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## Daratumumab Significantly Delays Smoldering Multiple Myeloma Progression

Silas Inman

**THREE YEARS OF TREATMENT** with subcutaneous daratumumab and hyaluronidase-fihj (Darzalex Faspro; Johnson & Johnson) significantly reduced the risk of progression from smoldering to active multiple myeloma without significantly impacting health-related quality of life (HRQOL), according to findings from the phase 3 AQUILA study (NCT03301220) presented at the 66th American Society of Hematology Annual Meeting and Exposition.<sup>1</sup>

In the study, which had 5 years of follow-up data available, progression was measured using International Myeloma Working Group SLiM-CRAB

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## Adding Daratumumab to VRd Significantly Boosts MRD Negativity for Patients With NDMM

Mary Caffrey

**ADDING SUBCUTANEOUS DARATUMUMAB** and hyaluronidase-fihj (Darzalex Faspro; Johnson & Johnson) to a standard backbone regimen significantly increased rates of sustained minimal residual disease (MRD) negativity in patients newly diagnosed with multiple myeloma for whom no transplant is planned, according to data presented at the

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## Daratumumab Significantly Delays Smoldering Multiple Myeloma Progression

(CONTINUED FROM COVER)

criteria. At 5 years, 63.1% of patients were progression-free with daratumumab compared with 40.8% undergoing active monitoring (HR, 0.49; 95% CI, 0.36-0.67;  $P < .001$ ). In those with high-risk factors, as identified by Mayo 2018 criteria, there was a 64% reduction in the risk of progression with daratumumab compared with active monitoring (HR, 0.36; 95% CI, 0.23-0.58). There was a trend toward improvement in HRQOL with daratumumab, according to lead investigator Meletios A. Dimopoulos, MD, professor and chairman of the Department of Clinical Therapeutics at the National and Kapodistrian School of Medicine University of Athens in Greece.

“We believe that, with this data, patients with high-risk smoldering myeloma may benefit from immediate treatment with daratumumab and that observation for this particular subset of patients may not be an adequate option,” Dimopoulos said during a presentation of the findings during a news briefing. “Despite that the treatment was discontinued at 3 years, even at 5 or 6 years there was a continuous benefit from treatment with daratumumab.”

In the study, investigators randomly assigned patients 1:1 to receive daratumumab monotherapy (n = 194) or active monitoring (n = 196), with the number of risk factors used as a stratification factor. Daratumumab was administered subcutaneously at 1800 mg weekly for cycles 1 and 2, followed by every 2 weeks for cycles 3 to 6, and every 4 weeks thereafter. Treatment was stopped after 3 years. All patients were monitored using a combination of laboratory tests, CT/PET and MRI, and bone marrow biopsy, which was conducted at least every 2 years.<sup>1</sup>

Smoldering multiple myeloma (SMM) has been an area of increased interest to researchers and was the topic of a symposium at the 2024 International Myeloma Society (IMS) meeting in Rio de Janeiro, Brazil, in September. During that session, S. Vincent Rajkumar, MD, professor of medicine at Mayo Clinic in Rochester, Minnesota, said SMM had emerged as an area where treatment could have greatest clinical benefit, and it is distinct biologically from an earlier disease stage, monoclonal gammopathy of undetermined significance (MGUS).

“Initially it was thought that smoldering myeloma is some in-between stage, between MGUS and smoldering multiple myeloma. But that’s not what it is,” Rajkumar said during the IMS meeting. “We now know that smoldering multiple myeloma is a heterogeneous clinical condition, clinically defined where one-third of the patients have high-risk smoldering myeloma. They actually have myeloma, but they don’t have the end organ damage, and two-thirds have MGUS.”<sup>2</sup>

### Results From AQUILA

The baseline patient characteristics were balanced between the groups, with a few discrepancies. Overall, patients were slightly younger in the daratumumab arm, with a median age of 63 years vs 64.5 years in the active monitoring group. More than half (54.6%) of patients were younger than

65 years in the daratumumab group compared with 50.0% in the control arm. Additionally, there were differences in the median time from diagnosis to randomization, which was 0.80 years in the daratumumab arm and 0.67 in the control arm.<sup>1</sup>

During the study, which was initiated in 2017, the criteria for smoldering multiple myeloma risk assessment were updated. To accommodate this, the investigator adjusted their enrollment to use the Mayo 2018 criteria, which involves examining serum M-protein greater than 2 g/L, involved:uninvolved free light chain ratio higher than 20, and clonal bone marrow plasma cells greater than 20%. Those with no factors were considered low risk, those with 1 were considered intermediate risk, and those with 2 or more were considered high risk. Overall, fewer patients were high risk in the daratumumab arm compared with the control arm (37.1% vs 43.9%).

