{177}$Lu-DTPA-omburtamab is identical to that used in $^{131}$I-omburtamab and the radioimmunotherapy is to be administered via the same route, i.e., an

indwelling device directly into the third or lateral ventricle. Hence, no new toxicities due to the monoclonal antibody or dose route are anticipated.

The nonclinical and clinical data package supporting this trial consists of $^{131}$I-omburtamab nonclinical data and previous human experience, as well as nonclinical safety data using $^{177}$Lu-DTPA-omburtamab and DTPA-conjugated antibody product (DTPA-omburtamab).

DTPA-omburtamab has been tested in a 28-day intracerebroventricular toxicity study in cynomolgus monkeys. DTPA-omburtamab, when administered as a single dose up to 1.5 mg/kg to juvenile cynomolgus monkeys, was well tolerated over the study period. All findings were considered unrelated to the test article and non-adverse. The NOAEL for DTPA-omburtamab in monkey was determined to be 1.5 mg/kg.

At the NOAEL following a single infusion of DTPA-omburtamab to juvenile cynomolgus monkeys, safety margins for a proposed total mass dose of up to 1 mg DTPA-omburtamab are 30-, 60-, and 75-fold in pediatric, adolescent, and adult humans, respectively (for more details, please see the Investigator's Brochure).

### 3.3.2. Selection of Lutetium-177 Dose for Organ Dosimetry

The dosimetry dose (Day 1 of Cycle 1, in Part 1 only) will be 5 mCi of lutetium-177. This is considered sufficient to deliver quality whole-body planar gamma camera (and SPECT, if possible) scans. If the dosimetry dose of 5 mCi turns out to deliver a too low acquisition of radioactivity count (see Section 7.2), the dosimetry dose will be increased to 10 mCi for subsequent patients, at the sponsor's discretion.

### 3.3.3. Selection of Lutetium-177 Treatment Dose

Lutetium-177 and iodine-131 predominantly emit β-radiation with a comparable half-life. From a pure radionuclide perspective, and considering small-volume tumors and minimal residual disease, lutetium-177 is expected to generate two thirds of the same β-ionizing radiation to the tumor compared to iodine-131 (Table 2). For larger tumors and normal organs, lutetium-177 is conservatively estimated to generate approximately 50% of the decay of iodine-131. The proposed escalation dose levels for $^{177}$Lu-DTPA-omburtamab take into account the energies of the pure radionuclide, the clinical data with $^{131}$I-omburtamab, and preclinical dosimetry estimations for a pediatric patient. Dosimetry calculations from the biodistribution of $^{177}$Lu-DTPA-omburtamab given intrathecally to rats predict lower absorbed doses to all organs except the liver and lower effective doses than $^{131}$I-omburtamab. However, given the myelosuppression observed in our mouse studies, a 10 mCi starting dose level is proposed which corresponds to an 8-fold safety margin over the highest no-adverse-events dose (200 µCi corresponds to 80 mCi in a 10-kg child).

**Table 2: Properties of Lutetium-177 and Iodine-131**

| Property | Lutetium-177 | Iodine-131 |
|---|---|---|
| Half-life (days) | 6.65 | 8.03 |
| Main beta energies (average) (keV) | 134 | 97 and 192 |
| Beta dose/decay (MeV/Bq-s) | 0.134 | 0.182 |
| X rays intensity >5% (keV) | None | 29-33 |
| Gamma energies (keV) | 113; 208 | 284; 364 |
| Auger cascade total energy (keV) | 0.67 | 0.37 |
| Chemistry | Lanthanide, chelates | Halogen, covalently bound |

Clinical safety data of intracerebroventricular administration of $^{131}$I-omburtamab are derived from clinical studies. The monoclonal antibody (omburtamab) used for lutetium-177 labeling is identical to that used for iodine-131 labeling. The radiopharmaceutical is to be administered via the same route (intracerebroventricular administration) via an indwelling device directly into the third or lateral ventricle. Hence, no new toxicities, either due to the monoclonal antibody or to the administration route, are anticipated. A single-center clinical trial at Memorial Sloan Kettering Cancer Center and a multicenter, international clinical trial are ongoing under the governance of Y-mAbs, where more than 200 patients have received the $^{131}$I-labeled omburtamab via intracerebroventricular administration. Most patients had neuroblastoma CNS/leptomeningeal metastases (n = 109); however, 23 patients had the diagnosis refractory/recurrent medulloblastoma. Overall, safety profiles were not markedly different in these patients as compared to the general exposed patient population. In these studies, the doses were reduced by 50% for patients ≤12 months old, and by 33% for patients >12 to <36 months old. However, based on the safety findings in the escalation phase, a flat treatment dose of 50 mCi $^{131}$I-omburtamab was administered to patients aged 3 years and older in the expansion phase. As treatment with $^{131}$I-omburtamab in the 03-133 trial appeared to be safe with manageable acute hematological toxicities, a similar approach will be used in the current trial with $^{177}$Lu-DTPA-omburtamab, which does not include patients under the age of 3 years.

# 4. SELECTION OF TRIAL POPULATION

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted. The World Health Organization 2016 classification are detailed in Louis et al. 2016[26].

## 4.1. Inclusion Criteria

Patients must satisfy all of the following criteria at the Screening Visit, unless otherwise stated:

1. Histologically confirmed diagnosis of medulloblastoma.
2. SHH, Group 3, or Group 4 according to World Health Organization 2016 classification.
3. Recurrent or refractory to frontline therapy, defined as:
    a. For Part 1 only: Recurrent (maximum of 2 recurrences) or refractory to frontline therapy. Prior frontline or second-line therapy may involve surgery, craniospinal irradiation, stereotactic radiosurgery, and multi-agent chemotherapy regimens.
    b. For Part 2 only: Recurrent (maximum of 1 recurrence) or refractory to frontline therapy. Patients with recurrent disease must have received second-line chemotherapy for progressive disease. Prior frontline or second-line therapy may involve surgery, craniospinal irradiation, stereotactic radiosurgery, and multi-agent chemotherapy regimens.
4. Have refractory disease, focal or multifocal recurrent disease, or pure leptomeningeal disease. Cytological or radiographic remission is allowed; however, not simultaneously.
5. Performance status score of 50 to 100, both inclusive, on the Lansky [<16 years] or Karnofsky [≥16 years] scales.
6. Aged 3 to 19 years, both inclusive, at the time of the first planned dose of trial treatment.
7. Life expectancy of at least 3 months, as judged by the investigator.
8. Acceptable hematological status prior to first dosing (hematological support is allowed if administered at least 1 week before administration of $^{177}$Lu-DTPA-omburtamab), defined as:
    a. Hemoglobin ≥8 g/dL
    b. White blood cell count ≥1000/µL
    c. Absolute neutrophil count ≥1000/µL
    d. Platelet count ≥75 000/µL.

9. Acceptable liver function prior to first dosing, defined as:

    a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 × upper limit of normal (ULN)

    b. Bilirubin ≤1.5 × ULN.

10. Acceptable kidney function prior to first dosing, defined as:

    a. Estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 $m^2$, calculated by the 2009 revised Bedside Schwartz Equation (Appendix 4).

11. Written informed consent from legal guardian(s) and/or child obtained in accordance with local regulations. Pediatric patients must provide assent as required by local regulations.

### 4.2. Exclusion Criteria

Patients will be excluded from the trial if they satisfy any of the following criteria at the Screening Visit unless otherwise stated:

1. Obstructive or symptomatic communicating hydrocephalus as determined by Ommaya patency/CSF flow assessment.

2. Any tumor lesion measuring >15 mm in the smallest diameter.

3. Ventriculoperitoneal (VP) shunts without programmable valves. Ventriculo-atrial or ventriculo-pleural shunts.

4. Grade 4 nervous system disorder. Stable neurological deficits due to brain tumor or surgery and hearing loss are allowed.

5. Uncontrolled life-threatening infection.

6. Received radiation therapy (focal or cranio-spinal irradiation), systemic or intrathecal cytotoxic chemotherapy, or immunotherapy (including monoclonal antibodies; corticosteroids not included) less than 3 weeks prior to the Dosimetry Dose (or until recovery from clinically significant adverse events). Received nitrosoureas less than 6 weeks prior to the Dosimetry Dose.

7. Received any prior anti-B7-H3 treatment.

8. Non-hematologic organ toxicity Grade 3 or above; specifically, any renal, cardiac, hepatic, pulmonary, and gastrointestinal system toxicity.

9. Other significant disease or condition that in the investigator's opinion would exclude the patient from the trial.

10. Females of childbearing potential (as defined in Appendix 5) who are pregnant, breast feeding, intend to become pregnant, or are not using highly effective contraceptive methods as defined in Appendix 5 or males who are not using highly effective contraceptive methods as defined in Appendix 5.

## 4.3. Discontinuation Criteria

### 4.3.1. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but do not meet all eligibility criteria and are not dosed in the trial. A minimal set of information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, reason for screen failure, eligibility criteria, and any SAEs.

Final assessment of the eligibility criteria is done prior to first dose. Patients who do not meet the criteria for participation in this trial may be rescreened.

### 4.3.2. End of Treatment

The end of treatment (EOT) is defined as the day the last dose of $^{177}$Lu-DTPA-omburtamab is received. The EOT Visit should occur 5 to 6 weeks after the last dose, whether this is a premature treatment discontinuation or treatment completion.

#### *4.3.2.1. Discontinuation of Trial Treatment*

Patients may withdraw from the trial treatment at any time at his/her own request or may be discontinued from trial treatment at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Additionally, patients may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records. Refer to the Schedule of Assessments (Appendix 3) for data to be collected at the time of treatment discontinuation (EOT visit) and follow-up and for any further evaluations that need to be completed.

The patient must be permanently discontinued from treatment if any of the following occur:

- After receiving the dosimetry dose only, Grade 3 or 4 non-hematologic AE (including an AE considered to be a Grade 3 or 4 nervous system disorder; see Section 7.1.5)
- DLT occurring before the end of Cycle 1 in each dose level in Part 1
- Grade 4 infusion-related reaction/anaphylaxis, or Grade 3 infusion-related reactions (excluding fever and Grade 3 abnormal laboratory values) that do not resolve to Grade ≤ 1 within 5 days of onset

- Grade 4 neurological AE
- Development of obstructive or symptomatic communicating hydrocephalus
- Grade 4 treatment-related AEs (excluding infusion-related fever, and non–life-threatening laboratory values)
- Disease progression before Cycle 2 in Part 1 or Cycle 5 in Part 2
- Any medical or safety reason, in the opinion of the investigator or sponsor
- Chemical meningitis (symptoms of clinical meningitis but cultures for infectious agents were negative) in which either: a) event is non-responsive to IV steroids, b) radiologic or operative intervention was indicated, or c) focal neurologic deficit was present
- The patient receives prohibited therapy and/or undergoes procedures during the trial that, in the opinion of the investigator, warrant treatment discontinuation
- Patient decision
- Pregnancy.

A patient who is discontinued from treatment, but for whom consent is not withdrawn, shall continue to be followed for the entire trial period.

#### *4.3.2.2. Completion of Trial Treatment*

Patients will be regarded as having completed the trial treatment if they received 2 cycles of IMP in Part 1 or up to 5 cycles in Part 2.

### 4.3.3. End of Trial

The end of the trial is defined as the date the last patient completes the last Visit or the date of death of the last patient, whichever comes first.

#### *4.3.3.1. Discontinuation from Trial*

A patient should be discontinued from the trial if:

- The patient or legal guardian withdraws informed consent for any reason.

#### *4.3.3.2. Completion of Trial*

Patients will be regarded as having completed the trial if they received all the planned cycles and attend the EOT visit (Part 1) and follow-up period (Part 2) until the end of trial.

#### *4.3.3.3. Lost to Follow-up*

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

If a patient fails to return to the clinic for a required trial visit, the site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the trial.

In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

Should the patient continue to be unreachable, he/she will be considered to have discontinued from the trial with a primary reason of lost to follow-up.

### 4.3.4. Replacement Procedures

Patients in Part 1, who discontinue treatment after the Dosimetry dose (i.e., prior to the first treatment dose), will be replaced. Patients in Part 1, who are discontinued during the DLT reporting period for reasons not related to IMP may be replaced following discussion between the investigator and the sponsor. If a patient is discontinued as a result of AEs considered to be related to the IMP, the DMC will be consulted as to whether the patient should be replaced.

### 4.3.5. Follow-up of Patients Discontinued from Trial Treatment or from the Trial

A patient discontinued from treatment should as soon as possible attend the EOT Visit, and be followed at all scheduled Follow-up Visits (Part 2) and for post-trial monitoring of secondary malignancies at least 10 years after end of trial, or until death, if sooner (Appendix 3).

