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)

Poster PD1-02

Uhlik M.[1], Bose N.[1], Cox J.[1], Mattson P.[1], Gargano M.[1], O'Day S.[2], Borges V.[3], Chmielowski B.[4], Rao R.[5], Abu-Khalaf M.[6], Stopeck A.[7], Chisamore M.[8], Osterwalder B.[9], Graff J.[1]

[1]Biothera Pharmaceuticals, Inc., Eagan, MN, USA; [2]John Wayne Cancer Institute, Santa Monica, CA, USA; [3]UCHealth University of Colorado, Aurora, CO, USA; [4]Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA;

[5]Rush University Medical Center, Chicago, IL, USA; [6]Sidney Kimmel Cancer Center, Philadelphia, PA, USA; [7]SUNY Stony Brook Cancer Center, Stony Brook, NY; [8]Merck & Co., Inc., Kenilworth, NJ, USA; [9]B.O. Consulting GmbH, Riehen, Switzerland

Correspondence: Jeremy Graff, PhD (jgraff@biothera.com)

Abstract

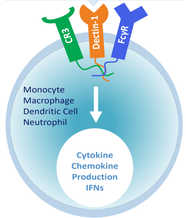
Background: Immune checkpoint inhibitor (ICI) monotherapy provides substantial, long-term clinical benefit to patients (pts) with many types of cancer. To date, chemo-refractory, metastatic TNBC pts have realized only limited clinical benefit from ICI monotherapy with ORR of ~5-6%, median overall survival (OS) ~9 months and 1 year OS rates ~37-40%. Such limited benefit may reflect a poor underlying immune response with inadequate T cell responses in these pts. Combining ICIs with innate immune modulators may provide a promising approach to initiating an immune response in these pts. Imprime PGG (Imprime) is a novel, systemically-delivered Dectin Receptor agonist that, mechanistically, activates the innate immune system to reprogram the immunosuppressive tumor microenvironment to stimulate antigen-specific T cell activation. In preclinical cancer models, Imprime significantly enhances the anti-cancer efficacy of ICI therapy. Accordingly, Imprime is currently being studied in combination with pembrolizumab (KEYTRUDA®, pembro), a humanized mAb against PD-1, in a Ph2 trial (NCT02981303) in chemo-refractory metastatic TNBC pts (Biothera in collaboration with Merck & Co., Inc.).

Methods: An open-label, Simon 2 stage study design was employed (12 pts in Stage 1; 32 pts in Stage 2) with full enrollment completed Nov. 2018. Pts received Imprime (4 mg/kg IV days 1, 8, 15 of each 3-week cycle) + pembro 200 mg on D1 of each cycle. CT scans were obtained at baseline and every 6 weeks thereafter until disease progression. Primary endpoints were ORR and safety. Secondary endpoints included PFS and OS. Biopsies and blood samples were collected to explore immune activation in tumor tissue and peripheral blood.

Results: Data presented here are from a primary analysis when all patients have been enrolled and through at least 12 weeks on therapy (2 CT scans/tumor assessments). In the intent-to-treat population (N=44; median duration of follow-up of 19.1 months as of 11/11/2019), confirmed ORR was 15.9% (1 CR, 6 PRs). Stable disease (SD) >12 wks as best response was observed in nearly 40% of pts (17/44). Four of these 17 were stable for≥24 wks. OS at 1 year are 57.6% with median OS currently at 16.4 months by K-M estimation (95% CI, 11.1 – 23.9 mos). A majority of pts (62.5%) showed target lesion (TL) reduction or stabilization. Treatment discontinuation due to progression often (22/41, 53.7%) resulted from new lesions (NL), or non-target lesion (NTL) progression, even while target lesions were shrinking or stable. Pts with this mixed response pattern showed increased overall survival. Specifically, enhanced OS was evident in pts showing a reduction in 1) any of their target lesions (HR 0.33; p=0.015), 2) in total tumor burden ≥10% at 12 wks (HR 0.14, p=0.001); or, 3) total tumor burden below baseline at any time (HR 0.44; p=0.064) independent of NL/NTL status. Analyses of biopsies and peripheral blood indicated profound infiltration of activated myeloid and T cells into tumor tissue after 6 wks of therapy. Pts at baseline were largely devoid of activated T cells. However, a significant fraction of pts (16/44) showed activated T cells as early as 3 wks on therapy which significantly correlated with improved OS (HR 0.26; p=0.008).

