2. JVBJ Synopsis

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Clinical Study Report Synopsis: Study I4T-IE-JVBJ

Title of Study: A Phase 2, Open-Label Study of IMC-1121B in Combination with Paclitaxel and Carboplatin as First-Line Therapy in Patients with Stage IIIB/IV Non-Small Cell Lung Cancer

Number of Investigators: This multicenter study included 8 principal investigators.

Study Centers: This study was conducted at 8 study centers in two countries.

Publications Based on the Study: Camidge DR, Ballas MS, Dubey S, Haignetz M, Rosen PJ, Spicer JF, West HJ, Shah GD, Youssoufian H, Mita AC. A phase 2, open-label study of ramucirumab (IMC-1121B), an IgG1 fully human monoclonal antibody targeting VEGFR-2, in combination with paclitaxel and carboplatin as first-line therapy in patients with stage IIIB/IV non-small cell lung cancer. [Abstract 7588 and poster] American Society of Clinical Oncology Annual Meeting; Jun 4-8, 2010; Chicago, IL

Camidge R, Doebele R, Ballas M, Jahan T, Haigentz M, Hoffman D, Spicer J, West H, Yurasov S, Mita AC. Final results of a phase 2, open-label study of ramucirumab (IMC-1121b;RAM, an IGg1 mab targeting VEGFR-2, with paclitaxel and carboplatin as first-line therapy in patients (pts) with stage IIIb/IV non-small cell lung cancer (NSCLC) (NCT00735696). [Abstract and poster] European Society for Medical Oncology Annual Meeting; September 28 – October 2, 2012; Vienna, Austria.

Length of Study:	**Phase of Development:** 2
Date of first patient enrolled: 21 January 2009 Date of last patient completed entire study: 06 January 2012	

Objectives: *Primary Objective*: To evaluate the progression-free survival (PFS) rate at 6 months of IMC-1121B (ramucirumab) administered in combination with paclitaxel and carboplatin as first-line therapy for Stage IIIB/IV non-small cell lung cancer (NSCLC).

Secondary Objectives: To assess the combination of ramucirmab plus paclitaxel and carboplatin in terms of: (1) safety (2) objective response rate (ORR), duration of response; overall survival (OS), OS rate at 1 year, and PFS, (3) pharmacokinetic (PK) profile and immunogenicity of ramucirumab

Exploratory analyses: To assess potential surrogate markers of ramucirumab pharmacodynamic activity, obtained from serum, and to assess potential biomarkers (including vascular endothelial growth factor) in tumor tissue and their potential association with clinical endpoints

Study Design: Single-arm, open-label, multi-center study of ramucirumab in combination with paclitaxel and carboplatin administered once every 3 weeks for up to 6 cycles in treatment-naïve, Stage IIIB/IV NSCLC patients

Number of Patients:

Planned: 40

Treated (at least 1 dose): 40 active drug

Completed: All patients continued treatment until there was evidence of disease progression, unacceptable toxicity, or other withdrawal criteria were met.

Diagnosis and Main Criteria for Inclusion: Female or male patients at least 18 years of age with histologically or cytologically confirmed, measurable, Stage IIIB or IV NSCLC. Eligible patients had to have adequate hepatic, renal and hematologic function, ECOG performance status ≤1, no evidence of major blood vessel invasion or encasement by cancer, no uncontrolled thrombotic or hemorrhagic disorders and no serious non-healing wounds.

Ramucirumab Dose and Mode of Administration, Lot Number

All patients received ramucirumab as a 1-hour intravenous (I.V.) infusion at 10 mg/kg on Day 1 every 3 weeks. ImClone Systems supplied ramucirumab injectable solution in single-use, 50-mL vials containing 250 mg (5.0 mg/mL) or 500 mg (10 mg/mL) of product.

Lot numbers: [redacted]

Paclitaxel Dose and Mode of Administration, Lot Number

All patients received **paclitaxel** as a 3-hour I.V. infusion at 200 mg/m^2, following the infusion of ramucirumab, every 3 weeks. Paclitaxel injectable solution was commerically available.

