Reprinted From

The NEW ENGLAND JOURNAL of MEDICINE

VOL. 391 NO. 17

ESTABLISHED IN 1812 OCTOBER 31, 2024 WWW.NEJM.ORG

ORIGINAL ARTICLE

Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

Thierry Facon, M.D., Meletios-Athanasios Dimopoulos, M.D., Xavier P. Leleu, M.D., Meral Beksac, M.D., Ludek Pour, M.D., Roman Hájek, M.D., Zhuogang Liu, M.D., Jiri Minarik, M.D., Philippe Moreau, M.D., Joanna Romejko-Jarosinska, M.D., Ivan Spicka, M.D., Vladimir I. Vorobyev, M.D., Britta Besemer, M.D., Tadao Ishida, M.D., Wojciech Janowski, M.D., Sevgi Kalayoglu-Besisik, M.D., Gurdeep Parmar, M.D., Pawel Robak, M.D., Elena Zamagni, M.D., Hartmut Goldschmidt, M.D., Thomas G. Martin, M.D., Salomon Manier, M.D., Mohamad Mohty, M.D., Corina Oprea, M.D., Marie-France Brégeault, M.D., Sandrine Macé, Ph.D., Christelle Berthou, M.S., David Bregman, M.D., Zandra Klippel, M.D., and Robert Z. Orlowski, M.D., for the IMROZ Study Group*

ABSTRACT

BACKGROUND

Bortezomib, lenalidomide, and dexamethasone (VRd) is a preferred first-line treatment option for patients with newly diagnosed multiple myeloma. Whether the addition of the anti-CD38 monoclonal antibody isatuximab to the VRd regimen would reduce the risk of disease progression or death among patients ineligible to undergo transplantation is unclear.

METHODS

In an international, open-label, phase 3 trial, we randomly assigned, in a 3:2 ratio, patients 18 to 80 years of age with newly diagnosed multiple myeloma who were ineligible to undergo transplantation to receive either isatuximab plus VRd or VRd alone. The primary efficacy end point was progression-free survival. Key secondary end points included a complete response or better and minimal residual disease (MRD)–negative status in patients with a complete response.

RESULTS

A total of 446 patients underwent randomization. At a median follow-up of 59.7 months, the estimated progression-free survival at 60 months was 63.2% in the isatuximab-VRd group, as compared with 45.2% in the VRd group (hazard ratio for disease progression or death, 0.60; 98.5% confidence interval, 0.41 to 0.88; P<0.001). The percentage of patients with a complete response or better was significantly higher in the isatuximab-VRd group than in the VRd group (74.7% vs. 64.1%, P=0.01), as was the percentage of patients with MRD-negative status and a complete response (55.5% vs. 40.9%, P=0.003). No new safety signals were observed with the isatuximab-VRd regimen. The incidence of serious adverse events during treatment and the incidence of adverse events leading to discontinuation were similar in the two groups.

CONCLUSIONS

Isatuximab-VRd was more effective than VRd as initial therapy in patients 18 to 80 years of age with newly diagnosed multiple myeloma who were ineligible to undergo transplantation. (Funded by Sanofi and a Cancer Center Support Grant; IMROZ ClinicalTrials.gov number, NCT03319667.)

Reprinted from THE NEW ENGLAND JOURNAL OF MEDICINE
(ISSN 0028-4793) Vol. 391:1597-1609 (October 31, 2024).

Printed in the U.S.A. Fax: (781) 893-8103 www.nejm.org

The authors' affiliations are listed in the Appendix. Dr. Facon can be contacted at thierry.facon@chu-lille.fr or at Centre Hospitalier Universitaire de Lille, Rue Michel Polonovski, 59037 Lille, France.

*A list of the investigators in the IMROZ Study Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 3, 2024, at NEJM.org.

N Engl J Med 2024;391:1597-609.
DOI: 10.1056/NEJMoa2400712

CME

A Quick Take is available at NEJM.org

Treatment with triplet therapies has historically improved outcomes in patients with newly diagnosed multiple myeloma, providing deep, durable disease control in most patients and delaying disease relapse.[1] The SWOG S0777 trial established bortezomib–lenalidomide–dexamethasone (VRd) as a standard, first-line treatment for patients with myeloma, regardless of their eligibility for transplantation,[2,3] and is commonly used in clinical practice.[2] Older patients with multiple myeloma benefit most when efficacious regimens are used early, given that some do not receive any subsequent lines of therapy after first-line treatment.[4-7]

Isatuximab, an IgG1 monoclonal antibody, targets a specific epitope of human CD38, inducing myeloma-cell death by means of multiple mechanisms.[8-10] Phase 3 trials have shown a benefit of isatuximab added to standard backbone regimens, with the combination therapies isatuximab–pomalidomide–dexamethasone (in the ICARIA trial) and isatuximab–carfilzomib–dexamethasone (in the IKEMA trial) being approved for the treatment of relapsed or refractory multiple myeloma in numerous geographic areas.[9,11-14]

Phase 3 trials showed improved outcomes with anti-CD38 quadruplet regimens including proteasome inhibitor–immunomodulatory drug backbones for patients with myeloma who were eligible to undergo transplantation, thus positioning quadruplets as a new standard treatment.[15-18] In patients who are ineligible for transplantation, the daratumumab–bortezomib–melphalan–prednisone quadruplet was approved on the basis of the results of the ALCYONE trial.[19] Trials of daratumumab-VRd (D-VRd; the CEPHEUS trial) and daratumumab, carfilzomib, lenalidomide, and dexamethasone (D-KRd; the GEM2017FIT trial) are ongoing.[20,21] The results of a phase 1b trial of isatuximab-VRd showed excellent clinical activity and deep responses in patients who had no immediate intention to undergo transplantation.[22] However, the efficacy of treatment with an anti-CD38 agent and VRd in the population of patients with newly diagnosed myeloma who are ineligible to undergo transplantation has been unclear. Here, we report a prespecified interim analysis of IMROZ, an international, phase 3 trial of the efficacy and safety of isatuximab-VRd as compared with VRd in patients with myeloma who were ineligible to undergo transplantation.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this randomized, open-label, phase 3 trial at 93 sites in 21 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The independent ethics committee or institutional review board at each site approved the trial protocol, which is available at NEJM.org. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice of the International Council for Harmonisation. All the patients provided written informed consent. Senior academic investigators designed the trial together with Sanofi, the sponsor. Sanofi compiled, maintained, and analyzed the data. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Sanofi funded medical writers to prepare the manuscript, and the authors critically reviewed, edited, and approved the manuscript for submission for publication. No confidentiality agreements were made that preclude the publication of trial findings.

