Background Colorectal cancer (CRC) is the third most prevalent cancer and the second leading cause of cancer-related death worldwide. CRC has elevated Wnt signaling activity in which DKK1 plays a regulatory role. DKN-01 is an IgG4 clinical stage antibody that specifically neutralizes DKK1. Fluorouracil (5FU)-based therapies are the standard backbone treatment for CRC and have demonstrated clinical activity in combination with DKN-01 in gastroesophageal adenocarcinoma (GEA). DKK1 expression has been shown to correlate with 5FU resistance in CRC tumors and cell lines. We evaluated the efficacy of DKN-01 alone and in combination with 5FU in parental and 5FU-resistant HCT116 and SW480 xenograft models. Further, given the established role of DKK1 on TME modulation, we also explored treatment with DKN-01 as a monotherapy and in combination with anti-PD-1 in a CT26 syngeneic CRC model.

Methods For the xenograft models, athymic nude mice were inoculated subcutaneously (SC) with either parental or 5FU-resistant colon cancer cell lines. Once tumors reached 50mm³, dosing was initiated with either isotype control, DKN-01, 5FU, or the combination. For the CT26 syngeneic model, BALB/c mice were inoculated SC with CT26 mouse colon cancer cells. Once tumors reached 50mm³, dosing initiated with either isotype control, a murinized version of DKN-01 (mDKN-01), anti-PD-1, or the combination.

Results In the parental HCT116 model, 30%, 39%, and 55% tumor growth inhibition (TGI) were observed in the DKN-01, 5FU, and combination treatment groups compared to isotype controls. Strikingly, in the HCT116 5FU-resistant model, 5FU had a negligible effect on TGI compared to DKN-01 monotherapy; and combination treatment groups in both 5FU-resistant models experienced 100% tumor regression. In the CT26 syngeneic model, mDKN-01 monotherapy resulted in 71% TGI with 47% of the group experiencing tumor regression at study termination unlike the anti-PD-1 monotherapy which had negligible TGI. The effect of mDKN-01 was further enhanced by the combination resulting in an additional 58% TGI with 73% of the group experiencing tumor regression. Notably, a robust inflammatory infiltrate was observed in the tumors of mDKN-01 monotherapy and combination groups, correlating with the level of necrosis. In addition, a significant increase in PD-L1 staining occurred with mDKN-01 monotherapy.

Conclusions In multiple models of CRC, DKN-01 showed strong anti-tumor effects. This included tumor regression in a 5FU-resistant setting reflective of second line CRC, as well as significant monotherapy efficacy and synergy with anti-PD-1.