2. JVBA Synopsis

Clinical Study Report Synopsis: Study I4T-MC-JVBA

Title of Study: A Randomized, Double-Blind, Phase 3 Study of Docetaxel and Ramucirumab versus Docetaxel and Placebo in the Treatment of Stage IV Non-Small Cell Lung Cancer Following Disease Progression after One Prior Platinum-Based Therapy

Number of Investigators: This multicenter study included 216 principal investigators.

Study Centers: This study was conducted at 216 study centers in 26 countries.

Publication Based on the Study:

Garon EB, Cao D, Alexandris E, John WJ, Yurasov S, Perol M. A randomized, double-blind, phase III study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small-cell lung cancer after disease progression after 1 previous platinum-based therapy (REVEL): Treatment rationale and study design. *Clin Lung Cancer*. 2012;13(6):505-509.

Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Gorbunova V, Kowalyszyn RD, Pikiel J, Czyzewicz G, Orlov SV, Lewanski CR, Thomas M, Bidoli P, Dakhil S, Gans S, Kim J-H, Grigorescu A, Karaseva N, Reck M, Cappuzzo F, Alexandris E, Sashegyi A, Yurasov S, Perol M. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014; published online 02 June 2014.

Length of Study:	**Phase of Development:** 3
Date of first patient enrolled: 03 December 2010 Date of data cutoff: 20 December 2013	

Objectives: The primary objective of this study was to compare the overall survival (OS) of ramucirumab administered in combination with docetaxel versus placebo with docetaxel as therapy for patients with Stage IV non-small cell lung cancer (NSCLC) who had disease progression during or after 1 prior first-line platinum-based chemotherapy for advanced/metastatic disease.

The secondary objectives of this study were to evaluate:

- Safety and toxicity profile
- Progression-free survival (PFS)
- Objective response rate (ORR)
- Disease control rate (DCR)
- Patient-reported outcomes (using Lung Cancer Symptom Scale [LCSS] and EuroQol 5-dimensions [EQ-5D]).

The additional prespecified objectives of this study were to evaluate:

- Anti-ramucirumab antibodies (immunogenicity) and serum levels of ramucirumab
- Potential surrogates of ramucirumab pharmacodynamic activity
- Biomarkers, such as single nucleotide polymorphisms (SNPs), deoxyribonucleic acid (DNA) mutations, and copy number variation in vascu
- lar endothelial growth factor (VEGF) Receptor 2 and other pathway related genes, relevant to the safety, efficacy, and mechanism of action of ramucirumab in germ line DNA and tissue.
- The association between biomarkers and clinical outcome.

Study Design: I4T-MC-JVBA (JVBA; REVEL) was a global, randomized, placebo-controlled, double-blind, multicenter Phase 3 study that compared ramucirumab plus docetaxel with placebo plus docetaxel in patients with Stage IV NSCLC who had progressed during or after 1 prior first-line platinum-based therapy for metastatic disease. Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1), gender (females vs. males), prior maintenance therapy (yes vs. no), and geographic region (Japan/East Asia vs. rest of the world [ROW; Japan did not enroll any patients, and East Asia included Republic of Korea (Korea) and Taiwan]). Randomization was performed separately within each of the 16 strata (or cells) defined by all combinations of these 4 variables.

Number of Patients:

Planned: 1242

Randomized (intent-to-treat [ITT] population): 1253 patients (628 patients in the ramucirumab plus docetaxel arm and 625 patients in the placebo plus docetaxel arm)

Safety population: 1245 patients (627 patients in the ramucirumab plus docetaxel arm and 618 patients in the placebo plus docetaxel arm)

Diagnosis and Main Criteria for Inclusion: Male and female patients (age ≥18 years) with histologically or cytologically confirmed NSCLC who had disease progression during or after 1 prior first-line platinum-based chemotherapy regimen with or without maintenance therapy for advanced/metastatic disease were included. Patients with squamous and nonsquamous histologies were also included. Prior bevacizumab as first-line and/or maintenance therapy was allowed.

