NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	A Multinational Active Safety Surveillance Study of Crizotinib in Europe and the United States
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Product reference	EU/1/12/793/001-004
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Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	To estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for hepatotoxicity, pneumonitis/interstitial lung disease, QT prolongation-related events, bradycardia, and vision disorders among lung cancer patients receiving crizotinib dispensing/prescription
Countries of study	Denmark, Finland, Sweden, the Netherlands, and United States of America

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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
ALK	Anaplastic lymphoma kinase
ATC	Anatomical therapeutic chemical
CI	Confidence interval
CVV	Classificatie van Verrichtingen
CPE	Centre of Pharmacoepidemiology
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescence in-situ hybridization
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practices
CPT	Current Procedural Terminology
GVP	Good Pharmacovigilance Practice
HCPCS	Healthcare Common Procedure Coding System
HGFR	Hepatocyte growth factor receptor
HUS	Helsinki and Uusimaa
ICD	International Classification of Diseases
ICPM	International Classification of Procedures in Medicine
IQR	Interquartile range
ISPE	International Society for Pharmacoepidemiology
IRB	Independent Review Board
ILD	Interstitial lung disease
MAH	Marketing Authorisation Holder
MET	Mesenchymal epithelial growth factor
NDC	National Drug Codes
NI	Non-interventional
NIS	Non-interventional study
NOMESCO	Nordic Medico-Statistical Committee
NSCLC	Non-small cell lung cancer
ORD	Optum Research Database
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PFS	Progression-free survival
PPV	Positive predictive value
QC	Quality control
RedCAP	Research Electronic Data Capture

Abbreviation	Definition
RCT	Randomized controlled trial
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
TKI	Tyrosine kinase inhibitor
TNM	Tumor, nodes, metastasis
US	United States

3. INVESTIGATORS

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5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	30 December 2014	4 March 2015	Actual date different from the Planned date owing to delayed data availability from data custodians
End of data collection	30 June 2017	30 June 2017	
Registration in the EU PAS register	02 December 2014	02 December 2014	
Interim report I	30 June 2015	30 June 2015	
Interim report II	30 June 2016	29 June 2016	
Final report of study results	30 June 2018	12 June 2018	

6. RATIONALE AND BACKGROUND

Lung cancer is the most common cancer in the world, accounting for 13% of all cancer cases. Lung cancer has poor prognosis (1). Non-small cell lung cancer (NSCLC), which represents approximately 85% of all lung cancer cases (2), is a leading cause of death in developed countries (3). NSCLC has low response rates to conventional chemotherapy regimens. Data from the United States (US) Surveillance, Epidemiology, and End-Results (SEER) show a merely 17% 5-year survival (4), and a median survival of less than 1 year following the diagnosis in this patient population (5).

Tyrosine kinase inhibitors (TKIs) enable targeted therapies for mutation/fusion-based NSCLC subtypes. Anaplastic lymphoma kinase (ALK) gene rearrangements are novel targets for the treatment of NSCLC (6). The translocated ALK gene induces generation of chimeric proteins, leading to deregulation of cell proliferation, cell survival and cell cycling (7). Up to 7% of patients with NSCLC harbor ALK rearrangements (6); presence of ALK rearrangement is a poor prognostic factor for untreated NSCLC (8). Crizotinib (Xalkori®) is an orally administered selective small-molecule TKI of the ALK, ROS1, and mesenchymal epithelial growth factor/hepatocyte growth factor receptor (MET/HGFR) and their oncogenic variants (e.g., MET/HGFR mutations and ALK or ROS1 fusion proteins). Crizotinib showed potent and selective growth-inhibitory activity against tumor cells with ALK rearrangements (9). In a phase III randomized controlled trial (RCT) of crizotinib versus chemotherapy in previously treated patients with ALK-positive NSCLC, median progression-free survival (PFS) was 7.7 months in the crizotinib arm and 3.0 months in the chemotherapy arm, with hazard ratio for progression or death of 0.49 (95% confidence interval [CI]: 0.37 - 0.64). (10). In a phase 3 RCT of crizotinib versus chemotherapy as first-line treatment for advanced ALK-positive NSCLC, the median PFS was 10.9 months in the crizotinib arm and 7.0 months in the chemotherapy arm, with hazard ratio for progression or death of 0.45 (95% CI: 0.35 - 0.60) (11).

Crizotinib received approval in the United States (US) in August 2011 for the treatment of patients with metastatic NSCLC that is ALK-positive as detected by a Food and Drug Administration (FDA)-approved test. Crizotinib also received approval in the European Union (EU) in October 2012 for the treatment of adults with previously treated - and subsequently with previously untreated - ALK-positive advanced NSCLC. Crizotinib has additionally received approvals for the treatment of ALK-positive advanced NSCLC in more than 90 countries worldwide.

Crizotinib received approval for a second indication of ROS1-positive advanced NSCLC in the US and the EU in March 2016 and August 2016, respectively. Crizotinib has additionally received approvals for the treatment of ROS1-positive advanced NSCLC in more than 60 countries worldwide, including Russia, Switzerland, Japan, and Canada, and marketing applications for this indication are currently planned or in review in several other countries (10-17). Current indications for crizotinib according to the Summaries of Product Characteristics (SmPC) of the European Medicines Agency (EMA) and the FDA are summarized in Table 1.

Table 1. Current Approved Indications of Crizotinib

EMA*	FDA**
Xalkori® as monotherapy is indicated for: • The first-line treatment of adults with ALK-positive advanced NSCLC; • The treatment of adults with previously treated ALK-positive advanced NSCLC; • The treatment of adults with ROS1-positive advanced NSCLC (15).	Xalkori® is a kinase inhibitor indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK or ROS1-positive as detected by an FDA-approved test (14).

* EU: previously treated ALK-positive NSCLC indication approved in October 2012; first-line ALK-positive NSCLC indication approved in November 2015; ROS1-positive NSCLC indication approved in August 2016.
** US: ALK-positive NSCLC indication approved in August 2011; ROS1-positive NSCLC indication approved in March 2016.

Adverse drug reactions of crizotinib therapy, listed in the SmPC, include hepatotoxicity, pneumonitis/interstitial lung disease (ILD), QT interval prolongation, bradycardia, vision effects, neuropathy, leukopenia, gastrointestinal (GI) effects, renal cysts, edema, and cardiac failure Photosensitivity, malignant melanoma, and reproductive toxicity are important potential risks (14, 15).

In addition to risks that may be observed in clinical trial settings or in animal studies, it is important to characterize risks associated with crizotinib therapy in routine practice and in subpopulations of patients that may be vulnerable to these risks. Therefore, ongoing monitoring of these risks is important to refine crizotinib's benefit/risk profile. Moreover, a number of populations, such as the elderly, were either not studied, or insufficiently studied, in the pre-authorization phase.

This multinational post-authorization active safety surveillance study using existing health care data sources in Europe and the US was designed to monitor safety of crizotinib in a real-world setting. Its primary objective is to estimate incidence rates of hepatotoxicity, pneumonitis/ILD, QT prolongation-related events, bradycardia, and vision disorders among lung cancer patients receiving crizotinib dispensing/prescription in routine clinical settings. It also aims to evaluate effectiveness of crizotinib and to further characterize the safety of crizotinib in subgroups, including lung cancer patients with brain metastases at baseline, renal or hepatic impairment at baseline, and the elderly (patients ages 65 years of age or older). Whenever a treated patient population is expected to be small, as is the case with crizotinib, and a study based on routinely collected real-world data is more efficient and less prone to selection bias than a study involving primary data collection.

To provide context to findings in patients treated with crizotinib, the events of interest were also assessed in patients with advanced primary lung cancer treated with other TKIs. Ceritinib (Zykadia®) was approved by the EMA in May of 2015 and by the FDA in August of 2014 for the

treatment of patients with ALK-positive, metastatic NSCLC previously treated with crizotinib (18, 19). Two TKIs of the epidermal growth factor receptor (EGFR) – erlotinib (Tarceva®) and gefitinib (Iressa®) among others – are currently used for treatment of advanced-stage NSCLC with activating EGFR mutations. Patients with primary lung cancer treated with these TKIs were used in this study to provide context to findings in patients treated with crizotinib.

This non-interventional (NI) study is designated as a Post-authorisation Safety Study (PASS) and was Marketing Authorisation Holder's (MAH) commitment to the EMA.

7. RESEARCH QUESTION AND OBJECTIVES

This active safety surveillance study using existing health care data sources in Denmark, Finland, Sweden, the Netherlands, and the US evaluated safety and effectiveness outcomes among patients with primary lung cancer patients receiving crizotinib dispensing/prescription over an approximately 3-year period under real-world conditions. To contextualize the findings, this study obtained data among patients with primary lung cancer receiving dispensing/prescription of ceritinib, erlotinib or gefitinib from the same data sources during the study period. In addition, the study also collected data on other cancer patients receiving crizotinib dispensing/prescription.

7.1. Primary Objectives

To estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for hepatotoxicity, pneumonitis/ILD, QT prolongation-related events, bradycardia, and vision disorders among lung cancer patients receiving crizotinib dispensing/prescription.

7.2. Secondary Objectives

- To estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for renal cysts, edema, leukopenia, neuropathy, malignant melanoma, GI perforation, cardiac failure, and photosensitivity among lung cancer patients receiving crizotinib dispensing/prescription.

- To estimate Kaplan-Meier one-year, two-year, and three-year survival among lung cancer patients receiving crizotinib dispensing/prescription.

- To estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for hepatotoxicity, pneumonitis/ILD, QT prolongation-related events, bradycardia, vision disorders, and other safety outcomes among lung cancer patients receiving dispensing/prescription of ceritinib, erlotinib or gefitinib.

- To estimate Kaplan-Meier one-year, two-year, and three-year survival among lung cancer patients receiving dispensing/prescription of ceritinib, erlotinib or gefitinib.

- To describe clinical characteristics, comorbidities, and concomitant medications of patients receiving dispensing/prescription of crizotinib, ceritinib, erlotinib or gefitinib.

- To describe demographics, clinical characteristics and comorbidities of patients receiving dispensing/prescription of crizotinib for other cancer.

8. AMENDMENTS AND UPDATES

Three amendments were made since the finalization of the Study Protocol, on March 29, 2013. The amendments are detailed in the Study Protocol (Appendix 2) and are summarized in Table 2.

Table 2. Summary of Amendments to the Study Protocol

Number	Date	Section of study protocol	Amendment or update	Reason
1.1	February 28, 2014	Sections 3; 7; 8.1.2; 9.3; 9.5; 9.6.3; 9.8; 11 Appendix 1 and Appendix 2	• Added malignant melanoma as one of secondary objectives • Amended section on the management and reporting of adverse events/adverse reactions • Inserted additional analyses on pneumonitis/ILD	• Malignant melanoma identified as a new potential risk by Pfizer • The adverse event reporting language was updated to ensure consistency with Pfizer internal Standard Operating Procedure (SOP) and the local laws and regulations • The additional analyses on pneumonitis/ILD were to further comprehend the risk in a real world setting
1.2	February 19, 2015	PASS information; Abstract; Sections 7; 8; 9, Appendix 1, and Appendix 2	• Norway removed from the study • Optum database in the US added to the study • GI perforation was added as a secondary study endpoint • Ceritinib was added as one of study drugs • Safety data presented in the background section were updated.	• Investigators in Norway decided to withdraw from this study due to competing obligations and lack of resources • Optum database in the US was added to ensure sufficient study size • GI perforation became recognized as a new risk • Ceritinib became approved for the treatment of patients with ALK- positive, metastatic NSCLC with disease progression intolerant to crizotinib. • Background section updated to include data from crizotinib phase III clinical trials since data presented in the previous version of this protocol was based on phase I and II trials
1.3	June 7, 2016	PASS information; Abstract; Sections 7; 8; 9	• Cardiac failure was added as a secondary study endpoint • An inclusion criterion for patients receiving dispensing of crizotinib or ceritinib was added	• As required by EMA, cardiac failure was added as a study endpoint • The new inclusion criterion was to ensure that patients receiving dispensing of crizotinib or ceritinib were new users

9. RESEARCH METHODS

This study was conducted according to the Amendment 3 of the Study Protocol, dated June 7, 2016 (Appendix 2) and to the Statistical Analysis Plan (SAP), dated July 19, 2017 (Appendix 4).

9.1. Study design

This was a non-interventional, active safety surveillance study using existing health care data sources in the EU and the US to evaluate safety and effectiveness outcomes among patients with primary lung cancer receiving dispensing/prescription of crizotinib, ceritinib, erlotinib, or gefitinib during an approximately 3-year period of observation.

9.2. Setting

The source population included persons in the coverage area of each database during the country-specific study period: the entire populations of Denmark (5.6 million), Finland (5.4 million) and Sweden (9.5 million); the population covered by the PHARMO Database Network in the Netherlands (4 million or ~25% of the total Dutch population); and the US insured population covered by the Optum Research Database (ORD) (12.6 million, or 3-4% of the total US population).

In the three Scandinavian countries, i.e., Denmark, Finland, Sweden, the various population-based nationwide databases are administered by government agencies and are set in their respective welfare states with universal tax-funded health care access (20).

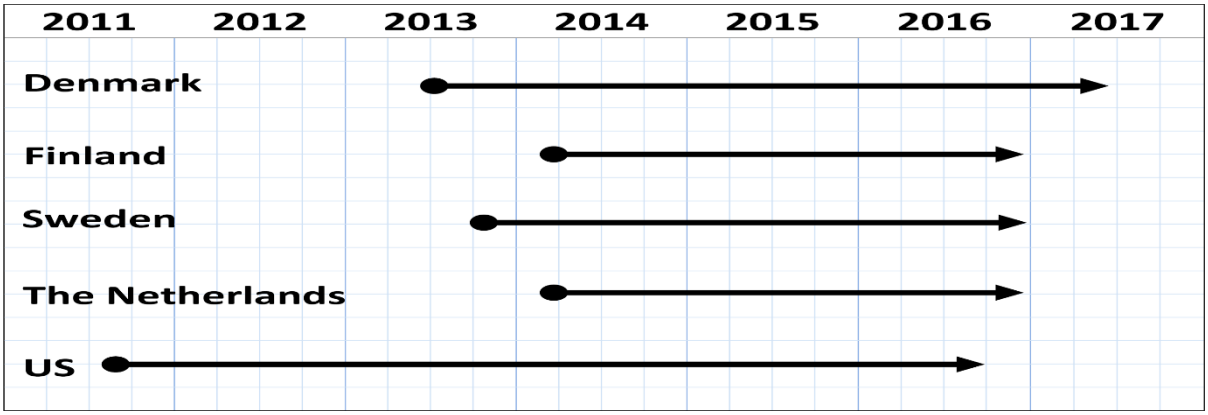
In the Netherlands, the data originated from the PHARMO Database Network, a population-based network of healthcare databases that combines data from different healthcare settings, including general practitioners, inpatient or outpatient pharmacy, clinical laboratory, hospitals and the National Pathology Registry (21). The Pathology Registry was used instead of the originally planned cancer registry because of its shorter lag time and availability of genotyping data. The Out-patient Pharmacy Database contains information from two settings: the community setting and hospital setting. Since 2011, the reimbursement budget of biologicals is transferred to the hospital setting and the community setting no longer dispenses biologicals. Therefore, for this study, patients were identified from the hospital outpatient setting.

In the US, the patients included in this study were identified in the ORD, a proprietary research database containing pharmacy and medical claims data from a large US commercial insurance health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US (22).

9.3. Subjects

The study population included eligible patients diagnosed with primary lung cancer who received, during the study period, a dispensing/prescription of crizotinib, ceritinib, erlotinib, or gefitinib as recorded in each country's relevant data source. In addition, the study population also included all other cancer patients receiving crizotinib dispensing/prescription. The overall study period, inclusive of follow-up, was from 1 September 2011 to 30 June 2017; country-specific periods varied according to crizotinib availability dates. Figure 1 shows country-specific study periods, inclusive of the follow-up and exclusive of the baseline. In each country, the patient inclusion period ended 6 months before the latest available follow-up date.

Figure 1. Study Period by Country, Including Follow-up



9.4. Inclusion criteria

Patients had to meet all of the following inclusion criteria to be eligible for inclusion in the study:

- At least 1 dispensing/prescription of crizotinib, ceritinib, erlotinib, or gefitinib no less than 6 months prior to the end of the follow-up date;
- A record of primary lung cancer diagnosis for patients receiving dispensing/prescription of erlotinib, gefitinib, or ceritinib prior to or at the time of the first dispensing/prescription;
- For patients receiving dispensing/prescription of erlotinib or gefitinib, no prior record of dispensing/prescription of erlotinib or gefitinib for at least 6 months before the first dispensing/prescription during the study period;
- For patients receiving dispensing/prescription of crizotinib or ceritinib, no prior record of dispensing/prescription of crizotinib or ceritinib for at least 6 months before the first dispensing/prescription during the study period;
- A record of at least a 6 months' length in the database prior to the first dispensing/prescription of crizotinib, ceritinib, erlotinib, or gefitinib (i.e., index date).

9.5. Exclusion criteria

There were no exclusion criteria not implied by the inclusion criteria.

9.6. Variables

9.6.1. Exposure

Exposure was defined by a dispensing/prescription of one of the study drugs: crizotinib, ceritinib, erlotinib, or gefitinib. Six study drug groups were defined based on the first and the subsequent study drug initiated during the inclusion period: the crizotinib group; the ceritinib

group; the erlotinib group; the gefitinib group; the crizotinib and ceritinib group; and the erlotinib and gefitinib group. Patients entering the study as initiators of crizotinib (ceritinib) who subsequently switched to ceritinib (crizotinib) before the end of the inclusion period contributed observation to the crizotinib (ceritinib) group until the switch. On the date of the switch, patients stopped contribution to the original study drug group and started contributing to the crizotinib and ceritinib group until censoring. The same procedure was followed for erlotinib and gefitinib. The index date for each study drug group was the date of the first dispensing/prescription of the study drug during the inclusion period. Co-occurrence of EGFR mutation and ALK rearrangement, although reported, is rare (23, 24). Therefore, for the purposes of this study, it was assumed that switching could primarily occur between the drugs with the same molecular target (ALK rearrangement: crizotinib to ceritinib or vice versa; EGFR mutation: gefitinib to erlotinib or vice versa). Observation time of patients switching between drugs with different molecular targets was censored on the date of the switch.

A patient was considered to be on-treatment in a given study drug group until the expiration of the days supplied plus 28 days. An on-treatment period was continuous as long as the start of a given dispensing/prescription was no more than 28 days apart from the expiration of the days supplied in the previous dispensing/prescription. Days supplied in the consecutive dispensings/prescriptions were “stacked”. Dispensing/prescription of a study drug different from the original drug ended a patient’s time contributed to the original study drug group. For a given patient, the total on-treatment period was the sum of all on-treatment periods during the study period. A patient was considered to be no longer on treatment in a given study drug group as soon as the time following the expiration of all dispensings/prescriptions exceeded 28 days. Based on the recommended dosing and size of packages, one package of a drug was assumed to last for 30 days, with the exception of erlotinib 25 mg, which was assumed to last for 10 days. In Denmark, where all oncology treatments are dispensed to patients directly at hospitals and were therefore defined using hospital treatment records rather than outpatient dispensings, there was no information about the package size or pill strength in a given dispensing. Furthermore, in the Danish data, the observed pattern of hospital dispensings did not follow a typical pattern expected to be seen with outpatient dispensings. Therefore, after examining the distribution of the recorded administrations of the study drugs in Denmark, the on-treatment period in each study drug group started on the date of the first dispensing of the drug and ended 58 days after the last dispensing of the drug, thus, assuming that the last dispensing contained a 30 days’ supply.

9.6.2. Outcomes

The study endpoints, described in the Study Protocol (Appendix 2) and the SAP (Appendix 4) and defined by diagnostic, drug or procedure codes specific for each country, were following:

9.6.2.1. Primary endpoints

- Hepatotoxicity;
- Pneumonitis/ILD;
- QT interval prolongation-related events;
- Bradycardia;
- Vision disorders.

9.6.2.2. Secondary endpoints

- Renal cysts;
- Edema;
- Leukopenia;
- Neuropathy;
- Photosensitivity;
- Malignant melanoma;
- GI perforation;
- Cardiac failure;
- All-cause mortality.

For the following endpoints, patients with a history of a given condition recorded up to 5-years baseline period before the index date were excluded from the analysis of the respective endpoint:

- Pneumonitis/ILD;
- QT interval prolongation-related events;
- Bradycardia;
- Vision disorders;
- Renal cysts;
- Neuropathy;
- Malignant melanoma;
- Cardiac failure.

9.6.3. Baseline characteristics

Baseline characteristics included demographics, and selected comorbidities, recorded during a baseline period extending up to 5 years before and including the index date, and concomitant medications dispensed/prescribed up to 6 months before and including the index date. The list, definitions, and categories of all baseline characteristics are provided in the SAP (Appendix 4).

9.6.4. Subgroups

Cumulative incidences and incidence rates were estimated overall and in the following subgroups:

- Age <65 years and ≥65 years on the index date;
- Brain metastases at baseline (yes/no);
- Renal impairment at baseline (yes/no);
- Hepatic impairment at baseline (yes/no).

9.7. Data sources and measurement

To construct country-specific analysis data sets, data were used from the sources described below.

Denmark: Danish Central Person Registry, Danish National Patient Registry, Danish Cancer Registry, Danish Pathology Database, and Danish Health Services Prescription Database.

Individual-level records from these databases with total population coverage are linkable via a unique personal identifier. All these data sources have been described in the literature, and many algorithms have been validated (25-31). Selected medications dispensed at hospitals (crizotinib and erlotinib, but not ceritinib or gefitinib) are assigned internal hospital treatment codes, which were used to identify treated patients in Denmark.

Finland: Finnish Care Register for Health Care, Register of Primary Health Care Visits, Population Register Centre, Prescription Registry, e-Prescription Registry, and Finnish Cancer Registry. Individual-level records from these databases with total population coverage are linkable via a unique personal identifier (2). Ceritinib is not reimbursed in Finland and therefore was not captured in this study, as only reimbursed medications generate dispensing records (32). These databases do not capture medications dispensed at hospitals.

Sweden: Swedish Total Population Register, Swedish Cause of Death Register, Swedish Patient Register, Swedish Cancer Register, and Swedish Prescribed Drug Register. Individual-level records from these databases with total population coverage are linkable via a unique personal identifier (20, 33, 34). These databases do not capture medications dispensed at hospitals or nursing homes.

The Netherlands: the longitudinal PHARMO Database Network enables follow-up of more than 4 million (25% of the total population) residents of a well-defined population in the Netherlands for an average of ten years. Data collection period, catchment area and overlap between the data sources differ. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Crizotinib is dispensed in pharmacies in the hospital outpatient setting. Those pharmacies are part of the Out-patient Pharmacy Database, which includes information from community settings and hospital settings. Pharmacies in the hospital setting were the main source to identify the study population. Records from different data sources were linked on a patient level through validated algorithms (35, 36).

US: The ORD consists of patients' longitudinal records of enrolment, inpatient and outpatient medical claims, pharmaceutical claims, and laboratory procedures (and, in 40% of the cases, results of the laboratory tests) for beneficiaries receiving medical insurance from a large US health insurer affiliated with Optum. In 2015, data relating to approximately 13.5 million individuals with both medical and pharmacy benefit coverage were available. This database consists of de-identified Health Insurance Portability and Accountability Act compliant patient records of enrollees of a large health insurance plan in the US. With appropriate permissions, patient and provider identifiers may be accessed and utilized for a subset of the patient population (approximately 20 to 40% of the ORD patient population). Access to patient and provider identifiers is required to request and obtain medical charts and to establish linkages to supplemental databases (e.g., the U.S. National Death Index).

Each of the EU databases routinely records patient characteristics; inpatient and outpatient hospital diagnoses; drug dispensings/prescriptions primarily in outpatient settings and in some situations in inpatient settings, and surgical procedures. All databases use standard classification systems, including the Anatomical Therapeutic Chemical (ATC) classification for medicines (and record the number of packages, date, strength, and route of administration, and the daily defined dose [DDD]); International Classification of Diseases (ICD) codes for diagnoses; and

local standard procedure classifications: the Nordic Medical-Statistical Committee (NOMESCO) classification (37) in the Scandinavian countries, and the Classificatie van Verrichtingen (CVV) classification based on the International Classification of Procedures in Medicine (ICPM), in the Netherlands.

In the US, pharmacy claims are recorded using the National Drug Codes (NDC) and include drug name, route of administration, strength, fill date, and days supplied. Medical claims or encounter data are collected from inpatient hospital, outpatient hospital, ER, physician's office, surgery center and other encounters for virtually all types of provided services, including specialty, preventive and office-based treatments. Medical claims and coding conform to insurance industry standards. Medical claims include: multiple diagnoses recorded with the International Classification of Diseases (ICD) 9th Revision Clinical Modification, and 10th Revision Clinical Modification (ICD-9-CM or ICD-10-CM) diagnosis codes; procedures recorded with ICD-9-CM or ICD-10-CM procedure codes, Current Procedural Terminology (CPT), or Healthcare Common Procedure Coding System (HCPCS) codes. Typically, facility claims do not include medications dispensed in hospitals.

9.8. Adjudication and validation of the primary endpoints

To evaluate the accuracy of the ICD diagnostic and/or procedure codes used to capture the primary endpoints, the latter were validated against available medical records in Sweden, the Central Region in Denmark, in the Helsinki Region of Finland, in the PHARMO catchment area in the Netherlands, and in the Optum Research Database in the US among patients with available patient and provider identifiers. All eligible patients in crizotinib group and an equally sized group from all other study drug groups combined (erlotinib, gefitinib, ceritinib) were assembled and their available medical records were abstracted into a secure electronic database, using a standard data collection form. Validation data were collected and managed using REDCap electronic data capture tools hosted at Aarhus University. REDCap (Research Electronic Data Capture) is a secure, web-based application, designed to support data capture for research studies, including validated data entry and automated import/export procedures with common statistical packages (38).

Obtaining records at departments of oncology and cardiology was prioritized for abstraction, as it was assumed that oncology records would reflect all relevant data on potential other safety events of interest. The electronic data abstraction results for each endpoint were reviewed by two specialist clinicians (cardiologists, ophthalmologists, hepatologists, and pulmonologists) at Aarhus University Hospital, in Denmark. Each case was classified as “definite case,” “possible case” or “noncase” or “cannot determine”. Cases adjudicated as “definite” or “possible” by both adjudicators were considered true cases. In the case of adjudicators’ disagreement, a third adjudicator served as a tie breaker. The adjudicators were blinded to drug exposure status. The initial case definitions used for adjudication purposes were based on those used in RCTs and were subsequently adapted, to the extent possible, in consultation with the adjudicators, to the type of information likely to be recorded in the available medical records. The Adjudication Charter is provided in Appendix 6.

9.9. Bias

Several potential sources of bias in this study present a challenge, as they do in observational studies in general, including those based on secondary data. Some types of bias are unique for studies of newly available treatments (39-41). The most important sources of bias for studies of newly marketed drugs are potentially prognosis-driven channeling of patients to new therapies; and changing of the patient populations over time, with the resulting treatment effect heterogeneity. For example, in this study, in the EU crizotinib was approved for use in the second line and subsequently in the first line; in the US, it was approved for use in the first line throughout the study period. To avoid exclusion of patients who discontinued medications because of early adverse events, only new users (as defined by the 6-month washout period) of all study drugs were eligible for inclusion in this study. To achieve an adequate study size and ensure representation of patients within different subgroups, the study spanned a period of approximately 3 years.

Sources of bias specific to use of secondary data important in the context of this study include inevitable misclassification of patients with respect to the intake and the timing of the treatment, and misclassification of the outcome status by routinely recorded diagnosis, procedure, or medication codes. In Denmark, an additional source of exposure misclassification stemmed from the fact that gefitinib and ceritinib were not identifiable via available routine data sources, patients in the study who were treated with gefitinib before the index date could not be excluded. For the same reason, the proportion of erlotinib initiators who switched to gefitinib or the proportion of crizotinib initiators who switched to ceritinib during follow-up was unknown and initiation of ceritinib was not identifiable. According to the aggregated sales data provided by the Danish Health Data Authority, in 2013-2016, erlotinib was more commonly used in Denmark than gefitinib, with respectively, 26,400 DDDs and 14,000 DDDs sold during that period. In 2015-2016, approximately 2,500 DDDs of ceritinib were sold in Denmark according to the aggregated sales data (42). Similarly, ascertainment of initiation of/switching to ceritinib was not possible in Finland because ceritinib is not reimbursed and therefore does not generate dispensing records.

9.10. Study size

All eligible patients with primary lung cancer receiving dispensing/prescription for crizotinib, ceritinib, erlotinib, or gefitinib, and all eligible cancer patients receiving crizotinib dispensing/prescription during the study period were included. As described in the Study Protocol (Appendix 2), 677 primary lung cancer patients with a dispensing/prescription for crizotinib and 2,006 lung cancer patients with a dispensing/prescription of erlotinib or gefitinib were projected for inclusion across all participating countries based on the population size, expected number of lung cancer cases, and prevalence of the ALK-positive and EGFR-positive NSCLC. The size of the ceritinib group was not estimated, but all identifiable patients were planned for inclusion.

9.11. Data transformation

Detailed methodology, including construction of the analysis dataset from the raw data, is documented in the SAP (Appendix 4).

9.12. Statistical methods

All planned analyses were conducted initially within each country's database and subsequently, combined to comprise the main statistical output for this report. Results were reported separately for the combined EU population and the US population. The main analyses were performed among the patients with primary lung cancer. Whenever the number of patients was sufficient to not require suppression by local laws, selected baseline characteristics were reported for patients without primary lung cancer. In country-specific output, counts that could allow identification of individuals from a combination of country-specific and combined tables were reported as "Suppressed≤5" (in Sweden) or "Suppressed ≤3" (in Denmark).

9.12.1. Descriptive statistics

Distributions of the baseline characteristics of patients with primary lung cancer were reported descriptively by study drug group, using appropriate summary statistics: frequencies and percent for categorical variables; means and standard deviations (SDs) and/or medians, quartiles, and ranges for continuous variables. One drug group referred to patients exposed to one study drug treatment during the study period and two drug group referred to patients exposed to two study drug treatments during the study period.

9.12.2. Incidence rates and cumulative incidences

The incidence proportions of the endpoints were estimated using cumulative incidences. For each endpoint, 1-, 2- and 3-year cumulative incidences were calculated in each country, whenever the required uniform follow-up was available for all patients. Death was used as a competing risk, according to a previously described method (43), so that a patient dying during the first-year follow-up ceased to be at risk for an endpoint in subsequent years. In the analysis combined across countries, cumulative incidences were combined for patients with the appropriate amount of follow-up available, i.e., because 3 years of follow-up was not available for three countries, the 3-year cumulative incidence was not computed.

Incidence rates of the endpoints were computed, within each study drug group, first using the entire follow-up time (whereby follow-up was censored by a given endpoint, death, emigration, or end of the study period) as time at risk and subsequently using only the on-treatment period as the time at risk (whereby follow-up was additionally censored by discontinuation or switch, as described in Section 9.6.1). The follow-up for incidence rates was not censored at 3 years; therefore, the number of endpoints included in the calculation of incidence rates with the entire follow-up as the time at risk may be greater than those included in calculation of the respective 3-year cumulative incidences.

The effectiveness of the study drugs was assessed descriptively by overall survival, estimated using the Kaplan-Meier product limit estimator of the survival function over 1-, 2-, and 3-years of follow-up in each study drug group.

The analyses were stratified, whenever feasible, by age at the index date (<65/≥ 65 years), baseline record of brain metastases, renal impairment at baseline, and hepatic impairment at baseline.

9.12.3. Combining results across databases

The results were combined across all databases and separately across the EU databases. Combined analyses of cumulative incidences and incidence rates were conducted using random-effects meta-analysis (44). To quantify heterogeneity of the estimates of cumulative incidence and incidence rates originating from the five databases, the I^2 was used. I^2 is a relative measure, corresponding to the proportion of the total variation in estimates from different sources that is attributable to heterogeneity (45-47). I^2 does not depend on the number of studies/databases in a meta-analysis (46). A rough recommendation is to qualify I^2 values of 25%, 50% and 75%, as indicative of "low", "medium", and "high" heterogeneity, emphasizing that I^2 is a relative, rather than absolute, measure of heterogeneity. As I^2 of the results combined across the EU and US populations, exceeded 80% in most analyses, those results are presented, for illustration only, in Section 15. For the purposes of reporting and interpretation, results combined across the EU databases are presented separately and alongside the results from the US.

