SYNOPSIS

Title of the study: A multicenter, randomized double-blind placebo-controlled Phase III study of the efficacy of xaliproden in preventing the neurotoxicity of oxaliplatin in first-line treatment of patients with metastatic colorectal cancer (MCRC) treated with oxaliplatin/5-FU/LV (EFC5505)

Coordinating Investigator: [redacted]

Study countries/centers: A total of 13 countries and 97 active centers including Argentina (3 centers), Australia (4 centers), Brazil (6 centers), Canada (4 centers), Chile (4 centers), Germany (6 centers), Hungary (5 centers), Italy (6 centers), Poland (7 centers), Portugal (7 centers), Spain (5 centers), UK (8 centers), and USA (32 centers)

Publications (reference): Not applicable

Study period: Date first patient enrolled: 16/Dec/2005; Date last patient completed: 30/Oct/2009

Phase of development: Phase 3

Objectives:

Primary

- Neuroprotection: To compare the risk of occurrence of Grade3-4 oxaliplatin-induced cumulative peripheral sensory neuropathy (PSN), relative to cumulative dose of oxaliplatin between:
  - the control arm A: oxaliplatin + 5-Fluorouracil/Leucovorin (5-FU/LV) + placebo
  - the experimental arm B: oxaliplatin + 5-FU/LV + xaliproden

Secondary

- Main secondary objective (chemotherapy efficacy): To compare the Response Rate (RR) between the control arm A and the experimental arm B in order to ensure that the efficacy of the chemotherapy is not compromised by the addition of xaliproden (non-inferiority)
- Other secondary objectives (neurotoxicity for each arm):
  - duration of oxaliplatin-induced PSN (Grades 2-4)
  - overall incidence of PSN during treatment by patient and by Grades (1-4)
  - time and dose to onset of PSN (Grades 1-4)
  - incidence of dose-reduction and dose-delay due to PSN
  - incidence of oxaliplatin treatment discontinuation due to PSN
  - change in nerve conduction studies (NCS)
- Chemotherapy efficacy:
  - progression free survival (PFS)
  - overall survival
- Safety profile other than PSN

Methodology: Multinational, multicenter, randomized, placebo controlled, 2-arms Phase III study of xaliproden or matching placebo in combination with oxaliplatin/5-FU/LV (modified FOLFOX6) in patients with MCRC, not previously treated for metastatic disease

Number of patients: Planned: 900 (450 per arm); Randomized: 879 (440 placebo, 439 xaliproden); Treated: 875; Efficacy: 879; Safety: 875

Pharmacokinetics : Not applicable

Diagnosis and main criteria for inclusion:

- Age ≥ 18 years
- World Health Organization (WHO) performance status (PS) : 0 or 1.
- Histologically or cytologically-proven metastatic cancer of the colon or rectum; metastatic disease not curable by surgery or amenable to radiation therapy with curative intent.
- Measurable disease: at least one unidimensionally measurable lesion with a diameter ≥ 20 mm using conventional computerized tomography (CT) or magnetic resonance imaging scans or ≥ 10 mm using spiral CT scans
- Prior adjuvant chemotherapy with 5-FU/LV, with Fluorouracil (5-FU)/levamizole, with irinotecan/5-FU/LV, with capecitabine allowed provided disease-free interval from end of the adjuvant therapy > 6 months, with oxaliplatin/5-FU/LV provided the PFS from end of adjuvant therapy > 12 months
- No PSN > grade 1

Investigational product: SR57746A (xaliproden) or matching placebo capsules

Dose: 1 mg

Administration:

- One capsule of 1mg SR57746A or matching placebo oral daily after breakfast
- Chemotherapy once every 2 weeks as modified FOLFOX6 (mFOLFOX6):
  -D1: Oxaliplatin 85 mg/m², intravenous (IV) over 2 hours, LV 350 mg/m², IV over 2 hours followed by 5-FU 400 mg/m², IV bolus
  -D1+ D2: Followed by 5-FU 2400 mg/m² over 46-hour continuous IV infusion

Treatment with bevacizumab was permitted in countries where it was specifically approved for use in combination with 5-FU based chemotherapy.

