

AJMC®

THE AMERICAN JOURNAL OF MANAGED CARE®

DECEMBER 2024

2024 YEAR IN REVIEW

MULTIPLE MYELOMA

Multiple Myeloma: Bispecifics and Beyond

MARY CAFFREY | DECEMBER 2024

Advances for patients with multiple myeloma (MM) in 2024 fell into 2 broad categories. First, FDA approved 2 new quadruplet regimens for groups of newly diagnosed patients, and second, and at the other end of the spectrum, advances with bispecific antibody combinations and even trispecifics may offer choices for patients who are refractory to existing regimens.

Earlier in the year, FDA's Oncologic Drugs Advisory Committee (ODAC) offered a boost for future clinical investigation when it voted 12-0 that minimal residual disease (MRD) negativity can be part of an accelerated approval end point in MM,¹ which promises to speed the process of getting new therapies to patients.

Later that month, data presented at the Academy of Managed Care Pharmacy 2024 annual meeting showed that talquetamab, the bispecific GRPC5D-directed CD3 T-cell

Continued on page 8

Talquetamab Is a Cost-Effective Breakthrough for RRMM

MAGGIE L. SHAW | APRIL 23, 2024

Data on talquetamab-tgvs (Talvey; Janssen) presented at the Academy of Managed Care Pharmacy 2024 annual meeting show the bispecific GRPC5D-directed CD3 T-cell engager is effective when administered to patients with relapsed/refractory multiple myeloma (RRMM) who have failed at least 4 prior lines of treatment, and that the cost to give the treatment is lower per responding patient compared with usual care.¹

For this analysis, the total cost of care with talquetamab encompassed the cost of the treatment itself—based on an average US patient weight in MM of 85 kg—inpatient

Continued on page 9

ALSO IN THIS ISSUE

At ASCO, MRD Negativity Rates in PERSEUS Are Linked to Improved PFS in Newly Diagnosed Transplant-Eligible Multiple Myeloma **10**

No CRS in First 10 Patients in Teclistamab Pilot With Prophylactic Tocilizumab **13**

CEPHEUS: SC Daratumumab With VRd Improves MRD Negativity, PFS in Myeloma When Transplant Is Deferred **14**

Talquetamab Combo Offers Durable Responses in Heavily Pretreated Patients, Updated Data Show **15**

From CARs to Trispecifics, More Choices to Come in Multiple Myeloma **17**

Opinions expressed by authors, contributors, and advertisers are their own and not necessarily those of Clinical Care Targeted Communications Group, LLC, the editorial staff, or any member of the editorial advisory board. Clinical Care Targeted Communications Group, LLC, is not responsible for accuracy of dosages given in articles printed herein. The appearance of advertisements in this publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. Clinical Care Targeted Communications Group, LLC, disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

EDITORIAL

Vice President, Content
Laura Joszt, MA

Executive Editor
Mary K. Caffrey

Associate Editorial Director
Christina Mattina

Senior Editor
Maggie L. Shaw

Associate Editor
Julia Bonavitacola

COPY & PRODUCTION

Vice President, Copy
Jennifer Potash

Copy Chief
Paul Silverman

Copy Supervisors
Angie DeRosa
Nicole Canfora Lupo

Substantive Editor
Georgina Carson

Senior Copy Editors
Cheney Baltz
Marie-Louise Best
Kelly King

Copy Editor
Kim Nir

Creative Director, Publishing
Melissa Feinen

Art Director
Julianne Costello

SALES & MARKETING

Director, Sales
Ben Baruch

Senior National Accounts Managers
Robert Foti
Kevin George
Shaye Zyskowski

National Accounts Managers
Michael Bachalis, MHA, MS
James Roskowsinski

National Accounts Associates
Bryn Fitchett
Whit Walter

Senior Vice President, Strategy
Jeff Prescott, PharmD

OPERATIONS & FINANCE

Circulation Director
Jon Severn
circulation@mjhassoc.com

Vice President, Finance
Leah Babitz, CPA

Controller
Katherine Wyckoff

CORPORATE

President & CEO
Mike Hennessy Jr

Chief Financial Officer
Neil Glasser, CPA/CFE

Chief Operating Officer
Beth Buehler

Chief Marketing Officer
Shannon Seastead

Chief Data Officer
Terric Townsend

Executive Vice President, Global Medical Affairs & Corporate Development
Joe Petroziello

Senior Vice President, Corporate Development
Gil Hernandez

Senior Vice President, Content
Silas Inman

Senior Vice President, Human Resources & Administration
Shari Lundenberg

Senior Vice President, Mergers & Acquisitions, Strategic Innovation
Phil Talamo

Executive Creative Director
Jeff Brown

FOUNDER

Mike Hennessy Sr | 1960-2021

Copyright © 2024 by Clinical Care Targeted Communications Group, LLC



AN **MJH** life sciences[®] BRAND

Continued from page 1

engager, is cost-effective for patients with relapsed/refractory MM who have failed at least 4 prior lines of treatment (See **COVER**).

Adverse events (AEs) have been one of the challenges of administering bispecific antibodies, so the early results from the OPTec trial presented at the American Society for Clinical Oncology (ASCO) were exciting. At that point, the first 10 patients who received tocilizumab ahead of teclistamab showed no signs of cytokine release syndrome (See **PAGE 13**).

Management of AEs was a topic of discussion during the 21st Annual Meeting of the International Myeloma Society (IMS) in Rio de Janeiro, Brazil, which took place September 25-27, 2024. A session featured updates on 2 trials of combinations, TRIMM-2, for talquetamab and daratumumab, and RedirecTT-1, featuring dual bispecifics talquetamab and teclistamab. (See **PAGE 15**). Still, the durability seen in RedirecTT-1 offers hope for an investigational trispecific which targets B-cell maturation antigen and GRPC5D, but with a less toxic punch at CD3 than the dual bispecific combination (See **PAGE 17**).

Advances in newly diagnosed MM (NDMM). MRD negativity was the focal point of a set of results presented at the June 3, 2024, session on multiple myeloma at ASCO, which featured 2 regimens that later received FDA approval.

Paula Rodriguez-Otero, MD, PhD, of the Department of Hematology, Cancer Center Clinica Universidad de Navarra in Pamplona, Spain, reviewed data on MRD negativity from the PERSEUS trial, which was first presented at the December 2023 meeting of the American Society of Hematology in San Diego, and published in the *New England Journal of Medicine (NEJM)* in January 2024.^{2,3} Thierry Facon, MD, professor of hematology, Department of Hematology at Lille University Hospital in France,

presented data from IMROZ, which also appeared in *NEJM*.⁴

These quadruplet regimens are based on different anti-CD38 monoclonal antibodies and treat different groups of newly diagnosed patients. PERSEUS, based on subcutaneous daratumumab (Darzalex Faspro), was approved July 30, 2024, for use with autologous stem cell transplant (ASCT), while IMROZ, based on isatuximab, was approved in September 2024 for patients not eligible for transplant (See **PAGE 10**).

Another regimen based on subcutaneous daratumumab, CEPHEUS, had positive results presented September 27, 2024, at IMS. Johnson & Johnson filed an application for a new indication for patients not planning a transplant on September 30, 2024 (See **PAGE 14**).

