Luspatercept promotes terminal differentiation of erythroblasts in late-stage erythropoiesis (EPO-dependent)
Luspatercept, a modified activin receptor type IB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other TGFβ family ligands to suppress Smad2/3 signaling; increased hemoglobin in healthy volunteers
In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia, and increased hemoglobin

A Phase 2, multicenter, open-label, 3-month-dose escalation study in adults with lower-risk MDS, followed by a 5-year extension study
- Base study 3 months (N=106); NCT01749514; Platebecker U, et al. Lancet Oncol 2017;18:338-47
- Extension study 5 years (N=70); NCT01266838
- Key eligibility criteria: low to interstitial (IPSS) MDS including non-transfusion dependent and transfusion dependent, ESA-naive and prior ESA; range of baseline EPO; RIS+ and non-RS patients
- Treatment: luspatercept 0.125 – 1.75 mg/kg (base study); 1.0 – 1.75 mg/kg (extension); SC q3; 2-month follow up
- Endpoints: IWG (2008) HE; Hgb increase ≥ 1.5 g/dL over 8 weeks for patients with < 4 units/wk and Hgb ≥ 10 g/dL; 4 RBC unit decrease over 8 weeks for patients with 2 – 3 units/wk; RBC-RCT independence ≥ 8 weeks; time to/duration of HE response

Majority of adverse events (AEs) were grade 1 or 2
- Eight possibly related grade 3 non-serious AEs in 1 patient each: ascites, blast cell count increase, blood bilirubin increase, bone pain, hypertension, myelosuppression, platelet count decrease, pleural effusion
- Four possibly related SAEs in 3 patients: general physical health deterioration (patient 1), muscular weakness & musculoskeletal pain (patient 1), and myalgia (1 patient)

Preliminary data as of 08 Sept 2017
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Table 3. Mutated Genes Per Patient at Baseline

| Patient | Mutation Type | Gene Frequency | N (%)
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Table 6. IWG Hi-E and RBC-TI Response by ESA, EPO Status

<table>
<thead>
<tr>
<th>ESA Status</th>
<th>IWG Hi-E (%)</th>
<th>RBC-TI (%)</th>
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<tbody>
<tr>
<td>None</td>
<td>46 (47%)</td>
<td>34 (34%)</td>
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<tr>
<td>Prior</td>
<td>38 (40%)</td>
<td>30 (30%)</td>
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Response

Figure 1. Duration of Transfusion Independence in RBC-TI Responders

Figure 3. Increase in Mean Hemoglobin in Low Hemoglobin Transfusion Patients

Figure 4. Response Rate by Cellular and Morphologic Parameters

Summary/Conclusions

- Lower-risk MDS patients treated with luspatercept continue to demonstrate sustained increases in hemoglobin and decreases in transfusion burden (per IWG HE) and a high rate of RBC transfusion independence
- HE responders had increased levels of bone marrow erythroid cells/erythropoiesis and soluble transferrin receptor and lower baseline myeloid/erythrocyt ratios
- Treatment benefit similar in ESA-naive and prior ESA-treated patients and benefit is observed in both RIS+ and non-RS patients
- The majority of patients had at least one mutation in the genes analyzed; co-mutations in SF3B1 and TET2 and in SF3B1 and DNMT3A were the most common

Acknowledgements/References

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Central Lab (Bone Marrow): D. Haase, H. Kreipe, U. Oelschlägel, A.Giagounidis

Central Lab (Bone Marrow): D. Haase, H. Kreipe, U. Oelschlägel, A.Giagounidis

References

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