

REVIEW

Latest Advances in Treatment of Lymphoproliferative Disorders: Key Highlights from ASH 2024

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ABSTRACT

The 66th American Society of Hematology (ASH) Annual Meeting and Exposition was held on December 7–10, 2024, in San Diego, California. This review article provides highlights of the meeting, focusing on studies with significant clinical implications that have the potential to influence treatment paradigms and improve patient outcomes in lymphoproliferative disorders. These include the AMPLIFY trial investigating fixed-duration venetoclax plus acalabrutinib in treatment-naïve chronic lymphocytic leukemia; the TRIANGLE trial that evaluated ibrutinib-based therapies in mantle cell lymphoma (MCL); the ENRICH study that established ibrutinib plus rituximab as a superior frontline regimen for older MCL patients; the GHSB HD21 study, which validated positron emission tomography (PET)-guided BrECADD in older patients with advanced Hodgkin lymphoma; and the inMIND trial investigating the combination of tafasitamab with rituximab and lenalidomide in relapsed/refractory follicular lymphoma.

Keywords: mantle cell lymphoma, Hodgkin lymphoma, chronic lymphocytic leukemia, older patients, immunotherapy

AMPLIFY: FIXED-DURATION VENETOCLAX PLUS ACALABRUTINIB IN UNTREATED CLL

The AMPLIFY trial was one of the key highlights of the meeting.^{1–3} For the first time, a regimen combining fixed-duration venetoclax with the second-generation Bruton tyrosine kinase inhibitor (BTKi) acalabrutinib was investigated in previously untreated patients with chronic lymphocytic leukemia (CLL). Currently, treatment-naïve CLL patients have several treatment options, including continuous BTKi therapy or fixed-duration venetoclax regimens, both with or without anti-CD20 monoclonal antibody (mAb) obinutuzumab.⁴ While the combination of fixed-duration venetoclax with ibrutinib can achieve deep durable responses, it is associated with cardiac toxicity, particularly in older patients.^{5–9} Acalabrutinib is a highly selective BTKi characterized with improved safety profile compared with ibrutinib.^{10–12} AMPLIFY aimed to evaluate the efficacy and safety of fixed-duration venetoclax plus acalabrutinib with or without obinutuzumab versus the investigator's choice of chemoimmunotherapy in fit, treatment-naïve patients with CLL without del(17p) or a TP53 mutation.²

This study followed a three-arm design.² A total of 867 patients aged ≥18 years were randomized 1:1:1 to receive 14 cycles of acalabrutinib plus venetoclax (AV), 14 cycles of AV plus obinutuzumab (AVO) or six cycles of chemoimmunotherapy with fludarabine-cyclophosphamide-rituximab (FCR) or bendamustine-rituximab (BR), depending on the patient's age and comorbidities. Patients with del(17p) or TP53 mutations, significant cardiovascular disease and a Cumulative Illness Rating Scale (CIRS)-Geriatric index >6 were excluded from the study. The primary endpoint was progression-free survival (PFS) of AV versus FCR/BR in the intent-to-treat (ITT) population. The secondary endpoints included PFS for AVO versus FCR/BR, undetectable measurable residual disease (uMRD) for AV and AVO versus FCR/BR and overall survival (OS) for AV and AVO versus FCR/BR.

The combination of acalabrutinib plus venetoclax met the primary endpoint, with significant PFS improvement compared with chemoimmunotherapy.² At a median follow-up of 40.8 months, the median PFS was not reached in the AV arm compared with 47.6 months with FCR/BR (HR: 0.65 [95% CI: 0.49–0.87]; $p=0.0038$) (**Figure 1**). Furthermore, PFS was not reached and improved in the AVO arm versus FCR/BR as well (HR: 0.42 [95% CI: 0.30–0.59]; $p<0.0001$). The 36-month PFS rates in the AV, AVO and FCR/BR arms were 76.5%, 83.1% and 66.5%, respectively.

