

## Shall We Dance: Evolving Partnerships of Targeted Therapies for AML

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In this issue of *Clinical Cancer Research*, Konopleva and colleagues (1) and Pollyea and colleagues (2) provide response and survival outcomes of two important genetic subsets of patients with newly diagnosed acute myeloid leukemia (AML) treated with the novel, and now standard, frontline regimen of venetoclax and azacitidine (VEN/AZA). These two reports detail how patients with mutations in the genes Fms-like tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase 1 and 2 (IDH1, IDH2) respond to VEN/AZA. These common, recurrent AML mutations are important therapeutic subgroups not only due to their prognostic role in disease response, but also because of the availability of molecularly targeted therapy that provide potential alternatives to the VEN/AZA approach, as well as options for future targeted combinations.

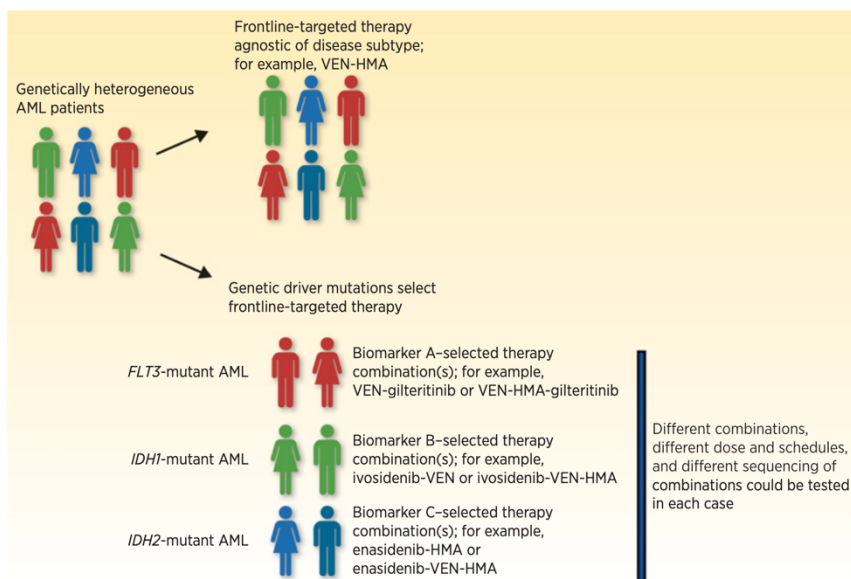
Single-agent, low-dose cytarabine or DNA methyltransferase-1 inhibitors (commonly known as hypomethylating agents, or HMA) such as AZA had traditionally served as a standard—albeit not very satisfactory—therapy for newly diagnosed patients with AML ineligible for intensive chemotherapy combining anthracycline and standard dose cytarabine combinations. A phase Ib trial combining the BCL2 inhibitor, venetoclax, with an HMA then showed dramatically higher and faster response rates, longer survival than historic experience, and a tolerable safety profile (3). The following phase III VIALE-A study was a double-blind, randomized controlled trial that compared VEN/AZA with AZA/placebo in newly diagnosed patients considered ineligible for intensive chemotherapy due to comorbidity or age over 75 years (4). In this trial, the VEN/AZA combination resulted in both a substantially higher composite complete remission rate as well as significantly longer overall survival than AZA/placebo. Because AML is primarily a geriatric cancer, these results changed the treatment paradigm in a large fraction of patients and established VEN/AZA the new standard of care in patients unsuitable for intensive chemotherapy. A number of novel agents recently entered the AML therapeutic armamentarium, including drugs that selectively inhibit the enzymatic function of oncoproteins arising from recurrent somatic driver mutations in IDH1, IDH2, or FLT3. Accordingly, clinical use of IDH or FLT3 inhibitors is predicated upon the detection of these mutations at the time of treatment. Functionally, mutant IDH1 and IDH2 encode distinct isoforms of a citric acid cycle enzyme. Pathogenic IDH mutations are present in up to 20% of patients with AML ineligible for intensive chemotherapy and lead to a neomorphic enzymatic function that generates high levels of the cancer-associated metabolite 2-hydroxyglutarate (2-HG; refs. 5, 6). 2-HG structurally resembles alpha ketoglutarate (αKG) and contributes to leukemogenesis by inhibiting a number of αKG-dependent dioxygenases, leading to epigenetic deregulation of genes involved in myeloid differentiation, such as TET2 and members of the Jumonji-C family of histone demethylases (7). In addition, 2-HG inhibits cytochrome-c oxidase, further increasing survival dependency upon BCL2 in IDH-mutated AML cells and predicting particular sensitivity of patients with these mutations to venetoclax-containing therapy (8). Tyrosine kinase-activating mutations in the hematopoietic cytokine receptor FLT3 occur in approximately 25% of newly diagnosed patients with AML (5). These constitutively activate multiple cascades of intracellular signal transduction, including PI3K/AKT, RAS-MAPK, and STAT5 to promote differentiation block, proliferation, and cell survival. Prognostically, internal tandem duplications in FLT3 (FLT3-ITD) are associated with high relapse rates and poor survival to standard chemotherapy regimens. Isoform-selective inhibitors of IDH1 and IDH2 (ivosidenib and enasidenib, respectively) were approved for single-agent use by the FDA and are effective for treatment of relapsed or refractory (R/R) patients with IDH mutations as single agents, based upon complete remission rates of approximately 30% in that setting with very favorable side-effect profiles. The FLT3 inhibitors midostaurin and gilteritinib were approved in combination with intensive chemotherapy in fit, newly diagnosed patients or as a single agent for R/R patients, respectively, based upon survival benefits seen in randomized, controlled trials (refs. 9, 10). Because of the success of drugs like midostaurin, newly diagnosed fit patients now undergo rapid determination of actionable mutations to select regimens that integrate novel agents into an intensive chemotherapy backbone. However, no mutation-driven strategy guides the treatment of patients with lower intensity approaches, such as VEN/AZA. The reports by Pollyea and Konopleva begin to inform how to assess whether using a regimen based upon a mutation-agnostic approach such as VEN/AZA should be the standard or frontline targeted therapies should be favored. By pooling datasets from the VEN/AZA arm of the VIALE-A trial (4) with those from the preceding phase Ib study (3), these two articles dissect the response and survival data from these two trials in the IDH- and FLT3-mutated subsets. Combining

