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MINI REVIEW

Advancements in the Treatment of High-Risk Smoldering Myeloma: News from ASH 2024

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Smoldering multiple myeloma (SMM) is a precursor to symptomatic multiple myeloma (MM), characterized by its asymptomatic yet progressive nature and significant risk of progression. The management of SMM has evolved considerably in recent years with the introduction of targeted therapies. While the traditional "watch and wait" strategy remains the standard approach for low-risk cases, early treatment for high-risk SMM has become increasingly favored, backed by clinical trials highlighting its ability to delay the progression to MM and reduce related complications.

The AQUILA trial, a phase III multicenter study, evaluated subcutaneous daratumumab as a monotherapy for high-risk SMM compared to active monitoring. With 390 participants, the trial demonstrated a significant reduction in the progression to MM or death, with a 51% risk reduction and favorable safety results.

By validating daratumumab monotherapy as an effective and safe early intervention for high-risk SMM, the AQUILA trial underscores a pivotal shift in disease management. These findings complement existing evidence from trials, such as QUIREDEX and E3A06, emphasizing the value of proactive treatment strategies. AQUILA also highlights the need for continued research into dynamic risk stratification, biomarker-driven approaches, and innovative therapies, paving the way for precision medicine in SMM care.

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Background

Smoldering multiple myeloma (SMM) is an asymptomatic plasma cell disorder with a significant risk of progression to MM.[1,2] It represents a transitional stage between monoclonal gammopathy of undetermined significance (MGUS) and symptomatic MM.[3,4] Historically, management has focused on observation until end-organ damage occurs, as defined by CRAB criteria (hypercalcemia, renal failure, anemia, bone lesions) or SLiM criteria (≥60% clonal bone marrow plasma cells, light chain ratio ≥100 or >1 focal bone lesion on magnetic resonance imaging [MRI]).[5,6] However, this "watch and wait" approach leaves high-risk patients vulnerable to disease progression and associated complications.[7] Patients with high-risk SMM have a greater than 50% likelihood of progressing to symptomatic MM within two years, which emphasizes the need for proactive treatment strategies.[4] Therefore, early intervention have emerged as an effective strategy for select subgroups of patients with SMM, with the goal to promote long-term disease control, delay progression to symptomatic MM and mitigate MM-associated morbidity and the risk of end-organ damage, such as fractures and renal failure.[8] Furthermore, it was hypothesized that intense treatment during the precursor stage may have the potential to eliminate the malignant clone, achieving prolonged remission or possibly even a cure.

SMM is a heterogeneous disease with varying progression rates and prognostic outcomes.[2] Accurate risk estimation is essential for guiding clinical surveillance and correctly identifying patients who will benefit from early intervention. The development of risk stratification models for SMM is based on the identification of key biomarkers that predict progression to symptomatic MM. The most widely used risk assessment tools, such as the Mayo Clinic 2018[1] and International Myeloma Working Group (IMWG)[9] risk stratification models, incorporate clinical and laboratory parameters to classify patients into low-, intermediate- and high-risk categories. These risk factors include serum M-protein concentration >2 g/dL, serum involved to uninvolved free light-chain ratio (FLCr) >20 and marrow plasma cell infiltration >20% as independent predictors of progression, along with the presence of cytogenetic abnormalities, such as t(4;14), t(14;16) +1q and/or del13q.[1,9] More recently, genomic profiling and next-generation sequencing (NGS) have provided additional insights into the mutational landscape of SMM, enabling the identification of high-risk molecular subtypes.[10]

Advances in risk stratification and treatment have shifted the focus to early therapeutic intervention in high-risk SMM.[2] Immunomodulatory drugs such as lenalidomide have demonstrated clear benefits, including improved progression-free survival (PFS) through early treatment.[11] However, toxicity concerns and the need for well-balanced strategies to align treatment intensity with patient benefit remain challenges. Monoclonal antibodies (mAbs) have emerged as promising options for SMM management due to their targeted

mechanisms of action and favorable safety profiles.[2,12] Daratumumab, an anti-CD38 antibody, represents a key advancement, with demonstrated efficacy in delaying MM progression while maintaining tolerability.[2,12]

