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**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**

**PNOC Protocol: PNOC 013 (CC#160825)**

**Regeneron Study R2810-ONC-1690**

**Amendment Number: 3**

**Version Date:** *See appended electronic signature page*


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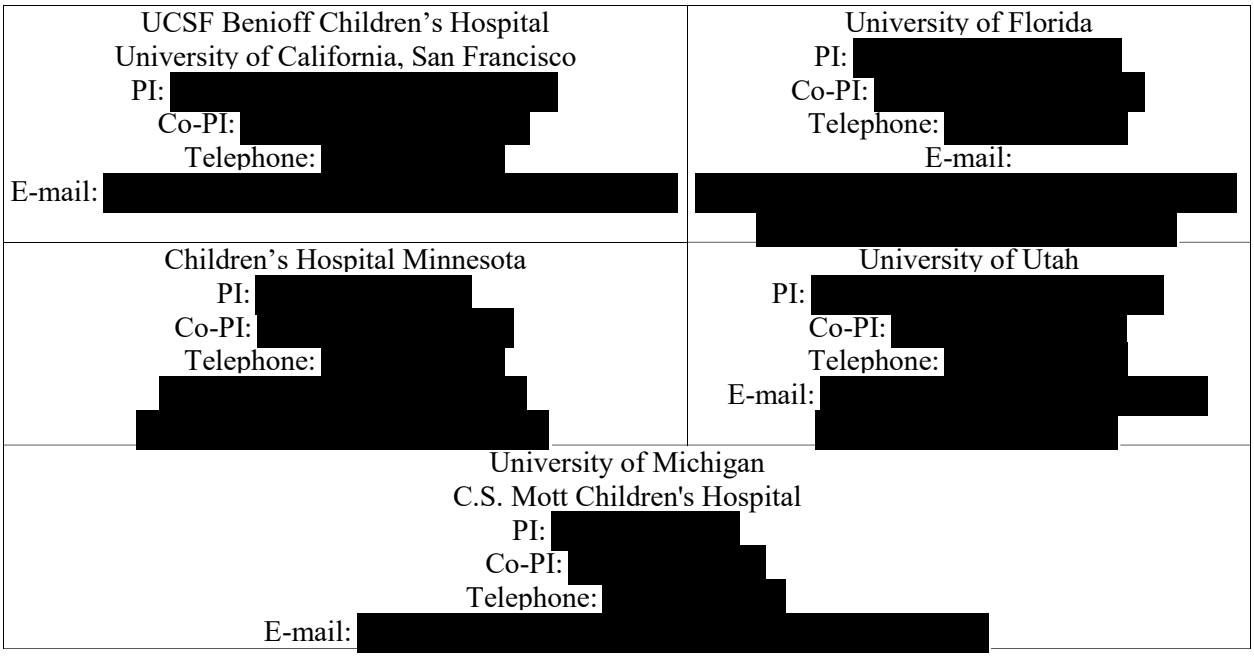


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# PROTOCOL SIGNATURE PAGE

**Protocol No.: PNOC 013 / Regeneron R2810-ONC-1690**

**Version Date:** *See appended electronic signature page*

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

**Study Chair**

_____
Printed Name

_____ _____
Signature Date

# PROTOCOL SIGNATURE PAGE – PARTICIPATING SITES

**Protocol No.: PNOC 013 / Regeneron R2810-ONC-1690**

**Version Date:** *See appended electronic signature page*

Participating Site(s)

I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.

| **Principal Investigator** | **Site** |
|---|---|
| _____ | _____ |
| Printed Name | Institution Name |
| _____ | _____ |
| Signature | Date |

# AMENDMENT HISTORY

## Amendment 3

The following is a summary of changes made for amendment 3 of the PNOC 013 (R2810-ONC-1690) protocol. The aim of this amendment is to streamline the structure and language of the protocol, to improve the clarity of the study design, and consistency of study conduct. Additionally, changes that impact the design of the study have been made.

The changes in this amendment and their rationale are detailed below. Changes are categorized as **changes to study design**, **clarifications of study design**, **structural changes**, and **other changes**, and are listed by order of first appearance in the protocol.

### Changes to Study Design

| *Changes to Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| If a patient treated with combination therapy experiences AE(s) that are likely to be related to only one of the therapies (in the opinion of the investigator), the patient may continue treatment with the therapy determined not to be the cause of the AE(s). In addition, if the AE is an infusion-related reaction that is likely only related to REGN2810 and not to combination therapy (in the opinion of the investigator), this will not be considered a DLT of the combination therapy. | Section 4.5 Off-Treatment Criteria |
| Amended the following regarding off-treatment criteria:<br>• Patients may be allowed to continue treatment after a treatment delay of ≥28 days, after discussion with the sponsor and The Pacific Pediatric Neuro Oncology Consortium (PNOC) | Section 4.5 Off-Treatment Criteria |
| Patients who begin an anticancer therapy not specified in protocol will be considered off study. | Section 4.6 Off-Study Criteria |
| Patients with documented allergic or acute hypersensitivity reaction attributed to antibody treatments are now permitted entry into the study. Upon further consideration and in light of the fully human nature of REGN2810, it is unlikely that patients with prior allergic reaction to antibody treatment will have an increased risk of reaction to REGN2810 compared with other patients. | Section 5.2 Exclusion Criteria<br>Section 7.2.1 Allergic Reaction or Hypersensitivity in Patients with Prior Reaction(s) to Antibody Treatment<br>Section 8.2.1.2 Medical History |

| *Changes to Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| To ensure appropriate management of these patients who are now permitted in the study, prior history of antibody reaction will be documented as medical history. In addition, treatment will be temporarily suspended following any evidence of an allergic reaction or hypersensitivity to REGN2810, and the sponsor should be informed as soon as possible to discuss patient management. | |
| Amended exclusion criteria to clarify that, for patients with newly diagnosed HGG, the first study treatment should occur within 28 days of the date of definitive surgery. This criterion was implied but not explicitly stated. | Section 5.1.3.2 Newly Diagnosed HGG (Cohorts G and H) Only<br>Section 10.5 Timing |
| Either serum or urine pregnancy test may be used to assess pregnancy during screening, and the window for a negative pregnancy test has been widened to 14 days from cycle 1 day 1 (C1D1). In addition, all subsequent pregnancy tests are allowed a window of +/-14 days. | Section 5.2 Exclusion Criteria<br>S<br>Table 11 Schedule of Events for Phase 1<br>Table 12 Schedule of Events for the Efficacy Phase: REGN2810 + Conventionally Fractionated Radiation<br>Table 13 Schedule of Events for the Efficacy Phase: REGN2810 + Hypofractionated Radiation or Re-Irradiation |
| Patients with prior idelalisib treatment are now permitted entry into the study. The cemiplimab risk-benefit profile has evolved and is now considered positive for patients who have had prior treatment with idelalisib. | Section 5.2 Exclusion Criteria |
| The infusion time for REGN2810 has been amended to provide greater institutional flexibility. REGN2810 infusion should occur over at least 30 minutes (window: +/-5 minutes). The infusion time may exceed 30 minutes as needed to conform with institutional standards. | Section 6.1 REGN2810 Administration<br>Table 9 REGN2810 Administration |
| Clarified that patients may not receive live vaccines while on therapy and for 3 months after stopping therapy. Patients are currently prohibited from receiving live vaccines within 28 days of study registration; this prohibition clarified the original intent of the study (on-treatment and post-treatment prohibition). | Section 6.3 Prohibited Therapies |

| *Changes to Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| On-treatment serum C-reactive protein (CRP) collection will be required only on the first day of each cycle. | Table 11 Schedule of Events for Phase 1<br>Table 12 Schedule of Events for the Efficacy Phase: REGN2810 + Conventionally Fractionated Radiation<br>Table 13 Schedule of Events for the Efficacy Phase: REGN2810 + Hypofractionated Radiation or Re-Irradiation |
| End of Treatment has been redefined as the day it is confirmed that a patient will discontinue future dosing, regardless of the reason for discontinuation. | Table 11 Schedule of Events for Phase 1<br>Table 12 Schedule of Events for the Efficacy Phase: REGN2810 + Conventionally Fractionated Radiation<br>Table 13 Schedule of Events for the Efficacy Phase: REGN2810 + Hypofractionated Radiation or Re-Irradiation<br>Table 14 PK and ADA Collection Schedule for Phase 1: Patients 0 to 2 Years of Age (or Per Institutional Guidelines)<br>Table 15 and PK and ADA Collection Schedule for Phase 1: Patients >2 to <18 Years of Age<br>Table 16 PK and ADA Collection Schedule for the Efficacy Phase<br>Section 8.1.5 Footnotes for Table 14, Table 15, and Table 16 (PK and ADA Collection Schedules), footnote #2, #5<br>Section 8.1.6 End of Treatment Visit |
| The following changes and clarifications have been made regarding the collection of samples for Pharmacokinetic (PK) and Anti-drug Antibodies (ADA) analysis:<br>• For patients who continue receiving REGN2810 beyond cycle 12, on-treatment PK samples will be collected on cycles 16 and 24 (rather than every 3 cycles)<br>• Clarified that in Phase 1, the time 1 PK sample should be collected pre-dose (rather than at the end of infusion)<br>•<br>• Clarified that a PK sample will be taken at the first in-clinic follow-up visit. Additional PK samples will be taken at in-clinic visits after End | Section 8.1.4 Pharmacokinetic and Anti-Drug Antibody Sample Collection<br>Table 14 PK and ADA Collection Schedule for Phase 1: Patients 0 to 2 Years of Age (or Per Institutional Guidelines)<br>Table 15 and PK and ADA Collection Schedule for Phase 1: Patients >2 to <18 Years of Age<br>Table 16 PK and ADA Collection Schedule for the Efficacy Phase<br>Section 8.1.5 Footnotes for Table 14, Table 15, and Table 16 (PK and ADA Collection Schedules), footnote #2, #5 |

| *Changes to Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| of Treatment (EOT) that are at least 3 weeks apart. | |
| Delineated that concomitant medications must be captured from signing of informed consent through the 30-day toxicity check. | Section 8.2.1.8 Concomitant Medications |
| Urinalysis will involve a dipstick urine test with reflex to microscopic urinalysis in the event of abnormal findings. | Section 8.2.3 Laboratory Procedures |
| Safety reporting requirements have been amended such that all AEs will be recorded/reported if they occur from the time the informed consent is signed until 90 days after the end of study treatment or until the patient receives another systemic anticancer therapy, whichever is earlier. In addition, clarified that AEs attributable to disease progression will not be recorded/reported. | Section 9.4.1 Adverse Events<br>Section 9.4.6 Follow-Up |
| Study endpoints have been updated in order to better differentiate them from study objectives. Endpoints now provide an explicit description of the outcomes that will be measured and the methods or criteria that will be used to measure them. These updates are in line with the current planned outcome analyses of the study and are not intended to represent deviations from the study's objectives. | Abstract – Primary Endpoints, Secondary Endpoints, Exploratory Endpoints<br>Section 12.1 Study Endpoints<br>Section 12.1.1 Primary Endpoints<br>Section 12.1.2 Secondary Endpoints<br>Section 12.1.3 Exploratory Endpoints<br>Section 12.7 Analysis of Primary Endpoints<br>Section 12.8 Analysis of Secondary Endpoints<br>Section 12.9 Analysis of Exploratory Endpoints |
| Study reservation and registration procedures have been updated to reflect current process. | Section 15.2 Reservation and Registration Process |

## Clarifications of Study Design

| *Clarifications of Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| Experimental design schema were updated to better clarify the design of the study. | Figure 1 Trial Enrollment in Phase 1: Recurrent or Refractory Solid or Central Nervous System<br>Figure 2 Trial Enrollment in the Efficacy Phase: Newly Diagnosed Diffuse Intrinsic Pontine Glioma |

| *Clarifications of Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| | Figure 3 Trial Enrollment in the Efficacy Phase: Newly Diagnosed High-Grade Glioma<br>Figure 4 Trial Enrollment in the Efficacy Phase: Recurrent High-Grade Glioma<br>Figure 5 Study Design, Phase 1<br>Figure 6 Study Design, Efficacy Phase |
| Amended exploratory quality of life objective to clarify that both younger and older cohorts will be assessed by quality of life instruments in this study. | Abstract – Exploratory Objectives<br>Section 1.3 Exploratory Objectives |
| Additional information was provided, and structural reorganizations were made, to clarify the design of the study, including:<br>• Letter designations for each cohort<br>• Dedicated sub-sections describing the dose escalation design (Phase 1 and Efficacy Phase), dose escalation rules (Phase 1 and Efficacy Phase), timing of enrollment (Efficacy Phase), and expansion cohorts (Efficacy Phase)<br>• Description of the dose escalation review committee and review process<br>• Description of the Simon two-stage design<br>• Explicit delineation of dose escalation rules according to both age cohort and study phase<br>• Dedicated sub-sections describing dose-limiting toxicity windows and definitions<br>• Dedicated sub-sections describing off-treatment and off-study criteria | Abstract – Study Design<br>Section 4 Study Design (and all sections therein)<br>Table 1 Patient Cohorts<br>Table 2 Patient Cohorts in Phase 1<br>Table 3 Patient Cohorts in the Efficacy Phase<br>Table 4 Dose Escalation Rules: Cohorts Age <12 Years, Phase 1<br>Table 5 Dose Escalation Rules: Cohorts Age <12 Years, Efficacy Phase<br>Table 6 Dose Escalation Rules: Cohorts Age ≥12 Years, Phase 1 and Efficacy Phase<br>Table 7 Criteria for Dose-Limiting Toxicity<br>Section 4.1 Characteristics (deleted)<br>Section 6.2 Definition of Dose-Limiting Toxicity (deleted)<br>Section 6.3 Dose Escalation Guidelines (deleted)<br>Section 9.5 Off-Treatment Criteria (deleted)<br>Section 9.6 Off-Study Criteria (deleted) |
| Clarified that expansion enrollment will include at least 100 patients (at least 40 patients with newly diagnosed DIPG, at least 40 with newly diagnosed HGG, and at least 20 with recurrent HGG). Additionally, clarified the breakdown of patients within each cohort, for both Phase 1 and the Efficacy Phase. | Abstract – Number of Patients<br>Section 4.7 Number of Patients<br>Section 12.2 Sample Size |
| To ensure adequate imaging collection while minimizing duplicative data, imaging requirements | Section 4 Study Design |

| *Clarifications of Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| have been clarified as follows (applies to both study phases):<br>• Imaging does not need to be taken or recorded every treatment cycle, but should occur once every 12 weeks (window: -2 weeks) while patients are on treatment<br>• Imaging should be performed at the EOT visit, and during the off-treatment follow-up period approximately once every 12 weeks (or per institutional standards) for up to 52 weeks<br>• Imaging should be performed at the time of disease progression<br>• Imaging during C1D1 is only required if prior imaging occurred more than 14 days from C1D1. If imaging has been taken within 14 days of C1D1 (ie, during the screening period), imaging does not need to be performed on C1D1 | Section 8.1.2 Footnotes for Table 10 (Schedule of Events for Phase 1) - Footnote #6<br>Section 8.1.3 Footnotes for Table 11 and Table 12 (Schedules of Events for the Efficacy Phase) - Footnote #7 |
| Clarified that quality of life will be measured by Pediatric Quality of Life (PedsQL) for patients 2 to <18 years of age) and by Functional Assessment of Cancer Therapy-Brain (FACT-Br) for adult patients (>18 years of age). | Section 4 Study Design<br>Section 8.1.2 Footnotes for Table 11 (Schedule of Events for Phase 1) - Footnote #2<br>Section 8.1.3 Footnotes for Table 12 and Table 13 (Schedules of Events for the Efficacy Phase) - Footnote #3<br>Section 8.2.1.9 Quality of Life Assessment |
| Clarified that cohorts are defined by both age and tumor type. | Section 4.1 Phase 1 Study Design<br>Section 4.2 Efficacy Phase Study Design |
| Clarified that cohort recommended phase 2 dose (RP2D) may be lower than the maximum tolerated dose (MTD) if indicated by pharmacokinetic analyses. | Section 4.1.2 Dose Escalation Rules in Phase 1<br>Section 4.2.2 Dose Escalation Rules in Efficacy Phase |
| Clarified that radiation centers must be approved by PNOC. | Section 4.2 Efficacy Phase Study Design<br>Section 8.2.2.2 Radiation Therapy<br>Section 10.1 General Guidelines |
| Clarified that the timing of enrollment for age 3 to <12 Efficacy Phase cohorts will begin once the RP2D is determined for the corresponding age within the Central Nervous System (CNS) tumor cohorts. | Section 4.2.3 Timing of Initial Enrollment |

| *Clarifications of Study Design* | |
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| **Change and Rationale** | **Sections Changed** |
| Clarified that disease progression must be confirmed before patient will be taken off treatment for disease progression | Section 4.5 Off-Treatment Criteria |
| Clarified that archival tissue is acceptable to satisfy biopsy requirement for both Phase 1 and the Efficacy Phase. | Section 5.1 Inclusion Criteria |
| Removed duplicative inclusion criterion regarding corticosteroid use. Retained corticosteroid exclusion criterion. | Section 5.1 Inclusion Criteria<br>Section 5.2 Exclusion Criteria |
| Clarification to inclusion/exclusion criteria: for newly diagnosed DIPG cohorts, patients should have no prior therapy or radiation before study registration | Section 5.1.3.1 Newly Diagnosed DIPG (Cohorts E and F) Only<br>Section 5.1.3.2 Newly Diagnosed HGG (Cohorts G and H) Only |
| Clarified that patients are excluded from the study if they have received an investigational anticancer agent (ie, investigational agents not intended to treat/palliate cancer are not exclusionary). | Section 5.2 Exclusion Criteria |
| Exclusion criterion describing contraception requirements has been updated to comply with Clinical Trial Facilitation Group (CTFG) guidance. | Section 5.2 Exclusion Criteria |
| Clarified that lengthening of REGN2810 infusion time may be considered in managing Grade 2 infusion-related reactions. | Table 10 Guidelines for Dose Modification and Re-Initiation of Treatment in Case of Suspected REGN2810 Toxicity<br>Section 7.2 Infusion-Related Reactions |
| To minimize redundancy and improve clarity/consistency regarding the required assessments and data collection timepoints in this study, the schedules of events have been updated as follows:<br>• The Efficacy Phase schedules and corresponding footnotes have been consolidated. There are now two Efficacy Phase tables in total, based on treatment arm (conventionally fractionated radiation versus hypofractionated radiation)<br>• Some assessments have been reordered to consolidate the number of assessment categories<br>• Clarification has been made that, except where noted in the footnotes, all visit days (including | Section 8 Schedule of Events and Procedures<br>Section 8.1 Schedule of Events / Treatment Plan<br>Table 11 Schedule of Events for Phase 1<br>Section 8.1.2 Footnotes for Table 11 (Schedule of Events for Phase 1)<br>Table 12 Schedule of Events for the Efficacy Phase: REGN2810 + Conventionally Fractionated Radiation<br>Table 13 Schedule of Events for the Efficacy Phase: REGN2810 + Hypofractionated Radiation or Re-Irradiation<br>Section 8.1.3 Footnotes for Table 12 and Table 13 (Schedules of Events for the Efficacy Phase)<br>Section 9.1Study Calendar for Phase 1 (deleted)<br>Section 9.2 Study Calendar for Efficacy Phase |

| *Clarifications of Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| study drug administration and assessments) are allowed a window of +/-3 days<br>• Line items have been added for height and weight<br>• "Toxicity Assessment" has been renamed "Adverse Events"<br>• To avoid duplicative data collection, the "baseline" column has been removed; these samples will be collected predose on C1D1<br>• To avoid schedule overlaps, the toxicity check visit has been defined as 30 days after the end of treatment visit<br>• The randomization column has been removed; randomization has been marked during the screening period<br>• The "tissue collection" column has been removed; collection time points for tumor tissue, genomic DNA, and circulating tumor DNA have been marked within the corresponding clinic visits<br>• All footnotes have been clarified to align sample collection requirements with the schedule provided in the tables<br>• Clarified that the visit window for follow-up visits is +/-7 days<br>• Various typographical, grammatical, formatting, and editorial changes were implemented | Table 6: CYCLES 1 & 2: DIPG Cohort Arm 1 (XRT 30 fractions, total 42 days) (deleted)<br>Table 7: CYCLES 1 & 2: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days) (deleted)<br>Table 8: CYCLES 1 & 2: Newly diagnosed HGG Cohort Arm 1 (XRT 33 fractions, total 45 days) (deleted)<br>Table 9: CYCLES 1 & 2: Newly diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days) (deleted)<br>Table 10: CYCLES 1 & 2: Recurrent HGG Cohort (XRT 10 fractions, 14 days) (deleted)<br>Table 11: CYCLE 3 and Future Cycles Thereafter (deleted) |
| Clarified that a) all patients must undergo a 30-day toxicity check, regardless of the reason for treatment cessation, and b) the 30-day toxicity check can be conducted by clinic visit, telemedicine encounter, or telephone encounter. | Section 8.1.7 30-Day Toxicity Check |
| Clarified that circulating tumor DNA (ctDNA) samples will be collected predose at C1D1 and at any time scheduled or repeat/confirmatory imaging is performed (except during screening). | Table 11 Schedule of Events for Phase 1<br>Section 8.1.2 Footnotes for Table 11 (Schedule of Events for Phase 1) - Footnote #9<br>Table 12 Schedule of Events for the Efficacy Phase: REGN2810 + Conventionally Fractionated Radiation |

| *Clarifications of Study Design* | |
|---|---|
| **Change and Rationale** | **Sections Changed** |
| | Table 13 Schedule of Events for the Efficacy Phase: REGN2810 + Hypofractionated Radiation or Re-Irradiation<br>Section 8.1.3 Footnotes for Table 12 and Table 13 (Schedules of Events for the Efficacy Phase) - Footnote #10 |
| Clarified that periodic meetings of the study safety monitoring team will be conducted to review emerging safety data of the study treatments. | Section 9.6 Safety Monitoring |
| Clarified language surrounding statistical analysis; analysis will be conducted based on each radiation therapy arm irrespective of cohort or age group. | Section 12.2 Sample Size<br>Section 12.3 Sample Size Justification and Accrual Rate |
| Clarified in the statistical analysis section that PK analysis is a primary objective in the Efficacy Phase. | Section 12.7.3 Efficacy Phase: Pharmacokinetics |
| Clarified the meaning of the term "enrollment" as appropriate (C1D1, screening, etc). | Throughout the protocol. |
| Clarified that data submission timelines represent targets, but may vary according to individual site. | Appendix 3 REQUIRED DATA AND TIME TABLE FOR SUBMISSION |

## Structural Changes

| *Structural Changes* | |
|---|---|
| **Change and Rationale for Change** | **Sections Changed** |
| Section headers were added and/or modified to the background and rationale sections of the protocol, and some text was reordered, to improve readability. | Section 2 Background (and sections therein) Section 3 Rationale (and sections therein) |
| The rationale for radiation therapy fractionation schedules selected for this study was moved from the background section to the rationale section. | Section 3.3 Radiotherapy Regimen Selection<br>Section 2.3 Radiotherapy (deleted) |
| Rationale, study procedures, and statistical considerations for correlative/biomarker analyses have been placed in the corresponding sections of the protocol related to rationale, study procedures, and statistical considerations. | Section 3.5 Correlative Exploratory Studies<br>Section 8.2.6 Exploratory Procedures<br>Section 12.4 Exploratory Endpoints<br>Section 12.9 Analysis of Exploratory Endpoints<br>Section 13 Biomarker, Correlative, and Special Studies (deleted) |
| To improve clarity of inclusion/exclusion criteria, the following changes have been made: | Section 5.1 Inclusion Criteria<br>Section 5.1.1 All Patients (Phase 1 and Efficacy Phase) |

| *Structural Changes* | |
|---|---|
| **Change and Rationale for Change** | **Sections Changed** |
| • Placed the criteria in a dedicated section of the protocol<br>• Moved inclusion under "all patients" sub-section to the top of the inclusion/exclusion criteria section, to clarify that these criteria apply to patients in both Phase 1 and the Efficacy Phase | Section 5.1.2 Phase 1<br>Section 5.1.3 Efficacy Phase<br>Section 5.1.3.1 5.1.3.1. Newly Diagnosed DIPG (Cohorts E and F) Only<br>Section 5.1.3.2 Newly Diagnosed HGG (Cohorts G and H) Only<br>Section 5.1.3.3 Recurrent HGG Cohorts (I and J) Only<br>Section 5.2 Exclusion Criteria<br><br>Section 4.3 Inclusion Criteria (deleted)<br>Section 4.3.1. Phase 1 – Safety/RP2D (deleted)<br>Section 4.3.2.1 DIPG Cohort (deleted)<br>Section 4.3.2.2 HGG Cohort (deleted)<br>Section 4.3.2.3 All Patients (deleted)<br>Section 4.4 Exclusion Criteria (For All Patients) (deleted) |
| To improve document organization, dosing modification guidelines have been merged with information concerning study drug administration. In addition, the section title was reworded to clarify that dose modification guidelines apply to both study phases. | Section 6.2 REGN2810 Dose Modifications and Delays<br>Section 8 Dosing Modifications and Delays for the Efficacy Phase of the Study (deleted) |
| To improve clarity, section headings were added to the supportive care/adverse event management section. | Section 6.3 Study Supportive Care and Adverse Event Management Guidelines |
| To improve ease of use, the following changes to PK tables and descriptions have been made:<br>• Sample collection tables for PK and ADA have been moved to the schedule of events section of the protocol<br>• Information pertaining to PK and ADA procedures has been moved to the study procedures section of the protocol<br>• Footnotes have been consolidated in a single set of footnotes for PK/ADA collection tables | Section 8.1.4 Pharmacokinetic and Anti-Drug Antibody Sample Collection<br>Table 14 PK and ADA Collection Schedule for Phase 1: Patients 0 to 2 Years of Age (or Per Institutional Guidelines)<br>Table 15 and PK and ADA Collection Schedule for Phase 1: Patients >2 to <18 Years of Age<br>Table 16 PK and ADA Collection Schedule for the Efficacy Phase<br>Section 8.1.5 Footnotes for Table 14, Table 15, and Table 16 (PK and ADA Collection Schedules)<br>Section 8.2.5 Pharmacokinetic and Immunogenicity Procedures |

| *Structural Changes* | |
|---|---|
| **Change and Rationale for Change** | **Sections Changed** |
| | Section 3.1.2 Anti-drug Antibody Measurements and Samples (deleted)<br>Section 12 PHARMACOKINETICS AND ANTI-DRUG ANTIBODY STUDIES (deleted)<br>Section 12.1. Drug Concentration Measurements and Samples (deleted)<br>Section 12.2. Analysis of Anti-Drug Antibody Data (deleted) |
| To avoid redundancy and internal inconsistencies, the study procedures section has been revised to include information concerning procedure execution and not timing of procedures. | Section 8.2 Study Assessments and Procedures (and all sections therein)<br>Section 9.3 Observations and Procedures (deleted) |
| To improve document flow, the dedicated sections describing the procedural guidelines for radiation therapy and disease assessment per Response Evaluation Criteria in Solid Tumors (RECIST) have been placed near each other and earlier in the protocol. | Section 10 Radiation Therapy Guidelines<br>Section 11 Evaluation Criteria |
| The per-protocol fractionation schedule for Efficacy Phase cohorts has been moved from the study procedures section to the radiation guidelines section, to avoid redundancy. Radiation therapy treatment lengths have also been moved into this section, from their previous location in the titles of schedules of events tables. | Section 10.2 Protocol-Defined Dose and Fractionation Schedules<br>Section 10.8.2 Prescribed Dose and Fractionation<br>Section 9.3.4. Cycle 1 Day 1 Visit and Weekly During Cycle 1 and Through the DLT Period (Within 3 Days of Therapy Initiation and +/-3 Days Thereafter) – All Patients (deleted) |
| Response criteria headings were renumbered to improve readability, and guidance schematic was reformatted. | Section 11.4 Response Criteria (and sections therein)<br>Figure 7 Additional Guidelines for Response Criteria for CNS Tumors |
| To improve document flow, trial registration procedures have been moved to a later section of the protocol, adjacent to information regarding reporting and exclusions. | Section 15 Registration Procedures<br>Section 5 Registration Procedures (deleted) |
| References and appendices have been reordered based on the order in which they are cited in the protocol. | Section 18 References<br>Appendix 1 PERFORMANCE STATUS CRITERIA<br>Appendix 2 ADVERSE EVENT MANAGEMENT<br>Appendix 3 REQUIRED DATA AND TIME TABLE FOR SUBMISSION |

| *Structural Changes* | |
|---|---|
| **Change and Rationale for Change** | **Sections Changed** |
| | Appendix 4 PNOC INSTITUTIONS, REQUIRED REGULATORY DOCUMENTS<br>Appendix 5 INFORMATION SHEET ON POSSIBLE DRUG INTERACTIONS |

### Other Changes

| *Other Changes* | |
|---|---|
| **Change and Rationale for Change** | **Sections Changed** |
| Duration of Study in abstract has been defined on a per-patient basis. | Abstract – Duration of Study (Per Patient) |
| Background section was updated to reflect most recent cumulative safety data and marketing authorization status for REGN2810, with other editorial changes and updates made to improve readability. | Section 2.3 REGN2810, a Human Monoclonal Antibody to Programmed Death-1 (PD-1)<br>Section 2.5 REGN2810 Clinical Studies |
| Specifications of REGN2810 infusion bag stability were removed; corresponding information can be found in the pharmacy manual. | Section 13.2.6 Stability |
| Typographical, grammatical, formatting, and other editorial updates were made as needed. | Throughout the protocol. |

## Amendment 2

The following is a summary of changes made for amendment 2 of the PNOC 013 (R2810-ONC-1690) protocol. This study is being run in collaboration with the Pacific Pediatric Neuro-Oncology Consortium (PNOC). The primary objective of this amendment is to improve the applicability of our adverse event management guidelines to a pediatric population. The changes and rationale for changes in this amendment are detailed below.

| **Change and Rationale for Change** | **Sections Changed** |
|---|---|
| Guidelines for treatment-emergent adverse events (TEAEs) management are detailed in Appendix 5, and all other sections that discuss TEAE management were revised to refer to Appendix 5 | Section 7 General Supportive Care Guidelines (revised title)<br>Section 8.1.1 Criteria for Dose-Modification in Case of Suspected REGN2810 Toxicity and Re-Initiation of Treatment<br>Appendix 5 Adverse Event Management<br>Table 5 Criteria for Dose Modification (deleted) |

| Change and Rationale for Change | Sections Changed |
|---|---|
| Updated the RECIST criteria with new references added to bring criteria to be more in line with the most recent RECIST guidelines and updated other imaging instructions as needed. | Section 14.2.1 Solid Tumors<br>Section 14.3.1 Chest X-Ray<br>Section 14.3.2 Conventional CT and MRI<br>Section 14.3.3 Ultrasound (addition)<br>Section 14.3.4 Positron Emission Tomography-Computed Tomography (formerly Section 14.3.3)<br>Section 14.5.2 Complete Response<br>Section 14.5.3 Non-complete response and Non-progressive disease<br>Section 14.5.4 Progressive Disease |
| A special consideration was added in the General Supportive Care Guidelines for pseudoprogression | Section 7 General Supportive Care Guidelines (revised title) |
| Changed specification that tumor imaging must be performed within 14 days of enrollment. Imaging must be repeated if performed >14 days from enrollment | Section 9.3.1 Screening Visit – Within 14 Days Prior to Enrollment – All Patients<br>Section 9.3.3 Baseline Prior to Therapy Initiation – Within 3 Days Prior to Starting Therapy – All Patients |
| Removed Surgery and Survival and removed weekly visits during 4-week post XRT DLT period from the Study Calendars | Table 6 CYCLES 1 & 2: DIPG Cohort Arm 1 (XRT 30 fractions, total 42 days) (formerly Table 7)<br>Table 7 CYCLES 1 & 2: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days) (formerly Table 8)<br>Table 8 CYCLES 1 & 2: Newly diagnosed HGG Cohort Arm 1 (XRT 33 fractions, total 45 days) (formerly Table 9)<br>Table 9 CYCLES 1 & 2: Newly diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days) (formerly Table 10)<br>Table 10 CYCLES 1 & 2: Recurrent HGG Cohort (XRT 10 fractions, 14 days) (formerly Table 11) |
| Added collection of ADA samples prior to infusion (pre-dose) at cycle 2 in response to request by health authorities for earlier ADA assessments | Table 12 Blood PK and ADA Collection Schedule in Phase 1 for Patients 0 to 2 Years of Age<br>Table 13 Blood PK and ADA Collection Schedule in Phase 1 for Patients >2 years of Age<br>Table 14 Blood PK and ADA Collection Schedule for the Efficacy Phase |
| Added a consent to the screening in the Study Calendar for the newly diagnosed HGG Cohort Arm 1, Arm 2, and the recurrent HGG Cohort | Table 8 CYCLES 1 & 2: Newly Diagnosed HGG Cohort Arm 1 (XRT 33 fractions, total 45 days) (formerly Table 9)<br>Table 9 CYCLES 1 & 2: Newly Diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days) (formerly Table 10) |

| Change and Rationale for Change | Sections Changed |
|---|---|
| | Table 10 CYCLES 1 & 2: Recurrent HGG Cohort (XRT 10 fractions, 14 days) (formerly Table 11) |
| Clarified that the younger age group applies to patients <12 years old | Section 6.3.1 Dose Escalation for the <12 years Age Cohorts of the Phase 1 and Efficacy Phases (revised title)<br>Table 2 Dose Escalation for the <12 Years Age Cohorts ( revised title) |
| Specified that tissue collection from biopsy or surgery will be performed per standard of care | Section 9.3.1 Screening Visit – Within 14 Days Prior to Enrollment – All Patients<br>Table 5 Study Calendar for Phase 1 (formerly Table 6) – Footnote a<br>Table 6 CYCLES 1 & 2: DIPG Cohort Arm 1 (XRT 30 fractions, total 42 days) (formerly Table 7) – Footnote a<br>Table 7 CYCLES 1 & 2: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days) (formerly Table 8) – Footnote a<br>Table 8 CYCLES 1 & 2: Newly diagnosed HGG Cohort Arm 1 (XRT 33 fractions, total 45 days) (formerly Table 9) – Footnote a<br>Table 9 CYCLES 1 & 2: Newly diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days) (formerly Table 10) – Footnote a<br>Table 10 CYCLES 1 & 2: Recurrent HGG Cohort (XRT 10 fractions, 14 days) (formerly Table 11) – Footnote a |
| Removed collection of blood for ADA and PK analysis at the screening visit | Section 9.3.1 Screening Visit – Within 14 Days Prior to Enrollment – All Patients |
| Clarified that disease status assessment on cycle 2 day 1 was to be performed as indicated per randomization | Section 9.3.5 Cycle 2 Day 1 Visit and Prior to Every Cycle Thereafter (Within 3 Days Prior to Each Cycle) – All Patients |
| Added references to 'legally authorized representative,' in addition to the patient, where applicable, since the study enrolls a pediatric patient population | Section 3.2.2 Biomarker Procedures<br>Section 4.3.2.3 All Patients<br>Section 5.1 General Guidelines<br>Section 9.5 Off-Treatment Criteria<br>Section 9.6 Off-Study Criteria<br>Section 13.2.2 Exploratory Biomarker Procedures<br>Section 17.2.4 Regulatory Documentation |

| Change and Rationale for Change | Sections Changed |
|---|---|
| Revised, added, or removed text, including redundant text, for clarity and accuracy. Made editorial revisions throughout. | List of Pacific Pediatric Neuro-Oncology Consortium Institutions)<br>Abstract- Number of Patients<br>Section 3 Rationale<br>Section 3.2.2 Biomarker Procedures<br>Section 3.2.3 Circulating Cytokine Procedures<br>Section 4.1 Characteristics<br>Section 4.3.2.3 All Patients<br>Section 5.2 Reservation and Registration Process<br>Section 7 General Supportive Care Guidelines (revised title)<br>Section 9.3.4 Cycle 1 Day 1 Visit and Weekly During Cycle 1 and Through the DLT Period (Within 3 Days of Therapy Initiation and +/-3 Days Thereafter) – All Patients<br>Section 9.3.5 Cycle 2 Day 1 Visit and Prior to Every Cycle Thereafter (Within 3 Days Prior to Each Cycle) – All Patients<br>Section 9.3.7 End of Treatment Visit<br>Section 9.5 Off-Treatment Criteria<br>Section 9.6 Off-Study Criteria<br>Section 10.7 Investigator Alert Notification<br>Section 13.2.2 Exploratory Biomarker Procedures<br>Section 13.2.3 Exploratory Circulating Cytokine Procedure<br>Section 14.1.1.3 Immunotherapy Response Assessment in Neuro-Oncology Criteria<br>Section 14.2.1 Solid Tumors<br>Section 14.2.1.3 Non-Measurable Disease<br>Section 14.2.2 Target Lesions<br>Section 14.2.3 Non-Target Lesions<br>Section 14.3 Methods for Evaluation of Measurable Disease<br>Section 14.3.5 Tumor Markers<br>Section 14.3.6 Cytology and Histology<br>Section 14.3.7 FDG-PET<br>Section 14.4 Response Criteria for Patients with Solid Tumors and Measurable Disease |

| Change and Rationale for Change | Sections Changed |
|---|---|
| | Section 14.4.1.3 Progressive Disease<br>Section 14.6.1 Metaiodobenzylguanidine-Positive Lesions<br>Section 14.6.5 Overall Response<br>Section 14.8 Response Criteria for Central Nervous System Tumors<br>Section 17.2.4 Coordinating Center Documentation Distribution (deleted)<br>Section 17.2.4 Regulatory Documentation<br>Table 1 Dose Scheme for Phase 1 and Efficacy Phase<br>Table 5 Study Calendar for Phase 1 (formerly Table 6)<br>Table 6 CYCLES 1 & 2: DIPG Cohort Arm 1 (XRT 30 fractions, total 42 days) (formerly Table 7)<br>Table 7 CYCLES 1 & 2: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days) (formerly Table 8)<br>Table 8 CYCLES 1 & 2: Newly diagnosed HGG Cohort Arm 1 (XRT 33 fractions, total 45 days) (formerly Table 9)<br>Table 9 CYCLES 1 & 2: Newly diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days) (formerly Table 10)<br>Table 10 CYCLES 1 & 2: Recurrent HGG Cohort (XRT 10 fractions, 14 days) (formerly Table 11)<br>Table 11 CYCLE 2 and Future Cycles Thereafter<br>Table 13 Blood PK and ADA Collection Schedule in Phase 1 for Patients >2 years of Age<br>Table 14 Blood PK and ADA Collection Schedule for the Efficacy Phase |

