A Phase 1 Open-Label, Dose-Escalation Study of Central Nervous System-Penetrant Cyclin Dependent Kinase (CDK)4/6 Inhibitor, PRT3645, in Patients With Select Advanced or Metastatic Solid Tumors

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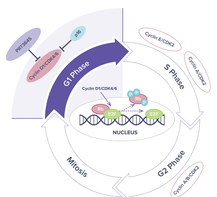
Background

- CDK4 and CDK6 are integral components of the cell cycle regulatory machinery, orchestrating the transition from G1 to S phase and regulating cell proliferation (Figure 1).[1]
- CDK4/6 inhibitors are approved for patients with advanced HR+/HER2– breast cancer (BC) but have inadequate tissue/brain penetration and are ineffective against primary or metastatic brain tumors.[2-4]
- PRT3645 is an investigational, highly selective, and potent CDK4/6 inhibitor, designed to achieve high tissue and brain penetration.[5]
- In preclinical models of glioblastoma (GBM) and BC brain metastasis, PRT3645 demonstrated anti-tumor activity and enhanced survival.[6]

Figure 1. CyclinD-CDK4/6-Rb-E2F Pathway



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Objective

- This phase 1 dose-escalation study (NCT05538572) aims to evaluate the safety, preliminary efficacy, and pharmacokinetic (PK) and pharmacodynamic profile of PRT3645.

Key Findings

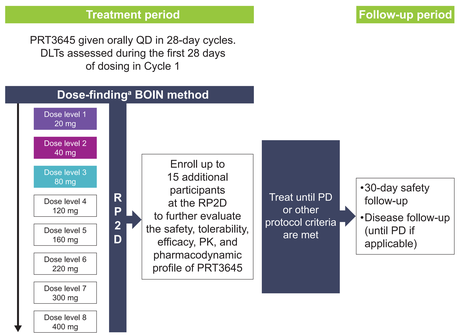
- PRT3645 exhibited evidence of target engagement and tolerable dose escalation in the initial three cohorts of patients with no significant gastrointestinal or hematologic events reported to date, leveraging its enhanced selectivity profile.

Methods

Study Design

- This is an open-label, multicenter, phase 1 dose-escalation study of PRT3645 in participants with select advanced solid tumors (Figure 2).
- The study drug, PRT3645, is a self-administered capsule taken orally once daily (QD) for a cycle of 28 days.
- Dose escalation employed a Bayesian optimal interval design (BOIN) to evaluate the safety, tolerability, and incidence of dose-limiting toxicities (DLTs). Intra-patient dose escalation was permitted.

Figure 2. PRT3645-01 Study Design



[a]Additional dose levels, intermediate dose levels, and/or alternate administration scheduled may also be explored based on observed toxicities, PK, and pharmacodynamic data. PD, progressive disease; RP2D, recommended phase 2 dose.

Patient Population

Key inclusion criteria

- Aged ≥18 years
- Histologically confirmed advanced recurrent or metastatic solid tumor malignancy that has either progressed or is ineligible for standard of care therapy:
  - HR+/HER2– or HR+ HER2+ BC
  - Recurrent GBM (*IDH* wild type) or *CDKN2A/B* homozygous deleted *IDH*-mutant astrocytoma
  - *KRAS*-mutant non-small cell lung cancer (NSCLC) or loss of *SMARCA4*
  - CDK pathway alteration in any of the following tumor types: malignant mesothelioma, human papillomavirus (HPV)-negative head and neck squamous cell carcinoma (HNSCC; including oral cavity, oropharynx, hypopharynx, and larynx), sarcoma, or NSCLC
  - Endometrial (endometroid) cancer
- Able to swallow and retain oral medication
- Tumor tissue sample for central laboratory analysis
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 or Karnofsky PS ≥80% (GBM only)
- Adequate organ function
- Treated and untreated brain metastases (lesion <1.5 cm), without neurological symptoms and not requiring immediate local treatment

Key exclusion criteria

- Primary malignancy of the central nervous system or uncontrolled central nervous system metastases
- Impaired cardiac function
- Chronic inflammatory bowel disease
- Prior anti-cancer therapy within 5 half-lives or 30 days (whichever is shorter) prior to Cycle 1 Day 1 (C1D1)

