Protocol 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)

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Approval Date: 31-Jan-2017

1. Protocol 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) and nivolumab (BMS-936558)

This is a multicentre, nonrandomised, open-label, dose-escalation Phase 1b study of galunisertib combined with nivolumab in patients with advanced refractory solid tumours followed by a 3-cohort expansion Phase 2 study in patients with refractory or recurrent non–small cell lung cancer or hepatocellular carcinoma.

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2. Synopsis

Transforming growth factor–β (TGF-β) is an important protein with tumour-promoting activity. Mechanisms to explain this activity include tumour neovascularisation (neoangiogenesis), immunosuppression, and loss of tumour-immune surveillance both through production of immunosuppressive cytokines and induction of immune suppressive cells and inhibition of antitumour immunity, and increased migration, invasion, and metastases (Akhurst and Derynck 2001; Derynck et al. 2001; Wick et al. 2001a, 2001b; Siegel and Massagué 2003). These combined effects on the tumour microenvironment by TGF-β promote tumour progression; inhibition of this cytokine by a TGF-β receptor type I kinase inhibitor is expected to arrest tumour growth and metastasis and improve immune function.

Programmed Cell Death–1 (PD-1) is expressed on activated T cells and can act to dampen the immune response. Tumour cells overexpress programmed cell death–1 ligand (PD-L1), which potentially leads to inhibition of local immune response. PD-1 is a hallmark of exhausted T cells in the tumour microenvironment. Targeting PD-1 provides the opportunity to restore T-cell immunity via blocking both its inhibitory interactions with PD-L1 and B7-1. Thus, blockade of both TGF-β and PD-1 could be expected to reverse the immune escape associated with these molecules and the combination to potentially provide immune restoration to improve tumour response. Indeed the combination of galunisertib and nivolumab may act synergistically via suppression of the immune suppressive function of TGF-β at the maximum tolerated dose or pharmacologically active dose.

This study is a Phase 1b/2 open-label study that will be conducted in 2 parts. The Phase 1b part of this study will consist of an open-label, dose-escalation assessment of the safety and tolerability of galunisertib administered at 50 mg daily (QD), 50 mg twice daily (BID), 80 mg BID, or 150 mg BID in combination with nivolumab 3 mg/kg in patients with advanced refractory solid tumours. The Phase 2 part of this study will be disease restricted and include 2 expansion cohorts of patients in tumours with documented monotherapy activity with nivolumab (non–small cell lung cancer; n = approximately 25 patients) or galunisertib (hepatocellular carcinoma [n = approximately 25 patients]). Patients in the 2 cohorts will be enrolled independently and will be assigned to treatment concurrently; enrolment for each cohort will be complete when that cohort has reached the prespecified enrolment target. Galunisertib will be used to attempt to augment nivolumab activity via suppression of the immune suppressive function of TGF-β at the maximum tolerated dose or pharmacologically active dose. Additional cohorts of patients with specific alternative tumour histologies may be added and will require an amendment.

3. Table of Contents

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)

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Attachments

List of Protocol Attachments

Attachment **Page**

4. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AFP	α-foetoprotein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{τ}	area under the concentration-time curve during 1 dosing interval
BID	twice daily
BNP	brain natriuretic peptide
CI	confidence interval
C_{max}	maximum observed drug concentration
$C_{max,ss}$	maximum observed drug concentration at steady state
C_{min}	minimum observed plasma concentration (trough)
CNS	central nervous system
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.

CR	complete response
CrCl	creatinine clearance
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form, a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician
CRS	clinical research scientist
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DC	dendritic cell
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
EMT	epithelial-mesenchymal transition
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enrol	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least 1 dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
GCP	good clinical practice
GI	gastrointestinal
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus

IB	Investigator's Brochure
ICD-O	International Classification of Diseases for Oncology
ICF	informed consent form
IFN-γ	interferon-γ
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalised ratio
interim analysis	an analysis of clinical study data that is conducted before the final reporting database is authorised for database lock
investigational product	a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial
investigator	a person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorised under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
Lilly Safety System	global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system
LLT	lower-level term
LV	left ventricular
MedDRA	*Medical Dictionary for Regulatory Activities*
MGMT	O6-methylguanine-DNA methyltransferase
monitor	a person responsible for ensuring the investigator site complies with the monitoring plan, applicable local standard operating procedures (SOPs) (if any), and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to patients, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

NK	natural killer
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
open-label	a study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
patient	a subject with a defined disease
PD	progressive disease
PD-1	programmed cell death–1
PD-L1	programmed cell death–ligand 1
PD-L2	programmed cell death–ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
pSMAD	phosphorylated SMAD
PT	preferred term
QD	daily
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumours
rescreen	to screen a patient who was previously declared a screen failure for the same study
Q2W	every 2 weeks
SAE	serious adverse event

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	a patient who does not meet 1 or more criteria required for participation in a trial
SD	stable disease
sponsor	the party who takes responsibility for the initiation, management and/or financing of a clinical study
study completion	occurs (that is, the scientific evaluation will be complete) following the final evaluation of patients' overall survival (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.
SUSAR	suspected unexpected serious adverse reactions
TGF-β	transforming growth factor–β
TPO	third-party organisation
TTP	time-to-progression
ULN	upper limit of normal
WHO	World Health Organization

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5. Introduction

5.1. Cancer Immunotherapy

Cancer immunotherapy rests on the premise that tumours can be recognised as foreign rather than as self and can be effectively attacked by an activated immune system. Tumour progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective, innate, and adaptive immune responses (Dunn et al. 2002; Pardoll 2003; Zitvogel et al. 2006; Jemal et al. 2011). An effective response in this setting is thought to rely on immune surveillance of tumour antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Current immunotherapy efforts attempt to reverse the immunosuppression to tumour cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system.

T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, costimulatory signals in addition to antigen recognition by the T-cell receptor (Greenwald et al. 2004). Collectively, these signals govern the balance between T-cell activation and tolerance. Programmed Cell Death–1 (PD-1) is a member of the CD28 family of T-cell costimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA (Nishimura and Honjo 2001). PD-1 signalling has been shown to inhibit CD-28–mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes (Sharpe et al. 2007). These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

5.2. Transforming Growth Factor–β

Transforming growth factor–β (TGF-β) has been shown to be a tumour promoter in advanced, metastatic cancer, while in normal tissue TGF-β inhibits epithelial cell proliferation (de Caestecker et al. 2000; Massagué et al. 2000; Derynck et al. 2001; Wakefield and Roberts 2002; Bierie and Moses 2010). TGF-β also modulates immune function by influencing T-cell, neutrophil, monocyte, macrophage, natural killer (NK)–cell, carcinoma-associated

fibroblast, and carcinoma-cell–autonomous signalling in the tumour microenvironment (Bierie and Moses 2006; Nagaraj and Datta 2010). Due to this regulation and the elevated TGF-β levels present in many tumour types, an environment favourable for immune escape and tumour progression is created. TGF-β inhibition is then a reasonable hypothetical treatment option in patients with advanced cancer (Yingling et al. 2004). Inhibiting TGF-β is a novel approach that should simultaneously inhibit tumour spread, neoangiogenesis and improve the host's antitumour immune response.

TGF-β also participates in down-regulation of the adaptive immune response (Ignotz and Massagué 1987; Bhowmick et al. 2004; Bierie and Moses 2006; Grady and Markowitz 2008; Padua and Massagué 2009) by inhibiting activity of antigen-presenting cells including dendritic cells (DCs) (Rotzer et al. 2001; Grady and Markowitz 2008), B cells and cytotoxic T cells. For example, by suppressing IFN-γ secretion from activated T cells, decreased proliferation of these T cells occurs and TGF-β, thereby, further compromises immune function.

TGF-β upregulates the expression and signalling of the immunoregulatory enzyme indoleamine 2,3-dioxygenase by plasmacytoid DCs. Other Treg-dependent mechanisms that impair the generation of host immunity also appear to be regulated by TGF-β, including CCL22 chemokine immunosuppression due to the ability of TGF-β to activate the CCL22 promoter. The cytokines regulated by CCL22 induce chemotaxis for monocytes, DCs, NK cells, and chronically activated T cells. These mechanisms suggest that inhibition of the TGF-β pathway will improve immune function by inhibiting production of immunosuppressive cytokines and restoring T-cell and other immune cell function (Hanks et al. 2013).

TGF-β promotes T-cell exhaustion, a state of T-cell dysfunction, which is identified by expression of markers including PD-1, LAG-3, TIM-3 and CTLA-4 (Wherry 2011).

5.3. Programmed Cell Death–1

PD-1 (cluster of differentiation 279) is a cell surface signalling molecule that delivers inhibitory signals that regulate the balance between T-cell activation and tolerance by interacting with its ligands, PD-L1 and PD-L2. It is a 55-kD type I transmembrane protein that is a member of the CD28 family of T-cell costimulatory receptors, which also includes CTLA-4, ICOS, and BTLA (Freeman et al. 2000). PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif and a membrane distal immunoreceptor tyrosine-based switch motif. PD-1 is primarily expressed on activated T, B, and myeloid cells (Nishimura and Honjo 2001). Its ligands, PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems (Latchman et al. 2001; Carter et al. 2002). PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the immunoreceptor tyrosine-based switch motif in its cytoplasmic region (Chemnitz et al. 2004; Shepherd et al. 2000).

In humans, PD-L1 is constitutively expressed on macrophage-lineage cells, activated T cells, lung, vascular endothelial cells, and placental syncytiotrophoblasts (Keir et al. 2008). Aberrant expression of PD-L1 by tumour cells has been reported in a number of human malignancies (Dong and Chen 2003; Konishi et al. 2004; Thompson et al. 2004; Ohigashi et al. 2005;

Thompson et al. 2005a, 2005b; Tsushima et al. 2006). PD-L1 expressed by tumour cells has been shown to enhance apoptosis of activated tumour-specific T cells in vitro (Chemnitz et al. 2004). Moreover, the expression of PD-L1 may protect the tumour cells from the induction of apoptosis by effector T cells (Azuma et al. 2008). Retrospective analyses of several human tumour types suggest that tumour overexpression (as measured by immunohistochemistry) of PD-L1 may permit immune evasion by tumours. In renal cell carcinoma, high surface expression levels of PD-L1 on tumour cells are related to tumour aggressiveness. Patients with high tumour and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than patients exhibiting low levels of PD-L1 expression (Thompson et al. 2004). In multivariate analysis, high expression of PD-L1 in melanoma is an independent predictor of vertical growth of primary melanomas and of worse outcome (Hino et al. 2010).

Following most viral infections, the host is capable of eliciting an effective innate and adaptive immune response to eliminate the virus and prevent reinfection. In some cases, chronic viral infection is established. In the setting of chronic viral infection, antigen specific CD8 T cells may demonstrate increased expression of PD-1 (Barber et al. 2006). These T cells have been termed "exhausted" due to their inability to control the infecting virus. Administration of an antibody that prevents PD-1 interaction with its ligands restores the ability of the cells to eliminate the virus infection and presumably restores immune function.

Thus blockage of both TGF-β and PD-1 could be expected to reverse the immunosuppression associated with these molecules; the combination of TGF-β and PD-1 blockade may be expected to act synergistically to induce immune restoration and to improve tumour control and response.

5.4. Rationale for H9H-MC-JBEF Protocol Amendment (a)

H9H-MC-JBEF protocol was amended to incorporate requests related to safety from the US Food and Drug Administration (FDA) submitted during review ending 26-Jun-2015. These consisted of:

- Addition of 2 cohorts to the Phase 1b part in order to lower the galunisertib starting dose. At the request of FDA, these additional cohorts are added to decrease any potential risks to patients in the absence of combination data with galunisertib and nivolumab to decrease patient risk. The revised galunisertib starting dose (in Cohort 1) will be 50 mg daily (QD) on a 14 day on/14 day off schedule; galunisertib dosing in the new Cohort 2 will be 50 mg twice daily (BID) on a 14 day on/14 day off schedule. Nivolumab dosing will remain the same.
- Addition of ≥ CTCAE Grade 3 thrombocytopenia with clinically significant bleeding to the list of AEs considered as DLTs to ensure patient safety
- Exclusion of concomitant use of strong cytochrome P450 (CYP)3A4 inhibitors and inducers in order to minimise the influence of potential drug interactions on the galunisertib/nivolumab combination in Phase 1b
- Clarification of galunisertib administration in regard to food intake

Other significant changes, modifications or clarifications made in this amendment but not requested by the FDA include:

- Modification of "glioma" to "glioblastoma" and removal of "multiforme" from "glioblastoma multiforme" to conform to the most recent World Health Organization (WHO) guidelines
- Addition of dosing information used in 2 Phase 2 studies (H9H-MC-JBAK [JBAK] and H9H-MC-JBAL [JBAL]) to galunisertib clinical background section
- Revision of Inclusion Criterion 3 to remove eligibility for patients with gliosarcoma
- Clarification added to Inclusion Criterion 3 to revise the documentation of the first recurrence of glioblastoma and to better define the requirement for patients with glioblastoma (International Classification of Diseases for Oncology [ICD-O] 9440/3, WHO grade IV)
- Clarification of Inclusion Criterion 4 that for biopsies, fine-needle aspirates or other cytology samples are not acceptable
- Revision of Inclusion Criterion 6 to require that patients with MGMT (O6-methylguanine-DNA methyltransferase) unmethylated newly diagnosed glioblastoma may have received radiotherapy only and not radiotherapy and temozolomide
- Clarification was added to Exclusion Criterion 45 to indicate that patients are to be excluded for a history of severe allergy to study drug components
- Clarifications for dose adjustments for galunisertib were added to Table JBEF.7.1 and within Section 7 to align with the additions of the DLT of ≥ CTCAE Grade 3 thrombocytopenia with clinically significant bleeding and the 2 Phase 1b dose levels
- Addition of on-study serum pregnancy tests to be conducted predose on Day 1 of every cycle
- Addition of the collection at baseline information on weight change for the previous 3 months and that weight and weight change from baseline would be assessed
- Inclusion on Phase 1b patients in assessment of overall survival (OS)
- Incorporation of additional information on different galunisertib formulations in consideration of the addition of the 50-mg galunisertib dose levels and corresponding 50-mg tablets
- Addition of pharmacokinetic (PK) time-matched electrocardiograms (ECGs)
- Modifications to the schedule of events (Attachment 1) and the PK and immunogenicity sampling schedule (Attachment 4) to improve consistency within the protocol and incorporate amendment changes

5.5. Rationale for H9H-MC-JBEF Protocol Amendment (b)

H9H-MC-JBEF protocol (a) was amended for the following reasons:

- To be consistent with other nivolumab clinical trials and to be able to assess toxicities between Study JBEF and other nivolumab clinical trials, this study was designed with a 56-day DLT period, consistent with 2 cycle lengths for galunisertib and 1 cycle length for nivolumab.

  Many Phase 1 patients travel an above-average distance to participate in trials at Phase 1 centres. In addition, many Phase 1 patients are more ill than those enrolled in Phase 2 clinical trials. These 2 issues have resulted in patients withdrawing from this trial prior to the end of the DLT period, for reasons not due to DLTs or AEs. To minimise the impact of withdrawal, 1 additional patient will be enrolled in each dose level, for a total of 4 patients per dose level to allow for unforeseen discontinuation not due to a DLT before the DLT period is completed. If at least 3 patients in each cohort dose level complete the DLT period and the fourth patient discontinues for non-DLT reasons prior to completing the DLT period, the dose level will be considered successfully completed. Thus, depending on the number of DLTs observed, the minimum number of evaluable patients will be 3, 6, or 9 at each dose level.

  Because of the progress of the study to date, this may affect Phase 1b Cohort 3 and will affect Cohort 4.

  The additional patient in each dose level will not impact the definition of the maximum tolerated dose (MTD), and it will assure adequate assessment of toxicity at each dose level and will allow more rapid determination of the appropriate dose of galunisertib to use in combination with nivolumab. Once this safety assessment is completed, the study can progress to the Phase 2 portion and allow patients with unmet medical needs, particularly those with hepatocellular carcinoma (HCC) and glioblastoma, to begin therapy with potential benefit.

- In Section 7.3, the eligibility check between the site and Lilly was removed. This was an error because the site monitor performs this review.
- The allowance of a 3-day window for ECG assessment before Day 1 of Cycles 2 and 3 and within 3 days before Day 1 of every other odd-numbered cycle thereafter has been removed because patients must travel to sites to have ECGs performed on machines calibrated for QTc Fridericia, and patients will be at the sites on Day 1 of these cycles.
- Collection and testing of high-sensitivity C-reactive protein was removed from this study because this is a nonspecific inflammatory marker that may reasonably be elevated in patients with malignancies and, if elevated, may not reflect abnormal cardiac status if this is the sole indicator of cardiac abnormality.
- Clarification has been added that pathology notes must accompany tissue biopsies.

- In Attachment 1, Study Schedules, a requirement was added for echocardiography (ECHO) at the 30-day follow-up visit, and, for the Phase 2 portion, clarification was provided that imaging is to be collected centrally [see clarification in Section 5.5].
- In Attachment 2, Clinical Laboratory Tests, clarification was added that clinical chemistries and thyroid tests will be performed by a central laboratory (Lilly-designated laboratory).

5.6. Rationale for H9H-MC-JBEF Protocol Amendment (c)

H9H-MC-JBEF protocol (b) was amended for the following reasons:

- Phase 2 portion of study: to remove the glioblastoma cohort and update protocol text to reflect this change. Results from 2 recently reported galunisertib trials, Studies H9H-MC-JBAI and H9H-MC-JBAL, have indicated a lack of sufficient efficacy with galunisertib in glioblastoma.
- To clarify the rationale for the changes to the ECHOs in Attachment 1 made in protocol amendment (b) (see Section 5.5 bullet 6): the requirement for ECHO (echocardiography) at the 30-day follow-up visit was restored into the protocol as this requirement had been inadvertently removed during Amendment A; for the Phase 2 portion, clarification was provided that imaging is to be collected centrally.
- Attachment 2: to add hepatitis B surface antigen testing to match what is already stated in Attachment 1, to add that hepatitis testing at baseline will be assayed by a local and a Lilly-designated laboratory and during the trial will be performed by a Lilly-designated laboratory; and to clarify in Attachment 2 the footnotes.
- Attachment 4: to add a ±10-minute window to the blood biomarker collection on Cycle 1 Day 1.

Minor editorial corrections or clarifications may have been made but not noted. A detailed list of changes may be found in Attachment 13.

5.7. Galunisertib

Galunisertib is an oral small molecule designed to selectively inhibit the serine/threonine kinase of the TGF-β receptor type I (see Section 5.10). The highest selected Phase 2 study dose for the JBAK and JBAL studies discussed below was 150 mg BID on a 14 days on/14 days off schedule (see the galunisertib Investigator's Brochure [IB] Section 6.1.1).

For detailed safety information, please refer to the galunisertib IB, Sections 3.2 and 6.2.

Non–Small Cell Lung Cancer

No studies have been conducted evaluating galunisertib in non–small cell lung cancer (NSCLC).

Hepatocellular Carcinoma

Study JBAK is a 4-part, Phase 2 study in HCC. In this ongoing study, an interim analysis for Part A has reported response to galunisertib in 109 patients with advanced, unresectable HCC who either failed or who were intolerant to sorafenib and had elevated α-fetoprotein (AFP) at

baseline (AFP≥1.5 times (x) upper limit of normal [ULN]) (Faivre et al. 2014; Giannelli et al. 2014). Patients were also evaluated for response based upon TGF-β1 serum levels at baseline (<, ≥3411 pg/mL).

- CCI

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

5.8. Nivolumab

Nivolumab (also referred to as BMS-936558) is a fully human monoclonal antibody (HuMAb; immunoglobulin G4–S228P) that targets the PD-1 cluster of differentiation 279 cell surface membrane receptor (see Section 5.10).

Safety

For detailed safety information, please refer to the nivolumab IB, Section 5.5.

The overall safety experience with nivolumab is based on experience in approximately 4000 patients as either monotherapy or in combination with other therapeutics. In general, for monotherapy, the safety profile is similar across tumour types.

The most frequently reported treatment-related AE is fatigue, which is almost always of low grade. Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of preferred terms (PTs) have been used to describe similar kinds of organ-related AEs, with the result being that AE frequency tables organised by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. To address this issue, select AE categories were created. Select AE categories group together the most common and impactful PTs by organ category. These categories include the following: pulmonary, gastrointestinal (GI), hepatic, skin, endocrine, hypersensitivity/infusion reaction, and renal AEs.

It is also useful to consider the management of nivolumab-related AEs by organ category, as the diagnostic work-up often requires excluding other potential diagnoses and, when appropriate, instituting specific management principles as outlined in Attachment 11.

For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be used. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and uses the same safety management algorithms.

NSCLC Efficacy

Nivolumab (Opdivo®; Bristol-Myers Squibb, Inc. [BMS], New York, New York, USA) was approved to treat patients with metastatic squamous cell NSCLC with progression on or after platinum-based chemotherapy (BMS 2014).

Study 209017 was a 1:1 randomised, open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after 1 prior platinum doublet-based chemotherapy regimen. Patients received nivolumab (n=135) administered intravenously (IV) at 3 mg/kg every 2 weeks (Q2W) or docetaxel (n=137) administered IV at 75 mg/m^2 every 3 weeks. The trial demonstrated a statistically significant improvement in OS (p=.00025) for patients randomly assigned to nivolumab as compared with docetaxel at the prespecified interim analysis (9.2 [95% CI: 7.3-13.3] months compared to 6.0 [95% CI: 5.1-7.3] months, respectively) (BMS 2014).

Study 209063 was a monotherapy Phase 2 study involving 117 patients with refractory squamous NSCLC. Based on an assessment by an independent review committee and with a minimum follow-up of at least 10 months for all patients, confirmed objective response rate

(ORR) was 15% (95% CI: 9%, 22%), of which all were PRs. The median time to onset of response was 3.3 months (range: 1.7 to 8.8 months) after the start of nivolumab treatment. Thirteen of the 17 patients (76%) with a confirmed response had ongoing responses with duration ranging from 1.9+ to 11.5+ months; 10 of these 17 (59%) patients had durable responses of 6 months or longer (BMS 2014).

Substantial monotherapy clinical activity has been observed in ≥ second-line NSCLC patients (n=129) treated in the completed Phase 1 multidose, dose-escalation study of nivolumab (CA209003). This study showed ORRs of 22% (squamous) to 26% (nonsquamous) at the 3-mg/kg dose, greater than the historical ORR for second-line docetaxel (approximately 8%-10%) (Fossella et al. 2000; Shepherd et al. 2000; Hanna et al. 2004) and similar to that for first-line platinum doublet chemotherapy (approximately 25%-30%) (Belani et al. 2008). In addition, the 48-week PFS rate among NSCLC patients treated at the 3 mg/kg dose was 30% (both nonsquamous and squamous). By comparison, the historical median PFS for second-line docetaxel is approximately 3 months (Fossella et al. 2000; Shepherd et al. 2000; Hanna et al. 2004) and that for first-line platinum doublet chemotherapy is approximately 4 to 5.5 months (Scagliotti et al. 2008). Among all CA209003 NSCLC patients with a response, the median duration of response was 17 months. Furthermore, the AE profile for nivolumab appears favourable versus platinum doublet chemotherapy, as haematologic toxicities are currently rare and the majority of nonhaematologic toxicities are low grade and manageable.