PATIENTS

We enrolled patients 18 years of age or older with symptomatic previously untreated myeloma (according to International Myeloma Working Group [IMWG] criteria[11]) and measurable disease who were ineligible to undergo transplantation owing to an age of 65 years or older or to coexisting conditions. Key exclusion criteria were an age of more than 80 years, an Eastern Cooperative Oncology Group (ECOG) performance-status score of more than 2 (on a 5-point scale, with higher scores indicating greater disability), or an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m^2 of body-surface area. Additional eligibility criteria are listed in the Supplementary Appendix.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 3:2 ratio to receive either isatuximab-VRd or VRd. 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).

Four induction cycles (with 6 weeks per cycle)

were followed by 4-week cycles of continuous treatment with isatuximab-Rd (in the isatuximab-VRd group) or Rd (in the VRd group) (see below), until the occurrence of disease progression, an unacceptable adverse event, or other discontinuation criteria. The dose-administration scheme is shown in the Supplementary Appendix.

During induction, all patients received VRd, which consisted of subcutaneous bortezomib (1.3 mg per square meter on days 1, 4, 8, 11, 22, 25, 29, and 32), oral lenalidomide (25 mg per day [or 10 mg per day if the estimated GFR was 30 to <60 ml per minute per 1.73 m^2] on days 1 to 14 and 22 to 35), and oral or intravenous dexamethasone (20 mg per day on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 [or on days 1, 4, 8, 11, 15, 22, 25, 29, and 32 in patients ≥75 years of age]). Patients in the isatuximab-VRd group received intravenous isatuximab (10 mg per kilogram of body weight once weekly in cycle 1, with subsequent cycles occurring every 2 weeks). Antibacterial prophylactic treatment was recommended for all patients during induction.

During continuous treatment, all patients received an Rd regimen that consisted of oral lenalidomide (25 mg per day [or 10 mg per day if the estimated GFR was 30 to <60 ml per minute per 1.73 m^2] on days 1 to 21) and dexamethasone (20 mg per day once weekly). Patients in the isatuximab-VRd group received intravenous isatuximab (10 mg per kilogram every 2 weeks, with monthly administration starting with cycle 18). Crossover from the Rd regimen to the isatuximab-Rd regimen during continuous treatment was allowed according to the investigator's discretion in the case of biochemical or clinical progression (see the Supplementary Appendix).

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was defined as the time from randomization to the first documented disease progression (on the basis of assessment by the independent review committee) or death, whichever occurred first (assessed in a time-to-event analysis). Key secondary end points included a complete response or better (defined as a complete response or stringent complete response); minimal residual disease (MRD)–negative status in patients with a complete or better response (assessed at 10^{-5} sensitivity by means of next-generation sequencing); a very good partial response or better; and overall survival, which was defined as the time from randomization to death from any cause (assessed in a time-to-event analysis). Other secondary end points included overall response (partial response or better), the time to disease progression, duration of response, the time to the first response, the time to the best response, second progression–free survival (defined as the time from randomization to second progression or death, whichever occurred first, assessed in a time-to-event analysis), progression-free survival according to MRD status, sustained MRD-negative status for at least 12 months, and quality of life.

Central laboratories performed disease and MRD assessments, as well as baseline cytogenetic analyses by means of fluorescence in situ hybridization. An independent review committee, whose members were unaware of the treatment assignments, determined disease response and progression according to efficacy data (assessed at a central laboratory), bone marrow assessment for plasma-cell infiltration (assessed at the local laboratory), and centrally reviewed imaging according to the IMWG criteria. Quality of life was assessed by means of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30), which included the global health status scale. Safety assessments included adverse events and laboratory variables, which were assessed according to the Common Terminology Criteria for Adverse Events, version 4.03, of the National Cancer Institute. Additional information on end points and assessments is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

All the efficacy analyses were conducted in the intention-to-treat population, which included all the patients who underwent randomization. The safety population included all the patients who had received at least one dose of trial drug. For the primary end point, between-group comparisons were conducted with the use of a stratified log-rank test procedure with the randomization stratification factors. The significance level at the interim analysis ($P=0.0074$) used an O'Brien–Fleming alpha-spending function to control the one-sided type I error at 2.5%, which resulted in the reported 98.5% confidence interval for the primary analysis. The significance level for the

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Isatuximab-VRd (N=265)	VRd (N=181)
Age		
Median (range) — yr	72 (60–80)	72 (55–80)
Distribution — no. (%)		
<65 yr	8 (3.0)	9 (5.0)
65–69 yr	73 (27.5)	47 (26.0)
70–74 yr	115 (43.4)	68 (37.6)
75–80 yr	69 (26.0)	57 (31.5)
Sex		
Female	122 (46.0)	87 (48.1)
Male	143 (54.0)	94 (51.9)
Race or ethnic group†		
American Indian or Alaska Native	4 (1.5)	1 (0.6)
Asian	31 (11.7)	17 (9.4)
Black	2 (0.8)	2 (1.1)
Native Hawaiian or other Pacific Islander	1 (0.4)	1 (0.6)
White	192 (72.5)	131 (72.4)
Not reported or missing data	35 (13.2)	29 (16.0)
ECOG performance-status score — no. (%)‡		
0 or 1	235 (88.7)	162 (89.5)
>1	30 (11.3)	19 (10.5)
Estimated GFR <60 ml/min/1.73 m^2 — no. (%)§	66 (24.9)	62 (34.3)
Extramedullary disease at trial enrollment — no. (%)¶	18 (6.8)	6 (3.3)
Median duration since initial diagnosis of multiple myeloma (range) — mo	1.2 (0.3–48.9)	1.2 (0.3–37.7)
Type of myeloma at baseline — no. (%)		
IgG	171 (64.5)	115 (63.5)
Non-IgG	94 (35.5)	66 (36.5)
IgA	57 (21.5)	41 (22.7)
Light chain only‖	32 (12.1)	21 (11.6)
R-ISS stage at baseline — no. (%)**		
Stage I or II	234 (88.3)	157 (86.7)
Stage III	29 (10.9)	21 (11.6)
Not classified	2 (0.8)	3 (1.7)
Cytogenetic risk at baseline — no. (%)		
Standard	207 (78.1)	140 (77.3)
High††	40 (15.1)	34 (18.8)
Unknown or missing data	18 (6.8)	7 (3.9)

interim analysis of overall survival was 0.0001, which resulted in the reported 99.97% confidence interval. The median progression-free survival, the probability of being free from disease progression, and corresponding confidence intervals were calculated by means of the Kaplan–Meier method. Hazard ratio estimates were obtained with the use of a stratified Cox propor-

Table 1. (Continued.)

