Protocol No.: JO29424

Version 1.2

Date prepared: October 1, 2017

Survival Follow Up of JO25567, a Randomized Phase 2 Study Comparing Erlotinib and Bevacizumab Combination with Erlotinib Alone in NSCLC Patients Harboring EGFR Mutation

Protocol

Chugai Pharmaceutical Co., Ltd.

Confidentiality Statement

Sponsor's Contact Details

Sponsor:

Chugai Pharmaceutical Co., Ltd.

2-1-1 Nihonbashi-Muromachi, Chuo-ku, Tokyo 103-8324, Japan

Study Leader:

Medical Science Dept., Chugai Pharmaceutical Co., Ltd.

Tel: +81-3-3273-2613 Fax: +81-3-3281-2656

Enrollment Center:

[redacted].

Address: [redacted], Japan

Tel: [redacted] Fax: [redacted]

SYNOPSIS

Name of Sponsor: Chugai Pharmaceutical Co., Ltd.	
Name of Study Drug: Erlotinib	
Name of Active Ingredient: Erlotinib hydrochloride	
Title of Study: Survival follow up of JO25567, a randomized phase 2 study comparing erlotinib and bevacizumab combination with erlotinib alone in NSCLC patients harboring EGFR mutation	
Principal Investigators/Study Sites: See Attachment 2.	
Medical Expert: [redacted] (Chugai Pharmaceutical Co., Ltd.)	
Planned Study Period: July 2014 to March 2018	Phase of Development: Phase IV
Objectives: The study will follow patients who completed Study JO25567 comparing bevacizumab plus erlotinib with erlotinib alone with the objective of comparing overall survival between these 2 treatment groups. Primary objective: Overall survival	
Methodology: The study is an open-label follow-up study of survival in patients who participated in Study JO25567.	
Planned Sample Size: Up to 121 patients	
Diagnosis and Main Criteria for Inclusion: Inclusion Criteria (1) Enrolled and received investigational medicinal product at least once in the previously conducted Study JO25567: "Open-Label, Randomized, Phase II Clinical Study to Compare Combination Therapy with Bevacizumab + RO5O-8231 (Erlotinib) and Monotherapy with RO5O-8231 as First-Line Therapy in Non-Small Cell Lung Cancer Patients with EGFR Gene Mutations" (excluding patients who died or were lost to follow-up in Study JO25567) (2) Provided written informed consent after having received a detailed explanation of the study	
Study Period: For each patient, participation in the study will extend from the day of informed consent to death or lost to follow-up (including withdrawal of consent). Study Completion/Withdrawal Criteria: Patients meeting criterion (1) below will be considered to have completed the study. Patients meeting criterion (2) below will be withdrawn from the study by the investigator. (1) Death (2) Lost to follow-up (including withdrawal of consent)	
Study Procedure: The study will not include any patient visits, drug administration, or testing. The outcome of patients (alive/died/lost to follow-up [including withdrawal of consent]) and subsequent treatment for NSCLC after the completion of Study JO25567 will be evaluated at the following time points. • Evaluation time point: Annually (generally in September of each year) Evaluations may also be performed at other time points depending on the occurrence of death events.	

Endpoints: Primary endpoint: Overall survival Survival outcome will be evaluated regularly until death or lost to follow-up (including withdrawal of consent). Detailed information on subsequent treatment received by patients will also be recorded.
Statistical Methods: Efficacy: In the analysis of the primary endpoint, overall survival (OS) will be compared by log-rank test using the pooled survival data from the current study and Study JO25567. The hazard ratio for OS in the bevacizumab + erlotinib group compared with the erlotinib alone group will also be determined using a Cox proportional hazards model.
Interim Analyses: Interim analyses of survival and subsequent treatment for NSCLC will be performed annually in the current study.

List of Abbreviations

Abbreviation	Full term
EGFR	epidermal growth factor receptor
GCP	Good Clinical Practice
GPSP	Good Post-Marketing Study Practice
IRB	institutional review board
MST	median survival time
OS	overall survival
PFS	progression-free survival
PS	performance status

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1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Study Sponsor

Study sponsor: Chugai Pharmaceutical Co., Ltd.

Address: 2-1-1 Nihonbashi-Muromachi, Chuo-ku, Tokyo 103-8324, Japan

Tel: +81-3-3273-2613 Fax: +81-3-3281-2656

1.2 Medical Expert

1. Main roles of the medical expert
   The medical expert will provide the sponsor with advice from a medical standpoint mainly with respect to the following matters in response to requests from the sponsor, and will sign the clinical study report after checking the contents.

   a. Preparation and amendment of the protocol
   b. Preparation and amendment of the informed consent form (sample)
   c. Preparation and amendment of the clinical study report (CSR) and study articles
   d. Study conduct

2. Name, title, and contact details of medical expert
   Name: [redacted]

   Title: [redacted], Chugai Pharmaceutical Co., Ltd.

   Contact details: [redacted], Japan

   Tel: [redacted] Fax: [redacted]

1.3 Sponsor's Administrative Structure

1.3.1 Post-Marketing Study Manager

Affiliation: Safety Real World Data Science Dept.

Name: [redacted]

1.3.2 Study Leader

1. Main duties of Study Leader
   a. Responsible for the study protocol (protocol signatory)

2. Affiliation, name, and contact details of Study Leader

See Attachment 1.

1.3.3 Monitors

1. Main duties of monitors
   a. Preparing the protocol
   b. Survey of study conduct by visiting the study sites, etc.

c. Study request and contract procedures
d. Collecting and reviewing case report forms (CRFs)
e. Gathering and providing information
f. Performing source document verification
g. Confirming the retention of study-related documents or records
h. Monitoring activities other than those specified above

2. Affiliations, names, and contact details of monitors
   See Attachment 1.

1.3.4 Other Duties of the Sponsor

The sponsor will perform the following tasks in accordance with standard operating procedures (SOPs) prepared and controlled by Chugai Pharmaceutical Co., Ltd.

1. Retaining records
   a. Retaining and managing study-related documents required to be retained by the sponsor
2. Statistical analysis
   a. Preparing the statistics section of the protocol

1.4 Study Sites and Principal Investigators

See Attachment 2 for a list of study sites and principal investigators.

1.5 Contract Research Organizations (CROs)

1.5.1 Monitoring and Enrollment Center Activities

See Attachment 1 for information on personnel at the monitoring CRO.

