Protocol I7H-MC-JNBA(b)

A Phase 1 Study of LY3164530, a Bispecific Antibody Targeting MET and EGFR, in Patients with Advanced or Metastatic Cancer

NCT02221882

Approval Date: 28-Sep-2015

1. Protocol I7H-MC-JNBA(b)

A Phase 1 Study of LY3164530, a Bispecific Antibody Targeting MET and EGFR, in Patients with Advanced or Metastatic Cancer

Anti-MET/EGFR Bispecific Antibody (LY3164530)

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study of intravenous LY3164530 in patients with advanced or metastatic cancer.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly 02 April 2014
Amendment (a) Electronically Signed and Approved by Lilly 11 August 2014
Amendment (b) Electronically Signed and Approved by Lilly on date provided below

Approval Date: 28-Sep-2015 GMT

2. Synopsis

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study of intravenous LY3164530 in patients with advanced or metastatic cancer.

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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.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
$AUC_{(0\text{-}tlast)}$	area under the serum concentration-time curve from time zero to last measurable serum concentration
$AUC_{(0\text{-}\infty)}$	area under the serum concentration-time curve from time zero to infinity
$AUC_{0\text{-}\tau}$	area under the serum versus time concentration-time curve over the dosing interval
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).
$C_{av,\tau}$	average serum concentration over the dosing interval
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	systemic clearance
C_{max}	maximum serum concentration
$C_{min,\tau}$	minimum serum concentration over the dosing interval
CNS	central nervous system

complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
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
CSF	colony-stimulating factor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	deescalate the dose
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DU	deescalate the dose due to unacceptable toxicity
E	escalate the dose
EC_{50}	the half maximal effective serum concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EGFR/ECD	epidermal growth factor receptor extracellular domain
EI	equivalence interval
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one 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.
FISH	fluorescence in situ hybridization
GCP	good clinical practice
HGF	hepatocyte growth factor
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IHC	immunohistochemistry
IV	intravenous
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.
interim analysis	An analysis of clinical study data that is conducted before the final 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.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition factor
MET/ECD	mesenchymal-epithelial transition factor extracellular domain
monitor	A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local 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
mRNA	microribonucleic acid
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI	National Cancer Institute
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.
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QTc	corrected QT interval
Q2W	once every 2 weeks
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
S	stay at the same dose
SAE	serious adverse event
SCCHN	squamous cell cancer of the head and neck
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
SE	standard error
Sponsor	The party who takes responsibility for the initiation, management, and/or financing of a clinical study.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TGF	transforming growth factor
TPO	third-party organization
ULN	upper limit of normal

V	volume of distribution

A Phase 1 Study of LY3164530, a Bispecific Antibody Targeting MET and EGFR, in Patients with Advanced or Metastatic Cancer

5. Introduction

5.1. Rationale and Justification for the Study

The epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition factor (MET) are receptor tyrosine kinases that each play a key role in cancer signaling. They are co-expressed in many tumors, and crosstalk between the signaling pathways controlled by these receptors has emerged as a major mechanism for cancer progression and resistance to therapy.

Mesenchymal-epithelial transition factor, also known as the hepatocyte growth factor (HGF) receptor, and its ligand HGF, have a significant role in tumor growth and metastasis. Aberrant MET signaling has been implicated in the development of many human cancers, including breast, cholangiocarcinoma, colorectal, endometrial, esophageal, head and neck, gastric, renal, pancreatic, bladder, liver, lung, prostate, melanoma, thyroid, and ovarian cancers (Gherardi et al. 2012). Mesenchymal-epithelial transition factor signaling alterations can result from the overexpression of HGF or MET, activating mutations in MET, transactivation, autocrine or paracrine signaling, or MET gene amplification (Graveel et al. 2013). In addition, MET/HGF is a critical player in developed resistance to targeted therapies, including therapies directed at EGFR (Remon et al. 2014).

Epidermal growth factor receptor signaling has a crucial role in tumor biology by modulating cellular proliferation, angiogenesis, metastasis, and survival of cancer cells. Therapies targeting EGFR signaling are used to treat non-small cell lung, colorectal, pancreatic, and head and neck cancers. Multiple mechanisms of resistance to EGFR-targeted therapies have been identified, and include mutations in EGFR and downstream proteins such as KRAS, histologic transformation, and the activation of alternative pathways, including the MET signaling pathway (Chong and Janne 2013).

Co-expression and activation of MET and EGFR are found in a number of tumor types, including non-small cell lung, colorectal, gastric, and head and neck cancers (Scheving et al. 2002; Bonine-Summers et al. 2007; Nanjo et al. 2013). Blocking one receptor tends to up-regulate the other, leading to resistance to single-agent treatment (Engelman et al. 2007). Amplification of *MET* and/or high levels of HGF expression has been observed in non-small cell lung cancer patients with intrinsic or acquired resistance to tyrosine kinase inhibitors of EGFR, including erlotinib and gefitinib (Engelman et al. 2007; Yano et al. 2011). Conversely, *MET*-amplified lung cancer cells exposed to MET-inhibiting agents for a prolonged period develop resistance via the EGFR pathway (McDermott et al. 2010).

The crosstalk between the MET and EGFR pathways suggests that dual inhibition of these targets may lead to improved outcomes for patients with an MET- and EGFR-positive cancer,

and that simultaneous inhibition may overcome or delay resistance compared to blockade of just 1 pathway.

Unlike early versions of bispecific antibodies, which simply aimed at crosslinking receptors on the surface of immune cells, LY3164530 is an engineered bispecific antibody designed to neutralize, internalize, and disrupt signaling via both the MET and EGFR receptors. It consists of an immunoglobulin G (IgG)4 antibody to MET and a single-chain variable fragment (scFv) to EGFR fused to the N-terminus of each heavy chain. LY3164530 consists of 2 identical heavy chains and 2 identical light chains.

This bispecific antibody may offer an advantage over combining 2 different antibodies since, as described below (Section 5.3) and in the Investigator's Brochure, the dual inhibition may lead to more efficient internalization and subsequent degradation of both the MET and EGFR receptors. The initial Phase 1 study with LY3164530, Study I7H-MC-JNBA (JNBA), will characterize the safety and determine the recommended Phase 2 dose (RP2D) of LY3164530 in patients with advanced or metastatic cancer.

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.

5.2. Objectives

5.2.1. Primary Objective

The primary objective of this study is to determine an RP2D and schedule of LY3164530 that may be safely administered to patients with advanced or metastatic cancer.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3164530
- to estimate the pharmacokinetic (PK) parameters of LY3164530
- to document any antitumor activity observed with LY3164530.

5.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- to explore the effect of LY3164530 on pharmacodynamic (PD) markers
- to identify exploratory biomarkers associated with tumor response and/or safety.

5.3. General Introduction to LY3164530

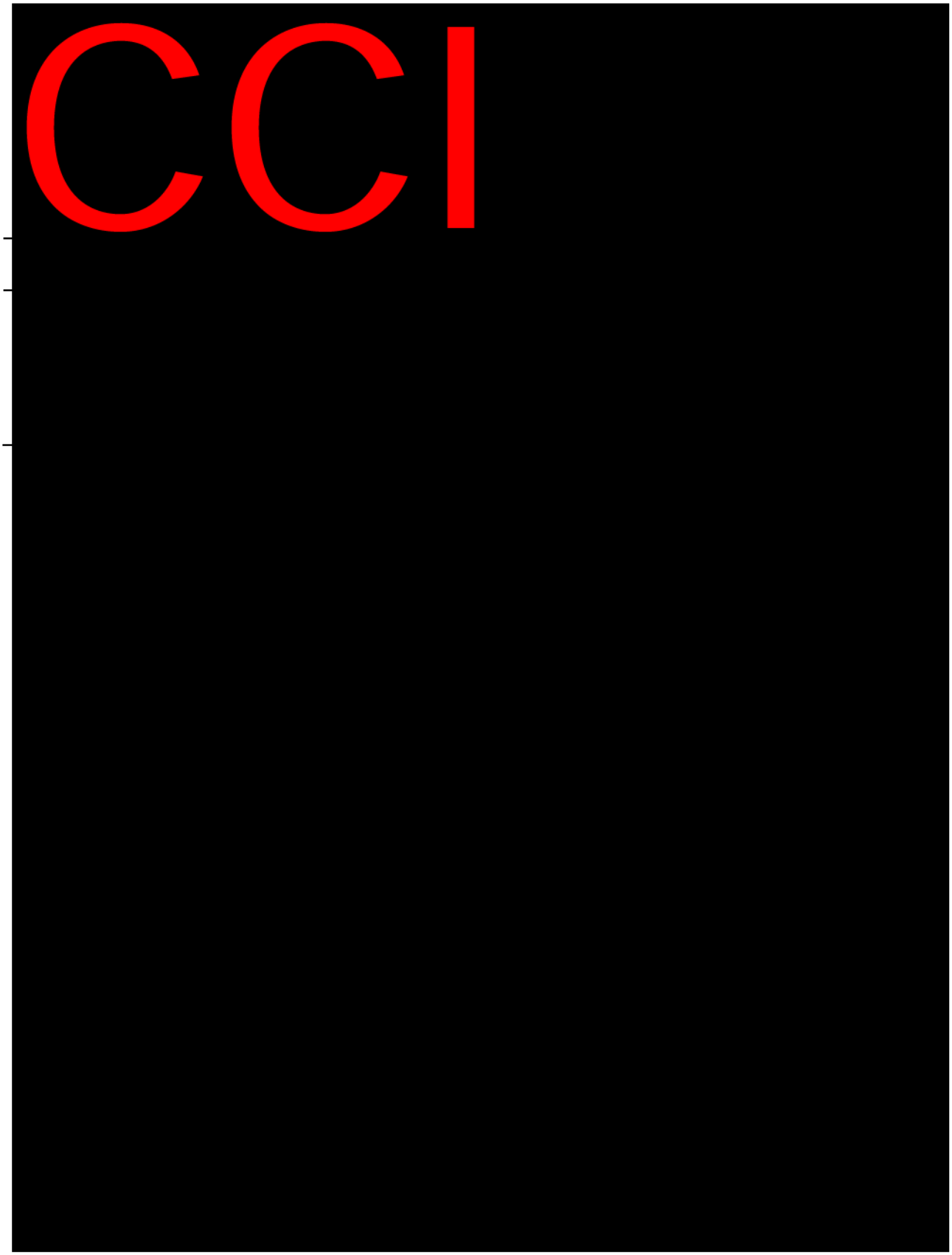
LY3164530 is an engineered bispecific antibody targeting MET and EGFR, derived from a MET antibody (LY2875358) and humanized cetuximab, an EGFR antibody. During Phase 1 dose

escalation, LY2875358 has been well tolerated. No dose-limiting toxicities (DLTs), serious adverse events (SAEs), or ≥Grade 3 adverse events (AEs) possibly related to LY2875358 were reported at doses up to 2000 mg administered every 2 weeks. The most frequent AEs possibly related to LY2875358 were nausea (8.7%), vomiting (8.7%), and diarrhea (8.7%) (Goldman et al. 2013). The toxicities of cetuximab have been well characterized, and include cutaneous AEs (rash, pruritus, and nail changes), diarrhea, and infusion-related reactions. It is expected that LY3164530 will have a toxicity profile consistent with these agents.

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

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

LY3164530 has high affinity for both MET and EGFR and binds both receptors simultaneously in tumor cells. As described in the Investigator's Brochure (Section 5.2.2), binding of LY3164530 to MET and EGFR blocks activation of both receptors by their respective ligands. In addition to its ligand-blocking activity, LY3164530 also leads to internalization and degradation of both receptors in tumor cells. The ability of LY3164530 to internalize both receptors is superior to the combination of individual monoclonal antibodies. The internalization of both receptors is most commonly observed in cells expressing high levels of MET. In addition, LY3164530 also increases the avidity binding to MET in cells expressing both MET and EGFR, leading to better neutralization of HGF compared to the parental MET antibody alone or in combination with cetuximab. The ability of LY3164530 to block ligand-receptor interactions and efficiently internalize MET and EGFR, and its increased avidity for MET, is believed to be responsible for the in vitro antiproliferative activity observed against a panel of tumor cell lines. In vivo, administration of LY3164530 results in dose-dependent antitumor activity in cell line-derived non-small cell lung cancer, gastric cancer, and squamous cell cancer of the head and neck (SCCHN) xenografts, as well as in colorectal cancer and SCCHN patient-derived xenografts.


CCI

5.3.4. Biomarkers

In order to assess the capacity of LY3164530 to inhibit the MET and EGFR pathways, pre- and post-treatment assessments of circulating biomarkers including, but not limited to, the MET ligand (HGF), EGFR ligands (eg, EGF, transforming growth factor [TGF]-alpha), MET extracellular domain (MET/ECD), and EGFR extracellular domain (EGFR/ECD) may be analyzed.

Mesenchymal-epithelial transition factor protein expression in tumors has been linked to clinical outcomes to MET therapy (Martens et al. 2006; Jin et al. 2008, Spigel et al. 2013). Therefore, pre-treatment tumor biopsy tissue should be obtained and prior archived tissue will be requested in order to retrospectively assess potential markers associated with response. However, for patients who have disease recurrence/metastasis in technically challenging sites to obtain biopsies or who have tissue available from a prior post-treatment biopsy and have not received intervening therapy, the investigator and Sponsor may agree to omit the pretreatment biopsy. In archived and pre-treatment tissue samples, analytes related to the MET and EGFR pathways and cancer pathobiology including, but not limited to, MET and EGFR protein expression may be evaluated. In tumor tissue and circulating deoxyribonucleic acid (DNA), somatic mutation status and/or copy number variations of MET and EGFR pathway-related genes (eg, KRAS, BRAF) or genes related to cancer pathobiology may be assessed. In addition, tumor samples may be evaluated for potential tumor gene signature(s), potentially employing targeted or high-throughput sequencing approaches.

A blood sample will be stored to study genetic variants in drug metabolism and transport, to measure levels of target pathway proteins, or for genetic analysis of pathway-related markers of either response or toxicity, if deemed necessary by the Sponsor.

5.4. Rationale for Selection of Dose

A fixed starting dose of 300 mg LY3164530 administered IV once every 2 weeks was selected based on data from nonclinical toxicology studies and modeling of PK/PD data from nonclinical studies of LY3164530. CCI [redacted] The starting dose is significantly lower than the corresponding weekly dose of cetuximab based on body surface area. CCI [redacted] See Section 5 of the LY3164530 Investigator's Brochure for additional details.

In addition, a starting dose of 300 mg is predicted to be in a range to achieve biological effects in humans. CCI [redacted] The PK/PD relationship (eg, the model structure and maximal effect) observed in MKN45 xenograft models was assumed to translate directly to patients with cancer. As a result, when administered IV every 2 weeks, LY3164530 doses greater than 100 mg are predicted to achieve biological effects in humans. Since weight-based dosing of monoclonal antibodies has not been correlated with a reduction in PK or PD variability, a fixed-dose strategy was chosen because it minimizes the potential for dosing errors in the clinic, eliminates the need for complex dosing algorithms based on body size, and is considered to be safe (Wang et al. 2009).

Based on the data from nonclinical toxicology studies and modeling of PK/PD data, the starting dose of LY3164530 in Study JNBA will be 300 mg administered IV once every 2 weeks.

5.5. Rationale for Amendment (b)

As of 27 July 2015, 15 patients have been treated in Study JNBA at doses of 300, 600, 1000, and 1250 mg on Days 1 and 15 of a 28 day cycle. One DLT (Cycle 1) has been reported in a patient at the 1000 mg dose level who experienced intolerable, Grade 2 rash. Two of the 3 patients treated at the 1250 mg dose level experienced AEs in Cycle 2 that would have met the criteria for a DLT had they occurred in Cycle 1 (DLT-equivalent toxicity). These events included Grade 3 pustular rash in one patient and Grade 3 dermatitis acneiform and Grade 4 hypomagnesaemia in another patient. As a result, a dose of 1250 mg was deemed to exceed the maximum tolerated dose. As of 27 July 2015, 6 patients have been treated at the 1000 mg dose level and enrollment will continue until 10-20 patients have been treated at the recommended Phase 2 dose.

