STATISTICAL ANALYSIS PLAN
VERSION: 1

Clinical Study Protocol Title: A Safety and Pharmacokinetic Study of Single Agent REGN2810 in Pediatric Patients with Relapsed or Refractory Solid or Central Nervous System (CNS) Tumors and a Safety and Efficacy Trial of REGN2810 in Combination with Radiotherapy in Pediatric Patients with Newly Diagnosed Diffuse Intrinsic Pontine Glioma, Newly Diagnosed High-Grade Glioma, or Recurrent High-Grade Glioma

Compound:	REGN2810
Protocol Number:	PNOC 013/ R2810-ONC-1690
Clinical Phase:	Phase 1 & 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Study Team Leader:	[redacted]
Study Medical Director:	[redacted]
Version:	1
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

Biostatistics

See appended electronic signature page

[redacted]

Clinical Sciences

See appended electronic signature page

[redacted]

Clinical Pharmacology

See appended electronic signature page

[redacted]

Bioanalytical Sciences

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[redacted]

Precision Medicine

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[redacted]

Biostatistics and Data Management

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ABBREVIATIONS AND DEFINITIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
BOR	Best overall response
CNS	Central nervous system
CR	Complete response
CRF	Case report form (electronic or paper)
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DIPG	Diffuse intrinsic pontine glioma
DLT	Dose-limiting toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FDA	Food and drug administration
HGG	High-grade glioma
ICF	Informed consent form
ICH	International Council for Harmonization
irRC	Immune-related response criteria
imAE	Immune-mediated adverse event
iRANO	Immunotherapy Response Assessment in Neuro-Oncology
IRR	Infusion related reaction
IV	Intravenous
IWRS	Interactive web response system
KM	
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NE	Not evaluable

ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononucleated cell
PDDD	Protocol deviation definition document
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R2810-ONC-1690 study for a clinical study report.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on review of the study and data, and a final plan will be issued prior to data lock.

R2810-ONC-1690 is a multicenter, phase 1 and early efficacy study conducted through the Pacific Pediatric Neuro-oncology Consortium (PNOC). Phase 1 will consist of 4 cohorts (Cohort A through Cohort D) as specified in Table 1 below.

Table 1: Patient Cohorts in Phase 1

Recurrent or refractory solid tumors	Recurrent or refractory CNS tumors
Cohort A: Age 0 to <12 years **Cohort B:** Age 12 to <18 years	**Cohort C:** Age 0 to <12 years **Cohort D:** Age 12 to <18 years

The Efficacy Phase will consist of 6 cohorts (Cohort E through Cohort J) of pediatric patients with either newly diagnosed DIPG, newly diagnosed HGG, or recurrent HGG, and defined according to patient age as specified in Table 2 below.

Table 2: Patient Cohorts in the Efficacy Phase

Newly diagnosed DIPG	Newly diagnosed HGG	Recurrent HGG
Cohort E: Age 3 to <12 years **Cohort F:** Age 12 to 25 years	**Cohort G:** Age 3 to <12 years **Cohort H:** Age 12 to 25 years	**Cohort I:** Age 3 to <12 years **Cohort J:** Age 12 to 25 years

In this phase of the study, REGN2810 will be given in combination with radiation therapy: REGN2810 + conventionally fractionated radiation) and REGN2810 + hypofractionated radiation.

1.1. Study Objectives

1.1.1. Primary Objectives

Phase 1

- To confirm the safety and anticipated recommended phase 2 dose (RP2D) of REGN2810 (cemiplimab) for children with recurrent or refractory solid or CNS tumors
- To characterize the pharmacokinetics (PK) of REGN2810 given in children with recurrent or refractory solid or CNS tumors

Efficacy Phase

- To confirm the safety and anticipated RP2D of REGN2810 to be given concomitantly with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG)
- To confirm the safety and anticipated RP2D of REGN2810 given concomitantly with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed high-grade glioma (HGG)
- To confirm the safety and anticipated RP2D of REGN2810 given concomitantly with re-irradiation in patients with recurrent HGG
- To assess PK of REGN2810 in pediatric patients with newly diagnosed DIPG, newly diagnosed HGG, or recurrent HGG when given in combination with radiation
- To assess anti-tumor activity of REGN2810 in combination with radiation in improving overall survival at 12 months (OS12) among patients with newly diagnosed DIPG
- To assess anti-tumor activity of REGN2810 in combination with radiation in improving progression-free survival at 12 months (PFS12) among patients with newly diagnosed HGG
- To assess anti-tumor activity of REGN2810 in combination with radiation in improving overall survival at OS12 among patients with recurrent HGG

1.1.2. Secondary Objectives

Phase 1

- To assess anti-tumor activity of REGN2810 monotherapy as identified by objective response in children with recurrent or refractory solid or CNS tumors
- To assess immunogenicity

Efficacy Phase

- To assess safety and tolerability profiles of REGN2810 given in combination with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed DIPG
- To assess safety and tolerability profiles of REGN2810 given in combination with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed HGG
- To assess safety and tolerability profiles of REGN2810 given in combination with re-irradiation among patients with recurrent HGG
- To assess immunogenicity

1.1.3. Exploratory Objectives

Phase 1 and Efficacy Phase

- To assess Quality of Life (QoL) in patients with solid or CNS tumors treated with REGN2810 as monotherapy or given concurrently with radiation followed by adjuvant monotherapy
- To investigate the biologic activity of REGN2810 and potentially identify biomarkers predictive of drug response using DNA, serum, plasma, and tumor biopsy samples

1.1.4. Modifications from the Statistical Section in the Final Protocol

Revision to this plan may be made if deemed necessary to the furtherance of the trial objectives. Such revision, if necessary, will be completed prior to the final data base lock.

