Background
ACTM-838 is a bacterial immunotherapy that encodes an engineered IL-15 (IL-15plex) and a constitutively active STING (eSTING). ACTM-838 is a highly modified, attenuated S. Typhimurium lacking several major inflammatory components on the microbial surface and designed to naturally and specifically enrich in the TME via auxotrophic dependency on metabolites of the adenosine pathway and purines, to achieve tumor-specific payload delivery.

Methods
ACTM-838 uptake, payload expression and activity were measured using qPCR, MSD, and flow cytometry across human and mouse samples. TME immune responses and payload effects were assessed using single cell RNAseq, flow cytometry and ELISA.

Results
In EMT6 tumor-bearing mice, ACTM-838 upon single IV dose was able to rapidly distribute and enrich in the TME compared to other tissues and exhibited specific uptake in the phagocytic antigen presenting cells such as monocytes, macrophages and neutrophils, whereas in liver, spleen and blood, neutrophils showed the highest uptake. This led to a significantly increased expression of human IL-15plex and murine IFNalpha in the tumor compared to other tissues. Ex vivo bactofection of EMT6 tumors exhibited a dose-dependent increase in cellular uptake of ACTM-838, maintaining its preferential uptake in the myeloid compartment. ACTM-838 showed a significantly decreased inflammatory cytokine profile compared to parental strain VNP20009.

ACTM-838 showed significantly prolonged anti-tumor efficacy in EMT6 breast cancer, MC38 colon tumor as well as MMTV-PyMT GEMM. Across multiple tumor models, ACTM-838 exhibited significant reprogramming in the TME as well as periphery with a decrease in exhausted T cells and Treg and an increase in activated CD8 T cells and MHCII-high proliferating myeloid cells. In addition, we observed a significant decrease in adenosine-generating enzyme CD73 across myeloid and T cell populations, suggesting reduced immunosuppression.

Human MDMs exhibited significantly reduced pro-inflammatory cytokines with high expression of co-stimulatory markers and MHCII with ACTM-838 compared to VNP20009. ACTM-838 was stable in human whole blood with minimal complement activation. Serum from healthy donors and cancer patients showed varying levels of anti-salmonella antibodies with minimal neutralization of ACTM-838. Indication prioritization analyses using the TCGA and MET500 datasets identified key indications with high myeloid content as well as adenosine and purine metabolism.

Conclusions
ACTM-838 is a novel immunotherapy delivering IL-15plex + eSTING payloads to phagocytic APCs, inducing a durable anti-tumor immune response, after IV dosing. IV-delivered ACTM-838 possesses a compelling safety profile in mice and primates and is currently entering clinical trials in cancer patients in Australia.