Protocol I7O-MC-JOBA(a)

A Phase 1 Study of LY3076226, a Fibroblast Growth Factor Receptor 3 (FGFR3) Antibody-Drug Conjugate, in Patients with Advanced or Metastatic Cancer

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1. Protocol I7O-MC-JOBA(a)

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LY3076226

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study of intravenous LY3076226 in patients with advanced or metastatic cancer.

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Protocol Electronically Signed and Approved by Lilly: 14 May 2015
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2. Synopsis

This Phase 1 study is a multicenter, outpatient, nonrandomized, open-label, dose-escalation study of intravenous (IV) LY3076226 in patients with advanced or metastatic cancer.

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4. Abbreviations and Definitions

Note: Terms used only once are not included in this table.

Term	Definition
ADA	anti-drug antibody(ies)
ADC	antibody-drug conjugate
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 plasma concentration-time curve
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).
C1D1	Cycle 1, Day 1
C_{max}	maximum (observed) plasma concentration
$C_{max,ss}$	maximum (observed) plasma concentration at steady state
CI	confidence interval
CL/F (or CL)	(apparent) systemic clearance
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation either will occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.
CR	complete response
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form, a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRM	continual reassessment method
CRP	clinical research physician
CRS	clinical research scientist
CSF	colony-stimulating factor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCSI	Development Core Safety Information
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DM4	A maytansine derivative that is the cytotoxic payload (drug) of LY3076226.
DM4-Me	S-methyl-DM4
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
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 (ICF) 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.
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FGFR3	fibroblast growth factor receptor 3
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GLS	(Lilly) generic laboratory system
HER2	human epidermal growth factor receptor 2
HNSTD	highest non-severely toxic dose
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)
Ig	immunoglobulin
IgG	immunoglobulin G
IgG1	immunoglobulin G, subclass 1
IHC	immunohistochemistry
IMC-D11	ImClone code name for an IgG1 monoclonal antibody against FGFR3 that is the antibody portion of LY3076226.
IMWG	International Myeloma Working Group
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 (ICF).
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for data lock.
investigational product (IP)	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.
IRR	infusion-related reaction
IV	intravenous(ly); also New York Heart Association classification
LC-MS	liquid chromatography-mass spectrometry
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LY3076226	fibroblast growth factor receptor 3 (FGFR3) antibody-drug conjugate (ADC)
MED	minimally efficacious dose
menopausal women	Women with: 1) spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators [SERMs], or chemotherapy) or 2) spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone (FSH) level greater than 40 mIU/mL. This language is relevant to the inclusion criteria.
MinTD	minimally toxic dose
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 guideline (ICH GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer

open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
ORR	overall response rate
patient	A subject with a defined disease.
PD	pharmacodynamic(s) (also progressive disease [in Attachments only])
PDX	patient-derived xenograft
PET	positron emission tomography
PK	pharmacokinetic(s)
PR	partial response; also an ECG interval (Note: "PR" is the abbreviation for pulse rate only in Attachment 1.)
prescreen	The act of determining if a patient meets the requirements for FGFR3 alteration status for Parts B and C in this study.
qd×1	single administration
q14d×2	2 administrations separated by a 14-day dosing interval
QT	an ECG interval
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	To screen a patient who was previously declared a screen failure for the same study
RP2D	recommended Phase 2 dose
RR	an ECG interval (Note: "RR" is the abbreviation for respiration rate only in Attachment 1.)
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic, x-rays, and blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	A patient who does not meet one or more criteria required for participation in a trial.

sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.
study completion	This study will be considered complete following the protocol-specified final analysis for the primary and secondary objectives.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TACC3	transforming acidic coiled-coil (fusion protein of FGFR3)
TCC	transitional cell carcinoma
TK	toxicokinetic(s)
TPO	third-party organization
ULN	upper limit of normal
V/F (or V)	(apparent) volume of distribution

A Phase 1 Study of LY3076226, a Fibroblast Growth Factor Receptor 3 (FGFR3) Antibody-Drug Conjugate, in Patients with Advanced or Metastatic Cancer

5. Introduction

5.1. Rationale and Justification for the Study

Fibroblast growth factor receptor (FGFR) is a receptor tyrosine kinase (RTK) involved in critical cellular activities such as angiogenesis, proliferation, survival, wound repair, and migration. Receptor dimerization initiates the tyrosine kinase cascade of diverse downstream signaling, such as SOS-GRB2-RAS-RAF-MAPK, GAB-1-PI3K-AKT, PLCγ-PIP3/DAG-PKC-RAF-MAPK, p38MAPK, JNK, STAT, and ribosomal protein S6 kinase 2 (as reviewed by Turner and Grose 2010). Activation of FGFR plays a pivotal role in cancer initiation and progression.

Fibroblast growth factor receptor 3 (FGFR3), 1 of 4 members of the FGFR family, is found to be constitutively active in bladder, multiple myeloma, non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), and cervical cancer through overexpression, point mutations, and translocations (Singh et al. 2012; Parker et al. 2013; Williams et al. 2013; Wu et al. 2013). Aberrant activation of FGFR3 through overexpression has been shown to be sufficient to induce oncogenic transformation in fibroblasts, hematopoietic cells, and murine bone marrow transplantation models (Plowright et al. 2000; Chesi et al. 2001; Ronchetti et al. 2001; Chen et al. 2005).

LY3076226 is an anti-FGFR3 antibody conjugated to a cytotoxic payload, DM4, a maytansine derivative that inhibits tubulin dynamics. The anti-FGFR3 antibody recognizes not only wild-type (WT) receptor, but also constitutively active mutant receptors (S249C, Y373C, and others) and transforming acidic coiled-coil (TACC3) fusion proteins of FGFR3 (Stewart et al. 2004; Kiemeney et al. 2010). This allows LY3076226 to selectively internalize the FGFR3 receptor and deliver the cytotoxin into the target cancer cells that are aberrantly activated by the FGFR3 receptor, regardless of mechanism. DM4 is catabolized once the receptor—antibody-drug conjugate (ADC) complex is internalized, providing specific killing of the unwanted cancer cell along with bystander killing of neighboring cells within the tumor microenvironment.

Maytansine was developed in 1972 and tested in Phase 1 and 2 studies as a cytotoxic agent for treatment across multiple cancer types, including breast, melanoma, lung, colorectal, and ovarian in the late 1970s and early 1980s (Blum et al. 1978a; Blum et al. 1978b; Cabanillas et al. 1978; Chabner et al. 1978; Cabanillas et al. 1979; Neidhart et al. 1980; Ravry et al. 1985). The adverse event (AE) profile was similar to other anti-tubulin agents, with gastrointestinal (GI) and central nervous system (CNS) toxicities being dose limiting. The doses selected to avoid and mitigate higher-grade toxicity did not demonstrate sufficient activity and development was stopped. Selectively targeting aberrant cells using an antibody that recognizes cancer-specific cell surface receptors to deliver a maytansine derivative directly into the cell has the potential to decrease the systemic exposure, thereby potentially decreasing dose-limiting GI and CNS effects while potentially increasing the efficacy. Another derivative of maytansine, DM1, has been

successfully conjugated to an anti-human epidermal growth factor receptor 2 (HER2) antibody for use in the treatment of HER2+ metastatic breast cancer (Kadcyla package insert, 2014). A number of other maytansine antibody-drug conjugates with either DM1 or DM4 payloads are currently in clinical trials (Trail 2013).

Urothelial carcinoma, a cancer involving the transitional epithelial lining of the urinary system, is a type of cancer that typically occurs in the urinary bladder (90% of cases), renal pelvis (8%), or ureters or urethra (remaining 2%, combined). For simplicity, the disease is often referred to as bladder cancer. Transitional cell carcinoma (TCC) is the predominant histologic type of urothelial carcinoma in North America and Europe, where it accounts for ≥90% of all bladder cancers (Billis et al. 2001; Chalasani et al. 2009). Other histologic subtypes are squamous cell, adenocarcinoma, and small-cell tumors. Urothelial tumors with a mixture of histologic subtypes and transitional cell predominance are generally treated similarly as urothelial (transitional cell) carcinomas (NCCN 2014).

Almost half of patients with urothelial carcinoma have FGFR3 genetic mutations. In 2015 in the United States, there will be an estimated 74,000 newly diagnosed cases of bladder cancer with 16,000 deaths (American Cancer Society 2015). Point mutations (S249C in the extracellular domain, R248C in the transmembrane domain, and Y373C and Y375C in the kinase domain) occur in 70% to 80% of patients with early stage TCC. Despite multimodal therapy with bacillus Calmette-Guérin (BCG)/radiation/surgery, the recurrence rate is 50% to 70%, with 10% to 20% of patients progressing to muscle-invasive disease (Al-Ahmadie et al. 2011). In muscle-invasive disease, activating mutations of FGFR3 are reported in 11% to 20% of patients (TCGA 2014) and FGFR3 overexpression is seen in 35% to 50% of patients. Taken together, these data make FGFR3 a particularly relevant target for the treatment of urothelial carcinoma (Guancial et al. 2014; Sung et al. 2014; Turo et al. 2015).

LY3076226 may overcome the dose-limiting toxicities (DLTs) of traditional cytotoxic therapy by selectively delivering the cytotoxic payload directly to the targeted cancer cells, resulting in greater tumor reduction/efficacy. This initial Phase 1 study with LY3076226, Study I70-MC-JOBA (JOBA), will characterize the safety and determine the recommended Phase 2 dose (RP2D) of LY3076226 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 a recommended Phase 2 dose and schedule of LY3076226 that may safely be 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 LY3076226
- to characterize the pharmacokinetics (PK) of LY3076226
- to document antitumor activity observed with LY3076226

5.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- to explore the effect of LY3076226 on pharmacodynamic (PD) markers
- to explore the association between biomarkers and clinical outcome

5.3. General Introduction to LY3076226

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

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

LY3076226 is an antibody-drug conjugate (ADC) composed of IMC-D11, an immunoglobulin G, subclass 1 (IgG1) monoclonal antibody against FGFR3, attached with a cleavable linker, sulfo-SPDB (disulfide N-succinimidyl 4-[2-pyridyldithio]butyrate), to the maytansine derivative DM4, a tubulin inhibitor. LY3076226 uses a selective, high-affinity, neutralizing, phage-derived, fully human IgG1 monoclonal antibody against the human FGFR3b/c protein. This IgG 1λ monoclonal antibody to FGFR3, IMC-D11, was generated for use in human cancer patients with FGFR3 amplifications, overexpression, and activating mutations. The antibody component of LY3076226, IMC-D11, blocks ligand-dependent as well as ligand-independent signaling in tumor-derived cell lines and in FGFR3 stably transfected cells. The anti-FGFR3 IMC-D11 epitope overlaps with heparin sulfate proteoglycan and FGFR3 ligand binding. IMC-D11 was selected for its ability to potently block primary FGFR3 ligand-dependent (ligands fibroblast growth factor [FGF]-1 and FGF-9 and all others) cancer cell proliferation and induce FGFR3 receptor internalization and degradation with similar potency, which results in FGFR3-mediated cancer cell death. Importantly, IMC-D11 is fully cross-reactive with human, cynomolgus

monkey, rat, and mouse FGFR3b/3c receptors binding with similar affinities. IMC-D11 has comparable activity against wild type and mutant FGFR3 and has demonstrable tumor growth inhibition in vivo in several bladder cancer cell lines and multiple myeloma models, with marked decreases in receptor phosphorylation, as well as a significant decrease in phosphorylation of mitogen-activated protein kinase (MAPK).

IMC-D11 is conjugated to the maytansine derivative DM4 (a tubulin inhibitor) via a cleavable linker moiety (sulfo-SPDB). LY3076226 binds specifically to the human FGFR3 protein with high affinity, and following internalization can deliver potent cytotoxic payload resulting in cell cycle arrest and cell death (Discovery, Eli Lilly and Company, preclinical in vitro study IMC37; LY3076226 Investigator's Brochure, Eli Lilly and Company, 2015). Sulfo-SPDB, the linker portion of LY3076226, was selected to balance the toxicity of the drug moiety by ensuring intracellular metabolism of the drug moiety (Discovery, Eli Lilly and Company, preclinical in vitro study IMC37; Discovery, Eli Lilly and Company, preclinical study 5404-12). Sulfo-SPDB conjugates, when metabolized intracellularly, generate 3 metabolic products (lysine-N[epsilon]-SPDB-DM4, DM4, and S-methyl-DM4), 2 of which are capable of promoting bystander cell killing of neighboring cells through the delivery of free drug (DM4 and S-methyl-DM4 [DM4-Me]), which can also increase toxicity through non-specific killing of proliferating, normal cells. Sulfo-SPDB was selected over other cleavable linkers due to its high processing efficiency (Zhao et al. 2011), superior efficacy in some tumor models, as well as toxicity/tolerability considerations (Discovery, Eli Lilly and Company, preclinical study 5404-12). However, due to this bystander killing mechanism, sulfo-SPDB conjugates can also increase toxicity through non-specific killing of normal cells (Erickson et al. 2012).

LY3076226 was studied in 3 bladder patient-derived xenograft (PDX) models with unknown FGFR3 expression (receptor density not determined), 21 NSCLC models of varying antigen density (determined by FGFR3 messenger ribonucleic acid [mRNA]), and 7 in-house cell-line-derived bladder xenograft models representative of FGFR3; wild type, S249C mutant, and TACC3 fusion-positive as defined by receptor density, mRNA expression, immunohistochemistry (IHC), and ModaPlex analysis. Preclinical in vivo efficacy data demonstrate that treatment with LY3076226 inhibits tumor growth in a number of cell-line-derived human bladder and multiple myeloma xenografts, as well as a squamous NSCLC PDX model (LXFE 2227) that is TACC3 fusion-positive as defined by ModaPlex analysis. The in vivo responses observed (including complete response [CR], partial response [PR], and stable disease [SD]) are durable and LY3076226 was demonstrated to mechanistically induce tumor cell apoptosis. Importantly, LY3076226 had no activity in xenograft models devoid of FGFR3 cell surface expression, which further supports the FGFR3 specificity of the molecule.

Significant cytotoxic activity of LY3076226 was observed when the molecule was used to treat each of the FGFR3-overexpressing bladder tumor cell lines. The compound was slightly more potent in the UMUC-14 tumor cell line, which overexpresses FGFR3 containing a mutation (S249C) in the extracellular domain that renders the receptor constitutively active. The negative control isotype-matched ADC showed no cytotoxicity in the concentration ranges seen with LY3076226 in any of the lines. A bladder tumor cell line, KU-19-19, that does not overexpress

FGFR3 was included in the experiment to assess nonspecific cytotoxicity. No cytotoxicity was observed with the KU-19-19 line, a cell line that is devoid of FGFR3 expression. It was concluded that specific in vitro cytotoxicity can be induced by LY3076226 in cell lines overexpressing FGFR3 wild type, FGFR3 S249C mutant, and FGFR3-TACC3 fusion.

In preclinical testing, LY3076226 has shown in vivo activity in bladder, squamous NSCLC, and multiple myeloma models containing wild type, mutated, and TACC3-fused FGFR3 that is overexpressed or constitutively active. LY3076226 may overcome the DLTs of traditional cytotoxic therapy by selectively delivering the cytotoxic payload directly to the targeted cancer cells, resulting in greater tumor reduction/efficacy.

5.3.2. Nonclinical Pharmacokinetics/Pharmacodynamics

Pharmacokinetics and/or toxicokinetics (TK) of LY3076226 have been studied in mice, rats, and cynomolgus monkeys following single intravenous (IV) administration of 3, 10, or 20 mg/kg or once-weekly repeat-dose administration of 1, 3, and 10 or 15 mg/kg. Plasma PK of LY3076226, either conjugated LY3076226 (LY3076226 with at least one DM4 payload) or total LY3076226 IgG, were characterized using enzyme-linked immunosorbent (ELISA) assays. Plasma concentrations of free DM (total free immunoreactive maytansine species) were quantified by unvalidated ELISA assays in preliminary experiments. In later studies, DM4 and DM4-Me were quantified with liquid chromatography-mass spectrometry (LC-MS) assays.

