# Ixazomib-based frontline therapy followed by ixazomib maintenance in frail elderly newly diagnosed with multiple myeloma: a prospective multicenter study

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## Summary

**Background** Frail elderly patients with newly diagnosed multiple myeloma (NDMM) have inferior survival and less benefit from high-dose therapies. This prospective study aimed to investigate the efficacy, safety, and quality of life (QoL) of induction treatment of ixazomib/lenalidomide/dexamethasone (IRd) and ixazomib/pegylated liposomal doxorubicin/dexamethasone (IDd) followed by ixazomib/dexamethasone (Id) maintenance therapy in frail, elderly patients with NDMM.

**Methods** From July 2019 to December 2021, this non-randomized concurrent controlled clinical study enrolled 120 NDMM patients aged ≥65 years with frailty defined by the International Myeloma Working Group (IMWG) frailty score or Mayo geriatric scoring system. The enrolled patients received 6–8 cycles of IRd or IDd followed by Id maintenance therapy for a minimum of 2 years at the discretion of physicians based on patient's clinical characteristics (chiCTR1900024917).

**Findings** The median age was 71 years and 55% of the patients were males. The overall response rate (ORR) was 82% and 77%, complete response (CR) rate was 25% and 12% for IRd and IDd groups, respectively. The difference in ORR of the Idd group minus the IRd group was −5.36% (95% CI: −18.9% to 8.19%), indicating that the ORR of the IDd group was neither inferior nor non-inferior to the IRd group. After a median follow-up of 34.3 months, the median progression-free survival (PFS) was 21.6 and 13.9 months, OS was not reached and 29.2 months in IRd and IDd groups, respectively. 28 and 33 patients discontinued induction therapy, 20 and 19 discontinued maintenance therapy in IRd and IDd groups, respectively. Cumulative Grade 3 or higher hematological adverse events (AEs) occurred in 10 of the 60 patients (17%) and non-hematological AEs occurred in 15 of the 60 patients (25%) in the IRd group, while 13 of the 60 patients (22%) and 21 of the 60 patients (35%) in the IDd group. Patients were observed with clinically significant improvement in QoL when compared with that at baseline in both IRd and IDd groups by evaluation per cycle ($P < 0.0001$).

**Interpretation** The results demonstrated that compared with IRd regimen, IDd regimen showed no significant advantage, but the survival of the IDd group was shorter than that of the IRd group, indicating an all-oral outpatient

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triplet regimen with IRd, which has low toxicity and has improved QoL, could be the viable first-line treatment option for frail NDMM patients.

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Keywords: Frail; Elderly; Multiple myeloma; All oral regimen; Quality of life

### Research in context

#### Evidence before this study

In contrast to the younger patients, the population of newly diagnosed multiple myeloma (NDMM) patients, aged ≥65 years is highly heterogeneous in terms of geriatric status and treatment discontinuation due to relapse and toxicity. As frail NDMM patients are usually excluded from randomized clinical trials due to strict inclusive criteria, our search in Pubmed revealed that data on frail NDMM patients were mainly from non-planned post-hoc analyses that did not classify frail patients accordingly to any recognized frailty score. The prospective clinical trials designed for frail patients classified according to the International Myeloma Working Group (IMWG) frailty score, including the HOVON-143 and UK-MRA Myeloma XIV Trial could not provide definitive indications for the most beneficial regimens for frail NDMM patients.

#### Added value of this study

Our study is the first study to report a prospective non-randomized concurrent controlled clinical study investigating ixazomib-based frontline therapy followed by ixazomib maintenance in a frail population defined by the IMWG frailty score. The results demonstrated that the ORR of the IDd group is similar to the one of the IRd regimen but the survival of the IDd group was shorter than that of the IRd group.

#### Implications of all the available evidence

Our results suggest that an all-oral outpatient triplet regimen with IRd could be a viable first-line treatment option for frail NDMM patients with low toxicity and improvement of quality of life.

## Introduction

Multiple myeloma (MM) is an incurable neoplastic disease that predominantly affects elderly patients with a median age of 69 years at diagnosis.[1,2] Compared with younger patients, MM patients aged ≥65 years are highly heterogeneous in terms of geriatric status and treatment discontinuation due to relapse and toxicity.[3–5] The International Myeloma Working Group (IMWG) has proposed a geriatric assessment (GA) of frailty score, which is based on age, comorbidities, and cognitive and physical conditions of (instrumental) activities of daily living ([i]ADL), and predicts mortality and the risk of toxicity in elderly MM patients.[3,6,7] The Mayo Clinic has also reported a simple frailty score (MAYO score), in which age ≥70 years, Eastern Cooperative Oncology Group performance status score (ECOG-PS) ≥2, and N-terminal pro-B type natriuretic peptide (NT-proBNP) ≥300 are independent predictors of overall survival (OS).[8] Despite the availability of these frailty score systems, treatment regimens with efficacy and low toxicity tailored to the frail patient population are scant.

Up to now, only a handful of prospective clinical trials have been designed for the frail patient population according to the IMWG frailty score or Mayo score. In the Hovon-143 study, frail NDMM patients defined by IMWG frailty score received 9 cycles of ixazomib/daratumumab/low-dose dexamethasone (DId regimen) followed by maintenance therapy with ixazomib/daratumumab (DI) for a maximum of 2 years. The results showed a median progression-free survival (PFS) of 13.8 months.[7] A Phase III clinical trial is currently underway (UK-MRA Myeloma XIV Trial) which evaluates frailty-adjusted induction therapy delivery with ixazomib/lenalidomide/dexamethasone (IRd), followed by maintenance therapy with either lenalidomide or ixazomib/lenalidomide (IR).[9]

Other daratumumab-based regimens have showed a preferred response and tolerance in patients with frailty, including daratumumab plus lenalidomide/dexamethasone (DRd) (overall response rate [ORR]: 87.2%)[10] and daratumumab/bortezomib/melphalan/prednisone (Dara-VMP) (ORR: 88.3%).[11] However, in these clinical trials, strict inclusion criteria and post-hoc analysis using relatively simple frailty scoring criteria defined by age and the Charlson comorbidity index (CCI) made frail subgroups unrepresentative of the real frail NDMM patients. Meanwhile, considering the limited availability and unaffordable cost of daratumumab for some patients, prospective clinical trials designed for frail patients using alternative regimens are also needed.