Study Endpoints and Assessments

- The primary endpoints of this analysis were to identify DLTs and establish the maximum tolerated dose and RP2D of PRT3645 based on incidence of DLTs, incidence and severity of adverse events (AEs), changes in laboratory parameters, and incidence of changes in dosing.
- Secondary endpoints include evaluation of the PK profile, pharmacodynamic effect, safety, and efficacy signal of PRT3645 based on overall response rate, progression-free survival (PFS), disease control rate, and duration of response.
- Blood samples were collected on C1D1, C1D8, C1D15, and C1D22 and C2D1, C4D1, C6D1, and C8D1.
  - C1D1, C1D15: pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours post-dose
  - C1D8, C1D22: pre-dose only
  - Subsequent cycles: pre-dose and then 2 hours post-dose
- Skin punch biopsies were collected C1D1 pre-dose and C1D15 approximately 4 hours post-dose.

Results

Patients

- At the time of data cutoff (August 4, 2023; median treatment duration of 8.0 [range, 5.4-25.4] weeks), 11 patients have been enrolled into the first three dose level cohorts (Table 1); 81.8% (n=9) of patients had discontinued PRT3645. The primary reason for discontinuation was PD (n=9, 100.0%).

Table 1. Patient Baseline Characteristics

Characteristic	PRT3645 20 mg (n=4)	PRT3645 40 mg (n=4)	PRT3645 80 mg (n=3)	Total (N=11)
Age, median (range), years	61.5 (57.0-66.0)	67.0 (55.0-76.0)	45.0 (36.0-62.0)	61.0 (36.0-76.0)
Female, n (%)	2 (50.0)	2 (50.0)	2 (66.7)	6 (54.5)
ECOG PS at baseline, n (%)				
0	0	0	1 (33.3)	1 (9.1)
1	1 (25.0)	2 (50.0)	1 (33.3)	4 (36.4)
Missing	3 (75.0)	2 (50.0)	1 (33.3)	6 (54.5)
Lines of prior systemic therapies, median (range)	2.5 (1.0-7.0)	2.5 (2.0-9.0)	3.0 (3.0-5.0)	3.0 (1.0-9.0)
Tumor type, n (%)				
Anaplastic astrocytoma	0	1 (25.0)	0	1 (9.1)
Breast	1 (25.0)	1 (25.0)	2 (66.7)	4 (36.4)
GBM	3 (75.0)	1 (25.0)	1 (33.3)	5 (45.5)
Sarcoma	0	1 (25.0)	0	1 (9.1)

Safety

- The most common treatment-emergent adverse events (TEAEs) observed in the study were typically grade 1/2 in severity; one grade 3 event was reported (Table 2 and Table 3).
- At the time of data cutoff:
  - The most common TEAEs were anemia, dizziness, and neutropenia (n=2 for each; Table 3).
  - No DLTs have been reported.
  - One grade 3 event (neutropenia in the 80 mg cohort), which was treatment related but not dose limiting, was ongoing at time of data cutoff.
- No deaths, serious AEs, dose reductions, dose interruptions, dose withdrawals, or DLTs related to treatment were observed.

Table 2. Overview of TEAEs

Events, n (%)	PRT3645 20 mg (n=4)	PRT3645 40 mg (n=4)	PRT3645 80 mg (n=3)	Total (N=11)
TEAEs				
Any grade	4 (100.0)	3 (75.0)	2 (66.7)	9 (81.8)
Grade ≥3	0	0	1 (33.3)	1 (9.1)
Treatment-related TEAEs				
Any grade	1 (25.0)	0	2 (66.7)	3 (27.3)
Grade ≥3	0	0	1 (33.3)	1 (9.1)

Table 3. All TEAEs/Treatment-Related TEAEs

Events, n (%)	TEAEs Total (N=11)			Treatment-related TEAEs Total (N=11)		
	Grade 1-2	Grade 3-5	Any grade	Grade 1-2	Grade 3-5	Any grade
TEAEs	8 (72.7)	1 (9.1)	9 (81.8)	2 (18.2)	1 (9.1)	3 (27.3)
Anemia	2 (18.2)	0	2 (18.2)	0	0	0
Dizziness	2 (18.2)	0	2 (18.2)	0	0	0
Neutropenia	1 (9.1)	1 (9.1)	2 (18.2)	0	1 (9.1)	1 (9.1)

