Highlights in Multiple Myeloma

From the 2025 American Society of Hematology Annual Meeting

December 6-9, 2025 • Orlando, Florida

Teclistamab/Daratumumab Combination Improves Survival in Relapsed/Refractory Myeloma

Progression-free survival (PFS) and overall survival (OS) in patients with relapsed or refractory multiple myeloma (RRMM) were better with a combination of the bispecific antibody teclistamab (Tecvayli, Janssen Biotech) and daratumumab (Darzalex, Janssen Biotech) (Tec-Dara) than with standard-of-care triplet therapy, according to initial results from the phase 3 MajesTEC-3 trial. María-Victoria Mateos, MD, PhD, of Hospital Universitario de Salamanca in Spain, presented the findings, which also appeared online in the *New England Journal of Medicine*.

The global randomized study enrolled 587 patients who had received 1 to 3 prior lines of therapy, including a proteasome inhibitor and lenalidomide. Patients were ineligible if they had received prior B-cell maturation antigen (BCMA)–directed treatment or had disease refractory to anti-CD38 therapy, although prior exposure to daratumumab was allowed. Participants were assigned in a 1:1 ratio to receive Tec-Dara or the investigator's choice of daratumumab plus pomalidomide (Pomalyst, Celgene) and dexamethasone (DPd) or daratumumab plus bortezomib and dexamethasone (DVd).

After a median follow-up of 34.5 months, median PFS was not reached with Tec-Dara vs 18.1 months in the control arm, and the 3-year PFS rates were 83.4% vs 29.7%, respectively (hazard ratio [HR], 0.17; 95% CI, 0.12-0.23; $P<.0001$). Benefits were consistent across all prespecified subgroups, including older patients, those with high-risk cytogenetics, and those with disease refractory to lenalidomide.

Rates of complete response (CR) or better were higher with Tec-Dara than with DPd/DVd, at 81.8% vs 32.1% ($P<.0001$), as were rates of measurable residual disease (MRD) negativity at a threshold of 10^{-5}, at 58.4% vs 17.1% ($P<.0001$). The 3-year OS rates were significantly higher with Tec-Dara than with DPd/DVd, at 83.3% vs 65.0% (HR, 0.46; 95% CI, 0.32-0.65).

Safety was manageable and consistent with known profiles. The rates of grade 3/4 adverse events (AEs) were similar in the 2 groups (95.1% vs 96.6%). Cytokine release syndrome (CRS), which was primarily grade 1, occurred in 60% of the Tec-Dara recipients, and immune effector cell–associated neurotoxicity syndrome was rare (1.1%). Infections were common in both arms, but the rates declined when immunoglobulin replacement therapy and antimicrobial prophylaxis protocols were reinforced.

The investigators concluded that Tec-Dara is a highly effective off-the-shelf immunotherapy combination and a potential new standard of care for RRMM as early as at first relapse.

Mateos MV, Bahlis N, Perrot A, et al. Phase 3 randomized study of teclistamab plus daratumumab versus investigator's choice of daratumumab and dexamethasone with either pomalidomide or bortezomib (DPd/DVd) in patients (Pts) with relapsed refractory multiple myeloma (RRMM): results of MAJESTEC-3 [ASH abstract LBA-6]. *Blood*. 2025;164(2)(suppl).

Costa LJ, Bahlis NJ, Perrot A, et al; MajesTEC-3 Trial Investigators. Teclistamab plus daratumumab in relapsed or refractory multiple myeloma [published online December 9, 2025]. *N Engl J Med*. doi:10.1056/NEJMoa2514663.

CAR T-Cell Therapy Achieves Early MRD-Negative Responses in Relapsed/Refractory Myeloma

A novel off-the-shelf gene therapy designed to generate BCMA-directed chimeric antigen receptor (CAR) T cells in vivo achieved rapid MRD-negative responses with manageable toxicity in the first 4 patients treated in a phase 1 trial, according to preliminary results presented by Phoebe Joy Ho, MBBS, DPhil, of the Peter MacCallum Cancer Centre in Melbourne. The investigational product, KLN-1010, which is intravenously administered, uses a T-cell–targeted lentiviral vector to engineer circulating T cells directly. This approach eliminates the need for apheresis, ex vivo cell manufacturing, and lymphodepleting chemotherapy.

The inMMyCAR study is enrolling patients with RRMM who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. All 4 initial participants were heavily pretreated, had high-risk cytogenetics, and were naive to BCMA-directed therapy.

Despite the absence of preparative chemotherapy, robust in vivo CAR T-cell expansion occurred, with peak absolute lymphocyte counts on days 13 to 18 ranging from 2.3 to 43.1 × 10^9/L. By day 15, 22% to 85% of $CD3^+$ lymphocytes were CAR T cells, and CAR T cells with a memory phenotype were detected in blood and bone marrow for at least 3 months in the first 2 patients.

