A Phase 1, Open-Label, Dose-Escalation Study of PRT1419, a Selective Induced MCL-1 Inhibitor, in Patients With Advanced/Metastatic Solid Tumors

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Background

- Induced myeloid leukemia cell differentiation protein (MCL-1) is a member of the B-cell lymphoma-2 (BCL2) family of apoptosis regulators and plays a critical role in maintaining cellular homeostasis (Figure 1).[1]
- Due to the crucial role of MCL-1 in promoting cell survival, it is frequently found to be amplified or overexpressed in both solid tumors and hematologic cancers and increased expression of MCL-1 is associated with a higher grade and poor prognosis in a number of cancer types.[2]
- PRT1419 is a novel, potent, and selective MCL-1 inhibitor that has demonstrated anti-tumor efficacy in various preclinical models and is currently being investigated in a phase 1, open-label, dose-escalation study in patients with advanced/metastatic solid tumors (NCT04837677).[3,4]

Figure 1. MCL-1 Mechanism of Action

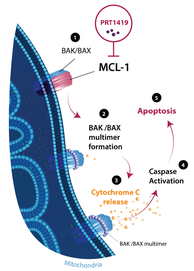


Figure reproduced with permission from Bhagwat N, et al.[3]
BAK, BCL2 antagonist/killer 1; BAX, BCL2 Associated X protein.

Objectives

- To establish the recommended phase 2 dose (RP2D) and evaluate the pharmacokinetic/pharmacodynamic profile, safety, and preliminary efficacy of PRT1419 in patients with advanced/metastatic solid tumors.

Key Findings

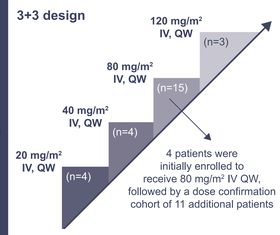
- In this phase 1, open-label, dose-escalation study, the MCL-1 inhibitor PRT1419 demonstrated acceptable safety and tolerability in patients with advanced/metastatic solid tumors.

Methods

- This is a multicenter, open-label, dose-escalation, phase 1 study of PRT1419 in patients with advanced/metastatic solid tumors (NCT04837677; Figure 2).
- Patients initially received a 30-min infusion for the 20 and 40 mg/m^2 dose levels followed by a 60-min infusion for the 80 and 120 mg/m^2 dose levels.
- Escalation occurred upon review of at least 3 patients safety data from Cycle 1 (28 days).
- PRT1419 dose increase was permitted up to 100% of the preceding dose for the first 3 dose escalations or until the initial dose-limiting toxicity (DLT), whichever occurred first; any escalations after this point were limited to a 50% increase from the preceding dose.
- Schedule, dose level, and infusion time for subsequent escalation was based on pharmacokinetic and pharmacodynamic data from the preceding dose levels.
- The primary endpoints of this analysis were to identify DLTs and to establish the maximum tolerated dose and RP2D of PRT1419.
- Secondary endpoints included evaluation of the safety, efficacy (per Response Evaluation Criteria in Solid Tumors v1.1), pharmacokinetic profile, and pharmacodynamic markers of PRT1419.
- The safety and efficacy analysis population included all patients who received at least 1 dose of PRT1419.
- All data are reported as descriptive analyses.

Figure 2. Study Design

Key inclusion criteria
- Adults (aged ≥18 years) with advanced/metastatic solid tumors who are relapsed or refractory, or who are intolerant to therapies with known benefit
- ECOG PS 0-2
- AST and ALT levels ≤3.0 × ULN (≤5 × ULN for patients with liver metastases)
- Total bilirubin <1.5 x ULN or direct bilirubin <1.5 × ULN if total bilirubin ≥1.5 × ULN
- Serum creatinine ≤1.5 × ULN or calculated creatinine clearance ≥50 mL/min
- LVEF ≥50% by echocardiogram or MUGA
- ANC >1.0 × 10/µL, platelet count >75,000/µL, and Hgb >9.0 g/dL within 14 days of treatment
- Absence of primary CNS malignancy or uncontrolled metastasis, active inflammatory disorders of the gastrointestinal tract, history of heart failure or risk of arrythmia, including mean QtCF of >480 ms



ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; Hgb, hemoglobin; IV, intravenous; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition scan; QW, once weekly; QtCF, QT interval corrected by Fridericia; ULN, upper limit of normal.

