CLINICAL TRIAL PROTOCOL

A Multicenter Phase 2/3 Trial of the Efficacy and Safety of Intracerebroventricular Radioimmunotherapy using ^{131}I-omburtamab for Neuroblastoma Central Nervous System/Leptomeningeal Metastases.

A Phase 2/3, International Clinical Trial

Clinical Trial ID: 101

EudraCT No.: 2017-001828-22

IND No.: 9351

ClinicalTrials.gov Identifier: NCT03275402

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1 PROTOCOL SYNOPSIS

Title	A Multicenter Phase 2/3 Trial of the Efficacy and Safety of Intracerebroventricular Radioimmunotherapy using ^{131}I-omburtamab for Neuroblastoma Central Nervous System/Leptomeningeal Metastases
EudraCT number	2017-001828-22
Investigational New Drug (IND)	9351
Investigational site(s)	Several sites in Europe and US
Investigator	**Trial Coordinating Investigator:** Kim Kramer, M.D. Memorial Sloan-Kettering Cancer Center 1275 York Ave. New York, NY 10065 USA
Sponsor	Y-mAbs Therapeutics Agern Allé 11 2970 Hørsholm Denmark
Trial ID	101
Trial design	Single-arm, open-label Phase 2/3 trial
Patient population	Pediatric neuroblastoma (NB) patients with central nervous system (CNS) relapse as evidenced by CNS/leptomeningeal (LM) metastases
Objectives	**Primary Objective** 1. To evaluate the overall survival (OS) rate at 3 years. **Secondary objectives:** 1. To evaluate CNS/LM progression-free survival (CNS/LM PFS) at 6 and 12 months 2. To evaluate Overall Survival (OS) at 12 months 3. To evaluate the objective response rate (ORR) at 6 months. 4. To evaluate dosimetry of ^{131}I-omburtamab. 5. To evaluate the pharmacokinetics of ^{131}I-omburtamab. 6. To evaluate safety of ^{131}I-omburtamab. 7. To evaluate the immunogenicity of ^{131}I-omburtamab.
Endpoints	**Primary Endpoint:** 1. OS rate at 3 years after the first treatment dose of ^{131}I-omburtamab. **Secondary Endpoints** 1. CNS/LM PFS at 6 and 12 months 2. OS at 12 months 3. ORR assessed as a combination of partial response and complete response as defined by the Response assessment in Neuro-Oncology (RANO) group criteria for brain metastasis (Lin et al, 2015) or leptomeningeal metastases as defined by EANO-ESMO criteria (Le Rhun et al, 2017). ORR will be assessed at 6 months after the first treatment dose of ^{131}I-omburtamab 4. ORR according to CSF cytology. Response is defined as a complete response when CSF converts from positive at baseline to negative after treatment with ^{131}I-omburtamab 5. Whole-body, organ, blood, and CSF radiation dosimetry. 6. Pharmacokinetic analysis of activity in blood and CSF including derivation of best-fit uptake and/or clearance parameters (half-times, maximum value) of time-activity concentration curves and of I-^{131} residence times (i.e., cumulated activity) concentrations (in μCi-h/g). 7. The frequency, type, and duration of treatment-emergent severe adverse events and serious adverse events, including clinically significant laboratory abnormalities. All

	adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. 8. Performance assessment to monitor gross changes in neurological function is performed at week 26 and subsequently every 6 months during trial period. 9. The rate of ADA occurrence assessed three weeks after the first and second treatment dose of ^{131}I-omburtamab
Patient selection criteria	**Inclusion criteria:** 1. Patients must have a histologically confirmed diagnosis of NB with relapse in the CNS or LM. 2. Patients need to have progressed in CNS/LM through induction therapy or have relapsed in CNS/LM following induction. CNS/LM progression/relapse is defined as LM disease or metastatic deposits in the CNS parenchyma, (excluding skull bone-based metastases). 3. Stable systemic disease not requiring chemo/immunotherapy as judged by the investigator. 4. Ventriculoperitoneal (VP) shunts (only shunts with programmable valves can be accepted) are allowed however should be closed (or adjusted to highest pressure setting) during Investigational Medicinal Product (IMP) infusion. It is recommended that the VP shunt remains closed for approximately 5 hours after treatment and then re-adjusted. The shunt readjustment times are at the discretion of the treating physician. Closure of 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. Patients with ventriculo-atrial or ventriculo-pleural shunts are not eligible. 5. Patients must be between birth and 18 years of age at the time of screening. 6. Patients must have a life expectancy of at least 3 months as judged by the investigator 7. Acceptable hematological status defined as: • Hemoglobin ≥8 g/dL • White blood cell (WBC) count ≥1000/µL • Absolute neutrophil count ≥500/µL • Platelet count ≥50,000/µL 8. Acceptable liver function defined as: • ALT and/or AST ≤ 5 times UNL • Bilirubin ≤ 3 x UNL • In case either AST or ALT ≥3 x ULN, bilirubin must be ≤ 2 UNL 9. Acceptable kidney function defined as: • Estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 calculated by the 2009 revised Bedside Schwartz Equation (Appendix 3) 10. Written informed consent from legal guardian(s) and/or child must be obtained in accordance with local regulations. Pediatric patients must provide assent as required by local regulations. **Exclusion criteria:** 1. Patients with primary NB in CNS. 2. Patients must not have obstructive or symptomatic communicating hydrocephalus. 3. Patients must not have worsening of neurologic function, according to the assessment by investigator, within 3 weeks prior to first dose of ^{131}I-omburtamab. 4. Patients must not have an uncontrolled life-threatening infection. 5. Patients must not have received cranial or spinal irradiation less than 3 weeks prior to first dose of ^{131}I-omburtamab in this trial. 6. Patients must not have received systemic chemo/immunotherapy (corticosteroids not included) less than 3 weeks prior to enrollment in this trial. 7. Patients must not have received any anti-B7-H3 treatment prior to enrollment in this trial. 8. Patients must not have severe major non-hematologic organ toxicity; specifically, any renal, cardiac, hepatic, pulmonary, and gastrointestinal system toxicity must fall below

	Grade 3 prior to enrollment in this trial. Patients with stable neurological deficits (due to brain tumor) are not excluded. Patients with Grade 3 or lower hearing loss are not excluded. 9. Patients must not be pregnant or breast-feeding. 10. Female patients of child-bearing potential (i.e. having experienced menarche) and male partners to female patients who do not agree to the use of effective contraception during treatment and for a period of 12 months after the last ^{131}I-omburtamab dose. Effective contraception for women is defined as intrauterine devices or hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release). Effective contraception for male partners is defined as use of condoms. To be exempt from the requirement to use contraception after ^{131}I-omburtamab treatment, one of the criteria described in section 9.2.11 of this protocol must be met. 11. Fertile male patients who do not agree to the use of condoms during treatment and for a period of 12 months after the last ^{131}I-omburtamab dose. For a sterilized male patient to be exempt from the requirement to use contraception after ^{131}I-omburtamab treatment, he must have undergone surgical sterilization (vasectomy).
Methodology	This Phase 2/3 trial is a single-arm, open-label, non-randomized, multi-center efficacy, safety, and dosimetry trial of intracerebroventricular (intracerebroventricular meaning administration of a medicinal product into the cerebral ventricles (cerebral ventricular system) of the brain) ^{131}I-omburtamab in pediatric NB patients with CNS/LM metastases. Patients will receive up to two cycles of ^{131}I-omburtamab. In case the patient has a subsequent relapse in the CNS/LM after ^{131}I-omburtamab therapy during the follow-up period, re-treatment to target minimal residual disease can be considered and allowed. Safety and efficacy will be investigated with short-term follow-up at 26 weeks after treatment and with long-term follow-up for up to 3 years following treatment.
Number of patients (planned)	Trial 101 plans to enroll at least 32 patients
Trial outline	Screening evaluations including medical history, physical and neurologic examination, hematology and clinical chemistry will be completed within 30 days of the first ^{131}I-omburtamab dose. MRI and CSF cytology will be completed within 3 weeks of the first ^{131}I-omburtamab dose and baseline performance testing is completed any time after diagnosis of CNS/LM metastases. ^{131}I-omburtamab is infused via an indwelling intracerebroventricular access device (e.g. Ommaya) and an Ommaya patency/CSR flow study is conducted prior to the first ^{131}I-omburtamab infusion. One ^{131}I-omburtamab cycle takes 4 weeks and includes a treatment dose, an observation period and post-treatment evaluations. An interim analysis, evaluating the dosimetry and pharmacokinetic endpoints as well as available safety and efficacy data, will be conducted on data from patients having received at least treatment cycle 1 (dosimetry and treatment dose) prior to January 1st, 2020. Starting January 1st, 2020, no further patients will be administered dosimetry doses. Patients can be treated in an outpatient setting or may be admitted as inpatients for the treatment infusions. Patients without Grade 4 toxicity, as described in section 6.1.4, and without objective disease progression (as determined by neurologic and/or radiographic examination) by MRI at week 4 in cycle 1 will be eligible to receive a second ^{131}I-omburtamab dosing cycle. Patients with Grade 3 toxicity will receive a second dosing cycle at the discretion of the investigator. Patients who finish both treatment cycles and complete week-8 assessments will enter the short-term follow up phase. Patients who finish only one treatment cycle will be registered as early treatment discontinuation and continue to the short-term follow-up visit at week 26. If week-8 assessments are not or cannot be completed, the next visit will be the short-term follow up visit at week 26. Patients will be monitored for adverse events during and after ^{131}I-omburtamab infusion. Patients will have pre- and post-treatment clinical assessments including neurologic examination, hematology and serum chemistry, blood and CSF cultures, endocrinology

	assessments, CSF analysis, and pre- and post ^{131}I-omburtamab performance testing. Performance testing will be performed at trial baseline, 3 months after the last ^{131}I-omburtamab infusion, and twice yearly thereafter at the discretion of the investigator.
IMP	Monoclonal antibody omburtamab is a murine immunoglobulin G1 (IgG1) antibody raised in BALB/c mice. Omburtamab recognizes tumor-associated antigen B7-H3. The purified antibody is stored in glass vials between -25 to -15ºC. The patients will receive omburtamab antibody radiolabelled with radioactivity calibrated to 50 mCi per treatment cycle. There will be a treatment dose reduction for patients younger than 3 years of age.
Trial period and duration	Trial duration will be up to 3 years for each patient. Safety and efficacy assessments will be performed for 26 weeks after the first ^{131}I-omburtamab cycle, with long-term follow up for up to 3 years after start of treatment.
Statistical considerations	An interim analysis to evaluate the dosimetry endpoint as well as available safety and efficacy data, will be performed on data from patients having received at least treatment cycle 1 (both dosimetry and treatment dose) prior to January 1st, 2020. Starting January 1st, 2020, no further patients will be administered dosimetry doses. Final analysis will be performed when at least 32 treated patients have completed long-term follow-up (3 years or until death). OS rate at 3 years and its 95% confidence interval will be estimated using Kaplan-Meier methods. [redacted] PFS will also be analyzed using Kaplan-Meier methods. Dosimetry will be summarized with descriptive statistics (n, mean, median, standard deviation (SD), minimum, maximum). Safety summaries will be provided for treatment exposure, patient disposition, adverse events, adverse events leading to discontinuation and serious adverse events, laboratory safety data (serum chemistry and hematology), vital signs, and physical examination. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance.