The drug-related, treatment emergent adverse events reported for LY3164530 are consistent with inhibition of EGFR and include skin reactions [maculo-papular rash, dermatitis acneiform, skin fissures, rash, skin exfoliation, and/or pustular rash] (n=14, 93.3%), hypomagnesaemia (n=7,

46.7%), and paronychia (n=4, 26.7%). The following drug-related events occurred in 2 patients each (13.3%): decreased appetite, dysgeuesia, fatigue, and hypokalaemia. One SAE (hypomagnesaemia) was considered to be related to LY3164530 by the investigator and the Sponsor. The event occurred in a metastatic cutaneous squamous cell carcinoma patient who had Grade 1 hypomagnesaemia at baseline that worsened and resulted in study drug discontinuation.

An interim analysis of the LY3164530 PK data was conducted from all of the 15 patients who received at least 1 dose of LY3164530 administered as a 1 or 2-hour infusion once every 2 weeks (Q2W) across the dose range of 300-1250 mg. Dose-dependent increases in the systemic exposure (AUC, C_{max}) of LY3164530 following single and multiple doses were observed. A minor amount of accumulation in serum was observed within Cycle 1 and between Cycles 1 and 2 of treatment after 1000 mg Q2W (mean accumulation ratio of 1.1 within and between cycles). The LY3164530 systemic clearance (CL) decreased by approximately 2-fold on average when the dose was escalated from 600 mg to 1000 mg, indicating the saturation of cell-surface receptors by LY3164530 and a slower non-receptor-mediated clearance predominating at doses >600 mg. While a more rapid receptor-mediated clearance (ie, target mediated drug disposition [TMDD]) predominates at low doses (ie, ≤600 mg). In addition, the LY3164530 exposure following 1000 mg Q2W appears to be in an exposure range expected to achieve biological effects based on the nonclinical MKN45 xenograft PK/PD model estimates for the MET and EGFR half maximal effective serum concentrations (EC_{50}) values. The LY3164530 maximum serum concentration (C_{max}) after 1000 mg in Cycles 1 and 2 is greater (mean C_{max} range: 295-394 µg/mL) than both the MET EC_{50} (79.5 µg/mL; 0.4 µM) and EGFR EC_{50} (7.95 µg/mL; 0.04 µM) concentrations. The average LY3164530 serum concentration over the dosing interval ($C_{av,\tau}$) during Cycles 1 and 2 is also greater (mean $C_{av,\tau}$ range: 102-132 µg/mL) than the MET EC_{50} and EGFR EC_{50}. However, the minimum serum concentration over the dosing interval ($C_{min,\tau}$) of LY3164530 following 1000 mg in Cycles 1 and 2 (mean $C_{min,\tau}$ range: 19-49 µg/mL) is lower than the MET EC_{50} (79.5 ug/mL), which is the desired concentration to maintain throughout the dosing interval in order to maximize the biological activity of LY3164530.

At a dose of 1000 mg, the mean terminal elimination-life ($t_{1/2}$) is approximately 100 hours (approximately 4 days). As a result, the administration of LY3164530 every 2 weeks may not be the optimal schedule of administration in order to achieve a LY3164530 $C_{min,\tau}$ near the MET EC_{50}. Therefore, it is hypothesized that weekly dosing of LY3164530 (ie, Days 1, 8, 15, and 22 of a 28 day cycle) will minimize the fluctuation between the peak (C_{max}) and trough ($C_{min,\tau}$) serum concentrations of LY3164530 leading to a more consistent inhibition of both MET and EGFR over the dosing interval (with minimal impact on the accumulation of LY3164530) and potentially greater pharmacologic activity (PD response). The MTD of LY3164530 when administered on Days 1 and 15 of a 28 day cycle is 1000 mg. As a result, the starting dose for the weekly schedule will be 500 mg. The safety, toxicity, PK, and PD associated with a weekly schedule will be assessed.

6. Investigational Plan

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

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. The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy (eg, available standard therapies have been used, the patient is not eligible for standard curative therapy, or the patient has refused standard therapies).

[2] Have the presence of measurable and/or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009).

[3] Are ≥18 years of age.

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

[5] Have adequate organ function, including:

- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x 10^9 cells /L, platelets ≥100 x 10^9/L, and hemoglobin ≥8 g/dL. Transfusions to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug.
- Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 times ULN. If the liver has tumor involvement, AST and ALT equaling ≤5 times ULN are acceptable.
- Renal: Serum creatinine ≤1.5 times ULN.

[6] Have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale.

[7] Prior Treatments

– **Systemic treatments:** Have discontinued previous systemic treatments for cancer and recovered from the acute effects of therapy. Prior to first dose of study treatment, patients must have discontinued:

- Cytotoxic therapies or targeted agents that are small molecule inhibitors for 5 half-lives or at least 28 days (whichever is shorter).
- Mitomycin-C or nitrosourea therapy for at least 42 days.
- Biologic agents (eg, antibodies) for at least 28 days.
- At the discretion of the investigator, hormone-sensitive prostate cancer patients receiving gonadotropin releasing hormone agonist therapy and breast cancer patients on antiestrogen therapy (eg, an aromatase inhibitor) may have that treatment continued while they are enrolled in Study JNBA. However, the treatment should have been started at least 3 months prior to first dose of study drug.

– **Radiation therapy:** Limited field therapy must be completed 2 weeks before the first dose of study drug. All other radiation therapy must be completed at least 4 weeks before the first dose of study treatment. Patients must have recovered from the acute toxic effects of the treatment prior to first dose of study treatment.

– **Major surgery (excluding biopsy):** Must be completed at least 4 weeks prior to first dose of study treatment and patient must have recovered from the acute effects of the surgery.

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

[9] *Men and women with reproductive potential:* Must agree to use a reliable method of birth control during the study and for 3 months following the last dose of study drug or country requirements, whichever is longer.

[10] *Females with childbearing potential:* Must have had a negative serum pregnancy test ≤7 days before the first dose of study drug and also must not be breastfeeding.

6.1.2. Exclusion Criteria

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

[11] Have received treatment within 28 days of the initial dose of study drug with an investigational product or non-approved use of a drug or device (other than the study drug/device used in this study) for non-cancer indications or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[12] Have serious preexisting medical conditions or concomitant disorders that, in the opinion of the investigator, would exclude the patient as a candidate for this study.

[13] Have active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of study entry. Patients with a history of a CNS metastasis previously treated with curative intent (eg, stereotactic radiation or surgery) that have not progressed on follow-up imaging, have been asymptomatic for at least 28 days and are not receiving corticosteroids and or/anticonvulsants, are eligible. Patients with signs or symptoms of neurological compromise should have appropriate radiographic imaging performed before study entry to rule out brain metastasis.

[14] Have current acute or chronic leukemia.

[15] Have an active symptomatic fungal, bacterial, and/or known viral infection including human immunodeficiency virus **(**HIV) or viral (A, B, or C) hepatitis (screening is not required).

[16] Have a second primary malignancy that, in the judgment of the investigator or Sponsor, may affect the interpretation of results.

[17] Have Bazett's corrected QT interval (QTc) of >470 msec on screening electrocardiogram (ECG) in repeated measurements.

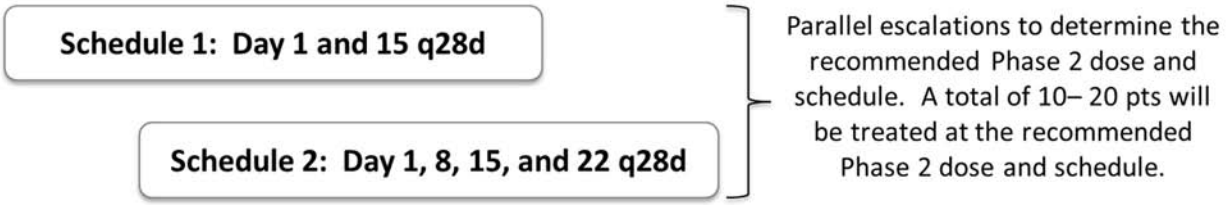
Note: Patients with permanent pacemakers may enter study if QTc is >470 msec if measured from a paced conduction and not an intrinsic (non-paced beat) conduction.

[18] Have a serious cardiac condition, such as congestive heart failure; New York Heart Association Class III/IV heart disease; unstable angina pectoris; myocardial infarction within the last 3 months; valvulopathy that is severe, moderate, or deemed clinically significant; or arrhythmias that are symptomatic or require treatment (not including patients with rate-controlled atrial fibrillation).

[19] Have a known allergy/history of hypersensitivity to any of the study drug components, or to monoclonal antibodies or other therapeutic proteins such as fresh frozen plasma, human serum albumin, cytokines, or interleukins.

6.2. Summary of Study Design

Study JNBA is a multicenter, nonrandomized, open label, dose escalation Phase 1 study of IV LY3164530 in patients with advanced and/or metastatic cancer. Eligible patients will receive LY3164530 as an infusion on Days 1 and 15 (Schedule 1) or on Days 1, 8, 15, and 22 (Schedule 2) of each cycle. A cycle will consist of 28 days and the schedules will enroll in parallel.



Dose escalation will be driven by a modified toxicity probability interval (mTPI) method. The RP2D and schedule will be determined once at least 10 patients, but no more than 20, are treated at a dose and schedule that is at or below the maximum tolerated dose (MTD). The actual sample size for Study JNBA is anticipated to be approximately 50 patients depending on the incidence of DLTs.

The planned duration of treatment is 2 cycles. Patients who are receiving benefit from study drug may continue to be treated with LY3164530 until 1 or more of the criteria for discontinuation have been fulfilled (Section 6.3.1).

6.2.1. Primary Endpoint Analysis, Study Completion, and End of Trial

The primary endpoint analysis will occur after the final patient enrolled has been evaluated for at least 1 cycle. Any patient enrolled that has completed at least 1 cycle of treatment or discontinued due to an AE (during Cycle 1), and completed the required post-treatment safety assessment, will be considered to have completed the study. However, additional cycles of therapy may continue as long as the patient is receiving benefit and no criteria for discontinuation have been met. All secondary/exploratory endpoint analyses will be updated at study completion.

Both the study completion and end of trial will be the date of the last visit or last scheduled procedure for the last patient.

6.3. Discontinuations

6.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who did not meet enrollment criteria and was inadvertently enrolled is identified, either by the Sponsor or investigator, a discussion must occur between the clinical research physician (CRP)/clinical research scientist (CRS) and the investigator to determine if the patient may continue in the study. The investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without treatment with study drug.

In addition, patients will be discontinued from the study drug and from the study 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
- Patient Decision
    - the 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
- The patient has radiographic progressive disease or significant symptomatic disease deterioration characterized as progression of disease, in the opinion of investigator, in the absence of radiographic evidence of progressive disease.
- The patient experiences unacceptable toxicity.
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).
- A dose cannot be administered within 28 days of the prior dose due to an AE (except as noted in Section 7.2.5.1).

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

LY3164530 is supplied for clinical trial use as a lyophilized powder in a glass vial. The vial is manufactured to deliver 75 mg of LY3164530. LY3164530 will be supplied to the investigative sites by Lilly. Detailed instructions for the reconstitution of the study drug and the preparation of the different dilutions will be provided separately by the Sponsor.

LY3164530 should be stored refrigerated at 2 to 8°C.

7.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent and planned duration of each individual's treatment to the site personnel or patient
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensation, destruction, and collection
- returning or destroying 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(s) so that the situation can be assessed.

7.2.1. Dosing Schedule

For doses ≤1000 mg, LY3164530 will be administered intravenously over approximately 60 minutes. The Sponsor may instruct sites to extend the infusion time for up to 3 hours for doses >1000 mg.

LY3164530 will be administered on Days 1 and 15 every 28 days (Schedule 1) or on Days 1, 8, 15, and 22 every 28 days (Schedule 2). The assigned dose, schedule, and duration of infusion of LY3164530 will be provided by the Sponsor on a patient registration form. A patient will be assigned to either Schedule 1 or Schedule 2 and will be maintained on that schedule for the duration of therapy. Subsequent doses and/or infusion times should be adjusted as described in Section 7.2.5.

7.2.2. Dose Escalation

7.2.2.1. Dose-Limiting Toxicity Determination

Dose-limiting toxicity is defined as an AE during Cycle 1 that is considered by the investigator to be at least possibly related to LY3164530 and fulfills any one of the following criterion using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03:

- ≥ Grade 3 non-hematological toxicity. Exceptions will be made for:

  - nausea, vomiting, diarrhea, and constipation that can be controlled with treatment. Grade 3 and Grade 4 nausea, vomiting, or diarrhea should be considered DLTs if persisting more than 48 hours despite supportive intervention.
  - Grade 3 rash that resolves with treatment to ≤Grade 1 within 14 days
  - Grade 3 or 4 asymptomatic electrolyte abnormalities that respond to standard treatment
  - Grade 3 elevations of ALT and/or AST lasting fewer than 8 days, without evidence of other hepatic injury, in the setting of preexisting hepatic metastasis and baseline elevation of these values, may not be considered a DLT if agreed by the study investigator and Lilly CRP/CRS.
- Grade 4 neutropenia or leukopenia, of >7 days duration.
- Grade 4 thrombocytopenia of any duration.
- Grade 3 thrombocytopenia with bleeding.
- Any febrile neutropenia.
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (eg, any toxicity that is possibly related to the study drug that requires the withdrawal of the patient from the study during Cycle 1).

7.2.2.2. DLT-Equivalent Toxicities

A DLT-equivalent toxicity is defined as an AE occurring in Cycle 2 and beyond that would have met the criteria for a DLT if it had occurred during Cycle 1. For individual patients experiencing a DLT-equivalent toxicity, dose adjustments will be made as outlined in Section 7.2.5.

At each interim analysis (as defined in Section 10.10), the rate of DLT-equivalent toxicities will be assessed. If the rate of DLT-equivalent toxicities is unacceptable (eg, a DLT-equivalent toxicity is observed in >33% patients at a given dose level), then a safety analysis will be triggered and the data will be reviewed by study investigators and the Lilly CRP/CRS. If the findings indicate that a dose level does not have an acceptable safety profile for chronic (Cycle 2 or later) administration, then a lower dose level will be chosen for further investigation. This decision will be documented in writing.

7.2.2.3. Dose Escalation Method

Dose escalation will be driven by a mTPI method (Ji and Wang 2013) (Attachment 7). A 3+3 design is commonly used in Phase 1 trials due to its simple, intuitive, and pre-specified escalation rules. However, the 3+3 method has been criticized for being conservative because the method is dictated by the observed DLT rate without acknowledging the variability arising from small cohort size.

Like the 3+3 design, the mTPI method incorporates pre-specified escalation rules. In contrast, the mTPI method is based on quantitative models that incorporate uncertainty into the decision

rules, thereby allowing more aggressive dose escalation. In the mTPI method, the number of patients in each cohort is not fixed, but a minimum of 3 patients are required for this study at each dose (unless the rule in the table indicates to deescalate the dose due to unacceptable toxicity [DU]). If 3 to 6 patients are enrolled in a cohort, the escalation rule parallels a traditional 3+3 design. However, the stay/deescalation rule of the mTPI is more aggressive than the 3+3 design. For instance, with 2 to 3 DLTs per 6 patients enrolled, the mTPI would recommend staying at the current dose, whereas the 3+3 design would recommend deescalation. Figure JNBA.1 provides the mTPI escalation rules for any cohort size up to 20 patients.

