Synergistic efficacy of the BRM/BRG1 ATPase inhibitor, FHD-286, and anti-PD-1 antibody in mouse sympathetic tumors

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Abstract

The BRM family of chromatin remodeling complexes are critical regulators of chromatin accessibility and gene expression, and BRM and BRG1 (also known as SMARCAD1 and SMARCAD4), two subunits of BRM, 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 (NCT04879107 and NCT04891757). BRM chromatin remodeling complexes are implicated in many immunologic responses, and previous studies have shown the involvement of BRM in the regulation of antitumor immunity [1]. Given the recent reports correlating SMARC4 deficiency and ICI response [2], we explored the combination of BRM/BRG1 ATPase inhibitors and anti-PD-1 antibody in syngeneic mouse models from various lineages and with different sensitivities to checkpoint inhibition. 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 MHC expression on B16F10 cells, and increases in IFN and Th1-type chemokine levels were observed in immunocompetent mice following treatment, suggesting that combinatorial activity may result from effects on both the tumor and the immune system. FHD-286 has the potential to sensitize tumor to immune-checkpoint inhibition and represents a novel combination approach for cancer immunotherapy.

Combination of FHD-286 and anti-PD-1 provides significant synergistic efficacy and survival benefit compared to anti-PD-1 alone in 3 syngeneic models

FHD-286 induced BRM/BRG1 inhibition transforms B16F10 tumor microenvironment

Figure 2. Changes in B16F10 tumor microenvironment (TME) induced by BRM/BRG1 ATPase inhibition. B16F10 tumor-bearing animals were dosed for 10 days (n=8 per group). Anti-PD-1, FHD-286, and FHD-286 + anti-PD-1 treatments were performed in a blinded fashion. Three different inhibitors were studied: the FHD-286 + ATP combination group due to small tumor volume (TV, ~5, 12, and 36 mm³). Statistical significance by one-way ANOVA. (A) MHC expression on B16F10 tumor cells (p=0.04). (B) MHC expression on B16F10 tumor cells (p=0.02). (C) Average number of CD8+ T-cells per gram of tissue in the TME. (D) A score of CD8+ T-cells and its kinetics in the TME. (E) MHC-I expression in memory, EM, effector memory. (F) Ratio of CD8+ cells to FOXP3+ Tregs in the TME (p=0.03). (G) Level of CD8+ T-cell activation, measured by CD69 MRI (Vehicle or anti-PD-1 vs FHD-286+anti-PD-1; p=0.013). (H) FHD-286 + anti-PD-1 (p=0.03). (I) Average fold change in cytokines and chemokines levels compared to the vehicle group (p<0.01, ****p<0.0001, **p<0.001, *p<0.01) in (M) tumor and (J) plasma, measured by 32plex Lumipulse panel. Cytokines with no detectable expression are excluded from the analysis.

FHD-286 induced BRM/BRG1 inhibition enhances antigen presentation

Figure 4. Enhanced expression of MHC-I in responses to BAP/A T cell inhibition. (A) Flow cytometry analysis of B16F10 cells treated with FHD-286 (0.1µM) or the combination of FHD-286 and IFNγ for 48h in vitro. (B) Idiograms representing the shift in MHC-I and PD-L1 MRI with treatment. (C) Enhanced MHC-I expression with the combination of FHD-286 + IFNγ. (D) PD-L1 expression in response to FHD-286 + IFNγ.

Conclusions

- Dual BRM/BRG1 ATPase inhibitor FHD-286 synergizes with anti-PD-1 antibody to promote tumor regression and animal survival in 3 unique syngeneic models.
- FHD-286 increases immune cell trafficking and infiltration into the TME. The combination with anti-PD-1 antibody enhances the activation of CD8+ T-cells and the expression of pro-inflammatory cytokines, transforming the TME.
- FHD-286 induced BAP inhibition enhances antigen presentation and sensitizes B16F10 cells to immune response.
- FHD-286 has the potential to sensitize tumor to immune-checkpoint inhibition and represents a novel combination approach for cancer immunotherapy.