2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BALB/c	BALB/c Mouse Sarcoma Virus
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CGCCR	Central German Childhood Cancer Registry
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSRCT	Desmoplastic Small-Round-Cell Tumor
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EAC	Event Adjudication Committee
EOT	End of Trial
FAS	Full Analysis Set
h	Hour
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IgG	Immunoglobulin G
I.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
MBq	Megabecquerel
LDH	Lactate Dehydrogenase
LM	Leptomeningeal
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
mCi	Millicurie
mg	Milligram
mGy	Milligray
mL	Milliliter
MRI	Magnetic Resonance Imaging
mSv	Millisievert
MSK	Memorial Sloan Kettering Cancer Center
MYCN	V-Myc Myelocytomatosis Viral Related Oncogene
NB	Neuroblastoma
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron emission tomography

PI	Principal Investigator
PFS	Progression Free Survival
PK	Pharmacokinetic
PO	Per Os (by mouth)
PPS	Per Protocol Analysis Set
RANO	Revised Assessment in Neuro-Oncology
RBC	Red Blood Cells
ROI	Regions-of-interest
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
sc	Subcutaneous
SD	Standard deviation
SPECT	Single-Photon Emission Computed Tomography
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
UNL	Upper Normal Limit
VP	Ventriculoperitoneal
WBC	White Blood Cells
WHO	World Health Organization

3 FLOW CHARTS

Table 1 Schedule of time and events

Dosing/Measurements/Evaluations	Trial Periods						
	Screening	^{131}I-omburtamab Treatment Period[1]				Follow-up[21]	Long Term Follow-up[21]
	Day –29 to 0	Week 1 & 5	Week 2 & 6	Week 3 & 7	Week 4 & 8	Week 26	Weeks 52, 78, 104, 130 & 156
Informed consent	X[2]						
Eligibility check	X						
Demographics, height, and body weight	X						
Medical, surgical and disease history	X						
Prior/concomitant medications	X	X	X	X	X	X[19]	X[19]
TSH/free and total T4[3]	X	X			X	X	X
Physical examination	X	X	X	X	X		
Vital signs[4]	X	X	X	X	X		
Clinical chemistry & Hematology	X	X	X	X	X		
Performance test[6]	X[5]					X	X
MRI of the brain and spine[7]	X[5]				X	X[22]	
Neurotoxicity[8]	X	X			X	X	
Placement of an indwelling intracerebroventricular access device (e.g. Ommaya)[9]	X						
Ommaya patency/CSF flow study	X						
CSF for cytology, total protein, glucose, and cell count[10]	X[5]				X	X	
Blocking of thyroid ^{131}I uptake[11]	X[12]	X	X		(X)[13]		
Premedication (oral dexamethasone or an i.v. equivalent)[14]		X					
Premedication with an anti-pyretic[15]		X					
Conditional blood and CSF for culture[16]		X[16]					
Intracerebroventricular ^{131}I-omburtamab treatment dose [17]		X					
Adverse events[18]	X	X	X	X	X	X	X

Dosing/Measurements/Evaluations	Trial Periods						
	Screening	^{131}I-omburtamab Treatment Period[1]				Follow-up[21]	Long Term Follow-up[21]
	Day –29 to 0	Week 1 & 5	Week 2 & 6	Week 3 & 7	Week 4 & 8	Week 26	Weeks 52, 78, 104, 130 & 156
Pregnancy testing	X[20]				X[20]	X[20]	
Clinical response assessment for CNS/LM metastasis[23]	X				X	X	
Collection of information on systemic disease progression[24]		X	X	X	X	X	X
Collection of information on CNS/LM disease progression[25]							X
ADA blood and CSF [26]	X				X		
PK blood and CSF [27]		X	X				

[1] The ^{131}I-omburtamab treatment periods is divided in 4-week cycles (if a patient will receive 1 or 2 cycles is at the discretion of the investigator). A cycle consists of a treatment dose in the first week, followed by observation, and samples are taken during week 2 and 3 where after post-treatment evaluations will take place during week 4. For more details about the ^{131}I-omburtamab cycles see section 6.1.4.

[2] Informed Consent must be obtained before any trial related procedures. Procedures or tests that are performed as a part of standard clinical care prior to informed consent, and therefore, not for the purpose of the trial, do not need to be repeated at screening if they have been performed within the allowed screening timelines. In these cases, source documents must show that these procedures or tests were performed as standard clinical practice and not for the purpose of the present trial. In case 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 can be done before the start of the screening period if necessary. The investigator is responsible for documenting this properly.

[3] Thyroid stimulating hormone (TSH)/ free and total T4 to be assessed at screening, pre-dose week 1 and 4, pre-dose week 5 and 8, week 26 if applicable and weeks 52, 78, 104 130 and 156.

[4] Measurements of pulse oximetry, heart rate, respiratory rate, temperature, and blood pressure.

[5] To be performed within 3 weeks prior first IMP infusion.

[6] Lansky Scale < 16 years, Karnofsky Scale ≥16 years. Post week 26 every 6 months.

[7] (Magnetic resonance imaging of the brain and spine to be completed before first IMP administration), at week 4 (± 4 days), 8 (± 4 days) and 26 (± 24-29 weeks)

[8] Gross investigation of cranial nerves by physical examination and radiographical investigation as described in section 6.1.3. Evaluating neurological Adverse Events (AEs), the National Cancer Institute clinical neurotoxicity criteria will be used. Any patient that develops a Grade 4 neurotoxicity must be discontinued from treatment. The clinical neurotoxicity evaluation is to be conducted at screening and weeks 1, 4, 5, 8 and 26. The radiographic assessment of neurotoxicity and disease progression (by MRI) is to be conducted at screening, weeks 4 and 8 and week 26.

[9] Only for patients who do not have an intracerebroventricular device already placed. The procedure must be conducted prior to first dose and after the patient has been assessed to be eligible to enter the trial.

[10] If CSF sample is positive for abnormal cells or outside reference ranges for any of the following: 1. total protein 2. glucose 3. cell count, it must be repeated within 4 weeks of the sample at screening. If abnormal CSF glucose (CTCAE ≥ Grade 2) is obtained, a fasting serum glucose is to be obtained at next patient visit. At week 26, the CSF analysis should include cytology only.

[11] Treatment with potassium iodide and Cytomel should be initiated 1 week prior to each ^{131}I- omburtamab infusion in a cycle and continue until 2 weeks after ^{131}I-omburtamab infusion in the same cycle. .

[12] Thyroid protection should be initiated 1 week prior to IMP administration. See section 7.2.5 for further details.

[13] Thyroid protection should be initiated 1 week prior to next IMP administration – this is only applicable for week 4 and not week 8. See section 7.2.5 for further details.

[14] Beginning 24 hours before ^{131}I-omburtamab administration please see section 6.1.2.

[15] Given 1-2 hours prior to ^{131}I-omburtamab administration, including oral acetaminophen/paracetamol and antihistamine (e.g., diphenhydramine), please see section 6.1.2[16] Drawn and held for culture if elevated body temperature after dosing suggests infection rather than expected response to intracerebroventricular dosing.

[17] Dose reduction: 50% (25 mCi) for patients < 1 of age and 33% (33.5 mCi) for patients age 1 year to < 3 years of age, respectively.

[18] Non-SAE's captured from signing the informed consent form (ICF) to dosing should be recorded as medical history. AEs should be reported until 3 weeks after the last IMP administration. SAE's should be captured from signing the ICF. Starting at week 4 (for patients receiving only one cycle) and starting at week 8 (for patients receiving both cycles) only SAEs considered related to ^{131}I-omburtamab or new onset of cancers regardless of causality should be reported.

[19] Limit to therapy related to cancer.

[20] In case fertile women (experienced menarche prior to screening or during treatment, until week 8) are enrolled; pregnancy testing should take place at screening, at week 4 and week 8, and at follow-up at week 26.

[21] Follow-up at week 26 (24-29 weeks after first treatment) and Long-term follow-up visits at Weeks 52, 78, 104, 130 & 156 (± 4 weeks) can be done at referral site.

[22] If done at referral site imaging parameters as required in the Imaging Manual should be followed to the extent possible.

[23] If this is the screening visit record any significant findings on the medical history page. For other visits evaluate the clinical status according to the following comparison to the previous assessment: Improved, Stable or Worse. See section 9.2.10.

[24] If systemic disease progression has occurred, this information is to be collected in the eCRF

[25] If CNS/LM disease progression has occurred, this information is to be collected in the eCRF

[26] Blood and CSF sampling for ADA will be done at baseline, 3 weeks after the 1st treatment (wk 4) and 3 weeks after the 2nd treatment dose (wk 8). 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

[27] Blood and CSF PK sample collection will be done 1h after treatment, 6h after treatment, 24h after treatment and 7 days after treatment (wk 2 & wk 6) for both cycles. 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, See section 9.1.2.7

4 INTRODUCTION

4.1 Medical background

NB is a rare cancer of neural crest origin. The neuroectodermal cells that comprise neuroblastic tumors originate from the neural crest during fetal development and are destined for the adrenal medulla and sympathetic nervous system. Neuroblasts can transform into NB, a term that may be used to describe a spectrum of neuroblastic tumors, including ganglioneurinoma (benign), NB (malignant), and ganglioneuroblastoma (borderline aggressive). In this text, NB refers to the malignant form if not specified otherwise. NB is a disease of childhood. About 37% of patients are diagnosed as infants, and 90% are younger than 5 years, with a median age of 19 months, at diagnosis (London et al. 2005). The highest incidence is seen in the first months of life (Howlader et al. 2012; Gurney et al.1997; London et al. 2005).

NB is a life-threatening disease that is associated with poor long-term survival. Generally, survival rates depend highly on whether the tumor is low risk, intermediate risk, or high risk:

- For patients with low-risk tumors, five-year OS was 97% in a large COG trial (Strother et al. 2012).
- For patients with intermediate-risk tumors, three-year OS rate was about 96% in a large COG trial (Baker et al. 2010).
- For high-risk patients, survival rates of 40-50% have not changed significantly during the last two decades (Pinto et al. 2015).

Conventional systemic treatment for newly diagnosed patients does not adequately treat the central nervous system and leptomeningeal (LM) space, , which may serve as a sanctuary site leading to relapse (Matthay et al. 2003; Kramer, Gerald, et al. 2001). In large series, the incidence of CNS/LM disease in relapsed patients is between 6-10% and the incidence of CNS/LM tumor will likely increase as better treatment options induce longer systemic remissions and increased frequency of CNS relapse. CNS relapses are almost uniformly lethal (Matthay et al. 2003; Choi et al. 2005; Zhu et al. 2015; Kellie et al. 1991; Shaw and Eden 1992; Wiens and Hattab 2014; Watts 1992; Sakata et al. 1993; Astigarraga et al. 1996; Kramer, Kushner, et al. 2001). Specific factors that can predict CNS/LM metastasis have not been identified.
Furthermore, general management guidelines for recurrent NB in CNS are lacking consensus in Europe and the US, and specific treatment for metastatic CNS NB has yet to be approved. Leptomeningeal cancer remains a challenging problem and the long-term outcome for children with leptomeningeal disease due to solid tumors remains poor with rapid progression over a period of weeks to months (Neville KA, Blaney SM. Leptomeningeal cancer in the pediatric patient. Cancer Treat Res. 2005; 125:87–106
). In addition, there are significant toxicities associated with therapy in those children who are ultimately cured. Various treatment combinations, comprising one or more of the following treatments, are currently used in the clinic:

- Surgery of bulky tumor prior to irradiation and chemotherapy to reduce symptoms, edema and hemorrhage or to correct CSF flow.
- Craniospinal or focal irradiation to alleviate symptoms and to obtain disease control and to correct CSF flow in case of obstruction.

- Standard systemic combination chemotherapy (e.g., irinotecan plus temozolomide) may improve outcome, but significant toxicity and complications typically limit this form of treatment to patients with high likelihood of benefit.

Memorial Sloan Kettering Cancer Center (MSK) has developed ^{131}I-omburtamab for the treatment of pediatric recurrent NB with CNS/LM metastases and ^{131}I-omburtamab has been studied in [redacted] clinical trials at MSK with more than [redacted] treated patients over 15 years. ^{131}I-omburtamab has been used as monotherapy for the treatment of NB patients with CNS)/LM metastases (trial 03-133) and patients with Desmoplastic Small Round Cell Tumor (DSRCT) (trial 09-090). In addition, ^{131}I-omburtamab has been used in a tumor detection trial (trial 00-066).

