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Sponsor/company:	sanofi-aventis	ClincialTrials.gov Identifier:	NCT00129870
		Study Code:	L_9444
Generic drug name:	Oxaliplatin	Date:	30/Oct/2009

Title of the study: CONcePT – A Phase IV, randomized, prospective multicenter comparison of an intermittent schedule of oxaliplatin (IO) combined with 5-fluorouracil/leucovorin (FOLFOX)/bevacizumab versus the conventional (CO) mode of administration of FOLFOX/bevacizumab plus neuroprophylaxis with calcium/magnesium for the optimization of first-line therapy of metastatic colorectal cancer

Investigators:

Axel Grothey, MD (The Mayo Clinic, Rochester, MN) and Howard Hochster, MD (New York University School of Medicine, New York, NY) were the Principal Investigators for this study.

Study centers: A total of 42 active centers in the United States

Publications (reference):

H.S. Hochster, A. Grothey, A. Shpilsky, B.H. Childs. Effect of intravenous (IV) calcium and magnesium (Ca/Mg) versus placebo on response to FOLFOX+bevacizumab (BEV) in the CONcePT trial. 2008 Gastrointestinal Cancers Symposium. Abstract # 280.

A. Grothey, L. Hart, K. Rowland, R. Ansari, S. Alberts, N. Chowhan, A. Shpilsky, H. Hochster. Intermittent oxaliplatin (oxali) administration and time-to-treatment failure in metastatic colorectal cancer (mCRC): final results of the phase III CONcePT trial. *Journal of Clinical Oncology*, 2008 ASCO. Annual Meeting Proceedings. Vol 26 (May 20 suppl; abstract # 4010, oral presentation).

Study period:

Date first subject enrolled: 08-Feb-2005

Date last subject completed: 24-Jul-2007

Phase of development: Phase IV

Objectives: The primary objective was to test the hypothesis that an intermittent oxaliplatin (IO) administration schedule of oxaliplatin combined with 5-fluorouracil (5-FU)/leucovorin (LV) (FOLFOX)/bevacizumab will allow subjects to remain on therapy for a longer period of time compared to a conventional oxaliplatin (CO) "treat-to-failure" administration schedule, by reducing the proportion of subjects who discontinue therapy for treatment-related toxicity. Secondary objectives were to evaluate the effect of calcium/magnesium (CaMg) infusions on the incidence and severity of neurotoxicity in subjects receiving either the IO or CO FOLFOX/bevacizumab treatment schedules as first-line treatment for metastatic colorectal cancer (MCRC) and to evaluate the safety and efficacy of the IO vs the CO schedule + CaMg infusions, as part of oxaliplatin-based first-line therapy for MCRC.

Methodology: This was a randomized, controlled, open-label, parallel group, multicenter Phase IV study. Initially, this was a 4-arm design, but due to slow enrollment the study was amended to a 2-arm design. The 4-arm design was placebo-controlled for CaMg. Both designs compared the CO schedule as the control to the IO schedule.

Number of subjects: Planned: 270 subjects total

Randomized: 180 subjects total: 140 subjects in Cohort 1 (34 subjects in the CO + Placebo [ConvPlacebo] group, 35 subjects in the CO + CaMg [ConvCaMg] group, 36 subjects in the IO + Placebo [ImttPlacebo] group, and 35 subjects in the IO + CaMg [ImttCaMg] group; and 40 subjects (20 subjects in each ConvCaMg and Imtt CaMg group) in Cohort 2.

Treated: 179 subjects total: 139 subjects in Cohort 1 (1 subject in the ConvCaMg group was not treated) and 40 subjects in Cohort 2.

Evaluated:

Efficacy: Intent-to-Treat (ITT) Population—140 subjects in Cohort 1 (34 ConvPlacebo, 35 ConvCaMg, 36 ImttPlacebo, 35 ImttCaMg)

As-treated Population—139 subjects in Cohort 1 (33 ConvPlacebo, 35 ConvCaMg, 36 ImttPlacebo, 35 ImttCaMg)

Safety: 179 subjects total: 139 subjects in Cohort 1 (1 subject in the ConvCaMg group was not treated) and 40 subjects in Cohort 2.

Pharmacokinetics: Not applicable.

