Protocol(a): H9H-MC-JBAL

A Phase 2 Study of LY2157299 Monohydrate Monotherapy or LY2157299 Monohydrate plus Lomustine Therapy compared to Lomustine Monotherapy in Patients with Recurrent Glioblastoma

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Approval Date: 18-Mar-2015

1. Protocol H9H-MC-JBAL(a)
A Phase 2 Study of LY2157299 Monohydrate Monotherapy or LY2157299 Monohydrate plus Lomustine Therapy compared to Lomustine Monotherapy in Patients with Recurrent Glioblastoma

LY2157299 Monohydrate

This is a 3-arm, randomized, multicenter, global, Phase 2 study of LY2157299 monohydrate monotherapy or LY2157299 monohydrate plus lomustine therapy compared to lomustine plus placebo therapy in patients with relapsed glioblastoma.

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Protocol Electronically Signed and Approved by Lilly: 11 November 2011
Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 18-Mar-2015 GMT

2. Synopsis

Study Rationale

Transforming growth factor beta (TGF-β) is an important protein that regulates immune response to and metastatic spread of tumor cells. It is also an important regulator of neoangiogenesis.

LY2157299 monohydrate is a small molecule designed to selectively inhibit the serine/threonine kinase of the TGF-β receptor type I (TGF-βRI). Thus, the antitumor effect of LY2157299 monohydrate is expected to result in an increased tumor immune surveillance, reduced metastatic spread, and decreased tumor-associated neoangiogenesis.

In glioblastoma (GB), anaplastic astrocytomas, anaplastic oligoastrocytoma, or anaplastic oligodendroglioma, LY2157299 monohydrate is expected to reduce neoangiogenesis, enhance antitumor cytotoxic T cells, and reduce fibrogenic remodeling associated with tumor necrosis, radiation, and surgery.

In a recent first-human-dose study, H9H-MC-JBAH (Study JBAH), single-agent administration of LY2157299 monohydrate has been associated with [redacted] complete and [redacted] partial tumor responses in [redacted] patients with relapsed and recurrent GB. Combination with lomustine and LY2157299 monohydrate was safe at the [redacted] mg/day and [redacted]-mg/day doses. Preliminary information indicated [redacted] partial responses in [redacted] patients who were treated with the combination of lomustine and LY2157299 monohydrate.

This clinical activity of LY2157299 monohydrate together with the scientific hypothesis that blocking the TGF-β signaling pathway in GB will have clinical benefit provide the justification to conduct a trial with LY2157299 monohydrate in patients who relapsed after first-line treatment for GB.

Clinical Protocol Synopsis: Study H9H-MC-JBAL

Name of Investigational Product: LY2157299 monohydrate	
Title of Study: A Phase 2 Study of LY2157299 Monohydrate Monotherapy or LY2157299 Monohydrate plus Lomustine Therapy compared to Lomustine Monotherapy in Patients with Recurrent Glioblastoma	
Number of Planned Patients: Entered: 180 Enrolled/Completed: CCI	**Phase of Development:** 2
Length of Study: CCI years Planned first patient visit: February 2012 Planned last patient visit: August 2014 Planned interim analysis: CCI (after the first CCI patients have completed 1 cycle, discontinued from study treatment, or died [safety assessment]; after CCI patients have completed at least 3 cycles, discontinued from study treatment, or died [treatment risk assessment]; after approximately CCI events have been observed [early efficacy assessment]).	

Objectives:

The **primary objective** of this study is to compare the overall survival (OS) distributions between LY2157299 monohydrate plus lomustine therapy with lomustine plus placebo therapy (control arm), in patients who have relapsed or have progressive GB after first-line treatment with chemoradiation.

The **secondary objectives** of the study are:

Pharmacokinetic (PK)

- To determine the population PK of LY2157299 monohydrate.

Safety

- To provide additional safety information on LY2157299 monotherapy and LY2157299 plus lomustine therapy and to evaluate the safety of LY2157299 monohydrate monotherapy and LY2157299 monohydrate plus lomustine therapy relative to lomustine plus placebo therapy.

Pharmacodynamic (PD) – prognostic and predictive marker assessment

- To investigate in tumor tissue, biomarkers associated with tumor growth and the TGF-β signaling pathway (phosphorylated SMAD [pSMAD] and other TGF-β-related biomarkers, O6-methylguanine-DNA methyltransferase [MGMT] promoter status, and other relevant tumor genetic information [eg, isocitrate dehydrogenase (IDH1) mutation]) and its association with clinical responses.
- To determine serum/plasma tumor markers and secreted proteins (eg, S100β, lactate dehydrogenase [LDH], TGF-β, and platelet factor 4 [PF4]) and their association with clinical responses.
- To determine T cell biomarker responses, including T regulatory cell counts (eg, $CD4^+CD25^+FoxP3^+$T cells) and their association with clinical responses.

Efficacy

- To estimate the OS and hazard ratio (HR) between lomustine plus placebo therapy and LY2157299 monohydrate monotherapy and between LY2157299 monohydrate plus lomustine therapy and LY2157299 monohydrate monotherapy.
- To estimate progression-free survival (PFS) distributions for each treatment arm and estimate additional parameters from both the OS distributions and PFS distributions for each treatment arm (such as median OS and PFS, OS and PFS rates at 6 months).
- To estimate tumor response rate based on Response Assessment in Neuro-Oncology (RANO) criteria for each treatment arm.

Health Outcomes

- To assess patient-reported symptoms using the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) and assess neurocognitive function using the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test Parts A and B, and Controlled Oral Word Association (COWA) for each treatment arm.

Study Design: This is a 3-arm, randomized (CCI), multicenter, global, Phase 2 study of LY2157299 monohydrate monotherapy or LY2157299 monohydrate plus lomustine therapy compared to lomustine plus placebo therapy in patients with relapsed GB. In contrast to the LY2157299 monohydrate monotherapy arm, patients and investigators will be blinded to the LY2157299 monohydrate or placebo assignment in either the LY2157299 plus lomustine or the lomustine plus placebo therapy arms.
Diagnosis and Main Criteria for Inclusion and Exclusions: Male and female patients at or older than 18 years and who have relapsed GB after first-line treatment with chemoradiation, have measureable disease (response to be based on RANO criteria), and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
Test Product, Dosage, and Mode of Administration: LY2157299 monohydrate, 300 mg/day, given orally for 14 days followed by 14 days of rest, for a 28-day cycle. LY2157299 monohydrate-matched placebo, given orally for 14 days, followed by 14 days of rest, for a 28-day cycle. Lomustine will be given orally once every 6 weeks. The first lomustine dose will be 100 mg/m^2, and all following doses can be escalated to a maximum of 130 mg/m^2, at the investigator's discretion.
Planned Duration of Treatment: Patients will receive study treatment until their disease has progressed, the patient has died, or the patient discontinues for adverse events (AEs), investigator's judgment, or other reasons. **Planned Follow-Up Observation Period Per Patient:** Patients who have discontinued study treatment without progression will continue to be followed for progression or until they start a new anticancer therapy. **Planned Continued Access Period**: Patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until 1 of the criteria for discontinuation is met.
Criteria for Evaluation: Efficacy: OS; PFS; response rate (using RANO criteria). Safety: AEs (using International Common Terminology Criteria for Adverse Events [CTCAE], version 4), clinical laboratory tests, electrocardiograms (ECGs), and echocardiography (ECHO)/Doppler. Health Outcomes: MDASI-BT; HVLT-R; Trail Making Test Parts A and B; and Verbal fluency COWA. Bioanalytical: Plasma LY2157299 monohydrate concentrations will be analyzed by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS).

Statistical Methods:

Efficacy: The primary analysis is to compare the HR between LY2157299 monohydrate plus lomustine therapy with lomustine plus placebo therapy based on OS using a Bayesian OS model which augments current control data with additional information from historical data. The same Bayesian OS model will be used to estimate the HR between LY2157299 monohydrate monotherapy and lomustine plus placebo therapy. Hazard rates and ratios of and between the 3 treatment arms will also be estimated for PFS. Response rates based on the RANO criteria will be estimated.

Safety: Summary statistics, plots, and listings for all safety data will be provided. Summaries of both acute toxicity (occurring in the first 3 cycles) and chronic toxicity will be provided by treatment arm.

Health Outcomes: Neurocognitive function will be compared to population norms, summarized for each assessment period, and change over time will be explored. Time-to-neurocognitive progression will be assessed between arms. Data from the MDASI-BT will be summarized for each assessment period. This summary will include descriptive statistics and change from baseline (including time to worsening of symptoms). The MDASI-BT will be reported as core symptoms, brain tumor symptoms, symptom interference, and symptom groupings.

Pharmacokinetic (PK): Exposure of LY2157299 monohydrate using population PK analysis will be compared. This analysis will explore the impact of covariates, such as demographic factors, on the relevant PK parameters. Exploratory PK/PD analyses may be conducted to identify the exposure-biomarker response (such as S100β and LDH) relationship.

Pharmacodynamic (PD): Tumor tissue for pSMAD, MGMT promoter status, and serum assessments for S100β, LDH, and T regulatory cells will be collected and correlated with clinical benefit.

Translational Medicine: Previously described genetic profile signatures will be studied for their relevance to the clinical outcome of LY2157299 monohydrate monotherapy or LY2157299 monohydrate plus lomustine and to the clinical outcome of recurrent malignant glioma.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
AA	anaplastic astrocytomas
ACNU	nimustine, (3-[4-amino-2-methyl-5-pyrimidinyl) methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration versus time curve; exposure
AUC(0-∞)	area under the plasma drug concentration versus time curve from time 0 to infinity
AUC(0-τ)	area under the plasma drug concentration versus time curve during 1 dosing interval
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BCNU	carmustine, 1,3-bis (2 chloroetyl)-1-nitrosurea
BID	twice daily
BNP	brain natriuretic peptide
BSA	body surface area
case report form (CRF) and electronic case report form (eCRF)	Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CIOMS	Council for International Organizations of Medical Sciences

clinical research physician (CRP)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CI	confidence interval
CL/F	apparent clearance
CL_{ss}/F	apparent clearance at steady state
$C_{max,ss}$	maximum observed concentration at steady state
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on investigational product who continue to experience clinical benefit and no undue risks may continue to receive investigational product until 1 of the criteria for discontinuation is met.
COWA	Controlled Oral Word Association
CR	complete response
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	variability estimates (percent coefficient of variation)
DCSI	Development Core Safety Information
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
end of trial	End of trial is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.

enter	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the Informed Consent Form directly or through their legally acceptable representatives.
EORTC	European Organisation for Research and Treatment of Cancer
ethical review board (ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
FFPE	formalin-fixed paraffin-embedded
FHD	first-in-human Dose
FSH	follicle-stimulating hormone
GB	glioblastoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HR	hazard ratio
HVLT-R	Hopkins Verbal Learning Test-Revised
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDH1	isocitrate dehydrogenase
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IVRS	interactive voice-response system
LC/MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDH	lactate dehydrogenase

legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
LLT	lower level term
LVEF	left ventricular ejection fraction
LY2157299	LY2157299 monohydrate
MDASI-BT	MD Anderson Symptom Inventory-Brain Tumor
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguanine-DNA-methyltransferase
MID	minimally important differences
MRI	magnetic resonance imaging
NF	neurofibromatosis
NOEL	no-observed-effect level
NYHA	New York Heart Association
OA	anaplastic oligodendroglioma
OAO	anaplastic oligoastrocytoma
ORR	overall response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	Pharmacodynamic; the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure. This includes expression of markers that may have prognostic or predictive value.
PDGFRα	platelet-derived growth factor receptor alpha
PF4	platelet factor 4
PFS	progression-free survival
PFS-6	progression-free survival rate at 6 months
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome

pSMAD	phosphorylated SMAD
PS	performance status
PT	preferred term
QTc	corrected QT interval
QTcB	QT interval – Bazett's correction
QTcF	QT interval – Fridericia's correction
RA	accumulation ratio
RANO	Response Assessment in Neuro-Oncology
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SD	stable disease
SOC	System Organ Class
study completion	This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis/evaluation of overall survival or after approximately CCI survival events have occurred. Study completion occurs before the end of trial.
SUSAR	suspected unexpected serious adverse reaction
TGF-β	transforming growth factor-beta
TGF-βRI	transforming growth factor-beta receptor type I
$t_{max,ss}$	time to maximum concentration at steady state
TMZ	temozolomide
TPO	third-party organization
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limits of normal

US	United States
VEGF-R	vascular endothelial growth factor receptor
V_{ss}	steady state volume of distribution
WHO	World Health Organization

A Phase 2 Study of LY2157299 Monohydrate Monotherapy or LY2157299 Monohydrate plus Lomustine Therapy compared to Lomustine Monotherapy in Patients with Recurrent Malignant Glioma

5. Introduction

5.1. Glioblastoma

Glioblastoma (GB) is the most common and most aggressive malignant primary brain tumor in humans, accounting for 52% of all parenchymal brain tumor cases and 20% of all intracranial tumors. Glioblastomas occur in 2 to 3 cases per 100,000 people in Europe and North America. Since 2007, the World Health Organization (WHO) has issued guidelines on the diagnosis of GB and other brain tumors (Louis et al. 2007). These guidelines acknowledge the diverse histologic background of GB.

The median survival time from the time of diagnosis without any treatment is 3 months, but even with therapy, prognosis is poor, with median survival time of approximately 14 months. Glioblastoma remains a disease with an unmet medical need associated with a poor prognosis.

5.2. First-line Treatment for Glioblastoma

Despite recent improvements in the first-line treatment, the outcome is dismal (Stupp et al. 2005). Standard therapy for GB (WHO-grade IV) is surgical resection of tumor (Hess et al. 1999) and postoperative radiochemotherapy with temozolomide (TMZ) (Walker et al. 1978; Laperriere et al. 2002; Stupp et al. 2005). Adjuvant nitrosourea-based radiochemotherapy has been shown to increase survival compared to radiation alone (Stewart 2002). Compared to not using TMZ, the concomitant and adjuvant TMZ therapy has been shown to increase the progression-free survival (PFS) rate to 6 months (PFS-6; 53.9% versus 36.4%) and median survival (14.6 versus 12.1 months with hazard ratio [HR] of 0.63, 95% confidence interval [CI]: 0.52-0.75) (European Organisation for Research and Treatment of Cancer [EORTC] 26981/22981-NCIC CE3 trial, Stupp et al. 2005) with encouraging long-term efficacy (Stupp and Roila 2009). Resistance against nitrosourea and TMZ may be caused by a DNA-repair enzyme O6-methylguanine-DNA-methyltransferase (MGMT) (Esteller et al. 2000; Gerson 2004). Epigenetic silencing of the MGMT gene by promoter methylation compromises DNA repair and has been associated with longer survival in patients who receive alkylating agents. The EORTC trial 26981 also showed that patients with GB containing a methylated MGMT promoter benefited from TMZ (Hegi et al. 2005).

The use of bevacizumab in this line of treatment has not been established.

5.3. Second-Line Treatment for Glioblastoma

Once patients relapse, several treatments have been used or approved: lomustine (CeeNU®), carmustine (1,3-bis (2 chloroetyl)-1-nitrosurea [BCNU]), including Gliadel® wafers), nimustine (3-[4-amino-2-methyl-5-pyrimidinyl] methyl)-1-(2-chloroethyl)-1-nitrosourea hydrochloride

[ACNU]), TMZ, and bevacizumab (Avastin®, United States [US] and many countries outside the European Union).

Lomustine, an oral nitrosourea agent, has been shown to be useful as a single agent in both primary and metastatic brain tumors. Because of the high lipid solubility and the relative lack of ionization at physiological pH, lomustine crosses the blood-brain barrier quite effectively. Common and severe adverse events (AEs) include bone-marrow suppression (most notably thrombocytopenia and leukopenia). At the time of writing this protocol, lomustine is considered the most accepted second-line treatment in GB.

Enzastaurin and cediranib (AZD2171) were other agents investigated in the same line of treatment and compared to lomustine (Batchelor et al. 2010b; Wick et al. 2010a), but which failed to show an improvement over lomustine treatment (Table JBAL.5.1).

A number of other chemotherapeutic agents, including erlotinib, cilengitide, carboplatin, irinotecan, or fotemustine (Reardon et al. 2004, 2005, 2008; van den Bent et al. 2009) have been used as salvage therapy either alone or in combination. For patients who progress on TMZ, other combination therapies may be possible. Several recent trials have evaluated various combinations containing angiogenesis inhibitors combined with cytotoxic chemotherapy. Using cytotoxic chemotherapy alone, the PFS-6 rate is about 15% (Wong et al. 1999). Compared to this PFS rate, the combination of bevacizumab with other chemotherapies have been reported to be around 50% (Vredenburgh et al. 2007) and summarized recently in a meta-analysis (Wong et al. 2011) as shown in Table JBAL.5.1.

As a consequence of these responses in second-line treatment, bevacizumab has been approved for recurrent/progressive GB in the US and many other countries outside the European Union (Wick et al. 2010b).

Table JBAL.5.1. Summary of Responses in Second-line Treatment

Compound (total patients)	ORR (95% CI)	SD (95% CI)	OS (95% CI)	PFS (95% CI)	PFS Rate at 6 months (95% CI)	References
Bevacizumab						
Bevacizumab 10 mg/kg + Irinotecan 340/125 mg/m^2 (48)	17% (35)	-	31 wks (21-54)	16 wks (12-26)	29% (18-48)	(Kreisl et al. 2009)
Bevacizumab 10 mg/kg (84)	28.2% (18.5-40.3)	-	9.2 mo (8.2-10.7)	4.2 mo (2.9–5.8)	42.6% (29.6–55.5)	(Friedman et al. 2009)
+ Irinotecan 340/125 mg/m^2 (82)	37.8% (26.5-50.8)	-	8.7 mo (7.8-10.9)	5.6 mo (4.4–6.2)	50.3% (36.8–63.9)	
Meta-analysis of 15 studies (548)	55% (2-61)	29% (20-38)	9.3 mo (7.9-10.6)	6.1 mo (4.2-8.1)	45% (34-57)	(Wong et al. 2011)
Enzastaurin						(Wick et al. 2010a)
Enzastaurin (174)	3% 4.14-9.63	38%	6.6 mo (5.2-7.7)	1.5 mo (1.45-2.10)	-	
Lomustine (92)	4% 2.79-9.62	36%	7.1 mo (6.0-8.8)	1.64 mo (1.48-2.79)	-	
Cediranib (2:2:1)						Batchelor et al. 2010a
Cediranib (30 mg/day) (131)	-	-	8 mo	92 days	16%	
Cediranib (30 mg/day) + lomustine 110 mg/m^2 (129)	-	-	9.4 mo	125 days	34%	
Placebo + lomustine 110 mg/m^2 (129)	-	-	9.8 mo	82 days	24%	

Abbreviations: CI = confidence interval; mo = months; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SD = stable disease; wks = weeks.

5.4. Gene Expression Profiling in Glioblastoma

Recent studies using gene expression profiles from GB tumor tissue have confirmed the diverse nature of GB as previously discovered by cytogenetic and standard histology (Louis et al. 2007).

One of the largest gene expression profiling studies identified 4 gene expression profiles designated as “Proneural,” “Neural,” “Classical,” and “Mesenchymal” subtypes (Verhaak et al. 2010). These subtypes appear to be characterized by specific mutations of the epidermal growth factor receptor (EGFR), neurofibromatosis (NF) 1, and platelet-derived growth factor receptor

alpha (PDGFRα) and isocitrate dehydrogenase (IDH1) genes. In addition, similar studies have identified stem cell-like CD133+ GBs as origin for malignant growth for GB (Prestegarden et al. 2010) and found that TGF-β-induced genes are associated with GBs of poor prognosis (Colman et al. 2010).

5.5. TGF-β Signaling and its Role in Glioblastoma

Transforming growth factor-beta (TGF-β) signals into the cell by engaging TGF-β Type I and Type II receptors and inducing phosphorylation of the TGF-β receptor kinases (Shi and Massague 2003). The Type I receptor kinase phosphorylates SMAD2 and SMAD3 resulting in the formation of SMAD complexes, which are subsequently translocated into the nucleus to stimulate gene transcription of TGF-β responsive genes (Derynck et al. 2001). Therefore, assessment of phosphorylated SMAD (pSMAD) after TGF-β activation can be used to determine the ability of the host to respond to TGF-β activation.

Several mechanisms have been proposed to explain the tumor-promoting activity of TGF-β such as increased neovascularization of the tumor causing increased nourishment to the tumor cells, immunosuppression leading to the escape of tumor immune surveillance, and increased migration and invasion resulting in metastasis (Akhurst and Derynck 2001; Derynck et al. 2001; Wick et al. 2001a, 2001b; Siegel and Massague 2003). These combined effects on the tumor microenvironment by TGF-β promote tumor progression and therefore, a TGF-β receptor type I (TGF-βRI) kinase inhibitor is expected to cause arrest of tumor growth and metastasis in patients.

In GB, recent studies suggest that TGF-β plays an important role in tumor progression (Schneider et al. 2006; Bruna et al. 2007; Peñuelas et al. 2009; Tritschler et al. 2009). For instance, the small molecule inhibitor of TGF-βRI kinase SD-208 blocks the inhibitory effect of glioma cell supernatants on immune cell function and delays the growth of syngeneic SMA-560 gliomas in VM/Dk mice (Uhl et al. 2004). A similar compound, SX-007, also had an anti-tumor effect in animal models. SX-007 improves median survival in a syngeneic orthotopic mouse model (VmDk/SMA-560) (Tran et al. 2007).

