Non-Interventional Study Protocol
A8081031

Xalkori Capsules: Special Investigation
–A Survey for *ALK*-Fusion-Gene-Positive Non-Small Cell Lung Cancer–

Statistical Analysis Plan

Version: 2.0

Author: PPD (Clinical Statistics, Pfizer Japan Inc.)

Date: 01-FEB-2017

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1. REVISION HISTORY

Version	Date	Author(s)	Summary of Changes/Comments
1.0	21-FEB-2014	PPD	Original SAP
2.0	01-FEB-2017	PPD	5.1. Safety Analysis Set • "Have an experience taking the drug" was deleted (as a writing error). 5.4. Subgroups • Reference subgroups for calculations of risk ratios were added. 6.3. Other Endpoints • Duration of treatment was added. 6.4. Covariates • The covariates concerning the development of hepatotoxicity were added. 7. HANDLING OF MISSING DATA • The handling of censor date in analyzing time period data (time-to-event data) was added. 8.2.1. Description of Patients • In "Summary of discontinuations/dropouts," preparation of a table of discontinued patients was added. 8.2.2. Patient Characteristics and Prior Treatments • The factor "ALK test detail" was added.

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.3.2. Subgroup Analyses • Subgroup analyses concerning the occurrence of hepatotoxicity, visual disturbance, neutropenia/leukopenia, and neuropathy were added. • The summarization in terms of n and % of patients for each of the predefined subgroups was added. CCI [redacted] [redacted] [redacted]. 8.2.4.3. Subgroup Analyses • The provision of ORR by patient characteristic was added. 9. LISTINGS • Listing of deaths was added. 10. REFERENCES • "Manuals for the Management of Individual Serious Adverse Drug Reactions" was added. Other minor changes were made including corrections of typos and clarifications of descriptions.

2. INTRODUCTION

This document is to describe the statistical analysis plan for a post-marketing surveillance (special investigation) of Xalkori® Capsules. In this SAP, statements cited from the protocol of the survey are indicated in italics.

2.1. Study Design

This survey is a non-interventional study in a cohort of 2000 patients with ALK fusion gene-positive non-small cell lung cancer (NSCLC) who took Xalkori capsules.

<Study Population>

Patients with ALK fusion gene-positive NSCLC who took Xalkori capsules (including those who participated in the Therapeutic Cost Coverage System for Combination Therapies Containing Therapies Not Covered by Insurance) will be evaluated with a target sample size of 2000 patients.

<Rationale for the Sample Size Determination>

The sample size was determined assuming that the incidence of interstitial lung disease (ILD) after treatment with Xalkori capsules is approximately 4%, considering the possibility that the incidence in Japanese patients might be higher than non-Japanese patients, and from the fact that the incidence of ILD in Japanese patients was approximately 3.6% (4/111) based on the data from the global studies of crizotinib (Studies A8081001, A8081005, A8081007, and A8081014).*

Guided by the results from relevant studies including a prospective investigation of gefitinib (special investigation) and a special investigation of erlotinib, we sought to determine a sample size that enables us to detect a risk factor with a high probability when the incidence of ILD in the higher risk population defined by this factor is ≥2-fold higher than the incidence in the lower risk population defined by the same factor, based on the relationship among the sample size necessary for a chi-square test, significance level (α), and power.

With α=0.15, the power-sample size curve almost reaches a plateau around n=2000. A sample size of 2000 would provide a statistical power of ≥90% even if the ratio of the lower and higher risk populations was 1:2 or 2:1, or a power of 86.3% if the ratio was 1:3. With α=0.05, a sample size of 2000 would provide powers of 83.8%, 77.5%, and 81.0% if the case ratio was 1:1, 1:2, or 2:1, respectively. Even if the ratio was 1:3 or 3:1, the power provided is 68.4% or 75.8%, respectively, indicating a certain level of power.

Taken together, a target sample size of 2000 may be adequate also for the purpose of determining risk factors that should be mentioned as a result of a multivariate analysis such as an analysis with a Cox proportional hazards model.

