Efficacy of Venetoclax-Based Therapy in t(11;14)-Positive Relapsed/Refractory Multiple Myeloma

SOHO 2026 ANNUAL MEETING

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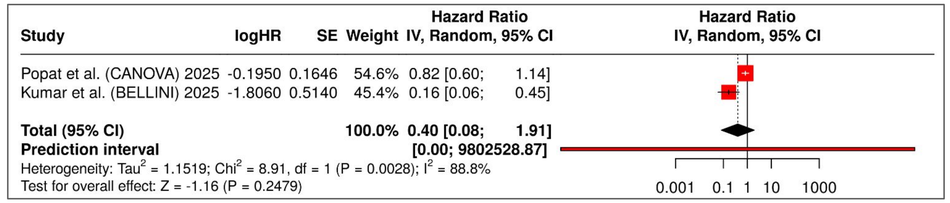
INTRODUCTION

Translocation between chromosomes 11 and 14 [t(11;14)] is one of the most common primary cytogenetic abnormalities in multiple myeloma. Venetoclax is a highly selective, oral BH3 mimetic that binds B-cell lymphoma-2 (BCL-2), inducing apoptosis in BCL-2–dependent plasma cells. Early phase studies suggested promising activity of venetoclax-based regimens, particularly in t(11;14) relapsed/refractory multiple myeloma (RRMM). However, venetoclax has not received FDA approval for the treatment of RRMM, in part due to results from two phase III randomized trials.

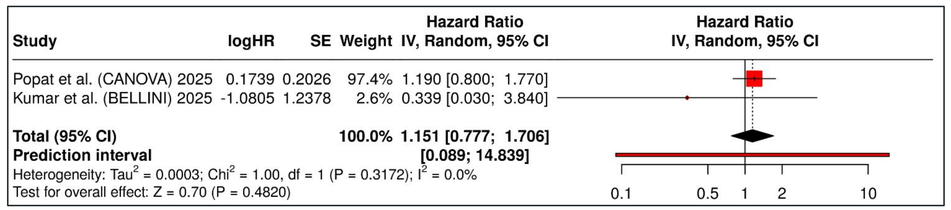
METHODS

A systematic literature search was performed across PubMed-MEDLINE, Embase-OVID, CENTRAL, ClinicalTrials.gov, and Web of Science databases up to January 1, 2025. Randomized phase III trials evaluating venetoclax-based therapy versus standard-of-care regimens in patients with t(11;14)-positive RRMM were included. Progression-free survival (PFS) was the primary outcome. Overall survival (OS) and time to deterioration in disease-related symptoms (TTDDS) were secondary outcomes. Hazard ratios (HRs) were pooled using a random-effects inverse-variance model with heterogeneity assessed using the I^2 statistic.

Progression-Free Survival (PFS)



Overall Survival (OS)



Time To Deterioration in Disease-Related Symptoms (TTDDS)

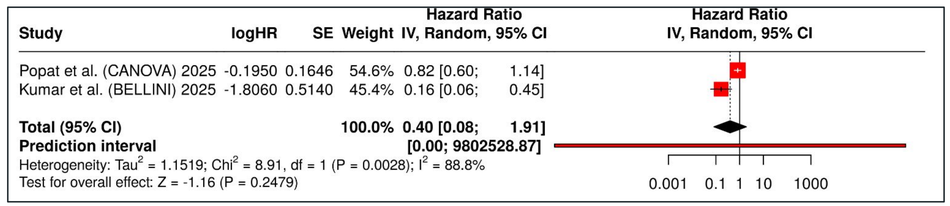


Figure 2 Summary of Pooled Outcomes

RESULTS

A total of 298 patients from two phase III randomized controlled trials (CANOVA and BELLINI) were included. Venetoclax-based therapy was associated with a directionally favorable improvement in PFS (pooled HR 0.40; 95% CI, 0.08–1.91). No pooled OS benefit was observed (HR 1.15; 95% CI, 0.78–1.71). Venetoclax-based regimens demonstrated a trend toward prolonged TTDDS (TTDDS HR 0.70; 95% CI, 0.46–1.05). Substantial heterogeneity was observed for PFS (I^2 = 88.8%), while heterogeneity was minimal for OS and TTDDS (I^2 = 0%). None of the pooled efficacy outcomes reached statistical significance.

CONCLUSIONS

Venetoclax-based therapy demonstrates a directionally favorable effect on PFS and TTDDS in t(11;14)-positive RRMM. In BELLINI, despite a small subgroup sample size, venetoclax demonstrated an effect size rarely observed in RRMM, whereas CANOVA was conducted against a highly active comparator. Future trials should prioritize t(11;14) populations and consider non-inferiority or combination-based comparator designs. The lack of statistical significance in pooled outcomes likely reflects differences in trial design and treatment backbone rather than absence of biological activity.

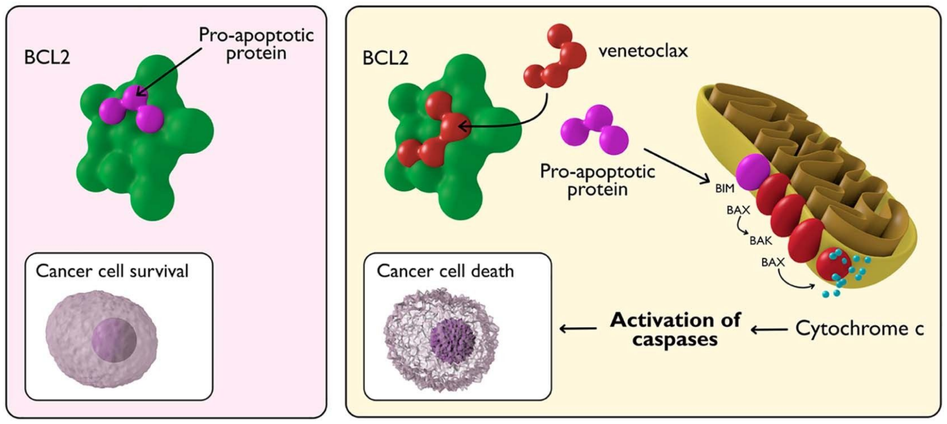


Figure 1 Mechanism of Action of Venetoclax

CLINICAL IMPORTANCE

Venetoclax is commonly used off-label in patients with relapsed/refractory multiple myeloma (RRMM) who harbor the t(11;14) translocation, despite lack of FDA approval.

Randomized trial results have been conflicting, leading to uncertainty among clinicians about how effective venetoclax truly is in this setting.

This meta-analysis shows that venetoclax demonstrates a biologically plausible, directionally favorable efficacy signal, but results vary substantially depending on trial design and comparator regimen.

Not all t(11;14) patients derive the same benefit, emphasizing the importance of patient selection, disease context, and treatment backbone.

REFERENCES