

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

¹Anissa Chan, ¹Nandita Bose*, ¹Nandita Bose, ¹Nadine Ottoson, ¹Xiaohong Qiu, ¹Ben Harrison, ¹Richard Walsh, ¹Paulette Mattson, ¹Michele Gargano, ¹Joanna Cox, ²Michael Chisamore, ¹Mark Uhlrik, ¹Jeremy Graff. ¹Biothera Pharmaceuticals, Eagan, MN, USA; ²Merck and Co., Inc., Rahway, NJ, USA

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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

¹Michele Maio*, ²Matteo Carlino, ³Anthony Joshua, ⁴Elaine McWhirter, ⁵Antoni Ribas, ⁶Paolo Ascierto, ⁷Wilson Miller, ³Marcus Butler, ⁸Pier Ferrucci, ⁹Robert Zielinski, ¹⁰Michele Del Vecchio, ¹¹Eduard Gasal, ¹²Razi Ghorri, ¹²Scott Diede, ¹²Elizabeth Croydton, ¹³Omid Hamid. ¹Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; ²Melanoma Institute Australia, The University of Sydney, Westmead and Blacktown Hospitals, Sydney, NSW, Australia; ³Kinghorn Cancer Centre, St. Vincent's Hospital, Sydney, NSW, Australia; ⁴Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; ⁵David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA; ⁶Istituto Nazionale Tumori IRCCS 'Fondazione G. Pascale', Naples, Italy; ⁷Lady Davis Institute for Medical Research, Jewish General Hospital, and McGill University, Montreal, QC, Canada; ⁸Istituto Europeo di Oncologia – IRCCS, Milan, Italy; ⁹Buffalo Medical Group, Williamsville, NY, USA; ¹⁰Fondazione IRCCS Istituto Nazionale, Milan, Italy; ¹¹Novartis, East Hanover, NJ, USA; ¹²Merck and Co., Inc., Kenilworth, NJ, USA; ¹³The Angeles Clinic and Research Institute, Los Angeles, CA, USA

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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

Abstract P863 Table 1 DLT, TRAE, and ORR in KEYNOTE-022 parts 4 and 5

Table. DLT, TRAE, and ORR in KEYNOTE-022 parts 4 and 5					
n (%)	cDL1 n=5	cDL2a n=16	cDL2b n=3	iDL1 n=3	iDL2 n=15
DLT	n=0	Grade 2 diarrhea, n=1; grade 1 thrombocytopenia, n=1; grade 2 dermatitis acneiform, n=1; grade 2 rash, n=1	Grade 4 thrombocytopenia, n=1; grade 2 mucosal inflammation, n=1	n=0	Grade 2 rash, n=2; grade 3 aseptic meningitis, n=1; grade 3 pneumonitis, n=1
Dose selected for confirmation in part 5	No	Yes	No	No	Yes
Any-grade TRAE	5 (100.0)	13 (81.3)	3 (100.0)	3 (100.0)	15 (100.0)
Grade 3-5 TRAE	5 (100.0)	5 (31.3)	2 (66.7)	0 (0)	7 (46.7)
ORR	2 (40.0)	0 (0)	0 (0)	1 (33.3)	4 (26.7)
CR	1 (20.0)	0 (0)	0 (0)	0 (0)	0 (0)
PR	1 (20.0)	0 (0)	0 (0)	1 (33.3)	4 (26.7)

cDL1: 4 weeks of trametinib 1.5 mg QD run-in, concurrent dosing of pembrolizumab 200 mg Q3W and trametinib 1.5 mg QD starting at week 5.

cDL2a: 2 weeks of trametinib 1.5 mg QD run-in, concurrent dosing of pembrolizumab 200 mg Q3W and trametinib 1.5 mg QD starting at week 3.

cDL2b: 4 weeks of trametinib 2 mg QD run-in, concurrent dosing of pembrolizumab 200 mg Q3W and trametinib 2 mg QD starting at week 5.

iDL1: 2 weeks of trametinib 1.5 mg QD run-in, pembrolizumab 200 mg Q3W dosing starting at week 3 with intermittent 1 week off trametinib, 2 weeks on trametinib 1.5 mg QD.

iDL2: 2 weeks of trametinib 2 mg QD run-in, pembrolizumab 200 mg Q3W dosing starting at week 3 with intermittent 1 week off trametinib, 2 weeks on trametinib 2 mg QD.

