

### Transcript Details

This is a transcript of an educational program accessible on the ReachMD network. Details about the program and additional media formats for the program are accessible by visiting: <https://reachmd.com/programs/medical-industry-feature/therapeutic-targets-in-acute-myeloid-leukemia/11611/>

### ReachMD

www.reachmd.com  
info@reachmd.com  
(866) 423-7849

---

## Therapeutic Targets in Acute Myeloid Leukemia

### ReachMD Announcer:

Welcome to ReachMD. The following program, "Therapeutic Targets in Acute Myeloid Leukemia" is developed and sponsored by AbbVie. This activity is intended for United States and Puerto Rico health care professionals only.

The US Medical Affairs department of AbbVie Inc. is the sole author and copyright owner of this presentation and has paid ReachMD to host this presentation. AbbVie is solely responsible for all written and oral content within this presentation. ©2020 AbbVie Inc. All rights reserved.

The following speaker has received compensation from the US Medical Affairs department of AbbVie Inc. to prepare and present the following information and is speaking on behalf of AbbVie.

### Dr. Erba:

I am Dr. Harry Erba, director of the Leukemia Program and Medical Director of the Hematologic Malignancies Inpatient Unit at Duke University in Durham, North Carolina.

For several decades, therapy for AML was rather straightforward based on the determination of whether a patient was fit or unfit for intensive chemotherapy, and then subsequent selection from among limited treatment options. Recently, a deeper understanding of the pathogenesis of AML has led to the identification of potential therapeutic targets that give us options in addition to our standard cytotoxic chemotherapy.

From the Cancer Genome Atlas study, 23 recurrently mutated genes in AML were identified and categorized, with each mutation representing a potential target for drug development in AML. Among these genes, signaling and kinase pathway genes are common, including fms-like tyrosine kinase 3, or FLT3, which is often associated with gain-of-function mutations. Activating FLT3 mutations contribute to constitutive activation of the receptor and subsequent constant transduction of proliferation signals to downstream pathways.

The tumor suppressor gene TP53 is important for the regulation of apoptosis and cell cycle integrity. Mutated TP53 contributes to uncontrolled cellular proliferation and the promotion of neoplasia.

Mutations in the isocitrate dehydrogenase (IDH) family, including IDH1 and IDH2, are often seen in older patients and in patients with intermediate-risk disease. Mutated IDH enzymes catalyze the reduction of  $\alpha$ -ketoglutarate to the oncometabolite, 2-hydroxyglutarate, which is associated with DNA and histone hypermethylation, altered gene expression, and blocked differentiation of hematopoietic cells. IDH inhibitors drive clinical efficacy via the induction of myeloblast differentiation.

The B-cell lymphoma-2, or BCL-2, family includes 12 or more proteins that either inhibit or promote apoptosis. The balance between the pro- and anti-apoptotic BCL-2 proteins determines whether a cell lives or dies. Pro-apoptotic proteins antagonize anti-apoptotic proteins, including BCL-2, by binding of the BH3 domain to the hydrophobic pocket of anti-apoptotic proteins. Molecules have been developed that mimic the BH3 domain to antagonize the effect of anti-apoptotic proteins.

In the past few years, the US Food and Drug Administration has approved eight therapies for patients with AML, targeting activating mutations of FLT3 and IDH, as well as expression of BCL-2, Smoothed in the Hedgehog Pathway, and the cell surface molecule CD33. Furthermore, synergistic activity between chemotherapy and these targeted agents has allowed for the development of additional regimens in AML that older and more infirm patients may be able to tolerate.

**ReachMD Announcer:**

This program was brought to you by AbbVie. If you missed any part of this discussion or to find others in this series, visit [ReachMD.com/SpotlightOn](https://ReachMD.com/SpotlightOn). This is ReachMD. Be part of the knowledge.

BCL2-US-00035-MC

Approved: November 2020