The AQUILA phase III trial builds on the latest evidence, investigating the efficacy of subcutaneous daratumumab as a monotherapy for high-risk SMM.[5] Results demonstrated that daratumumab significantly delays progression to MM while maintaining a manageable safety profile. Its subcutaneous administration fosters better patient adherence and convenience, further supporting its use as a first-line therapy for high-risk SMM.[5] Presented with more than five years of follow-up, the primary analysis of AQUILA results, shared at the 66th ASH Annual Meeting in 2024 by Prof. Dr Meletios-Athanasios Dimopoulos,[13] signals a paradigm shift from the traditional "watch and wait" strategy to proactive management in the high-risk SMM population.

This review highlights how evolving treatment strategies, including the AQUILA trial and other pivotal studies, reinforce the role of early intervention and signal the growing adoption of precision medicine, setting a foundation for improved outcomes in SMM care.

Evolving treatment strategies in SMM

The management of SMM has undergone significant evolution in recent years with the advent of targeted therapies. While low-risk cases typically follow an observation-based approach, early intervention for high-risk SMM has gained traction, supported by clinical trials demonstrating the potential benefits of delaying MM progression and associated complications.[2]

Immunomodulatory drugs such as lenalidomide have played a key role in the early treatment of SMM. The landmark phase III QUIREDEX trial (ClinicalTrials.gov identifier: NCT00480363) demonstrated that lenalidomide combined with dexamethasone (Rd) significantly prolonged PFS in high-risk SMM compared to observation.[11] After a median follow-up of 75 months, the median time to progression (TTP) was not reached in the treatment arm, compared to 23 months with observation. Importantly, this trial showed that early therapeutic intervention could lower the risk of transformation to MM, although toxicity and patient adherence remain a concern. With a median follow-up of 12.5 years, the median TTP to MM was 9.5 years in the Rd group, compared to just 2.1 years with observation.[14] Additionally, 58% of patients in the Rd group were alive at the data cut-off, compared to 40% in the active monitoring group, highlighting a survival benefit for early intervention. However, concerns about treatment-related toxicity and patient adherence remain, emphasizing the need to balance the benefits of delaying progression with potential side effects.[11,14]

Similarly, the ECOG-ACRIN E3A06 phase III trial (ClinicalTrials.gov identifier: NCT01169337) examined lenalidomide monotherapy in SMM, reporting a significant improvement in 3-year PFS (91% in the treatment group vs 66% in the observation group).[15] High-risk patients saw the greatest benefit, with a hazard ratio (HR) for progression reduced by 91% (HR: 0.09). Despite these promising results, the trial did not demonstrate a statistically significant PFS improvement in low- to intermediate-risk patients.[16] Adverse events, including grade 3–4 toxicities, led to a 40% treatment discontinuation rate, prompting recommendations to limit lenalidomide treatment to two years.[2,8] The lack of mature overall survival (OS) data and concerns about long-term toxicity remain barriers to broad implementation of this therapy.[2, 15,16]

Monoclonal antibodies (mAbs), such as daratumumab, have emerged as promising alternatives or adjuncts to immunomodulatory drugs in SMM treatment.[2] Daratumumab, a fully human anti-CD38 IgG1κ mAb, targets plasma cells through direct apoptosis induction, immune-mediated cytotoxicity, and modulation of the bone marrow microenvironment.[17] Its subcutaneous formulation minimizes side effects, reduces treatment burden, and enhances patient convenience. The CENTAURUS phase II trial (ClinicalTrials.gov identifier: NCT02316106) evaluated daratumumab monotherapy in intermediate- and high-risk SMM patients across different dosing strategies (intense, intermediate, and short).[12] The intermediate-dosing group, most aligned with the phase III AQUILA trial protocol,[5, 13] demonstrated an overall response rate of 58.5% and a 7-year OS rate of 81.3%.[12] Median PFS exceeded 24 months across all dosing groups, with 24-month PFS rates ranging from 75.3% to 89.9%. Notably, no new safety concerns emerged after the extended follow-up, supporting its use in this generally asymptomatic population. These findings, combined with the pharmacokinetic efficacy and manageable safety profile of daratumumab, have established its potential as a first-line therapy for high-risk patients with SMM. These results also set the foundation for the phase III AQUILA trial (ClinicalTrials.gov identifier: NCT03301220), which further explores daratumumab as a standalone early intervention for this population.[5,13]