The development of ^{131}I-omburtamab for the treatment of NB with CNS/LM metastases has entered phase 1/2, and an interim analysis (data reported through Aug-2017) based on [redacted] from the on-going trial 03-133 is available. The results hold promise for a potential breakthrough as evidenced by low toxicity, high rate of radiographic improvements, and long-term survival.

The median survival for the patients included in the interim analysis was 47 months versus 6 months in various historical cohorts (Kramer, Kushner, and Modak 2017; Berthold, Hömberg, and Baadsgaard 2017). Survival past 3 years historically is rare, less than 10% (Kramer et al. 2017), which is aligned with findings by (Berthold, Hömberg, and Baadsgaard 2017), demonstrating a 3-year survival rate of 8.2% (Berthold et al. 2017). In contrast, for NB patients in study 03-133, the estimated 3-year survival of 56% and an estimated 5-year survival of 43% is reported. Survivors have been followed for up to 11.1 years, with a current mean duration of follow up of 2.6 years. Fifty-one (54.8%) of the [redacted] patients treated with ^{131}I-omburtamab remained alive at their last follow up.

Late effects from ^{131}I-omburtamab are rare except for hypothyroidism related to ^{131}I-uptake and irradiation, which is easily treated with thyroid replacement therapy. Based on the information above, ^{131}I-omburtamab will be further investigated in the proposed phase 2/3 trial for treatment of pediatric NB patients with CNS/ LM metastases.

4.2 Drug profile

4.2.1 ^{131}I-omburtamab

^{131}I-omburtamab is a radiolabeled monoclonal antibody that targets cluster of differentiation 276 (CD276) (also known as B7-H3, (Modak, 2001 #471)(Xu et al. 2009). CD276 is a member of the B7/CD28 immunoglobulin superfamily which regulates T-cell functions in tumor surveillance, infections, and autoimmune diseases. CD276 is a tumor-associated antigen highly overexpressed on a wide range of human solid tumors, but minimally in normal tissues. CD276 is distributed on the cell membrane of solid 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. Upon administration, ^{131}I-omburtamab binds selectively to the B7-H3 antigen (CD276/B7-H3) expressed on tumor cell membranes. The iodine-131 emits beta radiation that causes deoxyribonucleic acid (DNA) damage and tumor cell death. Iodine-131 has a half-life of 8 days and the beta radiation penetrates up to 3 millimeters, with effects

not only on the antibody binding cell, but also on neighboring tumor cells (Larson et al. 2015). For further information, please see the current ^{131}I-omburtamab Investigator's Brochure (IB).

4.2.1.1 *Non-clinical pharmacology and toxicology*

Pharmacology

[redacted]

Toxicology

[redacted]

An overview of the studies is presented in the IB.

Non-clinical summary

[redacted]

4.2.1.2 *Effects on Humans*

Normal Organ Dosimetry

[redacted]

from an interim analysis of dosimetry show that absorbed dose estimates exhibit high inter-patient variability across all organs, consistent with previous results from previous trials with ^{131}I-omburtamab (Table 2). For more detailed information, please see the current ^{131}I-omburtamab investigator's brochure.

[redacted]

Previous clinical experience

To date the MSK-produced ^{131}I-omburtamab has been used in [redacted] clinical trials at MSK, U.S. [redacted]

- [redacted]
- [redacted]

4.2.2 Radiolabeling

Omburtamab will be radiolabeled with iodine-131 by a radiopharmacy connected to the treating institution or at a designated central radiopharmacy (section 7.1) according to a qualified procedure described in a manufacturing agreement.

5 RATIONALE, OBJECTIVE AND BENEFIT-RISK ASSESSMENT

5.1 Rationale for performing the trial

The proposed phase 2/3 international multi-center trial evaluates the efficacy and safety of intracerebroventricular (intracerebroventricular meaning administration of a medicinal product into the cerebral ventricles (cerebral ventricular system) of the brain) ^{131}I-omburtamab as well as the dosimetry in pediatric NB patients with CNS/LM metastases. The findings of the proposed trial will expand and be compared with the findings of the single center trial of intracerebroventricular ^{131}I-omburtamab in pediatric patients with NB CNS/LM metastases treated in the MSK Trial 03-133. The aggregate findings from the two trials evaluating patients from several centers in the US as well as Europe seek to provide a basis for establishing ^{131}I-omburtamab as the next generation treatment of NB patients with CNS/LM metastases.

5.2 Rationale for dose selection

5.2.1 ^{131}I-omburtamab

[redacted]

A second treatment cycle of ^{131}I-omburtamab was administered 5 weeks after the first dose under the condition that the first treatment cycle was tolerable and without objective disease progression. The administered dose was adjusted in children under 3 years of age, as is standard for intracerebroventricularly administered therapies (section 7.1).

5.3 Benefit-risk assessment

There are sufficient data to support an assessment of benefit and risk for the treatment of NB with CNS/LM metastases with ^{131}I-omburtamab. [redacted]

5.3.1 Trial objectives

5.3.2 Primary objective

1. To evaluate the overall survival (OS) rate at 3 years.

5.3.3 Secondary objectives

1. To evaluate CNS/LM progression-free survival (CNS/LM PFS) at 6 &12 months
2. To evaluate Overall Survival (OS) at 12 months
3. To evaluate the objective response rate (ORR) at 6 months.

4. To evaluate dosimetry of ^{131}I-omburtamab.
5. To evaluate the pharmacokinetics of ^{131}I-omburtamab.
6. To evaluate safety of ^{131}I-omburtamab.
7. To evaluate the immunogenicity of ^{131}I-omburtamab.

6 DESCRIPTION OF DESIGN AND TRIAL POPULATION

6.1 Overall trial design and plan

This single-arm, open-label, non-randomized trial includes a screening period followed by treatment and observation periods. At least 32 patients are expected to be enrolled. Before entering the screening period, patients are recommended to have received salvage therapy including surgery, irradiation (preferable craniospinal) and high dose chemotherapy (recommended modalities listed in Appendix 2).

Patients without an objective disease progression (as determined by radiographic examination) 4 weeks after the first infusion and without clinically significant Grade 4 toxicity, are eligible for a second dosing cycle. ^{131}I-omburtamab will be administered via an indwelling intracerebroventricular access device (e.g. Ommaya). In order to avoid an additional procedure and burden to the patient, it can be considered to place the intracerebroventricular access device in connection with the recommended tumor resection procedure (see section 13.4).

After ^{131}I-omburtamab treatment, safety and efficacy will be assessed as described in the flow charts in Table 1 Schedule of time and events with follow-up at week 26 followed by long-term follow up for up to 3 years with regards to survival. An interim analysis, evaluating the dosimetry and pharmacokinetic endpoints as well as available safety and efficacy data, has been conducted on data from patients having received at least treatment cycle 1 (both dosimetry and treatment dose) prior to January 1st, 2020. Starting January 1st, 2020, no further patients will be administered dosimetry doses. After completion of the interim analysis, the dosimetry doses have been removed from treatment cycles. After this, a treatment cycle will take 4 weeks, compared to the previous 5 weeks cycle and will include a treatment dose only followed by an observation period and post-treatment evaluations.

6.1.1 Screening

Screening evaluations (including medical history, physical and neurologic examination, hematology, clinical chemistry) must be completed within 30 days before the first ^{131}I-omburtamab dose at week 1. In case 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 MRI, CSF cytology and baseline performance testing are to be completed within 3 weeks before the first ^{131}I-omburtamab dose. Adequate CSF flow for ^{131}I-omburtamab intrathecal therapy is determined by Ommaya patency/CSF flow study as outlined in Appendix 4. Patients with obstructive or symptomatic communicating hydrocephalus will be excluded.

6.1.2 Treatment

Patients can be treated in an outpatient setting or may be admitted as inpatients for the treatment infusions. 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.

Thyroid protection must be ensured by adequate stable iodide saturation by use of e.g. oral potassium iodide and Cytomel (liothyronine sodium or equivalent). Thyroid protection should be initiated 1 week prior to first ^{131}I-omburtamab infusion in a cycle and continue until 2 weeks after last ^{131}I-omburtamab infusion in the same cycle. Thyroid protection is administered in relation to each treatment cycle. Please refer to section 7.2.5 for details.

[redacted]

[redacted]

A treatment dose of ^{131}I-omburtamab is administered during week 1. The treatment dose is followed by a 3-week observation period followed by MRI, CSF cytology, and safety monitoring.

6.1.3 Safety considerations

Patients will be monitored for AEs following signing of the informed consent form (ICF).

National Cancer Institute clinical neurotoxicity criteria will be used. All neurologic abnormalities (regardless CTCAE grade) present prior to intrathecal ^{131}I-omburtamab infusions will be recorded as Medical History. In the absence of clear evidence of tumor progression, it may be assumed that new neurological signs and symptoms are treatment related.

Neurotoxicity will also be assessed clinically and radiographically. Assessment of cranial nerves, gross motor function and sensory function will be performed by physical examination. Assessment and grading of radiographically cortical atrophy, cerebral ventricular size, white matter changes or other abnormalities will be made by a neuro-radiologist. Altered CSF flow will be interpreted by the trial nuclear medicine physicians.

Lansky (Karnovsky for children ≥ 16 years) performance score will be analyzed to evaluate gross neurologic function and a measure of a patient's overall function.

Expected risks are described in current ^{131}I-omburtamab IB and section 10.7.

Patients and guardians will be informed of the risk of uncommon or unexpected new side effects.

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

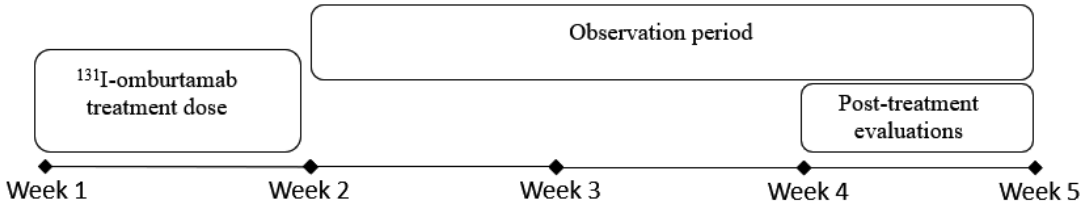
- Urticaria will be treated with antihistamines.

- During administration of ^{131}I-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 or granulocyte-colony stimulating factor according to local standard of care. If indicated, patients also may have banked stem cells reinfused. There is to be a minimum of one week between support for myelosuppression as a stated above and IMP administration.

6.1.4 Duration of treatment

A single treatment cycle will last 4 weeks and includes premedication, intracerebroventricular ^{131}I-omburtamab administration [redacted], an observation period, and post-treatment evaluations (see Figure 1 One ^{131}I-omburtamab treatment cycle after the interim analysis).

Figure 1 One ^{131}I-omburtamab treatment cycle after the interim analysis



Patients without Grade 4 toxicity and without objective disease progression (as determined by neurologic and/or radiographic examination) by MRI at week 4 in cycle 1 will be eligible to receive a second ^{131}I-omburtamab dosing cycle. Patients with Grade 3 toxicity will receive a second dosing cycle at the discretion of the investigator. For patients presenting with ongoing Grade 3 or 4 myelosuppression at week 4, a delay of dosing cycle 2 for up to 8 weeks can be introduced. Dose delay may be enforced at the discretion of the treating physician.

In case of a subsequent relapse in the CNS/LM during the follow-up period, re-treatment to target minimal residual disease can be considered and allowed in case the patient/parents provide written consent to this. In these cases, it is recommended that patients undergo the salvage treatment as specified in Appendix 2 before subsequent administration of ^{131}I-omburtamab. The administration of ^{131}I-omburtamab in these cases must follow the scheme of the treatment cycle as illustrated in Figure 2.

Patients who complete at least one treatment cycle will be evaluable. All patients who complete at least one treatment cycle (one dose of ^{131}I-omburtamab) will form part of the dataset. However, patients who do not continue to the second treatment cycle (for whatever reason) will be registered as “early treatment discontinuation” in the eCRF. Patients receiving both treatment

cycles of ^{131}I-omburtamab will be registered as "completed treatment" in the eCRF. All evaluable patients will first enter a follow-up period through week 26 (Figure 2) and thereafter the long-term follow-up where patients will be evaluated every half year for up to 3 years post-^{131}I-omburtamab treatment where after the trial is ended.

