Statistical Analysis Plan Version 1: 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 Glioblastom

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# 1. Statistical Analysis Plan: 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



TGF-β (LY2157299 Monohydrate) Glioblastoma

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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[Phase 2]

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on date provided below.

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# 2. Table of Contents

**Section** **Page**

## Table of Contents

## List of Tables

**Table** **Page**

# 3. Revision History

The first version of the Statistical Analysis Plan (SAP) was approved prior to first patient visit for this study.

This SAP includes the definitions of the analysis populations, the pharmacokinetics (PK), the pharmacodynamic (PD), efficacy and safety endpoints, the tables and figures for the analysis and is based on the study protocol approved on 10 November 2011.

Statistical analysis of this study will be the responsibility of both PharmaNet/i3 (under the direction of Eli Lilly and Company) and Lilly.

PharmaNet/i3 will produce all pre-planned standard tables, figures, and listings (TFLs) in the study. The documentation and validation of programs written by PharmaNet/i3 for the production of TFLs will follow all applicable Lilly SOPs.

The interpretation of the study results will be the responsibility of the investigator with Lilly CRP/CRS, Pharmacokinetist and Statistician. The CRP/CRS and Statistician will be also responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication by Lilly.

# 4. Study Objectives

## 4.1. 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 (glioblastoma) after first-line treatment with chemoradiation.

## 4.2. 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:
  - o pSMAD2 and other TGF-β-related biomarkers
  - o O6- MGMT promoter status
  - o other relevant tumor genetic information (eg, IDH1 mutation)
- To determine serum/plasma tumor markers and secreted proteins (eg, S100β, lactate dehydrogenase [LDH], TGF-β, 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:
  - o lomustine plus placebo therapy and LY2157299 monotherapy
  - o 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

# 5. Study Design

## 5.1. 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 LY2152799-matched placebo therapy in patients with relapsed or progressed GB.

CCI 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 LY2152799-matched placebo therapy. 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.

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.

Patients will receive treatment until disease progression, death, or discontinuation occurs. Patients will be followed for OS until death or study closure. Tumor assessments will be conducted at baseline (within 28 days before the first dose of study drug or 14 days prior to enrollment) and at the end of every 2 cycles (Day 26 ± 2) thereafter.

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.

CCI interim assessments are planned:


The planned duration of the study is CCI 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.

## 5.2. 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 the combination arm, LY2157299 plus lomustine therapy with the control arm, lomustine plus placebo using a Bayesian augmented control design. By incorporating historical information regarding the control arm (ie, lomustine plus placebo) into the Bayesian model, it is possible to improve the operating characteristics compared to a standard (frequentist) analysis using log rank test with the assumptions that the HR = CCI, Power = CCI%, Type I error = 0.1 (one-sided).

At the final analysis, the combination arm will be considered superior to the control arm 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 control arm is <1 (ie. Pr(Treatment HR < 1) CCI%).

This study is designed to observe approximately CCI events at the final analysis and approximately CCI events at the CCI interim analysis. 5000 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 Gamma distribution with a mean of CCI and a weight of 1 (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)
- 'True' hazard ratios (HR) of CCI (success), CCI (null) and CCI (failed) and CCI (extreme fail) arm observed at interim analysis
- 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) for the primary analysis at the end of the study and 12 weeks for CCI interim analyses

At the CCI interim analysis for a signal of early efficacy the same assumptions are used as for the final analysis, as described above.

The following table define the posterior probabilities of the different scenarios, for both CCI interim analysis and the final analysis.

**Table JBAL.5.1. Operating Characteristics for CCI Interim Analysis after Approximately CCI Events and for 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 = CCI; in "successful" model HR = CCI

At the CCI interim analysis either the combination arm or LY2157299 monotherapy arm may 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 monotherapy arm versus lomustine arm is less than CCI. Using the same assumptions as for the primary analysis at the end of the study, this analysis will take place approximately 5 months after the first patient is dosed. Table 5.2 and 5.3 provide the operating characteristics for different decision criteria to assess the likelihood of futility of the combination arm and the monotherapy arm respectively.

As an example, using the criteria that the combination arm may be declared futile if the pr(HR CCI, relative to the control)<0.1, then there is a CCI% probability of declaring the combination arm is futile when it is in fact successful. Conversely, with the same decision criteria, there is a CCI% probability of declaring the saying that the combination arm is futile when the hazard ratio is CCI i.e. the median OS of the combination arm is CCI times that of the control arm.

**Note that the comparison between the control arm and the monotherapy arm is based on fewer patients, given the randomization ratio.**

**Table JBAL.5.2. Interim Analysis for Futility of LY2157299 plus Lomustine Arm after CCI Patients Completed 3 Cycles**

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

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

**Table JBAL.5.3. Interim Analysis for Futility of LY2157299 Monotherapy Arm after CCI Patients Completed 3 Cycles**

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

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

## 5.3. 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. Randomization will be monitored periodically and the randomization parameter will be modified if necessary.

# 6. A Priori Statistical Methods

## 6.1. General Considerations

Statistical analysis of this study will be responsibility of both PharmaNet/i3 (under the direction of Eli Lilly and Company) and Lilly.

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 statistical analysis plan and/or clinical study report. The following terms and data handling conventions will be used in the analysis.

