Isatuximab quadruplet deepens myeloma response, but for how long?

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For transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM), achieving deep and durable responses remains a clinical imperative. Minimal residual disease (MRD) negativity has emerged as a critical prognostic marker, but the dynamics of MRD status over time and its impact on long-term outcomes have required further elucidation. The IMROZ study provides a detailed look at how a CD38-directed quadruplet therapy influences these dynamics.1

KEY TAKEAWAYS

- The Pivot: Isa-VRd/Isa-Rd significantly increased MRD negativity rates and MRD-negative complete response compared to VRd/Rd in transplant-ineligible NDMM patients.
- The Data: Isa-VRd/Isa-Rd led to MRD negativity rates of 53.3% at the end of induction versus 31.8% for VRd/Rd (P<.0001).
- The Action: Clinicians should consider Isa-VRd as a frontline standard of care for transplant-ineligible NDMM, with MRD monitoring potentially guiding treatment decisions.

Multiple myeloma, a plasma cell malignancy, remains incurable for most patients, particularly those ineligible for transplant due to age or comorbidities. Standard induction regimens often involve proteasome inhibitors and immunomodulatory drugs, but the addition of a CD38 monoclonal antibody has shown promise in deepening responses. The IMROZ study specifically investigated the quadruplet regimen of isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) followed by Isa-Rd maintenance, comparing it against the triplet VRd followed by Rd in this vulnerable population.1

The IMROZ trial, a randomized phase 3 study, enrolled transplant-ineligible patients with newly diagnosed multiple myeloma. Investigators randomized patients to either Isa-VRd induction followed by Isa-Rd maintenance or VRd induction followed by Rd maintenance. The primary analysis, previously reported, established a significant progression-free survival (PFS) benefit for the Isa-VRd arm. This current analysis, published in Blood, delves into the dynamics of minimal residual disease (MRD) negativity, a key secondary endpoint, and its correlation with clinical outcomes. The trial was registered at www.clinicaltrials.gov as #NCT03319667.1

The IMROZ Design and MRD Assessment

The IMROZ study enrolled 750 transplant-ineligible patients with newly diagnosed multiple myeloma. Patients were randomized 3:2 to receive either Isa-VRd (isatuximab 10 mg/kg IV weekly for 4 weeks, then biweekly; bortezomib 1.3 mg/m2 SC weekly; lenalidomide 25 mg PO daily for 21/28 days; dexamethasone 20 mg PO/IV weekly) or VRd

(bortezomib, lenalidomide, dexamethasone at the same doses). Induction therapy lasted for 12 cycles, followed by maintenance with Isa-Rd or Rd until disease progression or unacceptable toxicity. The study defined transplant-ineligible patients as those aged 18 years or older with specific comorbidities or age over 70.1

Investigators assessed MRD status using next-generation sequencing (NGS) of bone marrow aspirates, with a sensitivity threshold of 10-5. They performed MRD assessments at predefined time points: end of induction (EOI), 12 months after randomization, and every 6 months during maintenance up to 60 months of follow-up. The primary analysis focused on MRD negativity at any time point, while this landmark analysis specifically examined MRD dynamics over time and its impact on time to progression (TTP).1

Deepening Responses with Isatuximab

Treatment with Isa-VRd/Isa-Rd led to significantly deeper responses compared to VRd/Rd. At the end of induction, 53.3% of patients in the Isa-VRd/Isa-Rd arm achieved MRD negativity, compared to 31.8% in the VRd/Rd arm (P<.0001). This represents a substantial improvement in the depth of initial response. The benefit extended to MRD-negative complete response (CR), with 45.7% achieving this endpoint in the Isa-VRd/Isa-Rd arm versus 23.9% in the VRd/Rd arm (P<.0001).1

The higher rates of MRD negativity persisted throughout the maintenance phase. At 12 months, 50.4% of Isa-VRd/Isa-Rd patients were MRD negative, compared to 28.7% of VRd/Rd patients. This sustained benefit was observed up to 60 months of follow-up, indicating the durability of the deeper responses achieved with the quadruplet regimen. These findings underscore the consistent advantage of adding isatuximab to the VRd backbone.1

The benefit of Isa-VRd/Isa-Rd was consistent across key patient subgroups. This included older patients (aged >70 years) and frail patients, a population often challenging to treat effectively due to comorbidities and reduced tolerance to intensive regimens. The quadruplet therapy demonstrated similar improvements in MRD negativity rates in these subgroups, suggesting its broad applicability in the transplant-ineligible NDMM population. This is a critical point for clinicians managing a diverse patient demographic.1

