Isatuximab plus bortezomib, lenalidomide, and dexamethasone for transplant-ineligible newly diagnosed multiple myeloma patients: a frailty subgroup analysis of the IMROZ trial

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Abstract

Patients with multiple myeloma (MM) meeting frailty criteria have worse outcomes than those identified as non-frail. Here, we present a *post hoc* subgroup analysis of IMROZ, a global, phase III, open-label study investigating isatuximab (Isa) with bortezomib, lenalidomide, and dexamethasone (VRd) followed by Isa-Rd (N=265) *versus* VRd followed by Rd (N=181) in newly diagnosed transplant-ineligible MM (Ti NDMM) patients using the simplified International Myeloma Working Group (sIMWG) frailty score. Although patients aged >80 years were excluded, there was no exclusion for patients meeting frailty criteria. All patients received standard VRd/Rd dosing; Isa-VRd patients received intravenous Isa (cycle 1, 10 mg/kg once weekly; cycles 2-17, once every 2 weeks; subsequent cycles, once every 4 weeks). Patients with a frailty score of 0/1 were considered non-frail; scores ≥2 were frail. Using this scoring, 26.7% of patients were frail (26.0% Isa-VRd; 27.6% VRd), and 72.0% non-frail (72.8% Isa-VRd; 70.7% VRd). After a median follow-up of 59.7 months, Isa-VRd significantly improved progression-free survival *versus* VRd in frail patients (hazard ratio [HR] =0.518; 95% confidence interval [CI]: 0.294-0.912; *P*=0.0227) and non-frail patients (HR=0.615; 95% CI: 0.419-0.903; *P*=0.0131). Significantly more frail patients receiving Isa-VRd than VRd achieved minimal residual disease negativity and complete response (odds ratio=3.459; 95% CI: 1.495-8.006; *P*=0.0030 at 10^{-5} by next-generation sequencing). Rates of treatment-emergent adverse events leading to definitive discontinuation were similar between both arms regardless of frailty status. This *post hoc* subgroup analysis of the IMROZ trial demonstrated that Isa-VRd is an effective option with a manageable safety profile for frail patients with Ti NDMM (*clinicaltrials gov. Identifier: NCT03319667*).

Introduction

Isatuximab (Isa) is a monoclonal antibody that targets a specific epitope of CD38, induces myeloma cell death via multiple mechanisms, and is approved in several countries in combination with pomalidomide and dexamethasone, and carfilzomib and dexamethasone, for the treatment of relapsed/refractory multiple myeloma (RRMM) based on the phase III ICARIA-MM and IKEMA trials.[1-8] Recently, in the phase III IMROZ study (*clinicaltrials gov. Identifier: NCT03319667*), Isa in combination with bortezomib, lenalidomide, and dexamethasone (VRd) significantly improved progression-free survival (PFS) and induced deep and sustained responses in transplant-ineligible (Ti) newly diagnosed multiple myeloma (NDMM) patients aged ≤80 years.[9] Isa is now approved in numerous geographies in

combination with VRd for Ti NDMM patients on the basis of the IMROZ study.[10-12] However, the use of quadruplet therapies incorporating an anti-CD38 monoclonal antibody with a standard-of-care backbone regimen such as VRd has not been explored in frail patients.[13,14]

Frail myeloma patients do not tolerate MM treatment regimens as well as fit patients, making them harder to treat. These patients have higher rates of dose reductions and treatment discontinuations, which can lead to shorter PFS and overall survival (OS).[15] Frail patients have been shown to have worse outcomes than non-frail patients, and the current treatment recommendations for these patients are triplet regimens, such as VRd.[14,16] The criteria to identify frail patients have evolved over time; while frailty was previously determined based on chronologic age, research has demonstrated that age alone does not accurately capture the complexities of frailty.[15,17] Other factors, such as comorbidities and functional impairment, have thus been incorporated into frailty assessments.[15,17] However, there is no consensus on how to measure frailty, and different frailty indexes impact the prevalence of frailty due to the different measures incorporated.[18]

Several measures have been developed to assess frailty; one of them is the simplified International Myeloma Working Group (sIMWG) frailty score, which has been validated with data from numerous clinical trials.[19-21] The sIMWG frailty score is a modification of the IMWG frailty score and incorporates age, Eastern Cooperative Oncology Group performance status (ECOG PS) and the Charlson Comorbidity Index (CCI).[20] However, there is no consensus on the variables with which to measure frailty or which frailty score to use within clinical trials.

Here, we present a *post hoc* subgroup analysis of IMROZ investigating Isa-VRd followed by Isa-Rd *versus* VRd followed by Rd across frail and non-frail subgroups using the sIMWG frailty score.[20] This is the first analysis assessing the tolerability of the standard of care VRd with or without an anti-CD38 monoclonal antibody followed by Isa-Rd or Rd maintenance in frail Ti patients with NDMM.

Methods

Study design and patients

IMROZ (*clinicaltrials gov. Identifier: NCT03319667*) is a global, phase III, open-label study investigating an induction phase with Isa-VRd followed by a continuous treatment phase with Isa-Rd (N=265) *versus* VRd followed by Rd (N=181) in Ti NDMM patients aged ≤80 years. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The independent ethics committee or institutional review board at each site approved the trial protocol, and all patients provided written informed consent. The complete methodology of IMROZ has been previously described.[9] Briefly, patients with Ti NDMM who were aged ≤80 years were included. Patients with an ECOG PS >2 or estimated glomerular filtration rate <30 mL/min/1.73 m^2 were excluded.

Randomization and treatment

Patients (N=446) were randomized 3:2 to Isa-VRd followed by Isa-Rd, or VRd followed by Rd. Randomization was stratified according to country (not China *vs*. China), age (<70 *vs*. ≥70 years), and Revised International Staging System disease stage (stage I or II *vs*. III *vs*. not classified).

During induction, all patients received VRd, consisting of subcutaneous bortezomib (1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32), oral lenalidomide (25 mg/day) on days 1-14 and days 22-35, and oral or intravenous dexamethasone (20 mg/day on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33). Patients in the Isa-VRd arm received intravenous Isa (10 mg/kg once weekly in cycle 1 and every 2 weeks in subsequent cycles).

During continuous treatment, all patients received lenalidomide (25 mg/day) and dexamethasone (20 mg once weekly). Patients in the Isa-VRd arm received intravenous Isa (10 mg/kg every 2 weeks, every 4 weeks from cycle 18 onwards).

Patients were recommended to receive antibacterial prophylaxis, consisting of either oral cotrimoxazole or oral quinolone. This should start no later than day 1 of study treatment and continue until 6 weeks after the induction treatment period.

Frailty evaluation

Using the sIMWG frailty score, which has been validated in numerous publications,[19-21] frailty scores at baseline were calculated based on age (≤75 *vs*. 76-80 years), modified CCI score using medical history at baseline, and ECOG PS.[22-24] Patients with a frailty score of 0/1 were considered non-frail, and scores ≥2 were counted as frail.