**Table JBAL.6.1. Data Definitions and Rules**

| Term | Definitions or Rule |
|---|---|
| Entered | Patients who have signed the informed consent document directly. |
| Screen failures | Patients who have signed informed consent, do not meet eligibility criteria and are not randomized. |
| Randomized/ Enrolled | Patients who have been assigned to study treatment and but may have not received any study treatment (LY2157299, LY2152799-matched placebo, or lomustine). |
| Patients on therapy | Patients who have been randomized/enrolled to study treatment and have received at least 1 dose of study treatment (LY2157299, LY2152799-matched placebo, or Lomustine). |
| Study day | If assessment is on or after date of first LY2157299/ LY2152799-matched placebo dose then<br>(date of assessment) – (date of first study treatment dose) + 1<br>If assessment precedes first treatment dose then<br>(date of assessment) – (date of first study treatment dose) |

| | |
|---|---|
| | There is no study day 0. Study day 1 is the date of first dose and study day -1 is the day before the first dose. |
| Cycle day | If assessment is on or after date of first LY2157299/ LY2152799-matched placebo dose then<br>(date of assessment) – (date of first study treatment dose in cycle) + 1<br>If assessment precedes first treatment dose then<br>(date of assessment) – (date of first study treatment dose in cycle)<br>There is no cycle day 0. Cycle day 1 is the date of first dose in the cycle and cycle day -1 is the day before the first dose. |
| Baseline | For change from baseline analysis, baseline value is defined as the last reported measure on or before the first dose date (or discontinuation, if no treatment is given). For change from baseline within a cycle, the measure prior to the first dose if that cycle is baseline. |
| Study treatment period | Time from treatment start to discontinuation from study treatment |
| Post-discontinuation – short-term follow-up | The short term follow-up period begins 1 day after discontinuation of study treatment and lasts approximately 30 days (Visit 801). |
| Post-discontinuation – long-term follow-up | The long-term follow-up period begins 1 day after the short-term follow-up period (Visit 801) is completed and continues until death to collect survival data. |

### *6.1.1. Analysis Populations*

Primary time-to-event efficacy analyses will be conducted on all randomized patients. This set will group patients according to their allocated treatment.

All patients who entered the study will have measurable disease. However, should a patient be required to undergo a surgery for palliative reasons before objective tumor progression he/she will be excluded from analyses and summaries associated with tumor response  Such cases, will not be common in this disease setting. This set will group patients according to their allocated treatment.

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.

For all labroratory and biomarker assessments analyses, patients with at least one post-baseline assessment will be included for analysis. This set will group patients according to their allocated treatment.

## 6.2. Adjustments for Covariates

Additional exploratory analyses may be performed on efficacy measures to adjust for factors that may affect survival or disease progression. See section 6.17 on the covariates that will be considered in the survival models.

## 6.3. Handling of Dropouts or Missing Data

The number of patients that discontinued early from treatment and the reason for discontinuation will be summarized for each treatment arm. See Sections 6.5 and 6.6 on the method for handling these patients in the analyses.

The primary method for handling missing time-to-event data will be censoring. See details on censoring for each time-to-event endpoints in Section 6.10.

## 6.4. Multiple Comparisons/Multiplicity

No adjustment for multiplicity is planned for this study. The primary analysis will compare the OS distributions for only LY2157299 plus lomustine and placebo plus lomustine. Comparisons between other treatment arms will secondary or exploratory in nature.

## 6.5. Use of an "Efficacy Subset" of Patients

The efficacy analyses on time-to-event endpoints will be conducted on all patients who received at least 1 dose of any study drug. Patients that discontinued after randomization and did not receive study treatment for reasons other than not meeting entry criteria will be followed for survival till death occurs. Since the effect of the study drug is not realized in these patients, the time-to-event analyses will not include these patients.

Patients that did not meet entry criteria after receiving study treatment (for example, protocol violators) will be included in the main efficacy and safety analyses. However, a subanalysis will be conducted by excluding these patients who should have been otherwise discontinued to determine their influence on the final study results.

## 6.6. 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 in each arm. All entered patients will be accounted for in this summary of disposition. Screen failures and patients who died or discontinued before treatment begins will be specified.

A listing of primary reasons for both study treatment and study discontinuation will also be provided according to each treatment arm. A listing of patients who discontinued due to AE or death from treatment and study itself will also be provided with additional information on cause of death and the AE associated with discontinuation.

## 6.7. Patient Characteristics

Patient demographics and physical characteristics including age at consent, sex, race, height, screening weight, and body surface area (BSA) will be listed and summarized using descriptive statistics for all enrolled patients in each arm. Consumption habits of tobacco, alcohol and caffeine/xanthine use will also be included as appropriate.

Special instructions regarding presentation of race: patient may select more than one of the values for Race in the case report form (CRF). Derive Race to 'Multiple' if more than one race is selected. Otherwise, race equals the single race selected. For example, if a patient selects both 'White' and 'Asian' then RACE = 'Multiple'. However, if a patient select only 'Asian' then RACE = 'Asian'.

Baseline disease characteristics will be summarized, by presenting frequency counts and percentages, for pathological diagnosis (histological or cytological), ECOG PS, GB subtypes (primary or secondary) and disease grade.

