

Targeting leukemia stem cells in unfit acute myeloid leukemia with a CD70-directed third agent: promise and caveats from the ELEVATE trial. Comment on: "Cusatuzumab combined with venetoclax with or without azacitidine in unfit patients with newly diagnosed acute myeloid leukemia: phase Ib ELEVATE study"

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Targeting leukemia stem cells in unfit acute myeloid leukemia with a CD70-directed third agent: promise and caveats from the ELEVATE trial. Comment on: “Cusatuzumab combined with venetoclax with or without azacitidine in unfit patients with newly diagnosed acute myeloid leukemia: phase Ib ELEVATE study”

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Contributions

Both authors contributed equally to conceptualizing and writing this Comment.

In a recent issue of *Haematologica*, Roboz and colleagues report the phase Ib ELEVATE trial, in which the anti-CD70 monoclonal antibody cusatuzumab was added to venetoclax plus azacitidine (CVA, n=44), or to venetoclax alone (CV, n=16), in older or comorbid patients with newly diagnosed acute myeloid leukemia (AML) ineligible for intensive chemotherapy.¹ The CVA triplet achieved an overall response rate (ORR; CR+CRh+CRi) of 77.3% and a median overall survival (OS) of 12.0 months.¹ As one of the first clinical tests of a leukemia-stem-cell (LSC)-directed triplet in this setting, ELEVATE is encouraging, yet four issues warrant discussion before these signals are extrapolated: the place of CD70 among third agents, the hematologic and infectious price, the non-randomized cohort comparison, and the design of the confirmatory trial.

The mechanistic rationale is compelling. CD70 is overexpressed on CD34+ AML progenitors and LSCs, where CD70/CD27 signaling sustains blast stemness, whereas its expression on healthy tissues is limited.² Both azacitidine and venetoclax up-regulate CD70 on LSCs, sensitizing them to cusatuzumab, which in turn synergizes with venetoclax to eradicate the LSC reservoir that underlies relapse after BCL-2 inhibition.^{3,4} ELEVATE thus joins a broader effort to layer an LSC-targeting agent onto the azacitidine–venetoclax backbone established by VIALE-A.⁵ Whether CD70 blockade is differentiated from, for example, the anti-CD47 antibody magrolimab evaluated in ENHANCE-3 cannot yet be settled,⁶ but the convergent strategy—simultaneously targeting the bulk blast population, apoptotic dependence and the resistant LSC pool—is biologically coherent at a time when relapse after venetoclax-based therapy remains almost uniformly poor.^{7,8}

The efficacy signals are notable for a population with a median age of 75 years in which 61.4% had adverse-risk disease by ELN 2017.¹ The 47.7% CR rate (77.3% when CRh and CRi are included) compares favorably with the 27% CR rate of cusatuzumab–azacitidine in CULMINATE,⁹ and activity spanned genetic risk categories, with a 70.4% ORR even in adverse-risk patients.¹ Remission depth was also encouraging: 52.9% of CR/CRi responders (18/34) achieved measurable residual disease (MRD) negativity by centralized multiparameter flow cytometry, and 13.6% proceeded to allogeneic transplantation.¹ In an exploratory long-term analysis, roughly one-third of responders

were alive beyond two years.¹ Such signals are hypothesis-generating but meaningful in a disease in which durable disease control with low-intensity therapy remains exceptional.⁷

The cost was substantial myelosuppression and infection. Grade 3 or higher treatment-emergent adverse events occurred in 97.7% of CVA patients; grade 3 or higher neutropenia and thrombocytopenia each affected roughly three-quarters, febrile neutropenia 38.6%, sepsis 36.4%, and grade 5 events 13.6%.¹ Venetoclax relative dose intensity was only 41.9%, and from cycle 5 onward venetoclax was given for a median of just 14 days per cycle, while 95% of patients had cycle delays.¹ Although broadly comparable to other venetoclax-based triplets,⁶ this profile shows that successful delivery will depend on proactive infection surveillance, timely growth-factor and transfusion support, and individualized venetoclax scheduling—areas in which structured nursing and supportive-care pathways are decisive in patients this elderly.

Two interpretive caveats deserve emphasis. First, allocation to CVA or CV was left to investigator discretion rather than randomization, and CV patients were markedly frailer (75% aged over 75 years, 56% with ECOG performance status 2, 31% with prior hypomethylating therapy).¹ The contrast between 12.0-month OS with CVA and 3.4 months with CV therefore reflects confounding by indication as much as any contribution of azacitidine, and cannot establish that the doublet is ineffective or that azacitidine is indispensable. Second, as a single-arm phase Ib study with median follow-up of only 43.1 weeks and no planned cross-cohort comparison, ELEVATE cannot demonstrate superiority; juxtaposition with VIALE-A, CULMINATE or ENHANCE-3 remains confounded by differing populations, eras and supportive care.^{5,6,9} The MRD results likewise require careful denominators—52.9% among CR/CRi responders versus 23.8% among CR patients—and MRD status was not significantly associated with OS ($P=0.2$), whereas the striking 57.9-month median OS among two-year survivors is conditional on having already responded and survived.¹

These caveats do not diminish the signal; they define what the confirmatory step must resolve. The ongoing randomized phase II trial of CVA versus azacitidine–venetoclax (NCT06384261) is therefore welcome and should, in our view, pre-specify stratification by the 2024 ELN genetic classification¹⁰ and by key lesions such as TP53, harmonize

MRD methodology, and capture infectious burden and venetoclax delivery as core endpoints. If CD70-directed LSC eradication can independently deepen and prolong remissions in adverse-risk, unfit AML, ELEVATE will be recognized as a worthwhile first step.

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