796 A PHASE I/II TRIAL COMBINING AVELUMAB AND TRABECTEDIN FOR ADVANCED LIPOSARCOMA AND LEIOMYOSARCOMA

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Background Leiomyosarcoma (LMS) and liposarcoma (LPS) are soft tissue sarcoma subtypes that frequently express PD-L1 and are infiltrated with T cells. They are generally resistant to PD-1/PD-L1 inhibition, possibly due to infiltration with high levels of immunosuppressive tumor-associated macrophages (TAMs). Trabectedin is FDA-approved for refractory LMS and LPS. Prior studies demonstrated trabectedin activity against TAMs. We hypothesized that PD-L1 inhibition by avelumab would be enhanced by trabectedin through its inhibition of immunosuppressive TAMs.

Methods This is a single-arm, open-label, Phase I/II study of avelumab combined with trabectedin for patients with advanced LMS and LPS. In the phase I portion, we evaluated safety and feasibility at 3 trabectedin doses (1, 1.2 and 1.5 mg/m2) with avelumab at standard dosing (10 mg/kg) in a 3+3 design. Primary endpoint of the phase II portion was the objective response rate (ORR) by RECIST 1.1. 24 patients were included for phase II endpoints. Secondary objectives were duration of response, progression free survival (PFS), clinical benefit rate (CBR) at 12 weeks, and overall survival.

Results 37 patients enrolled; 34 were evaluable. 23 had LMS. 11 had LPS. In Phase 1, there were DLTs in 2 of 6 patients at both higher doses of trabectedin including grade 3 GGT elevation, bilirubin and alanine aminotransferase (ALT) elevation, small bowel obstruction, and reduced ejection fraction. The recommended Phase 2 dose was 1.0 mg/m2 trabectedin and 10 mg/kg avelumab. At the Phase 2 dose, the most common adverse events (AEs) attributed to study drug were fatigue, ALT increase, diarrhea, anorexia, nausea, and infusion reaction. There were 8 instances of PORT inflammation or infection. The most common Grade 3 AEs attributed to study drug were neutropenia and ALT increase. There were no grade 4/5 AEs at the Phase 2 dose. 23 patients were evaluable for primary ORR endpoint. 2 (8.7%) had partial response (1 confirmed), 11 had stable disease as best response. CBR (PR+SD) at 12 weeks was 56%. 6 month PFS was 50.1%; median PFS is 23.4 months. 9 patients remain on study treatment. In a secondary analysis of all patients, ORR was 8.6% (3/35 with PR), median PFS was 6.1 months.

Conclusions Administration of this combination was feasible with acceptable toxicity. The recommended Phase 2 dose was 1.0 mg/m2 trabectedin and 10 mg/kg avelumab. The combination failed to meet the primary endpoint of ORR, however the PFS appears favorable compared to prior studies of trabectedin in this population and warrants further study.

Trial Registration NCT03074318

Ethics Approval The study was approved by the Fred Hutch IRB, number 9717.

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797 SIGNIFICANT ANTI-TUMOR ACTIVITY OF HBI-8000, A CLASS I HISTONE DEACETYLASE INHIBITOR (HDACI) IN COMBINATION WITH NIVOLUMAB (NIVO) IN ANTI-PD1 THERAPY-NAÏVE ADVANCED MELANOMA (TN-MEL)

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Background Anti-PD1 based therapy has been the mainstay of treatment for advanced melanoma for several years. HBI-8000 is a Class I selective oral HDACi with immunomodulatory effects including enhanced cell-mediated toxicity, enhanced tumor infiltration by cytotoxic T-cells and reduced tumor infiltration by T-regulatory cells. In a phase 1b/2 trial in melanoma, kidney cancer and non-small cell lung cancer, the recommended phase 2 dose of HBI-8000 was determined to be 30mg orally twice weekly (BIW) combined with nivolumab administered at the approved dosing schedule (JITC 2018; P346). This report describes the tolerability of this combination in all enrolled melanoma patients, and efficacy in the expansion cohort of anti-PD1 TN-MEL.

Methods Patients with unresectable or advanced melanoma and measurable disease, of ECOG performance status 0-1, and with adequate hematologic and biochemical parameters were enrolled. Treated brain metastases not requiring steroids were permitted. Tumor response was assessed by RECIST v1.1 and iRECIST with staging every 8 weeks; treatment continued for 24 months, disease progression or unacceptable toxicity. Data cut-off was Jan 31, 2020 for the reported analyses

Results Forty-nine patients (32 anti-PD1 naïve, 17 with prior anti-PD1 therapy) were treated with HBI-8000 (47 patients at 30 mg BIW; 2 patients at 40mg BIW in Phase 1b) in combination with nivolumab. The median age was 63 years (range 28-84); 57% were male. In the anti-PD1 naïve cohort, most (30/32) had normal LDH. The most common all grade treatment related adverse events (AEs) included fatigue (n=25), diarrhea (n=24), abdominal pain (n=14), and lymphopenia (n=13). Although HBI-8000 related thrombocytopenia (n=25) and neutropenia (n=15) were common, clinically significant bleeding or febrile neutropenia were not observed. The most frequent >/= G3 AEs related to HBI-8000 were hypophosphatemia (n=7), neutropenia (n=4), thrombocytopenia (n=3) and lymphopenia (n=2). Twelve patients discontinued treatment for AEs. Among 31 anti-PD1 naïve patients evaluable for response, there were 23 objective responses (4 CR, 19 PR; ORR 74%), 5 stable disease (disease control rate 90%), and 3 progressive disease. Median time to response was 1.9 months. At a median follow-up for this cohort of 8.9 months (range, 0.9-35.5 months), the median duration of response and median progression-free survival have not been reached.