The investigator should:

- Ensure the safety of the patient. Follow any SAE and Grade 3 or higher non-serious AEs that are considered treatment related and still ongoing after withdrawal until the event has been resolved or the investigator assesses the SAE as being chronic or stable.

- Offer the best possible treatment outside of the trial based on clinical practice at the investigational site.

## 4.4. Data Monitoring Committee

An external DMC will be established to assure patient safety and will function independently of all other individuals associated with the conduct of the trial, including site investigators participating in the trial. The DMC will consist of a minimum of 2 physicians whose expertise covers relevant specialties.

During the conduct of Part 1, following completion of the first 5-week treatment cycle (Cycle 1) for the last patient in each dose level, the DMC will evaluate available safety information and recommend trial continuation or termination. If continuation is recommended, the DMC will recommend to the sponsor whether the dose should be escalated, de-escalated, or held at the same level. In the absence of DLT during the first two weeks of the first patient enrolled in each dose level, the enrollment to the dose level will continue without the need of feedback from the DMC.

If any of the side effects mentioned in the DLT definitions (Section 3.1.1.2) occurs during Cycle 2 in Part 1, these will be discussed at the first upcoming preplanned DMC meeting, and the internal Sponsor Safety Committee will evaluate the external DMC recommendations for further dosing. During Part 1 and until the DMC meeting in Part 2, the sponsor will share with the DMC all SAEs occurring during the trial and an unplanned DMC meeting can be held at the request of either the DMC or the Sponsor Safety Committee.

The DMC will evaluate the totality of cumulated absorbed dose calculated based on the dosimetry data from Part 1, and all available DLTs and other non-DLT toxicities from cycles 1 and 2 in all patients dosed in Part 1, to guide whether the maximum of five cycles is feasible in Part 2.

During the conduct of Part 2, an additional DMC meeting will be held when the eighth patient has completed dosing in Cycle 1 to evaluate whether the trial should be modified, stopped, or continue unchanged. The Sponsor Safety Committee will evaluate the recommendations from the DMC after each DMC meeting. Any significant finding/recommendation from the DMC and endorsed by the Sponsor Safety Committee will be communicated to the regulatory authorities and Institutional Review Board (IRB)/Ethics Committee (EC) as appropriate, and to the sites.

Responsibilities, procedures, content of the DMC packages, and workflow of the DMC are specified in the DMC Charter.

### 4.4.1. Trial Stopping Rules

If any of the following occur, administration of the IMP will be stopped, and recruitment will be put on hold at least temporarily until DMC feedback is received to confirm if the trial can continue:

1. AEs or frequency of AEs that, in the judgment of the sponsor, are deemed to warrant immediate review by the DMC

2. Any other safety finding assessed as related to $^{177}$Lu-DTPA-omburtamab that, in the opinion of the DMC or sponsor, contraindicates further dosing of trial patients.

If any of these occur, an immediate cumulative review of safety data with focus on the AE in question will be conducted by the DMC to determine whether dosing and further recruitment should be resumed, the protocol modified, or whether the trial should be discontinued. Review and approval of the Sponsor Safety Committee and approval by the regulatory authorities is

required for resumption of the trial, should the trial be interrupted due to one of the above-mentioned safety findings.

Any patients who have received the IMP and are currently in the trial at the time trial stopping criteria are met will continue to be followed by the investigator for safety.

### 4.5. Trial Termination

The sponsor reserves the right to close a trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed. Reasons for trial termination may include, but are not limited to:

- Related AEs not previously reported with any similar investigational trial treatment with respect to their nature, severity, and/or duration
- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs or pre-existing conditions
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients
- Cancellation of drug development.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a trial site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local regulatory authorities, the sponsor's procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of participants by the investigator.

# 5. TRIAL TREATMENTS

## 5.1. Treatments Administered

Omburtamab is a murine IgG1 monoclonal antibody that recognizes tumor-associated antigen B7-H3. DTPA-omburtamab will be radiolabeled with lutetium-177 at a dedicated GMP facility. $^{177}$Lu-DTPA-omburtamab is a clear, colorless to slightly yellow, and particle free solution.

$^{177}$Lu-DTPA-omburtamab will be administered via an indwelling intracerebroventricular access device (e.g., Ommaya catheter). The infusion reservoir must be flushed with human serum albumin (HSA) and autologous CSF after each infusion. For detailed instructions, please refer to the IMP manual. For all infusions, emergency support for anaphylaxis must be readily available, including epinephrine, diphenhydramine, hydrocortisone, and/or dexamethasone at the bedside.

In Part 1 Cycle 1, the dosimetry and treatment doses should be administered under controlled conditions with inpatient care for at least 24 hours after IMP administration. As a routine precaution, patients must be monitored during the infusion and with close observation for two hours after the infusion with readily available resuscitation equipment and access to emergency units. Staff should be qualified in resuscitation and the physician must be readily accessible for assistance during the day of the infusion. The infusion reservoir must be flushed with human serum albumin and CSF after each infusion. The patient must be observed regularly, and the patient can be discharged after 24 hours if no safety issues are observed.

In Part 1 Cycle 2 and in Part 2, patients can be treated in an outpatient setting or can be admitted as inpatients for infusions; however, all patients should be observed for a minimum of 2 hours after the end of infusion and can be released if no safety issues are observed.

For radiation safety, see Section 5.2.2.

In Part 1 only, for the first 5-week treatment cycle, a 5 mCi dosimetry dose will be administered on Day 1 and a treatment dose will be administered on Day 8. However, if a patient experiences a Grade 3 or 4 non-hematologic AE or other DLT after receiving the dosimetry dose, the treatment dose will not be administered, and the patient will be discontinued from trial treatment. If the dosimetry dose of 5 mCi turns out to deliver a too low acquisition of radioactivity count (see Section 7.2), the dosimetry dose may be increased to 10 mCi for subsequent patients, at the sponsor's discretion. In the second treatment cycle of Part 1 (if applicable) and throughout Part 2, a treatment cycle will consist of a treatment dose on the first day of each cycle. Patients who are not discontinued from treatment will be eligible for treatment at the same dose administered in the first cycle, up to a maximum of 2 cycles in Part 1 and 5 cycles in Part 2.

## 5.2. Preparation, Storage, Handling, and Accountability

Only patients enrolled in the trial may receive trial treatment and only authorized site staff may supply or administer trial treatment. The investigator, institution, or the head of the medical institution (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). There is no long-term storage of IMP at site, and the IMP will be prepared on demand when a patient is

found to be eligible for the trial and when further cycles (if applicable) are scheduled. The utensils used to ship, prepare, and administer the IMP will be radioactive and should be destroyed according to local regulations. The destruction can be performed without sponsor approval but only after accountability (see Section 5.5) has been conducted.

Doses must be aseptically prepared at a designated radiopharmacy by withdrawal of $^{177}$Lu-DTPA-omburtamab from the single-use vial into a sterile syringe to the target activity confirmed by dose calibration. The finished product in liquid form is drawn into a syringe and then placed in a lead container ("pig") that is then placed inside a lead-lined container and transported to the patient's bedside prior to administration. For detailed instructions, please refer to the IMP manual.

At each clinical site, the actual $^{177}$Lu-DTPA-omburtamab dose administered should be assayed immediately prior to administration to verify that the prescribed activity and the activity actually administered agree within ±10% (see Table 3). The amount of radioactivity infused in patients should be assessed by measuring radioactivity of the infusion syringe before and after $^{177}$Lu-DTPA-omburtamab infusion into the indwelling intracerebroventricular access device (e.g., Ommaya catheter) and subtracting the post infusion count from the pre infusion count. The radiolabeled $^{177}$Lu-DTPA-omburtamab is administered via a catheter with an inline filter.

**Table 3: Accepted Activity Ranges for Dosimetry and Treatment Doses**

| | Nominal Dose (Acceptable Range) of Lutetium-177 |
|---|---|
| Dosimetry Dose (Day 1, Cycle 1, prior to all treatment dose levels in Part 1) | 5 (4.5 – 5.5) mCi |
| Dose Level 1 Treatment Dose | 10 (9.0 – 11.0) mCi |
| Dose Level 2 Treatment Dose | 25 (22.5 – 27.5) mCi |
| Dose Level 3 Treatment Dose | 50 (45.0 – 55.0) mCi |
| Dose Level 4 Treatment Dose | 65 (58.5 – 71.5) mCi |
| Dose Level 5 Treatment Dose | 85 (76.5 – 93.5) mCi |

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit to the radiopharmacy. Temperature-controlled shipment from radiopharmacy to the clinical department is not required.

All trial treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

Further guidance and information for the final disposition of unused trial treatment will be provided in the IMP manual.

### 5.2.1. Radiolabeling of DTPA-omburtamab

$^{177}$Lu-DTPA-omburtamab is manufactured by conjugating the monoclonal antibody omburtamab with p-SCN-Bn-CHX-A''-DTPA followed by radiolabeling of the conjugate DTPA-omburtamab (DTPA-omburtamab drug product intermediate) with lutetium-177 to create the final $^{177}$Lu-DTPA-omburtamab drug product.

The conjugation of omburtamab is performed by a conjugation of p-SCN-Bn-CHX-A''-DTPA ([(R)-2-Amino-3-(4-isothiocyanatophenyl)propyl]-trans-(S,S)-cyclohexane-1,2-diamine-pentaacetic acid) to lysine side chains of the monoclonal antibody in a chelator-to-antibody ratio (CAR) of 3.

The DTPA-omburtamab drug product intermediate is then radiolabeled with the β-emitter lutetium-177, and shipped to the radio pharmacy affiliated with the clinical trial site.

The required activity should be withdrawn into a syringe using aseptic technique using a dose calibrator and the rest of the activity should be discarded in accordance with local regulations. Radiolabeled product is sterilized by filtration. Quality control is ensured according to a release specification, also including endotoxin testing, bioburden, and radioimmunoassay.

### 5.2.2. Radiation Safety

Local safety instructions for storage and handling of radioactive drug products must be strictly followed. Radiation safety precautions may include patient isolation and the use of lead shielding, or designated rooms to ensure that the dose rate in the surrounding areas meets regulatory requirements.

For treatment in Part 1 Cycle 1, see Section 5.1. In Part 1 Cycle 2 and in Part 2, patients can be treated in an outpatient setting or can be admitted for $^{177}$Lu-DTPA-omburtamab administration; however, all patients should be observed for a minimum of 2 hours after end of each infusion. When patients are admitted, the caregiving staff will be instructed in radiation safety steps required to minimize exposure to themselves according to local guidelines.

The dose rate from the patient will be measured after end of infusion and at later timepoints to define the need for overnight stay(s) using portable radiation detectors as described in the local safety instructions. Patient release timepoint following administration of a dose of $^{177}$Lu-DTPA-omburtamab will be determined based on the dose rate criterion specified in § 35.75 in NUREG 1556, Volume 9, Rev 3[27] and Regulatory Guide 8.39, Rev 1[28] (US sites) or based on local radiation safety requirements (sites outside US). Patients can be released following administration of dosimetry or treatment doses of $^{177}$Lu-DTPA-omburtamab if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 mSv (~ 500 mrem) or the value described by local safety instructions, whichever is the lowest. Patient isolation will remain in effect until the dose rate is below what is required in accordance with local patient release regulations.

The site's radiation safety service will manage the collection, shielding, and waste disposal, as appropriate, for patient excreta for each case. Following release of the patient, the site's radiation safety service will survey and perform decontamination procedures in the room to ensure that the room meets regulatory requirements.

Patients and legal guardians will be given instructions by radiation safety staff on how to handle waste and steps and procedures to follow to minimize radiation exposure to themselves, household contacts, the general public, and possible patient family caregiver(s), including pregnant women, and small children. Safety precautions will be taken to ensure that doses to

these caregivers are maintained as less than local safety instructions (e.g., 5 mSv [~ 500 mrem]). Patients and/or caregivers will be provided with a written instruction detailing radiation safety precautions as per the local requirements. The caregiver will agree to radiation safety instructions prior to administration of the IMP.

Safety instructions must include the following general precautions: Close contact (less than 1 meter) with other people should be limited for 7 days following an administration of $^{177}$Lu-DTPA-omburtamab. For other children and/or pregnant women, close contact (less than 1 meter) should be limited to less than 15 minutes per day for 7 days. Patients should sleep more than 1 meter from other people for 7 days and in a separate bedroom from other children and/or pregnant women for 15 days following an administration of $^{177}$Lu-DTPA-omburtamab.

### 5.2.3. Ventriculo-peritoneal Shunts

Ventriculo-peritoneal shunts with programmable valves are allowed; however, the VP shunt must be closed (or adjusted to highest pressure setting) during IMP infusion and up to approximately 5 hours after IMP administration and then re-adjusted. The shunt re-adjustment times are at the discretion of the treating physician. Closure of the VP shunt is done at the discretion of the treating physician and the VP shunt should at any time based on patient safety evaluation be re-opened at the assessment of the treating physician.

