Ixazomib maintenance therapy in transplant-eligible multiple myeloma: real-world evidence from three large German centers

For transplant-eligible multiple myeloma (TEMM) patients, maintenance therapy following autologous stem cell transplantation (ASCT) represents a pivotal element of current treatment strategies, enhancing both progression-free survival (PFS) and overall survival (OS).[1] The oral immunomodulatory drug lenalidomide is approved by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) and is the most widely used maintenance therapy worldwide.[2] However, prolonged administration may be restricted by cumulative toxicities - such as myelosuppression, increased risks of thromboembolism and secondary malignancies, as well as worsening of pre-existing peripheral neuropathy - underscoring the need, at least in some patients, for highly effective and better-tolerated maintenance strategies.[3] An alternative maintenance approach is parenteral administration of the proteasome inhibitor bortezomib, either as monotherapy or in combination with dexamethasone, which has shown particular efficacy in high-risk multiple myeloma. The principal limitations of prolonged bortezomib maintenance are its dose-dependent risk of peripheral neuropathy and the logistical requirement for parenteral administration at a specialized myeloma center.[4]

In this setting, ixazomib - an oral, second-generation proteasome inhibitor - has emerged as a promising option, combining clinical efficacy with the convenience of oral dosing. Its toxicity profile differs notably from that of bortezomib, with a higher incidence of gastrointestinal adverse events (AE) but a substantially lower risk of peripheral neuropathy.[5] The TOURMALINE-MM3 trial demonstrated that ixazomib maintenance significantly prolonged PFS compared to placebo in patients achieving at least a partial response after ASCT.[6] However, ixazomib has not yet been approved for post-ASCT maintenance by either the European or US regulatory authorities. Due to the lack of approval, clinical experience with ixazomib in the maintenance setting in many myeloma centers is limited. While robust real-world evidence (RWE) supports the use of ixazomib in combination therapy, for example with lenalidomide and bortezomib in relapsed/refractory multiple myeloma (RRMM), there is limited evidence for its use as maintenance monotherapy after ASCT outside of clinical trials.[7,8] To address this gap, we present multicenter RWE on the effectiveness, safety, and clinical utility of ixazomib maintenance in a European TEMM patient cohort treated at three high-volume academic myeloma centers in Germany.

We retrospectively evaluated 44 patients (36 newly diagnosed; 8 relapsed/refractory) who received ixazomib maintenance after ASCT between May 2018 and June 2024 (Table 1). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Technical University of Munich ethics committee (code: 2025-307-S-CB). AE, including neuropathy, were abstracted from medical records and graded per Common Terminology Criteria for Adverse Events (CTCAE) as documented during routine care. The median follow-up time for the cohort was 26.2 months (range, 7-81 months). High-risk cytogenetics, defined according to International Myeloma Working Group (IMWG) 2024 criteria, were identified

Table 1. Key patient characteristics at beginning of ixazomib maintenance therapy.

Characteristics	N=44
Age, years	
Median (range)	63.9 (36.2-79.0)
<65, N (%)	23 (52.3)
≥65, N (%)	21(47.7)
Sex, N (%)	
Male	29 (65.9)
Female	15 (34.1)
ECOG PS, N (%)	
0	14 (31.8)
1	24 (54.5)
2	6 (13.6)
Diagnosis, N (%)	
NDMM	36 (81.8)
RRMM	8 (18.2)
Type of myeloma, N (%)	
IgG	22 (50.0)
IgA	6 (13.6)
Light chain only	16 (36.4)
R-ISS, N (%)	
I	11 (25.0)
II	24 (54.5)
III	6 (13.6)
NA	3 (6.8)
Cytogenetics, IMWG 2024, N (%)	
Standard risk	23 (52.3)
High risk	18 (40.9)
NA	3 (6.8)

ECOG PS: Eastern Cooperative Oncology Group performance status; NDMM: newly diagnosed multiple myeloma; RRMM: relapsed/refractory multiple myeloma; Ig: immunoglobulin; R-ISS: revised International Staging System; NA: not available; IMWG: International Myeloma Working Group.

in 40.9% of the cohort.[9] All patients received standard induction therapy and all but one underwent ASCT prior to ixazomib. The most used induction regimen was bortezomib, cyclophosphamide, and dexamethasone (VCd), administered to 56.8% of patients (*Online Supplementary Table S1*), while quadruplet combinations including CD38 antibodies like daratumumab were less frequent (20.5%). A significant proportion of patients switched from lenalidomide to ixazomib maintenance (38.6%).