In addition, TGF-β released during radiation activates tumor-associated fibroblasts, which in turn can render tumor cells more resistant to subsequent therapies (Barcellos-Hoff et al. 2009). Thus, it is expected that an inhibitor to TGF-β should result in a reduction of the radiation-associated activation of tumor-associated fibroblasts (Shao et al. 2008).

Glioblastoma cells produce factors which can avert immunosurveillance (Kuppner et al. 1988). In the past, immunotherapy in malignant glioma may have failed in part because of strong immune inhibition mediated by elevated TGF-β activity and the proinvasive side effect of therapeutic radiation (Wild-Bode et al. 2001). In particular, increased T regulatory fraction has been observed in patients with GB (Fecci et al. 2006). Recent studies with cancer vaccines and TMZ suggest that TMZ-associated lymphocytopenia may selectively enhance the recovery of T regulatory cells ($CD4^+CD25^+Foxp3^+$) and negatively affect the cytotoxic $CD8^+$ T cells (Heimberger et al. 2008).

Finally, with the increased understanding of genetic expression profiles in GB, TGF-β inhibition has generated some interesting hypotheses, which need to be investigated in the clinic. For instance, the TGF-β inhibitor SD-208 has shown selective inhibition for some GB primary cell lines, but not in others (Xu and Kapoun 2009). Using the surrogate LY2109761 of the clinical compound LY2157299 monohydrate (abbreviated as LY2157299 for the remainder of this document), glioma-initiating cells expressing $CD44^{high}/Id1^{high}$ were inhibited which in turn had an anti-tumor effect (Anido et al. 2010).

5.6. LY2157299 – Nonclinical and Clinical Experience

5.6.1. Nonclinical Pharmacokinetics of LY2157299

In the studies using dogs, a gastric pH-dependent variability was observed suggesting that at acidic pH, LY2157299 had a less variable exposure. To reduce possible pharmacokinetic (PK) variability, LY2157299 will be administered on an empty stomach.

As determined by metabolism studies in rats, most of LY2157299 was excreted in feces. Three metabolites have thus far been identified. The function and activity of these metabolites have not been defined at this time.

Based on the nonclinical metabolism studies, LY2157299 is not anticipated to have the potential to accumulate in patients or have a risk of high hepatic metabolism.

Also, there is no indication that LY2157299 may interfere or have an altered PK profile when given with enzyme-inducing antiepileptic agents.

While parent drug is the dominating circulating product, metabolite analysis is ongoing in rat and dog disposition studies.

For details on the nonclinical PK of LY2157299, please see Section 5 in the LY2157299 Investigator's Brochure (IB).

5.6.2. Nonclinical Pharmacokinetic/Pharmacodynamic Model

A pharmacokinetic/pharmacodynamic (PK/PD) model was developed to characterize the relationship between drug concentrations and pSMAD levels (Bueno et al. 2008). This model was used to predict an anticipated dose range that is likely to be biologically effective in patients with cancer. The simulations from the rat and the mouse suggest that a range of CCI mg (total daily doses), administered twice daily (BID) are expected to produce the required percent inhibition of pSMAD that has been associated with tumor growth delay in the preclinical studies.

For details of predicted efficacy and exposure (area under the concentration versus time curve [AUC]), refer to Section 5 of the IB and Rodon Ahnert et al. (2011).

As shown in Figure JBAL.5.1, nonclinical pharmacology studies combining LY2157299 with lomustine have been conducted (Eli Lilly, data on file). In these studies, LY2157299 showed an additive, if not a synergistic effect when combined with lomustine (Yingling et al. 2011).

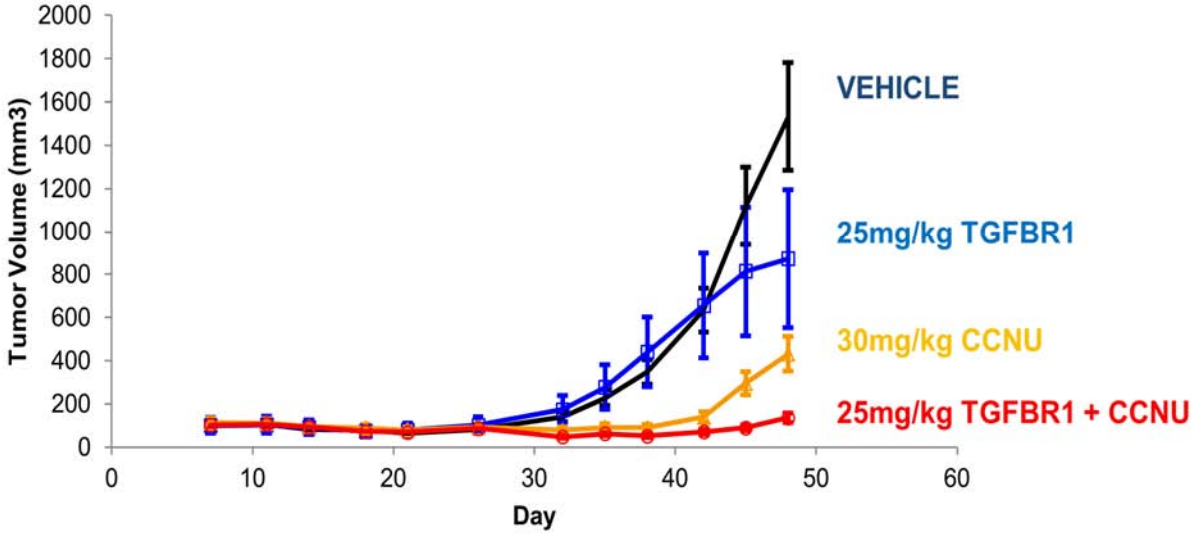

Figure JBAL.5.1. LY2157299 and lomustine (CCNU, CeeNU®) given orally to mice with subcutaneously implanted U87MG cells.

5.6.3. Nonclinical Toxicology of LY2157299

The toxicity of LY2157299 has been characterized in repeat- and intermittent-dose nonclinical safety studies up to 6 months duration in the rat and dog.

For additional information see Section 5 in the IB and the following brief summary:

The heart and great vessels are major target organs for toxicity in both F344 rats and beagle dogs following treatment with LY2157299. These effects include valvulopathy and vascular lesions of multiple blood vessels at the base of the heart in rat and dog, which in the rat appear to be partially reversible.

Changes in the base of the ascending aorta, characterized by minimal-to-marked degeneration, disorganization, and separation of intramural elastic laminae without an accompanying inflammatory response, were observed in the dog administered daily doses of CCI mg/kg for 6 months. The aortic mural degeneration was focally extensive or multifocal with no compound-related microscopic changes in the descending aorta. Although the microscopic changes likely compromised regional aortic structural integrity, there were no changes diagnostic of an aortic aneurysm, no gross dilation, no effects in the intimal layer, and a lack of free blood within the wall of the aorta. A cardiac valvulopathy, characterized by endothelial/stromal cell proliferation, inflammation, and increases in smooth muscle actin immunolabeling and hemorrhage is similar in rats and dogs. The cardiac valvulopathy observed in preclinical toxicology species has not been associated with extracardiac evidence of valvular insufficiency or dysfunction.

The no-observed-effect level (NOEL) for cardiac effects in the rat is CCI mg/kg administered on a 2-week-on/2-week-off schedule and 8 mg/kg in the dog in the 6-month study.

Administration of LY2157299 may produce dose-dependent hemodynamic side effects, measured by decreased blood pressure and increases in heart rate, which can be easily monitored in the clinic and are reversible upon cessation of treatment. The nonclinical data do not reveal any substantive clinical risk of QT/corrected QT interval (QTc) prolongation at doses that result in total plasma concentrations of at least CCI µg/mL.

LY2157299 was positive in an in vitro mammalian chromosome aberration test with and without metabolic activation. In the rat, additional important compound-related findings affecting the skeletal system, consisting of proliferation of trabecular bone or sternal cartilage, altered endochondral ossification, and slightly increased degeneration of articular cartilage were observed. In the rat, a continuum of changes in the gastrointestinal tract have been described, including inflammation of the mucosa, simple mucosal hyperplasia, and adenocarcinoma following 6 months of continuous treatment. The proliferative changes included simple mucosal hyperplasia that progressed to include adenomatous hyperplasia, adenoma, and, in 2 males at the high dose, adenocarcinoma. In the dog, corneal edema and episcleritis were noted in the eyes of dogs at the high dose (CCI mg/kg) during a scheduled ophthalmologic examination of all dogs on Day 176 of the 6-month study. Corneal endothelitis (inflammation of the most posterior cell layer of the cornea) was considered to be the primary change. Histologic evaluation of the eye was unremarkable. Additional important compound-related findings in the dog consisted of atrophy and/or inflammation of the mucosa of the stomach and large intestine, proliferation of sterna cartilage, and gallbladder mucification.

5.6.3.1. Overall Conclusions from the Nonclinical Toxicology Studies

The findings in the continuous 3- and 6-month daily dosing toxicity studies, particularly the degeneration of the large blood vessels, imply that long-term, daily dosing of LY2157299 may carry a risk in patients for developing aneurysms. Reversibility was not assessed in the 3- or 6-month toxicity studies, but in a non-Good Laboratory Practices (GLP) reversibility study in rats, data indicate the cardiovascular lesions are partially reversible but those that are still present following the recovery period are still adverse.

The intermittent dosing regimen in patients is based on the safety demonstrated in the rat and dog following 1 month of continuous daily dosing in which the NOEL for any effects in the heart was CCI and CCI mg/kg in the rat and dog, respectively, and a 3-month intermittent dosing study in the rat in which the NOEL for any effects in the heart was CCI mg/kg (see Table JBAL.5.2, below, for margin of safety calculations).

Although the likelihood of occurrence or the extent and timing of such a risk observed after daily dosing is not known in humans, LY2157299 will be administered as an intermittent-dosing regimen in this patient population which has a poor prognosis and rapidly advancing cancer.

Table JBAL.5.2. Margin of Safety Based on NOEL to Cardiovascular Effects in 30-Day Daily and 3-Month Intermittent Dosing GLP Toxicology Studies in Rat and Dog and Clinical AUC

Cohort	1	2	3	4	5
Clinical Dose (mg/day)	CCI				
Measured AUC(0-24 hr) (µg•hr/mL) from Day 1 QD dose					
Measured AUC(0-24hr) (µg•hr/mL) at steady state BID					
Simulated AUC(0-24 hr) (µg•hr/mL) at steady state QD[e]					
	Margin of Safety				
Rat NOEL[c] (CCI mg/kg) (30 days; Daily dosing) (R00244)					
AUC0-24 hr (µg•hr/mL)[a] CCI Measured (Day 1 QD Dose or Steady State BID)[d]	CCI				
Rat NOEL[c] (CCI mg/kg) (3-months intermittent; 2 weeks on/2 weeks off) (WIL353120)					
AUC0-24 hr (µg•hr/mL)[a] CCI Measured (Day 1 QD Dose or Steady State BID)[d]	CCI				
Dog NOEL[c] (CCI mg/kg) (30 days; Daily dosing) (D00052)					
AUC0-24 hr (µg•hr/mL)[b] CCI Measured (Day 1 QD Dose or Steady State BID)[d]	CCI				

Abbreviations: AUC = area under the concentration-time curve; AUC(0-24hr) = area under the concentration-time curve from 0 to 24 hours; BID = twice daily; GLP = good laboratory practice; NOEL = no-observed-effect level; QD = once daily.

a AUC from males were used to calculate margin of safety from Study #R00244.

b AUC from males and females were averaged since no exposure differences were noted.

c NOEL is based on absence of any cardiovascular changes at this dose.

d Margin of safety calculated based on measured AUC following a QD dose on day 1 (CCI) or measured AUC at steady state after BID (CCI).

e Simulations based on all clinical data (Cohorts 1 to 5) assuming QD dosing.

5.6.4. Clinical Safety of LY2157299

As reported in the 2011 IB, a total of CCI patients have been dosed with LY2157299 across 4 studies. Based on the observed toxicity in animals, all CCI patients have been asked to undergo regular echocardiography (ECHO)/Doppler evaluations to monitor possible risks to the valve function. All future studies will require that patients undergo ECHO/Doppler assessments to obtain a safety database of at least CCI patients with serial and long-term treatment (ie, over 3 months of treatment) with LY2157299.

LY2157299 is being investigated as a monotherapy in patients with GB in the first-in-human-dose (FHD) study (Study H9H-MC-JBAH [JBAH], Part A [CCI patients]) and in patients with hepatocellular carcinoma (Study H9H-MC-JBAK [JBAK], CCI patients). In addition, LY2157299 is being evaluated for safety in patients with GB when combined with lomustine (Study JBAH, Part B, CCI patients) or chemoradiation with TMZ (Study H9H-MC-JBAI [JBAI], CCI patients). Further, LY2157299 is being investigated in patients with pancreatic cancer when combined with gemcitabine (Study H9H-MC-JBAJ [JBAJ], CCI patients).

Study JBAH is a nonrandomized, open-label, dose-escalation, FHD/Phase 1 study of LY2157299 in patients with GB. The study is divided into 2 parts: Part A, focusing on the dose escalation of single-agent LY2157299 (doses [redacted] mg/day up to [redacted] mg/day); and Part B, the combination of LY2157299 with lomustine at doses of [redacted] mg/day and [redacted] mg/day.

As of 19 August 2011, 65 patients have been treated with LY2157299 or LY2157299 plus lomustine in Study JBAH, 3 of whom remain on study treatment in Part A and [redacted] patients remain on study treatment in Study Part B.

5.6.4.1. Part A of Study H9H-MC-JBAH – Monotherapy with LY2157299

Patients in Cohorts 1 and 2 of Part A were administered LY2157299 as a continuous treatment. Before dosing of Cohort 3, unexpected toxicities (based on preliminary findings) were observed in nonclinical toxicology 6-month continuous oral administration of LY2157299 studies in rats and dogs. These findings imply that a long-term, continuous administration of LY2157299 may carry a risk in patients for developing aneurysms with the potential of rupture and bleeding. Although the likelihood of occurrence, or the extent and timing of such a risk is not known in humans, the sponsor decided to change the administration of LY2157299 from a continuous- to an intermittent-dosing regimen. Additionally, the sponsor altered the study population from a general cancer population to a specific cancer indication of malignant glioma. Starting with Cohort 3, all patients were treated with an intermittent dosing schedule of 14 days on/14 days off.

In Cohorts 3 and 5, [redacted] patients ([redacted] patients in Cohort 3 and [redacted] patients in Cohort 5) were treated longer than 180 days. This exceeds the duration administered in any preclinical safety study. In Cohort 3, 4 patients received LY2157299 for over 1 year, with 3 patients being on study treatment for more than 18 months at a total mean drug dose across these patients of [redacted] mg per patient.

While Study JBAH Part A was not designed as an efficacy study, [redacted] patients ([redacted] treated with [redacted] mg/day and [redacted] treated with [redacted] mg/day LY2157299) have had complete responses and [redacted] patients ([redacted] patients treated with [redacted] mg/day and [redacted] patient treated with [redacted] mg/day LY2157299) have had partial responses. [redacted] patients ([redacted] each having stable disease, partial or complete responses) at the [redacted]-mg/day level were treated for more than 20 cycles. This suggests that LY2157299 has a possible single-agent activity. Additionally, preliminary response results for Study JBAH Part B indicate that [redacted] of [redacted] patients have had a partial response, suggesting that the combination of LY2157299 (at doses of either [redacted] or [redacted] mg/day) plus lomustine also may also have antitumor activity.

The most common treatment-emergent adverse events (TEAEs) possibly related to LY2157299 monohydrate monotherapy are asthenia and nausea (Studies JBAH [Part A] and JBAK). Other TEAEs observed primarily in Cohorts 1 and 2 of Study JBAH Part A that are possibly related to LY2157299 monohydrate monotherapy include anal inflammation, diarrhea, nausea, and gastritis.

5.6.4.2. Part B of Study H9H-MC-JBAH – Combination of LY2157299 Monohydrate with Lomustine

After establishing the safety of LY2157299 monohydrate as a monotherapy up to the exposure considered to be safe, 2 cohorts with each CCI -mg/day and CCI -mg/day dose were evaluated in combination with lomustine. In Study JBAH Part B, no distinction was made between relatedness of AEs to either LY2157299 monohydrate or lomustine, where the study therapy was LY2157299 monohydrate in combination with lomustine.

As of 19 August 2011, the most common TEAE related to study therapy was thrombocytopenia (CCI of CCI patients dosed [CCI %]). Other hematologic TEAEs related to study therapy included neutropenia, lymphopenia, and leucopenia affecting CCI to CCI patients (CCI % to CCI %). These are in line with the observed toxicity profile for lomustine. Other reported study therapy related TEAEs were fatigue, nausea, and dysgeusia, affecting CCI or CCI patients dosed (CCI % to CCI %). Of the TEAEs that were not considered related to study therapy, 1 patient had an isolated prolonged Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 QTc interval and was not considered serious because of its isolated observation.

Based on these observations the proposed dose for Phase 2 development is CCI mg/day given as a 14–days-on/14-days-off cycle.

More information about the known and expected benefits, risks and reasonably anticipated AEs may be found in the IB. Information on AEs expected to be related to the study drug may be found in Section 7 (Development Core Safety Information [DCSI]) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in Section 6 (Effects in Humans) of the IB.

5.6.5. Clinical Pharmacokinetics of LY2157299

5.6.5.1. Monotherapy with LY2157299 Monohydrate

Of the CCI patients treated with LY2157299 monotherapy in Study JBAH Part A, noncompartmental PK analysis has been performed on CCI patients (CCI patients from Cohort 1 [CCI mg/day], CCI patients from Cohort 2 [CCI mg/day], CCI patients from Cohort 3 [CCI mg/day], CCI patients from Cohort 4 [CCI mg/day] and CCI patients from Cohort 5 [CCI mg/day]). In Cohort 3, CCI patients were evaluable for PK in Cycle 1 Day 1 with 13 on Day 14 and 9 on both Days 1 and 14 on Cycle 2. In Cohort 4, 6 patients were evaluable for PK on Cycle 1 Day 1, 5 on Day 14, 4 on Cycle 2 Day 1, and 2 on Day 14. In Cohort 5, CCI patients were evaluable for PK on Cycle 1 Day 1 and 9 on Day 14, 6 on Cycle 2 Day 1 and 7 on Day 14.

Results from all 5 cohorts showed rapid absorption of LY2157299, as demonstrated by measurable plasma concentrations at the first sampling time (CCI to CCI hours). Plasma concentrations of LY2157299 were measurable for at least 48 hours, where available, following the administration of the CCI and CCI -mg doses of LY2157299.

Observed exposures of LY2157299 increased with dose increases in the studied dose range. Specifically, the ratio of geometric means for AUC from 0 to infinity (AUC[0-∞]) between

CCI mg/total dose and CCI mg/total dose was estimated as CCI (90% CI: CCI). A ratio of CCI would indicate ideal dose proportionality across the entire dose range tested. For a doubling of dose, the fold increases for AUC(0-∞) and maximal drug concentration at steady state ($C_{max,ss}$) are CCI-fold with corresponding CCI% confidence limits (CCI) and CCI-fold with CCI% confidence limits (CCI), respectively.

At steady state, on Day 14, the median time to maximum concentration at steady state ($t_{max,ss}$) ranged from CCI to CCI hours postdose, independent of dose. The terminal half-life of LY2157299 was estimated to be between CCI and CCI h^{-1}. Both $C_{max,ss}$ and exposure increased with dose. The geometric mean of the apparent clearance at steady state (CL_{ss}/F) was similar across Cohorts 3, 4, and 5, whereas for the first 2 cohorts the scheduled sampling time was only up to 8 hours post dose and the parameter could not be estimated with any degree of certainty.

Formal assessment of time-linear kinetics, that is, whether AUC(0-∞), Day 1 and AUC(0-∞), Day 14 are similar, was not possible, due to the limited PK sampling on Day 1. However, no accumulation of LY2157299 in the 5 cohorts was observed over the 14-day BID dosing regimen, as shown by the accumulation ratio (observed to be approximately 1). Additionally, the $C_{max,ss}$ on Day 1 and Day 14 in the same patient also appeared to be similar.

A population PK model, based on Cohort 1 through 5 data, was developed. A first order absorption linear 2-compartment model, with elimination from the central compartment provided the best fit to the plasma data. The mean population clearance of LY2157299 was CCI L/h with standard error, expressed as a percent coefficient of variation of CCI% and the steady state volume of distribution (V_{ss}) was CCI L. From the population PK analysis of all 5 cohort data, the between-patient variance was estimated to be CCI% on the population apparent clearance (CL/F). The between-occasion variability on CL/F was estimated at CCI%.

5.6.5.2. Combination of LY2157299 Monohydrate with Lomustine

In Part B of Study JBAH, LY2157299 was administered for 1 week and lomustine was co-administered on Day 7. Following BID multiple dosing for 6 days, LY2157299 would have achieved steady state distribution in patients due to it relatively short half-life. Hence, comparison of LY2157299 PK profiles on Day 6 against Day 7 (in presence of lomustine) will allow detection of any potential alterations in absorption and disposition. Pharmacokinetic profiles of LY2157299 following administration of CCI mg BID (Cohort 1) and CCI mg BID (Cohort 2) on Days 6 and 7 were similar. Hence, co-administration of lomustine did not appear to alter the LY2157299 PK profile.

Specifically, following administration of 80 mg BID, mean $C_{max,ss}$ of CCI and CCI µg/L and exposures (area under the concentration versus time curve during 1 dosing interval [AUC(0-τ)]) of CCI and CCI µg.h/L, respectively were achieved. For Cohort 2, mean $C_{max,ss}$ of CCI and CCI µg/L and exposures ($AUC_{0-\tau}$) of CCI and CCI µg.h/L, respectively were achieved.

