STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Open-label, Single-arm Study Evaluating the Efficacy, Safety and Tolerability of Oncolytic Polio/Rhinovirus Recombinant (lerapolturev) and the Immune Checkpoint Inhibitor Pembrolizumab in the Treatment of Patients with Recurrent Glioblastoma
Phase:	II
Protocol No.:	LUMINOS-101
Protocol Date(s):	Version 4.0: 26 May 2021
Analysis Plan Version and Date:	Version 1.0: 23 June 2022
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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the planned data summary and analysis of data from Protocol LUMINOS-101. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

This is an open-label, single-arm, non-randomized study characterizing the efficacy, safety, and tolerability of lerapolturev delivered via intratumoral infusion followed by pembrolizumab in patients with recurrent glioblastoma (rGBM). Approximately 30 eligible participants, 18 years of age or older, are planned to be enrolled and treated with lerapolturev and at least one dose of pembrolizumab in this study. The maximum planned duration of follow-up in this study is up to 24 months (104 weeks), and consists of the following treatments:

- Single lerapolturev infusion on Day 0
    - Note: retreatment with lerapolturev is allowed for qualifying participants who progress ≥ 6 months from initial lerapolturev infusion
- Pembrolizumab (200 mg intravenous (IV) infusion) initiated 14 days after lerapolturev infusion (up to 28 days, if necessary), given every 3 weeks, through Week 104 (23.5 months of treatment) or until immune-related AE (irAE) meeting criteria for dose interruption/discontinuation or confirmed progression (must consider clinical and radiographic assessments)

The study will occur in the following periods:

- Screening Period 1: Between 1 and 6 weeks prior to catheter placement
- Screening Period 2: Within 7 days prior to catheter placement
- Catheter Placement and Biopsy (if required) Period: Day 0
- Lerapolturev Infusion Period/Baseline: Single lerapolturev infusion on Day 0 or Day 1 (unless extension granted by Sponsor)
- Post-lerapolturev Infusion, Pembrolizumab Treatment and Follow-up Period: pembrolizumab starting at Week 2 (up to Week 4, max) and every 3 weeks thereafter, to a maximum of Week 104 (approximately 23.5 months maximum pembrolizumab treatment duration)

The study may be adapted or expanded in one or more larger cohorts of participants, in consultation with the Data and Safety Monitoring Board (DSMB), based on interim review and considering the totality of the study data.

1.2. SCHEDULE OF EVENTS

Table 1: Schedule of Assessments

Description	Screening[1]		Treatment and Follow-Up Periods[18]								
	Screen. Period 1	Screen Period 2	Catheter/ lerapolture v[2]	Post-lerapolturev infusion, pembrolizumab treatment and Follow-Up (± 7 days)[3]							
Week	Within 6 weeks of catheter placement	Within 1 week relative to catheter placement		1	2	U (3-4)[5]	5 or +3 weeks	8 or +3 weeks	11; + every 3 weeks to week104 max.	Follow-Up	End of Study visit
Day	-42 to 8	-7 to 1	0 (+1 day)	1	14	(28)	35 or +21	56 or +21	+21 up to max 730	From discontinuation of pembrolizumab	Anytime for permanent discontinuation
Visit	1	2	3	4	5	U	6	7	≥ 8	≥ 8	
General Evaluations											
Informed Consent	X										
Medical History	X	X	X								
Physical Exam[6,7]		X		X	X	X	X	X	X		X
Neurologic Exam[7]		X		X	X	X	X	X	X		X
NANO assessment[7]		X		X	X	X	X	X	X		X
KPS[7]		X		X	X	X	X	X	X		X
PRO[4]		X		X			X		X		
Adverse Events		Continuous (including AE due to non-SOC screening procedures)									
Concomitant Medications		Continuous (throughout the duration of the study)									
Lab Evaluations											
PV booster vaccine	X										
CBC w/diff	X	X	X	X	X	X	X	X	X		X
CMP	X	X		X	X	X	X	X	X		X
Pancreatitis labs (amylase, lipase)		X		X	X	X	X	X	X		

Description	Screening[1]		Treatment and Follow-Up Periods[18]								
	Screen. Period 1	Screen Period 2	Catheter/ lerapolturev[2]	Post-lerapolturev infusion, pembrolizumab treatment and Follow-Up (± 7 days)[3]							
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Day	-42 to 8	-7 to 1	0 (+1 day)	1	14	(28)	35 or +21	56 or +21	+21 up to max 730	From discontinuation of pembrolizumab	Anytime for permanent discontinuation
Visit	1	2	3	4	5	U	6	7	≥ 8	≥ 8	
PT, aPTT		X					X	X			
Pregnancy Test[8]			X								
Thyroid Panel[9]		X			X			X	X		
ATT IgG[10]	X										
LSQ[11]	X	X			X		X				
Whole blood, research analyses[12]	X	X			X		X		X		X
Disease Evaluations											
MRI[13]	X				(X)	X	X	X	X	X	X
CT Scan[14]			X								
Biopsy/Tumor research analyses[15]			X								
Unscheduled biopsy/tumor tissue collection[16]			Continuous								
ORR/DOR/OS			Continuous								
Treatment(s)											
Lerapolturev[17]			X								
Pembrolizumab[18]					X	X	X	X	X		