Following IV administration PK and TK studies, plasma concentration-versus-time profiles for conjugated LY3076226 and total LY3076226 IgG demonstrated similar maximum plasma concentration (C_{max}) values and elimination profiles. Plasma concentrations for both conjugated and total LY3076226 increased with increasing dose. In both the rat and monkey, there was limited evidence of super-proportionality observed in C_{max} and area under the plasma concentration-time curve (AUC) in some studies, but this was 2-fold or less across doses of 1 through 20 mg/kg. There were no apparent sex differences in the PK/TK of LY3076226. The mean elimination half-life ($t_{1/2}$) for conjugated LY3076226 was approximately 20 hours in the mouse, 16 to 42 hours after a single dose in the rat, and 45 to 101 hours after single or multiple doses in the monkey. The mean $t_{1/2}$ for total LY3076226 IgG was approximately 23 hours in the mouse, 9 to 31 hours following single-dose administration in the rat, and 45 to 138 hours after single or multiple doses in the monkey. In the rat, concentrations of conjugated and total LY3076226 IgG were variable (reduced or no longer quantifiable) in some animals after repeat administration, and no accumulation was apparent. These observations in the rat were possibly affected by anti-drug antibodies (ADA). In the monkey, once-weekly dosing at 1 or 3 mg/kg demonstrated little or no accumulation (2-fold or less).

Based on the validated LC-MS assay for DM4 and DM4-Me, plasma concentrations of these species in both rat and cynomolgus monkey increased with increasing dose and did not accumulate with repeated dosing. There were insufficient data for $t_{1/2}$ estimations for DM4 or DM4-Me in the monkey. In the rat, mean DM4 and DM4-Me $t_{1/2}$ estimates were 16 to 19 and 22 to 29 hours, respectively. DM4 and DM4-Me were a small fraction (generally less than 2.5% in the rat and 0.07% in the monkey on a molar basis) of conjugated LY3076226.

Metabolism studies have not been conducted with LY3076226. However, the metabolism of the molecule based on the construct and the PD activity of LY3076226 is expected to be ligand binding followed by receptor-mediated cellular uptake and degradation of the IgG portion of the molecule into component amino acids. The DM4 payload released by the proteolytic metabolism of the ADC is then available within the cell to bind to microtubules, inducing mitotic arrest and cytotoxicity (Erickson et al. 2010). Both DM4 and DM4-Me have been identified in the ADC literature as active metabolites released both in vitro and in vivo (Erickson et al. 2006; Erickson et al. 2010). Mouse studies suggest that active maytansine species are further detoxified by oxidation in the liver (Sun et al. 2011).

In vitro drug-drug interaction (DDI) studies have not been conducted with LY3076226. The in vitro DDI potential of DM4 has been evaluated (Davis et al. 2012). While the free sulfhydryl in DM4 has the potential to inactivate CYP3A4 in an NADPH-dependent manner, the low plasma concentrations observed clinically for free DM4 arising from ADCs suggest that this is of limited clinical concern.

5.3.3. Nonclinical Toxicology

To support clinical investigation of LY3076226, a package of nonclinical toxicology studies have been conducted with LY3076226. These studies are supplemented with data from prior nonclinical safety studies that investigated both the monoclonal antibody and drug conjugate parts of LY3076226.

The repeat-dose toxicology studies of LY3076226 consisted of 5-week studies in rats at dosages of 1, 3, or 10 mg/kg (equivalent to 6, 18, or 60 mg/m^2, respectively) or in cynomolgus monkeys at dosages of 1, 3, or 15 mg/kg (equivalent to 12, 36, or 180 mg/m^2, respectively). LY3076226 was given by IV injection (slow bolus) once weekly for 5 occasions (Days 1, 8, 15, 22, and 29). The dosing schedule used in the toxicology studies represents a more intense schedule than is planned in this Phase 1 clinical trial.

The main toxicities associated with IV administration of LY3076226 comprised changes in the skin, and cornea. In addition, there were effects on bone marrow, lymphoid tissue, GI tract, liver, and reproductive systems consistent with the cytotoxic effects of the DM4 payload. Toxicities at the lower doses (1 or 3 mg/kg) were of lower severity and frequency than those observed at the high dose in either species.

Adverse skin reactions with subsequent generalized debilitation resulted in the premature euthanasia of rats and monkeys at the highest dose of LY3076226 tested in each species (10 or 15 mg/kg, respectively). Although adverse skin reactions were seen at lower dosages (1 or 3 mg/kg) in both rat and monkey, these did not cause debilitation and premature euthanasia.

Dry, flaking, reddened, discolored and/or sloughing skin was seen in both rats (3 or 10 mg/kg) and monkeys (all dosages). Skin changes were seen on the limbs (including injection sites), dorsal and ventral surfaces, face, eyelids and/or eyebrows. In the monkey, microscopic changes in the skin comprised hyperkeratosis, dyskeratosis, necrosis, inflammation, and pigmentation at all dosages; in the rat, hyperplasia, ulceration, and inflammation were seen in the skin. In both

species, increased mitoses and single-cell necrosis were seen in the skin (and in many other tissues). After an 8-week reversibility period, skin lesions were still present in both rat and monkey, but the incidence and/or severity was reduced.

In the 5-week monkey study, haze at the corneal limbus was seen by slit-lamp examination after 5 treatments in all animals treated at 3 mg/kg and was accompanied by corneal pigmentation in the majority of the affected animals. Microscopically, increased mitoses and single-cell necrosis were present in the corneal epithelium at all dosages; dyskeratosis was seen in animals treated at 3 mg/kg or more. After the 8-week recovery period, the corneal hazing was not present, although pigmented corneas were still apparent – dyskeratosis and/or pigment were seen histologically. Corneal pigmentation observed in recovery animals is a likely sequelae of the corneal injury noted in terminal and early death animals. In the rat, although no corneal lesions were seen by ophthalmic examination, increased mitoses in the corneal epithelium were seen at all dosages after 5 weeks of treatment; this change was not apparent after the 8-week reversibility period.

Single-cell necrosis and increased mitoses were seen in the epithelium of some or all of the GI tract in both rats and monkeys at the highest dose; these changes were completely reversible after 8 weeks of recovery.

Effects on the bone marrow and lymphoid tissues, with concomitant effects on circulating red and white blood cells, were consistent with the cytotoxic activity of the DM4 payload. These changes were most severe at the high dose in rats and monkeys and comprised decreased erythroid and early myeloid progenitors and increased mitoses/single-cell necrosis in the bone marrow, increased mitoses and/or decreased cellularity of lymphoid tissue, decreased erythroid mass and decreased reticulocyte, neutrophil, lymphocyte, monocyte, and eosinophil counts; at the lower dosages, these effects were less severe and/or frequent in both species. Effects on bone marrow, blood, and lymphoid tissue showed complete or almost complete recovery during the 8-week reversibility period.

In male rats, tubular degeneration in the testis and hypospermia/inflammation in the epididymides were seen at the highest dose (10 mg/kg) and in 1 or 2 males at the 3-mg/kg dose; no similar changes were seen at 1 mg/kg. The effects on testes and epididymides were only partially reversible.

Increased mitoses and/or single-cell necrosis was seen in a number of other tissues, including the liver, gallbladder, pancreas, salivary glands, kidneys, epididymides, prostate, seminal vesicles, ovaries, cervix, uterus, mammary gland, and/or vagina in monkeys or rats. These changes were generally confined to the highest dose in either species and only rarely were these effects seen at the 3-mg/kg dose level. The changes in the liver of rats were accompanied by mild increases in liver transaminase levels.

Increased heart rate and decreased RR, PR, and QT intervals were seen in monkeys following treatment at 3 or 15 mg/kg; no decrease in corrected QT (QTc) interval was apparent and there were no unusual or abnormal rhythms or waveforms. Heart rates in monkeys treated at 3 or 15 mg/kg were approximately 25% or 60% higher than either prestudy values or time-matched

control values. No effects on heart rate were seen at 1 mg/kg. LY3076226 had no effect on body temperature, breathing rate, or neurological parameters.

Based on the nonclinical toxicology studies of LY3076226, the DLTs are expected to be skin lesions, corneal changes, myelosuppression, and/or GI toxicity. These changes are considered manageable, and at least partial reversibility has been demonstrated. Appropriate endpoints to monitor patient safety have been incorporated into this clinical protocol.

For Study JOBA, an initial clinical starting dose of 6 mg/m^2 (equivalent to 0.18 mg/kg for a patient with a body surface area of 1.8 m^2 and body weight of 60 kg) administered once every 21 days was selected based on the highest non-severely toxic dose (HNSTD) in the most sensitive animal species and on PK projections that suggest the exposure at this dose is comparable with the minimally efficacious exposure, while ensuring an adequate safety margin. The starting dose is one sixth of the HNSTD in the most sensitive species (based on a dose of 3 mg/kg or 36 mg/m^2 in cynomolgus monkeys). Table JOBA.1 shows the calculated exposure multiples for the clinical starting dose and highest planned dose relative to the exposure at the HNSTD in monkeys.

Table JOBA.1. Exposure Multiples for Intravenous Administration of LY3076226 Based on Administered Dose and Predicted Exposure in Humans

	Dose		$AUC_{(0\text{-}7\ d)}$		C_{max}	
	mg/m^2	Multiple[a]	µg·h/mL	Multiple[b]	µg/mL	Multiple[c]
Rat MinTD	18	-	1525	-	63.85	-
Monkey HNSTD	36	-	3473	-	63.85	-
Human:	**Dose**		$AUC_{(0\text{-}21\ d,ss)}$		$C_{max,ss}$	
	mg/m^2	Multiple[a]	µg·h/mL	Multiple[b]	µg/mL	Multiple[c]
Starting dose (0.18 mg/kg)	6	rat: 3× monkey: 6×	224	rat: 6.8× monkey: 15.5×	4.7	rat: 13.6× monkey: 13.6×
Highest dose (5 mg/kg)	165	rat: 0.11× monkey: 0.22×	15000	rat: 0.10× monkey: 0.23×	110	rat: 0.58× monkey: 0.58×

Abbreviations: AUC = area under the plasma concentration-time curve; C_{max} = maximum observed plasma concentration; $C_{max,ss}$ = maximum observed plasma concentration at steady state; HNSTD = highest non-severely toxic dose; MinTD = minimally toxic dose.

a Dose multiple is the dose in animals/dose in humans based on body surface area (mg/m^2).

b Exposure multiple is the mean AUC(0-7 d) on Day 1 in male and female animals/projected mean AUC(0-21 d,ss) in humans.

c Exposure multiple is the mean C_{max} on Day 1 in male and female animals/projected mean Cmax,ss in humans.

MinTD based on 5-week repeat-dose toxicity study in the rat (Study No. 5000859).

HNSTD based on 5-week repeat-dose toxicity study in the cynomolgus monkey (Study No. 20056864).

5.3.4. Biomarkers

FGFR protein expression and patient genetic data identifying constitutively active or overexpressed FGFR on the cell surface of tumors have been linked to clinical outcomes to other pan-FGFR therapy (André et al. 2013a; André et al. 2013b; Nogova et al. 2014; Dienstmann et al. 2014). Analytes related to the FGFR pathway, the DM4 mechanism of action, and cancer pathobiology including, but not limited to, FGFR3 protein expression, along with somatic mutation status and/or copy number variations of FGFR3 pathway-related genes or genes related to cancer pathobiology may be assessed.

In addition, induction of cell cycle arrest will be examined by measuring Ki-67 and phosphohistone H3 (pHH3) in patients with known alterations of FGFR3. CK18, a circulating marker in blood, will be analyzed as an indirect measurement of apoptosis.

5.4. Rationale for Selection of Dose

A dose range of 0.2 (rounded up from 0.18 for ease of calculation) to 5 mg/kg of LY3076226 administered IV on Day 1 of a 21-day cycle was selected based on nonclinical toxicology, efficacy, and PK data.

The starting dose for Study JOBA is a dose of 0.2 mg/kg (6 mg/m^2) administered on Day 1 of a 21-day cycle. As indicated in Table JOBA.1, when calculated on the basis of mg/m^2 dosing, this dose is approximately 3-fold lower than the minimally toxic dose (MinTD) of 3 mg/kg (18 mg/m^2) in rats and 6-fold lower than the HNSTD of 3 mg/kg (36 mg/m^2) in cynomolgus monkeys.

Table JOBA.2 gives the mean predicted maximum (observed) plasma concentration at steady state ($C_{max,ss}$) and $AUC_{(0\text{-}21\ d,ss)}$ for the various anticipated dose levels to be tested in Study JOBA. Exposure levels (C_{max} and $AUC_{(0\text{-}7\ d)}$) after multiple doses at the MinTD in rats and the HNSTD in cynomolgus monkeys are summarized in Section 5.3.3 (Nonclinical Toxicology). Based on a human starting dose of 0.2 mg/kg given once every 21 days and the exposure observed after multiple doses at the MinTD of 3 mg/kg (18 mg/m^2) in rats, the mean predicted exposure multiples are approximately 6.8 for $AUC_{(0\text{-}21\ d,ss)}$ and 13.6 for $C_{max,ss}$. When calculated using exposures observed at the HNSTD of 3 mg/kg (36 mg/m^2) in cynomolgus monkeys, the mean predicted exposure multiples are approximately 15.5 for $AUC_{(0\text{-}21\ d,ss)}$ and 13.6 for $C_{max,ss}$.

Preclinical efficacy associated with administration of LY3076226 was evaluated by investigating the exposure levels associated with xenograft tumor growth delay in mice. In an RT112 xenograft tumor model, the lowest dose associated with complete tumor regression in 4 out of 5 mice per dose group was 10 mg/kg administered either as a single IV administration (qd×1) or as two 5-mg/kg IV administrations separated by a 14-day dosing interval (q14d×2). A PK model developed for LY3076226 in mice indicates a mean $AUC_{(0\text{-}28\ d)}$ and C_{max} in plasma of approximately 3600 µg·h/mL and 123 µg/mL, respectively, for the 10-mg/kg qd×1 dose group. $AUC_{(0\text{-}28\ d)}$ and C_{max} were estimated at 3030 µg·h/mL and 61.2 µg/mL, respectively, after 5 mg/kg administered q14d×2.

The minimally efficacious dose (MED) in humans was subsequently projected using a human PK model obtained by allometric scaling performed on cynomolgus monkey PK data. This projected human PK model indicates that a dose of 1.6 to 1.8 mg/kg would be needed to achieve an $AUC_{(0\text{-}21\ d,ss)}$ in patients similar to the $AUC_{(0\text{-}28\ d)}$ observed in mouse. Likewise, human C_{max} values similar to those obtained in mice would be obtained at a dose ranging from 3.0 to 7.2 mg/kg.

Altogether, these results suggest a MED in humans ranging from 1.6 to 3.0 mg/kg. Based on the LY3076226 plasma exposures observed at the MinTD in rats, the mean AUC exposure multiples predicted at steady state for this MED projection range from 0.5 to 0.2. When using LY3076226 plasma exposures observed at the MinTD in rats, the mean projected AUC exposure multiples at steady state range from 1.1 to 0.4.

Based on data from the rat and nonhuman primate toxicology studies, the DLTs in humans are expected to be monitorable and reversible. The proposed dose-escalation strategy will thus be guided by safety assessments and the use of a human PK/PD model, which will be updated as human clinical PK data are available. The primary determinant, however, will be safety. The actual dose increment between cohorts and the example dose level of each cohort will be determined according to the constraints described in Section 7.2.2 (Dose Escalation).

Table JOBA.2. Mean Predicted Plasma Exposure Levels at the Example LY3076226 Dose Levels for Study I7O-MC-JOBA

LY3076226 Dose (mg/kg)	$C_{max,ss}$ (µg/mL)	$AUC_{(0\text{-}21\ d,ss)}$ (µg·h/mL)
0.2	4.7	224
0.4	8.16	521
0.8	16.4	1270
1.6	33.2	3220
2.4	50.5	5640
3.2	68.4	8430
4.0	86.9	11500
5.0	110	15500

Abbreviations: AUC = area under the plasma concentration-time curve; $C_{max,ss}$ = maximum plasma concentration at steady state.

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. Individuals may be re-screened one time. 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] Must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies have failed to provide clinical benefit for their disease or if the patient refuses standard therapy. Patients must be well informed about the benefit and risk of standard therapy prior to signing the informed consent.