## 5.3. Method of Treatment Assignment

This is an open-label trial and is not subject to randomization. After dose level 1 in Part 1, patients will be allocated to the highest dose level cleared by the DMC.

### 5.3.1. Dose Modification

Dose reductions will not be allowed in Part 1. If a dose reduction is needed in Part 1, the patient should be discontinued from treatment and all EOT Visit assessments completed.

In Part 2, dose reductions in individual patients are permitted where warranted due to toxicity. If dose reduction is needed in Part 2, the reduced dose will be decided upon agreement between the treating investigator and sponsor, guided by the safety and calculated absorbed doses to CSF and blood findings from Part 1.

For patients in Part 1 or 2 presenting with ongoing Grade 3 or 4 myelosuppression in the fifth week of a treatment cycle, and who are otherwise eligible for an additional treatment cycle, a delay of dosing in the next cycle for up to 8 weeks can be introduced, provided that the myelosuppression has sufficiently declined to Grade $\leq$2. Dose delay will be enforced at the discretion of the treating investigator.

## 5.4. Blinding

This is an open-label trial; blinding procedures are not applicable.

## 5.5. Treatment Compliance

Clinical personnel at the site will record in the source notes the timing and site of all administrations of IMP. Any reasons for non-compliance should be documented.

Drug accountability on a patient level will be documented by keeping copies of the IMP order form and the IMP administration form and the completed appendices to the IMP manual. The documentation will be reviewed periodically and verified by the Trial Monitor over the course of the trial.

### 5.5.1. Overdose, Medication Errors, and Misuse

An overdose is defined as a patient receiving a dose of the IMP in excess of that specified in this protocol.

Medication errors and uses outside what is foreseen in the protocol, including misuse of the product, may include:

- Administration of wrong drug
- Wrong route of administration, such as IV instead of intracerebroventricular
- Administration of an overdose with the intention to cause harm, or misuse of trial treatment
- Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial patient were likely to happen as judged by the investigator, although the clinical consequences did not necessarily occur.

Overdose/underdose and medication errors (exceeding ± 10% as compared to protocol-specified dose) should be reported in the electronic case report form (eCRF), including information on the quantity of the excess dose as well as the duration (if an overdose) and of the type (if a medication error).

If an overdose, medication error, or misuse result in an AE this should be reported as an AE in the eCRF and (if serious) to safetymailbox@ymabs.com using the clinical AE report form.

#### *5.5.1.1. Management of Overdose of $^{177}$Lu-DTPA-omburtamab*

Rescue medication to reverse the action of $^{177}$Lu-DTPA-omburtamab is not available. In case of overdose or other medication errors of $^{177}$Lu-DTPA-omburtamab patients, should receive supportive care according to local guidelines and potential side effects of $^{177}$Lu-DTPA-omburtamab should be treated systematically.

In the event of an overdose, the Investigator should:

- Contact Medical Monitor (for contact details, see the protocol front page)
- Closely monitor the patient for any AE and laboratory abnormalities
- In case of an AE, close medical supervision and monitoring should continue until the patient recovers.

## 5.6. Technical complaint

A technical complaint is any written or oral communication that states any dissatisfaction with the product characteristics and alleges a product defect. A complaint can be related to e.g., the product appearance (discoloration, presence of particles, or sediment), product container (damaged or missing seal), product label (damaged, missing, misleading), or consignment (wrong number of vials in the package). Complaint should also be initiated if the product is suspected to be falsified.

Please refer to the IMP manual for information regarding reporting of a technical complaint.

# 6. CONCOMITANT THERAPIES

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrolment or receives during the trial must be entered on the eCRF, including:

- reason for use
- dates of administration, including start and end dates, and
- dosage information including dose and frequency.

Prior anti-cancer therapy must be entered in the eCRF. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

## 6.1. Permitted Concomitant Therapy

Any treatment needed for patient wellbeing (including supportive care) that will not interfere with IMP administration may be given at the discretion of the investigator. Additional anti-cancer and supportive care treatments are allowed after the EOT Visit. If an MRI is scheduled at that visit, the MRI should be completed before starting the additional treatments. Medical marijuana is permitted if the patient was receiving this therapy prior to signing the ICF.

After discontinuation of the IMP, any treatment deemed safe and justified by the investigator can be administered according to clinical practice and at the discretion of the investigator.

## 6.2. Prohibited Concomitant Therapy

The following therapies are prohibited within 3 weeks prior to the first dose and until completion of the EOT Visit:

- Additional cytotoxic anti-cancer therapy.
- Any other IMP.
- Any live viral vaccines.
- Herbal medications with known risk of hepatotoxicity.

The following is prohibited in Part 1 Cycle 1 within 1 week prior to first IMP administration and until 5 weeks after:

- Additional hematological support.

## 6.3. Treatment of Expected Toxicities

### Premedication

Starting 24 hours prior to each $^{177}$Lu-DTPA-omburtamab infusion, dexamethasone will be administered orally at 0.6 mg/kg/day or an IV equivalent (subject to a maximum total dose of 20 mg/day) divided into twice-daily doses for a total of 3 days to alleviate infusion-related AEs.

An anti-pyretic (e.g., oral acetaminophen/paracetamol [15 mg/kg, 650 mg maximum]) and an antihistamine (e.g., diphenhydramine [1 mg/kg, 50 mg maximum]) or equivalents will be administered within 1 to 2 hours before all intracerebroventricular infusions.

### Expected Toxicities

Expected toxicities will be treated at the discretion of the investigator and could include the following:

- Urticaria will be treated with antihistamines.
- Fever will be treated with paracetamol/acetaminophen.
- During administration of $^{177}$Lu-DTPA-omburtamab, emergency support for anaphylaxis must be readily available, including epinephrine, diphenhydramine, hydrocortisone, and/or dexamethasone at the bedside.
- Patients with myelosuppression may be supported with blood products, GM-CSF, or granulocyte–colony-stimulating factor according to local standard of care. If indicated, patients also may have banked stem cells reinfused.

# 7. TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the Schedule of Assessments (Appendix 3). As protocol waivers or exemptions are not allowed, with the exception of immediate safety concerns, these should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue the IMP. Adherence to the trial design requirements, including those specified in the Schedule of Assessments, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure (Section 4.3.1), as applicable. Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the Schedule of Assessments (Appendix 3).

The maximum amount of blood collected from each dosed patient over the duration of the trial, including any extra assessments that may be required, will not exceed 300 mL, and the maximum amount of CSF collected from each dosed patient over the duration of the trial, including any extra assessments that may be required, will not exceed 20 mL. In case the patient will participate in the ctDNA analysis, additional 3-5 ml CSF will be collected. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 7.1. Vital Signs, Physical Examination, and Other Safety Evaluations

### 7.1.1. Demographics

The following demographic information will be entered in the eCRF during screening:

- Age or date of birth, if allowed by local legislation
- Gender
- Ethnic origin and race, if allowed by local legislation

### 7.1.2. Height and Body Weight

Height (without shoes and rounded to the nearest centimeter) and body weight (without overcoat and shoes and rounded to kilogram with 1 decimal) will be measured at screening and entered in the eCRF.

### 7.1.3. Vital Signs

Measurements of heart rate, respiratory rate, temperature, and blood pressure will be performed before and 30 minutes after the end of the IMP infusion on dosing days and at the times specified

in the Schedule of Assessments (Appendix 3). Temperature must be measured by using the same method on each occasion (e.g., an ear thermometer).

### 7.1.4. Physical Examinations

Physical examinations should be performed at screening and as clinically indicated and should include assessment of general appearance, mental status, and various organ systems (neurological, skin, head, eyes, ears, nose, mouth, throat, neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, and musculoskeletal systems).

### 7.1.5. Neurological Assessments

Neurological examination will be done according to the National Cancer Institute (NCI) criteria for clinical assessment of nervous system disorders (CTCAE version 5) at the timepoints detailed in the Schedule of Assessments (Appendix 3). Typical signs and symptoms of medulloblastoma will be entered in the eCRF. Signs and symptoms of medulloblastoma may include headaches, nausea, vomiting, tiredness, dizziness, double vision, poor coordination, unsteady walk, and other concerns. According to RAPNO, any clinical deterioration not attributable to other causes is, by definition, PD. In the absence of clear evidence of PD, it may be assumed that new signs and symptoms are treatment related. Any patient who develops an AE considered to be a Grade 3 or 4 nervous system disorder after the dosimetry infusion will not receive the treatment dose.

### 7.1.6. Performance Status

Since most if not all patients will have received prior craniospinal and/or whole-brain irradiation, late side effects for such previous therapies are difficult to distinguish from $^{177}$Lu-DTPA-omburtamab inflicted CNS AEs. However, to evaluate gross changes in neurological function, a performance test (Lansky [<16 years] or Karnofsky [≥16 years]) will be conducted at the Screening, EOT, and all Follow-up Visits in both parts of the trial.

## 7.2. Dosimetry, Pharmacokinetics, Imaging, and Laboratory Evaluations

### 7.2.1. Intracerebroventricular Access Device/CSF Flow Assessment

The patency of the intracerebroventricular access device shunt will be assessed at screening by injecting a small volume (about 0.3 mL) of a radiotracer into the shunt reservoir. The flow of CSF will be measured (for details, see Appendix 7). Only patients with sufficient flow should be dosed. Efforts to correct CSF flow can be installed and if sufficient flow is established, the patient can be dosed. Abnormal scan findings (ventricular outflow obstruction, obstruction within spinal canal, or failure to ascend to the convexities by 6 hours and spread over the convexities by 24 hours) will result in screening failure and must be documented in the patient's file.

### 7.2.2. Dosimetry and Calculation of Absorbed Radiation Doses (Part 1 only)

This will be conducted in Part 1 Cycle 1 only, and the timepoints for CSF/blood sampling and imaging scans are outlined in Table 4.

**Table 4: CSF and Blood Sampling and Scans in only Cycle 1 of Part 1**

| Time point (after dosimetry dose) | CSF | Blood | Whole-body planar Gamma Camera Scan | SPECT[a] |
|---|---|---|---|---|
| Baseline | × | × | | |
| 30 (± 10) min[b] | × | × | | |
| 1 h (± 10 min) | × | × | | |
| 4 h (± 10 min) | × | × | × (+ 1 h) | |
| 24 (± 2) h | × | × | × (± 2 h) | × (± 2 h) |
| 48 (± 2) h | × | × | × (± 2 h) | |
| 72 (± 4) h | × | × | | × (± 2 h) |
| Day 5-7[c] | × | × | × | × |
| Day 15 (± 12 h)[d] | × | × | × | × |

Abbreviations: CSF = cerebrospinal fluid.
[a] SPECT scan is optional.
[b] Both CSF and blood sampling; however, if both are not possible, CSF should be prioritized.
[c] Can be performed on Day 8; however, must be prior to the treatment dose.
[d] To be performed 7 days (± 12 h) after the treatment dose.

A dosimetry dose of 5 mCi was selected, with a possibility to increase to 10 mCi at the Sponsor's discretion in case of too low acquisition of radioactivity count.

**Organ Dosimetry**

Organ dosimetry by whole-body planar gamma camera scan (and regions of interest) will be conducted at site at the timepoints mentioned in Table 4 and calculation of the absorbed radiation doses will take place centrally. If a hybrid planar/SPECT imaging scanner is available, SPECT images may be acquired to improve the quantitative assessment of tumor target absorbed doses in particular.

Regions of interest in each planar dataset will be defined for the following source organs at each timepoint if signal is visibly above the immediate background: brain, spinal cord, liver, thyroid, salivary glands, lungs, kidneys, bladder, gallbladder, stomach, spleen, heart, gastrointestinal tract (large and small intestines), and any other organs demonstrating appreciable uptake. The mean absorbed radiation dose in CSF and whole blood will be estimated via imaging-based estimation (CSF) and serial sample-based estimation (CSF and blood) as described in the technical operations manual.

Whole-body planar gamma camera (and SPECT, if possible) scans will be performed using a dual-headed gamma camera (e.g., ADAC dual-headed VERTEX gamma camera, Milpitas, CA) for both planar gamma and SPECT scans) or comparable dual-detector system with medium-energy collimation. A photopeak energy window of 208 keV (±10%) and 113 keV (±10%) is used for lutetium-177. A known activity (e.g., 100 µCi) of $^{177}$Lu-DTPA-omburtamab is placed alongside the patient (a minimum of 10 cm from an extremity) and serves as a calibration standard. Whole body and regions of interest are manually drawn. Spinal CSF is manually drawn on the posterior whole-body images.

**Absorbed Radiation Doses in CSF and Blood**

The radioactivity in CSF and blood after administration of the dosimetry dose (seven measurements) and treatment dose (one measurement) in Part 1 Cycle 1 will be measured at site using a scintillation well counter, following qualified procedures outlined in the technical operations manual. The patients will have approximately 0.5 mL of CSF and 2 mL of peripheral blood drawn at each timepoint mentioned in Table 4.