At the median follow-up of 65.2 months, the median progression-free survival (PFS) was not yet reached with daratumumab compared with 41.5 months for active monitoring. There were 67 progression events with daratumumab and 99 with active monitoring. Death without disease progression was the same in both groups (n = 5) with the remaining progression events for daratumumab and active monitoring being related to CRAB criteria (19.4% vs 36.2%, respectively) and SLiM criteria (80.6% vs 69.1%, respectively).

At the 5-year analysis, 93.0% of patients were alive in the daratumumab group compared with 86.9% with active monitoring, representing a significant improvement in overall survival (HR, 0.52; 95% CI, 0.27-0.98). “You can see that the deaths were essentially doubled [with active monitoring],” Dimopoulos said. “Of course, further follow-up will be conducted in this.”

Prolonged PFS was also seen with the first-line treatment for active multiple myeloma, Dimopoulos noted. In this

group, which could include a variety of treatments, there was a 42% reduction in the risk of progression for those in the daratumumab arm (HR, 0.58; 95% CI, 0.35-0.96). This shows that using daratumumab earlier does not compromise the treatment for active myeloma down the road, which could be related to the fixed duration of treatment in the study, he said.

The median duration of adverse event (AE) reporting was 26 months with active monitoring and 35 months for daratumumab. A treatment-emergent AE (TEAE) of any grade occurred in 96.9% of patients taking daratumumab and in 82.7% with active monitoring. The rates of grade 3/4 TEAEs were 40.4% and 30.1% for daratumumab and active monitoring, respectively. Treatment discontinuation due to a TEAE occurred in 5.7% of patients on daratumumab. Dose modifications were required for 46.6% of patients.

Based on an earlier assessment of AQUILA, Johnson & Johnson, the developer of daratumumab and hyaluronidase-fihj, applied for regulatory approval in the United States and Europe.<sup>3</sup> A decision timeline for the application has not yet been released. ♦

#### REFERENCES

1. Dimopoulos M-A, Voorhees PM, Schjesvold F, et al. Phase 3 randomized study of daratumumab monotherapy versus active monitoring in patients with high-risk smoldering multiple myeloma: primary results of the AQUILA study. Presented at: ASH 2024 Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 773.
2. Caffrey M. Smoldering multiple myeloma risk factors: who to treat, how to treat. *AJMC.com*. September 25, 2024. Accessed December 12, 2024. <https://www.ajmc.com/view/smoldering-multiple-myeloma-risk-factors-who-to-treat-how-to-treat>
3. Johnson & Johnson submits applications in the U.S. and EU seeking approval of Darzalex Faspro/Darzalex as subcutaneous monotherapy for high-risk smoldering multiple myeloma. November 8, 2024. Accessed December 8, 2024. <https://bit.ly/3ZvIDeh>

## Adding Daratumumab to VRd Significantly Boosts MRD Negativity for Patients With NDMM

(CONTINUED FROM COVER)

66th American Society of Hematology Annual Meeting and Exposition (ASH 2024).<sup>1</sup>

The MRD negativity results for the CEPHEUS trial (NCT03652064) followed the earlier data from the study, which was presented in September during the International Myeloma Society Annual Meeting in Rio de Janeiro, Brazil. Those results showed that adding

subcutaneous daratumumab to bortezomib, lenalidomide, and dexamethasone (VRd) increased progression-free survival 43% over VRd alone.<sup>2</sup>

CEPHEUS is a phase 3, multicenter, randomized, open-label study that has enrolled 395 patients in 13 countries. It compares the efficacy and safety of daratumumab plus VRd vs VRd alone.<sup>2</sup>

At nearly 5 years of follow-up, the rate of MRD negativity in patients who received daratumumab plus VRd was 60.9% compared with 39.4% for those receiving VRd alone, at a sensitivity threshold of  $10^{-5}$ , according to Sonja Zweegman, MD, PhD, professor of immunology at Amsterdam University Medical Center, who presented the MRD negativity analysis at ASH 2024 (See Q&A, page 17).<sup>1</sup>

The rate of MRD negativity at the  $10^{-5}$  threshold is significant: In April, FDA's Oncologic Drugs Advisory Committee voted unanimously that MRD negativity should be accepted as part of a composite end point in clinical trials, and that vote was based on evidence involving MRD negativity measured at the  $10^{-5}$  threshold.<sup>3</sup>

**“These data further support the use of [daratumumab plus bortezomib, lenalidomide, and dexamethasone] as a new standard of care” for patients with newly diagnosed multiple myeloma who are either transplant ineligible or for whom transplant is deferred, the authors said.**

CEPHEUS randomly assigned 395 patients 1:1 between December 11, 2018, and October 7, 2019, to receive either daratumumab plus VRd or VRd alone. Results at  $10^{-5}$  showed an OR of 2.37; 95% CI, 1.58-3.55;  $P < .0001$ , favoring the daratumumab arm. Results at the more sensitive  $10^{-6}$  threshold were 46.2% vs 27.3%, respectively, for OR 2.24; 95% CI, 1.48-3.40;  $P = .0001$ .

