2. JVBH Synopsis (IMCL CP12-0709)

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Clinical Study Report Synopsis: Study I4T-IE-JVBH (IMCL CP12-0709)

Title of Study: An Open Label, Multicenter, Phase 2 Study Evaluating the Safety and Efficacy of IMC-1121B in Combination with 5 FU/FA and Oxaliplatin (Modified FOLFOX 6) as First line Therapy in Patients with Metastatic Colorectal Cancer
Number of Investigators: This multicenter study included 8 principal investigators.
Study Centers: This study was conducted at 8 study centers in 2 countries.
Publications Based on the Study: Garcia-Carbonero R, Rivera F, Maurel J, Ayoub JPM, Moore MJ, Cervantes-Ruiperez A, Asmis TR, Schwartz JD, Ballal S, Tabernero J. A phase 2, open-label study evaluating the safety and efficacy of ramucirumab combined with mFOLFOX‑6 as first‑line therapy in patients (pts) with metastatic colorectal cancer (mCRC) (CP12-0709/NCT00862784). Abstract and poster. 2012. ASCO GI conference.
Length of Study: Date of first patient enrolled (assigned to therapy): 24 April 2009 Date of last patient completed: 22 August 2011 — **Phase of Development:** 2
Objectives: The primary objective of this study was to evaluate the progression-free survival (PFS) in patients with mCRC when treated with the monoclonal antibody ramucirumab in combination with the mFOLFOX-6 chemotherapy regimen as first-line therapy. The secondary objectives of this study were to evaluate: • Objective response rate (ORR) • Overall survival (OS) • Duration of response • Safety profile • Pharmacokinetic (PK) profile and immunogenicity of ramucirumab
Study Design: An open-label, multicenter, multinational Phase 2 trial in which previously untreated patients with locally advanced or metastatic colorectal cancer received ramucirumab administered every 2 weeks in combination with mFOLFOX-6 therapy. Treatment continued until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision.
Number of Patients: Planned: 45 Treated (at least 1 dose): 48
Diagnosis and Main Criteria for Inclusion: Eligible patients were at least 18 years of age with histologically or cytologically confirmed treatment-naïve adenocarcinoma of the colon or rectum; locally advanced, unresectable or metastatic disease; at least 1 measurable target lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1; adequate renal, liver, hematologic, and coagulation function. Exclusion criteria included prior systemic chemotherapy (adjuvant therapy was permitted), prior biologic, investigational or anti-angiogenic systemic therapy for CRC; chronic systemic corticosteroid treatment; acute or subacute intestinal obstruction; symptomatic brain or leptomeningeal metastases; known dihydropyrimidine dehydrogenase (DPD) deficiency; ongoing or active infection, poorly controlled hypertension, or other poorly controlled illnesses.
Investigational Product, Dose, and Mode of Administration: Ramucirumab 8 mg/kg intravenous (IV) infusion on Day 1 of each 2-week cycle

Other Study Drugs, Dose, and Mode of Administration: Following administration of ramucirumab on Day 1 of each 2-week cycle, each patient received the following treatments, in the order shown, all by IV infusion: oxaliplatin at a dose of 85 mg/m2, folinic acid at a dose of 400 mg/m2, and 5-fluorouracil (5-FU) as a bolus injection of 400 mg/m2 immediately followed by a 46-hour continuous infusion of 2400 mg/m2.

Duration of Treatment: All treatments were to be administered every 2 weeks until disease progression, the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the patient (or until other criteria for treatment discontinuation were met).

Variables:

Efficacy: PFS; best ORR; duration of response; OS

Safety: Treatment-emergent adverse events (TEAE), serious TEAE, treatment discontinuations due to adverse events (AEs), deaths, physical examination, laboratory data (including serum chemistry and hematology evaluations), concomitant medications

Pharmacokinetic: including but not limited to predose and 1 hour post-end-of-infusion serum concentrations.

Immunogenicity (antibodies against ramucirumab): samples were collected prior to the initial infusion, prior to the ramucirumab infusion at Cycle 5, Cycle 9, and at the 30-day follow-up visits.

Evaluation Methods:

Efficacy: Efficacy data were analyzed for all treated patients. PFS, OS, and duration of response were analyzed using the Kaplan-Meier method to estimate the survival curves and determine the 95% confidence interval (CI) for medians using the Lifetest Procedure from SAS. Best overall response rates were summarized in terms of frequency and percentage, and an exact 95% CI was calculated.