9.12.4. Validation statistics

For the sets of diagnostic and procedure codes used to identify each primary endpoint, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were estimated using adjudicated cases based on data from medical charts as the reference standard (computed as described in the SAP, Appendix 4). In one analysis, only cases adjudicated as "definite" were considered true cases (2 "definite" adjudications). In another analysis, cases adjudicated as "definite" or "possible" were considered true cases (at least 1 "possible" adjudication).

9.12.5. Missing values

Within administrative data sources (such as claims, registries, and medical records), the absence of a diagnostic code or a drug code is presumed to indicate that the diagnosis or drug was not present in the patient's medical history. Because the missingness is likely to be unrelated to the study treatments in the routine databases used for this study, missing data were assumed to be random, and no method to impute missing data was used. Invalid records were discarded prior to constructing analysis datasets. Whenever applicable, a "Missing" or "Unknown" category was used descriptively.

9.12.6. Sensitivity analyses

None.

9.12.7. Amendments to the statistical analysis plan

There were the following deviations from the SAP:

1. Three-year cumulative incidences were not observed for all countries; therefore, only 2-year cumulative incidences were reported.

2. Because erlotinib was the largest study drug group and all other non-crizotinib study drug groups were small, even in the combined data, cumulative incidences and incidence rates were estimated for the crizotinib and the erlotinib groups only.

3. In the Netherlands, Pathology Registry was used to identify patients with primary lung cancer as it had shorter lag time than the Cancer Registry and allowed for identification of mutation status.

4. Overall survival was not reported for 2 drug groups (erlotinib/gefitinib and crizotinib/ceritinib) because of sparse data.

9.13. Quality control

In Denmark, data were managed and analyzed and quality control (QC) was conducted in accordance with the SOPs at the Department of Clinical Epidemiology and Aarhus University Hospital. Patient privacy was ensured according to the Danish Act on Processing of Personal Data (http://www.datatilsynet.dk/english/). Statistical quality control procedures entailed logic checks of statistical output, and review of the results and the report by the project epidemiologist and project statistician. All report drafts underwent internal review by a senior epidemiologist, a statistician, and a clinician and was to be approved by the Principal Investigator.

In Finland, all processes from data management to the creation of analysis results went through quality control checks including programs, results tables and written text, according to EPID Research's SOP ER-10510.03 "Data Management and Statistical Analysis". The programming quality control was performed by a statistician other than the original writer of the program for all programs related to the data management and statistical analyses. A detailed audit trail of all documents (programs, result tables, reports) along with quality control processes was maintained.

In Sweden, quality control was performed according to the guideline for QC of data and analysis and reporting, issued by the Centre for Pharmacoepidemiology (CPE) at Karolinska Institutet. The data received from the Swedish National Board of Health and Welfare were checked for completeness and consistency. The computer programming was in accordance with the CPE guideline for good programming practice. The output was reviewed by a senior epidemiologist.

In the Netherlands, SOPs for quality control included internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. All programming written by the executing researcher was reviewed independently by a senior researcher. All key study documents, such as the statistical analysis plan and study reports, underwent quality control and senior scientific review.

In the US, data were managed and analyzed according to Optum Epidemiology's internal SOPs that are consistent with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) (48) as well as the FDA Best Practice Guidance document (49). In particular, the SOPs in place described that processes and deliverables be documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

9.14. Protection of human subjects

Subject information and consent

Not applicable.

Other required approvals:

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the GPP, issued by the ISPE (48), the Guidelines for Good Pharmacovigilance Practice (GVP) Module VI and Module VIII, issued by the EMA (50); European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and the FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

In Denmark, the study received approval from the Danish Data Protection Agency (journal numbers 2014-41-3488, 2015-57-0002) for the analysis of registry-based data and an approval from the Danish Patient Safety Board to access medical records for the validation study (www.stps.dk, journal number 3-3013-1775/1).

In Finland, the study received approval from the office of the data protection Ombudsman for the use of nationwide registry data (journal number 1197/4225/16) and from the Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) (journal number 321/13/03/00/15).

In Sweden, the study was approved by the regional ethical board in Stockholm, Sweden (record number 2015/1548-31/4).

In the Netherlands, this study fulfilled the requirements as checked by the PHARMO Compliance Commission to use data from the PHARMO Database Network for this specific study.

In the US, all analyses were performed in accordance with applicable laws and regulations, with approvals by an Independent Review Board (IRB) and Privacy Board. Release of de-identified abstracted data from medical charts and analytical datasets received IRB and Deidentification Determination Program approval. The study received approval from the New England IRB (IRB# 120160394, Legacy IRB#15-319) for analyses and release of data.

10. RESULTS

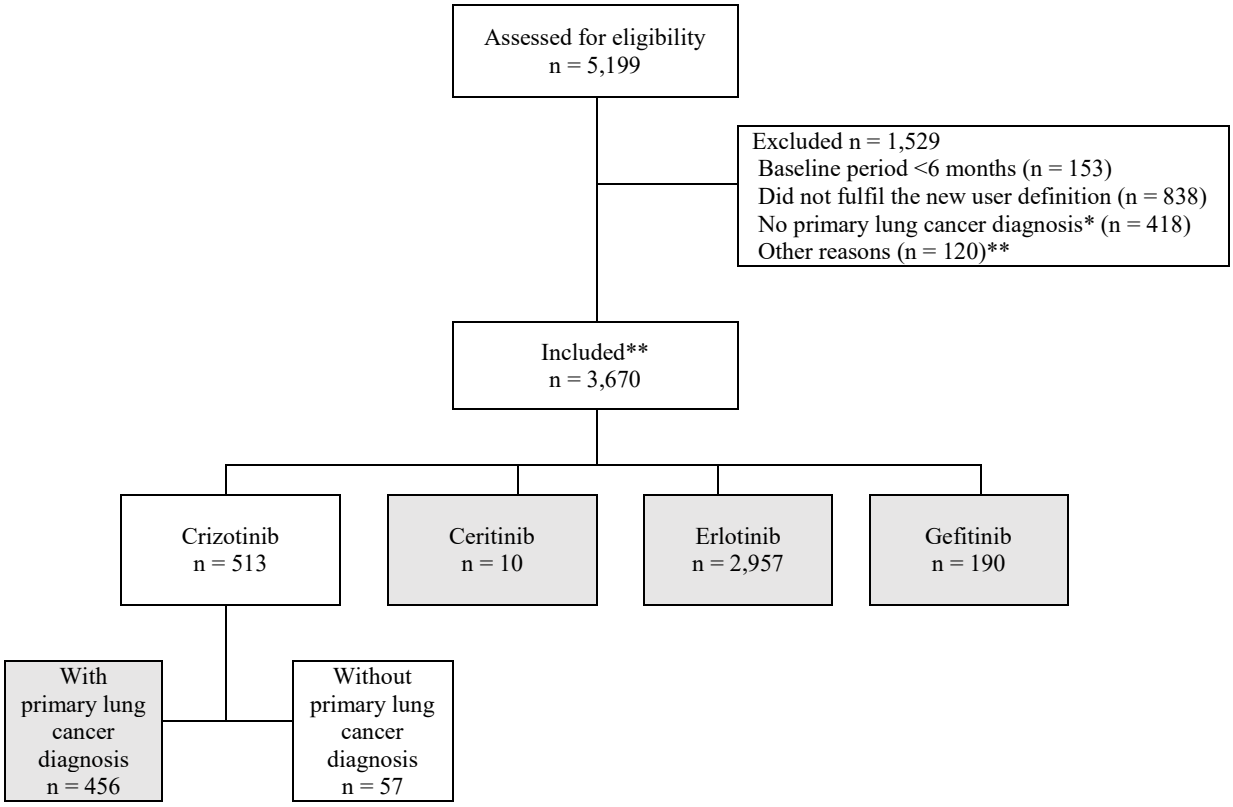
10.1. Participants

During the entire study period, 5,199 patients with a dispensing/prescription of a study drug accompanied by a record of primary lung cancer (except crizotinib group) before/on the index date were assessed for eligibility. Overall, 1,529 ineligible patients were excluded: 153 with <6 months baseline period (17 in crizotinib group, 3 in ceritinib group, 132 in erlotinib group, 1 in gefitinib group); 838 not fulfilling the new user definition (49 in the crizotinib group; 8 in the ceritinib group; 700 in the erlotinib group; 81 in the gefitinib group); 418 patients without a primary lung cancer diagnosis on/before index date; and 120 for other reasons (Figure 2). Thus, 3,670 patients were eligible for the study, of whom 513 patients received crizotinib and 3,157

received other study drugs. Of the 513 patients with a dispensing/prescription of crizotinib during the study period, 456 had a prior record of primary lung cancer and were included in the main analysis; 57 patients did not have a prior record of primary lung cancer and were included only in the off-label analysis.

The main analysis dataset of patients with primary lung cancer in all five countries included 456 patients in the crizotinib group; 10 patients in the ceritinib group; 2,957 patients in the erlotinib group; and 190 patients in the gefitinib group (Figure 2). Furthermore, 80 patients who entered the study in the crizotinib group or ceritinib group also contributed to the "crizotinib and ceritinib" group following the switch to the second drug; 52 patients who entered the study in the erlotinib group or gefitinib group also contributed to the "erlotinib and gefitinib" group following the switch. . Sweden and the US each contributed approximately one-third of all patients into the study. Country-specific enrollment is shown in country-specific output (Appendix 5).

Figure 2. Identification of the Study Population



* Applies only to patients with dispensing/prescription of study drugs other than crizotinib.
** Patients in Sweden with a qualifying dispensing of a study drug less than 6 months before the end of the follow-up
*** Enrolment shown according to the first study drug received on the index date during the study period; 80 patients who entered the study in the crizotinib group or ceritinib group also contributed to the "crizotinib and ceritinib" group following the switch to the second drug; 52 patients who entered the study in the erlotinib group or gefitinib group also contributed to the "erlotinib and gefitinib" group following the switch.
Source: Figure 15.1 and country-specific Supplemental Figures 1 (Appendix 5).

A full 3-year follow-up for all patients, required for computation of 3-year cumulative incidences, was available in Denmark and in the US. Table 3 shows the median and interquartile range (IQR) total follow-up and on-treatment time by country and by study drug group. IQR total follow-up time and IQR on-treatment time in the crizotinib group as well as in the erlotinib group were slightly longer in EU than that in US. Because patients with dispensing/prescription of erlotinib were the largest non-crizotinib study drug group (Figure 2), this group supplied the most stable estimates for the context of the findings for the crizotinib group. Therefore, this report focuses on the crizotinib group and the erlotinib group. In country-specific supplemental output (Appendix 5), results are presented for all study drug groups. Owing to the high level of heterogeneity between the EU and US data, as described above, and as provided in the SAP (Appendix 4), results were described and interpreted separately for the EU and the US data. Section 15 provides overall combined results to illustrate heterogeneity.

Table 3. Follow-up Time and On-treatment Time among Patients with Primary Lung Cancer, by Study Drug Group and by Country

	Total follow-up time, days, median (IQR)					
	Crizotinib	Ceritinib	Erlotinib	Gefitinib	Crizotinib and ceritinib	Erlotinib and gefitinib
Denmark	422 (183 - 597)	N/A	203 (78 - 442)	N/A	N/A	N/A
Finland	422 (283 - 779)	N/A	252 (114 - 477)	340 (194 - 561)	N/A	488 (279 - 670)
Sweden	274 (135 - 445)	N/A	207 (78 - 500)	328 (138 - 568)	124 (47 - 211)	319 (144 - 570)
The Netherlands	352 (203 - 639)	288 (268 - 423)	487 (344 - 830)	483 (354 - 813)	N/A	N/A
United States	262 (134 - 487)	403 (225 - 582)	234 (95 - 466)	285 (283 - 287)	250 (91 - 591)	141 (38 - 263)
	Total on-treatment time, days, median (IQR)					
	Crizotinib	Ceritinib	Erlotinib	Gefitinib	Crizotinib and ceritinib	Erlotinib and gefitinib
Denmark	247 (79 - 423)	N/A	100 (58 - 209)	N/A	N/A	N/A
Finland	314 (119 - 547)	N/A	127 (81 - 299)	238 (118 - 467)	N/A	382 (164 - 609)
Sweden	209 (93 - 364)	N/A	118 (58 - 293)	221 (107 - 407)	112 (48 - 188)	134 (77 - 336)
The Netherlands	151 (71 - 340)	266 (218 - 375)	238 (88 - 360)	147 (58 - 347)	N/A	N/A
United States	160 (74 - 323)	123 (92 - 345)	113 (58 - 230)	184 (135 - 232)	117 (58 - 385)	65 (31 - 104)

N/A not applicable (no or too few observations); IQR interquartile range. Rounded to the nearest integer.

10.2. Descriptive data

Table 4 shows baseline characteristics of patients with primary lung cancer by study drug group in the combined EU data. There were 278 patients in the crizotinib group; 4 patients in the ceritinib group; 2,121 patients in the erlotinib group; 188 patients in the gefitinib group; and 48 patients each in the crizotinib and ceritinib group and the erlotinib and gefitinib group. All 48 patients in the crizotinib and ceritinib group were from Sweden. Median (range) age at index date was 62.8 (23.7 - 84.0) years in the crizotinib group and 68.3 (24.0 - 91.2) years in the erlotinib group; 19.4% of the patients in the crizotinib group and 4.4% of the patients in the erlotinib group were younger than 50 years on the index date. Women comprised 56.1% of the

crizotinib group and 58.0% of the erlotinib group. A majority of the patients with available information on cancer stage at primary lung cancer diagnosis had lung cancer Stage IV. Primary lung cancer was diagnosed before 2011 in 8.3% of the patients in the crizotinib group, and in 7.6% of the patients in the erlotinib group. Mean time from primary lung cancer diagnosis until the index date was 15.6 (SD: 23.3) months (range: 0.0-153.4 months) in the crizotinib group; and 14.6 (SD: 18.8) months (range: 0.0-293.4 months) in the erlotinib group (Table 4, Table 15.2).

Data on ALK-testing and EGFR-testing results were available in Denmark and in the Netherlands. In Denmark, 67/79 (84.8%) patients in the crizotinib group had a record of an ALK-positive test, and 574/855 (67.1%) patients in the erlotinib group had a record of an EGFR-positive test; 2 patients were positive for both alterations (Denmark Supplemental Table 1, Appendix 5). In the Netherlands, 11/32 (34.4%) patients in the crizotinib group had a record of an ALK-positive test, and 33/61 (54.1%) patients in the erlotinib group had a record of an EGFR-positive test (The Netherlands Supplemental Table 1, Appendix 5).

Table 4. Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, EU Combined

	Study drug group					
Characteristics	Crizotinib (N= 278)	Ceritinib (N= 4)	Erlotinib (N=2,121)	Gefitinib (N= 188)	Crizotinib and Ceritinib (N= 48)	Erlotinib and Gefitinib (N= 48)
Age group at index date, years, n (%)						
<50	54 (19.4)	0 (0.0)	94 (4.4)	9 (4.8)	10 (20.8)	4 (8.3)
50 to 59	58 (20.9)	4 (100.0)	306 (14.4)	21 (11.2)	14 (29.2)	3 (6.3)
60 to 69	98 (35.3)	0 (0.0)	792 (37.3)	61 (32.4)	18 (37.5)	19 (39.6)
70 to 79	56 (20.1)	0 (0.0)	688 (32.4)	64 (34.0)	6 (12.5)	17 (35.4)
80+	12 (4.3)	0 (0.0)	241 (11.4)	33 (17.6)	0 (0.0)	5 (10.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age at index date, years						
Median (range)	62.8 (23.7-84.0)	55.0 (51.0-59.7)	68.3 (24.0-91.2)	70.5 (40.6-89.0)	60.0 (40.0-76.0)	68.9 (44.0-83.0)
Sex, n (%)						
Men	122 (43.9)	2 (50.0)	890 (42.0)	77 (41.0)	22 (45.8)	15 (31.3)
Women	156 (56.1)	2 (50.0)	1,231 (58.0)	111 (59.0)	26 (54.2)	33 (68.8)
Race/ethnicity, n (%)						
Unknown	278 (100.0)	4 (100.0)	2,121 (100.0)	188 (100.0)	48 (100.0)	48 (100.0)
Lung cancer morphology, n (%)						
Non-small cell lung cancer (NSCLC)	250 (89.9)	4 (100.0)	1,975 (93.1)	164 (87.2)	47 (97.9)	46 (95.8)
Small cell lung cancer	3 (1.1)	0 (0.0)	6 (0.3)	0 (0.0)	1 (2.1)	0 (0.0)
Unknown	25 (9.0)	0 (0.0)	140 (6.6)	24 (12.8)	0 (0.0)	2 (4.2)
Lung cancer histology (NSCLC only), n (%)						
Squamous cell carcinoma	6 (2.2)	0 (0.0)	171 (8.1)	4 (2.1)	1 (2.1)	0 (0.0)
Adenocarcinoma	220 (79.1)	4 (100.0)	1,628 (76.8)	150 (79.8)	42 (87.5)	42 (87.5)
Other	2 (0.7)	0 (0.0)	76 (3.6)	1 (0.5)	0 (0.0)	0 (0.0)
Unknown or not NSCLC	50 (18.0)	0 (0.0)	246 (11.6)	33 (17.6)	5 (10.4)	6 (12.5)
Stage at diagnosis, n (%)						
Stage I	13 (4.7)	0 (0.0)	138 (6.5)	10 (5.3)	2 (4.2)	5 (10.4)
Stage II	1 (0.4)	0 (0.0)	68 (3.2)	5 (2.7)	0 (0.0)	0 (0.0)
Stage III	17 (6.1)	0 (0.0)	224 (10.6)	4 (2.1)	1 (2.1)	0 (0.0)
Stage IV	161 (57.9)	0 (0.0)	1,114 (52.5)	65 (34.6)	34 (70.8)	33 (68.8)
Unknown or not reported as TNM stage (Finland[a])	86 (30.9)	4 (100.0)	577 (27.2)	104 (55.3)	11 (22.9)	10 (20.8)
Genotyping, n (%)						
ALK rearrangement	78 (28.1)	1 (25.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EGFR mutation	3 (1.1)	0 (0.0)	311 (14.7)	10 (5.3)	0 (0.0)	0 (0.0)
Both ALK and EGFR	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Not ALK or EGFR	6 (2.2)	1 (25.0)	6 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Unknown	191 (68.7)	2 (50.0)	1,801 (84.9)	177 (94.1)	48 (100.0)	48 (100.0)

Table 4. Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, EU Combined

Characteristics	Study drug group					
	Crizotinib (N= 278)	Ceritinib (N= 4)	Erlotinib (N=2,121)	Gefitinib (N= 188)	Crizotinib and Ceritinib (N= 48)	Erlotinib and Gefitinib (N= 48)
Year of lung cancer diagnosis, n (%)						
Before 2011	23 (8.3)	1 (25.0)	161 (7.6)	11 (5.9)	5 (10.4)	2 (4.2)
2011-2012	32 (11.5)	1 (25.0)	486 (22.9)	23 (12.2)	7 (14.6)	8 (16.7)
2013-2014	124 (44.6)	1 (25.0)	1,020 (48.1)	95 (50.5)	17 (35.4)	27 (56.3)
2015-2016	99 (35.6)	1 (25.0)	454 (21.4)	59 (31.4)	19 (39.6)	11 (22.9)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time since primary lung cancer diagnosis, months						
Mean (standard deviation)	15.6 (23.3)	36.2 (-)	14.6 (18.8)	11.4 (17.3)	16.8 (23.2)	8.7 (13.3)
Range[b]	0.0-153.4	7.2-69.5	0.0-293.4	0.1-148.0	0.8-115.3	0.5-75.9
Country, n (%)						
Denmark	79 (28.4)	0 (0.0)	855 (40.3)	0 (0.0)	0 (0.0)	0 (0.0)
Finland	25 (9.0)	0 (0.0)	323 (15.2)	77 (41.0)	0 (0.0)	8 (16.7)
Netherlands	32 (11.5)	3 (75.0)	61 (2.9)	18 (9.6)	0 (0.0)	0 (0.0)
Sweden	142 (51.1)	1 (25.0)	882 (41.6)	93 (49.5)	48 (100.0)	40 (83.3)

[a] For stage distribution in Finland, see Finland Supplemental Table 1, Appendix 5.
[b] Median not estimable from available combined data.
ALK anaplastic lymphoma kinase; EGFR epidermal growth factor receptor; NSCLC non-small cell lung cancer; TNM tumour, node, metastasis.
Source: Table 15.2

Table 5 shows baseline characteristics of patients with primary lung cancer by study drug group in the US population. There were 178 patients in the crizotinib group; 6 patients in the ceritinib group; 836 patients in the erlotinib group; 2 patients in the gefitinib group (expected given that gefitinib was re-approved in the US in 2015), 32 patients in the crizotinib and ceritinib group; and 4 patients in the erlotinib and gefitinib group. Median (range) age at index date was 55.0 (49.0 - 61.0) years in the crizotinib group and 61.0 (54.0 - 65.0) years in the erlotinib group; 25.8% of the patients in the crizotinib group and 11.5% of the patients in the erlotinib group were younger than 50 years at the index date. Women comprised 53.4% of the crizotinib group and 55.1% of the erlotinib group. Mean time from primary lung cancer diagnosis until the index date was 9.8 (SD: 14.5) months in the crizotinib group (range: 1.1-11.7 months); and 12.0 (SD: 13.6) months in the erlotinib group (range: 2.1-16.0 months) (Table 5, Table 15.3). Data on ALK-testing, EGFR-testing or on cancer stage were not available in the US.

Table 5. Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, US

Characteristics	Study drug group					
	Crizotinib (N= 178)	Ceritinib (N= 6)	Erlotinib (N= 836)	Gefitinib (N= 2)	Crizotinib and Ceritinib (N= 32)	Erlotinib and Gefitinib (N= 4)
Age group at index date, years, n (%)						
<50	46 (25.8)	3 (50.0)	96 (11.5)	0 (0.0)	9 (28.1)	0 (0.0)
50 to 59	72 (40.4)	3 (50.0)	280 (33.5)	1 (50.0)	15 (46.9)	1 (25.0)
60 to 69	51 (28.7)	0 (0.0)	338 (40.4)	0 (0.0)	7 (21.9)	2 (50.0)
70 to 79	8 (4.5)	0 (0.0)	78 (9.3)	0 (0.0)	1 (3.1)	0 (0.0)
80+	1 (0.6)	0 (0.0)	44 (5.3)	1 (50.0)	0 (0.0)	1 (25.0)
Age at index date, years						
Median (range)	55.0 (49.0-61.0)	46.5 (34.0-56.0)	61.0 (54.0-65.0)	70.5 (54.0-87.0)	56.0 (47.5-59.5)	63.0 (58.0-73.0)
Sex, n (%)						
Men	83 (46.6)	3 (50.0)	375 (44.9)	0 (0.0)	13 (40.6)	0 (0.0)
Women	95 (53.4)	3 (50.0)	461 (55.1)	2 (100.0)	19 (59.4)	4 (100.0)
Race/ethnicity, n (%)						
Asian	8 (4.5)	0 (0.0)	46 (5.5)	1 (50.0)	0 (0.0)	1 (25.0)
Black	14 (7.9)	0 (0.0)	71 (8.5)	0 (0.0)	5 (15.6)	1 (25.0)

Table 5. Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, US

	Study drug group					
Characteristics	Crizotinib (N= 178)	Ceritinib (N= 6)	Erlotinib (N= 836)	Gefitinib (N= 2)	Crizotinib and Ceritinib (N= 32)	Erlotinib and Gefitinib (N= 4)
Hispanic	11 (6.2)	0 (0.0)	52 (6.2)	0 (0.0)	2 (6.3)	1 (25.0)
White	128 (71.9)	5 (83.3)	602 (72.0)	1 (50.0)	21 (65.6)	1 (25.0)
Unknown	17 (9.6)	1 (16.7)	65 (7.8)	0 (0.0)	4 (12.5)	0 (0.0)
Lung cancer morphology, n (%)						
Unknown	178 (100.0)	6 (100.0)	836 (100.0)	2 (100.0)	32 (100.0)	4 (100.0)
Lung cancer histology (NSCLC only), n (%)						
Unknown	178 (100.0)	6 (100.0)	836 (100.0)	2 (100.0)	32 (100.0)	4 (100.0)
Stage at diagnosis, n (%)						
Unknown	178 (100.0)	6 (100.0)	836 (100.0)	2 (100.0)	32 (100.0)	4 (100.0)
Genotyping, n (%)						
Unknown	178 (100.0)	6 (100.0)	836 (100.0)	2 (100.0)	32 (100.0)	4 (100.0)
Year of lung cancer diagnosis, n (%)						
Before 2011	26 (14.6)	0 (0.0)	133 (15.9)	0 (0.0)	3 (9.4)	2 (50.0)
2011-2012	42 (23.6)	2 (33.3)	380 (45.5)	0 (0.0)	6 (18.8)	1 (25.0)
2013-2014	77 (43.3)	4 (66.7)	240 (28.7)	0 (0.0)	19 (59.4)	0 (0.0)
2015-2016	33 (18.5)	0 (0.0)	83 (9.9)	2 (100.0)	4 (12.5)	1 (25.0)
Time since primary lung cancer diagnosis, months						
Mean (standard deviation)	9.8 (14.5)	17.8 (8.4)	12.0 (13.6)	5.5 (4.1)	20.8 (16.7)	43.8 (26.0)
Median (range)	2.8 (1.1-11.7)	17.9 (10.3-23.7)	7.3 (2.1-16.0)	5.5 (2.5-8.4)	13.9 (9.2-26.5)	54.6 (27.3-60.3)

NSCLC non-small cell lung cancer, US United States
Source: Table 15.3

Patients in the EU were older than patients in the US, both in the crizotinib and in erlotinib groups. Furthermore, mean time from primary cancer diagnosis until starting treatment with a study drug was longer in the EU than in the US (Table 4, Table 15.2, Table 5, Table 15.3). For completeness, baseline characteristics combined across all countries are listed in Table 15.1.

Table 6 shows baseline comorbidities and concomitant medications among patients with primary lung cancer by study drug group in the combined EU population. In the crizotinib and erlotinib groups, respective prevalences of baseline bradycardia were 0.4% and 1.6%; prevalences of baseline hepatotoxicity were 0.7% and 0.3%; prevalences of baseline pneumonitis/ILD were 20.5% and 14.6%, prevalences of baseline QT interval prolongation-related events were 3.6% and 3.6%, and prevalences of baseline vision disorders were 6.8% and 6.2%. Patients in the crizotinib and erlotinib groups had, respectively, 11.2% and 11.1% prevalence of brain metastases at baseline; 4.0% and 1.8% prevalence of hepatic impairment at baseline; and 2.2% and 4.6% prevalence of renal impairment at baseline (Table 6).

The prevalence of high overall baseline comorbidity burden (Charlson Comorbidity Index score 3 or higher), was 51.8% in the crizotinib group and 51.5% in the erlotinib group. The prevalences of baseline use of concomitant medications in the crizotinib and erlotinib groups were, respectively, 5.8% and 11.9% for antidiabetic agents; 43.9% and 68.8% for any cardiovascular medication; 63.3% and 63.1% for steroids; 75.2% and 80.2% for systemic antibacterials; 5.4% and 4.5% for antipsychotics; 30.9% and 36.5% for anti-asthma medications; and 20.9% and 24.4% for ophthalmologicals (Table 6, Table 15.5).

Table 6. Comorbidities and Concomitant Medications among Patients with Primary Lung Cancer by Study Drug Group at Baseline, EU Combined

	Study drug group					
Characteristics	Crizotinib (N= 278)	Ceritinib (N= 4)	Erlotinib (N=2,121)	Gefitinib (N= 188)	Crizotinib and Ceritinib (N= 48)	Erlotinib and Gefitinib (N= 48)
Bradycardia	1 (0.4)	1 (25.0)	33 (1.6)	0 (0.0)	2 (4.2)	0 (0.0)
Hepatotoxicity	2 (0.7)	0 (0.0)	6 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Pneumonitis/ILD	57 (20.5)	1 (25.0)	309 (14.6)	47 (25.0)	17 (35.4)	12 (25.0)
QT interval prolongation-related events	10 (3.6)	1 (25.0)	77 (3.6)	10 (5.3)	3 (6.3)	3 (6.3)
Vision disorders	19 (6.8)	0 (0.0)	132 (6.2)	15 (8.0)	9 (18.8)	8 (16.7)
Renal cysts	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	8 (2.9)	0 (0.0)	44 (2.1)	6 (3.2)	3 (6.3)	1 (2.1)
Leukopenia	21 (7.6)	1 (25.0)	160 (7.5)	10 (5.3)	8 (16.7)	2 (4.2)
Neuropathy	27 (9.7)	0 (0.0)	247 (11.6)	26 (13.8)	13 (27.1)	5 (10.4)
Photosensitivity	2 (0.7)	0 (0.0)	11 (0.5)	2 (1.1)	1 (2.1)	7 (14.6)
Malignant melanoma	1 (0.4)	0 (0.0)	20 (0.9)	1 (0.5)	2 (4.2)	4 (8.3)
Gastrointestinal perforation	0 (0.0)	0 (0.0)	12 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure	3 (1.1)	0 (0.0)	75 (3.5)	2 (1.1)	0 (0.0)	1 (2.1)
Brain metastases	31 (11.2)	1 (25.0)	235 (11.1)	20 (10.6)	9 (18.8)	6 (12.5)
Hepatic impairment	11 (4.0)	1 (25.0)	38 (1.8)	3 (1.6)	2 (4.2)	1 (2.1)
Liver cirrhosis	1 (0.4)	0 (0.0)	10 (0.5)	0 (0.0)	0 (0.0)	1 (2.1)
Renal impairment	6 (2.2)	0 (0.0)	98 (4.6)	11 (5.9)	0 (0.0)	2 (4.2)
End-stage renal disease	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Diabetes type 1 or type 2	27 (9.7)	0 (0.0)	299 (14.1)	27 (14.4)	2 (4.2)	6 (12.5)
Chronic lung disease	25 (9.0)	1 (25.0)	333 (15.7)	22 (11.7)	4 (8.3)	7 (14.6)
Chronic obstructive pulmonary disease	15 (5.4)	0 (0.0)	267 (12.6)	8 (4.3)	1 (2.1)	3 (6.3)
Charlson comorbidity index[a]						
Low (0)	103 (37.1)	0 (0.0)	628 (29.6)	54 (28.7)	18 (37.5)	14 (29.2)
Medium (1-2)	31 (11.2)	0 (0.0)	401 (18.9)	28 (14.9)	3 (6.3)	8 (16.7)
High (3+)	144 (51.8)	4 (100.0)	1,092 (51.5)	106 (56.4)	27 (56.3)	26 (54.2)
Oral antidiabetics and insulin	16 (5.8)	0 (0.0)	252 (11.9)	20 (10.6)	2 (4.2)	5 (10.4)
Any cardiovascular medications	122 (43.9)	0 (0.0)	1,459 (68.8)	117 (62.2)	19 (39.6)	31 (64.6)
Diuretics	57 (20.5)	0 (0.0)	680 (32.1)	39 (20.7)	11 (22.9)	14 (29.2)
Beta blockers	55 (19.8)	0 (0.0)	696 (32.8)	66 (35.1)	7 (14.6)	16 (33.3)
Calcium-channel blockers	42 (15.1)	0 (0.0)	557 (26.3)	43 (22.9)	3 (6.3)	10 (20.8)
Angiotensin converting enzyme inhibitors	42 (15.1)	0 (0.0)	515 (24.3)	31 (16.5)	6 (12.5)	7 (14.6)
Angiotensin II receptor antagonists	35 (12.6)	0 (0.0)	393 (18.5)	39 (20.7)	4 (8.3)	4 (8.3)
Statins	55 (19.8)	0 (0.0)	706 (33.3)	63 (33.5)	12 (25.0)	11 (22.9)
Steroids	176 (63.3)	1 (25.0)	1,339 (63.1)	106 (56.4)	46 (95.8)	33 (68.8)
Antibacterials for systemic use	209 (75.2)	1 (25.0)	1,700 (80.2)	126 (67.0)	41 (85.4)	34 (70.8)
Anticonvulsants	25 (9.0)	0 (0.0)	271 (12.8)	17 (9.0)	6 (12.5)	3 (6.3)
Antipsychotics	15 (5.4)	0 (0.0)	96 (4.5)	2 (1.1)	0 (0.0)	1 (2.1)
Anti-asthma medications	86 (30.9)	1 (25.0)	775 (36.5)	47 (25.0)	21 (43.8)	17 (35.4)
Ophthalmologicals	58 (20.9)	1 (25.0)	517 (24.4)	44 (23.4)	9 (18.8)	19 (39.6)

[a] Excluding lung cancer.
ILD interstitial lung disease.
Source: Table 15.5

Table 7 shows baseline comorbidities and concomitant medications among patients with primary lung cancer by study drug group in the US. In the crizotinib and erlotinib groups, respective prevalences of baseline bradycardia were 15.7% and 14.5%; prevalences of baseline hepatotoxicity were 3.4% and 3.5%; prevalences of baseline pneumonitis/ILD were 43.3% and 41.5%, prevalences of baseline QT interval prolongation-related events were 55.1% and 49.5%, and prevalences of baseline vision disorders were 10.7% and 10.2%. Patients in the crizotinib

and erlotinib groups had, respectively, 30.3% and 31.9% prevalence of brain metastases at baseline; 24.2% and 18.9% prevalence of hepatic impairment at baseline; and 22.5% and 25.4% prevalence of renal impairment at baseline (Table 7).