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DOI:10.36000/HBT.OH.2024.22.172
ISSN: 2673-2092 (Print) and
2673-2106 (Online)

Peer reviewers:
Dr Veronika Ballova, Cantonal Hospital Baden, Baden, Switzerland
One anonymous peer reviewer

Schmidt A. Latest Advances in Treatment of Lymphoproliferative Disorders: Key Highlights from ASH 2024. *healthbook TIMES Onco Hema*. 2024;22(4):121–126.

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The secondary endpoint of OS was prolonged with the AV regimen versus FCR/BR (HR: 0.33 [95% CI: 0.18–0.56]; $p < 0.0001$), with 36-month OS rates of 94.1% versus 85.9%, respectively.² Adding obinutuzumab in the second arm also proved very effective; however, based on prior experience, patients treated with obinutuzumab during the COVID-19 pandemic generally had worse outcomes. This was also reflected in the AMPLIFY trial, where the majority of COVID-19-related deaths occurred in the obinutuzumab-containing arm. When censored for COVID-19-related deaths, the secondary endpoint of OS was improved both with the doublet (HR: 0.27 [95% CI: 0.11–0.60]) and the triple regimen (HR: 0.47 [95% CI: 0.22–0.95]) versus chemoimmunotherapy.

The highest uMRD rates at the end of treatment (EoT) were observed in the AVO arm (95.0% vs 45.0% with AV and 72.9% with FCR/BR).² PFS was prolonged in patients who achieved uMRD at EoT in all three treatment arms, with PFS rates ranging from 74.8% with FCR/BR to 87.1% with AV and 90.4% with AVO.

With respect to safety, grade ≥ 3 adverse events (AEs) were reported in 53.6%, 69.4% and 60.6% of patients in the AV, AVO and FCR/BR arms, respectively.² The most common AEs in the experimental arms included hematological toxicity and infections. Slightly higher rates of cardiac events were observed in both experimental arms (AV, 9.3%; AVO, 12%; FCR/BR, 3.5%), as well as more frequent hemorrhages. However, grade ≥ 3 AEs were manageable and did not raise significant concerns. The overall incidence of atrial fibrillation was low.

In conclusion, this study demonstrated good efficacy and manageable safety profile with AV versus FCR/BR, with similar outcomes for AVO versus FCR/BR.² A key advantage of the AV regimen is its fixed-duration therapy, which is advantageous for

patients and combines the two most effective drugs for this disease entity. While some patients may prefer monotherapy based on individual needs, this combination sets a new standard of care (SoC) and is a practice-changing approach for treatment-naïve CLL. Patients with unmutated IGHV-status may profit most from the addition of obinutuzumab to AV (AVO), but higher vulnerability against COVID-19-infection and grade 3 infections in general should be taken into account.

TRIANGLE: Ibrutinib with and without ASCT in MCL

The randomized TRIANGLE trial previously demonstrated high efficacy of adding ibrutinib during induction chemoimmunotherapy and as a maintenance therapy with and without autologous stem cell transplantation (ASCT) in younger patients with mantle cell lymphoma (MCL).^{13,14} The latest data presented at ASH 2024 provided further insights into the efficacy comparison of the ibrutinib-containing regimens with and without ASCT with prolonged follow-up of 55 months.^{15,16}

The study enrolled patients aged ≤ 65 years with previously untreated, advanced-stage (II–IV) MCL eligible for high-dose cytarabine and ASCT.^{15,16} Patients ($n=870$) were randomized 1:1:1 into three arms, all receiving six alternating cycles of chemoimmunotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) and rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP). In Arm A (control, $n=288$), chemoimmunotherapy was followed by ASCT. In the experimental arms, ibrutinib was added to chemoimmunotherapy followed by two years of ibrutinib maintenance with (Arm A+I, $n=292$) or without ASCT (Arm I, $n=290$). Rituximab maintenance was added following national guidelines. The primary endpoint was failure-free survival (FFS). The secondary outcomes included response rates, PFS, OS and safety.

