Statistical Analysis Plan 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

NCT02529553

Approval Date: 24-Jun-2015

1. Statistical Analysis Plan: 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

FGFR3 Antibody-Drug Conjugate (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 I7O-MC-JOBA
Phase 1

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

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3. Revision History

SAP Version 1 was approved prior to the first patient visit.

4. Study Objectives

4.1. 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.

4.2. 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

4.3. Exploratory Objectives

The exploratory objectives of this study are:

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

5. Study Design

5.1. Summary of Study Design

Study JOBA is a multicenter, outpatient, nonrandomized, open-label, dose-escalation Phase 1 study of intravenous (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. The initial dose levels will enroll one patient per cohort. 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). For more details, please refer to Protocol Section 6.2 and 7.2.2.

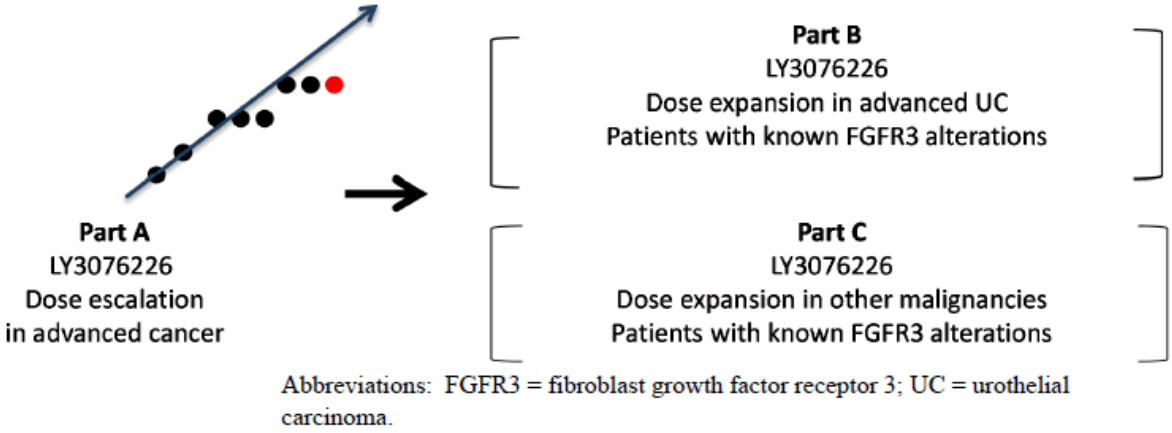
Once MTD is identified in Part A, up to approximately 15 patients who have known alterations of FGFR3 will be enrolled in each of Parts B (urothelial carcinoma) and C (other malignancies) to further evaluate the safety profile of LY3076226, characterize the exploratory biomarker assays, and document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

Figure JOBA.5.1 is a representative illustration of Study JOBA study design, showing the dose escalation design in advanced cancer (Part A) and MTD expansions Parts B and C.

5.2. Determination of Sample Size

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 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.



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

Figure JOBA.5.1. Illustration of Study JOBA study design.

5.3. 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 Eli Lilly and Company (Lilly) clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose, identification number, and cohort assignment for each patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly Clinical Research Physician/Clinical Research Scientist (CRP/CRS).

If investigators have eligible patients who have consented concurrently, more than 1 or 3 patients may be entered at a particular dose level (or 6 if the cohort has been expanded due to a DLT) provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.

6. A Priori Statistical Methods

6.1. General Considerations

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

The analyses for this study will be descriptive; no p-values will be calculated. Data analyses will be provided by cohort and overall 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. Exploratory analyses of the data that are not described in the protocol will be conducted as deemed appropriate.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feather of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the clinical study report (CSR).

The following data handling conventions will be used in the analysis (see Table JOBA.6.1).

Table JOBA.6.1. Data Handling Conventions

Term	Definition or Rule
Relative Study Day	If assessment is on or after date of first dose then (date of assessment)-(date of first study drug dose)+1
	If assessment precedes first dose of drug then (date of assessment) – (date of first study drug dose)
	There is no Study Day 0. Study Day 1 is the date of first dose and study day -1 is the day before the first dose.
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose date (prior to the dose administration), unless otherwise specified. For change from baseline within a cycle, baseline value is defined as the measure prior to the first dose of that cycle, unless otherwise specified. If more than one pre-dose measures are available, they may be averaged if appropriate.
Entered	Patients who have signed the informed consent document (ICD).
Enrolled	Patients who have been assigned to a study treatment and have received at least one dose of study treatment.

6.2. Handling of Dropouts or Missing Data

Missing data, except dates, will not be imputed. Historical data such as historical diagnosis, historical illness, pre-existing conditions and prior therapies should be collected in a sufficiently informative way. For example, in order to be considered as historical illness, events occurring in the same year as study entry should have at least a known month and year for the end date, while events occurring in previous years should have at least a known year for the end date. When dates need to be imputed, missing days will be replaced with 15th of the month and missing day/month with 01 JULY.