Upon local analysis, the data will be transferred to a vendor located in US for central evaluation of the radiation doses delivered to the CSF and blood (derived from radioactivity versus time data).

### 7.2.3. Magnetic Resonance Imaging

Brain and spine MRI for assessment of response should be done locally in accordance with the recommendations outlined by the RAPNO committee[10], including:

- Central review for eligibility by neuroradiologists (at site) with expertise in pediatric brain tumor imaging.
- Absence of movement artifacts- if judged necessary, the patient must be sedated.
- Available preoperative contrast-enhanced MRI, to allow sufficient delineation of primary tumor and assessment of leptomeningeal metastases.
- Slice thickness according to the recommendations in RAPNO (see Table 1 in Warren et al. 2018[10]).
- Spinal MRI with full visualization of the dural sac, performed in 2 planes without skip regions and with adequate slice thickness and resolution.
- Tumor measurements should be made using the sequence that best demonstrates the extent of tumor; non-enhancing and enhancing primary lesions should be measured similarly.

### 7.2.4. CSF for Cytology, Total Protein, Glucose, ctDNA, and Cell Count

Samples of CSF for cytology, total protein, glucose, ctDNA, and cell count should be collected according to the Schedule of Assessments (Appendix 3). The CSF is sampled from the intracerebroventricular access device (e.g., Ommaya).

#### *7.2.4.1. CSF Sampling for ctDNA Sequencing*

Samples of CSF for ctDNA will be collected in standard CSF collection kit via the Ommaya reservoir at screening and at the EOT Visit if the patient has given informed consent to DNA analysis. ctDNA will be sequenced using high-throughput DNA sequencing. Samples will be

stored at site until testing at a central facility. As per protocol version 8, this analysis will not be performed, and samples should no longer be shipped from sites.

### 7.2.5. Blood and CSF for Culture

Blood and CSF will be sampled up to 6 hours after each IMP dose and held for potential culture (including the dosimetry dose in Part 1). Samples will be cultured only if body temperature is elevated (defined as ≥38°C [≈100°F]) after dosing and clinical infection is suspected.

### 7.2.6. Clinical Chemistry and Hematology

Blood samples for biochemistry and hematology will be analyzed by local laboratories; see Appendix 1 for a list of analytes to be analyzed.

### 7.2.7. Archival Tumor Tissue

#### *7.2.7.1. Analysis of B7-H3*

Archival tumor tissue from primary tumor and/or from CNS/leptomeningeal metastasis (if available) obtained as standard of care at site should be sent to the central laboratory in the US for semi-quantitative immunohistochemistry analysis of B7-H3. The histological diagnosis will be confirmed. The analyses will be performed in batches. As per protocol version 8, this analysis will not be performed, and samples should no longer be shipped from sites.

At least 5 (preferably 10 to 15) formalin-fixed, paraffin-embedded slides of 3 to 5 µm thickness (or a paraffin-embedded tissue block [enough for at least 5 sections]) will be needed. A detailed description of the procedures for sampling, handling, storage, and shipment of the samples will be provided by the central laboratory. Date of sampling, etc. will be recorded in the eCRF.

#### *7.2.7.2. Analysis of Primary Tumor DNA (in case of separate Informed Consent)*

Archival tumor tissue from primary tumor (if available) obtained as standard of care at site should be sent to the central laboratory in the US for DNA sequencing and analysis for comparison with the ctDNA derived from the CSF. The analyses will be performed in batches. As per protocol version 8, this analysis will not be performed, and samples should no longer be shipped from sites.

At least 10 formalin-fixed, paraffin-embedded sections of 3 to 5 µm thickness (or a paraffin-embedded tissue block [enough for at least 10 sections]) will be needed. If less than 10 are available, fewer sections are accepted. A detailed description of the procedures for sampling, handling, storage, and shipment of the samples will be provided by the central laboratory. Date of sampling, etc. will be recorded in the eCRF.

Upon issuance of the report, any leftover material will be discarded.

### 7.2.8. Immunogenicity

The presence of ADAs to $^{177}$Lu-DTPA-omburtamab in serum and CSF will be measured at the timepoints specified in the Schedule of Assessments (Appendix 3). No more than 2 mL of blood and 0.5 mL of CSF will be collected per timepoint, and sampling will be conducted conservatively given the age of the patients. Unscheduled sampling triggered by suspected immunologically related AEs may be conducted and collected until ADAs return to baseline. Dependent on the clinical data and occurrence of ADAs in Part 1, an assay to determine whether ADAs in CSF are neutralizing will be developed for Part 2. Samples will be stored frozen until testing at a central laboratory. ADAs will be evaluated using a validated enzyme-linked immunosorbent assay (ELISA) method.

### 7.2.9. Pharmacokinetic Analysis

To test the potential effect of ADAs on blood and CSF clearance of $^{177}$Lu-DTPA-omburtamab, PK exposure differences between Cycle 1 and Cycle 2 will be compared. Blood and CSF PK samples will be drawn at the following timepoints after the treatment doses in Cycle 1 and 2 (Table 5). No more than 2 mL of blood will be collected per timepoint and sampling. Samples will be stored frozen until testing at a central laboratory. Procedures for collection, processing, and shipping of PK blood and CSF samples will be detailed in a separate document.

Serum and CSF concentrations of $^{177}$Lu-DTPA-omburtamab will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

**Table 5: Schedule for CSF and Blood Pharmacokinetic Sampling (Parts 1 and 2)**

| Time of sampling following Cycle 1 Treatment Dose | Cycle 2 Treatment Dose |
|---|---|
| Baseline (prior to the treatment dose) | Baseline (prior to the treatment dose) |
| 30 (±10) min[1] | 30 (±10) min |
| 1 h (±10 min) | 1 h (±10 min) |
| 4 h (±10 min) | 4 h (±10 min) |
| 24 (±2) h | 24 (±2) h |
| 48 (±2) h | 48 (±2) h |
| 7 (±1) days after (blood only)*,** | 7 (± 1) days after (blood only)* |

* Only drawn in Part 1; may be performed on Day 8; however, must be pre-dose.
** In Part 1, Cycle 1, this is Day 15 as treatment dose is administered on Day 8.
[1] Both CSF and blood sampling; however, if both are not possible, CSF should be prioritized.

## 7.3. Efficacy Assessments

### 7.3.1. Progression-free Survival

Progression-free survival (PFS) will be assessed by MRI, neurological examination, and CSF cytology. As detailed in the RAPNO criteria (Appendix 6), progression is defined when any of the PD criteria are met. The timeframe for assessment of PFS will be from the first treatment dose of $^{177}$Lu-DTPA-omburtamab to time of disease progression or death from any cause. Patients lost to follow-up without any sign of progression will be censored at the date of last PFS assessment.

### 7.3.2. Response Evaluation, Overall Response Rate, and Duration of Response

Response, as defined by the RAPNO criteria (Warren et al. 2018[10]; see Appendix 6) will be assessed in Part 1 at the EOT Visit. In Part 2, response will be assessed at end of Cycle 1 and Cycle 3, EOT Visit, then 26, 39, and 52 weeks post first dose, followed by 78 and 104 weeks post first dose of $^{177}$Lu-DTPA-omburtamab. Notably, objective response and stable disease requires that all criteria are met, while progression is defined when any of the PD criteria are met.

The ORR will be calculated from baseline MRI scans and from scans after the dosing of $^{177}$Lu-DTPA-omburtamab using 2 methods: firstly, by considering MRI data, neurological examination, and CSF cytology data together (RAPNO criteria); secondly, by considering CSF cytology data only. ORR will be defined as the proportion of all evaluable patients achieving a CR or PR as best overall response at the time of assessment.

Investigator-assessed DoR (Part 2) is defined as the time from response (CR or PR) to progression. Patients without any sign of progression will be censored at the date of their last PFS assessment.

In Part 1 and Part 2, the baseline CSF cytology assessment must be completed within 3 weeks prior to the first $^{177}$Lu-DTPA-omburtamab treatment dose infusion. Cerebrospinal fluid cytology should be assessed as positive/negative. Cerebrospinal fluid cytology will be assessed in Part 1 at screening, the EOT Visit, and in Part 2 at screening, end of Cycle 1 and Cycle 3, EOT Visit, and at each Follow-up Visit.

### 7.3.3. Overall Survival (Part 2 Only)

The timeframe for assessment of OS will be from the first dose of $^{177}$Lu-DTPA-omburtamab to date of death from any cause. OS will be estimated using Kaplan-Meier methods.

## 7.4. Adverse Events

### 7.4.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory AE: a clinical laboratory abnormality which is clinically significant, i.e., an abnormality that suggests a disease and/or organ toxicity and is of a severity that

requires active management. Active management includes interventional treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

A pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the medical history/physical examination form) should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed should, however, be reported if it meets the definition of an AE. For example, an acute appendicitis should be reported as the AE and not the appendectomy.

### 7.4.2. Definition of Serious Adverse Events

Each AE is to be classified by the investigator as either serious or non-serious. This classification of the seriousness of the AE determines the reporting procedures to be followed. An AE that meets 1 or more of the following criteria/outcomes is classified as serious:

- Is fatal or life threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event.[3]

[1] The term "life threatening" in the definition of "serious" refers to an event in which the patient, in view of either the investigator or sponsor, 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.
Death alone is not considered an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to death. However, sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

[2] Hospitalization is defined as admission to a hospital/inpatient (irrespective of the duration of physical stay) or is not admitted to a hospital/not an inpatient but stays at the hospital for treatment or observation for more than 24 hours. Events leading to hospitalizations for the following reasons should not be reported as SAEs:

- Trial-related purposes, not associated with any deterioration in condition
- Social reasons in the absence of any deterioration in the patient's general condition
- Elective surgery or other scheduled hospitalization periods that were planned before the patient was included in this trial.

[3] Medical and scientific judgment must be exercised in deciding whether an AE is believed to be "medically important". Medically important events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

### 7.4.3. Definition of Non-serious Adverse Events

A non-serious AE is any AE which does not fulfil the definition of an SAE.

### 7.4.4. Definition of Adverse Events of Special Interest

The following AEs (serious and non-serious) are selected as Adverse Events of Special Interest (AESIs) and should be reported within 24 hours to the sponsor:

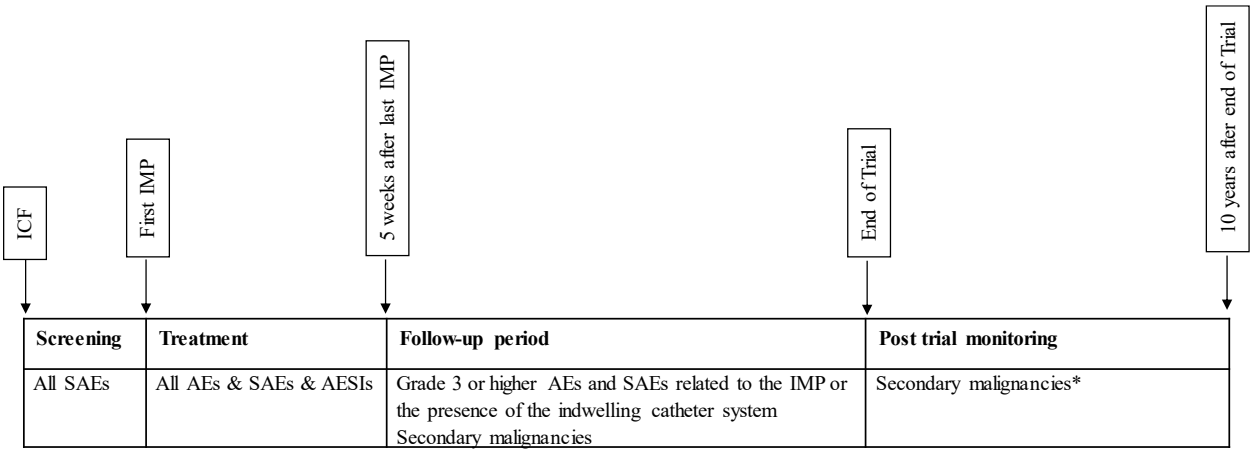
- Nervous system disorder Grade 3 and above (see Section 7.1.5)
- Severe infections related to placement of intracerebroventricular device.
- Chemical meningitis (symptoms of clinical meningitis but cultures for infectious agents were negative) in which either: a) event is non-responsive to IV steroids, b) radiologic or operative intervention was indicated, or c) presence of focal neurologic deficit.
- Suspicion of liver injury, defined as:
    - ALT or AST >3 × ULN and total bilirubin >2 × ULN* if baseline was within the normal reference ranges, or
    - ALT or AST increasing more than 3-fold from baseline value, if baseline was above normal reference ranges*

      *Either criterion requires that no other reason can be found to explain the increased laboratory parameters, such as viral hepatitis A, B, or C, pre-existing liver disease, or another drug capable of causing the observed injury.