data from two trials that used very similar enrollment criteria, the authors are able to show for the first time the outcomes of various different mutations within these genes, such as an analysis of IDH1 or IDH2 mutation specifically or the difference in response and survival among patients with FLT3-ITD or FLT3 tyrosine kinase domain (FLT3-TKD) mutations. They also examine the impact of comutation with NPM1, which is relatively commonly seen with each of these mutations and appears to positively modulate response rate and survival to VEN/AZA. Obviously, we should be cautious to avoid overinterpreting small subsets, particularly any comparisons with AZA, which was only included in one of the two trials analyzed. Still, these two reports suggest substantial heterogeneity in response and survival among patients with IDH and FLT3 mutations. Specifically, the authors show patients with IDH2 mutations and FLT3-TKD mutations had particularly high rates of remission and long survival when treated with VEN/AZA, not only in comparison with patients treated with AZA/placebo, but also when compared with those treated with VEN/AZA who had IDH1 or FLT3-ITD mutation. As FLT3-TKD mutation was relatively uncommon on these trials, the observed results with FLT3-ITD largely drive observations among all FLT3- mutated patients and suggest considerable room for improvement in that subset. There are at least 2 ways we can begin to look at these data. First, they raise the question of whether the standard karyotype and genomic classification used by European Leukemia Network (ELN; revised 2017) should be used to risk stratify patients treated with VEN/AZA. Because VEN/AZA's biologic mechanism of action is distinct from cytotoxic chemotherapy, it is conceivable that the ELN classification may suboptimally predict response and survival to this regimen. One could imagine that mutations like IDH2, FLT3-TKD, or NPM1 predict particularly favorable outcomes with the VEN/AZA regimen and might allow treatment discontinuation after a fixed duration of therapy. Conversely, mutations like TP53, FLT3-ITD in the absence of mutated NPM1, or persistent measurable residual disease might establish such patients as a higher risk group that requires augmented or alternative therapy. Further work is needed to validate this approach. The second way to consider these data is to put the outcomes of VEN/AZA in the context of alternative approaches using targeted therapy. Specifically, because VEN/AZA is a mutation-agnostic approach, should this be offered to all patients as initial therapy and then targeted therapy only added in sequence for suboptimal responders, or those who relapse? Or would an alternative, mutation-targeted therapy be the initial therapy? Or finally should the addition of a targeted agent to VEN/AZA be considered to improve outcome for certain, mutation-defined subsets (Fig. 1)? To address these questions, frontline data from studies of targeted agents in mutation-defined groups of patients ineligible for intensive chemotherapy have already begun. Results from some of these studies have been recently published or reported in abstract form. These studies generally combined an IDH or FLT3 inhibitor with an HMA ("doublet therapy"), or with VEN/AZA ("triplet therapy"). Although many such reports have design limitations or lack mature survival data, pivotal trials were also recently reported and may inform therapy. While results of a phase III, open-label randomized comparison of gilteritinib/AZA with AZA alone were disappointing (LACEWING trial, NCT02752035), a randomized, placebo-controlled, double-blind comparison of ivosidenib/AZA with AZA/placebo showed improved event-free and overall survival for ivosidenib/AZA (AGILE trial, NCT03173248). These results present a real challenge to VEN/AZA in terms of which approach should guide initial therapy of IDH1- mutated patients unsuitable for intensive chemotherapy. From a practical standpoint, if ivosidenib/AZA is preferred over VEN/AZA, one must consider whether the value of this alternative justifies delaying therapy for the vast majority of patients with AML while screening for a mutation seen in <10% of patients. In summary, these two studies provide a backdrop for major initiatives, underway in the United States and Europe, to test novel targeted therapies with a VEN/AZA backbone and consequently the implementation of rapid screening of all newly diagnosed patients with AML unsuitable for intensive chemotherapy. The subsets presented here by Pollyea and colleagues and Konopleva and colleagues will help power statistical comparisons for these studies. Hopefully these coming trials will define the next generation of prognostic scoring systems and treatment algorithms that address the key question of whether targeted agents should be combined with VEN-AZA or sequenced for patients with AML ineligible for intensive therapy. Finally, as combinations evolve and more targeted therapies come into play, it is likely we will use new clinical trial designs not only to efficiently test the safest and most effective combinations, but also the sequence in which they should be used.

#### Authors' Disclosures

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**Figure 1.**

Frontline treatment of a genetically heterogeneous group of newly diagnosed patients with AML can be either mutation agnostic as it is currently, with VEN-AZA, or could be based on mutations detected with different combinations and sequencing of targeted inhibitors. AML, acute myeloid leukemia; *FLT3*, Fms-like tyrosine kinase 3; HMA, hypomethylating agent; *IDH*, isocitrate dehydrogenase; VEN, venetoclax.