MRD was evaluated via next-generation sequencing using the clonoSEQ test. According to the abstract, in this test, bone marrow aspirate samples are obtained at baseline; at the time of suspected complete response; at 12, 18, 24, 30, and 36 months after the first dose; and annually thereafter in patients with complete response.

### MRD Negativity Consistent Across Most Subgroups

The authors reported that subgroup analyses showed that adding daratumumab to the VRd backbone produced a consistent MRD negativity benefit across most subgroups, with the exception of patients with high cytogenetic risk.

Rates of sustained MRD negativity for at least 12 months were also higher in the daratumumab arm at both sensitivity levels measured, as follows:

- At  $10^{-5}$ , the measure of sustained MRD activity favored the daratumumab arm 48.7% vs 26.3% (OR, 2.63; 95% CI, 1.73-4.00;  $P < .0001$ ).
- At  $10^{-6}$ , sustained MRD favored the daratumumab arm 32.0% vs 15.7% (OR, 2.52; 95% CI, 1.55-4.11;  $P = 0.0001$ ).

Sustained benefits favored the daratumumab arm at key milestones, as follows:

- At the 2-year mark, rates were 38.6% vs 21.2%, respectively, at  $10^{-5}$  and 24.9% vs 12.6% at  $10^{-6}$ .
- At 3 years, the benefit for daratumumab was 27.4% vs 13.6% at  $10^{-5}$ .

The estimated 54-month PFS rates were 81.0% for daratumumab plus VRd vs 69.5% for VRd in MRD-negative patients at  $10^{-5}$  compared with 46% vs 33.7% for MRD-positive patients.

“This deeper response translated into significant improvements in overall PFS in the [daratumumab] group,” the authors concluded. Of those who achieved MRD negativity at  $10^{-5}$ , more than 80% were alive and progression free at 54 months, they said.

“These data further support the use of [daratumumab plus VRd] as a new standard of care” for patients with newly diagnosed multiple myeloma who are either transplant ineligible or for whom a transplant is deferred, the authors emphasized. ♦

### REFERENCES

1. Zweegman S, Facon T, Hungria V, et al. Phase 3 randomized study of daratumumab (DARA) + bortezomib, lenalidomide and dexamethasone (VRd) vs VRd alone in patients with transplant ineligible newly diagnosed multiple myeloma or for whom transplant is not planned as initial therapy: analysis of minimal residual disease in the CEPHEUS trial. Presented at: 66th ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 362.
2. Durie BGM. A historic turning point: ODAC unanimously votes in favor of MRD testing as an early end point in myeloma clinical trials to support accelerated approvals of new treatments. International Myeloma Foundation. April 18, 2024. Accessed December 12, 2024. <https://www.myeloma.org/blog/dr-duries/odac-unanimously-in-favor-mrd-testing-early-endpoint-myeloma>
3. Usmani S. Daratumumab + bortezomib/lenalidomide/dexamethasone in patients with transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: results of the phase 3 CEPHEUS study. Presented at: International Myeloma Society 21st Annual Meeting and Exposition, September 27, 2024; Rio de Janeiro, Brazil. Abstract OA – 63.

# Access, Equity, and Quality of Life: Managed Care Data From ASH

Mary Caffrey

**BEYOND THE CLINICAL FINDINGS** presented at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition, sessions on quality of life in multiple myeloma; diversity, equity, and inclusion; and outcomes research highlighted abstracts focused on key topics in managed care, from factors affecting access to treatment to those impacting where clinicians set up practice.