Patients were excluded if they received prior treatment with docetaxel or if their only prior treatment for advanced disease was a tyrosine kinase inhibitor (eg, erlotinib). Patients with radiographic evidence of intratumor cavitaton and/or tumor invasion or encasement of major blood vessels were excluded. Patients were excluded if they had a history of gross hemoptysis within 2 months prior to randomization; had experienced any arterial thrombotic event within 6 months prior to randomization; had significant bleeding disorders, vasculitis, or experienced Grade 3-4 gastrointestinal (GI) bleeding within 3 months prior to randomization; or had a history of GI perforation and/or fistulae within 6 months prior to randomization.

Study Drug, Dose, and Mode of Administration:

Ramucirumab (10 mg/kg, 60-minute intravenous [IV]) in combination with docetaxel (75 mg/m^2, 60-minute IV) administered on Day 1 of a 21-day (3-week) cycle.

An independent data monitoring committee (IDMC) recommended a lower starting dose of docetaxel, 60 mg/m^2, for new patients enrolling in Korea and Taiwan beginning with Protocol Amendment (d).

Comparator, Dose, and Mode of Administration:

An equivalent volume of placebo (60-minute IV) in combination with docetaxel (75 mg/m^2, 60-minute IV) administered on Day 1 of a 21-day (3-week) cycle.

Duration of Treatment:

Patients were treated until there was radiographic or symptomatic disease progression, toxicity requiring cessation, withdrawal of consent, or death.

Variables:

Efficacy: The primary efficacy endpoint was OS. Secondary efficacy endpoints included PFS, ORR, and DCR.

Safety: Safety was evaluated based on reported adverse events (AEs), clinical laboratory assessments, vital signs, and physical examinations. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. Clinical laboratory toxicities were graded using NCI-CTCAE criteria, Version 4.0.

Immunogenicity: Serum samples were analyzed for antibodies to ramucirumab from all patients at baseline, at specified time points during treatment, and at the 30-day safety follow-up visit. In the event of an infusion-related reaction (IRR), a blood sample was collected for immunogenicity analysis as close to the onset of the reaction as possible, at the resolution of the event, and approximately 30 days following the event.

Pharmacokinetic (PK): Pharmacokinetic parameters included, but were not limited to, calculation of mean serum trough and peak concentrations.

Pharmacodynamic: Exploratory analyses of plasma proteins will be performed for patients for whom samples are available. The results will be provided once they become available.

Health Outcomes: All patients underwent assessment for symptoms, quality of life (QoL), and health status using LCSS and EQ-5D. Time to deterioration in ECOG PS was also assessed.

Statistical Evaluation Methods:

The sample size calculation was based on a superiority test for comparing OS between the 2 treatment arms. The sample size was based on the following assumptions:

- 869 deaths observed among 1242 patients (30% censoring rate)
- a 1-sided overall significance level of 0.025 (2-sided 0.05)
- 85% statistical power assuming OS hazard ratio (HR) = 0.816 (median OS of 7.5 months in the control group [placebo plus docetaxel] and 9.2 months in the test group [ramucirumab plus docetaxel])
- the randomization ratio is 1:1.

Efficacy: The primary efficacy analysis was performed on the ITT population. The primary analysis compared OS between the 2 treatment arms (with vs. without ramucirumab) using the p-value from a log-rank test stratified by ECOG PS (0 vs. 1), gender (females vs. males), maintenance therapy (yes vs. no), and geographic region (East Asia vs. ROW). The estimation of within-arm survival parameters for the 2 treatment arms was generated using the Kaplan-Meier methodology. Stratified Cox regression models to compare the treatments were performed to generate HR and 95% confidence limits (for primary OS and secondary PFS). Stratification was based on the same stratification factors included in the randomization. Tumor response rate (ORR: complete response [CR] + partial response [PR]) and DCR (CR+PR+ stable disease [SD]) was reported, each with a 95% confidence interval (CI). Gatekeeping was used for inferential purposes from OS to PFS to ORR. An IDMC was established prior to the inclusion of the first patient in the trial. The IDMC reviewed unblinded interim analyses of safety and efficacy data.

