H9H-MC-JBEF Statistical Analysis Plan v2

A Phase 1b/2 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of a Novel Transforming Growth Factor-β Receptor I Kinase Inhibitor (Galunisertib) Administered in Combination with Anti-PD-1 (Nivolumab) in Advance Refractory Solid Tumours (Phase 1b) and in Recurrent or Refractory Non-Small Cell Lung Cancer or Hepatocellular Carcinoma (Phase 2)

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Approval Date: 26-Oct-2017

1. Statistical Analysis Plan: H9H-MC-JBEF(c): A Phase 1b/2 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of a Novel Transforming Growth Factor–β Receptor I Kinase Inhibitor (Galunisertib) Administered in Combination with Anti–PD-1 (Nivolumab) in Advanced Refractory Solid Tumours (Phase 1b) and in Recurrent or Refractory Non–Small Cell Lung Cancer or Hepatocellular Carcinoma (Phase 2)

Galunisertib (LY2157299)

A Phase 1b/2 Dose Escalation and Cohort Expansion Study of Galunisertib Administered in Combination with Anti–PD-1 (Nivolumab) in Advanced Refractory Solid Tumours (Phase 1b) and in Recurrent or Refractory Non–Small Cell Lung Cancer or Hepatocellular Carcinoma (Phase 2).

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Protocol H9H-MC-JBEF(c)
Phase 1b/2

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on 5 October 2015.

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 26-Oct-2017 GMT

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3. Revision History

SAP Version 1 was approved prior to the first patient receiving study drug or any other protocol intervention.

SAP Version 2 overall changes and rationale for the changes are as follows:

1. Removed "glioblastoma" from Phase 2 of the study.
2. Section 5.1. Summary of Study Design, revised the second part (Phase 2) of the study to be disease restricted to include 2 rather than 3 expansion cohorts in recurrent or refractory NSCLC (n = approximately 25 patients) or HCC (n = approximately 25 patients) by removing glioblastoma (n = approximately 25 patients).
3. Section 5.2. Determination of Sample Size, revised the study design to be 3+3+3 rather 3+3 to be consistent with JBEF 05 Protocol (c).
4. Section 5.3. Method of Assignment to Treatment, Phase 1b of the study was revised to clarify that 3 patients for Cohorts 1 and 2 or 4 patients for Cohorts 3 and 4 may be entered at a particular dose level to be consistent with JBEF 05 Protocol (c).
5. Section 6.7.2. Analysis Methods, the analysis of individual changes in tumour values was removed for patients with glioblastoma. The evaluation of efficacy endpoints for IDH, ½ expression, serum TGFβ-1 levels, and tumour PD-L1 expression was removed. The use of [redacted] for sensitivity exploratory analysis was removed.

4. Study Objectives

4.1. Primary Objective

Phase 1b

The primary objective of the Phase 1b part of this study is to assess the safety and tolerability of orally dosed galunisertib 14 days on/14 days off in combination with IV nivolumab 3 mg/kg Q2W by identifying dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) or pharmacologically active dose (PAD) of the combination in patients with advanced refractory solid tumours during the first 2 cycles.

Phase 2

The primary objective of the Phase 2 part (expansion cohorts) of this study is to assess the safety of the combination of galunisertib and nivolumab in patients with refractory or recurrent non–small cell lung cancer (NSCLC) or hepatocellular carcinoma (HCC) who have failed 1 prior line of therapy.

4.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the pharmacokinetics (PK) of galunisertib and nivolumab when coadministered
- to characterize the immunogenicity of nivolumab when administered in combination with galunisertib
- to estimate the overall survival (OS) rate following the final analysis/evaluation of OS and the landmark OS at 6, 12, and 18 months following the start of therapy with the combination of galunisertib and nivolumab
- Phase 2 only: To assess the preliminary antitumour activity including progression-free survival (PFS), overall response rate (ORR), duration of response, and time to response of the combination of galunisertib and nivolumab in patients with NSCLC or HCC.