Assessments and statistical analyses

The primary endpoint was PFS, defined as time from randomization to the first documented disease progression or death, whichever occurred first. Key secondary endpoints included complete response or better (≥CR) and minimal residual disease negativity (MRD-) in patients with CR. MRD was assessed by central laboratories with next-generation sequencing in bone marrow samples from patients who achieved ≥CR at a threshold of 10^{-5}. M-protein quantification was performed at screening, at cycle 1 day 1 prior to study treatment administration, on day 1 of every remaining cycle during treatment until progression or discontinuation due to other reason, and at the end of treatment visit and during the follow-up period. For patients with suspected isatuximab interference on serum immunofixation electrophoresis, the Sebia Hydrashift 2/4 isatuximab IFE test was used by the central laboratory to specifically measure endogenous M-protein. Participants that met all other IMWG criteria for CR and for whom negative immunofixation was confirmed after using the Hydrashift isatuximab test, were considered complete responders.

Efficacy endpoints were assessed based on the intention-to-treat (ITT) population (all randomized patients). Safety was assessed in the safety population (patients who received ≥1 dose of study treatment). *Post hoc* analyses were performed by patient frailty status. PFS and OS were evaluated using the Kaplan-Meier method, and hazard ratios along with 95% confidence intervals (CI) were estimated using a Cox proportional hazards model. Stratification variables included age (<70 *vs.* ≥70 years) and Revised International Staging System disease stage (I or II *vs.* III or not classified). Odds ratios (OR) were determined using an unconditional maximum likelihood estimation. *P* values based on comparisons of 2x2 contingency tables were calculated using χ^2 or Fisher exact tests. Adverse events (AE) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-C30). All analyses were performed using SAS version 9.4 and Viya.

Results

Patient disposition and treatment

Using the sIMWG frailty score, 119 (26.7%) patients were

Table 1. Baseline patient characteristics in frail and non-frail subgroups in the intent to treat population.

Characteristic	Frail, N=119		Non-frail, N=321	
	Isa-VRd, N=69	VRd, N=50	Isa-VRd, N=193	VRd, N=128
Age in years, median (range)	75 (65-80)	76 (59-80)	71 (60-80)	71 (55-80)
Age in years by category, N (%)				
<65	0	2 (4.0)	8 (4.2)	6 (4.7)
65-74	31 (44.9)	17 (34.0)	154 (79.8)	96 (75.0)
≥75	38 (55.1)	31 (62.0)	31 (16.1)	26 (20.3)
ECOG PS, N (%)				
0	3 (4.4)	3 (6.0)	119 (61.7)	74 (57.8)
1	37 (53.6)	28 (56.0)	74 (38.3)	54 (42.2)
2	29 (42.0)	19 (38.0)	0	0
ISS stage at study entry, N (%)				
I	16 (23.2)	12 (24.0)	72 (37.3)	35 (27.3)
II	31 (44.9)	22 (44.0)	76 (39.4)	56 (43.8)
III	21 (30.4)	16 (32.0)	45 (23.2)	36 (28.1)
Unknown	1 (1.5)	0	0	1 (0.8)
Renal impairment at baseline, N (%)				
eGFR ≥15-<30 mL/min/1.73 m^2	1 (1.5)	2 (4.0)	5 (2.6)	2 (1.6)
eGFR <50 mL/min/1.73 m^2	11 (15.9)	11 (22.0)	26 (13.5)	20 (15.6)
Cytogenetic risk* at study entry, N (%)				
High	10 (14.5)	10 (20.0)	30 (15.5)	24 (18.8)
Standard	53 (76.8)	40 (80.0)	151 (78.2)	97 (75.8)
Unknown	6 (8.7)	0	12 (6.2)	7 (5.5)
Gain 1q21 at baseline, N (%)				
Present	12 (17.4)	16 (32.0)	50 (25.9)	29 (22.7)
Absent	52 (75.4)	33 (66.0)	130 (67.4)	91 (71.1)
Unknown	5 (7.3)	1 (2.0)	13 (6.7)	8 (6.3)
Amp 1q21 at baseline, N (%)				
Present	13 (18.8)	4 (8.0)	18 (9.3)	19 (14.8)
Absent	49 (71.0)	44 (88.0)	161 (83.4)	98 (76.6)
Unknown	7 (10.1)	2 (4.0)	14 (7.3)	11 (8.6)
Plasmacytoma at study entry, N (%)	15 (21.7)	12 (24.0)	34 (17.6)	21 (16.4)
Frailty score, N (%)				
2	55 (79.7)	44 (88.0)	-	-
3	12 (17.4)	5 (10.0)	-	-
4	2 (2.9)	1 (2.0)	-	-

*High risk was defined as presence of del(17p), t(4;14), or t(14;16) as detected by fluorescence *in situ* hybridization. Cytogenetics was performed by a central laboratory with a cutoff of 50% for del(17p) and 30% for t(4;14) or t(14;16). Amp: amplification; d: dexamethasone; ECOG PS: Eastern Cooperative Oncology Group performance status; eGFR: estimated glomerular filtration rate; ISS: International Staging System; Isa: isatuximab; ITT: intention-to-treat; R: lenalidomide; V: bortezomib.

classified as frail (69 [26.0%] Isa-VRd; 50 [27.6%] VRd), and 321 (72.0%) were classified as non-frail (193 [72.8%] Isa-VRd; 128 [70.7%] VRd). Six (1.4%) patients had missing data due to lack of medical history for the modified CCI score and were excluded from the frailty analysis. A breakdown of the variables contributing to the frailty score can be found in *Online Supplementary Table S1*. The range of scores in frail patients in both Isa-VRd and VRd arms was 2-4, and most patients classified as frail (83.2%) had a frailty score of 2 (Table 1).

At the time of data cutoff, for both the Isa-VRd and VRd cohorts, the proportion of patients who discontinued treatment was highest in the frail subgroup; 50 (72.5%) and 42 (84.0%) Isa-VRd and VRd patients, respectively, in the frail subgroup had discontinued treatment (*Online Supplementary Table S2*). Twenty-two (31.9%) and 20 (40.0%) of these discontinuations, respectively, were due to AE, while 16 (23.2%) and 17 (34.0%) were due to disease progression. In the non-frail subgroup, 89 (46.1%) and 93 (72.7%) Isa-VRd and VRd patients, respectively, had discontinued treatment at the time of data cutoff. Discontinuations due to AE occurred in 38 (19.7%) and 30 (23.4%) Isa-VRd and VRd patients, respectively, while 21 (10.9%) and 48 (37.5%) patients discontinued treatment due to disease progression. Baseline patient characteristics can be seen in Table 1. Frail patients had a median age of 75 (Isa-VRd) and 76 years (VRd), while non-frail patients had a median age of 71 years in both arms. More frail patients than non-frail patients had ISS stage III disease and renal dysfunction (estimated glomerular filtration rate <50 mL/min/1.73m^2); ECOG PS 2 was observed only amongst frail patients. The distribution of high-risk cytogenetic patients was comparable between the two subgroups.