Abbreviations: AE: adverse event; aPTT: activated partial thromboplastin time; ATT IgG: anti-tetanus toxoid immunoglobulin G; CBC with diff: Complete Blood Count with differential; CMP: Comprehensive Metabolic Panel; CT: computed tomography; DOR: duration of response; KPS: Karnofsky

performance status; LSQ: lymphocyte subset quantitation; MRI: Magnetic Resonance Imaging; NANO: Neurologic Assessment in Neuro-Oncology; PRO: patient-reported outcome; PT: prothrombin time; PV: poliovirus; SOC: standard of care; U: Unscheduled

1 At Screening Period 1, lab evaluations will occur first, followed by patients receiving their single PV booster vaccine.

2 Catheter placement and lerapolturev infusion (+1 day window or extension as approved by Sponsor). Lerapolturev infusion occurs only following confirmation of GBM at time of catheter placement or within 6 weeks of visit 3. If diagnosis of GBM is not confirmed/patient not infused, patient is a screen failure. Platelet count should be confirmed prior to catheter placement as well as at time of catheter removal and should remain consistent with inclusion criteria 11. Should the platelet count be less than 125 x 10^9/L on the day of catheter removal, a platelet transfusion should be administered and platelet count confirmed to be greater than 125 x 10^9/L prior to catheter removal.

3 Following Visit 4, all tests and procedures have a ±7-day window except for dose-limiting toxicity (DLT) assessment period for first 3 to 6 participants (21 days ± 3 days) post-first pembrolizumab infusion).

4 Questionnaires in support of PROs to occur at visits 2, 4, 6, 8 and then every 9-12 weeks per scheduled imaging visit follow-up.

5 Unscheduled (U): Visit occurs between visits 5 and 6 only if first dose of pembrolizumab is delayed from planned administration at visit 5. If first pembrolizumab infusion is delayed, the schedule of assessments shifts accordingly so the next visit occurs 3 weeks after the date of first pembrolizumab administration.

6 Includes height, weight, body surface area, vital signs (blood pressure, heart rate, respiratory rate, temperature).

7 Physical exam, neurologic exam with NANO and KPS daily after lerapolturev infusion until day of discharge from hospital.

8 Individuals of childbearing potential, pregnancy test (urine or serum) within 48 h of catheter placement. Repeat every 6 months or any time pregnancy suspected.

9 Thyroid panel (at a minimum: TSH and free T4; may include free and total T3) should occur every 6 weeks while participant is receiving pembrolizumab.

10 If undetectable anti-tetanus toxoid immunoglobulin G (ATT IgG) at screen, then Tdap booster vaccine > 1 week prior to biopsy/catheter placement.

11 LSQ analysis should include the following (both %, and ABS): CD3 T, CD4 T, CD8 T, CD19 B, CD56 NK cells. LSQ should be collected at visit 1 (pre-boost), visit 2 (post-boost), and before pembrolizumab doses at visits 5 and 6.

12 Collection of whole blood for biomarker analyses where indicated. Collected at visit 1 (pre-boost) and visit 2 (post-boost), before pembrolizumab doses at visits 5, 6, 8, and at End of Study visit for progression.

13 MRI with and without contrast. Screening MRI conducted within 14 days prior to catheter placement. If neurologic deficit presents at visit 5 and pembrolizumab dose is held to days 15 to 28, MRI should be conducted and precede pembrolizumab administration. After week 11, MRI to occur every 9-12 weeks or more frequently, at the discretion of the treating physician.

14 CT occurs before infusion to confirm placement criteria and after catheter is removed, post-infusion, to confirm no bleeding.

15 If possible, up to 3 additional core biopsies will be obtained for biomarker testing (if not available from archival tissue obtained within 6 weeks).

16 Results from an unscheduled or unplanned biopsy and/or surgical resection should be recorded in the eCRF, and remaining tissue may be requested for analysis.

17 Lerapolturev retreatment may be allowed for confirmed progression ≥ 6 months post-initial lerapolturev infusion with Sponsor/designee approval.

18 All visit assessments should be conducted before pembrolizumab administration. Pembrolizumab should be administered every 3 weeks ± 1 week through week 104, with the first dose at day 14 but up to day 28, if required. If pembrolizumab is permanently discontinued, then safety laboratory evaluations that are not SOC are no longer required 30 days after the date of pembrolizumab discontinuation.

