A PHASE I TRIAL OF INTRATUMORAL PVSRIPO IN PATIENTS WITH UNRESECTABLE TREATMENT REFRACTORY MELANOMA

Background While PD-1/PD-L1 antagonists have improved the prognosis for many patients with melanoma, the majority fail therapy. PVSRIPO is a novel immunotherapy consisting of a non-neurovirulent rhinovirus:poliovirus chimera that activates tumor-associated plasmacytoid dendritic cells (pDC) via TLR9 inducing type I interferons and anti-tumor innate immunity to facilitate a targeted anti-tumor immune response. Preclinical data show that PVSRIPO plus anti-PD-1 therapy leads to a greater anti-tumor response than either agent alone, warranting clinical investigation.

Methods An open-label phase I trial of intratumoral PVSRIPO in patients with unresectable melanoma (AJCC version 7 stage IIIb, IIIC, or IV) was performed. Eligible patients failed at least prior anti-PD-1 and BRAF/MEK (if BRAF mutant) therapy. The primary objective was to characterize the safety and tolerability of PVSRIPO. 12 patients in 4 cohorts received a total of 1, 2 (into 2 different lesions) or 3 (same lesion 3x or 3 different lesions) injections of PVSRIPO monotherapy, 21 days apart.

Results PVSRIPO injections were well tolerated with no SAEs or DLTs reported; all TEAEs were grade (G) 1 or 2 (grade 1 pruritus most common at 38%), with all but 2 PVSRIPO-related TEAEs localized to the injected or adjacent lesions (n=1 G1 hot flash, n=1 G1 fatigue). Despite the limited number of PVSRIPO treatments relative to the overall lesion burden (67% patients >5 lesions), 4 of 12 patients (33%) achieved an objective response per irRC, including 4/6 (66%) who received 3 injections (maximum administered). Pathologic complete response (ie, no viable tumor detected in injected and non-injected lesions biopsied) was observed in 2 of 4 (50%) patients with in-transit disease. PVSRIPO response relative to time since prior anti-PD-1 exposure is summarized in table 1. Following study completion/PVSRIPO therapy, 10/12 patients (83%) again received immune checkpoint inhibitor (ICI)-based therapy and 6/12 patients (50%) remained progression free at the data cutoff.

Conclusions Intratumoral PVSRIPO was well tolerated. When taken together with preclinical data, the anti-tumor responses observed relative to prior or subsequent ICI therapy suggests that PVSRIPO, either alone or in combination with anti-PD-1, may be an effective treatment in anti-PD-1 refractory melanoma. An amendment exploring higher PVSRIPO dose levels is ongoing and a phase 2 study with and without anti-PD-1 in the refractory population is initiating.

Ethics Approval This study (NCT03712358) was approved by WIRB; ID 20181772.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0302

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PHASE II TRIAL OF NEOADJUVANT NIVOLUMAB (NIVO) AND INTRA-TUMORAL (IT) CMP-001 IN HIGH-RISK RESECTABLE MELANOMA (NEO-C-NIVO): FINAL RESULTS

Background Neoadjuvant PD-1 blockade produces major pathologic responses (MPR) in ~30% of patients (pts) with high-risk resectable melanoma (MEL) with durable relapse-free benefit, and increased circulating activated CD8+ T cells. 1, 2 CMP-001 is a type A CpG packaged within a virus-like particle that activates tumor-associated plasmacytoid dendritic cells (pDC) via TLR9 inducing type I interferons and anti-tumor CD8+ T cells. CMP-001/pembrolizumab produces durable anti-tumor responses in PD-1 refractory melanoma. 3 We previously reported preliminary evidence of efficacy of neoadjuvant IT CMP/Nivo in high-risk resectable MEL; and herein present final results on 30 evaluable patients.

Results PVSRIPO injections were well tolerated with no SAEs or DLTs reported; all TEAEs were grade (G) 1 or 2 (grade 1 pruritus most common at 38%), with all but 2 PVSRIPO-related TEAEs localized to the injected or adjacent lesions (n=1 G1 hot flash, n=1 G1 fatigue). Despite the limited number of PVSRIPO treatments relative to the overall lesion burden (67% patients >5 lesions), 4 of 12 patients (33%) achieved an objective response per irRC, including 4/6 (66%) who received 3 injections (maximum administered). Pathologic complete response (ie, no viable tumor detected in injected and non-injected lesions biopsied) was observed in 2 of 4 (50%) patients with in-transit disease. PVSRIPO response relative to time since prior anti-PD-1 exposure is summarized in table 1. Following study completion/PVSRIPO therapy, 10/12 patients (83%) again received immune checkpoint inhibitor (ICI)-based therapy and 6/12 patients (50%) remained progression free at the data cutoff.

Conclusions Intratumoral PVSRIPO was well tolerated. When taken together with preclinical data, the anti-tumor responses observed relative to prior or subsequent ICI therapy suggests that PVSRIPO, either alone or in combination with anti-PD-1, may be an effective treatment in anti-PD-1 refractory melanoma. An amendment exploring higher PVSRIPO dose levels is ongoing and a phase 2 study with and without anti-PD-1 in the refractory population is initiating.

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