# A Phase 2 Safety and Efficacy Study of PRT3789 in Combination With Pembrolizumab in Patients With Advanced or Metastatic Solid Tumors and a *SMARCA4* Mutation

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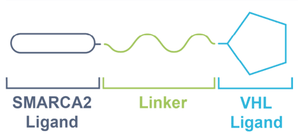
## BACKGROUND

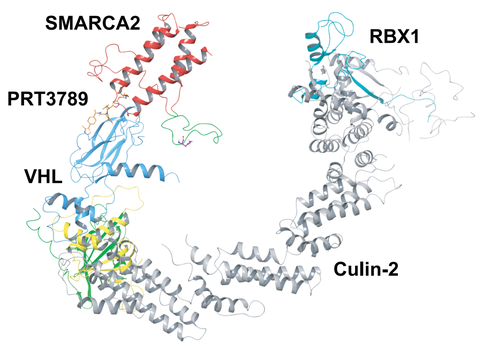
- Mutations in genes encoding subunits of the SWI/SNF chromatin remodeling complex have been observed in 20% of all human cancers[1,2]
  - The SWI/SNF complex contains 1 of 2 ATP enzymatic subunits, either SMARCA2 (also known as BRM) or SMARCA4 (also known as BRG1)[1]
  - Because SMARCA2 and SMARCA4 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]
- In NSCLC, *SMARCA4* mutations are observed in approximately 10% of cases and are associated with more aggressive and invasive disease and shorter survival[6-8]
- PRT3789 is a potent and selective, intravenous, VHL-based SMARCA2 degrader (**Figure 1**) which induces proteosome-dependent degradation of SMARCA2 and robust synthetic lethality in *SMARCA4*-deficient cancers

### Figure 1. Characterization of PRT3789




**PRT3789, a VHL-recruiting SMARCA2 degrader IV drug candidate**

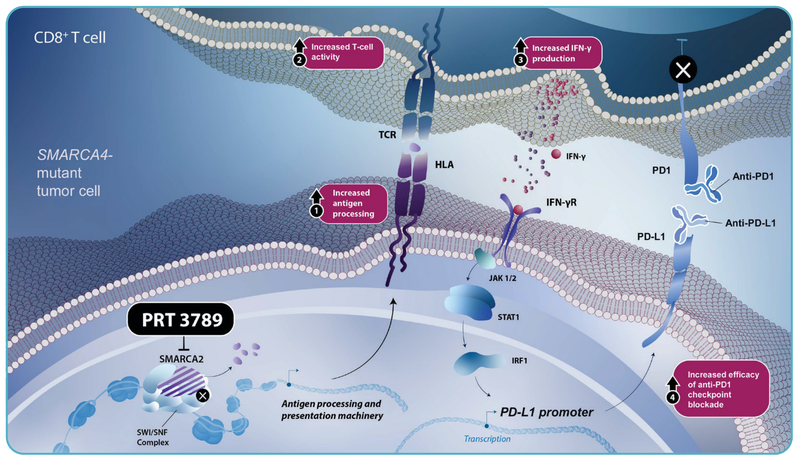
- Heterobifunctional SMARCA2 degrader
- Highly potent and selective for SMARCA2 vs SMARCA4
- Efficacious in *SMARCA4*-mutated CDX and PDX in vivo models at well-tolerated doses




3-Dimensional structure of SMARCA2 bromodomain and E3 ligase complex (VBC/CUL2/RBX1) formed by PRT3789 SMARCA2 degrader

- PRT3789 at doses up to 500 mg IV once weekly was well tolerated and demonstrated encouraging clinical activity in patients with NSCLC and upper gastric or esophageal cancers, with LOF *SMARCA4* mutations (PRT3789-01; NCT05639751)[9]
- Although ICIs have shown remarkable clinical activity across a broad range of tumor types, various resistance mechanisms contribute to limited effectiveness in some patients. These resistance mechanisms include altered antigen presentation, reduced T-cell infiltration, and altered immune signaling pathways[8]
- PRT3789 was shown to increase antigen processing and presentation of unique MHC class I peptides and increase T-cell activity and IFN-γ production in *SMARCA4*-mutated cancer cells
- PRT3789 in combination with pembrolizumab may re-sensitize patients with cancers resistant to subsequent anti–PD-L1 therapy (**Figure 2**)

