Combination therapy with selective SMARCA2 (BRM) degraders for treatment of SMARCA4 (BRG1)-deficient cancers

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**Background**

SMARCA2 and SMARCA4 are the core catalytic subunits of the SWI/SNF complexes, which play an important role in modulating gene expression by remodeling chromatin. SMARCA4 is mutated in multiple cancers and deregulation of SMARCA4 is one of the hallmarks of cancer. Deregulation of SMARCA2 and SMARCA4 expression leads to a synthetic lethal phenotype, where inhibitors of SMARCA2 or SMARCA4 induce tumor cell death. This suggests that SMARCA2 and SMARCA4 may be therapeutic targets in SMARCA4-deficient cancers.

**Objectives**

The objective of this study was to evaluate the efficacy of a selective SMARCA2 (BRM) degrader, PRT3789, in combination with KRAS G12C inhibitors and other MAPK pathway inhibitors in SMARCA4-deficient cancer models.

**Results**

Figure 1. PRT3789 inhibits SMARCA4-deficient tumor growth

- A) PRT3789, a highly potent and selective SMARCA2 protein degrader, inhibits proliferation of SMARCA4-del/KRAS G12C NCI-H2030 CDX model, at well tolerated doses.
- B) Selectivity Cell Proliferation >1000 (HiBiT) 40X Assay PRT3789
- CL (mL/min/kg) 66

Figure 2. PRT3789 synergizes with KRAS G12C, SHP2 and MEK inhibitors in vitro

- A) PRT3789 + KRAS G12C inhibitor (MRTX849) combination therapy increased TGI versus each constituent monotherapy in a SMARCA4-low expression/KRAS G12C NCI-H2030 CDX model, at well tolerated doses.
- B) PRT3789 + KRAS G12C inhibitor (MRTX849) combination therapy significantly inhibits tumor growth in a H838 NSCLC CDX model at well tolerated doses.
- C) PRT3789 + KRAS G12C inhibitor (MRTX849) combination therapy resulted in TGI of 89% in the H2030 NSCLC CDX model at well tolerated doses.

Figure 3. PRT3789 combination with KRAS G12C inhibitor shows enhanced efficacy in SMARCA4/KRAS G12C mutant cancers in vivo

- A) PRT3789 + KRAS G12C inhibitor combination therapy significantly inhibits tumor growth in a SMARCA4-deficient/SMARCA4-low-expressing cell line (H2030) and in a SMARCA4-deficient/KRAS G12C mutant cell line (NCI-H2030). A 90% TGI was observed in the H2030 NSCLC CDX model at well tolerated doses.

Figure 4. PRT3789 and KRAS G12C inhibitor induces unique transcriptional signatures

- A) PRT3789 + KRAS G12C inhibitor combination therapy induces unique transcriptional signatures.
- B) Volcano plots display Log2 fold change vs DMSO controls and adjusted p-value versus vehicle. **P<0.01 ***P<0.001, versus vehicle (two-tailed Mann-Whitney test).

Figure 5. PRT3789 downregulates cell cycle proteins and combines with the Next generation CDK9 inhibitor PRT2545 in vitro

- A) PRT3789 + CDK9 inhibitor PRT2545 combination therapy demonstrated synergy in vitro in the SMARCA4-deficient/SMARCA4-low-expressing cell line (H2030) and in the SMARCA4-deficient/KRAS G12C mutant cell line (NCI-H2030). A 90% TGI was observed in the H2030 NSCLC CDX model at well tolerated doses.

Figure 6. PRT3789 combination with the CDK9 inhibitor PRT2527 shows enhanced efficacy in vivo

- A) PRT3789 + CDK9 inhibitor PRT2527 combination therapy significantly inhibits tumor growth in the SMARCA4-deficient/SMARCA4-low-expressing cell line (H2030) and in the SMARCA4-deficient/KRAS G12C mutant cell line (NCI-H2030). A 90% TGI was observed in the H2030 NSCLC CDX model at well tolerated doses.

**Conclusions**

- Targeting SMARCA2 in SMARCA4-deficient cancers with PRT3789 monotherapy significantly inhibits growth and induces regression of SMARCA4- and SMARCA4+/del NSCLC PDX and CDX models at well tolerated doses.
- PRT3789 combines synergistically with agents that target the MAPK pathway, including KRAS G12C, SHP2 and MEK inhibitors.
- PRT3789 combines with CDK9 inhibitors to inhibit tumor growth and induce regression of SMARCA4-deficient CDX models.

References