1.1.5. Modifications from the Approved Statistical Analysis Plan

This is the first version of the SAP, based on the study protocol PNOC 013/ R2810-ONC-1690 Amendment 3.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a multi-center safety and efficacy study conducted through the PNOC. This study will consist of Phase 1 and Efficacy Phase conducted in parallel.

Phase 1

A 3+3 design will be used to confirm the anticipated RP2Ds of cemiplimab as monotherapy in patients age 0 to <18 years with recurrent/refractory solid or recurrent/refractory CNS tumors in Phase 1 of this study. The recurrent/refractory solid tumor and recurrent/refractory CNS tumor cohorts will each be sub-grouped by age (0 to <12 years and 12 to <18 years), due to concern that exposure may vary between lower body weight younger and higher body weight older patients. Based on the 3+3 design, for each age group of a tumor cohort, a minimum of 3 DLT evaluable patients who have completed the 28-day DLT period at a dose level will be required to derive DLT at that dose level. Refer the protocol for dose escalation/de-escalation rules.

Efficacy Phase

The Efficacy Phase will enroll patients aged 3 to 25 years with either newly-diagnosed DIPG, newly-diagnosed HGG, or recurrent HGG. Each of the three disease cohorts will be sub-grouped by age (3 to <12 years, 12 to 25 years). In this phase of study, cemiplimab will be given in combination with radiation therapy and continue cemiplimab monotherapy once radiation therapy is complete. All the patients in the recurrent HGG cohort will undergo re-irradiation (referred to as "rRT" hereinafter). Within each age group of newly diagnosed DIPG cohort and newly diagnosed HGG cohort, patients will be randomized 1:1 to either conventionally fractionated radiation (referred to as "RT" hereinafter) or hypofractionated radiation (referred to as "HfRT" hereinafter). There will be 5 treatment arms in the Efficacy Phase as follows:

Simon's two-stage design will be utilized in this phase. Up to 20 patients will be enrolled for each treatment arm at two stages. Enrollment and randomization within the younger age groups of 3 to <12 years occur once the RP2D for this age group from Phase 1 is confirmed. Enrollment and randomization within the age groups of 12 to <25 years will take place immediately in parallel with the Phase 1 since this age cohort will be enrolled at the anticipated RP2D (DL1).

To assess safety of cemiplimab combined with radiation, a 3+3 safety run-in will be initiated in this phase to confirm the RP2D of cemiplimab in combination with radiation for each age group of each disease cohort and radiation arm. The DLT period for the Efficacy Phase includes the length of radiation therapy (details are given in Section 2.3.1) plus 4 weeks after completion of radiation therapy. The same dose decision rules for Phase 1 patients will be followed. Once safety of the combination therapy is confirmed in 3-6 DLT-evaluable patients in each age group, the newly diagnosed DIPG cohort, newly diagnosed HGG cohort and recurrent HGG cohort will be fully opened for enrollment. Once PK, tolerability, and preliminary efficacy of the combination of cemiplimab and radiation are established in patients >3 years of age, patients ≤3 years of age will also be enrolled, if appropriate, in the Efficacy Phase at the determined RP2D for their age group.

2.2. Sample Size and Power Considerations

In Phase 1, a minimum of 30 patients will be enrolled. This will include at least 6 patients in the age 0 to <12 recurrent/refractory tumor cohort (Cohort A), at least 3 patients in the age 12 to <18 recurrent/refractory tumor cohort (Cohort B), at least 6 patients in the age 0 to <12 CNS tumor cohort (Cohort C), and at least 3 patients in the age 12 to <18 CNS tumor cohort (Cohort D), as well as 6 additional patients (at the corresponding identified RP2D) in each of the solid tumor cohorts.

In the Efficacy Phase, a minimum of 30 patients will initially be enrolled as part of the 3+3 design to assess the safety of the anticipated RP2D of REGN2810 in combination with either conventional or hypofractionated radiation. This will include at least 6 patients in the age 3 to <12 newly diagnosed DIPG (Cohort E; 3 in each treatment arm), at least 6 patients in the age 12 to 25 newly diagnosed DIPG cohort (Cohort F; 3 in each treatment arm), at least 6 patients in the age 3 to <12 newly diagnosed HGG cohort (Cohort G; 3 in each treatment arm), at least 6 patients in the age 12 to 25 newly diagnosed HGG cohort (Cohort H; 3 in each treatment arm), at least 3 patients in the age 3 to <12 recurrent HGG cohort (Cohort I), and at least 3 patients in the age 12 to 25 recurrent HGG cohort (Cohort J).

Once the RP2D of REGN2810 is confirmed for a given cohort (and treatment arm, where applicable), additional patients will be enrolled as part of expansion. During expansion, the total number of patients enrolled will be based on treatment regimen, irrespective of patient age or cohort. Additional patients will be enrolled until at least 20 evaluable patients are reached, based on a Simon two-stage design, in each of the following pooled treatment arms:

- Newly diagnosed DIPG with conventionally fractionated radiation + REGN2810 (DIPG Arm 1)
- Newly diagnosed DIPG with hypofractionated radiation + REGN2810 (DIPG Arm 2)
- Newly diagnosed HGG with conventionally fractionated radiation + REGN2810 (Newly Diagnosed HGG Arm 1)
- Newly diagnosed HGG with hypofractionated radiation + REGN2810 (Newly Diagnosed HGG Arm 2)
- Recurrent HGG with reirradiation + REGN2810 (Recurrent HGG Arm 1)

Sample size justification and accrual rate

The most recent Children's Oncology Group study that treated children with newly diagnosed DIPG with a combination of radiation therapy and temozolomide resulted in a mean OS12 rate of 40% (Standard Deviation +/-6.5%). We will apply these findings as historical controls for our DIPG treatment arms. The null hypothesis for each DIPG treatment arm is an OS12 of 40%, with a target alternative hypothesis of 70% OS12. Note that although DIPG cohorts will be randomized equally between arms 1 and 2, evaluations will be done within each arm as this trial is not powered for comparisons between arms.

