A Phase 1 Study of PRT2527, a Selective CDK9 Inhibitor, as Monotherapy and in Combination With Zanubrutinib in Relapsed/Refractory Lymphoid Malignancies: Updated Analysis

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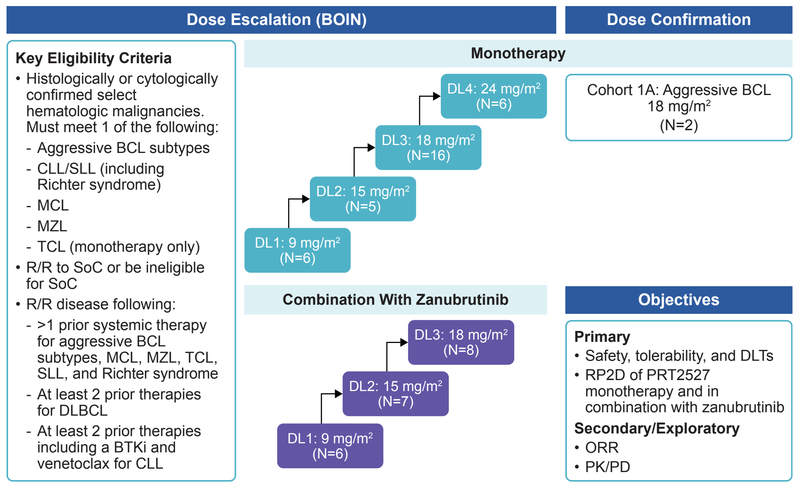
INTRODUCTION

- 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 updated analysis 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



BCL, B-cell lymphoma; BOIN, Bayesian optimal interval design; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DL, dose level; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; 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 cycle 1 day 1 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 (TLS) 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 April 28, 2025, 56 patients with R/R lymphoid malignancies were treated with PRT2527; 35 patients were treated with PRT2527 monotherapy and 21 with PRT2527 and zanubrutinib combination therapy (**Table 1**)
- Median duration of treatment was 6.0 weeks (range: 1-51) for monotherapy and 15 weeks (range: 4-57) for combination therapy
- Treatment is ongoing in 1 patient (3%) in the monotherapy cohort and 6 patients (29%) in the combination cohort. The most common reason for discontinuation was disease progression (25 [71%] monotherapy; 14 [67%] combination therapy) and adverse events (5 [14%] monotherapy; 0 combination therapy)

Table 1. Patient Demographics and Baseline Disease Characteristics

Characteristics	PRT2527 (n=35)	PRT2527 + Zanubrutinib (n=21)	Total (N=56)
Median age (range), years	62 (27-94)	70 (37-86)	64 (27-94)
Male, n (%)	23 (66)	10 (48)	33 (59)
ECOG PS, n (%)			
0	18 (51)	8 (38)	26 (46)
1	16 (46)	13 (62)	29 (52)
2	1 (3)	0	1 (2)
Diagnosis, n (%)			
DLBCL NOS	12 (34)	8 (38)	20 (36)
HGBCL[a]	0	4 (19)	4 (7)
Richter syndrome	2 (6)	0	2 (4)
CLL	1 (3)	2 (10)	3 (5)
SLL	0	1 (5)	1 (2)
MCL	0	6 (29)	6 (11)
TCL[b]	20 (57)	0	20 (36)
Median prior lines of therapy (range)	3 (1-7)	4 (1-6)	3 (1-7)
Prior CAR T therapy, n (%)	9 (26)	5 (24)	14 (25)
Prior TCE, n (%)	9 (26)	8 (38)	17 (30)

[a] Includes 3 patients with HGBCL with *BCL2/MYC* rearrangements and 1 patient with HGBCL NOS. [b] Includes 12 patients with PTCL-NOS, 5 patients with nodal TFH TCL, 2 patients with ALCL, and 1 patient with PCPTCL.
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; PCPTCL, primary cutaneous peripheral T-cell lymphoma; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma; TCE, T-cell engager; TCL, T-cell lymphoma; TFH, follicular T-cell helper 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)	4 (33)	6 (23)
Non-GCB	8 (57)	8 (67)	16 (62)
Unknown/test not performed	4 (29)	0	4 (15)
Molecular subtype for DLBCL,[a] n (%)			
Double expressor (*BCL2, MYC*)	8 (57)	1 (8)	9 (35)
DLBCL/HGBCL with rearrangements of *MYC* and *BCL2*	1 (7)	4 (33)	5 (19)
No rearrangements of *MYC* and *BCL2*	0	1 (8)	1 (4)
Unknown/test not performed	5 (36)	6 (50)	11 (42)

[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.