It has been demonstrated that the continuous use of proteasome inhibitors (PIs) or the use of higher cumulative doses can improve long-term prognosis. In the Phase 3, double-blind, placebo-controlled, multicenter TOURMALINE-MM2 study, ixazomib plus lenalidomide/dexamethasone (Rd) exhibited superior outcomes compared with placebo plus Rd in transplant-ineligible NDMM patients.[12] Given the limitations in the application of lenalidomide in certain circumstances such as those with renal insufficiency and deep venous thrombosis, one treatment option is pegylated liposomal doxorubicin, which is less cardiotoxic than cytotoxic agents and has shown a favorable response in the treatment of extramedullary disease.[13] Thus, we analyzed the efficacy and safety of two ixazomib-based frontline therapies in frail patients with NDMM defined by the IMWG frailty score–IRd and ixazomib/pegylated liposomal doxorubicin/dexamethasone (IDd) followed by ixazomib/dexamethasone (Id) maintenance therapy.

## Methods

### Patients

This was a prospective, multicenter, non-randomized concurrent controlled clinical study (ChiCTR1900024917) conducted in 15 hospitals throughout China. The key eligible criteria included age ≥65 years, newly diagnosed symptomatic multiple myeloma who adhered to a frail standard of IMWG frailty score[3] ≥2 or Mayo frailty index (combination of age ≥70, ECOG-PS ≥2, and NT-proBNP ≥300 ng/L simultaneously), a measurable disease with evaluable serum Monoclonal protein of blood (IgG ≥10 g/L, others ≥5 g/L) or urine (≥200 mg/24 h), or serum free light chain ≥10 mg/dL, or measurable extramedullary plasmacytoma. Patients were excluded from the study if they were allergic to any formulation of the study drugs, or had cardiovascular and cerebrovascular events such as acute myocardial infarction, acute heart failure, acute cerebral infarction, or acute cerebral hemorrhage within the past 15 days, or received live attenuated vaccine within 4 weeks before study drug administration.

### Ethics

All study procedures were approved by the institutional review board and ethics committees of Beijing Jishuitan Hospital before study initiation (No. 201907-04). The study was conducted in accordance with the Declaration of Helsinki and the principles of the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

### Study design and treatment

Patients received IRd or IDd at the discretion of physicians according to baseline clinical characteristics. The limitations of lenalidomide are patients with high risk of thrombosis and renal insufficiency, and the need for daily dosing, patients with renal dysfunction, paraplegia, and unsatisfactory medication compliance may be more inclined to receive IDd regimen. IRd regimen consisted of oral ixazomib 4 mg (Days 1, 8, and 15), oral lenalidomide 25 mg (Days 1–14; 10 mg was recommended if the patient's creatinine clearance was 30–60 mL/min; lenalidomide was to be postponed if the patient's creatinine clearance was <30 mL/min until it got improved) and oral dexamethasone 20 mg (Days 1, 8, 15, and 22) in a 28-day cycle. The IDd regimen also consisted ixazomib 4 mg (Days 1, 8, and 15), intravenous liposomal doxorubicin 40 mg (Day 1), and oral dexamethasone 20 mg (Days 1, 8, 15, and 22) in a 28-day cycle. All patients received four 28-day induction cycles. Patients who achieved a response better than very good partial response (VGPR) proceeded with two more cycles, and those who achieved a partial response (PR) and minimal response (MR) received four more cycles as consolidation therapy. As previous studies have demonstrated further improvement in response during maintenance treatment with ixazomib,[14] a 34.1% reduction in the risk of progression or death compared with placebo, and no cumulative toxicity,[15] we proposed the maintenance regimen of ixazomib (Days 1, 8, and 15) and dexamethasone 20 mg (Days 1, 8, 15, and 22) in a 4-week cycle until progression or unacceptable adverse events (AEs) for a minimum of 2 years (Appendix Fig B1). Antiviral prophylaxis and anti-thrombosis prophylaxis were recommended according to IMWG guidelines.[16] Other prophylactic treatments were permitted according to each institutional practice standard.

Bone lesions and extramedullary plasmacytoma were evaluated focally by CT or MRI and throughout the whole body by PET-CT scans. For disease evaluations, serum and urine samples were collected on Day 0 of every cycle for 2 years, then every 8 weeks thereafter until disease progression. Responses to study treatment and the progressive disease were evaluated based on IMWG criteria.[17] The cytogenetic risk was assessed locally (with no standard cutoff for clonal size) by fluorescence in situ hybridization (FISH) or karyotype analysis. The safety of the treatment was monitored continuously throughout the study until 30 days after the last dose of the study treatment. AEs were graded in severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 4.03).[18]

### Endpoints

The primary endpoint was the ORR with different induction regimens, defined as the proportion of patients who achieved partial response (PR) or above according to IMWG criteria. Key secondary endpoints were PFS, OS, early death (death within 60 days of enrollment), health-related quality of life (HRQoL), treatment discontinuation due to toxicity, and relative dose

intensity (RDI). AE was jointly assessed and intervened by a competent physician and a pharmacist according to CTCAE 4.0.[18] The calculation of RDI is described in the Appendix. The quality of life (QoL) was evaluated according to the European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30)[19] before each cycle for patients who were still receiving the study treatment.

### Statistical analysis

The non-inferiority tests for the ratio of two proportions design were used to calculate the sample size of the two subgroups that IDd was not inferior to IRd. ORR values of 90% for the IRd group and 80% for the IDd group were considered to be sufficient. With a non-inferiority margin of 10%, $\alpha = 0.025$, and a power of 80%, the sample size for each group was 48. Taking into account a 25% ineligibility rate, 60 frail patients should be screened for each group and there should be 120 frail patients in total.

The analysis population was the intent-to-treat population of patients who were assigned to the treatment group. Patients who received at least one dose of the treatment drug were included in the safety analysis. The determination analysis of the non-inferiority hypothesis was examined by the Newcombe-Wilson Score Confidence Interval (CI) of ORR between the two groups. The interpretation of the 95% CI of the ORR difference of IDd minus IRd was according to the previous report.[20] The sensitivity analyses included multivariate analysis and propensity score matching to address potential sources of bias. The chi-square test was used for univariate analysis and logistic regression analysis was for multivariate analysis of ORR between the two groups. Multivariate analysis and propensity score matching were performed for variables with statistically significant differences between the two groups in baseline characteristics, including ECOG score, International Staging System (ISS) stage, revised ISS (R-ISS) stage, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 $m^2$, and paraplegia. Time-to-event variables between the two treatment groups were estimated using the Kaplan–Meier method; 95% CI was also evaluated. Survival analyses were performed using Cox proportional hazard models. For PFS, patients were censored at the date of last disease assessment before next-line antimyeloma therapy or death from any causes, whichever occurred first. For OS, patients were censored at the last date on which they were known to be alive. The survival status included early death (within 60 days of registration), late death (60 days after registration), and survival (Appendix F). For AEs, patients who had multiple occurrences of one AE were counted only once in the numerator and the most severe grade was recorded. Changes in QoL over time were assessed by a linear mixed-effects model.