## HRQOL Results in PERSEUS Support Quadruplet as Standard

Pieter Sonneveld, MD, of the Erasmus MC Cancer Institute in Rotterdam, the Netherlands, last year presented the main findings of the PERSEUS trial (NCT03710603) at ASH; the results showed that adding subcutaneous daratumumab and hyaluronidase-fihj (Darzalex Faspro; Johnson & Johnson) to bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (VRd) was associated with a significantly higher rate of progression-free survival in transplant-eligible patients newly diagnosed with multiple myeloma (HR, 0.42; 95% CI, 0.30-0.59;  $P < .001$ ).<sup>1</sup>

On December 7, 2024, Sonneveld presented results from patient questionnaires in the phase 3 trial, which aimed to measure health-related quality of life (HRQOL), a secondary end point in PERSEUS. Patients completed 2 questionnaires on quality of life: the 30-question EORTC Core Quality of Life questionnaire (EORTC QLQ-C30), and the EuroQoL EQ-5D descriptive system and EQ visual analog scale (EQ VAS). They also completed 1 questionnaire on myeloma-specific symptoms, EORTC-MY-20.<sup>2</sup>

Baseline characteristics were well balanced between the 2 arms of PERSEUS. At the time of clinical cutoff, follow-up was 47.5 months. At maintenance cycle 34, there were 254 patients in the daratumumab group and 164 in the control arm of the study. Results showed the following<sup>1</sup>:

- Compliance on the questionnaires was above 94% on all 3 tests in both arms at baseline. It remained above 75% on all 3 tests in both arms at maintenance cycle 34, with slightly higher participation in the daratumumab arm.
- Patients in the daratumumab arm saw improvement in HRQOL between baseline and the start of maintenance that was intact through the start of

maintenance cycle 34 and comparable on most measures with patients in the control arm.

- Proportions of patients with clinically meaningful improvements in HRQOL at each cycle were similar across treatment arms: On the EORTC QLQ-C30, overall health, 37.8% vs 36.8%; physical functioning, 39.5% vs 41.1%; pain, 48.9% vs 50.0; fatigue, 46.5% vs 53.1%; EORTC-MY-20 disease symptoms, 47.3% vs 49.1%; EQ-5D-5L VAS, 49.7% vs 43.9%.

“Together with favorable efficacy outcomes data,” the authors wrote, the HRQOL data support the addition of daratumumab to a VRd triplet “as a new standard of care for [transplant-eligible] newly diagnosed multiple myeloma.”<sup>1</sup>

## As Training Progresses, Cancer Doctors Move Away From Black Patients

Researchers from Georgia, located at Wellstar Spalding Medical Center in Griffin and the Medical College of Georgia in Augusta, have created data to support a pattern observed anecdotally: As trainees in hematology and oncology progress through residency, fellowship, and their first attending positions, they migrate away from areas that serve high numbers of non-Hispanic Black patients. Among the factors that contribute to health care disparities are shortages of oncologists, particularly in areas that serve high numbers of Black patients.<sup>3,4</sup> As the authors note, “geographical distribution of hematology/oncology fellowship graduates is crucial for shaping health care delivery and highlighting regional health disparities in cancer care.”

Presented by Vishwanath Anil, MD, of Wellstar, the study digs into patterns of movement of these young physicians and identifies the career pivot points where many opt to move to less diverse locations.<sup>4</sup> For this study, the investigators analyzed transitions of 703 graduates of 65 accredited hematology and oncology fellowship programs from 2019 to 2022 that featured alumni data on their websites. The study team labeled 3 key transitions in medical training:

- T1: medical school to residency
- T2: residency to fellowship
- T3: fellowship to first attending position

They measured geographic relocation by straight-line distance and used US Census and zip code data to evaluate retention, and racial and socioeconomic data for locations. They divided the country into 4 regions to assess retention. Results showed the following<sup>4</sup>:

- **DISTANCE TRAVELED:** During T1, trainees traveled 674 miles, which decreased to 491 in T2 and 450 in T3 ( $P < .001$ ).
- **BEST RETENTION:** Regional retention was highest in the Western region from T1 (71.4%) to T2 (83%) to T3 (75.8%).
- **RURAL MOVEMENT:** Trainees moved less to rural areas during T1 and T2, but more to rural areas in T3. Fellows traveled less distance in T1 if they came from a rural region ( $P < .02$ ).
- **WEALTH DETERMINANTS:** Investigators found that “unemployment rates were directly correlated with greater miles traveled in all transitions,” that trainees migrated to areas with higher household incomes in their first transition, and this trend continued as careers progressed.
- **RACIAL DETERMINANTS:** The investigators determined, “There is a clear trend among trainees to move away from the non-Hispanic Black population as they progress from T1 to T2 to T3.”

The authors concluded that trainees may seek to diversify their educational experiences early in their training, but as time moves on, their preferences shift to “establishing roots,” possibly influenced by professional, personal, or network connections. The pattern of moving away from and then back to rural areas likely reflects a similar dynamic, they wrote, where “early training is sought in urban centers with more resources, but eventual practice might be to areas with lower cost of living, higher physician demand, and higher salaries which are classified as more rural areas.”

The patterns tracked call for policy solutions to address a workforce that is not moving to the areas of greatest need. “These findings underscore the need for targeted policies to mitigate geographic, socioeconomic, and racial inequality, ensuring equitable access to quality cancer care across all regions,” they write.