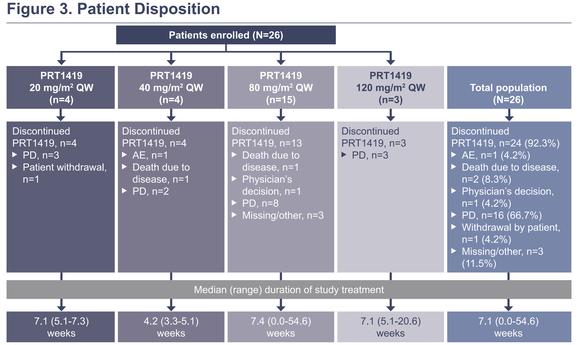
Results

- Patient baseline characteristics were generally well balanced between dose cohorts (Table 1).
- As of February 20, 2023, 92.3% of patients had discontinued PRT1419 (Figure 3).

Table 1. Patient Baseline Characteristics

Characteristic	PRT1419 20 mg/m^2 QW (n=4)	PRT1419 40 mg/m^2 QW (n=4)	PRT1419 80 mg/m^2 QW (n=15)	PRT1419 120 mg/m^2 QW (n=3)	Total (N=26)
Age, median (range), years	53 (51-59)	64 (47-77)	63 (32-77)	62 (55-78)	59.5 (32-78)
≥65 years, n (%)	0	2 (50.0)	6 (40.0)	1 (33.3)	9 (34.6)
Female, n (%)	2 (50.0)	1 (25.0)	10 (66.7)	3 (100.0)	16 (61.5)
ECOG PS at baseline, n (%)					
0	1 (25.0)	0	7 (46.7)	2 (66.7)	10 (38.5)
1	3 (75.0)	4 (100.0)	8 (53.3)	1 (33.3)	16 (61.5)
Lines of prior systemic therapies, median (range)	2.5 (2-6)	4.5 (1-8)	3 (1-8)	2 (1-5)	3 (1-8)
Tumor type, n (%)					
Cervical cancer	0	1 (25.0)	1 (6.7)	1 (33.3)	3 (11.5)
Esophageal cancer	1 (25.0)	1 (25.0)	2 (13.3)	0	4 (15.4)
Head and neck cancers	1 (25.0)	0	2 (13.3)	0	3 (11.5)
Melanoma	0	2 (50.0)	5 (33.3)	1 (33.3)	8 (30.8)
Non-small cell lung cancer	1 (25.0)	0	0	0	1 (3.9)
Sarcoma	1 (25.0)	0	3 (20.0)	1 (33.3)	5 (19.2)
Small cell lung cancer	0	0	1 (6.7)	0	1 (3.9)
Triple negative breast cancer	0	0	1 (6.7)	0	1 (3.9)

Figure 3. Patient Disposition



Primary reasons for discontinuation are presented. AE, adverse event.

Safety

- Any-grade treatment-emergent adverse events (TEAEs) occurred in 100.0% of patients (Table 2); the most common were diarrhea (65.4%), nausea (53.8%), and vomiting (53.8%; Table 3).
- Grade 3 TEAEs occurred in 46.2% of patients; the most common was neutropenia (11.5%).
  - In the 80 mg/m^2 QW cohort, 27% of patients had grade 1-3 neutropenia.
  - In the 120 mg/m^2 QW cohort, 1 patient had grade 3 neutropenia and 2 patients had grade 4 neutropenia; these were transient and did not meet the protocol DLT criteria, but the pattern suggested dose-relatedness.
  - Therefore, the 80 mg/m^2 QW dose was expanded to confirm tolerability.
- No DLTs, AEs of increased troponin or heart failure, serious treatment-related AEs (TRAEs), or grade 5 (fatal) TEAEs were observed.
- Cardiac safety was monitored with serial troponin levels, electrocardiograms, echocardiograms, and cardiac AEs. One patient had a single, asymptomatic elevation in troponin on Cycle 1 Day 8 that was not confirmed with repeat troponin testing and was not reproduced with subsequent dosing. This event was not considered clinically significant.

