

NT-I7, A LONG-ACTING IL-7, PLUS PEMBROLIZUMAB FAVORS CD8 T-CELL INFILTRATION IN LIVER METASTASES OF HEAVILY PRE-TREATED, IMMUNOLOGICALLY COLD, MSS-COLORECTAL AND PANCREATIC CANCER

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Background Checkpoint inhibitors (CPI) have null objective response (ORR) and dismal disease control rates (DCR) in microsatellite-stable colorectal (MSS-CRC) and pancreatic cancer (PaC), due to low mutation burden and sparse T-cell infiltration. Liver metastases are common in these indications and are harder to infiltrate, further reducing the efficacy of immunotherapy. NT-I7 (efineptakin alfa) in combination with pembrolizumab has been shown to increase T-cell infiltration. This study explores the ability of NT-I7 and pembrolizumab to support T-cell infiltration in subjects with liver metastasis as a correlate of clinical efficacy.

Methods Open-label, phase 2a study in subjects with relapsed/refractory (r/r) CPI-naïve MSS-CRC and PaC. Subjects received NT-I7 at 1200 µg/kg every 6 weeks (Q6W) plus pembrolizumab at 200 mg Q3W. Antitumor activity was assessed by RECIST v1.1 and iRECIST. Pre-treatment and on-treatment biopsies were analyzed by Lunit SCOPE IO, an artificial intelligence-powered H&E analyzer, and immunohistochemistry. For exome sequencing analysis, single nucleotide variants and indels were detected and filtered by GATK Mutect2.

Results As of April 29, 2022, 53 subjects were evaluable. 67.9% of subjects had ≥2 prior therapies; 73.6% had liver metastasis and median tumor mutation burden (TMB; n=18) was 3.22 mutations/megabase. ORR was 3.8% per RECIST and 9.4% per iRECIST. Total density of tumor-infiltrating lymphocytes (TIL) significantly increased on-treatment, despite low TMB. Subjects with metastasis to sites other than the liver had 28.6% iORR and 71.4% iDCR, a remarkable result considering the lack of response with anti-PD(L)1 monotherapy, and significantly higher overall survival (OS; p=0.0241). However, NT-I7 and pembrolizumab still demonstrated benefit for patients with liver metastasis; with an iDCR of 25.6%. CD8 T-cell infiltration increased with treatment regardless of tissue location, including liver biopsies (p=0.0032). Lymphoid aggregates containing CD8+TCF1+ lymphocytes, suggestive of tertiary lymphoid structures, were observed on-treatment (n=14) in both liver and non-liver biopsies, including all 3 patients with objective response. Moreover, CD8+ T-cell infiltration was directly associated with OS (p=0.0002), suggesting that NT-I7 plus pembrolizumab increases intratumoral TIL density and CD8 T-cell infiltration in primary and metastatic locations to mediate clinical benefit.

Conclusions NT-I7 plus pembrolizumab shows remarkable efficacy in immunologically cold CPI-naïve r/r MSS-CRC and PaC in the absence of liver metastasis. Furthermore, this combination also increases T-cell infiltration in immune-excluded liver biopsies, favoring a hot tumor microenvironment that contributes to the overall high iDCR observed in these hard-to-treat CPI-resistant indications.

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Ethics Approval The trial was approved by MD Anderson IRB, Advarra IRB, Mary Crowley IRB, and Integ Review IRB.

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