Patients who withdraw from the study before receiving study drug will be replaced and will not be included in the safety or efficacy assessments unless the withdrawl is due to a safety issue that is possibly related to study procedure.

In the following situations, patients will be considered non-evaluable and 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:

1. Any patient who is discontinued from the study before completing one cycle of therapy unless they experience a DLT prior to withdrawal.
2. Patients who are not evaluable for PK, but who complete one cycle of therapy.

6.3. Population for Analysis

Safety analyses will be conducted on all patients who have received at least one dose of LY3076226, regardless of whether they are deemed evaluable for the assessment of a dose level.

PK analyses will be conducted on patients who have received at least one dose of LY3076226 and have sufficient samples collected to allow the estimation of LY3076226 PK parameters.

PD analyses will be conducted on subjects who have received at least one dose of LY3076226 and have sufficient samples collected to allow the assessment of PD.

6.4. Patient Disposition

A detailed description of patient disposition will be provided. It will include summaries of the number and percentage of patients entered into the study, enrolled in the study, completing the study, and reasons for discontinuation from study treatment, as well as discontinuation from the study. Patients completing the study are defined as patients who received tumor assessments after 3 cycles. All patients entered in the study will be included in the summary. Reason for discontinuation from both study treatment and the study will be listed by the pre-determined categories. If the reason for discontinuation is adverse event (AE) or death, the associated AE or cause of death will be reported.

6.5. Patient Characteristics

Patient characteristics will be summarized and listed for all patients enrolled and will include:

- Patient demographics, including age, sex, race, ethnicity, screening height and weight, and screening body mass index (BMI).
- Baseline disease characteristics, including initial pathological diagnosis, basis for initial diagnosis, disease stage at initial diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status.
- Prior disease-related therapies including systemic, radiotherapy and cancer surgeries, if known, including dose, best response, date of progression.

Alcohol and tobacco historical consumption will be summarized. Other patient characteristics will be summarized as deemed appropriate.

6.6. Treatment Compliance

LY3076226 will be administered intravenously at the investigational site under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured.

6.7. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be listed and summarized using the preferred name by cohort and overall for all patients on therapy. If the concomitant medication use is due to an adverse event (AE), the associated National Cancer Institute's (NCI) Common terminology Criteria for Adverse Events (CTCAE) Version 4.0 term will be listed.

6.8. Safety Analyses

All patients who receive at least one dose of LY3076226 will be evaluated for safety and toxicity.

6.8.1. Extend of Exposure

Study drug exposure information will be summarized by cohort and overall for patients on therapy, including cycles received per subject, duration on therapy, and cumulative dose.

Dose adjustment information will be summarized by cohort and overall for patients on therapy, including dose reductions, dose delays, dose omissions, dose increases, and the reasons leading to dose adjustments.

Dose intensity, defined as the actual amount of drug taken per week, and relative dose intensity, defined as the actual amount of drug taken/planned amount of drug taken×100%, will also be summarized by cohort and overall.

6.8.2. Dose Limiting Toxicity

Dose limiting toxicities (DLTs) will be summarized and listed by cohort and overall for the safety population.

Dose-equivalent toxicities (DETs) will also be summarized and listed by cohort and overall for the safety population.

6.8.3. Adverse Events

AE terms and severity grades will be assigned by the investigator using CTCAE Version 4.0. In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs will be reported using a unified CTCAE/MedDRA reporting process:

- The CTCAE v4.0 term reported by the investigator will be mapped to the MedDRA preferred term (PT) and system organ class (SOC) of the corresponding MedDRA lowest level term (LLT), unless the reported CTCAE term is "Other-specify".
- If the reported CTCAE term is "Other-specify" the MedDRA LLT, PT and SOC mapped from the verbatim AE term will be used
- All listings and summaries will use the CTCAE terms when available or the MedDRA LLT, along with the MedDRA PT resulting from this process.

A treatment emergent adverse event (TEAE) is defined as any AE that begins on or after the day of the first dose of LY3076226 or any pre-existing condition that increases in CTCAE grade on or after the day of the first dose of LY3076226. Comparisons of pre-existing conditions to treatment events at the LLT level will be used in the treatment-emergent computation.

The number of patients who experienced a TEAE, SAE, or TEAE possibly related to study drug, will be summarized. TEAEs will be summarized by SOC, by PT terms of decreasing frequency within SOC, and by maximum CTCAE grade and grade categories.

Historical illnesses are defined as events which ended before completion of the screening visit. Pre-existing conditions are defined as AEs that begin but do not resolve prior to the first dose of study drug is administered. The pre-existing conditions will be presented by patient and can be combined with the adverse event listing, so that the history of the pre-existing conditions/adverse events can be traced. Historical illnesses and pre-existing conditions will be summarized and listed by cohort and overall for all patients on therapy.

