A PHASE II STUDY OF THE ANTI-GITR AGONIST INCAGN01876 AND THE PD-1 INHIBITOR INCMGA00012 IN COMBINATION WITH STEREOTACTIC RADIOSURGERY IN RECURRENT GLIOBLASTOMA

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The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

All information contained in this document is privileged and confidential. Any distribution, copying, or disclosure is strictly prohibited without prior written approval by the Sponsor.

List of Abbreviations

ADP: adenosine diphosphate

AE: Adverse event

AESI: Adverse event of special interest

AIDS: Acquired immunodeficiency syndrome

ALP: alkaline phosphatase

ALT: Alanine aminotransferase

ART: Antiretroviral therapy

AST: Aspartate aminotransferase

AUC: Area under the curve

BID: twice daily

C: Celsius

CBC: Complete blood count

CL: Plasma clearance

CL_{cr}: Creatinine clearance

CLIA: Clinical Laboratory Improvement Amendments

Cmax: mean peak observed concentration

CNS: Central Nervous System

CR: Complete response

CRF: Case report form

CT: Computed tomography

CTCAE: Common Terminology Criteria for Adverse Events

CV: Coefficient of variation

CYP: Cytochrome P450

DLT: Dose-limiting toxicity

DNA: Deoxyribonucleic acid

ECOG: Eastern Cooperative Oncology Group

eCRF: electronic case report form

EOT: end of treatment

FDA: Food and Drug Administration

FE: Food effect

FFPE: Formalin-fixed paraffin-embedded

FLAIR: fluid attenuation inversion recovery

GBM: Glioblastoma

GSCF: Granulocyte-colony stimulating factor

GGT: gamma-glutamyl transferase

GI: Gastrointestinal

GITR: Glucocorticoid-induced TNFR family related protein

GLP: Good Laboratory Practice

Gy: Gray

h: hour

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HCG: Human chorionic gonadotropin

hfRT: hypofractionated radiotherapy

Hgb: Hemoglobin

HIV: Human immunodeficiency virus

IB: Investigator's brochure

ICHL International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IDH: Isocitrate dehydrogenase

IHC: immunohistochemistry

IMRT: Intensity-modulated radiation therapy

INR: International normalized ratio

IRB: institutional review board

IU: International Units

IUD: intrauterine device

IV: Intravenous (ly)

kDa: kilodaltons

Kg: Kilograms

L: liter

LDH: Lactate dehydrogenase

LFTs: liver function tests

Mg: Milligrams

MGMT: O6-Methylguanine-methyltransferase

mL: milliliter

mM: millimolar

mRANO: modified Response Assessment in Neuro-Oncology Criteria

MRI: Magnetic Resonance Imaging

MTD: maximal tolerated dose

NA: Not available

NOAEL: no-observed-adverse-effect-level

ORR: Objective response rate

OS: Overall survival

PAD: pharmacologically active dose

PCR: polymerase chain reaction

PD: Progressive disease

PD-1: programmed cell death protein 1

PD-L1: programmed death-ligand 1

PFS: Progression-free survival

PFS-6mo: Progression-free survival rate at 6 months

P-gp: p-glycoprotein

PK: Pharmacokinetic (s)

PR: Partial response

PRO: Patient reported outcomes

PS: Performance status

PT: Prothrombin time

PTT: Partial thromboplastin time

QD: once a day

Qtc: corrected QT interval

RANO: Response Assessment in Neuro-Oncology Criteria

RNA seq: Ribonucleic acid sequencing

RT: Radiation therapy

SAE: Serious adverse event

SD: Stable disease

SMC: safety monitoring committee

SRS: stereotactic radiosurgery

$T_{1/2}$: half-life

TEAS: treatment emergent adverse events

TK: toxicokinetic

TMZ: Temozolomide

TRAE: treatment related adverse event

TTFields: Tumor-treating fields

UADE: Unanticipated Adverse Device Experience

ULN: upper limit of normal

VEGF: Vascular endothelial growth factor

Vss: volume of distribution at steady-state

WHO: World Health Organization

WOCBP: Women of child bearing potential

WT: Body weight

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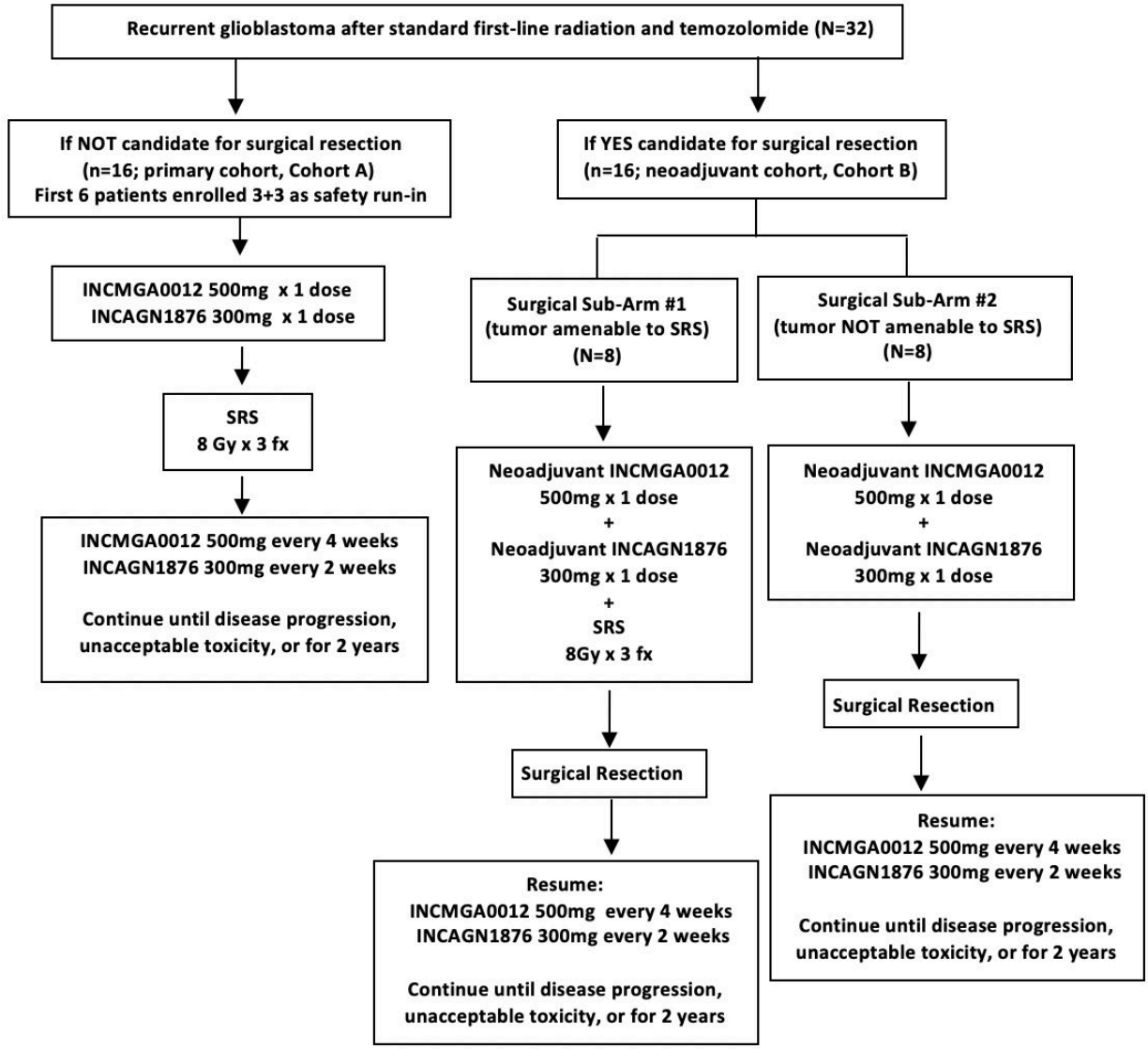
Study Synopsis

Title:	A PHASE II STUDY OF THE ANTI-GITR AGONIST INCAGN01876 AND THE PD-1 INHIBITOR INCMGA00012 IN COMBINATION WITH STEREOTACTIC RADIOSURGERY IN RECURRENT GLIOBLASTOMA
Short title:	GITR/PD1/SRS in GBM
IRB# and other Identifiers:	Penn IRB # 834197 [redacted]
Study Center:	Single center: University of Pennsylvania
Study Rationale:	Glioblastoma (GBM) is the most common primary malignant brain tumor in adults and is near uniformly fatal. Effective treatment options for recurrent disease remain elusive. GBM is characterized by a severely immunosuppressive tumor microenvironment and a paucity of intratumoral T cells. Combined inhibition of programmed death ligand 1 (PD-L1) and glucocorticoid-induced TNFR-related protein (GITR) augments the anti-tumor immune response in tumor-bearing mice, leading to durable responses, improved survival, and the development of T cells with a memory phenotype. In addition, preclinical data suggest that hypofractionated radiation using stereotactic radiosurgery (SRS) has immunostimulatory effects on the tumor immune microenvironment, potentially converting an immunologically "cold" tumor to "hot". The following protocol is a phase II study of the combination of the GITR agonist monoclonal antibody INCAGN01876, the anti-PD1 monoclonal antibody INCMGA00012, and SRS for recurrent GBM. We hypothesize that the proposed regimen will be safe and stimulate a robust anti-tumor immune response and result in improved tumor responses.
Investigational Products	1. INCAGN01876 (anti-GITR) 300mg IV every 2 weeks until disease progression, unacceptable toxicity, or 2 years, whichever occurs first 2. INCMGA00012 (anti-PD1) 500mg IV every 4 weeks until disease progression, unacceptable toxicity, or 2 years, whichever occurs first
Treatment Plan:	**The study has 2 arms:** **Arm A (Cohort A)** is a nonsurgical arm (N=16) that will serve as the primary study cohort and evaluated for the primary study endpoint. Subjects in this arm receive a single priming dose of both INCMGA00012 and INCAGN01876 prior to stereotactic radiosurgery (SRS), then undergo SRS (8 Gy x 3 fractions). Following SRS, INCMGA00012 (IV every 4 weeks) and INCAGN01876 (IV every 2 weeks) are resumed and continued until disease progression, unacceptable toxicity, or for 2 years, whichever occurs first.

Arm B (Cohort B) is a surgical arm (N=16) that will allow for evaluation of the effects on the tumor immune microenvironment of INCMGA00012, INCAGN01876, and SRS. In order to be enrolled on this arm, subjects must have a clinical indication for surgical resection of the recurrent GBM tumor. Prior to planned surgical resection, subjects receive neoadjuvant immunotherapy (one of two possible combinations, as outlined below). Subjects then undergo surgery. Postoperatively, the immunotherapy combination of INCMGA00012 (IV every 4 weeks) and INCAGN01876 (IV every 2 weeks) is resumed and continued until disease progression, unacceptable toxicity, or for 2 years, whichever occurs first. Subjects in the surgical arm with a focus of contrast-enhancing tumor that is amenable to SRS will be assigned to surgical sub-arm #1 of Cohort B (N=8). These subjects will receive neoadjuvant INCMGA00012 + INCAGN01876 + SRS. All other subjects enrolled on Cohort B (N=8) are treated with neoadjvuant INCMGA00012 + INCAGN01876 (without SRS).

Schema:



Objectives:

Primary Objective:

- To determine the efficacy of the combination of INCMGA00012, INCAGN01876, and SRS in recurrent GBM, as measured by the overall objective response rate (ORR)

Secondary Objectives:

- To evaluate the safety and tolerability of the combination of INCMGA00012, INCAGN01876, and SRS in recurrent GBM
- To determine the progression-free survival (PFS) and overall survival (OS) of patients with recurrent GBM treated with the combination of INCMGA00012, INCAGN01876, and SRS

Exploratory Objectives:

- To evaluate the biologic effect of the combination of INCMGA00012 and INCAGN01876 on the GBM tumor immunemicroenvironment
- To evaluate the biologic effect of the combination of INCMGA00012 and INCAGN01876, with or without SRS, on the GBM tumor immune microenvironment
- To evaluate the pharmacodynamic impact of the combination of INCMGA00012, INCAGN01876, and SRS on peripheral blood immune cell populations
- To evaluate the pharmacokinetics (PK) of INCAGN01876 in patients with glioblastoma
- To determine whether anti-drug antibodies (ADA) form against INCAGN01876 in patients with glioblastoma
- To detect tumor and/or blood biomarkers associated with the outcomes of OS, PFS, and/or ORR in patients with recurrent GBM treated with the combination of INCMGA00012, INCAGN01876, and SRS

Endpoints:

Primary Endpoint:

- Objective radiographic response (ORR), as measured by modified Response Assessment in Neuro-Oncology (RANO) criteria

Secondary Endpoints:

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs, and through clinical laboratory evaluations.
- OS, defined as the time from date of enrollment until death from any cause PFS, defined as the time from date of enrollment until the earliest date of disease progression (as determined by modified RANO criteria) or death due to any cause

Exploratory Endpoints:

- Comparison of the following immunocorrelative assays in subjects treated with INCMGA00012 + INCAGN01876, with or without SRS:
  - Multiplex immunohistochemistry on tumor tissue for CD4/8 T cell infiltration, Foxp3+ Treg infiltration, and PD-1/PD-L1 expression

  - Tumor cell and immune cell GITR expression by a validated immunohistochemistry stain
  - Flow cytometry/mass cytometry in tumor tissue and peripheral blood for T cell and monocyte phenotyping
  - RNA-Seq on tumor tissue for PD-1/PD-L1 and GITR expression, T cell- and interferon-γ-related gene expression, and cell-cycle-related gene expression
  - T cell receptor sequencing in tumor tissue and peripheral blood for assessment of TCR clonal diversity
- Association between the above tumor tissue and peripheral blood-based markers of immune activation, tumor genetic mutations, and clinical outcomes of OS, PFS, and ORR
- PK parameters for INCAGN01876 in patients with glioblastoma
- Detection of anti-drug antibodies (ADA) against INCAGN01876

Sample Size, Power, Statistical Analysis: The total sample size for this trial is 32 subjects.

- 16 subjects will comprise the non-surgical arm, Cohort A, which serves as the cohort for the primary study endpoint analysis (subjects do not have clinical indication for surgical resection).
- 16 subjects will comprise the surgical arm, Cohort B, which is the exploratory arm for correlative studies (subjects have clinical indication for surgical resection).
- Once a 3+3 safety run-in phase had been completed in Cohort A, the two cohorts will enroll simultaneously.

Cohort A (N=16):

The primary efficacy hypothesis of this study is that the proportion of subjects who experience an objective radiographic response will be 25% or higher. We will test this hypothesis against the null hypothesis of 5% of subjects experiencing an objective response using an exact single-stage phase II design for the primary study cohort (Cohort A; Non-surgical). A sample size of 16 evaluable subjects is required for 80% power. A one-sided significance level has been set at 0.05.

Cohort B (N=16)

This exploratory cohort will consist of subjects who meet all eligibility criteria for this trial but in whom surgical resection is clinically indicated at the time of study enrollment. These subjects will be assigned to two subarms (N=8 in each arm), with each subarm receiving a different neoadjuvant regimen prior to surgical resection as diagrammed above in the study schema. This sample size is not intended for detecting efficacy differences between the surgical subarms, or for detecting efficacy differences between the surgical Cohort B and the non-surgical Cohort A. Rather, 8 subjects per surgical subarm is the minimum necessary to provide enough patient tumor samples to make meaningful inferences from the exploratory/correlative tissue studies that will accompany this

trial. For efficacy endpoints in the surgical arm, only descriptive statistics will be used given the limited sample size.

Statistical analyses for additional secondary and exploratory endpoints: Descriptive analyses will be conducted to summarize subject characteristics and detect potential selection bias as a result of missing data or dropout. Variable distributions will be examined; if needed, appropriate transformations will be performed. Kaplan-Meier curves will be generated for PFS and OS. Paired t-tests will be used to assess change from pre- to post-treatment for exploratory endpoints that are normally distributed. Wilcoxon signed-rank tests will be used to assess change from pre- to post-treatment for exploratory endpoints that are not normally distributed. Multiple comparison adjustment using false discovery rate (FDR) will be used.

1 Background

1.1 Introduction

This document is a clinical research protocol. The described study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations, including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, and Good Clinical Practice: Consolidated Guidelines approved by the International Conference of Harmonization (ICH).

The study shall be conducted as described in this approved protocol. The investigator should not implement any deviation or change to the protocol without prior review and documented approval from the Sponsor (University of Pennsylvania) and IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

This is an open-label, single-institution, phase II study of the anti-GITR agonist INCAGN01876 and the PD-1 inhibitor INCMGA00012 in combination with stereotactic radiosurgery in recurrent glioblastoma. The primary objective of the study is to determine the efficacy of this regimen in this patient population.

1.2 Disease Background

GBM is the most common primary malignant brain tumor in adults and is near uniformly fatal (Ostrom et al, Neuro Oncol 2015). Standard first-line treatment for primary GBM includes surgical resection of the bulk tumor to the maximal extent possible consistent with neurological preservation, followed by radiotherapy, often in combination with temozolomide based on an overall survival (OS) benefit (referred to as the Stupp protocol; Stupp et al., 2005). Temozolomide is then continued as a maintenance therapy for 6 monthly cycles. In addition, tumor-treating fields (TTFields), manufactured by Novocure and branded as the Optune® device, is approved by the United States Food and Drug Administration (FDA) for use in combination with maintenance temozolomide in patients 22 year of age or older. Although this was also shown to improve OS compared to temozolomide alone, currently only about 15% of newly diagnosed patients in the US are treated with Optune as part of first-line treatment (Burri et al, Am J Clin Oncol 2018).

When relapse or progression inevitably occurs in patients who have undergone the Stupp protocol, therapeutic options are unfortunately limited and generally not effective; median OS for recurrent GBM is typically less than 12 months (Weller et al, Neuro Oncol 2013), and no therapeutic intervention has ever been demonstrated to prolong OS compared to supportive care alone. Surgery may be indicated in a minority of relapsed patients with disease that is symptomatic from mass effect, but it results in only limited prolongation of survival (Keles et al, J Neurosurg 2004). When repeat surgery is performed, survival may be improved by adding the Gliadel® (carmustine) implant at the time of surgery. However, the majority of patients with relapsed disease are not candidates for additional surgery (and hence are not candidates for Gliadel) (Weller et al., Neuro Oncol 2013). Avastin® (bevacizumab) is also FDA-approved for recurrent GBM based on achieving an overall radiographic response rate of 28% and a 6-month progression free survival (PFS) rate of 42.6% (Friedman et al., J Clin Oncol 2009). However, duration of response to bevacizumab is generally limited to several months, at which point tumors typically develop resistance to the agent and continue to progress. Furthermore, the

addition of bevacizumab to salvage cytocytoxic chemotherapies for recurrent GBM, such as lomustine (which has very limited efficacy itself, with a response rate <10%), has never been demonstrated to improve OS (Wick et al, N Engl J Med 2017). The Optune (TTFields) device is also FDA-approved for recurrent GBM (age 22 years and older) as a monotherapy based on a randomized controlled trial demonstrating similar OS between recurrent GBM patients treated with TTFields monotherapy versus physician's choice of chemotherapy, with a more favorable toxicity profile in the TTFields arm compared to chemotherapy (Stupp et al, Eur J Cancer 2012). Lastly, select patients may be candidates for reirradiation. In a large retrospective series, the median survival after re-irradiation was approximately 11 months (Fogh et al, J Clin Oncol 2010). However, the benefit of such therapy is unclear given the paucity of prospective data.

Based on the current lack of any therapy for recurrent GBM that has durable efficacy and/or results in improved OS compared to best supportive care, novel therapeutic options for recurrent GBM are desperately needed.

1.3 Name and Description of Investigational Drugs

1.3.1. INCMGA00012

INCMGA00012 is a humanized, hinge-stabilized, IgG4κ mAb that recognizes human PD-1. INCMGA00012 contains a human IgG4 Fc domain to limit effector function while retaining neonatal FcRn binding to extend circulating t½. INCMGA00012 is designed to target PD-1–expressing cells, including T cells, and sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2. INCMGA00012 drug product is formulated at a concentration of 25 mg/mL in sodium acetate trihydrate, acetic acid, sucrose, and polysorbate 80 at pH 5.1.

PD-1 is expressed on T cells (CD4+ and CD8+), B cells, NK cells and myeloid-derived cells. It is well-established that the interaction of PD-1 with its ligands, PD-L1 and PD-L2, forms a negative signaling axis in T cells (Chen and Flies 2013, Freeman et al 2000, Parry et al 2005). This PD-1–PD-L1/L2 inhibitory signaling pathway is one of several known "immune checkpoints" utilized by the immune system to maintain self-tolerance and modulate the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage. Extensive research has shown that cancer cells co-opt certain immune checkpoint pathways, including the PD-1 pathway, as a major mechanism of immune evasion/resistance, particularly against T cells that are specific for tumor antigens (Chen and Mellman 2013, Topalian et al 2015, Yao et al 2013). Disruptors of this pathway, including antibodies that inhibit PD-1 receptor-ligand interactions, have been shown to be effective inhibitors of tumor growth in murine models (Curran et al 2010, Iwai et al 2005, Pilon-Thomas et al 2010, Wong et al 2007). Moreover, clinical evaluation of these molecules has established them as a new class of antitumor agents, referred to collectively as checkpoint inhibitors, with several molecules targeting this pathway recently gaining marketing approval for several cancer indications (Keytruda® 2018, Opdivo® 2018, Libtayo® 2018, Bavencio® 2018, Imfinzi® 2018, Tencentriq® 2018).

1.3.1.1. Nonclinical data

Nonclinical data on INCMGA00012 are discussed in detail in the INCMGA00012 Investigator's Brochure (IB).

In vitro studies with INCMGA00012 have demonstrated high affinity binding to both recombinant human and cynomolgus monkey PD-1 as well as to PD-1 naturally expressed on the cell surface, including on T cells. Consistent with its intended mechanism of action and functional properties, INCMGA00012 has been shown to inhibit the binding of PD-L1 and PD-L2 to PD-1, to disrupt the PD-1–PD-L1 inhibitory axis, and to enhance IFN-γ secretion in human PBMCs stimulated with the superantigen, SEB. These studies also demonstrated that the in vitro biological activity of INCMGA00012 was comparable to that mediated by other anti–PD-1 mAbs, specifically, 2 mAb replicas of pembrolizumab and nivolumab generated by MacroGenics, Inc. based on the published sequences of these antibodies. Mean IC50 values of INCMGA00012, the nivolumab replica, and the pembrolizumab replica were 0.010, 0.016, and 0.014 μg/mL, respectively, for PD-L1 binding and 0.021, 0.028, and 0.028 μg/mL, respectively, for PD-L2 binding.

