Background Cancer patients include various populations with underlying immune dysfunction, like transplant patients or subjects with chronic infections, and subjects that are heavily pre-treated, receiving concurrent chronic steroid therapy, elderly, pregnant, or have poor performance status. Immune dysfunction curtails efficacy of immunotherapy. NT-I7 (efineptakin alfa), a long-acting IL-7, is a potent T cell amplifier that increases systemic stemness as monotherapy or in combination with checkpoint inhibitors (CPIs). Here, we explore the systemic beneficial effects of NT-I7 when combined with pembrolizumab.

Methods Open-label Phase 2a study in subjects with relapsed/refractory CPI-naïve MSS-CRC and PDAC; NT-I7 1200 µg/kg IM every 6 weeks (Q6W), pembrolizumab 200 mg IV Q3W. Correlative studies included single cell RNA and T cell receptor (TCR) sequencing (n=27) and flow cytometry (n=53) immunophenotyping of longitudinal peripheral blood samples.

Results As of 04-Nov-2022, 53 subjects were enrolled and evaluable; 41 (77.4%) were treated in fourth-line or beyond. Absolute lymphocyte counts, the main pharmacodynamic biomarker for NT-I7 biological activity, significantly increased following treatment (p<0.0001). The distribution of peripheral immune subsets changed on-treatment, shifting away from monocytes and dendritic cells and towards a strong T cell increase. Less differentiated T cell subsets (naïve, stem-cell memory, central memory) and Tpex showed high IL-7Rα expression levels; Tregs expressed very low levels and were considered unlikely to respond to NT-I7. At baseline, the CD8 T cell compartment included high levels of effector memory and terminally differentiated CD8+ T cells and low levels of less differentiated subsets. Treatment led to significant IL-7Rα downregulation in all subsets and concomitant increase in Ki67 expression (p=0.001 for all CD8 subsets, Tregs p=0.0292). Subset dynamics showed that stem-cell memory cells were differentially expanded (W0=5.2%, W3=38.8%); Tregs showed only a small, transient increase (W0=5.0%, W1=8.0%, W3=3.2%). At week 9, differentiated and not-differentiated subsets were balanced, with decreased Tregs (2.4%). Treatment significantly increased TCR diversity (18/26, p=0.0102) and frequency of costimulatory receptors, while reducing exhaustion markers. Cytotoxicity markers increased in subsets with effector abilities while decreasing for naïve and central memory T cells. Naïve and effector-memory cells showed early activation markers; late activation markers increased significantly only for effector subsets.

Conclusions NT-I7-driven T cell expansion, even when combined with an anti-PD-1 agent like pembrolizumab, promotes stemness and restores T cell fitness in heavily pretreated subjects showing signs of immune dysfunction. Combining NT-I7 with conventional immunotherapy or other anticancer agents has added systemic benefits that could impact long-term clinical response in these patients.

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Trial Registration NCT04332653

Ethics Approval This trial obtained approval from MD Anderson IRB (2020–0008), Advarra IRB (IRB00000971), and Mary Crowley IRB (20–13). Participants gave informed consent before taking part in this trial.

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