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## *on multiple myeloma*

CAR+ T-cell lymphoma after cilta-cel therapy for relapsed or refractory myeloma

*The New England Journal of Medicine, 2025 February 13; 392(7):677–85*

Belantamab mafodotin plus bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-7): updated overall survival analysis from a global, randomised, open-label, phase 3 trial

*The Lancet Oncology, 2025 August; 26(8):1067–80*

Venetoclax or placebo in combination with bortezomib and dexamethasone in relapsed or refractory multiple myeloma (BELLINI): final overall survival results from a randomised, phase 3 study

*The Lancet Haematology, 2025 August; 12(8):e574–87*

Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial

*Nature Medicine, 2025 April; 31(4):1195–20*

ISSUE 6, 2025

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**Art Design**
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**Layout and Printing**
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**Publisher**
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# CAR+ T-CELL LYMPHOMA AFTER CILTA-CEL THERAPY FOR RELAPSED OR REFRACTORY MYELOMA

*The New England Journal of Medicine, 2025 February 13; 392(7):677–85*

AUTHORS: Harrison SJ, Touzeau C, Kint N, et al.
CENTRE FOR CORRESPONDENCE: Clinical Haematology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

**BACKGROUND & AIM:** As of December 2023, 22 cases in which patients treated with approved chimeric antigen receptor (CAR) T-cell therapies developed T-cell malignant neoplasms had been reported to the US Food and Drug Administration, with CAR transgenes detected in malignant clones in three patients. In the phase 3 CARTITUDE-4 trial, patients with lenalidomide-refractory multiple myeloma were treated with ciltacabtagene autoleucel (cilta-cel), an anti-B-cell maturation antigen-directed CAR T-cell therapy produced by means of lentiviral transduction. The aim of this study was to conduct clinicogenomic characterization of clinically aggressive peripheral T-cell lymphoma–not otherwise specified, referred to as a CAR transgenic T-cell lymphoproliferative neoplasm (CTTLN), that developed in two CARTITUDE-4 participants after cilta-cel infusion.

**STUDY DESIGN:** Patient case studies.

**ENDPOINT:** Clinicogenomic features.

**METHOD:** After apheresis, both patients received two cycles of bridging therapy with daratumumab, pomalidomide and dexamethasone, and then lymphodepletion before receiving a single infusion of cilta-cel. The clinical follow-up protocol for CARTITUDE-4 has been described in a previous report.

**RESULTS:** Both patients had antimyeloma responses to cilta-cel therapy before developing CTTLN. The first patient developed a facial lesion 5 months after infusion, and imaging showed bilateral cervical lymphadenopathy. Lesion and lymph node biopsy samples revealed similar atypical T-cell infiltrates. Parvovirus B19 infection was detected in the second patient 84 days after infusion and was treated with high-dose intravenous immunoglobulin, with clearance by 8 months after cilta-cel infusion. CAR T-cell counts increased during the infection and did not return to preinfection levels. The patient developed several skin masses 16 months postinfusion and imaging showed progressive lesions in the bones, breasts, skin, lungs and lymph nodes. Monoclonal T cells from both patients showed CAR transgene expression and integration. Similar clinicogenomic features of the CTTLNs in both patients suggested that multiple intrinsic and/or extrinsic factors may have contributed to their pathogenesis, including cutaneous involvement, the presence of *TET2* anomalies around 2 years before cilta-cel infusion, viral infection (COVID-19 on day 31 postinfusion in patient 1) soon before CTTLN detection, and previous treatment with therapies associated with an increased risk of second primary malignant neoplasms.

**CONCLUSION:** Although CTTLNs appear to be rare events, vigilant monitoring for T-cell lymphomas should be implemented in patients treated with CAR T-cell therapy.

https://doi.org/10.1056/NEJMoa2309728

# BELANTAMAB MAFODOTIN PLUS BORTEZOMIB AND DEXAMETHASONE IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (DREAMM-7):

## UPDATED OVERALL SURVIVAL ANALYSIS FROM A GLOBAL, RANDOMISED, OPEN-LABEL, PHASE 3 TRIAL

*The Lancet Oncology, 2025 August; 26(8):1067–80*

AUTHORS: Hungria V, Robak P, Hus M, et al., on behalf of the DREAMM-7 study investigators
CENTRE FOR CORRESPONDENCE: Hospital Universitario de Salamanca/IBSAL/CIC/Ciberonc, Salamanca, Spain

**BACKGROUND & AIM:** Effective second-line therapy combinations that include new drug classes are required for patients with relapsed or refractory multiple myeloma (RRMM). In the first interim analysis of the ongoing DREAMM-7 trial (median follow-up 28.2 months), the combination of belantamab mafodotin, bortezomib and dexamethasone (BVd) demonstrated superior progression-free survival over daratumumab, bortezomib and dexamethasone (DVd) in patients with RRMM who had received at least one previous line of therapy (hazard ratio 0.41, 95% confidence interval 0.31–0.53; $p<0.001$). The aim of this article was to report efficacy data from the second interim analysis of DREAMM-7.