The AQUILA trial

The AQUILA trial is an ongoing, phase III, open-label, multicenter study that recruited 390 patients with high-risk SMM to assess the safety and effectiveness of subcutaneous daratumumab in comparison to active surveillance.[5,13] High-risk status was defined based on the International Myeloma Working Group (IMWG) criteria,[18] requiring at least 10% clonal bone marrow plasma cells (BMPCs) with one or more of the following additional factors: serum M-protein levels of 30 g/L or higher, a diagnosis of IgA SMM, immunoparesis with reduced levels of two uninvolved immunoglobulin isotypes, FLCr between 8 and 100 and/or clonal BMPCs

of 50–60%.[5,13] The primary endpoint of the study was PFS evaluated by an independent review committee (IRC) in line with the IMWG diagnostic criteria.[18]

Participants were randomized 1:1 to daratumumab monotherapy (1,800 mg) or active monitoring.[5,13] Disease progression was assessed using predefined IMWG criteria to ensure uniformity.[18] Imaging modalities like MRI and positron emission tomography-computed tomography (PET-CT) were included at baseline.[5,13]

A crucial aspect of the study design was its recognition of evolving definitions of high-risk SMM. Although the trial predates the Mayo 2018 risk model, it retrospectively classified 40.5% of participants under this system, ensuring relevance to modern clinical standards.[1]

Daratumumab delays MM progression, even in high-risk SMM populations

The baseline characteristics of the two treatment groups were generally comparable and reflected a typical high-risk SMM cohort.[5,13] The median age was 64 years, with 54.6% of participants in the daratumumab group and 50.0% in the active monitoring group aged 18 to under 65 years. The median time from SMM diagnosis to randomization was 0.80 years in the daratumumab group and 0.67 years in the active monitoring group. According to the Mayo 2018 criteria, 37.1% of patients in the daratumumab group and 43.9% in the active monitoring group were classified as having high-risk disease.

Key efficacy findings from AQUILA, at a median 65.2-month follow-up, demonstrated a significant benefit of daratumumab in delaying disease progression.[13] Overall, the intervention reduced the risk of MM progression or death by 51% compared to active monitoring (HR: 0.49 [95% CI: 0.36–0.67]; p<0.0001) (**Figure 1**). PFS outcomes confirmed the effectiveness of daratumumab in this cohort. The 5-year PFS rates were substantially higher for daratumumab-treated patients (63.1%) compared to those in the active monitoring group (40.8%). Notably, the median PFS was not reached in the daratumumab arm, while it was just 41.5 months in the active monitoring group. These outcomes align with earlier findings from the CENTAURUS trial,[12] which also highlighted the ability of daratumumab to delay MM progression in intermediate- and high-risk SMM populations. Subgroup analyses also supported consistent benefits of daratumumab, especially among patients with high-risk disease based on Mayo 2018 criteria (median PFS, not reached vs 22.1 months; HR: 0.36), showcasing daratumumab's efficacy regardless of risk stratification.[13]