In Figure JNBA.1, the number of patients dosed at a given dose level are shown in the columns (x-axis), while the number of DLTs experienced are shown in the rows (y-axis). The rules in this figure will be used for each dose level evaluated; the patient numbers and DLTs do not carry over from cohort to cohort. By locating the intersection of the number of patients dosed and the number of DLTs, 1 of 4 pre-defined rules is used:

- E: Escalate the dose
- S: Stay at the same dose
- D: Deescalate the dose
- DU: Deescalate the dose due to unacceptable toxicity. The dose cannot be re-escalated to this dose level at a future point in the escalation.

If agreed upon by the investigators and Sponsor (for instance, if PK/PD data suggest that increasing the dose further is not expected to yield additional benefit), a more conservative rule may be applied. For instance, if the rule indicates "E" to escalate, the dose may remain at the current dose level or be deescalated to a lower level.

As shown in Figure JNBA.1, if 1 of 3 patients experiences a DLT, the decision (located in column 3 row 1) is "S", stay at the same dose. Therefore, the next patient must be treated at the same dose level. If 1 of 6 patients experience a DLT, the decision (located at column 6 row 1) is "E", escalate the dose. However, if 2 of 3 patients experience a DLT the decision is "D" and the dose must be deescalated.

In the mTPI, the cohort size is not fixed. However, each cohort in this study will contain a minimum of 3 patients, unless the escalation rules dictate that the dose should be deescalated due to unacceptable toxicity ("DU"). Doses can be escalated, deescalated, and re-escalated following the rules in Figure JNBA.1. If the dose decision was "DU," the dose cannot be re-escalated to that level.

This study is designed to identify a dose level with a dose-limiting target toxicity rate of 30%. In reality, the exact target toxicity rate is almost never achieved for a dose. To this end, instead of using a single target rate, the mTPI method considers an equivalence interval (EI) around the target toxicity rate. For this study, the EI is calibrated to be (28.7%, 30.1%), resulting in the rules in Figure JNBA.1. If the observed toxicity rate exceeds 40% and the model is still recommending "S", the Sponsor, in discussion with the investigators, may choose to deescalate. Deescalation may not be required for toxicities confounded by patient comorbidities or other clinical factors that make direct attribution to study drug difficult to determine, particularly if

they are deemed non-serious (eg, fatigue, anorexia), reversible, or inconsistent with the known toxicities of MET or EGFR inhibitors by study investigators and the Lilly CRP/CRS.

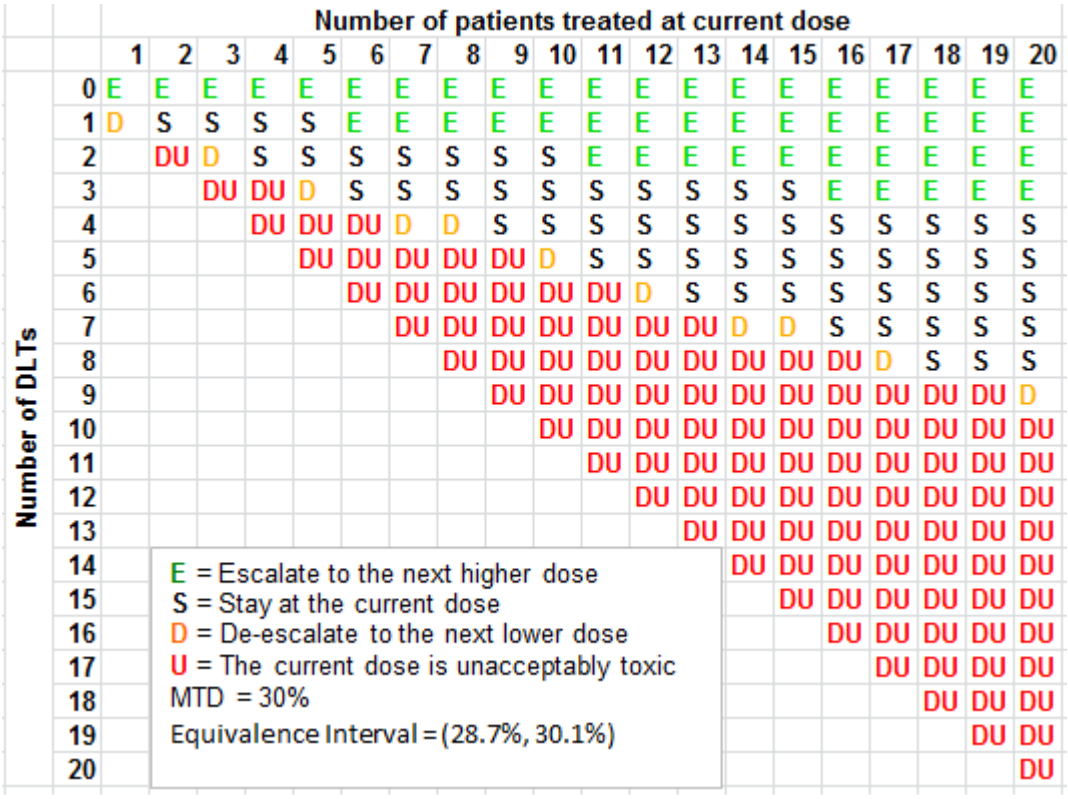


Figure JNBA.1. **Dose-finding spreadsheet of the modified toxicity probability interval method showing number of patients treated at a given dose vs. number of DLTs observed at that dose .**

The beginning dose level for Schedule 1 was 300 mg. The starting dose level for Schedule 2 will be 500 mg. The dose will be escalated by a maximum increment of 100%. If the beginning dose level is determined to be unacceptably toxic, a -1 dose level may be explored.

The exact increment will be determined by the investigators and Lilly CRP/CRS, and may be less than the maximum increment allowed in the protocol. Safety data will be the primary criteria for both the decision to dose-escalate and for selecting the dose to be administered in the next cohort. In addition, if available at the time of the dose escalation decision, PK (maximum serum concentration [C_{max}], area under the serum concentration-time curve [AUC], and CL) and/or PD results will be used as secondary/supporting data for dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly CRP or CRS; the decision will be documented in writing. Intrapatient dose escalations are not permitted.

Although an example escalation table is shown in Table JNBA.3, alternate doses may be selected.

Table JNBA.3. Sample Dose Escalation Schema

Dose Level (Cohort)	Schedule 1 Dose	Schedule 2 Dose
-1	100 mg	400 mg
1	300 mg	500 mg
2	600 mg	600 mg
3	1000 mg	700 mg
4	1250 mg	

In Cohort 1 for Schedule 1 only, the first patient is required to complete a full cycle (28 days) before subsequent patients can be dosed. Subsequent patients in Cohort 1 can be dosed concurrently. Beginning with Cohort 2 for Schedule 1 and for all cohorts with Schedule 2, patients within a cohort can be dosed concurrently.

The decision to stop dose escalation will be primarily driven by the appearance of DLTs and the rules in Figure JNBA.1. However, if PK/PD data suggest that increasing the dose further is not expected to yield additional benefit, escalation may cease.

7.2.3. Recommended Phase 2 Dose Determination

The RP2D will be a dose at which at least 10 patients, but no more than 20, have been enrolled. The RP2D will be agreed upon following discussion between the investigators and the Lilly CRP or CRS and will include an assessment of safety, PK, and PD data. At the RP2D, the intersection of the number of patients dosed and the number of DLTs at that dose level on the mTPI grid should indicate "S" or "E."

7.2.4. Monitoring and Treatment Guidance for the Investigator

7.2.4.1. Infusion-Related Reactions

Due to the risk of hypersensitivity reactions with any biological agents, all patients should continue to be closely monitored for signs and symptoms indicative of an infusion-related reaction both in the acute period (immediately or within 24 hours after dosing) and up to several days to a few weeks after dosing for delayed reactions. In Cycles 1 and 2, acute assessments should include an assessment of vital signs starting at the time of initiation of the infusion and continuing until at least 60 minutes after the end of the infusion. At a minimum, vital signs should be obtained prior to infusion, during infusion, and at 1 hour post-infusion. The exact frequency of the monitoring is left to the discretion of the investigator. Monitoring should be performed in an area where resuscitation equipment and other agents (eg, epinephrine, corticosteroids) are readily available.

Per the CTCAE v 4.03 definition of infusion-related reactions, symptoms occurring during or following infusion of investigational therapy may be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome. In the setting of symptoms occurring during or following infusion of investigational therapy, 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.

Section 7.2.5 and Table JNBA.4 detail the treatment recommendations for LY3164530 infusion-related reactions. If a patient should have an infusion-related reaction to LY3164530, all attempts should be made to obtain an anti-LY3164530 antibody blood sample (immunogenicity sample) as close to the onset of the event as possible, at the resolution of the event and 28 days following the event. In addition, these same samples may be assessed for levels of LY3164530 and for PD markers to provide information on the nature of the infusion-related reaction. Immunogenicity samples will be collected during the follow-up visit for all patients. The procedure for sample collection and handling is described in a separate procedural manual.

If infusion-related reactions are observed, premedication with diphenhydramine hydrochloride (or equivalent), dexamethasone (or equivalent), or other medications as medically indicated may be considered for future patients. The decision to implement premedication for drug administration in subsequent patients will be made following a discussion between the investigators and Sponsor and will be documented in writing.

7.2.4.2. Skin Reactions

Skin rash is a known toxicity of EGFR inhibitors, and skin effects were observed with LY3164530 in a 5-week repeat-dose toxicity study in monkeys. In Study JNBA, skin reactions were observed at all dose levels with Schedule 1 and were dose limiting at 1250 mg. As a result, prophylaxis is permitted for the initial dose of LY3164530. Institutional-approved standard of care premedication for EGFR inhibitors, such as dexamethasone and/or topical and/or oral antibiotics, may be administered for the initial and subsequent doses. .

Section 7.2.4.1 and Table JNBA.4 detail the treatment recommendations for LY3164530 skin reactions.

7.2.5. Dose Delays and Adjustments

7.2.5.1. Dose Delays and Omissions

The following rules should guide dosing:

- Before each cycle of LY3164530 the following parameters are required:
  - Hematologic: ANC ≥1.5 x 10^9/L, platelets ≥75 x 10^9/L, and hemoglobin ≥8 g/dL.
  - Non-hematologic: AEs must resolve to CTCAE v 4.03 Grade ≤1, or baseline. Exceptions will be made for: alopecia, fatigue, skin reactions, or other toxicities that can be controlled with standard treatment; these toxicities must resolve to ≤Grade 2.
- The start of a cycle is the date of the Day 1 dose.

  For Schedule 1: If the Day 15 dose cannot be administered within 21 days of the prior dose (by Day 22), it should be omitted. The interval between LY3164530 doses must not

be less than 14 days. If a dose is delayed (for toxicity or other circumstances), the next dose should be adjusted so that there is at least a 14-day interval.
–

For Schedule 2: If a dose cannot be administered within 10 days of the prior dose, it should be omitted. The interval between LY3164530 doses must not be less than 7 days. If a dose is delayed (for toxicity or other circumstances), the next dose should be adjusted so that there is at least a 7-day interval.If a dose cannot be administered within 28 days of the prior dose due to an AE, the patient should be removed from study drug treatment and should complete subsequent follow-up (Table JNBA.4).

- If the patient has completed the initial on-study radiographic assessment (eg, at the end of Cycle 2) and is continuing to receive benefit from therapy, delays of greater than 28 days may be acceptable if agreed upon by both the investigator and Sponsor. For instance, if a patient has a non–drug-related AE such as prolonged flu, the patient may continue on therapy if, in the opinion of the investigator, he/she is showing benefit from therapy and has recovered sufficiently from the AE.
- A delay of no more than 7 days because of holidays, weekends, inclement weather, or other justifiable events will be permitted and will not be counted as a protocol deviation.

7.2.5.2. Dose Adjustments

Dose adjustments should follow the guidance in Table JNBA.4.

For patients requiring dose reductions, reescalation to the original assigned LY3164530 dose is not allowed. The patient must be maintained at a reduced dose level for all remaining cycles.

Table JNBA.4. Dose Modifications and Treatment Alterations in Patients Treated with LY3164530

Toxicity	CTCAE Grade	Recommendations
Infusion-related reaction	Grade 1 First occurrence	Decrease the LY3164530 infusion rate by 50% and monitor closely for any worsening. For subsequent infusions, premedicate with diphenhydramine hydrochloride; additional premedication may be administered at the investigator's discretion.
	Grade 2 First occurrence	Stop LY3164530 infusion. Administer diphenhydramine hydrochloride and acetaminophen for fever and oxygen. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening. For subsequent infusions, premedicate with diphenhydramine hydrochloride; additional premedication may be administered at the investigator's discretion. The reduced rate should be used for all subsequent infusions.
	Grade 1 or 2 Second occurrence	Administer dexamethasone. For subsequent infusions, premedicate with diphenhydramine hydrochloride, acetaminophen, and dexamethasone. The reduced infusion rate should be used for all subsequent infusions.
	≥Grade 3	Stop LY3164530 infusion immediately and disconnect infusion tubing from the patient. Administer diphenhydramine hydrochloride, dexamethasone, bronchodilators for bronchospasm, and other medications/treatment as medically indicated. Patients must not receive any further LY3164530 treatment.
Skin reactions (eg, acne-like rash)	Grade 3 First occurrence	Delay or omit LY3164530 treatment until ≤Grade 1 following the rules in Section 7.2.5.1. Treatment with topical and/or oral antibiotics should be considered.
	Grade 3 Second occurrence	Delay or omit LY3164530 treatment until ≤Grade 1 following the rules in Section 7.2.5.1. Dose reduce to the dose level used for the previous cohort for second occurrence. Treatment with topical and/or oral antibiotics should be considered.
	Grade 3 Third occurrence Or Grade 4	Patients must not receive any further LY3164530 treatment.
Other toxicities	≥Grade 3 First occurrence	Delay or omit LY3164530 treatment until ≤Grade 1 or baseline following the rules in Section 7.2.5.1. Based on the investigator's discretion, the full dose of LY3164530 may be administered or the dose may be reduced to the next lowest dose level. If event recurs at same grade, then dose reduce LY3164530 to the next lowest dose.
	≥Grade 3 Second occurrence	Delay or omit LY3164530 treatment until ≤Grade 1 or baseline following the rules in Section 7.2.5.1. If event recurs at same grade, then dose reduce LY3164530 to the next lowest dose. Exceptions may be made for transient changes in electrolytes that respond to treatment.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

Note: In addition, the dose may be reduced to the next lower level for any toxicity at the discretion of the investigator.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3164530 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, schedule, infusion duration, and identification number assignment for each patient.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

In the absence of clinical experience with LY3164530, patients should be closely evaluated to ensure identification of exacerbations of known side effects of concomitant medications. These should be reported immediately to the Sponsor. No other chemotherapy, radiotherapy, immunotherapy, herbal supplements intended to treat the cancer, 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 antiestrogen therapy (eg, an aromatase inhibitor). However, the treatment should have been started at least 3 months prior to first dose of study drug. Patients on stable doses of bisphosphonates or denosumab are allowed to continue. These agents should not be initiated within the 4 weeks prior to study enrollment or at any point while on the study. Palliative radiotherapy of no more than 14 calendar days to a solitary (non-skull) skeletal metastasis will be permitted following discussions between the investigators and the Sponsor, so long as the skeletal metastasis is not the primary measurable lesion and the patient has not developed another reason for study discontinuation.

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

Patients should receive full supportive care during the trial. Routine prophylactic use of granulocyte colony-stimulating factors (G-CSF) is not permitted during this study. Should the use of hematopoietic colony-stimulating factors (CSFs) be necessary, follow the American Society of Clinical Oncology (ASCO) recommendations for the use of CSFs (Smith et al. 2015).

Erythropoietin and packed red blood cell (RBC) transfusion may be used according to ASCO guidelines (Rizzo et al. 2008) if clinically indicated at any time during the study. Platelet transfusions may be used according to ASCO guidelines (Schiffer et al. 2001).