Part A (dose escalation): Have histological or cytological evidence of a diagnosis of cancer (including multiple myeloma and lymphoma) that is advanced and/or metastatic.

Part B (dose expansion): Have histologically or cytologically confirmed, locally advanced, or unresectable or metastatic urothelial (transitional cell) carcinoma of the bladder, urethra, ureter, or renal pelvis, with locally determined overexpression or alterations of FGFR3 (refer to Attachment 11).

Part C (dose expansion): Have histological or cytological evidence of a diagnosis of cancer (including multiple myeloma and lymphoma) that is advanced and/or metastatic, with locally determined overexpression or alterations of FGFR3 (refer to Attachment 11).

[2] Part A: Have the presence of measurable and/or nonmeasurable disease as defined by the appropriate criteria: Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1 [refer to Attachment 9]; Eisenhauer et al. 2009), multiple myeloma criteria (International Myeloma Working Group [IMWG; refer to Attachment 5]; Rajkumar et al. 2011), or lymphoma criteria (Cheson et al. 2014).

Parts B and C: Have the presence of measurable disease as defined by the appropriate criteria: RECIST 1.1 (Eisenhauer et al. 2009), multiple myeloma criteria (IMWG; Rajkumar et al. 2011), or lymphoma criteria (Cheson et al. 2014).

[3] Parts B and C: Are willing to provide a pretreatment tissue sample. For patients who have disease recurrence/metastasis at body sites that are technically challenging for biopsy and who have available tissue from a previous regimen posttreatment biopsy and have not received intervening therapy, the investigator and sponsor may agree to omit the pretreatment biopsy.

[4] Are ≥18 years of age.

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

[6] Have adequate organ function, including:

- Hematologic: Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥9 g/dL and have not received blood or blood components transfusion within 2 weeks (≤2 weeks) prior to the laboratory test.

  In Part C only, patients with multiple myeloma are allowed the following: ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 50 \times 10^9$/L, and hemoglobin ≥8 g/dL.

- Hepatic: Total bilirubin ≤1.5 × upper limit of normal (ULN) in the absence of Gilbert's syndrome, direct bilirubin ≤1.5 × ULN in the presence of Gilbert's syndrome, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN.

- Renal: Serum creatinine ≤1.5 × ULN or a calculated or measured creatinine clearance of ≥50 mL/min/1.73 m^2 (refer to Attachment 8 for the Cockcroft and Gault formula to calculate creatinine clearance from local laboratory results).

[7] Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 7).

[8] Have discontinued previous treatments for cancer and have resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior chemotherapy, surgery, or radiotherapy to Grade ≤1 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (v 4.0) (CTEP 2009).

[9a] Male patients:

who are sterile (including vasectomy) or agree to use a reliable method of birth control and to not donate sperm during the study and for at least 12 weeks following last dose of study drug or country requirements, whichever is longer.

[9b] Female patients:

are women not of childbearing potential due to surgical sterilization (at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or due to menopause (refer to Section 4 for the definition of menopausal women).

OR

are women of childbearing potential who test negative for pregnancy within 7 days of enrollment based on a serum pregnancy test and agree to use a highly effective method of birth control* during the study and for 3 months following the last dose of the study drug and also must not be breastfeeding.

*A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

[10] Have an estimated life expectancy that, in the judgment of the investigator, will permit the patient to complete 3 cycles (9 weeks) of treatment.

6.1.2. Exclusion Criteria

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

[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) 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 (left to the discretion of the investigator).

[13] Have symptomatic CNS malignancy or metastasis (screening not required).

Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids for this indication and/or anticonvulsants, and their disease is asymptomatic and radiographically stable for at least 28 days.

[14] Have current acute or chronic leukemia.

[15] Have an active 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 and sponsor, may affect the interpretation of results.

Curatively treated nonmelanoma skin cancer or in situ carcinoma of any origin is allowed.

[17] Have Fridericia-corrected QT interval (QTcF) >480 msec on screening electrocardiogram (ECG).

[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 preexisting corneal diseases that may interfere with assessment of potential toxicity in the eyes during the study.

[20] Have skin disorders (for example, erythema, and dermatitis) of ≥Grade 2.

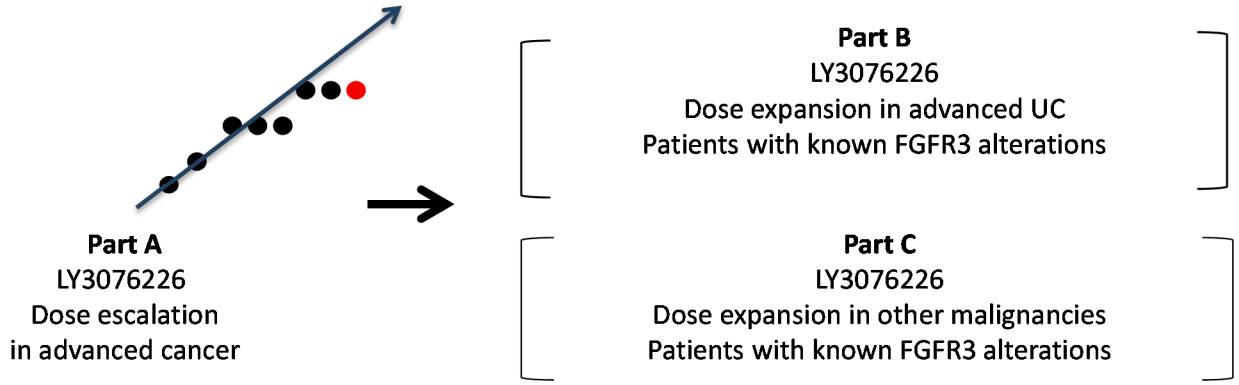
6.2. Summary of Study Design

Study JOBA is a multicenter, nonrandomized, open-label, dose-escalation Phase 1 study of IV LY3076226 in patients with advanced or metastatic cancer. Eligible patients will receive LY3076226 as an IV infusion on Day 1 of a 21-day cycle.

Dose escalation for LY3076226 in Part A will be driven by an accelerated dose-escalation scheme. Initial cohorts will enroll at least one patient each until a dose level of 1.6 mg/kg is reached, unless toxicity observed requires enrolling additional patients to a dose level. A modified 3+3 dose-escalation scheme will be followed in subsequent cohorts, with incorporation of a Bayesian model-based dose-escalation method (Neuenschwander et al. 2008) to assist in estimation of the DLT rate at recommended dose levels. Dose levels for Cohorts 2 and beyond will reflect a maximum increment of 100% from the prior dose level. The dose will be escalated until a maximum tolerated dose (MTD) has been identified. If the MTD has not yet been reached at the highest prespecified dose level, then additional dose levels may be investigated based on both safety and the available PK data.

Once MTD is identified in Part A, up to approximately 15 patients who have known alterations of FGFR3 will be enrolled in each of Parts B (urothelial carcinoma) and C (other malignancies) to further evaluate the safety profile of LY3076226, characterize the exploratory biomarker assays, and document any antitumor activity.

Figure JOBA.1 is a representative illustration of the JOBA study design, showing the dose-escalation design in advanced cancer (Part A) and MTD expansions focusing on selected patient populations with known alterations of FGFR3 in urothelial carcinoma (Part B) and other malignancies (Part C).



Abbreviations: FGFR3 = fibroblast growth factor receptor 3; UC = urothelial carcinoma.

Figure JOBA.1. Illustration of I7O-MC-JOBA study design.

To determine the recommended Phase 2 dose of LY3076226, an adequate sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as well as an evaluation of the relationship between exposure and pharmacological effects using descriptive statistics and appropriate modeling techniques, if data warrant.

The actual sample size of the dose escalation (Part A) will primarily be determined by the observed toxicity and the incidence of DLTs. Under the modified 3+3 dose-escalation scheme, each cohort will include 3 to 6 patients. The anticipated sample size for Part A ranges from approximately 20 to 35 patients, depending on the observed toxicity. Each of Parts B and C expansion cohorts will enroll up to approximately 15 patients. The overall sample size is thus estimated to be approximately 65 patients.

The planned duration of treatment is not fixed. Patients will have tumor assessments after receiving 3 cycles of treatment. Patients without evidence of disease progression may continue treatment until they fulfill one of the criteria for study discontinuation (Section 6.3).

Refer to Attachment 1 for the Study Schedule.

6.2.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the protocol-specified final analysis for the primary and secondary objectives.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.

6.2.2. Continued Access Period

All patients remaining on study treatment without disease progression following the final analysis for the primary and secondary objectives will be able to enter the continued access period of the study. The continued access period begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until disease progression, death, unacceptable toxicity, or start of new anticancer treatment. The continued access period includes a follow-up visit. The follow-up visit begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 28 days. If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

During the continued access period, all AEs, SAEs, study drug dosing, and dose reduction of treatment will be collected on the case report form (CRF).

Serious adverse events will also be reported to Lilly Global Patient Safety and collected in the pharmacovigilance system (Section 8.1.2.4). In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments.

6.3. Discontinuations

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

6.3.1. Discontinuation of Patients

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

In addition, patients will be discontinued from the study drug and/or from the study 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.
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug occurs prior to introduction of the other agent.
- 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).
- The patient's dosing is delayed for more than 2 weeks as the result of an AE that is at least possibly related to LY3076226. If this delay occurs for the start of Cycle 2, this will be considered a DLT.

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

LY3076226 drug product is supplied for clinical trial use as an aqueous solution (10mM acetate, 9% sucrose, 0.01% polysorbate 20, pH 5.0) at a concentration of 5.0 mg/mL (in terms of antibody weight). It is a clear to slightly opalescent, colorless to slightly brown or slightly yellow liquid. The drug product is supplied as a single-use vial containing 100 mg LY3076226 in 20 mL of solution (5.0 mg/mL). LY3076226 will be administered as an IV infusion and sterile dextrose (5%) solution only must be used as a diluent. Lilly instructions regarding dilution requirements should be followed.

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

7.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensation and collection, and
- 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 so that the situation can be assessed.

7.2.1. Dosing Schedule

For doses ≤250 mg, LY3076226 will be administered as an IV infusion over approximately 60 minutes on Day 1 of each 21-day cycle. The sponsor may instruct the sites to extend the infusion time for up to 2 hours for doses greater than 250 mg. The assigned dose and duration of infusion of LY3076226 will be provided by the sponsor on a patient registration form. Subsequent doses should be adjusted as described in Section 7.2.6.

Premedication is not permitted for the initial dose of LY3076226 for each patient so that any observed toxicities may be appropriately characterized.

7.2.2. Dose Escalation

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

Dose-limiting toxicity (DLT) is defined as an AE occurring during Cycle 1 that is at least possibly related to LY3076226 and fulfills any one of the following criteria using the NCI-CTCAE v 4.0:

- CTCAE Grade ≥3 non-hematological toxicity. Exceptions will be made for the following:
  - 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 for more than 48 hours, despite supportive intervention.)
  - Anorexia
  - Grade 3 fatigue lasting ≤5 days
- Grade 3 elevations of ALT and/or AST lasting >7 days.
- Concurrent elevation of ALT >3 × ULN and total bilirubin >2 × ULN in the absence of biliary obstruction or other causes that could reasonably explain the elevation.
- CTCAE Grade 4 neutropenia of >7 days' duration
- Any febrile neutropenia
- CTCAE Grade 3 thrombocytopenia with bleeding
- CTCAE Grade 4 thrombocytopenia with or without bleeding
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is at least possibly related to the study medication and that requires the withdrawal of the patient from the study during Cycle 1 or delays the start of Cycle 2 by >14 days).

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

7.2.2.2. DLT-Equivalent Toxicity

A DLT-equivalent toxicity is defined as an AE occurring during 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 7.2.6. 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 (for example, a DLT-equivalent toxicity is observed in >33% patients at a given dose level), the data will be reviewed by study investigators and the Lilly CRP/clinical research scientist (CRS) and a safety analysis may be triggered. 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

For Part A, the proposed starting dose level will be 0.2 mg/kg. Dose escalation will proceed at a maximum dose increment of 100%. An accelerated dose-escalation scheme will be used, as follows: initial cohorts will enroll at least one patient each until a dose level of 1.6 mg/kg is reached, unless a ≥Grade 2 toxicity that is at least possibly related to LY3076226 is observed requiring additional patients to be enrolled to a dose level. After which a modified 3+3 scheme, with incorporation of a Bayesian model-based, toxicity-band method (Neuenschwander et al. 2008), will be followed, wherein at least 3 patients will be enrolled in each of the subsequent cohorts. The Bayesian model-based, toxicity-band method incorporates the prior expectations of the dose-toxicity curve and the observed DLT data after each cohort and provides quantitative guidance on the determination of the dose level for the next cohort, with control of overdosing probability. This method will be applied to the observed data on an ongoing basis throughout the dose escalation. The toxicity-band method will stop if the prespecified maximum number of patients is reached or the recommended next dose level has been administered to at least 6 patients.

During the dose-escalation period, the investigators and Lilly CRP/CRS will consider both the model recommendation and the observed DLT rate at each cohort to determine the next dose level and determine when to stop dose escalation. Safety data, in particular, AEs, will be the primary criteria for dose escalation. In addition, if available at the time of the dose-escalation decision, PK (C_{max}, AUC, and systemic clearance [CL]) results will be used as secondary/supporting data for dose escalation. Additional patients may, therefore, be enrolled at a specific dose level to characterize PK/PD. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly CRP/CRS; the decision will be documented in writing. Intrapatient dose escalations are not permitted.

The example dose levels for Part A are shown in Table JOBA.3. Intermediate or higher dose levels may be explored, if deemed necessary, after discussion between the Lilly CRP/CRS and investigators. The toxicity-band method has the ability to accommodate additional dose levels naturally.

Details regarding the toxicity-band method for this study are provided in Attachment 10.

If, during dose escalation, a situation presents itself that is not described above, Lilly CRP/CRS and investigators will determine the best method to select the appropriate dose for the patient(s) involved, using all available information. The decision will be documented in writing. No dose escalation can occur without prior discussion and agreement between the site-specific investigator and the Lilly CRP/CRS. Written notification will be sent to the site specifying the dose to be used for each patient at each dose level.

Table JOBA.3. Example of LY3076226 Dose Levels for Part A

Cohort	LY3076226 Dose Level (mg/kg)
1	0.2
2	0.4
3	0.8
4	1.6
5	2.4
6	3.2
7	4.0
8	5.0

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

7.2.3. Dose Confirmation in Patients with Known Alterations of FGFR3 (Parts B and C)

Once the MTD has been defined in Part A, Parts B (urothelial carcinoma) and C (other malignancies) will be activated and will enroll up to approximately 15 patients who have known alterations of FGFR3, to further define the safety and tolerability of LY3076226 and to characterize the exploratory biomarker assays. The dose of LY3076226 in Parts B and C will not exceed the MTD of LY3076226, as defined during dose escalation in Part A. The exact sample size of this cohort will be dependent on the number of patients who have known FGFR3 alterations treated at the MTD during dose escalation in Part A, and will be adjusted so that a total of approximately 15 patients will be treated.

If a DLT-equivalent toxicity occurs in one third or more of patients during Cycle 1 (with a minimum of 6 patients enrolled), the enrollment of new patients will cease until the Lilly CRP/CRS and investigators assess the severity and nature of the toxicities. A data review will be performed to determine whether to continue at the current LY3076226 dose or whether the dose of LY3076226 should be reduced. The toxicity-band method used in the dose-escalation phase will be updated with the additional data observed in Parts B and C to confirm the MTD selection and/or to inform any need to further refine the MTD. This decision will be documented in writing.

7.2.4. Recommended Phase 2 Dose (RP2D)

The RP2D will be determined after the completion of Parts B and C. 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. This will not exceed the MTD.

7.2.5. 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 (IRR) 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. 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 (for example, epinephrine, corticosteroids) are readily available.

Per the CTCAE v 4.0 definition of IRRs, 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 7.2.6 provides treatment recommendations for IRRs.

If, at any time, a patient experiences an IRR to LY3076226, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of IRRs.

If IRRs 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.

7.2.6. Dose Adjustments and Delays

7.2.6.1. General Dose Adjustments and Delays

Once a patient has had a dose reduction (has started a new cycle at the reduced dose), all subsequent infusions will be at the reduced dose level; there will be no resumption to prior dose level(s). Any patient experiencing toxicity that would necessitate more than 2 dose reductions must discontinue treatment.