**) Because Studies A8081007 and A8081014 are ongoing open-label randomized trials, half the patients who had received study drug as of December 6, 2011 were assumed to have had crizotinib to calculate the incidence.*

2.2. Study Objectives

To determine whether another special investigation or post-marketing clinical study is needed or not by grasping the safety and effectiveness of Xalkori capsules in post-marketing real-world clinical settings with respect to:

1. *Occurrence of adverse reactions unexpected from the statements in Precautions in the package insert (ie, unlisted adverse reactions);*
2. *Occurrence of all adverse reactions, and*
3. *Factors affecting the safety/effectiveness of Xalkori capsules.*

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses will be performed on a regular basis for periodical safety reports. Among the analyses defined in this SAP, only those that are needed for periodic safety reports will be performed for interim analyses. A final analysis will be performed for an application of reexamination. For the final analysis, all analyses defined in the SAP will be performed.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

CCI [redacted]

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety of Xalkori capsules will be analyzed using the Safety Analysis Set that consists of all patients who meet the inclusion criteria for this study and are confirmed to have had at least one dose of Xalkori capsules, except those who:

- Had a contract defection;
- Had a contract violation;

- Never visited after first prescription;
- Never took the drug, or
- Are considered "indeterminate" for safety evaluation.

5.2. Effectiveness Analysis Set

Basically, the Effectiveness Analysis Set consists of all patients who have at least one measurable lesion and were evaluated for effectiveness. Patients are excluded from the effectiveness analysis set if they:

- Do not have a target disease;
- Are considered "indeterminate" for effectiveness evaluation, or
- Do not meet the effectiveness evaluation conditions.

5.3. Other Analysis Sets

Not applicable.

5.4. Subgroups

The safety of Xalkori capsules will also be analyzed for the subgroups defined by the following patient characteristics:

- Sex [male, female] (reference: male);
- Age group [<15 years, ≥15 years] (reference: <15 years);
- Age group [<65 years, ≥65 years] (reference: <65 years);
- Body weight [<40 kg, ≥40-<50 kg, ≥50-<60 kg, ≥60-<70 kg, ≥70-<80 kg, ≥80 kg] (reference: <40 kg);
- Body surface area [<1.2, ≥1.2-<1.4, ≥1.4-<1.6, ≥1.6-<1.8, ≥1.8] (reference: <1.2);
- Body mass index (BMI) [<18.5, ≥18.5-<25.0, ≥25.0] (reference: <18.5);
- Time from first diagnosis of NSCLC to treatment [≥0-≤12 months, ≥13-≤24 months, ≥25-≤48 months, ≥49-≤72 months, ≥73-≤96 months, ≥97 months] (reference: ≥0-≤12 months);
- Stage of target disease [IA, IB, IIA, IIB, IIIA, IIIB, IV] (reference: IA);
- M category of target disease [M0, M1a, M1b] (reference: M0);

- Metastasis (lung) [absent, present] (reference: absent);
- Metastasis (liver) [absent, present] (reference: absent);
- Metastasis (lymph node) [absent, present] (reference: absent);
- Metastasis (pleura) [absent, present] (reference: absent);
- Metastasis (bone) [absent, present] (reference: absent);
- Metastasis (brain) [absent, present] (reference: absent);
- Performance status (ECOG PS) [0, 1, 2, 3, 4] (reference: 0);
- Smoking status [never smoked, ex-smoker, smoker] (reference: never smoked);
- Brinkman index [never smoked, <200, ≥200-<400, ≥400-<600, ≥600-<800, ≥800-<1000, ≥1000-<1200, ≥1200] (reference: never smoked);
- History of occupational/environmental exposure to asbestos, pneumoconiosis, etc. [absent, present] (reference: absent)
- High concentration of oxygen for the treatment of respiratory disease [never received, currently receiving, previously received] (reference: never received);
- Past history (drug allergy) [absent, present] (reference: absent);
- Past history (other allergic diseases) [absent, present] (reference: absent);
- Past history (ILD, pulmonary fibrosis, or radiation pneumonitis) [absent, present] (reference: absent);
- Past history (lymphangiosis carcinomatosa, pleural effusion, pulmonary edema, or other respiratory diseases) [absent, present] (reference: absent);
- Past history (cardiovascular diseases) [absent, present] (reference: absent);
- Past history (autoimmune diseases) [absent, present] (reference: absent);
- Past history (hepatic impairment) [absent, present] (reference: absent);
- Past history (renal impairment) [absent, present] (reference: absent);
- Complication (drug allergy) [absent, present] (reference: absent);
- Complication (other allergic diseases) [absent, present] (reference: absent);

- Complication (ILD, pulmonary fibrosis, or radiation pneumonitis) [absent, present] (reference: absent);
- Complication (lymphangiosis carcinomatosa, pleural effusion, pulmonary edema, or other respiratory diseases) [absent, present] (reference: absent);
- Complication (cardiovascular diseases) [absent, present] (reference: absent);
- Complication (autoimmune diseases) [absent, present] (reference: absent);
- Complication (hepatic impairment) [absent, present] (reference: absent);
- Complication (renal impairment) [absent, present] (reference: absent);
- Treatment line with Xalkori capsules for NSCLC [1st-line, 2nd-line, 3rd-line, 4th-line, 5th-line, 6th-line, ≥7th-line] (reference: 1st-line);
- Severity of renal impairment (eGFR) [Grade <1, Grade 1, Grade 2, Grade ≥3] (reference: Grade <1).