An interim efficacy analysis for futility was to be performed after 150 OS events had been observed.

Safety: Safety analyses were performed on all randomized patients who received any quantity of study treatment grouped by actual treatment received (at any cycle). Patients who received any dose of ramucirumab at any time were analyzed in the ramucirumab arm for safety. Safety analyses included summaries of the incidences of AEs by maximum NCI-CTCAE grade (Version 4.0) that occurred during the study treatment period or within approximately 30 days after the decision was made to discontinue study treatment. Additionally, the following safety-related outcomes were summarized:

- study treatment discontinuations due to AEs
- deaths during the study treatment period or within 30 days after the decision was made to discontinue study treatment
- serious adverse events (SAEs) during the study treatment period or within 30 days after the decision was made to discontinue study treatment
- hospitalizations and transfusions during the study treatment period or within 30 days after the decision was

made to discontinue study treatment

Pharmacokinetic/Translational Research/Immunogenicity: Serum concentrations of ramucirumab at each sampling time point was summarized using descriptive statistics. Incidence of anti-ramucirumab antibodies (ADAs) was tabulated. Correlation to ramucirumab drug level, activity, and safety was assessed. Translational research analyses will be performed and reported at a later date.

Health Outcomes: For all randomized patients with baseline LCSS data, time to worsening of symptoms for each item was analyzed using the Kaplan-Meier methodology and treatments were compared using a Cox regression model to generate an HR. Lung Cancer Symptom Scale data were also analyzed with repeated measures. EuroQol-5 dimensions data were summarized for each assessment period.

Summary:

REVEL was a global study conducted at 216 investigative sites in 26 countries, with 1253 randomized patients (628 patients in the ramucirumab plus docetaxel arm and 625 patients in the placebo plus docetaxel arm), which constituted the ITT population. The Safety population consisted of 627 patients in the ramucirumab plus docetaxel arm and 618 patients in the placebo plus docetaxel arm. As of the data cutoff date (20 December 2013), 21 patients (11 patients in the ramucirumab plus docetaxel arm and 10 patients in the placebo plus docetaxel arm) were receiving study treatment. The majority of patients discontinued treatment due to disease progression: 54.3% in the ramucirumab plus docetaxel arm and 68.6% in the placebo plus docetaxel arm. The percentages of patients who discontinued treatment due to AEs were 15.0% for ramucirumab plus docetaxel and 8.8% for placebo plus docetaxel.

The demographic and baseline disease characteristics and prior therapies were well balanced between treatment arms. The median age was 62 years (range: 21 to 86); 82.1% of patients were White, 66.6% were male, and 63.7% were less than 65 years of age. The majority of patients had nonsquamous histology (72.9% 26.2% had squamous histology) and 79.2% had Stage IV (American Joint Committee on Cancer [AJCC], 7th Edition) disease at initial diagnosis. A majority of patients received systemic treatment for advanced/metastatic disease (55.1%) and as palliative therapy (32.7%); 10.7% of patients received adjuvant therapy, 22.2% had received maintenance therapy, and 14.4% had received prior bevacizumab. Almost all patients (99.4%) had received prior standard platinum-based chemotherapy (8 patients did not receive prior standard platinum-based chemotherapy).

Efficacy

Ramucirumab in combination with docetaxel reduced the risk of death in this population by 14.3% (HR = 0.857; 95% CI: 0.751, 0.979; p=0.024), with an improvement of 1.4 months in median survival in the ramucirumab plus docetaxel arm over the placebo plus docetaxel arm (10.5 months vs. 9.1 months, respectively). The statistical significance, magnitude of effect, and robustness of the primary OS analysis results were supported by prespecified sensitivity analyses, as demonstrated by consistent HRs between 0.81 and 0.86, all with $p \leq 0.027$.