### Mental Health Issues, Financial Limits Are Barriers to Transplant

Mental health challenges, financial pressures, and not having a caregiver at home are among the reasons patients delayed allogeneic hematopoietic cell transplantation

(HCT) when diagnosed with acute myeloid leukemia (AML), according to a study conducted by Knight Cancer Institute, Oregon Health & Science University (OHSU) in Portland, Oregon.<sup>5</sup>

Although being referred early for HCT is linked to improved survival for adults with intermediate and high-risk AML, many patients have delays in accessing this curative therapy for reasons unrelated to their disease. For this reason, investigators at OHSU sought to gain a deeper understanding of what keeps patients with AML who are clinically eligible from progressing to transplant.

The analysis involved 369 patients with HCT delays from 2019 through 2022. Through evaluations by social workers, the team uncovered multiple reasons, with many patients affected by more than 1 factor. Results showed the following<sup>6</sup>:

- The median age of the group studied was 63 years, with a range of 18 to 95 years; 47% of the patients were 65 years or older.
- Of the patients, 43% were female, and 10% were of a race or ethnicity other than non-Hispanic White. Almost half (45%) were from nonmetropolitan areas, with 46% living more than 60 miles from the transplant center.
- Of the patients, 44% were at or below the national poverty level; 39% of those younger than 65 years had public insurance, and 91% of those 65 years and older had public insurance. Uninsured patients accounted for 2.5%.
- For 153 patients (41%), 1 or more social determinants of health (SDOH) barriers were identified. The most common reasons listed were “psychiatric disorders interfering with daily living” (14%), financial stressors (12%), substance dependence (9%), and lack of a caregiver (7%).

Investigators reported that referral for human leukocyte antigen (HLA) typing was completed for 42% of the patients. The median time was 46 days from diagnosis, with a range of 0 to 280 days; 21% of the patients had HLA completed within 6 weeks of diagnosis.

HCT consults were completed for 45% of patients; the median time to HCT consultation was 58 days, with a range of 0 to 483 days. Of those who completed consults, 73% proceeded to HCT with a median of 154 days from diagnosis and a range of 64 to 1030 days.

The documented reasons for not having HLA typing or HCT consults were disease progression (37%), patient’s oncologist determined HCT was not indicated (32%),

comorbidities (16%), patient wishes (8%), and advanced age (4%). Nondisease-related factors that were associated with reduced likelihood of proceeding to HCT were being older than 70 years and not having private insurance, whereas factors such as gender, race/ethnicity, living in a nonmetropolitan or poverty area, being a long distance to the transplant center, and SDOH were not statistically significant. ♦

#### REFERENCES

1. Sonneveld P, Dimopoulos MA, Boccadoro M, et al; PERSEUS Trial Investigators. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;390(4):301-313. doi:10.1056/NEJMoa2312054
2. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Health-related quality of life in transplant-eligible patients with newly diagnosed multiple myeloma: data from the PERSEUS trial of subcutaneous daratumumab combined with bortezomib, lenalidomide, and dexamethasone (D-VRd). Presented at: 66th American Society of Hematology Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 2000.
3. Cavallo J. How ASCO is tackling the need to improve workforce diversity and the looming oncology workforce shortage. *The ASCO Post*. November 10, 2023. Accessed December 12, 2024. <https://bit.ly/4feLbn0>
4. Anil V, Patel R, Nulu C, Vuppala R. Unveiling regional disparities in cancer care—analysis of the geographical journey and relocation patterns of hematology/oncology fellowship graduates. Presented at: 66th American Society of Hematology Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 2443.
5. Khare S, Cook RJ, Desai A, et al. Impact of social determinants of health on access to blood and marrow transplantation for acute myeloid leukemia. Presented at: 66th American Society of Hematology Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 2292.

## Sonja Zweegman, MD, PhD, Says CEPHEUS Regimen Is Linked to Sustained MRD Negativity

Luke Halpern

**IN AN INTERVIEW**, Sonja Zweegman, MD, PhD, professor of hematology at Amsterdam University Medical Center, discussed her presentation on new data from the CEPHEUS trial (NCT03652064),<sup>1,2</sup> which demonstrated that the addition of daratumumab (dara) to bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (VRd) significantly increased minimal residual disease (MRD) negativity rates compared with VRd alone in patients with newly diagnosed multiple myeloma (NDMM) who are transplant-ineligible or transplant-deferred. The regimen was strongly associated with sustained MRD negativity and improvements in overall survival compared with the VRd regimen alone.

Zweegman elaborated on the clinical implications for the significantly improved depth and duration of MRD negativity in transplant-ineligible or transplant-deferred patients with NDMM and explained how the combination may be further effective in other patient populations.