The preplanned interim analyses have been conducted and have been published.[21] Observations were censored on August 15, 2023. Statistical analyses were performed by Prism (version 7.0), SPSS (version 24), and SAS (version 9.4).

### Role of funding source

The funding was used to support the follow-up of patients, data collection, data analyses, and consulting of statistical analysis.

## Results

### Baseline characteristics

From July 2019 to December 2021, a total of 132 patients were enrolled, of whom 12 were excluded due to ineligibility. Eligible patients were assigned to two groups to receive the IRd regimen (n = 60) or IDd regimen (n = 60) at the discretion of the physician (Fig. 1). All patients had a GA score ≥2, while 27.5% of them were also defined as frail according to the Mayo criterion. Details about CCI, ADL, and Mayo fragile scores are provided in Supplementary Data. Demographics and baseline clinical characteristics of the 120 eligible frail patients are presented in Table 1. The median age of patients was 71 years with a range of 65–88, of whom 38 (31.7%) patients were aged 75 years or older, 75 (62.5%) patients had ECOG score of 3 or 4, 48 (40.0%) patients had ISS stage of III disease, 34 (30.4%) of 112 patients with FISH detection had high-risk cytogenetic abnormalities [del 17p, t (4; 14) and t (14; 16)], and 20 (16.6%) patients had solitary bone plasmacytoma. The proportion of patient with ECOG score of 3 or 4, ISS stage of III, R-ISS stage of III, eGFR <30 mL/min/1.73 $m^2$, and paraplegia was significantly higher in the IDd group. Due to the limitations of lenalidomide, patients with insufficient renal function, thrombosis, eGFR <30 mL/min/1.73 $m^2$, or paraplegia were more likely to receive IDd regimen due to physician's initial treatment choices, which were not interfered with in this study. The unbalance might adversely affect the survival of the IDd group.

### Response

The ORR during induction was comparable in the IRd and IDd groups with a higher (stringent) complete response ([s]CR) in the IRd group (Table 2). The ORR was 82% (95% CI: 0.719–0.915) and 77% (95% CI: 0.660–0.834) in IRd and IDd groups, respectively, including 15 (25%) and 7 (12%) patients with a CR, 22 (37%) and 24 (40%) patients with a VGPR, and 12 (20%) and 15 (25%) patients with a PR. There was no statistical difference in efficacy between the two groups (Table 2). The depth of the clinical response increased during the treatment course for both IRd and IDd groups (Appendix Fig D1). Of the 22 patients who achieved CR, 18 (82%) were included in the minimal residual disease (MRD) analysis and 11 (50%) were MRD-negative.

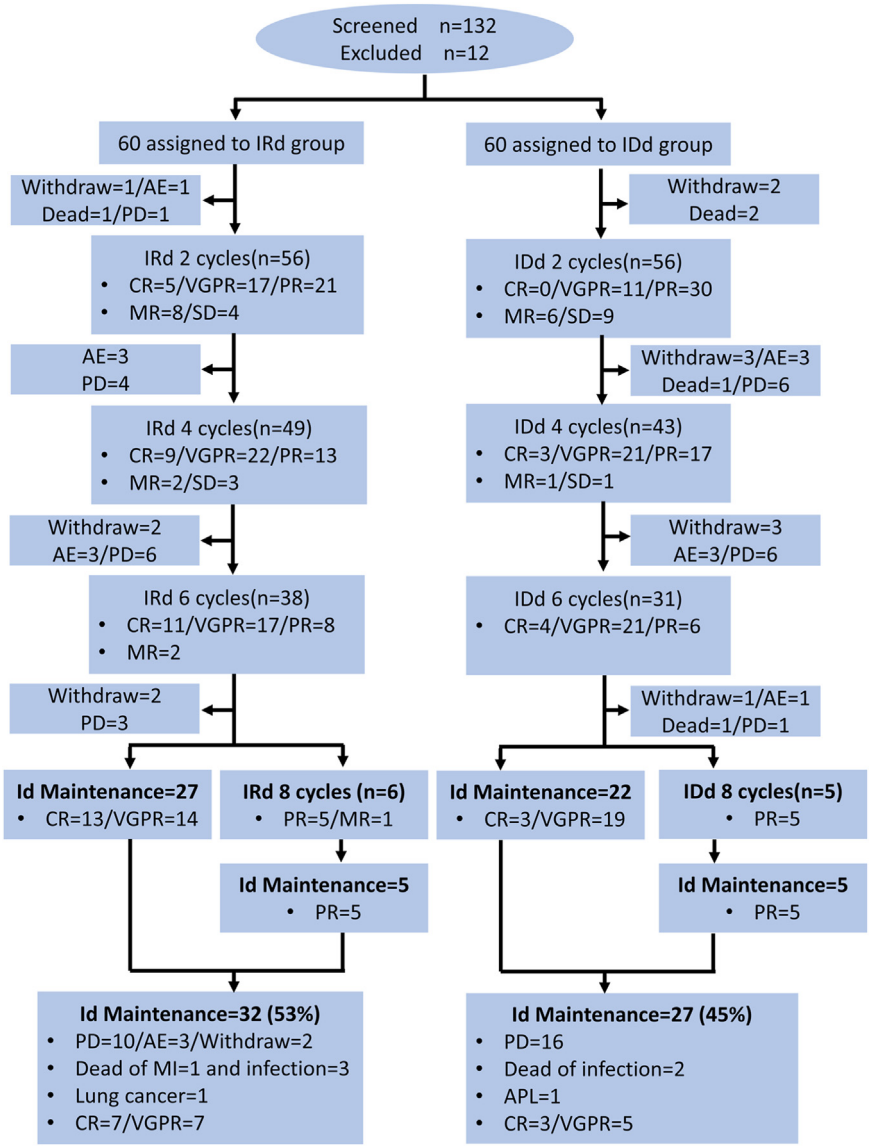


***Fig. 1:*** Diagram of the number of frail patients participating in the present study, the flow-through of the induction phase, the timing, and the rationale of treatment discontinuation.