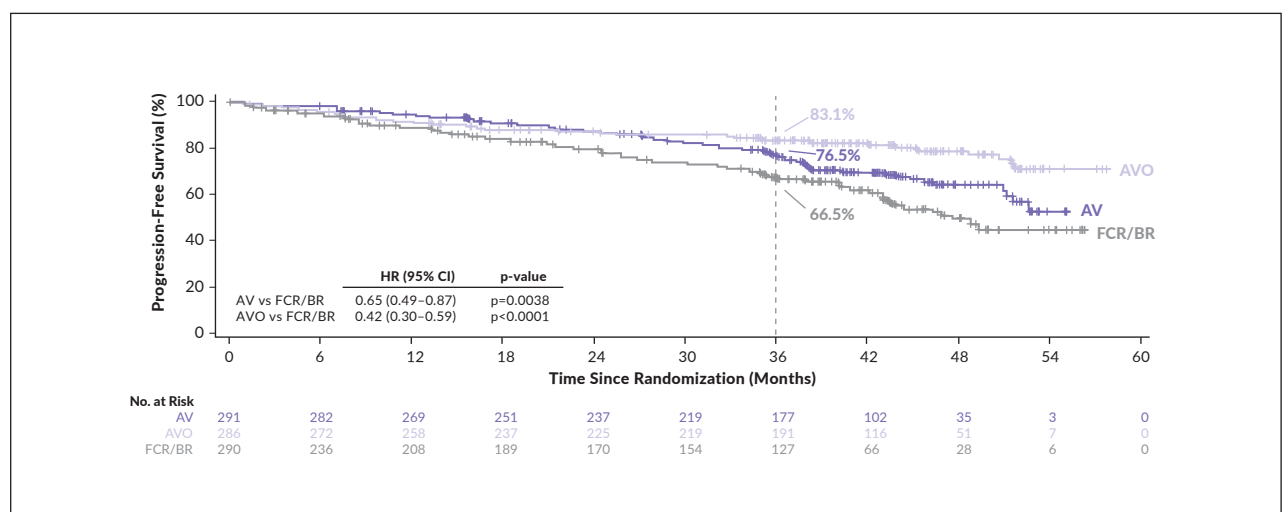


Figure 1. Progression-free survival (PFS) in the AMPLIFY study. AV, acalabrutinib plus venetoclax; AVO, acalabrutinib plus venetoclax and obinutuzumab; BR, bendamustine plus rituximab; FCR, fludarabine plus cyclophosphamide and rituximab. Adapted from Brown et al. 2024.^{1,2}

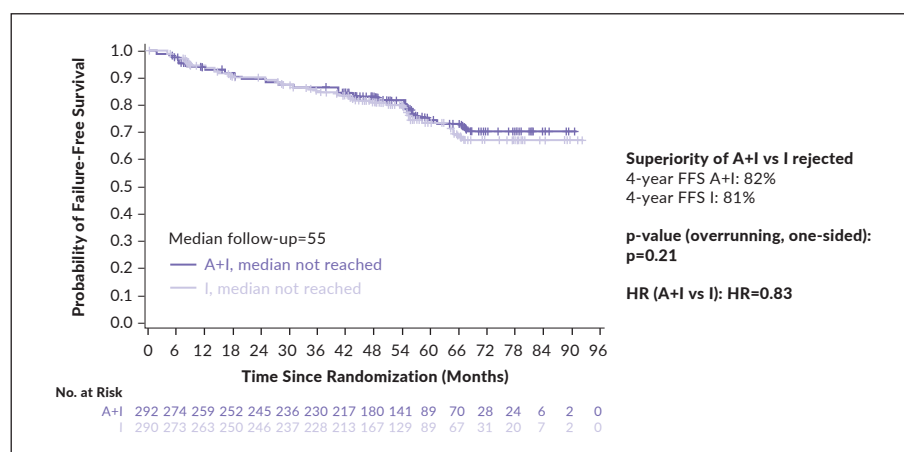


Figure 2. Failure-free survival in patients receiving ibrutinib plus chemoimmunotherapy with (A+I) or without (I) autologous stem cell transplantation (ASCT). Adapted from Dreyling et al. 2024.¹⁵

