could enable preemptive risk stratification. Emerging evidence suggests that pre-treatment serum autoantibody profiling may enable personalized irAE risk prediction. A recent multicenter study of 331 patients receiving ipilimumab/nivolumab combination therapy identified 47 autoantibodies predictive of subsequent irAEs, with distinct signatures for CTLA-4–based versus programmed cell death protein 1 (PD-1)–based regimens [5]. Specifically, anti-RPLP2 was associated with irAEs in combination therapy, while anti-KRT7 and anti-GPHN predicted toxicity in PD-1 monotherapy. Prospective integration of such biomarkers into future trial designs could enable preemptive toxicity monitoring and early intervention strategies, ultimately improving the safety profile of immunotherapy-based bladder-preserving approaches without compromising efficacy.

Conflicts of interest: The authors have nothing to disclose.

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Re: Fecal Microbiota Transplantation plus Pembrolizumab and Axitinib in Metastatic Renal Cell Carcinoma: The Randomized Phase 2 TACITO Trial

Porcari S, Ciccarese C, Heidrich V, et al
Nat Med. In press. https://doi.org/10.1038/s41591-025-04189-2

Experts' summary:

Porcari and colleagues [1] conducted the first randomized, double-blind, placebo-controlled phase 2 trial (TACITO trial) to investigate whether fecal microbiota transplantation (FMT) from complete responders could enhance the efficacy of first-line pembrolizumab plus axitinib in metastatic renal cell carcinoma (mRCC). Although the primary endpoint of 12-mo progression-free survival (PFS) rate narrowly missed statistical significance (70% vs 41%, p = 0.053), patients receiving donor FMT demonstrated a remarkably prolonged median PFS compared to those receiving placebo (24.0 vs 9.0 mo; hazard ratio = 0.50, p = 0.035), alongside a higher objective response rate (52% vs 32%). Utilizing deep shotgun metagenomic sequencing, the authors revealed that donor FMT successfully increased α-diversity and induced significant microbiome compositional shifts. Importantly, they demonstrated that clinical benefit was uncoupled from the total quantity of donor strain engraftment. Rather, it was driven by the acquisition of specific beneficial strains, such as *Blautia wexlerae*, and by the displacement of baseline recipient species. These findings provide compelling clinical evidence that targeted functional ecosystem engineering through FMT is safe and can significantly potentiate immune checkpoint inhibitor-based therapies in mRCC.

Experts' comments:

The advent of immune checkpoint inhibitors (ICIs) combined with tyrosine kinase inhibitors, such as pembrolizumab plus axitinib, has revolutionized the first-line treatment of mRCC. However, primary and acquired resistance remain major clinical hurdles. Given the established link between gut dysbiosis (often exacerbated by antibiotic exposure) and poor ICI outcomes in RCC [2], microbiome manipulation represents a promising therapeutic frontier. Further, previous proof-of-concept studies have demonstrated that FMT could overcome ICI resistance in melanoma, and its broader clinical translation has been hampered by variability in donor selection, engraftment efficiency, and ecological resilience [3]. Porcari et al [1] significantly advance this field by conducting the first randomized, placebo-controlled trial of FMT in treatment-naive mRCC. The substantial improvement in median PFS (24.0 vs 9.0 mo) strongly supports the clinical viability of microbiome-augmented immunotherapy.

A key conceptual advance of this study is its emphasis on qualitative ecological restructuring rather than simple total bacterial biomass transfer. The authors revealed that total quantitative engraftment did not correlate with clinical effi-

cacy. Instead, prolonged survival was dictated by the acquisition of specific donor strains, such as *Blautia wexlerae*, and the targeted displacement of baseline pro-inflammatory species like *Escherichia coli*. This highlights a profound metabolic rewiring of the gut-immune axis. *B. wexlerae* engraftment bolsters short-chain fatty acid (SCFA) production, supported by the retention of keystone species like *Ruminococcus bromii* that cross-feed SCFA-producing bacteria. Consequently, successful FMT acts as a functional ecological correction restoring metabolic homeostasis, challenging the assumption that maximal donor engraftment is the ultimate goal.

To optimize these interventions, integrating systemic biomarkers is crucial. Recently, soluble MAdCAM-1 (sMAdCAM-1) was identified as a circulating surrogate for immunosuppressive gut microbiota and poor ICI outcomes in mRCC [4]. Utilizing biomarkers like sMAdCAM-1 could help clinicians pre-select patients with dysbiosis who may require microbiome remodeling prior to therapy. Furthermore, the TACITO trial's reliance on a single "super-responder" donor highlights major scalability challenges, including donor standardization and the risk of variable engraftment [5], prompting parallel investigations into healthy donor FMTs. Ultimately, transitioning from whole-stool FMT toward rationally defined synthetic microbial consortia will be essential to integrate precision ecosystem engineering into standard oncological care.

Conflicts of interest: The authors have nothing to disclose.

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