Title: Phase II study of IDHI inhibitor ivosidenib and nivolumab in IDHI mutant gliomas and advanced solid tumors

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i. Abbreviations

Abbreviation	Definition
2-HG	2-Hydroxyglutarate
5-FU	5-Flurouracil
a-KG	Alpha-ketoglutarate
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC0-12h	Area under the concentration x time curve from Oto 12 h
BCRP	Breast cancer resistance protein
BID	Twice daily
BUN	Blood urea nitrogen
CxDx	Cycle X, Day X
CI	Confidence interval
CIMP	Cytosine-guanine dinucleotide island methylator phenotype
Cmax	Maximum concentration
CpG	Cytosine-guanine dinucleotide
CO2	Carbon dioxide
CR	Complete response
CRA	Clinical Research Associate
CSR	Clinical study report
CT	Computed tomography
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DME	Drug-metabolizing enzyme

Abbreviation	Definition
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EQT	End of treatment
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
HBV,HCV	Hepatitis (B/C) virus
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IDH, IDHI, IDH2	Isocitrate dehydrogenase protein, 1, 2
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
mSV	Millisievert
MTD	Maximum tolerated dose
NCICTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PAS	Pharmacokinetic analysis set
PD	Pharmacodynamic
PFS	Progression-free survival

Abbreviation	Definition
PFS6	Progression-free survival at six months
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PPS	Per protocol set
PR	Partial response
PS	Performance status
QD	Once daily
QTcB, QTcF	Heart-rate corrected QT interval (using Bazett's /Fridericia's formula)
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SD	Stable disease
	Elimination half-life
TEAE	Treatment-emergent adverse event
TIS	Tumor inflamed signature
TTR	Time to response
ULN	Upper limit of normal

ii. **Protocol Summary**

Title	Phase II study of IDHl inhibitor ivosidenib and nivolumab in IDHl mutant gliomas and advanced solid tumors
Short Title	Phase II of ivosidenib (AG-120) with nivolumab in IDHl mutant tumors
Protocol Number	HCC 19-096 / CA209-8U3
Phase	Phase II
Methodology	Interventional trial comparing response and progression-free survival to historical data Treatment groups: advanced solid tumor and select gliomas harboring an IDHl mutation
Estimated Enrollment Period	12 months
Estimated Study Duration	36 months
Study Centers	The UPMC Hillman Cancer Center and Memorial Sloan-Kettering Cancer Center
Primary Objective	• To describe the clinical response and six month progression-free survival of patients treated with ivosidenib in combination with nivolumab
Secondary Objectives	• To determine the safety of ivosidenib in combination with nivolumab • To summarize longitudinal clinical outcomes of patients treated with ivosidenib in combination with nivolumab
Exploratory Objective	• To evaluate biomaterial-based biomarkers and determine their association with treatment response

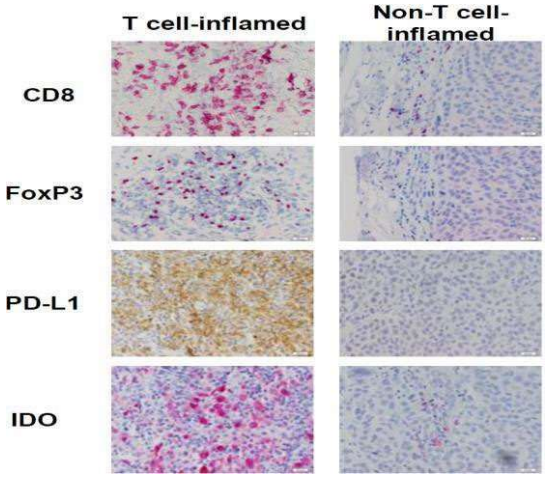
Primary Endpoints	• **Response** ▪ Advanced Solid Tumors: Best overall response by RECIST 1.1 as detailed in (Section 11.8) 8 weeks after the initiation of treatment ▪ Glioma: Best overall Response by Response Assessment in Neuro-Oncology (RANO), Criteria as detailed in (Section 11.9) 8 weeks after the initiation of treatment • **Six Month Progression-Free Survival (PFSG)** ▪ All tumor types: Survival to six months aftter the initiation of treatment without objective tumor progression
Secondary Endpoints	• The occurrence of dose-limiting toxicity (DLT), as defined in Section 7.5, in patients receiving ivosidenib plus nivolumab. • Adverse Events and Serious Adverse Events related to study treatment (per CTCAE vS.0) • Progression-free Survival (PFS) - Survival after the initiation of treatment without objective tumor progression up until 18 months after the last participant has initiated treatment
Exploratory Endpoints	• Biomarker Studies - quantitative measures of response biomarkers by Nanostring assay (or other available technologies at the time of analysis)

Number of Participants	Eighteen in the first stage and seventeen in the second stage, for a maximum of 35 patients
Investigational Product	Ivosidenib, Nivolumab, route of administration: intravenous (IV) and oral (po), respectively
Estimated average treatment duration per patient	6 months
Duration of Participation	Up to 2 years
Reference therapies	Ivosidenib or Nivolumab
Statistical Methodology	An optimal Simon two-stage design is employed, where the primary endpoint is a composite of response (RANO for glioma patients or RECIST for solid tumor patients) and PFS6. Dose-limiting toxicity (DLT) is monitored throughout the trial using a Bayesian beta-binomial model. In secondary objectives, adverse events, response over time and progression-free survival are assessed. In exploratory objectives, the relationship between baseline biomarkers and response are described.
Safety Evaluations	Physical examination and ECOG performance status, vital signs, safety laboratory assessments (Hematology, chemistry, thyroid studies, pregnancy test (all women of child-bearing potential [WOCBP]) must have a negative pregnancy test to be eligible. Pregnancy testing to be done every 4 ± 1 weeks while on study treatment), AEs.
Data and Safety Monitoring Plan	Investigator/sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, serious adverse events, participant safety issues, recruitment issues, accrual, protocol deviations, unanticipated problems, breaches of confidentiality Minutes of the disease center DSMB meetings are available to those who are unable to attend in person. A formal, sequential decision rule based on dose-limiting toxicity will be evaluated after every five participants have completed Cycle 1.

1.0 Introduction and Study Rationale

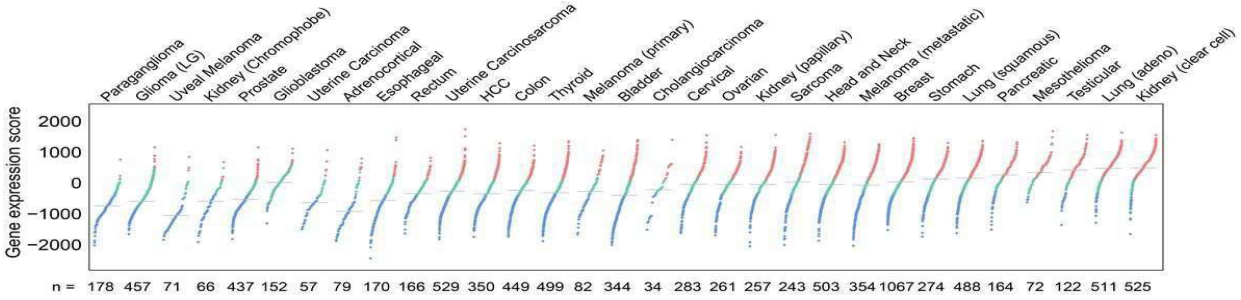
1.1 The T-Cell InflamedMicroenvironment

The T cell-inflamed tumor microenvironment has been described as a potential predictive biomarker for response to multiple immunotherapies including therapeutic vaccines, anti-cytotoxic T-lymphocyte-associated protein (CTLA}-4, and anti-programmed cell death protein 1 (PD-1}/PD-1 ligand 1 (PD-Ll} antibodies (Harlin, Meng et al. 2009, Gajewski, Louahed et al. 2010, Ji, Chasalow et al. 2012, Topalian, Hodi et al. 2012, Gajewski, Woo et al. 2013, Spranger, Spaapen et al. 2013). Analysis of the tumor microenvironment in patients with melanoma suggests that approximately 35-50% of cases show evidence of spontaneous priming of anti-tumor T cells, leading to migration of CD8+ effector T cells into tumor sites. This phenotype has been designated the T cell-inflamed tumor microenvironment and is characterized by expression of T cell markers, chemokines for T cell recruitment, and transcripts indicative of type I interferon (IFN) signaling (Harlin, Meng et al. 2009, Gajewski, Louahed et al. 2010, Gajewski, Woo et al. 2013} **(Figure 1}.**



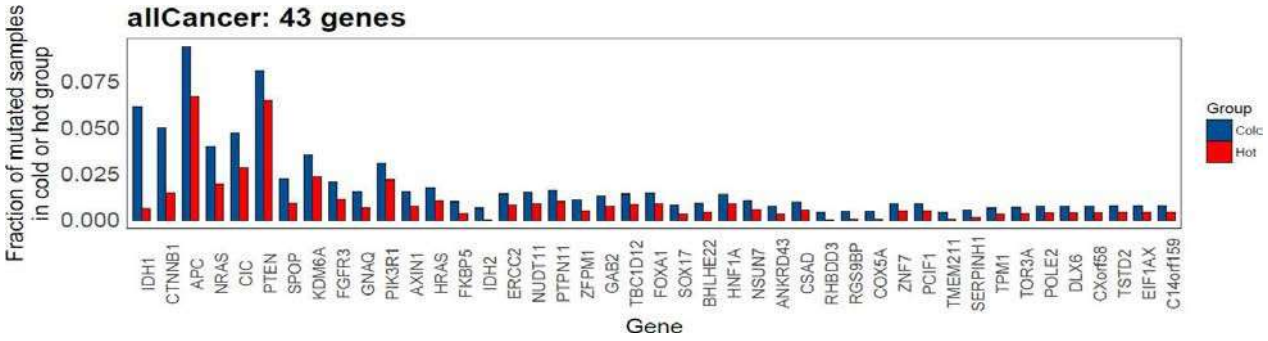
This phenotype may be most robustly predicted using gene expression profiling, which in addition to response prediction, may also potentially be useful in identifying those that will not respond. Patients harboring non-inflamed tumors may require treatment strategies which modulate the immune response to facilitate the influx of tumor infiltrating lymphocytes (TIL} and conversion from a non-inflamed to an inflamed tumor.

We have recently expanded this analysis of the T cell-inflamed tumor microenvironment to all tumor types via analysis of The Cancer Genome Atlas (TCGA) identifying subsets of inflamed and non-inflamed tumors across all histologies (Spranger, Luke et al. 2016) **(Figure 2).**

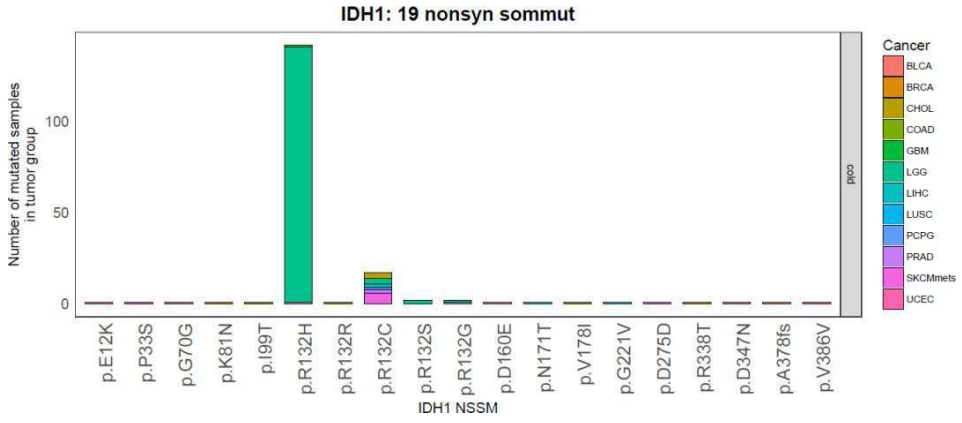


Additionally, our group was the first to identify tumor-intrinsic oncogene signaling pathways mediating immune exclusion and resistance to cancer immunotherapy. In a disease-specific fashion, we have identified WNT/ -catenin signaling (Spranger, Bao et al. 2015} and phosphatase and tensin homolog (PTEN) loss in melanoma as well as fibroblast growth factor receptor 3 (FGFR3} activation in urothelial bladder cancer (Sweis, Spranger et al. 2016). To more broadly assess the impact of oncogene signaling

pathways on immune exclusion, we recently separated all solid tumors of TCGA into T cell-inflamed and non-T cell-inflamed and looked for somatic alterations associated with the non-T cell-inflamed phenotype. Utilizing a cut off of at least a 10-sample difference for mutations between non-T cell-inflamed and T cell-inflamed, we identified isocitrate dehydrogenase 1 (IDHI) as having the most powerful association with non-inflamed tumors (while IDH2 also showed a less powerful association, **Figure 3).**



These IDHI alterations were present across tumor histologies with the vast majority being identified as R132H and minority of R132C **(Figure 4).** While glioma was the most highly represented tumor type others included breast cancer, cholangiocarcinoma, melanoma and other tumor types described previously to harbor IDHI alterations. This suggests that IDHI alterations may have a pan-cancer effect in driving immune exclusion.

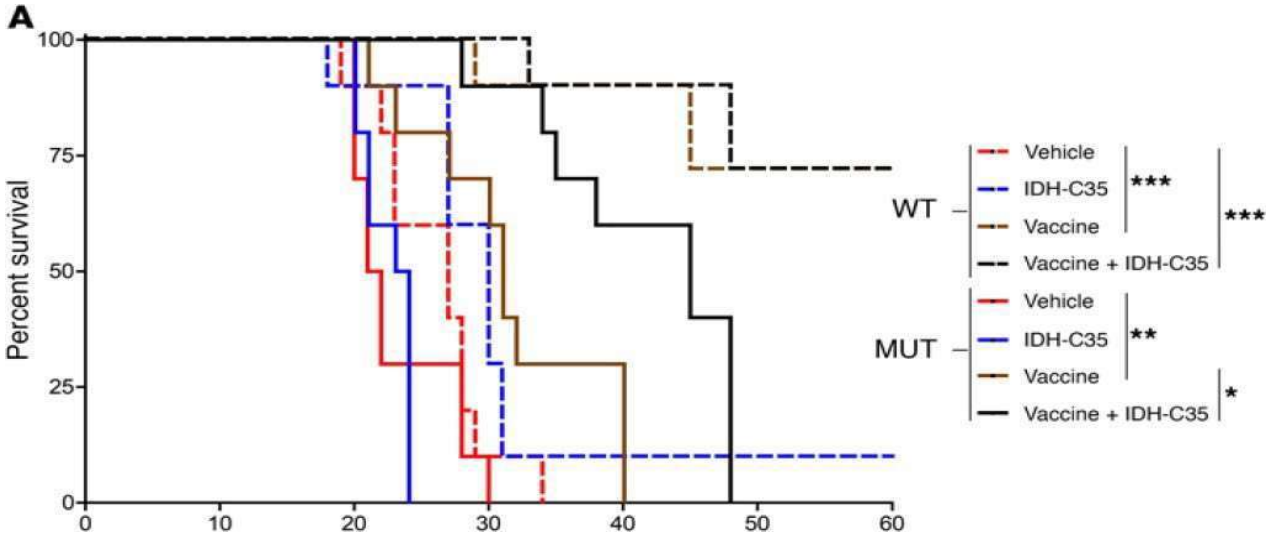


1.2 Study Rationale

While PDI-blocking immunotherapy has rapidly changed the landscape of cancer treatment, most patients do not benefit from this therapy. This is particularly evident for certain cancers that generally display the non-T cell-inflamed tumor microenvironment: gliomas, breast cancers and gastrointestinal cancers such as cholangiocarcinomas, among others. Our data suggest that aberrant IDH activity may play a role in in limiting the efficacy of immunotherapy and data from other groups appear to collaborate this finding. A previous study (Kohanbash, Carrera et al. 2017) described a role for mutant IDH in mediating immune exclusion in human glioma samples and recapitulated this effect in an IDH

mutant syngeneic mouse model. Mutations in IDH confer gain-of-function activity by converting a-ketoglutarate to the oncometabolite R-2-hydroxyglutarate, which coordinates epigenetic changes that promote malignant transformation (Dang, White et al. 2009).

Gene expression profiling of gliomas revealed reduced expression of T cell-associated genes and IFN-y-inducible cytokines in the IDH-mutated gliomas compared to gliomas with wild-type IDH. Mice possessing gliomas with mutated IDH recapitulated the immunophenotype of human IDH-mutated gliomas and demonstrated poor CD8 T cell infiltration. R-2-hydroxyglutarate limited intra-tumoral production of chemokines CXCL9 and CXCLl0, resulting in decreased T cell recruitment into IDH-mutated gliomas (Kohanbash, Carrera et al. 2017).
Finally, a selective inhibitor that blocks the ability of mutated IDH-1 to produce the oncometabolite R-2-hydroxyglutarate restored chemokine expression, promoted T cell infiltration, and increased the efficacy of therapeutic peptide vaccination against gliomas **(Figure S)** (Dang, White et al. 2009).



