Title of Trial: A double-blind, randomized, comparative, multicenter, exploratory, and placebo-controlled Phase II trial of FOLFIRI plus MSC1936369B or placebo with a safety run-in part as second-line treatment of metastatic KRAS mutated colorectal cancer subjects

Investigational Product: Pimasertib (MSC1936369B)

Trial No.: EMR 200066-004

Study Center: This study was conducted in total of 4 centers (2 in Spain, 1 in Belgium, and 1 in Italy)

Trial Dates:

Trial Initiation Date: 03 March 2010

Trial Completion Date: 25 May 2012

Development Phase: Phase II

Publication (reference): Macarulla T, Tabernero J, Cervantes A, et al. Phase I/II study of FOLFIRI plus the MEK1/2 inhibitor pimasertib (MSC1936369B) as second-line treatment for KRAS mutated metastatic colorectal cancer. Annals of Oncology 2012 June; 23 (Suppl 4): iv 27

Study Objectives:

Part 1: Safety run-in part

Primary Objective:

- To determine the maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D) of pimasertib combined with FOLFIRI (irinotecan, 5- fluorouracil [FU], and folinic acid) as second-line treatment in subjects with KRAS mutated metastatic colorectal cancer (mCRC).

Secondary Objective:

- To assess the pharmacokinetics of pimasertib and irinotecan, and 5-FU concentration when combined in subjects with mCRC.
- To explore the anti-tumor activity of pimasertib combined with FOLFIRI as second-line treatment for subjects with KRAS mutated mCRC.
- To explore candidate markers for tumor characteristics and predictive of anti-tumor activity.
- To explore circulating markers in serum.

Part 2: Phase II randomized part

Primary Objective

- To assess the anti-tumor activity of pimasertib combined with FOLFIRI as second-line treatment in subjects with KRAS mutated mCRC in terms of progression-free survival (PFS).

Secondary Objectives

- To determine safety and tolerability of pimasertib combined with FOLFIRI as second-line treatment in subjects with KRAS mutated mCRC.
- To assess the anti-tumor activity in terms of response rate, clinical benefit, overall survival, and time to progression.
- To explore candidate markers for tumor characteristics and predictive of anti-tumor activity.
- To explore circulating markers in serum.
- To assess the pharmacokinetics of pimasertib in subjects with mCRC.

Methodology:

This was a 2-part trial, where a safety run-in part of pimasertib combined with FOLFIRI was to be followed by a randomized, placebo-controlled Phase II part of FOLFIRI + pimasertib versus FOLFIRI + placebo.

The safety run-in part was an open-label, dose-escalation, multicenter trial, following a dose escalation "3 + 3" cohort design where 3 to 6 subjects were enrolled at each dose level. The pimasertib dose was escalated on the basis of the dose-limiting toxicity (DLT) assessments. DLTs were monitored centrally, and the decision to escalate to the next dose level was to be made by the safety monitoring committee.

During the trial, the decision was made not to perform the randomized, placebo-controlled Phase II part of the study. The reason for this decision was that 2 DLTs had been reported at the pimasertib dose of 60 mg/day and the dose therefore could not be escalated above this dose level as per the protocol. The MTD was defined at the first dose level (45 mg/day). The estimated probability of observing clinical benefit with this combination at the first dose level of 45 mg/day of Pimasertib was considered to be low. Therefore, the current report only provides the summary of the results for the safety run-in part of the trial.

Number of Subjects (Planned and Analyzed):

Twenty-two screened, 16 enrolled, and 16 treated in the safety run-in part of the trial.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Male or female subjects aged ≥ 18 years with histologically confirmed KRAS mutated colon/rectum cancer. The disease had to have progressed during or after a first-line treatment for metastatic disease with oxaliplatin and fluoropyrimidins based chemotherapy with or without bevacizumab. The metastatic measurable disease had to be evident at trial entry as per the Response Evaluation Criteria In Solid Tumors (RECIST) v1.0 (at least 1 measurable lesion).

