Managing Myeloma

The Emerging Role of CD38 in Multiple Myeloma

Human CD38 antigen is a transmembrane glycoprotein that is prominently expressed on multiple myeloma (MM) plasma cells, making it an ideal target for monoclonal antibody therapy. While naturally present in hematopoietic cells, including activated B- and T-cells, monocytes, natural killer cells, dendritic cells, and plasma cells, CD38 expression is significantly higher in MM cells, enhancing therapeutic efficacy of agents that target CD38 in MM. Additionally, CD38 is involved in several cellular processes such as signaling events, adhesion, and enzymatic activity, further supporting its role as a therapeutic target. As such, anti-CD38 therapies have shifted treatment paradigms by providing deeper and more sustained responses in both newly diagnosed and relapsed/refractory MM.

The American Society of Clinical Oncology (ASCO) Annual Meeting is a pivotal event where oncologists and researchers gather to discuss the latest advancements in cancer treatment. ASCO provides a platform for presenting new clinical data, debating treatment paradigms, and sharing innovative approaches. At the 2024 Annual Meeting, several key abstracts focused on anti-CD38 agents in MM. This e-newsletter features summaries of selected key abstracts that collectively emphasize the evolving role of anti-CD38 monoclonal antibodies in multiple myeloma, further establishing these agents as critical components of frontline and subsequent treatment strategies.

Highlighted Abstract Summaries

Phase 3 Study Results of Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone (Isa-VRd) Versus VRd for Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma (IMROZ)

Authors: *Thierry Facon, Meletios Athanasios Dimopoulos, Xavier P Leleu, et al.*

Background: Initial treatment is critical for patients with newly diagnosed multiple myeloma (NDMM), as opportunities for subsequent therapies may be limited in some patients. VRd (bortezomib, lenalidomide, and dexamethasone) is a current standard of care for NDMM. Isatuximab (Isa) is an anti-CD38 monoclonal antibody that induces myeloma cell death. The Phase 3 IMROZ study evaluated the efficacy and safety of Isa combined with VRd (Isa-VRd) compared to VRd alone in transplant-ineligible NDMM patients.

Study Overview and Results: The IMROZ study included 446 patients with active, measurable NDMM who were ineligible for transplant due to age or comorbidities. Patients were randomized to receive either Isa-VRd or VRd. The study found that Isa-VRd significantly improved progression-free survival (PFS) compared to VRd alone. Patients in the Isa-VRd arm had deeper and more sustained responses. The safety profile was consistent with the addition of Isa to VRd, with adverse events (AEs) being manageable and similar across both groups.

Relevance: The results from the IMROZ study suggest that adding isatuximab to the VRd regimen can significantly reduce the risk of disease progression or death in transplant-ineligible NDMM patients. This combination shows promise as a new standard of care, providing deeper and longer-lasting responses without significantly increasing toxicity. These findings highlight the potential for improved patient outcomes with Isa-VRd in this patient population.

Link: Abstract 7500

Phase 3 Randomized Study of Isatuximab (Isa) Plus Lenalidomide and Dexamethasone (Rd) With Bortezomib Versus IsaRd in Patients With Newly Diagnosed Transplant-ineligible Multiple Myeloma (NDMM TI)

Authors: *Xavier P. Leleu, Cyrille Hulin, Jerome Lambert, et al.*

Background: CD38-targeting immunotherapy combined with lenalidomide and dexamethasone is a current standard of care for transplant-ineligible newly diagnosed multiple myeloma (NDMM TI). The best treatment combinations are crucial as outcomes worsen with successive lines of therapy. This Phase 3 study, BENEFIT/IFM2020-05, evaluated the efficacy and safety of adding bortezomib to IsaRd (Isa-VRd) compared to IsaRd alone, aiming to improve the depth of response in NDMM TI patients.

Study Overview and Results: The prospective, multicenter, randomized trial included 270 non-frail patients aged 65-79 with NDMM TI. Patients were randomized to receive either Isa-VRd or IsaRd. The study found that Isa-VRd significantly improved minimal residual disease (MRD) negativity rates at 18 months compared to IsaRd. The addition of bortezomib led to deeper responses without significantly affecting the relative dose intensity of IsaRd. The safety profile was consistent, although there were more neurological adverse events in the Isa-VRd arm.

