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on multiple myeloma

Sequencing BCMA- and GPRC5D-targeting immunotherapies in multiple myeloma: practical guidance from the European Myeloma Network

HemaSphere, 2025 November 25; 9(11):e70260

Cilta-cel in lenalidomide-refractory multiple myeloma (CARTITUDE-4):
an updated analysis including overall survival from an open-label, multicentre, randomised, phase 3 trial

The Lancet Oncology, 2026 February; 27(2):254–68

Iberdomide plus low-dose cyclophosphamide and dexamethasone in patients with relapsed and refractory multiple myeloma (the ICON study):
a multicentre, single-arm, phase 2 trial

The Lancet Haematology, 2026 January; 13(1):e30–40

Patient-reported outcomes with belantamab mafodotin, pomalidomide, and dexamethasone versus bortezomib, pomalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-8):
a phase 3, open-label, randomised controlled trial

The Lancet Haematology, 2025 November; 12(11):e876–86

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SEQUENCING BCMA- AND GPRC5D-TARGETING IMMUNOTHERAPIES IN MULTIPLE MYELOMA:

PRACTICAL GUIDANCE FROM THE EUROPEAN MYELOMA NETWORK

HemaSphere, 2025 November 25; 9(11):e70260

AUTHORS: van de Donk NW, Moreau P, San-Miguel JF, et al., on behalf of the EMN Guidelines Committee
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BACKGROUND & AIM: In recent years, treatment options for heavily pretreated patients with relapsed or refractory multiple myeloma (RRMM) have become increasingly complex due to the availability of multiple agents such as novel B-cell maturation antigen (BCMA)- and GPRC5D (G-protein-coupled receptor, class C, group 5, member D)-directed therapies, including bispecific antibodies, antibody–drug conjugates and chimeric antigen receptor (CAR) T-cell therapy. Currently, there are no randomized trial data regarding the best treatment choices and sequences. The aim of this paper from the European Myeloma Network was to provide practical guidance on the sequential use of BCMA- and GPRC5D-directed therapies.

ARTICLE TYPE: Evidenced-based guidelines.

FINDINGS: The optimal choice and sequence of treatments for patients with RRMM should be guided by patient-related factors, patient preferences, treatment availability and reimbursement, disease characteristics and the type of prior treatment. The efficacy of sequential BCMA- and GPRC5D-directed immunotherapies can also be influenced by underlying mechanisms of relapse, such as antigen loss, reduced T-cell fitness or outgrowth of T-cell-resistant clones.

The preferred option in the early relapse setting is BCMA-directed therapy, with a strong recommendation to use CAR T-cell therapy first in patients eligible for this treatment. This is based on high response rates and durable remissions after a single CAR T-cell infusion, and the fact that previous therapy with BCMA-targeting bispecific antibodies or the antibody–drug conjugate belamaf can have a negative impact on CAR T-cell therapy. BCMA-targeting bispecific antibodies or belamaf can be effective if patients relapse after CAR T-cell therapy, particularly with a switch of target. However, a BCMA-free interval of 6–9 months is recommended when sequencing two BCMA-directed therapies.

GPRC5D-directed therapy with bispecific antibodies can be effectively used as a bridging therapy as long as it is initiated after apheresis so as not to negatively affect CAR T-cell manufacturing. This bridging therapy can significantly reduce tumour burden and thereby improve the efficacy of consecutive BCMA-directed therapy. Current data indicate that switching from BCMA- to GPRC5D-targeted therapies is more effective than sequential use of different BCMA-directed therapies. No data are available on the feasibility of sequential treatment with two different GPRC5D-directed therapies.

In patients not eligible for CAR T-cell therapy, belamaf-based combination regimens should be considered after first relapse based on efficacy and manageable toxicity.

CONCLUSION: These recommendations can be used to optimize the efficacy of BCMA- and GPRC5D-directed therapies in patients with RRMM.