Study Treatment:

Test Product: Dose and Mode of Administration:

At each dose level, subjects received:

Pimasertib orally once daily for a 5-day on / 2-day off schedule continuously during a 28-day cycle (Days 1 to 5, 8 to 12, 15 to 19, and 22 to 26). In the first cycle, dosing of pimasertib on Day 15 to 19 was shifted by 1 day to Day 16 to 20 to allow pharmacokinetic (PK) evaluations for potential drug-drug interaction. The starting dose of pimasertib was 45 mg per day.

and

FOLFIRI on Days 1 and 15 of a 28-day cycle:

1. FA / l-folinic acid / levoleucovorin 200 mg/m² i.v. infusion over 90 minutes or leucovorin (*dl*-leucovorin) 400 mg/m² IV infusion over 90 minutes

and

2. Irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector.

   followed by

3. Bolus 5-FU 400 mg/m² and a 46-hour infusion 5-FU 2400 mg/m².

Duration of Treatment: Beyond Cycle 1, subjects were allowed to continue the trial treatment until progressive disease or intolerable toxicity or investigator / subject decision. Cycles were planned to last 28 days.

Reference Therapies, Dose and Mode of Administration:

Not applicable

Criteria for Evaluation:

Efficacy:

Computed tomography (CT) (or magnetic resonance imaging [MRI] if there were contraindications to CT) scans of the chest and abdomen and pelvis (at a minimum) was performed in order to document the baseline status of the tumor disease. In the safety run-in part, the tumor assessments were performed every 6 weeks and at the EOT.

The efficacy was evaluated by assessing the tumor response measured as the best response per time point for each subject, which was derived programmatically, based on RECIST v1.0 and using the investigator overall assessment of target, non-target, and new lesions at the corresponding time point.

The best overall response per subject was derived as the best response recorded from the start of treatment until disease progression using the derived overall response per time point. The subject's best response assignment depended on the achievement of both measurement and confirmation criteria.

Pharmacokinetics:

Concentration-time profiles for pimasertib, irinotecan, and irinotecan metabolite SN-38 were obtained based on plasma samples. Pharmacokinetic parameters were calculated using standard non-compartmental analyses. In addition, concentrations of 5-FU were determined at individual time points in subjects who received the 46-hour infusion via electronic pump.

Pharmacodynamics:

Blood samples were collected for assessing circulating biomarkers such as cytokines in serum. Archived tumor tissue samples were collected during screening to explore tumor predictive and prognostic biomarkers.

Safety:

Safety was assessed by adverse events (AEs), deaths, clinical laboratory abnormalities, electrocardiograms, echocardiograms / multi-gated acquisition (MUGA) data, vital signs, and ophthalmologic assessments.

In this trial, DLT assessments were part of the overall safety assessments of the trial drug. DLTs were any protocol pre-defined toxicities including (1) any Grade 3 or more non-hematological toxicity except for Grade 4 asymptomatic increases in liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]) reversible within 7 days in subjects with liver involvement, Grade 3 asymptomatic increases in liver function tests (AST, ALT, and ALP) reversible within 7 days in subjects without liver involvement, Grade 3 vomiting controlled with adequate and optimal therapy and prophylaxis (e.g., 5HT3 antagonists and corticosteroids), and Grade 3 diarrhea controlled with adequate and optimal anti-diarrhea therapy; (2) any Grade

4 neutropenia lasing >5 days or febrile neutropenia lasting > 1 day; (3) any Grade 4 thrombocytopenia or Grade 3 with bleeding; or (4) any treatment delay > 2 weeks due to trial treatment-related adverse effects at any dose level and judged to be possibly or probably related to the trial treatment (i.e., related to pimasertib and / or FOLFIRI) by the investigator and / or the Sponsor and relevant for the combination treatment.

