haematologica
Journal of the Ferrata Storti Foundation

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Received: April 14, 2026.
Accepted: August 31, 2026.

Citation: Tamir Shragai, Noa Lavi, Iuliana Vaxman, Moshe E. Gatt, Evgeni Chubar, Chezi Ganzel, Hila Magen, Efrat Luttwak, Moshe Mittelman, Svetlana Trestman, Eyal Lebel, Revital Saban, Vladimir Vainstein, Tsila Zuckerman, Netanel Horowitz, Inna Tzoran, Nurit Horesh, Noa Lowenton-Spier, Natan Melamed, Ilana Pereg, Irit Avivi and Yael C. Cohen. Ixazomib, pomalidomide and dexamethasone in triple-class exposed multiple myeloma patients - a phase II study.
Haematologica. 2026 Sept 10. doi: 10.3324/haematol.2026.301067 [Epub ahead of print]

Ixazomib, pomalidomide and dexamethasone in triple-class exposed multiple myeloma patients - a phase II study

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Clinical trial registration:
Clinicaltrials.gov identifier: (NCT04790474).

Acknowledgments: The authors acknowledge Takeda pharmaceuticals for providing Ixazomib (Ninlaro®) and supporting this study through a research grant. The authors also wish to thank Irit Segalovich and Ella Krayzler from the Clinical trial units, Tel-Aviv sourasky medical center, for their support with coordination and monitoring.

Contribution: Y.C.C, N.L.S and T.S designed the study and wrote the protocol; T.S, Y.C.C, N.L, I.V, M.E.G, E.C, C.G, H.M, E.L, M.M, S.T, E.L. R.S, V.V, N.H, T.Z, I.T, N.H, and I.A enrolled the patients and conducted the study; T.S, Y.C.C and N.M analyzed the data; N.M performed the statistics; I.P monitored data at all sites; T.S, Y.C.C and N.M wrote the manuscript; I.A, I.V and N.L critically reviewed the manuscript; All authors read and approved the submitted version of the manuscript.

Conflict-of-interest disclosure:
T.S: Consulting & advisory role: GSK, Takeda; honoraria: J&J;
Y.C.C: Consulting & advisory role: J&J, Sanofi, BMS, Takeda, Pfizer, GSK; Speaker's Bureau: GSK, J&J; Research Funding: J&J, Takeda
All other co-authors declare no conflict of interest

Data-sharing statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Abstract:

Multi-class upfront regimens for multiple myeloma (MM) have improved outcomes, yet many patients become either triple-class exposed (TCE) or refractory (TCR) early in their disease course. This is a phase II, investigator initiated, open-label, single-arm, prospective, multicenter study evaluating all-oral Ixazomib-pomalidomide- dexamethasone (IPd) regimen for TCE RRMM patients. Sixty-one patients were enrolled between March 1st 2021 and March 17th 2024. The median age was 74 (range: 53-89) years; 25 (41%) were ≥75 years old. Fifty-seven percent had high-risk cytogenetics (t(4;14), t(14;16), +1q21, del17p). Twenty-six (43%) patients were frail. Refractoriness rates to bortezomib, lenalidomide and daratumumab were 51%, 85% and 96% respectively. Triple-class refractory (TCR) rate was 39%. Ninety-seven percent of the patients had ≥1 treatment emergent adverse event (TEAE) and 67% had a TEAE grade ≥3. The rate of Gr ≥3 AE was not increased in frail vs. non-frail patients (p=0.43). Overall response rate (ORR) was 58% (22% very good partial response or better). TCR patients had an ORR of 46% vs. 68% for non-TCR patients (p=0.12). The median progression-free survival was 8.1 (95% CI 3.9-12.3) months and the median overall survival was 30.4 (95% CI 21.5-39.4) months. To conclude, the all-oral IPd regimen for TCE RRMM patients showed high response rates and a manageable safety profile, in a cohort enriched with TCR, elderly and frail patients. (NCT04790474).

Introduction:

Progress in the treatment paradigm of multiple myeloma (MM) in recent years has resulted in marked improvements in patients' outcomes. The introduction of triplet and quadruplet regimens in the frontline setting resulted in improved progression-free survival (PFS) and higher minimal residual disease (MRD) negativity rates, both for transplant eligible(1–3) and transplant ineligible(4–7) patients. In recent years, due to incorporation of quadruplet regimens in the front-line setting, many patients are triple-class exposed (TCE) - that is, exposed to proteasome inhibitor (PI), immunomodulatory drug (IMiD) and CD38 monoclonal antibody (MoAb) at their 1st relapse - and almost all patients are TCE at their 2nd relapse. TCE patients exhibited unfavorable treatment outcomes, with PFS and overall survival (OS) of 4.6 months and 9.2 to 13.8 months, respectively, in real-world studies(8,9), prior to the introduction of T-cell redirectional therapy. While novel immunotherapies, mainly chimeric antigen receptor T-cell (CART) and bispecific antibodies, show promising efficacy in the early relapse setting(10–12), their use is sometimes challenged by toxicity, financial costs and logistic complexity.

Ixazomib is an oral 2nd generation PI, with proven efficacy as a part of combination regimens in newly diagnosed(13), and relapsed refractory (RR) MM(14).

Pomalidomide is an oral third generation IMiD with single-drug activity in RRMM patients (15). Adding pomalidomide to the PI bortezomib improved PFS in lenalidomide exposed RRMM patients(16). Pomalidomide was also used in various single arm trials for RRMM(15–18).

Ixazomib-pomalidomide-dexamethasone (IPd) combination is an all-oral triplet for TCE patients, which could be particularly suitable for older patients. Therefore, we designed a prospective trial to explore the safety and efficacy of this combination in patients with TCE myeloma.

Methods:

Ethics approval and consent to participate:

The IPOD-790 study is a phase II investigator-initiated study. It was conducted in 7 Israeli centers and was approved by Institutional Review Boards at each institution. All subjects signed informed consent prior to screening. Ixazomib was supplied by Takeda Inc. Pomalidomide was supplied by patients' health plan. This trial is registered at www.clinicaltrials.gov (NCT04790474).

Eligibility:

Patients ≥ 18 years of age with RRMM according to the international myeloma working group (IMWG) criteria(19). Patients had to have measurable disease and be triple-class exposed or refractory. Exposure was defined as receiving at least 1 full cycle of a drug; Refractoriness was defined as documented progression while receiving, or within 60 days of last dose of anti-myeloma drug(20). Patients had to have adequate bone marrow reserve (hemoglobin ≥8 gr/dl, platelet count ≥75×10^9/L and neutrophil count ≥1.0 ×10^9/L), creatinine clearance (using the MDRD(20) equation) >15 mL/min, and Eastern Cooperative Oncology Group (ECOG) score of 2 or less. The full inclusion/exclusion criteria are provided in the **supplementary materials**.