4.3. Exploratory Objectives

The exploratory objectives of this study are:

- to examine biomarkers, including pharmacodynamic markers, relevant to galunisertib, nivolumab, immune cells/immune functioning and the disease state, and to correlate these markers to clinical outcome
- Phase 1b only: To document the preliminary antitumour activity of the combination of galunisertib and nivolumab.

5. Study Design

5.1. Summary of Study Design

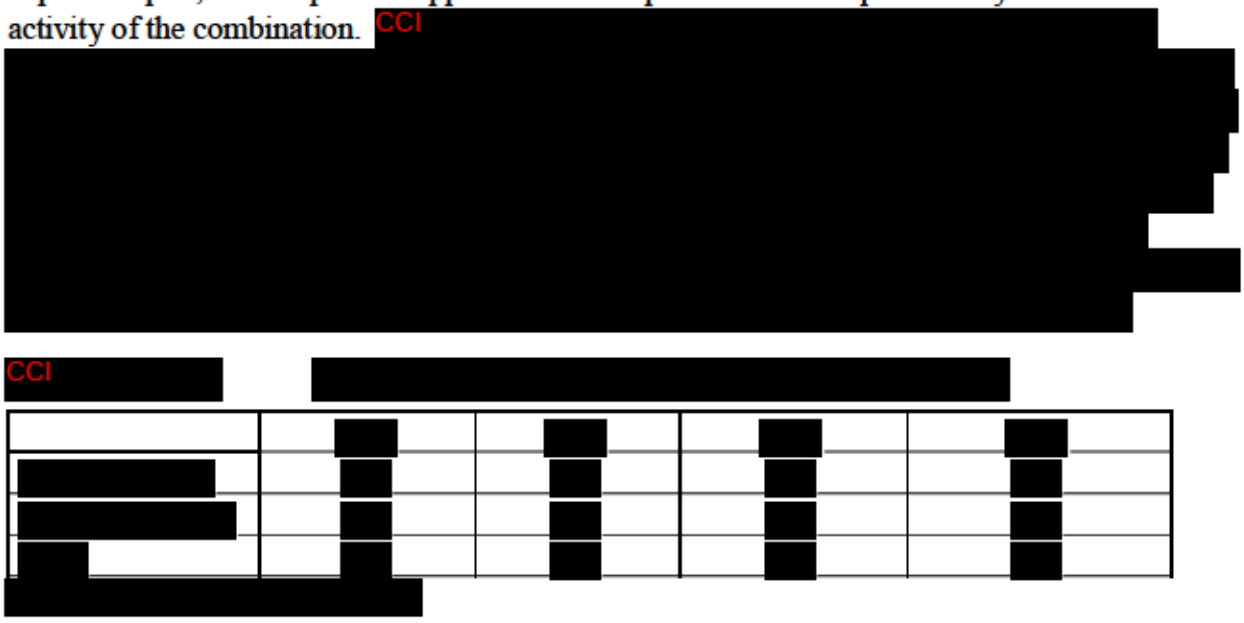
Please refer to the protocol for a full description of the study design. A brief description is provided below.

This is a Phase 1b / Phase 2 study that will be conducted in 2 parts. The first part (Phase 1b) of the study will consist of an open-label, dose-escalation assessment of the safety and tolerability of galunisertib administered at 50 mg QD (Cohort 1), 50 mg BID (Cohort 2), 80 mg BID (Cohort 3), and 150 mg BID (Cohort 4) administered with nivolumab 3 mg/kg Q2W in patients with advanced refractory solid tumours. The second part (Phase 2) of the study will be disease restricted to include 2 expansion cohorts in recurrent or refractory NSCLC (n = approximately 25 patients) or HCC (n = approximately 25 patients), all receiving nivolumab 3 mg/kg Q2W plus galunisertib at the dose determined from the Phase 1b part of the study. Additional expansion of individual cohorts may occur depending upon activity based upon a 2-stage design after 3 cycles.

5.2. Determination of Sample Size

For the Phase 1b dose escalation, a 3+3+3 design will be used to assess the safety of galunisertib in combination with nivolumab 3 mg/kg. Between 3 and 12 additional patients may be enrolled in a cohort to achieve the minimum of 3 evaluable patients if dropouts or dose interruptions or reductions occur that result in a patient being nonevaluable for DLTs.