DLT, dose-limiting toxicity; TRAE, treatment-related adverse event; ORR, objective response rate.

pembrolizumab+trametinib. Safety was analyzed for all patients who received ≥ 1 dose of study drug; patients treated during the trametinib run-in who discontinued study before receiving pembrolizumab were included; patients who did not complete trametinib run-in or receive $\geq 66\%$ of planned doses during the 6-week dose-limiting toxicity (DLT) evaluable period were not included for DLT evaluation. AEs were graded per NCI CTCAE v4.

Results Of 42 enrolled patients, most were female (61.9%); median age was 55.0 years; 57.1% had received ≥ 2 prior lines of therapy. At database cutoff (June 26, 2019), median follow-up was 9.0 months (range, 1.4-25.6 months). Of 38 DLT-evaluable patients, 10 had DLTs (table 1). Dosing regimens were selected for confirmation in part 5 based on safety data. Any-grade TRAEs occurred in 39 (92.9%) patients; grade 3-4 TRAEs occurred in 19 (45.2%), none were grade 5. TRAEs led to discontinuation in 8 (19.0%) patients. Immune-mediated AEs occurred in 12 (28.6%) patients, most commonly severe skin reactions (n=6; 14.3%), pneumonitis (n=3; 7.1%), hypothyroidism (n=2; 4.8%). The MTD of concurrent pembrolizumab+trametinib was pembrolizumab 200 mg Q3W plus trametinib 1.5 mg with 2 weeks of trametinib run-in (ORR, 0/16; 0%) and the MTD of intermittent pembrolizumab+trametinib was pembrolizumab 200 mg Q3W plus trametinib 2 mg with 2 weeks of run-in (ORR, 4/15; 26.7%).

Conclusions Both concurrent or intermittent pembrolizumab +trametinib dosing were feasible and the combination showed antitumor activity in patients with advanced solid tumors or advanced BRAF wild-type melanoma.

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COMBINATION OF FECAL MICROBIOTA TRANSPLANTATION FROM HEALTHY DONORS WITH ANTI-PD1 IMMUNOTHERAPY IN TREATMENT-NAÏVE ADVANCED OR METASTATIC MELANOMA PATIENTS

¹Saman Maleki*, ¹John Lenehan, ²Jeremy Burton, ¹Michael Silverman, ³Seema Nair Parvathy, ¹Mikal El-Hajjar, ¹Mithunah Krishnamoorthy. ¹Western University, London, Canada; ²Lawson Health Research Institute, London, Canada; ³St. Joseph's Health Care, London, Canada

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Background Checkpoint inhibitors have changed the outcomes for patients with advanced melanoma. However, many patients still show primary resistance to single-agent therapy. Recently, the role of the gut microbiome in influencing antitumor immunity has been established. Currently, various methods of modifying the gut microbiome of cancer patients are being explored. We report the initial safety results of the first two patients treated on a phase I study combining Fecal Microbiota Transplantation (FMT) with single-agent anti-PD1 in treatment-naïve patients with advanced melanoma.

Methods Two healthy donors were selected through our screening process and approximately 100 grams of fresh stool was processed and prepared for FMT as per our standardized protocol. FMT recipients were melanoma patients with unresectable or metastatic disease who were treatment naïve for their advanced disease. Bowel preparation was completed the day prior and FMT was performed using oral administration of approximately 40 capsules. Anti-PD1 was started at least 1 week after FMT to allow for microbiome engraftment. Blood