Treatment plan:

Eligible patients received ixazomib 3 mg (days 1,4,8,11), pomalidomide 4 mg (days 1-14), and dexamethasone 20 mg (days 1,2, 8,9, 15 and 16) every 21 days for 3 cycles (cycles 1-3), followed by 28-days cycles of ixazomib 4 mg (days 1,8 and 15), pomalidomide 4 mg (days 1-21) and dexamethasone 20 mg (days 1,2, 8,9, 15, 16, 22 and 23) every 28 days, for additional 21 cycles (cycles 4-24) (**Figure S1**). The initial doses of pomalidomide and dexamethasone could be decreased (to 3 and 10 mg, respectively) in patients older than 75 and/or with renal impairment (creatinine clearance of 15-50 mL/min), according to physician discretion. Doses may have been subsequently increased if the regimen was well tolerated. After completion of 24 treatment cycles, patients continued pomalidomide and dexamethasone as standard of care until progression or unacceptable toxicity. Mandatory supportive care included prophylactic antiviral therapy against varicella zoster virus and prophylactic anticoagulation (or antiplatelet therapy). The cut-off date for database lock was May 1st, 2025.

Definitions:

Revised international staging system (R-ISS) was calculated according to serum levels of albumin, beta2 microglobulin, lactate dehydrogenase and the presence of del(17p), t(4;14) or t(14;16)(21). Patients were considered to have high-risk (HR) cytogenetics if they had one of these alterations or +1q gain/amplification, as detected by fluorescence in situ hybridization (FISH) since diagnosis. Frailty score was calculated according to the modified IFM frailty score, based on age, ECOG and Charlson comorbidity score(22) according to Facon et al(23). Double refractory patients were defined as patients whose disease was refractory to both bortezomib and lenalidomide. Bortezomib-free interval and lenalidomide-free

interval were defined as time (in months) from last administration of the drug as a part of previous line to C1D1.

Endpoints:

The primary endpoint was PFS. Secondary endpoints included the safety profile of the regimen using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (24), the response rates according to IMWG criteria(25), duration of response (DOR; defined as time from 1st documented response to progression of disease [PD]), time to next treatment (TTNT; defined as time from 1st dose of study regimen to first dose of subsequent regimen), and OS.

Statistics:

Sample size determination: Assuming a PFS of at least 8 months in our study with IPd regimen , a sample size of 61 patients, enrolled over 24 months with an additional follow-up of 18 months, will allow to detect superiority over the historical control group(26) (POM/dex arm - PFS 4.7 months) with a power of 0.8 and type 1 error of 5%.

The estimation of median time-to-event data for PFS, OS, DOR and TTNT was done using the Kaplan-Meier method. Cox regression was used to model the relationship between predictor variables and time-to-event data. Association between categorical variables was determined using Chi-square or Fisher's exact test, depending on sample size. All the statistics were performed using IBM SPSS Statistics for Windows, version 29 (IBM Corporation, 2022).

Results:

Sixty-one patients (35 [57%] males) were enrolled between March 1st 2021 and March 17th 2024. The median age was 74 (range: 53-89); 13 patients (21%) were 80 years or older. The R-ISS score was I/II/III for 29%, 55% and 16%, respectively; 57% had high-risk cytogenetics. Twenty-six (43%) patients were frail according to simplified myeloma frailty score(23); Ten patients (16%) had a glomerular filtration rate ≤40 ml/min. All patients were exposed to bortezomib and lenalidomide and were included in the safety cohort. Sixty (98%) were DARA exposed and were included in the efficacy cohort (one DARA-naïve patient was excluded from the efficacy cohort). Refractoriness rates to bortezomib, lenalidomide and daratumumab were 51%, 85% and 96%, respectively. Thirty-nine percent of the patients were Triple-class refractory (all double-refractory patients were also triple refractory). Thirty percent had undergone autologous stem-cell transplantation. Median time from diagnosis to enrollment was 45 [interquartile range 28-74] months, median prior lines of therapy was 2 (range 1-4) (**Table 1**). The initial dose of pomalidomide was 4 mg in 50 (82.0%) patients. Eleven (18.0%) patients had reduced initial dose at physician discretion (3 mg in 10 patients and 2 mg in 1 patient). Thirty-five (57%) patients received anti-platelet therapy, 20 (33%) received anticoagulation therapy, 4 (7%) received both anti-coagulation and anti-platelet therapy and 2 patients (3%) did not receive anti-platelet nor anti-coagulation therapy.

At data cut-off date (May 1st, 2025), two patients (3%) remained on study treatment and 7 patients (11%) completed 2 years of study regimen and continued pomalidomide monotherapy as standard of care, as prespecified in the

protocol. Study regimen discontinuation occurred in 52 patients (85%): 34 (56%) due to (d/t) PD, 14 (23%) d/t AE, 3 (5%) withdrew consent and 1 (2%) d/t investigator decision. Seven (11%) patients died on treatment (see details below) (**Figure 1)**.

Safety:

Fifty-nine patients (97%) had ≥1 treatment emergent adverse event (TEAE) and 41 (67%) had a TEAE grade (Gr) 3 and above. Common (occurring in ≥15% of patients) TEAEs related to study regimen included neutropenia (39%, Gr≥3: 30%), fatigue (33%, Gr≥3: 2%), pneumonia (30%, Gr≥3: 26%, including 3% Gr 5), thrombocytopenia (31%, Gr≥3: 18%), gastrointestinal (GI) toxicity (33%, Gr≥3: 3%; including diarrhea 30%, Gr≥3: 3%; nausea and vomiting 13%, Gr≥3: 0%), anemia (30%, Gr≥3: 5%), peripheral edema (26%, Gr≥3: 2%), pain (23%, Gr≥3: 3%), rash (20%, Gr≥3: 0%), peripheral neuropathy (18%, Gr≥3: 2%) and COVID19 infection (15%, Gr≥3: 3%)**(Table 2)**. Thirty-two patients (52%) had a dose reduction: pomalidomide, ixazomib and dexamethasone doses were reduced in 18 (30%), 14 (23%) and 17 (28%) of patients, respectively. The reasons for ixazomib dose reductions were neutropenia (6 patients), thrombocytopenia (5 patients), peripheral neuropathy (2 patients) and constipation, nausea and urinary tract infection (UTI) (1 patient each). The reasons for pomalidomide dose reductions were: neutropenia (6 patients), rash (5 patients), anemia, thrombocytopenia (4 patients each), Sweet/ suspected Sweet syndrome (2 patients), deterioration in kidney function (2 patients), neuropathy, disequilibrium, fatigue, constipation, edema, UTI, pneumonia (1 patient each). For both drugs, some patients had multiple reasons for dose reductions. Twenty-two (36%) patients had at least one serious adverse event (SAE), mainly infectious

(28%, including pneumonia in 18%, febrile neutropenia 5% and bacterial meningitis 1.6%). Other SAEs included acute renal injury, acute febrile neutrophilic dermatosis and ischemic cerebrovascular accident (1.6% each). As mentioned above, 7 (11%) patients died while still on treatment: 1 d/t PD, and 6 (10%) patients died from AEs: one from CVA, and 5 (8%) patients died from infections: 3 pneumonia, 1 COVID19 infection and 1 septic shock. Three of these patients died during the first 3 cycles of therapy, without achieving response. Two died 6 and 12 months from treatment initiation, one in VGPR and one in stable disease (SD). Three of them had dose reduction prior to their death. All 6 patients who died from AEs were frail. Eight (13%) patients (2 frail, 6 non-frail) discontinued treatment d/t AEs. Six (10%) were potentially related to the study regimen: pneumonia, thrombocytopenia, meningitis, renal failure, blepharitis and upper GI bleeding. Two of them had a dose reduction (both had pomalidomide dose reduction, and one of them additionally had ixazomib dose reduction) prior to permanent discontinuation of the study protocol. Two (3%) patients discontinued protocol because of AEs deemed by investigator to be unrelated to treatment: adenocarcinoma of GI tract and dementia. No venous thromboembolic events were observed.

