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[1]
- 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[2]
- Single-agent cetuximab, in this setting, is associated with a 12.8% objective response rate (ORR) and median progression-free survival (PFS) of 3.7 months.[3] There remains an unmet medical need to improve quality of life and outcomes for patients with advanced, refractory CRC
- **Cetuximab** is a chimeric IgG1 monoclonal antibody that binds with high affinity to the extracellular region of human EGFR.[4] By binding EGFR, cetuximab prevents endogenous ligands from binding the receptor and disrupts the downstream cell signaling pathway that supports tumor survival and growth.[4] Cetuximab may also exert anti-tumor activity by inducing immunological responses such as antibody-dependent cellular cytotoxicity (ADCC) [4]
- **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) following targeting by anti-tumor antibodies. [5-11]

Rationale

- EGFR is highly expressed in over 75% of mCRC and has been associated with tumor formation and progression[13]
- Binding of cetuximab to EGFR can induce complement deposition (opsonization) in vivo[5]. Although complement-dependent cytotoxicity (CDC) is a potent mechanism of cell killing[14] CDC has not been identified as a significant mechanism of action for cetuximab[15]
- Imprime PGG is a novel innate immune cell modulator that primes neutrophils, monocytes and macrophages through a complement receptor 3 (CR3)-dependent mechanism to exert anti-tumor activity against complement opsonized tumor cells[6-11]
- In human colorectal cancer xenograft studies, the combination of Imprime PGG with cetuximab reduced tumor growth and prolonged survival compared to either agent alone[16]
- Thus, combining Imprime PGG with cetuximab is a rational investigational strategy to increase tumor response and improve clinical outcomes for patients with mCRC
- In a phase 2 single-arm clinical trial in metastatic, previously treated CRC, the combination of Imprime PGG with cetuximab resulted in 24% ORR, 62% disease control rate (DCR), and median time to progression (TTP) of 12 wks[17], which compared favorably against historical data (11% ORR, 32% DCR and median TTP of 6 weeks)[18]
- In a posthoc subgroup analysis of patients with KRAS WT tumors, the combination of Imprime PGG and cetuximab achieved a 45% ORR, 82% DCR and median TTP of 24 wks[17], representing substantial increases compared to outcomes achieved historically with cetuximab alone[4](12.8% ORR and median PFS of 3.7 months)
- **PRIMUS** is a randomized phase 3 clinical trial that examines if Imprime PGG can improve overall survival when given in combination with cetuximab to patients with relapsed or refractory KRAS WT mCRC
- This trial is registered with Clinicaltrials.gov: NCT01309126; EudraCT: 2010-023562-51

Mechanism of Action of Imprime PGG in Combination With an EGFR-Targeted Antibody

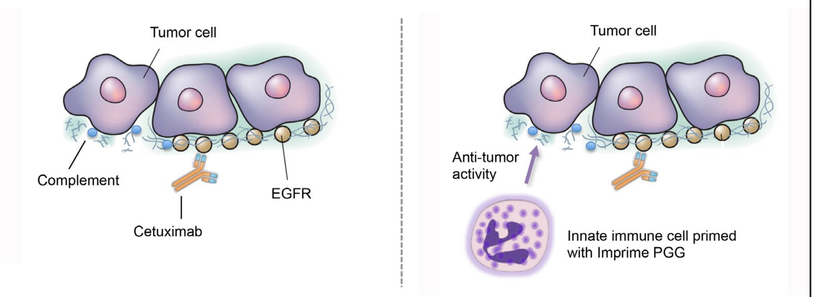


Image components adapted from Ferrara N et al, Nature Medicine 2003[12]

Hypothesis

- Imprime PGG in combination with cetuximab will improve overall survival (OS) compared to cetuximab alone in patients with advanced, refractory KRAS wild type mCRC

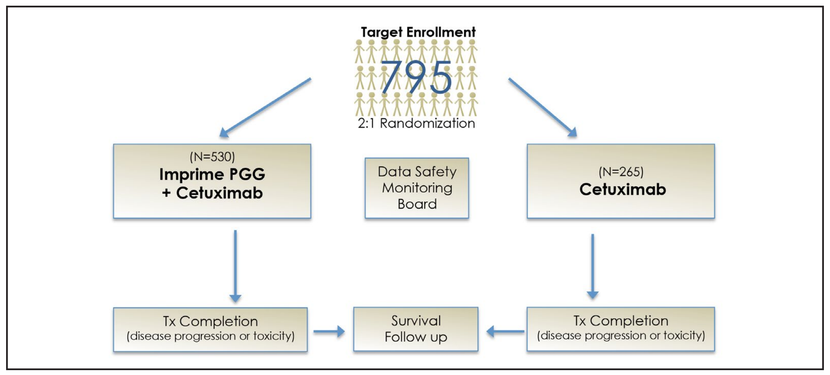
Study Design

- Study BT-CL-PGG-CRC1031 (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

Study Treatment:
- Imprime PGG 4 mg/kg IV is administered weekly preceding the administration of cetuximab
- Cetuximab is administered weekly at an initial dose of 400 mg/m^2 and subsequent doses of 250 mg/m^2
- 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
  - Response will be evaluated according to RECIST 1.1 by blinded, independent central radiology review
- Quality of Life will be assessed by FACT-C on day 1 of each cycle and post-treatment
- Sparse pk sampling 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
- Progression-Free Survival
- 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

