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Correlation Analyses of Imetelstat Exposure with Pharmacodynamic Effect, Efficacy and Safety in a Phase 2 Study in Patients with Higher-Risk Myelofibrosis Refractory to Janus Kinase Inhibitor Identified an Optimal Dosing Regimen for Phase 3 Study

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Background: Imetelstat is a first-in-class telomerase inhibitor currently in clinical development for hematologic myeloid malignancies. IMbark (MYF2001; NCT02426086) was a 2-dose (9.4 mg/kg or 4.7 mg/kg IV every 3 weeks), randomized Phase 2 study of imetelstat in intermediate-2/high-risk myelofibrosis (MF) relapsed or refractory to prior Janus kinase inhibitor treatment. Comparing the 9.4 mg/kg arm to the 4.7 mg/kg arm, the rate of symptom response (total symptom score [TSS] reduction ≥50%) at Week 24 was 32.2% and 6.3%, respectively (Mascarenhas et al, ASH 2018 #685), and median overall survival (OS) was 28.1 months (mos) (95% confidence interval [CI]: 22.8, 31.6) for the 9.4 mg/kg arm and 19.9 mos for the 4.7 mg/kg arm (95% CI: 17.1, 33.9) with an overall study follow up of 42 mos (Mascarenhas et al, EHA 2020, EP1107). Dose-dependent on-target pharmacodynamic (PD) activity of imetelstat was observed and it correlated with clinical responses and longer OS (Mascarenhas et al, EHA 2020 EP1098). Here we report the results of imetelstat exposure-response analyses from IMbark to further evaluate the benefit/risk profile and justify 9.4 mg/kg every 21 days as the optimal dosing regimen for the planned Phase 3 study of imetelstat in refractory MF.

Methods: The average plasma concentration (C_{avg}) of imetelstat was used to define the exposure. The C_{avg} values of 107 patients (pts) were grouped into 4 quartiles (Q1-4) representing different levels of imetelstat exposure regardless of the protocol-specified dose arm assignment. Optimal PD effect of imetelstat was defined as ≥50% reduction in telomerase activity or human telomerase reverse transcriptase (hTERT) from baseline. The exposure-response relationships between exposure quartiles and PD effect, symptom response, OS, and laboratory safety parameters were assessed.

Results: The association between the 4 exposure quartiles and dose levels showed that 89% of pts in Q1 (the lowest exposure quartile) were treated with 4.7 mg/kg, while 96% of pts in Q4 (the highest exposure quartile) were treated with 9.4 mg/kg. The pts in the 4.7 mg/kg arm who had higher exposure in Q3 and Q4 were mainly those with dose escalation to 9.4 mg/kg, and pts in the 9.4 mg/kg arm who had lower exposure in Q1-Q2 were mainly those with dose delay, reduction, or interruption. 51.9% of pts in Q1, 63% in Q2 (vs Q1, p=0.5826), 77.8% in Q3 (vs Q1, p=0.0861), and 80% in Q4 (vs Q1, p=0.0439) achieved the optimal PD effect, respectively, indicating exposure-dependent on-target activity of imetelstat. The symptom response rate for pts in exposure quartile Q1, Q2, Q3, and Q4 was 7.4%, 18.5% (vs Q1, p=0.4203), 18.5% (vs Q1, p=0.4203), and 38.5% (vs Q1, p=0.0091), respectively. Median OS was 18.9 mos in Q1, 23.6 mos in Q2 (hazard ratio [HR]=0.663; 95% CI: 0.350, 1.259; log-rank p=0.2097), 24.6 mos in Q3 (HR=0.656; 95% CI 0.348, 1.236; p=0.1920) and 30.6 mos in Q4 (HR=0.467; 95% CI: 0.236, 0.925; p=0.0260), respectively. The exposure-response analyses showed that pts in the highest exposure quartile were more likely to have better clinical outcome.

The relationship between exposure quartiles and hematological and liver function safety parameters was assessed. There were no significant differences between each imetelstat exposure quartile group on the change from baseline in hemoglobin concentration, platelet count, and neutrophil counts; or in the rate of Grade 3+ neutropenia, thrombocytopenia, and elevations in alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and bilirubin. Pts with higher imetelstat exposure had similar rates of Grade 3+ adverse events as pts with lower exposure, suggesting that the lower dose does not improve safety.

Conclusions: In summary, the exposure-response analysis results indicated 9.4 mg/kg and 4.7 mg/kg covered the therapeutic window of imetelstat in MF pts. Imetelstat 9.4 mg/kg every 21 days treatment yielded higher exposure, leading to higher rate of pts achieving the optimal PD effect, consistently better clinical benefits, such as higher symptom response and significantly longer median OS, and had a similar safety profile as 4.7 mg/kg with regard to hematologic and liver function parameters. This exposure-response analysis of benefit/risk profile supports 9.4 mg/kg

every 21 days as the optimal dosing regimen for the planned imetelstat Phase 3 study in refractory MF.

Disclosures

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