All concomitant medications, including premedication, should be recorded throughout the patient's participation in the study on the electronic case report form (eCRF).

7.6. Treatment Compliance

LY3164530 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 is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the eCRF.

7.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drug 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 1 cycle of LY3164530 treatment will be deemed non-evaluable for assessment of a dose level, unless they experience a DLT prior to withdrawal. However, patients who receive all doses of LY3164530, but discontinue from study drug before the end of Cycle 1, will be considered evaluable for the assessment of a dose level, provided it can be documented whether the patient experienced a DLT during Cycle 1.

If the patient is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered non-evaluable and may be replaced.

Patients that require a dose reduction or omission during Cycle 1 or have a dosing delay of more than 3 days for reasons other than a study drug-related AE may be deemed non-evaluable for DLT assessment.

Nonevaluable patients may be replaced to ensure that enough patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT.

Patients who are not evaluable for PK, but who complete 1 cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP or CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

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

8.1. Safety Evaluations

The safety and tolerability of LY3164530 have been assessed in nonclinical toxicology studies and this ongoing Phase 1 study. The results from these studies are detailed in the Investigator's Brochure. This Phase 1 study contains safety monitoring that will permit initial characterization of the safety profile of LY3164530 in patients with advanced or metastatic cancer. Study procedures and their timing, including collection of patient samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests will be performed as listed in Attachment 2. A urine or serum pregnancy test will be administered to female participants, if applicable. 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 are responsible for monitoring the safety of patients who have entered into this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator, but must meet the minimium requirements outlined in Table JNBA.5.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JNBA.5 presents a summary of AE and SAE reporting guidelines. Table JNBA.5 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 labs, 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 v 4.03.

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

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the Sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) 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 patient must be removed from the study and treatment with study drug must be stopped immediately.

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

If a patient's dosage is reduced, delayed, or omitted; or if 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 modification 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 and/or study drug via eCRF/electronic data entry.

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 elective 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 (eg, 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)
- a life-threatening experience (ie, 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.

Serious adverse events 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 Investigator's Brochure.

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

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 (eg, have not been exposed to LY3164530), 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 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 or protocol procedures, occurring during the follow-up visit (Visit 801) must be reported to Lilly or its designee. The follow-up visit starts following the last dose of study drug. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these assessments is 28 days ± 5 days after the last dose of study drug.

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

Following the safety assessments that mark the planned end of the follow-up visit (Visit 801), the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. Particular focus should be placed on patients that have abnormal electrolytes, as electrolyte depletion is known to occur for >6 weeks after EGFR monoclonal antibody therapy.

If a patient has an ongoing AE or SAE possibly related to LY3164530 (eg, abnormal electrolytes), the patient should be followed until the event is resolved, the event is no longer considered to be study 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. Any subsequent follow-up(s) for AEs will be no more than 28 days ± 5 days in duration.

After the follow-up visit (Visit 801), AEs are not required to be reported unless the investigator feels the AEs were related to either study drug, drug delivery system, or a protocol procedure. If an investigator becomes aware of an SAE believed to be related to protocol procedures or study drug, the investigator should report the SAE to the Sponsor (Attachment 6), and the SAE will be entered in the Lilly Safety System.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the Development Core Safety Information in the Investigator's Brochure and that the investigator identifies as related to study drug or procedure. The US 21 CFR 312.32, the EU 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 JNBA.5.

Table JNBA.5. Adverse Event and Serious Adverse Event Reporting Guidelines for Study JNBA

Study Period	Timing	Types of AEs/SAEs Reported	Database used for Collection
Screening/Baseline	Starts at the signing of informed consent and ends just before the first dose of study drug	Preexisting conditions All AEs and SAEs regardless of relatedness	Clinical database and LSS
On therapy	Starts at first dose of study drug and ends at last dose of study drug	All AEs and SAEs regardless of relatedness	Clinical database and LSS
Follow-up Visit (Visit 801)	Starts just after the last dose of study drug and ends when end of study safety assessments are completed 28 days (±5 days) after last dose of study drug	All AEs and SAEs regardless of relatedness	Clinical database and LSS
Subsequent Follow-ups , if necessary for patient monitoring for ongoing related AEs (continuation of Visit 801)	Follow-ups no more than 28 day intervals (±5 days) and are continued until the criteria in Section 8.1.2.2.3 are met	Ongoing AEs possibly related to study drug, or protocol procedures. All SAEs related to protocol procedures or study drug	Clinical database and LSS
Patient no longer on study		All SAEs related to protocol procedures or study drug that the investigator becomes aware of	LSS

Abbreviations: AE = adverse event; LSS = Lilly Safety System; SAE = serious adverse event.

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

For each patient, a 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1 and Attachment 4). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. During Cycle 1, triplicate ECGs will be done as specified in the Study Schedule (Attachment 1). Beginning with Cycle 2 and beyond, only a single ECG will be required (Attachment 4).

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

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

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (eg, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (eg, demographics and study details), and will then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

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

8.1.4. Safety Monitoring

The Lilly CRP or CRS will monitor safety data throughout the course of the study. Representatives from Lilly Global Patient Safety will specifically monitor SAEs.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 5).

- If a study patient experiences elevated ALT $\geq$5X ULN and elevated total bilirubin $\geq$2X ULN, clinical and laboratory monitoring should be initiated by the investigator.
- For patients entering the study with ALT $\geq$3X ULN, monitoring should be triggered at ALT $\geq$2X baseline.

8.1.5. Complaint Handling

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

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

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

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

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

8.2. Sample Collection and Testing

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

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

Attachment 3 lists the PK and PD sample collections.

Attachment 4 lists the ECG, chemistry, and hematology collection schedule.

8.2.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Investigators must document their review of each laboratory safety report and include a determination of the clinical significance of abnormal labs.

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

8.2.2. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

8.2.2.1. Pharmacokinetic Samples

At the visits and times specified in Attachment 3, blood samples will be collected to determine the serum concentrations of LY3164530. A maximum of 5 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and Lilly. Similarly, if sufficient data have been collected from other patients, a maximum of 5 samples may be removed if agreed upon between both the investigator and Lilly. Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

These samples will be analyzed at a laboratory designated by the Sponsor. Serum concentrations of LY3164530 will be assayed using a validated ELISA method.

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

Bioanalytical samples collected to measure LY3164530 will be retained for a maximum of 1 year following last patient visit for the study.

8.2.2.2. Pharmacodynamic Samples

At the visits and times specified in Attachment 3, serum and plasma samples will be collected. The effect of LY3164530 on MET and EGFR pathway-specific targets may be explored to determine changes in potential biomarkers such as circulating levels of the MET ligand HGF,

EGFR ligands (eg, EGF, TGFalpha), MET/ECD, and EGFR/ECD. These samples may be used for exploratory research on new biomarkers related to the MET/HGF and EGFR pathway. In addition, exploratory samples to assess proteomic panel may be collected. A maximum of 3 timepoints may be removed per dosing schedule during the study if warranted and agreed upon between both the investigator and Lilly.

Bioanalytical samples collected to measure PD biomarkers will be identified by the patient number (coded) and retained for a maximum of 15 years following last patient visit for the study at a facility selected by the Sponsor. Supplies and detailed instructions required for the collection, handling, and shipment of the patients' samples will be provided by the Sponsor. The samples will be analyzed at a laboratory designated by the Sponsor.

8.2.3. Samples for Tailoring Biomarkers

Collection of tumor samples for tailoring biomarker research is a component of this study.

The following samples are required for biomarker research:

- Pre-treatment tumor tissue
- Blood, plasma, and/or serum samples.

The following samples are optional samples and should be collected from patients in the study when possible:

- If a patient has available archived tumor tissue previously taken to evaluate the patient's disease, a small amount of this tissue will be requested for biomarker research
- On treatment and/or post-treatment tumor tissue.

These samples are described in the following sections.

8.2.3.1. Tumor Tissue

A pretreatment tumor biopsy should be obtained prior to the first dose of LY3164530. However, for patients who have disease recurrence/metastasis in technically challenging sites to obtain biopsies or who have tissue available from a prior post-treatment biopsy and have not received intervening therapy, the investigator and Sponsor may agree to omit the pretreatment biopsy. The decision must be documented in writing prior to the patient receiving the first dose of study drug and will not constitute a protocol violation. Tissue will be taken by core biopsy prior to starting treatment. Due diligence should be used to ensure that tumor specimen (not normal adjacent or tumor margins) is provided. Pathology notes accompanying the tissue may also be requested.

In addition to the new biopsy tissue, prior archived tissue will be requested. Pretreatment archived formalin-fixed paraffin-embedded tumor tissue should be in a whole block, partial block, or unstained slides. Bone samples should not be submitted. Any blocks or slides submitted for analysis will either be returned to the site upon request or discarded within 15 years after last patient visit for the trial.

Following treatment with LY3164530, optional on-treatment (eg, while still on study therapy) and/or post-progression biopsies (eg, following documentation of progressive disease on Study JNBA) for biomarker research from patients willing to consent may be collected if safe and feasible and upon notification and discussion with the Sponsor. In particular, post-treatment biopsies from lesions in patients who have received clinical benefit and subsequently progress may help identify mechanisms of resistance to LY3164530. Post-progression biopsies should be performed prior to the start of subsequent cancer treatment. However, the procedure should not impede or delay the planned cancer treatment.

In archived and pre-treatment tissue samples, an evaluation of analytes related to the mechanism of action of MET-EGFR inhibition and cancer pathobiology may be performed to assess any potential correlation with response to LY3164530. For example, the expression of MET protein, EGFR protein, HGF, and EGFR ligands may be assessed by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH). In addition, mutation status, allelic imbalance, and/or copy number variations of cancer-related genes including, but not limited to, *MET*, *HGF*, *EGFR*, *KRAS*, *HRAS*, *NRAS*, *BRAF*, may be analyzed at a laboratory designated by the Sponsor. Tumor samples may also be analyzed to explore potential tumor gene signature(s) associated with response to LY3164530 therapy.

8.2.3.2. Blood Samples for Pharmacogenetic Evaluations

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 LY3164530. 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.

The samples will be coded with the patient number and stored for up to a maximum of 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.

8.2.3.3. Exploratory Biomarker Blood Samples

In addition to blood samples, plasma samples to study circulating biomarkers associated with response to LY3164530 therapy, the underlying cancer, or cancer-related conditions will be collected. This analysis may include, but is not limited to, circulating microribonucleic acids (microRNAs) and cell-free tumor DNA. These analyses may employ targeted or high-throughput sequencing approaches. For this purpose, the results of these analyses will be correlated with clinical efficacy data. The samples will be coded with the patient number and stored for up to a maximum of 15 years.

8.2.4. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against LY3164530. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADAs) in the presence of LY3164530 antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3164530. The presence of ADAs and neutralizing ADAs may be compared to any changes in expected PK/PD parameters. In the event of any AE suspected of being related to immunogenicity, the presence of ADAs may also be evaluated. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Samples may be stored for up to 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 LY3164530. The duration allows the Sponsor to respond to regulatory requests related to LY3164530.

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 one or more of the following radiologic tests for tumor measurement:

- Computed tomography (CT) scan
- Magnetic resonance imaging (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
- Evaluation of the ECOG performance status.

In rare circumstances, historical radiologic exams for RECIST criteria that are obtained greater than 28 days prior to the first dose may be used, but this decision must be discussed with the Sponsor and documented in writing.

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

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, 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 and lab 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 eCRFs, 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 eCRF 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 ERB(s) 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.

For data handled by a data management third-party organization (TPO), eCRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

For data handled by the Sponsor internally, eCRF data and some or all data that are related will be managed by the Sponsor and stored electronically in the Sponsor's system.

9.2.2. Ancillary Data

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

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

Electrocardiogram data will be stored electronically in the central database system of Lilly's central review organization. Data may subsequently be transferred from the central review organization system to the TPO's system.

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

10. Data Analyses

10.1. General Considerations

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

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP/CRS, pharmacokineticist, and statistician. The CRP/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, standard error (SE), minimum, and maximum. Categorical endpoints will be summarized using N, frequency, percentages, and associated SE. Missing data will not be imputed. Exploratory analyses of the data that are not described in the protocol will be conducted as deemed appropriate.

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 mTPI method and determined by the occurrences of DLTs (up to 20 patients per cohort before establishing the RP2D and schedule). The total sample size is anticipated to be approximately 50 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. Discontinuations due to AE or death will be listed and summarized with cause of death further partitioned into AE, study disease, or other cause and summarized.

10.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics including age, sex, and screening height and weight
- 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 have been exposed to LY3164530 will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE v 4.03.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- dose adjustments (reductions, omissions, and delays)
- laboratory values
- vital signs
- DLTs at each dose level
- ECGs
- Extent of concomitant medications.

10.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have been exposed to study drug and have had samples collected.

Pharmacokinetic parameter estimates for LY3164530 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max}, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\tau}$, and $AUC_{0\text{-}\infty}$ of LY3164530. Other noncompartmental parameters, such as $t_{1/2}$, CL, volume of distribution (V), and accumulation ratios may be reported. Additional exploratory analyses will be performed if warranted by the data, and other validated PK software programs may be used if appropriate and approved by Lilly Global PK/PD management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Pharmacokinetic parameter estimates 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% confidence intervals (CIs).

10.6. Pharmacodynamic Analyses

Provided that the data allows, PD and immunogenicity data from all patients may be analyzed using linear and/or nonlinear fixed and mixed effects models as appropriate. Pharmacodynamic and immunogenicity data will be summarized by dose, drug concentrations, and time from dose for each schedule of administration. Potential PD markers and immunogenicity versus time data will be presented graphically for each patient and summarized by dose and schedule of administration. Absolute and/or percent change from baseline for the PD markers may also be evaluated. Data may be log-transformed prior to summarizing if necessary. The interpatient and intrapatient variability of the PD markers and immunogenicity responses may also be assessed where appropriate. Baseline measurements may be evaluated as potential covariates to assess their relationship to relevant PD responses.

10.7. Pharmacokinetic/Pharmacodynamic Analyses

In addition to a standard noncompartmental assessment, and provided that the data allows, the LY3164530 serum concentration-time data may be evaluated by model-based approaches as

warranted. Additional analyses, such as exposure-response modeling using the efficacy endpoints, may also be explored.

Additional exploratory analyses may be performed if warranted by the data.

10.8. Efficacy

The study was not designed to make an efficacy assessment. However, any tumor response data and duration of treatment will be tabulated.

10.9. Biomarker Analyses

Biomarker assessments in this study will focus on identifying markers and/or marker signatures that may indicate the patients most likely to respond or be resistant to LY3164530.

In archived and pre-treatment tissue samples, biomarker data related to the MET and EGFR pathways and cancer pathobiology may be analyzed to assess any potential correlation with response to LY3164530. These analyses may include, but are not limited to, MET and EGFR protein expression, circulating DNA, somatic mutation status, and/or copy number variations of MET and EGFR pathway-related genes (eg, KRAS, BRAF) or genes related to cancer pathobiology. In addition, tumor sample based gene signature(s) may be defined and evaluated to explore whether they are associated with response to LY3164530. In all analyses, adjustments may be made to account for other baseline patient characteristics, safety, and PK/PD data. Unless otherwise stated, given the small sample sizes involved, statistical analyses results will be considered exploratory and will not consider multiple comparison adjustments.

10.10. Interim Analyses

Since this is a dose-escalation study, data will be reviewed on an ongoing basis during the study until the RP2D is determined. The purpose of these ongoing reviews is to evaluate the safety data at each dose level. A review of the data will be completed approximately after 6 patients have been treated for at least 1 cycle at a dose level without a cohort analysis.

An interim analysis will be triggered when at least 15 patients have been dosed at a given dose level for 1 cycle of treatment to evaluate the safety and tolerability of LY3164530. The interim analysis may include, but are not limited to, an assessment of available safety, PK, and PD data.

