Protocol I7W-MC-JQBA(d)

# A Phase 1 Study of LY3127804 as Monotherapy and in Combination with Ramucirumab in Patients with Advanced Solid Tumors

NCT02597036

Approval Date: 11-Sep-2017

# 1. Protocol I7W-MC-JQBA(d)

# A Phase 1 Study of LY3127804 as Monotherapy and in Combination with Ramucirumab in Patients with Advanced Solid Tumors

## Confidential Information



LY3127804

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study, potentially followed by dose expansion of intravenous LY3127804 administered as monotherapy and in combination with ramucirumab (dependent on the safety and tolerability data under monotherapy) in patients with advanced solid tumors who have failed standard therapy or for whom no standard therapy is available.

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Protocol Electronically Signed and Approved by Lilly: 29 July 2015
Amendment (a) Electronically Signed and Approved by Lilly: 06 September 2015
Amendment (b) Electronically Signed and Approved by Lilly: 14 December 2015
Amendment (c) Electronically Signed and Approved by Lilly: 29 July 2016
Amendment (d) Electronically Signed and Approved by Lilly on approval date provided below

Approval Date: 11-Sep-2017 GMT

# 2. Synopsis

This Phase 1 first-in-human study is a multicenter, nonrandomized, open-label, dose-escalation study of intravenous LY3127804 in patients with advanced or metastatic solid tumors who have failed standard of care or for whom no standard of care is available. Study I7W-MC-JQBA (JQBA) will determine a recommended dose range and schedule for LY3127804 that may be safely administered as monotherapy and in combination with ramucirumab. The study will consist of a dose escalation for LY3127804 monotherapy (Part A) and combinations with ramucirumab (Parts B and C).

# 3. Table of Contents

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# 4. Abbreviations and Definitions

| Term | Definition |
|---|---|
| **ADA** | anti-drug 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 unfavorable 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** | alpha-fetoprotein |
| **ALT** | alanine aminotransferase |
| **ANC** | absolute neutrophil count |
| **Ang1/Ang2** | angiopoietin 1/2 |
| **assent** | agreement from a minor or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some Institutional Review Boards [IRBs]/ethical review boards [ERBs]). |
| **AST** | aspartate aminotransferase |
| **$AUC_{(\tau\text{-ss})}$** | area under the concentration versus time curve during a dosing interval at steady state |
| **$AUC_{(0\text{-}\infty)}$** | area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{(0\text{-tlast})}$** | area under the plasma concentration-time curve from time zero to last measurable plasma concentration |
| **audit** | a systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s) |
| **BIW** | twice a week |
| **BP** | blood pressure |
| **CI** | confidence interval |
| **$C_{max}$** | maximum observed drug concentration |
| **$C_{min}$** | minimal concentration over the dosing interval |

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|---|---|
| **CNS** | central nervous system |
| **collection database** | a computer database where clinical trial data are entered and validated |
| **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 |
| **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 |
| **DCE-MRI** | dynamic contrast-enhanced magnetic resonance imaging |
| **DCSI** | Development Core Safety Information |
| **DLT** | dose-limiting toxicity |
| **DNA** | deoxyribonucleic acid |
| **ECG** | electrocardiogram |
| **ECOG** | Eastern Cooperative Oncology Group |
| **end of trial** | End of trial is the date of the last visit/study contact or last scheduled procedure for the last patient last visit. |
| **enroll** | 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 |
| **FFPE** | formalin-fixed paraffin-embedded |
| **GCP** | good clinical practice |
| **GEJ** | gastro-esophageal junction |
| **GnRH** | gonadotropin-releasing hormone |
| **HCC** | hepatocellular carcinoma |
| **HED** | human equivalent dose |
| **HIV** | human immunodeficiency virus |
| **IB** | investigator's brochure |
| **IC50** | half-maximal inhibitory concentration |
| **ICF** | informed consent form |
| **ICH** | International Conference on Harmonisation |
| **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 normalized ratio |
| **interim analysis** | an analysis of clinical study data that is conducted before the final reporting database is authorized for data lock |
| **investigational product** | a pharmaceutical form of an active ingredient 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 |
| **Lilly Safety System** | global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system |
| **mAb** | monoclonal antibody |

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| **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 subjects, 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 |
| **N** | number of patients |
| **NCI** | National Cancer Institute |
| **NOAEL** | no-observed-adverse-effect level |
| **NOEL** | no-observed-effect level |
| **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 |
| **patient** | a subject with a defined disease |
| **PD** | pharmacodynamic |
| **PET** | positron emission tomography |
| **PFS** | progression-free survival |
| **PK** | pharmacokinetic |
| **PR** | partial response |
| **Q2W** | every 2 weeks |
| **QTcF** | corrected QT interval using Fridericia's correction |
| **QW** | weekly |
| **RECIST** | Response Evaluation Criteria in Solid Tumors |
| **reporting database** | a point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data. |
| **rescreen** | to screen a patient who was previously declared a screen failure for the same study |

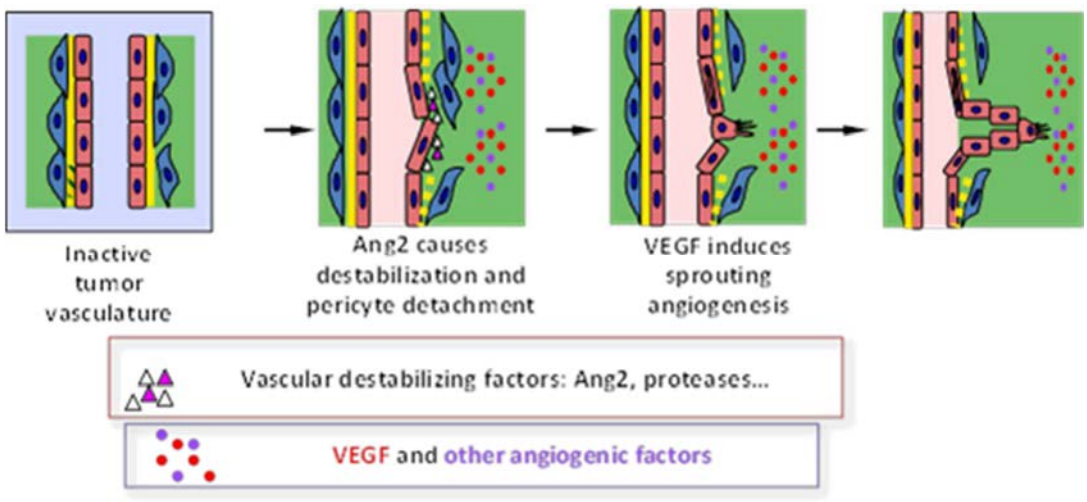
| | |
|---|---|
| **RP2D** | recommended Phase 2 dose |
| **RR** | respiratory rate |
| **SAE** | serious adverse event |
| **screen** | the act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial |
| **screen failure** | a patient who does not meet one or more criteria required for participation in a trial |
| **SOC** | standard of care |
| **sponsor** | the party who takes responsibility for the initiation, management and/or financing of a clinical study |
| **study completion** | This study will be considered complete after all parts (Parts A, B, and C) are complete. The dose-escalation and exploration phases of the study (Parts A, B, and C) will be considered complete after all patients required to determine the RP2D for LY3127804 have completed DLT treatment-observation period and the patients in Part C have completed 4 cycles of study therapy or discontinued from the treatment (last patient). |
| **SUSAR** | suspected unexpected serious adverse reaction |
| **% ΔT/ΔC** | % of treated tumor volume difference from baseline/control tumor volume difference from baseline |
| **$t_{1/2}$** | half-life |
| **T4** | thyroxine |
| **Tie2** | tunica interna endothelial tyrosine kinase 2 |
| **TPO** | third-party organization |
| **TSH** | thyroid-stimulating hormone |
| **ULN** | upper limit of normal |
| **VEGF/VEGFR** | vascular endothelial growth factor/vascular endothelial growth factor receptor |

# A Phase 1 Study of LY3127804 as Monotherapy and in Combination with Ramucirumab in Patients with Advanced Solid Tumors

# 5. Introduction

## 5.1. Rationale and Justification for the Study

Angiogenesis, the growth of new blood vessels, has been widely accepted to play a pivotal role in tumor growth, propagation, and metastasis. Anti-angiogenic therapy has become the focus of therapeutic interventions, which led to the approval of several therapies targeting vascular endothelial growth factor (VEGF)/vascular endothelial growth factor-receptor 2 (VEGFR2) pathways. Anti-VEGF pathway therapies primarily target immature blood vessels in tumors. However, emerging approaches to combine anti–VEGF/VEGFR2 therapies with therapies impacting the different stages of remodeling and vessel maturation are expected to improve clinical efficacy by expanding the target vessel population (Gerald et al. 2013). The ligands of vascular receptor tunica interna endothelial tyrosine kinase 2 (Tie2), angiopoietin1 (Ang1), and angiopoietin 2 (Ang2), play an important role in remodeling of tumor vasculature. Ang1 is produced by periendothelial cells including pericytes, to act in a paracrine manner; whereas Ang2 is produced by vascular endothelial cells and acts on endothelial cells in an autocrine manner (Scharpfenecker et al. 2005). Ang1- and Tie2-deficient mice die in mid gestation because of perturbed vessel remodeling and maturation. The phenotypic similarity between Ang1 ligand and Tie2 receptor-deficient mice suggests Ang1 to be an agonistic ligand for Tie2 (Dumont et al. 1994; Suri et al. 1996). Ang2 overexpressing transgenic mice phenocopy the mid-gestational embryonic lethal phenotype of Ang1-deficient mice inferring the antagonistic mode of action of Ang2 (Gerald et al. 2013). Ang2 promotes tumor angiogenesis and growth by destabilizing the Tie2-expressing vasculature enhancing the endothelial cells response to angiogenic stimuli such as VEGF (Figure JQBA.5.1) and by induction of Tie2-independent integrin-mediated sprouting tip cell migration (Scharpfenecker et al. 2005; Felcht et al. 2012).




Abbreviations: Ang2 = angiopoietin 2; VEGF = vascular endothelial growth factor.

**Figure JQBA.5.1. Ang2 promotes sprouting angiogenesis induced by angiogenic growth factors (eg, VEGF).**

Ang1 and Ang2 have been identified to exert opposing functions during vessel development, but recently Daly et al (Daly et al. 2013) also proposed the model wherein Ang2 functions to activate Tie2 signaling, particularly in endothelial cells that are not exposed to significant levels of pericyte-derived Ang1 (likely the majority of tumor endothelial cells). Thus, Ang2 can act on Tie2 at disparate ends of the angiogenesis process, both to initiate sprouting in a quiescent pericyte-covered vessel and to provide a weak survival activity in phases of angiogenesis prior to pericyte recruitment. As a hallmark of activated endothelium engaged in ongoing angiogenesis, Ang2 is a poor prognostic factor and is upregulated in several tumor types including colon, gastric, lung, and breast carcinoma correlating with disease progression and metastasis (Etoh et al. 2001; Sfiligoi et al. 2003; Ochiumi et al. 2004; Andersen et al. 2011). Ang2 has also been shown to promote pulmonary metastasis (in mice [Mazzieri et al. 2011]), and an increased expression of Ang2 has been observed in metastatic tumors as compared to primary tumors (Rigamonti and De Palma 2013). Several Ang2 pathway inhibitors, both small and large molecules, have significantly inhibited tumor growth in several preclinical tumor models. Combined inhibition of Ang2 and VEGF pathways has greater efficacy than monotherapy in preclinical models (Brown et al. 2010; Hashizume et al. 2010; Koh et al. 2010). In addition to the anti-angiogenic effect, Ang2 inhibitors also limit metastatic growth (Mazzieri et al. 2011; Srivastava et al. 2014).

Currently, there are several molecules targeting the Ang2 pathway in early to advanced clinical trials (Gerald et al. 2013). Amgen's Ang1/2 blocker, trebananib (formerly known as AMG 386), is a peptide-Fc fusion protein that blocks Ang1 and Ang2 binding to Tie2. Previous experience with AMG 386 indicated that combination therapies in advanced solid tumors were tolerated and that there were no interactions affecting the pharmacokinetic (PK) profiles of either AMG 386 or the other drugs (Hong et al. 2008). The most common adverse effects associated with AMG 386 plus bevacizumab (N=25), AMG 386 plus motesanib (AMG 706, an antagonist of VEGF receptors; [N=11]), and AMG 386 plus sorafenib (N=10) were diarrhea, hypertension, weight

decreased, hemorrhage, and rash. Two patients receiving AMG 386 plus bevacizumab experienced Grade ≥3 hemorrhage. One patient receiving AMG 386 plus motesanib experienced Grade ≥3 diarrhea. One patient each experienced Grade ≥3 diarrhea and weight decreased in an AMG 386 plus sorafenib cohort (Hong et al. 2008). In another study, the combination of AMG 386 with sorafenib (17 patients) or sunitinib (15 patients) was reported to be tolerated, had no marked effect on their individual PK profiles, and showed promising tumor response in renal cell carcinoma (Appleman et al. 2010). Three Phase III clinical trials have been performed in ovarian cancer with trebananib, of which the first trial (TRINOVA-1) reported initially encouraging progression-free survival (PFS) results; however, more recently this is complemented with non-significant overall survival (OS) results: median OS of 19.3 months in the trebananib arm versus 18.3 months in the control arm (Amgen news release [WWW]). The interest in the pathway however has been confirmed with the introduction of 2 additional monoclonal antibody (mAb) drugs against Ang2 (nesvacumab [REGN910] and MEDI3617). Both of these investigational drugs (nesvacumab [REGN910] as monotherapy; MEDI3617 as monotherapy and in combination with carboplatin/paclitaxel, paclitaxel, or bevacizumab) have shown acceptable safety profiles in cancer patients (Hyman et al. 2014; Kelley et al. 2014). While trebananib's ovarian cancer clinical development strategy is in combination with standard of care (SOC) chemotherapy, it is clear from clinical strategies and preclinical information that all Ang antibodies are intended for development in combination with anti-VEGF or anti-VEGFR2 therapy.

Simultaneous inhibition of Ang2/Tie2 and VEGFA/VEGFR2 pathways plays a role in vessel destabilization, while at the same time having an effect at the level of proliferation and migration of endothelial cells, respectively offering great promise in delivering the second-generation antiangiogenesis drugs to patients with angiogenesis-dependent malignant diseases.

Targeting the Ang2-Tie2 pathway by blocking the ability of Ang2 to bind to the Tie2 receptor may therefore provide cancer patients with a novel therapeutic to target the angiogenic aspect of their disease. LY3127804 is a humanized immunoglobulin G 4 (IgG4) mAb that targets Ang2 and prevents its binding to Tie2 receptor. More detailed information about the mechanism of action of LY3127804 is presented in Section 5.3.1.

Study I7W-MC-JQBA (JQBA) is the first-in-human Phase 1 dose-escalation study of LY3127804 designed to evaluate the safety and tolerability and the PK properties, as well as to gather evidence of pharmacodynamic (PD) effects and antitumor activity, of LY3127804 in patients with advanced solid tumors who have failed SOC or for whom no SOC is available and the feasibility to combine LY3127804 with the approved VEGFR2-blocking antibody ramucirumab (see Section 6.2).

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

### 5.1.1. Rationale for Protocol Amendment (a)

The protocol was amended prior to study initiation based on the United States Food and Drug Administration (FDA) feedback to clarify continuation criteria for patients experiencing elevated blood pressure.

### 5.1.2. Rationale for Protocol Amendment (b)

The protocol was amended to clarify dose rationale for LY3127804 and ramucirumab combination, rules of dose-escalation, timing of vital sign measurements, and infusion durations of LY3127804 based on feedback received from European regulatory authorities, from institutional review boards (IRBs), and during site initiations prior to study initiation. In addition, some minor editorial changes have been made to improve clinical practicality of the protocol and align with the intended study design.

### 5.1.3. Rationale for Protocol Amendment (c)

The protocol was amended to substitute the tumor specific expansion cohorts for gastric cancer and HCC with a safety confirmation cohort for LY3127804 in combination with ramucirumab at the RP2D level (Part D) and a cohort to explore the safety and tolerability of LY3127804 when given in combination with ramucirumab and paclitaxel (Part E).

As of 21 June 2016 there has been a total of 25 patients treated with LY3127804 at 4mg, 8mg, 12mg and 16mg dose levels including 12 patients treated with LY3127804 and ramucirumab combination therapy. To date no DLTs have been reported.

The revised Part D will include 6-12 additional patients to be treated at the RP2D of LY3127804 in combination with 8mg/kg ramucirumab to expand the safety and tolerability experience with this combination prior to exposing a larger population in phase 2 studies. In addition, expanding the number of patients exposed at the RP2D will allow to assess the PK/PD biomarker as an exploratory objective of this study in a more robust manner.

The revised Part E will include 9-12 patients to explore the safety and tolerability of LY3127804 when given in combination with ramucirumab and paclitaxel. Ramucirumab has been approved in combination with paclitaxel for treatment of 2nd line gastric cancer based on a successful Phase 3 study demonstrating significant OS benefit (Wilke et al. 2014). In preclinical studies, LY3127804 demonstrated additive activity in combination with ramucirumab and chemotherapy in several patient-derived tumor-xenograft models (Eli Lilly, data on file). Therefore, there is a scientific rationale to explore the feasibility of the triplet combination consisting of LY3127804, ramucirumab, and paclitaxel (more detailed information about part E in Section 6.2).

In addition, some minor editorial changes have been made to improve clarity and practicability of the protocol and secure alignment with the intended study design.

### 5.1.4. Rationale for Protocol Amendment (d)

The Sponsor implemented amendment (d) in order to eliminate Parts D and E from the current study protocol and to clarify that LY3127804 at a dose of 27 mg/kg was tested as monotherapy (Part A) and as combination therapy with ramucirumab (Part B).

The rationale for the elimination of Parts D and E was based on the following: (i) based on Lilly's current oncology portfolio strategies, it was concluded that combining paclitaxel with LY3127804 for treating second-line gastric cancer was no longer desired to be investigated in this particular study. Other regimens will be used to treat second-line gastric cancer in the foreseeable future, ii) the primary and secondary end points of this study were reached, and (iii) information collected from Parts A, B, and C (fully enrolled and ongoing as of August 21, 2017) was considered sufficient to conclude the primary objective of the study and to answer all scientific questions. Therefore, further accrual of patients was not required.

## 5.2. Objectives

### 5.2.1. Primary Objective

The primary objective of this study is to determine a recommended Phase 2 dose (RP2D) range and schedule of LY3127804, as monotherapy and in combination with ramucirumab that may be safely administered to patients with advanced solid tumors.

### 5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3127804 as monotherapy and in combination with ramucirumab.
- to assess the maximum tolerated dose (MTD) of LY3127804 monotherapy and in combination with ramucirumab based on the dose-limiting toxicity (DLT), if applicable.
- to assess the PK parameters of LY3127804 monotherapy and when administered in combination with ramucirumab.
- to assess limited PK (peak and trough concentration) of ramucirumab when given in combination with LY3127804.
- to evaluate the incidence and level of antibodies against LY3127804 (anti-drug antibodies [ADAs]) and ramucirumab.
- to document any antitumor activity of LY3127804 as monotherapy and in combination with ramucirumab.
- to estimate PFS of LY3127804 monotherapy and when given in combination with ramucirumab.

### *5.2.3. Exploratory Objectives*

- to evaluate tumor tissue, blood, and DNA for biomarkers related to the gene and gene products associated with mechanism of action of LY3127804, Tie2-Ang2-Ang1, and VEGF-signaling pathway and the tumor biology of the respective tumor types enrolled in the study, which may include but are not necessarily limited to tumor expression (eg, Ang-2, Tie-2, Tie-1,VEGFR-2) and circulating biomarker (eg, Ang-2, Ang-1, s-Tie-2, VEGF-A) and their potential association with the objectives of the study (including PK/PD biomarker relationship)
- to explore biological activity of LY3127804 as monotherapy and when given in combination with ramucirumab based on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

## 5.3. General Introduction to LY3127804

Detailed information about the characteristics of LY3127804 and the known and expected benefits and risks of LY3127804 may be found in the most recent version of the investigator's brochure (IB).

### *5.3.1. Mechanism of Action and In Vitro/In Vivo Activity*

LY3127804 is a humanized IgG4 mAb that targets Ang2 ligand. LY3127804 was selected for having high-affinity binding to Ang2 and for blocking the binding of human Ang2 to human Tie2-Fc in a dose-dependent manner with a half-maximal inhibitory concentration (IC50) of 0.0268 nM (95% confidence interval [CI]: 0.00089-0.8029). LY3127804 neutralizes the Ang2-induced phospho-Tie2 in CHO-Tie2 cells dose dependently with an IC50 of 0.773 nM (95% CI: 0.412-1.450).

The in vivo inhibition of blood vessel development in the mouse retina was used to study the evidence for repression of developmental angiogenesis by LY3127804. The results showed that LY3127804 similarly repressed vascular progression, reduced the number of endothelial tip cells and the vascular density while increasing the pericyte coverage, at 3 mg/kg, 10 mg/kg, and 30 mg/kg.

The antiangiogenic effect of DC101 (anti-mouse VEGFR-2, murine surrogate of ramucirumab), LY3127804, and the combination was assessed in mice bearing PC3 (prostate) xenograft tumors. Animals bearing PC3 xenograft tumors at approximately 250 $mm^3$ volume were either dosed with control immunoglobulin G 1 (IgG1), DC101, LY3127804, DC101+ LY3127804, or LSN3150895 (DC101-Ang2 bispecific antibody) for 6 days twice a week (BIW); and the tumors were collected, fixed, sectioned, and stained for CD105/endoglin (upregulated in actively proliferating endothelial cells; Nassiri et al. 2011) to determine the total vessel area. Overall total vessel area was reduced by 65% with DC101 ($p<.0001$), 69% with LY3127804 ($p<.0001$), 84% with the DC101 + LY3127804 combination ($p<.0001$), and 84% with LSN3150895 ($p<.0001$).

The antitumor efficacy of DC101, LY3127804, and its combination was further assessed in multiple in vivo xenograft models, including the triple-negative orthotopic breast cancer model (MDA-MB-231-MET2), subcutaneous triple-negative patient-derived breast cancer model (TNBC PDX), and subcutaneous ovarian xenograft model (SKOV3x.1). Antibodies were administered BIW for 4 consecutive weeks by intraperitoneal injection, and SOC was administered weekly (QW) for 4 consecutive weeks by either intraperitoneal or intravenous (IV) injection after tumors reached 250 to 400 $mm^3$ in volume. The impact on tumor growth was determined by 3-dimensional caliper measurements of the tumor volumes BIW during the course of treatment. The results from these assessments are summarized below.

Immuno-deficient mice bearing MDA-MB-231-MET2 breast xenografts orthotopically in mammary fat pad were treated with either vehicle control, DC101, LSN3052473 (unoptimized earlier version of LY3127804, specific and cross-reactive to human/mouse/rat Ang2), or the combination of DC101 + LSN3052473 antibody. The combination of DC101 with LSN3052473 and DC101 alone resulted in tumor regression by 61% and 63%, respectively. LSN3052473 alone resulted in a % $\Delta T/\Delta C$ (% of treated tumor volume difference from baseline/control tumor volume difference from baseline) of 24%. The OS of vehicle treatment and DC101 alone were similar. Anti-Ang2 Ab (LSN3052473) and the combination with DC101 improved the OS compared to vehicle or DC101 alone.

Immuno-deficient mice bearing EL1997 triple-negative breast patient–derived xenografts (TNBC PDX) were treated with either vehicle control; DC101; LY3127804; cyclophosphamide + doxorubicin; the combination of DC101 and LY3127804; or the combination of cyclophosphamide + doxorubicin, DC101, and LY3127804 BIW for 4 consecutive weeks. The combination of DC101 and LY3127804 resulted in $\Delta T/\Delta C$ of 19.9% compared to $\Delta T/\Delta C$ of 35.2% for DC101 and 56.7% for LY3127804 alone. The combination of cyclophosphamide, doxorubicin, DC101, and LY3127804 resulted in $\Delta T/\Delta C$ of 0.4% compared to $\Delta T/\Delta C$ of 32% for the combination of cyclophosphamide and doxorubicin.

### *5.3.2. Nonclinical Toxicokinetics*

LY3127804 toxicokinetics were evaluated in rats and monkeys following 5-weekly IV administrations of LY3127804. In both studies, increases in dose demonstrated roughly proportional increases in exposure, and there were no exposure differences between males and females. Elimination half-lives in monkeys were 281 and 248 hours for males and females, respectively.

### *5.3.3. Nonclinical Toxicology*

The nonclinical safety assessment of LY3127804 has been adequately assessed in a 5-week QW IV bolus dosing (5, 20, or 100 mg/kg) with an 8-week reversibility study in monkeys and in a 5-week rat study (10, 30, or 100 mg/kg).

In cynomolgus monkeys, LY3127804 was well tolerated at doses up to 100 mg/kg. No compound-related changes in electrocardiogram (ECG) parameters (PR interval, QRS duration, QT interval, or QTc interval), clinical pathology parameters (including urine biomarker

assessment), organ weights, or macroscopic or microscopic findings were present. Therefore, the no-observed-effect level (NOEL) is 100 mg/kg. After 5 weeks of dosing, a dose of 100 mg/kg corresponded to LY3127804 maximum observed drug concentration ($C_{max}$) and area under the plasma concentration-time curve from time zero to 168 hours ($AUC_{0\text{-}168hr}$) values of 4720 µg/mL and 518,000 µg·hr/mL, respectively, in males and 5210 µg/mL and 515,000 µg·hr/mL, respectively, in females as determined by antigen (Ang2) capture.

