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A Phase 1 Study of PRT3789, a Potent and Selective Degrader of SMARCA2 in Patients With Advanced or Metastatic Solid Tumors and a *SMARCA4* Mutation

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BACKGROUND

- Genes encoding subunits of the SWI/SNF chromatin remodeling complex have been observed in 20% of all human cancers[1,2]
  - The SWI/SNF complex contains 1 of 2 ATP enzymatic subunits: either SMARCA2 (also known as BRM) or SMARCA4 (also known as BRG1)
  - Because SMARCA2 and SMARCA4 function as mutually exclusive catalytic subunits of the SWI/SNF complex, cells exhibiting SMARCA4 loss rely on its paralog, SMARCA2, making SMARCA2 an attractive therapeutic target[3-5]
- *SMARCA4* mutations have been found in multiple tumor types, including thoracic sarcomas, lymphomas, and cancers of the lung, ovaries, and skin (**Table 1**)[2,6]

Table 1. *SMARCA4* Mutation by Cancer Indication[2,6]

Indication	Any *SMARCA4* mutation, %	*SMARCA4* LOF mutation, %
NSCLC	10.0	5
Esophageal	8.0	2.7
Gastric (stomach adeno)	8.3	2.3
Skin	21.0	2.0
Endometrial (Uterine corpus)	13.3	1.9
Squamous cell lung	7.7	1.9
Urinary (bladder)	9.0	1.5
Colorectal	6.0	1.3
Pancreatic	2.9	1.2
Melanoma	8.7	0.5

- In NSCLC, *SMARCA4* mutations are observed in ≈10% of cases and are associated with more aggressive and invasive disease and shorter survival[7,8]
- The most frequently co-mutated genes in *SMARCA4*-mutated NSCLC are *TP53*, *KRAS*, *KEAP1*, and *STK11*[7,8]
- *SMARCA4* mutation class is differentially associated with prognosis in patients with stage IV NSCLC; *SMARCA4* alterations can be divided into 2 clinically relevant genomic classes associated with differential protein expression as well as distinct prognostic and treatment implications[9]
  - **Class 1 mutations** include truncating mutations, fusions, and homozygous deletion
  - **Class 2 mutations** include missense mutations
- In patients with metastatic NSCLC, *SMARCA4* alterations have been associated with shorter OS, with truncating mutations, fusions, and homozygous deletion alterations being associated with the shortest survival times[9]
- Increased understanding of the relationship of *SMARCA4* in lung cancer may enable the development of new therapeutic opportunities
- Among NSCLCs treated with first-line chemoimmunotherapy, a *SMARCA4* mutation is associated with significantly worse ORR, mPFS, and mOS compared to those of first-line chemoimmunotherapy[9]
- *SMARCA4* LOF mutations include homozygous missense and hotspot mutations with known LOF, in addition to the other damaging mutations such as frameshift indels, nonsense (stop gain, stop loss), or splice site
- PRT3789 is an intravenous VHL-based SMARCA2 degrader (**Figure 1**) which induces proteosome-dependent degradation of SMARCA2 (**Figure 2**)
- Preclinical data indicate that PRT3789 is a potent and selective degrader of SMARCA2, which induces robust synthetic lethality in *SMARCA4*-deficient cancers

Figure 1. 3D Figure of SMARCA2 Bromodomain and E3 Ligase Complex (VBC/CUL2/RBX1) Formed by PRT3789 SMARCA2 Degrader

PRT3789

- Highly potent (plasma DC_{50}=21 nM)
- Highly selective for SMARCA2 over SMARCA4
  - Cellular assays >1000×
  - HiBit 40× selective
  - Selectivity confirmed in vivo
- Efficacious in H838 CDX model at well-tolerated doses
- Clean on hERG and safety 47
- Moderate CYP3A4 inhibition
- IC_{50} >10-fold expected C_{max}, with no TDI