Subgroup analyses of safety will also be performed for the following subgroups:

- Children (<15 years of age) vs adults (≥15 years);
- Elderly (≥65 years of age) vs non-elderly (<65 years);
- Pregnant vs not pregnant;
- With vs without renal impairment;
- With vs without hepatic impairment.

The effectiveness of Xalkori capsules will be analyzed for the subgroups defined by the following patient characteristics:

- Sex [male, female];
- Age group [<15 years, ≥15 years];
- Age group [<65 years, ≥65 years];
- Body surface area [<1.2, ≥1.2-<1.4, ≥1.4-<1.6, ≥1.6-<1.8, ≥1.8];
- BMI [<18.5, ≥18.5-<25.0, ≥25.0];
- Time from first diagnosis of NSCLC to treatment [≥0-≤12 months, ≥13-≤24 months, ≥25-≤48 months, ≥49-≤72 months, ≥73-≤96 months, ≥97 months];

- Stage of target disease [IA, IB, IIA, IIB, IIIA, IIIB, IV];
- M category of target disease [M0, M1a, M1b];
- Metastasis (lung) [absent, present];
- Metastasis (liver) [absent, present];
- Metastasis (lymph node) [absent, present];
- Metastasis (pleura) [absent, present];
- Metastasis (bone) [absent, present];
- Metastasis (brain) [absent, present];
- ECOG PS [0, 1, 2, 3, 4];
- Smoking status [never smoked, ex-smoker, smoker];
- Brinkman index [<200, ≥200-<400, ≥400-<600, ≥600-<800, ≥800-<1000, ≥1000-<1200, ≥1200];
- History of occupational/environmental exposure to asbestos, pneumoconiosis, etc. [absent, present];
- High concentration of oxygen for the treatment of respiratory disease [never received, currently receiving, previously received];
- Past history (drug allergy) [absent, present];
- Past history (other allergic diseases) [absent, present];
- Past history (ILD, pulmonary fibrosis, radiation pneumonitis, lymphangiosis carcinomatosa, pleural effusion, pulmonary edema, or other respiratory diseases);
- Past history (cardiovascular diseases) [absent, present];
- Past history (autoimmune disease) [absent, present];
- Past history (hepatic impairment) [absent, present];
- Past history (renal impairment) [absent, present];
- Complication (drug allergy) [absent, present];
- Complication (other allergic diseases) [absent, present];

- Complication (ILD, pulmonary fibrosis, radiation pneumonitis, lymphangiosis carcinomatosa, pleural effusion, pulmonary edema, or other respiratory diseases);
- Complication (cardiovascular diseases) [absent, present];
- Complication (autoimmune diseases) [absent, present];
- Complication (hepatic impairment) [absent, present];
- Complication (renal impairment) [absent, present];
- Treatment line with Xalkori capsules for NSCLC [1st-line, 2nd-line, 3rd-line, 4th-line, 5th-line, 6th-line, 7th-line, 8th-line, 9th-line, ≥10th-line];
- Severity of renal impairment (eGFR) [Grade <1, Grade 1, Grade 2, Grade ≥3].

Subgroup analyses of effectiveness will also be performed for the following subgroups:

- Children (<15 years of age) vs adults (≥15 years);
- Elderly (≥65 years of age) vs non-elderly (<65 years);
- Pregnant vs not pregnant;
- With vs without renal impairment;
- With vs without hepatic impairment.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

Safety endpoints include:

- Adverse reactions, ie, treatment-related adverse events (AEs) as assessed by the physician or company,
- Adverse events (all causality), and
- Events of special interest, which include:
    - Interstitial lung disease (ILD) (A separate analysis will also be performed for the data that only include the events judged by the adjudication committee as ILD);
    - QTc prolongation;
    - Bradycardia;

- Hepatotoxicity;
- Visual disturbance;
- Neutropenia/Leukopenia;
- Neuropathy;
- Complicated renal cyst;
- Photosensitivity.