The following criteria should guide dosing:

- Before the start of each cycle, the following parameters are required:
  - Hematologic: ANC $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥ 8 g/dL. (In Part C only, patients with multiple myeloma are allowed the following: ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 50 \times 10^9$/L, and hemoglobin ≥ 8 g/dL.)
  - Non-hematologic: AEs must resolve to CTCAE v 4.0 Grade ≤ 1 or baseline. Exceptions will be made for: alopecia, fatigue, or other toxicities that can be controlled with standard treatment; these toxicities must resolve to Grade ≤ 2.
- If subsequent cycles are delayed by more than 14 days due to an AE that is at least possibly related to LY3076226, the patient should be removed from study drug treatment and should complete subsequent follow-up.
- If the patient is in Cycle 3 or beyond and is continuing to receive benefit from therapy, delays of greater than 14 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.

Table JOBA.4 presents LY3076226 dosing guidelines for managing AEs of concern, which may or may not be associated with LY3076226 therapy.

Table JOBA.4. LY3076226 Dosing Guidelines for Managing Adverse Events of Concern for Study I7O-MC-JOBA

Event and Grade	Specifics	LY3076226 Dosing Guidelines, Including Dose Reductions and Delays
Infusion-Related Reactions		
Grade 1	First occurrence	Decrease LY3076226 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 LY3076226 infusion. Administer diphenhydramine hydrochloride and acetaminophen for fever. Supply oxygen. Resume infusion at 50% of previous rate once the 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.
Grade ≥3		Stop LY3076226 infusion 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 LY3076226 treatment.
Other Toxicities		
Grade ≥3	First occurrence	Delay LY3076226 treatment until Grade ≤1 or baseline following the rules in Section 7.2.6.1. Based on the investigator's discretion, the full dose of LY3076226 may be administered or the dose may be reduced to the next lowest dose level. If the event recurs at the same grade, then dose reduce LY3076226 to the next lowest dose level.
Grade ≥3	Second occurrence	Delay LY3076226 treatment until Grade ≤1 or baseline following the rules in Section 7.2.6.1. Dose reduce LY3076226 to the next lowest dose level.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3076226. 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 and identification number assignment and cohort for each patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP/CRS.

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

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

In the absence of clinical experience with LY3076226, 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, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. The need for any form of radiotherapy (including palliative) will be cause for early discontinuation from the study. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the CRF. Replacement hormonal therapy will be allowed. Patients on stable doses of bisphosphonates are allowed to continue.

Concomitant use of strong CYP3A4 inhibitors (for example, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with LY3076226 should be avoided due to the potential for an increase in DM4 exposure and toxicity. Where possible, consider an alternate medication with no or minimal potential to inhibit CYP3A4. Concomitant use of strong CYP3A4 inducers (for example, avasimibe [not commercially available], carbamazepine, phenytoin, rifampin, and St. John's wort) with LY3076226 should be avoided due to the potential for a decrease in DM4 exposure and potentially efficacy. Where possible, consider an alternate medication with no or minimal potential to induce CYP3A4. Concomitant use of strong CYP2D6 inhibitors (for example, bupropion, fluoxetine, paroxetine, and quinidine) with LY3076226 should be avoided

due to the potential for an increase in DM4 exposure and toxicity. Where possible, consider an alternate medication with no or minimal potential to inhibit CYP2D6. Refer to the Food and Drug Administration (FDA) website for a complete list (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm).

Patients should receive full supportive care with the exception that the routine use of granulocyte colony-stimulating factor (G-CSF) is not permitted during this study. Patients should not receive G-CSF prophylactically in any cycle. G-CSF may only be used for patients who have ANC $<0.5 \times 10^9$/L, neutropenic fever, or documented infections while neutropenic. G-CSF must be discontinued at least 24 hours before the start of the next cycle of treatment. 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). If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2010).

Premedication is not permitted for the initial dose of LY3076226 for each patient. Appropriate treatment with topical/oral corticosteroids and/or antibiotics may be instituted at the discretion of the investigator if skin reaction occurs.

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

7.6. Treatment Compliance

LY3076226 will be administered IV at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF.

7.6.1. 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 received at least one dose of 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 one cycle of LY3076226 treatment may be deemed non-evaluable for assessment of a dose level, unless they experience a DLT prior to withdrawal.

Patients who receive LY3076226 on Cycle 1, Day 1 (C1D1) but discontinue from study treatment before the end of Cycle 1 will be considered evaluable for the assessment of a dose level provided it can be documented if the patient experienced a DLT within 21 days of C1D1.

Nonevaluable patients may be replaced to ensure that enough patients complete one 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 one cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP/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 LY3076226 has been assessed in nonclinical toxicology studies and the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit initial characterization of the safety profile of LY3076226 in patients. Study procedures and their timing, including collection of blood and urine samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests, including chemistry, hematology, coagulation and urinalysis panels, will be performed. A serum pregnancy test will be administered 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.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JOBA.5 presents a summary of AE and SAE reporting guidelines. Table JOBA.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 4.0.

The National Cancer Institute (NCI)-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. All AEs observed will be graded using CTCAE v 4.0. Any minor version of CTCAE v 4.0 (for example, version 4.0X) 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 NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the CRF. This collection is in addition to verbatim text used to describe the AE.

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

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

Upon documentation of pregnancy, the 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 or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via electronic data entry the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or study drug via electronic data entry.

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

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

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

8.1.2.1. Serious Adverse Events

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

Planned 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 (for example, for the administration of study treatment 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 (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

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

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 IB.

Refer to Attachment 6 for recommendations for reporting SAEs.

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 prescreening and screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the ICF. For patients who do not enroll in the trial (that is, have not received at least one dose of study treatment), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.2.2. On-Study Treatment

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 begins the day after the patient and the investigator agree that the patient will no longer continue study treatment. The duration of the follow-up visit is 28 ± 5 days. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). 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, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

Following the safety assessments, which mark the 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. In this instance, 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.

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, and the SAE will be entered in the Lilly Safety System.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the DCSI in the IB and that the investigator identifies as related to study drug or procedure. The United States 21 Code of Federal Regulations (CFR) 312.32, the European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance 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 guidance.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JOBA.5.

Table JOBA.5. Adverse Event and Serious Adverse Event Reporting Guidelines for Study I7O-MC-JOBA

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (Starts at the signing of the ICF and ends just before the first dose of study drug)	Preexisting conditions All AEs All SAEs regardless of relatedness	x x x	 x
On therapy (Starts at first dose of study drug and ends at last dose of study drug)	All AEs All SAEs regardless of relatedness	x x	 x
Follow-up visit (Visit 801) (Begins the day after the patient and the investigator agree that the patient will no longer continue study treatment. The duration of the follow-up visit is 28 ± 5 days.)	All AEs All SAEs regardless of relatedness	x x	 x
Continued access period	All AEs All SAEs regardless of relatedness	x x	 x
Continued access period follow-up	All AEs All SAEs regardless of relatedness	x x	 x
Subsequent follow-up visits, if necessary for patient monitoring	Ongoing AEs at least possibly related to study drug, or protocol procedures All SAEs related to protocol procedures or study drug	x x	 x
Patient no longer on study	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; ICF = informed consent form; SAEs = serious adverse events.

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). Patients must be supine or semi-recumbent for approximately 5 to 10 minutes before ECG collection and remain supine or semi-recumbent but awake during ECG collection.

During Cycle 1, triplicate ECGs (consecutive replicate ECGs at approximately 1-minute intervals) will be done as specified in the Study Schedule (Attachment 1). Beginning with Cycle 2 and beyond, only a single ECG will be required. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. 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, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee 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 one 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 (for example, demographics and study details) 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/CRS will monitor safety data throughout the course of the study.

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures.

Ophthalmologist may perform additional examinations when visual changes or other ocular symptoms occur, at their discretion as clinically indicated.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. Potential for biliary obstruction should be assessed. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3). If a study patient experiences concurrent elevated ALT >3 × ULN and elevated total bilirubin >2 × ULN, clinical and laboratory monitoring should be initiated by the investigator. If this is determined to be in the absence of biliary obstruction or other causes than can reasonably explain the concurrent elevation, then the patient should be discontinued from LY3076226.

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 AE 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 (Study Schedule) lists the schedule for sample collections in this study.

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

Attachment 4 is the PK, PD, and immunogenicity sampling schedule for this study.

Required and optional sample collection for PD and patient tailoring (exploratory biomarkers) is as follows:

REQUIRED

Required samples to be collected in this study include:

- Parts A, B, and C
  - Whole blood (refer to Section 8.2.4)
  - Exploratory plasma sample (refer to Section 8.2.3)
- Part B only
  - Urine (refer to Section 8.2.3)
  - CK18 sample (refer to Section 8.2.2)
  - Pretreatment tissue biopsy (refer to Sections 8.2.2 and 8.2.3)

However, for patients who have disease recurrence/metastasis at body sites that are technically challenging for biopsy or who have available tissue from a prior regimen posttreatment biopsy and have not received intervening therapy, the investigator and sponsor may agree to omit the pretreatment biopsy.

- Part C only
  - CK18 sample (refer to Section 8.2.2)
  - Pretreatment tissue biopsy (refer to Sections 8.2.2 and 8.2.3)

However, for patients who have disease recurrence/metastasis at body sites that are technically challenging for biopsy or who have available tissue from a prior regimen posttreatment biopsy and have not received intervening therapy, the investigator and sponsor may agree to omit the pretreatment biopsy.

If the FGFR3 alteration status is not known for a patient who is a potential candidate for participating in Parts B or C and an archived tissue sample is not available, the patient may have a biopsy collected locally to determine the FGFR3 alteration status for eligibility. If the patient qualifies for the study, a portion of this biopsy sample may be used for the required centrally collected pretreatment biopsy for PD and exploratory biomarker evaluation.

OPTIONAL

Optional samples for biomarker research that should be collected from patients in the study, where possible, include:

- Parts A, B, and C
  - Archived tumor tissue (refer to Section 8.2.3)

If a patient has archived tumor tissue previously taken to evaluate the patient's disease, a small amount of this tissue will be requested, if available, for biomarker research.

- Parts B and C only
  - Posttreatment tissue biopsy (refer to Section 8.2.2)

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

Standard laboratory tests, including hematology and urinalysis panels, will be performed and analyzed by a local laboratory. Chemistry panels will be performed and analyzed centrally. Enrollment or dose adjustment decisions may be based upon chemistry results performed at a local laboratory; however, a sample must be sent to the central laboratory. These central chemistry laboratory results will be used for subsequent safety analyses. In the event of minor discrepancies between local and central laboratory results, the investigator may use the local results for treatment decisions, and the central laboratory results will remain part of the safety database. Discrepancies between local and central results that may have an impact on treatment decisions will not be considered protocol violations.

Investigators must document their review of each laboratory safety report.

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

8.2.1. Samples for Pharmacokinetics

At the visits and times specified in Attachment 4, venous blood samples of approximately 6 mL each will be collected to determine the plasma concentrations of conjugated LY3076226, total LY3076226 IgG, and the metabolites DM4 and DM4-Me.

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and Lilly. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

These samples will be analyzed at laboratories designated by the sponsor. Plasma concentrations of conjugated LY3076226 and total LY3076226 IgG will be assayed using validated ELISA methods. Plasma concentrations of DM4 and DM4-Me will be assayed using a validated LC-MS assay.

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

The remaining plasma from the samples collected for PK may be pooled and used for exploratory metabolism work as deemed appropriate.

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

8.2.2. Samples for Pharmacodynamics

Samples will be taken to measure cell cycle arrest and apoptosis. Tissue biopsy may be taken by core needle biopsy and/or surgical biopsy (pretreatment and posttreatment fresh tumor biopsies in Parts B and C). 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.

Bioanalytical tissue samples collected to measure Ki-67, pHH3, and caspase 3 will be identified by the patient number (coded) and retained for a maximum of 15 years or until testing is complete following last patient visit for the study at a facility selected by the sponsor.

In Parts B and C, bioanalytical blood samples will also be collected at visits and times indicated in Attachment 1 in order to measure CK18 levels. These blood samples will be identified by the patient number (coded) and retained for a maximum of 5 years or until testing is complete following last patient visit for the study at a facility selected by the sponsor.

8.2.3. Samples for Exploratory Biomarkers

Exploratory analysis may be conducted using blood (including ethylenediaminetetraacetic acid [EDTA] plasma), urine, and tumor tissue to explore potential biomarkers related to LY3076226 mechanism of action, the FGFR3 pathway, DM4 mechanism of action, and the cancer pathobiology, to better understand relationship with clinical outcomes. Tumor tissue samples may be analyzed to explore potential tumor gene signature(s) associated with response or resistance to LY3076226 therapy. These studies may be analyzed at a laboratory designated by the sponsor and may include IHC of proteins, fluorescence in situ hybridization (FISH) for copy number amplifications, ribonucleic acid (RNA) gene-expression profiling, and/or genetic analyses of the tumor specimen deoxyribonucleic acid (DNA). Such analyses may employ targeted or high-throughput sequencing approaches.

8.2.4. Samples for Pharmacogenetic Research

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis. In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to study drug. 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 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.

8.2.5. Samples for Immunogenicity Research

At the visits and times specified in Attachment 1, blood samples for immunogenicity testing will be collected to determine antibody production against study drug. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADA) in the presence of study drug. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of study drug.

In addition to planned sampling for immunogenicity testing, if at any time a patient experiences an IRR to study drug, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of IRRs.

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

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)
- For lymphoma patients only, positron emission tomography (PET)/CT is permitted if appropriate for standard of care (Cheson et al. 2014)

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

- Tumor measurement by RECIST 1.1 (Eisenhauer et al. 2009), international uniform response criteria for multiple myeloma (Rajkumar et al. 2011), or response criteria for lymphomas (Cheson et al. 2014).
- Evaluation of tumor markers, if indicated.
- Evaluation of performance status (refer to the ECOG scale, Attachment 7).

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. Every attempt should be made to adhere to the sample collection times in the first 3 cycles. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the CRF or laboratory requisition form. However, delays of ±1 day due to holidays, inclement weather, or other justifiable events will be permitted and will not be counted as a protocol deviation.

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

9. Data Management Methods

9.1. Data Quality Assurance

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

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

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

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

9.2. Data Capture Systems

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.

9.2.1. Case Report Form

Case report form data will be encoded and stored in a clinical trial database.

For data handled by a data management third-party organization (TPO), CRF 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 SAS for Drug Development (SDD) system, using Lilly Integration Broker file transfer processes.

For data handled by the sponsor internally, CRF 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 laboratory system (GLS).

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly GLS.

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

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

Up to approximately 65 patients may be enrolled in this multicenter, nonrandomized, open-label Phase 1 dose-escalation study of LY3076226. Patients will be enrolled into cohorts sequentially without randomization to dose. The Bayesian model-based, toxicity-band method will be followed to assist dose escalation. The toxicity-band method will provide quantitative guidance on the determination of the dose level for the next cohort based on the observed DLT data. Compared with the traditional 3+3 method, the toxicity-band method provides a lower underdosing rate and a higher MTD selection rate, with a well-controlled overdosing rate at a prespecified criterion. Refer to Attachment 10 for more details. The sample size for Part A will primarily be determined by the incidence of DLTs prior to establishing the MTD in Part A. The anticipated sample size for Part A ranges from approximately 20 to 35 patients. In each of Parts B and C, up to approximately 15 patients who have known alterations of FGFR3 will be enrolled. The sample sizes of Parts B and C have been selected to allow adequate assessment of safety at the recommended dose and to characterize the biomarker assay.

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

The analyses for this study will be descriptive; no p-values will be calculated. Data analyses will be provided by cohorts and for all study patients combined whenever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, standard error, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, percentages, and their standard errors. Missing data will not be imputed.

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.

Exploratory analyses of the data not described in Sections 10.2 through 10.9 will be conducted as deemed appropriate.

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.

Patients are expected to have tumor assessments after receiving 3 cycles of treatment. Patients completing the study are defined as patients who received tumor assessments after 3 cycles. Patient disposition will be summarized for patients not completing 3 cycles.