Conclusion: The combination of Imprime and pembro showed promising response rates and overall survival in chemo-refractory metastatic TNBC. Biopsy analyses consistently revealed activation of both myeloid and T cells with extensive infiltration into tumor tissue. Examination of response patterns and clinical benefit revealed extended OS even in pts not classified as responders by RECIST. Indeed, extended OS was most evident in pts with any reduction in TL, regardless of NL/NTLs. These data suggest that clinical benefit from the combination of Imprime and ICI therapy may not be adequately assessed using standard RECIST v1.1 and suggest a modified RECIST criteria might better determine clinical benefit of such a combination.

Imprime PGG: a Novel Innate Immune Activator



1. **Imprime PGG forms an immune complex**
   - Anti-β glucan antibodies (ABA)
     - patient selection biomarker, identifies ~50% of patients
   - Complement fragment (iC3b)
2. **Immune Complex binds Dectin-1 and Co-Receptors**
   - This immune complex is the "active" drug
3. **Innate Immune Cell Activation**
   - Alleviates immunosuppression
     - Promotes shift from immunosuppressive "M2" state
     - Drives infiltration of PD-L1+, CD80+ immune cells (M1)
   - Activates antigen presenting cells
     - Dendritic Cells, M1 APCs
     - Increases expression of co-stimulatory CD80, CD86 markers
   - Increases tumor specific T Cell activation and infiltration

Imprime PGG is a novel, IV administered Dectin-1 Receptor agonist that triggers an *integrated* anti-cancer immune response involving both innate and adaptive immunity to potentiate the efficacy of checkpoint inhibitor therapy

- **Immune checkpoint inhibitor (ICI) monotherapy trials have shown limited clinical benefit in previously treated mTNBC patients (Table 1).**
- **Imprime PGG is a novel, systemically administered DECTIN receptor agonist**
- **Imprime PGG-mediated innate activation requires Anti-Beta Glucan Antibody (ABA)**
- **Imprime PGG reprograms the immunosuppressive tumor microenvironment**
- **Imprime PGG activates antigen presenting cells**
- **Imprime PGG elicits increased anti-cancer T cell responses**
- **In preclinical tumor models, Imprime PGG enhances the efficacy of ICI monotherapy**

IMPRIME 1 (NCT02981303) Study Design

Patients (n=44)
- Histologically or cytologically confirmed diagnosis of metastatic/ stage IV TNBC
- ≥ 1 prior line of chemotherapy after the diagnosis of metastatic TNBC (mTNBC)
- No prior checkpoint inhibitor therapy (CPI-naïve)
- ECOG status 0-1
- Irrespective of PD-L1 status
- Baseline anti-beta glucan antibody (ABA) levels ≥ 20mcg/ml

Single arm, Combination study – Each Cycle = 21 Days
- Imprime PGG administered by IV infusion 4mg/kg, weekly
- Pembrolizumab administered by IV infusion 200mg, q3W

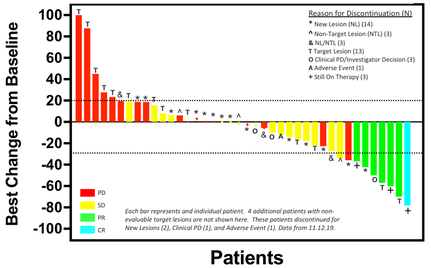
Clinical Endpoints:
- 1° endpoint - ORR by RECIST v1.1 and safety
- CT scans starting after 6 weeks on therapy and every 6 weeks until disease progression
- 2°/ exploratory endpoints included OS, PFS and DCR

Translational Endpoints- Immune Activation
- Tumor biopsies- preTx and 6 weeks on Tx (immunofluorescence)
- Peripheral Blood Samples (Pre-cycle 1, Pre-cycle 2, Pre-cycle 6)

❖ ***Data presented in this poster are primary data. IMPRIME1 is ongoing.***

❖ ***This trial also included a cohort of metastatic melanoma patients post-CPI therapy.***

Best Overall Response and Reason for Discontinuation

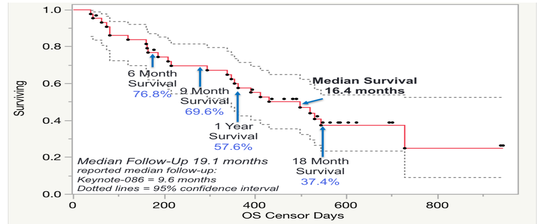


IMPRIME 1 Efficacy Data

	Bavencio[c] % (N=58)	Tecentriq[b] % (N=94)	Keytruda[a] % (N=170)	IMPRIME 1 % (N=44#)
Overall Response Rate (ORR)	5.2	6.4	5.3	**15.9**
Stable Disease (SD)	26.0	13.0	18	**38.6**
Progressive Disease (PD)	65.0	64.0	60.6	**40.9**
Disease Control Rate (DCR)				
- CR+PR+SD any time	31.2	19.4	23.3	**54.5**
- CR+PR+SD ≥ 24 weeks	NR	10.0	7.6	**25.0**
Median Overall Survival (mos)	9.2	7.3	9.0	**16.4***
Overall Survival Rate (%)				
- 6 month	NR	60.0	69.7	**76.8**
- 9 month	~50.0**	44.0	50.0	**69.6**
- 12 month	37.1	37.0	39.8	**57.6**