In cases of suspected liver injury, testing should be repeated within 48 to 72 hours for evaluation of the event course/confirmation. Furthermore, additional information needs to be provided by the site, such as physical examination, information on alcohol consumption, or concomitant therapy (including herbal medications). Aspects like abdominal pain/tenderness, nausea, vomiting, jaundice, fever, rash, hepatomegaly, splenomegaly, peripheral edema, and recent weight gain should be considered and described.

### 7.4.5. Adverse Event Reporting

**Figure 2: Adverse Event Reporting**




* This post-trial monitoring can be conducted by contacting the patient or the general practitioner, the referral site (if applicable), or by checking medical records or other sources.

Any related SAE that the investigator becomes aware of after end of trial must be reported to sponsor using the clinical AE report form, see Section 7.4.5.3.

**Non-serious Events:**

Non-serious AEs should be reported from the day of first IMP administration until 5 weeks after the patient's last dose. Thereafter and during the follow-up and post-trial monitoring periods, new onset of cancers regardless of causality, should be reported, until death or at least 10 years after end of trial, whichever comes first. During the follow-up period, Grade 3 or higher non-serious AEs considered related to IMP or related to the presence of the indwelling catheter system should be reported. Non-serious AEs occurring between signing the ICF and the first IMP administration must be recorded as medical history.

**Serious Adverse Events:**

Serious AEs should be reported from signing the ICF until 5 weeks after the patient's last dose. Thereafter and during both the follow-up and post-trial monitoring periods, only SAEs considered related to IMP or related to the presence of the indwelling catheter system, or new onset of cancers regardless of causality, should be reported, until death or at least 10 years after end of trial, whichever comes first.

All events meeting the definition of an AE must be collected and reported in the eCRF. SAEs, DLTs (Part 1), and AESIs (whether serious or non-serious) should be reported both in the eCRF and on the clinical AE report form.

During each contact with the trial site staff, the patient must be asked about AEs, for example by asking: "Have you experienced any problems since the last contact?" All AEs observed by the

investigator or patient must be reported by the investigator and evaluated unless specifically excluded. All SAEs and AEs leading to discontinuation of IMP either observed by the investigator or patient must be reported by the investigator and evaluated.

**Diagnosis**

The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

**Onset Date and Time**

Start date for an (S)AE is the date of occurrence of the first symptom. The time should be entered if the event starts on a dosing day or if the duration of the event is less than 24 hours.

**End Date and Time**

The end date should be entered if the outcome of an event is fatal, recovered/resolved, or recovered/resolved with sequelae. The time should be entered if the event starts on a dosing day or if the duration of the event is less than 24 hours.

**Severity**

The investigator will use NCI CTCAE Version 5.0 to describe the severity of the AE. The grade assigned by the investigator should indicate the grade at the onset of the event and the most severe grade that occurred during the AE period.

**Outcome**

The investigator must judge outcome of the AE by the following terms:

- Recovered
- Recovered with sequelae
    - Description of the sequelae should be provided
- Not recovered
- Recovering
- Fatal
- Unknown*

    * Should only be used if patient is lost to follow-up.

Instructions for reporting changes in an ongoing AE during a patient's participation in the trial will be provided in the instructions that accompany the AE form in the eCRF.

**Relationship to Investigational Medicinal Product**

The investigator must assess whether the event is related to the IMP. A suspected adverse drug reaction (ADR) is defined as one in which there is a reasonable possibility that the drug caused the AE. Relatedness must be assessed and reported from the first time the AE is being reported. When assessing the causal relationship of an AE to the IMP, the following should be taken into consideration:

**Not Related (Unlikely)**

The AE is not related to the IMP, which means the AE:

- Does not follow a reasonable temporal sequence from IMP administration.
- Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient.
- Is clearly not related to the IMP.

For AEs assessed as "Not Related", an alternative etiology should be stated detailing the more likely reason for the AE.

**Possibly Related**

The AE follows a reasonable temporal sequence from IMP administration but could have been produced by the patient's clinical state, medical history, or the trial procedures/conditions.

Alternative etiology should be provided for all AEs assessed as possibly related to IMP.

**Probably Related**

The AE is probably related to the IMP, which means the AE:

- Follows a reasonable temporal sequence from IMP administration.
- Abates spontaneously upon discontinuation of the IMP (de-challenge) without any curative treatment.
- Is confirmed by reappearance of the same reaction on repeat exposure (re-challenge) (if applicable).
- Cannot be reasonably explained by the known characteristics of the patient's clinical state or medical history.

**Action Taken with Investigational Medicinal Product**

The action taken with the IMP should be noted as:

- Dose Decreased*
- Dose Administration Rate Decreased
- Interrupted
- Postponed
- Discontinued
- None
- Not Applicable**
- Unknown.

*Only applicable in Part 2.

**Not Applicable should be used if the AE occurs before first treatment or after end of treatment (i.e., the IMP was already discontinued).

#### *7.4.5.1. Events Requiring Immediate Reporting*

The following events (for reporting periods, see Figure 2) require immediate reporting (within 24 hours) (for details, see Section 7.4.5.3):

- SAE
- DLT
- AESI
- Pregnancy.

Starting five weeks after the last dose, only SAEs or Grade 3 or higher AEs at least possibly related to $^{177}$Lu-DTPA-omburtamab or to the presence of the indwelling catheter system, or new onset of cancers regardless of causality, should be reported until end of trial. Subsequently, in the post-trial monitoring period, SAEs considered related to IMP or new onset of cancers regardless of causality, should be reported until death or at least 10 years after end of the trial, whichever comes first, using the clinical AE report form, see Section 7.4.5.3.

#### *7.4.5.2. Pregnancy*

Any pregnancy that occurs during trial participation must be reported to the sponsor within 24 hours of knowledge using the pregnancy form. Pregnant trial patients must be discontinued from treatment immediately. Should pregnancy of female partners of male patients occur, a separate informed consent will be obtained from the female partner for collection of information regarding the pregnancy. The pregnancy must be followed up to determine outcome and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

#### *7.4.5.3. Reporting Timelines and Contact Details*

- Initial SAEs (including DLTs and predefined AESIs, whether serious or not): The clinical AE report form must be reported from site to sponsor within 24 hours of the investigator's first knowledge of the event. The clinical AE report form is to be e-mailed as detailed below. The AE eCRF page should be updated in accordance with agreed data entry timelines and the eCRF completion instructions. New follow-up information available at site must be reported within 24 hours.

- Follow-up information requested from the sponsor must be replied to within 3 working days using a data clarification form. The AE eCRF page should be updated in accordance with agreed data entry timelines.

- If an ongoing SAE/AESI changes in intensity, relationship to IMP, or as new information becomes available for the event, a clinical AE report form should be completed and sent to the sponsor within 24 hours of the change in assessment.

**Contact Details for Reporting**

Completed clinical AE report forms and pregnancy forms must immediately be reported using the following e-mail address:

safetymailbox@ymabs.com

In emergency situations, the completed clinical AE report forms or pregnancy forms can be faxed to:

FAX:+45 7879 6060

#### *7.4.5.4. Reporting of SUSARs*

All relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to regulatory authorities in accordance with regulatory requirements.

Investigators will be notified of SUSARs in accordance with local requirements. Furthermore, investigators will be informed of any trial-related SAEs that may warrant a change in any trial

procedure. Labcorp will inform the IRBs/ECs of SUSARs in accordance with local requirements, unless locally this is an obligation of the investigator. The Sponsor assessment of expectedness for $^{177}$Lu-DTPA-omburtamab will be performed according to the current version of the investigator's brochure.

#### *7.4.5.5. Follow-up on Adverse Events*

Non-serious AEs should be followed until they are either resolved, returned to baseline, or until end of trial, whichever comes first. Grade 3 or higher non-serious AEs that are considered treatment related and all SAEs (including AESIs and DLTs) should be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator can assess it as chronic or stable. This includes follow-up during the long-term monitoring periods.

#### *7.4.5.6. Medical Monitoring and Communication of Significant Safety Issues*

In the event of any significant safety related issues, the investigator should:

- Closely monitor the patient
- Contact the Medical Monitor (for contact details, see the protocol front page)

Sponsor will decide upon immediate action to be taken including prompt notification of the DMC and will communicate to regulatory authorities, investigators, ECs/IRB, and patients as needed within regulatory timelines.

The Sponsor will ensure that all Investigators across sites and ongoing trials with the same IMP ($^{177}$Lu-DTPA-omburtamab) are promptly notified of significant safety issues and required actions including urgent safety measures (e.g., holding further dosing) to protect trial participants against an immediate hazard.

In addition, the Sponsor will inform all Investigators across sites and ongoing trials with the same IMP ($^{177}$Lu-DTPA-omburtamab) of DMC recommendations including dose escalation decisions.

# 8. SAMPLE SIZE AND DATA ANALYSES

## 8.1. Determination of Sample Size

In Part 1, the chosen sample size is customary for studies of this nature and is not based on statistical considerations. It is estimated that up to 25 patients will participate in Part 1, based on 5 dose levels being recruited. Actual number of patients will depend on the number of DLTs observed.

For Part 2, a sample size of 24 patients provides at least 90% probability to detect an AE occurring in 10% of exposed patients.

The assumption is that 20 out of the 24 patients in Part 2 are evaluable. With 20 patients evaluable for response and a response rate of 25% (~ to 5 responders out of 20), the lower limit of the 95% confidence interval will be 9%.

## 8.2. Analysis Populations

The following analysis sets will be included for this trial:

**Safety Analysis Set:** will consist of all patients who received at least 1 dose of trial treatment (treatment dose or dosimetry dose).

**DLT Evaluable Analysis Set:** will include patients in the dose escalation who as a minimum is evaluated during the 5 weeks DLT evaluation period, or who has a DLT during the DLT evaluation period. This analysis set is a subset of the Safety Analysis Set.

**Full Analysis Set (FAS):** will consist of all patients in the Safety Analysis Set.

**Dosimetry Analysis Set (Part 1 only):** will consist of all patients who received the dosimetry dose and have evaluable data for absorbed doses to CSF and blood or for whole-body planar scan.

**PK Analysis Set**: will consist of all patients who received at least 1 treatment dose of trial drug and have evaluable PK data.

Efficacy will be analyzed using the FAS. Safety will be analyzed using the Safety Analysis Set. Dosimetry and absorbed doses to CSF and blood will be analyzed using the Dosimetry Analysis Set. Pharmacokinetics will be analyzed using the PK Analysis Set.

## 8.3. General Considerations

Summary statistics, listings, and statistical analyses will be performed for patients included in the relevant analysis sets.

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number. For log-normal data (e.g., the PK parameters, the activity-time curve and elimination half-life of absorbed doses to CSF and

blood), the geometric mean and geometric coefficient of variation will be presented instead of mean and SD. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all patients up to the point of withdrawal, with any patients excluded from the relevant analysis set highlighted. For the calculation of summary statistics, listings, and statistical analysis, unrounded data will be used.

For the time to event efficacy endpoints, patients who do not have an event will be censored at the date of their last evaluation. If partial dates are present, a conservative approach will be used. If partial dates are present for efficacy time to event endpoints, missing months and/or days will be imputed as January and the first day of the month, respectively. AEs with a missing start date or time that leads to ambiguity in whether the AE is treatment-emergent will be considered treatment-emergent. It is unlikely that other missing of safety data will occur in the targeted patient population, but in case it happens the data will not be imputed.

When the last patient in Part 1 has completed the EOT visit, all available data for that part will be reported.

For Part 2, full efficacy and safety analyses will be performed when the last patient completes week 52 assessments, dies, or is lost to follow up. An updated long term survival analysis will be performed when the last patient has reached the 104 week visit, dies, or is lost to follow-up.

Data analysis will be performed using SAS® Version 9.3 or higher.

## 8.4. Efficacy Analysis

The FAS will be used for all efficacy endpoints.

### 8.4.1. Part 2 Efficacy Analysis

Overall survival at 1 and 2 years post first dose will also be estimated using Kaplan-Meier methods. Patients not deceased will be censored at the last date known to be alive. The median PFS time and the proportion of patients without PFS events at 1 and 2 years post first dose will be estimated using Kaplan-Meier methods, along with their 95% confidence intervals. Results will be displayed in Kaplan-Meier plots. The ORR according to RAPNO criteria (MRI, neurological examination, and CSF cytology), as well as according to CSF cytology alone, will be assessed. The 95% confidence intervals will be calculated using the Clopper-Pearson exact methodology. Investigator-assessed DoR will be estimated using Kaplan-Meier methods. The median DoR and corresponding 95% confidence interval will be calculated.

