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Beyond venetoclax and azacitidine: CD70-targeted triplet therapy in acute myeloid leukemia

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In this edition of *Haematologica*, Roboz and colleagues describe the results of the ELEVATE study combining Cusatuzumab with standard of care treatment in acute myeloid leukemia (AML) patients who are ineligible for intensive chemotherapy (1). This population, composed of older adults and patients with clinically significant comorbidities, frailty, or reduced functional reserve, remains a major clinical challenge. For decades, therapeutic options were limited and were associated with modest response rates, short remission duration, and poor overall survival. The introduction of lower-intensity regimens, particularly the combination of venetoclax and azacitidine (VEN-AZA), has substantially improved the therapeutic landscape and established a new standard of care for many patients who cannot tolerate intensive induction chemotherapy (2). However, despite this important progress, the benefits of VEN-AZA are not universal or permanent. Primary resistance occurs in a significant subset of patients, and relapse after an initial response remains frequent. Consequently, durable disease control continues to be difficult to achieve, highlighting the urgent need for treatment strategies that can deepen responses, eradicate residual disease, and prevent relapse.

In this context, triplet regimens are emerging as a promising next step in AML treatment development. By adding a third agent to the VEN-AZA backbone, these strategies aim to enhance antileukemic activity through complementary mechanisms of action. Several targeted triplets have already generated considerable interest, particularly in molecularly defined AML subgroups (3). Nevertheless, these strategies remain restricted to specific molecular subsets and therefore cannot address the broader population of patients with AML. This limitation is particularly relevant in older or unfit patients, whose disease is often characterized by complex clonal architecture, adverse-risk cytogenetics, and molecular heterogeneity. There is therefore a clear need for novel approaches that may be applicable beyond narrowly defined genomic categories.

Immunotherapeutic strategies, particularly monoclonal antibodies, have emerged as attractive approaches in oncology because of their ability to selectively target tumor-associated antigens

and, in some cases, enhance antitumor immune responses. In several hematologic malignancies, antibody-based therapies have transformed clinical practice and have demonstrated the value of targeting surface antigens expressed by malignant cells. In AML, however, the development of effective immunotherapeutic approaches has been more challenging. The majority of trials using antibodies targeting CD33, CD123, CD371 (CLL1/Clec12), and CD47 have failed. This can be explained by the biological heterogeneity of the disease, and because leukemic blasts often share antigenic features with normal hematopoietic progenitors, raising concerns about on-target off-leukemia toxicity. In addition, AML cells can evade immune surveillance through multiple mechanisms, including impaired antigen presentation, immunosuppressive microenvironmental interactions, and the persistence of leukemic stem and progenitor cell populations (4). These factors underscore the need for combinations capable of both enhancing antileukemic activity and targeting disease reservoirs responsible for relapse.

These limitations provide the rationale for developing more effective immune-based combinations capable of overcoming resistance and improving the durability of response. In this evolving therapeutic landscape, cusatuzumab, a monoclonal antibody targeting CD70, represents one of the most promising strategies (5,6). Its clinical relevance has been explored in the ELEVATE study, which evaluated cusatuzumab in combination with venetoclax and azacitidine (CVA). This triplet regimen is designed to address one of the major limitations of current treatment approaches: the persistence of leukemic stem cells, which is strongly implicated in therapeutic resistance and disease relapse. By integrating an immune-targeting agent with two established components of lower-intensity AML therapy, the CVA regimen seeks not only to induce remission but also to improve the quality and depth of response.

Cusatuzumab's mechanism of action is particularly relevant in AML. The antibody binds with high affinity to CD70 and disrupts CD70/CD27 signaling, a pathway that has been implicated in leukemic stem cell survival, proliferation, and immune escape. CD70 is overexpressed on AML progenitors and leukemic stem cells while showing more restricted expression in normal hematopoietic compartments, making it an appealing therapeutic target (7,8). Beyond direct pathway inhibition, cusatuzumab may also promote antibody-dependent cellular cytotoxicity and contribute to immune-mediated elimination of leukemic cells. Preclinical studies have provided a strong rationale for combining cusatuzumab with venetoclax and azacitidine. Venetoclax targets the anti-apoptotic protein BCL-2 and promotes apoptosis in AML cells, while azacitidine can modify epigenetic programs and potentially increase immune visibility (9,8). The synergy observed between these agents supports the hypothesis that CVA may more effectively target both bulk leukemic blasts and disease-propagating stem cell populations (**Figure**).

The results of the phase 1b ELEVATE study are therefore encouraging. The CVA regimen achieved a composite response rate of 77.3%, with 47.7% of patients attaining complete remission. These results are in line with other trials using a monoclonal antibody in addition with a VEN-AZA

backbone (**Table**). Importantly, 53% of responders reached measurable residual disease negativity, suggesting that responses were not only frequent but also deep. The safety profile appeared consistent with expectations for this patient group and with the known toxicities of VEN-AZA-based therapy, with hematologic and infectious adverse events that were generally manageable with appropriate supportive care and treatment modifications.

The comparison with the CV cohort, in which cusatuzumab was combined with venetoclax without azacitidine, further reinforces the importance of the triplet approach. The less favorable efficacy and survival observed with CV suggest that azacitidine remains a critical component of the regimen, potentially contributing both cytotoxic and immunomodulatory effects.

In summary, the ELEVATE study introduces a compelling therapeutic concept for vulnerable patients with AML by combining targeted immune intervention with established lower-intensity therapy. The CVA regimen offers a biologically rational approach aimed at improving response depth and addressing leukemic stem cell persistence, one of the central mechanisms of relapse. While these early clinical data are promising, they require confirmation in larger, randomized studies with longer follow-up and correlative analyses to better define predictive biomarkers, durability of response, and long-term safety. As AML treatment continues to move toward precision medicine and mechanism-based combinations, the integration of targeted therapies such as cusatuzumab may represent an important step toward improving outcomes, prognosis, and quality of life for patients who remain poorly served by current therapeutic options.