1. Main contracted services
   a. Survey of study conduct by visiting the study sites, etc.
   b. Study request and contract procedures
   c. Receiving patient enrollments, checking patient eligibility/ineligibility, and sending communications regarding these matters
   d. Collecting and reviewing CRFs
   e. Gathering and providing information
   f. Performing source document verification
   g. Confirming the retention of study-related documents and records
   h. Monitoring activities other than those specified above

2. Name, supervisor/personnel, and address of the CRO responsible for monitoring and enrollment center activities
   See Attachment 1.

1.5.2 Statistical Analysis

1. Main contracted services
   a. Preparing the statistical analysis plan (SAP)

b. Performing statistical analysis

2. Name and address of statistical analysis CRO
   Name: [redacted]

   Address: [redacted], Japan

   Tel: [redacted] Fax: [redacted]

1.5.3 Data Management

1. Main contracted services
   a. Preparing CRFs
   b. Preparing the data management plan and report
   c. Database design
   d. Data entry, data checking, and data lock
   e. Data verification

2. Name and address of data management CRO
   Name: [redacted]

   Address: [redacted], Japan

   Tel: [redacted] Fax: [redacted]

1.5.4 Retention of Records

1. Main contracted services
   a. Retaining and managing study-related documents required to be retained by the sponsor

2. Name and address of archiving CRO
   Name: [redacted]

   Address: [redacted], Japan

   Tel: [redacted] Fax: [redacted]

1.5.5 Clinical Study Report (CSR)

1. Main duties
   a. Preparing the CSR

2. Name and address of organization responsible for preparing the CSR
   Name: F. Hoffmann-La Roche Ltd.
   Address: Grenzacherstrasse 124, 4070 Basel, Switzerland

2. BACKGROUND

2.1 Japanese Phase II Clinical Study (JO22903)

A Phase II clinical study (JO22903) was conducted to evaluate the efficacy and safety of erlotinib monotherapy in 103 patients with treatment-naïve, advanced, metastatic, or postoperative recurrent NSCLC with EGFR mutations (exon 19 deletion or L858R mutation in exon 21).

The analysis of the primary endpoint of progression-free survival (PFS) showed PFS of 11.8 months (95% confidence interval [CI]: 9.7–15.3 months). PFS tended to be longer in patients with exon 19 deletions than patients with L858R mutations. The most common adverse events were rash (all grades: 83%) and diarrhea (all grades: 81%). The safety profile was consistent with the expected safety profile. Interstitial lung disease (ILD) was reported in 6 patients [17.1].

The analysis of the secondary endpoint, overall survival (OS), showed that OS-related events occurred in 50 patients (49.0%). The median OS was 36.3 months (95% CI: 29.4 months to not reached), and the estimated 1-year and 2-year survival rates were 92% (95% CI: 87%–97%) and 69% (95% CI: 60%–78%), respectively [17.2, 17.6].

2.2 Japanese Phase II Clinical Study (JO25567) [17.5]

A Phase II clinical study (JO25567) was conducted to compare bevacizumab in combination with erlotinib with erlotinib alone in the first-line treatment of patients with treatment-naïve, advanced, metastatic, or postoperative recurrent NSCLC with EGFR mutations (exon 19 deletion or L858R mutation in exon 21).

The analysis of the primary endpoint, PFS (assessed by an independent review committee), showed that the median PFS was statistically significantly longer in patients receiving bevacizumab plus erlotinib (hereinafter, “AT group”) than patients receiving erlotinib alone (hereinafter, “T group”) (16.0 months vs. 9.7 months; hazard ratio 0.54 [95% CI: 0.36–0.79 months]; P=0.0015). An analysis of PFS by baseline characteristics (sex, age category, smoking status, performance status, histopathological classification, disease stage, EGFR mutation) also showed greater benefit in the AT group than the T group across all subgroups of patients. The analysis of the secondary endpoint, OS, indicated that at the time that the 89 PFS events specified in the protocol were reached (June 30, 2013), 13 events had occurred in the AT group and 18 events had occurred in the T group, with the median OS not being reached.

The safety evaluation showed that the addition of bevacizumab resulted in an increase in adverse events specific to bevacizumab (hypertension, hemorrhagic events, and proteinuria), but the incidence of adverse events in the bevacizumab plus erlotinib group was not significantly different from that in the erlotinib alone group. No pattern of increased incidence of adverse events of rash and gastrointestinal symptoms specific to erlotinib was observed with the addition of bevacizumab, indicating that combination therapy with the 2 drugs was well tolerated [17.3].

Based on the findings of this study, F. Hoffman-La Roche Ltd. filed an application for marketing authorization with the European Medicines Agency (EMA) for combination

therapy with bevacizumab plus erlotinib for the indication of chemotherapy-naïve, unresectable, advanced/metastatic or recurrent NSCLC with EGFR mutations. Approval was received in June 2016.

2.3 Overseas Phase III Clinical Study (BeTa Lung Study, OSI3364g/BO20792)

BeTa Lung was a Phase III study conducted primarily to evaluate the efficacy of bevacizumab (15 mg/kg/3 wk) in combination with erlotinib (150 mg/day) compared with erlotinib alone for the second-line treatment of patients with histologically or cytologically confirmed advanced *NSCLC* who had received standard first-line chemotherapy. The primary endpoint was OS, and the secondary endpoints were PFS, response rate, response duration, pharmacokinetics, and correlation between biomarkers and efficacy.

A total of 636 patients (319 patients in the bevacizumab + erlotinib group and 317 patients in the erlotinib alone group) were randomized in the study. The final analysis was conducted when 418 deaths were observed. The median duration of follow-up was 19 months (range: 0.2–34 months).

The analysis of the primary endpoint, OS, showed that OS was 9.3 months in the bevacizumab plus erlotinib group versus 9.2 months in the erlotinib alone group, demonstrating that the addition of bevacizumab did not prolong OS (hazard ratio 0.97 [95% CI: 0.80–1.18]; *P*=0.7583). The analysis of the secondary endpoint, PFS, showed that PFS was 3.4 months in the bevacizumab plus erlotinib group versus 1.7 months in the erlotinib alone group (hazard ratio 0.62). The response rate was 13% in the bevacizumab plus erlotinib group and 6% in the erlotinib alone group.

The incidence of bevacizumab-related adverse events was not clearly different from that observed in previous clinical studies [17.4].

2.4 Summary of Known and Potential Risks and Benefits to Patients

The study is designed to evaluate the survival status and collect treatment history data only, without investigational medicinal product being administered or tests being performed. There are therefore no known or potential risks or benefits to patients.