10.3. Patient Characteristics

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

- Patient demographics including age, sex, screening height and weight, and screening body mass index (BMI)
- Baseline disease characteristics
- Prior disease-related therapies
- Concomitant medications

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least one dose of LY3076226 will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE v 4.0.

Safety analyses will include summaries of the following:

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

10.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of the study drug and have had samples collected.

Pharmacokinetic parameter estimates for conjugated LY3076226 and total LY3076226 IgG and metabolites DM4 and DM4-Me will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max} and AUC of conjugated LY3076226 and total LY3076226 IgG and metabolites DM4 and DM4-Me. Other noncompartmental parameters, such as $t_{1/2}$, CL, and volume of distribution (V) may be reported.

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

Pharmacokinetic parameter estimates will be evaluated to delineate effects of dose proportionality using methods described previously (Smith et al. 2000). 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

Pharmacodynamic data will be summarized by dose, drug concentrations, and time from dose. Potential PD markers-versus-time data will be presented graphically for each patient and summarized by dose. Absolute and/or percentage change from baseline may be evaluated. Data may be log-transformed prior to summarizing, if necessary. The interpatient and intrapatient variability of the PD markers may also be assessed where appropriate.

If the data allow, a PK/PD analysis may also be performed, wherein PD data from all patients would be analyzed using linear and/or nonlinear fixed and mixed effects models as appropriate.

10.7. Immunogenicity Analyses

Immunogenicity data will be summarized by dose, drug concentrations, and time from dose.

If the data allow, immunogenicity data from all patients may also be analyzed using linear and/or nonlinear fixed and mixed effects models as appropriate.

10.8. Efficacy

The study is not designed to make an efficacy assessment. However, any tumor response data will be tabulated. Particularly, the antitumor effect will be summarized by the overall response rate (ORR). A patient is considered to have a tumor response if they achieve a confirmed CR or PR according to RECIST 1.1 (Eisenhauer et al. 2009) or lymphoma criteria (Cheson et al. 2014); or a confirmed stringent complete response (sCR), CR, very good partial response (VGPR), or PR according to multiple myeloma (IMWG) criteria (Rajkumar et al. 2011). The ORR will be estimated by dividing the total number of confirmed complete and partial responders (CR+PR) by the total number of enrolled patients. A 90% exact CI will be constructed to determine the level of precision of the tumor response rate. Time-to-event variables will also be tabulated. For PFS and duration of response, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves, medians, and survival rates if applicable.

10.9. Tailoring Biomarker

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 LY3076226. Exploratory analysis may be conducted using blood, urine, and tumor tissue to explore potential biomarkers related to LY3076226 mechanism of action, the FGFR3 pathway, DM4 mechanism of action, and the cancer pathobiology, to better understand relationship with clinical outcomes. Tumor tissue samples may be analyzed to explore potential tumor gene signature(s) associated with response or resistance to LY3076226 therapy.

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

Once the LY3076226 MTD is defined for Part A, an interim analysis will be performed prior to opening Parts B and C.

At the end of Parts B and C, an analysis may be conducted to review available safety, PK, and efficacy data once all evaluable patients have either completed 3 cycles of study treatment or discontinued from the study treatment.

Because this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until the MTD is determined for Part A. The purpose of these cohort-by-cohort reviews is to evaluate the safety data and any available PK data at each dose level and determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

In Parts B and C, if a DLT-equivalent toxicity occurs in one third or more of patients during Cycle 1 (with a minimum of 6 patients enrolled), a data review will be performed to determine whether to continue at the current LY3076226 dose or whether the dose of LY3076226 should be reduced. Refer to Section 7.2.3 for more details.

If an unplanned interim analysis is deemed necessary, the sponsor will determine if it is necessary to amend the protocol.

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.

There may be 2 ICFs used in this study: a prescreening ICF and a study ICF. The prescreening ICF will provide relevant information and document that the patient is satisfied with his or her understanding of the collection and testing of the tumor sample for FGFR3 alterations, for potential study candidates when FGFR3 alteration status is unknown.

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

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

As used 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 site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

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

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

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) the ICH GCP guideline [E6]

3) applicable laws and regulations.

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

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

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

11.3.1. Investigator Information

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

11.3.2. Protocol Signatures

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

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

11.3.3. Final Report Signature

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

The investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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

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Attachment 1. Protocol JOBA Study Schedule

Baseline Assessments

Relative day to Cycle 1, Day 1	Pre-screening	Screening ≤28	Screening ≤14	Screening ≤7	Comments
Informed consent	X		X		ICF signed (prior to performance of any protocol-specific tests/procedures). Prescreening consent for Parts B and C only, for patients with unknown FGFR3 alteration status.
Collection of tumor tissue sample for local FGFR3 alteration testing for eligibility (Parts B and C only)	X				Archived tissue or biopsy if archived tissue is not available. If prescreening biopsy is performed and results are positive and patient signs study ICF, a portion of this biopsy may be used for pretreatment biopsy for the study.
Radiological tumor assessment according to RECIST 1.1			X		Radiological assessments obtained previously (≤28 d prior to C1D1) as part of routine clinical care may be used as the baseline assessment. Appropriate tumor assessment criteria should be used for patients with multiple myeloma (IMWG [Rajkumar et al. 2011; refer to Attachment 5]) or lymphoma (Cheson et al. 2014).
Medical history			X		Including alcohol/tobacco use and other relevant habits assessments.
Physical examination			X		Including height and weight.
Standard ophthalmic examination			X		Performed by an ophthalmologist.
Vital signs			X		Including temperature, BP, PR, RR.
ECOG performance status			X		
Central ECG			X		One set of triplicate ECGs.
Local hematology			X		Refer to Attachment 2.
Central serum chemistry			X		Refer to Attachment 2. Enrollment or dose adjustment decisions may be based upon chemistry results performed at a local laboratory; however, a sample must be sent to the central laboratory.
Coagulation (local)			X		Refer to Attachment 2.
Local urinalysis			X		
Tumor measurement (palpable or visible)			X		
CTCAE v 4.0 grading (preexisting conditions)			X		Refer to Section 8.1.2.

Baseline Assessments (continued)

Relative day to Cycle 1, Day 1	Pre-screening	Screening ≤28	Screening ≤14	Screening ≤7	Comments
Concomitant medications			X		
Local tumor markers			X		If applicable.
Central archived tissue sample			X		Collected only if patient has met inclusion/exclusion criteria.
Local pregnancy test, serum				X	For women of childbearing potential.
Central pretreatment tumor tissue biopsy (Parts B and C only)			X		Collected only if patient has met inclusion/exclusion criteria. If the patient had prescreening biopsy to assess FGFR3 alteration status, a portion of the prescreening biopsy may be used for pretreatment biopsy for the study.

Abbreviations: BP = blood pressure; C = cycle; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FGFR3 = fibroblast growth factor receptor 3; ICF = informed consent form; IMWG = International Myeloma Working Group; PR = pulse rate; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; RR = respiration rate.

During Study-Treatment Assessments

	Cycle 1					Cycle 2			Cycle 3					Cycles 4-n	Comments
Relative day within a cycle	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	Cycle duration = 21 d
LY3076226	X					X			X					X	
Physical examination	X			X	X	X	X	X	X			X	X	X	Performed on Day 1 of each cycle. Physical examination can be done ≤24 h prior to Day 1 of each cycle or ±24 h for other days.
Ophthalmic examination													X		Performed by an ophthalmologist anytime from Days 15-21. Additional monitoring may occur if clinically indicated at the discretion of the ophthalmologist.
Weight	X					X			X					X	
Vital signs	X			X	X	X	X	X	X			X	X	X	Temperature, BP, PR, RR. At a minimum, vital signs should be obtained prior to infusion, during infusion, and at 1 h following end of infusion. Refer to Section 7.2.5.
Central ECG	X					X			X						In Cycle 1, triplicate ECGs collected predose and at end of infusion. In Cycles 2 and 3, single ECG collected predose and at end of infusion. Refer to Attachment 4.
Local hematology	X			X	X	X	X	X	X			X	X	X	Can be drawn ≤24 h prior to Day 1 or ±24 h for other days.

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During Study-Treatment Assessments (continued)

	Cycle 1					Cycle 2			Cycle 3					Cycles 4-n	Comments
Relative day within a cycle	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	Cycle duration = 21 d
Central serum chemistry	X			X	X	X	X	X	X			X	X	X	Can be drawn ≤24 h prior to Day 1 of a cycle or ±24 h for other days. Enrollment or dose adjustment decisions may be based upon chemistry results performed at a local laboratory; however, a sample must be sent to the central laboratory.
Local urinalysis	X					X			X					X	Can be collected ≤24 h prior to Day 1 of a cycle.
CTCAE v 4.0 grading			X				X				X			X	Throughout study as needed. Refer to Section 8.1.2 for reporting guidelines. Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Concomitant medications			X				X				X			X	Throughout study as needed.
ECOG performance status	X					X			X					X	
Central PK sampling	X	X	X	X	X	X			X	X	X	X	X	X	Refer to Attachment 4 for exact timing.

- Table is continued on the next page. -

During Study-Treatment Assessments (continued)

	Cycle 1					Cycle 2			Cycle 3					Cycles 4-n	Comments
Relative day within a cycle	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	Cycle duration = 21 d
Tumor measurement (palpable or visible)	X					X			X					X	
Radiological tumor assessment													X	X	Use RECIST 1.1 (Eisenhauer et al. 2009), multiple myeloma criteria (IMWG [Rajkumar et al. 2011; refer to Attachment 5]), or lymphoma criteria (Cheson et al. 2014). The same method of imaging used at baseline should be used for each subsequent assessment. Imaging should be performed during the last wk of every third cycle; that is, Cycles 3, 6, 9, 12, and so on). May be omitted if patient has clear signs of progressive disease. In addition, any patient whose disease has not progressed by 1 y after entering the trial may be assessed every 18 wk.

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During Study-Treatment Assessments (continued)

	Cycle 1					Cycle 2			Cycle 3					Cycles 4-n	Comments
Relative day within a cycle	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	Cycle duration = 21 d
Local tumor markers						X			X					X	If applicable to patient's tumor type. May be drawn up to 3 d prior to the planned assessment.
Posttreatment tumor biopsy (Parts B and C only)			X												Optional. Posttreatment biopsy may be performed on C1D4 or C1D5 to allow flexibility for scheduling.
Central urine sample for biomarkers (Part B only)	X								X						Collect preinfusion on C1D1. Refer to Attachment 4 for exact timing.
Central CK18	X	X	X	X	X	X			X	X	X	X	X	X	Parts B and C only. Refer to Attachment 4 for exact timing.
Whole blood for central DNA storage	X														Collect once. Sample can be collected at any time if not collected on C1D1.
Central exploratory plasma sample	X	X	X	X	X	X			X	X	X	X	X	X	Refer to Attachment 4 for exact timing.

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During Study-Treatment Assessments (continued)

	Cycle 1					Cycle 2			Cycle 3					Cycles 4-n	Comments
Relative day within a cycle	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	Cycle duration = 21 d
Central immunogenicity sample	X					X			X					X	Refer to Attachment 4 for exact timing. Note that after Cycle 3, sample will be collected every other cycle (for example, C5, C7, etc). In addition to the scheduled samples, if a patient should have an IRR to LY3076226, all attempts should be made to obtain an immunogenicity sample as close to the onset of the event as possible, at the resolution of the event, and 30 d following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis.

Abbreviations: BP = blood pressure; C = cycle (as in C#D#); CK18 = cytokeratin 18; CTCAE = Common Terminology Criteria for Adverse Events; D = day (as in C#D#); DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IMWG = International Myeloma Working Group; IRR = infusion-related reaction; PK = pharmacokinetic(s); PR = pulse rate; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; RR= respiration rate; SAE = serious adverse event.

Posttreatment Discontinuation Follow-Up Assessments

	Study Period	Short-Term Follow-Up	
	Visit	801	The follow-up visit begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
	Duration	28±5 d	
Procedure			**Comments**
Weight		X	
Vital signs		X	Including temperature, BP, PR, RR.
ECOG performance status		X	
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		X	Use RECIST 1.1 (Eisenhauer et al. 2009), multiple myeloma criteria (IMWG [Rajkumar et al. 2011; refer to Attachment 5]), or lymphoma criteria (Cheson et al. 2014). 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.
CTCAE v 4.0 grading		X	Refer to Section 8.1.2. Report all AEs during the Short-Term Follow-Up period. After Visit 801, only study protocol- or drug-related events are reported. If a patient has an ongoing AE or SAE at least possibly related to LY3076226, 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.
Concomitant medication notation		X	

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Posttreatment Discontinuation Follow-Up Assessments (continued)

	Cycle	Short-Term Follow-Up	
	Visit	801	The follow-up visit begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
	Duration	28±5 d	
Procedure			**Comments**
Local hematology		X	
Central serum chemistry		X	
Central ECG		X	Single ECG.
Local urinalysis		X	
Local tumor markers		X	If applicable to tumor type of the patient.
Central immunogenicity sample		X	In addition to the scheduled sample, if a patient should have an IRR to LY3076226, all attempts should be made to obtain an immunogenicity sample as close to the onset of the event as possible, at the resolution of the event, and 30 d 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. Refer to Attachment 4 for exact timing.
Central PK sample		X	Refer to Attachment 4 for exact timing.
Central urine sample for biomarkers (Part B only)		X	
Central exploratory plasma sample		X	

Abbreviations: AE = adverse event; BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IMWG = International Myeloma Working Group; IRR = infusion-related reaction; PK = pharmacokinetic(s); PR = pulse rate; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; RR = respiration rate; SAE = serious adverse event.
Note: No follow-up procedures will be performed for patients who withdraw informed consent unless he or she has explicitly provided permission and consent.

Continued Access Schedule

Study Period	Continued Access Treatment Period	Continued Access Follow-Up	
Visit	**501-5XX**	**901**	**Comments**
Relative day within a cycle	**1**		
Procedure			
Weight	X		
LY3076226	X		
CTCAE v 4.0 grading	X	X	Refer to Section 8.1.2. In the event that SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE.
Central immunogenicity sample	If applicable		During the continued access period, if a patient should have an IRR to LY3076226, 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 d following the event. If a patient requires subsequent follow-ups (for example, 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.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; PK = pharmacokinetic(s); SAE = serious adverse event.

Attachment 2. Protocol JOBA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry**[b]:
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Magnesium
Leukocytes (WBC)	Potassium
Neutrophils	Total bilirubin
Lymphocytes	Direct bilirubin
Monocytes	Alkaline phosphatase
Eosinophils	Alanine aminotransferase
Basophils	Aspartate aminotransferase
Platelets	Blood urea nitrogen
	Creatinine
Coagulation[a]**:**	Creatinine clearance, calculated[c]
Prothrombin time (PT or INR)	Uric acid
Partial thromboplastin time (PTT or aPTT)	Calcium
	Ionized calcium
	Glucose, random
Urinalysis[a]**:**	Albumin
Specific gravity	Total protein
pH	Chloride
Protein	
Glucose	**Serum Pregnancy Test** (females only)[a]
Ketones	
Blood	
Urine leukocyte esterase	

Abbreviations: aPTT = activated partial thromboplastin time; PT/INR = international normalized ratio of prothrombin time; RBC = red blood cells; WBC = white blood cells.

a Local or investigator-designated laboratory.

b Lilly-designated (central) laboratory. Enrollment or dose adjustment decisions may be based upon chemistry results performed at a local laboratory; however, a sample must be sent to the central laboratory.

c Cockcroft and Gault formula will be used for calculated creatinine clearance. See Attachment 8.