Enrollment may continue during the interim analysis and the dose escalation rules as outlined in Figure JNBA.1 will continue to be followed.

Additional interim analyses may be triggered and may include, but are not limited to, assessment of available safety, PK, and PD data.

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11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. Informed Consent

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

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

The investigator is ultimately responsible for ensuring that informed consent is given by each patient 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 given by patients or their legal representatives.

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 Investigator's Brochure 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).

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

11.3.1. Investigator Information

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

11.3.2. Protocol Signatures

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

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

11.3.3. Final Report Signature

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

The investigator with the 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 JNBA Study Schedule

Baseline Schedule

Study Period	Baseline		
Cycle	BL		
Visit	0		
Duration	Up to 28 days		
Relative Day to C1D1	≤28	≤14	

Procedure Category	**Procedure**			**Comments**
Study Entry/ Enrollment	Informed consent form signed (prior to conducting any protocol-specific tests/procedures)	X		
	Inclusion/Exclusion evaluation		X	
Medical History	Initial history/preexisting conditions		X	
	Historical illnesses		X	Include HPV status if known in tumor as part of historical assessment and denote on eCRF.
Physical Examination	Physical examination (including height and weight)		X	
	ECOG performance status		X	
	Vital signs		X	Includes blood pressure, pulse, and temperature.
Tumor Assessment	Radiologic imaging according to RECIST 1.1	X		Radiologic assessments obtained previously as part of routine clinical care may be used as the baseline assessment. This may be CT scan or MRI.
	Tumor measurement (palpable or visible)		X	
Adverse Events Collection/CTCAE Grading		X		
Concomitant Medication Notation		X		

Baseline Schedule

	Study Period	Baseline			
	Cycle	BL			
	Visit	0			
	Duration	Up to 28 days			
	Relative Day to C1D1	≤28	≤14	**≤7**	
Procedure Category	**Procedure**				**Comments**
Lab/ Diagnostic Tests	Local hematology		X		
	Local chemistry		X		
	Local coagulation		X		
	Local urinalysis		X		
	Local pregnancy test			X	Must be done ≤7 days prior to the first dose of study drug if patient is a woman of child-bearing potential. May be urine or serum specimen.
	Central ECG		X		Triplicate ECG.
	Biopsy of pretreatment tumor tissue		X		Unless the Sponsor and investigator document that the biopsy may be omitted; sample should be taken only after study eligibility is confirmed
	Archived tumor tissue (only if available)		X		Only for those patients that meet inclusion/exclusion criteria
	Tumor markers		X		Only if appropriate for the tumor type of the patient.
	Exploratory biomarker blood sample		X		If possible, this sample should be collected on the same day as the biopsy.
	Immunogenicity sample	X			

During Treatment Study Schedule

	Study Period	Study Treatment Period														
	Cycle/Visit	1						2				3-X[a]				
	Duration	28 days						28 days				28 days				
	Relative Day within Dosing Cycle	1	2	3	8	15	22	1	8	15	22	1	8	15	22	
Procedure Category	**Procedure**															**Comments**
Physical Examination	Physical exam (including weight and skin inspections)	X						X				X				May be completed up to 7 days prior to the treatment infusion.
	Vital signs	X			X	X	X	X	X	X	X	X	X*	X	X*	Includes blood pressure, pulse, and temperature. For Cycles 1-2, at a minimum, vital signs should be obtained prior to infusion, during infusion, and at 1 hour EOI (Section 7.2.4.1). In Cycle 3-X, vital signs should be taken predose and when clinically indicated. * Only need to be collected for patients on Schedule 2
	ECOG performance status	X						X				X				May be completed up to 7 days prior to the treatment infusion
Lab/ Diagnostic Tests	Local hematology	X	X	X	X	X	X	X	X	X	X	X		X		. May be drawn up to 1 day prior to the planned assessment. On C1D1, post-dose samples should be drawn. See Attachment 4 **Schedule 2:** In Cycle 3-X, if clinically significant changes are observed, hematology should be obtained at least weekly until no longer clinically significant.
	Local chemistry	X	X	X	X	X	X	X	X	X	X	X		X		May be drawn up to 1 day prior to the planned assessment. On C1D1, post-dose samples should be drawn. See Attachment 4. **Schedule 2:** In Cycle 3-X, if clinically significant changes are observed, chemistry should be obtained at least weekly until no longer clinically significant.
	Local Urinalysis	X						X				X				May be assessed up to 3 days prior to the planned assessment.
	PK sampling	X						X				X				See Attachment 3.
	Immunogenicity Sample	X						X				X				In addition to the scheduled samples, if a patient should have an infusion-related reaction to LY3164530, all attempts should be made to obtain immunogenicity sample as close to the onset of the event as possible, at the resolution of the event and 28 days following the event. A portion of the sample

																taken for immunogenicity testing may be used for PK analysis.
	MET and EGFR ECD pharmacodynamic samples	X	X			X		X		X		X				See Attachment 3.
	MET and EGFR ligands pharmacodynamic samples	X	X			X		X		X		X				See Attachment 3.

During Treatment Study Schedule

		Study Period	Study Treatment Period														
		Cycle/Visit	1						2				3-X				
		Duration	28 days						28 days				28 days				
		Relative Day within Dosing Cycle	1	2	3	8	15	22	1	8	15	22	1	8	15	22	
Procedure Category	**Procedure**																**Comments**
Lab/ Diagnostic Tests (cnt'd)	Proteomic blood sample		X	X			X		X		X		X				See Attachment 3. Sample is only collected through Cycle 6.
	Stored sample for pharmacogenomics		X														Collect once. Sample can be collected at any time if not collected on C1D1.
	Exploratory biomarker blood sample		X										X				Sample to be collected C7D1.
	Central ECG		X	X	X	X	X	X	X	X	X	X	X	X*	X	X*	In Cycle 1, triplicate ECGs collected predose, at EOI, 2 hours EOI, and 6 hours EOI on the day of dosing . If possible, obtain prior to any associated blood draws. In Cycles 2-X, single ECGs should be obtained predose on the day of dosing. On non-dosing days,the ECG may be obtained at anytime, but if possible they should be obtained near to the same time of day as the C1D1 ECG. See Attachment 4. *Schedule 2 only
	Tumor markers								X				X				If applicable to tumor type of the patient; may be drawn up to 3 days prior to the planned assessment.
	Optional tumor biopsy		X														
Tumor Assessment	Tumor measurement (palpable or visible)											X			X		Perform at least every 8 weeks at the end of every even cycle.
	Radiologic imaging according to RECIST											X				X	The same method of imaging used at baseline should be used for each subsequent assessment. Perform at least every other cycle (approximately every 8 weeks). May be omitted if patient has clear signs of progressive disease.
Adverse Events Collection/CTCAE Grading			X						X				X				
Concomitant Medication Notation			X						X				X				
	LY3164530 – Schedule 1		X				X		X		X		X		X		

	LY3164530 – Schedule 2	X			X	X	X	X	X	X	X	X	X	X	X	

[a] Following discussion and agreement from the Sponsor, the frequency of some assessments may be reduced for patients that have been on treatment for more than 1 year and are continuing to derive benefit from treatment. This decision will be documented in writing.

Post-Treatment Discontinuation Schedule

	Study Period	Post-discontinuation Follow-Up	
	Visit 801		Post-treatment discontinuation follow-up should begin after the last dose of study therapy or, if study therapy has been omitted for an extended period, the date it is decided that the patient will not restart study therapy.
	Duration	28 ±5 days	
	Relative Day	**28**	

Procedure Category	Procedure		Comments
Physical Examination	Weight	X	
	Vital signs	X	Includes blood pressure, pulse, and temperature.
	ECOG performance status	X	
Tumor Assessment	Tumor measurement (palpable or visible)	X	Performed if lesion is assessed as target or non-target. Not required if progressive disease is documented while on treatment.
	Radiologic imaging according to RECIST	X	The same method of imaging used at baseline should be used for each subsequent assessment. Not required if progressive disease is documented while on treatment or if there are clear signs of clinical progression.
Adverse Events Collection/CTCAE Grading		X	After Visit 801, only study protocol- or drug-related events are reported. If a patient has an ongoing AE or SAE possibly related to LY3164530 (eg, abnormal electrolytes), 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. Any subsequent follow-up(s) for AEs will be no more than 28 days ±5 days in duration.
Concomitant Medication Notation		X	
	Local hematology	X	
	Local chemistry	X	Particular focus should be placed on patients that have abnormal electrolytes, as electrolyte depletion is known to occur for >6 weeks after EGFR monoclonal antibody therapy.
	Central ECG	X	Single ECG.
	Tumor markers	X	If applicable to tumor type of the patient.

Lab/ Diagnostic Tests	Optional tumor biopsy	X	From patients willing to consent.
	Exploratory biomarker blood sample	X	
	PK sample	X	
	Immunogenicity sample	X	In addition to the scheduled sample, if a patient should have an infusion reaction to LY3164530, all attempts should be made to obtain immunogenicity sample as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. If a patient requires subsequent follow-ups (eg, for an ongoing AE), an immunogenicity sample should be obtained, if possible. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
	MET and EGFR ECD pharmacodynamic samples	X	
	MET and EGFR ligand pharmacodynamic samples	X	
	Proteomic blood sample	X	Only if patient discontinues prior to Cycle 6.

Abbreviations: AE = adverse event; BL = baseline; C = cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECD = extracellular domain; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EGFR = epidermal growth factor receptor; EOI = end of infusion; HPV = human papillomavirus; MET = mesenchymal-epithelial transition factor; MRI = magnetic resonance imaging; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Attachment 2. Protocol JNBA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Basophils	**Serum Concentrations of:**
Eosinophils	Alanine aminotransferase
Erythrocyte count (RBC)	Albumin
Hematocrit	Alkaline phosphatase
Hemoglobin	Aspartate aminotransferase
Leukocytes (WBC)	Blood urea nitrogen
Lymphocytes	Calcium and ionized calcium
Monocytes	Chloride
Neutrophils (segmented and bands)	Cholinesterase
Platelets	Creatinine
Reticulocytes	Gamma-glutamyl transpeptidase
	Glucose, random
Coagulation: [a]	LDH
aPTT	Magnesium
PT/INR	Potassium
	Sodium
Urinalysis[a]	Total bilirubin; if total bilirubin is increased a direct bilirubin should be obtained.
Blood	Total protein
Glucose	Uric acid
Ketones	
pH	Tumor markers (if applicable)
Protein	
Specific gravity	**Serum or Urine Pregnancy Test** (females only)[a]
Urine leukocyte esterase	

Abbreviations: aPTT = activated partial thromboplastin time; INR = International Normalised Ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

[a] Local or investigator-designated laboratory

Attachment 3. Protocol JNBA Pharmacokinetic and Pharmacodynamic Sampling Schedule

Pharmacokinetic and Pharmacodynamic Sampling for Schedule 1

Cycle	Day	Collection Time	PK Sampling Time	MET ECD and EGFR ECD[a]	MET and EGFR Ligands[a]	Proteomic Blood Sample[a]
1 and 2	1	Predose	X	X	X	X
	1	Mid-infusion	X			
	1	End of infusion	X	X	X	X
	1	2 hours post end of infusion	X			
	1	4 hours post end of infusion	X			
	1	6 hours post end of infusion (Cycle 1 only)	X			
	2	24 ±4 hours post-end of infusion (Cycle 1 only)	X	X	X	X
	3	Anytime during day (Cycle 1 only)	X			
	8±1	Anytime during day	X			
	15	Predose	X	X	X	X
	15	End of infusion	X	X	X	X
	15	2 hours post end of infusion (Cycle 1 only)	X			
	15	4 hours post end of infusion (Cycle 1 only)	X			
	15	6 hours post end of infusion (Cycle 1 only)	X			
	22±2	Anytime during day (Cycle 1 only)	X			
3-6	1	Predose	X	X	X	X
	1	End of infusion	X			
Follow-ups		Occurs on the day the follow-ups occur.	X	X	X	

Abbreviations: ECD = extracellular domain; EGFR = epidermal growth factor receptor; MET = mesenchymal-epithelial transition factor; PK = pharmacokinetic; V = volume of distribution.

[a] Samples are requested to be taken immediately before the dose and immediately after the end of the LY3164530 infusion. Aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of LY3164530 dose and samples are recorded accurately on the appropriate forms.

Pharmacokinetic and Pharmacodynamic Sampling for Schedule 2Cycle	Day	Collection Time	PK Sampling Time	MET ECD and EGFR ECD[a]	MET and EGFR Ligands[a]	Proteomic Blood Sample[a]
1 and 2	1	Predose	X	X	X	X
	1	Mid-infusion	X			
	1	End of infusion	X	X	X	X
	1	2 hours post end of infusion	X			
	1	4 hours post end of infusion	X			
	1	6 hours post end of infusion	X			
	2	24 ±4 hours post-end of infusion	X	X	X	X
	3	Anytime during day	X			
	8	Predose	X			
	8	End of infusion	X			
	22	Predose	X	X	X	X
	22	End of infusion	X	X	X	X
	22	2 hours post end of infusion (Cycle 1 only)	X			
	22	4 hours post end of infusion (Cycle 1 only)	X			
	22	6 hours post end of infusion (Cycle 1 only)	X			
	23	24 ±4 hours post-end of infusion (Cycle 1 only)	X			
	24	Anytime during day (Cycle 1 only)	X			
3-6	1	Predose	X	X	X	X
	1	End of infusion	X			
Follow-up		Occurs on the day the follow-ups occur.	X	X	X	

Abbreviations: ECD = extracellular domain; EGFR = epidermal growth factor receptor; MET = mesenchymal-epithelial transition factor; PK = pharmacokinetic; V = volume of distribution.

[a] Samples are requested to be taken immediately before the dose and immediately after the end of the LY3164530 infusion. Aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of LY3164530 dose and samples are recorded accurately on the appropriate forms.

Attachment 4. Protocol JNBA ECG, Chemistry, and Hematology Collection Schedule

Schedule 1

Cycle	Day	Collection Time	Central Triplicate ECG	Central Single ECG	Local Hematology	Local Chemistry
Screening			X		X	X
1	1	Predose	X		X	X
	1	EOI (+ 10 min)	X		X[a]	X[a]
	1	2 ±0.25 hours EOI	X			
	1	6 ±0.25 hours EOI	X			
	2	24 ±4 hours EOI	X		X[a]	X[a]
	3	48 ±4 hours EOI	X		X[a]	X[a]
	8		X		X	X
	15	Predose	X		X	X
	15	EOI (+ 10 min)	X			
	15	2 ±0.25 hours EOI	X			
	15	6 ±0.25 hours EOI	X			
	22		X		X	X
2	1	Predose		X	X	X
	8			X	X	X
	15	Predose		X	X	X
	22			X	X	X
3-X	1	Predose		X	X	X
	15	Predose		X	X	X
Follow up	28			X	X	X

Abbreviations: ECG = electrocardiogram; EOI = end of infusion; min = minute.

[a] If an abnormality in hematology or chemistry is consistently observed in the 48 hours following the end of the first infusion, additional post-infusion laboratory samples (EOI, and 24 hours and 48 hours after EOI) must be repeated for subsequent infusions until they are normal or return to baseline levels.

Schedule 2

Cycle	Day	Collection Time	Central Triplicate ECG	Central Single ECG	Local Hematology	Local Chemistry
Screening			X		X	X
1	1	Predose	X		X	X
	1	EOI (+ 10 min)	X		X[a]	X[a]
	1	2 ±0.25 hours EOI	X			
	1	6 ±0.25 hours EOI	X			
	2	24 ±4 hours EOI	X		X[a]	X[a]
	3	48 ±4 hours EOI	X		X[a]	X[a]
	8	Predose	X		X	X
	8	EOI (+ 10 min)	X			
	8	2 ±0.25 hours EOI	X			
	8	6 ±0.25 hours EOI	X			
	15	Predose		X	X	X
	22	Predose		X	X	X
2-X	1	Predose		X	X	X
	8	Predose		X	X[b]	X[b]
	15	Predose		X	X	X
	22	Predose		X	X[b]	X[b]
Follow up	28			X	X	X

Abbreviations: ECG = electrocardiogram; EOI = end of infusion; min = minute.