As this non-randomized concurrent controlled clinical trial was conducted based on the non-inferiority hypothesis that "IDd is not inferior to IRd", we tested the hypothesis by Newcombe-Wilson Score CI. The result showed that the ORR difference of IDd minus IRd is –5.36% (95% CI: –18.9% to 8.19%). As the lower limit of 95% CI was less than –10% defined in the hypothesis, the non-inferiority assumption of this study was not held. Moreover, zero was included in the range of 95% CI which meant the IDd regimen was neither inferior nor non-inferior to the IRd regimen. The sensitivity analyses showed the (Appendix D2) variables with statistically significant differences between the two groups in baseline characteristics had no effect on the ORR of the two groups.

## Survival

After a median follow-up of 34.3 months (95% CI: 31.2–37.4), 38 (63%) patients in the IRd group and 50 (83%) patients in the IDd group had PFS events. Of the 38 patients in the IRd group, 10 (26%) were deaths (9 due to infection including 3 of COVID-19, the other one due to myocardial infarction) and 28 (74%) were disease progression events. Of the 50 patients who had PFS events in the IDd group, 13 (26%) PFS events were death (7 due to infection, 1 due to myocardial

| Parameter | Total (N = 120) | IRd (N = 60) | IDd (N = 60) | P value[b] |
|---|---|---|---|---|
| Age, years | 71 (65–88) | 70 (65–88) | 72 (65–88) | 0.956 |
| ≥75 | 38 (32%) | 19 (32%) | 19 (32%) | |
| Male/Female | 66/54 | 31/29 | 35/25 | 0.665 |
| ECOG score | | | | **0.003** |
| 1–2 | 45 (38%) | 26 (43%) | 19 (32%) | |
| 3–4 | 75 (63%) | 34 (57%) | 41 (68%) | |
| M protein subtype | | | | 0.682 |
| IgG/IgA/IgD | 61/33/3 | 33/16/0 | 28/17/3 | |
| κ/λ/non-secreting | 6/15/2 | 4/7/0 | 2/8/2 | |
| ISS stage | | | | **0.003** |
| Stage I | 24 | 16 | 8 | |
| Stage II | 48 | 26 | 22 | |
| Stage III | 48 | 18 | 30 | |
| R-ISS stage[a] | | | | **0.023** |
| Stage I | 16 | 11 | 5 | |
| Stage II | 79 | 37 | 42 | |
| Stage III | 17 | 4 | 13 | |
| Creatinine, μmol/l | 80 (21–740) | 80 (21–488) | 80 (44–740) | 0.227 |
| eGFR (mL/min) | 76 (8.5–134) | 75 (10–134) | 76 (9–108) | 0.338 |
| <30 mL/min/1.73 $m^2$ | 13 (11%) | 2 (3%) | 11 (18%) | **0.005** |
| Calcium, mmol/l | 2.27 (1.64–3.87) | 2.32 (1.85–3.87) | 2.20 (1.64–3.35) | 0.091 |
| Hemoglobin, g/L | 103 (43–149) | 102 (55–149) | 104 (43–149) | 0.924 |
| LDH, IU/L | 173 (59–3902) | 173 (79–446) | 172 (59–3902) | 0.706 |
| β2-microgloblin, mg/L | 4.33 (1.64–31.1) | 4.17 (1.69–27.4) | 5.2 (1.64–31.1) | 0.065 |
| Albumin, g/L | 36 (19–54) | 36 (20–54) | 35 (19–50) | 0.439 |
| NT-proBNP. pg/mL | 254 (10–6874) | 146 (25–3069) | 306 (10–6874) | 0.114 |
| Bone marrow plasma cells (%) | 25 (0–98) | 26 (1–80) | 24 (0–98) | 0.896 |
| [a]FISH (n = 112, IRD = 52) | | | | |
| Amp 1q21/Gain 1q21 | 47 (42%)/38 (34%) | 29 (56%)/19 (37%) | 18 (30%)/19 (32%) | 0.633 |
| del17p | 11 (10%) | 7 (14%) | 4 (7%) | 0.242 |
| t (4; 14) | 20 (18%) | 12 (24%) | 8 (13%) | 0.195 |
| t (14; 16) | 3 (3%) | 1 (2%) | 2 (3%) | 0.636 |
| Solitary bone plasmacytoma | 20 (17%) | 8 (13%) | 12 (20%) | 0.329 |
| Paraplegia | 6 (5%) | 1 (2%) | 6 (10%) | **0.012** |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; FISH, Fluorescence in situ hybridization; IDd, ixazomib/pegylated liposomal doxorubicin/dexamethasone; Ig, immunoglobulin; IRd, ixazomib/lenalidomide/dexamethasone; ISS, international staging system; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-B type natriuretic peptide; R-ISS, revised international staging system. [a]The FISH was undetected in 8 patients who received IRd treatment and 1 patient received IDd as no clonal plasma cells in bone marrow or no enough samples. [b]The P value represented the comparison of the IRd and IDd groups. The bold is represented of significance between two groups with a P value <0.05.

***Table 1:*** **The baseline characteristics of older NDMM patients.**

infarction, 6 due to treatment discontinuation of toxicity or withdrawal) and 37 (74%) PFS events were disease progression events. The median PFS for all patients was 18.5 months (95% CI: 15.4–21.6) (Fig. 2A), and 21.6 months (95% CI: 20.0–23.2) and 13.9 months (95% CI: 7.7–20.1) in the IRd and IDd groups, respectively (Fig. 2B). The PFS was significantly longer in the IRd group compared with that of the IDd group (P = 0.0097). The prespecified subgroup analyses of PFS are shown in Fig. 3. Male, age less than 75 years, ISS II, extramedullary plasmacytoma (EMP), Amp 1q21, no del 17p, not (4; 14) and standard-risk patients had longer PFS with the IRd regimen compared with the IDd regimen.

