614 MICROBIOME MODIFICATION WITH FECAL MICROBIOTA TRANSPLANT FROM HEALTHY DONORS BEFORE ANTI-PD1 THERAPY REDUCES PRIMARY RESISTANCE TO IMMUNOTHERAPY IN ADVANCED AND METASTATIC MELANOMA PATIENTS

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Background Microbiome-based interventions with fecal microbiota transplant (FMT) from treatment responders (R) have shown promising results in re-sensitizing anti-PD-1-refractory melanoma patients to anti-PD1 therapy. However, it is not currently known whether FMT can be used to prevent primary resistance. Here, we report results from the first phase I clinical trial (NCT03772899) that combines FMT with anti-PD1 therapy in anti-PD1-naïve melanoma patients.

Methods Twenty patients with advanced disease were treated with FMT with capsules from healthy donors one week before the standard of care anti-PD-1. A total of three donors were used. Fecal microbiota was profiled with 16S rRNA and metagenomics sequencing. ^{1}H-NMR/SMolESY was used to measure plasma metabolites, and flow cytometry was performed on PBMCs. Additionally, FMT in avatar murine models was performed.

Results The median age was 75.5 years, and eight were female. The median follow-up time was 12.2 months. No unexpected toxicities or grade 3/4 toxicities were observed with FMT. Grade 3 immune-related adverse events included nephritis, pneumonitis, and vasculitis. ORR was 65% (13/20), of which 3 were CR. Clinical benefit rate (includes SD lasting > 6 months) was 75% (15/20). There was no correlation between outcomes/toxicities and donors. Microbiome profiling revealed positive engraftment of all patients one week after FMT; however, sustainable engraftment was only observed in R at one month and maintained at three months. At the taxa level, R had enrichment of *Eubacterium rectale*, *Eubacterium ramuleus*, and *Firmicutes* while a loss of *Hungatella*. Metabolomics analysis uncovered that succinate levels were lower in R at baseline. A significant fold change increase in plasma propionate between pre- and post-FMT was observed in R but not non-responders (NR). Immune profiling showed an increase in conventional effector $CD8^+$ T-cells and an increase in $CD38^+CD8^+$ Mucosa-associated invariant T (MAIT) cells in R compared to NR post-FMT. Avatar mouse models in germ-free and antibiotic-treated mice confirmed our clinical observations in that pre-FMT stool from both NR and R patients did not induce a response to anti-PD1 therapy. However, the post-FMT stool from R or FMT using donor feces sensitized B16-OVA and MCA-205 tumors to anti-PD1. Post FMT alpha diversity in responder mice correlated with increased intratumor memory $CD8^+$ T-cells, $TIM3^+$ T-cells, and stronger anti-PD-1 response.

Conclusions Our findings show that combining FMT from healthy donors with anti-PD1 potentially reduces primary resistance to immunotherapy. Successful engraftment of donor microbiota in patients correlated with better outcomes, and this was corroborated by translational experiments.

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Trial Registration NCT03772899

Ethics Approval This study was approved by the Ethics Research Board (REB) at Western University, CHUM hospital, and The Jewish General Hospital. REB # 113131

All participants signed informed consent before participating in the trial.

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