Within each DIPG radiation arm, 20 eligible and evaluable DIPG patients will be randomized in order to achieve at least 80% power to detect the above absolute increase of 30% in OS12 within an arm using a one-sided 0.05 level exact binomial test. This phase of the study will follow a

two-stage design, where initially 7 patients are entered at the first stage in each arm. If no more than 3 deaths occur within 12 months in the initial cohort, the study will move to the second stage. In each arm, an additional 13 eligible patients will be randomized. If at the first stage, 4 or more patients die within 12 months in an arm, that arm will be temporarily closed and a detailed review performed. The study team together Regeneron and its delegates will determine if accrual will continue or enrollment be stopped in this arm. The arm will be considered a success (reject the associated null hypothesis) if at least 12 of the 20 patients survive beyond 12 months. There is a 71% chance of stopping early under the null hypothesis under this two-stage design. To allow for ineligibility, we anticipate there may be an additional 1-2 patients enrolled in this cohort overall to achieve the target number of eligible and evaluable patients.

It is expected that the study will not pause after the first stage accrual goals are met for each cohort, but that the first stage patients will be monitored with respect to the first stage futility rule above. However, given the requirement of 12 months of follow-up to determine the OS12 endpoint for each patient, should the accrual to the first stage be rapid and there is insufficient follow-up in the first stage cohort to obtain an OS signal before continuing to accrue to the second stage, consideration will be given to pausing accrual in order to gather information at the first stage. Furthermore, if before expansion to the second stage there is clear evidence for a need to pause accrual (eg, 2 or 3 deaths observed in the first cohort) then the study will halt accrual until it can be confirmed that it is warranted to move to the second stage.

The most recent Children's Oncology Group study that treated children with newly diagnosed HGG with a combination of radiation therapy, lomustine, and temozolomide resulted in a mean PFS12 rate of 49%. We will apply these findings as historical controls for our newly diagnosed HGG treatment arms. The null hypothesis for each arm is a PFS12 of 50% with a target alternative hypothesis of 80% PFS12. Note that although HGG cohorts will be randomized equally between arms 1 and 2, evaluations will be done within each arm as this trial is not powered for comparisons between arms.

Within each newly diagnosed HGG treatment arm, 20 eligible and evaluable newly diagnosed HGG patients at the RP2D level will be randomized in order to maintain 80% power to detect the alternative hypothesis using a one-sided 0.05 level exact binomial test. This phase of the study will also follow a two-stage design where initially 7 patients are entered at the first stage. If no more than 2 patients experience disease progression or death within 12 months in the initial cohort, the study will move to the second stage and an additional 13 patients will be entered. If at the first stage, 3 or more patients experience disease progression or death within 12 months, the arm will be temporarily closed and a detailed review performed. The study team together with Regeneron and its delegates will determine if accrual will continue or enrollment be stopped in this arm. The arm will be considered a success (reject the associated null hypothesis) if at least 14 of the 20 patients do not experience disease progression or death at or beyond 12 months. There is a 77% chance of stopping early under the null hypothesis under this two-stage design. To allow for ineligibility, there may be an additional 1-2 patients enrolled in this cohort overall to achieve the target eligible and evaluable number of patients.

Based on cumulative outcome data from a 20-year systematic review and meta-analysis[69], the cumulative median overall survival over the last decade was 8.5 months for recurrent pediatric HGG, which translates into OS12 of 37.6% under exponential distribution. We assume the OS12 of 40% as null hypothesis and OS12 of 70% as alternative hypothesis. The target sample size for

all recurrent HGG patients is 20 eligible and evaluable recurrent HGG patients at the RP2D level in order to maintain 80% power to detect the alternative hypothesis using a one-sided 0.05 level exact binomial test. This phase of the study will also follow a two-stage design where initially 7 patients are entered at the first stage. If no more than 3 deaths occur within 12 months in the initial cohort, the study will move to the second stage and an additional 13 patients will be entered. If at the first stage, 4 or more patients die within 12 months, the arm will be temporarily closed and detailed review performed. The study team together with Regeneron and its delegates will determine if accrual will continue or enrollment be stopped in this arm. The arm will be considered a success (reject the associated null hypothesis) if at least 12 of the 20 patients survive beyond 12 months. There is a 71% chance of stopping early under the null hypothesis under this two-stage design. To allow for ineligibility, there may be an additional 1-2 patients enrolled in this cohort overall to achieve the target number of eligible and evaluable patients.

It is expected that the study will not pause after the first stage accrual goals are met for these cohorts, but that the first stage patients will be monitored with respect to the first stage futility rule above. However, given the requirement of 12 months of follow-up to determine the OS12 or PFS12 endpoint for each patient, should the accrual to the first stage be rapid and there is insufficient follow-up in the first stage cohort to obtain an OS or PFS signal before continuing to accrue to the second stage, consideration will be given to pausing accrual in order to gather information at the first stage. Furthermore, if before expansion to the second stage there is clear evidence for a need to pause accrual (eg, 1 or 2 deaths observed in the first cohort) then the study will halt accrual until it can be confirmed that it is warranted to move to the second stage.

In the event that interim pharmacokinetic analysis indicates serum concentrations below goal trough exposure for any cohort or age group, study investigators along with study sponsors will determine appropriateness of additional dose escalation or expansion cohorts in Phase 1 or the Efficacy Phase.