**Q:** What are the key points of the CEPHEUS trial regarding long-term disease control and overall survival?

**ZWEEGMAN:** The CEPHEUS trial was a trial for [NDMM] patients who were not eligible for stem cell

transplantation, or in whom a stem cell transplantation was deferred. [A total of] 395 patients were [randomly assigned] between either bortezomib, lenalidomide [len], and dexamethasone [dex] for 8 cycles, followed by len-dex until progression, or dara added to VRd, and then, after 8 cycles, continuation of the therapy with dara/len-dex. That resulted in a superior progression-free survival. There was a 43% risk reduction in progression or death after the addition of [dara] to VRd. We presented a more detailed analysis on [MRD} negativity, so MRD-negative complete response (CR). That was also the primary end point of the study, and we showed that there was a 50% increase in reaching MRD negativity.

Now, in detail, the cumulative incidence of MRD negativity increased over time. The MRD CR-negative rates were obtained faster, they were deeper, and they continued to increase over time in the VRd arm until approximately 3 years. It seems that in the dara-VRd arm, there was a continuous increase over time further than 3 years. Also, the sustained MRD negativity rates were doubled. After more than 12, 24, or 36 months, the addition of dara led to a doubling of the sustained MRD negativity. That paves the way for quadruple therapy, also for older patients with [MM] who are not transplant-eligible, because the high

rate of MRD negativity and the deep MRD-negative CR rates led to a very good medium progression-free survival. Those patients who were treated with dara-VRd and obtained MRD negativity until the  $10^{-6}$ —more than 85% of the patients were still without progression and alive after 45 months. I think that's very good results, and again, that should lead to the implementation of quadruple therapy, also for all the patients with [MM], perfect.

**Q:** Are there specific patient populations beyond the one focused on in CEPHEUS that may benefit from D-VRd therapy?

**ZWEEGMAN:** Importantly, in this trial, frail patients were not included, and we know that many patients who are nontransplant-eligible are frail. It will be interesting to have a look at whether frail patients can also benefit from

quadruple therapy and, well, the jury is not out yet, so we'll have to investigate it in the future. ♦

*This interview first appeared on Pharmacy Times®.*

#### REFERENCES

1. Usmani S. Daratumumab + bortezomib/lenalidomide/dexamethasone in patients with transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: results of the phase 3 CEPHEUS study. Presented at: International Myeloma Society 21st Annual Meeting & Exposition; September 25-28, 2024; Rio de Janeiro, Brazil. Abstract OA-63.
2. Zweegman S, Facon T, Hungria V, et al. Phase 3 randomized study of daratumumab (DARA) + bortezomib, lenalidomide and dexamethasone (VRd) versus alone in patients with transplant-ineligible newly diagnosed multiple myeloma or for whom transplant is not planned as initial therapy: analysis of minimal residual disease in the CEPHEUS trial. Presented at: 66th American Society of Hematology Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Abstract 362.

## How Anti-CD-38 Antibodies Are Changing the Standard of Myeloma Care

Hayden E. Klein

**AT THE INSTITUTE FOR VALUE-BASED MEDICINE®** event in Houston, Texas, held just prior to the 66th American Society of Hematology Annual Meeting and Exposition, Hans Lee, MD, director of multiple myeloma clinical research and associate professor in the Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center, shared his insights on the evolving treatment pathways for multiple myeloma. Here, he highlights the transformative impact of bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapies on relapsed/refractory (R/R) multiple myeloma and discusses the incorporation of anti-CD-38 monoclonal antibodies into frontline therapy.

This transcript has been lightly edited for clarity.

**Q:** How has integrating bispecific antibodies and CAR T-cell therapies altered treatment sequencing for R/R multiple myeloma?

**LEE:** Bispecific T-cell antibodies and CAR T therapies have really transformed the treatment landscape for relapsed/refractory multiple myeloma over the last 2 to 3 years or so. Before their regulatory pools, we had very limited options

for treatment of [patients with] triple-class refractory multiple myeloma—these are patients who are refractory to IMiDs [immunomodulatory drugs], proteasome inhibitors, [and] anti-CD-38 monoclonal antibodies. And the advent of bispecific antibodies and CAR T therapies have really provided a very efficacious therapy with not only high overall response rates, but durable responses for this challenging patient population to treat.