**STUDY DESIGN:** International, open-label, randomized, phase 3 trial.

**ENDPOINTS:** Primary: overall survival. Secondary: overall response rate; minimal residual disease-negativity ($10^{-5}$ threshold) rate; duration of response; second progression-free survival; safety.

**METHOD:** Adults with RRMM were randomized to receive either BVd ($n=243$) or DVd ($n=251$) until disease progression, death, unacceptable toxicity, consent withdrawal or loss to follow-up. Belantamab mafodotin and daratumumab were administered intravenously at doses of 2.5 and 16 mg/kg, respectively.

**RESULTS:** At a median follow-up of 39.4 months (range 0.1–52.3 months), median overall survival was not reached in either group and the 3-year overall survival rate was 74% with BVd versus 60% with DVd (HR 0.58, 95% CI 0.43–0.79; $p=0.0002$). The overall response rate was 83% versus 71%, respectively. Minimal residual disease-negativity rates in those with a complete response or better were 25% with BVd and 10% with DVd, and the median duration of response was 40.8 and 17.8 months, respectively. More patients in the DVd versus the BVd group discontinued treatment owing to disease progression (64% versus 30%) and received subsequent therapies (52% versus 36%). Following subsequent antimyeloma therapy, median second progression-free survival was not reached with BVd versus 33.4 months with DVd (HR 0.59, 95% CI 0.45–0.77). Serious adverse events were seen in 53% of patients who received BVd and 38% who received DVd, and treatment-related serious adverse events resulted in death in 3% and 1%, respectively.

**CONCLUSION:** In the second interim analysis of DREAMM-7, BVd was associated with significant and clinically meaningful efficacy benefits compared with DVd.

https://doi.org/10.1016/S1470-2045(25)00330-4

# VENETOCLAX OR PLACEBO IN COMBINATION WITH BORTEZOMIB AND DEXAMETHASONE IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA (BELLINI):

## FINAL OVERALL SURVIVAL RESULTS FROM A RANDOMISED, PHASE 3 STUDY

*The Lancet Haematology, 2025 August; 12(8):e574–87*

AUTHORS: Kumar SK, Harrison SJ, Cavo M, de la Rubia J, Popat R, Gasparetto C, Hungria V, Salwender H, Suzuki K, Kim I, Onishi M, Ku G, Pothacamury R, Jalaluddin M, Zeng J, Ross JA, Dobkowska E, Moreau P
CENTRE FOR CORRESPONDENCE: Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA

**BACKGROUND & AIM:** The primary analysis (median follow-up 18.7 months) of the phase 3 BELLINI study in adults with relapsed or refractory multiple myeloma (RRMM) showed that triplet therapy with venetoclax, bortezomib and dexamethasone significantly improved progression-free survival and the overall response rate compared with placebo, bortezomib and dexamethasone. Median overall survival (OS) was not reached in either group, but early mortality was unexpectedly elevated with venetoclax. The aim of this study was to report the final OS analysis of BELLINI.

**STUDY DESIGN:** International, randomized, double-blind, phase 3 trial.

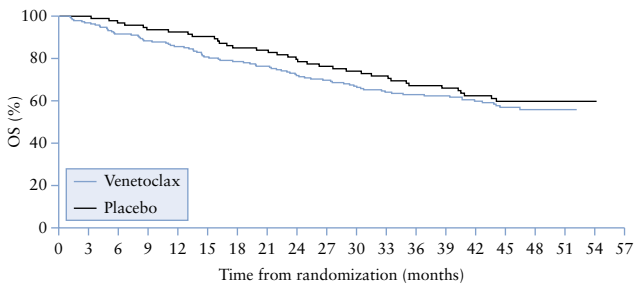
**ENDPOINTS:** OS; progression-free survival; overall response rate; duration of response; safety.

**METHOD:** Adults with RRMM and one to three prior lines of therapy were randomized to receive either venetoclax (800 mg/day; *n*=194) or placebo (*n*=97), plus bortezomib and dexamethasone, until progressive disease, unacceptable toxicity or patient withdrawal.