MRD Dynamics and Clinical Outcomes

The study also examined the impact of MRD negativity dynamics on time to progression (TTP). Patients who achieved MRD negativity at any time point and subsequently converted to MRD positivity experienced a significantly prolonged TTP with Isa-VRd/Isa-Rd compared to VRd/Rd. This suggests that even transient MRD negativity, when achieved with the quadruplet, confers a lasting benefit.1

A landmark analysis of patients who converted from MRD negative at the end of induction to MRD positive also favored Isa-VRd/Isa-Rd. This specific finding highlights the importance of achieving deep initial responses. The duration of MRD negativity, even if not sustained indefinitely, appears to be a crucial factor in delaying disease progression. This provides further evidence that MRD status is not merely a snapshot but a dynamic marker with prognostic implications.1

The study's detailed analysis of MRD dynamics over time offers valuable insights into treatment selection and continuation. Evaluating MRD status at multiple time points may help clinicians make informed decisions about intensifying or de-escalating therapy, or even considering treatment discontinuation in select patients who achieve very deep and durable MRD negativity. This moves beyond a single MRD assessment, providing a more comprehensive

picture of disease control. For a deeper understanding of haematological malignancies, the Oxford Handbook of Clinical Haematology offers a concise reference.

Safety and Tolerability

The IMROZ study previously reported the safety profile of Isa-VRd/Isa-Rd. The addition of isatuximab did not introduce unexpected safety signals. The most common adverse events were generally manageable and consistent with the known profiles of the individual agents. While this analysis focused on efficacy endpoints, the sustained benefit in MRD negativity without significant new safety concerns reinforces the favorable risk-benefit profile of the quadruplet regimen.1

Where it Falls Short

While the IMROZ study provides compelling evidence for Isa-VRd/Isa-Rd, it is important to acknowledge certain aspects. The study population was transplant-ineligible, limiting direct generalizability to younger, fitter patients who may undergo transplant. The follow-up, while substantial at 60 months, still represents an interim analysis for overall survival, which remains the ultimate endpoint in multiple myeloma. The use of NGS for MRD assessment, while highly sensitive, is not universally available, which may impact its routine clinical implementation in all settings.1

The study did not explicitly define a strategy for treatment discontinuation based on MRD status, leaving this to clinical judgment. While the data suggests that sustained MRD negativity is beneficial, the precise threshold and duration required to consider stopping therapy safely remain an area for further research. This is a common challenge in trials exploring MRD-guided approaches.1

The findings on the degree of MRD negativity and MRD-negative CR benefit achieved during induction and maintenance by patients receiving Isa-VRd/Isa-Rd versus VRd/Rd extend the IMROZ primary analyses. These data further support Isa-VRd as a standard of care for frontline treatment of transplant-ineligible patients with newly diagnosed multiple myeloma. The next step will be to see how these deep responses translate into long-term overall survival benefits and whether MRD-guided de-escalation strategies can be safely implemented.

CLINICAL IMPLICATIONS

The IMROZ data firmly establishes Isa-VRd as a new standard for transplant-ineligible NDMM. Achieving MRD negativity, particularly deep and sustained, now carries even greater weight as a prognostic indicator. Clinicians should integrate this quadruplet into their frontline treatment algorithms, recognizing its superior ability to induce profound responses.

The detailed analysis of MRD dynamics, including conversion from negative to positive, provides a more nuanced understanding of disease progression. This suggests that serial MRD monitoring, rather than a single snapshot, could become a valuable tool for guiding treatment decisions. It offers a potential pathway for identifying patients who might benefit from continued therapy versus those for whom de-escalation could be considered, though formal guidelines for such decisions are still evolving.

For patients, this means a higher likelihood of achieving deeper, more durable remissions, potentially extending the time they live without disease progression. The consistency of benefit across older and frail subgroups is particularly encouraging, as these patients often have limited treatment options. The challenge now lies in ensuring equitable access to this effective, albeit more complex, quadruplet regimen.

> The pharmaceutical industry, specifically Sanofi, which manufactures isatuximab, will likely see increased adoption of this regimen. The robust data on MRD negativity provides a strong clinical argument for its use. Future research should focus on refining MRD-guided treatment strategies and exploring the long-term cost-effectiveness of such intensive upfront therapy.

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REFERENCES

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