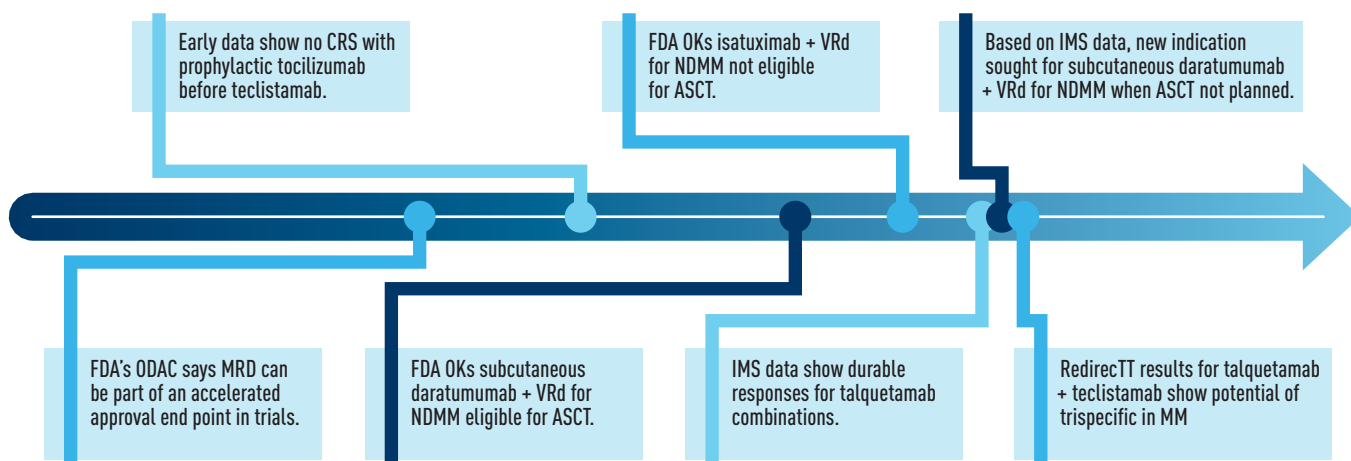
Ajai Chari, MD, professor of medicine at the University of California, San Francisco, summed up the progress in his talk in Rio de Janeiro during IMS.

“I think anybody who’s treating myeloma patients today is so gratified to see the improvement in their outcomes with these T-cell–redirection therapies.” Nonetheless, he said, “We have a lot of unmet needs.”⁵ ●

REFERENCES

1. Serani S. FDA’s ODAC votes 12 to 0 that MRD is a viable end point in myeloma trials. *Targeted Oncology*. April 12, 2024. Accessed November 26, 2024. <https://www.targetedonc.com/view/fda-odac-meeting-april-12-mrd-myeloma-trials>
2. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Phase 3 randomized study of daratumumab + bortezomib, lenalidomide, and dexamethasone (VRd) versus VRd alone in patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation: primary results of the PERSEUS trial. *Blood*. 2023;142(suppl 2):LBA-1. doi:10.1182/blood-2023-191911
3. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;390(4):301-313. doi:10.1056/NEJMoa2312054
4. Facon T, Dimopoulos MA, Leleu XP, et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;391(17):1597-1609. doi:10.1056/NEJMoa2400712
5. Caffrey M. From CARs to trispecifics, more choices to come in multiple myeloma. *AJMC.com*. October 1, 2024. Accessed November 26, 2024. <https://www.ajmc.com/view/from-cars-to-trispecifics-more-choices-to-come-in-multiple-myeloma>

KEY EVENTS OF 2024



ASCT, autologous stem-cell transplant; CRS, cytokine release syndrome; IMS, International Myeloma Society; MM, multiple myeloma; MRD, minimal residual disease; NDMM, newly diagnosed MM; ODAC, Oncologic Drugs Advisory Committee; VRd, Velcade (bortezomib) Revlimid (lenalidomide), and dexamethasone.

Continued from page 1

cost, adverse event management cost after step-up hospitalization, outpatient administrative and supportive care cost, and subsequent therapy cost. Treatment duration was based on progression-free survival.

The FDA granted Janssen an accelerated approval for talquetamab on August 9, 2023, for use among this patient population, with failed prior therapies that include a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Talquetamab had previously received priority review, breakthrough designation, and orphan drug designation.²

Results showed that talquetamab is both clinically effective and cost-effective for patients with relapsed/refractory multiple myeloma.

In this most recent analysis, the authors reiterated that most patients with MM, especially RRMM, endure multiple treatments and disease relapses, resulting in extreme clinical and economic burdens from poor disease control. However, talquetamab shows great promise in filling a treatment void for patients with severely refractory RRMM due to its previously demonstrated high overall response rate (ORR) among this population. Data are lacking, however, on its cost-effectiveness. For comparison with usual care, investigators used cost data for weekly and biweekly talquetamab from a recent study conducted among patients with RRMM and 4 prior lines of

therapy³ and ORR data on talquetamab and physician's choice from the MonumentAL-1 (NCT03399799) and LocoMMotion (NCT04035226) studies, respectively.

For weekly talquetamab administration, the total costs of care for 6 months of treatment were \$327,987, and for 12 months, \$521,567. Biweekly administration saw corresponding costs of \$341,217 and \$551,350. For usual care at these time points, the care costs were \$217,996 and \$435,993.

Per responder, 6-month costs were \$442,627 for weekly dosing and \$446,781 for biweekly dosing, and 12-month costs were \$703,869 and \$754,241, respectively, compared with \$764,900 and \$1,529,800 for usual care after 6 and 12 months.

A final analysis that considered costs per additional responder produced figures of \$241,207 and \$285,233 for 6 months of weekly or biweekly talquetamab, respectively, and \$187,663 and \$267,031, respectively, for 12 months of treatment.

The investigators concluded that talquetamab is both effective and cost-effective among patients who have RRMM, with superior per-responder costs compared with usual care. ●

REFERENCES

1. Lee H, Le H, Zhang X. Cost-per-responder analysis for patients with relapsed or refractory multiple myeloma treated with talquetamab compared with usual care. Poster presented at: Academy of Managed Care Pharmacy 2024 annual meeting; April 15-18, 2024; New Orleans, LA. Presentation C33.
2. FDA grants accelerated approval to talquetamab-tgvs for relapsed or refractory multiple myeloma. News release. FDA. August 9, 2023. Accessed April 22, 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-talquetamab-tgvs-relapsed-or-refractory-multiple-myeloma>
3. Martin T, Krishnan A, Yong K, et al. Comparative effectiveness of ciltacabtagene autoleucel in CARTITUDE-1 versus physician's choice of therapy in the Flatiron Health multiple myeloma cohort registry for the treatment of patients with relapsed or refractory multiple myeloma. *EJHaem*. 2021;3(1):97-108. doi:10.1002/jha2.312

At ASCO, MRD Negativity Rates in PERSEUS Are Linked to Improved PFS in Newly Diagnosed Transplant-Eligible Multiple Myeloma

MARY CAFFREY | JUNE 4, 2024

An in-depth analysis presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting highlighted links between rates of minimal residual disease (MRD) negativity and progression-free survival (PFS) seen among transplant-eligible patients treated with subcutaneous daratumumab (Darzalex Faspro; Janssen) and a standard backbone triplet in the phase 3 PERSEUS trial.^{1,2}