Although the primary objective remains safety of the combination for the Phase 2 cohort expansion part, the sample size appears to be adequate to evaluate preliminary antitumour activity of the combination. CCI



When the 25th patient from each cohort has completed at least 3 cycles, an interim analysis will be conducted. Two-stage design criteria (Simon 1989) will be used to evaluate whether additional patients for that cohort will be enrolled. The null hypothesis that the null response

rate is 20% will be tested against a 1-sided alternative. If there are 4 or fewer responses in the initial 25 patients who have been enrolled and either discontinued from their allocated treatment or completed at least 3 cycles, no additional patients will be enrolled. If there are ≥9 responses, then no additional patients will be enrolled into this cohort in Phase 2. If there are 5 to 8 responses, then approximately 16 additional patients may be accrued for a total of approximately 41 patients for that cohort. CCI [redacted]

5.3. Method of Assignment to Treatment

This study is open-label for Phase 1b and Phase 2. Before each patient's enrolment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrolment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose and identification number assignment and cohort for each patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement between the investigator and the responsible Eli Lilly and Company (Lilly) CRP or clinical research scientist (CRS); the decision will be documented in writing. All patients must begin study treatment within 7 days of enrolment by interactive web-response system (IWRS).

For Phase 1b, if investigators have eligible patients who have consented concurrently, more than 3 patients (Cohorts 1 and 2) or 4 patients (Cohorts 3 or 4) may be entered at a particular dose level provided that accrual has not ceased due to excessive toxicity. This enrolment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.

All patients who enter Phase 2 will be assigned to nivolumab/galunisertib combination therapy by IWRS.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly.

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

Additional exploratory analyses of the data not described in this plan will be conducted as deemed appropriate.

By default, listings will include the study part (Phase 1b/2), the dose cohort for Phase 1b and the histology cohort for Phase 2. Summaries will generally be split by part and cohort as well.

For continuous measures, summary statistics will include sample size, means, standard deviations and/or standard error, medians, minimums, and maximums. For categorical measures, summary statistics will include frequency counts and percentages. Any missing longitudinal data will not be imputed; rather statistics will be estimated from an appropriate mixed effects model, unless otherwise specified. 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.

All confidence intervals for clinical parameters that are estimated will have a nominal confidence grade of 95%, unless otherwise stated.

Statistical tests of treatment effects will be performed at a 2-sided significance level of 0.05, unless otherwise stated.

The following terms and data handling conventions (Table JBEF.6.1) will be used in the analysis.

Table JBEF.6.1. Terms and Data Handling Conventions

Term	Definitions or Rule
Study day	If assessment is on or after date of first study drug dose then (date of assessment) – (date of first study treatment dose) + 1. If assessment precedes first treatment dose then (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 study drug dose then (date of assessment) – (date of first study treatment dose in cycle) + 1. If SOE planned pre-dose assessment precedes first treatment dose date in that cycle then (date of assessment) – (date of first study treatment dose in cycle). 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 of that cycle is baseline.
Study treatment period	Time from treatment start to discontinuation from combination treatment or if the patient has previously discontinued from 1 of the 2 study drugs, ends on the date the decision to discontinue the patient from the remaining study drug.
Post-discontinuation – short-term follow-up (or safety follow-up)	Safety Follow-Up begins the day after the patient and the investigator agree that the patient will no longer continue combination treatment and includes 30-day and 100-day visits. o ***30-Day Follow-Up*** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days. o ***100-Day Follow-Up*** begins the day after the 30-day follow-up visit and lasts approximately 70 days or approximately 100 days after the patient is no longer receiving study treatment.
Post-discontinuation – long-term follow-up	Long-Term Follow-Up begins the day after 100-day follow-up is completed and continues until the patient's death or end of trial (the patient will be contacted approximately every 12 weeks ±7 days).

6.1.1. Analysis Populations

All safety and efficacy analyses will be conducted on the safety analysis set (ie, patients who received at 1 dose of either galunisertib or nivolumab).

