590 METAGENOMIC SEQUENCING REVEALS UNIQUE GUT MICROBIAL FEATURES ASSOCIATED WITH TERTIARY LYMPHOID STRUCTURES IN RESPONSE TO IMMUNE CHECKPOINT BLOCKADE IN SOLID CANCERS

[1]Manoj Chelvanambi*, [1]Nathaniel Deboever, [1]Elise Nassif, [1]Ashish Damania, [1]Lili Chen, [1]Cheuk Leung, [1]Emily Keung, [1]Chia-Chin Wu, [1]Russell Witt, [1]Michael White, [1]Sarah Johnson, [1]Matthew Wong, [1]Aditya Mishra, [1]Matthew Lastrapes, [1]Neeta Somaiah, [1]Humam Kadara, [1]Sreyashi Basu, [1]James Allison, [1]Padmanee Sharma, [1]Kevin McBride, [2]Wolf Fridman, [1]John Heymach, [1]Boris Sepesi, [1]Nadim Ajami, [1]Christina Roland, [1]Jennifer Wargo, [1]Tina Cascone. *[1]UT MD Anderson Cancer Center, Houston, TX, United States; [2]Centre de Recherche des Cordeliers, Paris, France*

Background Immune checkpoint blockade (ICB) therapy has significantly improved clinical outcomes; however, a significant proportion of patients fail to develop durable responses.[1] Therefore, novel targetable biomarkers are needed. Our group has previously shown that the composition of the gut microbiome and presence of intratumoral tertiary lymphoid structures (TLS) can influence response to ICB.[2-4] Here, we study three randomized phase II neoadjuvant ICB trials [melanoma (MEL; NCT02519322; n=23), non-small-cell lung cancer (NSCLC; NCT03158129; n=31)[5] and sarcoma (SARC; NCT02301039; n=17)] to investigate the relationship and interplay between these two established determinants of response.

Methods Patients were defined as responders (R) or non-responders (NR) based on major pathologic response (MPR; MEL and NSCLC-viable ≤ 10%; SARC-hyalinization ≥ 30%). Transcriptional profiles of tumor specimen collected pre-ICB (MEL and SARC) and post-ICB (MEL, SARC and NSCLC) were used to score and dichotomize patients (by median) based on a TLS gene signature (*LTA, LTB, TNFSF14, CXCL13, CCL18, CCL19, CCL21, CD79B, CR2, PAX54A1, MZB1*). Paired baseline stool samples were profiled via metagenomic sequencing to characterize the composition and the molecular and metabolic function using MetaPhlAn 3.0 and HUMAnN 3.0, respectively.

Results There were 21 R overall (NSCLC n=9; MEL n=9; SARC n=3). TLS signature was significantly higher in R vs NR on-treatment with ICB (p=0.032; unpaired t-test). Longitudinal evaluation of transcriptional profiles showed increased expression of the TLS signature with treatment in R (p=0.032; paired t-test) but not in NR (p>0.99; paired t-test). Following patient dichotomization by TLS score, analysis of baseline microbiome profiles revealed the presence of unique TLS-associated gut microbiome signatures, including enrichment of specific taxa such as *Holdemanella* and *Lactococcus* (ANCOM-BC; p<0.0001). Further analysis of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways in baseline stool metagenomes suggested enhanced function of membrane transport proteins (q=0.006) in TLS^{high}patients and increased carbohydrate metabolism (q=0.04) in TLS^{low}patients.

Conclusions Our data suggest that unique gut microbiome features are associated with TLS in the context of treatment with ICB in solid cancers. Future mechanistic and translational studies will seek to validate and parlay these novel findings into microbiome-based treatments to induce TLS and/or augment the efficacy of ICB in solid tumors.

Trial Registration NCT02519322, NCT03158129, NCT02301039

REFERENCES

1. Korman AJ, SC Garrett-Thomson, and N Lonberg. The foundations of immune checkpoint blockade and the ipilimumab approval decennial. *Nat Rev Drug Discov*, 2022. **21**(7): 509–528.
2. Gopalakrishnan V, *et al*. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science*, 2018. **359**(6371): 97–103.
3. Helmink BA, *et al*, B cells and tertiary lymphoid structures promote immunotherapy response. *Nature*, 2020;**577**(7791): 549–555.
4. Baruch EN, *et al*. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science*, 2021. **371**(6529): 602–609.
5. Cascone T, *et al*. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. *Nat Med*, 2021;**27**(3): 504–514.

Ethics Approval Patients were treated at the University of Texas MD Anderson Cancer Center and had tumor samples collected and analyzed under Institutional Review Board (IRB)-approved protocols (Melanoma: 2015-0041, 2012-0846, LAB00-063 and PA17-0261; NSCLC: 2016-0982; Sarcoma: 2017-0143)

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0590