- There are also two arms of nEach cohort in the Efficacy Phase will aso enroll minimum number of children in certain age groups defined as follows:

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998) the following population of analysis will be used for all statistical analysis.

3.1. The Dose Limiting Toxicity Set

The DLT analysis set includes

- Phase 1: All DLT-evaluable patients treated with monotherapy cemiplimab1
- Efficacy Phase: The first 6 DLT-evaluable patients of each disease cohort by age group who are treated with cemiplimab + radiotherapy during 3+3 safety run-in

DLT evaluable patients are defined as those patients who have completed the corresponding DLT observation period and those patients who discontinued early due to the development of a DLT. This population will be used for the assessment of DLTs.

3.2. The Full Analysis Set (FAS)

In Phase 1, the FAS includes all enrolled patients who have passed screening and are deemed to be eligible for this study.

In Efficacy Phase, the FAS includes two parts:

- All newly diagnosed DIPG and newly diagnosed HGG patients to whom the radiation treatment has been assigned by the IWRS at randomization. This is the intent to treat (ITT) population for these two disease cohorts. Per ITT principle, these patients will be analyzed according to the treatment they have been assigned to during the randomization.
- All recurrent HGG patients who have pass screening and are deemed to be eligible for this study.

FAS will be used for all baseline, demographic, and efficacy endpoints.

3.3. The Safety Analysis Set (SAF)

The SAF includes all enrolled patients who have received any study treatment (at least one dose of any component of study treatment in a combination therapy) in each study phase. Patients will be analyzed according to the study treatment received (as treated). Treatment administration and all clinical safety variables will be analyzed using the SAF.

3.4. The Pharmacokinetics Analysis Set (PKS)

The pharmacokinetic analysis set (PKS) includes all treated patients who received any amount of study drug cemiplimab (safety analysis set) and has at least one non-missing cemiplimab concentration following the first dose of cemiplimab up to the end of the study.

3.5. The Immunogenicity Analysis Set

The Anti-drug Antibody (ADA) analysis set includes all treated patients who received any amount of study drug cemiplimab and had at least 1 non-missing ADA result following the first dose of cemiplimab. The ADA analysis set is based on the actual treatment received.

4. ANALYSIS VARIABLES

4.1. Disposition of Patients

The following summaries regarding patient enrollment, randomization, discontinuation and completion will be provided to assess the patient disposition:

- Summary of analysis populations, patients screened.
- Number of patients randomized in Efficacy Phase
- Number of patients discontinued treatment and the reasons for treatment discontinuation
- Number of patients discontinued study participation and the reasons for study discontinuation.

4.2. Demographic and Baseline Characteristics

Patient demographic variables include:

- Age at screening in years (quantitative and qualitative variable: Phase 1: 0 to <12, 12 to <18 years; Efficacy Phase: 3 to 12 years, 12 to 25 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino, Not reported)
- Baseline weight (kg)
- Baseline height (cm)
- Performance status by Karnofsky score (quantitative variable)
- Performance status by Lansky score (quantitative variable)

Baseline disease characteristics variables include:

- Tumor type (Solid, CNS)
- Primary diagnosis
- Primary site of tumor
- Histological/cytologic type of tumor
- WHO grade at initial diagnosis and screening
- TNM stage at initial diagnosis and screening
- Time from initial diagnosis to first dose/randomization in months
- Time from most recent relapse/recurrence to first dose/randomization in months

4.3. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

4.4. Pre-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the study drug, particularly, prior cancer related surgery, prior cancer related radiotherapy, and prior cancer related systemic therapy: chemotherapy, targeted therapy, immunotherapy and others.

Concomitant medications/procedures: any treatment administered from the time of informed consent until 90 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and are ongoing during the study, as well as any therapies started in the follow-up period to treat a study drug-related AE. All concomitant treatments will be recorded in the study case report form (CRF) with the generic name, dose, dose unit, frequency, indication, and start/stop date, appropriate.

4.5. Treatment Exposure

Cemiplimab

Duration of treatment exposure to cemiplimab (in weeks) is calculated as the minimum of

- [date of last dose – date of first dose + 14] / 7

The actual dose intensity = total dose received / duration of treatment exposure (week)

The relative dose intensity = actual dose intensity / planned dose intensity, where planned dose intensity (in week) = planned dose / 2.

Duration of exposure to radiotherapy (RT, HfRT, rRT) will not be calculated for the combination therapy in Efficacy Phase.

4.6. Efficacy Variable

4.6.1. Primary Efficacy Variable(s) (Efficacy Phase Only)

OS is defined as the time from randomization (for newly diagnosed DIPG patients) or time from the first dose of study treatment (for recurrent HGG patients) to the date of death due to any cause. **OS12** is defined as the K-M estimated probability of patients who survived at 12 months after randomization (for newly diagnosed DIPG patients) or after the first dose of study treatment (for recurrent HGG patients). All deaths due to any cause occurring on or before cut-off date in

the FAS will be used in the OS analysis. A patient who has not died or is lost to follow up at the time of analysis cut-off date will be censored at the last date that patient is documented to be alive.

PFS is defined for newly diagnosed HGG patients as the time from randomization to the date of the first documented tumor progression, as determined per Response Assessment in Neuro-Oncology (RANO) criteria with integration of Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria, or death due to any cause, whichever is earlier. In PFS analysis, patients will be censored according to rules listed below:

- Patients without a documented tumor progression or death will be censored on the date of their last evaluable tumor assessment.
- Patients without a documented tumor progression or death before initiation of another anti-tumor therapy will be censored on the date of their last evaluable tumor assessment prior to or on the date of new anti-tumor therapy.
- Patients who withdraw consent before taking any study treatment, and as a consequence have no post-baseline tumor assessment, will be censored at the date of randomization
- Patients without any evaluable tumor assessments after randomization and did not die will be censored on the date of randomization.