Duration of exposure

The median treatment duration was 31.2 months and 19.2 months in frail Isa-VRd and VRd patients, respectively, *versus* 55.2 months and 38.1 months in non-frail patients. The median relative dose intensity (RDI) for Isa was 92.3% (interquartile range [IQR], 86.6-97.2) in the frail subgroup and 94.0% (IQR, 90.1-97.1) in the non-frail subgroup. The median RDI for bortezomib was 91.2% (Isa-VRd; IQR, 78.6-97.7) and 85.2% (VRd; IQR, 74.996.8) in frail patients, compared with 89.8% (Isa-VRd; IQR, 75.3-97.4) and 87.0% (VRd; IQR, 74.3-97.0) in non-frail patients. The median RDI for lenalidomide was 81.9% (Isa-VRd; IQR, 57.7-93.8) and 87.6% (VRd; IQR, 65.2-96.2) in frail patients *versus* 76.3% (Isa-VRd; IQR, 56.5-95.4) and 81.1% (VRd; IQR, 60.6-94.5) in non-frail patients. For dexamethasone, the median RDI was 84.5% (Isa-VRd; IQR, 59.2-94.1) and 81.9% (VRd; IQR, 67.6-95.8) in frail patients and 79.6% (Isa-VRd; IQR, 54.1-94.2) and 79.2% (VRd; IQR, 60.4-94.4) in non-frail patients.

Efficacy

Efficacy assessment was based on central review. After a median follow-up of 59.7 months, the PFS benefit of Isa-VRd *versus* VRd was maintained in frail (not reached *vs*. 28.91 months; HR=0.518; 95% CI: 0.294-0.912; *P*=0.0227) and non-frail (not reached *vs*. 59.70 months; HR=0.615; 95% CI: 0.419-0.903; *P*=0.0131; Figure 1) patients. In frail patients, the 60-month PFS rate was 52.6% in Isa-VRd patients compared with 36.2% in VRd patients. In non-frail patients, the 60-month PFS rate was 66.6% and 48.8% in Isa-VRd and VRd patients, respectively. When comparing within treatment arms, frail patients had a significantly worse PFS compared with non-frail patients (Isa-VRd:

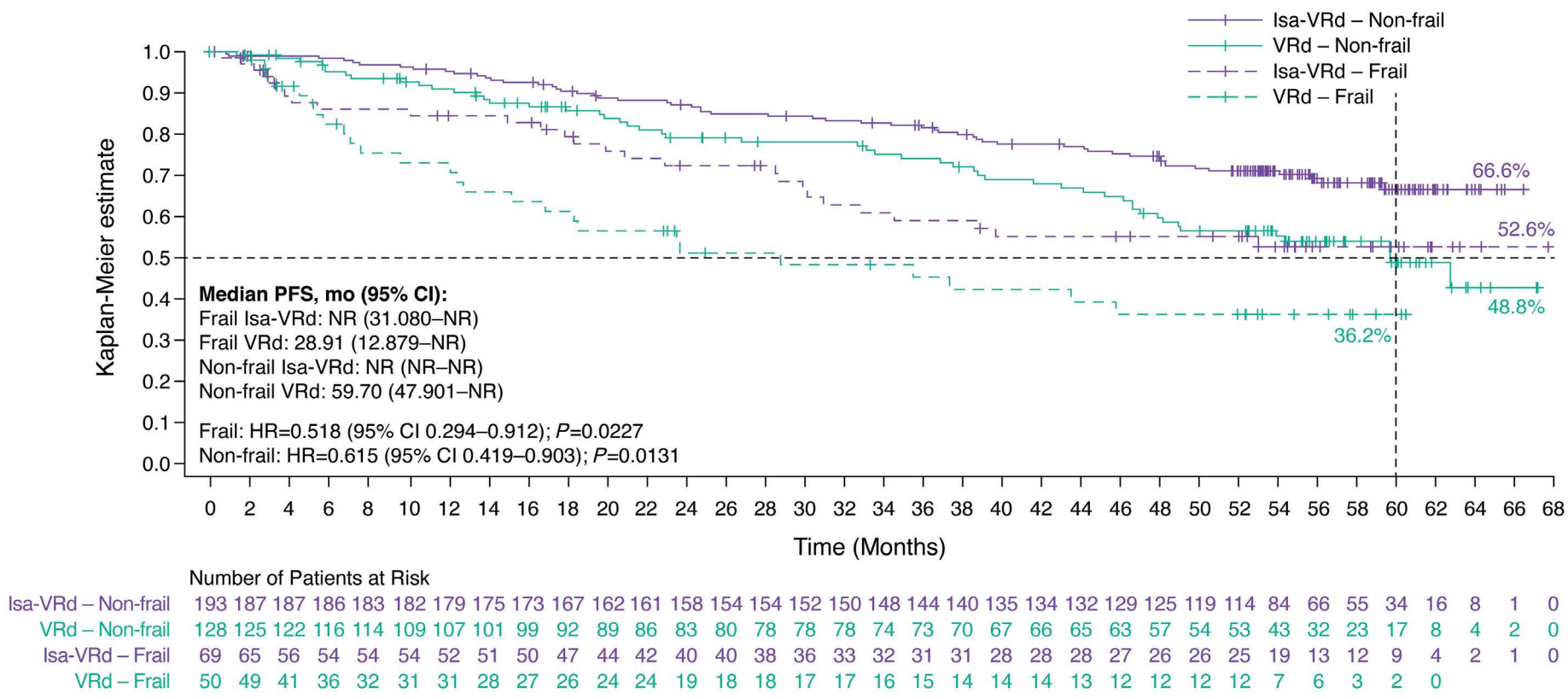
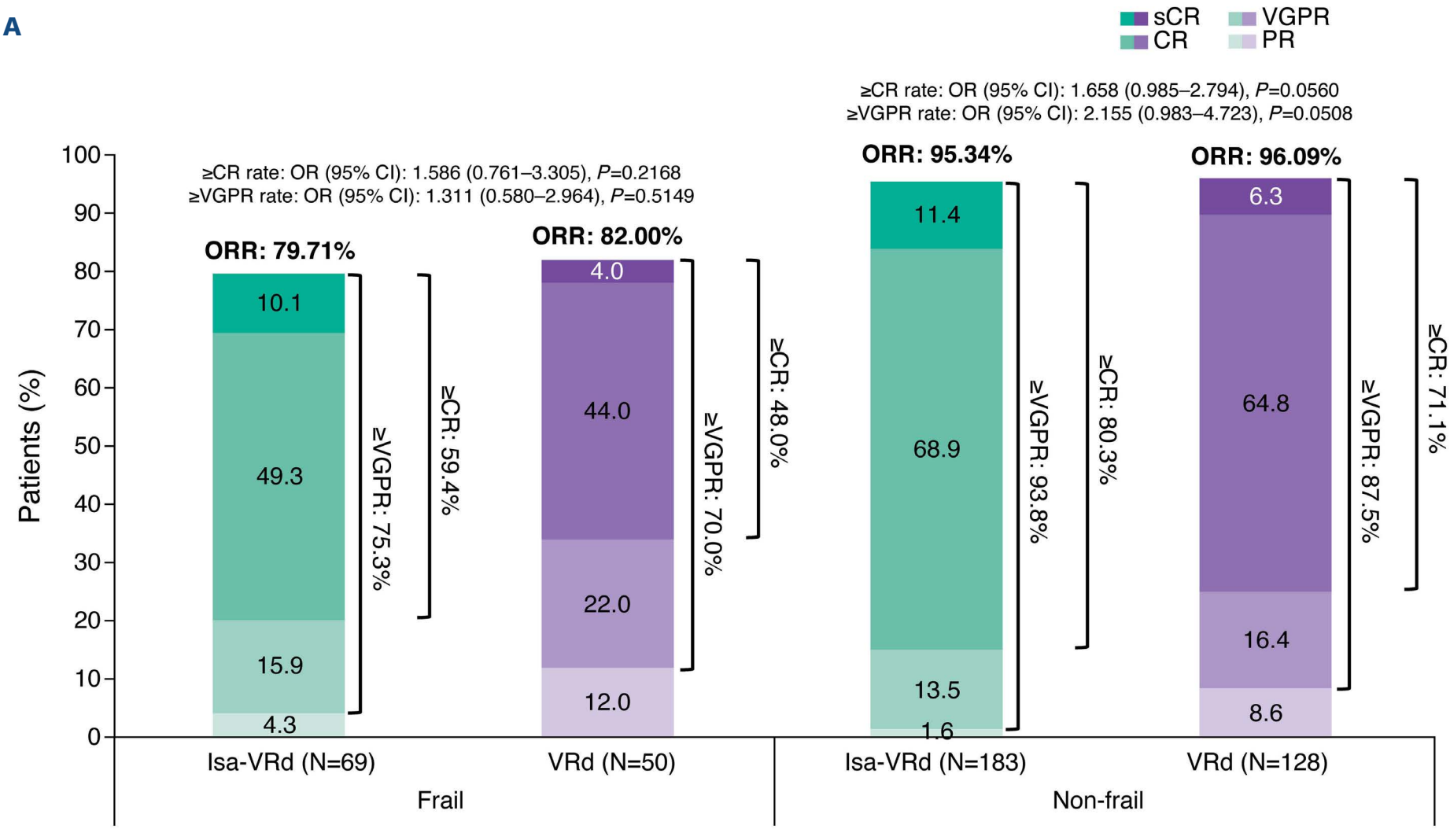