Characteristic	Isatuximab-VRd (N=265)	VRd (N=181)
High-risk chromosomal abnormalities and 1q21+ — no. (%)‡‡	19 (7.2)	15 (8.3)
Chromosomal abnormality — no. (%)§§		
1q21+	95 (35.8)	70 (38.7)
Amplification 1q21	32 (12.1)	23 (12.7)
Del(17p) with a 50% cutoff	15 (5.7)	9 (5.0)

* The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. VRd denotes bortezomib–lenalidomide–dexamethasone.
† Race and ethnic group were reported by the patient.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. A total of 112 patients (42.3%) in the isatuximab-VRd group and 83 (45.9%) in the VRd group had an ECOG performance-status score of 1 (indicating that strenuous physical activity was restricted but the patient was fully ambulatory and able to carry out light work). One patient in the isatuximab-VRd group had an ECOG performance-status score of 3 (indicating that the patient was capable of only limited self-care and was confined to bed or chair more than 50% of waking hours).
§ The estimated glomerular filtration rate (GFR) was calculated on the basis of the Modification of Diet in Renal Disease formula.
¶ Extramedullary disease only is reported. In addition, 67 patients (25.3%) in the isatuximab-VRd group and 49 (27.1%) in the VRd group had paramedullary disease; 1 patient in each group had both extra- and paramedullary disease. Status with regard to extramedullary disease was determined by an independent review committee.
‖ Light chains could be κ, γ, or both.
** The Revised International Staging System (R-ISS) stage at baseline was determined by means of interactive response technology for stratification. The stage was derived from the ISS stage at enrollment, cytogenetic abnormality (yes vs. no), and serum lactate dehydrogenase concentration.
†† High cytogenetic risk was defined as the presence of del(17p), t(4;14), t(14;16), or a combination of these, with cutoffs defined below.
‡‡ Abnormality was defined as present in at least 30% of abnormal bone marrow plasma cells for t(4;14), t(14;16), and 1q21+ (at least three copies) and at least 50% of abnormal plasma cells for del(17p). One patient in the isatuximab-VRd group had two high-risk chromosomal abnormalities (del[17p] and t[4;14]).
§§ The 1q21+ abnormality was defined as at least three copies of 1q21. The amplification 1q21 abnormality was defined as at least four copies of 1q21.

tional-hazards model. (The assumption assessment is discussed in the Supplementary Appendix.) Key secondary end points were assessed by means of a closed-test procedure and a stratified Cochran–Mantel–Haenszel test with 95% confidence intervals. For the primary end point of progression-free survival and the key secondary end points, we report confidence intervals that were adjusted for multiplicity, as well as two-sided P values. For all other end points, we report 95% confidence intervals without multiplicity control.

Continuous variables were summarized with the use of descriptive statistics, and categorical and ordinal variables were summarized as frequencies and percentages. Safety analyses and the extent of trial treatment were assessed according to the actual treatment received in the safety population. In this article, we report the second of three planned interim analyses, after 73% of the 222 events of disease progression or death for the planned final analysis had occurred.

RESULTS

PATIENTS AND TREATMENT

We enrolled patients from December 2017 through March 2019. Overall, 446 patients underwent randomization (265 to the isatuximab-VRd group and 181 to the VRd group). The demographic and disease characteristics of the patients at baseline were balanced across the two groups (Table 1, and see the Supplementary Appendix). The median age of the patients was 72 years (range, 55 to 80), 16.6% of the patients had high-risk cytogenetic features, 37.0% had a chromosomal 1q21+ abnormality (at least three copies of 1q21), and 28.7% had an estimated GFR of less than 60 ml per minute per 1.73 m^2. The representativeness of the patient population is described in Table S1 in the Supplementary Appendix.

As of the data-cutoff date (September 26, 2023), 47.2% of the patients in the isatuximab-VRd group and 24.3% of those in the VRd group were

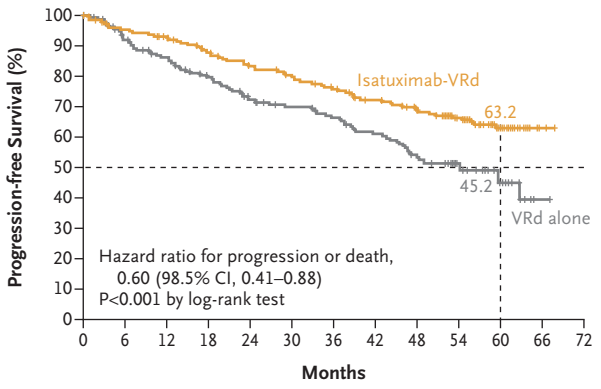


Figure 1. Progression-free Survival (Intention-to-Treat Population).

Shown are Kaplan–Meier estimates of progression-free survival among patients in the intention-to-treat population (defined as all the patients who underwent randomization). The interim analysis of progression-free survival was performed after 162 events of disease progression or death had occurred (which was 73% of the 222 events specified for the planned final analysis). The median progression-free survival was not reached (95% CI, not reached to not reached) in the isatuximab-VRd group (in which patients received isatuximab plus a regimen of bortezomib, lenalidomide, and dexamethasone) and 54.3 months (95% CI, 45.2 to not reached) in the VRd group (in which patients received bortezomib, lenalidomide, and dexamethasone). Tick marks indicate censored data.

continuing to receive treatment. A total of 138 patients (52.1%) in the isatuximab-VRd group and 137 (75.7%) in the VRd group had discontinued treatment, mostly because of adverse events or progressive disease. Two patients who had been randomly assigned to the isatuximab-VRd group did not receive trial treatment, and 25 patients in the VRd group switched to isatuximab-Rd therapy (Fig. S1). Among the adverse events that contributed to definitive treatment discontinuation, 8 (in 3.0% of the patients in the isatuximab-VRd group) and 4 (in 2.2% of those in the VRd group) were related to coronavirus disease 2019 (Covid-19).

The median treatment duration was 53.2 months (range, 0.5 to 68.8) in the isatuximab-VRd group and 31.3 months (range, 0.6 to 67.2) in the VRd group, and the median number of cycles started was 52 (range, 1 to 69) and 29 (range, 1 to 69), respectively. The median relative dose intensity for isatuximab was 93.6%. The median relative dose intensity for bortezomib was 90.3% in the isatuximab-VRd group and 86.7% in the VRd group; for lenalidomide, 77.7% and 83.5%, respectively; and for dexamethasone, 81.6% and 79.3%, respectively. Dose reductions are described in the Supplementary Appendix.

EFFICACY

At a median follow-up of 59.7 months (interquartile range, 56.0 to 63.2), disease progression or death had occurred in 162 patients (84 of 265 [31.7%] in the isatuximab-VRd group and 78 of 181 [43.1%] in the VRd group). At 60 months, progression-free survival as assessed on the basis of independent review was 63.2% in the isatuximab-VRd group, as compared with 45.2% in the VRd group (hazard ratio for disease progression or death, 0.60; 98.5% confidence interval [CI], 0.41 to 0.88; P<0.001) (Fig. 1 and Table S2). The results regarding progression-free survival according to investigator assessment were consistent with those of the primary analysis (Fig. S2). Prespecified subgroup analyses of progression-free survival are shown in Figure S3. A benefit was apparent in most subgroups, although the hazard ratio in the subgroup of patients with high-risk cytogenetic features was 0.97 (95% CI, 0.48 to 1.96). The time to disease progression was longer in the isatuximab-VRd group than in the VRd group (hazard ratio, 0.41; 95% CI, 0.29 to 0.60) (Fig. S4).

