Clinical Study Report Synopsis	
Drug Substance	Osimertinib
Study Code	D5160L00032
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RADIANCE: Resistance and **A**ctivating Mutations **DIA**gnosed Among **N**on-small Cell Lung Cancer, **C**ommunity Dwelling, **E**GFR Mutation Positive Patients

An Open-label, Non-randomized Prospective Biomarker Study to Assess Analytic Concordance Between Non-invasive Testing and Tissue Testing for EGFR T790M Mutation Detection in Patients with Non-small Cell Lung Cancer

Study dates: First patient enrolled: 24 October 2017
Last patient last visit: 10 November 2018
Date of early study termination: 12 December 2018
The analyses presented in this report are based on a database lock date of 07 January 2019.

Phase of development: Therapeutic use (IV)

Sponsor's Responsible Medical Officer: [redacted]

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study sites

This study was conducted at 23 sites: 20 sites in the United States and 3 sites in Canada.

This study was planned to be conducted at approximately 50 sites in the United States and Canada. However, only 44 sites were activated; of those, only 23 sites enrolled patients.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome measures

Objective		Outcome Measure
Priority	**Description**	**Description**
Primary	To evaluate the overall analytic concordance between non-invasive testing (via Guardant360 plasma and urine) versus cobas tissue testing in identifying EGFR T790M mutation status (positive or negative).	The OPA was estimated as analytic concordance between Guardant360 plasma and urine testing versus cobas tissue testing in identifying T790M status (positive or negative). The PPA was estimated as the percentage of cobas tissue positive patients who were also Guardant360 plasma and/or urine positive. The NPA was estimated as the percentage of cobas tissue negative patients who were also Guardant360 plasma and urine negative. An overall concordance of ≥70% was considered a meaningful analytic concordance for the joint non-invasive testing strategy.
Secondary	To evaluate the ORR, DoR, and PFS in patients who were T790M+ (via cobas tissue and/or cobas plasma testing) and received osimertinib. The ORR was defined as the number (%) of patients achieving a confirmed PR or CR from osimertinib treatment.	The ORR was measured according to RECIST v1.1 as assessed by the investigational team. The DoR and PFS were measured by the investigational team. Review by a central imaging laboratory was used as a sensitivity test.
Safety	Safety data were collected for Part 1 and Part 2 of the study as follows: • Part 1: Procedure-related safety events during Part 1; and • Part 2: Safety events occurring in patients treated with osimertinib.	Adverse events including SAEs and AESIs (for Part 2 only), physical examination, vital signs including BP and pulse, and ECG.

Objective		Outcome Measure
Priority	**Description**	**Description**
Exploratory	To singly examine the analytic concordance of each non-invasive test (Guardant360 plasma and urine) compared to cobas tissue testing.	The OPA was estimated as analytic concordance between cobas tissue and Guardant360 plasma, and cobas tissue and urine testing in identifying T790M status (positive or negative). The PPA was estimated as the percentage of cobas tissue positive patients who were also Guardant360 plasma positive, and cobas tissue positive patients who were urine positive. The NPA was estimated as the percentage of cobas tissue negative patients who were also Guardant360 plasma negative, and cobas tissue negative patients who were urine negative.
	To potentially assess additional biomarkers from the blood and/or tissue of NSCLC patients who had progressed during or following treatment with an EGFR TKI.	Biomarker results were assessed and compared to T790M status and/or clinical response.
	To evaluate the analytic concordance between non-invasive testing (via Guardant360 plasma and urine) versus cobas tissue testing in identifying additional EGFR mutation(s).	The OPA was estimated as analytic concordance between Guardant360 plasma and urine testing versus cobas tissue testing in identifying the status of specified EGFR mutations (positive or negative). The PPA was estimated as the percentage of cobas tissue positive patients who were also Guardant360 plasma and/or urine positive. The NPA was estimated as the percentage of cobas tissue negative patients who were also Guardant360 plasma and urine negative.

AESI = adverse event of special interest; BP = blood pressure; CR = complete response; DoR = duration of response; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; NPA = negative percent agreement; NSCLC = non-small cell lung cancer; OPA = overall percent agreement; ORR = objective response rate; PFS = progression-free survival; PPA = positive percent agreement; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T790M+ = epidermal growth factor receptor T790M mutation positive; TKI = tyrosine kinase inhibitor; v = version.