Figure 1. Kaplan-Meier curves of progression-free survival for the frail and non-frail subgroups. CI: confidence interval; d: dexamethasone; HR: hazard ratio; Isa: isatuximab; R: lenalidomide; V: bortezomib; NR: not reached; mo: months; PFS: progression-free survival.

A



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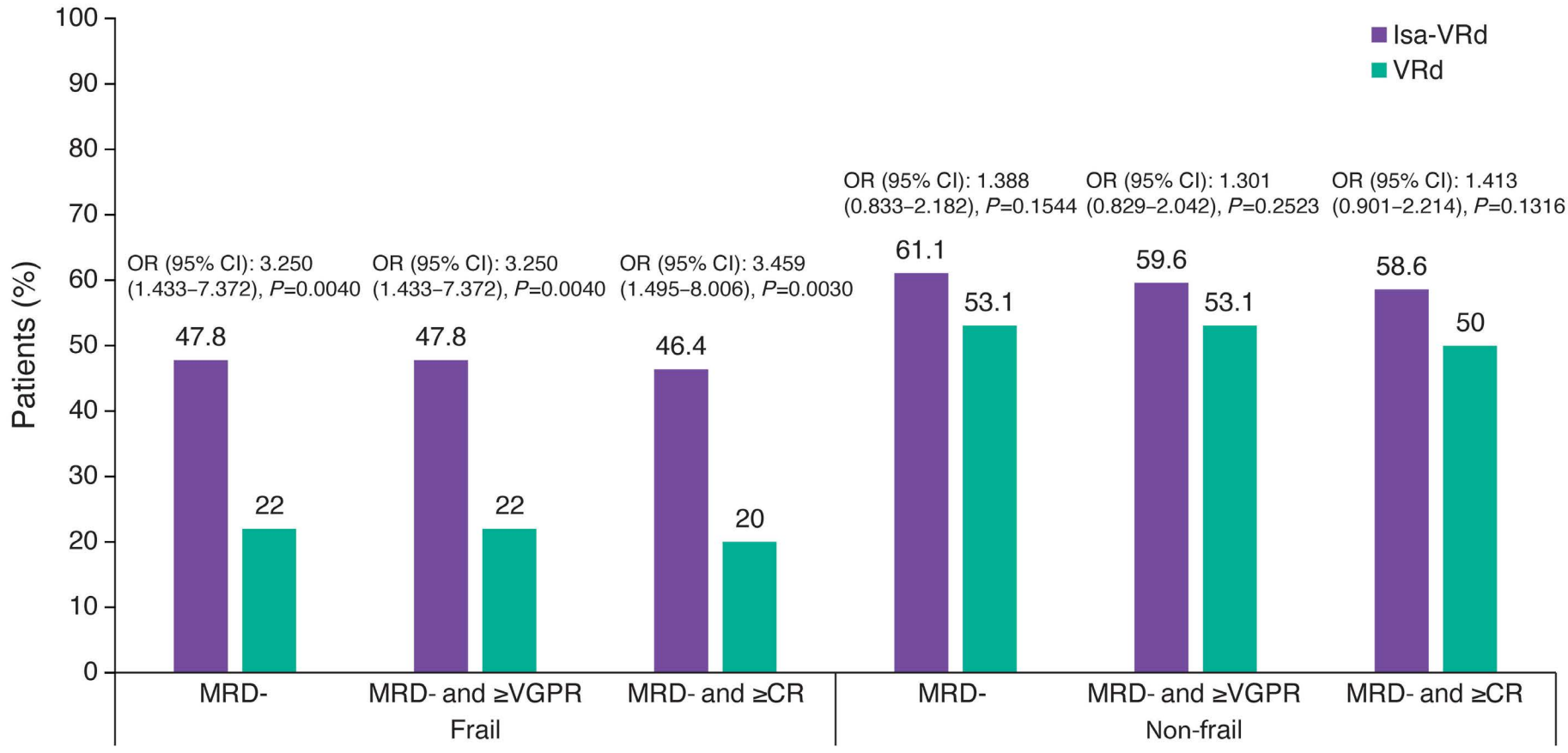

Figure 2. Summary of responses and minimal residual disease status for frail and non-frail subgroups. (A) Depth of response and (B) minimal residual disease negativity (MRD-) rates. CI: confidence interval; ≥CR: complete response or better; d: dexamethasone; Isa: isatuximab; OR: odds ratio; ORR: overall response rate; PR: partial response; R: lenalidomide; sCR: stringent complete response; V: bortezomib; ≥VGPR: very good partial response or better.