All patients who have received at least 1 dose of either galunisertib or nivolumab and have evaluable PK samples will be included in the analysis of PK.

Pharmacodynamics (PD) and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guidelines) has been obtained.

6.1.2. End of Study Definitions

Per protocol, the following definitions apply:

- **Study Completion** corresponds to the final analysis/evaluation of OS. The final evaluation may occur before all patients reach the OS endpoint if this earlier evaluation will not alter the statistical interpretation of OS. Investigators will continue to follow the study schedule for all patients until notified otherwise by Lilly.
- The term **"end of trial"** refers to the date of the last visit or last scheduled procedure for the last patient (includes follow-up periods). The end of trial occurs after study completion, and after the last patient has discontinued study treatment and completed the 100-day follow-up (if applicable).

6.2. Adjustments for Covariates

Additional exploratory analyses may be performed on safety or efficacy measures to adjust for factors that may affect outcomes.

6.3. Handling of Dropouts or Missing Data

Rules for handling dropouts or missing data are listed by type of analysis. Unless otherwise specified, observed data will be used and missing data will not be imputed or carried forward.

General rules for imputing dates related to adverse event (AE) or concomitant therapy (pre-dose):

- Onset date of an AE or start date of a concomitant therapy:
    - If only the day is missing, the date will be set to:
        - First day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment.
        - The day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment.
    - If both the day and month are missing, the complete date will be set to:
        - January 1 of the year of onset, if the onset year is after the year of the first study treatment.
        - The date of the first dose, if the onset year is the same as the year of the first study treatment.
- Resolution date of an AE or end date of a concomitant therapy:
    - If only the day is missing, the date will be set to the last day of the month of the occurrence, or to the date of death if the patient died in the same month.
    - If both the day and month are missing, the date will be set to 31 December of the year of occurrence.

If a date is completely missing, then the AE will be considered treatment emergent. In case of additional therapies, the therapy will be considered concomitant.

General rule for imputing other dates: If a date variable is needed for an analysis, use the following general rule to impute incomplete date:

- If the date has no missing year and month but the day is missing, then assign 1 to the day
- If the date has no missing year, but has missing month, then assign January to the month.

However, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make appropriate correction if necessary. For example, if a visit start date was 10 May 2015 and a tumour assessment date was xx May 2015 (missing day) but it was known that it occurred after that visit, then after imputation, the tumour assessment date became 01 May 2015. In this case, the imputed tumour assessment date should be compared to the visit start date and then corrected to be the visit start date, 10 May 2015.

Safety analysis: The following rule for missing data processing will apply for safety analysis:

- Missing classifications concerning study medication relationship will be considered as related to study medication (both components).
- If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication when determining whether or not the AE is present at baseline. In this case, the AE will be assumed to be treatment emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study medication.

Time-to-event analysis: All censored data will be accounted for using appropriate statistical methods as described in the efficacy section.

6.4. Patient Disposition

All patient discontinuation data collected on the eCRF will be listed, including the extent of the patient participation in the study. If known, a reason for their discontinuation from treatment and from study will be listed and summarized. All patients entered in the study will be included in the summary and listing.

All significant protocol violations will be listed by pre-determined categories (eg, inclusion/exclusion criteria, errors/missing data in the informed consent process, noncompliance with protocol procedures, patients continuing after meeting withdrawal criteria, or other violations as recorded on eCRFs or monitoring reports).

6.5. Patient Characteristics

Patient characteristics will include a summary and/or listing by cohort in Phase 1b and histology cohort in Phase 2 of the following:

- Patient demographics including (for example) age, sex, ethnicity/race, weight and change in weight from baseline, and screening height will be reported.

- baseline disease characteristics and in Phase 2, including histology
- prior disease-related therapies
- concomitant medications

6.5.1. Demographics

Patient demographics including age, sex, ethnicity, race, height at baseline, weight at baseline, body mass index (BMI) at baseline will be summarized for all treated patients using descriptive statistics and listed in a data listing.