### Figure 2. Scientific Rationale for Combination Treatment of PRT3789 and Anti-PD1/PD-L1 Therapy




- PRT3789 increases antigen processing and presentation machinery in *SMARCA4*-deficient NSCLC cells
- PRT3789 combined with pembrolizumab promotes T-cell activity and *SMARCA4*-deficient NSCLC cell killing
- SMARCA2 degradation promotes the effect of anti-PD1 therapy in a *SMARCA4*-deficient cancer syngeneic mouse model in vivo

## METHODS

### KEY OBJECTIVES

- PRT3789-02 (NCT06682806) is a phase 2, open-label, multicenter study of PRT3789 in combination with pembrolizumab in patients with advanced, recurrent, or metastatic solid tumors with a *SMARCA4* mutation (**Figure 3**)

#### Primary objectives

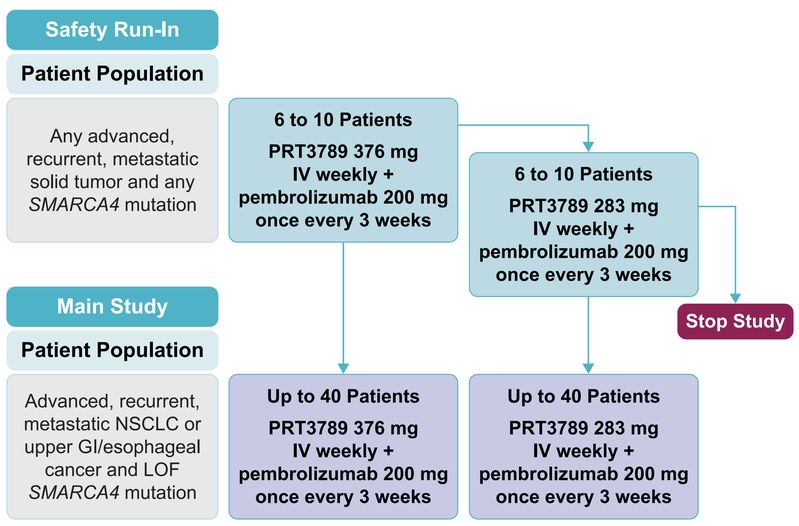
- **Part 1:** Evaluate the safety and tolerability of PRT3789 in combination with pembrolizumab in patients with advanced, recurrent, or metastatic solid tumors, with any *SMARCA4* mutation
- **Part 2:** Evaluate the efficacy of PRT3789 in combination with pembrolizumab in patients with advanced or metastatic NSCLC or upper GI/esophageal cancer, with a LOF *SMARCA4* mutation

#### Secondary objectives

- Evaluate the efficacy (ORR, DOR, CBR, PFS, and OS), safety and tolerability, and PK profile of PRT3789 in combination with pembrolizumab

