STATISTICAL ANALYSIS PLAN

Protocol XPORT-GBM-029

A Phase 1/2 Study of Selinexor (KPT-330) in Combination with Standard of Care (SoC) Therapy for Newly Diagnosed or Recurrent Glioblastoma

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	**Definition**
AE	Adverse event
BSA	Body surface area
C1D1	Cycle 1 day 1
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDx (e.g., C1D1)	Cycle x Day x (e.g., Cycle 1 Day 1)
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EoT	End of Treatment
EDC	Electronic data capture
EOT	End of Treatment
GBM	Glioblastoma multiforme
HR	Hazard ratio
ICF	Informed consent form
IRC	Independent Review Committee
K-M	Kaplan-Meier
KPS	Karnofsky Performance Score
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguanine-DNA-methyltransferase

Abbreviation	Definition
mITT	Modified intent-to-treat
mMGMT	Methylated O6-methylguanine-DNA-methyltransferase
uMGMT	Unmethylated O6-methylguanine-DNA-methyltransferase
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
nGBM	Newly diagnosed GBM patients
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDn	Pharmacodynamic
PFS	Progression-free survival
PFS3	Progression-free survival rate at 3 months
PFS6	Progression-free survival rate at 6 months
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per-protocol
PR	Partial response
PT	Preferred term
RT	Radiation Therapy
QW	Once weekly
QoL	Quality of life
rGBM	Recurrent GBM patients
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure

Abbreviation	Definition
SD	Stable disease
SOC	System organ class
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
TTP	Time to progression
ULN	Upper limit of normal
WBC	White blood cell
WHO	World health organization

1. OVERVIEW AND INVESTIGATIONAL PLAN

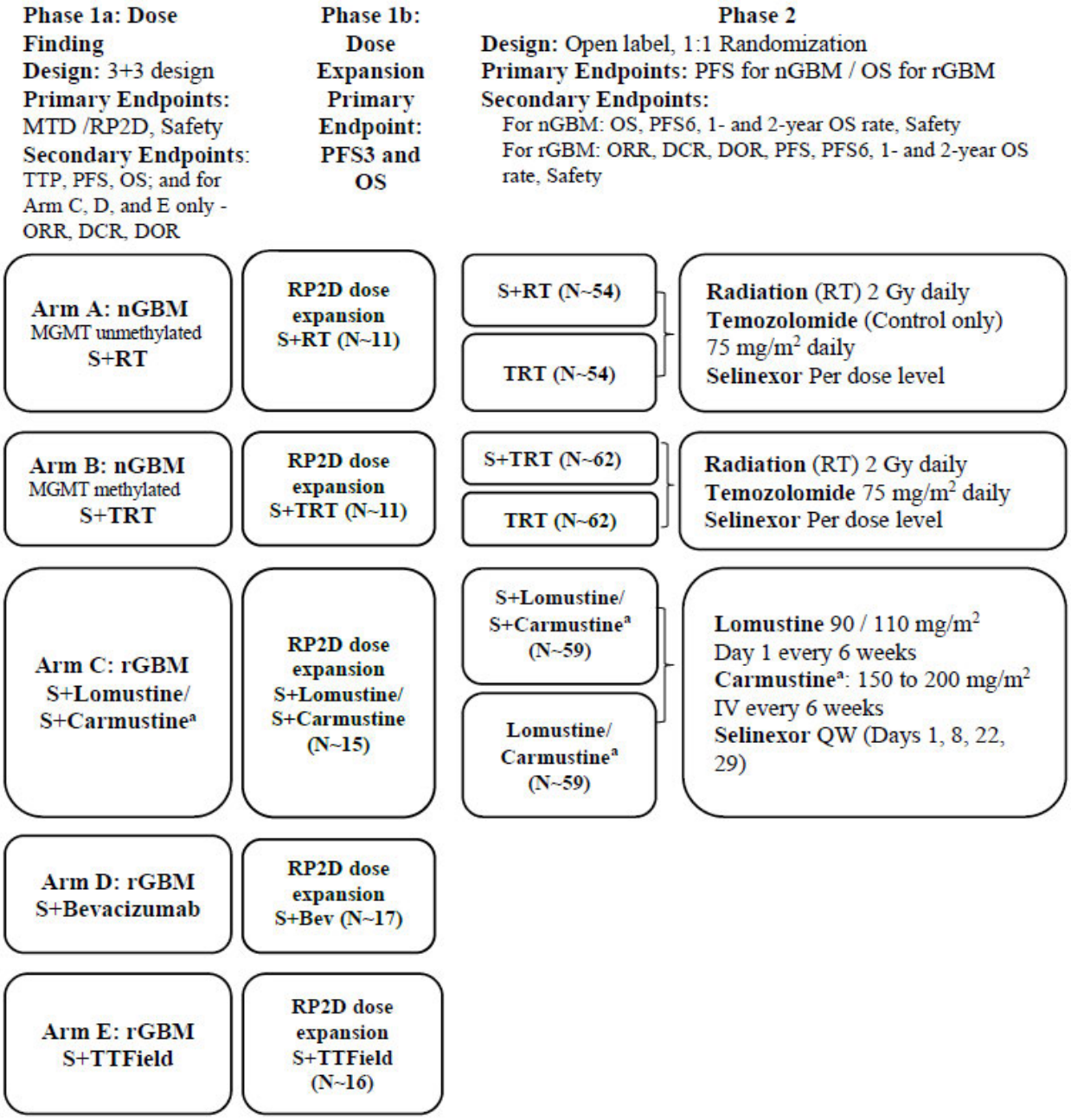
1.1. STUDY DESIGN

This is a global, multicenter, open-label, clinical study with Dose Escalation (Phase 1a) followed by Phase 1b (Dose Expansion) and (Phase 2 randomized efficacy exploration) to independently assess the MTD, efficacy, and safety of selinexor in combination with SoC therapy for nGBM or rGBM. The study will independently evaluate 5 different combination regimens in 5 treatment arms in patients with nGBM (Arms A and B) or with rGBM (Arm C, D, and E).