2.5 Appropriateness of Conducting the Study

The analysis of the primary endpoint, PFS (assessed by an independent review committee), in JO25567 showed that the median PFS was statistically significantly longer in patients receiving bevacizumab plus erlotinib (hereinafter, “AT group”) than patients receiving erlotinib alone (hereinafter, “T group”) (16.0 months vs. 9.7 months; hazard ratio 0.54; *P*=0.0015). However, at the time of the primary analysis of PFS, the length of the follow-up period of the secondary endpoint, OS, was insufficient and the median OS was not reached. No historical OS data for comparisons of tyrosine kinase inhibitors alone and in combination with bevacizumab for the first-line treatment of EGFR mutation-positive

NSCLC are currently available, and therefore, follow-up investigation of OS in the current study was determined to be scientifically appropriate.

2.6 Good Clinical Practice and Good Postmarketing Study Practice Compliance Statement

The study will be conducted in compliance with the Declaration of Helsinki; this study protocol; Paragraph 4 of Article 14-4 and Paragraph 4 of Article 14-6 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics; the Ministerial Ordinance on Good Postmarketing Study Practice (GPSP); and the Ministerial Ordinance on Good Clinical Practice for Drugs (GCP).

3. STUDY OBJECTIVES

Primary objective:

The study will follow patients who completed Study JO25567 comparing bevacizumab plus erlotinib with erlotinib alone with the objective of comparing overall survival between these 2 treatment groups.

4. STUDY DESIGN

4.1 Endpoints

1. Primary endpoint

Overall survival

4.2 Study Type and Design

4.2.1 Study Type

Phase IV (survival follow-up study)

4.2.2 Study Design

The study will be an open-label follow-up study of survival in patients who participated in Study JO25567.

4.3 Study Procedures

The study procedures are described below.

1. Selection of patients
   The investigator will enroll patients who were enrolled and received investigational medicinal product at least once in Study JO25567.

2. Informed consent
   Patients who are considered suitable for this study will be fully informed about the study by the investigator, and the investigator will obtain their written informed consent (for details, see section 12.1 “Informed Consent of Patients”).

3. Assessment of eligibility
   The investigator will determine patient eligibility based on the inclusion and exclusion criteria.

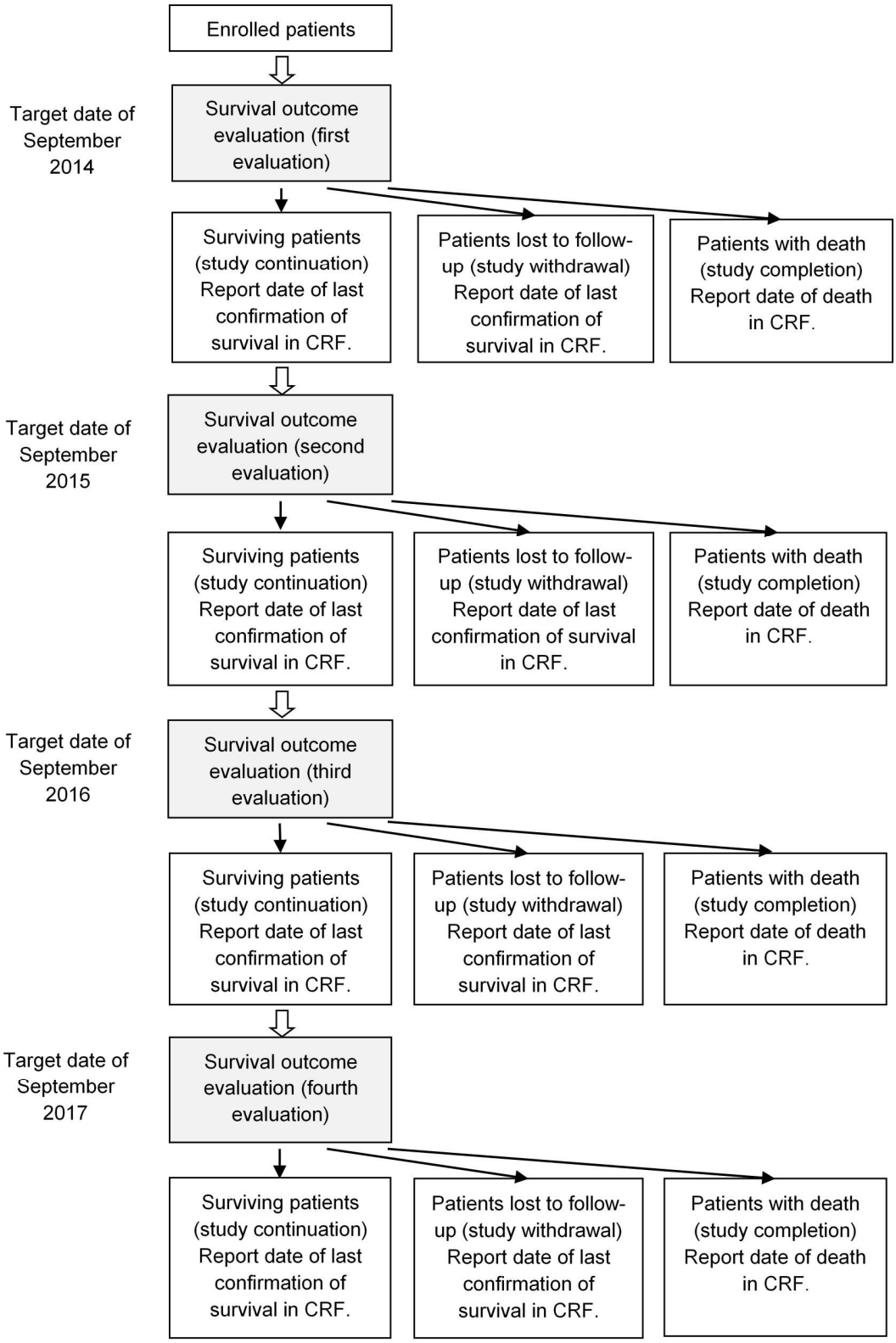
4. Enrollment
   The investigator (or a study collaborator under the guidance of the investigator) will complete the enrollment form (Form 3) with the required patient information and fax the completed form to the enrollment center ([redacted], fax: [redacted]). The enrollment center will review the enrollment form (Form 3) sent by the study site and notify the study site of the eligibility/ineligibility of the patient (along with the reason for ineligibility for patients determined to be ineligible) using the enrollment confirmation form (Form 3). The same patient numbers used in Study JO25567 will be used.

5. Procedures during the study period
   During the study period, the outcome of patients (alive/died/lost to follow-up [including withdrawal of consent]) and detailed information on subsequent treatment for NSCLC after the completion of Study JO25567 will be recorded in the CRF once per year, generally in September. Evaluations may also be performed at other time points depending on the occurrence of death events.