Hepatocellular Carcinoma

There are no data published with nivolumab in HCC. A Phase 1 dose-escalation study to investigate the safety, immunoregulatory activity, PK, and preliminary antitumour activity of nivolumab in advanced HCC in patients with or without chronic viral hepatitis (CA209040) is currently ongoing.

In a study of tremelimumab (an anti–CTLA-4 antibody) in HCC (Sangro et al. 2013), investigators reported a good safety profile; no patients needed steroids because of severe immune-mediated AEs. Some patients had a transient intense elevation of transaminases after the first dose but not following subsequent cycles. PR rate was 17.6% and disease control rate was 76.4%. TTP was 6.48 months (95% CI: 3.95–9.14). A significant drop in viral load was observed while new emerging variants of the hypervariable region 1 of hepatitis C virus (HCV). HCV replaced the predominant variants present before therapy, particularly in those patients with a more prominent drop in viral load. This antiviral effect was associated with an enhanced specific anti-HCV immune response.

Additional information may be found in the nivolumab IB, Section 5.4.

5.9. Objectives

5.9.1. 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 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 NSCLC or HCC who have failed 1 prior line of therapy.

5.9.2. Secondary Objectives

The secondary objectives of this study are:

- to characterise the PK of galunisertib and nivolumab when coadministered
- to characterise the immunogenicity of nivolumab when administered in combination with galunisertib
- to estimate the 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 PFS, ORR, duration of response, and time to response of the combination of galunisertib and nivolumab in patients with NSCLC or HCC

5.9.3. 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

5.10. General Introduction to Galunisertib and Nivolumab

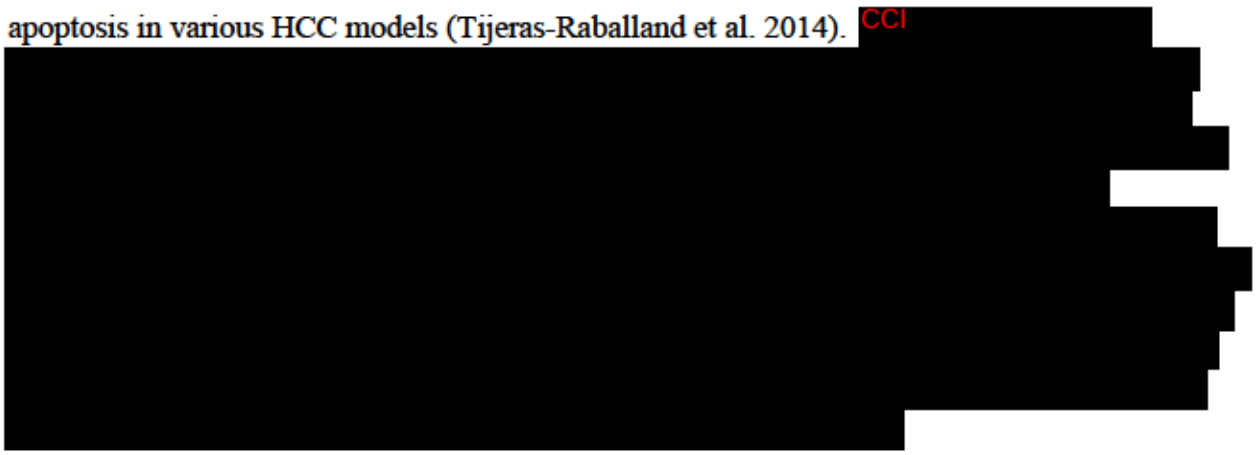
5.10.1. Mechanism of Action and In Vitro/In Vivo Activity of Galunisertib

TGF-β has been shown to be a tumour promoter in advanced, metastatic cancer (de Caestecker et al. 2000; Massagué et al. 2000; Derynck et al. 2001; Wakefield and Roberts 2002). Several mechanisms have been proposed to explain the tumour-promoting activity of TGF-β, such as increased neovascularisation of the tumour, immunosuppression leading to the escape of tumour-immune surveillance, and increased migration and invasion resulting in metastasis (Akhurst and Derynck 2001; Derynck et al. 2001; Siegel and Massagué 2003). These combined effects of immunosuppression and the tumour microenvironment changes induced by TGF-β promote tumour progression, and, therefore, a TGF-β receptor type I kinase inhibitor is expected to cause arrest of tumour growth and metastasis in patients.

TGF-β shifts the immune response from a Th1 (anti-inflammatory) response to a Th2 (proinflammatory) response, which can be tumour promoting. In vitro and animal studies have shown that inhibition of the TGF-β pathway can block activity mediated by T regulatory cells and enhance NK and CD8 T-cell activity (Lilly, data on file; Zhong et al. 2010). These data suggest that reversion of the pro-tumourigenic Th2-like milieu to a more Th1-like micro-environment by blockade of the TGF-β pathway may result in improved outcomes in tumours typically unresponsive to standard cytotoxic therapy as well as tumours sensitive to standard chemotherapy. In addition, the regulation of epithelial-mesenchymal transition (EMT) and suppression of neoangiogenesis further suggests that inhibition of TGF-β may regulate the control of a number of tumour types.

Galunisertib inhibits TGF-β–dependent cell signalling in HCC cell lines with either antiproliferative or anti-invasive effects depending on the model. In tumour samples from patients, inhibition of TGF-β signalling was associated with decreased AFP levels, inhibition of proliferation and apoptosis induction (Serova et al. 2013). Further, recent data from a study investigating the tumour effects of galunisertib ± sorafenib in various mouse models of HCC and in freshly grown HCC specimens from patients demonstrated that TGF-β signalling inhibition using galunisertib may prevent sorafenib-induced EMT, delay tumour growth, and induce

apoptosis in various HCC models (Tijeras-Raballand et al. 2014). CCI



5.10.2. Mechanism of Action and In Vitro/In Vivo Activity of Nivolumab

Blockade of the PD-1 pathway by nivolumab has been studied in a variety of preclinical in vitro assays, and antitumour activity using a murine analogue of nivolumab has been shown in a number of immunocompetent mouse cancer models (BMS Nonclinical Study Reports for Studies MDX1106-023-R [BMS 2006a], MDX1106-032-R [BMS 2006b], MDX1106-003-R [BMS 2006c], and MDX1106-006-R [BMS 2006d]). Based on these and other preclinical data, PD-1 blockade by nivolumab has been pursued as a promising therapeutic strategy to reverse immune tolerance and enhance T-cell effector function in several tumour types.

In vitro, nivolumab binds to PD-1 with high affinity (drug concentration that produces 50% of maximum effect = 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (drug concentration that reduces the maximum effect by 50% = ±1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a CMV re-stimulation assay with human peripheral blood mononuclear cells, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the antitumour immune response and result in tumour rejection in several immunocompetent mouse tumour models (MC38 and SA1/N) (Wolchok et al. 2009).

For more information, please refer to the nivolumab IB, Section 4.

5.10.3. Nonclinical Pharmacokinetics/Pharmacodynamics of Galunisertib

As determined by metabolism studies in rats, most of galunisertib was excreted in faeces, with 3 metabolites accounting for 39% of the dose excreted into urine and faeces. The function and activity of these metabolites have not been defined at this time.

Male and female Fischer 344 rats were given daily oral doses of galunisertib at 0, 15, 50, or 150 mg/kg for 1 month. Male and female beagle dogs were given daily oral doses of galunisertib

at 0, 50, 250, or 500 mg/kg for 1 month. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Nonclinical Pharmacokinetic/Pharmacodynamic Model

CCI [redacted]

CCI [redacted]

5.10.4. Nonclinical Toxicology

CCI [redacted]

5.10.5. Clinical Pharmacokinetics of Galunisertib

CCI [redacted]


CCI
CCI
CCI

5.10.6. Clinical Pharmacokinetics of Nivolumab

Single-dose PK of nivolumab was studied in 39 patients with cancer (BMS Clinical Study Report for Study MDX1106-01 [BMS, 2011]). The single-dose PK of nivolumab was linear and dose-proportional in the range of 0.3 mg/kg to 10 mg/kg (BMS Nonclinical Study Report for Study MDX1106-025-R [BMS, 2006e]). The mean terminal half-life of nivolumab ranged between 17 and 25 days across the dose range of 0.3 mg/kg to 10 mg/kg. Geometric mean total clearance varied from 0.13 mL/h/kg to 0.19 mL/h/kg, while mean volume of distribution varied between 83 mL/kg and 113 mL/kg across doses. The clearance and half-life of nivolumab are consistent with that of immunoglobulin G4. The multiple-dose PK of nivolumab given Q2W was determined by the MDX1106-03 study, as well as by population PK using data from 669 patients across nivolumab studies (BMS Clinical Study Report for Study MDX1106 [BMS, 2013]). Multiple-dose PK of nivolumab following Q2W dosing was linear with dose-proportional increase in C_{max} and area under the concentration-time curve (AUC) in 1 dosing interval (AUC_{τ}) in the studied range of 0.1 mg/kg to 10 mg/kg. Nivolumab accumulation with Q2W dosing frequency was in the range of 2.9 to 3.3 based on AUC_{τ}, 2.0 to 2.4 based on C_{max}, and 3.1 to 4.8 based on minimum observed plasma concentration (trough) (C_{min}). A population PK model was developed by nonlinear mixed effect modelling using data from 669 patients. Nivolumab concentration-time data were well described by a linear, 2-compartment, 0-order IV infusion model with first-order elimination. Nivolumab PK was found to be linear, dose independent, and time invariant. The geometric mean of terminal half-life was 25.6 days and the typical clearance was 8.8 mL/h, which are consistent with those of full human immunoglobulin antibodies. Clearance of nivolumab is independent of dose in the dose range (0.1 mg/kg to 10 mg/kg) and tumour types studied. Body weight normalised dosing showed approximately constant trough concentrations over a wide range of body weights.

5.11. Rationale for Selection of Dose

In the Phase 1b part of this study, 4 dosage levels of galunisertib (at 50 mg QD, 50 mg BID, 80 mg BID, or 150 mg BID, given on a 14 days on/14 days off schedule) will be administered orally with nivolumab 3 mg/kg IV in patients with advanced refractory solid tumours (1 cycle = 28 days). CCI

CCI [redacted]

In the nivolumab clinical development programme, the recommended nivolumab monotherapy dose and schedule of 3 mg/kg Q2W is the same across tumour types. CCI [redacted]

The safety profile of nivolumab combination therapy observed in cancer patients treated on clinical studies varies with the agent combined with nivolumab but is generally consistent with the safety profiles observed with either agent alone and, in some cases, the frequency of AEs may be greater than that observed with either agent alone. For nivolumab monotherapy and combination therapy, most high-grade events were manageable with use of low-dose corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in Attachment 11.

Based on the nonclinical safety profile for galunisertib, treatment in rats for 6 months resulted in a continuum of changes in the GI tract. These changes included inflammation of the mucosa, simple mucosal hyperplasia, and adenocarcinoma. These data suggest that there is potential for enhanced toxicity when nivolumab and galunisertib are administered in combination.

However, given the safety profile of nivolumab and galunisertib alone, the potential benefits of a combination study are expected to outweigh the potential risks.

6. Investigational Plan

6.1. Study Population

Patients who do not meet the criteria for participation within the 28-day screening period (screen failures) may be rescreened. Note that repeating laboratory tests during the 28-day screening period does not constitute rescreening (any test that does not meet eligibility may be repeated within the 28-day period and not considered a rescreening). Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the 28-day screening period. If a repeat laboratory value meets eligibility, that test must be repeated again to confirm eligibility.

Patients may be rescreened up to 2 times after the initial screening, if needed. The interval between rescreenings should be at least 1 week. If a patient does not meet eligibility within the first 28-day screening period, the patient may be rescreened beginning on Day 35. Each time rescreening is performed, the patient must sign a new informed consent form (ICF) and be assigned a new identification number. All required tests including laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), magnetic resonance imaging (MRI)/computed tomography (CT) scans with contrast must be repeated in patients who are rescreened in a new 28-day period (Attachment 1).

Prospective approval of protocol deviations to recruitment and enrolment criteria (also known as protocol waivers or exemptions) is not permitted. Any missing laboratory or test results precludes patient from being enrolled on this study until those laboratory or test results are available. Local laboratories will be used to assess eligibility.

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to first dose of study drug.

[1] For Phase 1b, must have advanced refractory solid tumours in any line of therapy.

[2] For Phase 2, must have 1 of the following tumour types: recurrent or refractory NSCLC (any histology) or HCC with AFP ≥200 ng/mL.

[3] For Phase 2, must have histological or cytological confirmation of recurrent disease based upon standard diagnostic criteria for the tumour type.

[4] New (nonarchived) baseline tumour biopsies (defined as a biopsy specimen taken since completion of the first-line treatment regimen) are required for all cohorts (see Section 8.2.1). In addition, in the Phase 2 part of the study, patients must agree to undergo an on-study biopsy; patients in the Phase 1b part of this study are strongly encouraged to agree to undergo an on-study biopsy. See Section 8.2.3.2.

For Phase 1b of the study, any glioblastoma patients must have either a new biopsy or archived tumour tissue available.

Fine-needle aspirates or other cytology samples are not acceptable.

[5] For NSCLC, HCC or other nonneuro-oncology tumours: have measurable disease as defined by RECIST version 1.1 (Eisenhauer et al. 2009; Attachment 8).

For any glioblastoma patient in Phase 1b of the study: have measurable disease as defined by RANO (Wen et al. 2010; Attachment 9). Patients with glioblastoma may have nonmeasurable disease if they have undergone resection and postresection radiation. If measurable disease is present, at least 1 measurable glioblastoma lesion present prior to randomisation must meet the following criteria:

- contrast-enhancing and clearly defined, bi-dimensionally measurable margins AND
- at least 2 perpendicular diameters measuring ≥10 mm x ≥10 mm (Note: MRI measurements will not include surgical cavities, cysts, or necrotic area)

[6] For Phase 2 only, have had disease progression or be refractory or intolerant to **1 prior line of therapy** (first-line therapy) for recurrent or refractory NSCLC or HCC and have refused currently approved second-line of therapy. First-line therapy is defined as therapy used to treat advanced disease. This may include multiple chemotherapeutic, targeted or immunotherapeutic agents with or without radiation therapy and/or surgery. Each subsequent line of therapy is preceded by disease progression. A switch of an agent within the same drug class (eg, cisplatinum to carboplatinum) within a regimen in order to manage toxicity does not define the start of a new line of therapy.

For NSCLC:

- Prior lines of therapy must include a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Patients who received platinum-based neoadjuvant or adjuvant therapy and subsequently received platinum-based therapy as first-line of therapy are eligible.
- Patients who have completed neoadjuvant or adjuvant therapy with a platinum doublet and have experienced disease recurrence within 6 months of completing the platinum doublet are eligible.
- Tumours with driver mutations (epidermal growth factor receptor mutation positive or anaplastic lymphoma kinase fusion oncogene positive) treated with a tyrosine kinase inhibitor or crizotinib are eligible. For patients who have progressed on a tyrosine kinase inhibitor or crizotinib or are intolerant to this targeted therapy, that patient must receive platinum-based therapy prior to enrolment in this study. Documentation of such mutations must be available and entered into the electronic case report form (eCRF).

- Maintenance or switch maintenance therapy after first-line chemotherapy will be considered part of the first-line regimen and is acceptable.
- Patients who completed and progressed on a platinum-containing regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy given from locally advanced disease and developed recurrent (local or metastatic) disease within the 6 months before screening would be counted as having received 1 prior platinum-containing regimen and therefore would not require retreatment with a platinum-containing regimen for Stage IIIB, IV, or recurrent disease and are eligible. However, patients must have received at least 2 cycles of platinum doublet-based chemotherapy before discontinuation for toxicity. If patients received only 1 cycle of a platinum doublet and discontinue due to clear progression, that regimen should be counted as a prior line of therapy.

For HCC:

- one prior line of therapy which must include sorafenib, or patient must have progressed or been intolerant to sorafenib for patients not eligible for transarterial chemoembolisation. Patients who had sorafenib for locally advanced disease or are intolerant to sorafenib are eligible. Patients may have had clinical progression only following sorafenib or local therapy.
- must have Child-Pugh A only. Patients may have any viral status (hepatitis B, hepatitis C, or none).
- have a viral load <100 IU/mL
- for hepatitis B patients, must be on a nucleoside analogue reverse transcriptase inhibitor (lamivudine, telbivudine, adefovir, tenofovir, or entecavir)

[7] Are ≥18 years of age

[8] Have given written informed consent prior to any study-specific procedures

[9] Have adequate organ function, including:

<u>For Phase 1b only:</u>

Have sufficient haematological function, defined as a platelet count of ≥100x10^9/L, haemoglobin concentration ≥9.0 g/dL or ≥5.6 mmol/L, and absolute neutrophil count (ANC) ≥1.5x10^9/L. Patients may receive erythrocyte transfusions to achieve this haemoglobin level at the discretion of the investigator (at least 3 days before starting treatment with study drug). Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of haemoglobin level ≥9 g/dL.

Have sufficient hepatic function, defined as bilirubin ≤1.5xULN (except patients with Gilbert Syndrome who must have a total bilirubin level of <3.0xULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≤3.0xULN.

Serum creatinine ≤1.5 × institutional ULN OR measured or calculated CrCl (glomerular filtration rate can also be used in place of creatinine or CrCl; Attachment 7) ≥50 mL/min for patients with creatinine levels ≤1.5x institutional ULN.

For Phase 2 only:

For all Phase 2 cohorts:

- Renal: Serum creatinine ≤1.5 × institutional ULN OR measured or calculated CrCl (glomerular filtration rate can also be used in place of creatinine or CrCl; Attachment 7) ≥50 mL/min for patients with creatinine levels ≤1.5x institutional ULN.
- Neurologic: Patients with ≤ Grade 2 neuropathy are eligible and may enrol.

For NSCLC cohort only:

- Haematologic: platelets ≥100x10^9/L, and haemoglobin ≥9 g/dL or ≥5.6 mmol/L, ANC ≥1.5x10^9/L. Patients may receive erythrocyte transfusions to achieve this haemoglobin level at the discretion of the investigator (at least 3 days before starting treatment with study drug). Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of haemoglobin level ≥9 g/dL.
- Have sufficient hepatic function, defined as bilirubin ≤1.5xULN (except patients with Gilbert Syndrome who must have a total bilirubin level of <3.0xULN) and ALT and AST levels ≤3.0xULN.

For HCC cohort only:

- Haematologic: platelets ≥50 x 10^9/L, haemoglobin ≥9 g/dL or ≥5.6 mmol/L, ANC ≥1.5x10^9/L. Patients may receive erythrocyte transfusions to achieve this haemoglobin level at the discretion of the investigator (at least 3 days before starting treatment with study drug). Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of haemoglobin level ≥9 g/dL.
- Hepatic: bilirubin ≤2.5xULN (except patients with Gilbert Syndrome who must have a total bilirubin level of <3.0xULN), ALT, and AST ≤5.0xULN. Prothrombin time/international normalised ratio (INR) ≤2.3; or prothrombin time 6 seconds above control.

[10] Patients with recent major surgery must have recovered, in the opinion of the investigator, from the toxicity and/or complications from the intervention before starting therapy.

[11] Have an INR or prothrombin time ≤1.5xULN, except as noted for HCC patients in Inclusion Criterion 9, unless patient is receiving stable dose anticoagulant therapy. These patients are eligible as long as prothrombin time or INR is within therapeutic range of the intended use of the anticoagulant.

[12] Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 6).

[13] Have discontinued previous treatments for cancer for at least 28 days and recovered from the acute effects of therapy and at least 42 days for mitomycin-C or nitrosoureas

[14] Are reliable and willing to be available for the duration of the study and are willing to follow study procedures

[15] Use an approved contraceptive method (for example, intrauterine device, birth control pills, or barrier device), if appropriate (male and female patients with reproductive potential) during the study and for 23 weeks for women of childbearing potential and 31 weeks for males sexually active with women of childbearing potential after discontinuation of study treatment. If condoms are used as a barrier contraceptive, a spermicidal agent should be added to ensure that pregnancy does not occur. The selected contraceptive method should have a failure rate of <1%.

[16] Women of childbearing potential must have a negative β-human chorionic gonadotropin pregnancy test documented within 7 days prior to treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should immediately discontinue study treatment and inform her treating physician immediately. If pregnancy is confirmed, patient will be discontinued from treatment.

[17] Have an estimated life expectancy of ≥12 weeks, in the judgement of the investigator

[18] Are able to swallow tablets

6.1.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.

[19] Have received treatment within 28 days or 5 half-lives (whichever is longer) of the initial dose of study drug with an investigational product or nonapproved use of a drug or device (other than the study drug/device used in this study) for noncancer indications or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[20] For Phase 2 only, more than 1 prior line of therapy for their tumour type.

[21] Have moderate or severe cardiovascular disease:

- have the presence of cardiac disease, including a myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension

- have baseline elevated cardiac enzymes as follows: brain natriuretic peptide (BNP) or Cystatin C elevated more than 2xULN or Troponin I elevated above the ULN
- have documented major ECG abnormalities (not responding to medical treatments)
- have major abnormalities documented by ECHO with Doppler:
  - moderate or severe heart valve function defect including moderate or severe valve stenosis or regurgitation
  - left ventricular (LV) ejection fraction <50%, evaluation based on the institutional lower limit of normal
  - have septal aneurysm or other heart aneurysm
  - any aneurysm of the major vessels

For additional details, refer to the attached ECHO guidelines (Attachment 10).

[22] Have a serious concomitant systemic disorder including active infection with human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

[23] Active infection with hepatitis B virus (HBV) (positive hepatitis B surface antigen); HCV is allowed only in HCC patients. HCC patients at risk for HBV reactivation (as defined by anti–hepatitis B core antibody positive) are only eligible in the HCC cohort; see Inclusion Criterion 6.

[24] Are receiving immunosuppressive agents (eg, cyclosporine) for any reason except for corticosteroids for transfusions. In the Phase 1b portion of the study, low-dose corticosteroids for glioblastoma are permitted (eg, prednisone 10 mg [approximately equivalent to 2 mg of dexamethasone] or less daily or equivalent dose of other corticosteroid).

[25] Have had prior monoclonal antibody therapy within 28 days before Study Day 1 or not recovered (≤ Grade 1 or at baseline) from AEs (except for fatigue or alopecia) due to agents administered more than 28 days earlier.

[26] Have had prior therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, or anti–cytotoxic T lymphocyte-associated antigen-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or a TGFβ R1 kinase inhibitor.

[27] Have a second concurrent primary malignancy that, in the judgement of the investigator and Lilly, may affect the interpretation of results.

[28] Have prior malignancies. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low (such as basal cell carcinoma), as judged by the Lilly clinical research physician (CRP), are eligible for this study. The Lilly CRP will approve enrolment of patients with prior malignancies in remission before these patients are enrolled.

[29] Receiving any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents).

[30] Have had prior radiotherapy within 2 weeks of therapy. Patients must have recovered from all radiation-related toxicities, not require more than low-dose corticosteroids (except for low-dose corticosteroids for glioblastoma in the Phase 1b portion of the study, eg, prednisone 10 mg or less daily or equivalent dose of other corticosteroid), and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNS disease with Lilly physician approval.

[31] For glioblastoma patients in the Phase 1b portion of the study only, have diffuse leptomeningeal disease.

[32] Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with stable, previously treated brain metastases may participate if neurologic symptoms have resolved, they have been off steroids for at least 7 days, and have no evidence of disease progression by imaging for at least 2 weeks before the first dose of study treatment.