HR=0.531; 95% CI: 0.335-0.842; *P*=0.0071; VRd: HR=0.487; 95% CI: 0.302-0.785; *P*=0.0031).

When examining PFS after stratifying by age, frail patients aged ≤75 years showed a clear separation of curves favoring Isa-VRd over VRd (HR=0.511; 95% CI: 0.232-1.125; *P*=0.0953; *Online Supplementary Figure S1*). However, among frail patients aged 76-80 years, even if a benefit is observed in favor of Isa-VRd, this benefit was not statistically significant (HR=0.733; 95% CI: 0.348-1.544; *P*=0.4139). Stratifying PFS by ECOG PS demonstrated favorable results for Isa-VRd over VRd in patients with ECOG PS of 1 (HR=0.653; 95% CI: 0.328-1.297; *P*=0.2236) or 2 (HR=0.571; 95% CI: 0.226-1.440; *P*=0.2349), although not significantly different (*Online Supplementary Figure S2*).

Numerically higher ≥CR rates were observed with Isa-VRd compared with VRd in both frail and non-frail subgroups, and the overall response rate (ORR) and very good partial response or better (≥VGPR) rate were comparable be-

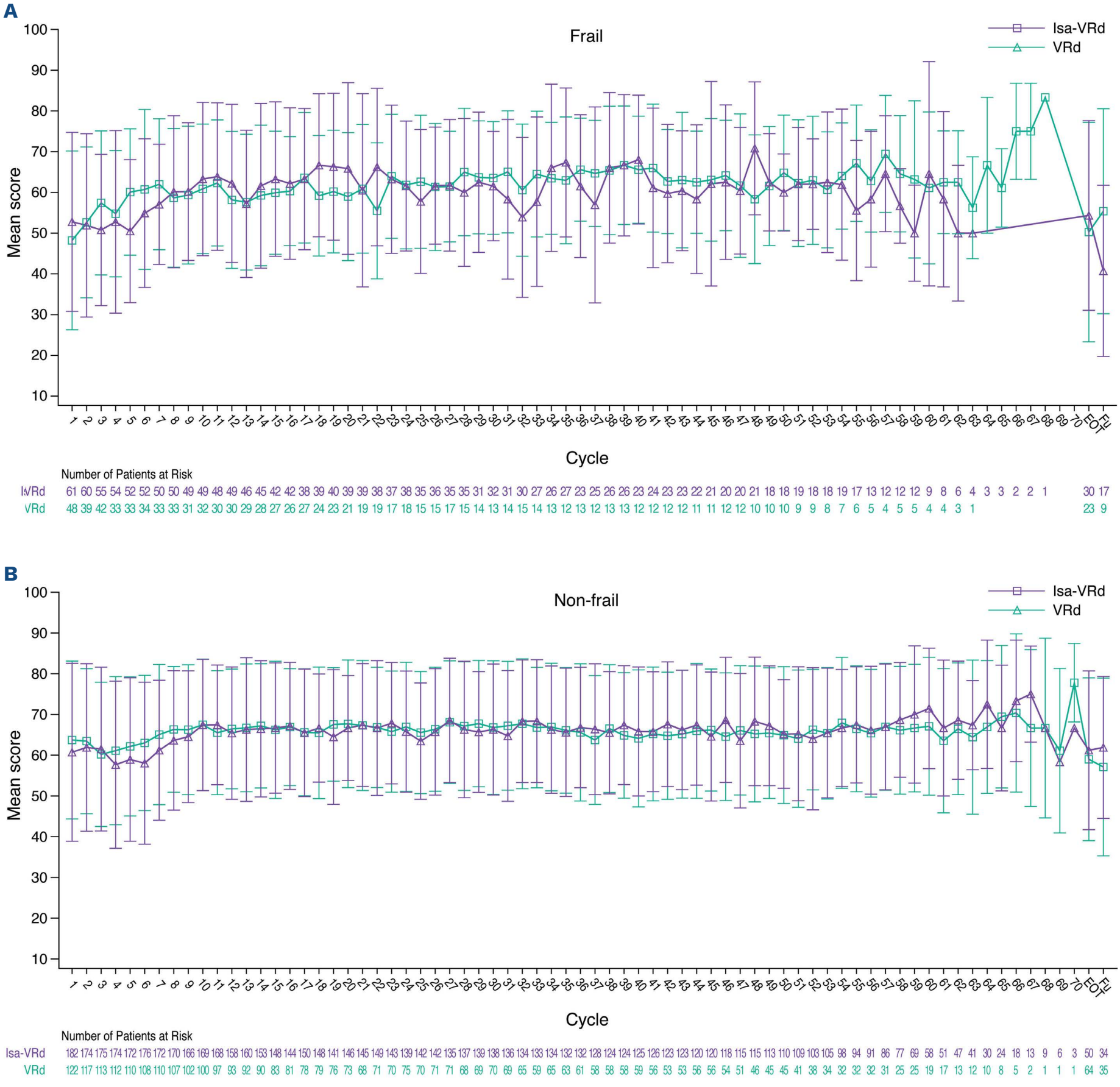

Figure 3. Quality of life as measured by EORTC-QLQ-C30 in the frail and non-frail subgroups. (A) Frail subgroup. (B) Non-frail subgroup. d: dexamethasone; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EOT: end of treatment; Fu: follow-up; Isa: isatuximab; R: lenalidomide; V: bortezomib.

tween subgroups (Figure 2A). Among frail patients, more than twice as many patients who received Isa-VRd *versus* VRd achieved MRD- in the ITT group (47.8% *vs*. 22.0%, OR=3.250; 95% CI: 1.433-7.372; *P*=0.0040) and in patients who achieved ≥CR (46.4% *vs*. 20.0%, OR=3.459; 95% CI: 1.495-8.006; *P*=0.0030, respectively at 10^{-5} by NGS) (Figure 2B). In non-frail patients, 58.6% of Isa-VRd and 50.0% of VRd patients achieved MRD- and ≥CR (OR=1.413; 95% CI: 0.901-2.214; *P*=0.1316). The sustained MRD (at 10^{-5} by NGS) rates at 12 months in frail Isa-VRd and VRd patients was 33.3% and 10.0%, respectively, and 51.3% and 30.5% in non-frail patients.

Quality of life, as measured by the EORTC-QLQ-C30 global health status domain score, remained stable over time in both the frail and non-frail subgroups, with no negative effects observed with the addition of Isa (Figure 3).

