Preliminary Results of a Phase 1, Dose-Escalation Study of PRT2527, a Potent and Highly Selective CDK9 Inhibitor, as Monotherapy and in Combination With Zanubrutinib in Patients With Relapsed/Refractory Lymphoid Malignancies

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INTRODUCTION

- Cyclin-dependent kinase 9 (CDK9) is a key regulator of transcription elongation and is a potential target in transcriptionally addicted cancers that are dependent on oncogenic drivers with short half-lives, such as MYC, MYB, and MCL1
- PRT2527, an investigational, potent, and highly selective CDK9 inhibitor, is being evaluated in select relapsed/refractory (R/R) hematologic malignancies as monotherapy and in combination with zanubrutinib or venetoclax
- Zanubrutinib is a Bruton tyrosine kinase (BTK) inhibitor that upregulates BCL2-modifying factor (BMF), a proapoptotic molecule physiologically inhibited by BCL2, BCLXL, and BCLW.[1] The combination of CDK9 and BTK inhibition may lead to a synergistic effect by enhancing apoptotic priming and shifting dependency toward the CDK9 targets, MCL1 and BFL1[2,3]
- Here, we report the preliminary data from the phase 1 study of PRT2527 as monotherapy or in combination with zanubrutinib in patients with select R/R lymphoid malignancies (NCT05665530)

METHODS

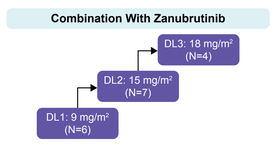
Figure 1. Study Design

Dose Escalation (BOIN)

Key Eligibility Criteria

- Histologically or cytologically confirmed select hematologic malignancies. Must meet one of the following:
  - Aggressive BCL subtypes
  - CLL/SLL (including Richter syndrome)
  - MCL
  - TCL (monotherapy only)
- R/R to SoC or be ineligible for SoC
- R/R disease following:
  - >1 prior systemic therapy for aggressive BCL subtypes, MCL, and Richter syndrome
  - At least 2 prior therapies including a BTKi and venetoclax for CLL

Monotherapy



Combination With Zanubrutinib

Objectives

Primary
- Safety, tolerability, and DLTs
- RP2D of PRT2527 monotherapy and in combination with zanubrutinib

Secondary/Exploratory
- ORR
- PK/PD

BCL, B-cell lymphoma; BOIN, Bayesian optimal interval design; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DL, dose level; DLT, dose-limiting toxicity; MCL, mantle cell lymphoma; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; SoC, standard of care; TCL, T-cell lymphoma.

Dosing and Administration

- Study treatment was given on a 21-day cycle
- PRT2527 was administered intravenously (IV) weekly
- Zanubrutinib was administered orally starting on C1D1 at 320 mg daily or 160 mg twice daily
- Dose-limiting toxicity (DLT) observation period was 21 days. Patients at high risk for tumor lysis syndrome may receive weekly ramp-up (DLT observation period of 35 days) or an accelerated ramp-up dosing of PRT2527 (DLT observation period of 28 days)

RESULTS

Patient Demographics and Baseline Disease Characteristics

- As of September 17, 2024, 46 patients with R/R lymphoid malignancies were treated with PRT2527; 29 patients were treated with PRT2527 monotherapy and 17 with PRT2527 and zanubrutinib combination therapy (**Table 1**)
- Median duration of treatment was 6.0 weeks (range: 1-30) for monotherapy and 7.3 weeks (range: 4-33) for combination therapy
- Treatment is ongoing in 7 (24%) patients in the monotherapy cohort and 9 (53%) patients in the combination cohort. The most common reason for discontinuation was disease progression (17 [59%] monotherapy; 8 [47%] combination therapy)