Table 2. Safety Summary

Events, n (%)	PRT1419 20 mg/m^2 QW (n=4)	PRT1419 40 mg/m^2 QW (n=4)	PRT1419 80 mg/m^2 QW (n=15)	PRT1419 120 mg/m^2 QW (n=3)	Total (N=26)
TEAE					
Any grade	4 (100.0)	4 (100.0)	15 (100.0)	3 (100.0)	26 (100.0)
Grade 3-4	1 (25.0)	3 (75.0)	6 (40.0)	2 (66.7)	12 (46.2)
Serious	0	2 (50.0)	5 (33.3)	1 (33.3)	8 (30.8)
Grade 5 (fatal)	0	0	0	0	0
Leading to study drug dose reduction	0	1 (25.0)	0	2 (66.7)	3 (11.5)
Leading to study drug interruption	0	1 (25.0)	8 (53.3)	2 (66.7)	11 (42.3)
Leading to study drug withdrawal	0	1 (25.0)	1 (6.7)	0	2 (7.7)
TRAEs					
Any grade	3 (75.0)	3 (75.0)	14 (93.3)	2 (66.7)	22 (84.6)
Grade 3-4	0	0	2 (13.3)	2 (66.7)	4 (15.4)
Serious	0	0	0	0	0

Table 3. Most Common AEs (in ≥15% of the Total Population)

Events, n (%)	PRT1419 20 mg/m^2 QW (n=4)	PRT1419 40 mg/m^2 QW (n=4)	PRT1419 80 mg/m^2 QW (n=15)	PRT1419 120 mg/m^2 QW (n=3)	Total (N=26)		
	Any grade	Any grade	Any grade	Any grade	Grade 1-2	Grade 3-4	Any grade
Any TEAE	4 (100.0)	4 (100.0)	15 (100.0)	3 (100.0)	14 (53.8)	12 (46.2)	26 (100.0)
Diarrhea	2 (50.0)	3 (75.0)	9 (60.0)	3 (100.0)	16 (61.5)	0	17 (65.4)
Nausea	0	3 (75.0)	8 (53.3)	3 (100.0)	14 (53.8)	0	14 (53.8)
Vomiting	1 (25.0)	3 (75.0)	9 (60.0)	1 (33.3)	13 (50.0)	1 (3.8)	14 (53.8)
Fatigue	1 (25.0)	1 (25.0)	4 (26.7)	2 (66.7)	7 (26.9)	1 (3.8)	8 (30.8)
Arthralgia	1 (25.0)	1 (25.0)	3 (20.0)	1 (33.3)	6 (23.1)	0	6 (23.1)
Constipation	1 (25.0)	0	4 (26.7)	2 (66.7)	7 (26.9)	0	7 (26.9)
Neutropenia	0	0	4 (26.7)	3 (100.0)	4 (15.4)	3 (11.5)	7 (26.9)
Injection site reaction	1 (25.0)	1 (25.0)	1 (6.7)	1 (33.3)	4 (15.4)	0	4 (15.4)
Any TRAE	3 (75.0)	3 (75.0)	14 (93.3)	2 (66.7)	18 (69.2)	4 (15.4)	22 (84.6)
Nausea	0	3 (75.0)	8 (53.3)	2 (66.7)	13 (50.0)	0	13 (50.0)
Diarrhea	2 (50.0)	3 (75.0)	6 (40.0)	1 (33.3)	12 (46.2)	0	12 (46.2)
Vomiting	1 (25.0)	2 (50.0)	8 (53.3)	1 (33.3)	12 (46.2)	0	12 (46.2)
Fatigue	0	0	2 (13.3)	2 (66.7)	3 (11.5)	1 (3.8)	4 (15.4)
Injection site reaction	1 (25.0)	1 (25.0)	1 (6.7)	1 (33.3)	4 (15.4)	0	4 (15.4)
Neutropenia	0	0	2 (13.3)	2 (66.7)	1 (3.8)	3 (11.5)	4 (15.4)

Pharmacodynamics/Pharmacokinetics

- Activation of BAX (Figure 4) and cleaved caspase 3 (data not shown) in peripheral blood monocytes was observed at 80 mg/m^2 QW and 120 mg/m^2 QW.
- At Week 3, mean clearance was 12.6 L/h and mean half-life was 2.5 hours; no PRT1419 accumulation was seen with QW dosing (Figure 5).