Overall, nearly half of the patients (46.8%) received additional systemic anticancer therapy after discontinuation from study therapy (45.4% in the ramucirumab plus docetaxel arm and 48.3% in the placebo plus docetaxel arm). Post-discontinuation anticancer treatments were balanced, and the usage of specific anticancer treatments was similar between treatment arms, suggesting that the observed prolongation of OS is due to a treatment effect of the combination of ramucirumab with docetaxel.

Treatment with ramucirumab significantly reduced the risk of disease progression or death by 23.8% (HR = 0.762; 95% CI: 0.677, 0.859; p<0.001), with a 1.5-month longer median PFS in the ramucirumab plus docetaxel arm than the placebo plus docetaxel arm (4.5 months vs. 3.0 months, respectively). The robustness of the main PFS analysis results was supported by prespecified sensitivity analyses, as demonstrated by consistent HRs between 0.75 and 0.80, all with p<0.001.

The ORR was significantly improved for the ramucirumab plus docetaxel arm as compared to the placebo plus docetaxel arm (22.9% versus 13.6%, respectively; p<0.001). The DCR for the ramucirumab plus docetaxel arm and placebo plus docetaxel arm were 64.0% and 52.6%, respectively, showing an improvement in DCR in the ramucirumab plus docetaxel arm (p<0.001).

The treatment effect of ramucirumab plus docetaxel was internally consistent across the multiple prespecified patient subgroups examined for both OS and PFS, including patients with squamous and nonsquamous histologies.

Patient-Reported Outcomes

The primary QoL analysis showed similar time to deterioration for all LCSS scores between treatment arms. Additional analyses found no consistent or clinically meaningful differences between treatment arms, suggesting that QoL was not negatively impacted by treatment with ramucirumab plus docetaxel relative to placebo plus docetaxel.

Time to Deterioration in ECOG Performance Status

The time to deterioration of ECOG PS to 2 or worse was similar between treatment arms (HR = 1.03; 95% CI: 0.85, 1.26). Approximately two-thirds of patients were censored in this analysis.

Pharmacokinetics

Administration of 10 mg/kg of ramucirumab once every-3-week as an IV infusion over approximately 1 hour in combination with docetaxel generated geometric mean (percent coefficient of variation) ramucirumab trough concentrations of 28.3 µg/mL (65%) and 38.4 µg/mL (63%) prior to doses 3 and 5.

Immunogenicity

Overall, the rates of treatment-emergent ADA responses and neutralizing antibodies in the ramucirumab plus docetaxel arm were low. Due to the low rate of formation of ADA, no conclusions could be drawn on the effect of ADA on PK.

Safety

Overall, the percentage of patients who experienced at least 1 treatment-emergent adverse event (TEAE) of any grade was similar between treatment arms (97.8% in the ramucirumab plus docetaxel arm vs. 96.1% in the placebo plus docetaxel arm). While a higher percentage of patients in the ramucirumab plus docetaxel arm than the placebo plus docetaxel arm experienced Grade ≥3 TEAEs (78.9% vs. 71.8%, respectively), the percentage of patients who experienced at least 1 SAE (42.9% vs. 42.4%, respectively) or TEAE leading to death (5.4% vs. 5.7%, respectively) was similar between the ramucirumab plus docetaxel arm and the placebo plus docetaxel arm.