1.3. GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
ATT	Anti-tetanus toxoid
CBC	Complete Blood Count
CE	Cerebral Edema
CI	Confidence Interval
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DSMB	Data and Safety Monitoring Board
EC	Exclusion Criteria
EGFR	Epidermal Growth Factor Receptor
EGFRvIII	Epidermal Growth Factor Receptor (variant III)
FLAIR	Fluid-Attenuated Inversion Recovery
GBM	Glioblastoma
GTR	Gross Total Resection
h	hour
IC	Inclusion Criteria
ICE	Intercurrent Events
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
irAE	Immune-related Adverse Event
iRANO	Immunotherapy Response Assessment in Neuro-Oncology
IV	Intravenous

kg	Kilogram
KPS	Karnofsky Performance Status
LS	Landmark Survival
LSQ	Lymphocyte Subset Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
n	Participants
NANO	The Neurologic Assessment in Neuro-Oncology scale
ORR	Objective Radiographic Response/Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PP	Per-Protocol
PR	Partial Response
PRO	Patient-reported Outcome
PT	Preferred Term
PTE	Peritumoral Edema
PV	Poliovirus
RDI	Relative Dose Intensity
rGBM	Recurrent Glioblastoma
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Stable Disease
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Events
TERT	Telomerase Reverse Transcriptase
ULN	Upper Limit Normal
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WHO-DD	WHO Data Dictionary

2. OBJECTIVES

Objective	Endpoint
Primary	
• Anti-tumor activity	• Objective response rate (ORR) • Duration of response (DOR)
• Safety/tolerability	• The frequency and severity of treatment-emergent adverse events (TEAEs) via Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 for participants receiving lerapolturev and at least one dose of pembrolizumab
Secondary	
• Anti-tumor activity	• Disease Control Rate (DCR)
• Survival	• Overall Survival (OS) • Landmark Survival (LS)

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

In an analysis of the ongoing Phase 1 study of lerapolturev in rGBM, an ORR of 11% was demonstrated (7/61 participants achieved a complete response (CR) or partial response (PR); data on file, Istari). With 30 participants planned to be treated in this study, there is a greater than 75% power to demonstrate a 20% or greater improvement in ORR (ORR > 31%, two-sided $P < 0.05$).

3.2. HANDLING OF DATA

3.2.1. Strata and Covariates

All analyses will be conducted without using strata.

3.2.2. Multiple Testing and Comparisons

All analyses will be conducted without adjustments for multiple comparisons.

3.2.3. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all participants who have been enrolled. In situations where it is not possible to obtain all data, it may be necessary to impute missing data. These situations are described below. Unless otherwise specified, all other missing data will not be imputed.

3.2.3.1. Missing Severity or Relationship for Adverse Events

Adverse events (AEs) with missing severity will have the severity imputed as "Grade 3" for the AE tabulations. AEs with missing relationship to study drug will have the relationship imputed as 'Definite' for the AE tabulations if the AE started on or after catheter placement.

3.2.3.2. Imputation of Incomplete Dates

An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a participant. The database contains data fields for month, day, and year. A date is incomplete if at least one of these three fields is not known. For many of the planned analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For the purposes of handling partially reported start and stop dates for an event the following algorithm will be applied:

1) For onset date:
   a) If only the day part of the onset date is missing and occurs in the same month and year as the date of dose of study drug, the date of dose of study drug will be used as the onset date. Otherwise, the first day of the month will be used to complete the onset date.
   b) If the day and month parts of the onset date are missing and occur in the same year as the dose of study drug, the date of the dose of study drug will be used as the onset date. Otherwise, January 1st will be used to complete the onset date.
   c) If the onset date is completely missing, the date of the dose of study drug will be used as the onset date.
2) For end date:
   a) If only the day part of the end date is missing, the last day of the month will be used to complete the end date.
   b) If the day and month parts of the end date are missing, December 31st will be used to complete the end date.
   c) If the end date is completely missing, the maximum of the participant's end of study date or date of last contact will be used as the end date.

If any imputed start date causes the start date to occur after the end date, the end date will be used for the imputation of the start date. If any imputed end date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date.

3.2.4. Presentations by Study Visit

When data are collected serially over time, individual data presentations may include by-study visit displays. By-study visit displays will only be summarized up to Week 104. Visits will be presented according to the nominal visit as obtained from the eCRF. If multiple observations are collected at a scheduled visit, the closest observation to the target day will be chosen. If two observations have equal distance from the target day but one is earlier and the other is later than the target day, the earlier observation will be chosen. Unscheduled assessments will be included in the listings.

3.2.5. Presentations by Worst Case

When data are collected serially over time, individual data presentations may include "worst case on study" displays. In those situations, both scheduled and unscheduled assessments up to 104 weeks will be included.

3.2.6. Definitions and Terminology

Age
Age is age at informed consent and is as captured on the eCRF.

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to calendar day of lerapolturev infusion.

Day 1 (Baseline)
Day 1 is the earliest day that study drug is initiated. Note that this is a change from the protocol where the first day of study drug administration was designated as Day 0.

Study Day
Study Day is defined relative to Baseline (Day 1). Thus, the study day of an event is calculated as:

Study Day = event date – date of Day 1 (+ 1, if event date ≥ date of Day 1).

Study Visit
Study Visit is the nominal visit as recorded on the eCRF.

