AMLGlobalPortal

IDH1/2

ASH 2018 | Ivosidenib or enasidenib in combination with induction and consolidation therapy in newly diagnosed acute myeloid leukemia with *IDH* or *IDH2* mutation

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Isocitrate dehydrogenase (*IDH*) mutations occur in approximately 20% of acute myeloid leukemia (AML) patients and the prevalence increases with patient age. *IDH* enzymes catalyze the conversion of isocitrate to α-ketoglutarate (αKG). However, mutations in *IDH1/2* lead to a reverse reaction of αKG to the oncometabolite D-2-hydroxyglutarate (D-2HG). The accumulation of 2HG competitively inhibits αKG, thus leading to alterations in TET2-dependent hydroxymethylation, chromatin modification, activation of the hypoxic response, and increased dependence on BCL2. Ivosidenib and enasidenib are oral inhibitors of mutant *IDH1* (*mIDH1*) and mutant *IDH2* (*mIDH2*), respectively, approved for the treatment of relapsed/refractory *IDH*-mutant AML.

At the 60th American Society of Hematology Annual Meeting & Exposition, Eytan Stein from the Memorial Sloan Kettering Cancer Center, New York, US, presented data from a phase I multicenter study (NCT02632708), which is evaluating the safety of enasidenib or ivosidenib in combination with standard induction and consolidation therapy in newly diagnosed patients with *mIDH1* or *mIDH2* AML.

A total of 154 patients with *mIDH1* or *mIDH2* newly diagnosed AML were treated with induction therapy (daunorubicin 60 mg/m^2/day or idarubicin 12 mg/m^2/day for 3 days with cytarabine 200 mg/m^2/day for 7 days) in combination with either ivosidenib (500mg daily; n = 60) for *mIDH1* or enasidenib (100 mg once daily; n = 93). After induction, patients may receive ≤ 4 cycles of consolidation therapy while continuing the *mIDH* inhibitor.

Key findings:

Safety

- Grade ≥ 3 *IDH* differentiation syndrome occurred in 3% (2/60) of patients treated in the ivosidenib/chemotherapy arm and 1% (1/93) in the enasidenib/chemotherapy arm
- Grade ≥ 3 QT interval prolongation occurred in one patient in the ivosidenib/chemotherapy arm
- Grade ≥ 3 adverse event of increased blood bilirubin occurred in 7% (4/60) of patients treated in the ivosidenib/chemotherapy arm and 14% (13/93) in the enasidenib/chemotherapy arm
- 30-day and 60-day mortality rate in patients in the ivosidenib/chemotherapy arm were 5% (4/60) and 8% (5/60) respectively
- 30-day and 60-day mortality rate in patients in the enasidenib/chemotherapy arm were 5% (5/93) and 9% (8/93) respectively

Efficacy in evaluable patients in the ivosidenib/chemotherapy arm

- Complete response (CR) plus CR with incomplete blood count (CRi)/CR with incomplete platelet recovery (CRp): 80% (39/49)
- CR rate in patients with *de novo* AML: 91% (31/24)
- CR rate in patients with secondary AML (sAML): 53% (8/15)
- Treatment failure occurred in 12% (6/49) of patients

Efficacy in evaluable patients in the enasidenib/chemotherapy arm

- CR plus CRi/CRp rate: 72% (64/89)
- CR rate in patients with *de novo* AML: 64% (36/56)
- CR rate in patients with sAML: 64% (21/33)
- Treatment failure occurred in 15% (13/89) of patients

Mutation clearance and measurable residual disease (MRD) assessment

- In patients who achieved a CR, *IDH*-mutation clearance (*IDH*-MC) by digital PCR was observed in 41% (12/29) of those with *mIDH1* and in 25% (15/59) of those with *mIDH2*
- In patients treated with ivosidenib who achieved a CR, 88% (15/17) became MRD- negative
- In patients treated with enasidenib who achieved a CR, 45% (9/20) became MRD-negative

Eytan Stein concluded by stating that the "combination of ivosidenib or enasidenib with induction and consolidation therapy is safe and well tolerated in patients with newly diagnosed AML with *IDH* mutation. In subsets of patients who achieved CR, ivosidenib, and enasidenib led to an MRD-negative CR and mutation clearance in a population of older, high-risk patients with *mIDH* AML."

References

1. Stein E. *et al*. Ivosidenib or enasidenib combined with induction and consolidation chemotherapy in patients with newly diagnosed AML with an IDH1 or IDH2 mutation is safe, effective, and leads to MRD-negative complete remissions. 2018 Dec 3; Oral Abstract #560: 60th ASH Annual Meeting and Exposition, San Diego, CA.