CONFIDENTIAL

CLINICAL TRIAL PROTOCOL

Safety and clinical activity of nivatrotamab, an anti GD2×CD3 bispecific antibody, in relapsed/recurrent metastatic small-cell lung cancer

An open-label, single-arm, multicenter, phase 1/2 trial

Clinical Trial ID: 402

IND No: 153595

EudraCT No: 2022-000201-27

Version 8.0_20-Jan-2022

Approval of Clinical Trial Protocol

Protocol Author		
Y-mAbs Therapeutics, Inc. [redacted] Director Clinical Operation	Please refer to the e-signature page	
Print Name:	Signature:	Date:

Medical Monitor/Expert		
Y-mAbs Therapeutics, Inc. [redacted] Chief Scientific Officer, Global Head, Translational Medicine	Please refer to the e-signature page	
Print Name:	Signature:	Date:

Biometrics		
Y-mAbs Therapeutics Inc. [redacted] Senior Project Statistician	Please refer to the e-signature page	
Print Name:	Signature:	Date:

Key Contact Information

Sponsor

Y-mAbs Therapeutics, Inc.
230 Park Avenue, Suite 3350
New York, NY 10169
USA

Sponsor's Medical Expert

[redacted]
SVP, Chief Scientific Officer
Global Head, Translational Medicine

E-mail: [redacted]
Phone: [redacted]

Contact Details for Reporting of SAE/AE

safetymailbox@ymabs.com

In emergency situations, the completed Clinical Adverse Events Report forms or pregnancy forms can be faxed to:

FAX +0045 7879 6060

Coordinating Investigator

[redacted]
UPMC Hillman Cancer Center
5150 Centre Ave. 5th Floor
Pittsburgh, PA 15232

Approval by signature of the Clinical Trial Report (CTR) on behalf of all Investigators

Information regarding Investigators conducting the trial, the trial monitor, clinical laboratories and/or technical departments and/or institutions involved in the trial will be provided as separate documents referencing the protocol.

TABLE OF CONTENTS

List of Tables

List of Figures

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABS	Absolute count
ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
AP	alkaline phosphatase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BiPAP	bilevel positive airway pressure
BOIN	Bayesian Optimal Interval design
BUN	blood urea nitrogen
CDR	complementarity-determining region
C_{max}	peak plasma concentration
CNS	central nervous system
CPAP	continuous positive airway pressure
CR	complete response
CRA	clinical research associate
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTR	clinical trial report
CV	coefficient of variation
DAS	DLT evaluable analysis set

DCR	disease control rate
DFS	disease free survival
DLT	dose-limiting toxicity
DMC	data monitoring committee
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	extensive stage disease
ECG	electrocardiogram
EEG	electroencephalography
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
F	fraction absorbed
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
FMOL	femtomole
FSH	follicle-stimulating hormone
H	hours
HCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
I	immune
IB	Investigator's brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICH	International Council for Harmonisation

ICP	intracranial pressure
ID	identification number
IEC	independent ethics committees
Ig	immunoglobulin
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
iRECIST	immune response evaluation criteria in solid tumors
IRR	infusion-related reaction
IV	intravenous
IVF	intravenous fluids
Ka	absorption rate constant
LD	limited stage disease
LDH	lactic dehydrogenase
LLOQ	lower level of quantification
LVEF	left ventricular ejection fraction
mAbs	monoclonal antibodies
mBOIN	modified Bayesian Optimal Interval Design
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N/A	not applicable
NOAEL	no-observed-adverse-effect level

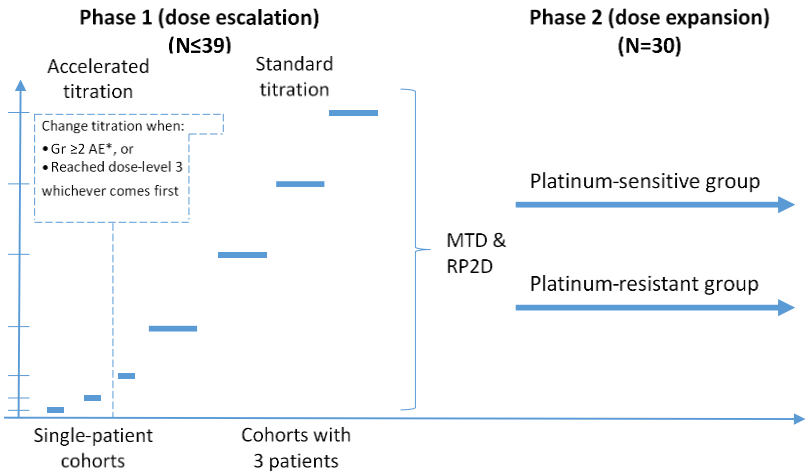
NSAID	nonsteroidal anti-inflammatory drug
PD	progressive disease
PDL1	anti-programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PKAS	PK analysis set
PO	per oral
PR	partial response
PT	preferred term
PTT	partial thromboplastin time
OR	overall response
ORR	objective response rate
OS	overall survival
RBC	red blood cell count
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SCR	screening
scFv	single-chain variable fragment
SCLC	small-cell lung cancer
SD	stable disease
SOC	system organ class
SNRI	selective norepinephrine reuptake inhibitors

SRS	stereotactic radiosurgery
SSRIs	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TCA	tricyclic antidepressants
TEAE	treatment-emergent AE
t.i.d	three times daily
TNM	tumor-node-metastasis
ULN	upper limit of normal
ULOQ	upper level of quantification
US	United States
VLD	very limited disease
WBC	white blood cell count
WBRT	whole brain radiotherapy

2 PROTOCOL SYNOPSIS

Title	Safety and clinical activity of nivatrotamab, an anti GD2×CD3 bispecific antibody, in relapsed/recurrent metastatic small-cell lung cancer - An open-label, single-arm, multicenter, phase 1/2 trial
Investigational New Drug (IND)	153595
Investigational site locations	USA and Europe
Co-ordinating Investigator	[redacted] [redacted] UPMC Hillman Cancer Center 5150 Centre Ave. 5th Floor Pittsburgh, PA 15232
Sponsor	Y-mAbs Therapeutics Inc. 230 Park Avenue, Suite 3350 New York, NY 10169 USA
Trial ID	402
Trial design	This is an open-label, multicenter, phase 1/2 trial with the aim to assess the safety and tolerability of increasing doses of nivatrotamab administered subcutaneously (SC) in patients with small-cell lung cancer (SCLC). The study will include a phase 1 dose escalation part to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D). This will be conducted following a modified Bayesian Optimal Interval Design (mBOIN) design. For the purpose of dose escalation, dose-limiting toxicities (DLTs) will be collected and assessed for a period of 28 days (the DLT evaluation period). A phase 2 dose expansion part will follow the phase 1 dose escalation. In phase 2, patients will be stratified according to whether they have platinum -sensitive or platinum-resistant SCLC. Phase 2 will assess the long-term safety and tolerability of nivatrotamab as well as the clinical activity of nivatrotamab when administered at the obtained MTD/RP2D in phase 1.

Figure: Trial design outline



* excluding toxicities clearly related to disease progression or intercurrent illness.

Patient population

The patient population for phase 1 of the trial will consist of patients with relapsed extensive or limited stage SCLC regardless of platinum sensitivity. Patients will be eligible after failure or intolerance of first-line platinum-containing treatment but not more than 3 lines of systemic therapy. Patients must be at least 18 years of age; however, there is no upper age limit as long as the patient meets the criteria for patient selection.

In phase 2, patients will be stratified into 2 groups based on whether they have platinum-sensitive or platinum-resistant disease. Platinum-sensitive disease is defined as a platinum-free interval of ≥90 days post last dose of frontline chemotherapy; platinum-resistant disease is defined as a platinum-free interval of <90 days.

Objectives

Primary Objective

Phase 1

- To determine the MTD and the RP2D of nivatrotamab
- To assess the safety and tolerability of different doses of nivatrotamab

Phase 2

- To assess the long-term safety of nivatrotamab administered at RP2D

	Secondary Objectives ***Phase 1*** • To assess the anti-tumor activity of nivatrotamab • To assess the pharmacokinetics (PK) of different doses of nivatrotamab • To assess the development of anti-drug antibodies to nivatrotamab ***Phase 2*** • To assess the anti-tumor activity of nivatrotamab • To assess the development of anti-drug-antibodies (ADA) against nivatrotamab **Exploratory Objectives** ***Phase 1 and Phase 2*** To explore GD2 expression from tumor tissue (optional)

Endpoints	**Primary Endpoints**
	Phase 1
	• The MTD (defined by a modified Bayesian Optimal Interval Design [mBOIN]) and the RP2D of nivatrotamab
	• The overall incidence and severity of adverse events (AEs) for different doses of nivatrotamab
	
	Phase 2
	• Incidence and severity of AEs for nivatrotamab dosed at RP2D
	
	Secondary Endpoints
	Phase 1
	• Anti-tumor activity
	  o Measured according to the response evaluation criteria in solid tumors (RECIST) version 1.1
	  ▪ Objective response rate (ORR)
	  ▪ Disease control rate (DCR): complete response (CR) + partial response (PR) + stable disease (SD) as well as the proportion of patients in disease control at 4, 8, 16, and 24 weeks
	  ▪ Duration of response (DoR)
	  ▪ Progression-free survival (PFS)
	  o Measured according to the immune response evaluation criteria in solid tumors (iRECIST)
	  ▪ iORR

	▪ iDCR: iCR + iPR + iSD as well as the proportion of patients in disease control at 4, 8, 16, and 24 weeks ▪ iDoR ▪ iPFS o Overall survival (OS) • PK of different doses of nivatrotamab • Proportion of patients who develop anti-drug-antibodies at any time ***Phase 2*** • Anti-tumor activity o Measured according to RECIST version 1.1 ▪ ORR ▪ DCR: CR + PR + SD as well as the proportion of patients in disease control at 4, 8, 16, and 24 weeks ▪ DoR ▪ PFS o According to iRECIST ▪ iORR ▪ iDCR: iCR + iPR + iSD as well as the proportion of patients in disease control at 4, 8, 16, and 24 weeks ▪ iDoR ▪ iPFS o OS • Proportion of patients who develop anti-drug-antibodies at any time **Exploratory Endpoints** ***Phase 1 and Phase 2*** Assessment of GD2 expression, from paraffin embedded tumor tissue (optional)
Patient selection criteria	**Inclusion criteria** 1. Signed and dated informed consent has been provided prior to any trial-related procedures. 2. Patient willing and able to comply with the trial protocol 3. Age ≥18 years at the time of informed consent 4. Histologically or cytologically proven SCLC. Radiographical relapse/progression after minimum 1 line of platinum-containing chemotherapy with PR or CR as the best response (only applicable for phase 2) and not more than 3 prior lines of therapy 5. Measurable disease according to RECIST v1.1

	6. Eastern Cooperative Oncology Group (ECOG) performance status 0–1 7. Expected survival >3 months 8. Platelet counts ≥100,000 cells/mm^3 9. Hemoglobin ≥9 g/dL 10. Absolute neutrophil count (ANC) ≥1000 cells/mm^3 11. Adequate liver function defined by aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) ≤3 × upper limit of normal (ULN), and serum bilirubin ≤1.5 × ULN with the following exceptions a. In patients with documented liver metastases, AST, ALT, and ALP ≤5 × ULN and serum bilirubin ≤1.5 × ULN 12. Adequate renal function with serum creatinine ≤1.5 mg/dL or creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault equation 13. Serum albumin >3.0 g/dL 14. Women of child-bearing potential must agree to appropriate contraception during treatment and for a period of 30 days after the last dose of study drug. Fertile male patients must agree to the use of condoms during treatment and for a period of 30 days after the last dose of the investigational medicinal product (IMP). For a sterilized male patient to be exempt from the requirement to use contraception after IMP treatment, he must have undergone surgical sterilization (vasectomy). **Exclusion criteria** 1. Systemic chemotherapy, radiotherapy, immunotherapy, or major surgery administered within 3 weeks prior to the first planned dosing of the IMP per protocol 2. Patients receiving any other investigational therapy for their cancer within 3 weeks prior to the first planned dosing of the IMP per protocol 3. Patients who never received platinum-containing regimen for SCLC (defined as less than 2 cycles of platinum doublet) 4. Persistent > grade 1 toxicity from previous treatment with checkpoint inhibitors 5. Any immunosuppressive concomitant medication (i.e., salazopyrine, methotrexate, steroids etc.) 6. Inability to wean off steroid, unless tapered to 0 mg/day minimum 10 days prior to the first treatment in case of prior use 7. Any active, uncontrolled viral, fungal, or bacterial infection

	8. Any medical history within 3 months prior to enrolment with need for anticonvulsant therapy 9. Patients with diagnosis of autoimmune diseases or immunodeficiencies or documented infection with human immunodeficiency virus (HIV) or hepatitis B or C virus (active) 10. Previous autologous stem cell transplantation or solid organ transplantation 11. Active heart disease including myocardial infarction within the last 6 months before first dose. This includes cardiac insufficiency with left ventricular ejection fraction (LVEF) <50% 12. Active CNS metastases. Patients with treated CNS metastases are eligible if they are clinically stable without any new neurological symptoms and if there is no radiological evidence of new or enlarging CNS metastases. CNS-directed treatment (surgery, radiation) must be completed 4 weeks prior to the first IMP administration. Furthermore, patients are excluded if they have: • Leptomeningeal carcinomatosis • Uncontrolled seizures. Patients with known seizure are eligible if they are stable and have been without seizure 4 weeks prior to the first IMP administration 13. Patients who experienced severe or recurrent (>grade 2) immune-mediated AEs or IRRs, including those that lead to permanent discontinuation while on treatment with immune-oncology agents 14. Prior treatment with anti-GD2 antibody or bispecific antibodies 15. Patients with Limited Disease (LD), who are candidates for local or regional therapy 16. Impending need for palliative radiotherapy or surgery for pathological fractures and/or for medullary compression up to 3 weeks prior to the first planned dosing of the IMP per protocol (palliative radiation for other reasons within 2 weeks) 17. History of other active malignancy within the past 3 years prior to the first planned dosing of the IMP per protocol (excluding non-melanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ of the breast, incidental prostate cancer (T1a, Gleason score ≤ 6, prostate specific antigen (PSA) less than 0.5 ng/ml) 18. Patients with a significant intercurrent illness (any ongoing serious medical problem unrelated to cancer or its treatment) that is not covered by the detailed exclusion criteria and that is expected to

	interfere with the action of the trial IMP or significantly increase the severity of the toxicities experienced from trial treatment 19. Patients who are pregnant or breastfeeding 20. Patients with a body weight of < 45 kg 21. Patients with prior orthostatic hypotension
Methodology	**Phase 1 (dose escalation):** The dose escalation phase will consist of up to 13 cycles (Cycles 1 to 13), each cycle being of 14 days' duration. Thus, patients will receive up to 26 weeks of treatment. In Cycle 1, [redacted] Intermediate dose levels can be introduced at any time after discussion with the data monitoring committee (DMC). There will be 13 treatment cycles, each cycle being of 2 weeks' duration. Thus, patients will receive up to 26 weeks of treatment. The dose escalation will be conducted following an mBOIN design. It will consist of 2 stages: the initial accelerated titration stage followed by a standard titration stage. In the accelerated titration stage, patients will be recruited and treated in single-patient cohorts. These single-patient cohorts may optionally be expanded with up to 2 additional patients for the purpose of obtaining additional PK and/or pharmacodynamic data. The accelerated titration stage will end and the standard titration stage begin if either, a) dose level 3 is reached, or b) during the DLT evaluation period (28 days), a patient is observed with i) any grade ≥ 2 AE (excluding toxicities clearly related to disease progression or intercurrent illness), or ii) a protocol-defined DLT, whichever occurs first. In the standard titration stage, patients will be allocated to dose-levels typically in cohorts of 3. However, as the mBOIN design allows cohort-sizes to vary, actual cohort sizes may differ from 3.

	Determination of MTD and RP2D: The mBOIN-based MTD will be preliminarily estimated statistically as the dose level with the observed DLT rate closest to the target toxicity level (i.e., 28%). After the mBOIN dose -escalation algorithm has been completed, the DMC and the Sponsor will determine the MTD and the RP2D. The selection of the RP2D will balance the frequency and severity of AEs with any observed dose response for clinical activity. It will be based on a review of the available safety information, including AEs and safety laboratory values, relevant PK data, and observations made after the end of the DLT evaluation period. The RP2D may not exceed the MTD. For the purpose of dose escalation, DLTs will be collected and assessed throughout Cycles 1 and 2, covering a treatment period of 4 weeks. This will allow for the evaluation of up to 3 IMP administrations. **Phase 2 (dose expansion):** In phase 2, the RP2D will be used to further assess safety and tolerability, as well as the clinical activity of nivatrotamab.
Number of patients (planned)	Up to 39 patients are planned to be dosed in phase 1 (dose escalation) and 30 additional patients in phase 2 (dose expansion). No more than 69 patients in total will be dosed in the trial.
Investigational Medicinal Product (IMP)	For this trial, the Sponsor, Y-mAbs, will provide nivatrotamab, 2 mg/mL. No other medicinal products or auxiliary medicinal products will be provided by Y-mAbs. The IMP, nivatrotamab, will be administered SC according to the treatment schedule.
Trial period(s) and duration	Pre-treatment evaluations should be completed within 21 days of the start of treatment. The dose escalation and expansion phases will consist of 13 cycles (Cycles 1 to 13), each cycle being of 14 days' duration with a 12-month follow-up after the end of treatment. It is estimated that at least 24 months will be needed to recruit the planned number of patients. The recruitment periods are estimated to be at least 18 months for phase 1 and 6 months for phase 2.
Statistical considerations	Up to 39 patients may be included in the dose escalation phase (phase 1). This number includes up to 10 additional patients who may be added to any dose-level in this phase. DLTs observed during the DLT evaluation period will be listed and summarized in a table by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The

information from the DLTs will be used to guide the escalation and de-escalation rules as per the mBOIN-design and ultimately determine the MTD.

Upon completion of the mBOIN-design, the MTD is preliminarily estimated as the dose for which the isotonic estimate of the DLT rate is closest to the target toxicity level. If there are ties, either the highest dose level when the estimate of the DLT rate is smaller than the target or the lowest dose level when the estimate of the DLT rate is greater than the target, will be selected from the ties.

The overall observation period for safety analyses (AEs) will be divided into 3 parts:

- Pre-treatment period: From the day of the patient's informed consent to the day before the first dose of nivatrotamab
- On-treatment period: From the day of the first dose of nivatrotamab to 30 days after the last dose of nivatrotamab
- Post-treatment period: From 31 days after the last dose of nivatrotamab and thereafter

Descriptive statistics will be presented for baseline values, absolute values, and changes from baseline in safety laboratory parameters. Vital signs will be listed. Abnormal electrocardiogram (ECG) observations will be listed and summarized. Clinical activity of nivatrotamab will be based on imaging data, response evaluation (according to both RECIST 1.1 and iRECIST), PFS, DoR, and OS. All imaging data will be listed. The OR rate will be presented including corresponding, for binomial distribution, exact 95% confidence intervals. The DCR as well as proportions of patients in disease control at 4, 12, and 28 weeks (± 7 days for each of the 3 timepoints) will be analyzed and presented in the same way as OR. PFS will be derived for all patients and presented graphically as well as summarized using survival analysis methods: distribution functions will be estimated using the Kaplan-Meier technique and plotted. The Kaplan-Meier quartile estimates of PFS including 2-sided 95% confidence intervals will be presented. The DoR will be calculated, censored, and presented in the same way as PFS. OS will be analyzed using the same Kaplan-Meier methodology as for PFS.