6. Completion of study and discontinuation for individual patients
   Patients who die will be considered to have completed the study. The study will be discontinued for patients who are lost to follow-up (including withdrawal of consent).

7. Completion of overall study
   The planned date of the last evaluation is September 2017, but the study may be completed earlier if the median OS and its 95% confidence interval in each group can be estimated from the results of evaluations conducted before this date.

Study Procedure



4.4 Study Period for Each Patient

For each patient, participation in the study will extend from the date of informed consent to death or lost to follow-up (including withdrawal of consent).

4.5 Planned Study Period

July 2014 to March 2018

(The study may, however, be completed earlier if the median OS and its 95% confidence interval in each group can be estimated from the results of evaluations conducted before the planned September 2017 evaluation.)

5. PATIENT INCLUSION AND WITHDRAWAL CRITERIA

Patients who meet the inclusion criteria listed in section 5.1 below at enrollment will be eligible to participate in the study.

5.1 Inclusion Criteria

Eligible patients must meet all of the following criteria.

1. Enrolled and received investigational medicinal product at least once in the previously conducted "Survival Follow Up of JO25567, a Randomized Phase 2 Study Comparing Erlotinib and Bevacizumab Combination with Erlotinib Alone in NSCLC Patients Harboring EGFR Mutation" (excluding patients who died or were lost to follow-up in Study JO25567)
2. Provided written informed consent after having received a detailed explanation of the study

Rationale

1. This criterion was established to enable pooled analysis of OS data from the current study and Study JO25567.
2. This criterion was established to ensure that the study is conducted in accordance with GCP and GPSP.

5.2 Withdrawal Criteria

5.2.1 Removal of Patients from Assessment

Patients who meet the following criterion will be withdrawn from the study by the investigator.

1. Lost to follow-up (including withdrawal of consent)

5.3 Observation and Test Schedule

5.3.1 Patient Baseline Characteristics

1. Variables evaluated: Patient number (same patient number used in Study JO25567), date of informed consent
2. Evaluation time point: At acquisition of informed consent

5.3.2 Subsequent Treatment for NSCLC

1. Variables evaluated: Treatment administered, date of initiation of treatment (during the period from completion of Study JO25567 to any time during the current study)
2. Evaluation time point: Annually (generally September of each year)

5.3.3 Survival Outcome Evaluation

1. Survival Outcome Evaluation
   a. Variables evaluated: Survival status (alive [date confirmed to be alive]), died (date of death, cause of death), or lost to follow-up (date last confirmed to be alive, reason for being lost to follow-up [including withdrawal of consent], date of evaluation [date signed])
   b. Evaluation time point: Annually (generally September of each year)
      Evaluations may also be performed at other time points depending on the occurrence of death events.

6. INVESTIGATIONAL MEDICINAL PRODUCT/TREATMENT OF PATIENTS

The study does not involve an investigational medicinal product or treatment of patients.

7. EFFICACY EVALUATION

7.1 Endpoints

1. Primary endpoint
   a. Overall survival
      Overall survival is defined as the time from entry into Study JO25567 until death of any cause. Patients without confirmed death at the analysis time point will be censored at the date they were last confirmed to be alive.

8. STATISTICAL ANALYSIS

8.1 Full Analysis Set (FAS)

All patients enrolled in Study JO25567

8.2 Analytical Methods

The CRO will perform the statistical analysis in accordance with the statistical analysis plan finalized before database lock. The analytical approach will be determined in consultation with the sponsor and medical expert when necessary.

8.2.1 Efficacy

The FAS will be the primary efficacy analysis population.

1. Primary endpoint: Overall survival
   The survival function will be estimated by the Kaplan-Meier method. Median OS and its 95% interval will then be calculated, and the 2 groups will be compared by log-rank

test. Confidence intervals will be calculated based on Greenwood's formula. The hazard ratio for OS in the AT group versus the T group will also be determined using a Cox proportional hazards model.

8.3 Target Sample Size

Up to 121 patients

Rationale:

Study JO25567 enrolled 152 patients who received treatment. At the time of the primary analysis, PFS, in Study JO25567 (June 30, 2013), 31 deaths had been reported. The target sample size in the current study was therefore set at a maximum of 121 patients.

8.4 Interim Analysis

Interim analysis of survival and subsequent treatment for NSCLC will be performed annually in the current study. Interim analysis may, however, be performed at other unscheduled time points depending on the occurrence of death events.

9. SAFETY EVALUATION

The study is designed as a follow-up investigation of survival after the completion of Study JO25567. The protocol does not mention any treatment of patients, hospital visits, or invasive testing. For this reason, safety information will not be collected or evaluated.

10. SOURCE DATA DOCUMENTATION/SOURCE DOCUMENT VERIFICATION

10.1 Source Data Documentation

The CRF entries will be considered the source data for the following information recorded directly in the CRF.

- Cause of death
- Detailed comments
- Reason for being lost to follow-up

10.2 Source Document Verification

During monitoring by the sponsor's monitors, auditing by the sponsor's auditors, and reviews by the institutional review board (IRB) and regulatory authorities, the principal investigators and study sites will make source documents and all other study-related records available to the monitors, auditors, IRB members, and GCP inspectors, and will cooperate with these parties.

The study sites will consult with the sponsor to identify the source documents, determine which parts will be subjected to verification, and decide how and when the verification will be performed.

11. STUDY QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Study Quality Control and Quality Assurance

The sponsor will perform study quality control and quality assurance under the sponsor's administrative structure described in section 1. "STUDY ADMINISTRATIVE STRUCTURE" in accordance with the various standard operating procedures and audit procedures based on the "Operating Procedures for Postmarketing Studies: Postmarketing Clinical Studies" specified by the sponsor.

The sponsor will perform study quality control and quality assurance by preparing operating procedures (including lists of assigned responsibilities) after discussion with the CROs.

11.2 Quality Control and Quality Assurance in this Study

The accuracy, consistency, integrity, and reliability of data will be assured as follows.

1. Before commencing the study, the sponsor will thoroughly explain the study protocol, etc., to the investigators and other relevant study personnel to make sure that it is properly understood and to ensure standardization of assessments and evaluations.
2. Patient eligibility will be checked by an external enrollment center ([redacted]) to eliminate any potential violations of the inclusion and exclusion criteria.
3. The monitors will check that the study is being conducted appropriately in accordance with the study protocol, GCP, GPSP, and relevant regulations, and will check the accuracy of the data.
4. As part of the study quality assurance, the auditors will assess whether the study is being conducted in compliance with the protocol, the SOPs stipulated by the sponsor, GCP, and GPSP, etc., in accordance with the "Audit Procedures" based on "Basic Rules on Regulatory Affairs Auditing" stipulated by the sponsor. This evaluation will be performed independently of and separately from routine monitoring and study quality control.
5. All source documents and source data will be made available in response to requests for access by the sponsor or Japanese or overseas regulatory authorities.