PFS12 is defined as the K-M estimated probability of patients who are progression-free at 12 months after randomization.

For OS variables, the time to event (day) is defined as the date of event/censor - the date of randomization + 1. For PFS variables, the time to event (day) is defined as the date of event/censor - the date of first study treatment +1.

4.6.2. Secondary Efficacy Variables

The secondary efficacy variables in Phase 1 includes the objective response rate (ORR), best overall response (BOR), duration of response (DOR).

ORR is defined as the percentage of patients who have a confirmed complete response (CR) or partial response (PR), as determined per standard criteria between the date of first study treatment and the date of the first objectively documented progression or the date of receiving another anti-cancer systemic therapy, whichever comes first.

BOR is defined as the best overall response, as determined per standard criteria between the date of first study treatment and the date of the first objectively documented progression or the date of receiving another anti-cancer systemic therapy, whichever comes first. For solid tumor, RECIST 1.1 will be used as the standard response criteria while also taking into consideration of immune-related RECIST (irRECIST) criteria. For CNS tumor, RANO with the integration of iRANO will be used as the standard response criteria.

- Best overall response of CR or PR needs to be confirmed by subsequent evaluations of overall response of CR or PR at time points at least 4 weeks apart.

- Best overall response of SD must have met the response SD criteria at least once >=39 days after start of study treatment.
- For solid tumor, best overall response of early PD does not require confirmation using RECIST 1.1. For CNS tumor, best overall response of PD should be confirmed on a 3-month follow-up scan to assess for true progressive disease versus pseudo progression as long as the patient is NOT experiencing significant neurological decline (defined as CTCAE grade 3 or higher)
- Best overall response for patients who do not have any post-baseline tumor assessment will not be evaluable (NE).

Duration of overall response (DOR) is defined for a patient whose BOR is CR or PR as the time from the time the criteria are met for a confirmed CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, or death, whichever occurs first. The same censoring rules as PFS will be applied to DOR.

4.7. Safety Variables

Beside the evaluations used to address the primary endpoint of the DLT evaluation period (the incidence of DLTs), safety endpoints include deaths due to adverse events, serious adverse events and adverse events, treatment-emergent adverse events, immune-related adverse events, and other events of special interest, laboratory evaluations, electrocardiograms (ECGs), and reasons off treatment.

4.7.1. Adverse Events and Serious Adverse Events

An **Adverse Event** (AE) is any untoward medical occurrence in a patient administered a study drug and which does not necessarily have to have a causal relationship with the study drug. A Serious Adverse Event **(SAE)** is an AE that is classified as "serious" according to the criteria specified in the protocol.

The investigator (or designee) will seek information on AEs at each patient contact. All AEs after initiation of study treatment and until 90 days after the last dose of study drug, or until the patient commences another anticancer systemic therapy, whichever is earlier, will be recorded on AE eCRF. After signing the informed consent but prior to initiation of study treatment, only the SAE and Non-SAEs associated with a protocol-mandated intervention (e.g., AEs related to an invasive procedure such as a biopsy) will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 90 days after last study treatment will be reported. Information for any non-SAE that starts during the treatment period or within 90 days after last study treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first.

The relationship of AEs to study drug will be assessed by the investigator and be determined based on protocol specified criteria.

All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, the Version 26.0 or the latest current available version). The revised National Cancer Institute

(NCI) CTCAE version 4.0 will be utilized for adverse events grading of severity. When specific AEs are not listed in the CTCAE they will be graded by the Investigator according to the following grades and definitions:

1. Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL **.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.7.2. Special Safety Variables of Interest

4.7.2.1. Adverse Events of Special Interest

An AE of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol. All AESIs must be reported within 24 hours of identification using the same reporting process as for SAE reporting. In this study, AESI are listed below (as provided in the protocol), along with each AESI detailed definition:

- Any AE that meets DLT criteria
- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 or greater immune-related AE (imAE) (or Grade 2 or greater Uveitis).

Note: An imAE can occur shortly after the first dose, several months after the last dose of treatment, or any time in-between. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an imAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an imAE.

4.7.2.2. Dose Limiting Toxicity

Dose-limiting toxicities (DLTs) are generally defined as any of the following study drug related toxicities observed during the DLT evaluation period (only for cohorts that include a DLT evaluation period).

For all Phase 1 and Efficacy Phase patients:

Non-Hematologic Dose-Limiting Toxicity**:**

- Any Grade ≥3 non-hematologic toxicity considered related to cemiplimab.
- Any cemiplimab-related AE during the first cycle of therapy that leads to a dose reduction or results in delay of treatment ≥7 days or which results in the permanent cessation of therapy will be considered dose limiting.

Hematologic Dose-Limiting Toxicity**:**

- Any grade 4 hematologic toxicity with the exception of lymphopenia and anemia considered related to cemiplimab
- Grade 3 neutropenia with fever considered related to cemiplimab
- Grade 3 thrombocytopenia considered related to cemiplimab

Immune-related Dose-Limiting Toxicity**:**

- Grade 3 immune-related AE considered related to cemiplimab. Examples include, but are not limited to, neurological toxicities, uveitis, endocrine toxicity, and colitis.