Efficacy:

Sixty patients were eligible for response assessment (one patient was not exposed to DARA and therefore excluded from the efficacy cohort). Overall response rate (ORR) was 58%. Complete response (CR), very good partial response (VGPR) and partial response (PR) rates were 7% (stringent CR in 2%), 15% and 36%, respectively.

The median follow-up time was 32 (95% CI 28.8-35.2) months. The median PFS was 8.1 (95% CI 3.9 – 12.3) months (**Figure 2A)**. The median DOR and TTNT were 10.7 (95% CI 8-13.5) and 11.7 (95% CI 8.5-14.9) months, respectively. Patients achieving VGPR or better had a median PFS and median DOR of 25.6 (95% CI 3-48.2) and 24.9 (95% CI 2.2-47.6) months, respectively. The median OS was 30.4 (95% CI 21.5-39.4) months **(Figure 2A)**. Response to treatment (achieving PR or better) was not significantly associated with OS in a time-dependent Cox regression model adjusted for age and sex, but a trend toward improved survival was observed (HR 0.46; 95% CI 0.20-1.05; p=0.065). Patients with high-risk cytogenetics had similar ORR as patients with standard risk cytogenetics, 59% vs. 60%, respectively (p=0.96), but shorter PFS and DOR (7.9 vs 13.8 months, p=0.036; 8.6 vs 13.1 months, p= 0.05) **(Figure 2B)**.

Impact of drug-refractoriness:

Single-class refractoriness: ORR rates were 52% and 66% for bortezomib refractory and non-refractory patients, respectively (p=0.31). Similarly, ORR was 56% and 75% for lenalidomide refractory and non-refractory patients, respectively (p=0.45). PFS and DOR did not differ significantly between bortezomib-refractory and bortezomib-sensitive patients (PFS: 7.1 vs 9.8 months, p=0.98; DOR: 11.5 vs 9.5 months, p=0.85) **(Figure 3A)**. Lenalidomide-refractory patients had shorter PFS and DOR compared to patients who were lenalidomide-sensitive (PFS: 6.2 vs 16.6 months, p=0.156; DOR: 9.1 vs 24.9 months, p=0.017) (**Figure 3B**). Lenalidomide-free interval and bortezomib-free interval had no impact on ORR, PFS and DOR (**appendix Table S1**).

Triple refractoriness: ORR was numerically lower for patients who were refractory to bortezomib, lenalidomide and daratumumab: 46% vs. 68% for patients who

were not triple-refractory, p=0.12. Median PFS and DOR in triple-refractory patients (4.0 and 7.4 months, respectively) were not significantly different from those in non-triple-refractory patients (**Figure 3C)**. OS of triple-refractory patients was shorter than that of non-triple-refractory patients (26.6 vs. 37.2 months), although at the time of data cut-off this did not reach statistical significance (p=0.09).

Impact of frailty:

Twenty-six (43%) of the study population had a frailty score of 2 or more according to the simplified frailty score(23). Frail patients had no increase in all AEs, Gr≥3 AEs, all infections, Gr≥3 infections, Gr≥3 anemia, renal failure and stroke (**appendix Table S2**), but, as mentioned above, had a significantly higher rate of fatal AEs compared to non-frail (6 vs none, p=0.001). Gr≥3 thrombocytopenia was higher in frail patients (46% vs. 17%, p=0.014), leading to treatment discontinuation in one patient only.

ORR of frail patients was 50% vs 65% for non-frail (p=0.30). Frail patients had numerically but not statistically significant shorter PFS (6.2 vs 9.8 months, p=0.14) **(Figure 2C)** and DOR (7.6 vs 11.5 months, p=0.13). A trend towards shorter OS in frail patients was noticed: median OS of 22.5 months vs 34.7 in the non-frail patients, p=0.065.

Combined effect of frailty and refractoriness:

Almost all frail patients were lenalidomide refractory (24/26, 92%). Half (13/26) of the frail patients were bortezomib-refractory and 38% (10/26) were TCR. Bortezomib-refractory and TCR frail patients had consistently numerically lower ORR and shorter PFS and DOR (**appendix Table S3**). None of these comparisons was statistically significant, except for DOR for TCR frail patients

compared to non-TCR frail patients: 3.3 months (95% CI 0.0-7.7) vs 10.7 months (95% CI 6.5-14.9), p=0.02.

Discussion:

In this phase II multi-site study of triple-exposed RRMM patients, an all-oral regimen of ixazomib-pomalidomide-dexamethasone resulted in a response rate of 58% and median DOR of 10.7 months. A twice-weekly ixazomib administration was used in the first three cycles, aiming to increase dose intensity in order to improve initial disease control in these hard-to-treat TCE patients. To date, three published prospective trials evaluated the combination of IPd for RRMM. The participants were younger and less frail than in our cohort, and most patients were not TCE: Krishan et al.(27) published a phase I/II trial of 32 bortezomib exposed, lenalidomide refractory patients. The median age was 62 (38-84) years, and the median number of previous lines was 2 (1-5). ORR was 48%, with a median PFS and DOR of 8.6 and 9.2 months, respectively. None of the patients was reported to be DARA exposed. The IFM 2014 trial was a multicenter, open-label, single arm, phase II study of IPd in 26 lenalidomide refractory MM patients with adverse genomic abnormalities, defined as t (4;14) and/or del 17p at 1st or 2nd relapse(28). Ixazomib was given twice weekly (3 mg on days 1,4,8,11 every 21 days) for 17 cycles and then switched to weekly administration (4 mg days 1,8, 15 every 28 days). Less than half of the patients were DARA exposed. The median age was 72 and 12 patients were 75 or older. ORR was 60%, DOR was 10.0 months and median OS was 23.7 months. Safety profile was manageable and demonstrated the tolerability of twice weekly 3 mg ixazomib administration(28). The ALLIANCE 061202(29) was a phase II randomized trial comparing IPd to pomalidomide-dexamethasone (Pd) in 1st relapse for

lenalidomide refractory, but PIs naïve or sensitive, MM patients. None of them were DARA exposed. Seventy-seven patients were randomized in a 1:1 ratio. The median age was 65 (with only 6 patients older than 75 in the IPd arm). The ORR for the IPd arm was 63% with median DOR of 23 months, both numerically better than the control arm but differences were not statistically significant. Patients in the IPd arm had significantly higher rate of deep responses (VGPR or better) - 29% vs. 5% ($p<0.00$). There was no difference in OS. Hematological and GI gr$\geq$ 3 AEs were higher in the IPd arm. Thus, the abovementioned studies reported ORR rates and DOR similar to our cohort. The longer DOR reported in the ALLIANCE 061202 trial(29) likely reflecting patient populations with lesser disease resistance, as TCE patients were not included. Other studies used different pomalidomide combinations for TCE patients: The SELECT(18) trial investigated the carfilzomib-pomalidomide combination in 52 RRMM patients. Sixty-seven percent were TCE and 37% were TCR. ORR was similar to ours with 58%, but responses were more durable: median PFS was 11.1 and median DOR was 20.3 months. The ALGONQUIN trial enrolled patients after a median of 3 (range 1-6) previous lines of therapy to receive belantamab mafodotin in combination with pomalidomide(30). In a post-hoc subgroup analysis of 69 TCE patients(31) ORR was 86% (with 64% VGPR or better). The median DOR was 22 months. Both studies included younger patients (median age 67-68) compared to our cohort.