The study demonstrated the ongoing superiority of the ibrutinib-containing regimen plus ASCT versus control (HR for A+I vs A: 0.64; $p=0.0026$), with the median FFS not reached in either arm and 4-year FFS rates of 82% versus 70%, respectively.^{15,16} The control regimen was not superior to ibrutinib-containing regimen without ASCT (HR for A vs I: 1.29; $p=0.9890$). In contrast, the retrospectively calculated two-sided p -value demonstrated FFS superiority of I over A ($p=0.0208$). When comparing the efficacy of the two ibrutinib-containing regimens, the addition of ASCT failed to show FFS superiority (HR for A+I vs I: 0.83; $p=0.21$; 4-year FFS rates: 82% vs 81%) (Figure 2).

There was a trend towards improved FFS in the A+I arm versus the I arm in high-risk patient groups; however, the toxicity profile was more favorable with ibrutinib without ASCT.^{15,16} OS was prolonged with both ibrutinib-containing regimens, with 4-year OS rates of 81%, 88% and 90% in Arms A, A+I and I, respectively (A vs I, HR: 0.565; $p=0.0019$; A vs A+I, HR: 0.587; $p=0.0036$).

These data indicate that high-dose chemotherapy can be avoided in younger MCL patients, with induction and maintenance ibrutinib (and maintenance rituximab) without ASCT as the preferred first-line option.

ENRICH: Rituximab plus ibrutinib in MCL

The median age at MCL diagnosis is 71 years,¹⁷ and aggressive treatment approaches are generally unsuitable for most patients.¹⁸⁻²⁰ The current first-line SoC for older MCL patients includes R-CHOP²¹ or BR.²² Rituximab maintenance following R-CHOP improves both PFS and OS, and real-world data suggest a similar benefit after BR.^{21,22} In the second line, BTKis such as ibrutinib are the SoC.²³ The addition of ibrutinib to first-line BR has been shown to improve PFS compared with BR alone.²⁴

ENRICH is the first phase II/III study that compared rituximab plus ibrutinib versus rituximab plus the investigator's choice of chemotherapy (either R-CHOP or BR).^{25,26} Eligible patients were aged ≥ 60 years with previously untreated stage II-IV MCL in need of treatment and not fit enough for high dose chemotherapy. A total of 397 patients were randomized to receive either ibrutinib

plus rituximab (IR, $n=199$) or chemotherapy plus rituximab (R-chemo, $n=198$). Maintenance rituximab was administered in both arms for two years, while patients in the ibrutinib arm continued ibrutinib later on as monotherapy until disease progression or unacceptable toxicity. The primary outcome was PFS.

Overall, rituximab plus ibrutinib demonstrated superior outcomes.^{25,26} At a median follow-up of 47.9 months, the median PFS was 65.3 months with IR compared with 42.4 months with R-chemo (HR: 0.69 [95% CI: 0.52–0.90]; $p=0.003$) (Figure 3A). Subgroup analyses further highlighted the advantage of IR particularly over R-CHOP (HR: 0.37 [95% CI: 0.22–0.62]), with 5-year PFS rates of 52.4% versus 19.2%, respectively (Figure 3B). The difference was less pronounced when IR was compared with BR (HR: 0.91 [95% CI: 0.66–1.25]; 5-year PFS rates, 50.8% vs 47.4%). PFS was numerically longer with IR in patients with *TP53* mutations, and a particular benefit of IR was observed in patients with a Ki67 index of $<30\%$. However, PFS tended to be inferior in the IR arm in patients with blastoid disease (consider small number of $n=25$). A trend toward improved OS was observed with IR compared with chemo (HR: 0.87 [95% CI: 0.64–1.18]), with 5-year OS rates of 57.7% versus 54.5%.