The prevalence of high overall baseline comorbidity burden (Charlson Comorbidity Index score 3 or higher), was 87.1% in the crizotinib group and 86.4% in the erlotinib group. The prevalences of baseline use of medications in the crizotinib and erlotinib groups were, respectively, 29.8% and 32.5% for antidiabetic agents; 44.4% and 41.1% for any cardiovascular medication; 56.2% and 58.3% for steroids; 64.6% and 68.2% for systemic antibacterials; 2.8% and 3.8% for antipsychotics; 48.3% and 44.6% for anti-asthma medications; and 1.1% and 1.8% for ophthalmologicals (Table 7, Table 15.6).

Table 7. Comorbidities and Concomitant Medications among Patients with Primary Lung Cancer by Study Drug Group at Baseline, US

	Study drug group					
Characteristics	Crizotinib (N= 178)	Ceritinib (N= 6)	Erlotinib (N= 836)	Gefitinib (N= 2)	Crizotinib and Ceritinib (N= 32)	Erlotinib and Gefitinib (N= 4)
Bradycardia	28 (15.7)	2 (33.3)	121 (14.5)	0 (0.0)	7 (21.9)	2 (50.0)
Hepatotoxicity	6 (3.4)	0 (0.0)	29 (3.5)	0 (0.0)	2 (6.3)	0 (0.0)
Pneumonitis/ILD	77 (43.3)	3 (50.0)	347 (41.5)	1 (50.0)	12 (37.5)	1 (25.0)
QT interval prolongation-related events	98 (55.1)	4 (66.7)	414 (49.5)	2 (100.0)	24 (75.0)	3 (75.0)
Vision disorders	19 (10.7)	2 (33.3)	85 (10.2)	0 (0.0)	8 (25.0)	0 (0.0)
Renal cysts	5 (2.8)	0 (0.0)	16 (1.9)	0 (0.0)	1 (3.1)	0 (0.0)
Edema	59 (33.1)	1 (16.7)	203 (24.3)	0 (0.0)	11 (34.4)	1 (25.0)
Leukopenia	48 (27.0)	1 (16.7)	313 (37.4)	0 (0.0)	9 (28.1)	3 (75.0)
Neuropathy	84 (47.2)	4 (66.7)	466 (55.7)	1 (50.0)	16 (50.0)	2 (50.0)
Photosensitivity	14 (7.9)	0 (0.0)	67 (8.0)	0 (0.0)	1 (3.1)	1 (25.0)
Malignant melanoma	0 (0.0)	0 (0.0)	9 (1.1)	0 (0.0)	1 (3.1)	0 (0.0)
Gastrointestinal perforation	10 (5.6)	0 (0.0)	81 (9.7)	1 (50.0)	4 (12.5)	1 (25.0)
Cardiac failure	14 (7.9)	1 (16.7)	70 (8.4)	0 (0.0)	5 (15.6)	1 (25.0)
Brain metastases	54 (30.3)	3 (50.0)	267 (31.9)	1 (50.0)	13 (40.6)	2 (50.0)
Hepatic impairment	43 (24.2)	0 (0.0)	158 (18.9)	1 (50.0)	6 (18.8)	0 (0.0)
Liver cirrhosis	19 (10.7)	0 (0.0)	61 (7.3)	0 (0.0)	2 (6.3)	0 (0.0)
Renal impairment	40 (22.5)	0 (0.0)	212 (25.4)	1 (50.0)	8 (25.0)	2 (50.0)
End-stage renal disease	1 (0.6)	0 (0.0)	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes type 1 or type 2	60 (33.7)	1 (16.7)	313 (37.4)	0 (0.0)	12 (37.5)	2 (50.0)
Chronic lung disease	56 (31.5)	3 (50.0)	384 (45.9)	0 (0.0)	10 (31.3)	1 (25.0)
Chronic obstructive pulmonary disease	27 (15.2)	2 (33.3)	290 (34.7)	0 (0.0)	6 (18.8)	1 (25.0)
Charlson comorbidity index[a]						
Low (0)	12 (6.7)	0 (0.0)	51 (6.1)	0 (0.0)	2 (6.3)	0 (0.0)
Medium (1-2)	11 (6.2)	0 (0.0)	63 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)
High (3+)	155 (87.1)	6 (100.0)	722 (86.4)	2 (100.0)	30 (93.8)	4 (100.0)
Oral antidiabetics and insulin	53 (29.8)	1 (16.7)	272 (32.5)	0 (0.0)	10 (31.3)	2 (50.0)
Any cardiovascular medications	79 (44.4)	2 (33.3)	344 (41.1)	1 (50.0)	12 (37.5)	2 (50.0)
Diuretics	33 (18.5)	1 (16.7)	158 (18.9)	0 (0.0)	6 (18.8)	0 (0.0)
Beta blockers	45 (25.3)	2 (33.3)	190 (22.7)	0 (0.0)	6 (18.8)	2 (50.0)
Calcium-channel blockers	22 (12.4)	1 (16.7)	132 (15.8)	1 (50.0)	3 (9.4)	1 (25.0)
Angiotensin converting enzyme inhibitors	27 (15.2)	0 (0.0)	106 (12.7)	1 (50.0)	4 (12.5)	2 (50.0)
Angiotensin II receptor antagonists	22 (12.4)	0 (0.0)	93 (11.1)	0 (0.0)	4 (12.5)	1 (25.0)
Statins	37 (20.8)	1 (16.7)	201 (24.0)	0 (0.0)	6 (18.8)	1 (25.0)
Steroids	100 (56.2)	1 (16.7)	487 (58.3)	1 (50.0)	14 (43.8)	2 (50.0)
Antibacterials for systemic use	115 (64.6)	4 (66.7)	570 (68.2)	2 (100.0)	15 (46.9)	3 (75.0)
Anticonvulsants	45 (25.3)	1 (16.7)	215 (25.7)	0 (0.0)	6 (18.8)	1 (25.0)
Antipsychotics	5 (2.8)	0 (0.0)	32 (3.8)	0 (0.0)	2 (6.3)	0 (0.0)
Anti-asthma medications	86 (48.3)	4 (66.7)	373 (44.6)	0 (0.0)	8 (25.0)	2 (50.0)
Ophthalmologicals	2 (1.1)	1 (16.7)	15 (1.8)	0 (0.0)	0 (0.0)	1 (25.0)

Table 7. Comorbidities and Concomitant Medications among Patients with Primary Lung Cancer by Study Drug Group at Baseline, US

	Study drug group					
Characteristics	Crizotinib (N= 178)	Ceritinib (N= 6)	Erlotinib (N= 836)	Gefitinib (N= 2)	Crizotinib and Ceritinib (N= 32)	Erlotinib and Gefitinib (N= 4)

[a] Excluding lung cancer.
ILD interstitial lung disease.
Source: Table 15.6

Patients in the EU had lower baseline prevalence of most recorded comorbidities than patients in the US, both in the crizotinib and in erlotinib groups, including brain metastases, renal impairment, and hepatic impairment. Patients in the EU, both in crizotinib and erlotinib groups, had lower than patients in the US prevalence of baseline use of antidiabetic agents, but higher prevalence of use of steroids or antibacterials for systemic use. Baseline prevalence of use of any cardiovascular medication was comparable in the EU and in the US in the crizotinib group, but was higher in the EU in the erlotinib group (Table 6, Table 15.5, Table 7, Table 15.6). For completeness, patients' baseline comorbidities and co-medications combined across all countries are listed in Table 15.4.

10.3. Outcome data

The total numbers of incident cases of the primary and secondary endpoints observed during follow-up, overall, EU combined, and US are shown in Table 15.18. Although the number of patients in the crizotinib and erlotinib groups was smaller in the US than that in the EU, the number of observed endpoints was lower in the EU than that in the US.

In the EU, during follow-up in the crizotinib group, there were 4 incident events of bradycardia; 2 incident events of hepatotoxicity; 18 incident events of pneumonitis/ILD; 5 incident QT prolongation-related events; and 7 incident events of vision disorders as identified by codes in the routinely collected data (Table 10).

In the EU, during follow-up in the erlotinib group, there were 10 incident events of bradycardia; 2 incident events of hepatotoxicity; 163 incident events of pneumonitis/ILD; 39 incident QT prolongation-related events; and 29 incident events of vision disorders as identified by codes in the routinely collected data (Table 10).

In the US, during follow-up in the crizotinib group, there were 21 incident events of bradycardia; 7 incident events of hepatotoxicity; 26 incident events of pneumonitis/ILD; 26 incident QT prolongation-related events; and 17 incident events of vision disorders as identified by codes in the routinely collected data (Table 10).

In the US, during follow-up in the erlotinib group, there were 65 incident events of bradycardia; 43 incident events of hepatotoxicity; 130 incident events of pneumonitis/ILD; 108 incident QT prolongation-related events; and 32 incident events of vision disorders as identified by codes in the routinely collected data (Table 10).

10.4. Main results

Results combined across the EU population and in the US were presented separately, focusing on 1- and 2-year cumulative incidences, as those were observed in all countries. No stratified analysis of 3-year cumulative incidence was undertaken. Three-year cumulative incidences of the endpoints in Denmark and the US, where 3-year follow-up was available, are reported in the Denmark Supplemental Table 3 and US Supplemental Table 3, Appendix 5).

10.4.1. Cumulative incidences of the endpoints during the follow-up period

Table 8 shows 1-year and Table 9 shows 2-year cumulative incidences of the primary and secondary endpoints, combined via meta-analysis across the 4 EU populations and separately for the US population, in the crizotinib group and erlotinib group. The number of patients at risk varied for a given endpoint owing to exclusion of patients with prevalent conditions before the index date. The 2-year cumulative incidences are inclusive of the respective 1-year cumulative incidences. For most endpoints, the majority of the events occurred during the first year (Table 8 and Table 9).

In the combined EU population, the 2-year cumulative incidences (95% CI) in the crizotinib and erlotinib group, respectively, for the primary endpoints were 1.1% (0.0 - 3.0) and 0.3% (0.0 - 0.7) for bradycardia; 0.8% (0.0 - 3.1) and 0.0% (0.0 - 0.1) for hepatotoxicity; 9.2% (4.5 - 15.0) and 7.0% (3.8 - 11.1) for pneumonitis/ILD; 1.0% (0.0 - 3.1) and 1.2% (0.7 - 1.8) for QT interval prolongation-related events; and 2.2% (0.4 - 5.1) and 1.1% (0.3 - 2.2) for vision disorder.

In the combined EU population, the 2-year cumulative incidences (95% CI) in the crizotinib and erlotinib group, respectively, for the secondary endpoints were 0.0% (0.0 - 0.5) and 0.0% (0.0 - 0.0) for renal cysts; 1.8% (0.0 - 5.3) and 1.2% (0.2 - 2.7) for edema; 2.2% (0.2 - 5.6) and 2.2% (0.2 - 6.0) for leukopenia; 8.8% (1.9 - 19.1) and 8.6% (3.8 - 14.9) for neuropathy; 0.0% (0.0 - 0.5) and 1.3% (0.1 - 3.5) for photosensitivity; 0.2% (0.0 - 1.6) and 0.4% (0.1 - 0.8) for malignant melanoma; 0.1% (0.0 - 1.2) and 0.3% (0.0 - 0.6) for GI perforation; and 0.5% (0.0 - 2.1) and 0.9% (0.1 - 2.2) for cardiac failure. Two-year all-cause mortality (95% CI) was 43.9% (28.4 - 60.0) in the crizotinib group and 64.2% (47.6 - 79.3) in the erlotinib group. In the EU combined analyses, heterogeneity varied by endpoint and I^2 exceeded 90% for leukopenia, neuropathy, and death of all causes in the erlotinib group (Table 9). Heterogeneity was lower in the crizotinib group than in the erlotinib group for all endpoints.

In the US, the 2-year cumulative incidences (95% CI) in the crizotinib and erlotinib group, respectively, for the primary endpoints were 16.9% (10.5 - 24.7) and 9.5% (7.4 - 12.0) for bradycardia; 3.8% (1.5 - 7.8) and 5.2% (3.8 - 7.0) for hepatotoxicity; 30.6% (20.0 - 42.0) and 27.4% (23.2 - 31.7) for pneumonitis/ILD; 26.8% (17.6 - 36.9) and 20.9% (17.1 - 24.9) for QT interval prolongation-related events; and 14.8% (8.3 - 23.1) and 4.3% (2.9 - 6.0) for vision disorder.

In the US, the 2-year cumulative incidences (95% CI) in the crizotinib and erlotinib group, respectively, for the secondary endpoints were 0.0% (0.0 - 0.0) and 0.2% (0.1 - 0.8) for renal cysts; 6.8% (3.4 - 11.9) and 3.1% (2.0 - 4.6) for edema; 14.3% (9.1 - 20.6) and 18.1% (15.4 - 21.0) for leukopenia; 32.7% (22.5 - 43.3) and 28.8% (24.0 - 33.9) for neuropathy; 1.3% (0.3 - 4.4) and 11.8% (9.7 - 14.2) for photosensitivity; 1.8% (0.5 - 4.8) and 0.4% (0.1 - 1.3) for malignant melanoma; 3.2% (1.2 - 6.9) and 3.2% (2.1 - 4.7) for GI perforation; and 6.8% (3.4 -

11.7) and 5.9% (4.3 - 7.8) for cardiac failure. Two-year all-cause mortality (95% CI) was 35.3% (21.5 - 49.3) in the crizotinib group and 49.8% (43.4 - 55.8) in the erlotinib group (Table 9).

Cumulative incidences of the endpoints in the combined EU/US data, combined EU data, and in the US data are listed in Table 15.7 (one year), Table 15.8 (two years).

Table 8. One-Year Cumulative Incidences of Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, EU Combined (Meta-analysis) and US

Endpoint	Population	Crizotinib n/N	Crizotinib Cumulative incidence, % (95% CI)	Crizotinib I^2 statistic, %	Erlotinib n/N	Erlotinib Cumulative incidence, % (95% CI)	Erlotinib I^2 statistic, %
Primary endpoints							
Bradycardia							
	EU	4/277	1.1 (0.0 - 3.0)	0.0	5/2,088	0.1 (0.0 - 0.3)	8.2
	US	14/150	9.7 (5.5 - 15.1)		52/715	7.3 (5.5 - 9.4)	
Hepatotoxicity							
	EU	0/278	0.0 (0.0 - 0.5)	0.0	2/2,121	0.0 (0.0 - 0.1)	0.0
	US	5/178	2.9 (1.1 - 6.2)		34/836	4.1 (2.9 - 5.6)	
Pneumonitis/ILD							
	EU	15/221	6.8 (3.3 - 11.1)	4.2	122/1,812	5.8 (3.6 - 8.5)	72.9
	US	21/101	21.5 (14.0 - 30.1)		99/489	20.3 (16.9 - 24.0)	
QT interval prolongation-related events							
	EU	4/268	1.0 (0.0 - 3.1)	0.0	28/2,044	1.2 (0.7 - 1.8)	0.0
	US	21/80	26.8 (17.6 - 36.9)		88/422	20.9 (17.1 - 24.9)	
Vision disorder							
	EU	6/259	1.8 (0.3 - 4.2)	0.0	22/1,989	0.9 (0.3 - 1.6)	40.0
	US	11/159	7.0 (3.7 - 11.7)		24/751	3.2 (2.1 - 4.7)	
Secondary endpoints							
Renal cysts							
	EU	0/278	0.0 (0.0 - 0.5)	0.0	0/2,120	0.0 (0.0 - 0.0)	0.0
	US	0/173	0.0 (0.0 - 0.0)		2/820	0.2 (0.1 - 0.8)	
Edema							
	EU	5/278	1.3 (0.0 - 3.5)	7.6	23/2,121	0.9 (0.2 - 2.0)	64.7
	US	8/178	4.7 (2.2 - 8.6)		16/836	1.9 (1.1 - 3.0)	
Leukopenia							
	EU	6/278	1.7 (0.2 - 3.9)	0.0	43/2,121	1.8 (0.1 - 5.3)	93.0
	US	19/178	11.1 (6.9 - 16.3)		116/836	13.9 (11.7 - 16.3)	
Neuropathy							
	EU	14/251	5.1 (0.9 - 11.7)	61.0	123/1,870	5.9 (1.8 - 12.0)	94.1
	US	23/94	25.6 (17.1 - 34.9)		81/370	21.9 (17.9 - 26.3)	
Photosensitivity							
	EU	0/278	0.0 (0.0 - 0.5)	0.0	42/2,121	1.3 (0.1 - 3.4)	87.1
	US	1/178	0.6 (0.1 - 2.9)		88/836	10.6 (8.6 - 12.7)	
Malignant melanoma							
	EU	2/277	0.2 (0.0 - 1.6)	0.0	9/2,101	0.3 (0.0 - 0.8)	49.6
	US	3/178	1.8 (0.5 - 4.8)		1/827	0.1 (0.0 - 0.7)	
Gastrointestinal perforation							
	EU	1/278	0.1 (0.0 - 1.2)	0.0	6/2,121	0.1 (0.0 - 0.4)	0.0
	US	4/178	2.3 (0.8 - 5.5)		22/836	2.6 (1.7 - 3.9)	
Cardiac failure							
	EU	3/275	0.5 (0.0 - 2.1)	0.0	16/2,046	0.6 (0.2 - 1.2)	31.1
	US	8/164	5.0 (2.3 - 9.2)		34/766	4.5 (3.1 - 6.1)	
Death of all causes[a]							
	EU	88/278	33.3 (27.6 - 39.2)	0.0	1,241/2,121	48.6 (36.2 - 61.0)	96.3
	US	14/62	25.6 (14.9 - 37.6)		111/265	41.9 (35.9 - 47.7)	

[a] Data on death may be incomplete in the Netherlands.
2-year cumulative incidence is inclusive of 1-year cumulative incidence and all estimates are computed excluding patients with corresponding prevalent conditions. For 3-year cumulative incidences (Denmark and US) see Denmark Supplemental Table 3 and US Supplemental Table 3, Appendix 5.
CI confidence interval; ILD interstitial lung disease; n=number of cases, N=number at risk.
Source: Table 15.7.

Table 9. Two-Year Cumulative Incidences of Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, EU Combined (Meta-analysis) and US

Endpoint	Population	Crizotinib n/N	Crizotinib Cumulative incidence, % (95% CI)	Crizotinib I^2 statistic, %	Erlotinib n/N	Erlotinib Cumulative incidence, % (95% CI)	Erlotinib I^2 statistic, %
Primary endpoints							
Bradycardia							
	EU	4/277	1.1 (0.0 - 3.0)	0.0	8/2,088	0.3 (0.0 - 0.7)	0.0
	US	20/150	16.9 (10.5 - 24.7)		63/715	9.5 (7.4 - 12.0)	
Hepatotoxicity							
	EU	2/278	0.8 (0.0 - 3.1)	0.0	2/2,121	0.0 (0.0 - 0.1)	0.0
	US	6/178	3.8 (1.5 - 7.8)		40/836	5.2 (3.8 - 7.0)	
Pneumonitis/ILD							
	EU	18/221	9.2 (4.5 - 15.0)	22.0	151/1,812	7.0 (3.8 - 11.1)	84.7
	US	25/101	30.6 (20.0 - 42.0)		123/489	27.4 (23.2 - 31.7)	
QT interval prolongation-related events							
	EU	5/268	1.0 (0.0 - 3.1)	0.0	37/2,044	1.2 (0.7 - 1.8)	0.0
	US	21/80	26.8 (17.6 - 36.9)		88/422	20.9 (17.1 - 24.9)	
Vision disorder							
	EU	7/259	2.2 (0.4 - 5.1)	9.0	27/1,989	1.1 (0.3 - 2.2)	61.7
	US	16/159	14.8 (8.3 - 23.1)		29/751	4.3 (2.9 - 6.0)	
Secondary endpoints							
Renal cysts							
	EU	0/278	0.0 (0.0 - 0.5)	0.0	0/2,120	0.0 (0.0 - 0.0)	0.0
	US	0/173	0.0 (0.0 - 0.0)		2/820	0.2 (0.1 - 0.8)	
Edema							
	EU	6/278	1.8 (0.0 - 5.3)	33.1	30/2,121	1.2 (0.2 - 2.7)	77.0
	US	10/178	6.8 (3.4 - 11.9)		22/836	3.1 (2.0 - 4.6)	
Leukopenia							
	EU	8/278	2.2 (0.2 - 5.6)	28.4	51/2,121	2.2 (0.2 - 6.0)	93.4
	US	22/178	14.3 (9.1 - 20.6)		139/836	18.1 (15.4 - 21.0)	
Neuropathy							
	EU	20/251	8.8 (1.9 - 19.1)	72.4	153/1,870	8.6 (3.8 - 14.9)	92.0
	US	27/94	32.7 (22.5 - 43.3)		99/370	28.8 (24.0 - 33.9)	
Photosensitivity							
	EU	0/278	0.0 (0.0 - 0.5)	0.0	43/2,121	1.3 (0.1 - 3.5)	87.8
	US	2/178	1.3 (0.3 - 4.4)		95/836	11.8 (9.7 - 14.2)	
Malignant melanoma							
	EU	2/277	0.2 (0.0 - 1.6)	0.0	11/2,101	0.4 (0.1 - 0.8)	0.0
	US	3/178	1.8 (0.5 - 4.8)		2/827	0.4 (0.1 - 1.3)	
Gastrointestinal perforation							
	EU	1/278	0.1 (0.0 - 1.2)	0.0	8/2,121	0.3 (0.0 - 0.6)	0.0
	US	5/178	3.2 (1.2 - 6.9)		25/836	3.2 (2.1 - 4.7)	
Cardiac failure							
	EU	3/275	0.5 (0.0 - 2.1)	0.0	24/2,046	0.9 (0.1 - 2.2)	70.9
	US	10/164	6.8 (3.4 - 11.7)		42/766	5.9 (4.3 - 7.8)	
Death of all causes[a]							
	EU	113/278	43.9 (28.4 - 60.0)	80.5	1,529/2,121	64.2 (47.6 - 79.3)	97.9
	US	17/62	35.3 (21.5 - 49.3)		128/265	49.8 (43.4 - 55.8)	

[a] Data on death may be incomplete in the Netherlands.
2-year cumulative incidence is inclusive of 1-year cumulative incidence and all estimates are computed excluding patients with corresponding prevalent conditions. For 3-year cumulative incidences (Denmark and US) see Denmark Supplemental Table 3 and US Supplemental Table 3, Appendix 5.
CI confidence interval; ILD interstitial lung disease; n=number of cases, N=number at risk.
Source: Table 15.8.

10.4.2. Incidence rates of the endpoints with time at risk being the total-follow-up

Table 10 shows incidence rates of the primary and secondary endpoints combined across the four EU populations and in the US, with time at risk being the total-follow-up.

In the combined EU population, for the primary endpoints, the overall incidence rates per 1,000 person-years (95% CI), in the crizotinib and erlotinib groups were, respectively, 12.0 (0.0 - 25.2) and 5.0 (1.8 - 8.2) for bradycardia; 7.2 (0.0 - 18.2) and 1.1 (0.0 - 2.8) for hepatotoxicity; 64.9 (22.1 - 107.8) and 74.3 (19.3 - 129.4) for pneumonitis/ILD; 13.9 (0.0 - 28.4) and 17.5 (6.5 - 28.4) for QT interval prolongation-related events; and 15.9 (0.0 - 33.3) and 12.5 (2.9 - 22.1) for vision disorders. For the secondary endpoints, the overall incidence rates per 1,000 person-years (95% CI), in the crizotinib and erlotinib groups, respectively, were 0.0 (0.0 - 8.0) and 0.0 (0.0 - 1.2) for renal cysts; 13.2 (0.2 - 26.1) and 13.8 (1.8 - 25.8) for edema; 21.3 (3.6 - 38.9) and 24.9 (3.7 - 46.0) for leukopenia; 60.4 (4.3 - 116.5) and 90.7 (28.8 - 152.7) for neuropathy; 0.0 (0.0 - 8.0) and 17.4 (0.0 - 35.2) for photosensitivity; 3.8 (0.0 - 14.5) and 4.6 (1.3 - 7.8) for malignant melanoma; 3.1 (0.0 - 12.6) and 4.2 (1.2 - 7.2) for GI perforation; and 11.3 (0.0 - 25.0) and 12.9 (4.6 - 21.2) for cardiac failure. The all-cause mortality rate (95% CI) was 334.2 (206.1 - 462.4) per 1,000 person-years in the crizotinib group and 663.0 (190.0 - 1,136.1) in the erlotinib group. The value of the I^2 statistics exceeded 75% for most endpoints and heterogeneity tended to be lower in the crizotinib group than in the erlotinib group (Table 10).

In the US for the primary endpoints, the overall incidence rates per 1,000 person-years (95% CI), in the crizotinib and erlotinib groups, respectively, were 147.9 (91.5 - 226.0) and 100.5 (77.5 - 128.1) for bradycardia; 40.0 (16.1 - 82.4) and 57.6 (41.7 - 77.6) for hepatotoxicity; 274.5 (179.3 - 402.2) and 312.6 (261.2 - 371.2) for pneumonitis/ILD; 374.6 (244.7 - 548.9) and 296.1 (242.9 - 357.5) for QT interval prolongation-related events; and 114.4 (66.7 - 183.2) and 47.8 (32.7 - 67.5) for vision disorders. For the secondary endpoints, the overall incidence rates per 1,000 person-years (95% CI), in the crizotinib and erlotinib groups, respectively, were 0.0 (0.0 - 21.0) and 2.6 (0.3 - 9.5) and for renal cysts; 57.6 (27.6 - 105.8) and 34.2 (22.3 - 50.1) for edema; 129.4 (81.1 - 195.9) and 221.6 (187.2 - 260.4) for leukopenia; 357.0 (239.1 - 512.7) and 393.3 (323.0 - 474.5) for neuropathy; 17.0 (3.5 - 49.8) and 147.6 (119.8 - 179.8) for photosensitivity; 17.0 (3.5 - 49.8) and 2.6 (0.3 - 9.5) for malignant melanoma; 28.7 (9.3 - 67.0) and 36.1 (23.8 - 52.5) for GI perforation; and 60.2 (28.9 - 110.7) and 65.7 (48.1 - 87.7) for cardiac failure. The all-cause mortality rate (95% CI) was 302.9 (176.5 - 485.0) per 1,000 person-years in the crizotinib group and 637.0 (533.0 - 755.5) in the erlotinib group (Table 10).

Incidence rates of the endpoints with time at risk being the total follow-up in the combined EU and in the US data are shown in Table 15.18.

Table 10. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, EU Combined (Meta-Analysis) and US (Time at Risk being Total Follow-up)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic, %	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic, %
Primary endpoints							
Bradycardia							
	EU	4/297.3	12.0 (0.0 - 25.2)	0.0	10/1,853.5	5.0 (1.8 - 8.2)	0.0
	US	21/142.0	147.9 (91.5 - 226.0)		65/647.0	100.5 (77.5 - 128.1)	
Hepatotoxicity							
	EU	2/300.5	7.2 (0.0 - 18.2)	0.0	2/1,885.5	1.1 (0.0 - 2.8)	0.0

Table 10. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, EU Combined (Meta-Analysis) and US (Time at Risk being Total Follow-up)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic, %	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic, %
	US	7/175.1	40.0 (16.1 - 82.4)		43/746.5	57.6 (41.7 - 77.6)	
Pneumonitis/ILD							
	EU	18/228.3	64.9 (22.1 - 107.8)	36.0	163/1,582.0	74.3 (19.3 - 129.4)	94.4
	US	26/94.7	274.5 (179.3 - 402.2)		130/415.9	312.6 (261.2 - 371.2)	
QT interval prolongation-related events							
	EU	5/287.7	13.9 (0.0 - 28.4)	0.0	39/1,816.0	17.5 (6.5 - 28.4)	62.5
	US	26/69.4	374.6 (244.7 - 548.9)		108/364.7	296.1 (242.9 - 357.5)	
Vision disorder							
	EU	7/278.2	15.9 (0.0 - 33.3)	11.1	29/1,753.8	12.5 (2.9 - 22.1)	63.9
	US	17/148.6	114.4 (66.7 - 183.2)		32/668.9	47.8 (32.7 - 67.5)	
Secondary endpoints							
Renal cysts							
	EU	0/301.8	0.0 (0.0 - 8.0)	0.0	0/1,885.4	0.0 (0.0 - 1.2)	0.0
	US	0/175.3	0.0 (0.0 - 21.0)		2/756.6	2.6 (0.3 - 9.5)	
Edema							
	EU	6/299.7	13.2 (0.2 - 26.1)	0.0	32/1,867.3	13.8 (1.8 - 25.8)	75.8
	US	10/173.7	57.6 (27.6 - 105.8)		26/760.5	34.2 (22.3 - 50.1)	
Leukopenia							
	EU	8/298.7	21.3 (3.6 - 38.9)	0.0	52/1,853.8	24.9 (3.7 - 46.0)	90.4
	US	22/170.1	129.4 (81.1 - 195.9)		147/663.4	221.6 (187.2 - 260.4)	
Neuropathy							
	EU	20/266.2	60.4 (4.3 - 116.5)	70.8	161/1,627.9	90.7 (28.8 - 152.7)	94.4
	US	29/81.2	357.0 (239.1 - 512.7)		109/277.1	393.3 (323.0 - 474.5)	
Photosensitivity							
	EU	0/301.8	0.0 (0.0 - 8.0)	0.0	45/1,834.7	17.4 (0.0 - 35.2)	87.8
	US	3/176.2	17.0 (3.5 - 49.8)		98/664.2	147.6 (119.8 - 179.8)	
Malignant melanoma							
	EU	2/299.7	3.8 (0.0 - 14.5)	0.0	11/1,856.1	4.6 (1.3 - 7.8)	3.5
	US	3/176.1	17.0 (3.5 - 49.8)		2/763.2	2.6 (0.3 - 9.5)	
Gastrointestinal perforation							
	EU	1/301.7	3.1 (0.0 - 12.6)	0.0	8/1,879.9	4.2 (1.2 - 7.2)	0.0
	US	5/174.2	28.7 (9.3 - 67.0)		27/747.7	36.1 (23.8 - 52.5)	
Cardiac failure							
	EU	4/298.9	11.3 (0.0 - 25.0)	0.0	27/1,822.0	12.9 (4.6 - 21.2)	53.2
	US	10/166.1	60.2 (28.9 - 110.7)		46/699.9	65.7 (48.1 - 87.7)	
Death of all causes[a]							
	EU	117/301.8	334.2 (206.1 - 462.4)	71.8	1,594/1,885.7	663.0 (190.0 - 1,136.1)	99.5
	US	17/56.1	302.9 (176.5 - 485.0)		132/207.2	637.0 (533.0 - 755.5)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
All estimates are computed excluding patients with corresponding prevalent conditions.
CI confidence interval; ILD interstitial lung disease; n=number of cases, PY=person-years.
Source: Table 15.18.

10.4.3. Stratified all-cause mortality

The stratified analyses of the all-cause mortality rate during follow-up are presented for patients younger than 65 years (Table 15.19) and 65 years or older (Table 15.20); with (Table 15.21) and without (Table 15.22) brain metastases at baseline; with (Table 15.23) and without (Table 15.24) hepatic impairment at baseline and with (Table 15.25) and without (Table 15.26) renal impairment at baseline.