Indeed, the unmet need among TCE patients was shown in recent real-world studies preceding the introduction of novel immunotherapies, including Mammoth(8) and Locommotion(9) that reported inferior results in this population, with ORR of 29-30%, and median PFS and OS of 4 and 12 months, respectively.

Our study population is highly enriched with elderly and frail patients, which would have precluded their enrollment in most interventional studies. Rates of TEAE related discontinuation and on-study death (23% and 11%, respectively) were in accordance with other early-relapse, non-immunotherapy trials with similar age distribution(18,32). Although response rates of frail patients were not significantly lower compared to the non-frail patients (50% vs. 65%, respectively, p=0.30) a trend towards shorter DOR and OS was noted, probably attributed to 6 frail patients who died without achieving response, thus uncontrolled myeloma could have also contributed to their death.

The ORR was lower among TCR patients, suggesting potential class-wide drug resistance. Of note, all double refractory patients in our efficacy cohort were also triple-refractory (as daratumumab is typically continued until progression, and discontinuation d/t AEs is uncommon). Nevertheless, nearly half of the TCR patients responded, and maintained response for more than 7 months (almost double than DOR for triple-class refractory patients in the Locommotion study(9)).

The recent introduction of T-cell redirectional therapy and anti B-cell maturation antigen (BCMA) CART significantly improved outcomes of TCE patients. Initial studies of novel immunotherapies enrolled TCE RRMM patients in late relapse (after 3 or more lines of therapy). These studies have demonstrated encouraging results: ORR was 63-98% and median DOR was 7.8-33 months(33–37). Novel Immunotherapy outcomes are superior to those in our IPd cohort and will likely change the treatment paradigm for relapsed TCE myeloma in the coming years. Combination studies may further improve efficacy outcomes(11,31,38) as may the introduction of novel immunotherapies in earlier treatment lines.

The place of IPd regimen nowadays needs to be considered in the context of these remarkable results. Nevertheless, the IPd regimen, being an all-oral

therapy, represents an alternative option for some of the TCE RRMM population, with a manageable safety and tolerability profile, no need for hospitalizations d/t risk of CRS and no hypogammaglobulinemia requiring IVIG administration (as opposed to immunotherapy), and no keratopathy (associated with belantamab-mafodotin). It may also be considered in between immunotherapy regimens, to allow for T cell recovery. An all-oral combination can potentially overcome social and mobility challenges that may interfere with adherence. However, frail patients did suffer from considerable toxicity, including fatalities, underscoring the need for careful patient selection and monitoring.

The response rate of 58% which we report in this study is encouraging in this TCE population, enriched with high-risk cytogenetics (57%), elderly (41% >75 years) and frail (43%) patients, which closely resembles “real-world” patients. However, most responses were not deep (22% VGPR or better), translating to a median duration of response (DOR) of 10.7 months. While still surpassing expectations for this cohort, these results remain inferior to immunotherapy or BPd regimens(10,31). Whether extending ixazomib biweekly administration beyond three cycles could lead to deeper and more durable responses remains unknown. In the IFM 2014 trial, twice weekly ixazomib for 17 cycles did not yield a longer DOR (median 10.0 months); notably, the study only included patients with high-risk cytogenetic aberrations. The more frequent administration did not result in added toxicity(28).

Limitations of this study include the small sample size and single arm design. The absence of pharmacokinetic samples, particularly during cycles with biweekly ixazomib administration, precluded determination of the optimal dosing schedule. Frailty was assessed using the simplified IFM frailty score, as the variables required for this tool were consistently available in our dataset, whereas more

comprehensive validated scores such as the IMWG frailty score were not assessed in our trial.

In conclusion, our study demonstrated the efficacy and safety of the all oral combination therapy of IPd in TCE and relapsed myeloma patients. The efficacy, safety and tolerability demonstrated in a cohort relatively enriched with elderly and frail patients, which are typically underrepresented in clinical trials, provide an alternative for patients who are not candidates for more intensive treatments.

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Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (N=61)

	n*	%
Age, years:		
<65	11	18
65-75	25	41
≥75	25	41
Sex		
Male	35	57
Female	26	43
ECOG		
0	25	41
1	31	51
2	5	8
Frail†	26	43
eGFR‡		
>60	31	51
30-60	25	41
<30	5	8
Myeloma type (n=55)		
IgG	26	47
IgA	9	16
Light chain only	20	36
ISS (n=48) I / II / III	20 / 12 / 16	42 / 25 / 33
R-ISS (n=44) I / II / III	13 / 24 / 7	29 / 55 / 16
FISH Cytogenetics§ (n=47)		
Any high-risk FISH	27	57
Double-hit myeloma	4	9
true EMD at study baseline (n=59)	3	7
Prior Drug Exposure and Resistance		
Prior lines of therapy		
1	6	10
2	44	72
3-4	11	18
Bortezomib – Exposed (E) / Refractory	61 / 31	100 / 51
Daratumumab - E / R	60 / 59	98 / 96
Lenalidomide - E / R	61 / 52	100 / 85
Carfilzomib - E / R	3 / 2	5 / 3
Post-ASCT	18	30
Triple-class refractory	24	39

* n=61 Unless otherwise specified

† Frailty status was determined using the simplified IFM frailty score based on age, ECOG, and Charlson Comorbidity Index according to Facon et al(23)
‡ eGFR was calculated using the MDRD equation(20)
§ High-risk cytogenetics defines as the presence of del(17p), t(4;14), t(14;16) or +1q gain/amplification. Double-hit myeloma was defined as the presence of two or more of these aberrations.

Table 2: Common Treatment Emergent Adverse Events (≥15%)

AEs	All grade		GR ≥3	
	n	%	n	%
Neutropenia	24	39	18	30
Fatigue	20	33	1	2
Pneumonia	19	31	16	26
Thrombocytopenia	19	31	11	18
Anemia	18	30	3	5
Diarrhea	18	30	2	3
Peripheral edema	16	26	1	2
Pain	14	23	2	3
Rash	12	20	0	0
Peripheral neuropathy	11	18	1	2
COVID-19 infection	9	15	2	3

Figure 1: CONSORT diagram of patient's disposition

Consort flow diagram for the IPoD study.