6.5.2. Baseline Disease Characteristics

Eastern Cooperative Oncology Group (ECOG) performance status, initial pathological diagnosis, basis for initial diagnosis and disease stage will be summarized for all treated patients using descriptive statistics and listed in a data listing.

6.5.3. Pre-existing Conditions and Medical History

Medical history (MH) conditions are historical illnesses, pre-existing conditions and relevant surgeries or other procedures that started prior to signing the informed consent document. All MH conditions will be coded using the MedDRA dictionary and by using the Common Terminology Criteria for Adverse Events (CTCAE).

A **historical condition** is a MH condition that has ended prior to the date of informed consent.

A **preexisting condition** is a MH condition that is either ongoing or has ended on or after the date of informed consent.

Historical and preexisting conditions will be summarized and listed for all treated patients. Summaries will be presented by System Organ Class (SOC) and by decreasing frequency of MedDRA Preferred Term (PT) within SOC.

The MH verbatim and MedDRA PT will be listed along with start and end dates. Additionally, CTCAE severity grade will be listed for preexisting conditions.

6.5.4. Prior Therapies

Prior therapies, including systemic therapy, radiotherapies, and surgeries will be listed for all treated patients.

The number of patients with prior therapies will be reported by category of prior therapy, as well as by reasons for regimen. Additionally, the number of prior regimens for prior systemic therapy will be reported.

6.6. Concomitant Therapy

All medications entered on the CRF will be coded according to the current WHO drug dictionary.

Concomitant medications will be listed and summarized for all treated patients. The WHO classification, start and end dates, and indication for which the medication was taken will be included in the listing.

Palliative radiotherapy treatment during treatment will also be summarized.

Post discontinuation therapy will be listed and summarized.

6.7. Efficacy Analyses

For the Phase 1b portion of the trial, one of the exploratory objectives is to document the preliminary antitumour activity of the combination of galunisertib and nivolumab.

For the Phase 2 portion of the trial, one of the secondary objectives is to evaluate preliminary antitumour activity of the combination including PFS, ORR, duration of response, and time to response of the combination of galunisertib and nivolumab in patients with NSCLC or HCC.

6.7.1. Endpoint Definitions

The following efficacy endpoints will be determined:

Overall response rate (ORR) is the proportion of patients who achieved a complete response (CR) or partial response (PR) as their best overall response out of all patients treated set.

Tumour responses will be assessed using the CCI guidelines for patients with NSCLC, HCC, and tumours other than glioblastoma.

Tumor responses will be assessed using the CCI guidelines for patients with glioblastoma.

Best response is determined from a sequence of responses assessed for each patient per the respective guidelines.

Disease Control Rate (DCR) is defined as the proportion of treated patients achieving a best overall response of complete response (CR), partial response (PR), or stable disease (SD) as their best overall response out of all patients treated set.

Change in tumour size (CTS) will be assessed in each patient using radiographic imaging. This endpoint will be based on tumour measurements collected by the centers according to the applicable guidelines.

- For patients with NSCLC, HCC, and tumours other than glioblastoma, tumour size is defined as the sum of the largest diameter for each target lesions at each tumour evaluation for CCI
- For patients with glioblastoma, tumor size is defined as the sum of the largest diameter for each measurable lesion at each tumor evaluation for CCI. Change in tumour size is defined as the percent change in tumour size from the baseline evaluation to the evaluation at the each tumour evaluation, only including the tumors present at baseline.

The change in tumour size corresponding to the best response for each patient will be represented in waterfall plots.

Time to Response is defined only for responders. It is measured from the date of first study treatment to the first documented response.

Duration of Response will be calculated for ORR and is defined only for responders. It is measured from the date of documented response to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease at the cut-off date, duration of response will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

Progression-free survival (PFS) is defined as the time from the date of first study treatment to the first date of documented progression or death due to any cause, whichever occurs first. For patients who are not known to have died or progressed as of the cut-off date, PFS time will be censored at the date of the last progression-free disease assessment prior to the date of any subsequent anticancer therapy.

Overall Survival (OS) is defined as the time from the date of first study treatment to the date of death from any cause. For each patient who is not known to have died as of the cut-off date, 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).

