Title: An Open-Label, Multi-Center Trial of INO-5401 and INO-9012 Delivered by Electroporation (EP) in Combination with REGN2810 in Subjects with Newly Diagnosed Glioblastoma (GBM)

ClinicalTrials.gov ID: NCT03491683

Sponsor: Inovio Pharmaceuticals

Document Date: Study Protocol Version 5.0: 30 November 2023



GBM-001

An Open-Label, Multi-Center Trial of INO-5401 and INO-9012 Delivered by Electroporation (EP) in Combination with REGN2810 in Subjects with Newly Diagnosed Glioblastoma (GBM)

Sponsored by:

Inovio Pharmaceuticals, Inc.

IND #: 17671

Protocol Version: 5.0

Protocol Version Date: 30Nov2023

MEDICAL MONITOR APPROVAL PAGE

Drug: INO-5401 + INO-9012
REGN2810

Sponsor: Inovio Pharmaceuticals, Inc.
660 W. Germantown Pike, Suite 110
Plymouth Meeting, PA 19462

Medical Monitor: [redacted] MD
[redacted]
Inovio Pharmaceuticals

Approval Signature:

(Signed and dated electronically)

[redacted] MD
[redacted]
Inovio Pharmaceuticals, Inc.

Date(dd/Mmm/yyyy)

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PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT

I have read and understood this Protocol and agree that it contains all necessary details to conduct the trial. I understand that it must be reviewed by the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) overseeing the conduct of the clinical trial and approved or given favorable opinion before implementation.

The Principal Investigator's (PI's) signature constitutes the PI's approval of this Protocol and provides the necessary assurances that this trial will be conducted in accordance with International Council on Harmonization (ICH)/Good Clinical Practice (GCP), International Organization for Standardization (ISO) guidelines, local legal and regulatory requirements, and all stipulations of the Protocol.

Principal Investigator Signature:

Principal Investigator Printed Name

Principal Investigator Signature

Date (ddMmmyyyy)

Clinical Trial Site Number:

Clinical Trial Site Name:

SUMMARY OF CHANGES

The following are significant protocol changes from version 4.0 dated 24Aug2022 to version 5.0 dated 30Nov2023. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. Study procedures will be limited to administration of study drugs INO-5401 + INO-9012 and cemiplimab per prior schedule. Assessments will be limited to standard-of-care assessments (i.e., vital signs, physical assessment, and safety labs) only. No further evaluation of efficacy or immunogenicity will be performed. The relevant sections of the protocol have been updated to reflect this change. The continuation of this protocol is solely for the potential benefit of prior subjects who continue to demonstrate clinical benefit from trial therapy.

The following is the list of protocol changes from version 3.0 03Jan2018 dated to version 4.0 dated 24Aug2022.

1. Subjects will no longer be followed for disease progression or survival after they have discontinued dosing with investigational product and have completed the End of Treatment visit. Previously specified imaging is no longer required. At this point the trial has met its secondary endpoints of evaluating overall survival at 18 months, and a median overall survival has been calculated for both Cohorts A and B. As such no further information is required with respect to these endpoints at this time, and the continuation of this protocol is solely for the potential benefit of prior subjects who continue to demonstrate clinical benefit from trial therapy. The protocol (Sections 6.10.1, 6.11.13, 6.12), and schedule of events have been amended to reflect this change.
2. Administrative and typographical errors have been corrected throughout the document.

The following is the list of protocol changes from version 2.1 dated 30Oct2017 to version 3.0 dated 03Jan2018.

1. All subjects will be administered temozolomide, if clinically indicated, in combination with radiotherapy and trial drug during the period of radiotherapy, regardless of cohort. Subjects whose tumors are determined to contain a methylated or indeterminate MGMT promoter will continue to receive temozolomide following radiation therapy, for up to six additional cycles, if clinically indicated. Subjects whose tumors are determined to contain an unmethylated MGMT promoter will not receive temozolomide following radiation therapy. Language has been added throughout the protocol to reflect this change.
2. In Section 3.7 *the following sentence was added, "Once the first three subjects of these six in each cohort have completed Week 9 assessments, in the absence of dose-limiting toxicity (DLT), following a review of all available safety data from these patients by the Medical Monitors from the Sponsor and from Regeneron Pharmaceuticals, and the coordinating Principal Investigator, enrollment to that cohort may begin in full."*
3. In section 5.2.3, Radiation Therapy, "*radiotherapy will be given Monday through Friday* for three weeks was changed to "*radiotherapy will be given for 3 weeks."*

4. In Appendix H Radiation Parameters, section 3 Dose, "*treatment shall be given daily"* was deleted.

The following is the list of protocol changes from version 2.0 dated 09Oct2017 to version 2.1 30Oct2017.

1. The protocol version is V 2.1. The protocol version date is 30Oct2017.
2. The description of the formulation for REGN2810 on page 11 has been changed from REGN2810: (350 mg every 3 weeks (Q3W)) A monoclonal, "*fully humanized"* to "*a fully human*" antibody to programmed death-1 (PD-1).
3. Exclusion criteria # 7 was changed from, "*Prior treatment with idelalisib at any point in the past, secondary to a known interaction between REGN2810 and idelalisib*" to "*Have received prior treatment with idelalisib at any point in the past".*
4. Exclusion criteria # 9 was changed from, "*Allergy or hypersensitivity to REGN2810 or its excipients; including doxycycline or tetracycline*" to "*Allergy or hypersensitivity to REGN2810 or to any of its excipients."*
5. Section 1.3.2 was changed from "*REGN2810 is a fully humanized human antibody, hinge-stabilized IgG4 (S228P) high affinity anti-PD1 antibody that potently blocks programmed death-1 (PD-1)-PD-1 ligand (PD-L1) functional interaction*" to "*REGN2810 is a hinge-stabilized IgG4 (S228P) high affinity anti-PD1 fully human antibody that potently blocks programmed death-1 (PD-1)-PD-1 ligand (PD-L1) functional interaction".*
6. Editorial updates were made to section 1.4.1.
7. Section 5.5.1.1 was changed from "*signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion*" to "*signs and symptoms usually develop during or shortly after drug infusion and generally resolve during the infusion or within one day after the infusion".*

The following is the list of protocol changes from version 1.0 dated 31Aug2017 to version 2.0 dated 09Oct2017.

1. All subjects will be administered temozolomide, if clinically indicated, in combination with radiotherapy and trial drug, regardless of cohort assignment. Language has been added throughout the protocol to reflect this change.
2. Additional language has been added to Section 3.7 Safety run-in to include a one week waiting period between subjects #1, 2 and 3 in both cohorts A and B. Language now reads, *"Enrollment will be staggered, with a waiting period of one week between enrollment of the first and second subject and again between the second and third subject in each cohort. Each subject will be assessed up to Week 9."*
3. Section 3.8: Stopping rules were added. Language now reads, *"Following the safety run-in period, if at any point during the course of this clinical study, ≥30% of subjects in either cohort experience a dose-limiting toxicity as defined in Section 3.7 deemed related to investigational trial drug(s), enrollment to one or both cohorts will stop, and the*

Sponsor's Medical Monitor, in addition to the Principal Investigator (PI) and Investigator(s) at the subjects' site(s) will discuss the safety profile of the trial drug(s), and a decision will be made whether to modify trial drug or concomitant drug (RT/TMZ) dose within one or both cohorts, or to cease further enrollment to one or both cohorts. If a change to the protocol is required, enrollment will only be re-initiated after amendment of the protocol and approval of the amended protocol by the IRB."

4. Grammar and punctuation has been corrected throughout.

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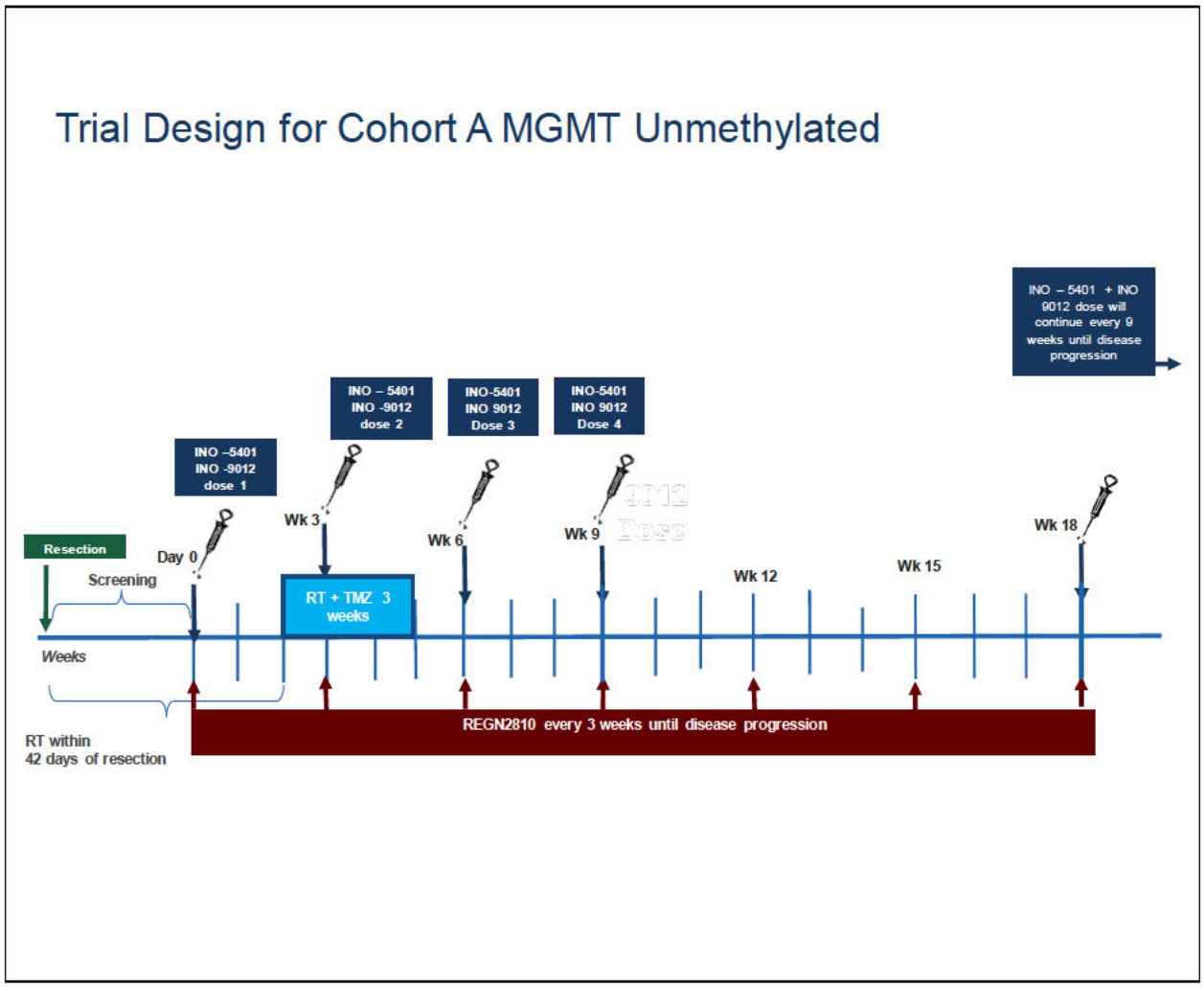
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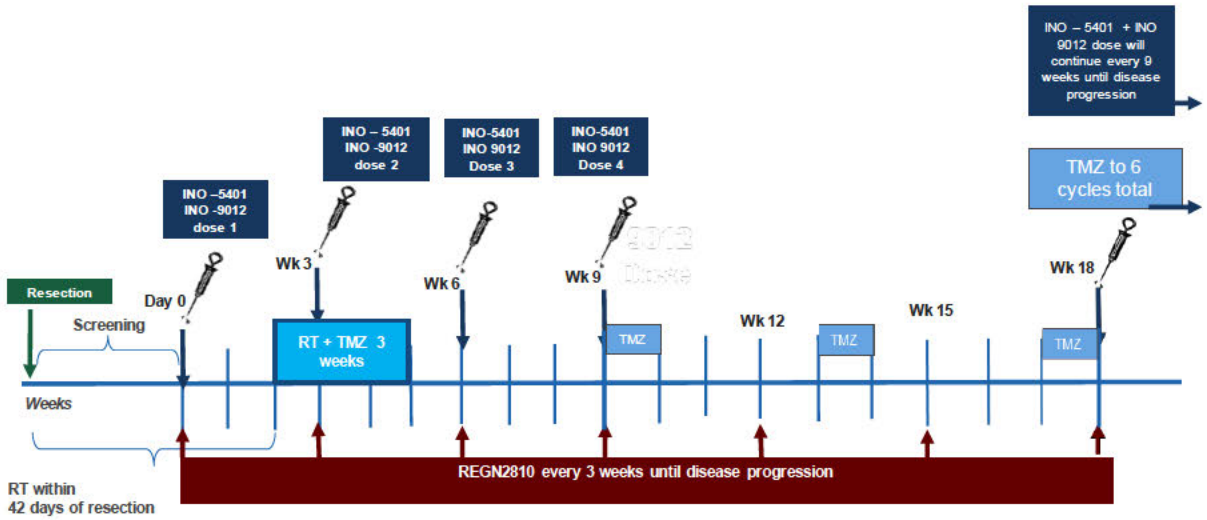
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CLINICAL PROTOCOL SYNOPSIS

Protocol Title: An Open-Label, Multi-Center Trial of INO-5401 and INO-9012 Delivered by Electroporation (EP) in Combination with REGN2810 in Subjects with Newly Diagnosed Glioblastoma (GBM)
Protocol Number: GBM-001
Clinical Trial Phase: 1/2
Estimated Number of Trial Centers and Countries/Regions: Approximately 25 sites in the U.S.
Clinical Trial Design: This is a Phase 1/2, open-label, multi-center trial to evaluate the safety, immunogenicity, and preliminary efficacy of INO-5401 and INO-9012 in combination with REGN2810 in subjects with newly diagnosed GBM. The following procedures were performed prior to execution of Protocol v5.0: Subjects will start immunotherapy with REGN2810 upon definitive histopathological diagnosis of GBM and adequate recovery from surgical intervention. The start of immunotherapy is designated as Day 0. REGN2810 will be administered intravenously (IV) every three weeks until disease progression defined by iRANO (Immune Response Assessment in Neuro-Oncology), unacceptable toxicity, withdrawal of consent, or death. On Day 0, subjects will also receive INO-5401 and INO-9012 intramuscularly (IM) followed by electroporation (EP). INO-5401 and INO-9012 will be administered, followed by EP, every three weeks for four doses, and then every 9 weeks until disease progression defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. Temozolomide will be administered to all subjects both with and without MGMT promoter methylation, unless clinically contraindicated, during radiation therapy. Radiation therapy (RT) will begin **no later than** 42 days after surgical intervention. Radiation therapy should start approximately 1 to 2 weeks after Day 0 and will continue for approximately three weeks. Temozolomide (TMZ) will be given daily during radiation therapy (TMZ/RT). Subjects with MGMT promoter methylation, or whose MGMT promoter methylation status is indeterminate, will then receive maintenance (adjuvant) TMZ for 6 cycles, following recovery from TMZ/RT. Maintenance (adjuvant) TMZ will be administered for the first 5 days of a 28-day cycle. This study will have two cohorts: Cohort A will consist of subjects with an unmethylated MGMT promoter, and Cohort B will consist of subjects with a methylated or indeterminate MGMT promoter.


Trial Design for Cohort A MGMT Unmethylated
INO – 5401 + INO 9012 dose will continue every 9 weeks until disease progression
INO – 5401 INO -9012 dose 2
INO-5401 INO 9012 Dose 3
INO-5401 INO 9012 Dose 4
INO –5401 INO -9012 dose 1
Wk 3
Wk 6
Wk 9
Wk 18
Resection
Day 0
Screening
RT + TMZ 3 weeks
Wk 12
Wk 15
Weeks
REGN2810 every 3 weeks until disease progression
RT within 42 days of resection

Trial Design for Cohort B MGMT Methylated or Indeterminate



The following procedures will be performed after execution of Protocol v5.0:

REGN2810 will be administered every 3 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or death. Confirmation of disease progression is not required.

INO-5401 + INO-9012 will be administered IM followed by EP every 9 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or death. Confirmation of disease progression is not required.

Criteria for Evaluation:

Research Hypothesis:

INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 will be safe, well-tolerated and immunogenic in adult subjects with newly diagnosed GBM.

Primary Objective:

To evaluate the safety and tolerability of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 in adult subjects with newly diagnosed GBM.

Primary Endpoint(s) and Assessments:

1. Incidence of adverse events (AE) graded per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03, classified by system organ class, preferred term, severity, and relationship to trial treatment.
2. Clinically significant changes in safety laboratory parameters from baseline.

Secondary Objective(s):

1. To evaluate preliminary clinical efficacy of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 in adult subjects with newly diagnosed GBM.
2. To evaluate preliminary immunogenicity of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 in adult subjects with newly diagnosed GBM.

Secondary Endpoint(s) and Assessments:

1. Overall survival at 18 months (OS18).
2. Antigen-specific cellular immune responses assessed by:
   - Interferon-γ secreting T lymphocytes in peripheral blood mononuclear cells (PBMC) by ELISpot
   - T-cell phenotype (e.g. activation and cytolytic cell, [redacted] in PBMC by Flow Cytometry

[redacted]

Exploratory Objective(s):

1. To explore correlative association between clinical efficacy and tumor genetics and/or biomarkers.
2. To further evaluate efficacy of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 and hypofractionated radiation therapy in adult subjects with newly diagnosed GBM.

Exploratory Endpoint(s):

1. Tumor infiltrating lymphocytes (TILs) and immunosuppressive elements, where feasible

2. Expression of tumor oncoproteins, [redacted]
7. Progression-Free Survival, as assessed by RANO (Response Assessment in Neuro-oncology) criteria and Immunotherapy Response Assessment in Neuro-oncology (iRANO) criteria
8. Overall Survival (OS)

Safety Assessment:

Adverse events (AE) graded per Common Toxicity Criteria for Adverse Events (CTCAE) v5.0, classified by system organ class, preferred term, severity, and relationship to trial treatment; and clinically significant changes in safety laboratory parameters from baseline.

A safety run-in will be performed using a modified Rolling 6 design, which will enroll up to six subjects to each Cohort (A and B up to 12 subjects total). Enrollment will be staggered, with a waiting period of one week between enrollment of the first and second subject and again between the second and third subject in each cohort. Each subject will be assessed up to Week 9. By Week 9 a subject will have received three doses of REGN2810, three doses of INO-5401 + INO-9012, and will have completed RT.

Once the first three subjects of these six in each cohort have completed Week 9 assessments, in the absence of dose-limiting toxicity (DLT), enrollment to that cohort may begin in full. However, if prior to the first three subjects in each cohort completing Week 9, a single subject from the first six in that cohort experiences a DLT then enrollment will be limited to six subjects in that cohort until all six subjects have reached Week 9 and are assessed for DLT.

If a second subject within the first 6 experiences a DLT in the same cohort within the first 9 weeks, enrollment to that cohort will stop, and the Sponsor's Medical Monitor, in addition to the Principal Investigator (PI) and Investigator(s) at the subjects' site(s) will discuss the case, and a decision will be made whether to modify trial drug or concomitant drug (RT/TMZ) dose within that cohort, or to cease further enrollment to that cohort. If a change to the protocol is required, enrollment will only be re-initiated after amendment of the protocol and approval of the amended protocol by the IRB.

Definition of DLT can be found in Section 3.7

Clinical Trial Population:

Adults with newly diagnosed GBM who are post-definitive surgery, and are able to receive standard therapy.

Estimated Number of Subjects: 52

Cohort A: MGMT promoter unmethylated (N=32 for 30 evaluable subjects)

Cohort B: MGMT promoter methylated or indeterminate (N=20 for 19 evaluable subjects)

A total sample size of 52 subjects is adequate to define the safety and tolerability profile of this combination, which is the primary endpoint of this trial.

The sample size of each cohort, using a one-sided significance level of 2.5%, provides 80% power to demonstrate an improvement in the percentage of subjects surviving at 18 months (OS18) in each cohort above historical control. Assuming a historical OS18 of 45% in MGMT unmethylated subjects, and of 60% in MGMT methylated or indeterminate subjects, in order to demonstrate a 30 percentage point improvement in OS18 (75% and 90%, respectively), 30 subjects are needed in Cohort A, and 19 subjects are needed in Cohort B.

Inclusion Criteria:

1. Subjects must provide written IRB approved informed consent in accordance with institutional guidelines;
2. Be 18 years of age or older on the day of signing the informed consent, and able and willing to comply with all trial procedures;
3. Newly diagnosed brain cancer with histopathological diagnosis of glioblastoma (GBM);
4. Karnofsky Performance Status (KPS) rating of ≥70 at baseline (Appendix B);
5. Receipt of dexamethasone equivalent dose ≤2 mg per day, stable or decreased for ≥ three days prior to Day 0;
6. Recovery from the effects of prior GBM surgery as defined by the Investigator;
7. ECG with no clinically significant findings as assessed by the Investigator performed within 28 days of signing the informed consent form (ICF);
8. Adequate organ function as demonstrated by hematological, renal, hepatic parameters as defined in the Table below, obtained within 28 days prior to the first trial treatment;

Absolute neutrophil count (ANC)	**≥1500/mm^3**
Platelets	≥100,000/mm^3
Hemoglobin	≥9 g/dL
Creatinine OR Measured or calculated creatinine clearance or GFR*	≤ 1.5 X upper limit of normal (ULN), OR ≥50 mL/min for subject with creatinine level > 1.5 X institutional ULN
Total bilirubin	≤ 1.5 X ULN

AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
*Creatinine clearance should be calculated per Cockcroft-Gault equation (Appendix E)	

9. Agree that during the trial, men will not father a child, and women cannot be or become pregnant if they are of child-bearing potential. Subjects must be of non-child bearing potential (≥12 months of non-therapy-induced amenorrhea, confirmed by follicle stimulating hormone [FSH], if not on hormone replacement); or surgically sterile (vasectomy in males or absence of ovaries and/or uterus in females); or agree to use one highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and at least through week 12 after last dose. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with an expected failure rate of < 1% per year include male sterilization and hormonal implants. Alternatively, proper use of combined oral or injected hormonal contraceptives and certain intrauterine devices (IUDs) or two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year (barrier methods must always be supplemented with the use of a spermicide);
10. Ability to tolerate magnetic resonance imaging (MRI).

Exclusion Criteria:

1. Presence of greater than 1 cm x 1 cm residual tumor enhancement on post-operative MRI;
2. Multifocal disease or leptomeningeal disease (LM) disease on post-operative MRI;
3. Are not able to start radiation within 42 days of surgical resection of their tumor;
4. Receive dexamethasone equivalent dose >2 mg per day;
5. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway at any point in the past;
6. Receipt of previous approved or investigative immune modulatory agent (for example, anti-TNF, therapeutic anti-cancer vaccines, cytokine treatments (other than G-CSF or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI3K-delta, or OX-40) within 28 days of receiving the first dose of treatment;
7. Have received prior treatment with idelalisib at any point in the past.
8. Past, current or planned treatment with tumor treatment fields (Optune; NovoTTF); oncolytic viral treatment; or prior exposure to an investigational agent or device, including Gliadel wafer (Carmustine) implant for chemotherapy; within 28 days of receiving the first dose of treatment;
9. Allergy or hypersensitivity to REGN2810 or to any of its excipients.

10. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments;
11. Ongoing or recent (within 5 years) evidence of autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs), with the exception of: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment;
12. Diagnosis of immunodeficiency or treatment with systemic immunosuppressive therapy within 28 days prior to the first dose of trial treatment, other than dexamethasone for the underlying disease under investigation, as noted in the inclusion criteria;
13. Positive serological test for human immunodeficiency virus (HIV), or a history of HIV infection; or positive tests for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating active or chronic infection, as these infections may interfere with the ability to mount an appropriate immune response to vaccination;
14. Current malignancy at another site, with the exception of adequately treated basal or squamous cell skin cancers, or carcinoma of the cervix *in situ*, with no evidence of disease within 3 years. Cancer survivors who have undergone curative therapy for a prior malignancy, have no evidence of disease for 3 years and are deemed at low risk for recurrence are eligible for the trial;
15. Receipt of any vaccine within 4 weeks prior to first dose of trial treatment with the exception of the inactivated influenza vaccine, which may be given up to 2 weeks prior;
16. History of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with trial assessments or endpoint evaluation, or otherwise impact the validity of the trial results (e.g. chronic renal failure, angina, myocardial ischemia or infarction, New York Heart Association (NYHA) class III/ IV cardiac disease); or any cardiac pre-excitation syndromes (such as Wolff-Parkinson-White; cardiomyopathy, or clinically significant arrhythmias);
17. History of pneumonitis within the last 5 years;
18. Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs, excluding over-the-counter aspirin or non-steroidal anti-inflammatory drugs, such as ibuprofen) within 2 weeks of Day 0;
19. Fewer than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:

- Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
- Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
- Metal implants or implantable medical device within the intended treatment site (i.e. EP area);

20. Active drug or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to trial requirements;
21. Imprisonment, or compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
22. Pregnant or current breastfeeding;
23. As determined by the Investigator, any medical or psychological or non-medical condition that might interfere with the subject's ability to participate or affect the safety of the subject.

Clinical Trial Treatment:

1. INO-5401 (3 mg of each WT1, PSMA and hTERT targeting plasmids) combined with 1 mg INO-9012, (total 10 mg of DNA) IM injection followed by EP with CELLECTRA® 2000 given every three weeks for four doses, then every 9 weeks; and
2. REGN2810 (350 mg IV every three weeks (Q3W))

Chemoradiation:

1. Radiation (RT), given in a hypofractionated schedule (40 Gy over three weeks).
2. Temozolomide (TMZ) concurrent with radiation (Cohorts A and B), followed by maintenance (adjuvant) cycles (Cohort B only).

Formulation:

1. INO-5401 (9 mg dose): A mixture of 3 separate synthetic plasmids that encode WT1, PSMA and hTERT proteins, respectively; and
2. INO-9012 (1 mg dose): A synthetic plasmid that encodes human IL-12; and
3. REGN2810: (350 mg every 3 weeks (Q3W)) A monoclonal, fully human antibody to programmed death-1 (PD-1).

TRIAL SCHEDULE OF EVENTS

Table 1: Trial Schedule of Events Prior to Execution of Protocol v5.0

Schedule of Events **Visit windows can be found in Protocol Section 6.0**	**Screening**	**Day 0**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 9**	**Q3 Weeks (Wk 12, 15, 18, etc.)**	**Q9 Weeks (Wk 18, 27, 36, etc.)**	**Q12 Weeks (Wk 21, 33, 45, etc.)**	**End of Treatment[k]**
Informed consent	X										
MGMT promoter status	MGMT promoter status should be determined prior to the completion of RT										
Medical history	X										
Inclusion/Exclusion criteria	X	X									
Concomitant medications and AEs	X	X	X	X	X	X	X	X			X
KPS	X	X	X			X	X	X			
Physical exam	X	X	X			X	X	X			
Neurological exam	X	X	X			X	X	X			
Vital Signs and Weight	X	X	X			X	X	X			
Height, BMI	X										
12-lead ECG	X										
MRI[a]	X[a]						X[b]			X[b]	
iRANO, RANO[b]							X[b]			X[b]	
NANO scale[c]	X						X			X	
CBC w/ differential	X	X	X			X	X	X			
Serum chemistry	X	X	X			X	X	X			
Urinalysis	X										
HCG Serum for Pregnancy	X	X	X			X	X	X			
TSH, Free T3, T4	X						X		X		
CPK	X										X
HIV/HCV/HBV serology	X										
REGN2810[d]		X	X			X	X	X			
INO 5401 + INO-9012[e]		X	X			X	X		X		
Immunology samples[f]	X[f]	X[f]	X[f]			X[f]	X[f]	Immunology samples are to be collected on Week 12 and then every 12 weeks (Weeks 24, 36, 48, etc.) until discontinuation			X
Assessment of EP Injection Site		X	X			X	X		X		
Download EP data		X	X			X	X		X		

Schedule of Events **Visit windows can be found in Protocol Section 6.0**	**Screening**	**Day 0**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 9**	**Q3 Weeks (Wk 12, 15, 18, etc.)**	**Q9 Weeks (Wk 18, 27, 36, etc.)**	**Q12 Weeks (Wk 21, 33, 45, etc.)**	**End of Treatment[k]**
Informed consent	X										
MGMT promoter status	MGMT promoter status should be determined prior to the completion of RT										
Medical history	X										
Inclusion/Exclusion criteria	X	X									
Concomitant medications and AEs	X	X	X	X	X	X	X	X			X
KPS	X	X	X			X	X	X			
Physical exam	X	X	X			X	X	X			
Neurological exam	X	X	X			X	X	X			
Vital Signs and Weight	X	X	X			X	X	X			
Height, BMI	X										
12-lead ECG	X										
MRI[a]	X[a]						X[b]			X[b]	
iRANO, RANO[b]							X[b]			X[b]	
NANO scale[c]	X						X			X	
CBC w/ differential	X	X	X			X	X	X			
Serum chemistry	X	X	X			X	X	X			
Urinalysis	X										
HCG Serum for Pregnancy	X	X	X			X	X	X			
TSH, Free T3, T4	X						X		X		
CPK	X										X
RT[g]			X	X	X						
TMZ[h]			X[h]	X[h]	X[h]		X[h]				
aPTT; INR	X										
Tumor sample	X										X[i]

IDH-1: isocitrate dehydrogenase-1; MGMT: O6-methylguanine DNA methyltransferase; AE: adverse event; KPS: Karnofsky Performance Status; ECG: electrocardiogram; MRI: magnetic resonance imaging; iRANO: Immune Response Assessment in Neuro-oncology; RANO: Response Assessment in Neuro-oncology; NANO: Neurological Assessment in Neuro-oncology scale; CBC: complete blood count; HCG: human chorionic gonadotropin; TSH: thyroid stimulating hormone; CPK: creatine phosphokinase; HIV: human immunodeficiency virus; HCV: hepatitis C virus; HBV: hepatitis B virus; EP: electroporation; RT: radiation therapy; TMZ: temozolomide; aPTT: activated partial thromboplastin time; INR: International Normalized Ratio.

a. Post-cranial resection.

b. After Week 9, tumor assessment every 12 weeks or earlier if indicated per standard of care. See Appendix G for information regarding Immunotherapy Response Assessment in Neuro-oncology (iRANO)/Radiologic Assessment for Neuro-Oncology (RANO).
c. The NANO scale is to be performed at baseline and at follow-up visits where MRI is performed.
d. REGN2810 will be given on Day 0 and then every 3 weeks, until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. REGN2810 should be administered prior to INO-5401 + INO-9012 for all treatment visits.
e. INO-5401 and INO-9012 will be given together on Day 0 and then every three weeks (±3 days) for a total of 4 doses. After 4 doses, INO-5401 and INO-9012 will be given every 9 weeks, until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death.
f. Immunology samples are to be drawn at Screening, Day 0, Weeks 3, 6, 9, 12, and then every 12 weeks (Weeks 24, 36, 48, etc.) until discontinuation. [redacted]
g. Radiation Therapy (RT) given for 3 weeks to begin no more than 42 days following surgical resection.
h. Temozolomide (TMZ) is given for 21 days with concomitant RT in all subjects, and then in MGMT promoter methylation positive or indeterminate subjects (Cohort B) TMZ is given x 5 days every 28 days x 6 cycles, following recovery from chemoradiation.
i. Optional tumor biopsy at progression.
j. End of Treatment visit to be performed within 30 days of confirmation of progression.

The table below (Table 2) highlights recommended assessments to be performed while a subject is on-study. These assessments are consistent with standard-of-care. The study will only collect information on trial treatment dosing, EP data, concomitant medications related to AEs, and study treatment discontinuation will be collected.

Table 2: Trial Schedule of Events Following Execution of Protocol v5.0

Schedule of Events Visit window can be found in Protocol Section 6.0	**Day 0**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 9**	**Q3 Weeks (Wk 12, 15, 18, etc.)**	**Q9 Weeks (wk 18, 27, 36, etc.)**	**End of Treatment[c]**
Concomitant medications and Adverse Events	X	X	X	X	X	X	X		X
Physical Exam	X	X			X	X	X		
Vital Signs and Weight	X	X			X	X	X		
CBC w/ Differential	X	X			X	X	X		
Serum Chemistry	X	X			X	X	X		
HCG Serum for Pregnancy	X	X			X	X	X		
TSH, Free T3, T4						X			
REGN2810[a]	X	X			X	X	X		
INO-5401 + INO-9012[b]	X	X			X	X		X	
Assessment of EP Injection Site	X	X			X	X		X	
Download EP Data	X	X			X	X		X	

IDH-1: isocitrate dehydrogenase-1; AE: adverse event; CBC: complete blood count; HCG: human chorionic gonadotropin; TSH: thyroid stimulating hormone; EP: electroporation.

a. REGN2810 will be given on Day 0 and then every 3 weeks, until disease progression, unacceptable toxicity, withdrawal of consent, or death. REGN2810 should be administered prior to INO-5401 + INO-9012 for all treatment visits.
b. INO-5401 and INO-9012 will be given together on Day 0 and then every three weeks (±3 days) for a total of 4 doses. After 4 doses, INO-5401 and INO-9012 will be given every 9 weeks, until disease progression, unacceptable toxicity, withdrawal of consent, or death.
c. End of Treatment visit to be performed within 30 days of progression.

1. INTRODUCTION

1.1. Overview: Glioblastoma

Glioblastoma (GBM) is the most common malignant primary tumor of the central nervous system in humans [1]. Based on the 2013 Central Brain Tumor Registry of the United States (CBTR US) report, the average annual age-adjusted incidence rate of GBM is 3.19/100,000 population [2]. Primary (de novo) GBMs account for 80% of GBMs and occur in older patients with a mean age of 62 years. The incidence rate of GBM is 1.6 times higher in males as compared with females, and Whites have the highest incidence rates for GBM, followed by Blacks, Asian/Pacific Islanders, and American Indian/Alaska Natives [2, 3].

GBM can arise either de novo (primary GBM) or develop from transformation of an already existing low-grade glioma (secondary GBM) [2]. The diagnosis is typically made by a combination of computerized tomography (CT) scan, magnetic resonance imaging (MRI) scan, and tissue biopsy. Secondary GBMs occur in younger patients (mean age, 45 years), and tend to contain mutations in isocitrate dehydrogenase-1 (IDH-1), which confers a worse prognosis [1, 4-6]. Many genetic and environmental factors have been studied in GBM but, with rare exception, risk factors have not been identified that lead to the development of GBM tumors, and therefore GBM tumors are felt to arise spontaneously [3, 7].

1.2. Background: Treatment of Glioblastoma

The current standard treatment for GBM is surgery, followed by concurrent radiation therapy (RT) and temozolomide (TMZ) chemotherapy administered daily during RT and then for 6-12 maintenance (adjuvant) cycles following the completion of RT [8].

Maximum, safe surgical resection is the initial step of GBM therapy because surgery serves to 1) confirm the histopathologic diagnosis; 2) relieve symptoms of mass effect 3) remove disease before secondary resistance to radiation and chemotherapy; and 4) prolong survival. Removal of 98% or more of the tumor is associated with a significantly longer disease-free interval and Overall Survival (OS) than if <98% is removed [9]. Following surgery, all patients undergo RT based on a pivotal trial conducted in the 1970s among 303 newly diagnosed GBM patients demonstrating that those who were randomized to receive RT had a median survival that doubled that of those who randomized to not receive RT [10]. RT is typically administered to a total dose of 60 Gy targeting enhancing and T2/FLAIR disease with a 1-2 cm margin via approximately 30 fractions (200 cGy/fraction), but other RT regimens have been assessed in the clinic [11].

The addition of TMZ to RT was based on a randomized phase 3 trial among 575 newly diagnosed GBM patients. In this trial, those who received TMZ daily for six weeks during RT followed by six cycles of maintenance (adjuvant) therapy had a median survival of 14.6 months compared to 12.1 months for those who received RT alone [8, 12]. Approximately two-thirds of GBM patients have tumors that express significant levels of O6-methylguanine methyltransferase (MGMT) due to lack of methylation of the MGMT promoter [13]. MGMT is a ubiquitous DNA repair protein whose expression is enhanced in some cancers, including the majority of GBM patients. These patients have been shown to derive minimal benefit from the addition of TMZ to standard RT. Specifically, in a phase 3 trial, patients with unmethylated

MGMT tumors who received radiation alone had median progression-free and OS of 4.4 months and 11.8 months, respectively, compared to 5.3 months and 12.7 months for those who received TMZ and RT [4]. The addition of TMZ increased both Progression-Free Survival (PFS) and OS for these patients by less than one month and was also associated with more adverse events including neutropenia, thrombocytopenia and infections. Nonetheless, unmethylated MGMT GBM patients are routinely offered TMZ treatment due to lack of more effective treatment options, and because their outcome is otherwise poor [14].

Attempts to improve survival for newly-diagnosed GBM patients in randomized phase III clinical trials evaluating dose-dense adjuvant TMZ [15] and the addition of bevacizumab to inhibit tumor associated angiogenesis[16, 17] have failed, although a recently reported trial demonstrated that the application of tumor-treating fields (TTF), a locoregional anti-mitotic therapy, improved both the median progression-free and OS of patients when administered following completion of RT/TMZ [18].

Supportive treatment focuses on relieving symptoms and improving patients' neurologic function. The primary supportive agents are anticonvulsants and corticosteroids. Historically, around 90% of patients with GBM received anticonvulsant treatment, although it has been estimated that only approximately 40% of patients required this treatment. Corticosteroids, usually dexamethasone, can reduce peritumoral edema, diminishing mass effect and lowering intracranial pressure, with a decrease in symptoms [19].

In addition to dexamethasone, bevacizumab has been shown to be efficacious in treating symptomatic cerebral edema. Inhibition of vascular endothelial growth factor (VEGF) signaling improves PFS among both newly diagnosed and recurrent glioblastoma patients [15, 20], and decreases cerebral edema in glioblastoma preclinical models as well as patients, leading to reduced need for corticosteroids [16, 21, 22]. For patients who develop progressive imaging and/or clinical findings consistent with progression of disease, or require treatment of symptomatic cerebral edema, bevacizumab can be used as initial therapy before corticosteroid therapy. Although dexamethasone can provide rapid symptomatic relief, it is associated with myriad sequelae, such as proximal myopathy, osteoporosis, truncal obesity, hypertension, hyperglycemia, mood alterations and importantly for this trial, immunosuppression. Growing data also links corticosteroid use as an independent predictor of poor prognosis among glioblastoma patients [23-25]. Furthermore, due to their immunosuppressive capability corticosteroids may compromise the anti-tumor activity of immunotherapies such as vaccines and checkpoint inhibitors. Corticosteroid use was associated with poorer outcome for recurrent GBM patients treated with nivolumab on a recently completed phase 3 trial [26].

VEGF inhibitors such as bevacizumab are associated with potential adverse events including hypertension, proteinuria, wound dehiscence, thrombosis, and hemorrhage, particularly following protracted therapy. Due to these concerns, the use of bevacizumab as initial therapy for symptomatic cerebral edema, is a recommended but not required guideline in this trial. Dexamethasone treatment for this indication is allowed for patients with symptomatic cerebral edema for whom bevacizumab is ineffective, contraindicated, not available or not preferred by treating physician/patient, however the lowest course of dexamethasone that is required should be administered when possible.

In summary, the prognosis for newly diagnosed GBM patients treated with current standard therapy remains extremely poor and varies based on MGMT status. Median OS among MGMT methylated patients treated with TMZ and RT is 21.9 months but is only 14.6 months among those with MGMT unmethylated tumors. For all patients, the two and five-year survival rates are only 27% and 9.8%, respectively [12]; thus, there remains a great need to develop better treatments for GBM.

1.3. Rationale for Trial Therapy

In recent years, the induction of anti-tumor cellular immunity has been shown to be an important modality for effective cancer therapy, with immune modulating agents that inhibit PD-1 or PD-L1 demonstrating durable therapeutic benefit across a spectrum of cancer indications [27]. The value of PD-1/PD-L1 inhibitors for glioblastoma patients remains to be determined. Although preliminary results of single-arm phase 2 studies have shown modest therapeutic benefit among recurrent GBM patients [28, 29], a recently reported randomized phase 3 trial failed to demonstrate a survival benefit for recurrent GBM patients treated with nivolumab, an anti-PD-1 antibody, when compared to bevacizumab [26]. A contributing explanation for these disappointing results may include that the recurrent setting, where GBM tumors are typically growing rapidly with aggressive destruction of adjacent brain tissue, may be a suboptimal setting to evaluate immunotherapies which require time to stimulate sufficient anti-tumor immune responses. For this reason, the current protocol will evaluate trial investigational immunotherapy among newly diagnosed GBM patients.

Another factor that may limit the therapeutic benefit of anti-PD-1 therapy among GBM patients is that the microenvironment of GBM tumors is typically immunologically devoid of effector cells, such as cytotoxic T cells, or immunologically “cold.” A recent analysis of lymphocyte infiltration among GBM tumors conducted through the Cancer Genome Atlas (TCGA) demonstrated that over half of GBM tumors lack detectable lymphocytes while only 11% had lymphocytes identified in over 50% of the tumor [30]. Growing evidence demonstrates patients with tumors that are immunologically “cold” and lack an immune infiltrate tend to have a lower rate of benefit from anti-PD-1 therapy [31, 32]. In the current trial, we will evaluate vaccination as a strategy to enhance T cell infiltration and thereby enhance the therapeutic benefit of anti-PD-1 therapy. Vaccination against tumor antigens has been shown to increase T cell infiltration into tumors in preclinical models [33] and in patients [34, 35] leading to enhanced anti-tumor activity when combined with immune checkpoint inhibitor therapy [36, 37] including against GBM tumors [38, 39]. Importantly, in pre-clinical studies tumor vaccination has been shown to lead to an upregulation of PD-L1 expression in the tumor microenvironment [40] providing further justification for combining anti-PD-1/anti-PD-L1 therapy with tumor vaccination.

1.3.1. INO-5401 and INO-9012: DNA-based Immunotherapy

DNA immunization has been recognized as a promising vaccine platform for almost 20 years for a number of reasons [41]. First, the immunogenicity of DNA vaccines is similar to what can be achieved with viral vectors [42]. Potent T-cell immune responses can be generated to virtually any antigenic sequence using DNA vaccines. DNA differs from live attenuated viral vector vaccines in that the viral approaches are associated with safety concerns on their vector

backbone, which DNA vaccines circumvent. Second, as opposed to viral-based vaccines which carry a risk of mutation back to a virulent state or spread to unintended individuals, DNA vaccines are not based on an intact natural pathogen and therefore cannot revert to a virulent form. Third, repeated dosing of viral-based vaccines is generally not feasible due to the neutralization of targeted viral vector sequences. DNA vaccines are associated with virtually no immune response to the plasmid backbone and efficacy of plasmid vectors is not influenced by pre-existing neutralizing antibodies [43], thus allowing repeated dosing to increase or maintain immune responses over long periods. Additionally, pre-existing anti-vector immunity can reduce the immunogenicity of the viral vector for future immunizations. Finally, DNA vaccines are simple and relatively easy to manufacture, are readily produced in large quantities, and are generally stable for long periods of time. Specifically, the ability to engineer specific targeting of multiple antigenic components allows the combination of specific immunogens, adjuvants or targeting sequences. These advantages make DNA-based immunizations a desirable vaccine modality for the prevention and treatment of disease.

To date, DNA vaccines have been well-tolerated in humans. In fact, clinical data from hundreds of subjects vaccinated with DNA plasmids show that Intramuscular (IM) administration primarily elicits local administration site reactions with few systemic AEs. Additionally, preclinical safety studies in the literature have not demonstrated evidence of plasmid integration [44, 45].

INO-5401 is a novel therapeutic consisting of DNA plasmids encoding three proteins whose expression is known to be upregulated in the majority of GBM tumors including human telomerase reverse transcriptase (hTERT; 3 mg), Wilms Tumor-1 (WT1; 3 mg) and prostate specific membrane antigen (PSMA; 3 mg).

In support of this platform, immunization with a full-length hTERT DNA plasmid was shown to be immunogenic and afforded antitumor effects. Immunotherapy elicited strong hTERT-specific CD8+ T-cell responses in mice and was associated with overcoming tolerance and the induction of potent cytotoxic responses in a non-human primate model [46]. Furthermore, hTERT DNA administered with CCL21 adjuvant demonstrated antigen-specific cellular and humoral immune responses and inhibited tumor growth in a mouse model of breast cancer [47]. These data highlight the broad therapeutic potential of hTERT DNA plasmids as cancer therapies.

hTERT is highly expressed in about 80% of GBM tumor samples as measured by Immunohistochemistry (IHC), with little or no expression in normal somatic cells [48, 49]. Loss of telomerase activity leads to hTERT-positive tumor cell death by apoptosis as expression of hTERT is directly linked to tumor cell growth and contributes crucially to the long-term survival of tumor cells [50]. In addition, targeting hTERT may have the potential to eliminate cancer stem cells as recent studies have suggested that cancer stem or stem-like cells express hTERT [51-53]. Therapeutic hTERT vaccines have been widely studied in the clinic because of their potential to stimulate the killing of tumor cells by enhancing the activity of telomerase-specific cytotoxic CD8+ T cells [54].

Similar to hTERT, WT1 is also an attractive target antigen as it is overexpressed in about 86% of GBM tumor samples as measured by IHC [55]. Preclinical studies have suggested that WT1 promotes cell migration and invasion, and that suppression of WT1 significantly decreases tumor proliferation [56, 57]. Treatment with WT1 antisense oligomer specifically inhibits the growth of

several GBM cell lines and it is hypothesized that WT1 may be a new molecular target for glioma therapy [58, 59]. Hashimoto et al. have shown that the WT1 peptide vaccination in combination with TMZ was tolerable and was able to induce CD8+ WT1-tetramer-positive T cells in GBM subjects [59].

PSMA is also highly expressed in approximately 89% of GBM tumors as measured by IHC. [60] In addition, Wernicke et al. demonstrated intensive PSMA staining on the vessels of most of GBM specimens (91%), while no PSMA expression was detected in normal vessels [61]. Preclinical studies have shown that loss of PSMA abrogates angiogenesis and PSMA is required for endothelial cell invasion [62]. Thus PSMA could serve as an effective therapy antigen to include because it is expressed by both GBM tumor cells and GBM-associated vasculature.

For additional information please see the Investigator's Brochure (IB) for INO-5401 + INO-9012.

1.3.1.1. Rationale for Addition of IL-12 Plasmid DNA Molecular Adjuvant

DNA vaccines historically were thought to primarily elicit CD4+ T-cell responses in humans, and there has been interest in discovering ways to boost the immune response. In addition to Electroporation (EP), Inovio has shown that Interleukin 12 (IL-12) DNA can be used as a molecular adjuvant to enhance immune responses. This has been done by co-delivering DNA plasmids expressing immune modulators. The IL-12 DNA adjuvant is a dual promoter expression plasmid encoding human IL-12 proteins p35 and p40 under separate regulatory controls.

In a clinical trial with a vaccine of HIV-1 DNA immunogen, co-administration of IL-12 DNA was associated with an enhanced CD8+ antigen-specific immune response [63, 64]. The use of IL-12 DNA has also been associated with expansion of antigen-specific Interferon Gamma (IFN-γ) positive effector cells, as well as granzyme B production. The induced immunity included both a CD8 as well a CD4 component [65, 66]. The safety information from these studies in humans, forms the preliminary basis for the predicted safety profile for its use as an adjuvant component of the immunotherapy in this proposed clinical trial.