Figure 2: Progression-free and overall survival

(A) Progression-Free Survival (PFS) and Overall Survival (OS) **(B)** PFS by Cytogenetics: Patients with high-risk cytogenetics (HR FISH), defined as: t(4:14), t(14:16), +1q21, or del17p) compared to standard-risk patients **(C)** PFS by Frailty Status: Frail patients (frailty score ≥2) compared to non-frail patients

Figure 3: Progression-free survival according to prior refractoriness

PFS according to bortezomib **(A)**, lenalidomide **(B)** and triple-class refractoriness status **(C)**.

Figure 1 – Consort diagram of patient disposition

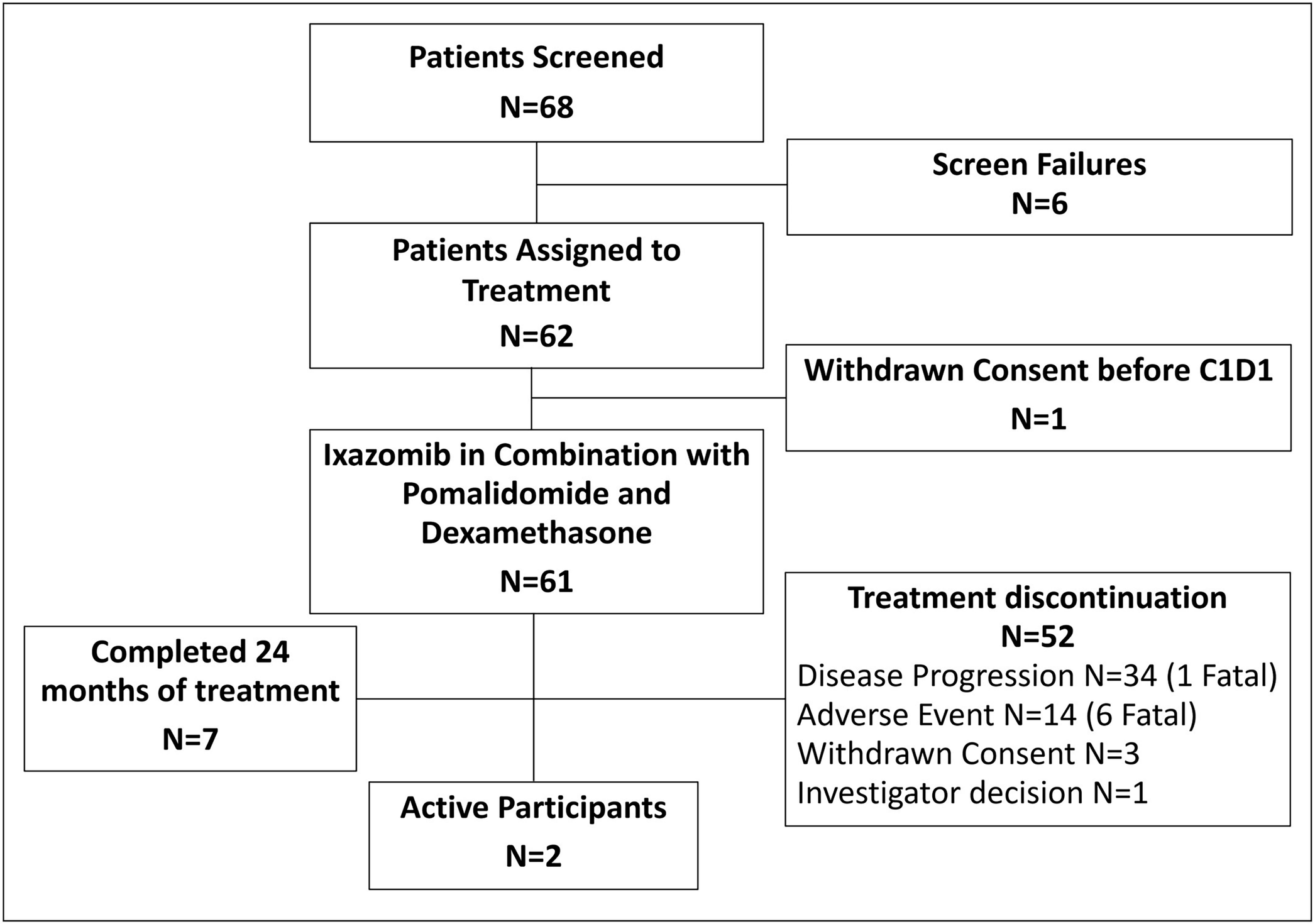
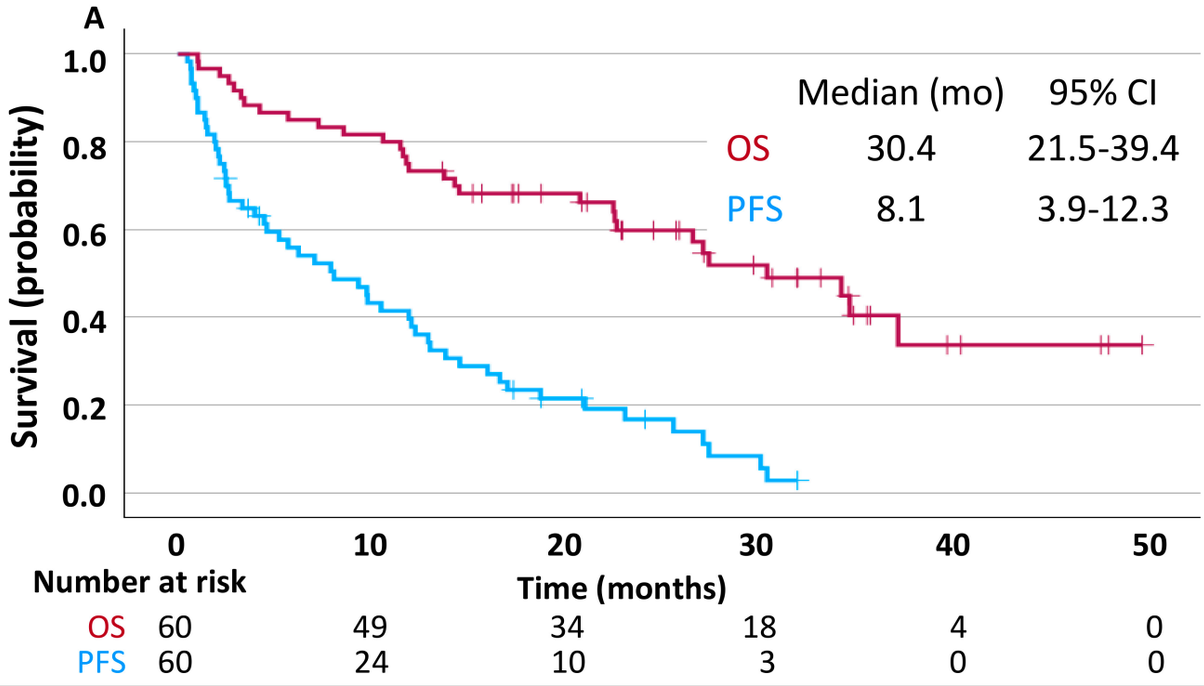
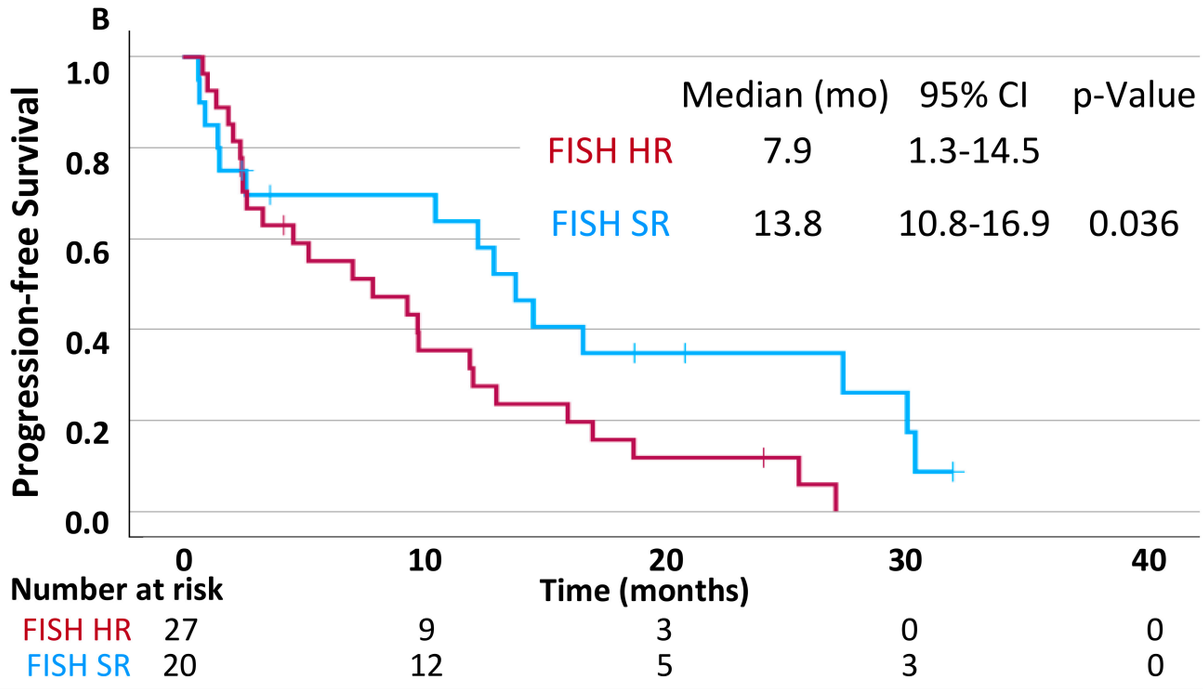