RESULTS *(Continued)*

Safety

- The most frequent treatment-emergent adverse events (TEAEs) observed in ≥20% of patients were neutropenia (46%), nausea (38%), and anemia (21%), and the most frequent grade ≥3 TEAEs (≥10% of patients) were neutropenia (45%) 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 27 patients (18 monotherapy; 9 combination therapy). Most dose interruptions were due to neutropenia and 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

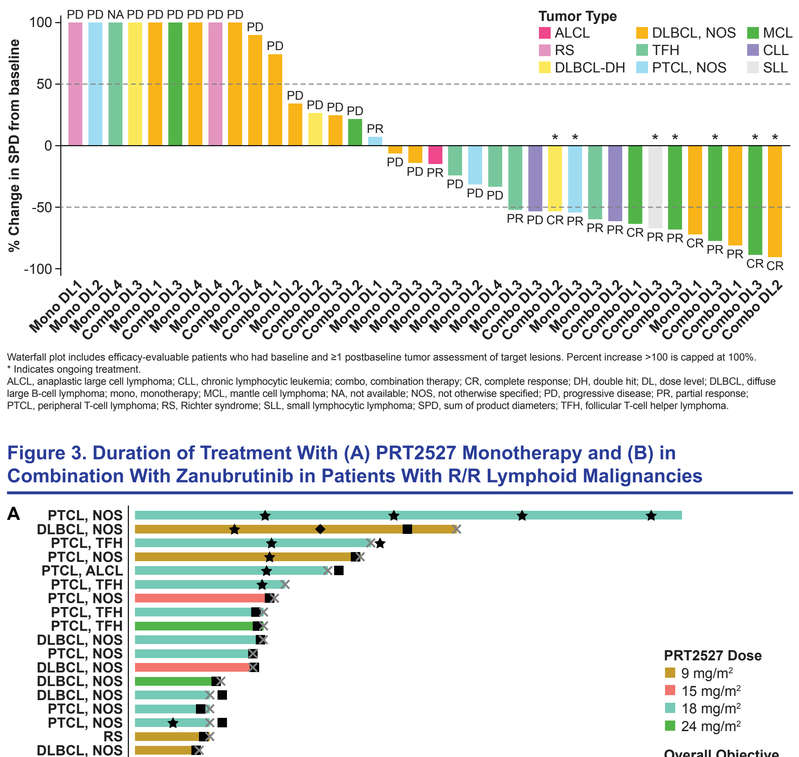
Table 3. TEAEs of ≥10% by Preferred Term

Preferred Term, n (%)	PRT2527 (n=35) Any Grade	PRT2527 (n=35) Grade ≥3	PRT2527 + Zanubrutinib (n=21) Any Grade	PRT2527 + Zanubrutinib (n=21) Grade ≥3	Total (N=56) Any Grade	Total (N=56) Grade ≥3
Any TEAEs	35 (100)	27 (77)	20 (95)	15 (71)	55 (98)	42 (75)
Neutropenia	15 (43)	15 (43)	11 (52)	10 (48)	26 (46)	25 (45)
Nausea	17 (49)	0	4 (19)	0	21 (38)	0
Anemia	8 (23)	2 (6)	4 (19)	4 (19)	12 (21)	6 (11)
Diarrhea	5 (14)	1 (3)	4 (19)	0	9 (16)	1 (2)
Constipation	6 (17)	0	2 (10)	0	8 (14)	0
Pyrexia	5 (14)	0	3 (14)	0	8 (14)	0
Vomiting	5 (14)	0	3 (14)	0	8 (14)	0
Thrombocytopenia	4 (11)	3 (9)	3 (14)	2 (10)	7 (13)	5 (9)
Asthenia	3 (9)	0	3 (14)	1 (5)	6 (11)	1 (2)
COVID-19	4 (11)	1 (3)	2 (10)	0	6 (11)	1 (2)
Fatigue	4 (11)	1 (3)	2 (10)	0	6 (11)	1 (2)

TEAE, treatment-emergent adverse event.