	Immunogenicity data will be listed and positive/negative host immune response to nivatrotamab and presence of binding antibodies will be summarized (positive/negative). PK information will also be listed and summarized. GD2 expression from tumor tissue will be summarized and presented graphically. The relationship between GD2 expression from tumor tissue and relative reduction in tumor size from baseline, OR, and PFS may be investigated by graphical presentations as well as non-parametric correlation, linear, logistic, and Cox-regression analyses, as appropriate. Covariates, such as dose may be included in the regression analyses. All statistical tests will be 2-sided with an α (significance) level of 0.05. No subgroups beyond the sensitivity/resistance to previous platinum therapy strata in phase 2 are defined. Missing safety data will in general not be imputed.

3 FLOW CHART

Table 3-1 Schedule of time and events: screening, treatment, and follow-up (phase 1 - dose escalation)

Treatment / Measurements / Evaluations	SCR	Cycle 1 (D1 to 14); 1 cycle = 14 days[a] *DLT evaluation period = 2 cycles*								Cycle 2 to 13				EOT ±4d	Follow up[d]
	<21 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Informed consent	X														
Eligibility check	X														
Demographics and baseline characteristics	X														
Medical history, concomitant illness	X														
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]
Physical examination	X[f]	X	X			X	X			X				X[f]	
Height	X														
Weight	X	X				X			X	X				X	
ECOG score	X	X								X				X	X
Vitals signs	X	X[q]	X[q]	X	X	X[q]	X[q]	X	X	X[q]	X[q]	X	X	X	
HCG in FOCP (urine or blood)	X									X[g]				X	
Urinalysis (dipstick)	X	X				X				X				X	
Cranial and Spinal MRI[h]	X														
ECG	X	X[s]	X			X[s]	X			X[s]	X				
Echocardiogram/MUGA	X								X[i]				X[i]		
Hospitalization[j]		X	X			X	X			X	X				
Premedication		X	X			X	X			X	X				
[redacted]		[redacted]													
[redacted]						X				X					
PK, see Table 8-1		X	X	X	X	X	X	X	X	X					
AE (CTCAE version 5)	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRS grading[l]		X	X	X	X	X	X	X	X	X	X	X	X		
ICE score[l]		X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistries	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Treatment / Measurements / Evaluations	SCR	Cycle 1 (D1 to 14); 1 cycle = 14 days[a] *DLT evaluation period = 2 cycles*								Cycle 2 to 13				EOT ±4d	Follow up[d]
	<21 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Clinical activity assessment[m] CT (baseline + from Cycle 3)	X													X[n]	X[o]
IL-6 assessment[r] (Dosing Day+1)		X	X				X				X				
ADA (including predose) [p]		X				X				X				X	

a: In cases of toxicities, for patients who remain eligible for further treatment, a treatment delay of up to 3 weeks is acceptable to allow for resolution of ≥ grade 3 hematological and non-hematological toxicities (that do not meet the treatment discontinuation criteria) down to ≤ grade 2 or returned to baseline value at study entry (e.g. lab values).

b: Cycles 2 (inpatient Days 1 and 2) and 3 only, unless patient is hospitalized due to cytokine release syndrome (CRS)

c: Cycle 2 only

d: All patients to be followed up for safety reporting for 30 days after the last investigational medicinal product (IMP) dosing. Thereafter, long-term safety will be recorded by registration of related SAEs up to 12 months after the last dose. Vital status and disease progression for follow up on progression-free survival (PFS) and overall survival (OS) will be up to 12 months after the last dose. The Investigator should collect CT scan reports for tumor assessments every 8 weeks or according to the local standard of care. The FU assessments can be done locally at the referral site.

e: This will only include anti-cancer therapy.

f: Physical examination at screening and the EOT visit should include a neurological examination.

g: Every second cycle (e.g., Cycle 2, 4, 6, 8, 10, and 12)

h: For baseline. In addition, an MRI must be performed if a patient develops a central nervous system (CNS) AE ≥ grade 2.

i: Echocardiogram/MUGA to be performed on Day 11 of treatment cycle 1, and Day 4 of cycle 2. Assessment must be analyzed and reviewed by Investigator prior to dosing in cycle 2 and cycle 3

j: Mandatory 48 hours hospitalization in Cycles 1 and 2; optional thereafter (pending clinical signs of possible CRS).

From Cycle 3 onward, the minimum patient monitoring time following dosing will be 6 h; the patient may be observed for this duration as an outpatient or be hospitalized depending on AEs and Investigator's judgement.

k: All AEs (including SAE, and AESIs) should be reported from the signing of the informed consent until 30 days after the patient's last dose of IMP. Thereafter and during the follow-up period, only SAEs considered related to IMP, study procedures and secondary malignancies (regardless of causality) should be reported. DLTs should be reported from the first dose of IMP and the following 28 days.

l: CRS grading and ICE score should be performed predose on dosing days and once per day when the patient is attending the ward for the first 3 cycles, thereafter only if clinically indicated. If the ICE score decreases from baseline, neurotoxicity should be assessed with the use of the ICANS grading system (see section 7.2.4).

m: CT scan of the neck, chest, and abdomen at screening and Week 4, 8, 16, and 24, with an assessment window of ±4days. Confirmatory scanning for patients who have obtained PR or CR will be undertaken approximately 4 weeks after the initial response.

n: Only if more than 6 weeks since last CT scan

o: Assessment of response by the Primary Investigator (progression and survival).

p: Pre-dose on Day 1 and 8 of Cycle 1, Day 1 of Cycles 2-13, and EOT.

q: Vital signs to be monitored and registered every 2 hours on Day 1 and Day 2 of cycle 1 and cycle 2 during daytime and every 4 h during nighttime.

r: Cycle 1 day 1 the IL-6 sample must be taken pre-dose (baseline), all other IL-6 samples should be taken the day after IMP administration (dosing day +1) and should be taken at the same time of the day (±60 min)

s: ECG performed pre-dose on dosing days.

Table 3-2 Schedule of time and events: phase 2 (dose expansion)

Treatment / Measurements / Evaluations	**SCR**	**Cycle 1 (D1 to 14); 1 cycle = 14 days[a]** *DLT evaluation period = 2 cycles*								**Cycle 2 to 13**				**EOT ±4d**	**Follow up[d]**
	<21 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Informed consent	X														
Eligibility check	X														
Demographics and baseline characteristics	X														
Medical history, concomitant illness	X														
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]
Physical examination	X[f]	X	X			X	X			X				X[f]	
Height	X														
Weight	X	X				X			X	X				X	
ECOG score	X	X								X				X	X
Vitals signs	X	X[q]	X[q]	X	X	X[q]	X[q]	X	X	X[q]	X[q]	X	X	X	
HCG in FOCP (urine or blood)	X									X[g]				X	
Urinalysis (dipstick)	X	X				X				X				X	
Cranial and Spinal MRI[h]	X														
ECG	X	X[s]	X			X[s]	X			X[s]	X				
Echocardiogram/MUGA	X								X[i]				X[i]		
Hospitalization[j]		X	X			X	X			X	X				
Premedication		X	X			X	X			X	X				
[redacted]		[redacted]													
[redacted]						X				X					
PK, see Table 8-1		X	X							X					
AE (CTCAE version 5)	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRS grading[l]		X	X	X	X	X	X	X	X	X	X	X	X		
ICE score[l]		X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistries	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical activity assessment[m] CT (baseline + from Cycle 3)	X													X[n]	X[o]
IL-6 assessment[r] (Dosing Day+1)		X	X				X				X				

Treatment / Measurements / Evaluations	SCR	Cycle 1 (D1 to 14); 1 cycle = 14 days[a] *DLT evaluation period = 2 cycles*								Cycle 2 to 13				EOT ±4d	Follow up[d]
	<21 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
ADA (including predose) [p]		X				X				X				X	

a: In cases of toxicities, for patients who remain eligible for further treatment, a treatment delay of up to 3 weeks is acceptable to allow for resolution of ≥ grade 3 hematological and non-hematological toxicities (that do not meet the treatment discontinuation criteria) down to ≤grade 2 or returned to baseline value at study entry (e.g. lab values).

b: Cycles 2 (inpatient Days 1 and 2) and 3 only, unless patient is hospitalized due to cytokine release syndrome (CRS).

c: Cycle 2 only.

d: All patients will be followed up for safety reporting for 30 days after the last IMP dosing. Thereafter, long-term safety will be recorded by registration of related SAEs up to 12 months after the last dose. Vital status and disease progression for follow up on PFS and OS will be up to 12 months after the last dose. The Investigator should collect CT scan reports for tumor assessments every 8 weeks or according to the local standard of care. The FU assessments can be done locally at the referral site.

e: This will only include anti-cancer therapy.

f: Physical examination at screening and the EOT visit should include a neurological examination.

g: Every second cycle (e.g., Cycle 2, 4, 6, 8, 10, and 12).

h: For baseline. In addition, an MRI must be performed if a patient develops a central nervous system (CNS) AE ≥ grade 2.

i: Echocardiogram/MUGA to be performed on Day 11 of treatment cycles 1, and Day 4 of cycle 2. Assessment must be analyzed and reviewed by investigator prior to dosing in cycle 2 and cycle 3.

j: Mandatory 48 hours hospitalization in Cycles 1 and 2; optional thereafter (pending clinical signs of possible CRS).

From Cycle 3 onward, the minimum patient monitoring time following dosing will be 6 h; the patient may be observed for this duration as an outpatient or be hospitalized depending on AEs and Investigator's judgement.

k: All AEs (including SAE, and AESIs) should be reported from the signing of the informed consent until 30 days after the patient's last dose of IMP. Thereafter and during the follow-up period, only SAEs considered related to IMP, study procedures and secondary malignancies (regardless of causality) should be reported. DLTs should be reported from the first dose of IMP and the following 28 days.

l: CRS grading and ICE score should be performed at predose on dosing days and once per day when the patient is attending the ward for the first 3 cycles, thereafter only if clinically indicated. If the ICE score decreases from baseline, neurotoxicity should be assessed with the use of the ICANS grading system (see section 7.2.4).

m: CT scan of the neck, chest, and abdomen at screening and Week 4, 8, 16, and 24, with an assessment window of ±4days. Confirmatory scanning for patients who have obtained PR or CR will be undertaken approximately 4 weeks after the initial response.

n: Only if more than 6 weeks since last CT scan.

o: Assessment of response by the Primary Investigator (progression and survival)

p: Pre-dose on Day 1 and 8 of Cycle 1, Day 1 of Cycles 2, 4 and 13, and/or EOT.

q: Vital signs to be monitored and registered every 2 h on Day 1 and Day 2 of cycle 1 and cycle 2 during daytime and every 4 h during night time

r: Cycle 1 day 1 the IL-6 sample must be taken pre-dose (baseline), all other IL-6 assessments should be taken the day after IMP administration (dosing day +1) and should be taken at the same time of the day (±60 min)

s: ECG performed pre-dose on dosing days.

4 MEDICAL AND SCIENTIFIC JUSTIFICATION FOR THE TRIAL

4.1 Disease Background

Lung cancer is the second most common cancer in both men and women with an estimate of more than 200,000 new cases diagnosed annually in the US [1]. Small-cell lung cancer (SCLC) accounts for approximately 13% to 15% of all lung cancers, hence about 30,000 cases per year in the US [1-4]. This high-grade neuroendocrine tumor is characterized by rapid growth and early development of metastases to both regional lymph nodes and distant sites, including the central nervous system (CNS) [5].

SCLC is often classified into staging systems, for example, limited stage disease (LD) vs. extensive stage disease (ED) or the tumor-node-metastasis (TNM) system [6]. Stage is the major prognostic factor for SCLC; however, a diagnosis of SCLC generally carries with it a poor prognosis: 20% to 40% of LD and less than 5% of ED patients survive 2 years or more [7].

At presentation, only a minority of patients (~5%) have operable TNM stage I disease (very limited disease, VLD); this group has the best prognosis with possibility of cure and a 5-year overall survival (OS) of 50% [8]. About 25% of patients present with unilateral thoracic involvement, TNM stages I to III (i.e., LD), allowing for an attempt at controlling the disease with concomitant chemo-radiotherapy, i.e., platinum-etoposide and radiotherapy. Most patients with LD relapse subsequently within 2 years due to lymphatic spread and failure of local therapy. Median survival at 2 years among LD patients varies from 15 to 20 months, with OS being 20% to 40% [4].

The majority of patients (≥70%) present with metastatic disease (i.e., stage IV) or ED, wherein the disease has most often spread within the lung tissue, to lymph nodes, and to the liver, bone, and brain. Patients with such advanced disease have, on average, disease-free survival (DFS) of 5.5 months and median survival of less than 10 months [8]. Five-year survivors are exceedingly rare [9].

Currently, the only approved first-line treatment approach for ED in SCLC is platinum-based chemotherapy with or without the addition of an immune checkpoint inhibitor, namely, atezolizumab or durvalumab [10, 11]. Platinum (cisplatin or carboplatin) remains the cornerstone for the treatment of SCLC of any stage, with high initial responses (including rapid responses and symptomatic improvement) reported in 70% to 80% of patients following first-line platinum- and immunotherapy-based treatment regimens; nevertheless, virtually all SCLC patients with ED develop tumor progression, mostly within 6 months [12, 13].

Until recently, in the second-line setting, the topoisomerase I inhibitor, topotecan, was the only drug approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In randomized clinical trials, topotecan has been associated with overall response (OR) rates of 16.9% to 21.9%, median progression-free survival (PFS) of 3.4 to

3.5 months, and median OS of 7.8 to 8.7 months [14, 15]. Outcomes are particularly poor among patients with platinum-resistant disease, generally indicated by tumor progression within 90 days of completion of first-line therapy [16]; the OR rates in these patients are usually below 10% [17]. In a typical clinical population, the response rate thus rarely exceeds 15%.

There is no globally approved therapeutic agent for patients with progressive SCLC following second-line treatment. However, for this patient population, FDA granted accelerated approvals to 2 compounds: nivolumab in August 2018 (based on the CheckMate 032 trial; ClinicalTrials.gov id: NCT01928394) and pembrolizumab in June 2019 (based on the Keynote trials 158 [NCT02628067] and 028 [NCT02054806]). Third-line treatment with checkpoint inhibitors are associated with benefit in a small percentage of patients, primarily in the platinum-sensitive subpopulation, with objective response rates (ORRs) ranging from 11% to 33% in clinical trials [18, 19]. Unfortunately, despite such response rates, most patients treated in these trials did not appear to benefit, as evidenced by median PFS of only 1.4 to 2 months. As a consequence to neither of the trials meeting the predefined endpoint of OS, the indication of checkpoint inhibitors in 3rd line for SCLC was subsequently withdrawn in December 2020 (nivolumab) [20] and March 2021(pembrolizumab) [21].

Recently, FDA granted accelerated approval to the RNA polymerase II inhibitor, lurbinectedin, as monotherapy for patients with metastatic SCLC with disease progression during or after platinum-based chemotherapy [22]. Efficacy of lurbinectedin was demonstrated in the PM1183-8B-005-14 trial (ClinicalTrials.gov id: NCT02454972), a multicenter open-label, multi-cohort (basket) trial enrolling 105 patients with metastatic SCLC. Among the 105 patients, the ORR was 30% with a median response duration of 5.1 months. The median PFS was 3.9 months and the 6-month PFS rate was 33.6%. In the subgroup of patients with platinum-resistant disease, the ORR was 22% (45% in platinum-sensitive patients), median PFS was 2.6 months, and the 6-month PFS rate was 18.8%. At a median follow-up of 17.1 months, the median OS with lurbinectedin was 9.3 months; the 12-month OS rate was 34.2%. The grade 3–4 adverse event (AE) frequency was 34% and events comprised mainly myelosuppression (hematological toxicities).

4.2 Rationale for the Development of GD2×CD3 Bispecific Antibody for the Treatment of SCLC

SCLC develops early resistance to conventional treatments, therefore, showing early progression and lack of sensitivity to further pharmacological treatment. As such, SCLC had been considered “a graveyard for drug development,” with chemotherapy remaining the standard treatment for first- and second-line management until quite recently. Thus, there is a considerable need to develop novel therapeutic approaches in SCLC.

It has been known for many years that SCLC cells, similar to those of many other tumors of neural crest origin, almost uniformly express GD2, a cell-surface glycolipid disialoganglioside [23, 24]. Recently, dinutuximab (Unituxin®), a chimeric anti-GD2 IgG1 (immunoglobulin G, subtype 1) antibody was tested in a clinical phase 3 trial (the DISTINCT trial, ClinicalTrials.gov id:

NCT03098030) in relapsed SCLC patients. In this trial, irinotecan or topotecan as monotherapy or irinotecan in combination with dinituximab was investigated. The trial failed to meet its OS endpoint. However, dinituximab was only administered once every 3 weeks at a dose of 10 mg/m^2 or approximately 18 mg total dose. This dose frequency likely was insufficient and represents only 14% of dose intensity as compared to the labelled dose schedule (17.5 mg/m^2 × 4 per treatment cycle for the label indication of neuroblastoma) [25]. The most common AEs in this trial were pain, thrombocytopenia, lymphopenia, infusion-related reactions (IRRs), hypotension, increased alanine aminotransferase (ALT), capillary leak syndrome, neutropenia as well as electrolyte disturbances and gastrointestinal symptoms.

Naxitamab (3F8), an anti-GD2 antibody, has been developed by Y-mAbs Therapeutics, Inc. (hereafter, Y-mAbs) for the treatment of relapsed/refractory neuroblastoma. In November 2020, the biological license application for naxitamab received approval from the FDA. Naxitamab has been shown to localize to all extracranial sites of the SCLC disease. Furthermore, using identical complementarity-determining region (CDR), Y-mAbs has developed an anti-GD2×CD3 T cell-redirecting bispecific antibody (BiClone^{TM}). BiClone comprises a novel tetravalent structure, humanized format, with an introduced mutation to reduce FcgR binding while retaining FcRn binding. Advantages of using the BiClone format include (i) possibility of using a very low dose (mcg range) and hence, a likely better safety profile; (ii) possibility of using a more frequent dosing regimen, which may potentially improve efficacy outcomes; and (iii) a subcutaneous (SC) administration approach, which may reduce the cytokine release syndrome (CRS). CRS is a key common dose-limiting side effect observed with CD3-based bispecific antibodies administered by the intravenous (IV) route. Pre-clinical efficacy of the BiClone format has been demonstrated *in vitro* in SCLC cell lines (e.g., NCI-H524, NCI-H69 [unpublished data]) and *in vivo* in neuroblastoma and melanoma xenograft models [26].

4.3 Nivatrotamab Profile

Nivatrotamab is a T-cell engaging antibody utilizing the BiClone format which is currently being evaluated in human clinical trials.

4.3.1 Non-clinical Data for Nivatrotamab

[redacted]

[redacted]

[redacted]

4.3.3 Nivatrotamab Dose Selection and Administration Schedule

[redacted]

[redacted]

4.4 Choice of Trial Population

For decades, the landscape of treatment options for patients with SCLC has been dominated by platinum-containing chemotherapeutic regimens, and chemotherapy remains the gold standard first line therapy. After disease progression, second line options have been associated with a modest chance of response and significant toxicity, and survival for the patient group with ED

has not improved significantly over the past many years. Thus, there is a strong rationale for exploring new treatment modalities in SCLC.

This trial will be conducted in 2 phases (phases 1 and 2, see section 6.2). The patient population for phase 1 of the trial will consist of patients with relapsed extensive or limited stage SCLC regardless of platinum sensitivity. Patients will be eligible after failure or intolerance of first-line platinum-containing treatment but not more than 3 lines of systemic therapy. Patients must be at least 18 years of age; however, there is no upper age limit as long as the patient meets the criteria of patient selection (see inclusion criteria, section 6.3.2.1). See also section 6.3.2.2 (exclusion criteria). In phase 2, patients will be stratified into 2 groups based on whether they have platinum sensitive or resistant disease.

