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


**BACKGROUND**

SMARCA2 and SMARCA4 are ATP enzymatic subunits of the SWI/SNF complex, which contains 1 of 2 ATP enzymatic subunits: either SMARCA2 (also known as BRM) or SMARCA4. Mutations, fusions, and homozygous deletions of SMARCA2 and SMARCA4 are associated with shorter OS, with truncating mutations, fusions, and homozygous deletions being associated with the shortest survival times. In NSCLC, alterations have been associated with shorter OS, with truncating mutations, fusions, and homozygous deletions being associated with the shortest survival times. Patients with NSCLC with driver alterations (eg, MET, RET, BRAF) or alterations in TP53, RB1, or CDKN2A are poor candidates for clinical trials using EGFR and ALK inhibitors. Patients with NSCLC with driver alterations (eg, MET, RET, BRAF, TP53, RB1, CDKN2A) are not eligible for this study.

**OBJECTIVES**

**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 CDK4a as surrogate endpoint for monitoring of disease response

**STUDY DESIGN AND ENDPOINTS**

**Study Entry**

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 (Table 1). Patients with NSCLC with driver alterations (eg, MET, RET, BRAF) or alterations in TP53, RB1, CDKN2A are poor candidates for clinical trials using EGFR and ALK inhibitors. Patients with NSCLC with driver alterations (eg, MET, RET, BRAF, TP53, RB1, CDKN2A) are not eligible for this study.

**Study Treatment**

PRT3789 will be administered IV once weekly for 3 weeks (1 cycle) ORR assessed during the first 21 days of dosing in cycle 1

**Key Exclusion Criteria**

- Patients with solid tumors with known susceptibility to SMARCA2 inhibition, or lack of protein expression
- Any prior therapy with PRT3789
- Uncontrolled bacterial or viral infection
- Patients who have received previous treatment with any investigational agents within 28 days of starting the study
- Patients with a history of or radiographic evidence of brain metastases or uncontrolled symptomatic brain metastases
- Patients with active or uncontrolled neuroendocrine tumor disease
- Patients with an ongoing active malignancy
- Patients with uncontrolled or symptomatic interstitial lung disease
- Patients with uncontrolled hormone-dependent tumor
- Patients with a history of active seronegative vasculitis
- Patients with cerebrovascular disease
- Patients with a history of uncontrolled hypertension

**Enrollment, Status, and Registration**

This study is registered at ClinicalTrials.gov (NCT05639751) and is active in the United States, France, Spain, and the Netherlands.

**References**

[1-20]

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