of 10^7 PFU/mL. Of the six patients treated with single agent RP2, three (50%) have ongoing partial responses. Objective responses (including in uninjected tumors) were observed in patients with uveal melanoma (prior ipilumumab/nivolumab; extensive liver metastases), mucoepidermoid carcinoma (prior carboplatin/paclitaxel, bicalutamide, ceralasertib), and esophageal cancer (prior durvalumab, M6620, capecitabine, oxaliplatin, cisplatin, chemoradiation; liver and abdominal node metastases). Enrollment is underway in HSV seronegative patients and in combination with nivolumab. Updated data including biomarker and biodistribution data will be presented.

Conclusions The Phase 1 clinical data supports the safety and efficacy of single agent RP2, including demonstration of uninjected tumor response in patients with difficult to treat advanced cancers. This data supports the hypothesis that anti-CTLA-4 delivered intra-tumorally through oncolytic virus replication, with accompanying antigen release and presentation, can provide potent anti-tumor effects.

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422 AN OPEN-LABEL, MULTICENTER, PHASE 1/2 CLINICAL TRIAL OF RP1, AN ENHANCED POTENCY ONCOLYTIC HSV, COMBINED WITH NIVOLUMAB: UPDATED RESULTS FROM THE SKIN CANCER COHORTS

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Background RP1 is an enhanced potency oncolytic HSV encoding a fusogenic protein (GALV-GP R-) and GM-CSF which has previously demonstrated tolerable safety and tumor regression alone and with nivolumab in patients with a number of tumor types. Updated data from the phase 1 expansion with nivolumab, melanoma phase 2 (enrollment complete) and non-melanoma skin cancer (NMSC; enrollment ongoing) cohorts will be presented (NCT03767348). Enrollment of a further 125 patient anti-PD1 refractory cutaneous melanoma cohort; and activation of a cohort of anti-PD1 refractory NSCLC is underway.

Methods Stage IIIb-IV melanoma patients for whom anti-PD-1 was indicated or who were refractory to prior anti-PD-1 alone or in combination with anti-CTLA-4, were enrolled. NMSC patients were anti-PD1 naïve. Patients received ≤8 doses of RP1 (≤10 mL/visit Q2W; first dose 10^6 PFU/mL then 10^7 PFU/mL) with nivolumab (240 mg IV Q2W for 4 months then 480 mg IV Q4W up to 2 years) from the second RP1 dose.

Results As of 24th June 2020, 36 melanoma and 16 NMSC patients had been enrolled with follow up of <1–17 months. Of the melanoma patients, 16 previously anti-PD1 treated cutaneous (8 also prior anti-CTLA-4), 8 anti-PD1 naïve cutaneous, 6 mucosal, and 6 uveal. Of the NMSC patients, 10 had squamous cell (CSCC), 3 had a basal cell, 1 had Merkel cell carcinomas, and 2 had angiosarcoma. Treatment emergent adverse events (TEAEs) remain consistent with phase 1, with RP1 side effects generally of Grade 1/2 constitutional-type symptoms, with no exacerbation of the side effects expected for nivolumab. At the data cut-off, 5 previously anti-PD1 treated (4 also anti-CTLA-4) cutaneous melanoma patients, 4 anti-PD1 naïve cutaneous melanoma patients, two mucosal melanoma patients (one anti-PD1 refractory) and one uveal melanoma patient (ipi/nivo refractory) have achieved response (WHO criteria for uveal). For NMSC, for the 13 patients with >8 weeks follow up, one of two angiosarcoma patients and seven of eight CSCC patients (5 CR) have achieved response (CSCC ORR 87.5%; CR rate 62.5%, including of uninjected visceral disease). Tumor biopsies in patients continue to routinely show immune activation, including robust recruitment of CD8+ T cells, reversal of T cell exclusion, and increased PD-L1 expression. Treatment remains ongoing, and current data will be presented.

Conclusions RP1 and nivolumab have continued to be well tolerated, with continued promising anti-tumor activity in patients with skin cancers, including those with anti-PD1 refractory and other difficult to treat melanomas, and in patients with CSCC.

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423 SAFETY AND PRELIMINARY EFFICACY OF INTRATUMORAL CAVROTOLIMOD (AST-008), A SPHERICAL NUCLEIC ACID TLR9 AGONIST, IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Spherical nucleic acids (SNAs) are nanostructures consisting of radially oriented, densely packed oligonucleotides arranged in a spherical 3D architecture. SNAs have different properties than linear oligonucleotides, including increased cellular uptake, which may enhance efficacy. Cavrotolimod (AST-008) is an SNA toll-like receptor 9 (TLR9) agonist designed to robustly activate innate and adaptive immune responses. Cavrotolimod is in development for the treatment of advanced solid tumors in combination with PD-1 blockade. Prior studies demonstrated that cavrotolimod, alone and in combination with PD-1 blockade, increased circulating levels of Th1-type cytokines and activated peripheral T cells and NK cells.