All patients achieved MRD negativity by month 1,

at a sensitivity of 10^{-6} in 3 patients and at a sensitivity of 10^{-5} in 1 patient, with deepening responses over time. The longest-treated patient maintained MRD negativity through month 3 and achieved a very good partial response (VGPR) at month 3, which progressed to a still-to-be confirmed CR at month 5.

Toxicity was manageable. Infusion-related reactions occurred in 2 patients, and grade 1 or 2 CRS occurred in 3 patients. No immune effector cell–associated neurotoxicity or delayed neurologic events were observed. Cytopenias were transient.

The investigators concluded that in vivo CAR T-cell generation with KLN-1010 is feasible and that the product is clinically active, with a safety profile distinct from those of conventional ex vivo CAR T-cell therapies. The trial is ongoing, with further dose escalation results expected.

Harrison S, Ho PJ, Lim S-L, et al. Minimal residual disease (MRD)-negative outcomes following a novel, in vivo gene therapy generating anti–B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T cells in patients with relapsed and refractory multiple myeloma (RRMM): preliminary results from inMMyCAR, the first-in-human phase 1 study of KLN-1010 [ASH abstract LBA-1]. *Blood*. 2025;164(2)(suppl).

Carfilzomib-Based Regimen Improves Outcomes Compared With Standard Therapy in Newly Diagnosed Myeloma

Outcomes were significantly better with carfilzomib (Kyprolis, Amgen), lenalidomide, and dexamethasone (KRd) than with bortezomib, lenalidomide, and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma (NDMM), according to interim results from the phase 3 COBRA trial. Although KRd is highly active, previous research had found no PFS difference when the combination was compared with VRd in NDMM without high-risk features.

The randomized international study enrolled 250 patients with NDMM between July 2019 and July 2024, assigning them in a 1:1 ratio to receive either KRd or VRd for 24 months, followed by lenalidomide maintenance until progression. The trial included patients regardless of their transplant eligibility or cytogenetic risk factors. Co-primary endpoints were MRD-negative CR at 12 months and PFS.

After a median follow-up of 53 months, the 2 co-primary endpoints were met. A significantly higher proportion of patients receiving KRd than of patients receiving VRd achieved MRD-negative CR or better at the standard threshold of 10^{-5} (31% vs 18%; *P*=.016), with even greater separation at the deeper threshold of 10^{-6} (19% vs 7%; *P*=.008). Median PFS was also significantly longer with KRd, at not reached vs 49 months for VRd (HR, 0.57; *P*=.0095). Regarding cytogenetics, KRd led to significantly improved PFS in the standard-risk group and a trend toward improved PFS in the high-risk group. Rates of CR or better also favored KRd vs VRd (71% vs 53%; *P*=.005), although the overall response rates were similar.

Grade 3 or higher AEs (specifically, neutropenia and cardiac events) occurred more frequently with KRd (73% vs 62%). Notably, any-grade peripheral neuropathy affected substantially fewer patients receiving KRd than patients receiving VRd (17% vs 56%).

Lead investigator Dominik Dytfeld, MD, PhD, of Poznan University of Medical Sciences in Poland, concluded that the findings support further evaluation of KRd-based induction regimens in NDMM.

Dytfeld D, Kubicki T, Tyczynska A, et al. Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma (NDMM) – interim results from the randomized phase III COBRA trial [ASH abstract 99]. *Blood*. 2025;164(1)(suppl).

Quadruplet Regimen Improves MRD Negativity Rates in Newly Diagnosed Myeloma

Sustained MRD negativity rates were significantly better with the addition of bortezomib to isatuximab (Sarclisa, Sanofi-Aventis), lenalidomide, and dexamethasone (Isa-VRd) than with isatuximab, lenalidomide, and dexamethasone alone (Isa-Rd) in transplant-ineligible patients with NDMM, according to updated results from the phase 3 BENEFIT trial (IFM 2020-05).

The multicenter trial randomized 270 transplant-ineligible patients aged 65 to 79 years with NDMM in a 1:1 ratio to receive Isa-Rd with or without bortezomib. In the Isa-VRd arm, bortezomib was administered weekly for 12 months and then twice weekly for up to 18 months, dexamethasone was discontinued after 12 months, and isatuximab-lenalidomide was continued until disease progression. The primary endpoint was MRD negativity.

After a median follow-up of 33.4 months, the MRD negativity rate at 24 months at a threshold of 10^{-5} was significantly higher in the Isa-VRd arm than in the Isa-Rd arm, at 44% vs 26% (odds ratio [OR], 2.26; 95% CI, 1.34-3.79; *P*=.002). Rates of sustained MRD negativity between 12 and 24 months at a threshold of 10^{-5} were also higher with Isa-VRd than with Isa-VRd, at 34% vs 16% (OR, 2.73; 95% CI, 1.50-4.80; *P*=.0007). Similar results were observed at the 10^{-6} threshold. The rate of VGPR or better at 24 months was 95% with Isa-VRd.

Of note, patients with t(11;14) NDMM had consistently lower MRD negativity rates at all points through 24 months, possibly owing to delayed conversion to MRD negativity. Isa-VRd was well tolerated, and its safety profile was consistent with the profiles of the individual agents.

