GVHD PROPHYLAXIS WITH KRP203, A SPHINGOSINE-1-PHOSPHATE RECEPTOR MODULATOR, IS SAFE AND MAY HAVE THE POTENTIAL TO IMPROVE SURVIVAL IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

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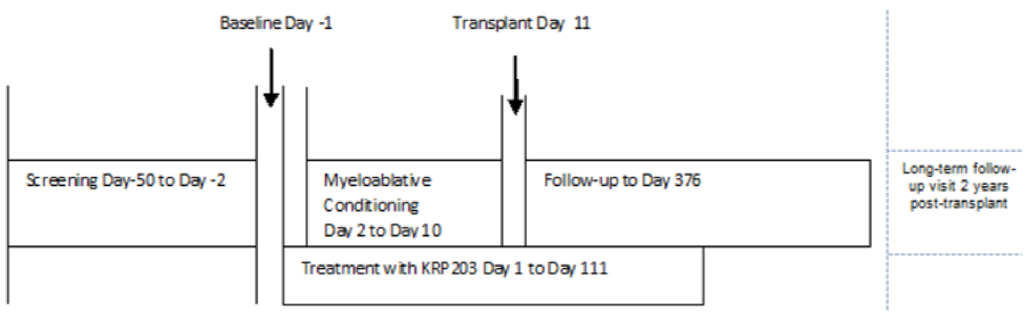
INTRODUCTION AND METHODS

Migration of allo-activated donor effector T-cells from lymphoid tissues to target organs is an important step in acute graft versus host disease (GvHD), a major complication of allogeneic hematopoietic stem cell transplantation (HSCT). The sphingosine-1-phosphate-1 (S1P1) receptor plays a crucial role in lymphocyte trafficking and data from animal models suggest that pharmacological modulation of the S1P1 receptor reduces GvHD and improves mortality. We, for the first time, investigated this mode of action by using the second-generation S1P1 modulator KRP203 for the prophylaxis of GvHD in a pilot clinical trial in patients undergoing allogeneic HSCT. A multi-centric, Phase 1b, prospective, open label, two-part study (ClinicalTrials.gov Identifier: NCT01830010) was conducted to evaluate the safety, tolerability and pharmacokinetics of KRP203 in intermediate to high risk patients undergoing allogeneic HSCT for hematological malignancies (Fig. 1).

Figure 1. Study design



Male or female patients between 18 to 65 years old were eligible for enrollment with a diagnosis qualifying for allogeneic HSCT with a HLA matched (10/10) stem cell source available. Primary endpoint was safety. Initial efficacy was explored based on the incidence of GvHD, mortality and relapse. Part 1 was a single arm open label study to investigate the safety of 3 mg/day KRP203 added to a standard of care GvHD prophylaxis (CsA/MTX) in 10 patients. Part 2 was a randomized two-arm open label study to compare the safety, efficacy and PK of 3 mg/day of KRP203 in combination with tacrolimus/MTX to 1 mg/day of KRP203 in combination with CsA/MTX in 13 patients. Patients receiving ATG prophylaxis were excluded from the study. In both parts, treatment with KRP203 was initiated 10 days before HSCT and continued for an additional 100 days. Patients were followed up for up to 2 years.

RESULTS

Twenty-three patients were included in the study and received KRP203. Sixteen of 23 patients completed the 110-day treatment with KRP203 at the assigned doses. Median duration of follow-up time was 264 days (interquartile range 153 to 271 days). Overall, KRP203 was safe and well tolerated. Eleven serious adverse events (SAEs) suspected to be related to KRP203 were observed. Macular edema (n=3) and peripheral edema (n=1) as S1P related adverse events occurred and resolved without sequelae. Of note, the incidence of macular edema in HSCT recipients undergoing myeloablative conditioning is not known. Neutrophil engraftment was confirmed in all patients with a median of 16 days after transplant (range 12 to 45 days) (Fig. 2). Five of 23 patients presented with Grade III or IV acute GvHD (on Days 50, 56, 68, 99 and 102), (Fig 3)