Batch numbers: [redacted]

Duration of treatment: Study drug (xaliproden or placebo) was initiated on Day 1 of the first cycle of chemotherapy and administered daily while the patient was under treatment with oxaliplatin. Study drug dose was not adjusted when the chemotherapy dose was delayed or reduced. The end of treatment with study drug depended on the patients' PSN status at the time oxaliplatin was discontinued. Patients reporting PSN ≤ Grade 1 at that time point discontinued study drug 15 days after the last administration of oxaliplatin. Patients reporting PSN > Grade 1 at that time point continued to be treated with study drug, as initially randomized, until resolution of symptoms of PSN, and up to a maximum of 3 months after the last administration of oxaliplatin

Duration of observation: The duration of study period per patient included:

- Anti-cancer therapy: intended to be administered up to disease progression
- Study drug (either xaliproden or placebo) up to 15 days following oxaliplatin discontinuation or up to a maximum of 3 months following oxaliplatin discontinuation as described above
- Post-study drug observation for all treatment emergent adverse events (TEAEs) up to 30 days after last administration of study drug
- Patients with persisting PSN at post-study drug period followed for PSN resolution once every 2 months (in case disease progression was not yet documented) or/then once every 3 months (after disease progression was documented)
- Follow-up for survival status up to death or cut-off date whichever came first

Reference therapy: Not applicable

Background: As no statistical significant difference was observed for the primary endpoint the decision was made by the Sponsor to stop development of xaliproden. Consequently, the current clinical study report (CSR) is an abbreviated report. Data cutoff date for the primary analysis was events driven (date of occurrence of 125th Grades 3-4 PSN) event and defined as May 15, 2009, with database lock (DBL) for analyses on June 30, 2009. Per Sponsor's decision, patients who were still under treatment at the time the results on primary endpoint were made available were to end treatment with xaliproden or placebo by August 31, 2009, have their last follow-up visit by September 30, 2009. The last patient completed treatment 30 October 2009. The final DBL took place on December 22, 2009, and safety and secondary efficacy data from baseline to study completion were updated for the CSR.

Criteria for evaluation and statistical methods: Safety data were evaluated and analyzed using descriptive statistics. Primarily, safety was evaluated via the analysis of adverse events (AEs) according to the National Cancer Institute Common Toxicity Criteria, version 3.0, dated 31 March 2003. For efficacy, the primary endpoint (probability of occurrence of Grade 3-4 PSN relative to the cumulative dose of oxaliplatin) was analyzed using the Kaplan-Meier method and comparison between groups was performed using a 2-sided logrank test. Neuroprotection was measured via grading of neurotoxicity (using the oxaliplatin specific scale for dose adjustment and by using NCS) and antitumoral efficacy assessed by using the Response Evaluation Criteria In Solid Tumors criteria and by measuring survival.

Summary:

Study population accountability and demographics

A total of 879 patients were randomized (440 placebo, 439 xaliproden), and 521 (59.3%) males and 358 (40.7%) females were included in all intention-to-treat (ITT) analyses. Median age was 62 years (range: 22 to 86) while WHO PS was 0 in 560 (63.7%) patients and 1 in 318 (36.2%) patients. A total of 875 received study drug treatment and were included in the safety analysis. Overall, patientdemographics and disease characteristics were evenly balanced across arms.

Primary tumor site was colon in 407 (54.9%) patients, rectosigmoid in 169 (19.2%) patients, rectum in 224 (25.5%) patients and "Other" in 3 (0.3%) patients. Organs involved included liver in 691(78.6%) patients, lungs only in 40 (4.6%) patients and "Other including lymph nodes" in 142 (16.2%) patients. Over half of the patients (517 [58.8%]) had ≥ 2 organs involved. Median time from diagnosis was 1.64 months (range: 0.1 to 83.9 months).

At baseline, a total of 165 (18.8%) patients had prior adjuvant therapy and 7 (0.8%) were receiving prior oxaliplatin while 26 had PSN Grade ≥ 1 and 112 had diabetes.

Safety results

The maximum duration of dosing with study drug was 107 weeks in the placebo arm and 129 weeks in the xaliproden arm with a median of 28.7 weeks for both arms. Compliance was within the interval of [95%:100%] for the majority of patients (699 patients or 79.9%). A total of 362 (82.5%) patients in the placebo arm versus 337 (77.3%) in the xaliproden arm had received the study treatment as planned in the protocol. Exposure to oxaliplatin/5-FU was similar in the 2 arms, with a median of 12 cycles each, respectively. Median cumulative dose of oxaliplatin was 894 and 927 mg/m² in the placebo and xaliproden arms, respectively. Relative dose intensity was of 85.1 and 88.6 % in the placebo and xaliproden arms, respectively. Bevacizumab treatment was reported for 95 (10.8%) patients (46 placebo, 49 xaliproden) during the study.

