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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SIGNIFICANT ANTI-TUMOR ACTIVITY OF HBI-8000, A CLASS I HISTONE DEACETYLASE INHIBITOR (HDACi) IN COMBINATION WITH NIVOLUMAB (NIVO) IN ANTI-PD1 THERAPY-NAÍVE 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. 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 adverse events 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.

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