Abstract: P605

Title: OLUTASIDENIB DEMONSTRATES CLINICAL ACTIVITY IN MUTATED IDH1 ACUTE MYELOID LEUKEMIA (AML) SECONDARY TO MYELOPROLIFERATIVE NEOPLASMS (MPN)

Abstract Type: Poster Presentation

Topic: Acute myeloid leukemia - Clinical

Background:

Acute myeloid leukemia (AML) arising from myeloproliferative neoplasms (MPNs) represents a subtype of secondary AML associated with poor response to available therapies and dismal outcomes with a complete response (CR) rate of 35% and median survival of 3.6 months. [Tefferi A, Mudireddy M, Mannelli F. et al. Leukemia. 2018;32(5):1200–1210.] To date, there are no standardized treatment options and there has been very little therapeutic advancement over time. A registrational phase 1b/2 multi-center, open-label, multi-cohort trial (NCT02719574) enrolled patients with mutated *IDH1* (*mIDH1*) AML, who were treated with olutasidenib, an oral small molecule inhibitor of *mIDH1*. The results of the Phase 2 pivotal cohort demonstrated a CR or CR with partial hematologic recovery (CRh) in 35% of patients with a 25.9 month duration of response, leading to FDA approval of olutasidenib (OLU) for the treatment of relapsed or refractory (R/R) AML. The trial included patients with secondary AML due to MPNs.

Aims:

To examine the clinical outcomes of post-MPN AML patients enrolled in the phase 1b/2 trial, conducted between Apr 2016 and Dec 2023.

Methods:

This analysis included patients with *mIDH1* AML secondary to MPN treated with OLU 150mg BID as monotherapy or in combination with azacitidine (AZA). Endpoints included response as per International Working Group modified response criteria in AML, durability of response, and overall survival. Adverse events were graded by NCI-CTCAE v4.03.

Results:

Among 336 patients enrolled in the study, 16 patients had a prior history of MPN that transformed to AML and were included in this analysis. Of those, 5 patients had newly diagnosed AML and 11 had R/R AML, including 6 from the pivotal cohort and 1 with MRD+ CRi in a maintenance cohort. 6 were treated with OLU monotherapy and 10 in combination with AZA. The median age at diagnosis was 68 years (range 48-83). Male to female ratio was 11 to 5. Primary MPN diagnoses were polycythemia vera in 3, essential thrombocythemia in 3, primary myelofibrosis in 7, and MPN not otherwise specified in 3 patients. Median baseline bone marrow blast % was 35% (range 1-90). IDH1 mutation type was R132C in 10, R132H in 5, and R132L/G/S in 1. Frequent co-mutations included *JAK2* in 10 patients, *ASXL1* in 7, *SRSF2* in 6, *RUNX1* in 4, *MPL* in 3, and 2 each in *CALR*, *TP53*, *STAG2*, and *FLT3*. Cytogenetic risk status was intermediate in 12, poor in 3, and unknown in 1.

OLU was well tolerated with grade 3-4 adverse events (AEs) occurring in 7 (44%) patients and only 2 patients stopping therapy due to AEs, 1 on monotherapy and 1 on the combination. Responses included CR in 6 (38%) patients, with a median duration of response of 9.8 months (range 1.7-27.5). 2 additional patients had a complete response with incomplete hematologic recovery (CRi), and 1 had morphologic leukemia free state (MLFS) giving a composite complete response (CRc; CR+CRi) in 8 (50%) and an overall response rate (ORR; CR+CRi+MLFS) in 9 (56.3%).Of the 8 patients who achieved a CRc, 3 were treated with OLU monotherapy and 5 were treated with OLU and AZA. 2 patients who responded with a CR later received a transplant. Table 1 shows survival estimates with OLU. Median overall survival was 13.8 months (95% CI: 3.70, 23.7; range 1.6-55.3).

Summary/Conclusion:

OLU was effective and well tolerated in patients with post-MPN mIDH1 AML. These results appear to be appreciably better than outcomes reported in the literature, supporting a role for OLU based therapy in mIDH1 AML secondary to MPN.

Table. Kaplan Meier estimated Percent Survival in Patients with Post-MPN AML Treated with Olutasidenib

DURATION	SURVIVAL PERCENTAGE (95% CI)
3 months	87% (56, 96)
6 months	67% (38, 85)
12 months	53% (26, 74)
24 months	23% (6, 47)

Keywords: Acute myeloid leukemia, Myeloproliferative disorder