The detailed algorithm for the censoring rules will be described in the analysis dataset requirements (Adam requirements).

6.7.2. Analysis Methods

Individual best overall response, time to and duration of response, PFS, and OS will be listed and summarised by dose for the Phase 1b and by disease cohort for the Phase 2. Additional analyses may be performed as deemed appropriate depending on the final number of patients treated in each dose cohort.

For the Phase 2 portion of the study, the following analyses will be performed:

- Rates including ORR and DCR will be computed for each cohort and the estimates will be reported with exact 95% confidence intervals.
- Time to events variables including PFS, DOR, and OS will be analysed using the Kaplan-Meier method (Kaplan and Meier 1958). Survival curves will be used to summarize the data and medians will be reported with the 95% confidence intervals for each cohort. In addition, for each time to event variable, survival rates at adequate time points may be reported (eg. 6, 12, 18 months).
- Time-to-response will be summarised using descriptive statistics by cohort.
- Individual changes in the tumour size over time will be presented graphically by tumour type using spider plots. The change in tumour size corresponding to the best response

based on target lesions (for CCI for each patient will be represented in waterfall plots by cohort.

- ECOG performance status over time will be presented graphically to explore changes over time.

To understand the impact of baseline biomarkers on efficacy, the following analyses may be considered:

- For the NSCLC cohort, efficacy endpoints may be evaluated by adjusting for baseline PD-L1 expression and serum TGFβ-1 levels.
- For the HCC cohort, efficacy endpoints may be evaluated by adjusting for serum AFP and TGFβ-1 levels and tumour PD-L1 expression.

In addition, sensitivity exploratory analyses may be conducted using arrests.

6.8. Bioanalytical and Pharmacokinetic/Pharmacodynamics Methods

6.8.1. Pharmacokinetics

Lilly PK will perform the PK analyses per the separate PK/PD analysis plan, except as indicated below.

Pharmacokinetics analyses will be conducted on patients who have received at least 1 dose of the study drug and have had samples collected. For galunisertib, population apparent clearance, volume of distribution, and exposure are steady state for galunisertib will be calculated. For nivolumab, C_{min} concentrations will be reported. If data warrants, dose proportionality of galunisertib when coadministered with nivolumab during Phase 1b may be assessed based on a power model. Nivolumab C_{min} concentration in Phase 1b will be tabulated by summary statistics.

Providing that the data allow (ie, PK parameters are available for more than 2 dose levels), the PK parameter estimates for galunisertib may be evaluated statistically. The degree of dose proportionality will be assessed by fitting the power model to the log transformed PK parameters. Different fold-ranges of doses will be chosen to provide estimates of ratios of dose-normalized geometric means, depending on the actual range of doses tested in the study (Smith et al. 2000).

In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated.

6.8.2. Pharmacodynamics and Tailoring Analyses

Biomarker data from all patients undergoing biomarker assessments will be analyzed using descriptive statistics. Biomarkers will be explored at baseline for prognostic value in efficacy or safety outcomes.

Further exploratory analyses of pharmacodynamic markers will be conducted as warranted.

6.8.3. Immunogenicity

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those patients with at least 1 positive ADA at any time point will be provided. The frequency of patients with at least 1 positive ADA assessment, and frequency of patients who develop ADA after a negative baseline assessment will be provided. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status by cohort in Phase 1b and by indication in Phase 2.

6.9. Safety Analyses

All safety summaries and analyses will be based upon the safety population that includes patients that have received at least 1 dose of study drug.

6.9.1. Extent of Exposure

All study drug information and dose level assignment will be listed for all patients on therapy.

The total number of cycles received and duration of treatment for each patient will be summarised by cohort (for example, using a napoleon plot).

The following exposure-related variables will be summarised by cohort (using dose for the Phase 1b portion and histology for the Phase 2) for each of the study drugs:

- Duration of treatment
- Number of cycles received
- Number of patients with dose adjustments
- Reasons for dose adjustments
- Dose intensity as a percentage of dose received relative to the planned dose
- Dose compliance as a percentage of dose received relative to the prescribed dose (this takes into account dose adjustments)

The detailed algorithms for the exposure variables will be described in the analysis dataset requirements (ADaM requirements).