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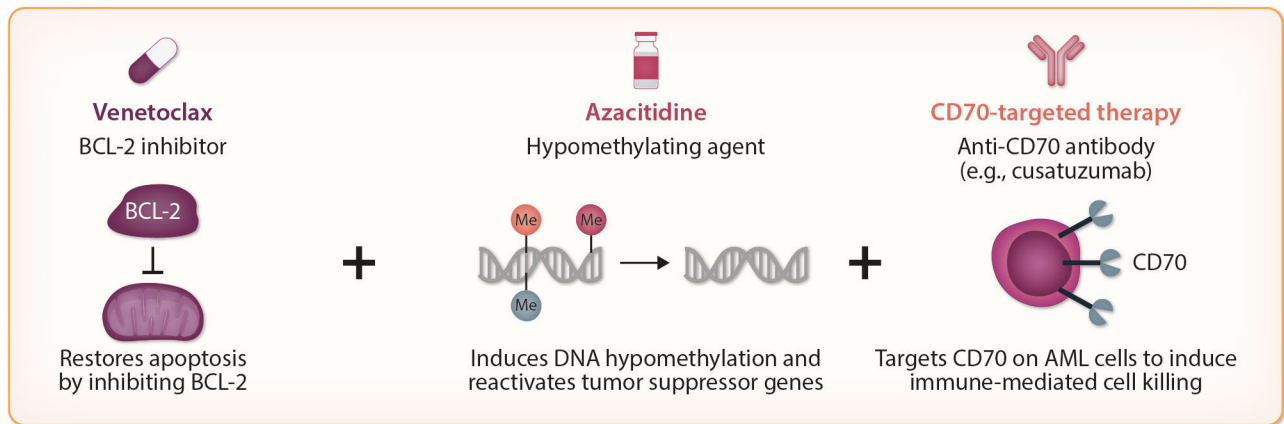
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Study	Drug	CR	CR/CRh/CRi	reference
ENHANCE-3 (NCT05079230)	Mogralimab	41.3%	47.6%	Daver, Blood 2025
EVICTON (NCT04243499)	ICT-01	68% (10 mg) and 44% (75mg)	84% (10 mg) and 69% (75mg)	Garciaz, ASH 2025
STIMULUS-AML1 (NCT04150029)	Sabatolimab	47.1%	69.5%	Zeidan, EHA 2025

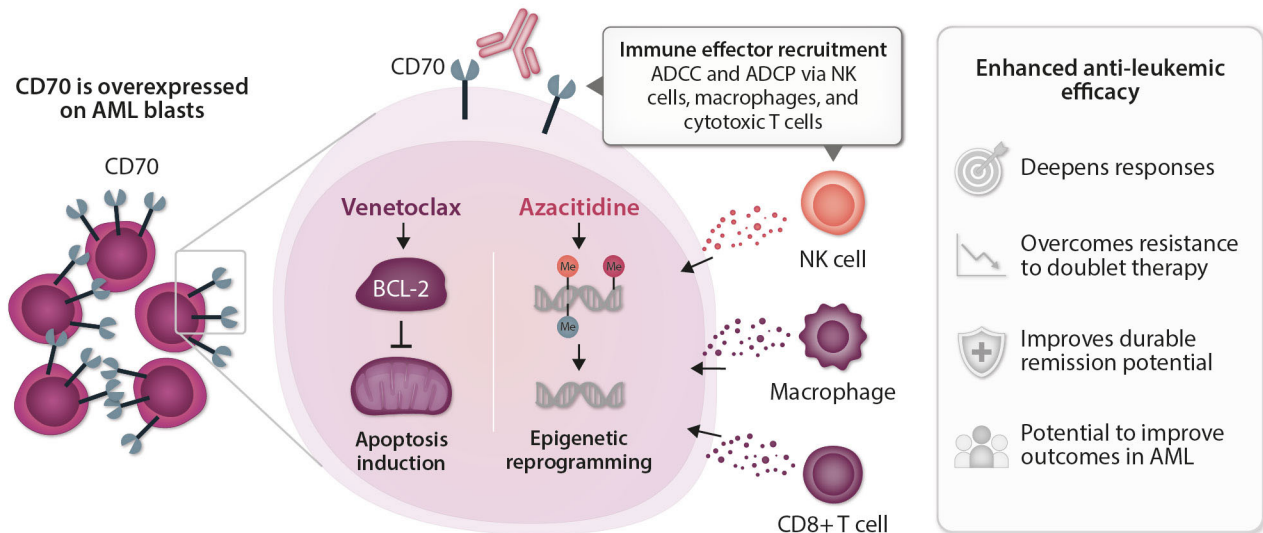
Table. Comparison of other triplets studies using VEN-AZA as a backbone and monoclonal antibodies in AML.

Legend : **Biological rationale and clinical evaluation of CD70-targeted triplet therapy in acute myeloid leukemia.** Cusatuzumab binds CD70 on acute myeloid leukemia (AML) blasts, progenitors, and leukemia stem cells, thereby blocking CD70/CD27 signaling and promoting immune-mediated cytotoxicity. Venetoclax inhibits BCL-2 at the mitochondria to restore apoptosis, whereas azacitidine induces DNA hypomethylation and epigenetic reprogramming. Together, these complementary mechanisms are intended to target both bulk leukemic cells and relapse-initiating stem-cell populations.

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Triplet therapy: Multimodal anti-leukemic activity



Targeting CD70 adds an immune-directed mechanism to the proven synergy of Venetoclax and Azacitidine, offering a rational next step to improve outcomes in AML.