Thus, inhibitors of mutant IDH are potential therapeutic candidates to reverse immune evasion in gliomas and potentially other tumor types. Collectively, these data indicate that it might be possible to therapeutically target mutant IDH1 within a non-inflamed tumor to re-engage anti-tumor immune defenses and potentially drive combinatorial benefit with anti-PD1 immunotherapy.

Ivosidenib is a novel, first-in-class compound targeted selectively to inhibit the mutated IDH1 enzyme. Small molecule inhibition of the mutant IDH enzyme represents a novel, targeted approach to cancer treatment. Direct inhibition of the gain-of-function activity of the IDH1 mutated protein is intended to inhibit the production of the oncogenic metabolite 2-HG. Ivosidenib has been extensively evaluated in nonclinical studies and has been shown in vitro and in vivo to effectively inhibit the gain-of-function activity of the mutated protein leading to> 95% inhibition of the production of the potential oncometabolite 2-HG. In clinical studies, up to 98% inhibition of plasma 2-HG has been observed in participants with solid tumors after QD dosing of ivosidenib.

Here, we propose a Phase II study of the IDH1 inhibitor ivosidenib and nivolumab in IDH1 mutant gliomas and advanced solid tumors to assess toxicity and assess the preliminary activity of this combination regimen. We hypothesize that safe doses will be observed for ivosidenib with nivolumab

and that a higher overall response rate and improved progression free survival relative to historical controls will be seen. Within this study we will integrate detailed immune monitoring, genomic profiling of the tumor, and systemic immune response. This study will lay the groundwork for potential subsequent randomized studies and has the potential to improve outcomes for a high-need patient population through expanding the utility of cancer immunotherapy.

1.2.1 Rationale for Primary Endpoint

The primary objectives are detailed in section 2.

In addition to safety, we propose the two co-primary endpoints of Response Evaluation Criteria in Solid Tumors (RECIST) or RANO Criteria for gliomas and six month progression-free survival (PFS). First, we propose response as an endpoint based on the low historical response rates seen in the proposed tumor histologies. The benefits of anti- PDl therapy, despite their advances across multiple cancers, have not appreciably advanced the field for many advanced solid tumors- including those enriched with IDHl mutations. In prior analyses of such tumor types, poor response rates correlated with a failure to improve overall survival (OS). For example, in the Phase lll Checkmate 143 study of nivolumab in glioblastoma (GBM), the noted response rate of 8% failed to show a survival benefit (Filley, Henriquez et al. 2017). Additionally, in breast cancer, the ORR was< 5% in those treated with avelumab anti-PDLl therapy (Dirix, Takacs et al. 2018). Within GI malignancies, trials assessing outcomes of cholangiocarcinoma and anti-PDl combinations are accruing; however, outcomes for other mismatch-repair proficient GI malignancies have been poor and expectations are guarded - the ORR was 0% in mismatch-repair proficient colorectal cancer when treated with pembrolizumab (Le, Uram et al. 2015).

We additionally propose the co-primary endpoint of six-month PFS. This is based on the concern that response alone may not adequately capture the clinical benefit the study treatments within certain tumor histologies. It has been recognized in the treatment of soft tissue sarcomas that tumors responding to therapy may be replaced with fibrotic tissue that can confound RECIST measurements (Verweij 2008). Additionally, in the Phase 1 study of ivosidenib in chondrosarcoma, a majority of patients achieved stable disease as their best overall response. This suggests a possible cytostatic effect of ivosidenib (Tap, et al. 2016) where RECIST response may not reflect the therapeutic effect of the study treatments. Given the heterogeneity of the tumor histologies involved, it is difficult to know if ivosidenib would have similar cytostatic effect across all tumor types - especially when combined with nivolumab. PFS has the potential to capture the benefit of the study treatments across these tumor types since the most commonly IDHl mutant tumors included have a PFS of< 4 months. This is based the following historical controls:

- **Cholangiocarcinoma:** A median PFS of 3.2 months (Brieau, Dahan et al. 2015)
- **Advanced Chondrosarcoma:** A median PFS of 3.5 months (Italiano, Le Cesne et al. 2013)
- **Enhancing glioma:** median duration on ivosidenib or AG-881 treatment of 1.9-3 months (Mellinghoff, Gregory Cote et al. 2016, Mellinghoff, Penas-Prado et al. 2018)

This study has selected diverse, aggressive tumor histologies unified by their low anticipated PFS. With this in mind, we see that the proposed a doubling of expected PFS to 6 months with combination ivosidenib and nivolumab to be a meaningful measure of the efficacy of these drugs.

1.3 Cellular Metabolism and Cancer

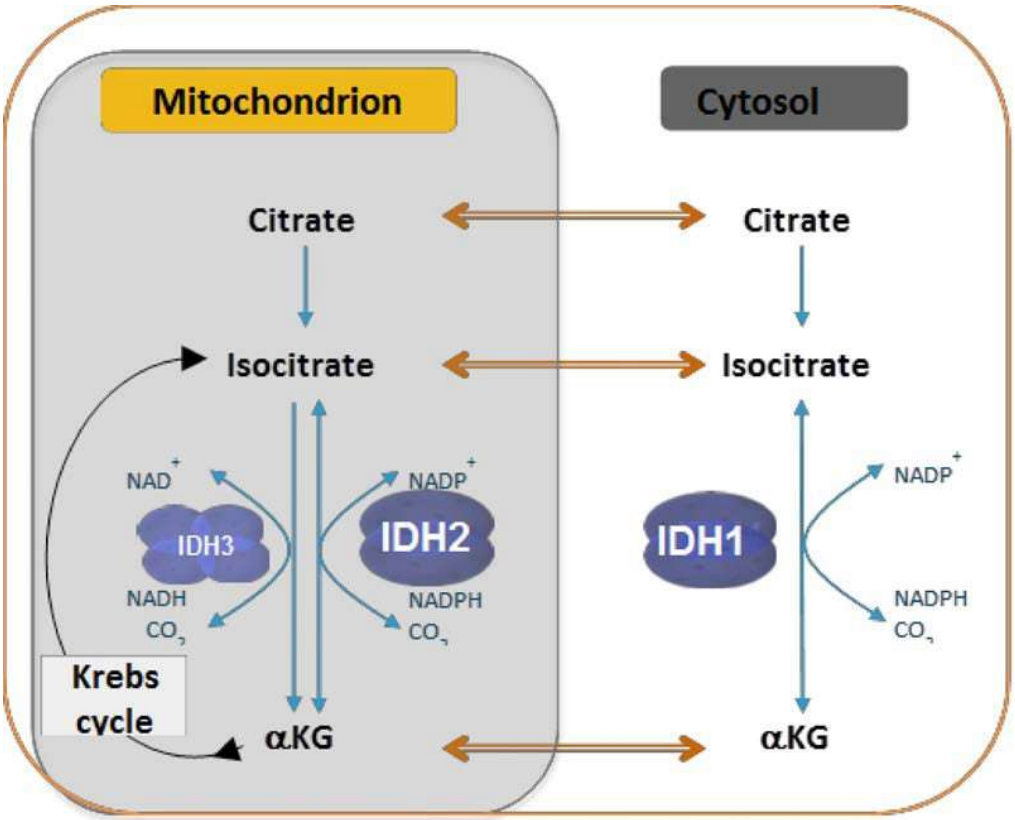
1.3.1 Role of Isocitrate Dehydrogenase

The IDH proteins are critical metabolic enzymes that exist as three isoforms: IDHI, IDH2, and IDH3 (Figure 1), which all catalyze the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO2) and alpha-ketoglutarate (a-KG). IDHI and IDH2 produce adenine dinucleotide phosphate (NADPH) whereas IDH3 only produces NADH.

Cancer-associated mutations have been identified in IDHI and IDH2; however, to date, no mutations have been described in IDH3 (Yen, Bittinger et al. 2010). One fundamental difference between IDHI and IDH2 is the subcellular localization of the two proteins. IDHI is localized in both peroxisomes and cytosol (Geisbrecht and Gould 1999, Yoshihara, Hamamoto et al. 2001). IDH2 is a mitochondrial isoform of IDH (Yoshihara, Hamamoto et al. 2001, Wang, Travins et al. 2013).

The genes encoding *IDHI* and *IDH2* are located on chromosome 2q33.3 and 15q26.1, respectively. Mutations in these IDH proteins most commonly lead to alterations affecting arginine-132 (R132H or R132C) in IDHI, and the analogous arginine residue (arginine-172 mutated to lysine [R172K]) or arginine-140 (R140Q) in IDH2.

Figure 6: Citric Acid Cycle



1.3.2 Tumorigenesis Hypothesis

Mutant IDH1 and IDH2 are not catalytically inactive enzymes, but rather possess novel enzymatic activities, consistent with a gain-of-function, reconciling the heterozygous nature of the point mutations (Dang, White et al. 2009). The mutated proteins themselves have a gain-of-function, neomorphic activity, catalyzing the reduction of a-KG to 2-hydroxyglutarate (2-HG) (Dang, White et al. 2009). The Sponsor's studies established that purified mutant protein efficiently catalyzes the proposed reduction of a-KG to 2-HG, while being unable to synthesize isocitrate (Dang, White et al. 2009). Mutations in IDH1 and IDH2 are almost always mutually exclusive and occur at very early stages of tumor development suggesting that they promote formation and progression of tumors (Welch, Ley et al. 2012).

Evidence supports that cancer-associated IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal production of 2-HG, a potential oncometabolite. High levels of 2-HG have been shown to inhibit a-KG-dependent dioxygenases including histone and deoxyribonucleotide demethylases, which play a key role in regulating the epigenetic state of cells (Chowdhury, Yeah et al. 2011, Xu, Yang et al. 2011, Koivunen, Lee et al. 2012). Consistent with 2-HG promoting tumorigenesis via an effect on chromatin structure, patients with IDH mutations display a cytosine-guanine dinucleotide (CpG) island methylator phenotype (CIMP) and several studies have shown that overexpression of IDH mutant enzymes can induce histone and deoxyribonucleic acid (DNA) hypermethylation as well as impair normal cellular differentiation (Figueroa, Abdel-Wahab et al. 2010, Lu, Ward et al. 2012, Turcan, Rohle et al. 2012).

Clinical studies of several tumor types including glioma and acute myelogenous leukemia (AML) have found elevated levels of 2-HG in cells with mutant IDH1 and IDH2 compared to cells with wild-type alleles (Gross, Cairns et al. 2010, Ward, Patel et al. 2010). In normal cells, 2-HG is present in low levels. However, IDH1/IDH2 mutations in cancer cells result in the excess accumulation of 2-HG to extremely high levels, which can alter a number of downstream cellular activities. The elevated levels of 2-HG also are present in the sera and urine of some affected patients. Efforts are underway in the ongoing Phase 1 study (AG120-C-002) to explore the association of plasma and tissue 2-HG with underlying tumor burden and tumor response in cholangiocarcinoma, enhancing glioma and other solid tumors.

1.3.3 IDH Mutations in Gliomas and Solid Tumors

IDH1 mutations continue to be identified in a variety of solid tumor subtypes, including gliomas, chondrosarcomas, and intrahepatic cholangiocarcinomas. Mutations in IDH1 have been found in approximately 70% of Grade 2 to 3 gliomas (Yan, Parsons et al. 2009), 50% of chondrosarcomas (Amary, Bacsi et al. 2011), and 20% of intrahepatic cholangiocarcinomas (Borger, Tanabe et al. 2012) and a smaller percentage of extra-hepatic cholangiocarcinomas (Kipp, Voss et al. 2012).

IDH1 mutations are found in a high percentage of low-grade (Grade 2/3) oligodendrogliomas and astrocytomas as well as secondary glioblastomas. IDH2 mutations occur less frequently. IDHI mutations occur early in gliomagenesis and are oncogenic, although the exact mechanism for this is unclear. In addition, IDH mutations lead to increased methylation in gliomas. Gliomas with IDH1 and IDH2 mutations also have a better prognosis than gliomas with IDH WT (Cohen, Holmen et al. 2013).

IDH1 mutations are relevant therapeutic targets in cholangiocarcinoma as they may play a role in the pathogenesis of the disease by blocking the differentiation of liver progenitor cells and promoting cellular proliferation (Saha, Parachoniak et al. 2014). The majority of available data suggest IDH1

mutations are not associated with prognosis in cholangiocarcinoma unlike IDHl mutations in glioma, which are associated with improved outcomes (Goyal, Govindan et al. 2015).

1.3.4 Biomarker Research

As described in Section 2.1, the T cell-inflamed phenotype is a potential predictive biomarker for response to immunotherapies. In addition to response prediction, this gene signature is also potentially useful in identifying those that will not respond. Patients harboring non-T cell-inflamed tumors therefore require treatment strategies which may modulate the immune response to facilitate the influx of tumor infiltrating lymphocytes (TIL) with the intent to convert from a non-T cell-inflamed to a T cell-inflamed tumor. Beyond the tumor microenvironment, aspects of the host (patient) may also have an essential impact on immunity in response to immunotherapy. Host factors of interest regarding the immune response include circulating immune subsets in the peripheral blood.

Further, evolving research in the presence circulating tumor DNA (ctDNA) have shown this to be a potentially predictive biomarker for patients undergoing anti-PDl therapy (Lee, Long et al. 2017). Given that all patients included in this study harbor a known IDHl mutation, this allows for circulating IDHl mutated ctDNA to be followed before and during therapy. As has been seen in melanoma patients followed for known mutations, changes in ctDNA on therapy can predict tumor response and PFS. Considering this background, we propose to collect peripheral blood for plasma, peripheral blood mononuclear cells, ctDNA and serum levels of 2-HG. Additionally, for at least the first 10 solid tumor patients we propose an analysis of baseline tumor tissue, and an additional tissue analysis at week 5 of therapy to assess changes in tumor microenvironment.

Additionally, it is requested that any patients who undergo tumor biopsy as part of their standard care during the study have any available tissue forwarded for analysis in comparison of pre-administration and on-/post-treatment tumor microenvironmental factors.

1.4 Ivosidenib

1.4.1 Overview

Ivosidenib is a potent and selective inhibitor of the IDHl mutant protein with no significant off-target activity observed. The compound has been demonstrated to reduce 2-HG levels by> 95%, to reverse growth factor-independent growth *in vitro,* and to induce differentiation in leukemia cell models. Clinical data in patients with advanced hematologic malignancies harboring an IDHl mutation (AG120-C-001) and with advanced solid tumors harboring an IDHl mutation (AG120-C-002) have shown the compound to be well tolerated at total daily doses up to 1200 mg with clinical activity observed in both solid and liquid tumors. The 500 mg dose level of ivosidenib was expanded and selected for future studies based on the available pharmacokinetic (PK)/pharmacodynamic (PD), safety profile, and preliminary clinical activity observed. In 2018, ivosidenib was approved by the US Food and Drug Administration (FDA) for the treatment of patients with relapsed refractory AML with and IDHl mutation.

1.4.2 Summary of Nonclinical Information

Details of the nonclinical development program for ivosidenib are provided in the Investigator's Brochure. A summary of the key information is provided below.

1.4.2.1 PK Drug Interactions

In vitro studies showed that ivosidenib is predominantly metabolized by cytochrome P450 3A4 (CYP3A4) and, therefore, co-administration with inhibitors or inducers of CYP3A4 has the potential to affect ivosidenib exposure. Co-administration of 250 mg ivosidenib with a strong CYP3A4 inhibitor itraconazole) increased single-dose AUC of ivosidenib by 169% with no change in Cmax- Based on physiologically based PK (PBPK) simulations, co-administration with ivosidenib and a strong CYP3A4 inhibitor (itraconazole) or moderate CYP3A4 inhibitor (fluconazole) is predicted to increase ivosidenib steady-state Cmax by up to 52% and AUC by up to 90%. Increased ivosidenib plasma concentrations may increase the risk of QTc interval prolongation.

Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with ivosidenib. If concomitant use of strong or moderate CYP3A4 inhibitors (eg, strong inhibitors such as: posaconazole, voriconazole, itraconazole, erythromycin, clarithromycin, and moderate inhibitors such as: fluconazole, erythromycin, isavuconazole, diltiazem, and grapefruit juice) is unavoidable, monitor participants for increased risk of QTc interval prolongation (refer to Section 6.4 for QTcF risk management and the monitoring plan in ivosidenib protocols). Based on a PBPK simulation, coadministration of ivosidenib with a strong CYP3A4 inducer (rifampin) is predicted to decrease ivosidenib steady-state AUC by 33% and Cmaxby 19%. Avoid coadministration of strong CYP3A4 inducers with ivosidenib.

Ivosidenib is an inducer of CYP3A4 and may also induce CYP2B6, CYP2C8, and CYP2C9. Coadministration of ivosidenib with narrow therapeutic index drugs that are extensively metabolized by CYP3A4 (eg, cyclosporine, fentanyl, everolimus, tacrolimus, sirolimus) or CYP2C9 (eg, phenytoin, warfarin) may result in decreased concentrations of these drugs. Investigators should consider alternative therapies that are not sensitive substrates of CYP3A4 or CYP2C9 during treatment with ivosidenib. Participants should be monitored for loss of therapeutic effect of these medications if coadministration with ivosidenib cannot be avoided.

