Impact of Gut Microbiome on Survival in Metastatic Melanoma Treated With TIL Therapy

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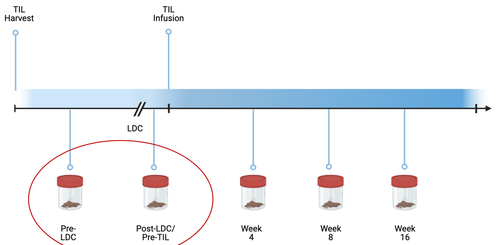
BACKGROUND

Checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer, though many patients still show resistance to ICIs. Tumor-infiltrating lymphocyte (TIL) therapy, approved for the treatment of advanced melanoma in 2024, shows a durable response in nearly 1/3 of pretreated patients with an overall response rate of 31.4%[1]. Studies show the gut microbiome may influence ICI response in both preclinical and clinical models[2-5]. The association between the gut microbiome and response to TIL therapy remains unexplored.

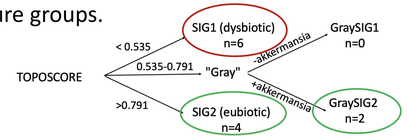
Recent studies have shown that the gut microbiome topography score (Toposcore) - a quantitative metric reflecting the ecological organization of gut microbial communities - is associated with ICI response and survival in melanoma[6]. Building on these findings, this study investigates the association between Toposcore and clinical outcomes in patients with metastatic melanoma treated with TIL therapy.

METHODS

We performed a retrospective analysis of 18 patients with metastatic melanoma who received TIL therapy and provided stool samples at predefined timepoints. The pre-lymphodepleting chemotherapy (pre-LDC) and pre-TIL timepoints had the highest sample availability, with stool from 12 patients analyzed and assigned a Toposcore.

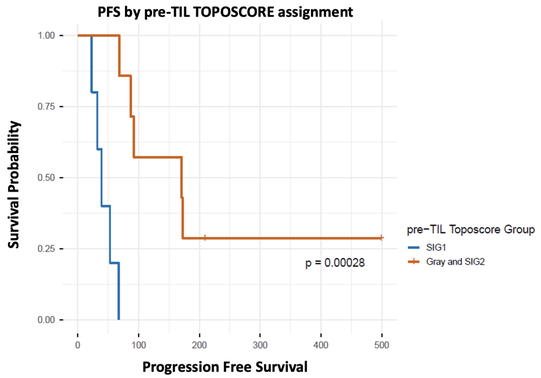


Based on microbial composition, patients were categorized into three gut community signatures: SIG1 (dysbiotic), SIG2 (eubiotic), and a gray zone intermediate group. Pearson correlation coefficients and p values were calculated to assess associations between Toposcore and both progression-free survival (PFS) and overall survival (OS). Kaplan-Meier analysis compared PFS between microbial signature groups.

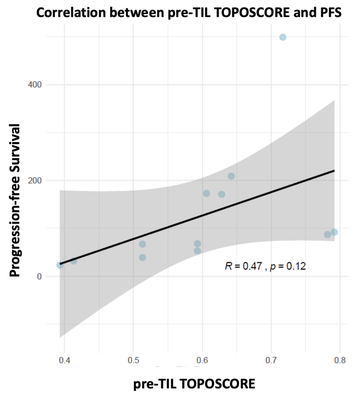


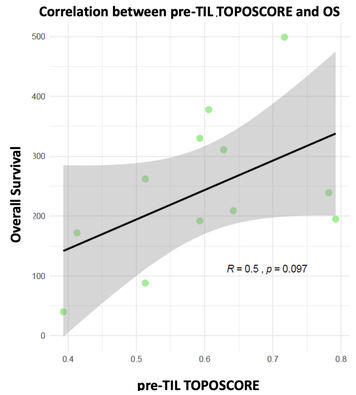
RESULTS

Higher Toposcores demonstrated moderate positive correlations with both PFS (r = 0.47, p = 0.12) and OS (r = 0.50, p = 0.10). Kaplan–Meier analysis revealed significantly longer PFS in patients with Gray/SIG2 microbial signatures compared to those with SIG1 (p = 0.00028). Although correlation analyses did not reach statistical significance, these trends collectively suggest that a more eubiotic microbiome, reflected by higher Toposcore and Gray/SIG2 classification, is associated with improved clinical outcomes.



Kaplan–Meier analysis revealed significantly longer PFS in patients with Gray/SIG2 (eubiotic) microbial signatures compared to those with SIG1 (dysbiotic) (p = 0.00028)





DISCUSSION

Toposcore and microbial signature classification were positively associated with PFS and OS in patients with metastatic melanoma treated with TIL therapy. These findings support emerging evidence that gut microbiome ecology influences antitumor immunity. Larger studies are warranted to validate Toposcore and microbial signatures as predictive biomarkers and to elucidate their mechanistic role in melanoma immunotherapy.

Conclusions:

- Higher Toposcores show positive correlation with both PFS and OS
- Patients with eubiotic microbiomes show statistically significant benefit in PFS compared to those with dysbiotic microbiomes
- Microbiome ecology may meaningfully influence therapeutic response to TIL therapy in melanoma

Clinical Implications:

- Microbiome could serve as a modifiable biomarker
- Microbiome-directed interventions - including dietary strategies, targeted antibiotics, or FMT - may represent future avenues to optimize patient selection and enhance response to TIL therapy

Future Directions:

- Validate findings in a larger prospective TIL cohort with SIG1 and SIG2
- Investigate whether microbiome optimization improves TIL outcomes

REFERENCES

1. Chesney J, Lewis KD, Kluger H, et al. Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study. J Immunother Cancer. 2022;10(12):e005755. doi:10.1136/jitc-2022-005755
2. Fernandez E, Wargo JA, Helmink BA. The Microbiome and Cancer: A Translational Science Review. JAMA. 2025;333(24):2188–2196. doi:10.1001/jama.2025.2191
3. Davar D, Dzutsev AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science. 2021;371(6529):595-602. doi:10.1126/science.abf3363
4. Baruch EN, Youngster I, Ben-Betzalel G, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science. 2021;371(6529):602-609. doi:10.1126/science.abb5920
5. Glitza IC, Seo YD, Spencer CN, et al. Randomized Placebo-Controlled, Biomarker-Stratified Phase Ib Microbiome Modulation in Melanoma: Impact of Antibiotic Preconditioning on Microbiome and Immunity. Cancer Discov. 2024;14(7):1161-1175. doi:10.1158/2159-8290.CD-24-0066
6. Derosa L, Iebba V, Silva CAC, et al. Custom scoring based on ecological topology of gut microbiota associated with cancer immunotherapy outcome. Cell. 2024;187(13):3373-3389.e16. doi:10.1016/j.cell.2024.05.029

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