Background BEMPEG is a pegylated interleukin-2 (IL-2) cytokine prodrug 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 (IFN\(\gamma\)), were also evaluated. Changes in% tumor cell PD-L1 expression, % CD8+ tumor-infiltrating lymphocytes (TILs), and% FOXP3+ cells from baseline to C1 Day 21 (C1D21) 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 IFN\(\gamma\) levels, from baseline to day 8 of C1 and C5, 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 IFN\(\gamma\) 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 C1D21 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+ TIL 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.

Acknowledgements The authors would like to thank the patients who participated in this trial and their families; the investigators, study coordinators, and study teams; and Lisa Panting and Yongliang Sun for their flow cytometry work. Editorial support was provided by Emily Motola, PharmD, of Spark Medica Inc.

Trial Registration NCT03635983

Ethics Approval The trial protocols were approved by site institutional review boards or independent ethics committees and conducted according to Good Clinical Practice guidelines, per the International Conference on Harmonisation. Patients provided written informed consent based on Declaration of Helsinki principles.

Consent Not applicable – no patient-identifiable data reported in this abstract