Grade ≥3 TEAEs occurring in more than 10% of patients in either treatment arm were fatigue, neutropenia, and febrile neutropenia. Of these, neutropenia (38.9% vs. 33.2%, respectively) and febrile neutropenia (15.9% vs. 10.0%, respectively) occurred more frequently (≥5%) in the ramucirumab plus docetaxel arm than in the placebo plus docetaxel arm. There were no Grade 5 events. Consolidated terms of neutropenia, any grade (55.0% vs. 46.0%) and Grade ≥3 (48.8% vs. 39.8%), and thrombocytopenia, any grade (13.4% vs. 5.2%), were reported with a higher (≥5%) incidence in the ramucirumab plus docetaxel arm than the placebo plus docetaxel arm. Additional analyses indicated that the higher incidence of thrombocytopenia was not associated with an increased risk of bleeding. The most frequently reported (≥1%) treatment-emergent serious adverse event (TE-SAE) with a higher incidence in the ramucirumab plus docetaxel arm was febrile neutropenia.

The incidence of febrile neutropenia was higher in the ramucirumab plus docetaxel arm than the placebo plus docetaxel arm (Grade 3: 61 patients [9.7%] vs. 40 patients [6.5%], respectively; Grade 4: 39 patients [6.2%] vs. 22 patients [3.6%], respectively). There was an association in both treatment arms between the TEAEs of neutropenia/febrile neutropenia and infection, with an odds ratio of 2.18 (95% CI: 1.56, 3.06) in the ramucirumab plus docetaxel arm and 1.81 (95% CI: 1.28, 2.56) in the placebo plus docetaxel arm.

Adverse events of special interest with a similar incidence between the treatment arms were IRR, arterial thromboembolic events, GI perforations, congestive heart failure, and fistula. Venous thromboembolic events occurred at a lower frequency in the ramucirumab plus docetaxel arm than the placebo plus docetaxel arm. No events of reversible posterior leukoencephalopathy syndrome or wound healing complications were observed in the study.

A greater incidence of hypertension was observed in patients receiving ramucirumab plus docetaxel (10.8%) than in patients receiving placebo plus docetaxel (4.9%). The incidence of Grade ≥3 hypertension also was higher in the ramucirumab plus docetaxel arm than the placebo plus docetaxel arm (5.4% vs. 2.1%, respectively).

Proteinuria was reported at a higher frequency in the ramucirumab plus docetaxel arm (3.3%) than in the placebo plus docetaxel arm (0.8%). One Grade 3 event was reported in the ramucirumab plus docetaxel arm.

Overall, bleeding events (any grade) were observed with a higher incidence in the ramucirumab plus docetaxel arm compared to the placebo plus docetaxel arm (28.9% vs. 15.2%, respectively). However, Grade ≥3 events were similar in the ramucirumab plus docetaxel arm compared to the placebo plus docetaxel arm (2.4% vs. 2.3%, respectively). The most frequently reported bleeding event in the ramucirumab plus docetaxel arm was epistaxis, and its incidence was higher than in the placebo plus docetaxel arm (18.5% vs. 6.5%, respectively), although the incidence of Grade ≥3 events was low and similar in the ramucirumab plus docetaxel arm compared to the placebo plus docetaxel arm (0.3% vs. 0.2%, respectively). Events of pulmonary hemorrhage (7.8% vs. 7.4%, respectively), including hemoptysis (5.7% vs. 5.2%, respectively) occurred at similar rates in the ramucirumab plus docetaxel arm compared to the placebo plus docetaxel arm.

A higher incidence (5.4% vs. 2.8%, respectively) of any-grade liver-related events (laboratory and clinical) was observed in the ramucirumab plus docetaxel arm compared to the placebo plus docetaxel arm. This difference was largely due to laboratory-related events in the ramucirumab plus docetaxel arm and the placebo plus docetaxel arm (4.9% vs. 2.4%, respectively). The incidence of Grade 3 and 4 liver failure/injury was similar for patients in both treatment arms. One Grade 5 event (hepatic failure) was observed in the placebo plus docetaxel arm.