12. ETHICS

12.1 Informed Consent of Patients

12.1.1 Informed Consent Form

1. The principal investigator must prepare an informed consent form in cooperation with the sponsor for use in obtaining the informed consent of patients to participate in the study.
2. The prepared document must be submitted to the sponsor and approved by the IRB before use.
3. The informed consent form must state the following minimum information:
   a. That the study involves research
   b. The objectives of the study
   c. The study method (the experimental aspects of the study, the inclusion and exclusion criteria)

d. The expected duration of the patient's participation in the study
e. The number of patients expected to participate in the study
f. The anticipated clinical benefits and risks or inconveniences (When there is no anticipated benefit to the patient, the patient should be made aware of this.)
g. The alternative treatments available to the patient, and their important potential benefits and risks
h. The compensation and treatment available to the patient in the event of study-related injury
i. That the patient's participation in the study is voluntary and the patient may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the patient is otherwise entitled
j. That the patient will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the study
k. The foreseeable circumstances or reasons under which the patient's participation in the study may be terminated
l. That the monitors, auditors, IRB, and regulatory authorities in Japan and outside Japan may access the patient's original medical records and that the results may be submitted to the regulatory authorities in Japan and outside Japan; that the patient's privacy will be protected at such times; and that, by signing or sealing a written informed consent form, the patient is authorizing such access
m. That if the results of the study are published, the patient's identity will remain confidential
n. The anticipated expenses, if any, to the patient for participating in the study
o. The name, administrator, and address of the IRB; that the study procedures, etc., can be accessed either on the IRB's website (if published on the website) or at the clinical study office, etc. (if not published on the website); and that the patient is encouraged to request this information if desired.
p. The names, titles, and contact details of the investigators
q. The study site's information service so that the patient can request further information on his/her rights, or notify/inquire about study-related injuries
r. The patient's responsibilities

12.1.2 Timing and Method of Obtaining Informed Consent

1. Before a patient can participate in the study, the investigator must thoroughly explain the study to the patient using the informed consent form approved by the IRB, and must obtain the patient's voluntary consent to participate in the study using the informed consent form.
2. Before informed consent can be obtained, the investigator must give the patient the opportunity to ask questions and sufficient time to decide whether or not to participate in the study. The investigator or any study collaborators who provide additional information must answer all questions to the satisfaction of the patient.
3. The patient and the investigator who explained the study will each sign and date the informed consent form. If a study collaborator provided supplementary information, the study collaborator will also sign and date the informed consent form.

4. The investigator will record the consent date in the CRF and give the patient a copy of the signed and dated informed consent form before the patient can participate in the study.
5. The investigator will inform the patient in a timely manner if any information becomes available that may affect the patient's willingness to continue participating in the study, and will confirm whether or not the patient still wishes to participate in the study.

12.1.3 Amendment of the Informed Consent Form

1. If significant new information becomes available that may affect the patient's willingness to consent to the study (typically information that necessitates amendment of the patient informed consent form), the investigator must promptly amend the patient informed consent form in consultation with the sponsor, and must obtain the prior approval of the IRB.
2. Each time the informed consent form is amended for the reason described in 1. above, the investigator must promptly convey the details of the amendment to patients who are already participating in the study, and must confirm whether they are willing to continue participating in the study before re-informing and re-consenting the patients using the amended informed consent form.
   The investigator must record the consent date in the CRF and give the patient a copy of the newly signed and dated informed consent form.

12.2 Institutional Review Boards

The study protocol and any amendments thereto will be reviewed by the IRB from the perspectives of ethical, scientific, and medical validity. The IRB will also continue to review whether the study is being conducted properly at least once a year. To facilitate this review, the principal investigator will submit a written summary of the study status to the head of the study site.

12.3 Protection of Patients' Human Rights

1. When selecting patients, the investigator will carefully consider whether patients are suitable for study participation from the perspective of human rights and compliance with the inclusion and exclusion criteria, taking into account their health, symptoms, age, sex, capacity to consent, dependence on the investigator and other study personnel, and participation in other clinical studies.
2. When reporting study-related data, the principal investigator will ensure patient confidentiality by using the patient number assigned in the study (same patient number used in Study JO25567).
3. The sponsor, IRB, and regulatory authorities will maintain patient confidentiality during source document verification. The identity of patients will also be kept confidential even if the results of the study are published.

13. DATA HANDLING AND RECORD RETENTION

13.1 Preparation, Revision, and Amendment of Case Report Forms

1. CRFs should be completed for all enrolled patients.

2. The investigator or a study collaborator will prepare the CRFs and revise or amend CRF entries in accordance with "Procedure for Revising and Amending Case Report Forms."

13.2 Electronic Data Storage and Management

The sponsor will retain the information contained in the CRFs as electronic data using an electronic data processing system, and will outsource the following tasks to [redacted].

1. Maintaining a record of any amendments to electronic data (i.e., the date of the amendment and the name of the person who made it)
2. Managing system security
3. Backing up data appropriately

13.3 Retention of Records

13.3.1 Institutional Review Boards

1. Documents to be retained
   The IRB administrator will retain records such as the standard operating procedures, the IRB members' register (including the qualifications of individual members), a list of member positions (i.e., job titles) and affiliations, submitted documents, meeting minutes, and letters.

2. Retention period
   The IRB administrator will retain these documents until the date on which reexamination is completed. However, if the sponsor requires the documents to be retained for longer, the retention period and archiving method will be determined by discussion with the sponsor. The records must be archived so that they can be presented in response to a request from the regulatory authorities.

3. Other matters
   The IRB administrator will comply with requests to view the IRB's standard operating procedures and members' register from the head of the study site (where the head of the study site is not the IRB administrator, and seeks the opinion of the IRB) or the sponsor.

13.3.2 Study Sites

1. Documents to be retained
   The head of the study site will retain the study-related documents and records that are required to be retained by the study site according to GCP and GPSP.

2. Retention period
   The head of the study site will retain these documents until the date on which reexamination is completed. However, if the sponsor requires the documents to be retained for longer, the retention period and archiving method will be determined by discussion with the sponsor. An archive manager will be designated for each record to be retained.

3. Other matters

The head of the study site or archive manager will take steps to ensure that these records are not lost or disposed of during this mandatory storage period, and that they can be presented on demand.

13.3.3 Principal Investigator

The principal investigator will retain documents and records related to the conduct of the study in accordance with the instructions of the head of the study site.