Fifty-three (44%) patients died during a median follow-up of 34.3 months, of whom 20 (33%) were in the IRd group and 33 (55%) were in the IDd group. Four patients died within 60 days from treatment initiation, all due to infection. The cause of death and characteristics stratified by survival status are listed in Appendix F. The relapse mortality was 18% (11/60) and 32% (19/60), while non-relapse mortality was 15% (9/60) and 23% (14/60) for IRd and IDd groups respectively. The median OS for all patients was 42.3 months (Fig. 2C), with not reached in the IRd group and 29.2 months (95% CI: 17.4–20.1) in the IDd group (Fig. 2D). The OS was significantly longer in the IRd group compared with the IDd group (P = 0.0039). As

| Response status | IRd (N = 60)[a] | IDd (N = 60)[a] | P value |
|---|---|---|---|
| ORR (≥PR), No. (%) | 49 (82%) | 46 (77%) | 0.580 |
| (s)CR | 15 (25%) | 7 (12%) | 0.079 |
| VGPR | 22 (37%) | 24 (40%) | 0.302 |
| PR | 12 (20%) | 15 (25%) | 0.878 |
| MR, No. (%) | 4 (7%) | 3 (5%) | 0.715 |
| SD, No. (%) | 3 (5%) | 7 (12%) | 0.097 |

Abbreviations: IDd, ixazomib/pegylated liposomal doxorubicin/dexamethasone; IRd, ixazomib/lenalidomide/dexamethasone; MR, minimal response; ORR, overall response rate; PR, partial response (s)CR (stringent) complete response; SD, stable disease; VGPR, very good partial response. [a]In the IRd group, four patients did not completed two cycles due to early death within 1 month (one patient), withdrawal (one patient), adverse events (one patient), and disease progression (one patient), so they were not evaluated for response. In the IDd group, 4 patients were not evaluated for response because of early death within 1 month (three patients) and study drug withdrawal (one patient).

*Table 2:* **Best response of treatment.**

shown in Fig. 4, the prespecified subgroup analyses indicated male, age >75 years, eGFR ≤60 mL/min/1.73 $m^2$, ISS II, non-IgG type, EMP, no del 17p, not (4; 14) and standard-risk patients had longer OS with the IRd regimen compared with the IDd regimen.

### Safety and tolerability

The patient flow-through of the study is summarized in Fig. 1. There were 28 patients discontinued treatment with IRd and 33 discontinued treatment with IDd before the initiation of the maintenance therapy. In the IRd group, 15 (25%) patients relapsed or were refractory, 1 (2%) died of infection, 7 (12%) had toxicity, and 5 (8%) did not comply with the study treatment. In the IDd group, 13 (22%) patients relapsed, 4 (7%) died of infection, 7 (12%) had toxicity, and 9 (15%) did not comply with the study treatment.

In the IRd group, the median RDI (interquartile range [IQR]) of the induction treatment was 0.87 (0.74–0.93) for ixazomib, 0.89 (0.77–0.93) for lenalidomide, and 0.88 (0.76–0.93) for dexamethasone. In the IDd group, the median RDI (IQR) was 0.82 (0.72–0.90) for ixazomib, 0.82 (0.70–0.89) for liposomal doxorubicin, and 0.82 (0.72–0.89) for dexamethasone. Ixazomib dose reduction was reported in 2 (3%) patients in the IRd group and 9 (15%) patients in the IDd group, which was related to infections, gastrointestinal toxicity, or peripheral neuropathy (PNP) (Supplementary Data). Lenalidomide dose reductions occurred in 4 (7%) patients in the IRd group. Dose withholds of dexamethasone was infrequently observed (Supplementary Data).

Thirty-two (53%) and 27 (45%) patients started maintenance treatment in the IRd and IDd groups, respectively. After a median follow-up of 26.3 months (95% CI: 18.5–34.2) from the start of the maintenance treatment in the IRd group, 18 patients (56%) discontinued therapy due to progression disease (PD) (10 patients), toxicity (3 patients), second onset of cancer (1 patient with lung cancer), sudden death (1 for myocardial infarction and 1 for car accident), and withdraw (2 patient). After a median follow-up of 21.7 months (95% CI: 19.3–24.0) from the start of the maintenance treatment in the IDd group, 19 (70%) patients discontinued therapy due to PD (16 patients), infection (2 patients),

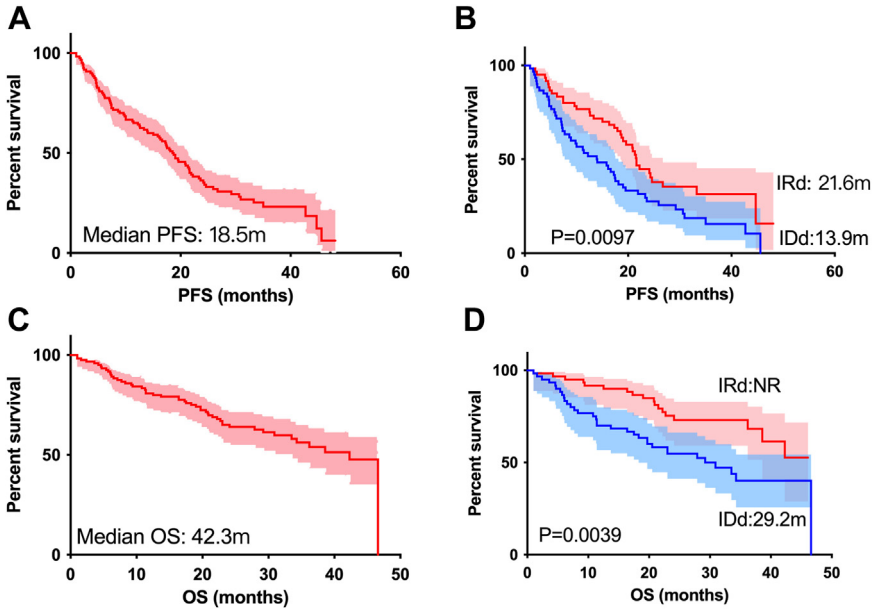


*Fig. 2:* Progression-free survival (PFS) and overall survival (OS). Kaplan–Meier estimates of PFS for all patients (A) and subgroup patients (B), OS for all patients (C) and subgroup patients (D). The P value shows that there is a statistical difference between IRd and IDd groups in both PFS (B) and OS (D).