Figure 2: Overall and Progression-free survival





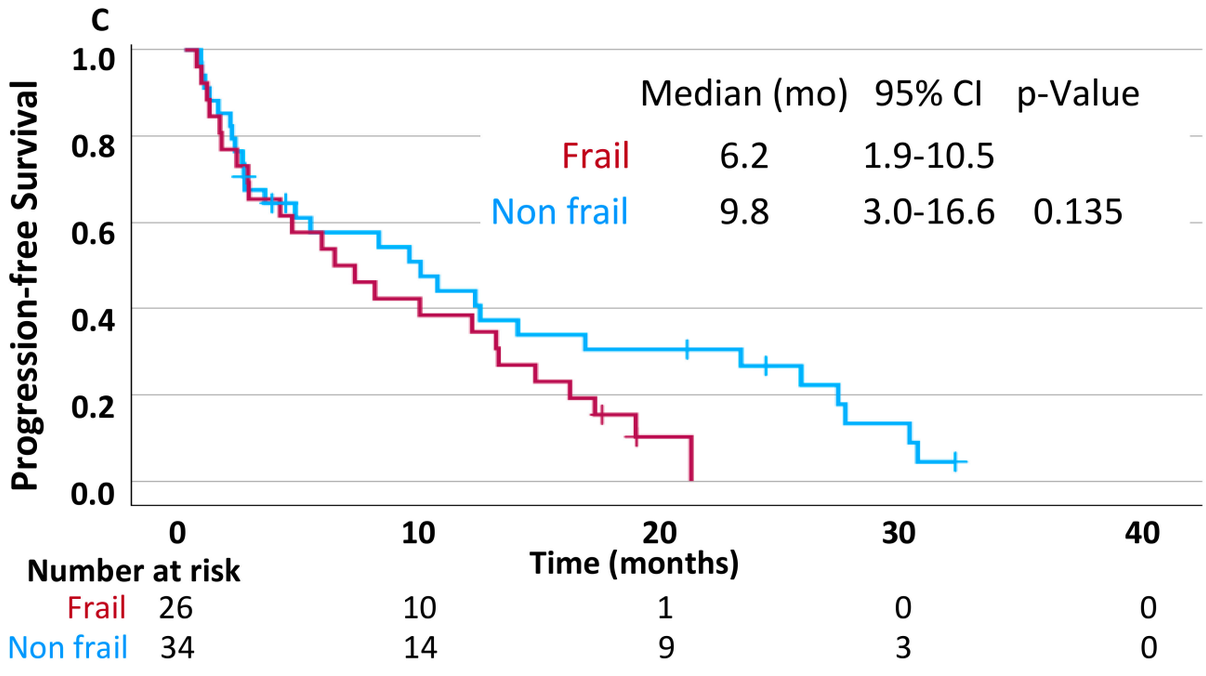
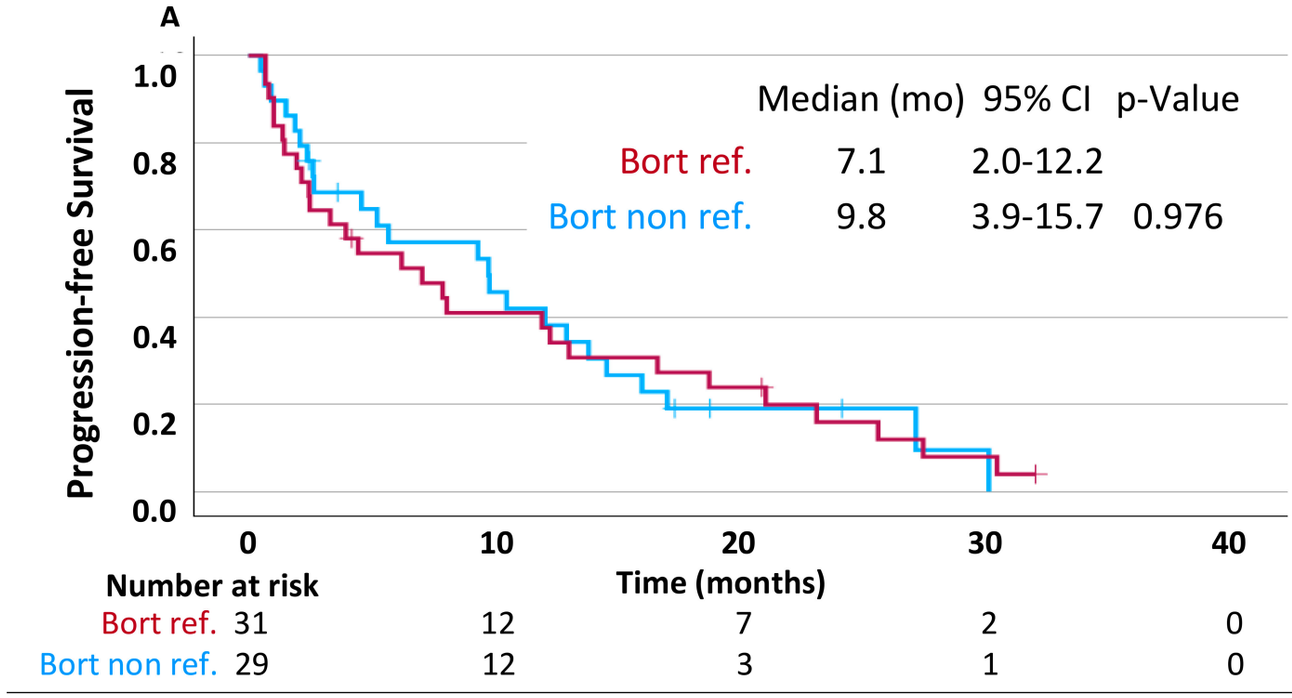
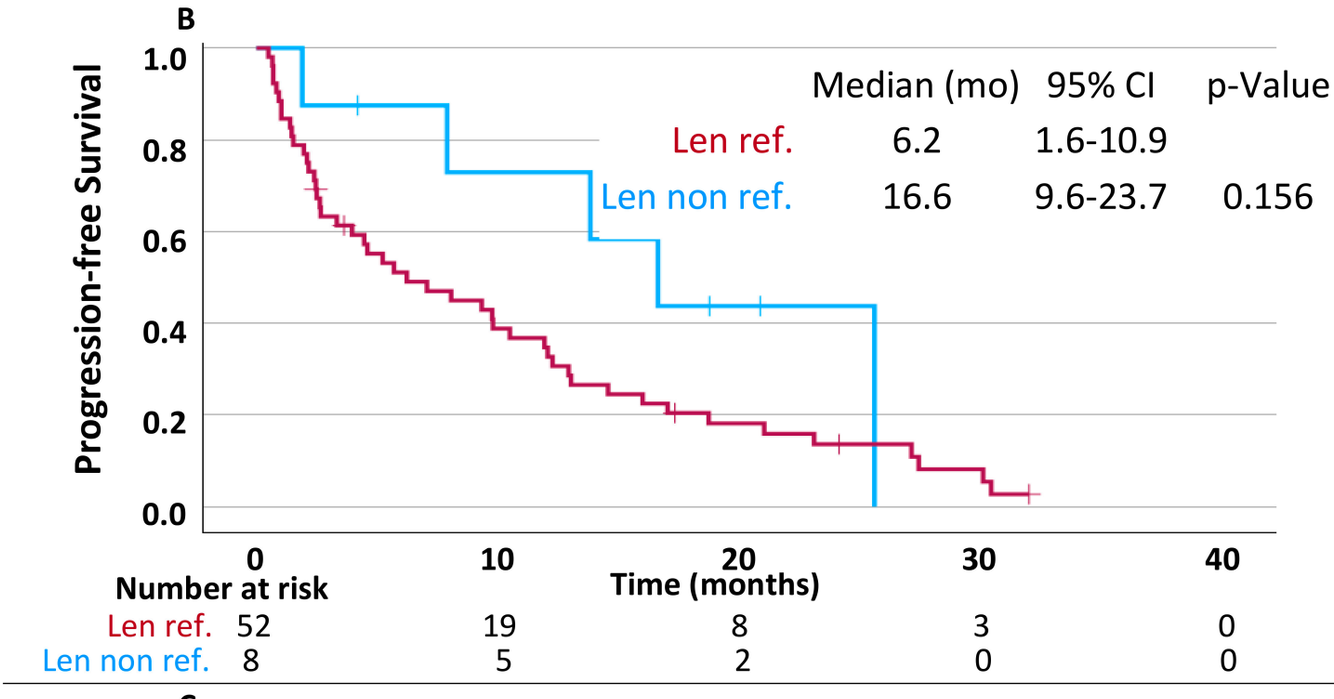