- Arm A: evaluating the combination of selinexor with RT (S-RT) in nGBM patients with uMGMT
- Arm B: evaluating the combination of selinexor with RT and TMZ (S-TRT) in nGBM patients with mMGMT
- Arm C: evaluating the combination of selinexor with lomustine (or carmustine if lomustine is not available) (S-L/C) in rGBM patients regardless of MGMT status
- Arm D: evaluating the combination of selinexor with bevacizumab in rGBM patients regardless of MGMT status
- Arm E: evaluating the combination of selinexor with TTField in rGBM patients regardless of MGMT status

An overview of all arms is provided in the Study Flow Chart (Figure 1-1).

Figure 1-1 Study Flow Chart



Bev: bevacizumab; DOR: duration of response; DCR: disease control rate; QW: once a week; nGBM: newly diagnosed GBM; ORR: objective response rate; OS: overall survival; MGMT: O6-methylguanine-DNA-methyltransferase; MTD: maximum tolerated dose; PFS: progression-free survival; PFS3: progression-free survival rate at 3 months; PFS6: progression-free survival rate at 6 months; RP2D: recommended Phase 2 dose S: selinexor; rGBM: recurrent GBM; RT: radiotherapy; S: selinexor; TRT: temozolomide + radiotherapy; TTP: time to progression; TTField: tumor treating fields.
[a] Carmustine may be substituted for lomustine if lomustine is not available.

1.1.1. Phase 1a - Dose Escalation Phase

For nGBM Arm A, B and rGBM Arm C, Arm D, and Arm E approximately 9 to18 evaluable patients will be enrolled for each arm for a total of 45 to 90 patients. With emerging data and upon Safety Review Committee (SRC) agreement, selected dose level can be expanded with additional patients to better understand the safety, anti-tumor activity and PK/pharmacodynamics (PDn) of that dose.

An independent 3+3 dose escalation of selinexor will be performed in each arm until the MTD and/or RP2D for that Arm is reached. Safety Review Committee meetings will occur between each dose level to review dose limiting toxicities (DLTs). Consensus among SRC to proceed to the next dose level will be documented. The SRC is comprised of Investigators and Sponsor Medical Monitors.

The RP2D to be used in the Phase 1b and Phase 2 portion for each Arm will be determined by the SRC, based on the MTD and the totality of efficacy and safety data seen in the Phase 1a dose escalation study.

Dose-escalation will follow the rules outlined below in **Error! Reference source not found.**.

Table 1-1 Dose Escalation Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enroll 3 patients at the next higher dose level
≥2 out of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose. Up to 3 additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enroll 3 more patients at this dose level. • If 0 of these 3 additional patients experience DLT, proceed to the next higher dose level. • If 1 or more of these 3 additional patients suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Up to 3 additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
≤1 out of 6 at highest dose level at or below the maximally administered dose	This is the MTD. RP2D can be at or below MTD and will be determined based on the totality of the available safety, efficacy, PK/PDn data from all dose levels. At least 6 patients must be entered at the RP2D.

DLT=dose-limiting toxicity; MTD=maximum tolerated dose.

The number of patients defined in this table are those patients considered evaluable for DLT and MTD evaluation unless they cannot complete the first cycle of therapy for any reason other than a DLT. A patient will be DLT-evaluable if the patient experiences a DLT in Cycle 1, or has taken at least 2 out of the 3, or at least 3 out of the 4, or at least 4 out of the 6 planned selinexor doses (depending on planned dosing frequency) or both doses if a patient is dosed twice only in Cycle 1 without experiencing a DLT. A patient who is not DLT-evaluable will be replaced. Dose level review discussions will be held by the Sponsor and Investigators to determine dose escalation, reductions, and dose level expansions.

Note: AEs that occur outside of Phase 1a are not dose-limiting toxicity (DLTs).

1.1.2. Phase 1b – Expansion Phase

The open label Dose Expansion Phase (Phase 1b), will confirm safety of the MTD/RP2D and preliminary signal of efficacy (PFS rate at 3 months [PFS3] compared to historical benchmarks) and OS in patients with nGBM and rGBM before proceeding to Phase 2. Patients will receive the RP2D determined in the Phase 1a in each arm and further information on safety and efficacy will be obtained.

- Arm A: nGBM uMGMT, approximately 11 patients are required with a 1-sided 95% confidence interval
- Arm B: nGBM mMGMT approximately 11 patients are required with a 1-sided 95% confidence interval
- Arm C: rGBM regardless of MGMT status, approximately 15 patients are required with a 1-sided 95% confidence interval
- Arm D: rGBM regardless of MGMT status, approximately 17 patients are required with a 1-sided 95% confidence interval
- Arm E: rGBM regardless of MGMT status, approximately 16 patients are required with a 1-sided 95% confidence interval

1.1.3. Phase 2 – Efficacy Exploration/Randomization Phase

During Phase 2, patients will receive the RP2D in each arm in an open-label, randomized design. The number of patients for each arm in the Phase 2 portion will be evaluated again at the end of the Phase 1 portion.

- Arm A: nGBM uMGMT approximately 108 patients (54 patients in S+RTexperimental arm and 54 patients in TRT control arm).
- Arm B: nGBM mMGMT approximately 124 patients (62 patients in S+TRT experimental arm and 62 patients in TRT control arm).
- Arm C: rGBM regardless of MGMT status, approximately 118 patients (59 patients in S+L/C experimental arm and 59 patients in L/C control arm).

Randomization in Arm C (Section 7.2) will be stratified based on:

- Number of prior lines of anti-GBM regimens (1 versus >1)

It is planned to randomize patients in a 1:1 allocation to treatment and control arm.
Patients will continue to receive treatment until disease progression (however, patients may stay on treatment if they have documented clinical benefit per the Investigator and after documented approval with the medical monitor), death, toxicity (i.e., AEs that cannot be managed with medical care), or withdrawal from the study.

1.2. OBJECTIVES

1.2.1. Primary Objective

This is a Phase 1/2 study of selinexor in combination with SoC therapy for nGBM or rGBM. This study will be conducted in 2 phases. The modified RANO criteria will be used for assessment in Arms A, B, and D; and RANO criteria for Arms C and E.