Table 1. Demographic andbaseline characteristics

		KRP203 1mg + CsA N=6	KRP203 3mg + CsA N=10	KRP203 3mg + Tac N=7	Total N=23
Age (years)	Mean (SD)	50.7 (8.87)	47.1 (10.22)	49.9 (14.90)	48.9 (11.13)
	Median	51.0	49.5	56.0	51.0
	Range	[35, 62]	[26, 60]	[23, 63]	[23, 63]
Sex - n(%)	Male	5 (83%)	5 (50%)	4 (57%)	14 (61%)
	Female	1 (17%)	5 (50%)	3 (43%)	9 (39%)
Race - n(%)	Caucasian	6 (100%)	9 (90%)	5 (71%)	20 (87%)
	Asian	0 (0%)	1 (10%)	0 (0%)	1 (4%)
	Other	0 (0%)	0 (0%)	2 (29%)	2 (9%)
Ethnicity - n(%)	Indian (India subc)	0 (0%)	1 (10%)	0 (0%)	1 (4%)
	Other	6 (100%)	9 (90%)	7 (100%)	22 (96%)
Weight (kg)	Mean (SD)	89.15 (14.931)	70.16 (8.933)	74.83 (15.159)	76.53 (14.449)
	Median	84.15	74.00	76.00	76.30
	Range	[79.0, 119.1]	[55.0, 80.0]	[56.0, 99.8]	[55.0, 119.1]
Height (kg)	Mean (SD)	175.0 (6.20)	169.2 (4.42)	171.6 (7.87)	171.4 (6.27)
	Median	173.5	168.5	172.0	171.0
	Range	[168, 183]	[161, 175]	[160, 185]	[160, 185]
BMI (kg/m2)	Mean (SD)	29.201 (5.2934)	24.466 (2.6759)	25.526 (5.4193)	26.024 (4.6090)
	Median	28.407	24.992	25.690	25.690
	Range	[24.60, 39.34]	[20.66, 29.03]	[18.29, 33.59]	[18.29, 39.34]

Table 2. Overall incidence of adverse events

	KRP203 1mg + CsA N=6 nE, nS (%)	KRP203 3mg + Tac N=7 nE, nS (%)	Part 2 Total N=13 nE, nS (%)	KRP203 3mg + CsA N=10 nE, nS (%)
AEs, Subjects with AEs	267, 6 (100)	267, 7 (100)	534, 13 (100)	179, 10 (100)
AEs of Grade 1/Mild intensity	117, 6 (100)	106, 5 (71)	223, 11 (85)	120, 10 (100)
AEs of Grade 2/Moderate intensity	94, 6 (100)	113, 7 (100)	207, 13 (100)	48, 9 (90)
AEs of Grade 3/Severe intensity	48, 6 (100)	43, 7 (100)	91, 13 (100)	11, 4 (40)
AEs of Grade 4/Life Threatening intensity	8, 4 (67)	4, 3 (43)	12, 7 (54)	0, 0 (0)
Study drug-related AEs	22, 4 (67)	14, 7 (100)	36, 11 (85)	19, 5 (50)
Serious AEs	13, 4 (67)	16, 6 (86)	29, 10 (77)	18, 5 (50)
Study drug-related serious AEs	4, 2 (33)	4, 3 (43)	8, 5 (38)	3, 1 (10)
AEs leading to discontinuation of study treatment	4, 2 (33)	2, 2 (29)	6, 4 (31)	8, 3 (30)
Study-drug related AEs leading to discontinuation of study treatment	4, 2 (33)	2, 2 (29)	6, 4 (31)	6, 2 (20)

N = number of subjects studied; nE = number of AE events in the category; nS = number of subjects with at least one AE in the category; % is based on the number of subjects

No GvHD or infection related death occurred during the first 100 days. 100-day survival was 96%, with no death occurring during KRP203 treatment. One death occurred on Study Day 90 due to lymphoma relapse. A second death occurred on Study Day 121 due to liver GvHD initially diagnosed as drug toxicity with all immunosuppressives including KRP203 withdrawn earlier. Four patients died in the follow-up period due to gastrointestinal GVHD (Day 265), aspiration pneumonia (Day 327), myelodysplastic syndrome (MDS) relapse (Day 533) and acute myeloid leukemia (Day 877). The Kaplan-Meier estimate of overall survival at 1 year was 0.75 and seemed favorable when comparing to historical controls (Figure 4). When comparing the data from the two dose groups (1 and 3 mg KRP203), no major differences in safety, engraftment, GvHD rate or mortality were observed.