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6.1.5 Screening/pretreatment evaluation

Pre-treatment evaluations should be completed within 30 days of start of treatment, unless otherwise specified, with regards to:

- Informed consent by the patient/patient's legal guardian(s) and assent by the patient as required by local EC/Institutional Review Board (IRB). Informed Consent must be obtained before any trial related procedures. Procedures or tests that are performed as a part of standard clinical care prior to informed consent, and therefore, not for the purpose of the trial do not need to be repeated at screening if they have been performed within the allowed screening timelines. In these cases, source documents must show that these procedures or tests were performed as standard clinical practice and not for the purpose of the present trial. In case 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 can be done before the start of the screening period if necessary and up to three months before the start of the screening period.

- Eligibility assessment
- Collection of patient demographic information
- Collection of disease history, including initial diagnosis, dates of initial diagnosis and recurrence, date of CNS/LM metastases diagnosis, prior treatments, and prior surgical interventions as well as outcome of such treatments/ interventions
- Physical examination (including height and weight)
- Vital signs
- Neurologic examination
- Performance testing

- Concomitant medications
- Complete medical and surgical history
- Hematology including complete blood count (CBC) with differential count (including eosinophils) and platelet count
- Clinical chemistry including serum electrolytes (K^+, Na^+, Cl^-), creatinine, blood urea nitrogen (BUN), AST, ALT, lactate dehydrogenase (LDH), total bilirubin, albumin, total protein, glucose, T4 and TSH
- CSF cytology, total protein, glucose cell count
- Baseline MRI of the brain and spine
- Placement of an indwelling intracerebroventricular access device (i.e. if not already in place)
- Ommaya patency/CSF flow study prior to the first infusion
- Pregnancy testing (only fertile women, experienced menarche prior to screening or during treatment, until week 8)

6.2 Data Monitoring Committee and Adjudication Committee

The data monitoring committee (DMC) is an external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial both ad hoc and when 25, 50 and 100% of patients have been enrolled with a maximum interval between meetings of 3 months. The DMC is established to assure patient safety and to evaluate benefit-risk balance during conduct of the trial. The DMC will provide recommendations on trial continuation, modification or termination. Responsibilities, procedures and workflow of the DMC are specified in the DMC charter.

[redacted] We keep the IB as source document for reference safety information and refer to this in the protocol. In addition to listing expected side-effects in protocol section 10.7, to further ensure patient safety, we have included AEs of special interest in protocol section 10.4.

Based on above, no stopping rule is introduced; however, single patient withdrawal criteria's are described in protocol section 6.9.3 in order to ensure patient safety.

Any significant finding/ significant recommendation from the DMC and endorsed by the Sponsors Safety Committee will be communicated to the regulatory authorities.

6.3 Follow-up

Short-term (26 weeks): will include SAE's considered related to ^{131}I-omburtamab or new onset of cancers regardless of causality, physical examinations, concomitant medications, neurological and performance test results and MRI of the brain and spine as described in details in flow charts

in Table 1 **Schedule of time and events**. Pregnancy testing at week 4 and 8 and 26 (only fertile women who have experienced menarche prior to screening or during treatment, until week 8.

Long term (3 years): clinical sites will provide status reports for each patient at 6-month intervals. Details of data collection procedures can be found in the trial flow chart (Table 1 **Schedule of time and events**).

For patients who have relocated back to their home country after the treatment period, the data that would normally be collected at the follow-up visits at the trial hospital can be collected at the referral hospital. The referral hospital is not an investigational site and will not be trained in the protocol. The trial investigator must coordinate the collection of the requested follow-up data every 6 months for up to 3 years following treatment. The safety, survival and relapse status including MRI assessments must be collected to be able to comply with the obligations while ensuring the best possible treatment and safety for the patient. In case the referral site evaluates MRI as to signify CNS/LM progression, this will supersede any other assessment. Ideally the referring oncologist should share the imaging report with the investigator but at the least, the investigator will add notes from the communication with the referring oncologist in the patient files, and the monitor will check consistency between eCRF entry and investigators notes in the patient files (see appendix 6).

6.4 Discussion of trial design

Available clinical data from a single-site trial indicates that treatment with ^{131}I-omburtamab may provide a robust and durable improvement in median survival of NB patients with CNS metastases from 6 to 47 months, providing a reasonable basis for undertaking the present trial when compared to survival for external controls receiving existing therapies. Consequently, an open, single-arm design has been chosen since any controlled design would be considered unethical.

6.5 Selection of trial population

Iodine-131 omburtamab is primarily developed for treatment of NB patients with CNS/LM metastases, a population whose median survival does not exceed 6 months with current treatment options. Patients need to have progressed through induction therapy or have relapsed in CNS/LM following induction.

6.6 Recruitment period

At least 12 months of recruitment time is estimated to be needed to enroll the planned number of patients.

6.7 End of trial

End of trial (EOT) will occur when all patients have been followed until the visit at 3 years, or death whichever comes first.

6.8 Number of participants

At least 32 and a maximum of 50 patients will be enrolled in this trial. With an estimated screen failure rate of 25% it is likely that 40-50 patients will be screened to reach 32 eligible. The patients will be recruited according to institutional guidelines.

6.9 Participant selection and withdrawal

Eligibility will require that the patient meet all inclusion criteria and is not violating any exclusion criterion.

6.9.1 Inclusion criteria

1. Patients must have a histologically confirmed diagnosis of NB with relapse in the CNS or LM.
2. Patients need to have progressed in CNS/LM through induction therapy or have relapsed in CNS/LM following induction. CNS/LM progression/ relapse is defined as LM disease or metastatic deposits in the CNS parenchyma, (excluding skull bone-based metastases).
3. Stable systemic disease not requiring chemo/ immunotherapy as judged by the investigator.
4. VP shunt (only shunts with programmable valves can be accepted) is allowed however should be closed (or adjusted to highest pressure setting) during IMP infusion. It is recommended that the VP shunt remains closed for approximately 5 hours after treatment and then readjusted. The shunt readjustment times are at the discretion of the treating physician. Closure of 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. Patients with ventriculo-atrial or ventriculo-pleural shunts are not eligible.
5. Patients must be between the ages of birth and 18 years at the time of screening.
6. Patients must have a life expectancy of at least 3 months as judged by the investigator.
7. Acceptable hematological status, defined as:
    - Hemoglobin ≥ 8 g/dL
    - WBC count ≥1000/µL
    - Absolute neutrophil count ≥500/µL
    - Platelet count ≥50,000/µL
8. Acceptable liver function defined as:
    - ALT and/or AST ≤ 5 times UNL
    - Bilirubin ≤ 3 x UNL
      In case either AST or ALT ≥3 x ULN, bilirubin must be ≤ 2 UNL
9. Acceptable kidney function defined as:
    - eGFR >60 mL/min/1.73 m^2 calculated by the 2009 revised Bedside Schwartz Equation (Appendix 3).

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

6.9.2 Exclusion criteria

1. Patients with primary NB in CNS.
2. Patients must not have obstructive or symptomatic communicating hydrocephalus as determined by Ommaya patency/CSF flow study.
3. Patients must not have worsening of neurologic function, according to assessment by investigator, within 3 weeks prior to first dose of ^{131}I-omburtamab.
4. Patients must not have an uncontrolled life-threatening infection.
5. Patients must not have received cranial or spinal irradiation less than 3 weeks prior to first dose of ^{131}I-omburtamab in this trial.
6. Patients must not have received systemic chemo/ immunotherapy (corticosteroids not included) less than 3 weeks prior to enrollment in this trial.
7. Patients must not have received any anti-B7-H3 treatment prior to enrollment in this trial.
8. Patients must not have severe major non-hematologic organ toxicity; specifically, any renal, cardiac, hepatic, pulmonary, and gastrointestinal system toxicity must fall below Grade 3 prior to enrollment in this trial. Patients with stable neurological deficits (due to brain tumor) are not excluded. Patients with Grade 3 or lower hearing loss are not excluded.
9. Patients must not be pregnant or breast-feeding.
10. Female patients of child-bearing potential (i.e. having experienced menarche) and male partners to female patients who do not agree to the use of effective contraception during treatment and for a period of 12 months after the last ^{131}I-omburtamab dose. Effective contraception for women is defined as intrauterine devices or hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release). Effective contraception for male partners is defined as use of condoms. To be exempt from the requirement to use contraception after ^{131}I-omburtamab treatment, one of the criteria described in section 9.2.11 of this protocol must be met.
11. Fertile male patients who do not agree to the use of condoms during treatment and for a period of 12 months after the last ^{131}I-omburtamab dose. For a sterilized male patient to be exempt from the requirement to use contraception after ^{131}I-omburtamab treatment, he must have undergone surgical sterilization (vasectomy).

6.9.3 Treatment discontinuation criteria

A patient must be discontinued from treatment if:

- Treatment-related CTCAE Grade 3 or 4 anaphylaxis.

- CTCAE Grade 4 neurotoxicity.
- Development of obstructive or symptomatic communicating hydrocephalus
- Unexpected, IMP-related and clinically significant Grade 4 toxicity.
- Disease progression before cycle 2.
- The investigator requests discontinuation of treatment for medical or safety reasons, including lack of treatment response; or
- The patient receives prohibited therapy and/or undergoes prohibited procedures during the trial.

Diagnosis of chemical meningitis (symptoms of clinical meningitis but cultures for infective 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. A patient discontinued from treatment should as soon as possible attend the week 4 or 8 visit as applicable, and subsequently be followed at the short and long-term follow-up visits. The investigator should follow any SAE still ongoing after discontinuation until the event has been resolved or the investigator assesses the SAE as being chronic or stable.

A patient should be withdrawn from the trial if:

- The patient or legal guardian withdraws consent for any reason;

If the patient is withdrawn from the trial, the investigator should:

- Ensure the safety of the patient.
- Offer the best possible treatment outside of the trial.

Furthermore, after withdrawal for any reason, the investigator, in consultation with the patient/legal guardian, will recommend future treatment based on clinical practice at the investigational site.

7 TREATMENTS

7.1 Investigational Medicinal Product

Screening assessments will be evaluated before any patient receives IMP. The patient and/or legal guardian must have received patient information and signed the ICF. Eligible patients must meet all inclusion criteria and must not violate any of the exclusion criteria (please see sections 6.9.1 and 6.9.2).

Monoclonal antibody omburtamab is a murine IgG1 antibody that is raised in BALB/c mice and recognizes tumor associated antigen B7-H3. Omburtamab will be radiolabeled with iodine-131 at a radiopharmacy connected to the treating institution or at a designated central radiopharmacy. At each clinical site, the ^{131}I-omburtamab dose should be assayed immediately prior to administration to verify that the prescribed activity and the activity actually administered agree within 10%. The residual activity in the dose syringe should then be assayed following administration to determine the net activity administered (= pre-administration activity – post-administration residual activity). The amount of radioactivity infused in patients should be assessed by measuring radioactivity of the infusion syringe before and after ^{131}I-omburtamab infusion into the indwelling intraventricular access device (e.g. Ommaya) and subtracting before and after counts. The radiolabeled ^{131}I-omburtamab is sterile filtered before administration. Patients will receive up to two cycles of ^{131}I-omburtamab.

7.1.1 Treatment

One 131I-omburtamab cycle takes 4 weeks and includes a treatment dose followed by an observation period and post-treatment evaluations. The treatment dose is administered on day 1 of the first week in a cycle (according to **Table 1**). The patient will be followed for 4 weeks after the treatment dose. A full treatment is achieved when both cycles have been completed. Patients who finish both treatment cycles and complete week-8 assessments will enter the short-term follow up phase. Patients who finish only one treatment cycle will be registered as early treatment discontinuation and continue to the short-term follow-up visit at week 26. Please see Duration of treatment section 6.1.4.