The percentage of patients who discontinued ramucirumab/placebo due to TEAEs was similar between treatment arms (1.4% in the ramucirumab plus docetaxel arm vs. 1.0% in the placebo plus docetaxel arm). The overall incidence of TEAEs leading to the discontinuation of any study drug was higher in the ramucirumab plus docetaxel arm (9.3%) compared to the placebo plus docetaxel arm (5.2%). This was most commonly due to discontinuation of docetaxel (ramucirumab plus docetaxel arm: 7.8% vs. placebo plus docetaxel arm: 4.2%).

The percentage of patients who were hospitalized was similar in both treatment arms (41.9% in the ramucirumab plus docetaxel arm and 42.6% in the placebo plus docetaxel arm). The median duration (range) of hospitalization was 9.0 days (1-128) in the ramucirumab plus docetaxel arm and 8.0 days (1-56) in the placebo plus docetaxel arm.

Conclusions:

REVEL is the first study to demonstrate a statistically significant and clinically meaningful improvement in OS for a novel agent in combination with a standard chemotherapy in advanced NSCLC patients with progression after platinum-based chemotherapy. Consistent survival benefit was observed in both squamous and nonsquamous patients. The REVEL study met its primary endpoint, with a significant improvement in median survival of 1.4 months, and a 14.3% reduction in the risk of death (HR = 0.857; 95% CI: 0.751, 0.979; p=0.024) in patients treated with ramucirumab plus docetaxel compared to placebo plus docetaxel. Treatment with ramucirumab plus docetaxel significantly reduced the risk of disease progression or death by 23.8% compared with placebo plus docetaxel (HR = 0.762; p<0.001), and improved median PFS by 1.5 months in patients treated with ramucirumab plus docetaxel compared to placebo plus docetaxel. A statistically significant improvement in the ORR was observed for the ramucirumab plus docetaxel arm over the placebo plus docetaxel arm (22.9% vs. 13.6%,respectively; p<0.001). Also, an improvement in DCR was observed for the ramucirumab plus docetaxel arm over the placebo plus docetaxel arm (64% vs. 52.6%, respectively; p<0.0001). The subgroup analyses showed consistent results across multiple prespecified patient subgroups.

Ramucirumab in combination with docetaxel was well tolerated in the advanced NSCLC population, with manageable side effects. Overall, the safety profile observed was consistent with the safety profile for ramucirumab established in previous pivotal studies in gastric cancer, as well as the established safety profile for docetaxel. The results of REVEL represent a significant new second line therapeutic option for patients with locally advanced or metastatic NSCLC with progression after platinum-based chemotherapy.

Ergänzende Angaben zur Synopse

1. Sponsor der Studie

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN46285, USA

2. Name des Endproduktes:

Cyramza® 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung

3. Name des Wirkstoffs:

Ramucirumab (IMC-1121B; LY3009806)

6. Prüfärzte + 7. Namen und Adressen aller Studienzentren

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City of Hope National Medical Center 1500 E Duarte Rd Duarte, CA 91010-0269 USA
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Portsmouth Regional Hospital 155 Borthwick Ave Portsmouth, NH 03801 USA
The West Clinic 100 N Humphreys Blvd Memphis, TN 38120 USA
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Smilow Cancer Hospital at Yale-New Haven 1075 Chase Parkway Waterbury, CT 06708 USA
Northeast Georgia Cancer Care, LLC 3320 Old Jefferson Road Athens, GA 30607 USA
Summit Cancer Care 225 Candler Dr Savannah, GA 31405 USA
Pennsylvania Oncology Hematology Associates 230 W Washington Sq Philadelphia, PA 19106 USA
Physicians Clinic of Iowa 202 10th Street SE Cedar Rapids, IA 52403 USA
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Comprehensive Cancer Center of Nevada 10001 S Eastern Ave Henderson, NV 89169 USA
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21. Datum der Berichterstellung

Approval der Synopse: 12-Jun-2014
Ergänzende Angaben: 07-Dec-2016