[33] Have active known or suspected autoimmune disease or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo, alopecia, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring thyroid replacement therapy (must be on a stable dose started prior to study entry), and/or psoriasis not requiring chronic and systemic immunosuppressive treatment, are permitted to enrol if the above listed conditions are not expected to recur in the absence of an external trigger.

[34] Patients requiring escalating or chronic supraphysiologic doses of corticosteroids for control of their disease at randomisation are excluded. However, patients with resolved childhood asthma/atopy, who require intermittent use of bronchodilators or local steroid injections, who have hypothyroidism stable on thyroid replacement therapy at study entry, or who have Sjögren's syndrome are eligible for the study.

[35] Patients with Crohn's disease are not eligible.

[36] For glioblastoma patients in the Phase 1b portion of the study only, previous treatment with carmustine wafer except when administered as first-line treatment and at least 6 months prior to randomisation.

[37] Concurrent treatment with Novo-Tumor Treating Fields® (Novocure; Haifa, Israel) is not permitted. Prior whole brain or gamma knife radiosurgery is permitted for the treatment of glioblastoma or metastatic brain lesions.

[38] Have evidence of interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity or active, noninfectious pneumonitis.

[39] Have an active infection requiring systemic therapy.

[40] Be a pregnant or nursing woman.

[41] Have received a live vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

[42] Have a GI condition that may affect drug absorption.

[43] Have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

[44] Have known psychiatric or substance abuse disorders that in the opinion of the investigator would interfere with cooperation with the requirements of the study.

[45] Have a history of severe allergy or hypersensitivity to study drug components (including monoclonal antibody therapy).

[46] For Phase 1b only: Concomitant use of strong CYP3A4 inhibitors and inducers is prohibited. See Attachment 12.

[47] For HCC patients only:

- have known HCC with fibro-lamellar or mixed histology
- have presence of clinically relevant ascites
- have a history of hepatic encephalopathy
- have had a liver transplant
- have experienced any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 GI bleeding or any variceal bleeding episode in the 3 months prior to enrolment requiring transfusion or endoscopic or operative intervention. (Patients with any bleeding episode considered life-threatening during the 3 months prior to enrolment are excluded, regardless of transfusion or intervention status.)
- have oesophageal or gastric varices that require immediate intervention (eg, banding, sclerotherapy) or represent a high bleeding risk in the opinion of the investigator or consulting gastroenterologist or hepatologist

6.2. Summary of Study Design

This is a Phase 1b/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 (Figure JBEF.6.1). The second part (Phase 2) of the study will be disease restricted to include 2 expansion cohorts in patients with recurrent or refractory NSCLC (n = approximately 25 patients) or HCC (n = approximately 25 patients) receiving nivolumab 3 mg/kg Q2W plus galunisertib at the dose determined from the Phase 1b part. Additional expansion of individual cohorts may occur depending upon activity based upon a 2-stage design after 3 cycles. Details are found in Section 10.1.1. NSCLC has a historically good activity under nivolumab monotherapy; HCC has documented activity with galunisertib therapy.

Additional cohorts of patients with specific alternative tumour histologies may be added, but this addition will require an amendment.

Safety assessments including laboratory assessments, PK blood draws, vital sign collection, medical history, weight and at baseline change in weight for previous 3 months, and physical examinations will be performed according to the schedule of events in Attachment 1. AEs will be assessed continuously during the study and for 100 days after the last dose of combination treatment. ECGs will be collected as described in Attachment 1 and Attachment 4. ECHOs will be collected at baseline and every 8 weeks (end of every other cycle). Additionally imaging examinations will be performed approximately every 8 weeks (end of every other cycle).

Efficacy measures will be assessed following every other treatment cycle (end of Cycles 2, 4, etc). Disease assessment with CT and/or MRI, as appropriate, will be performed at baseline and approximately between Days 22 and 28 of every other cycle and completed before the first dose in the next cycle (or approximately every 8 weeks), until disease progression or patient withdrawal from the study.

Treatment decisions related to patient management and whether to treat a patient with advanced refractory solid tumours with additional cycles of study therapy will be based on RECIST version 1.1 for all study patients except patients with glioblastoma, for whom treatment decisions will be based on RANO criteria.

At the sponsor's discretion, scans and measurements may be collected and reviewed by independent radiologists using RECIST version 1.1/RANO criteria at a later date, or at any time during the study.

The planned duration of treatment is not fixed; patients will remain on study treatment until they fulfil 1 of the criteria for study discontinuation (Section 6.3). Patients demonstrating a benefit from treatment may continue on combination therapy if the patient and investigator feel that the patient is benefiting from treatment. If a patient experiences an AE that requires the patient be discontinued from 1 of the 2 study drugs, the patient should continue on the other study drug

(Section 7.2.4). Landmark analysis of all study patients will occur at 6, 12, and 18 months, and OS will be assessed at the end of trial.

Patients who have discontinued from combination treatment will enter the Safety Follow-Up period with visits at approximately 30 and 100 days. If the patient has only discontinued from 1 of the 2 study drugs, the patient will continue on treatment until they discontinue from the second drug, at which time they will enter the Safety Follow-Up period as noted above. If patients have discontinued treatment for reasons other than disease progression, tumour assessments should continue every 8 weeks until disease progression occurs, initiation of a new anticancer therapy, the patient dies or is lost to follow-up. Patients will be followed for survival approximately every 12 weeks (±7 days) until death or end of trial. This follow-up may occur through a phone call, email, or visit by the patient or the patient's caretaker.

Refer to Attachment 1 for the study schedule.

Abbreviations: approx = approximately; BID = twice daily; IV = intravenous; HCC = hepatocellular carcinoma; n = number of patients; NSCLC = non–small cell lung cancer; Q2W = every other week; QD = daily; TBD = to be determined.

Figure JBEF.6.1. Study H9H-MC-JBEF design.

6.2.1. Phase 1b Dose Escalation

A 3 + 3 + 3 design will be used to assess the safety of galunisertib given in combination with nivolumab 3 mg/kg. Beginning with Cohort 3 or 4, 1 additional patient will be enrolled in each dose level for a total of 4 patients per dose level to allow for unforeseen discontinuation not due to a DLT before the DLT period is completed (see Section 7.2.2.2). A cycle length for the combination of nivolumab and galunisertib is defined for the purpose of this study to be 28 days. The dosages during dose escalation are provided in Table JBEF.6.1. The DLT observation period will last for 8 weeks or to the completion of Cycle 2, whichever is longer.

After determining the MTD, PAD, or if dose escalation is completed without identifying the MTD and to further explore pharmacodynamic/biomarker objectives, 3 to 12 additional patients may be enrolled in each dose level for a total of up to 15 patients at any dose level.

If at least 50 mg QD of galunisertib cannot be combined safely with nivolumab 3 mg/kg, then following the review of available safety, PK, and pharmacodynamic data at the dose escalation/cohort review meetings, a lower dose of nivolumab may be considered and tested with galunisertib at 50 mg oral QD.

Table JBEF.6.1. Phase 1b Dose Levels

Cohort/Dose Level	Total Number of Evaluable Patients	Galunisertib (PO)	Nivolumab (IV)
1	n=3 to approx 15	50 mg QD 14 days on/14 days off	3 mg/kg Q2W
2	n=3 to approx 15	50 mg BID 14 days on/14 days off	3 mg/kg Q2W
3	n=3 to approx 15	80 mg BID 14 days on/14 days off	3 mg/kg Q2W
4	n=3 to approx 15	150 mg BID 14 days on/14 days off	3 mg/kg Q2W
Total	n=12 to approx 60 total		

Abbreviations: approx = approximately; BID = twice daily; IV = intravenous; PO = orally; Q2W = every 2 weeks; QD = daily.

6.2.2. Phase 2 Cohort Expansion

The purpose of the cohort expansions is to gather additional safety, PK, tolerability, preliminary efficacy and pharmacodynamic information regarding the combination of galunisertib and nivolumab 3 mg/kg. Once the safety profile of all doses tested has been characterised and the MTD or PAD of combined administration of galunisertib and nivolumab has been defined in the Phase 1b part, the Phase 2 cohort expansions will be initiated at the MTD, or PAD. Treatment doses in the cohort expansion groups will not exceed the MTD. Two expansion cohorts will be tested in order to demonstrate efficacy of the combination in NSCLC and HCC. If DLT-equivalent toxicities occur in 33% or more of patients within a tumour-specific cohort expansion in the first 2 cycles, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. No additional patients will be accrued 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 NSCLC cohort (NSCLC has demonstrated activity with nivolumab monotherapy) and the HCC cohort (HCC has documented monotherapy activity with galunisertib) will be used to assess activity of the combination. Additional cohorts could be considered after reviewing the Phase 1b dose-escalation data to further explore activity of the combination. Any additions would require an amendment.

Approximately 25 patients will be initially enrolled in each cohort. These cohorts may be expanded depending upon activity observed in each individual cohort. These patients will be enrolled to allow for a more precise estimate of the ORR in these tumour types where preliminary data or Phase 3 data have suggested activity for monotherapy. See Section 7.2.3 for dosing information. For all tumour types, patients should receive a minimum of 6 cycles of therapy since responses may take up to 4 to 6 cycles unless they meet 1 of the discontinuation criteria. Patients may continue on combination therapy past 6 cycles if in the opinion of the investigator and the Lilly physician the patient is deriving benefit.

Continuous evaluation of toxicity in the cohort expansions will be performed throughout enrolment in the expansion cohorts. If the rate of DLT-equivalent events exceeds 33% in the first 2 cycles, the findings will be discussed and further enrolment may be interrupted. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level.

6.2.3. Study Completion and End of Trial

Study completion occurs (that is, the scientific evaluation will be complete) following the final evaluation of patients' 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.

"End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

6.2.4. Definitions of Study Periods

Terms used to describe the periods during the study are defined below:

- **Baseline or screening (= patient entering the study):** begins when the ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Treatment Period:** begins at the first study treatment **(= patient is enrolled in the study)** and ends on the date the decision to discontinue the patient from combination treatment or if the patient has previously discontinued from 1 or the 2 study drug, ends on the date the decision to discontinue the patient from remaining study drug.
- **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.
    - ***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.

- ***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.
- ***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 (approximately every 12 weeks ± 7 days the patient will be contacted).

- **Study Completion:** occurs (that is, the scientific evaluation will be complete) following the final analysis/evaluation of OS.
- **End of Trial:** 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).

6.3. Discontinuations

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorisation.

6.3.1. Discontinuation of Patients Inadvertently Enrolled

The criteria for enrolment must be followed explicitly. If the investigator site identifies a patient who did not meet enrolment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrolment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue on study treatment if the Lilly CRP does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

6.3.2. Discontinuation of Patients

Patients will be discontinued from the study drug and/or from the study in the following circumstances:

- Enrolment in any other clinical trial involving an investigational product or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/physician decision
    - the investigator/physician decides that the patient should be discontinued from the study or study drug(s)

  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) occurs prior to introduction of the other agent
- Patient decision
  - the patient or the patient's designee (for example, legal guardian) requests to be discontinued from the study or study drug.
- Sponsor decision
  - Sponsors stop the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).
- The patient experiences unacceptable toxicity. If the patient discontinues from 1 study treatment due unacceptable toxicity (see Section 7.2.4.1.3 for galunisertib discontinuation and Section 7.2.4.2.3 for nivolumab discontinuation), the patient should continue on the other study treatment.
- The patient becomes pregnant.

The reason for and date of discontinuation from study treatment will be collected for all patients. The Date of Discontinuation (for any of the above reasons) from study treatment is to be reported on the case report form (CRF). Patients who discontinue from study treatment will have follow-up procedures performed as shown in the study schedule (Attachment 1).

6.3.3. Patients Lost to Follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

6.3.4. Discontinuation of Study Sites

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

6.3.5. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges it necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7. Treatment

7.1. Materials and Supplies

7.1.1. Galunisertib

Galunisertib (50 mg) will be supplied in open-label blister packs or other appropriate packaging of uncoated, round white tablets. Galunisertib (80 and 150 mg) will be supplied in open-label blister packs or other appropriate packaging of film-coated, paracapsule-shaped tablets that are light yellow/yellow in appearance. No premedication is required for galunisertib.

All materials must be stored at room temperature within temperature range specified on the material label in the original container and to keep out of the reach of children. Tablets should not be opened, crushed, or dissolved. The material will be labelled according to regulatory requirements of the country. Should the type of clinical trial material packaging change, it will adhere to country-specific regulations.

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

Clinical study materials will be labelled according to the country's regulatory requirements.

7.1.2. Nivolumab

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) or 40 mg/4 mL (10 mg/mL), is a clear to opalescent, colourless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentaacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes a 0.7-mL overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminium seals. The only difference between the 2 drug product presentations is the vial fill volume.

Clinical study materials will be labelled according to the country's regulatory requirements.

7.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agents and planned duration of each individual's treatment to the site personnel or patient/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensation, destruction, and collection, and returning or destroying all unused medication to Lilly or its designee at the end of the study
- verifying completion of patient diary for galunisertib dosing during Cycles 1and 2 of both Phase 1b and 2

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

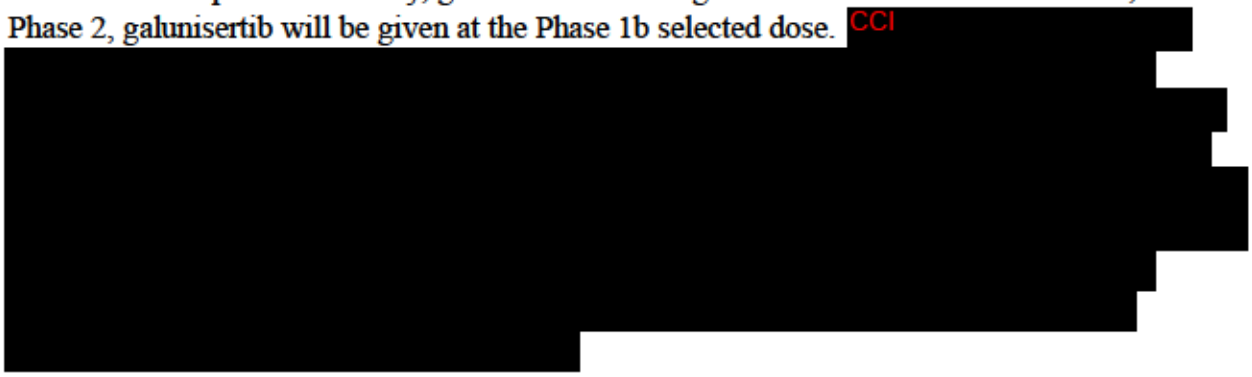
7.2.1. Dosing Schedule

This study defines 1 cycle as 4 weeks or 28 days.

The planned duration of treatment is not fixed; patients will remain on study treatment until they fulfil 1 of the criteria for study discontinuation (Section 6.3). Patients demonstrating a benefit from treatment may continue on the combination therapy.

Galunisertib

Each patient will take galunisertib orally 14 days on (Days 1 to 14)/14 days off (Days 15 to 28). In the Phase 1b part of the study, galunisertib will be given in a dose-escalation schema; in the Phase 2, galunisertib will be given at the Phase 1b selected dose. CCI



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Nivolumab

Patients should receive nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion, on Days 1 and 15 of each treatment cycle.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to recalculate subsequent doses if the patient's weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram.

Nivolumab may be dosed with no fewer than 12 days between doses and no more than 3 days after the scheduled dosing date. Dose given after the 3-day window is considered a dose delay. A maximum delay of 42 days *between doses* is allowed.

There are no premedications recommended for nivolumab on the first cycle.

Patients should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, patients should be managed according to Section 7.2.7.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the patient tolerates the treatment.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/mL (10 mg/mL)

Nivolumab injection is to be administered at a dose of 3 mg/kg as a 30-minute IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

No incompatibilities between nivolumab and polyvinyl chloride, non-PVC/ non-(di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

Clinical study materials will be labelled according to the country's regulatory requirements.

7.2.2. Phase 1b Dose Escalation

The MTD (or PAD) of galunisertib defined during Phase 1b will be used for Phase 2.

Four dose levels will be investigated (Table JBEF.6.1). Dose escalation is described in Section 7.2.2.2.

Because this is a dose-escalation part of the study, data will be evaluated on an ongoing basis until the MTD, or PAD, is determined.

Safety data, in particular AEs, will be the primary criteria for the dose escalation. In addition, if available at the time of dose-escalation decision, PK will be used as secondary/supporting data for dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly study teams; the decision will be documented in writing.

Based on the ongoing safety reviews, modifications to the dose-escalation strategy or other design elements may be made via protocol amendment to ensure patient safety.

No intrapatient dose escalation is allowed during Phase 1b within Cycles 1 or 2. Intrapatient dose reduction is permitted for a DLT if a lower dose of galunisertib has been established to be safe in combination with nivolumab and the patient, in the opinion of the investigator and the

Lilly physician, is deriving benefit. Subsequent cycles may be dose adjusted as outlined in Sections 7.2.4.1.1, 7.2.4.1.2, 7.2.4.2.1, and 7.2.4.2.2.

Dose escalation will be based on the number of DLTs experienced during Cycles 1 and 2.

7.2.2.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

DLT is defined as an AE during Cycles 1 or 2 (8 weeks) that is possibly related to either study drug and fulfils any 1 of the following criteria using the National Cancer Institute's (NCI's) CTCAE version 4.03:

- ≥CTCAE Grade 3 nonhaematologic toxicity. Exceptions that will not be considered a DLT are:
  - nausea, vomiting, diarrhoea, and constipation that can be controlled with treatment
  - fatigue relieved by rest, limiting self-care and/or activities of daily living
  - anorexia not associated with significant weight loss (weight loss of >10% baseline) or malnutrition (eg, inadequate oral caloric and/or fluid intake); tube feeding or total parenteral nutrition indicated
  - Grade 3 elevations of ALT and/or AST, without evidence of other hepatic injury, in the setting of preexisting hepatic metastasis and baseline elevation of these values may not be considered a DLT if agreed by the study investigator and Lilly CRP
- CTCAE Grade 4 haematological toxicity of >5 days duration
- any febrile neutropenia
- ≥ CTCAE Grade 3 thrombocytopenia with clinically significant bleeding
- for nivolumab, any toxicity occurring during Cycles 1 or 2 managed by discontinuation as described in Section 7.2.4.2.
- any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycles 1 or 2) or results in the patient getting <75% of the total doses or leads to holding galunisertib for >2 weeks

Although no intrapatient dose escalation or reduction is allowed, for the purposes of patient management, DLTs will lead to dose interruption regardless of the cycle in which a DLT occurs (see Section 7.2.2.2 for specific guidelines).

For the purpose of this study, the MTD is defined as the highest tested dose that has less than 33% probability of causing a DLT.

7.2.2.2. Dose-Escalation Method

Cohorts 1 and 2

A 3 + 3 +3 design will be used to assess the safety of galunisertib given in combination with nivolumab 3 mg/kg. The dosages during dose escalation are provided in Table JBEF.6.1. The DLT observation period will last for 8 weeks or to the completion of Cycle 2. Three patients will be treated initially at each dose level. If no DLTs occur in a cohort of 3 patients at the lower dose level, a new cohort of 3 patients will be treated at the higher dose level. If 1 of 3 patients experiences a DLT in either cohort, that cohort will be expanded to 6 patients. If 1 of 6 patients experiences a DLT in the lower cohort, a new cohort of 3 patients will be treated at the higher dose level. If 2 of 6 patients experience a DLT, that cohort will be expanded to 9 patients. If 2 of 3, 3 of 6, or 3 of 9 patients experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD or the intended maximum dose of galunisertib.

Additional patients will 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. Patients who withdraw from the study during the DLT period for reasons other than a DLT should be replaced within the same dose level. For the purpose of making decisions on dose escalation from a safety perspective, patients will be considered evaluable if they have received at least 3 out of the 4 scheduled nivolumab doses through the 8-week observation period and if at least 75% of the cohort-specified doses of galunisertib were taken (see Section 7.6.3). Patients who receive fewer than 3 out of 4 nivolumab doses or less than 75% of galunisertib doses for reasons other than AEs or DLTs should be replaced.

Cohorts 3 and 4

A 3 + 3 + 3 design will be used to assess the safety of galunisertib given in combination with nivolumab 3 mg/kg. The dosages during dose escalation are provided in Table JBEF.6.1. The DLT observation period will last for 8 weeks or to the completion of Cycle 2. One additional patient will be enrolled in each dose level for a total of 4 patients per dose level to allow for unforeseen discontinuation not due to a DLT before the DLT period is completed. If at least 3 patients in each dose level complete the DLT period and the fourth patient discontinues for non-DLT reasons prior to completing the DLT period, the dose level will be considered successfully completed. Thus, depending on the number of DLTs observed, the minimum number of evaluable patients will be 3, 6, or 9. For the cohort expansions, up to 4 patients will be enrolled to ensure the minimum number of evaluable patients is achieved (6 or 9 patients).

For the purpose of making decisions on dose escalation from a safety perspective, patients will be considered evaluable if they have received at least 3 of the 4 scheduled nivolumab doses through the 8-week observation period and if at least 75% of the cohort-specified doses of galunisertib were taken (see Section 7.6.3). Patients who receive fewer than 3 of 4 nivolumab doses or <75% of galunisertib doses for reasons other than AEs or DLTs should be replaced if the minimum number of evaluable patients has not been reached.

- If no DLTs occur in a cohort of 3 or 4 evaluable patients at the lower dose level, a new cohort of 4 patients will be treated at the higher dose level.
- If 1 of 3 or 4 evaluable patients experiences a DLT, up to 4 additional patients (dose level expansion) will be enrolled into the cohort so that a minimum of 6 patients will be evaluable. The dose escalation can proceed if the DLT rate is <33%. If the DLT rate is 33%, up to 4 additional patients (dose level expansion) will be enrolled into the cohort so that a minimum of 9 patients will be evaluable. The dose escalation can proceed if the DLT rate is <33%. If the DLT rate is ≥33%, then that dose level will be determined to have exceeded the MTD or the intended maximum dose of galunisertib.
- If the DLT rate is >33% (for example, 2 of 3 or 4 evaluable patients experiences a DLT), that dose level will be determined to have exceeded the MTD or the intended maximum dose of galunisertib.

7.2.2.3. Pharmacologically Active Dose

The PAD of a targeted agent is not necessarily the same as the MTD. The PAD of galunisertib will be assessed using an appropriate pharmacodynamic marker.

7.2.3. Phase 2 Cohort Expansion

Once the safety profile of all doses tested has been characterised and the MTD or PAD of combined administration of galunisertib and nivolumab has been defined in the Phase 1b part, the cohort expansions will be initiated.

The Phase 2 part of the study will initially include 2 expansion cohorts (NSCLC and HCC [n = approximately 25 patients per cohort]). Additional cohorts of patients with specific alternative tumour histologies may be added and would require a protocol amendment. 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 accrued 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. Treatment in all 3 cohorts will consist of 3 mg/kg nivolumab IV on Days 1 and 15 and galunisertib given orally at the dose determined during the Phase 1b part on a schedule of 14 days on/14 days off (taken on Days 1-14). A cycle is 28 days.

Continuous evaluation of toxicity in the cohort expansions will be performed throughout enrolment in the expansion cohorts. If the rate of DLT-equivalent events exceeds 33% in the first 2 cycles, the findings will be discussed and further enrolment may be interrupted. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level.

