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Poster Session

MYELODYSPLASTIC SYNDROMES POSTER II

An Open-Label Extension Study Evaluating the Long-Term Safety and Efficacy of Romiplostim in Thrombocytopenic Patients (Pts) with Myelodysplastic Syndromes (MDS).

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Background: Romiplostim is a peptibody protein that increases platelet production by binding to and activating the thrombopoietin receptor. Currently, platelet transfusion is the only supportive treatment for thrombocytopenia in MDS. In a phase 1/2 study of romiplostim in lower-risk thrombocytopenic MDS pts receiving supportive care only, about half achieved a platelet response (Sekeres et al., ASCO 2009, Kantarjian et al, JCO 2009, in press). We report results from an interim analysis of the subsequent ongoing open-label extension study evaluating the long-term safety and efficacy of romiplostim in MDS pts.

Methods: MDS pts who, after completing the parent study, had platelets '50x10^9/L and no evidence of disease progression were eligible to enroll in this extension. The primary endpoint of this extension was adverse event (AE) incidence with long-term use of romiplostim; incidence of bleeding events was a secondary endpoint. Pts received romiplostim at a dose of 250, 500, 750, 1000, or 1500 µg weekly or every two weeks based on previous dosing, with subsequent adjustment between 250 and 1000 µg. If after 4 weeks at the increased dose there was an inadequate platelet response (using IWG 2006 criteria), the dose could be further escalated (with 4 weeks at each dose) up to a maximum of 1000 µg/week. If no response was observed after 4 weeks at 1000 µg/week, treatment was discontinued.

Results: At the reference date of Feb 18, 2009, 28 pts had enrolled in this open-label extension study: 68% male, median age 71.5 y [interquartile range (Q1-Q3): 63.5-76.5 y], median baseline platelets 31x10^9/L (Q1-Q3: 20–41x10^9/L), 32% with platelets <20x10^9/L. During the parent study, 24 of the 28 pts had a platelet response. At the end of the parent study, there was a 4-week washout period. At initiation of the open-label extension study, IPSS status was low (13 pts), int-1 (12), int-2 (1), or missing (2), and MDS subtypes were RA (11 pts), RCMD (7), MDS-U (4), RAEB-1 (2), RCMD-RS (1), RARS (1), or missing (2). Ten pts (36%) had bleeding events in the previous year. Median duration of treatment in the extension study was 41 weeks (Q1-Q3: 23–58 weeks), with a median weekly dose of 748 µg (Q1-Q3: 493–821 µg). All 28 pts received µ8 weeks of romiplostim. Most AEs were mild-to-moderate; the most common being epistaxis (36%), arthralgia

(29%), anemia (21%), and cough (21%). No neutralizing antibodies to romiplostim or TPO were observed. Nine pts withdrew from the study, 6 of these due to AEs. By investigator assessment, five of these AEs were related to romiplostim: 3 pts with increased blast cells, 1 pt with early-stage chronic myeloid leukemia (CML) diagnosed 519 days after romiplostim initiation, with bcr-abl first detected 1 year after romiplostim initiation (negative at baseline), and 1 pt with a history of chronic obstructive pulmonary disease and congestive heart failure who subsequently experienced the acute and rapid development of fatal pulmonary fibrosis after treatment with romiplostim. Two of these AEs were severe (pulmonary fibrosis and CML). For the increased blast cells, in cases 1 and 2, peripheral blasts were detected: in case 1 bone marrow (bm) blasts of 7% fell to <1% after drug discontinuation, while in case 2, bm blasts were 3% (no follow-up blast count). In both cases 1 and 2, peripheral blasts disappeared after drug discontinuation. In case 3, increase in blasts was reported by the investigator, with no peripheral blasts detected (follow-up bm biopsy was not evaluable). One AE leading to study withdrawal was not related to romiplostim (follicular B-cell lymphoma). As of the reference date, no progression to AML was reported. Eighteen pts (64%) reported ≥1 bleeding events, with 6 pts (21%) reporting ≥1 clinically significant bleeding events (i.e., CTCAE grade ≥3, serious AE, or any bleeding AE requiring intervention). Eight pts (29%) received platelet transfusions. From Study Week 4 on, the median platelet count was $\geq 50 \times 10^9$/L. Twenty-three pts (82%) had a platelet response (per IWG 2006 guidelines), including 6 of 9 pts with baseline platelet counts $< 20 \times 10^9$/L. The median platelet response lasted 30 weeks (Q1-Q3: 16–52 weeks). Over half of pts (54%) demonstrated an initial platelet response by Study Week 3.

Conclusion: In this long-term, follow-up, open-label extension study in thrombocytopenic MDS pts, romiplostim demonstrated an acceptable toxicity profile, with the majority of pts achieving a durable platelet response.

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Footnotes

* Asterisk with author names denotes non-ASH members.