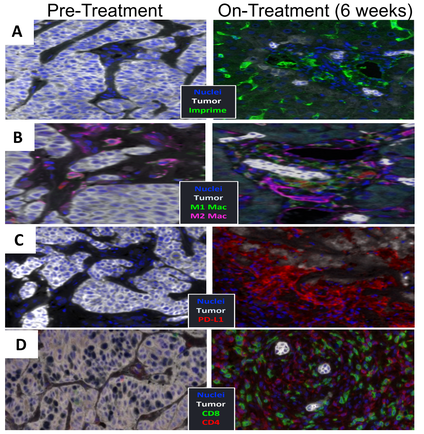
CR = Confirmed Complete Responder, PR = Confirmed Partial Responder, NR = Not Reported, #- ITT population, n = 44 patients, 2 not evaluable for response. Latest IMPRIME 1 data from July 9, 2019. * Median follow-up time 19.1 months, **Estimated from reported median OS, [a] Keynote-086 Adams et al., 2018- Merck, [b] PCD4989g Emens et al., 2019- Genentech , [c]Javelin Dirix et al., 2018- Pfizer

IMPRIME 1 Kaplan-Meier Overall Survival Plot



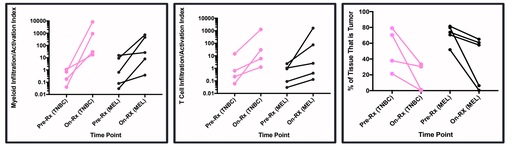
IMPRIME 1 Translational Research

IMPRIME 1 Tumor Biopsy Analyses: Liver Metastasis



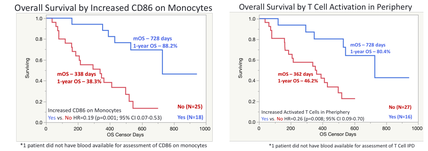
Tumor biopsies were taken from patients pre-treatment and again 6 weeks on treatment. Tumor samples were assessed by immunofluorescence using the Perkin Elmer Vectra 3.0 system for the markers shown in the insets. These images were taken from the same liver metastasis. **A**- Staining for Imprime+ Myeloid cells. **B**- Staining for M2 (pink, CD206) and M1 (green, CD80) markers. **C**- Staining for PD-L1 (red) in the tumor bed. **D**- Activated CD8 (green) and CD4 (red) T cells in the tumor bed after IMPRIME 1 therapy. Note: on treatment, tumor is evident as small tumor cell clusters vs the large tumor sheets pre-treatment. **This patient started therapy with 3 liver metastases, 2 breast metastases and bone metastases. She remained on therapy > 500 days and is now without evidence for any liver metastases**.

Myeloid Activation Index | T Cell Activation Index | Tumor Cell Content



Breast Patients shown in Pink, Melanoma Patients shown in Black. Myeloid and T cell activation indices reflect cell infiltration and activation (CD80/CD206 for myeloid activation-M1 state, CD3+/Ki67/GranzymeB for T cell activation) as a composite measure. Each bar represents a single patient pre- and on-treatment (6 weeks). All quantitation performed using the Perkin Elmer Vectra 3.0 imaging system. These data represent the total number of tumor biopsy pairs (pre and on-Tx) collected.