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

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

Hepatic Monitoring Tests

Hepatic hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

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

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

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

Attachment 4. Protocol JOBA Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule

Visit (Cycle)/Day	Sampling Time (relative to LY3076226 dosing)	Type of Sample or Assessment						
		PK: LY3076226 and metabolites	PD: CK18 (Parts B and C)	Exploratory plasma	PD: Tumor tissue biopsy (Parts B and C)	Urine for biomarkers (Part B only)	ECG	IG
V0/≤28 d	≤28 d prior to the first dose				x		x	
C1/Day 1	Prior to infusion	x	x	x		x	x	x
	Within 5 min post infusion	x					x[a]	
	1 ± 0.1 h post infusion	x						
	3 ± 0.25 h post infusion	x						
	6 ± 0.25 h post infusion	x						
C1/Day 2	24 ± 1 h post infusion	x	x	x				
C1/Day 4	72 ± 1 h post infusion	x	x	x	x[b]			
C1/Day 8	Anytime	x	x	x				
C1/Day 15	Anytime	x	x	x				
C2/Day 1	Within 15 min prior to infusion	x	x	x			x[c]	x
	Within 5 min post infusion	x					x[a]	
C3/Day 1	Within 15 min prior to infusion	x	x	x		x[d]	x[c]	x
	Within 5 min post infusion	x					x[a]	
	1 ± 0.1 h post infusion	x						
	3 ± 0.25 h post infusion	x						
	6 ± 0.25 h post infusion	x						
C3/Day 2	24 ± 1 h post infusion	x	x	x				
C3/Day 4	72 ± 1 h post infusion	x	x	x				
C3/Day 8	Anytime	x	x	x				
C3/Day 15	Anytime	x	x	x				
C4/Day 1	Within 15 min prior to infusion	x	x	x				
	Within 5 min post infusion	x						

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Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule (continued)

Visit (Cycle)/Day	Sampling Time (relative to LY3076226 dosing)	Type of Sample or Assessment						
		PK: LY3076226 and metabolites	PD: CK18 (Parts B and C)	Exploratory plasma	PD: Tumor tissue biopsy (Parts B and C)	Urine for biomarkers (Part B only)	ECG	IG
C5 and then every other cycle/Day 1	Within 15 min prior to infusion	X						X
	Within 5 min post infusion	X						
Short-Term Follow-Up (V801)	28 ± 5 d after treatment discontinuation decision	X		X		X		X

Abbreviations: C = cycle (as in C#D#); CK18 = cytokeratin 18; D = day (as in C#D#); ECG = electrocardiogram; IG = immunogenicity; PD = pharmacodynamic(s); PK = pharmacokinetic(s); V = visit.

[a] Post-infusion ECG can be done within 15 minutes after end of infusion.

[b] Posttreatment biopsy may be performed on C1D4 or C1D5 to allow flexibility for scheduling.

[c] Predose ECG can be obtained prior to predose blood samples.

[d] Predose urine biomarker sample (Part B only) can be obtained prior to predose blood samples.

Attachment 5. Protocol JOBA Multiple Myeloma Tumor Assessment

For patients with multiple myeloma enrolled to this trial, the International Myeloma Working Group (IMWG) uniform response criteria (Rajkumar et al. 2011) will be used for tumor assessment. Each patient with multiple myeloma will be assessed at baseline via serum and urine protein electrophoresis (SPEP or UPEP, respectively), serum and urine immunofixation electrophoresis (SIFE or UIFE, respectively), and serum free light chains (SFLC). Patients will have baseline imaging of plasmacytomas and, after eligibility criteria have been met, patients should have a skeletal survey and a bone marrow examination. Refer to the following tables for assessments and timing and a summary of IMWG response criteria.

Assessments and Timing for Patients with Multiple Myeloma

Myeloma Assessment	Baseline	C1 - CX	Short-Term Follow-Up (Visit 801)	Comments
Local quantitative immunoglobulins	X	X	X	Baseline performed ≤28 d prior to C1D1. On study: Performed on D1 of each cycle, prior to treatment. Short-term follow-up (Visit 801): May be omitted if progressive disease is previously documented or if there are clear signs of clinical progression.
Local SPEP/IFE	X	X	X	Baseline performed ≤28 d prior to C1D1. On study: Performed on D1 of each cycle, prior to treatment. Short-term follow-up (Visit 801): May be omitted if progressive disease is previously documented or if there are clear signs of clinical progression.
Local 24-h urine for UPEP/IFE	X	X	X	Baseline performed ≤28 d prior to C1D1. On study: Performed prior to D1 of each cycle. The urine collection should be completed as close to the visit as possible. Short-term follow-up (Visit 801): May be omitted if progressive disease is previously documented or if there are clear signs of clinical progression.
Local serum free light chains	X	X	X	Baseline performed ≤28 d prior to C1D1. On study: Performed on D1 of each cycle, prior to treatment. Short-term follow-up (Visit 801): May be omitted if progressive disease is previously documented or if there are clear signs of clinical progression.
Local bone marrow aspirate	X			A bone marrow aspirate is required prior to start of study therapy and to confirm CR, sCR, immunophenotypic CR, or molecular CR.
Skeletal survey	X			A skeletal survey should include skull, spine, pelvis, bilateral femur, and bilateral humerus. Skeletal survey should be repeated as clinically indicated or at least every 12 mo.
Plasmacytoma measurement	X	X		If a plasmacytoma is present, CT or MRI should be used to obtain bi-dimensional measurements at baseline, and the test used at baseline should be repeated to assess response. If a measureable plasmacytoma is present at baseline, plasmacytoma needs to be evaluated (perform a CT scan or MRI) every time that response is assessed.

Abbreviations: C# = cycle; CR = complete response; CT = computed tomography; D# = day; IFE = immunofixation electrophoresis (serum/urine); MRI = magnetic resonance imaging; sCR = stringent complete response; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

International Myeloma Working Group Uniform Response Criteria

Response	Criteria
CR[a,b,c,d]	Negative immunofixation of serum and urine AND disappearance of any soft tissue plasmacytomas AND <5% plasma cells in bone marrow Clarification: In patients in whom the only measurable disease is by serum FLC levels, normal FLC ratio of 0.26-1.65 is required, in addition to CR criteria.
sCR[a,b,c,d]	CR (as defined above) PLUS normal FLC ratio AND absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry
Immunophenotypic CR	sCR (as defined above) PLUS absence of phenotypically aberrant plasma cells (clonal) in bone marrow with a minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with >4 colors)
Molecular CR	CR (as defined above) PLUS negative ASO-PCR, sensitivity 10^{-5}
VGPR[a,b,c,d]	Serum and urine M-component detectable by immunofixation but not on electrophoresis OR ≥90% reduction in serum M-component plus urine M-component <100 mg/24 h Clarification: In patients in whom the only measurable disease is by serum FLC levels, a >90% decrease in the difference between involved and uninvolved FLC levels is required, in addition to VGPR criteria.
PR[a,b,c]	≥50% reduction of serum M-protein AND reduction in 24-h urinary M-protein by ≥90% or to <200 mg/24 h If serum and urine M-protein are not measurable, a decrease ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein and serum FLC assay are not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30%. In addition to the above criteria, if present at baseline, ≥50% reduction in size of soft tissue plasmacytomas is also required.
MR for relapsed refractory myeloma only[e]	≥25% but ≤49% reduction of serum M-protein AND reduction in 24-h urine M-protein by 50%-89% In addition to the above criteria, if present at baseline, 25%-49% reduction in size of soft tissue plasmacytomas is also required. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
SD[b,c,d]	Not meeting criteria for CR, VGPR, PR, or PD

- Table is continued on the next page. -

International Myeloma Working Group Uniform Response Criteria (continued)

Response	Criteria
PD[a,d]	Increase of 25% from lowest response value in any of following: • serum M-component (absolute increase must be ≥0.5 g/dL; serum M-component increases ≥1 g/dL are sufficient to define relapse if starting M component ≥5 g/dL) • urine M-component (absolute increase must be ≥200 mg/24 h) • only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC level: bone marrow plasma cell percentage (absolute percentage must be ≥10%) Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder Clarification: Bone marrow criteria for PD are to be used only in patients without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia, and the "lowest response value" does not need to be a confirmed value.

Abbreviations: ASO-PCR = allele-specific oligonucleotide polymerase chain reaction; CR = complete response; EBMT = European Group for Blood and Marrow Transplantation; FLC = free light chain; M= monoclonal; MR = minimal response; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.

[a] All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy.

[b] CR, sCR, VGPR, PR, and SD also require no known evidence of progressive or new bone lesions if radiographic studies were performed.

[c] VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. CR, sCR, VGPR, PR, and SD also require no known evidence of progressive or new bone lesions if radiographic studies were performed.

[d] Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

[e] Adopted from the EBMT criteria (Bladé et al. 1998).

Source: Rajkumar et al. 2011

Attachment 6. Protocol JOBA Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

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

Patient Demographics

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

Study Identification

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

Study Drug

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

Adverse Event

- description, date of onset, severity, treatment (including 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, investigator assessment of relationship to study drug and protocol procedures.

Attachment 7. Protocol JOBA ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Source: Oken et al. 1982.

Attachment 8. Protocol JOBA Creatinine Clearance Formula

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

Attachment 9. Protocol JOBA RECIST Criteria 1.1

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

Measurability of Tumor at Baseline

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

Measurable

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray

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

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone lesions:

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

Cystic lesions:

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

Lesions with Prior Local Treatment:

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

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

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

Non-target Lesions

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

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

Specifications by Methods of Measurement

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

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

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

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

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

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

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

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

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

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

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

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

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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

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

Evaluation of Non-target Lesions

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

Non-CR/ non-PD: Persistence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions is also considered progression.

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

Evaluation of Best Overall Response

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

Time Point Response

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

Table 1. Time Point Response: Patients with Target (± non-target) Disease

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

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; PD = progressive disease; NE = not evaluable.

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

Table 2. Time Point Response: Patients with Non-Target Disease Only

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

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; SD = stable disease.

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

Frequency of Tumor Re-Evaluation

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

Confirmatory Measurement/Duration of Response

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

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

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

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

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

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

Independent Review of Response and Progression

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

Attachment 10. Protocol JOBA Toxicity-Band Method for Phase 1 Dose Escalation

The need to minimize the number of patients treated below the biological active dose and the understanding of LY3076226 from earlier nonclinical and clinical studies supports a more efficient dose-escalation design for Study JOBA. Therefore, the Bayesian model-based method is used in this trial to determine the next dose level, based on the predicted probabilities of DLT rates. The exact dose-escalation increment will be determined by the investigators and Lilly CRP/CRS and may be different from the model recommendation. This section introduces the background of a model-based dose-escalation method and toxicity-band design (Neuenschwander et al. 2008) and describes the key elements for this trial. Simulation results from the toxicity-band design are presented. These results are also compared with that from the simulation of traditional 3+3 design to demonstrate the benefit of implementing a toxicity-band design in this trial. Fixed and Adaptive Clinical Trial Simulator (FACTS) software version 3.5 is used for all the simulations.

Introduction to Continual Reassessment Method (CRM) Approaches

The continual reassessment method (CRM; O'Quigley et al. 1990) is the first Bayesian model-based approach developed for dose-escalation studies. Compared to the traditional 3+3 design that only used current dose-level DLT data to estimate the MTD, CRM utilizes prior dose toxicity information and all available DLT data to effectively estimate the MTD. To improve the operating characteristics of CRM, Goodman et al. (1995), among others, have proposed modified CRM (MCRM) procedures to make the model-based designs more acceptable in practice. The major modifications include:

- Always start at the lowest dose level.
- Limit the escalation increment.
- Escalate by cohorts rather than single patients.

Babb et al. (1998) proposed the escalation-with-overdose-control method (EWOC) that directly controls the probability of overdosing during dose escalation. EWOC is also a CRM-type method. During the escalation, EWOC selects the next dose such that the predicted probability that the new dose exceeds the MTD is equal to a prespecified feasibility bound α=0.25. The connection between CRM and EWOC is that CRM typically uses the middle (mean or median) of the MTD's posterior distribution as the next recommended dose, whereas EWOC uses the 25th percentile. Therefore, EWOC is a more conservative method than the original CRM method.

Toxicity-Band Design

Neuenschwander et al. (2008) extended the concept of EWOC (Babb et al. 1998) and proposed considering the uncertainty of the posterior distributions and using interval estimates to make the dose recommendation, herein referred to as the toxicity-band design.

The Model

A 2-parameter logistic model is used to model the relationship between dose and probability of a DLT:

$$\text{logit}\{p(d)\} = \alpha + \beta \log\left(\frac{d}{d^*}\right), \quad \beta > 0. \quad (1.1)$$

In the model, d is the true dose and $p(d)$ is the probability of a DLT at dose d. d^* is the reference dose, such that α is interpreted as the log-odds of a DLT at d^*.

Toxicity Band

The probability of a DLT is categorized to 4 bands:

- Underdosing: $p(d)$ in (0, 0.20]
- Targeted toxicity: $p(d)$ in (0.20, 0.33]
- Excessive toxicity: $p(d)$ in (0.33, 0.60]
- Unacceptable toxicity: $p(d)$ in (0.60, 1.00]

Overdosing is defined as $p(d) > 0.33$.

Dose Recommendation

During the escalation, after each cohort of patients, the following will be done:

1. Calculate the posterior probabilities of the 4 toxicity bands for each dose.
2. Exclude the doses such that the posterior probabilities of overdosing are larger than 0.25 (overdosing control criteria). The remaining doses are the ones that satisfy the overdose control criteria.
3. Among the remaining doses, the dose with the highest posterior probability in the targeted toxicity band will be the model recommendation of the next dose.

The data will be evaluated on an ongoing basis until the MTD is determined. Once the MTD has been identified, a discussion between the sponsor and investigators may occur in order to treat additional patients at intermediate doses below the MTD.

Dose Range and Reference Dose

It is assumed that the starting dose level for the toxicity-band method is 1.6 kg/mg. Based on the preclinical data, the highest dose level that will be explored in this study is 5 mg/kg and the reference dose in model (1.1) is chosen as $\mathrm{d}^* = 5$ mg/kg.

The Prior Distribution on Model Parameters

A quantile-based uninformative prior (Neuenschwander et al. 2008) is used to derive a bivariate-normal prior on (α, logβ). Based on preclinical experience of LY3076226, the median probability of DLT for the dose levels from 1.6 mg/kg to 5 mg/kg was determined as in Table 1 of this attachment. Any intermediate dose level within the starting doses to 5 mg/kg can be explored.

Table 1. Prior Median Probability of DLT at Each Dose Level

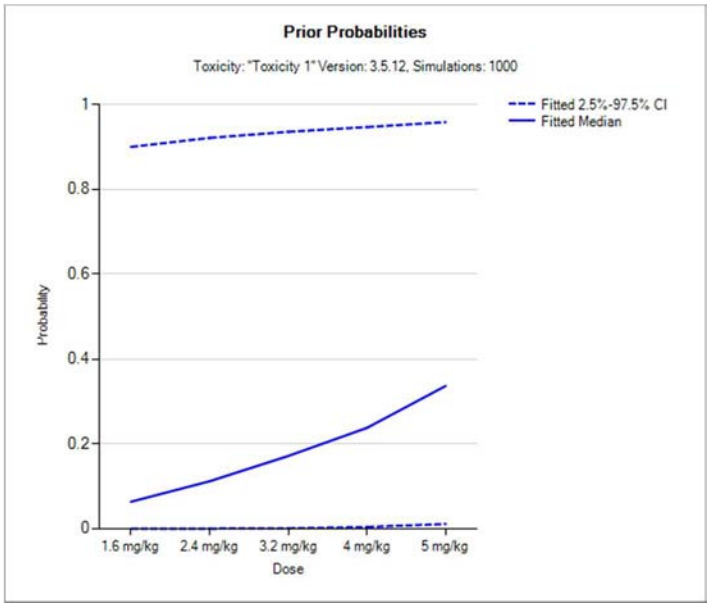
Dose (mg/kg)	Median Probability of DLT
1.6	0.075
2.4	0.125
3.2	0.175
4	0.225
5	0.35

Abbreviation: DLT = dose-limiting toxicity.

For each dose, the minimally informative unimodal Beta distribution (a,b) is derived as the prior distribution for the probability of DLT, so that the operating characteristics of the model are robust to the selected prior distribution of DLT:

- For median probability of DLT <0.5, b=1 and a(<1) are tuned to match the median.
- For median probability of DLT >0.5, a=1 and b(<1) are tuned to match the median.

Figure 1 shows the median and the 95% CI of the prior distribution of the DLT rate at each dose level.



Abbreviations: CI = confidence interval; DLT = dose-limiting toxicity.

Figure 1. The prior distribution of DLT rate at each dose level.

A bivariate normal distribution was derived on (α, logβ) that stochastically gives the best fit to the 2.5%, 50%, and 97.5% quantiles of the prior probability of DLT at each dose. The parameters (α, logβ) have a bivariate normal distribution with mean=(-0.69,0.39), SD=(1.95,1.05), and ρ=-0.25.