Safety: Adverse events were classified by type, incidence, severity, and causality. The incidence and percentage of patients with at least one occurrence of a preferred term were summarized, according to the most severe grade per the National Cancer Institute – Common Terminology Criteria for Adverse Events, (NCI-CTCAE) Version 3.0. Causality (relationship to any chemotherapy and ramucirumab only) was separately summarized. Adverse Events leading to discontinuation of therapy or dose modification were also summarized. Serious adverse events (SAEs) per the definition in the study protocol, were summarized by system organ class (SOC), preferred term (PT), and relationship to study drug. Laboratory findings (including laboratory abnormalities) were summarized, and laboratory toxicity grade changes from baseline to worst on study were summarized using shift tables.

Pharmacokinetic: ramucirumab concentrations were summarized by cycle and time point.

Pharmacodynamic: Potential exploratory pharmacodynamic markers including, but not limited to, VEGF, soluble VEGFR-1, soluble VEGR-2 were assayed using samples obtained from 9 patients. The results will be reported in an addendum to this report.

Immunogenicity: A report of immunogenicity results will be reported at a later date in an addendum to this report.

Summary:
Forty-eight (48) patients signed the Informed Consent Form (ICF) and were treated in this study. Twenty-five patients (52.1%) were men, and all 48 patients were white. The majority of patients (31 patients, 64.6%) were under age 65 years (median age, 60.5 years [range, 28 to 81 years]). Thirty patients (62.5%) had an ECOG PS of 0. All patients had metastatic disease. The liver was the most common site of metastatic disease (38 patients [79.2%]), and 13 patients (27.1%) had liver-only metastases. The majority of patients (33 patients [68.8%]) had undergone previous surgery for colorectal cancer.

The median PFS in this study (the study's primary endpoint) was 11.5 months (95% CI: 8.6, 13.1). Thirty-seven (37) patients (77.1%) had documented disease progression or death, and 11 patients (22.9%) were censored. Five (5) patients had lesions surgically resected during the study. In a sensitivity analysis of PFS, patients with surgical resection of lesions had their date of last tumor assessment prior to resection censored (33.3% censoring); median PFS was 9.8 months (95% CI: 8.2, 13.4).

The ORR was 58.3% (95% CI: 43.21, 72.39). One patient (2.1%) had a best overall response (BOR) of complete response (CR), and 27 patients (56.3%) had a BOR of partial response (PR). Median duration of response was 11.0 months (95% CI: 6.9, 12.6).

Median OS was 20.4 months (95% CI: 18.5, 25.1).

Pharmacokinetic samples were collected as a secondary objective of this study in a subset of 9 patients. Data from this study showed that mean trough levels after repeated dosing of 8 mg/kg of ramucirumab every 2 weeks exceeded the target concentration associated with antitumor activity in preclinical models at Cycle 5 and beyond.

The median duration of ramucirumab+mFOLFOX-6 therapy was 34.1 weeks (maximum 104.9 weeks [48 ramucirumab infusions]). The majority of patients (64.6%) received 80% or greater of the planned dose of ramucirumab and mFOLFOX-6. Although many patients discontinued oxaliplatin treatment after the initial 5 to 8 months of therapy, a substantial subset received continued ramucirumab/5-fluorouracil and folinic acid with ongoing disease control, including 28 patients (58.3%) who received this combination for 5 months or greater before discontinuing therapy because of disease progression or AEs.

All patients experienced at least one TEAE in the study, and 45 patients (93.8%) experienced at least one TEAE considered related to ramucirumab by the investigator.

The most commonly reported TEAE, occurring in greater than 50% of patients and regardless of causality, were from the SOC of General Disorders and Administration Site Conditions; Gastrointestinal Disorders; Nervous System Disorders; Blood and Lymphatic System Disorders; Vascular Disorders; Skin and Subcutaneous Disorders; and Respiratory, Thoracic and Mediastinal Disorders.

Grade 3 events were experienced by 34 patients (70.8%). The most common Grade 3 events, occurring in more than 5% of patients and regardless of causality, were neutropenia, hypertension, dysaesthesia, neurotoxicity, asthenia, and diarrhea. The only common (≥5%) Grade 3 TEAE considered related to ramucirumab was hypertension (in 7 patients; 14.6%). Grade 4 events were neutropenia (4 patients; 8.3%) and the following events in 1 patient each (2.1%): coagulopathy, febrile neutropenia, diarrhea, disease progression, GGT increased, nephrotic syndrome, and pulmonary embolism. Coagulopathy, GGT increased, nephrotic syndrome, and pulmonary embolism were considered by the investigator to be related to ramucirumab. Nine (9) patients (18.8%) had a Grade 1 or Grade 2 infusion-related reaction considered related to ramucirumab by the investigator. With premedication and/or reduced infusion rate, 8 of these 9 patients received subsequent ramucirumab successfully, without development of additional hypersensitivity symptoms.

Twenty-four (24) patients (50.0%) had TEAEs leading to discontinuation of any study treatment (primarily mFOLFOX-6), with the most common events being in the SOC of Nervous System Disorders. The majority of events were Grade 3 or lower. Of these 24 patients, 11 patients (22.9%) had TEAEs leading to discontinuation of only their ramucirumab treatment because of AEs, the most common events being pulmonary embolism (2 patients, 4.2%) and hypertension (2 patients; 4.2%).

