A Phase 1, Open-Label, Dose-Escalation Study of a CDK9 Inhibitor, PRT2527, in Adult Patients With Advanced Solid Tumors: An Updated Analysis

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Background

- Cyclin-dependent kinase 9 (CDK9) is a master regulator of transcription that controls paused RNA polymerase II (RNAP2) release through phosphorylation of its carboxy-terminal domain, resulting in transcription elongation (Figure 1).[1,2]
- Selective CDK9 inhibition may be a promising approach to treat transcription-addicted cancers that are dependent on oncogenic drivers with a short half-life, such as the oncogenes myelocytomatosis (*MYC*), myeloblastosis (*MYB*), and myeloid leukemia cell differentiation protein (*MCL1*).[2]
- PRT2527 is a potent and selective inhibitor of CDK9 with a biochemical half-maximal inhibitory concentration (IC_{50}) of 0.98 nM at 1 mM adenosine triphosphate that inhibits the enzymatic activity of human CDK9/CyclinT1 complex.[1] PRT2527 is highly selective among CDK family members and across 177 kinases.[1]
- Intermittent intravenous (IV) administration of PRT2527 demonstrated strong efficacy in preclinical models of solid tumors and hematological malignancies as monotherapy and in combination with other anticancer therapies.[1]

Figure 1. CDK9 Mechanism of Action

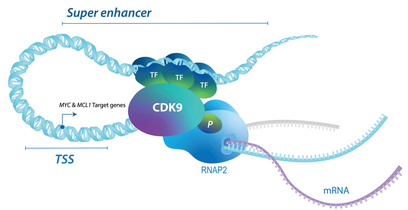


Figure reproduced with permission from Zhang Y, et al.[1] mRNA, messenger ribonucleic acid; P, phosphate; TF, transcription factor; TSS, transcription start site.

Objective

- To establish the recommended phase 2 dose (RP2D) and evaluate the pharmacokinetic/pharmacodynamic profile, safety, and preliminary efficacy of PRT2527 in patients with advanced solid tumors.

Key Findings

- In this updated analysis of a phase 1, open-label, dose-escalation study, the CDK9 inhibitor PRT2527 demonstrates acceptable safety and tolerability in patients with advanced solid tumors.

Methods

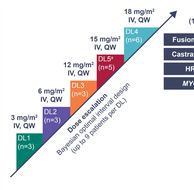
Study Design

- This is an open-label, multicenter, phase 1 dose-escalation study of PRT2527 in participants with select advanced solid tumors (NCT05159518; Figure 2).
- Dose escalation employed a Bayesian optimal interval design to evaluate the safety, tolerability, and incidence of dose-limiting toxicities (DLTs).

Figure 2. Study Design

Key inclusion criteria
- Adults (aged ≥18 years) with previously treated selected sarcomas, CRPC, HR+/HER2− breast cancer, NSCLC, or *MYC*-amplified solid tumors
- Prior systemic therapy
- Measurable (per RECIST v1.1) or evaluable (CRPC or sarcoma only) disease
- ECOG PS 0-1
- Adequate organ function
- Central nervous system disease is allowed if stable and adequately controlled

Key exclusion criteria
- Impaired cardiac function
- Chronic inflammatory bowel disease
- Prior exposure to CDK9 inhibitor
- Prior anti-cancer therapy within 5 half-lives or 28 days (whichever is shorter) prior to C1D1



Dose confirmation (15 mg/m² IV, QW; n=10)
- Fusion-positive selected sarcoma
- Castrate-resistant prostate cancer
- HR+ HER2− breast cancer
- *MYC*-amplified solid tumors

[a]DL5 (15 mg/m²) was evaluated as an intermediate DL following safety review of DL4 (18 mg/m²). PRT2527 was administered IV QW in a 3-week cycle until disease progression or unacceptable toxicity. C1D1, Cycle 1 Day 1; CRPC, castrate-resistant prostate cancer; DL, dose level; ECOG PS, Eastern Cooperative Oncology Group performance status; HR+/HER2−, hormone receptor positive, human epidermal growth factor receptor 2 negative; NSCLC, non-small cell lung cancer; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumors.