As expected, there was an increase in observed exposure with dose increase between the 2 cohorts. The variability estimates (percent coefficient of variation [CV%]) of PK parameters appear to be slightly higher in the presence of lomustine when compared with LY2157299 alone

(Days 6 and 7) and then again reduced on Day 12±2. This could be an artifact of the relatively small sample size in Study JBAH, Part B (n=13 Cohort 1 and n=8 Cohort 2) or a valid observation, and will be revisited during the planned first safety interim analysis of Study H9H-MC-JBAL (JBAL).

5.7. Rationale and Justification for the Study

Based on the above mentioned non-clinical and clinical observations, recent clinical studies with the first-generation antisense oligonucleotide against TGF-β2, AP12009 (trabedersen), in GB, anaplastic astrocytomas (AA), and anaplastic oligodendroglioma (OA) (Stauder et al. 2003; Bogdahn et al. 2004, 2011) the proposed study is justified because:

- TGF-β signaling has been identified as a driver of malignant growth in GB (see Section 5.5)
- Blocking TGF-β signaling (including with LY2157299) results in antitumor effects in nonclinical models supporting the importance of this pathway in tumor growth (see Section 5.5)
- LY2157299 has shown an acceptable safety profile in patients (Study JBAH, Part A) with no medically significant cardiovascular toxicities and with an interesting anti-tumor response in 4 patients (see Section 5.6.4)
- LY2157299 has shown no added toxicity when combined with lomustine (Study JBAH, Part B) (see Section 5.6.4)
- Lomustine remains a widely used and approved agent for second-line treatment in GB (see Section 5.3)
- LY2157299 has shown possible signs of single-agent activity against GB (see Section 5.6.4)
- Unmet medical need remains high to find treatment options that are at least as efficacious and better tolerated than lomustine

5.7.1. Rationale for Amendment (a)

The proposed protocol amendment(a) is aimed at facilitating the participation of the remaining patients in study JBAL. The protocol has been amended to include the concept of 'study completion' in the study design (see Section 8.1.4). This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis/evaluation of overall survival or after approximately CCI survival events have occurred.

The protocol has also been amended to add a continued access period to LY2157299 for patients who continue to experience clinical benefit, have no undue risks, and are on study treatment at the time of study completion (see Section 8.1.3). Patients in the continued access period will be followed for safety only and all other follow-up testing has been eliminated (See Attachment 1 for the study schedule for the continued access period). Based on the current safety profile of LY2157299, the reduction in the number of visits and tests will have no influence on the risk assessment.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply. Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

Minor editorial changes were made but not listed. Attachment 11 contains a detailed listing of changes made in the amendment.

6. Objectives

6.1. Primary Objective

To compare the overall survival (OS) distributions between LY2157299 plus lomustine therapy and lomustine plus placebo therapy (control arm) in patients who have relapsed or have progressive GB after first-line treatment with chemoradiation.

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

Pharmacokinetic:

- To determine the population plasma PK of LY2157299

Safety:

- To provide additional safety information on LY2157299 monotherapy and LY2157299 plus lomustine therapy and to evaluate the safety of LY2157299 monotherapy and LY2157299 plus lomustine therapy relative to lomustine plus placebo therapy

Pharmacodynamic – prognostic and predictive marker assessment:

- To investigate in tumor tissue, biomarkers associated with tumor growth and the TGF-β signaling pathway and its association with clinical responses:
  - pSMAD and other TGF-β-related biomarkers
  - MGMT promoter status
  - other relevant tumor genetic information (eg, IDH1 mutation)
- To determine serum/plasma tumor markers and secreted proteins (eg, S100β, lactate dehydrogenase [LDH], TGF-β, platelet factor 4 [PF4]) and their association with clinical responses
- To determine T cell biomarker responses, including T regulatory cell counts (eg, $CD4^+CD25^+FoxP3^+$ T cells) and their association with clinical responses

Efficacy:

- To estimate the HR from their OS distributions between:
  - lomustine plus placebo therapy and LY2157299 monotherapy
  - LY2157299 plus lomustine therapy and LY2157299 monotherapy
- To estimate PFS distributions for each treatment arm and estimate additional parameters from both the OS distributions and PFS distributions for each treatment arm (such as median OS and PFS, OS and PFS rates at CCI months)
- To estimate tumor response rate based on Response Assessment in Neuro-Oncology (RANO) criteria for each treatment arm

Health Outcomes:

- To assess patient-reported symptoms using the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) and assess neurocognitive function using the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test Parts A and B, and Controlled Oral Word Association (COWA) for each treatment arm

7. Study Population

Patients are eligible for enrollment if they have been diagnosed with recurrent, intracranial GB (WHO Grade IV) confirmed by histological evaluation. The investigator or a designee will obtain written informed consent from all patients or their legally authorized representatives before any protocol-specific procedure is performed.

For Eli Lilly and Company (Lilly) studies, the following definitions are used:

Enter: The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.

Enroll: The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment. For a randomized study, the act of assigning a patient to treatment is through the randomization schedule. A person who has been entered into the study is potentially eligible to be enrolled in the study, but must meet all criteria for enrollment specified in the protocol before being randomized (assigned to a treatment group). Individuals who are entered into the study but fail to meet the criteria for randomization are not eligible to participate in the study and will not be randomized.

7.1. Inclusion Criteria

Patients are eligible to be entered and enrolled in the study only if they meet **all** of the following criteria:

[1] Histologically confirmed diagnosis of relapsed intracranial GB (WHO Grade IV; including gliosarcomas). Patients may be entered based on local pathology from the original diagnostic tumor specimen.

Patients who have secondary GBs will also be eligible for this trial.

To confirm the original diagnosis for all patients, the original diagnostic tumor specimen must be made available for a central pathology review (this will be returned to the original pathology laboratory).

[2] Patients must have evidence of tumor progression as determined by RANO criteria (see Attachment 5) following standard chemoradiation (Stupp protocol).

- Magnetic resonance imaging (MRI) must be performed within 14 days prior to enrollment, and patients who are receiving steroids must be stable for at least 5 days prior to imaging. If the steroid dose is increased between the date of imaging and enrollment, a new baseline MRI is required. An MRI must be used throughout the period of study treatment for tumor measurement.
- Patients must have completed only 1 prior course of radiation therapy and must have experienced an interval of ≥12 weeks from the completion of radiation therapy to study entry.

- Patients may have received 1 prior TMZ-based chemotherapy regimen: chemotherapy treatment with concurrent radiotherapy or chemotherapy treatment in the adjuvant setting will each be considered 1 regimen.
- Patients must have experienced an interval of no less than 30 days from the last day of receiving a chemotherapy treatment prior to receiving study therapy (for biologics and targeted agents for at least 14 days) or shorter depending on their known PK plasma half-life).

[3] Patients may have undergone prior surgical resection and will be eligible if the following conditions apply:

- Patients must have recovered from the effects of surgery.
- Evaluable or measurable disease must be present (RANO criteria). To adequately assess the extent of residual disease postoperatively, MRI should be done:
  - In the immediate postoperative period (<72 hours).
    Note: if the 72-hour scan is performed more than 14 days prior to enrollment, the scan needs to be repeated. An optimal baseline scan is done 48 hours after surgery.

OR

- In the postoperative period (>4 weeks postoperatively and <14 days of enrollment). For patients receiving steroids, they must be on stable treatment for at least 5 days.
  Note: If the steroid dose is increased between the date of imaging and enrollment, a new baseline MRI is required on a stable steroid dosage of at least 5 days duration.

[4] Have available tumor tissue (mandatory) for additional prognostic and predictive biomarker evaluation (from initial pathological diagnosis tissueand/or from subsequent tumor tissues) .

[5] Have a performance status (PS) of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale. See Attachment 4.

[6] Have discontinued all previous treatments for cancer excluding palliative treatments and recovered from the acute effects of therapy (given the toxicity profile, mitomycin-C has to be discontinued at least 42 days and all other chemotherapies 30 days from last administration or for biologics and targeted agents for at least 14 days), or shorter depending on their known PK plasma half-life.

At the discretion of the investigator, hormone-refractory prostate cancer patients who are stable on gonadotropin-releasing hormone (GnRH) agonist therapy and breast cancer patients who are stable on antiestrogen therapy (for example, an aromatase inhibitor) may have that treatment continued while they are enrolled in this study.

[7] Have adequate organ function, including:

- Adequate bone marrow reserve: absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, and hemoglobin ≥9 g/dL (6.21 mmol/L).
- Hepatic: total bilirubin ≤2 x the upper limit of normal (ULN); alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≤3 x ULN.
- Renal: serum creatinine <1.5 x ULN.
- Eligibility for hemoglobin may be reached by transfusion. Patients with hemoglobin >8 g/dL but <9 g/dL may receive erythrocyte transfusions to achieve a hemoglobin level ≥9 g/dL. Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of hemoglobin level ≥9 g/dL.
- Note: Small changes from the outlined laboratory values, which are a result of biological or laboratory equipment variability as evidenced by historical values, will be deemed as consistent with the protocol-requirements provided that they are isolated values, are transient, and are not reflective of a medical condition. Repeat laboratory/hematological tests should be done prior to dosing the patient on Cycle 1 Day 1.

[8] Are males or females at least 18 years old at the time of screening.

[8a] Male patients:

- agree to use a reliable method of birth control during the study and for at least 12 weeks following last dose of study drug or country requirements, whichever is longer.

[8b] Female patients:

- are women of child-bearing potential who test negative for pregnancy at the time of enrollment based on a urine pregnancy test and agree to use a reliable method of birth control during the study and for 3 months following the last dose of the investigational product.
- are postmenopausal women, defined as:
  - at least 6 weeks post surgical bilateral oophorectomy with or without hysterectomy, confirmed by medical history.

OR

  - spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy).

OR

  - spontaneous amenorrhea 6 to 12 months and a follicle-stimulating hormone (FSH) level greater than 40 mIU/mL.

[9] Have given written informed consent/assent prior to any study-specific procedures.

[10] Are able to swallow capsules (lomustine) and tablets (LY2157299/placebo).

7.2. Exclusion Criteria

Patients will be excluded from entering or enrolling in the study if they meet **any** of the following criteria:

[11] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product (including vascular endothelial growth factor receptor [VEGF-R] inhibitors) or non-approved use of a drug or device (other than the study drug/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[12] Have previously completed or withdrawn from this study or any other study investigating LY2157299.

[13] Have moderate or severe cardiac disease:

a) Have the presence of cardiac disease, including a myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association (NYHA) Class III/IV congestive heart failure, or uncontrolled hypertension.
b) Have documented major electrocardiogram (ECG) abnormalities which are not controlled by medical treatments, for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, bundle branch blocks, ventricular hypertrophy, or recent myocardial infarction.
c) Have major abnormalities documented by ECHO with Doppler (for example, moderate or severe heart valve function defect and/or left ventricular ejection fraction [LVEF] <50%, evaluation based on the institutional lower limit of normal). For additional details, refer to ECHO protocol (Attachment 6).
d) Have predisposing conditions that are consistent with development of aneurysms of the ascending aorta or aortic stress (for example, family history of aneurysms, Marfan-Syndrome, bicuspid aortic valve, evidence of damage to the large vessels of the heart documented by chest computed tomography [CT] scan with contrast).

[14] Received prior nitrosourea (including lomustine or Gliadel®/local carmustine) therapy.

[15] Received prior bevacizumab as part of a first-line treatment for GB (if treatment was concluded 12 months prior to enrollment, the patient may be eligible to participate in the trial).

[16] Have a serious concomitant systemic disorder (for example, active infection including human immunodeficiency virus [HIV]) that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol.

[17] Have current acute or chronic myelogenous leukemia.

[18] Have a second primary malignancy that, in the judgment of the investigator and sponsor, may affect the interpretation of results (eg, slowly progressing tumors that in the past 3 years have shown an accelerated growth and are resistant to other treatments; for breast and prostate cancer patients see inclusion criterion [6]).

[19] Are pregnant or breast-feeding women.

[20] Are unwilling or unable to participate in the study.

7.3. Discontinuations

7.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly.

If a patient who does not meet enrollment criteria is inadvertently enrolled, Lilly or its designee must be contacted. In these cases, the investigator must obtain documented approval from Lilly to allow the patient to continue in the study enrollment or receive study drug (see additional guidance below).

Patients may be discontinued from the study or study drug treatment in the following circumstances to ensure their safety and to maintain the scientific integrity of the study:

- If Exclusion Criterion [13], [14], [15], [16], [17], [18], [19], or [20] is known after enrollment.
- Cases of pregnancy or failure to use adequate birth control (for women of reproductive potential) as outlined in [8] and [20]
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
    - The investigator/physician decides that the patient should be withdrawn from the study or study drug.
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug occurs prior to introduction of the new agent.
- Patient Decision
    - The patient requests to be withdrawn from the study or study drug.
- Sponsor Decision
    - The investigator or Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.
- The patient is significantly noncompliant with study procedures and/or treatment.

Exceptions will be granted in rare circumstances, because GB patients have a serious or life-threatening condition for which there is no effective alternative therapy. In such cases, the investigator has to provide information on the patient´s anticipated benefit or current benefit

from being entered in the study or receiving study drug. In these rare cases, the investigator must obtain documented approval from Lilly to allow the patient to continue in the study and/or receive study drug.

For cases involving continued treatment after objective disease progression (excluding cases in which pseudoprogression is assumed), the investigator needs to discontinue the patient as soon as he/she is made aware of this situation, but the patient will be followed until study objectives are met.

The reason and date for discontinuation from both study treatment and study itself will be collected for all patients. All patients enrolled will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

7.3.3. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study JBAL is a 3-arm, randomized, multicenter, global, Phase 2 study of LY2157299 monotherapy or LY2157299 plus lomustine therapy compared to lomustine plus LY2157299-matched placebo therapy in patients with relapsed or progressed GB. CCI [redacted] patients will be entered with the aim of randomizing CCI patients in a CCI fashion to LY2157299 monotherapy or LY2157299 plus lomustine therapy or lomustine plus LY2157299-matched placebo therapy (see Section 12.1). Figure JBAL.8.1 illustrates the study design. Patients and investigators will be blinded to the LY2157299 or placebo assignment for those patients who receive lomustine. One cycle is defined as 28 days in all treatment arms and constitutes 14 days on/14 days off of LY2157299/LY2157299-matched placebo.

Figure JBAL.8.2 illustrates an overview of the first 4 cycles for each treatment arm.

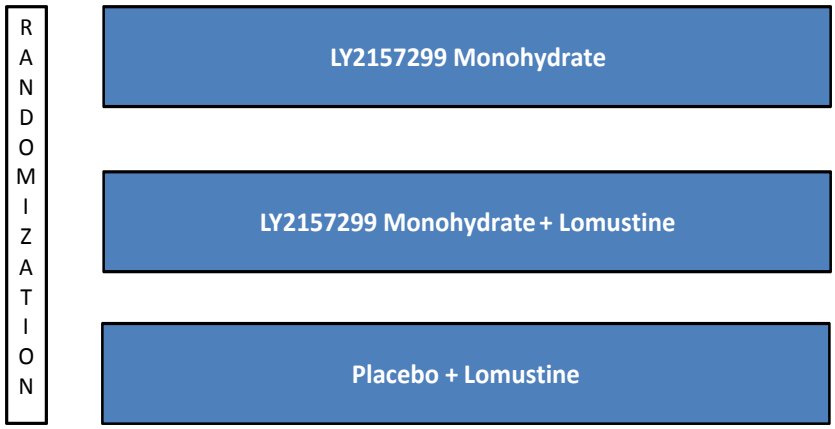

Figure JBAL.8.1. Illustration of study design for Protocol H9H-MC-JBAL.

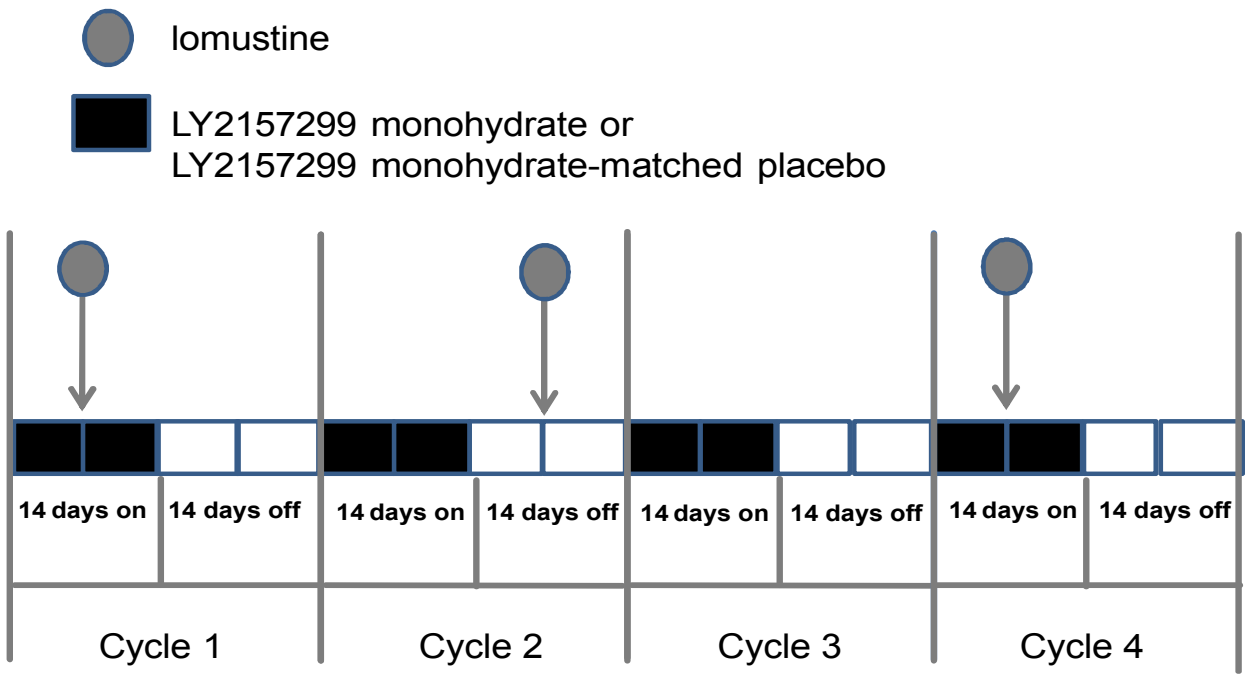

Figure JBAL.8.2. Illustration of LY2157299 and lomustine administration for the first 4 treatment cycles in Protocol H9H-MC-JBAL.

In Cycle 1, lomustine will be given after LY2157299 or placebo has been given for 7 days (on Day 7 of Cycle 1). After the first dose, lomustine will then be given once every 6 weeks to those patients assigned to either the LY2157299 plus lomustine or lomustine plus placebo treatment groups. The planned treatment with lomustine will be limited to 6 administrations. For details, see Section 9.1.

The primary comparison for efficacy is to compare OS between the LY2157299 plus lomustine therapy and lomustine plus placebo therapy. Additional endpoints (eg, PFS, response rate) will be estimated.

Further analyses will be carried out to estimate efficacy and safety endpoints for LY2157299 monotherapy and LY2157299 plus lomustine therapy. This secondary analysis will provide an assessment of whether the monotherapy treatment with LY2157299 is as active as lomustine alone. At the same time, this design will offer additional information whether LY2157299 monotherapy has a toxicity profile that warrants further investigation.

Patients will receive treatment until disease progression, death, or discontinuation (criteria defined in Section 7.3.1) occurs. Patients will be followed for OS until death or study completion (see Section 10.1.2). Tumor assessments will be conducted according to the Study Schedule (Attachment 1) and as denoted in Sections 10.1.1 and 10.1.2 to determine whether the patient continues to benefit from their treatment.

CCI interim assessments are planned (see Section 12.2.12 and Attachment 10):

CCI

The planned duration of the study is CCI years in order to follow all patients for OS. Overall survival will be collected for all patients, including those who started other therapies after discontinuation from study drug treatment.

Database lock for the final analysis of the primary endpoint will occur after approximately CCI events have occurred.

8.1.1. Baseline and Study Treatment Period Assessments

Terms used to describe the study baseline and treatment periods are defined below:

- **Baseline:** After signing Informed Consent and from the time of screening to first study treatment (or discontinuation, if no treatment is given)
- **Study Treatment Period:** Time from treatment start to discontinuation from study treatment (does not include the continued access period)

The Study Schedule (Attachment 1) describes the timing of baseline and study treatment period assessments.

Written informed consent must be obtained prior to any study-specific pretreatment evaluations. At baseline, within 28 days prior to dosing, and during the study treatment period, medical and physical examinations, ECOG PS evaluation, health outcome assessments (Section 10.2), ECG/ECG chemistry (Section 10.3.2.1), ECHO/Doppler and chest CT scans (Section 10.3.2.2), pregnancy test (as applicable), serum chemistry, urinalysis and hematology laboratory tests (Section 10.4.1) in addition to tumor measurements by MRI will be completed. In addition, pulmonary function tests will be conducted on those patients receiving lomustine at baseline and every 6 months thereafter (Section 10.3.2.3).

Tumor measurements will be performed by MRI every 2 cycles until objective progression is observed, per efficacy measurement criteria described in Section 10.1.1. Tumor responses will be confirmed. Imaging methods used at baseline must be consistently used during study.

All enrolled patients will be assessed for toxicity before each cycle using CTCAE, version 4.0. Trial-level safety monitoring will be done as specified in Table JBAL.10.3 (Section 10.3).

Pharmacokinetic sampling (Section 10.4.4) will be conducted during Cycle 1. Additionally, samples will be collected for biomarker, PD, and patient tailoring research (Section 10.4.3).