The specific primary objectives are as follows:

Objectives	Endpoints
Primary Objectives **Phase 1a** (for all arms) • To assess the MTD per arm • To evaluate the RP2D per arm	**Primary Endpoints** **Phase 1a** (for all arms) • MTD/RP2D per arm • The occurrence of Grade ≥3 AEs, all serious adverse events (SAEs), and all AEs leading to treatment discontinuation
Phase 1b (for all arms) • To determine the efficacy of selinexor in all patients as determined by the 3-month PFS (PFS3) rate with PFS assessment as per RANO/modified RANO per Investigator assessment	**Phase 1b** (for all arms) • All Arms: PFS3 (survival probability of having PFS ≥3 months as estimated by Kaplan-Meier method per Investigator assessment)

• To determine the efficacy of selinexor in all patients as determined by the OS	• OS, defined as the time from initiation of treatment until death due to any cause
Phase 2 • Arms A and B: to determine the efficacy of selinexor in all nGBM patients as determined by PFS per modified RANO per independent review committee (IRC) in patients randomized to the experimental arm (S-RT in Arm A and S-TRT in Arm B) vs the control arm treated with SoC regimen (TRT) in the targeted population	**Phase 2** • Arms A and B: PFS, defined as the time from date of randomization until the first date of PD or death due to any cause per IRC assessment
• Arm C: to compare OS in all rGBM patients randomized to the experimental arm (selinexor + lomustine/or carmustine) vs the control arm treated with SoC regimen (lomustine/carmustine) in the targeted population	• Arm C: OS, defined as the time from randomization until death due to any cause

1.2.2. Secondary Objectives

The specific secondary objectives are as follows. The modified RANO criteria will be used for assessment in Arms A, B, and D; and RANO criteria for Arms C and E.

Secondary Objectives	**Secondary Endpoints**
Phase 1a • To assess OS for each arm independently	**Phase 1a** • OS
Phase 1a/b • To assess time-to-progression (TTP) and PFS for each arm independently	**Phase 1a/b** • TTP, defined as time from date of first study treatment until progression or death due to progression • PFS

• For Arm C, D, and E only: To evaluate the overall response rate (ORR) and disease control rate (DCR) based on RANO/modified RANO criteria • For Arm C, D, and E only: To assess duration of response (DOR)	• For Arm C, D, and E only: ORR, defined as the proportion of patients who have a response of partial response (PR) or complete response (CR) • For Arm C, D, and E only: DCR, defined as the proportion of patients in whom the best overall response is determined as CR, PR or stable disease (SD) • For Arm C, D, and E only: DOR, defined as time from date of first occurrence of objective response (PR or CR) until progression
• To assess selinexor PK in plasma when administered with radiation therapy, temozolomide, and/or lomustine/ carmustine, bevacizumab, and TTField	• Selinexor PK parameters (e.g., clearance [CL], area under the concentration curve [AUC], maximum concentration [C_{max}])
Phase 1b • To obtain additional safety, tolerability data.	**Phase 1b** • To further characterize the occurrence of Grade ≥3 AE, all serious adverse events (SAEs), and all AEs leading to treatment discontinuation and confirm tolerability at the MTD/RP2D.

Phase 2 • Arms A and B: to determine the efficacy of selinexor in all nGBM patients as determined by PFS per modified RANO criteria per investigator assessment in patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population • Arms A and B: to compare OS in all nGBM patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population • Arm C: to determine PFS per RANO criteria per IRC and investigator assessment in all rGBM patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population. • Arm C only: to compare the ORR and DCR based on the response per RANO per Investigator assessment and per IRC in patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population. • Arm C only: to compare the DOR per RANO per Investigator assessment and per IRC in patients randomized to the experimental arm vs the control arm • All Arms: to determine the efficacy of selinexor in all patients as determined by the (PFS6) rate where PFS assessment is per RANO/modified RANO per IRC and investigator assessment • All Arms: to assess the 1 and 2-year OS rate of patients in experimental and control arm • All Arms: to assess the safety and tolerability of treatment in patients randomized to the experimental arm vs	**Phase 2** • Arms A and B: PFS per Investigator assessment • Arms A and B: OS for patients with nGBM • Arm C: PFS per IRC assessment • Arm C: PFS per Investigator assessment • Arm C only: ORR per IRC and Investigator assessment • Arm C only: DCR per IRC and Investigator assessment • Arm C only: DOR per IRC and Investigator assessment • All Arms: PFS6 (survival probability of having PFS ≥ 6 months as estimated by Kaplan-Meier method per IRC and investigator assessment) • All Arms: 1-year OS (OS1) and 2-year OS (OS2) rate as estimated by Kaplan-Meier method • All Arms: Safety • All Arms: Incidence of selected Grade ⩾3 AEs, including hematological abnormalities, gastrointestinal disorders (nausea, vomiting, and diarrhea), and fatigue • All Arms: Incidence of all SAEs. • All Arms: Incidence of AEs leading to treatment discontinuation