Primary results for PERSEUS (NCT03710603), presented in December 2023 at the American Society of Hematology meeting in San Diego, showed PFS was 84.3% at 4 years for patients treated with daratumumab and a triplet of bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone, known as VRd, vs 67.7% for VRd alone (HR, 0.42).²

In PERSEUS, 709 patients were randomly assigned 1:1 to receive the daratumumab-VRd combination or VRd alone. Patients in both arms received up to 6 cycles of VRd, with 4 prior to autologous stem cell transplant (ASCT) and 2 post ASCT consolidation. Subcutaneous (SC) daratumumab and placebo were administered on a separate schedule from VRd, with daratumumab SC and lenalidomide given as maintenance in the investigational arm; patients in the placebo arm received lenalidomide maintenance. Those in the investigational arm who achieved MRD negativity could stop daratumumab SC, with the chance to restart the therapy if there was a loss of CR or MRD negativity.²

Measures of MRD negativity could soon become even more important, as the FDA must weigh whether they can be used as surrogate end points following a unanimous endorsement from the Oncologic Drugs Advisory Committee (ODAC).³ As the number of therapies for multiple myeloma increases—along with the length of time needed to demonstrate overall survival—experts in the United States and Europe have demonstrated evidence that supports this change.^{4,5}

The presentation by Paula Rodriguez-Otero, MD, PhD, of the Department of Hematology, Cancer Center Clinica Universidad de Navarra in Pamplona, Spain, reviewed data on MRD negativity at sensitivity of both 10^{-5} and 10^{-6} . According to the Multiple Myeloma Research Foundation, this difference refers to MRD tests that can detect at least 1 myeloma cell in 100,000 healthy bone marrow cells (for a threshold of 1×10^{-5}) vs tests that can detect 1 myeloma cell in 1 million (1×10^{-6}).⁶

“In newly diagnosed multiple myeloma, minimal residual disease negativity has been associated with prolonged survival,” Rodriguez-Otero said during the oral abstract session at ASCO. “Moreover, deeper responses with a sensitivity level of 10^{-6} have been associated with superior outcomes compared to 10^{-5} and

10^{-4} current [MRD] testing. This sensitivity level of 10^{-6} and sustained for over 5 years translates into very good survival and a potential for cure for patients with newly diagnosed multiple myeloma.”

Data showed that 88% of transplant-eligible patients achieved a complete response (CR) or better, and 47% of patients treated with daratumumab-based induction, consolidation, and maintenance therapy remained MRD negative after 12 months. The MRD negativity rate, as measured by the clonoSEQ test, deepened over time, Rodriguez-Otero reported. The rate was defined as the share of intent-to-treat patients who achieved both a CR or better and MRD negativity.

Results. According to the ASCO abstract,¹ at the end of consolidation, MRD negativity rates were 44.5% for the daratumumab SC arm vs 34.7% for the VRd-only arm ($P = .0078$). Data from the abstract report overall MRD negativity rates of 87.9% for the daratumumab SC arm vs 70.1% for the VRd-only arm ($P < .0001$).

“Importantly, the rates of conversion from patients that were MRD-positive at the end of consolidation and converted to MRD negativity during maintenance was also higher with D-R treatment as compared to lenalidomide alone,” Rodriguez-Otero noted.

Rates of MRD negativity deepened over time as follows, all favoring the daratumumab SC-VRd arm (daratumumab SC) at both levels of sensitivity (all $P < .0001$). First, to a 10^{-5} sensitivity:

- At 12 months, rates were 65.1% for daratumumab SC vs 38.7% for VRd only.
- At 24 months, rates were 72.1% for daratumumab SC vs 44.9% for VRd only.
- At 36 months, rates were 74.6% for daratumumab SC vs 46.9% for VRd only.

Second, to a 10^{-6} sensitivity:

- At 12 months, rates were 43.9% for daratumumab SC vs 20.9% for VRd only.
- At 24 months, rates were 57.7% for daratumumab SC vs 27.4% for VRd only.
- At 36 months, rates were 63.9% for daratumumab SC vs 30.8% for VRd only.

During her presentation, Rodriguez-Otero focused on MRD negativity rates for patients with high-risk cytogenetic abnormalities; she noted that the rates of sustained MRD negativity at least 12 months out from the start of treatment were higher

in the daratumumab arm: 30% for daratumumab vs 14% in the VRd-only arm. “This translates into a prolonged progression-free survival for high-receptor genetic abnormality patients when treated with D-VRd followed by D-R maintenance.”

Will the MRD negativity rate take on greater meaning going forward? An official with Adaptive Biotechnologies, which makes the clonoSEQ test used in PERSEUS, weighed in with this statement to *The American Journal of Managed Care*[®] (*AJMC*[®]):

“In recent years, the significance of MRD as a prognostic biomarker has become increasingly clear. The unanimous recommendation by the FDA’s Oncologic Drugs Advisory Committee to accept MRD as a primary end point for accelerated approvals in multiple myeloma trials, based on its strong correlation with progression-free survival and overall survival, underscores the clinical benefit of specific and sensitive MRD testing with clonoSEQ, as highlighted by the data presented at the ASCO annual meeting,” said Adaptive Biotechnologies’ Susan Bobulsky, chief commercial officer, MRD.

The test, she continued, is “well positioned” to continue as the preferred testing option in clinical trials. “We are proud to contribute to this paradigm shift in clinical trial end point consideration, which may help bring us closer to a cure for people living with multiple myeloma.”

“MRD-negativity is an important measure in predicting long-term progression-free survival for patients with multiple myeloma,” Rodriguez-Otero said in a statement.⁷ The higher rates of deep and sustained MRD negativity with a subcutaneous daratumumab-based regimen show the potential of this quadruplet and daratumumab-based maintenance “to shift the treatment paradigm for transplant-eligible patients with newly diagnosed multiple myeloma and bring us closer to the potential for a functional cure.”

IMROZ Shows 40% Reduced Risk With Isatuximab Combo

Adding isatuximab (Sarclisa; Sanofi), an anti-CD38 monoclonal antibody, to both phases of the standard regimen for patients newly diagnosed with multiple myeloma not eligible for transplant cut the risk of disease progression or death by 40%, according to results presented June 3, 2024, at ASCO 2024.⁸

Results for the IMROZ trial (NCT03319667), presented in an oral session by Thierry Facon, MD, professor of hematology, Department of Hematology at Lille University Hospital in France, were simultaneously published in *The New England Journal of Medicine* (*NEJM*).⁹

Facon described IMROZ as the first worldwide phase 3 study of an anti-CD38 agent combined with the standard-of-care (SOC) combination of bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone to show significant improvements in progression-free survival (PFS), along with deep

responses based on measures of minimal residual disease (MRD), in transplant-ineligible patients newly diagnosed with multiple myeloma.

The triplet therapy that is the current standard regimen for these patients, known as VRd, is followed by maintenance with lenalidomide and dexamethasone only (Rd). In his presentation, Facon noted that several phase 3 trials are building off this triplet background therapy to seek even better results with quadruplet therapy.