Cerebrospinal fluid (CSF) may be collected by lumbar puncture.

8.1.2. Postdiscontinuation Follow-Up Period Assessments

Terms used to describe the postdiscontinuation of study treatment are defined below:

- **Postdiscontinuation Follow-Up:** Begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
    - **The *short-term follow-up period*** begins 1 day after discontinuation of study treatment and lasts approximately 30 days (Visit 801).
    - **The *long-term follow-up period*** begins 1 day after the short-term follow-up period (Visit 801) is completed and continues until death or study completion to collect survival data.

The Study Schedule (Attachment 1) describes all assessments for the post discontinuation and follow up periods. All patients should be followed and all AEs (Section 10.3) reported for a minimum of 30 days from the date of discontinuation or until completion of Visit 801.
At Visit 801, physical examinations, ECOG PS evaluation, health outcome assessments (Section 10.2), ECG/ECG chemistry (Section 10.3.2.1), ECHO/Doppler (Section 10.3.2.2), serum chemistry, urinalysis, and hematology laboratory tests (Section 10.4.1) will be completed. Additionally, after Visit 801, ECG/ECG chemistry and ECHO/Doppler will be performed as indicated in Section 10.3.2.1 and Section 10.3.2.2, respectively.

After discontinuation, tumor measurements will be performed as indicated in Section 10.1.2.

8.1.3. Continued Access Period

- Continued access: begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until 1 of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
- Continued access follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

The continued access period will apply to this study only if at least 1 patient is still on investigational product when study completion occurs.

Patients receiving investigational product and experiencing ongoing clinical benefit and no undue risks may continue to receive investigational product in the continued access period until 1 of the criteria for discontinuation is met (Section 7.3). Lilly will notify investigators when the continued access period begins. Patients must sign a new informed consent form (ICF) before continued access is provided.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and investigational product exposure will be reported on the case report form (CRF). Patient diaries for drug administration will no longer be required in the continued access period.

Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

8.1.4. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis/evaluation of overall survival or after approximately CCI survival events have occurred. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient on study treatment.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.

8.2. Discussion of Design and Control

CCI patients will be entered in order to randomly assign CCI patients to 1 of 3 treatment arms using a CCI allocation ratio in favor of the LY2157299 plus lomustine arm. A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. The study will use dynamic randomization for the known influence factors, such as age, PS, and primary or secondary GB.

Using an appropriate concurrent control arm (which is lomustine in combination with placebo) enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. The rationale behind favoring the combination arm in the randomization is that this is the primary treatment of interest to compare with lomustine alone. However, since there was some evidence of activity in patients with GB in Study JBAH where LY2157299 was administered as a monotherapy, there is medical interest in getting more information in terms of efficacy and safety for LY2157299 monotherapy. Therefore, a monotherapy arm is also included.

Since OS is not affected by pseudoprogression evaluations, OS is a preferred primary endpoint over PFS. A Bayesian design can be used to leverage survival data for lomustine alone from

historical clinical trials in order to benefit from the CCI randomization of the combination arm relative to lomustine alone with the goal of increasing power over an otherwise similar design.

Glioblastoma is a heterogenous tumor entity and treatment effects may be influenced by MGMT methylation, IDH1 gene mutatation status, or other genetic differences. Hence, to understand this influence on OS, all patients will be required to provide tumor tissue to determine the genetic make-up of the tumor and its impact on survival.

Poststudy treatment with bevacizumab may affect the OS. Collection of poststudy treatment will be limited to the first new regimen and any new subsequent therapy will not be collected.

Patients and investigators will be blinded to the administration of LY2157299 using a LY2157299-matched placebo. In contrast to the favorable toxicity profile of LY2157299, blinding of lomustine is difficult to ensure due to its well-characterized bone marrow toxicity. Given the other toxicity concerns, a blinding of lomustine is not warranted for this study.

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If a patient can no longer tolerate lomustine therapy but the patient is benefitting from the treatment, the patient may continue LY2157299 or placebo treatment after approval by the Lilly Clinical Research Physician (CRP). Treatment may continue until disease progression or additional unacceptable toxicity occurs (see Section 9.4.1).

After the trial is completed, biomarker assessment of the tumor tissue will be used to determine whether treatment with LY2157299 had a particular impact on subtypes with a gene expression profile associated with TGF-β-associated signaling. This retrospective evaluation will help to identify a possible subgroup of patients that may respond to LY2157299 treatment, either alone or in combination with lomustine. Hence, the collection of tumor tissue is important to design future Phase 3 studies or to enrich potential responders in future GB studies. Because PK may be associated with toxicity, sparse population PK sampling is being implemented in this study. Finally, the health outcome measures are important for evaluating patient reported outcomes and are needed for future Phase 3 study designs.

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study:

- LY2157299 Monotherapy:
  - LY2157299 300 mg/day, given orally as three 50-mg tablets BID for 14 days, followed by 14 days of rest, equaling a 28-day cycle.
- LY2157299 plus lomustine therapy:
  - The first lomustine dose will be given as 100 mg/m^2.
  - Remaining doses (starting with the second lomustine dose) are based on the investigator's discretion and will be given orally once every 6 weeks at 100 to 130 mg/m^2.
  - LY2157299 300 mg/day, given orally as three 50-mg tablets BID for 14 days, followed by 14 days of rest, equaling a 28-day cycle.
- Lomustine plus placebo therapy:
  - The first lomustine dose will be given as 100 mg/m^2.
  - Remaining doses (starting with the second lomustine dose) from 100 to 130 mg/m^2 are based on the investigator's discretion and will be given orally once every 6 weeks..
  - LY2157299 -matched placebo, given orally as 3 tablets BID for 14 days, followed by 14 days of rest, equaling a 28-day cycle.

Lomustine doses should be rounded to the lowest available capsule strength.

Weight is used to determine dose and should be assessed at each cycle, and dose should be recalculated for each cycle.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drug(s) and planned duration of each individual's treatment to the patient/site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

To be considered compliant, the minimum planned treatment of LY2157299 is 10 days and a maximum of 14 days per 28-day cycle and at least CC% of the allocated LY2157299 prescribed dose has to be administered within each cycle.

9.2. Materials and Supplies

9.2.1. LY2157299

LY2157299 will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements.

LY2157299 will be supplied in blister packs or other appropriate packaging of uncoated, round, white tablets (eg, 10 and 50 mg or other appropriate dosage forms). All materials must be stored at room temperature within temperature range specified on the material label.

The tablet should remain in the blister pack until just prior to administration.

If a patient vomits within 30 minutes of taking a dose of LY2157299, the LY2157299 dose should be repeated 1 time only, that same day, if nausea/vomiting permits (at the discretion of the investigator). If a patient vomits within 30 minutes of taking both the morning and evening dose of LY2157299, the LY2157299 is repeated 1 time only on that day as described above.

LY2157299 should be taken at approximately the same time in the morning and evening every day. At this time LY2157299 has not been evaluated on whether food intake may change the PK profile. Hence, patients should take LY2157299 on an empty stomach preferably 2 hours before a meal. Patients should wait at least 1 hour after taking LY2157299 before eating a meal (see Section 9.4).

Tablets should be swallowed whole and not split, crushed, or dissolved for administration.

9.2.2. Lomustine

Lomustine will either be provided by Lilly in 10-, 40-, or 100-mg capsules in blisters or bottles or obtained as commercial preparation according to local requirements. At each visit, an appropriate number of capsules will be dispensed. The drug should be stored at room temperature. The size of lomustine capsules may differ between countries due to marketing availability.

9.2.3. Placebo

A placebo formulation that will resemble the LY2157299 tablets will be supplied by Eli Lilly and Company to the sites.

9.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomly assigned in a CCI ratio to receive treatment on LY2157299 monotherapy, LY2157299 plus lomustine therapy, or lomustine plus placebo therapy using an interactive voice-response system (IVRS). This will occur before Cycle 1 Day 1. There is no plan to have an unblinded site representative for this study.

A dynamic allocation method, introduced by Pocock and Simon (1975) (and extended for unequal treatment group sizes by Han et al. [2009]), will be adopted to minimize imbalance between treatment arms according to the following factors:

- baseline ECOG PS (0, 1)
- age (≤60, >60 years)
- GB, primary or secondary at study entry

The randomization parameter P will be set at 0.9 to maximize the benefit of the allocation procedure, while keeping treatment assignments unpredictable.

The IVRS will be used to assign blisterpacks containing LY2157299/placebo to each patient. Site personnel will confirm that they have located the correct blisterpacks by entering a confirmation number found on the blisterpacks into the IVRS.

9.4. Selection and Timing of Doses

LY2157299 or placebo will be administered in tablet form on an empty stomach. Patients should take LY2157299 or placebo on an empty stomach preferably 2 hours before a meal. Patients should wait at least 1 hour after taking LY2157299 before eating a meal. Tablets should be swallowed whole and not split, crushed, or dissolved for administration. After intake of LY2157299 or placebo, lomustine will be administered in capsule form on empty stomach. Ingestion on empty stomach is recommended to reduce nausea and vomiting, which may appear about 6 hours after lomustine intake. Alternatively, lomustine may be taken based on institutional guidelines, which may be in the evening prior to bedrest, some hours after a light dinner.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

A patient will receive study drug treatment until the patient progresses, has toxicity, dies, or discontinues for any other reasons (as described in Section 7.3.1).

9.4.1. Dose Adjustments and Delays

The intended treatment for lomustine is 6 doses, each given 6 weeks apart.

9.4.1.1. Lomustine Hematologic Adverse Events

Blood counts should be monitored weekly and repeat doses of lomustine should given every 6 weeks due to possible delayed hematotoxicity. Dose adjustments at the start of a subsequent cycle of therapy will be based on the lowest platelet and ANC (nadir) counts. A repeat dose of lomustine should not be given until ANC and platelet counts return to baseline levels or Grade 1, which usually occurs within 6 weeks.

Any patient who requires a dose reduction due to hematologic AEs will continue to receive a reduced dose for the remainder of the study. Any patient with 2 prior dose reductions, who experiences a toxicity that would cause a third dose reduction, must be discontinued from

lomustine therapy. A patient who, for any reason, cannot be administered lomustine for 12 weeks from the last lomustine dose, must be discontinued from *lomustine therapy*.

If either of the foregoing occur and, in the judgment of the treating physician, it is felt that the patient is benefiting from the treatment and after approval by the Lilly CRP, the patient may continue LY2157299 or placebo treatment, until disease progression or additional unacceptable toxicity occurs.

Treating physicians at the investigative sites will dose adjust lomustine based upon the following suggested guidelines (refer to Table JBAL.9.1) or best institutional practices:

Table JBAL.9.1. Dose Adjustment Guide for Lomustine Based on Nadir Hematologic Values for Preceding Cycle

Nadir After Prior Dose		Percentage of Prior Dose to be Given
ANC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	
LLN – 1.5	>75	100%
1.5 – 1.0	25 – 75	70%
<1.0	<25	50%

Abbreviations: ANC = absolute neutrophil count; LLN = lower limit of normal.

9.4.1.2. Lomustine Nonhematologic Adverse Events

For nonhematologic toxicity greater than or equal to CTCAE Grade 3, treatment should be delayed until resolution to Grade 1 or equal to the patient's baseline values. Dose reductions for nonhematologic toxicities will be based on the previous administered dose level. If, after restarting therapy, the patient does not have recurrence of the event after 6 weeks of therapy, the patient may be re-escalated to the previous dose at the discretion of the investigator.

Upon resolution of Grade 3 or 4 CTCAE, lomustine treatment will resume as follows:

- Nausea and/or vomiting: treatment may resume without dose reduction. Grade 3 or 4 nausea and/or vomiting should be managed with appropriate changes in antiemetic regimen.
- Grade 3 transaminase elevations that return to baseline by Day 1 of the next cycle: treatment may resume without delay or dose reduction.
- Other Grade 3 or 4 nonhematologic toxicities considered clinically relevant: a 50% dose reduction should be administered if deemed appropriate by the treating physician.

9.4.1.3. LY2157299 Dose Adjustments and Delays

At the time of writing this protocol, no specific toxicities for LY2157299 have been identified in patients. Hence, the investigator is asked to contact the Lilly physician if there is a drug-related toxicity which is attributed to LY2157299.

While no bone marrow toxicities were detected in nonclinical toxicology studies, there was 1 case in a patient with GB in which a Grade 4 thrombocytopenia was observed and potentially

associated with administration of LY2157299 monotherapy. In similar cases, the drug should be discontinued until thrombocyte counts either return to Grade 1 or baseline.

Subsequent courses of LY2157299/placebo will be adjusted for any patient who experiences unacceptable toxicity based on nadir counts, maximal nonhematologic toxicities, or other severe events which are related to LY2157299 or its combination with lomustine. This decision will be made in the context of the known safety profile of lomustine monotherapy.

The first dose reduction of LY2157299 should be to approximately CCI mg/day and no re-escalation should be performed unless there is clinical benefit expected in the opinion of the investigator.

A further 50% dose reduction should only be considered in rare circumstances.

9.5. Continued Access to Study Drug

The intended treatment for lomustine is 6 doses, each given 6 weeks apart. If after 6 doses of lomustine, in the judgment of the treating physician, it is felt that the patient is benefiting from the treatment, then LY2157299 or placebo treatment may be continued after approval by the Lilly CRP until disease progression or unacceptable toxicity occur.

9.6. Blinding

Patients who are randomly assigned to receive LY2157299 monotherapy will not be blinded. Patients and investigators in the LY2157299 plus lomustine or lomustine plus placebo arms will be blinded to the LY2157299 or placebo assignment.

To preserve the blinding of the study, only Lilly personnel involved in the clinical trial material dispensation will be unblinded to LY2157299/placebo. The investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone.

9.7. Concomitant Therapy

Patients must receive full supportive care therapies concomitantly during the study, including antiemetic treatment as per institutional guidelines.

At each visit, appropriate documentation of all forms of premedication, supportive care, and concomitant medications must be captured on the study electronic case report form (eCRF). Concomitant medications and supportive care must also be documented until 30 days after the last dose of investigational product. No other chemotherapy, immunotherapy, radiation therapy, hormonal cancer therapy, surgery for cancer, or experimental medications will be permitted while the patients are participating in this study. Any disease progression requiring other forms of specific anti-tumor therapy will be cause for early discontinuation from the study.

Routine use of colony-stimulating factors is not permitted during this study. The American Society of Clinical Oncology (ASCO) guidelines for use of colony-stimulating factors should be followed (Smith et al. 2006). Granulocyte colony-stimulating factor (G-CSF) may be used for patients who have ANC $\leq 0.5 \times 10^9$/L, neutropenic fever, or documented infections while

neutropenic. Duration of uncomplicated neutropenia before initiation of G-CSF treatment is left to the investigator's discretion. Granulocyte colony-stimulating factor (G-CSF) must be discontinued at least 24 hours prior to the start of the next cycle of chemotherapy. Use of erythropoietin is allowed (Rizzo et al. 2007).

Patients assigned to receive lomustine therapy may receive antiemetic therapy prior to dosing and/or on subsequent days per investigator's discretion or according to institutional guidelines.

Patients who are at risk of being immunosuppressed may require a prophylaxis for opportunistic infections (eg, with pneumocystis jeroveci). Such prophylaxis is generally done with cotrimoxazole or following institutional guidelines. A sign of immunosuppression includes persistent low lymphocyte counts (CTCAE Grade >3) (ie, longer than 2 months, or co-treatment of lomustine and steroids longer than 2 months) or signs or multiple infections.

9.8. Treatment Compliance

Patient compliance will be assessed by direct questions and count of returned tablets. Deviations from the prescribed dosage regimen should be recorded in the comments section of the eCRF.

LY2157299 and lomustine will be administered orally. Lomustine should be administered under the direction of study personnel. The site, following institutional guidelines, may allow the patient to take the schedule lomustine dose at home.

Patients who are significantly noncompliant will be discontinued from the study after discussion between Lilly and the investigator. Significant noncompliance includes, but is not limited to the following:

- Compliance of LY2157299 will be determined by the use of at least CCI % of the prescribed/intended amount of drug per cycle (see details in Section 9.1).
- Patient refuses to inform about efficacy and survival measures.
- Patient misses several visits leading to dose delay and/or missed safety assessments.

10. Efficacy, Health Outcome Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures related to efficacy, safety, sample collection, and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Evaluations

10.1.1. Efficacy Assessments at Baseline and during Study

Within 28 days before the first dose of study drug or 14 days prior to enrollment, baseline tumor measurement(s) will be performed on each patient. All patients will have to undergo an MRI with contrast.

The method of assessment used at baseline must be used consistently for tumor assessment and will be repeated every other cycle.

During the continued access period, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

10.1.2. Efficacy Assessments during the Postdiscontinuation Period

After patients have discontinued study treatment, they may receive additional anticancer therapy at the discretion of the investigator.

For those patients who discontinue study treatment without objectively measured progressive disease, the investigative sites will continue to monitor patients approximately every 60 days (±14 days) to evaluate tumor response by the same method used at baseline and throughout the study, until objective progression or the patient starts a new anticancer therapy.

Once a patient has objective progression or starts a new anticancer therapy, they will be followed for OS approximately every 60 days (±14 days) until death or study completion.

10.1.3. Primary Efficacy Endpoint

The primary efficacy endpoint is OS. Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS time will be censored at the last contact date the patient was known to be alive prior to the cut-off date.

10.1.4. Secondary Efficacy Endpoints

The secondary time-to-event endpoints are defined in Table JBAL.10.1.

Table JBAL.10.1. Secondary Efficacy Endpoints

Endpoint	Definition
Progression-Free Survival	The time from the date of study enrollment (randomization) to the date of first observation of objective progression or death from any cause, whichever occurs first. For patients who are not known to have died or progressed as of the data-inclusion cut-off date, PFS time will be censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systematic anticancer therapy.
Progression-Free Survival at 6 months	Number of patients not having objective progression or death at 6 months after the time from date of study enrollment (randomization) estimated from the PFS distribution.
Survival at 12 months	Number of patients alive 12 months after start of treatment, even if they have progressed, estimated from the overall survival distribution

Abbreviation: PFS = progression-free survival.

The use of MRI is mandatory to determine tumor response and to assess when objective progressive disease has occurred (for use in estimating PFS). Recent guidelines have modified the MacDonald criteria and these new guidelines are attached in Attachment 5 and are referred to as the RANO criteria (Wen et al. 2010). The MRI scans will be collected and stored centrally; if necessary, independent review of all or a representative sample of scans may be considered following study completion.

Overall response rate (ORR) is the proportion of patients who achieved a complete response (CR) or partial response (PR) out of all randomly assigned patients.

Based on RANO criteria, a responder is defined by radiographic and clinical criteria (see Attachment 5). Complete response or PR will be first assessed by radiographic changes as determined by an improvement of the bi-dimensional evaluation of the tumor size. In addition, changes in neurologic function and steroid use will be considered to determine stable disease (SD).

10.2. Health Outcome Measures

Patient symptoms will be measured with the self-administered MDASI-BT (Attachment 8). Neurocognitive function will be measured by the HVLT-R, the Trail Making Test, Parts A and B, and COWA. The details of the neurocognitive test administration and implementation will be provided separately from the protocol during training.

The MDASI-BT and the neurocognitive function assessments will be completed at baseline, at the same time of the disease assessments (ie, MRI) post-baseline, and after discontinuation of study therapy.

The health outcome measures should be completed at the beginning of office visits, before any extensive contact and consultation with the clinician/study investigator in regards to the disease assessments. Consultation with the clinician may bias perceptions about symptoms and thus affect assessments. The MDASI-BT, Trail Making Test Parts A and B, and COWA can be completed during the 20-minute wait before the delayed recall for the HVLT-R; as a result of the

delayed recall, the total time for administration of health outcome measures will be approximately 25 minutes.

The health outcome measures will only be completed by patients for whom there is a valid translation in which the patient is fluent.

The neurocognitive assessments will be completed where training is available and feasible.

10.2.1. Neurocognitive Function

The healthcare professional (eg, nurse, psychologist) who is responsible for test administration in this study must complete training and follow administration procedures for the neurocognitive test battery. The tests in the neurocognitive test battery were selected because they are widely used standardized psychometric instruments that have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials (Meyers and Brown 2006). The tests have published normative data that take into account age, and where appropriate, education and gender. The tests are given by the certified site administrators, and the total time for the cognitive assessment is approximately 20 minutes (Table JBAL.10.2). These neurocognitive function tests have been found to be a valid and feasible method in GB patients (Wefel et al. 2011).

Table JBAL.10.2. Cognitive Assessment Tests Used in Study H9H-MC-JBAL

Cognitive Domain	Test Administration Time (minutes)
Memory	
Hopkins Verbal Learning Test-Revised	5
Cognitive Processing Speed	
Trail Making Test, Part A	3
Executive Function	
Trail Making Test, Part B	5
Controlled Oral Word Association	5

Hopkins Verbal Learning Test-Revised

The patient is asked to recall a list of 12 words over 3 trials. After a 20-minute delay the patient is asked to spontaneously recall the list words (Delayed Recall) and discriminate the list words from amongst a set of distracters (Delayed Recognition). The total time for this test, exclusive of the delay interval, is 5 minutes. There are 6 alternate forms of this test to minimize practice effects. The test measures learning and memory processes (Benedict et al. 1998).

Trail Making Test, Part A

This is a timed test of visual-motor cognitive processing speed, requiring the patient to connect dots in numerical order from 1 to 25 as fast as possible (Reitan 1992).

Trail Making Test, Part B

This timed test is similar to Trail Making Test Part A, with the additional requirement of shifting mental set (an executive function). The patient connects dots alternating numbers and letters as fast as possible (Reitan 1992).