Statistical Methods:

In this trial report, all analyses and data summaries were considered as descriptive statistics. The following descriptive statistics were used to summarize the trial data per dose level on the basis of their nature unless otherwise specified:

- Continuous variables: number of missing and non-missing observations, mean, standard deviation, median, minimum and maximum, and percentage change from baseline when applicable.

- Continuous variables for PK: number non-missing observations, mean, standard deviation, standard error of the mean, geometric mean, median, minimum and maximum, and coefficient of variation.

- Categorical variables: frequencies and percentages.

Results:

Subject Disposition:

Sixteen subjects were enrolled in the trial. All the 16 subjects participated in the safety run-in phase of the trial and received trial treatment, 10 being treated daily with 45 mg of pimasertib and 6 being treated daily with 60 mg of pimasertib.

All the 16 treated subjects were included in the safety analysis set. Fifteen (9 and 6 receiving 45 and 60 mg of pimasertib, respectively) of the 16 subjects were included in DLT analysis set and the efficacy analysis set.

Demographics and Baseline Characteristics:

The 16 enrolled subjects included 9 male (56.3%) and 7 female (43.8%) subjects. The mean age of the subjects was 61.6 years old with a range from 38 to 81 years old. All 16 subjects were white, with a mean body height of 166.9 cm, a mean body weight of 74.93 kg, and a mean body surface area (BSA) of 1.856 m^2. The ECOG performance status was 0 in 9 subjects (56.3%) and 1 in 7 subjects (43.8%).

The tumor histopathological diagnosis was adenocarcinoma of colon in 9 subjects (56.3%) and adenocarcinoma of rectum in 6 subjects (37.5%). An additional subject had a histopathological diagnosis of adenocarcinoma of cecum. At the time the primary tumor was diagnosed, most of the subjects had a T3 or T4 tumor classification, had the tumor already spread to regional lymph nodes (N1 or N2 classification), and had remote metastasis

(stage M1).

Efficacy Results:

Of the 15 subjects included in the efficacy analysis set, 2 (13.3%) had partial response, 9 (60.0%) had stable disease, and 3 (20.0%) had progressive disease as their best overall response. There was 1 subject whose best overall response status was not evaluable. Six subjects (40.0%) had a best overall response of stable disease, which lasted for at least 12 weeks.

Of the 15 subjects whose tumor response was evaluated, 9 subjects showed a reduction in tumor size and 3 subjects did not show a notable change in tumor size as compared with their respective baseline value assessed as the sum of target lesions. The tumor size enlarged during trial treatment in 3 subjects.

Pharmacokinetic Results:

Pharmacokinetic analysis of pimasertib, irinotecan, and SN-38, and evaluation of 5-FU concentrations suggested that there was no apparent pharmacokinetic drug-drug interaction between these compounds.

Pharmacodynamics Results:

The small population of subjects enrolled would not have provided enough statistical power to perform any analysis, therefore, the biomarker samples were not analyzed as part of the trial. These samples will be stored for 5 years as per the informed consent form (ICF) in the event proven useful in the framework of future biomarker studies. Any unused samples will be destroyed at the latest after 5 years.

Safety Results:

All 16 subjects experienced at least 1 treatment-emergent adverse event (TEAE) and treatment-related TEAE, 12 subjects (75.0%) experienced TEAEs of $\geq$ Common Terminology Criteria for Adverse Events (CTCAE) Grade 3, 8 subjects (50.0%) reported serious TEAEs, and 10 subjects (62.5%) had their trial treatment discontinued for TEAEs. No TEAEs leading to a fatal outcome were reported.

Diarrhea was the most frequently reported TEAE, which occurred in 13 of 16 subjects (81.3%). Other gastrointestinal disorders, such as nausea, vomiting, stomatitis, and abdominal pain were also each reported in several subjects with an incidence between 37.5% and 50.0%. Asthenia was the second most frequently reported TEAE after diarrhea, and occurred in 10 of the 16 subjects (62.5%). Other frequent TEAEs included rash reported in 8 subjects (50.0%), mucosal inflammation, neutropenia, and serous retinal detachment (preferred term for detachment of retinal pigment epithelium and macular degeneration), each being observed in 6 subjects (37.5%), and pyrexia and decreased appetite, each seen in 5 subjects (31.3%).

