Abstract Submission

16. Myeloproliferative neoplasms - Clinical

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A RANDOMIZED, DOUBLE BLIND PHASE 2 STUDY OF 3 DIFFERENT DOSES OF PRM-151 IN PATIENTS WITH MYELOFIBROSIS WHO WERE PREVIOUSLY TREATED WITH OR INELIGIBLE FOR RUXOLITINIB

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Does the study abide by applicable national and international regulations and guidelines, including but not limited to ethical committees, data protection and privacy regulations, informed consent and off-label use of drugs?: Yes

Background: PRM-151, a recombinant human pentraxin-2 molecule, prevents and reverses fibrosis in animal models of myelofibrosis (MF) in part by targeting differentiation of fibrocytes from monocytes. In the first stage of a two-stage trial, treatment of patients (pts) with primary (PMF), post-essential thrombocythemia/polycythemia vera (post-ET/PV) MF with PRM-151 ± ruxolitinib (Rux) was associated with decreases in bone marrow fibrosis (BMF), improvements in hemoglobin (Hgb) and platelets (PLT), reductions in transfusions and symptoms, and modest reductions in splenomegaly.

Aims: Here, we report efficacy and safety data from a stage 2 randomized, double-blind evaluation of single agent PRM-151.

Methods: Pts with DIPPS Int-1, Int-2, and high risk PMF or post-ET/PV MF who were ineligible for, intolerant of, or had an inadequate response to Rux were randomized between 0.3, 3, and 10 mg/kg of PRM-151 as a sole agent. PRM-151 was to be administered by IV infusion at one of the three assigned doses on Days 1, 3, and 5 of Cycle 1 and on Day 1 of each subsequent 28-day cycle for at least 9 cycles. Randomization was stratified according to baseline (BL) Hgb <100 g/L receiving transfusions and/or PLT <50 x 10^9/L. Bone marrow biopsies and imaging for spleen volume were obtained at BL, C4D1, C7D1, and C9D29. BMF score was evaluated centrally by three independent, blinded hematopathologists. The primary objective of the study was to determine the effect size of three different doses of PRM-151 on reduction in BMF by ≥ 1 grade at any time during the study.

Results: Of the 98 randomized patients, 97 were treated with 0.3 mg/kg (n=33), 3 mg/kg (n=32), or 10 mg/kg (n=32). BL characteristics are provided in Table 1. Forty-six pts discontinued treatment prior to Cycle 9. Decrease in BMF grade at any time was observed in 10 of 33 pts (30%) at 0.3 mg/kg, 9 of 31 pts (28%) at 3 mg/kg, and 8 of 32 pts (25%) at 10 mg/kg. Decrease in BM collagen grade was observed in 31-37% of pts. In pts who were RBC transfusion dependent or with Hgb <100 g/L and transfusion independent at BL, 16-29% of pts had ≥50% reduction in RBC transfusions or Hgb increases ≥10 g/L for ≥12 consecutive weeks. In pts who were PLT transfusion dependent or with PLT<25 or PLT25-<50 x 10^9/L and transfusion independent at BL, 31-40% of pts had ≥50% reduction in PLT transfusions, PLT ≥25 x 10^9/L or PLT ≥50 x 10^9/L or doubling of PLT count, without transfusions for ≥12 consecutive weeks. Improvement from BL in MPN-SAF TSS of ≥25% for ≥12 consecutive weeks was observed in 10-26% of pts. Reduction in spleen volume was observed with a maximum reduction of 34% in one pt. Response rates for BM collagen, Hgb, PLT, MPN-SAF, and spleen were generally similar across the three dose levels. The most common treatment emergent adverse events (AEs) were fatigue, cough, thrombocytopenia, and abnormal weight loss. A majority of the AEs were Grade 2 or lower in severity and consistent with disease progression. Grade 3 and 4 related AEs were reported in 12% and 6% of pts, respectively.

Image/Pictures:

Table 1. Baseline Characteristics

	PRM-151 0.3 mg/kg n = 33	PRM-151 3 mg/kg n = 32	PRM-151 10 mg/kg n = 32	All N = 97
Median age (years)	70	71	69	70
MF type, n (%)				
Primary	20 (61)	20 (63)	26 (81)	66 (68)
Post-PV MF	8 (24)	6 (19)	2 (6)	16 (16)
Post-ET MF	5 (15)	6 (19)	4 (13)	15 (15)
Fibrosis grade by central pathologist (n, %) MF 0/1/2/3	0/2/1/27/3 (0/6/36/58)	1/2/6/21 (3/7/20/70)	0/1/10/21 (0/3/31/66)	1/5/18/69 (1/5/19/64)
Number of prior medications for myelofibrosis				
n	27	28	29	84
1-2	21 (78)	22 (79)	21 (72)	64 (76)
3-5	4 (15)	6 (21)	8 (28)	18 (21)
≥ 6	2 (7)	0	0	2 (2)
Mean time from diagnosis, years (range)	3.48 (0-31.0)	3.28 (0-10.0)	4.69 (0-21.0)	3.81 (0-31.0)
DIPSS category, derived				
n (%) – Low	0	0	0	0
n (%) – Intermediate-1	8 (24)	7 (22)	2 (6)	17 (18)
n (%) – Intermediate-2	22 (67)	24 (75)	23 (72)	69 (71)
n (%) – High	3 (9)	1 (3)	7 (22)	11 (11)
Prior ruxolitinib therapy, n (%)	25 (76)	27 (84)	22 (69)	74 (76)
Intolerant	18 (72)	20 (74)	10 (45)	48 (65)
Inadequate response	16 (64)	7 (26)	14 (64)	37 (50)
Median hemoglobin, g/L (Q1, Q3) [range]	88 (81-94) [59-131]	86 (78-97) [60-129]	88 (77-95) [60-125]	87 (78-95) [59-131]
Median RBC transfusions 12 wk before BL, n (range)	3 (0-10)	3 (0-11)	3 (0-26)	3 (0-26)
Median PLT, x 10^9/L (Q1, Q3) (range)	97 (25-89) [13-402]	45 (24-132) [6-923]	44 (22-102) [11-686]	62 (24-102) [6-923]
Mean PLT transfusions 12 wk before BL, n (range)	0.48 (0-7)	1.00 (0-27)	2.84 (0-33)	1.43 (0-33)
Mean MPN-SAF Total Symptom Score, # (range)	30 (4-73)	31 (1-91)	27 (7-70)	29 (1-91)

Summary/Conclusion: The study enrolled a large proportion of MF pts with advanced disease (Int-2 or high risk, BMF grade 3, anemic/transfusion dependent, and PLT <50 x 10^9/L). Decrease in BMF and collagen grade were observed across all dose levels. Increases in Hgb and PLT count or reduction in transfusion requirements were also reported across all dose levels. Improvements in MPN-SAF TSS and spleen volume were observed in a proportion of pts. PRM-151 treatment for up to 9 cycles was well tolerated. These data warrant confirmation in a larger controlled study.

Keywords: None