## Amendment 1

The changes to the protocol are summarized in the table below and are primarily being implemented at the request of the FDA.

| Change and Rationale for Change | Sections Changed |
|---|---|
| Revised the 4+3 design to the standard 3+3 design | Abstract: Study Design, Number of Patients<br>Section 4.1 Characteristics<br>Section 4.2 Number of Patients<br>Section 6.2 Definition of Dose-Limiting Toxicity<br>Table 2: Dose Escalation for the Younger Age Groups<br>Table 3: Dose Escalation for the Older Groups |

| Change and Rationale for Change | Sections Changed |
|---|---|
| | Section 15.2 Sample Size/Accrual Rate |
| Added a physical examination on cycle 1 day 22, and cycle 2 days 1, 8, and 15 and weekly during the 4-week post XRT dose-limiting toxicity (DLT) period (procedure days vary with each table) | Table 7 Cycle 1: DIPG Cohort Arm 1 (XRT 30 fractions, total 42 days)<br>Table 8 Cycle 1: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 9 Cycle 1: Newly Diagnosed HGG Cohort Arm 1 (XRT 33 fractions, total 45 days)<br>Table 10 Cycle 1: Newly Diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 11 Cycle 1: Recurrent HGG Cohort (XRT 10 fractions, 14 days) |
| Added collection of blood samples for correlative studies (Peripheral blood mononucleated cell; [PBMC]) and cytokines at baseline | Table 6 Study Calendar for Phase 1 |
| Added the following assessments on cycle 2 day 15: vital signs, toxicity assessment, performance status, concomitant medications, survival, serum thyroid-stimulating hormone (TSH), serum amylase, serum lipase, serum C-reactive protein, serum chemistry (procedures vary with each table)<br>Cycle 2 day 1 (aka day 29): disease status (Table 9) | Table 7 Cycle 1: DIPG Cohort Arm 1 (XRT 30 fractions, total 42 days)<br>Table 9 Cycle 1: Newly Diagnosed HGG Cohort Arm 1 (XRT 33 fractions, total 45 days) |
| Added the following assessments:<br>Cycle 1 day 22: survival, urinalysis, serum TSH, serum free thyroxine, serum amylase, serum lipase, serum C-reactive protein Cycle 2 day 1 (aka day 29): survival, disease status<br>Cycle 2 day 15: vital signs, toxicity assessment, performance status, concomitant medications, survival, urinalysis, serum TSH, serum free thyroxine, serum amylase, serum lipase, serum C-reactive protein, serum chemistry<br>(procedures vary with each table) | Table 8 Cycle 1: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 10 Cycle 1: Newly Diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days) |
| Added administration of REGN2810 on Cycle 2 day 1 (aka day 29), Cycle 2 day 15<br>(procedure days vary with each table) | Table 7 Cycle 1: DIPG Cohort Arm 1 (XRT 30 fractions, total 42 days)<br>Table 8 Cycle 1: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 10 Cycle 1: Newly Diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 11 Cycle 1: Recurrent HGG Cohort (XRT 10 fractions, 14 days) |
| Added brain magnetic resonance imaging (MRI)/Spine MRI REGN2810 on Cycle 2 day 1 (aka day 29) | Table 8 Cycle 1: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 10 Cycle 1: Newly Diagnosed HGG |

| Change and Rationale for Change | Sections Changed |
|---|---|
| | Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 11 Cycle 1: Recurrent HGG Cohort (XRT 10 fractions, 14 days) |
| Deleted radiation on cycle 1 day 22, Cycle 2 day 1 (aka day 29) | Table 10 Cycle 1: Newly Diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days) |
| Deleted cycle 2 day 8 assessments due to redundancy with DLT period observations | Table 8 Cycle 1: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 10 Cycle 1: Newly Diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 11 Cycle 1: Recurrent HGG Cohort (XRT 10 fractions, 14 days) |
| Added the following assessments:<br>Cycle 1 day 22: survival, urinalysis, serum TSH,<br>Cycle 2 day 1 (aka day 29): survival Cycle 2 day 15: vital signs, toxicity assessment, performance status, concomitant medications, survival, urinalysis, serum TSH, serum amylase, serum lipase, serum C-reactive protein | Table 11 Cycle 1: Recurrent HGG Cohort (XRT 10 fractions, 14 days) |
| Added randomization to the recurrent High-grade glioma (HGG) cohort | Table 11 Cycle 1: Recurrent HGG Cohort (XRT 10 fractions, 14 days) |
| Specified that physical examinations will include a full neurological exam | Table 6 Study Calendar for Phase 1<br>Table 7 Cycle 1: DIPG Cohort Arm 1 (XRT 30 fractions, total 42 days)<br>Table 8 Cycle 1: DIPG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 9 Cycle 1: Newly Diagnosed HGG Cohort Arm 1 (XRT 33 fractions, total 45 days)<br>Table 10 Cycle 1: Newly Diagnosed HGG Cohort Arm 2 (XRT 13 fractions, total 17 days)<br>Table 11 Cycle 1: Recurrent HGG Cohort (XRT 10 fractions, 14 days)<br>Table 12 Cycle 2 and Future Cycles Thereafter<br>Section 9.3.5 Cycle 2 Day 1 Visit and Prior to Every Cycle Thereafter (Within 3 Days Prior to Each Cycle) – All Patients<br>Section 9.3.7 End of Treatment Visit |
| Updated information in the protocol regarding safety data on patients with DIPG treated concurrently with radiation | Section 3 Rationale |
| Added criteria to delay enrollment of children under 1 year of age | Section 4.1 Characteristics |

| Change and Rationale for Change | Sections Changed |
|---|---|
| Augmented safety oversight in the form of a safety monitoring team (SMT) and a Regeneron Safety Oversight Committee (RSOC) | Section 10.6 Safety Monitoring |
| Added a global stopping rule in the event of excessive toxicity | Section 10.6.1 Safety Monitoring for Irreversible Neurological Events |
| Clarified how disease response will be determined in patients with neuroblastoma with both Metaiodobenzylguanidine- (MIBG-) avid disease and bone marrow involvement | Section 14.6.1 Metaiodobenzylguanidine-Positive Lesions<br>Section 14.6.2 Primary Soft Tissue Disease<br>Section 14.6.3 Metastatic Soft Tissue and Bone Disease<br>Section 14.6.4 Bone Marrow Disease<br>Section 14.6.5 Overall Response |
| Added International Neuroblastoma Response Criteria | Section 14.6.1 Metaiodobenzylguanidine-Positive Lesions |
| Excluded urinary catecholamine levels from response assessment for patients with neuroblastoma | Section 14.4.1.1 Complete Response<br>Section 14.6.1 Metaiodobenzylguanidine-Positive Lesions |
| Clarified how Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria will be used to assess response in central nervous system tumors | Section 14.8 Response Criteria for Central Nervous System Tumors |
| Corrected the definition of progressive disease per the Response Assessment in Neuro-Oncology (RANO) criteria from a 50% increase to at least a 25% increase in the sum of the size of target lesions | Section 14.8.3 Response Criteria, per RANO Criteria and Allowing for Integration of iRANO Criteria to Supplement RANO Criteria as Appropriate |
| Added treatment criteria for determination of patient evaluability for efficacy and toxicity per Intention to Treat analyses, and Per Protocol Analyses | Section 15.3 Criteria to be Evaluable for Efficacy and Toxicity |
| Added replacement criteria for non-evaluable patients | Section 15.4 Replacement Criteria |
| Clarified the basis to support the assumption of the null hypothesis for the recurrent HGG cohort | Section 15.2 Sample Size/Accrual Rate<br>Section 15.2 Efficacy Phase-RP2D and Efficacy |

# ABSTRACT

| | |
|---|---|
| **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 |
| **Patient Population** | **Phase 1** will include patients age 0 to <18 years with recurrent/refractory solid tumors or recurrent/refractory CNS tumors.<br>**Efficacy Phase** will include patients age 3 to 25 years with newly diagnosed diffuse intrinsic pontine glioma (DIPG), newly diagnosed high-grade glioma (HGG), or recurrent HGG. |
| **Study Rationale** | The median survival for newly diagnosed DIPG and recurrent HGG in pediatric patients is <1 year, while only 20% of pediatric patients with newly diagnosed HGG are alive at 2 years. Immunotherapy is a novel therapeutic approach emerging as effective therapy for a variety of malignancies and may have significant potential in treating pediatric DIPG, HGG, and other solid tumors. Preclinical data show that radiation "primes" the immune system, as evidenced by increases in antigen presentation, major histocompatibility complex expression, and antigen-specific T cells in the tumor microenvironment. The collective data suggest that combining radiation with Programmed Death-1 (PD-1) inhibitory immunotherapy in pediatric patients with DIPG, HGG, and other solid tumors is clinically and biologically feasible. |

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| **Primary Objectives** | **Phase 1**<br>• To confirm the safety and anticipated recommended phase 2 dose (RP2D) of REGN2810 (cemiplimab) for children with recurrent or refractory solid or CNS tumors<br>• To characterize the pharmacokinetics (PK) of REGN2810 given in children with recurrent or refractory solid or CNS tumors<br>**Efficacy Phase**<br>• 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)<br>• 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)<br>• To confirm the safety and anticipated RP2D of REGN2810 given concomitantly with re-irradiation in patients with recurrent HGG<br>• To assess PK of REGN2810 in pediatric patients with newly diagnosed DIPG, newly diagnosed HGG, or recurrent HGG when given in combination with radiation<br>• 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<br>• 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<br>• To assess anti-tumor activity of REGN2810 in combination with radiation in improving overall survival at OS12 among patients with recurrent HGG |
| **Secondary Objectives** | **Phase 1**<br>• To assess anti-tumor activity of REGN2810 monotherapy as identified by objective response in children with recurrent or refractory solid or CNS tumors<br>• To assess immunogenicity<br>**Efficacy Phase**<br>• To assess safety and tolerability profiles of REGN2810 given in combination with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed DIPG<br>• To assess safety and tolerability profiles of REGN2810 given in combination with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed HGG<br>• To assess safety and tolerability profiles of REGN2810 given in combination with re-irradiation among patients with recurrent HGG<br>• To assess immunogenicity |

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| **Exploratory Objectives** | **Phase 1 and Efficacy Phase**<br>• To assess Quality of Life (QoL) in patients treated with REGN2810 as monotherapy or given concurrently with radiation followed by adjuvant monotherapy<br>• To investigate the biologic activity of REGN2810 and potentially identify biomarkers predictive of drug response using DNA, serum, plasma, and tumor biopsy samples |
| **Primary Endpoints** | **Phase 1**<br>• Safety, as measured by the incidence and severity of treatment-emergent adverse events (TEAEs)/immune-related adverse events (irAEs)/adverse events of special interest (AESIs) / serious adverse events (SAEs), deaths, and laboratory abnormalities (grade 3 or higher per version 4.0 of Common Terminology Criteria for Adverse Events (CTCAE v4.0), from initiation of study treatment until 90 days after the last study treatment (or until the patient receives another systemic anticancer therapy, whichever is earlier)<br>• Tolerability, as measured by the incidence of dose-limiting toxicities (DLTs) from the first dose of REGN2810 through the end of the DLT observation period for cemiplimab given as monotherapy<br>• PK for REGN2810 given as monotherapy in pediatric patients<br>**Efficacy Phase:**<br>• Incidence and severity of TEAEs, irAEs, AESIs, SAEs, deaths, and laboratory abnormalities (Grade 3 or higher per CTCAE v4.0) for REGN2810 given in combination with radiation therapy, from initiation of study treatment until 90 days after the last study treatment (or until the patient receives another systemic anticancer therapy, whichever is earlier)<br>• Incidence of DLTs during the DLT observation period for REGN2810 given in combination with radiation therapy<br>• PK for REGN2810 given as given in combination with radiation therapy in pediatric patients<br>• Overall survival at 12 months (OS12) among newly diagnosed DIPG patients and recurrent HGG patients, respectively.<br>• Progression-free survival at 12 months (PFS12) among newly diagnosed HGG patients. |
| **Secondary Endpoints** | **Phase 1**<br>• Objective response rate (ORR). ORR is defined as the percentage of patients who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR).<br>• Anti-drug antibody (ADA) assessments for REGN2810 given as monotherapy<br>**Efficacy Phase**<br>• ADA assessments for REGN2810 given in combination with radiation therapy |

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| **Exploratory Endpoints** | <u>Phase 1 and Efficacy Phase:</u><br>• Quality of Life (QoL), as measured using Pediatric Quality of Life (PedsQL) for younger age group 2 to <18 years<br>• QoL, as measured using the Functional Assessment of Cancer Therapy-Brain (FACT-Br) for older age group 18 to 25 years<br>• Circulating tumor cells, biomarker data, circulating cytokines, and peripheral blood mononucleated cells (PBMC), tumor expression of PD-L1 for biomarker and correlative studies |

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| **Study Design** | This is a multi-center safety and efficacy study conducted through The Pacific Pediatric Neuro Oncology Consortium (PNOC). This study will consist of 2 phases conducted in parallel. In both phases, treatment cycles will each last 28 days. Therapy will continue for a total of 12 cycles (or up to 24 cycles if, in the investigator's opinion, the patient would continue to derive clinical benefit). Patients who discontinue or complete therapy will undergo evaluation at an end of treatment visit, followed by a 30-day toxicity check. Patients will then enter long-term follow up, which will occur every 12 weeks from the last day of treatment and will last for up to 52 weeks.<br><br>To assess preliminary anti-tumor efficacy, patients will receive radiographic imaging (MRI/PET or CT) at least once every 12 weeks while on treatment and during follow up. Patients will also provide tumor tissue (either fresh or archival) at screening and will undergo biopsy at any time on-study at the time of disease progression. To assess the impact of treatment on quality of life (QoL), patients will also be asked to complete the PedsQL (age 2 to <18) or FACT-Br (age >18) questionnaire while on treatment and during follow up.<br><br>Phase 1 will consist of 4 cohorts, consisting of patients with recurrent/refractory solid tumors (Cohorts A and B) or recurrent/refractory CNS tumors (Cohorts C and D), with each cohort defined according to patient age (age 0 to <12 and age 12 to <18). Phase 1 will use a 3+3 design to confirm the anticipated recommended phase 2 dose (RP2D) of REGN2810 as monotherapy in pediatric patients. Cohorts will escalate through a series of dose levels (DL0, 1 mg/kg/dose; DL1, 3 mg/kg/dose; DL2, 4.5 mg/kg/dose), with dose escalation rules defined by age cohort. Younger cohorts (age 0 to <12) will begin at DL1 can escalate up to DL2 or de-escalate to DL0 based on toxicity. Older cohorts (age 12 to <18) will begin at DL1 and may not escalate further but may de-escalate to DL0 based on toxicity.<br><br>The DLT period for Phase 1 will be 28 days (2 doses of REGN2810 monotherapy). The RP2D will be determined separately for each of the 4 cohorts and may be lower than the identified maximum tolerated dose (MTD) if pharmacokinetically indicated.<br><br>The Efficacy Phase will consist of 6 cohorts, including pediatric patients with either newly diagnosed DIPG (Cohorts E and F), newly diagnosed HGG (Cohorts G and H), or recurrent HGG (Cohorts I and J), defined according to patient age (age 3 to <12 and age 12 to 25). The Efficacy Phase will use a 3+3 design to confirm the RP2D of REGN2810 in combination with radiation therapy in pediatric patients. Patients in newly diagnosed DIPG and newly diagnosed HGG cohorts will be randomized 1:1 to receive REGN2810 + conventionally fractionated radiation therapy (Arm 1) or REGN2810 + hypofractionated radiation therapy (Arm 2). Patients in recurrent HGG cohorts will receive REGN2810 + re-irradiation.<br><br>Each cohort in the Efficacy Phase will escalate through a series of dose levels defined by age cohort. Younger cohorts (age 3 to <12) will begin at the RP2D identified in the Phase 1 younger CNS tumor cohort and may not escalate further but may de-escalate to a lower dose level based on toxicity. Older cohorts (age 12 to 25) will begin at DL1 and may not escalate further but may de-escalate to DL0 based on toxicity.<br><br>The DLT period for the Efficacy Phase will be the length of radiation therapy + 28 days after completion of radiation therapy. DLT evaluation will occur according to both cohort and treatment arm. The RP2D will be confirmed for each of the 10 treatment arms and may be lower than the MTD if pharmacokinetically indicated. |

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| **Number of Patients** | In **Phase 1**, a minimum of 30 patients with recurrent/refractory solid tumors or CNS tumors will be enrolled, including at least 6 patients each in younger (age 0 to <12) cohorts and at least 3 patients in older (age 12 to <18) cohorts. Solid tumor cohorts will enroll an additional 6 patients each (12 total) for treatment at the corresponding RP2D.<br>In the **Efficacy Phase**, a minimum enrollment of 100 patients (at the respective confirmed RP2D for each cohort) is planned. This will include at least 40 patients with newly diagnosed DIPG patients, at least 40 patients with newly diagnosed HGG, and at least 20 patients with recurrent HGG. |
| **Duration of Therapy** | Patients in both Phase 1 and the Efficacy Phase will receive REGN2810 on study for 12 cycles from the time of study entry. REGN2810 may be continued for up to 24 cycles if a patient continues to derive clinical benefit. |
| **Duration of Follow-up** | Patients will be followed for at least 52 weeks from end of treatment or until death, whichever occurs first. |
| **Duration of Study (Per Patient)** | For each patient, the study is anticipated to last up to 3 years, which includes a maximum of 24 cycles of treatment and a maximum of 52 weeks of follow up. |
| **Study Drugs** | REGN2810, a human monoclonal antibody targeting the PD-1 receptor, to be administered every 14 days via 30-minute intravenous (IV) infusion. |
| **Safety Assessments** | Safety assessments will include DLTs, adverse events (AEs), clinical laboratory evaluations, physical examination, and vital signs. |
| **PK Assessments** | PK assessments will be included in both Phase 1 and the Efficacy Phase of the study. |
| **Efficacy Assessments** | Objective response, 12-month overall survival (OS12), 12-month progression-free survival (PFS). |
| **Unique Aspects of this Study** | This is the first study to:<br>• Evaluate the safety of PD-1 inhibition given with radiation in pediatric patients with newly diagnosed DIPG, newly diagnosed HGG, or recurrent HGG<br>• Assess and describe preliminary efficacy of PD-1 inhibition given with conventionally fractionated or hypofractionated radiation in newly diagnosed DIPG and newly diagnosed HGG<br>• Determine the PK of REGN2810 in pediatric patients |

## EXPERIMENTAL DESIGN SCHEMA

**Figure 1: Trial Enrollment in Phase 1: Recurrent or Refractory Solid or Central Nervous System**

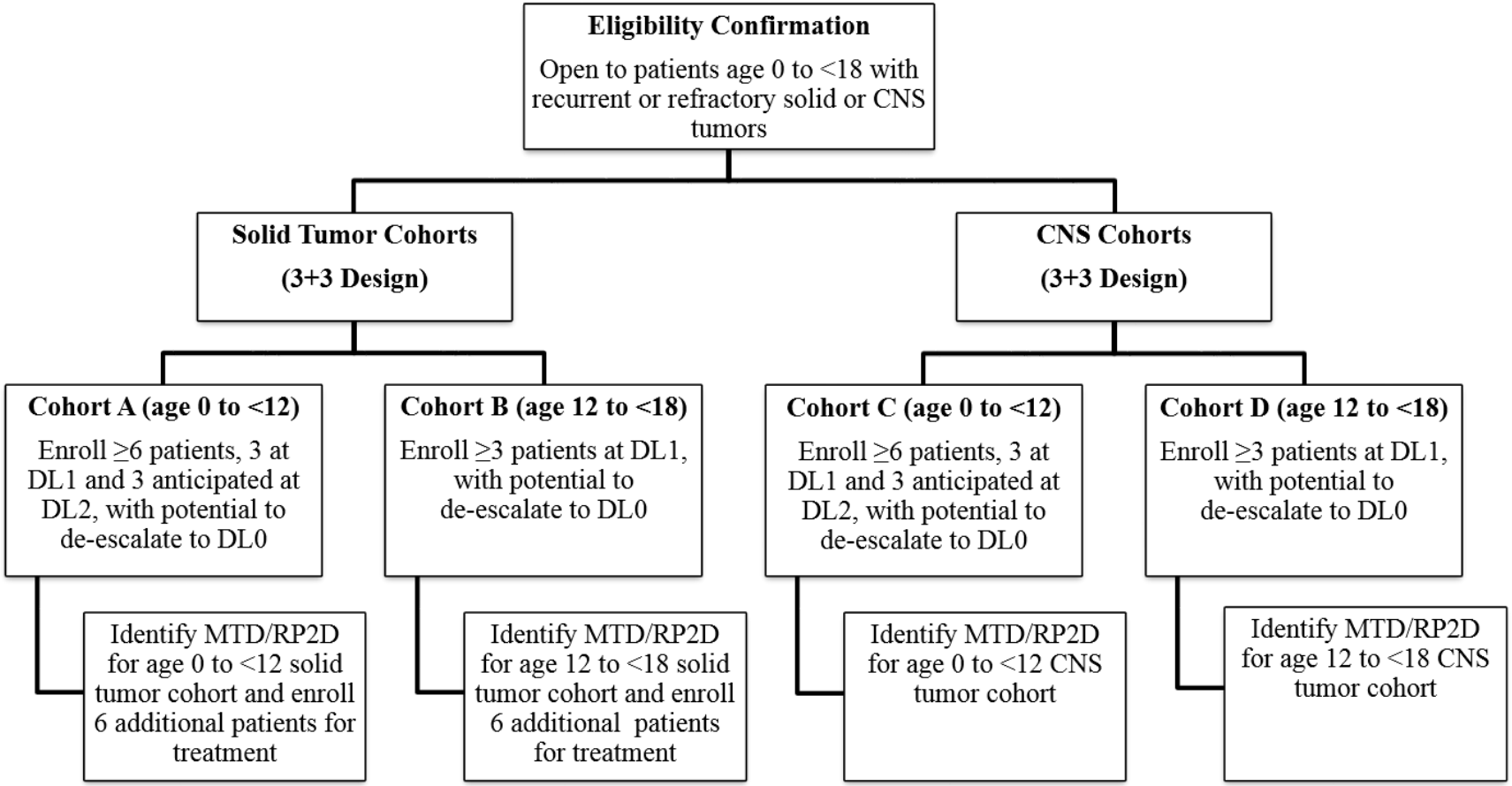

**Figure 2: Trial Enrollment in the Efficacy Phase: Newly Diagnosed Diffuse Intrinsic Pontine Glioma**

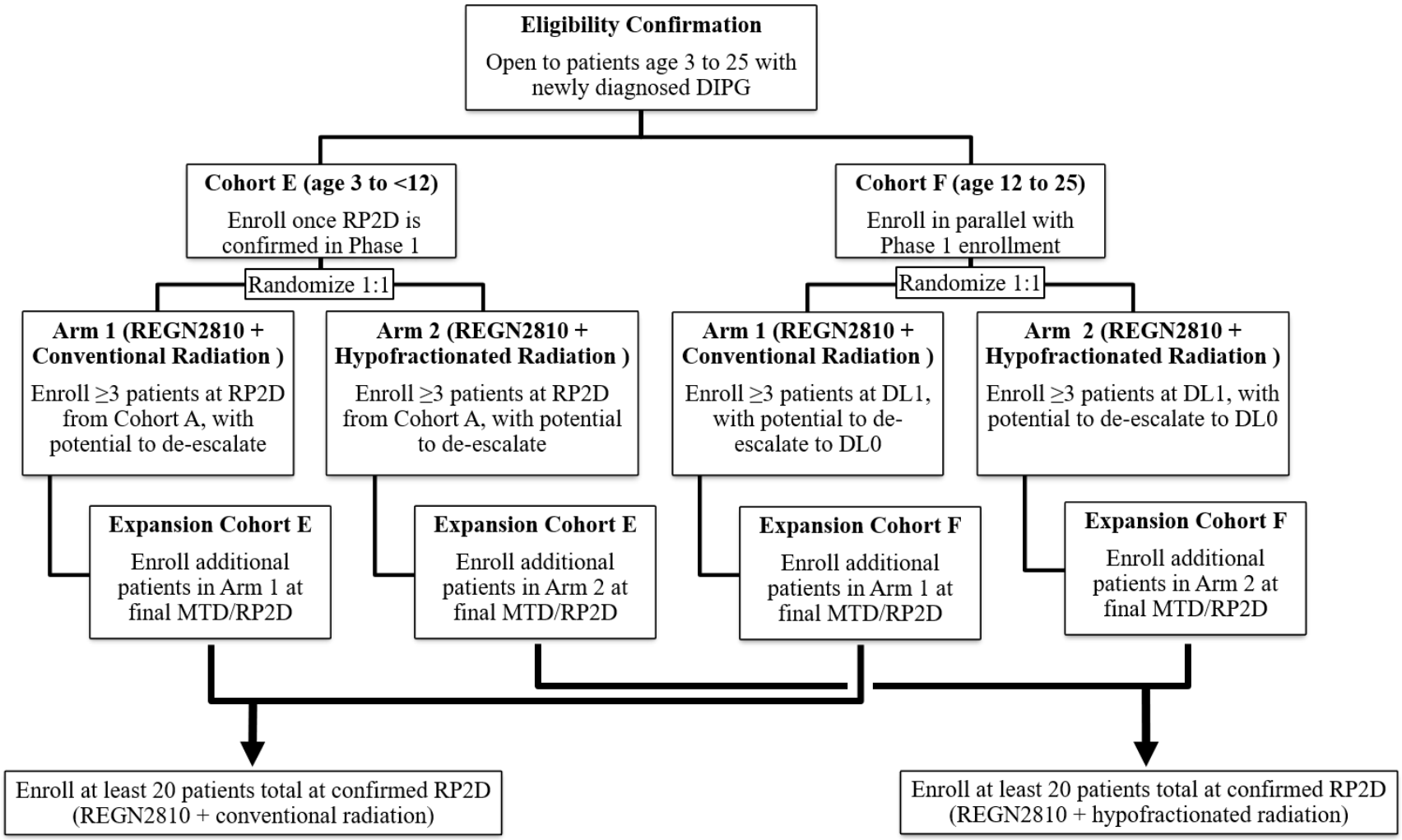

**Figure 3: Trial Enrollment in the Efficacy Phase: Newly Diagnosed High-Grade Glioma**

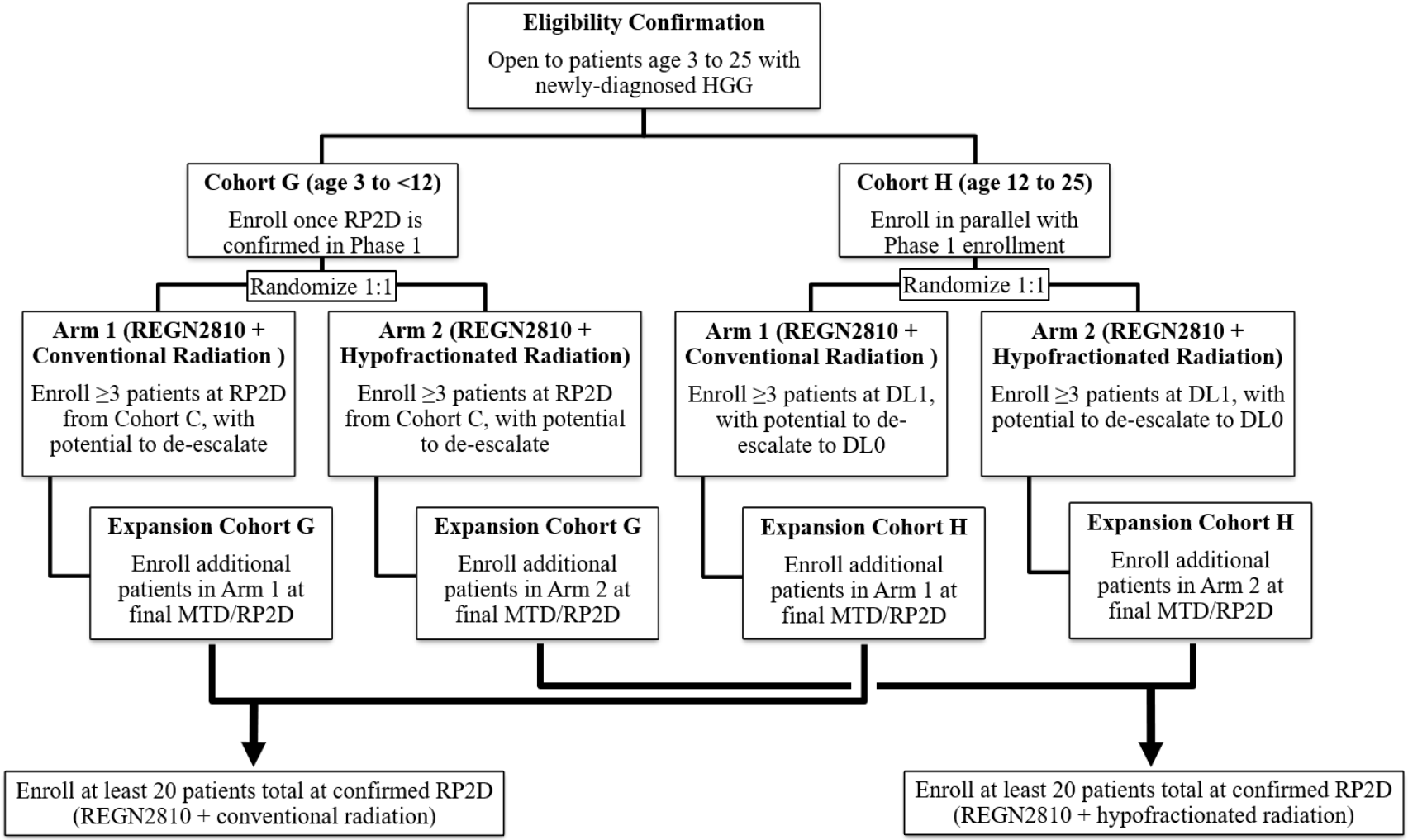

**Figure 4: Trial Enrollment in the Efficacy Phase: Recurrent High-Grade Glioma**

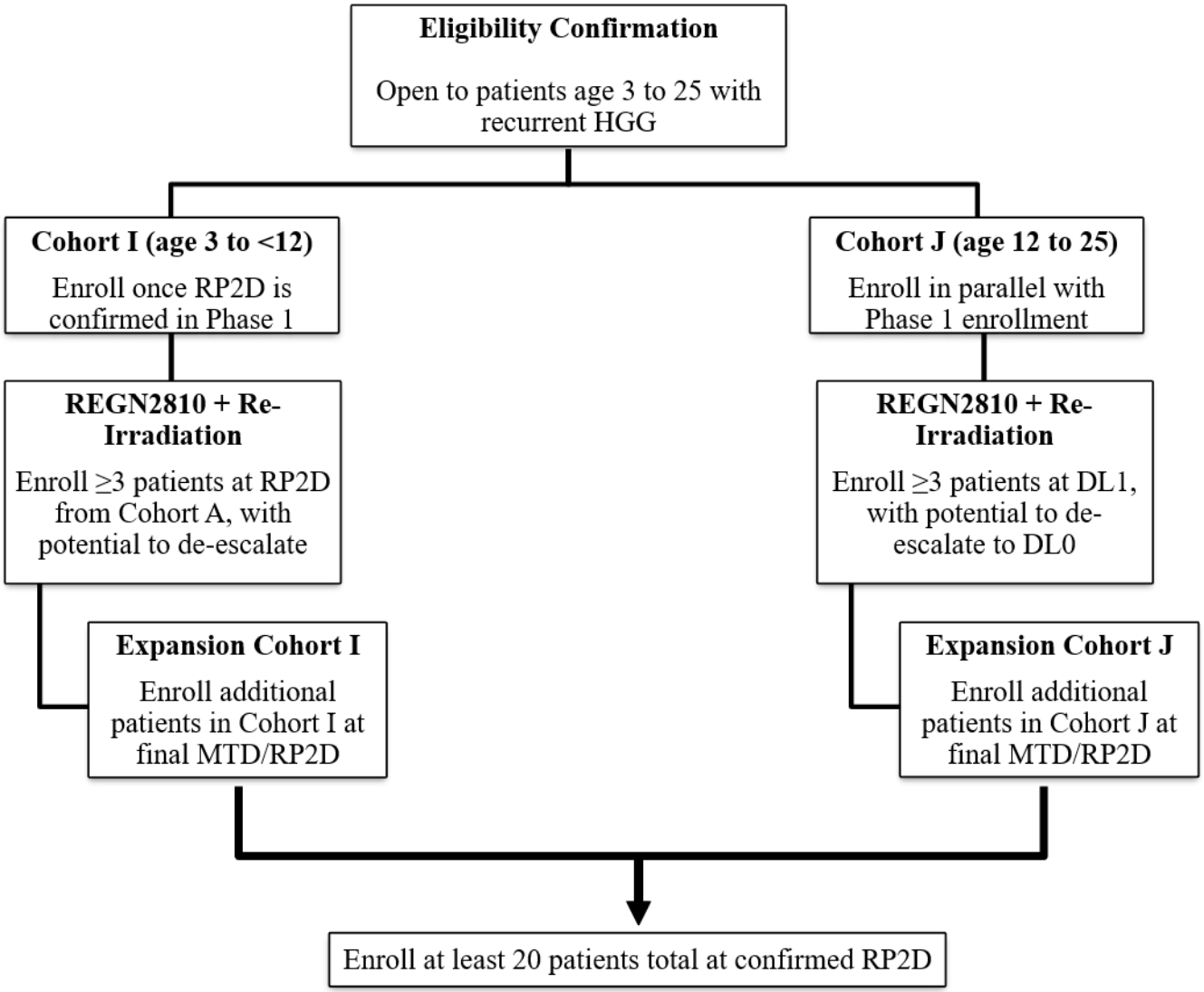

**Figure 5: Study Design, Phase 1**

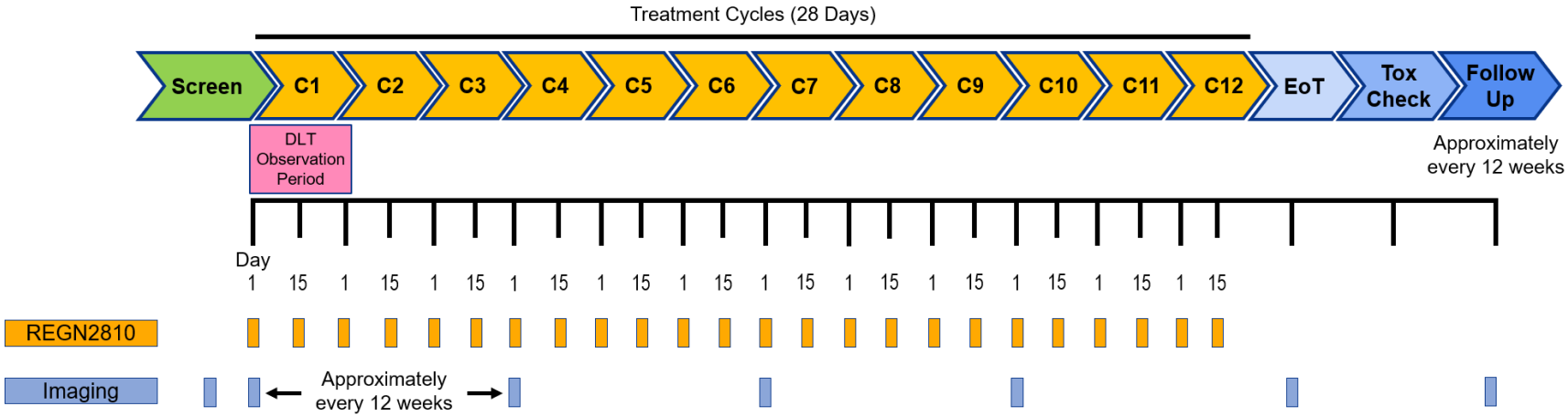

**Figure 6: Study Design, Efficacy Phase**

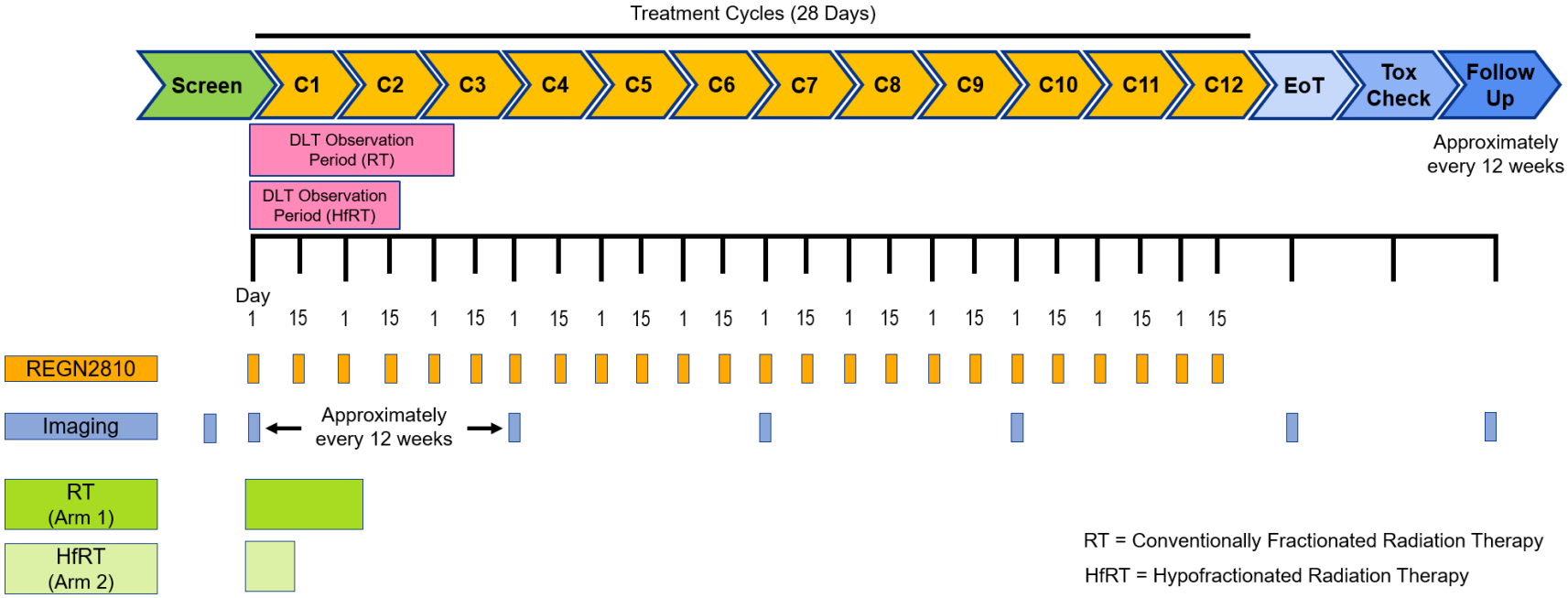

**Table 1: Patient Cohorts**

| Cohort | Study Phase | Tumor Type | Age Range |
|---|---|---|---|
| A | 1 | Solid Tumors | 0 to <12 |
| B | 1 | Solid Tumors | 12 to <18 |
| C | 1 | CNS Tumors | 0 to <12 |
| D | 1 | CNS Tumors | 12 to <18 |
| E | Efficacy | DIPG (Newly Diagnosed) | 3 to <12 |
| F | Efficacy | DIPG (Newly Diagnosed) | 12 to 25 |
| G | Efficacy | HGG (Newly Diagnosed) | 3 to <12 |
| H | Efficacy | HGG (Newly Diagnosed) | 12 to 25 |
| I | Efficacy | HGG (Recurrent) | 3 to <12 |
| J | Efficacy | HGG (Recurrent) | 12 to 25 |