Efficacy

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

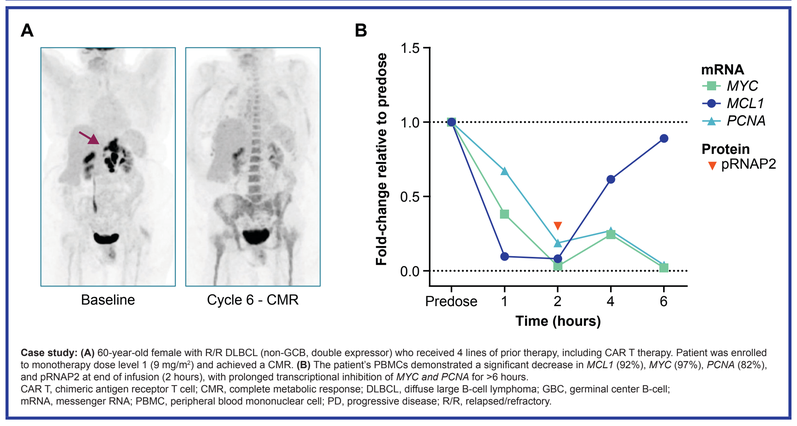


Waterfall plot includes efficacy-evaluable patients who had baseline and ≥1 postbaseline tumor assessment of target lesions. Percent increase >100 is capped at 100%.
* Indicates ongoing treatment.
ALCL, anaplastic large cell lymphoma; CLL, chronic lymphocytic leukemia; combo, combination therapy; CR, complete response; DH, double hit; DL, dose level; DLBCL, diffuse large B-cell lymphoma; mono, monotherapy; MCL, mantle cell lymphoma; NA, not available; NOS, not otherwise specified; PD, progressive disease; PR, partial response; PTCL, peripheral T-cell lymphoma; RS, Richter syndrome; SLL, small lymphocytic lymphoma; SPD, sum of product diameters; TFH, follicular T-cell helper lymphoma.

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

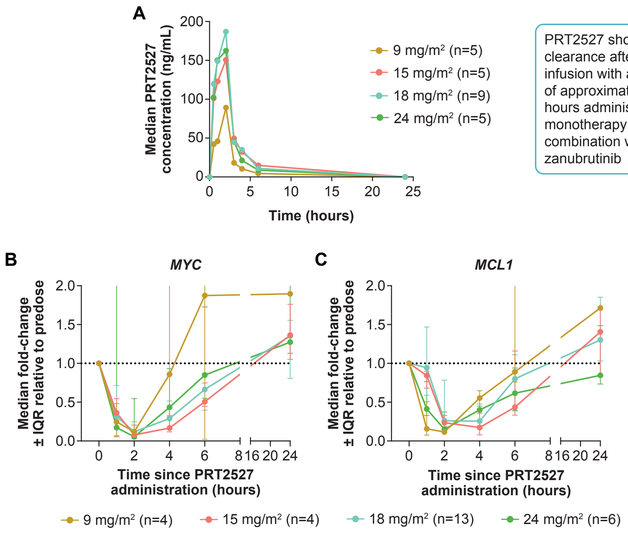
X denotes the end of treatment.
[a] Censored at last assessment.
ALCL, anaplastic large-cell lymphoma; CLL, chronic lymphocytic leukemia; CR, complete response; DH, double hit; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; NOS, not otherwise specified; PCPTCL, primary cutaneous peripheral T-cell lymphoma; PD, progressive disease; PR, partial response; PTCL, peripheral T-cell lymphoma; R/R, relapsed/refractory; RS, Richter syndrome; SD, stable disease; SLL, small lymphocytic lymphoma; TFH, follicular T-cell helper lymphoma; 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; mRNA, messenger RNA; 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; IV, intravenous; mRNA, messenger RNA; 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
- 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 in patients who received ramp-up dosing of PRT2527
  - No DLTs occurred in the combination therapy dose-escalation cohorts
- PRT2527 showed fast clearance and had 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* demonstrated 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

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