2. Synopsis

Clinical Study Report Synopsis: Study CP11-0602

Title of Study:
Open label, multicenter, phase II study evaluating the efficacy and safety of IMC-11F8 in combination with 5-FU/FA and oxaliplatin (mFOLFOX-6) in patients with treatment-naïve locally-advanced or metastatic colorectal cancer

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

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

Publications Based on the Study:

1. Tabernero J, Cervantes A, Delaunoit T, Hendlisz A, Youssoufian H, Zhu J, Rowinsky E, Sastre Valera J. A phase 2 study of IMC-11F8, a monoclonal antibody directed against the EGFR, in combination with mFOLFOX6 chemotherapy in the first-line treatment of advanced or metastatic colorectal carcinoma. Abstract 546 and poster presented at the ESMO Conference: 11th World Congress on Gastrointestinal Cancer; Jun 24-27, 2009; Barcelona, Spain. Abstract available at: http://www.postersessiononline.com/173580348_eu/congresos/11wgic/aula/-PD_7_11wgic.pdf

2. Tabernero J, Sastre Valera J, Delaunoit T, Cervantes A, Hendlisz A, Youssoufian H, Rowinsky EK, Wang G. A phase II multicenter study evaluating the efficacy and safety of IMC-11F8, a recombinant human IgG1 anti-epidermal growth factor receptor (EGFR) monoclonal antibody (Mab), combined with 5-FU/FA and oxaliplatin (mFOLFOX-6) as first- line therapy. Abstract 4066 and poster presented at the American Society for Clinical Oncology Annual Meeting: May 30-Jun 3, 2008; Chicago, IL. Abstract available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=35412

Length of Study:	**Phase of Development:** Phase 2
Date of first patient enrolled: 01 August 2007 Date of last patient completed: 29 October 2010	

Objectives:
The primary objective of this study was to evaluate the antitumor activity (best overall response rate [ORR]) of the anti-EGFR monoclonal antibody necitumumab (IMC-11F8) administered in combination with the mFOLFOX-6 chemotherapy regimen in treatment-naïve, locally advanced or metastatic colorectal cancer patients.

The secondary objectives of this study were to evaluate the overall survival, the progression-free survival, the safety profile, the duration of response, the pharmacokinetic profile of IMC-11F8, the immunogenicity of IMC-11F8, and the association between response to treatment and the presence or absence of *KRAS* mutations in tumor tissue

Study Design:
This study was a an open-label, single-arm, multicenter Phase 2 trial in which patients with treatment-naïve, locally advanced or metastatic colorectal cancer received necitumumab at an absolute dose of 800 mg, administered every 2 weeks in combination with modified FOLFOX-6 chemotherapy (ie, oxaliplatin [85 mg/m^2 on Day 1 of each 2-week cycle], folinic acid [400 mg/m^2 on Day 1 of each cycle], and 5-fluorouracil [400 mg/m^2 bolus on Day 1 of each 2-week cycle followed by 2400 mg/m^2 by continuous infusion over the next 46 hours]).

Approval Date: 20-Feb-2012 GMT

Number of Patients:
Planned: 40
Enrolled: 44
Treated (at least 1 dose): 44
Completed: 44

Diagnosis and Main Criteria for Inclusion:

Key inclusion criteria included the following:

- Histologically confirmed, EGFR-detectable or EGFR-undetectable colorectal cancer. Patients who do not have tissue available for EGFR testing were to undergo biopsy of an accessible tumor. A waiver was permitted for patients who did not wish to undergo a biopsy.
- Locally advanced unresectable or metastatic adenocarcinoma of the colon or rectum.
- At least one unidimensionally measurable target lesion.
- Age ≥ 18 years, life expectancy ≥ 6 months, and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2.
- Adequate hematologic, hepatic, and renal function.
- Adequate recovery from toxicities/effects of prior therapy

Key exclusion criteria included the following:

- Prior systemic chemotherapy for locally advanced unresectable or mCRC. Prior adjuvant chemotherapy was allowed if disease progression was documented > 6 months after the end of the last cycle of adjuvant chemotherapy or ≥ 12 months for oxaliplatin-containing regimens.
- Prior radiotherapy to > 25% of bone marrow. Radiation therapy as a part of standard adjuvant chemoradiotherapy for rectal cancer > 6 months prior to study entry was allowed.
- Documented and/or symptomatic brain metastases.
- Previous therapy with monoclonal antibodies, or any agent targeting the EGFR.
- Current use of chronic non-topical corticosteroid treatment for > 6 months at doses > 10 mg/day of prednisolone or equivalent before study entry, which in the opinion of the investigator could compromise the patient or the study.
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Acute or subacute intestinal occlusion.
- History of other malignancies, with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix.
- Pregnancy or breastfeeding.
- Prior autologous or allogeneic organ or tissue transplantation.
- Interstitial pneumonia or interstitial fibrosis of the lung.

Study Drug, Dose, and Mode of Administration:

Necitumumab (IMC-11F8) administered at an absolute dose of 800 mg by intravenous (I.V.) infusion on Day 1 of each 2-week cycle.

Reference Therapy, Dose, and Mode of Administration:

Following administration of necitumumab on Day 1 of each 2-week cycle, each patient received the following treatments, in the order shown, all by I.V. infusion: oxaliplatin at a dose of 85 mg/m^2, folinic acid at a dose of 400 mg/m^2, and 5-fluorouracil (5-FU) as a bolus injection of 400 mg/m^2 immediately followed by a 46-hour continuous infusion of 2400 mg/m^2.