International normalized ratio (INR) levels should be monitored more frequently in participants receiving warfarin (a CYP2C9 substrate) during initiation or discontinuation of ivosidenib.
Ivosidenib is a weak direct inhibitor of CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 with ICsovalues > 50 µM and shows little or no evidence of direct inhibition of CYP1A2, CYP2B6, or CYP2C9. Ivosidenib did not show time- or metabolism-dependent inhibition of any of the CYP enzymes evaluated and therefore, the likelihood of inhibition of CYP enzymes by ivosidenib is extremely low.

Ivosidenib is a substrate for P-glycoprotein (P-gp), but not for BCRP or hepatic transporters OATP1B1 and OATP1B3. Ivosidenib does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, and OCT2 at clinically relevant concentrations. Ivosidenib is an inhibitor of OAT3. A PBPK simulation predicted an increase (<30%) in the AUC of a sensitive OAT3 substrate, suggesting that the potential for clinically relevant drug interactions due to the inhibition of OAT3 appears to be low.

Ivosidenib does not contain ionizable groups under physiological condition and its aqueous solubility is pH independent. Thus, gastric acid reducing agents (eg, proton pump inhibitors, H2-receptor antagonists, and antacids) do not affect ivosidenib exposure.

Co-administration of ivosidenib may decrease the concentrations of hormonal contraceptives.

1.4.2.2 Safety Pharmacology and Toxicology

The toxicity profile of ivosidenib has been evaluated *in vitro* in the bacterial reverse mutation assay and *in vivo* in Sprague Dawley rats and cynomolgus monkeys. The compound was not mutagenic and was well tolerated at estimated efficacious exposures with a potential 4-fold therapeutic window.

Safety pharmacology

Individual animals with possible (30 ms) and probable (60 ms) test article-related QT prolongation corrected for heart rate using Bazett's formula (QTcB) (Morganroth 2001} have been noted in both the 28-day and 3-month Good Laboratory Practice (GLP) cynomolgus monkey studies at free maximum concentration (Cmax) values 0.7-fold the C2Dl 500 mg free Cmax human exposure (500 mg is the dose selected for the expansion phase of the ongoing Phase 1 clinical trial, Study AG120-C-001). In addition, prolonged QTcB was observed at the 45 and 135 mg/kg dose levels in a non-GLP single dose monkey CV safety pharmacology study, in which group mean Cmaxvalues were similar to that of individual animals in the 28-day and 3-month repeat-dose studies.

Toxicology

In GLP 28-day repeat-dose toxicology studies, oral doses of ivosidenib administered twice daily (BID) at the projected human efficacious exposure were well tolerated by both rats and monkeys. In rats, significant findings at 100 mg·kg-^{1}-day-^{1}were limited to minimal alterations in clinical pathology parameters, liver and thyroid findings consistent with autoinduction of metabolism, and splenic extramedullary hematopoiesis. In monkeys, significant findings at 30 mg·kg-^{1}-day-^{1}were limited to gastrointestinal clinical observations and sporadic emesis. In both species, all significant effects at projected efficacious exposures were reversible over the 14-day recovery period.

In the GLP 28-day rat study, dose-limiting toxicity (DLT) occurred at a dosage of 2000 mg·kg-^{1}-day-^{1}. At this dose level, significantly reduced exposures were observed, from 15-fold the projected efficacious exposure on Day Oto 5.4- to 7.8-fold on Day 27, which were consistent with autoinduction of metabolism. Most of the unscheduled deaths occurred early in the study, between Days 2 and 6, suggesting that these early mortalities were being driven by the higher exposures. The cause of this early DLT was multifactorial and included moderate, bridging, centrilobular hepatocellular degeneration and necrosis with additional contributing factors being tubular necrosis in the kidney; cortical and medullary tubular vacuolation in the kidney; atrophy of small intestines; hypocellularity, hemorrhage and necrosis of the femoral and/or sternal bone marrow; and erosions of the glandular stomach.

When DLT occurred later in the dosing period (the minority of the early mortality), it was due to mucosal atrophy of the intestines, erosions and ulcerations of the glandular stomach and/or rectum, and lymphoid depletion and necrosis in lymphoid organs with renal tubular necrosis being an additional contributing factor. Exposures at this time were likely closer to the Day 27 exposures. The Day 27 ivosidenib area under the concentration x time curve from Oto 12 h (AUCo-12h) value for this dosage was 69500 and 101000 h-g-^{1}-mL-^{1}, in males and females, respectively, which is 1.2- and 1.8-fold the human AUC0-10h, respectively. The next lower dose level tested in rats (500 mg·kg-^{1}-day-^{1}) resulted in an AUC0-12h values of 30100 and 59000 ng·h-^{1}-mL-^{1}in males and females, respectively, which is 0.5- and 1-fold the human AUC0-10h- No early mortality occurred and this exposure level was tolerated. All significant findings at this dose level were reversible.

In the GLP 3-month rat study, ivosidenib was well tolerated at dosage levels of 20, 100, and 500 mg-kg-^{1}·day-^{1}in rats and resulted in no test article-related deaths. Test article-related effects were qualitatively similar at 100 and 500 mg·kg-^{1}-day-^{1}. Most findings had resolved during the 4-week recovery period. At 500 mg·kg-^{1}·day-1,the Day 90 mean plasma AUC0-12h values were 29000 and 62000 ng·h-^{1}-mL-^{1}in males and females, respectively (0.5- and 1.1-fold the human AUCo-1oh value), and at 100 mg·kg-^{1}-day-^{1}were 12100 and 20000, respectively (0.2- and 0.3-fold the human AUC0-1oh value). At 500 mg·kg-^{1}-day-1,the

Day 90 mean plasma Cmaxvalues were 4650 and 9710 ng/ml in males and females, respectively, and at 100 mg·kg-^{1}-day-^{1}were 2770 and 5660 ng/ml, respectively. The Day 90 mean plasma AUC0-12h values at 20 mg-kg-^{1}-day-^{1}were 6880 and 7090 ng·h-^{1}-mL-^{1}in males and females, respectively (0.1-fold the human AUC0-10h value), and the Day 90 mean plasma Cmaxvalues were 1320 and 1580 ng/ml, respectively. The findings observed in the 3-month rat study are largely consistent with those noted at tolerable doses in the 28-day study with the exception of the novel finding of a higher potassium fractional urine excretion.

In the GLP 28-day monkey study, DLT occurred in male monkeys at an AUC0-12h value of 235000 (at a dose of 270 mg·kg-^{1}-day-^{1}), which is 4.1-fold the human AUC0-10h value. The cause of DLT was general malaise characterized by poor body condition and gastrointestinal clinical signs leading to emesis and secondary aspiration. In females at the same dose level, ivosidenib was tolerated and the Day 27 AUC0-12h value was 109000 ng·h-^{1}-mL-^{1}, which is 1.9-fold the human AUC0-10h value. The dosage of 270 mg·kg-^{1}·day-^{1}was associated with significant weight loss and moribundity; higher total, direct, and indirect bilirubin and triglycerides; lower hemoglobin and hematocrit values; lower phosphorous levels; lower albumin and total protein; higher mean specific gravity and lower total urine volume; ventricular bigeminy; prolonged QTcB in females; higher liver weights; and hepatocellular hypertrophy. All significant findings were reversible following the recovery period, with the exception of the cardiovascular findings, for which recovery was not assessed because the affected animals were assigned to the primary necropsy.

In the GLP 3-month monkey study, ivosidenib at dosage levels of 30, 90, and 180 mg·kg-^{1}-day-^{1}for up to 92 consecutive days was well tolerated at all dosage levels and resulted in no test article-related deaths. Test article-related effects included diarrhea in males at 30 mg-kg-^{1}-day-^{1}and females at 180 mg·kg-^{1}·day-1,and hepatocellular hypertrophy and higher liver weights at 30 mg·kg-^{1}-day-^{1}. Likely test article-related prolongations of QTcB were noted in individual animals in the 90 and 180 mg-kg-^{1}-day-^{1}dose groups at free Cmax exposure margins 1.3-fold that of the human 500 mg Cmax value. All test article-related changes resolved during the recovery period. The 180 mg·kg-^{1}-day-^{1}dose level was associated with gender combined Day 90 mean plasma Cmax and AUC0-12h values of 14800 ng/ml and 134000 ng·h-^{1}-mL-^{1}, respectively (2.3-fold the human AUC0-10h value). The findings observed in the 3-month monkey study are largely consistent with those noted at tolerable doses in the 28-day study.

1.4.3 Summary of Clinical Data

The ivosidenib clinical development program was initiated in March 2014 with two Phase 1 dose escalation studies, AG120-C-001 and AG120-C-002. Refer to the Investigator's Brochure for further details on each of these studies.

1.4.3.1 Study AG120-C-002

Study AG120-C-002 is evaluating the safety, PK, PD biomarker patterns, and clinical activity of ivosidenib in participants with advanced solid tumors, including cholangiocarcinoma, with an IDHI

mutation. The primary objectives of the study are to assess the safety and tolerability of treatment with ivosidenib administered daily as a single agent dosed orally in participants with advanced solid tumors, including glioma, and to determine the maximum tolerated dose(s) (MTD[s]) and/or the recommended Phase 2 dose(s) of ivosidenib in this population. The initial dosing regimen was 100 mg BID and doses up to 1200 mg once daily (QD) were assessed in a 3+3 dose escalation design; based on the favorable PK profile showing a long elimination half-life (t½), BID dosing was discontinued after the first cohort and a QD dosing regimen was implemented. The study is divided into a dose escalation phase, followed by an expansion phase to allow for a more robust evaluation of the safety profile and preliminary assessment of clinical activity. This study is currently ongoing.

Efficacy data for Study AG120-C-002 were analyzed separately based on the underlying disease and specific response criteria, including Response Evaluation Criteria in Solid Tumors (RECIST), Response Assessment in Neuro-Oncology (RANO), Response Assessment in Neuro-Oncology for low grade glioma (RANO-LGG): cholangiocarcinoma, chondrosarcoma, or glioma. As of March 10, 2017, 73 participants with cholangiocarcinoma received ivosidenib in the dose escalation and expansion cohorts, with 62 participants receiving ivosidenib at 500 mg QD. Overall, 5% (n=4) experienced a confirmed partial response and 56% (n=41) experienced stable disease.

The 6-month PFS rate was 38.5% and the 12-month PFS rate was 21% (Lowery, Abou-Alfa et al. 2017). As of September 23, 2016, 21 participants with chondrosarcoma had been treated with ivosidenib and 20 were efficacy-evaluable. Eleven (55%) participants experienced stable disease as their best overall response; the remaining participants experienced disease progression (30%) or were not assessed (15%). The 3-month PFS rate was 58% with a median ivosidenib treatment duration of 2.6 months (range, 0 to 24 months) (Tap, et al. 2016).

As of May 12, 2017, 66 participants with glioma had been treated with ivosidenib and enrollment of this subset was complete; of these participants, 35 had non-enhancing glioma. Two of these 35 participants (6%) had a minor response according to RANO-LGG. Twenty-nine (83%) participants had stable disease and 4 (11%) had progressive disease as their best response; the median treatment duration for non-enhancing glioma was 16 months with 63% of participants being treated for ;?:1 year. Volumetric analysis (conducted centrally) demonstrated stabilization or a decrease in tumor growth rate compared to the pretreatment rate in glioma participants with non-enhancing disease receiving ivosidenib (Mellinghoff and Gilbertson 2017).

Treatment with ivosidenib has been well tolerated; no DLTs have been reported. Overall, 101 (83%) of 122 participants have reported treatment-emergent AEs (TEAEs). To date, the most commonly reported AEs have been nausea (20%), fatigue (12%), diarrhea, (11%), prolonged QT interval (10%), and vomiting (10%). There was no evidence for an increase in the incidence of these commonly reported events with dose.

Two deaths within 30 days of study treatment termination have been reported in the 400 mg dose cohort. One was due to anemia and the other occurred due to acute respiratory failure. Both deaths were assessed as unrelated to study treatment. A total of 20 (16%) of the 122 participants have experienced serious AEs (SAEs). No individual SAE was reported in more than 1 participant, and none of these SAEs were assessed to be related to ivosidenib. The only SAE experienced by more than one participant was headache (2 participants, 2%); additional SAEs were reported in 1

participant each. Only an event of supraventricular extrasystoles was assessed as possibly related to study treatment.

Preliminary analysis of PK data at the 100 mg BID and, 300, 400, 500, 600, 800, 900, and 1200 mg QD dose levels demonstrated excellent oral ivosidenib exposure that on Cycle 1, Day 15 (C1D15) and Cycle 2, Day 1 (C2DI) was above the predicted efficacious exposure of 12.9 h·µg-1-mL-1 that was associated with 97% tumor 2-HG inhibition (direct IDHI pathway inhibition PD biomarker) in nonclinical models; meant½was from 38.4 to 86.2 h, which enables a QD oral dosing schedule. Evaluation of 2-HG as a direct inhibition of the IDHI pathway PD biomarker response following ivosidenib dosing in the 100 mg BID and 300, 400, 500, 600, 800, 900, and 1200 mg QD dose cohorts demonstrated sustained reduction in 2-HG plasma levels (up to 100% inhibition) by C2DI at all dose levels.

As of April 14, 2016, 48 participants with cholangiocarcinoma have been treated, including 24 participants in the dose escalation phase and 24 in the expansion phase. At the time of the data cutoff, 23 of the 48 participants remain on treatment and 25 have discontinued {19 due to disease progression and 2 each due to AE, withdrawal of consent, and other reasons). The overall safety profile of ivosidenib remains consistent with that reported in the most recent Investigator's Brochure. Of the 48 cholangiocarcinoma participants, 38 were evaluable for the analysis of efficacy (ie, had a baseline tumor measurement and at least 1 post-baseline response assessment or discontinued earlier).

Three participants {8%) with cholangiocarcinoma receiving ivosidenib (1 at 300 mg and 2 at 500 mg) had an objective partial response, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) vl.1 (Appendix 11.8). In addition, 22 participants {58%) had stable disease (SD), and 11 participants {29%) experienced disease progression as best response. Two participants {8%) were not assessed for response (discontinued treatment prior to a response assessment). At the 6-month time point, 60% of participants were progression free (PFS6) as assessed by the Kaplan-Meier method. As of the data cutoff, three participants remained on study drug> 1 year with an overall best response of SD.

There were no dose limiting toxicities. Based on the available PK (suggesting less than dose proportional increase in exposure beyond 500 mg and maximal plasma 2-HG suppression at 500 mg) and following review of data from the dose escalation phase of this study, ivosidenib 500 mg QD was determined to be a safe and potentially effective dose for further study.

1.4.3.2 Study AG120-C-001

Study AG120-C-001 is evaluating the safety, PK, PD biomarker patterns, and clinical activity of ivosidenib in participants with advanced AML and related hematologic malignancies that harbor an IDHI mutation. The primary objectives of the study are to assess the safety and tolerability of treatment with ivosidenib administered daily in participants with advanced hematologic malignancies, to determine the MTD and/or the recommended Phase 2 dose of ivosidenib in this population, and to assess the preliminary clinical activity of ivosidenib in participants with relapsed or refractory AML with an IDHI mutation. The initial dosing regimen was BID; based on the favorable PK profile showing a long t½, BID dosing was discontinued after the first cohort and a QD dosing regimen was implemented. Similar to the AG120-C-002 study, this study is divided into a dose escalation phase, followed by an expansion phase to allow for a more robust evaluation of the safety profile and preliminary assessment of clinical activity. This study is currently ongoing and has served as the basis for the 2018 FDA approval of ivosidenib in relapsed refractory AML. A summary of the data from this study is provided in the Investigator's Brochure for

ivosidenib.

1.5 Identified Risks of Ivosidenib

A summary of AEs reported in> 10% of participants overall is presented in Table 25 of the Investigator's Brochure. As of January 16, 2019, 165 (98.2%) of the 168 participants had reported at least one AE. The most commonly reported AEs (> 20% of participants) across all 168 participants were fatigue (33.9%), nausea (29.2%), diarrhea (26.2%), and vomiting (20.2%).

AEs of Grade 3 in severity have been reported in 59 (35.1%) of the 168 participants as of the data cutoff date. Grade 3 AEs reported in> 2 participants included ascites, hyponatremia, and hypophosphatasemia (five participants each); anemia (four participants); and abdominal pain, headache, hyperglycemia, and pulmonary embolism (three participants each).

As of the data cutoff date, AEs leading to discontinuation of study treatment were reported for two participants (cystitis and hyponatremia in one participant and hydronephrosis in the other). All events leading to discontinuation were assessed as unrelated to ivosidenib. No dose-limiting toxicities have been reported in the study and the MTD was not reached.

1.6 Nivolumab (BM-936558)

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (mAb, immunoglobulin (lg)G4-S228P) that targets the PD-1 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-LI and PD-L2, results in the downregulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for IV administration.

