P776 A PHASE 2, OPEN-LABEL, ASCENDING DOSE STUDY OF KER-050 FOR THE TREATMENT OF ANEMIA IN PATIENTS WITH VERY LOW, LOW, OR INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES

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Background:
Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis; many patients develop high transfusion burden (HTB) requiring ≥4 units RBCs every 8 weeks and have high unmet medical need. KER-050, an investigational modified activin receptor type IIA inhibitor, is designed to target TGF-β ligands to promote differentiation of erythroid and megakaryocyte lineages to improve anemia and thrombocytopenia.

Aims:
Evaluate safety, tolerability, pharmacodynamics (PD), efficacy of KER-050 in MDS in an open-label Phase 2 study.

Methods:
IPSS-R lower-risk anemic MDS patients are enrolled, including non-transfused, low-transfusion burden (LTB) and HTB patients. In Part 1 base study, ascending dose cohorts receive KER-050 subcutaneously q4w for 4 doses until a recommended Part 2 dose is determined. Safety endpoints include incidence of adverse events (AEs); erythroid efficacy endpoints (≥8 weeks duration) include rates of transfusion independence (TI) and reduction in RBC transfusions by ≥4 units (IWG 2006 HI-E) in HTB patients. Safety-set includes patients receiving ≥1 dose. PD/efficacy results are reported in efficacy evaluable (EE) patients who contributed ≥8 weeks of HGB and transfusion data. New analyses presented here describe response and markers of erythropoiesis and thrombopoiesis in HTB patients.

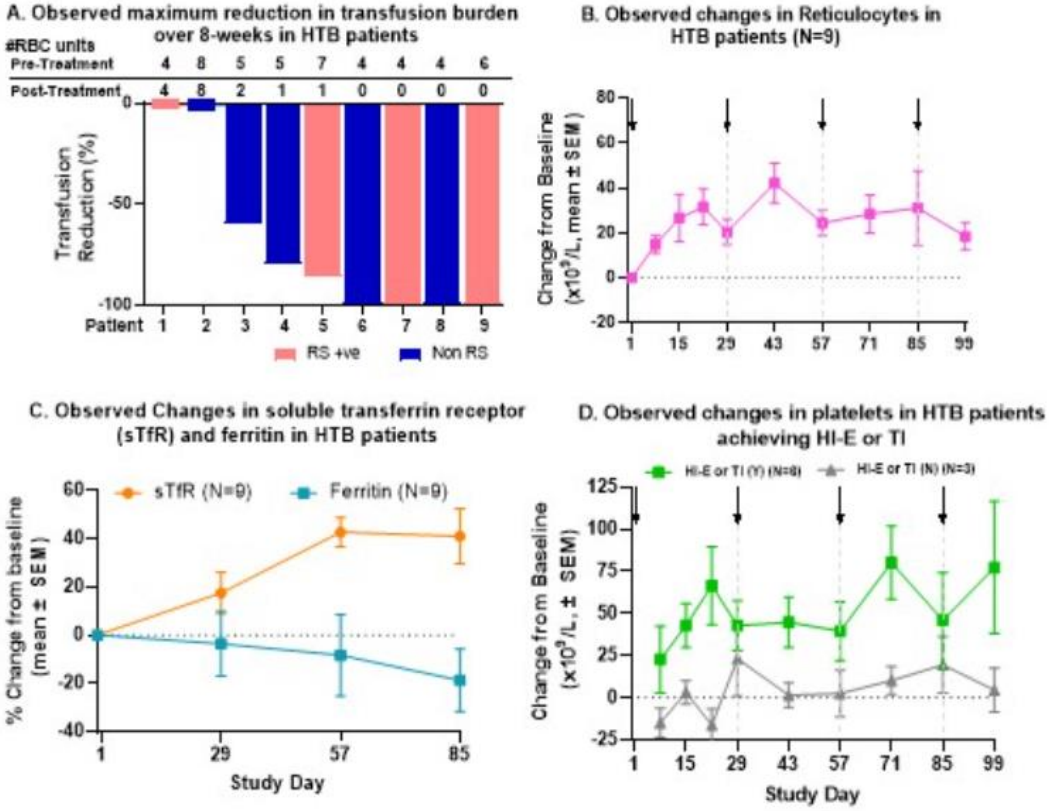
Results:
At data cut-off (25-Oct-2021), median follow-up was 124 days (range 10-217). 24 patients received ≥1 dose of KER-050 across 4 dose levels (0.75mg/kg to 3.75mg/kg q4W). Of these, 16

were EE (8 not EE due to: duration of treatment (n=6), death (n=1), study discontinuation (n=1)). Median time from diagnosis was 2.2 years (range 0.2 – 8.6), 14 (58.3%) were HTB. Of HTB patients, 7 were RS+, 6 were on iron chelators.

No DLTs were reported in the safety-set. 5 (20.8%) reported grade ≥3 treatment-emergent AEs (TEAEs), 5 (20.8%) reported SAEs (none related), 4 (16.7%) developed grade 1 or 2 treatment-related AEs. Most frequent TEAEs (≥10%) were diarrhea, dyspnea, fatigue, nausea, anemia, headache. 2 discontinued study drug: 1 participant decision, 1 death. 1 required dose modification due to unrelated TEAE; none required dose modification for increased HGB or thrombocytosis.

Results from 16 EE cohort 1-3 patients were presented at ASH 2021 (Poster #3675), 8 (50%) achieved HI-E or TI. New analyses focused on HTB patients found that 6 of 9 HTB, EE patients achieved HI-E and 4 achieved TI for ≥8 weeks (Panel A). Increases in reticulocytes (RETs) (Panel B) and sTfR and decreases in serum ferritin (Panel C) in these HTB patients were observed. Mean maximum RETs increase was 56.87 x109/L, range 15.7-142.5x109/L with mean maximum ferritin reduction of 29.7%, range -17 to 65% and mean maximum sTfR increases of 51%, range 29-90%. Increases in platelets were observed in HTB patients achieving HI-E or TI (Panel D). Maximum increase from baseline was 98 x109/L (mean), range 33-179 x109/L.

Figure 1. Treatment with KER-050 resulted in reduction in transfusion burden (A), increased erythropoiesis (B and C) and increased platelet counts (D) in HTB patients.
Mean baseline platelet count for patients achieving HI-E or TI was 202 x10^9/L (range 103-305 x10^9/L).
Arrow indicates dosing day.



Conclusion:

KER-050 was generally well-tolerated as of data cut-off date. HI-E and TI ≥8 weeks have been observed in HTB patients treated with KER-050. Observed PD effects in RETs, sTfR and ferritin support the proposed mechanism of action of increasing erythropoiesis. Increases in platelets have been observed in HTB patients achieving HI-E or TI which supports the potential of KER-050 as a treatment for multilineage cytopenias in difficult-to-treat HTB patients. Dose escalation is ongoing in this Phase 2 study of anemic patients with MDS; updated data from Part 1 with safety, PD and efficacy data from cohorts 4 and 5 will be presented for the first time at the meeting.

Keyword(s):

Clinical trial, MDS, TGF-