In the intention-to-treat population, the percentage of patients with an overall response was similarly high in the isatuximab-VRd group and the VRd group (91.3% and 92.3%, respectively) (Fig. 2A). A significantly higher percentage of patients had a complete or better response with isatuximab-VRd than with VRd (74.7% vs. 64.1%, P=0.01). The results regarding hierarchical testing and additional response data are shown in Tables S3 and S4. A significant improvement was seen for MRD-negative status in patients with a complete response at any time (55.5% in the with isatuximab-VRd group vs. 40.9% in the VRd group, P=0.003) (Fig. 2B). The percentage of patients with MRD-negative status was higher in the isatuximab-VRd group than in the VRd group (58.1% vs. 43.6%). A total of 46.8% of the patients in the isatuximab-VRd group and 24.3% of those in the VRd group had a sustained MRD-negative status lasting at least 12 months. Exploratory analysis of the percentage of patients with MRD-negative status and a complete response at 10^{-6} sensitivity showed results consis-

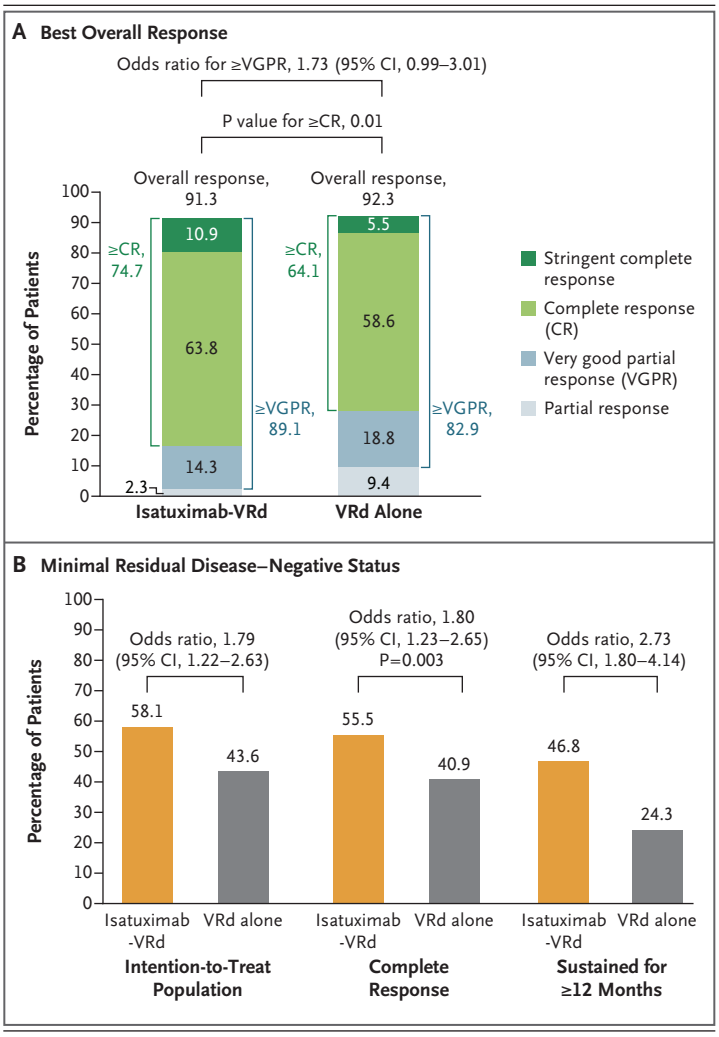


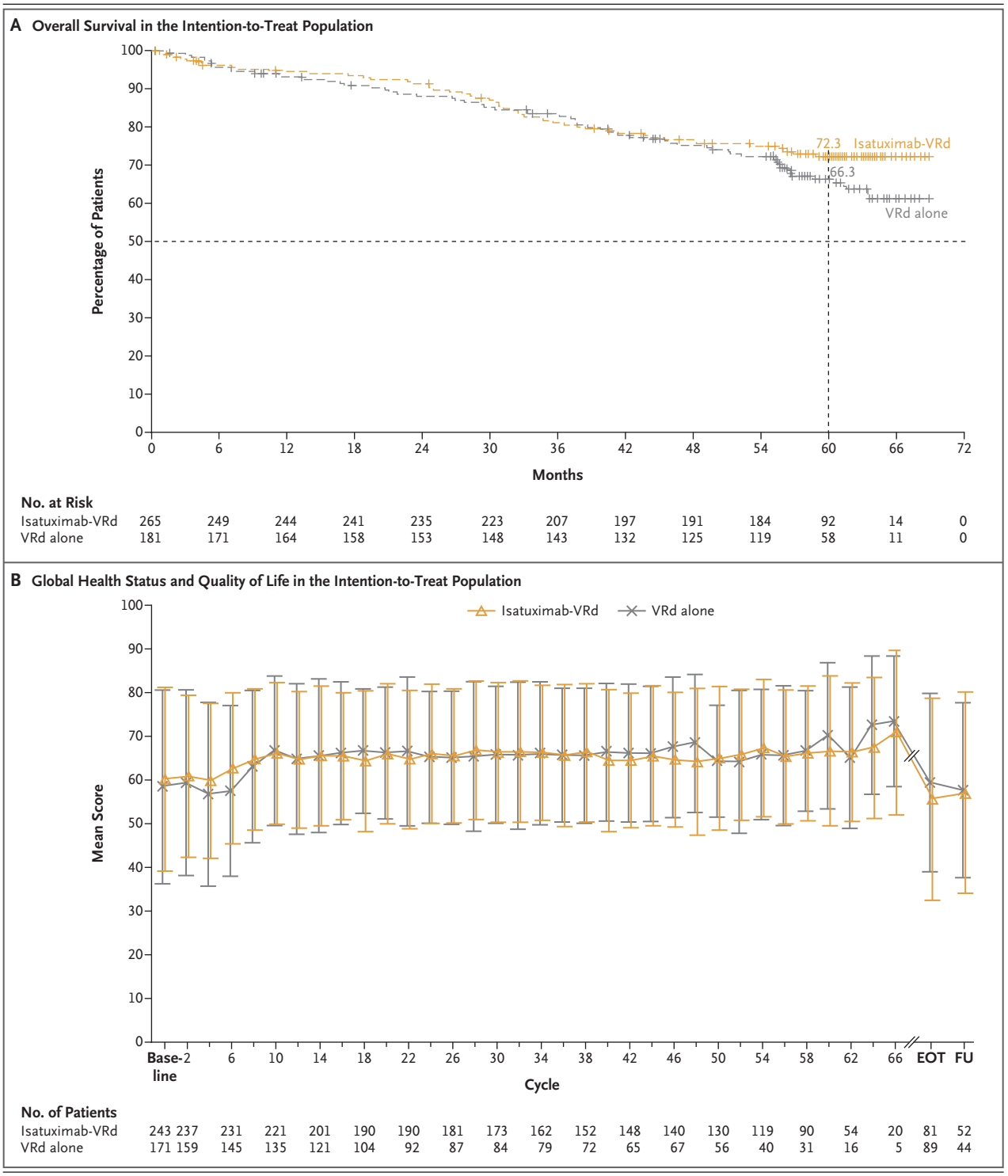
Figure 2. Summary of Responses and Minimal Residual Disease Status (Intention-to-Treat Population).