[a] If an abnormality in hematology or chemistry is consistently observed in the 48 hours following the end of the first infusion, additional post-infusion laboratory samples (EOI, and 24 hours and 48 hours after EOI) must be repeated for subsequent infusions until they are normal or return to baseline levels.

[b] In Cycle 2-X, if clinically significant changes are observed, hematology and/or chemistry should be obtained at least weekly until no longer clinically significant. Otherwise these samples are not required.

Attachment 5. Protocol JNBA Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**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 Normalised Ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

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

Attachment 6. Protocol JNBA Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When contacting Lilly to report a serious adverse event (SAE), please have the following information available:

Patient Demographics

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

Study Identification

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

Study Drug

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

Adverse Event

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

Relationship to Study Drug & Protocol Procedures

Concomitant Drug Therapy

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

In Case of Death

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

Attachment 7. Protocol JNBA mTPI and Simulation

The modified toxicity probability interval (mTPI) method employs a simple beta-binomial hierarchical model. Decision rules are based on calculating the unit probability mass (UPM) of 3 intervals corresponding to underdosing, proper dosing, and overdosing in terms of toxicity. Specifically, the underdosing interval is defined as $(0, p_T-\varepsilon_1)$, the overdosing interval as $(p_T+\varepsilon_2, 1)$, and the proper dosing interval as $(p_T-\varepsilon_1, p_T+\varepsilon_2)$, where ε_1 and ε_2 are small fractions, such as 0.05, to account for the uncertainty around the true target toxicity. A sensitivity analysis reported by Ji et al. (2010) showed that the mTPI design is robust to the specification of ε values.

In addition, ε_1 and ε_2 could take different values to reflect physician preference and the nature of the disease. For advanced diseases with few treatment options, higher toxicity rates might be considered acceptable, implying a specification of $\varepsilon_2>\varepsilon_1$. For less advanced diseases, the 2 ε values could be identical or ε_1 could be $>\varepsilon_2$. The 3 dosing intervals are associated with 3 different dose-escalation decisions. The under-dosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose deescalation (D), and proper dosing corresponds to staying at the current dose (S).

Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, decision E, to escalate, will be executed, and the next cohort of patients will be treated at the next-higher dose level. Ji et al. (2010) show that the decision based on the UPM is optimal in that it minimizes a subsequent expected loss. Under the mTPI design, a trial is terminated when either the lowest dose is above the maximum tolerated dose (MTD) or a pre-specified maximum sample size is reached.

Simulation

A small simulation study was conducted to compare the mTPI with 3+3 in identifying the right MTD. Six scenarios were run, each with 1000 simulated trials. As in Study JNBA, the MTD has a target toxicity probability of $P_T=0.3$ and ε_1 and ε_2 are set at 0.013 and 0.001 respectively. The scenarios assumed the true probabilities of six doses as follows: scenario 1= (0.1, 0.2, 0.3, 0.4, 0.5, 0.6); scenario 2= (0.08, 0.16, 0.24, 0.3, 0.38, 0.46); scenario 3= (0.04, 0.08, 0.12, 0.16, 0.2, 0.24); scenario 4= (0.4, 0.5, 0.6, 0.7, 0.8, 0.9); scenario 5= (0.04, 0.08, 0.12, 0.16, 0.2, 0.58); and scenario 6= (0.06, 0.46, 0.53, 0.6, 0.67, 0.74). For all scenarios, the probability of selecting each dose was summarized, the average number of patients treated at each dose and average number of patients experience DLT at each dose. The simulation demonstrates that, in general, mTPI method correctly identifies the MTD more than 3+3 and appears to be as safe as 3+3 method in that it puts a similar percentage of patients on toxic doses.

Scenario	Dose Level	True Prob (tox)	Selection Prob (%)		# of Subjects Treated		# of Toxicities	
			mTPI	3+3	mTPI	3+3	mTPI	3+3
1	1	0.1	5.8	24.4	3.53	4.42	0.38	0.44
	2	0.2	20.8	30.3	6.89	4.55	1.45	0.89
	3	0.3	35.1	19.4	8.21	3.43	2.39	1
	4	0.4	28.4	4.4	6.94	1.61	2.78	0.68
	5	0.5	7.2	0.5	2.99	0.43	1.54	0.22
	6	0.6	1.3	0	1.06	0.06	0.62	0.04
2	1	0.08	3.4	20.8	2.67	4.15	0.22	0.31
	2	0.16	13.2	26.4	5.17	4.49	0.83	0.75
	3	0.24	20.6	19.5	5.81	3.69	1.38	0.91
	4	0.3	29.2	10.8	7.29	2.32	2.22	0.67
	5	0.38	23.7	2.8	5.48	1.1	2.09	0.42
	6	0.46	9.5	1.6	3.48	0.36	1.63	0.17
3	1	0.04	0.8	7.3	1.6	3.52	0.07	0.14
	2	0.08	1.7	12.1	2.07	3.88	0.15	0.33
	3	0.12	3.6	18.3	2.73	3.91	0.34	0.48
	4	0.16	8.5	16.2	3.54	3.63	0.53	0.62
	5	0.2	14.5	11.4	4.65	2.77	0.94	0.58
	6	0.24	70.8	25.4	15.38	1.74	3.62	0.41
4	1	0.4	43.3	15.6	13.7	4.94	5.4	1.97
	2	0.5	10.5	1.5	5.25	1.34	2.63	0.69
	3	0.6	1.2	0	1.67	0.19	1	0.11
	4	0.7	0	0.1	0.44	0.01	0.3	0
	5	0.8	0	0	0.1	0.01	0.07	0.01
	6	0.9	0	0	0.02	0	0.02	0
5	1	0.04	0.8	5.9	1.48	3.49	0.05	0.14
	2	0.08	2.1	13.2	2.22	3.89	0.17	0.31
	3	0.12	4	16.8	2.85	3.95	0.35	0.51
	4	0.16	9.8	18.7	3.86	3.68	0.64	0.61
	5	0.2	75.7	24.6	14.12	3.37	2.86	0.67
	6	0.58	7.3	3.7	5.38	1.61	3.17	0.94
6	1	0.06	60.4	76.8	14.01	5.62	0.81	0.33
	2	0.46	31.2	8.5	10.5	4.43	4.83	2.07
	3	0.53	7.1	0.8	3.64	0.87	1.91	0.47
	4	0.6	0.8	0	1.21	0.09	0.73	0.05
	5	0.67	0	0.1	0.39	0.01	0.27	0
	6	0.74	0	0.1	0.11	0.01	0.08	0

Abbreviation: mTPI = modified toxicity probability interval.

Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. *Clin Trials*. 2010;7(6):653-663.

Attachment 8. Protocol JNBA Protocol I7-MC-JNBA(b) Amendment Summary A Phase 1 Study of LY3164530, a Bispecific Antibody Targeting MET and EGFR, in Patients with Advanced or Metastatic Cancer

Overview

Protocol I7-MC-JNBA, A Phase 1 Study of LY3164530, a Bispecific Antibody Targeting MET and EGFR, in Patients with Advanced or Metastatic Cancer has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

- Introduction of a new weekly schedule for dosing.
- Minor changes were made to increase the clarity and consistency of the document and to correct typographical errors.

Revised Protocol Sections

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

4.0 Abbreviations and Definitions

AUC	area under the serum ~~plasma~~ concentration-time curve
$AUC_{(0\text{-}tlast)}$	area under the serum ~~plasma~~ concentration-time curve from time zero to last measurable plasma concentration
$AUC_{(0\text{-}\infty)}$	area under the serum ~~plasma~~ concentration-time curve from time zero to infinity
$AUC_{0\text{-}\tau}$	area under the serum versus time concentration-time curve over the dosing interval
$C_{av,\tau}$	average serum concentration over the dosing interval
C_{max}	maximum serum ~~plasma~~ concentration
$C_{min,\tau}$	minimum serum concentration over the dosing interval
EC_{50}	the half maximal effective serum concentration
Q2W	once every 2 weeks

5.2.1 Primary Objective

The primary objective of this study is to determine an RP2D and schedule of LY3164530 that may be safely administered to patients with advanced or metastatic cancer.

5.3.1 Mechanism of Action and In Vitro/In Vivo Activity

LY3164530 has high affinity for both MET and EGFR and binds both receptors simultaneously in tumor cells. As described in the Investigator's Brochure (Section 5.2.2), binding of LY3164530 to MET and EGFR blocks activation of both receptors by their respective ligands. In addition to its ligand-blocking activity, LY3164530 also leads to internalization and degradation of both receptors in tumor cells. The ability of LY3164530 to internalize both receptors is superior to the combination of ~~the 2 component~~individual monoclonal antibodies. The internalization of both receptors is most commonly observed in cells expressing high levels of MET. In addition, LY3164530 also increases the avidity binding to MET in cells expressing both MET and EGFR, leading to better neutralization of HGF compared to the parental MET antibody alone or in combination with cetuximab. The ability of LY3164530 to block ligand-receptor interactions and efficiently internalize MET and EGFR, and its increased avidity for MET, is believed to be responsible for the in vitro antiproliferative activity observed against a panel of tumor cell lines. In vivo, administration of LY3164530 results in dose-dependent antitumor activity in cell line-derived non-small cell lung cancer, gastric cancer, and squamous

cell cancer of the head and neck (SCCHN) xenografts, as well as in colorectal cancer and SCCHN patient-derived xenografts.

5.5 Rational for Amendment (b)

As of 27 July 2015, 15 patients have been treated in Study JNBA at doses of 300, 600, 1000, and 1250 mg on Days 1 and 15 of a 28 day cycle. One DLT (Cycle 1) has been reported in a patient at the 1000 mg dose level who experienced intolerable, Grade 2 rash. Two of the 3 patients treated at the 1250 mg dose level experienced AEs in Cycle 2 that would have met the criteria for a DLT had they occurred in Cycle 1 (DLT-equivalent toxicity). These events included Grade 3 pustular rash in one patient and Grade 3 dermatitis acneiform and Grade 4 hypomagnesaemia in another patient. As a result, a dose of 1250 mg was deemed to exceed the maximum tolerated dose. As of 27 July 2015, 6 patients have been treated at the 1000 mg dose level and enrollment will continue until 10-20 patients have been treated at the recommended Phase 2 dose.

The drug-related, treatment emergent adverse events reported for LY3164530 are consistent with inhibition of EGFR and include skin reactions [maculo-papular rash, dermatitis acneiform, skin fissures, rash, skin exfoliation, and/or pustular rash] (n=14, 93.3%), hypomagnesaemia (n=7, 46.7%), and paronychia (n=4, 26.7%). The following drug-related events occurred in 2 patients each (13.3%): decreased appetite, dysgeuesia, fatigue, and hypokalaemia. One SAE (hypomagnesaemia) was considered to be related to LY3164530 by the investigator and the Sponsor. The event occurred in a metastatic cutaneous squamous cell carcinoma patient who had Grade 1 hypomagnesaemia at baseline that worsened and resulted in study drug discontinuation.

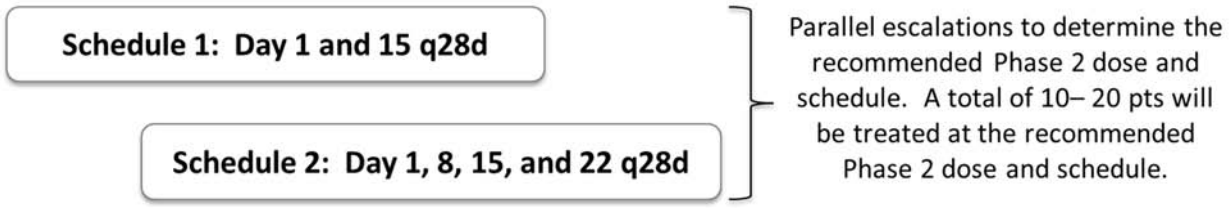
An interim analysis of the LY3164530 PK data was conducted from all of the 15 patients who received at least 1 dose of LY3164530 administered as a 1 or 2-hour infusion once every 2 weeks (Q2W) across the dose range of 300-1250 mg. Dose-dependent increases in the systemic exposure (AUC, C_{max}) of LY3164530 following single and multiple doses were observed. A minor amount of accumulation in serum was observed within Cycle 1 and between Cycles 1 and 2 of treatment after 1000 mg Q2W (mean accumulation ratio of 1.1 within and between cycles). The LY3164530 systemic clearance (CL) decreased by approximately 2-fold on average when the dose was escalated from 600 mg to 1000 mg, indicating the saturation of cell-surface receptors by LY3164530 and a slower non-receptor-mediated clearance predominating at doses >600 mg. While a more rapid receptor-mediated clearance (ie, target mediated drug disposition [TMDD]) predominates at low doses (ie, ≤600 mg). In addition, the LY3164530 exposure following 1000 mg Q2W appears to be in an exposure range expected to achieve biological effects based on the nonclinical MKN45 xenograft PK/PD model estimates for the MET and EGFR half maximal effective serum concentrations (EC_{50}) values. The LY3164530 maximum serum concentration (C_{max}) after 1000 mg in Cycles 1 and 2 is greater (mean C_{max} range: 295-394 µg/mL) than both the MET EC_{50} (79.5 µg/mL; 0.4 µM) and EGFR EC_{50} (7.95 µg/mL; 0.04 µM) concentrations. The average LY3164530 serum concentration over the dosing interval ($C_{av,\tau}$) during Cycles 1 and 2 is also greater (mean $C_{av,\tau}$ range: 102-132 µg/mL) than the MET EC_{50} and EGFR EC_{50}. However, the minimum serum concentration over the dosing interval ($C_{min,\tau}$) of LY3164530 following 1000 mg in Cycles 1 and 2 (mean $C_{min,\tau}$ range: 19-49 µg/mL) is lower

than the MET EC_{50} (79.5 ug/mL), which is the desired concentration to maintain throughout the dosing interval in order to maximize the biological activity of LY3164530.

At a dose of 1000 mg, the mean terminal elimination-life ($t_{1/2}$) is approximately 100 hours (approximately 4 days). As a result, the administration of LY3164530 every 2 weeks may not be the optimal schedule of administration in order to achieve a LY3164530 $C_{min,\tau}$ near the MET EC_{50}. Therefore, it is hypothesized that weekly dosing of LY3164530 (ie, Days 1, 8, 15, and 22 of a 28 day cycle) will minimize the fluctuation between the peak (C_{max}) and trough ($C_{min,\tau}$) serum concentrations of LY3164530 leading to a more consistent inhibition of both MET and EGFR over the dosing interval (with minimal impact on the accumulation of LY3164530) and potentially greater pharmacologic activity (PD response). The MTD of LY3164530 when administered on Days 1 and 15 of a 28 day cycle is 1000 mg. As a result, the starting dose for the weekly schedule will be 500 mg. The safety, toxicity, PK, and PD associated with a weekly schedule will be assessed.

6.2 Summary of Study Design

Study JNBA is a multicenter, nonrandomized, open label, dose escalation Phase 1 study of IV LY3164530 in patients with advanced and/or metastatic cancer. Eligible patients will receive LY3164530 as an infusion on Days 1 and 15 (Schedule 1) or on Days 1, 8, 15, and 22 (Schedule 2) of each cycle. A cycle will consist of 28 days and the schedules will enroll in parallel.



Dose escalation will be driven by a modified toxicity probability interval (mTPI) method. The RP2D and schedule will be determined once at least 10 patients, but no more than 20, are treated at a dose and schedule that is at or below the maximum tolerated dose (MTD). The actual sample size for Study JNBA is anticipated to be approximately 50 patients dependings on the incidence of DLTs ~~and is anticipated to be approximately 50 patients~~.