1.3.1.2. Clinical Experience

INCMGA00012 clinical data are discussed in detail in the INCMGA00012 IB.

Briefly, INCMGA00012 is currently under development as a therapeutic candidate for the treatment of multiple solid tumors, both as a monotherapy and in combination with other agents. As of 23 SEP 2018, INCMGA00012 has been administered to approximately 200 participants in a Phase 1 study (INCMGA 0012-101, formerly CP-MGA012-01) at weight-based doses ranging from 1 to 10 mg/kg Q2W or Q4W and at flat doses of 500 mg Q4W and 750 mg Q4W. Preliminary efficacy data demonstrate clinical activity of INCMGA00012 based on durable RECIST responses in multiple tumor types. The 500 mg Q4W dose was selected for further development based on favorable safety and PK profiles.

INCMGA00012 was well-tolerated at all doses tested in Study INCMGA 0012-101 with no dose-limiting toxicities observed in the dose-escalation phase. The MTD was not established. Treatment-related AEs were primarily immunologic in nature and representative of previous experience with other PD-1 inhibitors (Keytruda 2018, Opdivo 2018, Libtayo 2018). Among the 199 participants exposed to INCMGA00012 monotherapy in Study INCMGA 0012-101, the most frequently reported treatment-emergent adverse events (TEAEs; > 10%, regardless of attribution to treatment) were fatigue, anemia, nausea, diarrhea, pyrexia, and vomiting (NCT03059823). A complete list of treatment-emergent AEs occurring in >=10% of patients in Study INCAMGA0012-101 (cohort expansion phase, safety population) are displayed in **Table 1:**

Table 1. Treatment-emergent AEs occurring >=10% of patients in INCMGA0012-101 by tumor type and dosage

	3 mg/kg Q2W					Q4W Administration	
MedDRA Preferred Term	**Endometrial Cancer (n = 29)**	**Cervical Cancer (n = 34)**	**Sarcoma (n = 34)**	**NSCLC (n = 35)**	**Total (N = 132)**	**500 mg (n = 15)**	**750 mg (n = 15)**
Participants with at least 1 TEAE, n (%)	23 (79.3)	28 (82.4)	29 (85.3)	28 (80.0)	108 (81.8)	15 (100.0)	13 (86.7)
Fatigue	7 (24.1)	4 (11.8)	5 (14.7)	2 (5.7)	18 (13.6)	4 (26.7)	3 (20.0)
Diarrhoea	5 (17.2)	4 (11.8)	3 (8.8)	2 (5.7)	14 (10.6)	2 (13.3)	1 (6.7)
Dyspnoea	4 (13.8)	4 (11.8)	3 (8.8)	3 (8.6)	14 (10.6)	0	0
Anaemia	4 (13.8)	5 (14.7)	2 (5.9)	2 (5.7)	13 (9.8)	2 (13.3)	4 (26.7)
Nausea	3 (10.3)	6 (17.6)	2 (5.9)	1 (2.9)	12 (9.1)	0	3 (20.0)
Hypothyroidism	1 (3.4)	3 (8.8)	1 (2.9)	4 (11.4)	9 (6.8)	1 (6.7)	3 (20.0)
Pyrexia	5 (17.2)	1 (2.9)	3 (8.8)	0	9 (6.8)	2 (13.3)	1 (6.7)
Vomiting	5 (17.2)	3 (8.8)	1 (2.9)	0	9 (6.8)	1 (6.7)	3 (20.0)
Blood creatinine increased	5 (17.2)	2 (5.9)	0	1 (2.9)	8 (6.1)	0	2 (13.3)
Hyperthyroidism	0	3 (8.8)	3 (8.8)	2 (5.7)	8 (6.1)	1 (6.7)	3 (20.0)
Cough	1 (3.4)	3 (8.8)	2 (5.9)	1 (2.9)	7 (5.3)	0	3 (20.0)
Hypokalaemia	4 (13.8)	0	1 (2.9)	2 (5.7)	7 (5.3)	0	2 (13.3)
Decreased appetite	5 (17.2)	0	1 (2.9)	0	6 (4.5)	2 (13.3)	0
Pruritus	3 (10.3)	1 (2.9)	1 (2.9)	1 (2.9)	6 (4.5)	1 (6.7)	2 (13.3)
Blood alkaline phosphatase increased	3 (10.3)	0	0	0	3 (2.3)	3 (20.0)	1 (6.7)
Lymphopenia	2 (6.9)	0	0	0	2 (1.5)	2 (13.3)	0
Blood bilirubin increased	1 (3.4)	0	0	0	1 (0.8)	3 (20.0)	1 (6.7)
Hypertriglyceridaemia	0	0	1 (2.9)	0	1 (0.8)	0	2 (13.3)
Musculoskeletal pain	0	0	1 (2.9)	0	1 (0.8)	1 (6.7)	2 (13.3)

Note: TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of INCMGA00012.
Note: Participants were counted once under each MedDRA system organ class and preferred term.
Note: MedDRA preferred terms are presented in decreasing order of frequency using the Total 3 mg/kg Q2W column.

A complete list of treatment-emergent AEs occurring in >=5% of patients in Study INCAMGA0012-101 (cohort expansion phase, safety population) is displayed in **Table 2:**

Table 2. INCMGA00012 Monotherapy: Summary of Frequent (≥ 5%) Treatment-Emergent Adverse Events (Safety Population; N = 199)

MedDRA Preferred Term	INCMGA00012 Monotherapy n (%)
Fatigue	41 (20.6)
Anaemia	26 (13.1)
Nausea	23 (11.6)
Diarrhoea	20 (10.1)
Pyrexia	20 (10.1)
Vomiting	20 (10.1)
Cough	16 (8.0)
Hypothyroidism	16 (8.0)
Dyspnoea	15 (7.5)
Decreased appetite	14 (7.0)
Hyperthyroidism	14 (7.0)
Blood alkaline phosphatase increased	13 (6.5)
Blood creatinine increased	13 (6.5)
Pruritus	13 (6.5)
Urinary tract infection	12 (6.0)
Constipation	11 (5.5)
Pain in extremity	11 (5.5)
Rash	11 (5.5)
Arthralgia	10 (5.0)
Asthenia	10 (5.0)
Dehydration	10 (5.0)
Hypokalaemia	10 (5.0)
Weight decreased	10 (5.0)

Note: TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of INCMGA00012.
Note: Participants were counted only once under each MedDRA preferred term.
Note: MedDRA preferred terms are presented in decreasing order of frequency using the Overall column.

There were no fatal treatment-emergent AEs (TEAEs) related to INCMGA00012. In the cohort expansion phase participants receiving flat doses of INCMGA00012 Q4W, 3 participants each (20.0%) receiving 500 mg and 750 mg experienced serious TEAEs (hyperthyroidism, upper abdominal pain, large intestine perforation, pain, pyrexia, cholangitis, sepsis, blood bilirubin increased, and renal colic); each preferred term occurred in 1 participant. Serious TEAEs considered by the investigator to be at least possibly related to INCMGA00012 were blood bilirubin increased and hyperthyroidism.

The first-in-human Study INCMGA 0012-101 protocol specified the following adverse events of special interest (AESIs):
• _Grade 2 or greater immune related adverse events (irAEs)
• _Grade 3 or greater infusion reactions or cytokine relase syndrome
• _Abnormal liver enzymes that meet the criteria for potential Hy's law, defined as AST and/or ALT > 3 × ULN and total bilirubin > 2 × ULN and without any alternate etiology

As of 23 SEP 2018, a total of 27 participants in Study INCMGA 0012-101 have experienced at least 1 protocol-specified AESI (**Table 3**), described in detail below.

Table 3. Adverse Events of Special Interest Occurring in Participants in Study INCMGA 0012- 101 (Safety Population)

MedDRA Preferred Term	Dose Escalation Phase	Dose Expansion Phase		
	Total (N = 37)[a]	3 mg/kg Q2W (n = 132)	500 mg Q4W (n = 15)	750 mg Q4W (n = 15)
Participants with at least 1 AESI, n (%)	6 (16.2)	16 (12.1)	3 (20.0)	2 (13.3)
Colitis	0	3 (2.3)	0	0
Infusion-related reaction	1 (2.7)	3 (2.3)	0	1 (6.7)[b]
Liver function abnormality[c]	0	3 (2.3)	2 (13.3)	0
Endocrine disorders[d]	3 (8.1)	2 (1.5)	1 (6.7)	2 (13.3)
Rash[e]	1 (2.7)	2 (1.5)	0	0
Diarrhoea	0	1 (0.8)	0	0
Hyperglycemia	0	1 (0.8)	0	0
Myocarditis	0	1 (0.8)	0	0
Nephritis	0	1 (0.8)	0	0
Pain in extremity	0	1 (0.8)	0	0
Proctitis	1 (2.7)	0	0	0
Stomatitis	1 (2.7)	0	0	0
Mucosal inflammation	1 (2.7)	0	0	0
Lipase increased	1 (2.7)	0	0	0
Vulvovaginal inflammation	1 (2.7)	0	0	0

[a] Dose levels of 1 mg/kg, 3 mg/kg, or 10 mg/kg on a Q2W schedule or 3 mg/kg or 10 mg/kg on a Q4W schedule.
[b] Not categorized as an AESI.
[c] Liver function abnormality includes the following MedDRA preferred terms: autoimmune hepatitis, cholangitis, alanine aminotransferase increased, blood bilirubin increased, and transaminases increased.
[d] Endocrine disorders include the following MedDRA preferred terms: autimmune thyroiditis, hyperthyroidism, and hypothyroidism.
[e] Rash includes the following MedDRA terms: rash and rash maculopapular.

1.3.1.3. Potential Risks of INCMGA00012

INCMGA00012 is an investigational drug. Clinical experience with the PD-1 inhibitor class is well-described, and no major differences in the INCMGA00012 safety profile compared with other PD-1 inhibitors are anticipated based upon nonclinical and preclinical characterization of the molecule and the clinical experience as of the data cutoff date. As with any new product, however, administration of INCMGA00012 may involve safety concerns that are currently unforeseen, and appropriate precautions should be taken as described in the respective study protocols.

INCMGA00012 is an IgG4 humanized mAb that has been designed to restore T-cell immune function, similar to other PD-1 inhibitors that have been extensively studied. Therefore, safety

experience with other drugs should be considered when administering INCMGA00012. Potentially serious immune-related adverse events (irAEs) include:
• Pneumonitis
• Hepatitis
• Colitis
• Nephritis
• Endocrinopathies (thyroiditis, hypophysitis, Type I diabetes)
• Encephalitis
• Myocarditis
• Skin reactions (including SJS/TEN)
• Rejection of organ transplants
• Other reactions (including arthritis, uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, and hemolytic anemia)

As of the data cutoff date, irAEs in participants exposed to INCMGA00012 were generally consistent with approved PD-1 inhibitors in frequency and severity. Guidance for assessment, management, and reporting of these immune-related toxicities is provided in the remainder of the protocol.

Complete, detailed nonclinical and clinical data for INCMGA00012, including complete pharmacology, toxicology, and genotoxicity data, is available in the Investigator's Brochure.

1.3.2 INCAGN01876

INCAGN01876 is a recombinant, humanized immunoglobulin G1 (IgG1) kappa (κ) mAb that binds to the extracellular domain of the human tumor necrosis factor receptor superfamily member 18 (TNFRSF18), also known as glucocorticoid-induced TNFR-related protein (GITR). INCAGN01876 drug product is formulated at a concentration of 10 mg/mL in histidine, sucrose, and polysorbate 80 at pH 6.0. Agonist GITR antibodies have shown antitumor activity in in vivo studies in mice (Turk et al 2004, Ko et al 2005, Bulliard et al 2013). INCAGN01876 is an agonistic antihuman GITR mAb, with the potential to enhance the function of tumor-specific T cells and promote antitumor immunity in cancer patients. Recent clinical success with checkpoint inhibitors has provided rationale for investigating agonists, such as GITR, in order to extend clinical benefit to patients.

GITR belongs to the TNF receptor superfamily, and is activated by its cognate ligand, GITRL. GITR regulates a variety of immune cell functions including T-cell proliferation, differentiation, cytokine production, and survival (Smith et al 1994). GITR expression is generally restricted to normal tissues with high immune cell composition, including the peripheral blood, bone marrow, spleen, and thymus (Gurney et al 1999). GITR is expressed on some Tregs, is upregulated upon T-cell activation of both CD4+ and CD8+ T cells, and is a costimulator in the activation of these T cells (Allan et al 2007, Bianchini et al 2011, Schaer et al 2012).

In mice, the GITR-GITRL system is implicated in development of autoimmune and inflammatory responses, as well as promoting protective immunity to pathogens and tumors (Nocentini et al 2012). Animals treated with a GITR-Fc fusion protein leading to an attenuated GITR signaling showed signs of ameliorated autoimmunity. By contrast, an agonist anti-GITR antibody augmented an immune response to viral, bacterial, and parasitic infections. Unlike murine models, the cell surface expression of GITR is undetectable on the majority of human

peripheral blood immune cell populations. GITR expression among human immune cells seems to be exclusively reserved to subpopulations of Treg, transitional memory T cells, and recently activated T cells (Schaer et al 2012, Ronchetti et al 2015). This would suggest that an agonistic GITR mAb, such as INCAGN01876, would have a focused effect in the human immune response leading to the proliferation and augmentation of an ineffectually active antitumor immune response.

1.3.2.1. Nonclinical data

Nonclinical data on INCMGA01876 are discussed in detail in the INCMGA01876 Investigator's Brochure (IB).

INCAGN01876 binds to human GITR with a KD value of 0.21 nM and cross-reacts with African Green monkey (*Chlorocebus sabeus*) GITR with less than a 10-fold difference in affinity. Consistent with its binding epitope on human and African Green monkey GITR, INCAGN01876 does not recognize cynomolgus monkey (*Macaca fascicularis*) or rodent GITR. African Green monkey was therefore considered as a toxicologically relevant nonhuman primate species in which to evaluate this molecule.

INCAGN01876 does not bind to related TNFRSF members. INCAGN01876 functions as a GITR agonist antibody in human and African Green monkey cells, providing T cell costimulation in the context of suboptimal TCR activation that results in enhanced T cell proliferation and cytokine production.

Preclinical findings highlight the potential antitumor mechanisms of action of INCAGN01876: 1) costimulatory agonistic engagement of GITR-enhancing T-effector cells, and 2) coengagement of activating FcγRs to selectively deplete immune suppressive Tregs located within the tumor (Gonzalez et al 2016). Together, this would suggest that an agonistic GITR mAb such as INCAGN01876 would have a focused effect in the human immune response leading to the proliferation and augmentation of an ineffectually active antitumor immune response.

1.3.2.2. Clinical Experience

Complete clinical data on INCMGA01876 are discussed in detail in the INCMGA01876 Investigator's Brochure (IB).

In brief, as of 14 JAN 2019, 3 Phase 1/2 clinical studies of INCAGN01876 in participants with advanced malignancies are ongoing: Study INCAGN 1876-101 is a monotherapy study (96 participants exposed); Study INCAGN 1876-201 is a study of INCAGN01876 in combination with nivolumab (anti-PD1), ipilimumab (anti-CTLA4), or nivolumab + ipilimumab (115 participants exposed); Study INCAGN 1876-202 is a study of INCAGN01876 in combination with pembrolizumab (anti-PD1) + epacadostat (IDO inhibitor) (10 participants exposed).

As of the data cutoff date, a total of 221 participants with advanced or metastatic malignancies have been enrolled in the ongoing clinical studies and have received at least 1 dose of INCAGN01876.

INCAGN01876 Monotherapy

In Study INCAGN 1876-101, 96 participants have received INCAGN01876 IV doses of 0.03, 0.1, 0.3, 1.0, 3.0, 5.0, 10.0, or 20.0 mg/kg Q2W, 300 mg Q2W (RP2D), or 400 mg Q4W. The most frequently occurring TEAE was fatigue (37.7% in Part 1 [dose escalation and safety expansion], 47.4% in Part 2 [dose expansion]). Part 2 (dose expansion) included 19 participants treated at the RP2D of 300 mg Q2W IV. Preliminary, unaudited data as of the clinical data cutoff date show that INCAGN01876 is generally well-tolerated. Two DLTs were reported in Part 1: Grade 4 hypoxia at a dose of 3.0 mg/kg Q2W and Grade 3 pleurisy at a dose of 5.0 mg/kg Q2W.

Overall, 100% of participants in Part 1 and 89.5% of participants in Part 2 had TEAEs, with the most frequent being fatigue. **Table 4** and **Table 5** summarize the most frequently occurring TEAEs (> 10%) in Parts 1 and 2, respectively:

Table 4. Study INCAGN 1876-101 (Part 1): Summary of treatment-emergent adverse events occurring in >10% of participants

MedDRA Preferred Term, n (%)	INCAGN01876 Dose and Dose Regimen									Total (N = 77)
	0.03 mg/kg Q2W (N = 4)	0.1 mg/kg Q2W (N = 4)	0.3 mg/kg Q2W (N = 4)	1.0 mg/kg Q2W (N = 3)	3.0 mg/kg Q2W (N = 15)	5.0 mg/kg Q2W (N = 18)	10.0 mg/kg Q2W (N = 16)	20.0 mg/kg Q2W (N = 4)	400 mg Q4W (N = 9)	
Fatigue	0	0	1 (25.0)	1 (33.3)	7 (46.7)	6 (33.3)	7 (43.8)	2 (50.0)	5 (55.6)	29 (37.7)
Abdominal pain	0	1 (25.0)	1 (25.0)	2 (66.7)	3 (20.0)	4 (22.2)	8 (50.0)	3 (75.0)	2 (22.2)	24 (31.2)
Dyspnoea	0	0	0	2 (66.7)	7 (46.7)	4 (22.2)	3 (18.8)	1 (25.0)	2 (22.2)	19 (24.7)
Nausea	0	0	1 (25.0)	1 (33.3)	3 (20.0)	5 (27.8)	6 (37.5)	1 (25.0)	1 (11.1)	18 (23.4)
Pyrexia	2 (50.0)	0	2 (50.0)	1 (33.3)	2 (13.3)	3 (16.7)	5 (31.3)	0	2 (22.2)	17 (22.1)
Vomiting	1 (25.0)	1 (25.0)	1 (25.0)	0	3 (20.0)	3 (16.7)	5 (31.3)	2 (50.0)	1 (11.1)	17 (22.1)
Decreased appetite	0	1 (25.0)	0	1 (33.3)	4 (26.7)	2 (11.1)	3 (18.8)	2 (50.0)	2 (22.2)	15 (19.5)
Pruritus	0	0	0	1 (33.3)	5 (33.3)	5 (27.8)	3 (18.8)	0	1 (11.1)	15 (19.5)
Diarrhoea	1 (25.0)	0	1 (25.0)	0	4 (26.7)	4 (22.2)	2 (12.5)	1 (25.0)	0	13 (16.9)
Anaemia	1 (25.0)	0	1 (25.0)	0	2 (13.3)	4 (22.2)	3 (18.8)	0	1 (11.1)	12 (15.6)
Headache	0	1 (25.0)	2 (50.0)	1 (33.3)	2 (13.3)	4 (22.2)	0	0	0	10 (13.0)
Oedema peripheral	0	0	0	1 (33.3)	3 (20.0)	5 (27.8)	0	1 (25.0)	0	10 (13.0)
Constipation	0	0	0	0	1 (6.7)	5 (27.8)	1 (6.3)	2 (50.0)	0	9 (11.7)
Cough	0	0	2 (50.0)	0	5 (33.3)	1 (5.6)	1 (6.3)	0	0	9 (11.7)
Alanine aminotransferase increased	0	0	0	0	3 (20.0)	2 (11.1)	2 (12.5)	1 (25.0)	0	8 (10.4)
Aspartate aminotransferase increased	1 (25.0)	0	0	0	3 (20.0)	1 (5.6)	2 (12.5)	1 (25.0)	0	8 (10.4)
Back pain	1 (25.0)	0	2 (50.0)	2 (66.7)	1 (6.7)	0	2 (12.5)	0	0	8 (10.4)
Blood alkaline phosphatase increased	1 (25.0)	0	0	0	1 (6.7)	2 (11.1)	3 (18.8)	1 (25.0)	0	8 (10.4)

Table 5. Study INCAGN 1876-101 (Part 2): Summary of treatment-emergent adverse events occurring in >10% of participants

MedDRA Preferred Term, n (%)	INCAGN01876 300 mg Q2W (N = 19)
Fatigue	9 (47.4)
Cough	5 (26.3)
Oedema peripheral	5 (26.3)
Anaemia	4 (21.1)
Nausea	4 (21.1)
Decreased appetite	3 (15.8)
Dehydration	3 (15.8)
Dyspnoea	3 (15.8)
Hypokalaemia	3 (15.8)
Influenza like illness	3 (15.8)
Pyrexia	3 (15.8)
Blood alkaline phosphatase increased	2 (10.5)
Chills	2 (10.5)
Constipation	2 (10.5)
Diarrhoea	2 (10.5)
Dizziness	2 (10.5)
Gastrooesophageal reflux disease	2 (10.5)
Hyponatraemia	2 (10.5)
Hypotension	2 (10.5)
Muscular weakness	2 (10.5)
Pain in extremity	2 (10.5)
Paraesthesia	2 (10.5)
Pruritus	2 (10.5)
Upper respiratory tract infection	2 (10.5)
Urinary tract infection	2 (10.5)
Vomiting	2 (10.5)

INCAGN01876 Combination Therapy with immune checkpoint inhibitors

In Study INCAGN 1876-201, 115 participants have received INCAGN01876 IV doses of 1.0, 3.0, 5.0, or 10.0 mg/kg Q2W or 300 mg Q2W (RP2D) in combination with nivolumab and/or ipilimumab. 56 participants have received concurrent dosing of INCAGN01876 at the RP2D of 300 mg Q2W IV + nivolumab 240 mg Q2W IV (the FDA approved dose of nivolumab). Four participants at this dose level had DLTs: Grade 3 rash in 1 participant; Grade 3 hepatic enzyme increased in 1 participant; Grade 2 diarrhea and Grade 2 hyperthyroidism in 1 participant; and Grade 3 chest pain in 1 participant. Overall, 85 of the 86 participants receiving INCAGN01876 + nivolumab had TEAEs. The TEAEs occurring in > 20% of participants were fatigue, nausea, and anemia. The only TEAE leading to discontinuation of INCAGN01876 that occurred in more than 1 participant was vomiting in 2 participants (2.3%), both of whom received INCAGN01876 300 mg Q2W IV. **Table 6** summarizes TEAEs occurring in > 5% of participants.