13.3.4 Sponsor

1. Documents to be retained
   The sponsor will retain the study-related documents and records that are required by GCP and GPSP to be kept by the sponsor in accordance with standard operating procedures prepared and managed by Chugai Pharmaceutical Co., Ltd.

2. Retention period
   The sponsor will retain study-related documents and records for a period of 5 years from the date on which reexamination is completed.

3. Other matters
   If the study-related documents and records to be retained by the head of the study site or the IRB administrator no longer need to be retained, the sponsor will provide notice to that effect to the head of the study site or to the IRB administrator via the head of the study site.

14. PUBLICATION POLICY

The investigator must obtain the written approval of the sponsor before publishing any of the study findings externally, such as at academic conferences.

The sponsor is free to use information obtained from this study for the purpose of reexamination or reevaluation.

15. CHANGES TO THE PROTOCOL

15.1 Protocol Amendments

1. If a change to the protocol becomes necessary while the study is in progress, the sponsor will decide what changes need to be made in consultation with the medical expert, and will promptly seek the agreement of the investigators for the change and the reason for the change in writing. The same will also apply to amendments requested by the head of the study site based on the opinion of the IRB.
2. The sponsor will promptly submit the amended study protocol and, where applicable, the amended CRF to the head of the study site.

15.2 Deviations from or Changes to the Protocol

1. The investigator must not deviate from or change the study protocol without the prior written agreement of the investigator and the sponsor, and the prior written approval of the IRB based on a review.
2. However, the investigator may deviate from or change the protocol without the prior agreement of the sponsor and the prior approval of the IRB if there are compelling medical circumstances. In these situations, the principal investigator will record all actions that deviated from the study protocol, submit a record explaining the reasons for the deviation or change to the sponsor and the relevant head of the study site, and retain a copy thereof.
3. If the content and rationale of a protocol deviation or change made under the provision of the previous item are deemed to be valid, the principal investigator and the sponsor will discuss and reach agreement on a protocol amendment in accordance with section 15.1 "Protocol Amendments." The proposed protocol amendments will then be submitted to the heads of the study sites as soon as possible, and the approval of the IRBs will be sought.
4. The principal investigator will promptly submit a report to the sponsor, head of the study site, and IRB about any changes to the study that may have a material impact on the conduct of the study or that could increase the risk to patients.

16. PREMATURE TERMINATION OR COMPLETION OF THE STUDY

16.1 Premature Termination of the Study

The rules for partial or complete termination of the study are described below. In each case, the sponsor will compile and analyze the study results at the time of termination. Withdrawal criteria for individual patients are set out in section 5.2 "Withdrawal Criteria."

16.1.1 Premature Termination of the Entire Clinical Study

If, for some reason, the clinical study as a whole must be prematurely terminated, the sponsor will consult with the principal investigators and the medical expert, and will promptly provide written notification to the heads of the study sites and the regulatory authorities detailing the reasons for terminating the study. The head of the study site will notify the principal investigator and IRB that the study is to be terminated and will subsequently provide a detailed written explanation.

16.1.2 Premature Termination at Individual Study Sites

1. Premature termination by the sponsor
   If an investigator or study site interferes with the proper conduct of the study through serious or persistent non-compliance with GCP, GPSP, the study protocol, or the study agreement, the sponsor will terminate the agreement with the study site and terminate the study at that particular study site.

2. Premature termination by the principal investigator
   If the principal investigator terminates the study, the investigator will promptly notify the head of the study site to that effect and provide a detailed written explanation. The

head of the study site will then promptly notify the sponsor and IRB of this in writing and provide a detailed written explanation.

3. Premature termination by the IRB
   If the IRB decides during its continuing review of the ongoing study to withdraw its approval for a certain aspect of the study based on medical evidence or ethical grounds, and has notified the head of the study site of this decision, then the head of the study site will promptly notify the principal investigator and sponsor of his/her instructions and decisions based thereupon, and will provide them with a copy of a dated document regarding the IRB's withdrawal of approval. The head of the study site will also provide the principal investigator and sponsor with a detailed written explanation of the IRB's decision.

16.2 Study Completion

Upon completion of the study, the principal investigator will notify the head of the study site to that effect in writing, and will present a study completion report summarizing the study results. The head of the study site will then promptly notify the IRB and sponsor of the study completion in writing, and will provide a summary of the study results based on the study completion report.

17. REFERENCES

1. Goto K, Nishio M, Yamamoto N, Chikamori K, Hida T, Maemondo M, et al. A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC). Lung Cancer 2013;82(1):109–14.
2. Internal Evaluation Materials. Addendum to the clinical study report of the Phase II clinical study of Ro50-8231 (erlotinib) in the first-line treatment of patients with advanced, metastatic, or postoperative recurrent non-small-cell lung cancer with EGFR mutations. Prepared December 26, 2013.
3. Internal Evaluation Materials. Analysis results report of the open-label, non-randomized Phase II clinical study comparing bevacizumab plus Ro50-8231 (erlotinib) with Ro50-8231 alone in the first-line treatment of patients with non-small-cell-lung cancer with EGFR mutations (JO25567). Version 2. Prepared February 28, 2014.
4. Herbst RS, Ansari R, Bustin F, Flynn P, Hart L, Otterson GA, et al. Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial. Lancet 2011; 377(9780):1846–54.
5. Seto T, Kato T, Nishio M, Goto K, Atagi S, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol 2014;15(11):1236–44.
6. Yamamoto N, Goto K, Nishio M, Chikamori K, Hida T, et al. Final overall survival in JO22903, a phase II, open-label study of first‐line erlotinib for Japanese patients with EGFR mutation-positive non-small-cell lung cancer. Int J Clin Oncol 2017;22:70–78.