RESULTS *(Continued)*

Table 1. Patient Demographics and Baseline Disease Characteristics

Characteristics	PRT2527 (n=29)	PRT2527 + Zanubrutinib (n=17)	Total (N=46)
Median age (range), years	62 (27-94)	70 (56-86)	64 (27-94)
Male, n (%)	21 (72.4)	9 (52.9)	30 (65.2)
ECOG PS, n (%)			
0	14 (48.3)	6 (35.3)	20 (43.5)
1	14 (48.3)	11 (64.7)	25 (54.3)
2	1 (3.4)	0	1 (2.2)
Diagnosis, n (%)			
DLBCL NOS	12 (41.4)	8 (47.1)	20 (43.5)
HGBCL[a]	0	4 (23.5)	4 (8.7)
Richter syndrome	2 (6.9)	0	2 (4.3)
CLL	1 (3.4)	2 (11.8)	3 (6.5)
MCL	0	3 (17.6)	3 (6.5)
TCL[b]	14 (48.3)	0	14 (30.4)
Median prior lines of therapy (range)	4 (1-7)	3 (1-6)	3.5 (1-7)
Prior CAR-T, n (%)	9 (31.0)	5 (29.4)	14 (30.4)
Prior TCE, n (%)	9 (31.0)	8 (47.1)	17 (37.0)

[a] Includes 3 patients with HGBCL with *BCL2/MYC* rearrangements and 1 patient with HGBCL NOS. [b] Includes 9 patients with PTCL-NOS, 2 patients with AITL, 2 patients with ALCL, and 1 patient with PCPTCL.
AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; CAR-T, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBCL, high-grade B-cell lymphoma; MCL, mantle cell lymphoma; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; PCPTCL, primary cutaneous peripheral T-cell lymphoma; TCE, T-cell engager; TCL, T-cell lymphoma.

Table 2. Baseline Disease Characteristics for Aggressive BCL

Characteristics	PRT2527 (n=14)	PRT2527 + Zanubrutinib (n=12)	Total (N=26)
Cell of origin for DLBCL,[a] n (%)			
GCB	2 (14.3)	4 (33.3)	6 (23.1)
Non-GCB	8 (57.1)	8 (66.7)	16 (61.5)
Unknown/not done	4 (28.5)	0	4 (15.3)
Molecular subtype for DLBCL,[a] n (%)			
Double expressor (*BCL2, MYC*)	8 (57.1)	1 (8.3)	9 (34.6)
DLBCL/HGBL with rearrangements of *MYC* and *BCL2*	1 (7.1)	4 (33.3)	5 (19.2)
Unknown/not done	5 (35.7)	7 (58.3)	12 (46.1)

[a] Includes DLBCL NOS, HGBCL, and patients with Richter syndrome.
BCL, B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; HGBCL, high-grade B-cell lymphoma; NOS, not otherwise specified.

Safety

- The most frequent treatment-emergent adverse events (TEAEs) observed in ≥20% of patients were neutropenia (48%) and nausea (33%), and the most frequent grade ≥3 TEAEs (≥10% of patients) were neutropenia (46%) and anemia (11%) (**Table 3**)
- Five patients discontinued treatment due to TEAEs in the monotherapy cohort; 3 TEAEs in 1 patient were treatment related: grade 3 hypotension, grade 3 diarrhea, and grade 4 neutropenia (n=1 each). No TEAEs led to treatment discontinuation in the combination therapy cohort
- PRT2527 dose interruptions due to TEAEs occurred in 17 patients (11 monotherapy; 6 combination therapy). Most dose interruptions were due to neutropenia and were managed with growth factor support
- One DLT of grade 3 TLS occurred in a patient with primary cutaneous peripheral T-cell lymphoma who had extensive disease at the 24 mg/m² monotherapy dose level and did not receive ramp-up dosing. TLS was managed with rasburicase and IV fluids and resolved. Patient was able to resume study treatment as planned. No DLTs were observed in the combination therapy cohort
- Dose level 3 (18 mg/m²) was selected for dose confirmation for monotherapy and in combination with zanubrutinib due to higher rates of grade 3/4 neutropenia and of dose interruption and reductions in the 24 mg/m² dose level

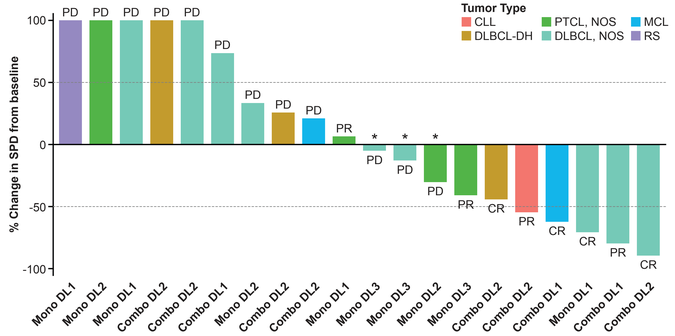
Table 3. TEAEs of ≥10% by Preferred Term

