Association of Immuno pharmacodynamic Responses of Imprime PGG Plus Pembrolizumab with Clinical Benefit in Metastatic Triple Negative Breast Cancer (TNBC) Subjects Failing Front-line Chemotherapy

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Abstract

Background: Checkpoint inhibitor (CT) monotherapies, including pembrolizumab (KEYTRUDA), pemetrexed, atezolizumab and discontinuation of treatment on average 11.3 months (SD: 3.4 months) in the pre-treatment group and 15.8 months (SD: 4.3 months) in these patients. The mean overall survival time was significantly longer in the pembrolizumab arm compared to the pemetrexed arm (17.8 vs. 14.1 months; p < 0.001).

Methods: The primary analysis of our Phase 2 study (NCT01803183), collaboration with Merck & Co., Inc. (to further refine chemotherapy-refractory/refractory TNBC patients treated with Imprime PGG (Imprime), a novel plant-derived, Dectin-1 agonist glucan PAMP in combination with pembrolizumab has shown enhanced disease control rate (DCR), N=11, CIR 0% for 8 months, and increased OS (12.6 months) vs the respective endpoints in previous preclinical and clinical trials. As part of exploratory translational objectives, peripheral blood was collected at baseline and imprinted and in the combination group in 3 cycles for 3 cycles at 30-day intervals. Results from serum and cellular immune responses were presented from these patients.

Results: Peak levels of serum circulating immune complexes (1 to 22-fold) and complement protein C5b-9 (1 to 41-fold) in stage 1 patients provided evidence for Imprime anti-angiogenic antibody activity. A significant increase in the frequency of HLA-DR+ myeloid cells was observed in the overall population (up to 7.4-fold). In pts showing disease control (DCR), a significant increase in complement function (CH50), 10.6-fold range, select chemokines such as MCP-1 production (up to 1000-fold), CDSB expression on monocytes (5.05-6 fold) and neutrophils (0.21-fold), and increased frequency of 6.7%-20.0% C3b-T cells (0.2-fold) were observed. Some IPD responses were associated with the 12 month landmark (N=29). Additionally, enhanced Leptin (51.1%, p=0.011) and mOS (HR 0.13, p=0.013) was observed in 18 pts with a 12.5-fold increase in CDSB expression on classical monocytes. Greater than 2-fold increase in the frequency of 0.47%-HILA-DR+/CD16+CD14+ cells in 16 pts was also associated with enhanced hNRs (HR 0.29, p=0.013) and mOS (HR 0.28, p=0.035). Additionally, the gene expression profile of these IPD responders was similar to the RECIST responders with ≥2-fold upregulation of several genes including IL1, CDSB, IL6, and CD52.

Conclusions: Overall, the strong association of the immune/adaptive IPD responses to the cellular responses are suggestive of interplay between the therapeutic mechanisms of Imprime and pembrolizumab.

Imprime PGG: A Novel Dectin Receptor Agonist (a PAMP) That Activates the Innate Immune System

Clinical Benefit in mTNBC: Previous CPI Monotherapies Studies and IMPRIME 1

Figure 1. Imprime activated monocytes and DCs in mTNBC patients.

Serum and Cellular IPD Evaluations in Imprime 1: TNBC

Figure 2. In vivo Evidence of Immune Complex Formation, Complement Activation and Cytokine Production

Figure 3. In vitro Evidence of Immune Complex Formation, Complement Activation and Cytokine Production

Figure 4. In vitro IPD responders vs RECIST responders

Figure 5. Imprime-mediated IPD effects mark patients with enhanced OS and PFS

Figure 6. Changes in IPD responders are associated with OS and PFS

Figure 7. Antibody mediated effects with pembrolizumab in patients with advanced NSCLC (© 2019 The American Association for Cancer Research).