the control arm treated with SoC regimen in the targeted population	

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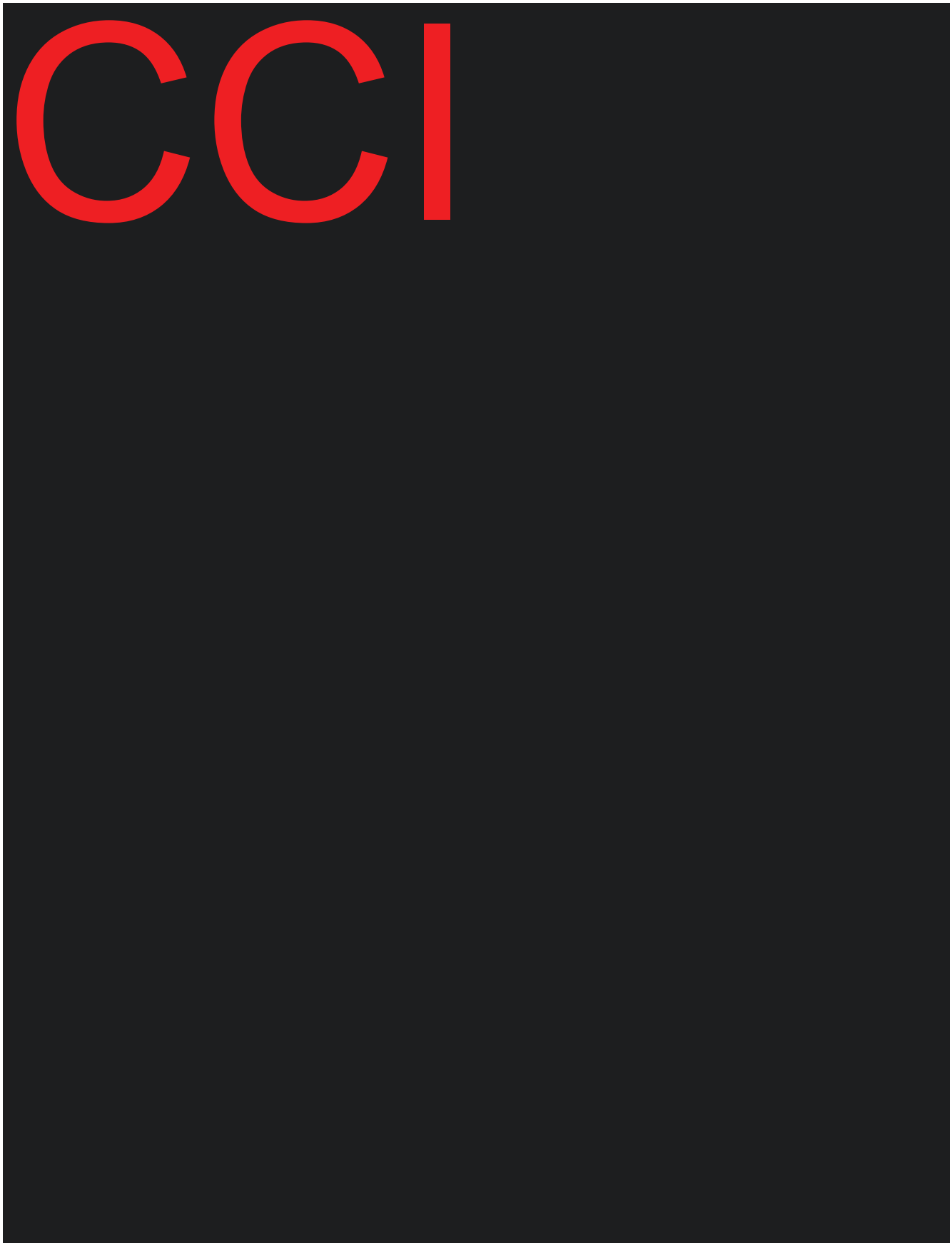
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1.4. STUDY PLAN

For each patient that signs the informed consent, the study consists of:

- Screening/baseline visit: occurs within 28 days prior to receiving the 1st dose of study treatment
- Treatment period: study treatment may continue until completing protocol defined treatment duration (for Arm A and B), disease progression determined by the treating physician per RANO/modified RANO criteria (however patients may stay on treatment if they have documented clinical benefit per the Investigator and after documented approval with the medical monitor), unacceptable AEs or failure to tolerate the study treatment, treatment delay of more than 28 days (except in specific cases with documented approval by the Sponsor), any medically appropriate reason or significant protocol violation (in the opinion of the Investigator), or patient decides to discontinue study treatment, withdraws consent, or becomes pregnant.

- Follow-up period: After discontinuation of study treatment, patients will be followed for safety up to 30 days after last dose, for PFS approximately every 3 months after end of treatment visit until PD, death or initiation of the subsequent anti-GBM treatment (if a patient discontinues from the treatment due to reasons other than PD), and for survival every 3 months after end of treatment visit until the end of study (i.e., when the last patient in the study has been followed on study treatment for at least 1 year or completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up, whichever occurs first).
- End of study: will occur after the last patient to be enrolled has been followed on study treatment for at least 1 year or completed the at least 6 months of survival follow-up period.

1.5. MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable. The current SAP is based on Protocol v6.0.

1.6. CHANGES IN THE STATISTICAL ANALYSIS PLAN

Not applicable. This is the original version of the SAP.

2. GENERAL STATISTICAL METHODS AND DATA HANDLING

This SAP outlines the methods to be used in the analysis of clinical data in order to answer the study objectives. Populations for analysis, data handling rules, and statistical methods are provided. This SAP does not include endpoints and methods to be used in the analysis of PK and PDn data; these will be included in a separate plan. This version of SAP is mainly to specify analyses for Phase 1a/b and more details of analyses for Phase 2 will be provided in later versions.

2.1. GENERAL ANALYSIS METHODS

All summary statistics will be computed and displayed among the corresponding analysis population, and by each assessment time point whenever applicable. Summary statistics for continuous variables will in general include n, median, mean, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be presented with the denominators for the percentages determined based on the analysis population used, unless otherwise specified. For time-to-event variables, the Kaplan-Meier (KM) method will be used for descriptive summaries. Graphical displays may be provided as appropriate.

2.2. OBSERVATION PERIOD

The observation period will be divided by the following:

- The pre-treatment period is defined as the time from the signed informed consent date up to the time before the first dose of study treatment
- The treatment period is defined as the time from the first dose of study treatment up to the date of last study treatment + 30 days, or the day before initiation of a new anti-neoplastic treatment, whichever comes first, inclusive
- The post-treatment period is defined as the time beyond the treatment period

The on-study observation period is the pre-treatment, treatment, and post-treatment period.

2.3. MISSING DATA HANDLING IN DATA PRESENTATION

In general, missing baseline values will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data will be summarized using counts (n) and percentages (%). The denominator will be the total number of people in the corresponding analysis group, based on the population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data: summaries will be based on observed data only

2.3.1. Handling of Computation of Treatment Duration if Study Treatment End of Treatment Date is Missing

For the calculation of treatment duration, the date of the last dose of study treatment is equal to the date of last study treatment dosing reported on the electronic case report form (eCRF) dosing page. If all the dosing dates are missing, then the duration is missing.