Prior disease-related regimens will also be listed detailing individual therapies within each regimen (Section 6.9) and summarized by the number of prior regimens.

A patient listing of historical illnesses (using preferred term from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA] and reported term captured in CRF) will also be provided.

Other patient characteristics will be summarized as deemed appropriate.

## 6.8. 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 with LY2157299 or placebo within a cycle means that the patient has taken their allocated LY2157299 or placebo treatment as prescribed for a minimum of 10 days and a maximum of 14 days per 28-day cycle and at least [redacted]% of the allocated LY2157299 prescribed dose has to be administered within each cycle. Exception is given to patients that discontinued early due to death or other reasons prior to completing a minimum of 10 dosing days in a cycle. These patients would be deemed compliant if at least [redacted]% of LY2157299 prescribed dose is administered up to the time of discontinuation. 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 6.13.1.

Treatment compliance within a cycle means that the patient has taken their allocated treatments as prescribed for that cycle. This information for LY2157299 and placebo will be collected on CRF through both tablet counts (for 50 mg and 10 mg tablets strength) and by the site querying the patient at the end of each cycle for each patient. The level of compliance in percent for a cycle will be calculated as follows:

**Compliance in percent** = 100% × [ 10 × (total tablets dispensed – total tablets returned) + 50 × (total tablets dispensed – total tablets returned) ]/ (10 × total tablets dispensed + 50 × total tablets dispensed)

The level compliance will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum) by cycle and treatment arm. Overall compliance will be averaged across cycles.

In addition, the number of tablets dispensed and returned will be listed with the level of compliance in each cycle for individual patient.

## 6.9. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications listings will include both the term reported in CRF and the WHO dictionary term for enrolled patients in each arm and if concomitant medication use is due to adverse event (AE), the associated AE will also be listed.

Enzyme-inducing and non-enzyme inducing anti-epileptic drug treatments will be determined retrospectively and indicated in the listings.

Patients with concomitant steroid use will be listed separately by each arm. Dose information including total daily dose and any dose modification at the start of each cycle will be provded in this listing.

Surgery for palliative reasons and carried out prior to discontinuation from study treatment will be captured separately.

Anti-cancer systemic therapy, radiotherapy and surgery that occurs post discontinuation of study treatment is captured separately from concomitant medication as the existence of such therapies can lead to censoring of time to event endpoints. Patients that received post discontinuation therapies will be listed by treatment arms.

## 6.10. Efficacy Analyses

The following are definitions of the primary and secondary efficacy endpoints:

**Primary Endpoint:**

- **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). For OS analysis, death is considered an event.

**Secondary Endpoints:**

- **Progression-Free Survival (PFS) duration** is measured 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 rate at** CCI is defined as the proportion of patients not having objective progression or death at CCI respectively after the time from date of study enrollment (randomization) estimated from the PFS distribution.
- **Survival rate at 12 months** is defined as the propotion of patients alive 12 months after start of treatment, even if they have progressed, estimated from the overall survival distribution.
- **Overall Response Rate (ORR)** is defined as the proportion of patients who achieved a best overall response of either complete response (CR) or partial response (PR). The overall response rate for each treatment group will be estimated by dividing the total number of confirmed responders by the number of patients who received at least 1 dose of study treatment. Response will be evaluated based on the Response Assessment in Neuro-Oncology (RANO).
- **Disease Control Rate** is defined as the proportion of patients who achieved a best response of CR, PR or stable disease (SD) per RANO criteria. This rate will be estimated for each treatment group by dividing the total number of patients that had CR, PR or SD by the number of patients who received at least 1 dose of study treatment. Best response of SD is defined as disease that does not meet the criteria for CR, PR, or progressive disease (PD) and has been evaluated at least one time, and at least 6 weeks after baseline assessment. Patients without a valid response assessment at least 6 weeks after baseline assessment are assigned a best response of nonevaluable unless progression has already occurred.

All primary and secondary efficacy endpoints will be analyzed for patients who received at least one dose of study treatment. All time-to-event endpoints will be analyzed using the Kaplan-Meier method. Covariates may also be included in these time-to-event models to account for variation in survival time. A Bayesian model will be used to estimate the hazard ratio of overall survival between the treatment arms.

**Table JBAL.6.10. An Overview of the Efficacy Analyses**

| Efficacy Endpoint | Statistical Analysis | SAS Procedures |
|---|---|---|
| Primary analysis: | | |
| Overall survival | A Bayesian OS model to estimate the hazard rates and ratios (HR) of OS and 90% predictive interval between LY2157299 plus lomustine therapy and lomustine plus placebo therapy | Non SAS - FACTS |
| Secondary analyses: | | |
| Overall survival | The same Bayesian OS model in the primary analysis is used in secondary analysis to estimate the HR between LY2157299 monotherapy and lomustine plus placebo therapy, and between LY2157299 plus lomustine therapy and LY2157299 monotherapy | Non SAS - FACTS |
| | Kaplan-Meier method will be used to estimate median survival time, OS rate at 12 months, and its 95% confidence interval for the treatment arms | LIFETEST |
| | Proportional hazard model will be used to estimate the hazard ratio of survival and 95% confidence interval between treatment arms, control for other factors | PHREG |
| Progression-free survival | Kaplan-Meier method will be used to estimate median PFS, PFS rates at CCI [redacted], and its 95% confidence interval for the treatment arms | LIFETEST |
| | Proportional hazard model will be used to estimate the hazard rate and ratio of PFS and 95% confidence interval of the 3 treatment arms and between the treatment arms | PHREG |
| Overall response rate (CR or PR)<br>Disease control rate (CR, PR or SD) | The overall response rate will be estimated from dividing the total number of responders ([CR or PR)] by the number of patients that have at least 1 dose of study drug in each treatment arm<br>The disease control rate will be estimated from dividing the total number of patients with CR, PR or SD by the number of patients that have received at least 1 dose of study drug in each treatment arm<br>The exact 95% confidence interval for ORR and disease control rate will also be provided for each arm | FREQ |