In a rat study, LY3127804 was well tolerated. No toxicologically important changes in clinical pathology parameters (including urine biomarker assessment) or macroscopic findings were present at the end of dosing phase. Increased thyroid/parathyroid weight parameters were present in males given ≥10 mg/kg and correlated with nonadverse microscopic findings of increased colloid in the thyroid. Effects on the thyroid organ are an expected potential pharmacologic effect based on antiangiogenic mechanism (Kamba and McDonald 2007); in clinical trials, patients will be monitored for thyroid function. Therefore, the no-observed-adverse-effect level (NOAEL) is 100 mg/kg. After 5 weeks of dosing (Day 29), a dose of 100 mg/kg corresponded to LY3127804 $C_{max}$ and $AUC_{0\text{-}168hr}$ values of 4160 µg/mL and 374000 µg·hr/mL, respectively, in males and 3450 µg/mL and 316000 µg·hr/mL, respectively, in females as determined by antigen (Ang2) capture.

The NOEL in monkeys treated for 5 weeks is 100 mg/kg which corresponds to a human equivalent dose (HED) of 32 mg/kg, and the proposed starting human dose based on monkey NOEL is 5.3 mg/kg (1/6th HED). The NOAEL in rats is 100 mg/kg, which corresponds to a HED of 16 mg/kg, and the proposed starting human dose based on rat NOAEL is approximately 1.6 mg/kg (1/10th HED). Therefore, based on monkey NOEL and rat NOAEL, the proposed starting dose is 4 mg/kg (1.6 – 5.3 mg/kg) and is approximately 8-fold lower than monkey NOEL and 4-fold lower than rat NOAEL. In addition, it should be noted that LY3127804 was administered QW in animal studies but will be administered once every 2 weeks (Q2W) in clinical studies. Thus, based on total dose received in a 2-week period, the dose multiples would be expected to be higher than expressed in Table JQBA.5.3.1. Please see Section 5.5.1 for a detailed rationale for selection of the starting dose.

**Table JQBA.5.3.1. Margins of Safety for Intravenous Administration of LY3127804 Based on Administered Dose and Predicted Exposure**

| | Dose (mg/kg) HED[a] | Dose Multiple[b] | AUC(μg h/mL) | Predicted Exposure Multiple[c] |
|---|---|---|---|---|
| **Human[a,d]** | | | | |
| Starting dose (HSD) Q2W | 4 | | 13800[c] | |
| Highest dose (HHD) Q2W | 20 | | 117000[c] | |
| **Rat NOAEL[e] 100 mg/kg QW** | 16 | | 117000[e] | |
| Multiple relative to HSD | | 4 | | 8 |
| Multiple relative to HHD | | <1 | | 1 |
| **Monkey NOEL[f] 100 mg/kg QW** | 32 | | 191000[f] | |
| Multiple relative to HSD | | 8 | | 14 |
| Multiple relative to HHD | | 1.6 | | 1.6 |

Abbreviations: AUC = area under the plasma concentration versus time curve; $AUC_{\tau ss}$ = area under the concentration versus time curve during one dosing interval at steady state; $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity; HED = human equivalent dose; HHD = human highest dose; HSD = human starting dose; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; Q2W = every 2 weeks; QW = weekly.

a Assuming a 70-kg person.

b Dose multiples is the dose in animals (as HED) / dose in humans based on mg/kg basis.

c Exposure multiple is the calculated AUC in animals / median predicted AUC in humans.

d Proposed starting and highest clinical dose, with the median and 5th to 95th percentile prediction for $AUC_{(0-\infty)}$ following a single dose (ie, equivalent to $AUC_{\tau ss}$ assuming time-independent PK, $\tau$ is 2-week period). The predictions for human $AUC_{(0-\infty)}$ are based on allometric scaling from preclinical species.

e NOAEL determined in a multiple-dose (QW) rat toxicity study (Study 8307246). The exposure reported is mean value following a single dose (ie, equivalent to $AUC_{\tau ss}$ assuming time-independent PK, $\tau$ is a week period).

f NOEL determined in a multiple-dose (QW) monkey toxicity study (Study 8307247) n=X recovery animals only. The exposure reported is mean value following a single dose (ie, equivalent to $AUC_{\tau ss}$ assuming time-independent PK, $\tau$ is a week period).

## 5.4. Ramucirumab

Ramucirumab (Cyramza®) is a recombinant human immunoglobulin G, subclass 1 mAb that specifically binds to the extracellular domain of VEGFR-2 with high affinity. This antibody potently blocks the binding of VEGF ligands to VEGFR-2, inhibits VEGF-stimulated activation of both VEGFR-2 and p44/p42 MAP kinases, and neutralizes VEGF-induced proliferation and migration of human endothelial cells.

Lilly obtained marketing authorization for ramucirumab in the European Union and in the United States for the treatment of adult patients with advanced gastric cancer or GEJ adenocarcinoma with disease progression after prior platinum and/or fluoropyrimidine chemotherapy, as a single agent (REGARD) (Fuchs et al. 2014) and in combination with paclitaxel (RAINBOW) (Wilke et al. 2014).

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of ramucirumab may be found in the IB. Information on AEs expected to be related to ramucirumab may be found in Section 7 (Development Core Safety Information

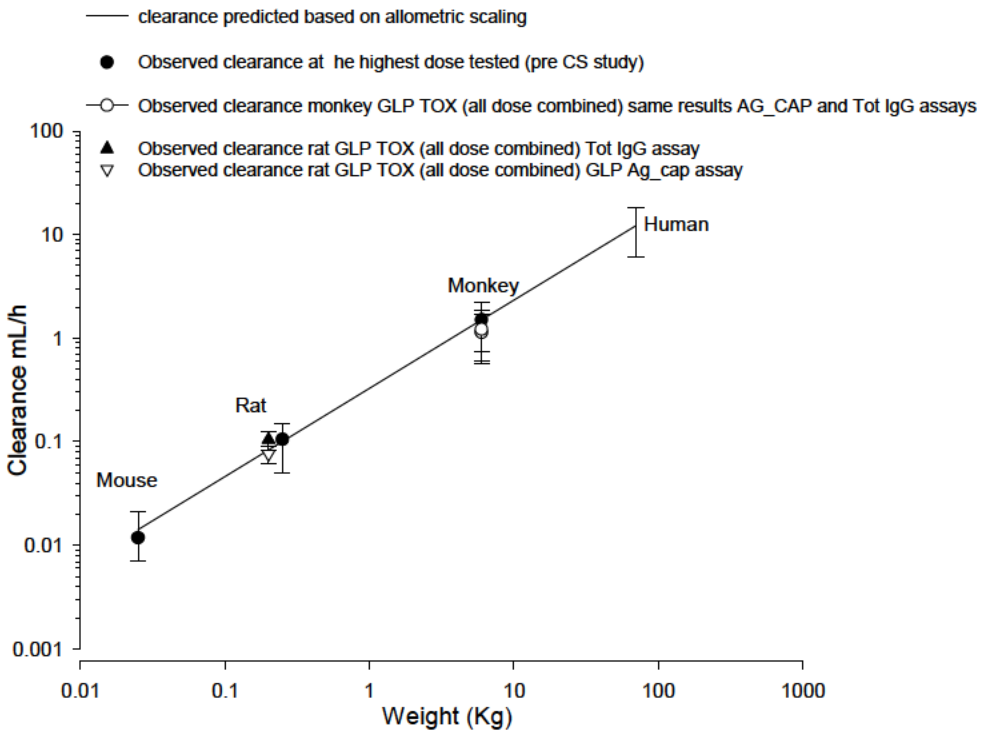
[DCSI]) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

## 5.5. Rationale for Selection of Dose

### *5.5.1. LY3127804 Dose*

At the beginning of the study, a dose range from 4 mg/kg up to 20 mg/kg of LY3127804 administered IV Q2W was selected based on nonclinical toxicology, PK, and PD/efficacy data (modeling). More details about the rationale for this dose selection are given below.

From a PK perspective, allometry scaling based on body weight was used to predict LY3127804 clearance and volume of distribution (and derived LY3127804 exposure) in humans based on mice, rat and monkey PK data. This methodology has successfully been used to predict human PK of large molecules such as monoclonal antibodies. There is a linear relationship between LY3127804 nonclinical PK parameters (clearance and volume of distribution in mice, rat, and monkey) and the animal species body weight (see Figure JQBA.5.2). Using this relationship, mean value for LY3127804 clearance, volume of distribution and half-life ($t_{1/2}$) in human are predicted to be 11.6 mL/h, 2.66 L, and 6.6 days, respectively.




Abbreviations: Ag_cap = antigen-capture assay; GLP = good laboratory practice; IgG = immunoglobulin G; Tot = total; TOX = toxicology.

**Figure JQBA.5.2. Allometric scaling.**

To predict LY3127804 dose range in humans that may lead to inhibitory effect on the Ang2 pathway and subsequently to antitumor activity, the assumption was made that LY3127804 exposure similar to "efficacious" exposure observed in mice should lead also to antitumor activity in humans. The preclinical mouse data indicate that the 3-mg/kg and 10- to 20-mg/kg dose can be considered, respectively, as minimal and optimal efficacious dose levels when given BIW to mice. Steady-state exposures for 2 weeks' treatment in mice following 3 mg/kg and 10 mg/kg (administered BIW) are 14800 µg.h/mL (4400 to 25200 µg.h/mL) (predicted mean [range] values based on 1 and 10 mg/kg data) and 84000 µg.h/mL (observed mean), respectively.

In humans, the planned dosing frequency of LY3127804 is Q2W based on the predicted $t_{1/2}$ of 6.6 days (90% CI: 5 to 9 days) in order to prevent significant drug accumulation (predicted accumulation ratio: approximately 1.2 and <1.5 following Q2W dosing).

Based on the predicted mean clearance in humans, 11.6 mL/h (5 to 18 mL/h, 95% prediction interval), the predicted human LY3127804 exposures at different human doses were derived and are presented in Table JQBA.5.5.1.

**Table JQBA.5.5.1. Predicted Human Exposure**

| Dose (mg/kg) Every 2 Weeks | Steady-State AUC (µg h/mL) over the Dose Interval 2 Weeks Median (5th - 95th Percentile) |
|---|---|
| 1 | **1661** (1015 - 4483) |
| 2 | **5135** (3182 – 12566) |
| 4 | **13828** (8501 – 34739) |
| 8 | **32941** (20190 – 78235) |
| 12 | **70000** (46667 – 168000) |
| 16 | **93333** (62222 – 224000) |
| 20 | **116667** (77778 – 280000) |

Abbreviation: AUC = area under the concentration versus time curve.

Table JQBA.5.5.1 indicates that a LY3127804 dose of 4 mg/kg and 16 mg/kg are predicted to deliver a human steady-state mean exposure (exposure over 2 weeks' treatment) of approximately 14000 and 93000 µg.h/mL (assuming human body weight of 70 kg and time-independent PK), respectively. These exposure values are similar to the predicted minimal and optimal efficacious exposures (over 2 weeks of treatment), 14800 and 84000 µg.h/mL, respectively, based on preclinical mouse data. The anticipated efficacious LY3127804 dose of 12 and 16 mg/kg are predicted to lead to a minimal concentration over the dosing interval ($C_{min}$) mean value of approximately 70 and 90 µg/mL, respectively, following Q2W dosing. These

predicted $C_{min}$ values compare favorably with the mouse data. Mouse PK data indicate a $C_{min}$ value of approximately 60 μg/mL following the efficacious dose of 10 mg/kg BIW.

Therefore, the proposed LY3127804 dose range to be investigated in this Study JQBA is 4 to 20 mg/kg given Q2W. This dose range will allow investigation of patient exposures that are anticipated to be efficacious based on preclinical data. This will permit full characterization of LY3127804 safety-tolerability and PK/PD versus dose-response relationship and, subsequently, optimal determination of the RP2D. The rationale for dose escalation up to 20 mg/kg (ie, beyond the anticipated predicted optimal effective dose of 16 mg/kg) is to generate the data package to optimally answer the study objectives (please refer to Section 5.1.3).

This dose range is supported by the 5-week toxicology study in the monkey and rat as illustrated by the margins of safety presented in Section 5.3.3, Table JQBA.5.3.1.

These dose and exposure multiples, presented in Table JQBA.5.3.1, result from a conservative calculation that does not take into account that the dose in human will be given half as frequently (Q2W) compared to the animal dosing (QW). If this difference in dosing frequency is factored in, then the dose multiples are 8- and 16-fold for the rat NOAEL and monkey NOEL relative to the human proposed starting dose, respectively. The exposure at the rat NOAEL dose and the monkey NOEL dose are 8- and 14-fold higher than the predicted exposure at the proposed 4-mg/kg starting dose in humans. This exposure results from that same conservative approach, which does not take into account that the dose in humans will be given half as frequently (Q2W) than the dose in the animal (QW). Furthermore, the single dose exposure in animal was taken for that calculation (excluding the accumulation from single dose to steady state).

Data from Cohort A5 (monotherapy) and B5 (combination with ramucirumab at 8 mg/kg) showed that 20 mg/kg LY3127804 did not result in any DLT. In such a case, the protocol allowed the investigation of additional dose levels with a maximum dose increment of 7 mg (please refer to Section 7.2.2). Consequently, the LY3127804 dose of 27 mg/kg was investigated in additional Cohorts A6 and B6. Later sections of the protocol (notably Section 6.2) have been amended, as needed, to clarify that LY3127804 was investigated up to a dose of 27 mg/kg.

### 5.5.2. Ramucirumab Dose

Ramucirumab is currently approved to be used at a dosage of 8 mg/kg Q2W.

In the Phase 1 dose-escalation study, Study I4T-IE-JVBM, weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated, and the MTD was identified as 13 mg/kg when given QW (Spratlin et al. 2010). The dosing regimen of 8 mg/kg administered Q2W was suggested for evaluation in further trials because clearance at this dose seemed to be saturated, and trough levels were >18 μg/mL, the level at which activity was seen in mouse xenograft models treated with a ramucirumab surrogate antibody. Data from both REGARD and RAINBOW confirmed that the ramucirumab dosing regimen of 8 mg/kg administered Q2W is a pharmacologically and clinically effective and safe dosage for the treatment of patients with advanced gastric cancer and offers a favorable benefit-risk profile for these patients. The first combination cohort in Part B will test LY3127804 and ramucirumab both administered at a dose

of 8 mg/kg (ie, at a 1:1 ratio). Based on pharmacological consideration, administering LY3127804 at least at the same dose as ramucirumab (ie, 1:1 ratio) is expected to be the minimal ratio leading to additional biological activity of LY3127804 when given in combination with ramucirumab. Therefore, Part B is designed to not study any dose lower than 8 mg/kg of LY3127804 in combination with the approved ramucirumab 8-mg/kg dose. This approach is fostered by the absence of any foreseeable toxic effects in vital organs based on nonclinical studies for the combination treatment at this ratio and the ethical consideration to minimize the number of patients exposed to combination therapy at ratios likely to be sub-therapeutic.

The dosage rationale for eventually using 12 mg/kg Q2W is based on the exposure-efficacy analyses from REGARD and RAINBOW, which indicated an association between efficacy and ramucirumab exposure. Additionally, the overall favorable safety profile of ramucirumab and the exposure-efficacy relationship observed in REGARD and RAINBOW suggested that there may be an opportunity to further improve efficacy while maintaining an acceptable safety profile in this combination therapy setting.

Hence, Study JQBA will be performed initially with a ramucirumab dosage of 8 mg/kg Q2W, and, if considered appropriate and safe, a ramucirumab dose of 12 mg/kg will be explored with a well-defined Ang2 combination dose.

# 6. Investigational Plan

## 6.1. Study Population

All patients will have to go through the entire screening process and fulfill all the criteria for enrollment in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once within 4 weeks of the initial screening. The interval between rescreenings should be at least 1 week and should not exceed 4 weeks. While performing a rescreening, all assessment time intervals will have to fit the timelines as mentioned in and Attachment 1. If a rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Repeating tests during the screening period (for example, blood pressure [BP] measurements or laboratory tests if medical conditions have changed) does not constitute rescreening.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

### *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] have histological or cytological evidence of a diagnosis of cancer that is advanced and/or metastatic. Patients must be, in the judgment of the investigator, an appropriate candidate for experimental therapy in the absence of a standard therapy or after available standard therapies have failed to provide clinical benefit for their disease, are refused by the patient, or the patient is not a candidate for those therapies. Patients entered into the trial for the combination setting may be patients for whom ramucirumab is considered SOC/appropriate treatment.

[2] have measurable and/or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1; Attachment 9) (Eisenhauer et al. 2009).

[3] Inclusion criteria [3] has been deleted

[4] are ≥18 years of age

[5] have given written informed consent prior to any study-specific procedures

[6] have adequate organ function, as demonstrated by:

- hematologic: absolute neutrophil count (ANC) ≥1.5 x $10^9$/L, platelets ≥100 x $10^9$/L, and hemoglobin level ≥9 g/dL (5.6 mmol/L). Transfusions are not allowed within 2 weeks prior to enrollment.

- hepatic: bilirubin level ≤1.5x upper limit of normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≤2.5x ULN. If the liver has tumor involvement, AST and ALT levels equaling ≤5x ULN are acceptable.
- renal: serum creatinine levels ≤1.5x ULN and calculated creatinine clearance >50 mL/min according Cockcroft and Gault (1976) (see Attachment 7).
- no major proteinuria:

  Patients with a urine dipstick analysis of ≥2+ at screening will need a 24-hour urine collection to confirm urine protein is ≤2g/24 hours prior to enrollment.
- albumin: albumin level ≥2.7 g/dL (27 g/L)
- coagulation: international normalized ratio (INR) or activated PTT ≤1.5x ULN

[7] have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 6)

[8] have discontinued previous treatments for cancer for at least 28 days or 5 half-lives prior to study enrolment, whichever is shorter, and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline or ≤ Grade 1, except alopecia and neuropathy, which should be resolved to ≤ Grade 2). Patients must have discontinued mitomycin-C or nitrosourea therapy for at least 42 days.

At the discretion of the investigator, an exception will be made for hormone-refractory prostate cancer patients continuing gonadotropin-releasing hormone (GnRH) agonist therapy and breast cancer patients continuing anti-estrogen therapy (for example, an aromatase inhibitor) while on Study JQBA as long as those therapies have been installed for at least 3 months and are known to have been well tolerated.

[9] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[10a] Male patients:

Agree to use a medically approved highly effective contraceptive method (Section 7.5) and to not donate sperm during the study and for at least 3 months following the last dose of study drug or country requirements, whichever is longer

[10b] Female patients:

Women of child-bearing potential must test negative for pregnancy within 7 days of enrollment based on a serum pregnancy test, agree to use a medically approved highly effective contraceptive method (Section 7.5) during the study and for 3 months following the last dose of the study drug(s), and also not be breastfeeding. A serum pregnancy test result above the reference range can be accepted if explained by disease history (and/or confirmed absence of pregnancy with echographic examination of the pelvis).

[11] have an estimated life expectancy, in the judgment of the investigator, that will permit the patient to complete 2 cycles of treatment

### 6.1.2. Exclusion Criteria

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

[12] have serious preexisting medical conditions (left to the discretion of the investigator) or have incompatibility with the exposure to LY3127804 or ramucirumab

[13] have received treatment with a drug predominantly targeting Ang2 activity (eg, tyrosine kinase inhibitors and/or antibody treatment)

[14] have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required)

Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids and/or anticonvulsants (for controlling the symptoms of the brain metastasis) and their disease is asymptomatic and radiographically stable for at least 30 days

[15] have current hematologic malignancies

[16] have an active fungal, bacterial, and/or known viral infection including

- human immunodeficiency virus (HIV, screening not required)
- hepatitis A (screening not required)
- hepatitis B or C (screening required; documentation of a negative test result within 6 months must be available for hepatitis B surface antigen and hepatitis C [antibodies or RNA according to local standard]). HCC patients with chronic viral (B or C) hepatitis are eligible if they retain adequate liver function per Child-Pugh score <7 (Child-Pugh class A only, Attachment 10).

[17] have a second primary malignancy that, in the judgment of the Investigator and sponsor, may affect the interpretation of results

[18] have a corrected QT interval using Fridericia's correction (QTcF) of >470 msec on screening electrocardiogram (ECG) at several consecutive days of assessment

[19] have a known sensitivity to mAbs or other therapeutic proteins, to agents of similar biologic composition as LY3127804 and ramucirumab, or to any products used in the formulation of LY3127804/ramucirumab (refer to the IB for LY3127804 and ramucirumab for details) or are incompatible with the treatment of LY3127804/ramucirumab.

[20] are patients receiving any of the following:

- full-dose (therapeutic) anticoagulation with warfarin and/or other anticoagulants like low-molecular weight heparin, thrombin inhibitors (dabigatran), and Factor Xa inhibitors (rivaroxaban)

  Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that they are on low-molecular-weight heparin or oral Factor Xa inhibitors or it is medically appropriate at the investigator's judgment that patients switch to low-molecular-weight heparin or oral Factor Xa inhibitors before initiation of study therapy.

- chronic daily treatment with aspirin at a daily dosage >325 mg/day or nonsteroidal anti-inflammatory medications known to inhibit platelet function (eg, indomethacin, ibuprofen, naproxen, or similar agents) or other antiplatelet agents (eg, clopidogrel, ticlopidine, dipyridamole, anagrelide) within 7 days prior to the first dose of study treatment. Patients receiving cyclooxygenase 2 (COX-2) inhibitors are eligible.

- low-dose methotrexate maintenance therapy

[21] have a significant bleeding disorder or vasculitis or had a Grade ≥3 bleeding episode within 12 weeks prior to receiving treatment

[22] have experienced any arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to receiving treatment

[23] have experienced any Grade 3 or 4 venous thromboembolic event that is considered by the investigator to be life-threatening or that is symptomatic and not adequately treated by anticoagulation therapy within 6 months prior to receiving treatment. Patients with chronic portal vein thrombosis who are asymptomatic and not considered to need anticoagulation therapy are eligible.

[24] have symptomatic congestive heart failure (New York Heart Association class ≥3) or symptomatic or poorly controlled cardiac arrhythmia

[25] have a serious nonhealing: (a) wound, (b) peptic ulcer, or (c) bone fracture, within 28 days prior to receiving treatment

[26] have undergone major surgery within 28 days prior to randomization or central venous access device placement within 7 days prior to receiving treatment

[27] plans to undergo elective major surgery during the course of the trial

[28] have a history of gastrointestinal perforation or fistula within 6 months prior to receiving treatment

[29] have a history of inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤12 months prior to receiving treatment

[30] have an acute or subacute bowel obstruction or history of chronic diarrhea that is considered clinically significant in the opinion of the investigator

[31] have liver cirrhosis with a Child-Pugh class B or worse or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. *Clinically meaningful ascites* is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

[32] have a history of hypertensive crisis or hypertensive encephalopathy or current poorly controlled hypertension (systolic BP ≥150 mm Hg and/or diastolic BP ≥95 mm Hg) despite standard medical management.

[33] have received treatment within 28 days of the initial dose of study drug with any 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

[34] for patients with non–small cell lung cancer only:

- The patient has radiographic evidence of intratumor cavitation regardless of tumor histology.

  For squamous cell histology or for centrally located mediastinal masses (<30 mm from the carina) identified by computed tomography (CT) scan or chest x-ray, the patient must undergo a magnetic resonance imaging (MRI) of the chest or IV contrast CT scan prior to study treatment to exclude major airway or blood vessel invasion by cancer.

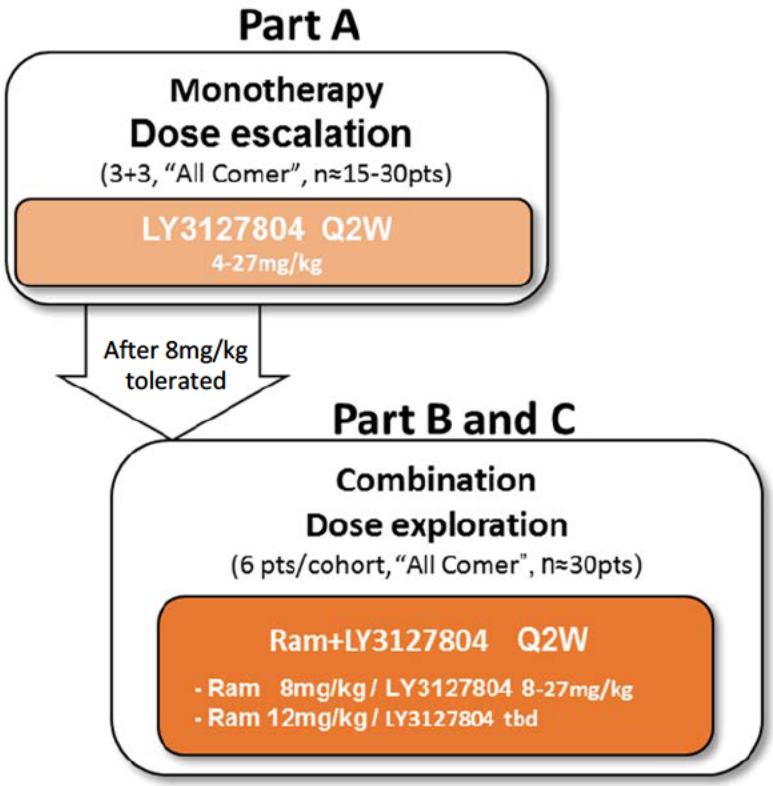
- The patient has a history of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months prior to study treatment.
- The patient has radiologically documented evidence of major blood vessel invasion or encasement by cancer

## 6.2. Summary of Study Design

Study JQBA is a multicenter, nonrandomized, open-label, dose-escalation Phase 1 study that will consist of 3 parts:

- Part A: dose escalation of LY3127804 to determine a RP2D range and schedule for LY3127804 monotherapy that may be safely administered to patients with advanced and/or metastatic cancer
- Part B: dose exploration of LY3127804 in combination with a fixed dose of ramucirumab 8 mg/kg to determine a RP2D range and schedule for LY3127804 that may be safely administered in combination with ramucirumab 8 mg/kg Q2W
- Part C: LY3127804 in combination with ramucirumab 12 mg/kg Q2W to determine a RP2D and schedule for LY3127804 that may be safely administered in combination with ramucirumab 12 mg/kg Q2W.