**RESULTS:** A total of 28 patients in the venetoclax group and five in the placebo group were still receiving treatment at the time of this analysis. At a median follow-up of 45.6 months (interquartile range 43.6–48.3 months), median OS was not reached in either group (hazard ratio 1.19, 95% confidence interval 0.80–1.77; not significant; Figure). However, patients in the venetoclax group had significantly longer median progression-free survival than those treated with placebo (23.4 versus 11.4 months; HR 0.58, 95% CI 0.43–0.78; *p*=0.00026), a higher overall response rate (84% versus 70%; *p*=0.0088) and a longer median duration of response (26.7 versus 12.8 months; HR 0.514, 95% CI 0.364–0.727; *p*=0.00012). The most common grade 3/4 treatment-emergent adverse events were thrombocytopenia (26% with venetoclax versus 40% with placebo), neutropenia (30% versus 8%) and pneumonia (22% versus 16%). Treatment-related adverse events led to death in four patients (2%) treated with venetoclax and none treated with placebo.

**CONCLUSION:** The final OS analysis of the BELLINI study showed no improvement in OS with the addition of venetoclax to bortezomib and dexamethasone in a non-biomarker-selected RRMM population.

OS in the intent-to-treat population




https://doi.org/10.1016/S2352-3026(25)00139-5

# DARATUMUMAB PLUS BORTEZOMIB, LENALIDOMIDE AND DEXAMETHASONE FOR TRANSPLANT-INELIGIBLE OR TRANSPLANT-DEFERRED NEWLY DIAGNOSED MULTIPLE MYELOMA:

## THE RANDOMIZED PHASE 3 CEPHEUS TRIAL

*Nature Medicine*, 2025 April; 31(4):1195–202

AUTHORS: Usmani SZ, Facon T, Hungria V, et al.
CENTRE FOR CORRESPONDENCE: Memorial Sloan Kettering Cancer Center, New York, New York, USA

**BACKGROUND & AIM:** The current standard of care for transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) is triplet therapy with daratumumab, lenalidomide and dexamethasone or bortezomib, lenalidomide and dexamethasone (VRd). The aim of this study was to investigate whether a quadruplet regimen with daratumumab added to VRd (D-VRd) improves efficacy over VRd alone in patients with NDMM who are either ineligible for transplantation or in whom transplantation is not planned as initial therapy (i.e. transplant deferred).

**STUDY DESIGN:** Multicentre, randomized, open-label, phase 3 trial.

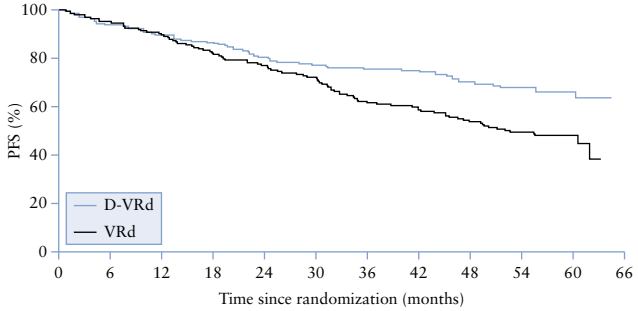
**ENDPOINTS:** Primary: overall minimal residual disease (MRD)-negativity ($10^{-5}$ threshold) rate. Secondary: sustained (≥12 months) MRD-negativity rate; rate of complete response or better; progression-free survival (PFS); overall survival; safety.

**METHOD:** Patients with transplant-ineligible or transplant-deferred NDMM were randomized to receive eight cycles of either D-VRd (*n*=197) or VRd (*n*=198), followed by lenalidomide and dexamethasone with or without daratumumab until progression.

**RESULTS:** Over a median follow-up of 58.7 months (range 0.1–64.7 months), patients treated with D-VRd versus VRd had a significantly higher overall MRD-negativity rate (60.9% versus 39.4%; odds ratio 2.37, 95% confidence interval 1.58–3.55; $p<0.0001$), sustained MRD-negativity rate (48.7% versus 26.3%; OR 2.63, 95% CI 1.73–4.00; $p<0.0001$) and rate of complete response or better (81.2% versus 61.6%; OR 2.73, 95% CI 1.71–4.34; $p<0.0001$). Median PFS was not reached with D-VRd versus 52.6 months with VRd (hazard ratio 0.57, 95% CI 0.41–0.79; $p=0.0005$) and the estimated 54-month PFS rate was 68.1% versus 49.5% (Figure). Overall survival data were immature but trended in favour of D-VRd (HR 0.85, 95% CI 0.58–1.24). Serious treatment-emergent adverse events occurred in 72.1% of patients treated with D-VRd and 67.2% with VRd, with no new safety signals.

**CONCLUSION:** In patients with transplant-ineligible or transplant-deferred NDMM, the addition of daratumumab to VRd was associated with deeper and more durable MRD responses and improved PFS compared with VRd alone.

Kaplan–Meier estimates of PFS

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