### *6.10.1. Primary Outcome and Primary Methodology*

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

A method of analysis for comparing OS between the combination arm, LY2157299 plus lomustine therapy and the control arm, lomustine plus placebo therapy 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.

### *6.10.2. Additional Analyses of the Primary Outcome*

Overall survival (OS) and OS rate at 12 months will be summarized by the combination arm (LY2157299 plus lomustine) and control arm (lomustine plus placebo) 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). Kaplan Meier plots of survival for each treatment group will also be provided.

Additional analyses of overall survival comparing LY2157299 monotherapy and lomustine plus placebo therapy and, between LY2157299 plus lomustine therapy and LY2157299 monotherapy are considered secondary efficacy analyses and described in the following section.

### *6.10.3. Secondary Efficacy Analyses/Outcomes/Comparisons*

A similar Bayesian analysis as described in Section 6.10.1 will also be carried out to provide the hazard rates and ratios including 90% predictive intervals of the HR between LY2157299 monotherapy and lomustine plus placebo therapy and, between LY2157299 plus lomustine therapy and LY2157299 monotherapy.

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
- Disease control rate

Progression-free survival (PFS) 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 using proportional hazards models. 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 pseudoprogression, 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 in each treatment group. Exact 95% CIs for each treatment arm will also be provided.

### *6.10.4. Sensitivity Analyses*

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. A subanalysis will be conducted by excluding such patients to determine their influence on the final study results.

Additional sensitivity analyses may also include the use of different censoring dates in the time-to-event analyses.

## 6.11. Health Outcomes/Quality-of-Life 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 or prorated questionnaires/number of expected questionnaires given those that are still on study).

Each health outcome parameter will be reported independently. Relationships (predictors or prognostic) among these parameters (patient reported symptoms and neurocognitive function) with other clinical parameters such as PS, OS, and disease assessments (based on MRI) may be explored. For example, relationship between change in neurocognitive function and prognostic and/or predictive nature of baseline assessments with OS or the relationship between change in neurocognitive function and change in MRI.

Health resource utitlization such as use of psychostimulants, steroids, anti-epileptic medications, etc will be assessed by treatment arms and exploratory analyses adjusting for these covariates may be performed.

### *6.11.1. Neurocognitive Function*

#### 6.11.1.1. Neurocognitive Outcome Measures

Neurocognitive function will be measured by the HVLT-R, the Trail Making Test, Parts A and B, and COWA.These tests in the neurocognitive test battery will be completed at prestudy (baseline), end of cycle 1 (26±2 days) and thereafter every 2 cycles starting at cycle 2 and after discontinuation of study therapy (Visit 801) during the study.

See table below for the administration time allocated to each test. 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.

**Table JBAL.6.11. Cognitive Assessment Tests Used in Study H9H-MC-JBAL**

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

**Hopkins Verbal Learning Test-Revised (HVLT-R)**
The patient is asked to recall a list of 12 words over 3 learning trials. After a 20-minute delay at then end of the third learning trial, the patient is asked to spontaneously recall the listed words (Delayed Recall trial) read in the 3 learning trials. The Delayed Recognition trial will follow immediately after the Delayed Recall trial and patient is asked to discriminate the listed words from amongst a set of distractors. 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).

The scoring for each of the 3 learning trials and the Delayed Recall trial is based on the number of correctly reported words in each trial. For the Delayed Recognition trial, scoring is based on the number of true-positives (listed words correctly recalled) and false-positives (listed words incorrectly recalled).

Four HVLT-R measures: Total Recall, Delayed Recall, Retention (%) and the Recognition Discrimination Index will be calculated based on the raw scoring from each trial. The total Recall score is the sum of three scores from the learning trials. The number of words correctly recalled during the Delayed Recall trial is the total score for Delayed Recall. The Retention score (percent retained) is calculated from the score of the Delayed Recall trial divided by higher of the two scores from the second and third learning trials. Lastly, the Recognition Discrimination Index is calculated by subtracting the total false positives score from the total true positives score.

**Trail Making Test, Part A (TMTA)**
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).

The measure of performance for this test is the time in seconds required to connect all 25 dots on the page.

**Trail Making Test, Part B (TMTB)**
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 (ie. 1-A-2-B) as fast as possible (Reitan 1992).

The measures of performance for this test is the time in seconds required to connect the dots alternating numbers and letters on the page.

**Controlled Oral Word Association (COWA)**
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).

Patients will be scored on the number of acceptable responses given on each letter and the sum of the number of acceptable responses from the 3 letters will be calculated as the patient's total score on the test.