IMPRIME 1 Peripheral Blood Analyses



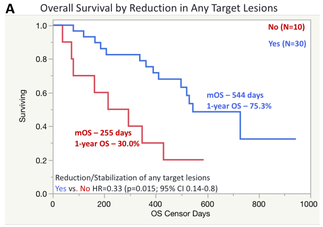
*1 patient did not have blood available for assessment of CD86 on monocytes

*1 patient did not have blood available for assessment of T Cell IPD

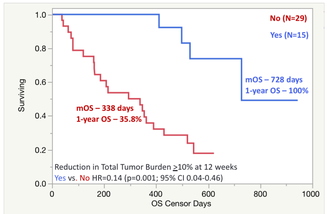
Peripheral blood from patients on IMPRIME 1 was taken at pre-cycle 2 (week 3) and pre-cycle 6 (week 15). ***Left panel***: Longitudinal blood samples from patients were collected and analyzed for CD86 expression on classical monocytes. Data shown represent a 1.25X or greater increase in CD86 expression vs baseline pre-treatment- an Imprime-mediated Immunopharmacodynamic (IPD) response . Overall survival was evaluated by Kaplan-Meier for those showing increased CD86 on monocytes at either pre-cycle 2 or 6. Sample not available from 1 patient. Note: N = 18 for those with increased activated T cells.
Right Panel: CD8 T cell activation is associated with benefit from pembrolizumab. Activated CD8 T cells (PD1+/HLA-DR+/Ki67+) were assessed on treatment by flow cytometry. Data shown represent ≥ 2X increase in CD8 T cells vs baseline pre-treatment. Sample not available from 1 patient. Note: N = 16 for those with increased activated T cells. Baseline samples showed very limited evidence for activated T cells in these mTNBC patients.

IMPRIME 1 Subgroup Analyses of Overall Survival

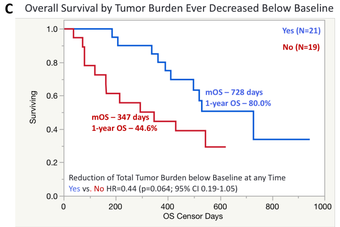
A Overall Survival by Reduction in Any Target Lesions



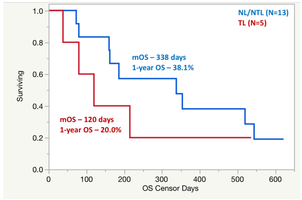
B Overall Survival by Reduction in Tumor Burden of ≥10% at 12 Weeks



C Overall Survival by Tumor Burden Ever Decreased Below Baseline



D OS by Discontinuation Reason in Early Progressors



*4 patients did not have target lesion assessments while on therapy

*4 patients did not have target lesion assessments while on therapy

Kaplan-Meier analyses of overall survival were performed on various subsets of patients. **A**- Overall survival of patients grouped by whether any of their target lesions showed a reduction from baseline ("Yes") or not ("No") at any point since the initiation of therapy. Note: 4 patients did not receive any CT scans or tumor assessments after initiation of therapy. **B**- Overall survival of patients grouped by whether their sum of total target lesions ("tumor burden") was decreased by >10% at 12 weeks ("Yes") or not ("No"). This analysis includes all early progressors (progressive disease, PD, as best overall response RECIST v1.1) in the "No" subgroup. Those patients who were still on therapy at 12 weeks but did not show a >10% decrease in tumor burden (a subset of the "No" group, N=13) had median OS of 475 days and 1 year OS rate of 66.7%. A comparison of these patients to patients with >10% tumor burden decrease at 12 weeks ("Yes" subgroup) also shows statistically different survival in favor of the "Yes" subgroup (HR 0.02, p=0.018 CI 0.05-0.76). **C**- Overall survival of patients grouped by whether their sum of the target lesions ("tumor burden") ever decreased below its original baseline at any point since initiation of therapy. Note: 4 patients did not receive any CT scans or tumor assessments after initiation of therapy. **D**- Overall survival of early progressor patients (PD as best response by RECIST v1.1) grouped by whether they discontinued therapy due to presence of new lesions or increased non-target lesions ("NL/NTL") or due to increased sum of target lesions ("TL").

IMPRIME 1 Study Summary

1. 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
2. Clinical response was evident as early as 6 weeks on treatment
3. A majority of patients discontinued due to appearance of new lesions or increased non-target lesions even while one or more of their target lesions were decreasing or stabilized. Increased overall survival was evident in these patients with "mixed responses" particularly if they had:
   - Reduction in any of their target lesions
   - Reduction of tumor burden of ≥10% at 12 weeks
   - Reduction in sum of target lesions below baseline at any time
4. Early progressors who discontinued from new lesions/increased non-target lesions (NL/NTL) showed increased survival compared with those that discontinued from target lesion (TL) increases
5. Tumor biopsy and peripheral blood analyses showed significant immune infiltration and activation at tumor site and in the periphery of IMPRIME-1 patients. Patients with peripheral activation of myeloid and T cells had significantly greater overall survival compared to those who do not

These data support the continued development of Imprime PGG with pembrolizumab for previously-treated mTNBC patients and suggest a modified RECIST criteria may be more appropriate for tumor assessment due to the "mixed" nature of responses observed.