## 8.5. Safety Analysis

### 8.5.1. Dose-Limiting Toxicities

DLTs observed during the DLT evaluation period, i.e., within 5 weeks after the dosimetry dose in Cycle 1 of the dose escalation will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). DLTs observed outside the DLT evaluation period will be presented in a listing. The information from

the DLTs will be used to guide the escalation and ultimately determine the MTD. Furthermore, the information will be used to make recommendations regarding the RP2D. The evaluation of DLTs will be based on the DLT evaluable analysis set.

### 8.5.2. Adverse Events

The Safety Analysis Set will be used for all safety analyses except for evaluations of DLTs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or later. Adverse events will be regarded as TEAEs if they occur after first administration of $^{177}$Lu-DTPA-omburtamab. Related AEs are defined as ADRs.

Listings will be made of all AEs. Non-TEAEs will be listed separately. All TEAEs, ADRs, AESIs, SAEs, and serious ADRs will be summarized by MedDRA SOC and preferred terms for each treatment group. The summaries will include number of AEs, number of patients, and percentage of patients reporting these AEs and will be tabulated by SOC and preferred term. TEAEs will also be summarized by severity and by relationship to IMP.

### 8.5.3. Other Safety Assessments

Changes in vital signs, hematology, and clinical chemistry parameters from baseline to the end of the trial will be examined. Treatment-emergent changes from normal values to abnormal values in key laboratory parameters may be identified. Development of ADA will be examined. Effects on cognitive functions will be assessed by summarizing changes from baseline in performance testing results using descriptive statistics.

Baseline is defined as the latest assessment prior to first dose.

## 8.6. Analysis for Calculation of Absorbed Doses to CSF and Blood (Part 1 only)

The mean absorbed radiation dose in CSF and blood will be calculated from radioactivity measured in CSF and blood samples taken at predefined timepoints after the dosimetry and the treatment doses in Cycle 1.

Analysis of lutetium-177 activity in blood and CSF will include derivation of best-fit uptake and/or clearance parameters (elimination half-times, maximum value) of time-activity curves and of residence times (i.e., cumulated activity in μCi·h/g). Blood and CSF time-activity curves will be modeled using exponential retention functions to estimate clearance following the last sampled timepoint, and cumulated activities for both will be computed using a combination of trapezoidal integration of sampling data and analytical integration of clearance curves (re-incorporating physical decay). Absorbed doses in the blood and CSF will then be derived from cumulated activity by applying the equilibrium absorbed dose constant for lutetium-177 under the assumption of complete local β-absorption, consistent with prevailing practice.

Individual and mean absorbed radiation dose to CSF and blood will be summarized using descriptive statistics for all patients in the Dosimetry Analysis Set and by trial site.

## 8.7. Dosimetry Analysis (Part 1 only)

Spinal cord, brain, and non-target region of interest absorbed radiation doses will be estimated and CSF mean absorbed radiation doses will be calculated on the basis of whole-body planar gamma camera scans. Tumor target absorbed doses will be calculated on the basis of SPECT scan, if possible. Additionally, the mean absorbed radiation dose in CSF and blood will be calculated from CSF and blood radioactivity measured in CSF and blood samples taken at predefined timepoints after the dosimetry and the treatment doses in Cycle 1.

Individual and mean dosimetry data will be calculated per trial site and will be summarized using descriptive statistics.

## 8.8. Pharmacokinetic Analysis

The serum and CSF PK parameters of $^{177}$Lu-DTPA-omburtamab following the treatment doses in Cycles 1 and 2 will be calculated using standard noncompartmental methods in both study parts. Standard PK parameters (such as $C_{max}$, AUC, half-life) will be calculated.

## 8.9. Interim Analysis

*Ad hoc* interim analyses will be performed in connection with communication with regulatory authorities.

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# 10. APPENDICES

## Appendix 1: Clinical Laboratory Evaluations

The following clinical laboratory analytes will be assessed locally at the site:

| Chemistry: | Hematology (CBC): |
|---|---|
| Albumin | Hematocrit |
| ALP | Hemoglobin |
| ALT | MCH |
| AST | MCHC |
| BUN | MCV |
| Calcium | Platelet count |
| Chloride | Red blood cell (RBC) count |
| Creatinine | White blood cell (WBC) count |
| Glucose | WBC differential |
| LDH | (% & absolute): |
| Potassium | Basophils |
| Sodium | Eosinophils |
| Total bilirubin | Lymphocytes |
| Total $CO_2$ (measured as bicarbonate) | Monocytes |
| Total protein | Neutrophils |
| Triglycerides | |
| Uric acid | For females of childbearing potential only: Urine or serum pregnancy test (only at the timepoints indicated in Appendix 3) |
| **CSF** | |
| Total protein | |
| Glucose | |
| Cell count | |
| Cytology | |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; $CO_2$ = carbon dioxide; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

If clinical signs of infection are observed following IMP infusion, the drawn CSF and blood samples must be cultured at the local microbiological laboratory.

## Appendix 2: Regulatory, Ethical, and Trial Oversight Considerations

### Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Ethical considerations for clinical trials on medicinal products conducted with minors[29]
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, patient information, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the trial is initiated.

- Any amendments to the protocol will require regulatory and IRB/EC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.

The investigator will be responsible for the following:

- Ensuring the trial is conducted in accordance with the procedures and evaluations described in this protocol. Deviations from the protocol should not occur. If deviations do occur, the investigator has to inform the CRA for discussion and decision on required action(s). Deviations should be documented in writing including an explanation. Documentation of deviations will be filled in the investigator's site file and a copy in the Sponsor's file. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority
- Providing written summaries of the status of the trial to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings as required by IRB/EC procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

**Finances and Insurance**

Financing and insurance will be addressed in a separate agreement. Insurance and liability will be in accordance with applicable local laws and regulations and GCP.

**Informed Consent**

The investigator or his/her designee must obtain the written informed consent from each patient, and/or the patient's acceptable authorized representative, before any trial-related procedures are performed, as applicable to local regulations. If the indwelling intracerebroventricular access device (e.g., Ommaya) is placed in connection with the tumor resection, the informed consent must be obtained prior to the surgery, and before the start of the screening period. However, if this is placed as part of a standard of care at site, this is not considered as a trial procedure and hence not requiring informed consent prior to the procedure. A separate ICF will be issued for the circulating tumor DNA (ctDNA) and primary tumor DNA assessments, for patients who wish to consent to that analysis. The written patient information must not be changed without prior discussion with the sponsor and approval by the IRB/IEC. Participant and legal representative (e.g., parent[s] or guardian[s]), if applicable, must receive full trial information, both verbally and written, before consent is given. A child or adolescent patient will be informed and included in the conversations with the parents, to the extent that he/she can understand given his/her age. A patient information sheet will be prepared addressing legal representative(s) and a version especially addressing the adolescent population will also be prepared, as and when applicable to local regulations.

The patient information will contain full and adequate information regarding the objective and procedures of the trial and the possible benefits and risks involved. This will include any information of possible transfer of biological materials, imaging, and other needed for central analysis. The consent shall be given in interest of the child, meaning that he/she is presumed willing to participate. Regardless of legal representative(s) written consent, the participation shall not take place if the patient objects. Objection can also be non-verbal and expressed by the child's attitude, body language, or resistance. Informed consent (parents or legal representative), and if applicable informed assent (child/adolescent), must be signed in accordance with local regulations. The patient information will be updated in case of new information that may affect a patient's decision to participate in or remain in the trial.

If applicable to local regulations: if a child turns 18 during his/her participation in the trial, a written consent must be obtained from him/her before the trial can continue.

Before signing the ICF, the patient/parents must be given sufficient time to consider the possible participation. Further, each patient must be informed about their right to withdraw from the trial at any time. Parents and patients will also be informed that research participation is voluntary but if they withdraw from the trial, their data will still be used. When the ICF has been signed, the patient/parent(s) receives a copy of the signed form and the original is retained in the investigative site file. A second copy may be kept in the patient's medical notes. The ICFs must be signed and dated both by the signee and by the person providing the information to the patient/parents. It is recommended to notify the patient's family doctor of the patient's consent to participate in the trial.

Informed consent must be obtained before any trial-related procedures. The placement of the indwelling intracerebroventricular access device (e.g., Ommaya reservoir) is a surgical procedure requiring general anesthesia. Having the neurosurgeon place the Ommaya in association with the anesthesia induced for the surgical resection of the tumor will reduce the burden of the trial procedures by avoiding an extra surgical procedure. Another consideration is that since the patient may receive high-dose chemotherapy in the period leading up to the screening period, this may be associated with myelosuppression rendering an invasive procedure like Ommaya placement not feasible. There is, therefore, a rationale for allowing placement of the Ommaya reservoir prior to screening for patients who are potential candidates for trial participation, in particular for patients who are not being resected to R0 classification. In cases where the potential patient is a referral patient, the investigator should discuss trial inclusion and exclusion criteria with the referring physician, and only patients deemed eligible for the trial should be considered for Ommaya placement in connection with tumor resection. In this case, the informed consent must be obtained prior to the surgery, and may be done so up to 2 months before the start of the screening period.

**Patient Data Protection**

Patients will be assigned a unique identifier and will not be identified by name in electronic case report forms (eCRFs), trial-related forms, study reports, or any related publications. Patient and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the trial protocol, study report, or trial data are included in a public registry, all identifiable information from individual patients or investigators will be redacted according to applicable laws and regulations.

The patient must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient. The patient must also be informed that his/her medical records may be examined by sponsor or Contract Research Organization auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

**Disclosure**

All information provided regarding the trial, as well as all information collected and/or documented during the course of the trial, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

**Data Quality Assurance**

The following data quality steps will be implemented:

- All patient data relating to the trial will be entered on eCRFs, unless directly transferred to the sponsor or designee electronically (e.g., laboratory data).
- All directly transferred data to the sponsor must be described in a Data Transfer Agreement (DTA) which must be signed by sponsor and the laboratory transferring data.

- The investigator must maintain accurate documentation (source data) and complete a source data list, defining where the specific source data that supports the information entered in the eCRF can be found.

- The investigator must permit trial-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this trial including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in Xcellerate Risk and Issue Management system (XRIM). Additional details of quality checking to be performed on the data may be included in the data management plan and the data review plan.

- Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, data management plan, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator in accordance with 21 CFR 312.62(c) (US sites) or in the trial site archive for at least 25 years after the end of the trial (European sites) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

**Investigator Documentation Responsibilities**

All individual, patient-specific trial data will be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF, containing edit checks on individual fields where deemed necessary, in a timely fashion. It is expected that data is entered in the eCRF within 5 working days; however, dosing and any AEs in Part 1 Cycle 1 should be entered within 24 hours. In case of data entry delay for Part 1 Cycle 1, the site is to confirm that the patient received the dose as per protocol and that any AEs (including DLTs) have been reported. All data generated from external sources (e.g., central laboratory, pharmacokinetics central readers) and transferred to the sponsor or designee electronically will be integrated with the patient's eCRF data in accordance with the data management plan and the applicable Data Transfer Agreements.

An eCRF must be completed for each patient who signs an ICF and undergoes any pre-screening or screening procedures, according to the eCRF completion instructions. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the trial staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the accuracy of the data on the eCRF, the data queries, and the site notifications. The data will be considered clean and final upon signature from the investigator.

**Publications**

If on completion of the trial the data warrant publication, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical trial agreement (CTA). Unless otherwise specified in the CTA, the following process shall occur:

The institution and investigator shall not publish or present data from an individual trial center until the complete multicenter trial has been presented in full or for 2 years after the termination of the multicenter trial, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the investigator expects to participate in the publication of data generated from this site, the institution and investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including (without limitation) the deletion of confidential information. The investigator shall act in good faith upon requested revisions, except the investigator shall delete any confidential information from such proposed publications. The investigator shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) file

## Appendix 3: Schedule of Assessments

### Table 6: Schedule of Assessments – Part 1, Screening and Cycle 1

| Dosing/Measurements/Evaluations | Screening | $^{177}$Lu-DTPA-omburtamab Treatment Period[1,2] – Cycle 1 | | | | |
|---|---|---|---|---|---|---|
| | Day -29* to -1 | Day 1 | Day 8 (±1) | Day 15 (±1) | Day 22 (±1) | End-of-Cycle Visit (Day 29 [±1]) |
| Informed consent[3] | X | | | | | |
| Eligibility check | X | | | | | |
| Demographics, height, body weight | X | | | | | |
| Medical, surgical, and disease history | X | | | | | |
| Prior/concomitant medications | X | X | X | X | X | X |
| Physical examination[4] | X | | | | | |
| Vital signs[5] | X | X | X | X | X | X |
| Performance test[6] | X[7] | | | | | |
| MRI of the brain and spine[8] | X[7] | | | | | |
| Neurological examination[9] | X | X | | | | |
| Placement of indwelling ICV access device | X[3] | | | | | |
| ICV access device patency/CSF flow assessment | X | | | | | |
| Premedication (oral dexamethasone/IV equivalent)[10] | | X | X | | | |
| Anti-pyretic and anti-histaminergic premedication[11] | | X | X | | | |
| ICV $^{177}$Lu-DTPA-omburtamab dosimetry dose | | X | | | | |
| ICV $^{177}$Lu-DTPA-omburtamab treatment dose | | | X | | | |
| Whole-body planar gamma camera scan[12] | | X[12] | X[12] | X[12] | | |
| Blood and CSF for calculation of absorbed doses[13] | | X[13] | | X[13] | | |
| Clinical chemistry and hematology[14] | X | X | X | X | X | X |
| CSF for cytology[15], total protein, glucose, and cell count | X[7] | | | | | |
| Blood and CSF for culture | | X[16] | X[16] | | | |
| Blood and CSF sampling for ADA[17] | X[17] | | | | | |
| Blood and CSF sampling for pharmacokinetics | | | X[18] | X[18] | | |
| Pregnancy testing[19] | X | X | X | | | |
| Adverse events[20] | X | X | | X | X | X |

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CSF = cerebrospinal fluid; ctDNA = circulating tumor deoxyribonucleic acid; EOT = end of treatment; HSA = human serum albumin; ICF = informed consent form; ICV = intracerebroventricular; IMP = investigational medicinal product; IV = intravenous; MRI = magnetic resonance imaging; NCI = National Cancer Institute; SAE = serious adverse event.