Table 6. Study INCAGN 1876-201: Summary of treatment-emergent adverse events occurring in >5% of participants receiving INCAGN01876 in combination with nivolumab

MedDRA Preferred Term, n (%)	INCAGN01876 + Nivolumab (N = 86)
Fatigue	24 (27.9)
Nausea	23 (26.7)
Anaemia	19 (22.1)
Decreased appetite	17 (19.8)
Diarrhoea	17 (19.8)
Dyspnoea	15 (17.4)
Pruritus	15 (17.4)
Abdominal pain	14 (16.3)
Vomiting	14 (16.3)
Oedema peripheral	13 (15.1)
Constipation	11 (12.8)
Rash	10 (11.6)
Arthralgia	9 (10.5)
Ascites	8 (9.3)
Cough	8 (9.3)
Headache	8 (9.3)
Pyrexia	8 (9.3)
Weight decreased	8 (9.3)
Asthenia	7 (8.1)
Back pain	7 (8.1)
Dysphagia	7 (8.1)
Urinary tract infection	7 (8.1)
Dizziness	6 (7.0)
Musculoskeletal pain	6 (7.0)
Hypercalcaemia	5 (5.8)
Hypokalaemia	5 (5.8)
Hypotension	5 (5.8)
Insomnia	5 (5.8)
Pneumonia	5 (5.8)
Pruritus generalised	5 (5.8)
Tachycardia	5 (5.8)

1.3.2.3. Potential Risks of INCAGN01876

Preclinical assessments used to evaluate theoretical safety concerns with INCAGN01876 eliciting adverse proinflammatory infusion reactions did not induce cytokines that in vivo would be predictive of cytokine release syndrome in participants, so the risk of significant infusion reactions is considered to be low. For participants who have an infusion reaction associated with administration of INCAGN01876, signs and symptoms would usually develop during or shortly

after drug infusion and generally resolve completely within 24 hours of completion of infusion. Specific infusion reaction treatment guidelines are provided in ***Section 5.8.2.***

INCAGN01876 is an immune modulator, and although no toxicities were identified in preclinical models, it is possible that immune related adverse events (irAEs; both nonserious and serious), similar to those described with approved immunotherapies, may occur. Adverse events of a potential immunologic etiology or irAEs may be defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on the nature of INCAGN01876, its mechanism of action, and based on reported experience with other immunotherapies. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Suspected irAEs should be discussed with the medical monitor when possible. Guidance for management of specific irAEs is provided in ***Section 5.8.1***.

Complete, detailed nonclinical and clinical data for INCAGN01876 is available in the Investigator's Brochure.

1.4 Study Rationale

This protocol uses the combination of the GITR agonist monoclonal antibody INCAGN01876, the anti-PD1 monoclonal antibody INCMGA00012, and stereotactic radiosurgery (SRS) in recurrent GBM. We hypothesize that this combination will lead to in immunostimulatory tumor microenvironment, increased anti-tumor CD8 T cell infiltration, and tumor cell death.

Among the array of cancer immunotherapeutics developed over the past decade, PD-1 monoclonal antibody blockade has yielded promising results in patients with multiple types of metastatic cancers (Chen, Nature 2017). PD-1 inhibition is thought to disrupt the engagement of PD-1 with its inhibitory ligands, spurring cytotoxic T cell-mediated tumor elimination (Topalian, Cancer Cell 2015). Survival benefits and regulatory approvals have been achieved in metastatic non-small cell lung cancer, metastatic melanoma, and other aggressive malignancies, including in patients with brain metastases (Gandhi, N Engl J Med 2018; Tawbi, N Engl J Med 2018). One of the main challenges has been to extend the benefit of PD-1 inhibitors to other cancers such as glioblastoma, which has not been responsive to single agent PD-1 inhibition in the trials conducted thus far (Reardon, Neuro Oncol 2017).

One proposed means of bolstering the response to PD-1 inhibition has been to agonize GITR (TNFRSF18), an immune costimulatory receptor. GITR activation leads to reduction in intratumoral regulatory T cells (Tregs) and enhances proliferation and activation of effector T cells (Mahne, Cancer Res 2017). GITR is upregulated in the GBM tumor microenvironment, expressed by virtually all brain-resident Tregs (Wainwright, Neuro Oncol 2011). In addition, we have shown through RNA-seq of bulk human GBM tumor samples that GITR expression is positively correlated with effector T cell cytolytic activity (as measured by a gene expression signature consisting of perforin and granzyme expression) (Bagley, J Neurooncol 2018) (**Figure 1**). INCAGN01876 is a GITR agonist antibody that promotes GITR signaling in recently activated T cells, resulting in increased T cell priming, enhanced tumor-specific T cell function, and selective depletion of intratumoral Tregs (Gonzalez et al, Cancer Res 2017).

Figure 1 In human GBM samples from The Cancer Genome Atlas, T cell cytolytic activity (gene expression signature comprised of *GZMA* and *PRF1* expression) is closely correlated with GITR mRNA expression, suggesting that GITR agonism would further increase the effector function of intratumoral CD8+ T cells

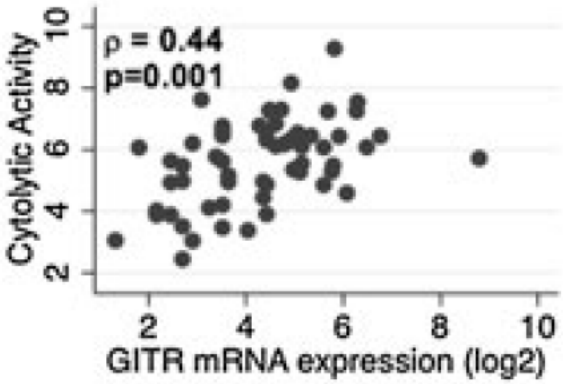
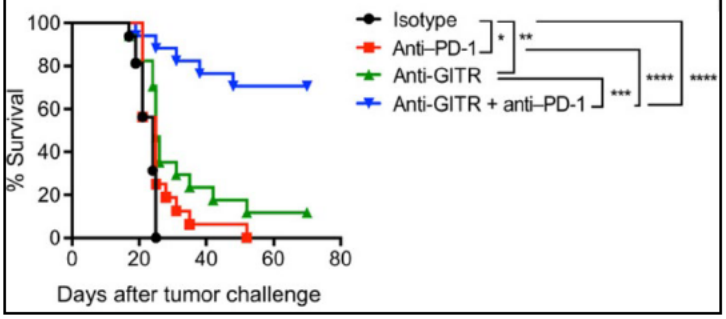


Figure 2 Survival curves of MC38 tumor-bearing mice treated with anti-GITR and/or anti-PD1 mAb



Recent preclinical data suggests that the combination of GITR agonism with PD-1 inhibition can rescue CD8+ T cell dysfunction and maintain a memory phenotype, leading to robust survival in mice bearing tumors unresponsive to single agent PD-1 blockade (**Figure 2**; Wang, Sci Immunol 2018).

In order to consider the combination of anti-PD1 and anti-GITR therapy as a rational treatment for GBM (a tumor with low mutational burden and a paucity of baseline intratumoral effector T cells), a T cell priming strategy must be used simultaneously to elicit antigen release and presentation (Garzon-Muvdi, Oncotarget 2018). Preclinical research from our institution and others demonstrated the immunostimulatory nature of hypofractionated radiation (i.e., SRS), functionating as an *in situ* vaccine and capable of converting "cold" tumors to "hot" (Shabason, J Semin Radiat Oncol 2017). The immunostimulatory mechanisms of radiation include, but are not limited to: (1) upregulation of MHC1 expression and release of tumor-associated antigens, (2) release of damage-associated molecular patterns (i.e., immunogenic cell death), (3) increased vascular permeability and extravasation of immune cells. In addition, there is preclinical data to support the specific combination of SRS and anti-GITR agonist therapy in GBM, as a recent study showed that systemic GITR agonist antibody therapy in combination with stereotactic radiosurgery (SRS, 10 Gy x 1 fraction) significantly improved survival over either treatment alone in an orthotopic GL261 glioblastoma mouse model (Patel, J Immunother Cancer 2016). This occurred in a T-lymphocyte dependent manner, with a cure rate of 24% (**Figure 3**). Finally,

in a separate, PD-1 resistant murine tumor model, treatment with anti-GITR, anti-PD1, and XRT led to significantly improved survival and abscopal responses, with half of the mice becoming tumor free (**Figure 4**; Schoenhals, Front Immunol 2018). These mice showed durable response and increased CD4+ and CD8+ effector memory on tumor rechallenge. Regulatory T cells (Tregs) expressed the highest level of GITR at the tumor site, and anti-GITR therapy drastically diminished Tregs at the tumor site.

Figure 3 Survival curves of GL261 tumor-bearing mice treated with anti-GITR

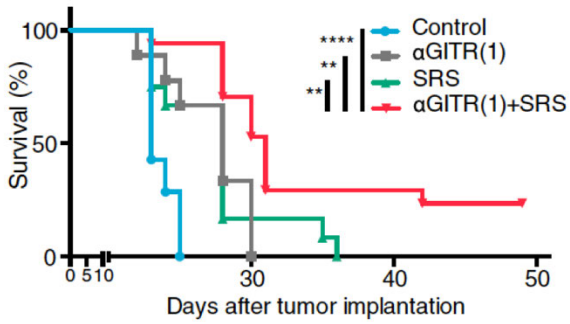
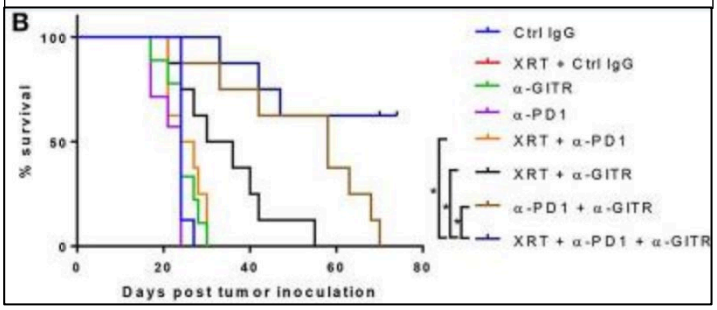


Figure 4 Anti-GITR combination therapy with anti-PD1 and XRT in 344SQ resistant tumors increases overall survival and promotes abscopal effects



Taken together, the above studies support a trial of anti-GITR agonism and PD-1 inhibition in combination with SRS for recurrent GBM.

1.5 Dose and schedule rationale

1.5.1. Investigational drugs

The dose and schedule of INCMGA00012 and INCAGN01876 used in this protocol are the recommended phase 2 doses (RP2Ds) derived from phase I studies of these compounds conducted by Incyte. As outlined in the above sections, there is sufficient experience and safety data for the combination of INCAGN01876 administered at the RP2D of 300mg IV every 2 weeks in combination with nivolumab, an FDA-approved PD-1 inhibitor, at its FDA-approved dose and schedule. The RP2D of the PD-1 inhibitor used in this protocol, INCMGA00012, is 500mg IV every 4 weeks. Therefore, the dose and schedule of investigational agents for this study is: INCAGN01876 300mg IV ever 2 weeks, and INCMGA00012 500mg IV every 4 weeks.

1.5.2. Stereotactic Radiosurgery

Subjects in Cohort A and in sub-arm #1 of Cohort B will receive hypofractionated radiation (stereotactic radiosurgery; SRS) to a dose of 8 Gy in 3 fractions. The dose of 8 Gy in 3 fractions was chosen based on preclinical evidence suggesting that it may maximally invoke an anti-tumor immune response (Vanpouille-Box, Nature Communications, 2017), compared to a variety of other fractionation schedules. For subjects treated in the nonsurgical cohort (Cohort A), a single dose of each systemic therapy (INCMGA00012 and INCAGN01876) is administered 3-7 days prior to SRS to prime the tumor immune microenvironment for optimal immune response to the SRS. Following SRS, the systemic agents are resumed according to their dosing schedule (i.e.,

INCMGA00012 is resumed 4 weeks from the date of the initial pre-SRS dose, and INCAGN01876 is resumed 2 weeks from the date of the initial pre-SRS dose). For the surgical arm (Cohort B; Surgical Sub-Arm #1 only), preclinical data suggests that in order to develop a maximal anti-tumor immune response the tumor needs to remain in situ for at least 7 days post radiation prior to surgical removal (De La Maza et al, Clinical Cancer Research, 2017). Thus, surgical resection (Cohort B; Surgical Sub-Arm #1 only) will take place 7-14 days following completion of radiation.

Overall, hypofractionated radiation has been shown to be safe and well-tolerated in recurrent GBM. For re-irradiation in general in recurrent GBM, the rate of grade 3 or higher AEs is less than 10% (Kazmi et al, *J Neurooncol* 2019). For SRS specifically in rGBM, prior studies have suggested a rate of grade 3 or higher AEs of ~3% (Holt et al, *J Cancer Res Ther* 2016; Clarke et al, *Int J Radiat Oncol Biol Phys* 2017). The rate of symptomatic radionecrosis from SRS in rGBM is estimated to be about 15-20% (Imber BS, et al, *Neurosurg* 2017).

The safety of brain-directed hypofractionated radiation with concurrent immune checkpoint blockade, as well as in the preoperative setting has been previously evaluated and is overall safe. There are numerous reports that have evaluated the safety of SRS with immune checkpoint blockade (primarily anti-PD-1 and anti-CTLA-4) in the treatment of brain metastases. Although the risk of radionecrosis may be higher in this setting and has been reported as high as 5-20% (Martin AM, JAMA Oncol 2018) (Lehrer EJ, Radiotherapy Oncology 2019), the therapy is overall safe and used routinely in the treatment of patients with brain metastases who are also on anti-PD-1 and anti-CTLA-4 agents. In addition, investigators have evaluated the use of neoadjuvant SRS for brain metastases and have not found any increase in morbidity, including wound healing complications (Asher AL, International Journal of Radiation Oncology Biology and Physics 2014; Patel Kr, Neurosurgery 2016).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective:

- To determine the efficacy of the combination of INCMGA00012, INCAGN01876, and SRS in recurrent GBM, as measured by the overall objective radiographic response rate (ORR)

2.1.2. Secondary Objectives:

- To evaluate the safety and tolerability of the combination of INCMGA00012, INCAGN01876, and SRS in recurrent GBM
- To determine the progression-free survival (PFS) and overall survival (OS) of patients with recurrent GBM treated with the combination of INCMGA00012, INCAGN01876, and SRS

2.1.3. Exploratory Objectives:

- To evaluate the biologic effect of the combination of INCMGA00012 and INCAGN01876, with or without SRS, on the GBM tumor immune microenvironment
- To evaluate the pharmacodynamic impact of the combination of INCMGA00012, INCAGN01876, and SRS on peripheral blood immune cell populations

- To evaluate the pharmacokinetics (PK) of INCAGN01876 in patients with glioblastoma
- To determine whether anti-drug antibodies (ADA) form against INCAGN01876 in patients with glioblastoma
- To detect tumor and/or blood biomarkers associated with the outcomes of OS, PFS, and/or ORR in patients with recurrent GBM treated with the combination of INCMGA00012, INCAGN01876, and SRS

2.2. Study Endpoints

2.2.1. Primary Endpoint:

- Objective radiographic response (ORR), as measured by modified Response Assessment in Neuro-Oncology (RANO) criteria

2.2.2. Secondary Endpoints:

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs, and through clinical laboratory evaluations.
- OS, defined as the time from date of enrollment until death from any cause
- PFS, defined as the time from date of enrollment until the earliest date of disease progression (as determined by modified RANO criteria) or death due to any cause

2.2.3 Exploratory Endpoints:

- Comparison of the following immunocorrelative assays in subjects treated with INCMGA00012 + INCAGN01876, with or without SRS:
  - Multiplex immunohistochemistry on tumor tissue for CD4/8 T cell infiltration, Foxp3+ Treg infiltration, and PD-1/PD-L1 expression
  - Tumor cell and immune cell GITR expression by a validated immunohistochemistry stain
  - Flow cytometry/mass cytometry in tumor tissue and peripheral blood for T cell and monocyte phenotyping
  - RNA-Seq on tumor tissue for PD-1/PD-L1 and GITR expression, T cell- and interferon-γ-related gene expression, and cell-cycle-related gene expression
  - T cell receptor sequencing in tumor tissue and peripheral blood for assessment of TCR clonal diversity
- Association between the above tumor tissue and peripheral blood-based markers of immune activation, tumor genetic mutations, and clinical outcomes of OS, PFS, and ORR
- PK parameters for INCAGN01876 in patients with glioblastoma
- Detection of anti-drug antibodies (ADA) against INCAGN01876

3 INVESTIGATIONAL PLAN

3.1. General Design

This is a single-center, phase II, open label study evaluating the efficacy and safety of the combination of INCMGA00012, INCAGN01876 and SRS for patients with recurrent GBM.

The overall study population will be broken down into two cohorts: Cohort A (N=16) and Cohort B (N=16). Subjects for whom surgical resection is not clinically indicated at the time of study

screening will be enrolled into Cohort A (non-surgical cohort). Subjects for whom surgical resection is clinically indicated at the time of study screening will be enrolled into Cohort B (surgical cohort).

The first 6 subjects enrolled onto the study must be enrolled onto Cohort A and will be enrolled in two groups of 3 subjects (i.e., a "3+3" design) as part of a safety run-in period. After enrollment of the first 3 subjects, enrollment is put on hold until all of the first 3 subjects have completed the safety monitoring period (completion of SRS and one cycle of INCMGA00012 and INCAGN01876). If only 0-1 of the first 3 subjects experiences a criterion for study drug discontinuation, as defined in **Section 5.7**, ***Study Drug Discontinuation Criteria,*** then the next 3 subjects will be enrolled. If 2 of the first 3 subjects experience a criterion for study drug discontinuation, the study will be paused for reconsideration of the dosing and schedule of investigational agents.

Of the first 6 subjects enrolled during the safety run-in, if 3 or greater subjects experience a criterion for study drug discontinuation, then the study will be paused for reconsideration of the dosing and schedule of investigational agents. If only 0-2 of the first 6 subjects enrolled during the safety run-in experience a criterion for study drug discontinuation, then enrollment to both cohorts A and B will commence uninterrupted.

If at any point during the safety run-in a stopping rule is met and the dose/schedule of investigational agents is changed, the safety run-in will start over again with another 6 patients. If Cohort A has reached enrollment of 12 subjects and the criteria to move beyond the safety run-in phase has still not yet been met (i.e., at least 6 patients have been treated at the same dose/schedule and only 2 or fewer have experienced a criterion for study drug discontinuation), the trial (including Cohort B) will be terminated due to intolerability of the study regimen.

If at any point during the safety run-in a stopping rule is met and the dose/schedule of investigational agents is changed, and the safety-run in phase is then successfully completed at the new dose/schedule, 16 additional subjects will be enrolled in Cohort A at the new dose/schedule to achieve the desire sample size of 16 subjects that are evaluable for the study's primary endpoint. Thus, the total sample size for Cohort A could potentially be more than 16 subjects (e.g., 6 subjects are enrolled in the initial safety run-in and 3 of them experience a toxicity requiring study drug discontinuation; an additional 6 subjects are then enrolled at the new dose/schedule that has been decided upon, and this time the safety run-is completed successfully with only 1 subject discontinuing study drug due to toxicity; we would then enroll 10 additional subjects at the current dose/schedule of study drugs to achieve 16 evaluable subjects treated at the final dose/schedule; the total sample size for cohort A in this example would be 22 subjects).

Cohort B will not start enrollment until the safety run-in phase has been successfully completed.

Details of treatment administered in each cohort are provided below in **Section 3.1.2**, ***Study Intervention Phase.***

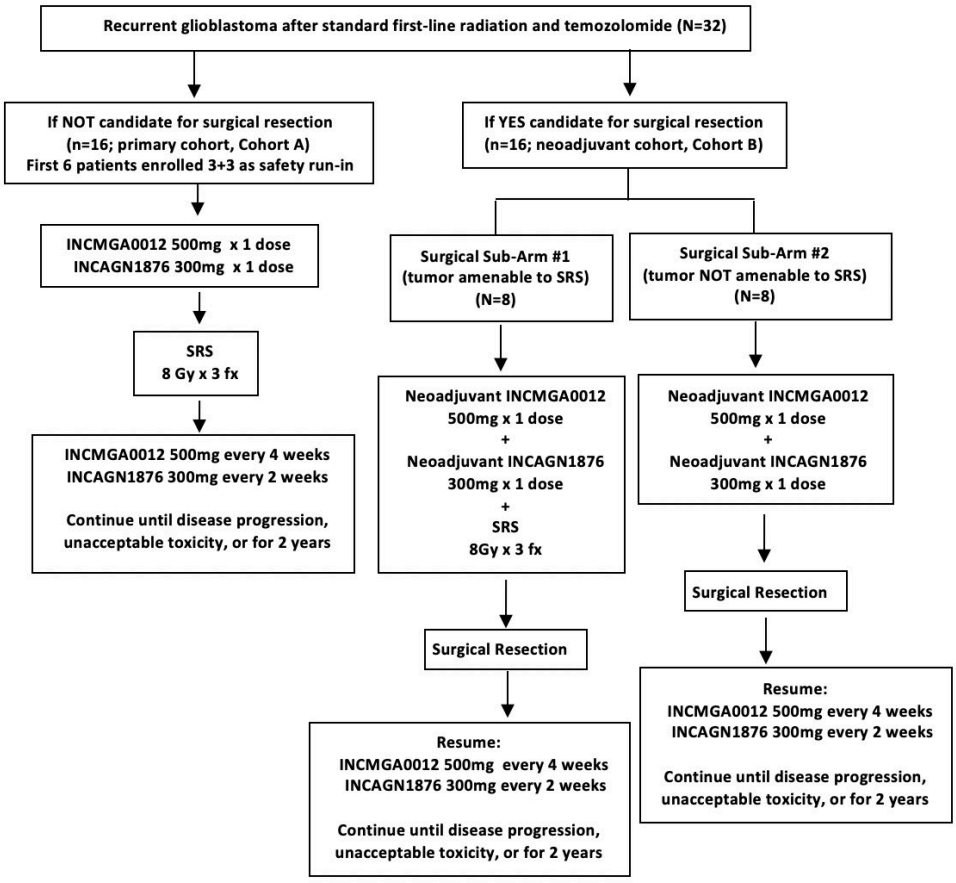
3.1.1. Screening Phase

Subjects will be recruited from the Medical Oncology, Radiation Oncology, and Neurosurgery practices at the University of Pennsylvania Health System. The treating physician will determine

if the patient is a potential research candidate. The treating physician will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating physician will contact a qualified member of the research team in the Neurosurgery Clinical Research Division at the University of Pennsylvania and request availability for enrollment. A sub-investigator will continue the formal consent process. This person will explain the requirements of the study and provide a copy of the Informed Consent Form. The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study before making her decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed after which screening procedures will be performed. Subject eligibility will be evaluated based upon the criteria outlined in the protocol. After eligibility is established, a subject study number will be issued. Eligibility is confirmed with a clinically-licensed study Investigator. All members of the research team will have successfully completed patient oriented research training.