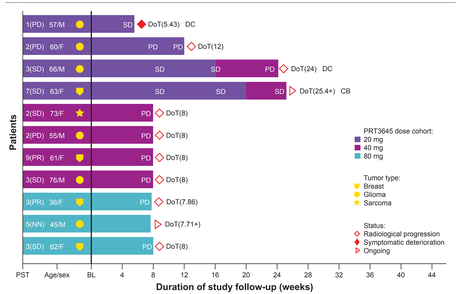
TEAEs with an incidence of >10% are presented in the table. The following grade 1-2 TEAEs were observed in 9.1% (n=1) of the population: blood creatinine increased, ear pain, eye pain, fatigue, constipation, gastroesophageal reflux disease, insomnia, hypoglycemia, nasal congestion, nephrolithiasis, leukopenia, thrombocytopenia, hemiparesis, paresthesia, headache, and seizure. The following grade 1-2 treatment-related TEAEs were observed in 9.1% (n=1) of the population: fatigue, leukopenia, and paresthesia.

Preliminary Efficacy

- No objective responses (per RECIST v1.1/Response Assessment in Neuro-Oncology) were observed in the 10 patients with one post-baseline scan (Figure 3): 3/10 (30.0%) had stable disease (SD) and median PFS was 1.77 months (95% confidence interval, 1.25-1.87).
  - A patient with BC, who received PRT3645 in combination with a gonadotropin-releasing hormone agonist, had SD for 24+ weeks.
- Overall, 9/11 (81.8) patients discontinued study treatment; all of those who discontinued did so due to PD.

Patient Status

Figure 3. Duration of Treatment

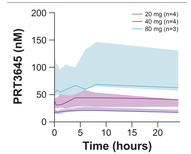


Status indicates the primary reason for treatment discontinuation. The text on the bars after baseline (SD/PD) indicates overall response assessed by the Investigator per the criteria corresponding to the underlying tumor type. The text (numbers) at the end of each row indicates DoT. DC/CB at the end of each line indicates the DC response, CB response, or overall response. BL, baseline; CB, clinical benefit; DC, disease control; DoT, duration of treatment; F, female; M, male; NN, non-complete response/non-PD; PR, partial response; PST, prior systemic therapy.

Pharmacokinetic Summary

- Dose-related increases in exposure were observed (Figure 4).
- Absorption of PRT3645 was slow with median time to maximum concentration (T_{max}) being observed between 7 to 24 hours across the dose levels after a single dose.
- Concentration–time profiles were relatively flat, indicating a long elimination phase after single and repeat dosing and half-life was not calculable.
- Steady state was achieved by Day 8, and significant accumulation was seen (4.25- to 6.25-fold across doses).

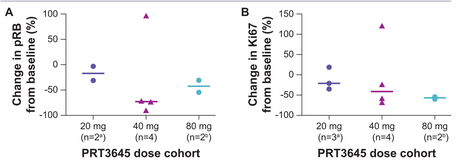
Figure 4. PRT3645 Median (Range) Concentration–Time Profiles at Steady State (Cycle 1, Day 15)



Pharmacodynamics

- A mean reduction in phosphorylated Rb (pRb) staining of 35% (>70% in 3 of 4 patients) and 41% (>50% reduction in 1 of 2 patients) was observed in patients who received 40 mg and 80 mg, respectively (Figure 5A).
- A mean reduction in Ki67 staining of 10% (>60% in 2 of 4 patients) and 60% (>50% reduction in 2 of 2 patients) was observed in patients who received 40 mg and 80 mg, respectively (Figure 5B).

Figure 5. Percentage Change in (A) pRb and (B) Ki67 From Baseline



[a]One patient in the 20 mg dose cohort had a baseline score of 0 and was therefore not evaluable for pRB but was evaluable for Ki67. A second patient in the 20 mg dose cohort had no evaluable samples for either pRB or Ki67. [b]One patient in the 80 mg dose cohort was not evaluable for pRB and Ki67.

Conclusions

- Treatment with the CDK4/6 inhibitor PRT3645 was associated with a substantial decrease in pRb and Ki67 expression, indicating a high level of target engagement at the doses evaluated; dose escalation is ongoing.
- PRT3645 exhibited tolerable dose escalation in the initial three cohorts of patients with no significant gastrointestinal, hematologic, or neurologic events reported to date, leveraging its enhanced selectivity profile.

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