[redacted]

7.2 Bleyer et al. 1977.Packaging and labelling of omburtamab

Packaging, labelling and release of omburtamab will be completed by KLIFO Supply in accordance with Good Manufacturing Practice (GMP) and national regulatory requirements. Label content will according to Annex 13, EudraLex, volume 4, local requirements and trial requirements. Each kit will be uniquely numbered.

7.2.1 Storage and handling

A description of IMP details is included in the IMP manual.

The Investigator or designee is responsible for ensuring that only eligible trial patients receive IMP. There is no storage of IMP at site, and the IMP is prepared on demand when a patient is found eligible for the trial and/or when subsequent cycles are being scheduled. The utensils used to ship, prepare and administer the IMP will be radioactive and should be destroyed according to local regulation. The destruction can be performed without sponsor approval
Drug accountability on a patient level is documented by keeping copies of the IMP Order Form, and the IMP Administration Form. The documentation will be reviewed periodically and verified by the CRA over the course of the trial.

7.2.2 Radiolabeling of omburtamab

Omburtamab will be radiolabeled with iodine-131 by a designated radio pharmacy following a qualified procedure outlined in a manufacturing agreement. Radiolabeling is performed by the iodogen method, which is based on previously published methods (Fraker and Speck 1978). Free iodine-131 is removed by ion exchange. Radiolabeled product will be pre-calibrated at the time of preparation to yield the prescribed activity at the projected time of administration as outlined in section 7.1 Radiolabeled product is sterilized by filtration to attain the target dose of 50 mCi, as applicable. Quality control is ensured according to a release specification, also including endotoxin testing, bioburden and radioimmunoassay.

7.2.3 Administration of ^{131}I-omburtamab

The radioactivity of the patient-specific unit doses must be within +/- 10 % of the intended dose (Table 4 Accepted activity ranges for treatment doses). Doses must be aseptically prepared by withdrawal of ^{131}I-omburtamab from the bulk vial into a sterile syringe. 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.

[redacted]

7.2.4 Radiation safety

Local safety instructions for storage and handling of radioactive IMP 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.

Patients can be treated in an outpatient setting or may be admitted for ^{131}I-omburtamab administration. When patients are admitted, the caregiving staff will be instructed in radiation safety about 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 time points 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 therapeutic amounts of ^{131}I-omburtamab will be determined based on the dose-rate criterion specified in Column 2 in table U.1 for I^{131} in NUREG 1556, Vol 9, Rev 1 (US sites) or based on local radiation safety requirements (sites outside US). That is, patients can be released following administration of therapeutic amounts of ^{131}I-omburtamab if the dose rate measured with a survey meter at 1 meter from the patient does not exceed 7 mrem per hour 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.

Patients and legal guardians must be advised of the risks of radiation exposure of household contacts, pregnant women, and small children and of the steps to be taken to reduce these risks. Legal guardians will be given instructions by radiation safety staff on how to handle waste and steps and procedures to follow to minimize exposure to themselves, household contacts, the general public and possible patient family caregiver(s). An evaluation of patient family caregiver doses will be performed, and appropriate radiation safety precautions will be taken to ensure that doses to these caregivers is maintained less than local requirements (e.g. 500 millirem or value determined by local safety instructions), in accordance with applicable regulations. Patients and/or caregiver will be provided with a written instruction detailing radio safety precautions as per the local requirements. The caregiver will agree to radiation safety instructions prior to administration of the therapeutic agent or the procedure may be delayed or declined.

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.

7.2.5 Protection of thyroid function

Blockade of ^{131}I-uptake in the thyroid gland is to be ensured by administration of stable iodine e.g. potassium iodide. For guidance on potassium iodide dosing, the investigators should refer to the FDA's guidance "Potassium iodide as a thyroid blocking agent in radiation emergencies" or the European Association of Nuclear Medicine (EANM) guidance on thyroid protection with potassium iodide during ^{131}I-meta-iodobenzylguanidine (^{131}I-mIBG) therapy (Giammarile et al. 2008, Eur J Nucl Med Mol Imaging). Alternative, more intensive thyroid protective schemes with potassium iodide that are according to institutional or local standard of care may be prescribed at the discretion of the investigator but must be documented. Potassium iodide may be given with juice or soft drink (e.g. cola) to mask taste.

In addition to potassium iodide, Cytomel (liothyronine sodium or equivalent) should be given at 25 µg/day if weight is less than 25kg or at 50 µg/day if weight $\geq$ 25 kg.

Treatment with potassium iodide and Cytomel should be initiated 1 week prior to each ^{131}I-omburtamab infusion in a cycle and continue until 2 weeks after ^{131}I-omburtamab infusion in the same cycle. Thyroid protection is administered in each treatment cycle. Sites will document the treatment regimen for thyroid protection prescribed and patients or caregivers will provide a written diary documenting that the potassium iodide and Cytomel has been taken as instructed by the site.

7.2.6 Participant 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.

7.3 Concomitant therapy

7.3.1 Therapy allowed during the trial

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. Detailed information about treatments administered following ^{131}I-omburtamab administration will be captured in the electronic case report form (eCRF). Additional anti-cancer and supportive care treatments are allowed after MRI has been assessed after the last dose at week 9.

- **Prohibited therapy and procedures during weeks -3 to 9**
    - Additional anti-cancer therapy during the treatment cycle(s) of ^{131}I-omburtamab
    - Additional IMP
    - Additional hematological support is not allowed if administered within 1 week prior to IMP administrations

7.4 Treatment after discontinuation of IMP

Any treatment deemed safe and justified by the investigator can be administered according to clinical practice and at the discretion of the investigator.

8 ENDPOINTS

8.1 Efficacy

8.1.1 Primary endpoint

1. OS rate at 3 years after the first treatment dose of ^{131}I-omburtamab.

8.1.2 Secondary endpoints

1. CNS/LM PFS at 6 and 12 months will be estimated based on the time from first treatment dose to CNS/LM progression or death from any cause. Patients alive without CNS/LM progression at time of analysis, will be censored at last date of disease evaluation without evidence of progression.
2. OS at 12 months will be estimated based on the time from first treatment dose to death by any cause. Patients alive at time of analysis, will be censored at last date known to be alive.
3. ORR assessed as a combination of partial response and complete response as defined by the Response assessment in Neuro-Oncology (RANO) group criteria for brain metastasis (Lin et al, 2015) or leptomeningeal metastases as defined by EANO-ESMO criteria (Le Rhun et al, 2017). ORR will be assessed at 6 months after the first treatment dose of ^{131}I-omburtamab
4. ORR according to CSF cytology. Response is defined as a complete response when CSF converts from positive at baseline to negative after treatment with ^{131}I-omburtamab
5. Whole-body, organ, blood, and CSF radiation dosimetry.
6. Pharmacokinetic analysis of activity in blood and CSF including derivation of best-fit uptake and/or clearance parameters (half-times, maximum value) of time-activity concentration curves and of I-131 residence times (i.e., cumulated activity) concentrations (in μCi-h/g).
7. The frequency, type, and duration of treatment-emergent severe adverse events and serious adverse events, including clinically significant laboratory abnormalities. All adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
8. Performance assessment to monitor gross changes in neurological function is performed at week 26 and subsequently every 6 months during trial period.
9. The rate of ADA occurrence assessed three weeks after the first and second treatment dose of 131I-omburtamab

8.2 Safety

8.2.1 Safety endpoints

Safety data will be collected via AE and SAE reporting during the trial and graded according to CTCAE, version 4.0. Abnormal findings at physical examination and vital signs will also be monitored and any clinically significant abnormalities should be reported as AEs. Adverse events including Clinical Laboratory Adverse Event (CLAE; as defined in section 10.1.1).

9 PROCEDURES AND ASSESSMENTS

9.1 Efficacy assessments

9.1.1 Primary endpoint

OS rate at 3 years. The time frame for assessment of OS will be from the first treatment dose of ^{131}I-omburtamab to time of death from any cause. OS will be censored at last date of contact. Survival at 3 years will be estimated by Kaplan-Meier methods.

9.1.2 Secondary endpoints

9.1.2.1 *CNS/LM Progression-Free Survival (CNS/LM PFS) at 6 and 12 months*

The time frame for CNS/LM PFS will be from first treatment dose of ^{131}I-omburtamab to time of documented CNS/LM progression or death from any cause. CNS/LM PFS will be censored at last date of disease evaluation without evidence of CNS/LM progression. CNS/LM PFS at 6 and 12 months will be estimated using Kaplan-Meier methods.

9.1.2.2 OS at 12 months

OS at 12 months will be estimated by Kaplan-Meier methods following the same time and censoring scheme as the primary endpoint.

9.1.2.3 *Objective response rate (ORR)*

Response will be assessed at 6 months (week 26 visit) after the first treatment dose of ^{131}I-omburtamab as a combination of best overall partial or complete response at 5, 10, and 26 weeks. Assessments will follow the Response assessment in Neuro-Oncology (RANO) group criteria for parenchymal metastasis (Lin et al, 2015) or as defined by EANO-ESMO for leptomeningeal metastases (Le Rhun et al, 2017). The evaluation comprises MRI scans, CSF cytology, and clinical assessments. ORR at week 26 is defined as the proportion of patients with response at week 26 from the total population of patients with radiographically evaluable disease at baseline.

9.1.2.4 *Dosimetry and PK analysis for ^{131}I-omburtamab*

An interim analysis, evaluating the dosimetry and pharmacokinetic endpoints as well as available safety and efficacy data, will be conducted on data from patients having received at least one treatment cycle1 (both dosimetry and treatment dose) prior to January 1st, 2020. Starting January 1st, 2020, no further patients will be administered dosimetry doses.

9.1.2.5 *Performance assessment*

Since most if not all patients will have received prior cranio-spinal and/or whole brain irradiation, late side effects for such previous therapies are difficult to distinguish from ^{131}I-Omburtamab inflicted toxicities in CNS. However, to evaluate gross changes in neurological

function, performance test will be conducted during screening and at weeks 26, 52, 78, 104, 130 and 156. The scales to be used are: Lansky < 16 years and Karnofsky ≥ 16 years.

9.1.2.6 *Anti-Drug-Antibodies characterization*

A quantitative assay to assess anti-drug antibodies (ADAs) will be developed. The assay will be developed and validated using "cold" labeled omburtamab (^{125}I-omburtamab).

9.1.2.7 *Anti-Drug-Antibody effects on PK and Safety.*

The ADA characterization will deliver occurrence rate of neutralizing antibodies in blood and cerebrospinal fluid (CSF) of exposed patients. Potential associated effects of any neutralizing ADA's on ^{131}I-omburtamab pharmacokinetics (PK) in blood and CSF and safety will be investigated.

9.1.2.7.1 ADA effects on PK

Radioactivity counts in blood and CSF will be measured at the following time points after treatment with ^{131}I-omburtamab:

- 1h after treatment
- 6h after treatment
- 24 after treatment
- 7 days after treatment.

The analysis will comprise an intra-patient comparison of PK parameters from the two dose administrations in patients with and without presence of neutralizing ADAs in blood or CSF.

9.1.2.7.2 ADA effects on Safety

The analysis will comprise a comparison of reported safety events after the second dose administration in patients with and without presence of neutralizing ADAs in blood or CSF.

9.2 Other assessments

9.2.1 Hematology and clinical chemistry

Hematology and clinical chemistry will be measured by a local laboratory during screening and in all following treatment cycles and will assess liver and kidney function (ALT, AST, alkaline phosphatase, albumin, bilirubin, BUN, glucose and creatinine), total protein and serum electrolytes (sodium, potassium, chloride and bicarbonate). Complete differential blood count, including eosinophils and platelets, will be performed during screening and in the cycles up to the follow-up at week 26. Thyroid stimulating hormone (TSH)/ free and total T4 to be assessed at screening, pre-dose week 1 and 4, pre-dose week 5 and 8, week 26 if applicable and weeks 52, 78, 104 130 and 156..

If abnormal serum glucose (CTCAE ≥ Grade 2) is obtained, a fasting serum glucose is to be obtained at next patient visit. AE reporting of hyperglycemia will require fasting values to assess CTCAE grading.

