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P1543 MITAPIVAT DECREASES THE NEED FOR TRANSFUSIONS SECONDARY TO POORLY TOLERATED ANEMIA AND ACUTE EVENTS COMPARED TO PLACEBO IN PATIENTS WITH PYRUVATE KINASE DEFICIENCY WHO ARE NOT REGULARLY TRANSFUSED

Topic: 28. Enzymopathies, membranopathies and other anemias

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Background: Pyruvate kinase (PK) deficiency is a rare, hereditary, chronic hemolytic anemia characterized by reduced activity of the red blood cell (RBC) PK (PKR) enzyme. A subset of patients (pts) require regular transfusions; however, transfusions may occasionally be needed in pts who are not regularly transfused due to hemolytic crisis, infections, and other acute events. Although transfusions can temporarily increase hemoglobin (Hb), they are associated with acute and chronic complications and can have a negative impact on quality of life. Mitapivat (AG-348) is a first-in-class, oral, allosteric activator of PKR which has demonstrated significant improvements in Hb, markers of hemolysis and hematopoiesis, and reduction in disease burden in pts who were not regularly transfused (ACTIVATE, NCT03548220) and significant reduction in transfusion burden in pts who were regularly transfused (ACTIVATE-T, NCT03559699) with PK deficiency.

Aims: Determine the effect of mitapivat on the number of transfusion episodes and RBC units transfused in pts with PK deficiency who were not regularly transfused, and randomized in the ACTIVATE trial.

Methods: ACTIVATE was a phase 3, global, double-blind, placebo (PBO)-controlled study of mitapivat in adults with PK deficiency who were not regularly transfused (≤4 transfusion episodes in prior year [yr]; none in prior 3 months). The proportion of pts requiring transfusions and the number of RBC units transfused were analyzed during the 24-week (wk) study (exploratory endpoint).

Results: 80 pts were randomized (mitapivat N=40; PBO N=40). The population was balanced between the mitapivat and PBO arms: mean age 36.6 yrs, 40% male, mean baseline Hb was 8.6 (mitapivat) and 8.5 (PBO) g/dL (Table). One pt in the PBO arm discontinued the study before being dosed. During the study, RBC transfusions were indicated for clinically significant or poorly tolerated anemia in 2 (5.0%) pts in the mitapivat arm (2 units in 1 pt and 4 units in the other pt) and 5 (12.8%) pts in the PBO arm (2 units per pt in 4 pts and 1 unit in 1 pt) (Table). Four (10.3%) pts in the PBO arm had transfusions (1–2 units per pt) due to an adverse event (AE) (viral upper respiratory tract infection, dyspnea, fatigue, presyncope). Two pts in the PBO arm received transfusions due to both an AE and clinically significant or poorly tolerated anemia. No pts in the mitapivat arm had transfusions due to an AE. One out of 11 (9.0%, mitapivat) and 6 out of 10 (60%, PBO) pts who received a transfusion in the 52 wks prior to study treatment required an on-study transfusion (Table).

Image:

Table. Baseline characteristics and on-treatment transfusion needs

Baseline characteristics[a]	Mitapivat N=40	Placebo N=40
Baseline Hb (g/dL), mean (SD)	8.6 (0.99)	8.5 (0.85)
Age (years), mean (range)	36.0 (18–70)	37.2 (19–78)
Sex (male), n (%)	16 (40)	16 (40)
On-treatment transfusion needs[b]	**Mitapivat N=40**	**Placebo N=39**
Reason for transfusion, n (%)	-	-
Adverse event[c]	0	4 (10.3)
Clinically significant or poorly tolerated anemia	2 (5.0)	5 (12.8)
Prior and on-treatment transfusions[a]	**Mitapivat N=40**	**Placebo N=40**
Pts with transfusions in the 52 weeks prior to study treatment, n (%)	11 (27.5)	10 (25.0)
Pts with prior transfusions who had on-treatment transfusions, n (%)	1/11 (9.0)	6/10 (60.0)

[a]Summarized based on full analysis set (all patients who were randomized to treatment). [b]Summarized based on safety analysis set (all patients who were received at least 1 treatment dose).[c]Adverse events requiring transfusion included viral upper respiratory tract infection, dyspnea, fatigue, presyncope. Hb=hemoglobin; Pts=patients; SD=standard deviation.

Summary/Conclusion: Mitapivat has the potential to decrease transfusion needs secondary to poorly tolerated anemia and acute events in pts with PK deficiency who are not regularly transfused, which is consistent with the decrease in transfusion burden previously observed in pts who are regularly transfused. This may in turn have a beneficial effect on reducing iron overload and improving the long-term disease burden and quality of life of pts with PK deficiency, across the disease spectrum. This analysis further adds to previously reported data showing beneficial effects of PK activation through mitapivat, the only disease-modifying drug therapy for adult pts with PK deficiency.