In the combined EU population, all-cause mortality rate per 1,000 person-years (95% CI) was lower in the crizotinib group in patients younger than 65 years: 271.0 (161.8 - 380.3) than in patients 65 years or older: 436.8 (218.1 - 655.5), while in the erlotinib group all-cause mortality rates were similar in both age groups: 655.4 (232.3 - 1,078.4) in the younger and 664.2 (140.7 - 1,187.7) in the older age group. Heterogeneity was greater in the older group than in the younger group and was smaller in the crizotinib than in the erlotinib group (Table 15.19 and Table 15.20).

In the US, the pattern for the all-cause mortality rates in the crizotinib group was the opposite, with greater all-cause mortality rates in the younger patients, however, there was only 1 death observed in patients ages 65 years or older; the all-cause mortality rate did not substantially vary by age group in the erlotinib group (Table 15.19 and Table 15.20).

In the combined EU population, all-cause mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 495.6 (216.7 - 774.5) in patients with and 313.6 (187.3 - 439.8) in patients without brain metastases at baseline. The corresponding estimates in the erlotinib group were 1,194.1 (815.4 - 1,572.7) and 628.8 (149.9 - 1,107.6). Heterogeneity was lower in the crizotinib group than in the erlotinib group in both strata (Table 15.21 and Table 15.22).

In the US, all-cause mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 342.6 (111.2 - 799.4) in patients with and 289.0 (149.3 - 504.8) in patients without brain metastases at baseline. The corresponding estimates in the erlotinib group were 929.7 (687.8 - 1,229.1) and 537.2 (427.9 - 666.0) (Table 15.21 and Table 15.22).

In the combined EU population, all-cause mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 600.4 (100.1 - 1,100.8) in patients with and 324.4 (192.2 - 456.5) in patients without hepatic impairment at baseline. The corresponding estimates in the erlotinib group were 643.4 (0.0 - 1,304.4) and 665.4 (197.0 - 1,133.7). Heterogeneity was lower in the crizotinib group than in the erlotinib group in both strata (Table 15.23 and Table 15.24).

In the US, all-cause mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 306.0 (63.1 - 894.2) in patients with and 302.3 (165.3 - 507.2) in patients without hepatic impairment at baseline. The corresponding estimates in the erlotinib group were 980.7 (661.7 - 1,400.0) and 577.5 (470.9 - 701.1) (Table 15.23 and Table 15.24).

In the combined EU population, all-cause mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 408.7 (0.0 - 1,110.2) in patients with and 327.9 (196.3 - 459.5) in patients without renal impairment at baseline. The corresponding estimates in the erlotinib group were 698.1 (292.7 - 1,103.4) and 667.7 (178.4 - 1,156.9). Heterogeneity was lower in the crizotinib group than in the erlotinib group in both strata (Table 15.25 and Table 15.26).

In the US, all-cause mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 388.6 (80.1 - 1,135.5) in patients with and 289.3 (158.1 - 485.3) in patients without renal impairment at baseline. The corresponding estimates in the erlotinib group were 766.1 (516.9 - 1,093.7) and 607.0 (494.9 - 736.8) (Table 15.25 and Table 15.26).

10.4.4. Incidence rates of endpoints during the on-treatment period

Table 11 shows incidence rates of the primary and secondary endpoints combined across the four EU countries and in the US, with time at risk being the on-treatment period.

In the combined EU population for the primary endpoints, the overall on-treatment incidence rates per 1,000 person-years (95% CI), in the crizotinib and erlotinib groups, respectively, were

12.0 (0.0 - 27.7) and 2.3 (0.0 - 5.3) for bradycardia; 2.3 (0.0 - 14.1) and 0.5 (0.0 - 2.7) for hepatotoxicity; 60.2 (8.8 - 111.7) and 67.4 (16.6 - 118.2) for pneumonitis/ILD; 21.5 (0.1 - 42.8) and 20.1 (11.7 - 28.5) for QT interval prolongation-related events; and 25.0 (1.5 - 48.5) and 14.9 (3.2 - 26.6) for vision disorders. For the secondary endpoints, the overall on-treatment incidence rates per 1,000 person-years (95% CI), in the crizotinib and erlotinib groups, respectively, were 0.0 (0.0 - 11.0) and 0.0 (0.0 - 2.0) for renal cysts; 15.5 (0.0 - 32.2) and 16.0 (0.0 - 32.0) for edema; 21.6 (0.7 - 42.5) and 17.4 (0.0 - 36.2) for leukopenia; 53.1 (8.9 - 97.3) and 88.8 (35.3 - 142.3) for neuropathy; 0.0 (0.0 - 11.0) and 26.9 (0.0 - 54.0) for photosensitivity; 6.7 (0.0 - 22.5) and 3.7 (0.0 - 9.4) for malignant melanoma; 5.0 (0.0 - 18.5) and 1.4 (0.0 - 4.7) for GI perforation; and 5.0 (0.0 - 18.6) and 11.4 (5.2 - 17.6) for cardiac failure. The all-cause mortality rate (95% CI) during the on-treatment period was 258.2 (183.7 - 332.8) per 1,000 person-years in the crizotinib group and 470.5 (212.8 - 728.2) in the erlotinib group. The value of the I^2 statistics exceeded 75% for most endpoints and heterogeneity tended to be lower in the crizotinib group than in the erlotinib group (Table 11).

In the US for the primary endpoints, the overall on-treatment incidence rates per 1,000 person-years (95% CI), in the crizotinib and erlotinib groups, respectively, were 142.2 (81.3 - 231.0) and 92.3 (65.7 - 126.2) for bradycardia; 36.5 (11.9 - 85.2) and 61.1 (40.9 - 87.8) for hepatotoxicity; 283.2 (175.3 - 432.9) and 332.2 (267.8 - 407.4) for pneumonitis/ILD; 387.0 (245.3 - 580.7) and 274.6 (214.5 - 346.3) for QT interval prolongation-related events; and 135.9 (77.7 - 220.7) and 37.2 (21.3 - 60.5) for vision disorders. For the secondary endpoints, the overall on-treatment incidence rates per 1,000 person-years (95% CI), in the crizotinib and erlotinib groups, respectively, were 0.0 (0.0 - 27.2) and 4.2 (0.5 - 15.1) for renal cysts; 74.0 (35.5 - 136.0) and 31.2 (17.4 - 51.4) for edema; 96.2 (51.2 - 164.4) and 201.0 (162.2 - 246.2) for leukopenia; 379.5 (247.9 - 556.0) and 377.2 (297.2 - 472.1) for neuropathy; 7.3 (0.2 - 40.6) and 199.9 (159.6 - 247.1) for photosensitivity; 22.0 (4.5 - 64.3) and 4.2 (0.5 - 15.0) for malignant melanoma; 29.6 (8.1 - 75.9) and 34.0 (19.4 - 55.2) for GI perforation; and 62.5 (27.0 - 123.2) and 53.9 (34.5 - 80.2) for cardiac failure. The all-cause on-treatment mortality rate (95% CI) was 194.0 (83.8 - 382.3) per 1,000 person-years in the crizotinib group and 526.1 (411.6 - 662.5) in the erlotinib group (Table 11).

Incidence rates of the endpoints during the on-treatment period in the combined EU and in the US data are listed in Table 15.27.

Table 11. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, EU Combined (Meta-analysis) and US(Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Primary endpoints							
Bradycardia							
	EU	3/209.1	12.0 (0.0 - 27.7)	0.0	4/1,163.7	2.3 (0.0 - 5.3)	0.0
	US	16/112.5	142.2 (81.3 - 231.0)		39/422.3	92.3 (65.7 - 126.2)	
Hepatotoxicity							
	EU	1/212.3	2.3 (0.0 - 14.1)	0.0	1/1,183.6	0.5 (0.0 - 2.7)	0.0
	US	5/136.9	36.5 (11.9 - 85.2)		29/474.5	61.1 (40.9 - 87.8)	
Pneumonitis/ILD							
	EU	13/162.0	60.2 (8.8 - 111.7)	37.6	92/992.9	67.4 (16.6 - 118.2)	89.2
	US	21/74.1	283.2 (175.3 - 432.9)		92/277.0	332.2 (267.8 - 407.4)	

Table 11. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, EU Combined (Meta-analysis) and US(Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic
QT interval prolongation-related events							
	EU	5/202.2	21.5 (0.1 - 42.8)	0.0	24/1,140.4	20.1 (11.7 - 28.5)	0.0
	US	23/59.4	387.0 (245.3 - 580.7)		71/258.6	274.6 (214.5 - 346.3)	
Vision disorder							
	EU	7/195.7	25.0 (1.5 - 48.5)	0.0	21/1,092.0	14.9 (3.2 - 26.6)	52.1
	US	16/117.7	135.9 (77.7 - 220.7)		16/429.7	37.2 (21.3 - 60.5)	
Secondary endpoints							
Renal cysts							
	EU	0/213.0	0.0 (0.0 - 11.0)	0.0	0/1,183.4	0.0 (0.0 - 2.0)	0.0
	US	0/135.6	0.0 (0.0 - 27.2)		2/478.3	4.2 (0.5 - 15.1)	
Edema							
	EU	5/211.4	15.5 (0.0 - 32.2)	0.0	22/1,172.5	16.0 (0.0 - 32.0)	73.2
	US	10/135.2	74.0 (35.5 - 136.0)		15/481.2	31.2 (17.4 - 51.4)	
Leukopenia							
	EU	5/211.7	21.6 (0.7 - 42.5)	0.0	26/1,180.5	17.4 (0.0 - 36.2)	85.1
	US	13/135.2	96.2 (51.2 - 164.4)		93/462.7	201.0 (162.2 - 246.2)	
Neuropathy							
	EU	13/186.2	53.1 (8.9 - 97.3)	32.3	97/1,032.5	88.8 (35.3 - 142.3)	85.3
	US	26/68.5	379.5 (247.9 - 556.0)		76/201.5	377.2 (297.2 - 472.1)	
Photosensitivity							
	EU	0/213.0	0.0 (0.0 - 11.0)	0.0	44/1,152.3	26.9 (0.0 - 54.0)	85.5
	US	1/137.3	7.3 (0.2 - 40.6)		85/425.3	199.9 (159.6 - 247.1)	
Malignant melanoma							
	EU	2/211.8	6.7 (0.0 - 22.5)	0.0	6/1,166.8	3.7 (0.0 - 9.4)	38.5
	US	3/136.4	22.0 (4.5 - 64.3)		2/480.5	4.2 (0.5 - 15.0)	
Gastrointestinal perforation							
	EU	1/213.0	5.0 (0.0 - 18.5)	0.0	4/1,181.2	1.4 (0.0 - 4.7)	13.0
	US	4/135.0	29.6 (8.1 - 75.9)		16/471.0	34.0 (19.4 - 55.2)	
Cardiac failure							
	EU	1/211.3	5.0 (0.0 - 18.6)	0.0	16/1,143.4	11.4 (5.2 - 17.6)	0.0
	US	8/128.0	62.5 (27.0 - 123.2)		24/445.2	53.9 (34.5 - 80.2)	
Death of all causes[a]							
	EU	59/213.0	258.2 (183.7 - 332.8)	12.9	718/1,183.7	470.5 (212.8 - 728.2)	97.5
	US	8/41.2	194.0 (83.8 - 382.3)		72/136.9	526.1 (411.6 - 662.5)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
All estimates are computed after excluding patients with corresponding prevalent conditions.
CI confidence interval; ILD interstitial lung disease; n=number of cases, PY=person-years.
Source: Table 15.27.

The stratified analyses of the incidence rates of death of all causes with time at risk as the on-treatment period are presented for patients younger than 65 years (Table 15.28) and 65 years or older (Table 15.29); with (Table 15.30) and without (Table 15.31) brain metastases at baseline; with (Table 15.32) and without (Table 15.33) hepatic impairment at baseline ; and with (Table 15.34) and without (Table 15.35) renal impairment at baseline.

In the combined EU population, all-cause on-treatment mortality rate per 1,000 person-years (95% CI) was lower in the crizotinib group in patients younger than 65 years: 171.8 (74.4 - 269.3) than in patients 65 years or older: 341.6 (153.1 - 530.1), while in the erlotinib group all-cause mortality rates were similar in both age groups: 461.3 (223.1 - 699.4) in patients younger than 65 years and 469.8 (163.9 - 775.8) in patients 65 years or older. Heterogeneity was greater

in the older group than in the younger group and was smaller in the crizotinib than in the erlotinib group (Table 15.28 and Table 15.29).

In the US, the pattern for the all-cause on-treatment mortality rates in the crizotinib group was the opposite, with greater all-cause mortality rates in the younger patients, however, there was only 1 on-treatment death observed in patients ages 65 years or older; the all-cause on-treatment mortality rate in the erlotinib group was greater for the younger 565.1 (429.1 - 730.5) than for the older 409.0 (223.6 - 686.3) patients (Table 15.28 and Table 15.29).

In the combined EU population, all-cause on-treatment mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 421.5 (49.1 - 794.0) in patients with and 249.7 (180.4 - 319.1) in patients without brain metastases at baseline. The corresponding estimates in the erlotinib group were 1,041.2 (771.5 - 1,310.9) and 432.0 (180.5 - 683.5). Heterogeneity was lower in the crizotinib group than in the erlotinib group in both strata and was considerably lower among patients with brain metastases than in patients without brain metastases in both drug groups (Table 15.30 and Table 15.31).

In the US, all-cause on-treatment mortality rate (95% CI) per 1,000 person-years in the crizotinib group was considerably higher in patients with 342.6 (111.2 - 799.4) than in patients without 123.0 (33.5 - 314.9) brain metastases at baseline. The corresponding estimates in the erlotinib group were 909.8 (618.1 - 1,291.3) and 398.9 (286.2 - 541.1) (Table 15.30 and Table 15.31).

In the combined EU population, all-cause on-treatment mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 354.0 (0.0 - 785.9) in patients with and 249.9 (172.0 - 327.9) in patients without hepatic impairment at baseline. The corresponding estimates in the erlotinib group were 597.5 (6.7 - 1,188.2) and 470.3 (215.8 - 724.8). Heterogeneity was lower in the crizotinib group than in the erlotinib group in both strata and lower in patients with preexisting hepatic impairment in both drug groups (Table 15.32 and Table 15.33).

In the US, all-cause on-treatment mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 212.4 (25.7 - 767.3) in patients with and 188.6 (69.2 - 410.4) in patients without preexisting hepatic impairment. The corresponding estimates in the erlotinib group were 1,012.5 (618.4 - 1,563.7) and 444.0 (331.6 - 582.3) (Table 15.32 and Table 15.33).

In the combined EU population, all-cause on-treatment mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 245.8 (0.0 - 1,082.3) in patients with and 257.2 (188.3 - 326.1) in patients without preexisting renal impairment at baseline. The corresponding estimates in the erlotinib group were 594.9 (109.7 - 1,080.1) and 469.0 (189.4 - 748.5). Heterogeneity was lower in the crizotinib group than in the erlotinib group in both strata and lower in the patients with renal impairment at baseline than in patients without in both drug groups (Table 15.34 and Table 15.35).

In the US, all-cause on-treatment mortality rate (95% CI) per 1,000 person-years in the crizotinib group was 281.0 (34.0 - 1,014.9) in patients with and 175.9 (64.5 - 382.8) in patients without renal impairment at baseline. The corresponding estimates in the erlotinib group were 557.4 (318.6 - 905.1) and 517.7 (391.1 - 672.3) (Table 15.34 and Table 15.35).

10.4.5. Overall survival

In the combined EU population, the 2-year overall survival was 49% (95% CI: 41 - 56) in the crizotinib group and 21% (95% CI: 19 - 23) in the erlotinib group (Figure 3). In the EU, the

overall survival was higher in the crizotinib group than in the erlotinib group in all subgroups examined (Figure 3, Figure 15.3). The overall survival was lower for both groups in the Scandinavian countries than in the Netherlands (Denmark Supplemental Figure 2, Finland Supplemental Figure 2, Sweden Supplemental Figure 2, Appendix 5, the Netherlands Supplemental Figure 2).

Figure 3. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Patients with Primary Lung Cancer, By Study Drug Group (One Drug), EU Combined

Source: Figure 15.3.

In the US population, the 2-year overall survival was 50% (95% CI: 30 - 68) in the crizotinib group and 35% (95% CI: 27 - 43) in the erlotinib group. In the US, the overall survival was higher in the crizotinib group than in the erlotinib group in all subgroups examined (Figure 4, Figure 15.4).

Figure 4. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Patients with Primary Lung Cancer, By Study Drug Group (One Drug), US

Source: Figure 15.4.

10.5. Patients in the crizotinib and ceritinib group

There were 80 patients in the crizotinib and ceritinib group: 48 in Sweden and 32 in the US. There were no patients in this group in the other countries.

In Sweden, 47/48 patients had a record of ceritinib after a record of crizotinib; the median age at switch was 60.0 years (range: 40.0 - 76.0), and 54.2% of the patients were women (Table 15.2). Among the 47 patients initiating crizotinib and switching to ceritinib, median time to switch was 323 days (range: 61 - 922). Patients who switched to ceritinib had higher baseline prevalence of bradycardia than patients in the overall crizotinib group (4.2% vs. 0.4%, respectively), pneumonitis/ILD (35.4% vs. 20.5%), QT interval prolongation-related events (6.3% vs. 3.6%) and vision disorders (18.8% vs. 6.8%) (Table 15.5). The maximum follow-up in this group was 445 days, during which there were 3 incident cases of pneumonitis/ILD; 1 incident case of QT interval prolongation-related events; 1 incident case of leukopenia; 1 incident case of neuropathy; 1 incident case or cardiac failure; and 22 all-cause deaths. The one-year all-cause mortality (95% CI) was 62.9% (41.7 - 78.3) (Sweden Supplemental Table 3, Sweden Supplemental Table 12, Appendix 5). No other endpoint was reported in the crizotinib and ceritinib group in Sweden. Mortality beyond one year was not available in this group in Sweden.

In the US, all 32 patients had a record of ceritinib after a record of crizotinib; the median age at switch was 56.0 years (range: 47.5 - 59.5), and 59.4% of the patients were women (Table 15.3). Among these patients, median time to switch was 332 days (range: 55 – 1,412). Patients switching to ceritinib group had higher baseline prevalence of bradycardia than patients in the overall crizotinib group (21.9% vs. 15.7%, respectively), hepatotoxicity (6.3% vs. 3.4%), QT interval prolongation-related events (75.0% vs. 55.1%) and vision disorders (25.0% vs. 10.7%) (Table 15.6). During the total follow-up, in this group there were 5 cases of bradycardia; 4 cases of hepatotoxicity; 4 cases of pneumonitis/ILD; 4 cases of QT prolongation-related events; 1 case of vision disorders; 2 cases of edema; 1 case of leukopenia; 2 cases of neuropathy; 2 cases of photosensitivity; 1 case of GI perforation; 1 case of cardiac failure; and 6 all-cause deaths in the 13 patients with complete data on death. The three-year all-cause mortality (95% CI) among these patients was 46.2% (19.2 - 69.6) (US Supplemental Table 3, US Supplemental Table 12, Appendix 5).

10.6. Use of crizotinib in patients without primary lung cancer

Of the 513 patients with dispensing/prescription of crizotinib, 57 (11%) did not have primary lung cancer diagnosis prior to the first crizotinib dispensing/prescription. Data were not combined for this analysis and are presented in Table 15.36.

In Denmark, there were 4 patients with a record of initiation of crizotinib and without record of primary lung cancer; all 4 patients were men younger than 50 years of age and had diagnoses of 4 different neoplasms, other than primary lung cancer.

In Finland, no data could be reported due to data protection regulations; there were more than 0, but fewer than 5 patients in this group.

In Sweden, there were 25 patients with a record of crizotinib dispensing and without prior diagnosis of primary lung cancer in the Swedish Cancer Register. Of those, 6 (24%) had a cancer diagnosis before the index date, however, 24/25 patients had lung cancer diagnosis in the Swedish Patient Register, but not in the Swedish Cancer Register. Since the Swedish Cancer Register was used as the source of data on lung cancer for the purposes of identifying the study population for the main analysis (as the most valid and complete source of data on primary cancer), patients without a lung cancer diagnosis in the Swedish Cancer Register were not included in the main analysis.

In the Netherlands, there were 2 patients in the crizotinib group who had no primary lung cancer diagnosis; no record of lung cancer was identified in the Hospitalisation Database or Pathology Registry.

In the US, 25 patients treated with crizotinib had no primary cancer diagnosis; majority were younger than 50 years and were men. Three quarters of these patients had a diagnosis “Other and Unspecified Malignant Neoplasms” (ICD-10 codes C69-C80).

10.7. Other analyses: validation of the primary endpoints

Overall, 667 patients were selected for the validation of the primary endpoints, as described in Section 9.8. The results reported herein reflect abstraction and adjudication results available

through 30 April 2018; chart abstraction of the remaining records could not be completed because of the time limitations. Adjudication results by two adjudicators was available, while adjudication of discordant cases by the third adjudicator is still ongoing. As of 30 April 2018, medical records from 425/667 (64%) patients have been abstracted. Among the 425 patients with abstracted records, 405 (95%) had adjudication completed by 2 experts for at least 1 of the endpoints. Table 12 shows distribution of completion of chart abstraction and adjudication by country and study drug group.

Table 12. Completed Chart Abstraction and Adjudication among 677 Patients with Primary Lung Cancer Identified for Validation of the Primary Endpoints, by Country and Study Drug Group

Country*	Study drug group	Selected for validation	Underwent chart abstraction	Completed adjudication by two experts in at least one** primary endpoint
Denmark	Crizotinib	79	48	48
	Other	79	45	44
Finland	Crizotinib	8	8	8
	Other	8	8	8
Sweden	Crizotinib	164	109	100
	Other	206	104	96
United States	Crizotinib	61	53	53
	Other	62	50	48
Total		**667**	**425**	**405**

*Data from the Netherlands were not available at the time of this analysis owing to administrative delays.
**Endpoint-specific population size may differ.

Records in which case status was marked as "cannot determine" by 1 adjudicator were excluded from the validation analysis. Table 13 shows the distribution of records included in the validation analysis of each endpoint by country and study drug group. The largest number of records was adjudicated in Sweden.

Table 13. Number of Patients Included in the Validation Analyses of the Primary Endpoints after Exclusion of the Records in which Case Status Could Not Be Determined, by Country and Study Drug Group

Country**	Study drug group	Primary endpoint*			
		Bradycardia	Hepatotoxicity	Pneumonitis/ILD	Vision Disorder
Denmark	Crizotinib	48	2	47	46
	Other	43	1	44	44
Finland	Crizotinib	8	5	7	5
	Other	7	5	8	8
Sweden	Crizotinib	99	37	87	95
	Other	96	32	90	91
United States	Crizotinib	53	39	53	51
	Other	48	30	44	48
Total		**402**	**151**	**380**	**388**

*QT prolongation-related events could not be validated owing to lack of access to relevant electrocardiograms
*Data from the Netherlands were not available at the time of this analysis

Electrocardiogram records before and after index date, both of which are necessary to adjudicate the primary endpoint "QT interval prolongation-related events", were not available. Therefore, it was not possible to adjudicate the primary endpoint "QT interval prolongation-related events". Laboratory test records, necessary for adjudication of the endpoint "Hepatotoxicity", were not available from medical charts in Denmark owing to restricted access to medical records. For

bradycardia and hepatotoxicity, planned analyses included stratification on the severity of the event, however, severity data were not available for most of the events and this analysis was not undertaken.

Among the 405 patients with results available for bradycardia, case status could not be determined for 3 patients by at least one of the adjudicators. Table 15.37 shows results of validity of diagnostic codes for bradycardia among the remaining 402 patients while counting as true cases those adjudicated as "definite" by 2 adjudicators. Sensitivity ranged from 0.00 in Finland to 0.50 in Denmark. PPV ranged from 0.08 in the US to 1.00 in Denmark. Counting as true cases those adjudicated as "possible" by one adjudicator and as "possible or definite" by the other adjudicator obtained did not change the results, as there was no discordance between the adjudicators (Table 15.38). Specificity and NPV were high.

Among the 271 patients with results available for hepatotoxicity, true case status could not be determined for 120 patients by at least 1 adjudicator, including 86 patients in whom it could not be determined by both adjudicators. Table 15.39 shows results of validity of diagnostic codes for hepatotoxicity among the remaining 151 patients, while counting as true cases those adjudicated as "definite" by 2 adjudicators. Sensitivity was zero, and PPV could not be estimated. Counting as true cases those adjudicated as "possible" by one adjudicator and as "possible or definite" by the other adjudicator obtained sensitivity of 0.09 and PPV 1.00 in the use (Table 15.40). The discordance between the adjudicators was high. The adjudication by a third adjudicator was not complete in time for inclusion for this analysis. Specificity and NPV were high.

Among the 398 patients with results available for pneumonitis/ILD, true case status could not be determined for 18 patients by at least one adjudicator, including 14 patients in whom it could not be determined by both adjudicators. Table 15.41 shows results of validity of diagnostic codes for pneumonitis/ILD among the remaining 380 patients, while counting as true cases only (i.e., defined as "definite" by two adjudicators). Sensitivity and PPV were both zero in this analysis. Counting as true cases those adjudicated as "possible" by one adjudicator and as "possible or definite" by the other adjudicator obtained sensitivity of 0.33 and PPV of 0.08 in Sweden and sensitivity of 0.14 and PPV of 0.06 in the US(Table 15.42). Specificity and NPV were high. There were no discordant adjudications in this analysis.

Table 15.43 and Table 15.44 for the adjudication of QT prolongation-related events were not populated.

Among the 405 patients with results available for vision disorder, true case status could not be determined for 17 patients by at least one adjudicator, including 2 patients in whom it could not be determined by both adjudicators. Table 15.45 shows results of validity of diagnostic codes for vision disorders among the remaining 388 patients, while counting as true cases only those adjudicated as "definite" by two adjudicators. Sensitivity and PPV were, respectively, 0.33 and 0.14 in the US and were both zero in the other countries. Counting as true cases those adjudicated as "possible" by one adjudicator and as "possible or definite" by the other adjudicator obtained both sensitivity and PPV of 1.00 in Finland; 0.06 and 0.50 in Sweden; and 0.24 and 0.71 in the US (Table 15.46). Specificity and NPV were high.

10.8. Adverse events/adverse reactions

This study used existing routine health care databases, in which it is generally not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual.

This Study Protocol (Appendix 2) required human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and vision depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. If allowed by local legislation, the reviewer was to report adverse events (AEs) with explicit attribution to any Pfizer drug appearing in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution was not inferred from merely a temporal relationship between drug administration and an AE, but had to be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

• All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

• Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product were to be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to (AEs) or associated with use of (other scenarios listed above), a Pfizer product, the data captured in the medical record were to constitute all clinical information known regarding these adverse events. No follow-up on related adverse events were to be conducted. Exposure during pregnancy cases was to be followed up, where possible, for pregnancy outcomes.

All research staff members completed the Pfizer requirements regarding training on the following: “Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)” and all relevant “Your Reporting Responsibilities” supplemental training. This training was provided to all research staff members prior to study start. All trainings included a “Confirmation of Training Certificate” (for signature by the trainee) as a record of completion of the training, was kept on file in a retrievable format. Copies of all signed training certificates were provided to Pfizer.

11. DISCUSSION

11.1. Key results

This active safety surveillance cohort study based on routinely collected data from 4 EU countries and from the US, included 3,613 patients with primary lung cancer with dispensing/prescription of one of the study drugs: crizotinib (N=456); ceritinib (N=10) erlotinib

(N=2,957), and gefitinib (N=190). Because of its largest size, patients in the erlotinib group were used to provide context to the findings in the crizotinib group.

Both in the combined EU population and in the US population, patients in the crizotinib group were younger than patients in the erlotinib group and had slightly higher proportions of women than men. In the EU population, patients in the crizotinib group were similar with respect to prevalence of brain metastases at baseline; had slightly higher prevalence of hepatic impairment at baseline and slightly lower prevalence of renal impairment at baseline. About half of the EU patients in both crizotinib and erlotinib groups had a high burden of comorbidity; patients in the crizotinib group tended to have lower or similar prevalence of concomitant medication use in the previous 6 months compared with the erlotinib group. Prevalence of high comorbidity burden in both crizotinib and erlotinib groups exceeded 85% in the US population, and baseline use of concomitant medication was comparably high in both groups. Proportions of patients with prevalent events corresponding to the endpoints tended to be lower in the EU population than in the US population in both crizotinib and erlotinib groups.

In the combined EU population, the 2-year cumulative incidences of all primary and all secondary endpoints other than death of all causes were lower than 10% and were highest for pneumonitis/ILD, with 9.2% in the crizotinib group and 7.0% in the erlotinib group and 8.8% and 8.6% for neuropathy, respectively. Death of all causes was the most frequently observed endpoint. The 2-year all-cause mortality was lower in the crizotinib group (43.9%) than in the erlotinib group (64.2%).

In the US, 2-year cumulative incidences were greater, often by orders of magnitude, than those in the EU population for most primary and secondary endpoints in both crizotinib and erlotinib groups. Among the primary endpoints, the highest 2-year cumulative incidences were observed in the crizotinib and erlotinib groups for pneumonitis/ILD (30.6% and 27.4%, respectively); QT interval prolongation-related events (26.8% and 20.9%, respectively); and bradycardia (16.9% and 9.5%, respectively). Among the secondary endpoints, the highest 2-year cumulative incidences were observed in the crizotinib and erlotinib groups for neuropathy (32.7% and 28.8%, respectively) and leukopenia (14.3% and 18.1%, respectively). Similarly to the EU population, death of all causes was the most common endpoint, and 2-year all-cause mortality was lower in the crizotinib group (35.3%) than in the erlotinib (49.8%) group.

In the combined EU population, the all-cause mortality rate was lower in the crizotinib group than in the erlotinib group (334.2 and 663.0 per 1,000 person-years, respectively). In the crizotinib group, the all-cause mortality rate was higher in patients ages 65 years or older (436.8 per 1,000 person-years), patients with brain metastases at baseline (495.6 per 1,000 person-years), in patients with hepatic impairment at baseline (600.4 per 1,000 person-years) and in patients with renal impairment at baseline (408.7 per 1,000 person-years). The corresponding stratified estimates were higher in the erlotinib group.

In the US population, the all-cause mortality rate was lower in the crizotinib group than in the erlotinib group (302.9 and 637.0 per 1,000 person-years). In the crizotinib group, the all-cause mortality rate was higher than the overall all-cause mortality rate in patients aged 65 years or older, but based on only 1 death in this patient group. Mortality rates were only slightly higher than the overall rates in the crizotinib group among patients with brain metastases at baseline

(342.6 per 1,000 person-years), in patients with hepatic impairment at baseline (306.0 per 1,000 person-years) and in patients with renal impairment at baseline (388.6 per 1,000 person-years). The corresponding stratified estimates were higher in the erlotinib group.

In the combined EU population, the 2-year overall survival was higher in the crizotinib (49%) than in the erlotinib group (21%) overall and in all subgroups.

Similarly, in the US population, the 2-year overall survival was higher in the crizotinib (50%) than in the erlotinib (35%) group, overall and in all subgroups.

In summary, based on incidence rates of the endpoints computed with time at risk as total follow-up time (the analysis that includes all observed events), the point estimates were numerically higher for crizotinib than for erlotinib, both in the EU and in the US data, for bradycardia and for vision disorder; the point estimates were numerically lower for crizotinib than for erlotinib, both in the EU and in the US data, for pneumonitis/ILD, neuropathy, photosensitivity, GI perforation, and death of all causes. The point estimates were similar for crizotinib and erlotinib in the EU and US data for cardiac failure. For hepatotoxicity, the point estimates for crizotinib were numerically higher than that for erlotinib in the EU data and lower in the US data. For QT interval prolongation-related events and malignant melanoma, the point estimates for crizotinib were numerically lower than that for erlotinib in both EU and US data. There were no cases of renal cysts in the EU data, and the point estimate for renal cysts was lower for crizotinib than for erlotinib in the US data.

There were 80 patients (48 in Sweden and 32 in the US) in the crizotinib and ceritinib group; nearly all of whom received crizotinib before receiving ceritinib. These patients represented a subset of crizotinib-treated patients. These patients had higher burden of baseline comorbidity than patients in the crizotinib group.

In addition, 57 patients with dispensing/prescription of crizotinib did not have a record of primary lung cancer in the database used to ascertain cancer status.

