Background Checkpoint inhibitor (CPI) monotherapies, including pembrolizumab (KEYTRUDA®, pembro), avelumab and atezolizumab have demonstrated modest clinical benefit in chemotherapy-relapsed/refractory TNBC patients (pts) with ~5-10% response rate, median overall survival (mOS) of 7-9 months, and 1 year OS ~37-40%. TNBC, although more immunogenic relative to the other breast cancer subtypes, is also the most heterogenous, resulting in substantial variability in immune responses. There is a dire need for immunotherapeutic agents that could consistently induce anti-cancer immune responses.

Methods The primary analyses of our Phase 2 study (NCT02981303; collaboration with Merck & Co., Inc.) in 44 (intent-to-treat) chemotherapy-refractory/relapsed TNBC pts treated with Imprime PGG (Imprime), a novel yeast derived, Dectin-1 agonist β -glucan PAMP in combination with pembro has shown enhanced disease control rate (25%, N= 11; 1 CR, 6 PR and 4 SD>24 weeks), 12-month OS rate (57.3%) and increased mOS (16.6 months) vs the respective endpoints in Keynote086 pts treated with pembro alone. As part of exploratory translational objectives, peripheral blood from pts receiving the combination in 3-week cycles were collected at various time points. Results from serum and cellular immunopharmacodynamic (IPD) evaluations from 41 pts are presented.

Results Peak levels of serum circulating immune complexes (~3 to 22-fold) and complement protein SC5b-9 (~1.4 to 41-fold) in stage 1 pts provided evidence for Imprime-anti beta glucan antibody immune complex formation. 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 (N=11), a significant increase in complement function (CH50, ~0.8-4 fold range), select chemokines such as MCP-1 production (up to 1000-fold), CD86 expression on monocyte (~0.5-6-fold) and DC subsets (~0.8-11-fold), and increased frequency of Ki-67+, HLA-DR/PD-1+ CD8 T cells (~0.4-14-fold) was observed. Some IPD responses were associated with the 12-month landmark OS analyses. Additionally, enhanced mPFS (HR 0.51; p=0.03) and mOS (HR 0.13; p=0.0013) was observed in 18 pts with >1.25-fold increase in CD86 expression on classical monocytes. Greater than 2-fold increase in the frequency of Ki-67+, HLA-DR/PD-1+ CD8 T cells in 16 pts was also associated with enhanced mPFS (HR 0.395; p=0.01) and mOS (HR 0.183; p=0.008). Additionally, the gene expression profile of these IPD-responders were similar to the RECIST responders with >2-fold upregulation of several genes including IFN γ , CD83, GZMA, GZMK, and CD3.

Conclusions Overall, the strong association of the innate/adaptive IPD responses to the clinical responses are suggestive of interplay between the therapeutic mechanisms of Imprime and pembro combination.

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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RESULTS FROM A COMBINATION OF OX40 (PF-04518600) AND 4-1BB (UTOMILUMAB) AGONISTIC ANTIBODIES IN MELANOMA AND NON-SMALL CELL LUNG CANCER IN A PHASE 1 DOSE EXPANSION COHORT

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Background PF-04518600 (PF-8600) and utomilumab (uto) are humanized agonist IgG2 monoclonal antibodies for the tumor necrosis factor superfamily receptors OX40 and 4-1BB, respectively. In a phase I dose escalation study (NCT02315066), this antibody combination was tolerable at all dose levels and induced responses in patients with melanoma resistant to immune checkpoint inhibitors. We report results from a dose expansion cohort of this study of patients with melanoma and non-small cell lung cancer (NSCLC) treated with PF-8600 (OX40 antibody) in combination with uto. Efficacy, safety, and the association of baseline and pharmacodynamic biomarkers with efficacy were examined.

Methods In this expansion cohort, patients with locally advanced/metastatic melanoma (n=10) and NSCLC (n=20) who progressed on prior anti-PD1/PD-L1 treatment and/or anti CTLA4 treatment (melanoma only) were enrolled. Patients received OX40 antibody 30 mg IV every 2wks in combination with uto 20 mg IV every 28d. Tumor assessments were performed every 8wks using RECIST1.1. Paired biopsy samples collected at baseline and 6wks were analyzed by immunohistochemistry and RNA sequencing to evaluate the pharmacodynamic effects of the OX40 antibody in combination with uto. Whole blood samples were collected longitudinally, from which DNA was extracted and submitted for high-throughput sequencing of the T cell receptor β -chain.

Results One patient with NSCLC achieved a confirmed and ongoing partial response lasting at least 6 months; Based on analyses of a subset of baseline biopsies, this patient's tumor had the lowest FOXP3 expression. A total of 7 (70%) melanoma patients and 7 (35%) NSCLC patients achieved a best overall response of stable disease (SD). The median duration of SD was 16.3 weeks (melanoma: 16.0 weeks; NSCLC: 24.1 weeks), for a disease control rate of 50%. Among patients with a defined response, paired biopsy analyses showed that the greatest increase in CD8 occurred in the NSCLC patient with the longest duration of stable disease. The most frequent treatment related adverse events (TRAEs) reported in $\geq 10\%$ of patients were pruritis, anemia, fatigue, decreased appetite, and rash. Grade 3 TRAEs, rash and lymphocyte count decreased, were reported in 5 patients and a grade 4 TRAE of lipase increased (asymptomatic) was reported in 1 patient.

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