Diagnosis and criteria for inclusion: Adult subjects who had: histologically or cytologically documented adenocarcinoma of the colon, rectum, or appendix that was inoperable metastatic or recurrent disease and for which they received no prior therapy (adjuvant therapy with 5-FU/LV or irinotecan was allowed if completed at least 6 months prior to registration); at least 1 unidimensionally measurable lesion with a diameter ≥20 mm using conventional computed tomography (CT) or magnetic resonance imaging (MRI) scans or ≥10 mm using spiral CT scans (single target lesions diagnostically confirmed); Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1; adequate hematologic renal and hepatic function; normal electrocardiogram (ECG); no other serious concomitant disease. Subjects with either Type I or Type II diabetes were considered eligible providing that the subject was otherwise fit to participate in the study and had no evidence of peripheral neuropathy ≥ Grade 1 (as defined by the NCI Common Terminology Criteria for Adverse Events version 3.0 [NCI CTCAE v3.0]).

Investigational product: Cohort 1 and 2: IO treatment schedule—FOLFOX/bevacizumab/CaMg alternating with 5-FU/LV/ bevacizumab maintenance

Dose: Oxaliplatin, 85 mg/m^2; LV, 200 mg/m^2; 5-FU, 2400 mg/m^2; bevacizumab, 5 mg/kg; CaMg, 1 g each of calcium gluconate and magnesium sulfate in 100 mL dextrose 5% injection (D5W) or normal saline. Maintenance treatment omits oxaliplatin and CaMg.

Administration: Intravenously (IV)

Duration of treatment: The IO treatment schedule consisted of eight 14-day cycles, alternating with 5-FU/LV/bevacizumab for eight 14-day cycles; the CO treatment schedule consisted of 14-day cycles ("treatment to failure") continued until death, disease progression, unacceptable toxicity, subject refusal, or treatment delay beyond that permitted for each treatment. For progressive disease on "maintenance" that fulfilled certain criteria, early reintroduction of oxaliplatin was permitted after consultation with the Sponsor.

Duration of observation: Observation consisted of a Prestudy Period (within 14 days prior to randomization), a Treatment Period (alternating eight 14-day cycles for the IO treatment schedule or 14-day cycles for the CO treatment schedule, repeated until discontinued as described above) and a Follow-up Period (3 years from the date of randomization).

Reference therapy: Cohort 1 only: CaMg placebo; Cohorts 1 and 2: CO treatment schedule—FOLFOX/bevacizumab/CaMg

Dose: CaMg placebo: normal saline; Oxaliplatin, 85 mg/m^2; LV, 200 mg/m^2; 5-FU, 2400 mg/m^2; bevacizumab, 5 mg/kg; CaMg, 1 g each of calcium gluconate and magnesium sulfate in 100 mL D5W or normal saline

Administration: IV

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was time to treatment failure (TTF) for the CO schedule in comparison with the IO schedule.

The secondary endpoints were:

Incidence of adverse events (AEs), including neurotoxicity, as determined using the NCI CTCAE v3.0.

Quality of Life, including oxaliplatin-specific neurologic symptoms, as determined using the Peripheral Neuropathy Questionnaire (oxaliplatin-specific) (PNQoxali).

Tumor response rate (overall and confirmed) based on application of the Response Evaluation Criteria in Solid Tumors (RECIST).

Time to tumor progression (TTP).

Time of tumor control (TTC), as discussed in Background and defined under Statistical Methods.

Overall Survival (OS).

Reasons for treatment discontinuation.

For all secondary endpoints the main comparison was between the CO and IO treatment schedules. The effect of CaMg on each of the tumor-specific endpoints was also determined in a secondary analysis, as discussed in the Statistical Methods section.

Safety: AEs (with an emphasis on neurotoxicity), hematology and blood chemistry, blood pressure, weight.

Pharmacokinetics: Not applicable.

Pharmacokinetic sampling times and bioanalytical methods: Not applicable.

Statistical methods: Prior to the first Data Monitoring Committee (DMC) meeting, enrollment was halted to modify the study design (removal of placebo arms), but subjects already enrolled in the study were allowed to continue treatment and follow-up procedures. Enrollment was restarted upon approval of the amendment by each study site. These subjects were identified as Cohort 2. After a planned review by the DMC, additional DMC-directed unplanned analyses resulted in suspension of enrollment. Subsequent unplanned additional, independent review and analyses followed in an attempt to confirm the DMC conclusion; it was not confirmed.

Study analysis populations included the ITT Population (as-randomized), the As-treated population, and the Safety Population. The ITT Population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received any study drug or received a different drug from that to which they were randomized. The As-treated Population consisted of all randomized subjects who had taken at least 1 dose of any of the study drugs (with the treatment assignment designated according to what was actually administered) and who provided sufficient efficacy data for a given endpoint. This population may be different for each selected endpoint. The Safety Population included all randomized subjects who received at least 1 dose of any of the study drugs with treatment assignment designated according to what was actually administered. The Safety Population was used for the analysis of all safety parameters.