In an interview with *AJMC* before ASCO, Facon said the results for isatuximab in IMROZ were highly significant in part because of the results in the comparator arm were so strong—a point also noted in the *NEJM* paper.

“ [Minimal residual disease]-negativity is an important measure in predicting long-term progression-free survival for patients with multiple myeloma. ”

—Paula Rodriguez-Otero, MD, PhD

“The PFS benefit, to be honest, is very significant, both from a clinical and a statistical point of view,” Facon said. “One thing is that the VRd control arm did very well; you will not see so many VRd regimens doing so well.”

He compared not only PFS but also the number of cycles of therapy between the 2 arms: “It’s totally true to say that the median duration on therapy is 31 months for VRd and 53 months for isatuximab. So the median number of cycles is 29 vs 52. That’s a big difference.”

In IMROZ, 446 patients aged 18 to 80 years were randomly assigned 3:2 to receive either isatuximab plus VRd or VRd alone; 4 induction cycles (6 weeks per cycle) were followed by 4-week cycles of continuous treatment of isatuximab-Rd for patients in the isatuximab-VRd group vs Rd for patients in the VRd group. Patients were treated until disease progression or an unacceptable adverse event (AE).

Results are as follows:

- The primary end point was PFS. At a median follow-up of 59.7 months, the median PFS with the isatuximab-VRd combination was not reached vs 54.3 months with VRd.
- The estimated PFS at 60 months was 63.2% in the isatuximab-VRd group vs 45.2% in the VRd group, for an HR of 0.60 for disease progression or death (98.5% CI, 0.41-0.88; $P < .001$).

- For the secondary end point of complete response (CR), 74.7% of patients receiving isatuximab-VRd achieved a CR or better vs 64.1% among those who received VRd alone ($P = .01$).
- For the secondary end point of MRD-negative status among those with a CR, the percentage of patients with MRD-negative status and a CR favored the isatuximab group (55.5% vs 40.9%; $P = .003$).
- No new safety signals were reported among patients taking the isatuximab-VRd regimen. Grade 3 or higher treatment-emergent AEs were seen in 91.6% of patients taking isatuximab-VRd and 84% of those taking VRd.
- The incidence of serious AEs leading to discontinuation was similar between the 2 groups; 22.8% of patients in the isatuximab-VRd group and 26% taking VRd.
- At the time of data cutoff, 47.2% of patients (125/263) receiving isatuximab-VRd and 24.3% of patients (44/181) treated with VRd were still on treatment. The median treatment duration for the isatuximab-VRd combination was 53.2 months compared with 31.3 months for VRd.

“The improved efficacy of [isatuximab] VRd, combined with a consistent safety profile, provides an important treatment option for frontline treatment in this population, establishing isa-VRd as a new standard of care for patients less than 80 years of age with transplant ineligible multiple myeloma,” Facon concluded.

In a commentary on 3 related presentations, Carl Ola Landgren, MD, PhD, of the University of Miami/Sylvester Comprehensive Cancer Center, agreed that isatuximab-VRd should be the standard of care, although he asked whether the lines between “transplant eligible” and “transplant ineligible” are still needed in the era of anti-CD38 therapy.

MRD status. The FDA is deciding whether to make MRD negativity a surrogate end point following a recent unanimous endorsement from the ODAC.³ The *NEJM* paper noted that 46.8% of those in isatuximab-VRd group and 24.3% of the VRd group had sustained MRD negative status for at least 12 months, based on a sensitivity of 10^{-5} . IMROZ also had an exploratory analysis of the share of patients with both MRD-negative status and CR at a sensitivity of 10^{-6} and results were consistent (40.0% vs 22.7%; with an OR of 2.27; 95% CI, 1.48-3.48).⁹

In addition, a PFS benefit was seen in the isatuximab-VRd group among MRD-negative patients compared with MRD-positive patients (HR, 0.22; 95% CI, 0.14-0.35), and this benefit was larger than what was seen among the VRd patients who were MRD-negative (HR, 0.31; 95% CI, 0.19-0.52).

During the interview, Facon was asked if the results provide evidence that MRD is a valid surrogate end point. “I think I

could tell you that FDA would be happy with the study results,” he replied. “They will not complain.”

Ahead of his ASCO presentation, Facon said he anticipated questions about results that show patients with high-risk cytogenetic features did not receive additional benefits from isatuximab vs VRd (HR, 0.97; 95% CI, 0.48-1.96). The *NEJM* paper said this area warrants “further analyses and longer follow-up.”

FDA UPDATES

On July 30, 2024, FDA approved subcutaneous daratumumab with bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant, based on phase 3 results from the PERSEUS trial.¹⁰

On September 20, 2024, FDA approved isatuximab plus VRd as a treatment for patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant.¹¹ ●

REFERENCES

- Rodriguez-Otero P, Moreau P, Dimopoulos MA, et al. Daratumumab (DARA) + bortezomib/lenalidomide/dexamethasone (VRd) in transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM): analysis of minimal residual disease (MRD) in the PERSEUS trial. *J Clin Oncol* 2024;42(suppl 16). Abstract 7502. doi:10.1200/JCO.2024.42.16_suppl.7502
- Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;390(4):301-313. doi:10.1056/NEJMoa2312054
- Durie BGM. A historic turning point: ODAC unanimously votes in favor of MRD testing as an early endpoint in myeloma clinical trials to support accelerated approvals of new treatments. International Myeloma Foundation. April 18, 2024. Accessed June 3, 2024. <https://www.myeloma.org/blog/dr-duries/odac-unanimously-in-favor-mrd-testing-early-endpoint-myeloma>
- Avet-Loiseau H, Ludwig H, Landgren O, et al. Minimal residual disease status as a surrogate end point for progression-free survival in newly diagnosed multiple myeloma studies: a meta-analysis. *Clin Lymphoma Myeloma Leuk*. 2020;20(1):e30-e37. doi:10.1016/j.clml.2019.09.622
- Cavo M, San-Miguel J, Usmani SZ, et al. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA. *Blood*. 2022;139(6):835-844. doi:10.1182/blood.2021011101
- Answers to FAQs from our 7/14/23 webinar on minimal residual disease. Multiple Myeloma Research Foundation. July 14, 2023. Accessed June 3, 2024. <https://themmrf.org/mmr-f-blogs/answers-to-faqs-from-our-7-14-23-webinar-on-minimal-residual-disease/>
- Darzalex-based regimens significantly improve clinical outcomes in both transplant-eligible and transplant-ineligible patients who are newly diagnosed with multiple myeloma. News release. Johnson & Johnson. June 3, 2024. Accessed June 3, 2024. <https://bit.ly/4b6Kz0J>
- Facon T, Dimopoulos MA, Leleu XP, et al. Phase 3 study results of isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) versus VRd for transplant-ineligible patients with newly diagnosed multiple myeloma (IMROZ). *J Clin Oncol*. 2024;42(suppl 16). Abstract 7500. doi:10.1200/JCO.2024.42.16_suppl.7500
- Facon T, Dimopoulos MA, Leleu XP, et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. Published online June 3, 2024. doi:10.1056/NEJMoa2400712
- FDA approves daratumumab and hyaluronidase-fihj with bortezomib, lenalidomide, and dexamethasone for multiple myeloma. News release. FDA. July 30, 2024. Accessed November 26, 2024. <https://tinyurl.com/jyc3btmb>
- FDA approves isatuximab-irfc with bortezomib, lenalidomide, and dexamethasone for newly diagnosed multiple myeloma. News release. FDA. September 20, 2024. Accessed November 26, 2024. <https://shorturl.at/B8d3c>

No CRS in First 10 Patients in Teclistamab Pilot With Prophylactic Tocilizumab

MARY CAFFREY | JUNE 3, 2024

The first 10 patients with multiple myeloma given a prophylactic dose of tocilizumab prior to treatment with teclistamab have not experienced cytokine release syndrome (CRS) or immune effector cell–associated neurotoxicity syndrome (ICANS), according to data from a pilot study presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting.¹

Early findings from the OPTec study (NCT05972135) could signal a breakthrough in patients' ability to receive teclistamab, a bispecific antibody sold as Tecvayli,² in community settings. More patients could access teclistamab if clinicians could prevent patients from experiencing an adverse event (AE) requiring hospital admission.