In the current trial, INO-5401 will be combined with INO-9012, a DNA plasmid encoding human interleukin-12 as a strategy to induce IL-12 expression localized to the vaccination site. IL-12 is a pro-inflammatory cytokine that regulates cell mediated immune responses via a wide array of mechanisms including 1) activation and recruitment of dendritic cells that facilitate cross priming of tumor antigen-specific T cells [67, 68]; 2) induction of T cell and Natural Killer Cells (NK) cell interferon-ɣ (IFNɣ) and tumor necrosis factor-α (TNFα) [69]; 3) differentiation of naïve T helper cells (Th0) to an inflamed (Th1) phenotype [70]; 4) differentiation of CD8+ T cells [71]; 5) reactivation and survival of memory CD4+ T cells [72].

1.3.1.2. Rationale for Electroporation (EP) with CELLECTRA® 2000 Device

Several groups are developing methods to improve the immune responses of DNA vaccines, using genetic optimization, cytokine adjuvants, and alternative cellular delivery with devices such as EP [73]. Inovio employs all these methods with an emphasis on improving the transfection of DNA using *in vivo* EP. This physical process exposes the target tissue to a brief

electric field pulse that induces temporary and reversible pores in the cell membrane to enhance the cellular uptake of large molecules such as DNA. By temporarily increasing the permeability of cell membranes, EP has been shown to be an efficient way to introduce DNA into cells [74, 75] and to increase the expression level of antigens encoded by DNA [76]. This technology has been used for more than three decades by molecular biologists for *in vitro* cell transfection.

The hypothesis is that EP will increase the uptake and expression of plasmid DNA (pDNA), generating significantly increased immunogenicity. Electroporation enhances both cellular and humoral immune responses, using less DNA than IM immunizations alone [77]. Studies have demonstrated the ability of EP to augment specific cellular immune responses in mice [78] and in macaques [79]. It has been found that simian immunodeficiency virus (SIV) DNA vaccines potency can be increased 50-200 fold [44] when delivered intramuscularly (IM) followed by EP. There are various means of delivering EP (i.e. constant current vs. constant voltage) and testing these strategies in mice and pigs has shown a constant current device may be the most effective at generating immune responses [80]. Studies in macaques found that EP of SIV DNA + IL-12 plasmids yielded 10-fold higher responses than DNA without EP [76], and that this immune response was boosted with additional doses. These responses are also polyfunctional, as defined by the ability of immune cells from treated animals to generate IFN-γ, tumor necrosis factor alpha (TNF-α) and Interleukin-2 (IL-2). Furthermore, the functional consequence of EP delivery of DNA encoding an antigen in combination with IL-12 is an improved ability of specific $CD8^+$ T cells to proliferate in culture in response to antigenic stimulation compared to delivery without EP [76]. Additionally, it has been shown that delivering DNA vaccines with EP has a significant dose-sparing effect, along with superior immunogenicity when compared to DNA vaccines delivered without the use of EP [81].

1.3.2. REGN2810

REGN2810 is a hinge-stabilized IgG4 (S228P) high affinity anti-PD1 fully human antibody that potently blocks programmed death-1 (PD-1)-PD-1 ligand (PD-L1) functional interaction. REGN2810 has been shown to reverse PD-1 dependent attenuation of T-cell receptor signaling in engineered T cells and enhances human primary T cell responses.

Pre-clinical and early clinical data provide proof-of-principal for the therapeutic potential of strategies to enhance the immune response against GBM. In a murine model of intracranial implantation of a glioma cell line, combined intracranial RT and systemic administration of an anti-PD-1 monoclonal antibody resulted in doubling of median OS, compared to either intervention alone. After combination therapy, re-challenge of the long-term survivors with the same tumor cells resulted in tumor clearance in 100% of the animals [82].

REGN2810 has been investigated in a phase 1 trial in combination with immune modulation, including hypofractionated radiation (hfRT), and/or GM-CSF, and/or low-dose chemotherapy. Thirty-six subjects received REGN2810 at 3 mg/kg/dose given every two weeks, of whom 24 received hfRT. No Dose-limiting toxicity (DLT) was seen, and the most common related AEs included fatigue, arthralgia, and nausea. Investigation of REGN2810 is ongoing in the clinic [83].

REGN2810 is currently being evaluated in a number of clinical trials for patients with advanced solid tumors. R2810-ONC-1423 includes cohorts for newly diagnosed and recurrent GBM. GBM may prevent an effective immune response by creating an immunosuppressive environment, including high expression of immunosuppressive cytokines, enrichment of Tregs, PD-1 expression on T cells, and PD-L1 expression on tumor cells and tumor-associated macrophages [84-86]. These factors suggest that PD-1 blockade should be studied in clinical trials for GBM, and preliminary activity has been observed with the anti-PD-1 antibody nivolumab [87]. For additional information, please see the IB for REGN2810.

1.4. Dose and Regimen Rationale

The doses of DNA chosen for this study are consistent with those shown to be immunogenic in animal studies of INO-5401 + INO-9012. The plasmids encoding PSMA, hTERT, alone and in combination with IL-12, are currently under clinical investigation in two separate trials.

PCa-001 (NCT#02514213) is investigating the tolerability and immunogenicity of the PSMA plasmid in subjects with prostate cancer, at 1 mg or 4.25 mg/dose, with or without INO-9012 at 1 mg/dose; this trial is fully enrolled. TRT-001 (NCT#02327468) is investigating the tolerability and immunogenicity of the hTERT plasmid at 2 mg or 8 mg/dose, with or without INO-9012 at 0.5 mg or 2 mg/dose in subjects with solid tumors, respectively. These studies are ongoing but current data from these studies suggest that both plasmids are well-tolerated and additional information can be found in the INO-5401 + INO-9012 IB.

The plasmid encoding WT1 has not been tested in humans however preclinical data are available. A phase 2 trial of a DNA fusion-gene vaccine encoding for WT1 was studied in 12 subjects with hematological malignancies [88]. In this trial, subjects with chronic myelogenous leukemia received 1 mg each of two DNA vaccines encoding for distinct Wilms' Tumor-1 (WT1) peptides, peptide 37 and peptide 126, followed by EP, administered 6 times every four weeks. These vaccines were well-tolerated, and there were no safety concerns raised by the trial. AEs reported included fatigue (4 subjects); and myalgia (3 subjects). One Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 AE was observed in an unvaccinated control group subject. No vaccine-related SAEs were observed; SAEs were only observed in the unvaccinated control group.

A phase 2 trial of a WT1 peptide vaccine was completed in 21 subjects with recurrent GBM [89]. In this trial, subjects received Intradermal (ID) injections of a modified 9-mer WT1 peptide weekly for 12 weeks. Treatment with the peptide vaccine was well-tolerated, with the only AE reported as local erythema at the vaccine site. Clinical responses as measured by change in tumor size were noted in two subjects.

1.4.1. Rational for REGN2810 Dose Selection

In the ongoing and planned phase 2 and phase 3 clinical studies, REGN2810 monotherapy at a dose of 350 mg every three weeks (Q3W) has been selected to allow for compatibility with many standard chemotherapeutic regimens that are dosed on a Q3W schedule, and to improve patient convenience. This REGN2810 dose of 350 mg Q3W was chosen based on the safety and preliminary anti-tumor activity observed in the ongoing first-in-human study R2810-ONC-1423

(NCT02383212) and was supported by modeling of REGN2810 exposure in serum based on data collected in this study.

Simulations of REGN2810 exposure in 1000 patients using population PK analysis indicated that: 1) the variability in REGN2810 exposure (CV%) was similar with body weight-adjusted as compared to fixed doses, therefore supporting the fixed dose selection; and 2) that a 350 mg Q3W dose resulted in similar (≤20% difference) pharmacokinetics, including Ctrough, AUC12 Week and Cmax as compared to a 3 mg/kg Q2W dose. The 350 mg Q3W dose of REGN2810 dose has therefore been selected for all phase 3 studies across the REGN2810 program.

1.4.2. Restricting Temozolomide to MGMT methylated patients in Maintenance

As noted above approximately two-thirds of GBM patients have tumors that express significant levels of methylguanine methyltransferase (MGMT) due to lack of methylation of the promoter [13], and these patients have been shown to derive minimal benefit from the addition of maintenance TMZ following standard RT. On the other hand, TMZ is a known radiosensitizer. Hence, TMZ dosing will be provided to all subjects for whom it is clinically indicated in combination with radiotherapy but will be restricted in maintenance only to subjects with MGMT promoter methylation, or whose MGMT promoter status is indeterminate, for up to six additional cycles following radiation therapy (Cohort B only).

1.4.3. Hypofractionated Chemoradiotherapy

Standard radiotherapy for newly diagnosed GBM consists of 60 Gy in 30 fractions, based on pre-temozolomide era studies which suggested improved survival and a dose response up to 60 Gy [90]. Multiple randomized trials exploring higher doses of irradiation have not shown a survival benefit [91, 92]. For this study a regimen of 40 Gy over 3 weeks has been selected.

The EORTC/NCIC trial [12] established the current standard of care of temozolomide chemoradiotherapy with an improved median OS of 14.6 months compared to 12.1 months with 60 Gy radiotherapy alone. Although this chemoradiotherapy regimen has become the standard treatment for newly diagnosed GBM, shortening the treatment or de-escalation of dose has never been studied in newly diagnosed, good performance status patients. Given the synergism between radiotherapy and temozolomide, less radiation dose, when combined with chemotherapy or immunotherapy, may be equivalent to 60 Gy of radiotherapy alone.

Dose de-escalation for newly diagnosed GBM in the TMZ era is supported by prospective single institution as well as international randomized data in those with advanced age or lower performance status. As background, a randomized trial of radiotherapy alone found that 40 Gy in 3 weeks had equivalent OS to 60 Gy in 6 weeks [93]. Initially, concern existed that combining radiotherapy of 40 Gy in 3 weeks with standard TMZ chemotherapy may lead to increased toxicity, given the greater daily dose of irradiation. However, in a single arm prospective trial of newly diagnosed patients older than 70 years, Minniti et al. found that 40 Gy in 15 fractions with concurrent TMZ was well tolerated, with a median survival comparable to historical outcomes without unexpected toxicity [94].

Recent randomized prospective data further support this shortened chemoradiotherapy regimen. In 562 patients older than 65 years with newly diagnosed GBM, median OS was longer in

patients randomized to 40 Gy in 15 fractions with concurrent and adjuvant TMZ (9.3 months) compared to 40 Gy in 15 fractions of radiotherapy without TMZ (7.6 months). Although assessed in both MGMT methylated and unmethylated patients, the addition of TMZ provided a statistically significant survival advantage only in MGMT methylated patients [95]. Other than the expected TMZ-related hematologic side effects, no other significant differences in toxicity were seen.

Given that hypofractionated chemoradiotherapy over 3 weeks is a standard of care for an elderly population of patients with newly diagnosed GBM, improvement in outcomes with this regimen may be realized with further intensification of treatment by the addition of immunotherapy.

For multiple reasons, specifically when combined with immunotherapy, a shorter treatment course is potentially beneficial compared to 6 weeks of radiotherapy. First, radiotherapy has potent immunosuppressive effects when given globally, such as in total body irradiation or total lymphoid irradiation as a preparatory regimen for stem-cell transplant. Similarly, localized immunosuppression may be seen in bone marrow and lymph nodes included in the irradiation field; irradiation of these stimulated nodes and immune pathways are likely counterproductive to the immunostimulatory goals of immune checkpoint inhibitors [96]. In patients with GBM treated with chemoradiotherapy, prospective data found that patients with lymphopenia and CD4 counts <200 cells/mm^3 had a median survival of 13.1 months compared to 19.7 months with higher CD4 counts [97-99]. Deaths were from early tumor progression, rather than immunosuppression-related infection, suggesting the important interplay between an intact immune system and tumor control. Furthermore, studies calculating the flow dynamics of the peripheral blood through the brain during a typical irradiation course suggest that the entire circulating blood lymphocyte compartment is irradiated in a 6 week radiotherapy course [100]. In other solid tumors, hypofractionation over a shorter course appears to decrease the rate of lymphopenia [101]. Therefore, a hypofractionated course over 3 weeks may lead to less immunosuppression, less lymphopenia, and improved outcomes, in general and particularly when combined with immunotherapy.

Second, the larger daily doses of radiotherapy with a 3-week regimen (2.67 Gy for 15 days) may be more immunostimulatory than 2 Gy per day. When combined with immunotherapy, radiotherapy may prime the immune system improving potential efficacy with study treatment [102, 103].

1.5. Potential Benefits and Risks

Several studies have demonstrated the potential utility of therapeutic vaccination in subjects with GBM, and there are several ongoing studies of checkpoint inhibitors in combination with radiation and chemotherapy in both newly diagnosed and relapsed GBM subjects. It is anticipated that the combination of a DNA vaccine designed to elicit a T cell response against common GBM tumor antigens, plus a checkpoint inhibitor, in combination with standard therapy will be tolerable and immunogenic, and potentially demonstrate superior efficacy and extend OS in this subject population, when compared historically to previous therapy.

INO-5401 + INO-9012, the device for EP, and REGN2810 are under clinical investigation, and the risk profile of these agents has yet to be determined. In addition to the risk of vaccination and

of receiving INO-5401 + INO-9012 and REGN2810, as described in their respective IBs, there is a risk that the combination of checkpoint inhibition with an antigen-specific T cell response induced by DNA vaccination may increase the risk of observing an AE as compared to either agent alone. In addition, EP also presents a risk of site administration AEs, commonly low-grade, as described in the IB.

Taken together, the data available for INO-5108 (PSMA), INO-1401 (hTERT) and INO-9012 (IL-12), as well as for REGN2810, support the clinical trial proposed, with risk mitigation and AE monitoring put forth in this protocol, given the potential for clinical benefit and improvement in outcome for subjects with GBM.

2. HYPOTHESIS

INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 will be safe, well-tolerated and immunogenic in adult subjects with newly diagnosed GBM.

3. TRIAL DESIGN, OBJECTIVES AND ENDPOINTS

This is a phase 1/2, open-label, multi-center trial to evaluate the safety, immunogenicity and preliminary efficacy, in subjects with newly diagnosed GBM, of INO-5401 (a combination of 3 separate DNA plasmids targeting WT1, PSMA and hTERT genes) and INO-9012 (DNA plasmid encoding human IL-12) delivered by IM injection followed by EP in combination with REGN2810 and chemoradiation or radiation.

There will be 2 cohorts in this trial. Cohort A (32 subjects) will be subjects with a tumor with an unmethylated MGMT promoter. Cohort B (20 subjects) will be subjects with a tumor with a MGMT methylated promoter or who have indeterminate MGMT status. Both cohorts will receive INO-5401 and INO-9012 and REGN2810 at the same doses and on the same dosing schedule, and both cohorts will receive upfront radiation and TMZ. Cohort B will also receive TMZ following radiotherapy for up to six cycles.

3.1. Primary Objective

To evaluate the safety and tolerability of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 in adult subjects with newly diagnosed GBM.

3.2. Primary Endpoint(s) and Assessments

1. Incidence of AEs, graded per CTCAE v4.03, and classified by system organ class, preferred term, severity, and relationship to trial treatment.
2. Clinically significant changes in safety laboratory parameters from baseline.

3.3. Secondary Objective(s)

1. To evaluate preliminary clinical efficacy of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 in adult subjects with newly diagnosed GBM.
2. To evaluate preliminary immunogenicity of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 in adult subjects with newly diagnosed GBM.

3.4. Secondary Endpoint(s) and Assessments

1. Overall survival at 18 months (OS18).
2. Antigen-specific cellular immune responses assessed by:
   - Interferon-γ secreting T lymphocytes in peripheral blood mononuclear cells (PBMC) by ELISpot
   - T-cell phenotype [redacted] in PBMC by Flow Cytometry

[redacted]

3.5. Exploratory Objective(s)

1. To explore correlative association between clinical efficacy and tumor genetics and/or biomarkers.
2. To further evaluate efficacy of INO-5401 and INO-9012 delivered by IM injection followed by EP with CELLECTRA® 2000 in combination with REGN2810 and hypofractionated RT in adult subjects with newly diagnosed GBM.

3.6. Exploratory Endpoint(s)

1. Tumor infiltrating lymphocytes (TILs) and immunosuppressive elements, where feasible
2. Expression of tumor oncoproteins, [redacted]

7. Progression-Free Survival, as assessed by RANO (Response Assessment in Neuro-oncology) criteria and Immunotherapy Response Assessment in Neuro-oncology (iRANO) criteria [104]
8. Overall Survival (OS)

3.7. Safety Run-in

A safety run-in will be performed using a modified Rolling 6 design, which will enroll up to six subjects to each Cohort (A and B up to 12 subjects total). Enrollment will be staggered, with a waiting period of one week between enrollment of the first and second subject and again between the second and third subject in each cohort. Each subject will be assessed up to Week 9. By Week 9 a subject will have received three doses of REGN2810, three doses of INO-5401 + INO-9012, and will have completed RT.

Once the first three subjects of these six in each cohort have completed Week 9 assessments, in the absence of dose-limiting toxicity (DLT), following a review of all available safety data from these patients by the Medical Monitors from the Sponsor and from Regeneron Pharmaceuticals, and the coordinating Principal Investigator, enrollment to that cohort may begin in full. However, if prior to the first three subjects in each cohort completing Week 9, a single subject from the first six in that cohort experiences a DLT then enrollment will be limited to six subjects in that cohort until all six subjects have reached Week 9 and are assessed for DLT.

If a second subject within the first 6 experiences a DLT in the same cohort within the first 9 weeks, enrollment to that cohort will stop, and the Sponsor's Medical Monitor, in addition to the Principal Investigator (PI) and Investigator(s) at the subjects' site(s) will discuss the case, and a decision will be made whether to modify trial drug or concomitant drug (RT/TMZ) dose within that cohort, or to cease further enrollment to that cohort. If a change to the protocol is required, enrollment will only be re-initiated after amendment of the protocol and approval of the amended protocol by the IRB.

A DLT is defined as:

Non-Hematologic Toxicity

1. Grade ≥2 uveitis.
2. Grade ≥3 non-hematologic toxicity; with the exception of:
    a. Grade 3 nausea, vomiting or diarrhea unless persistent (>7 days duration) despite maximal supportive care measures as prescribed by the treating physician.
    b. Grade ≥3 laboratory abnormalities that are considered clinically insignificant and do not meet criteria for an AE.
    c. Grade 3 infusion-related reactions that respond to medical management.
    d. Grade 3 Immune-Related Adverse Events (IRAE), other than uveitis, that improve within 14 days to Grade ≤2 with medical management (including treatment with steroids).

Hematologic Toxicity

1. Grade 4 neutropenia >7 days.
2. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding.
3. Grade ≥3 febrile neutropenia (fever ≥ 38.5°C with absolute neutrophil count [ANC] < 1000/mm^3), or Grade ≥ 3 neutropenia with documented infection.

Events considered by the treating Investigator to be related to underlying tumor, concurrent medication or co-morbid event, and events that are considered unlikely related to trial therapy (INO-5401, INO-9012 or REGN 2810), but at least probably related to either temozolomide or RT will not be considered a DLT.

Patients who experience DLT may be discontinued from further trial therapy and will enter the post-trial follow-up phase of the trial.

Adverse events that meet DLT criteria but occur outside the DLT window will be classified as unacceptable AEs and trial treatment may be discontinued.

3.8. Stopping Rules

Following the safety run-in period, if at any point during the course of this clinical study, ≥30% of subjects in either cohort experience a dose-limiting toxicity as defined in Section 3.7 deemed related to investigational trial drug(s), enrollment to one or both cohorts will stop, and the Sponsor's Medical Monitor, in addition to the Principal Investigator (PI) and Investigator(s) at the subjects' site(s) will discuss the safety profile of the trial drug(s), and a decision will be made whether to modify trial drug or concomitant drug (RT/TMZ) dose within one or both cohorts, or to cease further enrollment to one or both cohorts. If a change to the protocol is required, enrollment will only be re-initiated after amendment of the protocol and approval of the amended protocol by the IRB.

4. TRIAL POPULATION

4.1. Inclusion Criteria

1. Subjects must provide written IRB approved informed consent in accordance with institutional guidelines;
2. Be 18 years of age or older on the day of signing the informed consent, and able and willing to comply with all trial procedures;
3. Newly diagnosed brain cancer with histopathological diagnosis of glioblastoma (GBM);
4. Karnofsky Performance Status (KPS) rating of ≥70 at baseline (Appendix B);
5. Receive dexamethasone equivalent dose ≤2 mg per day, stable or decreased for ≥ three days prior to Day 0;
6. Recovery from the effects of prior GBM surgery as defined by the Investigator;
7. Electrocardiogram (ECG) with no clinically significant findings as assessed by the Investigator performed within 28 days of signing the informed consent form (ICF);

8. Adequate organ function as demonstrated by hematological, renal, hepatic parameters as defined in the table below, obtained within 28 days prior to the first trial treatment.

Table 3: Eligibility Laboratory Requirements

Absolute neutrophil count (ANC)	**≥1500/mm^3**
Platelets	≥100,000/mm^3
Hemoglobin	≥9 g/dL
Creatinine OR Measured or calculated creatinine clearance or GFR *	≤ 1.5 X upper limit of normal (ULN) OR ≥50 mL/min for subject with creatinine level > 1.5 X institutional ULN
Total bilirubin	≤ 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
*Creatinine clearance should be calculated per Cockcroft-Gault equation (Appendix E)	

9. Agree that during the trial, men will not father a child, and women cannot be or become pregnant if they are of child-bearing potential. Subjects must be of non-child bearing potential (≥12 months of non-therapy-induced amenorrhea, confirmed by follicle stimulating hormone [FSH], if not on hormone replacement); or surgically sterile (vasectomy in males or absence of ovaries and/or uterus in females); or agree to use one highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and at least through week 12 after last dose. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with an expected failure rate of < 1% per year include male sterilization and hormonal implants. Alternatively, proper use of combined oral or injected hormonal contraceptives and certain intrauterine devices (IUDs) or two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year (barrier methods must always be supplemented with the use of a spermicide);
10. Ability to tolerate magnetic resonance imaging (MRI).

4.2. Exclusion Criteria

1. Presence of greater than 1 cm x 1 cm residual tumor enhancement on post-operative MRI;
2. Multifocal disease or leptomeningeal disease (LM) disease on post-operative MRI;
3. Are not scheduled to start radiation within 42 days of surgical resection of their tumor;
4. Receive dexamethasone equivalent dose >2 mg per day;
5. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway at any point in the past;

6. Receipt of a previous approved or investigative immune modulatory agent (for example, anti-TNF, therapeutic anti-cancer vaccines, cytokine treatments (other than G-CSF or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI3K-delta, or OX-40) within 28 days of receiving the first dose of treatment;
7. Have received prior treatment with idelalisib at any point in the past;
8. Past, current or planned treatment with tumor treatment fields (Optune; NovoTTF); oncolytic viral treatment; or prior exposure to an investigational agent or device, including Gliadel wafer (Carmustine) implant for chemotherapy; within 28 days of receiving the first dose of treatment;
9. Allergy or hypersensitivity to REGN2810 or to any of its excipients;
10. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments;
11. Ongoing or recent (within 5 years) evidence of autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAE), with the exception of: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment;
12. Diagnosis of immunodeficiency or treatment with systemic immunosuppressive therapy within 28 days prior to the first dose of trial treatment, other than dexamethasone for the underlying disease under investigation, as noted in the inclusion criteria;
13. Positive serological test for human immunodeficiency virus (HIV), or a history of HIV infection; or positive tests for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating active or chronic infection, as these infections may interfere with the ability to mount an appropriate immune response to vaccination;
14. Current malignancy at another site, with the exception of adequately treated basal or squamous cell skin cancers, or carcinoma of the cervix *in situ*, with no evidence of disease within 3 years. Cancer survivors who have undergone curative therapy for a prior malignancy, have no evidence of disease for 3 years and are deemed at low risk for recurrence are eligible for the trial;
15. Receipt of any vaccine within 4 weeks prior to first dose of trial treatment with the exception of the inactivated influenza vaccine, which may be given up to 2 weeks prior;
16. History of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with trial assessments or endpoint evaluation, or otherwise impact the validity of the trial results (e.g. chronic renal failure, angina, myocardial ischemia or infarction, New York Heart Association (NYHA) class III/ IV cardiac disease); or any cardiac pre-excitation syndromes (such as Wolff-Parkinson-White; cardiomyopathy, or clinically significant arrhythmias);
17. History of pneumonitis within the last 5 years;

18. Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs, excluding over-the-counter aspirin or non-steroidal anti-inflammatory drugs, such as ibuprofen) within 2 weeks of Day 0;
19. Fewer than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    - Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
    - Metal implants or implantable medical device within the intended treatment site (i.e. EP area);
20. Active drug or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to trial requirements;
21. Imprisonment, or compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
22. Pregnant or current breastfeeding;
23. As determined by the Investigator, any medical or psychological or non-medical condition that might interfere with the subject's ability to participate or affect the safety of the subject.