In the present protocol, platinum-sensitive disease is defined as a platinum-free interval of ≥90 days post last dose of frontline chemotherapy; platinum-resistant disease is defined as a platinum-free interval of ≤90 days post last dose of frontline chemotherapy [16].

4.5 Choice of Trial Design and Dosing Strategy

This proposed trial is the second clinical trial with nivatrotamab. In this trial, a change in the route of administration from IV infusion to SC administration has been proposed to reduce possible IRRs, in particular CRS, which are known to occur with other bispecific, T-cell engaging mAbs; such reactions have also been seen in trial 18-034, the FIH trial with nivatrotamab. Based on the availability of safety data from the trial 18-034, a modified Bayesian Optimal Interval (mBOIN) design has been chosen for the phase1 part of the trial in order to identify the recommended phase 2 dose (RP2D) for further SC administration of nivatrotamab (in phase 2). In order to evaluate safety to direct exposure in a small number of patients, a flat-dose strategy has been chosen. The start dose will be lower than the dose in trial 18-034 that has been deemed safe by the internal review board at Memorial Sloan Kettering Cancer Center, New York, USA, the location of the FIH (18-034) trial.

The mBOIN design is similar to the standard 3+3 as well as 3+3+3 study designs [28]. Some features of the BOIN design include [29]:

- BOIN is devised to identify the MTD, while controlling the risks of observing DLTs.
- BOIN provides a better estimate of the MTD than the traditional 3+3 design, partly because BOIN allows dose levels to be revisited.
- The number of patients in a cohort may differ from 3, allowing flexibility in the conduct of the trial.

In this trial, the BOIN design will be modified to:

- Have an accelerated and standard titration part in phase 1 (the dose escalation phase)
- Allow stopping at a dose level with 6 DLT-evaluable patients

With a target toxicity level of 28 %, the design obtains characteristics that are similar to the 3+3+3 design, e.g., there are similarities in how 2 DLTs in 6 or 9 patients are addressed in Table 6-3.

See section 19, Appendix 1 for more details on the mBOIN design to be used in this trial.

To collect further data on the clinical activity, safety, tolerability, and PK, the selected dose (RP2D) from the dose escalation phase will be studied in phase 2 of the trial.

4.6 Benefit–Risk Assessment

Patients with relapsed/refractory SCLC have a marked unmet need with an estimated OS of less than 1 year. Thus far, only a few treatment options have been approved for use in patients subsequent to failure of or progression following frontline therapy.

The importance of T-cells has been substantiated by the efficacy of checkpoint inhibitors (anti-programmed death-ligand 1 [PDL1]) in the frontline setting, including in SCLC. Furthermore, GD2 is a membrane molecule expressed on the majority of SCLC cells. Hence, targeting SCLC through GD2 via a T-cell redirecting approach will potentially add benefit to a population failing the currently available treatment options.

Based on data from the 18-034 (FIH) trial and experience with other products having a similar mode of action, the safety profile of nivatrotamab is considered manageable with appropriate risk mitigation measures in place. The key potential risks are CRS, including potential CNS effects and GD2-mediated toxicities (e.g., hypotension and neuropathic pain).

In the FIH trial 18-034, where patients were exposed to nivatrotamab via the IV route, 2 subjects at dose level 6 (9.3 mcg/kg/cycle) experienced SAEs that were deemed related to treatment and evaluated as DLTs, namely, CTCAE grade 3 syncope and grade 3 sympathetic nerve neuropathy with orthostatic hypotension. These DLTs may represent a GD2-mediated neuropathy. No reports of severe pain (≥CTCAE grade 3) were reported. CRS events were graded in accordance with the grading system published by Lee et al. 2014[30] rather than CTCAE grading. Five patients at dose levels 4–6 experienced CRS with 2 events being serious: 1 grade 2 event at dose level 5 and 1 grade 3 event at dose level 6. All patients with CRS recovered. The types of CNS events seen due to the immune response with other CD3-engagers (e.g., seizures, speech disorders, confusion) were not observed. Other findings of note in the 18-034 trial include 3 subjects at dose levels 5–6 with SAEs of decreased lymphocyte count (CTCAE grade 4) considered related to nivatrotamab. The events resolved within 2 to 5 days and may be due to the migration of T lymphocytes into tissues following activation. Decreased lymphocyte count was the only CTCAE grade 4 event considered related to nivatrotamab. No AEs had a fatal outcome.

With respect to the safety of patients in this study, the starting dose is kept at a lower level than the dose level considered safe in the 18-034 trial. Administration of nivatrotamab will be performed in a clinical setting with immediate access to equipment and appropriately qualified

staff for resuscitating and stabilizing individuals in case of an acute emergency. Subjects will be closely monitored with hospitalization until 48 h after dosing for at least the first 2 treatment cycles in phase 1. [redacted] An external DMC will further assure patient safety and provide recommendations on dose escalation. Dosing of nivatrotamab will also be via the SC route, which may reduce the risk of developing both CRS and GD2-mediated toxicities.

Overall, the anticipated benefits for patients in the target indication are considered to outweigh the potential risks.

5 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Trial Objectives

5.1.1 Primary Objective

Phase 1

- To determine the MTD and the RP2D of nivatrotamab
- To assess the safety and tolerability of different doses of nivatrotamab

Phase 2

- To assess the long-term safety of nivatrotamab administered at the RP2D

5.1.2 Secondary Objectives

Phase 1

- To assess the anti-tumor activity of nivatrotamab
- To assess the PK of different doses of nivatrotamab
- To assess the development of anti-drug antibodies to nivatrotamab

Phase 2

- To assess the anti-tumor activity of nivatrotamab
- To assess the development of anti-drug-antibodies against nivatrotamab

5.1.3 Exploratory Objectives

Phases 1 and 2

- To explore GD2 expression from tumor tissue (optional)

5.2 Endpoints

5.2.1 Primary Endpoints

Phase 1

- The MTD (defined by an mBOIN design) and the RP2D of nivatrotamab
- The overall incidence and severity of AEs for different doses of nivatrotamab

Phase 2

- Incidence and severity of AEs for nivatrotamab dosed at the RP2D

5.2.2 Secondary Endpoints

Phase 1

- Anti-tumor activity
    - Measured according to the response evaluation criteria in solid tumors (RECIST) version 1.1
        - ORR
        - Disease control rate (DCR): complete response (CR) + partial response (PR) + stable disease (SD) as well as the proportion of patients in disease control at 4, 8, 16, and 24 weeks
        - Duration of response (DoR)
        - PFS
    - Measured according to the immune response evaluation criteria in solid tumors (iRECIST)
        - iORR
        - iDCR: iCR + iPR + iSD as well as the proportion of patients in disease control at 4, 8, 16, and 24 weeks
        - iDoR
        - iPFS
    - OS
- PK of different doses of nivatrotamab
- Proportion of patients who develop anti-drug-antibodies at any time

Phase 2

- Anti-tumor activity
    - Measured according to RECIST version 1.1
        - ORR
        - DCR: CR + PR + SD as well as the proportion of patients in disease control at 4, 8, 16, and 24 weeks
        - DoR
        - PFS

- Measured according to iRECIST
  - iORR
  - iDCR: iCR + iPR + iSD as well as the proportion of patients in disease control at 4, 8, 16, and 24 weeks
  - iDoR
  - iPFS
- OS

- Proportion of patients who develop anti-drug-antibodies at any time

5.2.3 Exploratory Endpoints

Phase 1 and Phase 2

Assessment of GD2 expression from archived paraffin-embedded tumor tissue (optional)

6 DESCRIPTION OF TRIAL DESIGN AND TRIAL POPULATION

6.1 Overall Trial Design

This is an open-label, multicenter, phase 1/2 trial with the aim to assess the safety and tolerability of increasing doses of nivatrotamab administered SC in patients with SCLC.

The study will include a phase 1 dose escalation part to determine the MTD and RP2D (Figure 6-1). This will be conducted following an mBOIN design (section 19, Appendix 1). For the purpose of dose escalation, DLTs will be collected and assessed for a period of 28 days (the DLT evaluation period, see section 6.2.3). Dose escalation rules will be based on the number of patients with DLTs (see section 6.2.1.4).

A phase 2 dose expansion part will follow phase 1 dose escalation. In phase 2, patients will be stratified according to whether they have platinum-sensitive or platinum-resistant SCLC (Figure 6-1). Phase 2 will assess longer-term safety and tolerability nivatrotamab as well as the clinical activity of nivatrotamab when administered at the obtained MTD/RP2D in phase 1.

Up to 39 patients with advanced and/or refractory solid malignancies are planned to be dosed in phase 1 (dose escalation) and 30 additional patients with similar malignancies in phase 2 (dose expansion). No more than 69 patients in total will be dosed in the trial.

Figure 6-1 Trial design outline for the 402 trial

Abbreviations: AE = adverse event; Gr = grade; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose* excluding toxicities clearly related to disease progression or intercurrent illness.

6.2 Overall Trial Plan

6.2.1 Phase 1: Dose Escalation

6.2.1.1 Dose Regimen

The dose escalation phase will consist of up to 13 cycles (Cycles 1 to 13), each cycle being of 14 days' duration. Thus, patients will receive up to 26 weeks of treatment. In Cycle 1 of phase 1, [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted] In addition, there is a possibility to add 2 additional intermediate dose levels. However, if the MTD is not reached and/or the RP2D cannot be established, the Sponsor will evaluate if the dose escalation is to be continued; this will be done after preparing a safety summary and presenting safety and PK data to an external DMC to reach an agreement. Any further dose escalation will be implemented via protocol amendment.

6.2.1.2 Dose Levels

The proposed dose levels in the dose escalation phase are shown in Table 6-2.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: CRS, cytokine release syndrome

6.2.1.3 Dose Escalation Stages

The dose escalation phase will consist of 2 stages: the initial accelerated titration stage followed by a standard titration stage (Figure 6-1).

In the accelerated titration stage, patients will be recruited and treated in single-patient cohorts. These single-patient cohorts may optionally be expanded with up to 2 additional patients for the purpose of obtaining additional PK and/or pharmacodynamic data.

The initial accelerated titration stage will end, and the single-patient cohort mandatorily expanded with (at least) 2 additional patients once either:

- Dose level 3 is reached, or
- During the DLT evaluation period (28 days), a patient is observed with:
  - any grade ≥ 2 AE (excluding toxicities clearly related to disease progression or intercurrent illness), or
  - a protocol defined DLT (section 6.2.3),

  whichever occurs first.

This will mark the end of the accelerated titration stage and the beginning of the standard titration stage. Hereafter, patients will be allocated to dose-levels typically in cohorts of 3. As the mBOIN design allows cohort-sizes to vary, the actual cohort sizes may differ from 3.

In the standard titration stage, cohorts will be allowed to include only 2 patients who are evaluable for DLT, provided that none of the 2 patients have experienced any related, grade ≥3 AE during the DLT evaluation period.

If patients are withdrawn prematurely without having experienced a DLT, they will be considered non-evaluable and may be replaced.

In cohorts that include more than 1 patient in the dose escalation part, there will be sequential enrolment. At a particular dose level, there must be at least 3 days between the first dose of the first patient and the first dose of the subsequent patients in the same cohort.

6.2.1.4 Dose Escalation Rules

The dose escalation will be conducted following an mBOIN design (for further details, see section 19, Appendix 1).

Table 6-3 Phase 1 dose escalation rules based on the number of patients with DLTs

Decision based on the number of patients with DLTs (N_{DLT})	Number of patients evaluable for DLT at the current dose level							
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Escalate if $N_{DLT} \leq$	0	0	0	1	1	1	1	2
Remain on dose level if $N_{DLT} =$	NA	1	1	NA	2	2	2	3
De-escalate if $N_{DLT} \geq$	1	2	2	2	3	3	3	4
Disallow dose-level if $N_{DLT} \geq$	NA	3	3	4	4	4	5	5

Abbreviations: DLT = dose-limiting toxicity; NA = not applicable

It will not be allowed to escalate or de-escalate to dose levels on which an unacceptable level of toxicity has been observed; these dose levels are disallowed, as addressed by the last row in Table 6-3 above.

Dose escalation will be recommended by the DMC and will be determined by the Sponsor's safety committee upon review of the safety data obtained during the DLT evaluation period as well as available data beyond the DLT evaluation period from all patients in the trial. Dose escalation will be allowed when the DMC has recommended the dose and the dosing schedule for the next dose level and the Sponsor's safety committee has approved it.

To better understand the safety, tolerability, PK, pharmacodynamics, or anti-tumor activity of nivatrotamab, up to 10 additional patients in total may be allocated in parallel to dose levels that are considered safe for such allocation (i.e., dose levels at or below the currently investigated one). This could be based on recommendations provided by the DMC. DLT information from patients in such additional cohorts will be taken into account for decisions on the dose level for the next cohort; the dose escalation rules shown in Table 6-3 can still be followed.

When a DLT in such an additional cohort is observed and the updated DLT information on a previously investigated lower dose level leads to decisions that come in conflict with previously taken decisions, the DMC will recommend the dose level for the next cohort. It will be possible to de-escalate from the starting dose, provided it is not disallowed due to toxicity.

6.2.1.5 Stopping Criteria for the Dose Escalation

The dose escalation will stop when either:

- The maximum sample size for phase 1 (N=39) has been reached (section 11.2).
- There are 9 DLT-evaluable patients at the current dose level, and according to the mBOIN rules, the decision is to remain at the same dose level.
- The lowest therapeutic dose is disallowed (i.e., the starting dose is considered too toxic).

The dose escalation may also stop if there are 6 DLT-evaluable patients with ≤1 DLT on the current dose-level, provided that a higher dose-level has been evaluated and the number of DLTs on that higher dose-level leads to a de-escalation.

6.2.1.6 Determination of MTD and RP2D

The mBOIN-based MTD will be preliminarily estimated statistically as the dose level with the observed DLT-rate closest to the target toxicity level (i.e., 28%%), as described in section 11.4.2.

After the mBOIN-based dose-escalation algorithm has been completed, the DMC and the Sponsor will determine the MTD and the RP2D, both of which may differ from the aforementioned preliminary statistical estimate. The RP2D cannot exceed the MTD.

The selection of the RP2D will be based on pharmacokinetic, pharmacodynamic, safety and efficacy data from Phase 1. The selection of RP2D will be informed by exposure-response analyses (cf. Section 11.4.9) and Frequency and severity of AEs will be balanced with any observed dose response for clinical activity. In the absence of compelling results as interpreted by the DMC and the Sponsor, the RP2D will be the highest dose administered that does not exceed the MTD. If there is evidence that a dose level lower than the MTD (which might not have been reached at this stage) has adequate clinical activity (whether determined by imaging data, pharmacodynamics endpoints, or predicted efficacious dose), the DMC and the Sponsor's safety committee may decide that the RP2D has been determined and that the dose escalation may be stopped.

Based on the available data, the DMC may recommend introduction of intermediate dose levels in between the pre-planned dose levels and may also suggest changing the dosing frequency.

6.2.2 Phase 2: Dose Expansion

6.2.2.1 Dose Regimen

In phase 2, the RP2D identified in phase 1 will be used (in order to assess the long-term safety and anti-tumor activity of nivatrotamab at this dose). It will be based on a review of the available safety information, including AEs and safety laboratory values, relevant PK data, and observations made after the end of the DLT evaluation period.

6.2.3 Definition of Dose-limiting Toxicity

DLTs include the following events:

Clinically significant AE (CTCAE version 5.0) or a significant laboratory abnormality (as defined below) that occurs during the DLT assessment period, excluding toxicities clearly related to disease progression or intercurrent illness. The established external, independent DMC will evaluate relatedness of an event in order for it to qualify for a DLT or not.

DLT criteria will be categorized as follows:

1. Thrombocytopenia grade 3 with clinically significant bleeding and neutropenia (i.e., myelosuppression) > grade 3, excluding neutropenia lasting <7 days and
2. Non-hematological toxicities ≥ grade 3, defined as
    a. Grade 3 non-hematological laboratory abnormalities requiring medical intervention, which are not mentioned in the list of exceptions below.
    b. Any non-hematological AE of ≥ grade 3 that is not mentioned in the list of exceptions below.
3. Death occurring during DLT evaluation period, not related to disease progression or complications or intercurrent illness as determined by the DMC
4. Injection site reaction ≥ grade 3
5. Dose delay of >21 days (failure to recover from any toxicity, which results in delayed dosing of the subsequent dose)
6. CRS grade 3 or higher
7. Immune effector cell-associated neurotoxicity syndrome (ICANS) grade 3 or higher
8. Peripheral sensory neuropathy grade 4
9. Peripheral sensory neuropathy grade 3 with no sign of clinical improvement within 21 days as evaluated by the investigator.
10. Pain grade 3 or higher lasting 24 h or more despite optimal analgesic therapy administered according to the local standard of care
11. Febrile neutropenia

12. Any AST/ALT and bilirubin elevation meeting Hy's law criteria (a,b,c and d)
    a. ALT or AST elevation > 3X upper limit of normal (ULN)
    b. Total bilirubin elevation > X2 ULN
    c. Absence of initial findings of cholestasis
    d. No other reason to be found i.e. due to infection (i.e. hepatitis), liver disease or other drug effect

List of exceptions: non-hematological exceptions

The following AEs will not constitute DLTs (however, they should be reported as AEs/SAEs according to the reporting guidelines).

- Grade 3 laboratory values considered not clinically significant
- Grade 3 headache, nausea, diarrhea, and vomiting, persisting for <48 h (with adequate supportive care)
- Grade 3 elevations of ALT/AST ≤ 8 x ULN or baseline ALT/ AST (in case baseline above ULN at study entry) improved to < grade 3 within 14 days)
- Grade 3 hypertension lasting <48 h
- Grade 3 Fever lasting <72 h
- Grade 3 Fatigue lasting < 7 days

AEs that are self-limited and resolve within a short time frame will not constitute DLTs; however, they should be reported as AEs/SAEs according to the reporting guidelines.

For the purpose of dose escalation, DLTs will be collected and assessed throughout Cycles 1 and 2, covering a treatment period of 4 weeks. This will allow for the evaluation of up to 3 investigational medicinal product (IMP) administrations.

DLTs must be entered in the clinical AE report form and reported from the site to the Sponsor within 24 h of the Investigator's first knowledge of the event. In case any of the side effects mentioned in the DLT definitions occur during Cycles 2 to 5 in Phase 1, these will be discussed at the first upcoming preplanned DMC meeting, and the Sponsor's safety committee will evaluate the DMC recommendations for further dosing.

6.2.4 Dose Modifications

Patients developing grade 3 toxicity not meeting the DLT criteria, that is not resolved/decreased to a lower grade within 36 h, will have treatment paused until toxicity is maximum grade 2 or returned to baseline value at study entry (e.g. lab values).

If the grade 3 toxicity is considered clinically significant by the investigator, patients will be planned for continued dosing at one lower dose level (dose level -1). No dose modification indicated for toxicities grade 1-2.

6.2.5 Trial Stopping Rules

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

1) One or more patients experience unexpected, sudden death during the treatment period

2) Treatment related death before the EOT visit

3) SAEs or frequency of AEs that, in the judgement of the Sponsor, are deemed to warrant immediate review by the DMC.

4) Any other safety finding assessed as related to nivatrotamab that, in the opinion of the DMC or Sponsor, contraindicates further dosing of trial patients.

If any of these occur, an immediate cumulative review of safety data with focus on the SAE/ AE in question will be conducted by the DMC to determine whether dosing and further recruitment should be resumed, the protocol modified, or whether the trial should be discontinued. Review and approval of the Sponsor Safety Committee is required for resumption of the trial in case the trial is interrupted due to one of the above-mentioned safety findings.

When applicable, regulatory authorities and ECs/IRBs will be notified of actions taken with the trial.