11.2. Limitations

Reliance on routinely collected administrative data is subject to a number of inherent limitations. Observed diagnostic codes, while in most cases indicative of the patient's disease state, especially in the discharge data used in the EU data of this study, may nevertheless include rare instances of incorrect diagnoses or, in the US data, may include rule-out diagnoses as a justification for billed tests or procedures. This can lead to an overestimation of event occurrence. The occurrence of all endpoints was higher in the US than in the EU, contributing to the heterogeneity seen in meta-analyses. In the Scandinavian countries and in the Netherlands, diagnoses came from inpatient and outpatient hospital encounters and did not include data on primary care encounters, implying that signs and symptoms (such as bradycardia, edema or photosensitivity) were less likely to be recorded in that setting than well-defined diagnoses, such as GI perforation, cardiac failure or malignant melanoma. For malignant melanoma, however, the available follow-up of 3 years (or 3 years in Denmark and the US) was likely be insufficient and results of malignant melanoma occurrence from this study should not be interpreted as indicative of the underlying risks in the population.

Dispensing of medicines, while more accurate than prescriptions, reflect medication receipt but not necessarily actual use. Certain amount of misclassification of treatment duration cannot be ruled out. In Denmark, neither gefitinib use before the index date nor its use during the follow-up period (to ascertain switching) could be captured based on the coding of the study drugs, which may have caused misclassification of the new user status in the erlotinib group and prevented identification of potential switching to gefitinib if such switching occurred. Based on the data from Sweden, the Netherlands and the US, in which all study drugs could be identified, the largest majority of enrolled patients were exposed to erlotinib. Data on ceritinib were not available in Denmark or Finland. Therefore initiation of ceritinib could not be ascertained in these countries. Finally elderly populations are likely under-represented in the US data originating from predominantly employed commercially insured population.

The overall mortality was low in the Netherlands and especially in the US. This may be attributable to larger proportion of patients treated with crizotinib in the first-line in the US, per US approval. In the Netherlands, data on deaths may be incomplete owing to long lag time in the National Date of Death Register. Finally, in all countries, the study population was likely to include patients treated with crizotinib and other drugs in both first and subsequent lines, which complicates interpretation, while data on line of treatment was not available in any of the countries.

Another important limitation of the study is that even using data from 5 countries, the projected number of the crizotinib group could not be achieved during the study period (677 projected vs. 456 for patients with primary lung cancer). Small numbers of patients treated with crizotinib have been reported in other studies, for example, in a multinational survey, physicians from 25 medical centers extracted information on only 158 patients from four regions over 1 calendar year; the survey reported high rates of crizotinib permanent discontinuation with a median duration of initial crizotinib treatment of 5.6 months (51).

The low values of sensitivity and PPV from the preliminary results of the validation of the primary endpoints are unlikely to reflect quality of the ICD-based definitions. They are more likely to reflect lack of data in routine medical charts details needed to adjudicate cases according to stringent clinical definitions of the endpoints (e.g., lack of data on electrocardiography necessary to adjudicate QT prolongation related events). Future validation studies may need to use real-world-based clinical definitions of the endpoints.

11.3. Strengths

One of the key strengths of this study was that the use of large data systems with routinely collected health care data, allowing for the possibility of studying a rare exposure (i.e. crizotinib) in a reasonable period of time and in the context of routine clinical care. Use of these data provided insight regarding safety outcomes in patients who were underrepresented in crizotinib RCTs, including elderly patients. Routinely recorded data on treatment with the study drugs had high correspondence with the drug use recorded in medical charts. In the validation subset with the data on crizotinib use available from medical charts, crizotinib treatment was recorded in the charts of nearly all patients with a database record of crizotinib initiation: in 45/48 (94%) patients in Denmark; in 8/8 (100%) patients in Finland; in 95/100 (95%) patients in Sweden, and in 52/53 (98%) patients in the US. In the validation subset with the data on erlotinib use available

from medical charts, erlotinib treatment was recorded in the charts of nearly all patients with a database record of erlotinib initiation: in 42/45 (93%) patients in Denmark; in 6/6 (100%) patients in Finland; in 91/100 (91%) patients in Sweden, and in 48/50 (96%) patients in the US. However, there is no reason to suspect that use of other study drugs would be recorded differently from crizotinib. In the Scandinavian countries, nearly 100% of the lung cancers during the study period could be ascertained and, owing to complete enumeration of the underlying population, there was no loss to follow-up. Therefore, results based on this population-based study are more generalizable than those obtained from clinical trials.

11.4. Interpretation

The results of this study in the combined EU population and in the US population should be interpreted in the light of differences in approvals for crizotinib (first-line for the entire study period in the US but not in the EU); heterogeneity of the underlying access to health care (universal in the EU vs. insurance-based in the US); differences in the record-generating types of health data (administrative healthcare data in the EU with diagnoses of events predominantly from the hospital setting vs. administrative claims data in the US with diagnoses of events from all healthcare sectors); and differences in the characteristics of the patients in the crizotinib and the erlotinib group, including diverse natural history of the underlying lung cancer types. Because the EU data stemmed primarily from the hospital settings, while the US data originated from all healthcare settings, the EU data may be more specific while the US data may be more sensitive in terms of capturing the true occurrences of the study endpoints. Incidence rates of nearly all endpoints in all drug groups were lower in the EU than in the US; however, within each healthcare setting the results were internally consistent.

Vision disorders and hepatotoxicity, two of the primary endpoints of this study, were the most commonly reported crizotinib-related toxicities in clinical studies with primary data collection (52), however, this was not uniformly observed in this study. The lower incidence of vision disturbances and hepatotoxicity in this study are expected because most vision disturbances are symptoms that are systematically under-recorded and some laboratory results, such as abnormal liver enzymes, are not well captured in the available administrative databases. Pneumonitis, on the other hand, is rarely reported in clinical studies (52), yet it was among the more common endpoints observed based on the pneumonitis/ICD algorithms used. At the same time, definitions of endpoint identification in routinely collected real-world data are likely to be less sensitive than those in clinical studies with primary data collection. Edema, renal cysts, and GI effects were reported as rare in crizotinib clinical trials (52), which was also the case in the present study. Neuropathy, relatively commonly observed in the present study, may be the result of cancer itself; indeed, in RCTs, neuropathy occurred with similar frequency in crizotinib-treated and chemotherapy-treated patients (10, 11). In a meta-analysis of 11 studies, it was concluded that crizotinib monotherapy was not less safe than chemotherapy in ALK-positive lung cancer patients, however, specific endpoints were not tabulated (53). In the present study, crizotinib-treated patients tended to be younger than erlotinib-treated patients. In the EU population, crizotinib-treated patients had lower prevalence of several comorbidities and concomitant medications than erlotinib-treated patients. In the US data, distributions of comorbidities and concomitant medications in the two groups were comparable.

The observed higher overall survival among the patients in the crizotinib group than those in the erlotinib group may reflect the fact that patients treated with crizotinib tend to be younger and have lower prevalence of smoking than the overall NSCKC population (54, 55). In the US a potentially higher proportion of crizotinib-treated patients were treated in the first- line. However, information about line of treatment in which the study drugs were given was not available in this study. These differences in survival in the crizotinib and erlotinib group should also be interpreted in the context of the knowledge that EGFR-positive and ALK-positive lung cancer represent different types of lung cancer. Among RCT participants, the 1-year overall survival in crizotinib-treated patients was 74%-84% (12) and was similar in patients EGFR-positive patients treated with erlotinib or gefitinib (56). The overall survival varied by country. It was higher in the Netherlands than in the Scandinavian countries, which may be partially an artefact of incomplete data on deaths in the PHARMO database for patients included in a recent period.

This study showed that crizotinib use was low, reflecting a low prevalence of its molecular target in the NSCLC population. By the descriptive nature of this study, no attempt has been made to formally estimate an association between treatment received and risks of the endpoints. Any observed differences in the occurrence of the endpoints between the drug groups may be subject to systematic treatment or prognosis-related differences in the patient populations, such as differences in age, comorbidity or the line of treatment. The results of this study should not be used for inferences about comparative safety or effectiveness of the study drugs.

11.5. Generalizability

The EU data sources used in this study were population-based and were therefore representative of its underlying source population. Results of the study could be generalized to the source population of each country.

In the US, patients were drawn from a commercially-insured patient population. The population covered by ORD is geographically diverse across the US, and therefore is fairly representative of the US population, with the exception of the elderly population, which is under-represented in the insured and employed population that give rise to the ORD records (22). Therefore, results from ORD in this study may be generalizable to the insured, relatively younger and employed NSCLC patients receiving crizotinib treatment in the US.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

The results of this study did not provide evidence for changing the current benefit/risk profile of crizotinib.

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15. LIST OF SOURCE TABLES AND FIGURES

Table 15.1 Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, Overall

	Study drug group					
Characteristics	Crizotinib (N= 456)	Ceritinib (N= 10)	Erlotinib (N=2,957)	Gefitinib (N= 190)	Crizotinib and Ceritinib (N= 80)	Erlotinib and Gefitinib (N= 52)
Age group at index date, years, n (%)						
<50	100 (21.9)	3 (30.0)	190 (6.4)	9 (4.7)	19 (23.8)	4 (7.7)
50 to 59	130 (28.5)	7 (70.0)	586 (19.8)	22 (11.6)	29 (36.3)	4 (7.7)
60 to 69	149 (32.7)	0 (0.0)	1,130 (38.2)	61 (32.1)	25 (31.3)	21 (40.4)
70 to 79	64 (14.0)	0 (0.0)	766 (25.9)	64 (33.7)	7 (8.8)	17 (32.7)
80+	13 (2.9)	0 (0.0)	285 (9.6)	34 (17.9)	0 (0.0)	6 (11.5)
Age at index date, years						
Mean (standard deviation)	58.5 (11.3)	48.9 (0.0)	72.5 (10.9)	69.4 (10.0)	56.9 (9.1)	68.3 (10.2)
Median (range)	59.8 (23.7-84.0)	52.9 (34.0-59.7)	66.2 (24.0-91.2)	70.5 (40.6-89.0)	57.2 (40.0-76.0)	68.6 (44.0-83.0)
Sex, n (%)						
Men	205 (45.0)	5 (50.0)	1,265 (42.8)	77 (40.5)	35 (43.8)	15 (28.8)
Women	251 (55.0)	5 (50.0)	1,692 (57.2)	113 (59.5)	45 (56.3)	37 (71.2)
Race/ethnicity, n (%)						
Asian	8 (1.8)	0 (0.0)	46 (1.6)	1 (0.5)	0 (0.0)	1 (1.9)
Black	14 (3.1)	0 (0.0)	71 (2.4)	0 (0.0)	5 (6.3)	1 (1.9)
Hispanic	11 (2.4)	0 (0.0)	52 (1.8)	0 (0.0)	2 (2.5)	1 (1.9)
White	128 (28.1)	5 (50.0)	602 (20.4)	1 (0.5)	21 (26.3)	1 (1.9)
Unknown[a]	295 (64.7)	5 (50.0)	2,186 (73.9)	188 (98.9)	52 (65.0)	48 (92.3)
Lung cancer morphology, n (%)						
Non-small cell lung cancer (NSCLC)	250 (54.8)	4 (40.0)	1,975 (66.8)	164 (86.3)	47 (58.8)	46 (88.5)
Small cell lung cancer	3 (0.7)	0 (0.0)	6 (0.2)	0 (0.0)	1 (1.3)	0 (0.0)
Unknown	203 (44.5)	6 (60.0)	976 (33.0)	26 (13.7)	32 (40.0)	6 (11.5)
Lung cancer histology (NSCLC only), n (%)						
Squamous cell carcinoma	6 (1.3)	0 (0.0)	171 (5.8)	4 (2.1)	1 (1.3)	0 (0.0)
Adenocarcinoma	220 (48.2)	4 (40.0)	1,628 (55.1)	150 (78.9)	42 (52.5)	42 (80.8)
Other	2 (0.4)	0 (0.0)	76 (2.6)	1 (0.5)	0 (0.0)	0 (0.0)
Unknown or not NSCLC)	228 (50.0)	6 (60.0)	1,082 (36.6)	35 (18.4)	37 (46.3)	10 (19.2)
Stage at diagnosis, n (%)						
Stage I	13 (2.9)	0 (0.0)	138 (4.7)	10 (5.3)	2 (2.5)	5 (9.6)
Stage II	1 (0.2)	0 (0.0)	68 (2.3)	5 (2.6)	0 (0.0)	0 (0.0)
Stage III	17 (3.7)	0 (0.0)	224 (7.6)	4 (2.1)	1 (1.3)	0 (0.0)
Stage IV	161 (35.3)	0 (0.0)	1,114 (37.7)	65 (34.2)	34 (42.5)	33 (63.5)
Unknown or not reported as TNM stage (Finland[b])	264 (57.9)	10 (100.0)	1,413 (47.8)	106 (55.8)	43 (53.8)	14 (26.9)
Genotyping, n (%)						
ALK rearrangement	78 (17.1)	1 (10.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EGFR mutation	3 (0.7)	0 (0.0)	311 (10.5)	10 (5.3)	0 (0.0)	0 (0.0)
Both ALK and EGFR	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Not ALK or EGFR	6 (1.3)	1 (10.0)	6 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)
Unknown	369 (80.9)	8 (80.0)	2,637 (89.2)	179 (94.2)	80 (100.0)	52 (100.0)
Year of lung cancer diagnosis, n (%)						
Before 2011	49 (10.7)	1 (10.0)	294 (9.9)	11 (5.8)	8 (10.0)	4 (7.7)
2011-2012	74 (16.2)	3 (30.0)	866 (29.3)	23 (12.1)	13 (16.3)	9 (17.3)
2013-2014	201 (44.1)	5 (50.0)	1,260 (42.6)	95 (50.0)	36 (45.0)	27 (51.9)
2015-2016	132 (28.9)	1 (10.0)	537 (18.2)	61 (32.1)	23 (28.8)	12 (23.1)
Time since primary lung cancer diagnosis, months						
Mean (standard deviation)	13.4 (19.8)	25.1 (.)	15.2 (18.8)	11.4 (17.1)	18.4 (20.6)	11.4 (14.3)

Table 15.1 Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, Overall

	Study drug group					
Characteristics	Crizotinib (N= 456)	Ceritinib (N= 10)	Erlotinib (N=2,957)	Gefitinib (N= 190)	Crizotinib and Ceritinib (N= 80)	Erlotinib and Gefitinib (N= 52)
Range[c]	0.0-153.4	7.2-69.5	0.0-293.4	0.1-148.0	0.8-115.3	0.5-75.9
Country, n (%)						
Denmark	79 (17.3)	0 (0.0)	855 (28.9)	0 (0.0)	0 (0.0)	0 (0.0)
Finland	25 (5.5)	0 (0.0)	323 (10.9)	77 (40.5)	0 (0.0)	8 (15.4)
Netherlands	32 (7.0)	3 (30.0)	61 (2.1)	18 (9.5)	0 (0.0)	0 (0.0)
Sweden	142 (31.1)	1 (10.0)	882 (29.8)	93 (48.9)	48 (60.0)	40 (76.9)
United States	178 (39.0)	6 (60.0)	836 (28.3)	2 (1.1)	32 (40.0)	4 (7.7)

[a] The EU Member States legislation prohibits the processing of personal data revealing racial or ethnic origin (57).
[b] For stage distribution in Finland, see Finland Supplemental Table 1, Appendix 5.
[c] Median not estimable from available combined data.
ALK anaplastic lymphoma kinase; EGFR epidermal growth factor receptor; NSCLC non-small cell lung cancer; TNM tumor, node, metastasis.
Source: country-specific Supplemental Tables 1, Appendix 5.

Table 15.2 Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, EU Combined

	Study drug group					
Characteristics	Crizotinib (N= 278)	Ceritinib (N= 4)	Erlotinib (N=2,121)	Gefitinib (N= 188)	Crizotinib and Ceritinib (N= 48)	Erlotinib and Gefitinib (N= 48)
Age group at index date, years, n (%)						
<50	54 (19.4)	0 (0.0)	94 (4.4)	9 (4.8)	10 (20.8)	4 (8.3)
50 to 59	58 (20.9)	4 (100.0)	306 (14.4)	21 (11.2)	14 (29.2)	3 (6.3)
60 to 69	98 (35.3)	0 (0.0)	792 (37.3)	61 (32.4)	18 (37.5)	19 (39.6)
70 to 79	56 (20.1)	0 (0.0)	688 (32.4)	64 (34.0)	6 (12.5)	17 (35.4)
80+	12 (4.3)	0 (0.0)	241 (11.4)	33 (17.6)	0 (0.0)	5 (10.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age at index date, years						
Mean (standard deviation)	60.7 (12.4)	55.0 (0.0)	68.2 (9.8)	69.4 (9.9)	59.1 (9.2)	68.5 (10.1)
Median (range)	62.8 (23.7-84.0)	55.0 (51.0-59.7)	68.3 (24.0-91.2)	70.5 (40.6-89.0)	60.0 (40.0-76.0)	68.9 (44.0-83.0)
Sex, n (%)						
Men	122 (43.9)	2 (50.0)	890 (42.0)	77 (41.0)	22 (45.8)	15 (31.3)
Women	156 (56.1)	2 (50.0)	1,231 (58.0)	111 (59.0)	26 (54.2)	33 (68.8)
Race/ethnicity, n (%)						
Unknown[a]	278 (100.0)	4 (100.0)	2,121 (100.0)	188 (100.0)	48 (100.0)	48 (100.0)
Lung cancer morphology, n (%)						
Non-small cell lung cancer (NSCLC)	250 (89.9)	4 (100.0)	1,975 (93.1)	164 (87.2)	47 (97.9)	46 (95.8)
Small cell lung cancer	3 (1.1)	0 (0.0)	6 (0.3)	0 (0.0)	1 (2.1)	0 (0.0)
Unknown	25 (9.0)	0 (0.0)	140 (6.6)	24 (12.8)	0 (0.0)	2 (4.2)
Lung cancer histology (NSCLC only), n (%)						
Squamous cell carcinoma	6 (2.2)	0 (0.0)	171 (8.1)	4 (2.1)	1 (2.1)	0 (0.0)
Adenocarcinoma	220 (79.1)	4 (100.0)	1,628 (76.8)	150 (79.8)	42 (87.5)	42 (87.5)
Other	2 (0.7)	0 (0.0)	76 (3.6)	1 (0.5)	0 (0.0)	0 (0.0)
Unknown or not NSCLC	50 (18.0)	0 (0.0)	246 (11.6)	33 (17.6)	5 (10.4)	6 (12.5)
Stage at diagnosis, n (%)						
Stage I	13 (4.7)	0 (0.0)	138 (6.5)	10 (5.3)	2 (4.2)	5 (10.4)
Stage II	1 (0.4)	0 (0.0)	68 (3.2)	5 (2.7)	0 (0.0)	0 (0.0)
Stage III	17 (6.1)	0 (0.0)	224 (10.6)	4 (2.1)	1 (2.1)	0 (0.0)
Stage IV	161 (57.9)	0 (0.0)	1,114 (52.5)	65 (34.6)	34 (70.8)	33 (68.8)
Unknown or not reported as TNM stage (Finland[b])	86 (30.9)	4 (100.0)	577 (27.2)	104 (55.3)	11 (22.9)	10 (20.8)
Genotyping, n (%)						
ALK rearrangement	78 (28.1)	1 (25.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EGFR mutation	3 (1.1)	0 (0.0)	311 (14.7)	10 (5.3)	0 (0.0)	0 (0.0)
Both ALK and EGFR	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Not ALK or EGFR	6 (2.2)	1 (25.0)	6 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Unknown	191 (68.7)	2 (50.0)	1,801 (84.9)	177 (94.1)	48 (100.0)	48 (100.0)
Year of lung cancer diagnosis, n (%)						
Before 2011	23 (8.3)	1 (25.0)	161 (7.6)	11 (5.9)	5 (10.4)	2 (4.2)
2011-2012	32 (11.5)	1 (25.0)	486 (22.9)	23 (12.2)	7 (14.6)	8 (16.7)
2013-2014	124 (44.6)	1 (25.0)	1,020 (48.1)	95 (50.5)	17 (35.4)	27 (56.3)
2015-2016	99 (35.6)	1 (25.0)	454 (21.4)	59 (31.4)	19 (39.6)	11 (22.9)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time since primary lung primary cancer diagnosis, months						
Mean (standard deviation)	15.6 (23.3)	36.2 (-)	14.6 (18.8)	11.4 (17.3)	16.8 (23.2)	8.7 (13.3)
Range[c]	0.0-153.4	7.2-69.5	0.0-293.4	0.1-148.0	0.8-115.3	0.5-75.9
Country, n (%)						
Denmark	79 (28.4)	0 (0.0)	855 (40.3)	0 (0.0)	0 (0.0)	0 (0.0)
Finland	25 (9.0)	0 (0.0)	323 (15.2)	77 (41.0)	0 (0.0)	8 (16.7)
Netherlands	32 (11.5)	3 (75.0)	61 (2.9)	18 (9.6)	0 (0.0)	0 (0.0)
Sweden	142 (51.1)	1 (25.0)	882 (41.6)	93 (49.5)	48 (100.0)	40 (83.3)

Table 15.2 Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, EU Combined

	Study drug group					
Characteristics	Crizotinib (N= 278)	Ceritinib (N= 4)	Erlotinib (N=2,121)	Gefitinib (N= 188)	Crizotinib and Ceritinib (N= 48)	Erlotinib and Gefitinib (N= 48)

[a] The EU Member States legislation prohibits the processing of personal data revealing racial or ethnic origin (57).
[b] For stage distribution in Finland, see Finland Supplemental Table 1, Appendix 5.
[c] Median not estimable from available combined data.
ALK anaplastic lymphoma kinase; EGFR epidermal growth factor receptor; NSCLC non-small cell lung cancer; TNM tumor, node, metastasis.
Source: country-specific Supplemental Tables 1, Appendix 5.

Table 15.3 Baseline Characteristics of Patients with Primary Lung Cancer by Study Drug Group, US

	Study drug group					
Characteristics	Crizotinib (N= 178)	Ceritinib (N= 6)	Erlotinib (N= 836)	Gefitinib (N= 2)	Crizotinib and Ceritinib (N= 32)	Erlotinib and Gefitinib (N= 4)
Age group at index date, years, n (%)						
<50	46 (25.8)	3 (50.0)	96 (11.5)	0 (0.0)	9 (28.1)	0 (0.0)
50 to 59	72 (40.4)	3 (50.0)	280 (33.5)	1 (50.0)	15 (46.9)	1 (25.0)
60 to 69	51 (28.7)	0 (0.0)	338 (40.4)	0 (0.0)	7 (21.9)	2 (50.0)
70 to 79	8 (4.5)	0 (0.0)	78 (9.3)	0 (0.0)	1 (3.1)	0 (0.0)
80+	1 (0.6)	0 (0.0)	44 (5.3)	1 (50.0)	0 (0.0)	1 (25.0)
Age at index date, years						
Mean (standard deviation)	55.1 (9.4)	44.8 (11.6)	60.5 (9.9)	70.5 (23.3)	53.6 (8.9)	65.5 (11.8)
Median (range)	55.0 (49.0-61.0)	46.5 (34.0-56.0)	61.0 (54.0-65.0)	70.5 (54.0-87.0)	56.0 (47.5-59.5)	63.0 (58.0-73.0)
Sex, n (%)						
Men	83 (46.6)	3 (50.0)	375 (44.9)	0 (0.0)	13 (40.6)	0 (0.0)
Women	95 (53.4)	3 (50.0)	461 (55.1)	2 (100.0)	19 (59.4)	4 (100.0)
Race/ethnicity, n (%)						
Asian	8 (4.5)	0 (0.0)	46 (5.5)	1 (50.0)	0 (0.0)	1 (25.0)
Black	14 (7.9)	0 (0.0)	71 (8.5)	0 (0.0)	5 (15.6)	1 (25.0)
Hispanic	11 (6.2)	0 (0.0)	52 (6.2)	0 (0.0)	2 (6.3)	1 (25.0)
White	128 (71.9)	5 (83.3)	602 (72.0)	1 (50.0)	21 (65.6)	1 (25.0)
Unknown	17 (9.6)	1 (16.7)	65 (7.8)	0 (0.0)	4 (12.5)	0 (0.0)
Lung cancer morphology, n (%)						
Unknown	178 (100.0)	6 (100.0)	836 (100.0)	2 (100.0)	32 (100.0)	4 (100.0)
Lung cancer histology (NSCLC only), n (%)						
Unknown	178 (100.0)	6 (100.0)	836 (100.0)	2 (100.0)	32 (100.0)	4 (100.0)
Stage at diagnosis, n (%)						
Unknown	178 (100.0)	6 (100.0)	836 (100.0)	2 (100.0)	32 (100.0)	4 (100.0)
Genotyping, n (%)						
Unknown	178 (100.0)	6 (100.0)	836 (100.0)	2 (100.0)	32 (100.0)	4 (100.0)
Year of lung cancer diagnosis, n (%)						
Before 2011	26 (14.6)	0 (0.0)	133 (15.9)	0 (0.0)	3 (9.4)	2 (50.0)
2011-2012	42 (23.6)	2 (33.3)	380 (45.5)	0 (0.0)	6 (18.8)	1 (25.0)
2013-2014	77 (43.3)	4 (66.7)	240 (28.7)	0 (0.0)	19 (59.4)	0 (0.0)
2015-2016	33 (18.5)	0 (0.0)	83 (9.9)	2 (100.0)	4 (12.5)	1 (25.0)
Time since primary lung cancer diagnosis, months						
Mean (standard deviation)	9.8 (14.5)	17.8 (8.4)	12.0 (13.6)	5.5 (4.1)	20.8 (16.7)	43.8 (26.0)
Median (range)	2.8 (1.1-11.7)	17.9 (10.3-23.7)	7.3 (2.1-16.0)	5.5 (2.5-8.4)	13.9 (9.2-26.5)	54.6 (27.3-60.3)

NSCLC non-small cell lung cancer, US United States
Source: US Supplemental Table 1, Appendix 5.

Table 15.4 Comorbidity and Comedication among Patients with Primary Lung Cancer by Study Drug Group, Overall

	Study drug group					
Characteristics	Crizotinib (N= 456)	Ceritinib (N= 10)	Erlotinib (N=2,957)	Gefitinib (N= 190)	Crizotinib and Ceritinib (N= 80)	Erlotinib and Gefitinib (N= 52)
Bradycardia	29 (6.4)	3 (30.0)	154 (5.2)	0 (0.0)	9 (11.3)	2 (3.8)
Hepatotoxicity	8 (1.8)	0 (0.0)	35 (1.2)	1 (0.5)	2 (2.5)	0 (0.0)
Pneumonitis/ILD	134 (29.4)	4 (40.0)	656 (22.2)	48 (25.3)	29 (36.3)	13 (25.0)
QT interval prolongation-related events	108 (23.7)	5 (50.0)	491 (16.6)	12 (6.3)	27 (33.8)	6 (11.5)
Vision disorders	38 (8.3)	2 (20.0)	217 (7.3)	15 (7.9)	17 (21.3)	8 (15.4)
Renal cysts	5 (1.1)	0 (0.0)	17 (0.6)	0 (0.0)	1 (1.3)	0 (0.0)
Edema	67 (14.7)	1 (10.0)	247 (8.4)	6 (3.2)	14 (17.5)	2 (3.8)
Leukopenia	69 (15.1)	2 (20.0)	473 (16.0)	10 (5.3)	17 (21.3)	5 (9.6)
Neuropathy	111 (24.3)	4 (40.0)	713 (24.1)	27 (14.2)	29 (36.3)	7 (13.5)
Photosensitivity	16 (3.5)	0 (0.0)	78 (2.6)	2 (1.1)	2 (2.5)	8 (15.4)
Malignant melanoma	1 (0.2)	0 (0.0)	29 (1.0)	1 (0.5)	3 (3.8)	4 (7.7)
Gastrointestinal perforation	10 (2.2)	0 (0.0)	93 (3.1)	1 (0.5)	4 (5.0)	1 (1.9)
Cardiac failure	17 (3.7)	1 (10.0)	145 (4.9)	2 (1.1)	5 (6.3)	2 (3.8)
Brain metastases	85 (18.6)	4 (40.0)	502 (17.0)	21 (11.1)	22 (27.5)	8 (15.4)
Hepatic impairment	54 (11.8)	1 (10.0)	196 (6.6)	4 (2.1)	8 (10.0)	1 (1.9)
Liver cirrhosis	20 (4.4)	0 (0.0)	71 (2.4)	0 (0.0)	2 (2.5)	1 (1.9)
Renal impairment	46 (10.1)	0 (0.0)	310 (10.5)	12 (6.3)	8 (10.0)	4 (7.7)
End-stage renal disease	1 (0.2)	0 (0.0)	5 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)
Diabetes type 1 or type 2	87 (19.1)	1 (10.0)	612 (20.7)	27 (14.2)	14 (17.5)	8 (15.4)
Chronic lung disease	81 (17.8)	4 (40.0)	717 (24.2)	22 (11.6)	14 (17.5)	8 (15.4)
Chronic obstructive pulmonary disease	42 (9.2)	2 (20.0)	557 (18.8)	8 (4.2)	7 (8.8)	4 (7.7)
Charlson comorbidity index[a]						
Low (0)	115 (25.2)	0 (0.0)	679 (23.0)	54 (28.4)	20 (25.0)	14 (26.9)
Medium (1-2)	42 (9.2)	0 (0.0)	464 (15.7)	28 (14.7)	3 (3.8)	8 (15.4)
High (3+)	299 (65.6)	10 (100.0)	1,814 (61.3)	108 (56.8)	57 (71.3)	30 (57.7)
Oral antidiabetics and insulin	69 (15.1)	1 (10.0)	524 (17.7)	20 (10.5)	12 (15.0)	7 (13.5)
Any cardiovascular medications	201 (44.1)	2 (20.0)	1,803 (61.0)	118 (62.1)	31 (38.8)	33 (63.5)
Diuretics	90 (19.7)	1 (10.0)	838 (28.3)	39 (20.5)	17 (21.3)	14 (26.9)
Beta blockers	100 (21.9)	2 (20.0)	886 (30.0)	66 (34.7)	13 (16.3)	18 (34.6)
Calcium-channel blockers	64 (14.0)	1 (10.0)	689 (23.3)	44 (23.2)	6 (7.5)	11 (21.2)
Angiotensin converting enzyme inhibitors	69 (15.1)	0 (0.0)	621 (21.0)	32 (16.8)	10 (12.5)	9 (17.3)
Angiotensin II receptor antagonists	57 (12.5)	0 (0.0)	486 (16.4)	39 (20.5)	8 (10.0)	5 (9.6)
Statins	92 (20.2)	1 (10.0)	907 (30.7)	63 (33.2)	18 (22.5)	12 (23.1)
Steroids	276 (60.5)	2 (20.0)	1,826 (61.8)	107 (56.3)	60 (75.0)	35 (67.3)
Antibacterials for systemic use	324 (71.1)	5 (50.0)	2,270 (76.8)	128 (67.4)	56 (70.0)	37 (71.2)
Anticonvulsants	70 (15.4)	1 (10.0)	486 (16.4)	17 (8.9)	12 (15.0)	4 (7.7)
Antipsychotics	20 (4.4)	0 (0.0)	128 (4.3)	2 (1.1)	2 (2.5)	1 (1.9)
Anti-asthma medications	172 (37.7)	5 (50.0)	1,148 (38.8)	47 (24.7)	29 (36.3)	19 (36.5)
Ophthalmologicals	60 (13.2)	2 (20.0)	532 (18.0)	44 (23.2)	9 (11.3)	20 (38.5)

[a] Excluding lung cancer.
ILD interstitial lung disease.
Source: country-specific Supplemental Tables 2, Appendix 5.