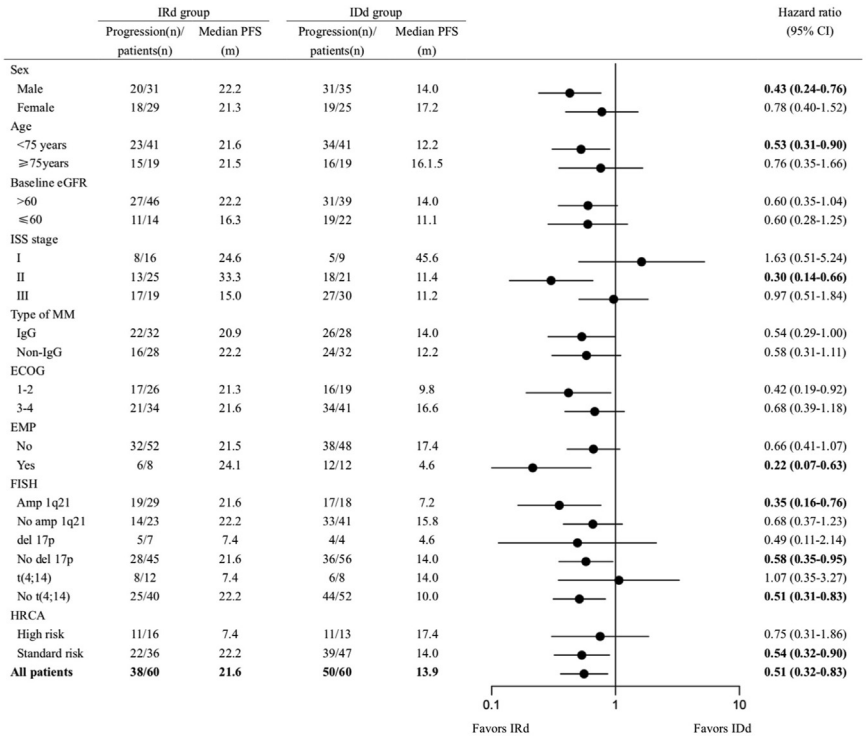


***Fig. 3:*** Prespecified subgroup analysis of progression-free survival (PFS) in the intent-to-treat population. ECOG, Eastern Cooperative Oncology Group. EMP, extramedullary plasmacytoma. FISH, fluorescence in situ hybridization. HRCA, high-risk cytogenetic abnormalities. Hazard ratios and 95% CIs were calculated from an unstratified Cox proportional hazards model with treatment as the sole explanatory variable.

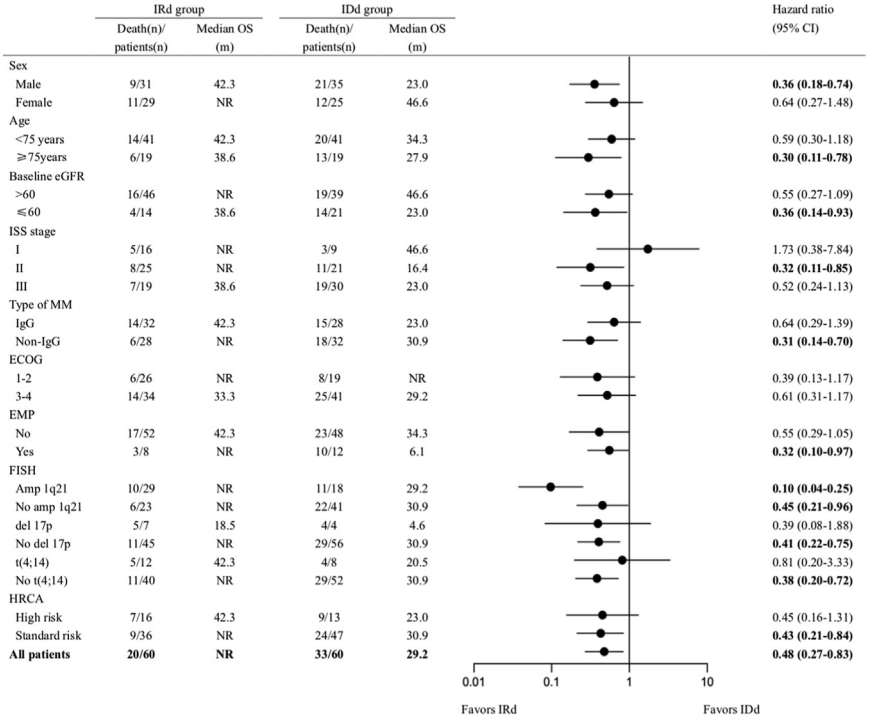


***Fig. 4:*** Prespecified subgroup analysis of overall survival (OS) in the intent-to-treat population. ECOG, Eastern Cooperative Oncology Group. EMP, extramedullary plasmacytoma. FISH, fluorescence in situ hybridization. HRCA, high-risk cytogenetic abnormalities. Hazard ratios and 95% CIs were calculated from an unstratified Cox proportional hazards model with treatment as the sole explanatory variable.

and the second onset of cancer (1 patient with acute promyelocytic leukemia).

For patients who discontinued the study treatment due to relapse, subsequent therapies are summarized in Appendix Table G. In the IRd group, 28 patients relapsed, of whom 12 patients received second-line therapy. In the IDd group, 38 patients relapsed, of whom 34 patients received second-line therapy. Among the patients who received subsequent therapy, 11 (50%) patients in the IRd group and 9 (26%) patients in the IDd group received a daratumumab-containing regimen.

Cumulative ≥ Grade 3 hematological AEs were reported in 10/60 (17%) and 13/60 (22%) patients, whereas Grade ≥3 non-hematological AEs were reported in 14/60 (23%) and 21/60 (35%) patients of IRd and IDd groups, respectively (Table 3). The most common non-hematological Grade ≥3 AEs were infections (21%) and gastro-intestinal AEs (13%). Only 1 (1%) patient experienced PNP with Grade 3. Most patients received antiviral prophylaxis (88% in the IRd group and 96% in the IDd group), while no patient received antibiotic prophylaxis. Eleven (18%) patients in the IRd group and 15 (25%) patients in the IDd group experienced serious adverse events (SAEs), of which 4 SAEs resulted in non-treatment-related deaths.

### Quality of life

A total of 970 questionnaires were acquired from patients and the median number of questionnaires per patient was 9 (range: 1–33). The baseline QoL score was 76.6 (IQR: 50.0–83.3) for the IRd group and 67.2 (IQR: 16.6–83.3) for the IDd group. After 8 cycles of induction treatment, the scores of the IRd group and the IDd group gradually increased to 165.2 and 157.2, respectively. Improvement in the QoL during induction treatment was statistically significant ($P < 0.001$) and was already clinically relevant after induction Cycle 2; the improvement in the QoL further increased over time during subsequent induction cycles (Fig. 5).