6.2.6 Recruitment Period

It is estimated that at least 24 months will be needed to recruit the planned number of patients. The recruitment periods are estimated to be at least 18 months for phase 1 and 6 months for phase 2.

6.2.7 Screening/Pre-treatment Evaluation

Pre-treatment evaluations should be completed within 21 days prior to the start of treatment (Day 1 of Cycle 1). Please refer to the screening (SCR) visit in the flowcharts for a summary of the procedures to be undertaken related to screening/pre-treatment evaluation in the trial (section 3).

Procedures to be performed only at screening:

(i) Eligibility check (based on inclusion and exclusion criteria [see section 6.3.2]; the most recent imaging and laboratory assessment must be used to evaluate eligibility)

(ii) Obtaining informed consent (written informed consent must be obtained from each patient within a reasonable time prior to the performance of any trial-related

procedure. Local recommendations regarding handling of informed consent will be followed)

(iii) Recording of medical history (including concomitant disease and smoking history) and data pertaining to demographic and baseline characteristics

Additionally, patients will undergo recording of information on concomitant medication and concurrent procedures, a physical examination (including a neurological examination [see section 8.1.3.1]), assessment of vital signs, height, body weight, Eastern Cooperative Oncology Group [ECOG] performance scoring, β-human chorionic gonadotropin [HCG] test (for pregnancy detection in females of childbearing potential), a 12-lead electrocardiogram (ECG), echocardiogram or multigated acquisition scan (MUGA), computed tomography (CT) scan of the primary tumor site, cranial and spinal magnetic resonance imaging (MRI) to evaluate CNS metastasis, clinical safety laboratory assessments (hematology, coagulation and clinical chemistry), assessment of SAEs, and urinalysis.

Any data that is generated within the screening period and is considered standard of care as per local procedures is permitted to be used for the evaluation of patient eligibility even if the evaluation is performed prior to signing of the informed consent form (see also section 8).

For phase 1, all patients will be locally screened and centrally treatment allocated (see also section 6.2.9). Results needed for inclusion of a patient in the trial must be available before a patient can be declared eligible for the study. Once the results of the screening evaluations become available and the patient is found to meet all eligibility criteria, the Investigator will complete an eligibility form and inform the Sponsor (for review and approval of eligibility of the patient).

6.2.8 Screening Failures and Re-screening

Screening failures are patients who consent to participate in the trial but are not subsequently enrolled to receive the trial treatment. For screening failure patients, the date of informed consent and reason for screening failure along with demographic data and data on any SAEs must be captured in the electronic case report form (eCRF).

Any SAEs must be followed up as described in section 9.

Re-screening of screening failures will be allowed (see section 6.2.10.1 regarding patients re-entering screening). If a patient is re-screened the patient should receive a new patient identifier (ID), i.e. a patient can have multiple screening IDs. If a patient is re-screened the patient must sign a new informed consent form (ICF).

6.2.9 Study Treatment Assignment

This being an open-label trial, the patient, the Investigator, and the Sponsor will know the administered treatment.

6.2.9.1 Phase 1

In phase 1, patients will be treated according to the dose levels indicated in section 6.2.1.2 [redacted] Patients will be allocated to the relevant dose level after completion of screening. The treatment assignment will be coordinated centrally. If an Investigator identifies a patient and confirms that the patient is eligible for enrollment into the study, he/she will accordingly give the Sponsor sufficient notice by sending an eligibility form by email.

The Sponsor will confirm in writing the patient enrollment number and the dose level at which the patient may be treated. The Investigator will complete the prescription form and send it to the pharmacy. The pharmacy will prepare the IMP accordingly.

6.2.9.2 Phase 2

In phase 2, the procedure of treatment assignment will be identical except that a uniform dose level will be administered to all patients (the RP2D). This being an open-label trial, the investigator, the patient, and the Sponsor will know the treatment.

6.2.10 Visit Schedule

6.2.10.1 Phase 1

The visit schedule for phase 1 is summarized in the flow chart in Table 3-1. The calculation of all study visits and time points of assessments are based on Day 1, which is defined as the first day of nivatrotamab injection.

Screening period (Day –20 to Day 0)

For details on the procedures to be performed at screening, see section 6.2.7. All patients who have signed the informed consent form will be recorded on the screening log. A patient is considered as being enrolled into the study as soon as the consent form is signed and will be assigned a unique subject identification number (ID). If a patient is screened but ultimately not treated, the reason will be recorded in the eCRF. A patient can re-enter screening for the study if at a later time point the inclusion/exclusion criteria are met. In this case, most recent screening evaluations will be used. If outside the screening period of 21 days repeated full screening must be effectuated.

During screening, if specific assessments are evaluated more than once, then the result of the most recent assessment will be relevant for eligibility evaluation.

[redacted]

[redacted]

[redacted]

6.2.10.2 Phase 2

The visit schedule for phase 2 is summarized in the flow chart in Table 3-2. The calculation of all study visits and time points of assessments are based on Day 1, which is defined as the first day of nivatrotamab injection. The visit schedule is similar to that of Phase 1.

6.2.11 End of Treatment Visit

At both phase 1 and phase 2, an "end of treatment" (EOT) visit should be made when the patient completes treatment or permanently discontinues the IMP. The EOT visit will be performed at the time of discontinuation, within 30 days after the last IMP dose and prior to initiation of any new anticancer treatment. In case of premature study discontinuation, the EOT visit should be performed immediately. The reason for discontinuation from treatment must be documented in the eCRF.

The EOT visit will include the following assessments: physical examination, vital signs and body weight, ECOG performance score, neurological examination, recording of concomitant medication and concurrent procedures, safety laboratory assessments (hematology, coagulation and clinical chemistry), HCG test (for females of childbearing potential), anti-drug antibodies, AEs/SAEs, urinalysis, and CT scanning of the primary tumor site (if the last prior tumor assessment was >6 weeks from date of the EOT visit).

6.2.12 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.

6.2.13 Follow-up

6.2.13.1 Phase 1

All patients will be followed up for safety reporting for 30 days after the last IMP dosing. Thereafter, long-term safety will be recorded by registration of related SAEs up to 12 months after the last dose. The Investigator must commit to provide data on vital status and disease progression for follow up on PFS and OS up to 12 months after the last dose. In phase 1, ORR will be assessed at predefined timepoints, including at Week 24. The Investigator should collect CT scan reports for tumor assessments every 8 weeks or according to the local standard of care. The FU assessments can be done locally at the referral site.

6.2.13.2 Phase 2

Follow up in phase 2 will be similar to that in phase 1. All patients will be followed up for safety reporting for 30 days after the last IMP dosing. Moreover, long-term safety will be recorded by registration of related SAEs up to 12 months after the last dose. Vital status and disease progression for follow up on PFS and OS will be up to 12 months after the last dose. In phase 2, ORR will be assessed at pre-defined timepoints, including at Week 24. The Investigator should collect CT scan reports for tumor assessments every 8 weeks or according to the local standard of care. The FU assessments can be done locally at the referral site.

6.2.14 End of Trial

End of trial is defined as last patient's last visit, follow-up contact or death in the long-term FU period.

6.3 Trial Population

6.3.1 Number of Patients

Up to 39 patients are planned to be dosed in phase 1 and 30 additional patients in phase 2. No more than 69 patients in total will be dosed in the trial.

6.3.2 Patient Selection

To be eligible, the patient must meet all the following inclusion criteria and must not violate any of the exclusion criteria (section 6.3.2.2).

6.3.2.1 Inclusion Criteria

1. Signed and dated informed consent has been provided prior to any trial-related procedures.
2. Patient willing and able to comply with the trial protocol
3. Age ≥18 years at the time of informed consent
4. Histologically or cytologically proven SCLC. Radiographical relapse/progression after minimum 1 line of platinum-containing chemotherapy with PR or CR as the best response (not required for phase I) and not more than 3 prior lines of therapy

5. Measurable disease according to RECIST v1.1
6. ECOG performance status 0–1
7. Expected survival >3 months
8. Platelet counts ≥100,000 cells/mm^3
9. Hemoglobin ≥9 g/dL
10. Absolute neutrophil count (ANC) ≥1000 cells/mm^3
11. Adequate liver function defined by AST, ALT, alkaline phosphatase (ALP) ≤3 × upper limit of normal (ULN), and serum bilirubin ≤1.5 × ULN with the following exceptions
    a. In patients with documented liver metastases, AST, ALT, and ALP ≤5 × ULN and serum bilirubin ≤1.5 × ULN
12. Adequate renal function with serum creatinine ≤1.5 mg/dL or creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault equation[31]
13. Serum albumin >3.0 g/dL
14. Women of child-bearing potential must agree to appropriate contraception during treatment and for a period of 30 days after the last dose of the study drug. Fertile male patients must agree to the use of condoms during treatment and for a period of 30 days after the last dose of the IMP. For a sterilized male patient to be exempt from the requirement to use contraception after IMP treatment, he must have undergone surgical sterilization (vasectomy).

6.3.2.2 Exclusion Criteria

1. Systemic chemotherapy, radiotherapy, immunotherapy, or major surgery administered within 3 weeks prior to the first planned dosing of the IMP per protocol
2. Patients receiving any other investigational therapy for their cancer within 3 weeks prior to the first planned dosing of the IMP per protocol
3. Patients who never received platinum-containing regimen for SCLC (defined as less than 2 cycles of platinum doublet)
4. Persistent > grade 1 toxicity from previous treatment with checkpoint inhibitors
5. Any immunosuppressive concomitant medication (i.e., salazopyrine, methotrexate, steroids etc.)
6. Inability to wean off steroid unless tapered to 0 mg/day minimum 10 days prior to the first treatment in case of prior use
7. Any active, uncontrolled viral, fungal, or bacterial infection
8. Any medical history within 3 months prior to enrolment with need for anticonvulsant therapy

9. Patients with a diagnosis of autoimmune diseases or immunodeficiencies or documented infection with human immunodeficiency virus (HIV) or hepatitis B or C virus (active)
10. Previous autologous stem cell transplantation (ASCT) or solid organ transplantation
11. Active heart disease including myocardial infarction within the last 6 months before the first dose. This includes cardiac insufficiency with left ventricular ejection fraction (LVEF) <50%
12. Active CNS metastases. Patients with treated CNS metastases are eligible if they are clinically stable without any new neurological symptoms and if there is no radiological evidence of new or enlarging CNS metastases. CNS-directed treatment (surgery, radiation) must be completed 4 weeks prior to the first IMP administration[32] Furthermore, patients are excluded if they have:
    - Leptomeningeal carcinomatosis
    - Uncontrolled seizures. Patients with known seizure are eligible if they are stable and have been without seizure 4 weeks prior to the first IMP administration
13. Patients who experienced severe or recurrent (>grade 2) immune-mediated AEs or IRRs, including those that lead to permanent discontinuation while on treatment with immuno-oncology agents
14. Prior treatment with anti-GD2 antibody or bispecific antibodies
15. Patients with Limited Disease (LD) who are candidates for local or regional therapy
16. Impending need for palliative radiotherapy or surgery for pathological fractures and/or for medullary compression up to 3 weeks prior to the first planned dosing of the IMP per protocol (palliative radiation for other reasons within 2 weeks)
17. History of other active malignancy within the past 3 years prior to the first planned dosing of the IMP per protocol (excluding non-melanoma skin canncers, carcinoma in situ of the cervix, ductal carcinoma in situ of the breast, incidental prostate cancer (T1a, Gleason score ≤6, prostate specific antigen (PSA) less than 0.5 ng/ml)
18. Patients with a significant intercurrent illness (any ongoing serious medical problem unrelated to cancer or its treatment) that is not covered by the detailed exclusion criteria and that is expected to interfere with the action of the trial IMP or significantly increase the severity of the toxicities experienced from trial treatment
19. Patients who are pregnant or breastfeeding
20. Patients with a body weight of < 45 kg
21. Patients with prior orthostatic hypotension

6.3.3 Premature Discontinuation of Treatment

6.3.3.1 Treatment Discontinuation Criteria

A patient should be discontinued from treatment with the IMP if any of the following situations occur:

- Any DLT (see section 6.2.3)
- Disease progression - confirmed PD (confirmed immune PD [iCPD]) or as clinically judged by the Investigator
- Patients with suspected progression, i.e., unconfirmed PD (unconfirmed immune PD [iUPD]), are allowed to continue treatment if they are considered to be clinically stable in the opinion of the Investigator until confirmatory radiological assessment (CT scan) is performed.
- In case of decreased ejection fraction (EF) of grade 3 (EF, 39%–20% or ≥20% drop from baseline), and the event is considered treatment-related.
- Investigator's decision for medical or safety reasons
- If the patient receives prohibited anti-tumor therapy/procedures during the trial
- Patient chooses to withdraw from the therapy at any time
- Pregnancy

6.3.4 Withdrawal from the Trial

A patient must be withdrawn from trial if one of the following applies:

- Patients may be withdrawn from the trial at the discretion of the Investigator or Sponsor due to a safety concern or if judged non-compliant with trial procedures.
- Patient chooses to withdraw from the trial at any time.
- Other circumstances that would endanger the health of the patient if he/she were to continue his/her participation in the trial.
- Patient becomes lost to follow-up

Reasons for withdrawal and discontinuation of any patient from the trial will have to be documented in the eCRF.

6.3.5 Patient Replacement

If patients are withdrawn pre-maturely without having experienced a DLT, they will be considered non-evaluable and may be replaced.

7 TREATMENTS

7.1 Investigational Medicinal Product

For this trial, the Sponsor, Y-mAbs, will provide nivatrotamab, 2 mg/mL. No other medicinal products or auxiliary medicinal products will be provided by Y-mAbs.

Please refer to the IMP manual for more details on preparation and administration of nivatrotamab. For further information on nivatrotamab, see the Investigator's brochure (IB).

Table 7-1 Investigational medicinal product (IMP)

IMP	Nivatrotamab 2 mg/mL
Route	Subcutaneous (SC)
Pharmaceutical form	Solution for SC use
Unit strength	2 mg/mL

7.1.1 Nivatrotamab Administration

The IMP, nivatrotamab, will be administered SC according to the treatment schedule (section 7.1.2). Nivatrotamab should only be administered in a hospital or clinic with immediate access to equipment, medications, and appropriately qualified staff for resuscitating and stabilizing individuals in an acute emergency, along with ready availability of an intensive care unit and other hospital facilities. Neurological consultation services should be readily available to address any neurological events that may arise as a result of IMP treatment. For the first 2 cycles in both the dose escalation phase of the study (phase 1) and the dose expansion phase (phase 2), patients will be admitted to a hospital inpatient unit on the day of injection and will remain hospitalized until 48 h after completion of the IMP injection. Hospitalization requirements for subsequent cycles will be determined on the basis of the clinical course during the first cycle; for example, patients who experience an injection-related reaction or CRS during Cycle 1 may require hospitalization for subsequent IMP doses and cycles.

IMP Administration Details

Nivatrotamab will be administered SC at a site easily visible for the patient, i.e., upper thigh, upper arm, or abdomen to allow observation of potential injection site reaction. The selected dose should be administered at 1 site only, i.e., it should not be divided into separately injected fractions. Moreover, the IMP must not be administered intramuscularly. The time of injection should be chosen carefully with regard to the time points for safety assessments, PK/pharmacodynamic measurements, and the required duration of in-house monitoring of the patient.

7.1.2 Treatment Schedule

[redacted]

[redacted]

7.1.2.1 Phase 1 (dose escalation)

[redacted]

7.1.2.2 Phase 2 (dose expansion)

All patients in the phase 2 part of the study will be treated at the recommended dose defined in the phase 1 part of the study (RP2D) (also see section 6.2.2).

7.1.2.3 Treatment Modification and Delays

In cases of toxicities, for patients who remain eligible for further treatment, a treatment delay of up to 3 weeks is acceptable to allow for resolution of ≥ grade 3 hematological and non-hematological toxicities (that do not meet the treatment discontinuation criteria) down to ≤ grade 2 or returned to baseline value at study entry (e.g. lab values).

7.1.2.4 Treatment after Discontinuation of IMP

After discontinuation of the IMP, the patient should be treated at the discretion of the Investigator.

7.1.3 Packaging and Labelling

Packaging and labelling of nivatrotamab will be outsourced to a clinical packaging contract manufacturing organization. All products will be labelled according to the rules governing medicinal products in the European Union (Annex 13, EudraLex, Volume 4) and local requirements. Each unit of the IMP will be uniquely numbered. The IMP provided must be used solely for this trial and as described in this protocol and for no other purpose. Further detailed information on packaging and labelling is provided in the IMP manual.

7.1.4 Storage and Handling

The IMP provided by the Sponsor must be stored according to the clinical label claim in a secure location with controlled access. It must be stored separately from normal clinical stock. The storage conditions must be monitored for adherence to the claims. Temperature monitoring data must be reviewed by the clinical research associate (CRA) during monitoring visits. Any deviations in storage temperature must be reported immediately, and the IMP must not be used until acceptance of such use is received. Monitoring must be done using a calibrated, stationary, and continuous recording system. As a minimum, a calibrated min/max thermometer is required for monitoring.

Detailed information on the storage and handling of the IMP is available in the IMP manual.

7.1.5 Drug Accountability and Compliance Check

Each trial site will be supplied with sufficient IMPs for the trial on an ongoing basis. The supplies will be ordered by the site in sufficient time to ensure that enough IMPs are available for treatment. Drug accountability must be documented in the eCRF.

The Investigator or designee is responsible for drug accountability and record maintenance (i.e., receipt, accountability, and final disposition records). All expired or damaged IMP must be stored separately from non-allocated trial products. Non-allocated IMP including expired or damaged IMP must be accounted as unused, at the latest at closure of the trial site. For more information on accountability procedures, please refer to the IMP manual.

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

Drug accountability on a patient level will be 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.

7.1.5.1 Medication Errors

Medication errors must be reported in the medication error page of the eCRF.

Medication errors and uses outside what is foreseen in the protocol may include:

- Administration of the wrong drug
- Wrong route of administration, such as intramuscular or IV instead of SC
- Accidental administration of a lower or higher dose than intended. An overdose is defined as an IMP dose received by the patient that exceeds the protocol -specified dose by at least 10%. An underdose is defined as an IMP dose received by the patient that is at least 10% lower than the protocol-specified dose.

If a medication error results in an AE, the AE must also be reported in the eCRF. If the event qualifies as an SAE, it must be reported using the paper clinical AE report form in addition to the AE form in the eCRF.

7.1.6 Device

Not applicable.

7.1.7 Technical Complaint

A technical complaint is any written or oral communication that states any dissatisfaction with the product characteristics and alleges a product defect. A technical complaint can be related to, for example, the product appearance (discoloration, presence of particles or sediment); product container (damaged or missing seal); product label (damaged, missing, misleading); or

consignment (wrong number of vials in the package). A technical complaint should be also initiated if the product is suspected to be falsified.

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

7.2 Other Therapies and Procedures

7.2.1 Concomitant Therapy

A concomitant medication is any medication received by the patient other than the IMP, including all pre-medication. All concomitant medications (including over the counter) that the patient is receiving at the time of enrollment or during the trial must be entered in the eCRF with the following information:

- Generic name
- Start date
- Stop date of administration or ongoing at trial termination
- Indication/reason for use
- Dose
- Frequency

Any changes to concomitant medication during the trial should be recorded in the eCRF. If a change is due to an AE/SAE, then this must be recorded according to section 9.

During follow up, only information on new anti-cancer therapy will be collected.

7.2.2 Pre-medications prior to nivatrotamab injection

All medications, pre-medication and supportive concomitant medication should be captured under concomitant medication in the eCRF.

7.2.2.1 Cytokine Release Syndrome

In order to mitigate expected reactions to administration of a monoclonal bispecific antibody and prevent CRS, premedication with dexamethasone should be administered before IMP dosing (via SC injection). In addition, the premedication package will contain a non-NSAID (nonsteroidal anti-inflammatory drug) antipyretic (acetaminophen or equivalent) and an antihistamine (loratadine or equivalent).