Figure JQBA.6.1 illustrates the planned study design.




Abbreviations: pts = patients; Q2W = every 2 weeks; Ram = ramucirumab.

Note: A treatment cycle is defined as an interval of 28 days.

**Figure JQBA.6.1. Study design.**

Eligible patients will receive LY3127804 as an IV infusion Q2W on a 28-day cycle (and discontinued as specified in Section 6.3.1). A 28-day period will be used for DLT observations

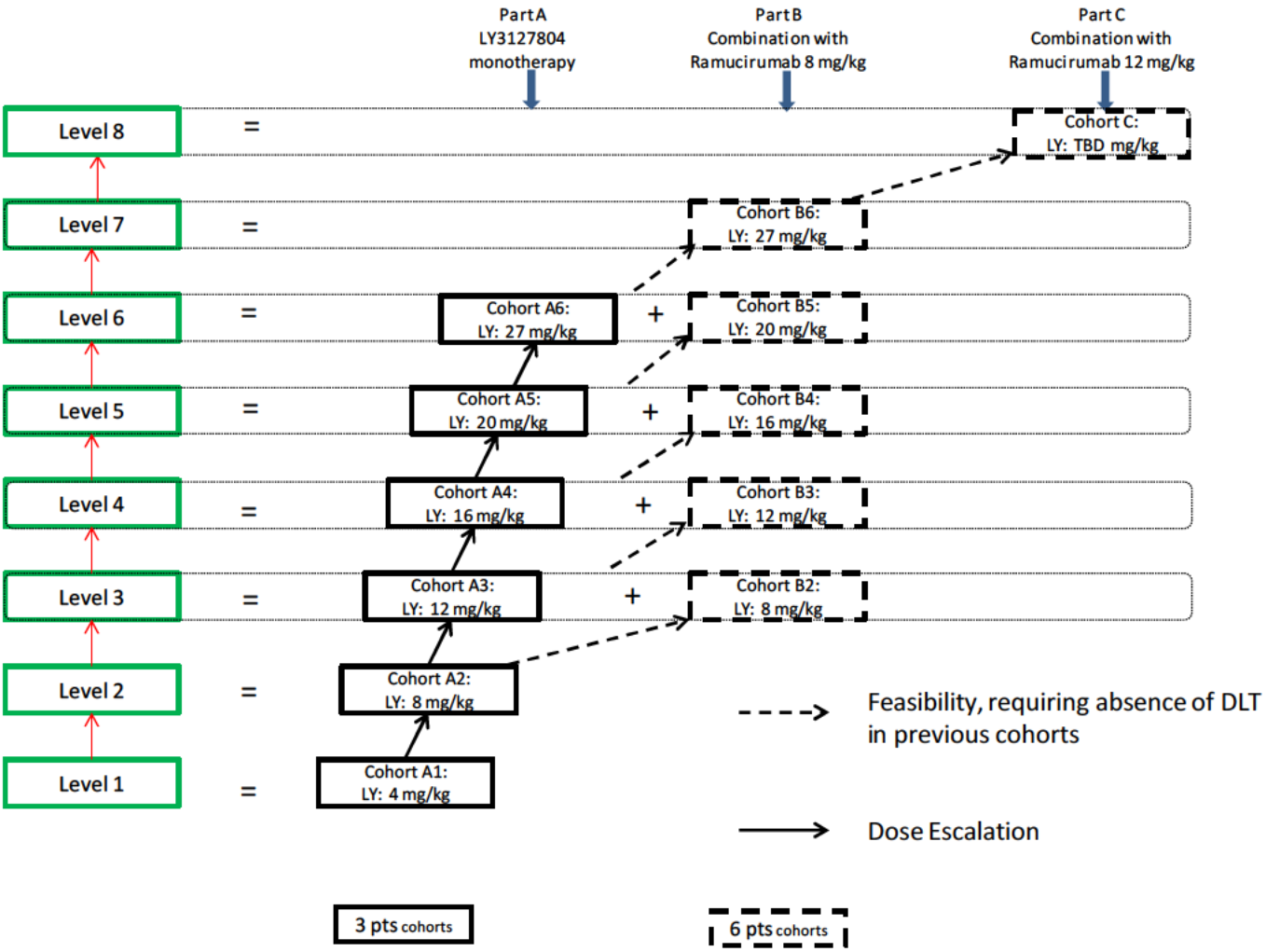
and an 8-week period will be used for efficacy assessments. LY3127804 will be investigated as a monotherapy and in combination with ramucirumab.

In **Part A,** the **LY3127804 single-agent, dose-escalation** part of the study, LY3127804 will be investigated as a monotherapy at a dose ranging from 4 mg/kg up to 27 mg/kg, given Q2W. Cohorts of 3 patients will be enrolled at each of the planned monotherapy dose levels. PK samplings and ECGs are being performed at expected time of maximal plasma concentration of LY3127804 to rule out the potential for LY3127804 to affect the QTc interval. The sponsor and the investigators will review and discuss all available patient safety data prior to dose escalation. In addition, available PK results from the previous cohort will be reviewed prior to dose escalation. The decision will be documented in writing.

**Part B (LY3127804 dose exploration with ramucirumab 8mg/kg)** will be opened after patients in Cohort A2 (ie, LY3127804 monotherapy at 8 mg/kg, Q2W) have completed the DLT period and the dose was assessed to be safe. An analysis of the data will be conducted, and feasibility to combine LY3127804 with ramucirumab dose of 8 mg/kg will be evaluated. Based on the results from this analysis, the dose exploration of B cohorts will be initiated (LY3127804 dose [ranging from 8 mg/kg up to 27 mg/kg] + ramucirumab at a fixed dose of 8 mg/kg) at the same time as LY3127804 monotherapy will be dose escalated at higher doses. Dose escalation for LY3127804 will occur up to 27 mg/kg Q2W or until the MTD has been reached; while for all dose levels starting from 8 mg/kg onwards, the feasibility of combining LY3127804 with ramucirumab will be explored. Cohorts of 6 patients will be scheduled at each of the planned combination dose levels. Safety data over the first 28 days of treatment with any LY3127804 dose and the available PK/PD data at that time will be reviewed prior to dose-escalation decision to the next dose level. More detailed information about the dose-escalation method and dosing decision in the course of Parts A to C of the study are available in Section 7.2.2.2 and Section 7.2.2.3.

**Part C (LY3127804 with ramucirumab 12 mg/kg)** will be opened once all the combination B cohorts (B2, B3, B4, B5 and B6) have been completed (unless prohibited by DLTs). After completion of Part B, an analysis will be triggered, and based on safety and tolerability data observed in Part B cohorts, it will be determined if and at which dose it is appropriate to combine LY3127804 with ramucirumab at a dose of 12 mg/kg. Based on the result from this analysis, a combination C cohort may be initiated (LY3127804 + ramucirumab dose of 12 mg/kg, 6 patients).

Figure JQBA.6.2 illustrates the planned dose-escalation scheme in Parts A through C of the study.




Abbreviations: DLT = dose-limiting toxicity; LY = LY3127804; pts = patients; TBD = to be determined.
Cohorts A, B, and C indicate, respectively, monotherapy LY3127804 or combination with 8 mg/kg or 12 mg/kg ramucirumab. The number in the cohort label (eg, 2 in Cohort A2) indicates the LY3127804 dose level 4 mg/kg (1), 8 mg/kg (2), 12 mg/kg (3), 16 mg/kg (4), 20 mg/kg (5), and 27 mg/kg (6).

**Figure JQBA.6.2. Study JQBA Parts A to C design: dose-escalation monotherapy and exploratory combination cohorts with ramucirumab.**

The planned duration of treatment is not fixed; patients will remain on study until they fulfill 1 of the criteria for study discontinuation (Section 6.3). All patients will undergo disease assessment every 8 weeks (prior to the onset of the subsequent treatment cycle). It is important that investigators consistently report lesions at all time points. In case of the observations of a new lesion, this new lesion will have to be reported in terms of location and size.

Refer to Attachment 1 for the Study Schedule.

### *6.2.1. Sample Size*

To determine the RP2D of LY3127804, an adequate sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as

well as an evaluation of the relationship between exposure and pharmacologic effects using descriptive statistics and appropriate modeling techniques, if data warrant. The overall sample size for this study is estimated to be a total of approximately up to 72 patients.

In Part A, approximately 15 to 30 patients (3 per cohort/dose level with 6 per cohort/dose level at which a DLT has been observed) are planned to be enrolled following a 3+3 dose-escalation scheme in this dose-escalation portion for LY3127804 monotherapy. The actual sample size will depend on the incidence of DLTs.

In Part B, approximately 24 patients (6 per cohort/dose level) are planned to be enrolled. The choice of having 6 patients per combination cohort is based on the assumption that this combination treatment can be beneficial for the patients (therapeutic dose of ramucirumab) and the intention to have a broad (safety) base before escalating to a higher dose of LY3127804 in the combination setting. In line, 6 patients will be enrolled in combination dose-exploration Cohort in Part C.

### *6.2.2. Study Completion and End of Trial*

This study will be considered complete after all parts (Parts A, B, and C) are complete. The dose-escalation and exploration phases of the study (Parts A, B, and C) will be considered complete after all patients required to determine the RP2D for LY3127804 have completed the DLT treatment-observation period and the patients in Part C have completed 4 cycles of study therapy or discontinued from the treatment (last patient). The unconfirmed objective responses of the patients in Part C need to be confirmed before the completion of the trial.

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

### *6.2.3. Continued Access Period*

All patients remaining on study treatment without evidence of disease progression or unacceptable toxicity, following the final analysis for safety or disease status, will be able to enter the continued access period of the study. The continued access period begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until disease progression, death, unacceptable toxicity, or start of new anticancer treatment. The continued access period includes a 30-day follow-up visit after last drug exposure. The follow-up visit begins on Day 1 after the cycle at which the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. 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.

A new patient ICF for the continued access period will need to be signed only if required by local law and regulations. Lilly will notify investigators when the continued access period begins.

During the continued access period, all AEs, SAEs, study drug dosing, and dose reduction and/or infusion duration continued access (due to infusion-related events) of treatment will be collected on the case report form (CRF).

SAEs will also be reported to Lilly Global Patient Safety and collected in the pharmacovigilance system. In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly to evaluate the reported SAE.

Investigators will perform any standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the Investigator's discretion; Lilly will not routinely collect the results of these assessments unless required for the safety follow-up of the patients.

## 6.3. Discontinuations

### *6.3.1. Discontinuation of Patients*

The criteria for enrollment must be followed explicitly. If the investigator site or the monitor at any time identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without investigational product, and this must be done prior to any further drug administration. 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 and in the best interest for that patient. The patient may not continue in the study (with or without investigational product) if the Lilly CRP does not agree with the investigator's determination that it is medically appropriate and indicated 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.

In addition, patients will be discontinued from the study drug and/or from the study (when specified) in the following circumstances:

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator/physician decision
    - the investigator/physician decides that the patient should be 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 the treatment of cancer,

discontinuation from the study drug(s) occurs prior to introduction of the other agent

- patient decision
    - patient requests to be discontinued from the study or study drug
- sponsor decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- patient has unequivocal evidence of progressive disease and will no longer benefit from trial treatment
- patient experiences unacceptable toxicity
- patient is noncompliant with study procedures and/or treatment (Section 7.6)
- patient becomes pregnant

The reason for and date of discontinuation 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 CRF and will represent the date of the onset of the 30-day safety follow-up. An exception to these discontinuation criteria may be granted in rare circumstances in which the patient has a serious or life-threatening condition for which there is no effective alternative therapy and, in the opinion of the investigator, is receiving benefit from study drug(s). In these rare cases, the investigator must obtain documented approval from Lilly to allow the patient to continue study treatment. Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

### 6.3.2. Discontinuation of Study Sites

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

### 6.3.3. 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. LY3127804*

LY3127804 for Injection is a lyophilized product supplied in a 75-mg vial (3 mL prior to lyophilization not including excess volume to enable withdrawal and delivery of the dose). This product is reconstituted with 3.2 mL of Sterile Water for Injection, resulting in 25 mg/mL of LY3127804. LY3127804 will be administered as an IV infusion by injection of the reconstituted drug product into sterile IV bags containing 250 to 500 mL normal saline. Lilly instructions regarding dilution requirements, infusion times, and appropriate use of filters during administration of LY3127804 should be followed.

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

### *7.1.2. Ramucirumab*

Ramucirumab, provided by Lilly, is a sterile, preservative-free solution for infusion formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50-mL vial). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80. Ramucirumab is a clear or slightly opalescent and colorless to slightly yellow liquid without visible particles. The pH is 6.0. The osmolality is 285 mmol/kg.

Ramucirumab must be stored under refrigeration at 2°C to 8°C with protection from direct light. DO NOT FREEZE AND/OR SHAKE RAMUCIRUMAB. Stability studies have demonstrated that the drug product can withstand transient excursion to room temperature without adverse effect; however, storage at this temperature is not recommended.

Ramucirumab should be prepared according to the manufacturer's instructions at dosages as specified in Table JQBA.7.2.2 and Section 7.2.1.2.

## 7.2. Study Drug Administration

The investigator or designee will be responsible for:

- the correct use of the investigational agent(s) and planned duration of each individual's treatment to the site personnel;
- verifying that instructions for preparation and administration are followed properly; and
- maintaining accurate records of study drug dispensation, destruction, and collection, and destroying or returning all unused medication to Lilly or its designee at the end of the study.

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

The date and time (start and end of infusion) of LY3127804 and ramucirumab administration will be recorded into the electronic CRF (eCRF).

### 7.2.1. Dosing Schedule

A treatment cycle is defined as an interval of 28 days. Treatment should continue on schedule if possible, but a variance of up to +3 days in Cycle 2 and beyond may be allowed to accommodate holidays and clinic scheduling conflicts. No shortening of the treatment cycle will be allowed.

#### 7.2.1.1. LY3127804 Dosing

The administered dose of LY3127804 will be dependent on the patient's baseline body weight in kilograms corresponding to the mg/kg dose given to the cohort the patient is allocated to. For repeated administration, the dose amount will be recalculated if there is a ≥10% change (increase or decrease) in body weight from baseline; thereafter subsequent doses will have to be calculated with this new body weight reference until there is another ≥10% change (increase or decrease) in body weight from this "new baseline" body weight for dose calculation. LY3127804 will be administered Q2W.

For patients undergoing repeated palliative drainage procedures to remove pleural or peritoneal fluid, the dry weight will be defined as weight obtained after the drainage procedure and before fluid reaccumulation. In such circumstances, dry weight will be used for dose calculation, if obtained within 30 days prior to dose. If no recent dry weight is available, actual weight will be used.

LY3127804 infusion time is to be determined based on an infusion rate not to exceed 25 mg/min and on the LY3127804 dose level administered. Table JQBA.7.2.1 provides an overview of the planned LY3127804 infusion duration. Patients receiving 4-mg/kg, 8-mg/kg, or 12-mg/kg doses should have infusion times not less than 60 minutes. Patients receiving 16-mg/kg, 20-mg/kg or 27-mg/kg doses should have drug infused in not less than 90 minutes. In addition, for patients receiving a LY3127804 dose up to a total dose of 1500 mg, LY3127804 IV infusions will last at least 60 minutes (±10 min) in order to not exceed an infusion rate of 25 mg/min of LY3127804. Total doses between 1500 and 2250 mg should be administered over at least 90 minutes (±15 min), and total doses above 2250 mg must be administered over at least 120 minutes (±20 min).

**Table JQBA.7.2.1. LY3127804 Infusion Duration**

| Dose Level | Total Dose | LY3127804 Infusion Duration |
|---|---|---|
| 4, 8, and 12 mg/kg | ≤1500 mg | 60 (±10) min |
| | >1500-2250 mg | 90 (±15) min |
| | >2250 mg-3000 mg | 120 (±20) min |
| 16, 20, and 27 mg/kg | ≤2250 mg | 90 (±15) min |
| | >2250 mg-3000 mg | 120 (±20) min |

Abbreviation: min = minutes.

The infusion rate must be reduced following an infusion-related reaction (see Section 7.2.2.8). The infusion duration must always be accurately recorded.

Aseptic techniques must be used when preparing and handling LY3127804. The dose of LY3127804 will be aseptically withdrawn from the vial and transferred to a commonly used

infusion container (see IB for details). A sufficient quantity of sterile normal saline (0.9% weight/volume) solution will be added to (or removed in the case of a prefilled bag such as AVIVA) the container so that the total/final volume of administration is 250 mL/500 mL. If the dose requires a volume 250 mL/500 mL, the addition of sterile normal saline is not required. The container must be gently inverted to ensure adequate mixing. Different LY3127804 drug product lots must not be mixed in a single infusion.

LY3127804 will be administered as an IV infusion using either a central or a peripheral venous line. A 0.22-micron in-line, sterile, non-pyrogenic filter should be used. Using 0.9% normal saline to flush the line at the end of the infusion or ensure overfill to ensure delivery of the calculated dose is recommended (but not mandatory). For more details regarding the administration of LY3127804, please refer to the pharmacy manual.

Premedication may be provided prior to LY3127804 infusion at the investigator's discretion. In case of infusion-related reaction suspected to be related to LY3127804, treatment (and further prophylaxis) is recommended and can be based on the ramucirumab recommendations for premedications. Recommended premedication agents include histamine H1 antagonists (IV or orally) such as diphenhydramine hydrochloride 50 mg (or equivalent). Additional premedication may be provided at investigator discretion. Premedication must be provided in the setting of a prior Grade 1 to 2 infusion-related reaction, as detailed in Section 7.2.2.8.

Patients will be observed closely for infusion-related or other AEs every 15 minutes during and following each administration of LY3127804 until 1 hour after the end of infusion. For patients receiving LY3127804 and ramucirumab, patients will be observed every 30 minutes during the ramucirumab infusion until 1 hour following the infusion. Afterwards, the patients should contact their treating physician as soon as possible in case of a late-occurring clinical event possibly related to the administration of LY3127804 or ramucirumab.

Observations should occur in an area containing resuscitation equipment and medications necessary for advanced life support and cardiopulmonary resuscitation, such as bronchodilators, vasopressor agents (eg, epinephrine), oxygen, glucocorticosteroids, antihistamine, and IV fluids. Vital signs will be collected as outlined in Attachment 1.

A written approval of the sponsor will be required in case the body weight of the patient indicates to administer a dose of LY3127804 exceeding 3000 mg on the day of treatment.

#### 7.2.1.2. Ramucirumab Dosing

Patients will receive ramucirumab by IV infusion over approximately 60 minutes (±10 min) at 8 mg/kg (or 12 mg/kg, according to cohort attributed to the patient) Q2W in the absence of disease progression or other withdrawal criteria.

On treatment days, ramucirumab will be administered **after** the LY3127804 infusion. The ramucirumab infusion should be started after a minimum of a 60-minute observation period (minimum of 30-minute observation period in Cycle 2 and beyond) **after** the end of the LY3127804 administration as specified in Section 7.2.1.1. Every attempt should be made in

order to start the ramucirumab infusion NO later than 60 minutes after the end of the LY3127804 infusion.

The administered dose of ramucirumab will be dependent on the patient's baseline body weight in kilograms. This dose will be recalculated if there is a ≥10% change (increase or decrease) in body weight from baseline; subsequent doses will have to be calculated with this new body weight reference unless there is another ≥10% change (increase or decrease) in body weight from "new baseline" dose calculation. Ramucirumab will be administered Q2W.

For patients undergoing repeated palliative drainage procedures to remove pleural or peritoneal fluid, the dry weight will be defined as weight obtained after the drainage procedure and before fluid reaccumulation. In such circumstances, dry weight will be used for dose calculation, if obtained within 30 days prior to dose. If no recent dry weight is available, actual weight will be used.

Ramucirumab administration guidelines can be found in the most recent pharmacy manual for ramucirumab. Aseptic technique is to be used when preparing and handling ramucirumab. Different drug product lots must not be mixed in a single infusion. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.

It is recommended that ramucirumab be diluted into normal saline in an IV infusion container to a final volume of 250 mL. Add to an empty IV container (or remove from AVIVA IV bag, which comes prefilled with 0.9% normal saline) a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to make the total volume 250 mL. Aseptically transfer the calculated dose of ramucirumab drug product at 10 mg/mL to the container. The container should be gently inverted to ensure adequate mixing. The use of a low protein-binding 0.22-micron in–line filter is required.

Prior to each ramucirumab infusion, all patients should be premedicated. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. For patients who have experienced a Grade 1 or 2 infusion-related reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen before each ramucirumab infusion. All premedication administered must be adequately documented in the eCRF.

### *7.2.2. Dose Escalation*

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD is reached or the RP2D is determined, whichever occurs first. RP2D can be concluded on appropriate biomarker or clinical evidence obtained during the period the patient is in the trial.

Safety data, in particular AEs, will be the primary criteria for dose escalation. The DLT period is defined as a 28-day period. Dose-escalation decision will be made based on safety data from Cycle 1 (observations of the first 28-day period). In addition, if available at the time of dose-escalation decision, PK ($C_{max}$, AUC, and systemic clearance) results will be used as secondary/supporting data for dose escalation. No dose escalation/opening of new cohort can

occur without prior discussion and agreement between the investigator and the Lilly CRP/Lilly study team; the decision will be documented in writing.

Different dose levels planned in Study JQBA are summarized in Table JQBA.7.2.2.

**Table JQBA.7.2.2. Planned Dose Levels and Treatment Schedule by Cohorts**

| Cohort | LY3127804[a] Day 1 and 15 | % Increase of LY3127804 | Ramucirumab[a] Day 1 and 15 |
|---|---|---|---|
| Cohort A-1 (3 pts) | 4 mg/kg | NA | NA |
| Cohort A-2 (3 pts) | 8 mg/kg | 100% | NA |
| Cohort A-3 (3 pts) | 12 mg/kg | 50% | NA |
| Cohort B-2 (6 pts) | 8 mg/kg | NA | 8 mg/kg |
| Cohort A-4 (3 pts) | 16 mg/kg | 33% | NA |
| Cohort B-3 (6 pts) | 12[b] mg/kg | 50% | 8 mg/kg |
| Cohort A-5 (3 pts) | 20 mg/kg | 25% | NA |
| Cohort B-4 (6 pts) | 16[b] mg/kg | 33% | 8 mg/kg |
| Cohort B-5 (6 pts) | 20[b] mg/kg | 25% | 8 mg/kg |
| Cohort A-6 (3 pts) | 27 mg.kg | 35% | NA |
| Cohort B-6 (6 pts) | 27 mg/kg | 35% | 8 mg/kg |
| Cohort C (6 pts) | TBD[b] mg/kg | NA | 12 mg/kg |

Note: "A" cohorts represent monotherapy cohorts; "B" cohorts represent combination cohorts with ramucirumab dose at 8mg/kg; and "C" cohort represent the combination cohort with ramucirumab dose at 12mg/kg.

Abbreviations: DLT = dose-limiting toxicity; NA = not applicable; TBD = to be determined.

[a] LY3127804 (and ramucirumab when mentioned) will be administered every 2 weeks, starting with LY3127804. A 28-day (2 infusions) period will be used for the observations of potential DLTs; an 8-week (4 infusions) period before a subsequent disease assessment is scheduled.

[b] To be performed only if required or indicated based on the observations from A and B cohorts. Dose may be modified if considered appropriate based on the data of the previous cohort. Final decision will be taken by the CRP in agreement with the investigators.

Intrapatient dose escalation will not be permitted at any time in this study. The first patient enrolled in Cohorts A1 and B2 (ie, first patients receiving any dose of LY3127804 monotherapy or in combination with ramucirumab) will be observed for a DLT (as defined in Section 7.2.2.1) during the first 2 weeks of Cycle 1, before subsequent patients are treated in these cohorts (ie, not prior to Cycle 1, Day 15, of the first patient). If the first patient does not experience a DLT during this period, subsequent patients may be concurrently enrolled at the initial cohort. In subsequent cohorts, all patients may be enrolled concurrently.

If the MTD has not yet been reached at the highest prespecified LY3127804 dose level (20 mg/kg), then additional dose levels can be investigated based on both safety and available PK data. However, dose increments beyond the highest prespecified dose level will never

exceed a maximum increment of 33% (ie, maximum increment of 7 mg) and patients will not be enrolled in the next cohort until safety data from the previous cohort have been assessed.

The LY3127804 dose level to be administered for patients in Cohort C (see Table JQBA.7.2.2) will be determined following a review of all safety and available PK/PD or antitumor activity data from previous cohorts. The data will be discussed between the sponsor and the investigators, and the decision will be documented in writing.

Based on the ongoing safety reviews, modifications to the dose-escalation strategy (as defined in Figure JQBA.6.2 and Table JQBA.7.2.2) or other design elements may be made via consensus between the CRP/clinical research scientist (CRS) and the investigators and/or via protocol amendment (to ensure patient safety). Intermediate dose levels for LY3127804 (or a dose below the starting dose) may be considered based on appearance of toxicity or PK/PD modeling, if deemed appropriate and following agreement between the investigators and the sponsor. During the dose escalation, if a new sequence of drug administration (eg, inverse order of administration or sequential dosing of the study drugs on separate days) should be indicated for safety or PK reasons, or preclinical data suggest that this may pose a better regimen, then the investigators together with the sponsor will decide on this change and inform the ERBs in writing.