7.2.4. Dose Adjustments, Delays, or Discontinuation from Study Drug

7.2.4.1. Galunisertib Dose Adjustments and Delays, Criteria for Resumption of Galunisertib Treatment, and Discontinuation for Phase 1b and 2

7.2.4.1.1. Galunisertib Dose Adjustments and Delays

During Phase 1b Cycles 1 and 2, no intrapatient dose escalation or reduction of galunisertib is allowed. Subsequent cycles may be dose adjusted as outlined in Sections 7.2.4.1.2 and 7.2.4.2.

Table JBEF.7.1 summarizes dose adjustment for patients experiencing the following events that are considered possibly related to galunisertib during Phase 1b Cycle 3 and beyond and during Phase 2. Galunisertib will be omitted until the event resolves.

Table JBEF.7.1. Dose Adjustments for Galunisertib

Events Possibly Related to Galunisertib	Adjustment
ANC $<0.5x10^9$/L for longer than 7 days, or ANC $<1.0x10^9$/L with a single temperature of >101°F/38.3°C or a sustained temperature of >100.4°F/38°C for >1 hour	Galunisertib will be omitted until the event resolves. In Phase 1b, no dose reduction is permitted; in Phase 2, galunisertib should be reduced by 1 (Phase 1b) cohort dose level (see Table JBEF.6.1). If the event has not recovered by Day 1 of the subsequent cycle, then galunisertib should be permanently discontinued.
Platelet count $<25x10^9$/L or platelet count $<50 \times 10^9$/L with bleeding	Galunisertib will be omitted until the event resolves. In Phase 1b, no dose reduction is permitted; in Phase 2, galunisertib should be reduced by 1 (Phase 1b) cohort dose level (see Table JBEF.6.1). If the event has not recovered by Day 1 of the subsequent cycle, then galunisertib should be permanently discontinued.
CTCAE Grade 3 or 4 nonhaematologic toxicity	Galunisertib will be omitted until the event resolves. In Phase 1b, no dose reduction is permitted; in Phase 2, galunisertib should be reduced by 1 (Phase 1b) cohort dose level (see Table JBEF.6.1). If the event has not recovered by Day 1 of the subsequent cycle, then galunisertib should be permanently discontinued.

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events.

7.2.4.1.2. Criteria to Resume Treatment with Galunisertib

Patients may resume treatment with galunisertib when the drug-related AE(s) resolve(s) to Grade ≤1 or baseline, with the following exceptions:

- Nonhaematologic toxicity must resolve to CTCAE Grade 0, 1, or baseline level before resuming treatment (with the exception of alopecia, fatigue, skin rash, nausea, vomiting, constipation, or diarrhoea that can be controlled with treatment).
- Haematologic toxicity must resolve to a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.

If dosing is delayed for galunisertib-related AEs such that the patient cannot resume galunisertib treatment by Day 1 of the next cycle, the patient should be withdrawn from galunisertib. At Cycle 3 and beyond in the Phase 1b part of the study, intrapatient dose reduction is permitted for a DLT if a lower dose of galunisertib has been established to be safe in combination with nivolumab, the patient has recovered by Day 1 of the next cycle, and the patient, in the opinion of the investigator and the Lilly physician, is deriving benefit. In the Phase 2 part only, patients who do recover by Day 1 of the next cycle may have the dosage reduced to the next lower (Phase 1b) dose level (see Table JBEF.6.1). If the Phase 2 galunisertib dose is 50 mg QD, no dose reduction will be allowed.

If galunisertib dosing is omitted during the 14-day dosing period, dosing with galunisertib may resume within that same 14-day dosing period, to conclude as originally scheduled, if the patient has adequately recovered from the toxicity that required the galunisertib to be held. If the galunisertib cannot resume during that 14-day dosing period, it should continue to be held until Day 1 of the next cycle.

If both galunisertib (see directions above) and nivolumab (see directions in Section 7.2.4.2.1) are held, each drug may be resumed per the directions for each individual drug.

In case of a dose delay of galunisertib, patients can continue nivolumab treatment (at investigator discretion).

No patient will have his/her galunisertib dose reduced more than once. Reescalation to the previous galunisertib dose is acceptable in the absence of continuing toxicities. If subsequent galunisertib dose reduction is required after reescalation, the patient must be maintained at the reduced dose level for all remaining cycles.

7.2.4.1.3. Discontinuation from Galunisertib

If dosing is delayed for galunisertib-related AEs such that the patient cannot resume galunisertib treatment by Day 1 of the next cycle, the patient should be withdrawn from galunisertib. In the Phase 1b part, intrapatient dose reduction is permitted for a DLT if a lower dose of galunisertib has been established to be safe in combination with nivolumab, the patient has recovered by Day 1 of the next cycle, and the patient, in the opinion of the investigator and the Lilly physician, is deriving benefit. In the Phase 2 part only, patients who do recover by Day 1 of the next cycle may have the dosage reduced to the next lower (Phase 1b) dose level (see Table JBEF.6.1). If the Phase 2 galunisertib dose is 50 mg QD, no dose reduction will be allowed. If in the investigator's opinion the toxicity is related to both study drugs, both drugs should be withheld.

If moderate or severe heart valve toxicities are observed or a patient develops an aneurysm, the patient must immediately be discontinued from galunisertib treatment (for definitions see Attachment 10, including references on the ECHO assessment based on the Guidelines of the American and European Societies of Cardiac Echocardiography). These events will be considered serious AEs (SAEs) and should be reported to Lilly per standard SAE reporting requirements (Table JBEF.8.1). Exceptions to this rule must be approved by the ERBs and Lilly.

Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.

If a patient experiences an AE that requires the patient be discontinued from galunisertib, the patient should continue on nivolumab (if the patient has not previously met discontinuation criteria for nivolumab). If in the investigator's opinion the toxicity is related to both study drugs, both drugs should be held.

7.2.4.2. Nivolumab Dose Adjustments and Delays, Criteria for Resumption of Nivolumab Treatment, and Discontinuation in Phase 1b and 2

Intrapatient dose escalations or reductions of nivolumab are not allowed in either Phase 1b or Phase 2.

7.2.4.2.1. Nivolumab Dose Adjustments and Delays

Dose delay criteria specified below apply for all nivolumab-related AEs. Nivolumab must be delayed until treatment can resume. There will be no dose reductions for nivolumab.

Nivolumab administration should be delayed for the following:

- Any Grade ≥2 nonskin, drug-related AE, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the Lilly CRP for Grade 3 amylase or lipase abnormalities, and to assess clinically relevant laboratory tests at more frequent intervals which will be determined by the investigator.
  - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥2 toxicity
  - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥3 toxicity
  - For HCC patients only, if a patient has baseline AST, ALT, or total bilirubin within the Grade 2 toxicity range, delay dosing if these become 2x baseline levels during the study.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the investigator, warrants delaying the dose of study medication

If nivolumab dosing is omitted on Days 1 or 15 of a cycle, dosing with nivolumab will be resumed 14 days later (next scheduled dose) as per the original schedule if the patient has

adequately recovered from the toxicity that required the nivolumab to be held. If the nivolumab cannot be resumed on the following Day 1 or 15, it should continue to be held until the next Day 1 or 15. Galunisertib should continue as scheduled.

If both galunisertib (see directions in Section 7.2.4.1.1) and nivolumab (see directions above) are held, each drug may be resumed per the directions for each individual drug.

7.2.4.2.2. Criteria for Resumption of Nivolumab Treatment

Patients may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤1 or baseline, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Drug-related pulmonary toxicity, diarrhoea, or colitis must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Lilly CRP
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Lilly CRP

Dose delay of nivolumab which results in treatment interruption of >6 weeks require treatment discontinuation, with exceptions as noted above.

7.2.4.2.3. Discontinuation from Nivolumab

Nivolumab treatment should be permanently discontinued for the following:

- any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the retreatment period OR requires systemic treatment
- any Grade 3 nonskin, drug-related AE lasting >7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation

- any drug-related liver function test abnormality that meets the following criteria require discontinuation:
  - AST or ALT >8xULN
  - total bilirubin >5xULN
  - concurrent AST or ALT >3xULN and total bilirubin >2xULN
  - for HCC patients only:
    - AST or ALT >10xULN for >2 weeks
    - AST or ALT >15xULN irrespective of duration
    - Total bilirubin >8xULN irrespective of duration for patients with elevated bilirubin at study entry or >5xULN for those with normal total bilirubin at entry
    - Concurrent AST or ALT >3xULN and total bilirubin >5xULN for patients entering treatment with a normal bilirubin and up to 8xULN for patients with elevated bilirubin
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤7 days
  - Grade 4 lymphopenia or leukopenia
  - isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Lilly CRP should be consulted for Grade 4 amylase or lipase abnormalities.
  - isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs (such as adrenal insufficiency, adrenocorticotropic hormone deficiency, hyperthyroidism or hypothyroidism, or glucose intolerance) which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Lilly CRP
- any event that leads to delay in dosing lasting >6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - *Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to reinitiating treatment in a patient with a dosing delay lasting >6 weeks from the previous dose, the Lilly CRP must be consulted. Tumour assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.*
  - *Dosing delays lasting >6 weeks from the previous dose that occur for nondrug-related reasons may be allowed if approved by the Lilly CRP. Prior to reinitiating treatment in a patient with a dosing delay lasting >6 weeks, the Lilly CRP must be consulted. Tumour assessments should continue as per protocol even if*

dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing

If a patient experiences an AE that requires the patient be discontinued from nivolumab, the patient should continue on galunisertib (if the patient has not previously met discontinuation criteria for galunisertib). If in the investigator's opinion the toxicity is related to both study drugs, both drugs should be held.

7.2.5. Study Treatment beyond Disease Progression by RECIST Version 1.1

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).

Nonglioblastoma Patients

Nonglioblastoma patients treated with nivolumab and galunisertib will be permitted to continue treatment beyond initial RECIST version 1.1–defined PD if they meet the following criteria:

- investigator-assessed clinical benefit and do not have rapid disease progression
- tolerance of study drugs
- stable performance status
- treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- patient provides written informed consent prior to receiving additional nivolumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options

The decision to continue treatment should be discussed with the Lilly CRP and documented in the study records. A radiographic assessment/scan should be performed within 8 weeks of original PD to determine whether there has been a decrease in the tumour size or continued PD. The assessment of clinical benefit should be balanced by clinical judgement as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab/galunisertib. If the investigator feels that the nivolumab/galunisertib patient continues to achieve clinical benefit by continuing treatment, the patient should remain on the trial and continue to receive monitoring according to Attachment 1. For the patients who continue nivolumab/galunisertib study therapy beyond progression, further progression is defined as an additional 10% increase in tumour burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression. New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short

axis of at least 15 mm). Any new lesion considered nonmeasurable at the time of initial progression may become measurable and therefore included in the tumour burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation from treatment.

Glioblastoma Patients

Standard treatment for glioblastomas (including radiation therapy and temozolomide) may result in a transient increase in tumour enhancement (pseudoprogression) in a subset of patients that eventually subsides without any change in therapy. Pseudoprogression may be difficult to differentiate from true tumour progression and may have important implications for patient management. In order to minimise premature discontinuation of study medication and distinguish pseudoprogression from PD, patients initially meeting radiologic criteria for disease progression may continue receiving study medication until confirmation of progression with an MRI performed approximately 12 weeks later.

In order to continue study treatment after assessment of initial radiological progression, the following criteria must be met:

1) The patient is believed to demonstrate clinical benefit as determined by the investigator.
2) The patient is tolerating study medication.

Patients with confirmed progression (approximately 12 weeks after initially assessed progression) will discontinue study medication and enter the follow-up/survival phase of the study. If progression is confirmed, then the date of disease progression will be the first date the patient met the criteria for progression. In those cases in which radiologic progression cannot be differentiated from pseudoprogression and it is the investigator's opinion that a surgical resection to obtain tumour tissue for histopathology is in the patient's best interests, a surgical resection may be performed following consultation with the Lilly CRP. Tumour biopsy samples (blocks or slides) must be submitted for central review by a neuropathologist to minimise any interobserver variation in the histopathologic assessment of progression versus treatment-related changes. If tumour pathology confirms progression, then the patient will be discontinued from study medication per protocol discontinuation criteria and the date of progression will be the day that it was first suspected. If tumour pathology reveals treatment-related changes and does not confirm disease progression, the patient may continue study medication. An MRI after the resection is required prior to treatment continuation. The patient will then continue all on-treatment tumour assessments as per the treatment schedule (Attachment 1).

Central Neuropathologic Review of Tumour Samples after Biopsy or Resection

In those cases in which radiologic progression cannot be differentiated from pseudoprogression and the patient undergoes a biopsy or diagnostic surgical resection to obtain tumour tissue for histopathology analysis, representative tumour tissue samples will be reviewed locally and submitted for central review by a neuropathologist. If there is discordance between the central and local neuropathologic determination of progression versus treatment-associated changes (pseudoprogression), then a second central neuropathologic review will be performed and serve as the final adjudicator of the histopathologic determination. Central review of histopathology will be blinded to the patient treatment arm assignment. Specific instructions will be provided to the investigative sites regarding the requirements for submission of tumour tissue for central neuropathologic review. If tumour tissue is not available for central neuropathology review, the reasons for not submitting tissue for central review must be clearly documented by the principle investigator and approval obtained from the Lilly CRP.

7.2.6. Management Algorithms for Immuno-Oncology Agents

Immuno-oncology agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- GI
- renal
- pulmonary
- hepatic
- endocrinopathy
- skin
- neurological

The above algorithms are found in Attachment 11.

7.2.7. Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigours, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Lilly CRP and reported as SAEs if any meet the criteria. Infusion reactions should be graded according to NCI CTCAE (version 4.03) guidelines. No blood sample will be collected with any infusion reaction.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For **Grade 1** symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For **Grade 2** symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of Solu-Cortef® or equivalent) may be used.

For **Grade 3 or 4** symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10 000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localised or generalised pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

7.3. Method of Assignment to Treatment

This study is open-label for Phase 1b and Phase 2. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement between the investigator and the responsible 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.

7.4. Blinding

The entire study is open label.

7.5. Concomitant Therapy

Growth factors and erythropoietin are allowed per American Society of Clinical Oncology or National Comprehensive Cancer Network guidelines. Granulocyte colony-stimulating factors must be discontinued at least 24 hours prior to the start of the next cycle of treatment. Transfusions are permitted. Patients may receive prophylactic corticosteroids (such as, prednisolone, methylprednisolone or dexamethasone) to prevent transfusion reactions. No other therapy, including routine use of growth factors or experimental medications (for example, immunotherapy or other not approved medication) will be permitted while the patients are on the study.

Immunosuppressive agents (eg, cyclosporine) will not be allowed, except for glioblastoma for which low-dose corticosteroids will be permitted (eg, prednisone 10 mg [approximately equivalent to 2 mg of dexamethasone] or less daily or equivalent dose of other corticosteroid). Immunosuppressive doses of systemic steroids will not be allowed except as outlined in Attachment 11.

Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents for treatment of NSCLC, HCC, or any other tumour type) will not be allowed.

Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses >10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Patients should receive full supportive care during the trial. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured for each cycle in the CRF. Concomitant palliative and supportive care for disease-related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study therapy. Prior palliative radiotherapy must have been completed at least 2 weeks prior to enrolment.

Palliative radiotherapy will be allowed. No toxicities have been observed when radiotherapy has been added to galunisertib. The potential for overlapping toxicities with radiotherapy and nivolumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving nivolumab. If palliative radiotherapy is required, then nivolumab should be withheld for at least 1 week before, during and 1 week after radiation. Patients should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤1 prior to resuming nivolumab. In the NSCLC cohort, nontarget brain lesions and nontarget bone lesions without lung tissue included in the planned radiation field may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and eCRF. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs. If warranted, symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression.

In addition, any disease progression requiring other forms of specific antitumour therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the CRF. Replacement hormonal therapy initiated before study entry will be allowed.

Concomitant use of strong CYP3A4 inhibitors and inducers is prohibited in Phase 1b to minimise the influence of potential drug interactions on the galunisertib/nivolumab combination. See Attachment 12 for guidance on restricted medications.

All concomitant medications should be recorded throughout the patient's participation in the study.

7.6. Treatment Compliance

7.6.1. Galunisertib Compliance

Patient compliance with galunisertib will be assessed at each visit. Compliance will be assessed by direct questioning, review of diary (diary for Cycles 1 and 2 only), and counting returned tablets. Deviations from the prescribed dosage regimen should be recorded on the CRF.

For patients who are significantly noncompliant (<75% of expected study drug taken in a visit interval), investigative site personnel must counsel patients on the importance of study drug compliance and drug accountability. Patients who are consistently out of the compliance range may be discontinued. If these patients are discontinued for reasons other than AEs or DLTs, they should be replaced. A Lilly representative should be contacted upon the second instance of treatment noncompliance.

The following procedures will be employed to ensure appropriate drug accountability:

- Drug accountability will be emphasised at the start-up meeting.
- Drug accountability will be monitored throughout the study.
- Each patient should be instructed to return all study-drug packaging and unused material to the study site at each visit. The study site will keep a record of all drug dispensed to and returned by the patients throughout the study. Study site personnel will return or destroy (as requested) all unused study drug for all patients.

Patients will keep a study diary for the first 2 cycles (56 days) to document that they are taking galunisertib as prescribed.

7.6.2. Nivolumab Compliance

Nivolumab will be administered IV at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF.

7.6.3. Evaluable Phase 1b Patients

For Phase 1b, any patient who discontinues from the study before completing the first 2 cycles of study treatment (56 days) will be deemed nonevaluable for assessment of a dose level and may be replaced within the same dose level, unless they experience a DLT prior to withdrawal. If the patient is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered nonevaluable and may be replaced. Nonevaluable patients may be replaced to ensure that at least 3 patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT. Safety analyses will be conducted on all patients who have received at least 1 dose of study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

For the purpose of making decisions on dose escalation from a safety perspective, patients will be considered evaluable if:

- they have received at least 3 of 4 scheduled nivolumab doses through first 2 cycles (56 days)
- they took at least 75% of the cohort-specified dose of galunisertib

Patients who have received less than 3 out of 4 nivolumab doses or less than 75% of galunisertib doses for reasons other than AEs or DLTs should be replaced. In addition, in Phase 1b, patients

with dosing delays in Cycles 1 and 2 of ≥3 weeks for non-DLT events will be considered not evaluable for making decisions on dose escalation and should be replaced.

Patients who are not evaluable for PK, but who complete 2 cycles of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP or CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

8. Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Data Collection

8.1. Safety Evaluations

Safety is the primary endpoint of this Phase 1b/2 study as determined by the NCI CTCAE version 4.03. All patients who receive at least one dose of galunisertib or nivolumab will be evaluated for safety as measured by the occurrence of AEs, SAEs, deaths, laboratory abnormalities, and weight and weight change from baseline, assessed during treatment and for approximately 100 days in follow-up.

Patients will have regularly scheduled study visits at the clinical site as shown in the study schedule (Attachment 1). Safety assessments including AE collection, laboratory assessments, vital sign collection, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable), weight, medical history (screening only) and physical examinations will be performed during the study. Additionally, peripheral blood will be assessed for HBV DNA, HCV RNA, and HCC antiviral activity.

Imaging studies will be performed every 8 weeks or sooner if clinically indicated. Liver function, as part of the routine clinical chemistry panel, will be tested every other week.

Standard laboratory tests, per the study schedule, will be performed. A serum pregnancy test will be administered if applicable. Other clinical laboratory tests will also be collected.

Study procedures and their timing are described in the study schedule (Attachment 1). Attachment 2 lists the specific tests that will be performed for this study.

8.1.1. Safety Data Collection and Review

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

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until:

- the event is resolved,
- the event is no longer considered to be drug-related,
- the event becomes stable or returns to baseline,
- a new treatment is initiated for the patient, or
- the patient dies or is lost to follow-up.

Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the study schedule (Attachment 1). Table JBEF.8.1 presents a summary of AE and SAE reporting guidelines. Table JBEF.8.1 also shows which database or system is used to store AE and SAE data.

8.1.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from laboratory results, vital sign measurements, etc, that occur should also be reported to Lilly or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using CTCAE version 4.03.

The NCI CTCAE version 4.03 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. All AEs observed will be graded using CTCAE version 4.0. Any minor version of CTCAE version 4.0 (for example, version 4.03) may be used for this study. Minor CTCAE version 4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI CTCAE version 4.03 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the CRF. This collection is in addition to verbatim text used to describe the AE.

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

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on foetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drugs must be stopped immediately.

In addition to AEs and pregnancy events as noted above, the following safety information is collected, even in the absence of an AE: overdose, medication error, drug-drug interaction and cases of suspected transmission of infectious agents via study drug and drug-induced liver injury.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition all AEs related to protocol procedures are reported to Lilly or designee.

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

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, study drug via CRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related:** a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related:** a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated:** without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.1.2.1. Serious Adverse Events

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalisations or elective procedures for underlying preexisting conditions that are already recorded in the patient's medical history at the time of study enrolment should not be considered SAEs. Hospitalisation or prolongation of hospitalisation without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

An SAE is any AE during this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalisation (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity

- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered SAEs when, based on appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

If an investigator becomes aware of SAEs occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAEs to the sponsor, and the SAEs will be entered in the Lilly Safety System.

Recommendations for reporting SAEs may be found in Attachment 5.

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

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

8.1.2.2.1. Prior to Administration of Study Drugs

AE or SAE collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an AE or SAE after signing informed consent but prior to receiving study drug, only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.2.2. On Therapy

All AEs and SAEs, regardless of relatedness to study drugs or protocol procedures, occurring while the patient is receiving study drug must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug to when he/she receives the last dose of study drug.

8.1.2.2.3. Follow-Up Visits

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the safety follow-up visits occurring at approximately 30 and 100 days after last dose of combination treatment must be reported to Lilly or its designee (Attachment 1).

For the Phase 1b part only, following the safety assessments (which occur after the patient discontinues from study treatment) which mark the end of the follow-up visit, the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug or protocol procedures. In this instance, the patient should be followed in subsequent follow-up visits until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

For the Phase 2 part only, following the safety assessments (which occur after the patient discontinues from study treatment) which mark the end of the follow-up visit, the patient will be followed only for survival (overall and 6, 12, and 18 months), unless there is an ongoing AE or SAE that is possibly related to study drug or protocol procedures. In this instance, the patient should be followed in subsequent follow-up visits until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

After the follow-up visits, AEs are not required to be reported unless the investigator feels the AEs were related to either study drug, drug delivery system, or a protocol procedure. If an investigator becomes aware of SAEs believed to be related to protocol procedures or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the Development Core Safety Information (galunisertib IB Section 7) or Reference Safety Information for Adverse Drug Reactions (nivolumab IB Section 5.6) and that the investigator identifies as related to study drug or procedure. The United States 21 CFR 312.32, the European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulatory regulations and the associated detailed guidances.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

The AE and SAE reporting guidelines are summarised in Table JBEF.8.1.

Table JBEF.8.1. Adverse Event and Serious Adverse Reporting Guidelines for Study H9H-MC-JBEF

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)	Preexisting conditions All AEs All SAEs regardless of relatedness	x x x	 x
On therapy (Starts at first dose of study drug[s] and ends at last dose of study drug[s])	All AEs All SAEs regardless of relatedness	x x	 x
Follow-up visits (Starts just after the last dose of combination treatment and ends when end of study safety assessments are completed [2 visits at approximately 30 and 100 days after last dose of study drugs])	All AEs All SAEs regardless of relatedness	x x	 x
Subsequent follow-up visits, if necessary for patient monitoring	Ongoing AEs possibly related to study drug(s) or protocol procedures All SAEs related to protocol procedures or study drug	x x	 x
Patient no longer on study	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

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

8.1.3. Other Safety Measures

8.1.3.1. Detection of Aneurysm Formation of the Ascending Aorta and Aortic Arch (Thoracic View)

MRI or CT scan with contrast of the chest will be performed and assessed locally at the site at baseline screening and every 6 months. For Germany, MRI of the chest is an acceptable alternative and may be used instead of CT scans. Each of the imaging techniques are used to detect aneurysms of the ascending aorta or aortic arch and must follow institutional guidelines. Once the method of assessment is chosen for a given patient, it must be used throughout the study for that patient.