2.3.2. Handling of Missing/partial Dates for Adverse Events or Concomitant Medications

In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates as late as possible. However, for categorization purposes, if the partial AE onset date information does not indicate whether the AE started prior to treatment, during the treatment period, or after the treatment period, the AE will be classified as treatment-emergent.

The data imputations are only for categorization purposes or calculation of AE duration, and will not be used in listings.

Refer to the *Karyopharm Biostatistics and Statistical Programming Rule Book Version 2.0* for details on imputation methods.

2.3.3. Handling of Missing Assessment of Relationship of AEs to Study Treatment

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment is considered as related.

2.4. STUDY TREATMENT DOSING DATE

Study treatment dosing date is the date on which a patient actually received study treatment (partial or complete), as recorded on the study drug exposure eCRF.

The start date of study treatment is defined as the earliest non-zero dose date of any study drug, and the end date of study treatment is defined as the latest non-zero dose date of any study drug.

2.5. STUDY DAY CALCULATION

Study Day 1 is the date of first study treatment. The day before Day 1 is considered Day -1. There is no Day 0.

A patient is considered as treated in a cycle if the patient received any non-zero dose of study drug in that cycle.

Study day for a given assessment is defined as

- the assessment date – the date of first study treatment + 1 if the assessment date is on or after Day 1, or
- The assessment date – the date of first study treatment if the assessment date is before Day 1

2.6. BASELINE MEASUREMENT

In general, the baseline value is defined as latest measured value prior to the first dose of study treatment.

In the event that an assessment is performed on the same date as the first dose and it cannot be determined whether it preceded the first dose, the evaluation time will be assumed to be prior to dosing.

2.7. VISIT WINDOWS

For safety data that are summarized/plotted by time points, non-missing assessments from all scheduled and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme. Analysis visit windows are defined in Table 2-1, Table 2-1.

If there are 2 or more assessments mapped to the same analysis visit for a patient, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments mapped to the same analysis visit with the same distance from the target visit day, the latest one will be selected for the analysis.

Table 2-1 Visit Windows for Clinical Laboratory Tests (for Arm A and Arm B)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline (C1)	Day 1	Prior to or on Day 1
Day 8	Day 8	Day 2 to 11
Day 15	Day 15	Day 12 to 18
Day 22	Day 22	Day 19 to 25
Day 29	Day 29	Day 26 to 32
Day 36	Day 36	Day 33 to 39
Day 43 (C2)	Day 43	Day 40 to 50
Day 57	Day 57	Day 51 to 64
Day 71 (C3)	Day 71	Day 65 to 78
Day 85	Day 85	Day 79 to 92
Day 99 (C4)	Day 99	Day 93 to 106
…		
(every 14 days)		

NOTE: Day 1 is the date of first study treatment. Analysis visit and visit window may change for certain parameters depending on the data availability.

Table 2-2 Visit Windows for Vital Signs (for Arm A, B)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline (C1)	Day 1	Prior to or on Day 1
Day 22	Day 22	Day 2 to 29
Day 36 (C1D36)	Day 36	Day 30 to 46
Day 57 (C2D15)	Day 57	Day 47 to 64
Day 71 (C3)	Day 71	Day 65 to 78
Day 85	Day 85	Day 79 to 92
Day 99 (C4)	Day 99	Day 93 to 106
Day 113	Day 113	Day 107 to 120
Day 127 (C5)	Day 127	Day 121 to 134
…		
(every 14 days)		
NOTE: Day 1 is the date of first study treatment. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 2-3 Visit Windows for Clinical Laboratory Tests (for Arm C)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline (C1)	Day 1	Prior to or on Day 1
Day 8	Day 8	Day 2 to 11
Day 15	Day 15	Day 12 to 18
Day 22	Day 22	Day 19 to 25
Day 29	Day 29	Day 26 to 32
Day 36	Day 36	Day 33 to 39
Day 43 (C2)	Day 43	Day 40 to 53
Day 64	Day 64	Day 54 to 74

Day 85 (C3)	Day 85	Day 75 to 95
Day 106	Day 106	Day 96 to 116
Day 127 (C4)	Day 127	Day 117 to 137
…		
(every 21 days)		
NOTE: Day 1 is the date of first study treatment. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 2-4 Visit Windows for Vital Signs (for Arm C)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline (C1)	Day 1	Prior to or on Day 1
Day 22	Day 22	Day 2 to 29
Day 36	Day 36	Day 30 to 39
Day 43 (C2)	Day 43	Day 40 to 53
Day 64	Day 64	Day 54 to 74
Day 85 (C3)	Day 85	Day 75 to 95
Day 106	Day 106	Day 96 to 116
Day 127 (C4)	Day 127	Day 117 to 137
Day 148	Day 148	Day 138 to 158
…		
(every 21 days)		
NOTE: Day 1 is the date of first study treatment. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 2-5 Visit Windows for Clinical Laboratory Tests (for Arm D and Arm E)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline (C1)	Day 1	Prior to or on Day 1
Day 15	Day 15	Day 2 to 22

Day 29 (C2)	Day 29	Day 23 to 36
Day 43	Day 43	Day 37 to 50
Day 57 (C3)	Day 57	Day 51 to 64
…		
(every 14 days)		
NOTE: Day 1 is the date of first study treatment. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 2-6 Visit Windows for Vital Signs (for Arm D and Arm E)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline (C1)	Day 1	Prior to or on Day 1
Day 22	Day 22	Day 2 to 25
Day 29 (C2)	Day 29	Day 26 to 39
Day 50	Day 50	Day 40 to 53
Day 57 (C3)	Day 57	Day 54 to 67
Day 78	Day 78	Day 68 to 81
Day 85 (C4)	Day 85	Day 82 to 95
…		
(every 21 days and 7 days)		
NOTE: Day 1 is the date of first study treatment. Analysis visit and visit window may change for certain parameters depending on the data availability.		

2.8. SUBGROUPS

No subgroup analysis is planned in Phase 1a or Phase 1b.

2.9. POOLING OF CENTERS FOR STATISTICAL ANALYSES

All participating centers in the study will be pooled together for analyses.

