Background CD8 T-cells (CD8s) mediate the effects of most cancer immunotherapies. CD8s are typically assessed by biopsy which is inherently limited by sample availability, intratumoral and intrapatient heterogeneity, and difficulty with repeated, longitudinal assessment. Non-invasive CD8 PET imaging with 89-Zr-Crefmirlimab Berdoxam (crefmirlimab) could circumvent these barriers and has previously demonstrated feasibility and safety.

Methods We conducted a Phase II, prospective multicenter study to test the correlation between crefmirlimab PET signal and CD8 cell quantity by immunohistochemistry (IHC) in patients with solid tumors receiving standard of care immunotherapy. Patients underwent a baseline CD8 PET scan within 1 week prior to starting immunotherapy. A second crefmirlimab scan was performed 4-6 weeks after starting immunotherapy. Pre-treatment tissue and a biopsy 4-6 weeks on-treatment were used for CD8 IHC assessment by SP-57 antibody stain. PET scan was performed 4-6 weeks after starting immunotherapy. Patients underwent a baseline CD8 PET scan within 1 week prior to starting immunotherapy. A second crefmirlimab scan was performed 4-6 weeks after starting immunotherapy. Pre-treatment tissue and a biopsy 4-6 weeks on-treatment were used for CD8 IHC assessment by SP-57 antibody stain. Bone biopsies and those with <5% tumor were excluded. The primary endpoint was the correlation between PET uptake in the biopsied tumors [SUVmax, SUVmean, SUVpeak; normalized to reference tissue] and CD8 IHC results [CD8 cells/mm²] using the Spearman's correlation coefficient.

Results Among 52 enrolled patients with ≥1 crefmirlimab scan and 48 patients had 35 baseline biopsies and 34 on-treatment biopsies evaluable for the primary endpoint. Eight solid tumor types were represented with renal cell carcinoma (RCC, n=21 samples), melanoma (n=23), and non-small cell lung cancer (NSCLC, n=17) being the most common. Among the examined imaging parameters, SUVmean of the biopsied tumor, normalized to Aorta (SUVmean/SUVaorta) provided the best correlation. For all 69 biopsied lesions, the SUVmean/SUVaorta correlated with CD8 cell density [cells/mm²] by IHC with a Spearman’s correlation coefficient of 0.58 (95% CI: 0.385 - 0.697). For the 35 baseline biopsies the correlation was 0.66 (95% CI: 0.387 - 0.825), and for the 34 on-treatment biopsies the correlation was 0.48 (95% CI: 0.148 - 0.713). The correlation for RCC, melanoma, and NSCLC was 0.77 (95% CI: 0.552 - 0.913), 0.55 (95% CI: 0.084 - 0.727), and 0.54 (95% CI: -0.121 - 0.774), respectively. The mean SUVmean lesion/SUVmean aorta and mean CD8 cell density were 1.71 (IQR: 0.93-1.55) and 509 (IQR:114-461) at baseline and 2.43 (IQR: 0.80-3.60) and 759 (IQR:158-963) post-treatment respectively.

Conclusions Non-invasive CD8 PET scanning with crefmirlimab correlates with CD8 assessment by IHC and permits whole patient, longitudinal CD8s assessment. Crefmirlimab imaging is under investigation as a biomarker for immunotherapy responsiveness in ongoing trials (NCT05013099) and could ultimately provide a useful tool for immunotherapy drug development and clinical management.

Trial Registration NCT03802123

Ethics Approval The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH-GCP) All patients provided written informed consent.