8.1.3.2. Electrocardiograms

For each patient, a 12-lead ECG will be collected as indicated in Attachment 1 and Attachment 4. Please see Attachment 4 for specific ECG times matched with PK blood draws.

For each patient, 12-lead digital ECGs will be obtained as single ECGs according to the study schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine during ECG collection. ECGs may be obtained at additional times

when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

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

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

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

It is recognised that ECG interpretations by the investigator (or qualified designee) and by the cardiologist at the central ECG laboratory may be different. When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator (or qualified designee) interpretation will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report-writing purposes.

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

Other safety measures include assessments of physical examinations, preexisting conditions, transfusions and hospitalisations, and AEs. Patients will be assessed before each visit by using the CTCAE v4.0.

8.1.3.3. Echocardiography/Doppler

Echocardiography with Doppler will be locally assessed for enrolment and safety decisions by physicians or a team of people who are qualified by experience or training. Individuals so qualified must be identified at each site. The same person should be responsible for reading the ECHOs on any individual study patient. ECHOs will be as indicated in Attachment 1. The ECHO will be electronically transmitted to a designated central laboratory for analysis. Data will be interpreted by the vendor cardiologist for data analysis and study report writing purposes.

Cardiotoxicity: ECHO/Doppler imaging will include the following assessments and other standard evaluations (see Attachment 10): an increase of 1 or more grades in the semiquantitative valvular insufficiency, LV function, or right ventricular systolic pressure (normal, mild, moderate, severe based on local laboratory limits). After a normal baseline

ECHO, if a subsequent ECHO demonstrates an abnormality, then a repeat ECHO should be performed after 14 days. If results confirm the abnormality at repeat ECHO, then the patient will be discontinued from study treatment. If findings are normal, then the patient will continue treatment per study protocol. If patient has clinically significant cardiac findings at 30-day follow-up visit, ECHO will be repeated every 2 cycles (approximately every 2 months). If no clinically significant cardiac findings at the last cardiac assessment conducted within the last 30 days and patient has started another treatment, 30-day follow-up visit will not be performed. If no clinically significant cardiac findings at 30-day follow-up visit, 1 more ECHO will be performed after 2 months unless the patient is receiving another treatment. If the patient is receiving another form of treatment, further cardiac assessments will not be performed.

8.1.3.4. Cardiotoxicity Serum Markers as Determined by Central Laboratory

In addition to ECHO/Doppler, the following serum markers will be followed for increases:

- BNP: an increase in BNP above 3 times the baseline value and above the ULN which is sustained at 2 consecutive, scheduled blood draws
- troponin I: above the ULN (with testing confirmation at the central laboratory)
- cystatin C

See Attachment 1 for timing.

8.1.3.5. Pulse Oximetry

Patients will have assessments of oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) at screening and during the study (Attachment 1). If a patient shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnoea, cough, fever) consistent with possible pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnoea, cough, fever) consistent with possible pulmonary AEs, the patient should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in Attachment 11.

8.1.4. Safety Monitoring

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

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures. The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or CRS, and periodically review:

- trends in safety data
- laboratory analytes
- AEs
- If a study patient experiences ≥ Grade 3 amylase or lipase, clinical and laboratory monitoring should be initiated by the investigator.

- Except for patients with liver metastases or HCC, for any patient who experiences elevated ALT >3xULN and elevated total bilirubin >2xULN, clinical and laboratory monitoring should be initiated by the investigator.
- For patients with liver metastases or HCC entering the study with ALT between ULN and 5xULN, monitoring should be triggered at ALT ≥2x baseline.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

8.1.5. Complaint Handling

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

Complaints related to nivolumab or concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

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

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

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

8.2. Sample Collection and Testing

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

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

Attachment 3 lists the hepatic monitoring tests for treatment-emergent abnormalities.

Attachment 4 contains the PK, biomarker, and immunogenicity sampling schedules.

8.2.1. Samples for Study Qualification and Health Monitoring

Blood will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

New baseline tumour biopsies (defined as a biopsy specimen taken since completion of the prior systemic regimen [see Inclusion Criterion 4 in Section 6.1.1]) are required at screening for all patients other than glioblastoma patients. For glioblastoma patients at screening, either new biopsy or archived tumour tissue is required.

Due diligence should be used to ensure that tumour specimen (not normal adjacent or tumour margins) is provided. Pathology notes accompanying the tissue will also be requested.

Investigators must document their review of each laboratory safety report.

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

8.2.2. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

PK and pharmacodynamic samples will be collected as specified in Attachment 4.

8.2.2.1. Pharmacokinetic Samples

At the visits and times specified in the study schedule, blood samples will be collected to determine the plasma concentrations of galunisertib and serum concentrations of nivolumab. Serum nivolumab PK concentrations will be measured to derive the C_{min} and at specified visits. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and Lilly. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. A patient diary will collect the time of all galunisertib doses taken during the first 2 cycles. In addition, the diary will record emesis to verify successful digestion of galunisertib. Dose information (dose time and amount of dose) must be collected for the day of sampling and the 2 days prior to the sampling day. This information should be obtained from the patient at the visit for blood sampling.

These samples will be analysed at a laboratory designated by the sponsor. Concentrations of galunisertib and nivolumab will be assayed using validated methods.

The PK samples will be stored at a facility designated by the sponsor.

The residual samples collected for PK may be pooled and used for exploratory metabolism work as deemed appropriate.

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

8.2.3. Samples for Biomarker Research

To understand the relationship between cancer, genetics, and response to therapy, this study may analyse biomarkers relevant to galunisertib, nivolumab, immune cells/immune functioning, and the disease state.

The following samples are mandatory (required), except as indicated otherwise:

- blood samples for biomarker research (see Section 8.2.3.1)
- tumour tissue (newly biopsied or archived) (see Section 8.2.3.2)
- whole blood for DNA collection (pharmacogenetic analysis) (see Section 8.2.4)

Sample collection including blood (serum, plasma, whole blood) and tumour tissue samples will occur at specified time points as indicated in Attachment 1 and Attachment 4.

8.2.3.1. Blood Samples

Blood (serum, plasma, peripheral blood mononuclear cells, and whole blood) will be used for the analyses of biomarkers related to galunisertib, nivolumab, immune cells/immune functioning within the disease state, and cancer-related conditions. Potential pharmacodynamic and/or circulating markers may include, but are not limited to: disease specific markers (eg, AFP in HCC), factors important in disease (eg, viruses in HCC), gene expression, exosome isolation and associated assays, and/or circulating tumour DNA isolation and associated assays.

Samples may be stored for a maximum of 15 years following last patient visit for the trial.

8.2.3.2. Tumour Tissue

Collection of tumour tissue samples (either newly biopsied or archived) is mandatory (required) for participation in this study, as follows:

In addition to the screening requirement of collecting newly biopsied tumour tissue, other biopsies during the study are also required for patients with cancers other than glioblastoma and are optional for patients with glioblastoma.

For nonglioblastoma patients, 2 treatment biopsy groups will be randomly assigned by IWRS at the time of the patient is originally enrolled by IWRS. For the Phase 1b part of the study, the 2 treatment biopsy groups will be randomly assigned; for the Phase 2 part, the 2 treatment biopsy groups will be randomly assigned within each cohort. These on-treatment biopsies are also mandatory:

- Approximately 50% of patients will have their on-treatment biopsy on Cycle 1 Day 15 +3 days (post second nivolumab treatment). If a patient's second nivolumab dose is delayed, the biopsy will still occur on Cycle 1 Day 15 +3 days.
- Approximately 50% of patients will have their on-treatment biopsy on Cycle 2 Day 1 +3 days (post third nivolumab treatment). If a patient's third nivolumab dose is delayed, the biopsy will still occur on Cycle 2 Day 1 +3 days.

If a patient with glioblastoma undergoes a biopsy for medical reasons during the study, an optional biopsy should be collected at that time.

Formalin-fixed paraffin-embedded tumour tissue should be provided as a block or (minimum of 20) unstained slides. Due diligence should be used to make sure that tumour specimen (not a normal adjacent or a tumour margin sample) is provided. Pathology notes accompanying archival tissue will also be requested. Archived tumour tissue blocks will be returned to the site.

Any block from an on-study biopsy, or slides submitted or cut from the block at a central laboratory will not be returned. Any new tumour tissue acquired for a patient on study that is obtained for study purposes is sent to central laboratory for processing (see laboratory manual for further instructions). If the local pathology laboratory prefers to process tissue, then a tissue block or minimum of 20 slides should be sent to the central laboratory.

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8.2.4. Whole Blood for Pharmacogenetics

A blood sample will be collected for pharmacogenetic analysis where local regulations and ERBs allow. These samples **are not** being collected to create a biobank for conducting unspecified disease or population genetic research either now or in the future.

Samples may be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to the TGF-β pathway and immunomodulatory mechanisms to evaluate their association with observed response to study treatment.

Where local regulations and ERBs allow, these samples will be collected for pharmacogenetic research as discussed below and specified in the sampling schedule (Attachment 1).

Samples will be retained for a maximum of 15 years after the last patient visit, or as local regulations and ERBs allow, for the study at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses. Regardless of the technology used, genotyping data generated will be used only for the specific research scope described in this section.

8.2.5. Samples for Immunogenicity Research

Blood samples to determine the occurrence of specific antidrug antibodies (ADAs) to nivolumab will be collected as indicated in Attachment 1 and Attachment 4.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of nivolumab.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to nivolumab. The duration allows the sponsor to respond to regulatory requests related to nivolumab.

8.3. Efficacy Evaluations

The following efficacy measures will be determined:

- ORR and best overall response, time to response, duration of response, and PFS
  — using RECIST version 1.1 (Attachment 8) for patients with NSCLC, HCC, and tumours other than glioblastoma
  — using RANO (see Attachment 9) for patients with glioblastoma
- survival at 6, 12, and 18 months following the start of treatment
- OS determined from the date of first treatment until death due to any cause
- change in ECOG performance status

Efficacy measures will be assessed as noted in Attachment 1. Disease assessment with CT and/or MRI, as appropriate, will be performed at baseline and every 8 weeks until disease progression per RECIST version 1.1 or until patients withdraw from the study. For patients who are being treated beyond initial progression, these patients should remain on study treatment until the next assessment period. Patients who are treated beyond progression will be evaluated on an 8 (nonglioblastoma patients)- or 12 (glioblastoma patients)-week basis to determine whether they should continue on treatment. The use of MRI is mandatory to determine tumour response when using RANO criteria. Brain imaging should be performed as clinically indicated. At the sponsor's discretion, scans and measurements may be collected and reviewed by independent radiologists using RECIST version 1.1/RANO criteria at a later date, or at any time during the study.

To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response, using the sample method that was used at baseline. If a patient is discontinued from the study, repeat radiology assessments may be omitted if clear clinical signs of PD are present.

To facilitate this effort the radiologist reading the baseline imaging study is asked to provide in the baseline report or in a supplemental report a comparison of the size of target lesions and nodes reported in the baseline study with the size of these same lesions and nodes, if present, in the reference study. The report should also make note of the date of the preceding referenced study. Reference study data provided in the radiologist's report should be entered into the eCRF by the investigator's staff.

8.4. Procedure/Sampling Compliance

Every attempt will be made to enrol patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study.

The collection times of safety assessments, PK samples, pharmacodynamic samples, and efficacy measurements are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the eCRF.

The scheduled collection times may be modified by the sponsor based on analysis of the safety and PK information obtained during the study. Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

9. Data Management Methods

9.1. Data Quality Assurance

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

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

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

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

9.2. Data Capture Systems

9.2.1. Case Report Form

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

CRF data collected by the third-party organisation (TPO) will be encoded by the TPO and stored electronically in the TPO's database system. Validated data will subsequently be transferred to Lilly data warehouse, using standard Lilly file transfer processes. For any data handled by the sponsor internally, it will be managed by the sponsor and stored electronically in the sponsor's data warehouse.

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

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect

patient-reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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

9.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system and TPO's system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly generic labs system and TPO's system.

ECG data will be stored electronically in the central database system of Lilly's central review organisation. Data will subsequently be transferred from the central review organisation system to the Lilly generic labs system and TPO's system.

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

10. Data Analyses

10.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company. Additional details of statistical assessments beyond what is detailed in this section will be provided in a statistical analysis plan.

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 authorised by Lilly for publication.

Descriptive statistics (including mean, standard deviation, and range) will be derived where appropriate.

10.1.1. Sample Size

For the Phase 1b Cohorts 1 and 2 (and possibly 3) 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.

For the Phase 1b Cohorts 3 and 4 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 or 4 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

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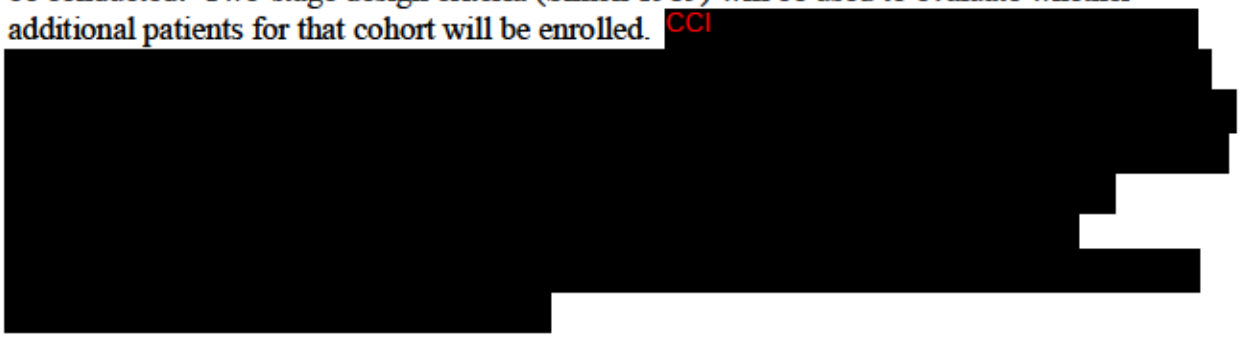
When the 25th patient from each cohort has completed at least 3 cycles, an interim analysis will be conducted. Two-stage design criteria (Simon 1989) will be used to evaluate whether additional patients for that cohort will be enrolled. CCI



10.2. Patient Disposition

All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for their discontinuation will be given. See Section 6.3.

Patient enrolment and disposition will be summarised and/or listed by cohort in Phase 1b and indication in Phase 2 for up to study completion (Section 6.2.4).

10.3. Patient Characteristics

Patient characteristics will include a summary and/or listing by cohort in Phase 1b and indication 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

Other patient characteristics will be summarised as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least 1 dose of either galunisertib or nivolumab will be evaluated for safety and toxicity. CTCAE terms (by entering the appropriate CTCAE code) and severity grades will be assigned by the investigator using CTCAE v4.03). Verbatim AE 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 system organ class 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 postbaseline and severity grades predose and postdose for preexisting conditions. Where CTCAE term is "Other," the matching MedDRA LLT will be used to determine treatment emergent.

Safety analyses may include, but are not limited to, summaries of the following:

- AEs, treatment-emergent AEs, and SAEs, including severity and possible relationship to study drug
- dose exposure and any adjustments
- laboratory values
- DLTs at each dose level for Phase 1b and DLT-equivalent AEs for Phase 2 for Cycles 1 and 2
- vital signs to include pulse oximetry readings and weight/change in weight from baseline
- ECGs
- ECHO readings and cardiotoxicity serum markers (BNP, troponin I, cystatin C)
- MRI/CT scans performed for detection of aneurysm formation of the ascending aorta and aortic arch

All recorded AEs, treatment-emergent AEs, and SAEs will be listed and tabulated by system organ class and CTCAE PT by cohort in Phase 1b and indication in Phase 2. Summaries of maximum grades of CTCAE PTs will be provided. The rate of DLTs will be summarised for each cohort in Phase 1b. Dose exposure and intensity will be calculated for both galunisertib and nivolumab for all patients and summarised by cohort in Phase 1b and by indication in Phase 2. Vital signs and clinical laboratory test results will be listed and summarised by indication. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECGs, collected as indicated in Attachment 1 and Attachment 4, and baseline and 8-week ECHO results will be evaluated by the investigator; abnormalities, if present, will be listed. Changes from baseline in ECG and ECHO parameters will be calculated and summarised at each visit. Safety data will be compared over time to assess change from baseline, during treatment, and follow-up.

10.5. Pharmacokinetic Analyses

PK 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.

Summary statistics will be tabulated for the PK parameters of galunisertib by dose and study day/week. Dose proportionality of galunisertib when coadministered with nivolumab during Phase 1b will be assessed based on a power model. Nivolumab C_{min} concentration in Phase 1b will be tabulated by summary statistics. In Phase 2, sparse PK data may also be pooled with other datasets for population PK analysis which will be part of a separate report. Exploratory

PK/pharmacodynamic analyses may be conducted to identify the exposure-response (biomarkers) relationship in this study.

Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Log-transformed C_{max} and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% CIs.

10.6. Biomarker Analyses

For details on biomarkers, see Section 8.2.3.

Pharmacodynamic data from all patients undergoing pharmacodynamic assessments will be analysed with appropriate standard nonlinear analytic software. Pharmacodynamic effects will be assessed by summary statistics, and investigated graphically to explore patterns of change over time, and how the patterns differ among dose levels or exposure. If there is a meaningful indication in the pattern over time, further analysis (eg, by linear mixed model) may be performed to characterise the relationship.

To identify and assess biomarkers for potential tailoring purpose, associations between baseline biomarker measures and clinical outcomes will be analysed using appropriate single-marker or multi-marker analysis approaches.

10.6.1. 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.

10.7. Efficacy

Disease response data will be compared over time to assess change from baseline, during treatment, and follow-up.

Individual best overall response, ORR, time to and duration of response, and PFS will be listed using RECIST version 1.1 or RANO criteria, as appropriate. Best overall response outcomes will be tabulated by disease type and dose. The ORR and PFS and the corresponding CI will be provided by tumour type, and by histology in the case of lung. The duration of response and PFS will be estimated by Kaplan-Meier methodology by tumour type, depending on data availability. PFS will be similarly estimated, based on Kaplan-Meier methodology. Presentations of efficacy will include patients in cohort expansion and patients in dose escalation matching those in cohort

expansion by tumour type and treatment. Individual changes in the tumour burden over time will be presented graphically within a tumour type. Landmark OS will also be assessed as part of the secondary efficacy analysis by Kaplan-Meier plots and medians for each tumour type.

For the NSCLC cohort, efficacy endpoints may be evaluated by adjusting for 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.

10.8. 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 2 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 interim analyses 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, 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.

The number of safety reviews in the Phase 2 part may be increased if data from the Phase 1b part suggest that increased monitoring would be appropriate; this will not require a protocol amendment.

11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. Informed Consent

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

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

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

11.2. Ethical Review

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

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

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

- the current IB and Package Insert, and updates during the course of the study
- ICF
- relevant curricula vitae

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
2) the International Conference on Harmonisation GCP Guideline [E6]
3) applicable laws and regulations

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

Some of the obligations of the sponsor will be assigned to a TPO.

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

11.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

11.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

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

11.3.3. Final Report Signature

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

The investigator with the greatest technical knowledge will serve as the final report coordinating investigator. If this investigator is unable to fulfil this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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

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Attachment 1. Protocol JBEF Study Schedule

Phase 1b Dose Escalation—Baseline/Screening Assessments

Relative Day Prior to Day 1 of Cycle 1[a]	≤28	≤14	≤7	Comments
Informed consent	X			Informed consent form signed (prior to performance of any protocol-specific tests/procedures)
Radiological tumour assessment	X			These scans can be performed locally. See Section 8.3 for details. Radiologic assessment should include appropriate body scan for tumour type.
Tumour biopsy	X			New tumour biopsy is required for patients with cancers other than glioblastoma. Archived tissue or new tumour biopsy is required for patients with glioblastoma. Biopsy should be taken only after study eligibility is confirmed.
Medical history		X		Including alcohol/tobacco use and other relevant habits assessments
Physical examination		X		
Vital signs		X		Including height (baseline only), temperature, blood pressure, pulse rate, respiration rate, and pulse oximetry reading
Weight and change in weight for previous 3 months		X		
ECOG performance status		X		
ECG		X		Single 12-lead ECGs. Must be done prior to initiation of therapy on Cycle 1 Day 1.
ECHO/Doppler imaging		X		Can be done up to 3 days before Cycle 1 Day 1; must be done prior to initiation of therapy on Day 1 and must meet Exclusion Criterion 21.
MRI/CT scan (of chest) with contrast		X		For safety: baseline and then every 6 months. NOTE: at screening, if a MRI or CT scan with contrast has been done to assess the status of the primary tumour, this scan may be used for safety screening if the scan has properly assessed the great vessels and the heart. Scans of other areas may be required for additional tumour assessment but not for safety.
Cardiac serum markers		X		BNP, troponin I, cystatin C
Haematology		X		See Attachment 2.
Serum chemistry		X		See Attachment 2.
HBV DNA sample		X		All patients: peripheral blood
HCV RNA sample		X		All patients: peripheral blood
HCC antiviral activity		X		HCC patients only: peripheral blood collection for qHBsAg
HBsAg, HCV, HIV serology		X		Required for all patients
PT/INR		X		
Tumour measurement (palpable or visible)		X		If appropriate for the tumour
CTCAE v 4.03 grading (preexisting conditions)		X		To be reported only after study eligibility is confirmed. See Section 8.1.2.4 for reporting expectations

Phase 1b Dose Escalation—Baseline/Screening Assessments

Relative Day Prior to Day 1 of Cycle 1[a]	≤28	≤14	≤7	Comments
Concomitant meds		X		
Blood biomarker samples		X		See Attachment 4.
Serum pregnancy test			X	
Whole blood for pharmacogenetics (DNA collection)	X			Must be collected prior to dosing on Cycle 1 Day 1

Abbreviations: BNP = brain natriuretic peptide; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiograph; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalised ratio; meds = medications; MRI = magnetic resonance imaging; PT = prothrombin time; qHBsAg = quantitative hepatitis B surface antigen; RNA = ribonucleic acid; SAEs = serious adverse events; v = version.

[a] With the exception of signing of the informed consent form (may be signed up to 3 days before initial visit), visit windows ±3 days.