Simulation Studies

Simulations were performed under different scenarios of possible dose-toxicity relationships to investigate the operational characteristics of the toxicity-band versus traditional 3+3 design:

- 3-patient cohorts starting from the lowest dose.
- Maximum number of patients: 24 for toxicity-band method and 30 for traditional 3+3 method.
- Stopping rules for toxicity-band method: maximum sample size reached or at least 6 patients have been treated at the recommended next dose level.

Assuming that the starting dose level is 1.6 mg/kg, 4 scenarios were considered to represent a wide range of possible dose-toxicity relationships as shown in Figure 2 and Table 2 of this attachment. DLT rates for the starting dose level are chosen to take into account single-patient cohorts before. The true DLT rate of the MTD is set at 20% to 33% across scenarios. Scenarios 1 and 2 have MTD at 5 mg/kg, and Scenarios 3 and 4 have MTD at 4 mg/kg. When the dose-toxicity curve is steep around MTD, the concern is the risk of overdosing; when the dose-toxicity curve is flat around MTD, the concern is underdosing. The simulation studies will access the performance of the toxicity-band method and compare it to the traditional 3+3 focusing on these concerns.

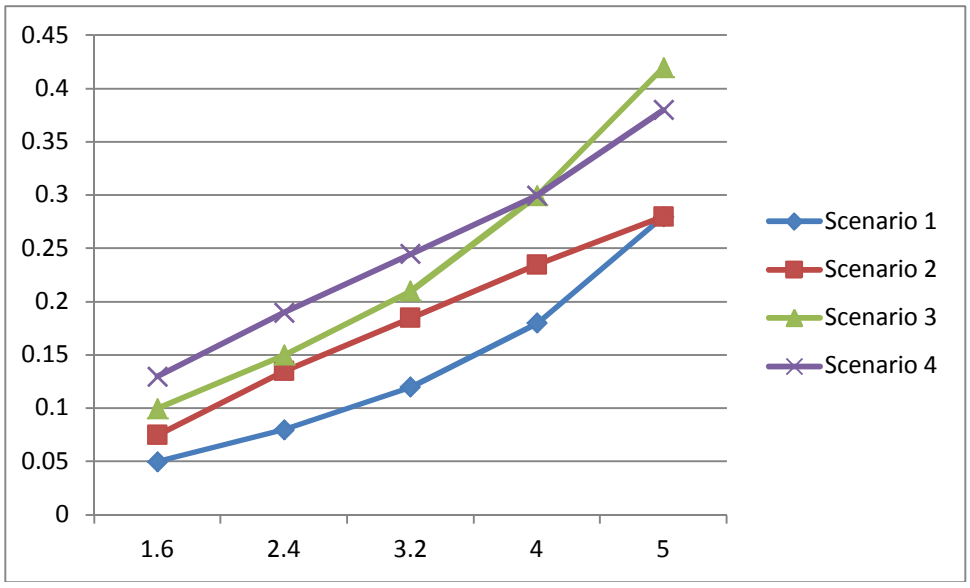


Figure 2. The dose-toxicity relationships under each scenario.

Table 2. The Dose-Toxicity Relationships under Each Scenario Starting from 1.6 mg/kg

Dose (mg/kg)	Scenarios			
	1	2	3	4
1.6	0.05	0.075	0.1	0.13
2.4	0.08	0.135	0.15	0.19
3.2	0.12	0.185	0.2	0.245
4	0.18	0.235	0.3	0.3
5	0.28	0.28	0.42	0.38

One thousand (1000) simulations were conducted under each scenario to investigate the operational characteristics of toxicity-band and traditional 3+3 methods. The results are summarized in Table 3 of this attachment.

Table 3. Comparison of Toxicity-Band and Traditional 3+3 Methods

Rate of Selected as MTD for Each Dose (mg/kg)	Scenarios							
	1		2		3		4	
	TB	3+3	TB	3+3	TB	3+3	TB	3+3
1.6	**0.079**	**0.08**	**0.185**	**0.192**	**0.25**	**0.258**	**0.392**	**0.394**
2.4	**0.078**	**0.119**	**0.155**	**0.199**	**0.209**	**0.208**	**0.195**	**0.233**
3.2	**0.134**	**0.183**	**0.122**	**0.214**	**0.257**	**0.242**	**0.196**	**0.177**
4	**0.305**	**0.285**	**0.198**	**0.177**	**0.22**	**0.209**	**0.143**	**0.135**
5	**0.404**	**0.333**	**0.34**	**0.218**	**0.064**	**0.083**	**0.074**	**0.071**
Rate of selecting Ph2 dose below true MTD	**0.596**	**0.667**	**0.66**	**0.782**	**0.611**	**0.671**	**0.783**	**0.818**
Rate of selecting Ph2 dose above true MTD	**0**	**0**	**0**	**0**	**0.064**	**0.083**	**0.074**	**0.071**
Rate of DLT events during the trial	**0.16**	**0.14**	**0.20**	**0.19**	**0.22**	**0.22**	**0.26**	**0.25**
Mean # subjects	**17.5**	**16.4**	**16.0**	**14.9**	**14.2**	**14.0**	**12.8**	**12.4**

Abbreviations: TB = toxicity-band method; DLT = dose-limiting toxicity; MTD = maximum tolerated dose.
Results based on 1000 simulations.

The traditional 3+3 design is generally conservative and has a higher rate of selecting a dose level below the true MTD to be recommended for future Phase 2 studies, increasing the risk of under-dosing and failure rate of Phase 2 studies. The toxicity-band method is slightly more aggressive in general and has a lower rate of MTD selection below the true level, and a higher rate of MTD selection at the true level. The mean percentages of a DLT event in each scenario are in general higher in the toxicity-band method, but strictly kept below the prespecified overdosing control criterion at 0.25.

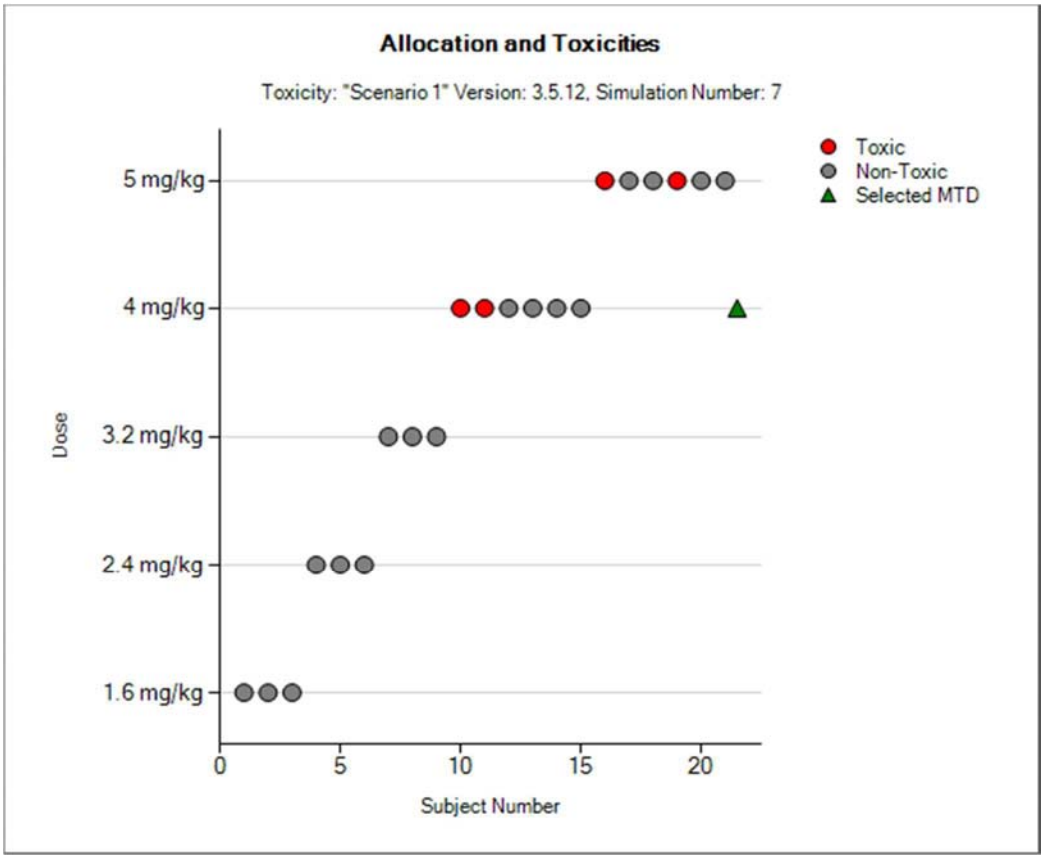
Examples

Examples from Scenario 1 and Scenario 4 are provided here to illustrate how the toxicity-band method operates under certain circumstances.

Example 1

Scenario 1 has a true MTD at 5 mg/kg with a DLT rate of 0.28 in Table 2. With a slowly increasing relationship between the dose level and the DLT rate, patients could be assigned to dose levels under MTD and cause underdosing when DLT occurs in the first few cohorts.

With the toxicity-band method, the next recommended dose level is 5 mg/kg after the 15th patient is treated (Figure 3a), although 2 DLTs are observed at 4 mg/kg, and 4 mg/kg will be declared as MTD after 21 patients are treated. However, using the traditional 3+3 method, dose de-escalation will be conducted after the 12th patient, since 2 DLTs have already been seen at the current dose level. The toxicity-band method has also allocated more patients at the MTD dose level.



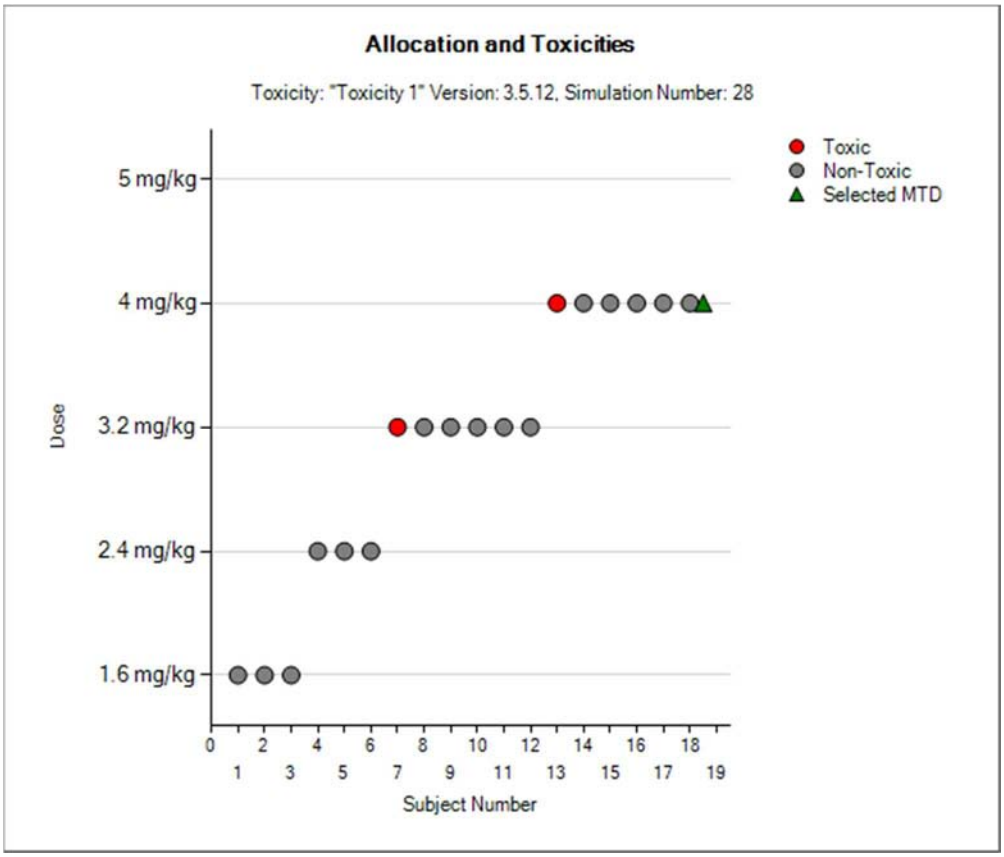
Abbreviation: MTD = maximum tolerated dose.

Figure 3a. A case study for Scenario 1.

Example 2

Scenario 3 has a true MTD at 4 mg/kg with a DLT rate of 0.3 in Table 2. With a relatively steep increasing relationship between the dose level and the DLT rate, patients could be assigned to dose levels above MTD and cause overdosing when few DLT occurs in the first few cohorts.

With the toxicity-band method, the next recommended dose level is still 4 mg/kg after the 18th patient is treated (Figure 3b), although 1 DLT is observed at 4 mg/kg. As 6 patients have already been treated at the next recommended dose level, the dose escalation is ceased and 4 mg/kg will be declared as MTD. However, using the traditional 3+3 method, the lower do se, 3.2 mg/kg, will be selected as MTD. Therefore, the selected MTD from the toxicity-band method is closer to the true MTD comparing to the traditional 3+3 method.



Abbreviation: MTD = maximum tolerated dose.

Figure 3b. A case study for Scenario 3.

Summary

As a conclusion, based on the simulation studies on a variety of scenarios and the illustrative examples, the toxicity-band method is slightly more aggressive than the traditional 3+3 design, and therefore provides a lower underdosing rate and a higher MTD selection rate, with a well-controlled overdosing rate at a prespecified criterion. Therefore, the modified 3+3 method that incorporates the principles of the toxicity-band method will be used in this study rather than the traditional 3+ 3 escalation paradigm.

Attachment 11. Protocol JOBA Alterations for FGFR3

Such as the following FGFR3 alterations:

R248C

S249C

G372C

Y375C

K650E

K652E

FGFR3-TACC3 fusion

t(4;14)(p16.3;q32.3)

Attachment 12. Protocol Amendment I7O-MC-JOBA(a) Summary
A Phase 1 Study of LY3076226, a Fibroblast Growth Factor Receptor 3 (FGFR3) Antibody-Drug Conjugate, in Patients with Advanced or Metastatic Cancer

Overview

Protocol I7O-MC-JOBA, A Phase 1 Study of LY3076226, a Fibroblast Growth Factor Receptor 3 (FGFR3) Antibody-Drug Conjugate, in Patients with Advanced or Metastatic Cancer, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- As requested by the Food and Drug Administration (FDA), patients with preexisting corneal diseases that may interfere with assessment of potential toxicity in the eyes during the study have been excluded in Section 6.1.2.
- As requested by the FDA, patients with skin disorders (for example, erythema, dermatitis) of ≥Grade 2 have been excluded in Section 6.1.2.
- As requested by the FDA, in reference to patients who may have refused standard therapy, wording has been added to Section 6.1.1 to state that these patients must be well informed about the benefit and risk of the standard therapy before signing the informed consent.
- As requested by the FDA, dose-limiting toxicity criteria (DLT) in Section 7.2.2.1 have been revised to indicate that the following events considered at least possibly related to LY3076226 will be DLTs: Grade 3 fatigue lasting >5 days, Grade 3 elevations in AST or ALT lasting >7 days, and concurrent elevation of ALT >3 × ULN and total bilirubin >2 × ULN in the absence of biliary obstruction or other causes that could reasonably explain the elevation. In addition, wording was added to Section 7.2.2.1 and Section 6.3.1 to indicate that significant related toxicity resulting in a >14-day delay in starting Cycle 2 would be considered a DLT.
- As requested by the FDA, infusion duration information was added to Section 7.2.1.
- As requested by the FDA, clarification that premedication is not permitted for the initial dose of LY3076226 for each patient was added to Section 7.2.1.
- As requested by the FDA, clarification on expanding one-patient cohorts when Grade 2 or greater events considered at least possibly related to study drug are observed has been added to Section 7.2.2.3.