ATTACHMENT 1

1. Sponsor's Administrative Structure

1.1 Sponsor's Administrative Structure

1.1.1 Post-Marketing Study Leader

(1) Study leader

Name: Chugai Pharmaceutical Co., Ltd. Medical Science Dept.
Person in charge: [redacted]
TEL: 03-3273-2613 FAX: 03-3281-2656

1.2 Contract Research Organizations (CROs)

1.2.1 Monitoring and Enrollment Center

(1) Name, responsible, and address of the monitoring

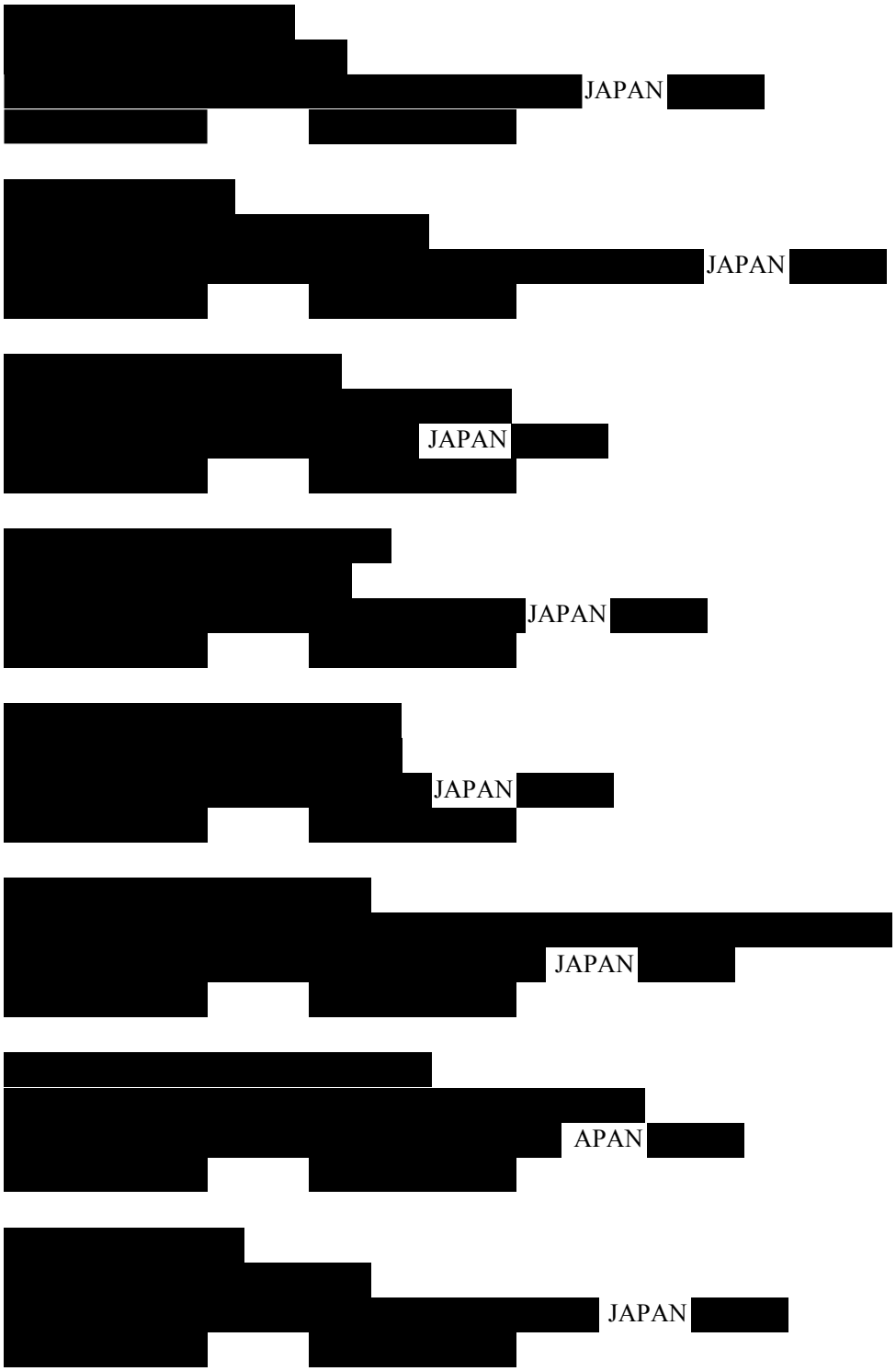
Name: [redacted].
Responsible: [redacted]
Person in charge: [redacted],
[redacted]
Address: [redacted], Japan
TEL: [redacted] FAX: [redacted]

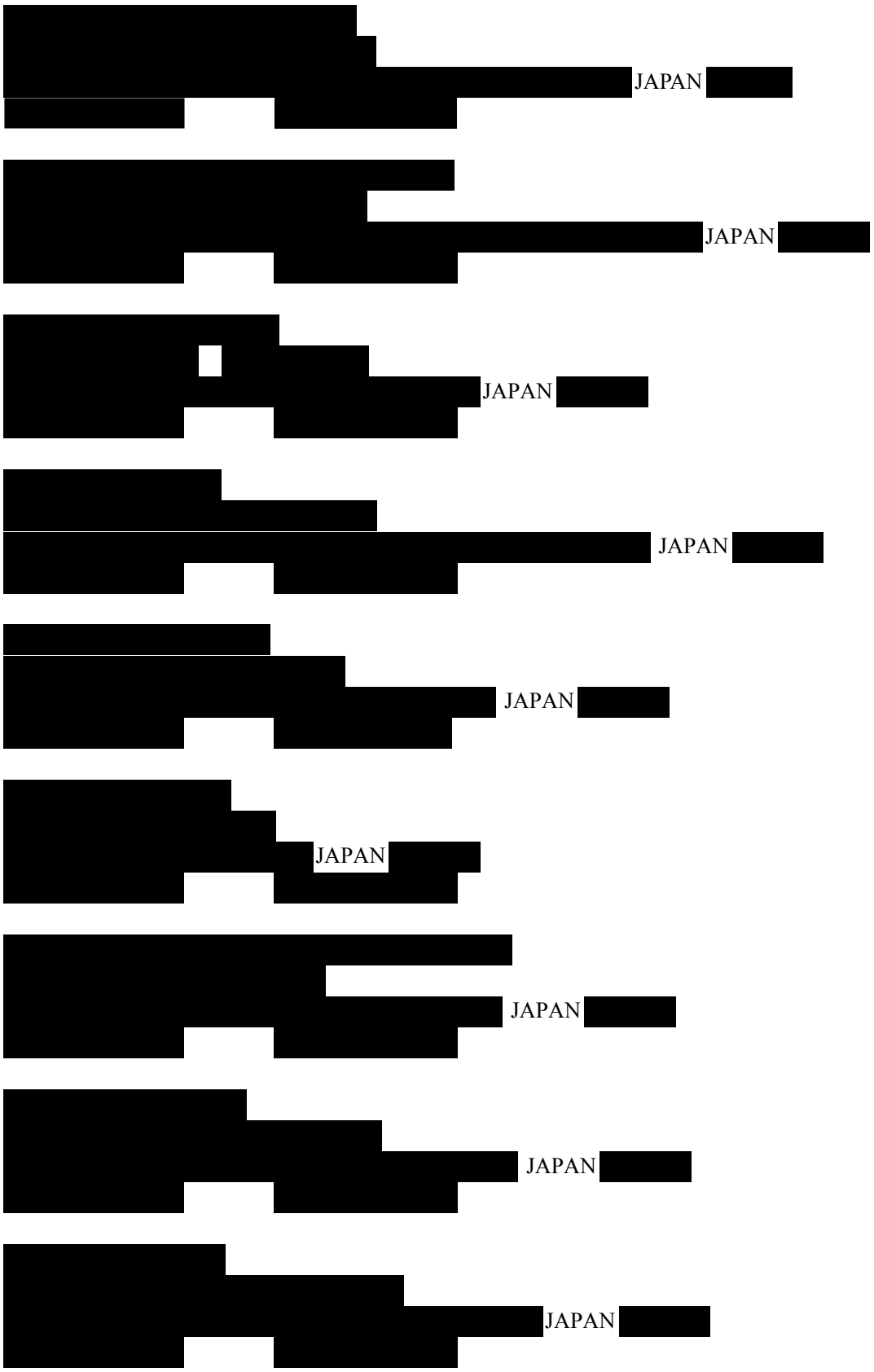
(2) Name, responsible, and address of the enrollment center