The majority of TEAEs were mild or moderate (Grade 1 or 2). Twelve subjects (75.0%) reported TEAEs of ≥ Grade 3. The most frequent ≥ Grade 3 TEAEs were neutropenia reported by 5 subjects (31.3%), diarrhea (reported by 3 subjects, 18.8%), and mucosal inflammation also reported by 3 subjects (18.8%). Specifically, grade 3 pimasertib-related mucosal inflammation occurred in 2 of the 6 subjects during cycle 1 of the pimasertib 60 mg/day cohort, and represented DLTs. Thus, the MTD was declared at 45 mg/day. All other ≥ Grade 3 TEAEs occurred in a single subject.

TEAEs considered related to pimasertib by the investigator were reported in all 16 subjects. The most frequent TEAEs related to pimasertib included diarrhea (62.5%), rash (50%), asthenia (37.5%), serous retinal detachment (preferred term for detachment of retinal pigment epithelium and macular degeneration) (37.5%), vomiting (31.3%), nausea (25.0%), mucosal inflammation (25.0%), stomatitis (18.8%), and neutropenia (18.8%). The ≥ Grade 3 TEAEs related to pimasertib were seen in 3 subjects for mucosal inflammation and neutropenia, in 2 subjects for diarrhea, and in 1 subject for iron deficiency anemia, hypomagnesemia, hyponatremia, ALT increased, and hyper transaminasemia.

Of the 15 subjects included in the DLT analysis set, 3 subjects experienced a DLT. One subject treated with pimasertib 45 mg/day (11.1%) reported hyponatremia and 2 subjects treated with pimasertib 60 mg/day (33.3%) each reported mucosal inflammation. All the 3 events in the 3 subjects were Grade 3 or more non-hematological toxicities that qualified as a DLT. Because 2 subjects experienced a DLT at the pimasertib 60 mg/day dose level, the dose level at 45 mg/day was considered as the MTD of pimasertib.

Ocular events and skin / rash events were considered AEs of special interest in this trial. Seven subjects (43.8%) reported ocular events during trial treatment. The ocular events observed included eye disorders of serous retinal detachment (preferred term for detachment of retinal pigment epithelium and macular degeneration) in 6 subjects (37.5%), maculopathy in 1 subject (6.3%), and visual impairment in 1 subject (6.3%) and nervous system disorders of visual field defect in 1 subject (6.3%). All these events were Grade 1 events except serous retinal detachment reported in 1 subject, which was considered a Grade 2 event.

Nine subjects (56.3%) experienced skin / rash events, which included rash in 8 subjects (50.0%), dermatitis acneiform in 2 subjects (12.5%), and dry skin in 1 subject (6.3%). The events of rash in 1 subject and dermatitis acneiform in 1 subject were considered Grade 2, and all other events were Grade 1 events.

Three subjects (18.8%) died, all due to disease progression and therefore considered unrelated to trial treatment by the investigators.

Eight subjects (50.0%) reported serious TEAEs. All serious TEAEs occurred in a single subject except for mucosal inflammation, which was observed in 2 subjects. No serious TEAEs led to a fatal outcome. Among all the serious TEAEs, those reported in 3 subjects (18.8%) were considered related to either pimasertib, or FOLFIRI, or both by the investigator. These included 2 cases of mucosal inflammation and asthenia,

cardiomyopathy, diarrhea, vomiting, electrocardiogram QT prolonged, and dehydration, each being reported in a single subject. The serious TEAEs that were considered related specifically to pimasertib treatment by the investigator were mucosal inflammation (2 subjects) and asthenia, cardiomyopathy, and electrocardiogram QT prolonged. The latter 3 events were reported in the same subject