The rates of grade ≥ 3 AEs were similar across the treatment arms, occurring in 63.1%, 67.8% and 69.2% of patients receiving IR, BR and R-CHOP, respectively.^{25,26} However, grade ≥ 3 cardiac events were more frequent with IR (22.2%) compared with BR (4.9%) and R-CHOP (13.5%). Grade ≥ 3 atrial fibrillation was reported in 6.1%, 0.7% and 0% of patients, respectively. Patients treated with IR had a significantly lower incidence of neutropenia (9.1%) than those treated with BR (18.9%) or R-CHOP (21.2%). Additionally, the quality of life (QoL) improved more rapidly in the IR arm.

In summary, ENRICH demonstrated improved PFS for ibrutinib plus rituximab versus chemoimmunotherapy plus rituximab in previously untreated MCL.^{25,26} This trial is highly relevant for treatment-naïve older patients who may benefit from avoiding chemotherapy.

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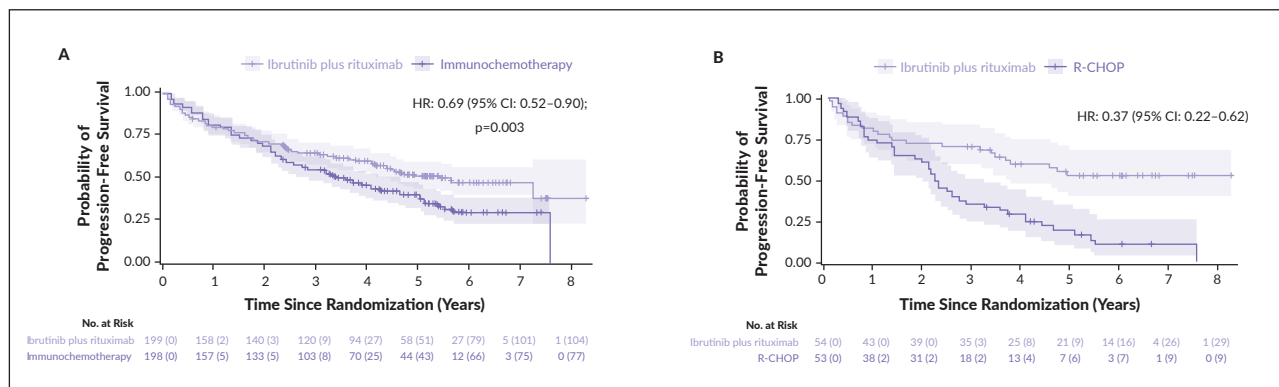


Figure 3. ENRICH: Ibrutinib plus rituximab improves progression-free survival (PFS) versus rituximab plus the investigator's choice of chemotherapy (A) or cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) (B). Adapted from Lewis et al. 2024.²⁵

GHSG HD21: PET-guided BrECADD in older patients with advanced HL

Older patients with advanced-stage classic Hodgkin lymphoma (HL) face a significant unmet need for effective therapy, as they have poorer outcomes and limited treatment options. Escalated-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (eBEACOPP) regimen is not feasible in this population due to high treatment-related mortality (~15%). Alternative regimens, such as brentuximab vedotin with doxorubicin, vinblastine and dacarbazine (A-AVD) or doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD), show suboptimal efficacy, with 5-year PFS rates of 67% and 62%, respectively.²⁷

The German Hodgkin Study Group (GHSG) HD21 trial had previously demonstrated high efficacy of positron emission tomography-computed tomography (PET-CT)-guided therapy with brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone (BrECADD) in HL patients.²⁸ At ASH 2024, results from a prospective, international, multicenter, single-arm add-on cohort of HD21 focusing on older patients with advanced HL were presented.^{29,30}

A total of 84 patients (median age 66.5 years, range 61–75 years) was included (ITT population). According to study design, they received two cycles of BrECADD followed by interim PET-CT restaging (PET2).^{29,30} Patients with PET2-negative disease received a total of four BrECADD cycles, whereas those with PET2-positive residuals completed six cycles. Consolidation radiotherapy was recommended for PET-positive residuals at EoT. The primary endpoint was the complete response (CR) rate at EoT. The secondary endpoints included AEs, treatment-related morbidity (TRMB), feasibility, PFS, OS and safety.