3.1.2. Study Intervention Phase

Schema (Figure 5):



Cohort A (non-surgical; N=16):
Within 7 days of enrollment, the subject will receive a single 500mg dose of INCMGA00012 and a single 300mg dose of INCAGN01876 on the same day. Within 3 to 7 days following these

doses, the subject will receive stereotactic radiosurgery (SRS), administered over the course of 3 consecutive business days (8 Gy x 3 fractions, one fraction per day, total dose 24 Gy). Subjects may receive 3 fractions every other day (non-consecutively) for logistical reasons relating to COVID-19. Following SRS, the two study drugs will be resumed according to their respective dosing schedule (INCMGA00012 500 mg IV every 4 weeks; INCAGN01876 300mg IV every 2 weeks). For example, INCAGN01876 will be resumed 2 weeks from the date that the first pre-SRS dose was given, and INCMGA00012 will be resumed 4 weeks from the date that the first pre-SRS dose was given. Subjects will continue on combined systemic treatment (INCMGA00012 500 mg IV every 4 weeks and INCAGN01876 300mg IV every 2 weeks) until disease progression, unacceptable AEs, or for 2 years, whichever occurs first.

Cohort B (surgical; N=16):
Subjects in cohort B are enrolled onto one of two surgical sub-arms (sub-arms 1 or 2; eight subjects per sub-arm), with each sub-arm receiving a different neoadjuvant regimen prior to surgical resection as diagrammed above in the study schema. The two possible neoadjuvant regimens are INCMGA00012 + INCAGN01876, or INCMAG00012 + INCAGN01876 + SRS. Subjects with a tumor that is amenable to SRS (i.e., as determined by the Investigator) are assigned to sub-arm 1 (INCMAG00012 + INCAGN01876 + SRS) until this arm has reached its total enrollment (N=8). All other subjects enrolled in Cohort B are assigned to the other surgical sub-arm (sub-arms 2; INCMGA00012 + INCAGN01876, without SRS).

In both surgical sub-arms, within 7 days of enrollment the subject will receive a single dose of the investigational systemic agent(s) according to the sub-arm to which he/she is assigned. In sub-arm # 1 (INCMAG0012 + INCAGN01876 + SRS), within 3 to 7 days following the neoadjuvant doses of the systemic study drugs, the subject will receive SRS, administered over the course of 3 consecutive business days (8 Gy x 3 fractions, one fraction per day, total dose 24 Gy). Subjects may receive 3 fractions every other day (non-consecutively) for logistical reasons relating to COVID-19. Within 7-14 days following administration of the study drug(s) (surgical sub-arms # 2) or within 7-14 days following SRS (surgical sub-arm # 1), the subject will undergo maximal safe surgical resection of the tumor. Following surgery, the subject will then resume systemic therapy with BOTH investigational agents INCMGA00012 and INCAGN01876 (regardless of which of the two sub-arms the subject was assigned to). The systemic agents should be started as soon as the investigator feels the subject has recovered adequately from surgery, but must be restarted within 5 weeks (35 days) from the date of surgery. Subjects will continue on combined systemic treatment (INCMGA00012 500 mg IV every 4 weeks and INCAGN01876 300mg IV every 2 weeks) until disease progression, unacceptable AEs, or for 2 years, whichever occurs first.

3.1.3. Follow Up Phase

Any subject who permanently discontinues the study drugs based on any reason outlined in ***Section 5.7*** will proceed to follow-up.

3.1.3.1. Safety Follow-Up

A scheduled safety follow-up visit occurs 30 (+/- 7) days after the EOT visit (the visit that occurs when subjects are taken off study treatment (see ***Section 6*****;Table 8** ***and*** **Table 9** for full schedule of events). Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period. If the subject cannot return to the site for

the safety follow-up visit, the subject is contacted by telephone for collection of AEs and SAEs, and this should be documented in the eCRF.

Following the scheduled 30-day safety follow-up visit, subjects are contacted by telephone, e-mail or visit one additional time 12 weeks (+/- 14 days) from the EOT visit to capture additional immune related AEs (see sections 1.3.1.3 and 1.3.2.3).

3.1.3.2. Disease Status Follow-Up

Subjects who discontinue study drug treatment but who have not yet met criteria for disease progression are assessed by radiologic imaging to monitor disease status. These assessments occur every 12 weeks (± 14 days). The imaging assessments occur at the study site if the subject continues to receive care at the University of Pennsylvania; otherwise, research staff will obtain subject's outside radiology reports and outside physician notes to determine disease status. If possible, the original images from radiology scans will also be obtained for formal radiologic interpretation by University of Pennsylvania Neuroradiology.

Every effort should be made to collect information regarding disease status until:
• The start of new antineoplastic therapy.
• Disease progression.
• Death.
• Termination of the study
• 5 years after removal from protocol therapy

3.1.3.3. Survival Follow-Up

Subjects are contacted by telephone, e-mail, or visit every 12 weeks (+/-14 days) from the 12-week safety follow-up visit to capture survival status until death, withdrawal of consent, termination of the study or 5 years after removal from protocol therapy, whichever occurs first. Public records/databases are searched if contact with the subject is lost.

For participants who are thought to be lost to follow-up, at least 3 documented attempts should be made to contact the participant before the participant is deemed lost to follow-up.

3.2 Replacement of Subjects

Cohort A: Any subject who is enrolled onto Cohort A of the study but meets one of the following criteria is replaced by enrollment of a new subject onto Cohort A:

- The subject is enrolled, but does not receive BOTH systemic agents (INCMGA00012, INCAGN01876)
- The subject is enrolled, but does not receive SRS
- The subject is enrolled as part of the safety run-in cohort and, for any logistical reason unrelated to the patient's clinical condition, does not receive all scheduled components of Cycle 1 treatment (i.e., a subject is enrolled on safety run-in cohort but does not receive all of the following: 3 fractions of radiation, C1D1 dose of INCMGA00012, C1D1 dose of INCAGN01876, and C1D15 dose of INCAGN01876). Examples of such logistical reasons include: the current lot of investigational product on site (INCMGA00012 or INCAGN01876) tests out of specification, the radiation machine breaks down in the midst of the subject's radiation, a spike in COVID-19 infections results in temporary suspension of clinical research at the study site, etc).

- The subject receives study drugs (+/- SRS), but becomes pregnant (and therefore is taken off study per study drug discontinuation criteria ***Section 5.7***) before the first response evaluation (MRI) occurs
- The subject receives study drugs (+/- SRS), but consent is withdrawn by the subject before the first response evaluation (MRI) occurs
- The subject receives study drugs (+/- SRS), but is subsequently found not to have met eligibility criteria, AND the Medical Director, in collaboration with the investigator, determined that the subject should be withdrawn from the study, AND the first response evaluation (MRI) has not yet taken place
- The subject receives study drugs (+/- SRS), but is then noncompliant with study procedures in the investigator's opinion, AND the sponsor has been consulted and has determined that the subject should be withdrawn from the study, AND the first response evaluation (MRI) has not yet taken place

As long as the subject has not withdrawn his/her consent, the non-treated (replaced) subject is followed for safety follow-up per **Table 10** **(see *Section 6*)** and all safety-related data collected for the subject is included in analysis of the study's secondary safety/tolerability endpoints. However, the subject is not included in the primary endpoint efficacy analysis or in analysis of secondary efficacy endpoints (see ***Section 8, Statistical Plan***). In addition, if the replaced subject was enrolled during the safety run-in phase, that subject will not be counted for purposes of determining whether the pre-specified safety criteria (see **Section 3.1; General Design**) have been met during the safety run-in phase to allow for successful completion of the safety run-in phase.

Subject replacement occurs up to and no more than 7 times for Cohort A [i.e., up to 23 subjects can be enrolled to obtain 16 subjects who receive both of the study drugs at the same dose and schedule AND SRS and are therefore evaluable for the primary endpoint].

Cohort B: Any subject who is enrolled onto Cohort B of the study but meets one of the following criteria is replaced by enrollment of a new subject onto Cohort B:

- The subject is enrolled, but does not receive either of the systemic agents (INCMGA00012, INCAGN01876)
- The subject is enrolled, but does not receive SRS (surgical subarm #1 only)
- The subject is enrolled, but does not undergo surgery

As long as the subject has not withdrawn his/her consent, the non-treated (replaced) subject is followed for safety follow-up per **Table 10** **(see *Section 6*)** and all safety-related data collected for the subject is included in analysis of secondary study endpoints.

Subject replacement occurs up to and no more than 10 times for Cohort B [i.e., up to 26 subjects can be enrolled to obtain 16 subjects who receive neoadjuvant therapy AND undergo surgery, with 8 patients assigned to each of the 2 sub-arms]. Subjects who need to be replaced in Cohort B, will be replaced by a subject enrolled onto the same sub-arm that the replaced subject was previously on.

Replaced subjects will be followed for safety only. These subjects will not be included in efficacy endpoint analyses, and they will not have tumor tissue available for correlative endpoint analyses.

3.3. Duration of Individual Subject Study Participation

After signing the ICF, screening procedures commence. Each enrolled subject begins study treatment. Treatment continues until the subject meets any one or more of the criteria for study drug discontinuation (see ***Section 5.7; Study Drug Discontinuation Criteria***). When a subject discontinues study drug but has not withdrawn consent, the subject enters the follow-up period. Subjects are taken off study if any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent
- Death
- Sponsor decides to terminate the study

3.4. Overall Study Duration

The study begins at the time that it becomes actively open to patient enrollment (i.e., the site is activated for the trial and screening for subjects has commenced). The study ends when all subjects have discontinued the study and the last follow-up visit has been performed.

In addition, the sponsor may terminate the study if required by regulatory decision, or upon review of emerging data. If the study is terminated prematurely, the sponsor will notify the principal investigator and the FDA of the decision and reason for termination of the study.

3.5 Total Number of Subjects and Sites

This is a single center study and subjects are only recruited from the University of Pennsylvania. Recruitment for Cohort A ends when (1) the safety run-in phase has been successfully completed AND (2) 16 subjects in Cohort A have received at least one dose of each study drug at the same dose/schedule as determined by the safety run-in phase. Greater than 16 total subjects may be enrolled on Cohort A if the stopping rule for toxicity is met during the safety run-in phase (see ***Section 3.1 General Design***). The maximum possible sample size for Cohort A is 22 subjects who are evaluable for the study's primary efficacy endpoint, which would occur if enrollment of 12 subjects (which is the maximum allowed for the safety run-in phase) is necessary to successfully complete the safety run-in phase and an additional 10 subjects are enrolled at the same finalized dose/schedule of study drugs that was given to the last 6 subjects enrolled on the safety run-on phase.

Recruitment for Cohort B ends with 16 subjects have received study drug(s) AND surgery.

4. INCLUSION AND EXCLUSION CRITERIA

4.1 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Prior histopathologically proven diagnosis of World Health Organization (WHO) grade IV glioblastoma, OR histopathologically proven diagnosis of gliosarcoma, OR molecular diagnosis of glioblastoma per c-IMPACT-NOW criteria ("diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV"; this requires presence of either amplification of *EGFR,* whole chromosome 7 gain AND whole chromosome 10 loss, or *TERT*

promoter mutation). Participants are eligible if the prior diagnosis was low-grade glioma and a subsequent histological diagnosis of glioblastoma was made (e.g. secondary GBM).

2. Participants must have glial tumor that is recurrent following prior first-line radiation therapy (prior dose must have been 40-75 Gy and may have been either photon or proton radiation), and must have unequivocal evidence of tumor progression by MRI scan

3. Cohort A and Sub-Arm 1 of Cohort B only: Patient must have at least one measurable (>=1cm x 1cm) contrast-enhancing tumor focus for which stereotactic radiosurgery (SRS) is clinically indicated, as determined by the Investigator, and must be able to achieve radiation target coverage without exceeding dose constraints. The contrast-enhancing target must not be larger than 4 cm in maximal diameter. Multifocal disease is allowed as long as this criterion is met

- Sub-Arms 2 of Cohort B can have any size tumor, and the tumor does not need to be amenable to SRS

4. Cohort B (surgical) patients only: patients must be undergoing surgery that is clinically indicated as determined by their care providers

5. Tumor O-6-methylguanine-deoxyribonucleic acid (DNA) methyltransferase (MGMT) methylation status must be available from any prior GBM tumor specimen; results of routinely used methods for MGMT methylation testing (e.g. mutagenically separated polymerase chain reaction [MSPCR] or quantitative polymerase chain reaction [PCR]) are acceptable)

6. Patients may have had treatment for an unlimited number of prior relapses but must not have had prior bevacizumab or other vascular endothelial growth factor (VEGF/VEGFR) inhibitors (exception: prior bevacizumab is allowed if it was administered for the treatment of radiation necrosis rather than progressive tumor and was stopped at least 4 weeks prior to MRI showing demonstrating tumor progression). Prior gliadel wafers are only allowed if placed during the first surgery for GBM at initial diagnosis.

7. Patients must have recovered from severe toxicity of prior therapy; the following intervals from previous treatments are required to be eligible:

- 12 weeks from completion of radiation
- 6 weeks from a nitrosourea cytotoxic chemotherapy
- 3 weeks from a non-nitrosourea cytotoxic chemotherapy
- 4 weeks from any investigational (not Food and Drug Administration [FDA]-approved for glioblastoma) agents, or within a time interval less than at least 5 half-lives of the investigational agent whichever is shorter
- 3 weeks from any major surgery, including brain surgery for recurrent tumor resection

8. If patient is on systemic corticosteroids to treat brain edema and/or brain edema-related symptoms, the dose must be 2mg of dexamethasone (or equivalent) daily or less for a minimum of 5 days prior to first dose of study drug.

9. Patients must be able to swallow oral medications

10. Age 18 or older

11. Karnofsky performance status >= 60

12. Life expectancy >3 months

13. Absolute lymphocyte count >= 500/uL

14. Adequate hepatic function within 7 days prior to start of study treatment, defined as follows
    - Total bilirubin (except patients with Gilbert's Syndrome, who are eligible for the study but exempt from the total bilirubin eligibility criterion) ≤ 2.0 mg/dl
    - ALT and AST ≤ 2.5x upper limit of normal (ULN)

15. Adequate renal function within 7 days prior to start of study treatment, defined as follows:
    - Serum creatinine <=1.5 x institutional ULN OR calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or CrCl) >=50 mL/min for subjects with creatinine levels >1.5x institutional ULN

16. Reproductive Status

    a) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to the start of study drug.
    b) Women must agree to not breastfeed during the study or for 180 days after the last dose of study treatment
    c) WOCBP must agree to use an adequate method to avoid pregnancy (as defined below) from the time of study screening through 180 days from last dose of study drug
    d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (as defined below) starting with the first dose of study drug through 180 days after the last dose of study
    e) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, these WOCBP must still undergo pregnancy testing as described in this section.

    At a minimum, participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception (as defined below) throughout their participation beginning with the time of consent, during the study treatment, and for 180 days after last dose of study treatment(s).

    HIGHLY EFFECTIVE METHODS OF CONTRACEPTION:

    - Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
    - Nonhormonal IUDs
    - Bilateral Tubal ligation
    - Vasectomy
    - Sexual Abstinence

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

17. Participant must, in the opinion of the Investigator, be able to comply with study procedures

18. Patients must be able to understand the study procedures and agree to participate in the study by providing written informed consent (or have legally authorized representative sign on patient's behalf if patient physically unable to sign consent due to neurologic deficit)

4.2 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Contrast-enhancing tumor in brainstem or spinal cord (subjects do not need spinal MRI for screening, but known spinal cord tumor is exclusionary)

2. Diffuse leptomeningeal disease

3. Prior bevacizumab or other vascular endothelial growth factor (VEGF/VEGFR) inhibitors (exception: prior bevacizumab is allowed if it was administered for the treatment of radiation necrosis rather than progressive tumor and was stopped at least 4 weeks prior to MRI showing demonstrating tumor progression).

4. Patients with clinically significant mass effect or midline shift (e.g., 1-2 cm of midline shift)

5. Use of any immunosuppressive medication other than steroids, including but not limited to antimetabolites, calcineurin inhibitors, and/or anti-TNF agents within six months of start of study drug

6. Prior diagnosis of immunodeficiency

7. Prior solid organ or bone marrow transplantation

8. Autoimmune or connective tissue disease that is EITHER (a) actively flaring OR (b) has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
EXCEPTIONS: Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, adrenal insufficiency requiring only replacement dose corticosteroids, skin disorders (such as vitiligo, psoriasis, pemphigus, or alopecia) controlled with topical medications, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Patients with asthma that is not actively flaring are allowed. Patients with history of Grave's disease that is previously treated with thyroidectomy or radioiodine are allowed. Patients with celiac disease whose symptoms are controlled with a gluten-free diet are allowed. Patients with rheumatoid arthritis and other arthropathies such as ankylosing

spondylitis, Sjogren's syndrome, Raynaud syndrome, and patients with positive serologies, such as antinuclear antibodies (ANA) or anti-thyroid antibodies, should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

9. History of non-infectious pneumonitis that required steroid treatment

10. Known active hepatitis B virus (HBsAg reactive) or active hepatitis C virus (HCV RNA detectable by PCR)

11. Human immunodeficiency virus (HIV)-positive patients on antiretroviral therapy

12. Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen are excluded from this trial. Otherwise, patients with prior or concurrent malignancy are eligible.

13. Any serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection that, in the opinion of the investigator, would put the subject at undue risk from the study treatment.

14. Patients with uncontrolled or significant cardiovascular disease including, but not limited to, any of the following are ineligible:

- Myocardial infarction or uncontrolled angina within 90 days prior to consent
- History of clinically significant arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or torsades pointes)
- History of cardiomyopathy, pericarditis, significant pericardial effusion, myocarditis, or New York Heart Association (NYHA) functional class III-IV congestive heart failure

15. Known hypersensitivity to another monoclonal antibody that cannot be controlled with standard measures (e.g., antihistamines and corticosteroids)

16. Prisoners or subjects who are involuntarily incarcerated

17. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

18. Pregnant women are excluded

19. Received a live vaccine within 30 days prior to first dose of study drug. Examples include but are not limited to measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Celmette-Guerin (BCG), and typhoid. Intranasal influenza vaccines are not allowed.

20. Participant must not be simultaneously enrolled in any interventional clinical trial

5 STUDY INTERVENTION

5.1 Description of Study Drugs

5.1.1. INCMGA00012

INCMGA00012 (also known as MGA012) is a humanized, hinge-stabilized, IgG4κ mAb that recognizes human PD-1. INCMGA00012 contains a human IgG4 Fc domain to limit effector function while retaining neonatal FcRn binding to extend circulating t½. INCMGA00012 is designed to target PD-1–expressing cells, including T cells, and sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2. INCMGA00012 is derived from a murine mAb clone that was generated using standard hybridoma technology from mice immunized with a His-tagged, human PD-1 extracellular domain molecule. INCMGA00012 drug product is formulated at a concentration of 25 mg/mL in sodium acetate trihydrate, acetic acid, sucrose, and polysorbate 80 at pH 5.1.

Complete physical, chemical, and pharmaceutical properties and formulations for INCMGA00012 are available in the Investigator's Brochure.

5.1.2. INCAGN01876

INCAGN01876 (previously designated as AGEN1876) is a recombinant, humanized immunoglobulin G1 (IgG1) kappa (κ) mAb that binds to the extracellular domain of the human tumor necrosis factor receptor superfamily member 18 (TNFRSF18), also known as glucocorticoid-induced TNFR-related protein (GITR). INCAGN01876 drug product is formulated at a concentration of 10 mg/mL in histidine, sucrose, and polysorbate 80 at pH 6.0.

Complete physical, chemical, and pharmaceutical properties and formulations for INCAGN01876 are available in the Investigator's Brochure.

5.2 Receipt of Investigational Agents

The investigational agents will be shipped from Incyte Corporation to:
Penn Investigational Drug Service Central
3400 Civic Center Blvd, 10th Floor (10-020)
Philadelphia, PA 19104
215-662-7911 (phone)
215-615-1308 (fax)

Receipt and product verification will be overseen by the Penn Investigational Drug Service (IDS). Shipments of study drugs will be arranged by Penn IDS on an as-needed basis. Certificates of delivery should be signed by Penn IDS.

5.3 Storage of study products

5.3.1. INCMGA00012

INCMGA00012 drug product should be stored under refrigeration at 2°C to 8°C.

5.3.2. INCMGA01876

INCAGN01876 drug product should be stored under refrigeration at 2°C to 8°C.

5.4 Study drug Accountability

Dispensation of study drugs from IDS should be recorded in the appropriate sections of the eCRF. IDS will only dispense study drugs to study subjects for whom the PI or delegated team member has signed an order. The study drugs provided for this study will be used only as directed in the study protocol.

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study. The study treatment accountability log includes information including a patient identifier, amount and date dispensed, and amount and date returned to the pharmacy. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed.

5.5 Study drug Administration

5.5.1 Administration of INCMGA00012

INCMGA00012 is administered as an IV infusion over 60 minutes for the first infusion. If well tolerated, it may be administered over 30 minutes for subsequent treatments. On days when both study drugs are due to be administered, INCMGA00012 study product is administered first prior to administration of INCAGN01876. The only dose of INCMGA00012 used for this study is 500mg. There is no dose escalation or reduction. A 1-hour observation period is recommended after the INCMGA00012 infusion prior to beginning the INCAGN01876 infusion.