The PK, clinical activity, and safety of nivolumab have been assessed in participants with non-NSCLC, MEL, and clear-cell RCC in addition to other tumor types. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

Opdivo® (nivolumab) is approved for the treatment of unresectable or metastatic MEL in multiple countries including Japan (Jul-2014), the US (Dec-2014), and the European Union (EU) (Jun-2015). Nivolumab is also approved for the treatment of metastatic squamous (SQ) NSCLC in the US (Mar-2015).

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 participants treated to date.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy and is manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical studies, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is the nivolumab and ipilimumab combination therapy, which is approved in participants with unresectable or metastatic MEL and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab and ipilimumab combination therapy is consistent with the individual mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs increase with the combination.

Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of nivolumab are provided in the nivolumab Investigator Brochure (1B).

1.6.1 Nivolumab Storage

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 8 h from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 h from the time of infusion preparation.

Do not freeze.

Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of nivolumab are provided in the nivolumab 1B.

2.0 Trial Objectives and Endpoints

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is:

- To describe the clinical response and six-month progression-free survival of patients treated with ivosidenib in combination with nivolumab

2.1.2 Secondary Objectives

The secondary objectives of the study are:

- To determine the safety of ivosidenib in combination with nivolumab
- To summarize longitudinal clinical outcomes of patients treated with ivosidenib in combination with nivolumab

2.1.3 Exploratory Objective

- To evaluate biomaterial-based biomarkers and determine their association with treatment

response.

2.2 Study Endpoints

2.2.1 Primary Endpoints

- **Response**
  - Advanced Solid Tumors: Best overall response by RECIST 1.1 as detailed in {Section 11.8) 8 weeks after the initiation of treatment
  - Glioma: Best overall Response by Response Assessment in Neuro-Oncology {RANO), Criteria as detailed in (Section 11.9) 8 weeks after the initiation of treatment
- **Six-Month Progression Free Survival (PFSG)**
  - All tumor types: All tumor types: Survival to six months after the initiation of treatment without objective tumor progression

2.2.2 Secondary Endpoints

- The occurrence of dose-limiting toxicity **{DLT),** as defined in Section 7.5, in patients receiving ivosidenib plus nivolumab.
- Adverse events in patients receiving the combination of ivosidenib and nivolumab based on CTCAEvS.0
- Progression Free Survival (PFS) - Survival with freedom from objective tumor progression from time of first treatment until up to 18 months after the last participant has initiated treatment.

2.2.3 Exploratory Endpoints

- The association between response biomarkers and clinical outcomes in patients treated with combination ivosidenib and nivolumab.

3.0 Investigational Plan

3.1 Overall Study Design

This is a Phase II study of orally administered ivosidenib in patients with advanced solid tumors {nonresectable or metastatic) or enhancing gliomas. Participants are required to have a histologically consistent diagnosis of *IDH1* gene-mutated tumor that is not eligible for curative therapy. Participants must have received appropriate standard of care treatment options {in the opinion of the treating investigator).

Each participant's course of treatment will be comprised of the following periods:

Pre-Treatment/Screening Period: Following informed consent, all potential participants will undergo Screening procedures to determine eligibility within 28 days prior to the start of study treatment on Cycle 1, Day 1 (C1D1), with the exception of baseline radiographic scans, which should be performed within 21 days prior to C1D1. In patients with advanced solid tumors excluding brain tumors, a tumor biopsy will be collected if not done so before screening. A second biopsy will be taken at the end of the first cycle of nivolumab (approximately week 4 ± 10 days). Additional Screening procedures are detailed in the study calendar in Section 6.1

Treatment Period and End of Treatment Visit: Participants who meet all study eligibility criteria will be eligible to start study treatment (criteria detailed in Section 4). Daily study treatment will begin on CIDI with planned concurrent dosing of ivosidenib and nivolumab. Cycles are 28 days (±2 days) in duration and dosing is continuous. Ivosidenib will be dosed daily on 28-day cycles and nivolumab will be infused IV every 28 days. All participants will continue to receive best supportive care according to institutional practice throughout the study, regardless of treatment arm. Study visits will be conducted every other week during Cycles 1-3 (Days 1 and 15), and Day 1 of each cycle thereafter. An end of treatment (EOT) Visit will be performed on the last day of study treatment (within 5 to 33 days of last dose of either study treatment to accommodate for potential dosing delays of up to 28 days).

Dosing		
Drug	ivosidenib	nivolumab
Dose Level 1	500 mg daily	480 mg IV q4
Dose Level -1	250 mg daily	480 mg IV q4

Schedule of Administration: Ivosidenib will be administered concurrently with nivolumab beginning on CIDI to patients with an IDHI mutant solid tumor or glioma selected by CUA certified sequencing for IDHI R132 mutations. Should toxicity monitoring suggest and intolerable dose, a dose de-escalation approach will be employed according to the above dose levels. Dosing will be continuous (once daily) on a 28-day cycle. After confirmation of tolerable dose, ivosidenib will be continued throughout the rest of the trial. Nivolumab will be dosed concurrently at 480 mg IV q4 weeks starting on CIDI. After collecting baseline peripheral blood, a research biopsy will also be collected in at least the first 10 patients with advanced solid tumors - ie, not in glioma - in whom a biopsy is deemed safe by the treating physician, pending available funding. Ivosidenib will then be administered concurrently with nivolumab on a Q28 day schedule. A second biopsy will be taken at the end of the first cycle of nivolumab (approximately week 4), pending funding. Treatment with ivosidenib will continue indefinitely per treating investigator discretion.

Nivolumab will be given for up to 1 year. Either agent will be discontinued upon severe toxicity, confirmed disease progression, confirmed pregnancy, death, withdrawal of consent, or if the participant is lost to follow-up.

Radiographic assessment (CT or MRI) for evaluation of disease response will be conducted every 8 weeks (±7 days) from C1D1, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. For participants who discontinue study drugs for reasons other than disease progression or start of another anticancer agent, an assessment will be conducted at the EOT Visit. Target and non-target lesion selection and objective tumor response assessments per Response Evaluation Criteria in Solid Tumors (RECIST) vl.1and RANO criteria for glioma patients.

Participants will be assessed at every visit for AEs and concomitant medications, starting from the first dose of study treatment. Toxicity severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Additional physical exam and laboratory will be conducted at each visit as detailed in the study assessments and biomarker table.

Participants may continue with their assigned study treatment until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, the participant is lost to follow-up, or the Lead Principal Investigator (PI} ends the study, whichever occurs first. For participants who are determined to be on ivosidenib upon radiographic disease progression and demonstrate clinical benefit, treating investigators, with consult from the Lead PI, may keep the participants on ivosidenib after the disease progression.

Post-Treatment Follow-up Visit: A Post-Treatment Follow-Up Visit for safety will occur 28 days (no more than 33 days) after the last dose of study drug. Every effort must be made to perform protocol-specified evaluations unless consent to participate in the study is withdrawn. Assessments to be performed at the Follow-up Visit are included under study assessments. If a participant's dose is interrupted for 28 days and then the participant discontinues study participation, the EOT Visit will serve as the Post-Treatment Follow-up Visit.

PFS Follow-up: Participants who discontinue study treatment for reasons other than disease progression or withdrawal of consent will be followed in PFS follow-up (every 8 weeks through week 48, and every 8 weeks thereafter) until documented disease progression, death, or the initiation of new cancer therapy. If a participant begins a new anticancer therapy during PFS follow-up, information on the new anticancer therapy will be collected.

End of Study: End of study is defined as the point in time when all participants have died, withdrawn consent, or been lost to follow-up.

3.2 Rationale for Dose Selected

3.2.1 Ivosidenib

Ivosidenib is FDA approved for relapsed refractory IDHI mutated AML. Data have shown ivosidenib to be well tolerated at total daily doses up to 1200 mg in solid tumors (AG120-C-002) and in hematologic malignancies (AG120-C-001}; the MTD was not reached in either study. As of a 16 January 2016,

122 participants have been treated with ivosidenib in the AG120-C-002 study, of which 84 participants received 500 mg QD; 119 participants have been treated with ivosidenib in the AG120-C-001 study, of which 89 participants received 500 mg QD. Based on a review of the available safety, PK/PD, and clinical activity data observed during dose escalation, 500 mg QD was selected as the ivosidenib dose for the expansion phases of both of these trials.

In these studies, there have been minimal dose interruptions, and without an apparent dose relationship for any commonly reported TEAEs or Grade 2:3 TEAEs. No DLTs have been reported in Study AG120-C-002. Dose-limiting toxicities of Grade 3 rash and Grade 3 QT prolongation were observed in the 1200 mg QD and 800 mg QD cohorts respectively in Study AG120-C-001; however, expansion of these dose cohorts did not result in identification of the MTD.

Plasma ivosidenib exposure increased in a less than proportional manner across doses from 100 mg BID

to 1200 mg QD, nearing a plateau at 500 mg QD, in both solid tumors and hematologic malignancies. Sustained and consistent plasma 2-HG inhibition was observed with plasma 2-HG levels reduced to the normal range of healthy volunteers (up to 98.0% inhibition in solid tumors, 99.7% in hematologic malignancies) at all doses, with no apparent dose response. The 500 mg QD dose has shown a maximum PD effect based on 2-HG levels for the majority of participants.

For Study AG120-C-002, efficacy data were analyzed separately based on the underlying disease and specific response criteria: cholangiocarcinoma, chondrosarcoma, or glioma (see Section 5.4.2 in Investigator's Brochure 7.0 for greater detail). As of March 10, 2017, 73 participants with cholangiocarcinoma received ivosidenib in the dose escalation and expansion cohorts, with 62 participants receiving ivosidenib at 500 mg QD. Overall, 5% (n=4) experienced a confirmed partial response and 56% (n=41) experienced stable disease. The 6-month progression-free survival (PFS) rate was 38.5% and the 12-month PFS rate was 20.7%. As of 23 September 2016, 21 participants with chondrosarcoma had been treated with ivosidenib and 20 were efficacy-evaluable. Eleven (55%) participants experienced stable disease as their best overall response; the remaining participants experienced disease progression (30%) or were not assessed (15%). The 3-month PFS rate was 58% with a median ivosidenib treatment duration of 2.6 months (range, 0 to 24 months).

As of May 12, 2017, 66 participants with glioma have been treated with ivosidenib and enrollment of this subset was complete; of these participants, 35 had non-enhancing glioma. Two of these 35 participants (6%) had a minor response according to RANO-LGG. Twenty-nine (83%) participants had stable disease and 4 (11%) had progressive disease as their best response; the median treatment duration for non-enhancing glioma was 16 months with 63% of participants being treated for 1 year. Volumetric analysis (conducted centrally) demonstrated stabilization or a decrease in tumor growth rate compared to the pretreatment rate in glioma participants with non-enhancing disease receiving ivosidenib.

3.2.2 Nivolumab

Nivolumab is approved as monotherapy for multiple solid tumors (NSCLC, melanoma, RCC, HCC) and in combination with ipilimumab for melanoma and RCC at doses of 480mg IV Q4 weeks. PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than proportionally with increasing weight, indicating that milligram/kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC participants has recently been updated, using data from 1,544 participants from 7 studies investigating nivolumab in the treatment of MEL, NSCLC, and RCC.

In this dataset, the median (minimum - maximum) weight was 77 kg (35 to 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80-kg participant, nivolumab 240 mg q2w was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg q2w, the PPK model was used to simulate nivolumab 3 mg/kg q2w and 240 mg q2w. In the simulations, the simulated participant populations consisted of 1,000 participants per treatment arm randomly sampled from aforementioned pooled database of cancer participants. Because no differences in PK were noted across ethnicities and tumor types, these simulated MEL and NSCLC data will be applicable to participants with other tumor types. The simulated measure of exposure of interest, time-averaged

concentrations for 240 mg q2w are predicted to be similar for all participants in reference to 80 kg participants receiving 3 mg/kg q2w.

Nivolumab is safe and well tolerated up to 10 mg/kg q2w dose level. AEs have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 to 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab (ie, 95th percentile following nivolumab 10 mg/kg q2w from Study CA209003). Thus, while participants in the lower body weight ranges would have greater exposures than 80 kg participants, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg q2w) used in the nivolumab clinical program and are not considered to put participants at increased risk.

For participants with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy because the exposures predicted following administration of a 240 mg q2w are on the flat part of the exposure- response curves for previously investigated tumors, **MEL** and NSCLC. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it has been expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

More recently, data on the clinical pharmacokinetics, safety, and efficacy of 480 mg IV over 30 min every 4 weeks has been collated and reviewed across tumor types, leading to FDA approval for the 480 mg dosing regimen. Hence, combination dosing of nivolumab for this study will be 480mg IV Q 4 weeks.

Investigational supply is being provided for this study. Please reference the nivolumab 1B for dosing information and proper storage conditions.

3.3 Criteria for Study Termination

In the event of such action, written notification documenting the reason for study termination will be provided to each Local Investigator. The study will be terminated if any of the following circumstances occur: Determination of unexpected, significant, or unacceptable risk to participants. Failure to enter participants at an acceptable rate. Insufficient adherence to protocol requirements. Plans to modify, suspend, or discontinue the development of the study treatment. Other administrative reasons.

4.0 Study Population

4.1 Inclusion Criteria

1. Be:::: 18 years of age.
2. Have a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) of an advanced solid tumor for which curative treatment is not available and have undergone appropriate standard of care treatment options (in the opinion of the treating investigator).
3. Have a documented *IDH1* gene-mutated disease (from a fresh tumor biopsy or the most recent banked tumor tissue available) based on CLIA certified sequencing (R132C/L/G/H/S mutation variants tested).

- For glioma, must have both 1) contrast enhancing disease and 2) WHO 2016 grade 2

4. Have an ECOG PS score of O or 1 (Appendix 11.1)
5. Have at least one evaluable and measurable lesion as defined by RECIST vI.1 (solid tumors) or Response Assessment in Neuro-Oncology (RANO) Criteria (glioma).
6. Have recovered from toxicities associated with prior anticancer therapy to baseline or :5 grade 1 unless stabilized under medical management per investigator.
7. Have adequate bone marrow function as evidenced by:
    - Absolute neutrophil count l,500/mm^3 or 1.5 x 10^9/L
    - Hemoglobin 8 g/dL
    - Platelets 100,000/mm^3 or 100 x 10^9/L
8. Have adequate hepatic function as evidenced by:
    - Serum total bilirubin :5 2 x upper limit of normal (ULN), unless considered due to Gilbert's disease
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) :5 5 x ULN in the presence of liver metastases (or primary hepatic tumor) OR :5 2x ULN within glioma patients
9. Have adequate renal function as evidenced by:
    - Serum creatinine < 1.5 x ULN OR Creatinine clearance 50 ml/min based on the Cockroft-Gault glomerular filtration rate (GFR) estimation: (140-Age) x (weight in kg) x (0.85 if female)/72 x serum creatinine
10. Be able to understand and willing to sign the informed consent form (or have legal representation) and to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling, biopsies, and urine sampling, during the study. A legally authorized representative may consent on behalf of a participant who is otherwise unable to provide informed consent if acceptable to and approved by the IRB/Independent Ethics Committee (IEC).
11. Female participants with reproductive potential must have negative serum pregnancy testing within 72 h prior to the initial administration of study drug, then every 4 weeks±l week, or a negative confirmation from an obstetrician in case of equivocal serum pregnancy results. Females of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who have not been naturally postmenopausal (ie, who have not menstruated) for at least 24 consecutive months (ie, have not had menses at any time in the preceding 24 consecutive months).

    Men with partners who are women with reproductive potential must agree that they or their partners will use two effective forms of contraception (including at least one barrier form) when engaging in reproductive sexual activity. Women of child-bearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab.

Effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

4.2 Exclusion Criteria

Participants who meet any of the following criteria will not be enrolled in the study:

1. Received a prior IDH inhibitor.
2. Received systemic anticancer therapy or an investigational agent< 2 weeks prior to Day 1). In addition, the first dose of study treatment should not occur before a period?: 5 half-lives (ti/2) of the investigational agent has elapsed.
3. For solid tumor patients: received radiotherapy to metastatic sites of disease< 2 weeks prior to Day 1 and for glioma patients have received radiation within 3 months prior.
4. For solid tumor patients, have underwent hepatic radiation, chemoembolization, and radiofrequency ablation< 4 weeks prior to Day 1.
5. Participants must not have a diagnosis of immunodeficiency or is receiving systemic steroid therapy at a dose of> 10 mg prednisone daily or equivalent at time of first dose of study treatment.
6. Participants must not have active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroids replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
7. Participants must not have a known history of non-infectious pneumonitis that required steroids for treatment.
8. Participants must not have evidence of interstitial lung disease.
9. For solid tumor patients, have known symptomatic brain metastases requiring steroids. Participants with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 1 week and have radiographically stable disease for at least 1 month prior to study entry.
10. Have a history of another primary cancer that is active requiring treatment, progressing or for which the treating investigator believes will make disease assessment unreliable.
11. Have evidence of intracranial or intra-tumoral hemorrhage either by MRI or computed tomographic (CT) scan. Participants with resolving post-surgical changes, punctate hemorrhage, or hemosiderin are eligible.
12. Underwent major surgery within 4 weeks of Day 1 or have not recovered from post-surgery toxicities.
13. Are pregnant or breastfeeding.