The study results were promising, with 60% of patients achieving CR after four cycles of therapy based on interim PET-CT, while 22% required six cycles, thus 82% reaching CR at EoT.^{29,30} As there were eight patients without centrally evaluated response assessment at EoT, the CR rate in the remaining 76

patients was even higher (87%). Overall, 85% of patients received the scheduled number of cycles – supported by pre-defined, per-protocol dose reductions – with 12% undergoing consolidating radiotherapy completed treatment. These high response rates translated into unprecedented PFS outcomes, with a 24-month PFS rate of 91.5% in the ITT population at a median follow-up of 23 months (**Figure 4**). OS rates at 12 and 24 months were 96.2% and 90.7%, respectively. No treatment-related deaths occurred.

The most common high-grade toxicities were hematologic AEs including anemia (69%) and thrombocytopenia (86%).^{29,30} Neutropenic fever occurred in 55% of patients. No grade 5 toxicity was observed. Initially impaired health-related QoL improved during treatment and normalized during the follow-up. These data demonstrate that the BrECADD regimen is feasible for older patients with advanced-stage HL with appropriate dose reductions, addressing an unmet need and offering a new promising SoC in this population, together with the recently published findings from the SWOG S1826-trial assessing the nivolumab plus AVD regimen in this patient population.³¹

inMIND: Tafasitamab plus rituximab and lenalidomide in relapsed/refractory follicular lymphoma

Finally, important results were reported in the phase III inMIND trial in patients with relapsed and refractory follicular lymphoma (R/R FL).^{32,33} Previous studies, such as RELEVANCE, had already shown that rituximab plus lenalidomide is effective as a first-line therapy for FL,³⁴ while L-MIND demonstrated the efficacy of anti-CD19 mAb tafasitamab plus lenalidomide in R/R diffuse large B-cell lymphoma (DLBCL).³⁵ The inMIND study further investigated a combination of rituximab, lenalidomide and tafasitamab versus rituximab plus lenalidomide in patients with FL and marginal zone lymphoma (MZL). At ASH 2024, the primary planned primary analysis of the study was presented.^{32,33}

This phase III, double-blind, placebo-controlled, international, multicenter, randomized study enrolled patients (aged ≥18 years) with grade 1–3A FL or MZL who had received ≥1 prior

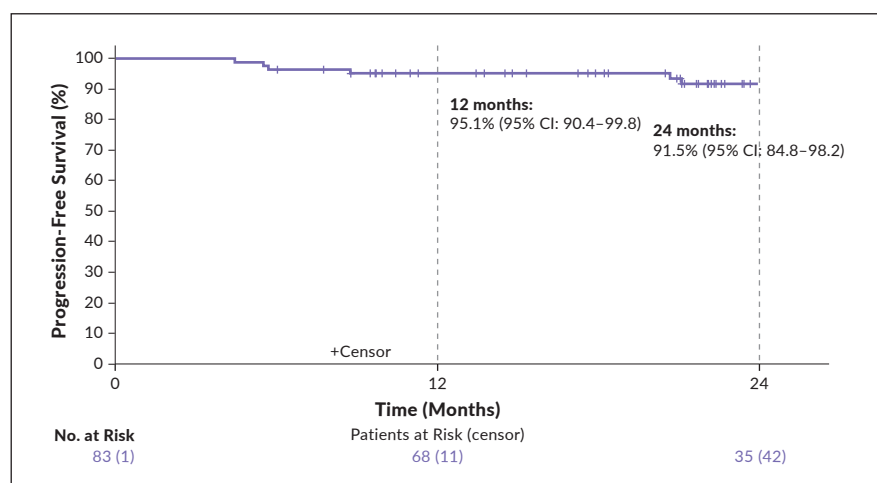


Figure 4. Progression-free survival in the GHSG HD21 trial. Adapted from Ferdinandus et al. 2024.²⁹