## Discussion

In this prospective non-randomized clinical study specifically designed for frail, elderly Chinese patients defined by the IMWG frailty score, the oral proteasome

| | IRd (n = 60) | | | IDd (n = 60) | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 1–2 | Grade 3 | Grade 4 |
| Hematological AE | | | | | | |
| Anemia | 7 (11.7%) | 1 (1.7%) | 0 | 0 | 1 (1.7%) | 0 |
| Thrombocytopenia | 4 (6.7%) | 4 (6.7%) | 0 | 5 (8.3%) | 3 (5.0%) | 1 (1.7%) |
| Neutropenia | 6 (10.0%) | 2 (3.3%) | 2 (3.3%) | 4 (6.7%) | 2 (3.3%) | 0 |
| lymphopenia | 1 (1.7%) | 1 (1.7%) | 0 | 1 | 0 | 0 |
| Non-hematological AE | | | | | | |
| Diarrhea | 10 (16.7%) | 3 (5.0%) | 0 | 4 (6.7%) | 7 (11.7%) | 1 (1.7%) |
| Constipation | 2 (3.3%) | 0 | 0 | 1 (1.7%) | 0 | 0 |
| Abdominal distension | 2 (3.3%) | 0 | 0 | 1 (1.7%) | 1 (1.7%) | 0 |
| Nausea/vomit | 6 (10%) | 3 (5%) | 1 (1.7%) | 10 (16.7%) | 2 (3.3%) | 0 |
| Decreased appetite | 2 (3.3%) | 2 (3.3%) | 0 | 7 (11.7%) | 3 (5.0%) | 1 (1.7%) |
| Peripheral neuropathy | 5 (8.3%) | 0 | 0 | 0 | 1 (1.7%) | 0 |
| Fatigue | 5 (8.3%) | 0 | 0 | 1 (1.7%) | 0 | 0 |
| Pneumonia | 0 | 9 (15%) | | 0 | 4 (6.7%) | 2 (3.3%) |
| Arrhythmia | 0 | 0 | 0 | 0 | 1 (1.7%) | 0 |
| Cardiac insufficiency | 0 | 1 (1.7%) | 0 | 0 | 2 (3.3%) | 0 |
| Anaphylactic rash | 5 (8.3%) | 4 (6.7%) | 1 (1.7%) | 0 | 0 | 0 |
| Herpes zoster | 1 (1.7%) | 0 | 0 | 2 (3.3%) | 2 (3.3%) | 0 |
| Delirium | 1 (1.7%) | 0 | 0 | 0 | 0 | 0 |
| Cerebral infarction | – | – | 1 (1.7%) | – | – | 1 (1.7%) |
| Thromboembolic | 2 (3.3%) | 1 (1.7%) | 0 | 0 | 0 | 0 |
| Elevated liver enzymes | 2 (3.3%) | 0 | 0 | 0 | 0 | 0 |
| Dropsy | 2 (3.3%) | 1 (1.7%) | 0 | 0 | 0 | 0 |
| Other infections | 2 (3.3%) | 3 (5%) | 0 | 7 (11.7%) | 1 (1.7%) | 0 |
| Fever | 1 (1.7%) | 0 | 0 | 1 (1.7%) | 0 | 0 |
| Second primary malignancy | 0 | 2 (3.3%) | 0 | 0 | 1 (1.7%) | 0 |

Abbreviations: AE, adverse event; IDd, ixazomib/pegylated liposomal doxorubicin/dexamethasone; IRd, ixazomib/lenalidomide/dexamethasone.

*Table 3:* **Adverse events during treatment.**

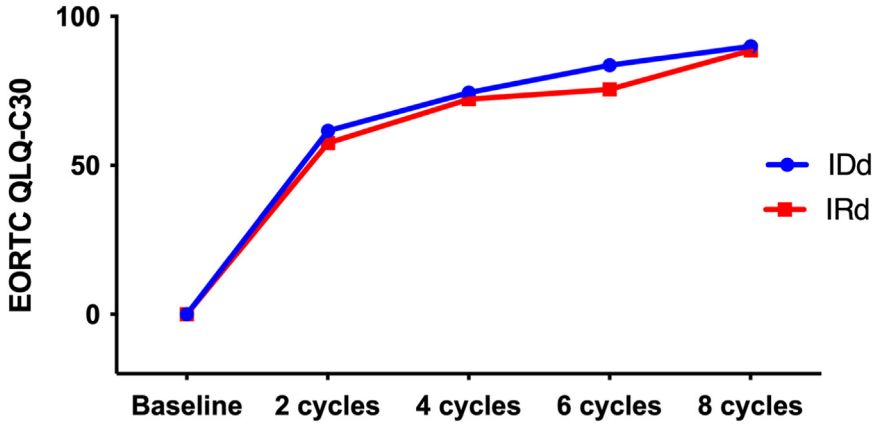


*Fig. 5:* Health-related quality of life (HRQOL) during induction. The estimated statistically significant changes in the global health status (GHS) and quality of life (QOL) over time from baseline until the end of induction cycle 8 in patients in IRd and IDd groups. The dotted horizontal lines were calculated as the score at this time point minus the baseline score. The P value represents the significant change in GHS or QOL over time in both the IRd and IDd groups assessed by ANOVA of repeated measurement data.

inhibitor and ixazomib-based regimens were investigated. After a median follow-up of 34.3 months, the ORR for the IRd and IDd groups was 82% and 77%, respectively, and a clinically relevant improvement of QoL was observed after 2 cycles of treatments. The ORR of the IDd group is neither inferior nor non-inferior to the IRd group, but the survival of the IDd group was shorter than that of the IRd group, indicating that this all-oral outpatient IRd regimen that improves the QoL over time with acceptable efficacy and fewer SAEs, is an option for geriatric NDMM patients.

With the current healthcare cost crisis around the world, ixazomib-based regimen has the advantage of being oral and administered in the outpatient setting. This convenient regimen also improved patient treatment compliance, particularly during the COVID-19 pandemic.[22] Although the RDI of ixazomib and lenalidomide was reduced due to complications and cycle delays, the ORR was still 82% and 77% for IRd and IDd groups, including 25% and 12% of CR, respectively. It is interesting to note the response in this study is comparable with other clinical trials of IRd regimens for transplant-ineligible NDMM patients (ORR: 74%–80%).[23,24] The response rate in this study is also similar to the response rate with the regimen of ixazomib combined with daratumumab followed by ixazomib maintenance in the HOVON-143 trial designed for frail NDMM patients (ORR of 77% and a CR rate of 8% post-induction).[7] However, the CR rates of this study were significantly lower than daratumumab-based regimens in post-hoc analysis for geriatric NDMM patients (44.2% for Dara-VMP and 43.6% for daratumumab/lenalidomide/dexamethasone [Dara-Rd]).[10,11] These results may be due to restrictive inclusion and exclusive criteria as well as the maintenance treatment of daratumumab.

