Naval Daver, MD
Assistant Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

What are the latest updates on the IDH1 and IDH2 inhibitor studies?

Welcome to *Managing AML*. I am Dr. Naval Daver. I am frequently asked, "What are the latest updates on the IDH1 and IDH2 inhibitor studies?" So, the IDH1 and IDH2 inhibitors have shown very promising activity in patients with acute myeloid leukemia (AML). The IDH2 inhibitors were the first ones to go into clinic about 2 years ago, and now, there have been about 200 plus patients enrolled on these studies.[1] The overall response rate is about 35% to 40%, including 20% that are complete response (CR) and an additional 15% to 20% that are partial responses and hematological improvements. One of the key features we have noticed is that a lot of the responses, including the partial responses or hematological improvements, have been very durable. This is a new era for acute myeloid leukemia where patients who do not achieve complete remission may have prolonged benefit from some of these agents.

The other benefit of these agents is that they are oral, therefore easy to administer, they have minimum toxicities, and are extremely well-tolerated. We have seen a few instances of transaminitis and usually it is reversible. So, all in all, I think the IDH1[2] and IDH2[1] inhibitors are a breakthrough for AML therapy, being oral agents, and targeting the particular mutations.

An important point to note is that the IDH2 mutation is present in about 8% to 10% of patients, and the IDH1 is present in about 10% to 12%. IDH inhibitors do not cover all AMLs, but they are good options for the 15% to 20% of patients who have an IDH1 or IDH2 mutation. Further, these drugs are now being developed in the front-line setting in combination with standard approved agents for AML, such as azacitidine plus IDH inhibitor for the older patients who are not fit for any intensive chemo,[3] and then 7+3* or high-dose chemo plus IDH inhibitor in the younger population.[4] I think these studies will be even more interesting to see if we can get more durable remissions that will then result in improved survival by using targeted therapies with chemotherapy upfront.

Note added post-recording: A randomized study of IDH2 inhibitor versus standard of care in older patients with late relapse of AML who harbor an IDH mutation is also currently accruing.[5]

**7+3, referred to in the video as 3+7, is most often used today as first-line induction therapy in AML, and consists of 7 days of standard dose cytarabine and 3 days of an anthracycline, most often daunorubicin.*

References

1. Phase 1/2 Study of AG-221 in Subjects With Advanced Hematologic Malignancies With an IDH2 Mutation. *https://clinicaltrials.gov/ct2/show/NCT01915498*
2. Study of Orally Administered AG-120 in Subjects With Advanced Hematologic Malignancies With an IDH1 Mutation. *https://clinicaltrials.gov/ct2/show/NCT02074839*
3. A Safety and Efficacy Study of Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus Subcutaneous Azacitidine in Subjects With Newly Diagnosed Acute Myeloid Leukemia (AML). *https://clinicaltrials.gov/ct2/show/NCT02677922*
4. Safety Study of AG-120 or AG-221 in Combination With Induction and Consolidation Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia With an IDH1 and/or IDH2 Mutation. *https://clinicaltrials.gov/ct2/show/NCT02632708*
5. An Efficacy and Safety Study of AG-221 (CC-90007) Versus Conventional Care Regimens in Older Subjects With Late Stage Acute Myeloid Leukemia Harboring an Isocitrate Dehydrogenase 2 Mutation (IDHENTIFY). *https://clinicaltrials.gov/ct2/show/NCT02577406*