# LIST OF ABBREVIATIONS

| | |
|---|---|
| 3D-CRT | 3D-conformal radiation therapy |
| ADA | Anti-drug antibody |
| ADL | Activities of Daily Living |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| AML | Acute myelocytic leukemia |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| CBC | Complete blood cell (count) |
| cGy | Centigray |
| CNS | Central nervous system |
| CR | Complete response |
| CRF | Case report form |
| CRO | Clinical Research Organization |
| CRP | C-reactive protein |
| CSCC | Cutaneous squamous cell carcinoma |
| CSF | Cerebral spinal fluid |
| CSI | Craniospinal irradiation |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumor DNA |
| CTEP | Cancer Therapy Evaluation Program |
| CTLA-4 | Cytotoxic T-lymphocyte-associated-4 |
| CTV | Clinical target volume |
| CTX | Cyclophosphamide |
| DFS | Disease-free survival |
| DIPG | Diffuse intrinsic pontine glioma |
| DLT | Dose-limiting toxicity |
| DVH | Dose volume histogram |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| EGFR | Estimated glomerular filtration rate |
| EOI | End of infusion |

| | |
|---|---|
| FACT-Br | Functional Assessment of Cancer Therapy-Brain Inventory |
| FDA | Food and Drug Administration |
| FFPE | Formalin fixed-paraffin embedded |
| GBM | Glioblastoma |
| GCP | Good Clinical Practice |
| GFR | Glomerular filtration rate |
| GI | Gastrointestinal |
| GM-CSF | Granulocyte Macrophage Colony-Stimulating Factor |
| GTV | Gross tumor volume |
| hfRT | Hypofractionated radiation therapy |
| HGG | High-grade glioma |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| ICRU | International Commission on Radiation Units and Measurements |
| IF | Immunofluorescence |
| IHC | Immunohistochemistry |
| IMRT | Intensity modulated radiation therapy |
| IND | Investigational new drug application |
| irAE | Immune-related adverse event |
| iRANO | Immunotherapy Response Assessment in Neuro-Oncology |
| IRB | Institutional Review Board |
| irRECIST | Immune-related response evaluation criteria in solid tumors |
| IV | Intravenous |
| IWRS | Interactive web response system |
| LAG-3 | Lymphocyte activation gene 3 |
| LAR | Legally authorized representative |
| LFT | Liver function test |
| MDS | Myelodysplastic syndrome |
| MIBG | Metaiodobenzylguanidine |
| mAb | Monoclonal antibody |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| NOAEL | no-observed-adverse-effect level |
| NSCLC | Non-small cell lung cancer |
| OS | Overall survival |
| OS12 | Overall survival at 12 months |

| | |
|---|---|
| PBMC | Peripheral blood mononucleated cell |
| PedsQL | Pediatric Quality of Life Inventory |
| PD | Progressive disease |
| PD-1 | Programmed Death-1 |
| PD-L1 | Programmed death ligand 1 |
| PD-L2 | Programmed death ligand 2 |
| PET | Positron Emission Tomography |
| PET-CT | Positron Emission Tomography-Computed Tomography |
| PFS | Progression-free survival |
| PFS12 | Progression-free survival at 12 months |
| PK | Pharmacokinetics |
| PNOC | Pacific Pediatric Neuro Oncology Consortium |
| PR | Partial response |
| PTV | Planning target volume |
| QOL | Quality of Life |
| Q2W | Every 2 weeks |
| RAPNO | Response Assessment in Pediatric Neuro-Oncology |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RCC | Renal cell cancer |
| RP2D | Recommended phase 2 dose |
| RT | Radiation therapy |
| SAE | Serious adverse event |
| SD | Stable disease |
| SGPT | Serum glutamic pyruvic transaminase |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment-emergent adverse event |
| TSH | Thyroid-stimulating hormone |
| t1/2 | Terminal half-life |
| ULN | Upper limit of normal |
| VEGF | Vascular endothelial growth factor |

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# 1. OBJECTIVES

Study objectives are provided below. Study endpoints are provided in Section 12.1.

## 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

## 1.2. 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

## 1.3. 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

# 2. BACKGROUND

## 2.1. Unmet Need in Pediatric DIPG and HGG

Brain tumors are the most common solid pediatric malignancy and result in more deaths than any other pediatric cancer. Diffuse intrinsic pontine gliomas (DIPG) and high-grade gliomas (HGG) account for the majority of these deaths. Pediatric HGGs are relatively rare, comprising approximately 4% of all brain tumors diagnosed in children age 0-14 and up to 14% in children age 10-19[1]. Histologically, the vast majority of pediatric HGGs are either anaplastic astrocytomas (World Health Organization [WHO] grade III) or glioblastomas (WHO grade IV). Diffuse intrinsic gliomas are gliomas (typically grade II-IV) arising in the brainstem. Even with multi-modality therapies, survival curves remain dismal and stagnant for these diagnoses[2-5]. The 2-year survival for patients with DIPG and HGG is less than 10% and 20%, respectively[6,7]. The median survival for DIPG and other brainstem HGG remains less than 1 year[8]. For children with HGG older than 3 years of age, combination therapy with surgical resection, radiation, and chemotherapy remains the standard of care[2,5]. Radiation is typically spared in children younger than 3 years due to the deleterious effects on neurocognition. Regardless, extent of surgical resection best correlates with both progression-free and overall survival[2,6,9]. Surgical resection though is not a viable option for patients with DIPG due to the brainstem location and infiltrative nature of the tumor. In these patients, radiation has proven to have the most lasting effect at slowing tumor growth; however, even this intervention does not prolong overall survival beyond 1 year[2,6].

## 2.2. Targeting of Programmed Death-1 (PD-1) as a Treatment Paradigm in Cancer

Enhancement of the anti-tumor immune response with cancer immunotherapy agents has emerged as a highly effective and complementary approach to the therapeutic mainstays of surgery, cytotoxic drugs, targeted therapeutics, and radiation. Moreover, induction of durable and extensive tumor regressions suggest that immunotherapy may convert previously fatal diseases into chronic,

manageable ones for some patients. Under chronic stimulation, T-cells lose proliferative and effector function capacity, often due to signal down-modulation via the increased expression of proteins such as PD-1, an inhibitory checkpoint receptor of the CD28 receptor family. The ligand for the PD-1 receptor, PD-L1, is expressed in a variety of human malignancies, and its high level of expression has been previously correlated with poor patient prognosis and resistance to treatment in non-small-cell lung cancer[10], glioblastoma multiforme[11], and squamous-cell carcinoma of head and neck[12]. Binding of ligand (PD-L1 or PD-L2), often expressed on tumor cells, to PD-1 imparts an inhibitory signal to the T-cell, thus down-modulating the anti-tumor T-cell response[13]. Blockade of the PD-1/PD-L1/PD-L2 T-cell checkpoint pathway is an effective and well-tolerated approach to stimulating the immune response and has achieved significant objective responses in advanced melanoma, renal cell cancer (RCC), and non-small-cell lung cancer (NSCLC), among others[14]. However, optimal therapy will likely require combining anti-PD-1 monoclonal antibody (mAb) treatment with conventional therapies and novel immunotherapy approaches. Combinatorial approaches to stimulate convergent aspects of host immunity by employing complementary immunomodulators as well as immune-stimulatory aspects of conventional modalities such as radiation and chemotherapy may result in the development of more effective cancer therapies. Combination blockade of PD-1 and the cytotoxic T-lymphocyte antigen 4 (CTLA-4) is effective in controlling growth of syngeneic mouse tumors of ID8-VEGF ovarian carcinoma and CT26 colon carcinoma cell lines in immune-competent mice, providing support to this notion[15]. Furthermore, adding blockade of CTLA-4 to PD-1 blockade in melanoma patients achieves response rates twice of that achieved with anti-PD-1 alone (ie, >50%)[16]. In a subset of patients with PD-L1+ tumors, preliminary results demonstrated an enhanced systemic response when treatment with an anti-PD-L1 antibody (MPDL3280A) coincided with palliative local irradiation[17].

## 2.3. REGN2810, a Human Monoclonal Antibody to Programmed Death-1 (PD-1)

**Investigational agent:** REGN2810

**IND:** 123950

**IND Sponsor:** Regeneron Pharmaceuticals, Inc.

For more information on this agent, please refer to the current Investigator's Brochure.

REGN2810 (cemiplimab) is a high-affinity, human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2. In syngeneic tumor models in immunocompetent mice humanized for PD-1, the anti-tumor activity of REGN2810 delivered as a monotherapy against a mouse colon adenocarcinoma tumor line is similar to that observed with antibodies generated in-house based on the publicly-available genetic sequences of pembrolizumab and nivolumab, anti-PD-1 antibodies approved for the treatment of melanoma, RCC, NSCLC, and in late-stage development for use against several other malignancies.

Libtayo® (cemiplimab) has received marketing authorization and is now approved in the United States (US), the European Union (EU), Canada, and Brazil for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation. In the US, it is approved as cemiplimab-rwlc.

This study is a multi-center study with the aim of assessing the safety, pharmacokinetics, and preliminary efficacy of REGN2810 as monotherapy and in combination with radiation therapy, in pediatric patients with newly diagnosed DIPG, newly diagnosed HGG, and recurrent HGG.

## 2.4. REGN2810 Pre-Clinical Studies

The starting dose chosen for the first-in-human study using REGN2810 was based on the similar *in vitro* and *in vivo* potency of REGN2810 compared to antibodies generated with publicly available sequences of 2 approved anti-PD-1 antibodies, nivolumab and pembrolizumab. When compared to REGN1672 (primary sequence identical to nivolumab) and REGN2626 (primary sequence identical to pembrolizumab) in both *in vitro* and cell-based assays, REGN2810 demonstrated similar *in vitro* PD-1 binding affinity, blocking efficiency for PD-1/PD-L1 and PD-L2 interactions *in vitro*, and ability to antagonize PD-1-induced T-cell inhibitory signaling in a cell-based bioassay. Additionally, REGN2810 demonstrated similar *in vivo* anti-tumor efficacy to REGN1672 and REGN2626 in humanized-PD-1 mouse tumor model bioassays. Furthermore, the PK profile for REGN2810 in monkeys is similar to that of nivolumab[18].

In a 4-week toxicology study in monkeys at the no-observed-adverse-effect level (NOAEL) of 50 mg/kg per week, the area under the concentration-time curve (AUC) over the last dosing interval was estimated at 6170 day•mg/mL, a greater than 12-fold higher exposure than steady-state exposures predicted with 1 mg/kg, and a 14% higher exposure than that anticipated with 10 mg/kg administered to human patients every 14 days. Based on preclinical activity and toxicology data and greater than 10-fold exposure margin over 1 mg/kg REGN2810, in addition to the clinical efficacy and safety data from other anti-PD-1 mAbs at similar doses/dosing intervals, a dosage of 1 mg/kg REGN2810 every 14 days was expected to have an acceptable safety profile and to be active, and was therefore chosen as a starting dosage in the first human trials, with plans to de-escalate if necessary. Experience with other anti-PD-1 antibodies suggested that REGN2810 dosage can be escalated safely. In PK studies of 1, 5, and 15 mg/kg REGN2810 administered to cynomolgus monkeys, estimates of the beta-phase terminal half-life ($t_{½}$) of REGN2810 were comparable across dose groups: 9.84, 10.9, and 12.4 days, respectively. Accordingly, REGN2810 will be administered every 14 days in this study to maintain targeted blood concentrations over the dosing interval.

## 2.5. REGN2810 Clinical Studies

REGN2810 is being evaluated in several phase 1, 2 and 3 clinical studies, as monotherapy and in combination with other antibodies, bispecific antibodies, radiation, and chemotherapy, among other treatment modalities. For an up-to-date list, please refer to the current Investigator's Brochure(s).

R2810-ONC-1423 is a Phase 1, first-in-human study of repeat dosing with REGN2810 as single therapy and in combination with other anticancer therapies in patients with advanced malignancies. The study has 10 dose escalation cohorts in patients with advanced solid tumors, followed by 26 expansion cohorts explored in select indications. The primary objective of this investigation is to characterize the safety, tolerability, and dose-limiting toxicities (DLT) of REGN2810 as monotherapy or in combination with hypofractionated radiation therapy (hfRT) and/or cyclophosphamide (CTX), with hfRT, CTX, and Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), or in combination with chemotherapy agents (low dose carboplatin plus

docetaxel, low dose docetaxel, full dose carboplatin plus paclitaxel or carboplatin plus pemetrexed) (IND 123950; Study REGN2810-ONC-1423). Fifty-two (52) weeks is the proposed study length for the current study, similar to the treatment duration in the first-in-human study of REGN2810.

As of 20 Jan 2017, a total of 353 (dose escalation, n = 60; expansion, n = 293) patients have been enrolled in this first-in-human study and treated at 4 different dose levels (1 mg/kg, 3 mg/kg, 10 mg/kg, and a flat dose of 200 mg) of REGN2810 as monotherapy as well as in combination. There were no protocol defined dose limiting toxicities observed. REGN2810 was generally well tolerated; the most common treatment emergent adverse events (TEAEs) occurring in 10% or more patients were fatigue, nausea, anemia, decreased appetite, arthralgia, constipation diarrhea, dyspnea, cough, pyrexia, vomiting, asthenia and back pain.

REGN2810 has demonstrated promising efficacy in a variety of tumor types, most notably as monotherapy in cutaneous squamous cell carcinoma, as presented at ASCO 2017[19].

**Cumulative Safety Profile of REGN2810**

The emerging safety profile of REGN2810 is consistent with that described for other antibodies directed against PD-1 and evidence of rapid and durable responses with REGN2810 has been similar to the observations with other PD-1 inhibitors[20,16].

As of 20 January 2019, 885 patients have been treated with REGN2810 either as monotherapy or in combination with radiotherapy and/or other cancer therapy in 7 of the ongoing studies. A total of 615 patients (69.5%) experienced at least 1 treatment-related adverse event (AE) of which 121 patients (13.7%) experienced grade 3 or higher treatment-related AEs. Seventy-six patients (8.6%) experienced investigator-attributed treatment-related serious adverse events (SAEs). Nine patients (1.0%) experienced fatal treatment-related AEs: hepatic failure (1 patient with hepatocellular carcinoma [HCC]) and acute hepatic failure (1 patient with diffuse large B-cell lymphoma [DLBCL]), paraneoplastic encephalomyelitis (1 patient with soft tissue sarcoma), toxic epidermal necrolysis (TEN), 1 patient with follicular lymphoma [FL] ), nosocomial pneumonia secondary to grade 4 mucositis (1 patient with FL), pneumonitis (2 patients: 1 with NSCLC and 1 with cervical cancer), myelodysplastic syndrome (1 patient with NSCLC and subsequent treatment with KEYTRUDA), and unknown cause of death that could not rule out REGN2810 (1 patient with locally advanced head and neck CSCC).

Additional details regarding the REGN2810 clinical development program and safety profile can be found in the Investigator's Brochure.

**Studies of REGN2810 in Glioblastoma**

In the R2810-ONC-1423 study, there are 2 cohorts of adult patients with glioblastoma: 1 with newly diagnosed patients and 1 with patients with recurrent disease. In these cohorts, patients are treated with a starting dose of REGN2810 at 1 mg/kg/dose every 14 days and dose escalated to 3 mg/kg/dose every 14 days and in combination with hypofractionated radiation of 6 Gy x 5 doses.

**Newly Diagnosed Glioblastoma:** As of 20 Jan 2017, 6 patients with newly diagnosed glioblastoma (GBM) were treated (3 patients at 1 mg/kg and 3 patients at 3 mg/kg REGN2810). The first 3 run-in patients in this cohort, at the starting dose level of 1 mg/kg REGN2810 experienced no DLTs; therefore the dose was escalated to 3 mg/kg REGN2810 for the next 3 patients. Patients at the 3 mg/kg dose level experienced CNS necrosis probably related to radiation

therapy (RT), a serious grade 3 infusion related reaction after receiving first dose of REGN2810, and a grade 3 SAE of Nervous System Disorder Inflammation, and have recovered from these reactions. As of the data cut, 2/5 patients received treatment with bevacizumab in the newly diagnosed GBM cohorts.

A total of 47 TEAEs of all grades occurred in 5/6 (83%) patients with newly diagnosed GBM, treated with either dose level of REGN2810 in combination with RT (1 patient receiving 1 mg/kg REGN2810 did not experience any AE thus far). Seven of the 47 TEAEs are suspected to be caused by REGN2810 occurring in 4/6 (66%) patients: grade 1 aspartate aminotransferase (AST) [1] and alanine aminotransferase (ALT) elevation [1]; grade 2 headache [2] and inflammation [1]; grade 3 inflammation [1] and infusion related reaction [1].

Two patients came off treatment: 1 patient in the 3 mg/kg REGN2810 cohort due to infusion related reaction and 1 in the 1 mg/kg REGN2810 cohort due to progressive disease.

**Recurrent Glioblastoma:** As of 20 January 2017, 9 patients were treated (6 patients at 1 mg/kg and 3 patients at 3 mg/kg REGN2810). One patient treated with 1 mg/kg REGN2810 developed grade 2 inflammation in the brain, which was considered by the investigator to be related to both RT and REGN2810. Due to the nature of the first AE of grade 2 inflammation of the brain, a decision was made to expand the 1 mg/kg cohort from 3 patients to 6 patients prior to escalating to 3 mg/kg. Among the 3 patients enrolled in the 3 mg/kg dose level, there have been no protocol-defined DLTs and the cohort has been expanded to enroll an additional 3 patients. Five of the 9 patients came off treatment due to progressive disease. Of these 5 patients, 4 received 1 mg/kg and 1 received 3 mg/kg REGN2810. One patient had progressive disease at the end of the first cycle (study day 54) and died on study day 105.

A total of 78 TEAEs of all grades occurred in 8/9 (88.9%) patients with recurrent GBM, treated with either dose level of REGN2810 in combination with RT (1 patient receiving 3 mg/kg REGN2810 did not experience any AE thus far). Among the 78 TEAEs, 19 are suspected to be related to REGN2810 alone or in combination with RT occurring in 5/9 (55.6%) patients. Most of these treatment-related TEAEs are grade ½ with 3 grade 3 events: headache, worsening back pain and hyponatremia. There are 17/78 TEAEs considered to be related to radiotherapy alone occurring in 4/9 (44%) patients. Among these, 15 of the TEAEs are grade 1 or 2, and 1 grade 3 headache and 1 grade 3 CNS necrosis, which have been resolved with bevacizumab treatment.

# 3. RATIONALE

## 3.1. Use of Anti-PD-1 Therapy in DIPG and HGG Patient Populations

Given the stagnant survival curves of pediatric DIPG and recurrent HGG, despite multi-modal therapies over decades, this population remains a high-risk group deserving of novel, investigational therapeutic approaches. Previous therapeutic attempts have included tumor resection or debulking, re-irradiation, standard chemotherapy, and targeted approaches[22-28]. Additionally, multiple phase 1 and 2 clinical trials have demonstrated poor outcomes for patients with these high-risk tumors. There remains limited published data on population-based outcomes of recurrent pediatric HGGs, but anecdotal evidence and some published data support an estimated 50% overall survival at 12 months for this high-risk group.

Immunotherapy is a novel therapeutic approach that is emerging as effective therapy for a variety of malignancies and may have significant potential in the treatment of pediatric DIPG and HGG. PD-1 receptors are expressed predominantly on T-cells and the corresponding ligands, PD-L1 and PD-L2, modulate T-cell function and diminish immune responses[29]. Evidence of PD-L1 and PD-L2 expression on various cancers as well as on tumor-infiltrating immune cells offers a potential pathway that can be targeted with anti-neoplastic immunotherapy. Recent preclinical studies have demonstrated that immunotherapy with PD-1 blockade prolongs overall survival and leads to durable responses in glioma mouse models[30,31]. These responses seem to correlate with T-cell lymphocyte infiltration and PD-L1 and –L2 expression in the tumor microenvironment.[32,33] A high percentage of human glioma cell lines express PD-L1, supporting that this inhibitory pathway is a key mechanism in HGG subversion of the immune system[34-37]. This is further supported through studies illustrating that PD-L1 levels within cerebral spinal fluid (CSF) and tumor tissues positively correlate with both grade and malignancy of gliomas[38]. The culmination of the above evidence, combined with findings of tumor-infiltrating lymphocytes and PD-L1 expression in HGG, reinforce use of PD-1 inhibitors in DIPG and HGG treatment[31,39].

Preliminary studies and animal models have suggested that PD-1 inhibition and radiation may synergize to produce local and systemic effects[40-45]. More specifically, preclinical data have shown that radiation "primes" the immune system as evidenced by increased antigen presentation, increased major histocompatibility complex expression, and antigen-specific T-cells in the tumor microenvironment[43]. Hypofractionated radiation may capitalize on these immune stimulating effects[46]. This priming of the immune system can then be further exploited by PD-1 inhibition, which is supported by prolonged survival in mouse models undergoing combined PD-1 inhibition and radiation compared to mice undergoing monotherapy with either agent[45]. Children may be particularly suited to exploit inherent immunity against tumor cells through the plasticity and robustness of their developing immune systems[47].

Early analyses of adult patients with melanoma, lung, or renal cancers at the Dana-Farber Cancer Institute treated with radiation and PD-1 pathway inhibitors concurrently or in close temporal proximity have revealed no unexpected or severe toxicities. This includes several patients treated with hypofractionated stereotactic radiosurgery to the brain or whole brain radiation therapy (PMID 28463153). Similarly, a recently published experience of patients treated with stereotactic radiosurgery and PD-1 inhibition revealed promising evidence in brain control with no unexpected toxicity or radionecrosis requiring surgery (PMID 26712903). At the University of California, San Francisco, a small cohort of patients with recurrent DIPG has been treated with nivolumab administered concurrently with reirradiation. To date, no patients have experienced significant toxicity. One patient experienced subacute onset of ataxia, dysarthria, and dysphagia early in treatment. Symptoms were treated with a 7-day course of oral dexamethasone, no doses of nivolumab were held and the patient went on to receive several months of therapy with nivolumab before again experiencing disease progression. The patient also experienced an acneiform rash that was treated with topical steroids[48]. Various studies evaluating combinations of PD-1 pathway blockade and radiation in adult patients are recently open or currently in development, including the combination of radiation and PD-L1 inhibition for the treatment of newly diagnosed glioblastoma (NCT02336165), also supporting this approach.

In the R2810-ONC-1423 study, there are 2 dose escalation cohorts of adult patients with GBM — 1 cohort of patients with newly diagnosed GBM and 1 cohort of patients with recurrent GBM. In both cohorts, patients are treated with a starting dose of REGN2810 1 mg/kg/dose every 14 days

and escalated to 3 mg/kg/dose every 14 days and in combination with hypofractionated radiation of 6 Gy for 5 fractions (total 30 Gy). As of 20 January 2017, 6 patients with newly diagnosed GBM and 9 patients with recurrent GBM have been treated, as discussed above.

Given the evidence, there is strong rationale to treat children with DIPG and newly diagnosed and recurrent HGG with hypofractionated radiation in combination with PD-1 inhibition.

## 3.2. REGN2810 Dose Selection

As REGN2810 has not yet been evaluated in children, Phase 1 of this investigation will include children with relapsed or refractory solid or CNS tumors in order to confirm the anticipated RP2D dose for our target population. Inclusion of children with refractory or recurrent solid or CNS tumors will allow more rapid definition of the dose of REGN2810 to be used in combination with radiation. The starting dose of 3 mg/kg/dose was chosen for Phase 1 and the Efficacy Phase based on similar dosing in the commercially available anti-PD-1 antibodies, nivolumab and pembrolizumab, and on the comparable *in vitro* and *in vivo* potency of REGN2810 to these compounds, as well as on the safety and tolerability of 3 mg/kg/dose that was demonstrated in the first-in-human and phase 1 expansion cohorts using REGN2810 (see Section 2.5). The efficacy phase of this study will evaluate the feasibility, safety, and potential efficacy of administering the PD-1 inhibitor, REGN2810 in combination with radiation therapy and adjuvantly in three cohorts of pediatric patients with high-risk intracranial malignancies: newly diagnosed diffuse intrinsic pontine gliomas randomized to conventionally fractionated or hypofractionated radiation, newly diagnosed HGG randomized to conventionally fractionated or hypofractionated radiation and recurrent high-grade gliomas receiving hypofractionated dosing in the re-irradiation setting.

Based on the phase 1 data, dose escalation experience with REGN2810, preclinical activity, toxicology data with greater-than-10-fold exposure margin over 1 mg/kg/dose REGN2810, and clinical efficacy and safety data from other anti-PD-1 monoclonal antibodies at similar doses/dosing intervals in global populations; a dosage of 3 mg/kg/dose every 14 days is expected to have an acceptable safety profile and to be active, and was therefore chosen as the anticipated RP2D in pediatrics. Additionally, at UCSF, PD-1 inhibition with nivolumab has been used concomitantly with upfront or reirradiation in nearly 10 pediatric patients with high-grade brain tumors. A 3 mg/kg/dose every 14 days has been employed at UCSF in all patients, with good tolerability observed for this regimen. Only 1 patient experienced symptomatic pseudoprogression including dysphagia and worsening ataxia; symptoms were alleviated with a 7-day course of oral dexamethasone and did not require holding of any drug. Ongoing multi-institutional trials also use similar dosing of PD-1 inhibitors in pediatric patients including trials led by the Children's Oncology Group and Pediatric Brain Tumor Consortium, further supporting the anticipated RP2D dose for REGN2810 in pediatrics.

Body weight-adjusted dosing of monoclonal antibodies may result in lower exposure in children with low body weight than in adults. This can lead to under-exposure in young pediatric patients with low body weight. In addition, based on REGN2810 clinical data and data in literature, toxicity of PD-1 inhibitors does not appear to correlate with increased dose[14,21]. Thus, the current study proposes a starting dose of REGN2810 of 3 mg/kg every 14 days, with a planned dose escalation to 4.5 mg/kg in younger children. If pharmacokinetics and drug exposure data suggest that dosing could be adjusted, then dosing may be altered. The 3 mg/kg every 2 weeks (Q2W) is consistent with the dose used for maintenance therapy in adult patient populations, and was found to be

clinically efficacious in several adult indications in study R2810-ONC-1423. This dose is consistent with current dosing used at UCSF for the similar PD-1 inhibitor, nivolumab, in conjunction with radiation and other pediatric protocols using nivolumab (NCT02304458).

The results of this study will provide insight to optimally guide the development of REGN2810 for DIPG and newly diagnosed and recurrent HGG and in combination with radiation, and potentially as treatment for other pediatric brain tumors.

## 3.3. Radiotherapy Regimen Selection

The optimal fractionated regimen for augmenting immunogenicity of tumors in human patients is unknown, therefore we propose four fractionated regimens in this current study, varying according to the arm and cohort of enrollment. We include both conventionally fractionated and hypofractionated regimens in this protocol, all of which represent acceptable standards of care in these populations.

Patients with newly diagnosed DIPG will be randomized to receive either conventionally fractionated radiation as 1.8 Gy administered 5 times a week for 30 fractions to a total of 54 Gy (DIPG cohort-arm 1), or hypofractionated radiation delivered as 3 Gy administered 5 times a week for 13 fractions for a total of 39 Gy (DIPG cohort-arm 2). This hypofractionated schema is supported by other pediatric studies that have found hypofractionation radiation alone for DIPG to be well tolerated[49-51].

Patients with newly diagnosed HGG will be randomized to receive either conventionally fractionated radiation as 1.8 Gy administered 5 times a week for 33 fractions to a total of 59.4 Gy, or hypofractionated radiation delivered as 3 Gy administered 5 times a week for 13 fractions for a total of 39 Gy.

In the recurrent HGG cohort, targeted focal re-irradiation is currently planned as 3.5 Gy administered 5 times a week for 10 fractions for a total of 35 Gy in recurrent HGG. This regimen has previously been used in patients with recurrent HGG who have received prior radiation therapy.

While both treatment regimens in the DIPG and HGG cohort are acceptable standards of practice, the hypofractionated regimens being evaluated may offer advantages in terms of immunopotentiating effects[52]. In contrast, more extremely hypofractionated regimens such as 25 Gy in 5 fractions have not been as well tolerated in this population and are therefore, not being tested in this study, despite their potential immune stimulating effects.

In this study, radiation will be administered within +/-3 days of initial administration of REGN2810. The time course between radiation and REGN2810 initiation is based on previous literature illustrating that concomitant radiation with PD-1 inhibition, as opposed to sequential pairing of these therapies, leads to increased immune response and survival in mouse models[41]. The study proposes a single course of radiation, as the objective is to provide this treatment as the equivalent of a potent, autologous tumor vaccine aimed to augment the response achieved by PD-1 blockade and as part of standard of care approach for our selected brain tumor populations.

## 3.4. Pharmacokinetic Assessment of REGN2810

Assessment of REGN2810 PK in blood will be performed in all patients enrolled in the Phase 1 and efficacy phases of this study. Because the PK profile of this agent is unknown in the pediatric population, this information will be essential to relate drug exposure in blood to toxicity and disease response in pediatrics and for refining dosing in future clinical trials of REGN2810.

## 3.5. Correlative Exploratory Studies

There is great utility to identifying mechanisms of response and resistance to PD-1 blockade as well as evaluating potential biomarkers that may be associated with clinical benefit. REGN2810 is thought to work by stimulating an immune mediated attack on cancer cells, and based on prior preliminary studies conducted in patients across several disease types, PD-L1 expression and greater numbers of infiltrating lymphocytes may predict response to PD-1 / PD-L1 / PD-L2 inhibitors in certain settings[14,32,53,54]. Systemic immune responses engendered by immunologic checkpoint blockade therapy may be predictive of response[53,55,56]. However, it is unknown to what degree tumor and circulating factors such as PD-L1 and PD-L2 expression, infiltrating and circulating T-cell populations, myeloid derived suppressor cells, and immunologic cytokines may predict responses to combined radiation-PD-1 blockade in patients with pediatric brain tumors. Tumor mutational burden may also be predictive of response to immune therapy and specifically PD-1 blockade, as has been observed in patients with lung cancer, glioblastoma, and mismatch repair deficient tumors.

Patients enrolled in this trial will have tissue samples collected at baseline when feasible, and therefore available for potential correlative analyses. In recurrent disease cohorts, archival tissue collected from initial diagnoses will be acceptable. Additionally, serial blood collections of serum and peripheral blood mononuclear cells will evaluate additional correlative endpoints.

We hypothesize that PD-L1 expression and CD8+ T-cell infiltration in baseline tumor biopsies will correlate with response to combined immunotherapy radiation approaches. We further hypothesize that CD8+ T-cell infiltration and PD-L1 expression as well as other immunologic factors such as PD-L2 expression, number of infiltrating CD68+ macrophages, and CD4+/FoxP3+ regulatory T cells may differ in biopsies taken in responding and non-responding patients and may therefore help guide future combination therapies. Favorable clinical responses may also be associated with measurable changes in circulating immune factors such as T-cell subsets, and immune chemokines/cytokines that may be of potential value in monitoring responses in future patients treated with this regimen.

Procedures and descriptions of the proposed analyses can be found in Section 8.2.6. Statistical considerations can be found in Section 12.4.

# 4. STUDY DESIGN

This is a multi-center safety and efficacy study conducted through The Pacific Pediatric Neuro Oncology Consortium (PNOC). This study will consist of 2 phases conducted in parallel. After a screening period of 14 days, therapy will begin for a total of 12 cycles (or up to 24 cycles if, in the investigator's opinion, the patient would continue to derive clinical benefit). In both phases, treatment cycles will each last 28 days. Patients who discontinue therapy or complete therapy will

undergo evaluation at an end of treatment visit, followed by a 30-day toxicity check. Patients will then enter long-term follow up, which will occur every 12 weeks from the last day of treatment and will last for up to 52 weeks.

To assess preliminary anti-tumor efficacy, patients will receive radiographic imaging (MRI/PET or CT) once every 12 weeks while on treatment and during follow up. Patients will also provide tumor tissue (either fresh or archival) at screening and will undergo biopsy at any time on-study at the time of disease progression. To assess the impact of treatment on quality of life (QoL), patients will also be asked, while on treatment and during follow up, to complete the PedsQL (age 2 to <18) or FACT-Br (age >18) questionnaire.

## 4.1. Phase 1 Study Design

Phase 1 will consist of 4 cohorts (Cohort A through Cohort D), consisting of patients with recurrent/refractory solid tumors or recurrent/refractory CNS tumors and defined according to patient age (see the Experimental Design Schema and Table 2; for more information on patient population criteria, see Section 5). Cohorts are divided by age because drug metabolism and exposure may vary between younger and older patients. In this phase of the study, REGN2810 will be given as monotherapy (ie, no radiation therapy will be given). The Schedule of Events for Phase 1 is provided in Table 11.