Efficacy

- Stable disease was the best response observed in 6 (23.1%) patients (Figure 6).
- Tumor shrinkage was seen in 1 patient with melanoma (a 10% reduction) and 1 patient with lung cancer (a 4% reduction) but did not meet the criteria for partial response (PR).

Figure 4. Target Engagement Was Demonstrated by BAX Activation (A) and a Decrease in Peripheral Blood Monocytes (B) at 80 and 120 mg/m^2 QW PRT1419

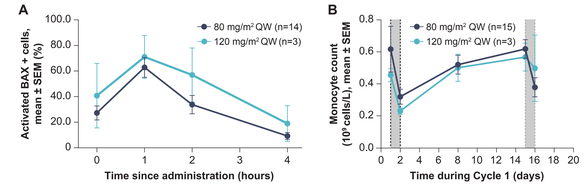
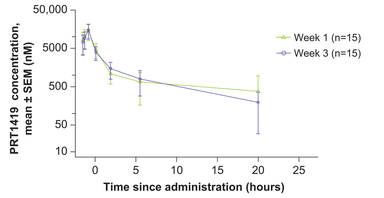
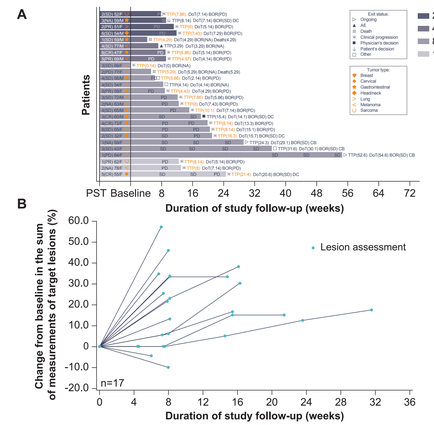


Figure 5. Pharmacokinetic profile of 80 mg/m^2 QW PRT1419



The data are representative of 10-15 patients depending upon the timepoint.

Figure 6. Duration of Study Treatment With Clinical Outcome (A) and Change From Baseline in the Sum of Measurements of Target Lesions (B)



Panel A: The text on the bars after baseline (stable disease [SD]/ progressive disease [PD]) indicate overall response assessed by the Investigator per the criteria corresponding to the underlying tumor type. The text (numbers) at the end of each line indicate the best overall response (BOR) assessed by the Investigator and the time to PD (orange colored text indicating a real event), respectively. The duration of treatment (DoT) was defined as the time interval from Day 1 to last dose date for discontinued patients and last clinical visit for ongoing patients.

Panel B: This plot only includes patients with a baseline and ≥1 post-baseline tumor assessment of target lesions.
CB, clinical benefit; CD, clinical benefit; CR, complete response; DC, disease control; NA, not applicable; PST, prior systemic therapy.

Conclusions

- PRT1419 demonstrated acceptable safety and tolerability in patients with advanced/metastatic solid tumors, with the most common TRAEs of nausea, and vomiting, and diarrhea.
  - Neutropenia was deemed to be dose related.
  - No cardiac toxicity was observed.
- Pharmacokinetics/pharmacodynamics and safety data in the 80 mg/m^2 QW PRT1419 dose cohort support further evaluation of this dose in future studies.
- Induction of activated-BAX and cleaved caspase-3 was observed at 80 and 120 mg/m^2 QW PRT1419, suggesting successful MCL-1 inhibition.
- No tumor reductions met response criteria.
- Further investigation of PRT1419 in patients with hematologic malignancy is ongoing (NCT05107856).

References
[1]Campbell KJ, et al. *Open Biol.* 2018;8:180002; [2]Beroukhim R, et al. *Nature.* 2010;463:899-905; [3]Bhagwat N, et al. *Cancer Res* 2021;81(13_Supplement):983; [4]Fuitang N, et al. *Cancer Res.* 2022;82(12_Supplement):420.

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