Selective and Novel ALDH1 Inhibitor Improves Immune Checkpoint Blockade Therapy in Preclinical MSS Colorectal Cancer Models

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Background

Microsatellite stable (MSS) colorectal cancer (CRC) is largely resistant to immune checkpoint blockade (ICB) due to its immune-cold microenvironment. Aldehyde dehydrogenase 1 (ALDH1) is implicated in tumor progression, immune evasion, and maintenance of cancer stem-like features. Targeting ALDH1 may remodel the tumor microenvironment and enhance responsiveness to ICB. This study explores the therapeutic potential of combining ALDH1 inhibitor with anti-PD-1 ICB in MSS CRC.

ABD0171: A highly selective ALDH1 inhibitor (ALDH1i)

Advanced Biodesign has developed a highly selective ALDH1 inhibitor (ALDH1i)[1]. ALDH1 catalyzes the conversion of retinal to retinoic acid (RA), which activates nuclear retinoic acid receptors (RARs) and drives the expression of genes involved in cell differentiation and survival. High ALDH1 expression in tumors is associated with increased tumorigenicity, drug resistance, and cancer stem cell-like phenotype. Elevated RA levels resulting from ALDH1 overexpression have also been linked to immune evasion in the tumor microenvironment[2].

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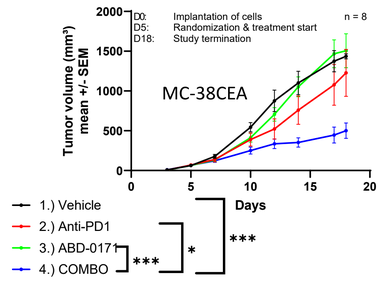
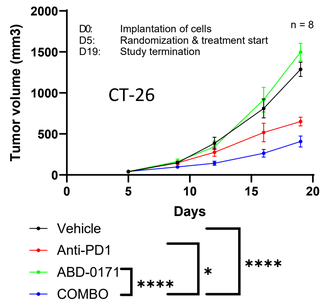
1. Pequerul et al., 2025. bioRxiv 2024.10.18.619128; doi: https://doi.org/10.1101/2024.10.18.619128
2. Devalaraja et al., 2020. Cell. https://doi.org/10.1016/j.cell.2020.02.042

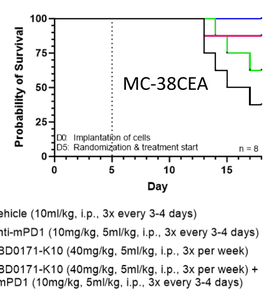
Results

In vivo data

ABD0171 improves the therapeutic benefit of anti-PD-1 in CRC mouse models





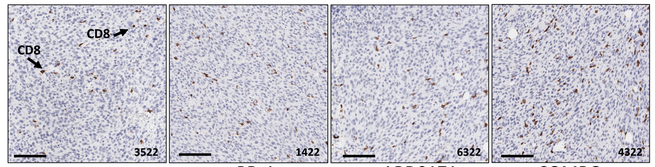


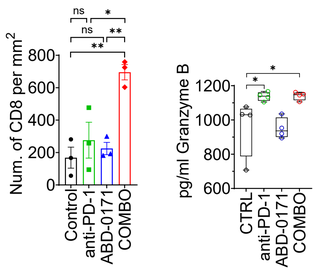
- ABD0171 synergizes with anti-PD-1 to effectively inhibit tumor growth in two CRC mouse models, CT-26 and MC-38CEA.
- The tumor growth inhibition observed in the MC-38 model is associated with a significant improvement of mouse survival.

Results

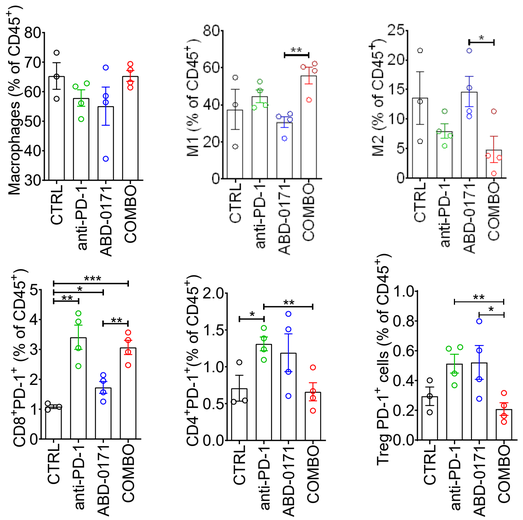
In vivo data

Combination of ABD0171 and anti-PD-1 increases the frequency of CD8⁺ T cells within MC-38CEA tumors and enhances Granzyme B release





Combination of ABD0171 and anti-PD-1 reshapes the immune landscape of MC38 colorectal tumors



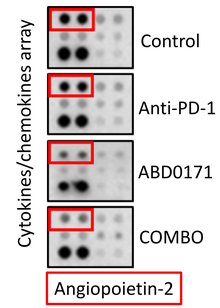
Immune phenotyping of MC38CEA tumors treated with the ABD0171/anti-PD-1 combination (COMBO) therapy, compared to untreated controls or monotherapy (anti-PD-1 or ABD0171 alone), revealed the following:

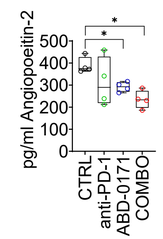
Results

In vivo data

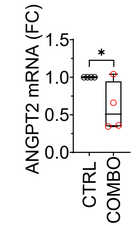
- An increased frequency of M1 macrophages, accompanied by a reduction in M2 macrophages.
- Elevated levels of PD-1+ CD8⁺ T cells, a decrease in PD-1+ CD4⁺ T cells, and a reduction in PD-1⁺ regulatory T cells (Tregs).

Combining ABD0171 with anti-PD-1 downregulates both the mRNA expression and the release of Angiopoietin-2 in MC-38 tumors.





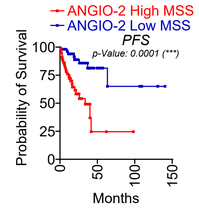
ELISA on tumors

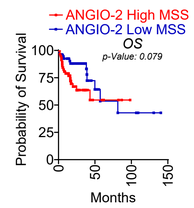


RT-qPCR on tumors

Patient data

MSS CRC patients with low Angiopoietin-2 levels exhibit improved survival compared to those with high expression levels





ANGIO-2: Angiopoeitin-2
PFS: Progression free survival
OS: Overall survival

Conclusions

- Selective inhibition of ALDH1 by ABD-0171 synergizes with anti-PD-1 therapy and enhances its therapeutic efficacy in MSS CRC mouse model.
- This enhanced response is associated with a reshaping of the tumor immune microenvironment, marked by an increased frequency of CD8⁺ T cells and M1 macrophages, alongside a reduction in M2 macrophages and regulatory T cells (Tregs).
- Angiopoietin-2 (ANGPT2) is a potential target downregulated in tumors treated with the combination therapy. This effect is primarily driven by ABD-0171, as tumors treated with ABD-0171 alone also exhibited reduced ANGPT2 expression.
- The mechanism by which ABD-0171 downregulates ANGPT2, and whether this downregulation directly contributes to the remodeling of the tumor immune landscape and the enhanced efficacy of anti-PD-1 therapy, is under investigation.

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