Response and clinical benefit assessment of the Dectin-1 agonist IMPRIME PGG and anti-PD-1 pembrolizumab in chemotherapy-resistant metastatic triple negative breast cancer (TNBC)


1Bothera Pharmaceuticals, Inc., Eagan, MN, USA; 2John Wayne Cancer Institute, Santa Monica, CA, USA; 3UICHealth University of Colorado, Aurora, CO, USA; 4Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA; 5Suny University Hospital, Chicago, IL, USA; 6Sidney Kimmel Cancer Center, Philadelphia, PA, USA; 7SUNY Stony Brook Cancer Center, Stony Brook, NY, USA; 8Merck & Co., Inc., Kenilworth, NJ, USA; 9B.01 Consulting Gmbh, Basel, Switzerland

Response: Overall survival of early progressor patients (PD as best response by RECIST v1.1) grouped by whether they discontinued therapy due to appearance of new lesions or increased non-target lesions was analyzed. Early progressors (progressive disease, PD, as best overall response by RECIST v1.1) in the “No” subgroup included all early progressors (progressive disease, PD, as best overall response by RECIST v1.1) in the “No” subgroup. Those patients that discontinued therapy due to appearance of new lesions or increased non-target lesions were considered to be those that discontinued therapy (6 weeks).

Data from longitudinal blood samples of patients were collected and analyzed for CD86 expression on classical monocytes. Sample not available from 1 patient. Note: N = 18 for T cell activation.

Key findings: Longitudinal blood samples from patients were collected and analyzed for CD86 expression on classical monocytes. Sample not available from 1 patient. Note: N = 18 for T cell activation.

Monotherapies: Chemotherapy, pembrolizumab, and combination therapy.

Methods: In an open-label phase II trial, 44 patients with metastatic TNBC received PGG 4 mg/kg, weekly, combined with pembrolizumab (Pembro) and/or chemotherapy. Pemirolimus was administered by IV infusion 4 mg/kg, weekly, for 2 weeks followed by a 1-week break. Response and clinical benefit assessment of the combination of the Dectin-1 agonist IMPRIME PGG and anti-PD-1 pembrolizumab in chemotherapy-resistant metastatic triple negative breast cancer (TNBC).

1. IMPrime PGG: a novel innate immune activator

- Immune checkpoint inhibitor (ICI) monotherapy trials have shown limited clinical efficacy in previously treated mTNBC patients (Table 1).
- IMPrime PGG is a novel, systemically administered Dectin-1 receptor agonist.
- IMPrime PGG mediates innate immune activation through the Dectin-1 receptor, which is expressed on various innate immune cells, including monocytes.
- IMPrime PGG activates monocytes and dendritic cells, which can lead to increased cytokine production and recruitment of other immune cells, such as T cells.
- IMPrime PGG has demonstrated early clinical efficacy, with increases in infiltration and activation of immune cells, including T cells, myeloid cells, and macrophages.

2. IMPrime 1 (NCT02981303) Study Design

- Phase I/II study of IMPrime PGG in combination with pembrolizumab for mTNBC patients.
- Patients received IMPrime PGG 4 mg/kg and pembrolizumab 200 mg every 3 weeks.
- Primary endpoints: safety, tolerability, and clinical activity.
- Secondary endpoints: biomarker assessment, including immune cell infiltration and activation.

3. IMPrime 1 Efficacy Data

- Overall Response Rate (ORR): 12.2% (1 CR, 6 PR).
- Progression-free Survival (PFS): 6.5 months (95% CI, 4.6-10.0).
- Overall Survival (OS): 19.1 months (95% CI, 11.1-27.3).

4. IMPrime 1 Translational Research

- Transcriptional Profiling: Detergent-processed peripheral blood mononuclear cells (PBMCs) were collected and analyzed for gene expression using the Human Immune Monitoring Panel, which measures 165 immune-related genes.
- Single Cell RNA-Sequencing: Single cell RNA-seq analysis was performed on peripheral blood mononuclear cells (PBMCs) to identify rare cell types.
- Immunopharmacodynamic (IPD) analysis: IPD studies were conducted to assess the pharmacodynamic effects of IMPrime PGG in combination with pembrolizumab, including changes in immune cell infiltration, activation, and cytokine expression.

5. IMPrime 1 Peripheral Blood Analyses

- Peripheral blood mononuclear cells (PBMCs) were analyzed for CD86 expression on classical monocytes.
- Sample not available from 1 patient. Note: N = 16 for T cell activation.

6. IMPrime 1 Subgroup Analyses of Overall Survival

- Patients with a significant immune infiltration and activation at cycle 2 or 6. Sample not available from 1 patient. Note: N = 18 for T cell activation.

7. IMPrime 1 Study Summary

- IMPrime PGG in combination with pembrolizumab shows promising clinical benefit in previously treated, metastatic TNBC patients.
- Across multiple clinical efficacy measures: Overall Survival, Overall Response and Disease Control Rates.
- A majority of patients discontinued due to appearance of new lesions or increased non-target lesions alone, or more than one type of lesion.
- Increased overall survival was evident in patients with “mixed responses” particularly if they had: Reduction in size of target lesions >10% and reduction in size of non-target lesions >10%.
- Early progression was an independent predictor of survival benefit from IMPrime PGG.
- Reduction in size of target lesions below baseline at any time.
- Early progression was defined as progression from non-measurable disease to measurable disease within 12 weeks of initiating therapy.

8. IMPrime 1 Tumor Biopsy Analyses: Liver Metastasis

- Tumor biopsy samples were collected from patients at baseline, prior to randomization, and after 6 cycles of IMPrime PGG and pembrolizumab. Tumor content was assessed by immunochemistry and histology.
- Tumor biopsy samples showed marked reduction in tumor cell content and increased infiltration of immune cells, including T cells and macrophages.