2.10. COMPUTING AND CODING STANDARDS

Activities will be performed using the following tools:

Table, listing, and figure production	SAS Version 9.4 or higher
Coding	
AEs	MedDRA Version 24.0 or higher
Medical Histories	MedDRA Version 24.0 or higher
Prior and Concomitant Medications	WHO DDE Version September 2018 or higher
Grading	
AEs	CTCAE Version 4.03
Labs	CTCAE Version 4.03

3. PATIENT INFORMATION

3.1. ANALYSIS POPULATIONS

Dose Escalation Population (per Arm in Phase 1a)

The dose escalation population will consist of all patients in the Dose Escalation Phase 1a who have either had a DLT prior to completion of 1 cycle of therapy, or who have completed a cycle of therapy.

RP2D Population (per Arm in Phase 1a/b)

The RP2D population will consist of all patients in the Dose Expansion Phase 1b and those in Phase 1a receiving RP2D dose who receive at least 1 dose of study treatment.

mITT Population (per Arm in Phase 1a/b)

The mITT population will consist of patients in Phase 1a and Phase 1b who have been assigned to study intervention and who have received ≥1 dose of study drug.

Safety Population (per Arm in Phase 1a/b)

The safety population will consist of patients in Phase 1a and Phase 1b who have been assigned to study intervention and who have received ≥1 dose of study drug. Participants will be analyzed according to the intervention actually received.

3.2. DISPOSITION OF PATIENTS

The following variables may be used to summarize patient disposition:

- Patients who received at least one dose of study treatment (partial or complete)
- End of treatment status:
    - Patients still on treatment (if applicable)
    - Patients who discontinued treatment and primary reason for treatment discontinuation
- Survival follow-up status
    - Patients in survival follow-up
    - Patients who have completed 1-year survival follow-up
    - Patients who died during survival follow-up
    - Patients who discontinued from the study without completing 1-year survival follow-up
- End of study status:

- Patients still on study (if applicable)
- Patients who discontinued study and primary reason for study discontinuation

The number of patients in each analysis population will be presented.

3.3. PROTOCOL DEVIATIONS

Major protocol deviations will be presented in a listing.

3.4. DEMOGRAPHICS, MEDICAL HISTORY AND BASELINE CHARACTERISTICS

Demographics, medical history and baseline characteristics will generally be summarized among dose escalation Population, RP2D Population and safety populations, unless otherwise specified.

3.4.1. Demographic Data

The demographic characteristics to be summarized will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic origin, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

3.4.2. Prior Treatment

There are 3 types of prior treatments for GBM: radiation therapy, antineoplastic therapy and surgery. Number and percentage of prior radiation therapy, prior antineoplastic therapy, and prior surgery will be summarized.

3.4.3. Medical History - Conditions and Procedures

Medical history other than GBM will be summarized by system organ class (SOC) and preferred term (PT) using the number and percentage of patients who have at least one occurrence of a SOC and PT.

Medical history information may also be provided in a data listing.

3.4.4. Disease History

The following summary statistics will be summarized using descriptive statistics:

- Number and percentage of initial diagnosis
- Time since initial diagnosis to first recurrence/relapse
- Time since initial diagnosis to most recent recurrence/relapse
- Time since initial diagnosis to informed consent
- Time since most recent recurrent/relapse to informed consent

3.5. PRIOR AND CONCOMITANT MEDICATIONS

All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE).

Prior medications are any medications received by the patient prior to the first dose of study drug. Prior medications can be discontinued before the first dose of study treatment or can be ongoing during treatment period.

Concomitant medications are any treatments received by the patient concomitantly with study treatment, from first dose of study treatment to last dose of study treatment + 30 days.

Note that a medication can be classified as both a prior medication and a concomitant medication.

Concomitant medications will generally be summarized among mITT and safety populations, unless otherwise specified. Concomitant medications will be summarized according to the WHO DDE by the ATC level 2 (therapeutic level), level 4 (generic level) and preferred name. A patient taking the same drug multiple times will only be counted once.

The use of prior and concomitant medications and procedures may also be provided in a data listing.

Please refer to Section 2.3.2 for details on data handling rules related to computation, dates and imputation for missing dates.

3.6. EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

Extent of exposure and compliance will be summarized for dose escalation population, RP2D population and safety populations, unless otherwise specified.

3.6.1. Extent of Study Treatment Exposure

The extent of exposure for the study treatment will be assessed using the following variables:

- Duration of study treatment exposure (continuous and categorized)
- Occurrence of selinexor dose escalation

The following will be assessed separately for each study drug (selinexor, Temozolomide, Lomustine and etc.):

- Duration of exposure (continuous and categorized)
- Total dose received (continuous)
- Average dose received per week (continuous)
- Occurrence of dose reduction
- Occurrence of dose interruption
- Occurrence of missed dose

Duration of study treatment exposure is defined as the date of last study treatment – date of first study treatment + 1.

Average dose received per week is defined as total dose received divided by duration of exposure.

3.6.2. Treatment Compliance

Study treatment compliance is defined as

$$\frac{\text{number of actual study treatment doses taken}}{\text{number of study treatment doses prescribed}} \times 100$$

A study treatment dose is considered prescribed if any study drug is prescribed. The number and percentage of patients with study treatment compliance ≥80% will be provided. Note that the number of prescribed study treatment doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

Selinexor compliance is similarly defined as

$$\frac{\text{number of actual selinexor doses taken}}{\text{number of selinexor doses prescribed}} \times 100$$

The number of scheduled selinexor doses does not include doses missed due to treatment interruption or other reasons not related to patient choice. The number and percentage of patients with selinexor compliance ≥80% will be provided.

Lomustine and other drug (if applicable) compliance will be defined and summarized in the same manner.

4. EFFICACY

Objective disease response assessment will be made according to modified RANO in Arms A, B, D or RANO in Arms C and E. The data used for Phase 1 primary analysis will be based on Investigator assessment and that of Phase 2 primary statistical analysis will be provided by the IRC.

Documentation of response requires two consecutive assessments of the disease, performed at time with 4 weeks interval required between the two assessments. The date of response or PD will be assigned to the earlier date of the two independent assessments, unless PD is based on an unambiguous criterion such as a clinical deterioration not attributable to other causes apart from tumor or attributable to changes in steroid dose.