Although ixazomib-based regimens had similar response, the PFS and OS did not substantially improve compared with other regimens in frail NDMM patients. In our study, the median PFS was 18.5 months for all patients, with 21.6 and 13.9 months in the IRd and IDd groups, respectively. The post-hoc analysis of frail NDMM patients showed that the combined regimens consisting of daratumumab achieved an impressive PFS of 36.4 months in Dara-VMP and NR in Dara-Rd regimens in MAIA study.[25–27] These clinical trials that were designed for non-frail patients excluded the most vulnerable groups, such as those with eGFR <30 mL/min/1.73 $m^2$, platelet count <50 × $10^9$/L, or ECOG >2 score. The difference in survival may also be partly treatment-related. However, the prospective trial of DID for frail NDMM defined by IMWG frailty score reported a PFS of 13.8 months, which was similar to this study.[7] Although the median age of NDMM patients in our cohort was younger than HOVON-143 (71 vs. 81), the population was equal in frailty because IMWG frailty score was used as evaluation criteria for both studies.[28] Patients in this study had more dependency on ADLs compared with HOVON-143 (Appendix Table E1). Therefore, further research is needed to demonstrate whether a daratumumab-based regimen could improve PFS in frail NDMM patients as strictly defined by IMWG frailty score.

It should be added that another reason for the shorter PFS may be a lower number of induction cycles, leading to early relapse. Patients achieved PR and above after 4 cycles in this study, and continued for 2 cycles of induction regimen, whereas other studies were designed for 9 cycles of DID in HOVON-143[7] and DVMP in ALCYONE[11] or continue DRd in MAIA until relapse.[10] We believe additional induction therapy may further improve the depth of response and prolong survival in this study. Given the toxicity and tolerance of the 3–4 drug used in the induction treatment, GA-score-based dose adjustment is currently under investigation

in the UK-MRA Myeloma XIV Trial (NCT03720041).[9] The adaptive dosing or reactive dosing and whether to prolong the course of treatment in geriatric NDMM patients remain to be elucidated in future research.

The subgroup analysis comparing IRd and IDd groups in PFS and OS demonstrated that frail NDMM patients benefited from the IRd regimen with comparable response, especially for patients without high-risk cytogenetic abnormalities (HRCA). Similar results were reported in the MAIA study, in which it was found that the DRd regimen could not improve the survival of patients with HRCA compared with the Rd regimen.[29] The regimen appropriate for frail NDMM patients with HRCA needs to be further explored. Unexpectedly, patients with renal dysfunction (eGFR $\leq$60 mL/min/1.73 $m^2$) and EMP did not gain survival benefit from the IDd regimen, these patients tended to use IDd regimen at diagnosis. Previous research reported that pegylated liposomal doxorubicin as an immunogenic cell death (ICD) inducing agent combined with ixazomib offered a chemo-immunotherapy treatment without AEs caused by anthracyclines.[30] The data from this study indicated that compared with the IRd group, frail NDMM patients in the IDd group had a lower response rate, a shorter survival, and more infections, which may lead to early death. For this vulnerable population, even the low dose and toxicity of chemotherapy agents should be used cautiously with more support.

In terms of safety, the proportion of patients with AEs and non-hematological AEs was 17% and 23% in the IRd group, and was 22% and 35% in the IDd group, respectively. The proportion of patients with Grade 3 or 4 AEs (19%) and non-hematological AEs (29%) observed in this study was comparable to that of EMN10 (47% and 37%, respectively), but was lower than that of the HOVON-143 trial (74% and 73%, respectively) and MAIA trial (DRd: 94.6% and 83.9%; Rd: 89.2% and 81.9%, respectively) analyzed in frail NDMM patients.[7,10,31] The younger age of the patients in this study could partly explain the difference observed with the latter two trials (71 vs. 81 vs. 77 years in this study, HOVON-143 study, and MAIA study, respectively), which led to less comorbidity. The regimen without daratumumab could also partly explain this difference. Pneumonia and diarrhea were the most commonly reported Grade 3 or higher SAEs in the IDd group. Different from the antibacterial prophylaxis of levofloxacin with or without co-trimoxazole used for the first 3 months of treatment in the DId group,[7] patients were only provided with valaciclovir for prophylaxis of herpes zoster. The IRd group had more neurotoxicity and psychiatric symptoms, which may be caused by lenalidomide. Thus, the use of intensive care, antibacterial pretreatment, and dosing adjustment of ixazomib and lenalidomide may reduce the incidence of Grade 3 or 4 AEs and early toxicity-related deaths.

The limitation of the study design as a non-randomized, concurrent, controlled clinical study resulted in bias in the baseline disease characteristics of the two regimen groups shown in Table 1. Although sensitivity analyses were conducted, the non-inferior hypothesis was unable to identify whether the ORR of the IDd regimen was inferior to IRd. This result may be due to a higher ORR setting in the study design than the actual value, resulting in a small sample size. Therefore, comparing PFS and OS in the subgroups should be interpreted with caution. The difference in subsequent therapy between the two groups may also affect the analysis of OS. The results of non-inferior hypothesis test also need to be validated by subsequent large-scale, high-quality, multi-center randomized clinical trials to avoid confounding factors and improve power. Otherwise, both the IMWG frail score and Mayo score were used as inclusion criteria in this study, resulting in 100% and 27.5% frail respectively. Although the Mayo score was only an objective index, it lacks assessment of function and comorbidities and is limited to screening for the potentially frail MM patients.

Although there was no statistical improvement in the IRd group compared with the IDd group, the IRd group had longer survival in both PFS and OS than the IDd group. In conclusion, this study was designed specifically for frail NDMM patients strictly defined by IMWG frailty score or MAYO score, indicating an all-oral induction regimen IRd followed by maintenance Id had a higher response rate and improved the QoL with relatively low toxicity. This is also the application of the IMWG frailty score in clinical practice and trial settings to accurately evaluate the treatment and outcomes in frail MM patients. Greater access to affordable treatment and better supportive care may improve survival and QoL for vulnerable myeloma patients.

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**All authors read and approved the final version of the manuscript**.

#### Data sharing statement

The data supporting this study's findings are not publicly available due to containing information that could compromise the privacy of research participants; nevertheless, some data are available from Li Bao. Email: baoli@jst-hosp.com.cn.

#### Declaration of interests

The authors have no conflict of interest.

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**Appendix A. Supplementary data**

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102431.

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