Intratumoral PVSRIPO therapy leads to a greater anti-tumor response than either response. Preclinical data show that PVSRIPO plus anti-PD-1 activates innate immunity to facilitate a targeted anti-tumor immune response. 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 immunity. CMP-001/pembrolizumab produces durable benefit, and increased circulating activated CD8+ T cells.12

**Conclusion**

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.

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.

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Methods 30 pts with stage III B/C/D MEL were enrolled. Preoperatively, CMP-001 was dosed at 5 mg subcutaneous (SC, 1st), then 10 mg IT (2nd-7th) weekly; Nivo was dosed 240 mg q2 weeks for 3 doses – both agents given for 7 weeks. Post-operatively, Nivo was dosed 480 mg q4 weeks with CMP-001 5 mg q4 weeks SC for 48 weeks. Primary end-points included major pathologic response rate (MPR), and incidence of dose-limiting toxicities (DLT). Secondary end-points were radiographic response, relapse-free survival (RFS) and overall survival (OS). Pathological response was scored blinded by pathologists based on residual volume of tumor (RVT) using prior specified cutoffs.4 0% (complete response, pCR); 0%<rvt<rvt50% (non-response, pNR). Radiographic response was assessed using RECIST v1.1. Sequential blood draws and tumor biopsies were collected and analyzed for CD8+ T cell infiltrate (TIL), multiparameter flow cytometry (MFC) and multiplex immunofluorescence (mIF).

Results 30 pts with regionally advanced MEL were enrolled, of stages III B (57%), IIIC (37%), IIID (7%). 29/ 30 (97%) of pts completed 7 weeks of neoadjuvant Nivo/ CMP; while 1 pt had a delay in surgery related to a pre-operative infection unrelated to therapy. No DLTs were reported; grade 3/4 irAE were reported in 3 pts (11%) leading to CMP-001 discontinuation in 2 pts (7%). Radiographic responses were seen in 13 pts (43%), while 9 pts (30%) had stable disease and 8 pts (27%) had progressive disease. Pathological responses (RVT <50%) were seen in 70% of pts: pCR 15 (50%), pMR 3 (10%), 3 pPR (10%); only 9 (30%) had pNR. Pathological responders (pCR/ pMR) had increased CD8+ TIL and CD303+ pDC intra-tumoral by mIF; and peripherally activated PD1+ /Ki67+ CD8+ T cells by MFC.

Conclusions Neoadjuvant CMP/Nivo has acceptable toxicity and promising efficacy. MPR is 60% in 30 pts. 1-year RFS was 82% (all pts) and 89% (among those with pCR/pMR); median RFS is 9 months (among pNR/pPR) and not reached (among pCR/pMR). Response is associated with evidence of immune activation intra-tumorally and peripherally. IT CMP001 increases clinical efficacy of PD-1 blockade with minimal additional toxicity in pts with regionally advanced MEL. Further study of this combination in high-risk resectable MEL is planned.

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Trial Registration Clinical trial information: NCT03618641

Ethics Approval The study was approved by University of Pittsburgh’s Institutional Review Board, approval number MOD19040237-002.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

REFERENCES

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304 INTRATUMORAL INJECTION OF CMP-001, A TOLL-LIKE RECEPTOR 9 (TLR9) AGONIST, IN COMBINATION WITH PEBROLIZUMAB REVERSED PROGRAMMED DEATH RECEPTOR 1 (PD-1) BLOCKADE RESISTANCE IN ADVANCED MELANOMA

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Background Therapeutic options are limited for patients with advanced melanoma that is refractory to PD-1 blockade. This study was performed in this patient population to assess the safety and antitumor activity of CMP-001, a CpG-A TLR9 agonist packaged within a virus-like particle.

Methods Patients were eligible for this 2-part, open-label, multicenter, phase 1b study if they had metastatic/unresectable melanoma and stable disease after =12 weeks or progressive disease (PD) on/after anti-PD-1 therapy. Part 1 evaluated CMP-001 plus pembrolizumab dose-escalation and dose-expansion. Part 2 evaluated CMP-001 monotherapy. Accessible lesion(s) were injected intratumorally with CMP-001, at a polysorbate 20 (PS20) concentration of either 0.01% or 0.00167%. The Part 1 primary objective was to identify the recommended phase 2 dose (RP2D) and schedule of CMP-001 plus pembrolizumab, while the Part 2 primary objective was to assess the safety of CMP-001 monotherapy. Secondary objectives for both parts were a preliminary assessment of antitumor activity of CMP-001 plus pembrolizumab and CMP-001 monotherapy, and the overall safety profile and pharmacodynamics of the combination.

Results In Part 1 (N=159) and Part 2 (N=40), 93.1% and 80.0% of patients had PD as their last response to prior anti-PD-1 therapy, respectively. The most common treatment-related adverse events (TRAEs; >25%) were flu-like symptoms (Parts 1 and 2) and injection-site reactions (Part 1). Grade 3/4 TRAEs were reported in 36.5% (Part 1) and 22.5% (Part 2) of patients, the most common being hypotension (Part 1: 43.3%) and hypophosphatemia (Part 1: 11%).