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Sponsor / Company: Sanofi **Drug substance(s):** oxaliplatin	**Study Identifiers:** NCT01087658, UTN U1111-1116-9494 **Study code:** OXALI_L_03768
Title of the study: A multicentre, randomized, open-label, phase III study comparing the efficacy of oral glutamine and calcium-magnesium with calcium-magnesium alone in the prevention of oxaliplatin-induced neurotoxicity in patients with colorectal cancer treated with oxaliplatin in adjuvant or 1st line metastatic settings.	
Study center: Multicenter: 13 Canadian centers randomized patients (14 sites were opened)	
Study period: Date first patient enrolled: 16/Feb/2010 Date last patient completed: 18/Mar/2013	
Phase of development: Phase 3	
Objectives: Primary Objective: To assess the benefit of glutamine when added to calcium-magnesium (CaMg) on the occurrence of grade 2, 3, and 4 peripheral sensory neuropathy (PSN) related to oxaliplatin with the National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE) scale taking into account the time from the start of oxaliplatin at which the first event occurred. Secondary Objectives: ▪ To determine the cumulative dose of oxaliplatin when the first occurrence of grade 2, 3 or 4 PSN. ▪ To determine the incidence of dose-reductions, dose-delays and discontinuations of oxaliplatin due to PSN grade 3 or 4. ▪ To assess effects of glutamine when added to Ca-Mg on patients-reported outcomes using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12 items questionnaire (FACT/COG NTX-12) subscale. ▪ To determine Progression-Free Survival (PFS) for metastatic patients. ▪ To evaluate the incidence of diarrhea.	
Methodology: Canadian multicenter, randomized (randomization 1:1), open-label, 2 parallel arms, Phase 3 study. Oxaliplatin-based chemotherapy (5-fluorouracil, leucovorin and oxaliplatin [FOLFOX-4]; modified FOLFOX-6 [mFOLFOX-6]; or capecitabine plus oxaliplatin [XELOX]) with open-label glutamine and CaMg or CaMg alone.	

Number of patients:	Planned: 200 Randomized: 200 Treated: 200
Evaluated:	Efficacy: 200 (intent-to-treat [ITT]) Safety: 200

Diagnosis and criteria for inclusion: Colorectal cancer (CRC) (adjuvant or 1st line metastatic setting) diagnosed patients ≥18 years of age, with an Eastern Cooperative Oncology (ECOG) ≤2, without any major surgical procedure in the prior 4 weeks, with normal electrocardiogram, adequate liver, kidney and hematological function with life expectancy of >6 months according to the investigator.

Study treatments

Investigational medicinal product(s): glutamine, calcium gluconate, magnesium sulfate.

Formulation: Tablets: glutamine. Solution: calcium gluconate, magnesium sulfate.

Route of administration: Per orem (PO): glutamine. Intravenous: calcium gluconate, magnesium sulfate.

Dose regimen:

ARM A: Glutamine 10 g PO three-times-a day (TID) beginning at Day 2 for 7 consecutive days during each chemotherapy cycle. 1 g of calcium and 1 g of magnesium will be delivered IV over 30 minutes just before the chemotherapy and repeated at the same dose after the completion of the oxaliplatin infusion.

ARM B: 1 g of calcium and 1 gram of magnesium will be delivered IV over 30 min just before the chemotherapy and repeated at the same dose after the completion of the oxaliplatin infusion.

Noninvestigational medicinal product(s): Oxaliplatin, 5-fluorouracil (5-FU), capecitabine, leucovorin (LV), bevacizumab.

Formulation: Tablets: capecitabine. Solution: oxaliplatin, 5-FU, LV, bevacizumab.

Route of administration: PO: capecitabine. Intravenous: oxaliplatin, 5-FU, LV, bevacizumab.

Dose regimen: FOLFOX-4: every 2 weeks, Day 1: oxaliplatin (85 mg/m2) with LV (200mg/m2) for 2 hours followed by 5-FU

bolus (400 mg/m2) followed by continuous infusion for 22 hours (600 mg/m2), Day 2: similar to day 1 without oxaliplatin infusion.

mFOLFOX-6: every 2 weeks, Day 1: oxaliplatin (85 mg/m2) with LV (400mg/m2) for 2 hours followed by 5-FU bolus (400 mg/m2) followed by continuous infusion for 46 hours (2400 mg/m2).