Administer the following pre-dose medications to reduce the risk of acute injection-related reactions, CRS, allergic reactions, nausea/vomiting to all patients prior to every injection of nivatrotamab:

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

Pre-medication in Cycle 2 and subsequent cycles

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Day 2

- [redacted]
- [redacted]
- [redacted]

7.2.2.2 Pain

Injection of nivatrotamab may be followed by development of neuropathic pain. The clinical manifestations are varied and could involve the abdomen, lower back, and extremities.
Pain is expected to develop by onboarding of IMP to GD2, with estimated onset on Day 1-2 after IMP administration. As many patients might already receive opioids and/or medication for neuropathic pain at enrolment, the below recommendations should be considered as a guideline, and treatment accommodated to each patient at the investigators' discretion.
To prevent the development of severe neuropathic pain, the following pre-emptive analgesia with peroral gabapentin is recommended and should be followed (at home) prior to dosing in all cycles:

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.3 Recommended supportive medication

[redacted]

[redacted]

[redacted]

7.2.4 Management of Selected Adverse Reactions

7.2.4.1 Grading and Management of Cytokine Release Syndrome

CRS should be graded in accordance with CRS Revised Grading System by Lee et al.[27] shown in Table 7-2 below.

Table 7-2 CRS Revised Grading System

CRS parameter	CRS Grading[1]			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Fever*	Temperature ≥38°C (≥100.4°F)	Temperature ≥38°C (≥100.4°F)	Temperature ≥38°C (≥100.4°F)	Temperature ≥38°C (≥100.4°F)
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[2]		
Hypoxia	None	Requiring low-flow nasal cannula[3] or blow-by oxygen delivery	Requiring high-flow nasal cannula,[3] face mask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)

Organ toxicities associated with CRS do not influence the grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS and then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever will no longer be required to grade subsequent CRS severity. In this case, CRS grading will be driven by hypotension and/or hypoxia.

[1] CRS with a fatal outcome should be recorded as a grade 5 event.

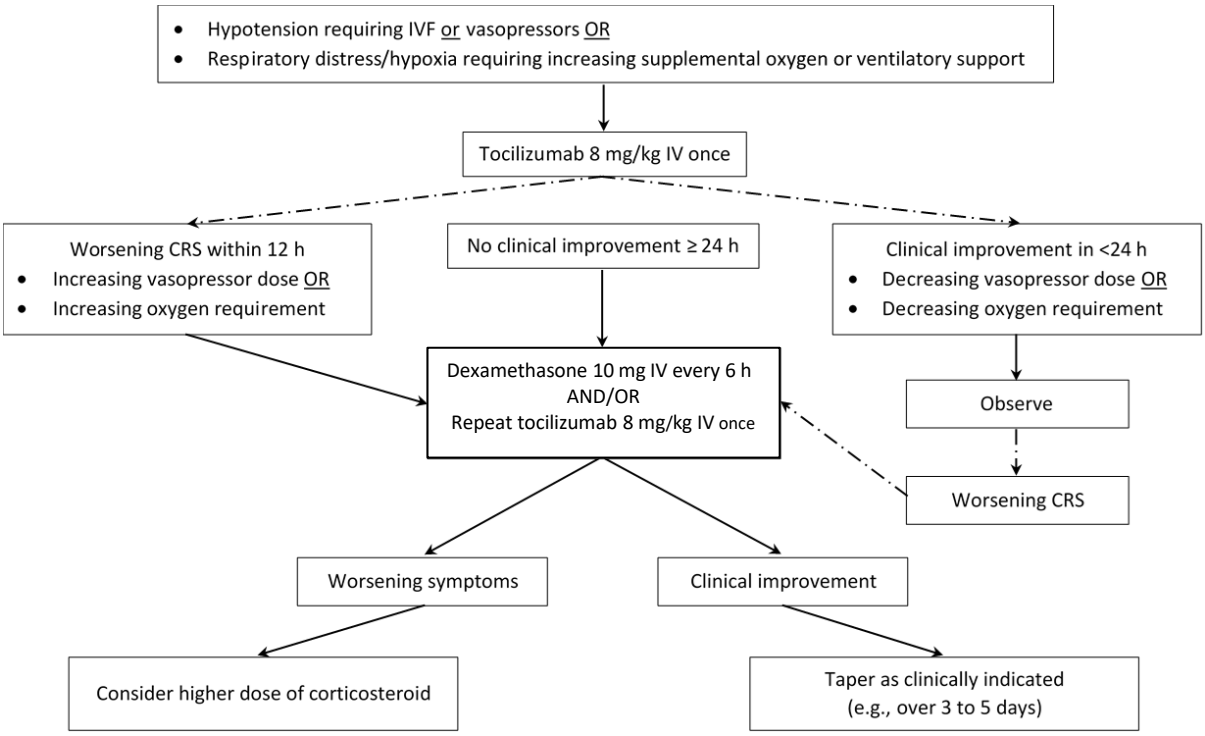
[2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[3] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

CRS should be managed according to the management algorithm described in Figure 7-2 below.

Tocilizumab (anti-cytokine therapy) should be dosed at 8 mg/kg (maximum 800 mg/dose) infused over 1 h with appropriate pre-medications. In the absence of clinical improvement within 24 h or should rapid deterioration occur, a second dose of tocilizumab could be administered; however, a second-line agent (e.g., a corticosteroid) should also be introduced simultaneously (Figure 7-1).

Figure 7-1 Cytokine release syndrome (CRS) management algorithm (CRS grade ≥2)



Abbreviations: IV = intravenous; IVF = intravenous fluids
This algorithm is based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome and neurologic toxicity [27]

7.2.4.2 Grading and Management of Immune effector-cell associated neurotoxicity

The neurotoxicity assessments should be performed and graded in accordance with the ASTCT immune effector cell-associated neurotoxicity syndrome, ICANS, consensus grading scheme for adults[27], as presented in Table 7-3.

The immune effector cell-associated encephalopathy (ICE) score is calculated as per Table 7-4.

Any neurological AEs observed as part of the assessment (e.g., seizures) should be recorded as described in section 9.

Table 7-3 ASTCT ICANS consensus grading for adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[1]	Awakens Spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[2]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[3]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; EEG = electroencephalography; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; N/A = not applicable

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause, for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia; however, a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[1] Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication)

[2] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE version 5.0; however, they do not influence ICANS grading.

[3] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE version 5.0.

Table 7-4 ICE assessment tool for the grading of ICANS

Domain	Assessment(s)	Points
Orientation	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects (e.g., point to clock, pen, button)	3
Following commands	Ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1
Writing	Ability to write a standard sentence (e.g., "Our national bird is the bald eagle")	1
Attention	Ability to count backwards from 100 by 10	1

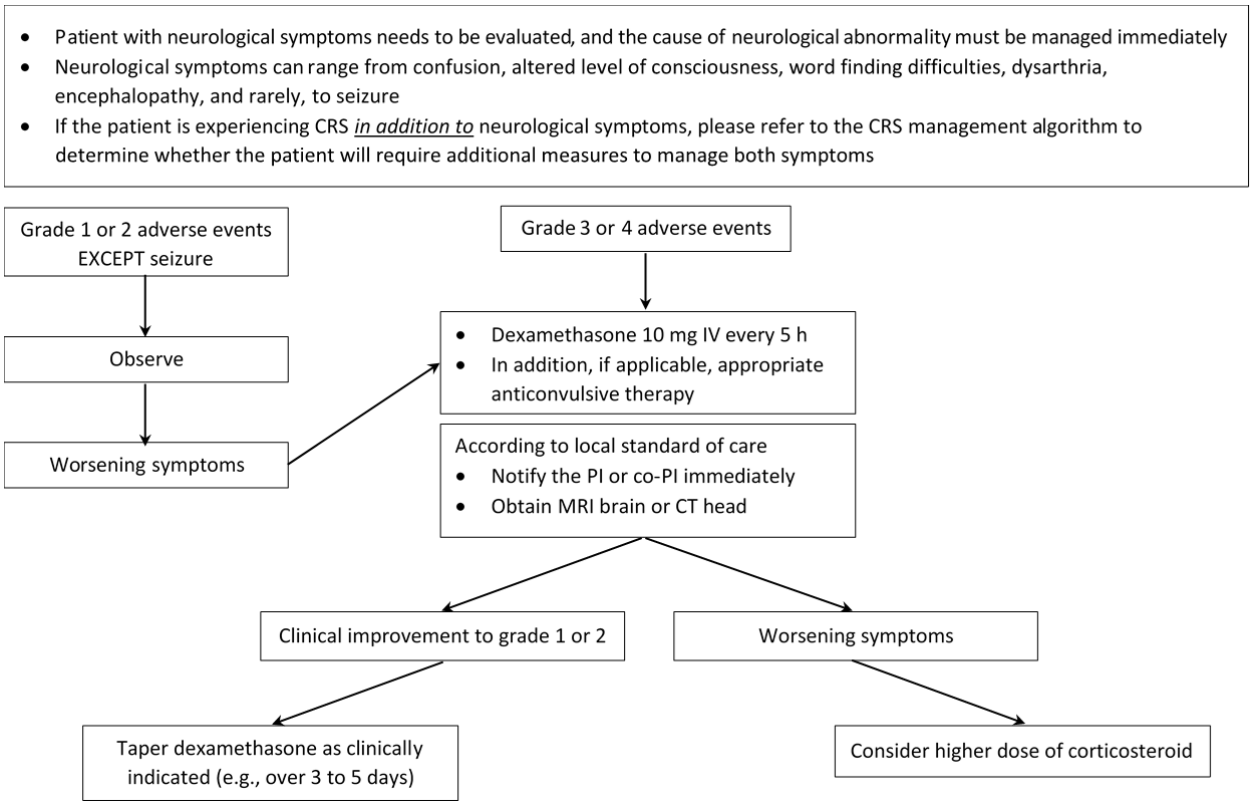
Abbreviations: ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy

Scoring

- 10 = no impairment
- 7–9 = grade 1 ICANS
- 3–6 = grade 2 ICANS
- 0–2 = grade 3 ICANS
- 0 due to patient unarousable and unable to perform ICE assessment = grade 4 ICANS

Management of neurotoxicity will be based on the following algorithm (Figure 7-2).

Figure 7-2 Treatment algorithm for the management of neurotoxicity (ICANS) in the 402 trial



Abbreviations: ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous
This algorithm is based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome and neurologic toxicity [27]

7.2.4.3 Management of Hypotension

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.4.4 Management of Orthostatic Hypotension

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

7.2.4.5 Management of Neuropathic Pain

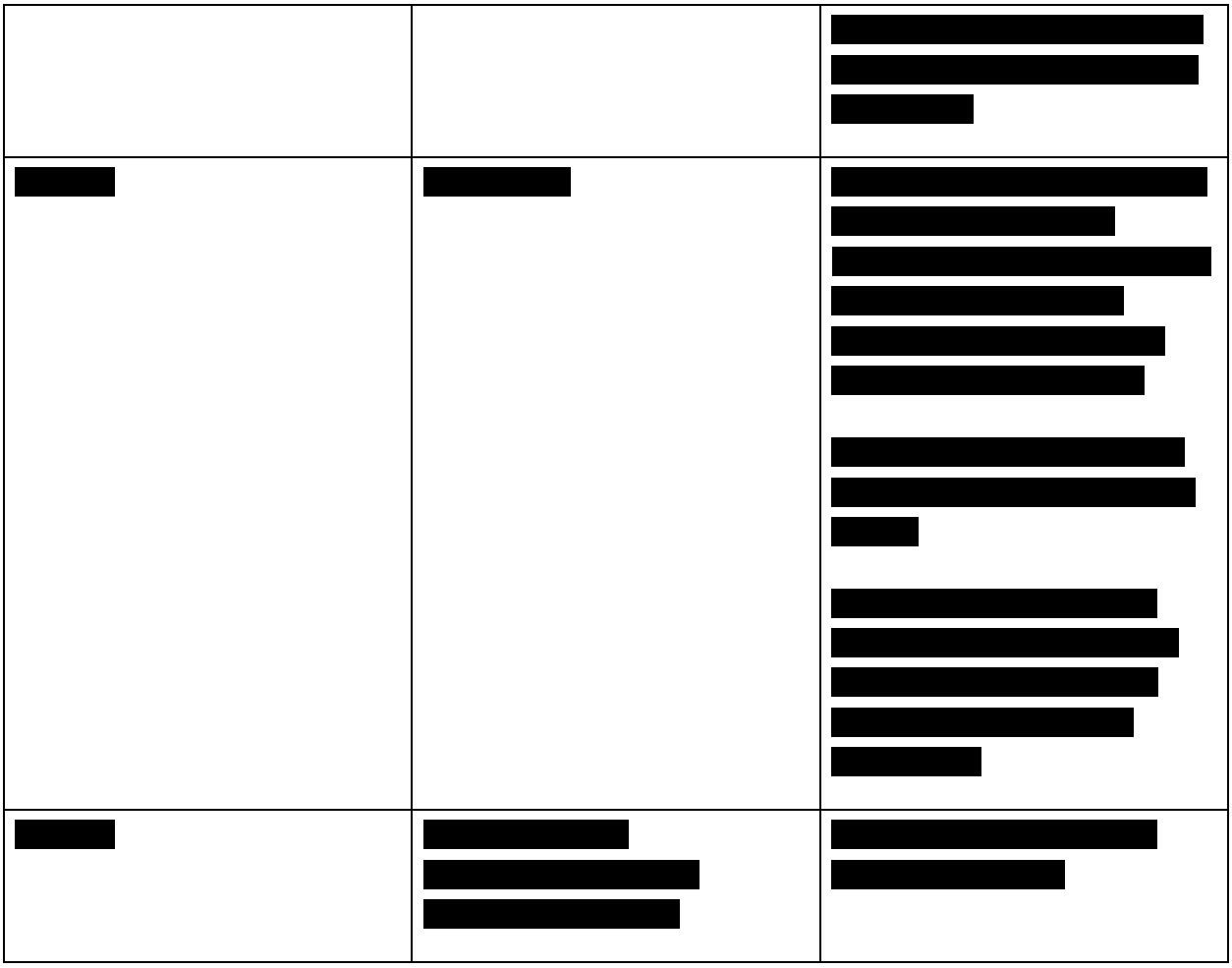
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



7.2.5 Therapy and Procedures 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.

7.2.6 Prohibited Therapy and Procedures During the Trial

The following are prohibited during the trial:

- Any anti-tumor therapy other than the IMP and mandatory concomitant medications, for example:
    - Cytotoxic and/or cytostatic drugs
    - Radiation therapy to primary tumor, CNS, or other target lesions
    - Immunotherapy
- Any other investigational agent
- Chronic (>7 days) systemic high-dose corticosteroid therapy (i.e., >10 mg dexamethasone daily)
- Any other immunosuppressive therapies (except for transient use of corticosteroids)

- Substrates of CYP450 isozymes considered by the investigator to have narrow therapeutic index must be paused or not initiated for 9 days after first dose and 2 days after second dose (corresponding to day 1 to 9, both included)

8 PROCEDURES AND ASSESSMENTS

An overview of all trial-related procedures and assessments at each visit is provided in the visit schedule flow charts, Table 3-1(phase 1) and Table 3-2 (phase 2). Written informed consent must be obtained from each patient prior to undertaking any trial specific procedure.

8.1 Eligibility and Safety Assessments

Assessment of the patient's eligibility criteria will be performed as outlined in sections 6.2.7 and 6.3.2, including a review of all laboratory measurements performed during the screening period.

8.1.1 Demographics

Information on the patient's demographics will be collected in the eCRF during screening.

The following demographic information will be entered:

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

Current and prior smoking status must be recorded for each patient.

8.1.2 Medical History/Current Medical Conditions

Medical history will include general and disease-specific medical history, including a history of past and current medical conditions and a full history of the course of the patient's SCLC, including all prior treatments such as prior systemic regimens and radiotherapy.

All concomitant illnesses should be recorded. A concomitant illness is defined as any illness, other than the disease being investigated (SCLC), which is present at the start of the trial or is found as a result of the screening procedure.

The information to be collected for SCLC medical history and concomitant illnesses will include

- Diagnosis
- Date of onset
- Date of resolution
- Date of relapse (for SCLC)

8.1.3 Physical Examination

Comprehensive physical examinations of all body systems will be performed as outlined in section 3. Physical examination should include an assessment of the general appearance and a review of systems (dermatologic; head; eyes; ears; nose; mouth, throat, and neck; extremities; thyroid; lymph nodes; and respiratory, cardiovascular, gastrointestinal, musculoskeletal, and neurologic systems).

8.1.3.1 Neurological Examination

During the screening and at the end-of-study visit, a neurological examination according to local standards will be performed. It will include examination of the following functions: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extrapyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, and neuropsychological findings (e.g., speech, cognition and emotion). The presence of tremors should also be evaluated.

8.1.3.2 Height and body weight

Height (without shoes) must be measured at screening and entered in the eCRF rounded to nearest centimeter.

Body weight must be measured without overcoat and shoes and entered in the eCRF rounded to nearest kilogram; see flowchart (section 3).

8.1.4 ECOG Performance Status

Patients' performance status will be assessed using the ECOG performance score (see section 3).

8.1.5 Vital Signs

Body temperature (e.g., tympanic or rectal), heart rate, oxygen saturation, and blood pressure (systolic/diastolic, patients should be supine/sitting for 5 mins before assessment) will be measured as part of vital signs. The Investigator is recommended to monitor the patient's vital signs continuously (in Cycles 1 and 2); see flowchart (section 3).

On Day 3 and 4 (Cycle 1 and 2), vital signs should be measured during the outpatient visit; moreover, from Cycle 3 onward, vital signs should be measured once on dosing day (Day 1). In case the patient's symptomatology or body temperature measurements rises suspicion of orthostatic hypotension (for definition, see section 7.2.4.3), it is recommended that the patient stay hospitalized for monitoring (this monitoring will not qualify as a DLT).

8.1.6 Echocardiogram, MUGA, and ECG

In order to exclude pre-existing or developing cardiac failure, an LVEF of ≥50% is required at screening, assessed by either echocardiogram or MUGA. Monitoring of cardiac function is required during the trial including repeat ECG (12-lead) to be performed as outlined in section 3. Monitoring of LVEF should be done by either repeat echocardiogram or MUGA (same modality per patient); for the time of assessments, see section 3. In case of decreased ejection fraction (EF) of grade 3 (EF, 39%–20% or ≥20% drop from baseline), if this event is considered treatment-related, the patient should discontinue treatment and proceed into follow up.

8.1.7 CT of the Neck, Thorax, and Abdomen

Assessment of SCLC target lesions and tumor burden must be performed via CT scanning, and the date of completion of the first CT should not exceed 21 days prior to the first dosing. Screening CT scanning result should be measurable according to RECIST 1.1

8.1.8 Cranial/Spinal MRI

MRI evaluation of the CNS is mandatory at baseline in order to evaluatebrain or leptomeningeal metastasis and assure absence of spinal metastasis; in addition, an MRI must be performed if a patient develops a neurological (CNS) AE ≥ grade 2 during the trial.

8.1.9 Clinical Laboratory Assessments

All clinical laboratory assessments must be conducted in accordance with the flowcharts in section 3.

8.1.9.1 Hematology

Hemoglobin; hematocrit, red blood cell (RBC), white blood cell (WBC) count; differential blood count to determine the absolute numbers of lymphocytes (absolute (ABS), %), neutrophils(ABS, %), eosinophils (ABS, %)and monocytes (ABS, %); basophils (ABS, %), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelet count are to be performed for safety analyses. Blood samples will be taken at screening, at the start of a treatment cycle (prior to the start of IMP administration), at different time points during the treatment and treatment-free periods, and at the EOT visits.

