A Phase 1 Dose Escalation Study of Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor PRT543 in Patients With Myeloid Malignancies

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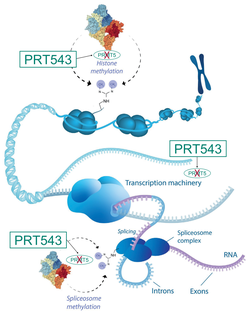
Background and Objectives

- PRMT5 catalyzes symmetric arginine dimethylation of protein substrates that play important roles in the cell cycle, including histone modification, transcription, and spliceosome assembly, and is overexpressed in a variety of cancers[1]
  - Notably, specific splicing mutations confer poor prognosis in myeloid malignancies[2]
- PRT543 is a potent, selective, oral inhibitor of PRMT5[3]
- An open-label phase 1 dose escalation study of PRT543 was conducted in unselected patients with myeloid malignancies (NCT03886831)
- The key objectives of this study were to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary clinical signals and to determine the recommended expansion dose



Study Design

- This was an open-label phase 1 study of 23 unselected patients with relapsed/refractory myelofibrosis (MF, n=12) or myelodysplastic syndrome (MDS, n=11) (Fig. 1)

Figure 1. Dose Escalation in Patients With Relapsed/Refractory MF or MDS[a]

[a]Dosing in 28-day cycles for all patients. Accelerated 3+3 design. [b]Dosing at 5, 10, 20, and 40 mg BIW.
Data cutoff October 1, 2021.
BIW, 2 times a week; QD, once daily; TIW, 3 times a week.

Results

Table 1. Demographics

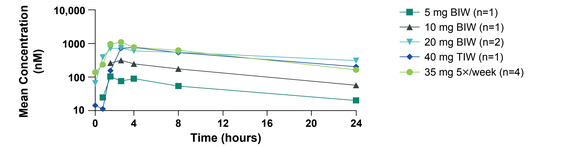
	MF (n=12)	MDS (n=11)
Age, years, median (range)	71 (61-78)	75 (68-84)
Female, n (%)	6 (50)	2 (18)
ECOG PS, n (%)		
0	3 (25)	0
1	9 (75)	10 (91)
2	0	1 (9)
Race, n (%)		
White or Caucasian	11 (92)	11 (100)
Other	1 (8)	0
IPSS-MF risk,[a] n (%)		
Intermediate 2	2 (20)	--
Not applicable	8 (80)	--
IPSS-MDS risk, n (%)		
High	--	3 (27)
Intermediate 1	--	4 (36)
Intermediate 2	--	2 (18)
Low	--	1 (9)
Not applicable	--	1 (9)
Platelet count (10^3/µL), median (range)	177 (33-655)	52 (14-359)
Hemoglobin (g/L), median (range)	92 (59-131)	80 (68-117)
Spleen[b] (cm below costal margin), median (range)	17 (10-20)	--
Prior lines of systemic therapy, median (range)	2 (0-6)	2 (0-6)
Prior ruxolitinib, n (%)	10 (83)	--
Splicing factor mutation–positive,[c] n (%)	5 (42)	6 (55)
JAK2 V167F mutation–positive, n (%)	10 (83)	--

[a]Data not available for 2 patients. [b]n=7. [c]Mutations were in (n=3 MF; 2 MDS), SRSF2 (n=1 MF; 3 MDS), U2AF1 (n=1 MF), and ZRSR2 (n=1 MDS). Splicing factor mutation status unevaluable for 3 MF patients.
ECOG PS, Eastern Cooperative Oncology Group performance status; IPSS, International Prognostic Scoring System.

