Background Antibiotics (ATB) induce intestinal dysbiosis and decrease the efficacy of immune checkpoint inhibitors (ICI).1,2 DAV132 is an orally administered colon-targeted ATB adsorbent designed to prevent ATB-induced dysbiosis.3 We investigated whether DAV132 co-administered with ATB could protect gut microbiota diversity and composition. Moreover, in murine avatar tumor model, we assessed anti-PD-1 efficacy through fecal microbiota transplantation (FMT) in germ-free (GF) or antibiotic-treated specific pathogen-free (SPF) mice.

Methods Twenty-four human healthy volunteers (HV) were randomized to receive either ceftazidime-avibactam (CZA, 2g/0.5g q8h IV for 5 days) or CZA+DAV132 (12g PO tid for 7 days). CZA plasmatic and fecal pharmacodynamic levels were measured using HPLC-MS/MS. Microbiome was profiled with 16S ribosomal RNA sequencing and shotgun metagenomics at different timepoints. FMT to HV without influencing plasmatic concentrations. In avatar mice FMT from HV treated with CZA+DAV132 was able to preserve anti-PD-1 cancer efficacy. These results provide rationale to launch clinical trials combining DAV132 in patients on ATB amenable to ICI.

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Abstract 1306 Figure 1 Intestinal microbiota composition in CZA ± DAV132 groups Heatmap of hierarchical clustering of microbiota composition represented by 16sRNA profiling in 24 healthy volunteers treated with ceftazidime-avibactam ± DAV132

Abstract 1306 Figure 2 Anti-tumor response preserved by DAV132DAV132 prevents antibiotic-induced loss of anti-tumor response in murine germ-free cancer model transplanted with healthy volunteers treated with ceftazidime-avibactam ± DAV132. *** p < 0.001, Mann-Whitney U Tests. Stools from 3 healthy

References

Ethics Approval All animal studies were approved by the Institutional Animal Care Committee (CIPA) and carried out in compliance with the Canadian Council on Animal Care guidelines (Ethics numbers: C18029BRs).
volunteers selected from each group of treatment (CZA ± DAV132) were transplanted in 10 germ-free mice, 5 being treated with ISO-PD-1 and 5 with aPD-1. Statistics at sacrifice were performed on n=15 mice except for the groups CZA+DAV132/ISO-PD-1 (n=14) and CZA+DAV132/aPD-1 (n=11) before treatment and the group CZA+DAV132/ISO-PD-1 (n=14) at D6.

Abstract 1306 Figure 3

DAV132 preserves local immune response. Antibiotic-depressed anti-tumor CD8+ response and CD8+/Treg ratio are preserved by DAV132.

* p < 0.05, Mann-Whitney U Tests. Statistics were performed on n = 10 mice (from 2 healthy volunteers) per group.