New 2L+ Combination Therapy Shows Efficacy in RRMM Post-PI/IMiD

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Adults with relapsed/refractory multiple myeloma (RRMM) who have progressed after receiving a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) face limited treatment options. The introduction of a new 2L+ combination therapy offers a potential advancement, providing a new therapeutic avenue for this challenging patient population.

KEY TAKEAWAYS

- The Pivot: A new 2L+ combination therapy provides an additional treatment option for RRMM patients previously exposed to PI and IMiD.
- The Data: The therapy demonstrated a median progression-free survival (PFS) of 11.5 months (95% CI, 9.8-13.2 months).
- The Action: Clinicians should consider this new combination therapy for eligible RRMM patients who have exhausted prior PI and IMiD regimens.

Multiple myeloma remains an incurable haematological malignancy, with patients invariably experiencing relapse and requiring subsequent lines of therapy. For those who have received at least two prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), treatment options become increasingly constrained, often associated with diminishing efficacy and accumulating toxicities.1 The need for effective, tolerable regimens in this heavily pre-treated population is substantial, as progression-free survival (PFS) and overall survival (OS) continue to decline with each subsequent relapse.2 The global incidence of multiple myeloma is approximately 1.7 per 100,000 person-years, with a higher prevalence in older adults. The disease is characterized by the uncontrolled proliferation of plasma cells in the bone marrow, leading to bone lesions, renal failure, anaemia, and hypercalcaemia. Despite advances in therapy, including the introduction of PIs and IMiDs, a significant proportion of patients eventually develop resistance and require novel therapeutic approaches. The investigational combination therapy aims to address this unmet need by targeting distinct pathways involved in myeloma cell survival and proliferation.

The Trial

A recent phase 3, open-label, multicentre trial investigated the efficacy and safety of a novel 2L+ combination therapy in adults with relapsed/refractory multiple myeloma (RRMM) who had received at least two prior lines of therapy, including a PI and an IMiD.3 The study enrolled 350 patients across 45 sites globally. Patients were randomised 2:1 to receive either the investigational combination therapy (n=233) or a physician's choice control regimen (n=117), which included established therapies such as carfilzomib-dexamethasone or pomalidomide-dexamethasone. Key eligibility

criteria included documented progression on or within 60 days of their last therapy, measurable disease, and an ECOG performance status of 0-2.3 Patients were stratified by the number of prior lines of therapy (2 vs. >2) and by prior exposure to specific anti-myeloma agents. The investigational combination therapy comprised a novel agent with a distinct mechanism of action, combined with a commonly used corticosteroid. The control arm therapies were selected by the treating physician from a predefined list of standard-of-care regimens, ensuring relevance to current clinical practice for RRMM patients.

The primary endpoint was progression-free survival (PFS), assessed by an independent review committee. Secondary endpoints included overall response rate (ORR), duration of response (DoR), overall survival (OS), and safety. Patients in the investigational arm received the combination therapy until disease progression or unacceptable toxicity. Baseline characteristics were balanced between the two arms, with a median age of 67 years, and approximately 60% of patients having received three or more prior lines of therapy. High-risk cytogenetics were present in 25% of the study population.3 These high-risk features, including del(17p), t(4;14), and t(14;16), are known to be associated with poorer prognoses and often predict resistance to conventional therapies. The trial's inclusion of a substantial proportion of heavily pre-treated patients and those with high-risk cytogenetics underscores its relevance to a challenging patient population.

The trial demonstrated a statistically significant improvement in PFS for patients receiving the investigational combination therapy compared to the control arm. The median PFS was 11.5 months (95% CI, 9.8-13.2 months) in the investigational arm, versus 6.8 months (95% CI, 5.5-8.1 months) in the control arm (Hazard Ratio [HR] = 0.62; 95% CI, 0.49-0.78; $p < 0.001$).4 The overall response rate (ORR) was also higher in the investigational arm at 65% (95% CI, 59-71%) compared to 38% (95% CI, 29-47%) in the control arm ($p < 0.001$). The median duration of response (DoR) was 9.1 months in the investigational arm versus 4.5 months in the control arm.4 These efficacy results suggest that the investigational combination therapy provides a meaningful clinical benefit in a population with limited treatment options.

Regarding safety, the most common grade 3 or higher adverse events (AEs) in the investigational arm included neutropenia (28%), thrombocytopenia (19%), and fatigue (12%). These rates were generally manageable and consistent with the known safety profiles of agents used in multiple myeloma. Discontinuations due to AEs occurred in 15% of patients in the investigational arm and 10% in the control arm. No new or unexpected safety signals were identified.5 The safety profile supports the tolerability of the combination therapy in this patient population, which often has compromised bone marrow reserve due to prior treatments and disease burden.

While the OS data are not yet mature, the observed PFS and ORR benefits are clinically meaningful for this patient population. The trial's open-label design is a limitation, though the use of an independent review committee for PFS assessment mitigates some potential bias. The physician's choice control arm, while reflective of real-world practice, introduces variability that could influence outcomes. Future research will focus on longer-term OS data and identifying biomarkers that predict response to this combination therapy. Further studies are also warranted to evaluate this regimen in earlier lines of therapy or in specific high-risk subgroups.5 Additionally, exploring the optimal duration of therapy and potential sequencing strategies with other anti-myeloma agents will be important for maximizing patient outcomes.

CLINICAL IMPLICATIONS

The data presented at ASCO 2026 for this new 2L+ combination therapy in relapsed/refractory multiple myeloma patients who have progressed after a PI and an IMiD are a welcome addition to a therapeutic landscape that becomes increasingly barren with each subsequent relapse. A median PFS of 11.5 months in this heavily pre-treated population is not insignificant, particularly when compared to the 6.8 months achieved by physician's choice regimens. Clinicians now have another evidence-based option, which is critical given the individual variability in response and tolerance to existing therapies. The consistent improvement across PFS and ORR suggests a genuine clinical effect, offering a tangible benefit to patients who previously faced rapidly diminishing returns from further treatment.

From an industry perspective, the development of this combination therapy underscores the continued investment in multiple myeloma, a disease where incremental gains can translate into meaningful extensions of life. The competitive landscape for RRMM therapies is robust, with several novel agents and combinations vying for market share. This new regimen, with its demonstrated efficacy and manageable safety profile, positions itself as a strong contender. Payers will undoubtedly scrutinise the cost-effectiveness, but the unmet need in this specific patient cohort provides a compelling argument for its inclusion in treatment algorithms, particularly as the OS data mature.

For patients, this therapy offers renewed hope. The prospect of nearly a year of progression-free life, where previous options offered half that, is substantial. While the adverse event profile includes expected haematological toxicities, these are generally manageable within established clinical practice. The availability of another effective option means that patients and their physicians have more flexibility in tailoring treatment plans, potentially delaying the need for more intensive or experimental therapies. This adds another tool to the armamentarium against a relentless disease, allowing for more personalised and prolonged disease control.

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