With regard to blood samples taken at screening, samples taken for standard procedures up to 48 h prior to screening can be used. As regards samples collected prior to the start of IMP administration, these samples may be obtained up to 48 h before the start of treatment; however, the results must be available before treatment start.

8.1.9.2 Safety Laboratory Evaluations

Serum chemistry

AST, ALT, alkaline phosphatase (AP), lactic dehydrogenase (LDH), total bilirubin, albumin, creatinine, urea/blood urea nitrogen (BUN) (as applicable), glucose, calcium, sodium, potassium, chloride, phosphorus, and magnesium will be assessed.

Coagulation

Coagulation parameters will include international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen, and D-dimer.

8.1.10 Urinalysis

The presence of glucose, protein, and blood in urine will be assessed by dipstick.

If proteinuria is suspected (repeated protein on dipstick at 2 consecutive tests), a 24 h collection of urine should be performed and analysed for protein content.

8.1.10.1 Creatinine Clearance

An estimated glomerular filtration rate (eGFR) using creatinine clearance will be used to detect any kidney function impairment.

8.1.11 Pregnancy Test

A urine or serum pregnancy test (HCG) will be performed in all female pre-menopausal women (unless of non-childbearing potential); see flowchart (section 3).

Non-child-bearing potential in female patients will be confirmed by one of the following:

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

Pregnancy and contraceptive requirements for female patients of child-bearing potential

Women of child-bearing potential must have a negative pregnancy test at screening and will be excluded if they do not agree to use highly effective contraception during treatment and for a period of 30 days after the last nivatrotamab administration.

Highly effective contraceptive methods are those that can achieve a failure rate of <1% per year when used consistently and correctly. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner[1]

[1] Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the female patient and that the vasectomised partner has received medical assessment of surgical success.

- Sexual abstinence[2]

Contraceptive requirements for male patients

Male patients with female partners of child-bearing potential must use contraception (condom) during treatment and for 30 days after the last IMP treatment.

8.1.12 Peripheral Blood Cytokines

Serum cytokine levels (IL-6) will be monitored in all patients enrolled in phase 1 and phase 2, in accordance with the flowcharts in section 3. Blood samples for the measurement of peripheral blood cytokines will be taken pre-dose on cycle 1 day 1 and on dosing day (+1) and should optimally be taken at the same time of the day (± 60 min) as the blood sample were taken cycle 1 day 1.

8.1.13 Anti-Drug-Antibodies

Blood samples for the assessment of binding anti-drug antibodies will be taken in accordance with the flowchart in section 3. . For further details, see the laboratory manual.

8.1.14 Concomitant Medication

All concomitant medications will be recorded, starting on the first day of screening and until the EOT visit. Administration of subsequent anti-cancer therapy during the follow up period will be recorded.

8.1.15 Adverse Events

AEs and SAEs should be recorded and reported in accordance with section 9.

8.2 Response Assessments

Responses will be assessed at predefined timepoints (see section 3). Response assessment will be based on the criteria described in RECIST version 1.1 [34]. Application of the iRECIST criteria in the evaluation of PD will also be done in order to protect patients from going off treatment in case of unconfirmed PD (according to RECIST1.1) and iUPD (according to iRECIST) due to pseudo-progression/tumor flare [35]. Confirmatory scanning for patients who have obtained PR or CR will be undertaken approximately 4 weeks after the initial response.

For definitions of response, please see section 11.

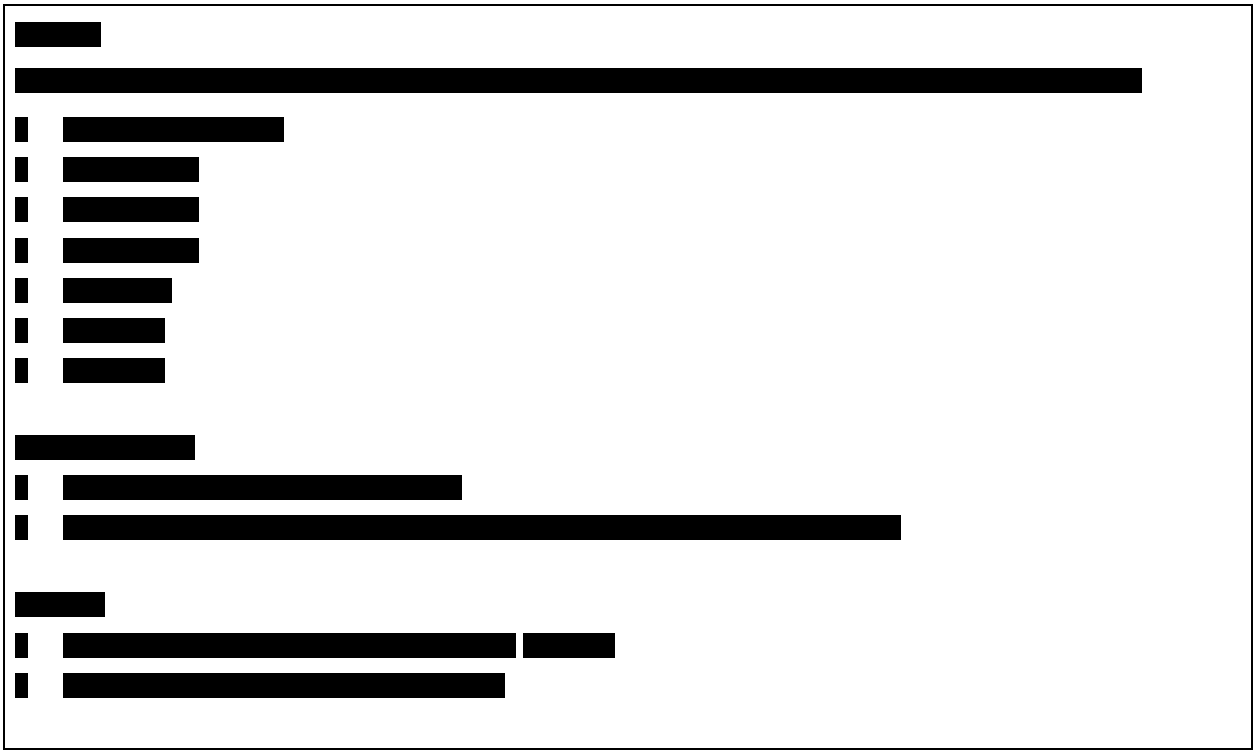
8.3 Pharmacokinetics Assessment

Nivatrotamab serum concentration will be measured in all patients dosed in both phase 1 and phase 2. Such measurements will occur at baseline (predose) and at regular intervals during the treatment period (see section 3). During the inpatient period, samples will be taken prior to

[2] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

treatment start (baseline) and at defined time points after IMP administration (see Table 8-1). The time window for these samples are also shown in Table 8-1. It is important that the actual time of sampling is documented precisely in the eCRF. For further details, see the laboratory manual.

Table 8-1 Pharmacokinetics assessment time points



Abbreviations: PK = pharmacokinetics

8.4 Assessment of GD2 Expression (optional)

Collection of tumor specimens from archival paraffin embedded tissue (minimum 5 to 10 slides) will be done for immunohistochemical analysis of GD2 expression. This will be done for patients with available tissue and who have provided a separate consent for this procedure. Please refer to the laboratory manual for further details.

9 ADVERSE EVENTS

9.1 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 laboratory abnormality that is clinically significant, i.e., an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes interventional treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.

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

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

9.2 Definition of Serious Adverse Events

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

- It is fatal or life-threatening.[3]

[3] The term “life-threatening” in the definition of “serious” refers to an event in which the patient, in view of either the Investigator or the Sponsor, was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Death alone is not considered an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to death. However, sudden death or death due to unexplainable cause should be reported as an SAE, while follow-up is pursued to determine the cause.

- It requires inpatient hospitalization or prolongation of existing hospitalization.[4]
- It results in persistent or significant disability/incapacity.
- It is a congenital anomaly/birth defect.
- It is a medically important event.[5]

9.3 Definition of Non-serious Adverse Events

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

9.4 Definition of Predefined Adverse Events of Special Interest

The following AEs (serious and non-serious) graded according to CTCAE v5.0 Revised CRS Criteria according to Lee et al.[27] for CRS are selected as adverse events of special interest (AESIs) in this trial:

- CRS grade 2 or higher
- Hypotension grade 3 or higher not in connection with CRS
- Neuralgia grade 3 or higher
- Peripheral neuropathy grade 3 or higher

[4] Hospitalization is defined as admission to a hospital/inpatient stay (irrespective of the duration of the physical stay) or no admission to a hospital/no inpatient stay but stay at the hospital for treatment or observation for more than 24 h. Events leading to hospitalizations for the following reasons should not be reported as SAEs:

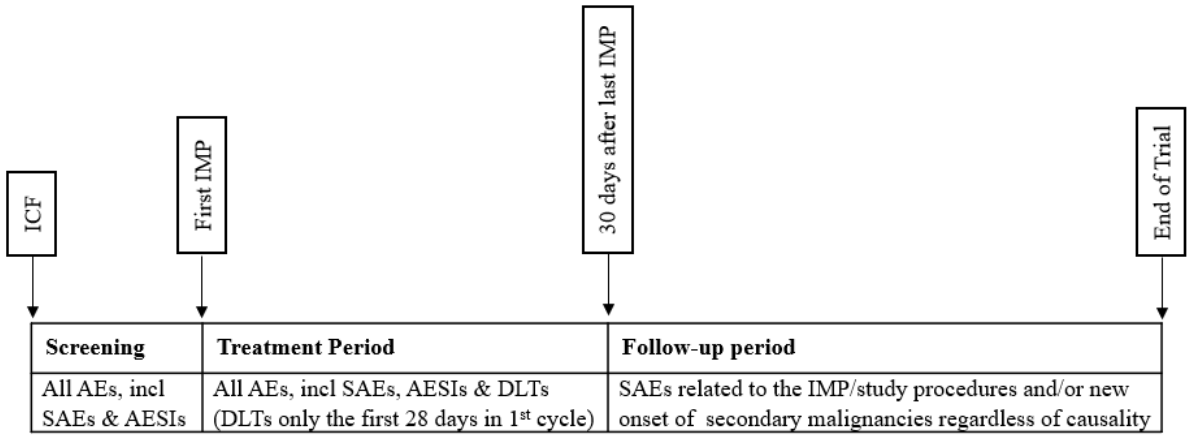
- Trial-related purposes not associated with any deterioration in the condition
- Social reasons in the absence of any deterioration in the patient's general condition
- Elective surgery or other scheduled hospitalization periods that were planned before the patient was included in this trial.

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

9.5 Adverse Event Reporting Period

The AE reporting period is shown in Figure 9-1.

Figure 9-1 Adverse event reporting



Abbreviations: AE = adverse event; AESI = adverse events of special interest; IMP = investigational medicinal product; SAE = serious adverse event

9.5.1 Non-serious Adverse Events Reporting

Non-serious AEs (including non-serious AESIs) should be reported from signing informed consent until 30 days after the last IMP administration.

9.5.2 Serious Adverse Events Reporting

Serious AEs should be reported from signing the informed consent until 30 days after the last IMP administration.

9.5.3 Adverse Events During Follow-Up

During the follow-up period, SAEs at least possibly related to nivatrotamab or to the study procedures and new onset of secondary malignancies regardless of causality, should be reported the until end of the trial.

9.5.4 Adverse Events with Onset After End-of-trial

If the Investigator becomes aware of an SAE after the end of the trial with a suspected causal relationship to the IMPs, it should immediately be reported to the Sponsor.

9.6 Recording of Adverse Events

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

During each contact with the trial site staff, the patient must be asked about AEs, for example, by asking: “Have you experienced any problems since the last contact?” All AEs, observed by the Investigator or the patient, must be reported by the Investigator and evaluated unless specifically excluded (see section 9.6.4).

9.6.1 Diagnosis

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

Further instructions on the recording of CRS and neurological AEs are provided below.

9.6.1.1 Cytokine release syndrome

AEs that are considered to be consistent with CRS should be recorded as “cytokine release syndrome” on the AE page of the eCRF. Associated signs and symptoms should be recorded on the dedicated CRS eCRF. Cytokine Release Syndrome grade 2 or higher should also be reported as an AESI and CRS grade 3 or higher should be reported as a DLT.

The severity grading of AEs of CRS should be performed in accordance with the CRS grading scheme presented in Table 7-2 in section 7.

9.6.1.2 Neurological Adverse Events

Neurological AEs (e.g., seizures) should be assessed and graded as per CTCAE version 5.0. The Investigator should indicate in the eCRF if the event is considered to be a symptom of ICANS. ICANS grade 3 or higher should also be reported as a DLT.

9.6.2 Onset Date and Time

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

9.6.3 End Date and Time

The end date should be filled in if the outcome of an AE is fatal, recovered/resolved, or recovered/resolved with sequelae. The end time should be entered for all events for which start time should be entered, i.e., if the event starts on a dosing day or if the duration of the event is less than 24 h.

9.6.4 Signs and Symptoms of the Cancer Disease

Signs and symptoms which, according to the Investigator, are expected and well-known consequences of the indication both in intensity and frequency, should not be reported as AEs or SAEs except for events with a fatal outcome. Any unexpected change in the intensity or frequency should be reported as an AE or SAE as applicable. In addition, all deaths (including death caused by PD and secondary cancers) must be reported as SAE.

9.6.5 Severity

The Investigator will use CTCAE version 5.0 to describe the severity of the AE apart from AEs of CRS (see section 9.6.1.1). If the severity changes over the course of the event, the grade assigned by the Investigator should be the most severe that occurred during the AE period. For grading of CRS and neurological AEs please see section 7.2.4.

9.6.6 Outcome

The Investigator must judge the outcome of an AE by the following terms

- Recovered
- Recovered with sequelae (description of the sequelae should be provided)
- Not recovered
- Fatal
- Unknown*

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

9.6.7 Relationship to Investigational Medicinal Product

The Investigator must assess whether the event is related to the IMP.

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

Not related (unlikely)

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

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

Possibly related

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

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

Probably Related

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

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

9.6.8 Action Taken with the Investigational Medicinal Product

The action taken with the IMP should be noted as:

- Dose decreased
- Drug postponed
- Drug discontinued
- None
- Not Applicable*
- Unknown

* Should be used if the AE occurs before the first treatment, IMP has been discontinued for other reasons, or after the EOT

9.7 Events Requiring Immediate Reporting

The following events (for reporting periods, see Figure 9-1) require reporting to the Sponsor within 24 h of knowledge (for details, see section 9.5):

- SAE
- AESI
- DLT
- Pregnancy

9.7.1 Pregnancy

Any pregnancy, including partner pregnancy, that occurs during trial participation must be reported to the Sponsor within 24 h of knowledge using the pregnancy form. Pregnant trial patients must be discontinued from IMP treatment immediately (see section 6.3.3). The pregnancy must be followed up to determine the outcome and status of the mother and the child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective

terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

9.8 Initial Reporting of Adverse Events

SAEs/AESIs/DLTs

- The paper clinical AE report form must be reported from the site to the Sponsor within 24 h 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.

All AEs

- The eCRF AE form should be updated in accordance with agreed data entry timelines (see section 14.1.2).

The eCRF completion instructions for reporting of AEs should be followed.

9.8.1 Contact Details for Adverse Event Reporting

Completed paper clinical AE report forms and paper pregnancy forms must immediately be reported to:

safetymailbox@ymabs.com In emergency situations, the completed clinical AE report forms or pregnancy forms can be faxed to: FAX +0045 7879 6060

9.9 Follow Up on Adverse Events

SAEs/AESIs/DLTs

- New follow-up information available at the site must be reported within 24 h of knowledge.
- Follow-up information requested from the Sponsor must be replied to within 3 working days. The eCRF AE form should be updated in accordance to agreed data entry timelines (see section 14.1.2).
- If an ongoing SAE/AESI changes in intensity, relationship to IMP, or as new information becomes available for the event, the paper clinical AE report form should be completed and sent to the designated drug safety provider within 24 h of the change in assessment.
- Grade 3 or higher non-serious AEs that are considered treatment related and all SAEs, AESIs, and DLTs should be followed on a regular basis, according to the Investigator's

clinical judgment, until the event has been resolved or until the Investigator can assess it as chronic or stable. This includes follow-up after EOT.

Non-SAEs

Non-serious AEs should be followed until they are either resolved, returned to baseline, or until the end of trial for the patient, whichever comes first.

9.9.1 Reporting of SUSARs

The Sponsor will ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) is reported to the regulatory authorities in accordance with regulatory requirements.

The contract research organization (CRO) appointed by the Sponsor will notify the Investigators of SUSARs in accordance with local requirements. Furthermore, the Investigators will be informed of any trial-related SAEs that may warrant a change in any trial procedure. The CRO appointed by the Sponsor 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.

The Sponsor's assessment of expectedness for nivatrotamab will be performed according to the current version of the IB.

9.9.2 Communication of significant safety issues

In the event of any significant safety-related issues, the Sponsor will decide upon immediate action to be taken, including prompt notification of the DMC, and will communicate to the regulatory authorities, Investigators, IECs/IRB, and patients, as needed, within regulatory timelines.

9.9.3 Data Monitoring Committee

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

During the conduct of phase 1 of the trial, after completion of the DLT evaluation period (2 treatment cycles/28 days) for the last patient in each dose level, the DMC will evaluate the available safety information and recommend trial continuation or termination. If continuation is recommended, the DMC will recommend to the Sponsor whether the dose should be escalated, de-escalated, or held at the same dose level.

During phase 1 and until the DMC meeting in phase 2, the Sponsor will share with the DMC all SAEs occurring during the trial, and an unplanned DMC meeting can be held at the request of either the DMC or the Sponsor safety committee.

During the conduct of phase 2, an additional DMC meeting will be held when the 10th patient across cohorts has completed Cycle 1 to evaluate whether the trial should be modified, stopped, or continue unchanged.

The Sponsor safety committee will evaluate the recommendations provided by the DMC after each DMC meeting. Any significant finding/recommendation from the DMC and endorsed by the Sponsor safety committee will be communicated to the regulatory authorities and IRB/IEC as appropriate, and to the sites.

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

10 LABORATORIES

Laboratory assessments are outlined in detail in section 8.

10.1 Clinical Laboratory Assessments

See section 8.1.9

10.2 Pharmacokinetic Assessments

See section 8.3.

10.3 Immunogenicity

See section 8.1.13.

11 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1 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 counts and percentages for categorical data. Data will also be listed as deemed appropriate. All statistical analyses will be performed and data appendices created by using SAS™ version 9.4 or later.

Any statistical tests will be 2-sided with an α (significance) level of 0.05.

Data from patients who were screened but never started treatment will be listed. Screening failures will not be included in any of the analyses and summary tables.

The results will be presented by groups and total. In the dose escalation phase of the trial, groups will be defined by dose-levels, and in the dose expansion phase, groups will be defined by sensitivity/resistance to previous platinum therapy.

Patients in the dose escalation phase, for whom major inclusion/exclusion criteria and dose regimen are the same as for the patients in the dose expansion phase, may be included in the analyses and presentations of the dose expansion results.

For the sake of the statistical analyses and summaries, the baseline value is defined as the value collected at the time closest to, but prior to, the start of the first nivatrotamab administration. Measurements made on the same day as the first nivatrotamab administration are assumed to have been performed pre-treatment, unless recorded, or by this trial protocol stipulated, otherwise.

The statistical analysis plan (SAP) will describe in further detail the analyses presented below. Furthermore, handling and presentation of data, including demographics, baseline data, and other trial assessments, will be described in more detail in the SAP.

11.2 Sample Size

Up to 39 patients may be included in the dose escalation phase. This number is based on the operational characteristics in Appendix 1, including the up to10 additional patients who may be added to any dose-level as described in section 6.2.1.4.