### 4.1.1. Dose Escalation Design in Phase 1

Cohorts will escalate through a series of dose levels (DLs), which are provided in Table 8. For all cohorts, doses will be given every 14 days (see dose administration information in Table 9). All cohorts in Phase 1 will start REGN2810 at DL1 (3 mg/kg/dose). If DL1 is tolerated, the subsequent age cohorts 0 to <12 years may escalate to DL2 (4.5 mg/kg/dose). Age cohorts 0 to <12 years may also de-escalate to DL0 (1 mg/kg/dose) if de-escalation criteria are met (see Table 4). Age cohorts 12 to <18 years cannot escalate beyond DL1, but may de-escalate to DL0 if de-escalation criteria are met (see Table 6).

**Table 2: Patient Cohorts in Phase 1**

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

### 4.1.2. Dose Escalation Rules in Phase 1

Phase 1 will use a 3+3 design to confirm the anticipated RP2D of REGN2810 as a single agent among children with solid or CNS tumors. Dose escalation rules for Phase 1 are provided in Table 4 (age cohorts <12 years) and Table 6 (age cohorts ≥12 years). A minimum of 3 patients will be required at each DL to be evaluable for DLT. Tolerability of a dose level will be achieved if all 3 DLT-evaluable patients complete the 28-day DLT period and 0 out of 3 experience a DLT. If 1 out of 3 DLT-evaluable patients experience a DLT, 3 more patients will be enrolled for a total of 6 patients. If 1 out of 6 evaluable patients experience a DLT, the DL will be considered tolerable. If ≥2 out of 6 evaluable patients experience a DLT, the DL will have exceeded the maximum tolerated dose (MTD). The RP2D will be confirmed separately for each of the 4 cohorts and may

be lower than the MTD if pharmacokinetically indicated. DLT windows for this study are provided in Section 4.4.1; DLT definitions are provided in Section 4.4.2.

Dose escalation, de-escalation, and/or confirmation of RP2D will occur once all initial patients enrolled in a cohort have been observed for the DLT period and the data have been reviewed at a dose escalation review meeting. This meeting will include (at a minimum) the Regeneron medical/study director, the Regeneron risk management lead, the PNOC chair or co-chair, and a representative PNOC statistician. Other individuals, such as the individual site investigators, may also be included. Note that screening for the next dose cohort may begin prior to the dose escalation review meeting.

For any cohort, if a dose level is considered tolerable but data from PK analyses indicate blood levels are above desired levels, a lower pre-specified dose level (Table 8) may be considered for that cohort.

For each of the solid tumor cohorts, an additional 6 patients will be enrolled at the corresponding identified RP2D.

Enrollment of patients <1 year of age will be allowed only after at least 3 patients ≥1 to <12 years of age have been enrolled and have demonstrated tolerability in the DLT period (ie, no DLTs).

## 4.2. Efficacy Phase Study Design

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 (see the Experimental Design Schema and Table 3; for more information on patient populations criteria see Section 5). In this phase of the study, REGN2810 will be given in combination with radiation therapy. The Schedule of Events for the Efficacy Phase is provided in Table 12 (REGN2810 + conventionally fractionated radiation) and Table 13 (REGN2810 + hypofractionated radiation).

**Table 3: Patient Cohorts in the Efficacy Phase**

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

In the Efficacy Phase of the study, patients in newly diagnosed DIPG and newly diagnosed HGG cohorts will be randomized 1:1 to receive REGN2810 + conventionally fractionated radiation therapy (Arm 1) or REGN2810 + hypofractionated radiation therapy (Arm 2). Patients in recurrent HGG cohorts will receive REGN2810 + re-irradiation. After radiation therapy (in combination with REGN2810) is complete, patients will continue to receive REGN2810 according to the respective Schedule of Events.

Radiation therapy guidelines, including dose schedules for each cohort, are provided in Section 9. All radiation will be done in a PNOC institution or PNOC-approved radiation center, due to frequent safety monitoring and the need to follow protocol radiation guidelines.

### 4.2.1. Dose Escalation Design in the Efficacy Phase

Similar to Phase 1, in the Efficacy Phase cohorts (and treatment arms, as applicable) will need to establish a RP2D for REGN2810 in combination with radiation. For all cohorts, doses will be given every 14 days (see dose administration information in Table 9).

Age cohorts 3 to <12 years (Cohorts E, G, and I) will start at the RP2D for this age group as determined by the corresponding CNS tumor cohort (Cohort C) in Phase 1, which is anticipated to be DL2 (4.5 mg/kg/dose). These cohorts may de-escalate if de-escalation criteria are met (see Table 5) but may not dose escalate above the Phase 1 RP2D of REGN2810.

Age cohorts 12 to 25 years will start REGN2810 at DL1 (3 mg/kg/dose). Age cohorts 12 to 25 years cannot escalate beyond DL1, but may de-escalate to DL0 if de-escalation criteria are met (see Table 6).

### 4.2.2. Dose Escalation Rules in Efficacy Phase

Similar to Phase 1, the Efficacy Phase will use a 3+3 design. This design will assess safety by observing for toxicity in the same manner as Phase 1 of the study. Dose escalation will proceed separately for each of the 6 cohorts per the dose escalation rules provided in Table 4 (age cohorts <12 years) and Table 6 (age cohorts ≥12 years). A minimum of 3 patients will be required at each DL to be evaluable for DLT. Tolerability of a dose level will be achieved if all 3 potentially DLT-evaluable patients complete the DLT period (length of radiation plus 28 days) and 0 out of 3 experience a DLT. If 1 out of 3 DLT-evaluable patients experience a DLT, 3 more patients will be enrolled for a total of 6 patients. If 1 out of 6 evaluable patients experience a DLT, the DL will be considered tolerable. If ≥2 out of 6 evaluable patients experience a DLT, the DL will have exceeded the maximum tolerated dose (MTD). DLT evaluation will occur according to both cohort and treatment arm. The RP2D will be confirmed for each of the 10 treatment arms and may be lower than the MTD if pharmacokinetically indicated. DLT windows for this study are provided in Section 4.4.1; DLT definitions are provided in Section 4.4.2.

Similar to Phase 1, dose escalation, de-escalation, or confirmation of MTD/RP2D will occur once all initial patients enrolled in a cohort have been observed for the DLT period and the data have been reviewed at a dose escalation review meeting or discussion, as appropriate. This will include (at minimum) the Regeneron medical/study director, the Regeneron risk management lead, the PNOC chair or co-chair, and a representative PNOC statistician. Other individuals, such as the individual PNOC site investigators, may also be included. Note that screening for the next dose cohort may begin prior to the dose escalation review meeting.

As in Phase 1, if a dose level is considered tolerable but data from PK analyses indicate blood levels are above desired levels, a lower pre-specified dose level (Table 8) may be considered for that cohort.

### 4.2.3. Timing of Initial Enrollment

For cohorts enrolling patients 3 to <12 years, Efficacy Phase enrollment (and for newly diagnosed DIPG or newly diagnosed HGG cohorts, randomization) will begin once the RP2D of REGN2810 is determined in Phase 1 for their corresponding age group in the CNS tumor cohort (Cohort C).

For cohorts enrolling patients 12 to 25 years of age, Efficacy Phase enrollment (and for newly diagnosed DIPG or newly diagnosed HGG cohorts, randomization) will begin immediately (in parallel with Phase 1). These cohorts will begin treatment at DL1.

Once PK, tolerability, and preliminary efficacy of REGN2810 + radiation therapy are established in patients >3 years of age, patients ≤3 years and will also be enrolled, if appropriate, at the corresponding RP2D for their age group.

### 4.2.4. Expansion Enrollment

Once the RP2D of REGN2810 in combination with radiation is confirmed for a given cohort, enrollment of expansion cohorts will open to further investigate the safety and efficacy of REGN2810 + radiation therapy. Patients in expansion cohorts will follow the same Schedule of Events as patients in the initial 3+3 enrollment of the Efficacy Phase (Table 12, REGN2810 + conventionally fractionated radiation, and Table 13 , REGN2810 + hypofractionated radiation).

During expansion, the total number of patients enrolled will be based on treatment arm, irrespective of patient age or cohort. Patients will be enrolled until at least 20 evaluable patients are reached per treatment arm, based on a Simon two-stage design. During the first stage, 7 patients will be enrolled per treatment arm. For DIPG and recurrent HGG, if no more than 3 deaths occur within 12 months, the second stage will be opened. If 4 or more deaths occur within 12 months, the arm will be temporarily closed for review. For newly diagnosed HGG, if no more than 2 patients experience disease progression or death, the second stage will be opened, but if 3 or more patients experience disease progression or death, the arm will be temporarily closed for review. For more information on expansion enrollment and statistical considerations, see Section 12.

## 4.3. Dose Escalation Rules

Dose escalation will follow the rules provided below. Dose escalation rules for both Phase 1 and the Efficacy Phase of the study are subdivided according to age cohorts. Younger cohorts (<12 years of age) will follow the rules outlined in Table 4 (Phase 1) and Table 5 (Efficacy Phase). All older cohorts (≥12 years of age) will follow the rules outlined in Table 6.

**Table 4: Dose Escalation Rules: Cohorts Age <12 Years, Phase 1**

| **DL1 Rules** | |
|---|---|
| **No. of Patients with DLT** | **Dose Decision Rule** |
| 0 out of 3 | May stop enrollment at this level and escalate to DL2 |
| 1 out of 3 | Enroll 3 more patients at DL1 |
| 1 out of 6 | DL1 will be considered the MTD for the cohort |
| ≥2 out of 6 | Dose will de-escalate to DL0 and subsequent patients will follow DL0 rules |
| ≥2 out of 3 | Dose will de-escalate to DL0 and subsequent patients will follow DL0 rules |
| **DL0 Rules** | |
| **No. of Patients with DLT** | **Dose Decision Rule** |
| 0 out of 3 | Enroll 3 more patients at DL0 |
| ≤1 out of 6 | DL0 will be considered the MTD for the cohort |
| ≥2 out of 6 | Trial will be stopped for toxicity and discussed with sponsor |
| 1 out of 3 | Enroll 3 more patients at DL0 |
| 1 out of 6 | DL0 will be considered the MTD for the cohort |
| ≥2 out of 6 | Trial will be stopped for toxicity and discussed with sponsor |
| ≥2 out of 3 | Trial will be stopped for toxicity and discussed with sponsor |
| **DL2 Rules** | |
| **No. of Patients with DLT** | **Dose Decision Rule** |
| 0 out of 3 | Enroll 3 more patients at DL2 |
| ≤1 out of 6 | DL2 will be considered the MTD for the cohort |
| ≥2 out of 6 | DL1 will be considered the MTD for the cohort |
| 1 out of 3 | Enroll 3 more patients at DL2 |
| 1 out of 6 | DL2 will be considered the MTD for the cohort |
| ≥2 out of 6 | DL1 will be considered the MTD for the cohort |
| ≥2 out of 3 | DL1 will be considered the RP2D for the cohort |

**Table 5: Dose Escalation Rules: Cohorts Age <12 Years, Efficacy Phase**

Note that, during the Efficacy Phase, patients <12 years will initially be enrolled to confirm the RP2D identified in Phase 1, which is anticipated to be DL2. Patients may not escalate above their respective Phase 1 RP2D, but may de-escalate. See Section 4.2 for more information.

| **DL2 Rules** | |
|---|---|
| **No. of Patients with DLT** | **Dose Decision Rule** |
| 0 out of 3 | Enroll 3 more patients at DL2 |
| ≤1 out of 6 | DL2 will be considered the MTD for the cohort |
| ≥2 out of 6 | Dose will de-escalate to DL1 and subsequent patients will follow DL1 rules |
| 1 out of 3 | Enroll 3 more patients at DL2 |
| 1 out of 6 | DL2 will be considered the MTD for the cohort |
| ≥2 out of 6 | Dose will de-escalate to DL1 and subsequent patients will follow DL1 rules |
| ≥2 out of 3 | Dose will de-escalate to DL1 and subsequent patients will follow DL1 rules |
| **DL1 Rules** | |
| **No. of Patients with DLT** | **Dose Decision Rule** |
| 0 out of 3 | Enroll 3 more patients at DL1 |
| ≤1 out of 6 | DL1 will be considered the MTD for the cohort |
| ≥2 out of 6 | Dose will de-escalate to DL0 and subsequent patients will follow DL0 rules |
| 1 out of 3 | Enroll 3 more patients at DL1 |
| 1 out of 6 | DL1 will be considered the MTD for the cohort |
| ≥2 out of 6 | Dose will de-escalate to DL0 and subsequent patients will follow DL0 rules |
| ≥2 out of 3 | Dose will de-escalate to DL0 and subsequent patients will follow DL0 rules |
| **DL0 Rules** | |
| **No. of Patients with DLT** | **Dose Decision Rule** |
| 0 out of 3 | Enroll 3 more patients at DL0 |
| ≤1 out of 6 | DL0 will be considered the MTD for the cohort |
| ≥2 out of 6 | Trial will be stopped for toxicity and discussed with sponsor |
| 1 out of 3 | Enroll 3 more patients at DL0 |
| 1 out of 6 | DL0 will be considered the MTD for the cohort |
| ≥2 out of 6 | Trial will be stopped for toxicity and discussed with sponsor |
| ≥2 out of 3 | Trial will be stopped for toxicity and discussed with sponsor |

**Table 6: Dose Escalation Rules: Cohorts Age ≥12 Years, Phase 1 and Efficacy Phase**

| **DL1 Rules** | |
|---|---|
| **No. of Patients with DLT** | **Dose Decision Rule** |
| 0 out of 3 | Enroll 3 more patients at DL1 |
| ≤1 out of 6 | DL1 will be considered the MTD for the cohort |
| ≥2 out of 6 | Dose will de-escalate to DL0 and subsequent patients will follow DL0 rules |
| 1 out of 3 | Enroll 3 more patients at DL1 |
| 1 out of 6 | DL1 will be considered the MTD for the cohort |
| ≥2 out of 6 | Dose will de-escalate to DL0 and subsequent patients will follow DL0 rules |
| ≥2 out of 3 | Dose will de-escalate to DL0 and subsequent patients will follow DL0 rules |
| **DL0 Rules** | |
| **No. of Patients with DLT** | **Dose Decision Rule** |
| 0 out of 3 | Enroll 3 more patients at DL0 |
| ≤1 out of 6 | DL0 will be considered the MTD for the cohort |
| ≥2 out of 6 | Trial will be stopped for toxicity and discussed with sponsor |
| 1 out of 3 | Enroll 3 more patients at DL0 |
| 1 out of 6 | DL0 will be considered the MTD for the cohort |
| ≥2 out of 6 | Trial will be stopped for toxicity and discussed with sponsor |
| ≥2 out of 3 | Trial will be stopped for toxicity and discussed with sponsor |

## 4.4. Dose-Limiting Toxicities

### 4.4.1. DLT Period

**Phase 1**: The DLT period for Phase 1 is defined as the first cycle of therapy (cycle length 28 days, having received 2 doses of REGN2810) and will include weekly toxicity monitoring (physical examination, vital signs, adverse event monitoring, CBC with differential, and serum chemistry).

**Efficacy Phase:** The DLT period for the Efficacy Phase is defined as the length of radiation therapy + 28 days after completion of radiation therapy. All patients in the DIPG and HGG cohorts of the efficacy phase will undergo weekly toxicity monitoring (described above) for the entire length of the DLT period.

### 4.4.2. Definition of Dose-Limiting Toxicity

Criteria for establishing dose-limiting toxicity are presented in Table 7. Treatment-emergent adverse events that appear to meet the DLT definition will be discussed between Regeneron and the investigator. The final decision of whether or not the AE meets the DLT definition will be based on a careful review of all relevant data and consensus between the medical monitor and the designated risk management lead from the Pharmacovigilance & Risk Management department.

The investigator will also be consulted. 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 entire DLT period.

Management and dose modifications associated with the AEs described below are outlined in Section 6.2**.**

**Table 7: Criteria for Dose-Limiting Toxicity**

| | |
|---|---|
| Non-Hematologic | • Any grade 3 or 4 non-hematologic toxicity considered related to REGN2810.<br>• Any REGN2810-related AE during the first cycle of therapy that leads to a dose reduction, or results in delay of treatment ≥7 days, or results in permanent cessation of therapy |
| Hematologic | • Any grade 4 hematologic toxicity considered related REGN2810, with the exception of lymphopenia and anemia<br>• Grade 3 neutropenia with fever considered related to REGN2810<br>• Grade 3 thrombocytopenia considered related to REGN2810 |
| Immune-Related | • Grade 3 immune-related AE considered related to REGN2810. Examples include, but are not limited to, neurological toxicities, uveitis, endocrine toxicity, and colitis |
| Interruption of Planned Radiation (Efficacy Phase Only) | • For newly diagnosed DIPG and HGG receiving conventionally fractionated radiation: interruption of radiation for 5 consecutive fractions, or 10 fractions total, due to REGN2810-related toxicity (and not due to technical issues)<br>• For newly diagnosed DIPG and HGG receiving hypofractionated radiation: interruption of radiation for 2 consecutive fractions, or 4 fractions total, due to REGN2810-related toxicity (and not due to technical issues)<br>• Recurrent HGG, reirradiation: 2 consecutive fractions or 3 fractions total due to REGN2810-related toxicity (and not due to technical issues) |

## 4.5. Off-Treatment Criteria

REGN2810 treatment may occur for up to 12 cycles (or up to 24 cycles if, in the opinion of the investigator, the patient would continue to derive clinical benefit from extended treatment). Patients must discontinue therapy if 1 or more of the following criteria are met:

- Confirmed disease progression
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Treatment delays (≥28 days) from anticipated dosing schedule of REGN2810; however, note that treatment may be continued after discussion with the sponsor and PNOC

- Unacceptable AE(s)
- The patient or LAR refuses further treatment on this protocol
- Pregnancy

Note that, in the Efficacy Phase, if a patient treated with combination therapy experiences unacceptable AE(s) that are (in the opinion of the investigator) reasonably likely to be related to only one of the therapies, the patient may continue treatment with the therapy determined not to be the cause of the AE(s). In addition, if the AE is an infusion-related reaction that (in the opinion of the investigator) is reasonably likely to be related to REGN2810 and not combination therapy, this will not be considered a DLT of the combination therapy.

The off-treatment information and reason for discontinuation must be documented by the attending investigator in the medical record and recorded in the eCRF.

## 4.6. Off-Study Criteria

Patients will be considered off study for the following reasons:

- Patients begins new anticancer therapy not specified in protocol
- Patient is determined to be ineligible
- Patient or LAR withdraws consent for continued participation
- Patient dies while on study
- Completion of the follow-up period specified in the protocol

The date and reason for the patient coming off study must be documented in the eCRF. No data will be collected after the "off study" date.

## 4.7. Number of Patients

In Phase 1, a minimum of 30 patients will be enrolled. In the Efficacy Phase, a minimum of 100 patients will be enrolled. A complete description of patient sample size can be found in Section 12.2.

### 4.7.1. Minimum Enrollment Requirements

Cohorts in the Efficacy Phase will have minimum enrollment requirements for certain age groups. DIPG cohorts will include a minimum of 30 patients age <18 years (15 in each treatment arm) and a minimum of 20 patients age <12 years (10 in each treatment arm). Newly diagnosed HGG cohorts will include a minimum of 20 patients age <18 years (10 in each treatment arm) and a minimum of 4 patients age <12 years (2 in each treatment arm). Recurrent HGG cohorts will include a minimum of 5 patients <18 years, with no minimum requirement for patients age <12 years. These minimum cutoffs are tailored to the age-related incidence of each tumor type.

# 5. STUDY POPULATION

## 5.1. Inclusion Criteria

To be eligible for this study, all patients must meet the criteria outlined in Section 5.1.1. Inclusion criteria applicable only to Phase 1 or the Efficacy Phase are provided in Section 5.1.2 and Section 5.1.3, respectively. Performance status criteria can be found in Appendix 1. For mandatory radiation dose constraints, see Section 10.

*The inclusion criteria provided below are to be interpreted literally and cannot be waived.*

### 5.1.1. All Patients (Phase 1 and Efficacy Phase)

- Karnofsky performance status ≥50 (patients >16 years) or Lansky performance status ≥50 (patients ≤16 years)
  - Patients who are unable to walk due to paralysis, but who are able to use a wheelchair, will be considered ambulatory for the purpose of assessing performance score
- Life expectancy >8 weeks
- Adequate bone marrow function, defined as:
  a. Peripheral absolute neutrophil count (ANC) ≥1000/mm$^3$
  **and**
  b. Platelet count ≥100,000/mm$^3$ (transfusion independent, defined as not receiving platelet transfusions for ≥7 days prior to study registration)
  **and**
  c. Hemoglobin ≥8 g/dL (transfusion independent)
- Adequate renal function, defined as:
  a. Creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥70 mL/min/1.73 m$^2$
  **or**
  b. Serum creatinine based on age/gender as follows:

| Age | Maximum Serum Creatinine (mg/dL) | |
|---|---|---|
| | Male | Female |
| 0 to 2 months | 0.9 | 0.9 |
| 2 months to <2 years | 0.6 | 0.6 |
| 2 to <6 years | 0.8 | 0.8 |
| 6 to <10 years | 1 | 1 |
| 10 to <13 years | 1.2 | 1.2 |
| 13 to <16 years | 1.5 | 1.4 |
| ≥16 years | 1.7 | 1.4 |
| Threshold creatinine values derived from the Schwartz formula for GFR estimation, which utilizes child body length/stature data from the Centers for Disease Control[57] | | |

- Adequate liver function, defined as:

a. Bilirubin (sum of conjugated + unconjugated) ≤1.5x upper limit of normal (ULN) for age
**and**
b. Alanine transaminase (ALT, also referred to as SGPT) ≤110 U/L
**and**
c. Serum albumin ≥2 g/dL

- Adequate neurologic function: patients with seizure disorder may be enrolled if well controlled
- Patient or legally authorized representative (LAR) able to understand, and willing to sign, a written informed consent

### 5.1.2. Phase 1

- Age 0 to <18 years
- Diagnosis of recurrent or refractory solid or CNS tumor
- Histologic confirmation of malignancy at original diagnosis or relapse
- Multifocal DIPG will be eligible for Phase 1
  - Exception: patients with metastatic spine disease and gliomatosis, as documented by diffuse involvement of >2 lobes, are not eligible
- Available tumor tissue from biopsy or resection; archived tissue is acceptable
- Radiation therapy: for solid tumors outside of the CNS, an interval of ≥14 days between local palliative radiation therapy and study registration; for CNS tumors, interval of ≥12 weeks between radiation therapy and study registration
  - Note: these requirements are due to concerns of pseudo-progression in the CNS and challenges that may arise from delineating toxicity related to radiation versus drug

### 5.1.3. Efficacy Phase

#### 5.1.3.1. Newly Diagnosed DIPG (Cohorts E and F) Only

- Age 3 to 25 years
- Histological confirmation of newly diagnosed DIPG
  - Patients with or without H3K27M mutations are eligible
  - Patients with infiltrating astrocytomas within the pons, consistent with DIPG, are eligible
  - Patients with disseminated spine disease are not eligible. Magnetic resonance imaging (MRI) of the spine must be performed if the treating physician suspects disseminated disease
- Available tumor tissue from biopsy or resection; archived tissue is acceptable
- No prior therapy before study registration

- No prior radiation before study registration
- First study treatment administration ≤28 days from the date of radiographic diagnosis

#### 5.1.3.2. Newly Diagnosed HGG (Cohorts G and H) Only

- Age 3 to 25 years
- Histological confirmation of newly diagnosed high-grade glioma (WHO grade III-IV) within the cerebrum and/or the cerebellum, including but not limited to infiltrating astrocytomas outside of the pons
  - Patients with or without H3K27M mutations are eligible
  - Patients with disseminated disease anywhere outside of the cerebrum or cerebellum are not eligible
  - Patients whose primary diagnosis is high-grade glioma of the spinal cord are not eligible
  - Patients with DIPG are excluded from this cohort
- Available tumor tissue from biopsy or resection; archived tissue is acceptable
- No prior therapy before study registration
- No prior radiation before study registration
- First study treatment administration ≤28 days of the date of definitive surgery

#### 5.1.3.3. Recurrent HGG (Cohorts I and J) Only:

- Age 3 to 25 years
- Diagnosis of recurrent high-grade glioma (WHO grade III-IV) within the cerebrum and/or the cerebellum, including but not limited to infiltrating astrocytomas outside of the pons
  - Patients with or without H3K27M mutations are eligible
  - Recurrent lesions must be treatable within a single radiation field that can meet mandatory radiation dose constraints
  - Patients will be limited to first or second recurrence
  - Patients with disseminated disease anywhere outside of the cerebrum or cerebellum are not eligible. Patients whose primary diagnosis included high-grade glioma of the spinal cord are not eligible. Patients with DIPG are excluded from this cohort
  - Histological confirmation of recurrent high-grade glioma (WHO grade III-IV) is preferred
- Available tumor tissue from biopsy or resection; archived tissue is acceptable
- Patients must have had previous irradiation as therapy for HGG diagnosis

- Patients are allowed to have undergone prior therapy including surgery, chemotherapy, and radiation therapy. Patients must have fully recovered from acute side effects related to previous anticancer therapies
- Patients must have:
  - Had their last fraction of local irradiation to primary tumor ≥6 months prior to study registration; investigators are reminded to review potentially eligible cases to avoid confusion with pseudo-progression
  - Had their last dose of myelosuppressive chemotherapy ≥21 days prior to study registration (≥42 days if nitrosourea therapy)
  - Had their last dose of hematopoietic growth factor ≥14 days (long-acting growth factor) or ≥7 days (short-acting growth factor) prior to study registration, or beyond the time during which adverse events (AEs) are known to occur
  - Had their last dose of biologic (anti-neoplastic agent) ≥7 days prior to study registration, or beyond the time during which AEs are known to occur
  - Had their last dose of monoclonal antibodies ≥21 days prior to study registration

## 5.2. Exclusion Criteria

The exclusion criteria below apply to all patients in this study, in both Phase 1 and the Efficacy Phase.

*The exclusion criteria provided below are to be interpreted literally and cannot be waived.*

- Patients with bulky metastatic disease of the CNS causing any of the following:
  - Uncal herniation or symptomatic midline shift
  - Significant, symptomatic mass effect
  - Uncontrolled neurological symptoms such as seizures or altered mental status
- Patients with metastatic spine disease and gliomatosis as documented by diffuse involvement of >2 lobes
- Patients who are receiving any other investigational anticancer agent(s)
- Patients on greater than dexamethasone 0.1 mg/kg/day (maximum 4 mg/day) or equivalent dose in alternate corticosteroid, or actively undergoing corticosteroid dose escalation in the last 7 days
- Patients with a history of allogeneic stem cell transplant
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

- Human immunodeficiency virus (HIV)-positive patients are ineligible if HIV therapy regimen has not been stable for ≥4 weeks, or there is intent to change the regimen within 8 weeks prior to study registration
- Patients who are unable to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy
- Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related AEs
- Prior treatment with an agent that blocks the PD-1/PD-L1/PD-L2 pathway
- History of pneumonitis within the last 5 years or any history of thoracic radiation
- Patients who have received prior craniospinal irradiation (CSI) or have prior radiation fields that overlap the lung
- History of documented allergic reactions or acute hypersensitivity reaction attributed to agents used in the study
- Patients who have received live vaccines within 28 days (4 weeks) prior to study registration
- Continued sexual activity in males or women of childbearing potential (WOCBP)[1] who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose

  Examples of highly effective contraceptive measures in WOCBP include: intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner[2]; stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; and/or sexual abstinence[3,4]

  Male study participants with WOCBP partners are required to use condoms unless they are vasectomized[2] or practice sexual abstinence[3,4]

  [1] WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy

  [2] Vasectomized partner or vasectomized study participant must have received medical assessment of the surgical success

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

  [4] Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together

- WOCBP who are pregnant or breast-feeding. WOCBP must have a negative pregnancy test (serum or urine) within 14 days prior to study registration

# 6. STUDY DRUG ADMINSTRATION AND DOSE MODIFICATIONS

## 6.1. REGN2810 Administration

REGN2810 dosing and information is provided in Table 8 and Table 9. Appropriate dose modifications are described in Section 6.2. REGN2810 will be infused intravenously every 2 weeks. REGN2810 infusion should occur over at least 30 minutes (window: +/-5 minutes). The infusion time may exceed 30 minutes as needed to conform with institutional standards. Patients should be observed post-infusion as per institutional standards. Post-infusion observations should be documented in the eCRF.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. REGN2810 should be initiated within 14 days of screening and within +/-3 days of radiation start.

**Table 8: REGN2810 Dose Levels**

| Dose Level | Dose of REGN2810[1] |
|---|---|
| DL0 | 1 mg/kg/dose |
| DL1 | 3 mg/kg/dose |
| DL2 | 4.5 mg/kg/dose |

[1] The dose of REGN2810 must be adjusted at the start of each cycle for changes in body weight of ≥10%. Dose adjustments for changes in body weight of <10% will be at the discretion of the investigator.

**Table 9: REGN2810 Administration**

| Agent (Phase 1 and Efficacy Phase) | Premedications or Precautions | Dose | Route | Schedule | Cycle Length |
|---|---|---|---|---|---|
| REGN2810 | None | See Table 8 | IV for at least 30 minutes (+/-5 minutes); may exceed 30 minutes per institutional standards | Dose on days 1 and 15 of 28-day cycles | 28 days (4 weeks) |

## 6.2. REGN2810 Dose Modifications and Delays

All toxicities will be graded per Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (see Section 9.5.1). Table 10 provides general guidelines for dose modification in the event of suspected toxicity related to REGN2810. Please see Appendix 2 for dose-modification guidelines for specific organ-related toxicities.

**NOTE:** If a patient experiences several AEs and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose the most.

The PNOC Study Chair, Co-Chair, and Medical Monitor **must** be notified prior to any dose modifications and prior to the implementation of a dose modification.

**Table 10: Guidelines for Dose Modification and Re-Initiation of Treatment in Case of Suspected REGN2810 Toxicity**

| Toxicity | Grade | Recommended Action |
|---|---|---|
| Non-hematologic toxicity[1] | 1 | No change in REGN2810 dose |
| | 2 | • Consider holding REGN2810 until grade ≤1<br>• Discontinue REGN2810 if toxicity is intolerable to patient<br>• Discontinue REGN2810 if toxicity remains and does not return to grade ≤1 within 4 weeks |
| | 3/4 | Discuss with study chairs regarding specific recommendations for REGN2810 dose modification. |
| Infusion-related reactions | 1 | • No change in REGN2810 dose<br>• Consider premedication with acetaminophen and diphenhydramine, as per institutional standards, prior to future infusions<br>• For patients with a documented history of allergic reaction/hypersensitivity to antibody therapy, temporarily suspend study treatment and notify sponsor |
| | 2 | • No change in REGN2810 dose<br>• Recommend premedication with acetaminophen and diphenhydramine, as per institutional standards, prior to future infusions<br>• For patients with a documented history of allergic reaction/hypersensitivity to antibody therapy, temporarily suspend study treatment and notify sponsor |
| | 2 (Recurrent)[2] | Discontinue REGN2810 |
| | 3/4 | Discontinue REGN2810 |

[1] Outside of specific organ-related toxicities listed in Appendix 2.

[2] Recurrent grade 2 that occurs a second time despite premedication.

## 6.3. Prohibited Therapies

Patients may not receive live vaccines while on therapy and for 3 months after stopping therapy.

# 7. STUDY SUPPORTIVE CARE AND ADVERSE EVENT MANAGEMENT GUIDELINES

## 7.1. Supportive Care

Supportive care may include, but is not limited to, antibiotics, antiemetics, antidiarrheals, topical treatments, blood products, intravenous or oral fluids, and electrolyte repletion. These measures will be used as clinically indicated.

## 7.2. Infusion-Related Reactions

Guidance for managing infusion-related reactions is provided in Table 10. Infusion-related reactions should be managed per institutional guidelines with treatment including, but not limited to, corticosteroids, antihistamines, epinephrine, and intravenous fluids. Lengthening of the infusion time for subsequent REGN2810 administration may also be considered, after discussion with the sponsor.

### 7.2.1. Allergic Reaction or Hypersensitivity in Patients with Prior Reaction(s) to Antibody Treatment

For patients with a documented allergic reaction or hypersensitivity attributed to antibody therapy, study treatment will be temporarily suspended following any evidence of an allergic reaction or hypersensitivity to REGN2810. The sponsor should be informed as soon as possible to discuss further management of the patient.

## 7.3. Management of Specific Organ-Related Toxicities

In general, treatment emergent adverse events should be provided symptomatic care per institutional standards. For grade 2 to 4 adverse events, corticosteroids may be considered, as described in Appendix 2. Grade 3 to 4 irAEs can be fatal if not aggressively treated. In most cases, this means instituting systemic corticosteroid therapy before ruling out all competing diagnoses. For adult patients, recommended initial systemic corticosteroid therapy is 0.5 to 1 mg/kg daily for grade 3 irAEs and 1 to 2 mg/kg daily for grade 4 irAEs. For pediatric patients, initiation of corticosteroids per institutional standards is appropriate. See Appendix 2 for additional AE management guidelines.

## 7.4. Special Considerations: Pseudoprogression

For symptoms and imaging consistent with pseudoprogression of tumors in the CNS, use of supportive care measures including bevacizumab and corticosteroids will be allowed, with recommended dosing as follows and in order of study preference, as possible per institutional availability and acuity of symptoms:

- Bevacizumab for up to 3 doses, dosing per institutional standard
- Dexamethasone, per institutional standard

For symptoms of pseudoprogression of solid tumors outside of the CNS (Phase 1 only), use of supportive care measures including corticosteroids will be allowed, with recommended type and

dosing as follows: methylprednisolone intravenous (IV) or oral equivalent per institutional standards, depending on severity of symptoms

# 8. SCHEDULE OF EVENTS AND PROCEDURES

## 8.1. Schedule of Events / Treatment Plan

### 8.1.1. Schedule of Events

The Schedule of Events is provided below for Phase 1 (Table 11) and the Efficacy Phase (Table 12 and Table 13). Table 12 describes cohorts in the Efficacy Phase receiving REGN2810 + conventionally fractionated radiation. Table 13 describes cohorts in the Efficacy Phase receiving REGN2810 + hypofractionated radiation. Additional information on long-term follow-up is provided in Section 8.1.8. Detailed descriptions of study observations and procedures are provided in Section 8.2. Specific fractionation schedules for each cohort/tumor type are provided in Section 10.2.

Windows for each visit are provided in the Schedule of Events. The window for REGN2810 administration is +/-3 days. Unless otherwise noted, the window for assessments is also +/-3 days. REGN2810 should be initiated within 14 days of screening and (for Efficacy Phase cohorts) +/-3 days of radiation start.

## Table 11: Schedule of Events for Phase 1

| Visit | Screening | Treatment Cycles (28 days) | | | | | | End of Treatment (EOT) | Toxicity Check | Follow-up[2] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | C2 to C12[1] | | | | | |
| Day | -14 to -1 | 1 +/-3d | 8 +/-3d | 15 +/-3d | 22 +/-3d | 1 +/-3d | 15 +/-3d | Day of decision to stop treatment +14d | 30 days after EOT +7d | Every 12 weeks after last treatment +/-7d |
| **CLINICAL PROCEDURES** | | | | | | | | | | |
| Consent Form | X | | | | | | | | | |
| Medical History | X | | | | | | | | | |
| Physical w/Full Neurologic Exam | X | X | X | X | X | X | | X | | |
| Vital Signs | X | X | X | X | X | X | X | X | | |
| Height | | X | | | | X | | X | | |
| Weight | X | X | X | X | X | X | X | X | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X |
| Performance Status | X | X | X | X | X | X | | X | | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | |
| Quality of Life Assessment[3] | | X[3] | | | | X[3] | | X[3] | | X[3] |
| Survival | | | | | | | | | | X |
| **AGENT ADMINISTRATION** | | | | | | | | | | |
| REGN2810 (cemiplimab) | | X[4] | | X[4] | | X[4] | X[4] | | | |
| **LABORATORY PROCEDURES** | | | | | | | | | | |
| CBC w/Differential | X | X | X | X | X | X | X | X | | |
| Serum Chemistry[5] | X | X | X | X | X | X | X | X | | |
| Serum or Urine Pregnancy Test (women of childbearing potential only)[6] | X | X | | | | X | | | | |
| Urinalysis | | X | | | | X | | X | | |
| Serum TSH | | X | | | | X | | X | | |
| Serum Free Thyroxine, T4 | | X | | | | X | | X | | |
| Serum Amylase | | X | | | | X | | X | | |
| Serum Lipase | | X | | | | X | | X | | |
| Serum C-reactive Protein (CRP) | | X | | | | X | | X | | |
| **IMAGING AND DISEASE ASSESSMENT PROCEDURES** | | | | | | | | | | |
| MRI/PET or CT | X[7] | X[7] | | | | X[7] | | X[7] | | X[7] |
| Disease Status Assessment | X[7] | X[7] | | | | X[7] | | X[7] | | X[7] |
| **PHARMACOKINETIC (PK) AND ANTI-DRUG ANTIBODY (ADA) PROCEDURES** | | | | | | | | | | |
| PK and ADA | | Sample collection schedule varies by cohort. See Section 8.2. | | | | | | | | |
| **EXPLORATORY PROCEDURES** | | | | | | | | | | |
| Tumor Tissue[8] | X[8] | | | | | | | | | |
| Genomic DNA (Saliva/Buccal) | X[9] | | | | | | | | | |
| Circulating Tumor DNA [10] | | X[10] | | | | X[10] | | X[10] | | X[10] |
| Peripheral Blood Mononuclear Cells[11] | | X[11] | | | | X[11] | | | | |
| Cytokines/Biomarkers[12] | | X[12] | | | | X[12] | | | | |

### 8.1.2. Footnotes for Table 11 (Schedule of Events for Phase 1)

1. Patients who continue beyond 12 cycles should undergo all observations listed under C2 to C12 with the exception of PBMC and cytokine sample collection.
2. All indicated follow-up assessments, with the exception of QoL assessments, should occur every 12 weeks after a patient has stopped receiving treatment, up to 52 weeks.
3. Quality of life assessment should occur at the following visits: prior to the first dose of REGN2810, prior to receiving REGN2810 on cycle 7, day 1, at the end of treatment visit, and during every other follow up visit (ie, every 24 weeks) during the off-treatment period. Quality of life will be measured using PedsQL (patients 2 to <18 years of age) or FACT-Br (patients >18 years of age) as described in Section 8.2.1.9.
4. REGN2810 should be given every 14 days, starting on cycle 1 day 1, for up to 12 cycles. REGN2810 may continue to be given every 14 days for up to 24 cycles if, in the investigator's opinion, the patient would continue to derive clinical benefit. On days when REGN2810 is given, all other assessments and procedures should be performed first. In Phase 1, the DLT period occurs during the first two doses of REGN2810 (ie, cycle 1 day 1 [C1D1] to C1D28).
5. For more information on serum chemistry tests that must be performed, see Section 8.2.3.
6. For all visits in which pregnancy testing is required, the procedure window is +/-14 days.
7. Imaging does not need to be taken or recorded every treatment cycle, but should occur once every 12 weeks (window: -2 weeks) while patients are on treatment. Imaging should also be performed during the EOT visit (window: +/-30 days) and during the off-treatment follow-up period approximately once every 12 weeks (or per institutional standards) for up to 52 weeks. Imaging should also be performed at the time of disease progression.