A composite score, Clinical Trial Battery Composite (CTB COMP), will be calculated based on the standardized scores from the above tests. This is calculated as a sum of all the following 6 standardized scores (HVLT-R Total Recall + Delayed Recall + Delayed Recognition Discrimiinability+ TMTA + TMTB + COWA) and divide this by number of non-missing score to get the average standardized score.

### 6.11.1.2. Neurocognitive Analyses

Compliance rate will be calculated as the number of completed or prorated questionnaires divided by the number of expected questionnaires given those that are still on study. For Trail Making Tests A and B, patients with completed and prorated tests will be included in analysis. A test score can be prorated if test was discontinued or maximum time was used due to a neurological difficulty.

Each neurocognitive test will be converted to a standardized score (mean = 0, SD = 1) using published healthy control data. To prorate discontinued Trail Making Tests A and B, the raw scores will be divided by the number of circles correctly completed and then multiplying the resulting "time per circle" figure by 25. [Wefel et. al. 2011; Heaton RK et. al. 2004]. For each neurocognitive test, standardized scores will be summarized at each assessment. Repeated measures ANOVA will be performed for each measure to assess the mean differences in change from baseline standardized scores between treatment arms, adjusting for baseline score if needed. The change in standardized score from baseline will be calculated and using the Reliable Change Index (RCI) [Wefel et. al. 2011], the neurocognitive status over time will be categorized into improved, stable or decline. The RCI is a threshold that measures improvement or decline in neurocognitive function and represents a 90% confidence interval for the difference in raw score between baseline and the next assessment assuming no real change occurred. It is derived as follows:

$RCI = 1.64 (SEdiff)$ where $SEdiff = [2(SEM^2)]^{1/2}$ and $SEM = SD_1[(1 - r_{xy})^{1/2}]$

where SEdiff is the standard error of difference in raw score from baseline to the next assessment, SEM is the standard error of measurement, SD is the standard deviation, and $r_{xy}$ is the test-retest reliability statistic. All derived RCI will be rounded to the nearest whole number and compared with changes from baseline assessments to determine the change in neurocognitive status. Those changes that did not meet the RCI threshold will be considered stable performance. Any changes from baseline neurocognitive status showing improvement or decline will need to be confirmed at the next assessment if available. In the absence of a confirmatory assessment, any sign of improvement or decline in neurocognitive status will be deemed as stable.

The proportion of patients with number of tests indicating stable, improved or decline in neurocognitive status will be summarized at each assessment by treatment arm.

The relationship between survival/tumor response and change in cognitive function will also be assessed in subgroups of patients with PFS > 6 months, OS > 12 months and patients with objective response. Proportion of patients in the above subgroups showing stable or improvement on all neurocognitive tests, or decline on at least one test at the time of PFS (at 6 months), OS (at 12 months) or at time of response will be provided and summarized for each treatment arm. Significant p-values comparing the proportion of patients with stable or improved tests on all tests will be reported.

The proportion of time patients spent in a stable/improved neurocognitive function during 6 months progression-free or 12 months survival will be assessed for each treatment arm. The area under the curve, where x-axis is the progression-free or survival time and y-axis is neurocognitive state will be used to calculate this proportion for individual patient.

Differences in neurocognitive progression (RCI determined) will be assessed between arms using Cox proportional hazards regression and adjusting for covariates such as use of psychostimulants, steroids, anti-epileptic medications, etc). Neurocognitive progression duration is measured from randomization to the time of RCI determined neurocognitive decline or death from any cause.

## *6.11.2. MD Anderson Symptom Inventory – Brain Tumor Module*

### 6.11.2.1. MDASI-BT Outcome Measures

Patient symptoms will be measured with the self-administered MD Anderson Symptom Index (MDASI-BT) (Armstrong et. al. 2006). The MDASI-BT will be completed at baseline, end of cycle 1 and thereafter every 2 cycles (26±2 days) starting at cycle 2 and after discontinuation of study therapy (Visit 801) during the study.

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. The core items are pain, fatigue, nausea, disturbed sleep, distress (emotional), shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling (MDASI1 to MDASI13). The brain tumor specific items (MDABTS1 to MDABTS9)

are weakness on one side of body, difficulty understanding,difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel pattern, and irritability. For the 22 symptom items, 0 equals “not present” and 10 equals “as bad as you can imagine” in the last 24 hours. The 6 interference items measures general activity, mood, work, relations with other people, walking, enjoyment of life where 0 equals “did not interfere” and 10 equals “interfered completely”.

The 22 symptom items may also be grouped by their underlying constructs: (1) affect consists of distress, fatigue, sleep, sad, and irritability; (2) cognition comprises of difficulty understanding, remember, difficulty speaking and difficulty concentrating; (3) focal neurologic deficit comprises of seizures, numbness, pain and weakness; (4) treatment-related symptoms such as dry mouth, drowsiness, and appetite; (5) generalized/disease status symptoms such as change in appearance, change in vision, change in bowel patterns and shortness of breath; and (6) gastrointestinal symptoms like nausea and vomiting.

The MDASI-BT will be scored by reporting the individual items and 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.