Table 15.5 Baseline Comorbidity and Comedication among Patients with Primary Lung Cancer by Study Drug Group, EU combined

	Study drug group					
Characteristics	Crizotinib (N= 278)	Ceritinib (N= 4)	Erlotinib (N=2,121)	Gefitinib (N= 188)	Crizotinib and Ceritinib (N= 48)	Erlotinib and Gefitinib (N= 48)
Bradycardia	1 (0.4)	1 (25.0)	33 (1.6)	0 (0.0)	2 (4.2)	0 (0.0)
Hepatotoxicity	2 (0.7)	0 (0.0)	6 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Pneumonitis/ILD	57 (20.5)	1 (25.0)	309 (14.6)	47 (25.0)	17 (35.4)	12 (25.0)
QT interval prolongation-related events	10 (3.6)	1 (25.0)	77 (3.6)	10 (5.3)	3 (6.3)	3 (6.3)
Vision disorders	19 (6.8)	0 (0.0)	132 (6.2)	15 (8.0)	9 (18.8)	8 (16.7)
Renal cysts	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	8 (2.9)	0 (0.0)	44 (2.1)	6 (3.2)	3 (6.3)	1 (2.1)
Leukopenia	21 (7.6)	1 (25.0)	160 (7.5)	10 (5.3)	8 (16.7)	2 (4.2)
Neuropathy	27 (9.7)	0 (0.0)	247 (11.6)	26 (13.8)	13 (27.1)	5 (10.4)
Photosensitivity	2 (0.7)	0 (0.0)	11 (0.5)	2 (1.1)	1 (2.1)	7 (14.6)
Malignant melanoma	1 (0.4)	0 (0.0)	20 (0.9)	1 (0.5)	2 (4.2)	4 (8.3)
Gastrointestinal perforation	0 (0.0)	0 (0.0)	12 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure	3 (1.1)	0 (0.0)	75 (3.5)	2 (1.1)	0 (0.0)	1 (2.1)
Brain metastases	31 (11.2)	1 (25.0)	235 (11.1)	20 (10.6)	9 (18.8)	6 (12.5)
Hepatic impairment	11 (4.0)	1 (25.0)	38 (1.8)	3 (1.6)	2 (4.2)	1 (2.1)
Liver cirrhosis	1 (0.4)	0 (0.0)	10 (0.5)	0 (0.0)	0 (0.0)	1 (2.1)
Renal impairment	6 (2.2)	0 (0.0)	98 (4.6)	11 (5.9)	0 (0.0)	2 (4.2)
End-stage renal disease	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Diabetes type 1 or type 2	27 (9.7)	0 (0.0)	299 (14.1)	27 (14.4)	2 (4.2)	6 (12.5)
Chronic lung disease	25 (9.0)	1 (25.0)	333 (15.7)	22 (11.7)	4 (8.3)	7 (14.6)
Chronic obstructive pulmonary disease	15 (5.4)	0 (0.0)	267 (12.6)	8 (4.3)	1 (2.1)	3 (6.3)
Charlson comorbidity index[a]						
Low (0)	103 (37.1)	0 (0.0)	628 (29.6)	54 (28.7)	18 (37.5)	14 (29.2)
Medium (1-2)	31 (11.2)	0 (0.0)	401 (18.9)	28 (14.9)	3 (6.3)	8 (16.7)
High (3+)	144 (51.8)	4 (100.0)	1,092 (51.5)	106 (56.4)	27 (56.3)	26 (54.2)
Oral antidiabetics and insulin	16 (5.8)	0 (0.0)	252 (11.9)	20 (10.6)	2 (4.2)	5 (10.4)
Any cardiovascular medications	122 (43.9)	0 (0.0)	1,459 (68.8)	117 (62.2)	19 (39.6)	31 (64.6)
Diuretics	57 (20.5)	0 (0.0)	680 (32.1)	39 (20.7)	11 (22.9)	14 (29.2)
Beta blockers	55 (19.8)	0 (0.0)	696 (32.8)	66 (35.1)	7 (14.6)	16 (33.3)
Calcium-channel blockers	42 (15.1)	0 (0.0)	557 (26.3)	43 (22.9)	3 (6.3)	10 (20.8)
Angiotensin converting enzyme inhibitors	42 (15.1)	0 (0.0)	515 (24.3)	31 (16.5)	6 (12.5)	7 (14.6)
Angiotensin II receptor antagonists	35 (12.6)	0 (0.0)	393 (18.5)	39 (20.7)	4 (8.3)	4 (8.3)
Statins	55 (19.8)	0 (0.0)	706 (33.3)	63 (33.5)	12 (25.0)	11 (22.9)
Steroids	176 (63.3)	1 (25.0)	1,339 (63.1)	106 (56.4)	46 (95.8)	33 (68.8)
Antibacterials for systemic use	209 (75.2)	1 (25.0)	1,700 (80.2)	126 (67.0)	41 (85.4)	34 (70.8)
Anticonvulsants	25 (9.0)	0 (0.0)	271 (12.8)	17 (9.0)	6 (12.5)	3 (6.3)
Antipsychotics	15 (5.4)	0 (0.0)	96 (4.5)	2 (1.1)	0 (0.0)	1 (2.1)
Anti-asthma medications	86 (30.9)	1 (25.0)	775 (36.5)	47 (25.0)	21 (43.8)	17 (35.4)
Ophthalmologicals	58 (20.9)	1 (25.0)	517 (24.4)	44 (23.4)	9 (18.8)	19 (39.6)

[a] Excluding lung cancer.
ILD interstitial lung disease.
Source: country-specific Supplemental Tables 2, Appendix 5.

Table 15.6 Baseline Comorbidity and Comedication among Patients with Primary Lung Cancer by Study Drug Group, US

	Study drug group					
Characteristics	Crizotinib (N= 178)	Ceritinib (N= 6)	Erlotinib (N= 836)	Gefitinib (N= 2)	Crizotinib and Ceritinib (N= 32)	Erlotinib and Gefitinib (N= 4)
Bradycardia	28 (15.7)	2 (33.3)	121 (14.5)	0 (0.0)	7 (21.9)	2 (50.0)
Hepatotoxicity	6 (3.4)	0 (0.0)	29 (3.5)	0 (0.0)	2 (6.3)	0 (0.0)
Pneumonitis/ILD	77 (43.3)	3 (50.0)	347 (41.5)	1 (50.0)	12 (37.5)	1 (25.0)
QT interval prolongation-related events	98 (55.1)	4 (66.7)	414 (49.5)	2 (100.0)	24 (75.0)	3 (75.0)
Vision disorders	19 (10.7)	2 (33.3)	85 (10.2)	0 (0.0)	8 (25.0)	0 (0.0)
Renal cysts	5 (2.8)	0 (0.0)	16 (1.9)	0 (0.0)	1 (3.1)	0 (0.0)
Edema	59 (33.1)	1 (16.7)	203 (24.3)	0 (0.0)	11 (34.4)	1 (25.0)
Leukopenia	48 (27.0)	1 (16.7)	313 (37.4)	0 (0.0)	9 (28.1)	3 (75.0)
Neuropathy	84 (47.2)	4 (66.7)	466 (55.7)	1 (50.0)	16 (50.0)	2 (50.0)
Photosensitivity	14 (7.9)	0 (0.0)	67 (8.0)	0 (0.0)	1 (3.1)	1 (25.0)
Malignant melanoma	0 (0.0)	0 (0.0)	9 (1.1)	0 (0.0)	1 (3.1)	0 (0.0)
Gastrointestinal perforation	10 (5.6)	0 (0.0)	81 (9.7)	1 (50.0)	4 (12.5)	1 (25.0)
Cardiac failure	14 (7.9)	1 (16.7)	70 (8.4)	0 (0.0)	5 (15.6)	1 (25.0)
Brain metastases	54 (30.3)	3 (50.0)	267 (31.9)	1 (50.0)	13 (40.6)	2 (50.0)
Hepatic impairment	43 (24.2)	0 (0.0)	158 (18.9)	1 (50.0)	6 (18.8)	0 (0.0)
Liver cirrhosis	19 (10.7)	0 (0.0)	61 (7.3)	0 (0.0)	2 (6.3)	0 (0.0)
Renal impairment	40 (22.5)	0 (0.0)	212 (25.4)	1 (50.0)	8 (25.0)	2 (50.0)
End-stage renal disease	1 (0.6)	0 (0.0)	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes type 1 or type 2	60 (33.7)	1 (16.7)	313 (37.4)	0 (0.0)	12 (37.5)	2 (50.0)
Chronic lung disease	56 (31.5)	3 (50.0)	384 (45.9)	0 (0.0)	10 (31.3)	1 (25.0)
Chronic obstructive pulmonary disease	27 (15.2)	2 (33.3)	290 (34.7)	0 (0.0)	6 (18.8)	1 (25.0)
Charlson comorbidity index[a]						
Low (0)	12 (6.7)	0 (0.0)	51 (6.1)	0 (0.0)	2 (6.3)	0 (0.0)
Medium (1-2)	11 (6.2)	0 (0.0)	63 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)
High (3+)	155 (87.1)	6 (100.0)	722 (86.4)	2 (100.0)	30 (93.8)	4 (100.0)
Oral antidiabetics and insulin	53 (29.8)	1 (16.7)	272 (32.5)	0 (0.0)	10 (31.3)	2 (50.0)
Any cardiovascular medications	79 (44.4)	2 (33.3)	344 (41.1)	1 (50.0)	12 (37.5)	2 (50.0)
Diuretics	33 (18.5)	1 (16.7)	158 (18.9)	0 (0.0)	6 (18.8)	0 (0.0)
Beta blockers	45 (25.3)	2 (33.3)	190 (22.7)	0 (0.0)	6 (18.8)	2 (50.0)
Calcium-channel blockers	22 (12.4)	1 (16.7)	132 (15.8)	1 (50.0)	3 (9.4)	1 (25.0)
Angiotensin converting enzyme inhibitors	27 (15.2)	0 (0.0)	106 (12.7)	1 (50.0)	4 (12.5)	2 (50.0)
Angiotensin II receptor antagonists	22 (12.4)	0 (0.0)	93 (11.1)	0 (0.0)	4 (12.5)	1 (25.0)
Statins	37 (20.8)	1 (16.7)	201 (24.0)	0 (0.0)	6 (18.8)	1 (25.0)
Steroids	100 (56.2)	1 (16.7)	487 (58.3)	1 (50.0)	14 (43.8)	2 (50.0)
Antibacterials for systemic use	115 (64.6)	4 (66.7)	570 (68.2)	2 (100.0)	15 (46.9)	3 (75.0)
Anticonvulsants	45 (25.3)	1 (16.7)	215 (25.7)	0 (0.0)	6 (18.8)	1 (25.0)
Antipsychotics	5 (2.8)	0 (0.0)	32 (3.8)	0 (0.0)	2 (6.3)	0 (0.0)
Anti-asthma medications	86 (48.3)	4 (66.7)	373 (44.6)	0 (0.0)	8 (25.0)	2 (50.0)
Ophthalmologicals	2 (1.1)	1 (16.7)	15 (1.8)	0 (0.0)	0 (0.0)	1 (25.0)

[a] Excluding lung cancer.
ILD interstitial lung disease.
Source: US Supplemental Table 2, Appendix 5.

Table 15.7 One-year Cumulative Incidence of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, Overall and EU Combined (Meta-analysis), and US

Endpoint	Population	Crizotinib			Erlotinib		
		n/N	Cumulative incidence, % (95% CI)	I^2 statistic, %	n/N	Cumulative incidence, % (95% CI)	I^2 statistic, %
Primary endpoints							
Bradycardia	Overall	18/427	2.7 (0.2 - 7.2)	70.1	57/2,803	1.0 (0.0 - 4.2)	96.4
	EU	4/277	1.1 (0.0 - 3.0)	0.0	5/2,088	0.1 (0.0 - 0.3)	8.2
	US	14/150	9.7 (5.5 - 15.1)		52/715	7.3 (5.5 - 9.4)	
Hepatotoxicity	Overall	5/456	0.2 (0.0 - 1.8)	41.6	36/2,957	0.4 (0.0 - 2.2)	94.1
	EU	0/278	0.0 (0.0 - 0.5)	0.0	2/2,121	0.0 (0.0 - 0.1)	0.0
	US	5/178	2.9 (1.1 - 6.2)		34/836	4.1 (2.9 - 5.6)	
Pneumonitis/ILD	Overall	36/322	9.8 (3.8 - 17.8)	70.9	221/2,301	7.8 (3.4 - 13.7)	94.6
	EU	15/221	6.8 (3.3 - 11.1)	4.2	122/1,812	5.8 (3.6 - 8.5)	72.9
	US	21/101	21.5 (14.0 - 30.1)		99/489	20.3 (16.9 - 24.0)	
QT interval prolongation-related events	Overall	25/348	4.5 (0.0 - 15.5)	90.3	116/2,466	3.2 (0.0 - 10.1)	97.7
	EU	4/268	1.0 (0.0 - 3.1)	0.0	28/2,044	1.2 (0.7 - 1.8)	0.0
	US	21/80	26.8 (17.6 - 36.9)		88/422	20.9 (17.1 - 24.9)	
Vision disorder	Overall	17/418	3.0 (0.9 - 6.0)	37.4	46/2,740	1.2 (0.4 - 2.5)	76.6
	EU	6/259	1.8 (0.3 - 4.2)	0.0	22/1,989	0.9 (0.3 - 1.6)	40.0
	US	11/159	7.0 (3.7 - 11.7)		24/751	3.2 (2.1 - 4.7)	
Secondary endpoints							
Renal cysts	Overall	0/451	0.0 (0.0 - 0.2)	0.0	2/2,940	0.0 (0.0 - 0.1)	0.0
	EU	0/278	0.0 (0.0 - 0.5)	0.0	0/2,120	0.0 (0.0 - 0.0)	0.0
	US	0/173	0.0 (0.0 - 0.0)		2/820	0.2 (0.1 - 0.8)	
Edema	Overall	13/456	2.2 (0.6 - 4.6)	30.4	39/2,957	1.1 (0.5 - 2.0)	64.2
	EU	5/278	1.3 (0.0 - 3.5)	7.6	23/2,121	0.9 (0.2 - 2.0)	64.7
	US	8/178	4.7 (2.2 - 8.6)		16/836	1.9 (1.1 - 3.0)	
Leukopenia	Overall	25/456	3.0 (0.2 - 7.7)	73.5	159/2,957	3.4 (0.1 - 10.1)	97.9
	EU	6/278	1.7 (0.2 - 3.9)	0.0	43/2,121	1.8 (0.1 - 5.3)	93.0
	US	19/178	11.1 (6.9 - 16.3)		116/836	13.9 (11.7 - 16.3)	
Neuropathy	Overall	37/345	8.8 (1.6 - 20.1)	86.5	204/2,240	8.4 (2.8 - 16.5)	96.6
	EU	14/251	5.1 (0.9 - 11.7)	61.0	123/1,870	5.9 (1.8 - 12.0)	94.1
	US	23/94	25.6 (17.1 - 34.9)		81/370	21.9 (17.9 - 26.3)	
Photosensitivity	Overall	1/456	0.0 (0.0 - 0.6)	0.0	130/2,957	2.5 (0.2 - 6.9)	96.5
	EU	0/278	0.0 (0.0 - 0.5)	0.0	42/2,121	1.3 (0.1 - 3.4)	87.1
	US	1/178	0.6 (0.1 - 2.9)		88/836	10.6 (8.6 - 12.7)	
Malignant melanoma	Overall	5/455	0.6 (0.0 - 1.9)	0.0	10/2,928	0.2 (0.0 - 0.6)	49.3
	EU	2/277	0.2 (0.0 - 1.6)	0.0	9/2,101	0.3 (0.0 - 0.8)	49.6
	US	3/178	1.8 (0.5 - 4.8)		1/827	0.1 (0.0 - 0.7)	
Gastrointestinal perforation	Overall	5/456	0.6 (0.0 - 1.8)	0.0	28/2,957	0.5 (0.0 - 1.7)	86.9
	EU	1/278	0.1 (0.0 - 1.2)	0.0	6/2,121	0.1 (0.0 - 0.4)	0.0
	US	4/178	2.3 (0.8 - 5.5)		22/836	2.6 (1.7 - 3.9)	
Cardiac failure	Overall	11/439	1.2 (0.0 - 3.7)	48.5	50/2,812	1.1 (0.1 - 2.9)	89.3
	EU	3/275	0.5 (0.0 - 2.1)	0.0	16/2,046	0.6 (0.2 - 1.2)	31.1
	US	8/164	5.0 (2.3 - 9.2)		34/766	4.5 (3.1 - 6.1)	
Death of all causes[a]	Overall	102/340	31.9 (26.8 - 37.2)	0.0	1,352/2,386	47.0 (35.5 - 58.7)	96.4
	EU	88/278	33.3 (27.6 - 39.2)	0.0	1,241/2,121	48.6 (36.2 - 61.0)	96.3
	US	14/62	25.6 (14.9 - 37.6)		111/265	41.9 (35.9 - 47.7)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
All estimates are computed excluding patients with corresponding prevalent conditions
CI confidence interval; EU European Union; ILD interstitial lung disease; US United States
n=number of cases, N=number at risk
Source: country-specific Supplemental Tables 3, Appendix 5.

Table 15.8 Two-year Cumulative Incidence of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, Overall and EU Combined (Meta-analysis), and US

Endpoint	Population	Crizotinib n/N	Crizotinib Cumulative incidence, % (95% CI)	Crizotinib I^2 statistic, %	Erlotinib n/N	Erlotinib Cumulative incidence, % (95% CI)	Erlotinib I^2 statistic, %
Primary endpoints							
Bradycardia	Overall	24/427	3.5 (0.0 - 11.1)	85.7	71/2,803	1.7 (0.0 - 6.2)	96.5
	EU	4/277	1.1 (0.0 - 3.0)	0.0	8/2,088	0.3 (0.0 - 0.7)	0.0
	US	20/150	16.9 (10.5 - 24.7)		63/715	9.5 (7.4 - 12.0)	
Hepatotoxicity	Overall	8/456	1.8 (0.4 - 3.8)	0.0	42/2,957	0.5 (0.0 - 2.7)	95.3
	EU	2/278	0.8 (0.0 - 3.1)	0.0	2/2,121	0.0 (0.0 - 0.1)	0.0
	US	6/178	3.8 (1.5 - 7.8)		40/836	5.2 (3.8 - 7.0)	
Pneumonitis/ILD	Overall	43/322	12.9 (4.7 - 24.0)	79.0	274/2,301	9.9 (3.9 - 18.0)	96.3
	EU	18/221	9.2 (4.5 - 15.0)	22.0	151/1,812	7.0 (3.8 - 11.1)	84.7
	US	25/101	30.6 (20.0 - 42.0)		123/489	27.4 (23.2 - 31.7)	
QT interval prolongation-related events	Overall	31/348	4.5 (0.0 - 15.5)	90.3	138/2,466	3.2 (0.0 - 10.1)	97.7
	EU	5/268	1.0 (0.0 - 3.1)	0.0	37/2,044	1.2 (0.7 - 1.8)	0.0
	US	21/80	26.8 (17.6 - 36.9)		88/422	20.9 (17.1 - 24.9)	
Vision disorder	Overall	23/418	4.2 (0.4 - 10.6)	76.8	56/2,740	1.6 (0.5 - 3.2)	83.2
	EU	7/259	2.2 (0.4 - 5.1)	9.0	27/1,989	1.1 (0.3 - 2.2)	61.7
	US	16/159	14.8 (8.3 - 23.1)		29/751	4.3 (2.9 - 6.0)	
Secondary endpoints							
Renal cysts	Overall	0/451	0.0 (0.0 - 0.2)	0.0	2/2,940	0.0 (0.0 - 0.1)	0.0
	EU	0/278	0.0 (0.0 - 0.5)	0.0	0/2,120	0.0 (0.0 - 0.0)	0.0
	US	0/173	0.0 (0.0 - 0.0)		2/820	0.2 (0.1 - 0.8)	
Edema	Overall	16/456	3.1 (0.6 - 7.0)	54.9	52/2,957	1.6 (0.5 - 3.0)	80.2
	EU	6/278	1.8 (0.0 - 5.3)	33.1	30/2,121	1.2 (0.2 - 2.7)	77.0
	US	10/178	6.8 (3.4 - 11.9)		22/836	3.1 (2.0 - 4.6)	
Leukopenia	Overall	30/456	4.8 (0.5 - 11.8)	80.8	190/2,957	4.2 (0.2 - 12.5)	98.3
	EU	8/278	2.2 (0.2 - 5.6)	28.4	51/2,121	2.2 (0.2 - 6.0)	93.4
	US	22/178	14.3 (9.1 - 20.6)		139/836	18.1 (15.4 - 21.0)	
Neuropathy	Overall	47/345	13.2 (3.5 - 27.3)	87.0	252/2,240	11.9 (4.8 - 21.6)	96.6
	EU	20/251	8.8 (1.9 - 19.1)	72.4	153/1,870	8.6 (3.8 - 14.9)	92.0
	US	27/94	32.7 (22.5 - 43.3)		99/370	28.8 (24.0 - 33.9)	
Photosensitivity	Overall	2/456	0.1 (0.0 - 0.8)	0.0	138/2,957	2.6 (0.2 - 7.5)	96.9
	EU	0/278	0.0 (0.0 - 0.5)	0.0	43/2,121	1.3 (0.1 - 3.5)	87.8
	US	2/178	1.3 (0.3 - 4.4)		95/836	11.8 (9.7 - 14.2)	
Malignant melanoma	Overall	5/455	0.6 (0.0 - 1.9)	0.0	13/2,928	0.4 (0.2 - 0.8)	0.0
	EU	2/277	0.2 (0.0 - 1.6)	0.0	11/2,101	0.4 (0.1 - 0.8)	0.0
	US	3/178	1.8 (0.5 - 4.8)		2/827	0.4 (0.1 - 1.3)	
Gastrointestinal perforation	Overall	6/456	0.7 (0.0 - 2.1)	12.2	33/2,957	0.7 (0.0 - 2.0)	85.4
	EU	1/278	0.1 (0.0 - 1.2)	0.0	8/2,121	0.3 (0.0 - 0.6)	0.0
	US	5/178	3.2 (1.2 - 6.9)		25/836	3.2 (2.1 - 4.7)	
Cardiac failure	Overall	13/439	1.3 (0.0 - 4.6)	64.8	66/2,812	1.6 (0.2 - 4.1)	91.7
	EU	3/275	0.5 (0.0 - 2.1)	0.0	24/2,046	0.9 (0.1 - 2.2)	70.9
	US	10/164	6.8 (3.4 - 11.7)		42/766	5.9 (4.3 - 7.8)	
Death of all causes[a]	Overall	130/340	42.3 (29.2 - 55.9)	78.4	1,657/2,386	61.1 (44.2 - 76.7)	98.2
	EU	113/278	43.9 (28.4 - 60.0)	80.5	1,529/2,121	64.2 (47.6 - 79.3)	97.9
	US	17/62	35.3 (21.5 - 49.3)		128/265	49.8 (43.4 - 55.8)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
All estimates are computed excluding patients with corresponding prevalent conditions.
CI confidence interval; EU European Union; ILD interstitial lung disease; US United States.
n=number of cases, N=number at risk.
For 3-year cumulative incidences (Denmark and the US) see Denmark Supplemental Table 3 and US Supplemental Table 3, Appendix 5.
Source: country-specific Supplemental Tables 3, Appendix 5.

Table 15.9 Three-year Cumulative Incidence Of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.10 Three-year Cumulative Incidences of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer Aged <65 Years at Index Date by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.11 Three-year Cumulative Incidences of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer Aged ≥65 Years at Index Date by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.12 Three-year Cumulative Incidences of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Brain Metastases at Baseline by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.13 Three-year Cumulative Incidences of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Brain Metastases at Baseline by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.14 Three-year Cumulative Incidences of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Hepatic Impairment at Baseline by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.15 Three-year Cumulative Incidences of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Hepatic Impairment at Baseline by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.16 Three-year Cumulative Incidences of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Renal Impairment at Baseline by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.17. Three-year Cumulative Incidences of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Renal Impairment at Baseline by Study Drug Group, Overall, EU Combined, US

Table not produced as 3-year follow-up is not available in all countries. Refer to country-specific Supplemental Output, Appendix 5.

Table 15.18. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

		Crizotinib			Erlotinib		
Endpoint	Population	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic, %	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic, %
Primary endpoints							
Bradycardia	Overall	25/439.3	30.9 (0.0 - 62.8)	77.6	75/2,500.5	19.4 (5.1 - 33.7)	93.2
	EU	4/297.3	12.0 (0.0 - 25.2)	0.0	10/1,853.5	5.0 (1.8 - 8.2)	0.0
	US	21/142.0	147.9 (91.5 - 226.0)		65/647.0	100.5 (77.5 - 128.1)	
Hepatotoxicity	Overall	9/475.6	11.5 (0.2 - 22.8)	10.6	45/2,632.0	6.6 (0.0 - 13.6)	90.3
	EU	2/300.5	7.2 (0.0 - 18.2)	0.0	2/1,885.5	1.1 (0.0 - 2.8)	0.0
	US	7/175.1	40.0 (16.1 - 82.4)		43/746.5	57.6 (41.7 - 77.6)	
Pneumonitis/ILD	Overall	44/323.0	105.3 (31.5 - 179.0)	79.5	293/1,997.9	119.1 (45.9 - 192.3)	96.9
	EU	18/228.3	64.9 (22.1 - 107.8)	36.0	163/1,582.0	74.3 (19.3 - 129.4)	94.4
	US	26/94.7	274.5 (179.3 - 402.2)		130/415.9	312.6 (261.2 - 371.2)	
QT interval prolongation-related events	Overall	31/357.1	42.0 (0.0 - 87.1)	84.2	147/2,180.7	57.2 (22.1 - 92.3)	96.1
	EU	5/287.7	13.9 (0.0 - 28.4)	0.0	39/1,816.0	17.5 (6.5 - 28.4)	62.5
	US	26/69.4	374.6 (244.7 - 548.9)		108/364.7	296.1 (242.9 - 357.5)	
Vision disorder	Overall	24/426.8	35.9 (1.7 - 70.1)	73.8	61/2,422.7	18.7 (5.2 - 32.1)	83.4
	EU	7/278.2	15.9 (0.0 - 33.3)	11.1	29/1,753.8	12.5 (2.9 - 22.1)	63.9
	US	17/148.6	114.4 (66.7 - 183.2)		32/668.9	47.8 (32.7 - 67.5)	
Secondary endpoints							
Renal cysts	Overall	0/477.1	0.0 (0.0 - 5.6)	0.0	2/2,642.0	0.3 (0.0 - 1.4)	0.0
	EU	0/301.8	0.0 (0.0 - 8.0)	0.0	0/1,885.4	0.0 (0.0 - 1.2)	0.0
	US	0/175.3	0.0 (0.0 - 21.0)		2/756.6	2.6 (0.3 - 9.5)	
Edema	Overall	16/473.4	26.8 (5.8 - 47.7)	45.3	58/2,627.8	18.0 (5.4 - 30.7)	82.5
	EU	6/299.7	13.2 (0.2 - 26.1)	0.0	32/1,867.3	13.8 (1.8 - 25.8)	75.8
	US	10/173.7	57.6 (27.6 - 105.8)		26/760.5	34.2 (22.3 - 50.1)	
Leukopenia	Overall	30/468.8	42.4 (5.4 - 79.3)	75.5	199/2,517.2	66.0 (25.5 - 106.5)	97.5
	EU	8/298.7	21.3 (3.6 - 38.9)	0.0	52/1,853.8	24.9 (3.7 - 46.0)	90.4
	US	22/170.1	129.4 (81.1 - 195.9)		147/663.4	221.6 (187.2 - 260.4)	
Neuropathy	Overall	49/347.4	115.3 (30.3 - 200.3)	87.5	270/1,905.0	146.6 (64.0 - 229.3)	96.8
	EU	20/266.2	60.4 (4.3 - 116.5)	70.8	161/1,627.9	90.7 (28.8 - 152.7)	94.4
	US	29/81.2	357.0 (239.1 - 512.7)		109/277.1	393.3 (323.0 - 474.5)	
Photosensitivity	Overall	3/478.0	2.5 (0.0 - 9.9)	0.0	143/2,498.9	41.1 (9.4 - 72.9)	96.2
	EU	0/301.8	0.0 (0.0 - 8.0)	0.0	45/1,834.7	17.4 (0.0 - 35.2)	87.8
	US	3/176.2	17.0 (3.5 - 49.8)		98/664.2	147.6 (119.8 - 179.8)	
Malignant melanoma	Overall	5/475.8	6.9 (0.0 - 16.3)	0.0	13/2,619.3	3.7 (1.3 - 6.0)	0.0
	EU	2/299.7	3.8 (0.0 - 14.5)	0.0	11/1,856.1	4.6 (1.3 - 7.8)	3.5
	US	3/176.1	17.0 (3.5 - 49.8)		2/763.2	2.6 (0.3 - 9.5)	
Gastrointestinal perforation	Overall	6/475.9	6.4 (0.0 - 15.4)	1.9	35/2,627.6	8.4 (0.8 - 16.0)	80.5
	EU	1/301.7	3.1 (0.0 - 12.6)	0.0	8/1,879.9	4.2 (1.2 - 7.2)	0.0
	US	5/174.2	28.7 (9.3 - 67.0)		27/747.7	36.1 (23.8 - 52.5)	
Cardiac failure	Overall	14/465.0	18.4 (0.0 - 37.0)	44.4	73/2,521.9	22.6 (6.2 - 39.0)	88.9
	EU	4/298.9	11.3 (0.0 - 25.0)	0.0	27/1,822.0	12.9 (4.6 - 21.2)	53.2
	US	10/166.1	60.2 (28.9 - 110.7)		46/699.9	65.7 (48.1 - 87.7)	
Death of all causes[a]	Overall	134/357.9	329.7 (227.7 - 431.7)	63.7	1,726/2,092.9	657.8 (263.8 - 1,051.8)	99.3
	EU	117/301.8	334.2 (206.1 - 462.4)	71.8	1,594/1,885.7	663.0 (190.0 - 1,136.1)	99.5
	US	17/56.1	302.9 (176.5 - 485.0)		132/207.2	637.0 (533.0 - 755.5)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations..
All estimates are computed excluding patients with corresponding prevalent conditions.
CI confidence interval; EU European Union; ILD interstitial lung disease; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 12, Appendix 5.