…

7.2.1 Dosing Schedule

For doses ~~less than~~ ≤1000 mg, LY3164530 will be administered intravenously over approximately 60 minutes. ~~on Days 1 and 15 of each 28-day cycle.~~ The Sponsor may instruct sites to extend the infusion time for up to 3 hours for doses ≥ ≥1000 mg.

LY3164530 will be administered on Days 1 and 15 every 28 days (Schedule 1) or on Days 1, 8, 15, and 22 every 28 days (Schedule 2). The assigned dose, schedule, and duration of infusion of

LY3164530 will be provided by the Sponsor on a patient registration form. A patient will be assigned to either Schedule 1 or Schedule 2 and will be maintained on that schedule for the duration of therapy. Subsequent doses and/or infusion times should be adjusted as described in Section 7.2.5.

7.2.2.3 Dose Escalation Method

…

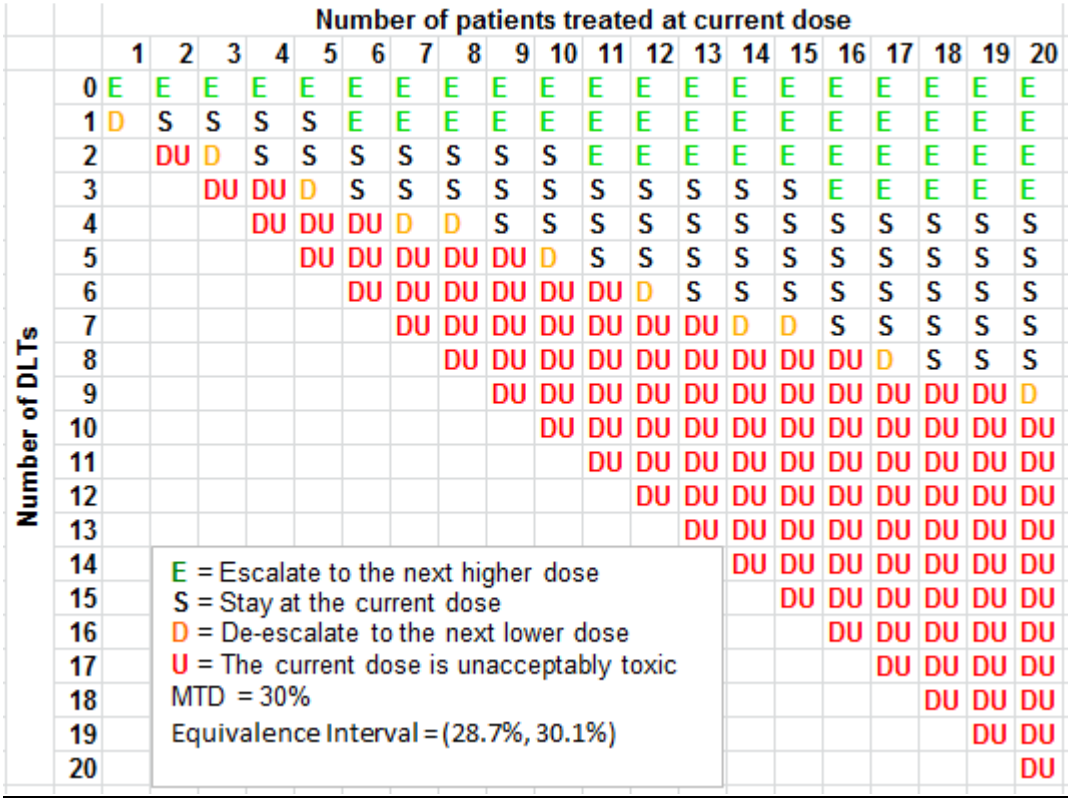


Figure JNBA.1. Dose-finding spreadsheet of the modified toxicity probability interval method showing number of patients treated at a given dose vs. number of DLTs observed at that dose .

The beginning dose level for Schedule 1 was ~~will be~~ 300 mg. The starting dose level for Schedule 2 will be 500 mg. The dose will be escalated by a maximum increment of 100%. If the beginning dose level is determined to be unacceptably toxic, a -1 dose level may be explored.

The exact increment will be determined by the investigators and Lilly CRP/CRS, and may be less than the maximum increment allowed in the protocol. Safety data will be the primary criteria for both the decision to dose-escalate and for selecting the dose to be administered in the next cohort. In addition, if available at the time of the dose escalation decision, PK (maximum ~~plasma~~ serum concentration [C_{max}], area under the ~~plasma~~ serum concentration-time curve [AUC], and CL) and/or PD results will be used as secondary/supporting data for dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator

and the Lilly CRP or CRS; the decision will be documented in writing. Intrapatient dose escalations are not permitted.

Although an example escalation table is shown in Table JNBA.3, alternate doses may be selected.

Table JNBA.3. Sample Dose Escalation Schema

Dose Level (Cohort)	**Schedule 1 Dose**	**Schedule 2 Dose**
-1	100 mg	400 mg
1	300 mg	500 mg
2	600 mg	600 mg
3	1000 mg	700 mg
4	~~1400~~ 1250 mg	
~~5~~	~~1700 mg~~	
~~6~~	~~2000 mg~~	

In Cohort 1 for Schedule 1 only, the first patient is required to complete a full cycle (28 days) before subsequent patients can be dosed. Subsequent patients in Cohort 1 can be dosed concurrently. Beginning with Cohort 2 for Schedule 1~~,~~ and for all cohorts with Schedule 2, patients within a cohort can be dosed concurrently.

…

7.2.4.1 Infusion-Related Reactions

Due to the risk of hypersensitivity reactions with any biological agents, all patients should continue to be closely monitored for signs and symptoms indicative of an infusion-related reaction both in the acute period (immediately or within 24 hours after dosing) and up to several days to a few weeks after dosing for delayed reactions. In Cycles 1 and 2, ~~A~~acute assessments should include an assessment of vital signs starting at the time of initiation of the infusion and continuing until at least 60 minutes after the end of the infusion. At a minimum, vital signs should be obtained prior to infusion, during infusion, and at 1 hour post-infusion. The exact frequency of the monitoring is left to the discretion of the investigator. Monitoring should be performed in an area where resuscitation equipment and other agents (eg, epinephrine, corticosteroids) are readily available.

…

7.2.4.2 Skin ~~Rash~~ Reactions

Skin rash is a known toxicity of EGFR inhibitors, and skin effects were observed with LY3164530 in a 5-week repeat-dose toxicity study in monkeys. In Study JNBA, skin reactions were observed at all dose levels with Schedule 1 and were dose limiting at 1250 mg. As a result, ~~P~~prophylaxis is ~~not~~ permitted for the initial dose of LY3164530. ~~so that the toxicities of LY3164530 may be appropriately characterized. However, i~~Institutional-approved standard of

care premedication for EGFR inhibitors, such as dexamethasone and/or topical and/or oral antibiotics, may be administered for the initial and subsequent doses.

~~If skin rash is identified as a DLT, prophylaxis may be permitted for the Cycle 1 Day 1 dose. Since LY3164530 is a bispecific antibody with a fixed stoichiometry for EGFR/MET, in the case of skin rash-only DLT, prophylaxis may be explored to maximize the chances of effective combined MET/EGFR. This decision will be made following discussions with the investigators and the Lilly CRP/CRS and will be documented in writing. The dose escalation rules in Figure JNBA.1 would be followed if this change is implemented.~~

…

7.2.5.1 Dose Delays and Omissions

The following rules should guide dosing:

- Before each ~~dose~~ cycle of LY3164530 the following parameters are required:
  - Hematologic: ANC ≥1.5 x 10^9/L, platelets ≥75 x 10^9/L, and hemoglobin ≥8 g/dL.
  - Non-hematologic: AEs must resolve to CTCAE v 4.03 Grade ≤1, or baseline. Exceptions will be made for: alopecia, fatigue, skin reactions, or other toxicities that can be controlled with standard treatment; these toxicities must resolve to ≤Grade 2.
- The start of a cycle is the date of the Day 1 dose.

  For Schedule 1: If the Day 15 dose cannot be administered within 21 days of the prior dose (by Day 22), it should be omitted. The interval between LY3164530 doses must not be less than 14 days. If a dose is delayed (for toxicity or other circumstances), the next dose should be adjusted so that there is at least a 14-day interval.

  For Schedule 2: If a dose cannot be administered within 10 days of the prior dose, it should be omitted. The interval between LY3164530 doses must not be less than 7 days. If a dose is delayed (for toxicity or other circumstances), the next dose should be adjusted so that there is at least a 7-day interval.

  ~~The interval between LY3164530 doses must not be less than 14 days. If a dose is delayed (for toxicity or other circumstances), the next dose should be adjusted so that there is at least a 14-day interval.~~

If a dose cannot be administered within 28 days of the prior dose due to an AE, the patient should be removed from study drug treatment and should complete subsequent follow-up (Table JNBA.4).

- If the patient has completed the initial on-study radiographic assessment (eg, at the end of Cycle 2) ~~is in Cycle 3 or beyond~~ and is continuing to receive benefit from therapy, delays of greater than 28 days may be acceptable if agreed upon by both the investigator and Sponsor. For instance, if a patient has a non–drug-related AE such as prolonged flu, the patient may

continue on therapy if, in the opinion of the investigator, he/she is showing benefit from therapy and has recovered sufficiently from the AE.

- A delay of no more than 7 days because of holidays, weekends, inclement weather, or other justifiable events will be permitted and will not be counted as a protocol deviation.

7.2.5.2 Dose Adjustments

Dose adjustments should follow the guidance in Table JNBA.4.

For patients requiring dose reductions, reescalation to the original assigned LY3164530 dose is not allowed. The patient must be maintained at a reduced dose level for all remaining cycles.

Table JNBA.4. Dose Modifications and Treatment Alterations in Patients Treated with LY3164530

Toxicity	CTCAE Grade	Recommendations
Infusion-related r~~R~~eaction	Grade 1 First occurrence	Decrease the LY3164530 infusion rate by 50% and monitor closely for any worsening. For subsequent infusions, premedicate with diphenhydramine hydrochloride; additional premedication may be administered at the investigator's discretion.
	Grade 2 First occurrence	Stop LY3164530 infusion. Administer diphenhydramine hydrochloride and acetaminophen for fever and oxygen. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening. For subsequent infusions, premedicate with diphenhydramine hydrochloride; additional premedication may be administered at the investigator's discretion. The reduced rate should be used for all subsequent infusions.
	Grade 1 or 2 Second occurrence	Administer dexamethasone. For subsequent infusions, premedicate with diphenhydramine hydrochloride, acetaminophen, and dexamethasone. The reduced infusion rate should be used for all subsequent infusions.
	≥Grade 3	Stop LY3164530 infusion immediately and disconnect infusion tubing from the patient. Administer diphenhydramine hydrochloride, dexamethasone, bronchodilators for bronchospasm, and other medications/treatment as medically indicated. Patients must not receive any further LY3164530 treatment.
Skin reactions (eg, acne-like rash)	Grade 3 First occurrence	Delay or omit LY3164530 treatment until ≤Grade 1 following the rules in Section 7.2.5.1. Treatment with topical and/or oral antibiotics ~~may~~ should be considered.
	Grade 3 Second occurrence	Delay or omit LY3164530 treatment until ≤Grade 1 following the rules in Section 7.2.5.1. Dose reduce ~~by 20% from assigned dose~~ to the dose level used for the previous cohort for second occurrence. Treatment with topical and/or oral antibiotics ~~may~~ should be considered.
	Grade 3 Third occurrence Or Grade 4	Patients must not receive any further LY3164530 treatment.
Other toxicities	≥Grade 3 First occurrence	Delay or omit LY3164530 treatment until ≤Grade 1 or baseline following the rules in Section 7.2.5.1. Based on the investigator's discretion, the full dose of LY3164530 may be administered or the dose may be reduced to the next lowest dose level. If event recurs at same grade, then dose reduce LY3164530 to the next lowest dose.
	≥Grade 3 Second occurrence	Delay or omit LY3164530 treatment until ≤Grade 1 or baseline following the rules in Section 7.2.5.1. If event recurs at same grade, then dose reduce LY3164530 to the next lowest dose. Exceptions may be made for transient changes in electrolytes that respond to treatment.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

Note: In addition, the dose may be reduced to the next lowest level for any toxicity at the discretion of the investigator.

7.3 Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3164530 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, schedule, infusion duration, and identification number assignment for each patient.

7.5 Concomitant Therapy

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Patients should receive full supportive care during the trial. Routine prophylactic use of granulocyte colony-stimulating factors (G-CSF) is not permitted during this study. Should the use of hematopoietic colony-stimulating factors (CSFs) be necessary, follow the American Society of Clinical Oncology (ASCO) recommendations for the use of CSFs (Smith et al. ~~2006~~ 2015).

…

8.1 Safety Evaluations

The safety and tolerability of LY3164530 have been assessed in nonclinical toxicology studies and this ongoing Phase 1 study. ~~and t~~The results from these studies are detailed in the Investigator's Brochure. This Phase 1 study contains safety monitoring that will permit initial characterization of the safety profile of LY3164530 in patients with advanced or metastatic cancer. Study procedures and their timing, including collection of patient samples, are described in the Study Schedule (Attachment 1).

…

8.2.2.2. Pharmacodynamic Samples

At the visits and times specified in Attachment 3, serum and plasma samples will be collected. The effect of LY3164530 on MET and EGFR pathway-specific targets may be explored to determine changes in potential biomarkers such as circulating levels of the MET ligand HGF, EGFR ligands (eg, EGF, TGFalpha), MET/ECD, and EGFR/ECD. These samples may be used for exploratory research on new biomarkers related to the MET/HGF and EGFR pathway. In addition, exploratory samples to assess proteomic panel may be collected. A maximum of 3 timepoints may be removed per dosing schedule during the study if warranted and agreed upon between both the investigator and Lilly.

…

8.2.3.3 Exploratory Biomarker Blood Samples

…

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 one or more of the following radiologic tests for tumor measurement:

- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)
- ~~Chest x-ray.~~

…

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 mTPI method and determined by the occurrences of DLTs (up to 20 patients per cohort before establishing the RP2D and schedule). The total sample size is anticipated to be approximately 50 patients.

10.5 Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have been exposed to study drug and have had samples collected.

Pharmacokinetic parameter estimates for LY3164530 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max}, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\tau}$, and $AUC_{0\text{-}\infty}$ of LY3164530. Other noncompartmental parameters, such as $t_{1/2}$, CL, volume of distribution (V), and accumulation ratios may be reported. Additional exploratory analyses will be performed if warranted by the data, and other validated PK software programs may be used if appropriate and approved by Lilly Global PK/PD management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Pharmacokinetic parameter estimates 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% confidence intervals (CIs).

10.6 Pharmacodynamic Analyses

Provided that the data allows, PD and immunogenicity data from all patients may be analyzed using linear and/or nonlinear fixed and mixed effects models as appropriate. Pharmacodynamic and immunogenicity data will be summarized by dose, drug concentrations, and time from dose

for each schedule of administration. Potential PD markers and immunogenicity versus time data will be presented graphically for each patient and summarized by dose and schedule of administration. Absolute and/or percent change from baseline for the PD markers may also be evaluated. Data may be log-transformed prior to summarizing if necessary. The interpatient and intrapatient variability of the PD markers and immunogenicity responses may also be assessed where appropriate. Baseline measurements may be evaluated as potential covariates to assess their relationship to relevant PD responses.

10.7. Pharmacokinetic/Pharmacodynamic Analyses

In addition to a standard noncompartmental assessment, and provided that the data allows, the LY3164530 serum concentration-time data may be evaluated by model-based approaches as warranted. Additional analyses, such as exposure-response modeling using the efficacy endpoints, may also be explored.

Additional exploratory analyses may be performed if warranted by the data.