Name: [redacted].
Responsible: [redacted].
Address: [redacted], Japan
TEL: [redacted] FAX: [redacted]

ATTACHMENT 2

Listing of Investigators by Site

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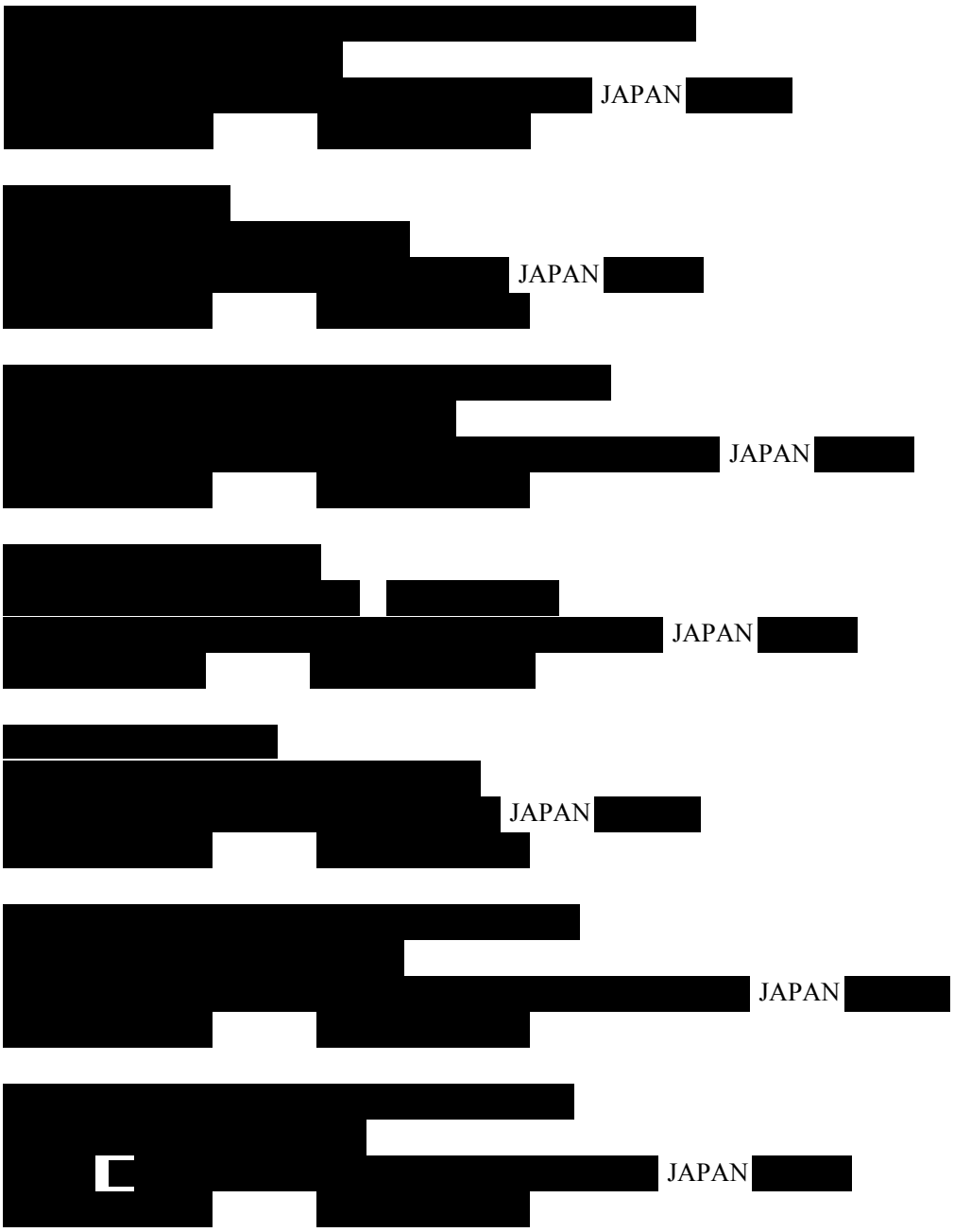
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ATTACHMENT 3　SUBJECT ENROLLMENT FORM

Postmarketing Clinical Study to Follow up Survival Outcomes for the JO25567 Study
(Bevacizumab + Erlotinib Combination Therapy and Erlotinib Monotherapy)
Subject Enrollment Form

JO29424 Study Enrollment Center **FAX:** [redacted] (Contact Tel: [redacted])

※

Name of institution and department	
Name of principal (sub-) investigator	
Date of birth [in Western calendar]	
Sex	☐ Male　☐ Female
Date informed consent was obtained [in Western calendar]	
JO25567 study subject number	

※

Inclusion criteria (Please check □.)	Yes	No
(1) Patients enrolled in the "Open-label, Randomized, Phase III Clinical Study to Compare Bevacizumab + Erlotinib Combination Therapy and Erlotinib Monotherapy as First-line Therapies for Non-small Cell Lung Cancer Patients with EGFR Gene Mutations" performed ahead of the present study, and treated at least once with an investigational product (excluding patients who died during the JO25567 study or who are untraceable)	□	□
(2) Fully informed written consent to the details of the study has been obtained from the subject.	□	□

*If either of the gray sections [ ] is applicable, the patient may not be enrolled.

Note: For inquiries concerning current subject enrollment (must be completed).

Phonetic reading	Telephone number
Department and name	(　　) – (Extension　　)

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Enrollment Certificate

To: Person in charge at institution

※

Date of enrollment	XXXX XX, 201X

Result: Eligible/Ineligible

If ineligible:

Reason for ineligibility	