9.2.2 CSF for cytology, total protein, glucose and cell count

CSF for cytology, total protein, glucose and cell count should be assessed during screening and at week 4, 8, and 26. If positive, it must be repeated within 4 weeks of the positive sampling.

9.2.3 Blood and CSF for culture

Blood and CSF will be sampled and held for potential culture after treatment doses in both cycle 1 and the conditional cycle 2. Samples will be cultured only if body temperature is elevated (defined as ≥ 38º C [≈ 100.4ºF]) after dosing and clinical infection is suspected.

9.2.4 Demographics

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

1. Age or date of birth if allowed by local legislation
2. Gender
3. Ethnic origin
4. Race
5. Other baseline characteristics, if applicable

9.2.5 Height and body weight

Height (without shoes and rounded to the nearest centimeter) must be measured at screening and recorded in the eCRF. Body weight (without overcoat and shoes and rounded to kilogram with one decimal) will be measured and recorded in the eCRF.

9.2.6 Medical and surgical history

Medical and surgical history if any relevant medical and/or surgical event(s) previously have been experienced by the patient. Information on the patient's medical history and general health will be collected during screening and comprises of, but is not limited to:

- General medical history
- Metastases location and characterization (unifocal parenchymal, multifocal parenchymal, leptomeningeal, parenchymal and leptomeningeal)
- Tumor characteristics that allow calculation of risk classification, e.g. V-Myc Myelocytomatosis Viral Related Oncogene (MYCN) status, DNA diploidy, disease stage and LDH at the time of diagnosis, and pathology classifications.
- Any prior treatment for neuroblastoma, e.g. frontline therapy and salvage regimens, responses to prior therapy, duration of responses, sites of relapse etc.

A concomitant illness is any illness, other than the disease being investigated, which is present at trial start or found as a result of the screening procedure.
The information collected for medical history and concomitant illnesses includes:

- Diagnosis
- Date of onset
- Date of resolution
- Date of relapse, including date of CNS relapse

Any clinically significant worsening of a concomitant illness must be reported as an AE (see section 10).

9.2.7 Concomitant medication

A concomitant medication is any medication other than the IMP. All concomitant medications must be recorded in the eCRF with the following information:

- Start date
- Stop date of administration or ongoing at trial termination
- Indication/ reason for use
- Dose
- Frequency
- Outcome (for anti-cancer treatments)

Any changes to concomitant medication during the trial will be recorded in the eCRF. All doses of allowed pain relief medication should be recorded as concomitant medication in the eCRF.

9.2.8 Physical examination

Physical examination should be performed as clinically indicated from screening to the EOT and includes assessment of general appearance, mental status and various organ systems (skin, head, eyes, ears, nose, mouth, throat, neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, and neurologic systems).

9.2.9 Vital signs

Pulse oximetry and measurements of heart rate, respiratory rate, temperature, and blood pressure before and 30 minutes after ^{131}I-omburtamab infusion. Temperature must be measured by using the same method (e.g., an ear thermometer).

9.2.10 Neurotoxicity

Neurotoxicity will be assessed by the National Cancer Institute clinical neurotoxicity criteria during screening and weeks 1, 4, 5, 8, 26. All neurologic abnormalities present prior to ^{131}I-omburtamab infusions will be recorded as medical history. Any neurologic changes during the trial period which meet the criteria for Grade 3 or 4 neurotoxicity will be assessed by the trial physicians as being unrelated, possibly or probably caused by the infusion. In the absence of clear evidence progressive disease (PD), it may be assumed that new signs and symptoms are

treatment related. Any patient that develops Grade 4 neurotoxicity after the IMP infusion is to be discontinued from treatment.

Neurotoxicity also will be assessed clinically and radiographically. Assessment of cranial nerves, gross motor function and sensory function will be performed. Assessment and grading of radiographically cortical atrophy, cerebral ventricular size, white matter changes or other abnormalities will be made by a neuro-radiologist. Altered CSF flow will be interpreted by the trial nuclear medicine physicians.

Clinical neurotoxicity evaluation is to be conducted at screening and weeks 1, 4, 5, 8 and 26, as indicated in the flowchart. The radiographic assessment of neurotoxicity and disease progression (by MRI) is to be conducted at screening, weeks 4 and 8 and week 26 only.

Lansky (Karnovsky for children ≥ 16 years) performance score will be analyzed to evaluate gross neurologic function and a measure of a patient's long-term function.

9.2.11 Non-childbearing potential

Non-childbearing potential in women will be confirmed by one of the following:

- Women/girls who have not reached menarche or
- Women/girls who have not had menses within the past 12 months and who do have a follicle-stimulating hormone level ≥40 IU/L or
- Women/girls who have not had menses within the past 24 consecutive months if a follicle-stimulating hormone measurement is not available
- Women/girls who have undergone surgical sterilization (e.g., hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy).

9.2.12 Unscheduled visits

If any assessments need re-evaluation, an additional response assessment is needed, or follow up on an (S)AE is required, the patient can be called for an unscheduled visit at the discretion of the Investigator. Data obtained during unscheduled visits pertaining to the clinical trial will be collected as unscheduled visits in the eCRF.

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 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 adverse event (CLAE): 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 active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

Throughout the clinical trial a DMC will monitor the patients' safety according to the DMC charter (section 6.2).

10.2 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 event determines the reporting procedures to be followed.
An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Medical important medical
- Results in death
- Is life threatening

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, which 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 the outcome of 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.

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. Exceptions are hospitalizations for

administrative, surgical procedures planned before trial inclusion, trial-related and social purposes do not constitute AEs.

Elective surgery or other scheduled hospitalization periods that were planned before the patient was included in this trial are not to be considered serious. However, the event must be reported on the AE page in the eCRF and commented upon.

Medical and scientific judgment must be exercised in deciding whether an AE is believed to be "medically important". Medical 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.

10.3 Definition of non-serious AE

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

10.4 Pre-defined AEs of Special Interest

The following AEs are selected as Adverse Events of Special Interest (AESIs)based on previously experience with ^{131}I-Omburtamab and should be reported within 24 hours to sponsor:

- Neurotoxicities Grade 3 and above
- Severe infections related to placement of cerebroventricular device
- Chemical meningitis

10.5 Adverse Event Recording

10.6 Pre-existing conditions

In this trial, 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.

10.6.1 Procedures

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. Additionally, any procedures pre-planned before entering the trial (e.g. for pre-existing conditions) can be excluded.

10.6.2 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 product.
- 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 and medication errors (exceeding ± 10% as compared to protocol-specified dose) should be reported as protocol deviations to the sponsor . If an overdose, medication error, or misuse results in an AE, the AE must also be reported in the eCRF. If the event qualifies as serious it must be reported using the paper the clinical AE report form in addition to the AE form in the eCRF.

10.6.2.1 *Management of Overdose of ^{131}I-omburtamab*

Rescue medication to reverse the action of ^{131}I-omburtamab is not available. In case of overdose or other medication errors of ^{131}I-omburtamab patients, should receive supportive care according to local guidelines and potential side effects of ^{131}I-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.

10.6.3 Pregnancy

Any pregnancy that occurs during trial participation must be reported to sponsor within 24 hours of learning of its occurrence using the pregnancy form. Pregnant trial patients must be withdrawn from treatment immediately. 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 one 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.

10.6.4 Severity

The Investigator will use the National Cancer Institute (NCI) CTCAE version 4.0 to describe the maximum severity of the AE, see below (US Department of Health and Human Services 2010). The grade assigned by the investigator should be the most severe, which occurred during the AE period:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living.
    - Instrumental Activities of Daily Living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living.
    - Self-care Activities of Daily Living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Any change in severity grade represents a new AE subsequently, when an AE change severity, a new AE should be created with the changed severity.

10.6.5 Relationship to IMP

The Investigator must assess the AE as either Related or Not Related to IMP. A suspected adverse reaction is defined as one in which there is a reasonable possibility that the drug caused the adverse event. Relatedness has to 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 event:

- 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.
- The AE 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 AE.

Related (possible/probable)
The AE is related to the IMP, which means the event:

- 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).
- Cannot be reasonably explained by the known characteristics of the patient's clinical state or medical history.
- Alternative etiology should be provided for all AEs assessed as possible related to IMP

10.6.6 Outcome

Investigator must judge outcome of the AE by the following terms:

- Recovered
- Recovered with sequelae
    - Description of the sequelae should be provided
- Not recovered
- Death
- 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 are provided in the instructions that accompany the AE case report forms.

10.7 Expected side-effects related to ^{131}I-omburtamab and dexamethasone

^{131}I-omburtamab:
For detailed description, please refer to current IB.

The risks of ^{131}I-omburtamab include thyroid suppression, neutropenia and myelosuppression requiring red blood cell and/or platelet transfusions. Expected toxicities in the acute phase include the known risks associated with intraventricular infusions: headache, vomiting, and fever in the first few hours post-infusion.

Dexamethasone:
The expected toxicities of dexamethasone include lymphopenia, anemia and hyperglycemia.

10.8 Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported in the eCRF. AEs occurring between Screening and first treatment must be recorded as Medical History.
SAEs and AESIs (whether serious or non-serious) should be reported both in the eCRF and on the paper clinical AE report form. SAEs must be reported from the first trial related activity after the patient has signed the informed consent until 3 weeks after last IMP administration.
Subsequent SAE reporting (occurring later than after 3 weeks after last IMP administration)

and during the long-term FU period (3 years) only SAEs considered related to the trial medication or new onset of cancers regardless of causality should be reported. The investigator should report these SAEs within the same timelines as for SAEs during the trial.

For patients withdrawn from the trial, please see section 6.9.3.

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 trial product either observed by the investigator or patient must be reported by the investigator and evaluated. All AEs must be recorded by the investigator on an AE form in the eCRF. 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. All pre-defined Adverse Events of Special Interest must be reported as SAEs.

For SAEs & AESIs, the clinical AE report form must be completed in addition to the AE form in the eCRF. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs. For all non-serious AEs, the applicable forms in the eCRF should be signed when the event is resolved or at the end of the trial at the latest.

Timelines for initial reporting of AEs:

- Initial SAEs & AESIs: The paper clinical AE report form must be reported from site to sponsor within 24 hours of the investigator's first knowledge of the event. The paper clinical AE report form is to be sent to the designated drug safety provider by e-mail or courier. Please ensure the eCRF AE form is updated in accordance to agreed data entry timelines. New FU information available at site must be reported within 24 hours
- FU information requested from Sponsor must be replied to within three working days by using the paper data clarification form. Please ensure the eCRF AE form is updated in accordance to agreed data entry timelines.
- If the eCRF is unavailable, the concerned SAE information must be entered when the eCRF becomes available again.

Contact details for reporting:
SAEintake@covance.com

In emergency situations the completed safety reporting forms or pregnancy forms can be faxed to:
FAX +1-888-887-8097

Sponsor assessment of AE expectedness:
The sponsor assessment of expectedness for ^{131}I-omburtamab is performed according to the current version of the Investigator's Brochure.

Reporting of trial product related SUSARs by Sponsor CRO
Sponsor CRO Covance Inc. will inform the regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) in accordance to regulatory requirements. Sponsor CRO Klifo A/S will notify investigators 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. Sponsor CRO Klifo A/S will inform the Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs) of SUSARs in accordance with local requirement, unless locally this is an obligation of the investigator.

10.9 Follow-Up on AEs

All non-serious AEs should be followed until they are either resolved, i.e., returned to baseline or until the end of the post-treatment FU period (3 weeks after last IMP administration) whichever comes first. AEs meeting one of the serious criteria (including AEs of Special Interest), still ongoing after ending trial participation, 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.

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

If the investigator becomes aware of an SAE after the long-term FU period with a suspected causal relationship to the IMP, the investigator should report this SAE within the same timelines as for SAEs during the trial.