10.10 Interim Analyses

Since this is a dose-escalation study, data will be reviewed on an ongoing basis during the study until the RP2D is determined. The purpose of these ongoing reviews is to evaluate the safety data at each dose level. A review of the data will be completed approximately after ~~5~~ 6 patients have been treated for at least 1 cycle at a dose level without a cohort analysis.

An interim analysis will be triggered when at least ~~10~~ 15 patients have been dosed at a given dose level for 1 cycle of treatment to evaluate the safety and tolerability of LY3164530. The interim analysis may include, but are not limited to, an assessment of available safety, PK, and PD data.

Enrollment may continue during the interim analysis and the dose escalation rules as outlined in Figure JNBA.1 will continue to be followed.

Additional interim analyses may be triggered and may include, but are not limited to, assessment of available safety, PK, and PD data.

12 References

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Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. 2015 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol*. 2015. doi: 10.1200/JCO.2015.62.3488.

~~Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24(19):3187-3205.~~

Attachment 1 Protocol JNBA Study Schedule

Baseline Schedule

	Study Period	Baseline			
	Cycle	BL			
	Visit	0			
	Duration	Up to 28 days			
	Relative Day to C1D1	≤28	≤14	**≤7**	
Procedure Category	**Procedure**				**Comments**
Lab/ Diagnostic Tests	Local hematology		X		
	Local chemistry		X		
	Local coagulation		X		
	Local urinalysis		X		
	Local pregnancy test		~~X~~	X	Must be done ≤~~14~~7 days prior to the first dose of study drug if patient is a woman of child-bearing potential. May be urine or serum specimen.
	Central ECG		X		Triplicate ECG.
	Biopsy of pretreatment tumor tissue		X		Unless the Sponsor and investigator document that the biopsy may be omitted; sample should be taken only after study eligibility is confirmed
	Archived tumor tissue (only if available)		X		Only for those patients that meet inclusion/exclusion criteria
	Tumor markers		X		Only if appropriate for the tumor type of the patient.
	Exploratory biomarker blood sample ~~for pharmacogenomics~~		X		If possible, this sample should be collected ~~at the time~~on the same day as ~~of~~the biopsy.
	Immunogenicity sample	X			

During Treatment Study Schedule

	Study Period		Study Treatment Period													
	Cycle/Visit	1						2				3-Xa				
	Duration	28 days						28 days				28 days				
	Relative Day within Dosing Cycle	1	2	3	8	15	22	1	8	15	22	1	8	15	22	
Procedure Category	**Procedure**															**Comments**
Physical Examination	Physical exam (including weight and skin inspections)	X						X				X				May be completed up to 7 days prior to the treatment infusion.
	Vital signs	X			X	X	X	X	X	X	X	X	X*	X	X*	Includes blood pressure, pulse, and temperature. For Cycles 1-2, ~~A~~at a minimum, vital signs should be obtained prior to infusion, during infusion, and at 1 hour EOI (Section 7.2.4.1). In Cycle 3-X, vital signs should be taken predose and when clinically indicated. * Only need to be collected for patients on Schedule 2
	ECOG performance status	X						X				X				May be completed up to 7 days prior to the treatment infusion
Lab/ Diagnostic Tests	Local hematology	X	X	X	X	X	X	X	X	X	X	X		X		~~On C1D1, both pre-dose and post-dose samples should be drawn. See Attachment 4. In Cycles 3-X M~~May be drawn up to 1 day prior to the planned assessment. On C1D1, post-dose samples should be drawn. See Attachment 4 **Schedule 2:** In Cycle 3-X, if clinically significant changes are observed, hematology should be obtained at least weekly until no longer clinically significant.
	Local chemistry	X	X	X	X	X	X	X	X	X	X	X		X		~~On C1D1, both pre-dose and post-dose samples should be drawn. See Attachment 4. Beginning with Cycles 3-X, lab m~~May be drawn up to 1 day prior to the planned assessment. On C1D1, post-dose samples should be drawn. See Attachment 4 **Schedule 2:** In Cycle 3-X, if clinically significant changes are observed, chemistry should be obtained at least weekly until no longer clinically significant.
	Local Urinalysis	X						X				X				May be assessed up to 3 days prior to the planned assessment.
	PK sampling	X						X				X				See Attachment 3.
	Immunogenicity Sample	X						X				X				In addition to the scheduled samples, if a patient should have an infusion-related reaction to LY3164530, all attempts should be made to obtain

																immunogenicity sample as close to the onset of the event as possible, at the resolution of the event and 28 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
	MET and EGFR ECD pharmacodynamic samples	X	X			X		X		X		X				See Attachment 3.
	MET and EGFR ligands pharmacodynamic samples~~,~~	X	X			X		X		X		X				See Attachment 3.

During Treatment Study Schedule

		Study Period		Study Treatment Period													
		Cycle/Visit	1						2				3-X				
		Duration	28 days						28 days				28 days				
		Relative Day within Dosing Cycle	1	2	3	8	15	22	1	8	15	22	1	8	15	22	
Procedure Category	**Procedure**																**Comments**
Lab/ Diagnostic Tests (cnt'd)	Proteomic blood sample		X	X			X		X		X		X				See Attachment 3. Sample is only collected through Cycle 6.
	Stored sample for pharmacogenomics		X														Collect once. Sample can be collected at any time if not collected on C1D1.
	Exploratory biomarker blood sample ~~for pharmacogenomics~~		X										X				Sample to be collected C7D1.
	Central ECG		X	X	X	X	X	X	X	X	X	X	X	X*	X	X*	In Cycle 1, triplicate ECGs collected predose, at EOI, 2 hours EOI, and 6 hours EOI on the day of dosing . If possible, obtain prior to any associated blood draws. In Cycles 2-X, single ECGs should be obtained predose on the day of dosing. On non-dosing days,the ECG may be obtained at anytime, but if possible they should be obtained near to the same time of day as the C1D1 ECG. See Attachment 4. *Schedule 2 only.
	Tumor markers								X				X				If applicable to tumor type of the patient; may be drawn up to 3 days prior to the planned assessment.
	Optional tumor biopsy		X														
Tumor Assessment	Tumor measurement (palpable or visible)											X			X		Perform at least every 8 weeks at the end of every even cycle.
	Radiologic imaging according to RECIST											X			~~X~~	X	The same method of imaging used at baseline should be used for each subsequent assessment. Perform at least every ~~8 weeks~~ other cycle (approximately every 8 weeks) ~~between D22-28~~. May be omitted if patient has clear signs of progressive disease.
Adverse Events Collection/CTCAE Grading			X						X				X				
Concomitant Medication Notation			X						X				X				
	LY3164530 – Schedule 1		X				X		X		X		X		X		

	LY3164530 – Schedule 2	X			X	X	X	X	X	X	X	X	X	X	X	

[a] Following discussion and agreement from the Sponsor, the frequency of some assessments may be reduced for patients that have been on treatment for more than 1 year and are continuing to derive benefit from treatment. This decision will be documented in writing.

Post-Treatment Discontinuation Schedule

	Study Period	Post-discontinuation Follow-Up	
	Visit 801		Post-treatment discontinuation follow-up should begin after the last dose of study therapy or, if study therapy has been omitted for an extended period, the date it is decided that the patient will not restart study therapy.
	Duration	28 ±5 days	
	Relative Day	**28**	

Procedure Category	Procedure		Comments
Physical Examination	Weight	X	
	Vital signs	X	Includes blood pressure, pulse, and temperature.
	ECOG performance status	X	
Tumor Assessment	Tumor measurement (palpable or visible)	X	Performed if lesion is assessed as target or non-target. Not required if progressive disease is documented while on treatment.
	Radiologic imaging according to RECIST	X	The same method of imaging used at baseline should be used for each subsequent assessment. Not required if progressive disease is documented while on treatment or if there are clear signs of clinical progression.
Adverse Events Collection/CTCAE Grading		X	After Visit 801, only study protocol- or drug-related events are reported. If a patient has an ongoing AE or SAE possibly related to LY3164530 (eg, abnormal electrolytes), 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. Any subsequent follow-up(s) for AEs will be no more than 28 days ±5 days in duration.
Concomitant Medication Notation		X	
	Local hematology	X	
	Local chemistry	X	Particular focus should be placed on patients that have abnormal electrolytes, as electrolyte depletion is known to occur for >6 weeks after EGFR monoclonal antibody therapy.
	Central ECG	X	Single ECG.
	Tumor markers	X	If applicable to tumor type of the patient.
	Optional tumor biopsy	X	From patients willing to consent.

Lab/ Diagnostic Tests	Exploratory biomarker blood sample	X	
	PK sample	X	
	Immunogenicity sample	X	In addition to the scheduled sample, if a patient should have an infusion reaction to LY3164530, all attempts should be made to obtain immunogenicity sample as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. If a patient requires subsequent follow-ups (eg, for an ongoing AE), an immunogenicity sample should be obtained, if possible. A portion of the sample taken for immunogenicity testing may be used for PK analysis.
	MET and EGFR ECD pharmacodynamic samples	X	
	MET and EGFR ligand pharmacodynamic samples	X	
	Proteomic blood sample	X	Only if patient discontinues prior to Cycle 6.

Abbreviations: AE = adverse event; BL = baseline; C = cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECD = extracellular domain; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EGFR = epidermal growth factor receptor; EOI = end of infusion; HPV = human papillomavirus; MET = mesenchymal-epithelial transition factor; MRI = magnetic resonance imaging; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Attachment 3 Protocol JNBA Pharmacokinetic and Pharmacodynamic Sampling Schedule

Pharmacokinetic and Pharmacodynamic Sampling for Schedule 1

Cycle	Day	Collection Time	PK Sampling Time	MET ECD and EGFR ECD[a]	MET and EGFR Ligands[a]	Proteomic Blood Sample-[a]
1 and 2	1	Predose	X	X	X	X
	1	Mid-infusion	X			
	1	End of infusion	X	X	X	X
	1	2 hours post end of infusion	X			
	1	4 hours post end of infusion	X			
	1	6 hours post end of infusion (Cycle 1 ~~O~~only)	X			
	2	24 ±4 hours post-end of infusion (Cycle 1 only)	X	X	X	X
	3	Anytime during day (Cycle 1 only)	X			
	8±1	Anytime during day	X			
	15	Predose	X	X	X	X
	15	End of infusion	X	X	X	X
	15	2 hours post end of infusion (Cycle 1 only)	X			
	15	4 hours post end of infusion (Cycle 1 only)	X			
	15	6 hours post end of infusion (Cycle 1 ~~O~~only)	X			
	22±2	Anytime during day (Cycle 1 only)	X			
3-6	1	Predose	X	X	X	X
	1	End of infusion	X			
Follow-ups		Occurs on the day the follow-ups occur.	X	X	X	

Abbreviations: ECD = extracellular domain; EGFR = epidermal growth factor receptor; MET = mesenchymal-epithelial transition factor; PK = pharmacokinetic; V = volume of distribution.

a Samples are requested to be taken immediately before the dose and immediately after the end of the LY3164530 infusion. Aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of LY3164530 dose and samples are recorded accurately on the appropriate forms.

Pharmacokinetic and Pharmacodynamic Sampling for Schedule 2

Cycle	Day	Collection Time	PK Sampling Time	MET ECD and EGFR ECD[a]	MET and EGFR Ligands[a]	Proteomic Blood Sample[a]
1 and 2	1	Predose	X	X	X	X
	1	Mid-infusion	X			
	1	End of infusion	X	X	X	X
	1	2 hours post end of infusion	X			
	1	4 hours post end of infusion	X			
	1	6 hours post end of infusion	X			
	2	24 ±4 hours post-end of infusion	X	X	X	X
	3	Anytime during day	X			
	8	Predose	X			X
	8	End of infusion (Cycle 1 only)	X			X
	15	Predose (Cycle 1 only)	X	X		X
	15	End of infusion (Cycle 1 only)	X			X
	22	Predose(Cycle 1 only)	X	X	X	X
	22	End of infusion (Cycle 1 only)	X	X	X	X
	22	2 hours post end of infusion (Cycle 1 only)	X			
	22	4 hours post end of infusion (Cycle 1 only)	X			
	22	6 hours post end of infusion (Cycle 1 only)	X			
	23	24 ±4 hours post-end of infusion (Cycle 1 only)	X			
	24	Anytime during day (Cycle 1 only)	X			
3-6	1	Predose	X	X	X	X
	1	End of infusion	X			
Follow-ups		Occurs on the day the follow-ups occur.	X	X	X	

Abbreviations: ECD = extracellular domain; EGFR = epidermal growth factor receptor; MET = mesenchymal-epithelial transition factor; PK = pharmacokinetic; V = volume of distribution.

[a] Samples are requested to be taken immediately before the dose and immediately after the end of the LY3164530 infusion. Aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of LY3164530 dose and samples are recorded accurately on the appropriate forms.

Attachment 4 Protocol JNBA ECG, Chemistry, and Hematology Collection Schedule

Schedule 1

Cycle	Day	Collection Time	Central Triplicate ECG	Central Single ECG	Local Hematology	Local Chemistry
Screening			X		X	X
1	1	Predose	X		X	X
	1	EOI (+ 10 min)	X		X[a]	X[a]
	1	2 ±0.25 hours EOI	X			
	1	6 ±0.25 hours EOI	X			
	2	24 ±4 hours EOI	X		X[a]	X[a]
	3	48 ±4 hours EOI	X		X[a]	X[a]
	8		X		X	X
	15	Predose	X		X	X
	15	EOI (+ 10 min)	X			
	15	2 ±0.25 hours EOI	X			
	15	6 ±0.25 hours EOI	X			
	22		X		X	X
2	1	Predose		X	X	X
	8			X	X	X
	15	Predose		X	X	X
	22			X	X	X
3-X	1	Predose		X	X	X
	15	Predose		X	X	X
Follow up	28			X	X	X

Abbreviations: ECG = electrocardiogram; EOI = end of infusion; min = minute.

[a] If an abnormality in hematology or chemistry is consistently observed in the 48 hours following the end of the first infusion, additional post-infusion laboratory samples (EOI, and 24 hours and 48 hours after EOI) must be repeated for subsequent infusions until they are normal or return to baseline levels.

Schedule 2

Cycle	Day	Collection Time	Central Triplicate ECG	Central Single ECG	Local Hematology	Local Chemistry
Screening			X		X	X
1	1	Predose	X		X	X
	1	EOI (+ 10 min)	X		X[a]	X[a]
	1	2 ±0.25 hours EOI	X			
	1	6 ±0.25 hours EOI	X			
	2	24 ±4 hours EOI	X		X[a]	X[a]
	3	48 ±4 hours EOI	X		X[a]	X[a]
	8	Predose	X		X	X
	8	EOI (+ 10 min)	X			
	8	2 ±0.25 hours EOI	X			
	8	6 ±0.25 hours EOI	X			
	15	Predose		X	X	X
	22	Predose		X	X	X
2-X	1	Predose		X	X	X
	8	Predose		X	X[b]	X[b]
	15	Predose		X	X	X
	22	Predose		X	X[b]	X[b]
Follow up	28			X	X	X

Abbreviations: ECG = electrocardiogram; EOI = end of infusion; min = minute.

[a] If an abnormality in hematology or chemistry is consistently observed in the 48 hours following the end of the first infusion, additional post-infusion laboratory samples (EOI, and 24 hours and 48 hours after EOI) must be repeated for subsequent infusions until they are normal or return to baseline levels.

[b] In Cycle 2-X, if clinically significant changes are observed, hematology and/or chemistry should be obtained at least weekly until no longer clinically significant. Otherwise these samples are not required.

Leo Document ID = 5b2565df-ce44-4304-ba4b-959e67a3df66

Approver:PPD
Approval Date & Time: 28-Sep-2015 17:31:23 GMT
Signature meaning: Approved

Approver:PPD
Approval Date & Time: 28-Sep-2015 21:59:40 GMT
Signature meaning: Approved