line of therapy, including anti-CD20 mAb.^{32,33} Patients (n=548) were randomized 1:1 to receive tafasitamab (12 mg/kg; n=273) or placebo (n=275) intravenously (on days 1, 8, 15 and 22 of 28-day cycles 1–3 and days 1 and 15 of cycles 4–12) in combination with the standard dosing of lenalidomide plus rituximab for up to 12 cycles. The primary endpoint was PFS in the FL population. Secondary endpoints included CR rate by PET in fluorodeoxyglucose (FDG)-avid population, OS, PFS, overall response rate (ORR), duration of response, safety, QoL and time to next treatment (TTNT).

The data revealed a clear benefit with respect to the primary endpoint of PFS with the triple therapy.^{32,33} At a median follow-up of 14.1 months, the median PFS was 22.4 months with tafasitamab plus lenalidomide and rituximab versus 13.9 months with placebo plus lenalidomide and rituximab (HR: 0.43 [95% CI: 0.32–0.58]; $p < 0.0001$) (**Figure 5**). Consistent benefits with tafasitamab were observed across all prespecified subgroups, including difficult-to-treat populations such as patients with POD24 or those refractory to prior anti-CD20 mAb.

Furthermore, tafasitamab significantly improved the PET-CR rate (49.4% vs 39.8%; odds ratio [OR]: 1.5 [95% CI: 1.04–2.13]; $p = 0.0286$) and ORR (83.5% vs 72.4%; OR: 2.0 [95% CI: 1.3–3.02]; $p = 0.0014$) versus placebo.^{32,33} TTNT was also significantly prolonged with tafasitamab compared with placebo, with a median not reached versus 28.8 months (HR: 0.45 [95% CI: 0.31–0.64]; $p < 0.0001$). The OS data were immature at the time of this analysis, with a trend favoring tafasitamab (HR: 0.59 [95% CI: 0.31–1.13]).

In summary, the first study to evaluate a combination of two mAbs targeting CD19 and CD20 in FL demonstrated a 57% reduction in the risk of progression, relapse or death with tafasitamab plus lenalidomide and rituximab, suggesting that the triple therapy combination could become a new SoC for this patient population.^{32,33}

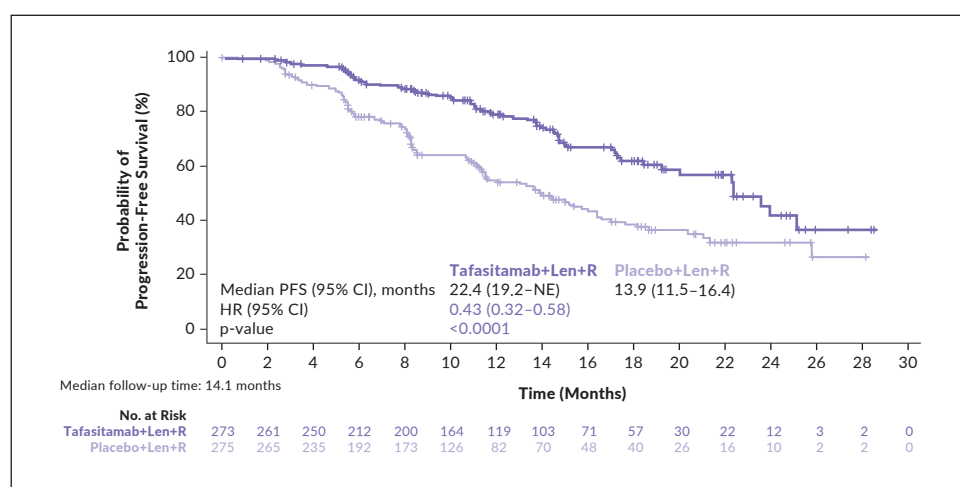


Figure 5. Progression-free survival (PFS) in the inMIND trial. Len, lenalidomide; NE, not evaluable; R, rituximab. Adapted from Sehn et al. 2024.³²

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CONCLUSIONS

At the 66th ASH Annual Meeting and Exposition, several studies with potentially practice-changing results for the treatment of leukemia and lymphoma were presented.

