# Therapy for acute myeloid leukemia in older and unfit adults

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The therapy of acute myeloid leukemia (AML) has experienced a renaissance in the past 5 years with the approval of nine new targeted agents and over 12 regimens.[1] Historically, therapy for AML was the domain of healthy, young, 'fit' individuals.[2] In 1973 the "7+3" regimen achieved an unprecedented 63% remission rate.[2] However, this intense regimen confines patients to the hospital for a month with one study showing that 12.3% of patients died during this time.[3] With the average age at the diagnosis of AML being 68 years, this therapy is not a viable option for many patients.[3] In the 44 years after this breakthrough, there were minimal changes, with many challenges facing additional agents such as the approval, subsequent withdrawal and re-approval of gemtuzumab ozogamicin.[1] Then, in 2017, a flurry of Food and Drug Administration approvals for targeted therapies began with midostaurin (NCT00782067).[1] However, these therapies were mostly relegated to the relapsed/refractory setting or as inclusions in intensive regimens for fit patients. That was until the landmark VIALE-A trial.[4] In this double-blinded, randomized trial venetoclax was added to azacitidine and compared to azacitidine alone (at the time the standard of care for older adults). The venetoclax plus azacitidine group had a significant and clinically meaningful improvement in response rates and survival, as compared with the azacitidine-only group, in treatment-naïve, predominantly elderly patients with AML ineligible for intensive therapy. The primary endpoint was overall survival, which was a median of 14.7 months with venetoclax plus azacitidine and 9.6 months with azacitidine alone. Serious adverse events occurred in 83% and 73% of the patients, respectively, and the composite complete remission rates were 66.4% and 28.3% in the two groups. With a similar safety profile and significantly improved results, the venetoclax plus azacitidine combination became the new standard of care for older adults. Despite their age these patients achieve excellent responses and frequently proceed to stem cell transplantation, extending their overall survival to become comparable to that of their counterparts treated with intensive therapy.[4] For this reason, expanding the use of venetoclax in combination with a hypomethylating agent to younger and fit patients who are also candidates for intensive chemotherapy is being actively studied in a clinical trial (MM1OA-EA02).[5] Not only did this trial move the remission rate of older unfit adults into the realm of the rates achieved by the "7+3" regimen, but it also did so in a mostly genetically agnostic way. Venetoclax is a first-in-class targeted medicine designed to selectively bind and inhibit the B-cell lymphoma-2 (BCL-2) protein, preventing the binding and releasing BAX and inducing apoptosis.[4] The venetoclax/azacitidine combination is not targeted against a single mutation but rather against a fundamental survival mechanism that leukemic cells are highly dependent upon. While subsequent research has shown that some mutations and variants, such as *RAS* mutations, *FLT3* mutations and monocytic subtypes, are less sensitive to venetoclax, the drug still has efficacy in these patients.[1] This allowed the benefits of the trial to be applied to the diverse landscape of *de novo* AML. In 1973 the care of young healthy AML patients took a massive leap forward; 44 years later VIALE-A helped older unfit AML patients to catch up.

## Disclosures

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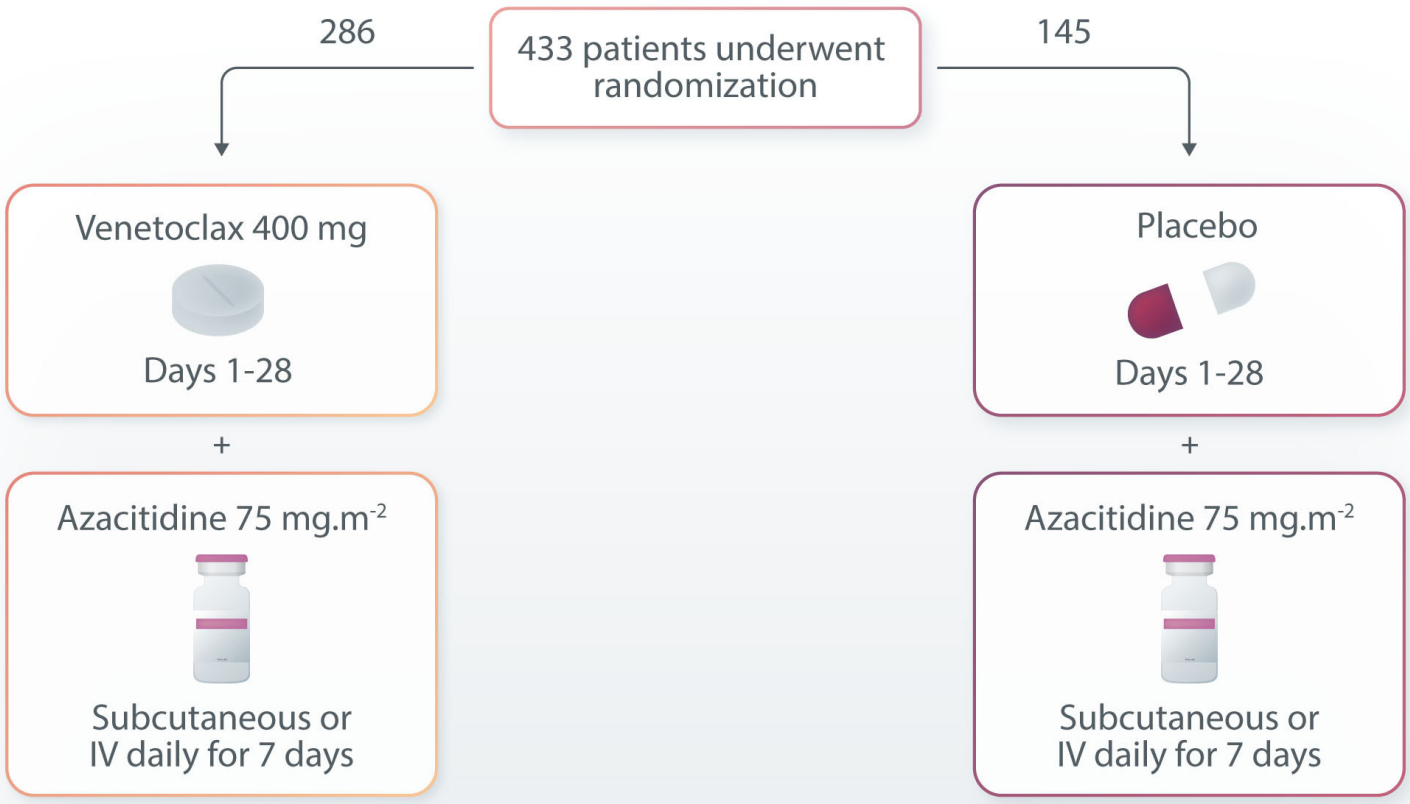


**Figure 1. The protocol and main result of the VIALE-A trial.** A simplified protocol scheme for the VIALE-A trial is shown above the Kaplan-Meier analysis of the findings. The hazard ratio for death was estimated using the Cox proportional hazard method. The data were subject to a cutoff date of January 4, 2020. The solid line indicates the 50% overall survival probability. *Figure adapted, with permission, from DiNardo et al.*[4]

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**Contributions**

*Both authors contributed equally.*

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