11 LABORATORIES

Nuclear scanning (whole-body planar gamma camera scans) and radioactivity measurements in CSF and blood will take place on-site following qualified procedures outlined in respective manuals. The calculation of the absorbed radiation doses will take place centrally following a predefined methodology. Pharmacokinetic parameter derived from radioactivity concentration vs. time data will be calculated centrally.

A detailed description of the procedures for sampling, handling, storage, and measurement of the specimen and all material such as test tubes and labels will be provided in the Technical Binder. Blood samples for biochemistry and hematology will be analyzed by local laboratories.

11.1 Clinical chemistry and hematology

Chemistry Panel
Liver and renal function tests (ALT, AST, alkaline phosphatase, TSH, T4, albumin, total bilirubin, total protein, LDH, BUN, and creatinine), serum glucose and serum electrolytes (sodium, potassium, chloride, and bicarbonate). If abnormal serum glucose (CTCAE ≥ Grade 2) is obtained, a fasting serum glucose is to be obtained at next patient visit.

Hematology Panel
Complete blood count will be performed during screening and during all treatment cycles with regards to hematocrit, hemoglobin, Mean Cell Hemoglobin (MCH), Mean Cell Hemoglobin Concentration (MCHC), Mean Cell Volume (MCV), platelets, red blood cells (RBC), WBC, basophils, eosinophils, lymphocytes, monocytes and neutrophils. All Grade 4 laboratory abnormalities must be retested within 24 hours of receiving results.

12 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1 General Overview

The data will be summarized in tables, as appropriate, showing the number of patients with non-missing data (n), mean, standard deviation, median, minimum, and maximum for continuous data and showing counts and percentage for categorical data. Data will also be listed as deemed appropriate. All statistical analyses will be performed and data appendices will be created by using SAS version 9.0 or later.

All statistical tests will be two-sided with an α level of 0.05.

The Statistical Analysis Plan (SAP) will describe in detail the analyses presented below. Furthermore, handling and presentation of data including baseline data and other trial assessments will be described in the SAP. The selection of an appropriate control group from available external data is briefly described below but will be described in full detail in the SAP. Patient characteristics that may be considered in the selection of the control group include, but are not limited, age at diagnosis, MYCN amplification status, International Neuroblastoma Staging System stage at diagnosis, International Neuroblastoma Pathology Classification (favorable vs. unfavorable), time to first relapse, site of relapse, and lactase dehydrogenase level.

12.2 Populations of Interest

- Full Analysis Set

  The full analysis set (FAS) will include all patients enrolled in the trial who begin an infusion of ^{131}I-omburtamab

- Per Protocol Analysis Set (PPS)

  The PPS will include all FAS patients who have no major protocol violations. Additional patients with other protocol violations may be uniformly excluded on the basis of data review. The precise reasons for excluding patients from the PPS will be fully defined and documented before data lock

- Safety Analysis Set

  The safety analysis set will include all enrolled patients who receive at least one dose of IMP

- External control group

External controls will be primarily obtained from a query to the Central German Childrens Cancer Registry (CGCCR). CGCCR initiated in 1980, registers approximately 2,000 children per year who are diagnosed with a malignant disease. CGCCR receives patient data from all paediatric oncology centers across Germany. 99% of all paediatric patients diagnosed with cancer in Germany were included in the national trials, with continuous update of the clinical data within the CGCCR.

The CGCCR data will be used to obtain an estimate of the 3-year survival rate in a contemporary systemically treated cohort of children. To explore the development of systemic treatment we will employ cut-offs in 2000 and 2004.

[redacted]

12.3 Efficacy Analysis

The FAS will be used for all efficacy endpoints. Additionally, the primary and secondary endpoint analyses will also be performed on the PPS. The primary endpoint of the OS rate at 3 years as well as OS at 12 months, and CNS/LM PFS at 6 and 12 months with corresponding 95% confidence intervals, will be estimated using Kaplan-Meier methods using the FAS. The comparison to external controls (OS only) will be exploratory and performed using multiple cox regression taking into account the most important prognostic factors identifiable in the historic data. The median OS and CNS/LM time and associated 95% confidence interval will be calculated. Results will be displayed with Kaplan Meier plots. ORR according to RANO criteria and CSF cytology as well as CSF cytology alone, will be assessed, 95% confidence intervals will be calculated using the Clopper-Pearson exact methodology.

12.4 Safety Analysis

The safety analysis set will be used for all safety analyses. Adverse event data will be listed individually, and the incidence of adverse events will be summarized by system organ class (SOC) and preferred terms for each treatment group. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later. AEs will be regarded as treatment-emergent adverse events (TEAEs) if they occur after first administration of ^{131}I-omburtamab. Related AEs are defined as adverse drug reactions (ADRs).

Listings will be made of all AEs, including non-TEAEs. All TEAEs, ADRs, SAEs and serious adverse reactions (SARs) will be summarized. The summaries will include number of events, number of patients, and percentage of patients reporting these events and will be tabulated by SOC and preferred term (PT). TEAEs will also be summarized by severity and by relationship to IMP. When calculating the incidence of adverse events, each adverse event will be counted only once for a given patient within a specified SOC, preferred term. If the same adverse event occurs on multiple occasions for a patient, the occurrence with the highest severity and relationship to IMP will be reported. 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 will be identified. Effects on cognitive functions will be assessed summarizing changes from baseline in performance testing results with descriptive statistics.

12.5 Dosimetry Analysis

Spinal cord, brain and non-target ROI absorbed radiation doses will be estimated and CSF mean absorbed radiation doses will be calculated on the basis of nuclear imaging scans (whole-body planar gamma camera scans). 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 pre-defined timepoints (section 9.1.2.4) after the dosimetry and the treatment doses in cycle 1 from all patients enrolled before January 1st, 2019.

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

12.6 Pharmacokinetic Analysis

The radioactivity measurements in CSF and blood that are used for calculation of the mean absorbed radiation dose after administration of the dosimetry and treatment doses are also used for pharmacokinetic analysis. C_{max} in blood is determined and the elimination half-life as well as the areas under the radioactivity vs. time curves are calculated.

Individual and mean pharmacokinetic parameter (if applicable) will be summarized with descriptive statistics for all patients and by trial site.

12.7 Interim Analysis

An interim analysis, evaluating the dosimetry and pharmacokinetic endpoints as well as available safety and efficacy data, will be conducted on data from patients having received at least treatment cycle 1 prior to January 1st, 2020. Starting January 1st, 2020, no further patients will be administered dosimetry doses. Progression in CNS/LM will be assessed at 6 and 12 months for the full analysis. The primary efficacy endpoint for the interim analysis will be CNS/LM PFS at 6 months.

12.8 Sample Size

Assuming an [redacted]

Power was estimated by simulation using an exponential model and an assumed lost to follow-up rate of 10%.

12.9 Handling of missing data

For the primary time to event efficacy endpoint, patients who do not have an event will be censored at their date of their last evaluation. It is unlikely that missing of safety data will occur in the targeted patient population, but in case it happens the data will not be imputed.

13 ETHICS

13.1 Independent ethics committee or institutional review board (IRB)

This protocol and any accompanying material to be provided to the patient (such as patient information sheets and/or descriptions of the trial used to obtain informed consent) will be submitted by the Investigator to an IRB/IEC. Approval from the IRB/IEC must be obtained before starting the trial and should be documented in a letter to the Investigator.
It is the responsibility of the Investigator or his/her representative to obtain approval of the trial protocol/protocol amendments, the patient information and the Informed Consent from the IRB/IEC before enrolment of any patient into the trial.

13.2 Ethical conduct of the trial

The trial will be conducted in accordance with the protocol, applicable regulatory requirements, ICH GCP and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and sub-sequent versions.
The trial will be conducted according to Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population (recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use). The guideline is referenced in Appendix 5.

13.3 Participant information and informed consent

The investigator or his/her designee must obtain the written informed consent from each patient, and/or the patients acceptable authorized representative, before any trial related procedures are performed as applicable to local regulations. Patients deemed eligible for the trial should be presented with the patient information in their native language. 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)) 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 verbal and written 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), and if applicable informed assent (child/adolescent), must be signed in accordance with local regulations.

If applicable to local regulations: if the 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 Informed Consent, the patient/parents must be given sufficient time to consider the possible participation. Further, each patient must be informed about their right to with-draw 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 informed consent form has been signed, the patient/parent(s) receives a copy of the signed form and the original is retained in the investigator site file. A second copy may be kept in the patient's medical notes. The informed consent forms 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 participant's family doctor of the participant's consent to participate in the trial.

13.4 Special considerations for patients having the Ommaya reservoir implanted at the referring hospital or locally but before entering the screening period.

The Ommaya reservoir is to be placed after the written informed consent has been obtained.
In cases where placing of the Ommaya is considered in association with the surgical procedure that is recommended before enrollment in the trial, informed consent may be obtained up to three months before the start of the screening period. This is considered acceptable since placing of the Ommaya in association with the anesthesia induced for the surgical resection of the tumor will reduce the burden to the patient by avoiding an extra surgical procedure. Furthermore, the patient may receive high dose chemotherapy in the period leading up to the screening period which may be associated with myelosuppression and therefore rendering an invasive procedure like Ommaya placement not feasible.
In cases where the potential patient is a referral patient, the investigator must as a first step discuss inclusion and exclusion criteria with the referring physician. Additionally, the Investigator must arrange for an information meeting where patients and parents have an opportunity to discuss details of the trial with the investigator. The meeting can be a telephone conference call with participation of patient, parents and referring doctor prior to Ommaya placement. The investigator is responsible for the documentation of this. In addition to the signature from patients/ parents and the investigator, the referring doctor must sign the ICF to testify that he/she has been present at the information meeting. Confidentiality
The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties according to local requirements. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

The investigator agrees that the IMPs and all information received from sponsor including but not limited to the IB, this protocol, data, eCRFs, and other trial information, remain the sole and exclusive property of sponsor during the conduct of the trial and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the trial or as required by law) without prior written consent from sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the trial site to any third party or otherwise into the public domain.

14 MONITORING AND QUALITY ASSURANCE

14.1 Compliance with Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, Washington, Seoul, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the trial patient.

14.1.1 Protocol compliance

The investigator is responsible for ensuring the trial is conducted in accordance with the procedures and evaluations described in this protocol.

14.1.2 Training of personnel

Training of personnel will be conducted during the site initiation visit. If change of personnel occurs, it is the responsibility of the Principal Investigator (PI) to train new personnel and it should be documented by e.g. completion of training log form. If the protocol or any trial specific procedures are updated, it is the responsibility of the CRA and PI to ensure documented training of all personnel.

14.2 Monitoring

In accordance with the principles of ICH GCP and the sponsor or its designee's SOPs, monitoring of the trial will be arranged. During the trial, the CRA will have regular contacts with the trial site, including visits to ensure that the trial is conducted and documented properly in compliance with the protocol, ICH GCP, and applicable local regulations. The extent of monitoring will be based on a risk assessment and will be described in a monitoring plan produced by the contract research organization (CRO). CRA will ensure that accountability of IMPs is performed and will review source documents for verification of consistency with the data recorded in the eCRFs (source data verification). The CRA will also provide information and support to the investigational sites.
In order to assure quality standards, the trial sites may be audited by the sponsor or its designee as well as inspected by a Regulatory Authority. The investigator and other responsible personnel must be available during the monitoring visits, audits and inspections and should devote sufficient time to these processes.
The investigator should provide a curriculum vitae or equivalent documentation of suitability to be responsible for the trial including valid GCP training, a copy of current licensure, and should sign a financial disclosure on conflict of interests. All investigators and other responsible personnel should be listed together with their function in the trial on the signature and delegation list to be filed in the investigator site file.

During these contacts, the monitoring activities will include:

- Drug accountability
- AE identification/review
- Checking and assessing the progress of the trial

- Reviewing trial data collected to date for completeness and accuracy
- Conducting source document verification by reviewing each patient's eCRF against source documents (e.g. medical records, ICF, laboratory result reports, raw data collection forms)
- Identifying any issues and addressing resolutions

These activities will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of the patients are being protected
- Trial is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements

The investigator will allow the CRA direct access to all relevant documents and allocate ample time and the time of the personnel to the CRA to discuss findings and any relevant issues.
In addition to contacts during the trial, the CRA will contact the site prior to the start of the trial to discuss the protocol and data collection procedures with the site personnel.