Teclistamab is the only FDA-approved therapy with weight-based dosing to target B-cell maturation antigen (BCMA) on multiple myeloma cells and CD3 on T cells to activate an immune response.² The therapy has a step-up dosing schedule, which allows some flexibility on when it is administered to deal with CRS or ICANS.

The pilot, led by Robert M. Rifkin, MD, medical oncologist/hematologist of Rocky Mountain Cancer Centers of Denver, Colorado, is based on findings from a cohort of the MajesTEC-1 study,³ which led to approval for teclistamab in patients who have received at least 3 therapies for multiple myeloma. CRS was seen in 72% of patients in cycles 1 and 2, with 33% seeing recurrent CRS. However, among a group of patients who had a prophylactic dose of tocilizumab, only 26% of patients had CRS.

The purpose of the pilot is to evaluate whether giving a prophylactic dose of tocilizumab can prevent neurologic AEs when teclistamab is administered in a community setting. This requires carefully following patients to ensure that tocilizumab, normally given at the onset of CRS, does not alter the efficacy of the therapy.

"All of the safety end points are early," cautioned Rifkin, who explained the pilot's methodology.

This process required investigators to treat 5 patients, present findings to the data review committee (DRC); treat 5 more patients, then present those findings to the DRC. Under the study's protocol, with the DRC's blessing, the study can then expand from 4 sites to 12 and enroll an additional 40 patients.

"We've completed our first 10 patients," Rifkin said in an interview. "The next data review committee will be within the next 2 weeks, and we're optimistic we'll be able to then open it up and accrue the remaining 40 patients."

In addition, he said, "a talquetamab arm will be added," referencing the bispecific antibody sold as Talvey, which is a GPRC5D-directed CD3 T-cell engager.

Both teclistamab and talquetamab are made by Johnson & Johnson, which sponsored the study with the Sarah Cannon Research Institute.

Rifkin was enthusiastic about the results, but he noted that giving patients teclistamab will still require a community practice to have resources to properly administer the therapy, which is given through subcutaneous injection. Patients must still have a caregiver present, there is still the likelihood of fever, and results show that other AEs such as headaches or nausea remain.

"It's still a team effort," Rifkin said. One approach being considered is that after a few weekly doses, patients in the study could return to their local oncologist, because the window for CRS or ICANS to appear will have passed.

The pilot is based on findings from a cohort of the MajesTEC-1 study, which led to approval for teclistamab in patients who have received at least 3 therapies for multiple myeloma.

Methods. Study protocol call for the following¹:

- Patients eligible for the pilot must be at least aged 18 years and have received at least 4 prior lines of therapy for multiple myeloma.
- Those with rapidly progressing multiple myeloma, active infection, or central nervous system involvement are excluded.
- Tocilizumab is given in doses of 8 mg/kg intravenously 2 to 4 hours prior the first dose of teclistamab in an outpatient setting; teclistamab is then given weekly for 12 cycles until disease progression or unacceptable toxicity.

Results: Data presented at ASCO include the following¹:

- Median age was 70 years (range, 53-83).
- Six female patients and 5 male patients have enrolled.
- Patients received a median of 8 (range, 5-11) prior systemic therapies.
- Criteria for stopping, which are grade 3 or higher CRS or neurotoxicity/ICANS, were not met for the first 11 patients.
- Common AEs were headache (5), nausea (5), neutropenia (4), and injection site reaction (4).
- No patient had CRS or ICANS.

- No patient was hospitalized due to tocilizumab or teclistamab.
- One patient had a grade 2 infection of the upper respiratory tract and urinary tract; 2 patients had 1 each of respiratory tract or yeast infection.
- Ten patients completed the step-up dosing regimen.
- One patient with diffuse bony lesions and pain did not complete the regimen and withdrew due to physician's decision; the patient later died. ●

REFERENCES

1. Rifkin RM, Schade HH, Simmons G, et al. OPTec: a phase 2 study to evaluate outpatient (OP) step-up administration of teclistamab (Tec), a BCMA-targeting bispecific antibody, in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol*. 2024;42(suppl 16). Abstract 7528. doi:10.1200/JCO.2024.42.16_suppl.7528
2. Tecvayi (teclistamab-cqyv) biweekly dosing approved by the U.S. FDA for the treatment of patients with relapsed or refractory multiple myeloma. News release. Johnson & Johnson. February 20, 2024. Accessed June 3, 2024. <https://bit.ly/3V5EQ53>
3. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med*. 2022;387(6):495-505. doi:10.1056/NEJMoa2203478

CEPHEUS: SC Daratumumab With VRd Improves MRD Negativity, PFS in Myeloma When Transplant Is Deferred

MARY CAFFREY | SEPTEMBER 27, 2024

Patients with newly diagnosed multiple myeloma must decide whether to pursue a bone marrow transplant if they are eligible. But if they defer this option, the anti-CD38 antibody daratumumab (Darzalex; Johnson & Johnson), given subcutaneously (SC) with a standard backbone combination, offers superior results in both progression-free survival (PFS) and in bone marrow tests to detect cancer cells.¹

Those are the findings of the CEPHEUS trial, which were presented at the 21st International Myeloma Society Annual Meeting (IMS 2024). CEPHEUS (NCT03652064) is an ongoing, phase 3, multicenter, randomized, open-label study that has enrolled 396 patients in 13 countries. It compares the efficacy and safety of daratumumab plus bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (D-VRd) vs VRd in patients with newly diagnosed multiple myeloma who are either ineligible for a transplant or who defer transplant as their initial treatment.

CEPHEUS' primary end point is minimal residual disease (MRD) at the 10⁻⁵ sensitivity threshold; this measure uses highly sensitive testing to see whether there are cancer cells in the bone marrow. Secondary end points include PFS, complete response (CR) rate, MRD-negative rate at 1 year, durable MRD negativity, and overall response rate. Overall survival (OS) measures were reported and favored D-VRd, but data were not yet mature.