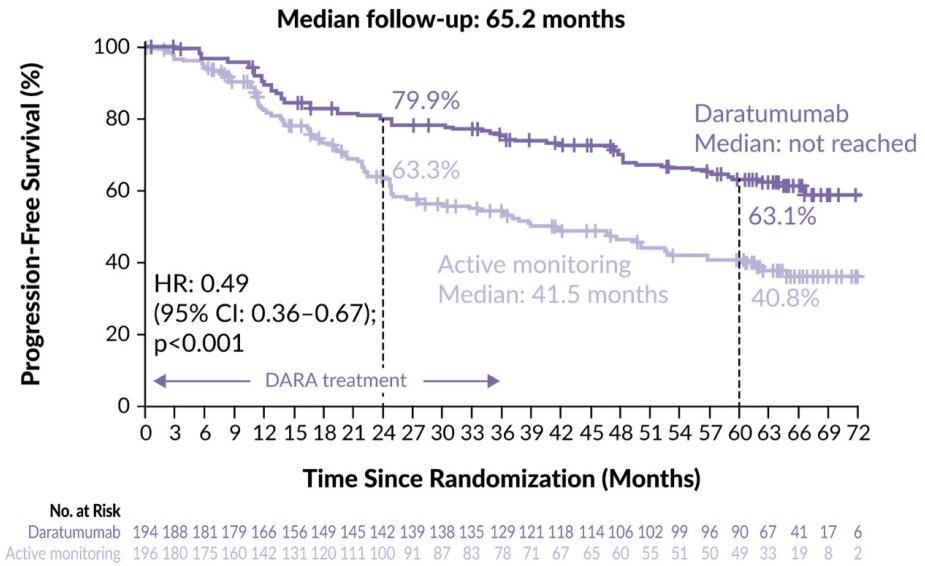

Figure 1. Progression-free survival in the AQUILA trial.

DARA, daratumumab. Adapted from Dimopoulos et al. 2024.[13]

Benefits of early intervention in high-risk SMM

Importantly, the time to first MM therapy, a secondary endpoint, was significantly prolonged in the daratumumab treatment group versus the active monitoring group (not reached vs 50.2 months; HR: 0.46 [95% CI: 0.33–0.62]).[5] Fewer daratumumab-treated patients required transition to first-line MM treatment (33.2% vs 53.6% for active monitoring), further underscoring its role in mitigating disease progression. Although the OS differences were less striking, they still indicated a favorable trend. The 5-year OS rate in the daratumumab group was 93.0%, compared to 86.9% in the active monitoring group (HR: 0.52 [95% CI: 0.27–0.98]). These results build on prior evidence from the QUIREDEX[11] and E3A06[15] trials, highlighting the benefits of early intervention in high-risk patients.

Balancing effectiveness with a manageable safety profile

An essential strength of AQUILA lies in its ability to demonstrate safety alongside efficacy.[5] Subcutaneous daratumumab monotherapy exhibited a manageable safety profile with low discontinuation rates in the daratumumab group (5.7%) due to adverse events (AEs). Grade 3–4 AEs were reported in 40.4% of the daratumumab group, which was slightly higher than that in the active monitoring group (30.1%) but within acceptable limits for oncology therapeutics. Hypertension was the most frequent grade 3–4 AE (5.7% for daratumumab, 4.6% for active monitoring). Serious AEs (SAEs), reported in 29.0% versus 19.4% in the daratumumab and active monitoring groups, respectively, were manageable, with pneumonia being the most common SAE

(3.6% for daratumumab, 0.5% for active monitoring). Notably, infection-related AEs were transient and treatable in the majority of cases. The rate of grade 3–4 infections was 16.1% in the daratumumab group. Fatal treatment-emergent AEs (TEAEs) were rare and balanced between the groups (1.0% with daratumumab vs 2.0% with active monitoring). These safety findings from AQUILA support daratumumab's established tolerability as observed in previous trials like CENTAURUS[12] and further position subcutaneous administration as a feasible alternative to intravenous therapies.[5]

Broader clinical implications

The question of whether high-risk SMM should be treated remains a subject of debate, with multiple studies investigating early interventions using different therapeutic agents. While earlier studies failed to demonstrate a clear benefit, the QUIREDEX trial showed that treatment with lenalidomide and dexamethasone significantly prolonged the median TTP compared to observation.[11] Similarly, the E3A06 trial reported improved PFS with lenalidomide monotherapy versus observation; however, it failed to demonstrate an improvement in OS.[15] Given the absence of data on OS benefits from both trials, as well as methodological inconsistencies across different published studies, particularly regarding the classification of progression events, definitive evidence supporting early treatment in SMM is lacking. Furthermore, uncertainty remains regarding the optimal treatment regimen for early intervention and whether initiating MM-effective therapies in SMM provides a greater advantage than reserving treatment for disease progression.

