

Early Intervention Versus Observation in High-Risk Smoldering Multiple Myeloma: Pooled Evidence from Randomized Trials and Real-World Cohorts

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INTRODUCTION

- High-risk smoldering multiple myeloma (SMM) carries substantial progression risk
- Optimal management remains debated.
- Multiple randomized trials and real-world cohorts now provide mature comparative efficacy and safety data.

OBJECTIVES

To compare efficacy and safety of early pharmacologic intervention versus observation in high-risk SMM.

DESIGN

- Evidence synthesis of PubMed-indexed studies (2020 to 2026) with dual-reviewer screening
- Pooled hazard ratios from a random-effects meta-analysis of 5 trials (844 patients)
- Supplementary data from a Cochrane review (7 trials, 1,096 participants)
- Flatiron Health real-world cohort.

Methodology

Phase 2 and 3 randomized clinical trials and a US real-world oncology database (Flatiron Health).

Adults with high-risk or intermediate-risk SMM defined by Mayo 2018 or IMWG 2020 criteria; trial follow-up 29 to 150 months.

INTERVENTIONS

Daratumumab, lenalidomide with or without dexamethasone, alkylating agents, and cytokine inhibitors, each compared with observation or placebo.

MAIN OUTCOMES MEASURES

Progression-free survival, time to symptomatic progression, overall survival, and serious adverse events.

CONCLUSIONS

- Early intervention significantly reduces progression and improves survival in high-risk SMM with daratumumab demonstrating the most durable benefit.
- The 3.5-fold increase in serious adverse events necessitates careful patient selection and shared decision-making.
- Treatment outside trials should remain individualized.

RESULTS

- Early intervention reduced progression or death by 60% (HR 0.40; 95% CI 0.29 to 0.55); restricting to observation-only controls deepened this (HR 0.34; 95% CI 0.21 to 0.56).
- Daratumumab monotherapy in CENTAURUS (n=123; 85.2 months follow-up) yielded median PFS not reached.
- In the phase 3 AQUILA trial (n=390), daratumumab SC versus active monitoring significantly reduced progression risk (HR 0.49; 95% CI 0.36 to 0.67), providing the strongest phase 3 confirmation of early intervention benefit.
- OS improved by 45% in two mature trials (HR 0.55; 95% CI 0.37 to 0.82).
- Lenalidomide-based regimens showed conflicting results with substantial heterogeneity.
- Early treatment carried a 3.5-fold higher rate of serious adverse events by pooled analysis (OR 3.53; 95% CI 1.14 to 10.91), requiring prominent weight in shared decision-making.
- The most common serious adverse events were infections (22%), neutropenia (24%), and thromboembolic events (8%); lenalidomide-based regimens also carried second primary malignancy risk.

KEYWORDS

smoldering multiple myeloma, early intervention, observation, daratumumab, lenalidomide, progression-free survival, overall survival, risk stratification

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