Carboplatin Dose and Mode of Administration, Lot Number:

All patients were to receive **carboplatin** as a 30-minute I.V. infusion at area under the curve (AUC) = 6, following the infusion of paclitaxel, every 3 weeks. Carboplatin injectable solution was commercially available. .

Duration of Treatment:
Combination treatment with chemotherapy and study medication continued until there was evidence of disease progression, unacceptable toxicity, or another withdrawal criterion was met, for a maximum of 6 cycles.
After completing the initial 6 cycles of treatment, in the absence of any withdrawal criteria, patients could continue to receive ramucirumab monotherapy every 3 weeks, provided there was evidence of benefit (tumor stabilization or shrinkage as radiographically measured during cytotoxic chemotherapy or ongoing symptomatic control) reviewed every 6 weeks.

Variables:
Efficacy: PFS rate at 6 months, ORR (complete response [CR] + partial response [PR]) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.0), duration of response, OS rate at one year, PFS, and OS
Pharmacokinetics: Parameters included, but were not limited to, Cmax, AUC, t½, Cl, and Vss of ramucirumab using noncompartmental methods of analysis.
Pharmacodynamic: Exploratory analyses assessed potential association of biomarkers (including VEGF) in tumor tissue and peripheral blood with clinical endpoints which included, but were not limited to PlGF, HGF, SDF1α, bFGF, VEGF, soluble VEGFR-1, soluble VEGFR-2, PDGF A, VEGFR-2, FCGR2A, and FCGR3A.
Immunogenicity: Determination of anti-ramucirumab antibodies.
Safety: Adverse events (according to National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0 [NCI-CTCAE v 3.0]), serious adverse events, physical examinations, vital sign measurements, clinical laboratory evaluations, neurological assessments, and treatment discontinuation due to toxicity.

Statistical Methods:
Approximately 40 evaluable patients were to be enrolled in this study. This sample size provided 80% power to demonstrate the assumed response rate at a 5% significance level.
The modified Intent-to-Treat (mITT) population included patients who enrolled and were treated with any study therapy . All efficacy analyses were performed on the mITT population.
The safety population included all enrolled patients who received any quantity of investigational product, regardless of their eligibility for the study. For this study, mITT and Safety populations were identical.
The PFS was defined as the time from date of first dose of study medication to the date of first documented disease progression as defined by RECIST 1.0, or death from any cause, whichever was first. Patients who did not progress were censored based on censoring rules specified in the Statistical Analysis Plan. The PFS rate at 6 months was the proportion of patients that experienced a PFS event during the first 6 months of the study. Median PFS and PFS rate at 6 months along with their 95% CI were estimated using the Kaplan-Meier method
ORR, defined as the proportion of all patients with confirmed PR or CR according to RECIST 1.0 from the start of the treatment until disease progression/recurrence, was presented with 95% CI. Frequency and percentage were used to summarize best objective response (classified as CR, PR, stable disease [SD], progressive disease [PD], or not applicable [NA] according to RECIST).
OS was defined as the time from the first dose of study medication to the date of death from any cause. OS rate at 1 year, defined as the proportion of patients that were alive 1 year following the date of first dose of study medication, were analyzed in the same manner as the PFS rate at 6 months.
Duration of response, measured from the time measurement criteria were first met for CR/PR (whichever was first recorded) until the first date that the criteria for PD were met, initiation of other/additional antitumor therapy is first reported, or death, was estimated by the Kaplan-Meier method, including a 95% CI for the median duration of response.
Adverse events were summarized by MedDRA® System Organ Class and preferred term, classified from verbatim terms. The incidence and percentage of patients with at least one occurrence of a preferred term were included, according to the most severe NCI-CTCAE v 3.0 grade. Causality (relationship to study medication) was separately summarized. Listing include duration of AE .
Laboratory results were classified according to NCI-CTCAE v 3.0. Incidence of laboratory abnormalities were summarized. Laboratory results not corresponding to an NCI-CTCAE v 3.0 term were not graded.
Descriptive statistics summarized the biomarkers by each biomarker platform. Statistical analyses were performed to explore the relationships between the biomarkers (Spearman correlation, Fisher's exact test, Wilcoxon rank sum test) and between biomarkers and clinical outcomes (Cox regression and logistic regression; with and without maximal chi-square method). Plots were generated to further explore these relationships.