### STUDY DESIGN AND ENDPOINTS

#### Figure 3. PRT3789-02 Study Design




### PATIENT ELIGIBILITY

#### Key inclusion criteria

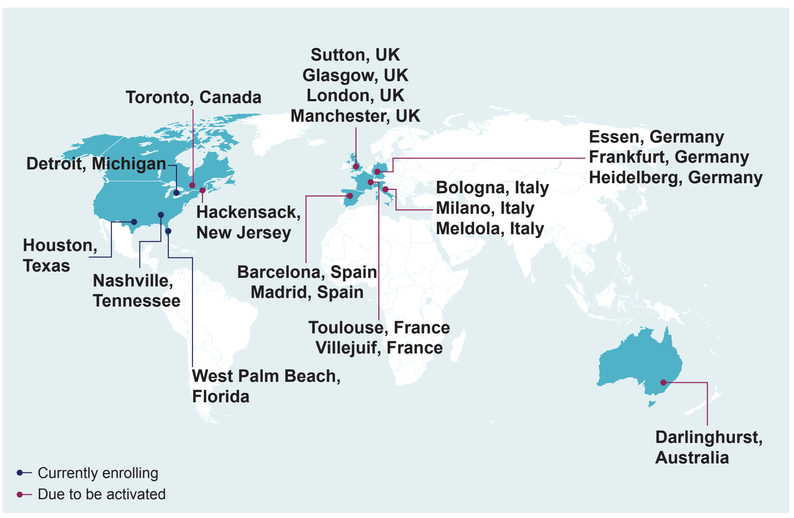
- **Part 1 safety run-in:** Patients aged ≥18 years with histologically or cytologically confirmed advanced, recurrent, or metastatic solid tumor malignancy with any *SMARCA4* mutation by local NGS testing or SMARCA protein expression loss per IHC. Patients must have measurable or nonmeasurable but evaluable disease
- **Part 2 main study:** Patients aged ≥18 years with histologically or cytologically confirmed advanced, recurrent, or metastatic NSCLC or upper GI/esophageal cancer with a LOF *SMARCA4* mutation by local NGS testing or SMARCA protein expression loss per IHC. Patients must have measurable disease
- Patients must meet 1 of the following criteria
  - Primary resistance to prior anti–PD1/PD-L1, defined by disease that did not respond at all and instead progressed (eg, best response of progressive disease per RECIST 1.1)
  - Acquired resistance to prior anti–PD1/PD-L1, defined as patients who received anti–PD1/PD-L1 therapy and had a partial or complete response, then progressed within 6 months
  - Received prior standard-of-care therapy but did not receive prior anti–PD1/PD-L1 therapy because the tumor PD-L1 expression was negative
  - Prior anti–PD1/PD-L1 therapy was discontinued for reasons other than disease progression, and subsequent progression >6 months following prior anti–PD1/PD-L1 therapy
- Patients must either progress on standard-of-care therapy or be ineligible for standard-of-care therapy. Patients with driver mutation in oncogenes (eg, *EGFR*, *MET*, *RET*, *ALK*, *BRAF*, *KRAS*, *ROS1*, *HER2*) are eligible after progression on approved targeted therapies, as applicable
- Adequate organ function

#### 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 and/or carcinomatous meningitis
- History of or current noninfectious pneumonitis or interstitial lung disease
- Active autoimmune disease or diagnosis of immunodeficiency disease/disorder
- Concurrent treatment with strong or moderate CYP3A4 inhibitor or inducer
- Patients who received prior treatment with an agent directed to a stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX40, CD137) other than an anti–PD1, anti–PD-L1, or anti–PD-L2 agent

## ENROLLMENT AND STATUS

This study is currently active with approximately 20 sites in North America, Europe, and Asia Pacific




## REGISTRATION

This study is registered at ClinicalTrials.gov (NCT06682806)

## ABBREVIATIONS

ALP, alkaline phosphate; ALT, alanine aminotransferase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ATP, adenosine triphosphate; BRG1, Brahma-related gene 1; BRM, Brahma; CBR, clinical benefit rate; CD137, tumor necrosis factor receptor superfamily member 9; CDX, cell-derived xenograft; CNS, central nervous system; CrCl, creatinine clearance; ctDNA, circulating tumor DNA; CTLA-4, cytotoxic t-lymphocyte-associated protein 4; CUL2, Cullin 2; CYP3A4, cytochrome P450 3A4; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; GI, gastrointestinal; ICI, immune checkpoint inhibitor; IFN-γ, interferon gamma; IFN-γR, IFN-γ receptor; IHC, immunohistochemistry; INR, international normalized ratio; IV, intravenous; LOF, loss of function; MHC, major histocompatibility complex; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; OX40, tumor necrosis factor receptor superfamily member 4; PD, pharmacodynamics; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDX, patient-derived xenograft; PFS, progression-free survival; PK, pharmacokinetics; PT, prothrombin time; RBX1, ring-box 1; RECIST, response evaluation criteria in solid tumors; SCCOHT, small-cell carcinoma of the ovary hypercalcemic type; SMARCA, SWI/SNF related matrix associated actin dependent regulator of chromatin subfamily a member; SWI/SNF, switch/sucrose non-fermentable; ULN, upper limit of normal; VBC, VHL binding complex; VHL, Von Hippel-Lindau.

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