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ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Efficacy and Safety of Roxadustat for Treatment of Anemia in Patients with Lower-Risk Myelodysplastic Syndrome (LR-MDS) with Low Red Blood Cell (RBC) Transfusion Burden: Results of Phase III Matterhorn Study

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Presented on behalf of all MATTERHORN (FGCL-4592-082) study investigators

Introduction: For patients (pts) with LR-MDS, anemia poses a major clinical challenge, with limited response to first-line erythropoietin (EPO)-stimulating agents (ESAs) and a median duration of response ≤2 years. Further, pts with RBC transfusion dependence (≥2 packed RBC [pRBC] units every 8 weeks [Q8W]) are less likely to respond to ESAs. Anemia treatments with novel mechanisms of action enabling transfusion independence (TI) are needed to reduce frequent RBC transfusion burden. Roxadustat is a first-in-class, hypoxia-inducible factor prolyl hydroxylase inhibitor for treatment of anemia with chronic kidney disease. In the MATTERHORN (NCT03263091) dose-selection stage, roxadustat was well-tolerated, and 37.5% of pts (9/24) with LR-MDS and low RBC transfusion burden ([LTB] 1 pRBC unit Q8W for two consecutive 8-week periods or 2-4 pRBC units Q8W) achieved TI. In the MATTERHORN double-blind stage, TI response rate and safety of roxadustat were further assessed.

Methods: MATTERHORN is an ongoing, double-blind, Phase III, randomized, placebo (PBO)-controlled trial. Eligible adult pts (≥18 years of age) had very low-, low-, or intermediate-risk primary MDS per Revised International Prognostic Scoring System (IPSS-R) classification (<5% bone marrow blasts); hemoglobin (Hb) ≤10.0 g/dL at baseline (BL); and LTB. Prior ESA use (>8 weeks before randomization) was permitted. Pts were randomized 3:2 to roxadustat or PBO, then stratified by serum EPO concentration (≤200 or 200-400 mIU/mL), IPSS-R risk, and transfusion burden. Pts received oral roxadustat (starting dosage: 2.5 mg/kg three times weekly based on the dose-selection stage) or PBO with best supportive care (BSC; per institutional criteria, including RBC transfusion) for a 52-week treatment period, followed by a 4-week follow-up period. Primary efficacy endpoint was percentage of pts with TI (the absence of RBC transfusion) for ≥56 consecutive days during the first 28 treatment weeks (TI responder). The percentage of pts with TI and mean Hb increase of ≥1.0 and ≥1.5 g/dL (averaged over 8 weeks) compared with BL pretransfusion Hb was also assessed (to be reported separately). Safety (including treatment-emergent adverse events [TEAEs] and serious TEAEs) was evaluated throughout the study.

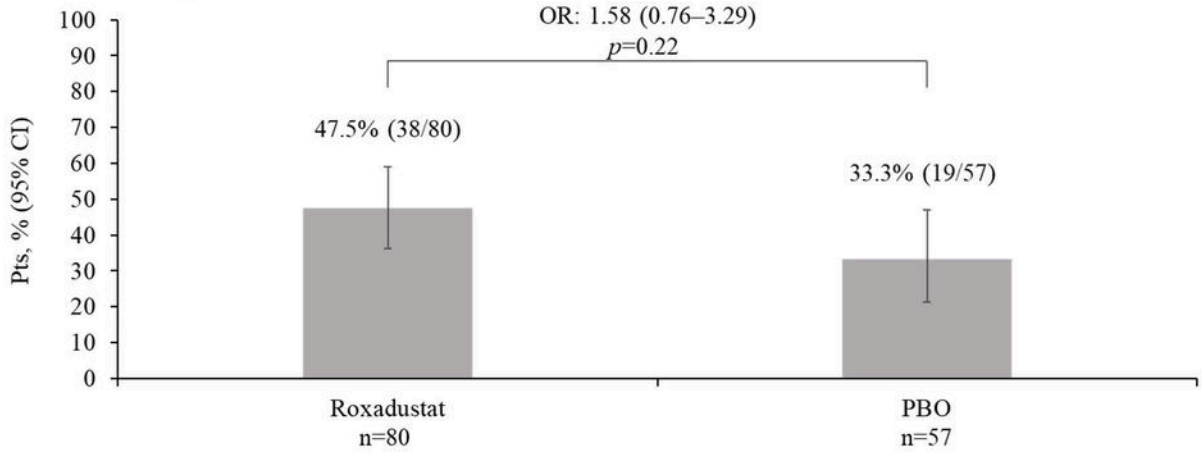
Results: As of the final 28-week interim analysis of the double-blind stage (data cutoff: April 24, 2023), 140 pts (82 roxadustat, 58 PBO) were randomized and treated. Across arms, median age was 71.5 years (range, 26-96), 59.3% (83/140) were male, and 80.0% (112/140) were white. Most pts (72.1% [101/140]) had IPSS-R low-risk disease and a transfusion burden of 2-4 pRBC units Q8W (92.1% [129/140]). Median (range) BL transfusion burden was 2.5 (1-10) pRBC units. Seventy pts (50.0%) received prior ESAs (98.6% [69/70] were ESA-refractory). Eighty-four pts (41/82 [50.0%] roxadustat, 43/58 [74.1%] PBO) completed 28 weeks of treatment, and 15 pts (6/82 [7.3%] roxadustat, 9/58 [15.5%] PBO) were continuing treatment. Median (range) treatment duration was 24.1 (1.1-28.0) weeks for the roxadustat arm and 28.0 (0.1-28.0) weeks for the PBO arm.