Study Endpoints

- The primary endpoint was to identify DLTs and establish the maximum tolerated dose and RP2D of PRT2527 based on incidence of DLTs, adverse events (AEs), changes in laboratory parameters, and changes in dosing.
- Secondary endpoints include evaluation of the pharmacokinetic profile, safety, and efficacy signal of PRT2527 based on overall response rate, disease control rate, duration of response, and progression-free survival (PFS).
- Exploratory endpoints included the pharmacodynamic assessment of the expression of CDK9 transcriptional targets (*MYC*, *MCL1*) in peripheral blood mononuclear cells (PBMCs) that may be associated with response to CDK9 inhibition. Phosphorylation of RNAP2 (p-RNAP2) was assessed by capillary electrophoresis and monitoring changes in absolute monocyte and neutrophil counts using clinical complete blood count.

Results

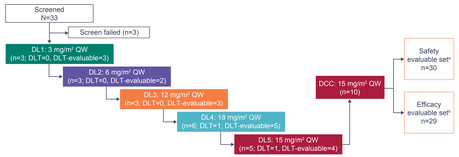
Patients

- Patient baseline characteristics are presented in Table 1 and patient disposition is presented in Figure 3.
- At the time of data cutoff (August 4, 2023; median treatment duration of 5.4 [range, 1.0-66.0] weeks), 93.3% of patients had discontinued PRT2527.
- The primary reasons for discontinuation were progressive disease (PD; n=22, 78.6%), AEs (n=5, 17.9%), and withdrawal by patient (n=1, 3.6%). One treatment-related AE led to discontinuation in the 15 mg/m² cohort.

Table 1. Patient Baseline Characteristics

Characteristic	PRT2527 3 mg/m² (n=3)	PRT2527 6 mg/m² (n=3)	PRT2527 12 mg/m² (n=3)	PRT2527 15 mg/m² (n=15)	PRT2527 18 mg/m² (n=6)	Total (N=30)
Age, median (range), years	64 (59-64)	64 (57-70)	72 (71-73)	58 (23-82)	71 (37-86)	65 (23-86)
Female, n (%)	1 (33.3)	3 (100.0)	0	9 (60.0)	1 (16.7)	14 (46.7)
ECOG PS at baseline, n (%)						
0	1 (33.3)	2 (66.7)	0	4 (26.7)	0	7 (23.3)
1	2 (66.7)	1 (33.3)	3 (100.0)	11 (73.3)	6 (100.0)	23 (76.7)
Lines of prior systemic therapies, median (range)	5 (4-8)	4 (1-5)	7 (3-8)	4 (2-9)	5 (1-8)	5 (1-9)
Tumor type, n (%)						
Breast	1 (33.3)	1 (33.3)	0	3 (20.0)	1 (16.7)	6 (20.0)
NSCLC	0	0	0	2 (13.3)	0	2 (6.7)
Pancreatic	0	0	0	2 (13.3)	0	2 (6.7)
Prostate	2 (66.7)	0	3 (100.0)	2 (13.3)	4 (66.7)	11 (36.7)
Sarcoma	0	2 (66.7)	0	6 (40.0)	1 (16.7)	9 (30.0)
MYC amplification						
Yes	1 (33.3)	0	0	5 (25.0)	1 (16.7)	7 (23.3)
No	2 (66.7)	3 (100.0)	3 (100.0)	10 (75.0)	5 (83.3)	23 (76.7)

Figure 3. Patient Disposition



[a]Includes all patients who received at least 1 dose of PRT2527. [b]Includes all patients in the safety evaluable set who had ≥1 post-baseline response assessment or discontinued the study due to death, AE, or PD. DCC, dose confirmation cohort.

Safety

- The most common treatment-emergent AEs (TEAEs) were nausea (46.7%), vomiting (40.0%), neutropenia (33.3%), diarrhea (23.3%), and fatigue (23.3%; Table 3).
  - Two DLTs of grade 4 neutropenia were observed during dose escalation in the 15 and 18 mg/m² QW cohorts.
  - No grade 3/4 hepatotoxicity was observed.
  - 9 serious AEs were reported (Table 2); 1 (pneumonia staphylococcal) was considered related to study treatment.
- The most common treatment-related AEs were nausea (43.3%), vomiting (36.7%), and neutropenia (33.3%).
  - Anti-emetic or growth factor prophylaxis was not required per protocol.
  - Three patients received growth factor support for neutropenia.
- No deaths related to treatment were observed.

