**Background** An unmet need exists for novel therapies that produce deep and durable responses in more patients with metastatic melanoma (metMEL). Encouraging clinical activity was observed with the CD122-preferential IL-2 pathway agonist bempegaldesleukin (BEMPEG) plus nivolumab (NIVO) in first-line metMEL in the phase 1/2 PIVOT-02 trial (NCT02983045), leading to FDA Breakthrough Therapy Designation. We present updated clinical results from PIVOT-02 in first-line metMEL, and biomarkers of response.

**Methods** 41 patients with previously untreated stage IV melanoma (known PD-L1 status by immunohistochemistry; 28–8 PharmDx) received ≥1 dose of BEMPEG (0.006 mg/kg) plus NIVO (360 mg) q3wks; 38 patients were efficaciously evaluable (≥1 post-baseline tumor scan). Primary endpoints were safety and objective response rate (ORR; RECIST v1.1; BICR); other endpoints included PFS, OS, and biomarkers. Polyfunctional and TIL in baseline tumor biopsies were analyzed for correlation with ORR and PFS.

**Results** At median follow-up of 25.7 months (15 May 2020), ORR by BICR was 53% (20/38 patients). Complete response occurred in 13/38 patients (34%): 23% PD-L1-negative (<1% tumor cell expression); 41% PD-L1-positive (≥1% tumor cell expression). Further deepening of response was observed, with 17/38 patients (45%) achieving 100% reduction in target lesions and a 79% median reduction from baseline in tumor size (previously 62%). Median time to response and time to complete response was 2.0 and 7.9 months, respectively. Median PFS and OS were not reached. 2-year OS rate was 77% (95% CI: 60–87; ITT). Safety was consistent with previous reports. IFNγ GEP and CD8+ TIL in baseline tumor biopsies were significantly associated with ORR and PFS. Analysis of Cycle1-Day8 blood samples demonstrated significant increases in CD4+PSI, CD8+PSI, and eosinophils from baseline. Increased CD8+PSI was significantly associated with higher ORR and PFS; increased eosinophils were significantly associated with higher ORR.

**Conclusions** BEMPEG plus NIVO was well tolerated in first-line metMEL, with durable and further deepening of responses, regardless of baseline PD-L1 status. At 25.7 months’ follow-up, mPFS and mOS were not reached. Early on-treatment (Day8) increases in CD8+PSI and eosinophils in blood were identified as non-invasive biomarkers of response that are detectable well before clinical measures of response. A phase 3 trial evaluating BEMPEG plus NIVO in first-line metMEL is enrolling (NCT03635983).

**Trial Registration** NCT02983045

**Ethics Approval** The study was approved by the institutional review board of each participating site.

**REFERENCE**


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**Abstracts**

**421 INITIAL RESULTS OF A PHASE 1 TRIAL OF RP2, A FIRST IN CLASS, ENHANCED POTENCY, ANTI-CTLA-4 ANTIBODY EXPRESSING, ONCOLYTIC HSV AS SINGLE AGENT AND COMBINED WITH NIVOLUMAB IN PATIENTS WITH SOLID TUMORS**

**Background** RP2 is an enhanced potency oncolytic HSV-1 expressing granulocyte-macrophage colony-stimulating factor (GM-CSF), a fusogenic protein (GALV-GP R), and an anti-CTLA-4 antibody-like molecule which is being tested in an open-label, multicenter, phase 1 study alone and combined with PD-1 blockade (NCT04336241).

**Methods** The objectives were to assess initial safety and efficacy and determine the recommended phase 2 dose (RP2D) of RP2 alone and combined with nivolumab. Patients were to be treated using a 3+3 dose escalation at two dose levels of up to 10 mL of RP2 Q2W up to 5 times (dose level 1: 10^5 PFU/mL then 4 doses of 10^6 PFU/mL; dose level 2: 10^5 PFU/mL then 4 doses of 10^7 PFU/mL). Following determination of the RP2D, additional HSV-1 seronegative patients were to be enrolled such that ≥3 had been dosed with RP2 at the RP2D, and a combination cohort of up to 30 patients dosed up to 8 times with RP2 at the RP2D combined with nivolumab (240 mg Q2W for 4 months from the second RP2 dose, then 480 mg Q4W for 20 months) opened. Lesions were injected directly or under imaging guidance used for visceral lesions. Tumor biopsies were obtained for biomarker analysis. Viral shedding and anti-HSV antibody titers were also monitored.

**Results** Six HSV seropositive patients were enrolled in the dose-escalation phase with primarily Grade 1–2 adverse events, including febrile and other constitutional symptoms, local inflammation, and erythema observed. There were no DLTs requiring dose level expansion. The RP2D was selected as up to 10 mL of 10^5 PFU/mL followed Q2W by multiple doses
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 therapy 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 ulcer. 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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