INITIAL BIOMARKER AND CLINICAL DATA OF A PHASE 2A STUDY OF NT-I7, A LONG-ACTING INTERLEUKIN-7, PLUS PEMBROLIZUMAB: COHORT OF SUBJECTS WITH CHECKPOINT INHIBITOR-NAÏVE ADVANCED MSS-COLORECTAL CANCER

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Background Checkpoint inhibitor (CPI) monotherapy is ineffective for microsatellite stable colorectal cancer (MSS-CRC). NT-I7 (efineptakin alfa) is the first-in-class long-acting IL-7 that can increase T-cell infiltration in the tumor microenvironment (TME). We hypothesize that NT-I7 may create a favorable immune-reactive TME to enhance the efficacy of CPI when combined with pembrolizumab (pembro).

Methods This is an open-label, phase 2a study in subjects with relapsed/refractory (R/R) tumors, including CPI-naïve R/R MSS-CRC. Subjects received the recommended-phase-2-dose of NT-I7 intramuscularly at 1200 µg/kg every 6 weeks (Q6W) plus pembro 200 mg intravenously Q3W. Preliminary anti-tumor activity based on Overall Response Rate (ORR) was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as a primary objective and by iRECIST as an exploratory objective. Biomarker analyses in peripheral blood and tumor biopsies were performed.

Results As of 15-July-2021, 19 subjects were enrolled in the CPI-naïve R/R MSS-CRC cohort. Six subjects are ongoing. Median age 58 years [37–81], ECOG PS 0 (26%), 1 (74%). Sixteen (84%) subjects received ≥ 2 prior therapies. All subjects had metastatic or locally advanced disease at enrollment. The median duration of follow-up was 4.64 months. Among 15 evaluable subjects, disease-control rate (DCR) based on RECIST1.1 was 47% and 1 subject achieved partial response per iRECIST (iPR) with 33% tumor reduction. Treatment-related adverse events (AEs) occurred in 14 (73.7%) subjects, 9 (47.4%) G1–2 events and 5 (26.3%) G3 events; no G4 or G5 AEs were reported. No subjects discontinued from the study due to AE. NT-I7 + pembro elicited a significant increase in the absolute lymphocyte count that peaked at week 3 (>3X from baseline, $p < 0.0001$) and was sustained at least until week 18. CD4+/CD8+ T-cell subsets followed the same response pattern. Importantly, Stem-Cell Memory CD8+ T-cells (TSCM), the potential target for CPIs that differentiate into effectors, were remarkably increased post-study treatment (>25X from baseline, $p < 0.01$). Plasmatic chemokines (CXCL9, CXCL10, CXCL11 and CCL9) were significantly increased after the first dose. The iPR subject had an enhanced T-cell infiltration in the TME at week 5. Subject's follow-up continues and more updated data will be presented.

Conclusions The chemo-free combination of NT-I7 + pembro was well tolerated and showed encouraging anti-tumor activity in subjects with CPI-naïve R/R MSS-CRC. Increased TSCM and CD8+ T-cell infiltration in TME may be the underlying mechanisms of action for the observed efficacy. These results support continued evaluation of NT-I7 + pembro in CPI-naïve subjects with R/R MSS-CRC.

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Trial Registration NCT04332653

Ethics Approval The trial was approved by MD Anderson IRB (#2020–0008_MOD001), Mary Crowley IRB (#20–13) and Advarra IRB (#Pro00042639). All participant gave informed consent prior to study enrollment.

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