Methods AST-008-102 is an ongoing Phase 1b/2 study (NCT03684785). The Phase 1b dose escalation stage examined intratumoral (IT) cavrotolimod at doses of 2, 4, 8, 16, and 32 mg in combination with pembrolizumab in patients with advanced solid tumors. Cavrotolimod was dosed once weekly for 8 weeks and once every 3 weeks thereafter. The Phase 2 dose expansion stage is examining cavrotolimod 32 mg IT in combination with IV pembrolizumab for the treatment of advanced Merkel cell carcinoma (MCC) and in combination with IV cemiplimab for the treatment of advanced cutaneous squamous cell carcinoma (CSCC). Both cohorts are enrolling patients with documented progression of disease on PD-(L)1 blockade. This analysis provides interim results of the Phase 1b stage.

Results In the Phase 1b stage, 20 patients were enrolled across all planned dose levels. No dose-limiting toxicities, grade (G)4 toxicities, or treatment-related serious adverse events (AEs) were observed. The most common AEs were injection site reactions (ISRs) and flu-like symptoms. All treatment-related AEs were < G3 except agitation and ISR (1 each). At data cutoff, ORR is 21% (4 of 19 evaluable patients) in a heterogeneous population with solid tumors. All 4 responders (2 melanoma and 2 MCC patients) have ongoing responses, with duration of response exceeding 52 weeks in 2 patients. Three of 4 responders had disease progression on PD-1 blockade at the time of enrollment, and one patient had a prior response to PD-1 blockade, but subsequently relapsed off therapy. Regression of both injected and noninjected lesions was observed. Gene expression analyses demonstrated increased IT infiltration by cytotoxic immune cells in both injected and noninjected tumors. The highest dose (32 mg) was selected for the Phase 2 stage.

Conclusions IT administration of cavrotolimod appears to be safe and well tolerated in combination with pembrolizumab. Durable responses have occurred in patients previously experiencing progressive disease on PD-1 blockade.

Trial Registration NCT03684785

Ethics Approval The study was approved by Institutional Review Boards of Dana-Farber Cancer Institute (IRB #18-584), John Wayne Cancer Institute (WIRB #20183064), University of Miami (IRB #20180957), University of Iowa (IRB #201810763), University of Cincinnati (WIRB #20183064), University of Washington (WIRB #20183064), MSKCC (IRB #20-174), UC San Francisco (WIRB #20183064), U Colorado (WIRB #20183064), Northwestern (IRB #STU00211083), U Arizona (WIRB #20183064), UC Irvine (WIRB #20183064), U Pitt (WIRB #20183064), and Washington University (WIRB #20183064).

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425 INVESTIGATION OF WNT LIGAND SIGNALING REGULATORS AS A PREDICTOR OF ANTI-PD-1 RESPONSE IN METASTATIC MELANOMA

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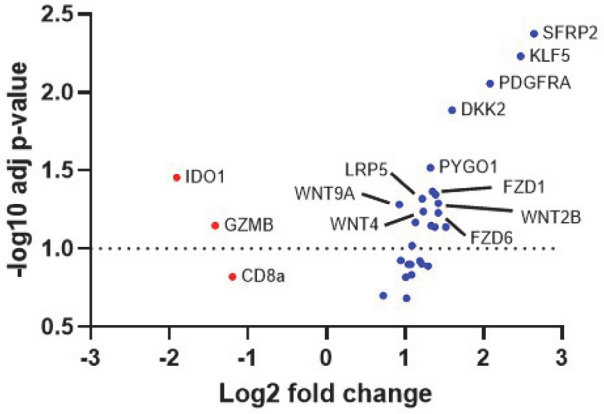
Background Responses to anti-PD-1 antibodies (aPD1) have changed the therapeutic landscape of metastatic melanoma, however predictive biomarkers of resistance are lacking. Beta-catenin pathway activation has been inversely correlated with tumor-infiltrating T lymphocytes in melanoma as well as several other solid tumors.[1] However, activating mutations involving this pathway are rare, implying that the modulation of upstream Wnt ligand/Fzd receptor (Wnt/Fzd) signaling could be a critical regulator of anti-tumor immunity. Indeed, expression of certain Wnt ligands has been associated with inferior responses to checkpoint inhibitor immunotherapy in metastatic melanoma patients.[2] In addition, we have further found tumor-derived paracrine and autocrine Wnt ligand signaling to drive dendritic cell tolerization and to be associated with escape from aPD1 therapy in transgenic mouse models.[3 4] No studies to date have focused on the impact of the various regulators and components of proximal Wnt/Fzd receptor signaling on resistance to aPD1 therapy in melanoma patients. We therefore developed a unique Wnt/Fzd pathway panel using Nanostring technology to examine alterations in Wnt ligands, their receptors, and regulators as a predictor of aPD1 resistance.

Abstract 425 Table 1 Most significantly upregulated Wnt ligands, receptors, and pathway components in patients that do not respond to aPD1

Gene Category	Genes Upregulated in NRs
Wnt Receptor	*FZD1*
Wnt Receptor	*FZD6*
Wnt Co-Receptor	*LRP5*
Wnt Ligand	*WNT2B*
Wnt Ligand	*WNT4*
Wnt Ligand	*WNT9A*
Wnt Activator	*PYGO1*
Wnt Regulator	*SFRP2*
Wnt Regulator	*DKK2*



Abstract 425 Figure 1 Volcano plot of the top 30 genes from the nanostring panel comparing responders (red) and nonresponders (blue)

Results Several components of both canonical and non-canonical Wnt ligand signaling, including regulators of autocrine/paracrine signaling, were upregulated in aPD1 NR pts