Infusion-related reactions (including anaphylaxis or cytokine release syndrome) may be associated with the administration of therapeutic antibodies. Of 199 prior study participants who have received infusions of INCMGA00012 in Study INCMGA 0012-101, 5 participants have experienced 1 infusion-related reaction each (see IB). This does not exceed the expected incidence of IRRs for the PD-1 inhibitor class. Infusion-related reactions were observed in Study INCMGA 0012-101 regardless of whether prophylaxis was administered; therefore, routine prophylaxis is not recommended. Secondary prophylaxis is recommended for participants who have experienced IRRs to INCMGA00012. Participants who experience life-threatening infusion reactions should not be retreated with INCMGA00012. Infusions reactions should be managed according to the guidelines in ***Section 5.8.2*.**

5.5.2 Administration of INCAGN01876

INCAGN01876 is administered as an IV infusion over 60 minutes for the first infusion. If well tolerated, it may be administered over 30 minutes for subsequent treatments. On days when both study drugs are due to be administered, INCMGA00012 study product is administered first prior to administration of INCAGN01876. The only dose of INCAGN01876 used for this study is 300mg. There is no dose escalation or reduction. A 1-hour observation period is recommended after the INCMGA00012 infusion prior to beginning the INCAGN01876 infusion.

Preclinical assessments used to evaluate theoretical safety concerns with INCAGN01876 eliciting adverse proinflammatory infusion reactions did not induce cytokines that in vivo would be predictive of CRS in participants, so the risk of significant infusion reactions is considered to be low. For participants who have an infusion reaction associated with administration of INCAGN01876, signs and symptoms would usually develop during or shortly after drug infusion

and generally resolve completely within 24 hours of completion of infusion. Infusions reactions should be managed according to the guidelines in ***Section 5.8.2***.

5.6 Concomitant Medications:

1) Following start of study drug, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the subject records and on the appropriate case report form. This includes corticosteroids of any dosage for the management of brain edema related to the tumor and/or study drugs. The administration of any other anticancer agents including chemotherapy and biologic agents (such as bevacizumab) is NOT permitted. Similarly, the use of other concurrent investigational drugs is not allowed.

2) List of medications that are prohibited during this study:

- Any anticancer medications, including chemotherapy or biologic therapy other than the study medications
- Any immunological-based treatment for any reason, with the exception of corticosteroids
- Any investigational agents other than INCAGN01876 and INCMGA00012
- Radiation therapy other than the SRS (8Gy x 3 fractions) administered as part of this protocol
    - Live vaccines. Examples include but are not limited to measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Celmette-Guerin (BCG), and typhoid. Intranasal influenza vaccines are not allowed.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

5.7 Study Drug Discontinuation Criteria

Subjects **must** be permanently discontinued from BOTH study drugs (INCMGA00012 and INCAGN01876) if any one or more of the following occurs:

- Grade 2 or higher toxicity [per NCI CTCAE v 5.0] that is at least possibly related to one of the study drugs AND does not improve with optimal medical management to grade 1 or less within 12 weeks from last dose of study drugs or results in subject being unable to taper off corticosteroids (or, if on corticosteroids prior to the toxicity, unable to taper down to subject's baseline/pre-toxicity dose) within 12 weeks from last dose of study drugs, with the following exceptions:
    - Grade 2 Nervous System toxicity (e.g., leg weakness, aphasia, etc) that is *due to* to intratumoral/peritumoral enlargement (contrast-enhancing or T2/FLAIR) or intratumoral/peritumoral cerebral edema
    - Grade 3-4 Nervous System toxicity (e.g., leg weakness, aphasia, etc) that is *due to* to intratumoral/peritumoral enlargement (contrast-enhancing or T2/FLAIR) or intratumoral/peritumoral cerebral edema AND improves to grade 2 or less within 7 days of optimal medical management
    - Grade 3 Cerebral Edema
    - Grade 4 Cerebral edema that improves to grade 3 within 7 days of optimal medical management

  - Any grade endocrinopathy that is controlled by hormone replacement
- Grade 4 irAE, as defined in **Section 9.1.2**, ***Immune-Related Adverse Events,*** with the following exception:
  - Grade 4 endocrinopathy that is controlled by hormone replacement
- Grade 3 hepatitis, pneumonitis, nephritis, myocarditis, pericarditis, encephalitis, myasthenia gravis, posterior- or pan-uveitis, episcleritis, peripheral neuropathy (including Guillain-Barre syndrome), autoimmune hemolytic anemia, acquired hemophilia, or autonomic neuropathy
- Recurrent Grade 2 pneumonitis
- Any grade transverse myelitis
- The subject becomes pregnant.
- Consent is withdrawn by the subject.

  Note: Consent withdrawn means that the subject can no longer be followed and no additional data can be collected. Subjects may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- Confirmed radiographic progression of disease per modified RANO criteria (as defined in ***Section 7***).
  - Exception: If subject meets radiographic criteria for PD but then undergoes a surgical resection of the area of radiographic PD per their treating oncologist's recommendation, the patient may stay on study and resume study drugs postoperatively if (i) histopathology from this surgery demonstrates only therapy-related changes and no viable tumor (scattered/rare atypical glial cells only would not count as viable tumor) AND (ii) there are no other, separate sites of PD on the immediate post-operative MRI.
  - Exception: If radiologic imaging *within the first 6 months* from the first dose of immunotherapy shows confirmed PD by mRANO criteria, participants not experiencing significant clinical decline may be allowed to continue study treatment for up to 3 months from the time of the scan showing confirmed PD. It is at the discretion of the treating physician whether to continue a participant on study treatment for up to 3 months pending confirmation of PD on follow-up imaging. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of PD if they are not experiencing significant clinical decline and if:
    - the subject is believed to demonstrate clinical benefit from the study regimen as determined by the treating physician;
    - the subject is adequately tolerating study therapy
- The study is terminated by the Sponsor.
- The IRB withdraws approval for the study

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Occurrence of any AE that is related to either study drug that, in the judgment of the Investigator and/or Medical Director, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.

A subject **may** be permanently discontinued from BOTH study drugs (INCMGA00012 and INCAGN01876) as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study treatment in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

A subject **must** be permanently discontinued from ONE study drug (either INCMGA00012 OR INCAGN01876) and **may continue** the other study drug if any of the following occurs:

- The subject has a grade 3 or higher infusion reaction that is clearly linked to only **one** of the study drugs. The temporal relationship between study drug administration and the reaction must be such that no other reasonable explanation exists for the subject's reaction beyond that specific study drug. If a subject has a grade 3 or higher infusion reaction and it is unclear which study drug was responsible, both study drugs must be permanently discontinued.

Reasons and procedures for replacing subjects are detailed in ***Section 3.2 Replacement of Subjects.***

5.8 Management of Study Drug Toxicities

5.8.1. Supportive care for Immune-Related Adverse Events (irAEs)

GITR represents an important immune control receptor. It is anticipated that combining GITR agonism PD-1 inhibition could cause more frequent, more severe, and/or new immune-related toxicities compared to the well-described immune-related toxicity for single agent PD-1 inhibition (Brahmer et al, J Clin Oncol 2018). For this reason, a variety of measures are included to mitigate these potential risks. These measures are consistent with published guidelines for immune-related AEs associated with anti−PD-1 drugs, but are meant to apply to any suspected immune-related AEs from other immuno-oncology agents such as the combination of INCMGA00012 and INCAGN01876

Immune-related AEs may be defined as an AE of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the INMGA0012 and INCAGN01876 compounds, their mechanism of action, and the extensive reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE. Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the principal investigator.

Recommendations for management of *specific* immune-mediated AEs such as pneumonitis, enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and other immune-mediated AEs, and are based on recently published guidelines for the management of immunotherapy-related toxicities that have recently been published by the National Comprehensive Cancer Network (NCCN) in partnership with the American Society of Clinical Oncology (ASCO), available here:
https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
and here:
http://ascopubs.org/doi/10.1200/JCO.2017.77.6385
and described in detail in **Appendix 1** with specific application to this protocol. These recommendations include management of the toxicity itself, as well as guidance for dose interruptions/delays of the investigational agents. There are no dose reductions or dose escalations permitted for either investigational agent.

5.8.2. Management of infusion-related 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 INCMGA00012 and INCAGN01876 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.

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 or severe bronchospasm
• Chest pain
• Seizure

5.8.3. Management of cerebral edema

Due to the immunologic nature of anti-PD-1 and GITR therapy, cerebral edema could theoretically result as a consequence of immune infiltration of the brain. In addition, SRS is expected to elicit cerebral edema. Symptoms related to cerebral edema may include headache or neurologic deficit that is either new or worsened. Participants with any signs or symptoms of cerebral edema in the investigator's judgment should be treated as clinically appropriate including initiation or increased dosing of systemic corticosteroids, osmotic diuretics, and/or surgical decompression. Subsequent study drug treatment should be immediately interrupted if significant clinical symptoms attributable to cerebral edema in the investigator's judgment develop. Treatment with additional study drug may only be re-initiated if clinically significant symptoms attributable to cerebral edema have stabilized or significantly resolved in the investigator's judgment.

Participants who develop grade 4 cerebral edema (CTCAE v5) attributable to study drug administration should not receive further study drug. Grade 4 cerebral edema is defined as life-threatening or requiring urgent intervention. For this study, urgent intervention refers to urgent/emergent intensive care unit admission, intubation for hyperventilation, administration of hypertonic or hyperosmotic agents, and/or urgent/emergent surgical decompression.

5.9 Disposal of Investigational Products

Study drug containers should not be destroyed until permitted by the Sponsor. Any unused study drug will be destroyed at the study site, per SOP.

5.10 Surgical Resection (Cohort B only)

For subjects enrolled onto cohort B, surgical resection for maximal safe tumor resection will be performed according to standard clinical practice. There is no aspect of this surgery that is different from standard practice.

5.11 Radiation Planning and Delivery (Cohort A; Cohort B, sub-arm #1 only)

Treatment will consist of 24 Gy delivered in 3 fractions over 3 consecutive business days. Subjects may receive 3 fractions every other day (non-consecutively) for logistical reasons relating to COVID-19. Therapy will be delivered according to standard guidelines of brain

directed SRS using the Cyberknife system or other linear accelerators commissioned for SRS. Patients will be simulated as per standard procedures with a CT and MRI scan in the treatment position with the patient immobilized in a thermoplastic mask. CT scan slice thickness will be 1.5mm. MRI images obtained at the time of simulation or diagnostic images will be fused as per department guidelines by a qualified physicist or dosimetrist and alignment confirmed by the treating radiation oncologist. For daily treatments patients will be immobilized in the custom thermoplastic masks created at simulation and undergo standard image guidance per routine care (6D skull tracking for Cyberknife treatments and volumetric cone beam CT for LINAC based treatments).

The gross tumor volume (GTV) will be defined as the enhancing tumor on the T1 post Gadolinium MRI scan. No expansion to a clinical target volume (CTV) will be applied (ie GTV=CTV). A planning target volume (PTV) expansion to account for setup uncertainty will be 1-2mm. Normal tissues to be contoured include the brainstem, optic nerves, optic chiasm, eyes, lens, cochlea. All radiation plans will undergo standard peer review prior to imitation of therapy. Target coverage and dose constraints are listed below in **Table 7**:

Table 7. Radiation Guidelines

Dose Metric	Per Protocol	Variation excepted
PTV_2400	Greater than or equal to 95% of the PTV should receive greater than or equal to 22.8 Gy. Max dose less than 28.8 Gy.	Greater than or equal to 90% of the PTV should receive greater than or equal to 22.8 Gy. Max dose less than 28.8 Gy.
Brainstem	Maximum dose from current plan (0.03cc) <23 Gy Maximum dose from combined plans (0.03cc)< 68Gy	
Optic Chiasm	Maximum dose from current plan (0.03cc) <17 Gy Maximum dose from combined plans (0.03cc)< 63Gy	
Optic Nerve	Maximum dose from current plan (0.03cc) <17 Gy Maximum dose from combined plans (0.03cc)< 63Gy	
Eyes	Maximum dose from current plan (0.03cc) <14 Gy	

	Maximum dose from combined plans (0.03cc)< 58Gy	
Cochlea	Maximum dose from current plan (0.03cc) <17 Gy Maximum dose from combined plans (0.03cc)< 53Gy Mean dose from combined plans (0.03cc)< 50Gy	Maximum dose from current plan (0.03cc) <25 Gy Maximum dose from combined plans (0.03cc)< 60Gy Mean dose from combined plans (0.03cc)< 55Gy

6 STUDY PROCEDURES

Screening assessments are to be conducted within 14 days prior to initiating protocol therapy unless otherwise specified. Screening assessments occurring prior to initiating study treatment do not need to be repeated on Cycle 1 Day 1 unless otherwise specified. Screening laboratory assessments must be done within 7 days prior to initiating protocol therapy.

For women of childbearing potential, as defined in the eligibility criteria, a pregnancy test must be completed within 7 days prior to initiating protocol therapy. If a urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

The schedule of study procedures for the screening and intervention phases of the study for Cohort A is displayed in **Table 8** and for Cohort B in **Table 9.** The schedule of procedures for the follow-up phase of the study for both cohorts is displayed in **Table 10.**

Table 8: COHORT A (N=16): Schedule of Study Procedures, SCREENING AND INTERVENTION

Study Week	**Screen**	**W1**	**W1**	**W2**	**W3**	**W5**	**W7**	**Q 4 weeks**		**Q 8 weeks**	**EOT§**
Cycle # (28-day cycles)		Cycle 1	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle X	Cycle X	Cycle X (pre-odd cycles only)	
Day (and window)	-14 to 1	1	5 ± 2	8	15 ± 2	1 ± 2	15 ± 2	1 ± 2	15 ± 2	1 ± 2	
Informed Consent	X										
Review Inclusion/Exclusion Criteria (Section 4)	X										
Karnofsky Performance Status (Section 7)	X	X			X	X	X	X	X		X
Demographics/Medical History (Section 7)	X										
Physical Assessment (targeted after screening visit) (Section 7)	X	X			X	X	X	X	X	X	X
Vital Signs: BP, HR, RR (Section 7)	X	X			X	X	X	X	X		X
ECG (Section 7)											
Weight (Section 7)	X	X				X		X			X
Height (Section 7)	X										
Pregnancy Test (Section 7; within 7d of first dose of study drug)	X							X			X
Concomitant Medications (Section 7)	X	X			X	X	X	X	X		X

Study Week	**Screen**	**W1**	**W1**	**W2**	**W3**	**W5**	**W7**	**Q 4 weeks**		**Q 8 weeks**	**EOT§**
Cycle # (28-day cycles)		Cycle 1	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle X	Cycle X	Cycle X (pre-odd cycles only)	
Day (and window)	-14 to 1	1	5 ± 2	8	15 ± 2	1 ± 2	15 ± 2	1 ± 2	15 ± 2	1 ± 2	
Clinical Laboratory Evaluation – non-endocrine (CBC, CMP, Mag, Phos, LDH) (Section 7; within 7d of first dose of study drug; Labs can be collected up to -3 days prior to treatment).	X	X			X	X	X	X	X		X
HBV/HCV screening (Section 7)	X										
Clinical laboratory Evaluation – endocrine (TSH, T4) (Section 7) Labs can be collected up to -3 days prior to treatment.	X									X	X
Urinalysis (Section 7)	X										X
Blood collected for INCAGN01876 PK (Section 7)		X***		X	X		X	X***†	X***†		
Blood collected for INCAGN01876 ADA (Section 7)		X			X		X		X		
Blood collected for correlatives (Section 7)		X				X				X	X

Study Week	**Screen**	**W1**	**W1**	**W2**	**W3**	**W5**	**W7**	**Q 4 weeks**		**Q 8 weeks**	**EOT§**
Cycle # (28-day cycles)		Cycle 1	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle X	Cycle X	Cycle X (pre-odd cycles only)	
Day (and window)	-14 to 1	1	5 ± 2	8	15 ± 2	1 ± 2	15 ± 2	1 ± 2	15 ± 2	1 ± 2	
Adverse Event / Unanticipated Problems Assessment (Section 7)	X	X			X	X	X	X	X		X
INCMGA00012 Administration (Section 5)		X				X		X			
INCAGN01876 Administration (Section 5)		X			X	X		X	X		
MRI brain (tumor assessment by mRANO criteria) (Section 7)	X									X*	X††
SRS planning (Section 5)	X										
SRS delivery** (Section 5)			X								

* MRI scan should be performed within 7 days prior to the cycle start (and ideally within 3 days prior). Adjustments to this 7 day window are allowable per the treating physician's discretion; however restaging scans MUST BE performed and reviewed before the subsequent cycle's dose may be initiated
**SRS delivery: Total 24 Gy delivered over 3 consecutive days (8 Gy per day). Subjects may receive 3 fractions every other day (non-consecutively) for logistical reasons relating to COVID-19. Must start between 3 and 7 days after first dose of study drugs
*** PK samples for INCAGN01876 collected pre-dose and at end of infusion on Cycle 1 Day 1 and Cycle 3 Day 15. All other PK draws for INCAGN01876 are pre-dose.
† After the first 2 cycles, PK samples for INCAGN01876 are drawn only on Cycle 3 Day 15, Cycle 4 Day 1, Cycle 4 Day 15, and then only on day 15 of each cycle starting with Cycle 5
†† MRI and mRANO assessment at EOT are only necessary if this has not already been performed within 28 days of the EOT visit
§ EOT visit occurs within 14 days from when the subject is taken off study.

Table 9: COHORT B (N=16): Schedule of Study Procedures, SCREENING AND INTERVENTION

Study Week	**Screen**	**Neo-adjuvant week**		**Peri-op weeks**		**W1**	**W2**	**W3**	**W5**	**W7**	**Q 4 weeks**		**Q 8 weeks**	**EOT§**
Cycle # (28-day cycles)		Neo- adjuvant cycle		Pre-Op	Post-Op	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle X	Cycle X	Cycle X (pre-odd cycles only)	
Day (and window)	-14 to 1	1	5 ± 2	Within 1 day of surgery	Up to 3 days from surgery	1 ± 2	8	15 ± 2	1 ± 2	15 ± 2	1 ± 2	15 ± 2	1 ± 2	
Informed Consent	X													
Review Inclusion /Exclusion Criteria (Section 4)	X													
Karnofsky Performance Status (Section 7)	X	X				X		X	X	X	X	X		X
Demographics/ Medical History (Section 7)	X													
Physical Assessment(targeted after screening (Section 7)	X	X				X		X	X	X	X	X	X	X

Study Week	**Screen**	**Neo-adjuvant week**		**Peri-op weeks**		**W1**	**W2**	**W3**	**W5**	**W7**	**Q 4 weeks**		**Q 8 weeks**	**EOT§**
Cycle # (28-day cycles)		Neo- adjuvant cycle		Pre-Op	Post-Op	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle X	Cycle X	Cycle X (pre-odd cycles only)	
Day (and window)	-14 to 1	1	5 ± 2	Within 1 day of surgery	Up to 3 days from surgery surgery	1 ± 2	8	15 ± 2	1 ± 2	15 ± 2	1 ± 2	15 ± 2	1 ± 2	
Vital Signs: BP, HR, RR (Section 7)	X	X		X		X		X	X	X	X	X		X
ECG (Section 7)	X													
Weight (Section 7)	X	X				X			X		X			X
Height (Section 7)	X													
Pregnancy Test (Section 7; within 7d of first dose of study drug)	X										X			X
Concomitant Medications (Section 7)	X	X		X		X		X	X	X	X	X		X
Clinical Laboratory Evaluation – non-endocrine (CBC, CMP, Mag, Phos, LDH) (Section 7; within 7d of first dose of study drug; Labs can be collected up to -3 days prior to treatment)	X	X			X	X		X	X	X	X	X		X

Study Week	**Screen**	**Neo-adjuvant week**		**Peri-op weeks**		**W1**	**W2**	**W3**	**W5**	**W7**	**Q 4 weeks**		**Q 8 weeks**	**EOT§**
Cycle # (28-day cycles)		Neo- adjuvant cycle		Pre-Op	Post-Op	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle X	Cycle X	Cycle X (pre-odd cycles only)	
Day (and window)	-14 to 1	1	5 ± 2	Within 1 day of surgery	Up to 3 days from surgery	1 ± 2	8	15 ± 2	1 ± 2	15 ± 2	1 ± 2	15 ± 2	1 ± 2	
Clinical laboratory Evaluation – endocrine (TSH, T4) (Section 7) Labs can be collected up to -3 days prior to treatment.	X					X							X	X
Urinalysis (Section 7)	X													X
HBV/HCV screening (Section 7)	X													
Blood collected for INCAGN01876 PK (Section 7)						X***	X	X		X	X†	X***†		
Blood collected for INCAGN01876 ADA (Section 7)						X		X		X		X		
Blood collected for correlatives (Section 7)		X				X			X				X	X

Study Week	**Screen**	**Neo-adjuvant week**		**Peri-op weeks**		**W1**	**W2**	**W3**	**W5**	**W7**	**Q 4 weeks**		**Q 8 weeks**	**EOT§**
Cycle # (28-day cycles)		Neo- adjuvant cycle		Pre-Op	Post-Op	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle X	Cycle X	Cycle X (pre-odd cycles only)	
Day (and window)	-14 to 1	1	5 ± 2	Within 1 day of surgery	Up to 3 days from surgery	1 ± 2	8	15 ± 2	1 ± 2	15 ± 2	1 ± 2	15 ± 2	1 ± 2	
Adverse Event / Unanticipated Problems Assessment (Section 7)	X	X		X	X	X		X	X	X	X	X		X
INCMGA00012 Administration (Section 5)		X††				X			X		X			
INCAGN01876 Administration (Section 5)		X††				X		X	X	X	X	X		
MRI brain (tumor assessment by mRANO criteria) (Section 7)	X												X*	X†††
SRS planning** (Section 5)	X													
SRS delivery** (Section 5)			X											
Surgical Resection; tissue for correlatives (Section 7)				X										

* MRI scan should be performed within 7 days prior to the cycle start (and ideally within 3 days prior). Adjustments to this 7-day window are allowable per the treating physician's discretion; however restaging scans MUST BE performed and reviewed before the subsequent cycle's dose may be initiated

**SRS delivery: Total 24 Gy delivered over 3 consecutive days (8 Gy per day). Subjects may receive 3 fractions every other day (non-consecutively) for logistical reasons relating to COVID-19. Must start between 3 and 7 days after first dose of study drugs
*** PK samples for INCAGN01876 collected pre-dose and at end of infusion on Cycle 1 Day 1 and Cycle 3 Day 15. All other PK draws for INCAGN01876 are pre-dose.
† After the first 2 cycles, PK samples for INCAGN01876 are drawn only on Cycle 3 Day 15, Cycle 4 Day 1, Cycle 4 Day 15, and then only on day 15 of each cycle starting with Cycle 5
†† For the neoadjuvant dose(s) of study drugs INCMGA00012 and INCAGN01876, the subject will be assigned to receive the combination of INCMGA00012 and INCAGN01876, or the combination of INCMGA00012 and INCAGN01876 plus SRS. After surgery ALL subjects will resume the combination of both INCMGA00012 and INCAGN01876
††† MRI and mRANO assessment at EOT are only necessary if this has not already been performed within 28 days of the EOT visit
§ EOT visit occurs within 14 days from when the subject is taken off study

Table 10: Schedule of study procedures, FOLLOW-UP			
Procedure	Safety visit	Safety follow-up	Disease Status and Survival
	30 d after EOT (+/- 7 d)	12 W (+/-14 d) after EOT	Q12W after EOT (+/- 14d)
Karnofsky Performance Status (Section 7)	X		
Targeted Physical Assessment (Section 7	X		
Vital Signs: BP, HR, RR, weight (Section 7)	X		
Prior/Concomitant Medications (Section 7)	X	X	
Clinical Laboratory Evaluation (CBC, CMP, Mag, Phos, LDH) (Section 7)	X		
Urinalysis (Section 7)	X		
Clinical laboratory Evaluation – endocrine (TSH, T4) (Section 7)	X		
Urine Pregnancy Test (Section 7)	X		
Adverse Event / Unanticipated Problems Assessment (Section 7)	X	X*	
MRI brain (tumor assessment) (Section 7)			X
Subject Vital Status (Collection of survival information every 3 months until death, lost to follow-up, or withdrawal of study consent)			X

* Only immune related Adverse Events are to be collected at the 12-week safety follow- up timepoint (see sections 1.3.1.3 and 1.3.2.3).