Preferred Term, n (%)	PRT2527 (n=29)		PRT2527 + Zanubrutinib (n=17)		Total (N=46)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAEs	27 (93)	21 (72)	15 (88)	11 (65)	42 (91)	32 (70)
Neutropenia	14 (48)	14 (48)	8 (47)	7 (41)	22 (48)	21 (46)
Nausea	12 (41)	0	3 (18)	0	15 (33)	0
Anemia	7 (24)	3 (10)	2 (12)	2 (12)	9 (20)	5 (11)
Diarrhea	5 (17)	1 (3)	3 (18)	0	8 (17)	1 (2)
Pyrexia	4 (14)	0	3 (18)	0	7 (15)	0
Constipation	4 (14)	0	2 (12)	0	6 (13)	0
Asthenia	2 (7)	0	3 (18)	1 (6)	5 (11)	1 (2)
Fatigue	3 (10)	0	2 (12)	0	5 (11)	0
Hypokalemia	2 (7)	0	3 (18)	0	5 (11)	0
Thrombocytopenia	2 (7)	2 (7)	3 (18)	2 (12)	5 (11)	4 (9)
Vomiting	2 (7)	0	3 (18)	0	5 (11)	0

TEAE, treatment-emergent adverse event.

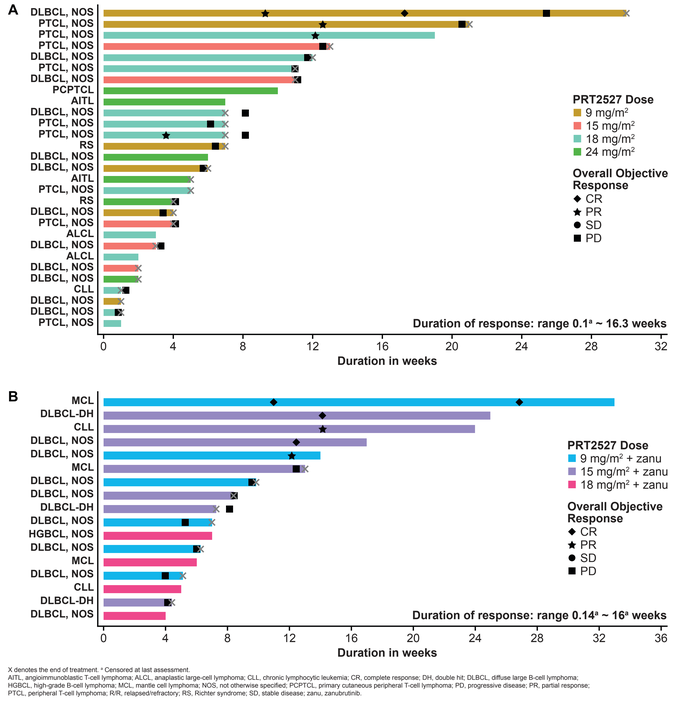
Preliminary Efficacy

Figure 2. Change in Tumor Burden With PRT2527 Monotherapy and Combination With Zanubrutinib



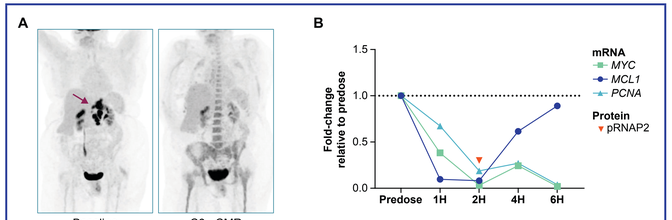
Waterfall plot includes efficacy-evaluable patients who had baseline and ≥1 postbaseline tumor assessment of target lesions. Percent increase >100 is capped at 100%.
* PD determined by appearance of new lesions and/or PET imaging.
CLL, chronic lymphocytic leukemia; combo, combination therapy; CR, complete response; DH, double hit; DL, dose level; DLBCL, diffuse large B-cell lymphoma; mono, monotherapy; MCL, mantle cell lymphoma; NOS, not otherwise specified; PD, progressive disease; PET, positron emission tomography; PR, partial response; PTCL, peripheral T-cell lymphoma; RS, Richter syndrome; SPD, sum of product diameters.