During and Post-Study Assessments—Phase 1b Dose Escalation

	Cycle 1				Cycle 2				Cycle 3-n				Follow-Up (days)			Comments
Relative Week Within a Cycle	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**				
Relative Day Within a Cycle[a]	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Short-term**		**Long-term[c]**	
													30[b]	**100**		
Galunisertib	X				X				X							14 days on/14 days off. Orally once or twice daily, depending on cohort.
Nivolumab	X		X		X		X		X		X					Administered by IV at site
Dispensing patient diary	X				X											First 2 cycles only for recording galunisertib dosing and any emesis episodes
Collecting patient diary			X				X									
Physical exam	X				X				X				X	X		
Weight	X				X				X				X	X		
Vital signs	X		X		X		X		X		X		X	X		Temperature, pulse rate, RR, BP, pulse oximetry
Serum pregnancy test	X				X				X							Predose
Cardiotoxicity serum markers	X				X				X				X	X	X	Troponin I, BNP, and cystatin C on Day 1 of every cycle
12-lead ECG					X	D 14 only			X*							Collect predose (if applicable): See Attachment 4 for timing of PK time-matched ECGs * Starting at Cycle 3 Day 1, ECGs will be performed at every odd-numbered cycle thereafter (Cycles 5, 7, 9, etc)
ECHO								X				*	X			Performed every other cycle within 5 days of when next cycle begins, beginning at the end of Cycle 2 (eg, Cycle 2 Days 23-28=*). Must be done predose. After a normal baseline ECHO, if a subsequent ECHO demonstrates an abnormality, then a repeat ECHO should be performed after 14 days. If results confirm the abnormality at repeat ECHO, then the patient will be discontinued from study treatment. If findings are normal, then the patient will continue treatment per study protocol. If patient has clinically significant cardiac findings at 30-day FUP Visit, ECHO will be repeated every 2 cycles (approximately every 2 months). If no clinically significant cardiac findings at the last cardiac assessment conducted within the last 30 days and patient has started another treatment, 30-day FUP Visit will not be performed. If no clinically significant cardiac findings at 30-day FUP Visit, 1 more ECHO will be performed after 2 months unless the patient is receiving another treatment. If the patient is receiving another form of treatment, further cardiac assessments will not be performed.

During and Post-Study Assessments—Phase 1b Dose Escalation

	Cycle 1				Cycle 2				Cycle 3-n				Follow-Up (days)			Comments
Relative Week Within a Cycle	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**				
Relative Day Within a Cycle[a]	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Short-term**		**Long-term[c]**	
													30[b]	**100**		
MRI/CT scan (of chest) with contrast												**				Every 6 months during treatment (eg, just prior to beginning Cycle 6=**). If there were no clinically significant findings at the last assessment conducted within the last 30 days and the patient has started another treatment, 30-Day FUP Visit MRI or CT scan with contrast will not be performed.
Haematology	X		X		X		X		X		X		X	X		See Attachment 2.
Serum chemistry	X	X*	X	X*	X	X*	X	X*	X		X		X	X		See Attachment 2. *Only performed if the last assessment prior to this assessment had an elevated value for liver function compared to baseline. See Section 8.1.4.
HBV DNA	X		X		X		X		X							All patients to be tested. Peripheral blood. Predose.
HCV RNA	X		X		X		X		X							All patients to be tested. Peripheral blood. Predose.
HCC antiviral activity									X							HCC patients only. Peripheral blood collection for assessment of qHBsAg. Predose Day 1 at every other cycle (Cycles, 3, 5, n).
CTCAE v 4.03 Grading	X		X		X		X		X		X		X	X	X	Refer to Section 8.1.2.4 for reporting guidelines.
Concomitant meds	X		X		X		X		X		X		X	X	X	Throughout study as needed.
ECOG performance status	X				X				X				X	X		
PK sampling	X	D 14	X		X	D14	X		C4 only							See Attachment 4 for timing.
Tumour measurement (palpable or visible)								X				*X*	X			To occur on or between Days 22 to 28 of every other cycle. At long-term FUP, every 12 weeks as appropriate.
Radiological tumour assessment								X				*X*	X			MRI/CT scan. To occur on or between Days 22 to 28 of every other cycle. At short-term FUP, every 8 weeks as appropriate.
Radiological tumour assessment for pseudoprogression																For patients who are being treated beyond initial progression, these patients should remain on study treatment until the next assessment period. Patients who are treated beyond progression will be evaluated on an 8- (nonglioblastoma) or 12- (glioblastoma) week basis to determine whether they should continue on treatment.
Survival													X			At FUP, at least every 12 weeks±7 days until death.
Immunogenicity	X	D 14	X		X				*					X		Window of ±7 days for 100-day FUP. *Collected at Week 13 and every 16 weeks thereafter (ie, Week 29, 45, etc.)

During and Post-Study Assessments—Phase 1b Dose Escalation

		Cycle 1				Cycle 2				Cycle 3-n				Follow-Up (days)			Comments
Relative Week Within a Cycle		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**				
Relative Day Within a Cycle[a]		**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Short-term**		**Long-term[c]**	
														30[b]	**100**		
Bio-marker samples	Tumour biopsy			1/2		1/2											Required for patients with cancers other than glioblastoma, with half of patients randomly assign to biopsies on either Cycle 1 D15 or Cycle 2 D1 post nivolumab dosing. If a patient with glioblastoma undergoes a biopsy during the study for other medical reasons, tissue should be collected at that time. Note glioblastoma patients are in Phase 1b only. For glioblastoma patients only (Phase 1b), if tumour biopsy is performed to distinguish between radiologic progression and pseudoprogression (not required), see Section 7.2.5 for instructions for proper handling of specimen.
	Blood bio-marker samples	D1 and D2	X	X		X		X		C4 only				X			See Attachment 4 for sampling times.

Abbreviations: BNP = brain natriuretic peptide; BP = blood pressure; BSA = body surface area; C = cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiography; ECOG = Eastern Cooperative Oncology Group; FUP = Follow-Up Period; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = heart rate; hrs = hours; IV = intravenous; MRI = magnetic resonance imaging; n = cycle number; PK = pharmacokinetic; qHBsAg = quantitative hepatitis B surface antigen; RNA = ribonucleic acid; RR= respiration rate; SAEs = serious adverse events; v = version.

a Visit windows ±3 days.

b Sometimes referred to as the end of treatment visit.

c 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 (approximately every 12 weeks ± 7 days the patient will be contacted).

Phase 2 Dose Expansion—Baseline/Screening Assessments

Relative Day Prior to Day 1 of Cycle 1[a]	≤28	≤14	≤7	Comments
Informed consent	X			Informed consent form signed (prior to performance of any protocol-specific tests/procedures)
Radiological tumour assessment	X			These scans can be performed locally and transmitted to a central imaging vendor. See Section 8.3 for details. Radiologic assessment should include appropriate body scan for tumour type.
Tumour biopsy	X			New tumour biopsy is required. Biopsy should be taken only after study eligibility is confirmed.
Medical history		X		Including alcohol/tobacco use and other relevant habits assessments
Physical exam		X		
Vital signs		X		Including height (baseline only), temperature, blood pressure, pulse rate, respiration rate, and pulse oximetry reading
Weight and change in weight for previous 3 months		X		
ECOG performance status		X		
ECG		X		Single 12-lead ECG. Must be done prior to initiation of therapy on Cycle 1 Day 1.
ECHO/Doppler imaging		X		Can be done up to 3 days before Cycle 1 Day 1; must be done prior to initiation of therapy on Day 1 and must meet Exclusion Criterion 21.
MRI/CT scan (of chest) with contrast		X		For safety: baseline and then every 6 months. NOTE: At screening, if a MRI or CT scan with contrast has been done to assess the status of the primary tumour; this scan may be used for safety screening if the scan has properly assessed the great vessels and the heart. Scans of other areas may be required for additional tumour assessment but not for safety.
Cardiac serum markers		X		BNP, troponin I, cystatin c
Haematology		X		See Attachment 2.
Serum chemistry		X		See Attachment 2.
HBV DNA sample		X		All patients: peripheral blood
HCV RNA sample		X		All patients: peripheral blood
HCC antiviral activity		X		HCC patients only: peripheral blood collection for qHBsAg
HBsAg, HCV, HIV serology		X		Required for all patients
PT/INR		X		
Tumour measurement (palpable or visible)		X		
CTCAE v 4.03 grading (preexisting conditions)		X		To be reported only after study eligibility is confirmed. See Section 8.1.2.4 for reporting expectations.
Concomitant meds		X		

Relative Day Prior to Day 1 of Cycle 1[a]	≤28	≤14	≤7	Comments
Blood biomarker samples		X		See Attachment 4.
Serum pregnancy test			X	
Whole blood for pharmacogenetics (DNA collection)	X			Must be collected prior to dosing on Cycle 1 Day 1

Abbreviations: BNP = brain natriuretic peptide; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiograph; ECOG = Eastern Cooperative Oncology Group; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalised ratio; meds = medications; MRI = magnetic resonance imaging; qHBsAg = quantitative hepatitis B surface antigen; PT = prothrombin time; RNA = ribonucleic acid; SAEs = serious adverse events; v = version.

[a] With the exception of signing of the informed consent form (may be signed up to 3 days before initial visit), visit windows ±3 days.

During and Post-Study Assessments—Phase 2 Dose Expansion

	Cycle 1				Cycle 2				Cycle 3-n				Follow-Up (days)			Comments
Relative Week Within a Cycle	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**				
Relative Day Within a Cycle[a]	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Short-term**		**Long-term[c]**	
													30[b]	**100**		
Galunisertib	X				X				X							14 days on/14 days off. Orally once or twice daily depending on dosing regimen from Phase 1b
Nivolumab	X		X		X		X		X		X					Administered by IV at site
Dispensing patient diary	X				X											First 2 cycles only for recording galunisertib dosing and any emesis episodes
Collecting patient diary			X				X									
Physical examination	X				X				X				X	X		
Weight	X				X				X				X	X		
Vital signs	X		X		X		X		X		X		X	X		Temperature, pulse rate, RR, BP, pulse oximetry
Serum pregnancy test	X				X				X							Predose
Cardiotoxicity serum markers	X				X				X				X	X	X	Troponin I, BNP, and cystatin C on Day 1 of every cycle
12-lead ECG					X	D 14 only			X*							Collect predose (if applicable): See Attachment 4 for timing of PK time-matched ECGs. * Starting at Cycle 3 Day 1, ECGs will be performed at every odd-numbered cycle thereafter (Cycles 5, 7, 9, etc)
ECHO								X				*	X			Performed every other cycle within 5 days of when next cycle begins, beginning at the end of Cycle 2 (eg, Cycle 2 Days 23-28=*). Must be done predose. After a normal baseline ECHO, if a subsequent ECHO demonstrates an abnormality, then a repeat ECHO should be performed after 14 days. If results confirm the abnormality at repeat ECHO, then the patient will be discontinued from study treatment. If findings are normal, then the patient will continue treatment per study protocol. If patient has clinically significant cardiac findings at 30-day FUP Visit, ECHO will be repeated every 2 cycles (approximately every 2 months). If no clinically significant cardiac findings at the last cardiac assessment conducted within the last 30 days and patient has started another treatment, 30-day FUP Visit will not be performed. If no clinically significant cardiac findings at 30-day FUP Visit, 1 more ECHO will be performed after 2 months unless the patient is receiving another treatment. If the patient is receiving another form of treatment, further cardiac assessments will not be performed.

During and Post-Study Assessments—Phase 2 Dose Expansion

	Cycle 1				Cycle 2				Cycle 3-n				Follow-Up (days)			Comments
Relative Week Within a Cycle	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**				
Relative Day Within a Cycle[a]	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Short-term**		**Long-term[c]**	
													30[b]	**100**		
MRI/CT scan with contrast												**				Every 6 months during treatment (eg, just prior to beginning Cycle 6=**). If there were no clinically significant findings at the last assessment conducted within the last 30 days and the patient has started another treatment, 30-Day FUP Visit MRI or CT scan with contrast will not be performed.
Haematology	X		X		X		X		X		X		X	X		See Attachment 2.
Serum chemistry	X		X		X		X		X		X		X	X		See Attachment 2.
HBV DNA	X		X		X		X		X							All patients to be tested. Peripheral blood. Predose
HCV RNA	X		X		X		X		X							All patients to be tested. Peripheral blood. Predose
HCC antiviral activity									X							HCC patients only: peripheral blood collection for assessment of qHBsAg. Predose Day 1 at every other cycle (Cycles, 3, 5, n)
CTCAE v 4.03 grading	X		X		X		X		X		X		X	X	X	Refer to Section 8.1.2.4 for reporting guidelines.
Concomitant meds	X		X		X		X		X		X		X	X	X	Throughout study as needed
ECOG performance Status	X				X				X				X	X		
PK sampling	X	D 14	X		X	D 14	X		C4 only							See Attachment 4 for timing.
Tumour measurement (palpable or visible)								X				*X*	X			To occur on or between Days 22 to 28 of every other cycle. At long-term FUP, every 12 weeks as appropriate.
Radiological tumour assessment								X				*X*	X			MRI/CT scan. These scans can be performed locally and transmitted to a central imaging vendor. To occur on or between Days 22 to 28 of every other cycle. At short-term FUP, every 8 weeks as appropriate.
Radiological tumour assessment for treatment past initial progression																MRI/CT scan. These scans can be performed locally and transmitted to a central imaging vendor. For patients who are being treated beyond initial progression, these patients should remain on study treatment until the next assessment period. Patients who are treated beyond progression will be evaluated on an 8-week basis to determine if they should continue on treatment.
Survival													X			At FUP, at least every 12 weeks until death.
Immunogenicity	X	D 14	X		X				*					X		Window of ±7 days for 100-day FUP. * Collected at Week 13 and every 16 weeks thereafter (ie, Week 29, 45, etc.)

During and Post-Study Assessments—Phase 2 Dose Expansion

		Cycle 1				Cycle 2				Cycle 3-n				Follow-Up (days)			Comments
Relative Week Within a Cycle		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**				
Relative Day Within a Cycle[a]		**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Short-term**		**Long-term[c]**	
														30[b]	**100**		
Bio-marker samples	Tumour biopsy			1/2		1/2											Required, with half of patients randomly assign to biopsies on either Cycle 1 D15 or Cycle 2 Day 1 post nivolumab dosing.
	Blood Bio-marker sample	D1 & D2	X	X		X		X		C4 only				X			See Attachment 4 for sampling times.

Abbreviations: BNP = brain natriuretic peptide; BP = blood pressure; C = cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECHO = echocardiography; ECOG = Eastern Cooperative Oncology Group; FUP = Follow-Up Period; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = heart rate; hrs = hours; n = cycle number; PK = pharmacokinetic; qHBsAg = quantitative hepatitis B surface antigen; RNA = ribonucleic acid; RR= respiration rate; SAEs = serious adverse events; v = version.

a Visit windows ±3 days.

b Sometimes referred to as the end of treatment visit.

c 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 (approximately every 12 weeks ± 7 days the patient will be contacted).

Attachment 2. Protocol JBEF Clinical Laboratory Tests

Clinical Laboratory Tests

Haematology[a]	**Clinical Chemistry**[a,b]
Haemoglobin	**Serum Concentrations of:**
Haematocrit	Sodium
	Magnesium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase
Monocytes	Aspartate aminotransferase
	Gamma-glutamyl transpeptidase
Eosinophils	Blood urea nitrogen
Basophils	Creatinine
Platelets	Uric acid
	Calcium
	Glucose, random
PT/INR[a]	Albumin
	Total protein
	Chloride
	Bicarbonate
	Amylase
	Lipase
	Thyroid-stimulating hormone[a,b,c]
	Reflex to fT3/fT4[a,b,c]
	Troponin I[b]
	BNP[b]
	Cystatin C[b]
	HBsAg[a,b]
	qHBsAg[d]
	HBV DNA[d]
	Hep C Ab[a,b]
	HCV RNA[d]
	HIV[b]
	Serum Pregnancy Test (females only)[a]

Abbreviations: aPTT = activated partial thromboplastin time, BNP = brain natriuretic peptide; DNA = deoxyribonucleic acid; fT3 = free triiodothyronine; fT4 = free thyroxine; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; Hep C Ab = hepatitis C antibody; HIV = human immunodeficiency virus; PT/INR = international normalised ratio of prothrombin time; qHBsAg = quantitative hepatitis B surface antigen; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

[a] Assayed by local laboratory.

[b] Assayed by Lilly-designated laboratory.

Clinical Laboratory Tests

[c] If thyroid-stimulating hormone test is abnormal, reflex to fT3/fT4 test must be performed.

[d] Baseline tests (screening) will be assayed by a local and a Lilly-designated laboratory. Testing during the trial will be performed by a Lilly-designated laboratory.

Attachment 3. Protocol JBEF Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly CRP.

Hepatic Monitoring Tests

Hepatic haematology[a]	**Haptoglobin[a]**
Haemoglobin	
Haematocrit	**Hepatic coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Antinuclear antibody[a]**
AST	
GGT	**Anti–smooth muscle antibody[a]**
CPK	

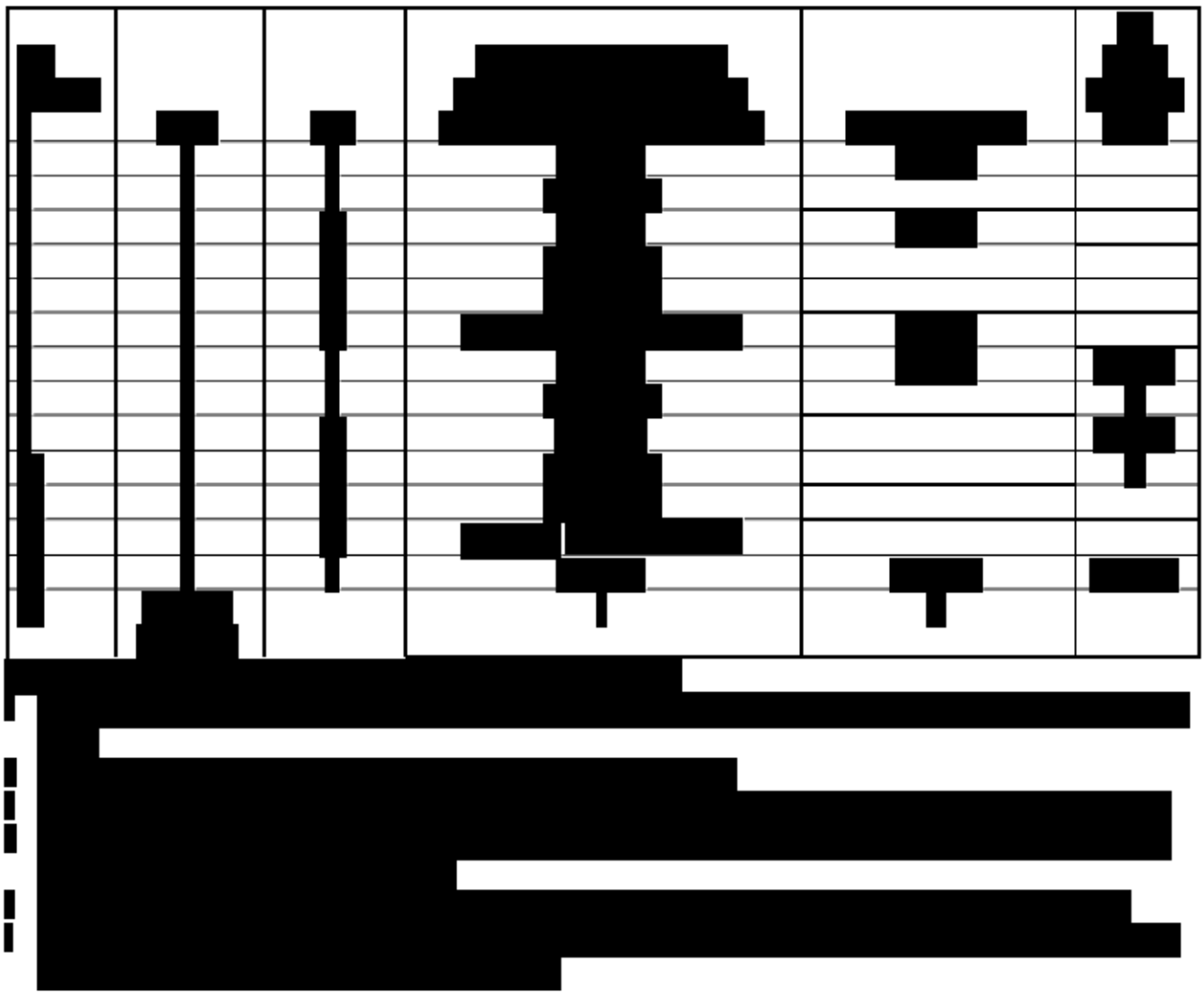
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated and local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JBEF Pharmacokinetic, Biomarker, PK Time-Matched ECG, and Immunogenicity Sampling Schedule

CCI



Blood Biomarker Sampling Schedule

Pharmacodynamic Sample #	Cycle	Day	Sampling Windows for Blood Collection
1	1	1	Predose
2	1	1	2 hours postdose ± 10 minutes
3	1	2	Predose
4	1	8	Predose
5	1	15	Predose
6	2	1	Predose
7	2	15	Predose
8	4	1	Predose
9	Follow-Up		

Abbreviation: V = visit.

Attachment 5. Protocol JBEF Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When contacting Lilly to report an SAE, please have the following information available:

Patient Demographics

- patient identification (number), sex, date of birth, origin, height, and weight

Study Identification

- full trial protocol number, investigator's name, investigator's number

Study Drug

- drug code or drug name, unit dose, total daily dose, frequency, route, start dose, cycle details, start date and last dose date (if applicable)

Adverse Event

- description, date of onset, severity, treatment (including hospitalisation), action taken with respect to study drug, clinical significance, test and procedure results (if applicable)

Relationship to Study Drug & Protocol Procedures

Concomitant Drug Therapy

- indication, total daily dose, duration of treatment, start date, action taken

In Case of Death

- cause, autopsy finding (if available), date, relationship to study drug and protocol procedures

Attachment 6. Protocol JBEF ECOG Performance Status

ECOG Performance Status

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

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
Source: Oken et al. 1982.

Attachment 7. Protocol JBEF Creatinine Clearance Formula

Note: This formula is to be used for calculating CrCl from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ (\mu mol/L)}$$

Abbreviation: CrCl = creatinine clearance.

[a] Age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

-OR-

$$GFR(mL/min/1.73m^2) = 170 \times [PCr]^{-0.999} \times [age]^{-0.176}$$

$$\times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}]$$

$$\times [SUN]^{-0.17} \times [Alb]^{+0.318}$$

PCr = plasma creatinine, mg/dL; SUN = serum urea nitrogen, mg/dL; Alb = serum albumin, g/dL.

Source: Murray and Ratain 2003.