6.1 Unscheduled Visits

During the conduct of the study, there are multiple situations that may require the subject to come to the research site for an unscheduled visit. Reasons for an unscheduled visit include but are not limited to the following:

- Subject missed the visit window
- Subject experienced an AE and needed to be seen for follow-up
- Due to lab results, the investigator has determined that for the welfare of the subject, she or he should be seen sooner than previously scheduled

The data from these visits will be recorded just as any study visit.

6.2. Subject Withdrawal from the Study

Subjects may withdraw consent for the study at any time for any reason without impact to their care. In addition, a subject may be withdrawn by the investigator or the sponsor if enrollment in the study is inappropriate, lack of adherence to the intervention or study procedures or visit schedules, the study plan is violated, or for administrative and/or other safety reasons. It is documented whether or not each subject completes the clinical study. If the subject actively withdraws consent for collection of follow-up data (i.e., subsequent anticancer treatments, safety follow-up, and survival), then no additional data collection occurs; however, all subjects are informed of the option to discontinue treatment and/or study assessments but allow collection of information in the follow-up period of the study. In the event that the latter occurs, the end-of-treatment (EOT) visit should be conducted (see **Table 8** and **Table 9** for EOT visit procedures). Thereafter, the subject will return for follow-up visits for safety and disease/survival status, with procedures as outlined above in **Table 10.**

If a subject withdraws from the study and has not yet received a dose of study drug, that subject is replaced according to the procedure outlined in ***Section 3.2; Replacement of Subjects***.

7 STUDY EVALUATIONS AND MEASUREMENTS

7.1 Demographic and Medical Record Review

The following variables will be collected at screening and abstracted from the electronic medical chart:

- Date of birth
- Height
- Weight
- Medical History, Prior and Concomitant Medications, and Allergies
    - All concomitant medications must be recorded, and any medication received within 30 days before screening must be recorded.
    - Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period.
- Karnofsky Performance Status, as defined in **Table 11**:

Table 11. KARNOFSKY PS
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 but unable to carry on normal activity or to do active work
60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
20—Very ill; hospitalization and active supportive care necessary 10—Moribund
0—Dead

7.2 Physical Assessment

Physical assessments will be performed according to the assessment schedules.

Full physical assessments will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, musculoskeletal (including spine and extremities), neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at Screening only. Targeted physical assessments are to be utilized by the investigator and/or research nurse on the basis of clinical observations and symptomatology. Clinically notable abnormalities that are considered clinically significant in the judgement of the investigator are to be reported as AEs.

7.3 Vital Signs

Height will be assessed at screening only. Weight will be assessed according to the Study Schedule (**Tables 8 and 9**) and as clinically indicated at any other time.

Vital signs (BP, pulse, temperature, and respiratory rate) will be evaluated according to the assessment schedules **Table 8 and Table 9**). Any changes in vital signs should be recorded as an AE, if applicable. Body temperature: Body temperature will be measured in degrees Celsius at the times indicated in the Study Schedule (**Table 8 and Table 9**).

On infusion days, subjects will be monitored during and after infusion of each investigational product(s) as presented in the bulleted list below. Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the subject has rested for at

least 5-10 minutes. BP and pulse will be collected from subjects before, during, and after each infusion at the following times (based on a 60-minute infusion):
• Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
• Approximately 30 minutes during 60-minute infusions (halfway through infusion). Vitals should be obtained at approximately 15 minutes during subsequent 30-minute infusions (halfway through infusion).
• At the end of the infusion (approximately 60 or 30 minutes ±5 minutes)
• A 1-hour observation period is recommended after the INCMGA00012 infusion prior to beginning the INCAGN01876 infusion.

7.4 Electrocardiogram (ECG)

A 12-lead electrocardiogram will be performed at screening only.

7.5 Clinical Laboratory Evaluations

Blood sampling will be performed for the following laboratory evaluations (**Table 12**) according to the schedule outlined in **Table 8 and Table 9:**

- Hematology
- Chemistry and Liver Function
- Additional electrolytes
- Endocrine
- Hepatitis screening
- Urinalysis

Table 12: Clinical Laboratory Tests

Category	Tests
Hematology	RBC, hemoglobin, hematocrit, platelet count, WBC with differential
Chemistry and Liver function tests (comprehensive metabolic panel)	Basic metabolic panel, LDH, AST, ALT, total Bilirubin (with direct and indirect components), alkaline phosphatase
Additional electrolytes	Magnesium, phosphorus
Endocrine	TSH, free T4
Hepatitis screening	HBV surface antigen (HBsAg), HCV viral load (RNA quant)
Urine	Microscopic Urinalysis

7.6 Pregnancy Testing

WOCBP are required to have a urine or serum pregnancy test performed during screening and this test must be completed within 7 days before the first dose of study drug. WOCBP must exhibit a negative serum or urine pregnancy (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to the start of study drug. Pregnancy testing will be performed as outlined in **Table 8** and **Table 9**; this includes the EOT visit, although a pregnancy test is not

required if a subject is going to hospice. Urine pregnancy tests will be conducted during the intervention phase of the study only as medically indicated. If a urine pregnancy test is positive or cannot be confirmed as negative, the results should be confirmed with a serum pregnancy test. If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study. A serum pregnancy test should also be repeated at the EOT visit.

7.7 Efficacy Evaluations

7.7.1. Anti-Tumor Effect Definitions

Modified Response Assessment in Neuro-Oncology (RANO) criteria (Ellingson et al, Neurotherapeutics 2017) will be used to assess for tumor response and progression, with definitions as outlined below. Radiologic response will be assessed by comparing the pretreatment baseline and on-treatment MRI scans. Radiologic progression will be determined by using the smallest tumor measurement at either the pretreatment baseline or after initiation of study medication. MRI scans will be performed no less frequently than every 8 weeks. The MRI scan should be performed within 7 days prior to a cycle start (and ideally within 3 days prior). Adjustments to this 7 day window are allowable per the treating physician's discretion; however restaging scans MUST BE performed and reviewed before the subsequent cycle's dose may be initiated. MRIs will be interpreted by the attending neuro-radiologist at the University of Pennsylvania assigned as a sub-investigator on this study.

Measurable disease should be defined as contrast enhancing lesions with a minimum size of *both* perpendicular measurements greater than or equal to 10mm. For example, if the largest diameter is 15 mm but the perpendicular diameter is 8 mm, this would constitute *non-measurable disease*. Up to a total of five target measurable lesions should be defined and ranked from largest to smallest. Non-measurable disease should be defined as lesions that are too small to be measured (less than 1 cm in both perpendicular dimensions), lesions that lack contrast enhancement (non-enhancing disease), or lesions that contain a poorly defined margin that cannot be measured or segmented with confidence.

7.7.2. Response/Progression Categories

The following definitions for disease response and progression will be used according to the following MRI and clinical criteria:

Complete Response (***CR***): Requires ***all*** of the following:

1. Disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan at least 4 weeks later, this scan will be considered only stable disease.
2. No new lesions
3. Stable or improved non-enhancing (T2/FLAIR) lesions
4. Patients must be off corticosteroids (or on physiologic replacement doses only).
5. Stable or improved clinical assessments

Partial Response (***PR***): Requires ***all*** of the following:

1. ≥50% decrease in sum of products of perpendicular diameters of all measurable enhancing lesions compared with baseline, sustained for at least 4 weeks. In the absence of a confirming scan at least 4 weeks later, this scan will be considered only stable disease.
2. No progression of non-measurable disease
3. No new lesions
4. Stable or improved non-enhancing (T2/FLAIR) lesions
5. Steroid dose should be the same or lower compared with baseline scan.
6. Stable or improved clinical assessments.

Progressive Disease (PD) is defined by *any* of the following:

1. ≥25% increase in sum of products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement [obtained either at baseline (if no decrease) or best response], on stable or increasing doses of corticosteroids.
2. Any new enhancing measurable lesion
3. Clear clinical deterioration not attributable to other causes apart from tumor (e.g. seizures, medication adverse effects, therapy complications, stroke, infection) or attributable to changes in steroid dose. The definition of clinical deterioration is left to the discretion of the investigator.
4. Clear progression of non-measurable disease
5. Failure to return for evaluation as a result of death or deteriorating condition.

Stable Disease (***SD***): Requires ***all*** of the following:

1. Does not qualify for CR, PR, or PD as defined above.
2. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan
3. Clinically stable

The response and progression criteria to be used in this study are summarized in **Table 13**:

Table 13. Summary of the RANO response Criteria:

Criterion	CR	PR	SD	PD
T1w CE	None	≥ 50 % ↓	<50%↓ but <25 %↑	≥25% ↑*
T2w/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑
New lesions	None	None	None	Present *
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Response requirement	All	All	All	Any *

The arrows indicate the direction of measured change from last exam. Abbreviations: RANO: Response Assessment in Neuro-Oncology, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, T1w: T1 weighted. T2w: T2 weighted, CE: contrast enhancement, FLAIR: fluid-attenuated inversion recovery, NA: not applicable. * Progression occurs when this criterion is present.

Of note, patients who require increased corticosteroids within 2 weeks of MRI assessment (relative to the dose taken at the time of the prior assessment) cannot be classified as CR, PR, or SD and should be classified as non-evaluable at that time point. Conversely, patients who decrease corticosteroids within 2 weeks of MRI assessment (relative to the dose taken at the time of the prior assessment) cannot be classified as PD and should be classified as non-evaluable.

Unscheduled Assessments:
If an unscheduled assessment was performed and the subject has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of first study drug infusion).

7.7.3. Study continuation beyond initial progressive disease

Immunotherapeutic agents including PD-1 inhibitors such as INCMGA00012 may produce antitumor effects by potentiating endogenous cancer-specific immune response, which may manifest as initial worsening of enhancement on MRI (i.e., pseudoprogression). In addition, the response patterns seen with immunotherapeutics may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. For these reasons, the immune-related response criteria (irRC) have endorsed continuation of study therapy beyond radiographic evidence of progression for clinically stable patients undergoing immune based therapies (Seymour et al, Lancet Oncol 2017).

Therefore, the following adaptations of the RANO criteria, as reflected in the recently published Immunologic Response Assessment in Neuro-Oncology (iRANO) criteria (Okada et al, Lancet Oncol 2015), will be used to assess tumor progression for patients treated on this study:

- Potential Pseudoprogression: If radiologic imaging *within the first 6 months* from the first dose of immunotherapy shows confirmed PD by mRANO criteria, as defined in the above section, participants not experiencing significant clinical decline

may be allowed to continue study treatment for up to 3 months from the time of the scan showing confirmed PD. Patients who have radiographic evidence of further progression after 3 months, or who decline significantly any time, will be classified as progressive disease with the date of disease progression back-dated to the first date the participant met criteria for PD and such participants will be discontinued from study therapy. In participants who have initial evidence of radiographic PD, it is at the discretion of the treating physician whether to continue a participant on study treatment for up to 3 months pending confirmation of PD on follow-up imaging. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of PD if they are not experiencing significant clinical decline and if:

- the subject is believed to demonstrate clinical benefit from the study regimen as determined by the treating physician;
- the subject is adequately tolerating study therapy

Subjects who have been on the study drugs for *more than 6 months* must come off study for disease progression at the first time that radiologic criteria for confirmed PD are met.

7.7.4. MRI Procedures

MRI of the brain is performed once every 8 weeks on study as per standard of care for the management of recurrent GBM. The MRIs performed for this study do not include experimental sequences or coils or any experimental contrast. These MRIs do require the use of an FDA-approved gadolinium-based contrast agent. The gadolinium will be used in accordance with the FDA label for gadolinium-based contrast.

IV Line Placement – This is required to administer the contrast agent. Multiple needle-sticks may be necessary if a vein cannot be properly accessed and this will be carried out with the subjects' permission.

IV Contrast Risks- As mention above, part of the MRI study will require the injection of a gadolinium contrast agent into the blood stream. There is a rare possibility that the subject could have an adverse reaction to the contrast agent such as rash, hives, itching, mild headache and nausea. The subject may also experience some minor discomfort and low risk of bleeding, infection and bruising associated with Intravenous catheter placement. Recently, FDA has also required a new class warning for all gadolinium-based contrast agents (GBCAs) for MRI concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these drugs. The long-term risks of this retention are not well elucidated; Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and the FDA has concluded that the benefit of all approved GBCAs continues to outweigh any potential risks. Also, there is a possible risk of nephrogenic systemic fibrosis (NSF, also

referred to as nephrogenic fibrosing dermopathy or NFD) occurring following administration of a GBCA in subjects with known moderate to severe renal disease (with a glomerular filtration rate or GFR < 30 mL/min/1.73m2). However, such patients are not eligible for this trial (see ***Section 4*****; *Eligibility Criteria***). In addition, serial creatinine values will be checked for each subject once monthly throughout the course of the trial. If at any point a subject's GFR falls below 30 mL/min/1.73m2 or a rise in creatinine above baseline suggests an acute kidney injury, that subject must undergo a repeat serum creatinine test within 24 hours prior to the next planned MRI scan with contrast. This MRI with contrast should not be performed until the GFR is above 30 mL/min/1.73m2 and is stable improving on two additional tests each separated by 48 hours.

Pregnancy Clause - Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is potential danger to the fetus from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative urine or serum pregnancy test will be required before a woman of child-bearing potential can participate in this study. If the subject is post-menopausal for at least one year or has undergone a hysterectomy, the subject will not be required to undergo a pregnancy test prior to enrolling in this study and undergoing MRI scans. Gadolinium-based IV contrast agents are not approved in pregnant women (pregnant women will be excluded from this trial).

Metallic Foreign Fragments/Flying Object Clause -The known risks associated with this study are minimal. Implanted medical devices and metallic foreign fragments inside the body may pose a risk if you were to enter the MRI magnet room. Therefore, questions regarding medical and work history will be asked prior to the exam. The greatest risk is a magnetic object flying through the air toward the magnet and hitting the subject. To reduce this risk, we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once subject is in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.

Magnetic Fields Health Risks Statement--There is no known health risk associated with exposure to magnetic fields during an MRI. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. We shall provide the subject with protective earplugs as necessary and make every attempt to ensure comfort with blankets, etc. during time in the scanner.

7.8 Safety Assessments

Subjects are evaluated for safety according to the office visit and laboratory evaluation schedule outlined in **Table 8** and **Table 9** (***Section 6***). Safety and AE definitions, recording, and reporting are outlined in detail in ***Section 9***.

7.9 Tissue/Blood collection for correlative analyses, PK, and ADA

For all subjects in this study (both Cohort A and Cohort B), informed consent will be obtained to collect a formalin-fixed, paraffin-embedded (FFPE) preserved component of tumor tissue from the subject's initial surgical tumor resection for exploratory correlative analyses. This surgery

will have already been performed prior to their enrollment on this protocol as part of standard of care therapy for glioblastoma.

For subject in the surgical arm only (Cohort B, N=16), both fresh frozen and FFPE preserved components of tumor tissue will also be collected from the surgery that subjects will undergo as part of this protocol (i.e., the subject's surgery for recurrent GBM).

In addition, in both Cohorts A and B 60 mL of peripheral blood will also be collected for future exploratory correlative analyses. These 60 mL blood samples will be collected at the time points outlined in the SOE (**Table 8** and **Table 9**).

All subjects will be asked to consent to collection of an FFPE preserved component of tumor tissue from any surgical brain tumor resection or brain tumor biopsy that is performed (as clinically indicated) after the subject has discontinued the study treatment. If a subject comes off study for progressive disease, initiates another treatment regimen per standard of care, and then has another tumor resection, collection of FFPE preserved tissue will not occur.

The exploratory endpoints of this study are outlined in ***Section 2*****.** All correlative analyses will be performed in University of Pennsylvania laboratories with the following exceptions**:** pharmacokinetic (PK) and anti-drug antibody (ADA) measurements will be performed by Syneos Health, and GITR expression by IHC will be performed by Mosaic Laboratories. In addition to the correlative assays listed in ***Section 2***, other assays relevant to understanding mechanisms or predictors of clinical benefit and/or resistance to INCMGA00012 and INCAGN01876 in GBM may be performed on these tissue and blood samples in the future based upon emerging data and future hypotheses. The informed consent form reflects this flexibility for future research use of subject biospecimens collected during the course of this study.

No results of tissue or blood correlatives will be recorded in the subject's electronic medical record and will not be used in any way to guide treatment or clinical decision making.

7.10 Protocol exceptions (prospective action)

An ***exception*** is defined as a one-time, intentional action or process that departs from the approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcomes may be compromised, or the action compromises the safety and/or welfare of study subjects, advance documented approval from the Regulatory Sponsor and local regulatory review committees, per institutional guidelines, is required. Approval from the Regulatory Sponsor must be received prior to submission to the local regulatory review committees.

7.11 Protocol Deviations (retrospective action)

A ***deviation*** is defined as a one-time, unintentional action or process that departs from the approved study protocol, involving one incident and identified retrospectively. If the deviation disrupts study progress, such that the study design or outcomes may be compromised, or the deviation compromises the safety and/or welfare of study subjects, the deviation must be reported to the Regulatory Sponsor within 24 hours of PI knowledge and to local regulatory review committees per institutional guidelines.

Report the following information on the Sponsor's exception/deviation form:

- Protocol number
- Subject number
- Description of the exception or deviation
- Impact on subject safety
- Impact on data integrity

Deviations that are assessed by the PI to not disrupt the study progress, such as not affecting the study design or outcome, or compromising the safety and/or welfare of study subjects, should be documented in site records and contain documentation of the PI's assessment.

8 STATISTICAL PLAN

8.1 Definition of Primary Endpoint

The primary efficacy endpoint of this study is objective radiographic response (ORR), as defined by modified Response Assessment in Neuro-Oncology (mRANO) criteria (Ellingson et al, Neurotherapeutics 2017). Per mRANO criteria, ORR is defined as the presence or absence of an objective radiographic tumor response, either a) partial or complete response; OR b) absence of partial or complete response, i.e., a binary endpoint. A two-sided 95% confidence interval for ORR will be calculated.

Only subjects enrolled on Cohort A who have (1) not been replaced AND (2) received SRS and at least one dose of both study drugs are evaluable for the primary endpoint.

8.2 Statistical Methods

8.2.1 Primary Endpoint Analysis (Efficacy of Regimen)

The primary efficacy hypothesis of this study is that the proportion of subjects who experience an objective radiographic response will be 25% or higher. We will test this hypothesis against the null hypothesis of 5% of subjects experiencing an objective response using an exact single-stage phase II design for the primary study cohort (Cohort A; Non-surgical). A sample size of 16 evaluable subjects is required for 80% power. A one-sided significance level has been set at 0.05. A subject is considered evaluable for the primary endpoint if (a) the subject is one of the 16 subjects enrolled onto Cohort A at the same dose and schedule of study drugs that is determined to be the final dose/schedule based on the safety run-in phase, AND (b) the subject has received at least one dose of BOTH study drugs AND has received at least one fraction of SRS.

In one of the largest series of patients with recurrent high-grade glioma treated with hypofractionated stereotactic radiation therapy alone, ~10% of patients experienced a minimal response of the irradiated tumor by MacDonald Criteria; no patients experienced a partial response (Fogh, J Clin Oncol 2010). For patients who have one tumor site irradiated while other sites of tumor are not irradiated, such as some of the subjects who will be enrolled in the current protocol, no responses would be expected in non-irradiated tumor. With these data in mind,

coupled with the historic overall response rate of ~10% to single-agent lomustine (a standard of care) in recurrent GBM (Batchelor TT, et al. *J Clin Oncol* 2013), we have designated ORR=5% as the null hypothesis.

The alternative hypothesis, a 25% ORR, would be a clinically significant difference that would suggest this regimen is worthy of further investigation.

8.2.2 Analysis of Secondary and Exploratory endpoints

Descriptive analyses will be conducted to summarize subject characteristics and detect potential selection bias as a result of missing data or dropout.

All subjects who sign informed consent will be included in safety analyses and in calculation of the rate of AEs, regardless of whether and how much study drug was received. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Safety summaries will be provided for both cohorts. Immune-related adverse events (irAEs, as defined in **Section 9**), are prespecified events of interest. These events will be summarized in separate tables from other AEs by toxicity grade and will include the counts, percentages, and 95% CI. AEs (specific terms as well as system organ class terms) that are not pre-specified as events of interest will be summarized with descriptive statistics (counts, percentage, mean, standard deviation, etc).

Progression-free survival (PFS) and overall survival (OS) will be estimated using the Kaplan-Meier product-limit method, with subjects censored at their last known date alive. Standard error for the Kaplan-Meier estimate will be calculated according to the formula of Peto, et al (Br J Cancer 1977) and a two-sided 95% confidence intervals for the median PFS and median OS, respectively, will also be calculated.

Comparisons of PFS and OS in subjects on Cohort A (nonsurgical) vs. PFS and OS in subjects on Cohort B (neoadjuvant therapy) will be exploratory in nature, as the study is not adequately powered for these comparisons. Log-rank tests will be used to explore differences in PFS/OS between these two groups.