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CILTA-CEL IN LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA (CARTITUDE-4):

AN UPDATED ANALYSIS INCLUDING OVERALL SURVIVAL FROM AN OPEN-LABEL, MULTICENTRE, RANDOMISED, PHASE 3 TRIAL

The Lancet Oncology, 2026 February; 27(2):254–68

AUTHORS: Einsele H, San-Miguel J, Dhakal B, et al.
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BACKGROUND & AIM: Ciltacabtagene autoleucel (cilta-cel) is a B-cell maturation antigen-directed chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of lenalidomide-refractory multiple myeloma based on the ongoing phase 3 CARTITUDE-4 trial, which is comparing the efficacy and safety of cilta-cel versus standard of care (SoC) regimens. The aim of this paper was to provide an updated analysis of efficacy and safety in the CARTITUDE-4 population.

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

ENDPOINTS: Progression-free survival (PFS); complete response rate; overall survival (OS); safety.

METHOD: The CARTITUDE-4 trial randomized adults with lenalidomide-refractory multiple myeloma to receive either a single infusion of cilta-cel therapy (apheresis, at least one cycle of SoC bridging therapy, lymphodepletion, then 0.75×10^6 CAR T cells per kg; *n*=208) or SoC (pomalidomide, bortezomib and dexamethasone, *n*=28; daratumumab, pomalidomide and dexamethasone, *n*=183). This paper reports the prespecified second interim analysis of OS and an updated analysis of PFS.

RESULTS: At a median follow-up of 33.6 months (interquartile range 20.3–35.0 months), PFS events had occurred in 43% of patients treated with cilta-cel versus 73% receiving SoC. Median PFS was not reached versus 11.8 months, respectively (hazard ratio 0.29, 95% confidence interval 0.22–0.39). Median OS was not reached in either group (HR 0.55, 95% CI 0.39–0.79; *p*=0.0009). The complete response rate was 77% in the cilta-cel group and 24% with SoC. The safety population comprised 208 patients in each group. Grade 3 treatment-emergent adverse events (TEAEs) occurred in 14% of patients treated with cilta-cel and 37% receiving SoC; the most common event was anaemia in the cilta-cel group (35%) and neutropenia in the SoC group (28%). Grade 4 TEAEs were seen in 75% and 56% of patients, respectively, most frequently neutropenia in both groups (73% and 54%). The serious TEAE rate was 47% in both groups. There were six (3%) treatment-related deaths in the cilta-cel group and five (2%) in the SoC group, mostly due to infection.

CONCLUSION: This interim analysis of CARTITUDE-4 after a median follow-up of nearly 3 years showed significantly improved PFS and OS with cilta-cel versus SoC therapies in patients with lenalidomide-refractory multiple myeloma.

https://doi.org/10.1016/S1470-2045(25)00653-9

IBERDOMIDE PLUS LOW-DOSE CYCLOPHOSPHAMIDE AND DEXAMETHASONE IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (THE ICON STUDY):

A MULTICENTRE, SINGLE-ARM, PHASE 2 TRIAL

The Lancet Haematology, 2026 January; 13(1):e30–40

AUTHORS: Korst CL, Plattel W, de Kort EA, et al.
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BACKGROUND & AIM: Iberdomide, a novel potent cereblon E3 ligase modulator, has shown promising clinical activity in combination with dexamethasone in patients with relapsed or refractory multiple myeloma (RRMM). The aim of this study was to evaluate the efficacy and safety of iberdomide combined with low-dose cyclophosphamide (which has been shown to potentiate the effects of immunomodulatory drugs) and dexamethasone in patients with RRMM.

STUDY DESIGN: Prospective, single-arm, open-label, phase 2 study.

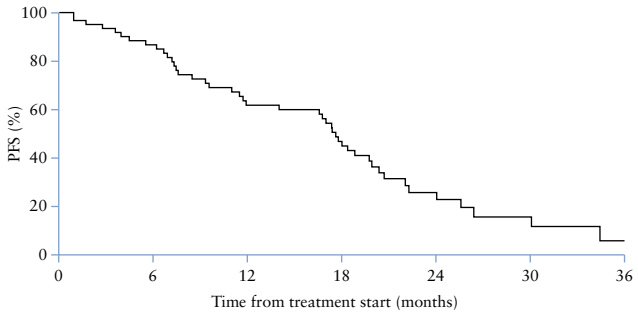
ENDPOINTS: Primary: progression-free survival (PFS). Secondary endpoints included the overall response rate, duration of response, overall survival and safety.