Controlled Oral Word Association
This is a test of phonemic verbal fluency. The patient is asked to produce as many words as possible in 60 seconds beginning with a specified letter. There are 2 alternate forms of this test (Ruff et al. 1996).

10.2.2. MD Anderson Symptom Inventory – Brain Tumor Module

The MDASI-BT is a reliable and valid instrument to assess symptoms in primary brain tumor patients (Armstrong et al. 2006). The MDASI-BT consists of 22 symptom items (13 items of the core MDASI plus 9 items specific to brain tumors) plus 6 interference items, all with 11-point rating scales. For the symptom items, 0 equals "not present" and 10 equals "as bad as you can imagine." For the interference items, 0 equals "did not interfere" and 10 equals "interfered completely." The MDASI-BT may be scored by reporting the individual items or by calculating the means of all symptom items and of all interference items. The means of the core and brain tumor items may be reported separately. The 22 symptom items may also be grouped by their underlying constructs: (1) affect; (2) cognition; (3) focal neurologic deficit; (4) treatment-related symptoms; (5) generalized/disease status symptoms; and (6) gastrointestinal symptoms.
The MD Anderson Symptom Inventory user guide will be used for scoring and analyses purposes.

Minimally important differences (MIDs) for the MDASI-BT have not been reported, but there are some guidelines available for the MDASI in general and can be found in the user manual.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JBAL.10.3 describes AE and SAE collection with regard to the type of events to be collected in each study period.

Table JBAL.10.3. Adverse Event and Serious Adverse Event Reporting Guidelines for Study H9H-MC-JBAL

Treatment Period	Types of AEs/SAEs Collected/Reported
Baseline (pretreatment)	Procedure-related AEs/SAEs
Study treatment period (on therapy)	All AEs/SAEs
30-day postdiscontinuation follow-up visit (Visit 801)	All AEs/SAEs
Subsequent postdiscontinuation follow-up visits, if necessary	SAEs are required to be reported only if the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure.
Continued access period	All AEs/SAEs
Continued access follow-up (approximately 30 days)	All AEs/SAEs

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from ECGs, labs, vital sign measurements, or any other procedure that results in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal or paternal exposures to study drug or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or designee.

In addition, all AEs occurring after the patient receives the first dose of study drug must be reported to Lilly or its designee via electronic data entry.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, study drug, and/or drug delivery system via electronic data entry.

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To

assess the relationship of the AE to the study drug or procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Does not know**: the investigator cannot determine
- **Not related**: without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The National Cancer Institute CTCAE version 4 (includes all minor versions) will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the CTCAE version 4 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the eCRF. This collection is in addition to verbatim text used to describe the AE.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA).

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via electronic data entry the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert Lilly or its designee of any **serious** adverse event within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. An SAE is any adverse event from this study that results in 1 of the following outcomes:

- death

- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

Death due to disease progression should not be reported as an SAE unless the investigator also deems there to be a possible contribution related to the study drug.

Serious adverse events occurring after a patient has taken the last dose of study drug will be collected in the pharmacovigilance system and clinical data collection database for 30 days after discontinuation from study treatment, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in the IB.

In the recurrent GB population, the occurrence of major cardiovascular events (eg, thromboembolic events) and serious infections are reasonably anticipated due to disease state and concomitant medications.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the DCSI in the IB and that the investigator identifies as related to the study drug or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Collection of Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Study Schedule (Attachment 1) as single ECGs for overread. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator (or qualified designee's) interpretation will be used for study entry and immediate patient management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

10.3.2.2. Collection of Echocardiographs with Doppler and Chest CT Scans

Because of the cardiotoxicity monitoring in this study, echocardiographs with Doppler and chest CT scans are being performed (see Attachment 1 and Attachment 6). Echocardiography with Doppler will be locally assessed at screening for enrollment and throughout the study according to the Study Schedule (Attachment 1) for safety decisions by a physician or a person who is qualified by experience or training. The individual must be identified at each site. A central reading will be performed for the data used in the study report.

Chest CT scan with contrast of thorax and abdomen to evaluate the large vessels of the heart will be locally assessed at screening for enrollment and throughout the study according to the schedule of events (Attachment 1) for safety decisions by a physician or a person who is qualified by experience or training. Alternatively, a chest MRI is allowed instead of chest CT scans. An MRI imaging protocol has been added to provide a general pratice guideline (Attachment 9). However, the procedure provided by the central reviewer of the images must be followed where and when it differs from the guidelines in Attachment 9. CT or MRI scan with contrast of abdomen may be indicated at baseline only and may be required in some patients depending on the investigator´s opinion.

If the patient has clinically significant cardiac findings at discontinuation (Visit 801), ECHO, ECG, and ECG chemistry will be repeated every 2 months for 6 months.

If there are no clinically significant cardiac findings at discontinuation (Visit 801), 1 more ECHO, ECG, and ECG chemistry will be performed after 2 months. If a patient receives another treatment, cardiac assessments will not be performed.

10.3.2.3. Pulmonary Function Tests

Pulmonary function tests will be performed at baseline and approximately every 6 months, according to the institution's guidelines, for those patients receiving lomustine. This will ensure that potential of lomustine toxicity on pulmonary tissue is being detected.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP, will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes including cystatin C, troponin I, brain natriuretic peptide (BNP)
- AEs including monitoring of cardiac symptoms, infection

10.3.4. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

10.4.1. Samples for Standard Safety Laboratory Testing

Standard laboratory tests, including chemistry, hematology, and urinalysis panels will be performed.

Attachment 2 lists the specific tests that will be performed for this study. For all women with reproductive potential, a serum or urine pregnancy test will be performed at the investigative site or at a local laboratory to determine the patient's eligibility. In addition, a serum pregnancy test will be done at a central laboratory and may be used instead of a local laboratory evaluation.

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1).

Blood serum and plasma will be collected by venipuncture or through a central line.

Cerebrospinal fluid may be collected by lumbar puncture. It is estimated that per CSF assessment, approximately 100 µl are needed. See Attachment 3 for sample collection times.

To confirm the original diagnosis for all patients, the original diagnostic tumor specimen must be made available for a central pathology review. This will be returned to the original pathology laboratory.

A small amount of preserved tissue previously taken to diagnose the patient's disease (diagnostic pathological tumor tissue/slides and if available, subsequent tumor tissue/slide) will be obtained for evaluating the TGF-β-associated pathways and the GB subsets. This will include genetic, protein, or biochemical research. If both (initial diagnostic tissue and subsequent tissue) are available, both should be provided. The tissue is currently preserved in wax and will be sent to specific laboratories. Tissue block or 10 slides (minimum of 9 slides) is needed. Tissue/slides obtained for this purpose will not be returned to the site after testing. Patients who do not have adequate tissue for the PD part will be allowed to continue in the study.

Routine laboratory tests will be analyzed by a central laboratory selected by Lilly. Patients may be enrolled on local laboratory values only.

Other clinical laboratory tests, which are specialized for safety and efficacy, will be analyzed by a central laboratory.

Laboratory or analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid.

Investigators must document their review of each laboratory safety report.

All clinical laboratory samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, as outlined in Attachment 2, including hematology will be performed at a central laboratory and urinalysis profiles will be performed at a local laboratory.

Other clinical laboratory tests such as S100β, LDH, TGF-ß, PF4, high-sensitivity C-reactive protein, troponin I, and BNP will be analyzed by a central laboratory. Further, markers associated with target modulation will be assessed in T cells (T cell counts, $CD4^+CD25^+FoxP3^+$, whole blood FoxP3).

Investigators must document their review of each laboratory safety report.

10.4.2. Pharmacogenetic Samples

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow, a blood sample will be collected for pharmacogenetic analysis. It is a 1-time collection, as noted in the Study Schedule (Attachment 1).

In the event of an unexpected AE or the observation of unusual response, the samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY2157299. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be identified by the patient number (coded) and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

10.4.3. Biomarkers, Pharmacodynamic, and Patient Tailoring Sampling (TGF-β Functionality, RNA Microarray, MAP, TGF-β, and PF4)

Collection of samples for biomarker, pharmacodynamic, and patient tailoring research is required for this study to link gene expression of the targeted signaling pathway with OS. Samples will be collected at the times specified in the Study Schedule (Attachment 1 and Attachment 2, as applicable).

The research on stored samples from this study may look at the proteins or other biochemical markers to learn more about compound specific disease states or how patients respond to or tolerate treatment with LY2157299 or other compounds/medications administered during this study. Stored samples may also be used in validating diagnostic tools or assay(s) related to patient tailoring and disease state.

The samples for whole-blood and plasma will be 10 to 20 mL of blood (approximately 1 to 2 tablespoons) collected at times before treatment with LY2157299. Tissue samples will be formalin-fixed paraffin-embedded (FFPE; preferred, with the second preference, FFPE partial block and the third preference, a minimum of 10 positively charged slides).

Samples will be identified by patient number (coded) and will be stored for a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor.

10.4.4. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

Pharmacokinetic collection is critical for the evaluation of safety risks for patients receiving LY2157299. Hence, population PK sampling will be required in this study and combined with ECG evaluation.

Sparse blood samples (2 mL) for the measurement of LY2157299 used for PK/PD evaluation will be collected during Cycle 1 for each patient in the study (see Attachment 1 and Attachment 3).

The actual time of dosing on the day of sampling and the actual time of sampling for each of the samples must be collected. Dose information (time and amount of LY2157299 dose recording in patient diaries) must be collected for the day of sampling and the 2 days prior to the sampling day. This information can be obtained from the patient diary at the visit for blood sampling.

Additionally, PK draws may be obtained for patients who show high variability of LY2157299. This is required to evaluate PK-related toxicity risks. Such PK draws will be discussed with the investigator and documented in the eCRF.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Plasma samples will be analyzed for LY2157299 using a validated method.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

10.4.5. Exploratory Samples and Work

Exploratory PK assessments, for example in CSF or urine, and exploratory imaging studies may be conducted in this study.

10.5. Appropriateness of Measurements

There are no regulatory approved surrogate endpoints used in this study. All efficacy and safety assessments used in this study are standard and appropriate for study.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data collected by the third-party organization (TPO) will be encoded by the TPO and stored electronically in the TPO's database system. Validated data will subsequently be transferred using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

CCI patients will be entered with the aim of randomizing CCI patients to 1 of 3 treatment arms in this multicenter study. The randomization will be in CCI (CCI patients in LY2157299 monotherapy, CCI patients in LY2157299 plus lomustine therapy, and CCI patients in lomustine plus placebo therapy).

The primary objective is to compare the OS distributions between of LY2157299 plus lomustine therapy with lomustine plus placebo therapy (control arm) using a Bayesian augmented control design. By incorporating historical information regarding the control group (ie, lomustine plus placebo) into the Bayesian model, it is possible to improve the operating characteristics compared to a standard (frequentist) analysis.

The primary comparison will be considered successful if, after CCI patients have completed at least 2 years of follow-up, the posterior probability is greater than CCI% that the HR for OS of the combination arm versus lomustine plus placebo is <1.

The study is designed to observe approximately CCI events. Simulations (FACTS v2.4) assuming the following were carried out:

- Exponential survival model using summary hazard rates from 2 previous lomustine trials (Study H6Q-MC-JCBF [data on file and Wick et al.2010a], Batchelor et al. 2010a;) along with data from the lomustine plus placebo arm in this study.
    - The average median OS time is 8.5 months giving an average control hazard rate across these 2 studies of CCI week
    - The fixed prior distribution for the control hazard rate has a mean of CCI and a weight of CCI (weak prior)
- The prior distribution of the log HR between the combination arm and lomustine plus placebo is assumed to be Normally distributed with a mean of zero and a standard deviation of 100 (weak prior)
- A 'true' OS HR of CCI
- Patients are randomized in a CCI ratio (favoring the LY2157299 plus lomustine arm)
- Enrollment rate is CCI patients/month (CCI patients/week)
- Minimum follow-up for last subject is approximately 2 years (94 weeks)

The simulations indicate that, by enrolling CCI patients, the posterior probability of concluding superiority of LY2157299 plus lomustine arm over lomustine plus placebo arm is approximately CCI%. Assuming an HR of CCI, the posterior probability of concluding superiority of LY2157299 plus lomustine arm over lomustine plus placebo arm is approximately CCI%. See Attachment 10 for more details.

Additional details for each of the below outlined statistical assessments will be provided in the Statistical Analysis Plan (SAP).

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

Time-to-event efficacy analyses will be conducted on all patients who received at least 1 dose of study drug treatment. This set will group patients according to their allocated treatment.

Only patients with measurable disease will be included in summaries of tumor response.

Safety analyses will be based on the safety population, defined as all randomized patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in Cycle 1. A subanalysis will be conducted by excluding patients who should have been otherwise discontinued to determine their influence on the final study results.

Patients from all sites will be pooled for the purposes of analysis. Inference about survival will be made using a Bayesian posterior probability for the superiority of LY2157299 plus lomustine arm survival over lomustine plus placebo arm. The remaining analyses of this study will estimate differences between arms where appropriate, including exploratory analyses. Descriptive statistics by treatment arm will also be provided.

Results of descriptive analyses and estimates from inferential analyses will be presented by treatment arm. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Any missing longitudinal data will not be imputed, rather estimated from an appropriate random mixed effects model. Transformations will be applied where assumptions behind any analysis are better satisfied by data being transformed onto an alternative scale. All results from any of these analyses will be back transformed to the original scale. Alternatively, nonparametric methods will be applied.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol or additional exploratory analyses deemed appropriate, and the justification for making the change and additions, will be described and justified in the SAP and/or clinical study report.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients discontinuing (overall and by reason for discontinuation) from both study treatment and study itself. A summary of all important protocol violations will be provided.

For the purpose of clinical trial registry reporting, patients who have died or are still in the study but off treatment at primary data base lock will be considered a completer. Those who withdrew

consent for all procedures, including follow-up, or were lost to follow up, will be considered as early discontinuers. Patients who remain on treatment will be counted as continuing treatment.

12.2.3. Patient Characteristics

Patient demographics including age, sex, screening height and weight, and screening body surface area will be listed and summarized using descriptive statistics.

Baseline disease characteristics will be summarized, by presenting frequency counts and percentages, such as pathological diagnosis (histological or cytological) and disease grade.

Prior disease-related regimens will also be listed and summarized by regimen, detailing individual therapies within each regimen (Section 12.2.4.1).

Other patient characteristics will be summarized as deemed appropriate.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population using generic names and class of drugs using standard dictionary, such as the WHO drug dictionary.

Enzyme-inducing and non-enzyme inducing anti-epileptic drug treatments will be collected and reported separately.

Steroid drug intake will be collected and reported separately.

12.2.4.1. Prior Regimens

Listings of patients' prior regimen will be provided, such as chemoradiation with TMZ. Listings will include regimen number indicating which different therapies and/or types of therapies are included in the same regimen. The numbers and percentages of patients reporting prior regimens will be provided.

12.2.4.2. Postdiscontinuation Regimens

Listings of patients reporting postdiscontinuation therapies will be provided.

Bevacizumab treatment after poststudy drug discontinuation will be listed and included in the OS analyses to detect any potential influence on OS.

Listings will include regimen number indicating which different therapies and/or types of therapies are included in the same regimen. The numbers and percentages of patients reporting postdiscontinuation regimens will be provided overall.

12.2.5. Treatment Compliance

The number of dose omissions, reductions, delays, number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm. Summarized data will be provided for the treatment period.

Treatment compliance within a cycle means that the patient has taken their allocated treatments as prescribed for that cycle (see Section 9.1). (This is distinct from dose intensity which

calculates the amount of drug taken per cycle compared to the dose the patient was initially assigned at the start of the study and is defined in Section 12.2.10).

Treatment compliance information for LY2157299 and placebo will be collected through both pill counts and by the site querying the patient at the end of each cycle for each patient. The number of tablets taken relative to the number expected to be taken will be summarized by cycle and treatment arm.

12.2.6. Primary Outcome and Methodology

Overall survival (OS) duration is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data inclusion cutoff date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

A method of analysis for comparing OS between the treatment arms will use a Bayesian exponential-likelihood model with possibly a hierarchical random-effects distribution on treatment effects. The model incorporates historical data from 2 studies (Study H6Q-MC-JCBF [data on file and Wick et al. 2010a]; Batchelor et al. 2010a) with a lomustine plus placebo arm to augment the prospective control arm data. If the Bayesian posterior probability of superiority of LY2157299 plus lomustine therapy over lomustine plus placebo therapy (control) (ie, HR CCI [redacted], then it will be concluded that the combination arm is superior. A similar Bayesian analysis will be carried out to provide 90% predictive intervals of the HR between the lomustine plus placebo and LY2157299 monotherapy. See Attachment 10 for more details.

12.2.7. Additional Efficacy Analyses

Overall survival (OS) is the primary outcome of interest and the primary analysis is as described above.

Overall survival (OS) and OS rate at 12 months will be summarized by treatment arm using Kaplan-Meier estimates of the median survival times (including 95% CIs) to inform assumptions for use in future trial planning (Kaplan and Meier 1958). Additional exploratory analyses using proportional hazards models to control for other factors may be performed, including, but not limited to, adding a covariate indicating the extent of lomustine exposure, PD marker assessment of the tumor tissue, the known influence factors, such as age, PS, and primary or secondary GB and whether patients had poststudy treatment with bevacizumab.

The following secondary efficacy parameters will be summarized for each treatment group:

- PFS distribution parameters and PFS rate
- ORR

Progression-free survival and PFS rate will be summarized (at CCI [redacted]) using Kaplan-Meier estimates of the median survival times (including 95% CIs) to inform assumptions for use in future trial planning (Kaplan and Meier 1958). Estimates of HRs between

the 3 arms will also be provided. Additional exploratory analyses using proportional hazards models to control for other factors may be performed.

Overall response rate (ORR) and, additionally, disease control rate given the risk of pseudo progression, will be estimated by dividing the total number of responders ([CR or PR] or [CR or PR or SD]) by number of randomly assigned patients. Exact 95% CIs for each treatment arm will be provided.

Additional analyses may be carried out to judge the influence of any patients who did not meet enrollment criteria but were inadvertently enrolled and continued on treatment after obtaining approval from the sponsor and/or patients who have continued treatment after objective disease progression (see Section 7.3.1). A subanalysis will be conducted by excluding such patients to determine their influence on the final study results.

12.2.8. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the investigational product and have had samples collected.

Population-based PK analysis will be performed using sparse PK data with validated PK software programs (for example, NONMEM). The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Pharmacodynamic data from all patients undergoing PD assessments will be analyzed. Pharmacodynamic data will be documented in the study report by dose, exposure, and time from dose. Exploratory PK/PD analyses will be conducted as data become available to determine the relationship between exposure and PD effect. The PK/PD data will be analyzed using validated software programs (for example, WinNonlin and NONMEM). The version of software used for the analysis will be documented and will meet the Lilly requirements of software validation.

12.2.9. Health Outcome Analyses

Patients with at least baseline and 1 post-baseline assessment will be included in the analyses. Compliance with completing the questionnaires will be summarized at the group-level at each assessment period (defined as the number of completed questionnaires/number expected questionnaires given those that are still on study).

Each health outcome parameter will be reported independently. Relationships (predictors or prognostic) among these parameters and with other clinical parameters such as PS, OS, and disease assessments (based on MRI) may be explored.

12.2.9.1. Neurocognitive Function

Each neurocognitive test will be converted to a standardized score (mean = 0, SD = 1) using published healthy control data. Data will be summarized for each assessment period and change over time will be explored. Differences in neurocognitive progression will be assessed between arms using Cox proportional hazards regression.

Further analyses will be specified in the SAP.

12.2.9.2. MD Anderson Symptom Inventory – Brain Tumor Module

The MDASI-BT will be analyzed as described in the MDASI user manual. Data will be summarized for each assessment period and compared between arms. This summary will include mean, standard deviation, median, minimum, maximum, and change from baseline (including time to worsening of symptoms). A minimally important difference of 1.2 (as defined in the MDASI user manual) will be used in the time to worsening analyses. The MDASI-BT will be reported as core symptoms, brain tumor symptoms, symptom interference, and symptom groupings (affect, cognition, focal neurologic deficit, treatment-related symptoms, generalized/disease status symptoms, and gastrointestinal symptoms).

Further analyses will be specified in the SAP.

12.2.10. Safety Analyses

All safety summaries and analyses will be based upon the safety population as defined in Section 12.2.1.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be used to report AEs. The MedDRA Version 14.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA lower level term (LLT) will be used in the treatment-emergent computation.

A TEAE is defined as an event that first occurred or worsened in severity after baseline, based on the MedDRA LLT and CTCAE severity grade. This means that any episode of the same AE with the same grade as at baseline that starts after the first dose of study treatment will not be defined as treatment emergent, even if now considered possibly drug related.

An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study medication, and repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Fisher's exact test. These analyses and summaries will be repeated for TEAEs.

The TEAEs will be summarized separately for both MedDRA and CTCAE dictionaries, by their respective System Organ Class (SOC) terms and by decreasing frequency of their respective preferred term (PT) within SOC.

The number of evaluable patients who experienced a TEAE, SAE, AE related to study drug, died, or discontinued from the study due to an AE will be summarized by treatment.

The CTCAEs, separated by those defined as laboratory and non-laboratory CTCAEs, will be summarized by CTCAE term and maximum CTCAE grade, including the total for maximum Grade 3 and 4. These summaries will be provided for events regardless of study drug causality,

and repeated for events deemed by the investigator to be possibly related to study medication. These summaries will be repeated for TEAEs.