   Imaging during C1D1 is only required if prior imaging occurred more than 14 days from C1D1. If imaging has been taken within 14 days of C1D1 (ie, during the screening period), imaging does not need to be performed on C1D1.

   For a given patient, the same imaging modality should be used throughout the study. Details on imaging procedures and disease assessment are provided in Section 11.
8. Available tumor tissue, either archival or fresh, must be confirmed prior to study eligibility. Tumor tissue will also be collected if the patient undergoes repeat surgical resection or biopsy at any time while the patient is on-study, including in the setting of disease progression. See Section 5.1 for tumor biopsy requirements.
9. Saliva/buccal sample for genomic DNA may be collected at any time. Saliva/buccal sample is only required if a tumor sample (either archival or from biopsy) is taken.
10. Blood for circulating tumor DNA (ctDNA) should be collected pre-dose on C1D1 and at any time scheduled or repeat/confirmatory imaging is performed (except during screening).
11. Blood for correlative peripheral blood mononuclear cell (PBMC) studies should be collected pre-dose on day 1 of cycles 1, 2, and 3.
12. Blood for correlative serum/plasma biomarker studies should be collected pre-dose on day 1 of cycles 1 through 5 and at the time of disease progression.

## Table 12: Schedule of Events for the Efficacy Phase: REGN2810 + Conventionally Fractionated Radiation

| Visit | Screening | Treatment Cycles (28 days) | | | | | | | | | End of Treatment (EOT) | Toxicity Check | Follow-up[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | | C2 | | | C3 to C12[1] | | | | |
| Day | -14 to -1 | 1 +/-3d | 8 +/-3d | 15 +/-3d | 22 +/-3d | 1 +/-3d | 8 +/-3d | 15 +/-3d | 1 +/-3d | 15 +/-3d | Decision to stop future dosing +14d | 30 days after EOT +7d | Every 12 weeks after last treatment +/-7d |
| **CLINICAL PROCEDURES** | | | | | | | | | | | | | |
| Consent Form | X | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | |
| Randomization | X[3] | | | | | | | | | | | | |
| Physical w/Full Neurologic Exam | X | X | X | X | X | X | X | X | X | | X | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | | |
| Height | | X | | | | X | | | X | | X | | |
| Weight | X | X | X | X | X | X | X | X | X | X | X | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X |
| Performance Status | X | X | X | X | X | X | X | X | X | | X | | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | | X | X | |
| Quality of Life Assessment[4] | | X[4] | | | | | | | X[4] | | X[4] | | X[4] |
| Survival | | | | | | | | | | | | | X |
| **AGENT ADMINISTRATION** | | | | | | | | | | | | | |
| REGN2810 (cemiplimab) | | X[5] | | X[5] | | X[5] | | X[5] | X[5] | X[5] | | | |
| Radiation[6] | | C1D1 to C2D8: 5 times each week w/ cohort-specific dosing (Section 10.2) | | | | | | | | | | | |
| **LABORATORY PROCEDURES** | | | | | | | | | | | | | |
| CBC w/Differential | X | X | X | X | X | X | X | X | X | X | X | | |
| Serum Chemistry | X | X | X | X | X | X | X | X | X | X | X | | |
| Serum or Urine Pregnancy Test[7] | X | X | | | | X | | | X | | X | | |
| Urinalysis | | X | | | | X | | | X | | X | | |
| Serum TSH, Serum Free T4 | | X | | X | | X | | X | X | | X | | |
| Serum Amylase | | X | | X | | X | | X | X | | X | | |
| Serum Lipase | | X | | X | | X | | X | X | | X | | |
| Serum C-reactive Protein (CRP) | | X | | | | X | | | X | | X | | |
| **IMAGING AND DISEASE STATUS ASSESSMENT PROCEDURES** | | | | | | | | | | | | | |
| Brain MRI/Spine MRI[8] | X[8] | X[8] | | | | | | | X[8] | | X[8] | | X[8] |
| Disease Status Assessment | X[8] | X[8] | | | | | | | X[8] | | X[8] | | X[8] |
| **PHARMACOKINETIC (PK) AND ANTI-DRUG ANTIBODY (ADA) PROCEDURES** | | | | | | | | | | | | | |
| PK and ADA | | Sample collection schedule varies by cohort. See Section 8.2. | | | | | | | | | | | |
| **EXPLORATORY PROCEDURES** | | | | | | | | | | | | | |
| Tumor Tissue[9] | X[9] | | | | | | | | | | | | |
| Genomic DNA (Saliva/Buccal) | X[10] | | | | | | | | | | | | |
| Circulating Tumor DNA[11] | | X[11] | | | | | | | X[11] | | X[11] | | X[11] |
| Peripheral Blood Mononuclear Cells[12] | | X[12] | | | | X[12] | | | X[12] | | | | |
| Cytokines/Biomarkers[13] | | X[13] | | | | X[13] | | | X[13] | | X[13] | | |

## Table 13: Schedule of Events for the Efficacy Phase: REGN2810 + Hypofractionated Radiation or Re-Irradiation

| Visit | Screening | Treatment Cycles (28 days) | | | | | | | | End of Treatment (EOT) | Toxicity Check | Follow-up[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | | C2 | | C3 to C12[1] | | | | |
| Day | -14 to -1 | 1 +/-3d | 8 +/-3d | 15 +/-3d | 22 +/-3d | 1 +/-3d | 15 +/-3d | 1 +/-3d | 15 +/-3d | Decision to stop future dosing +14d | 30 days after EOT +7d | Every 12 weeks after last treatment +/-7d |
| **CLINICAL PROCEDURES** | | | | | | | | | | | | |
| Consent Form | X | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | |
| Randomization | X[3] | | | | | | | | | | | |
| Physical w/Full Neurologic Exam | X | X | X | X | X | X | X | X | | X | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | | |
| Height | | X | | | | X | | X | | X | | |
| Weight | X | X | X | X | X | X | X | X | X | X | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X |
| Performance Status | X | X | X | X | X | X | X | X | | X | | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | |
| Quality of Life Assessment[4] | | X[4] | | | | | | X[4] | | X[4] | | X[4] |
| Survival | | | | | | | | | | | | X |
| **AGENT ADMINISTRATION** | | | | | | | | | | | | |
| REGN2810 (cemiplimab) | | X[5] | | X[5] | | X[5] | X[5] | X[5] | X[5] | | | |
| Radiation[6] | | C1D1 to C1D15: 5 times each week w/ cohort-specific dosing (Section 10.2) | | | | | | | | | | |
| **LABORATORY PROCEDURES** | | | | | | | | | | | | |
| CBC w/Differential | X | X | X | X | X | X | X | X | X | X | | |
| Serum Chemistry | X | X | X | X | X | X | X | X | X | X | | |
| Serum or Urine Pregnancy Test[7] | X | X | | | | X | | X | | X | | |
| Urinalysis | | X | | | | X | | X | | X | | |
| Serum TSH, Serum Free T4 | | X | | X | | X | X | X | | X | | |
| Serum Amylase | | X | | X | | X | X | X | | X | | |
| Serum Lipase | | X | | X | | X | X | X | | X | | |
| Serum C-reactive Protein (CRP) | | X | | | | X | | X | | X | | |
| **IMAGING AND DISEASE STATUS ASSESSMENT PROCEDURES** | | | | | | | | | | | | |
| Brain/Spine MRI[8] | X[8] | X[8] | | | | X[8] | | X[8] | | X[8] | | X[8] |
| Disease Status Assessment | X[8] | X[8] | | | | X[8] | | X[8] | | X[8] | | X[8] |
| **PHARMACOKINETIC (PK) AND ANTI-DRUG ANTIBODY (ADA) PROCEDURES** | | | | | | | | | | | | |
| PK and ADA | | Sample collection schedule varies by cohort. See Section 8.2. | | | | | | | | | | |
| **EXPLORATORY PROCEDURES** | | | | | | | | | | | | |
| Tumor Tissue[9] | X[9] | | | | | | | | | X[9] | | X[9] |
| Genomic DNA (Saliva/Buccal) | X[10] | | | | | | | | | | | |
| Circulating Tumor DNA[11] | | X[11] | | | | X[11] | | X[11] | | X[11] | | X[11] |
| Periph. Blood Mononuclear Cells[12] | | X[12] | | | | X[12] | | X[12] | | | | |
| Cytokines/biomarkers[13] | | X[13] | | | | X[13] | | X[13] | | X[13] | | X[13] |

### 8.1.3. Footnotes for Table 12 and Table 13 (Schedules of Events for the Efficacy Phase)

1. Patients who continue beyond 12 cycles should undergo all observations listed under C2 to C12 with the exception of PBMC and cytokine sample collection.
2. All follow-up assessments, with the exception of QoL assessments, should occur every 12 weeks after a patient has stopped receiving treatment, up to 52 weeks.
3. For more information on randomization in this study, please refer to Section 4.2.
4. Quality of life assessment should occur at the following visits: prior to the first dose of REGN2810, prior to receiving REGN2810 on cycle 7, day 1, at the end of treatment visit, and every 24 weeks during the off-treatment follow-up period. Quality of life will be measured using PedsQL (patients 2 to <18 years of age) or FACT-Br (patients >18 years of age) as described in Section 8.2.1.9.
5. REGN2810 should be given every 14 days starting on cycle 1 day 1, for up to 12 cycles. REGN2810 may continue to be given every 14 days for up to 24 cycles if, in the investigator's opinion, the patient would continue to derive clinical benefit. On days when REGN2810 is given, all other assessments and procedures should be performed first.
6. Radiation will be given 5 times weekly according to a fractionation and dosing schedule specific to each disease cohort. Radiation should be administered within +/-3 days of initial administration of REGN2810, and should be started no more than 3 days after initial administration of REGN2810. See Section 10.2 for more information.

   During the DLT period (the length of radiation therapy + 28 days), weekly toxicity monitoring must be performed, including physical examination, vital signs, adverse event monitoring, CBC with differential, and serum chemistry. For more information on serum chemistry tests that must be performed, see Section 8.2.3.
7. For all visits in which pregnancy testing is required, the procedure window is +/-14 days.
8. MRI should occur within 2 to 4 weeks after completion of radiation. Subsequently, imaging does not need to be taken or recorded every treatment cycle, but should occur once every 12 weeks (window: -2 weeks) while patients are on treatment. Imaging should also be performed during the EOT visit (window: +/-30 days) and during the off-treatment follow-up period approximately once every 12 weeks (or per institutional standards) for up to 52 weeks. Imaging should also be performed at the time of disease progression. Spine imaging should be performed as clinically indicated and should occur during the same visits as brain MRI.

   Imaging during C1D1 is only required if prior imaging occurred more than 14 days from C1D1. If imaging has been taken within 14 days of C1D1 (ie, during the screening period), imaging does not need to be performed on C1D1.

   For a given patient, the same imaging modality should be used throughout the study. Details on imaging procedures and disease assessment are provided in Section 11.
9. Available tumor tissue, either archival or fresh, must be confirmed prior to study eligibility. Tumor tissue will also be collected if the patient undergoes repeat surgical resection or

biopsy at any time while the patient is on-study, including in the setting of disease progression. See Section 5.1 for tumor biopsy requirements.

10. Saliva/buccal sample for genomic DNA may be collected at any time. Saliva/buccal sample is only required if a tumor sample (either archival or from biopsy) is taken.
11. Blood for circulating tumor DNA (ctDNA) should be collected pre-dose on C1D1 and at any time scheduled or repeat/confirmatory imaging is performed (except during screening).
12. Blood for correlative peripheral blood mononuclear cell (PBMC) studies should be collected pre-dose on day 1 of cycles 1, 2, and 3.
13. Blood for correlative serum biomarker studies should be collected pre-dose on day 1 of cycles 1 through 5 and at the time of disease progression.

### 8.1.4. Pharmacokinetic and Anti-Drug Antibody Sample Collection

Collection time points for PK and ADA samples are provided in Table 14, Table 15, and Table 16. For details on procedures for PK and ADA collection and analysis, refer to Section 8.2.5.

**Table 14: PK and ADA Collection Schedule for Phase 1: Patients 0 to 2 Years of Age (or Per Institutional Guidelines)**

| Visit[1] | Cycle 1 | | | | Cycles 2, 4, 6, 8, 10, 12, 16, 24[2] | End of Treatment (EOT)[3] | Follow-up[3] |
|---|---|---|---|---|---|---|---|
| | Day 1 | Day 2 | Day 8 | Day 15 | Day 1 | Decision to stop future dosing | Every 12 weeks after last treatment |
| Time 1 PK | X (pre-dose) | X (24 hours post-dose)[4] | X (any time during visit) | X (pre-dose) | X (pre-dose) | X (pre-dose, if applicable) | X (any time during visit)[5] |
| Time 1 ADA | X (pre-dose) | | | | X (pre-dose, cycles 2, 4, 8, 12, 16, and 24 only)[7] | X (pre-dose, if applicable) | X (first visit only; any time during visit)[6] |
| Time 2 PK | X (EOI)[4] | | | | X (EOI)[4] | | |

EOI=end of infusion.

**Table 15: PK and ADA Collection Schedule for Phase 1: Patients >2 to <18 Years of Age**

| Visit[1] | Cycle 1 | | | | Cycles 2, 3, 4, 5, 6, 8, 10, 12, 16, 24[2] | | End of Treatment (EOT)[3] | Follow-up[3] |
|---|---|---|---|---|---|---|---|---|
| | Day 1 | Day 2 | Day 8 | Day 15 | Day 1 | Day 15 (ages 12 to <18 only)[8] | Decision to stop future dosing | Every 12 weeks after last treatment |
| Time 1 PK | X (pre-dose) | X (24 hours post-dose)[4] | X (any time during visit) | X (pre-dose) | X (pre-dose) | X (pre-dose) | X (pre-dose, if applicable) | X (any time during visit)[5] |
| Time 1 ADA | X (pre-dose) | | | | X (pre-dose, cycles 2, 4, 8, 12, 16, and 24 only)[7] | | X (pre-dose, if applicable) | X (first visit only; any time during visit)[6] |
| Time 2 PK | X (EOI)[4] | | | | X (EOI)[4] | | | |
| Time 3 PK | X (8 hours post-dose)[4] | | | | | | | |

EOI=end of infusion.

**Table 16: PK and ADA Collection Schedule for the Efficacy Phase**

| Visit[1] | Cycle 1 | | | | Cycles 2, 3, 4, 5, 6, 8, 10, 12, 16, 24[2] | End of Treatment (EOT)[3] | Follow-up[3] |
|---|---|---|---|---|---|---|---|
| | Day 1 | Day 2 | Day 8 | Day 15 | Day 1 | Decision to stop future dosing | Every 12 weeks after last treatment |
| **Time 1 PK** | X (pre-dose) | X (24 hours post-dose)[4] | X (any time during visit) | X (pre-dose) | X (pre-dose) | X (pre-dose, if applicable) | X (any time during visit)[5] |
| **Time 1 ADA** | X (pre-dose) | | | | X (pre-dose, cycles 2, 4, 8, 12, 16, and 24 only)[7] | X (pre-dose, if applicable) | X (first visit only; any time during visit)[6] |
| **Time 2 PK** | X (EOI)[4] | | | | X (EOI)[4] | | |
| **Time 3 PK** | X (8 hours post-dose)[4] | | | | | | |

EOI=end of infusion.

### 8.1.5. Footnotes for Table 14, Table 15, and Table 16 (PK and ADA Collection Schedules)

1. Visit windows are as follows: on-treatment cycles: +/-3 days; end of treatment (EOT), day of decision to stop treatment +14 days; toxicity check: 30 days after EOT +7 days; follow-up visit: every 12 weeks after last treatment +/-7 days.
2. On-treatment PK and ADA samples will only be collected at cycles 16 and 24 for patients who continue receiving REGN2810.
3. End of treatment (EOT) and follow-up visits are the same visits as those listed in the Schedules of Events.
4. Windows for PK sample collection time are as follows: end of infusion, +15 to 30 minutes; 8 hours post-dose, +/-1 hour; 24 hours post-dose, +/-3 hours.
5. A PK sample will be taken at the first in-clinic follow-up visit. Additional PK samples will be taken at in-clinic visits after EOT that are at least 3 weeks apart.
6. An ADA sample will be taken at the first in-clinic follow-up visit.
7. On-treatment ADA samples should only be collected on cycles 1, 2, 4, 8, 12, and (for patients receiving REGN2810 beyond cycle 12) at cycles 16 and 24.
8. In Phase 1, PK samples on day 15 of cycles 2 and beyond should only be collected from patients age 12 to <18.

#### 8.1.6. End of Treatment Visit

The End of Treatment visit is defined as the day it is confirmed that a patient will discontinue future dosing, regardless of the reason for discontinuation (window: +14 days).

#### 8.1.7. 30-Day Toxicity Check

All patients who discontinue therapy (for any reason) or who complete therapy will have a 30-day toxicity check, consisting of an evaluation of adverse events and concomitant medications. This evaluation can be conducted via a clinic visit, telemedicine encounter, or telephone encounter.

Toxicity assessment-related AEs must be followed until resolution or until return to baseline. For more information on AE management and reporting, see Section 7 and Section 9.

#### 8.1.8. Long Term/Survival Follow-up

All patients in Phase 1 and the Efficacy Phase who have completed therapy or are off treatment (as defined in Section 4.5) will enter the follow-up period of the study. Patients will be followed every 12 weeks, up to 52 weeks or when a patient starts a new therapy or comes off study (as defined by criteria in Section 4.6). The follow-up period may end at any time per investigator discretion. Information will be collected by chart review and/or by telephone.

Information to be collected during the follow-up period is provided in the Schedules of Events (Table 11, Table 12, and Table 13). In addition, the following information should be collected as applicable: disease status information, the date of progression, date of commencement of any new anticancer therapy, date of last contact, and date of death. Patients who die without confirmation of disease status will be considered to have had PD at the time of death.

## 8.2. Study Assessments and Procedures

The section below provides information on performing study assessments and procedures. For frequency of assessments and procedures at each visit, see the Schedules of Events and PK/ADA collection tables listed in Section 8.1.

### 8.2.1. Clinical Procedures

#### 8.2.1.1. Consent Form

Informed consent/assent must be obtained in accordance with the guidelines described in Section 16.2.

#### 8.2.1.2. Medical History

A complete medical history should be taken and should include baseline symptoms, history of prior treatments, and any residual toxicity related to prior treatment. Any history of prior allergic reaction or hypersensitivity to antibody treatment should also be documented, including the name of the antibody therapy and a description of the reaction.

#### 8.2.1.3. Randomization (Efficacy Phase)

Newly diagnosed DIPG and newly diagnosed HGG patients will be randomized to either conventional radiotherapy (Arm 1) or hypofractionated radiation (Arm 2). The recurrent HGG cohort assignment is to re-irradiation therapy; there is no randomization for these patients. For more information, please refer to Section 4.2.

#### 8.2.1.4. Physical Examination with Full Neurological Exam

Physical examination should include an examination of head and neck, lungs, heart, abdomen (including liver and spleen), lymph nodes, extremities, and skin, as well as a complete neurologic examination, according to the visits listed in the Schedule of Events.

#### 8.2.1.5. Vital Signs, Height, and Weight

Vital signs should include temperature, blood pressure, pulse, and respiration rate. Height and weight will also be measured, as indicated in the Schedules of Events.

#### 8.2.1.6. Toxicity Assessment

Adverse events should be managed and reported as described in Section 7 and Section 9.

#### 8.2.1.7. Performance Status

Patients should be measured using Karnofsky criteria if >16 years of age, or Lansky criteria if ≤16 years of age). Performance status criteria are provided in Appendix 1. To be eligible for the study patients must have a Karnofsky or Lansky (as applicable) score of ≥50 at the time of screening.

#### 8.2.1.8. Concomitant Medications

Any procedure performed or treatment administered (both prescription medications and over-the-counter preparations), from the time of informed consent until the 30-day toxicity check, will be considered concomitant treatment. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

#### 8.2.1.9. Quality of Life Assessment

In patients 2 to <18 years of age, quality of life will be measured using the Pediatric Quality of Life Inventory (PedsQL). In patients 18 to 25 years of age, quality of life will be measured using the Functional Assessment of Cancer Therapy-Brain (FACT-Br) instrument.

#### 8.2.1.10. Survival Data Collection

Every effort will be made to collect survival data (by phone or chart review) on all patients, including patients who withdraw from the study for any reason but have not withdrawn consent to collect survival information. Follow up will continue until death, loss to follow up, or withdrawal of consent. If a patient is lost to follow-up, they will be considered to have died of progressive disease after their last completed survival assessment.

### 8.2.2. Agent Administration

#### 8.2.2.1. REGN2810

Dosing information for REGN2810 is provided in Section 6.1 and Section 6.2. For additional information pertaining to REGN2810 dosing in combination with radiation therapy, see Section 10.

#### 8.2.2.2. Radiation Therapy

Radiation therapy guidelines, including dose schedules for each cohort, are provided in Section 10. All radiation must be done in a PNOC-approved radiation center, due to the frequent safety monitoring and need to follow protocol radiation guidelines.

### 8.2.3. Laboratory Procedures

*Complete Blood Count:* should include differential and platelet count

*Serum Chemistry:* should include alkaline phosphatase, ALT, AST, total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN/urea), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate (carbon dioxide), and magnesium.

*Urinalysis:* a dipstick urine test should be performed, with reflex to microscopic urinalysis in the event of abnormal findings.

*Serum or Urine Pregnancy Test:* must be collected for women of childbearing potential.

Additional laboratory tests may also include urinalysis, serum TSH, serum thyroxine/T4, serum amylase, serum lipase, and serum CRP.

### 8.2.4. Imaging and Disease Status Assessment

A detailed description of imaging procedures and disease/response assessment is provided in Section 11.

In Phase 1 of the study, MRI/PET is the preferred imaging modality, but CT scans may be used for patients with a solid tumor diagnosis. In the Efficacy Phase, brain MRI (and spine MRI where clinically indicated) will be performed.

In all cases, imaging should be based on institutional guidelines appropriate for underlying tumor diagnosis and should include the primary site of disease as well as known measurable sites of metastases. For a given patient, the same imaging modality should be used throughout the study.

### 8.2.5. Pharmacokinetic and Immunogenicity Procedures

Sample collection time points for PK and ADA analysis are provided in Table 14, Table 15, and Table 16.

#### 8.2.5.1. Pharmacokinetics Procedures

REGN2810 PK parameters will be determined by measuring REGN2810 concentrations in blood samples using a validated assay. Blood samples for PK should be taken as close as feasible to the indicated PK sampling times. The actual time of each blood draw must be recorded. On days when study drug is not administered, all PK sampling times will be based on time of last administered

study drug dose. If for any reason a blood sample cannot be drawn at the proposed PK time point, then draw blood for PK as soon as possible and the actual time of PK sampling should be recorded.

Any unused blood samples collected for drug concentration measurements may be used for future research, which may include but are not limited to: exploratory biomarker research or to investigate unexpected AEs.

#### 8.2.5.2. Immunogenicity Procedures

Formation of ADA will be assessed in individual patients by dose level/dose cohort. The actual time of each blood draw must be recorded.

Any unused samples collected for ADA assessment may be used for future research, which may include but is not limited to exploratory biomarker research and/or investigation of unexpected SAEs.

### 8.2.6. Exploratory Procedures

Blood samples, saliva/buccal samples, and tumor tissue samples will be used for exploratory analyses as described in the sub-sections below.

Tissue biopsy/resection, as per standard of care therapy, is required for study enrollment. Surgical samples collected prior to screening including archived tissue will be acceptable. Tissue from this standard of care surgery will be submitted per sample processing standard operating procedure (SOP) found on the PNOC SharePoint Members Site. Tissue samples to be sent with sample for genomic DNA when possible.

#### 8.2.6.1. Exploratory Biomarker and Cytokine Procedures

Exploratory predictive and pharmacodynamic biomarkers related to REGN2810 treatment exposure, clinical activity, or underlying disease will be investigated from collected DNA, serum, plasma, PBMC, archived tumor tissue (as available) and tumor biopsy samples (as available). These results may be used to:

- Explore biomarkers of REGN2810 activity
- Identify ctDNA and cytokines that may have prognostic or predictive utility
- Assess tumor expression of PD-L1
- Analyze changes in the tumor microenvironment
- Perform immunohistochemistry for PD-L1 pathway components
- Identify somatic mutations through targeted mRNA sequencing to discover other factors that may modulate responses to immune therapy through PD-1/PD-L1 pathway interactions

Gene expression panels including the defined “tumor inflammation gene signature” panel, as well as a broader tumor immune-related expression profile will be investigated.

Formalin fixed-paraffin embedded (FFPE) tumor slides will be prepared and H&E stained for assessment of tumor infiltrating lymphocytes in all tumor samples. To identify subsets of different immune populations (effector/memory CD8 cells, T-regulatory cells, tumor-associated

macrophages, and potentially others such as dendritic cells, and Tie-2 expressing monocytes), IHC staining will be performed on FFPE tumor slices using some or all of the following antibodies:

Core set: CD3, CD4, CD8, PD-1, PD-L1, PD-L2, CD68, FoxP3, and Ki67.

Other potential antibodies to be used: CD25, Indoleamine 2,3 deoxygenase-1 (IDO1), CD11c, CD83, CD86, CD56, CD14, CD16, and Tie2

#### 8.2.6.2. Exploratory Biomarker Procedures

Protein expression of a set of pre-specified markers of immune cell infiltration and activity may be analyzed by IHC on evaluable archival samples taken at baseline and biopsies on study (as available). During the screening period, after patients or their LARs have given informed consent, they will be requested to arrange to provide any available archival tumor samples. Samples will be collected according to directions in the study Sample Processing SOP in the PNOC Members SharePoint Site.

For correlative studies, samples will be collected and prepared according to directions in the study reference manuals. The following markers may be assayed in archived and/or biopsy tumor tissue samples using IHC: CD3, CD4, CD8, FoxP3, CD274 (PD-L1), CD279 (PD-1), TIM-3, LAG-3, IDO, and GZMB. PD-L1 expression on tumor-associated immune cells, tumor associated macrophages and myeloid suppressor cells may be performed. Additional immune cell markers and/or tumor markers specific to DIPG and HGG may be included.

#### 8.2.6.3. Exploratory Circulating Cytokine Procedures

Circulating cytokine levels that may relate to REGN2810 treatment exposure, clinical activity, or underlying disease will be assessed at time points according to the Schedules of Events. Serum and plasma samples will be collected for measurement of cytokines. Cytokines to be analyzed may include, but are not limited to, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, GM-CSF, IFNγ, and TNFα. Serology analysis for anti-tumor specific antibody responses may include, but are not limited to survivin, 5T4, galectin-3, estimated glomerular filtration rate (EGFR), and MUC-1. Serum antibody levels in patients receiving Prevnar as standard of care will be used for positive controls.

#### 8.2.6.4. Peripheral Blood Mononucleated Cell Assay

Peripheral blood mononucleated cells will be assessed by fluorescence-activated cell sorting for changes in cell subsets including, but not limited to, naïve and memory CD8 and CD4 T-cells, MDSCs, NK, and B cells. Any unused blood samples collected for drug concentration measurements may be used for future research, which may include but are not limited to: exploratory biomarker research or to investigate unexpected AEs.

Baseline and post-treatment PBMC will be collected in cell preparation tubes (CPT) and red top blood collection tubes to monitor peripheral immunologic changes in response to therapy during the course of the trial. Primary analyses will be performed to quantify specific T-cell populations (composition and functioning), using flow cytometry in conjunction with peripheral markers such as CD3/CD4/CD8, and checkpoint receptors such as PD-1, Tim-3, and Lag-3. Baseline and post-treatment blood will be collected to identify potential therapeutic targets, biomarkers, and predictors of response.

#### 8.2.6.5. Tissue/Blood Banking

All leftover tissue or blood specimens will be banked, such that they can be used for additional or future analyses as needed. These analyses may include exploratory biomarker research, investigation of unexpected AEs, and RNA analyses using the most current and informative methodologies at the time that correlative science is performed on all specimens. NanoString signatures and comprehensive RNA sequencing may be used.

Additionally, available specimens, may be used for whole exome sequencing to determine mutational burden and neoantigen detection, T-cell receptor sequencing to determine intratumoral T-cell receptor diversity and flow cytometry to quantify immune populations.

# 9. SAFETY DEFINITIONS, REPORTING AND MONITORING

## 9.1. Obligations of Investigator

The investigator must promptly report to the IRB/Ethics Committee (EC) any information as required by local IRB/ECs. This includes all unanticipated events involving risks to patients. An unanticipated event is defined as any unexpected, serious event that has implications for the conduct of the study (e.g., requiring a significant and usually safety-related change in the protocol, such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or Investigator's Brochure).

## 9.2. Obligations of Regeneron

During the course of the study, the sponsor and/or the Clinical Research Organization (CRO) will inform health authorities, ECs/IRBs, and the participating investigators of any suspected unexpected serious adverse reactions (SUSARs), occurring in other study centers or other studies of the active study drug, REGN2810, as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Event expectedness for study drug (REGN2810) is assessed against the Reference Safety Information section of the Investigator's Brochure, using the version that is effective for expedited safety reporting.

At the completion of study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and ECs/IRBs as appropriate.

## 9.3. Definitions

### 9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug, which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in Section 9.4.

### 9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death – includes all deaths, even those that appear to be completely unrelated to study drug (e.g., a car accident in which a patient is a passenger).
- Is life-threatening – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Inpatient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event — Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered an SAE.

Criteria for reporting SAEs must be followed for these events. See Section 9.4.2 for more information on recording and reporting SAEs.

### 9.3.3. Adverse Events of Special Interest

An AE of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the

event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

### 9.3.4. Infusion Reactions

Infusion-related reactions are known to occur with protein therapeutic infusions and have been observed in REGN2810 studies.

Acute infusion reactions can include cytokine release syndrome, angioedema, or anaphylaxis, and differ from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 9.3.1) and graded using the grading scales as instructed in Section 9.5.1. Refer to Section 6.2 for guidelines on management of infusion reactions.

## 9.4. Recording and Reporting Adverse Events

### 9.4.1. Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 90 days after the end of study treatment (or until the patient receives another systemic anticancer therapy, whichever is earlier), except in cases where the AE is attributable to disease progression (see Section 9.3.1). Prior to initiation of study treatment, only the following categories of AEs should be reported on the AE eCRF:

- SAEs
- Non-SAEs associated with a protocol-mandated intervention (eg, AEs related to an invasive procedure such as a biopsy)

Other AEs that occur prior to first treatment should be reported on the medical history CRF.

All AEs after initiation of study treatment and until 90 days after the last study treatment (or until the patient receives another systemic anticancer therapy, whichever is earlier) will be reported on the AE CRF, except in cases where the AE is attributable to disease progression (see Section 9.3.1). 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 should be reported.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or electrocardiogram (ECG) abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

### 9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- All SAEs within the safety follow-up window should be reported. After this window, only SAEs that are deemed related should be reported. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.

### 9.4.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

**Symptomatic Overdose of Study Drug**: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE

**Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 6 months of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

**Adverse Events of Special Interest:** All AESI, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2. Adverse events of special interest for this study include the following:

- 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 (irAE) (or grade 2 or greater Uveitis). Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

### 9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

### 9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- The test result is associated with accompanying symptoms, and/or
- The test result requires additional diagnostic testing or medical/surgical intervention, and/or
- The test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Other criterion; for example, all grade 3 or higher lab abnormalities – if required for a particular study

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

### 9.4.6. Follow-Up

Information for any non-SAE that starts during the treatment period or within 90 days after last 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. Information does not need to be collected for any non-SAE attributable to disease progression (see Section 9.3.1)

Serious adverse event information will be collected until the event is considered chronic and/or stable.

## 9.5. Evaluation of Severity and Causality

### 9.5.1. Evaluation of Severity

The descriptions and grading scales found in the revised National Cancer Institute (NCI) CTCAE version 4.0 will be utilized for AE grading of severity. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. This can be downloaded from the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

When specific AEs are not listed in the CTCAE they will be graded by the Investigator according to the following grades and definitions:

**Table 17: NCI-CTCAE Grading System (v4.0)**

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

[1] Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care activities of daily living (ADL) refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

***Infusion Reactions***

The severity of infusion reactions will be graded NCI CTCAE version 4.0.

### 9.5.2. Evaluation of Causality

***Relationship of Adverse Events to Study Drug:***

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

- **Not Related:** There is no reasonable possibility that the event may have been caused by the study drug
- **Related:** There is a reasonable possibility that the event may have been caused by the study drug

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the AE may have been caused by the study drug?

No:

- Due to external causes such as environmental factors or other treatment(s) being administered

- Due to the patient's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- Does not reappear or worsen when dosing with study drug is resumed
- Is not a suspected response to the study drug based upon preclinical data or prior clinical data

Yes:

- Could not be explained by environmental factors or other treatment(s) being administered
- Could not be explained by the patient's disease state or clinical condition
- Follow a reasonable temporal sequence following the time of administration of the dose of study drug
- Resolve or improve after discontinuation of study drug
- Reappear or worsen when dosing with study drug
- Are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

***Relationship of Adverse Events to Study Conduct:***

The relationship of AEs to study conduct will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

- **Not Related:** There is no reasonable possibility that the event may have been caused by study conduct
- **Related:** There is a reasonable possibility that the event may have been caused by study conduct

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the AE may have been caused by the study conduct?

No:

- Due to external causes such as environmental factors or other treatment(s) being administered
- Due to the patient's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the course of the study
- Does not reappear or worsen when dosing with study participation is resumed

Yes:

- Could not be explained by environmental factors or other treatment(s) being administered
- Could not be explained by the patient's disease state or clinical condition
- Follow a reasonable temporal sequence following the course of the study
- Resolve or improve after discontinuation from study participation.
- Reappear or worsen when study participation is resumed

## 9.6. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with Regeneron or delegate(s) in a timely fashion. Regeneron or delegate(s) will monitor the safety data from across all study sites. Regeneron will have primary responsibility for the emerging safety profile of the compound. Safety monitoring will be performed on an ongoing basis (e.g., individual review of SAEs) and on a periodic cumulative aggregate basis.

Periodic (at least semi-annually or ad hoc as needed) meetings of the study safety monitoring team (SMT) will be conducted to review emerging safety data of the study treatments. The SMT will include at a minimum the Regeneron study monitor, Regeneron Risk Management lead for the study and the PNOC study chair or their designee. Other members of PNOC leadership may attend on an as needed basis.

Safety issues identified by the SMT can be escalated to the Regeneron Safety Oversight Committee (RSOC) per Regeneron's usual procedures. The RSOC is a standing committee that meets periodically or on an ad hoc basis, and includes senior leadership from clinical development, regulatory affairs, and pharmacovigilance. The RSOC serves as the Safety Oversight Committee for all Regeneron studies. The RSOC is empowered to require changes to a study, up to and including stopping a study or a specific cohort of a study, based on its assessment of the risks and potential benefits to study subjects. Any changes to this study will be communicated to Health Authorities and IRBs/ECs per regulatory requirements.

In addition, for this study, Regeneron is modifying their usual procedures in 2 ways: 1) any case of irreversible focal or non-focal neurologic toxicity, as described below, will be automatically escalated to RSOC for further consideration and 2) RSOC membership for safety matters related to this study will include, at a minimum, the PNOC study chair, or their designee. Other members of PNOC may attend on an as needed basis. The latter will ensure expertise at RSOC relevant to this study.