The results answered a question that remained following the phase 3 MAIA trial (NCT02252172), which compared daratumumab plus lenalidomide and dexamethasone (D-Rd) with Rd alone in patients with untreated myeloma, which had shown that giving daratumumab with another version of backbone therapy offered a median OS of 7.5 years in transplant-ineligible patients.²

"The addition of daratumumab to VRd improved the depth of response in terms of MRD negativity being overall at 10⁻⁵ or 10⁻⁶, as well as sustained MRD negativity at 10⁻⁵, defined as by

more than 12 months," said Saad Z. Usmani, MD, MBA, FASCO, of Memorial Sloan Kettering Cancer Center in New York, New York, and the lead investigator for CEPHEUS. "The risk of disease progression or death was lower in D-VRd."

He added, "CEPHEUS complements MAIA or D-Rd in supporting a daratumumab-based induction therapy for transplant-ineligible or transplant-deferred patients."

The trial broke ground in a few ways: It's among the first trials to measure MRD negativity as the primary end point, and the regimen's sponsors will head to FDA after its Oncologic Drug Advisory Committee (ODAC) voted unanimously in April to use MRD-negativity CR as an end point for accelerated approval.

But because the trial began years before the ODAC vote, investigators also accumulated enough PFS events to show these data to regulators, Usmani said in response to a question.

IMS President Philippe Moreau, MD, of the University Hospital of Nantes, France, in introducing the abstract, said if CEPHEUS continued the trend seen in recent multiple myeloma trials, involving triplet and quadruplet combinations, "We will have the confirmation that quadruplet is here, probably, to stay."

Moreau said the reason the myeloma field needs better regimens is that too many patients are lost after the first relapse. "So the best treatment up front for [older] patients is very important," he said.

However, Usmani cautioned that a patient's level of frailty was a consideration when deciding on a regimen, and CEPHEUS did not enroll overly frail patients in the study.

Methods and Results

To enroll, patients had to be 18 years or older with transplant-ineligible or transplant-deferred multiple myeloma. All received eight 21-day cycles of VRd, followed by 28-day cycles of Rd until disease progression.

The patients were randomly assigned to D-VRd and received SC daratumumab, which was given weekly in cycles 1 and 2, every 3 weeks for cycles 3 through 8, and every 4 weeks after that until disease progression.

Results were as follows¹:

- The D-VRd group had 197 patients; 198 were in the Rd group.
- Median age was 70 years (range, 31-80).
- Among all patients, 28.1% had International Staging System stage III disease; 13.2% had high-risk cytogenetics.
- At a median follow-up of 58.7 months, the overall MRD-negativity rate was 60.7% for D-VRd vs 39.4% for VRd (OR, 2.37; 95% CI, 1.58-3.55; $P < .0001$).
- PFS was significantly improved with D-VRd vs VRd (HR, 0.57; 95% CI, 0.41-0.79; $P = .0005$). Median PFS was not reached for D-VRd vs 52.6 months for VRd; estimated 54-month PFS rates were 68.1% vs 49.5%, respectively, favoring D-VRd.
- The CR rate was 81.2% vs 61.6%, favoring D-VRd ($P < .0001$).
- Sustained MRD-negativity rate was 48.7% vs 26.3%, also favoring D-VRd ($P < .0001$).
- Patients taking daratumumab were able to stay on treatment longer, for a median duration of 22 more months (56.3 vs 34.3 months).

- OS was trending in favor of D-VRd (HR 0.85; 95% CI, 0.58-1.24). After a sensitivity analysis to censoring deaths due to COVID-19, which was at its peak during enrollment, HR was 0.69 (95% CI, 0.45-1.05) favoring D-VRd. Data are not mature.

Data presented at IMS did not include results by race. In response to a question about results for Black and Latino patients, Usmani said, "This is on our docket of analyses to perform and report on in the future."

FDA UPDATE

On September 30, 2024, Johnson & Johnson announced it had submitted a supplemental Biologics License Application with FDA seeking a new indication for subcutaneous daratumumab with VRd for the treatment of patients newly diagnosed with multiple myeloma for whom autologous transplant is not planned. ●

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: 21st International Myeloma Society Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Abstract OA - 63.
2. Facon T, Kumar S, Plesner T, et al; MAIA trial investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249

Talquetamab Combo Offers Durable Responses in Heavily Pretreated Patients, Updated Data Show

MARY CAFFREY | SEPTEMBER 27, 2024

Talquetamab, the bispecific GPRC5D-directed CD3 T-cell engager, offered durable responses when used in different combinations, according to data from a pair of trials involving patients with multiple myeloma who had received 4 to 5 prior lines of therapy.

Updated phase 1b results for the TRIMM-2 (NCT04108195) and RedirecTT (NCT04586426) trials were presented during an oral abstract session at the 21st International Myeloma Society Annual Meeting (IMS 2024). Earlier results for both studies were reported during the 2023 meeting of the American Society of Clinical Oncology (ASCO 2023) and in the July 2023 issue of *Evidence-Based Oncology*.^{1,2}

The FDA approved talquetamab (Talvey; Johnson & Johnson) on August 8, 2023, for the treatment of relapsed or refractory multiple myeloma in patients who have received at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.³

TRIMM-2 Update: After Therapies Fail, Try Triplet

At ASCO 2023, phase 2 results for 1 arm of TRIMM-2 showed an overall response rate (ORR) of 78% for a combination of talquetamab and subcutaneous daratumumab (Darzalex; Johnson & Johnson), with 12-month progression-free survival (PFS) at 77.4% among patients taking the larger talquetamab dose (0.8 mg/kg biweekly).¹

At IMS 2024, Nizar J. Bahlis, MD, of Arnie Charbonneau Cancer Institute at the University of Calgary in Alberta, presented phase 1b results for a triplet arm, which tested talquetamab, daratumumab, and pomalidomide (Pomalyst; Bristol Myers Squibb) in patients who had on average at least 1 more line of therapy than patients in the earlier phase 2 study.⁴

In this phase 1b study, 93.5% of patients had received an anti-CD38 therapy, with 83.1% refractory (including 80.5% refractory to daratumumab). Also, 83.1% had received pomalidomide, with 75.3% refractory, and 39.0% had received a bispecific, with 37.7%

refractory. In addition, 31.2% had prior treatment with chimeric antigen receptor T-cell therapy.

As in the prior phase 2 study, patients received talquetamab doses of either 0.4 mg/kg weekly or 0.8 mg/kg biweekly. Daratumumab dosing was 1800 mg, with pomalidomide 2 mg, starting in cycle 2.^{1,4}

Results as of April 10, 2024, showed the following⁴:

- Seventy-seven patients received the triplet of talquetamab, daratumumab, and pomalidomide, with a median follow-up of 17.5 months.
- Median prior lines of therapy was 6, over a median of 6.8 years since diagnosis. Most patients were penta-drug exposed (68.8%) and triple-class refractory (77.9%).
- At baseline, 26.2% had high-risk cytogenetic features, and 23.4% had extramedullary disease.
- ORR was 81.8%; 53.2% of patients had a complete response or better. Median duration of response was 22.1 months (95% CI, 13.6–27.0). Median time to first response was 1.0 month, with a range of 0.9 to 6.7 months. Median PFS was 15.5 months (95% CI, 11.7–24.4).

Bahlis discussed the strengths and prior evidence for each therapy in the triplet in the current study.