Lead investigator Arthur Bobin, MD, of CHU Poitiers in France, concluded that these data support the quadruplet-based regimen of Isa-VRd as a new standard of care for transplant-ineligible patients with NDMM.

Bobin A, Lambert J, Corre J, et al. Sustained minimal residual disease (sMRD) negativity in transplant ineligible newly diagnosed multiple myeloma treated with isatuximab plus lenalidomide and dexamethasone with bortezomib (Isa-VRd) versus Isa-Rd: 12-24-month data from the phase 3 BENEFIT trial (IFM 2020-05) [ASH abstract 368]. *Blood*. 2025;164(1)(suppl).

Belantamab Mafodotin Triplet Delivers Deep, Durable Responses in Relapsed/Refractory Myeloma

A triplet regimen containing belantamab mafodotin (Blenrep, GSK) deepened responses and extended PFS in patients with RRMM after at least one prior line of therapy, according to updated results from the phase 3 DREAMM-8 trial presented by Suzanne Trudel, MD, of Princess Margaret Cancer Centre in Toronto, Canada.

DREAMM-8 randomized 302 patients who had RRMM after at least one prior line of therapy, including lenalidomide, to receive belantamab mafodotin plus pomalidomide and dexamethasone (BPd) or a control regimen of bortezomib plus pomalidomide and dexamethasone (PVd).

After a median follow-up of 35.8 months, median PFS was more than doubled with BPd, reaching 32.6 months vs 12.5 months with PVd (HR, 0.49; 95% CI, 0.36-0.67). The rate of CR or better was also higher with BPd than with PVd, at 43% vs 17%. The MRD negativity rate at 10^{-5} was higher with BPd than with PVd, at 28% vs 6%, and MRD negativity was sustained for at least 12 months in 15% of BPd-treated patients.

The median duration of response was not reached with BPd vs 16.4 months with PVd, and 65% of BPd responders remained in response at 24 months. The median PFS2, defined as the time from randomization to disease progression after the initiation of new antimyeloma therapy or death from any cause, was 47.1 months with BPd vs 21.7 months with PVd. The safety profile was consistent with earlier analyses, although grade 3/4 AEs were more frequent with BPd (91% vs 74%). Discontinuation rates were modest and aligned with the known toxicities of belantamab.

Dr Trudel concluded that these extended follow-up results demonstrate deep and durable responses with BPd and support its use as an outpatient, off-the-shelf, BCMA-directed option at first relapse. Ongoing follow-up will clarify the effect on OS.

Trudel S, Beksac M, Pour L, et al. Deep responses and durable outcomes in patients treated with belantamab mafodotin plus pomalidomide and dexamethasone from long-term follow-up of the phase 3 DREAMM-8 study [ASH abstract 368]. *Blood*. 2025;164(1)(suppl).

Adding Bortezomib to Daratumumab Maintenance Does Not Improve PFS in Transplant-Ineligible Myeloma

Adding bortezomib to daratumumab maintenance therapy failed to improve PFS in transplant-ineligible patients with NDMM, according to interim results from the phase 3 JCOG1911/B-DASH study. The trial was terminated early on the basis of futility analysis and tolerability concerns.

The Japanese multicenter study enrolled 224 patients with NDMM aged 65 years or older, or younger patients who had declined autologous stem cell transplant. After receiving daratumumab plus melphalan, prednisolone, and bortezomib (D-MPB) induction therapy, 143 patients who had achieved at least a partial response were randomized in a 1:1 ratio to receive maintenance with either daratumumab alone or daratumumab plus bortezomib for up to 24 cycles.

After a median follow-up of 1.3 years since randomization, neither the interim analysis nor the updated analysis showed a better 2-year PFS rate with the combination than with daratumumab alone. In fact, the updated analysis demonstrated better-than-expected 2-year PFS with daratumumab alone, at 81% vs the assumed rate of 65%. There was no apparent difference in OS between the 2 arms.

Grade 2 or higher AEs during maintenance were more common with combination therapy than with daratumumab alone, including higher rates of lymphopenia (38.5% vs 27.1%) and sensory peripheral neuropathy (18.5% vs 8.6%). Treatment discontinuation due to AEs occurred in 12 patients receiving combination therapy and in 4 receiving daratumumab alone.

Lead investigator Tomotaka Suzuki, MD, of Nagoya City University in Japan, concluded that adding bortezomib to daratumumab maintenance therapy did not improve PFS and was associated with increased toxicities in patients with transplant-ineligible NDMM. The researchers are conducting further evaluations, including detailed subgroup analyses.

Suzuki T, Machida R, Sano Y, et al. Role of bortezomib maintenance therapy in the anti-CD38 antibody era: interim analysis results of a randomized phase III study for transplant-ineligible newly diagnosed multiple myeloma (JCOG1911/B-DASH Study) [ASH abstract 370]. *Blood*. 2025;164(1)(suppl).