If a patient had one PD assessment but was not subsequently confirmed, unless IRC considers the progression assessment unambiguous, it is not considered a PD event per modified RANO.

4.1. PRIMARY EFFICACY ENDPOINT

4.1.1. Rate of 3-Month Progression Free Survival (PFS3) – Ph1b

The analysis of PFS3 will be performed by calculating the estimated survival probability of having PFS $\geq$ 3 months based on Kaplan-Meier method, where PFS will be calculated from the date of start of study treatment to the date of progression, or date of death should progression not have occurred. The outcome and censoring definitions of PFS are provided in OS will be calculated from the date of start of study treatment to the date of death. Patients who are still alive prior to the data cutoff for efficacy analysis, or who dropout prior to study end, will be censored on the day they were last known to be alive. The analysis of OS will be based on the Kaplan-Meier method for estimation of summary statistics including 50^{th} percentiles (median) and associated 95% CIs.

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The target day of 3-month assessment in Arm A and B is Cycle 3 Day 22 (day 92) with a window of ±3 days. The target day of 3-month assessment in Arm C is Cycle 2 Day 36 (day 78) with a window of ±3 days. The target day of 3-month assessment in Arm D and E is Cycle 3 Day 22 (day 78) with a window of ±3 days. To accommodate potential changes in individual patient's visit schedules, disease assessments on or before day 97 will be used for the primary analysis of rate of 3-month PFS. Actual times of events (progression or death) will be used for the Kaplan-Meier statistical summary of PFS.

A sensitivity analysis of the primary endpoint of PFS3 will be performed to assess the potential influence of causality of deaths on study, where deaths due to causes that are clearly unrelated to the disease or study drug would not be considered as a PFS event and instead would be censored on the last response assessment before a censoring event.

4.1.2. OS – Ph1b

OS will be calculated from the date of start of study treatment to the date of death. Patients who are still alive prior to the data cutoff for efficacy analysis, or who dropout prior to study end, will be censored on the day they were last known to be alive. The analysis of OS will be based on the Kaplan-Meier method for estimation of summary statistics including 50th percentiles (median) and associated 95% CIs.

4.2. SECONDARY EFFICACY ENDPOINTS

4.2.1. OS - Ph1a

OS will be calculated similarly to that in primary endpoint.

4.2.2. PFS - Ph1a/b

PFS is defined as the duration from date of first dose until the date of first confirmed PD or death due to any cause on or before EOT + 30 days, whichever occurs first. The outcome and censoring definitions are provided in OS will be calculated from the date of start of study treatment to the date of death. Patients who are still alive prior to the data cutoff for efficacy analysis, or who dropout prior to study end, will be censored on the day they were last known to be alive. The analysis of OS will be based on the Kaplan-Meier method for estimation of summary statistics including 50^{th} percentiles (median) and associated 95% CIs.

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If a patient has preliminary PD without a confirmed PD per mRANO, and has EOT due to clinical PD, then EOT is treated as confirmed PD.

The number and percentage of censored patients will be reported. The 25th, 50th (median), and 75th percentiles for PFS and associated 95% CIs will be estimated based on the K-M method, and the K-M curves will be provided.

Table 4-1 Outcome and Censoring Definition for DOR and PFS

Situation	**Date of event or censoring**	**Outcome**
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of first dose	Censored
Death before PD without a gap of 2 or more consecutively missed scheduled disease status assessments before death	Date of death	Event
Confirmed PD without a gap of 2 or more consecutively missed scheduled disease status assessment before progression	Date of PD (first preliminary PD per Modified RANO)	Event
No confirmed PD or death on or before a. database cut, b. withdrawal of informed consent, c. lost to follow-up, d. start of new GBM treatment, whichever occurs first	Date of last adequate disease assessment prior to the earliest occurrence of the events (a. – d.) listed in the left column	Censored
No confirmed PD or death before a gap of 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

4.2.3. TTP - Ph1a/b for Arm C, D and E only

TTP is defined as the duration from start of study treatment to time of PD or death due to disease progression, whichever occurs first. Details on the outcome and censoring definitions are provided in Table 4-2.

The number and percentage of censored patients will be reported. The median TTP and associated 95% CI will be estimated based on the K-M method, and the K-M curve will be provided.

Table 4-2 Outcome and censoring definition for TTP

Situation	Date of event or censoring	Outcome
No adequate post-baseline disease status assessment unless death due to disease progression occurs prior to first post-baseline assessment	Date of first dose	Censored
Death due to disease progression before PD without a gap of 2 or more consecutively missed scheduled disease status assessments before death	Date of death	Event
Confirmed PD without a gap of 2 or more consecutively missed scheduled disease status assessment before progression	Date of PD (first preliminary PD per Modified RANO)	Event
No confirmed PD or death due to disease progression on or before a. death due to reasons other than disease progression, b. database cut, c. withdrawal of informed consent, d. lost to follow-up, e. start of new GBM treatment, whichever occurs first	Date of last adequate disease assessment prior to the earliest occurrence of the events (a. – e.) listed in the left column	Censored

No confirmed PD or death due to disease progression before a gap of 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

4.2.4. ORR - Ph1a/b for Arm C, D and E only

ORR is defined as either complete response (CR) or partial response (PR), calculated as a proportion and including a 95% exact CI.

4.2.5. DCR - Ph1a/b for Arm C, D and E only

DCR is defined as defined as the proportion of patients in whom the best overall response is determined as CR, PR, or stable disease (SD), calculated as a proportion and including a 95% exact CI. The duration of stable disease, which is calculated from C1D1 to first PD, death due to any cause or initiating a new anti-GBM treatment, is required no shorter than 16 weeks.

4.2.6. DOR - Ph1a/b for Arm C, D and E only

DOR is defined, for patients with a confirmed PR or better as the duration from the date of first confirmed PR or better to the date of first confirmed PD or death due to any cause, whichever occurs first. Details on the outcome and censoring definitions used for DOR are provided are provided in OS will be calculated from the date of start of study treatment to the date of death. Patients who are still alive prior to the data cutoff for efficacy analysis, or who dropout prior to study end, will be censored on the day they were last known to be alive. The analysis of OS will be based on the Kaplan-Meier method for estimation of summary statistics including 50^{th} percentiles (median) and associated 95% CIs.