6.9.2. Adverse Events

All patients who receive at least 1 dose of either galunisertib or nivolumab will be evaluated for safety and toxicity. The CTCAE terms (by entering the appropriate CTCAE code) and severity grades will be assigned by the investigator using CTCAE). Verbatim adverse event terms will be mapped to corresponding MedDRA lower-level term (LLT) terminology within the MedDRA dictionary.

Both the CTCAE terms and MedDRA LLT will be mapped using the MedDRA dictionary hierarchy to provide PTs and body SOC terms for each dictionary. For CTCAE terms where "Other" is indicated, the CTCAE PTs will be the same as the PTs of the MedDRA PTs created from mapping through the verbatims. All safety summaries will report the PTs created from mapping the investigator assigned CTCAE term.

Treatment-emergent AEs will be identified using the CTCAE terms by comparing which events are present at baseline and post baseline and severity grades pre-dose and post-dose for pre-existing conditions. Where CTCAE term is "Other," the matching MedDRA LLT will be used to determine treatment emergent. Details algorithm to identify TEAEs will be described in the analysis dataset requirements (ADaM requirements).

A listing of all AEs by patient will be presented. This listing will include patient number, AE, event start and end dates, CTCAE grade, relationship to study drug/procedure, seriousness, and outcome. A listing of serious adverse events (SAEs) will be produced using the similar format.

An overall summary will be provided for AEs. The number and percent of evaluable patients will be summarized for each category below. The summary will provide counts for all AEs, and AEs possibly related to study treatment.

- Patients with at least 1 TEAE
- Patients with at least 1 grade 3 or 4 TEAE
- Patients with at least 1 SAE
- Patients who discontinued due to AE
- Patients who discontinued due to SAE
- Patients who died due to AE on study treatment
- Patients who died due to AE within 30 days of discontinuation from study treatment

The treatment-emergent adverse events (TEAEs) will be summarized by decreasing frequency of SOC by PT and by maximum CTCAE grade regardless of causality and related to any study drug separately. The incidence of TEAE will also be summarized by dose cohort (Phase 1b) and by histology cohort (Phase 2). Additional analyses of TEAEs may be performed as deemed appropriate.

6.9.2.1. Dose Limiting Toxicities

A dose-limiting toxicity (DLT) is defined as an AE during Cycles 1 or 2 (8 weeks) that is possibly related to either study drug and fulfils the predefined criteria described in Section 7.2.2.1 of the protocol.

All DLTs, as defined in the protocol, will be listed and summarized by dose level for all patients on therapy in the Phase 1b portion of the study. Similarly, DLT-equivalent AEs occurring during Cycles 1 and 2 in the Phase 2 portion of the study will be listed and summarized.

6.9.3. Deaths, Serious Adverse events and Other Notable Events

All deaths in this study, including the reasons for death, will be listed by dose cohort (Phase 1b) and by histology cohort (Phase 2). 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.

Serious adverse events will be summarized by PT and repeated for events deemed by the investigator to be possibly related to study medication, with consolidated summary performed if

needed. The SAEs will be summarized both up to 30 and 100 days after end of therapy. A listing of SAEs will be produced.

In addition, additional analyses may be performed for TEAEs of special interest.

6.9.4. Clinical Laboratory Evaluation

All laboratory results will be reviewed using Spotfire to assess changes over time and differences across cohorts. Key findings will be illustrated graphically using line plots over time or box plots for example.

Abnormal laboratory results will be listed for all patients on therapy.

Calculated CTCAE grade using CTCAE v4.0 (or higher) will be summarised for laboratory parameters where CTCAE grades are available by dose cohort (phase 1b) and by histology cohort (Phase 2).

6.9.5. Vital Signs and Other Physical Findings

All vital signs will be reviewed using Spotfire to assess changes over time and differences across cohorts. Key findings will be illustrated graphically using line plots over time or box plots for example.

Any significant physical examination findings and results of clinical laboratory tests will be listed.