Shown are the results for best overall response (Panel A) and minimal residual disease (MRD) status (Panel B) at any time during the trial among patients in the intention-to-treat population. The median time to MRD-negative status was 14.7 months (95% CI, 11.5 to 24.1) in the isatuximab-VRd group and 32.8 months (95% CI, 17.5 to 45.1) in the VRd group. Response was assessed on the basis of International Myeloma Working Group (IMWG) recommendations (see the protocol). The following secondary end points were tested sequentially, each with an overall two-sided alpha level of 0.05, with the use of a hierarchical testing approach: complete response or better, MRD-negative status in patients with a complete response, and a very good partial response or better. The criteria for a stringent complete response included the criteria for a complete response plus a normal free light-chain ratio and an absence of clonal plasma cells, as assessed by means of immunofluorescence or immunohistochemical analysis or by means of two-color to four-color flow cytometry. The sensitivity threshold for MRD was defined as 1 in 10^5 nucleated cells at any time during the trial. Bone marrow aspiration was conducted for central laboratory assessment at baseline and, in the case of a complete response or a very good partial response, at the end of the induction period and during the period of continuous treatment. MRD status was based on a postrandomization assessment performed on bone marrow samples by means of a Food and Drug Administration–approved next-generation sequencing assay (clonoSEQ Assay, version 2.0; Adaptive Biotechnologies) in accordance with IMWG guidelines regarding the assessment of MRD.[23] For the analyses of a complete response or better and of MRD-negative status among patients with a complete response, a two-sided P value was calculated with the use of the stratified Cochran–Mantel–Haenszel chi-square test. A P value is not reported for the analyses of MRD-negative status in the intention-to-treat population and MRD-negative status sustained for at least 12 months because these analyses were not key secondary end points.

tent with those at 10^{-5} sensitivity (40.0% vs. 22.7%; odds ratio, 2.27; 95% CI, 1.48 to 3.48).

A progression-free survival benefit was observed in patients with MRD-negative status as compared with those with MRD-positive status in the isatuximab-VRd group (hazard ratio for disease progression or death, 0.22; 95% CI, 0.14 to 0.35) and to a lesser extent in the VRd group (hazard ratio, 0.31; 95% CI, 0.19 to 0.52). Patients who had a sustained MRD-negative status lasting at least 12 months had a progression-free survival benefit as compared with those who had MRD-negative status for less than 12 months (Tables S5 and S6 and Figs. S5 and S6).

As of the data-cutoff date, 128 patients (69 [26.0%] in the isatuximab-VRd group and 59 [32.6%] in the VRd group) had died (Fig. 3A). The estimated overall survival at 60 months was 72.3% in the isatuximab-VRd group and 66.3% in the VRd group (hazard ratio for death, 0.78; 99.97% CI, 0.41 to 1.48); the upper boundary of the confidence interval for the hazard ratio passed the prespecified futility threshold (>1.1), and follow-up is ongoing. The overall incidence of death (including from adverse events that occurred during the treatment and post-treatment periods) tended to favor the isatuximab-VRd group over the VRd group (26.2% vs. 32.6%), owing largely to the lower mortality from disease progression in the isatuximab-VRd group (4.9% vs. 12.2%); this finding was supported by the time to death ac-



cording to a cause-specific analysis of competing risks (Fig. S7). Death not due to disease progression occurred in 21.1% of the patients in the isatuximab-VRd group and in 20.4% of those in the VRd group.

As of the data-cutoff date, further antimyeloma therapy had been initiated in 19.6% of the patients in the isatuximab-VRd group and in 44.2% of those in the VRd group. Among these patients, the percentage who received an anti-

Figure 3 (facing page). Overall Survival and Quality of Life (Intention-to-Treat Population).

Shown are the results of the Kaplan–Meier estimates of overall survival (Panel A) and quality of life on the basis of disease assessment by investigators and including symptomatic deterioration among patients in the intention-to-treat population and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 global health status and quality-of-life score (Panel B). Scores range from 0 to 100, with higher scores indicating a better health status and quality of life. The median follow-up was 59.7 months. The 128 deaths represent a 63% information fraction of the final overall survival analysis. As of the data-cutoff date, 25 patients from the VRd group had crossed over to isatuximab-Rd treatment after confirmation of a first disease progression. Among these patients, 12 (48%) had died by the data-cutoff date. I bars represent the standard deviation. Data are shown slightly offset at each time point for better visibility. Cycles in which fewer than 20 patients overall received treatment are not presented. The end-of-treatment (EOT) assessment occurred at 30 days after the last administration of trial treatment, and follow-up (FU) lasted until 90 days after the last administration of trial treatment.

CD38 agent was lower in the isatuximab-VRd group than in the VRd group (34.6% vs. 68.8%) (Table S7). At 60 months, second progression–free survival was 65.4% in the isatuximab-VRd group and 54.9% in the VRd group. The benefit with isatuximab-VRd therapy continued through a subsequent line of therapy (hazard ratio for disease progression or death in the second progression–free survival analysis, 0.70; 95% CI, 0.51 to 0.95) (Fig. S8). The time to the next treatment appeared to be longer in the isatuximab-VRd group than in the VRd group (hazard ratio, 0.38; 95% CI, 0.26 to 0.53) (Fig. S9). The EORTC QLQ-C30 global health status domain score remained stable over time in the two trial groups, with no negative effect observed with the addition of isatuximab (Fig. 3B).

SAFETY

Table 2 summarizes hematologic laboratory abnormalities and common adverse events. A summary of safety analyses is provided in Table S8. The incidence of adverse events leading to definitive discontinuation was 22.8% with isatuximab-VRd and 26.0% with VRd (Table S9). Serious adverse events were reported in 70.7% of the patients who received isatuximab-VRd and in 67.4% of those who received VRd (Table S10).

The incidence of infection of grade 3 or higher was 44.9% with isatuximab-VRd and 38.1% with VRd. The incidence of infection of grade 3 or higher was lower among patients who received antibiotic prophylaxis than among those who did not (43.5% vs. 51.0% in the isatuximab-VRd group, and 35.2% vs. 48.7% in the VRd group).