Table 15.19. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer Aged <65 Years at Index Date by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	75/241.8	281.6 (195.2 - 368.1)	37.5	629/809.3	650.6 (322.9 - 978.4)	97.3
	EU	59/191.8	271.0 (161.8 - 380.3)	51.2	526/646.8	655.4 (232.3 - 1,078.4)	98.0
	US	16/50.0	c		103/162.5	633.7 (517.2 - 768.5)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 13, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.20. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer Aged ≥65 Years at Index Date by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	59/116.1	388.7 (187.3 - 590.1)	64.7	1,097/1,283.6	661.3 (201.9 - 1,120.7)	99.2
	EU	58/110.0	436.8 (218.1 - 655.5)	65.5	1,068/1,238.9	664.2 (140.7 - 1,187.7)	99.4
	US	1/6.1	163.1 (4.1 - 908.9)		29/44.7	649.3 (434.8 - 932.5)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 14, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.21. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Brain Metastases at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	20/39.1	424.7 (220.4 - 629.0)	0.0	249/197.3	1,130.4 (805.6 - 1,455.3)	74.1
	EU	15/24.5	495.6 (216.7 - 774.5)	0.0	200/144.6	1,194.1 (815.4 - 1,572.7)	69.8
	US	5/14.6	342.6 (111.2 - 799.4)		49/52.7	929.7 (687.8 - 1,229.1)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 15, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.22. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Brain Metastases at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	114/318.8	310.8 (208.7 - 412.9)	61.2	1,477/1,895.6	610.5 (208.3 - 1,012.8)	99.4
	EU	102/277.3	313.6 (187.3 - 439.8)	70.2	1,394/1,741.1	628.8 (149.9 - 1,107.6)	99.5
	US	12/41.5	289.0 (149.3 - 504.8)		83/154.5	537.2 (427.9 - 666.0)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 16, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.23. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Hepatic Impairment at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	9/19.0	401.4 (116.6 - 686.2)	0.0	56/59.5	714.5 (153.4 - 1,275.6)	86.8
	EU	6/9.2	600.4 (100.1 - 1,100.8)	0.0	26/28.9	643.4 (0.0 - 1,304.4)	83.9
	US	3/9.8	306.0 (63.1 - 894.2)		30/30.6	980.7 (661.7 - 1,400.0)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 17, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.24. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Hepatic Impairment at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	125/338.9	321.6 (215.3 - 427.8)	65.5	1,670/2,033.4	647.8 (257.7 - 1,038.0)	99.3
	EU	111/292.6	324.4 (192.2 - 456.5)	73.7	1,568/1,856.8	665.4 (197.0 - 1,133.7)	99.4
	US	14/46.3	302.3 (165.3 - 507.2)		102/176.6	577.5 (470.9 - 701.1)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 18, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.25. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Renal Impairment at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	6/12.0	394.3 (21.0 - 767.6)	0.0	101/125.7	709.8 (411.9 - 1,007.8)	74.0
	EU	3/4.3	408.7 (0.0 - 1,110.2)	0.0	71/86.5	698.1 (292.7 - 1,103.4)	79.8
	US	3/7.7	388.6 (80.1 - 1,135.5)		30/39.2	766.1 (516.9 - 1,093.7)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 19, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.26. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Renal Impairment at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = Total Follow-up)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	128/345.8	321.9 (215.9 - 428.0)	65.8	1,625/1,967.2	655.6 (245.0 - 1,066.1)	99.3
	EU	114/297.4	327.9 (196.3 - 459.5)	73.3	1,523/1,799.2	667.7 (178.4 - 1,156.9)	99.5
	US	14/48.4	289.3 (158.1 - 485.3)		102/168.0	607.0 (494.9 - 736.8)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 20, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.27. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer by Study Drug Group, United States, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic
Primary endpoints							
Bradycardia	Overall	19/321.6	33.6 (0.0 - 70.0)	70.4	43/1,586.0	14.1 (1.3 - 27.0)	89.6
	EU	3/209.1	12.0 (0.0 - 27.7)	0.0	4/1,163.7	2.3 (0.0 - 5.3)	0.0
	US	16/112.5	142.2 (81.3 - 231.0)		39/422.3	92.3 (65.7 - 126.2)	
Hepatotoxicity	Overall	6/349.2	8.8 (0.0 - 22.9)	15.4	30/1,658.1	6.9 (0.0 - 15.6)	86.2
	EU	1/212.3	2.3 (0.0 - 14.1)	0.0	1/1,183.6	0.5 (0.0 - 2.7)	0.0
	US	5/136.9	36.5 (11.9 - 85.2)		29/474.5	61.1 (40.9 - 87.8)	
Pneumonitis/ILD	Overall	34/236.1	100.9 (20.2 - 181.6)	76.3	184/1,269.9	115.6 (40.1 - 191.1)	95.2
	EU	13/162.0	60.2 (8.8 - 111.7)	37.6	92/992.9	67.4 (16.6 - 118.2)	89.2
	US	21/74.1	283.2 (175.3 - 432.9)		92/277.0	332.2 (267.8 - 407.4)	
QT interval prolongation-related events	Overall	28/261.6	56.2 (0.0 - 114.9)	81.2	95/1,399.0	53.4 (15.8 - 91.0)	93.5
	EU	5/202.2	21.5 (0.1 - 42.8)	0.0	24/1,140.4	20.1 (11.7 - 28.5)	0.0
	US	23/59.4	387.0 (245.3 - 580.7)		71/258.6	274.6 (214.5 - 346.3)	
Vision disorder	Overall	23/313.4	47.6 (4.4 - 90.8)	67.0	37/1,521.7	19.1 (6.6 - 31.7)	65.6
	EU	7/195.7	25.0 (1.5 - 48.5)	0.0	21/1,092.0	14.9 (3.2 - 26.6)	52.1
	US	16/117.7	135.9 (77.7 - 220.7)		16/429.7	37.2 (21.3 - 60.5)	
Secondary endpoints							
Renal cysts	Overall	0/348.6	0.0 (0.0 - 7.5)	0.0	2/1,661.7	0.4 (0.0 - 2.3)	0.0
	EU	0/213.0	0.0 (0.0 - 11.0)	0.0	0/1,183.4	0.0 (0.0 - 2.0)	0.0
	US	0/135.6	0.0 (0.0 - 27.2)		2/478.3	4.2 (0.5 - 15.1)	
Edema	Overall	15/346.6	34.1 (6.0 - 62.2)	44.9	37/1,653.7	19.4 (4.6 - 34.2)	77.3
	EU	5/211.4	15.5 (0.0 - 32.2)	0.0	22/1,172.5	16.0 (0.0 - 32.0)	73.2
	US	10/135.2	74.0 (35.5 - 136.0)		15/481.2	31.2 (17.4 - 51.4)	
Leukopenia	Overall	18/346.9	36.3 (6.1 - 66.5)	47.6	119/1,643.2	55.1 (19.4 - 90.7)	96.3
	EU	5/211.7	21.6 (0.7 - 42.5)	0.0	26/1,180.5	17.4 (0.0 - 36.2)	85.1
	US	13/135.2	96.2 (51.2 - 164.4)		93/462.7	201.0 (162.2 - 246.2)	
Neuropathy	Overall	39/254.7	104.3 (16.8 - 191.9)	82.4	173/1,234.0	140.1 (57.7 - 222.4)	94.1
	EU	13/186.2	53.1 (8.9 - 97.3)	32.3	97/1,032.5	88.8 (35.3 - 142.3)	85.3
	US	26/68.5	379.5 (247.9 - 556.0)		76/201.5	377.2 (297.2 - 472.1)	
Photosensitivity	Overall	1/350.3	2.7 (0.0 - 11.4)	0.0	129/1,577.6	58.3 (11.5 - 105.0)	95.4
	EU	0/213.0	0.0 (0.0 - 11.0)	0.0	44/1,152.3	26.9 (0.0 - 54.0)	85.5
	US	1/137.3	7.3 (0.2 - 40.6)		85/425.3	199.9 (159.6 - 247.1)	
Malignant melanoma	Overall	5/348.2	11.1 (0.0 - 24.4)	0.0	8/1,647.3	3.2 (0.0 - 7.0)	27.1
	EU	2/211.8	6.7 (0.0 - 22.5)	0.0	6/1,166.8	3.7 (0.0 - 9.4)	38.5
	US	3/136.4	22.0 (4.5 - 64.3)		2/480.5	4.2 (0.5 - 15.0)	
Gastrointestinal perforation	Overall	5/348.0	9.4 (0.0 - 21.7)	0.0	20/1,652.2	6.6 (0.0 - 14.9)	77.9
	EU	1/213.0	5.0 (0.0 - 18.5)	0.0	4/1,181.2	1.4 (0.0 - 4.7)	13.0
	US	4/135.0	29.6 (8.1 - 75.9)		16/471.0	34.0 (19.4 - 55.2)	
Cardiac failure	Overall	9/339.3	12.7 (0.0 - 32.2)	39.8	40/1,588.6	20.6 (6.3 - 35.0)	76.1
	EU	1/211.3	5.0 (0.0 - 18.6)	0.0	16/1,143.4	11.4 (5.2 - 17.6)	0.0
	US	8/128.0	62.5 (27.0 - 123.2)		24/445.2	53.9 (34.5 - 80.2)	
Death of all causes[a]	Overall	67/254.2	246.2 (183.4 - 309.1)	4.7	790/1,320.6	481.4 (268.4 - 694.5)	96.6
	EU	59/213.0	258.2 (183.7 - 332.8)	12.9	718/1,183.7	470.5 (212.8 - 728.2)	97.5
	US	8/41.2	194.0 (83.8 - 382.3)		72/136.9	526.1 (411.6 - 662.5)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
All estimates are computed excluding patients with corresponding prevalent conditions.
CI confidence interval; EU European Union; ILD interstitial lung disease; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 12, Appendix 5.

Table 15.28. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer Aged <65 Years at Index Date by Study Drug Group, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	36/172.2	176.4 (99.8 - 252.9)	31.8	288/498.9	482.5 (294.5 - 670.6)	88.9
	EU	29/136.9	171.8 (74.4 - 269.3)	47.8	230/396.3	461.3 (223.1 - 699.4)	91.5
	US	7/35.3	198.1 (79.7 - 408.2)		58/102.6	565.1 (429.1 - 730.5)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 13, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.29. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer Aged ≥65 Years at Index Date by Study Drug Group, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	31/82.1	310.2 (152.4 - 468.1)	32.6	502/821.6	458.6 (193.6 - 723.6)	96.7
	EU	30/76.2	341.6 (153.1 - 530.1)	42.2	488/787.4	469.8 (163.9 - 775.8)	97.5
	US	1/5.9	169.4 (4.3 - 943.9)		14/34.2	409.0 (223.6 - 686.3)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 14, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.30. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Brain Metastases at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	11/22.2	436.9 (149.8 - 724.0)	0.0	147/136.6	1,017.1 (809.3 - 1,224.9)	26.2
	EU	7/13.5	421.5 (49.1 - 794.0)	0.0	116/102.5	1,041.2 (771.5 - 1,310.9)	34.6
	US	4/8.7	459.4 (125.2 - 1,176.3)		31/34.1	909.8 (618.1 - 1,291.3)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 15, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.31. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Brain Metastases at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	56/232.0	215.9 (144.7 - 287.1)	25.4	643/1,183.9	425.6 (216.5 - 634.8)	96.6
	EU	52/199.5	249.7 (180.4 - 319.1)	0.0	602/1,081.1	432.0 (180.5 - 683.5)	97.4
	US	4/32.5	123.0 (33.5 - 314.9)		41/102.8	398.9 (286.2 - 541.1)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 16, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.32. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Hepatic Impairment at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	5/16.7	257.4 (13.9 - 500.9)	0.0	34/38.7	718.0 (201.9 - 1,234.1)	68.3
	EU	3/7.3	354.0 (0.0 - 785.9)	0.0	14/18.9	597.5 (6.7 - 1,188.2)	57.2
	US	2/9.4	212.4 (25.7 - 767.3)		20/19.8	1,012.5 (618.4 - 1,563.7)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 17, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.33. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Hepatic Impairment at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib			Erlotinib		
		n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic	n/PY	Incidence rate per 1,000 PY (95% CI)	I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	62/237.5	241.3 (175.9 - 306.7)	7.2	756/1,281.9	465.3 (254.5 - 676.0)	96.5
	EU	56/205.7	249.9 (172.0 - 327.9)	19.1	704/1,164.8	470.3 (215.8 - 724.8)	97.3
	US	6/31.8	188.6 (69.2 - 410.4)		52/117.1	444.0 (331.6 - 582.3)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 18, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.34. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer with Renal Impairment at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	4/10.3	274.7 (0.0 - 628.5)	0.0	49/81.9	569.9 (232.0 - 907.8)	75.6
	EU	2/3.2	245.8 (0.0 - 1,082.3)	0.0	33/53.2	594.9 (109.7 - 1,080.1)	79.5
	US	2/7.1	281.0 (34.0 - 1,014.9)		16/28.7	557.4 (318.6 - 905.1)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 19, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.35. Incidence Rates of the Primary and Secondary Endpoints among Patients with Primary Lung Cancer without Renal Impairment at Baseline by Study Drug Group, Overall, EU Combined, US (Time at Risk = On-treatment Period)

Endpoint	Population	Crizotinib n/PY	Crizotinib Incidence rate per 1,000 PY (95% CI)	Crizotinib I^2 statistic	Erlotinib n/PY	Erlotinib Incidence rate per 1,000 PY (95% CI)	Erlotinib I^2 statistic
Secondary endpoints							
Death of all causes[a]	Overall	63/243.9	241.4 (179.2 - 303.6)	1.3	741/1,238.7	478.4 (243.9 - 713.0)	97.1
	EU	57/209.8	257.2 (188.3 - 326.1)	0.5	685/1,130.5	469.0 (189.4 - 748.5)	97.8
	US	6/34.1	175.9 (64.5 - 382.8)		56/108.2	517.7 (391.1 - 672.3)	

[a] Data on death may be incomplete in the Netherlands; in the US, only patients with complete data on death are included in computations.
CI confidence interval; EU European Union; US United States.
n=number of cases, PY=person-years.
Source: country-specific Supplemental Tables 20, Appendix 5.
Output on endpoints other than Death of All Causes not produced owing to low number of events.

Table 15.36. Baseline Characteristics and Comorbidity of Patients with a Dispensing/Prescription for Crizotinib without a Diagnosis of Primary Lung Cancer, Overall

DENMARK	Crizotinib dispensing/prescription (N=4)
Age group, years, n (%)	
<50	4 (100.0)
50 to 59	0 (0.0)
60 to 69	0 (0.0)
70 to 79	0 (0.0)
80+	0 (0.0)
Unknown	0 (0.0)
Age, years	
Mean (standard deviation)	25.4 (18.9)
Median (range)	25.6 (5.9-44.3)
Sex, n (%)	
Women	0 (0.0)
Men	4 (100.0)
Year of crizotinib initiation, n (%)	
Before 2011	Suppressed ≤3*
2011-2012	Suppressed ≤3
2013-2014	Suppressed ≤3
2015-2016	Suppressed ≤3
Cancer diagnoses up to 5 years before crizotinib initiation, n (%)	Suppressed ≤3 (4 different diagnoses)
Charlson Comorbidity Index score, (%)	
Low (0)	Suppressed ≤3
Medium (1,2)	Suppressed ≤3
High (3+)	Suppressed ≤3

Reporting suppressed to avoid identification of individuals
Source: Denmark Supplemental Table 21, Appendix 5.

FINLAND: Results not reported for the purpose of protecting identification of individuals based on the local law

SWEDEN	Crizotinib dispensing/prescription (N=25)
Age group, years, n (%)	
<50	7 (28.0)
50 to 59	4 (16.0)
60 to 69	8 (32.0)
70 to 79	4 (16.0)
80+	2 (8.0)
Age at index date, years	
Mean (standard deviation)	57.8 (17.5)
Median (range)	64.0 (14.0 - 86.0)
Sex, n (%)	
Men	11 (44.0)
Women	14 (56.0)
Year of crizotinib initiation, n (%)	
2014	3 (12.0)
2015	4 (16.0)
2016	18 (72.0)
Lung cancer diagnosis in the Swedish Patient Register (prior to index date), n (%)*	24 (96.0)
Any cancer diagnosis in cancer register (prior to index date), n (%)	6 (24.0)
Charlson Comorbidity Index score, n (%)	
Low (0)	8 (32.0)
Medium (1,2)	3 (12.0)
High (3+)	14 (56.0)

Source: Sweden Supplemental Table 21, Appendix 5.

* In the inclusion criteria the Swedish Cancer Register was used to define primary lung cancer. The register was only updated to 31 Dec 2015 at the time of data extraction. But cohort inclusion ended 30 Jun 2016. Hence some of the patients with index dates in 2016 were regarded as having no lung cancer diagnosis, even though there might be lung cancer diagnosis registered in the cancer register after the data extraction.

THE NETHERLANDS	Crizotinib dispensing/prescription (N=2)
Age group, years, n (%)	
<50	2 (100.0)
50 to 59	0 (0.0)
60 to 69	0 (0.0)
70 to 79	0 (0.0)
80+	0 (0.0)
Age, years	
Mean (standard deviation)	16.7 (11.3)
Median (range)	16.7 (8.7-24.7)
Sex, n (%)	
Women	2 (100.0)
Men	0 (0.0)
Year of crizotinib initiation, n (%)	
Before 2011	0 (0.0)
2011-2012	0 (0.0)
2013-2014	0 (0.0)
2015-2016	2 (100.0)
Charlson Comorbidity Index score, (%)	
Low (0)	0 (0.0)
Medium (1,2)	2 (100.0)
High (3+)	0 (0.0)

Source: The Netherlands Supplemental Table 21, Appendix 5.

	Persons with crizotinib dispensing/prescription (N=25)
UNITED STATES	
Age group, years, n (%)	
<50	17 (68.0)
50 to 59	4 (16.0)
60 to 69	4 (16.0)
70 to 79	0 (0.0)
80+	0 (0.0)
Age, years	
Mean (standard deviation)	33.8 (21.1)
Median (range)	31.0 (14.0- 53.0)
Sex, n (%)	
Men	17 (68.0)
Women	8 (32.0)
Race/ethnicity, n (%)	
Asian	0 (0.0)
Black	3 (12.0)
Hispanic	1 (4.0)
White	21 (84.0)
Unknown	0 (0.0)
Year of Crizotinib initiation following cancer diagnosis, n (%)	
2011-2012	4 (16.0)
2013-2014	11 (44.0)
2015-2016	10 (40.0)
Cancer diagnoses up to 5 years before Crizotinib initiation, n (%)	
Other and Unspecified Malignant Neoplasms (C69-C80)	19 (76.0)
Digestive (C15-C26)	11 (44.0)
Lymphoid and hematopoietic (C81-C96)	10 (40.0)
Bone and connective tissue (C40-C41, C47)	9 (36.0)
Metastatic Lung Cancer	6 (24.0)
Respiratory (C30-C39, C45)	4 (16.0)
Genital (C51-C63)	3 (12.0)
Neuroendocrine (C7A-C7B)	3 (12.0)
Oral (C00-C14)	2 (8.0)
Skin (C43-C44)	1 (4.0)
Breast (C50)	1 (4.0)
Charlson Comorbidity Index score, n (%)	
Low (0)	0 (0.0)
Medium (1,2)	4 (16.0)
High (3+)	21 (84.0)

Source: US Supplemental Table 21, Appendix 5.

Table 15.37. Validity of Diagnostic Codes for Bradycardia among 208 Primary Lung Cancer Patients in the Crizotinib Group and a Matched Sample of 194 Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Noncases)

			Source of reporting							
Analysis set	Country	Total	Medical record= Y, Database ICD codes=Y	Medical record= N, Database ICD codes=Y	Medical record= Y, Database ICD codes=N	Medical record= N, Database ICD codes=N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Bradycardia, Overall										
	Denmark	91	1	0	1	89	0.50 (0.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	0.99 (0.97 - 1.00)
	Finland	15	0	0	2	13	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.87 (0.69 - 1.00)
	Sweden	195	1	1	2	191	0.33 (0.00 - 0.87)	0.99 (0.98 - 1.00)	0.50 (0.00 - 1.00)	0.99 (0.98 - 1.00)
	United States	101	1	12	9	79	0.10 (0.00 - 0.29)	0.87 (0.80 - 0.94)	0.08 (0.00 - 0.22)	0.90 (0.83 - 0.96)

CI confidence interval
ICD International Classification of Diseases
NPV negative predictive value
PPV positive predictive value
Y=yes, N=No
Results from the Netherlands were not available at the time of the analysis
Stratification on severity not possible because of sparse data

Table 15.38. Validity of Diagnostic Codes for Bradycardia among 208 Primary Lung Cancer Patients in the Crizotinib Group and a Matched Sample of 194 Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Cases)

			Source of reporting							
Analysis set	Country	Total	Medical record= Y, Database ICD codes=Y	Medical record= N, Database ICD codes=Y	Medical record= Y, Database ICD codes=N	Medical record= N, Database ICD codes=N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Bradycardia, Overall										
	Denmark	91	1	0	1	89	0.50 (0.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	0.99 (0.97 - 1.00)
	Finland	15	0	0	2	13	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.87 (0.69 - 1.00)
	Sweden	195	1	1	2	191	0.33 (0.00 - 0.87)	0.99 (0.98 - 1.00)	0.50 (0.00 - 1.00)	0.99 (0.98 - 1.00)
	United States	101	1	12	9	79	0.10 (0.00 - 0.29)	0.87 (0.80 - 0.94)	0.08 (0.00 - 0.22)	0.90 (0.83 - 0.96)

CI confidence interval
ICD International Classification of Diseases
NPV negative predictive value
PPV positive predictive value
Y=yes, N=No
Results from the Netherlands were not available at the time of the analysis
Stratification on severity not possible because of sparse data

Table 15.39. Validity of Diagnostic Codes for Hepatotoxicity among 81 Primary Lung Cancer Patients in the Crizotinib Group and a Matched Sample of 70 Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Noncases)

			Source of reporting							
Analysis set	Country	Total	Medical record=Y, Database ICD codes=Y	Medical record=N, Database ICD codes=Y	Medical record=Y, Database ICD codes=N	Medical record=N, Database ICD codes=N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Hepatotoxicity, Overall										
	Denmark	3	0	0	0	3	-	1.00 (1.00 - 1.00)	-	1.00 (1.00 - 1.00)
	Finland	10	0	0	2	8	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.80 (0.55 - 1.00)
	Sweden	69	0	0	7	62	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.90 (0.83 - 0.97)
	United States	69	0	4	0	65	-	0.94 (0.89 - 1.00)	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)

CI confidence interval
ICD International Classification of Diseases
NPV negative predictive value
PPV positive predictive value
Y=yes, N=No
Results from the Netherlands were not available at the time of the analysis
Stratification on severity not possible because of sparse data

Table 15.40. Validity of Diagnostic Codes for Hepatotoxicity among 81 Primary Lung Cancer Patients in the Crizotinib Group and a Matched Sample of 70 Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Cases)

			Source of reporting							
Analysis set	Country	Total	Medical record=Y, Database ICD codes=Y	Medical record=N, Database ICD codes=Y	Medical record=Y, Database ICD codes=N	Medical record=N, Database ICD codes=N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Hepatotoxicity, Overall										
	Denmark	3	0	0	1	2	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.67 (0.13 - 1.00)
	Finland	10	0	0	9	1	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.10 (0.00 - 0.29)
	Sweden	69	0	0	44	25	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.36 (0.25 - 0.48)
	United States	69	4	0	40	25	0.09 (0.01 - 0.18)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	0.38 (0.27 - 0.50)

CI confidence interval
ICD International Classification of Diseases
NPV negative predictive value
PPV positive predictive value
Y=yes, N=No
Results from the Netherlands were not available at the time of the analysis
Stratification on severity not possible because of sparse data

Table 15.41. Validity of Diagnostic Codes for Pneumonitis/ILD among 194 Primary Lung Cancer Patients in the Crizotinib Group and a Matched Sample of 186 Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Noncases)

			Source of reporting							
Analysis set	Country	Total	Medical record=Y Database ICD codes=Y	Medical record=N Database ICD codes=Y	Medical record=Y Database ICD codes=N	Medical record=N Database ICD codes=N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Pneumonitis/ILD										
	Denmark	91	0	12	1	78	0.00 (0.00 - 0.00)	0.87 (0.80 - 0.94)	0.00 (0.00 - 0.00)	0.99 (0.96 - 1.00)
	Finland	15	0	0	0	15	-	1.00 (1.00 - 1.00)	-	1.00 (1.00 - 1.00)
	Sweden	177	0	26	0	151	-	0.85 (0.80 - 0.91)	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)
	United States	97	0	17	1	79	0.00 (0.00 - 0.00)	0.82 (0.75 - 0.90)	0.00 (0.00 - 0.00)	0.99 (0.96 - 1.00)

CI confidence interval
ICD International Classification of Diseases
NPV negative predictive value
PPV positive predictive value
Y=yes, N=No
Results from the Netherlands were not available at the time of the analysis

Table 15.42. Validity of Diagnostic Codes for Pneumonitis/ILD among 194 Primary Lung Cancer Patients in the Crizotinib Group and a Matched Sample of 186 Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Cases)

			Source of reporting							
Analysis set	Country	Total	Medical record=Y Database ICD codes=Y	Medical record=N Database ICD codes=Y	Medical record=Y Database ICD codes=N	Medical record=N Database ICD codes=N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Pneumonitis/ILD										
	Denmark	91	0	12	2	77	0.00 (0.00 - 0.00)	0.87 (0.79 - 0.94)	0.00 (0.00 - 0.00)	0.97 (0.94 - 1.00)
	Finland	15	0	0	0	15	-	1.00 (1.00 - 1.00)	-	1.00 (1.00 - 1.00)
	Sweden	177	2	24	4	147	0.33 (0.00 - 0.71)	0.86 (0.81 - 0.91)	0.08 (0.00 - 0.18)	0.97 (0.95 - 1.00)
	United States	97	1	16	6	74	0.14 (0.00 - 0.40)	0.82 (0.74 - 0.90)	0.06 (0.00 - 0.17)	0.93 (0.87 - 0.98)

CI confidence interval
ICD International Classification of Diseases
NPV negative predictive value
PPV positive predictive value
Y=yes, N=No
Results from the Netherlands were not available at the time of the analysis

Table 15.43. Validity of Diagnostic Codes for QT Interval Prolongation-related Conditions among Primary Lung Cancer Patients in the Crizotinib Group and a Matched Sample of Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Noncases)

Validation of QT interval prolongation-related events was not feasible owing to unavailability of electrocardiogram data from the medical charts.

Table 15.44. Validity of Diagnostic Codes for QT Interval Prolongation-related Conditions among Primary Lung Cancer Patients in the Crizotinib Group and a Matched Sample of Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Cases)

Validation of QT interval prolongation-related events was not feasible owing to unavailability of the required electrocardiogram data from the medical charts.

Table 15.45. Validity of Diagnostic Codes for Vision Disorders among 197 Lung Cancer Patients in the Crizotinib Group and a Matched Sample of 191 Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Noncases)

			Source of reporting							
Analysis set	Country	Total	Medical record=Y, Database ICD codes=Y	Medical record=N, Database ICD codes=Y	Medical record=Y, Database ICD codes=N	Medical record=N, Database ICD codes=N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Vision Disorders, Overall										
	Denmark	90	0	0	2	88	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.98 (0.95 - 1.00)
	Finland	13	0	2	0	11	-	0.85 (0.65 - 1.00)	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)
	Sweden	186	0	4	2	180	0.00 (0.00 - 0.00)	0.98 (0.96 - 1.00)	0.00 (0.00 - 0.00)	0.99 (0.97 - 1.00)
	United States	99	1	6	2	90	0.33 (0.00 - 0.87)	0.94 (0.89 - 0.99)	0.14 (0.00 - 0.40)	0.98 (0.95 - 1.00)

CI confidence interval
ICD International Classification of Diseases
NPV negative predictive value
PPV positive predictive value
Y=yes, N=No
Results from the Netherlands were not available at the time of the analysis

Table 15.46. Validity of Diagnostic Codes for Vision Disorders among 197 Lung Cancer Patients in the Crizotinib Group and a Matched Sample of 191 Primary Lung Cancer Patients from Other Study Drug Groups (Possible Cases Count as Cases)

			Source of reporting							
Analysis set	Country	Total	Medical record=Y, Database ICD codes=Y	Medical record=N, Database ICD codes=Y	Medical record=Y, Database ICD codes=N	Medical record=N, Database ICD codes=N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Vision Disorders, Overall										
	Denmark	90	0	0	5	85	0.00 (0.00 - 0.00)	1.00 (1.00 - 1.00)	-	0.94 (0.90 - 0.99)
	Finland	13	2	0	0	11	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
	Sweden	186	2	2	30	152	0.06 (0.00 - 0.15)	0.99 (0.97 - 1.00)	0.50 (0.01 - 0.99)	0.84 (0.78 - 0.89)
	United States	99	5	2	16	76	0.24 (0.06 - 0.42)	0.97 (0.94 - 1.00)	0.71 (0.38 - 1.00)	0.83 (0.75 - 0.90)

CI confidence interval
ICD International Classification of Diseases
NPV negative predictive value
PPV positive predictive value
Y=yes, N=No
Results from the Netherlands were not available at the time of the analysis

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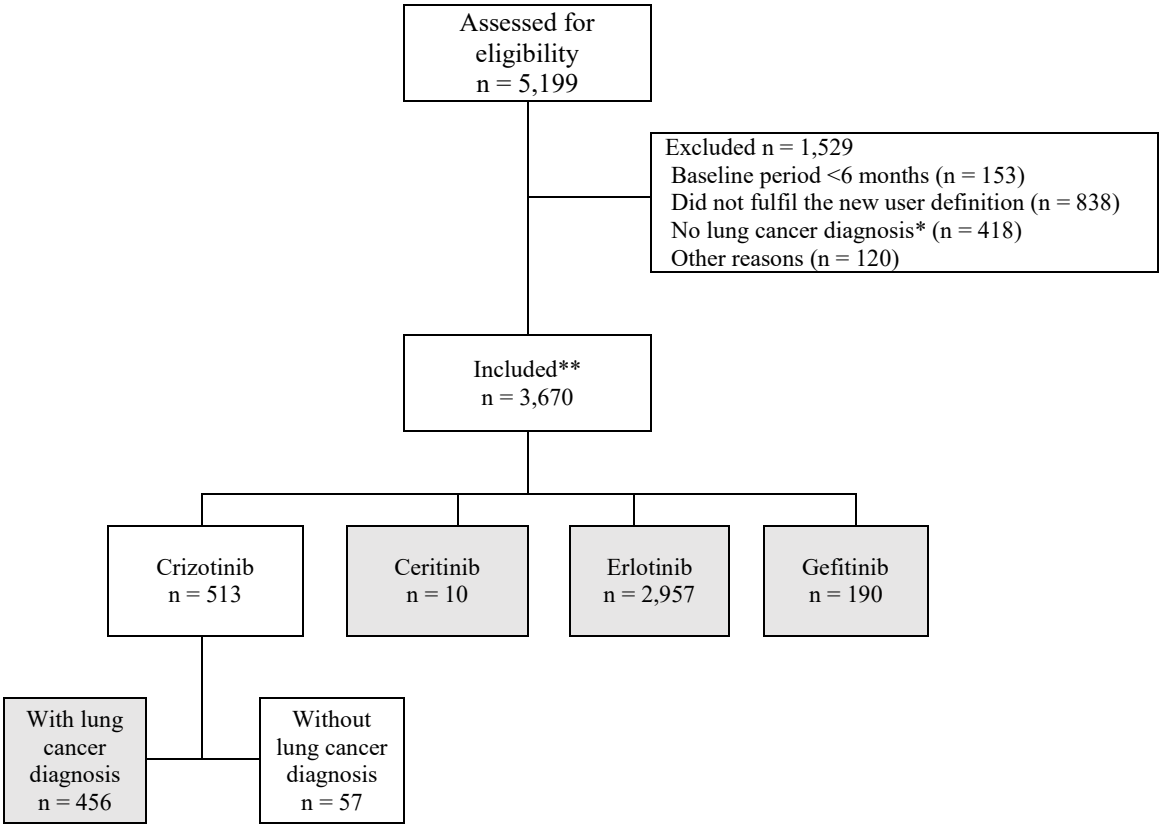
Figure 15.1. Identification of the Study Population



* Applies only to patients with dispensing/prescription of study drugs other than crizotinib

** Enrolment shown according to the first study drug received on the index date during the study period; 80 patients who entered the study in the crizotinib group or ceritinib group also contributed to the "crizotinib and ceritinib" group following the switch to the second drug; 52 patients who entered the study in the erlotinib group or gefitinib group also contributed to the "erlotinib and gefitinib" group following the switch.

Source: Country-specific Supplemental Figures 1, Appendix 5.

