Somatic mutations in the aspartate-d Dehydrogenase (DH) 2 and 3 genes occur in ~20% of patients with acute myeloid leukemia (AML). The methyltransferase 2 (DNMT2) enzyme catalyzes the reduction of alpha-ketoglutarate to the inosimabile 2,3-dihydroxyglutarate (2HG), and the resulting 2HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation.

Azacitidine reduces DNA methylation by inhibiting DNA methyltransferases.

An overall response rate (ORR) of 41.6% (95% CI 32.9, 50.8).

An ongoing phase 1b/2 study is assessing the combination of ivosidenib or enasidenib with azacitidine in patients with mIDH1/2 inhibitors + azacitidine in patients with ND-AML who are ineligible for intensive chemotherapy.

The ivosidenib + azacitidine combination was well tolerated in patients with mIDH1.

The majority of patients with CR also had CRh, as assessed by the sponsor, and defined as CR except absolute neutrophil count ≤ 0.1 × 10^9/L and platelet count ≤ 100 × 10^9/L.

A median duration of CR or CRh of 8.2 months.

The ivosidenib + azacitidine combination is being further studied in a phase 1b/2 open-label, randomized, multicenter trial to assess the safety and tolerability of the ivosidenib + azacitidine combination in patients with mIDH1/2 inhibitors + azacitidine in patients with ND-AML who are ineligible for intensive chemotherapy.