Study design

The **R**esistance and **A**ctivating Mutations **DIA**gnosed Among **N**on-small Cell Lung Cancer (NSCLC), **C**ommunity Dwelling, **E**pidermal Growth Factor Receptor (EGFR) Mutation Positive Patients (RADIANCE) study was an open-label, prospective biomarker study to assess analytic concordance between non-invasive testing (Guardant360 plasma and urine) and cobas tissue testing for the EGFR T790M mutation.

This was a 2-part study consisting of a diagnostic analytic validity assessment in Part 1 and a planned assessment of clinical outcomes in Part 2. During Part 1, all eligible and enrolled patients underwent tissue, plasma, and urine collection for EGFR T790M mutation analysis. In cases of insufficient samples (e.g., insufficient amount or failure to undergo sample collection) for biomarker testing or invalid test results from any of the 4 testing modalities (cobas tissue, cobas plasma, Guardant360 plasma, or urine), another sample may have been acquired from that patient, if feasible, including the patient's decision to undergo a second biopsy.

Patients who demonstrated EGFR T790M mutation positive (T790M+) cobas tissue and/or cobas plasma testing were offered treatment with osimertinib by their healthcare provider (no investigational drugs were provided for this study). If osimertinib was administered, those patients continued to Part 2 of the study. If osimertinib was not administered, the patients had completed the study. Patients with a T790M negative cobas tissue test AND a T790M negative cobas plasma test had completed the study. If the cobas plasma test result was T790M negative, the patient must have waited until the result from the cobas tissue test became available before treatment was discussed with their healthcare provider.

In Part 2, patients were assessed for the secondary endpoints of objective response rate (ORR), progression-free survival (PFS), and duration of response (DoR), and safety data continued to be collected.

Target patient population and sample size

Eligible patients included male and female adults ≥18 years of age with a primary diagnosis of NSCLC with evidence of disease progression during or following treatment with an EGFR tyrosine kinase inhibitor (TKI) and an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients who had been on EGFR therapy continued EGFR therapy until results of T790M cobas testing were available and further treatment was selected.

The planned sample size was not based on any particular formal hypothesis testing but on the precision of the primary endpoint. A sample size of 400 patients with evaluable biomarker test results for analytic concordance was selected in order to achieve a precision of no more than ±5% around the estimated concordance rate. If a 15% inflation factor was applied (~70 patients) to this sample size to take into account those patients who may not have been evaluable for concordance estimates, a total of approximately 470 patients would have been enrolled.

During the course of the study, osimertinib received expanded Food and Drug Administration approval (approval was granted for first line use and the number of EGFR mutations was expanded) and the standard of care in identifying EGFR mutations evolved. These positive changes for the oncology community operationally impacted the study and impacted the

interest by sites and patients. In September 2018, further enrollment for the study was terminated, prior to enrollment meeting the planned totals described above. The study only enrolled approximately 10% of the planned patient goal: 44 of the approximately 470 planned patients were enrolled in the study.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

If the EGFR T790M mutation was confirmed by at least 1 of the cobas tests (tissue or plasma), treatment options were discussed with the patient. These standard of care options may have included osimertinib. The patient may have elected to undergo treatment with osimertinib with the medical guidance of their healthcare provider. It was anticipated that approximately 95% of patients who were T790M+ (demonstrated by cobas tissue and/or cobas plasma analysis) would receive osimertinib (recommended dose of 80 mg once per day, administered orally, according to the package insert) because it was currently the only EGFR TKI that specifically targets T790M in this patient population and represented current treatment distribution estimates. Patients who received at least 1 dose of osimertinib (and demonstrated T790M+ cobas tissue and/or cobas plasma testing) were assessed for clinical outcomes. The remaining 5% of T790M+ patients who did not receive osimertinib completed the study and were not assessed for clinical outcomes. In Part 2, osimertinib-related adverse event data were collected.

Duration of treatment

All eligible and enrolled patients were tested for the EGFR T790M mutation using tissue, plasma, and urine collected during the Screening/Enrollment Period.

Patients who demonstrated T790M+ cobas tissue and/or cobas plasma testing results may have elected to receive osimertinib in consultation with their healthcare provider. These patients were to be assessed for the secondary endpoints (ORR, PFS, and DoR), and safety data continued to be collected. Follow-Up Visits occurred according to standard of care but at a minimum of every 12 weeks for the first 12 months (Weeks 12, 24, 36, and 48; ±14 days). A Final Study Visit was planned to occur at 18 months (Week 72; ±14 days) or upon early withdrawal.