Grade 5 adverse events during the treatment period were reported in 29 of 263 patients (11.0%) in the isatuximab-VRd group and in 10 of 181 (5.5%) in the VRd group. Four deaths (in 1.5% of the patients) in the isatuximab-VRd group and 1 death (in 0.6%) in the VRd group occurred within 60 days after the receipt of the first dose. The difference was driven in part by different treatment exposures (0.031 grade 5 adverse events per patient-year in the isatuximab-VRd group and 0.019 events per patient-year in the VRd group) (Tables S11, S12, and S13). During treatment, grade 5 adverse events were caused mainly by infection (in 17 patients [6.5%] in the isatuximab-VRd group and in 7 [3.9%] in the VRd group), including Covid-19 (in 8 patients [3.0%] and in 2 [1.1%], respectively). (The effect of Covid-19–related adverse events is reported in Fig. S10 and Table S14.)

Invasive solid-tumor second primary cancer was reported in 22 patients (8.4%) in the isatuximab-VRd group and in 8 (4.4%) in the VRd group (Table 2). Additional data are provided in the Supplementary Appendix.

DISCUSSION

Results from this interim analysis of the international, phase 3 IMROZ trial showed that the addition of isatuximab to a VRd regimen led to a significant 40% lower risk of progression or death at a median follow-up of 5 years. The estimated progression-free survival at 60 months was 63.2% in the isatuximab-VRd group, as compared with 45.2% in the VRd group — a finding that highlights the profound progression-free survival benefit with the isatuximab-VRd regimen in patients 80 years of age or younger with previously untreated myeloma who were ineligible for transplantation. Progression-free survival with VRd was longer in this trial than in other phase 3 trials involving comparable patient populations.[3,24] The progression-free survival benefit with isatuximab-VRd was maintained through the subsequent line of therapy and the time to

Table 2. Hematologic Laboratory Abnormalities, Adverse Events of Any Grade, and Second Primary Cancers (Safety Population).*

Event	Isatuximab-VRd (N = 263)		VRd (N = 181)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Hematologic laboratory abnormalities†				
Anemia	260 (98.9)	46 (17.5)	177 (97.8)	29 (16.0)
Lymphopenia	251 (95.4)	158 (60.1)	167 (92.3)	96 (53.0)
Neutropenia	230 (87.5)	143 (54.4)	145 (80.1)	67 (37.0)
Leukopenia	256 (97.3)	83 (31.6)	160 (88.4)	30 (16.6)
Thrombocytopenia	251 (95.4)	79 (30.0)	153 (84.5)	50 (27.6)
Nonhematologic adverse events				
Infection‡				
Pneumonia	79 (30.0)	53 (20.2)	35 (19.3)	23 (12.7)
Bronchitis	58 (22.1)	7 (2.7)	32 (17.7)	3 (1.7)
Upper respiratory tract infection	90 (34.2)	2 (0.8)	61 (33.7)	2 (1.1)
Diarrhea	144 (54.8)	20 (7.6)	88 (48.6)	15 (8.3)
Peripheral sensory neuropathy	143 (54.4)	19 (7.2)	110 (60.8)	11 (6.1)
Cataract	100 (38.0)	41 (15.6)	46 (25.4)	20 (11.0)
Constipation	94 (35.7)	6 (2.3)	74 (40.9)	3 (1.7)
Fatigue	91 (34.6)	21 (8.0)	48 (26.5)	12 (6.6)
Peripheral edema	86 (32.7)	0	59 (32.6)	2 (1.1)
Infusion-related reaction	62 (23.6)	1 (0.4)	2 (1.1)	0
Covid-19§	78 (29.7)	23 (8.7)	37 (20.4)	12 (6.6)
Insomnia	59 (22.4)	10 (3.8)	44 (24.3)	4 (2.2)
Back pain	58 (22.1)	9 (3.4)	31 (17.1)	3 (1.7)
Asthenia	57 (21.7)	7 (2.7)	44 (24.3)	4 (2.2)
Invasive second primary cancer¶				
Solid tumor‖	22 (8.4)	14 (5.3)	8 (4.4)	6 (3.3)
Hematologic cancer	3 (1.1)	1 (0.4)	2 (1.1)	2 (1.1)

* The safety population included all the patients who received at least one dose of trial treatment. The grading of adverse events was based on the Common Terminology Criteria for Adverse Events, version 4.03, of the National Cancer Institute. Adverse events of any grade that were reported in at least 20% of patients in either treatment group are listed. Events are listed according to preferred term. The worst grade of event in each patient is reported.

† The laboratory abnormalities listed here were those that occurred during the treatment period.

‡ The three categories of infection events that are presented are not exclusive.

§ The adverse event of coronavirus disease 2019 (Covid-19) included both Covid-19 and Covid-19–related pneumonia. Two patients in the isatuximab-VRd group and one in the VRd group had both Covid-19–related pneumonia and Covid-19. These patients are counted only once for all events of Covid-19–related adverse events that occurred during treatment.

¶ The presence of a second primary cancer was prespecified in the protocol as an adverse event of special interest. This event was identified with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA) Custom MedDRA Query "second primary malignancies." The events shown included those that occurred during treatment and after the treatment period.

‖ Solid tumor included melanoma and one case of metastasis to the peritoneum. In addition, 19 patients in the isatuximab-VRd group and 7 in the VRd group had nonmelanoma skin cancer. In the isatuximab-VRd group, 2 of the 19 patients also had melanoma. In the VRd group, 1 of the 7 patients also presented with adenocarcinoma of the colon.

next treatment. The results for patients with high-risk cytogenetic features in this analysis did not show a progression-free survival benefit with isatuximab-VRd. Further analyses and longer follow-up are warranted on the basis of the observed benefits with isatuximab-based combinations in patients with high-risk cytogenetic features in the contexts of first-line therapy and relapsed disease.[15,25-27]

In patients with previously untreated myeloma, deep and sustained responses are associated with improved progression-free and overall survival, and MRD-negative status is an important prognostic factor.[28,29] In this trial, treatment with isatuximab-VRd resulted in deep and sustained responses, with significant improvements in patients with MRD-negative status and a complete response and higher percentages of patients with MRD-negative status and sustained MRD-negative status for at least 12 months (at any point, in the intention-to-treat population). In addition, MRD-negative status was associated with improved progression-free survival.