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

A DLT is defined as an AE during Cycle 1 (first 28 days of exposure) in Parts A, B, and C that is possibly related to the study drug(s) and fulfills any 1 of the following criteria using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (NCI 2009) :

- ≥ CTCAE Grade 3 nonhematological toxicity despite maximal medical management. Exceptions will be made for:
  - nausea, vomiting, anorexia, diarrhea, or constipation that can be appropriately controlled and does not persist for more than 72 hours with treatment.
  - hypertension in which systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg persist <7 days after intensified antihypertensive therapy
  - asymptomatic electrolyte disturbance that can be treated with oral substitution therapy or by IV infusions requiring less than a 24-hour hospitalization
  - transient Grade 3 elevations of ALT and/or AST, without evidence of other hepatic injury (as defined by normal bilirubin levels and an ALT/AST ratio <1), in the setting of preexisting hepatic metastasis may be considered as not a DLT if agreed by the study investigator and Lilly CRP/CRS
- CTCAE Grade 4 hematological toxicity of >5 days' duration
- any febrile neutropenia (ANC <1.0x$10^9$/L, fever ≥38.5°C)

- CTCAE Grade 4 thrombocytopenia (unless recovered in 24 hours and in the absence of bleeding) or Grade 3 thrombocytopenia complicated with ≥ Grade 2 bleeding
- evidence of newly developed edema characterized by a body weight increase >10% as compared to the onset of therapy
- nephrotic syndrome or proteinuria exceeding 3.5 g/24 hours
- 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 Cycle 1)

Infusion-related reactions (including hypersensitivity reactions and anaphylaxis) should not be considered DLTs unless the investigator or Lilly medical monitor provides compelling rationale to support their inclusion as a DLT.

At the time of DLT reporting, special attention will be given to determine whether the DLT observed is primarily related to LY3127804, ramucirumab, or the combination of study drugs..

For the purpose of this study, the MTD is defined as the highest tested dose in a single-agent setting that has <33% probability of causing a DLT. MTD in the combination setting will be determined based on the nature and timing of the DLTs in the combination setting.

Patients in Parts A through C (Cycle 2 or greater) will be evaluated on an ongoing basis for AEs. In these patients, a DLT-equivalent toxicity will be defined based on trends of any clinical significant toxicity deemed by the study investigators and Lilly clinical research personnel to be dose limiting and related to study drug(s). The investigators and Lilly CRP/CRS will have to agree as to whether such AEs are considered as DLT-equivalent.

#### 7.2.2.2. Dose-Escalation Method for LY3127804 monotherapy in Part A

In this part of the study, a 3+3 dose-escalation paradigm will be used. If 1 of 3 patients at any dose level experiences a DLT in Cycle 1, then up to 3 additional patients will be enrolled at that dose level. If 2 (or more) out of a maximum of 3 patients at any dose level experience a DLT, dose escalation will cease and either the previous dose level will be declared the MTD or, following discussions between the investigators and the sponsor, additional patients may be treated at the previous or intermediate dose levels.

If a DLT is observed in 2 out of a maximum of 6 patients at any given dose, the sponsor, together with the investigators, will examine the safety. Following consultation, the sponsor and the investigators will decide if the dose level is intolerable or, in the case of confounding events (eg, ambiguity whether any toxicity with a potential DLT characteristic is possibly related to study treatment, the underlying tumor disease, or concomitant medication), additional patients may be enrolled at the current dose level or an intermediate dose level to further investigate the tolerability. If >2 patients experience a DLT at any time, dose escalation will cease, and the MTD will be defined at 1 dose level down. Following discussions between the investigators and

the sponsor, additional patients may be treated at previous dose levels to confirm the MTD or explore an intermediate dose level.

#### 7.2.2.3. Dose-Exploration Method for LY3227804 + ramucirumab in Parts B and C

This part of the study will consist of testing different dosages of LY3127804 in combination with a "fixed" dose of ramucirumab (either 8 mg/kg or 12 mg/kg).

Combination cohorts of LY3127804 and ramucirumab will be determined to be safe if the incidence of DLTs (Section 7.2.2.1) is <33%. Six patients per combination cohort will be enrolled to determine safety and tolerability. If a DLT is observed in 2 out of 6 patients at any combination cohort, the sponsor, together with the investigators, will examine the safety. Following consultation, the sponsor and the investigators will decide if the dose level is intolerable or, in case of confounding events (eg, ambiguity whether any toxicity with a potential DLT characteristic is possibly related to study treatment, the underlying tumor disease, or concomitant medication), additional patients may be enrolled at the current combination dose level to further investigate the tolerability. If >2 patients experience a DLT at any time, further dose exploration of combination treatment will cease, and the MTD for combination treatment will be defined at 1 combination dose level down.

In combination with ramucirumab 8 mg/kg, different dose levels of LY3127804 will be explored but only if considered safe from previous cohorts in monotherapy setting. It is planned that the combination of LY3127804 with ramucirumab 8 mg/kg will be started at the LY3127804 dose level of 8 mg/kg. Thereafter, the dose-escalation decision for LY3127804 from dose X to X+1 in combination with ramucirumab 8 mg/kg, will only be possible if:

- the proposed LY3127804 monotherapy dose level X+1, has been tested and assessed to be safe
- the previous combination cohort (LY3127804 X mg/kg + ramucirumab 8 mg/kg) have been tested and judged to be safe

In combination with ramucirumab 12 mg/kg, a single dose level of LY3127804 may be explored if considered appropriate (ie, Cohort C). LY3127804 dose selected will be based on the results from the combinations with ramucirumab 8 mg/kg and the monotherapy LY3127804 dose escalation. The dose selected will have to be agreed between the sponsor and the investigators and will be communicated to the ERB/IRB/ethics committee in writing.

#### 7.2.2.4. Biologically Effective Dose Range

The biologically effective dose of a targeted agent is not necessarily the same as the MTD. The biologically effective dose will be explored based on PK, PD, and clinical safety/efficacy data after consultation with the investigator to inform the recommended dose range for LY3127804 monotherapy and in combination with ramucirumab.

#### 7.2.2.5. Dose Adjustments and Delays

In Cycle 1, no dose adjustments or delays of LY3127804 or the combination of LY3127804 and ramucirumab will be allowed (ie, DLT assessment period), except in case of any DLT or safety concerns following discussion and written approval by the study CRP.

In Cycle 2 or beyond, if a patient experiences a toxicity warranting a dose adjustment or delay of study drug(s) in the investigator´s opinion, study drug(s) may be dose reduced or held for up to 2 consecutive doses (approximately 28 days) to allow sufficient time for recovery from the toxicity. This approximate 28-day time period begins on the day that the next dose of study treatment should have been administered but was withheld for toxicity.

In Parts B and C, if both study drugs were held due to a toxicity, study treatment with both study drugs should be resumed as soon as that toxicity is resolved, provided that the patient did not meet any discontinuation criteria. In case the toxicity in any of the combination cohorts is specifically attributable to 1 of the 2 study drugs in the opinion of the investigator, the patient may continue to receive the other study drug following the regularly scheduled Q2W treatment time points. In this setting, treatment of the withheld study drug should be resumed at the next regularly scheduled Q2W treatment time point of the continued study drug following the resolution of the event causing the hold. "Make-up doses" of the withheld antibody occurring between regularly scheduled Q2W treatment time points are not permitted in order to keep the administration of study drugs synchronized to the same study days (ie, Day 1 or 15 of a cycle). In situations in which >2 consecutive doses have been missed, events related to the missed doses have resolved, and there is evidence of ongoing disease control, continuation of ramucirumab and/or LY3127804 may be considered and must be discussed with the Lilly clinical team.

It is recognized that, in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions precisely 2 weeks following a prior infusion (ie, because of holidays, travel difficulties, or other circumstances). Accordingly, study-drug(s) infusions administered within the timing window as indicated in the Study Schedule (see Attachment 1) relative to the regularly scheduled Q2W treatment time point will be considered acceptable. Moreover, in Cycle 5 or beyond, study drug(s) dosing may be delayed for up to approximately 14 days because of holidays, weekends, inclement weather, or other justifiable events and will not counted as a protocol violation. This approximate up to 14-day time period begins on the day that the next dose of study treatment should have been administered. To keep the administration of both study drugs synchronized in the combination cohorts, the next dose of study drugs should be administered at the same study day to continue the regularly scheduled Q2W treatment time points.

In the event of dosing delays or missed doses, disease assessment and imaging studies should be undertaken according to the original Study Schedule, regardless of the actual number of on-study treatments received.

#### 7.2.2.6. Dose Modifications—LY3127804

LY3127804 may be dose reduced to the previous successfully explored dose level in case the investigators see the benefit for the patient to continue treatment and when the observed toxicity indicates that the administered LY3127804 dose is considered inappropriately high. For instance, if a patient suffers from toxicity primarily related to LY3127804 that is considered to be dose dependent and the exposure to LY3127804 is planned to continue in the patient's best interest for tumor control, treatment can be continued at 1 dose level below the dose at which the patient was entered into the trial (unless the patient was enrolled at the 4-mg/kg dose level).

Dose adjustments of LY3127804 should be discussed and agreed on between the CRP and the investigator.

#### 7.2.2.7. Dose Modifications—Ramucirumab

Toxicities assumed to be related to ramucirumab and potentially requiring dose delays or adjustments will have to be dose handled according to the guidelines in the most recent ramucirumab IB and pharmacy manual.

The ramucirumab dose may be delayed and/or reduced if the patient experiences an AE. Doses may be delayed to allow time for the patient to recover from the event. If a patient receiving 8 mg/kg experiences toxicity requiring ramucirumab dose modification, the dosage will be reduced to 6 mg/kg Q2W. If a second dose reduction becomes necessary, the dosage will be reduced to 5 mg/kg Q2W. Table JQBA.7.2.3 presents the dose reductions applicable to ramucirumab.

**Table JQBA.7.2.3. Ramucirumab Dose Reductions**

| Starting Dose | First Dose Reduction | Second Dose Reduction |
|---|---|---|
| 8 mg/kg | 6 mg/kg | 5 mg/kg |

Any patient who requires a ramucirumab dose reduction will continue to receive a reduced dose until discontinuation from ramucirumab or discontinuation from the study. Any patient who has had 2 ramucirumab dose reductions and who experiences an event that would cause a third dose reduction must be discontinued from ramucirumab.

For patients eventually entered at ramucirumab 12 mg/kg Q2W, the same toxicity criteria as used for 8 mg/kg will be used. If a patient at 12 mg/kg experiences toxicity requiring ramucirumab dose modification, the dose will be reduced to 10 mg/kg Q2W. If a second dose reduction becomes necessary, the dose will be reduced to 8 mg/kg Q2W.

Table JQBA.7.2.4 provides an overview of the criteria for ramucirumab dose modifications applicable if the patient experiences an AE.

**Table JQBA.7.2.4. Dose-Modification Guidelines for Ramucirumab for Adverse Events at Least Possibly Related to Ramucirumab, including Adverse Events of Special Interest (see also Ramucirumab IB)**

| | Adverse Event | CTCAE Grade | Dose-Modification Guidelines |
|---|---|---|---|
| 1. | **Infusion-related reaction** | | |
| 1.a. | Infusion-related reaction | 2 | Interrupt and reduce the infusion rate by 50% for the duration of the infusion and for all future infusions. Prior to all future infusions of ramucirumab, premedicate with:<br>• a histamine H1 antagonist, such as diphenhydramine hydrochloride<br>• dexamethasone or equivalent<br>• acetaminophen/paracetamol |
| 1.b. | Infusion-related reaction | 3-4 | Immediately and permanently discontinue ramucirumab |
| 2. | **Hypertension** | | |
| 2.a. | Hypertension (non–life-threatening and associated with symptoms) | 3 | • Delay ramucirumab until the hypertension is controlled with medication and is resolved to Grade 0-2.<br>o If controlled with medication and resolved to Grade 0-2, then may resume ramucirumab at current dose.<br>o If NOT controlled with medication and not resolved to Grade 0-2 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. |
| 2.b. | Uncontrolled hypertension, hypertensive crisis, or hypertensive encephalopathy | 4 | Immediately and permanently discontinue ramucirumab. |
| 3. | **Proteinuria** | | |
| 3.a. | Proteinuria = 2+ (dipstick or routine urinalysis)[a] | | • Administer ramucirumab at the current dose if clinically indicated.<br>• Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose.<br>o If urine protein is <2 g/24 h, administer ramucirumab at the patient's current dose.<br>o If urine protein is ≥2 g/24 h, modify the ramucirumab dose based on 24-hour collection. See Proteinuria ≥2 g/24 h (24-hour urine collection), Line 3.c. in this table. |

**Dose-Modification Guidelines for Ramucirumab for Adverse Events at Least Possibly Related to Ramucirumab, including Adverse Events of Special Interest (see also Ramucirumab IB)**

| | Adverse Event | CTCAE Grade | Dose-Modification Guidelines |
|---|---|---|---|
| 3.b. | Proteinuria >2+ (dipstick or routine urinalysis)[a] | | • Delay ramucirumab until urine protein returns to <2 g/24 h.<br>• Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose.<br>o If urine protein is <2 g/24 h, no further dose delay or dose reduction is required.<br>o If urine protein remains ≥2 g/24 h and is not resolved within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. |
| 3.c. | Proteinuria ≥2 g/24 h (24-hour urine collection)[a] | | • **First or second occurrence:** delay ramucirumab until urine protein returns to <2 g/24 h.<br>o If urine protein returns to <2 g/24 h, reduce ramucirumab dose.<br>o If urine protein remains ≥2 g/24 h and is not resolved within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.<br>• **Third occurrence:** discontinue ramucirumab. |
| 3.d. | Proteinuria >3 g/24 h or in the setting of nephrotic syndrome[a] | | Immediately and permanently discontinue ramucirumab. |
| 4. | **Arterial thromboembolic events, venous thromboembolic events** | 3 or 4 | Immediately and permanently discontinue ramucirumab. |
| 5. | **Bleeding/hemorrhage** | 3 or 4 | Immediately and permanently discontinue ramucirumab. |
| 6. | **Gastrointestinal perforation** | | Immediately and permanently discontinue ramucirumab. |
| 7. | **Reversible posterior leukoencephalopathy syndrome** | | Immediately and permanently discontinue ramucirumab. |
| 8. | **Congestive heart failure** | 3-4 | Immediately and permanently discontinue ramucirumab. |
| 9. | **Fistula formation** | | Immediately and permanently discontinue ramucirumab. |
| 10. | **Impaired wound healing** | | |
| 10.a. | Prior to planned surgery | | Withhold ramucirumab. |
| 10.b | After surgery | | Resume ramucirumab based on clinical judgment. |
| 10.c. | Wound-healing complications developed during study treatment | | Delay ramucirumab dosing until the wound is fully healed. |
| 11. | **Liver injury/liver failure** | | |
| 11.a. | Hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis | | Immediately and permanently discontinue ramucirumab. |

**Dose-Modification Guidelines for Ramucirumab for Adverse Events at Least Possibly Related to Ramucirumab, including Adverse Events of Special Interest (see also Ramucirumab IB)**

| | Adverse Event | CTCAE Grade | Dose-Modification Guidelines |
|---|---|---|---|
| 12. | **Hypothyroidism** | 2-4 | Therapy with ramucirumab can be continued while treatment for the thyroid disorder is instituted. |
| 13. | **Other adverse events considered at least possibly related to ramucirumab[b]** | | |
| 13.a. | Non–life-threatening and reversible adverse event | 3 | May delay ramucirumab until resolved to Grade 0-1.<br>• If resolved to Grade 0-1, may reduce ramucirumab dose.<br>• If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. |
| 13.b. | | 4 | Permanently discontinue treatment immediately, with the exception of Grade 4 fever or Grade 4 laboratory abnormality, in which case:<br>• **First occurrence:** Delay ramucirumab until resolved to Grade 0-1.<br>o If resolved to Grade 0-1, may resume ramucirumab original dose at the discretion of the investigator.<br>o If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.<br>• **Second occurrence:** Delay ramucirumab until resolved to Grade 0-1.<br>o If resolved to Grade 0-1, reduce ramucirumab dose.<br>o If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. |

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events (version 4.0; NCI 2009); h = hour(s); IB = investigator's brochure.

[a] If 24-hour urine collection is also performed the results of 24-hour urine collection should be used for clinical decision making.

[b] Patients who enter the study with symptoms or laboratory values equivalent to CTCAE Grade 1 or 2 adverse events should not necessarily have dose delays or reductions related to the persistence or mild worsening of those symptoms or laboratory values. If the patient experiences Grade 2 toxicities that represent clinically significant worsening of symptoms from baseline, the ramucirumab dose may be delayed at the discretion of the investigator.

### 7.2.2.8. Infusion-Related Reactions

As with other mAbs, infusion-related reactions may occur during or following LY3127804 monotherapy and in combination with ramucirumab administration. Infusion-related reactions will be defined according to the NCI-CTCAE 4.0 definition of infusion-related reactions (refer to "General disorders and administration site conditions" in NCI-CTCAE 4.0), as detailed below.

Symptoms occurring during or after infusion of study drug(s) may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (refer to "Immune System Disorders" in NCI-CTCAE 4.0). If symptoms occur during or after infusion of LY3127804, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event. Those described above should be graded as shown in Table JQBA.7.2.5.

**Table JQBA.7.2.5. NCI-CTCAE 4.0 Infusion-Related Reactions**

| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Infusion-related reaction | Mild transient reaction; infusion interruption not indicated; intervention not indicated | Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr | Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae | Life-threatening consequences; urgent intervention indicated | Death |
| Definition: A disorder characterized by an adverse reaction to the infusion of pharmacologic or biologic substances. | | | | | |
| Allergic reaction | Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated | Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hr | Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates) | Life-threatening consequences; urgent intervention indicated | Death |
| Definition: A disorder characterized by an adverse local or general response from exposure to an allergen. | | | | | |
| Anaphylaxis | — | — | Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension | Life-threatening consequences; urgent intervention indicated | Death |
| Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death. | | | | | |

**NCI-CTCAE 4.0 Infusion-Related Reactions (continued)**

| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Cytokine-release syndrome | Mild reaction; infusion interruption not indicated; intervention not indicated | Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr | Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates) | Life-threatening consequences; pressor or ventilator support indicated | Death |
| Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells. | | | | | |

Abbreviations: hr = hours; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

Consistent with usual medical practice, selected parenteral medications may be used for Grade 2 allergic/hypersensitivity reaction as detailed below. The Lilly CRP/study team must be contacted immediately.

The following are treatment guidelines for infusion-related reactions:

Grade 1

- Slow the infusion rate by 50% (by doubling the infusion time).
- Monitor the patient for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

Grade 2

- Stop the infusion.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen.
- Resume the infusion at 50% of the prior rate (by doubling the infusion time) once the infusion-related reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 4 hours.
- Monitor for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

For a second Grade 1 or 2 infusion-related reaction, administer dexamethasone 8 to 10 mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8 to 10 mg IV (or equivalent).

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.
- Patients who have a Grade 3 infusion-related reaction will not receive further treatment with LY3127804 but will continue to be followed per protocol.

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.
- Hospital admission for observation may be indicated.
- Patients who have a Grade 4 infusion-related reaction will not receive further treatment with LY3127804 but will continue to be followed in the study.

If a patient should have an infusion-related reaction to study drugs, all attempts should be made to obtain an anti-LY3127804 and anti-ramucirumab antibody blood sample as close to the onset of the event as possible, at the resolution of the event, and 30 days after the onset of the event. The procedure for sample collection and handling is described in a separate procedural manual.

The investigator will have to ensure that all therapy given for the infusion-related events are reported accordingly.

#### 7.2.2.9. Hypertension

Monitoring of BP is required during LY3127804 and ramucirumab therapy as outlined in Attachment 1. Every attempt should be made to control systolic BP to <140 mm Hg and diastolic BP to <90 mm Hg before starting treatment with LY3127804 and ramucirumab. Routine clinical and laboratory monitoring is required in patients who again develop hypertension or experience a deterioration in previous hypertension. Patients are allowed to continue either investigational drug as long as they experience ≤ CTCAE Grade 2 hypertension (ie, systolic BP <160 mm Hg and/or diastolic BP <100 mm Hg) or obtain such BP within 7 days following initiation of intensified antihypertensive therapy.

## 7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment in this trial will be assigned to receive LY3127804 as monotherapy or in combination with ramucirumab as presented in Table JQBA.7.2.2 in this study. Before each patient's enrollment into the study, an eligibility check must be conducted

between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose cohort and identification number assignment for each patient.

If investigators have eligible patients who have consented concurrently, more patients may be entered at a particular monotherapy dose level or combination dose level provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event needs to be approved by the sponsor following discussions with the investigators.

## 7.4. Blinding

This is an open-label study with data evaluation at the end of each cohort.

## 7.5. Concomitant Therapy

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. An exception will be made for:

- prostate cancer patients continuing GnRH agonist therapy or breast cancer patients continuing anti-estrogen therapy (for example, an aromatase inhibitor) as long as those therapies have been installed for at least 3 months and are known to have been well tolerated
- palliative radiotherapy of ≤14 calendar days in Cycles 2 and beyond following discussions between the investigators and the sponsor (eg, for pain control of a solitary [non-skull] skeletal metastasis) and written approval by the sponsor, as long as the patient has not developed another reason for study discontinuation

The need for any other form of radiotherapy will be the cause for early discontinuation from the study unless an agreement existed prior to enrollment for a painful bone lesion (to be irradiated in the first 2 weeks of the study). In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications (with special attention for antihypertensive and therapy for infusion related events) must be captured on the CRF.

Patients should receive full supportive care with the exception that the routine use of granulocyte colony–stimulating factors is not permitted during Parts A, B, and C of this study. The use of colony-stimulating factors may be given as needed for patients in Part E and follow local guidelines. If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to American Society of Clinical Oncology guidelines (Rizzo et al. 2008).

The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of antiplatelet therapy (eg, clopidogrel, ticlopidine, prasugrel, dipyridamole, picotamide, indobufen,

anagrelide, triflusal, or similar agents) and NSAIDs with a high risk of bleeding (for example, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged but is at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the patient. Chronic use of analgesic agents with no or low bleeding risk (for example, paracetamol/acetaminophen, metamizole, dipyrone, or propyphenazone) is acceptable.

Patients receiving therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents are excluded from participation. Anticoagulant low-molecular-weight heparin therapy may be instituted during the course of treatment on study (eg, following an asymptomatic or treatable deep vein thrombosis or pulmonary embolism), provided that no evidence of portal hypertension (including splenomegaly) or any prior history of variceal bleeding exists.

Males and females with reproductive potential must agree to use medically approved highly effective contraceptive precautions during the trial and for 3 months following the last dose of study drug. Female patients who are of child-bearing potential will be required to use 1 of the following highly effective contraceptive methods: combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives, intrauterine device, or contraceptive patch (only women <198 lb or 90 kg). Both males and females receiving LY3127804 may use total abstinence. Males receiving LY3127804 or males who have had a vasectomy who are the partners of females receiving LY3127804 do not need further contraception.

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

## 7.6. Treatment Compliance

LY3127804 and ramucirumab will be administered intravenously at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration should be 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.

### *7.6.1. Evaluable Patients*

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have been exposed to study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

Any patient who is discontinued from the study before completing the DLT cycle period will be deemed nonevaluable for assessment of a dose level, unless they experience a DLT prior to withdrawal.

If the patient is noncompliant, missed a dose, or had a dose administered outside of the 3-day time window 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 (single-agent cohorts) or 6 (combination cohorts) patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to DLTs.

Patients who are not evaluable for PK but who complete 1 cycle of therapy may be replaced upon consultation with the investigator(s), the Lilly CRP or CRS, and the PK/PD scientist 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

The safety and tolerability of LY3127804 have been assessed in nonclinical toxicology studies, and the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit initial characterization of the safety profile of LY3127804 in patients. Study procedures and their timing, including collection of blood/urine samples, are described in the Study Schedule (Attachment 1). The safety profile of ramucirumab is fully described in the ramucirumab IB.

Standard laboratory tests, including chemistry, hematology, coagulation, and urinalysis panels, will be performed. A serum pregnancy test will be performed if applicable at baseline and monthly during the study. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study.

### *8.1.1. Safety Data Collection and Review*

Investigators will be 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 will be responsible for the appropriate medical care of the patient during the study.

The investigator will remain 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 JQBA.8.1.1 presents a summary of AE and SAE reporting guidelines. Table JQBA.8.1.1 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 unfavorable 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 findings, vital sign measurements, and so on, 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 v4.0, and the investigator should make an effort to try to allocate the observed AEs to the underlying disease, LY3127804, ramucirumab, or the combination of treatments.

The NCI-CTCAE v4.0 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 v4.0. Any minor version of CTCAE v4.0 (for example, version 4.0X) may be used for this study. Minor CTCAE v4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI-CTCAE v4.0 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 fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

Upon documentation of pregnancy, the female patient must be removed from the study, and treatment with study drug(s) must be stopped immediately. The patient (mother and fetus) will be followed throughout gestation, birth, and for a short time postnatally for safety assessment.

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 must be reported to Lilly or its 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 designated data transmission methods 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 or study drug via designated data transmission methods.

The investigator will decide whether he or she interprets the observed AEs as either related to disease, the study medications (if possible), 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 primary cause-and-effect relationship between at least one of the study treatments and the AE is likely.
- **Possibly related:** a primary cause-and-effect relationship between at least one of the study treatments 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 any of the study treatments.

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

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

- death
- initial or prolonged inpatient hospitalization (except for study drug administration or underlying preexisting conditions that didn't change during therapy)
- 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 hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize 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.

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 Drug(s)*

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the ICF. For patients who do not enroll in the trial (that is, have not received at least 1 dose of LY3127804), 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 drug(s) 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 Visit*

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the 30-day follow-up visit (Visit 801) must be reported to Lilly or its designee. The 30-day follow-up visit starts the day after the patient and the investigator agree that the patient will no longer continue study treatment. At the end of the 30-day follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments will be 30 ± 3 days after the patient has discontinued treatment.

The continued access period follow-up visit (Visit 901) begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

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.

Once the new anticancer therapy is initiated, any subsequent AEs or SAEs should no longer be assigned to the study drug(s) in this protocol.