Change from Baseline
Change from baseline for a given endpoint is defined as the Study Day X value minus the Baseline Value.

Days on Study
Days on study is the number of days from Day 1 to the date of study completion as recorded on the End of Study eCRF page.

Adverse Event
An AE is an untoward or medical occurrence associated with the use of study treatment (drug, biologic, or device) in clinical investigation participants, which does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended symptom, sign, disease or condition, or test abnormality (although diagnosis should always be reported as the AE if known) regardless of the relationship to study treatment. AEs that do not meet the definition for a serious AE (SAE) are considered non-serious AEs.

Treatment-emergent Adverse Event (TEAE)
A TEAE will be an AE that occurred during the study on or after catheter placement. Additionally, it is assumed that an AE which was reported to have started on Day 1 without an associated onset time occurred on or after catheter placement.

Adverse Event of Special Interest (AESI)
AESIs for lerapolturev are defined as cerebral spinal fluid leakage, aseptic meningitis, cerebral edema (CE), peritumoral edema (PTE).

irAE
An AE of immunologic etiology associated with pembrolizumab

Dose limiting toxicity (DLT)
DLTs are defined per protocol as any of the following events related to lerapolturev:

1) ≥ Grade 3 neurologic events related to PTE or CE within the first 3 weeks of the first pembrolizumab administration that:
   a) Do not resolve to ≤ Grade 1 with the management practices outlined herein (≤ 4mg/dexamethasone or 7.5 mg/kg bevacizumab) within 3 weeks of initiating such treatments,

   and/or
   b) Require surgical debulking of the PVSRIPO infused tumor within 3 weeks of the first pembrolizumab administration
2) Any of the following SAEs:
   a) Treatment-related death
   b) Treatment-related life-threatening event
   c) A medically significant condition (defined as an event that compromises patient safety or may require medical or surgical intervention to prevent one of the outcomes above).
   d) Requires inpatient hospitalization or prolongation of existing hospitalization
   e) Results in persistent or significant incapacity or substantial disruption to conduct normal life functions
3) Any Grade 4 non-hematologic toxicity
4) Any Grade 3 non-laboratory-based toxicity that is not reversible to its pre-PVSRIPO treatment baseline within 2 weeks of onset with the following exceptions:
   a) Grade 3 fatigue lasting ≤ 3 days or Grade 3 fatigue in a participant with Grade 1 fatigue at baseline
   b) Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care
   c) Grade 3 adrenal insufficiency due to suboptimal steroid replacement therapy
   d) Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care
5) Grade 3 or Grade 4 non-hematological laboratory values only if meets one of the serious criteria outlined in 1 above or
   a) the abnormality persists for > 1 week
   b) The abnormality results in a drug-induced liver injury

   Note: Treatment-emergent, non-clinically significant laboratory abnormalities that are treatable with routine measures, or reversible (≤ 1 week of onset) laboratory abnormalities in and of themselves (including liver function tests, uric acid, etc.), are not considered DLTs.
   Exceptions (these laboratory values are DLT):
   - Grade 4 thrombocytopenia of any duration
   - Grade 3 thrombocytopenia associated with bleeding requiring a platelet transfusion
6) Febrile neutropenia meeting following criteria:

a) Grade 3: ANC < 1000/µl with a single temperature of > 38.3° C (101° F) or a sustained temperature of ≥ 38° C (100.4°F) for ≥ 1 hour
b) Grade 4: ANC < 1000/µl with a single temperature of > 38.3° C (101° F) or a sustained temperature of ≥ 38° C (100.4°F) for ≥ 1 h, with life-threatening consequences and urgent intervention indicated

Concomitant Medications
Concomitant medications are those medications taken on or after catheter placement. This definition includes medications started prior to catheter placement but continuing concomitantly with lerapolturev.

Prior Medications
Prior medications are defined as medications taken or therapies received by participants prior to catheter placement.

Immunotherapy Response Assessment in Neuro-Oncology (iRANO):
Note: While a modified version of iRANO is described in Section 8.4.6.1, Table 3 of the protocol, the definitions below, and used in the efficacy analyses, were based on iRANO without the modifications described in the protocol.

iRANO are guidelines that incorporate criteria previously defined by the RANO working committee to define CR, PR, SD, and progressive disease (PD) for participants with malignant glioma, low-grade glioma, and brain metastases. The key component of iRANO is specific additional guidance for the determination of PD among neuro-oncology participants undergoing immunotherapy. iRANO guidelines require confirmation of progression on follow-up imaging 3 months after initial radiographic progression if:

1. No new or significantly worsened neurologic deficits not due to co-morbid event or concurrent medication AND
2. ≤ 6 months from initiation of immunotherapy

If follow-up imaging confirms progression, the date of actual progression should be backdated to the date of initial radiographic progression. Appearance of new lesions solely does not define PD ≤ 6 months from initiation of immunotherapy. The lesions are added to the total lesion areas for follow-up assessments.