Pharmacokinetics

- At the recommended expansion dose (35 mg 5×/week), half-life ($t_{½}$) was 10 hours, and plasma drug exposures, ie, maximum observed plasma concentration (C_{max}) and area under the curve (AUC), were 1480 nM and 15,557 nM.hr, respectively (Fig. 2)

Figure 2. Dose-dependent Increases in C_{max} and AUC[a]



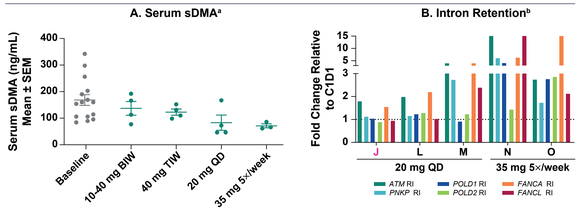
	5 mg BIW	10 mg BIW	20 mg BIW	40 mg TIW	35 mg 5×/week
C_{max}, nM	114	345	808 (4)	841	1480 (5)
AUC, nM.hr	1231	3763	12,522 (18)	11,045	15,557 (37)
$t_{½}$, hours	10	10	20	N/A	10 (45)

[a]Data are from C1D25 and are considered steady state. Data are not available for patients treated with 40 mg BIW or 20 mg QD. Values in parentheses in the table are coefficient of variation (CV%). C, cycle; D, day; N/A, not applicable.

Pharmacodynamics

- PRT543 exhibited dose-dependent reduction of serum symmetric dimethylarginine (sDMA), a marker of PRMT5 target engagement, with a 58% decrease at the recommended expansion dose of 35 mg 5×/week (Fig. 3A)
- PRT543 decreased PRMT5 functional activity in peripheral blood mononuclear cells (PBMCs) at the recommended expansion dose of 35 mg 5×/week (Fig. 3B), as demonstrated by increased intron retention of transcripts known to be regulated by PRMT5

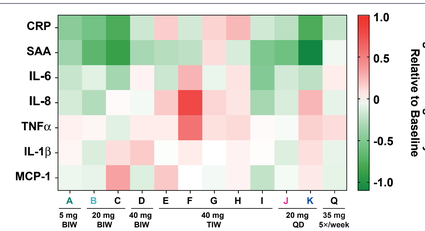
Figure 3. Confirmation of Target Engagement and Reduction in PRMT5 Functional Activity



[a]Serum sDMA was measured on C1D25 in 35 mg 5×/week and all BIW dose groups, and on C1D15 in 40 mg TIW and 20 mg QD dose groups. In BIW and TIW schedules, samples were not collected at steady state; n=15.
[b]Expression of retained introns known to be regulated by PRMT5 was evaluated in PBMCs on C1D25 for 35 mg 5×/week and on C2D1 for 20 mg QD. All are patients with MDS, except Patient J with MF. RI, retained intron.

- Reductions in inflammatory serum markers and cytokines were observed in MF patients (Fig. 4)

Figure 4. Reductions in Inflammatory Serum Markers and Cytokines in MF Patients



Assessments on C2D1.
CRP, C-reactive protein, IL, interleukin; MCP, monocyte chemoattractant protein; SAA, serum amyloid A; TNF, tumor necrosis factor.

Safety

- Three of 23 patients (13%) had a single occurrence of dose-limiting thrombocytopenia (1 each at 40 mg TIW, 35 mg 5×/week, and 20 mg QD)
- Eighteen patients discontinued treatment, primarily because of disease progression or investigator decision. One patient (35 mg 5×/week) discontinued due to an adverse event (performance status decreased/weakness)
- No treatment-related deaths were reported
- Grade ≥3 treatment-related adverse events of anemia and thrombocytopenia (Table 2) were reversible with dose modification

Table 2. Most Common Treatment-Related Adverse Events of Any Grade Occurring in ≥5% of Patients

	All Patients (N=23)		Recommended Expansion Dose 35 mg 5×/week (n=5)	
Adverse Event, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with events	14 (61)	6 (26)	2 (40)	1 (20)
Thrombocytopenia	5 (22)	4 (17)	1 (20)	1 (20)
Nausea	5 (22)	0	1 (20)	0
Anemia	4 (17)	4 (17)	0	0
Diarrhea	4 (17)	0	0	0
Fatigue	3 (13)	0	0	0
Bone pain	2 (9)	0	0	0