Summary:
Forty (40) patients were enrolled and treated with at least one dose of ramucirumab. Twelve (12) patients (30.0%) discontinued treatment due to an AE; 24 patients (60.0%) discontinued due to PD; 2 patients each

(5.0%) withdrew consent and discontinued due to other reasons

The majority of population was female (25 patients; 62.5%) with median age 59.5 years (range: 35 – 78 years). Thirty four (34) of 40 patients had adenocarcinoma; 2 had large-cell cancer, 1 squamous NSCLC, and 3 patients had other histologies. The majority of patients (27 of 40) had Stage IV disease at baseline (as assessed by American Joint Committee on Cancer Staging Manual, Sixth Edition) and the most common sites of metastatic disease at baseline were lung (39 pts), lymph nodes (24 pts), and pleura (18 pts). Nine patients had liver metastases at baseline. Twenty-five (25) patients (62.5%) had metastases in >2 sites.

Efficacy:

The PFS rate at 6 months was 59.0% (95% CI, 41.3 to72.9) as estimated by the Kaplan-Meier method. Median Kaplan-Meier estimate of PFS was 7.85 months (95% CI: 5.49 to 9.86). Objective response rate was 55.0% (95% CI: 38.5 to 70.7). One patient had a CR and 21 patients had a PR. Disease control rate (CR + PR + SD) was 90.0% (95% CI, 76.3 to 97.2). Median duration of response was 5.54 months (95% CI: 4.27 to 8.21). Kaplan-Meier estimate of 1-year survival rate was 74.6% (95% CI: 57.9 to 85.4).

Median overall survival time was 16.85 months (95% CI: 14.82 to 28.58) with 26 patients dying and 14 remaining alive at the time of the data cut-off date (06 Jan 2012).

Safety:

Forty patients (100.0%) experienced at least one TEAE, of which 85.0% were considered related to ramicurumab. A total of 31 patients (77.5%) experienced a ≥ Grade 3 TEAE. Nineteen patients (47.5%) experienced a serious TEAE, of which 8 patients (20.0%) had serious TEAEs that were considered related to ramicurumab. There were no deaths on study or within 30 days of discontinuation.

The most common TEAEs by preferred term were fatigue (75.0%), peripheral neuropathy (67.5%), nausea and alopecia (57.5% each), constipation and arthralgia (40.0% each), diarrhea and neutropenia (35.0% each).

The most common ramucirumab related events were fatigue (52.5%; 3 [7.5%] Grade 3 events), peripheral neuropathy (33%; 2 [5.0%] Grade 3 events), nausea (27.5%), epistaxis, and myalgia (22.5% each). Eight patients (20%) experienced related serious adverse events: 2 patients with febrile neutropenia and 1 each with neutropenia, fatigue, cholecystitis, convulsion, vasovagal syncope, pneumothorax, and pulmonary embolism.

Conclusions: In this Phase 2 study in advanced nonsmall cell lung cancer, 40 patients were treated with ramucirumab plus caroboplatin and paclitaxel.

The PFS rate at 6 months was 59% and disease control rate was 90%. Median PFS was 7.85 months and median OS was 16.85 months. The ORR was 55%.

Ramucirumab administered at 10 mg/kg once every 3 weeks in combination with caroboplatin and paclitaxel was safe and well tolerated. The AEs reported were consistent what would be expected with ramucirumab and with the combination of carboplatin and paclitaxel individually. There was no evidence of augmentation of toxicity or of any new or unexpected toxicity.

These data suggest possible enhancement of chemotherapy activity with the addition of ramucirumab and support additional evaluation of ramucirumab in combination with chemotherapy as 1st line treatment of advanced or metastatic NSCLC.