**Q:** How do you see anti-CD-38 monoclonal antibodies changing the standard of care in multiple myeloma?

**LEE:** Anti-CD-38 monoclonal antibodies like daratumumab and isatuximab have really transformed the landscape for the treatment of multiple myeloma, both in the relapsed setting [and] the newly diagnosed setting. And I think one of the most exciting things recently in the last couple years has been the incorporation of anti-CD-38 monoclonal antibodies in frontline therapy. Now we have multiple studies [with data] showing the addition of anti-CD-38 monoclonal antibodies with the backbone of bortezomib/lenalidomide/dexamethasone, or even carfilzomib/



dexamethasone, really adds benefit in terms of not only MRD [minimal residual disease]–negative rates, but also in some studies, progression-free survival as well.

I think most of us would consider that the standard of care for newly diagnosed multiple myeloma

should incorporate an anti-CD-38 monoclonal antibody plus a protease inhibitor [and] IMiD backbone as standard of care for both transplant-eligible and even transplant-ineligible patients who are fit to receive a quadruple-based therapy. ♦

## Phase 2 Trial Data Highlight 100% Complete Response With Cilta-Cel in Smoldering Myeloma

Gina Mauro

### DURING THE 66TH AMERICAN SOCIETY OF HEMATOLOGY

Annual Meeting and Exposition, findings from the single-arm phase 2 CAR-PRISM trial (NCT05767359) revealed that ciltacabtagene autoleucel (cilta-cel; Carvykti) induced a complete response (CR) in 100% of patients with high-risk smoldering multiple myeloma.<sup>1</sup>

At a median follow-up of 10.5 months in the safety run-in cohort, all 6 enrolled patients experienced a CR. The minimal residual disease (MRD)–negativity rate ( $10^{-6}$ ) was 100%. Additionally, stem cell collection was successful in all eligible patients, demonstrating an average stem cell yield of  $8.94 \times 10^6$  CD34-positive (+) cells/kg.<sup>1</sup>

Data also showed that the responses deepened over time. Lead study author Omar Nadeem, MD, clinical director of the Center for Early Detection and Interception of Blood Cancers and clinical director of the Myeloma Immune Effector Cell Therapy Program at Dana-Farber Cancer Institute in Boston, Massachusetts, noted in a presentation during the meeting that MRD negativity occurred early before achieving best serological response.

“The first 3 patients have sustained MRD negativity after 1 year of follow-up. The remainder of patients remain MRD negative at the time of their last follow-up,” said Nadeem, noting that no patients had developed biochemical or SLiM-CRAB progression to date.

The International Myeloma Working Group (IMWG) risk stratification model for smoldering multiple myeloma (SMM) score is used to predict risk of progression in smoldering myeloma, which is a heterogenous disease, to multiple myeloma. Prior phase 2 and 3 studies have evaluated early intervention in patients with high-risk smoldering multiple myeloma; however, CAR-PRISM marks the first trial of a chimeric antigen receptor (CAR) T-cell therapy being evaluated for this patient population.

In April 2024, the FDA approved cilta-cel for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), and who are refractory to lenalidomide (Revlimid).<sup>2</sup> This followed an earlier indication granted for the treatment of adult patients with relapsed/refractory multiple myeloma after at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.<sup>3</sup>

**At a median follow-up of 10.5 months in the safety run-in cohort, all 6 enrolled patients experienced a complete response. Data also showed that the responses deepened over time.**

For the CAR-PRISM study, investigators hypothesized that cilta-cel could be used to achieve MRD-negative disease without induction therapy. Nadeem explained that this is because the immune system is less altered in patients with smoldering multiple myeloma, allowing CAR T-cell therapy to potentially provide even greater

benefit compared with patients with relapsed/refractory myeloma. Additionally, the tumor burden in smoldering multiple myeloma is generally lower and less genomically complex, allowing for potentially greater efficacy and reduced toxicity.

In CAR-PRISM, patients underwent apheresis after screening and then received lymphodepletion with cyclophosphamide at 300 mg/m<sup>2</sup> and fludarabine at 30 mg/m<sup>2</sup> on days 5 to 3 before the trial start. Cilta-cel was then infused at a target dose of 0.5 or 0.75 x 10<sup>6</sup> CAR+ viable T cells/kg on day 1. Postinfusion assessments for safety, efficacy, pharmacokinetics, pharmacodynamics, and biomarkers were carried out on days 1 to 100. Posttreatment assessments for the above outcome measures were performed on days 101 up to the end of cohort, and follow-up continued thereafter.

The first 3 patients were treated at a lower target dose of 0.5 x 10<sup>6</sup> CAR+ viable T cells/kg, with an FDA review of safety prior to the dose escalation. Enrollment was staggered, with 1 patient receiving a dose every 60 days.

To be eligible for enrollment, patients had to have IMWG high-risk disease, defined as having 2 of the following criteria: serum M spike of at least 2 g/dL; an involved to uninvolved free light chain ratio of at least 20; and bone marrow plasma cells of at least 20%.

