Abstract: S182

Title: IVOSIDENIB MONOTHERAPY IN IDH1 MUTATED MYELODYSPLASTIC SYNDROME, FINAL RESULTS OF THE IDIOME TRIAL, A GFM STUDY

Abstract Type: Oral Presentation

Session Title: Immune and targeted therapies in MDS

Background:

Ivosidenib (IVO) is an oral, targeted, small-molecule inhibitor of mutant*IDH1* (*IDH1m*) approved in association with azacytidine (AZA) for unfit adult patients with acute myeloid leukemia (AML) and as a single agent for relapse/refractory AML. Little is known about its efficacy in patients with *IDH1m* myelodysplastic syndromes (MDS). Here we report the final results of a Phase 2 single-arm study evaluating IVO in three cohorts of MDS patients: High-risk (HR-) having failed (R/R) AZA (cohort A), HR- as a first-line treatment (cohort B) and low-risk (LR-) having failed EPO (cohort C). (ClinicalTrials.gov NCT03503409).

Aims:

To evaluate the safety and efficacy of IVO in*IDH1m* HR-MDS, and evaluate the feasibility and toxicity of IVO in *IDH1m* LR-MDS.

Methods:

Subjects enrolled in cohort A, B or C received continuous 28-day cycles of IVO - 500 mg PO QD. In cohort B, AZA (75 mg/m2/d x 7 days, SC) was added to IVO after 3 cycles, in the absence of IWG 2006 response. The primary endpoint was the overall hematological response (OR) within 6 months. Secondary endpoints of the trial included safety, duration of response (DOR), overall survival (OS) and translational project evaluating the role of biomarkers on responses.

Results:

Between March 2019 and February 2023, 64 patients were screened, 48 were included (22, 23 and 3 in cohort A, B and C respectively), of whom 43 were evaluable for the primary endpoint. Median age was 76.5 years (IQR 72-80) and 50% were female. According to WHO 2016, 3 (6%) had MDS-MLD, 5 (10%) MDS-EB1, 23 (48%) MDS-EB2, one (2%) CMML and 16 (33%) low-blast AML. IPSS-R was low, intermediate, high and very high in 3 (6%), 12 (25%), 14 (29%) and 19 (40%) respectively. *IDH1m* variants were p.R132C (60%), p.R132H (17%), p.R132S (13%), p.R132G (8%) and p.R132L (2%). The median VAF of *IDH1m* in bone marrow at screening was 21%.

In R/R cohort A, ORR after 3 cycles was achieved in 63.6% patients (95%CI, 40.7-82.8) including 3 (21%) CR, one (7%) PR, and 10 (71%) HI, with a median DOR of 4.8 months. At data cut-off (Sept. 2023), 20 patients had died (mainly from disease) and 2 were still alive on therapy (Figure 1). Median OS was 8.9 months, and the 12-month OS rate was 15.2% (95%CI, 5.4-42.5).

In cohort B, ORR after 3 cycles was achieved in 78.3% patients (95%CI, 56.3-92.5) including 11 (61%) CR, 2 (11%) PR and 5 (28%) HI. AZA was added to IVO only in 3 patients after 3, 3 and 5 cycles, without additional response. Five patients have been bridged to transplant. At data cut-off, 8 patients (6 after progression, one after HSCT, and one from suicide) had died, 4 were still alive in CR after HSCT, 8 were still alive on therapy in CR, 2 alive after progression, one is still alive in CR but after IVO discontinuation after cycle 13, due to QTC prolongation.

With a median follow-up of 25.2 months, median OS and DOR were not reached and the 12-month OS rate was 91.3% (95%CI, 80.5-100).

In cohort C, two of the three patient achieved CR, one after 3 cycles, and one after 9 cycles. One patient died 2

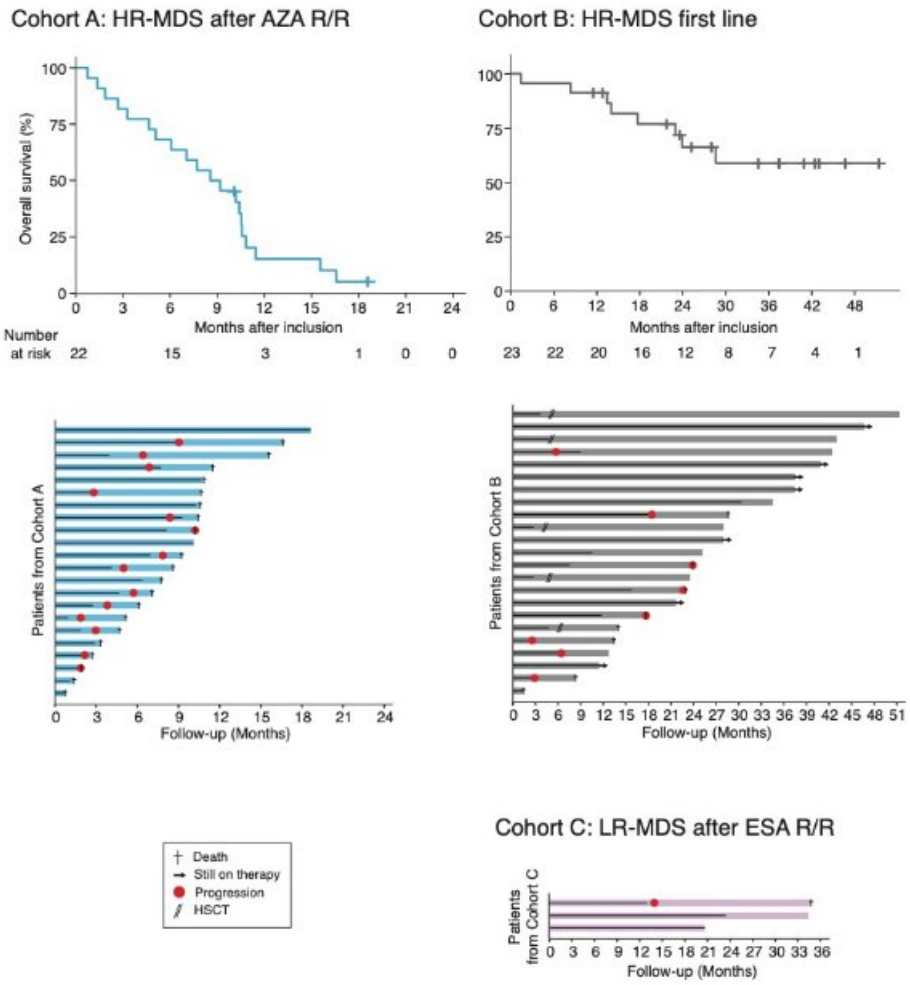
years after inclusion from progression after 13 cycles (DOR, 10 months), the two others are still alive without progression, one still in CR on therapy (20 cycles).

IVO was well tolerated, with 21 adverse events (AE) related to IVO reported in 9 patients, mainly differentiation syndrome, reversible in all cases.

Summary/Conclusion:

IVO monotherapy was associated with significant responses in all*IDH1m* MDS patients cohorts and, in this frail population, was well tolerated. The high OR rate and prolonged OS observed in treatment naive HR-MDS patients suggest that IVO monotherapy could be a first-line treatment in this population including in candidates for HSCT.

Figure 1:



Keywords: Myelodysplastic syndrome, Ivosidenib