4.3. Discontinuation or Withdrawal of Subjects

A subject will be considered to have completed the trial treatment when their disease has progressed.

A subject should not receive any further investigational product(s) (IP) if any of the following occur:

- Withdrawal of consent or lost to follow-up;
- Disease progression;
- An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing of any trial medication;
- Pregnancy;
- Subject noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal;
- Initiation of new anticancer therapy.

Investigators should discuss the reason for any discontinuation of trial treatment with the Sponsor's Medical Monitor as soon as possible when information becomes available.

The Investigator or study coordinator must notify the Sponsor as soon as possible when a subject has been discontinued or withdrawn. If a subject discontinues from the trial or is withdrawn from the trial prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.1 Safety Parameters.

4.4. Co-Enrollment Into other Trials

Enrollment into other trials (including, but not limited to, tissue repositories) while enrolled on GBM-001 is prohibited without approval from Sponsor's Medical Monitor.

4.5. Trial Discontinuation

The Sponsor reserves the right to discontinue the trial at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Additionally, the trial may be discontinued at any time by an IRB, Inovio, the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

Should the trial be terminated and/or the site closed for any reason, all investigational drugs and devices must be returned to Inovio or its representative. The PI should ensure their site file documents are complete prior to archiving, and provide copies of any requested documents to Inovio for its trial master file (TMF).

5. TRIAL TREATMENT

5.1. Investigational Drug Products

The trial drug products to be used in this clinical trial are listed in Table 4.

Table 4: Investigational Drug Products

Product	Formulation	Unit
INO-5401	[redacted]	[redacted]
INO-9012	[redacted]	[redacted]
REGN2810	[redacted]	[redacted]

5.1.1. INO-5401 + INO-9012

The active pharmaceutical ingredients (APIs) in INO-5401 are DNA plasmid sequences that were designed and constructed using proprietary synthetic consensus (SynCon®) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. The INO-5401 plasmids are as follows:

[redacted]

Both DNA plasmid products INO-5401 and INO-9012, are administered using a syringe and the investigational CELLECTRA® 2000 EP device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA plasmid, which increases cell membrane permeability and improves uptake of the DNA. [75, 106] Details about the CELLECTRA® 2000 device are found in the IB and device User Manual.

5.1.2. REGN2810

REGN2810 is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kDa based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region in Fc portion of the molecule. The REGN2810 heavy chain possesses an IgG4 isotype-constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody.

[redacted]



5.2. Treatment Regimens

Prior to Execution of Protocol v5.0:

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will start immunotherapy with REGN2810 and INO-5401 + INO-9012 on Day 0. REGN2810 will be administered IV every three weeks at a dose of 350 mg per dose, in the absence of dose holding, until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. INO-5401 and INO-9012 IM followed by EP will be administered every three weeks for four doses, and then every 9 weeks, at a dose of 10 mg/DNA per dose, in the absence of dose holding, until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. RT will begin no later than 42 days after surgical intervention and should start approximately 1 to 2 weeks after Day 0. RT will continue for approximately three weeks. The total dose of RT will be 40 Gy and it will be given over 3 weeks.

Daily TMZ with radiation therapy (TMZ/RT) will begin no later than 42 days after surgical intervention and should start approximately 2 weeks after Day 0. TMZ/RT should continue for approximately three weeks. TMZ will be given at a dose of 75 mg/m^2/dose, in the absence of dose reduction. Subjects should then receive maintenance (adjuvant) TMZ for an additional 6 cycles. Cohort B will also receive TMZ following radiotherapy for up to six cycles. Maintenance (adjuvant) TMZ should be administered to subjects in Cohort B for the first 5 days of a 28-day cycle at 150-200 mg/m2/dose, following peripheral blood count recovery from TMZ/RT per standard guidelines TMZ treatment.

Day 0 (first dose of INO 5401, INO 9012 and REGN2810) should be at least 14 days after completion of resection of primary tumor and the subject has recovered from surgery, but no later than post-operative day 28.

For subjects who discontinue one therapy (either INO-5401 + INO-9012 or REGN2810) for reasons other than progression, the other therapy may continue after consultation with the Medical Monitor.

Following Execution of Protocol v5.0:

REGN2810 will be administered via IV every three weeks at a dose of 350 mg per dose, in the absence of dose holding, until disease progression, unacceptable toxicity, withdrawal of consent, or death. Confirmation of disease progression is not required.

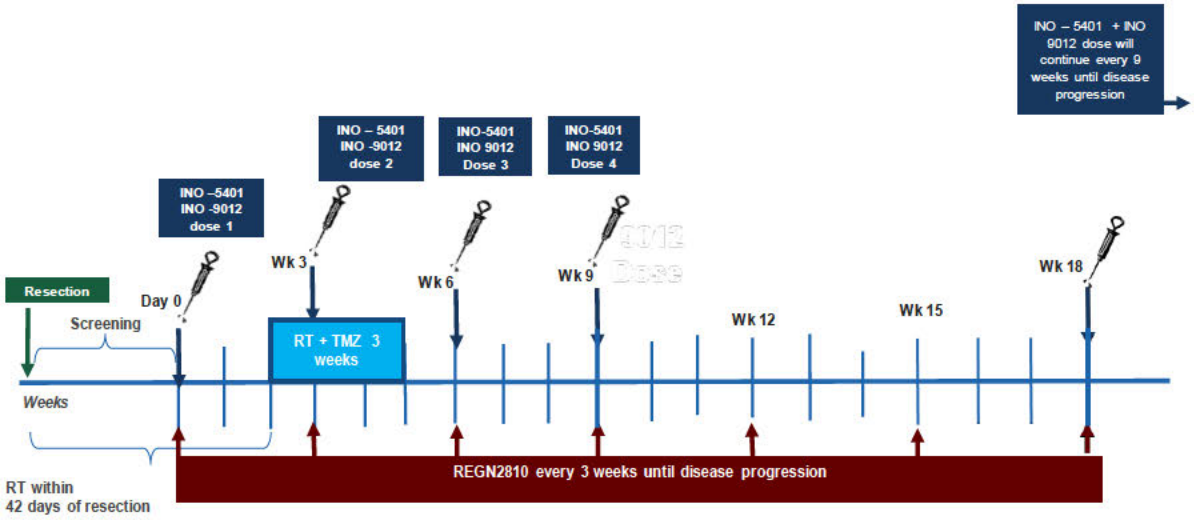
INO-5401 and INO-9012 will be administered via IM followed by EP every three weeks for four doses, and then every 9 weeks, at a dose of 10 mg/DNA per dose, in the absence of dose holding,

until disease progression, unacceptable toxicity, withdrawal of consent, or death. Confirmation of disease progression is not required.

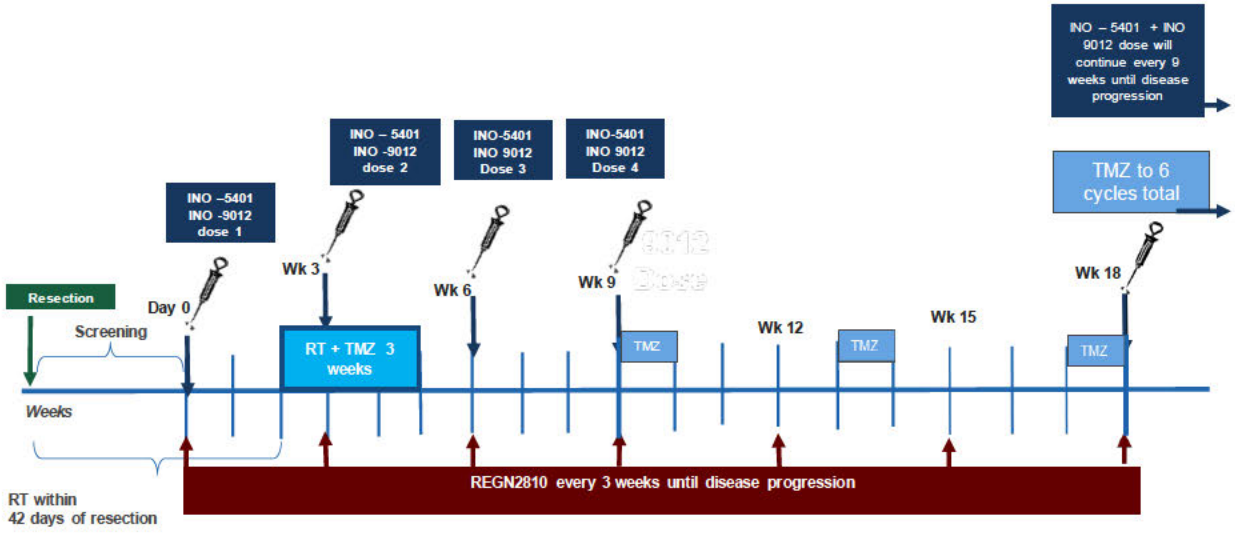
For subjects who discontinue one therapy (either INO-5401 + INO-9012 or REGN2810) for reasons other than progression, the other therapy may continue after consultation with the Medical Monitor.

The following schema describes the overall treatment regimen:

Trial Design for Cohort A MGMT Unmethylated



Trial Design for Cohort B MGMT Methylated or Indeterminate



5.2.1. REGN2810

Prior to Execution of Protocol v5.0:

REGN2810 will be administered IV at a dose of 350 mg every three weeks (Q3W) over approximately 30 minutes, starting at Day 0, and continued until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. Further dosing instructions for REGN2810 can be found in the pharmacy manual.

Following Execution of Protocol v5.0:

REGN2810 will be administered via IV at a dose of 350 mg every three weeks (Q3W) over approximately 30 minutes until disease progression, unacceptable toxicity, withdrawal of consent, or death. Confirmation of disease progression is not required. Further dosing instructions for REGN2810 can be found in the pharmacy manual.

5.2.2. INO-5401 + INO-9012

Prior to Execution of Protocol v5.0:

INO-5401 is a mixture of three separate synthetic plasmids that target WT1, PSMA and hTERT proteins. Each plasmid is dosed at 3 mg DNA, for a total of 9 mg DNA per dose of INO-5401. INO-5401 will be administered IM at Day 0, Week 3, Week 6, and Week 9, and then every 9 weeks thereafter, and continued until disease progression as defined by iRANO, unacceptable toxicity, withdrawal of consent, or death. INO-9012 is a synthetic plasmid that expresses human IL-12, and is dosed at 1 mg DNA, and will be administered IM together with INO-5401. The total dose of DNA in each dose of INO-5401 + INO-9012 when mixed and administered together is 10 mg. Further dosing instructions for INO-5401 and INO-9012 can be found in the pharmacy manual.

Following Execution of Protocol v5.0:

INO-5401 is a mixture of three separate synthetic plasmids that target WT1, PSMA and hTERT proteins. Each plasmid is dosed at 3 mg DNA, for a total of 9 mg DNA per dose of INO-5401. INO-5401 will be administered IM every 9 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or death. Confirmation of disease progression is not required. INO-9012 is a synthetic plasmid that expresses human IL-12, and is dosed at 1 mg DNA, and will be administered IM together with INO-5401. The total dose of DNA in each dose of INO-5401 + INO-9012 when mixed and administered together is 10 mg. Further dosing instructions for INO-5401 and INO-9012 can be found in the pharmacy manual.

5.2.3. Radiation therapy

All subjects will receive a total of 40 Gy in 15 fractions (three weeks). Hypofractionated radiation therapy (hfRT) must begin no later than 42 days after surgery. Radiotherapy will be given for three weeks. Please see Appendix H for details regarding administration of radiation; dose modification to hfRT is discussed below in Section 5.3.

5.2.4. Temozolomide therapy

All patients will receive TMZ, regardless of MGMT methylation status, unless clinically contraindicated, during radiotherapy. TMZ will be administered at 75 mg/m^2 daily by mouth for 21 days concomitant (7 days a week for three weeks) with hfRT therapy.

Following radiation therapy, subjects with MGMT promoter methylation or indeterminate methylation status (Cohort B) will continue TMZ maintenance therapy at a starting dose of 150 mg/m^2/day for 6 cycles on the first 5 days of a 28-day cycle (5 days “on,” 23 days “off”), and increased each maintenance cycle by 50 mg/m^2/dose to a maximum of 200 mg/m^2/dose, in the absence of hematologic toxicity (See Section 5.3.4). Maintenance (adjuvant) TMZ will start approximately four weeks after the last dose of RT (± 3 days) and following peripheral blood count recovery, per TMZ treatment guidelines. The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of each treatment cycle. The daily dose will be rounded to the nearest 5 mg.

5.3. Dose Modifications

5.3.1. REGN2810

The general approach to REGN2810 toxicity management is dose interruption rather than dose modification. REGN2810 treatment may be held at any time upon occurrence of a treatment-related AE. Missed doses of systemic therapy will not be made up, unless ≤3 days from the scheduled date.

Subjects will generally remain on the assigned dosage of REGN2810 throughout the course of trial treatment. General guidelines for REGN2810 treatment modifications due to AEs and irAEs are provided in Table 5 and Table 6 These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual subject. For additional information regarding irAEs, reference Appendix C. Acute infusion reactions to REGN2810 are discussed separately in Section 5.5.1.1. Please see Table 5 and Table 6 below, and Appendix C for specific guidance.

Table 5: General Guidelines for REGN2810 Treatment Modifications or Discontinuations Due to Treatment Related Adverse Events

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Discontinuation Criteria
Hematological Toxicity (other than Grade 3 thrombocytopenia greater than 7 days or associated with bleeding)	1, 2, 3	No	N/A	N/A
	4	Yes	Toxicity resolves to Grade ≤1 or baseline	Toxicity does not resolve within 84 days of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Grade 3 thrombocytopenia greater than 7 days or associated with bleeding	3	Yes	Toxicity resolves to Grade ≤1 or baseline	Toxicity does not resolve within 84 days of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-hematological Toxicity	1	No	N/A	N/A
Note: Exceptions to be treated as for Grade 1 toxicity: Grade 2 alopecia Grade 2 fatigue Clinically insignificant lab abnormality not meeting AE criteria	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0–1 or baseline	Toxicity does not resolve within 84 days of last infusion
	3	Yes	Toxicity resolves to Grade 0–1 or baseline	Toxicity does not resolve within 84 days of last infusion
	4	Yes	N/A	Subject must be discontinued

Table 6: General Treatment Hold Guidelines for Immune-Related Adverse Events

Severity	Withhold or Discontinue Treatment?	Supportive Care
Grade 1	No action	Provide symptomatic treatment.
Grade 2	May withhold treatment	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.

Severity	Withhold or Discontinue Treatment?	Supportive Care
Grade ≥3	Withhold treatment; discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. For any severe (Grade 3-4) irAE, if symptoms worsen or do not improve on adequate corticosteroids within 48 to 72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as infliximab, cyclophosphamide, cyclosporine, mycophenolate mofetil). Referral of the subject to a specialized unit for assessment and treatment should be considered.

5.3.1.1. Resumption of REGN2810 After Treatment Hold, or Discontinuation

Resumption of REGN2810 after resolution of AE to ≤Grade 1 (or baseline) is allowed at the discretion of the Investigator in accordance with the toxicity management guidelines in this protocol if resumption of treatment is thought to be in best interest of the subject. Treatment after an AE may resume, at the discretion of the Investigator, if the AE is felt to be manageable through supportive/medical therapy (eg, Grade 3 hypertension that can be controlled with the addition of a second anti-hypertensive agent). However, REGN2810 treatment resumption is not allowed in the following circumstances:

- Subjects with events that require REGN2810 to be permanently discontinued or held for more than 84 days from last scheduled dose.
- Subjects with ≥Grade 2 uveitis. Subjects with Grade 2 uveitis will generally be discontinued from REGN2810 treatment, unless there is resolution to ≤Grade 1 AND approval from the Medical Monitor at the Sponsor prior to resumption of treatment.

If REGN2810 is held, other treatments may be continued at the discretion of the treating clinician.

5.3.2. INO-5401 + INO-9012

There are no dose modifications for INO-5401 and INO-9012, however doses of INO-5401 and INO-9012 may be held secondary to AEs thought related to INO-5401 + INO-9012. Missed doses greater than 3 days past the scheduled dose should be made up as soon as possible but no later than 2 weeks before the next scheduled INO -5401 + INO-9012 dose. Please notify the Medical Monitor with rationale for missed doses.

The principal expected INO-5401 + INO-9012-related toxicities are:

- Local injection site reactions (common) characterized by erythema, pruritus, swelling, pain, rash, induration, urticarial, and rarely, vesicles.
  - If mild to moderate (NCI CTCAE Grade 1 or 2) reactions are felt to interfere with activities of daily living based on patient tolerability, dose omission may be

considered if there is residual toxicity at the time of re-treatment. Further vaccine doses should be discontinued in the event of a NCI CTCAE Grade ≥3 injection site reaction.

- Hypersensitivity reactions (theoretical).
  - Patients who experience Grade 3 or 4 allergic reactions should not receive further vaccination. Patients who experience Grade 2 allergic reactions should discontinue vaccine therapy unless the Investigator, after discussion with the Inovio Medical Monitor, determines that it is in the best interest of the patient to continue with therapy. Any Grade 2 or greater hypersensitivity/allergic reaction following vaccination should be reported to Inovio (or designee) as an "adverse event of special interest (AESI)" within 24 hours of the site's awareness of the event.
- If any other significant toxicity (eg, CTCAE Grade 3) is observed, and there is a reasonable likelihood that the event may be associated with administration of INO-5401 + INO-9012, the next immunization for that patient should be withheld until the toxicity improves to ≤Grade 1 or baseline. If the significant toxicity is observed again or is not reversible, all further immunizations should be discontinued.

If vaccinations are discontinued for any reason, other trial treatments may continue at the Investigator's discretion.

5.3.3. Radiation therapy

There are no planned dose modifications to hfRT. Radiation may be held for radiation-induced toxicity per institutional guidelines, but the total dose of radiation must be 40 Gy, even if elongation of the treatment period with hfRT is required. If radiation is held, continuation of trial investigational therapy and TMZ may be continued if felt to be in the best interest of the subject as determined by the treating physician after consultation with the trial Medical Monitor.

5.3.4. Temozolomide

The following information regarding temozolomide was obtained from the package insert for TEMODAR® [107].

5.3.4.1. Temozolomide concomitant with Radiation Therapy

Dose reductions are not recommended when TMZ is administered together with radiotherapy however dose interruptions or discontinuation may occur based on toxicity (Table 7).

During the radiotherapy treatment phase, radiotherapy will not be administered on Saturday and Sunday. TMZ dose should be taken 7 days a week including on these weekend days (Saturday and Sunday).

If the administration of TMZ requires interruption, radiotherapy and trial investigation therapy may proceed if felt to be in the best interest of the subject as determined by the treating physician after consultation with the trial Medical Monitor. Missed doses of TMZ will not be made up.

Table 7: Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	Temozolomide interruption	Temozolomide discontinuation
Absolute Neutrophil Count	500/mm^3 ≤ANC<1500/mm^3	<500/mm^3
Platelet Count	10,000/mm^3≤PLT<100,000/mm^3	<10,000/mm^3
Non-hematological toxicity*	CTCAE Grade 2	CTCAE Grade 3 or 4

*Excluding alopecia, nausea or vomiting.

Resuming treatment with concomitant TMZ may be continued when all of the following conditions are met: absolute neutrophil count (ANC) ≥1,500/mm^3; platelet count ≥100,000/mm^3; non-hematological toxicity ≤Grade 1 (except for alopecia, nausea, vomiting).

5.3.4.2. Temozolomide Maintenance (Adjuvant) Phase (Cohort B Only)

Approximately four weeks after completing the concomitant TMZ with radiotherapy phase, and following recovery, TMZ is administered for an additional 6 cycles of maintenance (adjuvant) treatment in subjects with MGMT promoter methylation or indeterminate methylation status (Cohort B).

During maintenance (adjuvant) TMZ treatment, a CBC should be obtained on Day 22 (21 days after the first dose of TMZ) or within 48 hours of that day, and, if necessary, weekly until the ANC is ≥1,500/mm^3 and the platelet count ≥100,000/mm^3. The next cycle of TMZ should not be started until the ANC and platelet count exceed these levels.

TMZ dosing in Cycle 1 is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the TMZ dose can be escalated to 200 mg/m^2 once daily for 5 days if during Cycle 1 the following were true:

- Absolute neutrophil count (ANC) ≥1,500/mm^3
- Platelet count ≥100,000//mm^3
- CTCAE non-hematological toxicity ≤Grade 2 (except for alopecia, nausea, or vomiting)

The TMZ dose should remain at 200 mg/m^2 per day for the first 5 days of each subsequent cycle unless a toxicity that requires dose reduction occurs.

Dose reductions or discontinuations during the maintenance phase should be applied according to Table 8 and Table 9, in the presence of hematological or non-hematological toxicity. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. If a dose reduction is required, the TMZ dose should be reduced by 50 mg/m^2/dose, to a minimum of 100 mg/m^2/dose. No dose reductions are permitted after reducing the dose to 100 mg/m^2; if further toxicity develops, TMZ must be discontinued.

Table 8: Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 9: Temozolomide Dose Reduction or Discontinuation during Maintenance Treatment for Treatment-Related Toxicity

Toxicity	Reduce TMZ by 1 Dose Level	Discontinue TMZ
Absolute Neutrophil Count	<1,000/mm^3	See footnote*
Platelet Count	<100,000/mm^3	See footnote*
Non-hematological toxicity (except for alopecia, nausea, vomiting)	CTCAE Grade 3	CTCAE Grade 4

*TMZ is to be discontinued if dose reduction to less than 100 mg/m2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

5.4. Concomitant Medications

5.4.1. REGN2810

No concomitant medications are required to be provided with REGN2810.

5.4.2. INO-5401 + INO-9012 with EP

5.4.2.1. Topical Anesthetic

Subjects may be offered topical anesthetic [redacted]

5.4.2.2. Sedatives

Subjects may be offered a mild sedative [redacted]

5.4.3. Anti-Inflammatory medications

5.4.3.1. Steroids

Systemic oral steroids (dexamethasone) may be given to subjects during the treatment and follow-up phases of this trial, but dexamethasone doses should be limited to 2 mg/day. Investigators are encouraged to use as low a dose of systemic corticosteroids for as short a duration as possible. Higher doses of dexamethasone or equivalent should be discussed with the Medical Monitor.

5.4.3.2. Bevacizumab

Bevacizumab or its biosimilar may be used at the discretion of the investigator for the treatment of symptomatic cerebral edema [108]. Bevacizumab should be initially dosed at 5 mg/kg biweekly until symptoms sufficiently regress and may be increased to 10 mg/kg as needed.

There are no reductions in the bevacizumab dose for subjects while on trial therapy for treatment of symptomatic cerebral edema or concern for clinical and/or radiologic progression. Guidelines for holding or discontinuing bevacizumab due to adverse events considered at least possibly related to bevacizumab are summarized in Appendix F. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Subjects who require bevacizumab hold or discontinuation are permitted to continue to receive other trial therapy. Any toxicity associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the trial, treatment with bevacizumab should be discontinued.

5.4.4. Pneumocystis prophylaxis

Prophylaxis for Pneumocystis jirovecii Pneumonia (PJP) during radiation will be per clinical guidelines and is suggested for patients who receive TMZ and are at risk for significant lymphocytopenia. PJP prophylaxis should be started and continued in subjects who develop lymphocytopenia until recovery from lymphocytopenia (CTCAE Grade ≤1). Prophylaxis should also be considered for patients who require chronic corticosteroid dosing.