Complete Response (CR)
CR is defined as:
- Disappearance of all enhancing disease for ≥ 4 weeks AND
- No greater than physiologic steroids AND
- No new lesions AND
- Stable/improved T2/FLAIR AND
- Stable improved clinically

Partial Response (PR)
PR is defined by:
- ≥ 50% decrease in the sum of biperpendicular diameters of enhancing disease for ≥ 4 weeks AND

- No new lesions AND
- Stable/improved T2/FLAIR AND
- Stable/improved steroids AND
- Stable/improved clinically

Stable Disease (SD)
SD is defined by:
- Does not qualify for CR, PR, or PD AND
- No new lesions AND
- Stable/improved T2/FLAIR AND
- Stable/improved steroids AND
- Stable/improved clinically

Progressive Disease (PD) which must be confirmed as described below
Initial PD by RANO is defined by:
- ≥ 25% increase in the sum of biperpendicular diameters of enhancing disease OR
- New lesions OR
- Significant worsened T2/FLAIR OR
- Significant clinical decline

Confirmation of progression on follow-up imaging 3 months after initial radiographic progression is required in the following situations
- No new or significantly worsening neurologic deficits not due to co-morbid event or concurrent medication AND
- ≤ 6 months from initiation of immunotherapy

If follow-up imaging confirms progression, the date of actual progression should be backdated to the date of initial radiographic progression. Also note that the appearance of new lesion solely does not define progressive disease if they occur ≤ 6 months from initiation of immunotherapy. Rather the lesions are added to the total lesion areas for follow-up assessments.

Objective Response Rate (ORR)
ORR is defined as the proportion of participants achieving CR or PR based on iRANO criteria.

Duration of Response (DOR)
DOR is defined as time from objective response (CR or PR per iRANO criteria) until confirmed PD or death; censoring at the date of the last imaging without confirmed PD prior to the date the subject is considered off study.

Disease Control Rate (DCR)
DCR is defined as the proportion of participants achieving CR, PR, or SD for ≥ 6 months (all per iRANO criteria).

Overall Survival (OS)
OS is defined as time from first lerapolturev infusion to death from any cause, or last follow-up if participant is alive.

Landmark Survival (LS)
LS is defined as the proportion of participants alive at ≥ 6 and ≥ 12 months from time of first lerapolturev infusion. This will be calculated as survival rate from the OS curve at 6 and 12 months.

Treatment Period
Treatment period is defined as the period from catheter placement to Week 104.

3.3. TIMING OF ANALYSES

The final analysis will be completed after the last participant completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

4. ANALYSIS POPULATIONS

Data analyses will be based on the efficacy, safety (SAF) and screening analysis sets.

4.1. EFFICACY ANALYSIS SET

The primary efficacy analysis set includes all participants who received at least one dose of lerapolturev and ≥ 1 dose of pembrolizumab. This will be the primary population used for the efficacy analyses. Analyses using the efficacy set will be conducted based on the treatment received.

4.2. SAFETY ANALYSIS SET

The SAF includes all enrolled participants who had an infusion catheter placed. This will be the primary population used for the safety analyses. Participants in the SAF set will be analyzed based on the treatment received.

4.3. SCREENING ANALYSIS SET

A screening analysis set will include all participants who signed the ICF and include screen failures who failed up until catheter placement (e.g., considered a screen failure if biopsy at time of catheter placement does not confirm rGBM). This will be the primary population for the disposition tables and listings. Participants in the screening set will be analyzed based on the treatment assigned.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term “descriptive statistics” refers to number of participants (n), mean, median, standard deviation, minimum and maximum for continuous data and frequencies and percentages for categorical data. Survival endpoints will be analyzed with Kaplan-Meier method and summarized with median, twenty-fifth and seventy-fifth percentiles, and 95% confidence intervals (CI), if applicable.

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment, participant, and then by date within each participant number.

All summary tables and figures will be presented by summarizing the overall population.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e., ICH-E3, will be used for all tables and listings. Upon completion, all SAS® programs will be validated by an independent programmer within the staff of the third-party vendor doing the primary analysis. The validation process will be used to confirm that statistically valid methods have been implemented and that all data transformations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

5.1. PARTICIPANT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Participant disposition will be presented for the screening analysis set. A summary table will be generated for the overall population. The number of participants who were screened, screen failures, and the reason for screen failure will be summarized. Additionally, the number of participants in each analysis population will be summarized. The end of treatment status including reasons for treatment discontinuation, as well as end of study status including reasons for study discontinuation reason will be provided. Similarly, the death status and primary reason for death will be presented. The number of days on study will also be summarized. Participant disposition including analysis population, end of treatment status and reason, end of study status and reason, and death status (including date of death) and reason will be listed.

Demographic data and baseline characteristics including age at informed consent, gender, race, ethnicity, Karnofsky performance status (KPS) at baseline, and baseline height, and weight will be summarized using descriptive statistics. Frequency of KPS scores < 70, 70, 80, 90, and 100 will be summarized for the safety population set. Demographic data and baseline characteristics will be listed.