Preliminary Clinical Activity

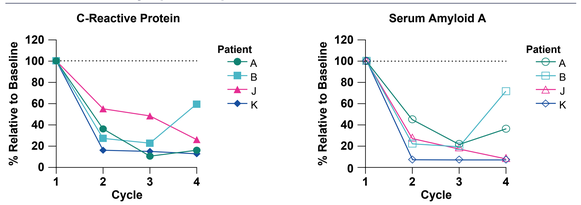
- Early signals of clinical activity were detected in 5 of 23 patients (Table 3) across assessments that included:
  - International Working Group (IWG) response (n=3/23; Table 3);
  - investigator-reported symptom response with concomitant improvements in inflammatory serum markers (n=3/23; Fig. 5);
  - sustained increases in hemoglobin with reductions in transfusion frequency (n=3/23; Fig. 6); and
  - improvement in bone marrow reticulin fibrosis (n=1/23; Fig. 7)

Table 3. Patients With IWG Response and/or Symptom Improvement

Patient	Initial PRT543 Dose[a]	Time on Treatment (Days)[b]	Splicing Factor Mutation	Prior Ruxolitinib (Years)	Best IWG Response	Symptom Improvement[d]
A (MF)	5 mg BIW	382 PD	No	1.5	Anemia response[4]	Yes C4
B (MF)	20 mg BIW	704 PD	No	4.0	None	Yes C4
J (MF)	20 mg QD	141 Other[c]	SRSF2 P95L	1.0	None	Yes C2 + C4
K (MF)	20 mg QD	365+ SD	SF3B1 K700E	0	Anemia response[4]	Yes C3 to C13
P (MDS)	35 mg 5×/week	188+ PD	SRSF2 P95L	N/A	Hematologic improvement-erythropoietic[5]	N/A

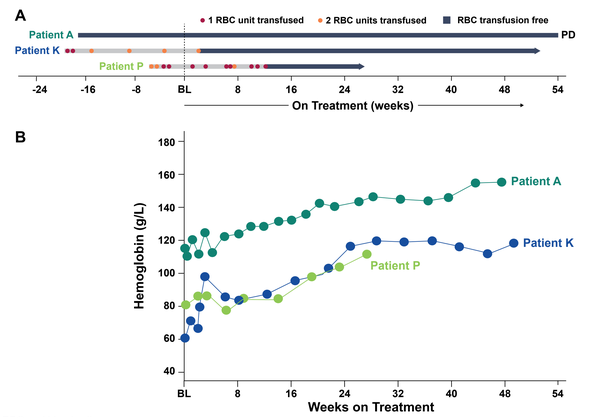
[a]Modification of initial dose occurred in all 5 patients (dosing range, 5 mg BIW to 20 mg QD). [b]Response at data cutoff on October 1, 2021. [c]Patient underwent off-study allogeneic transplant. [d]Per investigator assessment.
PD, progressive disease; SD, stable disease; +, ongoing.

Figure 5. Concomitant Reductions in Inflammatory Serum Markers in Patients With Symptom Improvement[a]



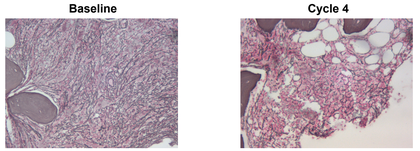
[a]Baseline assessments on C1D25.

Figure 6. Reduction in Transfusion Frequency (A) and Sustained Increase in Hemoglobin (B) in Patients A, K, and P



RBC, red blood cell.

Figure 7. Improvement in Bone Marrow Reticulin Fibrosis (+2-3 to +1-2) in Patient B



Conclusions

- PRT543 was well tolerated with a favorable safety profile
- Dose-dependent inhibition of PRMT5 target engagement and functional activity were observed
- Preliminary signals of clinical activity, including hematological responses and symptomatic improvements with concomitant reductions in serum inflammatory makers, were noted
- 35 mg 5×/week was determined to be the recommended expansion dose, and the expansion phase of the study is ongoing (NCT03886831)

References

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