Attachment 8. Protocol JBEF [redacted]

[redacted]


CCI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Attachment 9. Protocol JBEF [redacted]

CCI

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- CCI [redacted]
- [redacted]
- [redacted]
- [redacted] CCI [redacted]

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CCI

[redacted]

Table 1: CCI

[redacted]

Table 2: CCI

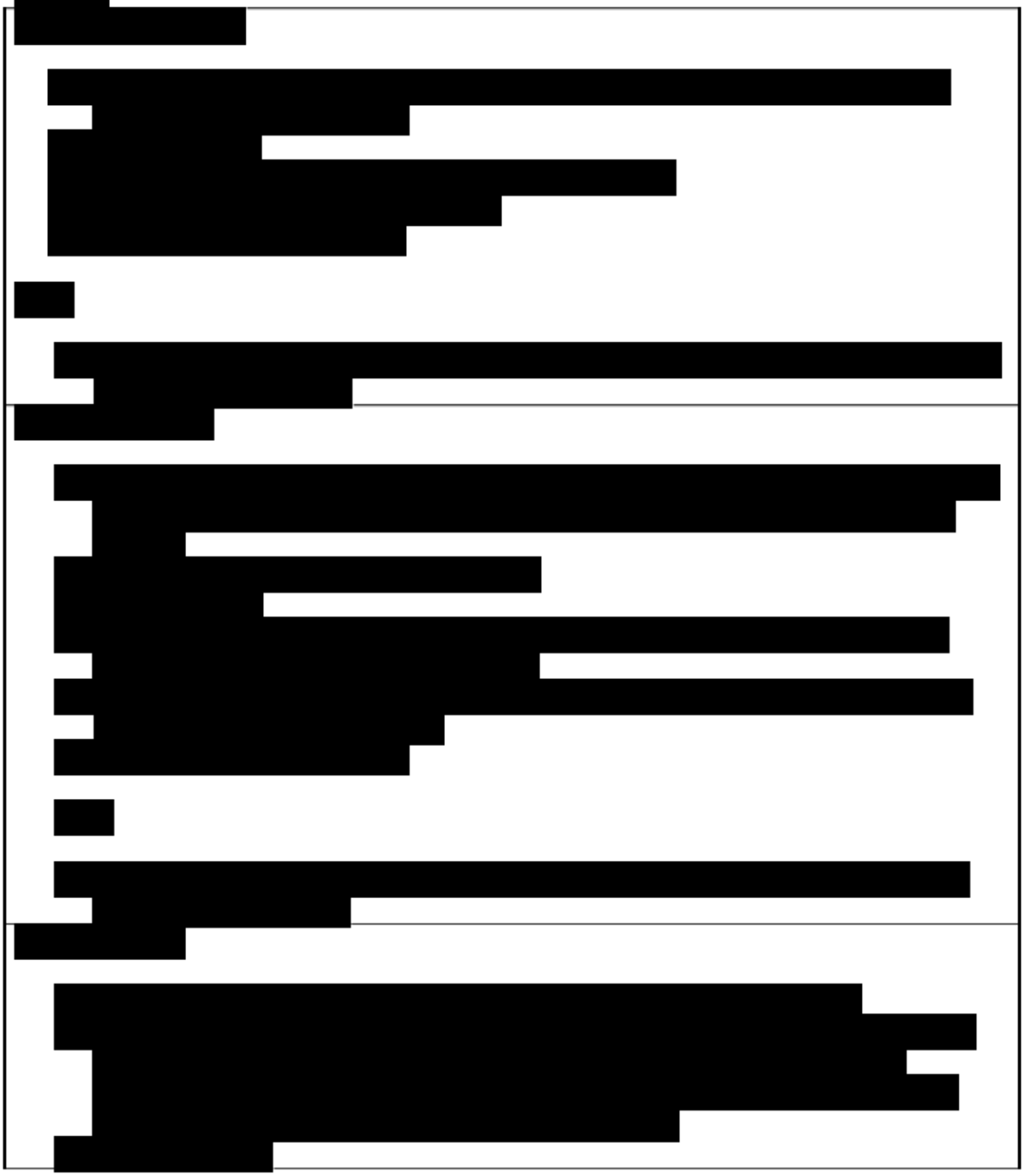


Table 3: CCI

Reference

CCI [redacted]

Attachment 10. Protocol JBEF Echocardiographic Guidelines

Echocardiography

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

In addition to qualitative assessment of valvular regurgitation when or if detected (trace, mild, moderate, or severe according to Singh et al. [1999] and Zoghbi et al. [2003] [see below]) and qualitative/quantitative assessment of valvular stenosis when or if detected (mild, moderate, or severe, using mean and peak pressure gradient in mm Hg and orifice area in cm^2 as applicable), other ECHO parameters to be serially quantified are: LV cavity size (diameters, volumes), LV ejection fraction, LV mass and mass index, diastolic function based on mitral flow velocity, mitral deceleration time, pulmonary venous flow pattern, tissue Doppler, extrapolation of LV end-diastolic pressure by E/Em, left atrial volume index, and extrapolation of pulmonary artery systolic pressure when obtainable.

An ECHO with no clinically significant abnormalities is one defined specifically as: the LV (Schiller et al. 1999) internal dimension in diastole should be ≤2.8 cm/m^2, the left atrial (Tsang et al. 2002) end-systolic volume should be ≤36 mL/M^2, the LV ejection fraction (Oh et al. 2006) should be ≥50% without regional wall motion abnormalities, 2-dimensional ECHO-derived LV mass index[1] should be ≤115 g/M^2 for males and ≤99 g/M^2 for females, the pulmonary artery pressure should be normal (tricuspid regurgitation jet velocity ≤2.5 m/s and/or pulmonary valve flow acceleration time ≥120 ms), the LV diastolic function (Khouri et al. 2004) should be normal (screening: mitral deceleration time ≥150 ms and ≤250 ms, mitral E/A ratio ≥0.75 and ≤1.5, mitral E velocity divided by Doppler mitral annular velocity [E/Em] <15), and there should be no evidence for pericardial or congenital or heart disease. In addition, there should be no evidence for more than mild mitral or aortic stenosis (mitral valve area should be >2.0 cm^2 and aortic valve area should be >1.5 cm^2) and no evidence of more than mild mitral or aortic regurgitation (Singh et al. 1999; Zoghbi et al. 2003). Patients enrolled in the study may have evidence for tricuspid (trace or mild), pulmonary, mitral (trace or mild), or aortic (trace or mild) regurgitation by Doppler techniques (Singh et al. 1999; Zoghbi et al. 2003).

References

Khouri SJ, Maly GT, Suh DD, Walsh TE. A practical approach to the echocardiographic evaluation of diastolic function. *J Am Soc Echocardiogr.* 2004;17(3):290-297.

Oh JK, Seward JB, Tajik AJ. The echo manual. 3rd ed. Philadelphia: Lippincott, Williams Wilkins; 2006.

Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reicheck N, Sahn D, Schnittger I, Silverman NH, Tajik AJ. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2(5):358-367.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol.* 1999;83(6):897-902.

Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol.* 2002;90(12):1284-1289.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16(7):777-802.

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

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

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol.* 1999;83(6):897-902.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16(7):777-802.

References

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

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

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

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

Sorensen AG, Batchelor TT, et al. Response criteria for glioma. *Nat Clin Pract Oncol.* 2008.

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

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

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

Attachment 11. Protocol JBEF Management Algorithms for Immuno-Oncology Agents

These general guidelines constitute guidance to the investigator and may be supplemented by discussions with the Lilly CRP. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Noninflammatory aetiologies should be considered and appropriately treated.

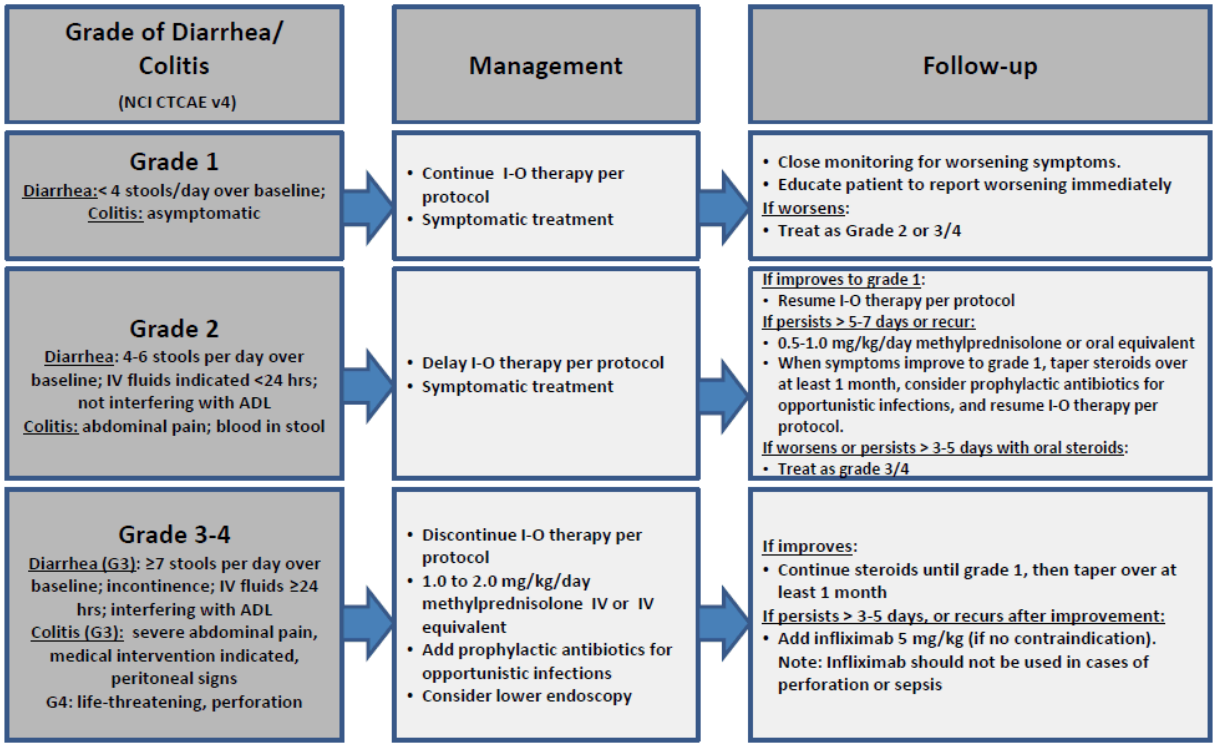
Corticosteroids are a primary therapy for immuno-oncology drug-related AEs. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related AEs covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

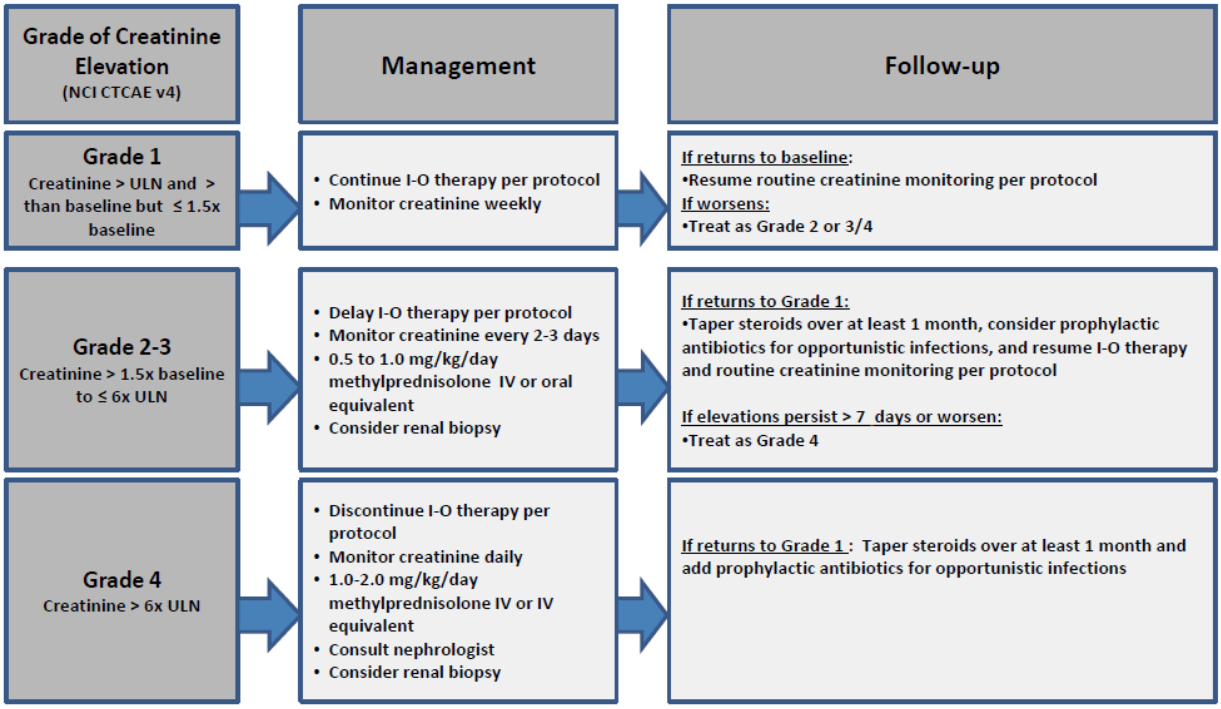
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

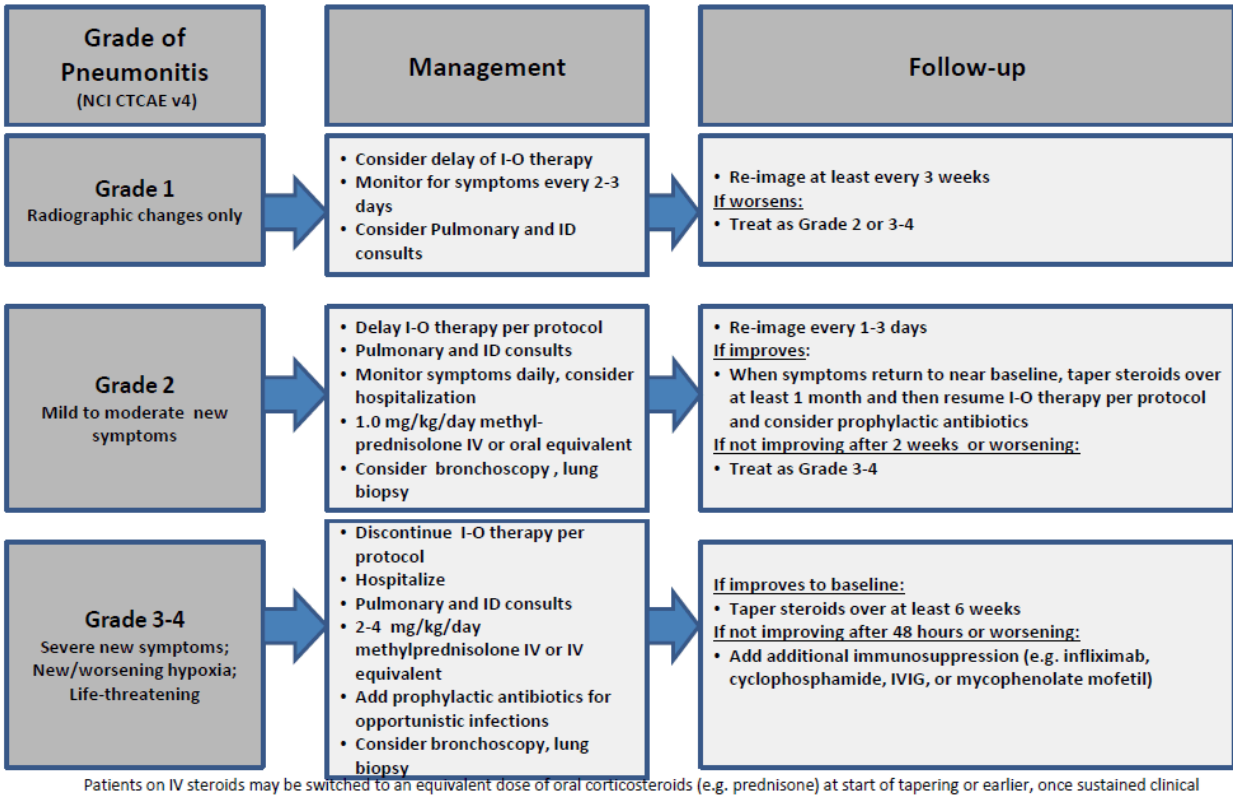
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

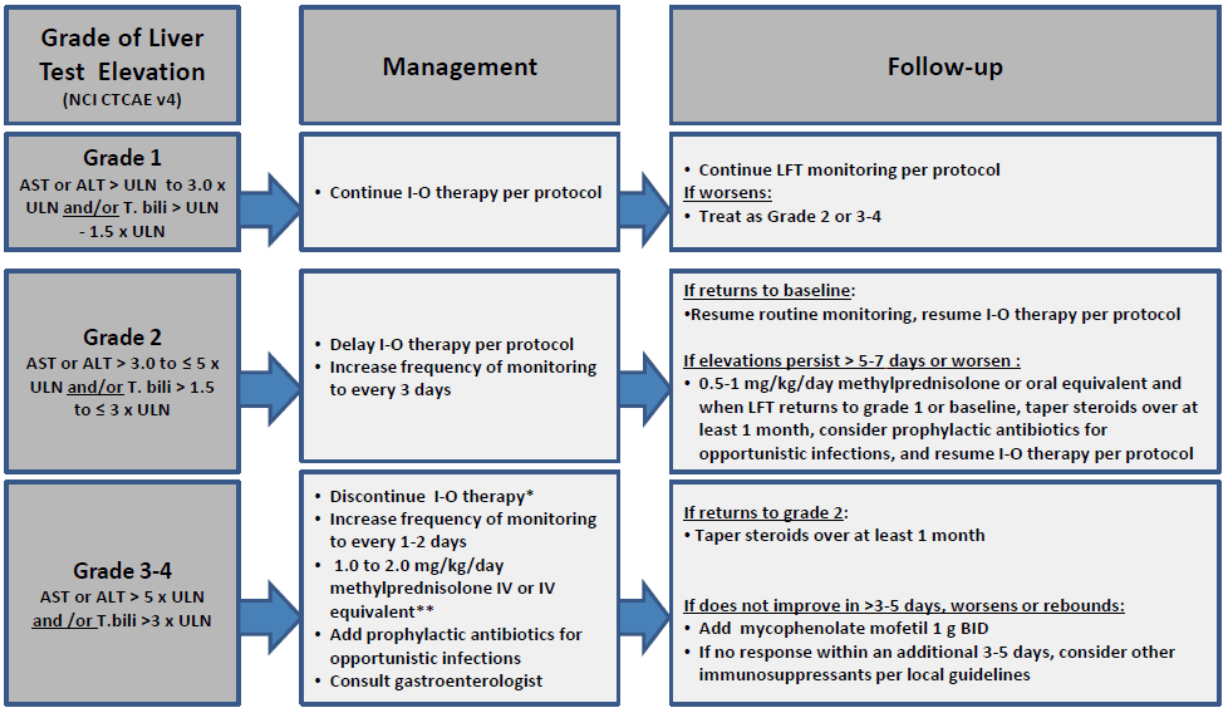
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



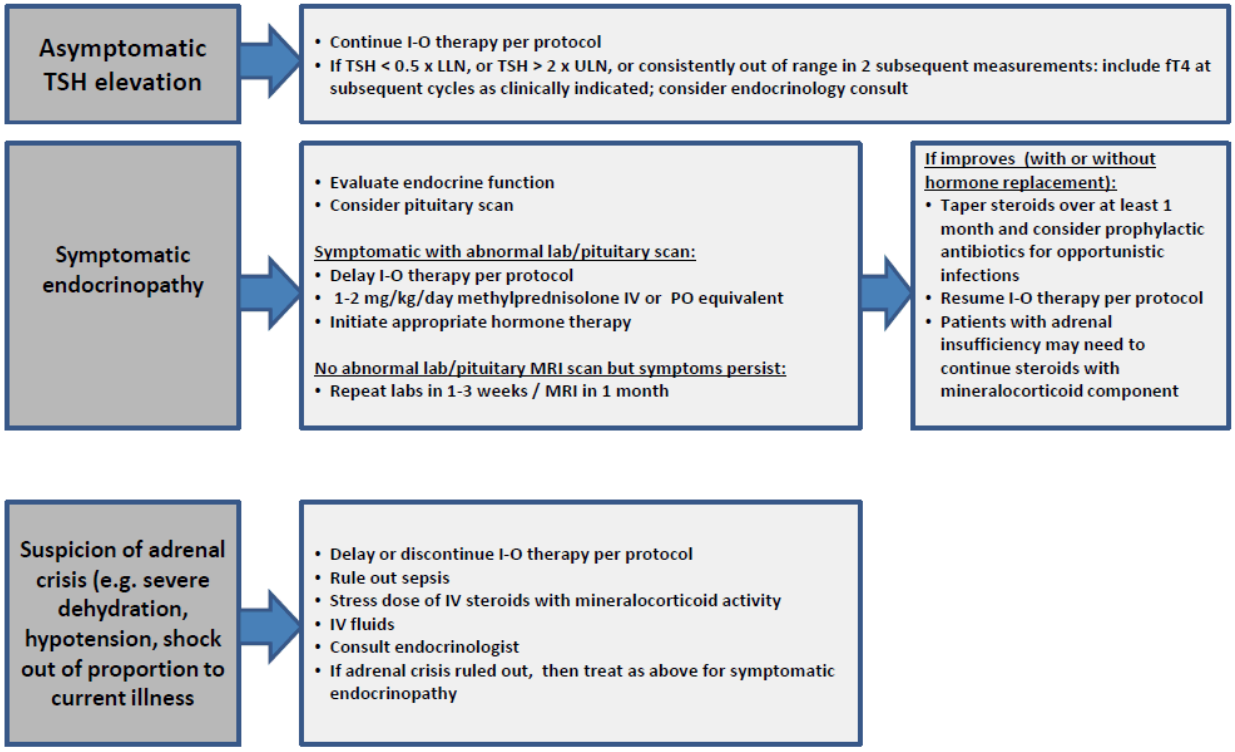
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

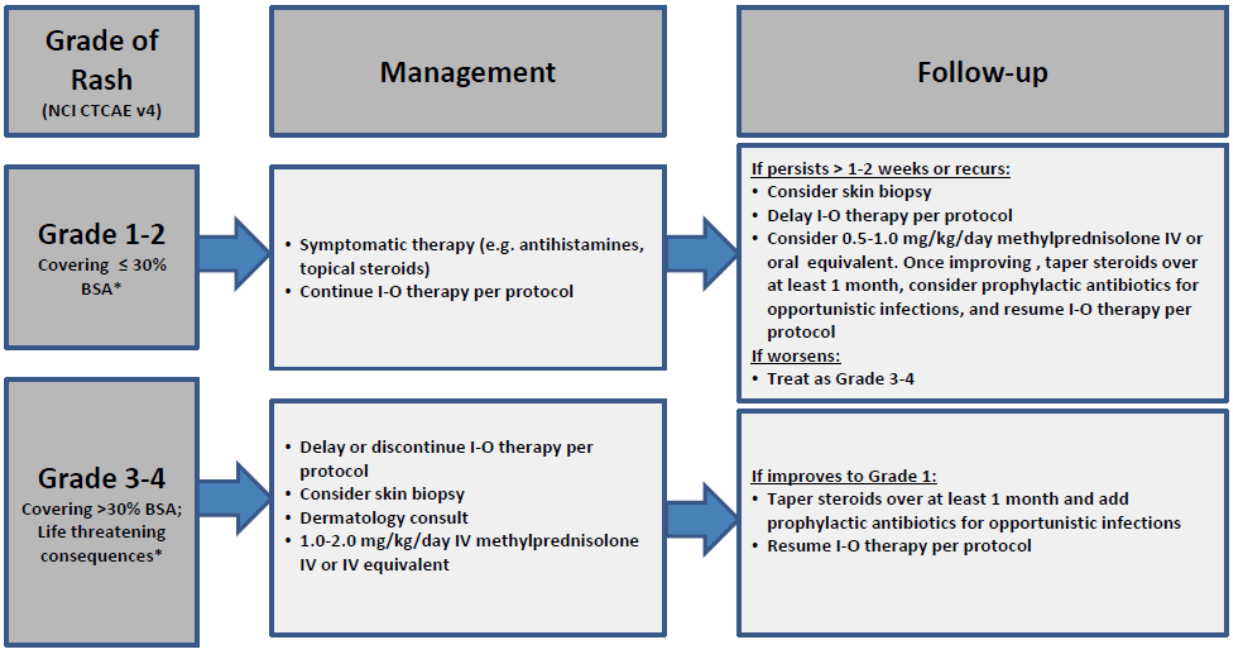
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Attachment 12. Protocol JBEF CYP3A4 Modulators

CYP3A4 Inducers	Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
aminoglutethimide	clarithromycin	amiodarone
bosentan	chloramphenicol	amprenavir
carbamazepine	cobicistat	aprepitant
efavirenz (in liver only)	conivaptan	atazanavir
fosphenytoin	Cremophor EL	cimetidine
nafcillin	cyclosporine	ciprofloxacin
nevirapine	delavirdine	clotrimazole
oxcarbazepine	diclofenac	darunavir
pentobarbital	diltiazem	darunavir and ritonavir
phenobarbital	elvitegravir and ritonavir	desipramine
phenytoin	enoxacin	doxycycline
primidone	erythromycin	dronedarone
rifabutin	fosamprenavir	efavirenz
rifampin	grapefruit juice	erythromycin
rifapentine	indinavir	FK1706
St. John's wort	indinavir and ritonavir	fluconazole
	itraconazole	fluvoxamine
	ketoconazole	haloperidol
	lopinavir and ritonavir	imatinib
	mibefradil	metronidazole
	miconazole	norfloxacin
	nefazodone	protease inhibitors
	nelfinavir	quinidine
	nicardipine	*Schisandra sphenanthera* extract
	posaconazole	sertraline
	quinidine	tetracycline
	ritonavir	tofisopam
	saquinavir	verapamil
	telithromycin	
	theophylline	
	troleandomycin	
	voriconazole	

Attachment 13. Protocol JBEF Protocol Amendment H9H-MC-JBEF(c) Summary 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)

Overview

Protocol H9H-MC-JBEF(b) has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

H9H-MC-JBEF protocol (b) was amended for the following reasons:

- Phase 2 portion of study: to remove the glioblastoma cohort and update the protocol text to reflect this change. Results from 2 recently reported galunisertib trials, Studies H9H-MC-JBAI and H9H-MC-JBAL, have indicated a lack of sufficient efficacy with galunisertib in glioblastoma.
- To clarify the rationale for the changes to the ECHOs in Attachment 1 made in protocol amendment (b) (see Section 5.5 bullet 6): the requirement for ECHO (echocardiography) at the 30-day follow-up visit was restored into the protocol as this requirement had been inadvertently removed during Amendment A; for the Phase 2 portion, clarification was provided that imaging is to be collected centrally.
- Attachment 2: to add hepatitis B surface antigen testing, which was inadvertently excluded previously; to clarify that all hepatitis testing at baseline will be assayed by a local and a Lilly-designated laboratory and during the trial will be performed by a Lilly-designated laboratory; and to clarify footnotes.
- Attachment 4: to add a ±10-minute window to the blood biomarker collection on Cycle 1 Day 1.