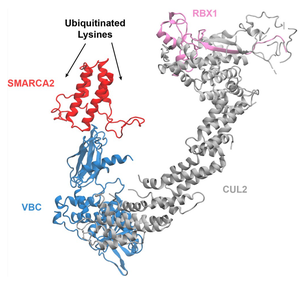


Figure 2. Mechanism of Action

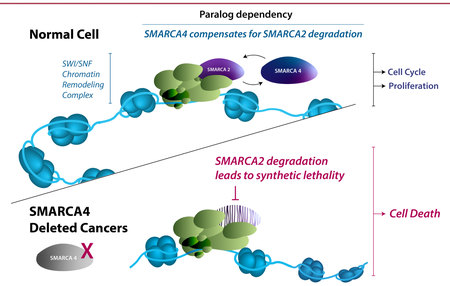
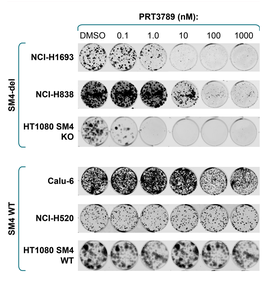
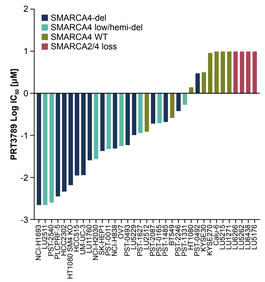


Figure 3. PRT3789 Inhibits Proliferation of SMARCA4-Del/Knockout Cancer Cell Lines, but Not SMARCA4 WT Cancer Cell Lines in a Clonogenic Assay



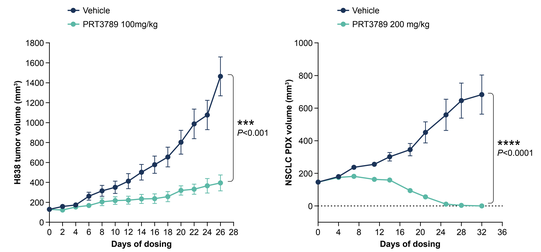
- PRT3789 selectively inhibits SMARCA4-deficient cancer cell proliferation in vitro (**Figure 3**)

Figure 4. SMARCA4-Del Cancer Cell Lines and PDX Models Are More Sensitive to PRT3789 vs WT and SMARCA2/4 Dual Loss Models



- There is none or limited response in SMARCA4 WT and SMARCA2/4 dual-loss cancer cells (**Figure 4**)

Figure 5. PRT3789 Significantly Inhibits Growth of SMARCA4-Del Lung Cancer CDX and PDX Models at Well-Tolerated Doses



- PRT3789 is efficacious as a single agent at well-tolerated doses in *SMARCA4*-deficient NSCLC in preclinical models in mice (**Figure 5**)

OBJECTIVES

PRT3789-01 (NCT05639751) is an open-label, multicenter, dose-escalation, first-in-human, phase 1 study of PRT3789, a SMARCA2 degrader, for participants with select advanced or metastatic solid tumors with any SMARCA4 mutation for dose escalation cohorts and a SMARCA4 LOF mutation for backfill cohorts (**Figure 6**)

Primary Objectives

- To evaluate the safety, tolerability, and DLTs of PRT3789
- To determine the RP2D of PRT3789

Secondary Objectives

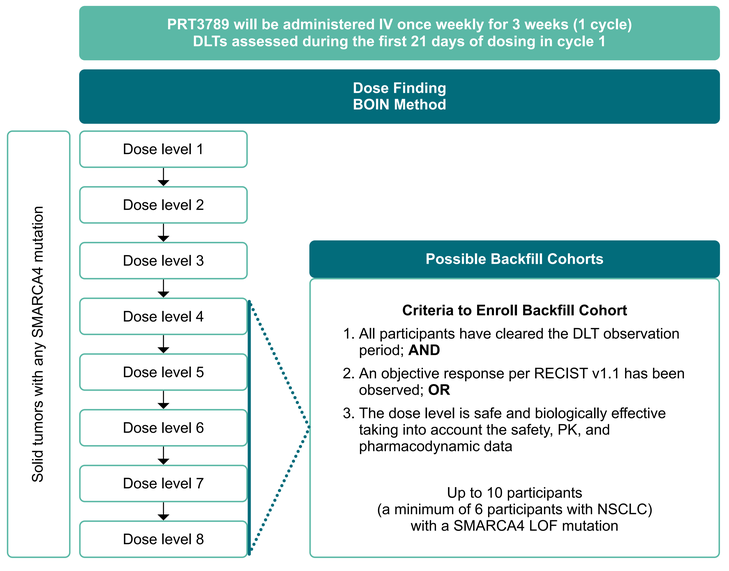
- To evaluate the efficacy (ORR, PFS, CBR, and DOR) of PRT3789 per investigator assessment per RECIST v1.1
- To evaluate the PK profile of PRT3789
- To evaluate the pharmacodynamic effect of PRT3789

Exploratory Objectives

- To evaluate additional markers of PRT3789 target engagement
- To understand baseline tumor biomarker profiles
- To explore potential role of ctDNA as surrogate endpoint for monitoring of disease response

