Conclusions The combination of PF-8600 and uto had a tolerable safety profile and demonstrated clinical benefit, including in an NSCLC patient who had progressed on anti-PD1 therapy and achieved a durable partial response. Further combinations with one or both of these immune costimulatory receptor agonist antibodies might enhance their efficacy.

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Trial Registration ClinicalTrials.gov: NCT02315066

Ethics Approval The study was approved by the institutional review board at each study center and conducted in accordance with the ethical principles of the Declaration of Helsinki.

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CLINICAL BENEFIT POTENTIALLY EVIDENT WITH IMMUNOPHARMACODYNAMIC RESPONSES IN PRIOR-CHECKPOINT FAILED METASTATIC MELANOMA PATIENTS TREATED WITH IMPRIME PGG AND PEMBROLIZUMAB

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Background Checkpoint inhibitor (CPI) monotherapy has revolutionized the treatment of melanoma, yet most patients are primary nonresponders or develop secondary resistance. Lack of antigen-specific T cell priming and/or immunosuppressive mechanisms leading to T cell exhaustion are critical cancer-extrinsic factors contributing to CPI resistance mechanisms. Immunotherapeutic agents capable of sparking de novo anti-tumor T cell responses or reinvigorating pre-existing exhausted T cell immunity could help reinstate the activity of CPI.

Methods Our Phase 2, multi-center, open label study, NCT02981303 in collaboration with Merck & Co., Inc., is evaluating Imprime PGG (Imprime), a novel yeast derived, Dectin-1 agonist, β -glucan PAMP in combination with pembrolizumab (KEYTRUDA®, pembro) in heavily CPI pre-treated melanoma patients (20 patients; 65% had >2 prior CPI regimens with 17/20 having previously progressed on pembro). Patients received Imprime (4 mg/kg) + pembro (200 mg) intravenously in a 3-week cycle. Here, we present the immunopharmacodynamic (IPD) responses elicited by Imprime and pembro in the peripheral blood of 19 patients.

Results In the intent-to-treat population (ITT; N=20), the disease control rate was 45% (1 CR and 8 SD), 6-month and 12-month OS rates were 65% and 45% respectively, and median OS (mOS) was 8.8 months. In the patients showing disease control, a significant increase in CH50, the classical pathway complement function (~0.7-2.6-fold), HLA-DR expression on classical monocytes (~0.61-1.94-fold) and reduction of frequency of PD-1+Tbet-EOMES+ exhausted CD8 T cells (~0.9-4-fold) was observed. Stimulation of peripheral blood mononuclear cells from a subset of patients by CD3/CD28 beads showed enhanced production of IL-2 and IFN-gamma in the CD8 T cells. Some of these IPD responses were also associated with 6-month landmark OS analyses. Additionally, whole blood gene expression analyses showed >2-fold upregulation of several myeloid and T cell

activation genes including IFN γ , CD83, IP-10, and IL-2RA. Enhanced OS was observed in patients with >1.3 fold increase in CH50 (8/19; HR 0.385; p=0.1) or >1.5-fold reduction in the frequency of exhausted CD8 T cells (8/19; HR 0.102; p=0.001). The IPD responses observed in the ITT population included formation of circulating immune complexes (peak levels ranging from ~4.5-16.1-fold) and production of complement activation protein SC5b9 (~3.4-25.6-fold), and increase in the frequency of HLA-DR+ myeloid cells (~0.43-3.71-fold).

Conclusions Overall, these data, albeit in a small population, demonstrate that Imprime/pembro combination can drive the innate/adaptive IPD responses that are critical for providing clinical benefit to the patients who have progressed through prior CPI treatments.

Ethics Approval The study was approved by central and local ethics committees depending on site requirements. The central IRB for the study is Western Institutional Review Board (WIRB), approval number 20162506; all sites received IRB approval before opening the study at the respective sites.

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KEYNOTE-022 PARTS 4 AND 5: PEMBROLIZUMAB PLUS TRAMETINIB FOR PATIENTS WITH SOLID TUMORS OR BRAF WILD-TYPE MELANOMA

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Background Pembrolizumab+dabrafenib+trametinib demonstrated promising antitumor activity and acceptable tolerability in BRAF-mutant melanoma in phase 1/2 KEYNOTE-022 parts 1 and 2 (NCT02130466). Pembrolizumab+dabrafenib+trametinib numerically prolonged PFS and DOR versus placebo+dabrafenib+trametinib but had a higher grade 3-5 TRAE rate in part 3. KEYNOTE-022 parts 4 and 5 evaluated pembrolizumab+trametinib.

Methods In part 4 (open-label, 3+3 dose-finding) patients with advanced solid tumors (irrespective of BRAF status) or unresectable/metastatic BRAF wild-type melanoma received pembrolizumab 200 mg Q3W with trametinib as concurrent (2 or 4 weeks of trametinib run-in [1.5 or 2 mg QD], then pembrolizumab+trametinib [1.5 or 2 mg QD]) or intermittent dosing (2 weeks of trametinib run-in [1.5 or 2 mg QD], then pembrolizumab+trametinib [1.5 or 2 mg QD; 1 week off/2 weeks on]). Interim MTDs identified in part 4 were confirmed in part 5 using a modified toxicity probability interval design. The primary objectives were safety, tolerability, and ORR by investigator assessment per RECIST v1.1 of the maximum administered or tolerated dose (MAD/MTD) of