14. Are taking known strong CYP3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window (Appendix 11.2), unless they can be transferred to other medications within 2'.5 *t112* prior to dosing.

15. Are taking P-glycoprotein (P-gp) transporter-sensitive substrate medications with a narrow therapeutic window (Appendix 11.2), unless they can be transferred to other medications within 2'. 5 t112 prior to administration of study treatment.

16. Have an active infection requiring systemic anti-infective therapy or with an unexplained fever> 38.5°C within 7 days of Day 1 (at the discretion of the treating investigator) participants with tumor fever may be enrolled).

17. Have any known hypersensitivity to any of the components of ivosidenib or nivolumab.

18. Have significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) Class III or IV congestive heart failure (Appendix 11.3); myocardial infarction; unstable angina; and/or stroke.

19. Have a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) (Appendix 11.4) 2'. 480 ms or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome). Bundle branch block and prolonged QTcF interval are permitted with approval of the PI.

20. Are taking medications that are known to prolong the QT interval (Appendix 11.5), unless they can be transferred to other medications within 2'. 5 t112 prior to dosing or unless the medications can be properly monitored during the study. (If equivalent medication is not available, QTcF should be closely monitored.)

21. Have known active hepatitis B (HBV) or hepatitis C (HCV) infections, known positive human immunodeficiency virus (HIV) antibody results, or acquired immunodeficiency syndrome (AIDS)-related illness. Participants with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Participants with chronic HBV that is adequately suppressed per institutional practice will be permitted.

22. Have any other acute or chronic medical or psychiatric condition, including recent (within 12 months of Day 1) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the treating investigator, would make the participant inappropriate for entry into this study.

23. Have known active inflammatory gastrointestinal disease, chronic diarrhea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).

24. Have been committed to an institution by an order issued either by the judicial or administrative authorities.

4.3 Subject Recruitment and Registration

Participants who are candidates for enrollment into the study will be evaluated for eligibility by the treating investigator to ensure that the inclusion and exclusion criteria have been satisfied and that the participant is eligible for participation in this clinical study.

4.3.1 Registration Procedures

When registering a participant, patients must not start protocol treatment prior to registration. The registration will be conducted using a clinical trials management system.

Registration will require the following information: 1) protocol name and number; 2) date treatment begins; 3) participant name; 4) date of birth; 5) participant hospital medical record number; 6) primary study physician; 7) confirmation of eligibility; 8) copies of the informed consent signature page; 9) verification that the informed consent was signed.

4.4 Subject Withdrawal Criteria

Participants have the right to withdraw from the study at any time for any reason. A participant's discontinuation of study treatment or withdrawal from the study will not jeopardize the relationship with their healthcare providers or affect their future care. Participants may choose to discontinue study treatment but agree to remain on study for follow-up contact. This decision must be recorded in writing at the study site.

Should a participant decide to withdraw, all efforts will be made to complete and report the protocol-defined study observations as completely as possible and to determine the reason for withdrawal.

4.4.1 Withdrawal from Study Treatment

Participants may discontinue or be discontinued from study treatment at any time. In this situation, a participant without documented progressive disease by the treating investigator should be followed for tumor assessments until the development of progressive disease and/or survival. Participants will be discontinued from study treatment for the following reasons:

- Grade 4 QTcF prolongation.
- Disease progression (participants who are, in the opinion of the treating investigator, benefiting from treatment [e.g., slow progression or immune-related response evaluation] may be allowed to continue on study treatment)
- Severe or unacceptable toxicity
- Death
- Lead Investigator decision
- Subject decision to withdraw from treatment
- Protocol violation: non-adherence to study treatments as required for evaluability (detailed in section 8.1.1) or other protocol requirements.
- Confirmed pregnancy (study therapy should be immediately interrupted based upon a positive urinary human chorionic gonadotropin [hCG] test, and permanently discontinued if confirmed by a serum -hCG test)
- Lost to follow-up

All AEs should be followed until resolution or for a period of 28 days from the last dose of study treatment, whichever is shorter. If the participant withdrew from treatment because of an AE, every

effort must be made to perform protocol-specified safety follow-up procedures. All SAEs that occur up to 100 days post last dose of nivolumab must be reported to BMS World Wide Safety.

4.4.2 Study Participation Termination

Participants who discontinue treatment without disease progression or death will continue to be followed for PFS every 8 weeks after the EOT Visit (±5 days) until disease progression, death, start of subsequent anticancer therapy, or withdrawal of consent until 6 months after the last enrolled patient begins treatment. Participants will be terminated from the study for the following reasons:

- Death
- Withdrawal of consent for follow-up
- Loss to follow-up
- Termination of the study

5.0 Study Treatment

5.1 Description of Study Treatment

Ivosidenib will be administered orally at a dose of 250 mg or 500 mg (provided as 250 mg strength tablets) daily.

Nivolumab will be administered at 480 mg IV every 28 days.

5.2 Study Treatment Packaging and Labeling

Ivosidenib will be supplied in appropriate containers with child resistant closures and labeled appropriately as the investigational product for this study.

Packaging and labeling will be prepared to meet all regulatory requirements.

5.3 Study Treatment Storage

Ivosidenib and nivolumab must be stored according to the package label.

Ivosidenib should be stored in a secure area according to local regulations. It is the responsibility of the local PI to ensure that ivosidenib is only dispensed to study participants. Ivosidenib must be dispensed only from official study site by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity). If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed.

Investigational product (IP) documentation must be maintained and includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration, and as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets). A temperature excursion form will be provided at study activation. All temperature excursion must be reported to BMS.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

Details regarding preparation and administration are provided in the site training materials for AG-120.

For nivolumab, investigational supply is being provided for this study. Please only refer to the nivolumab IB for drug storage, preparation, and administration guidelines to include in the protocol.

5.4 Study Treatment Preparation and Administration of Ivosidenib

Daily treatment with ivosidenib will begin on C1D1. Dosing is continuous; there are no planned inter-cycle rest periods. Participants should be instructed to take their QD dose at approximately the same time each day.

Participants should be instructed to swallow tablets whole and to not chew the tablets. Participants may take ivosidenib tablets with or without food. Participants should be advised that if ivosidenib tablets are taken with food, the participant should avoid grapefruit or grapefruit products and avoid consuming a high-fat meal.

If the participant forgets to take the daily dose, then they should take ivosidenib within 12 h after the missed dose. If more than 12 h have elapsed, then that dose should be omitted, and the participant should resume treatment with the next scheduled dose.

Participants will continue to receive best supportive care throughout the study, regardless of treatment arm. Participants may continue with their assigned study treatment until any of the conditions for withdrawal of study treatments are met - as detailed in Section 4.4.1. For participants who are determined to be on ivosidenib upon radiographic disease progression and demonstrate clinical benefit, Pis, with consult from the Sponsor, may keep the participants on ivosidenib after the disease progression.

5.5 Criteria for Dose Modification, Discontinuation of Study Treatment, and Continuation Beyond Radiographic Progression

5.5.1 Study Treatment Dose Modification and Discontinuation Criteria

5.5.1.1 Dose Modifications and Delays

Dose reductions or dose escalations of nivolumab are not permitted. Nivolumab may continue if the ivosidenib is held unless the hold of ivosidenib is for more than 28 days. If a safety issue arises that is related to nivolumab, the nivolumab should be withheld or permanently discontinued (Section 5.9). In such a case, continuing ivosidenib may be allowed after consultation with the PI.

For any AE, including AEs not specifically mentioned in Table 1, the treating investigator may decide to delay dosing or modify the dose of ivosidenib based on clinical judgment. Dose modifications of ivosidenib from 500 mg to 250 mg will be permitted on study for management of AEs (Table 1). If more than one AE occurs that would require a dose modification, upon resolution of all AEs to baseline or Grade 1, ivosidenib should be dose reduced to 250 mg. Dose reductions below 250 mg are not permitted. If the AE is thought to be related to the ivosidenib, the nivolumab will continue to be dosed as per protocol schedule.

Dose delays for reasons other than management of AEs are discouraged. Dose delays up to 28 days will be permitted at the discretion of the lead investigator.

If the participant cannot resume ivosidenib within 28 days, the participant should be discontinued from both study medications. If ivosidenib is discontinued, the participant will complete the EOT and Follow-up Visits, and then enter PFS follow-up (if disease has not progressed). Exemptions may be considered

for those participants who are determined by the investigator to have received clinical benefit from treatment. If a dose is delayed for the management of an AE, the participant should resume the study at the next planned visit within a dosing cycle. This determination will be at the discretion of the treating physician.

Table 1: Management of Ivosidenib-related Adverse Events (AEs)

AEs	Action
Grade 2 nausea or vomiting (related or unrelated)	• Consider holding dose of ivosidenib until resolution of AE to Grade 1 within 28 days of supportive therapy. • Manage with supportive therapy according to the institutional standard of care. • May resume ivosidenib at same dose.
Grade 3 AEs (related, first event)	• Hold dose of ivosidenib until resolution to Grade 1 or baseline within 28 days of supportive therapy and then resume dose. • Manage with supportive therapy according to the institutional standard of care. • If the Grade 3 AE recurs (a second time), consider reducing ivosidenib to 250 mg. Re-escalation may be permitted after discussion with the Lead Investigator. • If the Grade 3 AE recurs (a third time) despite dose reduction of ivosidenib, then consider discontinuing ivosidenib in consultation with the Lead Investigator.
Grade 4 AEs (related, first event)	• Hold ivosidenib • Manage with supportive therapy according to the institutional standard of care. • If the AE resolves to Grade 1 or baseline within 28 days, then restart ivosidenib dosing at 250 mg in consultation with the Lead Investigator. • If the AE does not resolve to Grade 1 or baseline within 28 days, consider discontinuing study treatment in consultation with the Lead Investigator. • If the Grade 4 AE recurs (a second time), despite dose reduction, ivosidenib should be discontinued in consultation with the Lead Investigator.

*See Table 2 for specific dose modifications for QTcF prolongation.

5.5.2 Continuation of Treatment beyond Radiographic Progression

Accumulating evidence indicates that a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

- Participants will be permitted to continue treatment beyond initial RECIST Version 1.1 (solid tumors) or Response Assessment in Neuro-Oncology (RANO) (gliomas)-defined PD, assessed by the investigator, if they meet the following criteria:
- Investigator-assessed clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of PD (e.g., CNS metastases).

A radiographic assessment/scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment.

If the treating investigator deems that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the study and continue to receive monitoring according to the study schedule.

For the participants who continue study treatment beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological LNs, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and, therefore, included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological LNs, which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions, which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

5.6 Guidelines for Management of QT Prolongation

The following are guidelines for the management of AEs of special interest based on the ivosidenib non-clinical and clinical safety findings in participants with solid tumors to date.

Prolongation of QTcF interval has been observed in monkeys at relatively high doses of ivosidenib (see Section 7.2.7.1) and has been identified as an expected risk of treatment with ivosidenib (see the Investigator's Brochure, Version 7.0). Cumulatively, QT prolongation has been experienced by 37 (17%) of the 223 participants in Study AG120-C-001 (8 participants [4%] had SAEs) and by 17 (10%) of the 168 participants in Study AG120-C-002 (no SAEs reported). There has been one report of QT prolongation in Study AG120-221-C-001, as of April 18, 2017.

Participants may be at increased risk for the development of QT prolongation when treated with ivosidenib in combination with fluoroquinolones, azole antifungal agents, or serotonin (5-HT3)

antagonists. Investigators need to be vigilant; refrain from administering concomitant medications associated with QT prolongation and if no other therapeutic options are available, monitor participants receiving study treatment with the combination of these drugs, and evaluate ECG and electrolytes (including potassium, magnesium, and calcium) particularly in participants presenting with nausea, vomiting, or diarrhea.

Participants who experience prolongation of the QTcF interval to> 480 ms (CTCAE Grade;::: 2} while receiving study treatment, should be promptly evaluated for causality of the QTcF prolongation and managed according to the following guidelines and Table 2:

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects.
- If no other cause is identified and the treating investigator believes it is appropriate, particularly if QTcF remains elevated (after above measures have been implemented, or as determined by the Investigator}, study treatment may be interrupted, and an ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed or more frequently as clinically indicated. If QTcF has recovered or improved and the Investigator believes it is safe to do so, re-challenge with study treatment should be considered if held.
- ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTcF reduction 480 ms.

Participants who experience prolongation of the QTcF interval to> 500 ms (CTCAE Grade;::: 3} while receiving study treatment, should be promptly evaluated for causality of the QTcF prolongation and managed according to the following guidelines and Table 2:

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects.
- If no other cause is identified and the treating investigator believes it is appropriate, particularly if QTcF remains elevated (after above measures have been implemented, or as determined by the Investigator}, study treatment may be interrupted, and an ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed or more frequently as clinically indicated. If QTcF has recovered or improved and the Investigator believes it is safe to do so, re-challenge with study treatment should be considered if held.
- ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTcF reduction 480 ms.

Table 2: Management of QT Prolongation by CTCAE Grade

CTCAE Grade	Management
Grade 2 (QTcF > 480 and :5 500 ms)	• The dose of study treatment may be reduced to 250 mg QD without interruption of dosing. The dose of study treatment may be re-escalated to the prior dose in 14 days after QT prolongation has decreased to :5Grade 1.
Grade 3 (QTcF > 500 ms on at least two separate ECGs)	• Hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. • Dosing with study treatment will be interrupted. If QTcF returns to within 30 ms of baseline or< 450 ms for males and< 470 ms for females within 14 days, treatment may be resumed at a reduced dose of 250 mg. • The dose of study treatment cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.
Grade 4 (QTcF > 500 ms or> 60 ms change from baseline with Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	• Participants should be admitted to a hospital for continuous cardiac monitoring and discharged only after review by a cardiologist. • Dosing with study treatment should be permanently discontinued.

5.7 Treatment of Study Drug-related Infusion Reactions

Nivolumab and the combination therapies may induce infusion or hypersensitivity reactions. If such a reaction were to occur, it may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms.

Infusion reactions should be graded according to CTCAE vs guidelines. Any Grade 3 or Grade 4 infusion reaction should be reported within 24 h to the PI or designee and reported as an SAE if it meets the criteria.

The nivolumab 30-min infusion will be administered first, with a 30-min rest, followed by the administration of ivosidinib. It may be unclear if an infusion reaction is due to the combination therapy, nivolumab, or to both study drugs. Therefore, one set of treatment recommendations (based on the most conservative treatments for infusion reactions due to either study drug) is

provided below and may be modified based on clinical judgment, local treatment standards and guidelines, and/or specific symptoms, as appropriate:

For Grade 1 symptoms: Mild reaction (e.g., localized cutaneous reactions including mild pruritus, flushing, rash), requires infusion rate to be decreased; intervention may be indicated.

Decrease the rate of the study drug infusion until recovery from symptoms.

Remain at bedside and monitor the participant's vital signs until resolution of symptoms. Diphenhydramine 50 mg may be administered at the discretion of the treating physician.

When symptoms resolve, restart the infusion at the original infusion rate.

If a participant has an infusion reaction with nivolumab, combination therapy can be given (without prophylactic medications) if the infusion reaction resolves within 3 h. For scheduling purposes, infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.

If a participant has an infusion reaction, prophylactic pre-infusion medications should be given prior to all subsequent infusions.

The following prophylactic pre-infusion medications are recommended prior to future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1,000 mg at least 30 min before additional study drug administrations.

For Grade 2 symptoms: Moderate reaction (i.e., any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, and hypotension with systolic blood pressure (BP) > 80 mmHg), requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids); prophylactic pre-infusion medications indicated for 24 h.

Interrupt the study drug infusion.

Begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 to 1,000 mg.

Remain at bedside and monitor the participant's vital signs until resolution of symptoms. Corticosteroid therapy may be administered at the discretion of the treating physician.

When symptoms resolve, restart the infusion at 50% of the original infusion rate; if no further complications ensue after 30 min, the rate may be increased to 100% of the original infusion rate.

Monitor the participant closely. If symptoms recur, immediately discontinue the infusion; no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the participant until resolution of symptoms.

If a participant has an infusion reaction with nivolumab infusion, combination therapy infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 h. For scheduling purposes, the combination therapy infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.

If a participant has an infusion reaction with a combination therapy, prophylactic pre-infusion medications should be given prior to all subsequent infusions.

The following prophylactic pre-infusion medications are recommended prior to future infusions: diphenhydramine 50 mg (or equivalent} and/or paracetamol (acetaminophen} 325 to 1,000 mg should be administered at least 30 min before additional study drug administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent} may be used.

The amount of study drug infused must be recorded.

For Grade 3 or Grade 4 symptoms: Severe reaction such as bronchospasm, generalized urticaria, systolic BP< 80 mmHg, or angioedema; Grade 3 symptoms including prolonged symptoms, which require 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae, such as renal impairment, pulmonary infiltrates; Grade 4: life-threatening; pressor or ventilation support indicated.

Immediately discontinue the study drug infusion. No further study drug will be administered. The amount of study drug infused must be recorded on the case report form (CRF}.

Begin an IV infusion of normal saline, and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1.0 mg of a 1:1,000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent}, as needed.