Events of special interests will be identified according to a separate risk management plan.

6.2. Effectiveness Endpoints

Effectiveness endpoints include:

- Best Response: Per RECIST version 1.1[1], disease response will be determined as:
- Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or indeterminate.
- Objective Response Rate (ORR), which is the proportion of patients with best response being CR or PR.
- Overall Survival (OS), which is the time from the initiation of treatment with Xalkori capsules to death during this survey. All deaths observed in this survey will be considered as relevant events, and patients who survived during the survey period will be censored at the last time point of observed survival.

6.3. Other Endpoints

Duration of Treatment, which is the time from the initiation of treatment with Xalkori capsules to the end of treatment with Xalkori capsules during the survey, will be analyzed as an endpoint. Patients who continue to use Xalkori capsules after the end of the survey period will be censored at the end of treatment during the survey period.

6.4. Covariates

Covariates for the analysis of the occurrence of ILD include:

- Age group (reference: <65 years);
- Sex (reference: male);
- ECOG PS (reference: 0);

- Brinkman index (reference: never smoked);
- Past history (ILD, pulmonary fibrosis, radiation pneumonitis, lymphangiosis carcinomatosa, pleural effusion, pulmonary edema, or other respiratory diseases) (reference: absent);
- Past history (cardiovascular diseases) (reference: absent);
- Complication (ILD, pulmonary fibrosis, radiation pneumonitis, lymphangiosis carcinomatosa, pleural effusion, pulmonary edema, or other respiratory diseases) (reference: absent);
- Complication (cardiovascular diseases) (reference: absent).

Covariates for the analysis of the occurrence of hepatotoxicity include:

- Age group (reference: <65 years);
- Sex (reference: male);
- ECOG PS (reference: 0);
- Past history (drug allergy) (reference: absent);
- Past history (other allergic diseases) (reference: absent);
- Past history (hepatic impairment) (reference: absent);
- Complication (drug allergy) (reference: absent);
- Complication (other allergic diseases) (reference: absent);
- Complication (hepatic impairment) (reference: absent).

Covariates may be added or deleted according to the results of an interim analysis of this study or based on new findings. If this occurred, this SAP will be revised.

7. HANDLING OF MISSING DATA

If the data for seriousness, action taken, and/or outcome for an AE are missing, they are handled as "unknown" when summarizing data.

If data within the window period (Appendix 1: Details of Data Collection) of each measurement time are missing for an effectiveness endpoint, they are handled as missing data and will not be imputed. In the analysis of OS, an unknown censor date will be imputed with the last date of observed survival, eg, the end of treatment or last time of effectiveness evaluation. In the analysis of duration of treatment, an unknown censor date will be

imputed with 12 weeks, 24 weeks, or 52 weeks after the initiation of treatment, according to the status of questionnaire collection.

8. STATISTICAL METHODS AND ANALYSES

8.1. Statistical Methods

8.1.1. Continuous Data

Data for continuous variables will be summarized using summary statistics (n, mean, standard deviation [SD], median, max, min).

8.1.2. Categorical Data

Data for categorical variables will be summarized in terms of the number and percentage of patients.

8.1.3. Binary Data

Data for binary variables will be summarized in terms of the number and percentage of patients. When presenting a confidence interval (CI) for a percentage, a two-sided 95% CI calculated based on an exact method will be presented.

For a comparison of percentages between subgroups, the risk ratio and its 95% CI will be calculated.

If a statistical test is performed, nominal scale data will be tested using Fisher's exact test, while ordinal scale data will be tested using the Cochran-Armitage test (exact method). In case of too much time required for output because of computation ability, or being unable to perform required calculations, the chi-square test and Cochran-Armitage test will instead be used for nominal and ordinal scale data, respectively.

8.1.4. Time Period (time to event) Data

For time period data (or time-to-event data), the median, 1st quartile, and 3rd quartile points will be calculated for each variable using the Kaplan-Meier method. The Kaplan-Meier curve will also be presented.

Using a Cox proportional hazard model, the covariate-adjusted hazard rate and its 95% CI will be estimated for each time-to-event variable. Using log-log plots, whether the assumption of proportional hazard is realized or not will be determined.

8.2. Statistical Analyses

A patient who was transferred from another hospital will be handled as the same patient as the one treated in the previous hospital if the data for birth date (a difference of one year or less allowed), sex, transferred hospital and transferring hospital coincide. In principle, the data in the previous hospital will be adopted for the patient characteristics and start of

treatment. As for the data after the start of treatment, those in both previous and present hospitals will be used.