“Talquetamab is a first-in-class bispecific antibody that targets an orphan molecule, GPRC5D, that is aberrantly expressed on clonal plasma cells as a single agent,” Bahlis said. “It reported high activity with an overall response rate of 70% in the MonumentAL-1 study [NCT03399799]. Daratumumab is a first-in-class anti-CD38 antibody with known direct antimyeloma activity as well as immunomodulatory effects. Pomalidomide is a third-generation immunomodulator that also has direct antimyeloma activity as well as immunomodulation effects. Preclinical studies suggest that the combination of a bispecific antibody with daratumumab or with an immunomodulator has synergistic effects.”

Investigators described the responses to the triplet as “deep and durable” in anti-CD38–refractory and prior T-cell redirection–exposed patients. Bahlis said responses were consistent among patients despite any therapy they may have had in the past, even if they were double refractory.

Adverse events. Despite the success of the trial, 45% of the patients stopped taking 1 of the therapies in week 2. In response to a question, Bahlis delineated that 24 patients stopped taking pomalidomide in week 2, compared with 3 who stopped talquetamab and 5 who stopped daratumumab. He did not have information available on what pomalidomide adds to the regimen.

All patients had at least 1 adverse event (AE), with 94.8% grade having a grade 3/4 AE. Most common AEs were dysgeusia

(79.2%; NA, grade 3/4), neutropenia (77.9%; 68.8%, grades 3/4), cytokine release syndrome (CRS; 74.0%; all grades, 1/2), dry mouth (64.9%; 2.6%, grades 3/4), and fatigue (57.1%; 5.2%, grades 3/4).

Median onset of CRS was 1 day after receiving talquetamab; median duration was 2 days. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 3.9% (1.3% grades 3/4). Infections occurred in 74.0% (29.9% grades 3/4); onset of most grade 3 or higher infections occurred within the first 6 months (18/23 events). Two patients died due to sepsis or hemorrhagic transformation stroke.

Investigators concluded that among patients with relapsed/refractory multiple myeloma, the triplet of talquetamab, daratumumab, and pomalidomide was “promising depth and durability of response,” even in patients who were refractory to daratumumab and pomalidomide in the past.

Based on the results, the triplet is being tested in the phase 3 MonumentAL trial (NCT05455320),⁵ Bahlis said.

RedirecTT-1: Strong Responses in EMD With Dual Bispecific

Prior to its approval of talquetamab, with its anti-GPRC5D mechanism, the FDA authorized teclistamab (Tecvayli, Johnson & Johnson), an anti-B-cell maturation antigen (BCMA) CD3 T-cell engager for patients who have received at least 3 prior therapies for multiple myeloma. In RedirecTT-1, investigators led by Yael C. Cohen, MD, of Tel Aviv University in Israel, are examining the potential advantages of combining these mechanisms, especially in high-risk patients.⁶

“The dual targeting of GPRC5D and BCMA can avoid antigen escape and clonal resistance,” Cohen explained during the session.

Earlier work allowed investigators to determine the recommended phase 2 dose of teclistamab at 3.0 mg/kg and talquetamab at 0.8 mg/kg every 2 weeks.² Results reported at IMS 2024 updated data from RedirecTT-1 with a longer median follow-up, according to the abstract.⁶

As of March 15, 2024, investigators reported results for 94 patients, with 44 patients at recommended phase 2 dose, as follows²:

- The median follow-up was 20.3 months, and 18.2 months for patients at the recommended dose.
- Median age was 64.5 years.
- Patients had 4 median prior lines of therapy; 86.2% were triple-class refractory and 64.9% were penta-drug exposed.
- Overall, 41.2% (21/51) patients had high-risk cytogenetic features; 34 (36.2%) had extramedullary disease (EMD), defined as more than 1 bone-independent lesion of at least 2 cm.
- ORR at 18 months for the intent-to-treat population at the recommended dose was 79.5%; among patients with EMD at the recommended dose, it was 61.1%.

Cohen said durability of response was a defining feature of the combination therapy. The probability of patients at the recommended dose who had a response retaining it at 12 months was 91.0%; at 18 months, it was 85.9% for these patients.

Among patients with EMD at the recommended dose, 81.1% of patients in response retained it at 12 months.

PFS was 73.7% at 12 months for the recommended dose and 69.8% at 18 months. At 12 months, PFS was 52.9% at the recommended dose for patients with EMD.

Dose-limiting toxicities occurred in 3 patients across all dose levels: 1 had grade 3 oral herpes, 1 had grade 3 elevated alanine aminotransferase/aspartate aminotransferase, and 1 had grade 4 thrombocytopenia at the recommended dose.

Adverse events. Fourteen patients (14.9%) died due to AEs; this included 11 due to infection, of which 6 (6.4%) deaths were related to the drug. The most common AE was CRS (78.7%; grade 3, 2.1%; no patient had grade 4/5). Other common AEs were neutropenia (73.4%; grade 3/4, 68.1%), taste changes (64.9%; grade 3/4, not applicable), and nonrash skin AEs (60.6%; no grade 3/4).²

Grade 3/4 infections occurred in 63.8% of patients at all dose levels and 47.7% at the recommended dose level. ICANS occurred in 3.2% of patients (none grades 4/5). In total, 15 (16.0%) patients discontinued 1 of the 2 drugs due to AEs, of which 7 (7.4%) were drug-related (5 due to infections).

“This is the first dual-targeting bispecific antibody combination” in relapsed/refractory multiple myeloma, the investigators wrote in the abstract, noting that the combination had a safety profile that was similar to each agent as monotherapy. Responses to dual bispecific were consistent across doses, with robust durability of response at the recommended dose.

“Efficacy in patients with EMD closely approximates outcomes in all patients, potentially overcoming the poor prognosis in

high-risk populations,” the investigators noted, saying the results support further study in a larger trial.

Cohen said the results for patients with EMD are highly favorable to anything seen previously. “When you test the new regimen—if you test it against your toughest patients, you can get a true sense of what the potency of this regimen is,” she said. “So 81% of the EMD patients remained in response after 12 months; looking at PFS again, similarly, we see here encouraging results in the total population, [with] 69.8% of the patients remaining progression free at 18 months.”

She added, “With EMD, PFS at 1 year was 52%. If you compare these EMD results [with] those that have been reported for nonimmunotherapeutics and even for monotherapies, with bispecifics and [chimeric antigen receptor T-cell therapy], these are far more favorable than what has been previously reported.” ●

REFERENCES

1. Dholaria BR, Weisel K, Mateos MV, et al. Talquetamab (tal) + daratumumab (dara) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Updated TRIMM-2 results. *J Clin Oncol*. 2023;41(suppl 16):8003. doi:10.1200/JCO.2023.41.16_suppl.8003
2. Cohen YC, Morillo D, Gatt ME, et al. First results from the RedirecTT-1 study with teclistamab (tec) + talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol*. 2023;41(suppl 16):8002. doi:10.1200/JCO.2023.41.16_suppl.8002
3. FDA D.I.S.C.O. Burst Edition: FDA approvals of Talvey (talquetamab-tgvs) for relapsed, refractory multiple myeloma, and Elrexfio (elranatamab-bcmm) for relapsed or refractory multiple myeloma. News release. FDA. Updated September 26, 2023. Accessed September 27, 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approvals-talvey-talquetamab-tgvs-relapsed-or-refractory-multiple>
4. Bahlis NJ. Talquetamab (tal) + daratumumab (dara) + pomalidomide (pom) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): results from the phase 1b TRIMM2 study. Presented at: 21st International Myeloma Society Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Abstract OA – 01.
5. Cohen YC, Moreau P, Tolbert J, et al. MonumentAL-3: phase 3 trial of talquetamab + daratumumab ± pomalidomide versus daratumumab + pomalidomide + dexamethasone in relapsed/refractory multiple myeloma following ≥1 prior line of therapy. *Blood*. 2022;140(suppl 1):4418-4419. doi:10.1182/blood-2022-162733
6. Cohen YC. Talquetamab (tal) + teclistamab (tec) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): updated phase 1B results from RedirecTT-1 with >1 year of follow-up. Presented at: 21st International Myeloma Society Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Abstract OA – 03.