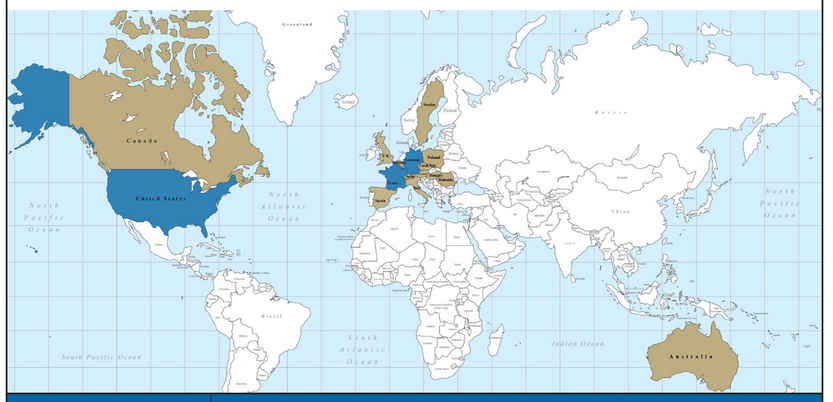
Exploratory biomarker analyses will be conducted, including tissue expression of EGFR as well as levels of cytokines, chemokines, and other factors associated with innate immune activation, and these biomarker levels will be correlated with outcomes.

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/FA or capecitabine) and prior irinotecan
  - *In All Other Countries*: at least 2 prior chemotherapeutic 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

- Patient screening and enrollment is underway.



Currently Enrolling:	Additional Countries Being Considered:		
USA France Germany	Australia Austria Belgium Canada Czech Republic	Hungary Israel Italy Poland Romania	Spain Sweden Switzerland United Kingdom

General Statistical Methods

- This study has 80% power to detect an increase in median OS from approximately 32 weeks in the control group to approximately 40 weeks in the Imprime PGG group (a hazard ratio of approximately 0.8) at a two-sided 5% significance level
- The primary analysis will occur when approximately 709 patients have died
- Analysis of efficacy parameters will be performed on the intent-to-treat population
  - Time to event endpoints (OS and PFS) will be estimated using Kaplan-Meier methodology and analyzed using a Cox proportional hazards model. Between-group differences will be assessed using a 2-sided log rank test.
  - ORR will be compared using 2-sided Fisher's Exact tests or chi-square tests where appropriate
- Quality of life changes from baseline as assessed by FACT-C will be compared between treatment groups using a mixed-effects model
- Analysis of safety parameters will be performed on the intent-to-treat population
  - The incidence of adverse events will be compared between treatment groups using Fisher's Exact tests or chi-square tests where appropriate

Study Oversight

- An independent Data Safety Monitoring Board is conducting regular safety reviews for this study.

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References

1. International Agency for Research on Cancer, World Health Organization; GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012; accessed at http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (08 September 2014); 2. Benson, AB 3rd, Venook, AP, Bekaii-Saab T, et al. Colon cancer, version 3.2014. J Natl Compr Canc Netw 12(7):1028-59, 2014; 3. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. N Engl J Med. 2008;359:1757-65; 4. Erbitux® (Cetuximab) Summary of Product Characteristics; 5. Hsu Y-F et al, 2010 Mol Cancer. 2010 Jun 7;9:139; 6. Bose N et al, Front Immunol. 2013 Aug 12;4:230; 7. Antonysamy M et al, J Immunol. 2014 May 1;192:73.9; 8. Li B et al, J Immunol. 2006 Aug 1;177(3):1661-9; 9. Qi C et al, Blood. 2011 Jun 23;117(25):6825-36; 10. Salvador C et al, Clin Cancer Res. 2008 Feb 15;14(4):1239-47; 11. Zhong W et al, J Immunother. 2009 Sep;32(7):703-12; 12. Ferrara N et al, Nat Med. 2003 Jun;9(6):669-76; 13. Spano J, et al, Ann Oncol. 2005 Jan;16(1):102-8; 14. Walpart M, N Engl J Med. 2001 Apr 5;344(14):1058-66; 15. Dechant M et al, Cancer Res. 2008 Jul 1;68(13):4998-5003; 16. Li B et al, Cancer Res. 2007 Aug 1;67(15):7421-30; 17. Tamayo M et al, Ann Oncol. 2010 21 (Suppl 6): Abstract PD0009; 18. Cunningham D et al, N Engl J Med. 2004 Jul 22;351(4):337-45