Phase Ib Study of PRT543, an Oral Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor, In Patients With Relapsed or Refractory, Splicing Factor-Mutant Myeloid Malignancies

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INTRODUCTION

- Mutations in RNA splicing factors (SF) are common in MDS and secondary AML but there are currently no targeted therapies.[1]
- PRMT5 catalyzes symmetrical dimethylation of arginines, a post-translational modification required for normal RNA splicing. Pre-clinical studies identified synthetic lethality between PRMT5 inhibition and SF-mutant myeloid malignancies.[2]
- The oral PRMT5 inhibitor PRT543 is safe at a dose of 35 mg 5x/week.[3] As responses were seen primarily in pts with SF mutations, we performed a multicenter, open-label phase Ib study of PRT543 monotherapy in pts with R/R, SF-mutant MDS, AML and MDS/MPN overlap (NCT03886831).

AIM

- To evaluate the safety and efficacy of PRT543 monotherapy in pts with R/R, SF-mutant myeloid malignancy
- To analyze the *in vivo* effect of PRT543 on splicing in patient samples

METHOD

- Phase Ib dose-escalation/expansion trial of pts with SF-mutant, R/R MDS, AML and MDS/MPN overlap syndromes.
- The primary endpoint was the best overall response rate (composite of CR, PR, mCR, and HI per IWG 2006 criteria for MDS and MDS/MPN pts or composite of CR, CRi, PR, and MLFS per ELN 2017 criteria for AML pts).
- Secondary endpoints included duration of response, PFS, and overall survival (OS).
- Correlative studies analyzing symmetric dimethyl arginine (SDMA) abundance and differential gene expression and RNA splicing from RNA-seq were performed in peripheral blood at baseline and C1D25.

RESULTS

40 pts (19 lower-risk MDS, 10 higher-risk MDS, 7 AML, and 4 MDS/MPN) enrolled with most common SF mutations being *SF3B1* (n=13; 31.0%), *U2AF1* (12; 30.0%), and *SRSF2* (8; 20.0%).

Table 1. Baseline patient and disease characteristics

Variable	Total cohort (n = 40)	MDS and MDS/MPN overlap (n = 33)	AML (n = 7)
Age (median; range)	74 years (46 – 84)	74 years (59 - 84)	66 years (46 – 80)
Male sex (n; %)	27 (67.5%)	22 (66.7%)	5 (71.4%)
Lines of prior therapy (n; %)			
-- 0	2 (5.0%)	1 (3.0%)	1 (14.3%)
-- 1	7 (17.5%)	7 (21.2%)	0
-- 2	11 (27.5%)	10 (30.3%)	1 (14.3%)
-- ≥3	20 (50.0%)	15 (42.3%)	5 (71.4%)
Prior allogeneic hematopoietic stem cell transplant (n; %)	4 (9.5%)	1 (2.9%)	3 (42.9%)
IPSS-R (n; %)			
-- very low	1 (2.5%)	1 (2.9%)	
-- low	8 (20.0%)	8 (22.9%)	
-- intermediate	10 (25.0%)	10 (28.6%)	
-- high	5 (12.5%)	5 (14.3%)	
-- very high	7 (17.5%)	7 (20.0%)	
-- Unknown/not available	3 (7.5%)	3 (8.6%)	N/A
ELN 2017 AML risk category (n; %)	0		0
-- favorable	1 (2.5%)		1 (14.3%)
-- intermediate	5 (12.5%)		5 (71.4%)
-- adverse	1 (2.5%)	N/A	1 (14.3%)
-- Unknown/not available			
Baseline molecular abnormalities (n; %)			
-- *SF3B1*	13 (32.5%)	11 (33.3%)	2 (28.6%)
-- *SRSF2*	8 (20.0%)	6 (18.2%)	2 (28.6%)
-- *U2AF1*	12 (30.0%)	9 (27.3%)	3 (42.9%)
-- *ZRSR2*	2 (5.0%)	2 (6.1%)	0
-- *EIF1AX*	0	0	0
-- *TP53*	5 (12.5%)	4 (12.1%)	1 (14.3%)
-- *RUNX1*	4 (10.0%)	2 (6.1%)	2 (28.6%)
-- *ASXL1*	13 (32.5%)	11 (33.3%)	2 (28.6%)
-- *IDH1*	2 (5.0%)	2 (6.1%)	0
-- *IDH2*	2 (5.0%)	1 (3.0%)	1 (14.3%)
-- *FLT3*	1 (2.5%)	1 (3.0%)	0
-- *NPM1*	0	0	0
-- *TET2*	12 (30.0%)	10 (30.3%)	2 (28.6%)
-- *KRAS/NRAS*	9 (22.5%)	6 (18.2%)	3 (42.9%)
-- *ETV6*	8 (20.0%)	7 (21.2%)	1 (14.3%)
-- *DNMT3A*	4 (10.0%)	4 (12.1%)	0

- Median duration of treatment with PRT543 was 3.6 months (R: 0.4 – 17.6 months). Best response:
  - MDS and MDS/MPN pts: mCR in 1 pt (3.0%) and HI in 3 pts (9.1%; 2 HI-erythroid and 1 trilineage HI).
  - AML: 1 CRi (14.3%), 1 SD with platelet transfusion independence from a baseline of requiring 9 units of platelets over 8 weeks
  - All patients with HI and the AML patients with CRi and platelet transfusion independence had mutations in *SRSF2* or *U2AF1*
- 6-month survival rates were 89% (95% CI: 69-97%) for MDS pts and 69% (95% CI: 21-91%) for AML pts.