For the purposes of determining the statistical superiority of the IO treatment schedule to the CO treat-to-failure schedule, the full analysis set (ITT Population) comprising the CaMg treatment arms was the primary population for the assessment of efficacy according to the protocol. However, more than 50% of subjects in Cohort 2 were discontinued due to study closure and differences in censoring patterns, making the placebo groups incomparable with the CaMg groups in the pooled analyses of both Cohorts. Therefore, the analysis of protocol-specified treatment approaches based on the ITT Population subjects treated with CaMg was no longer the primary analysis; exploratory analyses based on all treated subjects and pooling all subjects from both cohorts was not performed.

The primary efficacy endpoint was TTF for the CO treatment schedule in comparison with the IO treatment schedule. This was further limited to the As-treated Population of Cohort 1.

Secondary efficacy endpoints included: tumor response rate (overall and confirmed) based on application RECIST, TTP, TTC, as discussed in the Background section of the study protocol and defined under the Statistical Methods section of the study protocol, OS, and reasons for treatment discontinuation.

For all secondary endpoints the main comparison was planned between the CO and IO treatment schedules. However, motivated by unplanned analyses performed by the DMC in June 2007, the effect of CaMg on each of the tumor-specific endpoints was also examined in a secondary analysis, as discussed in the Statistical Methods section.

Quality of life assessments related to oxaliplatin-specific neurologic symptoms were made using the subject-based psychometric instrument called the PNQoxali, which consisted of two 5-point Likert-type scales asking responders to indicated their level of: numbness, pain, burning, tingling, or change in sense of touch in hands/fingers, or feet/toes, or mouth area; difficulty in swallowing, breathing, drinking, or chewing food, or muscle spasms in the mouth/jaw, hands/fingers, or feet/toes.

Assessments of safety were based on the incidence of AEs, including neurotoxicity, as classified using the NCI CTCAE v3.0.

There were no interim analyses, but there were 2 DMC meetings (up to 3 meetings could have been held at the discretion of the DMC as set forth in the study protocol). An unplanned Independent Radiology Review Committee (IRRC) analysis was also conducted after study closure but before the blind was broken.

Summary:

Efficacy results:

According to the 2-factor Cox regression model, the IO treatment schedule is associated with statistically significant improvement of TTF when compared with the CO schedule, while the CaMg effect was found to not be significant. Similarly, by log-rank tests when stratified by neuroprophylaxis factor (CaMg vs. Placebo), or without stratification, TTF prolongation with the IO treatment schedule was found to be statistically significant. Similar effects were found with respect to TTP.

As an effect of CaMg treatment was not demonstrated, the treatment groups were collapsed, ie, the ImttPlacebo and ImttCaMg groups were combined, and the ConvPlacebo and ConvCaMg groups were combined. Median TTF was 18.1 weeks for the combined Conv treatment group and 24.6 weeks for the combined Imtt treatment group. The respective 95% confidence intervals (CIs) were 16.1 to 24.0 weeks for the combined Conv group and 20.6 to 30.7 weeks for the combined Imtt group. TTF ranged from 10.9 to 27.1 weeks for the combined Conv treatment group and from 17.3 to 39.4 weeks for the combined Imtt treatment group.

TTF was significantly longer for subjects receiving the IO treatment schedule compared with subjects receiving the CO treatment schedule (p=0.002 unstratified, p=0.003 stratified by neuroprophylaxis treatment; log-rank test).Neither the 2-factor logistic regression exploratory model, nor the Fisher's exact test performed on the IRRC response data showed any significant relationship to tumor response (sequentially confirmed response, subsequently confirmed response, or unconfirmed response) with respect to treatment schedule (IO vs. CO) or use of CaMg.

No significant effect of CaMg on response rate was observed, regardless of the criteria used for response rate determination. Similarly,

neither treatment schedule nor neuroprophylaxis treatment had an effect on time to first response.

Neurotoxicity, as assessed using PNQoxali, was affected favorably by Imtt treatment for both chronic and acute peripheral sensory neuropathy (PSN), and was affected favorably by CaMg for chronic PSN.

Safety results:

The effect of CaMg infusion on the incidence and severity of neurotoxicity in subjects receiving treatment using either the IO or CO administration schedule could not be determined due to the small sample size and because the study was not designed to answer this question. Benefit relative to placebo also could not be determined because the study was amended to discontinue the placebo arms due to poor enrollment and existing standard of care practices. The CO treatment schedule was associated with a higher number of Grade 3 to 4 PSN events, as well as neurotoxicity events leading to dose reductions or discontinuations from the study treatment, when compared with the IO treatment schedule.

No new safety signals with regard to oxaliplatin emerged from this study.

Pharmacokinetic results: Not applicable.

Date of report: 29-Oct-2009