8.2.1. Description of Patients

- **Number of investigated sites and number of investigated patients by type of site establisher.**

In patients from whom questionnaire was collected, the number and percentage of sites and the number and percentage of patients will be presented for each of the following site types:

- National or private university hospitals;
- National hospitals established by the Ministry of Health, Labour and Welfare (MHLW);
- Prefectural or municipal hospitals;
- Public institutions;
- Hospitals established by a corporation/individual other than the four categories above;
- Clinics/practices.

The mean, minimum, and maximum number of patients per site will also be calculated.

- **Patient disposition**

In questionnaire-collected patients, the number of patients included in the safety analysis and the number of patients included in the effectiveness analysis will be presented. In addition, the number of patients excluded from the safety analysis and the number of patients excluded from the effectiveness analysis will be presented; these patients will also be summarized by reason for exclusion.

- **Summary of discontinuations/dropouts**

Using the safety analysis set and effectiveness analysis set, patients for whom follow-up was discontinued will be summarized by time of discontinuation [≤12 weeks, >12-≤24 weeks, >24 weeks posttreatment] in terms of the number and percentage. In addition, the discontinued patients will also be summarized by reason for discontinuation, using the number and percentage.

A table of discontinued patients with specific reasons for discontinuation other than inadequate clinical response, AE, death, no revisit, or hospital/department transfer will be presented.

- **Listing of excluded patients**

Listings of patients who were excluded from the safety analysis set and from the effectiveness analysis set will be presented with their reasons for exclusion.

8.2.2. Patient Characteristics and Prior Treatments

- **Patient characteristics**

Using the safety analysis set and effectiveness analysis set, patient characteristics will be summarized according to Section 8.1, with respect to the following factors:

- Sex [male, female];
- Age (continuous);
- Age group [<15 years, ≥15 years];
- Age group [<65 years, ≥65 years];
- Age group [<25 years, ≥25-<35 years, ≥35-<45 years, ≥45-<55 years, ≥55-<65 years, ≥65-<75 years, ≥75 years];
- Body height (continuous);
- Body height [<150 cm, ≥150-<160 cm, ≥160-<170 cm, ≥170 cm];
- Body weight (continuous);
- Body weight [<40 kg, ≥40-<50 kg, ≥50-<60 kg, ≥60-<70 kg, ≥70-<80 kg, ≥80 kg];
- Body surface area (continuous);
- Body surface area [<1.2, ≥1.2-<1.4, ≥1.4-<1.6, ≥1.6-<1.8, ≥1.8];
- BMI (continuous);
- BMI [<18.5, ≥18.5-<25.0, ≥25.0];
- Inpatient/outpatient status at the start of treatment [inpatient, outpatient];
- Investigated disease [ALK fusion gene-positive unresectable advanced/recurrent NSCLC, others];
- Time from first diagnosis of NSCLC to treatment (continuous);

- Time from first diagnosis of NSCLC to treatment [≥0-≤12 months, ≥13 -≤24 months, ≥25-≤48 months, ≥49-≤72 months, ≥73-≤96 months, ≥97 months];
- History of ALK test [never tested, FISH, PCR, IHC, FISH → PCR, FISH → IHC, PCR → FISH, PCR → IHC, IHC → FISH, IHC → PCR, FISH → PCR → IHC, FISH → IHC → PCR, PCR → FISH → IHC, PCR → IHC → FISH, IHC → FISH → PCR, IHC → PCR → FISH];
- ALK test detail [FISH, PCR, IHC, FISH + PCR, FISH + IHC, PCR + IHC, FISH + PCR + IHC];
- Stage of target disease [IA, IB, IIA, IIB, IIIA, IIIB, IV];
- M category of target disease [MX, M0, M1a, M1b];
- Metastasis (lung) [absent, present];
- Metastasis (liver) [absent, present];
- Metastasis (lymph node) [absent, present];
- Metastasis (pleura) [absent, present];
- Metastasis (bone) [absent, present];
- Metastasis (brain) [absent, present];
- Examination for histopathologic diagnosis [performed, unperformed];
- Histopathologic diagnosis (multiple choices allowed) [acinar adenocarcinoma, papillary adenocarcinoma, bronchioloalveolar carcinoma, mucin-producing solid adenocarcinoma, signet-ring cell carcinoma, unclassifiable adenocarcinoma, squamous cell carcinoma, large cell carcinoma, adenosquamous carcinoma, others];
- ECOG PS [0, 1, 2, 3, 4];
- Smoking status [never smoked, ex-smoker, smoker];
- Brinkman index (continuous);
- Brinkman index [<200, ≥200-<400, ≥400-<600, ≥600-<800, ≥800-<1000, ≥1000-<1200, ≥1200];
- History of occupational/environmental exposure to asbestos, pneumoconiosis, etc. [absent, present];