From CARs to Trispecifics, More Choices to Come in Multiple Myeloma

MARY CAFFREY | OCTOBER 1, 2024

Choices and combinations in multiple myeloma are proliferating, which is good news for both patients and physicians, according to Ajai Chari, MD, professor of medicine at the University of California, San Francisco, was the opening presenter during a September 27, 2024, symposium on immunotherapy at the 21st International Myeloma Society Annual Meeting (IMS 2024).

“I think anybody who’s treating [patients with myeloma] today is so gratified to see the improvement in their outcomes with these T-cell–redirection therapies,” Chari said. He highlighted

results from recent trials involving bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapies. Chari said that patients have had responses of 60% to 98% and progression-free survival (PFS) ranging from ≥11 months to 3 years.

Nonetheless, he said, “We have a lot of unmet needs.”

Chari noted positive news heard earlier during IMS 2024 regarding several high-risk conditions, such as treatment of extramedullary disease and patients with prior T-cell redirection “and, of course, global access to all these agents.”

“So how do we improve upon what we have?” Chari asked. “Targeting more than 1 antigen is one approach for the T cell with CARs. There are efforts to change the binding domains, the T-cell populations, and the source of T cells, including allogeneic [T cells],” he said.

Other strategies call for moving treatment into earlier lines of care. Additionally, Chari said, many studies are taking bispecific antibodies and working in a third target to create trispecifics.

In what one panel chair called a “whirlwind,” Chari took the audience on a rapid tour of recent approvals in myeloma and a view of what’s in the pipeline. With CAR T cells, for example, improvements will come not just through new products but also through alternative manufacturing processes that could save time and cut costs.

A trispecific engager under development combines B-cell maturation antigen and GPRC5D targeting with less toxicity than 2 separate therapies.

There are also new types of CARs: human single-chain variable fragments and allogeneic CARs. Chari showed early results from small studies with strong overall response rates and promising, if immature, PFS results. The question, he said, is how to “contextualize” what’s occurring compared with current therapies.

“It’s hard to make too many comparisons from single-arm small studies,” he said. “But we’re already seeing some interesting results.”

He compared recent phase 3 studies involving combinations of anti-CD38 therapies, pomalidomide, dexamethasone, and B-cell maturation antigen (BCMA)-targeting products. Chari noted that at the recent American Society of Clinical Oncology meeting, data from the phase 3 DREAMM-7 (NCT04246047)¹ and DREAMM-8 (NCT04484623)² studies were presented and showed the benefits of adding the BCMA-targeting antibody-drug conjugate belantamab mafodotin (Blenrep) to backbone regimens. Chari once again urged caution when comparing PFS with earlier trials.

“We’re looking at anywhere from 1 to 3 lines of prior therapy,” he said, noting that HRs are the more meaningful metric. “We should commend all of these studies [for] moving away from the doublet comparisons of yesteryear,” he said. “We’re now moving to triplet comparisons, and...we’re getting very impressive hazard ratios.”

Improvements in adverse event (AE) profiles are important, too. Chari noted that results for the phase 3 CARTITUDE-4 (NCT04181827) trial, presented at IMS 2024, answered questions “that we were concerned about.” For instance, he said, neurotoxicity AEs

were seen in 30% of patients, but there was only a single case of Parkinsonism, which had been a lingering issue.³

Coming in CAR T

“We have novel targets,” he said, including non-BCMA targets such as GPRC5D and CD70, and dual targets, including the combinations of BCMA with CD19 and GPRC5D.

“We have really exciting in vivo CARs, which are viral injections directly into the patient to avoid the leukapheresis manufacturing,” Chari said. “At UCSE, we’ll soon be having a CRISPR nonviral CAR,” referring to the gene-editing technology that allows scientists to modify living organism DNA.

Some clinical data for GPRC5D are coming in, he said, and responses are exciting, but again, he cautioned that numbers are small. Of concern, Chari said, is that so far the durability of PFS has been suboptimal.

CAR T-cell combinations are also being studied, but Chari said this concept removes one of the chief advantages of the CAR T approach, which is to give patients a break from treatment.

He reviewed a series of bispecific and trispecific engagers under development, including JNJ-7965322, which combines BCMA and GPRC5D targeting.⁴ As Yael C. Cohen, MD, explained the following day in a session on emerging therapies, this treatment essentially does the job of the talquetamab (Talvey) and teclistamab (Tecvayli) combination being studied in the RedirecTT-1 trial (NCT04586426); however, because it’s a trispecific, it does so with far less toxicity.⁵

Chari concluded with data on the use of prophylactic tocilizumab (Actemra) with bispecific antibodies; this is being studied in community practice due to the interest in bringing these therapies to a broader patient population.

Overall, early results show this strategy reduces rates of cytokine release syndrome (CRS), “but what you see is a bigger drop in the grade 1s than the grade 2s. So what remains to be worked up further is [how] we’re going to be moving this to outpatient,” Chari said. Also, he said, the drop in CRS comes with “a hint” of more neutropenia. ●

REFERENCES

1. Hungria V, Robak P, Hus M, et al; DREAMM-7 Investigators. Belantamab mafodotin, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;391(5):393-407. doi:10.1056/NEJMoa2405090
2. Dimopoulos MA, Beksac M, Pour L, et al; DREAMM-8 investigators. Belantamab mafodotin, pomalidomide, and dexamethasone in multiple myeloma. *N Engl J Med*. 2024;391(5):408-421. doi:10.1056/NEJMoa2403407
3. Mateos MV, San-Miguel J, Dhakal B, et al. Overall survival (OS) with ciltacabtagene autoleucel (cilta-cel) versus standard of care (SoC) in lenalidomide (len)-refractory multiple myeloma (MM): phase 3 CARTITUDE-4 study update. Presented at: 21st International Myeloma Society Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Abstract OA-65.
4. A study of JNJ-79635322 in participants with relapsed or refractory multiple myeloma or previously treated amyloid light-chain (AL) amyloidosis. ClinicalTrials.gov. Updated October 9, 2024. Accessed October 15, 2024. <https://clinicaltrials.gov/study/NCT05652335>
5. Cohen YC. Talquetamab (tal) + teclistamab (tec) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): updated phase 1B results from RedirecTT-1 with >1 year of follow-up. Presented at: 21st International Myeloma Society Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Abstract OA - 03.