METHOD: Adults with lenalidomide-refractory RRMM and two to four previous lines of therapy (n=61) were given oral iberdomide (1.6 mg/day on days 1–21), cyclophosphamide (50 mg/day on days 1–28) and dexamethasone (20–40 mg once weekly) in 28-day cycles. Treatment was continued until disease progression, unacceptable toxicity or death.

RESULTS: At a median follow-up of 25.4 months (interquartile range 19.7–31.6 months), median PFS was 17.6 months (Figure), median overall survival was 33.7 months, the overall response rate was 82% (with a very good partial response or better in 49% and a complete response in 15%) and median duration of response was 17.9 months. Subgroup analysis showed significantly shorter median overall survival in patients with versus without triple-class refractory disease (27.1 months versus not reached; p=0.038). The most frequent haematological adverse event (AE) was neutropenia (grade 2: 5%, grade ≥3: 56%) and the most frequent non-haematological AE was infection (grade 2: 39%, grade ≥3: 34%). Treatment-related serious AEs occurred in 41% of patients, of which infections were the most common (71% of 48 serious AEs). There was one treatment-related death due to COVID-19 in an unvaccinated patient.

CONCLUSION: The combination of oral iberdomide, cyclophosphamide and dexamethasone showed clinical activity with a manageable toxicity profile among late-line patients with RRMM.

Kaplan–Meier estimate of PFS



https://doi.org/10.1016/S2352-3026(25)00298-4

PATIENT-REPORTED OUTCOMES WITH BELANTAMAB MAFODOTIN, POMALIDOMIDE, AND DEXAMETHASONE VERSUS BORTEZOMIB, POMALIDOMIDE, AND DEXAMETHASONE IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (DREAMM-8):

A PHASE 3, OPEN-LABEL, RANDOMISED CONTROLLED TRIAL

The Lancet Haematology, 2025 November; 12(11):e876–86

AUTHORS: Dimopoulos MA, Beksac M, Pour L, et al., on behalf of the DREAMM-8 investigators
CENTRE FOR CORRESPONDENCE: Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

BACKGROUND & AIM: The DREAMM-8 study demonstrated that lenalidomide-exposed patients with relapsed or refractory multiple myeloma (RRMM) who received belantamab mafodotin, pomalidomide and dexamethasone had a significantly lower risk of disease progression or death than those who received bortezomib, pomalidomide and dexamethasone. The aim of this secondary analysis was to evaluate patient-reported health-related quality of life (QoL) among DREAMM-8 participants.

STUDY DESIGN: Secondary analysis of an international, open-label, randomized controlled, phase 3 trial.

ENDPOINTS: Change from baseline in QoL scores; safety.

METHOD: In DREAMM-8, lenalidomide-exposed adults with RRMM were randomized to receive 28-day cycles of intravenous belantamab mafodotin (*n*=155) or 21-day cycles of subcutaneous bortezomib (*n*=147), with both groups also receiving oral pomalidomide and oral dexamethasone. Treatment was continued until progressive disease, unacceptable toxicity, withdrawal of consent or death. QoL was measured using the general EORTC QLQ-C30 questionnaire and the myeloma-specific EORTC QLQ-MY20 questionnaire.

RESULTS: In both treatment groups, changes from baseline in EORTC QLQ-C30 and QLQ-MY20 scores were stable across a median follow-up of 21.8 months (interquartile range 13.2–27.6 months), although more belantamab mafodotin than bortezomib recipients experienced meaningful improvements (≥10 points) at most study visits. In the first year of therapy, the most frequent patient-reported severe or very severe adverse events were blurred vision (affecting 43% of belantamab mafodotin recipients versus 9% of bortezomib recipients), followed by fatigue (38% versus 35%). Among all symptomatic adverse events, fatigue was found to have the greatest negative impact on QoL measures. Decreased appetite also impacted QoL, but blurred vision had a relatively minor effect on patient-reported health outcomes. Patients generally reported low levels of bother by treatment side effects.

CONCLUSIONS: Among lenalidomide-exposed adults with RRMM, treatment with either intravenous belantamab mafodotin or subcutaneous bortezomib, both in combination with oral pomalidomide and dexamethasone, was generally well tolerated and patient-reported health-related QoL was stable across nearly 2 years of follow-up. However, blurred vision was more common with belantamab mafodotin.

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