A calculated CTCAE grade will be provided for all laboratory results which can be used independently of clinical judgment to determine a CTCAE severity grade. These will be summarized by CTCAE grade in a separate table, linking the CTCAE term to the laboratory term in question.

Reasons for death will be summarized separately for on-therapy, within 30 days of last dose of study drug and during the long-term follow-up periods. The SAEs will be summarized by MedDRA and CTCAE PT.

Hospitalizations and transfusions during the study treatment period or during the 30-day postdiscontinuation follow-up period will be summarized by treatment group.

12.2.10.1. Cardiac Safety Analyses

Refer to Attachment 1 and Attachment 2 for timing of ECGs, ECG chemistry, and ECHOs.

Echocardiography/Doppler assessments will be done as outlined in Attachment 6.

Baseline ECGs are ECGs performed either during screening or predose during the study. Changes in QT from baseline, delta QT, will be calculated by subtracting the respective reading taken at the same nominal time during screening from the reading taken after LY2157299 dosing on specified days in Attachment 1. Similarly, changes in RR from baseline, delta RR, will be calculated. Delta QT will then be analyzed using a linear mixed-effects model (Dmitrienko and Smith 2003).

In addition, listings and summaries of outlying corrected QT intervals (QTc [QTc – Bazett's correction (QTcB) and QTc – Fridericia's correction (QTcF)]) will be provided for each scheduled time point.

If data warrant, additional exploratory analyses may be conducted using appropriate modeling techniques.

The ECG chemistry laboratory values will be listed and summarized separately from other laboratory values.

Individual patient listings and summaries by treatment arm will be provided for all echocardiograph variables. Shift tables indicating maximum changes from baseline will be provided for qualitative variables and absolute and/or percent change from baseline for quantitative variables.

12.2.11. Subgroup Analyses

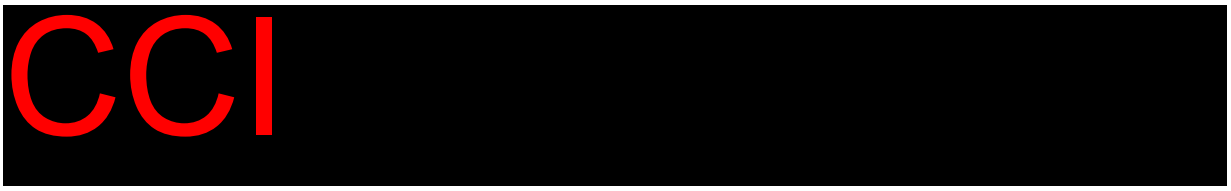
There are no planned subgroup analyses. However, exploratory analyses may be performed to generate hypotheses about the efficacy of study therapy in certain subgroups to be tested in future clinical trials.

12.2.12. Interim Analyses

CCI interim assessments are planned:

The combination arm or LY2157299 monotherapy arm could be considered futile if, after CCI patients have completed 3 cycles, the posterior probability is less than 10% that the HR for OS of combination arm or LY2157299 arm versus lomustine arm is less than CCI.

See Attachment 10 for the operating characteristics for this analysis.



See Attachment 10 for the operating characteristics for this analysis.

The plan is to continue enrolling patients into the study during each interim analysis unless ongoing safety reviews have raised safety concerns.

The safety/tolerability and efficacy results from the interim analyses will be reviewed only by an internal Assessment Committee consisting of the Lilly Medical Director, a Lilly CRP not in contact with study sites, a Lilly statistician, and a PK scientist, if needed. The assessment committee members will review unblinded safety and/or efficacy data at each interim analysis to determine whether there are sufficient safety or futility concerns to justify the termination of a

study treatment arm. Results of the interims will not be communicated to the study sites, unless the interim analysis shows evidence of harm.

Unblinding details are specified in the unblinding plan section of the SAP.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s).

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

The study site's ERB(s) should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

All or some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.4. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

13.4.1. Protocol Signatures

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.4.2. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most qualified will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The sponsor's responsible medical officer and responsible statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. JBAL Study Schedule

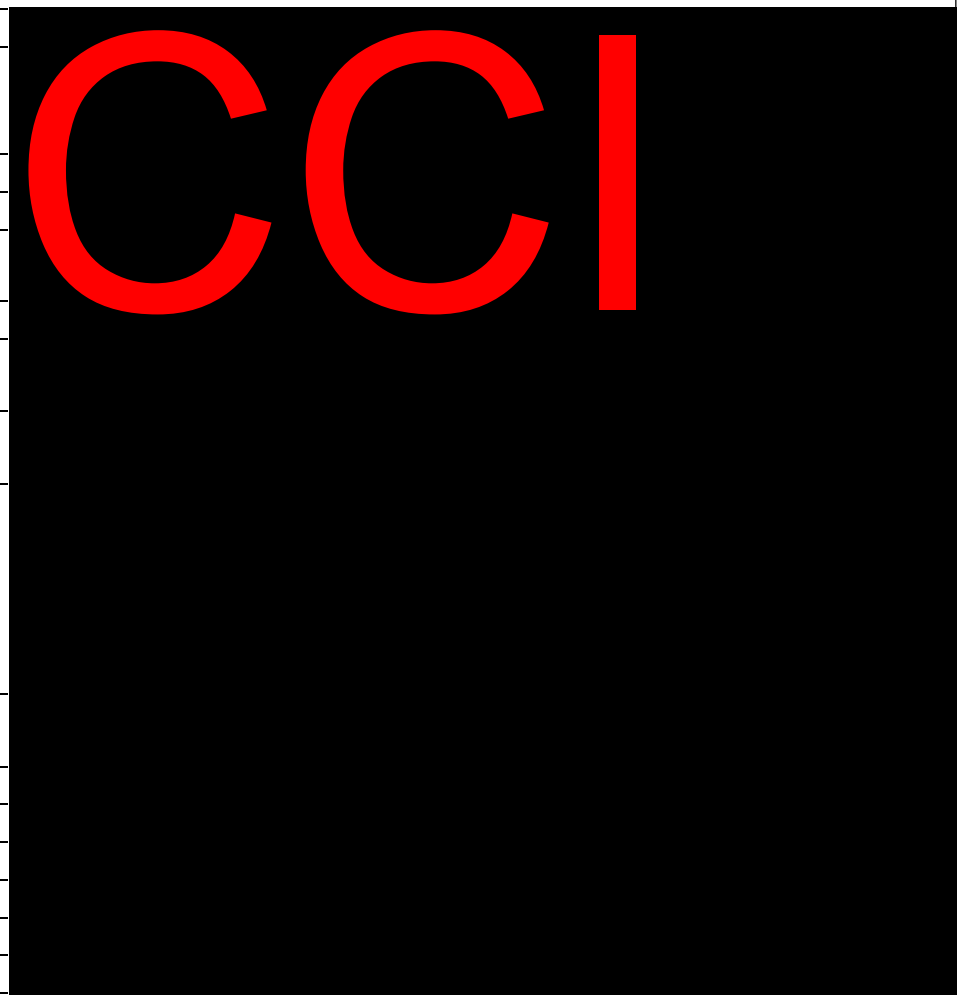
Study Schedule for Protocol H9H-MC-JBAL – Prestudy and Cycle 1

Cycle	Prestudy			Cycle 1								Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1**	**3**	**7±2**	**12±2**	**14**	**15**	**16**	**26±2**	
Treatment												
Lomustine						X						CCI
LY2157299 monohydrate or matched placebo				X	X	X	X	X				
Procedures												
Informed consent	X											
Medical history		X										
Pregnancy test		X										CCI
Physical Examination		X		X								
Vital signs (heart rate, blood pressure)		X		X								
CTCAE		X		X								
Concomitant medications		X		X								

Cycle	Prestudy			Cycle 1							Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1**	**3**	**7±2**	**12±2**	**14**	**15**	**16**	**26±2**	
ECOG performance status		X		X								
Health outcome measures		X									X	CCI
Imaging Procedures												
Echocardio-graphy with Doppler		X										
Radiological tumor assessment		X										
Chest CT scan or chest MRI		X										
Laboratory/Diagnostic Tests												
PFT			X									
ECG		X		X	X			X	X		X	
Troponin I and BNP			X								X	
Hematology			X								X	
Urinalysis			X								X	
Fox P3			X									

Cycle	Prestudy			Cycle 1							Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1**	**3**	**7±2**	**12±2**	**14**	**15**	**16**	**26±2**	
Serum chemistry			X								X	
ECG chemistry		X		X	X			X	X			
Serum hs-CRP			X								X	
PK sampling				X	X			X	X	X		
CSF												
MAP				X			X					
Affymetrix				X								
Whole blood for PGx		X										
Whole blood/ plasma				X								
Tumor tissue		X										

Study Schedule for Protocol H9H-MC-JBAL – Cycles 2, 5, 8, 11

Cycle	Cycles 2, 5, 8, 11					Comments
Relative Day Within a Cycle	**1±2**	**6±2**	**12±2**	**21±2**	**26±2**	
Treatment						
Lomustine				X		
LY2157299 monohydrate or matched placebo	X	X	X			
Procedures						
Physical examination	X		X			
Vital signs (heart rate, blood pressure)	X					
CTCAE	X					
Concomitant medications	X					
ECOG performance status	X					
Health outcome measures					X	
Echocardiography with Doppler					X	
ECG					X	
Troponin I and BNP					X	
Hematology					X	
Urinalysis					X	
Fox P3					X	
Serum chemistry					X	

ECG chemistry					X	
Cycle	**Cycles 2, 5, 8, 11**					**Comments**
Relative Day Within a Cycle	**1±2**	**6±2**	**12±2**	**21±2**	**26±2**	
Serum hs-CRP					X	
Radiological tumor assessment					X	CCI [redacted]
MAP			X			
Affymetrix					X	

Study Schedule for Protocol H9H-MC-JBAL – Cycles 3, 6, 9, 12

Cycle	Cycles 3, 6, 9, 12				Comments
Relative Day Within a Cycle	**1±2**	**6±2**	**12±2**	**26±2**	
Treatment					
Lomustine					[redacted]
LY2157299 monohydrate or matched placebo	X	X	X		
Procedures					
Physical examination	X				
Vital signs (heart rate, blood pressure)	X				
CTCAE	X				
Concomitant medications	X				
ECOG performance status	X				
Health outcome measures				X	
Echocardiography with Doppler				X	
ECG				X	
PFT				X	
Troponin I and BNP				X	
Hematology				X	
Fox P3				X	

Cycle	Cycles 3, 6, 9, 12				Comments
Relative Day Within a Cycle	**1±2**	**6±2**	**12±2**	**26±2**	
Serum chemistry				X	CCI
ECG chemistry				X	
Serum hs-CRP				X	
Radiological tumor assessment				X	
Chest CT scan or chest MRI				X	
MAP				X	
Affymetrix				X	

Study Schedule for Protocol H9H-MC-JBAL – Cycles 4, 7, 10, Visit 801, Follow-Up

Cycle	Cycles 4, 7, 10				Visit 801	Follow Up	Comments
Relative Day Within a Cycle	**1±2**	**6±2**	**12±2**	**26±2**			
Treatment							
Lomustine		X					
LY2157299 monohydrate or matched placebo	X	X	X				
Procedures							
Physical examination	X				X		
Vital signs (heart rate, blood pressure)	X				X		
CTCAE	X				X		
Concomitant medications	X				X		
ECOG performance status	X				X		
Health outcome measures				X	X		
Echocardiography with Doppler				X	X	X	
ECG				X	X	X	
Troponin I and BNP				X	X		

Hematology				X	X		CCI .
Cycle	**Cycles 4, 7, 10**				**Visit 801**	**Follow Up**	**Comments**
Relative Day Within a Cycle	**1±2**	**6±2**	**12±2**	**26±2**			
Urinalysis				X	X		CCI
Serum chemistry				X	X		
ECG chemistry				X	X	X	
Fox P3				X			
Serum hs-CRP				X			
Radiological tumor assessment				X			
MAP				X			
Affymetrix				X			

Abbreviations: BNP = brain natriuretic peptide; COWA = Controlled Oral Word Association; CSF = cerebrospinal fluid; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GB = glioblastoma; hs-CRP = high-sensitivity C-reactive protein; HVLT-R = Hopkins Verbal Learning Test – Revised; MAP = multi-analyte panel; MDASI-BT = MD Anderson Symptom Inventory-Brain Tumor; MRI = magnetic resonance imaging; PFT = pulmonary function test; PGx = pharmacogenetics; PK = pharmacokinetic; TGF-β = transforming growth factor – beta.

Study Schedule for the continued access period only, Protocol H9H-MC-JBAL

Cycle	Continued Access[a] Visit 501-5XX				Follow-Up[b] Visit 801	Comments
Relative Day Within a Cycle	**1±2**	**6±2**	**12±2**	**26±2**		
Treatment						
Lomustine		X				CCI
LY2157299	X	X	X			
Procedures						
Physical examination	X				X	
Vital signs (heart rate, blood pressure)	X				X	
CTCAE	X				X	
Echocardiography with Doppler				X	X	
ECG				X	X	
Troponin I and BNP				X	X	
ECG chemistry				X	X	
Serum hs-CRP				X		

Abbreviations: BNP = brain natriuretic peptide; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; hs-CRP = high-sensitivity C-reactive protein.

[a] No follow-up procedures will be performed for patients who withdraw informed consent unless he or she has explicitly provided permission and consent.

[b] Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately [30] days.

Note: Efficacy assessments will be done at the investigator's discretion based on the standard of care.

Attachment 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry**[a]:
Hemoglobin	Sodium
Erythrocytes	Potassium
Platelets	Total bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented + bands	Alanine aminotransferase / serum glutamic pyruvic transaminase (ALT/SGPT)
Eosinophils	Aspartate aminotransferase / serum glutamic oxaloacetic transaminase (AST/SGOT)
Monocytes	Blood urea nitrogen (BUN)
Basophils	Creatinine
Lymphocytes:	Uric acid
• Total T- and B-cell counts	Calcium
• CD8 T cell counts	Glucose, random
• CD4 T cell counts	Albumin
• T regulatory counts (eg, $CD4^+CD25^+FoxP3^+$)	Total protein
	Phosphorus
FoxP3[a]	S100ß
	LDH
Troponin I[b]	Cystatin C
	TGFβ
Serum Pregnancy Test (females only)[a,b]	PF4
BNP[a]	**ECG Chemistry**[a]:
	Lipase
High-sensitivity C-reactive protein (hs-CRP)[a]	Thyroid Stimulating Hormone (TSH)
	Tri-iodothyronine (T3)
Urinalysis[b]:	Thyroxine (T4)
pH	Albumin[c]
Protein	Glucose, random (non-fasting)[c]
Specific gravity	Calcium[c]
Glucose	Sodium[c]
Ketones	Potassium[c]
Blood	Phosphorus[c]
Leukocyte esterase	Magnesium[c]

Abbreviations: BNP = brain natriuretic peptide; ECG = electrocardiogram; LDH = lactate dehydrogenase; PF4 = platelet factor 4; TGFβ = transforming growth factor-beta; WBC = white blood cells.

a All samples will be discarded within 60 days of validated test results. Validation will either occur immediately after initial testing, or will require that samples be held to be retested at some defined time point. Laboratory tests will be analyzed by a central laboratory selected by Lilly.

b All samples will be discarded within 60 days of validated test results. Validation will either occur immediately after initial testing, or will require that samples be held to be retested at some defined time point. Patients may be enrolled on local laboratory values only.

c Test not performed if both chemistry and ECG chemistry required at same time point. See Attachment 1.

Attachment 3. Pharmacokinetic Sampling

In conjunction with the Study Schedule of Events, the following PK draws will be conducted.

Sparse PK Sampling Schedule for Phase 2

Sample Number	Cycle	Day	Sampling Windows for plasma PK	ECG and ECG Chemistry	Optional CSF collection[b]
1	1	1	Predose[a]	X	
2	1	1	0.5 to 2 hours		0.5 hours[b]
3	1	1	3.5 to 5 hours	X	4 hours
4	1	3	Predose[a]	X	Predose
5	1	14	Predose[a]	X	Predose
6	1	14	0.5 to 2 hours		0.5 hours
7	1	14	3.5 to 5 hours	X	4 hours
8	1	15	Morning	X	Morning
9	1	16	Morning		

Abbreviations: CSF = cerebrospinal fluid; ECG = electrocardiogram; PK = pharmacokinetic.

[a] The predose sample has to be taken before receiving any LY2157299 monohydrate.

[b] CSF collection time as close as possible to plasma sample.

Attachment 4. ECOG Performance Status

ECOG Performance Status

Activity Status	Description
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, e.g., 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 et al. 1982.

Attachment 5. Response Assessment in Neuro-Oncology

Criteria for Determining First Progression Depending On Time from Initial Radiochemotherapy

Twenty percent to 30% of patients develop "pseudoprogression" following radiochemotherapy, especially within the first 3 months following completion of radiotherapy. Given the difficulty of differentiating "pseudoprogression" from true progression in the first 3 months after irradiation, we propose excluding these patients from clinical trials for recurrent disease unless the progression is clearly outside the radiation field (eg, beyond the high dose region or 80% isodose line) or if there is pathologic confirmation of disease progression. Table 2 summarizes these recommendations.

Criteria for Entry into Clinical Trials for Recurrent High-grade Glioma

Currently patients with any worsening of their imaging studies are eligible for entry into clinical trials for recurrent gliomas, even if the change is minimal. It is proposed that patients will be required to have a 25% increase in the sum of the products of perpendicular diameters of the contrast-enhancing lesions on stable or increasing doses of corticosteroids before they are considered to have progressive disease for entry into clinical trials for recurrent/progressive disease. Patients with new contrast-enhancing non-measurable disease may be considered for clinical trials where progression-free survival is the primary endpoint. Clinical deterioration alone would not be sufficient to indicate progressive disease for entry into clinical studies.

A particularly difficult problem involves patients receiving first-line anti-angiogenic agents who develop predominantly non-enhancing disease at progression. This can be difficult to differentiate from treatment effects. If it seems clear that the non-enhancing changes represent tumor progression, these patients would also be eligible for enrollment into clinical trials for recurrent disease, although their tumor will be considered non-measurable. As noted previously, while it would be preferable to have a more objective measure of progressive non-enhancing recurrent disease similar to contrast-enhancing disease, the Response Assessment in Neuro-Oncology (RANO) working group felt that this was not possible at present given the limitations of current technology.

Definition of Radiographic Response

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement following initiation of therapy for determination of progression. Table 3 outlines the criteria for radiographic changes following therapy. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patients closely, for example at 4 weekly intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the scan at which this issue was first raised. All measurable and non-

measurable lesions must be assessed using the same techniques as baseline. Ideally patients should be imaged on the same MRI, or least the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

- **Complete Response**: Complete response is defined as complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease. There should be no new lesions. Stable or improved non-enhancing (T2/FLAIR) lesions. Patients must be off corticosteroids and stable or improved clinically.
- **Partial Response**: Greater than or equal to 50% decrease, compared to baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease. No progression of non-measurable disease. No new lesions. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.
- **Stable Disease**: This occurs if the patients did not qualify for complete response, partial response, or progression (see below). There should be stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose. The patient should be stable clinically.
- **Progression:** Progression is defined as ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions (over baseline if no decrease) on stable or increasing doses of corticosteroids and/or a significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events. The appearance of any new lesions. Clear progression of non-measurable lesions. Definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose. Failure to return for evaluation due to death or deteriorating condition should also be considered as progression. Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression.

The definition of clinical deterioration is left to the discretion of the treating physician but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20% from 80 or less, or a decline in KPS from any baseline to 50% or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group (ECOG) and the World Health Organization (WHO) scores from 0 or 1 to 2, or 2 to 3 would be considered neurologic deterioration.

Patients with non-measurable enhancing disease whose lesion has significantly increased in size and becomes measurable (minimal bidirectional diameter of ≥10 mm, and visible on 2 axial slices which are preferably at most 5 mm apart with 0 mm skip) will be considered to have progressed. The transition from a non-measurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (eg, a 9 x 9 mm lesion [non-measurable] increasing to 10 x 11 mm [measurable]). Ideally, the change should be significant (>5 mm increase in maximal diameter or ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation, for example at 4 weekly intervals. If subsequent evaluations suggest that the patient is in fact progressing, the date of progression should be the time point at which this issue was first raised.

Multifocal Tumors

For multifocal lesions, progressive disease is defined as 25% or greater increase in the sum of products of perpendicular diameters of all measurable lesions compared to the smallest tumor measurements following initiation of therapy (Table 3). Partial response is defined as equal to 50% or greater decrease compared to baseline in the sum of products of perpendicular diameters of all measurable lesions sustained for at least 4 weeks with stable or decreasing corticosteroid doses.

Role of Volumetric and Functional Imaging Assessment

Given the limitations of 2-dimensional (2D) tumor measurements, there is significant interest in volumetric anatomical assessment. The use of volumetric assessment would allow more accurate determination of the contrast-enhancing and non-enhancing volumes, and overcome the limitations of 2D measurements of lesions surrounding a surgical cavity. (Sorensen et al. 2001; Henson et al. 2008; Sorensen et al. 2008). However, the RANO working group and colleagues in neuroradiology did not believe that there is sufficient standardization and availability to recommend adoption of volumetric assessment of tumor volume at present. Nonetheless this is an important area of research. Eventually, as volumetric imaging becomes more standardized and widely available, and as data validating this approach emerges, it may be possible to incorporate volumetric measurements in the response assessment of high-grade gliomas.