Figure 3. Duration of Treatment With (A) PRT2527 Monotherapy and (B) in Combination With Zanubrutinib in Patients With R/R Lymphoid Malignancies



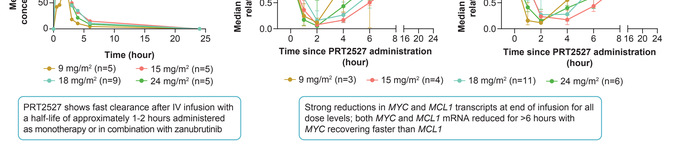
X denotes the end of treatment. ª Censored at last assessment.
AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; CLL, chronic lymphocytic leukemia; CR, complete response; DH, double hit; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; MCL, mantle cell lymphoma; NOS, not otherwise specified; PCPTCL, primary cutaneous peripheral T-cell lymphoma; PD, progressive disease; PR, partial response; PTCL, peripheral T-cell lymphoma; R/R, relapsed/refractory; RS, Richter syndrome; SD, stable disease; zanu, zanubrutinib.

Figure 4. Patient Case Study – R/R DLBCL With Prior CAR-T Therapy and Mutated *MYD88*, *CD79B*, and *CDKN2A*



Case study: (**A**) 60-year-old female with R/R DLBCL (non-GCB, double expressor) who received 4 lines of prior therapy, including CAR-T therapy. Patient was enrolled to monotherapy dose level 1 (9 mg/m²) and achieved a CMR. (**B**) The patient's PBMCs demonstrated a significant decrease in *MCL1* (92%), *MYC* (97%), *PCNA* (82%), and pRNAP2 at end of infusion (2 hours), with prolonged transcriptional inhibition of *MYC* and *PCNA* for >6 hours.
CAR-T, chimeric antigen receptor T-cell; CMR, complete metabolic response; DLBCL, diffuse large B-cell lymphoma; GBC, germinal center B-cell; H, hour; PBMC, peripheral blood mononuclear cell; PD, progressive disease; R/R, relapsed/refractory.

Figure 5. (A) PRT2527 Pharmacokinetics and Transcriptional Inhibition of CDK9 Targets (B) *MYC* and (C) *MCL1* in PBMCs



PRT2527 shows fast clearance after IV infusion with a half-life of approximately 1-2 hours administered as monotherapy or in combination with zanubrutinib

Strong reductions in *MYC* and *MCL1* transcripts at end of infusion for all dose levels; both *MYC* and *MCL1* mRNA reduced for >6 hours with *MYC* recovering faster than *MCL1*

CDK9, cyclin-dependent kinase 9; IQR, interquartile range; PBMC, peripheral blood mononuclear cell.

CONCLUSIONS

- PRT2527 demonstrated activity and acceptable safety profile as monotherapy and in combination with zanubrutinib across a range of R/R lymphoid malignancies, including patients who received prior CAR-T therapy
- The most common treatment-related adverse event was neutropenia, which was managed with growth factor support. Gastrointestinal side effects were managed with supportive care. No liver function abnormalities were observed
- One DLT (grade 3 TLS) was observed in the monotherapy dose-escalation cohort at the 24 mg/m² dose
  - No other clinical TLS events were observed, including patients who received ramp-up dosing of PRT2527
  - No DLTs occurred in the combination therapy dose-escalation cohorts
- PRT2527 shows fast clearance and has a short half-life of approximately 1 to 2 hours when given as monotherapy or in combination with zanubrutinib
- Transcriptional inhibition of *MYC* and *MCL1* demonstrates target engagement
- Data support further evaluation of PRT2527 at 18 mg/m² as monotherapy in peripheral T-cell lymphoma and in combination with zanubrutinib in aggressive B-cell lymphomas
- Dose escalation of PRT2527 as monotherapy and in combination with venetoclax in patients with myeloid malignancies is ongoing

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