Statistical methods

Full analysis sets: The full analysis set in Part 1 included all patients enrolled in the study except those with (1) invalid (or missing) cobas tissue results or (2) invalid (or missing) Guardant360 plasma and urine test results. The full analysis set in Part 2 included patients who demonstrated T790M+ cobas tissue and/or cobas plasma testing and were treated with at least 1 dose of osimertinib (i.e., all patients in Part 2).

Safety analysis sets: The safety analysis set in Part 1 included all patients in the study that had cobas tissue, cobas plasma, Guardant360 plasma, or urine tests performed. The safety analysis set in Part 2 included patients who demonstrated T790M+ cobas tissue and/or cobas plasma testing and were treated with at least 1 dose of osimertinib (i.e., all patients in Part 2).

The analyses of the data collected within this study were descriptive only, with no formal statistical testing. Continuous variables were summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized by frequency counts and percentages for each category.

The concordance rate between non-invasive testing and cobas tissue testing was presented as the point estimate together with the exact 95% confidence interval (CI) estimated using the Clopper Pearson method. Objective response, DoR, and PFS were listed by patient.

Patient population

A total of 44 patients enrolled at 23 sites in the United States and Canada (20 sites in the United States and 3 sites in Canada). A total of 26 (59.1%) patients withdrew from the study prior to Part 2, primarily due to negative T790M results (16 (36.4%) patients). A total of 18 (40.9%) patients continued into Part 2 of the study and received treatment with osimertinib.

No patients completed the study; in Part 2, 2 (11.1%) patients discontinued the study due to disease progression and 16 (88.9%) patients discontinued the study due to study termination by the Sponsor.

Summary of efficacy results

The T790M overall percent agreement (OPA) between the joint non-invasive test (urine and Guardant360 plasma) and cobas tissue test was 18/30 (60.0% OPA; 95% CI (40.6%, 77.3%)). The T790M positive percent agreement (PPA) between the joint non-invasive test and cobas tissue test was 13/16 (81.3% PPA; 95% CI (54.4%, 96.0%)). The T790M negative percent agreement (NPA) between the joint non-invasive test and cobas tissue test was 5/14 (35.7% NPA; 95% CI (12.8%, 64.9%)).

Summary of safety results

During Part 2, a total of 18 patients received osimertinib; the mean duration of osimertinib exposure was 5.4 months. During Part 2, dose interruptions occurred in 2 (11.1%) patients, and no patients experienced a dose reduction. Based on the evaluation of adverse events (AEs), vital signs, and electrocardiograms (ECGs), treatment with osimertinib was generally well tolerated in this patient population.

During Part 1, a total of 11 (26.2%) patients experienced AEs. In total, 4 (9.5%) patients experienced serious adverse events (SAEs), 1 (2.4%) patient experienced an AE that led to

discontinuation of the study, and 1 (2.4%) patient experienced an AE (aspiration; Common Terminology Criteria for Adverse Events (CTCAE) Grade 5) with the outcome of death. Three (7.1%) patients experienced AEs (pneumonia, embolism, esophageal stenosis, back pain, and aspiration) of CTCAE Grade 3 or higher.

During Part 2, a total of 13 (72.2%) patients experienced treatment-emergent AEs (TEAEs). In total, 1 (5.6%) patient experienced a treatment-emergent SAE (ECG QT prolonged; CTCAE Grade 3), which was considered causally related to osimertinib by the Investigator. No patients experienced TEAEs that led to discontinuation of osimertinib or death. One (5.6%) patient experienced a TEAE (ECG QT prolonged) of CTCAE Grade 3 or higher. The most commonly reported TEAEs causally related to osimertinib were diarrhea (4 (22.2%) patients) and rash (3 (16.7%) patients).

Conclusions

Based on the evaluation of AEs, vital signs, and ECGs, treatment with osimertinib was generally well tolerated in this patient population.

The T790M OPA between the joint non-invasive test (urine and Guardant360 plasma) and cobas tissue test was 18/30 (60.0% OPA; 95% CI (40.6%, 77.3%)). The T790M PPA between the joint non-invasive test and cobas tissue test was 13/16 (81.3% PPA; 95% CI (54.4%, 96.0%)). The T790M NPA between the joint non-invasive test and cobas tissue test was 5/14 (35.7% NPA; 95% CI (12.8%, 64.9%)).

In Part 2, no patients experienced TEAEs that led to discontinuation of osimertinib or death. In total, 1 patient experienced a treatment-emergent SAE (ECG QT prolonged; CTCAE Grade 3), which was considered causally related to osimertinib by the Investigator. The most commonly reported TEAEs causally related to osimertinib were diarrhea and rash.