

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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Wang F, Morita K, DiNardo CD, Furudate K, Tanaka T, Yan Y, Patel KP, MacBeth KJ, Wu B, Liu G, Frattini M, Matthews JA, Little LD, Gumbs C, Song X, Zhang J, Thompson EJ, Kadia TM, Garcia-Manero G, Jabbour E, Ravandi F, Bhalla KN, Konopleva M, Kantarjian HM, Andrew Futreal P, Takahashi K. **Leukemia stemness** and co-occurring mutations drive resistance to IDH inhibitors in acute myeloid leukemia. Nat Commun. 2021 May 10;12(1):2607. doi: 10.1038/s41467-021-22874-x. PMID: 33972549.

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