A greater percentage of pts in the roxadustat arm compared with the PBO arm were TI responders (47.5% vs. 33.3%). However, this difference did not reach statistical significance (p=0.22; figure). Percentages of pts with TEAEs of any grade, serious TEAEs, and TEAEs leading to treatment discontinuation were similar across arms (table). Six deaths occurred on study (rox-

adustat: pneumonia [n=2], acute myocardial infarction and ischemic stroke [n=1], multiorgan failure [n=1]; PBO: urosepsis [n=1], disease progression [n=1]). Three pts (all in roxadustat arm) progressed to acute myeloid leukemia.
The study was terminated by the sponsor and is currently being completed.
Conclusions: Despite not meeting the primary endpoint, roxadustat plus BSC was well-tolerated, and a high percentage of pts with LR-MDS and LTB were TI responders. The high TI response rate in the PBO arm, historically poor outcomes in pts with ESA-refractory disease, and the inclusion of pts who were not transfusion-dependent (1 pRBC unit Q8W) may have contributed to the lack of a statistically significant difference in TI response rates between arms. MATTERHORN outcomes highlight the continued unmet need for effective and safe therapies that reduce RBC transfusion burden in LR-MDS.

Disclosures Mittelman: *Silence:* Other: advisory boards; *Astellas:* Other: advisory boards; *Janssen:* Research Funding; *Onconova:* Other: advisory boards; *Roche:* Research Funding; *Medison/Amgen:* Research Funding; *Novartis:* Other: participated in clinical trials, advisory boards, Research Funding, Speakers Bureau; *Celgene/BMS:* Other: participated in clinical trials, Research Funding, Speakers Bureau; *MDS HUB:* Consultancy; *Media Digital:* Speakers Bureau; *Geron:* Other: participated in clinical trials; *FibroGen:* Other: participated in clinical trials; *Takeda:* Other: participated in clinical trials, advisory boards; *Gilead:* Consultancy, Research Funding; *AbbVie:* Other: participated in clinical trials, Research Funding. **Henry:** *FibroGen:* Research Funding. **Glaspy:** *FibroGen:* Research Funding. **Tombak:** *GSK:* Other: institution received research funding; *Dr. Reddy's:* Other: institution received research funding; *BeiGene:* Other: institution received research funding; *FibroGen:* Other: institution received research funding. **Harrup:** *F. Hoffmann-La Roche Ltd, Beigene:* Research Funding; *F. Hoffmann-La Roche Ltd, Takeda:* Current equity holder in publicly-traded company; *FibroGen:* Research Funding. **Madry:** *AbbVie:* Other: advisory boards, lecture fees; *BMS:* Other: advisory boards, lecture fees; *Teva:* Other: lecture fees. **Grabowska:** *FibroGen:* Research Funding. **Platzbecker:** *Jazz:* Consultancy, Honoraria, Research Funding; *Servier:* Consultancy, Honoraria, Research Funding; *Syros:* Consultancy, Honoraria, Research Funding; *Geron:* Consultancy, Research Funding; *Merck:* Research Funding; *Janssen Biotech:* Consultancy, Research Funding; *AbbVie:* Consultancy; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support; medical writing support, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *Curis:* Consultancy, Research Funding; *MDS Foundation:* Membership on an entity's Board of Directors or advisory committees; *Silence Therapeutics:* Consultancy, Honoraria, Research Funding; *Fibrogen:* Research Funding; *Amgen:* Consultancy, Research Funding; *Roche:* Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Celgene:* Honoraria; *BeiGene:* Research Funding; *BMS:* Research Funding. **Lee:** *FibroGen, Inc.:* Current Employment, Current holder of *stock options* in a privately-held company, Other: stock. **Modelska:** *FibroGen, Inc.:* Current Employment, Current holder of *stock options* in a privately-held company, Other: stock.

Figure. TI responders[a]



CI, confidence interval; OR, odds ratio; PBO, placebo; pts, patients; TI, transfusion independence.
Full analysis population (all pts who were randomized and received ≥1 dose of treatment).
[a]TI responders defined as pts with TI ≥56 consecutive days during the first 28 treatment weeks.

Table. Safety summary

TEAEs, n (%)	Roxadustat (n=82)	Placebo (n=58)
TEAEs, any grade	73 (89.0)	52 (89.7)
TEAEs, grade ≥3	31 (37.8)	12 (20.7)
Serious TEAEs	22 (26.8)	9 (15.5)
TEAEs leading to treatment discontinuation	12 (14.6)	5 (8.6)
TEAEs leading to death	4 (4.9)	2 (3.4)
Most common TEAEs[a], any grade		
Nausea	19 (23.2)	7 (12.1)
Fatigue	15 (18.3)	6 (10.3)
Constipation	11 (13.4)	1 (1.7)
Dizziness	10 (12.2)	9 (15.5)
Asthenia	10 (12.2)	7 (12.1)
ALT increased	10 (12.2)	6 (10.3)
Peripheral edema	9 (11.0)	4 (6.9)
Diarrhea	6 (7.3)	8 (13.8)
COVID-19	5 (6.1)	7 (12.1)

ALT, alanine aminotransferase; COVID-19, coronavirus disease of 2019; pts, patients; TEAE, treatment-emergent adverse event.
Safety population (all pts who received ≥1 dose of treatment).
[a]TEAEs occurring in ≥10% of pts in either treatment arm and listed in descending order of frequency in the roxadustat arm.

Figure 1

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