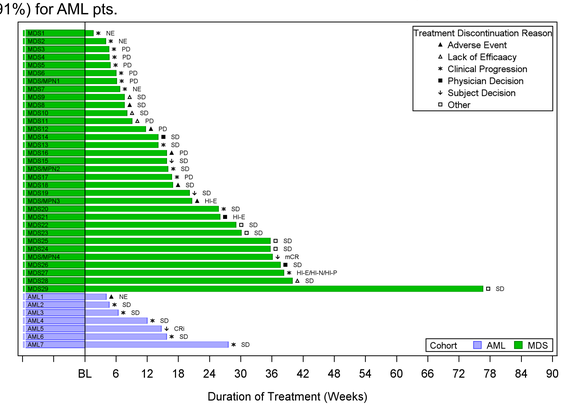

Figure 1. Swimmer's plot of MDS, MDS/MPN overlap, and AML patients treated with PRT543. Duration of study treatment in weeks of individual patients treated with PRT543 is shown. Best response and reason for treatment discontinuation are also shown. Abbreviations: AML – acute myeloid leukemia, CRi – complete remission with incomplete hematologic recovery, HI-E – hematologic improvement – erythroid, HI-N – hematologic improvement – neutrophil, HI-P – hematologic improvement – platelets, mCR – marrow complete remission, MDS – myelodysplastic syndrome; NE – not evaluable, PD – progressive disease; SD – stable disease

Table 2. Overview of treatment-emergent adverse events occurring in ≥ 10% of patients.

	MDS (N=33) CTC Grade			AML (N=7) CTC Grade			Total (N=40) CTC Grade		
Adverse Event	1-2 n	3-5 n	Any n (%)	1-2 n	3-5 n	Any n (%)	1-2 n	3-5 n	Any n (%)
Number (%) of Subjects With Any TEAE	4	29	33 (100)	2	5	7 (100)	6	34	40 (100)
Anemia	0	18	18 (54.5)	0	2	2 (28.6)	0	20	20 (50.0)
Thrombocytopenia	1	10	11 (33.3)	0	1	1 (14.3)	1	11	12 (30.0)
Nausea	9	0	9 (27.3)	2	0	2 (28.6)	11	0	11 (27.5)
Diarrhea	7	1	8 (24.2)	2	1	3 (42.9)	9	2	11 (27.5)
Fatigue	6	0	6 (18.2)	2	0	2 (28.6)	8	0	8 (20.0)
Constipation	6	1	7 (21.2)	0	0	0	6	1	7 (17.5)
Decreased appetite	6	0	6 (18.2)	1	0	1 (14.3)	7	0	7 (17.5)
Dizziness	7	0	7 (21.2)	0	0	0	7	0	7 (17.5)
Dyspnea	4	0	4 (12.1)	3	0	3 (42.9)	7	0	7 (17.5)
Pneumonia	2	3	5 (15.2)	1	1	2 (28.6)	3	4	7 (17.5)
Headache	2	0	2 (6.1)	4	0	4 (57.1)	6	0	6 (15.0)
Contusion	5	0	5 (15.2)	1	0	1 (14.3)	6	0	6 (15.0)
Neutropenia	0	5	5 (15.2)	0	1	1 (14.3)	0	6	6 (15.0)
Cough	4	0	4 (12.1)	2	0	2 (28.6)	6	0	6 (15.0)
Oedema peripheral	5	0	5 (15.2)	1	0	1 (14.3)	6	0	6 (15.0)
Pyrexia	5	0	5 (15.2)	1	0	1 (14.3)	6	0	6 (15.0)
Epistaxis	4	0	4 (12.1)	1	0	1 (14.3)	5	0	5 (12.5)
Hypertension	2	2	4 (12.1)	1	0	1 (14.3)	3	2	5 (12.5)
Back pain	4	0	4 (12.1)	0	0	0	4	0	4 (10.0)
Hypophosphatemia	3	0	3 (9.1)	1	0	1 (14.3)	4	0	4 (10.0)
Petechiae	3	0	3 (9.1)	1	0	1 (14.3)	4	0	4 (10.0)

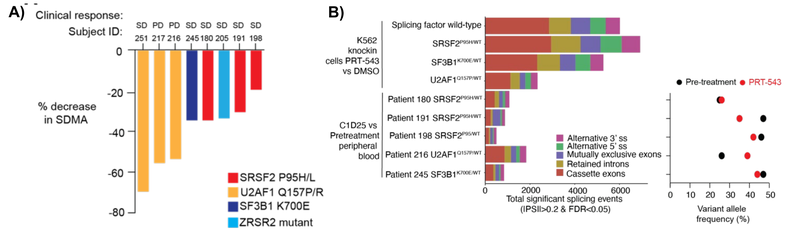

Figure 2. *In vitro* and *in vivo* splicing changes induced by PRT543. (A) Serum levels of symmetric dimethylarginine (SDMA) decrease post-treatment (C1D25) vs. pre-treatment levels in 8 patients treated with PRT543. Colors denote splicing factor mutations. **(B)** Enumeration of statistically significant alternative splicing events (defined as absolute value of percent spliced-in (PSI) > 0.2 and FDR < 0.05) on PRT543 treatment versus DMSO in cell lines or pre-treatment in patient samples. Colors denote distinct categories of RNA splicing events. Right, changes in variant allele fractions of splicing factor mutations in patient samples pre-treatment (black) vs. on PRT543 (red).

CONCLUSIONS

- PRT543 monotherapy among patients with R/R splicing factor-mutant MDS, MDS/MPN overlap, and AML was safe and showed encouraging activity.
- Patients with *SRSF2* and *U2AF1* mutations may be particularly sensitive to treatment with PRT543
- For the first-time, we have confirmed target engagement and global RNA splicing perturbations in patients treated with a PRMT5 inhibitor providing proof-of-concept for PRMT5 inhibition as a therapeutic target in patients with myeloid malignancies.

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