### 9.6.1. Safety Monitoring for Irreversible Neurological Events

A potential toxicity that is relatively unique to the pediatric brain tumor population set forth in this study is the potential for treatment-related (radiation + PD-1 blockade) intracranial swelling/edema that can result in irreversible focal or non-focal neurologic toxicity. This toxicity can occur/persist even after standard of care therapy for brain swelling, i.e., steroids and anti-angiogenic agents, has

been initiated. It is unknown if and how often such toxicity may occur. The natural history of these diseases also frequently involves irreversible neurologic deficit. Therefore, particular attention will be paid to the emergence of this potential toxicity.

For the purposes of this study, neurologic toxicity will be defined as intolerable grade 2 or any grade 3 or worse, treatment emergent focal or non-focal neurological toxicity that is not clearly due to either pseudo-progression or disease progression. Irreversible will be defined as toxicity that remains unimproved after 8 weeks of therapy including steroids and anti-angiogenic agents as described in Section 6.2.

Distinguishing irreversible neurologic toxicity that is directly related to drug versus disease status is difficult and best left to experts in this field. For this study, the primary responsibility for making this determination will be the PNOC study chair and co-chair or their designees.

## 9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the reference safety information in the Investigator's Brochure, and has a reasonable suspected causal relationship to the study drug by either investigator or sponsor).

## 9.8. Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- Leukemia secondary to oncology chemotherapy (eg, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

## 9.9. Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

# 10. RADIATION THERAPY GUIDELINES

## 10.1. General Guidelines

This study includes an efficacy study of REGN2810 in combination with radiation in patients with newly diagnosed DIPG and newly diagnosed and recurrent HGG. All patients in the efficacy phase

will receive radiation therapy with the targeted volume based on the extent of disease defined by neuroimaging prior to radiation therapy. This study specifies a 0 to 2 cm clinical target volume (CTV) margin (described in Section 10.7.2) and mandates the use of computed tomography-magnetic resonance (CT-MR) registration to define the target volume. The allowed treatment methods are restricted to conformal or intensity-modulated radiation therapy using photons and electronic data submission is required. Proton therapy is not allowed. All radiation is required to be done within a PNOC institution or PNOC-approved radiation center, due to the frequent safety monitoring and the need to follow protocol radiation guidelines.

## 10.2. Protocol-Defined Dose and Fractionation Schedules

The protocol-defined radiation therapy dose is specified according to tumor type and treatment arm.

**Newly Diagnosed DIPG Cohorts:**

- Arm 1, conventionally fractionated radiation:
  - Dose: 1.8 Gy fraction administered 5 times a week for 30 fractions; 54 Gy administered in total
  - Treatment Length: 42 days
- Arm 2, hypofractionated radiation delivered:
  - Dose: 3 Gy fraction administered 5 times a week for 13 fractions; 39 Gy administered in total
  - Treatment Length: 17 days

**Newly Diagnosed HGG Cohorts:**

- Arm 1, conventionally fractionated radiation:
  - Dose: 1.8 Gy fraction administered 5 times a week for 33 fractions; 59.4 Gy administered in total
  - Treatment Length: 45 days
- Arm 2: hypofractionated radiation:
  - Dose: 3 Gy fraction administered 5 times a week for 13 fractions; 39 Gy administered in total
  - Treatment Length: 17 days

**Recurrent HGG Cohorts:**

- Focal re-irradiation:
  - Dose: 3.5 Gy fraction administered 5 times a week for 10 fractions; 35 Gy administered in total
  - Treatment Length: 14 days

## 10.3. Treatment Planning Specifics

The goal of the treatment planning process is to develop a plan to deliver a uniform dose to the planning target volume that includes all known tumor plus the specified clinical target volume margin. The protocol-specified total dose for each cohort is listed in Section 10.2. The total dose does not exceed the recommended dose limits for the spinal cord and optic chiasm for the DIPG cohorts and so for these cohorts, volume reductions are not required nor recommended. Radiation therapy will be administered using photons. Required photon methods include 3D-conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT). Investigators using IMRT will be required to comply with the guidelines developed for the use of IMRT in National Cancer Institute sponsored cooperative group trials. These guidelines are available through www.qarc.org. These guidelines require that the protocol explicitly state their requirements and methods for localization and immobilization; the use of volumetric imaging; target and organ motion management; nomenclature, definitions and rationale for targets and organs at risk; target volume coverage and normal tissue dose constraints; effects of heterogeneity in tissues; and quality assurance.

## 10.4. Indications for Radiation Therapy

All patients enrolled on the efficacy phase of this protocol will receive concurrent REGN2810 and radiation therapy.

## 10.5. Timing

All patients should be seen in consultation by a radiation oncologist at the time of study enrollment. The purpose of the consultation is to participate in the initial evaluation and to review the adequacy of the initial diagnostic imaging studies that will be used for subsequent RT planning and the feasibility of reirradiation in the recurrent HGG cohort to the dose mandated in the protocol while maintaining brainstem, optic, and spinal cord tolerance. If additional imaging studies are pursued, thin section MR (T2-weighted and FLAIR) sequences should be obtained for registration to the CT dataset to assist in treatment planning.

Radiation should be administered within +/-3 days of initial administration of REGN2810.

Bevacizumab or corticosteroids should be used as clinically indicated and tapered as soon as possible.

Please see Section 6 and Section 6.2 for details of timing of REGN2810 administration. REGN2810 will be administered intravenously every 14 days and can be administered before or after each day's radiation therapy fraction.

### 10.5.1. Emergency Irradiation

Patients are not allowed to have received radiation therapy prior to enrollment on this protocol and urgent irradiation is not envisioned under any circumstance.

## 10.6. Equipment and Methods of Delivery and Verification

| Equipment | Photons (any energy) | IMRT (4-10MV) |
|---|---|---|
| Linear Accelerator | X | X |

### 10.6.1. Treatment Planning

Computed tomography (CT) (volumetric)-based planning is required to optimize dose to the planning target volume (PTV) while protecting normal tissues. Organs at risk within the irradiated volume should be contoured. A dose volume histogram (DVH) is necessary to determine target coverage and evaluate dose to normal tissues. Computed tomography section thickness should be ≤5 mm although 1-3 mm is preferred.

Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. Orthogonal paired (AP and lateral) portal images (MV or kV) are required for IMRT and 3D-CRT to verify that the isocenter is in correct alignment relative to the patient position.

Volumetric imaging is allowed in this study. This includes in-room kV or cone beam or conventional CT imaging. Please submit DICOM representative axial images showing the isocenter and the correct alignment in relationship to the patients' position. For CT here isocenters are not used, isodoses overlaid on the fused CT images can be submitted to demonstrate in-room verification.

## 10.7. Target Volumes

### 10.7.1. General Comments

International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62 (www.icru.org) define prescription methods and nomenclature that will be utilized for this study where applicable. Although the MRI obtained immediately prior to radiation therapy should be used for treatment planning, the target volumes for this study will be determined by the collective information that delineates the extent of disease before and after surgical resection or CSF shunting procedure. The investigators recognize that resection and shunting are unlikely for these patients. The sequence that best defines the extent of disease and post- operative tumor bed (when applicable) should be used to determine the gross tumor volume (GTV) and registered to the treatment planning CT. Most patients with DIPG and HGG require a combination of MR sequences to delineate the extent of disease. MR T2 and FLAIR sequences are most likely to be those chosen for registration to the treatment planning CT data set. The GTV, CTV, PTV and normal tissues must be outlined on all axial imaging slices on which the structures exist.

### 10.7.2. Definitions for Gross Tumor Volume, Clinical Target Volume, and Planning Target Volume

Gross tumor volume is based on the most recent MRI and/or post-operative MRI examination (if resection was done) and includes gross residual tumor and the tumor bed at the primary site. In defining the GTV, the investigator should consider all imaging studies that have defined the extent of tumor and the tissues involved anatomically. The GTV in most cases will be the T2 or FLAIR abnormality on the appropriate MR sequence. Tissue defects resulting from surgical approaches, when undertaken, will not be included as part of the GTV when not previously involved by tumor. Investigators should register the immediate pre-irradiation MR imaging sequences that demonstrated tumor and contour the GTV.

For patients enrolled in the newly diagnosed HGG cohort and randomized to conventional radiation, GTV1 and GTV2 can be developed as follows:

- The GTV1 is the enhancing and non-enhancing primary tumor volume as visualized on the treatment planning scan plus additional volume as characterized by tumor infiltration on the presurgical imaging. This should be outlined by translating the extent of presurgical infiltration using anatomical references onto the current treatment planning scans. The GTV2 is the enhancing and non-enhancing primary tumor volume as visualized on the treatment planning scan plus the surgical bed. This volume may be larger or smaller than the tumor visualized at diagnosis. Both GTV1 and GTV2 should only include imaging highly suspicious for gross tumor.
- Clinical target volume includes the GTV with an added margin of 1 cm for the DIPG cohort (DIPG patients) and an optional 0.5 cm for the recurrent HGG cohort (recurrent HGG patients). For the newly diagnosed HGG cohort, patients randomized to conventional fractionation will have a 2 cm CTV1 margin added to the GTV1 volume and a 1cm margin added to the CTV2 volume. For patients randomized to the hypofractionated regimen, the CTV will be created with an individualized 1-2 cm margin at the discretion of the treating radiation oncologist. For all cohorts the CTV expansion is meant to treat subclinical microscopic disease and is anatomically confined (ie, the CTV is limited to the confines of the bony calvarium, falx and tentorium where applicable, or extends up to but not beyond neuroanatomic structures through which tumor extension or invasion is certain not to have occurred). The CTV may be manually moved inward to the inner table of the bony calvarium. When the GTV approaches the boundary of an anatomic compartment, the CTV will extend up to and include the boundary. The CTV margin chosen for this study requires treatment planning MR and/or diagnostic MR imaging data with image section thickness ≤5 mm.
- PTV includes a margin that is added to the CTV in 3-dimensions. For the newly diagnosed HGG cohort randomized to conventional fractionation, a PTV1 corresponding to CTV1 and a PTV2 corresponding to CTV2 will be generated. PTVs are geometric and not anatomically defined. The PTV has two components, the internal margin (IM) and the set- up margin (SM). The IM is meant to compensate for all movements and variations in size and shape of the tissues contained within the CTV. The SM is meant to account for set-up, mechanical and dosimetric uncertainties related to daily patient positioning, treatment equipment and software. For this study, the PTV margin should be 3 or 5 mm. The use of a PTV margin of 3 mm requires written documentation that image-guided radiation therapy (IGRT) methods are used on a daily basis or alternatively that a head fixation system or verification system is used with weekly or more frequent imaging. For this study, IGRT is defined as 2- or 3-dimensional digital imaging positioning. Given that the CTV is generally confined to the intracranial space, the PTV may extend into or beyond bone but is unlikely to extend beyond the surface of the patient. The PTV margin chosen by the treating investigator requires treatment planning MR and/or diagnostic MR imaging data with imaging section thickness ≤ the chosen PTV margin.

## 10.8. Target Dose

### 10.8.1. Dose Definition

Photon dose is to be specified in centigray (cGy)-to-water.

### 10.8.2. Prescribed Dose and Fractionation

The total dose to the isodose surface encompasses the PTV will be as follows:

- **Newly diagnosed DIPG Cohorts (Arm 1):** 5400 cGy administered in 30 fractions of 180 cGy
- **Newly diagnosed DIPG Cohorts (Arm 2):** 3900 cGy administered in 13 fractions of 300 cGy
- **Newly diagnosed HGG Cohorts (Arm) 1:** 5940 cGy administered in 33 fractions of 180 cGy for PTV2, and 4500 in 25 fractions to PTV1
- **Newly diagnosed HGG Cohorts (Arm 2):** 3900 cGy administered in 13 fractions of 300 cGy
- **Recurrent HGG Cohorts:** 3500 cGy administered in 10 fractions of 350 cGy

The patient should be treated with 1 fraction per day. All fields should be treated each day.

### 10.8.3. Dose Uniformity

At least 95% of the protocol-specified dose should encompass 100% of the PTV and no more than 10% of the PTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. Wedges, compensators and other methods of generating more uniform dose distributions are encouraged.

### 10.8.4. Tissue Heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. For questions about heterogeneity corrections or approved algorithms, please contact the Study Chairs or refer to www.QARC.org.

### 10.8.5. Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for life threatening infection, severe hematological toxicity defined as ANC <300/μL or platelets less than 40,000/μL, or symptomatic pseudoprogression during the course of treatment. Blood product support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than 3 treatment days should be recorded in the patient treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size.

## 10.9. Treatment Technique

### 10.9.1. Beam Configuration

Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar) or IMRT are required to minimize dose to normal tissues.

### 10.9.2. Field Shaping

Field shaping will be done with either customized cerrobend blocking or multileaf collimation.

### 10.9.3. Simulation Including Patient Positioning and Immobilization

#### 10.9.3.1. Patient Positioning

Reproducible setups are critical. The patient may be treated in any appropriate, stable position. Consideration should be given to implications for inter- and intra-fraction motion when using non-standard position approaches.

#### 10.9.3.2. Immobilization Devices

Standard immobilization devices for the brain or head and neck are to be used. For IMRT delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the target volume with the patient in the treatment position.

#### 10.9.3.3. Special Considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

### 10.9.4. Motion Management and Margins to Account for Target Volume Changes During Treatment

Considering motion of target volumes is important. Brain tumors susceptible to cyst expansion should be monitored closely. Any change in clinical condition or anatomy related to hydrocephalus, VP shunt placement, subdural fluid, pseudomeningocele, or steroid use should be monitored carefully with repeat imaging when indicated.

## 10.10. Organs at Risk

The organ at risk guidelines in this section are recommendations. If the recommended doses to the organs at risk are exceeded because of target volume coverage requirements or other conditions, an explanation should be included in the quality assurance documentation. In some cases, photon IMRT may be the preferred treatment method to meet these recommendations and the required target volume coverage guidelines.

### 10.10.1. Dose Constraints

#### 10.10.1.1. Cochleae

- D50% ≤3500 cGy – Goal (each cochlea)
- D50% ≤2000 cGy – Preferred (each cochlea)
- Comment – There is no dose maximum for the cochleae.

- Structure definition — Each cochlea will be contoured on the treatment planning CT as a circular structure within the petrous portion of the temporal bone. The contour should appear on at least two successive CT images.

#### 10.10.1.2. Optic Globes

- D10% ≤3500 cGy – Goal
- D10% ≤5400 cGy – Maximum
- Comment – Effort should be made to avoid direct treatment of the anterior chamber of the eye and minimize dose to the entire eye without compromising target volume coverage. In the event that the recommended maximum dose constraints provided in this section would be exceeded, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure definition — Each eye should be separately contoured on the treatment planning CT or MR as a circular structure from the most superior to inferior aspect.

#### 10.10.1.3. Right and Left Optic Nerves and Chiasm

- Newly diagnosed DIPG and HGG cohort:
  - D10% ≤5600 cGy – Goal
  - D90% ≤5400 cGy, D50% ≤5600 cGy and D10% ≤5800 cGy – Maximum
- Recurrent HGG cohort
  - D90% ≤1000 cGy, Dmax ≤1200 cGy – Maximum
- Comment – These parameters apply to each of the separate three structures, not the combined volume of the three structures. Effort should be made to avoid direct treatment of the optic nerves and chiasm without compromising target volume coverage. In the event that the recommended maximum dose constraints provided in this section would be exceeded, the treating radiation oncologist may use his/her discretion to reduce target volume coverage.
- Structure definitions – The optic nerves and chiasm may be contoured on CT or MR. The contours should appear on at least two successive CT or MR images.
- Note: Dose constraints specified for the recurrent HGG cohort are only applicable in cases where a significant prior dose (Dmax<=42 Gy) was delivered to the optic nerves and chiasm or the prior dose to the optic nerves and chiasm is uncertain. In cases where a lower previous dose was administered to these structures and can be documented, a higher constraint will be considered on a case by case basis.

#### 10.10.1.4. Spinal Cord

- Newly diagnosed DIPG cohort:
  - D10% ≤5700 cGy – Goal
  - D10% ≤5900 cGy – Maximum

- Newly diagnosed HGG cohort
  - Dmax = 5000 cGy — Maximum
- Recurrent HGG cohort:
  - D90% ≤1000 cGy, Dmax ≤1200 cGy – Maximum
- Comment – Effort should be made to minimize dose to the spinal cord without compromising target volume coverage.
- Structure Definition — For the purposes of this study, the upper aspect of the spinal cord begins at the inferior border of the foramen magnum and should be contoured on the treatment planning CT. For purposes of comparison and consistency with dose volume data, the spinal cord should be contoured on a number of images to be determined by the image section thickness (CT section thickness, n=number of images; 2 mm, n=30; 2.5 mm, n=24; 3 mm, n=20). Using these guidelines, only the superior-most 6 cm of anatomic spinal cord is contoured.
- Note: Dose constraints specified for the recurrent HGG cohort are only applicable in cases where a significant prior dose (Dmax<=33 Gy) was delivered to the spinal cord or the prior dose to the spinal cord is uncertain. In cases where a lower previous dose was administered to these structures and can be documented, a higher constraint will be considered on a case by case basis.

#### 10.10.1.5. Brainstem

- Recurrent HGG cohort (recurrent HGG patients):
  - D90% ≤1000 cGy, Dmax ≤1200 cGy – Maximum
- Newly diagnosed HGG cohort
  - Effort should be made to minimize the amount of brainstem, if any, receiving more than 5400 cGy
- Comment – Effort should be made to minimize dose to the brainstem without compromising target volume coverage.
- Structure Definition — For the purposes of this study, the lower aspect of the brainstem begins above the inferior border of the foramen magnum and should be contoured on the treatment planning CT.
- Note: Dose constraints specified for the recurrent HGG cohort are only applicable in cases where a significant prior dose (Dmax≤42 Gy) was delivered to the brainstem or the prior dose to the brainstem is uncertain. In cases where a lower previous dose was administered to these structures and can be documented, a higher constraint will be considered on a case by case basis.

## 10.11. Dose Calculations and Reporting

### 10.11.1. Prescribed Dose

The dose prescription and fractionation shall be reported. The total dose delivered shall also be reported. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry.

### 10.11.2. Normal Tissue Dosimetry

The dose to the critical organs indicated (Table 18) should be calculated whenever they are directly included in a radiation field. The total dose shall be calculated and reported. The appropriate dose-volume histograms should be submitted. If IMRT is used for the primary tumor, a DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

**Table 18: Required DVH data**

| Required DVH |
|---|
| Total Brain |
| Optic Nerves (L+R) |
| Optic Chiasm |
| Optic Globes (L+R) |
| Brainstem |
| Spinal Cord |
| Cochleae (L+R) |
| Unspecified Tissue |

## 10.12. Quality Assurance Documentation

On-treatment review is NOT required for this study. Within 1 week of the completion of radiation therapy, detailed treatment data shall be submitted.

### 10.12.1. External Beam Treatment Planning System

- Digitally reconstructed radiographs (DRR) or simulator films for each treatment field and orthogonal (anterior/posterior and lateral) images for isocenter localization for each group of concurrently treated beams. When using IMRT, orthogonal isocenter images are sufficient.
- Isodose distributions for the treatment plan in the axial, sagittal and coronal planes at the center of the treatment or planning target volume. The planning target volume, isocenter and the normalization method must be clearly indicated.

- DVH for all target volumes and required organs at risk. A DVH shall be submitted for the organs at risk specified in Section 10.10. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Beams-eye-view (BEV) of portals showing collimator, beam aperture, target volume and critical structures are required when not using IMRT.

#### 10.12.2. Digital Data

Submission of the treatment plan and all data in DICOM format is required. The information should be transferred via a secure Partners Healthcare Interface (transfer.partners.org). Participating centers will be invited to create an account within this system by study staff. If there are any problems with digital data submission, please contact the Study Chairs.

#### 10.12.3. Supportive Data

A complete digital representation of the radiotherapy treatment plan, sufficient to fully reconstruct the plan in our system, must be uploaded in DICOM/DICOM RT format. This includes all diagnostic imaging (CT or MR PRIOR to surgical resection or primary tumor) and DICOM RT formatted files for the RT PLAN, RT STRUCTURE SET, and RT DOSE. If image registration was used to link CT to MR images, the image data may be uploaded either as reformatted images co-registered to the same frame of reference OR by providing the spatial registration in DICOM format. The RT Dose file should contain the dose matrix representing the total dose for all fields in the treatment plan in absolute dose. Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.

If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the radiation oncology reviewers.

If a PTV margin of 3 mm is used, written documentation that IGRT methods are used on a daily basis or alternatively that a head fixation system or verification system was used with weekly or more frequent imaging will be provided. See Section 10.12.

# 11. EVALUATION CRITERIA

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria.

## 11.1. Definitions

### 11.1.1. Evaluable for Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with REGN2810.

### 11.1.2. Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

### 11.1.3. Immunotherapy Response Assessment in Neuro-Oncology (iRANO) Criteria

Immunotherapeutic approaches for children with gliomas are a relatively new era and therefore we have limited experience on how to monitor response. Recently the Immunotherapy Response Assessment in Neuro-Oncology (iRANO) working group has proposed guidelines on how to monitor and assess efficacy in adult brain tumor patients treated with immunotherapy as a development of the iRANO criteria that were established to better account for the phenomenon of pseudo-progression in adult patients[58,59]. The pediatric neuro-oncology (RAPNO) working group is currently working on their guidelines for response criteria for pediatric neuro-oncology patients[60]. Our limited experience with immunotherapies have shown that early radiological changes could be misinterpreted as progression due to therapy-induced inflammation, and long-term benefit can still be seen even after initial progression or even after the appearance of new lesions[61,62].

## 11.2. Disease Parameters

### 11.2.1. Solid Tumors

The parameters below are adopted directly from published Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[63]

#### 11.2.1.1. Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with computed tomography (CT) scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

#### 11.2.1.2. Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

#### 11.2.1.3. Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. This includes bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI).

Cystic lesions that meet the criteria for radiographically-defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

### 11.2.2. Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should a) be selected based on the largest measurable lesions, b) appropriately represent involved organs, and c) be reproducibly measurable. The longest diameter of target lesions should be measured in the plane from which the images were taken. The longest measured diameters for each lesion should be recorded as the baseline sum diameters and used to objectively measure treatment response.

### 11.2.3. Non-Target Lesions

All other lesions (or sites of disease) including measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions is not required. These lesions will be followed as "present," "absent," or "unequivocal progression."

## 11.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline assessments should be done as close as possible to treatment start and per study requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

### 11.3.1. Chest X-Ray

Chest computed tomography (CT) is the preferred method of assessment for lesions in the chest, specifically when assessing treatment response. Lesions on chest x-ray can be considered measurable if they are clearly defined and surrounded by aerated lung.

### 11.3.2. Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain

situations (e.g. for body scans). Ideally, the same acquisition protocol should be followed as closely as possible to comparison scans.

### 11.3.3. Ultrasound

Ultrasound is not considered a useful modality to assess lesion size and should not be used for target lesion measurement.

### 11.3.4. Positron Emission Tomography-Computed Tomography

At present, the low dose or attenuation correction CT portion of a combined Positron Emission Tomography-CT (PET-CT) scan is limited in its use for diagnostic and treatment effect evaluations and should not substituted for a complete diagnostic CT. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements. The PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

### 11.3.5. Tumor Markers

Tumor markers alone cannot be used to assess objective response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

### 11.3.6. Cytology and Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases such as residual lesions in tumor types, i.e. germ cell tumors, where known residual benign tumors can remain.

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

### 11.3.7. FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions based on FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progressive disease (PD) based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing based on the anatomic images, this is not

PD. A 'positive' FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

## 11.4. Response Criteria

### 11.4.1. Response Criteria for Patients with Solid Tumors and Measurable Disease: Evaluation of Target Lesions

Response criteria for primary tumors outside the CNS will be evaluated per RECIST1.1. Immune-related RECIST (irRECIST) will also be considered.

**Complete Response**

Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology.

**Partial Response**

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease**

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

**NOTE:** The appearance of 1 or more new lesions is also considered progression. See Section 11.4.5.4 for exceptions.

**NOTE:** In the presence of stable disease (SD) or PR in target disease but "unequivocal progression" in non-target lesions, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

**Stable Disease**

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

### 11.4.2. Response Criteria for Patients with Solid Tumors and Evaluable Disease

**Evaluable Disease**

The presence of at least 1 lesion, with no lesion that can be accurately measured in at least 1 dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

**Complete Response**

Disappearance of all evaluable disease and normalization of tumor markers, as appropriate. All lymph nodes must be non-pathological in size (<10mm short axis).

**Non-complete Response and Non-progressive Disease**

Persistence of >1 non-target lesion and/or maintenance of tumor markers above normal limits.

**Progressive Disease**

Unequivocal progression of non-target lesions and/or the appearance of 1 or more new lesions and/or elevation in tumor markers.

### 11.4.3. Response Criteria for Neuroblastoma Patients with Metaiodobenzylguanidine-Positive Lesions

#### 11.4.3.1. Metaiodobenzylguanidine-Positive Lesions

Per the International Neuroblastoma Response Criteria, assessment of disease response will incorporate response in the primary tumor as well as soft tissue and bone metastases, the following assessments are adopted directly from these recommendations.[64] Primary and metastatic soft tissue sites will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) and iodine-123 [$^{123}$I]–metaiodobenzylguanidine (MIBG) scans or [$^{18}$F]fluorodeoxyglucose–positron emission tomography scans if the tumor is MIBG nonavid. $^{123}$I-MIBG scans, or [$^{18}$F]fluorodeoxyglucose–positron emission tomography scans for MIBG-nonavid disease should be done instead of technetium-99m diphosphonate bone scintigraphy for osteomedullary metastasis assessment.

Bone marrow will be assessed by histology or immunohistochemistry and cytology or immunocytology. Bone marrow with ≤5% tumor involvement will be classified as minimal disease.

Urinary catecholamine levels will *not* be included in response assessment.

Overall response will be defined as complete response, partial response, minor response, stable disease, or progressive disease.

#### 11.4.3.2. Primary Soft Tissue Disease

**Complete Response**

<10 mm residual soft tissue at primary site AND complete response of MIBG or FDG-PET uptake (for MIBG-nonavid tumors) at primary site

**Partial Response**

≥30% decrease in longest diameter of primary site AND MIBG or FDG-PET uptake at primary site stable, improved, or resolved

**Stable Disease**

Neither sufficient shrinkage for partial response nor sufficient increase for progressive disease at the primary site

**Progressive Disease**

>20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5 mm in longest diameter

#### 11.4.3.3. Metastatic Soft Tissue and Bone Disease

**Complete Response**

Non-primary target and nontarget lesions measure <10 mm AND lymph nodes identified as target lesions decrease to a short axis <10 mm AND complete response of MIBG or FDG-PET uptake (for MIBG-nonavid tumors) at non-primary lesions

**Partial Response**

≥30% decrease sum of diameters of nonprimary target lesions compared with baseline AND nontarget lesions may be stable or smaller in size AND no new lesions AND ≥50% reduction in MIBG absolute bone score or ≥50% reduction in number of FDG-PET-avid bone lesions

**Stable Disease**

Neither sufficient shrinkage for partial response nor sufficient increase for progressive disease at the nonprimary lesions

**Progressive Disease**

Any new soft tissue lesion detected by CT/MRI that is also MIBG- or FDG-PET-avid OR any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be neuroblastoma or ganglioneuroblastoma OR any new bone site that is MIBG-avid OR a new bone site that is FDG-PET-avid (for non-MIBG-avid tumors) and also has CT/MRI findings consistent with tumor or if confirmed by histology OR ≥20% increase in the longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) and minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions OR relative MIBG score ≥1.2

#### 11.4.3.4. Bone Marrow Disease

**Complete Response**

Bone marrow with no tumor involvement on reassessment, independent of baseline tumor involvement

**Minimal Disease**

Bone marrow with ≤5% tumor involvement and remains >0 to ≤5% tumor involvement on reassessment OR bone marrow with >20% tumor involvement that has >0 to ≤5% tumor involvement on reassessment

**Stable Disease**

Bone marrow with tumor infiltration that remains positive with >5% tumor involvement on reassessment that does not meet other disease criteria

**Progressive Disease**

Bone marrow without tumor infiltration that becomes >5% tumor involvement on reassessment OR bone marrow with tumor involvement that increases by >2-fold and has >20% tumor involvement on reassessment

#### 11.4.3.5. Overall Response

- **Complete Response:** All components that meet the criteria for complete response

- **Partial Response:** Partial response in at least one component and all other components are either complete response, minimal disease (bone marrow), partial response (soft tissue or bone), or no involvement; no component of progressive disease
- **Minor Response:** Partial response or complete response in at least one component but at least one other component with stable disease; no component of progressive disease
- **Stable Disease:** Stable disease in one component with no better than stable disease or no involvement in any other component; no component of progressive disease
- **Progressive Disease:** Any component with progressive disease

#### 11.4.3.6. Scoring Based on Relative Curie Score

Relative score is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

- **Complete Response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a CR.
- **Partial Response:** Relative score ≤0.2 (lesions almost disappeared) to ≤0.5 (lesions strongly reduced).
- **Stable Disease:** Relative score >0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
- **Progressive Disease:** New lesions on MIBG scan.

### 11.4.4. Response Criteria for Solid Tumor Patients with Bone Marrow Involvement

Bone marrow involvement is defined as bone marrow obtained within 28 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on 1 bone marrow sample.

Bone marrow responses are determined by H&E staining of bilateral bone marrow biopsies and aspirates.

**Complete Response**

No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

**Progressive Disease**

Patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by

morphology must increase to ≥25% tumor to have progressive disease; a patient entering with 30% tumor must increase to >60%.) Patients who enroll without evidence of neuroblastoma in bone marrow will be defined as having progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 21 days apart.

**Stable Disease**

Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

### 11.4.5. Response Criteria for Central Nervous System Tumors

Response criteria for CNS tumors will be evaluated per RANO criteria with the addition of iRANO criteria as a supplement to evaluation, as appropriate.[65,66] Patients will have their response classified according to the definitions stated below.

#### 11.4.5.1. Measurable Disease

Measurable disease is defined as the lesions (or lesions) that can be accurately measured in at least 2 dimensions by MRI (no less than double the slice thickness). All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Tumor response criteria for this study are to be determined by changes in size using the maximal 2-dimensional cross-sectional tumor measurements, T x W (product of the longest diameter of the tumor [width (W)] and its longest perpendicular diameter [transverse (T)]), using either T1 or T2 weighted images (which ever gives the best estimate of tumor size).

The following section describes the methodology:

1. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow-ups.
2. The longest measurement of the tumor (or width, W) should be determined.
3. The 2 perpendicular measurements should be determined (transverse [T]) measurement-perpendicular to the width (W) in the selected plane

**Target Lesions**

All measurable lesions up to a maximum of 5 lesions total, representative of all involved areas, should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (largest) and their suitability for accurate repeated measurements.

#### 11.4.5.2. Non-Measurable Disease

Non-measurable disease is all other lesions (or sites of disease), including leptomeningeal disease.

#### 11.4.5.3. Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up.

#### 11.4.5.4. Response Criteria, per RANO Criteria and Allowing for Integration of iRANO Criteria to Supplement RANO Criteria as Appropriate

**Complete Response**

Disappearance of all enhancing lesions, determined by two separate observations conducted not less than 4 weeks apart. Stable or improved T2/FLAIR non-enhancing lesions. There can be no appearance of new lesions.

**Partial Response**

At least a 50% decrease in the size of enhancing target lesions, taking as reference to the baseline MRI and determined by two separate observations conducted not less than 4 weeks apart. Stable or improved T2/FLAIR non-enhancing lesions. There can be no appearance of new lesions.

**Stable Disease**

Neither sufficient shrinkage to qualify for complete response or partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest target size since the treatment started. Stable or improved T2/FLAIR non—enhancing lesions. There can be no appearance of new lesions.

**Progressive Disease**

At least a 25% increase in the sum of the size of enhancing target lesions, taking as reference the smallest target size since the treatment started that is confirmed on a 3-month follow-up scan as long as the patient is NOT experiencing significant neurological decline (defined as CTCAE grade 3 or higher). The confirmatory scan requirement will assure that patients are not prematurely assigned to have progressive disease while receiving immune-based therapy. In addition, the appearance of new lesions might be part of an immune response and if the patient is clinically stable, these should be confirmed on a 3-month follow-up scan to assess for true progressive disease versus pseudoprogression. This will apply to patients that demonstrate worsening of the MRI within 6 months of start of therapy. Patients who develop worsening radiographic findings >6 months from start of immunotherapy are expected to have a low likelihood of ultimately deriving benefit from the therapy and should be considered PD based on imaging if they have a 50% increase in size of the target lesion or if new lesions appear.

Patients who experience significant clinical decline or those who have radiographic progression on the 3-month follow-up scan should be classified as progressive disease and the date of progression should be entered as the first MRI that showed progressive disease.

If the follow-up 3-month scan shows stabilization or reduction of tumor size in the setting of stable clinical examination and absence of increased use of steroid treatment, the patient will be classified as having pseudoprogression and will continue on study therapy.

If feasible, we recommend to obtain tissue if imaging is concerning for progression as tissue evaluation remains the gold standard to differentiate between pseudoprogression versus true progression. If pathology mainly consists of recurrent tumor, the patient should be considered to have true tumor progression and be taken off study. If the tissue mainly consists of gliosis and

inflammation (consistent with treatment effect) the patient should be classified has having pseudoprogression and should remain on study. Patients that have tissue available will be centrally reviewed at UCSF.

In cases for which it remains difficult to differentiate between progression versus pseudo-progression, the PI should discuss with the study chair the possibility of continuation of therapy. Images will also be centrally reviewed at UCSF. Continuation of therapy might be considered if the patient derives clinical benefit with acceptable toxicity.

This is applicable for imaging findings within the first 6 months since start of immunotherapy.

## 11.5. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment to the end of the study. The reference for progressive disease is the smallest measurements recorded since the treatment started. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

## 11.6. Duration of Response

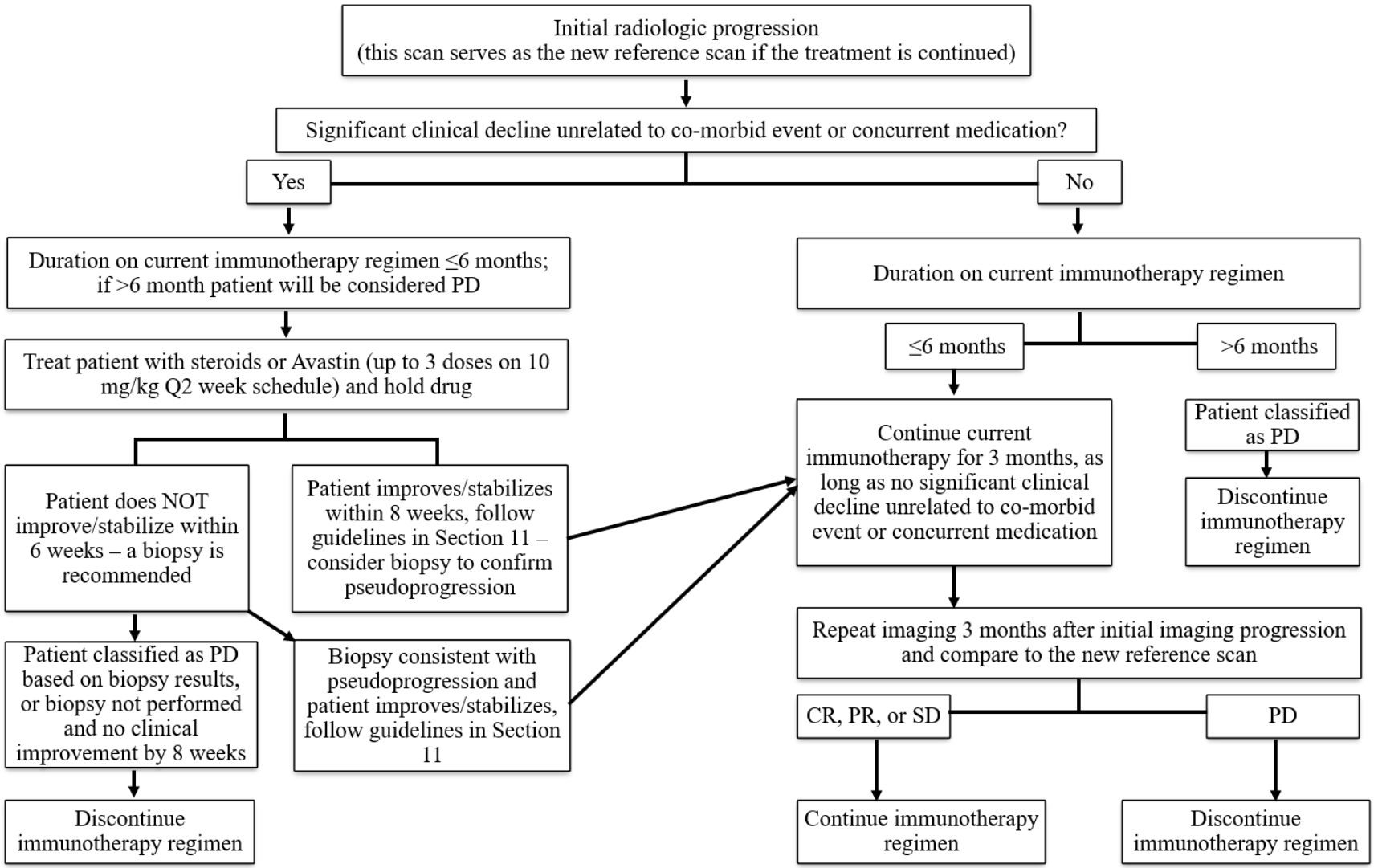
Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

## 11.7. Additional Guidelines for Response Criteria for CNS Tumors

**Figure 7: Additional Guidelines for Response Criteria for CNS Tumors**



# 12. STATISTICAL CONSIDERATIONS

## 12.1. Study Endpoints

Study endpoints are provided below. Study objectives are provided in Section 1. Evaluation criteria definitions are provided in Section 11.4.