### 6.11.2.2. MDASI-BT Analyses

The rate of compliance with completing MDASI-BT will be summarized at the group-level at each assessment: prestudy (baseline), end of cycle 1 and thereafter every 2 cycles (26±2 days) starting at cycle 2 and at discontinuation (Visit 801). Compliance is defined as the number of completed questionnaire/number of expected questionnaire to be completed at the time of the study.

For those patients who had completed at least one assessment, descriptive statistics will be provided for the 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) at each assessment period by treatment arms. This summary will include number of patients in each arm, number of patients with completed questionnaire, mean, standard deviation, median, minimum, maximum scores and change from baseline.

For those patients who completed a baseline and one post-baseline questionnaire, change from baseline on core symptoms, brain tumor symptoms, symptom interference, and symptom groupings will be assessed.Repeated measures ANOVA will be performed to assess the mean differences in change from baseline between treatment arms, adjusting for baseline score if needed. Least squares mean, mean differences, including 95% confidence interval and p-values indicating significant differences between treatment arms will be provided. Plots of mean and standard deviation for core symptoms, brain tumor symptoms, symptom interference, and symptom groupings over time and change from baseline plots will be provided.

The minimally important difference (MID) is used to assess and interpret mean score differences between treatment arms. A minimally important difference of 1.2 (as defined in the MDASI user manual) will be used as a reference in the time to worsening analysis. Data from each treatment

arm will be analyzed using Kaplan-Meier plots with censoring at the last assessment for patients with no worsening. Median time to worsening with 95% confidence interval will be provided. The proportion of patients who experienced a change from baseline score of 1.2 will also be summarized for each treatment arm and compared between treatment arms.

Relationships (predictors or prognostic) among patient-reported symptoms and with other clinical parameters such as performance status, overall survival, and disease assessments (based on MRI) may be explored. MDASI-BT analyses may also be adjusted for neurocognitive function of the patient.

Other exploratory longitudinal analyses may be performed.

## 6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Several pharmacokinetic (PK) analyses will be conducted to support this study using both noncompartmental and population pharmacokinetic approaches.

Population-based PK analysis will be performed on sparse PK data (LY2157299 measurements from cycle 1) using non-linear mixed effect modeling from validated PK software programs (for example, NONMEM).

Pharmacodynamic (PD) data from all patients undergoing PD assessments will be analyzed. Pharmacodynamic (PD) 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 any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Lilly Pharmacokineticist will be responsible for these analysis. Details on the analysis can be found in the Pharmacokinetic Plan.

## 6.13. Safety Analyses

All safety summaries and analyses will be based upon the safety population that includes patients that have received at least one dose of study drug.

Safety data will be listed and summarized with patient counts and percentages in each treatment arm. Details of the analyses are described in the following sections.

### *6.13.1. Extent of Exposure*

The numbers of patients completing each cycle will be summarized for each treatment arm. In addition, descriptive statistics (mean, median, standard deviation, minimum and maximum) for the number number of cycles completed will be presented. A patient is considered having completed a 28 day cycle if they have received at least 10 days and up to a maximum of 14 days of LY2157299 monohydrate or LY2157299 monohydrate-matched placebo therapy in that cycle.

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 for all treated patients per treatment arm, as will the reasons for dose adjustments.

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 will summarized by cycle and treatment arm for LY2157299 and lomustine therapy. LY2157299 and placebo-matched LY2157299 dosing will be captured on CRF based on the protocol schedule of events: Days 1, 3, 7 +/-2, 12 +/-2, and 14 of cycle 1 (these align with PK sample draws at Cycle 1) and Day 1 +/-2, 6 +/-2, and 12 +/-2 of cycle 2 on. The calculations for LY2157299 planned and prescribed cumulative dose and dose intensity are as follows:

**Planned cumulative LY2157299 dose (mg):**

*PLC* = number of cycles started multiplied by assigned dose on cycle 1 day 1 multiplied by 14 where 14 is the planned number of dosing days per cycle.

**Prescribed cumulative LY2157299 dose (mg):**

*PRC* =sum prescribed doses taken in all cycles
Note: any dose omission, adjustment or early discontinuation in a cycle need to be taken into account in calculating the cumulative prescribed dose. Treatment end date defined as last dose date will estimate the number of doses patient has taken in the discontinued cycle.

**Planned cumulative lomustine dose (mg):**

*PLC* = assigned dose on day 7 of cycle 1 multiplied by 6
where 6 is the number of administrations planned for lomustine.

**Prescribed cumulative lomustine dose (mg):**

*PRC* =sum prescribed doses taken in all administrations
Note: any dose omission, reduction or early discontinuation from lomustine need to be taken into account in calculating the cumulative prescribed dose.

**Dose intensity in percent** is then calculated by taking the prescribed cumulative dose divided by planned cumulative dose and multipled by 100% respectively for both LY2157299 and lomustine.

### *6.13.2. Adverse Events*

The Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be used to report adverse events in CTCAE terms. The current MedDRA Version 14.0 (or higher) at the time of reporting will be used when reporting adverse events by MedDRA terms. The MedDRA Lower Level Term (LLT) will be used in the treatment-emergent computation.