There is also emerging data suggesting that advanced MRI techniques such as perfusion imaging (dynamic susceptibility MRI), permeability imaging (dynamic contrast enhanced MRI), diffusion imaging, magnetic resonance spectroscopy, and (18)F-fluorothymidine and amino acid positron emission tomography may predict tumor response or allow the differentiation of non-enhancing tumor from other causes of increased FLAIR signal. These techniques will require rigorous clinical validation studies before they can be incorporated into response criteria used in clinical trials in high-grade gliomas.

Other Methods of Determining Efficacy

There is growing data suggesting that other endpoints such as neuro-cognitive function, quality of life and corticosteroid use may be used to measure clinical benefit. At present, these endpoints are not sufficiently validated to be incorporated into the current response criteria but could be added in the future as further data emerges.

Table 1: **Criteria for Determining First Progression Depending On Time from Initial Radiochemotherapy**

I. Definition of Progressive Disease Less Than 12 Weeks from Completion of Radiochemotherapy

a) Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high dose region or 80% isodose line).

or

b) If there is unequivocal evidence of viable tumor on histopathologic sampling (eg, solid" tumor areas (ie, >70% tumor cell nuclei in areas), high or progressive increase in MIB-1 proliferation index compared to prior biopsy, or evidence for histologic progression or increased anaplasia in tumor.

Note: Given the difficulty of differentiating true progression from "pseudoprogression", clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks following completion of XRT/TMZ.

II. Definition of Progressive Disease at and Beyond 12 Weeks of Radiochemotherapy Completion

a) New contrast-enhancing lesion outside of radiation field on decreasing, stable or increasing doses of corticosteroids.
b) Increase by 25% or greater in the sum of the products of perpendicular diameters between the first post-radiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids.
c) Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment, but not for entry on a clinical trial for recurrence.
d) For patients receiving anti-angiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, and not due to co-morbid events (eg, effects of RTX, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).

Table 2: **Criteria for Response Assessment Incorporating MRI and Clinical Factors**

All measurable and non-measurable lesions must be assessed using the same techniques as baseline.

Complete Response:

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks.
b) No new lesions.
c) Stable or improved non-enhancing (T2/FLAIR) lesions
a) Patients must be on no corticosteroids.
b) Stable or improved clinically.

Note:

1) Patients with non-measurable disease only cannot have a complete response. The best response possible is stable disease.

Partial Response:

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks.
b) No progression of non-measurable disease.
c) No new lesions.
d) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.

a) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
b) Stable or improved clinically.

Note:

g) Patients with non-measurable disease only cannot have a partial response. The best response possible is stable disease.

Stable Disease:

a) Does not qualify for complete response, partial response, or progression.

b) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
a) Stable clinically.

Progression:

a) ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids

and/or

b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (eg, RTX, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c) Any new lesion
d) Clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose.
e) Failure to return for evaluation due to death or deteriorating condition
f) Clear progression of non-measurable disease.

Table 3: Summary of the RANO Response Criteria

	CR	PR	SD	PD
T1-Gd +	**None**	**≥ 50% ↓**	**< 50% ↓ - < 25% ↑**	≥ 25% ↑*
T2/FLAIR	**Stable or ↓**	**Stable or ↓**	**Stable or ↓**	↑*
New Lesion	**None**	**None**	**None**	Present*
Corticosteroids	**None**	**Stable or ↓**	**Stable or ↓**	**NA**
Clinical Status	**Stable or ↑**	**Stable or ↑**	**Stable or ↑**	↓*
Requirement for response	all	all	all	Any*

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
↓ = decrease
↑ = increase
* Progression occurs when any of the criteria with * is present.
NA: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of clinical deterioration.

Reference:

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28(11):1963-1972.

Attachment 6. Echocardiography Protocol

Echocardiography

In this study, echocardiographic images are acquired with the purpose of ascertaining that patients enrolled in the study have baseline (and maintain during the study) normal cardiac structure and function, normal pulmonary artery pressure, and absence of significant valvular disease (defined herein as no valvular regurgitation except for mild tricuspid, mild mitral, mild aortic regurgitation, and no more than mild mitral or aortic valvular stenosis). Repeated echocardiograms in each subject are performed to establish the cardiac safety of LY2157299 monohydrate by comparison with the initial studies. Determination of normalcy status requires objective evaluation of cardiac chamber size and function and attention to the use of appropriate techniques in the performance of the echocardiographic examinations, in particular the use of standardized settings during the acquisitions of color flow Doppler imaging. Therefore, because quantitative echocardiography is the goal, stringent criteria for image quality and reproducibility are essential.

In addition to qualitative assessment of valvular regurgitation when or if detected (trace, mild, moderate, or severe according to Singh, et al. and Zoghbi, et al. (see below) and qualitative/quantitative assessment of valvular stenosis when or if detected (mild, moderate, or severe, using mean and peak pressure gradient in mmHg and orifice area in cm^2 as applicable), other echocardiographic parameters to be serially quantified are: left ventricular (LV) cavity size (diameters, volumes; assisted by intravenous injection of left-sided contrast echocardiographic agents). LV ejection fraction (EF), LV mass and mass index, diastolic function based on mitral flow velocity, mitral deceleration time, pulmonary venous flow pattern, tissue Doppler, extrapolation of LV end-diastolic pressure by E/Em, left atrial (LA) volume index, and extrapolation of pulmonary artery systolic pressure based on contrast-enhanced tricuspid regurgitation Doppler data.

An echocardiogram with no clinically significant abnormalities is one defined specifically as: the left ventricular[1] internal dimension in diastole should be ≤2.8 cm/M^2, the left atrial[2] end-systolic volume should be ≤36 mL/M^2, the left ventricular ejection fraction[3] should be ≥50% without regional wall motion abnormalities, 2-dimensional echocardiographic-derived left ventricular mass index[1] should be ≤115 g/M^2 for males and ≤99 g/M^2 for females, the pulmonary artery pressure should be normal (tricuspid regurgitation jet velocity ≤2.5 m/s and/or pulmonary valve flow acceleration time ≥120 ms), the left ventricular diastolic function[4] should be normal (screening: mitral deceleration time ≥150 ms and ≤250 ms, mitral E/A ratio ≥ 0.75 and ≤1.5, mitral E velocity divided by Doppler mitral annular velocity [E/Em] <15), and there should be no evidence for pericardial or congenital or heart disease. In addition, there should be no evidence for more than mild mitral or aortic stenosis (mitral valve area should be greater than 2.0 cm^2 and aortic valve area should be greater than 1.5 cm^2), no evidence of more than mild mitral or aortic regurgitation.[5, 6] Patients enrolled in the study may have evidence for tricuspid (trace or mild), pulmonary, mitral (trace or mild), or aortic (trace or mild) regurgitation by Doppler techniques.[5, 6]

References:

1 Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Reicheck N, Sahn D, Schnittger I, Silverman NH, Tajik AJ. Recommendations for quantitation of the left ventricle by two dimensional echocardiography. *J Am Soc Echocardiogr.* 1989;2:358-367.

2 Tsang TSM, Barnes, ME, Gersh, BJ, Bailey, KR, Seward, JB. Left atrial volume as morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol.* 2002:90:1284-1289.

3 Oh JK, Seward JB, Tajik AJ. The Echo Manual. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.

4 Khouri SJ, Maly GT, Suh DD, Walsh TE. A practical approach to the echocardiographic evaluation of diastolic function. *J Am Soc Echocardiogr.* 2004;17:290-297.

5 Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). *Am J Cardiol.* 1999;83:897-902.

6 Zoghbi WA, Enriquez Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777-802.

Echocardiographic Certification Process

To ensure protocol adherence, each study center will be required to complete echocardiography training and submit a certification echocardiogram to the central imaging core laboratory. The certification echocardiogram will be completed on the first study patient at each site. Certification approval must be received prior to performing echocardiograms on additional study patients.

General Instructions for Echocardiography

- Allow 1 hour for the performance of the echocardiographic examination in each patient.
- Do not enter the patient's name in the initial video screen of the echocardiographic imaging system or protocol. Only the patient's screen and or randomization number is to be entered and visible during the echocardiogram recording.
- Set the echocardiography imaging system (create preset "*Lilly*" and use in subsequent visits of patients in the study) to acquire and store digital 3 cardiac cycles loops for 2-dimensional (2D) echocardiographic image per screen and obtain at least 3 or more cardiac cycles per each M-Mode or Doppler spectral image screen.
- This protocol calls for the use of both, **harmonic imaging** (for all views; native or tissue harmonics, using high (>1.3) mechanical index, with the appropriate highest transmitted frequency possible for that transducer) as well as **fundamental imaging** (this for limited views of the aortic and mitral valve on parasternal long axis).
- Obtain the patient's height and weight at the time of the examination and include with the study data.
- Obtain and record with the study data the patient's **arterial blood pressure** in right arm while undergoing echocardiography in the recumbent left-lateral position.
- Display the electrocardiogram (ECG) at all times during echocardiographic sequence recordings.
- Obtain all image sequences at **held expiration** (for up to 5 seconds at a time).
- Record images (2D and color flow Doppler cine loops, frames for M-Mode and Doppler spectral) in digital form and copy to a CD-ROM or MO-disk for each patient per visit.
- Choose the best transmit gain, TGC's, mechanical index and compression setting for each patient. Record these settings and use them at all future visits for each specific patient.

- Always, obtain all images (except subcostal) at held-end expiration with the patient lying on the left side (45o to 60o) at 16 cm depth of field. In the rare instance when the apical view silhouette of the heart (including the atria) exceeds 16 cm, then employ a 20 cm depth setting and make a note of this to employ 20 cm depth for that patient in subsequent visits.
- Employ Doppler color-flow imaging from all views (long axis, short axis, apical 4-chamber, apical 2-chamber and apical long axis) and note presence of valvular regurgitation. For Doppler color flow, employ a Nyquist limit of 50 to 60 cm/s, and set the color gain at a level that just eliminates random color speckle from non-moving regions. Before recording Doppler color flow image data for the first time in each patient at each visit, record continuously in videotape while the adjustment of color gain is performed to document in the videotaped data that gain settings have been properly obtained. Avoid using very high or very low levels of pulse repetition frequency (PRF). Also, employ a color sector or color region of interest as narrow as possible for each valve examination, and with the least depth, to maximize lateral and temporal resolution.
- Spectral Doppler and M-Mode echocardiography data are to be recorded at a display speed of 50 or 100 mm/second (use discretion considering heart rate; videotape) using optimal gain control and minimal filter setting (at least 3 beats), also at held expiration.
- Before starting the second or subsequent visit echocardiogram for a given patient:

  A. Retrieve the cine loop, from the patient's first study digital data set, 2D images of the left ventricle (short axis) as acquired in the original study.

  B. Utilize this cine loop as part of a split screen to use as a guide to obtain the same imaging plane of the short axis again for this and subsequent visits of the same patient.

     After obtaining the current image, acquire a new image of both, short axis LV images
- Keep a set of the digital images of each echocardiogram obtained for that particular patient into a "master" file to remain in the site's echocardiography laboratory and send via courier mail a CD-ROM or MO-disk copy of each study to the Core Echocardiography Laboratory at Biomedical Systems, St. Louis. Use the provided preprinted shipping forms included with this manual. If additional forms are required please contact Biomedical Systems Echocardiography Laboratory in St. Louis.

Echocardiography Protocol; Required Views

Parasternal Long Axis View, 16 cm depth

- Record 3 beats **(held-expiration)** of the entire 2D image with **harmonic imaging**.
- Employ color flow Doppler to evaluate for aortic and mitral regurgitation (using here and at each time that color flow Doppler is used, the procedures described above regarding Nyquist limits, gain and PRF) and record 3 beats **(held-expiration)**
- Obtain M-Mode views of the LV as close as possible to the minor axis of the ventricle, avoiding the papillary muscle and obtain a freeze-frame M-Mode image (50-100 mm/s display).
- Switch to **fundamental imaging** (this is the only sequence of the protocol that requires fundamental imaging) by turning off the harmonic imaging mode, then place a small region of 2-D sector or region of interest (2D only without color flow; at >45 Hz frame rate) that includes both the aortic and mitral valve leaflets, and record 3 beats **(held-expiration)**.

Parasternal Short Axis view, 16 cm depth

- Record 2D harmonic imaging views of the aortic, mitral valve, and papillary muscle level of the left ventricle and record a sweep-sequence of 5 beats.
- Employ color flow Doppler to evaluate for aortic regurgitation (record 3 beats in held-expiration), then for mitral regurgitation at the level of the aortic root/left atrium (record 3 beats in held-expiration)
- Obtain pulsed spectral Doppler of the pulmonary valve flow at the level of the right ventricular outflow tract, freeze, and record spectral display of 3 to 5 beats at held expiration.
- If this is the second study in this patient, compare to previous image in the same patient (loop) to ensure obtaining the same left ventricular papillary muscle level. This procedure entails retrieving from digital data of the site's laboratory master storage of the same patient's previous echocardiogram tape that contains the short axis view
- Once it has been ascertained that the same papillary muscle level is being obtained today, as before, acquire (end-expiration) and save "today's" short axis LV papillary muscle level, record both for 3 beats

Apical 4-Chamber View, 16 cm or 20 cm depth

- Avoid foreshortening of the image by maximizing the length of the LV cavity with the transducer placed as lateral and leftward as possible (toward the axilla and at a lower interspace in the left chest wall). Likewise, obtain the widest possible LV cavity to ensure optimal assessment of LV volumes.
- Pay special attention to optimal visualization of the endocardium of the lateral wall and septum and avoid visualization of the papillary muscle in this view. Record 5 beats with harmonic imaging at held-expiration.
- Employ color flow Doppler to evaluate for mitral and tricuspid regurgitation (using procedures described above for settings, etc) and record 3 beats for each valve.
- Record at least 3 beats of the pulsed Doppler trans-mitral flow velocity with the sample volume (smallest size possible) positioned both at the mitral leaflet tips and at the mitral annulus level with the left atrium; (displayed at 100 mm/s).
- Then measure the flow velocity across the mitral valve employing continuous wave Doppler (3 beats, spectral display recording, 50 to 100 mm/s).
- Record at least 3 beats of the pulmonary venous flow velocities (pulsed Doppler spectral) with the sample volume at the right upper pulmonary vein entrance into the left atrium.
- Record at least 3 beats of the pulsed Doppler trans-tricuspid flow velocity with the sample volume positioned at the tips of the tricuspid valve.
- Then measure the flow velocity spectra across the tricuspid valve employing continuous wave Doppler (tricuspid regurgitation peak flow velocity; 3 beats, spectral display recording, 50 to 100 mm/s).
- If the tricuspid regurgitation jet is incompletely visualized or truncated (examples to be discussed and shown at investigators' meeting), this calls for the use of agitated saline contrast echocardiography (harmonic imaging, high mechanical index) to be employed to enhance the detection of the peak velocity of the tricuspid regurgitation jet. For this purpose, start a 20 gauge or larger peripheral IV (antecubital vein preferred). Draw 9 mL of sterile saline into a 10-mL syringe, connect it to a 3-way stopcock, and connect an empty 10-mL syringe to the other port. Leave 1 mL of air in the saline syringe. Agitate the solution by rapidly transferring the volume from one syringe to the other. Expel all visible bubbles from the syringe that will be used for injection (for contrast, it is not necessary to inject visible air, and it is dangerous and contraindicated to do so). Before injecting, point the syringe with saline downward so any remaining visible bubbles may rise towards the plunger (away from the patient). Inject only 7 mL of the 9 mL of saline in the syringe, leaving a residual of 2 mL in that syringe. This avoids the injection of visible bubbles.

- For recording of the tricuspid regurgitation peak jet after saline enhancement, be prepared to quickly reduce the Doppler spectral gain to avoid noise artifact blooming of the signal once the saline contrast effect is detected at the tricuspid valve inlet. Using continuous wave Doppler, obtain at least 3 beats with the enhanced Doppler signal; freeze the spectral display and record for 5 seconds.
- Obtain by Tissue Doppler echocardiography (initially by real-time 2D color display to facilitate placement of the sample volume within the LV myocardium) the spectral data of myocardial velocities at the level of the mitral annulus (lateral wall, or interventricular septum site) and freeze a spectral display (50 mm/s; at least 3-4 beats, held end-expiration) and record (apply procedures for specific manufacturers regarding presets with optimal settings for map, gain, power, dark background in the display, etc.). Ensure that the ECG is displayed above the Doppler tissue spectral data.

Apical 5-Chamber View, 16 cm

- Record 3 beats of the apical 5-chamber view harmonic imaging Color Flow Doppler (to evaluate for aortic regurgitation);
- Place a sample volume within 1 cm of the aortic valve in the left ventricular outflow tract and record (at held expiration) at least 3 beats of spectral pulsed Doppler of the flow velocity in the outflow tract (displaying the closing [but not the opening] valve clicks, at 50 or 100 mm/s spectral display speed).
- Then measure the flow velocity across the aortic valve employing continuous wave Doppler (3 beats, spectral display recording, 50-100 mm/s) displaying both systolic and any diastolic flow velocity spectra (held expiration).

Apical 2-Chamber View, 16 cm or 20 cm

- Obtain 3 beats at held-expiration (or held inspiration, if necessary for this view only) of the harmonic imaging apical 2-chamber view. Avoid foreshortening of the view by obtaining the longest possible major axis length displayed and the widest possible cavity.
- Employ color flow Doppler to evaluate for mitral regurgitation and record 3 beats.

Apical Long Axis View, 16 cm or 20 cm

- Record 3 beats of the harmonic imaging apical long-axis 2D examination employing held expiration. Again, avoid foreshortening the view by obtaining the longest as well as the widest possible LV cavity area.
- Employ color flow Doppler to evaluate for mitral and aortic regurgitation and record 3 beats for each valve image.

Subcostal view, 20 cm or 24 cm depth if necessary

- Record 3 beats continuously with harmonic imaging of the inferior vena cava while asking the patient to abruptly sniff once.

Appendix: Qualitative and Quantitative Parameters for Grading Valvular (Mitral and Aortic) Regurgitation Severity

Please refer to references below for information on qualitative and quantitative parameters for grading valvular (mitral and aortic) regurgitation severity.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). *Am J Cardiol.* 1999;83:897-902.

Zoghbi WA, Enriquez Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777-802.

References:

Henson JW, Ulmer S, et al. Brain tumor imaging in clinical trials. *Am J Neuroradiol.* 2008;29(3):419-424.

Kreisl TN, Kim L, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol.* 2009;27(5):740-745.

Shi Y, Massagué J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell*. 2003;113(6):685-700.

Sorensen AG, Patel S, et al. Comparison of diameter and perimeter methods for tumor volume calculation. *J Clin Oncol.* 2001;19(2):551-557.

Sorensen AG, Batchelor TT, et al. Response criteria for glioma. *Nat Clin Pract Oncol*. 2008;5(11):634-644.

Verhaak RG, Hoadley KA, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell.* 2010;17(1):98-110.

Wick W, Puduvalli VK, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol.* 2010;28(7):1168-1174.

Wong ET, Gautam S, et al. Bevacizumab for recurrent glioblastoma multiforme: a meta-analysis. *J Natl Compr Canc Netw.* 2011;9(4):403-407.

Attachment 7. Tailoring Strategy based on Mutations

Tailoring Strategy based on Mutations

Slides from Tumor Tissue will be assessed using 384-well point mutation detection panel(array) SA Biosciences/Qiagen

In addition to IDH1 mutation analysis, the following assays are being evaluated:

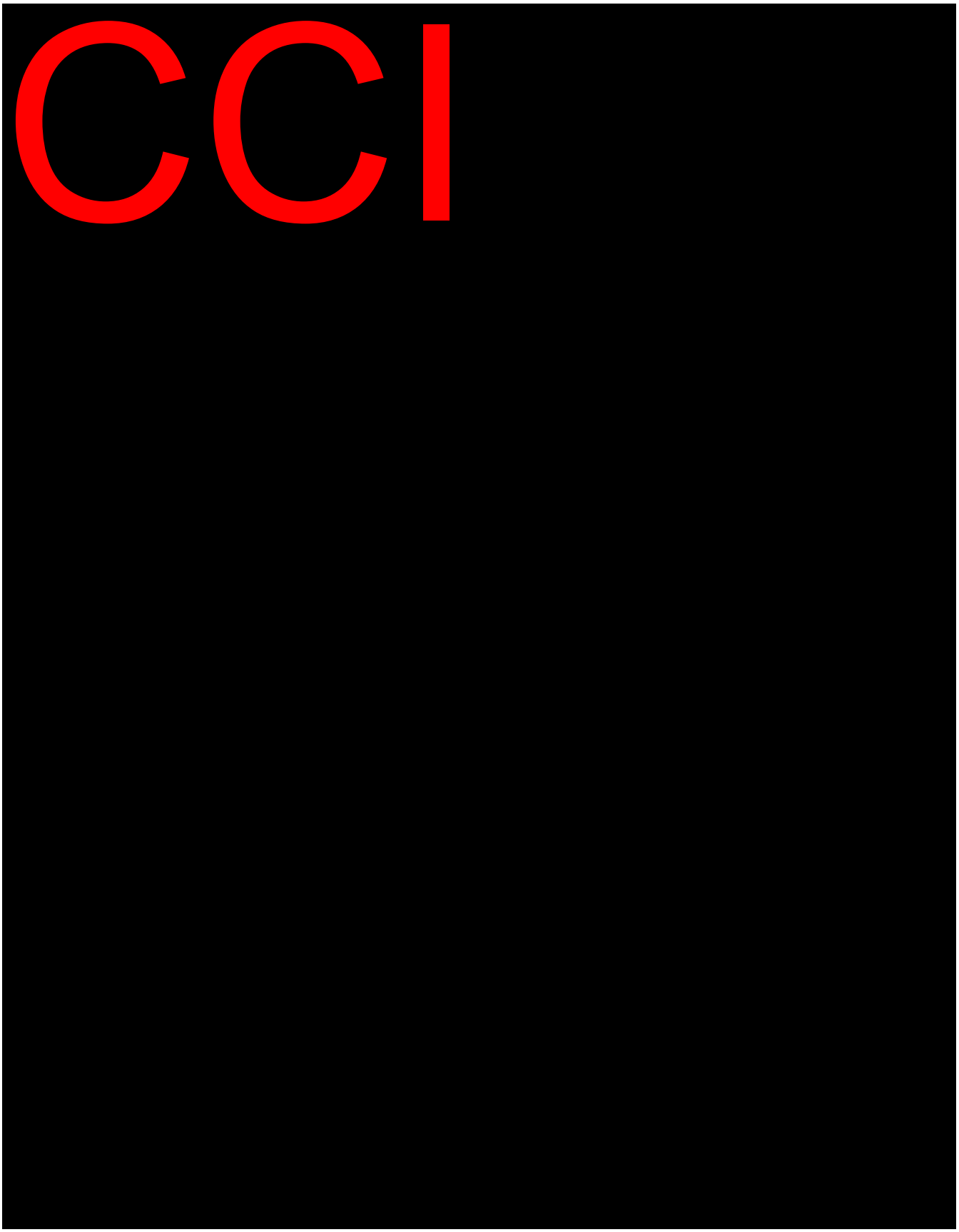
9 assays **have been validated**, and printed on Lilly phase I arrays (having a total of 64 mutation assays and 11 copy number assays). These arrays have been run with the FFPE samples from ProteoGenex and reported here.