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5. SAFETY

Safety analyses will be based on the reported AEs and other safety information, such as ECG, vital signs, physical examination, Karnofsky performance status, and clinical laboratory assessments. Safety analyses will be performed using the safety population and will be descriptive; no statistical testing is planned.

5.1. ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

All AEs (including serious adverse events [SAEs]) will be coded to a PT and associated primary SOC using the Medical Dictionary for Regulatory Activities (MedDRA).

The severity of all AEs will be graded according to the NCI CTCAE Grading Scale. An AE with a CTCAE grade of 3 or higher is considered a severe AE. The severity of the AE is different from the seriousness of the AE.

5.1.1. Definitions

- A ***treatment-emergent AE (TEAE)*** is an AE that was not present prior to the initiation of study treatment or was present and worsened in intensity or frequency following exposure to study treatment, from the first dose to 30 days after the last dose (inclusive). Additionally, any AE that occurs 30 days after the last dose of study treatment is considered a TEAE if considered by the Investigator as related to any study treatment.
- A ***serious AE (SAE)*** is any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e., an event in which the patient 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); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect
- A ***treatment-emergent treatment-related AE (TRAE)*** is any TEAE that is considered by the Investigator to be related to any study treatment.

5.1.2. Analysis Methods

Analyses of AEs will be performed only for TEAEs.

If an AE date/time of onset (occurrence or worsening) is incomplete, an imputation algorithm will be used to classify the AE is treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is

definitive information to determine it is not treatment emergent. Details on classification of AEs with missing or partial onset dates are provided in Section 2.3.2.

AE summaries will include number and percentage of patients who have experienced a TEAE. The denominator for percentages is the total number of patients in the treatment Arm. Multiple occurrences of the same event in the same patient will be counted only once in the tables.

Unless otherwise specified, sorting order will follow the alphabetic order in SOC, and further by decreasing frequency of PTs within each SOC. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

The summary of AEs by causality will generally include the following categories of causality.

- Related to any study drug
- Related to Selinexor only
- Related to Temozolomide only (Arm A and B)
- Related to Lomustine only (Arm C)
- Related to Bevacizumab only (Arm D)
- Related to Tumor Treating Fields only (Arm E)
- Not related to any of the above drug

5.1.2.1. Analysis of TEAEs

A TEAE overview summary table will be provided, which will include the number of patients with any:

- TEAEs
    - Grade 3/4
    - Serious
    - Leading to dose modification (i.e., reduction or interruption) of any study drug
    - Leading to dose reduction of any study drug
    - Leading to dose interruption of any study drug
    - Leading to study treatment discontinuation
    - Leading to death
- TRAEs
    - Same subcategories as for TEAEs

TEAEs will also be summarized by primary SOC and PT and will include the following categories:

- All
    - By maximum grade
    - By causality
- Grade ≥3
- Leading to dose modification of any study drug
- Leading to dose reduction of any study drug
- Leading to dose interruption of any study drug
- Leading to study treatment discontinuation

5.1.2.2. Analysis of SAEs

Treatment-emergent SAEs will be summarized by primary SOC and PT and will include the following categories:

- All
- Leading to dose modification of any study drug
- Leading to dose reduction of any study drug
- Leading to dose interruption of any study drug
- Leading to study treatment discontinuation

Data listings will be provided for SAEs.

5.1.2.3. Analysis of DLTs

DLTs will be summarized in the dose escalation population. A data listing will be provided for DLTs.

5.2. DEATH

The following summaries on death events will be provided:

- An overview of all death events and primary cause of death
- TEAEs leading to death (death as an outcome on the AE page as reported by the Investigator), by primary SOC and PT
- TEAEs leading to death and are related to study treatment, by primary SOC and PT
- Listing of all TEAEs leading to death

- Listing of all death events

5.3. LABORATORY SAFETY VARIABLES

5.3.1. Definitions

Blood samples for clinical laboratory tests will be taken as specified in the study protocol, and measurements in conventional units will be converted using the international system of units (SI).

5.3.2. Analysis of Laboratory Variables

For each dose level, the actual value and change from baseline (Day 1, prior to the first administration of study drug) to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry. In the event of repeat values, the last non-missing value per study day/time will be used.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g., those measures that have a corresponding CTCAE grade classification). Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced.

5.4. VITAL SIGNS, KARNOFSKY PERFORMANCE STATUS, AND PHYSICAL EXAMINATION VARIABLES

Full physical examinations (PEs) are performed at Screening and at the end-of-treatment (EoT) visit; at other visits, symptom-directed physical exams may be conducted.

Examinations include height, weight, BSA calculated by the Dubois method (Dubois and Dubois, 1916), and vital signs (heart rate, systolic and diastolic blood pressure, and body temperature). A Karnofsky performance status (KPS) assessment will be performed at Screening, Day 1 of each cycle, and the EoT visit.

The actual value and change from baseline over time will be summarized for vital signs. Abnormal vital signs results will be summarized in the threshold/range analyses.

Shift tables that present changes from baseline to worst on-study and last on-study KPS status will be presented.

5.5. ELECTROCARDIOGRAM (ECG)

Standard 12-lead ECG will be performed at Screening (or predose on cycle 1 day 1 [C1D1]) and the EoT visit.

Changes from baseline for PR interval, QRS interval, and QT corrected using Fridericia's formula will be summarized using shift tables. For heart rate, changes from baseline will be presented. Abnormal ECG results will be summarized in the threshold/range analyses.

Electrocardiogram data for each patient may also be provided in a data listing.

6. REFERENCES

Ellingson, Benjamin M., Patrick Y. Wen, and Timothy F. Cloughesy. "Modified criteria for radiographic response assessment in glioblastoma clinical trials." Neurotherapeutics 14.2 (2017): 307-320.

Karyopharm Biostatistics and Statistical Programming Rule Book v2.0, Karyopharm Therapeutics Inc.

Document Approvals

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