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: Best overall response rate (ORR); progression-free survival (PFS); duration of response; overall survival (OS)

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

Pharmacokinetic (PK): PK methods and results will be described in a separate PK report.

Pharmacodynamic: *KRAS* mutation status; *EGFR* status by immunohistochemistry.

Evaluation Methods:

Efficacy: Efficacy data were analyzed for all patients who received any study drug (mITT population). ORR was also calculated for the evaluable population. All patients underwent radiographic assessment of disease status approximately every 8 weeks throughout the study. The ORR was presented with a 95% confidence interval (CI). The Kaplan-Meier method was used to estimate the median duration of response (for patients with a best response of partial or complete response only), OS, and PFS with 95% CI. ORR, OS, and PFS were also presented by *KRAS* mutation status by PCR and EGFR status by immunohistochemistry.

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 included, according to the most severe grade per the National Cancer Institute – Common Terminology Criteria for Adverse Events, Version 3.0. Causality (relationship to study drug) was separately summarized. Duration of AE was determined and included in the listings along with action taken and outcome. AEs leading to dose modification or discontinuation of therapy were also summarized. Serious adverse events (SAEs) per the definition in the study protocol, were tabulated by system organ class, preferred term, and relationship to study drug. Laboratory findings (including laboratory abnormalities) were tabulated.

Pharmacokinetic/Pharmacodynamic: PK methods and results will be described in a separate PK report.

Summary:

A total of 44 patients (25 male, 19 female; median age = 64.0 years) were enrolled and treated at a total of five investigative sites. All patients had a diagnosis of adenocarcinoma, originating from the colon (29 patients; 65.9%) or rectum (34.1%), and either metastatic (42 patients; 95.5%) or locally advanced (2 patients; 4.5%). Patient disposition is summarized below.

	N = 44
Reasons for Discontinuation of Study Treatment	
Adverse Event	10 (22.7%)
Death	1 (2.3%)
Protocol Noncompliance	0
Progressive Disease	18 (40.9%)
Withdrew Consent	0
Other	15 (34.1%)

There were major protocol violations related to 30 of 44 patients (68.2%). The majority of these violations concerned missing procedures or medication errors. None of these violations is considered to have affected the safety of patients or evaluation of the efficacy endpoints. No patient was excluded from the evaluable population due to a protocol violation.

The combined treatment with mFOLFOX6 and necitumumab induced in 44 patients a best overall response rate (ORR) of 63.6% (95% CI = 47.8% to 77.6%), a median PFS of 10 months (95% CI = 7.0 months – 12.0 months) and a median OS of 22.5 months (95% CI = 11.0 months to 30.0 months).

The subgroup analysis in patients with *KRAS* wild-type tumors revealed a higher ORR and prolonged median PFS and OS compared to patients with mutant tumors (ORR: 87.5% vs. 55.6%; median OS: 30.0 months vs. 7.0 months; and PFS: 12.0 months vs. 7.0 months).

The most frequently reported treatment emergent AEs were from the System Organ Classes of General Disorders (mainly asthenia), Skin Disorders (mainly rash), Nervous System Disorders (mainly signs of sensory peripheral neuropathy), Gastrointestinal Disorders (mainly diarrhea), and Blood and Lymphatic System Disorders (mainly neutropenia); the most frequently reported Grade 3-4 events, occurring in more than 10% of patients, were asthenia, neutropenia, rash and paresthesia. Five patients died while on treatment (including four AEs with an outcome of death, none of which was considered related to necitumumab or chemotherapy).

Hypersensitivity reactions, skin toxicity, hypomagnesemia, thromboembolic events as well as hematologic toxicity and sensory peripheral neuropathy were analyzed as AEs of special interest with regard to necitumumab and mFOLFOX6 chemotherapy, respectively. Frequency and severity of skin toxicities, hypomagnesemia, hematologic and neurological toxicities did not exceed the range expected for the constituent agents. With regard to hypersensitivity reactions, one patient developed a hypersensitivity reaction considered related to necitumumab, assessed as serious event of Grade 2. Concerning thromboembolism, there were nine thromboembolic events reported; one case was considered related to necitumumab, a serious event of Grade 2 thrombosis in device. There were no other serious thromboembolic events or thomboembolic events of Grade 4-5, and there were no reports of cardiac ischemia.

Conclusions:

In this study, the combination of mFOLFOX6 and necitumumab was associated with high efficacy in terms of ORR (63.6%; 95% CI = 47.8% to 77.6%), median PFS (10 months; 95% CI = 7.0 months to 12.0 months), and median OS (22.5 months; 95% CI = 11.0 months to 30.0 months).

A historical comparison of necitumumab plus mFOLFOX6 as evaluated in this study with mFOLFOX6 alone suggested an add-on effect, with clinically relevant improvement in all observed efficacy parameters (ORR, median PFS, median OS).

The safety profile of the combination of necitumumab and mFOLFOX6 chemotherapy was shown to be acceptable and manageable, consistent with the established toxicity profile of the constituent chemotherapeutic agents and with the safety profile expected for an EGFR inhibitor, confounded by the underlying disease. The safety findings obtained in this study do not provide evidence to suggest that necitumumab aggravated the known toxicities of mFOLFOX6 or vice versa.

In conclusion, necitumumab in combination with mFOLFOX6 was associated with clinically relevant improvement in observed ORR, median PFS, and OS with an an acceptable safety profile as compared to mFOLFOX6 alone.