Figure 3: Progression-free survival according to prior refractoriness





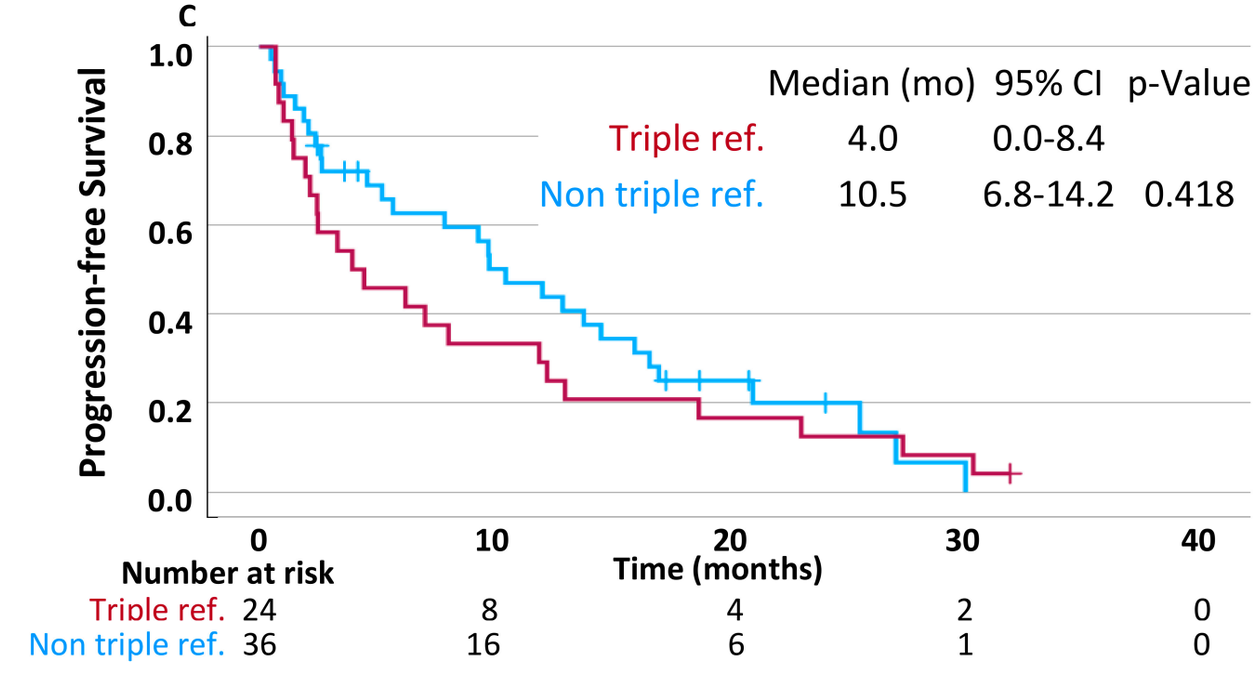


Table S1: Impact of bortezomib and lenalidomide-free intervals on efficacy:

	HR (95% CI)	p-value
Bortezomib-free interval:		
ORR	1.022 (0.998-1.048)	0.075
PFS	0.992 (0.981-1.002)	0.113
DOR	0.998 (0.975-1.002)	0.094
Lenalidomide-free interval:		
ORR	1.030 (0.978-1.085)	0.261
PFS	0.989 (0.966-1.013)	0.378
DOR	0.979 (0.949-1.009)	0.168