Remain at bedside and monitor the participant's vital signs until recovery from symptoms.

The participant should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment}, symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids}.

5.8 Nivolumab AEs

Nivolumab treatment should be permanently discontinued for the following:

Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the OR requires systemic treatment

Any Grade 3 non-skin, drug-related AE lasting> 7 days or recurs, with the following exceptions for laboratory abnormalities, diarrhea, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:

- Grade 3 drug-related diarrhea, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.

- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except for the following:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
        - Grade 3 drug-related AST, ALT, or total bilirubin requires discontinuation
        - Concurrent AST or ALT> 3x ULN and total bilirubin > 2x ULN

Any drug-related Grade 4 endocrinopathy and Grade 3 adrenal insufficiency requires discontinuation.

Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events, which do not require discontinuation:

- Grade 4 neutropenia :::; 7 days
- Grade 4 lymphopenia or leukopenia
- Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 h of their onset

Any drug-related Grade 4 endocrinopathy and Grade 3 adrenal insufficiency requires discontinuation.

Any event that leads to delay in dosing lasting> 8 weeks from the previous dose requires discontinuation, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Lead Investigator.

Prior to re-initiating treatment in a participant with a dosing delay lasting> 6 weeks, the Lead Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Any AE, laboratory abnormality, or intercurrent illness, which presents a substantial clinical risk to the participant with continued nivolumab dosing as assessed by the treating investigator.

5.9 Management of Nivolumab AEs

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to nivolumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- Pneumonitis:
    - For **Grade 2 events,** treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events,** immediately treat with IV steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- Diarrhea/Colitis:

Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All participants who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists> 1 week, treat with IV steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Type 1 diabetes mellitus **(if** new onset, including diabetic ketoacidosis [DKA]) or Grade 3 Hyperglycemia, **if** associated with ketosis (ketonuria) or metabolic acidosis (DKA)
    - For **TIDM or Grade 3-4** hyperglycemia

Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

Evaluate participants with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- Hypophysitis:
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor participants for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- Hepatic:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with IV corticosteroids for 24 to 48 h.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- Renal Failure or Nephritis:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.10 Duration of Subject Participation

5.10.1 Treatment Duration

Treatment with ivosidenib and nivolumab will continue until any of the conditions for withdrawal of study treatments are met - as detailed in 4.4.1.

Following discontinuation of study treatment, participants are to attend a Follow-up Visit at least 28 days and no more than 33 days after the last dose for study assessments. When study treatment is withheld from a participant to resolve toxicity and the participant does not subsequently restart treatment, EOT is defined as the date when the study drug was first held. Participants should proceed with EOT assessments, safety and PFS follow-up. If the decision to not restart study treatment occurs outside of the 28-day safety follow-up window, the participant should proceed with PFS follow-up.

5.11 Treatment Compliance

Participants will be dispensed the appropriate number of labeled bottle(s) of ivosidenib for at least 28 days of dosing on Day 1 of each cycle. The ivosidenib should be taken at approximately the same time each day. On clinic days, the ivosidenib should be taken any time prior to the nivolumab infusion. The participant will be asked to return all bottles and unused tablets (or empty bottles) on Day 1 of each cycle or at their next study visit for assessment of compliance with the dosing regimen.

Participants will be given a dosing diary for each treatment cycle. They should record relevant information regarding their study treatment in the diary (e.g., confirmation that each daily dose was taken, reasons for missed doses). Treatment compliance will be assessed based on return of unused drug and the dosing diary.

5.12 Study Treatment Accountability

Accountability for the study treatment at the study site is the responsibility of the Investigator. The Investigator will ensure that the study treatment is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each participant, and disposal of the drug. These records will adequately document that the participants were provided the doses as specified in the protocol and should reconcile all study treatment Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and participant numbers.

Study treatment must not be used for any purpose other than the present study. Study treatment that has been dispensed to a participant and returned unused must not be re-dispensed to a different participant.

Participants will receive instructions for home administration of study treatment along with a diary to record the date and time of each dose, as well as the number of tablets taken.

All unused and used study treatment should be retained at the site until they are inventoried and verified by study site personnel and/or the study monitor. All used, unused, or expired study treatment

will be returned to the Drug Manufacturer or its designee or if authorized, disposed of at the study site per the site's Standard Operating Procedures (SOPs) and documented. All material containing ivosidenib will be treated and disposed of as hazardous waste in accordance with governing regulations.

5.13 Prior and Concomitant Medications and Treatments

5.13.1 Prior Medications and Procedures

All medications administered, and procedures conducted within 28 days prior to the first day of study treatment administration are to be recorded in the medical record. In addition, all prior treatments for the underlying malignancy should be recorded.

5.13.2 Concomitant Therapy Requiring Careful Monitoring

Concomitant use of drugs with a potential QT prolongation should be avoided and replaced with alternative treatments. If this is not possible, participants receiving these drugs should be adequately monitored.

These medications include but are not limited to:

- Fluoroquinolones such as ciprofloxacin and moxifloxacin
- Azole antifungals such as fluconazole and posaconazole
- Serotonin (S-HT3) antagonists such as granisetron and ondansetron

Other examples of drugs known to prolong the QT interval are listed in Appendix 11.5.

5.13.3 Prohibited Concomitant Therapy

Anticancer therapy other than the treatment outlined in the protocol is not permitted during the study. If alternative therapy is required for treatment of the participant's disease, the participant should be discontinued from the study treatment.

5.13.4 Allowed Concomitant Medications, Procedures, and Treatments

Medications and treatments other than those specified above are permitted during the study. All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care.

If clinically indicated, palliative biliary decompression procedures will be permitted on-study after discussion with the PI.

Participants should receive analgesics, antiemetics, anti-infectives, antipyretics, blood products, and any other best supportive care measures (excluding anticancer therapy) as necessary, assuming no drug interaction potential.

Growth factors (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]) can be used to support participants who have developed dose-limiting Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection. The use of erythropoiesis stimulating agents is permitted according to the American Society of Clinical Oncology Guidelines (Rizzo, Brouwers et al. 2010).

All concomitant medications and any procedures performed during the study, including those used to treat AEs, are to be recorded.

6.0 Study Processes and Assessments

6.1 Schedule of Events

Table 3 provides the schedule of assessments for this study. Pre-screening or screening for IDH1 will occur via CLIA certified standard of care sequencing. After obtaining written informed consent for the study overall, all participants will undergo Screening procedures to determine eligibility within 28 days prior to the start of study treatment on C1D1. Participants are to attend study center visits as outlined in the Schedule of Assessments (Table 3).

An EOT Visit will be conducted as soon as possible after discontinuing study treatment (within 5 days of last dose of study treatment, if study drug dosing has not been delayed); in addition, participants are to attend a Follow-up Visit 28 days (no more than 33 days) after the last dose of study treatment for final safety assessments. If a participant's dose is held and it is subsequently decided to discontinue treatment, the EOT Visit should be conducted as soon as possible, within 28 days (and no more than 33 days) after the last dose of study drug.

Table 3: Study Calendar Showing Schedule of Assessments

Visit/Cycle:	**Screening**	**Cycle 1 (±2 days)**		**Cycle 2 (±2 days)**		**Cycle 3 (±2 days)**		**Cycle 4+[7] (±2 days)**	**EOT**	**Post Treatment Follow-up**	**PFS Follow- up**
Study Day:	**D-28**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D+28**		
Informed Consent	X										
Review Entry Criteria	X										
Demographics	X										
Disease History	X										
Medical and Surgical History	X										
Medication History	X	X	X	X	X	X	X	X	X		
Complete Physical Exam	X	X				X		X	X		X
Symptom Directed Physical Exam			X	X	X						
Vital Signs	X	X	X	X	X	X		X	X		X
ECG	X	X	X	X	X	X		X	X		

Visit/Cycle:	Screening	Cycle 1 (±2 days)		Cycle 2 (±2 days)		Cycle 3 (±2 days)		Cycle 4+[7] (±2 days)	EOT	Post Treatment Follow-up	PFS Follow- up
Study Day:	**D -28**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D +28**		
ECOG PS	X	X		X		X		X	X		X
Fresh/Banked Tumor Tissue[1, 11]	X			X							
Laboratory Evaluations[12]											
Hematology	X	X	X	X	X	X	X	X	X		
Serum Chemistry	X	X	X	X	X	X	X	X	X		
Thyroid Studies	X			X		X		X[10]	X		
Pregnancy Test[2]	X			X		X		X			
Correlative Blood – PBMC, serum[3]		X	X	X		X		X	X		
Germline DNA		X									

Visit/Cycle:	Screening	Cycle 1 (±2 days)		Cycle 2 (±2 days)		Cycle 3 (±2 days)		Cycle 4+ (±2 days	EOT	Post Treatment Follow-up	PFS Follow- up
Study Day:	D-28	D1	D15	D1	D15	D1	D15	D1	D+28		
Correlative Blood - ctDNA		X	X			X		X	X		
2-HG PD Analysis (plasma)[4]		X		X				X	X		
Stool	X										

reening	Cycle 1 (±2 days)		Cycle 2 (±2 days)		Cycle 3 (±2 days)		Cycle 4 +[7] (±2 days)	EOT	Post Treatment Follow-up	PFS Follow- up
D-28	D1	D15	D1	D15	D1	D15	D1	D+28		
Registration and Treatment:										
X										
	X		X		X		X			
			X		X		X	X		
Tumor Assessments										
X	8 weeks(± 7 days) after Cycle 1 including EOT and PFS follow-up									
Other Clinical Assessments										
	X	X	X	X	X		X	X		xs
	X	X	X	X	X		X	X		X

Abbreviations: D = Day; DNA= deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EQT= end of treatment; PFS = progression-free survival; PS= performance status; RECIST = Response Evaluation Criteria in Solid Tumors

Archival tissue to be submitted on all patients. At least 10 (solid tumor) patients to be biopsied, pending funding

[2]Female participants with reproductive potential must have negative serum pregnancy testing within 24 h prior to the initial administration of study drug, then every 4 ± 1 week, or a negative confirmation from an obstetrician in case of equivocal serum pregnancy results. Females of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who have not been naturally postmenopausal (ie, who have not menstruated) for at least 24 consecutive months (ie, have not had menses at any time in the preceding 24 consecutive months).

[3] ctDNA to be collected C1D1, C1D15, C3D1, C4D1 (time of pt response assessment) and at time of progression. PBMCs to be collected C1D1, C1D15, C2D1, C3D1, C4D1 (time of pt response assessment) and at time of progression.

Germline DNA to be collected C1D1

Serum to be drawn C1D1, C1D15, C2D1, C3D1, C4D1 (time of pt response assessment) and at the time of progression.

[4]Modification for 2-HG levels: Drawn on C1D1 (as baseline), at 1 month (C2D1), 3 months (C4D1) and at time of disease progression

[5]Submit all required materials (eligibility checklist, source documentation, and signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 h prior to the participant's scheduled therapy start date. Full details listed in Registration Procedures

Note that nivolumab will be dosed Q28 days via IV infusion, while ivosidenib will be continuous PO daily dosing

After cycle 3 (i.e., from C4 onwards), study visits will be monthly.

[8] SAEs occurring within 100 days post last study drug dose must be reported to BMS World Wide Safety and Agios

[9] Specific imaging modalities detailed under section 6.5 (Efficacy Assessments)

[10] As clinically indicated

[11] See Section 1.3.4 for research blood draw time points

[12] See Section 6.4.3 - Safety Laboratory Assessments

6.2 Informed Consent

A complete description of the study is to be presented to each potential participant and a signed and dated informed consent is to be obtained before any study specific procedures are performed. A legally authorized representative may consent on behalf of a participant who is otherwise unable to provide informed consent if acceptable to and approved by the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Demographic Data and Medical, Surgical, and Medication History

Subject demographic data, including gender, date of birth, age, race, and ethnicity, will be obtained during Screening, according to applicable local regulations.

A complete medical and surgical history, including the site of underlying sites of malignancy and the date of confirmation of the histologic diagnosis of the underlying malignancy will be obtained during Screening. The medical history is to include all relevant prior medical history as well as all current

medical conditions.

All medications administered and procedures conducted within 28 days prior to C101 should be reported in the medical record. In addition, all prior treatment regimens for the underlying malignancy will be reported.

6.3 Gene Mutation Analysis and Molecular Characterization

Tissue from a pre-treatment fresh or banked tumor biopsy will be required for all screened participants. Corresponding pathology report is also required if available.

6.4 Safety Assessments

6.4.1 Physical Examination and ECOG Performance Status

A complete physical examination, including assessment of weight, will be obtained at Screening, C1D1, C301 and every Day 1 of each cycle thereafter, EOT and post treatment follow up visit and PFS follow up. A symptom directed physical examination should be completed on C1D15, C2D1, and C2D15. Height will be obtained at the Screening Visit only. Participants should be monitored for rash at physical examinations and during assessments of adverse reactions.

Determination of ECOG PS will be performed at Screening, on Day 1 of each treatment cycle thereafter, at the EOT Visit, at the Post Treatment Follow-up Visit, and PFS follow up. See Appendix 11.1 for ECOG PS scoring.

6.4.2 Vital Signs and ECG

Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, will be obtained at Screening, Days 1 and 15 of Cycles 1 and 2, on Day 1 of each treatment cycle thereafter, EOT and post treatment follow up Visit and PFS follow up. Assessments should be conducted while the participant is seated or supine.

ECG will be obtained at Screening, Days 1 and 15 of Cycles 1 and 2, on Day 1 of each treatment cycle thereafter, EOT and post treatment follow up Visit. Refer to section 5.7 for management of QT prolongation.

6.4.3 Safety Laboratory Assessments

Clinical laboratory evaluations are to be performed by the local laboratory.

Clinical laboratory evaluations are to be conducted according to the Schedule of Assessments (Table 3). Clinical laboratory evaluations may be collected up to 24 h prior to study visit as long as the labs were collected within the visit window (±2 days). In addition, all clinically significant laboratory abnormalities noted on testing will be followed by repeat testing and further investigated according to the judgment of the Treating Investigator.

The safety laboratory parameters to be evaluated by the Treating Investigator are:

Hematology: Hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count and differential{% neutrophils, % bands), platelet count with differential

Chemistry: Sodium, potassium, calcium, magnesium, phosphorus, albumin, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase (LOH), alkaline phosphatase (ALP), AST, ALT, total bilirubin, direct bilirubin

Thyroid Studies: Thyroid stimulating hormone (TSH), total triiodothyronine (T3, *If TSH is abnormal},* free thyroxine (T4, *If TSH is abnormal)*

Blood for hematology and chemistries is to be obtained at screening, Cl - C3 days 1 and 15, on Day 1 of every treatment cycle thereafter, and at the EOT Visit. If assessments for hematology and serum chemistry were performed within 3 days prior to ClDI, these do not need to be repeated at the ClDl Visit.

Pregnancy Test: All WOCBP must have a negative pregnancy test to be eligible. Pregnancy testing to be done every 4 weeks±l week while on study treatment.

Adverse Events

All AEs will be graded using the NCI CTCAE version 5 grading system (Appendix 11.7).

6.5 Efficacy Assessments

6.5.1 Response to Treatment

The efficacy of ivosidenib and nivolumab will be evaluated by assessing response to treatment according to RECIST vl.1 (Appendix 11.8) or RANO Criteria (Appendix 11.9) (Eisenhauer, Therasse et al. 2009).

Radiographic assessments (CT or MRI) to obtain tumor measurements are to be conducted every 8 weeks (±7 days) from ClDI, independent of dose-delays and/or dose interruptions, and/or at any time when progression of disease is suspected. CT imaging of the chest, abdomen, and pelvis (torso) with triphasic IV contrast (30 millisieverts [mSv] per scan) should be performed at baseline and on study for solid tumor patients (not glioma patients). For participants with allergy to IV iodine contrast, CT of the chest without IV contrast and MRI of the abdomen with IV contrast should be performed at baseline and on study. For patients with solid tumors, brain scans with CT (2 mSv per scan) or MRI should be performed at baseline in participants with known treated brain metastases and on study at the same imaging time points as Torso imaging.

For the glioma cohort, MRI with contrast is required for baseline and response assessments, and CT is only allowed if an MRI is contraindicated (in the view of the treating physician). Bone scans (4 mSv per scan) will be performed at baseline if disease is suspected and on study as appropriate as the same imaging time points as Torso imaging. Any ancillary findings on the radiographic assessments will be communicated to the appropriate physician for notification to the participant. The same method (CT or MRI) should be used consistently for any given participant. For participants who discontinue study drug for reasons other than disease progression, an assessment will be conducted at the EOT Visit and every 8 weeks thereafter (with the exception of those participants who initiate a new cancer therapy after discontinuing study treatment) until any of the conditions for withdrawal of study treatments are met - as detailed in 4.4.1.

6.6 Correlative Studies

6.6.1 Nanostring Assays of Paired Samples

Morphologic predictors of response include expression of PD-Ll, an interferon gamma target indicative of an active inflammatory response to tumor, and the presence of tumor infiltrating CD8 T cells, dendritic cells, and NK cells of particular phenotypes. The therapeutic hypothesis for this study centers on the possibility that treatment with ivosidenib will either induce or augment an antitumor inflammatory response, and/or will induce production of neoantigen presenting MHC class I in the

tumor.

