Background

The BAF family of chromatin remodeling complexes are critical regulators of chromatin accessibility and gene expression, and BRM and BRG1 (also known as SMARCA2 and SMARCA4), the catalytic subunits of BAF, provide the enzymatic activity required for chromatin remodeling activity. We have previously identified and characterized a series of novel dual inhibitors of the BRM/BRG1 ATPases, and FHD-286, a potent and selective BRM/BRG1 inhibitor, is currently under clinical investigation for the treatment of metastatic uveal melanoma and advanced hematological malignancies (NCT04879017 and NCT04891757). BAF chromatin remodeling complex activities are implicated in many immunologic responses, and previous studies have shown the involvement of PBAF in the regulation of antitumor immunity.1

Methods

Given the recent reports correlating SMARCA4 deficiency and ICI response,2 we explored the combination of BRM/BRG1 ATPase inhibition and anti-PD-1 antibody in syngeneic mouse models from various lineages and with different sensitivities to checkpoint inhibition.

Results

The combination of FHD-286 and anti-PD-1 antibody provided synergistic efficacy and survival benefit compared to anti-PD-1 alone in A20, CT26, and the immunologically barren B16F10 melanoma model. FHD-286 increased MHCI expression on B16F10 cells, and increases in IFNγ and Th1-type chemokine CXCL10 levels were observed in immunocompetent mice following treatment, suggesting that combinatorial activity may result from effects on both the tumor and the immune system.

Conclusions

FHD-286 has the potential to sensitize tumor to immune-checkpoint inhibition and represents a novel combination approach for cancer immunotherapy.

REFERENCES