5.5. Administration Instructions

REGN2810 should be administered prior to INO-5401 + INO-9012 for all treatment visits.

5.5.1. REGN2810

REGN2810 will be administered via IV over approximately 30 minutes. [redacted]

5.5.1.1. Management Of Acute Infusion Reactions

Emergency equipment and medication for the treatment of potential adverse effects (e.g. antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and or epinephrine) secondary to infusion of REGN2810 must be available for immediate use.

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Grade 2 or greater infusion-related reactions are considered AEs of special interest (AESI) and must be reported within 24 hours of identification by the Investigator.

In the event of an infusion reaction of Grade 3 or greater severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must be permanently discontinued from REGN2810 treatment.

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 during the infusion or within one day after the infusion.

Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

The infusion should be interrupted if any of the following AEs are observed:

- Cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If Investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure

5.5.2. INO-5401 + INO-9012

INO-5401 in combination with INO-9012 will be administered as a mix in a volume of approximately 1 mL by IM injection followed immediately by EP. Both deltoid and quadriceps muscles can be considered for the sites of injection and EP. A site for injection/EP is not acceptable if there are tattoos, keloids or hypertrophic scars within 2 cm of the intended site of injection or if there is an implanted metal within the same limb. Any device implanted in the chest (e.g., cardiac pacemaker or defibrillator) excludes the use of the deltoid muscle on the same side of the body.

Injections and EPs will be given in the outpatient units or clinical offices. The trial treatment procedure will be performed by qualified personnel. An individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to subjects (e.g. MD, DO, RN, PA, NP) in addition to satisfactorily completing device training from the Sponsor personnel.

Procedures for the preparation of INO-5401 in combination with INO-9012 are provided within the pharmacy manual.

5.5.3. Use of CELLECTRA® 2000 Electroporation Device

The instructions for use of the CELLECTRA® 2000 device are located in the User Manual. Each clinical site will receive training for the use of the CELLECTRA® 2000 device. The following specifications will be used during the trial:

[redacted]

5.5.4. Downloading of EP Data from CELLECTRA® Device

Following each treatment with INO-5401 and INO-9012, data should be downloaded from the EP device, and the data file that is created should be sent to Inovio Pharmaceuticals, Inc. or

designee. Instructions on how to download the data and contact information will be provided in the User Manual and during training.

5.6. Packaging and Labeling

This trial is open label. Therefore the subject, the investigator site personnel and the Sponsor or its designee are not blinded to trial treatment. Each vial of IP will be labeled with a single panel label. At minimum, the following information will appear on the drug product labels:

Table 10: Example Investigational Product Labels

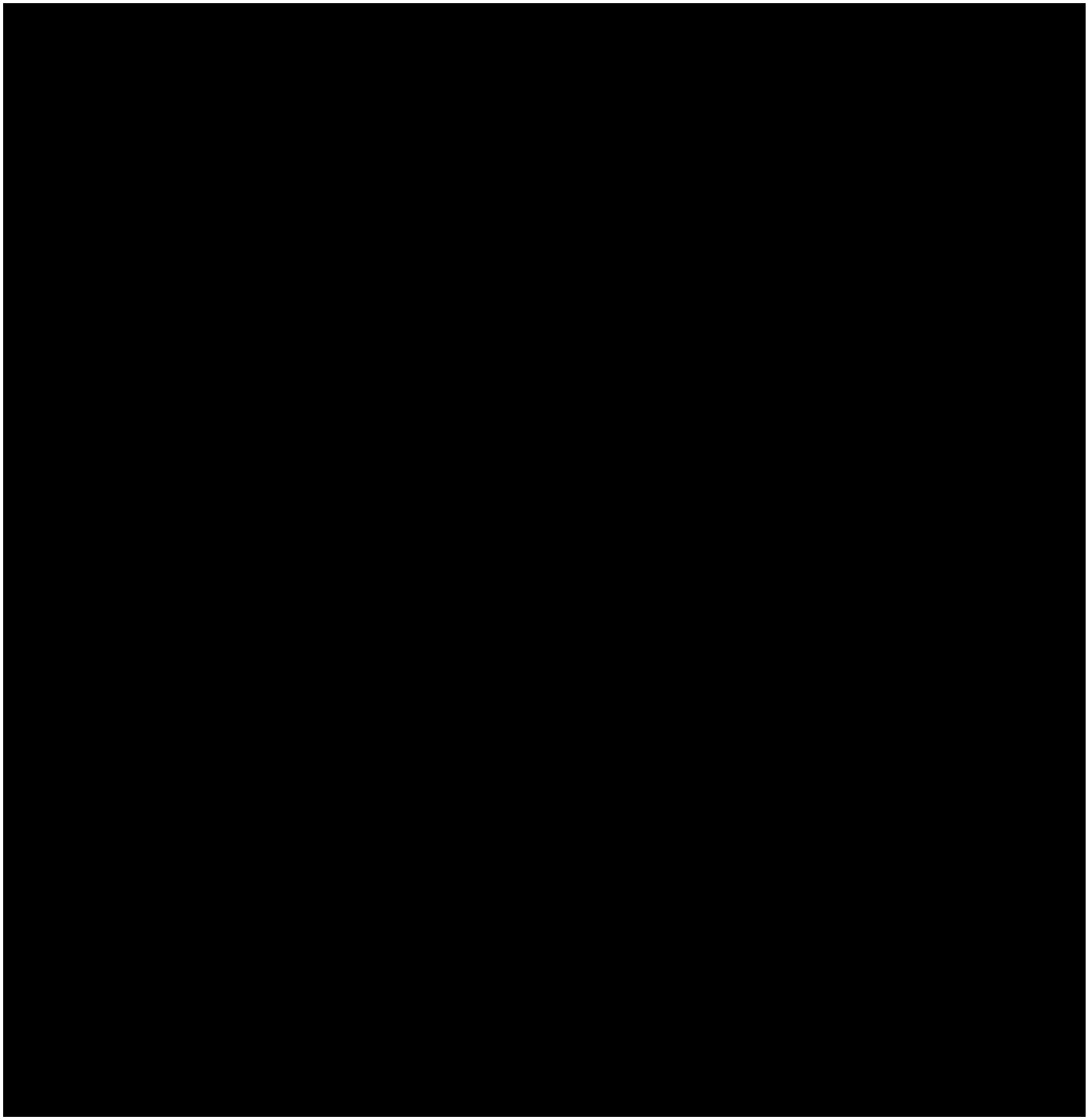
Drug Product	Label Content
INO-5401 **INO-9012**	Product Name [strength mg/mL] Single Use Vial Expiry Date, Storage conditions CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY Inovio Pharmaceuticals, Inc.
REGN2810	Product Name [strength mg/mL] Single Use Vial Expiry Date, Storage conditions CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY

5.6.1. The CELLECTRA® 2000 device

The CELLECTRA® 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA® 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. [redacted]

The CELLECTRA® 2000 device, and its components, will be shipped directly from the manufacturer to 1) the trial sites or 2) the trial depot prior to shipping to the trial site. The investigational labels in Table 11 below are presented as examples. Additional or replacement language may be required in countries outside the United States. Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record IP accountability during trial conduct.





5.6.2. Temozolomide

Temozolomide is commercially available and will be supplied by each study site as per chemotherapy standards at the respective institution and will not be provided by the Sponsor. The commercial labels for TMZ will not be altered.

5.7. Handling and Storage

5.7.1. INO-5401 + INO-9012

Inovio will be responsible for assuring the quality of the IP is adequate for the duration of the trial. [redacted]

5.7.2. REGN2810

[redacted]

5.8. Investigational Drug and Device Accountability

5.8.1. INO-5401 + INO-9012 and REGN2810

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each trial site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number or batch number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor or its designee;
- Amount destroyed at trial site, if applicable.

5.8.2. Investigational Device

Each clinical site is responsible for maintaining investigational device accountability. This includes recording the CELLECTRA® 2000 serial number, IM Applicator serial number, and IM Array lot number used for injection/EP of each subject. Site personnel will be required to download EP data and provide to Inovio after each treatment.

Each subject will be assigned a unique CELLECTRA® 2000 IM applicator, [redacted]

The used Sterile Disposable Array should be disposed of in accordance with institutional policy after each EP.

5.9. Return and Destruction of Investigational Drug and Device

5.9.1. INO-5401 + INO-9012, and REGN2810

Upon completion or termination of the trial, all unused and/or partially used investigational drug product must be returned to Inovio, if not authorized by Inovio or local regulations to be destroyed at the site.

All IPs returned to Inovio must be accompanied by the appropriate documentation. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused IP(s) should be arranged by the responsible trial Monitor if on site destruction is not possible.

If IPs are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused IP(s) can only be destroyed after being inspected and reconciled by the responsible trial Monitor.

5.9.2. Investigational Device

Upon completion or termination of the trial, all CELLECTRA® 2000 devices must be returned to Inovio. The EP Applicators used for each patient will be destroyed by each site and should not be returned. Any unused applicators and/or arrays should be returned to Inovio.

6. TRIAL PROCEDURES AND SCHEDULE

The Trial Schedule of Events (Table 1) summarizes the trial procedures to be performed at each visit, prior to execution of Protocol v5.0. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator.

To be eligible for screening, subjects must have a histopathological diagnosis of GBM. Subjects will be assigned to a cohort based on the results of the MGMT gene methylation assay performed in a CLIA-certified laboratory, which should be available prior to the completion of RT. The time required to result MGMT is variable by site and it is essential to have these results to determine which trial cohort will be assigned to the subject. Sites should be aware of how long it takes to result MGMT at their individual site and plan accordingly.

Sites should be mindful that since recovery time from definitive cranial tumor resection will vary by subject, "Day 0" will not be on the same post-operative day for every subject. Therefore, the first dose of REGN2810 and INO-5401 + INO-9012 will be considered Day 0 (Visit #1). Inclusion criteria require that radiotherapy be planned to initiate within 42 days of definitive tumor resection.

The first dose of REGN2810 and INO-5401+INO-9012 will be administered approximately 2 weeks prior to the initiation of radiotherapy. Since subjects will unlikely be consented before receiving histopathology results from tumor resection, the time between completing the ICF and screening process and the start of radiotherapy may be short. All screening labs and assessments, ECG, and other procedures are required to be completed within 28 days prior to Day 0.

Both cohorts will receive REGN2810 and INO-5401 + INO-9012 on the same dosing schedule(s). All treatment visits, and safety laboratory assessments have a window of ±3 days. Radiographic assessments and contacts determining OS have a window of ±7 days.

Immunology samples are to be drawn at Screening, Day 0, Weeks 3, 6, 9, 12, and then every 12 weeks (Weeks 24, 36, 48, etc.).

Upon execution of Protocol v5.0, study procedures will be limited to administration of study drugs INO-5401 + INO-9012 and cemiplimab as per prior schedule. Please see Table 2 for the Schedule of Events that summarizes the trial procedures that are suggested.

6.1. Informed Consent

All subjects must sign the ICF prior to any trial related procedures being performed. The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified trial personnel will meet with prospective trial participants, explain the trial, and provide them with an ICF that describes the screening tests, eligibility criteria for entering the trial, trial treatments and follow-up procedures, in a language understandable to the subject. Explanation of the trial includes, but is not limited to, trial objectives, potential benefits and risks, discomforts/inconveniences, and the subject's rights and responsibilities. The subject or subjects' legally acceptable representative is then requested to sign and date the ICF. A copy of the signed ICF must be provided to the subject or subjects' legally acceptable representative. The qualified trial personnel will document the process of obtaining informed consent within the

source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.2. Medical History/Existing Events/Illness

Investigators should document all significant illnesses that the subject has experienced within 6 months of signing ICF, as Medical History. Illnesses first occurring or detected after signing of ICF and/or worsening of an existing illness during the trial are to be documented as AEs on the CRF.

6.3. Prior treatments

Prior treatments are defined as administered prior to first trial treatment and no longer ongoing, up to 6 months prior, should be recorded in the CRF as prior medications. Concomitant treatments, defined as treatments continued by the subject after the first trial treatment and new treatments taken after the first trial treatment, should be recorded in the CRF as concomitant medications.

6.4. Subject Registration Procedure

6.4.1. Assignment of Subject Identification Numbers

Each subject who consents will be assigned (by the Sponsor) a unique subject identification number (SID), which identifies the subject for all trial-related procedures. Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the eCRF.

6.5. Safety Evaluations

Safety evaluations and management of toxicities are detailed in Section 7. Assessments for safety are described within this section.

6.5.1. Medical and Clinical Assessments

Concomitant medications will be collected from the time of signing the ICF and at all subsequent trial visits through trial discharge.

Assessment of all AEs will be collected from the time of signing of ICF until 30 days post last dose of INO-5401 + INO-9012 or REGN2810, whichever is later, with the exception of AESIs, and SAEs as defined in this protocol, which will be collected until 6 months post last dose of INO-5401 + INO-9012 or REGN2810, whichever is later. AEs will be assessed using the NCI CTCAE v4.03.

6.5.2. Physical Assessments

Prior to Execution of Protocol v5.0:

A full examination including complete neurologic exam (cranial nerve assessment, deep tendon reflexes, muscle strength and sensation), and Karnofsky Performance Scale (KPS) will be conducted every 3 weeks.

Following Execution of Protocol v5.0:

A physical examination will be conducted every 3 weeks. No neurological examination will be conducted.

6.5.2.1. Medical Post-Treatment Reaction Assessment

On Day 0, vital signs will be collected prior to both REGN2810 and INO-5401 + INO-9012 treatment, at the end of the REGN2810 infusion, and every 30 minutes for the first 4 hours post-REGN2810 infusion, as well as 30 minutes after the INO-5401 + INO-9012 injection with EP. At all other visits, the Investigator will assess local and systemic reactions for 30 minutes post-each treatment (REGN2810 and/or INO-5401 + INO-9012) and at specified visits as per the Schedule of Events.

6.5.3. Vital Signs

Vital signs including body temperature, respiration rate, blood pressure and heart rate will be measured at all the trial treatment visits.

6.5.4. Weight, Height, and Body Mass Index

Weight (kg) and height (cm) will be collected at the screening visit. Weight will be collected at each additional treatment visit from Day 0 through end of treatment. Body Mass Index will be assessed at Day 0, weeks 3, 6, 9, 18, and every 9 weeks after week 18 while the subject is receiving the EP procedure, secondary to the need to assess needle gauge.

6.5.5. 12-lead ECG

An ECG will be performed at screening within 28 days prior to Day 0 for all subjects to determine subject eligibility. Abnormal ECGs should be interpreted as clinically significant or not clinically significant. Abnormal ECGs at screening should be discussed with the trial medical monitor to determine subject eligibility.

6.5.6. Pregnancy Test

For women of reproductive potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be obtained at the screening visit and prior to each administration of INO-5401 + INO-9012 and REGN2810. If at any point, the β-HCG (pregnancy) test is positive, indicating that the subject is pregnant, no additional trial treatment will be administered, but the subject will be followed for the duration of the trial and beyond to determine the outcome of the pregnancy (with the subject's consent).

6.5.7. Laboratory Evaluations

Blood samples will be collected as specified in the Trial Schedule of Events. Screening labs may be used for Visit #1 (Day 0) if they are within 7 days of Day 0. Otherwise, all labs associated

with any treatment visit (CBC and chemistry) should be collected no more than 72 hours prior to treatment and reviewed/evaluated by the Investigator prior to treatment.

Complete blood count (CBC) should include:

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count
- Serum chemistries should include:
- Glucose
- Albumin
- Total protein
- SGPT (serum glutamic-pyruvic transaminase; ALT)
- SGOT (serum glutamic-oxaloacetic transaminase; AST)
- Alkaline phosphatase
- Bilirubin (total)
- Direct bilirubin
- BUN (blood urea nitrogen)
- Calcium
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Lipase
- Amylase

Assessments to be performed at <u>screening only</u>:

- HIV screening test (antibody immunoassay test); or documentation of these results in the medical record;
- Hepatitis B Serology: HBsAg (hepatitis B surface antigen); or documentation of these results in the medical record;
- Hepatitis C antibody immunoassay; or documentation of these results in the medical record;
- Urinalysis including specific gravity, glucose, blood and ketones;
- Activated partial thromboplastin time (aPTT), INR.

6.6. Assessment Of Laboratory Abnormalities

When evaluating laboratory abnormalities throughout the trial, the Investigator will be instructed to use CTCAE v5.0. Only clinically significant laboratory abnormalities will be reported as adverse events.

6.7. Peripheral Blood Immunogenicity Assessments

Prior to Execution of Protocol v5.0:

Whole blood and serum samples will be obtained. Immunology samples are to be drawn at Screening, Day 0, Weeks 3, 6, 9, 12, and then every 12 weeks (Weeks 24, 36, 48, etc.) until discontinuation. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

T cell responses may be assessed using antigen-specific IFN-γ ELISpot assay using overlapping peptide libraries covering the INO-5401 antigens. Additionally, PBMC responses against a pool of known antigenic epitopes combined from Cytomegalovirus, Epstein Barr Virus and Influenza (CEF) may be evaluated in order to track general cellular immune competence during the trial.

T cell responses may be additionally assessed via flow cytometry overlapping peptide libraries covering the INO-5401 antigens. Flow cytometric assays may include an examination of the influence of immunotherapy on the ability of subject T cells to exhibit phenotypic markers associated with cytolytic potential, activation or exhaustion after stimulation by peptides corresponding to INO-5401 antigens. [redacted]

Assessment of the presence of cells that are known to play a role in immune suppression may occur via the application of flow cytometry. Flow cytometric assays may include an examination of the influence of these cells on the induction or expansion of an immune response after immunotherapy. [redacted]

Post execution of Protocol v5.0, serum and whole blood samples will not be collected.

6.8. Tissue Immunology

Following execution of Protocol v5.0, no further samples will be collected for tissue for immunology and/or biomarkers assessment. Those samples collected prior to this may be used as described below.

Immune infiltration and the presence of immunomodulatory factors in neoplastic tissue prior to and following INO-5401 dosing may be examined via a number of assessments which may include:

[redacted]

6.9. Biomarkers

Following execution of Protocol v5.0, no further samples will be collected for tissue, whole blood, and urine for immunology and/or biomarkers assessment. Those samples collected prior to this may be used as described below.

Biomarker assessments may be performed from peripheral and tissue samples referenced above and collected per lab manual instructions.

Immunohistochemical assessment of the expression of the hTERT, WT1 and/or PSMA proteins within tissue samples from enrolled subjects may occur contingent on the presence of sufficient sample quantity and continued relevance as supported by available data. IDH-1 status may be performed on tumor tissue if available.

[redacted]

6.10. Clinical Assessments

Prior to Execution of Protocol v5.0:

Clinical evaluations for disease response will be conducted at all of the trial visits (as assessed by clinical signs and symptoms of disease progression). MRI for disease progression will be obtained for all subjects 9 weeks after Day 0 (± 3 days) and every 3 months thereafter, until End of Treatment, unless considered pseudo-progression by iRANO assessment. In that case, the repeat confirmatory MRI scan will be performed at 3 months after the suspected pseudo-progression.

Following Execution of Protocol v5.0:

Clinical evaluations for disease response will be conducted at all of the trial visits (as assessed by clinical signs and symptoms of disease progression). MRI scans will no longer be performed.

6.10.1. Overall Survival

All subjects will be followed for survival. After the End of Treatment visit has been completed, if it has not already occurred, documentation of survival status is required at month 18 post Day 0. The following methods are acceptable to document survival: phone call; personal contact; certified letter; or documentation of a visit confirmed in the medical record.

6.10.2. Progression

Prior to Execution of Protocol v5.0:

Progression will be assessed by both RANO and iRANO. Patients that withdraw prior to progression should be followed for progression and survival.

6.10.2.1. RANO And iRANO: (Immunotherapy) Response Assessment In Neuro-Oncology

As oncology treatments have expanded beyond cytotoxic therapy, the effect of therapeutics on tumor imaging findings has become less straight forward than applying traditional imaging response assessment methods like RECIST and Macdonald criteria. For neuro-oncology, pseudo-progression after radiotherapy and TMZ chemotherapy and pseudo-response after anti-angiogenic drugs, underline challenges with the interpretation of imaging changes. The Radiologic Assessment for Neuro-Oncology (RANO) criteria were proposed in 2010 to improve assessment of the evolving complexities of imaging for subjects with malignant glioma [109]. A key cornerstone of the RANO criteria is guidance for the occurrence of pseudo-progression, which occurs in about 10-20 % of newly-diagnosed subjects with GBM after radiotherapy and TMZ therapy. Clinical benefit, including long-term survival and tumor regression, can still occur after initial disease progression or after the appearance of a new lesion.

Important issues regarding progressive imaging findings in subjects with neuro-oncologic malignancies treated with immunotherapy suggest that further adaptation of RANO criteria is warranted. To that end, both RANO and iRANO criteria are being utilized in this trial.

The iRANO criteria were developed by a multinational and multidisciplinary panel of neuro-oncology immunotherapy experts (RANO Working Group) who established a guidance for the determination of tumor progression in immunotherapy trials in neuro-oncology [104, 110] The iRANO working committee recommends that for subjects with early progressive findings

(treatment with immunotherapy less than 6 months), including subjects who develop new lesions but who do not have substantial neurologic decline, confirmation of radiographic progression by follow-up imaging should be sought 3 months after initial radiographic evidence of progressive disease to decrease the likelihood of prematurely declaring progressive disease in subjects with pseudo-progression or delayed response. In such subjects, those with confirmation of further radiographic progression based comparison with the scan that first showed evidence of disease progression, or who develop substantial clinical decline at any time, should be classified as having progressive disease with the date of disease progression back dated to the first date that the subjects met criteria for radiographic progression.

In this study, Investigators should utilize iRANO criteria when making a decision as to whether to stop study drug in the face of suspected progression, however all subjects will be assessed for progression by both RANO and iRANO criteria for progression.

The RANO and iRANO criteria are provided in Appendix F.

6.10.3. NANO Scale: Neurologic Assessment in Neuro-Oncology

The NANO scale is used only in conjunction with the iRANO and RANO criteria. Although both the RANO and the iRANO scales specify that clinical status must be incorporated for overall assessment, neither scale provides specific parameters to do so. An international group of neuro-oncologists convened to draft the NANO criteria as an objective and quantifiable metric of neurologic function evaluable during a routine examination. The NANO scale involves evaluation of eight relevant neurologic domains based on direct observation/testing conducted during routine office visits. The score defines criteria for domain-specific and overall scores of response, progression, stable disease and “not assessed.” These criteria provide a more detailed and objective measure of neurologic function that can be assessed across clinical trials and therapeutic interventions [111].

This trial will include clinical assessment utilizing the NANO scale when RANO and iRANO is assessed. The NANO scale and scoring tool are located in Appendix A.

Following execution of Protocol v5.0:

Following radiographic progression, trial treatment should be stopped, and confirmation of disease progression is not required.

6.11. Procedure By Visit

Prior to execution of Protocol v5.0, procedures by visit are outlined in Trial Schedule of Events (Table 1).

After Week 9, some trial procedures occur every 3 weeks, some every 9 weeks and others every 12 weeks. Please refer to Schedule of Events table in addition to the schedule below. For example, during the Week 18 visit all “every 3 week” events will be performed along with any additional events that occur during the “every 9 week” visits. For the Week 21, visit all “every 3 week” events will be performed with any additional events that occur during all “every 12 week” visits, and so on.

MGMT promoter methylation status should be determined prior to the completion of RT.