Conclusions The combination of HBI-8000 and nivolumab is well tolerated and demonstrates very encouraging efficacy in patients with anti-PD1-naïve advanced melanoma. Follow-up to assess durability of response is ongoing, and further investigation of this promising combination is planned.

Trial Registration NCT02718066

Ethics Approval The study was approved by participating study sites' Institutional Review Boards and the Sponsor has conducted the trial in full compliance with all GCP and FDA regulations.

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Clinical trials in-progress

798 SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MRNA-4157 IN COMBINATION WITH PEMBROLIZUMAB IN SUBJECTS WITH UNRESECTABLE SOLID TUMORS (KEYNOTE-603): AN UPDATE

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Background T-cell targeting of mutation-derived epitopes (neoantigens) has shown to drive anti-tumor responses. Immunizing patients against such neoantigens in combination with a checkpoint inhibitor (CPI) may elicit greater anti-tumor responses than CPI alone. Mutations are rarely shared between patients, thus requiring a personalized approach to vaccine design. mRNA-4157 is a lipid encapsulated mRNA based personalized cancer vaccine encoding neoantigens selected using a proprietary algorithm to induce neoantigen specific T cells and associated anti-tumor responses. This report includes updates from the mRNA-4157 Phase1(P1) study. The initial data was presented at ASCO2019.[1]

Methods This study evaluates the safety and efficacy of mRNA-4157 as monotherapy in patients with resected solid tumors (Part A) and in combination with pembrolizumab in patients with advanced/metastatic solid tumors (Parts B). The selected solid tumors in Part A-B includes melanoma, bladder carcinoma, HPV-negative (HPV-neg) HNSCC, NSCLC, SCLC, MSI-High (MSI-h), or TMB-High cancers. Expansion cohorts includes patients with CPI-naïve MSS-CRC and HPV-neg HNSCC (Part C) and with resected melanoma (Part D). Patients receive up to 9 cycles (Q3W) of mRNA-4157 by intramuscular injection at up to 1 mg alone (Part A) or in combination with pembrolizumab (200 mg IV Q3W, Parts B-D). Pembrolizumab is administered for two cycles before the first dose of mRNA-4157 and may continue after 9 cycles of combination. Endpoints include safety, tolerability, efficacy and biomarker assessments.

Results 79 patients received mRNA-4157; 16 as monotherapy and 63 in combination with pembrolizumab. Only low grade and reversible treatment related AEs were reported. 14/16 Part A patients (3 melanoma, 11 NSCLC, 2 MSI-h CRC) remained disease free on study. 28 patients in Parts B (6 bladder, 2 HNSCC, 3 melanoma, 10 NSCLC, 2 SCLC, 4 MSI-h tumor, 1 TMB-h tumor), 27 patients in Part C (10 HNSCC and 17 MSS-CRC), and 8 patients with resected melanoma (Part D) received combination. 3 CR (1 HNSCC, 1 MSI-h CRC and 1 MSI-h prostate), and 8 PR (1 bladder, 4 HNSCC, 2 SCLC and 1 MSI-h endometrial) were observed with combination. Of 10 CPI-naïve HPV-neg HNSCC patients, the response rate was 50% (1CR, 4PR, 4SD) mPFS 9.8months, which compared favorably to published rates of ~14.6% mPFS 2.0months for pembrolizumab monotherapy.[2 3] Biomarker assessments including immune gene expression profiling will be presented.

Conclusions mRNA-4157 has an acceptable safety profile along with observed clinical responses in combination with pembrolizumab. Preliminary efficacy analysis from CPI-naïve relapsed/refractory HPV-neg HNSCC cohort suggests activity of this combination. Study is ongoing.

Trial Registration NCT03313778

Ethics Approval The study was approved by each participating sites' local IRB.

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799 DURABLE RESPONSES AND IMMUNE ACTIVATION WITH INTRATUMORAL ELECTROPORATION OF PIL-12 PLUS PEMBROLIZUMAB IN ACTIVELY PROGRESSING ANTI-PD-1 REFRACTORY ADVANCED MELANOMA: KEYNOTE 695 INTERIM DATA

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Background Electroporated plasmid IL-12 (TAVO or tavokinogene telseplasmid) is a novel pro-inflammatory intratumoral therapy with substantial single agent activity in melanoma, which has been shown to synergize with anti-PD-1 antibodies in patients predicted as non-responders to anti-PD-1.[1 2] Interim data from patients with stage III/IV melanoma actively progressing on anti-PD-1 antibody are presented herein.

Methods Patients with confirmed disease progression by RECIST v1.1 after at least 12 weeks of treatment on pembrolizumab or nivolumab (or combination checkpoint blockade) and within 12 weeks of last dose (with no intervening