5.2. DISEASE CHARACTERISTICS

Disease characteristics including GBM type, disease status, description (Unifocal or Multifocal), lesion site and side, surgical pathology diagnosis, histologic grade, and the number of prior progressions will be summarized using the safety set. Disease characteristics will also be listed.

5.3. CONCOMITANT MEDICATIONS

All medication verbatim terms collected will be coded to Anatomical Therapeutic Classification (ATC) and preferred term (PT) using the World Health Organization (WHO) Data Dictionary (DD) Version Sep2020.

Concomitant medications, including bevacizumab and dexamethasone, will be summarized by presenting the number and percentage of participants by PT and ATC, using the safety set. Participants taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class.

The number of participants who receive bevacizumab will be tabulated along with the number of doses administered, and dose levels received. Cumulative actual dose will be summarized. A participant's bevacizumab administration record will be included if it occurred after catheter placement and prior to the participant's Week 104, start date of subsequent anticancer therapy, or end of study/last contact date -- whichever occurs first. If a participant has bevacizumab listed as a post-study systemic monotherapy record, these data will be included in the analysis if the start and stop dates occur prior to any other type of subsequent anticancer therapy (eg, lomustine, pembrolizumab, irinotecan, nivolumab, carboplatin, etc.).

The number of participants who receive dexamethasone will be tabulated. The days on dexamethasone, cumulative actual dose, and average daily dose will also be summarized. Exposure will only be calculated from catheter placement to Week 104, start date of subsequent anticancer therapy, or until the participant's end of study/last contact date -- whichever occurs first.

5.4. BRAIN SURGERY, RADIOTHERAPY AND SYSTEMIC THERAPY

Brain surgery data will be listed. The number and percentage of participants with prior brain surgery will be summarized; data to be included in the summary are type of procedure, histologic diagnosis, Central Nervous System (CNS) site, and CNS side.

The prior and subsequent radiotherapy will be listed. The number and percentage of participants with prior radiotherapy will be summarized; data to be included in the summary are CNS site, radiation therapy type, and total dose delivered. If a participant experiences more than one prior radiotherapy, the worst-case will be used for numerical summaries and all cases will be presented for categorical summaries. A participant will only be included in a single category once.

All verbatim terms collected for both prior and subsequent systemic therapy will be coded to ATC and PT using the WHO-DD Version Sep2020.

The prior and subsequent systemic therapy will be listed. The prior systemic therapy data will be summarized by presenting the number and percentage of participants by PT and ATC and total number of cycles. Participants taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class. Additionally, the total number of cycles will be summarized. If a participant experiences more than one prior systemic therapy, the worst-case will be used for numerical summaries and all cases will be presented for categorical summaries. A participant will only be included in a single category once.

5.5. TISSUE BIOMARKERS

Tissue biomarker and core biopsy data will be listed. The following information will be summarized:

- EGFR IHC
- EGFRvIII IHC
- MGMT IHC
- MGMT promoter methylation
- IDH1 R132H
- IDH1 molecular diagnostics
- IDH1 mutation type
- IDH2 molecular diagnostics
- IDH2 mutation type
- TERT molecular diagnostics
- TERT mutation type
- PVR IHC

5.6. EXPOSURE

The number of participants who received study drug (lerapolturev and pembrolizumab) and cumulative actual dose received will be summarized. The number of cycles of pembrolizumab administered will be summarized using 0 cycles, 1-5 cycles, > 5 cycles. The relative dose intensity (RDI) of pembrolizumab will be summarized using the percentage of drug a participant received compared to the planned amount of drug received, such that if the RDI is 100% the participant received all the planned doses. To calculate the RDI is (actual cumulative dose / planned cumulative dose) * 100.

5.7. EFFICACY

5.7.1. Primary Efficacy Endpoints

The primary efficacy endpoints are ORR and DOR.

5.7.1.1. Statement of Estimand

The **population for the trial** is defined through appropriate inclusion/exclusion criteria (IC/EC) to reflect the targeted participant population for approval. The analysis population is based on the efficacy analysis set.

The **treatment** of interest is lerapolturev + pembrolizumab.

The **variable** of interest for ORR is the binary response value for a participant. For DOR, the variables of interest are the time from first response to confirmed progression/death/censoring.

The ability to evaluate treatment effect using the variables may be impacted by **intercurrent events** (ICEs). Death and use of additional cancer treatments may all impact the interpretation of treatment effect. For ORR, a composite strategy will be used to address intercurrent events (ICEs)

of potential death and start of additional cancer treatments, meaning occurrence of any of these events prior to a participant achieving CR or PR will mean the participant is considered a non-responder. DOR will use a composite strategy as well, treating death as an event that ends response, and the start of additional cancer treatments medications will be censored under the strategy.

The **population level summary measures** are the ORR, and the Kaplan Meier (KM) estimated median DOR, and associated CI for treatment.