6.11.1. Screening Evaluations

Screening evaluation visits to be performed within 28 days prior to first trial treatment:

1. Signed written ICF;
2. Review and confirm all inclusion/exclusion criteria;
3. Complete medical history including surgical history, previous non-cancer treatments, previous cancer related treatments, present conditions, baseline events, concomitant illnesses and current medications;
4. Document KPS status;
5. Collect demographics, including gender and ethnic origin;
6. Complete physical examination (PE) including, but not limited to, height, weight, BMI, and vital signs [heart rate (HR), blood pressure (BP), and oral temperature];
7. Complete neurologic exam, including NANO scale and:
    i. Cranial nerve assessment
    ii. Deep tendon reflexes
    iii. Muscle strength
    iv. Sensation
8. Document all current medications and medications within the last 6 months;
9. Clinical laboratory testing including, but not limited to: CBC with differential; serum chemistry (glucose, albumin, sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO_3), calcium (Ca); blood urea nitrogen (BUN), creatinine (Cr), or Measured or calculated creatinine clearance or GFR total serum bilirubin (TBIL), alkaline phosphatase (ALK P), AST, ALT);
10. Thyroid stimulating hormone (TSH), free T3, free T4;
11. CPK;
12. Urinalysis (screening only);
13. HIV/HCV/HBV serology;
14. Serum pregnancy test for beta Human Chorionic Gonadotropin (β-HCG) for female subjects of child bearing potential;
15. 12-lead ECG;
16. MRI; a post-surgery MRI will be acceptable if within 28 days prior to Day 0;
17. Whole blood and serum for baseline immunologic assays;
18. Paraffin-embedded tumor tissue or unstained slides, if available;
19. Inclusion/exclusion criteria signed off by Investigator;

20. aPTT, INR.

6.11.2. Day 0

1. Review and confirm all inclusion/exclusion criteria;
2. Medical/clinical assessment, including concomitant medications/treatments and AEs;
3. Document KPS status;
4. Complete PE including, but not limited to, weight, BMI, and vital signs [HR, BP, and oral temperature];
5. Complete neurologic exam;
6. Clinical laboratory testing including, but not limited to: CBC with differential; serum chemistry (glucose, albumin, Na, K, Cl, (HCO3), (Ca); (BUN), Cr, or Measured or calculated creatinine clearance or GFR TBIL, alkaline phosphatase ALK P, AST, ALT);
7. Assessment of clinical laboratory results: CBC, creatinine, GFR, AST, ALT
8. Serum pregnancy test for beta β-HCG for female subjects of child bearing potential;
9. Confirm negative pregnancy result;
10. Whole blood and serum for baseline immunologic assays, collected **before** treatment with INO-5401 + INO-9012;
11. Administration of REGN2810;
12. Assessment requirement for REGN2810.
13. Administration of INO-5401 + INO-9012;
14. Assessment of EP injection site;
15. Download EP data;

6.11.3. Week 3

1. Medical/clinical assessment, including concomitant medications/treatments and AEs;
2. Document KPS status;
3. Complete PE including, but not limited to, weight, BMI, and vital signs [HR, BP, and oral temperature];
4. Complete neurologic exam;
5. Clinical laboratory testing including, but not limited to: CBC with differential; serum chemistry (glucose, albumin, Na, K, Cl, HCO3, Ca; BUN, Cr, or Measured or calculated creatinine clearance or GFR, TBIL, ALK P, AST, ALT);
6. Assessment of clinical laboratory results: CBC, creatinine, GFR, AST, ALT;
7. Serum pregnancy test for β-HCG for female subjects of child bearing potential;
8. Confirm negative pregnancy result;

9. Whole blood and serum for immunologic assays;
10. Administration of REGN2810;
11. Assessment requirement for REGN2810;
12. Administration of INO-5401 + INO-9012;
13. Assessment of EP injection site;
14. Download EP data;
15. RT;
16. TMZ concurrent with RT.

6.11.4. Week 4

1. RT;
2. TMZ concurrent with RT.

6.11.5. Week 5

1. RT;
2. TMZ concurrent with RT.

6.11.6. Week 6

1. Medical/clinical assessment, including concomitant medications/treatments and AEs;
2. Document KPS status;
3. Complete PE including, but not limited to, weight, BMI, and vital signs [HR, BP, and oral temperature];
4. Complete neurologic exam;
5. Clinical laboratory testing including, but not limited to: CBC with differential; serum chemistry (glucose, albumin, Na, K, Cl, HCO3, Ca; BUN, Cr, or Measured or calculated creatinine clearance or GFR, TBIL, ALK P, AST, ALT);
6. Assessment of clinical laboratory results: CBC, creatinine, GFR, AST, ALT;
7. Serum pregnancy test for β-HCG for female subjects of child bearing potential;
8. Confirm negative pregnancy result;
9. Whole blood and serum for immunologic assays;
10. Administration of REGN2810
11. Assessment requirement for REGN2810;
12. Administration of INO-5401 + INO-9012;
13. Assessment of EP injection site;
14. Download EP data.

6.11.7. Week 9

1. Medical/clinical assessment, including concomitant medications/treatments and AEs;
2. Document KPS status;
3. Complete PE including, but not limited to, weight, BMI, and vital signs [HR, BP, and oral temperature];
4. Complete neurologic exam;
5. MRI;

6. iRANO, RANO and NANO scale assessments;
7. Clinical laboratory testing including, but not limited to: CBC with differential; serum chemistry (glucose, albumin, Na, K, Cl, HCO3, Ca; BUN, Cr, or Measured or calculated creatinine clearance or GFR TBILALK P, AST, ALT);
8. Assessment of clinical laboratory results: CBC, creatinine, GFR, AST, ALT;
9. Serum pregnancy test for β-HCG for female subjects of child bearing potential;
10. Confirm negative pregnancy results;
11. Whole blood and serum for immunologic assays;
12. Administration of REGN2810;
13. Assessment requirement for REGN2810.
14. Administration of INO-5401 + INO-9012;
15. Assessment of EP injection site;
16. Download EP data;
17. Maintenance TMZ, Cohort B only (See Section 5.2.4 for description / schedule details of Maintenance TMZ).

6.11.8. Every 3 Weeks after Week 9 (Week 12, 15, 18, etc.)

For Week 12 whole blood and serum will need to be collected for immunologic assays. After Week 12, immunology samples are collected every 12 weeks (Weeks 24, 36, 48, etc.) until discontinuation.

1. Medical/clinical assessment, including concomitant medications/treatments and AEs;
2. Document KPS status;
3. Complete PE including, but not limited to, weight and vital signs [HR, BP, and oral temperature];
4. Complete neurologic exam;
5. Clinical laboratory testing including, but not limited to: CBC with differential; serum chemistry [glucose, albumin, Na, K, Cl, HCO3, Ca; BUN, Cr, or Measured or calculated creatinine clearance or GFR TBILALK P, AST, ALT];
6. Assessment of clinical laboratory results: CBC, creatinine, GFR, AST, ALT;
7. Serum pregnancy test for β-HCG for female subjects of child bearing potential;
8. Administration of REGN2810;
9. Assessment requirement for REGN2810.

6.11.9. Every 9 Weeks after Week 9 (Week 18, 27, 36, etc.)

It is important to note that several weeks will occur on multiple trial visits, i.e. Week 18 occurs during the "every 3 week" visit as well as the "every 9 week" visit. On weeks that overlap it is important to perform all of the necessary events that occur for all visit schedules. For example, for the Week 18 visit, one must perform all events that take place for the "every 3 week" visits, as well as any additional events that occur during the "every 9 week" visits.

1. BMI
2. TSH, free T3, free T4
3. Administration of INO-5401 + INO-9012;
4. Assessment of EP injection site;
5. Download EP data.

6.11.10. Every 12 Weeks after Week 9 (Week 21, 33, 45, etc.)

Please see note under Section 6.11.8 and Section 6.11.9 regarding whole blood collection and overlapping weeks.

1. MRI;
2. iRANO, RANO and NANO scale assessments.

6.11.11. Every 12 Weeks after Week 12 (Week 24, 36, 48, etc.)

Immunology samples are to be drawn at Screening, Day 0, Weeks 3, 6, 9, 12, and then every 12 weeks after week 12 (Weeks 24, 36, 48, etc.) until discontinuation.

6.11.12. End of Treatment

1. End of treatment visit to be performed within 30 days of confirmation of progression.
2. Medical/clinical assessment, including concomitant medications/treatments and AEs;
3. Whole blood and serum for immunologic assays;
4. CPK
5. Optional tumor biopsy sample at progression.

6.11.13. Survival

1. Survival to be confirmed every 6 months post progression, until End of Treatment. Survival also to be confirmed at 18 months post Day 0 if it has not already occurred by End of Treatment.

Following execution of Protocol v5.0, procedures by visit are outlined in Trial Schedule of Events (Table 2), as well as below.

6.11.14. Every 3 Weeks

1. Medical/clinical assessment, including concomitant medications/treatments and AEs;
2. Complete PE including, but not limited to, weight and vital signs [HR, BP, and oral temperature];
3. Clinical laboratory testing including, but not limited to: CBC with differential; serum chemistry [glucose, albumin, Na, K, Cl, HCO3, Ca; BUN, Cr, or Measured or calculated creatinine clearance or GFR TBILALK P, AST, ALT];
4. Assessment of clinical laboratory results: CBC, creatinine, GFR, AST, ALT;
5. Serum pregnancy test for β-HCG for female subjects of child bearing potential;
6. Administration of REGN2810;
7. Assessment requirement for REGN2810.

6.11.15. Every 9 Weeks

It is important to note that several weeks will occur on multiple trial visits, i.e. Week 18 occurs during the "every 3 week" visit as well as the "every 9 week" visit. On weeks that overlap it is important to perform all of the necessary events that occur for all visit schedules. For example, for the Week 18 visit, one must perform all events that take place for the "every 3 week" visits, as well as any additional events that occur during the "every 9 week" visits.

1. TSH, free T3, free T4;
2. Administration of INO-5401 + INO-9012;
3. Assessment of EP injection site;
4. Download EP data.

6.11.16. End of Treatment

1. End of treatment visit to be performed within 30 days of progression.
2. Medical/clinical assessment, including concomitant medications/treatments and AEs.

6.11.17. Survival

1. Survival to be confirmed every 6 months post progression, until End of Treatment. Survival also to be confirmed at 18 months post Day 0 if it has not already occurred by End of Treatment.

6.12. Duration on Study

Subjects will continue to be followed for survival for every 6 months until End of Treatment. Subjects will be assessed for new AEs for 30 days following the last dose of trial drug, and for new SAEs and AESIs for 6 months following the last dose of trial drug.

7. EVALUATION OF SAFETY

7.1. Safety Parameters

The safety of the IPs will be measured and graded in accordance with National Cancer Institute (NCI) CTCAE v5.0.

7.2. Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In this study, AEs will be monitored, classified, and summarized. Medical condition/diseases present before starting the investigational products will be considered AEs only if they worsen after starting study treatment. An unexpected AE is one not identified in reference safety documents of the study drugs, or corresponding sections of the IBs. Throughout the course of the study, all AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to IP(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure.
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the trial drug phase of a human clinical trial.
- Complications of pregnancy.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure may be considered an AE.
- Diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose of study drug without clinical sequelae

- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed is not an AE, unless it worsens. It is documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason (documented on a pregnancy CRF).

All AEs that occur from the time of signing of consent onwards and throughout the duration of the trial, and 30 days (6 months for immune-related AEs; irAEs) post-last dose will be recorded.

7.2.1. Adverse Events of Special Interest (AESI)

AEs of Special Interest (AESI) are AEs that may or may not meet serious adverse event criteria (see below) but are of specific clinical interest to the Sponsor in this study. In this study, AESIs will include:

- Immune-related AEs (irAEs) as noted below in Section 7.2.2;
- Grade ≥2 REGN2810 infusion-related reactions;
- Grade ≥3 injection site reactions;
- Dose-limiting toxicities (DLTs) as defined in Section 3.7.

AESIs will require discussion with the Sponsor's Medical Monitor, and should be reported following the same guidelines provided for SAE reporting described below, and reported to the Sponsor within 24 hours.

7.2.2. REGN2810 Immune-related adverse events (irAE)

Investigators must be extremely vigilant and be ready to intervene early in the management of immune-related AEs (irAE), as the onset of symptoms of irAEs may be subtle. Guidance of management of irAEs is provided in Appendix C.

Based on the emerging safety profile of REGN2810 and other antibodies targeting the PD-1/PD-L1 axis, the following working case definitions are provided to help Investigators distinguish irAEs from non-immune AEs. These case definitions pertain to the more commonly reported irAEs associated with PD-1 inhibition [112, 113], and are not exhaustive of all possible irAEs. Clinical presentations of less common irAEs, including neurologic, musculoskeletal, cardiac, renal, and ocular events [114, 115], should be reviewed in subjects with concerning presentations.

The case definitions below have not been validated, and are intended only as guidance for Investigators to help distinguish irAEs from non-immune AEs. Investigators' clinical judgment may include other factors when determining immune-relatedness. The case definitions for irAEs may evolve as clinical experience increases with REGN2810 and other antibodies targeting the PD-1/PD-L1 axis.

- Immune-related rash: Skin examination demonstrates a rash that is usually maculopapular, but other presentations may occur, including papulopustular, follicular, or urticarial dermatitis. Consider dermatologic consultation and biopsy for atypical presentations. Exclude other causes such as virally-induced rash or contact dermatitis.
- Immune-related diarrhea/colitis: These events are on a continuum, with diarrhea defined as increased stool frequency, while colitis involves abdominal pain and/or radiologic evidence of colonic inflammation [112]. Onset at 4 to 6 weeks is common [113]. A CT scan usually demonstrates diffuse colitis [116]. Exclude clostridium dificile or other infectious etiologies and exclude laxative misuse.
- Immune-related hepatitis: Laboratory studies are notable for elevated ALT and/or AST that is usually asymptomatic. Viral or other drug-induced hepatitis is excluded. Exclude alcohol-related liver toxicity. If clinically appropriate, consider radiologic imaging to exclude malignant causes. If clinically appropriate, exclude worsening of underlying cirrhosis.
- Immune-related hypothyroidism: Laboratory studies are notable for elevated TSH associated with low serum free thyroxine (free T4). If elevated TSH is detected, it is recommended that free T4 level also be tested. Elevated TSH with low free T4 establishes the diagnosis of hypothyroidism. Hypothyroidism may be asymptomatic or associated with symptoms such as fatigue, constipation, cold intolerance, dry skin, weight gain, and/or bradycardia. Exclude other causes of hypothyroidism, such as prior RT to the neck. In subjects with prior history of hypothyroidism, exclude noncompliance with thyroid replacement medication.
- Immune-related hyperthyroidism: Hyperthyroidism should be managed with standard anti-thyroid pharmacotherapy, and consultation with an endocrinologist is recommended.
- Immune-related pneumonitis: Pneumonitis, defined as inflammation of the lung parenchyma, may present as shortness of breath, cough, fever, and/or chest pain. Median time from start of anti-PD-1 therapy to onset of pneumonitis is 2.6 months [117], but delayed onset of pneumonitis has been reported. The most common radiologic pattern on CT chest has been described as cryptogenic organizing pneumonia, but other radiographic patterns may occur [117]. If performed, biopsy may demonstrate lymphocyte-predominant interstitial pneumonitis with areas of organizing pneumonia [117]. Exclude infectious causes of pneumonitis.
- Immune-related encephalitis: Encephalitis may present with change in mental status, new-onset (or change in) seizures, or other new neurological symptoms. The frequency of immune-mediated encephalitis is <1% [118] and time to onset is unknown. If symptoms of encephalitis are present, study drugs should be stopped, and steroids should be administered. Work-up should include radiographic assessment and, if feasible, CSF assessment, to assess for the presence of auto-immune antibodies. Further information is provided in Appendix C.

AEs that meet the criteria above should be entered using the appropriate terms (see Appendix C for terms corresponding to common potential irAEs). Such related events will be assumed to be irAEs in the database unless medical review of data raises questions regarding the attribution and are queried. If AEs corresponding to the common terms are attributed as not related to REGN2810, additional information should be provided substantiating an alternative attribution. If not provided at the outset, this information may be requested by immediate edit checks or in subsequent queries.

These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual subject.

7.3. Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol (excluding death due to disease progression);
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred);
- Requires a subject's hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened does not constitute an SAE;
- Results in persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions).
- Results in congenital anomaly or birth defect;
- Is otherwise an important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include:
  - Allergic bronchospasm requiring intensive treatment in an emergency room or at home;
  - Blood dyscrasias or convulsions that do not result in hospitalization;
  - The development of drug dependency or drug abuse.

Note the following clarifications of SAEs:

- Death is an outcome of an AE, and not an AE in itself.
- The subject may not have been on IP when the event occurred.

- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time.

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

7.4. Unanticipated (Serious) Adverse Device Effect (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

A UADE is a type of SAE that requires expedited reporting on the part of the sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the trial investigator within 24 hours.

7.5. Causal Relationship of Clinical Material to Adverse Events (AEs)

All AEs are to be assessed for causal relationship with the one or more of IPs and/or the investigational device. An AE may be assessed as related or not related to the IP and/or the investigational device. Because the Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting AEs and judging the relationship between the administration of the IP and EP and a subsequent AE. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the Trial Subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the IP and/or the investigational device indicating "yes" or "no" accordingly, and should provide justification of causality should be assessed by the Investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there are facts, evidence or arguments that administration of the Trial Treatment (drug or device or both drug and device) contributed to the event;

- No – there are no facts, evidence or arguments that administration of the Trial Treatment contributed to the event;

The following should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or EP;
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable);
- Known association of the event with the IP, EP or with similar treatments;
- Known association of the event with the disease under trial or any co-morbidities;
- Presence of risk factors in the Trial Subject or use of concomitant medications known to increase the occurrence of the event.

7.6. Methods and Timing of the Collection and Recording of Safety Data

Subjects will be queried regarding the occurrence of any possible AEs, concomitant medications and new onset chronic disease during their trial visits. Subjects will be reminded to contact study site personnel and immediately report any event that may happen for the duration of the trial. These events will be recorded on the appropriate CRF.

7.7. Adverse Event (AE) Reporting

7.7.1. Trial Reporting Period of Adverse Events (AEs)

The reporting period for non-immune related AEs (without regard to causality or relationship) is comprised of the period following the signing of the ICF until 30 days following the last dose of trial treatment. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the Investigator should report this event to the Sponsor within 24 hours of becoming aware of the event.

All AEs will be collected and recorded in the Electronic Data Capture (EDC) system. The Study Report will analyze and summarize all AEs throughout the trial.

7.7.2. Trial Reporting Period of Serious Adverse Events (SAEs) and AESIs

The reporting period for SAEs and AESIs without regard to causality or relationship is comprised of the period following the signing of the ICF until 6 months following the last dose of trial treatment. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, or is considered an AESI the Investigator should record this event to the Sponsor within 24 hours of becoming aware of the event.

The Investigator will also directly report this event to the local IRB or Ethics Committee, if required, according to its standard operating procedures.

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating Investigators in a written safety report of any adverse event associated with the use of the product that is both serious and unexpected. All Investigators will

receive an expedited safety report notifying them of any Suspected Unexpected Serious Adverse Reaction (SUSAR). The Investigator should notify the Ethics Committee as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy. At any time after completion of the SAE reporting period, if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to the trial drug, the event will be reported to the Sponsor or its designee.

In the event of death, if an autopsy is performed, a copy of the report will be sent to the Sponsor.

7.7.3. Reporting Of Serious Adverse Events (SAEs) and AESIs To Regulatory Authorities

The Sponsor will assess each serious adverse event report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating Investigators as an expedited report, in accordance with the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

Reports will be made as soon as possible, and in no event later than seven (7) calendar days if the event is a death or is life threatening and 15 calendar days for all other reportable events after the Sponsor's initial receipt of the information. The Sponsor may notify a regulatory authority of a death or a life-threatening event associated with the use of the drug within seven (7) calendar days by telephone or facsimile. Each written notification may be submitted on a CIOMS-I form, a FDA Form 3500A, or in a tabular or narrative format in accordance with regulatory requirements.

7.7.4. SAE Contact Information

Please report (via email or fax) all SAE information to:

[redacted]

The preferred method for providing SAE forms or SAE supporting documents to the Sponsor or designee is as an attachment to an e-mail message, to the email address as indicated above. Any SAE supporting documents provided by facsimile (Fax) are to include a fax coversheet that identifies the contact information of the study site.

All supporting documents for SAE reports, including medical records and diagnostic test results, will include reference to the trial subject number. The trial site should redact all other patient identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

In addition to providing the SAE report to the Sponsor within 24 hours of becoming aware of the event, the AE that is serious must be recorded in the Adverse Event eCRF. The entry into the eCRF should occur as soon as possible.

In the event of a pregnancy, the investigator will submit a Pregnancy Form to the Sponsor or designee to the safety email address or fax number within 24 hours of learning of the pregnancy.

If there is a need to directly contact the Medical Monitor, please contact:

Medical Monitor	[redacted] **MD or designee**
Telephone	[redacted]
Email	[redacted]
Mailing address	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462

The SAE report should contain as much clinical safety information as possible, and a more detailed follow-up report should be sent as soon as more information becomes available. Each SAE must be followed up until resolution or stabilization and for a reported death, the Investigator will supply the Sponsor and the IRB/EC with any additional requested information (e.g., autopsy reports and terminal medical reports). The original SAE form must be kept at the trial site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements. SAEs must be followed by the Investigator until resolution, even if this extends beyond the trial-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

7.8. Reporting of Device Related Complaints or Deficiencies

A product complaint/device deficiency is defined as any written, electronic, or oral communication that alleges deficiencies or inadequacies of the device or components related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the device or components after it is released for distribution within the clinical investigation. All product complaints that meet this definition (with the exception of SAEs requiring 24 hour reporting) must be reported to the Sponsor with 10 days of discovery.

Device Deficiencies include malfunctions, use errors and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled or marketed, or for which it is under clinical investigation.

Any problems experienced during the treatment procedure including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting or complaint form must be completed and emailed to the Sponsor at [redacted].

7.9. Abnormal Laboratory Values

The investigator will annotate each lab report or otherwise identify those values that are clinically significant. Abnormal laboratory values that are not clinically significant in the opinion of the Investigator should not be reported as an adverse event.

7.10. Post-Trial Reporting Requirements

All AEs regardless of cause or relationship, must be reported for subjects on treatment until 30 days post-last study treatment.

All SAEs and AESIs, including irAEs, regardless of cause or relationship, must be reported for subjects on treatment until 6 months post-last trial treatment.

If the Investigator learns of an SAE that occurs after the completion or termination visit and the event is deemed by the Investigator to be related to the trial treatment, he/she should promptly document and report the event to the Sponsor.

7.11. Procedures Regarding Pregnancy During the Trial

Should a subject become pregnant after enrolling in the trial, she will not be given any further treatments with the IPs. A Pregnancy Form will be completed by the investigator and submitted to the sponsor trial team and medical monitor within 24 hours after learning of the pregnancy. The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the trial will continue to be followed for trial assessments without receiving further IP for up to 6 months following the last dose of trial treatment. Investigators should use clinical judgment regarding subsequent trial-related blood collection based on the presence or absence of anemia in each subject.

All pregnancies that occur from the time of consent through the follow up visits must be reported. If the end of the pregnancy occurs after the trial has been completed, the outcome will be reported to the Sponsor.

Male subjects will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant until the end of follow-up period. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts will be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to IP. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical and Analytical Plan

The documentation of the statistical and analytical plan is presented below.

8.2. General Considerations

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative. This is a single-arm (INO-5401 + INO 9012 in combination with REGN2810), open-label, multi-center trial in subjects with newly diagnosed GBM with a tumor with an unmethylated MGMT promoter (Cohort A) and with a tumor with a MGMT methylated promoter or indeterminate MGMT status (Cohort B). The trial's primary analyses regard the safety and tolerability of INO-5401 and INO-9012 in combination with REGN2810. The trial's secondary analyses will assess the efficacy of INO-5401 and INO-9012 in combination with REGN2810 using OS18 and using immunogenicity biomarkers (ELISpot/flow cytometry/[redacted]). Exploratory analyses concern the correlative association between clinical response and tumor genetics and biomarkers. Progression-Free Survival as assessed by RANO (Response Assessment in Neuro-oncology) criteria and Overall Survival will also be assessed as exploratory endpoints.

