IDH inhibitor

IDH inhibitors have shown good clinical response in AML patients. Based on phase 1/2 clinical trials, enasidenib and ivosidenib have been approved by the Food and Drug Administration (FDA) on 1 August 2017 and 20 July 2018 for the treatment of adult R/R AML with IDH2 and IDH1 mutations, respectively.

Allosteric inhibitors of mutant IDH1 or IDH2 induce terminal differentiation of the mutant leukemic blasts and provide durable clinical responses in approximately 40% of acute myeloid leukemia (AML) patients with the mutations. However, primary resistance and acquired resistance to the drugs are major clinical issues. To understand the molecular underpinnings of clinical resistance to IDH inhibitors (IDHi), Wang et al. performed multipronged genomic analyses (DNA sequencing, RNA sequencing, and cytosine methylation profiling) in longitudinally collected specimens from 60 IDH1- or IDH2-mutant AML patients treated with the inhibitors. The analysis reveals that leukemia stemness is a major driver of primary resistance to IDHi, whereas selection of mutations in RUNX1/CEBPA or RAS-RTK pathway genes is the main driver of acquired resistance to IDHi, along with BCOR, homologous IDH gene, and TET2. These data suggest that targeting stemness and certain high-risk co-occurring mutations may overcome resistance to IDHi in AML. [1)]

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