### 12.1.1. Primary Endpoints

**Phase 1**

- Safety, as measured by the incidence and severity of treatment-emergent adverse events (TEAEs)/immune-related adverse events (irAEs)/adverse events of special interest (AESIs) / serious adverse events (SAEs), deaths, and laboratory abnormalities (grade 3 or higher per version 4.0 of Common Terminology Criteria for Adverse Events (CTCAE v4.0), from initiation of study treatment until 90 days after the last study treatment (or until the patient receives another systemic anticancer therapy, whichever is earlier)
- Tolerability, as measured by the incidence of DLTs from the first dose of REGN2810 through the end of the DLT observation period for cemiplimab given as monotherapy
- PK for REGN2810 given as monotherapy in pediatric patients

**Efficacy Phase**

- Incidence and severity of TEAEs, irAEs, AESIs, SAEs, deaths, and laboratory abnormalities (Grade 3 or higher per CTCAE v4.0) for REGN2810 given in combination with radiation therapy, from initiation of study treatment until 90 days after the last study treatment (or until the patient receives another systemic anticancer therapy, whichever is earlier)
- Incidence of DLTs during the DLT observation period for REGN2810 given in combination with radiation therapy
- PK for REGN2810 given as given in combination with radiation therapy in pediatric patients
- Overall survival at 12 months (OS12) among newly diagnosed DIPG patients and recurrent HGG patients, respectively.

  OS is defined as the time from randomization to the date of death due to any cause. A patient who has not died will be censored at the last date that patient is documented to be alive.
- Progression-free survival at 12 months (PFS12) among newly diagnosed HGG patients.

  PFS is defined as the time from randomization to the date of the first documented tumor progression, as determined per RANO/iRANO criteria, or death due to any cause. 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

### 12.1.2. Secondary Endpoints

**Phase 1**

- Objective response rate (ORR). ORR is defined as the percentage of patients who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR).

  BOR is defined as the best overall response, as determined per RECIST 1.1/irRECIST criteria for solid tumors and per RANO/iRANO criteria for CNS tumors, between the date of first dose of REGN2810 and the date of the first objectively documented progression or the date of receiving another anticancer systemic therapy, whichever comes first.
- Anti-drug antibody (ADA) assessments for REGN2810 given as monotherapy

**Efficacy Phase**

- ADA assessments for REGN2810 given in combination with radiation therapy

### 12.1.3. Exploratory Endpoints

**Phase 1 and Efficacy Phase**

- Quality of Life (QoL), as measured using Pediatric Quality of Life (PedsQL) for younger age group 2 to <18 years
- QoL, as measured using the Functional Assessment of Cancer Therapy-Brain (FACT-Br) for older age group 18 to 25 years.
- Circulating tumor cells, biomarker data, circulating cytokines, and peripheral blood mononucleated cells (PBMC), tumor expression of PD-L1 for biomarker and correlative studies

## 12.2. Sample Size

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)

In total, a minimum of 100 patients (20 patients per pooled treatment arm at the respective confirmed RP2D) will be enrolled in the Efficacy Phase. The justification of sample size is described in Section 12.3.

## 12.3. 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%)[67]. 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%[68]. 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.

## 12.4. Criteria to be Evaluable for Efficacy and Toxicity

As per *Intention to Treat* analyses, any patient who receives at least one dose of REGN2810 will be evaluable for efficacy and toxicity.

As *Per Protocol* analyses, there will be separate criteria to be considered evaluable for efficacy and DLT. Patients who receive less than 85% of the prescribed dose of REGN2810 or who receive less than the required percentage of radiation during the DLT period within each cohort (as per description and tables below), may not be evaluable for efficacy or toxicity in the *Per Protocol* analyses (and may be replaced by another enrollee as per replacement criteria).

Due to the known role of radiation in the treatment of newly diagnosed DIPG and HGG, we will require patients receive at least 90% of intended radiation dosing to be evaluable for toxicity or efficacy in the *Per Protocol* analyses. This includes the following minimum fractions for each newly diagnosed cohort:

| **Cohort** | **Minimum # of radiation fractions for *Per Protocol* analyses** | |
|---|---|---|
| Newly diagnosed DIPG | *Conventional fractionation* | 27 |
| | *Hypofractionation* | 12 |
| Newly diagnosed HGG | *Conventional fractionation* | 30 |
| | *Hypofractionation* | 12 |

Due to the lesser known role of radiation in the treatment of recurrent HGG, we will require patients received at least 80% of intended radiation dosing to be evaluable for toxicity or efficacy in the *Per Protocol* analyses. This includes the following minimum fractions for each newly diagnosed cohort:

| Cohort | Minimum # of radiation fractions for *Per Protocol* analyses |
|---|---|
| Recurrent HGG | 8 |

## 12.5. Replacement Criteria

Patients who come off study during the DLT period for reasons other than a DLT or progression and who receive less than 85% of the prescribed dose of REGN2810 or who receive less than the required percentage of radiation during the DLT period within each cohort may not be applied toward the final enrollment number and may be considered for replacement by another enrollee. Final decisions for replacement will be determined by the study chairs.

The study team will review all instances of patients coming off study for reasons other than DLT or progression during the DLT period in order to ensure that patients are being treated with adequate therapy, before moving into the expansion phase of each cohort.

## 12.6. Stratification Factors for the Efficacy Phase of the Study

Within the efficacy phase of the study, the trial will enroll into cohorts based on disease: newly diagnosed DIPG cohort, newly diagnosed HGG cohort, and recurrent HGG cohort. The newly diagnosed DIPG and newly diagnosed HGG cohorts will include 2 radiation arms: Arm 1 will follow a conventionally fractionated radiation schedule; Arm 2 will follow a hypofractionated radiation schedule. Randomization within the 3 to <12 years age group of the newly diagnosed DIPG and HGG cohorts will occur once the RP2D has been confirmed for this age group in Phase 1. Randomization within the 12 to 25 years age group will occur at the anticipated RP2D at time of enrollment.

## 12.7. Analysis of Primary Endpoints

### 12.7.1. Phase 1: RP2D and Pharmacokinetics

- RP2D will be determined based on the MTD in each age and disease cohort, as applicable. It is possible more than 1 RP2D will be identified in each age cohort and between solid or CNS tumors.
- PK parameters will include but will not be limited to concentrations at pre-dose, end-of Infusion (Ceoi) after the first dose and during treatment. $AUC_{2w}$ and estimated t1/2 after the first dose will be determined by non-compartmental analysis.
- The PK analysis set will include all enrolled patients who received any study drug (safety population) and who had at least 1 REGN2810 concentration following the first dose.

### 12.7.2. Efficacy Phase: RP2D and Efficacy

- RP2D will be determined based on the MTD in each age group of each CNS tumor cohort and radiation arm. It is possible more than 1 RP2D will be identified in each CNS tumor cohort and each radiation arm.
- For the DIPG cohort, assuming 20 eligible patients in each arm, if in each arm 12 or more patients are alive at 12 months, the null hypothesis for that arm will be rejected and efficacy as demonstrated by improving OS12 will have been demonstrated. See Section 12.2 and Section 12.3 for details of sample size considerations.
- For the newly diagnosed HGG cohort, assuming 20 eligible patients in each arm, if 14 or more patients do not experience disease progression at 12 months, the null hypothesis for that arm will be rejected and efficacy as demonstrated by improving PFS12 will have been demonstrated. See Section 12.2 and Section 12.3 for details of sample size considerations.
- For the recurrent HGG cohort, assuming 20 eligible patients, if 12 or more patients are alive at 12 months, the null hypothesis for that arm will be rejected and efficacy as demonstrated by improving OS12 will have been demonstrated. See Section 12.2 and Section 12.3 for details of sample size consideration.
- Safety and toxicity measurements of repeated administration of REGN2810 using CTCAE version 4.0 in children.

### 12.7.3. Efficacy Phase: Pharmacokinetics

- PK parameters will include but will not be limited to concentrations at pre-dose, Ceoi after the first dose and during treatment. $AUC_{2w}$ and estimated t1/2 after the first dose will be determined by non-compartmental analysis.
- The PK analysis set will include all randomized patients who received any study drug (safety population) and who had at least 1 REGN2810 concentration following the first dose.

## 12.8. Analysis of Secondary Endpoints

### 12.8.1. Phase 1: Objective Response

- Objective response will be for descriptive purposes only in the phase 1 of this study. No formal hypothesis testing will be performed on efficacy. Objective tumor response is determined according to Section 10.

### 12.8.2. Efficacy Phase: Toxicity Profile

- All AEs reported in this study will be listed and summarized according to CNS tumor type and radiation arm.
- AEs will be collected for descriptive purposes. No formal hypothesis will be performed on the AEs. Results will potentially be used as reference for future clinical trials.

### 12.8.3. Phase 1 and Efficacy Phase: ADA

- ADA analysis will be conducted on serum samples for anti-REGN2810 antibody at time points according to the Schedules of Events
- The ADA population includes all treated patients who received any amount of study drug and who had at least 1 non-missing result in the ADA assay following the first dose of the study drug.

Anti-drug antibody variables include ADA response status and titer as follows:

- Total patients with preexisting immunoreactivity
- Total patients with treatment-emergent response
- Total patients with treatment-boosted response
- Titer values (Titer value category)
    - Low (Titer <1000)
    - Moderate (1,000 ≤ Titer ≤10,000)
    - High (Titer >10,000)

## 12.9. Analysis of Exploratory Endpoints

### 12.9.1. Phase 1 and Efficacy Phase: Quality of Life

- Quality of life will be measured using the Pediatric Quality of Life Inventory (PedsQL) in patients aged 2 to <18 years
- Quality of life will be measured using the Functional Assessment of Cancer Therapy-Brain (FACT-Br) in patients aged 18 to 25 years
- Quality of life will be collected for descriptive purposes. No formal hypothesis will be performed on the Quality of Life. Results will potentially be used as reference for future clinical trials.

### 12.9.2. Phase 1 and Efficacy Phase: Biology Studies

- Circulating tumor cells will be analyzed using standard scientific and statistical methods and summarized by phase, age, tumor type, and radiation arm
- Biomarker data, circulating cytokines, and PBMC results will be analyzed using standard scientific and statistical methods and summarized by phase, age, tumor type, and radiation arm
- Analyses of correlative scientific endpoints are largely exploratory and hypothesis generating. Any promising findings will be tested in future studies. All analyses will be descriptive in nature; however, statistical power is provided below in order to provide a sense of precision for the proposed analyses.

Regarding PD-L1 expression in tumor tissue, an unpaired t-test will be used to compare % positive tumor cells in responders compared to non-responders. Responders will be determined using the

primary endpoint of the trial – overall survival at 12 months. Based on prior data obtained in adult gliomas it is assumed that approximately 60% of tumors will express PD-L1[35].

To give a sense of power for studies to be done on paired blood samples (paired within patient comparing baseline and on-treatment) for analyses of T-cell subsets, myeloid-derived suppressor cells, immunologic cytokines and antibodies, differences will be taken for all measures and the hypothesis is that markers of immune response (e.g., antibody titer, levels of antigen reactive T-cells) should increase post-therapy. Assuming that within each cohort we will obtain the accrual of at least 20 patients, using a one-sided 0.10 level paired t-test, there is at least 80% power to detect a 0.58 standard deviation change in mean of a quantitative correlative parameter using a one-sided test with 5% type I error. Thus, with a modest level of consent for these studies there is sufficient power for meaningful analyses. Power for these tests will be further improved with greater numbers.

# 13. PHARMACEUTICAL INFORMATION

## 13.1. Agent

### 13.1.1. Agent - REGN2810

**Product description:** REGN2810 is an investigational agent supplied by Regeneron.

REGN2810 will be supplied as a liquid in sterile, single-use vials. Each vial will contain REGN2810 at a concentration of 50 mg/mL.

Instructions on dose preparation are provided in the study reference manuals.

REGN2810 will be administered in an inpatient or outpatient setting as a 30-minute IV infusion. Each patient's dose will depend on individual body weight. The dose of REGN2810 must be adjusted each cycle for changes in body weight of ≥10%. Dose adjustments for changes in body weight of <10% will be at the discretion of the investigator. REGN2810 will be administered alone or in combination with radiation. A pharmacist or other qualified individual will be identified at each site to prepare REGN2810 for administration.

## 13.2. Treatment Logistics and Accountability

### 13.2.1. Drug Ordering

Study drug supply will be managed by an IWRS, which will assign treatment for each patient dosing visit. Member sites should refer to SharePoint about details for drug ordering.

### 13.2.2. Packaging, Labeling and Storage

Open-label study drug will display the product lot number on the label. Study drug will be stored at the site at a temperature of 2°C to 8°C; storage instructions will be provided in the pharmacy manual.

### 13.2.3. Supply and Disposition

Study drug will be shipped at a temperature of 2° to 8°C to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

### 13.2.4. Solution Preparation

Detailed preparation and administration instructions will be provided to the sites in the study reference manuals.

### 13.2.5. Storage Requirements

Open-label REGN2810 will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. Each vial will contain REGN2810 at a concentration of 50 mg/mL. REGN2810 will be refrigerated at the site at a temperature of 2° to 8°C, and refrigerator temperature will be logged daily. Further storage instructions will be provided in the study reference manual.

### 13.2.6. Stability

Details regarding RENG2810 infusion bag stability are provided in the pharmacy manual.

### 13.2.7. Route of Administration

REGN2810 will be administered in an outpatient setting as a 30-minute IV infusion every 14 days. Each patient's dose will depend on individual body weight. The dose of REGN2810 must be adjusted each cycle for changes in body weight of ≥10%. Dose adjustments for changes in body weight of <10% will be at the discretion of the investigator.

### 13.2.8. Accountability

The investigator, or a responsible party designated by the investigator, will be responsible for drug accountability and this should be managed per each PNOC institutions' guidelines.

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

### 13.2.9. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

# 14. REPORTING AND EXCLUSIONS

## 14.1. Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with REGN2810.

## 14.2. Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned 1 of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (**Note:** By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.)

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

# 15. REGISTRATION PROCEDURES

## 15.1. General Guidelines

Patients must meet all inclusion criteria and cannot meet any exclusion criteria. The patient or LAR must have signed and dated an approved, current version of all applicable consent forms. To allow non-English speaking patients to participate in this study, bilingual health services will be provided in the appropriate language when feasible.

Registration materials will be submitted to the PNOC Operations Office as described below. The PNOC Operations Office will check the registration materials for completeness and contact the site with any discrepancies.

The PNOC Operations Office will forward the eligibility checklist, including source documentation to the Study Chair or Co-Chair as well as the Project Leader or Co-Project Leader of PNOC for review of eligibility and signoff.

Patient eligibility will be reviewed in OnCore®. Once eligibility is confirmed via email from the PNOC Operations Office to the registering site, the site will enroll the patient via the Interactive Web Response System (IWRS). Enrollment into the IWRS and treatment initiation on protocol therapy cannot occur unless eligibility has been reviewed and confirmed with receipt of the registration confirmation email from the PNOC Operations Office.

## 15.2. Reservation and Registration Process

The wait-list for study slots will be maintained by the PNOC Operations Office. Investigators can view updated information about slot availability and registration process updates on the PNOC Member's SharePoint homepage using their secure login and password, or by emailing a request to PNOC_Registration@ucsf.edu.

To place a patient on the waitlist, please complete the Qualtrics survey (link available on SharePoint). An automatic screening ID will be generated, and emailed to both the Operations Office and the person submitting the form. This screening ID will be used for registration and patient tracking purposes.

To register a patient for the study, limited patient information (confirmation of screening ID, gender, ethnicity, race, month & year of birth, ZIP or country code, disease site, histology, diagnosis date, name of treating physician and study specific information) along with a signed consent form and HIPAA authorization (if applicable to your institutional regulatory guidelines) should be emailed to the PNOC Operations Office at PNOC_Registration@ucsf.edu. All subject PHI must be redacted, and the screening ID included on each source document or consent form page. The patient will be given the status of consented in OnCore®.

When the eligibility checklist has been completed, the member institution PI and/or Coordinator will upload the completed eligibility checklist (along with copies of any supporting documents) into the patient's OnCore® record.

Once the necessary documents have been received and patient eligibility has been confirmed, the PNOC Operations Office will send a confirmation e-mail to the institutional PI(s) and Research Coordinator(s) to proceed with enrollment via IWRS.

The ICON Clinical Trial Manager will maintain the Master Enrollment Tracker.

# 16. DATA REPORTING / REGULATORY REQUIREMENTS

## 16.1. Data Reporting

### 16.1.1. Method

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs; throughout this protocol, CRF refers to either a paper CRF or an electronic CRF) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into eCRFs using single data entry with a secure access account. The electronic data capture (EDC) system used for this study is Medidata Rave. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained at each PNOC site. For participating sites, source documents will be maintained per institutional guidelines. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate. This signed declaration will accompany each set of patient CRFs that will be provided to Regeneron.

All source documentation and Clinical Trial Management System data will be available for review/monitoring by Regeneron and delegates, and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, Regeneron, and the PNOC Project Leader.

### 16.1.2. Responsibility for Data Submission

Please refer to Appendix 3 for data submission timelines.

## 16.2. Oversight and Monitoring Plan

This is a multicenter trial. Regeneron and delegates will be responsible for overall safety and data monitoring on this study.

The study monitor and/or designee (e.g., CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study.

### 16.2.1. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file. Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

### 16.2.2. Multicenter Communication

The PNOC Operations Office provides administration and organizational support for the participating sites in the conduct of the clinical trial. The PNOC Operations Office will coordinate, at minimum, quarterly conference calls with the PNOC member institutions to discuss risk assessment. The following items will be discussed, as appropriate:

- Enrollment information
- Cohort updates (i.e., DLTs)
- Adverse events (i.e., new AEs and updates on unresolved AEs and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

### 16.2.3. Record Keeping and Record Retention

The Principal Investigator for each PNOC institution is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by patients, as well as written records of the disposition of the drug when the study ends per institutional guidelines.

The site Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (eg, protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, each PNOC member institution must retain records and all essential study documents, including Informed Consent Forms (ICFs), source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The PNOC member institution must consult with Regeneron before

discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the PNOC member institution's situation is such that archiving can no longer be ensured, the PNOC member institution must inform Regeneron and/or its delegates and the relevant records will be transferred to a mutually agreed-upon destination.

### 16.2.4. Regulatory Documentation

Prior to implementing the protocol at each PNOC institution, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be first approved by Regeneron and/or its delegates. Prior to implementing this protocol at the participating sites, approval for the protocol must be obtained from the participating site's IRB.

It is the responsibility of the investigator to obtain written informed consent from each patient (or LAR, if patient is a minor) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained in language that the patient or LAR can understand. The ICF should be signed and dated by the patient or LAR and the same investigator or designee who explained the ICF.

If the patient is a minor, local law must be observed in deciding whether 1 or both parents or LAR consent is required. The patient may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients (and/or LARs) who can write but cannot read will have the assent form read to them before writing their name on the form.
- Patients (and/or LARs) who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient's LAR.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients (and their LARs, for patients who are minors) must be informed of the new information, and patients who wish to continue in the study must provide their written consent. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient. For patients who are minors, an LAR must provide written consent for a patient to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient's LAR.

The investigator may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment and approval of Regeneron.

Appendix 4 lists the documents which must be provided to Regeneron and/or its delegates before the participating site can be initiated and begin enrolling participants.

# 17. DEFINITIONS OF DEVIATIONS IN PROTOCOL PERFORMANCE

| **DEVIATION** | |
|---|---|
| **Minor** | **Major** |
| **Prescription Dose** | |
| Difference in prescribed or computed dose is 6-10% of protocol specified dose | Difference in prescribed or computed dose is >10% of protocol specified dose |
| **Dose Uniformity and Coverage** | |
| >10% PTV received >110% of the protocol dose *or* 95% isodose covers <100% of CTV | >20% of PTV received >110% of the protocol dose *or* 90% isodose covers <100% of CTV |
| **Volume** | |
| CTV or PTV margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV) or without written justification (PTV) | GTV does not encompass MR-visible residual tumor |
| **Organs at Risk** | |
| Dose to any OAR exceeds the goal dose stated in Section 10.6.1 | Dose to any OAR exceeds the maximum dose stated in Section 10.6.1 |

# 18. REFERENCES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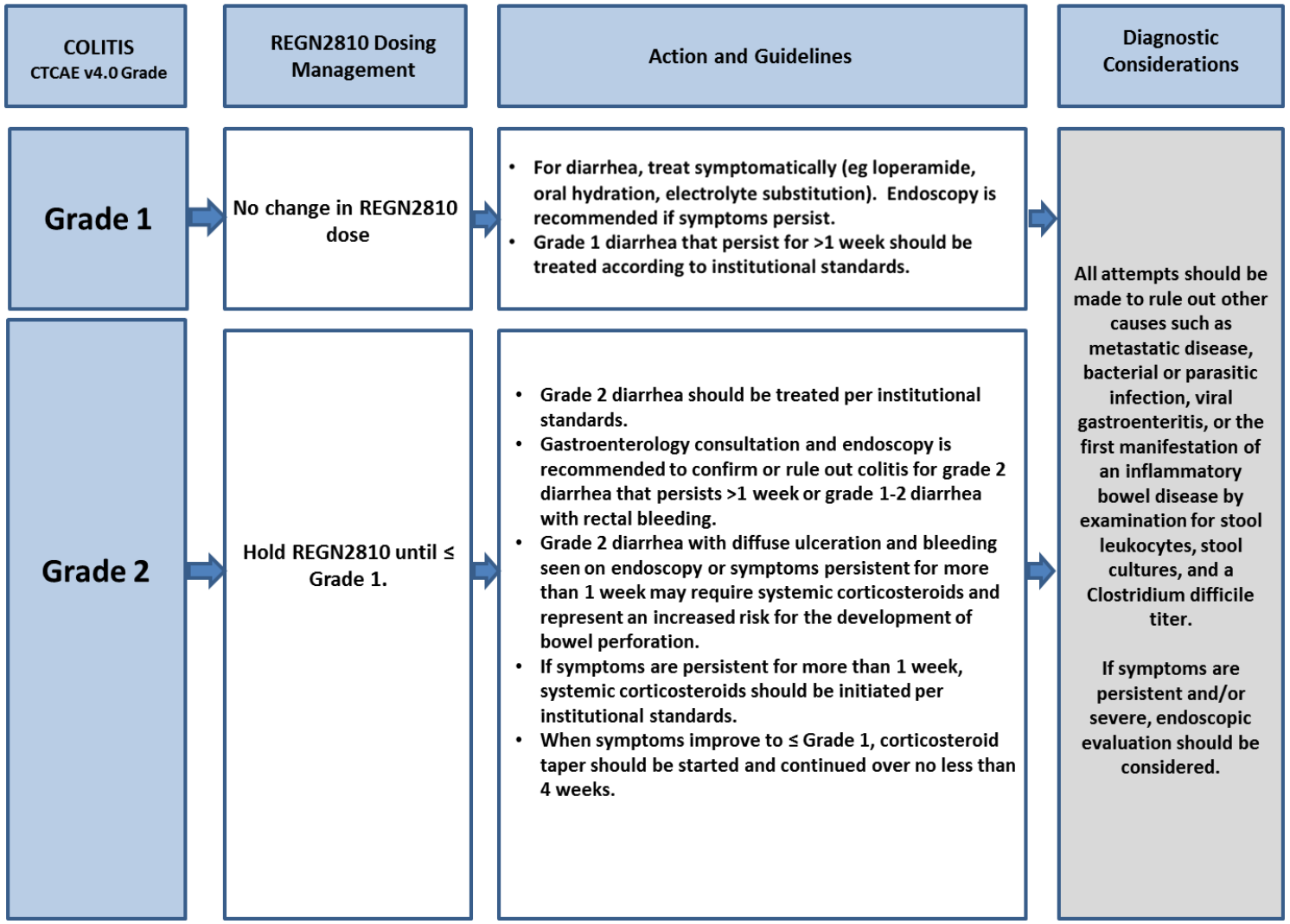
# APPENDIX 1. PERFORMANCE STATUS CRITERIA

| **Karnofsky** | | **Lansky** | |
|---|---|---|---|
| Score | Description | Score | Description |
| 100 | Normal, no complaints, no evidence of disease | 100 | Fully active, normal. |
| 90 | Able to carry on normal activity, minor signs or symptoms of disease. | 90 | Minor restrictions in physically strenuous activity. |
| 80 | Normal activity with effort; some signs or symptoms of disease. | 80 | Active, but tires more quickly |
| 70 | Cares for self, unable to carry on normal activity or do active work. | 70 | Both greater restriction of and less time spent in play activity. |
| 60 | Required occasional assistance, but is able to care for most of his/her needs. | 60 | Up and around, but minimal active play; keeps busy with quieter activities. |
| 50 | Requires considerable assistance and frequent medical care. | 50 | Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities. |
| 40 | Disabled, requires special care and assistance. | 40 | Mostly in bed; participates in quiet activities. |
| 30 | Severely disabled, hospitalization indicated. Death not imminent. | 30 | In bed; needs assistance even for quiet play. |
| 20 | Very sick, hospitalization indicated. Death not imminent. | 20 | Often sleeping; play entirely limited to very passive activities. |
| 10 | Moribund, fatal processes progressing rapidly. | 10 | No play; does not get out of bed. |

# APPENDIX 2. ADVERSE EVENT MANAGEMENT

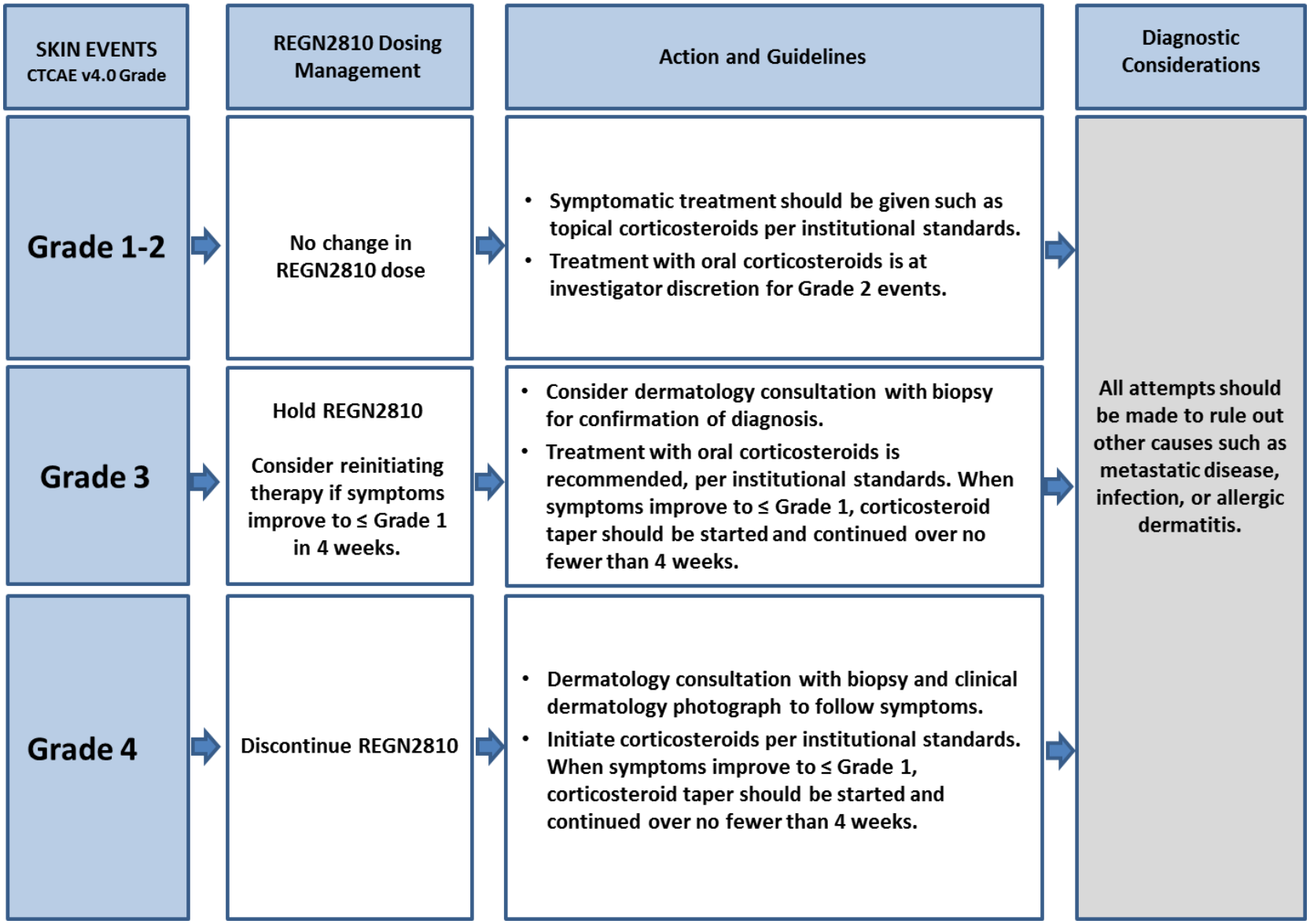
## Colitis Adverse Event Management



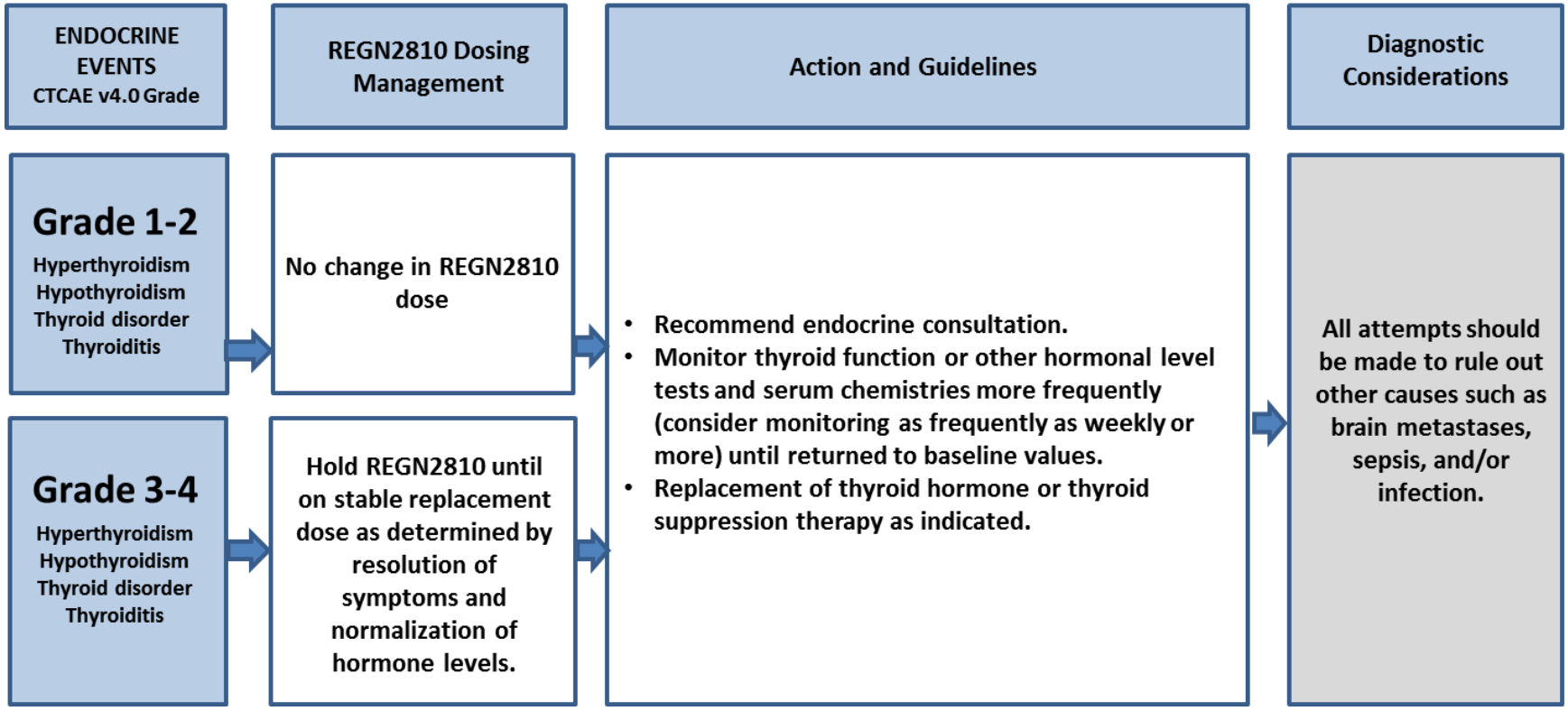
## Colitis Adverse Event Management (Cont)

| COLITIS CTCAE v4.0 Grade | REGN2810 Dosing Management | Action and Guidelines | Diagnostic Considerations |
|---|---|---|---|
| **Grade 3-4** | Hold REGN2810 until ≤ Grade 1<br><br>Discontinue REGN2810 if unable to reduce corticosteroid dose to below physiologic replacement within 4 weeks of toxicity | • Patients with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated per institutional standards. When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 4 weeks.<br><br>For Grade 3-4 diarrhea (or Grade 2 diarrhea that persists after initial corticosteroid treatment),<br>• Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful.<br>• Consultation with gastroenterologist and confirmation biopsy with endoscopy is recommended.<br>• Treat with intravenous (IV) steroids, per institutional standards. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over no less than 4 weeks. Taper over 6-8 weeks in patients with diffuse and severe ulceration and/or bleeding.<br>• If IV corticosteroids followed by high-dose oral corticosteroids does not reduce initial symptoms within 48-72 hours, consider treatment with infliximab. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 6-8 weeks. If symptoms worsen during corticosteroid reduction, initiate a retapering of corticosteroids starting at a higher dose followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis.<br>• If symptoms persist despite the above treatment a surgical consult should be obtained. | All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer.<br><br>If symptoms are persistent and/or severe, endoscopic evaluation should be considered. |

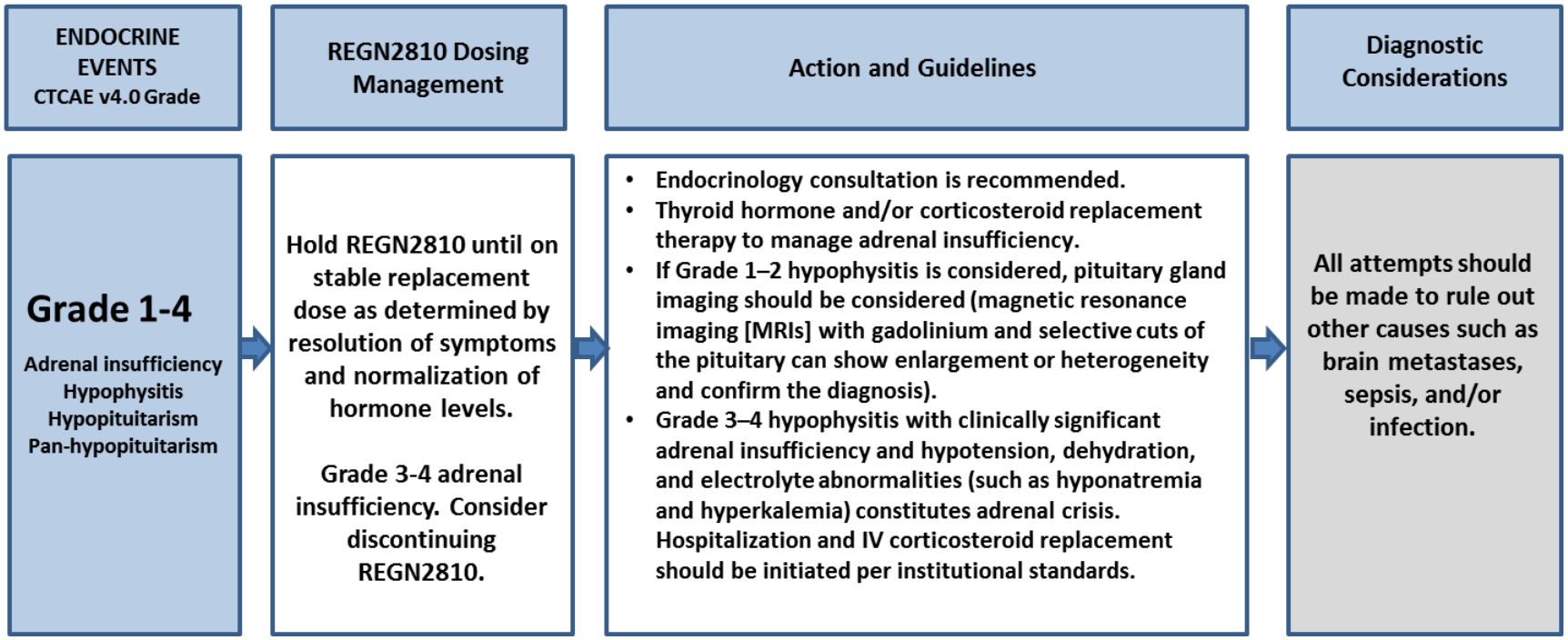
## Dermatologic Adverse Event Management