- As requested by the FDA, Section 8.1.4 has been modified to indicate that patients who have a concurrent elevation of ALT >3 × ULN and total bilirubin >2 × ULN and who, following assessment by the investigator, have no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation, will be discontinued from the study. Additionally, Section 7.2.2.1 was revised as noted above for consistency with Section 8.1.4.
- As requested by the FDA, additional ophthalmic examinations as clinically indicated at the ophthalmologist's discretion were added to Section 8.1.4 and Attachment 1.
- As requested by the FDA, information about FGFR3 alteration types has been added in Attachment 11 and is referenced in Section 6.1.1 Inclusion Criteria.
- As requested by the FDA, a section has been added to specifically address the RP2D determination, Section 7.2.4.
- As requested by the FDA, wording regarding avoidance of strong inducers and inhibitors of CYP3A and strong inhibitors of CYP2D6A has been added to Section 7.5.
- Additional 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. Abbreviations and Definitions

Term	Definition
C1D1	Cycle 1, Day 1
FDA	Food and Drug Administration
RP2D	recommended Phase 2 dose

6.1.1. Inclusion Criteria

[1] Must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies have failed to provide clinical benefit for their disease or if the patient refuses standard therapy. Patients must be well informed about the benefit and risk of standard therapy prior to signing the informed consent.

Part A (dose escalation): Have histological or cytological evidence of a diagnosis of cancer (including multiple myeloma and lymphoma) that is advanced and/or metastatic.

Part B (dose expansion): Have histologically or cytologically confirmed, locally advanced, or unresectable or metastatic urothelial (transitional cell) carcinoma of the bladder, urethra, ureter, or renal pelvis, with locally determined overexpression or alterations of FGFR3 (refer to Attachment 11).

Part C (dose expansion): Have histological or cytological evidence of a diagnosis of cancer (including multiple myeloma and lymphoma) that is advanced and/or metastatic, with locally determined overexpression or alterations of FGFR3 (refer to Attachment 11).

[2] Part A: Have the presence of measurable and/or nonmeasurable disease as defined by the appropriate criteria: Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1 [refer to Attachment 9]; Eisenhauer et al. 2009), multiple myeloma criteria (International Myelo ma Working Group [IMWG; refer to Attachment 5]; Rajkumar et al. 2011), or lymphoma criteria (Cheson et al. 20~~07~~14).

Parts B and C: Have the presence of measurable disease as defined by the appropriate criteria: RECIST 1.1 (Eisenhauer et al. 2009), multiple myeloma criteria (IMWG; Rajkumar et al. 2011), or lymphoma criteria (Cheson et al. 20~~07~~14).

6.1.2. Exclusion Criteria

[13] Have symptomatic CNS malignancy or metastasis (screening not required).

Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids for this indication and/or anticonvulsants, and their disease is asymptomatic and radiographically stable for at least 28 days.

[19] Have preexisting corneal diseases that may interfere with assessment of potential toxicity in the eyes during the study.

[20] Have skin disorders (for example, erythema, and dermatitis) of Grade ≥2.

6.3.1. Discontinuation of Patients

In addition, patients will be discontinued from the study drug and/or 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.
  - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug occurs prior to introduction of the other agent.
- 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).
- The patient's dosing is delayed for more than 2 weeks as the result of an AE that is at least possibly related to LY3076226. If this delay occurs for the start of Cycle 2, this will be considered a DLT.

7.2.1. Dosing Schedule

For doses ≤250 mg, LY3076226 will be administered as an IV infusion over approximately 60 minutes on Day 1 of each 21-day cycle. The sponsor may instruct the sites to extend the infusion time for up to 2 hours for doses greater than 250 mg. The assigned dose and duration of infusion of LY3076226 will be provided by the sponsor on a patient registration form. Subsequent doses should be adjusted as described in Section 7.2.6.

Premedication is not permitted for the initial dose of LY3076226 for each patient so that any observed toxicities may be appropriately characterized.

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

Dose-limiting toxicity (DLT) is defined as an AE occurring during Cycle 1 that is at least possibly related to LY3076226 and fulfills any one of the following criteria using the NCI-CTCAE v 4.0:

- CTCAE Grade ≥3 non-hematological toxicity. Exceptions will be made for the following:
  - 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 for more than 48 hours, despite supportive intervention.)
  - ~~Fatigue and a~~Anorexia
  - Grade 3 fatigue lasting ≤5 days
- Grade 3 elevations of ALT and/or AST lasting ≥7 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 or clinical research scientist (CRS)~~.
- Concurrent elevation of ALT >3 × ULN and total bilirubin >2 × ULN in the absence of biliary obstruction or other causes that could reasonably explain the elevation.
- CTCAE Grade 4 neutropenia of >7 days' duration
- Any febrile neutropenia
- CTCAE Grade 3 thrombocytopenia with bleeding
- CTCAE Grade 4 thrombocytopenia with or without bleeding
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is at least possibly related to the study medication and that requires the withdrawal of the patient from the study during Cycle 1 or delays the start of Cycle 2 by >14 days).

7.2.2.2. DLT-Equivalent Toxicity

If the rate of DLT-equivalent toxicities is unacceptable (for example, a DLT-equivalent toxicity is observed in >33% patients at a given dose level), the data will be reviewed by study investigators and the Lilly CRP/clinical research scientist (CRS) and a safety analysis may be triggered.

7.2.2.3. Dose-Escalation Method

For Part A, the proposed starting dose level will be 0.2 mg/kg. Dose escalation will proceed at a maximum dose increment of 100%. An accelerated dose-escalation scheme will be used, as follows: initial cohorts will enroll at least one patient each until a dose level of 1.6 mg/kg is reached, unless a ≥Grade 2 toxicity that is at least possibly related to LY3076226 is observed ~~requires~~ requiring ~~enrolling~~ additional patients to be enrolled to a dose level. After which a modified 3+3 scheme, with incorporation of a Bayesian model-based, toxicity-band method (Neuenschwander et al. 2008), will be followed, wherein at least 3 patients will be enrolled in each of the subsequent cohorts. The Bayesian model-based, toxicity-band method incorporates the prior expectations of the dose-toxicity curve and the observed DLT data after each cohort and provides quantitative guidance on the determination of the dose level for the next cohort, with control of overdosing probability. This method will be applied to the observed data on an ongoing basis throughout the dose escalation. The toxicity-band method will stop if the prespecified maximum number of patients is reached or the recommended next dose level has been administered to at least 6 patients.

7.2.4. Recommended Phase 2 Dose (RP2D)

The RP2D will be determined after the completion of Parts B and C. 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. This will not exceed the MTD.

7.2.6.1. General Dose Adjustments and Delays

- Before the start of each cycle, the following parameters are required:
  - Hematologic: ANC $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥8 g/dL. (In Part C only, patients with multiple myeloma are allowed the following: ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 50 \times 10^9$/L, and hemoglobin ≥8 g/dL.)
  - Non-hematologic: AEs must resolve to CTCAE v 4.0 Grade ≤1 or baseline. Exceptions will be made for: alopecia, fatigue, or other toxicities that can be controlled with standard treatment; these toxicities must resolve to Grade ≤2.
- If subsequent cycles are delayed by more than 14 days due to an AE that is at least possibly related to LY3076226, the patient should be removed from study drug treatment and should complete subsequent follow-up.

7.5. Concomitant Therapy

Concomitant use of strong CYP3A4 inhibitors (for example, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with LY3076226 should be avoided due to the potential for an increase in DM4 exposure and toxicity. Where possible, consider an alternate medication with no or minimal potential to inhibit CYP3A4. Concomitant use of strong CYP3A4 inducers (for example, avasimibe [not commercially available], carbamazepine, phenytoin, rifampin, and St. John's wort) with LY3076226 should be avoided due to the potential for a decrease in DM4 exposure and potentially efficacy. Where possible, consider an alternate medication with no or minimal potential to induce CYP3A4. Concomitant use of strong CYP2D6 inhibitors (for example, bupropion, fluoxetine, paroxetine, and quinidine) with LY3076226 should be avoided due to the potential for an increase in DM4 exposure and toxicity. Where possible, consider an alternate medication with no or minimal potential to inhibit CYP2D6. Refer to the Food and Drug Administration (FDA) website for a complete list (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm).

Premedication is not permitted for the initial dose of LY3076226 for each patient. Appropriate treatment with topical/oral corticosteroids and/or antibiotics may be instituted at the discretion of the investigator if skin reaction occurs.

7.6.1. Evaluable Patients

Any patient who is discontinued from the study before completing one cycle of LY3076226 treatment ~~will~~ may be deemed non-evaluable for assessment of a dose level, unless they experience a DLT prior to withdrawal.

Patients who receive LY3076226 on Cycle 1, Day 1 (C1D1) but discontinue from study treatment before the end of Cycle 1 will be considered evaluable for the assessment of a dose level provided it can be documented if the patient experienced a DLT within 21 days of C1D1.

8.1.2.2.3. Follow-Up Visit

Following the safety assessments, which mark the 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. In this instance, the patient should be followed ~~in subsequent follow-up visits (Visits 802 through 8XX),~~ 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.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

Table JOBA.5. Adverse Event and Serious Adverse Event Reporting Guidelines for Study I7O-MC-JOBA

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (Starts at the signing of the ICF and ends just before the first dose of study drug)	Preexisting conditions All AEs All SAEs regardless of relatedness	x x x	 x
On therapy (Starts at first dose of study drug and ends at last dose of study drug)	All AEs All SAEs regardless of relatedness	x x	 x
Follow-up visit (Visit 801) (Begins the day after the patient and the investigator agree that the patient will no longer continue study treatment. The duration of the follow-up visit is 28 ± 5 days.)	All AEs All SAEs regardless of relatedness	x x	 x
Continued access period	All AEs All SAEs regardless of relatedness	x x	 x
Continued access period follow-up	All AEs All SAEs regardless of relatedness	x x	 x
Subsequent follow-up visits, if necessary for patient monitoring	Ongoing AEs <u>at least</u> possibly related to study drug, or protocol procedures All SAEs related to protocol procedures or study drug	x x	 x
Patient no longer on study	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; ICF = informed consent form; SAEs = serious adverse events.

8.1.4. Safety Monitoring

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

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures.

Ophthalmologist may perform additional examinations when visual changes or other ocular symptoms occur, at their discretion as clinically indicated.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. Potential for biliary obstruction should be assessed. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3). If a study patient experiences concurrent elevated ALT ≥~~>~~5~~-~~3 × ULN and elevated total bilirubin ≥~~>~~2 × ULN, clinical and laboratory monitoring should be initiated by the investigator. If this is determined to be in the absence of biliary obstruction or other causes than can reasonably explain the concurrent elevation, then the patient should be discontinued from LY3076226.

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

8.3. Efficacy Evaluations

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)
- For lymphoma patients only, positron emission tomography (PET)/CT is permitted if appropriate for standard of care (Cheson et al. 20~~07~~14)

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

- Tumor measurement by RECIST 1.1 (Eisenhauer et al. 2009), international uniform response criteria for multiple myeloma (Rajkumar et al. 2011), or response criteria for lymphomas (Cheson et al. 20~~07~~14).

10.8. Efficacy

The study is not designed to make an efficacy assessment. However, any tumor response data will be tabulated. Particularly, the antitumor effect will be summarized by the overall response rate (ORR). A patient is considered to have a tumor response if they achieve a confirmed CR or PR according to RECIST 1.1 (Eisenhauer et al. 2009) or lymphoma criteria (Cheson et al. 20~~07~~14); or a confirmed stringent complete response (sCR), CR, very good partial response (VGPR), or PR according to multiple myeloma (IMWG) criteria (Rajkumar et al. 2011). The ORR will be estimated by dividing the total number of confirmed complete and partial

responders (CR+PR) by the total number of enrolled patients. A 90% exact CI will be constructed to determine the level of precision of the tumor response rate. Time-to-event variables will also be tabulated. For PFS and duration of response, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves, medians, and survival rates if applicable.

12. References

~~Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.~~

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research and Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Linformas y Trasplantes de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations fo r initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.

Attachment 1. Protocol JOBA Study Schedule

Baseline Assessments

Relative day to Cycle 1, Day 1	Pre-screening	Screening ≤28	Screening ≤14	Screening ≤7	Comments
Radiological tumor assessment according to RECIST 1.1		X			Radiological assessments obtained previously (≤28 d prior to C1D1) as part of routine clinical care may be used as the baseline assessment. Appropriate tumor assessment criteria should be used for patients with multiple myeloma (IMWG [Rajkumar et al. 2011; refer to Attachment 5]) or lymphoma (Cheson et al. 20~~07~~14).
Central ~~P~~pretreatment tumor tissue biopsy (Parts B and C only)			X		Collected only if patient has met inclusion/exclusion criteria. If the patient had prescreening biopsy to assess FGFR3 alteration status, a portion of the prescreening biopsy may be used for pretreatment biopsy for the study.

During Study-Treatment Assessments

	Cycle 1					Cycle 2			Cycle 3					Cycles 4-n	Comments
Relative day within a cycle	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	Cycle duration = 21 d
Ophthalmic examination													X		Performed by an ophthalmologist anytime from Days 15-21. Additional monitoring may occur if clinically indicated at the discretion of the ophthalmologist.
Local urinalysis	X					X			X					X	Can be collected ≤24 h prior to Day 1 of a cycle.
Radiological tumor assessment													X	X	Use RECIST 1.1 (Eisenhauer et al. 2009), multiple myeloma criteria (IMWG [Rajkumar et al. 2011; refer to Attachment 5]), or lymphoma criteria (Cheson et al. 20~~07~~14). The same method of imaging used at baseline should be used for each subsequent assessment. Imaging should be performed during the last wk of every third cycle; that is, Cycles 3, 6, 9, 12, and so on). May be omitted if patient has clear signs of progressive disease. In addition, any patient whose disease has not progressed by 1 y after entering the trial may be assessed every 18 wk.

	Cycle 1					Cycle 2			Cycle 3					Cycles 4-n	Comments
Relative day within a cycle	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	Cycle duration = 21 d
Central urine sample for biomarkers (Part B only)	X								X						Collect preinfusion on C1D1. Refer to Attachment 4 for exact timing.

Posttreatment Discontinuation Follow-Up Assessments

	Study Period	**Short-Term Follow-Up**	
	Visit	**801**	The follow-up visit begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
	Duration	28±5 d	

Procedure		**Comments**
Radiologic imaging	X	Use RECIST 1.1 (Eisenhauer et al. 2009), multiple myeloma criteria (IMWG [Rajkumar et al. 2011; refer to Attachment 5]), or lymphoma criteria (Cheson et al. 20~~07~~14). 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.
CTCAE v 4.0 grading	X	Refer to Section 8.1.2. Report all AEs during the Short-Term Follow-Up period. After Visit 801, only study protocol- or drug-related events are reported. If a patient has an ongoing AE or SAE at least possibly related to LY3076226, 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 (Visits 802-8XX) will be no more than 28 d ± 5 d in duration.~~

Attachment 2. Protocol JOBA Clinical Laboratory Tests

Clinical Laboratory Tests

Creatinine clearance, calculated[c]

[c] Cockcroft and Gault formula will be used for calculated creatinine clearance. See Attachment 8.

Attachment 4. Protocol JOBA Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule

[a] Post-infusion ECG can be done within 15 minutes after end of infusion.
[b] Posttreatment biopsy may be performed on C1D4 or C1D5 to allow flexibility for scheduling.
[c] Predose ECG can be obtained prior to predose blood samples.
[d] Predose ~~U~~urine biomarker sample (Part B only) can be obtained prior to predose blood samples.

Attachment 5. Protocol JOBA Multiple Myeloma Tumor Assessment

Assessments and Timing for Patients with Multiple Myeloma

Myeloma Assessment	Baseline	C1 - CX	Short-Term Follow-Up (Visit 801)	Comments
~~Central~~Local quantitative ~~IgG, IgA, IgM~~immunoglobulins	X	X	X	Baseline performed ≤28 d prior to C1D1. On study: Performed on D1 of each cycle, prior to treatment. Short-term follow-up (Visit 801): May be omitted if progressive disease is previously documented or if there are clear signs of clinical progression.

Abbreviations: C# = cycle; CR = complete response; CT = computed tomography; D# = day; IFE = immunofixation electrophoresis (serum/urine); ~~Ig = immunoglobulin;~~ MRI = magnetic resonance imaging; sCR = stringent complete response; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Attachment 8. Protocol JOBA Creatinine Clearance Formula

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

Attachment 11. Protocol JOBA Alterations for FGFR3

Such as the following FGFR3 alterations:

R248C

S249C

G372C

Y375C

K650E

K652E

FGFR3-TACC3 fusion

t(4;14)(p16.3;q32.3)