8.3. Statistical Hypotheses

Each cohort for this trial will have a separate independent hypothesis to evaluate the secondary endpoint overall survival at 18 months (OS18). We define the true treatment effect for OS18 as p, where p denotes the true population probability of OS18 in each cohort. Then, for the MGMT promoter unmethylated subjects (Cohort A), the hypothesis of superiority to the historical control is: H0: $p \leq 0.45$ vs. H1: $p > 0.45$, and for the MGMT promoter methylated or indeterminate subjects (Cohort B), the hypothesis of superiority to the historical control is: H0: $p \leq 0.60$ vs. H1: $p > 0.60$.

8.4. Analysis Populations/datasets

Analysis populations will be:

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of the trial treatment. The mITT population will be used for analysis of the secondary endpoint of OS18 as well all of the exploratory efficacy endpoints, including OS and PFS.

The per-protocol (PP) population is comprised of subjects who receive at least three of the first four doses of the trial treatment, and who have no protocol violations. Analyses on the PP population will be considered supportive of the corresponding mITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to locking the trial database.

The safety analysis set includes all subjects who receive at least one dose of either INO-5401 or INO-9012 or REGN2810 trial treatment. Subjects will be analyzed as to the treatment they received.

8.5. Description of Statistical Methods

8.5.1. Analysis of Primary Safety Endpoint

The primary analyses for this trial are safety analyses of Treatment Emergent Adverse Events (TEAE) and clinically significant changes in safety laboratory parameters from baseline.

TEAEs are defined for this trial as any AEs that occur on or after Day 0 up to 30 days after the last dose of trial treatment, with the exception of irAEs, AESIs and SAEs, which may occur up to 6 months after the last dose of trial treatment. All TEAEs will be summarized for the subjects in the safety analysis set by frequency, percentage and 95% Clopper-Pearson confidence intervals within each cohort and across both cohorts combined. These frequencies will be presented overall and separately by dose number, and will depict overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to trial treatment. Multiple occurrences of the same AE in a single subject will be counted only once following a worst-case approach with respect to severity and relationship to trial treatment. All serious TEAEs will also be summarized as above.

Any AEs with missing or partial onset/stop dates will be included in the overall AE summaries but excluded from the calculation of AE duration. AE duration will be calculated as AE Stop date - AE start date + 1 day. AEs, irAEs, AESIs and SAEs that are not TEAEs or serious TEAEs will be presented in listings.

Laboratory response variables will be descriptively summarized per time point and as changes from baseline including 95% confidence intervals. Shifts from baseline according to the CTCAE will also be presented. Laboratory values considered clinically significant will be presented in listings.

All of the safety analyses will be conducted on the subjects in the safety analysis set.

8.5.2. Analysis of Secondary Efficacy Endpoint

The secondary endpoint of OS18 will be summarized using frequency, percentage, 95% Clopper-Pearson confidence interval and p-value for each cohort. A subject will be considered a survivor if they are determined to be alive after 18 months (548 days). Superiority will be concluded if the one-sided p-value is < 0.025. OS18 will be analyzed on subjects in both the mITT and per protocol population and all mITT/PP subjects will be included in the OS18 denominator.

Cellular [redacted] immune responses will be presented using descriptive statistics at each time point and for changes from baseline.

8.5.3. Analysis of Other Safety Data

The percentage of subjects with abnormal medical history findings will be summarized by body system and preferred term for each cohort for subjects in the safety population.

Prior medications are those that were used before the start of the trial (within 28 days prior to Day 0). Concomitant medications are those used during the course of trial (on or after day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest

possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages for each cohort for subjects in the safety population.

Measurements for vital signs as well as changes from baseline will be descriptively summarized by time point for each cohort for subjects in the safety analysis set. The percentage of subjects with abnormal physical examination findings at each time point will be descriptively summarized overall and within each cohort by body system for subjects in the safety analysis set.

ECG and viral serology at screening, and serum pregnancy at each time point will be descriptively summarized overall and within each cohort.

8.5.4. Disposition

Subject disposition will be summarized by cohort and overall for all enrolled subjects and will include the number and percentage enrolled, the number and percentage who received each planned dose and the number who completed the trial. The number and percentage of subjects who discontinued treatment will be summarized overall and by reason. The number in each analysis population will also be presented.

8.5.5. Demographic and Other Baseline Characteristics

Demographic and baseline characteristic data will be descriptively summarized by cohort for subjects in the safety analysis set.

8.5.6. Interim Analyses

No formal interim analyses will be performed for this trial. However, safety and tolerability will be assessed as noted above for up to the first six patients per Cohort, in order to assess Dose Limiting Toxicities.

8.5.7. Multiplicity

No adjustment for multiplicity will be made in this trial.

8.5.8. Missing Values

Missing data will not be imputed or replaced, and calculations will be done on reported values.

8.5.9. Exploratory Analyses

Progression-free survival as assessed by RANO (defined as the time from Day 0 until the date of death from any cause or progression whichever occurs first) and OS (defined as the time from Day 0 until the date of death from any cause) will be summarized with Kaplan-Meier statistical methods within each cohort and overall. Subjects will be censored for PFS at withdrawal of consent or the last progression assessment date where the subject was considered to have not progressed. Subjects who are not recorded as having died will be censored for OS at withdrawal of consent or the last date the subject was known to be alive. Progression free survival and OS will be analyzed in the mITT and Per Protocol populations.

Exploratory tumor genetics and/or biomarker responses will be presented using descriptive statistics at each time point and as changes from baseline for the mITT population and per protocol population.

OS18, PFS, and OS will be modeled using logistic regression models and Cox PH models against the exploratory responses to examine associations. Baseline variables such as patient demographics or patient disease characteristics will be included in the models as potential confounders. Separately, cellular [redacted] immune responses will be used as explanatory variables.

8.6. Sample Size/Power

Estimated number of subjects: 52
Cohort A: MGMT promoter unmethylated (N=32)
Cohort B: MGMT promoter methylated or indeterminate (N=20)

A total sample size of 52 subjects is adequate to assess the safety and tolerability profile of this combination, which is the primary endpoint of this trial. In general, a sample size of three to six patients per dose cohort on a dose escalation trial is sufficient to assess safety and tolerability [105]; this study will enroll 32 patients to Cohort A, and 20 to Cohort B.

Although this study's primary endpoint is safety and tolerability, the sample size of each cohort has been chosen to achieve adequate power to assess the efficacy hypotheses regarding OS18. The sample size of each cohort, using a one-sided significance level of 2.5%, provides 80% power to demonstrate an improvement in the percentage of subjects surviving at 18 months (OS18) in each cohort above historical control. Assuming an historical OS18 of 45% in MGMT promoter unmethylated subjects, and of 60% in MGMT promoter methylated or indeterminate subjects, in order to demonstrate a 30 percentage point improvement in OS18 (75% and 90%, respectively), 30 subjects are needed for Cohort A, and 19 subjects are needed for Cohort B. Thus enrolling 52 subjects should provide a necessary 49 subjects, given the potential for drop-outs, while meeting the needs of both the primary and secondary (efficacy) endpoints.

8.7. Randomization and Blinding

Because this is an open-label trial, site personnel, individual subjects and Inovio or its representative trial personnel will be aware of the treatment allocations for this trial. Because this is a single - arm trial, randomization does not apply.

9. ETHICS

9.1. Investigator and Sponsor Responsibilities

The Investigator and Sponsor are responsible for ensuring that the clinical trial is performed in accordance with the protocol, the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable regulatory requirements.

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable Institutional Review

Board or Ethics Committee (IRB/EC) and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/EC include the following:

- Submit progress reports to the IRB/EC as required, and request re-review and approval of the trial at least once a year during the conduct of the trial.
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects.
- Notify the IRB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events.
- Obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required.
- Submit reports on, and reviews of, the trial and its progress to the IRB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of trial-related information (refer to trial files) that includes all correspondence with the IRB/EC.
- After trial completion (within three (3) months is recommended) provide the IRB/EC with a final report on the trial.
- Compliance with Electronic Records/Signatures Regulations (21CFR Part 11)
- Compliance with Protocol: Subjects will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviations, should a major deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting subject safety must be reported to the Medical Monitor immediately.
- Changes to the Protocol: The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB/EC of a protocol amendment, except where necessary to eliminate immediate hazards to trial subjects, or when the changes involve only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers). Vulnerable Subjects: This trial will not enroll any subjects considered to be vulnerable subjects per ICH E6. Vulnerable subjects are individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.
- Protection of Human Subjects.
- Compliance with Informed Consent Regulations: Written informed consent is to be obtained from each subject prior to enrollment into the trial, and/or from the subject's

legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

9.2. Office of Biotechnology Activities (OBA)

The investigator and Sponsor are responsible for ensuring that the clinical trial is reviewed and approved according to local and applicable global regulations (e.g., NIH Office of Biotechnology Activities) governing research that involves recombinant or synthetic nucleic acid molecules.

10. DATA COLLECTION, MONITORING, AND REPORTING

10.1. Confidentiality and Privacy

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the trial products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the trial sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the trial records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the trial, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA)).

Information about trial subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI
- In the event that a subject revokes authorization to collect or use PHI, the sponsor retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled trial period.

11. SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation

of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial. The Investigator/institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents related to this trial.

11.1. Records Retention

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the Investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRF. Subjects will be identified by their subject identification number (SID).

It is the Investigator's responsibility to retain trial essential documents for at least two (2) years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least two (2) years have elapsed since the formal discontinuation of clinical development of the IP. This retention period may be superseded by country requirements. The Sponsor will inform the Investigator/institution as to when these documents are no longer needed to be retained.

11.2. Safety and Quality Monitoring

The Safety Review Committee (SRC) of this trial will include the Sponsor's Medical Monitor, a Medical Representative from Regeneron Pharmaceuticals, the trial's Principal Investigator, and for reported DLTs or SAEs, the Principal Investigator from the site at which the event was reported. The SRC will be responsible for reviewing DLTs, SAEs, and AESIs. This trial is an open-label trial, and subjects, Investigators and the Sponsor are not blinded as to treatment allocation.

Clinical Monitoring

Clinical Monitoring of the clinical trial will be performed by experienced Clinical Monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the trial.
- The Clinical Monitor will address and document the following trial conduct activities and obligations:

- Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies.
- Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
- Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
- Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate, and complete (ALCOAC).
- Assure that the trial facilities continue to be acceptable.
- Compare the trial CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed.
- Assure that investigational drug and device accountability and reconciliation of records are complete and accurate.
- Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements.

12. FINANCING AND INSURANCE

Financing and insurance will be addressed outside of this protocol.

13. PUBLICATION POLICY

Publication of the results of this trial in its entirety will be expected, following completion of the Clinical Study Report.

All data or results arising out of the performance of this trial shall be considered Confidential Information and shall not be used for the commercial benefit of the Clinical Site or Principal Investigator. The Clinical Site and Principal Investigator agree that the Sponsor shall have the right to the first publication of the results of the trial which is intended to be a joint, multi-center publication of the trial results made by Sponsor in conjunction with the principal investigators and Clinical Sites from all appropriate sites contributing data, analysis and comments. Notwithstanding the foregoing, following the first publication, the Clinical Site and/or Principal Investigator may publish data or results from the trial; provided, however, that the Clinical Site and /or Principal Investigator submits the proposed publication to Inovio for review at least sixty (60) days prior to the date of the proposed publication, as indicated in the Clinical Trial Agreement. Inovio may remove from the proposed publication any information that is considered confidential and/or proprietary other than trial data and results. However, if a multi-center trial publication is not submitted within twenty-four (24) months after conclusion, abandonment or termination of the trial at all sites, or if Inovio confirms there will be no multi-

center trial publication, the Clinical Site and/or Principal Investigator may publish the trial results subject to Inovio's rights as set forth herein. The Clinical Site and the Principal Investigator agree not to publish any trial related material other than in accordance with this Section.

14. LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse event of special interest
ALK P	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
APIs	Active pharmaceutical ingredients
aPTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
bp	Blood Pressure
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete Blood Count
CFR	Code of Federal Regulations
Cl	Chloride
CPK	Creatine Phosphokinase
Cr	Creatinine
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen 4
CTV	clinical target volume
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
EP	Electroporation
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GBM	Glioblastoma
GCP	Good Clinical Practice

AE	Adverse Event
GTV	gross tumor volume
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HBV sAg	hepatitis B virus surface antigen
HCV	Hepatitis C Virus
HCV RNA	Hepatitis C virus ribonucleic acid
hfRT	Hypofractionated radiotherapy
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hTERT	Human telomerase reverse transcriptase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Intradermal
IDH-1	Isocitrate dehydrogenase-1
IEC	International Ethics Committee
IF	Immunofluorescence
IFN- γ	Interferon Gamma
IgG	Immunoglobulin G
IGRT	image-guided radiation
IHC	Immunohistochemistry
IL-12	Interleukin 12
IM	Intramuscular
IMRT	Intensity modulated radiation
IND	Investigational New Drug
INOVIO	Inovio Pharmaceuticals Inc.
INR	International Normalized Ratio
IP	Investigational Product (including drug and device)
IRAE	Immune-Related Adverse Events
iRANO	Immunotherapy Response Assessment in Neuro-oncology
IRB	Institutional Review Board
IRB/EC	Institutional Review Board or Ethics Committee
IUDs	Intrauterine devices

AE	Adverse Event
IV	Intravenous
KPS	Karnofsky Performance Status
LM	leptomeningeal disease
[redacted]	[redacted]
MGMT	Methylguanine DNA methyltransferase
mITT	Modified Intent to Treat
MRI	Magnetic Resonance Imaging
NANO	Neurologic Assessment In Neuro-oncology
NCI	National Cancer Institute
NCT	National Clinical Trial
NE	Non-evaluable
NIH	National Institutes of Health
NYHA	New York Heart Association
OAR	Organs at Risk
OBA	Office of Biotechnology Activities
OS	Overall Survival
OS18	Overall survival at 18 months
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed death-1
pDNA	Plasmid DNA
PE	Physical examination
PFS	Progression-Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PJP	Pneumocystis jirovecii Pneumonia
PR	Partial Response
PSMA	Prostate-specific membrane antigen
PTV	planning target volume
RANO	Radiologic Assessment for Neuro-Oncology
RNA	Ribonucleic Acid
RT	Radiation Therapy
SAE	Serious Adverse Event

AE	Adverse Event
SD	Stable Disease
SID	Subject Identification Number
SIV	Simian Immunodeficiency Virus
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAA	Tumor Associated-Antigen
TBIL	Total Serum Bilirubin
[redacted]	[redacted]
TEAE	Treatment Emergent Adverse Event
TILs	Tumor-infiltrating lymphocytes
TMZ	Temozolomide
TMZ/RT	TMZ with radiation therapy
TSH	Thyroid stimulating hormone
UADE	Unanticipated (serious) Adverse Device Effect
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WT1	Wilms Tumor 1

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16. APPENDICES

APPENDIX A. NEUROLOGIC ASSESSMENT IN NEURO-ONCOLOGY (NANO) SCALE

Adapted from: Nayak L, DeAngelis LM, Brandes AA, Peereboom DM, Galanis E, Lin NU*, et al.* The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. *Neuro Oncol* 2017,**19**:625-635.

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Patient ID: _____

Date of Assessment Performed (dd/Mmm/yyyy):_____

Study time point (i.e. Screening, Day 0, week 3, etc):_____

Assessment performed by (please print name):_____

Domains	**Key Considerations**
Gait 0 ☐ Normal 1 ☐ Abnormal, but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps

Strength

0 ☐ Normal

1 ☐ Movement present, but decreased against resistance

2 ☐ Movement present, but non against resistance

3 ☐ No movement

☐ Not assessed

☐ Not evaluable

- Test each limb separately
- Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups
- Score should assess worst performing area
- Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb

Ataxia (upper extremity)

0 ☐ Able to finger to nose touch without difficulty

1 ☐ Able to finger to nose touch but difficult

2 ☐ Unable to finger to nose touch

☐ Not assessed

☐ Not evaluable

- Non-evaluable if strength is compromised
- Trunk and lower extremities assessed by gait domain
- Particularly important for patients with brainstem and cerebellar tumors
- Score based on best response of 3 attempts

Sensation

0 ☐ Normal

1 ☐ Decreased but aware of sensory modality

2 ☐ Unaware of sensory modality

☐ Not assessed

☐ Not evaluable

- Recommend evaluating major body areas separately (face, limbs and trunk)
- Score should reflect worst performing area
- Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception
- Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

Visual Fields

0 ☐ Normal

1 ☐ Inconsistent or equivocal partial hemianopsia (≥quandrantopsia)

2 ☐ Consistent or unequivaocal partial hemianopsia (≥quandrantopsia)

3 ☐ Complete hemianopsia

☐ Not assessed

☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

0 ☐ Normal

1 ☐ Mild/moderate weakness

2 ☐ Severe facial weakness

☐ Not assessed

☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrows

Language

0 ☐ Normal

1 ☐ Abnormal but easily conveys meaning to examiner

2 ☐ Abnormal and difficulty conveying meaning to examiner

3 ☐ Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)

☐ Not assessed

☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologism/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

0 ☐ Normal

1 ☐ Drowsy (easily arousable)

2 ☐ Somnolent (difficult to arouse)

3 ☐ Unarousable/coma

☐ Not assessed

☐ Not evaluable

- None

Behavior

0 ☐ Normal

1 ☐ Mild/moderate alteration

2 ☐ Severe alteration

☐ Not assessed

☐ Not evaluable

- Particularly important for frontal love tumors
- Alteration includes, but is not limited to, apathy, disinhibition, and confusion
- Consider subclinical seizures for significant alteration

APPENDIX B. KARNOFSKY PERFORMANCE SCALE (%)

Adapted from: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET*, et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am.J.Clin.Oncol.* 1982,**5**:649-655.

100 Normal, no complaints; no evidence of disease.

90 Able to carry on normal activity; minor signs or symptoms of disease.

80 Normal activity with effort; some signs or symptoms of disease.

70 Cares for self; unable to carry on normal activity or to do active work.

60 Requires occasional assistance, but is able to care for most of his/her personal needs.

50 Requires considerable assistance and frequent medical care.

40 Disabled; requires special care and assistance.

30 Severely disabled; hospital admission is indicated although death not imminent.

20 Very sick; hospital admission necessary. Active support treatment necessary.

10 Moribund; fatal processes progressing rapidly.

0 Dead.

APPENDIX C. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC IMMUNE RELATED ADVERSE EVENTS

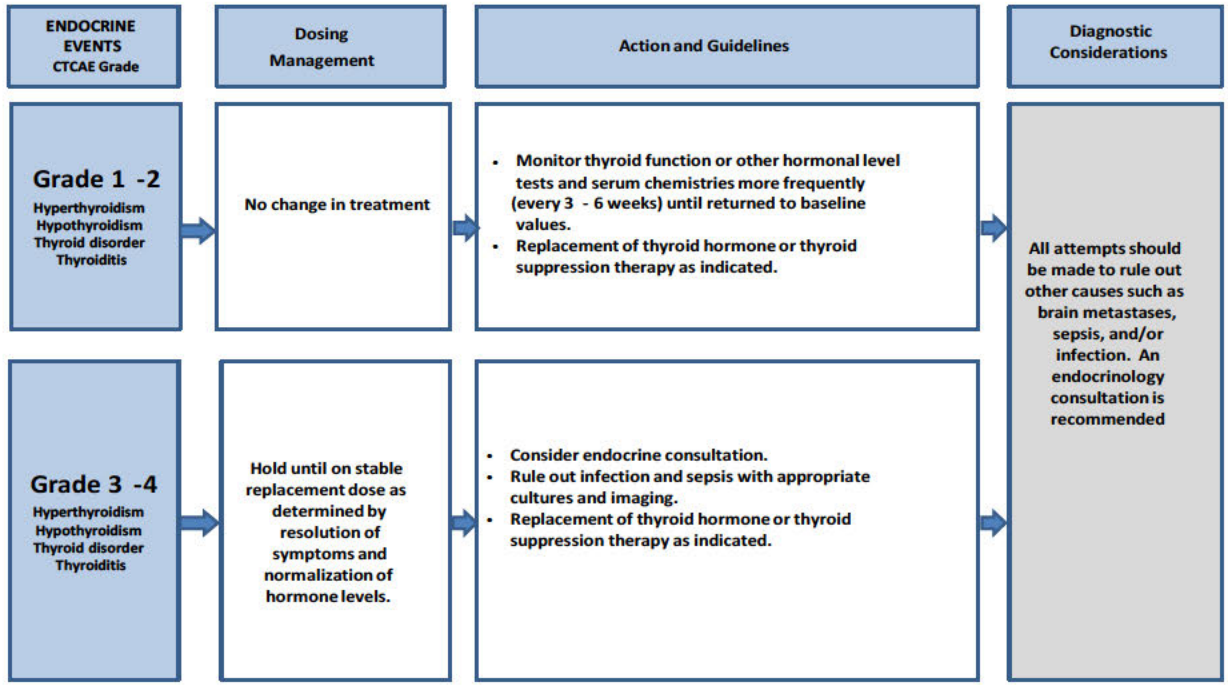
Colitis Adverse Event Management

COLITIS CTCAE Grade	Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1 Bowelobstruction Colitis Colitismicroscopic	No change in treatment	• For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily	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
Grade 2 Enterocolitis hemorrhagic Gastrointestinal (GI) perforation Necrotizing colitis Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and Electrolytes should be substituted via IV infusion.	Hold until ≤Grade 1.	• GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1 -2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, dosing should be withheld and anti -diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.	

