

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.

P864 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

and stool were analyzed at baseline (pre-FMT), before immunotherapy, and three weeks after it.

Results Patient 1 was diagnosed with recurrent melanoma of the lower limb with multiple in-transit lesions refractory to control with surgery and a single intralesional injection of IL-2. Patient received stool from Donor 1 and did not experience any adverse effects from FMT. At the time of treatment #4, a solitary large cutaneous lesion stabilized but the patient experienced grade 1 diarrhoea, grade 2 nausea, and grade 2 fatigue, and grade 2 depression (NCI-CTCAE v5.0). Patient 2 was diagnosed with recurrent melanoma of the parotid gland with metastatic lesions in the lungs. Patient 2 received stool from Donor 2 and experienced only grade 1 flatulence from FMT. At the time of treatment #3, the patient experienced grade 1 constipation. Both patients had a vigorous immune response to FMT measured by changes in the immune subpopulations in peripheral blood one week after FMT, including an increase in CD28+ CD8+ T cells and a decrease in PDL1 + CD3- cells. Following anti-PD1 therapy, both patients had an increase in CD39+ CD8+ T cell population. The PD1+ CD38+ CD8+ dysfunctional T cell levels decreased in both patients post-FMT and anti-PD1 therapy.

Conclusions FMT combined with anti-PD1 therapy in patients with advanced melanoma appears to be safe. A measurable immune response was observed one week after FMT in both patients. One patient experienced several grade 2 toxicities with stabilization of a large cutaneous lesion.

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Trial Registration NCT03772899

Ethics Approval The study was approved by Western University Institution's Ethics Board, approval number 113131, date of approval March 15, 2019.

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SAFETY & EFFICACY OF LIFILEUCEL (LN-144) TUMOR INFILTRATING LYMPHOCYTE THERAPY IN METASTATIC MELANOMA PATIENTS AFTER PROGRESSION ON MULTIPLE THERAPIES – INDEPENDENT REVIEW COMMITTEE DATA UPDATE

¹Amod Sarnaik, ¹Nikhil Khushalani, ²Jason Chesney, ³Harriet Kluger, ⁴Brendan Curti, ⁵Karl Lewis, ⁵Theresa Medina, ⁶Sajeve Thomas, ⁷Anna Pavlick, ⁸Eric Whitman, ⁹Salvador Algarra, ¹⁰Pippa Corrie, ¹¹Omid Hamid, ¹²Jose Lutzky, ¹³Judit Olah, ⁷Jeffrey Weber, ¹⁴James Larkin, ¹⁵Wen Shi, ¹⁵Kelly DiTrapani, ¹⁵Harry Qin, ¹⁵Mariam Mirgoli, ¹⁵Renee Wu, ¹⁵Toshimi Takamura, ¹⁵Maria Fardis, ¹⁶John Kirkwood*. ¹H. Lee Moffitt Cancer Center, Tampa, FL, USA; ²James Graham Brown Cancer Center, Louisville, KY, USA; ³Yale University School of Medicine, New Haven, CT, USA; ⁴Providence Cancer Institute, Portland, OR, USA; ⁵University of Colorado, Aurora, CO, USA; ⁶Univ. of Florida Health Cancer Center, Orlando, FL, USA; ⁷NYU Langone Medical Center, New York, NY, USA; ⁸Atlantic Health System Cancer Care, Morristown, NJ, USA; ⁹Clinica Universitaria de Navarra, Pamplona, Spain; ¹⁰Addenbrooke's Hospital, Cambridge, UK; ¹¹The Angeles Clinic and Research Institute, Los Angeles, CA, USA; ¹²Mount Sinai Comprehensive Cancer Center, Miami Beach, FL, USA; ¹³Szegedi Tudományegyetem Szent-Györgyi, Szeged, Hungary; ¹⁴The Royal Marsden NHS Foundation Trust, London, UK; ¹⁵Iovance Biotherapeutics, San Carlos, CA, USA; ¹⁶University of Pittsburgh Medical Center, Pittsburgh, PA, USA

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Background Treatment options are limited for patients with advanced melanoma who have progressed on checkpoint

inhibitors and targeted therapies such as BRAF/MEK inhibitors (if BRAF-V600E mutated). Adoptive cell therapy utilizing tumor-infiltrating lymphocytes (TIL) has shown antitumor efficacy with durable responses in heavily pretreated melanoma patients. Safety and efficacy of lifileucel, a centrally manufactured cryopreserved autologous TIL therapy assessed by both investigator and an independent review committee (IRC), are presented.

Methods C-144-01 is a global Phase 2 open-label, multicenter study of the safety and efficacy of lifileucel in patients with unresectable metastatic melanoma. We report on Cohort 2 (N = 66) patients with Stage IIIC/IV unresectable melanoma who received lifileucel. Tumors resected at local institutions were processed in central GMP facilities for TIL production in a 22-day process. Final TIL infusion product was cryopreserved and shipped to sites. Patients received one week of cyclophosphamide/fludarabine preconditioning lymphodepletion, a single lifileucel infusion, followed by up to 6 doses of IL-2. All responses were assessed by RECIST 1.1.

Results 66 patients had the following baseline characteristics: 3.3 mean prior therapies (anti-PD1 100%; anti-CTLA-4 80%; BRAF/MEK inhibitor 23%), relatively high tumor burden (106 mm mean target lesion sum of diameters), 44% with liver and/or brain lesions, median LDH 244 U/L. Objective Response Rate (ORR) by investigator was 36.4% (2 CR, 22 PR, 1 previously confirmed PR is now changed to SD) and Disease Control Rate (DCR) of 80.3%. At a median follow up of 9.7 months, median Duration of Response (DOR) has not been reached. The adverse event profile was generally consistent with the underlying advanced disease and the profile of the lymphodepletion and IL-2 regimens.

The ORR per IRC was 34.8% (2 CR, 21 PR) and DCR was 72.7%. At a median follow up of 6.9 months, the median IRC DOR has not been reached. Overall concordance rate of investigator and IRC read of response was 89.4%. The concordance compares favorably with literature reports in a metastatic disease.¹

Conclusions Lifileucel treatment resulted in a 36.4% ORR in heavily pretreated metastatic melanoma patients with high baseline disease burden who had received prior anti-PD1 and BRAF/MEK inhibitors, if tumor BRAF mutated. The high concordance of 89.4% between investigator and IRC confirms the original assessment of lifileucel efficacy in metastatic melanoma.²

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Trial Registration ClinicalTrials.gov Identifier: NCT02360579

Ethics Approval Ethics Approval This trial was approved by Western Institutional Review Board - IRB Tracking Number: 20160198.

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