For Efficacy Phase patients only:

Interruption of Planned Radiation:

- Newly diagnosed DIPG and HGG Arm 1 (conventionally fractionated radiation): 5 consecutive fractions or 10 fractions total due to cemiplimab attributable toxicity (and not due to technical issues)
- Newly diagnosed DIPG and HGG Arm 2 (hypofractionated radiation): 2 consecutive fractions or 4 factions total due to REGN2810 attributable toxicity (and not due to technical issues)
- Recurrent HGG with reirradiation: 2 consecutive fractions or 3 fractions total due to REGN2810 attributable toxicity (and not due to technical issues)

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays, will be analyzed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

4.7.3. Laboratory Safety Variables

The clinical laboratory data consists of hematology, serum chemistry, serum or urine pregnancy test, and other. Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

- Complete blood count (CBC) with differential and platelet count
- Serum chemistry, including alkaline phosphatase, ALT, AST, total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN/urea), creatinie, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, and magnesium
- Urinalysis including glucose, pH, ketones, blood, specific gravity, spot urine protein
- Serum or urine pregnancy test for females of childbrearing age
- Serum thyroid stimulating hormone (TSH)
- Serum free Thyroxine T4
- Serum amylase
- Serum lipase
- Serum C-reactive protein (CRP)

4.8. Pharmacokinetic Variables

Pharmacokinetic variables are cemiplimab concentrations in serum over time.

4.9. Anti Drug Antibody Variables(ADA)

The immunogenicity variables include ADA status and titer at nominal sampling time/visit.

4.10. Variables for Correlative Studies

For both Phase 1 and Efficacy Phase, correlative variables include the summary of PD-L1 expression level (%Tumor cell, %TC), and efficacy (OS, ORR and DOR) in subsets according to PD-L1 expression (>=1%TC, <1%TC).

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. In addition, 25th percentile and 75th percentile will be provided.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. The denominator will be determined by the analysis population used for the summary.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its 95% confidence intervals will be summarized by the Kaplan-Meier method.

Summary analyses will be presented as follows unless otherwise specified:

- For study population
  - For Phase 1 by solid and CNS tumors,
  - For efficacy phase by newly diagnosed DIPG (ndDIPG) crossed over with conventional radiation therapy (CRT) and hypofractionated radiation therapy (HYRT), newly diagnosed HGG (ndHGG) by CRT and HYRT, recurrent HGG (rHGG), and
  - Overall.
- For efficacy:
  - Phase 1: by solid and CNS tumors on ORR,
  - Efficacy Phase: by ndDIPG crossed over with CRT and HYRT, and by rHGG; by ndHGG crossed over with CRT and HYRT, for other efficacy parameters
- For safety: the same as the study population
- PK: by Cohort (see Table 1 and Table 2) and by dose, and overall
- ADA: by Cohort (see Table 1 and Table 2) and by dose, and overall

5.1. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics variables listed in Section 4.2 will be listed and summarized by cohort and/or treatment arm based on the study phase specific FAS population.

Assessments made before the first dose of study treatment will be used as baseline measurements for the purposes of statistical analysis and reporting unless otherwise specified.

5.2. Medical History

Medical history will be listed and summarized based on the FAS population. Listing of medical history will include SOC, PT, investigator verbatim, start date, and end date. The summaries will be presented by primary system organ class and preferred term in descending of frequency of SOC followed by PT.

5.3. Protocol Deviations

Protocol deviations will be defined in a separate protocol deviation definition document (PDDD). Listing of all patients with protocol deviations and the description of deviation will be provided. The major protocol deviation, such as violation of inclusion/exclusion criteria, post-enrollment deviations which may impact assessment of efficacy, or safety endpoints will be determined before database lock and be summarized for Phase 1 and Efficacy Phase, respectively.

5.4. Prior/Concomitant Medications and Procedures

Prior medications and procedures will be summarized and listed based on the FAS. Listing of prior cancer related medications will include generic name and ATC Levels 2 and 4, indication, start and end dates. Listing of prior cancer related radiotherapy will include type of radiation therapy, site of radiation, intent of treatment, start and end dates, and total dose. Listing of prior cancer related surgery will include type of procedure, date of surgery, and surgery location. The number and percentage of patients who received any prior cancer related medications, prior cancer related radiotherapy, or prior cancer related surgery will be summarized.

Concomitant medications and procedures will be listed and summarized by cohort based on the SAF. Listing of concomitant medications will include generic name, ATC levels 2 and 4, indication, start and end dates, dose, route, frequency, and ongoing status and summarized by ATC level 2 and ATC level 4. The number and proportion of patients taking concomitant medications will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC Level 4. Patients will be counted once in all ATC categories linked to the medication.

New anti-tumor treatment received after disease progression will be listed and summarized by cohort and/or treatment arm based on the SAF.

5.5. Patient Disposition

The following summaries by table will be provided for patient disposition:

- Number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- Number of randomized patients (Efficacy Phase only)
- Number of patients in SAF
- Number of patients who discontinued the study treatment and the reasons for the treatment discontinuation
- Number of patients who discontinued the study, and the reasons for the study discontinuation

Listing of patient disposition will include dates of the first and the last cemiplimab administration, date of the end of treatment and end of study visits, and reasons for treatment and study discontinuation.

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Compliance with study treatment cemiplimab will be calculated as follows:

- Treatment Compliance = (Number of doses of cemiplimab administered during treatment period) / (Number of doses of cemiplimab planned to be administered during treatment period) × 100%,

  where temporary dose discontinuation is ignored.

Treatment compliance will be summarized and listed by study part specific FAS. The following will be summarized by solid and CNS tumors for Phase 1 patients, by cohort and radiation type for Efficacy Phase patients:

- Number of doses administered
- Number and percentage of patients who have <60%, >=60 to <80%, >=80 to <=100%, and >100% compliance will be summarized for each treatment arm, or by study drugs
- Wrong dose table (if applicable).

5.6.2. Exposure to Investigational Product

Exposure to Investigational Product will be summarized and listed based on SAF by study phase.