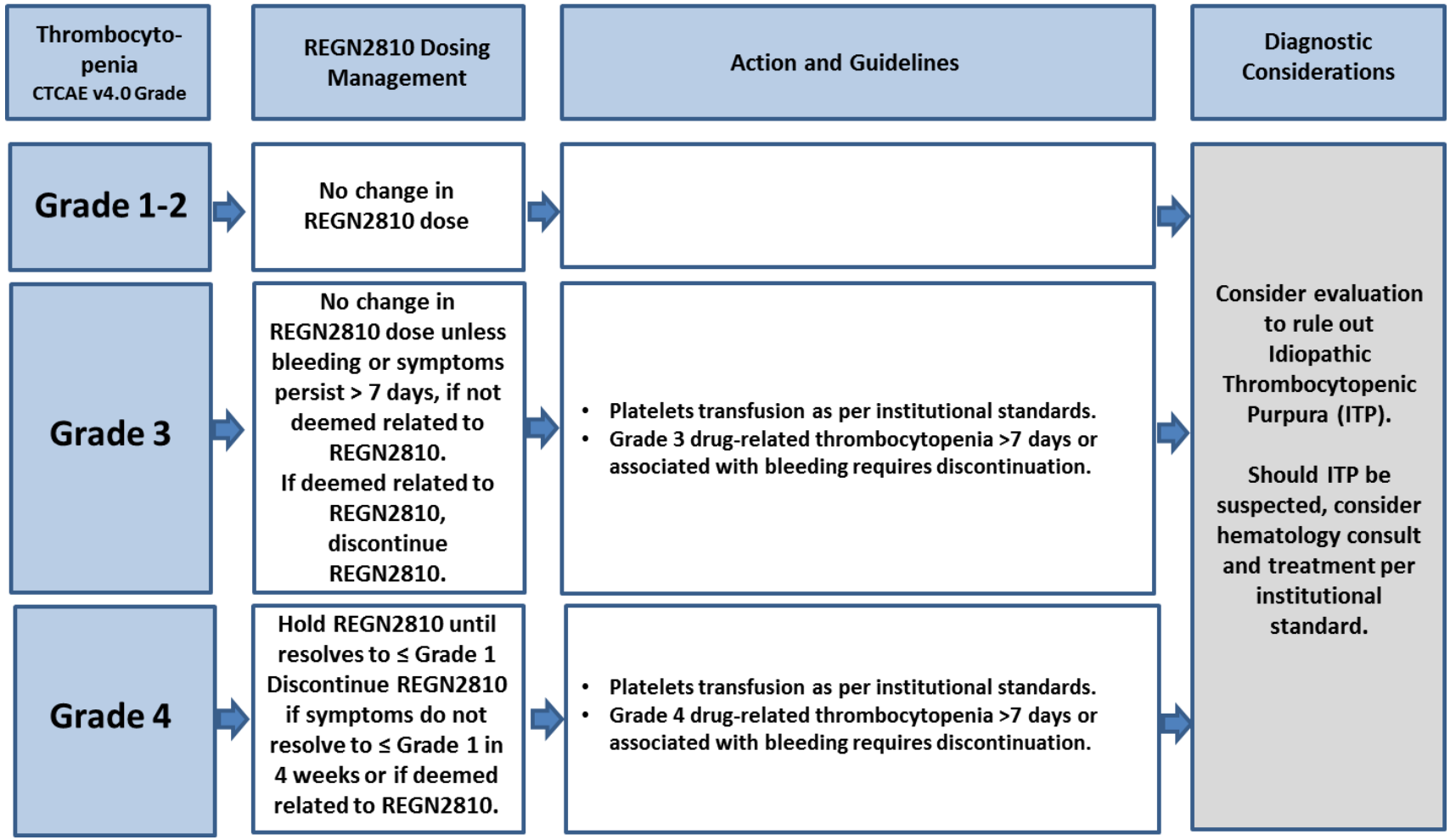
## Endocrine Adverse Event Management



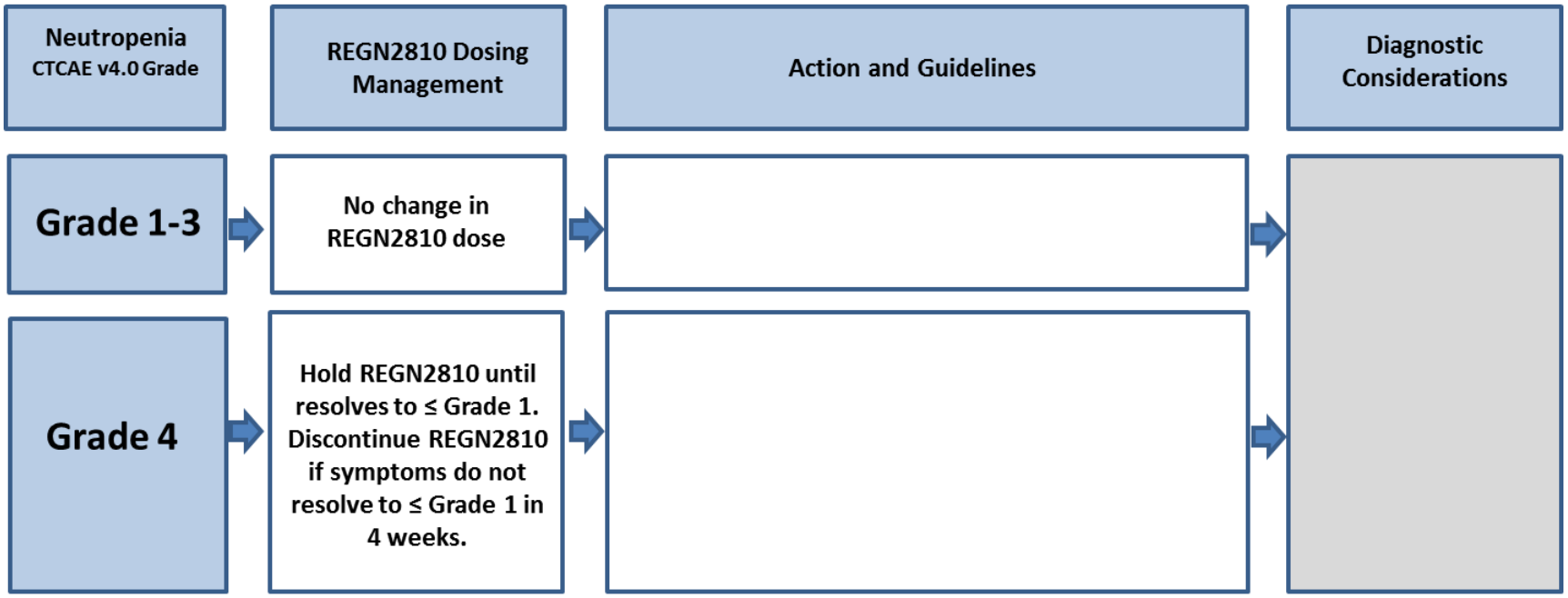
## Endocrine Adverse Event Management (Cont)



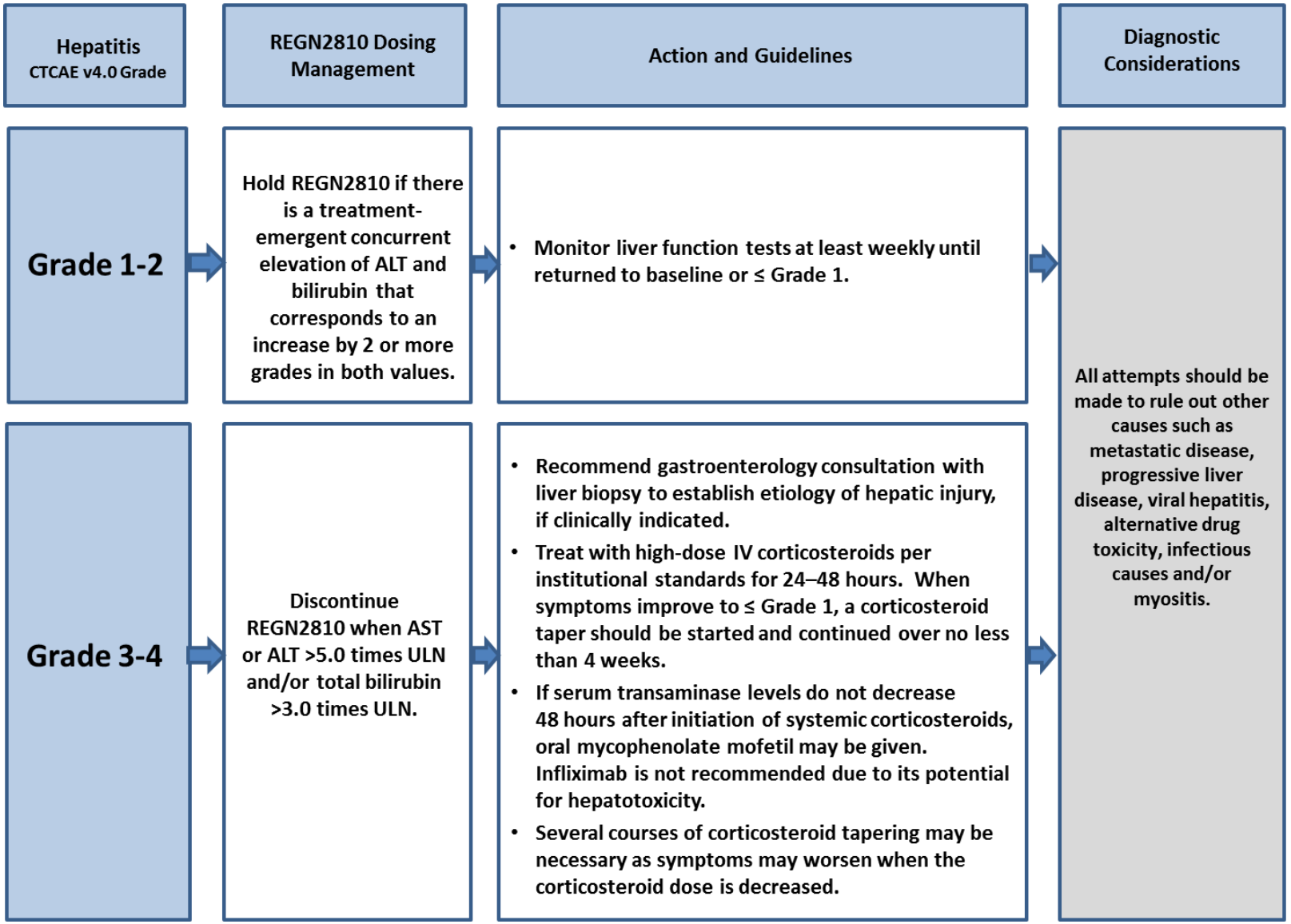
## Hematologic Adverse Event Management



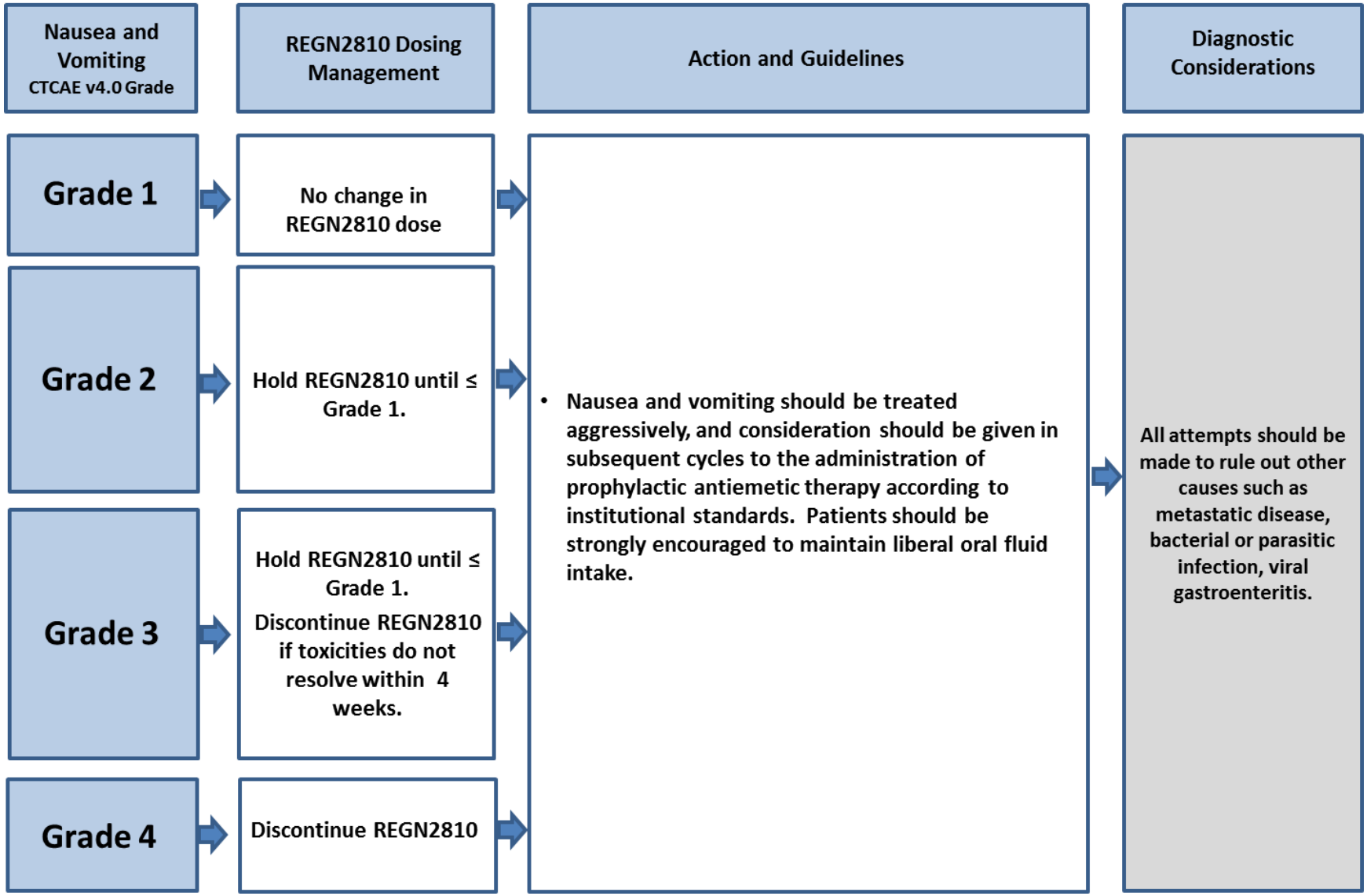
## Hematologic Adverse Event Management (Cont)



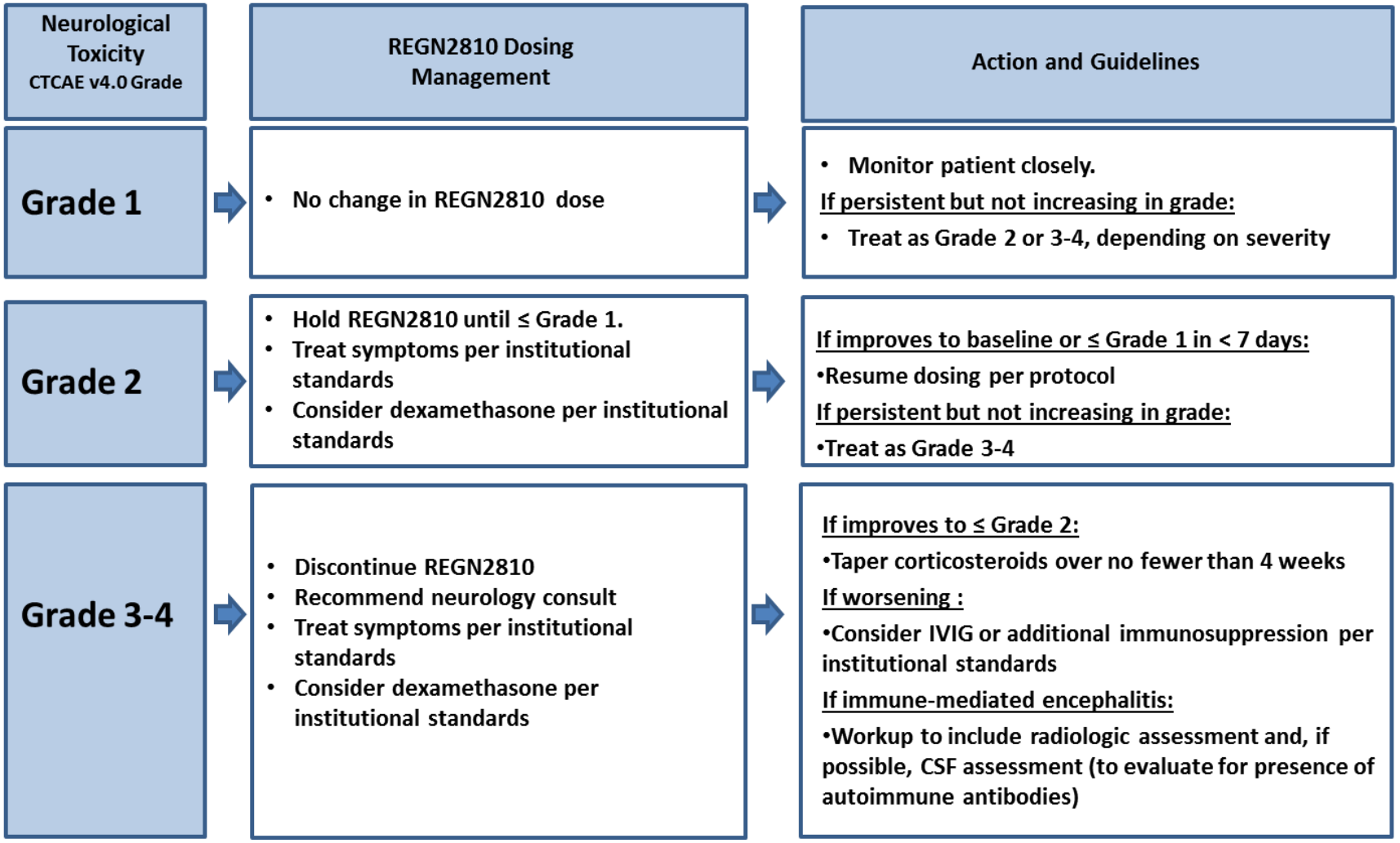
## Hepatitis Adverse Event Management



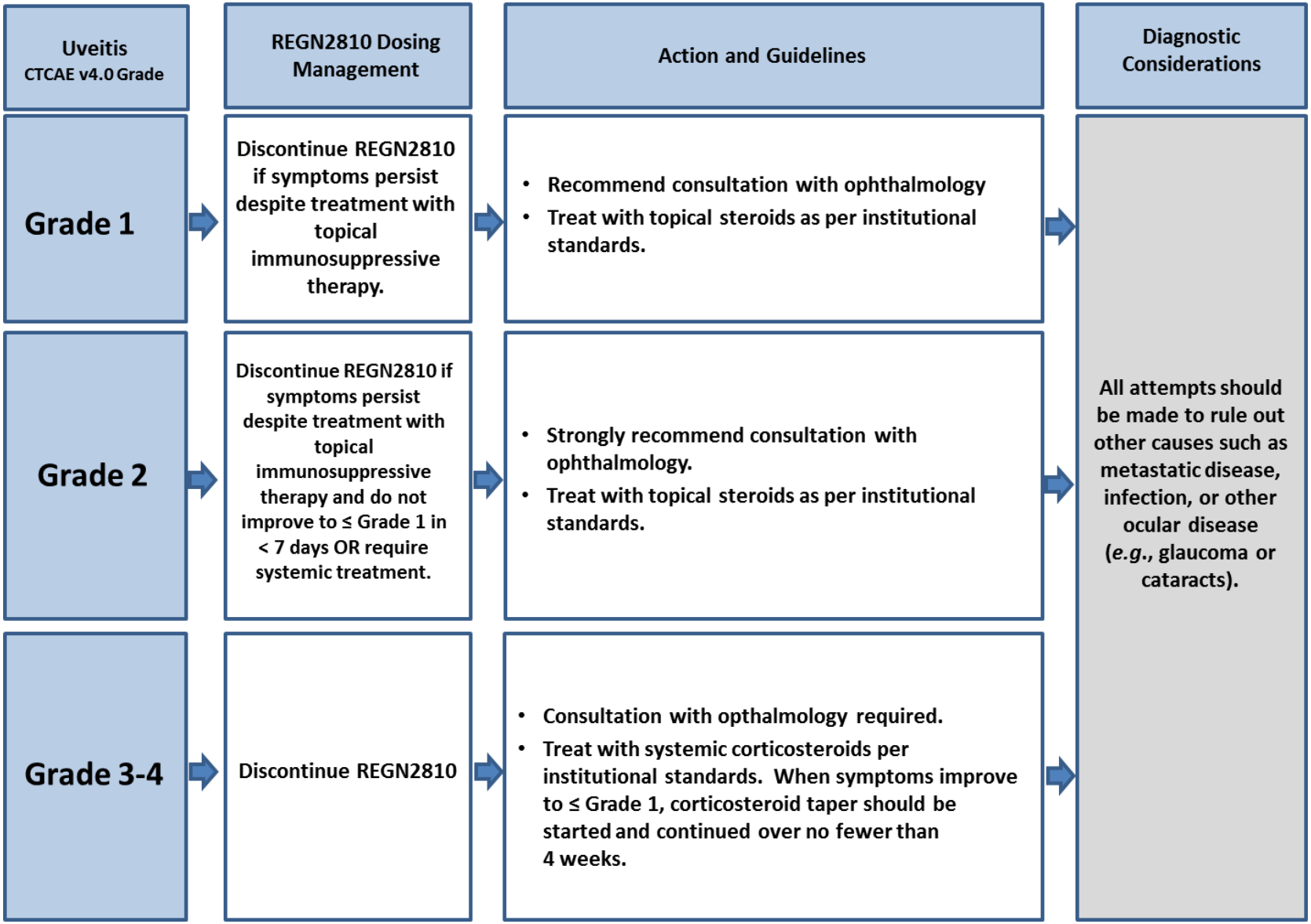
## Nausea and Vomiting Adverse Event Management



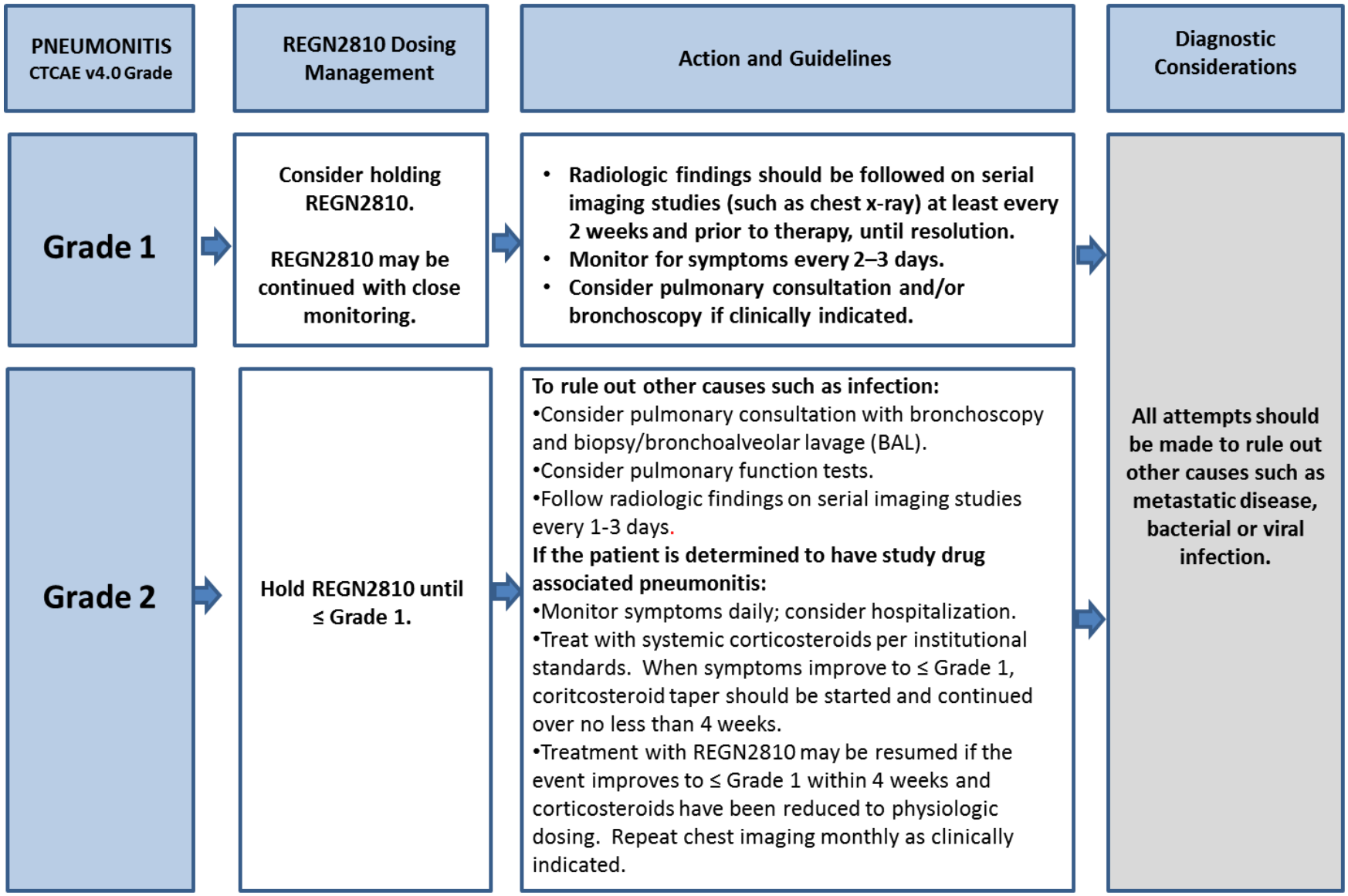
## Suspected Immune Related Neurological Adverse Event Management (see protocol for specific management of Pseudoprogression, Section 7)



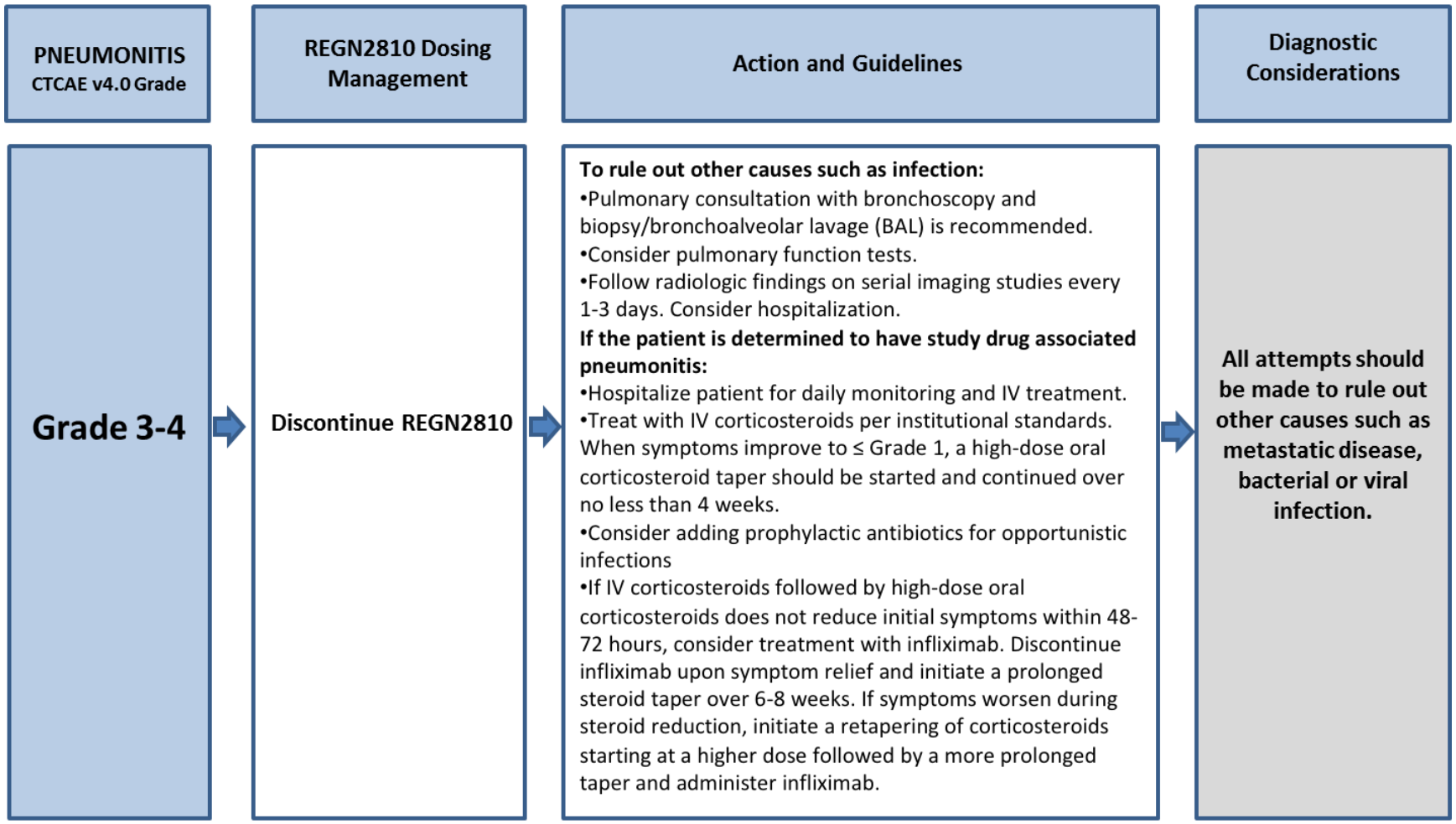
## Ophthalmologic (Uveitis) Adverse Event Management



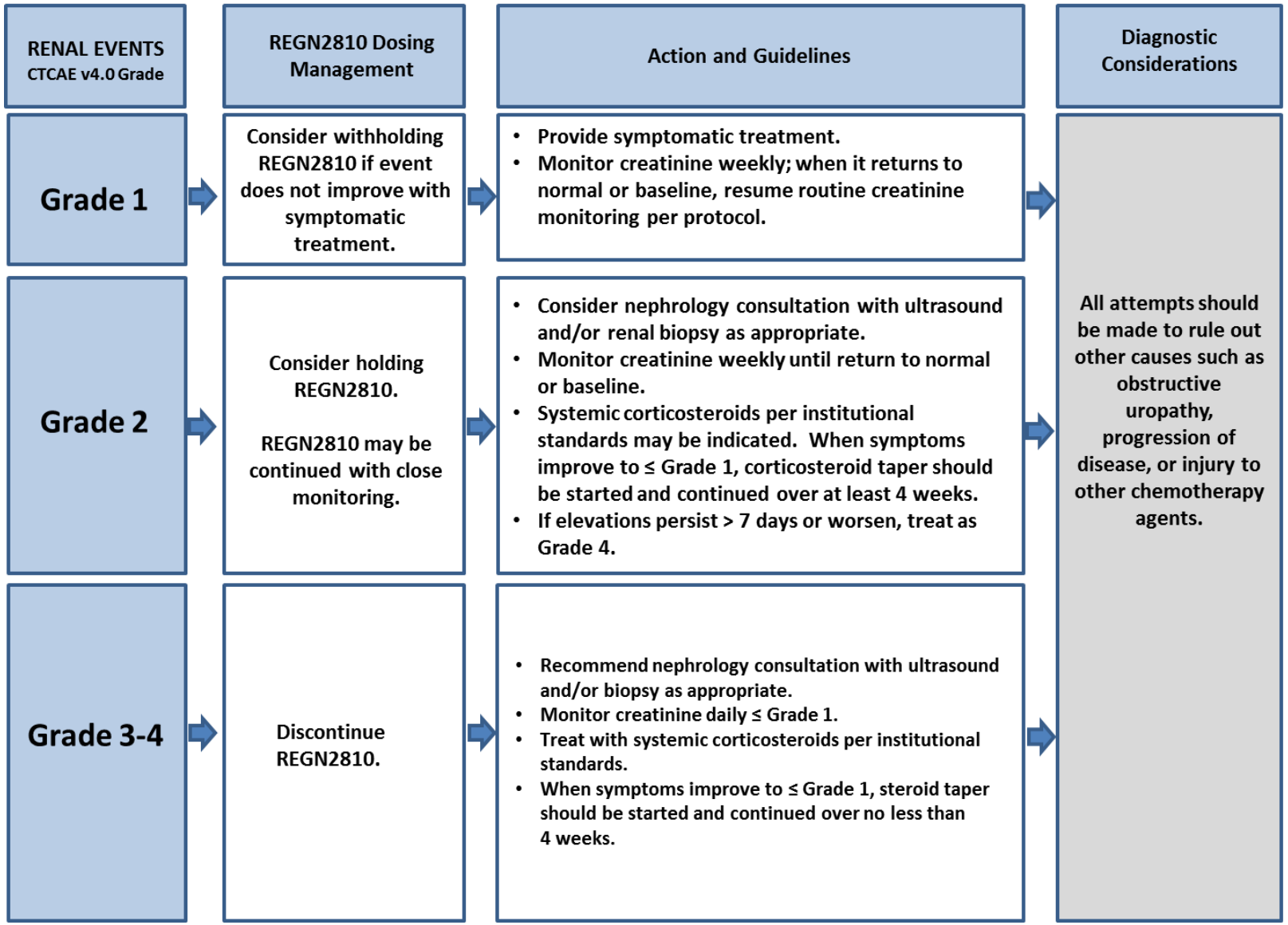
## Pneumonitis Adverse Event Management



# Pneumonitis Adverse Event Management (Cont)



## Renal Adverse Event Management



# APPENDIX 3. REQUIRED DATA AND TIME TABLE FOR SUBMISSION

The submission timelines listed below represent target timelines; however, timing may vary according to individual site.

| Form | Submission Timeline |
|---|---|
| Eligibility Checklist | Complete prior to registration |
| On Study Forms | Within 14 days of registration |
| Baseline Assessment Forms | Within 14 days of registration |
| Treatment Forms | Within 10 days of the last day of the cycle |
| Adverse Event Report Forms | All AEs are due within 10 business days of the date of assessment. |
| Serious Adverse Event Reporting | Within 1 business day of first PI awareness |
| Response Assessment Forms | Within 10 days of the completion of the cycle required for response evaluation |
| Off Treatment/Off Study Forms | Within 14 days of completing treatment or being taken off study for any reason |
| Follow-up/Survival Forms | Within 14 days of the protocol defined follow-up visit date |

# APPENDIX 4. PNOC INSTITUTIONS, REQUIRED REGULATORY DOCUMENTS

**Prior to opening a study at any member institution, the following regulatory documents must be submitted to Regeneron or its delegates:**

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals
- Signed copy of the completed delegation of authority log
- Signed copy of the protocol signature page
- Signed copy of the final contract
- Completed Form 1572

Upon receipt of the required documents, Regeneron or its delegates will formally contact the site and grant permission to proceed with enrollment.

Sites will upload new or revised documents as applicable to reflect any changes, including changes in staff and approved/expired documents.

# APPENDIX 5. INFORMATION SHEET ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.]

The patient _____ is enrolled on a clinical trial using the experimental agent REGN2810. This clinical trial is sponsored by the Pacific Pediatric Neuro-Oncology Consortium and Regeneron. This form is addressed to the patient but includes important information for others who care for this patient.

REGN2810 has no known drug interactions.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. Bring this paper with you and keep the attached information card in your wallet. These are the things that you and they need to know:

Other medicines can be a problem with your study drugs.

You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at

_____.

# SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

**(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)**

*To the best of my knowledge, this report accurately describes the conduct of the study.*

Study 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

Protocol Number: R2810-ONC-1690

Protocol Version: Amendment 3

*See appended electronic signature page*

Sponsor's Responsible Medical/Study Director

*See appended electronic signature page*

Sponsor's Responsible Regulatory Liaison

*See appended electronic signature page*

Sponsor's Responsible Clinical Study Team Lead

*See appended electronic signature page*

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00102228 v1.0

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| ESig Approval | [redacted]<br>16-Mar-2020 21:30:59 GMT+0000 |

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