A total of 865 (98.8%) patients experienced TEAE during the study. The body systems with the most frequently reported (≥ 10%) clinical TEAEs (all grade events) in both arms were: gastrointestinal disorders (diarrhea, nausea, vomiting, constipation, abdominal pain, stomatitis), general disorders and administration site conditions (fatigue/asthenia, pyrexia, mucosal inflammation), nervous system disorders (dysguesia, headache), metabolism and nutrition disorders (anorexia), respiratory, thoracic and mediastinal disorders (cough, epistaxis), skin and subcutaneous tissue disorders (alopecia), musculoskeletal and connective tissue disorders (back pain) and psychiatric disorders (insomnia). Considering treatment with xaliproden/placebo, discontinuation due to AEs was similar in both arms (34 [7.7%] for placebo and 35 [8.0%] for xaliproden).

Generally, on a system organ class (SOC) basis, the incidence of AEs across both arms was similar, with the exception of vascular disorders where Grades 3-4 events were reported in 26 (6.0%) patients in the xaliproden arm versus 9 (2.1%) patients in the placebo arm. This difference was mostly due to events of hypertension. Hypertension events were reported in 22 (5.0%) and 51 (11.7%) patients in the placebo and xaliproden arm, respectively. These events were of Grade 3-4 in 2 (0.5%) and 10 (2.3 %) patients in the placebo and xaliproden arms, respectively. In the vascular disorder body system, all grades AEs were reported in 23.6% of the patients in the xaliproden treatment arm and in 19.1 of the patients in the placebo arm. Incidence of hypertension events mostly account for this difference (11.7% vs 5%). Considering the pooling of selected AE of interest, no imbalance in the rate of venous thrombotic events and more particularly in the rate of pulmonary embolism was reported.

Deaths within 30 days of last treatment (either oxaliplatin or xaliproden/placebo) were reported for 55 (6.3%) patients (25 placebo, 30 xaliproden) and among them, 21 died from progression disease (6 placebo, 15 xaliproden) while the remaining 34 patients (19 placebo, 15 xaliproden) died from fatal AEs.

Serious TEAEs (mostly Grade 3 or 4) were reported in 280 patients: 125 (28.5%) patients under placebo and 155 (35.6%) patients under xaliproden. Serious TEAEs were more common in the gastrointestinal disorders SOC (diarrhea, intestinal obstruction), infections and infestations (pneumonia, sepsis), general disorders and administration site conditions (disease progression, pyrexia), blood and lymphatic system disorders (febrile neutropenia, anemia), respiratory, thoracic and mediastinal disorders (pulmonary embolism) and vascular disorders (deep vein thrombosis). Serious AEs were more frequent in the xaliproden treatment group (35.6% vs 28.5% all grades and 29.1%, 24.8% Grade 3-4). This difference is mostly due to a higher incidence from the vascular disorders (3.4% vs 0.9%) and cardiac disorders (2.3% vs 0.7%) SOCs.

Efficacy results

No statistically significant difference was observed for the primary endpoint of probability of occurrence of Grade 3-4 PSN relative to the cumulative dose of oxaliplatin (p =0.1089, hazard ratio: 0.76, 95%CI: 0.54, 1.07).

Nerve conduction studies were to be performed at baseline, at the end of treatment with oxaliplatin and at the end of treatment with the study drug. At baseline and at the end of treatment with oxaliplatin, the 2 groups were comparable for compound muscle action potential (CMAP) and for sensory action potential (SAP). Median changes CMAP or SAP amplitude were comparable between treatment arms.

At the primary cutoff for analysis, the incidence by patient of PSN events showed a total of 713 (81%) patients in the ITT population with PSN during the study. The incidence of Grade 3 PSN was slightly higher in the placebo arm with 73 (16.6%) patients reporting Grade 3 events versus 59 (13.4%) in the xaliproden arm. In addition, oxaliplatin was discontinued due to PSN with a higher incidence in the placebo arm (66 patients or 15.0%) than in the xaliproden arm (54 patients or 12.4%),

Patients who reported PSN > Grade 1 at the end of treatment with oxaliplatin had to continue treatment with xaliproden/placebo (as intially randomized) up to recovery or for a maximum of 3 months following oxaliplatin discontinuation. Continuation of xaliproden after discontinuation of oxaliplatin did not influence the rate or the time to recovery of PSN as shown by similar probability of partial and full recovery over time in the placebo and xaliproden treatment groups.

In the ITT population the RR was 50.9 % and 51.3 % in the placebo and xaliproden arms, respectively. No difference between arms was noted on time related parameters.

Conclusions

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Date of report: 15-Oct-2010