The impact of sample size on the detectability of AEs during dose escalation (when N=3, 6, or 9 patients at a dose level) and during dose expansion (when N=30) is shown in Table 11-1.

Table 11-1 Probabilities of observing adverse events

Probability of an event	Probability of making at least 1 observation of an event in N patients			
	N=3	N=6	N=9	N=30
30%	66%	88%	96%	100%
10%	27%	47%	61%	96%
5%	14%	26%	37%	79%
2%	6%	11%	17%	45%
1%	3%	6%	9%	26%
0.1%	0%	1%	1%	3%

11.3 Analysis Populations of Interest

11.3.1 Full Analysis Set

The full analysis set (FAS) will include all patients enrolled in the trial who received at least 1 dose of nivatrotamab. Patients who do not fulfil relevant inclusion criteria (e.g., no baseline measurable disease) but still receive the study drug, may be excluded from the FAS.

11.3.2 Safety Analysis Set

The safety analysis set (SAF) will include all enrolled patients who receive at least 1 dose of nivatrotamab.

Unless stated otherwise, the SAF will be used for the analyses related to the primary objective.

11.3.3 DLT Evaluable Analysis Set

The DLT evaluable analysis set (DAS) is a subset of the SAF. This analysis population will include patients in the dose escalation phase who receive at least 80% of the planned doses on each of the 4 administrations in the DLT evaluation period and who had sufficient safety evaluations, or who had a DLT during the DLT evaluation period.

11.3.4 PK Analysis Set

The PK analysis set (PKAS) consists of all patients who receive at least 1 dose of nivatrotamab and have at least 1 evaluable concentration measurement of nivatrotamab. Patients will be removed from the estimation of certain PK parameters on an individual basis due to, for example, missing PK samples or inadequate dosing such that the PK parameters cannot be appropriately derived or summarized. These patients will be identified at the time of the analyses along with the reason for their removal.

11.4 Statistical Analysis

11.4.1 Dose-limiting Toxicities

DLTs observed during the DLT evaluation period will be listed and summarized in a table by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The information from the DLTs will be used to guide the escalation and de-escalation rules as per the mBOIN-design and ultimately determine the MTD. The evaluation of DLTs will be based on the DAS.

Patients with and without DLTs will be plotted in a graph with dose level on the vertical axis and patient number on the horizontal axis.

11.4.2 Maximum Tolerated Dose

Upon completion of the mBOIN-design, the MTD is preliminarily estimated as the dose for which the isotonic estimate of the DLT rate is closest to the target toxicity level. If there are ties, either the highest dose level when the estimate of the DLT rate is smaller than the target or the lowest dose level when the estimate of the DLT rate is greater than the target, will be selected from the ties.

This MTD will be estimated using the select.mtd()-function in the BOIN-package for the R software (R software package 'BOIN' v 2.7.0 or later [36]).

11.4.3 Adverse Events

The overall observation period for AEs will be divided into 3 parts:

- Pre-treatment period: From the day of the patient's informed consent to the day before the first dose of nivatrotamab
- On-treatment period: From the day of the first dose of nivatrotamab to 30 days after the last dose of nivatrotamab
- Post-treatment period: From 31 days after the last dose of nivatrotamab and thereafter

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, the respective data will be assigned to the on-treatment period.

Additional analyses and presentations will be included in the SAP.

AEs will be presented descriptively in summary tables and listings.

AEs will be regarded as Treatment-emergent AEs (TEAEs) if they occur after the start of the first IMP administration.

A TEAE is defined as an AE that emerges during treatment having been absent pre-treatment (i.e., has onset on or after the first dose of study treatment).

AEs with onset during the pre- and post-treatment periods will be listed. AEs with onset during the on-treatment period will be summarized as follows:

- Summaries of AEs by MedDRA SOC and PT will be presented for all TEAEs, related TEAEs, CTCAE grade 3 or higher TEAEs, related CTCAE grade 3 or higher TEAEs, injection-related TEAEs, SAEs, related SAEs, CTCAE grade 3 or higher SAEs, related CTCAE grade 3 or higher SAEs, TEAEs leading to treatment discontinuation, and AEs leading to death.

11.4.4 Safety Laboratory Parameters

Descriptive statistics will be presented for baseline values, absolute values, and changes from baseline in safety laboratory parameters. Laboratory data will be summarized in tables and presented in figures by the type of laboratory test.

11.4.5 Vital Signs

Vital signs will be listed.

11.4.6 Electrocardiogram

Abnormal ECG-observations will be listed and summarized. The ECG data will be summarized for the SAF.

11.4.7 Analyses of Anti-tumor Activity

The efficacy analyses will be based on the FAS.

11.4.7.1 Imaging Data

All imaging data will be listed. Reduction in tumor sizes will be analyzed by summarizing the measures of the target lesions, including the relative change (%) from baseline. Graphs of the individual patient profiles over time of the (i) sum of measures and (ii) relative change in the sum of measures from baseline will be presented.

The best relative change from baseline will be presented in a waterfall plot.

11.4.7.2 Response Evaluation

The responses will be evaluated according to both RECIST 1.1 and iRECIST.

RECIST 1.1

The OR is the best timepoint response recorded from the start of the study treatment until the EOT. Patients who obtain CR and PR are considered responders. Both confirmed and unconfirmed responses will be presented. Patients are considered non-responders if they obtain SD, PD, or “Not evaluable” as OR.

SD requires that post-baseline measurements have met the SD criteria at least once and for a minimum period of 4 weeks (± 7 days).

The OR rate will be presented including corresponding, for binomial distribution, exact 95% confidence intervals.

The DCR as well as proportions of patients in disease control at 4, 8, 16, and 24 weeks (± 7 days for each of the timepoints) will be analyzed and presented in the same way as OR.

iRECIST

Responses assigned using iRECIST have a prefix of "i" (immune): iCR, iPR, iSD, iUPD, or iCPD to differentiate them from responses assigned using RECIST 1.1. Patients who obtain iCR and iPR are considered responders. Patients are considered non-responders if they obtain iSD, iUPD, iCPD or Not Evaluable as iOR. For iDCR, patients are considered to be in disease control if the corresponding response is iCR, iPR, or iSD. iSD requires that post-baseline measurements have met the iSD criteria at least once and for the same time-period as SD.

The iRECIST response endpoints are analyzed using the same statistical methodology and the results presented in the same way as for the corresponding RECIST 1.1 endpoints.

11.4.7.3 Progression-free Survival

PFS and iPFS are derived as the time from the first dose administration until progression or death, whichever occurs first.

The progression date to be used for calculation of iPFS should be the first date at which progression criteria are met (i.e, the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, the iUPD date should still be used if:

- the patient stops protocol treatment because they were not judged to be clinically stable, or
- no further response assessments are done (because of patient refusal, protocol non-compliance, or patient death), or
- the next timepoint responses are all iUPD, and iCPD never occurs, or
- the patient dies from their cancer.

PFS and iPFS will be derived for all patients and presented graphically as well as summarized using survival analysis methods: distribution functions will be estimated using the Kaplan-Meier technique and plotted. The corresponding Kaplan-Meier quartile estimates including 2-sided 95% confidence intervals will be presented.

PFS and iPFS will be censored on the date of the last adequately evaluable tumor assessment for patients who do not have an event (progression or death), for patients who start new anti-cancer

treatment prior to an event, or for patients with an event after 2 or more consecutive missing tumor assessments.

Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the date of the first treatment unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

11.4.7.4 Duration of Response

The DoR and iDoR are calculated, censored, and presented in the same way as PFS and iPFS, respectively, above with the following differences:

- DoR and iDoR are derived for responders only
- DoR and iDoR begin at the timepoint when the criteria for response are first met.

11.4.8 Overall Survival

OS is defined as the time from the first dose administration until death. OS will be analyzed using the same Kaplan-Meier methodology as for PFS above, except that in the absence of an observed event, OS is censored on the latest day that the patient is known to be alive as per assessment or contact.

11.4.9 PK Analysis

The PK information will be summarized for the PKAS.

All PK-concentrations and PK-parameters will be presented in listings.

Individual curves of nivatrotamab concentrations, including information on actual dose, will be presented for all patients. All available data will be shown in these figures. Both actual as well as ln (log)-transformed values will be presented. In the graphical presentations, values below the lower level of quantification (LLOQ) will be set to LLOQ/2 and marked with a "<LLOQ." Any values above the upper level of quantification (ULOQ) will be marked with a ">ULOQ."

PK parameters (Table 11-2) will be calculated based on non-compartmental methods.

Table 11-2 List of PK parameters

Parameter	Description
C_{max}	The maximum (peak) observed drug concentration after a single dose administration
T_{max}	The time to reach maximum (peak) drug concentration in serum after a single dose administration.
AUC_{0-T}	The area under the serum concentration–time curve from time zero to the last quantifiable timepoint (T).
$AUC_{0-\infty}$	The area under the serum concentration–time curve from time zero to infinity
$T_{1/2}$	The elimination half-life associated with the terminal slope (λ_z) of a semi-logarithmic concentration–time curve.
CL	The total body clearance of drug from serum.
V_d	Volume of distribution

The relation between derived PK parameters and covariates such as actual dose, weight, and selected parameters will be evaluated graphically.

If deemed applicable, compartmental modeling approaches to parameter estimation will be applied.

The PK-parameters will be presented in summary tables where AUC and C_{max} will be summarized using the geometric mean and the coefficient of variation (CV) that is based on a log-normal distribution: $CV(\%)=100 \cdot \sqrt{e^{\sigma_{ln}^2} - 1}$.

The half-life will be summarized using the harmonic mean.

In support of the RP2D-selection, analyses of a relation between exposure and response will be performed:

- Exposure after Cycle 1
  - C_{max}
  - $AUC_{0-\infty}$
- Response
  - Efficacy at weeks 4 and 8
    - Disease control [RECIST & iRECIST] (yes/no)
    - Reduction in tumor size (Section 11.4.7.1)
  - Safety after Cycle 1, 2 and 4
    - CRS (yes/no)
    - Highest grade of CRS
    - SAE (yes/no)

by means of logistic regressions (with ordinal response variable for highest grade of CRS, as appropriate) or linear regression for Reduction in tumor size. Non-linear PK/PD-modelling of the above will be considered.

Further details of the analyses and results presentations will be presented in a separate plan.

11.4.10 Analysis of Anti-Drug Antibody Formation

Immunogenicity data will be listed and positive/negative host immune response to nivatrotamab and presence of binding antibodies will be summarized (positive/negative).

The immunogenicity information will be summarized for the SAF.

11.4.11 Exploratory Objectives

GD2 expression from tumor tissue will be summarized and presented graphically.

The results from these exploratory analyses may be presented in a separate report.

11.4.12 Interim Analysis

No formal interim analyses are planned. Ad-hoc interim analyses may be performed in relation to health authority interactions.

11.4.13 Subgroup Analyses

No subgroups beyond the sensitivity/resistance to previous platinum therapy strata in phase 2 are defined.

11.4.14 Handling of Missing Data

Missing safety data will in general not be imputed. In the analyses of OR, patients with evaluable disease at baseline but who cannot be evaluated for response will be considered as non-responders.

11.5 Reporting of Trial Results

The results from this trial will be presented in a clinical trial report (CTR) after the last patient in the dose expansion has reached the end of the trial.

12 ETHICS

12.1 Independent Ethics Committee (IEC) 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 from the IRB/IEC before enrollment of any patient into the trial for the trial protocol/protocol amendments, advertisements, the patient information and the Informed Consent, including any written material to be given to the patient.

12.2 Ethical Conduct of the Trial

The trial will be conducted in accordance with the protocol, applicable regulatory requirements, International Council on Harmonisation (ICH) Good Clinical Practice ([37]) (GCP) and the ethical principles of the Declaration of Helsinki ([38]) as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and sub-sequent versions.

The trial will be conducted according to FDA regulations relating to GCP and clinical trials, Protection of Human Subjects (21 CFR Part 50) and as per Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population (recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to GCP in the conduct of clinical trials on medicinal products for human use). The guideline is referenced on internet address http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf.

12.3 Patient Information and Informed Consent

The Investigator or his/her designee must obtain the written informed consent from each patient, before any trial related procedures are performed as applicable to local regulations. The written patient information must not be changed without prior discussion with the Sponsor and approval by the IRB/IEC.

Patient must receive full trial information, both verbally and written, before consent is given.

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.

Before signing the ICF, the patient 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. The 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 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. It is recommended to notify the patient's family doctor of the patient's consent to participate in the trial.

12.4 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 patient will be identified only by a subject ID number.

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.

13 MONITORING AND QUALITY ASSURANCE

13.1 Compliance with Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki [38] (as amended in Edinburgh, Tokyo, Venice, Hong Kong, Washington, Seoul, and South Africa), International Council for Harmonisation (ICH) guideline [37], or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the trial patient.

13.2 Protocol Compliance

The Investigator is responsible for ensuring the trial is conducted in accordance with the procedures and evaluations described in this protocol. Deviations from the protocol should not occur. If deviations do occur, the Investigator has to inform the CRA for discussion and decision on required action(s). Deviations should be documented in writing including an explanation. Documentation of deviations will be filed in the Investigator's site file and a copy in the Sponsor's file. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority.

13.3 Changes 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 regulatory authorities and IRB/IECs. Approval must be obtained before changes can be implemented.

13.4 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 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 Principal Investigator to ensure documented training of all personnel.

13.5 Monitoring

In accordance with the principles of ICH GCP and the Sponsor or its designee's standard operating procedures, 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.

The CRA will ensure that accountability of IMPs is performed and will review source documents for verification of consistency with the data entered 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 (i.e. within the previous 2 years), 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 attributable, legible, contemporaneous, original, and accurate
- 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.

13.5.1 Monitoring of Pharmacies

If a pharmacy is needed to be involved at the site, then monitoring of the records kept here will be described in the monitoring plan.

13.6 Source Data Verification

13.6.1 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 reported in the hospital records:

- Clinical trial identification
- Patient identification
- Date when patient information was given and when the signed informed consent was obtained
- Diagnosis
- Fulfilment of eligibility criteria
- Specification of treatment with IMP
- Specification of visit dates, concomitant medications 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

13.6.2 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.

13.6.3 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 entered 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.

13.6.4 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 CRA immediately. The Investigator agrees to provide to representatives of a regulatory authority or Sponsor direct access to source documentation, facilities, and personnel for the effective conduct of any inspection or audit.

13.6.5 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 source documents, will provide a guided tour of the facilities and will allocate ample time and the time of the personnel to the auditor as may be required to have interviews and discuss findings and potential issues.

14 DATA HANDLING AND RECORD KEEPING

14.1 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 an 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 demographic data and any SAE must be captured in the eCRF.

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 eCRF data 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 entered in the eCRFs.

14.1.1 Corrections to Data

Corrections to the eCRF data can be made by the Investigator or the Investigator's delegated staff. The eCRF will contain an audit trail capturing as a minimum: the original and corrected/changed data, identification of the person correcting/changing the data, date and time of the correction/change and reason for the correction.

If corrections are made by the Investigator's delegated staff after the date the Investigator has signed the eCRF, the Investigator must re-sign the eCRF.

14.1.2 Data Entry Timelines

The Investigator must ensure that data is entered in the eCRF as soon as possible after the trial visit and no later than 5 working days after the trial visit. Detailed requirements for data entry will be specified in the eCRF completion guideline. Timeliness of data entries are monitored in the eCRF system. Data entry later than 5 days after the trial visit does not qualify as protocol non-compliance (section 13.2) and does not need to be documented by the Investigator; however, the CRA will address lateness during monitoring visits.

14.2 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 2 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. 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).

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.

All clinical trial documents must be retained by the Investigator until at least 25 years after the clinical trial. 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 inspection.

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 (for ADA, PK and tumor tissue assessments) will be discarded after the analysis has been completed and no later than at the finalization of the full Clinical Trial Report. If requested by the local sites, the tumor tissue material may be returned before End of Trial.

14.3 Data Management

All data, except IL-6, ADA, PK and tumor tissue data, will be collected using an eCRF compliant with 21 CFR Part 11 regulation. IL-6, ADA, PK and tumor tissue data centrally collected 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. The Investigator will approve the data using an electronic signature and thereby confirm the accuracy of the data entry. Medical history and AEs will be coded using the MedDRA dictionary. Concomitant medication will be coded using the World Health Organization (WHO) Drug dictionary.

15 PREMATURE TERMINATION OF THE TRIAL

15.1 Sponsor Criteria for Pausing Patient Enrolment

Enrolment will be paused if one of the following criteria is met:

- One or more patients experience unexpected, sudden death during the treatment period
- SAEs or frequency of AEs that, in the judgement of the Sponsor, are deemed to warrant immediate review by the DMC.
- One or more patients experience treatment-related death before EOT visit

If an above-mentioned criterion is met, the DMC will review the safety results and determine how to proceed as described in section 9.9.3.

Patients already included at the time of clinical trial pause, will continue in the clinical trial but further dosing will be postponed until a decision has been reached by the DMC.

15.2 Criteria for Termination of the Trial

The Sponsor reserves the right to close a trial site or terminate the trial at any time for the reasons below at the sole discretion of the Sponsor. If the trial is suspended or terminated, the Investigator must inform the patients promptly and ensure that adequate considerations is given to the protection of the patient's interest. The Sponsor must promptly inform the regulatory authorities and provide a detailed explanation of the termination. Furthermore, the Investigator or Sponsor will inform IECs/IRBs.

Trial site(s) will be closed upon completion. A trial site is considered closed when it has been verified that all eCRFs have been completed as far as possible, that all required documents are filed as required and that the IMP have been destroyed and a trial site closure visit has been performed.

The Investigator may initiate trial site closure at any time, provided there is a reasonable cause and sufficient notice in advance of the intended termination.

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

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, in accordance with applicable regulatory requirements. 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 [39] (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.

16.2 Use of Information

Sponsor will make 1 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 REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.
2. Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol. 2006;24(28):4539-44.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30.
4. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet. 2011;378(9804):1741-55.
5. Kalemkerian GP. Small Cell Lung Cancer. Semin Respir Crit Care Med. 2016;37(5):783-96.
6. Micke P, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer. 2002;37(3):271-6.
7. Osterlind K, Hansen HH, Hansen M, Dombernowsky P, Andersen PK. Long-term disease-free survival in small-cell carcinoma of the lung: a study of clinical determinants. J Clin Oncol. 1986;4(9):1307-13.
8. Foster NR, Qi Y, Shi Q, Krook JE, Kugler JW, Jett JR, et al. Tumor response and progression-free survival as potential surrogate endpoints for overall survival in extensive stage small-cell lung cancer: findings on the basis of North Central Cancer Treatment Group trials. Cancer. 2011;117(6):1262-71.
9. Nicholson AG, Chansky K, Crowley J, Beyruti R, Kubota K, Turrisi A, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(3):300-11.
10. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018;379(23):2220-9.
11. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394(10212):1929-39.
12. Hanna N, Bunn PA, Jr., Langer C, Einhorn L, Guthrie T, Jr., Beck T, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol. 2006;24(13):2038-43.
13. Lara PN, Jr., Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol. 2009;27(15):2530-5.
14. Eckardt JR, von Pawel J, Pujol JL, Papai Z, Quoix E, Ardizzoni A, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol. 2007;25(15):2086-92.