Table 2. Overview of TEAEs

Events, n (%)	PRT2527 3 mg/m² (n=3)	PRT2527 6 mg/m² (n=3)	PRT2527 12 mg/m² (n=3)	PRT2527 15 mg/m² (n=15)	PRT2527 18 mg/m² (n=6)	Total (N=30)
TEAEs						
Any grade	3 (100.0)	3 (100.0)	3 (100.0)	15 (100.0)	6 (100.0)	30 (100.0)
Grade ≥3	1 (33.3)	0	1 (33.3)	9 (60.0)	5 (83.3)	16 (53.3)
Serious	0	1 (33.3)	0	4 (26.7)	3 (50.0)	8 (26.7)
Grade 5 (fatal)	0	0	0	0	2 (33.3)	2 (6.7)
Leading to study dose reduction	0	0	0	1 (6.7)	3 (50.0)	4 (13.3)
Leading to study dose interruption	0	0	1 (33.3)	6 (40.0)	3 (50.0)	10 (33.3)
Leading to study dose withdrawal	0	0	0	2 (13.3)	3 (50.0)	5 (16.7)
Leading to a DLT	0	0	0	1 (6.7)	1 (16.7)	2 (6.7)
Treatment-related TEAEs						
Any grade	2 (66.7)	2 (66.7)	3 (100.0)	14 (93.3)	5 (83.3)	26 (86.7)
Grade ≥3	0	0	0	4 (26.7)	2 (33.3)	6 (20.0)
Serious	0	0	0	1 (6.7)	0	1 (3.3)
Grade 5 (fatal)	0	0	0	0	0	0
Leading to study dose reduction	0	0	0	1 (6.7)	3 (50.0)	4 (13.3)
Leading to study dose interruption	0	0	1 (33.3)	3 (20.0)	2 (33.3)	6 (20.0)
Leading to study dose withdrawal	0	0	0	1 (6.7)	0	1 (3.3)
Leading to a DLT	0	0	0	1 (6.7)	1 (16.7)	2 (6.7)

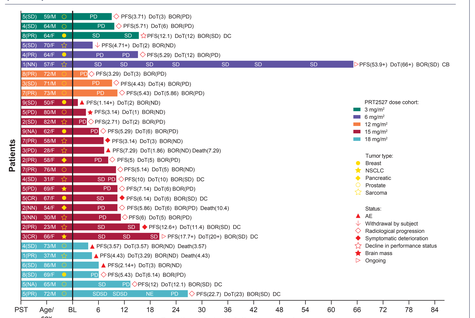
Table 3. TEAEs/Treatment-Related AEs in ≥10% of the Total Population

Events, n (%)	TEAE Total (N=30)			Treatment-related TEAE Total (N=30)		
	Grade 1-2	Grade 3-5	Any grade	Grade 1-2	Grade 3-5	Any grade
Any TEAE	14 (46.7)	16 (53.3)	30 (100.0)			
Any treatment-related TEAE				20 (66.7)	6 (20.0)	26 (86.7)
Nausea	13 (43.3)	1 (3.3)	14 (46.7)	12 (40.0)	1 (3.3)	13 (43.3)
Vomiting	12 (40.0)	0	12 (40.0)	11 (36.7)	0	11 (36.7)
Neutropenia	5 (16.7)	5 (16.7)	10 (33.3)	5 (16.7)	5 (16.7)	10 (33.3)
Fatigue	6 (20.0)	1 (3.3)	7 (23.3)	5 (16.7)	0	5 (16.7)
Decreased appetite	4 (13.3)	0	4 (13.3)	2 (6.7)	0	2 (6.7)
Diarrhea	7 (23.3)	0	7 (23.3)	4 (13.3)	0	4 (13.3)
Headache	5 (16.7)	0	5 (16.7)	2 (6.7)	0	2 (6.7)
Anemia	0	4 (13.3)	4 (13.3)	0	1 (3.3)	1 (3.3)
Dehydration	3 (10.0)	0	3 (10.0)	1 (3.3)	0	1 (3.3)
Dizziness	4 (13.3)	0	4 (13.3)	1 (3.3)	0	1 (3.3)
Leukopenia	2 (6.7)	1 (3.3)	3 (10.0)	2 (6.7)	1 (3.3)	3 (10.0)
Lymphopenia	2 (6.7)	1 (3.3)	3 (10.0)	2 (6.7)	0	2 (6.7)
Non-cardiac chest pain	3 (10.0)	0	3 (10.0)	1 (3.3)	0	1 (3.3)
Thrombocytopenia	2 (6.7)	1 (3.3)	3 (10.0)	1 (3.3)	1 (3.3)	2 (6.7)

Preliminary Efficacy

- Of the 29 patients with ≥1 post baseline scan or who discontinued due to death, AE, or progressive disease, no objective responses (per RECIST v1.1) were observed: 8 (27.6%) patients had stable disease (SD) as the best response.
  - Prolonged SD for 66+ weeks was observed in a patient with chondrosarcoma who received PRT2527 at a starting dose of 6 mg/m². This patient was dose escalated to 12 mg/m².
- Median PFS was 1.25 (95% confidence interval, 1.02-1.64) months.
- Duration of study follow-up in all patients is shown in Figure 4.

