Background BEMPEG is a pegylated interleukin-2 (IL-2) cytokine produe engineered to deliver a controlled and sustained IL-2 pathway stimulation, with the goal of preferentially expanding CD8+ T and natural killer (NK) cells over immunosuppressive regulatory T cells (Tregs) in the tumor microenvironment. In the phase 3 PIVOT IO-001 clinical trial (NCT03635983), BEMPEG+NIVO demonstrated no added clinical benefit over NIVO. This first disclosure of comprehensive biomarker analysis from a randomized controlled trial comparing a next-generation IL-2 agonist+NIVO with NIVO aims to gain mechanistic insights underlying the efficacy results.

Methods Patients with previously untreated, unresectable, or metastatic melanoma were randomized 1:1 to receive BEMPEG 0.006 mg/kg+NIVO 360 mg IV Q3W or NIVO 360 mg IV Q3W. Longitudinal changes within Cycle 1 (C1) and 3 (C3) in CD4+ and CD8+ T, NK, and Treg (CD4+CD25+FOXP3+) cell counts, and proliferating (Ki67+) populations, were characterized in blood by flow cytometry. Changes in systemic cytokines, including interferon gamma (IFNγ), were also evaluated. Changes in% tumor cell PD-L1 expression, %CD8+ tumor-infiltrating lymphocytes (TILs), and% FOXP3+ cells from baseline to C1 Day 21 (CID21) were assessed in tumor biopsies by immunohistochemistry.

Results In peripheral blood, BEMPEG+NIVO mediated statistically significant increases in CD8+ and CD4+ T, NK, and Treg cell counts, as well as IFNγ levels, from baseline to day 8 of C1 and C3, with limited changes observed with NIVO. Compared with NIVO, BEMPEG+NIVO led to significant increases in proliferating Tregs and NK cells from baseline to D8 of C1 and C5. While significant increases in proliferating CD8+ and CD4+ T cells were observed in C1 and C5 following BEMPEG+NIVO, these effects were attenuated in C5. Systemic IFNγ increases, although significant, were attenuated in C5 with BEMPEG+NIVO. Changes in biomarkers measured in the tumor, including increases in CD8+ TILs, from baseline to CID21 were similar between treatment arms.

Conclusions Observations in peripheral blood demonstrated that, in comparison with limited changes with NIVO, BEMPEG+NIVO increased all immune cell subsets interrogated. Despite greater expansion of peripheral CD8+ T cells within C1 following BEMPEG+NIVO vs NIVO, there was no substantive difference in CD8+ T cell increase between the two arms, suggesting no synergistic/additive tumor activity for BEMPEG+NIVO over NIVO. These observations, together with attenuation of peripheral T-cell proliferation over time, potentially explain the lack of added clinical benefit for BEMPEG+NIVO vs NIVO in PIVOT IO-001. Results from this study should be taken into consideration and interrogated further as next-generation IL-2 agonists are developed.