For analysis of correlative data, variable distributions will be presented graphically and descriptively at each time point; if needed, appropriate transformations will be performed. Paired t-tests will be used to assess change from pre- to post-treatment for exploratory endpoints that are normally distributed. Wilcoxon signed-rank tests will be used to assess change from pre- to post-treatment for exploratory endpoints that are not normally distributed. Multiple comparison adjustment using false discovery rate (FDR) will be used. The sample size of 16 subjects in the surgical arm of the study (Cohort B), with N=8 per sub-arm provides 85% power with one-sided alpha of 0.05 to detect the difference between the null hypothesis of a CD8+ tumor-infiltrating lymphocyte score of 1 and the alternative hypothesis of a CD8+ tumor-infiltrating lymphocyte score of 1.85. These numbers are based on the pre- and post- CD8+ tumor-infiltrating lymphocyte scoring system (scored 0 to 3, least to most CD8+ T cell infiltration) used in our prior CAR T cell trial in recurrent GBM (O'Rourke, Sci Transl Med 2017), which is one of the few immunotherapies shown to increase tumor T cell infiltration in this disease. In that study,

pre-CAR T cell GBM specimens had a mean score of 1 (standard deviation 0.1) and post-CAR T cell GBM specimens had a mean score of 1.85 (standard deviation 0.80).

9 SAFETY AND ADVERSE EVENTS

9.1 Definitions

9.1.1. Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study, whether or not considered drug related. This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for assessing the severity of AEs, as follows in **Table 14**:

Table 14: CTCAE version 5.0 for assessment of the severity of AEs

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

The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each adverse event. The CTCAE v5.0 is available on the NCI/NIH website.

Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy, or require changes in the study drug(s). Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

9.1.2 Immune-Related Adverse Events

Immune-related AEs (irAEs)may be defined as an AE of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. irAEs may be predicted based on the nature of the INCMGA00012 and INCAGN01876 compounds, their mechanism of action, and extensive reported experience with immunotherapies that have a similar mechanism of action.

Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

Of note, intratumoral/peritumoral edema and any resultant AEs (seizure, e.g.), even if attributed to the study drug(s), are NOT considered irAEs in this study. Such edema may be a desired effect of the treatment, as it may represent immune infiltration of the tumor.

9.1.3 Serious Adverse Events

Serious Adverse Event (SAE):
Adverse events are classified as serious or non-serious. An **SAE** is any AE that is at least one of the following:

- fatal
- life-threatening
- requires hospitalization or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- is considered to be an important medical event, which are those that may not be immediately life threatening but are clearly of major clinical significance. These may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

Events **not** considered to be SAEs in this trial are:

- Progression of the cancer under study (GBM)
- A visit to the emergency room or another hospital department that does not result in a hospitalization of >24 hours (unless considered an important medical or life-threatening event)
- Hospitalization for any of the following:
    - Elective procedures, including routine health assessment (e.g. routine colonoscopy) or elective/pre-planned treatment for a pre-existing condition that did not worsen while on study
    - Seizure, if felt related to subject's underlying disease
    - Scheduled tumor debulking surgery

9.1.4 Unanticipated problem

Any incident, experience, or outcome that meets <u>all</u> of the following criteria is defined as an **unanticipated problem:**

- <u>Unexpected in nature, severity, or frequency</u> (i.e., not described in protocol or consent form, the drug package insert, or the investigators brochure; a summary of expected AEs related to INCMGA00012/INCAGN01876 can be found in the ***Investigator's Brochure***)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

9.2 Collecting and recording of Adverse Events

Adverse event collection will occur from signing of the informed consent form until the 12-week safety follow-up visit. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the 12-week safety follow-up, any new clinically significant findings/abnormalities that meet the definition of an immune related adverse event must also be recorded and documented as an adverse event (see sections 1.3.1.3 and 1.3.2.3).

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. AEs may also be volunteered spontaneously by the study patient. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the electronic case report form (eCRF).

Each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug(s)
- The event outcome (e.g, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in ***Section 9.1.2***
    - Per the Investigator, whether the event is definitely related, probably related, possibly related, unlikely related, or unrelated to the study drug(s) and/or SRS. In order to be unrelated, a causal relationship between the drug(s)/SRS and the AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

All adverse events occurring between the time the informed consent form is signed and the end of the safety follow up phase will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the 12-week safety follow-up period will continue to be followed to determine the final outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

For AEs associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s)

should be reported as an SAE(s). In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The study's principal investigator is ultimately responsible for the recording, and reporting, unanticipated problems related to the research, which occur during the study.

9.3 Reporting of Adverse Events

The study period during which adverse events must be reported is defined as the period from the signing of the informed consent form to the 12-week safety follow-up visit.

9.3.1 Follow-up reporting for SAEs

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's or Sponsor's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the FDA and IRB. The PI and Sponsor are responsible for ensuring that all SAEs are followed until either resolved or stable.

9.3.2 Investigator Reporting: Notifying the Study Sponsor

All investigators should report **all** AEs to the study PI. The PI must report all AEs to the Sponsor (University of Pennsylvania) regardless of whether they are serious or not, as well as all unanticipated problems.

Any SAEs are notified to the study Sponsor and Medical Director by email or phone within 24 hours of the event. The PI will keep a copy of the SAE reporting form on file.

The PI then provides further information on the SAE as information becomes available in a SAE form. This includes the following:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Significant new information on ongoing SAEs should be provided promptly to the Principal Investigator and Sponsor.

9.3.3 Investigator Reporting: Notifying the Penn IRB

The investigator will report to the IRB following institutional policies requirements.

9.3.4 Reporting to Incyte

All SAEs and follow up information must be notified by phone or e-mail to Incyte within one (1) business day of Sponsor becoming aware of the initial event or follow-up information.

The Sponsor Institution will provide a causality assessment and must sign and date all SAE Report Forms. SAE reports should be for a single subject. SAE forms will be emailed with a cover sheet and and additional attachments to the address for Incyte listed below.

If supporting documentation is included in the submission to Incyte (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), all patient identifiers (including Medical Record number) will be redacted.

Incyte SAE and Pregnancy Reporting Information
Email: SafetyReporting@incyte.com Fax: 1-866-981-2057

On at least an annual basis, the Sponsor Institution will provide a copy of the safety reports submitted to applicable Regulatory Authorities or IRB. Annual reports should be provided to Incyte within 3 business days of submission to the applicable regulatory body.

9.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

If an event is assessed by the Sponsor Institution as a Suspected Unexpected Serious Adverse Reaction (SUSAR), the Sponsor will send a complete report to Incyte within 2 additional business of the assessment. The Sponsor will follow regulatory requirements regarding reporting of safety events.

In addition, the SUSAR will be distributed to the Investigators/sites per regulatory requirement.

9.5 Reporting Product Complaints for INCMGA00012 and INCAGN01876

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the Sponsor Institution or qualified designee within one (1) business day of first becoming aware of the possible defect to Incyte. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

9.6 Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

- The study drugs must be discontinued immediately (female subjects only)

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including

spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit.

An elective abortion without complications should not be regarded as an AE. Therapeutic abortions should be reported as a treatment procedure and as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

The Sponsor Institution must report all pregnancies associated with Incyte products including follow up outcomes to Incyte within one (1) business day of awareness.

9.7 Special Situations: Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose with a Incyte product, the Sponsor Institution and Incyte should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be reported.
- **Accidental /Occupational exposure:** is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of misuse, medication error, overdose, and accidental or occupational exposure associated with an Incyte product must be reported on a Special Situations Report Form to the Sponsor and from Sponsor to Incyte within 5 business days of awareness regardless of whether or not an AE or SAE has occurred. If the misuse, medication error, overdose, or accidental / occupational exposure is associated with an AE, a safety form must also be submitted to the Sponsor Institution and from Sponsor to Incyte within one (1) business day of awareness.

10 STUDY ADMINISTRATION, DATA HANDLING, AND RECORD KEEPING

10.1 Confidentiality

Information about study 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 study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a 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 investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

10.2 Data Collection and Management

Data will be managed using the clinical trial data management system Clinical Trial Management Systems (CTMS). Access to the trial project in CTMS is granted by the Penn Office of Clinical Research (OCR) to all persons with the appropriate roles in the study.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. If a space on the eCRF is left blank because the procedure was not done or the question was not asked, type "N/D". If the item is not applicable to the individual case, type "N/A". Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Each subject will be assigned a unique study ID number (unique for this project) in CTMS
To ensure that strict confidentiality is maintained, password-protected access to the CTMS project and a file linking medical record numbers (MRNs) to study ID number will be granted only to the clinical research coordinators and research nurses/assistants assigned to this study.

10.3. Records Retention

HIPAA Retention Period (45 CFR164.530(j):
Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain until Sponsor provides approval to destroy.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of release, to whom the information was released, and the circumstances of the release. Retain until Sponsor provides approval to destroy.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will be maintained until Sponsor provides approval to destroy.

11 STUDY MONITORING, AUDITING, and INSPECTING

11.1 Study Monitoring Plan

This study will be monitored by the Sponsor according to the monitoring plan.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12 ETHICAL CONSIDERATIONS

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to the University of Pennsylvania Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study and throughout the study.

12.1 Risks

The primary risks to subjects enrolled on this protocol include the following:

- That the experimental regimen will be ineffective against glioblastoma, thus permitting the tumor to continue to grow
- Study drug-related adverse events, which, in the worst case, could lead to permanent toxicity/injury or death. Detailed descriptions of the types and rates adverse reactions previously reported with INCMGA00012 and INCAGN01876 are outlined in detailed in the Investigator's Brochure. The risk that is most likely to result in an SAE related to the study drug(s) is cerebral edema (and resultant neurologic toxicity), which is outlined in detail in both this protocol (***Section 5.8.3***).
    - Serious harm or death due to an unexpected adverse event that occurs due to the combination of INCMGA00012 and INCAGN01876 with stereotactic radiosurgery. The risk that is most likely to result in an SAE related to the study drug(s) is cerebral edema (and resultant neurologic toxicity), which is outlined in detail in both this protocol (***Section 5.8.3***).

12.2 Benefits

Although no benefit can be guaranteed to subjects as a result of enrolling on this protocol, the investigational regimen has strong preclinical rationale for being studied in subjects with GBM. Therefore, there is a reasonable possibility that subjects enrolled on this study will receive therapy that is more efficacious than current standard of care for recurrent GBM; at present, there

is no systemic therapy that has been proven to prolong overall survival in recurrent GBM. In addition, even if the study is negative and does not reach its primary endpoint, there is benefit to medical knowledge and society as a whole from the correlative studies that accompany this trial. These studies are designed to improve our understanding of mechanisms of response and resistance to immunotherapy in GBM.

12.3 Risk Benefit Assessment

There continues to be a significant unmet need for patients with recurrent GBM. The potential benefit to subjects in this study is that the combination regimen of INCMGA00012, INCAGN01876, and SRS may be clinically active and would add additional progression-free and/or overall survival time compared to if the subject did not enroll on the trial. The primary risk to subjects is of adverse events occurring related to the individual use or the combination of the study drugs.

Overall, the current lack of any available systemic therapy that has been shown to improve OS in recurrent GBM, in combination with the relatively high level of safety and tolerability of INCMGA00012, INCAGN01876, and SRS in prior studies, the risk benefit assessment for enrolling in this clinical trial is in favor of benefit.

12.4 Informed Consent Process/HIPAA Authorization

Subjects will be recruited from the Radiation Oncology, Neurosurgery, and Medical Oncology practices at the University of Pennsylvania Health Systems. The treating physician will determine if the patient is a potential research candidate. The treating physician will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating physician will contact a qualified member of the research team in the Neurosurgery Clinical Research Division at the University of Pennsylvania and request availability for enrollment. A sub-investigator of the research team will continue the formal consent process. This person will explain the requirements of the study and provide a copy of the Informed Consent Form. The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study before making her decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed after which screening procedures will be performed. Subject eligibility will be evaluated based upon the criteria outlined in the protocol. After eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study PI.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Sponsor. 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 study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

13 STUDY FINANCES

13.1 Funding Source

This clinical trial is financed through a grant from Incyte.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14 PUBLICATION PLAN

This is an investigator-initiated trial and Penn holds the IND. The Sponsor holds the primary responsibility for publication of the results of the study.

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APPENDIX 1. Management guidelines for Immune-Related Adverse Events (irAEs)*

*ICPi = immune checkpoint inhibitor; in this protocol, this refers to BOTH study drugs INCMGA00012 and INCAGN01876.
*These tables are copied directly from the original publication for convenience (Brahmer et al, J Clin Oncol 2018).

Table 1. Management of Skin irAEs in Patients Treated With ICPis

1.0 Skin Toxicities

1.1 Rash/inflammatory dermatitis

Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [eg, Sweet syndrome], and others)

Diagnostic work-up

- Pertinent history and physical examination
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder
- If needed, a biologic checkup, including a blood cell count and liver and kidney tests
- Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms
- Skin biopsy
- Consider clinical monitoring with use of serial clinical photography
- Review full list of patient medications to rule out other drug-induced cause for photosensitivity

Grading	Management
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPi Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level

1.2 Bullous dermatoses

Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction

Diagnostic work-up

- Physical examination
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease
- If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases
- Referral to dermatology for blisters that are not explained by infectious or transient other causes (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister)
- Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)

Grading	Management
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations

(continued on following page)

Table 1. Management of Skin irAEs in Patients Treated With ICPis (continued)

1.0 Skin Toxicities	
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for grade > 2 Blisters covering 10%-30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions: • Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements • Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc
1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS	
Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug	
Diagnostic work-up Total body skin examination with attention to examining all mucous membranes as well as complete review of systems Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pusulosis Consider following patients closely using serial clinical photography If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management Primer on monitoring for complicated cutaneous adverse drug reactions: Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN	

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Table 1. Management of Skin irAEs in Patients Treated With ICPis (continued)

1.0 Skin Toxicities	
Grading	Management
All grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥ 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting of DRESS/DIHS)	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations
Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate	

Abbreviations: ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; G, grade; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; NA, not applicable; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TENS, toxic epidermal necrolysis.

Table 2. Management of GI irAEs in Patients Treated With ICPis

2.0 GI Toxicities

2.1 Colitis

Definition: A disorder characterized by inflammation of the colon

Diagnostic work-up

G2

- Work-up of blood (CBC, comprehensive metabolic panel, TSH, ESR, CRP), stool (culture, *Clostridium difficile*, parasite, CMV or other viral etiology, ova and parasite) should be performed
- Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow up on disease activity)
- Screening laboratories (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation
- Imaging (eg, CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid-refractory course, which may require early infliximab
- Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy

G3-4

- All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately
- Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICPi

Grading (based on CTCAE for diarrhea, as most often used clinically)	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits Fever, abdominal distention, obstipation, constipation For G2 or higher, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases
G1: Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi; alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed G1 Monitor for dehydration and recommend dietary changes Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline	Should hold ICPi temporarily until patient's symptoms recover to G1; can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (< 10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for G2 or higher Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent When symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases grade ≥ 2 to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of G2 or higher to differentiate functional *v* inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers Repeat colonoscopy is optional for cases of G2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections

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Table 2. Management of GI irAEs in Patients Treated With ICPis (continued)

2.0 GI Toxicities

Additional considerations

- The use of vedolizumab may be considered in patients refractory to infliximab and/or contraindicated to TNF-α blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results[13-15]
- Patients with hepatitis and irAE colitis are rare, and management should include permanently discontinuing ICPi and offering other immunosuppressant agents that work systemically for both conditions
- Currently, enteritis alone as the cause of diarrhea is uncommon and requires small bowel biopsy as the evaluation tool. It may be managed similar as colitis, including corticosteroid and/or infliximab, etc

2.2 Hepatitis

Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma

Diagnostic work-up

- Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if G1 liver function test elevations. No treatment is recommended for G1 liver function test abnormality
- For G2 or higher:
  - Work-up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANAs, antismooth muscle antibodies, antineutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, γ-glutamyl transferase should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies

Grading	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Yellowing of skin or whites of the eyes Severe nausea or vomiting Pain on the right side of the abdomen Drowsiness Dark urine (tea colored) Bleeding or bruising more easily than normal Feeling less hungry than usual
G1: Asymptomatic (AST or ALT > ULN to 3.0 × ULN and/or total bilirubin > ULN to 1.5 × ULN)	Continue ICPi with close monitoring; consider alternate etiologies Monitor laboratories one to two times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5 × ULN and/or total bilirubin > 1.5 to ≤ 3 × ULN)	Hold ICPi temporarily and resume if recover to G1 or less on prednisone ≤ 10 mg/d For grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days Increase frequency of monitoring to every 3 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 × ULN and/or total bilirubin 3-10 × ULN)	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated TB 3 × ULN Increase frequency of monitoring to every 1-2 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-α agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 × ULN and/or total bilirubin > 10 × ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil Monitor laboratories daily; consider inpatient monitoring Avoid the use of infliximab in the situation of immune-mediated hepatitis Hepatology consult if no improvement was achieved with corticosteroid Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear Consider transfer to tertiary care facility if necessary

All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations is moderate.

Abbreviations: ADL, activities of daily living; ANA, antinuclear antibody; CK, creatine kinase; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-cell lymphocyte-4; EGD, esophagogastroduodenoscopy; ESR, erythrocyte sedimentation rate; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; PD-1; programmed death 1; PD-L1, programmed death ligand 1; TB, tuberculosis; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Table 3. Management of Lung irAEs in Patients Treated With ICPis

3.0 Lung Toxicities	
3.1 Pneumonitis	
Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging) No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis	
Diagnostic work-up Should include the following: CXR, CT, pulse oximetry For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	
Grading	Management
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management
Additional considerations GI and *Pneumocystis* prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines[34-37] Consider calcium and vitamin D supplementation with prolonged corticosteroid use The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines[33] Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest x-ray; DLCO, diffusing capacity of lung for carbon monoxide; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; PPI, proton pump inhibitor.

Table 4. Management of Endocrine irAEs in Patients Treated With ICPis

4.0 Endocrine Toxicity	
Counsel patients to inform their health care provider immediately if they experience any changes in their health since their last visit, especially any of the following: Headaches that will not go away or unusual headache patterns Vision changes Rapid heartbeat Increased sweating Extreme tiredness or weakness Muscle aches Weight gain or weight loss Dizziness or fainting Feeling more hungry or thirsty than usual Hair loss Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness Feeling cold Constipation Voice gets deeper Urinating more often than usual Nausea or vomiting Abdominal pain	
4.1 Thyroid	
4.1.1 Primary hypothyroidism	
Definition: Elevated TSH, normal or low FT4	
Diagnostic work-up	
TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients	
Grading	Management
G1: TSH < 10 mIU/L and asymptomatic	Should continue ICPi with close follow-up and monitoring of TSH, FT4
G2: Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	May hold ICPi until symptoms resolve to baseline Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2
Additional considerations For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 μg/kg/d For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 μg Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase) Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated	
4.1.2 Hyperthyroidism	
Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine	
Diagnostic work-up Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (eg, ophthalmopathy) Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism	
Grading	Management
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until symptoms return to baseline Consider endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease

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Table 4. Management of Endocrine irAEs in Patients Treated With ICPis (continued)

4.0 Endocrine Toxicity	
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy Endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks; consider also use of SSKI or thionamide (methimazole or PTU).
Additional considerations Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above. Graves disease is generally persistent and is due to increased thyroid hormone production that can be treated with antithyroid medical therapy. Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral.	
4.2 Adrenal – primary adrenal insufficiency	
Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone	
Diagnostic work-up for patients in whom adrenal insufficiency is suspected: Evaluate ACTH (AM), cortisol level (AM) Basic metabolic panel (Na, K, CO_2, glucose) Consider ACTH stimulation test for indeterminate results If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically: Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage	
Grading	**Management**
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Initiate outpatient treatment at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation(hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1
Additional considerations Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3. Patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see next section on hypophysitis). Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg. All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS. Endocrine consultation prior to surgery or any procedure for stress-dose planning.	
4.3 Pituitary - hypophysitis	
Definition: Inflammation of the pituitary with varying effects on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism.	
Diagnostic work-up Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH. Testing: Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes	

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Table 4. Management of Endocrine irAEs in Patients Treated With ICPis (continued)

4.0 Endocrine Toxicity	
Grading	Management
G1: Asymptomatic or mild symptoms	Considering holding ICPi until patient is stabilized on replacement hormones Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (eg, hydrocortisone 10-20 mg orally in the morning, 5-10 mg orally in early afternoon; levothyroxine by weight) Testosterone or estrogen therapy as needed in those without contraindications Endocrine consultation Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis Follow FT4 for thyroid hormone replacement titration (TSH is not accurate)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1 Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks
Additional considerations Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS Corticosteroid use can cause isolated central adrenal insufficiency Work-up cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.	
4.4 Diabetes	
Definition: T2DM is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. It may be new onset or exacerbated during therapy for nonimmunologic reasons, such as corticosteroid exposure. Autoimmune T1DM results from islet cell destruction and is often acute onset, with ketosis and an insulin requirement	
Diagnostic work-up Monitor patients for hyperglycemia or other signs and symptoms of new or worsening DM, including measuring glucose at baseline and with each treatment cycle during induction for 12 weeks, then every 3-6 weeks thereafter. To guide the work-up in new-onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM. Laboratory evaluation in suspected T1DM should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti–glutamic acid decarboxylase, anti–islet cell, or anti–insulin antibodies are highly specific for autoimmune diabetes. Insulin and C-peptide levels can also assist in the diagnosis.	
Grading	Management
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow-up and laboratory evaluation May initiate oral therapy for those with new-onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value > 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL G3: > 250-500 mg/dL (> 13.9-27.8 mmol/L) G4: > 500 mg/dL (> 27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all patients Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to see endocrinology
Additional considerations Insulin therapy can be used as the default in any case with hyperglycemia. Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting. Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/d). In T2DM, sliding-scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs.	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ACTH, adrenocorticotropic hormone; ADL, activities of daily living; CT, computed tomography; DKA, diabetic ketoacidosis; DM, diabetes mellitus; EMS, emergency medical services; FSH, follicle-stimulating hormone; FT4, free thyroxine; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; LH, luteinizing hormone; MRI, magnetic resonance imaging; PTU, propylthiouracil; SSKI, potassium iodide; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; ULN, upper limit of normal.

Table 5. Management of Musculoskeletal irAEs in Patients Treated With ICPis

5.0 Musculoskeletal Toxicities

5.1 Inflammatory arthritis

Definition: A disorder characterized by inflammation of the joints

Clinical symptoms: Joint pain accompanied by joint swelling; inflammatory symptoms, such as stiffness after inactivity or in the morning, lasting > 30 minutes to 1 hour; improvement of symptoms with NSAIDs or corticosteroids but not with opioids or other pain medications may also be suggestive of inflammatory arthritis.