Patients were also eligible if they had an IMWG total score of 9 using the following scoring system:

- Free light chain ratio: > 10-25 = 2; > 25-40 = 3; > 40 = 5
- Serum M protein (g/dL): > 1.5-3 = 3; > 3 = 4
- Bone marrow plasma cell percentage: > 15%-20% = 2; > 20%-30% = 3; > 30%-40% = 5; > 40% = 6
- Fluorescence in situ hybridization (FISH) abnormality t(4;14), t(14;16), gain of chromosome 1q (1q gain), or 13q deletion = 2

Patients also could be eligible to enroll if there was presence of at least 10% bone marrow plasma cells and at least 1 of the following criteria: evolving pattern; abnormal plasma cell immunophenotype; at least 95% of bone marrow plasma cells are clonal and reduction of at least 1 uninvolved immunoglobulin isotype; and high-risk FISH, which could include the presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, or 1q gain.

Patients could not have SLiM-CRAB criteria present for active multiple myeloma, have bone marrow plasmacytosis greater than 40%, have been diagnosed or treated for another malignancy within 2 years of enrollment, have received prior directed therapy for smoldering multiple myeloma within 6 months of beginning study treatment,

or have experienced a stroke or seizure within 6 months of beginning treatment. Patients also could not have an uncontrolled intercurrent illness, including, but not limited to the following: ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or any psychiatric illness/social situations that would limit adherence to study requirements.

Baseline characteristics were reported for the first 6 enrolled patients. The median age was 55 years (range, 53-66), half the patients were male, 4 had IgG as their heavy-chain type, and 5 had high-risk FISH. FISH abnormalities comprised monosomy 13 (n = 4), 1q gain (n = 3), t(4;14) (n = 2), t(11;14) (n = 1), t(14;20) (n = 1), and t(14;16) (n = 1).

The primary end point was safety; secondary end points were overall response rate, CR rate, MRD negativity, and progression-free survival, as well as incidence and severity of adverse effects.

Regarding safety, no dose-limiting toxicities were observed in the safety run-in cohort. Cytokine release syndrome occurred in all 6 patients but was grade 1 (n = 4) or grade 2 (n = 2). Four patients received tocilizumab (Actemra), and the other 2 received dexamethasone.

Additionally, 1 patient experienced grade 1 Bell palsy that was found to be self-limiting and resolved within 2 weeks. There was 1 case of grade 4 immune-related thrombocytopenia, which also resolved within 2 weeks.

Hematologic toxicities included grade 3 neutropenia, which was transient without any febrile neutropenia. One patient experienced transient grade 3 increased aspartate aminotransferase and alanine aminotransferase levels, which resolved. Additionally, there were no grade 3 infections or any secondary malignancies to date.

Further findings showed that variable CAR-positive T-cell expansion and persistence were observed in this patient population. Nadeem added that at peak expansion, the majority of T cells were CAR+ T cells at a mean of 83% (SD, 14; range, 57%-97%). Also, when CAR-positive CD4+ and CAR+ CD8+ T cells expanded following infusion of cilta-cel, there was a preferential expansion of CAR-positive CD4+ T cells; this also occurred at the time of peak expansion.

Nadeem also discussed an individual patient who was treated with cilta-cel on study. This was a 54-year-old active man diagnosed with κ light chain high-risk smoldering multiple myeloma in 2023. The patient experienced a rise in κ light chains and an increase in bone marrow plasmacytosis in 2024. He had high-risk disease per 20-2-20 criteria with evolving pattern. ♦

*This article first appeared on OncLive®.*

## REFERENCES

1. Nadeem O, Nikiforow S, DeBraganca K, et al. Early safety and efficacy of CAR T-cell therapy in precursor myeloma: results of the CAR-PRISM study using ciltacabtagene autoleucel in high-risk smoldering myeloma. *Blood*. 2024;144(suppl 1):1027. doi:10.1182/blood-2024-202676
2. Carvykti is the first and only BCMA-targeted treatment approved by the US FDA for patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy. News release. Johnson & Johnson. April 5, 2024. Accessed December 10, 2024. <https://www.jnj.com/media-center/press-releases/carvykti-is-the-first-and-only-bcma-targeted-treatment-approved-by-the-u-s-fda-for-patients-with-relapsed-or-refractory-multiple-myeloma-who-have-received-at-least-one-prior-line-of-therapy>
3. FDA approves ciltacabtagene autoleucel for relapsed or refractory multiple myeloma. FDA. February 28, 2022. Accessed December 10, 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ciltacabtagene-autoleucel-relapsed-or-refractory-multiple-myeloma>

# NOTES

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