6.9.6. Electrocardiograms and Cardiac Assessment Data

Electrocardiogram (ECG) and echocardiogram (ECHO) results will be evaluated by the investigator and abnormalities, if present, will be listed.

Changes from baseline in ECG and ECHO parameters will be calculated and summarised at each visit. The ECG and ECHO parameters will be compared over time to assess change from baseline, during treatment, and during follow-up.

Myocardial information and quantitative results including PR, QRS, QTcB (Bazett's correction), QTcF (Fridericia's correction) and RR intervals will provided in patient listings for absolute and change from baseline. In addition, summaries of outlying corrected QT intervals (QTc, QTcB and QTcF) will be provided by treatment. Outlying intervals include absolute values >450, >480, and >500 msec and change from baseline >30 and >60 msec.

Cardiotoxicity serum markers (BNP, troponin I, high-sensitivity, C-reactive protein, cystatin C) will be reviewed using Spotfire to assess changes over time and differences across cohorts. All parameters will be tabulated and summarized using tables and graphs.

In addition, the results from MRI/CT scans performed for detection of aneurysm formation of the ascending aorta and aortic arch will be summarised.

Further exploratory analyses may be conducted as warranted.

6.10. Subgroup Analyses

Exploratory subgroup analyses not described in this SAP will be performed as deemed appropriate to further our understanding of the clinical trial data.

6.11. Protocol Violations

Protocol violations will be identified based on information recorded on the investigator log. In addition, a list of data dependent protocol violations will be programmatically derived to ensure systematic check of key significant protocol violations in the following categories:

- Inclusion/exclusion criteria not met
- Study drug administration non-compliance
- Informed consent violations
- Protocol violation leading to study discontinuation

Details of significant protocol violations to be checked programmatically will be detailed in the programming requirements.

6.12. Interim Analyses

Since the Phase 1b part is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until the MTD (or PAD) is determined. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and determine whether a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

After all patients who are deemed evaluable for the assessment of dose levels complete a DLT evaluation period or when MTD is determined, an interim safety and PK analysis may be conducted for planning next studies.

For the Phase 2 part, if DLT-equivalent toxicities occur in 33% or more of patients within a tumour-specific cohort expansion, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. No additional patients will be enrolled until this safety review is completed and a decision is made either to continue at the current dose or to deescalate the dose and define a new dose for the expansion phase. The safety review and decision will be documented in writing. Trial-level safety reviews will be conducted approximately 3 months after the first patient begins study drug on Cycle 1 Day 1, approximately 6 months after the first patient begins study drug on Cycle 1 Day 1, and approximately every 6 months thereafter. These evaluations will not be assessed by any formal statistical test; only listings and summaries will be carried out.

After enrolment has completed in a cohort (n = approximately 25) and the last enrolled patient in that cohort has completed or had the opportunity to complete 3 cycles of treatment, an interim analysis will be conducted for that particular cohort (for a total of 3 separate interim analyses to be conducted when each cohort reaches 25 patients complete at least 3 cycles of treatment). The intent of the interim analysis is to evaluate preliminary antitumour activity of galunisertib in

combination of nivolumab. These interims may be combined with the ongoing trial-level safety review. Pending review of the interim data, approximately 16 additional patients may be enrolled in that particular cohort if there are more than 4 and fewer than 9 patients who demonstrate responses (determined by ORR for the NSCLC cohort and by ORR or survival for the HCC cohort). Enrolment of the other cohort(s), if not completely enrolled, will not be stopped during the interim analysis. No independent data monitoring committee will be required for this study. The interim analysis will be conducted by an assessment committee consisting of at least 1 physician and 1 statistician.

6.13. Annual Report Analyses

The following reports are needed for the DSUR:

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

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

6.14. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a 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 term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

Analyses provided for the EudraCT requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file, in accordance with EudraCT requirements.
- Categorical breakdown of age across the entire study, represented planned and actual number of patients for the following age groups: adults (18-64 years, 65-84 years, and 85 years and over).

For the purpose of CTR/ EudraCT reporting, patients who have died, or are still in the study but off treatment, at primary DBL will be considered a completer. Those that 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.

7. References

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