The AQUILA trial's findings underscore a significant paradigm shift in managing high-risk SMM.[5] By demonstrating that daratumumab can effectively delay disease progression without major safety concerns, the trial challenges established reliance on a "watch and wait" strategy for this patient population. For clinicians, this marks a transition to proactive management, potentially preventing endpoints, such as organ damage or advanced-stage myeloma. It is also worth noting how AQUILA paves the way for the broader adoption of daratumumab. Unlike earlier trials using combination regimens like lenalidomide plus dexamethasone (as in QUIREDEX),[11] AQUILA validated the efficacy of a monotherapy approach.[5] This simplicity reduces treatment burden and appeals to both patients and healthcare systems.[5]

Despite the trial's success, AQUILA raises important questions for further research. One limitation is its reliance on high-risk definitions predating the Mayo 2018 guidelines — a challenge compounded by the lack of longitudinal risk assessment data.[5] Future studies should explore refined biomarkers and dynamic risk models to further enhance patient stratification.

Combination therapies and future research opportunities

Combination regimens incorporating proteasome inhibitors, immunomodulatory drugs, and antibodies are being explored to achieve deeper responses. For instance, the phase II GEM-CESAR (ClinicalTrials.gov identifier: NCT02415413)[19] and ASCENT (ClinicalTrials.gov identifier: NCT03289299)[20] trials are exploring intensive quadruplet therapies aimed at minimal residual disease (MRD)-negative status, a potential new benchmark in SMM management. GEM-CESAR,[19] which evaluated carfilzomib, lenalidomide, and dexamethasone (KRd) alongside autologous stem cell transplantation (ASCT), reported MRD-negative status in over 50% of patients post-consolidation.[5] This raises the possibility of curative therapy for some high-risk SMM cases, albeit with significant treatment intensity and associated risk.[5] Another ongoing phase II trial, ASCENT, builds upon the findings of AQUILA by integrating anti-CD38 mAbs like daratumumab into existing KRd regimens.[20] Early data suggest improved depth of response, although long-term follow-up will determine whether these interventions translate into superior survival outcomes.[20] Similarly, the phase III DETER-SMM trial (ClinicalTrials.gov identifier: NCT03937635) builds on the QUIREDEX and E3A06 trials by comparing triplet therapy using daratumumab, lenalidomide, and dexamethasone (DRd) with Rd alone, aiming to establish whether adding mAbs enhances improves survival and delays disease progression.[21]

Conclusion

The classification of high-risk SMM has evolved significantly, bringing this disease entity into closer alignment with multiple myeloma. Consequently, the therapeutic approach appears to be transitioning toward more aggressive management strategies, as shown in recent studies.[5,11,19]

The AQUILA trial represents a major milestone in managing high-risk SMM, challenging the passive "watch and wait" approach with evidence for early intervention. This highlights daratumumab monotherapy as a safe and effective treatment, significantly delaying progression to symptomatic MM. Its simplified subcutaneous formulation offers a manageable safety profile, reduces treatment burden, and enhances patient convenience, prioritizing quality of life and accessibility for early intervention.

These findings, along with advances from trials such as QUIREDEX and E3A06, solidify the case for proactive management of high-risk SMM, although challenges persist. The absence of standardized risk definitions and limited racial diversity in clinical studies remains a barrier to their widespread application. AQUILA highlights the need for dynamic, biomarker-driven stratification models to better identify patients who will benefit most from early treatment while minimizing overtreatment risks.

Notably, when the AQUILA study was initiated, high-risk SMM was primarily defined based on traditional clinical markers. However, in recent years, cytogenetic abnormalities and more refined risk stratification models have become increasingly important in identifying patients at the highest risk of progression to symptomatic MM. These include high-risk chromosomal abnormalities such as t(4;14), t(14;16) and t(14;20) (IGH translocations), as well as 17p deletion and 1q amplification. As a result, the definition of high-risk SMM has become more precise which has enabled better identification of patients who are at increased risk of progressing to MM.

Future research will likely expand on AQUILA's foundation by exploring innovative combination regimens, deeper response benchmarks, such as MRD negativity, and precision-based approaches. These efforts aim to balance treatment effectiveness with patient quality of life, potentially shifting SMM care towards a more personalized and curative standard. AQUILA stands as both a milestone and call to action for next-generation strategies in SMM management.

Conflict of interest

The author has declared that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author has created and approved the final manuscript.

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