A biomarker signature differentiates immune status in patients with cold gastrointestinal tumors, predicting clinical benefit of NT-I7 (efineptakin alfa, a long-acting interleukin-7) and pembrolizumab

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BACKGROUND:
Microsatellite-stable colorectal (MSS-CRC) and pancreatic cancers (PDAC) are hard to treat with immunotherapy. NT-I7+pembrolizumab shows promising pharmacodynamic indicators (significant increases in lymphocytes, stemness, immune fitness, and lymphocyte tumor infiltration). However, efficacy is modest and understanding underlying causes is critical. We previously described a potentially predictive biomarker enriching for higher clinical benefit by identifying patients with existing anti-tumor responses susceptible to immunotherapy boost.

METHODS:
Open-label Phase 2a study with relapsed/refractory checkpoint inhibitor (CPI)-naïve MSS-CRC and PDAC and CPI-pretreated non-small cell lung cancer (NSCLC); NT-I7 1200µg/kg intramuscular every 6 weeks (Q6W), pembrolizumab 200mg intravenous Q3W. Correlative studies included peripheral blood proteomics and flow cytometry, and tissue immunofluorescence. Biomarker thresholds were determined by comparing separation of Kaplan-Meier survival curves with outcome-based analysis.

RESULTS:
We identified TGFA, HGF and CXCL8 as potential biomarkers associated with existing anti-tumor responses. These factors are known to be associated with uncontrolled tumor growth. We used a training set, 53 CPI-naïve MSS-CRC (n=27) and PDAC (n=26) patients, to optimize threshold values. ≥2 baseline biomarkers below threshold were anticipated to indicate existing immune response (IR); ≥2 biomarkers above threshold were considered to indicate loss of immune response (LIR). IR had significantly higher median overall survival (mOS) than LIR (114 vs 36 weeks, $p<0.001$) in both MSS-CRC (not-reached vs 38.7 weeks, $p=0.004$) and PDAC (114 vs 16 weeks, $p<0.001$). IR had higher CD8 tumor infiltration on-treatment, consistent with existing immune responses boosted by NT-I7+pembrolizumab. An independent cohort (MSS-CRC n=23; PDAC n=22) validated this result, showing higher mOS in IR versus LIR (not-reached vs 16.7 weeks, $p<0.001$). In CPI-pretreated NSCLC, where CPI resistance was present alongside existing immune responses, the biomarker failed to identify patients with higher clinical benefit (n=26, $p=0.356$). When analyzing all MSS-CRC and PDAC patients (n=98), IR had significantly longer mOS (91 vs 26.7 weeks, $p<0.001$) and progression-free survival by iRECIST (59.6 vs 9 weeks, $p=0.044$), and higher response (9.3% vs 2.3%, $p<0.001$) and disease control rates (40.7% vs 22.7%, $p<0.001$). In this trial, IR patients were older (64 vs 59 years), with fewer liver metastases (55.5% vs 84.1%), and higher CD8 TPEX frequency (CD8+TCF1+PD1+), expressing similar CD127 levels. Additional investigation is planned to understand the complex nature of these biomarkers.

CONCLUSIONS:
Depleted immune responses in advanced hard-to-treat CPI-naïve cold indications could be an

insurmountable barrier to immunotherapy. These biomarkers enable identification of patients with greater likelihood of response to NT-I7+CPI, and suggest that treatment combinations enhancing immunity may also improve response.

Acknowledgments: This study was conducted in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The authors also thank ICON Plc for their assistance in conducting this study.