**Treatment-emergent adverse events (TEAE)** are defined as follows:

- Any event that first occurred or worsened in severity after baseline, based on the MedDRA LLT term 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.
- Or any PEC (emerged prior to informed consent) or any AE (emerged after signed informed consent) that were still present prior to first dose but has increased in severity (CTCAE grade) following the start of treatment, regardless of causation.

A listing of all adverse events by patient,including pre-existing conditions, will be presented. This listing will include patient number, adverse event (actual term, CTCAE term, and preferred term), event start and end dates, CTCAE grade, relationship to study drug/procedure, seriousness, and outcome. A listing of SAE will be produced using the similar format.

An overall summary will be provided for possibly drug-related AEs. The number and percent of evaluable patients will be summarized by treatment for each category below.

- Patients with at least one AE
- Patients with at least one TEAE
- Patients with at least one grade 3 or 4 AE
- Patients with at least one SAE
- Patients who discontinued due to AE
- Patients who discontinued due to SAE
- Patients who died on therapy
- Patients who died within 30 days of last dose of study drug (LY2157299/placebo or lomustine)

The AEs deemed by the investigator to be possibly related to study drug 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) or CTCAE term within SOC. These summaries will be 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 SAEs will be summarized by MedDRA PT and CTCAE term by decreasing frequency within each SOC, regardless of causality.

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.

### 6.13.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

All deaths in this study, including the reasons for death, will be listed by treatment. The reasons for death will be also summarized separately for on-therapy, within 30 days of last dose of study drug and during the long term follow-up periods.

### 6.13.4. Clinical Laboratory Evaluation

Listings of all laboratory results will be provided (using SI units [International System of Units], when available) by treatment, separately for hematology, chemistry, urinalysis, special chemistry, ECG chemistry, immune phenotype, whole blood for Fox3p, and urine C-terminal telopeptides of Type 1 collagen. Normal reference ranges, percent of the result outside of range (result divided by lower limit if result is less than lower limit; result divided by higher limit if result is greater than higher limit) and percent change from baseline will also be included.

A calculated CTCAE grade using CTCAE version 4 will be provided for all laboratory results which can be used independently of clinical judgment to determine a CTCAE severity grade. These summaries will be repeated for abnormal laboratory results.

The CTCAE term will be summarized by CTCAE grade in separate tables, linking these AEs to the laboratory term.

### 6.13.5. Vital Signs and Other Physical Findings

Vital signs measurements including height, weight, respiratory rate, temperature, blood pressure and post-baseline ECOG performance status will be listed by treatment arm.

### 6.13.6. Electrocardiograms

Electrocardiogram (ECG) assessment of normality and clinical significance will be listed by treatment group. Myocardial information and quantitative results including PR, QRS, QTcB (Bazett's correction), QTcF (Fridericia's correction) and RR intervals will provided in patient listings. In addition, listings and summaries of outlying corrected QT intervals (QTc, QTcB and QTcF) will be provided for each scheduled time point.

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 as per protocol schedule. Similarly, changes in RR from baseline (ie.delta RR) will be calculated. Delta QT will then be analyzed using a linear mixed-effects model with treatment arm, timepoint and delta RR as fixed effects, treatment-by-time interaction and patient as a random effect (Dmitrienko and Smith 2003). Least square means by timepoint and treatment arm together with 90% confidence intervals will be provided. Mean differences and 90% confidence intervals between treatment arms will be estimated from the model.

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.

### 6.13.7. Echocardiograms/Doppler

Echocardiograms assessment of normality and clinical significance will be listed by treatment arm. Results of echocardiograms, including LV dimension, LA volume, LV mass, left ventricular ejection fraction (LVEF), valvular regurgitation and wall motion will also be provided in patient listings. Absolute or percent change from baseline for quantitative variables will be included. Shift tables on maximum change from baseline severity will be provided for each valvular regurgitation. Graphical representation of LVEF may be provided if necessary.

### 6.13.8. Pulmonary Function Tests

Pulmonary function tests (PFT) will be performed at baseline and approximately every 6 months for those patients receiving lomustine. Changes from baseline for PFT variables (FEV1, FVC, FEV1/FVC ratio, DLCO) will be listed and summarized by treatment arm.

### 6.13.9. Hospitalizations and Blood Transfusions

Patients who were hospitalized due to SAE will be included in the AE listings.

Patients that received blood transfusions, including the blood products received (that is packed red blood cells, platelets, fresh frozen plasma, or whole blood) during the study treatment period or during the 30-day postdiscontinuation follow-up period will also be listed.

## 6.14. Subgroup Analyses

Subgroup analyses on health outcome measures are described in Section 6.11. In addition, exploratory analyses may be performed to generate hypotheses about the efficacy of study therapy in certain subgroups to be tested in future clinical trials.