The primary goal of the biopsy analysis is to determine whether the tumor has sustained an infiltration by innate and adaptive immune cells, and/or increased tumor expression of antigen expression apparatus such as components of MHC Class I, consistent with the therapeutic hypothesis. The secondary goal is to determine whether either the baseline level of inflammatory infiltrate or the level induced by ivosidenib treatment is predictive of immediate an extended response to the combination of ivosidenib with nivolumab.

The primary assays for analysis of the paired biopsies are the Nanostring 10 360 assay, an extensively validated transcript profiling assay used for semi-quantitative cell enumeration and transcriptional response in biopsies (Danaher, Warren et al. 2017), as well as immunofluorescence based direct enumeration of immune cells and their spatial co-localization. Assay is subject to change based on available technologies at the time of analysis.

The primary hypothesis for statistical analysis of the paired biopsies is to accept or reject the hypothesis that the tumor inflammation signature (TIS, or T cell-inflamed GEP), a function calculated from the abundance of 18 transcripts detected in the sample (Table below), has changed in the tumor due to therapy. This function is highly correlated with anti-PDl antibody treatment outcome (Ayers, Lunceford et al. 2017).

Table 4: Eighteen Component Transcripts of Tumor Inflamed Signature (TIS) Score

TIGIT	PD-LI	PSMBIO	STATI
CD27	CXCR6	IDO1	HLADRBI
CD8A	CMKLRI	CXCL9	HLAE
PD-L2	NKG7	HLADQAI	
LAG3	CCIS	CD276	

Several outcomes may be envisaged:

- Ivosidenib causes an increase in TIS in a subset of patients and that increase is associated with an increase in PFS.
- Baseline TIS is associated with PFS, and changes induced ivosidenib treatment are not associated with changes in PFS.
- Ivosidenib does not affect TIS in any patient.

7.0 Safety and AEs Assessing, Recording, and Reporting

AEs will be monitored throughout the study (once participants have received study drug); SAEs that are assessed as related to study treatment that occur> 100 days post treatment also are to be reported. All AEs should be monitored until they are resolved or are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

Adverse Event Reporting Period

Investigators will seek information on AEs at each participant contact, as outlined below. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record.

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive study procedures such as biopsies).

After initiation of study drug, all AEs and SAEs regardless of attribution will be collected at every visit until 100 days following the last administration of study treatment or until study discontinuation/termination or until initiation of subsequent anticancer therapy, whichever occurs first. Participants will be assessed at the Follow-up Visit to determine if any new AEs have occurred. After this period, Investigators should report only SAEs that are considered to be related to study treatment.

All Serious Adverse Events (SAEs) that occur following the participant's first does of study treatment through 100 days of discontinuation of dosing must be reported to according to section 7.3, whether related or not related to study drug.

Following the participant's first dose of study treatment, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.

7.1 Definition of AEs

7.1.1 AEs

An AE (also referred to as an adverse experience) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any of the following:

Any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug.

Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).

Recurrence of an intermittent medical condition (eg, headache) not present at baseline.

Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.

AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, screening invasive procedures such as biopsies).

An AE can arise from any use of the drugs (eg, off-label and in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.1.2 Progression of Underlying Malignancy

Progression of underlying malignancy should not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST vI.1 (solid tumor) or RANO

(glioma). Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the participant's underlying malignancy or does not fit the expected pattern of progression for the disease.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

7.1.3 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE except as outlined below.

The following hospitalization scenarios are **not considered** to be SAEs:

- Hospitalization for respite care
- Standard procedure for protocol therapy administration; however, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- Administration of blood or platelet transfusion as routine treatment of studied indication; however, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling); however, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

7.1.4 Persistent or Recurrent AEs

A persistent AE is one that extends continuously, without resolution, between participant evaluation time points. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens in intensity or grade.

A procedure that is planned (i.e., planned prior to start of treatment on study); must be documented in the source document and the eCRF; hospitalization or prolonged hospitalization for a complication remains a reportable SAE

An elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline

7.1.5 Related AES

A related AE is any AE for which there is a reasonable possibility that the drug(s) caused the AE.

Assessment of Causality of AEs

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered

to be related to the study treatment, per Table 5 below. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, considering especially the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (where applicable)
- Known association of the event with the study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5: Causal Attribution Guidance

• **Is the adverse event suspected to be caused by the study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?**	
Definitely related	There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.
Probably related	There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge.
Possibly related	There is a reasonable possibility that the drug caused the adverse event. The investigator can provide a rationale or evidence to suggest a causal relationship between the study drug and the adverse event other than just a temporal relationship.
Unlikely related	There is only a temporal relationship to study drug, but not a reasonable causal relationship between the investigational product and the AE.
Unrelated	There is no temporal relationship to study drug; there is a reasonable causal relationship to another drug product, concurrent disease, or circumstance.

7.1.6 Serious AEs (SAEs)

An AE or suspected adverse reaction is considered a serious AE (SAE) if, in the view of either Investigator, it could result in any of the following outcomes:

- Fatal (i.e., the AE actually causes or leads to death).
- Life-threatening. Life-threatening means that the participant was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form.

- In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned}.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect in a neonate/infant born to a mother or father exposed to study treatment.
- Important medical event. An important medical event is an event that may not result in death, be life- threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to NCI CTCAE criteria}; the event itself may be of relatively minor medical significance (such as severe headache without any further findings}.

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

7.2 Procedures for Reporting AEs and SAEs

7.2.1 Routine AE Reporting

All AEs (serious and non-serious} spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded. The Investigator must determine the intensity of any adverse events according to the NCI CTCAE version 5 and their causal relationship to study treatment. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

7.2.2 SAE Reporting

All events meeting the definition of a serious adverse events, which occur after the date of first dose of study treatment and within 100 days of the last dose of study treatment, should be reported according to the departmental SAE checklist and SAE form. The initial SAE form should be sent to the following within 1 business day of the Principal Investigator becoming aware:

1. Sponsor-Investigator: Jason Luke, lukejj@upmc.edu
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.
4. BMS SAE Email Address: Worldwide.Safety@BMS.com or facsimile +1 609-818-3804
5. Servier SAE Email Address: pharmacovigilance-US@servier.com

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections Band C of the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Pregnancies and overdoses must also be reported and submitted as instructed above.

Follow-up reports:

Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form. All SAEs should be followed to resolution or stabilization.

The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

7.2.3 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded rather than only individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded.

7.2.4 AEs Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events.

7.2.4.1 QT Prolongation

Prolongation of heart-rate corrected QT (QTc) interval has been observed in monkeys at relatively high doses of ivosidenib as well as in patients while receiving ivosidenib. Please refer to the current ivosidenib 1B for detailed information.

Participants may be at increased risk for the development of QT prolongation when treated with ivosidenib in combination with fluoroquinolones, azole antifungal agents, or serotonin (S-HT3) antagonists. Investigators need to be vigilant regarding concomitant medications associated with QT

prolongation, and if no other therapeutic options are available, monitor participants receiving AG-120 with the combination of these drugs, and evaluate ECG and electrolytes (including potassium, magnesium, and calcium) particularly in participants presenting with nausea, vomiting, or diarrhea.

Participants who experience prolongation of the heart-rate corrected QT interval, Fridericia's correction (QTcF) to> 480 ms (Grade 2) while treated with ivosidenib, should be promptly evaluated for causality of the QTc prolongation and managed according. For details, refer to the current Investigator brochure. Once the signs and symptoms resolve and the participant's clinical condition improves, ivosidenib may be reinitiated.

7.2.4.2 Leukoencephalopathy

Leukoencephalopathy is a potential risk associated with ivosidenib treatment based on clinical safety findings observed across the ivosidenib clinical development program. Progressive multifocal leukoencephalopathy (PML) and posterior reversible encephalopathy syndrome (PRES), both Grade 3 SAEs, have each been reported in one participant.

The signs and/or symptoms of PML may begin gradually, usually worsen rapidly, and vary depending on which part of the brain is infected. Signs and symptoms may include difficulty with walking and other movements, progressive weakness, decline in mental function, visual field deficits, and speech and language disturbances. Rarely, headaches and seizures occur. Participants should be monitored for onset of signs or symptoms suggestive of PML. Diagnostic evaluations may include consultation with a neurologist, MRI of the brain, lumbar puncture, and/or brain biopsy as clinically warranted. The Investigator should immediately contact the Study Medical Monitor when PML is a suspected or confirmed diagnosis. Treatment with ivosidenib should be suspended in the setting of suspected PML and permanently discontinued in participants with confirmed PML.

PRES is a rare clinico-radiological neurological syndrome (Linda and von Heijne 2015). Clinical characteristics may include sub-acute onset of headache, hypertension, seizures, altered mental status, visual disturbances, and occasionally other focal neurological signs. Radiologically, signs of vasogenic edema are usually seen bilaterally in the white mater of the parieto-occipital lobes, but changes can also be seen in frontal and temporal lobes, brainstem, cerebellum, and in cortical as well as deep gray matter. Participants should be monitored for onset of neurological signs and/or symptoms that are clinically associated with PRES. Diagnostic evaluations may include consultation with a neurologist, MRI of the brain, and other recognized standard of care measures as clinically warranted. Additionally, the Investigator should consult with the Study Medical Monitor for management guidelines to be utilized in the setting of suspected or confirmed PRES.

Refer to Section 6.5.8.1 (PML) and Section 6.5.8.2 (PRES) in the AG-120 IB for further details on these events.

7.2.4.3 Sensorimotor Neuropathy/Polyneuropathy

Sensorimotor neuropathy/polyneuropathy is a potential risk associated with ivosidenib treatment based on safety findings observed across the ivosidenib clinical development program. Guillain-Barre syndrome (Grade 2 SAE in one participant; Grade 3 SAE in one participant) and lumbosacral plexopathy (Grade 2 SAE in one participant) are rare, serious syndromes that affect the central and peripheral nervous systems.

Participants should be monitored for onset of new signs or symptoms or motor and/or sensory

neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. If a participant experiences signs or symptoms suggestive of sensorimotor neuropathy, Guillain-Barre syndrome, or lumbosacral plexopathy, diagnostic evaluation may include a consultation with a neurologist, lumbar puncture, and electromyography. The Investigator should immediately contain the Study Medical Monitor when Guillain-Barre syndrome is a suspected or confirmed diagnosis. Ivosidenib should be permanently discontinued in participants with a confirmed diagnosis of Guillain-Barre syndrome.

Refer to Section 7.2.4.3 (Sensorimotor Neuropathy/Polyneuropathy) in the AG-120 1B for further details on these events.

7.2.5 Overdose or Incorrect Administration

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects. If the associated AE fulfills serious criteria, the event should be reported to the Lead Investigator within 1 business day after learning of the event. All occurrences of overdose of nivolumab must be reported as an SAE to Agios and BMS World Wide Safety.

7.2.6 Review of Safety Information: Sponsor Responsibilities

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

7.2.7 IND Safety Reports

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND} in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under Sections 7.2.10.1 to 7.2.10.4 below. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

7.2.7.1 Serious and unexpected suspected adverse reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those

events occur more frequently in the drug treatment group than in a concurrent or historical control group.

7.2.7.2 Findings from other studies

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section 1.5.1), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

7.2.7.3 Findings from animal or in vitro testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

7.2.7.4 Increased rate of occurrence of serious suspected adverse reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

7.2.8 Submission of IND safety reports

The sponsor must submit each IND safety report in a narrative format or on Form FDA 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a Form FDA 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

7.2.8.1 Unexpected fatal or life-threatening suspected adverse reaction reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

7.2.8.2 Reporting format or frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting

format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

7.2.8.3 Investigations of marketed drugs

A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements.

7.2.8.4 Reporting study endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under Section 1.7 third bullet of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under Serious and unexpected suspected adverse reaction as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

7.2.9 Follow-up

- The sponsor must promptly investigate all safety information it receives.
- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under section IND safety reports of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

7.2.10 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

The principal investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

7.2.11 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is

determined to be 1) associated with the investigational drug or study treatment(s); 2) serious; and 3) unexpected. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) associated with the investigational drug or study treatment(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

7.3 Pregnancy Reporting

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (e.g., spontaneous abortion, which may qualify as an SAE).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant or partner of a male participant occurring while the participant is on study treatment, within 28 days or during at least 5 ti12 after product administration of the participant's last dose of study treatment, are considered immediately reportable events. If a female partner of a male participant taking investigational product becomes pregnant, the male participant taking study treatment should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. In pregnant female participants, study treatment is to be discontinued immediately and the participant instructed to return any unused study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately to the Lead PI. The Investigator must follow-up and document the course and outcome of all pregnancies even if the participant was discontinued from the study or if the study has finished. The female participant or partner of a male participant should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy.

All outcomes of pregnancy (from a female participant or the sexual partner of a male participant) must be reported by the Investigator to the Lead PI as an SAE within 28 days after he/she has gained knowledge of the delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 h in accordance with the procedure for reporting SAEs.

Females of reproductive potential must have a negative serum pregnancy test prior to the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results. Women of reproductive potential, as well as fertile men and their partners who are female with reproductive

potential, must agree to use two effective forms of contraception (including at least one barrier form) from the time of giving informed consent throughout the study and 7 months (both females and males) following the last dose of study drug. Women of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy or bilateral oophorectomy or who have not been naturally postmenopausal (ie, who have not menstruated at all) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Men with partners who are women with reproductive potential must agree that they or their partners will use two effective forms of contraception (including at least one barrier form) when engaging in reproductive sexual activity throughout the study and will avoid conceiving 7 months after the last dose of study treatment.

Effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

7.3.1 Specific BMS Pregnancy Reporting

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 *ti12* after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported.

Any pregnancy that occurs in a female study participant or a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected. The female participant or female partner must sign an informed consent form for disclosure of this information.

7.4 Follow-up of Participants after AEs

7.4.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all SAEs considered related to study treatment or trial-related procedures until a final outcome can be reported.

7.4.2 Post-study Adverse Events

At the treatment discontinuation visit, the Investigator should instruct each participant to report to the Investigator any subsequent AEs that the participant's personal physician believes could be related to prior study treatment or study procedures.

The Investigator should notify the Sponsor of any death, SAE, or other AE of concern occurring at any time after a participant has discontinued study participation if the event is believed to be related to prior study treatment or study procedures. The Sponsor should also be notified if the Investigator

becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a participant that participated in this study.

7.5 Definition of DLT

AEs will be graded according to the NCI CTCAE version 5.0.

A DLT is defined as any AE (except clearly attributable to an extraneous cause, such as disease progression) occurring in Cycle 1 (only) that satisfies at least one of the following criteria:

Non-hematologic AEs:

- Grade 3 or 4 nausea or vomiting:
    - If no anti-emetic prophylaxis was administered, Grade 3 or 4 nausea or vomiting is considered a DLT only if lasting> 3 days despite maximum supportive care.
    - Grade 3 or 4 nausea or vomiting despite anti-emetic prophylaxis of any duration will be considered a DLT.
- Grade 3 or 4 diarrhea:
    - If no anti-diarrheals were administered, Grade 3 or 4 diarrhea is considered a DLT only if lasting> 3 days despite maximum supportive care.
    - Grade 3 or 4 diarrhea despite the administration of anti-diarrheals of any duration will be considered a DLT.
- Any other Grade 3 or 4 non-hematological AE, with the exception of asymptomatic amylase/lipase or other biochemical marker that does not resolve with adequate treatment and/or within a week.

Hematologic AEs:

- Absolute neutrophil count (ANC) < 500/mm^3 for more than 7 days
- Febrile neutropenia (a disorder characterized by an ANC < 1,000/mm^3 and single temperature 2: 38.3 °C or sustained temperature of 2: 38.0 °C for more than 1 h)
- Platelets < 25,000/mm^3
- Hemoglobin< 8.0 g/dL
- Grade 3 hemorrhage associated with thrombocytopenia less than Grade 4 (ie, grade 3 hemorrhage with platelets> 25,000/mm^3).

General:

- Interruption of ivosidenib dosing for more than a total of 2 weeks (not necessarily consecutive) during Cycle 1, if due to AEs related to ivosidenib.
- Delay of starting Cycle 2 for> 2 weeks, if due to AEs related to ivosidenib.

All safety data in Cycle 1 and subsequent cycles will be monitored on an ongoing basis.

A patient who experiences a DLT at any dose level will receive appropriate treatment and supportive

care as necessary and will be monitored closely until resolution of the AE to Grade Oto 1 severity or Baseline severity, whichever is more abnormal, or until the AE is stabilized at any acceptable grade.

Patients who experience a DLT but who, in the opinion of the Investigator, are deriving clinical benefit will be permitted to continue treatment with ivosidenib at a lower dose that has been demonstrated to be well tolerated upon reasonable resolution of the DLT.

AEs will be tabulated by type, severity, and attribution. Immune responses, as assessed at baseline, post ivosidenib lead in, and week 9 (first restaging) will be analyzed by mixed effects regression for longitudinal data. Baseline and post-treatment values will also be compared between responders and non-responders.