Figure 4. Duration of Study Follow-up With Current Status in All Patients (N=30)

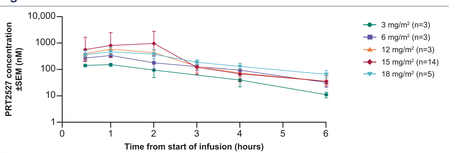


Status indicates the primary reason for treatment discontinuation. The text on the bars after baseline (SD/PD) indicates overall response assessed by the Investigator per the criteria corresponding to the underlying tumor type. The text (numbers) at the end of each row indicates PFS time, DoT, BOR, and death time. The DoT was defined as the time interval from Day 1 to the date of last IV infusion plus 6 days. DC/CB/R at the end of each line indicates the DC response, CB response, or overall response. BL, baseline; BOR, best overall response; CB, clinical benefit; CR, complete response; DC, disease control; DoT, duration of treatment; F, female; M, male; NA, not applicable; ND, not determined; NE, not evaluable; NN, non-CR/non-PD; PR, partial response; PST, prior systemic therapy.

Pharmacokinetics

- PRT2527 demonstrated dose-dependent increases in exposure (Figure 5).
- The mean half-life of PRT2527 was 3.8 hours after a single dose of 18 mg/m².
- Consistent with the short half-life, no accumulation was observed with QW dosing.

Figure 5. Pharmacokinetic Profile

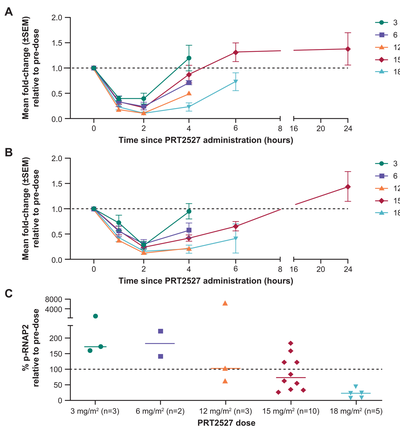


SEM, standard error of the mean.

Pharmacodynamics

- A dose-dependent downregulation of *MYC* and *MCL1* mRNA expression in PBMCs was observed (Figure 6A-B).
  - Maximum inhibition of CDK9 transcriptional targets – *MYC* and *MCL1* at doses ≥12 mg/m² – is consistent with the degree of target engagement required for preclinical efficacy.
- A dose-dependent inhibition of p-RNAP2 was observed in PBMCs at 15 and 18 mg/m² doses (Figure 6C).
  - Median decrease of 27.0% (n=10) at 15 mg/m²
  - Median decrease of 77.2% (n=5) at 18 mg/m²

Figure 6. PRT2527-Associated Inhibition of CDK9 Transcriptional Targets *MYC* (A), *MCL1* (B), and p-RNAP2 at 2 Hours (C) in PBMCs



In panels A, B, and C, the dotted line represents pre-dose baseline levels. In panel C, individual measurements are shown and the solid line represents the median value.

Conclusions

- In adults with advanced solid tumors, PRT2527 demonstrated favorable tolerability with manageable neutropenia and absence of significant gastrointestinal events or hepatotoxicity.
- The short half-life of PRT2527 enables acute CDK9 inhibition over a defined period.
- The observed dose-dependent downregulation of CDK9 transcriptional targets – *MYC* and *MCL1* mRNA expression in PBMCs isolated from patients treated with PRT2527 – was consistent with the degree of target engagement required for preclinical efficacy.
- As predicted by the preclinical model, 12 mg/m² QW dosing and higher showed optimal target inhibition.
- The overall safety profile observed in this study supports further development of PRT2527 in hematologic malignancies (NCT05665530).

References

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Acknowledgments

Funding support for PRT2527 was provided by Prelude Therapeutics.

We thank the patients and their caregivers for participating in PRT2527-01.

We thank the study investigators, coordinators, and healthcare staff at each study site.

We thank Megan Henry, an employee of Prelude Therapeutics, for contributions to the execution of PRT2527-01.

Medical writing and editorial support was provided by Russell Craddock, PhD, of Parexel, Uxbridge, UK, and was funded by Prelude Therapeutics.