Figure 2. Time to neutrophil recovery (days)

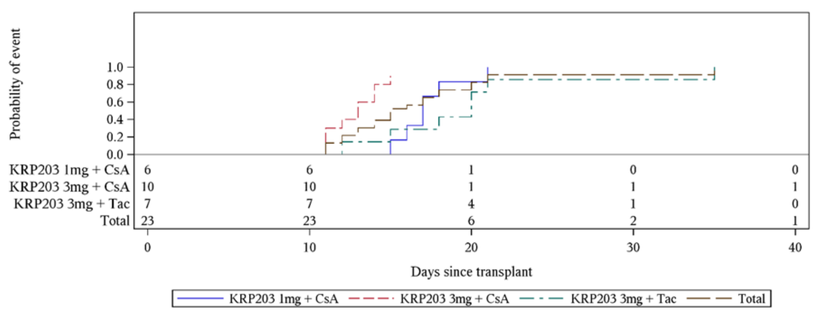


Figure 3. Time to severe GvHD (days)

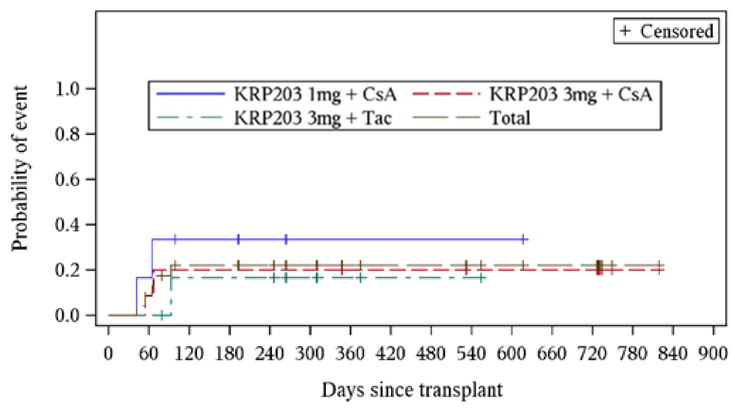
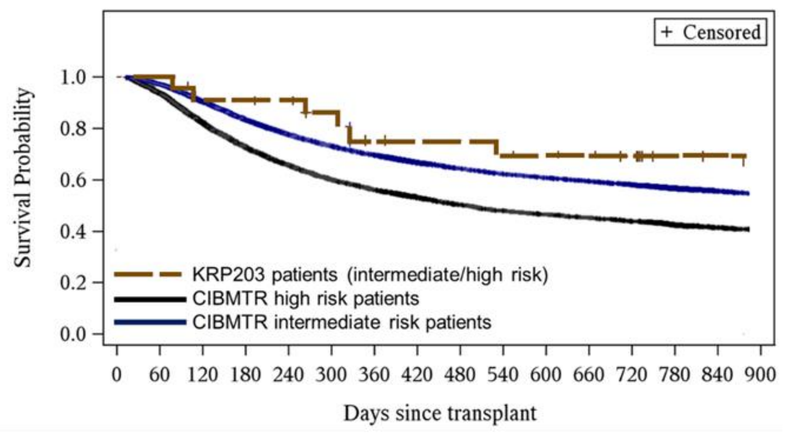


Figure 4. Overall survival on KRP203 vs CIBMTR database



CIBMTR: Center for International Blood and Marrow Transplant Research

CONCLUSION

This clinical trial was the first to test S1P modulation in this population. Our data suggest that KRP203, when administered prophylactically 10 days prior to transplant, and continued for an additional 100 days, had no negative impact on engraftment and overall, was safe, and well tolerated. KRP203 may also have potential to have favorable effects on overall survival. Further large, controlled studies are warranted to confirm the safety and assess the efficacy of this novel modality in patients undergoing allogeneic stem cell transplant.

DISCLAIMERS

KRP203 is an investigational drug owned by Kyorin Pharma. The clincal study was sponsored by Novartis AG.