Disease control in the context of first-line therapy is critical in older patients with myeloma.[4,6,7] Early use of efficacious regimens that include an anti-CD38 agent is warranted, given that the median progression-free survival and overall survival progressively decrease with successive treatments and the duration of response shortens with each relapse.[4,30,31] The phase 3 MAIA trial of Rd, with or without the anti-CD38 daratumumab (i.e., D-Rd vs. Rd),[32] established D-Rd as a standard regimen in patients with previously untreated myeloma who were ineligible for transplantation, including in those older than 80 years of age. Although we acknowledge the limitations of cross-trial comparisons, we note that at a median follow-up of 60 months in the IMROZ trial, 31.7% of the patients (84 of 265) in the isatuximab-VRd group had disease progression or died, as compared with 43.5% of the patients (160 of 368) in the D-Rd group in the MAIA trial, at a similar follow-up of 56.6 months.[33] Of note, in the MAIA trial, nearly 45% of the patients were 75 years of age or older, whereas our trial excluded patients older than 80 years of age.

The safety profile of isatuximab-VRd in the IMROZ trial was consistent with that among patients eligible for transplantation in the phase 3 GMMG-HD7 trial of isatuximab-VRd as compared with VRd,[17] with no new safety signals and with a similar incidence in the two groups of serious adverse events during the treatment period and of adverse events leading to definitive discontinuation. The incidence of infection of grade 3 or higher was 44.9% with isatuximab-VRd and 38.1% with VRd, and the incidence of neutropenia of grade 3 or higher (assessed as laboratory abnormalities) was 54.4% and 37.0%, respectively. In both groups, the incidence of infection of grade 3 or higher was lower with antibiotic prophylaxis (starting at induction) than with no prophylaxis. The incidence of peripheral sensory neuropathy was not higher with isatuximab-VRd than with VRd in this trial.

Overall, 78 patients (29.7%) in the isatuximab-VRd group and 37 (20.4%) in the VRd group had Covid-19–related adverse events. Despite the trial occurring during the Covid-19 pandemic, the incidence of Covid-19 (including Covid-19–related pneumonia) of grade 3 or higher was low (8.7% in the isatuximab-VRd group and 6.6% in the VRd group). During continuous treatment, 8 patients (3.0%) in the isatuximab-VRd group and 2 (1.1%) in the VRd group died from Covid-19, with the imbalance observed mainly in 2021.

In a Spanish phase 3 trial involving patients younger than 80 years of age with newly diagnosed multiple myeloma who were considered to be fit but were ineligible for transplantation, toxic effect–related mortality was higher with D-KRd than with KRd, mostly from infections, including more Covid-19–related deaths.[21] Furthermore, patients with frailty, who were identified on the basis of higher Geriatric Assessment in Hematology scale scores, were more likely to discontinue treatment because of toxic effects and generally had worse progression-free survival than those without frailty, which suggests that such metrics may help guide therapeutic selection.[21] Post hoc analyses of patients with frailty who were enrolled in our trial are under way.

The incidence of death from an adverse event was higher in the isatuximab-VRd group (11.0%) than in the VRd group (5.5%), including more Covid-19–related deaths. The overall incidence of death from any cause appeared to be lower in the isatuximab-VRd group than in the VRd group (26.2% vs. 32.6%), as did the incidence of death from disease progression (4.9% vs. 12.2%). Overall, the imbalance between the groups in the incidence of infection of grade 3 or higher and of grade 5 adverse events is probably attributable to

differences in treatment exposure and an imbalance in the occurrence of Covid-19–related events. The higher incidence of second cancer in the isatuximab-VRd group than in the VRd group is unexplained. Other trials involving patients with newly diagnosed myeloma (e.g., MAIA and FIRST [Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide]) have shown an incidence of second cancer similar to that observed in the IMROZ trial, but the contributing factors are undefined.[32,34]

Currently, VRd and D-Rd are the preferred regimens for patients with previously untreated myeloma who are ineligible for transplantation.[2] Although not designed specifically for older patients, the SWOG S0777 trial[3] showed significantly improved outcomes with VRd as compared with Rd in patients with previously untreated multiple myeloma without an intention to undergo immediate transplantation. IMROZ is an international, phase 3 trial of an anti-CD38 agent combined with VRd in patients with previously untreated myeloma who are ineligible for transplantation, and the results of this trial complement those from a phase 1b trial involving patients with no immediate intention to undergo transplantation and those from the phase 3 GMMG-HD7 trial involving patients who were eligible to undergo transplantation, showing the benefit of isatuximab-VRd across the disease continuum.[17,22] The ongoing BENEFIT trial of isatuximab-VRd as compared with isatuximab-Rd in patients with newly diagnosed multiple myeloma who do not have frail status and are ineligible to undergo transplantation is investigating the effects of bortezomib on a triplet regimen of an anti-CD38 agent, lenalidomide, and dexamethasone (ClinicalTrials.gov number, NCT04751877). We acknowledge that Black patients were underrepresented in the IMROZ trial, which is a limitation.

In this phase 3 trial, we found a progression-free survival benefit and consistent deep responses with first-line isatuximab-VRd treatment over standard VRd therapy. The toxicity of the regimen was similar to that of the current standard regimens.

Supported by Sanofi. Enrollment at the University of Texas M.D. Anderson Cancer Center was supported by a Cancer Center Support Grant (P30 CA16672).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participating patients, their families, and the staff at the trial centers; Michele Cavo, M.D.; Wendell Lamar Blackwell, Ph.D. (of Sanofi), for coordination of the development of the manuscript, facilitation of author discussion, and critical review of the manuscript; and Erin Burns-Tidmore, Ph.D., Kirsty Lee, M.P.H., Richard J. Hogan, Ph.D., Sara Mariani, M.D., Ph.D., and Camile Grubor, Ph.D. (all of Envision Pharma Group), for medical writing assistance with an earlier version of the manuscript, funded by Sanofi.

APPENDIX

The authors' affiliations are as follows: the Department of Hematology, Centre Hospitalier Universitaire (CHU) de Lille, University of Lille, Lille (T.F., S. Manier), the French National Academy of Medicine (T.F.), and the Department of Hematology, Hôpital Saint-Antoine, Sorbonne University and INSERM (M.M.), Paris, Service d'Hématologie et Thérapie Cellulaire, CHU and Centre d'Investigation Clinique INSERM Unité 1402, Poitiers (X.P.L.), the Department of Hematology, University Hospital Hôtel-Dieu, Nantes (P.M.), and Sanofi, Research and Development, Vitry-sur-Seine (C.O., M.-F.B., S. Macé, C.B.) — all in France; the Plasma Cell Dyscrasia Unit, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens (M.-A.D.); the Department of Hematology, Ankara University, and the Istinye University Ankara Liv Hospital, Ankara (M.B.), and the Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul (S.K.-B.) — all in Turkey; the Department of Internal Medicine, Hematology, and Oncology, University Hospital Brno, Brno (L.P.), the Department of Hemato-Oncology, University Hospital Ostrava, and the Faculty of Medicine, University of Ostrava, Ostrava (R.H.), the Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc (J.M.), and the Charles University and General Hospital in Prague, Prague (I.S.) — all in the Czech Republic; Shengjing Hospital of China Medical University, Shenyang, China (Z.L.); the Department of Lymphoid Malignancies, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw (J.R.-J.), and the Department of General Hematology, Copernicus Memorial Hospital, Comprehensive Cancer Center and Traumatology, Łódź (P.R.) — both in Poland; the S.P. Botkin Moscow City Clinical Hospital, Moscow (V.I.V.); the Department of Hematology, Oncology, Immunology, and Rheumatology, University Hospital of Tübingen, Tübingen (B.B.), and the Department of Internal Medicine V, University of Heidelberg, Heidelberg (H.G.) — both in Germany; the Japanese Red Cross Medical Center, Tokyo (T.I.); Calvary Mater Newcastle, Newcastle, NSW (W.J.), and the Illawarra Cancer Care Centre, Wollongong, NSW (G.P.) — both in Australia; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," and Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy (E.Z.); the Division of Hematology–Oncology, University of California, San Francisco, San Francisco (T.G.M.); Sanofi, Patient Safety and Pharmacovigilance, Bridgewater, NJ (D.B.); Sanofi, Cambridge, MA (Z.K.); and the Department of Lymphoma and Myeloma, University of Texas M.D. Anderson Cancer Center, Houston (R.Z.O.).