After the 30-day follow-up visit (Visit 801), AEs are not required to be reported unless the investigator feels that the AEs were related to either study drug, drug delivery system, or protocol procedure. If an investigator becomes aware of an SAE 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 DCSI in the IB 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 summarized in Table JQBA.8.1.1. Refer to Attachment 5 for SAE reporting recommendations.

**Table JQBA.8.1.1. Adverse Event and Serious Adverse Reporting Guidelines for Study JQBA**

| 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<br>All AEs<br>All SAEs regardless of relatedness | x<br>x<br>x | <br><br>x |
| On therapy (starts at first dose of study drug[s] and ends at last dose of study drug[s]) | All AEs<br>All SAEs regardless of relatedness | x<br>x | <br>x |
| 30-Day follow-up visit (Visit 801) (starts the day after the patient has discontinued treatment and ends when end-of-study safety assessments are completed [30 ± 3 days after the patient has discontinued treatment]) | All AEs<br>All SAEs regardless of relatedness | x<br>x | <br>x |
| Continued access period | All AEs<br>All SAEs regardless of relatedness | x<br>x | <br>x |
| Continued access period follow-up | All AEs<br>All SAEs regardless of relatedness | x<br>x | <br>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. Electrocardiograms

Safety **local** 12-lead ECGs will be collected according to the Study Schedule (Attachment 1). Patients should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs should be recorded before collecting any blood for safety or PK tests. Additionally, the local ECG obtained during screening should assess QTcF on consecutive replicate ECGs (triplicates) obtained at approximately 1-minute intervals.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point will be allowed 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 at the relevant visit(s) 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 enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether 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 from at least 1 of the replicate ECGs from each time point.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless an over-read of the ECGs is conducted prior to completion of the final study report (in which case, the over-read data would be used).

For patients in Parts A, B, and C, PK sample-time match **digital central 12-lead ECGs** will be collected as replicates (triplicates) according to the Study Schedule (Attachment 1; for more precise timing, see Attachment 4). All digital ECGs designated for central evaluation will be electronically transmitted to a central ECG laboratory designated by Lilly. If indicated, Lilly may trigger a conduct of a central over-read of these stored ECGs by a cardiologist at the central ECG laboratory (including all intervals). In this case, all data from the central over-reads will be placed in a Lilly database for analytical and study report purposes. When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

#### 8.1.3.2. Thyroid Function

Some thyroid observations have been noted in the rat preclinical toxicology study. The clinical relevance of this is uncertain at this time. The thyroid function will be monitored at baseline and during the study as outlined in the Study Schedule (Attachment 1).

### *8.1.4. Safety Monitoring*

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

Lilly will review SAEs within time frames mandated by company standard operating procedures and will review trends, laboratory analytes, and AEs at periodic intervals.

If a study patient experiences elevated ALT ≥5x ULN and elevated total bilirubin ≥2x ULN, clinical and laboratory monitoring should be initiated by the investigator.

For patients entering the study with ALT ≥3x ULN, monitoring should be triggered at ALT ≥2x baseline.

Details for hepatic monitoring depend on the severity and persistence of observed laboratory test abnormalities (see Attachment 3). 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 2).

Patients suspected of tumor bleeding will have to be monitored closely with regular hemoglobin assessments to document the impact of the bleeding and the overall safety of the patient.

Decisions for additional assessments (eg, endoscopy), as well as the requirement for transfusion, will be left to the investigator but should preferably be discussed with the CRP.

A 24-hour urine collection will be required at screening for any patients with a urine dipstick (or equivalent) of ≥2+ to document the proteinuria to be <2 g/24 hours (as a proteinuria of >2 g/24 hours will exclude the patient from study participation). During trial treatment, worsening in the proteinuria (urine dipstick result: ≥2+) will trigger an additional 24-hour urine collection to exclude a (treatment-related) proteinuria >3.5 g/24 hours (which will require the study treatment to be stopped).

### *8.1.5. Complaint Handling*

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

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

The investigator or his/her designee will be 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 8 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

### *8.2.1. Samples for Study Qualification and Health Monitoring*

Blood (serum/plasma) and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health throughout the study.

Tumor samples will be labeled with patient number and tissue of origin and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drugs. Tumor specimens submitted as an FFPE tissue block will be sectioned and returned to the sites by the end of study or upon request. Slides will not be returned. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission.

Investigators must document their review of each laboratory safety report.

Blood and urine samples collected for specified safety 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 PD samples will be collected as specified in the Pharmacokinetic and Pharmacodynamic Sampling Schedule (Attachment 4).

#### 8.2.2.1. Pharmacokinetic Samples

For LY3127804, blood will be collected and processed to plasma for measuring LY3127804 concentrations. For ramucirumab, blood will be collected and processed to serum for measuring ramucirumab concentrations.

At the visits and times specified in the Study Schedule and PK sampling scheme (Attachment 4), venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of LY3127804 or serum concentrations of ramucirumab. A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed on 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 (on the laboratory requisition form).

These samples will be analyzed at laboratories designated by the sponsor. Plasma concentrations of LY3127804 and serum samples of ramucirumab will be assayed using validated antigen capture enzyme-linked immunosorbent assays.

All PK samples will be stored at a facility in the United States designated by the sponsor.

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

Important note: each date and time (start and end) of infusion of LY3127804 and ramucirumab will be recorded in the eCRF. This is required to derive the actual PK profile (ie, to derive the actual time of the PK samples relative to the dose).

#### 8.2.2.2. Pharmacodynamic Samples

Blood samples collected to measure the biomarkers will be identified by the patient number (coded) and retained for a maximum of 15 years or until testing is considered complete following last patient visit for the study at a facility selected by the sponsor.

PD samples will be collected as specified in the Study Schedule and PD sampling scheme (Attachment 4). Venous blood samples of approximately 10 mL each will be collected. The

samples may be analyzed for, including but not limited to, Ang2/Ang1 ratio, PlGF, VEGF (VEGFA, VEGFC, and VEGFD), and soluble receptors (VEGFR2, sTie2, sTie1). Blood biomarker levels from the study treatment period may be compared with baseline (screening). In addition, the time course of blood biomarker levels during the study and PK/PD biomarker relationship may be evaluated. Additional analysis can be added at any time point to better understand the impact of the treatment on the body and tumor as well as understanding the cancer pathway. In case of volume shortness of PD samples, PK samples can also be considered for PD assessments.

### 8.2.3. Samples for Biomarker Research

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; the mechanism of action of the drug; the disease etiology; and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped, and analysis may be performed to evaluate a genetic association with response to LY3127804. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Collection of samples for other biomarker research is an integral part of this study. Blood and tissue samples will be collected. Assessments of these samples may include analysis for exploratory biomarkers related to the mechanism of action of LY3127804; angiogenesis; and the Ang1, Ang2, Tie2, and VEGF pathways to better understand relationships of cellular-signaling defects with clinical outcomes and mechanism of cancer and cancer-related conditions (paraneoplastic conditions and cancer pathobiology). These analyses may include, but are not limited to, candidate gene/genome-wide analysis for RNA, DNA, serum/plasma analytes (including any of these components derived from exosomes), or tissue biomarkers. The association of biomarkers with the objectives of the study may be assessed. The exploratory biomarker sampling times are listed in Attachment 1. The exploratory biomarker analysis may be performed by the sponsor or at a laboratory selected by the sponsor.

Samples for exploratory biomarkers include the following type of samples:

- blood (including whole blood for pharmacogenetics and plasma/serum for other circulating factors as described in Section 8.2.2.2; mandatory for all patients)
- tumor tissue samples:
  - archival and/or fresh pretreatment tumor samples (optional for all patients)
  - "on-treatment biopsies" (optional for all patients): for patients willing to consent, additional on-study biopsies may be collected at any time during the

study if safe and feasible (preferably core tumor biopsies; alternatively, cytology or fine-needle aspiration). In particular, patients progressing on study therapy are encouraged to have biopsies performed, provided no other cancer treatment has been started and the procedure does not impede or delay planned cancer treatment.

Tumor specimen samples may be of any type of tissue, with the exception of bone or CNS metastases. Submission of a tissue block is preferred. Alternatively, serially cut unstained sections from the FFPE block can be submitted. Tumor tissue specimens must have adequate evaluable tumor cells. Due diligence should be used to make sure that tumor specimens (not a normal adjacent or a tumor margin sample) are provided. An associated pathology report may also be requested to be sent with the samples. Tumor specimens submitted as an FFPE tissue block will be sectioned and returned to the sites by end of study or upon request. Slides will not be returned. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

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

Samples will be destroyed according to a process consistent with local regulation.

### *8.2.4. Samples for Immunogenicity Research*

Blood samples for immunogenicity testing will be collected to determine antibody production against study drugs (please refer to the Study Schedule, Attachment 1). The actual date of each sampling will be recorded. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of study drugs from the moment this assay is available. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of study drugs.

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 study drugs. The duration allows the sponsor to respond to regulatory requests related to both study drugs.

## 8.3. Efficacy Evaluations

A secondary objective of the study is to document any antitumor activity. Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

Each patient will be assessed by 1 or more of the following radiologic tests for tumor measurement:

- CT scan
- MRI

Each patient's full extent of disease will also be assessed with:

- tumor measurement by RECIST 1.1 (Eisenhauer et al. 2009)
- evaluation of tumor markers, if indicated.

Radiological images may be collected centrally and overread.

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 6 to 8 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 progressive disease are present and documented accordingly. Patients should be followed for survival (investigator contacting patients after evidence of disease progression) for the length of the study duration.

Optional DCE-MRI may be performed but will be subject to agreement between sponsor and investigator. For those patients, a DCE-MRI should be performed prior to study entry, after approximately 2 weeks of therapy, and eventually after approximately 4 weeks of therapy. The timing of the on-treatment DCE-MRI might be adjusted based on emerging information and following discussion between the sponsor and the investigators. Centralized independent reviewers will be involved in reviewing the imaging (DCE-MRI) data to minimize any bias in radiological assessment.

## 8.4. Procedure/Sampling Compliance

Every attempt will be made to enroll 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 (including ECGs), PK samples, PD 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 or laboratory requisition form.

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

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.

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

The analyses for this study will be descriptive, except for possible exploratory analyses as deemed appropriate. Data analyses will be provided by dose levels and for all patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients (N), mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using N, frequency, and percentages. Missing data will not be imputed. Exploratory analyses of the data that are not described in the protocol will be conducted as deemed appropriate. A detailed description of data analyses will be provided in a separate statistical analysis plan document for this study.

This is a Phase 1 study with an open-label, dose-escalation design. Patients will be enrolled into cohorts sequentially without randomization to dose level. During dose escalation, the total sample size per cohort will be guided by the standard oncology 3+3 method and determined by the occurrences of DLTs for the monotherapy-treated patients. The LY3127804 plus ramucirumab combination cohorts will enroll 6 patients per dose level. The size of 6 patients per combination cohort will ensure a broad (safety) base before exploring a higher dose of LY3127804 in the combination setting and is assumed to be beneficial for the patients (therapeutic dose of ramucirumab). The total sample size is estimated to be approximately up to 72 patients.

## 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.

Additional summary of patient participation flow will be performed for the purpose of fulfilling the Clinical Trial Registry requirements. A participant flow will describe how many enrolled patients completed the study, and for those who did not, the frequency of each reason for not completing.

## 10.3. Patient Characteristics

Patient characteristics will include a summary/listing of the following:

- patient demographics, including age, sex, screening height and weight, and screening body mass index
- baseline disease characteristics
- prior disease-related therapies

- concomitant medications

Other patient characteristics will be summarized as deemed appropriate.

## 10.4. Safety Analyses

All patients who receive at least 1 dose of LY3127804 and/or ramucirumab will be evaluated for safety and toxicity. AE terms and severity grades will be assigned by the investigator using CTCAE, version 4.0.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- dose adjustments
- laboratory values
- vital signs
- DLTs at each dose level
- ECGs readings
- concomitant medications

## 10.5. Pharmacokinetic Analyses

PK analyses will be conducted on patients who have received at least 1 dose of the study drug(s) and have had samples collected.

PK parameter estimates for LY3127804 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum observed drug concentration ($C_{max}$) and area under the concentration-time curve (from time zero to time t, for which *t* is the last time point with a measurable concentration [$AUC_{0\text{-}tlast}$], from time zero to infinity [$AUC_{0\text{-}\infty}$]) of LY3127804. Other noncompartmental parameters, such as $t_{1/2}$, systemic clearance, and volume of distribution may be reported.

PK parameter estimates $AUC_{0\text{-}\infty}$, area under the concentration versus time curve during a dosing interval at steady state ($AUC_{\tau\text{-}ss}$), and $C_{max}$ will be evaluated to delineate effects of dose proportionality and temporal linearity. Log-transformed $C_{max}$ and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% CIs. Summary descriptive statistics of the PK parameters will be carried out by dose group and also per monotherapy/combination therapy.

The limited ramucirumab PK information collected following administration of ramucirumab in combination with LY3127804 will be summarized by time point ($C_{min}$ and $C_{max}$) and compared with historical data following ramucirumab monotherapy.

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.

## 10.6. Pharmacodynamic Analyses

All patients enrolled in this trial will undergo blood sampling during the extent of their treatment. PD samples will be taken at the same time as PK samples are scheduled.

PD data from all patients undergoing PD assessments will be analyzed.

## 10.7. Pharmacokinetic/Pharmacodynamic Analyses

Relationship will be explored between LY3127804 concentration and biomarkers/PD response such as, but not limited to, Ang2/Ang1 ratio and other biomarkers (eg, markers of either Tie2-Ang2-Ang1 and VEGF pathways activity or tumor activity). Nonlinear mixed-effect modelling using software such as NONMEM may be used if appropriate to derive those relationships.

The PD endpoints versus time information will be analyzed (summary statistic performed by time point), and the change relative to pretreatment-baseline value will also be considered in the analysis.

In addition, if deemed appropriate based on the ECG read out, the central ECG database may be built using the stored digital central 12-lead ECGs. From those data, the relationship between LY3127804 concentration and ECG numerical results (QTcF and change in QTcF relative to baseline) may be explored to identify whether LY3127804 may lead to QTcF prolongation and to support/supplement the analysis of the cardiac safety monitoring.

## 10.8. Immunogenicity

Immunogenicity data will be summarized, and any relationship of immunogenicity to study drug level, activity, and safety will be explored as appropriate.

## 10.9. Efficacy

The study was not designed to make an efficacy assessment. However, any tumor response data and PFS data will be summarized if appropriate and will be listed.

Reported lesion data (target/nontarget or measurable/nonmeasurable) will be listed for all enrolled patients.

## 10.10. Safety Reviews and Interim Analyses

Since this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study until the RP2D range or MTDs are determined for monotherapy and combination dose level. The purpose of these cohort-by-cohort reviews (Safety Reviews) is to evaluate the safety data at each dose level/combination and determine if 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 on their review of the safety and tolerability data as described in this protocol for the dose escalation of LY3127804 as well as the feasibility of the different combination settings.

Safety and/or PK data (when available) will be reviewed during the study if needed for dose escalation, modifications to the dose-escalation strategy, or other design elements.

After all patients who are deemed evaluable for the assessment of dose levels complete the DLT evaluation period or MTD is determined in Parts A and B, an interim safety and available PK data review will be conducted. A further safety review is planned after completion of Part C.

If it is deemed that enough data is obtained to assess the primary objective and the secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data until the data-cutoff date will be used for the analysis of safety, efficacy, PK, and PD biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after the data-cutoff date. These data may be reported separately, and the analyses on all patients including these data may not be performed.

# 11. Informed Consent, Ethical Review, and Regulatory Considerations

## 11.1. Informed Consent

The investigator will be 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 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.

In this protocol, the term "informed consent" includes all consent and assent given by patients.

## 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 ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). 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 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 (CIOMS) International Ethical Guidelines
2) the ICH GCP Guideline [E6]
3) applicable laws and regulations

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

Some of the obligations of the sponsor will be assigned to a third-party organization (TPO).

An identification code assigned 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 most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill 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 JQBA Study Schedule

## Baseline Assessments

| | Relative Day Prior to Day 1 of Cycle 1 | | | |
|---|---|---|---|---|
| | ≤28 | ≤14 | ≤7 | Comments |
| Informed consent | | | | Informed consent form signed (prior to performance of any protocol-specific tests/procedures) |
| Radiological tumor assessment | X | | | These scans can be performed locally and may be from prior to consent if taken within 28 days of Day 1, Cycle 1. PET/CT allowed if CT portion is of diagnostic quality |
| Functional tumor imaging (DCE-MRI) | X | | | DCE-MRI can be scheduled pending agreement between sponsor and investigator |
| Hepatitis B and C screening | X | | | See Attachment 2 may be from prior to consent if done within 6 months of Day1, Cycle 1; hepatitis B surface antigen and hepatitis C (antibodies or RNA according to local standard) |
| Tumor sample (optional) | X | | | See Sections 8.2.1 and 8.2.3. |
| Whole blood for pharmacogenetics (mandatory) | X | | | See Section 8.2.3; may be obtained, if allowed by local law |
| Medical history | | X | | Including alcohol/tobacco use and age at baseline as well as concomitant medication |
| Physical examination | | X | | Including height and weight |
| Vital signs | | X | | Including temperature, blood pressure, pulse rate, respiration rate |
| Performance status | | X | | Per ECOG scale |
| Chest x-ray | | X | | X-ray is not required if a CT of the chest has been obtained |
| ECG | | X | | One set of local triplicate ECGs |
| Hematology | | X | | See Attachment 2 |
| Coagulation | | X | | See Attachment 2 |
| Serum chemistry | | X | | See Attachment 2 |
| Urinalysis | | X | | If the preliminary urinalysis shows trace protein levels (a urine dipstick analysis of ≥2+), the patient must have 24-hour urine collection |
| HbA1c | | X | | See Attachment 2 |
| TSH and fT4 | | X | | See Attachment 2 |
| Immunogenicity | | X | | Sampling for ADAs against LY3127804 (all patients) and ramucirumab (only patients receiving LY3127804 + ramucirumab) |
| CTCAE v4.0 grading (preexisting conditions) | | X | | To be reported only after study eligibility is confirmed. See Section 8.1.2 |

| | Relative Day Prior to Day 1 of Cycle 1 | | | |
|---|---|---|---|---|
| | ≤28 | ≤14 | ≤7 | Comments |
| Concomitant meds | | X | | |
| Tumor markers | | X | | To be collected based on initial diagnosis (for example, α-fetoprotein for HCC; CA-125 for ovarian cancer) |
| Sampling for exploratory blood biomarkers (mandatory) | | X | | See Section 8.2.3 |
| Pregnancy test (WOCBP) | | | X | Negative serum pregnancy test result required prior to dosing for women of child-bearing potential |

Abbreviations: ADA = anti-drug antibody; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; fT4 = free thyroxine; GEJ = gastro-esophageal junction; HbA1c = glycosylated hemoglobin; HCC = hepatocellular carcinoma; INR = international normalized ratio; meds = medications; PD = pharmacodynamic; PET = positron emission tomography; PSA = prostate-specific antigen; SAEs = serious adverse events; TSH = thyroid stimulating hormone; WOCBP = women of child-bearing potential.

## During and Poststudy Assessments

| | Cycle 1 | | | | | | | Cycle 2 | | | | Cycle 3-n | | | Follow-Up | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | 30-day (V801) | |
| ***Relative Day Within a Cycle*** | **1** | **2** | **4 or 5** | **8** | **15** | **16** | **22** | **1** | **8** | **15** | **22** | **1** | **8** | **15** | | In Cycle 2 and beyond, visits may be performed ±3 days around scheduled visits. No shortening of the treatment cycles is allowed |
| LY3127804 | X | | | | X | | | X | | X | | X | | X | | |
| Ramucirumab | X | | | | X | | | X | | X | | X | | X | | Only patients in Parts B and C |
| | | | | | | | | | | | | | | | | |
| Physical examination | X | | | X | X | | | X | | X | | X | | | X | |
| Weight | X | | | | X | | | X | | X | | X | | | X | |
| Vital signs | X | X | | X | X | | X | X | X | X | X | X | | X | X | Temperature, pulse rate, RR, and BP. On study drug infusion days, measure pulse rate and BP within 15 min prior to infusion(s), after completion of each infusion(s), and 1h after completion of the last antibody infusion. Additional measurements as clinically indicated. Day 2 Cycle 1 only for patients in Parts A, B, and C |
| Central ECG (12 lead) | X | X | | | X | | | X | | X | | | | | | **Only for patients in Parts A, B, and C** during Cycle 1 and 2; see Attachment 4 for exact timing; triplicate ECGs to be conducted |
| Hematology | X | | | X | X | | | X | X | X | | X | X | X | X | See Attachment 2; may be done within 3 days prior to administration of study drugs (except Cycle 1, Day 1 [within 3 days]); **Only patients in Part A-C**: Day 8 only in Cycle 1 and Day 15 in Cycle 3 and beyond only if abnormal (different from previous assessment) on Day 1 |

| | Cycle 1 | | | | | | | Cycle 2 | | | | Cycle 3-n | | | Follow-Up | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | 30-day (V801) | |
| ***Relative Day Within a Cycle*** | **1** | **2** | **4 or 5** | **8** | **15** | **16** | **22** | **1** | **8** | **15** | **22** | **1** | **8** | **15** | | In Cycle 2 and beyond, visits may be performed ±3 days around scheduled visits. No shortening of the treatment cycles is allowed |
| Coagulation | X | | | X | X | | | X | | X | | X | | X | X | See Attachment 2; may be done within 3 days prior to administration of study drugs (except Cycle 1, Day 1 [within 3 days]); in Cycle 3 and beyond, Day 15 only if abnormal (different from previous assessment) on Day 1 |
| Serum chemistry | X | | | X | X | | | X | X | X | | X | X | X | X | See Attachment 2; may be done within 3 days prior to administration of study drugs (except Cycle 1, Day 1 [within 3 days]); **Only patients in Part A-C**: Day 8 only in Cycle 1, and Day 15 in Cycle 3 and beyond only if abnormal (different from previous assessment) on Day 1 |
| Urinalysis | X | | | X | X | | | X | | X | | X | | X | X | See Attachment 2; 24-hour collection if dipstick worsened after initiation of study treatment; in Cycle 3 and beyond, Day 15 only if abnormal (different from previous assessment) on Day 1 |
| TSH +fT4 | | | | | | | | | | | | X | | | X | See Attachment 2; Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter |
| Adverse event reporting | X | | | | | | | X | | | | X | | | X | Throughout study as needed (according CTCAE v4.0 grading). Refer to Section 8.1.2.2 for reporting guidelines |
| Concomitant medications | X | | | | | | | X | | | | X | | | X | Throughout study as needed. |
| ECOG performance status | X | | | | | | | X | | | | X | | | X | See Attachment 6 |
| PK/PD sampling | see Attachment 4 for timing of PK/PD sampling | | | | | | | | | | | | | | X | See Section 8.2.2 |

| | Cycle 1 | | | | | | | Cycle 2 | | | | Cycle 3-n | | | Follow-Up | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | 30-day (V801) | |
| ***Relative Day Within a Cycle*** | **1** | **2** | **4 or 5** | **8** | **15** | **16** | **22** | **1** | **8** | **15** | **22** | **1** | **8** | **15** | | In Cycle 2 and beyond, visits may be performed ±3 days around scheduled visits. No shortening of the treatment cycles is allowed |
| Fresh tumor biopsy (optional) | X | | | | | | | | | | | | | | | Throughout the study, see Section 8.2.3; |
| Radiological tumor assessment | | | | | | | | | | | X | X | | | | Assessment performed at the end of every even cycle until discontinuation, preferentially between Days 22 and 29. After Cycle 8, every 2 to 4 cycles as clinically indicated |
| Functional tumor imaging (DCE-MRI) | X | | | | | | | | | | | | | | | DCE-MRI can be scheduled pending agreement between sponsor and investigator |
| Tumor markers | X | | | | | | | | | | | X | | | | If applicable to tumor type and patient; Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter |
| Immunogenicity | X | | | | X | | | X | | | | X | | | X | Sampling for ADAs against LY3127804 (all patients) and ramucirumab (only patients receiving LY3127804 + ramucirumab); after Cycle 4, every 2 cycles. **If a patient experiences an infusion-related reaction**, immunogenicity samples and PK samples will be taken as close to the onset of the event as possible, at the resolution of the event, and approximately 30 days following the event |
| Pregnancy test (WOCBP) | | | | | | | | X | | | | X | | | X | See Attachment 2 |

Abbreviations: ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; exam = examination; fT4 = free thyroxine; h = hour(s); HCC = hepatocellular carcinoma; INR = international normalized ratio; PD = pharmacodynamic; PK = pharmacokinetic; RR= respiration rate; SAEs = serious adverse events; TSH = thyroid stimulating hormone; WOCBP = women of child-bearing potential.

### Study Schedule for the Continued Access Period Only, Protocol I7W-MC-JQBA

Perform procedures as indicated.

| | | | Patients on Study Treatment | Continued Access Period Follow-Up |
|---|---|---|---|---|
| | | **Cycle** | **n** | **Follow-Up[a]** |
| | | **Visit** | 501-5XX | 901 |
| | | **Duration (days)** | 28 | 30 |
| | | **Relative day within a cycle** | 1 | |
| **Procedure Category** | **Procedure** | **Protocol Reference** | | |
| **Informed consent form[d]** | | Section 11 | X | |
| **Adverse events collection/CTCAE grading[b]** | | Section 8.1.2 | X | X |
| **Study drugs** | LY3127804/ramucirumab[c] | Section 7 | X | |

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; SAEs = serious adverse events.

[a] The continued access period begins after study completion and ends at the end of trial.

[b] Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.

[c] Patients in the combination cohorts will receive ramucirumab on the same schedule as LY3127804 (Table JQBA.7.2.2).