- High concentration of oxygen for the treatment of respiratory disease [never received, currently receiving, previously received];
- Chest CT examination [performed, unperformed];
- Chest X ray examination [performed, unperformed];
- Past history [absent, present];
- Past history (drug allergy) [absent, present];
- Past history (other allergic diseases) [absent, present];
- Past history (ILD) [absent, present];
- Past history (pulmonary fibrosis) [absent, present];
- Past history (radiation pneumonitis) [absent, present];
- Past history (lymphangiosis carcinomatosa) [absent, present];
- Past history (pleural effusion) [absent, present];
- Past history (pulmonary edema) [absent, present];
- Past history (COPD) [absent, present];
- Past history (pulmonary emphysema) [absent, present];
- Past history (lung infection (including bacterial and fungal)) [absent, present];
- Past history (other respiratory diseases) [absent, present];
- Past history (ILD, pulmonary fibrosis, radiation pneumonitis, lymphangiosis carcinomatosa, pleural effusion, pulmonary edema, or other respiratory diseases) [absent, present];
- Past history (cardiovascular diseases) [absent, present];
- Past history (autoimmune diseases) [absent, present];
- Past history (hepatic impairment) [absent, present];
- Past history (renal impairment) [absent, present];
- Complication [absent, present];

- Complication (drug allergy) [absent, present];
- Complication (other allergic diseases) [absent, present];
- Complication (ILD) [absent, present];
- Complication (pulmonary fibrosis) [absent, present];
- Complication (radiation pneumonitis) [absent, present];
- Complication (lymphangiosis carcinomatosa) [absent, present];
- Complication (pleural effusion) [absent, present];
- Complication (pulmonary edema) [absent, present];
- Complication (COPD) [absent, present];
- Complication (pulmonary emphysema) [absent, present];
- Complication (lung infection (including bacterial and fungal)) [absent, present];
- Complication (other respiratory diseases) [absent, present];
- Complication (ILD, pulmonary fibrosis, radiation pneumonitis, lymphangiosis carcinomatosa, pleural effusion, pulmonary edema, or other respiratory diseases) [absent, present];
- Complication (cardiovascular diseases) [absent, present];
- Complication (autoimmune diseases) [absent, present];
- Complication (hepatic impairment) [absent, present];
- Complication (renal impairment) [absent, present];
- Treatment line with Xalkori capsules for NSCLC [1st-line, 2nd-line, 3rd-line, 4th-line, 5th-line, 6th-line, 7th-line, 8th-line, 9th-line, ≥10th-line];
- Severity of renal impairment (eGFR) [Grade <1, Grade 1, Grade 2, Grade ≥3];

Using the safety analysis set, each of the following factors will be summarized by System Organ Class (SOC) and Preferred Term (PT), in terms of the number and percentage of patients:

- Past history;

- Complication.

Using the safety analysis set and effectiveness analysis set, each of the following factors will be summarized in terms of the number and percentages of patients:

- Concomitant medication;
- History of surgical treatment for NSCLC (primary or metastatic lesion);
- History of radiation therapy for NSCLC;
- History of drug therapy for NSCLC;

  1st-line treatment [amrubicin hydrochloride, irinotecan hydrochloride hydrate, erlotinib hydrochloride, carboplatin, gefitinib, gemcitabine hydrochloride, cisplatin, tegafur/gimeracil/oteracil potassium combination, docetaxel hydrate, nedaplatin, paclitaxel, vinorelbine ditartrate, bevacizumab, pemetrexed sodium hydrate, others];

  2nd-line treatment [amrubicin hydrochloride, irinotecan hydrochloride hydrate, erlotinib hydrochloride, carboplatin, gefitinib, gemcitabine hydrochloride, cisplatin, tegafur/gimeracil/oteracil potassium combination, docetaxel hydrate, nedaplatin, paclitaxel, vinorelbine ditartrate, bevacizumab, pemetrexed sodium hydrate, others];

  3rd-line treatment [amrubicin hydrochloride, irinotecan hydrochloride hydrate, erlotinib hydrochloride, carboplatin, gefitinib, gemcitabine hydrochloride, cisplatin, tegafur/gimeracil/oteracil potassium combination, docetaxel hydrate, nedaplatin, paclitaxel, vinorelbine ditartrate, bevacizumab, pemetrexed sodium hydrate, others];