5.7.1.2. Primary Efficacy Analysis

All efficacy endpoints for participants receiving lerapolturev and ≥ 1 dose of pembrolizumab will be summarized for the overall population.

The number of participants in each category of best overall response (CR, PR, SD, PD), and ORR will be summarized. ORR along with their associated exact 95% two-sided confidence intervals (CIs) using Clopper Pearson method will be computed.

The number of participants with disease progression or death and the number of censored participants will be summarized. DOR will be summarized using Kaplan-Meier methods, and the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs will be calculated. The Kaplan-Meier survival curve will also be plotted.

Supportive data listings will also be provided.

5.7.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study are:

- DCR
- OS (including median OS and LS)

5.7.2.1. Secondary Efficacy Analysis

OS, including LS rates at ≥6 and ≥12 months will be summarized using Kaplan-Meier method to estimate the median, 25% and 75% percentiles along with their 95% CIs.

In addition to the quartile summary from Kaplan-Meier method, Kaplan-Meier estimates will be provided for the survival rates at 6 and 12 months along with the 95% CIs for OS.

Analysis of DCR will be conducted in a similar manner to ORR in Section 5.7.1.2.

5.8. SAFETY

Values for all safety variables will be listed by participant and visit (as applicable). Safety summaries by visit will use scheduled visits up to Week 104.

5.8.1. Adverse Events

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 by system organ class and PT. If a participant experiences multiple events that map to a single PT, the greatest severity and strongest assessment of relation to a study drug will be assigned to the PT for the appropriate summaries. AE severity will be assessed according to the CTCAE version 5. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

The number of participants for the following groups will be summarized by overall:

- Any TEAE
- Any TEAE related to a study drug or catheter with sub bullets for TEAEs related to catheter placement, lerapolturev or pembrolizumab
- Any TESAE
- Any TESAE related to a study drug or catheter with sub bullets for TESAEs related to catheter placement, lerapolturev or pembrolizumab
- Any DLTs
- Any AESIs for lerapolturev
- Any irAEs for pembrolizumab
- Any TEAEs leading to discontinuation of study treatment
- Any TEAE with grade ≥ 3
- Any TEAE with grade ≥ 3 related to study drug or catheter with sub bullets for TEAEs with grade ≥ 3 related to catheter placement, lerapolturev or pembrolizumab
- Any Grade 5 TEAEs
- Any Grade 5 TEAEs related to study drug or catheter with sub bullets for Grade 5 TEAEs related to catheter placement, lerapolturev or pembrolizumab

The occurrence of TEAEs and TEAEs related to study drug or catheter will be summarized by PT, system organ class, and severity. All AEs reported will be listed for individual participants showing both verbatim and PT. All AEs that occurred prior to catheter placement will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 3.2.3.2 as required to determine TEAEs.

5.8.2. Clinical Laboratory Assessments

AEs for clinical labs will be characterized according to CTCAE version 5 (when possible) and shift in grade from baseline to the worst post-baseline value will be summarized. Both scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- Alanine Aminotransferase (ALT) and/or Aspartate Aminotransferase (AST) > 3 x upper limit normal (ULN), Alkaline Phosphatase (ALP) < 2 x ULN, and Total Bilirubin ≥ 2 x ULN

- AST > 3, 5, 8, 10, and 20 x ULN, and 5 x ULN for more than 5 weeks
- ALT > 3, 5, 8, 10, and 20 x ULN, and 5 x ULN for more than 5 weeks
- Total Bilirubin > 1.5 or ≥ 2 x ULN

Listings of all laboratory data with normal reference ranges, and CTCAE grades (when possible) will be provided.

5.8.3. Vital Signs

For vital sign parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, body temperature, and weight) the observed values and change from baseline will be summarized using descriptive statistics at each visit. The maximum post-baseline values and the change from baseline by visit will also be summarized.

A listing of all vital sign data will be provided.

5.8.4. KPS

The observed values and the change from baseline in the KPS will be summarized using descriptive statistics at each visit. The maximum post-baseline values and the change from baseline by visit will also be summarized.

A listing of KPS data will be generated.

5.8.5. NANO

The number of participants and percentage in each category of the Neurologic Assessment in Neuro-Oncology (NANO) scale score.

A listing of NANO data will be generated.

6. CHANGES IN THE PLANNED ANALYSES

1. Day 0 is the earliest day that study drug is initiated but will be designated as Day 1 based on implementation standards for the analysis.
2. Central imaging review was not completed; therefore, results from this will not be presented.
3. The following analyses will not be completed:
   a. Durable radiographic response (DRR)
   b. Duration of disease control (DDC)
   c. Progression-free survival (PFS)
   d. Analysis of Per-Protocol population
   e. Analyses based on participant strata (prior anti-VEGF agents, prior chemotherapy use)
   f. Analyses on the efficacy set and PP set for the following subgroups: baseline NANO score, KPS, prior bevacizumab and chemotherapy or other treatment use/failure, extent of surgery at diagnosis, MGMT promoter methylation status and/or other tumor genetic factors at diagnosis and baseline, lesion cross-sectional area at baseline, number of prior progressions, age, gender.