Colitis Adverse Event Management

COLITIS CTCAE Grade	Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 3-4	Withhold treatment Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	• Patients with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. For Grade 34 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment), • Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 68 weeks in patients with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by highdose oral steroids does not reduce initial symptoms within 48 -72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis. • 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 If symptoms are persistent And/or severe, endoscopic evaluation should be considered

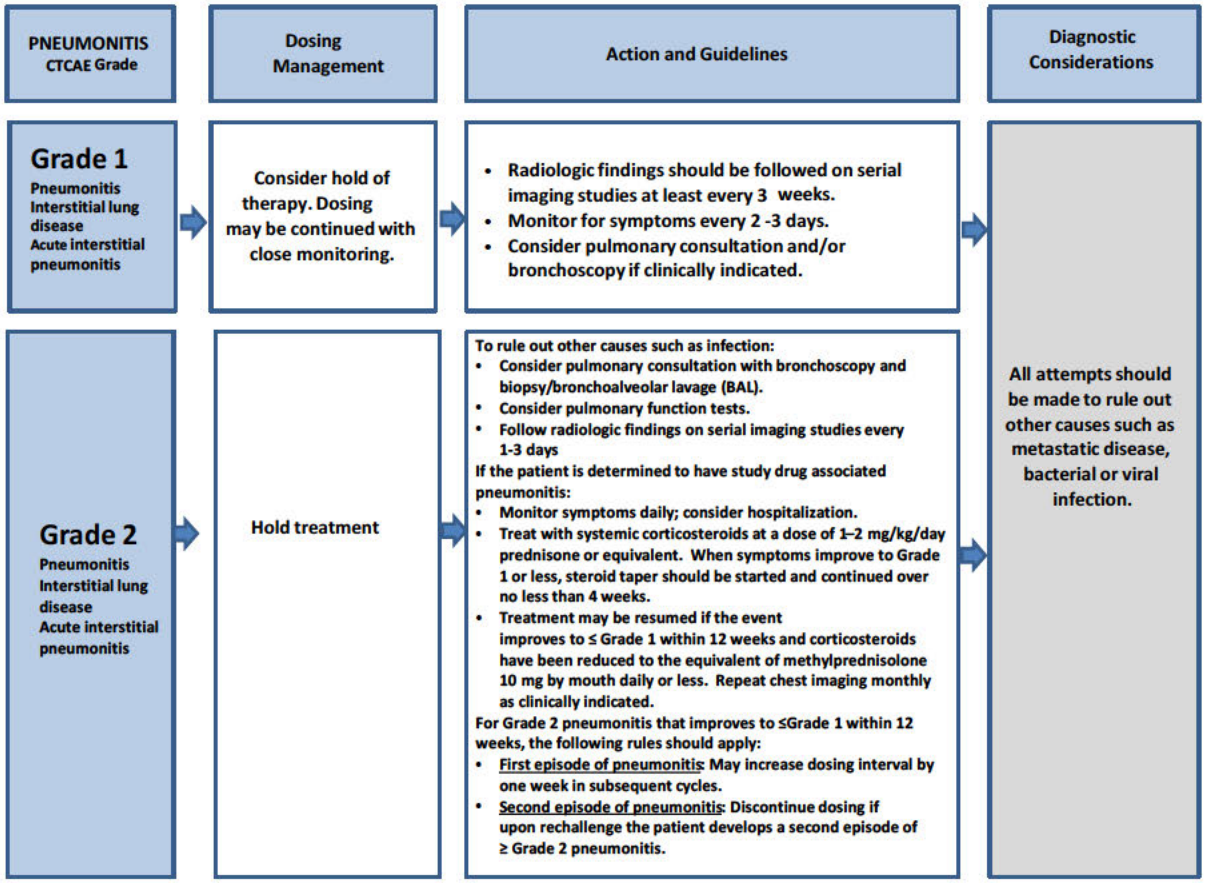
Endocrine Adverse Event Management



Endocrine Adverse Event Management (Cont)

ENDOCRINE EVENTS CTCAE Grade	Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1-4 Adrenal insufficiency Hypophysitis Hypopituitarism Pan-hypopituitarism	Hold until on stable replacement dose	• Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended

Pneumonitis Adverse Event Management



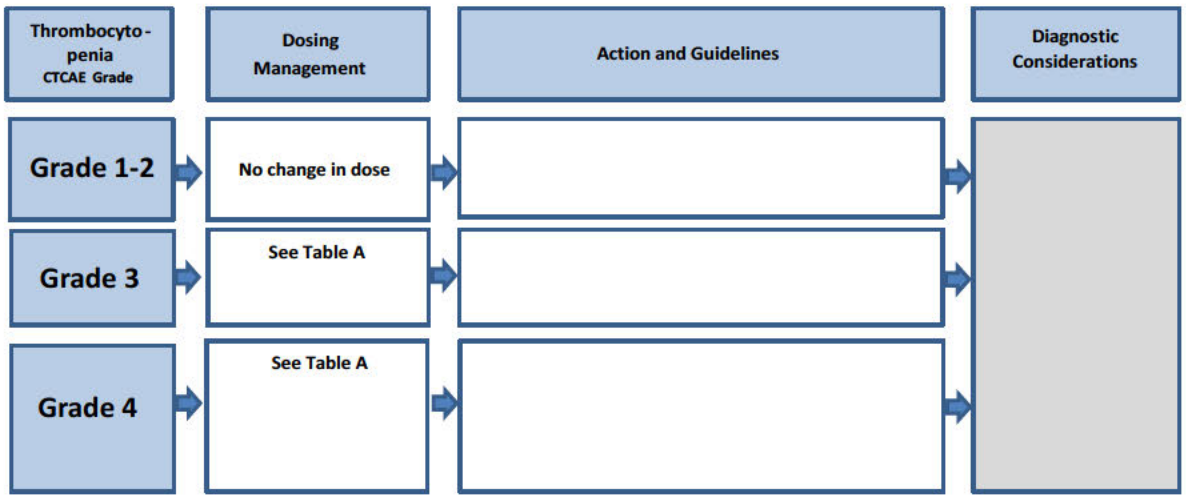
Pneumonitis Adverse Event Management (Cont)

PNEUMONITIS CTCAE Grade	Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 3 -4 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Discontinue treatment	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (methylprednisolone 125 mg). When symptoms improve to grade 1 or less, a high -dose oral steroid (prednisone 1- 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections • If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 -72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.

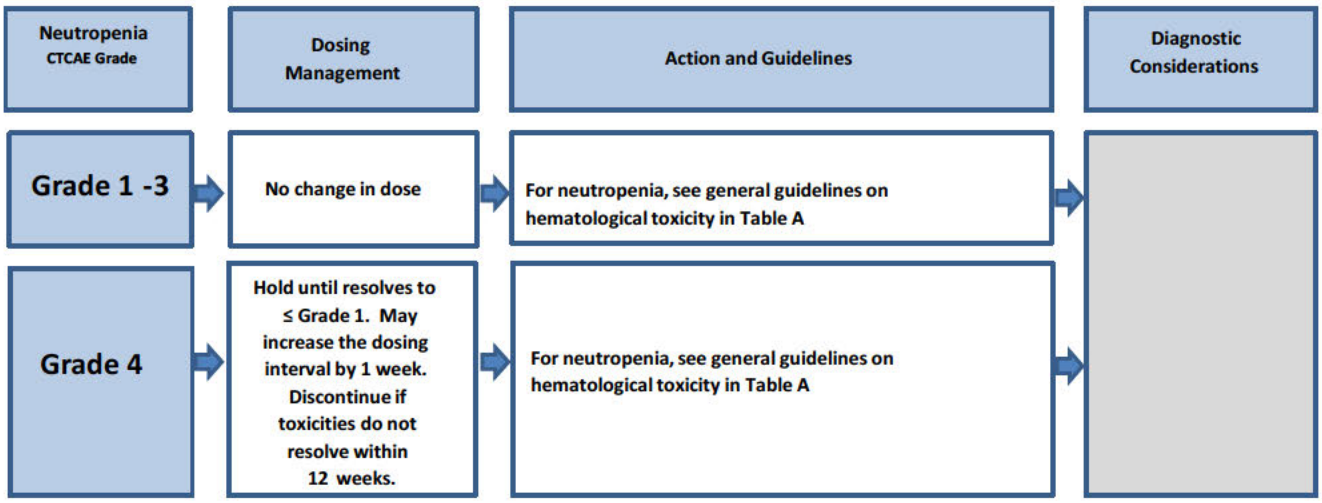
Renal Adverse Event Management

RENAL EVENTS CTCAE Grade	Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1 Nephritis Nephritis autoimmune	Consider withholding treatment if event does not improve with symptomatic treatment	• Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol.	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
Grade 2 Renal failure	Consider withholding treatment	• Systemic corticosteroids at a dose of 1-2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • If elevations persist >7 days or worsen, treat as Grade 4.	
Grade 3-4 •Renal failure acute	Discontinue treatment	• Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1-2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue treatment if unable to reduce corticosteroid dose for irAEs to ≤ 10 mg. • Treatment may be restarted and the dose modified as specified in the protocol.	

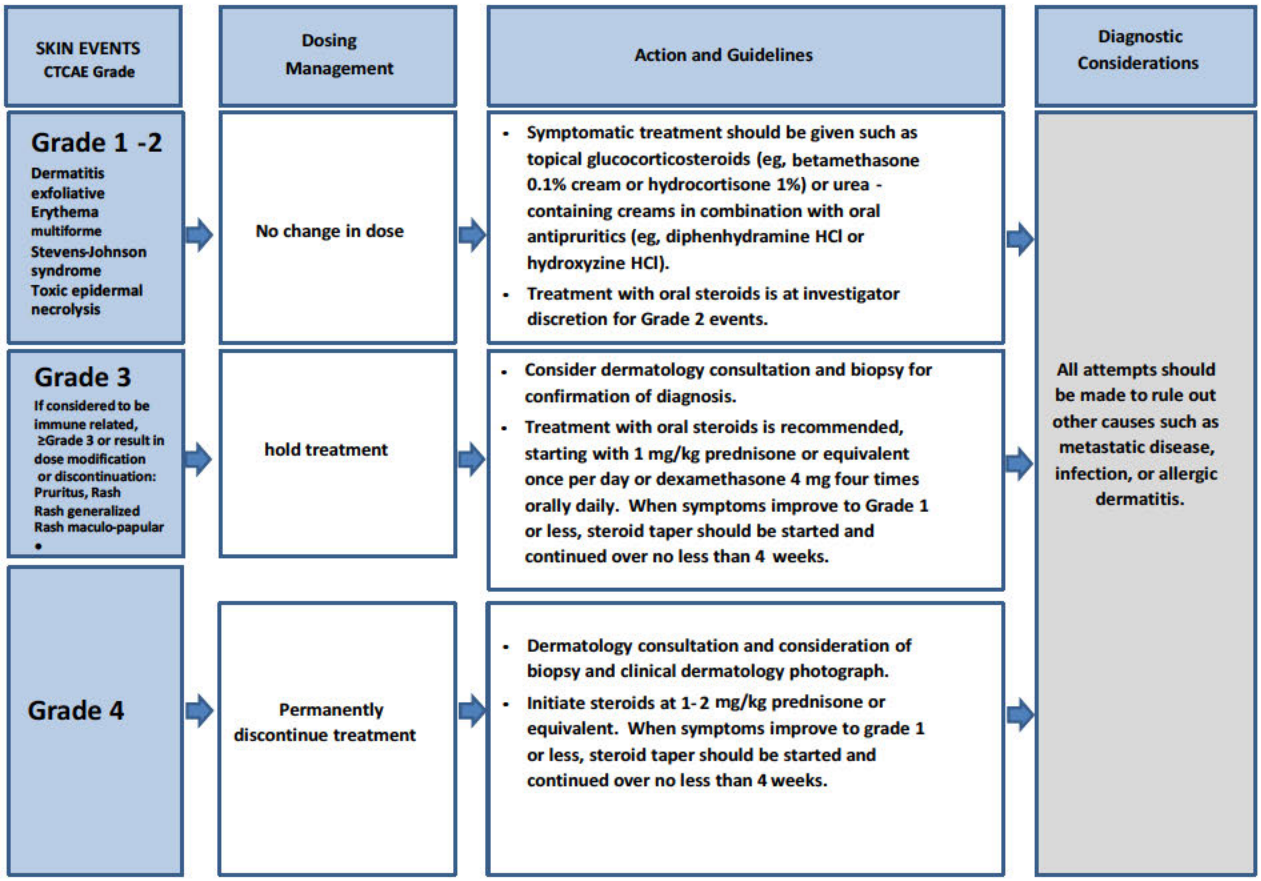
Hematologic Adverse Event Management



Hematologic Adverse Event Management (Cont)



Dermatologic Adverse Event Management



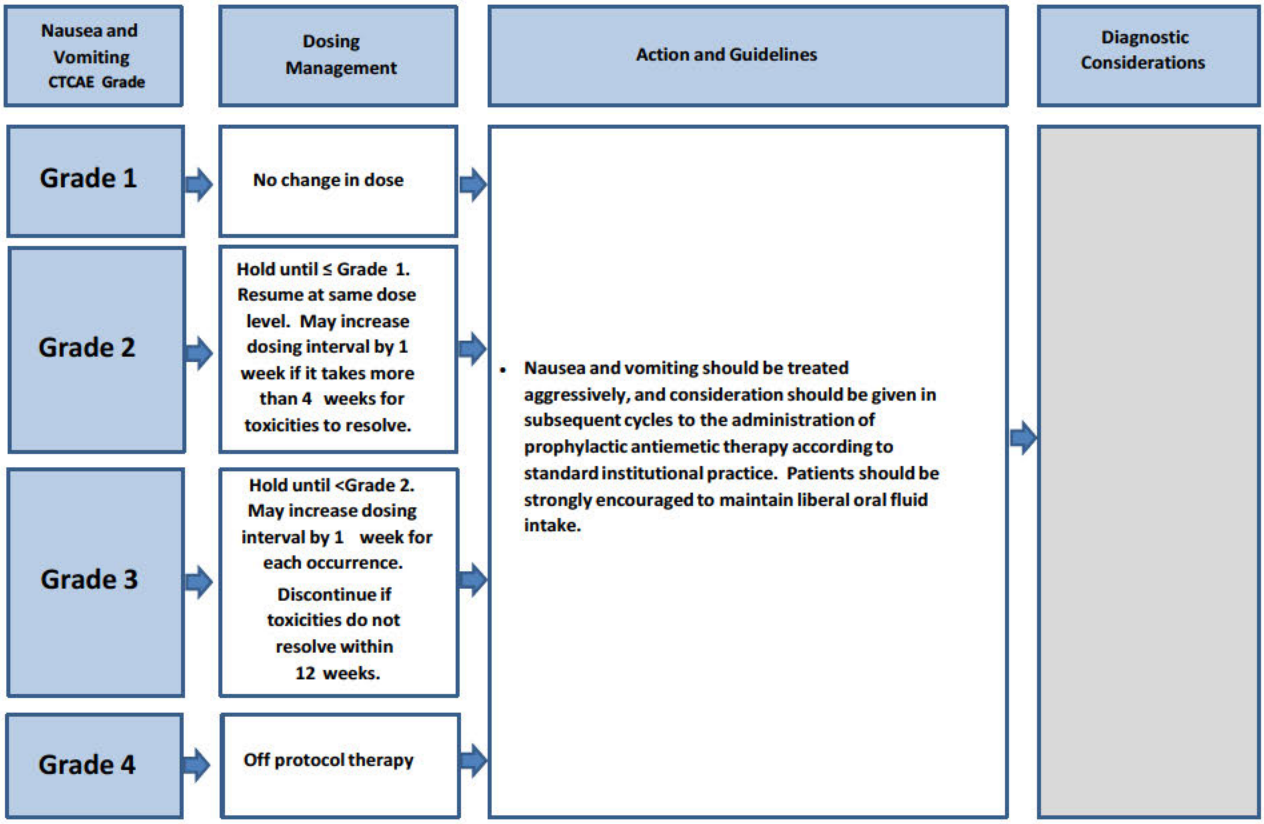
Hepatitis Adverse Event Management

Hepatitis CTCAE Grade	Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1 -2 Hepatitis Hepatitis, Autoimmune	Withhold treatment if there is a treatment - emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters.	• Monitor liver function tests more frequently until returned to baseline values.	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
Grade 3 -4	Discontinue treatment when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	• Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. • Treat with high -dose IV glucocorticosteroids for 24 –48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 –2 mg/kg should be started and continued over no less than 4 weeks. • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity. • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased	

Ophthalmologic (Uveitis) Adverse Event Management

Uveitis CTCAE Grade	Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1 iritis, iridocyclitis	Discontinue treatment if symptoms persist despite treatment with topical immunosuppressive therapy	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (*e.g.*, glaucoma or cataracts).
Grade 2	Discontinue treatment if symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	
Grade 3 -4	Discontinue treatment	• Treat with systemic corticosteroids such as prednisone at a dose of 1 - 2 mg/kg per day. When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks	

Nausea and Vomiting Adverse Event Management



Neurological Adverse Event Management

Adapted from: Larkin J, Chmielowski B, Lao CD, Hodi FS, Sharfman W, Weber J, *et al*. Neurologic Serious Adverse Events Associated with Nivolumab Plus Ipilimumab or Nivolumab Alone in Advanced Melanoma, Including a Case Series of Encephalitis. *Oncologist* 2017;**22**:709-718.

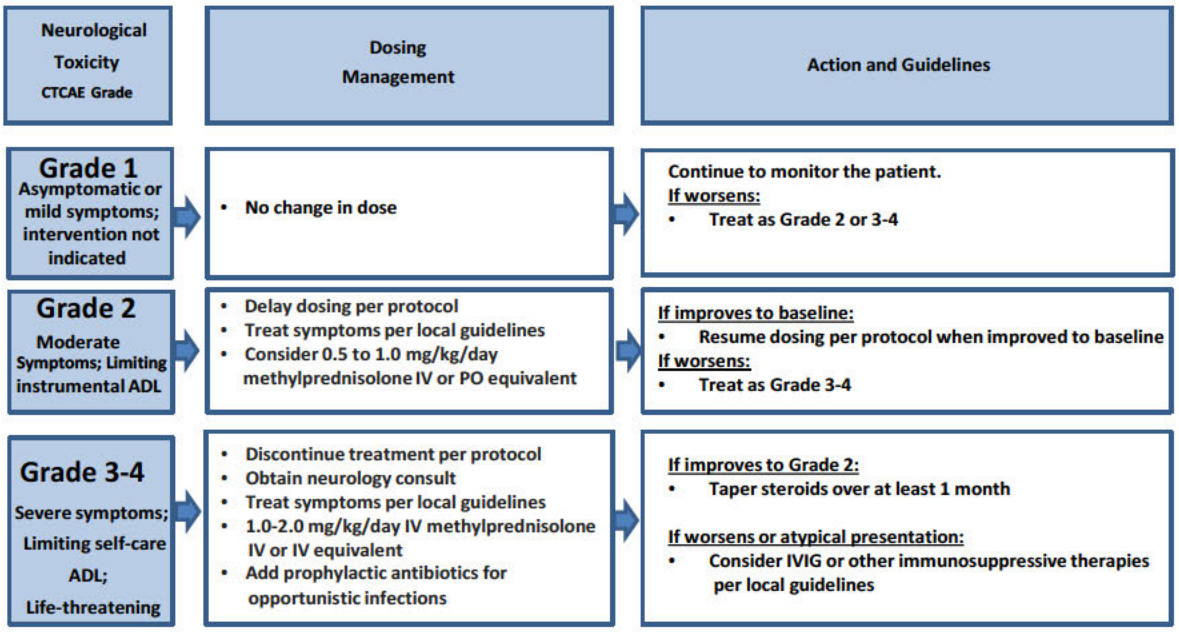


Table A: General Guidelines on Hematological Toxicity

Severity	Withhold/Discontinue Treatment?	Supportive Care
Grade 1	No action	Provide symptomatic treatment.
Grade 2	May withhold treatment	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade ≥3	Withhold treatment; discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. For any severe (Grade 3-4) irAE, if symptoms worsen or do not improve on adequate corticosteroids within 48 to 72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as infliximab, cyclophosphamide, cyclosporine, mycophenolate mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered.

APPENDIX D. COCKCROFT-GAULT FORMULA

Creatinine clearance (mL/minute) is estimated by the Cockcroft-Gault formula as:
[(140 – age in years) * weight in kilograms / (72 * serum creatinine)] * 0.85 if female.

Cockcroft, D.W. and M.H. Gault. Prediction of creatinine clearance from serum creatinine. Nephron. 1976. 16(1):31-41.

APPENDIX E. BEVACIZUMAB DOSE MANAGEMENT DUE TO ADVERSE EVENTS

Event	CTCAE Grade	Action to be Taken with Bevacizumab Dose
Hypertension	Grade 3	If not controlled with medication, discontinue bevacizumab
	Grade 4 (including reversible posterior leucoencephalopathy confirmed by MRI, or hypertensive encephalopathy)	Discontinue bevacizumab
Hemorrhage	Grade ≥ 1 new CNS hemorrhage	Discontinue bevacizumab
	Grade > 1 non-CNS hemorrhage	Discontinue bevacizumab
Venous Thrombosis	Grade 3 or Asymptomatic Grade 4	Hold bevacizumab. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if the following criteria is met: The participant must be therapeutically anti-coagulated with an approved anticoagulant agent according to standard prescribing guidelines.
	Symptomatic Grade 4	Discontinue bevacizumab
Arterial Thromboembolic event (Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	Any Grade	Discontinue bevacizumab
Congestive Heart Failure (left ventricular systolic dysfunction)	Grade 3	Hold bevacizumab until resolution to Grade ≤1
	Grade 4	Discontinue bevacizumab
Proteinuria	Grade 3	Hold bevacizumab treatment until ≤ Grade 2, as determined by 24 hour protein urine collection ≤ 3.5 g
	Grade 4	Discontinue bevacizumab
GI Perforation	Any Grade	Discontinue bevacizumab
Bowel Obstruction	Grade 1	Continue patient on bevacizumab for partial obstruction not requiring medical intervention

Event	CTCAE Grade	Action to be Taken with Bevacizumab Dose
	Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution
	Grade 3 or 4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Wound dehiscence	Any Grade	Discontinue bevacizumab if requires medical or surgical therapy
Infusion Related Reaction	Grade 1 or 2	Slow bevacizumab infusion to 50% or less or interrupt. When symptoms have completely resolved, the infusion may be continued at not more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. bevacizumab infusions may be restarted at the full rate during the next cycle
	Grade 3 or 4	Discontinue bevacizumab

APPENDIX F. RANO AND IRANO CRITERIA

iRANO Criteria

Response	Radiographic Findings	MRI Findings	Steroid Requirement	Clinical Status
Complete Response (CR)	Disappearance of all enhancing disease for ≥4 weeks in the absence of new lesions	Stable or improved T2/FLAIR	Physiological or less	Stable or improved
Partial Response (PR)	≥50% decrease in the sum of biperpendicular diameters of enhancing disease for ≥4 weeks in the absence of new lesions	Stable or improved T2/FLAIR	Stable or decreased	Stable or improved
Stable Disease (SD)	No CR, no PR, no PD	Stable or improved T2/FLAIR	Stable or decreased	Stable or improved
Progressive Disease (PD)	≥25% increase in the sum of biperpendicular diameters of enhancing disease, or new lesions	Worsened T2/FLAIR	Any	Substantial clinical decline

Adapted from: Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W*, et al.* Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol* 2015,**16**:e534-542.

RANO Criteria

Summary of the Proposed RANO Criteria				
Criterion	**CR**	**PR**	**SD**	**PD**
T1 galdolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA †
Clinical Status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neruo-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
*Progression occurs when this criterion is present.
† Increase in corticosteroids alone will not be taken into account in determining progression in absence of persistent clinical deterioration.

Adapted from: Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E*, et al.* Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010,**28**:1963-1972.

APPENDIX G. RADIATION PARAMETERS

40 Gy in 15 daily fractions:

1. Positioning, Immobilization and Simulation:
    a. The patient will be simulated in the supine position in most situations, immobilized typically with a thermoplastic mask. The treatment planning simulation CT scan will be acquired in the treatment position. The treatment volumes will be defined by fusion with the pre- and post-resection MRI scans.
    b. CT contrast may be omitted if medically indicated. The MRI sequences should include a T1-weighted post-contrast sequence (preferably stereotactic, thin slice, contiguous). Additionally, a T2/FLAIR sequence is helpful to identify non-enhancing tumor.
2. Equipment and Technique:
    a. Radiation will be delivered with megavoltage equipment, typically of 4MV or greater energy.
    b. Intensity modulated radiation (IMRT) via any method (eg, VMAT, static field IMRT, tomotherapy) is required. 3D planning is not allowed.
    c. Daily image-guidance is recommended to allow smaller planning target volume (PTV) margins, but is not required. The PTV margin should reflect if image-guided radiation (IGRT) is used.
3. Target Volume Delineation:
    a. A gross tumor volume (GTV) will be defined using the CT and MRI images.
    b. The GTV includes any enhancing tumor, if present following resection, as well as the post-operative resection cavity. The GTV also includes any non-enhancing tumor as identified on T2/FLAIR. T2/FLAIR signal consistent with edema is <u>not</u> specifically included in the GTV. Therefore a distinction is made between T2 edema (typically without mass effect, sparing the cortical ribbon, obeying the grey/white junction, etc) and T2 tumor (mass effect with sulcal effacement, involvement of the grey/white junction, obliteration of the cortical ribbon). Fusion of the pre-operative MRI to determine initial extent of the tumor is helpful.
    c. The clinical target volume (CTV) is created by anatomically expanding the GTV by 15 to 20 mm, per physician preference. The CTV should be trimmed at anatomic boundaries to rational tumor spread, such as the tentorium, falx if not near the corpus callosum, and skull. At these boundaries, the CTV may be 0 mm.
    d. A geometric PTV expansion of 3 to 5 mm will be applied to the CTV that is justified based on image guidance and immobilization. For treatment utilizing IGRT techniques, the PTV may be as small as 3mm. For non-IGRT approaches, a 5 mm expansion is recommended.
4. Organs at Risk (OAR) and OAR Constraints
    a. OARs shall be contoured, including: optic nerves, optic chiasm, eye globe, brainstem, and cochlea.

b. Radiation plan heterogeneity shall be constrained so that the above OARs all receive less than or equal to 41 Gy Dmax (102.5% of prescribed dose).

5. Dose:

a. A total dose of 40 Gy in 15 fractions of 2.67 Gy per day shall be delivered. Greater than or equal to 95% of the PTV should receive greater than or equal to 40 Gy. Undercoverage of the PTV at greater than or equal to 90% at 40 Gy is an acceptable variation in order to meet OAR constraints as above.
b. IMRT plan heterogeneity should ideally be 110% (44 Gy Dmax) or less and preferably under 105% (42 Gy Dmax). A Dmax of 114% (45.6 Gy) is an acceptable variation.