15. von Pawel J, Jotte R, Spigel DR, O'Brien ME, Socinski MA, Mezger J, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol. 2014;32(35):4012-9.
16. Gong J, Salgia R. Managing Patients With Relapsed Small-Cell Lung Cancer. J Oncol Pract. 2018;14(6):359-66.
17. Ardizzoni A, Hansen H, Dombernowsky P, Gamucci T, Kaplan S, Postmus P, et al. Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. J Clin Oncol. 1997;15(5):2090-6.
18. Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. J Clin Oncol. 2017;35(34):3823-9.
19. Regzedmaa O, Zhang H, Liu H, Chen J. Immune checkpoint inhibitors for small cell lung cancer: opportunities and challenges. Onco Targets Ther. 2019;12:4605-20.
20. Bristol Myers Squibb. Bristol Myers Squibb Statement on Opdivo (nivolumab) Small Cell Lung Cancer U.S. Indication 2020 [Available from: https://news.bms.com/news/details/2020/Bristol-Myers-Squibb-Statement-on-Opdivo-nivolumab-Small-Cell-Lung-Cancer-US-Indication/default.aspx.
21. Merck. Merck Provides Update on KEYTRUDA® (pembrolizumab) Indication in Metastatic Small Cell Lung Cancer in the US 2021 [Available from: https://www.merck.com/news/merck-provides-update-on-keytruda-pembrolizumab-indication-in-metastatic-small-cell-lung-cancer-in-the-us/.
22. Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020;21(5):645-54.
23. Nazha B, Inal C, Owonikoko TK. Disialoganglioside GD2 Expression in Solid Tumors and Role as a Target for Cancer Therapy. Front Oncol. 2020;10:1000-.
24. Yoshida S, Fukumoto S, Kawaguchi H, Sato S, Ueda R, Furukawa K. Ganglioside G(D2) in small cell lung cancer cell lines: enhancement of cell proliferation and mediation of apoptosis. Cancer Res. 2001;61(10):4244-52.
25. United Therapeutics Corp. Unituxin® (dinutuximab) [package insert]. U.S. Food and Drug Administration website. www.accessdata.fda.gov/drugsatfda_docs/label/2015/125516s000lbl.pdf (accessed November 16, 2020). [
26. Xu H, Cheng M, Guo H, Chen Y, Huse M, Cheung NK. Retargeting T cells to GD2 pentasaccharide on human tumors using Bispecific humanized antibody. Cancer Immunol Res. 2015;3(3):266-77.
27. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.
28. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst. 2009;101(10):708-20.
29. Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. Clin Cancer Res. 2016;22(17):4291-301.

30. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95.
31. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
32. Lin NU, Prowell T, Tan AR, Kozak M, Rosen O, Amiri-Kordestani L, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Brain Metastases Working Group. J Clin Oncol. 2017;35(33):3760-73.
33. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72.
34. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
35. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e52.
36. Yuan Y, Liu S. Bayesian Optimal Interval (BOIN) Design for Single-Agent and Drug - Combination Phase I Clinical Trials, software package for R, v 2.7.0, September 2020, https://cran.r-project.org/web/packages/BOIN/ (last accessed November 02, 2020) [
37. International Council for Harmonisation. S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals2011. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals.
38. World Medical Association. WMA Declaration of Helsinki-Ethical principles for medical research involving human subjects. Fortaleza, Brazil; 2013.
39. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals (ICMJE recommendations). 2019.
40. Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. Journal of the Royal Statistical Society Series C (Applied Statistics). 2015;64(3):507-23.

19 APPENDICES

Appendix 1 Statistical properties of the modified BOIN-design

The BOIN design is described in statistical detail in [40] as well as in clinical application in [28]. It can be considered as a generalization of the 3+3, accelerated titration and 3+3+3 designs and is quite similar to these designs [28]).

Let $\hat{p}$ denote the observed DLT-rate (number of patients with DLT/number of patients treated) at the current dose level.

The BOIN design shares the simplicity of the 3+3 design, which makes the decision of dose escalation/de-escalation by comparing $\hat{p}$ with 0/3, 1/3, 2/3, 0/6, 1/6, and 2/6. In the BOIN design this decision is based on a comparison of $\hat{p}$ with 2 pre-determined fixed boundaries, λ_e and λ_d.

In this study, the target toxicity level, i.e. the target DLT rate, is 28%% and the boundaries $\boldsymbol{\lambda_e}$=0.229 and $\boldsymbol{\lambda_d}$=0.334. This choice gives the design escalation and de-escalation rules that are similar to the 3+3 and 3+3+3 designs, e.g, note the similarities in how 2 DLTs in 6 or 9 patients are addressed in Table 6-3. While not directly comparable, in a standard 3+3 design the DLT rate of the MTD is <33%.

The λ_e=0.229 and λ_d=0.334 are based on:

- p_{saf}= 0.65 × 28% = 18% (the highest toxicity probability that is deemed subtherapeutic [i.e., below the MTD] such that dose escalation should be undertaken)
- p_{tox}= 1.4 × 28% =39% (the lowest toxicity probability that is deemed overly toxic such that de-escalation is required)

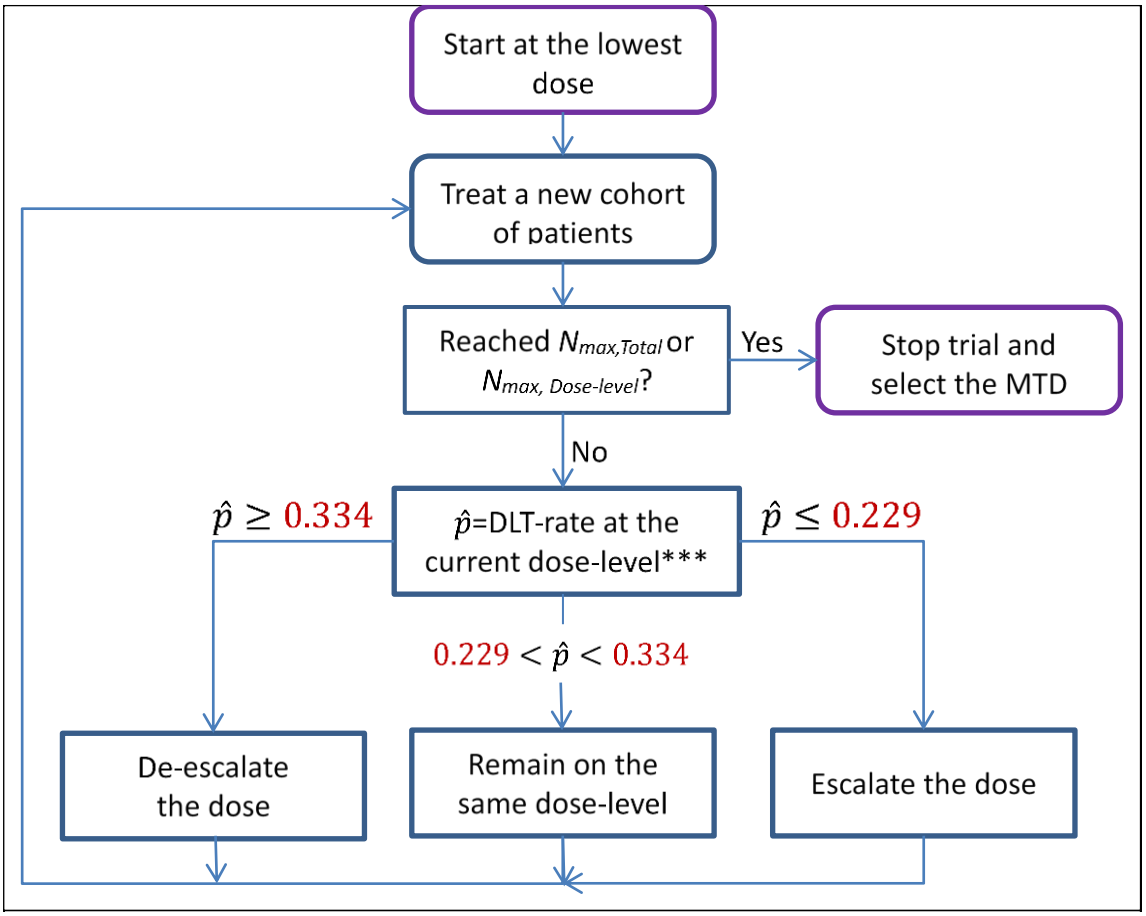
In this trial, the BOIN has been modified in 2 ways:

- The single-patient cohorts in the initial accelerated stage allocates fewer patients to low dose-levels with low chance of therapeutic effect.
- A declaration of the MTD on a dose-level based on ≤1 DLT in 6 patients in a situation where a higher dose-level has been evaluated and the number of DLTs on that higher dose-level lead to a de-escalation.

For operational simplicity, the rules based on the comparisons of the DLT-rate $\hat{p}$ with the rate-boundaries, λ_e and λ_d have been translated into number of patients and patients with DLTs and presented in Figure 19-1 below. While the disallowing of dose-levels is not described in [28], it is described in the implementation of BOIN in R provided by Yuan and (R package 'BOIN' v 2.7.0, Yuan Y and Liu S, 2020).

When a large number of patients have been assigned to a dose-level (here 9 seems to be an appropriate number, the dose-finding algorithm has approximately converged, and one can stop early and select the MTD).

Figure 19-1 Flow-chart of the BOIN-design



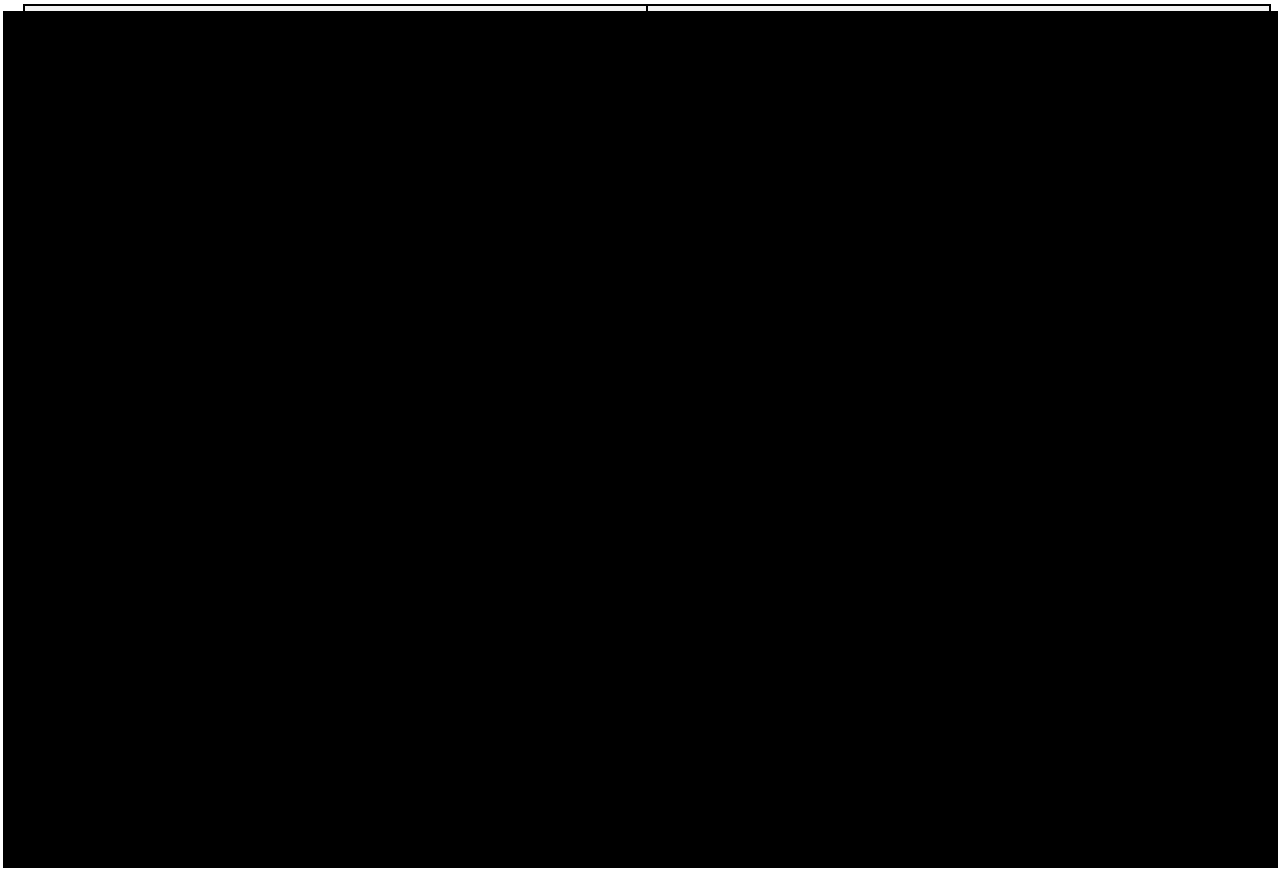
$N_{max,Total}$:maximum total number of patients in the dose-escalation (39).
$N_{max,\ Dose\text{-}level}$: maximum number of patients on a dose-level (9).
If either $N_{max,Total}$ is reached or $N_{max,\ Dose\text{-}level}$ is reached (*** and the decision rule recommends to remain on the same dose-level), the trial dose escalation should stop and the MTD be selected.

The remainder of this section investigates the operational characteristics of the mBOIN design implemented in R (v 3.6.0) including the BOIN package [36] with the accelerated titration design option set to true (Titration=True) , based on 20000 simulations. The simulation results have the following limitations, reflecting the limitations and available features of the BOIN package v2.7.0:

- The number of dose-levels in the accelerated titration part are not limited
- The probability of the first grade>=2 toxicity is the same as for a DLT

The operating characteristics are estimated based on simulations under 4 different scenarios.

Figure 19-2 Dose-toxicity scenarios used for assessment of operating characteristics



A brief description of the dose-toxicity relationships in the 4 scenarios:

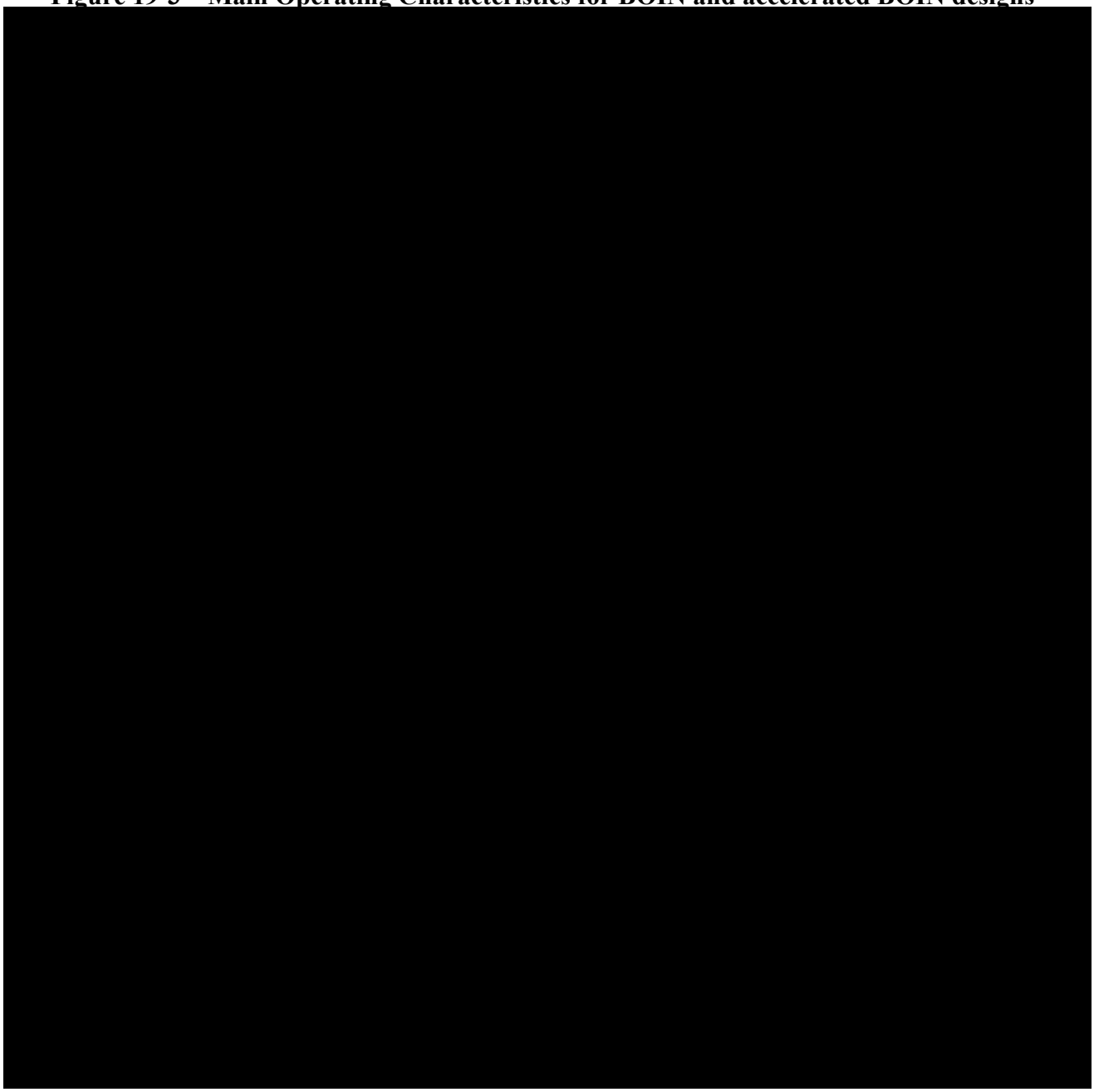
All 7 dose-levels under investigation are safe and the probability of DLT is very low (≤7%) on all of them.

A linear-like dose-tox ranging from 5% to 35%. The true MTD comes “late”: on the sixth dose-level.

A sigmoid-like dose-toxicity relationship, where the true MTD is on the fourth dose-level.

Toxicity is seen early and most dose-levels are quite toxic.

Figure 19-3 Main Operating Characteristics for BOIN and accelerated BOIN designs



The expected total number of patients ranges between 18 and 23 patients. The actual sample size may vary: it may be lower or higher, depending on the real trial data.

Figure 19-4 Expected number of patients per dose-level

The expected number of patients per dose-level reflects the assumptions for dose-toxicity-relationship in the different scenarios. Approximately half of the expected number of patients are allocated to dose-levels near the MTD.

Figure 19-5 Expected number of patients with DLTs per dose-level

The expected number of patients with DLTs per dose-level reflects the assumptions for dose-toxicity-relationship in the different scenarios. Fewer patients with DLTs are observed on dose-levels with toxicity rates above the MTD: the trial design stops the escalation in due time.

Appendix 2 **Protocol amendment summary of key changes**

Version	Date	Description of document
1.0	04-Dec-2020	Final Protocol
2.0	07-Jan-2021	Final Protocol -FDA requested amendment during IND evaluation
3.0	12-Jan-2021	Final Protocol -FDA requested amendment during IND evaluation
4.0	14-Jan-2021	Final Protocol -FDA requested amendment during IND evaluation
5.0	15-Jan-2021	Final Protocol -FDA requested amendment during IND evaluation
6.0	09-Feb-2021	Protocol amendment to introduce the Current concepts in the diagnosis and management of cytokine release syndrome, to introduce pre-medication and management of pain and to introduce temporary withdrawal of antihypertensive medication. Furthermore, minor changes are included to clarify ambiguous wording and ensure consistency across protocol sections.
7.0	23-Jun -2021	FDA requested amendment to replace the Current concepts in the diagnosis and management of cytokine release syndrome with ASTCT CRS consensus grading system. Furthermore, to remove section regarding temporary withdrawal of antihypertensive medication. In addition, minor changes are included to clarify ambiguous wording and ensure consistency across protocol sections.
8.0	20-Jan-2022	Exclusion criteria #12 updated according to recommendations from American Society of Clinical Oncology. Frequency of CRS grading and ICE-scoring/neurotoxicity assessments updated in flow chart, section 3.

Signature Page for CLIN-000151 v8.0

Approval	[redacted] 20-Jan-2022 09:46:10 GMT+0000

Approval	[redacted]y 20-Jan-2022 13:21:35 GMT+0000

Approval	[redacted] 20-Jan-2022 13:33:23 GMT+0000

Signature Page for CLIN-000151 v8.0