Table S2: Comparison of TEAEs between frail and non-frail patients:

	Frail n (%)	Non frail n (%)	P value
Any TEAE	26 (100)	33 (94)	0.503
TEAE GR 3-5	18 (69)	23 (66)	0.772
Common TEAEs in frail patients:			
Thrombocytopenia	10 (39)	9 (26)	0.29
Thrombocytopenia GR≥3	6 (23)	5 (14)	0.50
Diarrhea	12 (46)	6 (17)	0.014
Neutropenia	8 (31)	16 (46)	0.24
Neutropenia GR≥3	6 (23)	12 (34)	0.34
Anemia	7 (27)	11 (31)	0.70
Anemia GR≥3	1 (4)	2 (6)	1
Peripheral edema	7 (27)	9 (26)	0.92
Rash	5 (19)	7 (20)	0.94
Pneumonia	8 (31)	11 (31)	0.96
AKI	3 (12)	1 (3)	0.30
Stroke	1 (4)	2 (6)	1
All infections	17 (65)	25 (71)	0.6

Table S3: Refractoriness status in frail patients:

	Refractory	Non refractory	p-value
Bortezomib	n=13 (50.0%)	n=13 (50.0%)	
ORR (%)	38.5%	61.5%	0.24
PFS (months): median (95% CI)	6.23 (2.60-9.87)	9.77 (0.00-21.82)	0.53
DOR (months): median (95% CI)	5.53 (0.67-10.40)	9.30 (2.69-15.90)	0.28
Lenalidomide	n=24 (92.31%)	n=2 (7.69%)	
ORR (%)	50.0%	50.0%	1
PFS (months) median (95% CI)	5.70 (1.98-9.42)	7.90 (N/A)	0.22
DOR (months) median (95% CI)	5.97 (2.40-9.53)	N/A	N/A
Triple-Class	n=10 (38.46%)	n=16 (61.54%)	
ORR (%)	40.0%	56.3%	0.420
PFS (months) median (95% CI)	4.47 (0.95-7.98)	7.90 (0.00-15.87)	0.243
DOR (months) median (95% CI)	3.27 (0.00-7.74)	10.73 (6.54-14.92)	0.022

Figure S1: Treatment Schedule

Study Population:
Adult patients with a confirmed diagnosis of symptomatic and relapsed and/or refractory MM, after receiving bortezomib, lenalidomide and daratumumab during first and second lines, will be eligible to be enrolled in this study.
For the purposes of this study, refractory disease is defined as disease progression on treatment or progression within 60 days after the last dose of a given therapy.
Inclusion criteria:
Patients must meet all of the following inclusion criteria:
1. Male or female patients, 18 years of age or older.
2. Multiple myeloma diagnosed according to standard IMWG criteria
3. Patients must have measurable disease defined by at least one of the following five
measurements:
• Serum M-protein >1 g/dL (>10 g/L).
• Urine M-protein >200 mg/24 hours.
• Serum free light chain assay: involved free light chain level at least 100 mg/L), provided that the serum free light chain ratio is abnormal.
• A biopsy proven evaulble plasmacytoma
• Bone marrow plasmacytosis > 30% of total marrow cells
4. Patients received one or two prior lines of therapy which must have included bortezomib, lenalidomide-and daratumumab.

NOTE: A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. Autologous transplants are permitted.

5. Patients must meet the following clinical laboratory criteria:
• Absolute neutrophil count (ANC) ≥1,000/mm3 and platelet count≥75,000/mm3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days of enrollment.
• Total bilirubin ≤1.5 the upper limit of the normal range (ULN).
• Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 ULN.
• Calculated creatinine clearance ≥15 mL/min

NOTE: Patients with creatinine clearance of 15-50 mL/min will receive pomalidomide at a reduced dose (3 mg), which may subsequently be increased if well tolerated.

6. ECOG performance status of 0, 1 or 2.
7. Female patients who:
• Are postmenopausal for at least 24 months before the screening visit, OR
• Are surgically sterile, OR
• Who are of childbearing potential, and agree to practice two effective methods of contraception (1 highly effective method and 1 additional effective method) AT THE SAME TIME, from the time of signing the informed consent through 90 days after the last dose of study treatment, OR agree to completely abstain from heterosexual intercourse, AND
• Must also adhere to the guidelines of the pomalidomide pregnancy prevention program
Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 to 14 days of initiation of Cycle 1 and again within 24 hours of starting Cycle 1. FCBP must also agree to ongoing pregnancy testing. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.
8. Male patients, even if surgically sterilized (i.e., status postvasectomy), who:
• Agree to completely abstain from heterosexual intercourse, OR
• Agree to practice effective barrier contraception (i.e., latex condom) during sexual contact with a FCBP, even if they have had a successful vasectomy, throughout the entire study treatment period and through 4 months after the last dose of study treatment AND
• Must also adhere to the guidelines of the pomalidomide pregnancy prevention program.
9. Must be able to take concurrent aspirin 100mg daily (or enoxaparin 40 mg subcutaneously daily [or its equivalent] if allergic to aspirin) as prophylactic anticoagulation.
NOTE: For patients with prior history of deep-vein thrombosis, low molecular weight heparin (LMWH) or alternative anticoagulation (coumadine / NOAC) according to physician discretion, is advised.
10. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
11. Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

Exclusion criteria:
Patients meeting any of the following exclusion criteria are not eligible to participate in the study:
1. Patient underwent an allogeneic transplantation
2. Female patients who are lactating or pregnant.
3. Major surgery within 14 days before enrollment.

4. Central nervous system involvement
5. Concomitant use of any other antineoplastic treatment with activity against MM (with the exception of ≤40 mg Dexamethasone per day or equivalent for no longer than 4 days).
6. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before enrollment
7. Diagnosis of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.
8. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
9. Anti-myeloma therapy as follows prior to screening bone marrow aspiration:
• Targeted therapy, epigenetic therapy, within 14 days or at least 5 half-lives,whichever is less;
• Monoclonal antibody treatment for multiple myeloma within 21 days;
• Cytotoxic therapy within 14 days;
• Proteasome inhibitor therapy within 14 days;
• Immunomodulatory agent therapy within 7 days.
• Radiotherapy within 14 days (with the exception of radiotehrapy for spinal cord compression or for pain control that should be discussed and approved by the sponsor- investigator prior to study enrollment). However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.
10. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before enrollment in the study.
11. Ongoing or active systemic infection, active hepatitis B virus infection, active hepatitis C infection, or known human immunodeficiency virus (HIV) positive.
12. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
13. Psychiatric illness/social situation that would limit compliance with study requirements.
14. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

15. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or known GI disease or planned gastrointestinal (GI) procedure that could interfere with the oral absorption or tolerance of treatment.
16. Diagnosed or treated for another malignancy within 2 years before enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
17. Failure to have fully recovered (ie, ? Grade 1 toxicity) from the reversible effects of prior chemotherapy.
18. Patient has ? Grade 3 peripheral neuropathy during the screening period.
19. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.
20. Patients that have previously been treated with ixazomib or pomalidomide