420 PROGRESSION-FREE SURVIVAL AND BIOMARKER CORRELATES OF RESPONSE WITH BEMPEG PLUS NIVO IN PREVIOUSLY UNTREATED PATIENTS WITH METASTATIC MELANOMA: RESULTS FROM THE PIVOT-02 STUDY

[1]Adi Diab*, [2]Scott Tykodi, [3]Gregory Daniels, [4]Michele Maio, [5]Brendan Curti, [6]Karl Lewis, [7]Sekwon Jang, [8]Ewa Kalinka, [9]Igor Puzanov, [10]Alexander Spira, [11]Daniel Cho, [12]Shanhong Guan, [12]Erika Puente, [12]Ute Hoch, [12]Sue Currie, [12]Tuan Nguyen, [12]Wei Lin, [12]Mary Tagliaferri, [12]Jonathan Zalevsky, [13]Mario Sznol, [13]Michael Hurwitz. *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]University of California, La Jolla, CA, USA; [4]Azienda Ospedaliera Universitaria Senese, Siena, Italy; [5]Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR, USA; [6]University of Colorado, Aurora, CO, USA; [7]Inova Fairfax Hospital, Fairfax, VA, USA; [8]Santa Familia Medical Institute, Lodz, Poland; [9]Roswell Park Cancer Institute, Buffalo, NY, USA; [10]Virginia Cancer Specialists, Fairfax, VA, USA; [11]NYU Medical Oncology Associates, New York, NY, USA; [12]Nektar Therapeutics, San Francisco, CA, USA; [13]Yale School of Medicine, New Haven, CT, USA*

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),[1] 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 efficacy-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 strength index (PSI) of circulating lymphocytes (determined using single-cell cytokine analysis [Isoplexis]) and eosinophil count (determined from hematology analysis) at baseline and Cycle1-Day8 were analyzed using the median cut-off for correlations with ORR and PFS. Biomarkers, including $CD8^+$tumor infiltrating lymphocytes (TIL) and interferon-gamma (IFNg) gene expression profile (GEP), were measured in baseline tumor biopsies and analyzed for correlation with ORR and PFS.

Results At median follow-up of 25.7 months (15May2020), 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%).[1] 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.[1] IFNg 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

1. Diab A, Puzanov I, Maio M, *et al*. Clinical activity of BEMPEG plus NIVO in previously untreated patients with metastatic melanoma: updated results from the phase 1/2 PIVOT-02 study. Oral presentation at SITC; November 6–10, 2019; National Harbor, MD, USA. Abstract #O35.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0420

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

[1]Francesca Aroldi, [2]Joseph Sacco, [3]Kevin Harrington, [2]Anna Olsson-Brown, [3]Pablo Nanclares, [4]Lavita Menezes, [4]Praveen Bommareddy, [4]Suzanne Thomas, [5]Howard Kaufman, [4]Selda Samakoglu, [4]Robert Coffin, [1]Mark Middleton*. *[1]University of Oxford, Oxford, UK; [2]University of Liverpool, Wirral, UK; [3]The Institute of Cancer Research, London, UK; [4]Replimune Inc., Woburn, MA, USA; [5]Massachusetts General Hospital, Cambridge, MA, USA*

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-cytotoxic T lymphocyte antigen 4 (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: 10^6 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 10^6 PFU/mL followed Q2W by multiple doses