Relevance: The BENEFIT study supports Isa-VRd as a new standard of care for transplant-ineligible, non-frail NDMM patients. The addition of bortezomib significantly increased MRD negativity rates, suggesting deeper and more sustained responses. These findings highlight the potential of Isa-VRd in improving outcomes for this patient population.

Link: Abstract 7501

Clinical Outcomes of Retreatment with Daratumumab-based Regimens in Anti-CD38-refractory Multiple Myeloma

Authors: *Carlyn Rose Co Tan, Colin Rueda, Tala Shekarkhand, et al.*

Background: Daratumumab (Dara)-based regimens have led to significant responses and improved outcomes in both newly diagnosed (NDMM) and relapsed/refractory multiple myeloma (RRMM). With increasing use of Dara in these settings, understanding the effectiveness of retreating patients with Dara-based therapy becomes crucial. Previous studies indicated potential benefits from Dara-based retreatment in patients initially treated with Dara-based induction therapy.

Study Overview and Results: This retrospective study at Memorial Sloan Kettering evaluated 128 patients with RRMM who were retreated with Dara-based regimens. The study included a diverse patient population with a significant proportion having high-risk cytogenetics. Patients had undergone a median of five prior lines of therapy before retreatment. The overall response rate to retreatment was comparable to the initial response, with notable responses even in patients previously refractory to Dara. The progression-free survival varied based on the number of prior treatments, with better outcomes seen in those who had fewer lines of therapy before retreatment. The timing between initial treatment and retreatment did not significantly impact progression-free survival.

Relevance: This study demonstrates that retreatment with Dara-based regimens can yield similar response rates in RRMM patients, even for those who are Dara-refractory. These findings suggest that combining Dara with other active multiple myeloma agents can provide beneficial responses, emphasizing the potential of Dara retreatment strategies in managing RRMM.

Link: Abstract 7570

Daratumumab (DARA) + Bortezomib/Lenalidomide/Dexamethasone (VRd) in Transplant-eligible (TE) Patients With Newly Diagnosed Multiple Myeloma (NDMM): Analysis of Minimal Residual Disease (MRD) in the PERSEUS Trial

Authors: *Paula Rodríguez-Otero, Philippe Moreau, Meletios Athanasios Dimopoulos, et al.*

Background: In the Phase 3 PERSEUS study, subcutaneous daratumumab (DARA SC) combined with VRd (D-VRd) during induction/consolidation and D-R maintenance demonstrated improved progression-free survival (PFS) and increased depth of response compared to VRd alone in transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM) patients. This analysis focuses on the impact of D-VRd on minimal residual disease (MRD) during maintenance therapy.

Study Overview and Results: The PERSEUS trial included 709 TE NDMM patients who were randomized to receive either D-VRd or VRd. The study found that D-VRd significantly improved MRD negativity rates compared to VRd at multiple time points (12, 24, and 36 months). Additionally, more patients achieved sustained MRD negativity for 12 months or more with D-VRd. These improvements in MRD negativity were associated with better progression-free survival. The safety profile was consistent with previous findings, supporting D-VRd as a potential new standard of care for TE NDMM patients.

Relevance: The results from the PERSEUS study suggest that D-VRd induction/consolidation and D-R maintenance can significantly enhance MRD negativity rates and improve progression-free survival in transplant-eligible NDMM patients. These findings highlight the potential of DARA SC in maintenance therapy and support its use as a new standard of care, providing deeper and sustained responses.

Link: Abstract 7502

Importance of Staying Current with New Data

In the ever-evolving field of oncology, it is critical for clinicians to stay abreast of the latest research and clinical developments. The treatment landscape for MM is rapidly changing, with new therapies and combinations being explored and validated through ongoing clinical trials. Integrating new data into clinical practice is essential to providing the best possible care for patients. By staying informed of the latest findings, you have the potential to effectively implement the most up-to-date treatment strategies for your patients with MM.

To further explore the emerging importance of anti-CD38 agents in MM, we encourage you to review an important new accredited series, ***The Cutting Edge of MM: The Evolving Role of CD38-directed Strategies,*** available now on the *Managing Myeloma* website. In this fast-paced podcast series featuring rapid-fire discussion of clinical trials and their translation to practice, you'll learn about the most up-to-date data in CD38-targeting agents in multiple myeloma and new insights into how the CD38 monoclonal antibodies are changing the treatment of myeloma.

The Cutting Edge of MM:
The Evolving Role of CD38-directed Strategies

References

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