STUDY DESIGN AND ENDPOINTS

Figure 6. PRT3789-01 Phase 1 Study Design



PATIENT ELIGIBILITY

Key Inclusion Criteria

- Patients aged ≥18 years with histologically confirmed advanced, recurrent, or metastatic solid tumor malignancy with any SMARCA4 mutation for dose escalation cohorts and a SMARCA4 LOF mutation for backfill cohorts by local testing that have either progressed on or are ineligible for SOC therapy are eligible to enroll
- *SMARCA4* mutation must be confirmed by local NGS or IHC in tumor tissue or blood using a clinically validated laboratory test
- Patients with NSCLC with driver alterations (eg, *EGFR*, *MET*, *RET*, *ALK*, *BRAF*, *KRAS*, *ROS1*, etc) are eligible after progression on approved targeted therapies
- Patients may have measurable or nonmeasurable, but evaluable, disease
- Tumor tissue sample from a core or excisional/surgical biopsy
- Adequate organ function laboratory values as defined in **Table 2**
- ECOG PS of 0 or 1

Table 2. Adequate Organ Function Laboratory Values

System	Laboratory value
Hematology[a]	
ANC	≥1.0 × 10^9/L
Platelets	≥75,000/µL
Renal	
Calculated creatinine clearance	≥50 mL/min according to the Cockcroft-Gault equation or other standard institutional method
Hepatic	
Total bilirubin	<1.5 × ULN for reference laboratory OR direct bilirubin <1.5 × ULN for participants with total bilirubin levels ≥1.5 × ULN, (≤3 × ULN if Gilbert disease)
AST and ALT	≤3.0 × ULN for reference laboratory unless there is hepatic involvement by the underlying malignancy as documented by either CT or ultrasound, in which case <5 × ULN is acceptable

[a]Patients who do not meet the criteria for hematologic function due to disease-related cytopenias and/or due to extensive bone marrow involvement may be enrolled into the study provided the ANC is ≥0.5 × 10^9/L and platelet count is ≥50,000/µL.

Key Exclusion Criteria

- Participants with solid tumors with known concomitant *SMARCA2* mutation or loss of protein expression (eg, SCCOHT-small-cell carcinoma of the ovary hypercalcemic type or thoracic sarcomatoid tumors)
- Clinically significant or uncontrolled cardiac disease, uncontrolled electrolyte disorders, uncontrolled or symptomatic CNS metastases or leptomeningeal disease
- Participant has not recovered to grade ≤1 from toxic effects of prior treatments (systemic, radiation, or surgery)
- History of another malignancy within 3 years except for adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancies, or malignancies previously treated with curative intent and not on active therapy or expected to require treatment or recurrence during the study
- Concurrent treatment with strong or moderate CYP3A4 inhibitor or inducer
- Has a known history of hepatitis B or known active hepatitis C virus infection
- Pregnant or breastfeeding

ENROLLMENT, STATUS, AND REGISTRATION

- This study is registered at ClinicalTrials.gov (NCT05639751) and is active in the United States, France, Spain, and the Netherlands
- Study is enrolling well with treatment commencing at the 4th dose level, with a promising early safety profile and SMARCA2 degradation data

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ABBREVIATIONS

ANC, absolute neutrophil count; ATP, adenosine triphosphate; BOIN, Bayesian optimal interval; BRG1, brahma-related gene-1; BRM, brahma; CBR, clinical benefit rate; CDX, cell line-derived tumors xenograft; C_{max}, maximum concentration; CNS, central nervous system; CT, computed tomography; ctDNA, circulating tumor DNA; CYP3A4, cytochrome P450 3A4; DC_{50}, half-maximal degradation concentration; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; hERG, human ether-a-go-go-related gene; HIBiL, a small 11 amino acid peptide tag; IC_{50}, half-maximal inhibitory concentration; IHC, immunohistochemistry; IV, intravenous; KEAP1, kelch-like ECH-associated protein 1; KRAS, kirsten rat sarcoma viral oncogene homolog; LOF, loss of function; mOS, median overall survival; mPFS, median progression-free survival; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; QW, every 1 week; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dosing; sc, subcutaneous; SCCOHT, small cell carcinoma of the ovary, hypercalcemic type; SMARCA2, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2; SMARCA4, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4; SWI/SNF, switch/sucrose nonfermentable; TDI, time dependent inhibition; TYK2, tyrosine kinase 2; VHL, von Hippel-Lindau; WT, wild type.

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