The majority of patients (95.8%) had TEAEs leading to dose modification of any study treatment (primarily mFOLFOX-6), the most common events being in the SOC of Blood and Lymphatic Systemic Disorders and Nervous System Disorders. Thirty-six (36) patients (75.0%) had TEAEs leading to dose modification of ramucirumab.

The overall incidence of neuropathy was analyzed by means of an assessment employing a consolidated terminology for neuropathy (incorporating the MedDRA preferred terms: dysaesthesia, paraesthesia, neuropathy peripheral, peripheral sensory neuropathy and hypoaesthesia). Thirty-one patients (64.6%) experienced any grade neuropathy (as assessed via the consolidated term) and of these, Grade 3 neuropathy was observed in 6 patients (12.5%). No patients discontinued ramucirumab therapy due to adverse events related to neuropathy. Ten patients (20.8%) discontinued chemotherapy due to any grade neuropathy. Of these, 6 patients (12.5%) discontinued chemotherapy due to Grade 3 neuropathy.

Two AEs leading to death occurred within 30 days of the last study drug dose. Both occurred either during or shortly following the 46-hour 5-flurouracil continuous infusion. One event occurred following the initial dose of study therapy, the other occurred after approximately 15 weeks of therapy. One occurred in a patient without a history of coronary artery disease (CAD), the other in a patient with known ischemic cardiomyopathy. In addition to mCRC, both patients had some history of hypertension and were receiving omeprazole. In one case, this occurred in the absence of prior reported symptoms; in the other, death was preceded by vomiting and pain in the chest and upper back. Very limited additional diagnostic information is available. Although cardiopulmonary arrest and myocardial infarction have been reported in patients receiving investigational ramucirumab therapy (detailed in Section 3.8.1 of the Development Core Safety Information [DCSI] of the Investigator's Brochure (IB), Version 6.0), these events have been infrequent and have largely occurred in patients with underlying cardiovascular disorders; the relative contribution of IMC-1121B to these events is unclear. It has been shown that the anti-VEGF antibody bevacizumab, administered in combination with cytotoxic chemotherapy, is associated with a higher incidence of arteriothromboembolic events relative to chemotherapy without bevacizumab. Although the 2 events described above may have very distinct etiologies, the possibility also exists that the addition of IMC-1121B to cytotoxic chemotherapy (including infusional fluorouracil regimens) may be associated with a higher incidence of cardiovascular or cardiopulmonary toxicity. It should be noted that continuous infusion of 5-FU is also associated with (infrequent) cardiac toxicity, including ischemia. The incidence of these sudden-onset Grade 5 events, consistent with (but not conclusively proven to be) artertiothromboembolic events, occurring in the absence of demonstrable disease progression, was higher on CP12-0709 than has been observed on other studies investigating ramucirumab. Additional studies involving ramucirumab combination therapy with oxaliplatin- and infusional fluorouracil-containing regimens are underway; data safety committees and investigators for these studies are aware of this finding from study CP12-0709. Phase 3 randomized trials will more definitively delineate the incidence of arteriothromboembolic events (ATEs) in patients receiving ramucirumab.

No clinically significant patterns were observed with respect to clinical laboratory toxicity, vital signs, or other physical findings.

The important protocol violations identified are not believed to have substantially influenced or modified the presented results and conclusions.

Conclusions:
Despite the small number of patients enrolled in this trial, the combination of ramucirumab and mFOLFOX-6 suggested efficacy in patients with mCRC. The primary objective was to evaluate PFS. The ORR (58%), disease control rate (94%) and median PFS (11.5 months) suggest that ramucirumab may enhance the efficacy of mFOLFOX-6 in mCRC.

The incidence of most AEs in patients receiving ramucirumab + mFOLFOX-6 is consistent with the known AE profile of mFOLFOX-6 in mCRC. Hypertension (including Grade 3) and proteinuria (including Grade 4 nephrotic syndrome) were observed and considered related to ramucirumab. Severe arteriothromboembolic events (including Grade 5 and suspected arteriothromboembolic events) were observed. Phase 3 randomized trials will more definitively delineate the incidence of AEs in patients receiving ramucirumab. In conclusion, the overall AE profile in this study is consistent with the established toxicity profile of the constituent chemotherapeutic agents and with side effects associated with VEGF/VEGFR inhibitors, and with the known safety profile of ramucirumab to date. The safety results in this study do not suggest any marked enhancement of the known toxicities of mFOLFOX-6 when administered with ramucirumab, although the modest sample size and single-arm design of the study preclude definitive assessment regarding this conclusion.

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