Our initial analysis focused on the reasons for using ixazomib maintenance, acknowledging that it is not approved by the FDA or EMA. As shown in Figure 1A, the primary rationale was prior treatment toxicity from bortezomib and lenalidomide: peripheral neuropathy was the most frequent reason, affecting 34.1% of patients. Renal impairment and intolerance to lenalidomide played a key role in 27.3% and 20.5% of cases, respectively. Lenalidomide-induced cytopenias (11.4%) and thromboembolic complications (9.1%) also necessitated a change in maintenance strategy. Four patients (9.1%) were classified as lenalidomide-resistant because of insufficient response during induction treatment (4.5%) or during previous maintenance treatments for RRMM patients (4.5%).

Ixazomib maintenance therapy was generally well tolerated, demonstrating a manageable safety profile, particularly following dose reductions. The most frequently reported AE were thrombocytopenia (11.4%) and neutropenia (9.1%), while gastrointestinal side effects such as nausea and diarrhea occurred in 6.8% of patients (Figure 1B). Additional AE included hepatic transaminase elevations (4.5%), thromboembolic events (4.5%), allergic reactions (2.3%), and worsening peripheral neuropathy (2.3%). Severe AE (grade 3 or higher) were rare. Secondary hematologic malignancies were observed in three patients (6.8% of the cohort), comprising one case of acute myeloid leukemia (AML) and two of myelodysplastic syndrome (MDS). Of these patients, none had a del(17p) and two had prior lenalidomide exposure. All three patients exhibited hyperdiploidy involving trisomy/tetrasomy of chromosome 9 and/or 11.

Dose modifications during treatment were relatively frequent (*Online Supplementary Table S1*). Overall, 52.3% of patients received the standard 4 mg dose, whereas 43.2% received a reduced dose of 3 mg. The leading reasons for dose reductions were renal impairment (18.2%), thrombocytopenia (13.6%), and neutropenia (9.1%).

At the start of ixazomib maintenance therapy, 52.3% of patients were in complete remission (CR) and 34.1% in very good partial remission (VGPR) (*Online Supplementary Table S2*). Of note, 13.6% of patients experienced further deepening of response during ixazomib maintenance with improvements from partial remission (PR) or VGPR to CR (*Online Supplementary Figure S1A*). Overall, disease progression occurred in 15 patients (34.1%) during follow-up. This rate reflects a real-world cohort that included 18.2% pre-treated relapsed/refractory patients and 38.6% who switched from lenalidomide to ixazomib maintenance