The OS data are still immature. However, the 60-month survival rate was 48.8% and 43.7% in the Isa-VRd and VRd arms in frail patients and 79.9% and 74.9%, respectively, in non-frail patients (Figure 4). A total of 32 (46.4%) Isa-VRd *versus* 27 (54.0%) VRd patients in the frail subgroup and 37 (19.2%) Isa-VRd and 31 (24.2%) VRd patients in the non-frail subgroup had died at time of data cutoff. A survival analysis at the time of data cutoff stratified by cause of death due to disease progression *versus* not due to disease progression indicated that fewer patients receiving Isa-VRd, compared with VRd, died due to disease progression in the frail subgroup (8.7% *vs.* 20.0%; HR=0.426; 95% CI: 0.155-1.172; *P*=0.983; see mortality cumulative incidence function curves by cause of death in *Online Supplementary Figure S3*) and the non-frail subgroup (3.6% *vs.* 9.4%; HR=0.379; 95% CI: 0.149-0.963; *P*=0.0414). The mortality rates attributed to factors besides progressive disease were similar between arms in both frail (Isa-VRd, 37.7% *vs*. VRd, 34.0%; HR=1.075; 95% CI: 0.583-1.982; *P*=0.8174) and non-frail subgroups (Isa-VRd, 15.5% *vs*. VRd, 14.8%; HR=1.030; 95% CI: 0.580-1.830; *P*=0.9189).

Safety

The incidence of any treatment-emergent AE (TEAE) was similar in both arms across frail and non-frail populations, while the incidence of grade ≥3 TEAE was also similar between frail and non-frail patients, occurring in 91.2% (Isa-VRd) and 88.0% (VRd) of frail patients and 91.7% (Isa-VRd) and 82.0% (VRd) of non-frail patients. More frail patients had an incidence of any treatment-emergent serious AE (77.9% Isa-VRd, 86.0% VRd) than non-frail patients (69.3% Isa-VRd, 60.9% VRd). The rates of TEAE leading to definitive discontinuation in the safety population were similar between arms in both frail and non-frail subgroups (Table 2), including when adjusted for exposure. The most common TEAE leading to definitive discontinuation in the frail subgroup was pneumonia, which led to 3 patients in each arm (Isa-VRd 4.4%, VRd 6.0%) to discontinue treatment.

Grade 5 TEAE occurred in nine (13.2%) Isa-VRd patients and five (10.0%) VRd patients in the frail subgroup and 20 (10.4%) and five (3.9%) Isa-VRd and VRd patients in the non-frail subgroup, respectively. The grade 5 TEAE occurring in frail patients corresponded to an event rate per patient-year of 0.050 and 0.048, respectively. Eight of the 14 grade 5 TEAE occurring in the frail subgroup were due to infections and infestations, including Candida sepsis and pneumonia.

In the frail subgroup, neutropenia was the most common

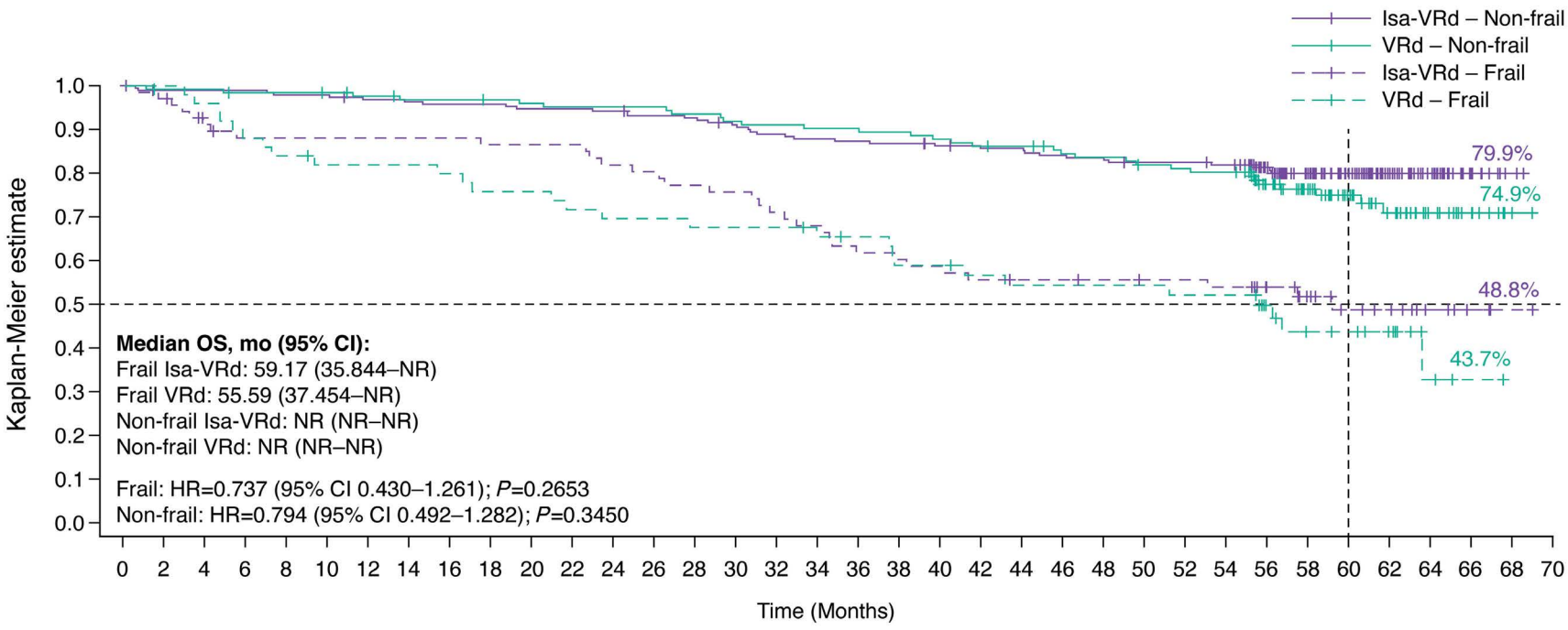

Figure 4. Kaplan-Meier estimates of overall survival for the frail and non-frail subgroups. CI: confidence interval; d: dexamethasone; HR: hazard ratio; Isa: isatuximab; R: lenalidomide; V: bortezomib; NR: not reached.

grade 3 or higher TEAE and occurred in 36.8% of Isa-VRd patients *versus* 16.0% of VRd patients (Table 3). All grade peripheral sensory neuropathy occurred in 27 (39.7%) and 28 (56.0%) of Isa-VRd and VRd patients, respectively, in the frail subgroup and was lower compared to the non-frail subgroup, while grade ≥3 peripheral neuropathy occurred in one patient in both arms (1.5% and 2.0%, respectively). In the non-frail subgroup, peripheral sensory neuropathy occurred in 114 (59.4%) Isa-VRd and 80 (62.5%) VRd patients. Corresponding grade ≥3 occurrences were 18 (9.4%) and ten (7.8%) patients, respectively.