[d] A new patient informed consent form for the continued access period will need to be signed only if required by local law and regulations.

# Attachment 2. Protocol JQBA Clinical Laboratory Tests

## Clinical Laboratory Tests

**Hematology**[a]
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Leukocytes (WBC)
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

**Coagulation**[a]
activated partial thromboplastin time
Prothrombin time/INR

**Urinalysis**[a]
Specific gravity
pH
Protein[d]
Glucose
Ketones
Blood
Urine leukocyte esterase

**Hepatitis tests**[a]
Hepatitis B surface antigen
Hepatitis C

**Tumor marker**[a]
As applicable to tumor type and patient

**Clinical chemistry**[a]
**Serum concentrations of:**
Sodium
Potassium
Magnesium
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Gamma-glutamyl transpeptidase[b]
Lactate dehydrogenase
Blood urea nitrogen/blood urea
Creatinine[e]
C-reactive protein
Uric acid[b]
Calcium
Chloride
Total protein
Albumin

HbA1c (at baseline only)

**Hormone panel**[a]
Thyroid stimulating hormone
Free thyroxine

**Pregnancy test** (females only)[a,c]

Abbreviations: HbA1c = glycosylated hemoglobin; HCC = hepatocellular carcinoma; INR = international normalized ratio; pts = patients; RBC = red blood cells; WBC = white blood cells.

a Assayed by local laboratory.

b Gamma glutamyl transferase and uric acid will be optional. To be measured if part of the routine panel.

c For women of childbearing potential only (as judged by the investigator). Serum pregnancy test result will be required within 7 days prior to enrollment. Values above the reference range can be accepted if explained by disease history (and/or confirmed absence of pregnancy with echographic examination of the pelvis). Urine or serum test may be performed prior to treatment at all other time points.

d If urine dipstick or routine urinalysis indicates proteinuria ≥2+ at screening and/or worsening relative to baseline while receiving study drugs, a 24-hour urine collection must be obtained to locally assess urine protein concentrations.

e For patients in Part E, creatinine clearance will be calculated according the formula by Cockcroft and Gault (1976) (see Attachment 7).

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

Selected tests may be obtained in the event of a treatment emergent hepatic abnormality (clinically relevant ALT/AST increase and/or bilirubin >ULN range) and may be required in follow up with patients in consultation with the Lilly CRP.

### Hepatic Monitoring Tests

| | |
|---|---|
| **Hepatic hematology[a]** | **Haptoglobin[a]** |
| Hemoglobin | |
| Hematocrit | **Hepatic coagulation[a]** |
| RBC | Prothrombin time |
| WBC | Partial prothrombin time, INR |
| Neutrophils, segmented | |
| Lymphocytes | **Hepatic serologies[a]** |
| 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 | **Anti-nuclear 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 normalized ratio; RBC = red blood cells; ULN = upper limit of normal; WBC = white blood cells.

[a] Assayed by local laboratory.

# Attachment 4. Protocol JQBA Pharmacokinetic and Pharmacodynamic Sampling Schedule

**Table 1: PK and PD sampling schedule for LY3127804 (LY, all cohort) and ramucirumab (combination cohorts only) and centralized ECG monitoring[e] for part A, B and C**

| Study Period Cycle[a]/Day | | Approximate Running Time (h)[b] | ID Sample[c] | Sample Description | LY3127804 PK and PD | Ramucirumab PK[d] | Centralized ECG[e] |
|---|---|---|---|---|---|---|---|
| Cycle 1 | Day 1 | 0 | 1 | Predose LY | X | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | | |
| | | 1-2 | 2 | EOI | X | | X |
| | | *Ramucirumab infusion (Parts B and C only)* | | | | | |
| | | 3-4 | 3 | 2 h post LY (EOI)[f] | X | X | X |
| | Day 2 | 24 | 4 | Any time during Day 2 | X | X | X |
| | Days 4-5 | 96 | 5 | Any time during Days 4-5 | X | X | |
| | Day 8 | 168 | 6 | Any time during Day 8 | X | X | |
| | Day 15 | 0 | 7 | Predose LY | X | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | | |
| | | 1-2 | 8 | EOI | X | | X |
| | | *Ramucirumab infusion (Parts B and C only)* | | | | | |
| | Day 16 | 24 | 9 | Any time during Day 16 | X | | |
| | Day 22 | 168 | 10 | Any time during Day 22 | X | | |
| Cycle 2 | Day 1 | 0 | 11 | Predose LY | X | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | | |
| | | 1-2 | 12 | EOI | X | | X |
| | | *Ramucirumab infusion (Parts B and C only)* | | | | | |
| | | 3-4 | 13 | 2 h post LY (EOI)[f] | X | X | X |
| | Day 8 | 168 | 14 | Any time during Day 8 | X | | |
| | Day 15 | 0 | 15 | Predose LY | X | | X |
| | | *LY3127804 infusion (60-120 min)* | | | | | |
| | | 1-2 | 16 | EOI | X | | X |
| | | *Ramucirumab infusion (Parts B and C only)* | | | | | |
| | Day 22 | 168 | 17 | Any time during Day 22 | X | | |
| Cycle 3 | Day 1 | 0 | 18 | Predose LY | X | | |
| Cycle 4 | Day 1 | 0 | 19 | Predose LY | X | X | |
| Visit 801 follow up | | 720 | 20 | 30 days post study discontinuation | X | X | |

Note: PK/PD samples and ECGs up to 4 hours after the end of LY3127804 should be obtained within ±10 minutes of the scheduled sampling time. It is essential that the actual date and times of ALL LY3127804 and ramucirumab doses are recorded accurately in the eCRF and date and times of collection of PK samples are recorded accurately on the appropriate forms.

Abbreviations: ECG = electrocardiogram; EOI = end of LY infusion; h = hour; IV = intravenous; LY = LY3127804; PK = pharmacokinetic; PD = pharmacodynamic;

a Cycle length = 28 days.

b Approximate time relative to start of last LY3127804 dose given (except for predose).

c Up to 5 additional PK samples can be drawn from each patient during the study, at the discretion of the sponsor after communication with the investigator. The number of sampling time points might be reduced if PK/PD has been sufficiently characterized and if approved in writing by the sponsor.

d Ramucirumab PK sample only to be analyzed for combination cohorts (LY3127804 + ramucirumab).

e Centralized ECGs will be collected in triplicates. The centralized ECGs are to be obtained in place of the local ECGs in Attachment 1(Study Schedule).

f For patients receiving LY3127804 + ramucirumab (Parts B and C), this sample should be taken immediately after the end of ramucirumab infusion.

# Attachment 5. Protocol JQBA Recommendations for Reporting Serious Adverse Events

**Recommendations for Reporting Serious Adverse Events**

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

**Patient Demographics**

- patient identification (number), sex, date of birth, origin, height, 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 hospitalization), action taken with respect to study drug, clinical significance, test and procedure results (if applicable)

**Relationship to Study Drug and 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 JQBA 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 JQBA Creatinine Clearance Formula

*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:*

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

Abbreviations: CrCl = creatinine clearance; wt = weight.

[a] age in years, weight in kilograms.

Reference: Cockcroft and Gault 1976.

# Attachment 8. Protocol JQBA Sampling Summary

This table summarizes the maximum number of samples, volumes for all sampling, and tests during the study. The summary below provides estimates for patient completing 6 cycles of treatment. More samples could be required in the case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, patients who discontinue from the study).

### Protocol I7W-MC-JQBA Sampling Summary

| Purpose | Sample Type | Maximum Amount per Sample | Maximum Number Samples | Maximum Total Amount |
|---|---|---|---|---|
| Study qualification[a] | Blood | 5 mL | 6 | 30 mL |
| Health monitoring (may be more than 1 tube)[b] | Blood | 5 mL | 52 | 260 mL |
| PD/tailoring biomarkers | Tissue biopsy | 5 mm, 0.5 oz, 1 cc | 2 | 10 mm<br>1 oz<br>2 cc |
| Drug concentration | Blood | 3.5 mL | 28 | 98 mL |
| PD biomarkers | Plasma | 10 mL | 19 | 190 mL |
| Pharmacogenetics | Blood | 10 mL | 1 | 10 mL |
| Immunogenicity | Blood | 8.5 mL | 14 | 119 mL |
| Hepatic monitoring[b] | Blood | 3 - 30 mL | — | — |
| Total | | | | Blood: 517 mL<br>Tissue biopsy: 10 mm, 1 oz, 2 cc<br>Plasma: 190 mL |

Abbreviation: PD = pharmacodynamic.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor

# Attachment 9. Protocol JQBA RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

### Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

***Measurable***

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

- 10 mm by CT or MRI scan (slice thickness ≤5 mm)
- 10-mm caliper measurement by clinical examination (nonmeasurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

***Nonmeasurable***

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical examination that is not measureable by reproducible imaging techniques.

***Special Considerations for Lesion Measurability***

Bone lesions

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are nonmeasurable.

Cystic lesions

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are nonmeasurable unless there has been demonstrated progression in the lesion.

### Baseline Documentation of Target and Nontarget Lesions

***Target Lesions***

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Nonnodal target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters (or decimal fractions of centimeters [cm]).

***Nontarget Lesions***

All other lesions (or sites of disease) should be identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

### Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical examination.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to the best effect and a consistent method is used on subsequent examinations for any given patient. If, prior to enrollment, it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

*Clinical Lesions:* Clinical lesions will only be considered measurable when they are superficial and ≥10-mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

*Chest X-ray*: Chest CT is preferred over chest x-ray when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

*CT and MRI*: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

*Ultrasound:* Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

*Endoscopy, Laparoscopy*: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials in which recurrence following CR or surgical resection is an endpoint.

*Tumor Markers*: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the ULN, they must normalize for a patient to be considered in CR. Specific guidelines for both prostate-specific antigen response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

*Cytology, Histology*: These techniques can be used to differentiate between PRs and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell

tumors, in which known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytologic confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or to differentiate between response (or stable disease) and progressive disease.

*Pet Scan (FDG-PET, PET CT)*: PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

*Bone Scan*: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a CR or PR in target disease or when progression in bone is suspected.

### Response Criteria

***Evaluation of Target Lesions***

*Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

*Partial Response (PR):* At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

*Progressive Disease:* At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

*Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

*Not Evaluable:* When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

***Evaluation of Nontarget Lesions***

*Complete Response:* Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological or normal in size (<10-mm short axis).

*Non-CR/nonprogressive Disease:* Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

*Progressive Disease:* Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

*Not Evaluable*: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

### Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The best overall response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

#### *Time Point Response*

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

**Table 1. Time Point Response: Patients with Target (± Nontarget) Disease**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 is to be used when patients have *nonmeasurable* disease only.

**Table 2. Time Point Response: Patients with Nontarget Disease Only**

| Nontarget Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD[a] |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease.

[a] Non-CR/non-PD is preferred over SD for nontarget disease.

### Frequency of Tumor Reevaluation

A baseline tumor evaluation must be performed within 4 weeks before the patient begins study treatment. Frequency of tumor reevaluation while on and adapting to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6 to 8 weeks is reasonable. Normally, all target and nontarget sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

### Confirmatory Measurement/Duration of Response

*Confirmation*
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (PR/CR) is the primary endpoint. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in a *randomized trial* (Phase 2 or 3) or studies in which SD or progression is the primary endpoint, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies that are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 8 weeks measured from first dose.

*Duration of Overall Response*
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

*Duration of Stable Disease*
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of progressive disease).

### Independent Review of Response and Progression

When objective response (CR + PR) is the primary endpoint and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

# Attachment 10. Protocol JQBA Child-Pugh Score

**Child-Pugh Score**

| Clinical and Biochemical Parameters | Points | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| Bilirubin (mg/dL) | <2 | 2-3 | >3 |
| Albumin (g/dL | >3.5 | 2.8-3.5 | <2.8 |
| Ascites | Absent | Moderate | Tense |
| Encephalopathy | Absent | Moderate (Stage I-II) | Severe (Stage III-IV) |
| Prothrombin time | | | |
| Seconds prolonged | <4 | 4-6 | >6 |
| % | >60 | 40-60 | <40 |
| INR[a] | <1.7 | 1.7-2.3 | >2.3 |
| **In case of primary biliary cirrhosis** | | | |
| | **1** | **2** | **3** |
| Bilirubin (mg/dL) | <4 | 4-10 | >10 |

Total points:

- 5 to 6: Child-Pugh class A
- 7 to 9: Child-Pugh class B
- 10 to 15: Child-Pugh class C

[a] INR (International Normalized Ratio) is an expression of prothrombin time, corrected by the sensitivity of the reactive to anticoagulants and should be validated as an alternative to prothrombin time in liver insufficiency.

Source: Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-649.

# Attachment 11. Protocol JQBA Protocol Amendment I7W-MC-JQBA(d) Summary A Phase 1 Study of LY3127804 as Monotherapy and in Combination with Ramucirumab in Patients with Advanced Solid Tumors

## Overview

Protocol I7W-MC-JQBA, A Phase 1 Study of LY3127804 as Monotherapy and in Combination with Ramucirumab in Patients with Advanced Solid Tumors, has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Part D was removed from the study since the primary and secondary end points were met and data collected from Parts A-C were adequate to fulfil primary objective of this study. Additional patient enrollment was not required.
- Part E was removed from the study since it was concluded based on Lilly's current oncology portfolio strategies that combining paclitaxel with LY3127804 for treating second-line gastric cancer was no longer desired to be investigated in this particular study.
- The necessary corrections were made in all sections and subsections of this protocol to align with the deletion of Parts D and E from the current study design.
- Clarified the testing of the higher dose 27 mg/kg through the addition of new cohorts of LY3127804 to Parts A and B to confirm MTD from expected DLTs at that particular dose.
- In Attachment 8, Protocol JQBA Sampling Summary was corrected to be inline with the rest of the protocol.
- Other minor corrections and editorial changes were made throughout the protocol to improve clarity and to secure alignment with the intended study design. These changes are not documented below.
- Corresponding changes (eg. study arms, sample size, etc.) were made in the standalone Protocol synopsis of Study JQBA to ensure consistency with the current amendment in the protocol.

# Revised Protocol Sections

| | |
|---|---|
| **Note:** | All deletions have been identified by ~~strikethroughs~~.<br>All additions have been identified by the use of underscore. |

## 2. Synopsis

This Phase 1 first-in-human study is a multicenter, nonrandomized, open-label, dose-escalation study of intravenous LY3127804 in patients with advanced or metastatic solid tumors who have failed standard of care or for whom no standard of care is available. Study I7W-MC-JQBA (JQBA) will determine a recommended dose range and schedule for LY3127804 that may be safely administered as monotherapy and in combination with ramucirumab. The study will consist of a dose escalation for LY3127804 monotherapy (Part A) and combinations with ramucirumab (Parts B and C). ~~followed by a safety confirmation of the RP2D for LY3127804 in combination with ramucirumab (Part D) and a safety exploration for the combination of LY3127804 plus ramucirumab and paclitaxel (Part E).~~

## 4. Abbreviations and Definitions

| | |
|---|---|
| **RR** | respiratory rate |
| **Study Completion** | This study will be considered complete after all parts (Parts A, B and C) are complete. The dose-escalation and exploration phase of the study (Parts A, B, and C) will be considered complete after all patients, required to determine the RP2D for LY3127804 have completed DLT treatment-observation period and the patients in Part C have completed four cycles of study therapy or discontinued from the treatment (last patient)<br><br>~~all parts (Parts A, B, C, D, and E) are complete. The dose-escalation and exploration phase of the study (Parts A, B, and C) will be considered complete after all patients, required to determine the RP2D for LY3127804 have completed DLT treatment-observation period. The safety-confirmation phase of the study (Part D) and combination with ramucirumab and paclitaxel (Part E) will be considered complete if the study objectives have been reached or patients have discontinued from the treatment (last patient~~) |

## 5.1. Rationale and Justification for the Study

Study I7W-MC-JQBA (JQBA) is the first-in-human Phase 1 dose-escalation study of LY3127804 designed to evaluate the safety and tolerability and the PK properties, as well as to gather evidence of pharmacodynamic (PD) effects and antitumor activity, of LY3127804 in patients with advanced solid tumors who have failed SOC or for whom no SOC is available and ~~,~~ ~~T~~the feasibility to combine LY3127804 with the approved VEGFR2-blocking antibody ramucirumab (see Section 6.2) ~~with and without paclitaxel will also be investigated in this study~~

## 5.1.4. Rationale for Protocol Amendment (d)

The Sponsor implemented amendment (d) in order to eliminate Parts D and E from the current study protocol and to clarify that LY3127804 at a dose of 27 mg/kg was tested as monotherapy (Part A) and as combination therapy with ramucirumab (Part B).

The rationale for the elimination of Parts D and E was based on the following: (i) based on Lilly's current oncology portfolio strategies, it was concluded that combining paclitaxel with LY3127804 for treating second-line gastric cancer was no longer desired to be investigated in this particular study. Other regimens will be used to treat second-line gastric cancer in the foreseeable future, ii) the primary and secondary end points of this study were reached, and (iii) information collected from Parts A, B, and C (fully enrolled and ongoing as of August 21, 2017) was considered sufficient to conclude the primary objective of the study and to answer all scientific questions. Therefore, further accrual of patients was not required.

### 5.2.1. Primary Objective

The primary objective of this study is to determine a recommended Phase 2 dose (RP2D) range and schedule of LY3127804, as monotherapy and in combination with ramucirumab ~~+/- paclitaxel~~ that may be safely administered to patients with advanced solid tumors

### 5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3127804 as monotherapy and in combination with ramucirumab ~~+/- paclitaxel~~
- to assess the maximum tolerated dose (MTD) of LY3127804 monotherapy and in combination with ramucirumab ~~+/- paclitaxel~~ based on the dose-limiting toxicity (DLT), if applicable
- to assess the PK parameters of LY3127804 monotherapy and when administered in combination with ramucirumab ~~+/- paclitaxel~~
- to assess limited PK (peak and trough concentration) of ramucirumab when given in combination with LY3127804 ~~+/- paclitaxel~~
- to evaluate the incidence and level of antibodies against LY3127804 (anti-drug antibodies [ADAs]) and ramucirumab ~~when given in combination +/- paclitaxel~~
- to document any antitumor activity of LY3127804 as monotherapy and in combination with ramucirumab ~~+/- paclitaxel~~
- to estimate PFS of LY3127804 monotherapy and when given in combination with ramucirumab ~~+/- paclitaxel~~

### 5.2.3. Exploratory Objectives

- to explore biological activity of LY3127804 as monotherapy and when given in combination with ramucirumab ~~+/- paclitaxel~~ based on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

### 5.3.1. Mechanism of Action and In Vitro/In Vivo Activity

~~Immuno-deficient mice bearing SKOV3x.1 ovarian xenografts were treated with either different doses of LY3127804, vehicle control, paclitaxel, or the combination of paclitaxel + LY3127804~~

~~BIW for 4 consecutive weeks. Percentage ΔT/ΔC values for 3 , 10 , and 30 mg/kg doses of LY3127804 are 39.1, 32.5, and 27.3, respectively, with p values of <0.001 compared with the control. The combination of paclitaxel plus LY3127804 resulted in a ΔT/ΔC of 7.1% compared to a ΔT/ΔC of 20.3% for paclitaxel alone and 32.5% for LY3127804 alone at 10 mg/kg.~~

~~Immuno-deficient mice bearing SKOV3x.1 ovarian xenografts were treated with vehicle control; DC101; paclitaxel; the combination of DC101 and LY3127804; or the combination of paclitaxel, DC101, and LY3127804 BIW for 4 consecutive weeks. The combination of DC101 and LY3127804 resulted in ΔT/ΔC of 0.1% compared to ΔT/ΔC of 9.6% for DC101 alone. The combination of paclitaxel, DC101 and LY3127804 resulted in regression (33%) compared to ΔT/ΔC of 17.8% for paclitaxel.~~

## 5.4. Ramucirumab

~~For HCC, ramucirumab has not been approved so far. Ramucirumab was studied in a randomized, controlled Phase 3 trial (Study I4T-IE-JVBF; Study JVBF, also known as REACH) of ramucirumab monotherapy versus placebo in a second-line setting (post-sorafenib) for patients with advanced HCC (Zhu 2015). The study did not meet its primary endpoint of OS; although the OS results favored the ramucirumab arm, they were not statistically significant. Encouraging single-agent ramucirumab activity was observed, with meaningful improvements in key secondary endpoints of PFS, ORR, and time to progression (TTP). Subgroup analyses suggest that an elevated baseline concentration of α-fetoprotein might identify patients more likely to derive an OS benefit from ramucirumab. A follow-up Phase 3 study focusing on HCC patients with an elevated baseline concentration of α-fetoprotein is planned~~.

### 5.5.1. LY3127804 Dose

At the beginning of the study, ~~A~~ a dose range from 4 mg/kg up to 20 mg/kg of LY3127804 administered IV Q2W was selected based on nonclinical toxicology, PK, and PD/efficacy data (modeling).

Data from Cohort A5 (monotherapy) and B5 (combination with ramucirumab at 8 mg/kg) showed that 20 mg/kg LY3127804 did not result in any DLT. In such a case, the protocol allowed the investigation of additional dose levels with a maximum dose increment of 7 mg (please refer to Section 7.2.2). Consequently, the LY3127804 dose of 27 mg/kg was investigated in additional Cohorts A6 and B6. Later sections of the protocol (notably Section 6.2) have been amended, as needed, to clarify that LY3127804 was investigated up to a dose of 27 mg/kg.

### 5.5.2. Ramucirumab Dose

~~Although exposure-safety analyses in RAINBOW also suggested that increasing exposure of ramucirumab (when given in combination with paclitaxel) is associated with increased risk of Grade ≥3 hypertension, neutropenia, and leukopenia, the association of neutropenia with ramucirumab exposure increase does not appear to translate to an increased risk of febrile neutropenia~~

~~Currently, Study I4T-MC-JVCZ is being performed in patients with metastatic or locally advanced gastric or gastroesophageal junction adenocarcinoma to compare the standard ramucirumab dose (8 mg/kg) and a new, higher ramucirumab dose (12 mg/kg), both administered on Days 1 and 15, in combination with paclitaxel (80 mg/m$^2$) administered on Days 1, 8, and 15 of a 28-day cycle in order to examine the potential improvement in efficacy as measured by PFS. The new ramucirumab dosing regimen (12 mg/kg) is predicted to produce approximately 50% higher exposure relative to the 8-mg/kg standard dose based on linear PK assumption and, therefore, is expected to improve PFS. However, it is unknown whether the dosage of 12 mg/kg Q2W will result in an acceptable toxicity profile~~.