- Fixed-duration venetoclax plus acalabrutinib significantly improved PFS in treatment-naïve CLL.¹⁻³
- Ibrutinib-based therapy without ASCT is an effective first-line option for younger patients with MCL.^{15,16}

- Ibrutinib plus rituximab was established as a superior frontline regimen for older MCL patients compared to chemoimmunotherapy.^{25,26}
- PET-guided BrECADD was validated as a feasible and highly effective regimen for older patients with advanced HL.^{29,30}
- The addition of tafasitamab to rituximab and lenalidomide significantly improved PFS in R/R FL.^{32,33}

Disclosures

Conflict of interest

Adrian Schmidt received honoraria from Takeda, Janssen, Celgene, Sobi, Roche, Sanofi, Amgen, BeiGene, Novartis, Incyte, Eli Lilly and Bayer. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way.

Funding

The author has declared that no financial support was received from any organization for the submitted work.

Author contributions

The author has created and approved the final manuscript.

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MINI REVIEW

Advancements in the Treatment of High-Risk Smoldering Myeloma

Kaveh Samii^{1*}

ABSTRACT

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.

Keywords: smoldering myeloma, SMM, daratumumab, high-risk patients, AQUILA

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 ($\geq 60\%$ 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 20181 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

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10.36000/HBT.OH.2024.22.173

ISSN: 2673-2092 (Print) and
2673-2106 (Online)

Peer reviewers:

Dr Thomas Lehmann, Cantonal Hospital
St. Gallen, St. Gallen, Switzerland
One anonymous peer reviewer

Samii K. Advancements in the Treatment of
High-Risk Smoldering Myeloma.
healthbook TIMES Onco Hema. 2024;22(4):
127-132.

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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 IgG1k 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

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

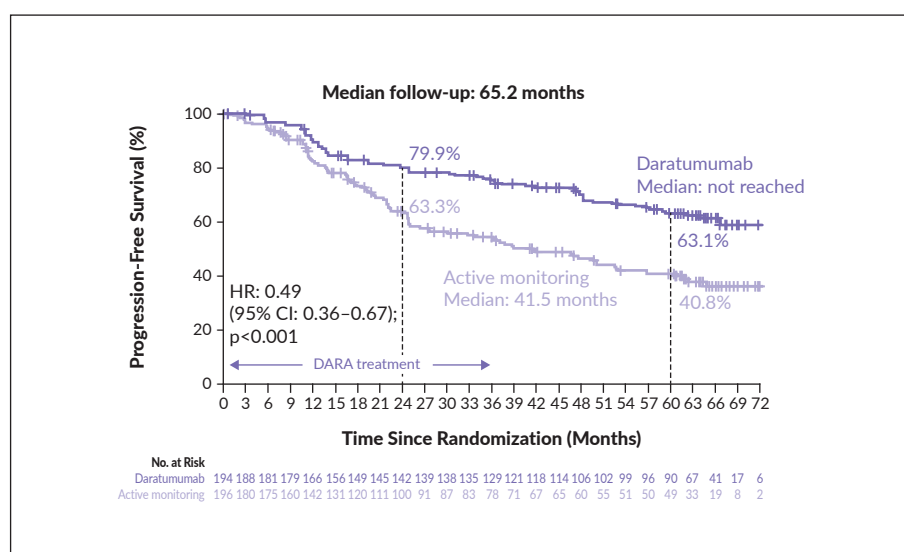


Figure 1. Progression-free survival in the AQUILA trial. DARA, daratumumab. Adapted from Dimopoulos et al. 2024.¹³

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the QUIREDEX¹¹ and E3A06¹⁵ 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 adverse events (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 CENTAURUS¹² 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.

Disclosures

Conflict of interest

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

Funding

The author has declared that no financial support was received from any organization for the submitted work.

Author contributions

The author has created and approved the final manuscript.

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