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

Myra I Patchen, Michele A Gargano, Michele A Grady, Jamie Lowe, Richard D Iuhn, Ada Braun

Background

• Colorectal cancer (CRC) is one of the most common malignancies worldwide and is the second leading cause of cancer death in the United States.

• In the United States, the age-adjusted incidence rate of CRC is approximately 14.5 per 100,000 males and 8.9 per 100,000 females.

• Patients with advanced disease have a poor prognosis, with a median survival of 12-18 months and a 5-year survival rate of approximately 10%.

• KRAS mutations are detected in approximately 40% of CRC patients and are associated with a poor response to anti-EGFR therapy.

• In a post-hoc subgroup analysis of subjects with KRAS WT tumors, the combination of Imprime PGG and cetuximab achieved a 45% ORR, 82% DCR and median TTP of 24 wks, compared favorably against historical data (11% ORR and median PFS of 3.7 months).

• 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 25% improvement).

Study Design

• Study BT-CL-PGG-CRC1031 (PRIMUS) is an international, phase 3, open-label, randomized, controlled study.

• Subjects will receive treatment until documented disease progression (PD) per RECIST 1.1 or intolerable toxicity.

• Randomization will be 2:1 to Imprime PGG and cetuximab: 795 subjects will be randomized in a 2:1 ratio to Imprime PGG + Cetuximab: (N=530) Imprime PGG + Cetuximab: (N=265) Cetuximab.

• Subjects will receive 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/m² followed by maintenance 250 mg/m² weekly.

• Treatment will be stopped if there is PD, unacceptable toxicity or loss to follow-up.

Hypothesis

• Imprime PGG and cetuximab will be centrally tested to confirm KRAS WT status and EGFR expression.

• Subjects with KRAS WT tumors will be randomized in a 2:1 ratio to Imprime PGG + Cetuximab: (N=530) Imprime PGG + Cetuximab: (N=265) Cetuximab.

• The trial is designed to determine if Imprime PGG can improve overall survival, progression-free survival, and disease control when combined with cetuximab to subjects with metastatic CRC with KRAS WT.

• The primary endpoint of this study is overall survival (OS).

Study Schema

Key Study Endpoints

Primary Efficacy Endpoints:

- Overall Survival
- Progression Free Survival
- Objective Response Rate

Secondary Efficacy Endpoints:

- Safety
- Quality of Life
- Biomarker Analysis

Safety Endpoints:

- Adverse events (AEs)
- Serious AEs
- Treatment-emergent adverse events (TEAEs)

Study Oversight

- This trial is sponsored by Biothera. Author disclosures: Patchen ML, Gargano MA, Grady MM, Lowe J, Huhn RD, Braun A are sponsor employees holding stock options and/or grants.

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

- Imprime PGG is a nucleotides-in-a-needle composition used in combination with cetuximab, a monoclonal antibody that binds to the extracellular domain of the epidermal growth factor receptor 3 (EGFR) on innate immune cells (including neutrophils, monocytes and macrophages) and prevents ligands from binding the receptor.

- The monoclonal antibody cetuximab disrupts the cell signaling pathway that supports tumor survival and growth.

- Cetuximab may also exert anti-tumor activity by inducing apoptosis, which compared favorably against historical data (11% ORR and median PFS of 3.7 months).

- Imprime PGG may also exert anti-tumor activity through the activation of the complement system, which is a key component of the innate immune response.

- Imprime PGG exerts anti-tumor activity against complement opsonized tumor cells and macrophages through a complement receptor 3 (CR3)-dependent mechanism to inhibit macrophage activity.

- Imprime PGG achieves this by binding to tumoral tissue factor, which activates the complement system, leading to the formation of a membrane attack complex on tumor cells.

- This membrane attack complex causes cell lysis.

- Thus, combining Imprime PGG with cetuximab is a rational investigational strategy to further enhance the anti-tumor activity of cetuximab.