A Phase 3 Open-Label, Randomized, Multicenter Study of Imprime PGG in Combination with Cetuximab in Patients with KRAS Wild Type Colorectal Cancer

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Background

Colorectal cancer (CRC) is one of the most common malignancies worldwide and the second leading cause of cancer-related deaths in Europe. For patients with KRAS wild type (WT), epidermal growth factor receptor (EGFR) expressing, metastatic colorectal cancer (mCRC) who failed oxaliplatin- and irinotecan-based therapy or who are intolerant of irinotecan, EGFR-targeted antibodies with or without irinotecan are a standard of care.

Cetuximab is a chimeric IgG1 monoclonal antibody that binds with high affinity to the extracellular domain of human EGFR. By binding EGFR, cetuximab prevents endogenous ligands from binding the receptor and disrupts the downstream cell signaling pathway that supports tumor survival and growth. Cetuximab may also exert anti-tumor activity by inducing immunological responses such as antibody-dependent cell-mediated cytotoxicity (ADCC).

Imprime PGG is a novel investigational immune modulator (complex carbohydrate biologic), which harnesses innate immune cells to enhance killing of antibody-targeted tumor cells. Imprime PGG binds complement receptor 3 (CR3) on innate immune cells (including neutrophils, monocytes and macrophages) and primes these cells to exert anti-tumor activity against tumor cells that have been opsonized by complement (iC3b) by following targeting by anti-tumor antibodies.

Rationale

EGFR is highly expressed in over 75% of mCRC and has been associated with tumor formation and progression. Binding of cetuximab to EGFR can induce complement deposition (opsonization) in vivo. Although complement-dependent cytotoxicity (CDC) is a potent mechanism of cell killing, CDC has not been identified as a significant mechanism of action for cetuximab. Imprime PGG is a novel innate immune cell modulator that primes neutrophils, monocytes and macrophages and primes these cells to exert anti-tumor activity against tumor cells that have been opsonized by complement (iC3b) by following targeting by anti-tumor antibodies.

Study Design

Study BT-CL-PGG-CRC103 (PRIMUS) is an international, phase 3, open-label, randomized, active-controlled study.

- Approximately 795 patients will be randomized in a 2:1 ratio to:
  - Imprime PGG plus Cetuximab, or
  - Cetuximab alone

Study Treatment:

- Imprime PGG 75 mg/kg IV is administered weekly preceding the administration of cetuximab
- Cetuximab is administered weekly at an initial dose of 400 mg/m² and subsequent doses of 250 mg/m²
- Patients will receive treatment until documented disease progression (PD) per RECIST 1.1 or intolerable toxicity
- Following treatment discontinuation, patients will be monitored for survival until death or loss to follow-up

Study Assessments:

- Overall Survival (OS): Following treatment discontinuation, patients will be monitored every three months until death or loss to follow-up
- Objective response: CT or MRI of chest, abdomen and pelvis will be performed every 6 weeks initially, and every 12 weeks following 1 year of treatment
- Quality of life will be evaluated according to FACT-C on day 1 of each cycle and post-treatment
- Sparse blood samples will be assessed on Cycle 1 Day 1 or Cycle 2 Day 1
- Tumor tissue samples from the patient’s historical biopsy will be centrally tested to confirm KRAS WT status and EGFR expression

Study Schema

Key Study Endpoints

Primary Efficacy Endpoint

- Overall Survival

Secondary Efficacy Endpoints

- Objective Response Rate (evaluated by blinded, independent radiology, central radiology review)

Quality of Life Endpoints

- Functional Assessment of Cancer Therapy – Colorectal (FACT-C) scores

Safety Endpoints

- Incidence of treatment-emergent adverse events
- Incidence of laboratory abnormalities

Pharmacokinetic Endpoints

- Pharmacokinetic profile of Imprime PGG and cetuximab

Exploratory biomarker analyses will be conducted, including tissue expression of EGFR as well as levels of cytokines, chemokines, and other factors associated with innate immune activation, and these biomarker levels will be correlated with outcomes.

Key Eligibility Criteria

- Adults with KRAS wild type recurrent or metastatic carcinoma of the colon or rectum
- Measurable disease (at least 1 measurable lesion according to RECIST 1.1)
- Received prior chemotherapy regimens for CRC
- In Germany; prior oxaliplatin-based regimen and prior irinotecan-based regimen unless irinotecan is contraindicated
- In France: prior oxaliplatin and fluoropyrimidines (5-FU/LA or capecitabine) and prior irinotecan in All Other Countries: at least 2 prior chemotherapy regimens for colorectal cancer;
- No prior cetuximab or panitumumab
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Documented informed consent
- Life Expectancy of > 3 months

Current Status

- This trial is registered with Clinicaltrials.gov: NCT01309126; EudraCT: 2010-023562-51
- In a phase 2 single-arm clinical trial in metastatic, previously treated CRC, the combination of Imprime PGG with cetuximab achieved a 45% ORR, 82% DCR and median TTP of 24 wks (11% ORR, 32% DCR and median TTP of 6 weeks)
- Although complement-dependent cytotoxicity (CDC) is a potent mechanism of cell killing, CDC has not been identified as a significant mechanism of action for cetuximab
- Imprime PGG is a novel innate immune cell modulator that primes neutrophils, monocytes and macrophages and primes these cells to exert anti-tumor activity against tumor cells that have been opsonized by complement (iC3b) by following targeting by anti-tumor antibodies.

References