REFERENCES

1. Rajkumar SV, Kumar S. Multiple myeloma current treatment algorithms. Blood Cancer J 2020;10:94.
2. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021; 32:309-22.
3. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet 2017;389:519-27.
4. Fonseca R, Usmani SZ, Mehra M, et al. Frontline treatment patterns and attrition rates by subsequent lines of therapy in patients with newly diagnosed multiple myeloma. BMC Cancer 2020;20:1087.
5. Bruno AS, Willson JL, Opalinska JM, et al. Recent real-world treatment patterns and outcomes in US patients with relapsed/refractory multiple myeloma. Expert Rev Hematol 2020;13:1017-25.
6. Raab MS, Cavo M, Delforge M, et al. Multiple myeloma: practice patterns across Europe. Br J Haematol 2016;175:66-76.
7. Facon T, Leleu X, Manier S. How I treat multiple myeloma in geriatric patients. Blood 2024;143:224-32.
8. Jiang H, Acharya C, An G, et al. SAR650984 directly induces multiple myeloma cell death via lysosomal-associated and apoptotic pathways, which is further enhanced by pomalidomide. Leukemia 2016;30:399-408.
9. Sarclisa. Bridgewater, NJ: Sanofi, 2021 (https://products.sanofi.us/Sarclisa/sarclisa_patient_information.pdf).
10. Tai Y-T, Anderson KC. Targeting CD38 alleviates tumor-induced immunosuppression. Oncotarget 2017;8:112166-7.
11. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol 2022;97:1086-107.
12. Sanofi. Sarclisa highlights of prescribing information, November 2023 (https://products.sanofi.us/Sarclisa/sarclisa.pdf).
13. Sarclisa, INN-Isatuximab. Summary of product characteristics. 2021 (https://www.ema.europa.eu/en/documents/product-information/sarclisa-epar-product-information_en.pdf).
14. Sarclisa (isatuximab). Prescribing information. 2021. (In Japanese) (https://www.pmda.go.jp/drugs/2021/P20211111001/780069000_30200AMX00511000_A100_1.pdf).
15. Gay F, Roeloffzen W, Dimopoulos MA, et al. Results of the phase III randomized iskia trial: isatuximab-carfilzomib-lenalidomide-dexamethasone vs carfilzomib-lenalidomide-dexamethasone as pre-transplant induction and post-transplant consolidation in newly diagnosed multiple myeloma patients. Blood 2023; 142:Suppl:4. abstract.
16. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet 2019; 394:29-38.
17. Goldschmidt H, Mai EK, Bertsch U, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. Lancet Haematol 2022;9(11):e810-e821.
18. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2024; 390:301-13.
19. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med 2018;378:518-28.
20. Zweegman S, Usmani SZ, Chastain K, et al. Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab (DARA) in patients (pts) with newly diagnosed multiple myeloma (NDMM) for whom transplant is not planned as initial therapy: a multicenter, randomized, phase III study (CEPHEUS). J Clin Oncol 2019;37:Suppl 15:TPS8056 (https://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.TPS8056). abstract.
21. Mateos M-V, Paiva B, Cedena Romero MT, et al. GEM2017FIT Trial: induction therapy with bortezomib-melphalan and prednisone (VMP) followed by lenalidomide and dexamethasone (Rd) versus carfilzomib, lenalidomide and dexamethasone (KRd) plus/minus daratumumab (D), 18 cycles, followed by consolidation and maintenance therapy with lenalidomide and daratumumab: phase III, multicenter, randomized trial for elderly fit newly diagnosed multiple myeloma (NDMM) patients aged between 65 and 80 years. Blood 2023; 142:Suppl:209. abstract.
22. Ocio EM, Perrot A, Bories P, et al. Efficacy and safety of isatuximab plus bortezomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma ineligible/with no immediate intent for autologous stem cell transplantation. Leukemia 2023;37:1521-9.
23. Kumar S, Paiva B, Anderson KC, et al. International myeloma working group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17(8): e328-e346.
24. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 2020;21:1317-30.
25. Leypoldt LB, Tichy D, Besemer B, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone for the treatment of high-risk newly diagnosed multiple myeloma. J Clin Oncol 2024;42: 26-37.
26. Spicka I, Moreau P, Martin TG, et al. Isatuximab plus carfilzomib and dexamethasone in relapsed multiple myeloma patients with high-risk cytogenetics: IKEMA subgroup analysis. Eur J Haematol 2022;109:504-12.
27. Harrison SJ, Perrot A, Alegre A, et al. Subgroup analysis of ICARIA-MM study in relapsed/refractory multiple myeloma patients with high-risk cytogenetics. Br J Haematol 2021;194:120-31.
28. Paiva B, van Dongen JJM, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. Blood 2015;125:3059-68.
29. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: a meta-analysis. JAMA Oncol 2017; 3:28-35.
30. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol 2016; 175:252-64.
31. Verelst SGR, Blommestein HM, De Groot S, et al. Long-term outcomes in patients with multiple myeloma: a retrospective analysis of the Dutch Population-based HAematological Registry for Observational Studies (PHAROS). Hemasphere 2018; 2(4):e45.
32. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med 2019;380:2104-15.
33. Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:1582-96.
34. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014; 371:906-17.

The NEW ENGLAND JOURNAL of MEDICINE

The *New England Journal of Medicine* (ISSN 0028-4793) is published weekly in the English language from Editorial Offices at 10 Shattuck Street, Boston, MA 02115-6094 USA – Fax: (617) 734-4457. Business and Subscription Offices are at 860 Winter Street, Waltham, MA 02451-1412 USA – Tel: (781) 893-3800 x5515; website: www.nejm.org.

NEJM GROUP

2409101023555KD - 04/2025 N°VISA : 25/01/66510210/PM/001