g. Landmark survival at month 24
h. Exploratory analyses including analysis of efficacy based on modified iRANO criteria in Section 8.4.6.1, Table 3 of the protocol, identification of biomarkers of anti-tumor response to lerapolturev following by pembrolizumab or assessment of patient reported outcomes

4. The entire anticipated sample size of patients was not enrolled.

7. REVISION HISTORY

Date	Revision	Rationale
23 June 2022	NA	Original Document

8. REFERENCES

9. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.0" boundary on the left and right edges. The top and bottom margins are 1.0" for tables and listings but may vary for figures. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all participants.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of participants summarized within any given summary module; some participants in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of participants contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of participants in the analysis population due to missing data.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted participant number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- Numerical Values: The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
    - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.

- Means will be reported to the same number of significant digits as the parameter.
- Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).

10. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

Accountability and Baseline Characteristics

14.1.1.1 Participant Disposition, Screening Set
14.1.2.1 Demographics and Baseline Characteristics, Safety Set
14.1.3.1 Disease Characteristics, Safety Set
14.1.3.2 Summary of Prior Anti-Cancer Therapy, Safety Set
14.1.3.3 Summary of Tissue Biomarkers, Safety Set
14.1.4.1 Concomitant Medications, Safety Set
14.1.4.2 Bevacizumab Administration, Safety Set
14.1.4.3 Dexamethasone Use, Safety Set
14.1.5.1 Summary of Study Drug Exposure, Safety Set

Efficacy

14.2.1.1 Summary of Best Overall Tumor Response and Duration of Response by iRANO Criteria, Efficacy Set
14.2.2.1 Summary of Overall Survival, Efficacy Set

Safety

14.3.1.1 Overall Summary of Treatment-Emergent Adverse Events, Safety Set
14.3.1.2 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.1.3 Treatment-Emergent Adverse Events by Preferred Term in Descending Frequency, Safety Set
14.3.1.4 Treatment-Emergent Adverse Events Related to Study Drug or Catheter by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.1.5 Treatment-Emergent Adverse Events Related to Study Drug or Catheter by Preferred Term in Descending Frequency, Safety Set
14.3.1.6 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Greatest Severity, Safety Set
14.3.1.7 Treatment-Emergent Serious Adverse Events Related to Study Drug or Catheter by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.1.8 Treatment-Emergent Dose Limiting Toxicities by System Organ Class, Preferred Term and Greatest Severity, Safety Set
14.3.1.9 Treatment-Emergent Adverse Events of Special Interest for Lerapolturev by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.1.10 Treatment-Emergent irAEs for Pembrolizumab by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.1.11 Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.4.1 Summary of Grade Shifts in Laboratory Abnormalities – Hematology, Safety Set
14.3.4.2 Summary of Grade Shifts in Laboratory Abnormalities – Chemistry, Pancreatic and Thyroid, Safety Set

14.3.4.3 Number of Participants with at Least One ALT, AST, or Total Bilirubin Above Upper Limit of the Normal Range Post-Baseline, Safety Set
14.3.4.4 Summary of Vital Signs by Visit, Safety Set
14.3.4.5 Summary of Karnofsky Performance Status by Visit, Safety Set
14.3.4.6 Summary of Neurologic Assessment in Neuro-Oncology Score by Visit, Safety Set

Summary Figures

Efficacy

14.2.1.2 Overall Survival – Kaplan Meier Curve, Safety Set
14.2.2.2 Duration of Response – Kaplan Meier Curve, Safety Set

Data Listings

16.2.1.1 Participant Enrollment
16.2.1.2 Participant Disposition
16.2.3.1 Analysis Sets
16.2.4.1 Demographics and Baseline Characteristics
16.2.4.2 Medical History
16.2.4.3 Disease Status
16.2.4.4 Prior Progressions
16.2.4.5.1 Brain Surgery
16.2.4.6.1 Prior Radiation Therapy
16.2.4.6.2 Post-Study Radiation Therapy
16.2.4.7.1 Prior Systemic Therapy
16.2.4.7.2 Post-Study Systemic Therapy
16.2.4.8.1 Prior and Concomitant Medications
16.2.4.9.1 Tissue Biomarkers/ Disease History
16.2.5.1.1 Catheter Placement
16.2.5.1.2 Lerapolturev Infusion
16.2.5.1.3 Pembrolizumab Infusion
16.2.6.1 Lesion Description & Assessment
16.2.6.2 Lesion Response
16.2.6.3 Follow-Up
16.2.7.1 Adverse Events
16.2.8.1 Laboratory Values – Hematology
16.2.8.2 Laboratory Values – Chemistry
16.2.8.3 Laboratory Values – Coagulation
16.2.8.4 Pregnancy Test
16.2.8.5 COVID-19 Impact
16.2.9.1 Vital Signs
16.2.10.1 Neurologic Assessment in Neuro-Oncology