  4th-line treatment [amrubicin hydrochloride, irinotecan hydrochloride hydrate, erlotinib hydrochloride, carboplatin, gefitinib, gemcitabine hydrochloride, cisplatin, tegafur/gimeracil/oteracil potassium combination, docetaxel hydrate, nedaplatin, paclitaxel, vinorelbine ditartrate, bevacizumab, pemetrexed sodium hydrate, others];

  5th-line treatment [amrubicin hydrochloride, irinotecan hydrochloride hydrate, erlotinib hydrochloride, carboplatin, gefitinib, gemcitabine hydrochloride, cisplatin, tegafur/gimeracil/oteracil potassium combination, docetaxel hydrate, nedaplatin, paclitaxel, vinorelbine ditartrate, bevacizumab, pemetrexed sodium hydrate, others];

  6th-line treatment [amrubicin hydrochloride, irinotecan hydrochloride hydrate, erlotinib hydrochloride, carboplatin, gefitinib, gemcitabine hydrochloride, cisplatin, tegafur/gimeracil/oteracil potassium combination, docetaxel hydrate, nedaplatin, paclitaxel, vinorelbine ditartrate, bevacizumab, pemetrexed sodium hydrate, others].

- **Status of the treatment with Xalkori capsules**

Using the safety analysis set, the status of the treatment with Xalkori capsules will be summarized by each of the following factors:

- Treatment duration [≤12 weeks, >12-≤24 weeks, >24-≤52 weeks, >52 weeks] (and as a continuous variable, as well);
- Initial dose per day [<400 mg, 400 mg, >400-<500 mg, 500 mg, >500 mg];
- Total dose (continuous).

The treatment duration is defined as the period from the initial dose to the last observed dose during the survey, including non-dosing periods.

8.2.3. Safety Analyses

8.2.3.1. Adverse reactions

- **All adverse reactions**

Patients who experienced adverse reactions will be summarized by SOC and PT, using the number and percentage.

- **Serious adverse reactions**

Patients who experienced serious adverse reactions will be summarized by SOC and PT, using the number and percentage.

- **Details of adverse reactions**

Patients who experienced adverse reactions will be summarized by each of the following factors, using the number and percentage within each SOC and PT:

- Seriousness [serious, non-serious];
- Listed/Unlisted [listed, unlisted];
- Action taken [discontinuation, interruption/dose reduction];
- Outcome [not recovered, recovered with sequelae, recovering, resolved/recovered, unknown];
- CTCAE Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5];
- CTCAE Grade [Grade ≤2, Grade ≥3].

If a patient experienced the same adverse reaction (same PT) multiple times, those events will be counted as follows:

- If a patient experienced both serious and non-serious events of the same adverse reaction, the patient will be counted as having a serious adverse reaction;
- If a patient experienced both listed and unlisted events, the patient will be counted as having an unlisted event;
- If multiple actions were taken for the event(s), one action will be selected from discontinuation, interruption, dose reduction, or others, with this order of priority (ie, discontinuation is the highest priority, the others lowest); and
- The outcome is defined as that of the last event.

- **Time to adverse reaction**

Patients who experienced adverse reactions will be summarized by time to first occurrence [≤12 weeks, >12-≤24 weeks, >24-≤52 weeks, >52 weeks], using the number within each SOC and PT.

In addition, time to first occurrence of the adverse reaction of ILD will be summarized according to Section 8.1.4. Patients who did not experience ILD will be censored at the discontinuation or last observation date of this survey.

- **Events of special interest**

Data for the occurrence of the events of special interest will be summarized in terms of the number and percentage of patients.

In addition, the data will also be summarized in the same manners described in "Details of adverse reactions" and "Time to adverse reaction".

- **Adverse reactions in patients excluded from the safety analysis set**

In questionnaire-collected patients who were excluded from the safety analysis set, patients who experienced adverse reactions will be summarized using the number within each SOC and PT.

8.2.3.2. Adverse Events

- **All adverse events**

Patients who experienced AEs will be summarized by SOC and PT, using the number and percentage.

- **Serious and non-serious adverse events**

Patients who experienced SAEs will be summarized by SOC and PT, using the number and percentage. Patients who experienced non-serious AEs will be summarized in a similar manner.