6.8.4. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

A summary of deaths will be presented for all patients who died on study. Reasons for death will be summarized separately for deaths on therapy, within 30 days of discontinuation of study therapy and after 30 days of discontinuation of study therapy. Other listings include:

- Listing of Deaths
- Listing of Serious Adverse Events
- Listing of Subjects who Discontinued due to Adverse Events of Death

6.8.5. Clinical Laboratory Evaluation

Abnormal laboratory parameters will be listed by cycle for patients on therapy. In addition to the investigator-reported AEs, relevant hematology and chemistry laboratory values will be graded according to CTCAE v4.0. These abnormal lab parameters with derived CTCAE grades will be summarized by visit and cohort.

6.8.6. Vital Signs and Other Physical Findings

All vital signs data, height and weight will be summarized and listed by visit/time points and cohort for patients on therapy.

6.8.7. Electrocardiograms

Electrocardiogram (ECG) data will be summarized by visit and parameter for patients on therapy. Any abnormal ECG data will be listed by patient. Number and percentage of subjects with AEs that could be associated with abnormal ECGs will be presented, if appropriate.

The number of patients meeting the following criteria with respect to QTc will be presented for maximum on-study value:

- QTc, >480 to 500 msec, and >500 msec and delta QTc >30 to 60 msec, and >60 msec.

All instances when a patient met the above criteria will be listed. Maximum absolute and change from baseline QTc data will be summarized as a continuous variable. Frequency of patients with Normal (≤480 msec) or High (>480 msec) QT/QTc interval at baseline and post baseline nominal time points will be summarized by shift table. Summaries of other ECG parameters (for example, RR, PR, and QRS) will be presented, if appropriate.

6.9. Pharmacokinetic Analyses

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

6.10. Pharmacodynamic Analyses

Pharmacodynamic data will be summarized by dose, and time from dose. Potential PD markers-versus-time data will be presented graphically for each patient and summarized by dose. Absolute and/or relative 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 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.

6.11. 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.

6.12. Efficacy Analyses

The study is not designed to make an efficacy assessment. However, any tumor response data will be listed and summarized. Particularly, the antitumor effect will be summarized by the overall response rate (ORR, defined by the total number of responses divided by the number of patients on therapy) and disease control rate (defined by the total number of stable disease + responses divided by the number of patients on therapy) by cohort and overall. Mean, median, range, and exact 90% confidence intervals (CI) will be provided. A patient is considered to have a tumor response if they achieve a confirmed complete response (CR) or partial response (PR) according to RECIST 1.1 or lymphoma criteria (Cheson et al. 2007) 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). Reported lesion measurement data, including sum of target lesions, change and/or percent change form baseline sum at each visit will be listed for all patients on therapy. Investigator-determined response by cycle will be listed.

Time-to-event variables, such as progression-free survival (PFS) and duration of response, will be listed and summarized. PFS time is defined as the time from the first dose of the study drug to progressive disease (PD, either due to objective progressive disease or symptomatic deterioration) or death due to any cause, occurring without observed disease progression. Duration of response (DoR) is defined as the time from the first assessment of any tumor response to PD or death due to any cause, occurring without observed disease progression. Patients not known to have progressed or died while on study will have their PFS and DoR time censored at the date of the last objective progression-free disease assessment. Patients for whom there is no record of progression, death, or post baseline radiographic assessment will have their PFS time censored on the day of first dose of any study drug. The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves, medians with 90% CI, and PFS rates at various time points if applicable. For Part C, time-to-event variables may be summarized by different tumor types if the data warrant.

6.13. Tailoring Biomarker Analyses

Biomarker assessments in this study will focus on identifying markers and/or marker signatures that may indicate the patients most likely to respond or be resistant to 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 analysis results will be considered exploratory and will not consider multiple comparison adjustments.

6.14. Protocol Violations

All major protocol violations will be summarized by cohort and reason. These violations will include those defined by, for example:

- Inclusion/Exclusion Criteria
- Dosing
- Noncompliance with other protocol procedures
- Informed consent/assent process

6.15. Interim Analyses and Data Monitoring

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 Protocol 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.

6.16. Annual Report Analyses

The following reports are needed as requested for annual reporting purposes.

Clinical Investigator brochure:

- Summary of SAE
- Summary of Deaths
- Listing and Summary of TEAE
- Listing of Subjects Who Discontinued Due to Adverse Event or Death

Development Safety Update Report:

- Cumulative Subject Exposure by Age Group and Sex
- Cumulative Subject Exposure by Racial Group
- Estimated Cumulative Subject Exposure
- Exposure Information
- Listing of Discontinuations Due to Adverse Event During the Reporting Period
- Listing of Subjects Who Died During the Reporting Period

6.17. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

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

- An AE is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.

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

A participant flow will be created that will describe how many entered patients completed the study, and for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation.

7. References

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