14.3 Source data verification

14.3.1 Source data

All digital or paper hospital records regarding the treatment of the patient included in the trial are considered source data. The following minimum amount of information should be recorded in the hospital records:

- Clinical trial identification.
- Participant identification.
- Date when patient information was given and when signed Informed Consent was obtained.
- Diagnosis.
- Fulfilment of inclusion criteria.
- Specification of visit dates, concomitant medication and any (S)AEs.
- Specification of the patient's cessation in the trial (e.g. premature withdrawal).
- Specification of the patient's outcome in the trial.

14.3.2 Direct access to source data/documents

The investigator(s)/institution(s) will permit trial-related monitoring, audits, review and regulatory inspection(s), access to source data/hospital records. The CRA verifies that each patient has consented in writing to direct access to the original source data/hospital records by the use of written patient information and signed informed consent. During monitoring, the data recorded in the eCRFs by the investigator will be compared for consistency with the source data/hospital records by the CRA. Any discrepancies of data will be documented and explained in the monitoring reports.

14.3.3 Access to information for monitoring

In accordance with ICH GCP guidelines, the CRA must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency. The CRA is responsible for routine review of the eCRFs at regular intervals throughout the trial to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered into the eCRF. The CRA should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the CRA to ensure that any problems detected in the course of these monitoring visits are resolved.

14.3.4 Access to information for auditing or inspections

Representatives of regulatory authorities or of sponsor may conduct inspections or audits of the clinical trial. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

14.4 Quality assurance

At its discretion, the sponsor (or designee) may conduct a quality assurance audit of this trial. Auditing procedures of the sponsor (or designee) will be followed in order to comply with GCP guidelines and ensure acceptability of the trial data for registration purposes. If such an audit occurs, the investigator will give the auditor direct access to all relevant documents and will allocate ample time and the time of the personnel to the auditor as may be required to discuss findings and potential issues.

15 DATA HANDLING AND RECORD KEEPING

15.1 Electronic case report forms

For each patient enrolled, an eCRF must be completed and signed by the investigator. This also applies to records for those patients who fail to complete the trial. If a patient withdraws from the trial, the reason must be noted in the eCRF. If a patient is withdrawn from the trial because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome. For screening failure patients, the date of informed consent and reason for failure to enroll must be captured in the eCRF.

15.1.1 eCRF

An eCRF will be established to collect data in a validated and effective way and in compliance with ICH guidelines including audit trail and a query module. The patient's identity must always remain confidential. All information in the eCRFs should be in English.
The completed original eCRF data are the sole property of the sponsor and should not be made available in any form to third parties (except for authorized representatives of appropriate regulatory authorities) without written permission from the sponsor.

The investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs.

15.2 Trial documents at site and record retention

The investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's site file, and (2) patient clinical source documents. The investigator's site file will contain the protocol/amendments, and IRB/IEC approval with correspondence, informed consent, drug records, personnel curriculum vitae and authorization forms, and other appropriate documents and correspondence. During the trial, the investigator will have full access to the eCRF. After the trial is completed, the investigator will receive a copy of the eCRF on CD-ROM or other appropriate electronic storage device. The investigator is required to complete a source data list, defining where the specific source data can be found (patient record/trial specific patient record). All clinical trial documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with sponsor. The investigator must notify sponsor before destroying any clinical trial records. Should the investigator wish to assign the trial records to another party or move them to another location, sponsor must be notified in advance.
If the investigator cannot guarantee this archiving requirement at the trial site for any or all of the documents, special arrangements must be made between the investigator and sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site. Biological

samples at the conclusion of this trial may be retained in storage by the sponsor for a period up to 10 years for purposes of this trial.

15.3 Data management

All data, except laboratory data, will be collected using an eCRF compliant with 21 CFR Part 11 regulation. Laboratory data will be transferred to data management facility for inclusion in the clinical database. Data management will be performed in accordance with applicable standards and data cleaning procedures. Only authorized access to the eCRF will be possible using encrypted username and password. Roles in the system are given according to functions. All tasks performed in the eCRF are logged in an audit trail. The eCRF will contain validation checks to maintain an ongoing quality check of data entered, these checks will be programmed by CRO. Manual medical checks as well as programmed validation checks must be signed off by Y-mAbs Data Management and Y-mAbs Clinical Project Management. The investigator will approve the data using an electronic signature and thereby confirm the accuracy of the data recorded. Medical history and AEs will be coded using the MedDRA dictionary. Concomitant medication will be coded using the World Health Organization (WHO) Drug dictionary.

16 REPORTING AND COMMUNICATION OF RESULTS

16.1 Publication

The data collected in this trial are the property of the sponsor. Sponsor commits to communicate and make available for public disclosure, the results of the clinical trial regardless of outcome at latest 1 year after final CSR is completed. Public disclosure implies publication in scientific journals, abstract submission for scientific meetings and other types of disclosure (e.g. via ClinicalTrials.gov). Co-authorship from Investigators will be in accordance with International Committee of Medical Journal Editors (ICMJE) rules:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A predefined publication committee will follow the entire process; decide on publication, manuscript authorship for the entire clinical trial and authorship of potential additional manuscripts based on sub- studies. All manuscripts relating to sub-studies will state that they are sub-studies and cite the main publication. The publication committee will also decide on which journal(s) to submit to. Positive, negative as well as inconclusive results will be published e.g. at www.clinicaltrials.gov or www.clinicaltrialsregister.eu.

16.2 Use of information

Sponsor will make one main publication from the clinical trial and all other publications should come afterwards and refer to the main clinical trial publication.
All information not previously published concerning the IMPs, including patent applications, manufacturing processes, basic scientific data, clinical trial data and results, etc., is considered confidential and remains the sole property of the sponsor. The investigator agrees to use this information only in connection with this trial and will not use it for other purposes without written permission from the sponsor.
No such communication, presentation, or publication will include sponsor's confidential information. All presentation and publications will be governed by the publication committee. Proposed publication(s) or presentation(s) along with the respective scientific journal or presentation forum should be provided to the sponsor at least 30 days prior to submission of the publication or presentation. Publication authors will comply with sponsor's request to delete references to its confidential information (other than the trial results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

17 INSURANCE

Insurance and liability will be in accordance with applicable local laws and regulations and GCP.

18 CHANGES AND DEVIATIONS TO THE PROTOCOL

Protocol modifications, except those intended to reduce immediate risk to trial patients, may only be made by sponsor. Protocol modifications will follow local requirements for submission to the competent authorities and IRB/IECs. Approval must be obtained before changes can be implemented.

Any protocol or other deviations that occur during the trial will be documented and reported to the sponsor. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority.

No change in the trial procedures shall be effectuated without the mutual agreement of the investigator and the sponsor (except where necessary to eliminate an immediate hazard to patients).

19 PREMATURE TERMINATION OF THE TRIAL

This trial may be terminated by the sponsor. The trial may also be terminated prematurely at any time when agreed to by both investigators and the sponsor as being in the best interest of patients and justified by either medical or ethical grounds. In terminating the trial, sponsor and investigators will ensure that adequate consideration is given to the protection of the patient's interest.

19.1 Criteria for halting participant enrollment

Enrolment will be halted if the following criteria is met:

- One or more patients experience IMP-related, unexpected, clinically life-threatening toxicity (excluding Grade 4 lab values without clinically significant symptoms)
- One or more patients experience unexpected, sudden death during a treatment cycle

If the abovementioned criteria are met, the DMC will review the safety results and determine how to proceed as described in section 6.2.
Patients already included at the time of clinical trial halt, will continue in the clinical trial but further dosing will be postponed until a decision has been reached by the DMC.

19.2 Criteria for termination of the trial

The sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients but intends to exercise this right only for valid scientific or administrative reasons. After such a decision, all delivered unused investigational medicinal products and other trial-related materials must be collected without delay and all eCRFs must be completed as far as possible.
The trial could be prematurely discontinued in the following situations (examples):

- New findings about the IMPs that is considered significantly to worsen the benefit/risk ratio.
- Compliance with the trial protocol proves difficult.
- Recruitment of eligible patients is far too low or slow.
- Level of investigator, sponsor or patient compliance becomes unacceptable.
- Critical changes are observed in sponsor or trial site personnel, administrative or scientific standards.
- The DMC recommends discontinuation.

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Appendix 1 Contact details of clinical trial team

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[redacted]
Chief Executive Officer
[redacted]

Appendix 2 Salvage Treatments Recommended Prior to Trial 101 Entry*

Time	Treatment
Week -12	Resection of CNS disease when possible
Week -11	Irinotecan 50 mg/m2/dose IV daily x5
Week -10	Craniospinal irradiation 2160 cGy/boost at tumor bed to 3000 cGy **
Week -5	Irinotecan 50 mg/m2/dose IV daily x5
	Temozolamide 250 mg/m2/dose daily x5
	Carboplatin 500 mg/m2/dose daily x2 (only if systemic NB present)
	Stem cell rescue ***
Trial start	First administration of IMP

* all salvage treatments will be depending on patient's condition and are ultimately at the treating physician's discretion
** to be acknowledged and agreed to by the local radiation-oncologist. For patients with unifocal resected CNS disease, a reduction in the craniospinal radiation dose to 1800cGy is recommended
*** if needed

Appendix 3 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 4 Ommaya patency/CSF flow study

CSF CISTERNOGRAM INDICATIONS:	Evaluate CSF circulation 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) or Technetium-99m Diethylenetriamine Pentaacetic Acid (^{99m}Tc-DTPA)
Dose:	0.5 mCi for cisternal infusion via indwelling intracerebroventricular access device (e.g. Ommaya).
Instrument:	Dual detector Gamma Camera
Collimator:	Medium Energy General Purpose (MEGP)
Isotope Energy Peak:	173, 247 keV
Energy Window Width:	20%

Technique

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 may be recorded at 4, 24 48 and 72 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. SPECT images (optional) may be recorded in a 128x128 matrix for 30 seconds/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, and spread over the convexities by 24 hours

Appendix 5 Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population

http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf

Appendix 6 Template letter to referring oncologist

Dear Colleague,

Thank you for referring patient (*patient name*) to the Y-mAb's 101 study for which I am responsible at (*site name*).

I am pleased to inform you that your patient now has the opportunity to receive re-treatment with 131I- omburtamab equivalent to two cycles in case your patient is suffering from subsequent relapse in the CNS/LM after the initial 131I-omburtamab therapy during the follow-up period.

As your patient has relocated back to your clinic, we need to make an agreement under which we can coordinate collection of the follow-up data stated below every six months.

From completion of the initial treatment in the 101 study, safety and efficacy must be investigated with follow-up visits every six months for up to three years. to ensure the best possible treatment and safety for your patient – and possibility of re-treatment in the event of re-lapse. This also comprises patients referred by other oncologists from other hospitals and other countries,

To be able to fulfill this, please provide the following information at the indicated time points:

	Date of Week 26	Date of Week 52	Date of Week 78	Date of Week 104	Date of Week 130	Date of Week 156
Any safety concerns						
Cancer related medications used since						
Status of TSH (free and total T^4						
Status of performance (test by using Lansky Scale < 16 years, Karnofsky Scale ≥16 years),						
MRI assessment report of the brain and spine for week 26						
Collection of information on systemic disease progression and CNS/LM disease						

I kindly ask you to return with confirmation, that your patient has received the information about the possibility to be re-treated if suffering from subsequent relapse in the CNS/LM.

Thank you for your attention and willingness to enter into this collaboration so we can give your patient the best possible follow-up and in the event of relapse the possibility of re-treatment.

Sincerely yours,

Signature Page for CLIN-000005 v10.0

Approval	[redacted] 01-May-2020 13:24:35 GMT+0000

Approval	[redacted] 01-May-2020 14:33:29 GMT+0000

Signature Page for CLIN-000005 v10.0