Ten subjects (62.5%) experienced TEAEs that led to premature trial treatment discontinuation of at least 1 study drug. Half of the cases (5 subjects; 31.3%) were due to ≥ grade 3 events. Trial treatment of at least 1 study drug was discontinued in 8 subjects (50.0%) who had TEAEs considered related to pimasertib treatment by the investigator. Three of these 8 subjects had ≥ grade 3 events. Among these events, diarrhea, neutropenia, and mucosal inflammation each caused 2 subjects to discontinue at least 1 study drug, while all other events, including nausea, vomiting, cardiomyopathy, electrocardiogram QT prolongation, hyponatremia, and rash, each led a single subject to withdraw from at least 1 study drug.

During trial treatment, shifts of hematology parameter values were observed. The worst Common Toxicity Criteria (CTC) grade was < Grade 3 in most of the cases. Grade 3 hematology abnormalities were seen for hemoglobin in 2 subjects (12.5%), for white blood cell count in 4 subjects (25.0%), for neutrophil count in 3 subjects (18.8%), for lymphocyte count in 3 subjects (18.8%), and for platelet count in 1 subject (6.3%). In addition, a Grade 4 neutrophil count abnormality occurred in 2 subjects (12.5%).

During trial treatment, the worst liver function and creatinine abnormalities were < Grade 3 in most of the subjects. One subject (401-0002) (6.3%) experienced a transient Grade 3 ALT abnormality. This subject, who had liver metastasis, also had Grade 3 gamma-glutamyl transferase (GGT) and Grade 3 ALP abnormalities without significant elevations in total bilirubin values. The Grade 3 GGT abnormalities maintained until the last study assessment and the ALP value decreased to a Grade 2 abnormality in the subsequent assessments. It should be noted that 10 of 16 subjects had GGT abnormalities during trial treatment, and 3 of the 16 subjects had a Grade 3 GGT abnormality. Of the 3 subjects with a Grade 3 GGT abnormality, 2 already had Grade 3 GGT and the other subject had Grade 2 GGT at baseline.

The majority of abnormal blood electrolyte values were < Grade 3. Grade 3 abnormalities during trial treatment were observed for hyponatremia and hypocalcemia, each in a single subject (6.3%); Grade 4 abnormalities were observed for hyperkalemia in 2 subjects (12.5%), hypomagnesemia in 1 subject (6.3%), and hypermagnesemia in 1 subject (6.3%).

A degree of changes in vital signs, body weight, ECG signals, and results based on echocardiogram was observed during the trial. Some of these changes reflected daily fluctuations of the parameters and some other changes were more likely related to the underlying disease.

Conclusions:

In combination with FOLFIRI, dose escalation of pimasertib from 45 to 60 mg/day was

limited by toxicity (mucosal inflammation), and the MTD of pimasertib in combination with FOLFIRI was 45 mg/day. At this dose level, pimasertib was adequately tolerated in subjects with mCRC, and no unexpected or new safety signals / concerns were identified.

The most frequent TEAEs were diarrhea and other gastro-intestinal events. The other frequently reported Grade 1 or 2 events were skin rash, asthenia, and serous retinal detachments, as well as Grade 3 or 4 events of mucosal inflammation and neutropenia

Pharmacokinetic analysis of pimasertib, irinotecan/SN-38, and evaluation of 5-FU concentrations suggested that there were no apparent pharmacokinetic drug-drug interactions between these compounds

Pimasertib treatment at both doses of 45 and 60 mg/day in combination with FOLFIRI showed early signs of clinical activity in subjects with advanced CRC. The majority of treated subjects had a partial response (2 subjects) or stable disease (9 subjects, in which 6 had a disease stabilization lasting at least 12 weeks) as their best response to trial treatment and showed their tumor size reduced or unchanged during trial treatment. However, conduct of the Phase II part in the present trial was not recommended because of the estimated probability of observing clinical benefit with this combination at the first dose level of 45 mg/day of Pimasertib was considered to be low.