Duration of exposure will be summarized by dose level/cohort for Phase 1 patients and by cohort /treatment arm for patients in Efficacy Phase. For cemiplimab, the following will be summarized:

- Duration of exposure
- Number of doses administered
- Cumulative dose administered
- Actual dose intensity
- Relative dose intensity

Cemiplimab dose delays and dose interruptions will be summarized by dose level/cohort for Phase 1 patients and by cohort /treatment arm for patients in Efficacy Phase.

Listing of treatment exposure will include duration of exposure, number of doses administered, cumulative dose administered, actual dose intensity, and relative dose intensity. A listing of dose administration will be provided and will include date of administration, actual dose, dose delay, infusion interruption, and dose modification.

5.7. Analyses of Efficacy Variables

All efficacy analyses will be based on FAS according to the assigned treatment group and stratification factors used to randomize patients (from the IVR data).

5.7.1. Analysis of Primary Efficacy Variable(s)

Newly diagnosed DIPG cohort and recurrent HGG cohort:

The primary analysis of OS is the estimate of OS12 rate.

OS will also be summarized by median and displayed by Kaplan-Meier approach.

Newly diagnosed HGG cohort:

The primary analysis of PFS is the estimate of PFS12 rate. PFS will also be summarized by median and displayed by Kaplan-Meier approach.

5.7.2. Analysis of Secondary Efficacy Variables

The overall response rate, and the response of CR, PR, SD, PD, NE will be summarized for groups as specified for study population and efficacy population.

5.8. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2. The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs etc.). The analysis will comprise the basis upon which conclusions will be drawn regarding cemiplimab.

5.8.1. RP2D

For both Phase 1 and Efficacy Phase, a minimum of 3 patients at each dose level will be required to be evaluable for DLT. Tolerability of a dose level will only be determined when all potentially DLT-evaluable patients complete the 28-day DLT period. Number and proportion of patients with DLTs will be summarized using the Dose Limiting Toxicity Set.

In Phase 1, RP2D will be determined based on the MTD after DLT evaluation in A, B, C, and D cohort, as applicable.

In Efficacy Phase, RP2D will be determined based on the MTD after DLT evaluation in each E, F, G, and H cohort by radiation type; and in each I and J group by age (3 to <12, and 12 to 25), respectively.

5.8.2. Adverse Events

Period of observation:

For safety variables, 3 observation periods are defined as follows:

- The pre-treatment period is defined as the time from signing the informed consent form to before the first dose the study drug
- The on-treatment period is defined as the time from the day of first dose of study drug to the day of the last dose of study drug of original treatment plus 90 days, or to 1 day before patients receive another anticancer systemic therapy, whichever is earlier
- The post-treatment period is defined as the time starting 1 day after the end of on-treatment period

Day 1 is the first day of patient receiving study treatment, Day-1 is the day before, and there is no Day 0.

- **Pre-treatment AEs** are defined as AEs that developed during the pre-treatment period.
- **Treatment-emergent AEs** (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occur during the post-treatment period but prior to initiation of other anticancer therapy.
- **Post-treatment AEs** are defined as AEs that developed or worsened during the post-treatment period and are not considered drug related by the investigator.
- **Infusion-related reaction** (IRR) is any AE that occurs during administration of the study drug or within 2 hours after the infusion of the study drug is completed. All IRR will be reported as AEs and graded using CTCAE.
- **Immune-mediated AE** (imAE) is any AE with unknown etiology associated with drug exposure and consistent with an immune phenomenon. imAEs are identified for the study drug by investigator assessment.

The focus of adverse event reporting will be on TEAEs. For details on handling missing data and partial dates, see Section 6. Summaries of adverse events will include: TEAEs, Treatment related TEAEs, Serious TEAEs, Treatment-related Serious TEAEs, AESI, immune-related AEs (imAE), and infusion related reaction (IRR). For AEs (TEAEs, AESIs, imAEs and IRRs), the following will be summarized:

- The number and proportions of patients reporting at least 1 AE, presented by SOC and PT
- AEs by severity (CTCAE, latest available version), presented by SOC and PT
- AEs by relationship to treatment (related, not related), presented by SOC and PT
- AEs occurring in > x% patients, presented by SOC and PT
- AEs leading to permanent treatment discontinuation, presented by SOC and PT
- AEs leading to death, presented by SOC and PT

For each AE summary presented by SOC and PT, the summary table will be sorted by decreasing frequency of SOC and PT. For AE summary presented by PT, the summary table will be sorted by decreasing frequency of PT.

The imAEs reported by investigator will be summarized. Additionally, imAEs identified by the sponsor will be summarized. The sponsor-defined imAEs are listed in a separate document. The list may be updated to include all possible imAEs. All imAEs occurred during the on-treatment and post-treatment periods will be included.

For AE listings, the following variables will be displayed:

- Age/gender
- Verbatim Term

- PT
- SOC
- AE start date and end date/ongoing (and corresponding study day)
- AE duration
- Relationship to study drug: unrelated or related
- Seriousness (Serious AE or not)
- NCI CTCAE grade: mild, moderate, severe, life-threatening or fatal
- Action taken: none, dose decreased, dose temporarily stopped or discontinued
- Treatment for AE: none, medication, surgery or others
- Outcome: recovered/resolved, recovered/resolved with residual effects, recovering/ resolving, not recovered/not resolved, fatal, or unknown

Counts will be provided for each PT within each SOC. Percentages will be calculated using the number of patients from the safety set.

5.8.3. Analysis of Adverse Events of Special Interest

Treatment emergent adverse events of special interest as defined in Section 4.7.2.1 will be presented by SOC and PT. The summaries will be sorted by decreasing incidence of PT within each SOC in the total.

5.8.4. Clinical Laboratory Measurements

Listings of laboratory values, normal ranges, grade, date, and visit/cycle will be provided. For numeric lab variables, values and change from baseline to each visit/cycle will be summarized. Listings of abnormal lab values by patient and visit/cycle will also be constructed.