Most Isa-VRd patients received antibiotic prophylaxis (60 frail patients, 151 non-frail patients; *Online Supplementary Tables S3* and *S4*), and the incidence of grade ≥3 infections was lower among patients who received antibiotic prophylaxis than those who did not. Granulocyte-colony stimulating factor was administered to 24 (35.3%) Isa-VRd and 9 (18.0%) VRd patients in the frail subgroup, and to 74 (38.5%) and 26 (20.3%) in the non-frail subgroup. Within each arm, there were no significant differences in the occurrence of upper respiratory tract infections between frail and non-frail patients, for both all grades and grade ≥3. All grade pneumonia was not significantly different within each arm between frail and non-frail patients. However, grade ≥3 pneumonia was found to be significantly different in frail patients receiving VRd (22%) *versus* non-frail patients (8.59%; OR=3.000; 95% CI: 1.206-7.460; *P*=0.0216) but was not significantly different in Isa-VRd patients (26.47% *vs*. 18.23%; OR=1.615; 95% CI: 0.842-3.098; *P*=0.1626).

Discussion

In this *post hoc* analysis of the IMROZ trial by frailty status, Isa-VRd followed by Isa-Rd led to favorable PFS benefits to all patients regardless of frailty status, with HR consistent with the ITT population.[9] After a median follow-up of 59.7 months, the median PFS estimate was not reached in Isa-VRd patients regardless of frailty. Isa-VRd also resulted in deep response rates, with more than twice as many patients in the frail subgroup achieving MRD- *versus* VRd (51% *vs*. 23%; *P*=0.0012). These results highlight the potential for Isa-VRd to help frail patients aged younger than 80 years achieve a level of disease control that translates into PFS benefits.

Patient quality of life was also consistent across the Isa-VRd and VRd arms, regardless of frailty status, and frail patients receiving Isa-VRd had a longer median treatment duration than those receiving VRd. Although the OS data are not yet mature, there seems to be no added mortality with the addition of Isa to VRd, and the Kaplan-Meier curve estimate for OS shows a separation in the frail and non-frail subgroups. The survival analysis looking at cause-specific mortality indicated that while fewer frail patients receiving Isa-VRd died due to disease progression than those receiving VRd, a similar proportion of frail patients died due to reasons other than disease progression across treatment arms.

Anti-CD38 monoclonal antibodies are commonly used for the treatment of MM, and Isa has demonstrated efficacy in combination with pomalidomide and dexamethasone (Pd) in frail patients with RRMM.[25] In Ti NDMM, triplet regimens are commonly used in clinical practice, one of which is a combination of a different CD38 monoclonal antibody, daratumumab (Dara), with Rd as evidenced from the phase III MAIA trial, which included patients up to 90 years old.[19] While cross-trial comparisons should be made with caution, a frailty analysis of MAIA also using the sIMWG frailty score

Table 2. Overview of treatment-emergent adverse events in the safety population by patient-year.

	Frail, N=118				Non-frail, N=320			
	Isa-VRd, N=68		VRd, N=50		Isa-VRd, N=192		VRd, N=128	
	N (%)	Event rate per patient-year	N (%)	Event rate per patient-year	N (%)	Event rate per patient-year	N (%)	Event rate per patient-year
Patients with any TEAE	68 (100.0)	16.416	49 (98.0)	18.188	191 (99.5)	12.574	126 (98.4)	11.154
Patients with any grade ≥3 TEAE	62 (91.2)	1.388	44 (88.0)	1.609	176 (91.7)	1.111	105 (82.0)	0.846
Patients with any grade 5 TEAE	9 (13.2)	0.050	5 (10.0)	0.048	20 (10.4)	0.027	5 (3.9)	0.012
Patients with any TEAE leading to definitive treatment discontinuation	21 (30.9)	0.119	20 (40.0)	0.202	39 (20.3)	0.054	27 (21.1)	0.065
Patients with any treatment-emergent SAE*	53 (77.9)	0.582	43 (86.0)	0.889	133 (69.3)	0.338	78 (60.9)	0.351

*TEAE with a start date before the operational cutoff date and becoming serious after the operational cutoff date were not counted as serious TEAE in this analysis. d: dexamethasone; Isa: isatuximab; R: lenalidomide; SAE: serious adverse event; TEAE: treatment-emergent adverse event; V: bortezomib.

found that Dara-Rd reduced the risk of disease progression or death by 38% in frail patients (HR=0.62; 95% CI: 0.45-0.85; *P*=0.003) after a median follow-up of 36.4 months.[19] The addition of Isa to the VRd regimen in our trial after a median follow-up of 59.7 months also led to significantly improved PFS in frail patients, with a 48% reduction in the risk of disease progression or death (HR=0.518; 95% CI: 0.294-0.912; *P*=0.0227), although patients aged >80 years were excluded, in contrast to MAIA. However, rates of MRD- were not as high in MAIA as compared to IMROZ (23.8% Dara-Rd *vs*. 10.1% Rd).[19] Between the two trials, there were similar proportions of patients who had ISS stage III disease in frail patients between treatment arms, and only frail patients had ECOG 2.[19] Rates of treatment discontinuations due to TEAE and incidences of grade 5 TEAE were also similar in the frail populations of MAIA and IMROZ.[19] The phase III ALCYONE trial was the first trial to show the role of a quadruplet, Dara-bortezomib-melphalan-prednisone (Dara-VMP), in Ti patients and showed efficacy in a frail population analysis (median PFS: Dara-VMP, 32.9 months *vs*. VMP, 19.5 months) after a median follow-up of 40.1 months.[21] However, this was done with a VMP backbone, which is no longer the current standard of care. The phase III CEPHEUS trial, investigating Dara in combination with VRd, is currently ongoing.[26] However, CEPHEUS will not be able to demonstrate whether the Dara-VRd quadruplet is efficacious in frail patients as it excludes patients with a frailty index score ≥2 (by Myeloma Geriatric Assessment score).[27]

The use of a quadruplet regimen in patients who are frail may also lead to toxicity concerns, particularly infections, which could represent a major cause of morbidity and mortality, and physicians must balance efficacy with safety in this population.[28] This analysis demonstrated that the safety profile of Isa-VRd was generally consistent with the ITT population of IMROZ, and most Isa-VRd patients received antibiotic prophylaxis, which lowered the incidence of grade ≥3 infections.[9] There were no significant differences in the occurrence of grade ≥3 upper respiratory tract infections (*P*>0.999) or pneumonia (*P*=0.163) between non-frail and frail patients receiving Isa-VRd, regardless of severity, and rates of neutropenia were generally similar between arms

Table 3. Treatment-emergent adverse events with an incidence ≥20% in the Isa-VRd arm.