## 6.15. Protocol Violations

Protocol violations will be identified based on information recorded on the investigator log and through statistical programming of the data. A list of data dependent protocol violations in general and specific to this study is as follows:

**General:**

- Not meeting protocol inclusion/exclusion criteria [2], [3], [5] to [9], [11], [13] to [17]
- If patient with “entry criteria not met” is marked at screening (visit 0) but patient moves on to cycle 1
- Use of prohibited concomitant therapy (See Protocol Section 9.7):
  - Chemotherapy;
  - Radiation therapy;
  - Immunotherapy;
  - Cancer-related hormonal therapy;
  - Surgery for cancer;
  - Experimental/investigational medication;

  - Routine use of granulocyte colony-stimulating factors. They may be used for patients who have ANC ≤0.5 x 109/L,, neutropenic fever, or documented infections at investigator's discretion, but cannot be used during Visit 0 to meet hematological inclusion criteria and must be discontinued at last 24 hours prior to the start of therapy.
  - Any disease progression requiring other forms of specific anti-tumor therapy will be cause for early discontinuation from the study.
- Treatment compliance with LY2157299 is less than CCI % of the prescribed/intended amount of drug per cycle
- Incorrect dose administered (e.g., more than intended)
- Informed consent violations, including patients that have had cerebral spinal fluid (CSF) collected but informed consent for CSF not signed

**Study specific:**

- Visit outside visit intervals specified in protocol:
  - lomustine therapy is held for ≥ 12 weeks from the last dose of lomustine due to any reason and the patient is not discontinued from the study
- If the patient had two prior dose reductions in lomustine therapy and needs a third reduction due to toxicities but is not discontinued from lomustine therapy
- Failure to perform PK collections
  - only collections "not done" are considered significant protocol violations.
- Failure to collect samples of tumor tissue (at screening only)
- Failure to perform safety procedures or missing safety measurements per requirements in Study Schedule (Attachment 1 in Protocol)
  - Hematology/chemistry
  - ECG
  - ECHO

  Note: only collections "not done" are considered significant protocol violations.

This list of these protocol violations may be included in a patient listing, and patients with missing safety assessments will identified from a tabular display of individual patient assessment according to study schedule. These data dependent protocol violations, together with the data from the investigator log will be summarized to include only important protocol violations for the final study report.

## 6.16. Interim Analyses and Data Monitoring

CCI interim assessments are planned:

CCI


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.

## 6.17. Planned Exploratory Analyses

Exploratory analyses on efficacy endpoints such as overall survival or progression-free survival will be carried using data from the treatment arms. Covariates may be added to the time-to-event models to explain the variability in survival times. Selection of covariates will be determined from Cox proportional hazard model. These covariates may include but are not limited to the following prognostic/predictive factors:

- Use of corticosteroids at randomization
- Baseline ECOG performance status
- Age

- Primary or secondary GB
- Post-surgical status (fully resected, partially resected)
- MGMT promoter methylation status, Fox3p+ status
- Baseline biomarker/Biomarker response

Point estimates and 95% confidence intervals for median survival (OS or PFS) may be provided for the model where the prognostic factor is found to influence variability in survival times.

The pharmacodynamic markers that will be evaluated include tumor markers (LDH, S100β), TGF-beta related markers (TGF-beta1, PF4) and changes in T cell subpopulation (for example T regulatory cells as evaluated by CD4+CD25+Fox3p+ and total concentration in Fox3p).

Pre- and post-dose values of the various biomarkers whose data are continuous will be analyzed using a mixed effects model with time, treatment arm and their interaction as fixed effects and patient as a random effect, after applying appropriate transformation (log scale to concentration data). Least square means (geometric means if log transformation is used) by time and treatment arm together with 90% confidence intervals will be provided. Mean differences (or ratio of means) and 90% confidence intervals between pre- and post-dose timepoints will be estimated from the model.

For biomarkers with categorical data, frequency and percentages will be used to summarize the data.

## 6.18. Annual Report Analyses

The Annual Report is replaced by Development Safety Update Report (DSUR). The following reports will be produced for the DSUR:

- Estimated cumulative subject exposure
- Cumulative exposure to investigational drug, by demographic characteristics for ongoing unblinded clinical trials and completed clinical trials
- Exposure information for ongoing clinical trials and clinical trials that completed during the reporting period
- Listing of subjects who died during the DSUR period
- Discontinuations due to adverse event during the DSUR Period.

For further details on these reports, see the DSUR collaboration site: http://lillynetcollaboration.global.lilly.com/sites/GMRS_GPS/Surv/dsur/default.aspx?PageView=Shared

## 6.19. Clinical Trial Registry Analyses

The efficacy and safety analyses on the primary and secondary outcomes for CTR disclosure will be consistent with other document disclosure, for example CSR, manuscript and so forth. These results will be published on www.clinicaltrials.gov.

Analyses provided for the CTR requirements include a summary of adverse events, provided as a dataset in XML file and will be presented as follows:

- Both Serious Adverse Events and 'Other' Adverse Events will be summarized by treatment arm and MedDRA preferred term.
- An adverse event is considered 'Serious' regardless of whether it is a treatment emergent adverse event (TEAE).
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious.
- For each Serious AE and 'Other' AE, for each event term and treatment arm, the following are provided:
    - Number of patients at risk of an event
    - Number of participants who experiences each event term
    - Number of events experienced

Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

Additional analyses will be performed for the purpose of fulfilling the CTR requirements.

# 7. Unblinding Plan

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, a minimum number of Lilly personnel will see the treatment assignments before the study is complete and Lilly personnel involved in the clinical trial material dispensation will be unblinded to LY2157299/placebo.

Emergency unblinding for adverse events may be performed through an IVRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IVRS. 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.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician for the patient to continue in the study.

Details of the process to be undertaken and the composition of the assessment committees for each interim analysis will be provided in the assessment charter.

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