Minor editing was made but not necessarily listed below.

A detailed list of text changes is below.

Revised Protocol Sections

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

Title page

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 ~~, or Glioblastoma~~ (Phase 2)

…

This is a multicentre, nonrandomised, open-label, dose-escalation Phase 1b study of galunisertib combined with nivolumab in patients with advanced refractory solid tumours followed by a 3-cohort expansion Phase 2 study in patients with refractory or recurrent non–small cell lung cancer or hepatocellular carcinoma~~, or glioblastoma~~.

…

Protocol Electronically Signed and Approved by Lilly: 17 April 2015
Amendment (a) Electronically Signed and Approved by Lilly: 24 July 2015
Amendment (b) Electronically Signed and Approved by Lilly: 30 August 2016
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below
~~Approval Date: 30-Aug-2016 GMT~~

Synopsis

…

This study is a Phase 1b/2 open-label study that will be conducted in 2 parts. The Phase 1b part of this study will consist of an open-label, dose-escalation assessment of the safety and tolerability of galunisertib administered at 50 mg daily (QD), 50 mg twice daily (BID), 80 mg BID, or 150 mg BID in combination with nivolumab 3 mg/kg in patients with advanced refractory solid tumours. The Phase 2 part of this study will be disease restricted and include 2~~3~~ expansion cohorts of patients in tumours with documented monotherapy activity with nivolumab (non–small cell lung cancer; n = approximately 25 patients) or galunisertib (hepatocellular carcinoma [n = approximately 25 patients]~~ and glioblastoma [n = approximately 25 patients]~~). Patients in the 2~~3~~ cohorts will be enrolled independently and will be assigned to treatment concurrently;~~, and~~ enrolment for each cohort will be complete when that~~all~~ cohort has~~ve~~ reached the prespecified enrolment target. Galunisertib will be used to attempt to augment nivolumab activity via suppression of the immune suppressive function of TGF-β at the

maximum tolerated dose or pharmacologically active dose. Additional cohorts of patients with specific alternative tumour histologies may be added and will require an amendment.

3. Table of Contents

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~~, or Glioblastoma~~ (Phase 2)

…

5. Introduction

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~~, or Glioblastoma~~ (Phase 2)

5.5. Rationale for H9H-MC-JBEF Protocol Amendment (b)

…

- In Attachment 1, Study Schedules, a requirement was added for echocardiography (ECHO) at the 30-day follow-up visit, and, for the Phase 2 portion, clarification was provided that imaging is to be collected centrally [see clarification in Section 5.5].

…

~~A detailed list of changes may be found in Attachment 13.~~

5.6. Rationale for H9H-MC-JBEF Protocol Amendment (c)

H9H-MC-JBEF protocol (b) was amended for the following reasons:

- Phase 2 portion of study: to remove the glioblastoma cohort and update the protocol text to reflect this change. Results from 2 recently reported galunisertib trials, Studies H9H-MC-JBAI and H9H-MC-JBAL, have indicated a lack of sufficient efficacy galunisertib in glioblastoma.

- To clarify the rationale for the changes to the ECHOs in Attachment 1 made in protocol amendment (b) (see Section 5.5 bullet 6): the requirement for ECHO (echocardiography) at the 30-day follow-up visit was restored into the protocol as this requirement had been inadvertently removed during Amendment A; for the Phase 2 portion, clarification was provided that imaging is to be collected centrally.
- Attachment 2: to add hepatitis B surface antigen testing, which was inadvertently excluded previously; to clarify that all hepatitis testing at baseline will be assayed by a local and a Lilly-designated laboratory and during the trial will be performed by a Lilly-designated laboratory; and to clarify footnotes.
- Attachment 4: to add a ±10-minute window to the blood biomarker collection on Cycle 1 Day 1.

Minor editorial corrections or clarifications may have been made but not detailed above. A detailed list of changes may be found in Attachment 13.

5.6.5.7. Galunisertib

…

~~Glioblastoma~~

~~In glioblastoma (GB), anaplastic astrocytomas, anaplastic oligoastrocytoma, or anaplastic oligodendroglioma, galunisertib is expected to reduce neoangiogenesis; enhance antitumour cytotoxic T cells; and reduce fibrogenic remodelling associated with tumour necrosis, radiation, and surgery. Of 32 patients with relapsed and recurrent GB who received galunisertib monotherapy and were assessed using either RECIST version 1.1 or MacDonald criteria in a recent first-in-human dose study (Study H9H-MC-JBAH [JBAH]), partial tumour responses were reported in 5 patients. Based upon these data, second- and first-line studies are ongoing assessing the efficacy of blockade of the TGF-β signalling pathway in GB.~~

~~Based on preclinical data suggesting an additive antitumour effect of a TGF-β inhibitor and lomustine and the Study JBAH clinical data, a Phase 2 study, Study JBAL, was initiated to evaluate the activity of this combination in patients with GB after first progression. In this study, 158 patients were randomly assigned to 3 treatment arms: galunisertib + lomustine (n=79), galunisertib alone (n=39), and placebo + lomustine (n=40) (Brandes et al. 2015).~~

- ~~The median OS (95% CI) was 6.7 months (5.3, 8.5) for the galunisertib + lomustine arm, 8.0 months (5.7, 11.7) for the galunisertib arm, and 7.5 months (5.6, 10.3) for the placebo + lomustine arm. Success criteria for superiority of the galunisertib + lomustine arm over the placebo + lomustine arm was not met (p [hazard ratio<1]<85%).~~
- ~~The median progression-free survival (PFS) (95% CI) was 1.8 months (1.7, 1.8) for the galunisertib + lomustine arm, 1.8 months (1.6, 3.0) for the galunisertib arm, and 1.9 months (1.7, 1.9) for the placebo + lomustine arm.~~

- ~~Best overall response as determined using Response Assessment in Neuro-Oncology (RANO) criteria included 1 CR in the galunisertib + lomustine arm and 2 PRs in the galunisertib arm.~~
- ~~Thirty-four patients (24% patients in the galunisertib + lomustine arm; 13% in the galunisertib arm; 26% in the placebo + lomustine arm) had Grade 3/4 AEs related to study drug. The most common drug-related Grade 3/4 AEs (galunisertib + lomustine, galunisertib, placebo + lomustine, respectively) were thrombocytopenia (8%, 0%, 13%), lymphopenia (9%, 3%, 0%), and neutropenia (8%, 0%, 5%).~~

~~Study JBAL efficacy outcomes including OS and PFS were similar in all 3 treatment arms. The treatment was safe and well tolerated. Outcomes of an IDH-1 mutated subgroup is being analysed for clinical outcome to determine whether it is different from the general glioblastoma population. In addition, in Study JBAL, higher baseline expression of MDC/CCL22 was a prognosticator of improved outcome, and patients whose CCL22 remained higher over the course of treatment had better outcomes (Hanks et al. 2013). In addition, higher baseline levels of CD3, CD4, CD4CD25, CD8, and FoxP3 correlated with improved outcome, suggesting that a more intact immune function improves outcome.~~

~~Study H9H-MC-JBAI is an ongoing Phase 1b study evaluating galunisertib in the first-line setting in combination with temozolomide and radiation.~~

…

~~5.7.~~5.8. Nivolumab

…

~~Glioblastoma~~

~~Recent improvements in OS achieved with immunotherapeutics in melanoma and prostate cancer suggest that immunotherapy approaches may offer promise in other difficult to treat cancers such as GB (Heimberger and Sampson 2011). More specific immunologic data in support of this hypothesis include the longer survival observed in patients with elevated IgE levels compared to those with normal levels (Lin et al. 2011; Schlehofer et al. 2011; Schwartzbaum et al. 2012; Turner 2012) and upregulation of immune checkpoint receptors such as PD-L1 in glioblastomas (Parsa et al. 2007; Jacobs et al. 2009). Studies have also suggested an association between malignancy grade of astrocytic tumours and tumour cell PD-L1 expression (Wilmotte et al. 2005; Yao et al. 2009). Additionally, use of an inhibitor of PD-L1 in mouse glioblastoma models suggests benefit in combination with radiation therapy (Zeng et al. 2013).~~

~~Although the efficacy of check point inhibitors such as nivolumab and ipilimumab have not previously been studied in GB, a multicentre, Phase 2 study to evaluate the response of brain tumour metastases to ipilimumab was previously performed (CA184042). Patients (n=71) with advanced Stage IV melanoma and measurable active brain metastases were randomly assigned to ipilimumab monotherapy. The study demonstrated that ipilimumab had clinical activity in patients with melanoma brain metastases with some patients showing prolonged clinical~~

~~responses, disease control, and prolonged survival. Ipilimumab did not cause unexpected neurological toxicity in patients with brain metastases.~~

~~Nivolumab monotherapy is being evaluated in Study CA209143.~~

…

5.9.1. Primary Objective

…

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 NSCLC or~~,~~ HCC~~, or glioblastoma~~ who have failed 1 prior line of therapy.

5.9.2. Secondary Objectives

The secondary objectives of this study are:

…

- Phase 2 only: To assess the preliminary antitumour activity including PFS, ORR, duration of response, and time to response of the combination of galunisertib and nivolumab in patients with NSCLC or~~,~~ HCC~~, or glioblastoma~~

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to first dose of study drug.

…

[2] For Phase 2, must have 1 of the following tumour types: recurrent or refractory NSCLC (any histology) or~~,~~ HCC with AFP ≥200 ng/mL~~, or glioblastoma (primary)~~.

[3] For Phase 2, ~~M~~must have histological or cytological confirmation of recurrent disease based upon standard diagnostic criteria for the tumour type.

~~For glioblastoma, patients must have:~~

~~1) previous or current histologically confirmed diagnosis of WHO glioblastoma (ICD-O 9440/3, WHO grade IV); and~~

~~2) first recurrence of glioblastoma as determined by RANO criteria (see Attachment 9) following standard chemoradiation (Stupp protocol [Stupp et al. 2009]). If first recurrence of glioblastoma is documented by MRI, an interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either: i) histopathologic confirmation of recurrent tumour, or ii) new~~

~~enhancement on MRI outside of the radiotherapy treatment field (beyond the high-dose region or 80% isodose line) (Wen et al. 2010). For glioblastoma patients, biopsy confirmation of recurrent disease is not required as long as new enhancement on MRI outside of the radiotherapy treatment field is documented.~~

[4] ~~For patients other than glioblastoma patients, n~~New (nonarchived) baseline tumour biopsies (defined as a biopsy specimen taken since completion of the first-line treatment regimen) are required for all cohorts (see Section 8.2.1). In addition, in the Phase 2 part of the study, patients must agree to undergo an on-study biopsy; patients in the Phase 1b part of this study are strongly encouraged to agree to undergo an on-study biopsy. See Section 8.2.3.2.

For Phase 1 of the study, any ~~For~~ glioblastoma patients must~~,~~ have either a new biopsy or archived tumour tissue available.

Fine-needle aspirates or other cytology samples are not acceptable.

[5] For NSCLC, HCC or other nonneuro-oncology tumours: have measurable disease as defined by RECIST version 1.1 (Eisenhauer et al. 2009; Attachment 8).

For any ~~For~~ glioblastoma patient in Phase 1 of the study: have measurable disease as defined by RANO (Wen et al. 2010; Attachment 9)~~.~~ ~~for the first 25 patients. If the cohort is expanded per the 2-stage design, then patients with either measurable or nonmeasurable disease as defined by RANO are eligible.~~ Patients with glioblastoma may have nonmeasurable disease if they have undergone resection and postresection radiation. …

[6] For Phase 2 only, have had disease progression or be refractory or intolerant to **1 prior line of therapy** (first-line therapy) for recurrent or refractory ~~for~~ NSCLC or ~~,~~ HCC~~, or glioblastoma~~ and have refused currently approved second-line of therapy. …

~~For glioblastoma:~~

- ~~previous first-line of therapy with at least radiotherapy and temozolomide except for patients with MGMT-unmethylated newly diagnosed GB (Stupp et al. 2009). Patients with MGMT-unmethylated newly diagnosed GB may have received radiation therapy only (Hegi et al. 2005).~~

…

[9] Have adequate organ function, including:

…

For Phase 2 only:

…

~~For glioblastoma cohort only:~~

- ~~Haematologic: platelets ≥100x10^9/L, and haemoglobin ≥9 g/dL or ≥5.6 mmol/L, ANC ≥1.5x10^9/L. Patients may receive erythrocyte transfusions to achieve this haemoglobin level at the discretion of the investigator (at least 3 days before starting study drug). Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of haemoglobin level ≥9 g/dL.~~
- ~~Hepatic: total bilirubin ≤1.5xULN (except patients with Gilbert Syndrome who must have a total bilirubin level of <3.0xULN); alkaline phosphatase, AST, and ALT ≥3.0xULN.~~

6.1.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.

…

[24] Are receiving immunosuppressive agents (eg, cyclosporine) for any reason except for corticosteroids for transfusions. In the Phase 1b portion of the study, l~~L~~ow-dose corticosteroids for glioblastoma are permitted (eg, prednisone 10 mg [approximately equivalent to 2 mg of dexamethasone] or less daily or equivalent dose of other corticosteroid).

…

[29] Receiving any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents ~~for treatment of NSCLC, HCC, or glioblastoma~~).

[30] Have had prior radiotherapy within 2 weeks of therapy. Patients must have recovered from all radiation-related toxicities, not require more than low-dose corticosteroids (except for low-dose corticosteroids for glioblastoma in the Phase 1b portion of the study, eg, prednisone 10 mg or less daily or equivalent dose of other corticosteroid), and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNS disease with Lilly physician approval.

[31] For glioblastoma patients in the Phase 1b portion of the study only, have diffuse leptomeningeal disease.

[32] ~~For nonglioblastoma patients, p~~Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with stable, previously treated brain metastases may participate if neurologic symptoms have resolved, they have been off steroids for at least 7 days, and have no evidence of disease progression by imaging for at least 2 weeks before the first dose of study treatment.

…

[36] For glioblastoma patients in the Phase 1b portion of the study only, previous treatment with carmustine wafer except when administered as first-line treatment and at least 6 months prior to randomisation.

6.2. Summary of Study Design

. … The second part (Phase 2) of the study will be disease restricted to include 2~~3~~ expansion cohorts in patients with recurrent or refractory NSCLC (n = approximately 25 patients) or HCC (n = approximately 25 patients~~) or glioblastoma (n = approximately 25 patients~~) ~~all~~ receiving nivolumab 3 mg/kg Q2W plus galunisertib at the dose determined from the Phase 1b part. Additional expansion of individual cohorts may occur depending upon activity based upon a 2-stage design after 3 cycles. Details are found in Section 10.1.1. NSCLC has a historically good activity under nivolumab monotherapy; HCC ~~and glioblastoma have~~has documented activity with galunisertib therapy.

…

[[Updated design figure]]

Figure JBEF.6.1. Study H9H-MC-JBEF design.

6.2.2. Phase 2 Cohort Expansion

… . ~~Three~~ Two expansion cohorts will be tested in order to demonstrate efficacy of the combination in NSCLC and~~,~~ HCC~~, and glioblastoma~~. If DLT-equivalent toxicities occur in 33% or more of patients within a tumour-specific cohort expansion in the first 2 cycles, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. No additional patients will be accrued 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 NSCLC cohort (NSCLC has demonstrated activity with nivolumab monotherapy)~~,~~ and the ~~glioblastoma and~~ HCC cohorts~~s~~ (HCC has documented monotherapy activity with galunisertib)~~,~~ will be used to assess activity of the combination. …

7.2.3. Phase 2 Cohort Expansion

…

The Phase 2 part of the study will initially include 2~~3~~ expansion cohorts (NSCLC and ~~,~~HCC~~, and glioblastoma~~ [n = approximately 25 patients per cohort]). …

7.5. Concomitant Therapy

…

Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents for treatment of NSCLC, HCC, or ~~glioblastoma~~any other tumour type) will not be allowed.

…

8.1.4. Safety Monitoring

…

The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or CRS, and periodically review:

…

- Except for patients with liver metastases or HCC, for any patient who~~If a study patient with NSCLC or glioblastoma~~ experiences elevated ALT >3xULN and elevated total bilirubin >2xULN, clinical and laboratory monitoring should be initiated by the investigator.
  …

10.1.1. Sample Size

…
For HCC ~~and glioblastoma~~, the response is defined based on ORR or survival at 10 months. …

10.7. Efficacy

…

~~For the glioblastoma cohort, efficacy endpoints may be evaluated by adjusting for IDH 1/2 expression, serum TGFβ-1 levels, and tumour PD-L1 expression.~~

10.8. Interim Analyses

…

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 2~~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 interim analyses 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 ~~and glioblastoma~~ cohort~~s~~). Enrolment of the other cohort~~(s)~~, if not completely enrolled, will not be stopped during the interim analysis. ...

12. References

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Attachment 1. Protocol JBEF Study Schedule

…

During and Post-Study Assessments—Phase 1b Dose Escalation

	Cycle 1				Cycle 2				Cycle 3-n				Follow-Up (days)			Comments
Relative Week Within a Cycle	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**				
Relative Day Within a Cycle[a]	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Short-term**		**Long-term[c]**	
													30[b]	**100**		

. . .

12-lead ECG					X	D 14 only			X*							Collect predose (if applicable): See Attachment 4 for timing of PK time-matched ECGs * Starting at Cycle ~~5~~3 Day 1, ECGs will be performed at every odd-numbered cycle thereafter (Cycles 5, 7, 9, etc)

. . .

Bio-marker samples	Tumour biopsy			1/2		1/2										Required for patients with cancers other than glioblastoma, with half of patients randomly assign to biopsies on either Cycle 1 D15 or Cycle 2 D1 post nivolumab dosing. If a patient with glioblastoma undergoes a biopsy during the study for other medical reasons, tissue should be collected at that time. For glioblastoma patients only (Phase 1b), if tumour biopsy is performed to distinguish between radiologic progression and pseudoprogression (not required), see Section 7.2.5 for instructions for proper handling of specimen.

. . .

Phase 2 Dose Expansion—Baseline/Screening Assessments

Relative Day Prior to Day 1 of Cycle 1[a]	≤28	≤14	≤7	Comments
…				
Tumour biopsy	X			New tumour biopsy is required ~~for patients with NSCLC and HCC. Archived tumour tissue or new tumour biopsy is required for patients with glioblastoma~~. Biopsy should be taken only after study eligibility is confirmed.
…				
Tumour measurement (palpable or visible)		X		~~If appropriate for the tumour~~
…				

During and Post-Study Assessments—Phase 2 Dose Expansion

	Cycle 1				Cycle 2				Cycle 3-n				Follow-Up (days)		Comments
Relative Week Within a Cycle	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**			
Relative Day Within a Cycle[a]	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Short-term**	**Long-term[c]**	
. . .															
12-lead ECG					X	D 14 only			X*						Collect predose (if applicable): See Attachment 4 for timing of PK time-matched ECGs. * Starting at Cycle 3~~5~~ Day 1, ECGs will be performed at every odd-numbered cycle thereafter (Cycles 5, 7, 9, etc)
. . .															
Radiological tumour assessment for ~~pseudoprogression~~treatment past initial progression															MRI/CT scan. These scans can be performed locally and transmitted to a central imaging vendor. For patients who are being treated beyond initial progression, these patients should remain on study treatment until the next assessment period. Patients who are treated beyond progression will be evaluated on an 8~~ (nonglioblastoma) or 12 (glioblastoma)~~ week basis to determine if they should continue on treatment.
. . .															
Bio-marker samples	Tumour biopsy			1/2		1/2									Required ~~for patients with cancers other than glioblastoma~~, with half of patients randomly assign to biopsies on either Cycle 1 D15 or Cycle 2 Day 1 post nivolumab dosing. ~~If a patient with glioblastoma undergoes a biopsy during the study for other medical reasons, tissue should be collected at that time.~~ ~~For glioblastoma patients only, if tumour biopsy is performed to distinguish between radiologic progression and pseudoprogression (not required), see Section 7.2.5 for instructions for proper handling of specimen.~~
. . .															

Attachment 2. Protocol JBEF Clinical Laboratory Tests

Clinical Laboratory Tests

Haematology[a]	Clinical Chemistry[a,b,~~c~~]
Haemoglobin	**Serum Concentrations of:**
…	
	Thyroid-stimulating hormone[a,b,c]
	Reflex to fT3/fT4[a,b,~~c~~]

…

c ~~Assayed by local and investigator-designated laboratory.~~

~~d~~ If thyroid-stimulating hormone test is abnormal, reflex to fT3/fT4 test must be performed.

d Baseline tests (screening) will be assayed by a local and a Lilly-designated laboratory. Testing during the trial will be performed by a Lilly-designated laboratory.

Attachment 4. Protocol JBEF Pharmacokinetic, Biomarker, PK Time-Matched ECG, and Immunogenicity Sampling Schedule

…

Blood Biomarker Sampling Schedule

Pharmacodynamic Sample #	Cycle	Day	Sampling Windows for Blood Collection
1	1	1	Predose
2	1	1	2 hours postdose ± 10 minutes
...			

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