[*] A longer screening period (e.g., due to logistics, COVID-19 situations etc.) are allowed; however, eligibility evaluation must be re-confirmed. Screening period of >60 days with individual patient considerations to be discussed with the sponsor.

[1] The $^{177}$Lu-DTPA-omburtamab Treatment Period is divided into 5-week cycles. In Part 1, the patient can receive up to 2 cycles at the discretion of the investigator. Cycle 1 starts with a dosimetry dose on Day 1 and continues with the first treatment dose on Day 8 (adjustments to the dosing schedule will be accommodated on a patient-by-patient basis depending on the clinical condition of the patient). The infusion reservoir must be flushed with HSA and CSF after each infusion. On dosing days, all assessments are done before dosing.

[2] If the IMP is discontinued after Cycle 1, the Day 29 Visit is replaced by the EOT Visit.

[3] Informed consent must be obtained before any trial-related procedures. If the indwelling ICV access device (e.g., Ommaya) is placed in connection with the tumor resection, the informed consent must be obtained prior to the surgery, and before the start of the screening period, unless this is placed as part of a standard of care procedure at site. If any procedures/tests are from before informed consent is obtained, it must be clear from source documents that this was not performed for the purpose of the present trial. In these cases, the procedures/tests do not need to be repeated at the Screening Visit if they were performed within the allowed timelines. The investigator is responsible for documenting this properly.

[4] Physical examinations to be performed at screening and as clinically indicated.

[5] Measurements of heart rate, respiratory rate, temperature, and blood pressure. On dosing days, measurements to be taken before and 30 min after the end of the IMP infusion.

[6] Lansky Scale <16 years, Karnofsky Scale ≥16 years.

[7] To be performed within 3 weeks prior to the first IMP infusion. May be performed on the first dosing day but it must be before IMP administration.

[8] MRI of the brain and spine will be completed before first IMP administration, at the EOT Visit (preferably ±4 days of the actual visit date). MRI can be performed on a separate day to the other visit assessments, if required, in accordance with investigational site standards.

[9] Will be used to evaluate safety and efficacy.

[10] Beginning 24 hours before IMP administration, divided into twice-daily doses for a total of 3 days.

[11] Given 1-2 hours prior to IMP administration, including oral acetaminophen/paracetamol and antihistamine (e.g., diphenhydramine).

[12] Following the dosimetry dose, whole-body planar gamma camera scans will be performed at 4 h (4-5 h), 24 h (22-26 h), 48 h (46-50 h), and Day 5-7 (may be performed on Day 8; however, must prior to the treatment dose), and on Day 15 (±12 hours), i.e., 7 days after administration of the treatment dose (see Table 4). SPECT imaging is optional at 24 h (22-24 h), 72 h (70-74), Day 5-7 (or Day 8 pre-dose), and on Day 15 (±1) (i.e., 7 days after the treatment dose).

[13] Approximately 0.5 mL of CSF and 2 mL of peripheral blood will be drawn at each timepoint (see Table 4), i.e., before treatment (baseline; to avoid withdrawing too high volumes of CSF on the day of the dosimetry dose, baseline sample should be drawn in the time between placement of the ICV access device and 1 day before dosing) and following the dosimetry dose at 30 min (±5 min), 1 h (±10 min), 4 h (±10 min), 24 h (±30 min), 48 h (±1 h) and 72 h (±4 hour) In addition, samples are drawn on Day 5-7 (may be on Day 8; however, must be prior to the treatment dose) and on Day 15 (±12 hr), i.e., 7 days after administration of the treatment dose.

[14] In accordance with Appendix 1.

[15] If CSF cytology sample is positive, it must be repeated within 4 weeks of the positive sampling.

[16] Drawn and held for culture only if elevated body temperature after dosing suggests infection rather than expected response to ICV dosing. Samples to be taken within 6 hours after completion of IMP infusion.

[17] The baseline ADA samples must be drawn prior to the dosimetry dose and to avoid withdrawing too high volumes of CSF on the day of the dosimetry dose, the samples should be drawn in the time between placement of the ICV access device and 1 day before dosing. Serum and CSF samples for ADA analyses will be drawn at baseline and after last treatment. Presence of ADA will be analyzed at a central laboratory.

[18] Blood and CSF samples for pharmacokinetics will be drawn as per Table 5. On Day 15 (i.e., 7 days after the treatment dose), blood collection only.

[19] Pregnancy testing (serum or urine) is mandatory for women of childbearing potential at screening, within one week prior to each dose, and at the EOT Visit.

[20] Non-serious AEs should be reported from the day of first IMP administration until 5 weeks after the patient's last dose of IMP. Non-serious AEs occurring between signing the ICF and the first IMP administration must be recorded as medical history. Serious AEs should be reported from signing the ICF until 5 weeks after the patient's last dose of IMP. Thereafter and during the follow-up period, only SAEs or Grade 3 or higher AEs at least possible related to $^{177}$Lu-DTPA-omburtamab or to the presence of the indwelling catheter system should be reported until end of trial. In the post-trial monitoring period, new onset of cancers, regardless of causality, should be reported.

**Table 7: Schedule of Assessments – Part 1, Cycle 2 (if Applicable) through Follow-up**

| Dosing/Measurements/Evaluations | $^{177}$Lu-DTPA-omburtamab Treatment Period[1,2] – Cycle 2 | | EOT and End of Trial |
|---|---|---|---|
| | Day 1 of cycle | Day 8 (±1), Day 15 (±1) of cycle | 5 to 6 weeks after last dose |
| Prior/concomitant medications | X | X | X |
| Physical examination[3] | | | |
| Vital signs[4] | X | X | X |
| Performance test[5] | | | X |
| MRI of the brain and spine[6] | | | X |
| Neurological examination[7] | X | | X |
| Premedication (oral dexamethasone/IV equivalent)[8] | X | | |
| Anti-pyretic and anti-histaminergic premedication[9] | X | | |
| ICV $^{177}$Lu-DTPA-omburtamab treatment dose | X | | |
| Clinical chemistry and hematology[10] | X | X | X |
| CSF for cytology[11], total protein, glucose, and cell count | | | X |
| Blood and CSF for culture | X[12] | | |
| Blood and CSF sampling for ADA | X[13] | | X |
| Blood and CSF sampling for pharmacokinetics | X[14] | X[14] | |
| Pregnancy testing[15] | X | | X |
| Adverse events[16] | X | X | X |

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CSF = cerebrospinal fluid; ctDNA = circulating tumor deoxyribonucleic acid; EOT = end of treatment; HSA = human serum albumin; ICF = informed consent form; ICV = intracerebroventricular; IMP = investigational medicinal product; IV = intravenous; MRI = magnetic resonance imaging; NCI = National Cancer Institute; SAE = serious adverse event.

[1] The $^{177}$Lu-DTPA-omburtamab Treatment Period is divided into 5-week cycles. In Part 1, the patient can receive up to 2 cycles at the discretion of the investigator. Cycle 2 will start 35 days (adjustments to the dosing schedule will be accommodated on a patient-by-patient basis depending on the clinical condition of the patient.) after the first dose (dosimetry dose) of Cycle 1 and will consist of a treatment dose only (i.e., no dosimetry dose), on Day 1 of the cycle. The infusion reservoir must be flushed with HSA and CSF after each infusion.

[2] If the IMP is discontinued after Cycle 1, the Cycle 2 visits should be skipped, and after the EOT Visit should be done.

[3] Physical examinations to be performed as clinically indicated.

[4] Measurements of heart rate, respiratory rate, temperature, and blood pressure. On dosing day, measurements to be taken before and 30 min after the end of the IMP infusion.

[5] Lansky Scale <16 years, Karnofsky Scale ≥16 years.

[6] MRI of the brain and spine will be completed before first IMP administration, at the EOT Visit (preferably ±4 days of the actual visit date). MRI can be performed on a separate day to the other visit assessments, if required, in accordance with investigational site standards.

[7] Will be used to evaluate safety and efficacy.

[8] Beginning 24 hours before $^{177}$Lu-DTPA-omburtamab administration, divided into twice-daily doses for a total of 3 days.

[9] Given 1-2 hours prior to $^{177}$Lu-DTPA-omburtamab administration, including oral acetaminophen/paracetamol and antihistamine (e.g., diphenhydramine).

[10] In accordance with Appendix 1.

[11] If CSF cytology sample is positive, it must be repeated within 4 weeks of the positive sampling.

[12] Drawn and held for culture only if elevated body temperature after dosing suggests infection rather than expected response to ICV dosing. Samples to be taken within 6 hours after completion of $^{177}$Lu-DTPA-omburtamab infusion.
[13] The ADA samples must be drawn prior to the Cycle 2 dose. The analysis can be performed from the samples drawn with the purpose of PK.
[14] Blood and CSF samples for pharmacokinetics will be drawn as per Table 5. On Day 8, blood collection only.
[15] Pregnancy testing (serum or urine) is mandatory for women of childbearing potential at screening, within one week prior to each dose, and at the EOT Visit.
[16] Non-serious AEs should be reported from the day of first IMP administration until 5 weeks after the patient's last dose of IMP. Non-serious AEs occurring between signing the ICF and the first IMP administration must be recorded as medical history. Serious AEs should be reported from signing the ICF until 5 weeks after the patient's last dose of IMP. Thereafter and during the follow-up period, only SAEs or Grade 3 or higher AEs at least possible related to $^{177}$Lu-DTPA-omburtamab or to the presence of the indwelling catheter system should be reported until end of trial. During the post-trial monitoring period, new onset of cancers, regardless of causality, should be reported.

**Table 8: Schedule of Assessments – Part 2 (All Cycles)**

| Dosing/Measurements/Evaluations | Screening | $^{177}$Lu-DTPA-omburtamab Treatment Period[1,2] | | | EOT | Follow-up[3] | |
|---|---|---|---|---|---|---|---|
| | | Cycles 1 through 5 | | | | | |
| | Day -29* to -1 | Day 1 of cycle | Day 15 (±1) of cycle | End-of-Cycle Visit (Day 29 [±1] of cycle) | 5 to 6 weeks after last dose | 26, 39, and 52 (±2) weeks post first dose | 78 and 104 (±2) weeks post first dose |
| Informed consent[4] | X | | | | | | |
| Eligibility check | X | | | | | | |
| Demographics, height, body weight | X | | | | | | |
| Medical, surgical, and disease history | X | | | | | | |
| Prior/concomitant medications | X | X | X | X | X | X[5] | X[5] |
| Physical examination[6] | X | | | | | | |
| Vital signs[7] | X | X | X | X | X | X | X |
| Performance test[8] | X[9] | | | | X | X[8] | X[8] |
| MRI of the brain and spine[10] | X[9] | | | X[10] | X | X | X |
| Neurological examination[11] | X | X | | X | X | X | X |
| Placement of an indwelling ICV access device | X[4] | | | | | | |
| ICV access device patency/CSF flow assessment | X | | | | | | |
| Premedication (oral dexamethasone/IV equivalent)[12] | | X | | | | | |
| Anti-pyretic and anti-histaminergic premedication[13] | | X | | | | | |
| ICV $^{177}$Lu-DTPA-omburtamab treatment dose[1] | | X | | | | | |
| Clinical chemistry and hematology[14] | X | X | X | X | X | X | |
| CSF for cytology[15], total protein, glucose, and cell count | X[9] | | | X[16] | X | X | X |
| Blood and CSF for culture | | X[17] | | | | | |
| Blood and CSF sampling for ADA | X[18] | X[18] | | | X | | |
| Blood and CSF sampling for pharmacokinetics | | X[19] | | | | | |
| Pregnancy testing[20] | X | X | | X | X | | |
| Adverse events[21] | X | X | X | X | X | X | X |

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CSF = cerebrospinal fluid; ctDNA = circulating tumor deoxyribonucleic acid; EOT = end of treatment; HSA = human serum albumin; ICF = informed consent form; ICV = intracerebroventricular; IMP = investigational medicinal product; IV = intravenous; MRI = magnetic resonance imaging; NCI = National Cancer Institute; SAE = serious adverse event.