Gene	COSMIC ID	Nucleotide Change	Amino Acid Change
ERBB2	35496	c.2330T>C	p.V777A
ERBB2	684	c.2740G>A	p.E914K
ERBB2	35804	c.146T>A	p.L49H
NF1	24466	c.4600C>T	p.R1534*
NF1	39161	c.6852_6855delTTAC	p.Y2285fs*5
NF1	36883	c.5305C>T	p.R1769*
PDGFRA	13348	c.2485G>A	p.G829R
PDGFRA	35395	c.1047G>C	p.W349C
PDGFRA	42897	c.704G>A	p.C235Y

The following **additional** 9 assays have been validated and are scheduled to be included on phase II arrays

Gene	COSMIC ID	Nucleotide Change	Amino Acid Change
EGFR	21686	c.865G>A	p.A289T
EGFR	21688	c.971G>T	p.R324L
PDGFRA	43059	c.1607T>A	p.V536E
PTEN	39513	c.1133_1136delGATA	p.R378fs*>25
TP53	13120	c.626_627delGA	p.R209fs*6
PIK3R1	43101	c.1726_1728delACG	p.T576del
EGFR	21685	c.866C>A	p.A289D
EGFR	35508	c.664C>T	p.R222C
TP53	10756	c.827C>T	p.A276V

Attachment 8. Health Outcomes


CCI


CCI

Attachment 9. Suggested MRI Protocol for Brain Tumors Based on EORTC Recommendations

Suggested MRI protocol for Brain Tumors based on EORTC recommendations

MR Scanners: 1.5T and 3T MR scanners only

0. Localizer / Scout

1. 3D T1w pre-contrast (MPRAGE, 3D IR FSPGR T1w)

- minimum TE
- TI, TR and flip angle according to manufacturer specific / field strength specific recommendations for optimum image quality
- SENSE / SMASH / GRAPPA / ASSET allowed
- Slice/3D slab orientation: sagittal or transverse
- FOV: 256 mm x 256 mm
- Matrix: 256x256
- Slice thickness: ≤ 1.5 mm
- Full brain coverage

2. DWI

- single shot EPI sequence
- minimum TE
- TR > 3000 ms
- Spectral fat suppression
- b: 0 and 1000 s/mm^2 (3 directions)
- SENSE / SMASH / GRAPPA / ASSET: optional for 1.5 T, obligatory for 3 T.
- Slice orientation: transverse
- Slice thickness: 5mm
- Slice gap: 0
- Number of slices: Full brain coverage
- FOV: 240 mm x 240 mm
- Matrix: 128 x 128 or higher
- Postprocessing: Calculation of ADC maps (diffusion trace maps)

3. 2D FLAIR, transverse

- Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence, turbo factor ≤17
- TE: 90-140ms
- TR: 6000-10000 ms
- TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)
- SENSE / SMASH / GRAPPA / ASSET allowed
- Slice orientation: transverse
- Slice thickness: 5mm
- Slice gap: 0
- Number of slices: same as sequence **2**
- FOV: 240 mm x 240 mm
- Matrix: 256 x 256 or higher
- Slice positioning as in sequence **2**

OPTIONAL

4. 3D FLAIR

- 3D Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence, turbo factor ≤17
- TE: 90-140ms
- TR: 6000-10000 ms
- TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)
- SENSE / SMASH / GRAPPA / ASSET / ARC allowed
- Slice orientation: sagittal or transverse
- Slice thickness: ≤ 1.5 mm
- Number of slices: Full brain coverage
- FOV: 250 mm x 250 mm
- Matrix: 224 x 224 or higher
- Slice positioning as in sequence **1**

5. Contrast agent injection, (0.1 mmol/kg BW of a Gd-based contrast agent)

6. T2w-TSE

- Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence, turbo factor ≤7
- TE: 80-120ms
- TR: ≥ 2500 ms
- SENSE / SMASH / GRAPPA / ASSET allowed
- Slice orientation: transverse
- Slice thickness: 5mm
- Slice gap: 0
- Number of slices: same as sequence **2**
- FOV: 240 mm x 240 mm
- Matrix: 256 x 256 or higher
- Slice positioning as in sequence **2**

7. 3D T1w post-contrast (MPRAGE, 3D IR FSPGR T1w)

- Sequence parameters and slice positioning as in sequence **1**

Further sequences can be added to the protocol according to the preferences of the respective center. If a 3D FLAIR is used, please adhere to the sequence parameters as specified in SEQUENCE 4. Also, respect the order and timing of prescribed sequences after contrast administration.

Attachment 10. Details of Statistical Survival Model and Simulation Results

A Bayesian Augmented Control (BAC) model is used that allows information borrowing from a previous study to augment the data on the control arm in the current study. The primary endpoint of this trial is overall survival (OS) time. OS is modeled using an exponential-likelihood model (constant baseline hazard) as specified below:

$\lambda_T = \lambda \exp(\theta_T)$
$\lambda \sim$ Gamma (α,β)
$\theta_T \sim$ Normal (μ, σ^2)

Where λ_T is the hazard rate for the combination arm, and λ is the hazard rate for the current control arm and θ_T is the log hazard ratio (HR) between the 2 hazard rates.

Historical Controls

Patient-level data from 2 previous randomized trials (H6Q-MC-JCBF [data on file and Wick et al. 2010a]; Batchelor et al. 2010b), which included lomustine as a control group were available for use as historical data. The patients in these studies are considered to be from a similar population as those in the current study. The Kaplan-Meier estimates of median OS from the 2 studies are 7.1 and 9.8 months respectively (average = 8.5 months). Between these 2 studies, the unweighted mean observed hazard rate for OS is CCI per week.

Operating Characteristics

There are 3 arms in this study and the primary analysis is to compare the combination arm, LY2157299 plus lomustine, and the control arm, lomustine plus placebo. The simulations assume that the HR for OS between the control arm and LY2157299 monohydrate monotherapy is CCI and the HR between the combination arm and the control arm is CCI.

At the final analysis, the combination arm will be considered superior to the control arm if the posterior probability is greater than CCI% that the HR for OS of combination arm versus control is (Pr[Treatment HR CCI %).

At the CCI interim analysis either the combination arm or LY2157299 monotherapy arm could be considered futile if, after CCI patients have completed 3 cycles, the posterior probability is less than CCI% that the HR for OS of combination arm or LY2157299 monotherapy arm versus lomustine arm is less than CCI.

Five thousand simulations (FACTS v2.4) assuming the following were carried out per scenario:

- Exponential survival model using summary hazard rates from 2 previous lomustine trials (H6Q-MC-JCBF [data on file and Wick et al.2010a]; Batchelor et al. 2010b), along with data from the lomustine plus placebo arm in this study.

    - The average median OS time is 8.5 months giving an average control hazard rate across these 2 studies of CCI /week.
    - The fixed prior distribution for the control hazard rate has a Gamma distribution with a mean of CCI and a weight of [redacted] (weak prior) or a weight of 10 (strong prior).
- The prior distribution of the log HR between the combination arm and lomustine plus placebo is assumed to be Normally distributed with a mean of zero and a standard deviation of 100 (weak prior).
- OS HR of CCI (success), [redacted] (null), CCI (failed), and [redacted] (extreme fail) are observed.
- Patients are randomized in a CCI ratio (favoring the LY2157299 plus lomustine arm).
- Enrolment rate is CCI patients/month (CCI patients/week).
- Minimum follow-up for last subject is as follows:
    - 94 weeks for the primary analysis
    - 12 weeks for interim analyses CCI
- 4000 Markov chain Monte Carlo burn-in for each simulation

The following tables define the posterior probabilities of the different scenarios.

Table 1. Operating Characteristics for Interim Analysis after Approximately CCI Events and Final Analysis after Approximately CCI Events

n	allocation	Control rate Prior	Timing of analysis	Posterior p(HR CCI	No. of events*
CCI					

Note: in "null" model HR = [redacted]; in "successful" model HR = CCI

For comparison, a frequentist analysis using the log rank test would give the following for the final analysis (FACTs results): Assuming the HR=CCI Power = 74%, Type I error = 0.1 (1-sided).

Table 2. Interim Analysis for Futility of LY2157299 Plus Lomustine Arm after CCI Patients

n	Allocation	Control rate Prior	Timing of Analysis	Model*	No. of events	Futile if posterior p(HR CCI < p p		
						5%	10%	20%
CCI								

Note: In "failed" model HR = CCI; in "null" model HR = CCI; in "successful" model HR = CCI.

Table 3. Interim Analysis for Futility of LY2157299 Monotherapy Arm after CCI Patients

n	Allocation	Control rate Prior	Timing of Analysis	Model*	No. of events	Futile if posterior p(HR CCI) < p p		
						5%	10%	20%
CCI								

Note: In "extreme failure" model HR = CCI; in "failed" model HR = CCI; in "null" model HR = CCI.

Attachment 11. Protocol JBAL Protocol Amendment H9H-MC-JBAL(a) Summary A Phase 2 Study of LY2157299 Monohydrate Monotherapy or LY2157299 Monohydrate plus Lomustine Therapy compared to Lomustine Monotherapy in Patients with Recurrent Glioblastoma

Overview

Protocol H9H-MC-JBAL, A Phase 2 Study of LY2157299 Monohydrate Monotherapy or LY2157299 Monohydrate plus Lomustine Therapy compared to Lomustine Monotherapy in Patients with Recurrent Glioblastoma, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- The addition of a continued access period to allow patients who continue to experience clinical benefit and no undue risks to continue to receive study treatment until 1 of the criteria for discontinuation is met.
- Additional clarifications to the protocol were made:
    - Removing the requirement to follow patients for overall survival until death.
- Minor editorial changes were made for clarity and consistency.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Clinical Protocol Synopsis: Study H9H-MC-JBAL…

Study Design: This is a 3-arm, randomized (CCI), multicenter, global, Phase 2 study of LY2157299 monohydrate monotherapy or LY2157299 monohydrate plus lomustine therapy compared to lomustine plus placebo therapy in patients with relapsed GB. In contrast to the LY2157299 monohydrate monotherapy arm, patients and investigators will be blinded to the LY2157299 monohydrate or placebo assignment in either the LY2157299 plus lomustine or the lomustine plus placebo therapy arms.
Diagnosis and Main Criteria for Inclusion and Exclusions: Male and female patients at or older than 18 years and who have relapsed GB after first-line treatment with chemoradiation, have measureable disease (response to be based on RANO criteria), and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
Test Product, Dosage, and Mode of Administration: LY2157299 monohydrate, 300 mg/day, given orally for 14 days followed by 14 days of rest, for a 28-day cycle. LY2157299 monohydrate-matched placebo, given orally for 14 days, followed by 14 days of rest, for a 28-day cycle. Lomustine will be given orally once every 6 weeks. The first lomustine dose will be 100 mg/m^2, and all following doses can be escalated to a maximum of 130 mg/m^2, at the investigator's discretion.
Planned Duration of Treatment: Patients will receive study treatment until their disease has progressed, the patient has died, or the patient discontinues for adverse events (AEs), investigator's judgment, or other reasons. **Planned Follow-Up Observation Period Per Patient:** Patients who have discontinued study treatment without progression will continue to be followed for progression or until they start a new anticancer therapy. ~~All patients will be followed until death.~~ **Planned Continued Access Period**: Patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until 1 of the criteria for discontinuation is met.
Criteria for Evaluation: Efficacy: OS; PFS; response rate (using RANO criteria). Safety: AEs (using International Common Terminology Criteria for Adverse Events [CTCAE], version 4), clinical laboratory tests, electrocardiograms (ECGs), and echocardiography (ECHO)/Doppler. Health Outcomes: MDASI-BT; HVLT-R; Trail Making Test Parts A and B; and Verbal fluency COWA. Bioanalytical: Plasma LY2157299 monohydrate concentrations will be analyzed by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS).

Abbreviations and Definitions

Term	Definition
continued access period	**The period between study completion and end of trial during which patients on investigational product who continue to experience clinical benefit and no undue risks may continue to receive investigational product until 1 of the criteria for discontinuation is met.**
end of ~~study~~ trial	**End of ~~study~~ trial is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.**

study completion	**This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis/evaluation of overall survival or after approximately CCI survival events. Study completion occurs before the end of trial.**

5.7. Rationale and Justification for the Study

5.7.1. Rationale for Amendment (a)

The proposed protocol amendment(a) is aimed at facilitating the participation of the remaining patients in study JBAL. The protocol has been amended to include the concept of 'study completion' in the study design (see Section 8.1.4). This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis/evaluation of overall survival or after approximately CCI survival events have occurred.

The protocol has also been amended to add a continued access period to LY2157299 for patients who continue to experience clinical benefit, have no undue risks, and are on study treatment at the time of study completion (see Section 8.1.3). Patients in the continued access period will be followed for safety only and all other follow-up testing has been eliminated (See Attachment 1 for the study schedule for the continued access period). Based on the current safety profile of LY2157299, the reduction in the number of visits and tests will have no influence on the risk assessment.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply. Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

Minor editorial changes were made but not listed. Attachment 11 contains a detailed listing of changes made in the amendment.

8.1. Summary of Study Design

… Patients will receive treatment until disease progression, death, or discontinuation (criteria defined in Section 7.3.1) occurs. Patients will be followed for OS until death or ~~study closure~~ study completion (see Section 10.1.2). Tumor assessments will be conducted according to the Study Schedule (Attachment 1) and as denoted in Sections 10.1.1 and 10.1.2 to determine whether the patient continues to benefit from their treatment. …

8.1.1. Baseline and Study Treatment Period Assessments

Terms used to describe the study baseline and treatment periods are defined below:

- Baseline: After signing Informed Consent and from the time of screening to first study treatment (or discontinuation, if no treatment is given)
- Study Treatment Period: Time from treatment start to discontinuation from study treatment (does not include the continued access period) …

8.1.2. Postdiscontinuation Follow-Up Period Assessments

Terms used to describe the postdiscontinuation of study treatment are defined below:

- Postdiscontinuation Follow-Up: Begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
  - The short-term follow-up period begins 1 day after discontinuation of study treatment and lasts approximately 30 days (Visit 801).
  - The long-term follow-up period begins 1 day after the short-term follow-up period (Visit 801) is completed and continues until death or study completion to collect survival data.

The Study Schedule (Attachment 1) describes all assessments for the post discontinuation and follow up periods. All patients should be followed and all AEs (Section 10.3) reported for a minimum of 30 days from the date of discontinuation or until completion of Visit 801.
At Visit 801, physical examinations, ECOG PS evaluation, health outcome assessments (Section 10.2), ECG/ECG chemistry (Section 10.3.2.1), ECHO/Doppler (Section 10.3.2.2), serum chemistry, urinalysis, and hematology laboratory tests (Section 10.4.1) will be completed. Additionally, after Visit 801, ECG/ECG chemistry and ECHO/Doppler will be performed as indicated in Section 10.3.2.1 and Section 10.3.2.2, respectively.

After discontinuation, tumor measurements will be performed as indicated in Section 10.1.2.

~~This study will be considered closed when the final study report has been completed (that is, complete following the final analysis for OS which will be when approximately CCI events have occurred). Patients who are still benefitting from treatment may continue to receive study drug for long-term durations, even after the study has closed and final database lock has occurred. In such cases, the sponsor may amend the protocol to allow for a safety extension to follow such patients after the end of the trial or may open a substudy which would be defined in a subsequent amendment.~~

8.1.3. Continued Access Period

- Continued access: begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until 1 of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
- Continued access follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

The continued access period will apply to this study only if at least 1 patient is still on investigational product when study completion occurs.

Patients receiving investigational product and experiencing ongoing clinical benefit and no undue risks may continue to receive investigational product in the continued access period until

1 of the criteria for discontinuation is met (Section 7.3). Lilly will notify investigators when the continued access period begins. Patients must sign a new informed consent form (ICF) before continued access is provided.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and investigational product exposure will be reported on the case report form (CRF). Patient diaries for drug administration will no longer be required in the continued access period.

Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

8.1.4. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis/evaluation of overall survival or after approximately CCI survival events have occurred. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.

9.4. Selection and Timing of Doses

LY2157299 or placebo will be administered in tablet form on an empty stomach. Patients should take LY2157299 or placebo on an empty stomach preferably 2 hours before a meal. Patients should wait at least 1 hour after taking LY2157299 before eating a meal. Tablets should be swallowed whole and not split, crushed, or dissolved for administration. After intake of LY2157299 or placebo, lomustine will be administered in capsule form on empty stomach. Ingestion on empty stomach is recommended to reduce nausea and vomiting, which may appear about 6 hours after lomustine intake. Alternatively, lomustine may be taken based on institutional guidelines, which may be in the evening prior to bedrest, some hours after a light dinner. ~~While patients receive treatment in the first cycle, they will be required to record the time and amount of study drug intake. Also, they need to record the time of food consumption before and after each dose in a daily diary.~~

…

9.8. Treatment Compliance

Patient ~~compliance with study medication will be recorded by the patient via a patient diary and will be assessed at each visit. In addition,~~ compliance will be assessed by direct questions and count of returned tablets. Deviations from the prescribed dosage regimen should be recorded in the comments section of the eCRF.

…

10.1.1. Efficacy Assessments at Baseline and during Study

Within 28 days before the first dose of study drug or 14 days prior to enrollment, baseline tumor measurement(s) will be performed on each patient. All patients will have to undergo an MRI with contrast.

The method of assessment used at baseline must be used consistently for tumor assessment and will be repeated every other cycle.

~~For patients continuing treatment after final database lock, efficacy assessments (frequency, type of assessments, and data reporting) will be based on the protocol as outlined above.~~

During the continued access period, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

10.1.2. Efficacy Assessments during the Postdiscontinuation Period

After patients have discontinued study treatment, they may receive additional anticancer therapy at the discretion of the investigator.

For those patients who discontinue study treatment without objectively measured progressive disease, the investigative sites will continue to monitor patients approximately every 60 days (±14 days) to evaluate tumor response by the same method used at baseline and throughout the study, until objective progression or the patient starts a new anticancer therapy.

Once a patient has objective progression or starts a new anticancer therapy, they will be followed for OS approximately every 60 days (±14 days) until death or ~~study closure~~ study completion.

Table JBAL.10.3. Adverse Event and Serious Adverse Event Reporting Guidelines for Study H9H-MC-JBAL

Treatment Period	Types of AEs/SAEs Collected/Reported
Baseline (pretreatment)	Procedure-related AEs/SAEs
Study treatment period (on therapy)	All AEs/SAEs
30-day postdiscontinuation follow-up visit (Visit 801)	All AEs/SAEs
Subsequent postdiscontinuation follow-up visits, if necessary	SAEs are required to be reported only if the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure.
Continued access period	All AEs/SAEs
Continued access follow-up (approximately 30 days)	All AEs/SAEs

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients discontinuing (overall and by reason for discontinuation) from both study treatment and study itself. A summary of all important protocol violations will be provided.

For the purpose of clinical trial registry reporting, patients who have died or are still in the study but off treatment at primary data base lock will be considered a completer. Those who withdrew consent for all procedures, including follow-up, or were lost to follow up, will be considered as early discontinuers. Patients who remain on treatment will be counted as continuing treatment.

Attachment 1 JBAL Study Schedule

Study Schedule for the continued access period only, Protocol H9H-MC-JBAL

Cycle	Continued Access[a] Visit 501-5XX				Follow-Up[b] Visit 801	Comments
Relative Day Within a Cycle	1±2	6±2	12±2	26±2		
Treatment						
Lomustine		X				CCI
LY2157299	X	X	X			
Procedures						
Physical examination	X				X	

Vital signs (heart rate, blood pressure)	X				X	
CTCAE	X				X	
Echocardiography with Doppler				X	X	CCI
ECG				X	X	
Troponin I and BNP				X	X	
ECG chemistry				X	X	
Serum hs-CRP				X[c]		

Abbreviations: BNP = brain natriuretic peptide; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; hs-CRP = high-sensitivity C-reactive protein.

[a] No follow-up procedures will be performed for patients who withdraw informed consent unless he or she has explicitly provided permission and consent.

[b] Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately [30] days.

Note: Efficacy assessments will be done at the investigator's discretion based on the standard of care.

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