Preferred term, N (%)	Frail, N=118				Non-frail, N=320			
	Isa-VRd, N=68		VRd, N=50		Isa-VRd, N=192		VRd, N=128	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any event	68 (100)	62 (91.18)	49 (98.0)	44 (88.0)	191 (99.5)	176 (91.7)	126 (98.4)	105 (82.0)
Diarrhea	33 (48.5)	6 (8.82)	22 (44.0)	4 (8.0)	111 (57.8)	14 (7.3)	64 (50.0)	11 (8.6)
Peripheral sensory neuropathy	27 (39.7)	1 (1.47)	28 (56.0)	1 (2.0)	114 (59.4)	18 (9.4)	80 (62.5)	10 (7.8)
Neutropenia	25 (36.8)	25 (36.76)	8 (16.0)	8 (16.0)	53 (27.6)	53 (27.6)	29 (22.7)	27 (21.1)
Upper respiratory tract infection	22 (32.4)	0	14 (28.0)	1 (2.0)	67 (34.9)	2 (1.0)	45 (35.2)	1 (0.8)
Pneumonia	21 (30.9)	18 (26.47)	12 (24.0)	11 (22.0)	57 (29.7)	35 (18.2)	22 (17.2)	11 (8.6)
Cataract	20 (29.4)	8 (11.76)	5 (10.0)	2 (4.0)	77 (40.1)	30 (15.6)	39 (30.5)	17 (13.3)
Constipation	20 (29.4)	1 (1.47)	24 (48.0)	0	74 (38.5)	5 (2.6)	48 (37.5)	3 (2.3)
Fatigue	20 (29.4)	4 (5.88)	14 (28.0)	1 (2.0)	71 (37.0)	17 (8.9)	33 (25.8)	11 (8.6)
Peripheral edema	18 (26.5)	0	20 (40.0)	0	68 (35.4)	0	39 (30.5)	2 (1.6)
Asthenia	16 (23.5)	2 (2.94)	10 (20.0)	3 (6.0)	41 (21.4)	5 (2.6)	33 (25.8)	1 (0.8)
Decreased appetite	16 (23.5)	1 (1.47)	8 (16.0)	1 (2.0)	18 (9.4)	1 (0.5)	22 (17.2)	1 (0.8)
Bronchitis	15 (22.1)	3 (4.4)	5 (10.0)	0	43 (22.4)	4 (2.1)	25 (19.5)	3 (2.3)
Infusion-related reaction	15 (22.1)	0	1 (2.0)	0	47 (24.5)	1 (0.5)	1 (0.8)	0
Fall	14 (20.6)	5 (7.4)	11 (22.0)	2 (4.0)	36 (18.8)	8 (4.2)	18 (14.1)	5 (3.9)
Rash	14 (20.6)	1 (1.5)	6 (12.0)	1 (2.0)	38 (19.8)	7 (3.7)	30 (23.4)	3 (2.3)
Insomnia	12 (17.7)	0	9 (18.0)	0	47 (24.5)	10 (5.2)	343 (25.8)	4 (3.1)
Back pain	10 (14.7)	3 (4.4)	10 (20.0)	0	48 (25.0)	6 (3.1)	21 (16.4)	3 (2.3)
COVID-19	10 (14.7)	2 (2.9)	6 (12.0)	1 (2.0)	49 (25.5)	0	24 (18.8)	4 (3.1)

COVID-19: Coronavirus disease 2019; d: dexamethasone; Isa: isatuximab; R: lenalidomide; TEAE: treatment-emergent adverse event; V: bortezomib.

in frail patients. Incidence of grade ≥3 Coronavirus disease 2019 was also low across both treatment arms and independent of frailty status. Patients tolerated bortezomib and lenalidomide well, with similar median RDI across arms and frailty status. Of note, we observed a median RDI of 81.9% for lenalidomide in frail patients receiving Isa-VRd, which was similar to that of such patients in the VRd arm (87.6%). In MAIA, frail patients receiving Dara-Rd had a median lenalidomide RDI of 65.4% *versus* 92.9% in the Rd arm. The exposure-adjusted rates of peripheral sensory neuropathy were also similar between arms and between frail and non-frail patients. Further, the exposure-adjusted rates of TEAE leading to discontinuation of treatment were similar between treatment arms. Patients receiving Isa-VRd, compared with VRd, also had a longer median treatment duration (31.2 *vs*. 19.2 months). Moreover, Isa-VRd has been evaluated in the BENEFIT trial, which had a flexible dosing schedule that could be more optimal for frail patients, as bortezomib was administered weekly and dexamethasone could be discontinued after cycle 12.[29]

While this analysis adds to the body of evidence validating the sIMWG frailty score, the use of reported medical history for the retrospective CCI calculations is a limitation of this study as it may contain missing data. In future, clinical trials could be designed to measure frailty prospectively or to incorporate dynamic measurements of frailty, particularly which patients would derive the most benefit from receiving a quadruplet regimen. Currently, there are numerous frailty scores that take into account various clinical factors and variables, although with wide heterogeneity in categorization and cutoff for frailty.[30,31] A standardized frailty score that is easy to use in the real-world setting and incorporated into clinical trial designs is needed to evaluate treatment outcomes in frail patients.[30] Although IMROZ excluded patients aged >80 years, and thus excludes patients who are frail due to their age, the use of the sIMWG frailty score was able to identify approximately one-third of the IMROZ population as frail, largely due to their comorbidities and performance status, and was not driven by age. Few patients, however, were identified as ultra-frail, which have been known to have the worst outcomes. Further, approximately 70% of the IMROZ population was aged ≥70 years, which reflects the patient population in real-world clinical practice. However, the exclusion of patients aged >80 means these data should be interpreted with caution in this patient population, and more data is needed to inform the use of quadruplets in the very elderly. Furthermore, in the real-world, frail patients are known to have poor outcomes and thus may not be reflective of this *post-hoc* frailty analysis. The frail population in the IMROZ study displayed characteristics that are expected of their frailty, with shorter median treatment duration and worse outcomes in PFS and response as compared with the non-frail population. The frail population in IMROZ is not driven by age but represents a population that is frail by factors beyond age and thus is expected to have a worse prognosis. A quadruplet of Isa-VRd for 24 weeks followed by Isa-Rd was tolerated by patients regardless of frailty status, and no new safety signals were observed. This *post hoc* subgroup analysis of the IMROZ trial by frailty status demonstrated that Isa-VRd is an effective option with a manageable safety profile for frail patients aged ≤80 years, with Ti NDMM, accounting for approximately one-third of patients in IMROZ. This is the first demonstration of a quadruplet regimen consisting of an anti-CD38 monoclonal antibody in combination with VRd that is safe and efficacious in all patients aged ≤80 years not eligible for transplant regardless of frailty status.

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Contributions

TF, MC, RZO, HG and M-FB were on the steering committee. SM, M-AD, XPL, PM, MC, HG, RZO, MB and TF performed research and recruited patients to the trial. M-FB and AS performed data analysis. All authors wrote/critically revised the manuscript and approved the final version.

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Data-sharing statement

Qualified researchers can request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access are at: https://www.vivli.org.

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