### ~~5.5.3. Paclitaxel Dose~~

~~Ramucirumab in combination with paclitaxel (80 mg/m² intravenously on days 1, 8 and 15 of a 28-day cycle) is approved by FDA and EMA. Paclitaxel at this dose and schedule is an accepted standard of care in advanced cancer patients in several tumor types and patients with no other treatment options.~~

~~In the randomized phase 3 study "RAINBOW" the combination of ramucirumab and paclitaxel demonstrated an overall favourable safety profile and significantly increased overall survival in 2nd line gastric cancer patients (Wilke et al. 2014). The same dose and schedule of paclitaxel will be used in JQBA Part E (ie, 80 mg/m² intravenously on days 1, 8, and 15 of a 28-day cycle) to explore the safety and tolerability when given in combination with ramucirumab and LY3127804. As outlined in Section 5.5.2 the dose of ramucirumab and LY3127804 to be given in combination with paclitaxel in Part E will depend on the safety and tolerability observed in Part B and C and the ongoing study JVCZ.~~

## 6.1.2. Exclusion Criteria

~~[35] for patients in Part E (LY3127804 +ramucirumab/paclitaxel) only:~~

- ~~The patient received previous systemic chemotherapy with a cumulative dose of >900 mg/m² of epirubicin or >400 mg/m² of doxorubicin~~
- ~~The patient has sensory peripheral neuropathy ≥ Grade 2~~
- ~~have a known allergy or hypersensitivity to paclitaxel or to any products used in the formulation of paclitaxel or are incompatible with the treatment of paclitaxel~~

## 6.2. Summary of Study Design

Study JQBA is a multicenter, nonrandomized, open-label, dose-escalation Phase 1 study that will consist of ~~4~~ 3 parts:

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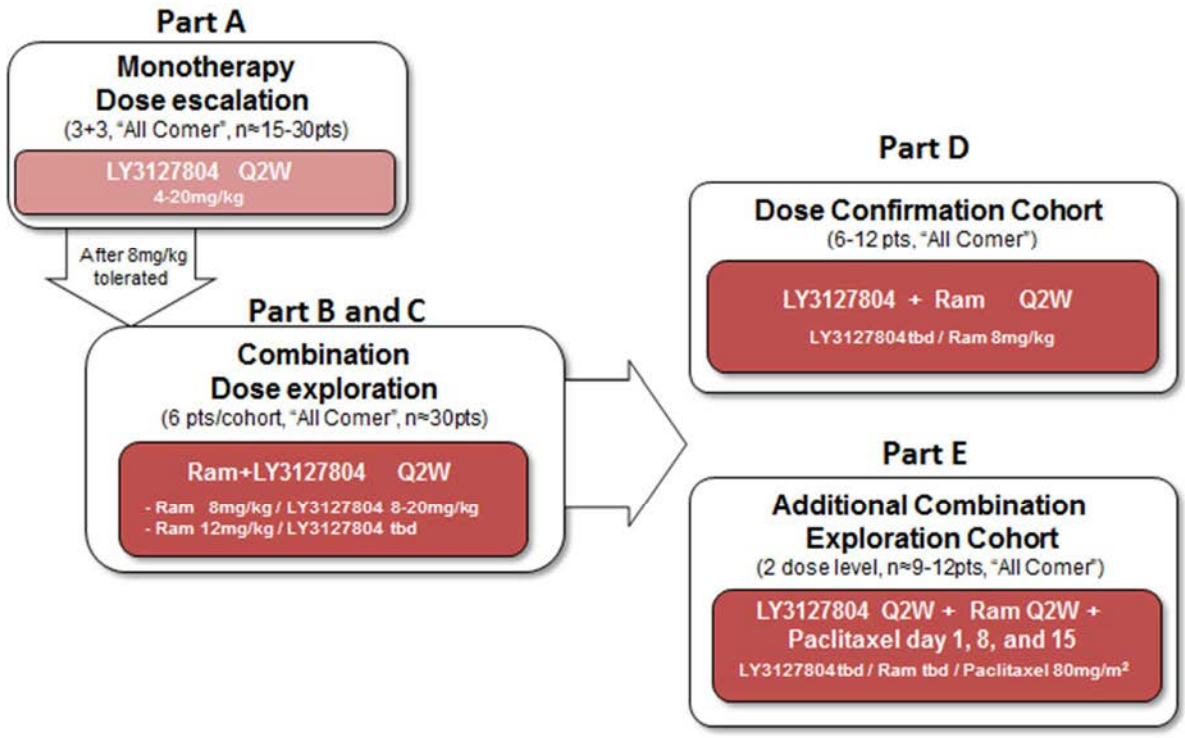
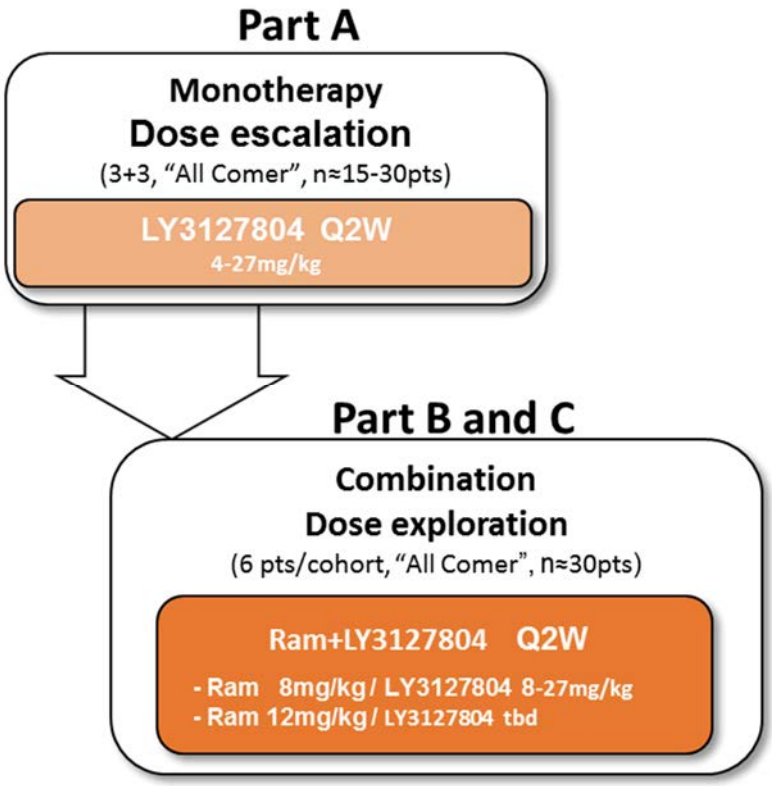


**New Figure Inserted**




Abbreviations: ~~GEJ = gastroesophageal junction~~; ~~HCC = hepatocellular carcinoma~~; ~~PD = pharmacodynamics; PK = pharmacokinetics~~; pts = patients; Q2W = every 2 weeks; Ram = ramucirumab.

- ~~Part D: safety confirmation cohort for LY3127804 at RP2D in combination with ramucirumab 8mg/kg Q2W~~
- ~~Part E: dose exploration of LY3127804 in combination with ramucirumab and paclitaxel to determine a RP2D range and schedule for LY3127804 that may be safely administered in combination with ramucirumab Q2W (dose tbd) and paclitaxel (80 mg/m2 day 1, 8, and 15)~~

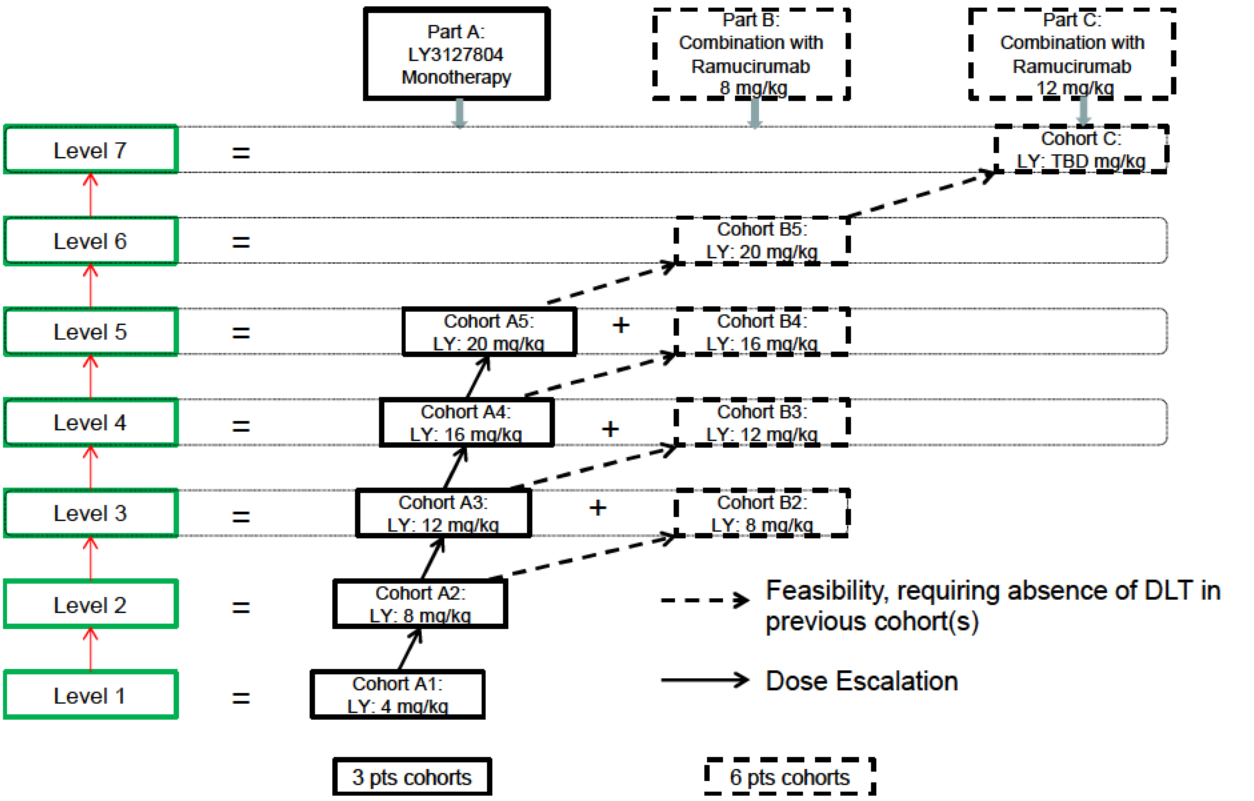
In **Part A,** the **LY3127804 single-agent, dose-escalation** part of the study, LY3127804 will be investigated as a monotherapy at a dose ranging from 4 mg/kg up to ~~20~~ 27 mg/kg, given Q2W. Cohorts of 3 patients will be enrolled at each of the planned monotherapy dose levels

**Part B (LY3127804 dose exploration with ramucirumab 8mg/kg)** will be opened after patients in Cohort A2 (ie, LY3127804 monotherapy at 8 mg/kg, Q2W) have completed the DLT period and the dose was assessed to be safe. An analysis of the data will be conducted, and feasibility to combine LY3127804 with ramucirumab dose of 8 mg/kg will be evaluated. Based on the results from this analysis, the dose exploration of B cohorts will be initiated (LY3127804 dose [ranging from 8 mg/kg up to ~~20~~ 27 mg/kg] + ramucirumab at a fixed dose of 8 mg/kg) at the

same time as LY3127804 monotherapy will be dose escalated at higher doses. Dose escalation for LY3127804 will occur up to 27 mg/kg Q2W or until the MTD has been reached~~ (defined in Section7.2.1.3)~~;

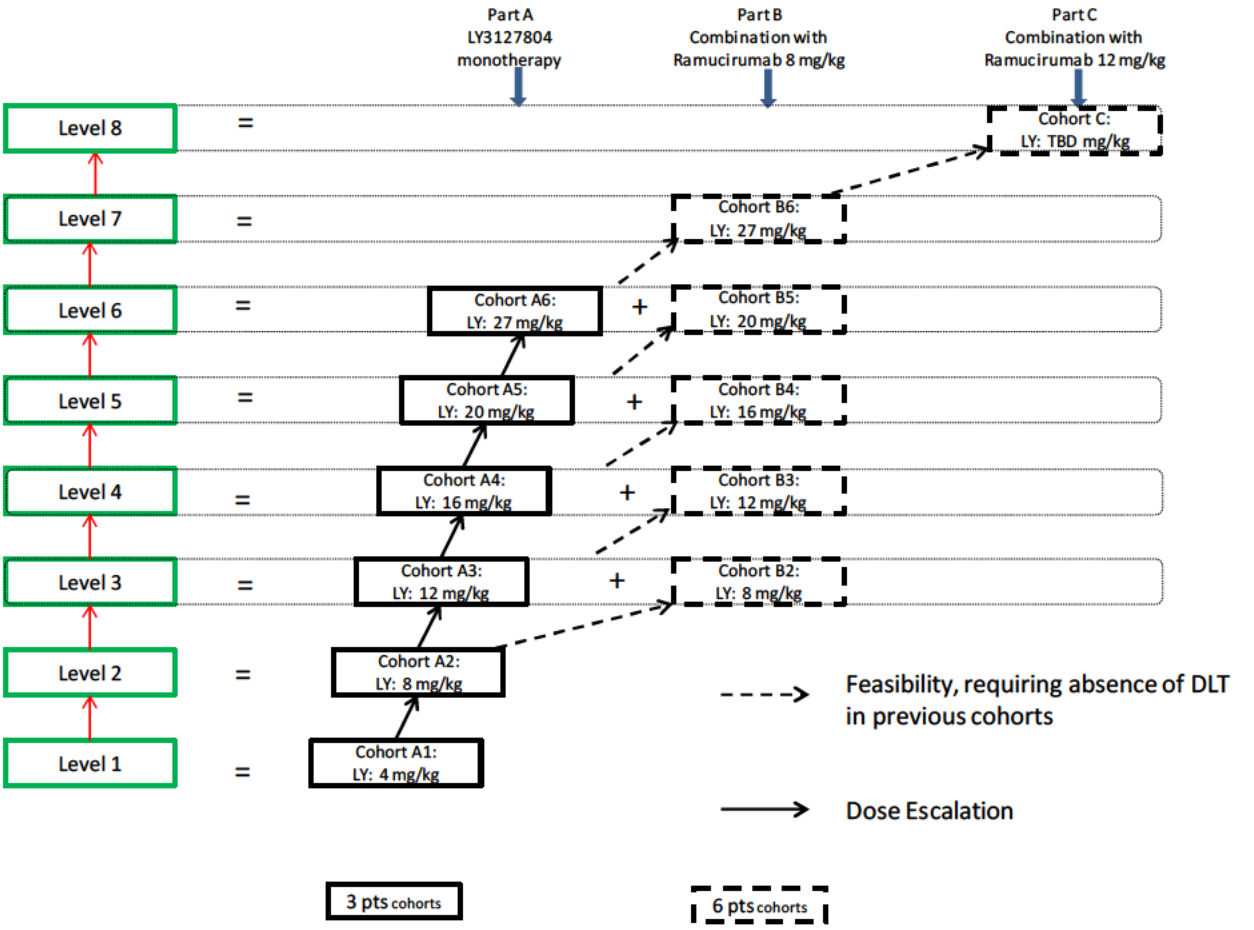
**Part C (LY3127804 with ramucirumab 12 mg/kg)** will be opened once all the combination B cohorts (B2, B3, B4, B5 and B6) have been completed (unless prohibited by DLTs).

**Old Figure JQBA. 6.2. Deleted**




~~Abbreviations: DLT = dose limiting toxicity; LY = LY3127804; pts = patients; TBD = to be determined; Cohort A, B, and C indicate, respectively, monotherapy LY3127804 or combination with 8 mg/kg or 12 mg/kg ramucirumab. The number in the cohort label (eg, 2 in Cohort A2) indicates the LY3127804 dose level 4 mg/kg (1), 8 mg/kg (2), 12 mg/kg (3), 16 mg/kg (4), 20 mg/kg (5) and 27 mg/kg (6).~~

**New Figure JQBA. 6.2. Inserted**




Abbreviations: DLT = dose-limiting toxicity; LY = LY3127804; pts = patients; TBD = to be determined.

Cohorts A, B, and C indicate, respectively, monotherapy LY3127804 or combination with 8 mg/kg or 12 mg/kg ramucirumab. The number in the cohort label (eg, 2 in Cohort A2) indicates the LY3127804 dose level 4 mg/kg (1), 8 mg/kg (2), 12 mg/kg (3), 16 mg/kg (4), 20 mg/kg (5), and 27 mg/kg (6).

~~**Part D (safety confirmation cohort of LY3127804 with ramucirumab 8 mg/kg)** will be initiated once Part B has been completed. In this part, approximately 6-12 patients will be enrolled to receive LY3127804 at the RP2D in combination with ramucirumab 8 mg/kg Q2W. The RP2D dose of LY3127804 to be evaluated in combination with ramucirumab in Part D will be defined based on safety, PK/PD, and antitumor activity observed in Parts A and B. The sponsor, in collaboration with the investigators, will review Parts A and B results prior to determining the recommended schedule and dose of study drugs to be studied in Part D. The decision will be documented in writing, and a written notification will be sent to the IRB prior to enrollment of patients into Part D. No amendment will be required.~~

~~**Part E (LY3127804 dose exploration with ramucirumab/paclitaxel)** will be opened once Parts B and Part C have been completed. In this part, approximately 9-12 patients will receive ramucirumab and paclitaxel at a fixed dose in combination with LY3127804. The first cohort of 3 patients will receive paclitaxel and ramucirumab in combination with LY3127804 starting at least 1 dose level below the RP2D of LY3127804 with ramucirumab for Part D. If tolerated, the LY3127804 dose will be increased to the RP2D for Part D and administered in combination with ramucirumab plus paclitaxel.~~

~~The dose levels of ramucirumab and LY3127804 to be explored in Part E will be defined based on safety data observed in Parts A through C as well as in Study JVCZ (see Section 5.5.2). The sponsor, in collaboration with the investigators, will review all the data prior to determining the recommended schedule and dose of LY3127804 and ramucirumab to be explored in Part E. The decision will be documented in writing, and a written notification will be sent to the IRB prior to enrollment of patients into Part E. No amendment will be required. Paclitaxel will be administered according to its label (80mg/m$^2$ day 1, 8, and 15). More detailed information is available in Section7.2.2.6.~~

~~The protocol for Study JQBA may be amended prior to commencement of Part D and Part E, depending on the safety, tolerability, and preliminary clinical activity observed in Parts A through C. In addition, further expansion cohorts for other tumor types and combination treatments may be added by a protocol amendment if indicated by emerging scientific data from preclinical and ongoing clinical studies~~

## 6.2.1. Sample Size

To determine the RP2D of LY3127804, an adequate sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as well as an evaluation of the relationship between exposure and pharmacologic effects using descriptive statistics and appropriate modeling techniques, if data warrant. The overall sample size for this study is estimated to be a total of approximately up to ~~84~~72~~-~~patients.

~~In Part D, a total of approximately 6-12 patients will be enrolled to confirm safety and tolerability of the RP2D of study drugs.~~

~~In Part E, a total of approximately 9-12 patients will be enrolled to explore the safety and tolerability of LY3127804 when given in combination with ramucirumab and paclitaxel (3 per cohort/dose level and a total of approximately 6 per cohort/dose level at the MTD level).~~

## 6.2.2. Study Completion and End of Trial

This study will be considered complete after all parts (Parts A, B, and C) are complete. The dose-escalation and exploration phases of the study (Parts A, B, and C) will be considered complete after all patients required to determine the RP2D for LY3127804 have completed the DLT treatment-observation period and the patients in Part C have completed 4 cycles of study therapy or discontinued from the treatment (last patient). The unconfirmed objective responses of the patients in Part C need to be confirmed before the completion of the trial. ~~(that is, the~~

~~scientific evaluation will be complete [study completion]) all parts (Parts A, B, C, D and E) are complete. The dose escalation and exploration phase of the study (Parts A, B, and C) will be considered complete after all patients, required to determine the RP2D for LY3127804 (in a single agent setting and in a combination setting with ramucirumab) have completed a DLT treatment observation period. The safety confirmation (Part D) and combination with ramucirumab and paclitaxel (Part E) phase of the study will be considered complete if the study objectives have been reached or the last patient has discontinued from treatment.~~

### 6.2.3. Continued Access Period

Investigators will perform any standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the Investigator's discretion. ~~Investigators may perform other standard procedures and tests needed to treat and evaluate patients~~; ~~however,~~ Lilly will not routinely collect the results of these assessments unless required for the safety follow-up of the patients.

## ~~7.1.3. Paclitaxel~~

~~Paclitaxel will be provided by Lilly and will be labeled according to the country's regulatory requirements. Refer to the manufacturer's instructions on preparation, handling, and storage of paclitaxel.~~

## 7.2.1. Dosing Schedule

A treatment cycle is defined as an interval of 28 days. Treatment should continue on schedule if possible, but a variance of up to +3 days in Cycle 2 and beyond, may be allowed to accommodate holidays and clinic scheduling conflicts. No shortening of the treatment cycle will be allowed.

### 7.2.1.1. LY3127804 Dosing

LY3127804 infusion time is to be determined based on an infusion rate not to exceed 25 mg/min and on the LY3127804 dose level administered. Table JQBA.7.2.1 provides an overview of the planned LY3127804 infusion duration. Patients receiving 4-mg/kg, 8-mg/kg, or 12-mg/kg doses should have infusion times not less than 60 minutes. Patients receiving 16-mg/kg, 20-mg/kg or 27-mg/kg doses should have drug infused in not less than 90 minutes.

**Table JQBA. 7.2.1. LY3127804 Infusion Duration**

| Dose Level | Total Dose | LY3127804 Infusion Duration |
|---|---|---|
| 4, 8, and 12 mg/kg | ≤1500 mg | 60 (±10) min |
| | >1500 - 2250 mg | 90 (±15) min |
| | >2250 mg-3000 mg | 120 (±20) min |
| 16, ~~and~~ 20 and 27 mg/kg | ≤2250 mg | 90 (±15) min |
| | >2250 mg-3000 mg | 120 (±20) min |

Abbreviation: min = minutes.

### 7.2.1.2. Ramucirumab Dosing

On treatment days, ramucirumab will be administered **after** the LY3127804 infusion. The ramucirumab infusion should be started after a minimum of a 60-minute observation period (minimum of 30-minute observation period in Cycle 2 and beyond) **after** the end of the LY3127804 administration as specified in Section ~~7.2.1.2~~.7.2.1.1. Should it be 7.2.1.1Every attempt should be made in order to start the ramucirumab infusion NO later than 60 minutes after the end of the LY3127804 infusion.

~~**7.2.1.3. Paclitaxel Dosing**~~

~~Patients will receive paclitaxel by IV infusion over approximately 60 minutes at 80 mg/m$^2$ on Days 1, 8, and 15, every 28 days.~~

~~On treatment days the paclitaxel will be administered **after** the ramucirumab infusion. Refer to the manufacturer's instructions for complete prescribing information and follow institutional procedures for administration of paclitaxel.~~

~~The patient's first dose of paclitaxel is dependent upon the patient's baseline body surface area (BSA). Subsequent doses of paclitaxel must be recalculated if the patient's BSA changes by ≥10% from his or her baseline BSA.~~

~~On Day 1 of each cycle, the patient must meet the criteria shown in Table 7.2.2prior to administration of paclitaxel. On Day 8 and Day 15, the patient must meet the criteria shown inTable 7.2.3.~~

~~**Table 7.2.2. Criteria to Be Met Prior to Paclitaxel Administration On Day 1 of Each Cycle**~~

| ~~**Laboratory Test**~~ | ~~**Required Value**~~ |
|---|---|
| ~~Neutrophils~~ | ~~≥1.5 × 10$^9$/L~~ |
| ~~Platelets~~ | ~~≥100 × 10$^9$/L~~ |
| ~~Hemoglobin~~ | ~~≥8.0 g/dL~~ |
| ~~Serum creatinine or CrCl~~ | ~~≤1.5 × ULN or CrCl ≥50 mL/min~~ |
| ~~Bilirubin~~ | ~~≤1.5 × ULN~~ |
| ~~AST/ALT~~ | |
| ~~• if the patient has liver metastases~~ | ~~≤5 × ULN~~ |
| ~~• if the patient does not have liver metastases~~ | ~~≤3 × ULN~~ |
| ~~Paclitaxel-related toxicities/AEs (except for clinically insignificant events, as determined by the investigator)~~ | ~~CTCAE Grade <2 or the patient's baseline level~~ |

~~Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; CTCAE = Common Toxicity Criteria for Adverse Events; ULN = upper limit of normal.~~

~~**Table7.2.3. Criteria to Be Met Prior to Paclitaxel Administration On Day 8 and Day 15 of Each Cycle**~~

| ~~Laboratory Test~~ | ~~Required Value~~ |
|---|---|
| ~~Neutrophils~~ | ~~≥1.0 × $10^9$/L~~ |
| ~~Platelets~~ | ~~≥75 × $10^9$/L~~ |
| ~~Hemoglobin~~ | ~~≥8.0 g/dL~~ |
| ~~Bilirubin~~ | ~~≤1.5 × ULN~~ |
| ~~AST/ALT~~ | |
| ~~• if the patient has liver metastases~~ | ~~≤5 × ULN~~ |
| ~~• if the patient does not have liver metastases~~ | ~~≤3 × ULN~~ |
| ~~Paclitaxel-related toxicities/AEs (except for clinically insignificant events, as determined by the investigator)~~ | ~~CTCAE Grade <2 or the patient's baseline level~~ |

~~Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Toxicity Criteria for Adverse Events; ULN = upper limit of normal.~~

~~Premedication is required prior to infusion of paclitaxel according to the manufacturer's instructions and local standards. Recommended premedication include:~~

- ~~dexamethasone 8 to 20 mg (or equivalent) administered:~~
  - ~~orally 12 hours and 6 hours prior to paclitaxel, or~~
  - ~~intravenously 30 to 60 minutes prior to paclitaxel~~
- ~~an antihistamine (H1-antagonist) such as diphenhydramine hydrochloride (or equivalent) 50 mg~~
- ~~cimetidine (H2 antagonist) (or equivalent) 300 mg~~

~~Additional premedication may be provided at the investigator's discretion. On treatment days with paclitaxel, premedication administered for ramucirumab need not be repeated for premedication for paclitaxel. An antiemetic, such as ondansetron 8 mg administered orally or intravenously (or equivalent) 30 to 120 minutes before paclitaxel, is recommended.~~

## 7.2.2. Dose Escalation

**Table JQBA.7.2.2. Planned Dose Levels and Treatment Schedule by Cohorts**

| Cohort | LY3127804[a] Day 1 and 15 | % Increase of LY3127804 | Ramucirumab[a] Day 1 and 15 | ~~Paclitaxel Day 1, 8, and 15~~ |
|---|---|---|---|---|
| Cohort A-1 (3 pts) | 4 mg/kg | NA | NA | ~~NA~~ |
| Cohort A-2 (3 pts) | 8 mg/kg | 100% | NA | ~~NA~~ |
| Cohort A-3 (3 pts) | 12 mg/kg | 50% | NA | ~~NA~~ |
| Cohort B-2 (6 pts) | 8 mg/kg | NA | 8 mg/kg | ~~NA~~ |
| Cohort A-4 (3 pts) | 16 mg/kg | 33% | NA | ~~NA~~ |
| Cohort B-3 (6 pts) | 12[b] mg/kg | 50% | 8 mg/kg | ~~NA~~ |
| Cohort A-5 (3 pts) | 20 mg/kg | 25% | NA | ~~NA~~ |
| Cohort B-4 (6 pts) | 16[b] mg/kg | 33% | 8 mg/kg | ~~NA~~ |
| Cohort B-5 (6 pts) | 20[b] mg/kg | 25% | 8 mg/kg | ~~NA~~ |
| Cohort A-6 (3 pts) | 27 mg.kg | 35% | NA | |
| Cohort B-6 (6 pts) | 27 mg/kg | 35% | 8mg/kg | |
| Cohort C (6 pts) | TBD[b] mg/kg | NA | 12 mg/kg | ~~NA~~ |
| ~~Cohort D (6-12 pts)~~ | ~~TBD mg/kg~~ | ~~NA~~ | ~~8 mg/kg~~ | ~~NA~~ |
| ~~Cohort E-1 (3-6 pts)~~ | ~~TBD mg/kg~~ | ~~TBD~~ | ~~TBD mg/kg~~ | ~~80 mg/m²~~ |
| ~~Cohort E-2 (3-6 pts)~~ | ~~TBD mg/kg~~ | ~~TBD~~ | ~~TBD mg/kg~~ | ~~80 mg/m²~~ |

Note: "A" cohorts represent monotherapy cohorts; "B ~~and D~~" cohorts represent combination cohorts with ramucirumab dose at 8mg/kg; and "C" cohort represent the combination cohort with ramucirumab dose at 12mg/kg. ~~"E" cohorts represent combination cohorts with ramucirumab and paclitaxel. The route of administration will be intravenous for all cohorts.~~

If the MTD has not yet been reached at the highest prespecified LY3127804 dose level (20 mg/kg), then additional dose levels can be investigated based on both safety and available PK data.