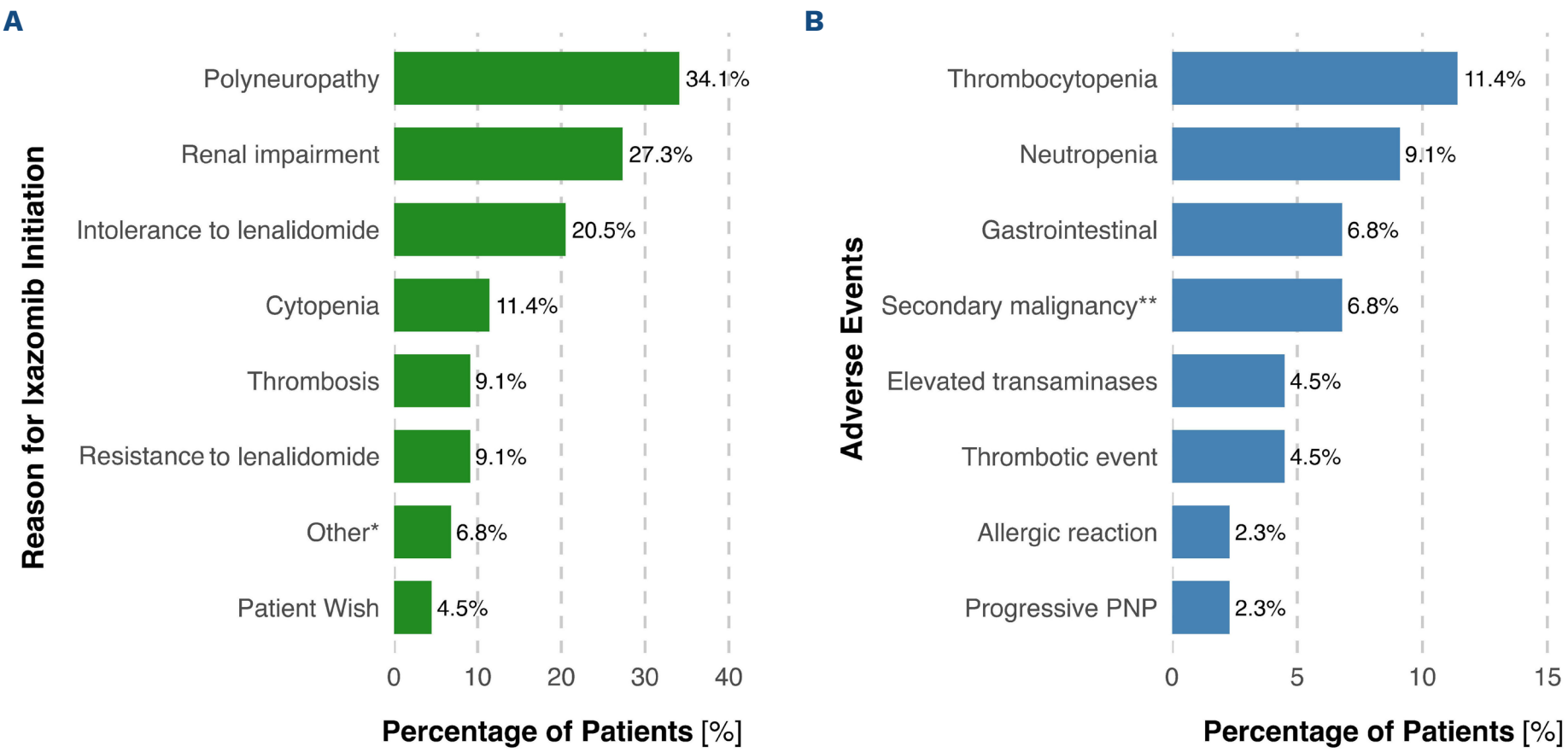

Figure 1. Reasons for ixazomib initiation and adverse event profile. (A) Primary reasons for initiating ixazomib maintenance therapy. (B) Frequency of common adverse events observed during ixazomib maintenance. Data represent the percentage of patients (N=44) in each category; multiple entries were allowed per patient. *One patient with psoriatic arthritis, 1 patient with cardiac involvement of amyloidosis, 1 not specified. **Without definite causal link to ixazomib (1 patient with acute myeloid leukemia and 2 patients with myelodysplastic syndrome).