8.2.3.3. Subgroup Analyses

Patients who experienced at least one event of adverse reaction of ILD will be summarized for each subgroup defined in Section 5.4, using the number and percentage. To assess the relationship between patient characteristics and occurrence of adverse reactions, risk ratios and their 95% CIs will be calculated and statistical tests performed as described in Section 8.1.3.

In addition, if at least one event of adverse reaction of hepatotoxicity, visual disturbance, neutropenia/leukopenia, or neuropathy developed, a similar summary will be presented for each of the adverse reaction types that were observed at least one time.

Furthermore, for each of the patient subgroups defined in Section 5.4, patients who experienced adverse reactions, serious adverse reactions, adverse reactions of Grade ≥3, and SAEs will be summarized by SOC and PT, using the number and percentage.

CCI [redacted]

- CCI [redacted]

[redacted]

8.2.4. Effectiveness Analyses

8.2.4.1. Objective Response Rate

The best responses after 52 weeks of treatment and at the end of treatment with Xalkori capsules will be summarized by presenting the number and percentage of patients within each category of response.

In addition, the number of patients with objective response (OR = CR or PR), objective response rate (ORR) and its 95% CI will be presented.

8.2.4.2. Overall Survival

Overall survival (OS) will be summarized according to Section 8.1.4.

8.2.4.3. Subgroup Analyses

A subgroup analysis of ORR will be performed for each of the factors defined in Section 5.4.

In addition, for each of the subgroups defined in Section 5.4, the distribution of best responses will be summarized using the numbers and percentages of patients, and the number of patients with OR, the ORR, and its 95% CI will be presented.

CCI [redacted]

[redacted]

9. LISTINGS

Following subject listings will be provided:

- Listing of patients;
- Listing of patients with adverse reactions;
- Listing of patients with serious adverse reactions;
- Listing of patients with SAEs;
- Listing of patients with AEs;

[redacted]

- Listing of patients excluded from the safety analysis set who experienced adverse reactions;
- Listing of patients who experienced adverse reactions of special interest;
- Listing of patients with hepatic impairment who experienced adverse reactions;
- Listing of patients with renal impairment who experienced adverse reactions;
- Listing of elderly patients (≥65 years) who experienced adverse reactions;
- Listing of pediatric patients (<15 years) who experienced adverse reactions;
- Listing of pregnant patients who experienced adverse reactions;
- Listing of events of special interest;
- Listing of deaths.

In addition, the following tables that correspond to some of the Attachment forms for the periodic safety update report will be provided:

- Attachment Form 3 (Tabulated Summary of the Investigated Patients);
- Attachment Form 2 (Summary Table of Adverse Reactions/Infections);
- Attachment Form 10 (Attachment Form 2-2) (Summary Table of Serious Adverse Events).

10. REFERENCES

1. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).

2. Manuals for the Management of Individual Serious Adverse Drug Reactions (In Japanese, available at http://www.info.pmda.go.jp/juutoku/juutoku_index.html).

11. APPENDICES

11.1. Appendix 1: Details of Data Collection

A1.1 DEFINITIONS OF VISITS

Visit	Endpoints	Definition [window period]
Start of Treatment	Effectiveness endpoints	From 30 days before the first dose (treatment initiation) to the date of first dose during this survey
Week 12	Effectiveness endpoints	From one week (one day) to 18 weeks (126 days) after the start of treatment
Week 24	Effectiveness endpoints	From 19 weeks (127 days) to 38 weeks (266 days) after the start of treatment
Week 52	Effectiveness endpoints	From 39 weeks (267 days) to 54 weeks (378 days) after the start of treatment
End of Treatment	Effectiveness endpoints	From 2 weeks before the last dose to 2 weeks after the last dose during this survey

11.2. Appendix 2: Formulae

Body Surface Area = (Weight [kg]) $^{0.425}$ × (Height [cm]) $^{0.725}$ × 0.007184

Body Mass Index (BMI) = Weight [kg]/ (Height [m]) ^{2}

Stage of the Investigated Disease:

TNM classification	N0	N1	N2	N3
Tis	0			
T1a, T1b	IA	IIA	IIIA	IIIB
T2a	IB	IIA	□A	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIB
T4	IIIA	IIIA	IIIB	IIIB
M1a, M1b	IV	IV	IV	IV

Brinkman index = (Number of cigarettes smoked per day) × (Years of smoking)

Renal impairment severity (eGFR) = 194 × (Serum creatinine [mg/dL])$^{-1.094}$ × (Age [years])$^{-0.287}$ × (1 for male or 0.739 for female).