* A longer screening period (e.g., due to logistics, COVID-19 situations etc.) are allowed; however, eligibility evaluation must be re-confirmed. Screening period of >60 days with individual patient considerations to be discussed with the sponsor.

[1] The $^{177}$Lu-DTPA-omburtamab Treatment Period is divided into 5-week cycles. In Part 2, a cycle consists of a treatment dose on Day 1. The patient can receive up to 5 cycles at the discretion of the investigator. The infusion reservoir must be flushed with HSA and CSF after each infusion. The patient will be observed post treatment to decide if further cycles can be administered.
Day 1, 15, and 29 for Cycles 2 to 5 correspond to Day 36, 50, and 64 (for Cycle 2), Day 71, 85, 99 (for Cycle 3), 106, 120, 134 (for Cycle 4), and 141, 155, and 169 (for Cycle 5). Adjustments to the dosing schedule will be accommodated on a patient-by-patient basis depending on the clinical condition of the patient.

[2] If the IMP is discontinued prior to completion of all scheduled visits of the cycle (i.e., up to and including Day 29), the treatment visits that fall after the date of the EOT Visit should be skipped, and the patient should move directly into the follow-up phase. If the IMP is discontinued after Cycle 1, an unscheduled visit (including MRI etc.) should be done at 13 weeks post first dose.

[3] All patients who are dosed with $^{177}$Lu-DTPA-omburtamab in Part 2 should be followed up regularly (every 13 [±2] weeks, i.e., 26, 39, and 52 weeks post first dose, then every 26 [±2] weeks, i.e., 78 and 104 weeks post first dose, and thereafter annually) for monitoring of secondary malignancies during the trial and for at least 10 years after the end of trial, or until death, if sooner.

[4] Informed consent must be obtained before any trial-related procedures. If the indwelling ICV access device (e.g., Ommaya) is placed in connection with the tumor resection, the informed consent must be obtained prior to the surgery, and before the start of the screening period, unless this is placed as part of a standard of care procedure at site. If any procedures/tests are from before informed consent is obtained, it must be clear from source documents that this was not performed for the purpose of the present trial. In these cases, the procedures/tests do not need to be repeated at the Screening Visit if they were performed within the allowed timelines. The investigator is responsible for documenting this properly.

[5] Only anti-cancer therapy.

[6] Physical examinations to be performed at screening and as clinically indicated.

[7] Measurements of heart rate, respiratory rate, temperature, and blood pressure. On dosing days, measurements to be taken before and 30 min after the end of the IMP infusion.

[8] Lansky Scale <16 years, Karnofsky Scale ≥16 years.

[9] To be performed within 3 weeks prior to first IMP infusion. May be performed on the first dosing day but it must be before IMP administration.

[10] MRI of the brain and spine will be completed before first IMP administration and at the End-of-Cycle (Day 29) Visit for Cycles 1 and 3 only (±4 days of the actual visit date), EOT Visit (preferably ±4 days of the actual visit date), and each Follow-up Visit (±2 weeks of the actual visit date). MRI can be performed on a different day to the other visit assessments, in accordance with investigational site standards.

[11] Will be used to evaluate safety and efficacy.

[12] Beginning 24 hours before $^{177}$Lu-DTPA-omburtamab administration, divided into twice-daily doses for a total of 3 days.

[13] Given 1-2 hours prior to $^{177}$Lu-DTPA-omburtamab administration, including oral acetaminophen/paracetamol and antihistamine (e.g., diphenhydramine).

[14] In accordance with Appendix 1 and until the first follow-up visit.

[15] If CSF cytology sample is positive, it must be repeated within 4 weeks of the positive sampling.

[16] Cycles 1 and 3 only.

[17] Drawn and held for culture only if elevated body temperature after dosing suggests infection rather than expected response to ICV dosing. Samples to be taken within 6 hours after completion of $^{177}$Lu-DTPA-omburtamab infusion.

[18] The ADA samples must be drawn prior to dosing. Serum and CSF samples for ADA analyses will be drawn at baseline, at the start of Cycle 2 (predose), and after last treatment. Presence of ADA will be analyzed at a central laboratory.

[19] Blood and CSF samples for pharmacokinetics will be drawn in Cycles 1 and 2 only, as per Table 5.

[20] Pregnancy testing (serum or urine) is mandatory for women of childbearing potential at screening, prior to each dose, and at the EOT Visit.

[21] Non-serious AEs should be reported from the day of first IMP administration until 5 weeks after the patient's last dose of IMP. Non-serious AEs occurring between signing the ICF and the first IMP administration must be recorded as medical history. Serious AEs should be reported from signing the ICF until 5 weeks after the patient's last dose of IMP. Thereafter and during the follow-up period, only SAEs and Grade 3 or higher AEs at least related to $^{177}$Lu-DTPA-omburtamab or to the presence of the indwelling catheter system, should be reported. In the post-trial monitoring period, new onset of cancers, regardless of causality, should be reported.

## Appendix 4: Creatinine-based 2009 Revised Bedside Schwartz Equation

eGFR = 0.413 x (height/Scr) if height is expressed in centimeters

Abbreviations / Units

eGFR (estimated glomerular filtration rate) = mL/min/1.73 $m^2$

Scr (standardized serum creatinine) = mg/dL

## Appendix 5: Contraceptive Guidance

### Definitions

**Women of Childbearing Potential:** premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

**Women of Nonchildbearing Potential:**

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, bilateral tubal occlusion, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 3 months prior to screening.

**Fertile male:** a male that is considered fertile after puberty.

**Infertile male:** permanently sterile male via bilateral orchiectomy.

### Contraception Guidance

### Female Patients

Female patients who are of nonchildbearing potential will not be required to use contraception. Female patients of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the ICF until 9 weeks after the last dose of investigational medicinal product (IMP). Primary (non-barrier) methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- hormonal implant
- hormonal or non-hormonal intrauterine device
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening Visit, with verbal confirmation of surgical success, and the sole partner for the female patient).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female patients of childbearing potential should refrain from donation of ova from screening until 9 weeks after the last dose of IMP.

**Male Patients**

Male patients will be surgically sterile for at least 90 days, with documented azoospermia, or when sexually active with female partners of childbearing potential will be required to use a male condom with spermicide from screening until 17 weeks after the last dose of IMP. Sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 17 weeks after the last dose of IMP. Male patients are required to refrain from donation of sperm from screening until 17 weeks after the last dose of IMP.

**Sexual Abstinence and Same-sex Relationships**

Patients who practice true abstinence, because of the patient's lifestyle choice (i.e., the patient should not become abstinent just for the purpose of trial participation), are exempt from contraceptive requirements. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a patient who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For patients who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a patient who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

## Appendix 6: Assessment in Pediatric Neuro-oncology (RAPNO) Criteria

| Response definitions: patients must meet **ALL** criteria in each response/stable disease category, or **ANY** criteria in the progressive disease category | | | | |
|---|---|---|---|---|
| | **Complete Response (CR)** | **Partial Response (PR)** | **Stable Disease** | **Progressive Disease (PD)** |
| Criteria | Must meet **ALL** criteria | Must meet **ALL** criteria | Must meet **ALL** criteria | Must meet **ANY** criteria |
| MRI-brain | Complete disappearance of all disease (enhancing and non-enhancing, measurable and nonmeasurable) for a minimum of 4 weeks; no new lesions | ≥50% decrease (compared with baseline) in the sum of the products of perpendicular diameters of all (up to 4) measurable lesions sustained for at least 4 weeks; no progression of nonmeasurable disease | Does not meet criteria for CR, PR, or PD | ≥25% increase (compared with smallest measurement at any timepoint) in the sum of the products of perpendicular diameters of all measurable lesions; significant progression of nonmeasurable disease not attributed to prior therapy; any new tumor (any new lesions suspected to be treatment related should be confirmed by biopsy) |
| MRI-spine | Complete disappearance of all disease (enhancing and non-enhancing, measurable and nonmeasurable) for a minimum of 4 weeks; no new lesions | ≥50% decrease (compared with baseline) in the sum of the products of perpendicular diameters of all measurable lesions sustained for at least 4 weeks; no progression of nonmeasurable disease. If negative at baseline, must remain negative | Does not meet criteria for CR, PR, or PD | ≥25% increase (compared with smallest tumor measurement at any timepoint) in the sum of the products of perpendicular diameters of all (up to 4) measurable lesions; significant progression of nonmeasurable disease not attributed to prior therapy; any new tumor (any new lesions suspected to be treatment related should be confirmed by biopsy) |
| CSF cytology | If tumor cells are present at baseline, must be negative × 2 (sampling at least 2 weeks apart) | If absent (negative) at baseline, must remain absent. If present at baseline, can be present or absent | If absent at baseline, must remain absent. If present at baseline, can be present or absent | Previously absent tumor cells in CSF now present (positive) |
| Neurologic exam[a] | Stable or improving | Stable or improving | Stable or improving | Clinical deterioration not attributable to other causes |
| Steroid use | Off steroids or physiologic replacement doses only | Stable or less than baseline dose | Stable or less than baseline dose | |
| Extra-CNS disease | If positive at any timepoint, must be re-evaluated and have no evidence of disease | No new sites of disease | No new sites of disease | New sites of disease |
| Serum or CSF AFP, βhCG (if obtained, eg, germ cell tumors) | Must be within normal range for age | | | A previously negative (normal) assessment becomes positive |

Abbreviations: βhCG=beta human chorionic gonadotropin; AFP=alpha-fetoprotein; CNS=central nervous system; CSF=cerebrospinal fluid; MRI=magnetic resonance imaging.
[a] If it is unclear that the patient has disease progression, it may be a reasonable option to keep the patient on study until subsequent assessments (e.g., MRI, CSF cytology) confirm progression. If subsequent testing confirms progression, the date of progression should be backdated to the onset of neurologic deterioration.
Adapted from Warren et al. 2018[10]. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5761545/

## Appendix 7: Intracerebroventricular Access Device/CSF Flow Assessment

The following is an example of intracerebroventricular access device (e.g., Ommaya)/CSF flow assessment. Local assessment may be used in case this fulfils similar requirements.

| | |
|---|---|
| CSF CISTERNOGRAM: | Evaluate CSF circulation |
| INDICATIONS: | Determine patency and flow from indwelling intracerebroventricular access device (e.g., Ommaya) |
| PATIENT PREPARATION: | None |
| Radiopharmaceutical: | Indium (In) 111 Diethylenetriamine Pentaacetic Acid ($^{111}$In-DTPA) |
| Dose: | 0.5 mCi for cisternal infusion via indwelling intracerebroventricular access device (e.g., Ommaya) |
| Instrument: | Dual-detector gamma camera |
| Isotope Energy Peak: | $^{111}$In-DTPA: Medium Energy General Purpose (MEGP) 173, 247 keV |
| Energy Window Width: | 20% |

1. Only fresh, undiluted radiopharmaceutical from a newly opened vial should be used.
2. Patients infused in an indwelling intracerebroventricular access device (e.g., Ommaya) should have anterior, posterior, and lateral images of the head as well as anterior and posterior images of the spine and chest recorded immediately following infusion. Additional views should be recorded at 4, 6, and 24 hours as necessary.
3. The collimator should be placed as close as possible to the patient. Ten-minute acquisitions are obtained for each pair of views (anterior posterior and lateral views of the head, as well as anterior and posterior views of the spine are obtained at each time period).
4. Single-photon emission computed tomography (SPECT) images (optional) may be recorded in a 128 × 128 matrix for 30 seconds per stop, 3-degree steps, using a 360-degree acquisition. The detectors should be as close as possible to the head – preferably positioning the detectors above the shoulders.
5. Data are reviewed to determine the timing and of tracer entry and clearance from each of the cisterns and the region of the pacchionian granulations in region of the superior sagittal sinus.

Abnormal scan findings:

a) Ventricular outflow obstruction - no egress beyond basal cisterns;

b) Obstruction within spinal canal;

c) Failure to ascend to the convexities by 6 hours (after infusion of the radiopharmaceutical), and spread over the convexities by 24 hours.

Only patients with sufficient flow should be dosed. Efforts to correct CSF flow can be installed and if sufficient flow is established, the patient should be dosed (see exclusion criterion # 1.

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