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Evaluating safety and efficacy of AMG 531 for the treatment of thrombocytopenic patients with myelodysplastic syndrome (MDS): Preliminary results of a phase 1/2 study.

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Abstract: Background: The prevalence of thrombocytopenia in MDS ranges from 40% to 65%, hemorrhagic complications range from 3% to 53%, and hemorrhagic deaths range from 14% to 24% (Kantarjian 2006). Platelet transfusion can lead to reactions, infection, and alloimmunization. AMG 531 is a thrombopoiesis-stimulating peptibody that increases platelet production. This phase 1/2 study evaluated the safety and efficacy of AMG 531 in thrombocytopenic MDS patients. Methods: A minimum of 5 subjects with low risk MDS (IPSS low or intermediate-1) and a platelet count of $\leq 50 \times 10^9/L$ were enrolled to receive 3 QW SC injections of AMG 531 in each of 4 sequential dose cohorts. After evaluation at week 4, subjects could continue AMG 531 in an optional treatment extension at their assigned dose or escalated to a responding dose. Erythroid growth factors were allowed, but no other active treatment. Results: 28 subjects (9 transfusion-dependent) have been enrolled to date. All subjects were evaluable for response and entered the extension; 17 continue treatment. Dose-limiting toxicity (DLT) was defined as a drug-related grade 3 or 4 adverse event (AE) or a platelet count $> 600 \times 10^9/L$. Two DLTs occurred, both due to elevated platelet counts. No treatment-related severe AEs occurred. There was 1 treatment-unrelated death. Overall, 17 subjects (61%) achieved a platelet response. Median baseline platelet count for responders was $25 \times 10^9/L$ with a median peak platelet count of $130 \times 10^9/L$ during the 4 week treatment period. Of the 18 subjects to date completing at least 12 weeks of treatment, 11 (48%) achieved a durable response of at least 8 consecutive weeks (revised IWG criteria, Cheson 2006). A total of 90 clinically significant thrombocytopenic events (39 bleeding, 51 transfusions) were observed over both treatment phases. There were 16 such events (12 bleeding, 4 transfusions) in 6 subjects with a durable response, 6 events (6 minor bleeds, 0 transfusions) during the durable response period. There were 74 events (27 bleeding, 47 transfusions) in 11 subjects without a durable response. Conclusions: These preliminary data suggest that bleeding and transfusion events can be reduced in thrombocytopenic low risk MDS patients who respond to AMG 531.