Summary tables for new or worsened laboratory values with all grade and NCI CTCAE grade ≥ 3 will be generated.

Summary of Shift tables from baseline to post-treatment worst NCI CTCAE grade will be generated. The shift tables include the overall and individual Hematologic Test (Hemoglobin, Platelet counts, Red blood cells, White Blood cells, and differential of Neutrophils, Lymphocytes and Monocytes).

Baseline clinical laboratory analytes and change from baseline in selected clinical laboratory analytes to each scheduled assessment time will be summarized with descriptive statistics. Summary statistics will include the number of patients, mean, median, standard deviation, quartiles, minimum, and maximum.

5.9. Analysis of Pharmacokinetic and Antibody Data

5.9.1. Analysis of the Pharmacokinetic Variables

Cemiplimab concentrations in serum over time will be reported at nominal timepoints as individual values (together with patients' baseline body weight) and with descriptive statistics, by

age group and dose. PK parameters after the first dose will be determined by non-compartmental analysis. The PK parameters will include but will not be limited to concentrations at pre-dose and Ceoi after the first dose and during treatment. Additional PK parameters after the first dose include AUC2w and estimated t1/2, estimated over the 2-week dosing interval.

5.9.2. Analysis of ADA Data

The immunogenicity variables described in Section 1.9 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA status, ADA category, and maximum titer observed in patients in the ADA analysis set. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥9-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients/Subjects/Participants that are treatment-emergent will be further categorized as follows:

Treatment-emergent is further sub-categorized as:

- Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 12/16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
- Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
- Transient - Not persistent or indeterminate, regardless of any missing samples

The maximum titer category of each patient is classified as:

- Low (titer <1,000)
- Moderate (1,000≤ titer ≤10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of pre-existing patients

- Number (n) and percent (%) of treatment-emergent ADA positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to cemiplimab will be explored by treatment groups. Plots of individual cemiplimab concentration time profiles may be provided to examine the potential impact of ADA category and maximum titer category on these profiles.

5.10.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

The safety analyses mentioned above will be conducted using the following categories:

- ADA Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category in ADA positive patients

5.10.3. Analysis of Exploratory Biomarker Data

The tumor expression of PD-L1 will be reported as % Tumor cell staining in individual patients with available PD-L1 IHC result. The efficacy variables (OS, ORR and DOR) will be summarized according to PD-L1 expression in following subsets of patients:

- All patients with available PD-L1 result (PD-L1 biomarker subset)
- Patients with PD-L1 expression score >=1%TC (PD-L1 positive biomarker subset)

- Patients with PD-L1 expression score <1%TC (PD-L1 negative biomarker subset)

All other biomarker endpoints are exploratory, and the analysis plan will be described in a separate Biomarker analysis plan (BAP) document.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

Incomplete date of death in OS analysis

- If the day of death is missing, it will be imputed to the first day of the month except if the date of patient's last contact is the same month as the death date. In this case, the death date will be imputed to the date of the last contact + 1 day.
- If the day and month of death are missing, date of death will be imputed to the 1st of January of the year, except if date of patients' last contact is the same year as death date. In this case, the death date will be imputed to the date of the last contact + 1 day.

Last contact date

Last contact date will be used for censoring patients in the OS analysis. The last contact date will be derived for patients alive at the analysis cut off using the latest complete date among the following:

- 'Last known date alive' recorded on the 'Survival status' eCRF page.
- Assessments with non-missing values corresponding to actual patient contact (including: retreatment screening, vital signs assessments, performance status assessments, physical examinations, tumor imaging, brain MRI, chest X-ray, scans, laboratory, ECG, pregnancy test, immunoglobulin, HIV testing, sample collection dates, AE start date, AE resolution date, and other dates on AE CRF, concomitant medication, procedures, post treatment anti-cancer procedure, study drug administration, cyclophosphamide administration, chemotherapy administration, radiation therapy administration, GM-CSF administration, inform consent tracking)

Non-evaluable response in ORR analysis

Patients who are deemed NE according to RECIST version 1.1. or unevaluable by the other response criteria will be considered as not reaching CR/PR in calculating ORR, i.e. they are not considered as responders in the numerator of ORR, but they are counted in the denominator of ORR.

6.3. Data Handling Convention for Missing Data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to date of the first study treatment, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be imputed in medication listings.

Missing AE severity and relationship with treatment

If the intensity of a TEAE is missing, it will be classified as "Grade 3" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

Missing AE and concomitant medication dates

- Imputation of AE and concomitant medication missing/partial start dates:

Every effort will be made to collect the start dates of all AEs and concomitant medications. However, in the case the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the first dose of study medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the first dose of study medication date, then the start date of the first dose will be imputed. Otherwise, the missing day or month by the first day or the first month will be imputed. However, if the imputed start date is after the non-missing end date, the start date will be imputed to the end date.

- Imputation of AE and concomitant medication missing/partial end dates:

When only year is present, missing AE/concomitant medication end day and month will be imputed to the earlier of (study end date, 31DECYYYY). When both month and year present, missing AE/concomitant medication end day will be imputed to the last day of the month. There will be no attempt to impute completely missing AE or concomitant medication end dates.

This represents the most conservative approach in the handling of missing or partial AE/concomitant medication start and end dates as well as missing AE severity.

- Date of first / last infusion

The date of first administration of study drug is derived as the first date when a non-zero dose of any component of study treatment was administered on the eCRF. The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study drug was administered and recorded on the eCRF. If a patient's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

6.4. Unscheduled Assessments

Unscheduled visit measurements may be used to provide a measurement for a baseline or endpoint value if appropriate according to their definition. The measurements may also be used to determine abnormal laboratory values.

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

7. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

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