The LY3127804 dose level to be administered for patients in Cohort C ~~through E~~ (see Table JQBA.7.2.2) will be determined following a review of all safety and available PK/PD or antitumor activity data from previous cohorts. The data will be discussed between the sponsor and the investigators, and the decision will be documented in writing

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

A DLT is defined as an AE during Cycle 1 (first 28 days of exposure) in Parts A, B, and C ~~and E,~~ that is possibly related to the study drug(s) and fulfills any 1 of the following criteria using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (NCI 2009):

At the time of DLT reporting, special attention will be given to determine whether the DLT observed is primarily related to LY3127804, ramucirumab, ~~paclitaxel~~ or the combination of study drugs. ~~For patients in Part E, toxicities that are clearly associated with paclitaxel (eg peripheral sensory neuropathy) should not be considered DLTs following discussion between the sponsor and the investigators~~

Patients in Parts A through C (Cycle 2 or greater) and Part D through E will be evaluated on an ongoing basis for AEs. .

**7.2.2.5. Dose Confirmation for LY3127804 + ramucirumab in Part D**

The dose and schedule of LY3127804 in combination with ramucirumab 8mg/kg for combination treatment in Part D will be defined based on safety, PK/PD, and antitumor activity observed in Parts A and B. The sponsor, in collaboration with the investigators, will review Parts A and B results prior to determining the recommended schedule and dose of LY3127804 to be studied in Part D. The decision will be documented in writing and a written notification will be sent to the IRB prior to enrollment of patients into Part D. No amendment will be required. If indicated by safety, PK/PD, and/or emerging clinical data, the recommended schedule and dose of LY3127804 and ramucirumab in Part D might be adjusted following written notification by the sponsor. Patients in Part D will be treated at a dose and schedule of LY3127804 in combination with ramucirumab no greater than the dose and schedule explored in Part B.

**7.2.2.6. Dose Exploration for LY3127804 + ramucirumab/Paclitaxel in Part E**

This part of the study will consist of evaluating 2 different doses of LY3127804 in combination with a "fixed" dose of ramucirumab (either 8 mg/kg or 12 mg/kg) and paclitaxel (80mg/$m^2$).

The sponsor, in collaboration with the investigators, will review the results of Parts A through C prior to determine the recommended dose for LY3127804 and for ramucirumab (ramucirumab 8 or 12mg/kg; Q2W) to be evaluated in combination with paclitaxel 80mg/$m^2$ (day 1, 8, and 15). Available safety data from Study JVCZ combining ramucirumab 12 mg/kg Q2W and paclitaxel 80mg/$m^2$ day 1, 8, and 15 will be reviewed as well (see also Section 5.5.2). The decision for dose levels of ramucirumab and LY3127804 to be explored in Part E will be documented in writing, and a written notification will be sent to the IRB prior to enrollment of patients into Part E. No amendment will be required. Based on the results from this review, patients in Part E will receive ramucirumab and paclitaxel at a fixed dose in combination with LY3127804 starting at least 1 dose level below the RP2D for LY3127804 in combination with ramucirumab in Part D. If tolerated in the initial cohort of 3 patients, the LY3127804 dose will be increased to the RP2D for LY3127804 in combination with ramucirumab and a total of 6 patients will be enrolled at this dose level.

The cohorts of LY3127804 in combination with ramucirumab and paclitaxel will be determined to be safe if the incidence of DLTs (Section7.2.2.1) is <33%. If a DLT is observed in 1 out of 3 patients in the initial cohort, the sponsor, together with the investigators, will examine the safety. Following consultation, the sponsor and the investigators will decide if the dose level is intolerable or, in case of confounding events (e.g., ambiguity whether any toxicity with a potential DLT characteristic is possibly related to study treatment, the underlying tumor disease, or concomitant medication), additional patients may be enrolled at the this dose level to further investigate the tolerability. If >2 patients experience a DLT at either cohort, further dose exploration of this combination treatment will cease, and lower dose levels of LY3127804 and/or ramucirumab may be explored in combination with paclitaxel. No amendment will be required in this case.

## ~~7.2.2.7.~~7.2.2.5. Dose Adjustments and Delays

In Cycle 1, no dose adjustments or delays of LY3127804 or the combination of LY3127804 and ramucirumab ~~+/- paclitaxel~~ will be allowed (ie, DLT assessment period), except in case of any DLT or safety concerns following discussion and written approval by the study CRP.

In Parts B ~~through~~ and ~~D~~C, if both study drugs were held due to a toxicity, study treatment with both study drugs should be resumed as soon as that toxicity is resolved, provided that the patient did not meet any discontinuation criteria.

~~In Part E, initiation of a new treatment cycle will be defined by administration of paclitaxel. If paclitaxel cannot be administered on the planned Day 1 of the next cycle, LY3127804 + ramucirumab will be administered within the current cycle. Once paclitaxel can be administered, the new treatment cycle will start, and LY3127804, ramucirumab and paclitaxel administration should be synchronized. If a patient cannot be treated with 1 component of the study therapy (LY3127804, ramucirumab, or paclitaxel) for more than 28 days from the last administered dose, that component will be permanently discontinued. The other component should be continued, with the patient remaining on study, if clinically indicated.~~

### ~~7.2.2.8.~~7.2.2.6. Dose Modifications—LY3127804

### ~~7.2.2.9.~~7.2.2.7. Dose Modifications—Ramucirumab

### ~~7.2.2.10.~~7.2.2.8. Infusion-Related Reactions

### ~~7.2.2.11.~~7.2.2.9. Hypertension

### ~~7.2.2.12. Dose Modifications Paclitaxel~~

~~This section provides instructions for paclitaxel dose modifications applicable if the patient experiences AEs or laboratory toxicities possibly related to paclitaxel.~~

~~On Days 8 and 15 of each cycle, the patient must meet the criteria shown inTable 7.2.3. If the patient does not meet these criteria, omit the paclitaxel dose.~~

~~If the patient experiences any of the following CTCAE toxicities, reduce the paclitaxel dose by 10 mg/m$^2$ beginning at the next cycle:~~

- ~~Grade 4 hematological toxicity~~
- ~~Grade 3 paclitaxel-related nonhematological toxicity that is clinically significant (as determined by the investigator)~~

~~Discontinue paclitaxel if the patient experiences Grade 4 nonhematological toxicity that is related to paclitaxel.~~

~~No reductions of the paclitaxel dose are allowed within a given cycle. Any patient who requires a paclitaxel dose reduction will continue to receive a reduced dose.~~

~~Any patient who has had 2 paclitaxel dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from paclitaxel.~~

## ~~7.5. Concomitant Therapy~~

Patients should receive full supportive care with the exception that the routine use of granulocyte colony–stimulating factors is not permitted during Parts ~~parts~~ A, B, and C~~, and D~~ of this study. The use of colony-stimulating factors may be given as needed for patients in Part E and follow local guidelines.

## 7.6. Treatment Compliance

LY3127804~~,~~ and ramucirumab, ~~and paclitaxel~~ will be administered intravenously at the investigational site, under the direction of the investigator.

## 8.1.2. Adverse Events

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 v4.0, and the investigator should make an effort to try to allocate the observed AEs to the underlying disease, LY3127804, ramucirumab, ~~paclitaxel,~~ or the combination of treatments.

In ~~addition~~ addition, all AEs related to protocol procedures must be reported to Lilly or its designee

The investigator will decide whether he or she interprets the observed AEs as either related to disease, ~~to which one of~~ the study medications (if possible), ~~to~~ study procedure, or ~~to~~ other concomitant treatment or pathologies.

## 8.1.4. Safety Monitoring

A 24-hour urine collection will be required at screening for any patients with a urine dipstick (or equivalent) of ≥2+ to document the proteinuria to be <2 g/24 hours (as a proteinuria of >2 g/24 hours will exclude the patient from study participation). ). During trial treatment, worsening in the proteinuria ~~assessments~~ (urine dipstick~~)~~ result: ~~s~~ ≥2+) will trigger an additional 24-hour urine collection to exclude a (treatment-related) proteinuria >3.5 g/24 hours (which will require the study treatment to be stopped)

## 8.3. Efficacy Evaluations

Each patient will be assessed by 1 or more of the following radiologic tests for tumor measurement:

- CT scan
- MRI

Each patient's full extent of disease will also be assessed with:

- tumor measurement by RECIST 1.1 (Eisenhauer et al. 2009)
- evaluation of tumor markers, if indicated

Radiological images may be collected centrally and overread.

Optional DCE-MRI may be performed but will be subject to agreement between sponsor and investigator. For those patients, a DCE-MRI should be performed prior to study entry, after approximately 2 weeks of therapy, and eventually after approximately 4 weeks of therapy. The timing of the on-treatment DCE-MRI might be adjusted based on emerging information and following discussion between the sponsor and the investigators. Centralized independent reviewers will be involved in reviewing the imaging (DCE-MRI) data to minimize any bias in radiological assessment.

### 10.1. General Considerations

This is a Phase 1 study with an open-label, dose-escalation design. Patients will be enrolled into cohorts sequentially without randomization to dose level. During dose escalation, the total sample size per cohort will be guided by the standard oncology 3+3 method and determined by the occurrences of DLTs for the monotherapy-treated patients. The LY3127804 plus ramucirumab combination cohorts will enroll 6 patients per dose level. The size of 6 patients per combination cohort will ensure a broad (safety) base before exploring a higher dose of LY3127804 in the combination setting and is assumed to be beneficial for the patients (therapeutic dose of ramucirumab). The total sample size is estimated to be approximately up to ~~84~~ 72 patients. ~~In Parts A through C, the sample size is estimated to be approximately 45 to 60 patients. In Part D, a total of approximately 6-12 patients has been selected to confirm safety of selected RP2D. In Part E, a total of approximately 9-12 patients has been estimated to explore and confirm RP2D range and schedule of LY3127804 in combination with ramucirumab and paclitaxel.~~

## 10.10. Safety Reviews and Interim Analyses

After all patients who are deemed evaluable for the assessment of dose levels complete the DLT evaluation period or MTD is determined in Parts A and B, an interim safety and available PK data review will be conducted. ~~for planning Part D.~~ A further safety review is planned after completion of Part C ~~to inform dosing in Part E or next studies. The decision to proceed to Part D and E will be made following discussions between the investigators and Lilly clinical research personnel.~~

~~During Part D and E, interim analyses may be conducted to review available safety, PK, and PD. The goal of the interim analyses is to aid in the planning of future trials. Further interim analysis may be considered if deemed appropriate by the sponsor.~~

## 12. References

~~Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014 Oct;15(11):1224-35.~~

~~therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015 Jul;16(7):859-70~~.

# Attachment 1. Protocol JQBA Study Schedule

## During and Poststudy Assessments

| | Cycle 1 | | | | | | | Cycle 2 | | | | Cycle 3-n | | | Follow-Up | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | 30-day (V801) | |
| ***Relative Day Within a Cycle*** | **1** | **2** | **4 or 5** | **8** | **15** | **16** | **22** | **1** | **8** | **15** | **22** | **1** | **8** | **15** | | In Cycle 2 and beyond, visits may be performed ±3 days around scheduled visits. No shortening of the treatment cycles is allowed |
| LY3127804 | X | | | | X | | | X | | X | | X | | X | | |
| Ramucirumab | X | | | | X | | | X | | X | | X | | X | | Only patients in Parts B and C~~, D, and E~~ |
| ~~Paclitaxel~~ | ~~X~~ | | | ~~X~~ | ~~X~~ | | | ~~X~~ | ~~X~~ | ~~X~~ | | ~~X~~ | ~~X~~ | ~~X~~ | | ~~Only patients in Part E~~ |
| Physical examination | X | | | X | X | | | X | | X | | X | | | X | |
| Weight | X | | | | X | | | X | | X | | X | | | X | |
| Vital signs | X | X | | X | X | | X | X | X | X | X | X | | X | X | Temperature, pulse rate, RR, and BP. On study drug infusion days, measure pulse rate and BP within 15 min prior to infusion(s), after completion of each infusion(s), and 1h after completion of the last antibody infusion. Additional measurements as clinically indicated. Day 2 Cycle 1 only for patients in Parts A, B, and C |
| Central ECG (12 lead) | X | X | | | X | | | X | | X | | | | | | **Only for patients in Parts A, B, and C** during Cycle 1 and 2; see Attachment 4 for exact timing; triplicate ECGs to be conducted |
| ~~Local ECG (12 lead)~~ | ~~X~~ | | | | ~~X~~ | | | ~~X~~ | | ~~X~~ | | ~~X~~ | | | ~~X~~ | ~~Single ECGs to be conducted predose; if a central ECG is performed at the same time point for patients in Parts A, B, and C during Cycle 1 and 2, no additional local ECG needs to be performed~~ |

| | Cycle 1 | | | | | | | Cycle 2 | | | | Cycle 3-n | | | Follow-Up | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | 30-day (V801) | |
| ***Relative Day Within a Cycle*** | **1** | **2** | **4 or 5** | **8** | **15** | **16** | **22** | **1** | **8** | **15** | **22** | **1** | **8** | **15** | | In Cycle 2 and beyond, visits may be performed ±3 days around scheduled visits. No shortening of the treatment cycles is allowed |
| Hematology | X | | | X | X | | | X | X | X | | X | X | X | X | See Attachment 2; may be done within 3 days prior to administration of study drugs (except Cycle 1, Day 1 [within 3 days]); **Only patients in Part A ~~D~~C**: Day 8 only in Cycle 1 and Day 15 in Cycle 3 and beyond only if abnormal (different from previous assessment) on Day 1 |
| Coagulation | X | | | X | X | | | X | | X | | X | | X | X | See Attachment 2; may be done within 3 days prior to administration of study drugs (except Cycle 1, Day 1 [within 3 days]); in Cycle 3 and beyond, Day 15 only if abnormal (different from previous assessment) on Day 1 |
| Serum chemistry | X | | | X | X | | | X | X | X | | X | X | X | X | See Attachment 2; may be done within 3 days prior to administration of study drugs (except Cycle 1, Day 1 [within 3 days]); **Only patients in Part A ~~D~~C**: Day 8 only in Cycle 1, and Day 15 in Cycle 3 and beyond only if abnormal (different from previous assessment) on Day 1 |
| Urinalysis | X | | | X | X | | | X | | X | | X | | X | X | See Attachment 2; 24-hour collection if dipstick worsened after initiation of study treatment; in Cycle 3 and beyond, Day 15 only if abnormal (different from previous assessment) on Day 1 |
| TSH +fT4 | | | | | | | | | | | | X | | | X | See Attachment 2; Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter |
| Adverse event reporting | X | | | | | | | X | | | | X | | | X | Throughout study as needed (according CTCAE v4.0 grading). Refer to Section 8.1.2.2 for reporting guidelines |
| Concomitant medications | X | | | | | | | X | | | | X | | | X | Throughout study as needed. |

## Study Schedule for the Continued Access Period Only, Protocol I7W-MC-JQBA

Perform procedures as indicated.

| | | | Patients on Study Treatment | Continued Access Period Follow-Up |
|---|---|---|---|---|
| | | **Cycle** | **n** | **Follow-Up[a]** |
| | | **Visit** | 501-5XX | 901 |
| | | **Duration (days)** | 28 | 30 |
| | | **Relative day within a cycle** | 1 | |
| **Procedure Category** | **Procedure** | **Protocol Reference** | | |
| **Informed consent form[d]** | | Section 11 | X | |
| **Adverse events collection/CTCAE grading[b]** | | Section 8.1.2 | X | X |
| **Study drugs** | LY3127804/ramucirumab[c] ~~paclitaxele~~ | Section 7 | X | |
| ~~**Serum chemistry**~~ | | ~~Attachment 2~~ | ~~X~~ | |
| ~~**Hematology**~~ | | ~~Attachment 2~~ | ~~X~~ | |

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; SAEs = serious adverse events.

[a] The continued access period begins after study completion and ends at the end of trial.

[b] Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.

[c] Patients in the combination cohorts will receive ramucirumab on the same schedule as LY3127804 (Table JQBA.7.2.2).

[d] A new patient informed consent form for the continued access period will need to be signed only if required by local law and regulations.

~~[e] Patients in Part E will receive paclitaxel on Days 1, 8, and 15.~~

# Attachment 4. Protocol JQBA Pharmacokinetic and Pharmacodynamic Sampling Schedule

**Table 1: PK and PD sampling schedule for LY3127804 (LY, all cohort) and ramucirumab (combination cohorts only) and centralized ECG monitoring[e] for part A, B and C**

| Study Period Cycle[a]/Day | | Approximate Running Time (h)[b] | ID Sample[c] | Sample Description | LY3127804 PK and PD | Ramucirumab PK[d] | Centralized ECG[e] |
|---|---|---|---|---|---|---|---|
| Cycle 1 | Day 1 | 0 | 1 | Predose LY | X | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | | |
| | | 1-2 | 2 | EOI | X | | X |
| | | *Ramucirumab infusion (Parts B and C only)* | | | | | |
| | | 3-4 | 3 | 2 h post LY (EOI)[f] | X | X | X |
| | Day 2 | 24 | 4 | Any time during Day 2 | X | X | X |
| | Days 4-5 | 96 | 5 | Any time during Days 4-5 | X | X | |
| | Day 8 | 168 | 6 | Any time during Day 8 | X | X | |
| | Day 15 | 0 | 7 | Predose LY | X | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | | |
| | | 1-2 | 8 | EOI | X | | X |
| | | *Ramucirumab infusion (Parts B and C only)* | | | | | |
| | Day 16 | 24 | 9 | Any time during Day 16 | X | | |
| | Day 22 | 168 | 10 | Any time during Day 22 | X | | |
| Cycle 2 | Day 1 | 0 | 11 | Predose LY | X | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | | |
| | | 1-2 | 12 | EOI | X | | X |
| | | *Ramucirumab infusion (Parts B and C only)* | | | | | |
| | | 3-4 | 13 | 2 h post LY (EOI)[f] | X | X | X |
| | Day 8 | 168 | 14 | Any time during Day 8 | X | | |
| | Day 15 | 0 | 15 | Predose LY | X | | X |
| | | *LY3127804 infusion (60-120 min)* | | | | | |
| | | 1-2 | 16 | EOI | X | | X |
| | | *Ramucirumab infusion (Parts B and C only)* | | | | | |
| | Day 22 | 168 | 17 | Any time during Day 22 | X | | |
| Cycle 3 | Day 1 | 0 | 18 | Predose LY | X | | |
| Cycle 4 | Day 1 | 0 | 19 | Predose LY | X | X | |
| Visit 801 follow up | | 720 | 20 | 30 days post ~~last dose~~ study discontinuation | X | X | |

**Table 2: PK and PD sampling schedule for LY3127804 and ramucirumab for part D.**

| Study Period Cycle[a]/Day | | Approximate Running Time (h)[b] | ID Sample[c] | Sample Description | LY3127804 PK and PD | Ramucirumab PK |
|---|---|---|---|---|---|---|
| Cycle 1 | Day 1 | 0 | 1 | Predose LY | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | |
| | | 1-2 | 2 | EOI | X | |
| | | *Ramucirumab infusion* | | | | |
| | | 3-4 | 3 | 2 h post LY (EOI)[d] | X | X |
| | Day 8 | 168 | 4 | Any time during Day 8 | X | X |
| | Day 15 | 0 | 5 | Predose LY | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | |
| | | 1-2 | 6 | EOI | X | |
| | | *Ramucirumab infusion* | | | | |
| | Day 22 | 168 | 7 | Any time during Day 22 | X | |
| Cycle 2 | Day 1 | 0 | 8 | Predose LY | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | |
| | | 1-2 | 9 | EOI | X | |
| | | *Ramucirumab infusion* | | | | |
| | | 3-4 | 10 | 2 h post LY (EOI)[d] | X | X |
| | Day 8 | 168 | 11 | Any time during Day 8 | X | |
| | Day 15 | 0 | 12 | Predose LY | X | |
| | | *LY3127804 infusion (60-120 min)* | | | | |
| | | 1-2 | 13 | EOI | X | |
| | | *Ramucirumab infusion* | | | | |
| | Day 22 | 168 | 14 | Any time during Day 22 | X | |
| Cycle 3 | Day 1 | 0 | 15 | Predose LY | X | |
| Cycle 4 | Day 1 | 0 | 16 | Predose LY | X | X |
| Visit 801 follow-up | | 720 | 17 | 30 day post last dose | X | X |

Note: PK/PD samples and ECGs up to 4 hours after the end of LY3127804 should be obtained within ±10 minutes of the scheduled sampling time. It is essential that the actual date and times of ALL LY3127804 and ramucirumab doses are recorded accurately in the eCRF and date and times of collection of PK samples are recorded accurately on the appropriate forms.

Abbreviations: ECG = electrocardiogram; EOI = end of LY infusion; h = hour; IV = intravenous; LY = LY3127804; PK = pharmacokinetic; PD = pharmacodynamic;

a Cycle length = 28 days.

b Approximate time relative to start of last LY3127804 dose given (except for predose).

c Up to 5 additional PK samples can be drawn from each patient during the study, at the discretion of the sponsor after communication with the investigator. The number of sampling time points might be reduced if PK/PD has been sufficiently characterized and if approved in writing by the sponsor.

d This sample should be taken immediately after the end of ramucirumab infusion

**Table 3: PK and PD sampling schedule for LY3127804 and ramucirumab for part E**

| Study Period Cycle[a]/Day | | Approximate Running Time (h)[b] | ID Sample[c] | Sample Description | LY3127804 PK and PD | Ramucirumab PK |
|---|---|---|---|---|---|---|
| Cycle 1 | Day 1 | 0 | 1 | Predose LY | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | |
| | | 1-2 | 2 | EOI | X | |
| | | *Ramucirumab infusion and paclitaxel infusion* | | | | |
| | | 3-4 | 3 | 2 h post LY (EOI)[d] | X | X |
| | Day 8 | 168 | 4 | prior to paclitaxel infusion | X | X |
| | Day 15 | 0 | 5 | Predose LY | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | |
| | | 1-2 | 6 | EOI | X | |
| | | *Ramucirumab infusion and paclitaxel infusion* | | | | |
| | Day 22 | 168 | 7 | Any time during Day 22 | X | |
| Cycle 2 | Day 1 | 0 | 8 | Predose LY | X | X |
| | | *LY3127804 infusion (60-120 min)* | | | | |
| | | 1-2 | 9 | EOI | X | |
| | | *Ramucirumab infusion and paclitaxel infusion* | | | | |
| | | 3-4 | 10 | 2 h post LY (EOI)[d] | X | X |
| | Day 8 | 168 | 11 | prior to paclitaxel infusion | X | |
| | Day 15 | 0 | 12 | Predose LY | X | |
| | | *LY3127804 infusion (60-120 min)* | | | | |
| | | 1-2 | 13 | EOI | X | |
| | | *Ramucirumab infusion and paclitaxel infusion* | | | | |
| | Day 22 | 168 | 14 | Any time during Day 22 | X | |
| Cycle 3 | Day 1 | 0 | 15 | Predose LY | X | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cycle 4 | Day 1 | 0 | 16 | Predose LY | X | X |
| Visit 801 follow up | | 720 | 17 | 30 day post last dose | X | X |

Note: PK/PD samples and ECGs up to 4 hours after the end of LY3127804 should be obtained within ±10 minutes of the scheduled sampling time. It is essential that the actual date and times of ALL LY3127804 and ramucirumab doses are recorded accurately in the eCRF and date and times of collection of PK samples are recorded accurately on the appropriate forms.

Abbreviations: EOI = end of LY infusion; h = hour; IV = intravenous; LY = LY3127804; PK = pharmacokinetic; PD = pharmacodynamic;

a Cycle length = 28 days.

b Approximate time relative to start of last LY3127804 dose given (except for predose).

c Up to 5 additional PK samples can be drawn from each patient during the study, at the discretion of the sponsor after communication with the investigator. The number of sampling time points might be reduced if PK/PD has been sufficiently characterized and if approved in writing by the sponsor.

d This sample should be taken immediately after the end of ramucirumab infusion.

# Attachment 8. Protocol JQBA Sampling Summary

| Purpose | Sample Type | Maximum Amount per Sample | Maximum Number Samples | Maximum Total Amount |
|---|---|---|---|---|
| Study qualification[a] | Blood | ~~10~~5 mL | ~~4~~6 | ~~40~~ 30 mL |
| Health monitoring (may be more than 1 tube)[b] | Blood | ~~10~~ 5 mL | ~~24~~52 | ~~240~~ 260 mL |
| PD/tailoring biomarkers | Tissue biopsy | 5 mm, 0.5 oz, 1 cc | 2 | 10 mm<br>1 oz<br>2 cc |
| Drug concentration | Blood | ~~4~~ 3.5 mL | 28 | ~~112~~ 98 mL |
| PD biomarkers | ~~Serum~~/~~p~~Plasma | 10 mL | ~~12~~19 | ~~120~~ 190 mL |
| ~~Tailoring biomarkers~~Pharmacogenetics | Blood | ~~3~~ 10 mL | ~~3~~1 | ~~9~~ 10 mL |
| Immunogenicity | Blood | ~~10~~ 8.5 mL | ~~4~~ 14 | ~~40~~ 119 mL |
| Hepatic monitoring[b] | Blood | 3 - 30 mL | — | — |
| Total | | | | Blood: ~~441~~517 mL<br>Tissue biopsy: 10 mm, 1 oz, 2 cc<br>~~Serum~~/~~p~~Plasma: ~~120~~ 190 mL |

**Leo Document ID = 696ee745-9b5a-4b24-a3ee-6d1689c87454**

**Approver:** PPD
**Approval Date & Time: 08-Sep-2017 18:46:07 GMT**
**Signature meaning: Approved**

**Approver:** PPD
**Approval Date & Time: 11-Sep-2017 09:19:12 GMT**
**Signature meaning: Approved**