Figure 15.2. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Patients with Primary Lung Cancer, By Study Drug Group (One Drug), Overall and in Subgroups

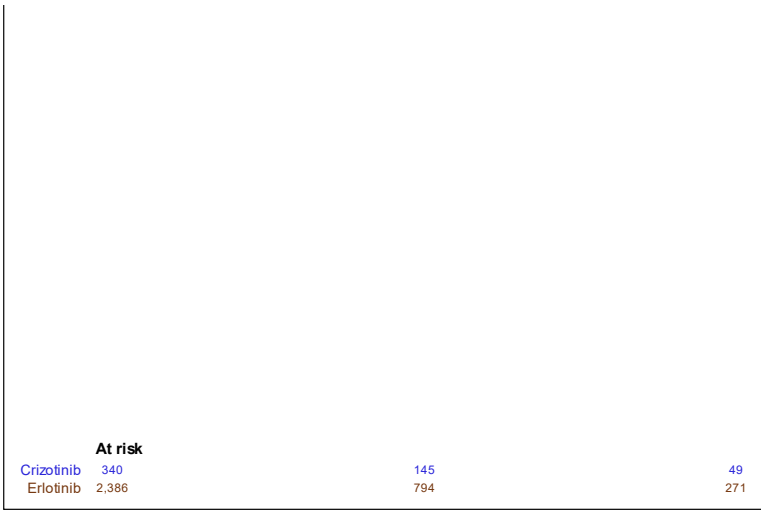


Figure 15.2a. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients Aged 65 Years or more at Index Date, By Study Drug Group (One Drug), Overall

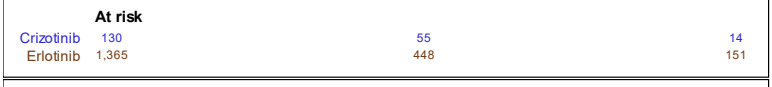


Figure 15.2b. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients Aged less than 65 Years at Index Date, By Study Drug Group (One Drug), Overall

Figure 15.2c. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Brain Metastases at Baseline, By Study Drug Group (One Drug), Overall

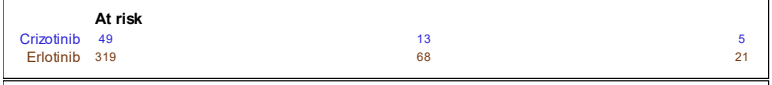


Figure 15.2d. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Brain Metastases at Baseline, By Study Drug Group (One Drug), Overall

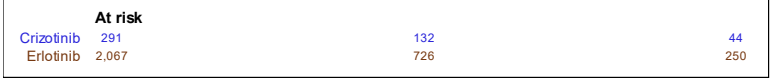


Figure 15.2e. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Hepatic Impairment at Baseline, By Study Drug Group (One Drug), Overall

Figure 15.2f. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Hepatic Impairment at Baseline, By Study Drug Group (One Drug), Overall

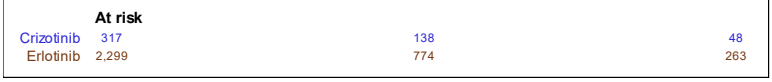


Figure 15.2g. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Renal Impairment at Baseline, By Study Drug Group (One Drug), Overall

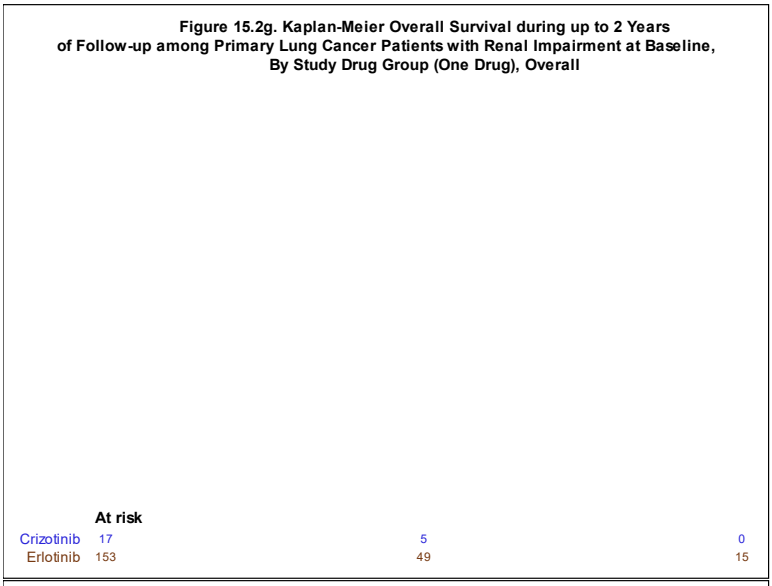
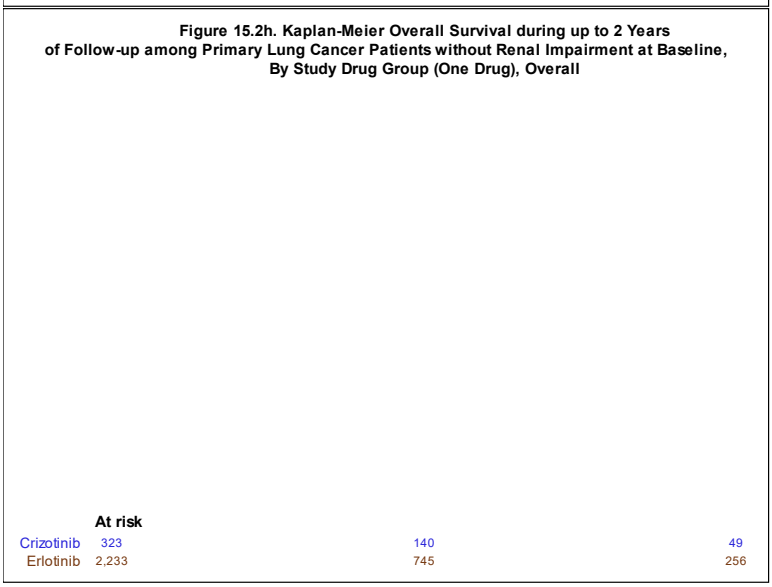


Figure 15.2h. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Renal Impairment at Baseline, By Study Drug Group (One Drug), Overall



Source: Country-specific Supplemental Figures 2, Appendix 5

Figure 15.3. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients, by Study Drug Group (One Drug), EU Combined and in Subgroups

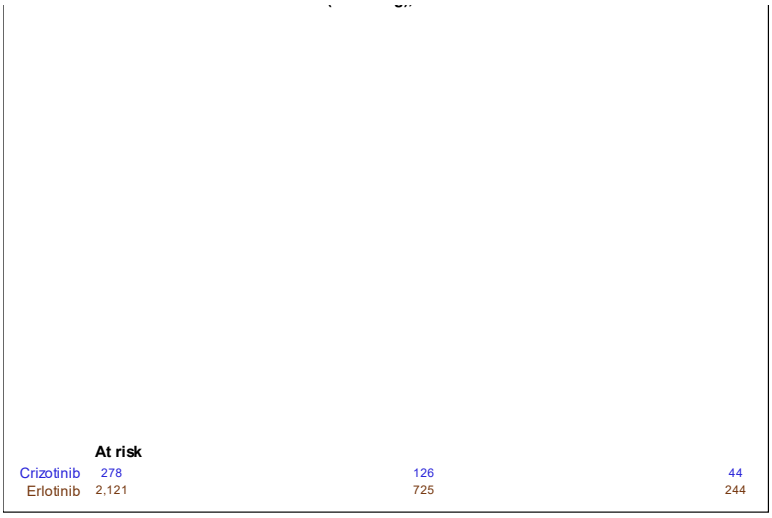


Figure 15.3a. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients Aged 65 Years or more at Index Date, By Study Drug Group (One Drug), EU Combined

Figure 15.3b. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients Aged less than 65 Years at Index Date, By Study Drug Group (One Drug), EU Combined

Figure 15.3c. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Brain Metastases at Baseline, By Study Drug Group (one drug), EU Combined

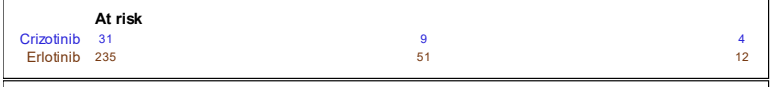
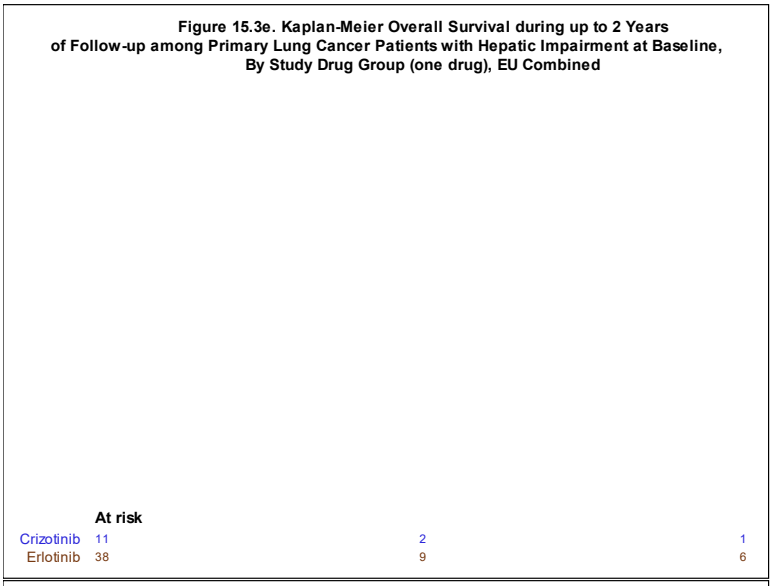


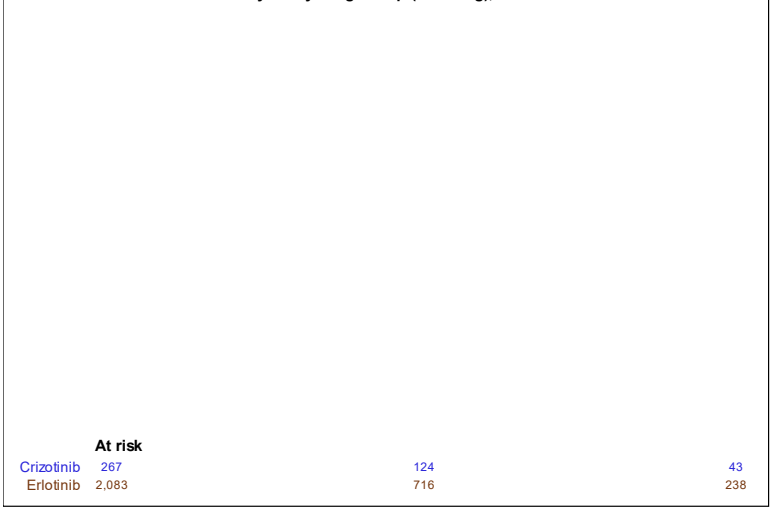
Figure 15.3d. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Brain Metastases at Baseline, By Study Drug Group (one drug), EU Combined

Figure 15.3e. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Hepatic Impairment at Baseline, By Study Drug Group (one drug), EU Combined



At risk			
Crizotinib	11	2	1
Erlotinib	38	9	6

Figure 15.3f. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Hepatic Impairment at Baseline, By Study Drug Group (one drug), EU Combined



At risk			
Crizotinib	267	124	43
Erlotinib	2,083	716	238

Figure 15.3g. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Renal Impairment at Baseline, By Study Drug Group (one drug), EU Combined

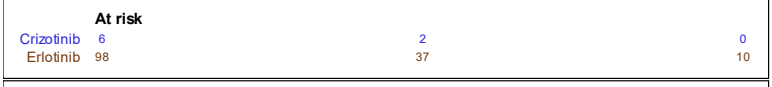
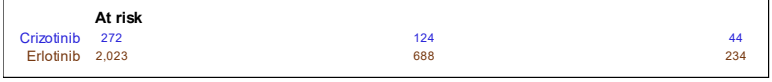


Figure 15.3h. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Renal Impairment at Baseline, By Study Drug Group (one drug), EU Combined



Source: Country-specific Supplemental Figures 2, Appendix 5

Figure 15.4. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients, by Study Drug Group (One Drug), US and in Subgroups

Figure 15.4a. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients Aged 65 Years or more at Index Date, By Study Drug Group (one drug), US

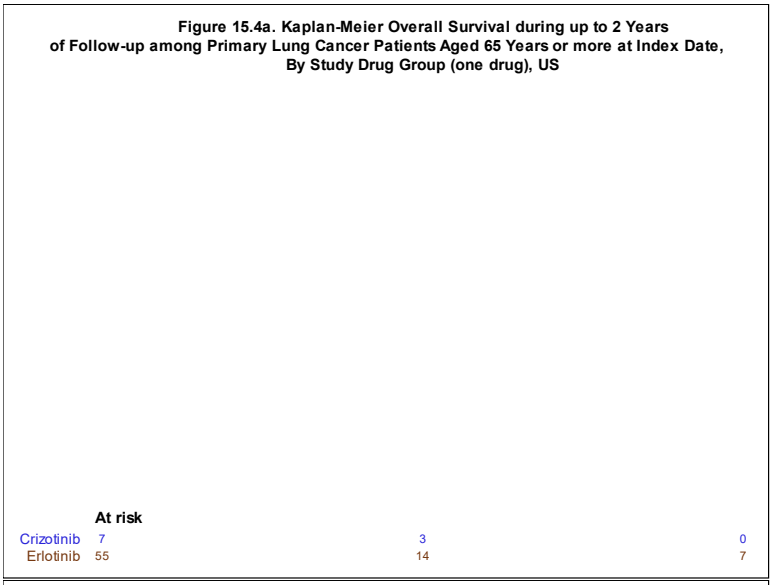


Figure 15.4b. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients Aged less than 65 Years at Index Date, By Study Drug Group (one drug), US

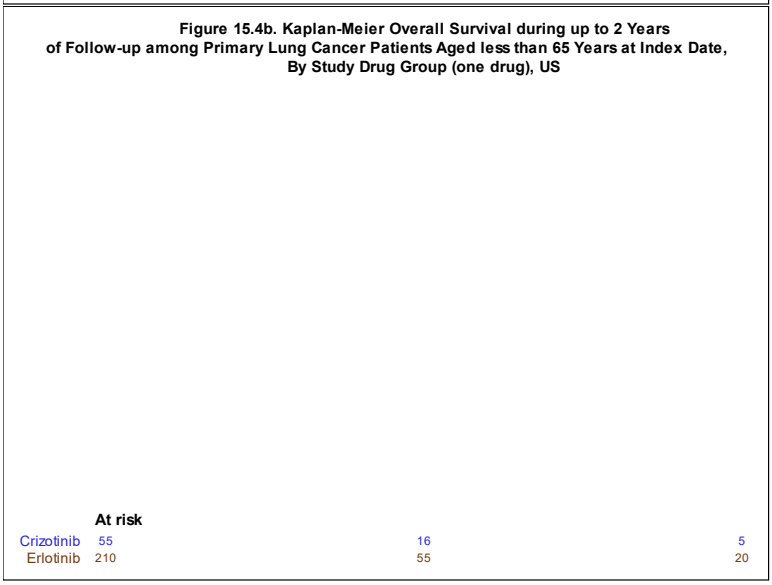


Figure 15.4c. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Brain Metastases at Baseline, By Study Drug Group (one drug), US

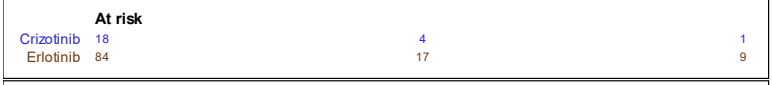


Figure 15.4d. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Brain Metastases at Baseline, By Study Drug Group (one drug), US

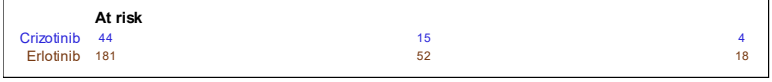


Figure 15.4e. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Hepatic Impairment at Baseline, By Study Drug Group (one drug), US

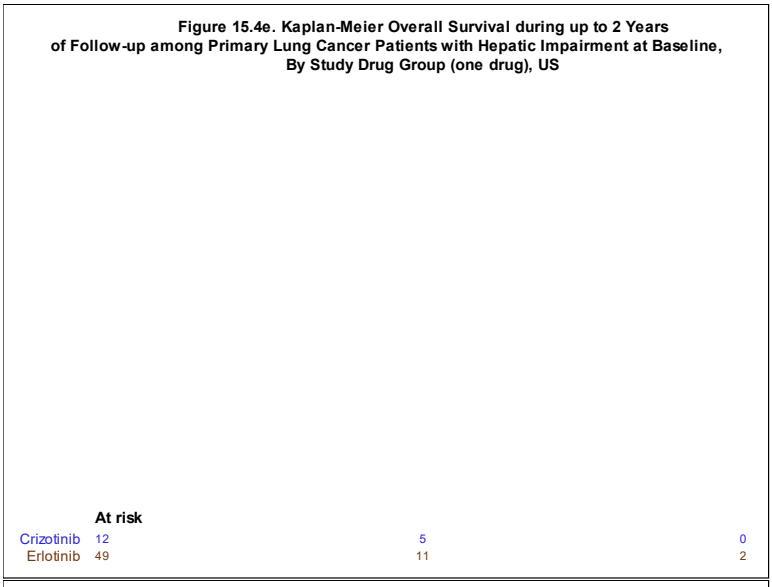


Figure 15.4f. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Hepatic Impairment at Baseline, By Study Drug Group (one drug), US

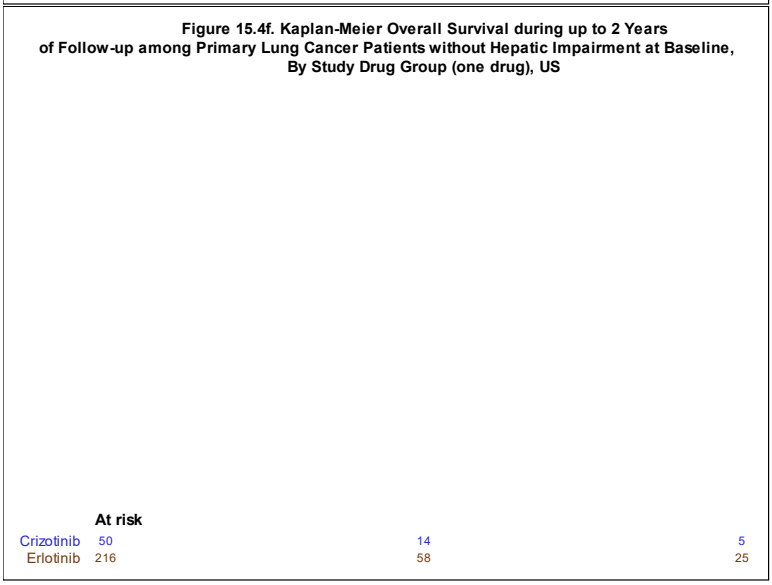


Figure 15.4g. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Renal Impairment at Baseline, By Study Drug Group (one drug), US

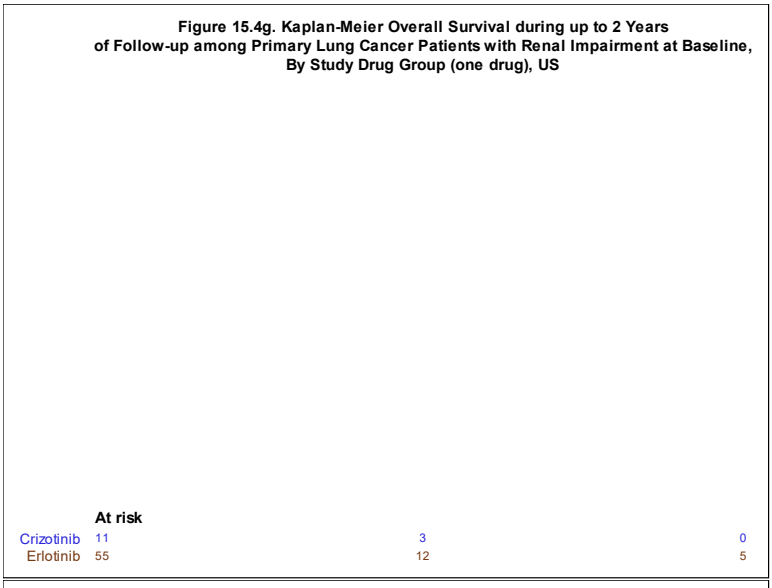
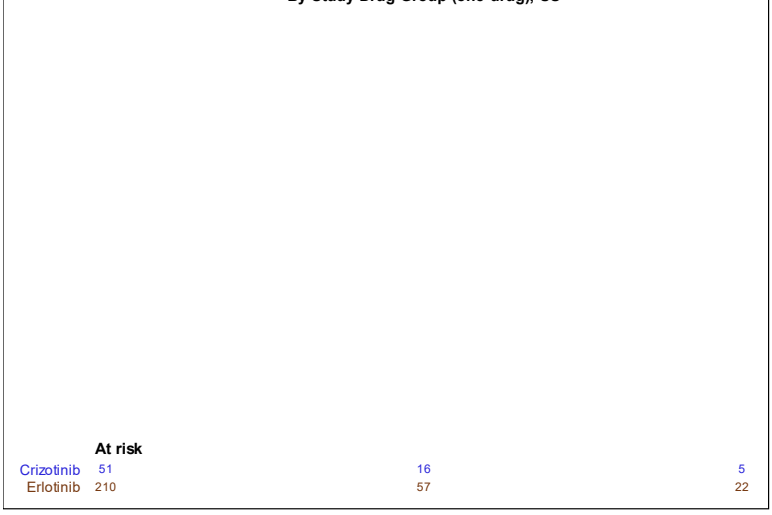


Figure 15.4h. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Renal Impairment at Baseline, By Study Drug Group (one drug), US



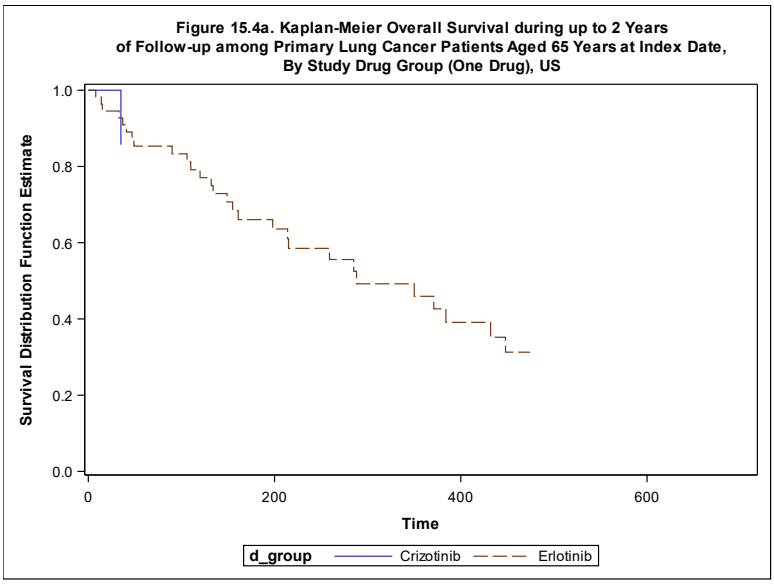


Figure 15.4a. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients Aged 65 Years at Index Date, By Study Drug Group (One Drug), US
Survival Distribution Function Estimate
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
Time
d_group
Crizotinib
Erlotinib

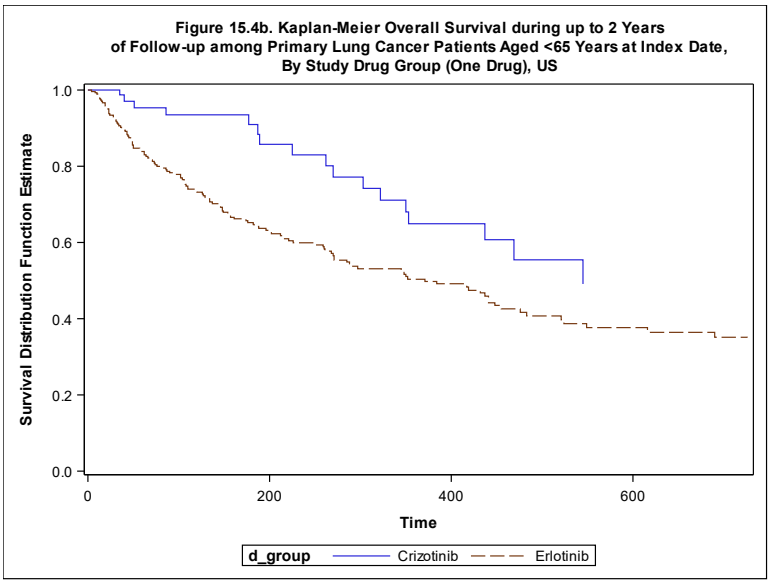


Figure 15.4b. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients Aged <65 Years at Index Date, By Study Drug Group (One Drug), US
Survival Distribution Function Estimate
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
Time
d_group
Crizotinib
Erlotinib

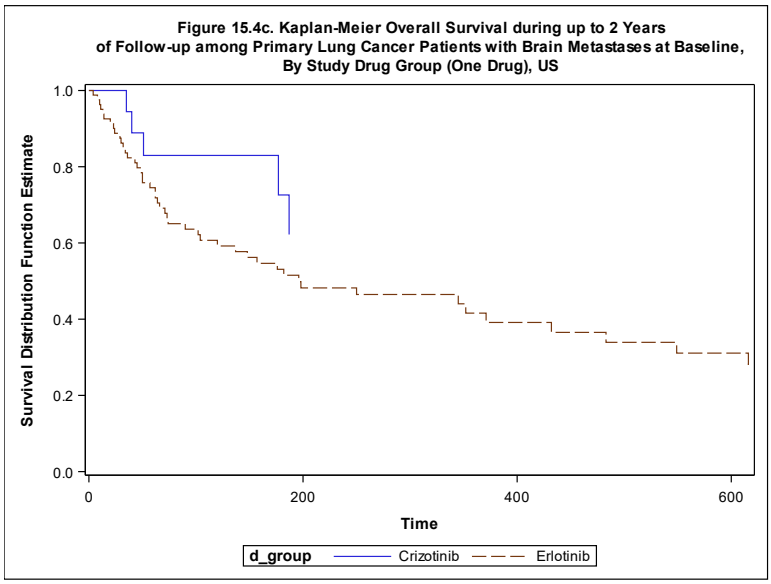


Figure 15.4c. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Brain Metastases at Baseline, By Study Drug Group (One Drug), US
Survival Distribution Function Estimate
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
Time
d_group
Crizotinib
Erlotinib

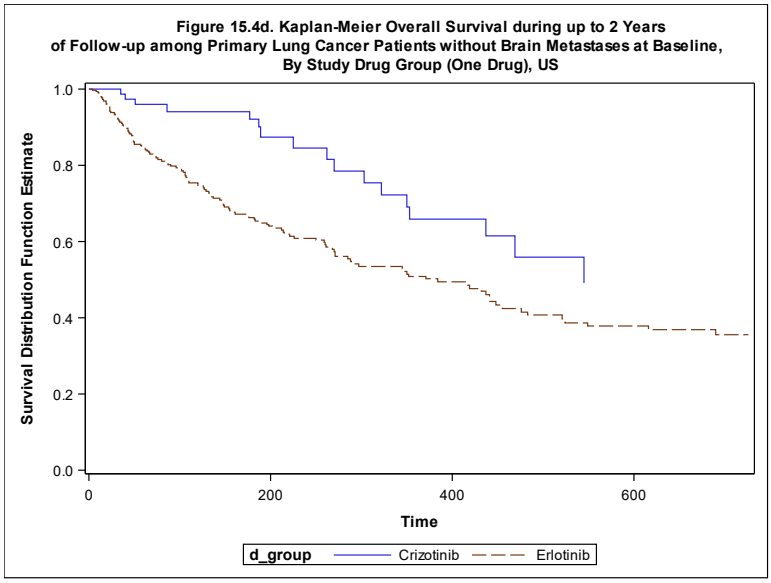


Figure 15.4d. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Brain Metastases at Baseline, By Study Drug Group (One Drug), US
Survival Distribution Function Estimate
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
Time
d_group
Crizotinib
Erlotinib

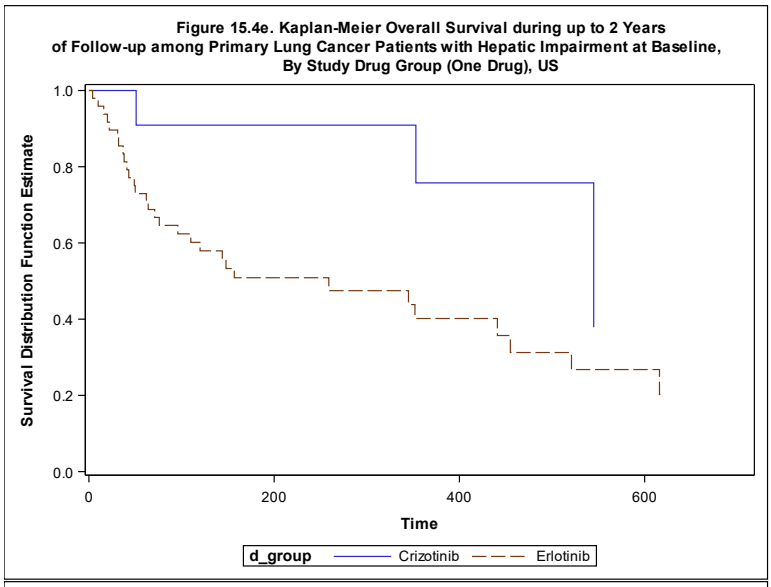


Figure 15.4e. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients with Hepatic Impairment at Baseline, By Study Drug Group (One Drug), US
Survival Distribution Function Estimate
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
Time
d_group
Crizotinib
Erlotinib

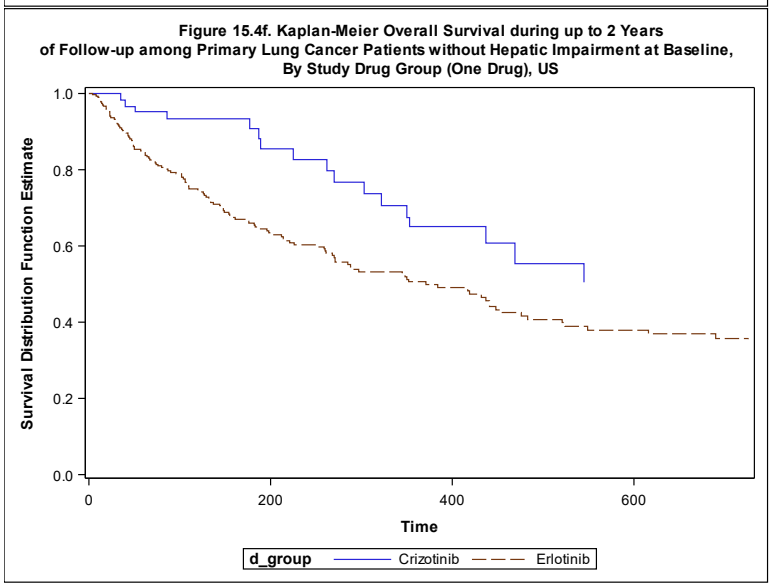
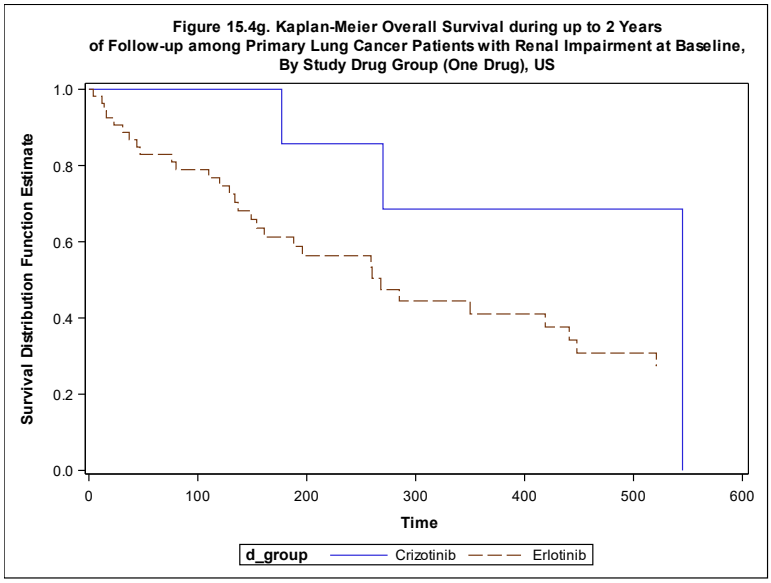
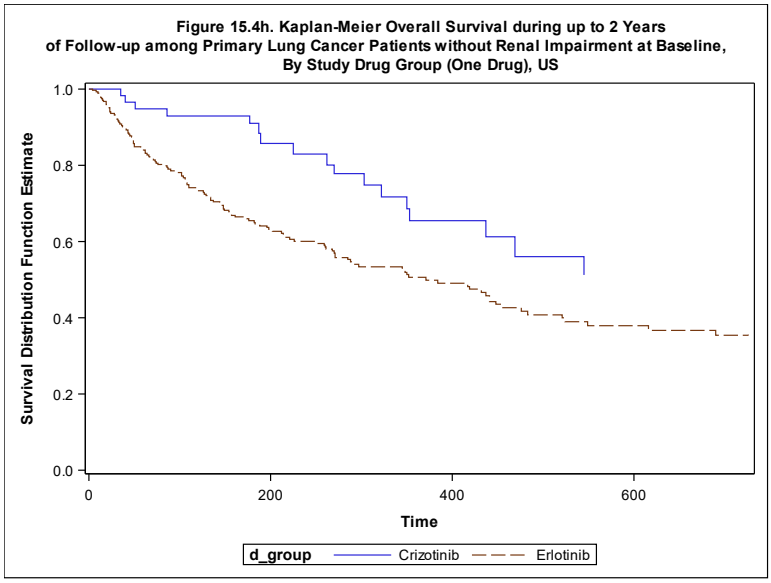


Figure 15.4f. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients without Hepatic Impairment at Baseline, By Study Drug Group (One Drug), US
Survival Distribution Function Estimate
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
Time
d_group
Crizotinib
Erlotinib





Source: Country-specific Supplemental Figures 2, Appendix 5

Figure 15.5. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Patients with Primary Lung Cancer, By Study Drug Group (Two Drugs), Overall and in Subgroups

Data too sparse to report.

Figure 15.6. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients, by Study Drug Group (Two Drugs), EU Combined and in Subgroups

Data too sparse to report.

Figure 15.7. Kaplan-Meier Overall Survival during up to 2 Years of Follow-up among Primary Lung Cancer Patients, by Study Drug Group (Two Drugs), US and in Subgroups

Data too sparse to report.