Venetoclax in MDS: From breakthrough to bottleneck

Market Event Summary

Vidhi Khosla | August 2025

Venetoclax is at the intersection of setback and strategy

Background

- **Venetoclax**, marketed as Venclexta in the United States and Venclyxto in Europe, is a pioneering oral **BCL-2 inhibitor** developed by AbbVie and Genentech (Roche). It targets the anti-apoptotic BCL-2 protein, reactivating programmed cell death in BCL-2–driven hematologic malignancies. It is globally approved for treating CLL, SLL, and AML.

Event summary

- On June 16, 2025, AbbVie announced that the **Phase 3 VERONA** trial (NCT04401748), evaluating Venetoclax + azacitidine in newly diagnosed higher-risk MDS, **did not meet its primary endpoint of OS** (HR = 0.908; p = 0.3772).
- No new safety concerns emerged, and the combination remained tolerable.
- Secondary endpoints (mOR, CR) and full results will be disclosed at upcoming medical conferences or in peer-reviewed publications.

Clinical results in MDS

- **Phase 1b M15-531 trial (NCT02942290):** Venetoclax + azacitidine showed efficacy, with an 80.4% marrow response rate, 50.5% mCR, and a median OS of 26 months in untreated high-risk MDS patients. Transplant candidates achieved higher responses (CR: 41%, mCR: 45%). However, 94.4% experienced grade ≥ 3 adverse events—mainly neutropenia, thrombocytopenia, and febrile neutropenia.
- **The ongoing Phase 1/2 (NCT04550442):** Venetoclax + azacitidine in high-risk MDS and R/R CMML showed a 48% response rate in 33 patients enrolled between September 2020 and January 2024, including those with prior HMA failure and elevated blasts. At a median follow-up of 4 months, grade ≥ 3 infectious complications—pneumonia (12%), febrile neutropenia (9%), sepsis (9%), and cellulitis (9%)—were commonly observed.

Clarivate's takeaways

Key opinion leaders interviewed by Clarivate identified venetoclax + azacitidine as a potential new SOC for high-risk MDS, based on compelling early data. However, the Phase 3 VERONA trial early results disrupt expectations.

Treatment void in high-risk MDS deepens: The Phase 3 VERONA trial setback stalls a promising front-line therapy for newly diagnosed high-risk MDS—a population already burdened by scarce treatment options. This outcome narrows therapeutic flexibility for clinicians in the frontline setting—reinforcing the unmet need for novel treatments in this underserved segment.

The road ahead - navigating the impact of VERONA in MDS: AbbVie's anticipated 2026 launch of venetoclax in high-risk MDS now faces uncertainty, following trial failure that disrupted regulatory momentum and weakened its clinical narrative. Comprehensive results from the VERONA trial may help clarify the drug's development path and future positioning. Should positive results emerge from other endpoints or ongoing trials, venetoclax could launch later in our forecast period (2024-2034)—but the timing shift could dampen peak-year sales expectations, while emerging therapies on the distant horizon may further impact venetoclax's market uptake.

AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CMML: chronic myelomonocytic leukemia; CR: complete remission; HMA: hypomethylating agents; HR: hazard ratio; mCR: marrow complete response; MDS: myelodysplastic syndromes; mOR: modified overall response; OS: overall survival; R/R: relapsed/refractory; SOC: standard of care; SLL: small lymphocytic lymphoma

About the author

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Ms. Khosla has several years of experience providing consulting, research, and analytic support in the pharmaceutical and healthcare domains and has worked in numerous therapy areas, including neurology, women's health, metabolic disorders, and rare diseases. She earned her bachelor's and master's (gold medalist) degrees in biochemistry from Delhi University and Kurukshetra University, respectively, and an M.B.A. from Symbiosis International University.

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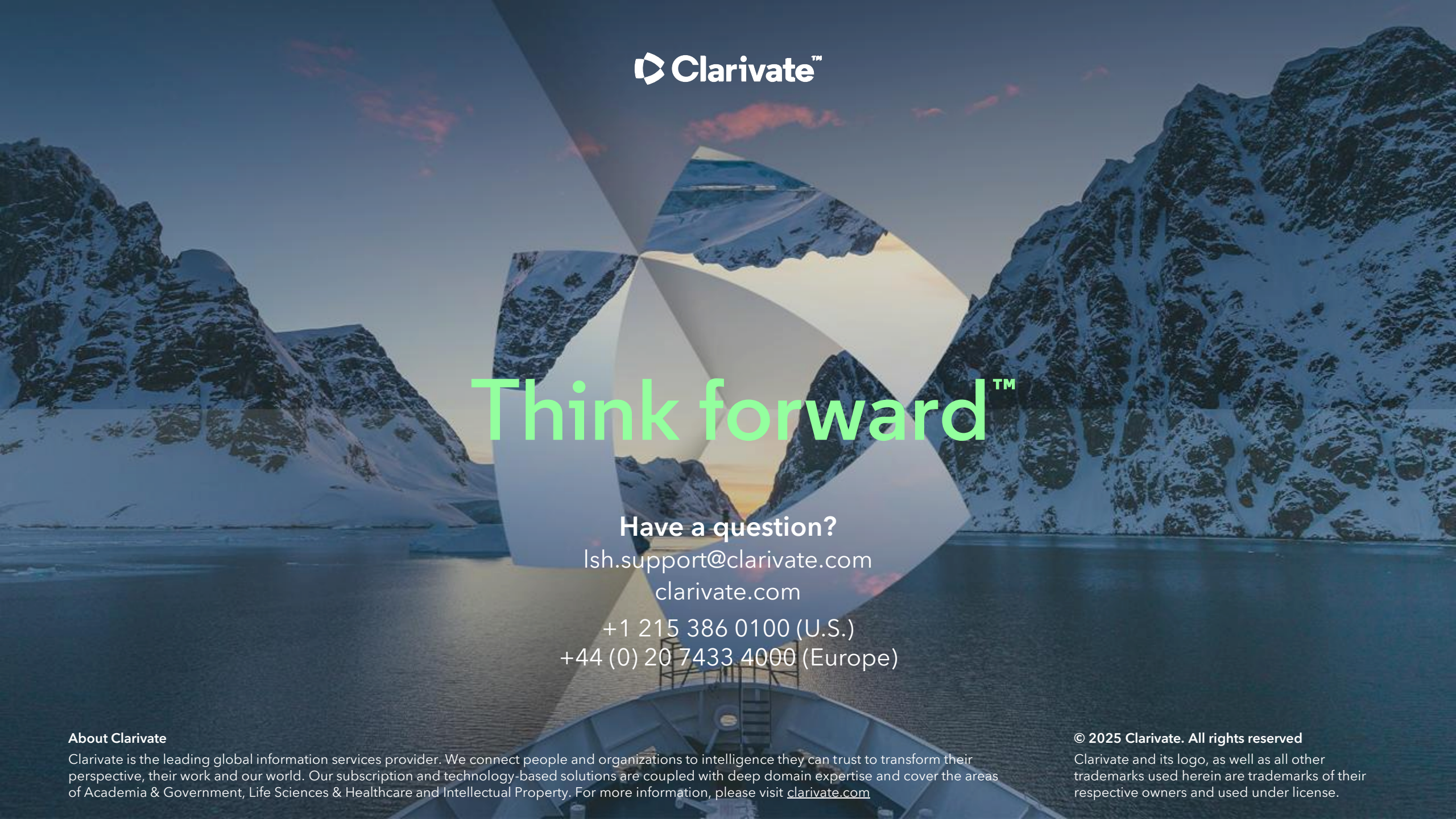

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