XELOX: every 3 weeks, Day 1: oxaliplatin (130 mg/m2) for 2 hours with capecitabine (1000 mg/m2) twice, Days 2-14:

capecitabine (1000 mg/m2) twice a day.

Bevacizumab (5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks) use is at the discretion of the treating physician.

Duration of treatment: 6 months

Duration of observation: 7 months

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint was the occurrence of PSN grade 2, 3 or 4 NCI-CTCAE (Version 4.0) taking into account the time from start of oxaliplatin at which the first event occurred. The main secondary endpoints were cumulative dose of oxaliplatin and time of onset of PSN grade 2, 3 and 4, dose-reduction, dose-delay and discontinuation due to PSN grade 3 or 4, patient self-report neurotoxicity scale for chronic peripheral neuropathy with the FACT/GOG NTX-12 questionnaire and PFS.

Safety:

Adverse events (AEs) and serious adverse events (SAEs) were collected, with special interest in the incidence of diarrhea.

Statistical methods:

The primary efficacy endpoint was analyzed in the ITT population defined as all randomized patients. The primary analysis was to compare Kaplan-Meier curves for both the glutamine with CaMg and the CaMg groups of patients using the log-rank statistic. When the sample size is 100 patients per arm, there is an 83% chance of detecting a statistically significant difference of 20.3% based on two-sides type 1 error of 5% when taking into account when the first PSN with a grade >1 occurred.

Summary:

Population characteristics:

Patients had a median age of 60 years old, were mostly man (59.0%) and were mostly white (95.0%). There was no statistical difference in population characteristics between groups. More patients had a tumor located in the colon (77.5%) than in the rectum (22.5%), with a similar distribution between groups. The median duration of colon or rectal cancer was 1.8 months (range 0.1 to 156.7 months). At study entry, 29.0% of patients had a metastatic disease while the remaining 71.0% received chemotherapy in adjuvant settings. Patients were mainly treated with mFOLFOX-6 (87.9% of total metastatic patients and 89.2% of patient receiving chemotherapy in adjuvant settings). Use of previous chemotherapy, previous therapy other than chemotherapy and prior/concomitant medication was distributed evenly between groups. There was no statistically significant difference between treatment groups with regard to the number of discontinued patients and the reasons for discontinuation

Efficacy results:

There was no statistically significant difference between the two treatment groups in the time to first occurrence PSN of grade 2, 3 or 4. The median time of first occurrence PSN grade 2, 3, 4 was 174 days in patients treated with CaMg and 162 days in patients treated with CaMg+glutamine. There was no statistical difference between groups for the cumulative dose of oxaliplatin at first occurrence of grade 2, 3 or 4 PSN, the incidence of dose-reductions, dose-delays and discontinuations of oxaliplatin due to PSN grade 3 or 4, patients-reported outcomes using the FACT/GOG NTX-12 subscale, the PFS of metastatic patients and the incidence of diarrhea.

Safety results:

Display of treatment-emergent adverse events (TEAEs) was separated based on the observation period of CaMg and/or glutamine (Glu) or oxaliplatin.

CaMg/Glu:

All TEAEs occurred in 99.0% of patients with TEAs possibly related to CaMg/Glu occurred more frequently in patients treated with CaMg+Glu (31.1%) compared to patients treated with CaMg (6.2%). All SAEs were reported in 14.0% of patients and possibly related to CaMg/Glu in 2.0% of patients with an even distribution between groups. No TEAE leading to death was reported. A similar proportion of patients with a TEAE leading to permanent treatment discontinuation was reported in each group.

Oxaliplatin:

All TEAEs occurred in 99.5% of patients with TEAE possibly related to oxaliplatin occurred more frequently in patients treated with CaMg+Glu (94.2%) compared to patients treated with CaMg (85.6%). All SAEs were reported in 17.5% of patients and possibly related to oxaliplatin in 4.0% of patients with an even distribution between groups. One TEAE leading to death was reported each group. A similar proportion of patients with aTEAE leading to permanent treatment discontinuation were reported in each group.

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