Diagnostic work-up

G1
- Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion; examination of the spine
- Consider plain x-ray/imaging to exclude metastases and evaluate joint damage (erosions), if appropriate
- Consider autoimmune blood panel including ANA, RF, and anti-CCP, and anti-inflammatory markers (ESR and CRP) if symptoms persist; if symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing

G2
- Complete history and examination as above; laboratory tests as above
- Consider US ± MRI of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis)
- Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms of arthralgia persist > 4 weeks

G3-4
- As for G2
- Seek rheumatologist advice and review

Monitoring: Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.

Grading	Management
All grades	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-α or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.

Additional considerations
- Early recognition is critical to avoid erosive joint damage.
- Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other irAEs
- Oligoarthritis can be treated early on with intra-articular corticosteroids; consider early referral.
- Consider PCP prophylaxis for patients treated with high dose of corticosteroids for > 12 weeks, as per local guidelines.

5.2 Myositis

Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life threatening if respiratory muscles or myocardium are involved

Diagnostic work-up
- Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider preexisting conditions that can cause similar symptoms.
- Blood testing to evaluate muscle inflammation
- CK, transaminases (AST, ALT), LDH, and aldolase can also be elevated
- Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed
- Inflammatory markers (ESR and CRP)
- Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected
- Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis
- Monitoring: CK, ESR, CRP

(continued on following page)

Table 5. Management of Musculoskeletal irAEs in Patients Treated With ICPis (continued)

5.0 Musculoskeletal Toxicities	
G1: Complete examination and laboratory work-up as above	
G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI of affected joints Early referral to a rheumatologist or neurologist	
G3-4: As for G2 Urgent referral to a rheumatologist or neurologist	
Grading	**Management**
G1: Mild weakness with or without pain	Continue ICPi If CK is elevated and patient has muscle weakness, may offer oral corticosteroids, and treat as G2 Offer analgesia with acetaminophen or NSAIDs if there are no contraindications
G2: Moderate weakness with or without pain, limiting age-appropriate instrumental ADL	Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose < 10 mg; if worsens, treat as per G3 NSAIDs as needed Referral to rheumatologist or neurologist If CK is elevated three times or more), initiate prednisone or equivalent at 0.5-1 mg/kg May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3-4: Severe weakness with or without pain, limiting self-care ADL	Hold ICPi until G1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration
Additional considerations: Caution is advised with rechallenging	
5.3 Polymyalgia-like syndrome	
Definition: Characterized by marked pain and stiffness in proximal upper and/or lower extremities and no signs of true muscle inflammation such as CK elevation or EMG findings of myositis. No true muscle weakness, difficulty in active motion related to pain	
Diagnostic work-up G1 Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin Check for symptoms of temporal arteritis, such as headache or visual disturbances; refer to ophthalmologist if present, and consider temporal artery biopsy ANA, RF, anti-CCP CK to evaluate differential diagnosis of myositis Inflammatory markers (ESR, CRP) Monitoring: ESR, CRP	
G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis; early referral to a rheumatologist	
G3-4: As for G2; see rheumatologist advice and review	
Grading	**Management**
G1: Mild stiffness and pain	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications
G2: Moderate stiffness and pain, limiting age-appropriate instrumental ADL	Consider holding ICPi and resuming upon symptom control, prednisolone < 10 mg; if worsens, treat as per G3 Initiate prednisone 20 mg/d or equivalent; if symptoms improve, start to taper dose after 3-4 weeks If no improvement or need for higher dosages after 4 weeks, escalate to G3 Consider referral to rheumatology
G3-4: Severe stiffness and pain, limiting self-care ADL	Hold ICPi and may resume, in consultation with rheumatology, if recover to G1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. Referral to rheumatology Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; ANA, antinuclear antibodies; CCP, citrullinated protein antibody; CK, creatine kinase; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; EMG, electromyography; ESR, erythrocyte sedimentation rate; ICPi, immune checkpoint inhibitor; IL, interleukin; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drug; PCP, *Pneumocystis* pneumonia; RF, rheumatoid factor; TNF, tumor necrosis factor.

Table 6. Management of Renal irAEs in Patients Treated With ICPis

6.0 Renal Toxicities	
Nephritis and renal dysfunction: diagnosis and monitoring For any suspected immune-mediated adverse reactions, exclude other causes Monitor patients for elevated serum creatinine prior to every dose Routine urinalysis is not necessary, other than to rule out UTIs, etc; nephrology may consider further If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy Swift treatment of autoimmune component important	
6.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading	Management
G1: Creatinine level increase of > 0.3 mg/dL; creatinine 1.5-2.0 × over baseline	Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still < 1.5 ULN could be meaningful
G2: Creatinine 2-3 × above baseline	Hold ICPi temporarily Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc); if other etiologies ruled out, administer 0.5-1 mg/kg/d prednisone equivalents If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment If improved to G1 or less, taper corticosteroids over 4-6 weeks If no recurrence of chronic renal insufficiency, discuss resumption of ICPI with patient after taking into account the risks and benefits.
G3: Creatinine > 3 × baseline or > 4.0 mg/dL; hospitalization indicated	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated	Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent)
Additional considerations Monitor creatinine weekly Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted	
6.2 Symptomatic nephritis: follow-up	
Grading	Management
G1	If improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist > 3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate)
G4	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist > 2-3 days or worsen, consider additional immunosuppression (eg, mycophenolate)
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AKI, acute kidney injury; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; ULN, upper limit of normal; UTI, urinary tract infection.

Table 7. Management of Nervous System irAEs in Patients Treated With ICPis

7.0 Nervous System Toxicities

7.1 Myasthenia gravis

Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.

Diagnostic work-up

- AChR and antistriated muscle antibodies in blood; if AChR antibodies are negative, consider muscle specific kinase and lipoprotein-related 4 antibodies in blood
- Pulmonary function assessment with NIF and VC
- CPK, aldolase, ESR, CRP for possible concurrent myositis
- Consider MRI of brain and/or spine, depending on symptoms to rule out CNS involvement by disease or alternate diagnosis
- If respiratory insufficiency or elevated CPK, troponin T, perform cardiac examination with ECG and TTE for possible concomitant myocarditis
- Neurologic consultation
- Electrodiagnositic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis

Grading	Management
All grades	All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADL MGFA severity class 1 (ocular symptoms and findings only) and MGFA severity class 2 (mild generalized weakness)	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve[87] Should consult neurology Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment Daily neurologic review

Additional considerations

- Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides
- Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days
- 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement
- Pyridostigmine, wean based on improvement
- ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required

7.2 Guillain-Barré syndrome

Definition: Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.

Diagnostic work-up

- Neurologic consultation
- MRI of spine with or without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening)
- Lumbar puncture: CSF typically has elevated protein and often elevated WBCs; even though this is not typically seen in classic Guillain-Barré syndrome, cytology should be sent with any CSF sample from a patient with cancer.
- Serum antiganglioside antibody tests for Guillain-Barré syndrome and its subtypes (eg, anti-GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia)
- Electrodiagnostic studies to evaluate polyneuropathy
- Pulmonary function testing (NIF/VC)
- Frequent neurochecks

Grading	Management
All grades	Warrant work-up and intervention given potential for progressive Guillain-Barré syndrome to lead to respiratory compromise Note: There is no G1 toxicity
G1: Mild, none	NA
G2: Moderate, some interference with ADL, symptoms concerning to patient G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms	Discontinue ICPi Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis Frequent neurochecks and pulmonary function monitoring Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus

(continued on following page)

Table 7. Management of Nervous System irAEs in Patients Treated With ICPis

7.0 Nervous System Toxicities

7.1 Myasthenia gravis

Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.

Diagnostic work-up
- AChR and antistriated muscle antibodies in blood; if AChR antibodies are negative, consider muscle specific kinase and lipoprotein-related 4 antibodies in blood
- Pulmonary function assessment with NIF and VC
- CPK, aldolase, ESR, CRP for possible concurrent myositis
- Consider MRI of brain and/or spine, depending on symptoms to rule out CNS involvement by disease or alternate diagnosis
- If respiratory insufficiency or elevated CPK, troponin T, perform cardiac examination with ECG and TTE for possible concomitant myocarditis
- Neurologic consultation
- Electrodiagnositic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis

Grading	Management
All grades	All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADL MGFA severity class 1 (ocular symptoms and findings only) and MGFA severity class 2 (mild generalized weakness)	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve[87] Should consult neurology Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment Daily neurologic review

Additional considerations
- Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides
- Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days
- 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement
- Pyridostigmine, wean based on improvement
- ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required

7.2 Guillain-Barré syndrome

Definition: Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.

Diagnostic work-up
- Neurologic consultation
- MRI of spine with or without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening)
- Lumbar puncture: CSF typically has elevated protein and often elevated WBCs; even though this is not typically seen in classic Guillain-Barré syndrome, cytology should be sent with any CSF sample from a patient with cancer.
- Serum antiganglioside antibody tests for Guillain-Barré syndrome and its subtypes (eg, anti-GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia)
- Electrodiagnostic studies to evaluate polyneuropathy
- Pulmonary function testing (NIF/VC)
- Frequent neurochecks

Grading	Management
All grades	Warrant work-up and intervention given potential for progressive Guillain-Barré syndrome to lead to respiratory compromise Note: There is no G1 toxicity
G1: Mild, none	NA
G2: Moderate, some interference with ADL, symptoms concerning to patient G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms	Discontinue ICPi Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis Frequent neurochecks and pulmonary function monitoring Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus

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Table 7. Management of Nervous System irAEs in Patients Treated With ICPis (continued)

7.0 Nervous System Toxicities	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms
7.6 Encephalitis	
Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (ie, HSV). Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality	
Diagnostic work-up Neurologic consultation MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels. May see elevated WBC count with lymphocytic predominance and/or elevated protein EEG to evaluate for subclinical seizures Blood: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits As above for aseptic meningitis, suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology
7.7 Transverse myelitis	
Definition: Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes	
Diagnostic work-up Neurologic consultation MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies Blood: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG Evaluation for urinary retention, constipation	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3-5 days Strongly consider IVIG
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AChR, acetylcholine receptor; ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ANCA, antineutrophil cytoplasmic antibodies; CPK, creatine phosphokinase; CRP, C-reactive protein; EMG, electromyography; ESR, erythrocyte sedimentation rate; HSV, herpes simplex virus; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; IgG, immunoglobulin G; IV, intravenous; IVIG, intravenous immunoglobulin; irAE, immune-related adverse event; MGFA, Myasthenia Gravis Foundation of America; MRI, magnetic resonance imaging; NA, not applicable; NCS, nerve conduction study; NIF, negative inspiratory force; PCR, polymerase chain reaction; RPR, rapid plasma reagin, TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram; VC, vital capacity.

Table 8. Management of Hematologic irAEs in Patients Treated With ICPis

8.0 Hematologic Toxicities

8.1 Autoimmune hemolytic anemia

Definition: A condition in which RBCs are destroyed and removed from the blood stream before their normal lifespan is over. Symptoms include weakness, paleness, jaundice, dark-colored urine, fever, inability to do physical activity, and heart murmur.

Diagnostic work-up

- History and physical examination (with special consideration of history of new drugs and insect, spider, or snake bites)
- Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear; LDH, haptoglobin, bilirubin, reticulocyte count, free Hgb
- DIC panel, which could include PTINR infectious causes
- Autoimmune serology
- Paroxysmal nocturnal hemoglobinuria screening
- Direct and indirect bilirubin; LDH; direct agglutinin test; and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate for myelodysplastic syndromes
- Evaluation for viral/bacterial (mycoplasma, etc) causes of hemolysis studies
- Protein electrophoresis, cryoglobulin analysis
- Work-up for bone marrow failure syndrome if refractory, including B12, folate, copper, parvovirus, FE, thyroid, infection
- Glucose-6-phosphate dehydrogenase
- Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc)
- Assessment of methemoglobinemia

Grading	Management
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2 to 4.9 mmol/L; < 100 to 80 g/L	Hold ICPi and strongly consider permanent discontinuation Administer 0.5-1 mg/kg/d prednisone equivalents
G3: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Permanently discontinue ICPi Should use clinical judgment and consider admitting the patient Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms/speed of development) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue ICPi treatment Consider RBC transfusion per existing guidelines; do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe Hgb range (7-8 g/dL in stable, noncardiac inpatients) Should offer patients supplementation with folic acid 1 mg once daily
G4: Life-threatening consequences, urgent intervention indicated	Permanently discontinue ICPi Admit patient Hematology consult IV prednisone corticosteroids 1-2 mg/kg/d If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporin A, and mycophenolate mofetil RBC transfusion per existing guidelines; discuss with blood bank team prior to transfusions that a patient with possible ICPi serious AE is in house.
Additional considerations: Monitor Hgb levels on a weekly basis until the corticosteroid tapering process is complete; thereafter, less-frequent testing is needed[164]	

8.2 Acquired TTP

Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurologic abnormalities, such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.

Diagnostic work-up

- History with specific questions related to drug exposure (eg, chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine)
- Physical examination, peripheral smear
- ADAMTS13 activity level and inhibitor titer
- LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes
- PT, activated PTT, fibrinogen
- Blood group and antibody screen, direct antiglobulin test, CMV serology
- Consider CT/MRI brain, echocardiogram, ECG
- Viral studies
- Note: This disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously

Grading	Management
All grades	The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition; hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity. Initially, the patient should be stabilized and any critical organ dysfunction stabilized
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy
G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	Hematology consult Administer 0.5-1 mg/kg/d prednisone

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Table 8. Management of Hematologic irAEs in Patients Treated With ICPis (continued)

8.0 Hematologic Toxicities	
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency > 2) G4: Life-threatening consequences (eg, CNS hemorrhage or thrombosis/embolism or renal failure)	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy Hematology consult In conjunction with hematology, initiate PEX according to existing guidelines with further PEX dependent on clinical progress[94-96] Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX May offer rituximab
8.3 Hemolytic uremic syndrome	
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include: Bloody diarrhea Decreased urination or blood in the urine Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, shiga toxin, *Escherichia coli* 0157, etc Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc) Evaluation for concurrent confusion	
Grading	Management
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia grade 2	Continue ICPi with close clinical follow-up and laboratory evaluation Supportive care
G3: Laboratory findings with clinical consequences (eg, renal insufficiency, petechiae) G4: Life-threatening consequences (eg, CNS thrombosis/embolism or renal failure)	Permanently discontinue ICPi Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, then 1,200 mg every 2 weeks Red blood transfusion according to existing guidelines
8.4 Aplastic anemia	
Definition: Condition in which the body stops producing enough new blood cells	
Diagnostic work-up History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections) CBC, smear, reticulocyte count Viral studies, including CMV, HHV6, EBV, parvovirus Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D Serum LDH, renal function Work-up for infectious causes Identify marrow hypo/aplasia Bone marrow biopsy and aspirate analysis Peripheral blood analysis, including neutrophil count, proportion of GPI-negative cells by flow for PNH Flow cytometry to evaluate loss of GPI-anchored proteins Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	
Grading	Management
G1: Nonsevere, > 0.5 polymorphonuclear cells × 10^9/L hypocellular marrow, with marrow cellularity < 25%, peripheral platelet count > 20,000, reticulocyte count > 20,000	Hold ICPi and provide growth factor support and close clinical follow-up, and laboratory evaluation Supportive transfusions as per local guidelines
G2: Severe, hypocellular marrow < 25% and two of the following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte colony-stimulating factor may be added in addition

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Table 8. Management of Hematologic irAEs in Patients Treated With ICPis (continued)

8.0 Hematologic Toxicities	
G3-4: Very severe, ANC < 200, platelet count < 20,000, reticulocyte count < 20,000, plus hypocellular marrow < 25%	Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 Hematology consult, growth factor support Horse ATG plus cyclosporine If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide For refractory patients, consider eltrombopag plus supportive care
8.5 Lymphopenia	
Definition: An abnormally low level of lymphocytes in PB; for adults, counts of < 1,500/mm^3	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc, as well as history of autoimmune disease, family history of autoimmune disease) Evaluation of nutritional state as cause Spleen size CBC with differential, peripheral smear and reticulocyte counts CXR for evaluation of presence of thymoma Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)	
Grading	Management
G1-2: 500-1,000 PB lymphocyte count	Continue ICPi
G3: 250-499 PB lymphocyte count	Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening
G4: < 250 PB lymphocyte count	Consider holding ICPi Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV/hepatitis screening if not already done May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease
8.6 Immune thrombocytopenia	
Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy) Family history of autoimmunity or personal history of autoimmune disease History of viral illness CBC Peripheral blood smear, reticulocyte count Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and *Helicobacter pylori* Direct antigen test should be checked to rule out concurrent Evan syndrome Nutritional evaluation Bone marrow evaluation if other cell lines affected and concern for aplastic anemia	
Grading	Management
G1: Platelet count < 100/μL	Continue ICPi with close clinical follow up and laboratory evaluation
G2: Platelet count < 75/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1 Administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.
G3: Platelet count < 50/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1
G4: Platelet count < 25/μL	Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia[97]; consult for further details)
8.7 Acquired hemophilia	
Definition: Disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors	
Diagnostic work-up Full blood count to assess platelet number, fibrinogen, PT, PTT, INR; the typical finding in patients with acquired hemophilia A is a prolonged activated PTT with a normal PT MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding Medication review to assess for alternative causes Determination of Bethesda unit level of inhibitor	

(continued on following page)

Table 8. Management of Hematologic irAEs in Patients Treated With ICPis (continued)

8.0 Hematologic Toxicities	
Grading	Management
G1: Mild, 5%-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Administer 0.5-1 mg/kg/d prednisone Transfusion support as required Treatment of bleeding disorders with hematology consult
G2: Moderate, 1%-5% of normal factor activity in blood, 0.01-0.05 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Hematology consult Administration of factor replacement (choice based on Bethesda unit of titer) Administer 1 mg/kg/d prednisone ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab *v* cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor
G3-4: Severe, < 1% of normal factor activity in blood, < 0.01 IU/mL of whole blood	Permanently discontinue ICPi Admit patient Hematology consult Administration of factor replacement, choice based on Bethesda unit level of inhibitor Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity); caution should be taken in the elderly and those with coronary artery disease Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d). Transfusion support as required for bleeding If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption
Additional considerations: Acquired hemophilia A requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established.[98]	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AE, adverse event; ANC, antineutrophil cytoplasmic antibodies; ATG, antithymocyte globulin; CMV, cytomegalovirus; CT, computed tomography; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; G, grade; GPI, glycosylphosphatidylinositol; Hgb, hemoglobin; HHV6, human herpesvirus 6; ICPi, immune checkpoint inhibitor; INR, international normalized ratio; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; LLN, lower limit of normal; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PB, peripheral blood; PEX, plasma exchange; PNH, paroxusmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; TTP, thrombotic thrombocytopenic purpura.

Table 9. Management of Cardiovascular irAEs in Patients Treated With ICPis

9.0 Cardiovascular Toxicities

9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis

Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue

Diagnostic work-up
- At baseline
  - ECG
  - Consider troponin, especially in patient treated with combination immune therapies
- Upon signs/symptoms (consider cardiology consult)
  - ECG
  - Troponin
  - BNP
  - Echocardiogram
  - CXR
- Additional testing to be guided by cardiology and may include
  - Stress test
  - Cardiac catherization
  - Cardiac MRI

Grading	Management
G1: Abnormal cardiac biomarker testing, including abnormal ECG	All grades warrant work-up and intervention given potential for cardiac compromise
G2: Abnormal screening tests with mild symptoms	Consider the following:
G3: Moderately abnormal testing or symptoms with mild activity	Hold ICPi and permanently discontinue after G1
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms) Admit patient, cardiology consultation Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin

Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.[108]

9.2 Venous thromboembolism

Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing, or hemoptysis for PE

Diagnostic work-up
- Evaluation of signs and symptoms of PE or DVT may include
  - Clinical prediction rule to stratify patients with suspected venous thromboembolism
  - Venous ultrasound for suspected DVT
  - CTPA for suspected PE
- Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler are not available or appropriate
- Ventilation/perfusion scan is also an option when CTPA is not appropriate
- Consider other testing, including ECG, CXR, BNP and troponin levels, and arterial blood gas

Grading	Management
G1: Venous thrombosis (eg, superficial thrombosis)	Continue ICPi Warm compress Clinical surveillance
G2: Venous thrombosis (eg, uncomplicated DVT), medical intervention indicated	Continue ICPi Management according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
G3: Thrombosis (eg, uncomplicated PE [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	
G4: Life-threatening (eg, PE, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated	Permanently discontinue ICPi Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology Respiratory and hemodynamic support LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term Further clinical management as indicated based on symptoms

Additional considerations
- While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents given the severity and life-threatening potential of G4 complications. Clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to discontinue ICPi treatment.
- Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission.[109,110]

All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; CT, computed tomography; CTPA, computed tomography pulmonary angiography; CXR, chest x-ray; DVT, deep vein thrombosis; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; PE, pulmonary embolism; VKA, vitamin K agonist.

Table 10. Management of Ocular irAEs in Patients Treated With ICPis

10.0 Ocular Toxicities	
Counsel all patients to inform their health care provider immediately if they experience any of the following ocular symptoms Blurred vision Change in color vision Photophobia Distortion Scotomas Visual field changes Double vision Tenderness Pain with eye movement Eyelid swelling Proptosis	
Evaluation, under the guidance of ophthalmology Check vision in each eye separately Color vision Red reflex Pupil size, shape, and reactivity Fundoscopic examination Inspection of anterior part of eye with penlight	
Prior conditions Exclude patients with history of active uveitis History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy	
Additional considerations Ocular irAEs are many times seen in the context of other organ irAEs High level of clinical suspicion as symptoms may not always be associated with severity Best to treat after ophthalmologist eye examination	
10.1 Uveitis/iritis	
Definition: Inflammation of the middle layer of the eye	
Diagnostic work-up: as per above	
Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Medical intervention required, anterior uveitis	Hold ICPi temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity Re-treat after return to G1 or less
G3: Posterior or panuveitis	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and intravitreal/periocular/topical corticosteroids
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment[121,122]	
10.2 Episcleritis	
Definition: Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection	
Diagnostic work-up: As per 10.0	
Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Vision 20/40 or better	Hold ICPi therapy temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids
G3: Symptomatic and vision worse than 2/40	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment[121,122]	
10.3 Blepharitis	
Definition: Inflammation of the eyelid that affects the eyelashes or tear production	
Diagnostic work-up: As per 10.0	
Grading	Management
No formal grading system	Warm compresses and lubrication drops Continue therapy unless persistent and serious
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous, TNF, tumor necrosis factor.