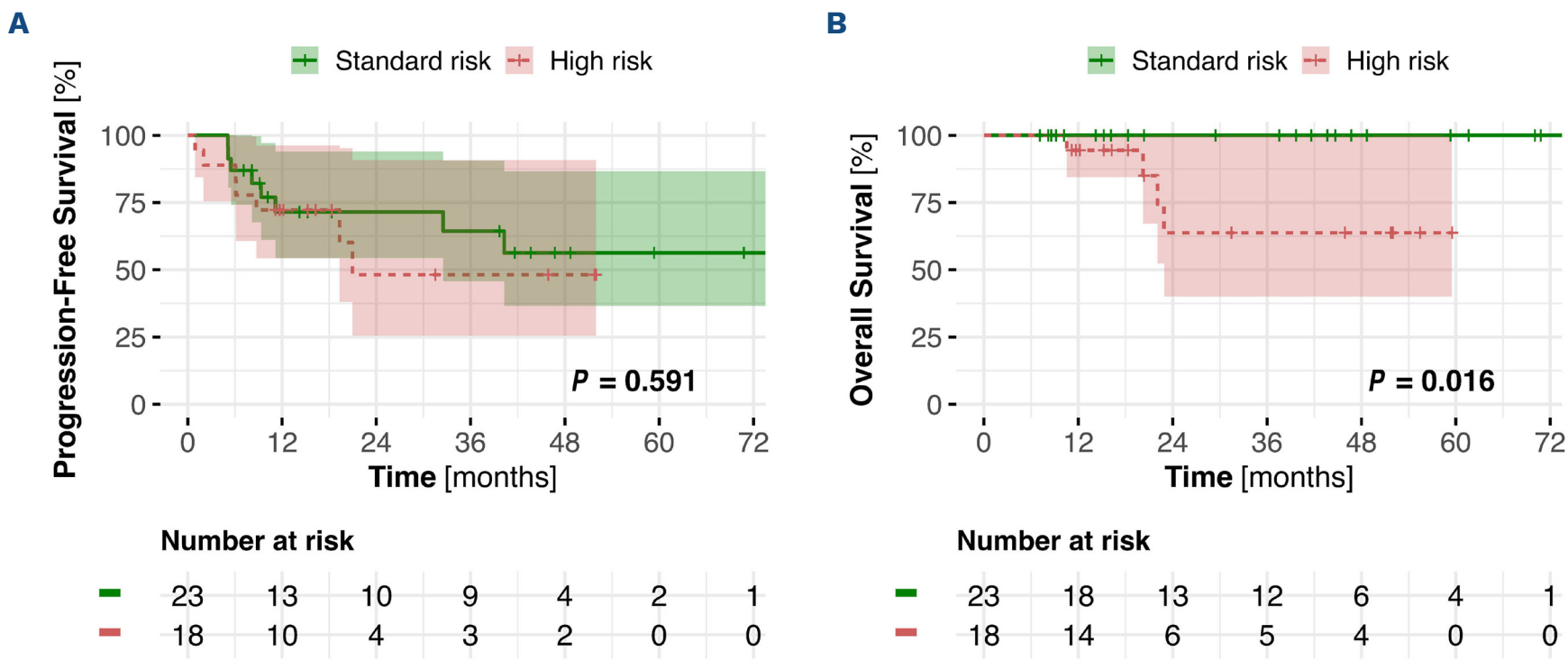

Figure 2. Kaplan-Meier estimates of survival outcomes. (A) Progression-free survival and (B) overall survival stratified by baseline risk status according to International Myeloma Working Group 2024 (standard risk, N=23; high risk, N=18). Three patients with unknown risk status are excluded. Shaded areas indicate 95% confidence intervals. Vertical ticks represent censored observations. *P* values comparing risk groups (log-rank test) are shown.

due to side effects. When considering newly diagnosed patients exclusively, the progression rate was markedly lower at 19.4%.

Median PFS and OS were not reached, indicating sustained disease control with ixazomib maintenance. The 2-year PFS rate was 64%, declining to 56% at 5 years, while OS remained stable at 86% at both time points. Subgroup analysis based on cytogenetic risk profiles according to 2024 criteria revealed no significant difference in PFS (Figure 2A) between high-risk and standard-risk patients (*P*=0.591). Nonetheless, we did observe a significant difference in OS, with poorer outcomes for the high-risk cohort (*P*=0.016; Figure 2B). A swimmer plot complements these survival analyses by visualizing individual patient treatment durations and PFS across risk groups (*Online Supplementary Figure S1B*).

In summary, this multicenter real-world study contributes to the growing body of evidence supporting ixazomib maintenance therapy as an effective and well-tolerated option for TEMM patients. Notably, it provides valuable RWE by including patients with renal impairment, prior bortezomib-induced peripheral neuropathy, and those intolerant to lenalidomide. These findings align with results from Shen *et al*., who also reported that ixazomib is particularly beneficial for patients transitioning from bortezomib-based regimens due to its oral administration and lower neurotoxicity.[10] Ixazomib demonstrated a favorable safety profile, characterized by manageable AE and a low incidence of severe toxicity with appropriate dose reductions, aligning with previous findings.[6] Thrombocytopenia and neutropenia were the most common toxicities, followed by gastrointestinal side effects. The low incidence of peripheral neuropathy (2.3%) further supports ixazomib's suitability for long-term maintenance, particularly for patients previously treated with neurotoxic agents like bortezomib.

Another key finding of our study is the comparable PFS between high-risk and standard-risk cytogenetic groups, suggesting that ixazomib may mitigate the negative impact of adverse genetic features. This result is consistent with recent findings by Xu *et al*., who observed no significant differences in outcomes between cytogenetic subgroups in a single-center study.[11] Moreover, Goldschmidt *et al*. highlighted that ixazomib maintenance led to deepened responses and extended PFS in both high-risk and standard-risk TEMM.[12]

Key limitations include the retrospective design, modest cohort size, and lack of a direct comparator. Future prospective studies, such as those incorporating patient-reported outcomes and health-economic analyses, are needed to validate these findings and further establish ixazomib's role in maintenance therapy. Emerging therapeutic alternatives like daratumumab-based maintenance and bispecific T-cell engagers reshape the treatment landscape.[13,14] The optimal niche of ixazomib is therefore likely in smaller patient subsets - those who are intolerant of lenalidomide, suffer from peripheral neuropathy, unable to receive doublet maintenance, and would most benefit from a convenient, all-oral, well-tolerated maintenance regimen.

In conclusion, our results support ixazomib as a feasible and effective maintenance option for TEMM patients, including those with high-risk cytogenetics or prior treatment-related toxicities. Its favorable safety profile and convenient oral administration make ixazomib a valuable addition to the spectrum of MM maintenance strategies.

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Contributions

RW, ST, ME, FB, and JJ designed the study. MR, MH, WS, and BS collected clinical data. AGM performed data visualization. PM and JJ performed data analysis and wrote the manuscript.

Data-sharing statement

The datasets generated during the current study are available from the corresponding author upon reasonable request.

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