8.0 Statistical Analysis Plan and Sample Size Justification

The primary and secondary objectives and endpoints are in Section 2. The accrual goal for this trial is 35 participants evaluable for both safety and efficacy.

8.1 Evaluability

8.1.1 Evaluability for Safety

Participants will be evaluable for safety if they receive a minimum of 75% of the first cycle of ivosidenib and have received one dose of nivolumab, unless they experience a DLT. The DLTwindow will be defined as from first dose through completion of the first 28-day cycle.

8.1.2 Evaluability for Efficacy

Patients will be evaluable for the co-primary efficacy objectives of response and PFS at the time of first radiographic assessment at week 12 of the study. Patients must receive a minimum of 75% of the first cycle of ivosidenib and have received one dose of nivolumab to be considered evaluable. Any patient having taken 75% of ivosidenib with clear clinical progression prior to first restaging at will also be evaluable for this objective.

8.2 Statistical Analysis Plan

8.2.1 Primary Objective: Efficacy

Given that the response rate would be expected to be< 10% and PFS < 3.5 months in this patient population of IDHI mutant advanced solid tumors or gliomas, we will consider a participant to have had a positive outcome if they have a positive PFS6 (PFS6 is scored as either No or Yes) *and* they have had at least a partial response (evaluated by RANO in glioma patients and RECIST in patients with solid tumors) at the 12 week scan.

An Optimal Simon two-stage design is employed, where a probability of positive outcome less than 0.1 would not be promising and a probability of positive outcome 0.3 would warrant further interest. In the first stage, 18 participants will be accrued. If three or more participants have positive outcomes, 17 more participants will be accrued. If 7 or more out of the 35 participants have positive outcomes, the null hypothesis p<0.I will be rejected at a=0.05. This design has 90% power if p > 0.3.

For all tumor types, six-month progression-free survival (PFS6) is defined as survival to six months after the initiation of treatment without objective tumor progression

The probability of positive outcome and 95% confidence interval will be estimated using the method of Koyama and Chen (Koyama and Chen 2008).

8.2.2 Secondary Objective: Safety

Summary tables and listings for adverse events will include treatment-emergent adverse events (AEs), where AE is defined as any AE that occurred between the first dose of any study drug and 28 days following the last dose of any study drug. The incidence of AEs (new or worsening from baseline) will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and/or preferred term, severity (based on NCI CTCAE vS.0 grading as assessed by the Investigator), seriousness, and relation to study treatment. All tabulations will be accompanied by probability of events and exact (Clopper-Pearson) 95% confidence intervals. The following summaries will be produced:

- All AEs
- AEs leading to dose modifications
- Treatment-related AEs
- Grade 3 or higher AEs
- Grade 3 or higher treatment-related AEs
- The most commonly reported AEs (ie, those events reported by 10% of all participants)
- SAEs
- Discontinuations due to AEs

By- participant listings will be provided for on-treatment deaths (on-treatment is defined as the period starting from the first dose to 100 days after the last dose), AEs, SAEs, and AEs leading to discontinuation of treatment.

8.2.2.1 Laboratory Abnormalities

For laboratory tests included in the NCI CTCAE version 5.0, laboratory data will be graded accordingly; a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by NCI CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, serum chemistry and coagulation studies, and urinalysis laboratory tests:

- Descriptive statistics for the actual values and/or change from baseline of clinical laboratory parameters over time.
- Shift tables using NCI CTCAE grades to compare baseline to the worst on-treatment value (for laboratory tests where NCI CTCAE grades are not defined, shift tables using the low/normal/high/[low and high] classification to compare baseline to the worst on-treatment may be generated).
- Listing of all laboratory data with values flagged to show the corresponding NCI CTCAE grades and the classifications relative to the laboratory normal ranges.

8.2.2.2 Other Safety Data

- Descriptive statistics for the actual values and/or the changes from baseline of vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) over time will be summarized.
- Descriptive statistics of ECOG PS over time will be summarized by frequency. Shift tables

may be provided for ECOG PS from baseline to worst value of post-baseline assessments.

- Categorical analysis of QTcF intervals may be performed. Maximum QTcF intervals and maximum changes from baseline may also be summarized similarly in a separate display. ECG abnormalities if collected will be presented in a data listing.
- Additional safety analyses may be performed if deemed necessary.

8.2.3 Secondary Objective: Longitudinal Clinical Outcomes

The distribution of adverse events over time (during and after Cycle 1) will be tabulated and described graphically. Surviving participants without progression will be censored as of the date of the last negative examination. Progression-free survival, defined from the beginning of treatment as survival without objective tumor progression, up until 18 months after the last efficacy-evaluable participant has initiated treatment will be characterized by the product-limit (Ka-plan-Meier} method with a 95 confidence region.

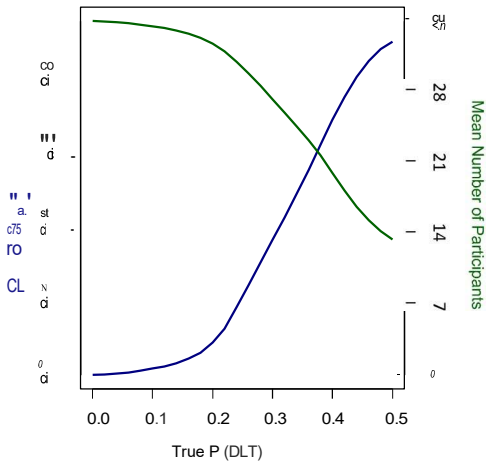
8.2.4 Exploratory Objective: Biomarkers and Response to Treatment

DLT (defined in Section 7.5} will be monitored throughout the trial and a stopping rule will be evaluated after every five participants have started Cycle 1. If the number of participants experiencing DLT equals or exceeds the number specified in the following table, the trial will be paused and the dosing reconsidered:

# Participants	# DLTs
5	3
10	5
15	7
20	8
25	10
30	**12**

8.3 Justification of Design

This trial employs an optimal Simon two-stage design with a= 0.05, assuming that the treatment is not worthy of further consideration if the probability of patients achieving a positive outcome (at least partial response and PFS 6 months} is less than 0.1. The design has 90% power if the true probability of positive outcome is 0.3 or greater. The stopping rule is designed to pause the trial if P(P[DLT > 0.3] > 0.7}, using a beta-binomial model with a=l and =4; that is, our prior expectation based on information equivalent to a total of five patients is that the P(DLT} = 0.2. The operating characteristics of the stopping rule, derived from a Monte Carlo simulation, are presented in the figure, where it is seen that, for instance, if the true probability of DLT is 0.3, the probability that the trial pauses is 0.4 and the expected number of participants accrued is 12.



9.0 Study Management, Agreement, and Ethical Considerations

9.1 IRB Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 FDA Approval

This study will be conducted under an IND held by Dr. Jason Luke at the UPMC Hillman Cancer Center, which will be responsible for facilitating all communications with the FDA on behalf of the IND holder.

9.3 Required Documentation

Prior to the commencement the study the UPMC Hillman Cancer Center audit and trial oversight processes must be reviewed and approved by the Protocol Review and Monitoring System or Protocol Review Committee (PRMS/PRC).

Before the study can be initiated, the following documentation must be provided to PRMS/PRC at the UPMC Hillman Cancer Center:

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the PI and any sub-investigators who will be involved in the

study.

- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Financial disclosure forms for the PI and any sub-investigators who will be involved in the study
- Investigational drug accountability standard operating procedures

Additionally, before the study can be initiated, the required executed research contract/subcontract must be on file with the UPMC Hillman Cancer Center. Once all required documents are received, reviewed and approved by the Coordinating Center's designated representative(s), a patient may be enrolled.

9.4 Data and Safety Monitoring Plan

Investigators, Sub-investigators and clinical research staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- Serious adverse events
- Subject safety issues
- Recruitment issues
- Accrual
- Protocol deviations
- Unanticipated Problems
- Breaches of confidentiality

Minutes from the disease center DSMB meetings are available to those who are unable to attend in person or participate via teleconference.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria Version 5.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be

reviewed bi-annually.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

9.5 Amendments to the Protocol

All modifications to the protocol, consent form, or questionnaires will be submitted to the University of Pittsburgh IRB (Pitt IRB) for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the Pitt IRB, the Regulatory Specialist will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Specialist indicating that the amendment was received by the institution and that it will be submitted to the local IRB.
- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.
- **The UPMC Hillman Cancer Center version date, amendment number, or both must appear on the affiliate consent form and the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Pittsburgh IRB (Pitt IRB) amendment approval letter that is sent with the protocol/amendment mailing.

The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated CRS Regulatory Specialist as soon as it is received.

9.6 Annual IRB Renewals, Continuing Review, and Final Reports

A continuing review of the protocol will be completed by the Pitt IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Specialist. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

9.7 Record Retention

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

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

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Study Site Investigators

The PI is responsible for the conduct of the clinical trial in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study PI is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site PI will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

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11.0 Appendix

11.1 Eastern Cooperative Oncology Group Performance Status Scoring

Grade	Symptomatology
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: (Oken, Creech et al. 1982)

11.2 Prohibited Concomitant Medications

Prohibited medications and certain foods are not allowed in this study while participants are receiving study drug.

Strong CYP3A Inducers	CVP3A Substrates with a Narrow Therapeutic Window
Avasimibe, carbamazepine, phenytoin, rifampin, rifabutin, St. John's wort	Alfentanil, astemizole1, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, everolimus, sirolimus, tacrolimus, terfenadine[1]
	Sensitive P-gp Substrates with a Narrow Therapeutic Window
	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, maraviroc, ranolazine, sirolimus talinolol, tolvaptan, topotecan

Note that this is not an exhaustive list. For an updated list, see the following **link:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

CYP or P-gp substrates with a narrow therapeutic window refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes). [1] Withdrawn from the US market because of safety reasons.

11.3 New York Heart Association Classification

Class	Symptomatology
	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

11.4 Fridericia's Formula

$QTcF=QT/RR$[113]

11.5 Medications Known to Prolong the QT Interval

amiodarone	citalopram	Escitalopram	methadone	sevoflurane
astemizole	clarithromycin	Flecainide	moxifloxacin	sotalol
azithromycin	disopyramide	Halofantrine	pentamidine	sparfloxacin
bepridil	dofetilide	Haloperidol	pimozide	terfenadine
chloroquine	domperidone	Ibutilide	probucol	thioridazine
chlorpromazine	droperidol	Levomethadyl	procainamide	
cisapride	erythromycin	Mesoridazine	quinidine	

Please note that this is not an exhaustive list. For an updated list, see the following link: http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm

11.6 Representative Examples of Low-Fat and High-Fat, High-CalorieMeals

Low-fat breakfast:

A} 2 slices of white bread toast, 1 tablespoon light fat margarine, 1 tablespoon of jelly, and 8 ounces of skim milk (319 calories and 8.2 grams of fat}.

B) 1 cup of cereal, 1 slice of toast with jam, 8 ounces of skim milk, and 1 cup of decaffeinated coffee or tea (520 calories and 2 grams of fat).

A high-fat breakfast consists of the following and may be adapted to the local regional preference: 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk. This representative high-fat breakfast contains approximately 1000 calories and 58 grams of fat.

11.7 National Cancer Institute Common Terminology Criteria for Adverse Events

The NCI CTCAE, version 5.0, can be accessed using the following link:

http://evs.nci.nih.gov/ftpl/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.Sx11.pdf

11.8 RECIST vl.1

Tumor lesions are to be categorized as measurable versus non-measurable and target versus non-target based on RECIST vl.1 (Eisenhauer, Therasse et al. 2009).

Measurable Lesions:

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15mm on the short axis when assessed by CT scan.

Non-measurable Lesions:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions, including leptomeningeal disease, ascites, pleural or pericardia! effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target Lesions:

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Pathological lymph nodes that are defined as measurable and identified as target lesions must have a short axis of 15 mm by CT scan. Only the short axis of these nodes contributes to the baseline sum.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions:

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent' or 'unequivocal progression.'

The following criteria outlined in Table 6 will be used to assess response to treatment.

Table 6: Disease Response Criteria for Target and Non-target Lesions

Category	Response Criteria	
	Target Lesions	**Non-Target Lesions/Tumor Markers**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm	Disappearance of all non-target lesions, and normalization of tumor marker level All lymph nodes must be non-pathological in size (<10 mm short axis).
Partial Response (PR)	A 30% decrease in the sum of the diameter of target lesions, taking as reference the baseline sum diameter	**N/A**
Stable Disease (SD)/ Incomplete Response	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameter since the treatment started	Persistence of 1 or more non-target lesion(s) and/or Maintenance of tumor marker levels above the normal limits

Progressive Disease	A 20% increase in the sum of the diameter of target lesions, taking as reference the smallest sum diameter recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm, or The appearance of 1 or more new lesions	Appearance of 1 or more new lesions, and/or Unequivocal progression of existing non-target lesions

Table 7: Overall Disease Response Criteria

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Incomplete response/Non-Progressive disease	No	PR
SD	Incomplete response/Non-Progressive disease	No	SD
Progressive disease	Any	Yes or no	Progressive disease
Any	Progressive disease	Yes or no	Progressive disease
Any	Any	Yes	Progressive disease

Abbreviations: CR= complete response; PR= partial response; SD= stable disease.

11.9 RANO Criteria

Table 11.9.1: RANO Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteriaa
Complete response	Requires all of tbe following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (Tl/FLAIR) lesions; subjects must be off corticosteroids (or on physiologic replacement doses only)· and stable or improved clinically. ote: subjects with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: 2:'. 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable dis ase· no new lesions; stable or .improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Subjects with nonmeasurable d.isease *only* cannot have a partial response; the best response possible is stable disease.
Stable disease	Requir s a!] of the following: does not qualify for complete response, partial response, or progression; stab.le nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroi.maging, aud subsequent follow-up imaging shows that thi increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ;:,: 25% increase in sum of the products of perµ nd..icular 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•; significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation oftberapy' not cause by comorbid events (eg, radiation therapy, demyelination, ischernic injury, infection, seizures, post-operative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

NOTE: Radiologic interpretation guidelines, definitions and rumor measurement instructions will be provided separately in a separate imaging manual. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.

Abbreviations: MRI, magnetic resonance imaging· FLAIR, fluid-attenuated inversion r covery

* Stable doses of corticosteroids include subjects not 011 corticosteroids

[a] From: Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorenson AG, Galanis E, et al. Updated Response Assessment Criteria for High-Grade Gbomas: Response Assessment in euro-Oncology Working Group; J Clin Oncol. 2010 Apr IO; 28(11):1963-72.

Table 8: Assessment of Best Overall Response

Best Overall Response	Criteria
Complete Response (CR)	CR observed in consecutive assessments 2'. 4 weeks apart per RANO
Partial Response (PR)	PR observed in consecutive assessments 2'. 4 weeks apart per RA 0
Stable Disease (SD/	SD observed and does uot qualify for CR or PR **or** Suspected PD followed with histologic results not confinning PD, and no CR, PR or SD observed
Not valuable ( )	Insufficient data to detennine disease progression or response
Progressive Disease (PD)	No CR, PR, or SD prior to PD

a To qualify for SD there must be a minimum on-treatment period of 10 weeks.

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11.10 Patient Pill Diary

Study name: Testing AG-120 in Combination with Immunotherapy

Please carefully read and follow these instructions:

- Bring this Pill Diary and any remaining AG-120 pills to clinic visits so your doctor can make sure that you are taking the pills correctly.
- Store the pills at room temperature at 20°C to 25°C (68°F to 77°F).
- Each dose is__ pills. Take each dose by mouth at the same time every day with one glass of water. Tablets should be swallowed whole. *You can toke the pills with or without meals.*

  If you miss taking a pill on time (a dose is missed) or you vomit after taking the pill, please do not repeat the dose.

  A dose is missed when more than 2 hours from the normal scheduled dosing time has elapsed.
- In the boxes below, note the date and time each day you take the AG-120 study drug pills:

Patient Initials **(FML):**

Start Date **(mm/dd/yyyy):**

/ /

Cycle Number_____Dose _____

Research Assistant Signature:_____

Date: _____

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Day 1 Date:_____ Time:	Day2 Date:_____ Time:	Day3 Date:_____ Time:	Day4 Date:_____ Time:	Day 5 Date:_____ Time:	Day6 Date:_____ Time:	Day7 Date:_____ Time:
Days Date:_____ Time:	Day9 Date:_____ Time:	Day 10 Date:_____ Time:	Dayll Date:_____ Time:	Day 12 Date:_____ Time:	Day 13 Date:_____ Time:	Day 14 Date:_____ Time:
Day 15 Date:_____ Time:	Day 16 Date:_____ Time:	Day 17 Date:_____ Time:	Day 18 Date:_____ Time:	Day 19 Date:_____ Time:	Day 20 Date:_____ Time:	Day 21 Date:_____ Time:
Day22 Date:_____ Time:	Day23 Date:_____ Time:	Day 24 Date:_____ Time:	Day25 Date:_____ Time:	Day 26 Date:_____ Time:	Day 27 Date:_____ Time:	Day 28 Date:_____ Time: