ORIGINAL ARTICLE

Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

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ABSTRACT

BACKGROUND

In patients with newly diagnosed multiple myeloma, the effect of adding autologous stem-cell transplantation (ASCT) to triplet therapy (lenalidomide, bortezomib, and dexamethasone [RVD]), followed by lenalidomide maintenance therapy until disease progression, is unknown.

METHODS

In this phase 3 trial, adults (18 to 65 years of age) with symptomatic myeloma received one cycle of RVD. We randomly assigned these patients, in a 1:1 ratio, to receive two additional RVD cycles plus stem-cell mobilization, followed by either five additional RVD cycles (the RVD-alone group) or high-dose melphalan plus ASCT followed by two additional RVD cycles (the transplantation group). Both groups received lenalidomide until disease progression, unacceptable side effects, or both. The primary end point was progression-free survival.

RESULTS

Among 357 patients in the RVD-alone group and 365 in the transplantation group, at a median follow-up of 76.0 months, 328 events of disease progression or death occurred; the risk was 53% higher in the RVD-alone group than in the transplantation group (hazard ratio, 1.53; 95% confidence interval [CI], 1.23 to 1.91; P<0.001); median progression-free survival was 46.2 months and 67.5 months. The percentage of patients with a partial response or better was 95.0% in the RVD-alone group and 97.5% in the transplantation group (P=0.55); 42.0% and 46.8%, respectively, had a complete response or better (P=0.99). Treatment-related adverse events of grade 3 or higher occurred in 78.2% and 94.2%, respectively; 5-year survival was 79.2% and 80.7% (hazard ratio for death, 1.10; 95% CI, 0.73 to 1.65).

CONCLUSIONS

Among adults with multiple myeloma, RVD plus ASCT was associated with longer progression-free survival than RVD alone. No overall survival benefit was observed. (Funded by the National Heart, Lung, and Blood Institute and others; DETERMINATION ClinicalTrials.gov number, NCT01208662.)

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*A list of the DETERMINATION Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The most appropriate use of induction therapy,[1-8] autologous stem-cell transplantation (ASCT),[1,9] and maintenance therapy[5,10] for patients with newly diagnosed multiple myeloma who are eligible to undergo ASCT continues to evolve.[11,12] The Intergroupe Francophone du Myélome (IFM) 2009 trial, in which patients received induction treatment with triplet therapy (lenalidomide, bortezomib, and dexamethasone [RVD]) alone or with high-dose melphalan plus ASCT, followed by lenalidomide maintenance therapy for 1 year,[1] showed superior progression-free survival with the use of ASCT.[9] These findings provided support for the benefit of ASCT in patients with newly diagnosed myeloma. In that trial, in which patients had multiple effective treatment options at relapse and in which many received ASCT after RVD alone, no overall survival benefit of RVD plus ASCT was evident after a median follow-up of more than 7 years.[9]

Further improvement in first-line treatment with both non-ASCT and ASCT-based approaches to increase progression-free and overall survival is an important goal. In addition, determination of whether individual patients may benefit from a particular approach is essential for improving treatment. We report primary data from the phase 3 DETERMINATION trial, which was originally designed as a parallel study to the IFM 2009 trial but was amended to include the use of lenalidomide maintenance therapy until disease progression in both the RVD-alone group and the RVD-plus-ASCT (transplantation) group.

Methods

Trial Design and Oversight

This randomized, open-label trial was conducted at 56 clinical sites in the United States. Patients were recruited between October 1, 2010, and January 30, 2018. The trial protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board or ethics committee at each participating site. All the patients provided written informed consent before treatment. The trial was designed by the senior academic investigators. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. Preparation of an earlier version of the manuscript was paid for by the Dana–Farber Cancer Institute and the R.J. Corman Multiple Myeloma Research Fund. Information on trial oversight is provided in the Oversight section in the Supplementary Appendix, available at NEJM.org.

A Quick Take is available at NEJM.org

Patients

Eligible patients were 18 to 65 years of age and had symptomatic, measurable, newly diagnosed myeloma and an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability). Exclusion criteria included the previous use of systemic therapy for myeloma, central nervous system involvement, primary amyloidosis, and inadequate hematologic, hepatic, renal, or cardiac function (Table S1 in the Supplementary Appendix). Full eligibility criteria are provided in the protocol.

Treatment

All the patients received one cycle of RVD. After this cycle, the patients were randomly assigned, in a 1:1 ratio, to the RVD-alone group or the transplantation group. Randomization was stratified according to International Staging System (ISS) disease stage (I, II, or III, with higher stages indicating a poorer prognosis) and cytogenetic risk profile, with high risk defined by the presence of a 17p deletion, a t(4;14) translocation, or a t(14;16) translocation, as determined by fluorescence in situ hybridization (FISH); standard risk by the absence of high-risk abnormalities; and undetermined risk by test failure. A screening bone marrow sample was assessed locally to determine cytogenetic risk, with thresholds for test positivity determined in accordance with institutional standards.

Patients in both groups received two additional cycles of RVD, followed by stem-cell collection. Patients in the RVD-alone group then received five additional RVD cycles, whereas those in the transplantation group received high-dose melphalan (at a dose of 200 mg per square meter of body-surface area, adjusted for ideal body weight) plus ASCT and, on recovery (approximately day 60), two additional RVD cycles. Each 21-day cycle of RVD therapy consisted of the following: oral lenalidomide (at a dose of 25 mg on days 1 through 14); intravenous or, after a protocol amendment, subcutaneous bortezomib (1.3 mg per square meter on days 1, 4, 8, and 11); and oral dexamethasone (20 mg in cycles 1 to 3 and

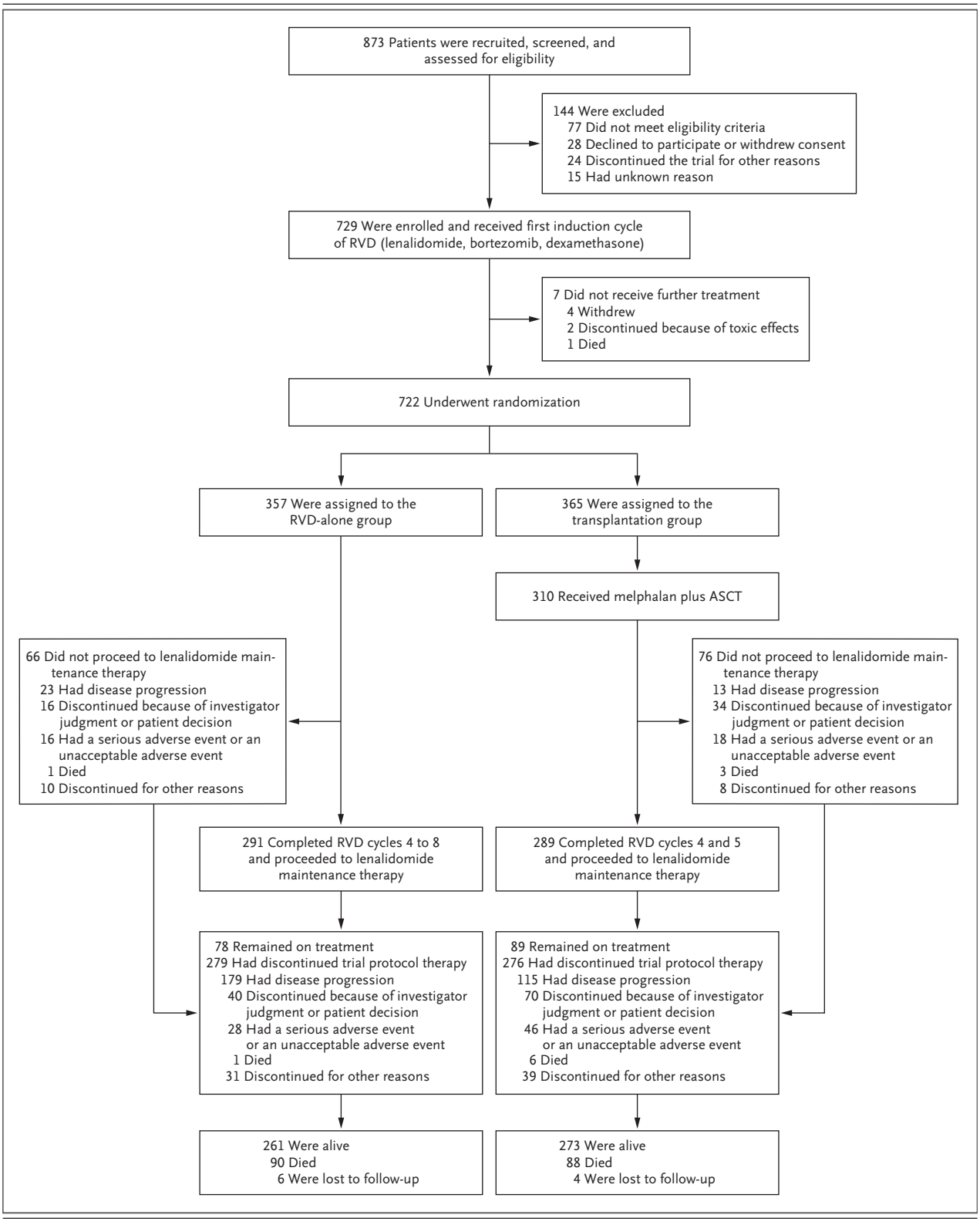

Figure 1 (facing page). Screening, Randomization, Treatment, and Follow-up.

Of the 77 patients who did not meet eligibility criteria, 32 did not have measurable disease or had minimal measurable disease, 9 did not have end-organ damage as defined by the CRAB criteria (i.e., hypercalcemia, renal insufficiency, anemia, or bone lesions),[13] 26 had laboratory values outside permitted cutoff levels, 4 had exceeded the limit of previous therapy, and 6 had screening failure. Of the 24 patients who discontinued the trial for other reasons, 9 had another complicating disease, 8 had insurance issues, 4 discontinued because of physician decision, 2 were unable to adhere to the trial protocol, and 1 had received an alternative therapy. The 76 patients who did not receive lenalidomide maintenance therapy included the 55 patients who had not received melphalan and undergone autologous stem-cell transplantation (ASCT). Of the 31 patients in the RVD (lenalidomide, bortezomib, dexamethasone)–alone group who discontinued the trial therapy for other reasons, 10 (2 before maintenance therapy) had received therapy outside the trial protocol for another cancer, 2 (1 before maintenance therapy) had received therapy outside the trial protocol for multiple myeloma, 4 (2 before maintenance therapy) had a treatment delay of more than 6 weeks, 7 (4 before maintenance therapy) withdrew consent, 1 had other reasons for discontinuation before maintenance therapy, and 7 had missing data. Of the 39 patients in the transplantation group who discontinued the trial therapy for other reasons, 13 (1 before maintenance therapy) had received therapy outside the trial protocol for another cancer, 2 (1 before maintenance therapy) had received therapy outside the trial protocol for multiple myeloma, 15 (4 before maintenance therapy) had a treatment delay of more than 6 weeks, 5 (2 before maintenance therapy) withdrew consent, and 4 had missing data.

10 mg starting in cycle 4 on days 1, 2, 4, 5, 8, 9, 11, and 12) (Fig. S1).

Maintenance therapy in both groups consisted of daily lenalidomide (at a dose of 10 mg, with a possible increase to 15 mg thereafter, depending on side effects) until disease progression, unacceptable toxic effects, or withdrawal from treatment or the trial. After completion of the protocol-specified treatment, off-trial salvage transplantation was recommended but not mandated for patients in the RVD-alone group at relapse; patients in the transplantation group could undergo a second transplantation. The selection of subsequent therapies was made in accordance with patient and physician decision.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival. Secondary end points included response rates, the duration of response, the time to disease progression, overall survival, quality of life, and adverse events. End points, planned correlative studies, and schedules of assessments are described fully in the Objectives, End Points, and Definitions section in the Supplementary Appendix.

Disease response and progression were assessed according to the International Myeloma Working Group response criteria[13] on day 1 of each RVD cycle; after ASCT and before RVD cycle 4 (in the transplantation group); and before lenalidomide maintenance therapy and every 4 weeks while the patients were receiving this maintenance therapy. A confirmatory assessment was conducted in all patients with a response. The schedule for obtaining bone marrow aspirate samples for evaluation of responses and for correlative analyses is described in the Supplementary Appendix. Patients who discontinued treatment before disease progression were followed every 2 months until progression; all the patients were followed for survival.

Safety was evaluated throughout trial treatment, including ASCT, and through 30 days after receipt of the last dose of a trial drug. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; the relationship of adverse events to the trial treatment was assessed in accordance with the World Health Organization–Uppsala Monitoring Centre system for causality assessment (https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf). Patients were asked to complete three outcome instruments at eight time points during the treatment period. Full details of the assessments and patient-reported outcome instruments are provided in the protocol.

Quality of life was assessed with the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30), which includes five function scales, nine symptom scales, and a global health status and quality-of-life scale; results for the global health status and quality-of-life scale and

Table 1. Baseline Characteristics of the Patients.*

Characteristic	RVD-Alone Group (N=357)	Transplantation Group (N=365)
Median age (IQR) — yr	57 (25–66)	55 (30–65)
Age category — no. (%)		
<60 yr	235 (65.8)	263 (72.1)
≥60 yr	122 (34.2)	102 (27.9)
Male sex — no. (%)	202 (56.6)	215 (58.9)
Race — no./total no. (%)†		
White	268/351 (76.4)	272/359 (75.8)
Black	66/351 (18.8)	66/359 (18.4)
Asian	8/351 (2.3)	12/359 (3.3)
Other	9/351 (2.6)	9/359 (2.5)
Ethnic group — no./total no. (%)†		
Hispanic	19/355 (5.4)	23/355 (6.5)
Non-Hispanic	336/355 (94.6)	332/355 (93.5)
ECOG performance-status score — no./total no. (%)‡		
0	153/357 (42.9)	164/364 (45.1)
1	177/ 357 (49.6)	161/364 (44.2)
2	27/357 (7.6)	39/364 (10.7)
Median BMI (IQR)§	28.5 (25.3–32.8)	29.0 (25.5–32.8)
BMI — no. (%)§		
<25	80 (22.4)	81 (22.2)
25 to <30	141 (39.5)	127 (34.8)
≥30	136 (38.1)	157 (43.0)
Type of multiple myeloma — no./total no. (%)¶		
IgG	220/330 (66.7)	200/337 (59.3)
IgA	72/330 (21.8)	95/337 (28.2)
Light chain only	34/330 (10.3)	41/337 (12.2)
Other	4/330 (1.2)	1/337 (0.3)
Serum β_2-microglobulin level — no./total no. (%)		
<3.5 mg/liter	211/357 (59.1)	224/363 (61.7)
3.5 to <5.5 mg/liter	95/357 (26.6)	91/363 (25.1)
≥5.5 mg/liter	51/357 (14.3)	48/363 (13.2)
ISS disease stage — no. (%)‖**		
I	178 (49.9)	184 (50.4)
II	130 (36.4)	134 (36.7)
III	49 (13.7)	47 (12.9)
Lactate dehydrogenase level — no./total no. (%)		
Not elevated, <225 U/liter	260/356 (73.0)	270/362 (74.6)
Elevated, ≥225 U/liter	96/356 (27.0)	92/362 (25.4)
Cytogenetic risk category — no./total no. (%)**††‡‡		
High risk	66/334 (19.8)	66/340 (19.4)
Standard risk	268/334 (80.2)	274/340 (80.6)

Table 1. (Continued.)

Characteristic	RVD-Alone Group (N=357)	Transplantation Group (N=365)
Cytogenetic abnormalities — no./total no. (%)‡‡§§		
t(4;14)	32/333 (9.6)	28/340 (8.2)
t(14;16)	10/333 (3.0)	15/340 (4.4)
del17p	38/333 (11.4)	34/340 (10.0)
Other	261/333 (78.4)	272/340 (80.0)
Revised ISS disease stage — no./total no. (%)¶¶		
I	103/333 (30.9)	105/337 (31.2)
II	202/333 (60.7)	211/337 (62.6)
III‖‖	28/333 (8.4)	21/337 (6.2)

* RVD therapy consists of lenalidomide, bortezomib, and dexamethasone. Percentages may not total 100 because of rounding. ASCT denotes autologous stem-cell transplantation, and IQR interquartile range.
† Race or ethnic group was reported by the patients.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability.
§ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
¶ The type of myeloma was not determined for 9 patients in the RVD-alone group and 5 patients in the transplantation group, missing for 2 and 1, and not available owing to serum immunofixation–negative status in 16 and 22, respectively.
‖ The International Staging System (ISS) consists of three stages: stage I, serum β_2-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and serum albumin level 3.5 g per deciliter or higher; stage II, neither stage I nor III; and stage III, serum β_2-microglobulin level 5.5 mg per liter or higher (≥470 nmol per liter). Higher stages indicate more severe disease.
** This variable was a stratification factor.
†† A total of 23 patients in the RVD-alone group and 25 patients in the transplantation group could not be evaluated by means of fluorescence in situ hybridization (FISH).
‡‡ Cytogenetic risk was based on FISH or karyotype analysis; patients who had a high-risk cytogenetic profile had at least one high-risk abnormality (t[4;14], t[14;16], or del17p). Patients with standard risk had no high-risk cytogenetic abnormalities.
§§ Individual abnormalities were unknown for 1 patient in the RVD-alone group. The "other" category includes patients in whom any other cytogenetic abnormality was reported but not those in whom no abnormalities were reported.
¶¶ The revised ISS consists of three stages: stage I, serum β_2-microglobulin level lower than 3.5 mg per liter, serum albumin level of 3.5 g per deciliter or higher, an absence of high-risk cytogenetic abnormalities, and a normal lactate dehydrogenase level (here defined as <225 U per liter); stage II, neither revised stages I or III; and stage III, serum β_2-microglobulin level 5.5 mg per liter or higher and high-risk cytogenetic abnormalities or a high lactate dehydrogenase level (≥225 U per liter) or both. The revised ISS disease stage was not available for 24 patients in the RVD-alone group and for 28 patients in the transplantation group because 23 patients in the RVD-alone group and 25 patients in the transplantation group could not be evaluated by means of FISH and the lactate dehydrogenase level was missing in 1 patient in the RVD-alone group and in 3 patients in the transplantation group.
‖‖ Among the 49 patients with stage III disease, 8 (16%) had a t(4;14) translocation, 2 (4%) had a t(14;16) translocation, 11 (22%) had a 17p deletion, and 36 (73%) had an elevated lactate dehydrogenase level.

selected function scales are included in this report. Scores on these scales range from 0 to 100 after linear transformation of the raw scores, with higher scores representing better global health status and quality of life. The threshold for a clinically meaningful difference (which was not prespecified) was a change of 10 or more points from baseline. Quality of life was also assessed with the EORTC QLQ-MY20 multiple myeloma module, which includes four scales of disease symptoms, side effects of treatment, body image, and future perspective. Scores on these scales range from 0 to 100, with higher scores representing worse symptoms and side effects of treatment.

STATISTICAL ANALYSIS

We estimated that a sample of 720 patients would provide the trial with 90% power to detect a 30% lower risk of disease progression or death in the transplantation group than in the RVD-alone group; for the primary end point of progression-free survival, this would correspond to a hazard ratio for disease progression or death of 1.43 in

the RVD-alone group as compared with the transplantation group.

The primary analysis of progression-free survival was conducted with the use of a stratified two-sided log-rank test with an overall type I error rate (alpha) of 0.05. Confidence intervals and P values for the seven secondary efficacy analyses were adjusted for multiplicity testing with the use of Bonferroni's procedure to control the family-wise error rate at 0.05. The results of subgroup analyses and preliminary analyses of minimal residual disease and correlative analyses of genetic mutations are reported as point estimates and 95% confidence intervals; the widths of the confidence intervals have not been adjusted for multiplicity (and are denoted as unadjusted), so intervals should not be used in place of a hypothesis test. For quality-of-life evaluations, testing for the between-group difference in the mean change from baseline was conducted at seven time points; P values were adjusted for multiplicity testing with the use of Bonferroni's procedure.

An analysis was planned after full information (329 events of disease progression or death) had been obtained in the planned sample of 720 patients who had undergone randomization. On the basis of simulations, the power calculations were adjusted for the potential to crossover from the RVD-alone group to the transplantation group before disease progression. Two interim analyses were planned after 33% and 69% of the prespecified total number of events of disease progression or death had occurred. The data-cutoff date for the full-information analysis was December 10, 2021, when 328 of 329 events of disease progression or death (99.7%) had occurred. The history of the trial design and the planned interim analyses is summarized in the Supplementary Appendix.

The primary analysis was performed in the intention-to-treat population. Time-to-event end points were estimated by means of the Kaplan–Meier method, with the use of stratified log-rank tests to compare the treatment groups. A multivariable stratified Cox proportional-hazards model was used to estimate hazard ratios and 95% confidence intervals. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and the R software package (R Foundation for Statistical Computing; https://www.r-project.org/).

RESULTS

PATIENTS

Of 873 patients who were recruited, 357 were randomly assigned to the RVD-alone group and 365 were randomly assigned to the transplantation group (Fig. 1). Baseline patient and disease characteristics were balanced between the two groups. The median age was 57 years (interquartile range, 25 to 66) in the RVD-alone group and 55 years (interquartile range, 30 to 65) in the transplantation group, and 122 patients (34.2%) and 102 patients (27.9%), respectively, were 60 years of age or older. The ISS disease stage was II or III in 179 patients in the RVD-alone group (50.1%) and in 181 patients in the transplantation group (49.6%); a high-risk cytogenetic profile was identified in 66 of 334 patients (19.8%) and 66 of 340 patients (19.4%), respectively, with data that could be evaluated by means of FISH (Table 1).

TREATMENT

The median duration of treatment was 28.2 months (95% confidence interval [CI], 21.1 to 36.3) in the RVD-alone group and 36.1 months (95% CI, 28.5 to 41.5) in the transplantation group. In the transplantation group, 310 of 365 patients (84.9%) underwent ASCT (Fig. 1). Among the 291 patients (81.5%) in the RVD-alone group and 289 patients (79.2%) in the transplantation group who received lenalidomide maintenance therapy, the median duration of maintenance therapy was 36.4 months (95% CI, 25.7 to 40.8) and 41.5 months (95% CI, 34.0 to 47.1); 78 patients (26.8%) and 89 patients (30.8%), respectively, were still receiving maintenance therapy at the data-cutoff date. The median percentage of maintenance cycles in which the average lenalidomide dose was at least 10 mg was 87.0% in the RVD-alone group and 60.0% in the transplantation group. The mean lenalidomide dose per cycle in years 1 to 3 of maintenance therapy is summarized in Figure S2.

Among the patients who received lenalidomide maintenance therapy, 259 patients (89.0%) in the RVD-alone group and 264 patients (91.3%) in the transplantation group had at least one dose modification, with 9854 dose modifications reported during maintenance therapy after RVD alone and 13,695 dose modifications reported during maintenance therapy after RVD plus ASCT. The

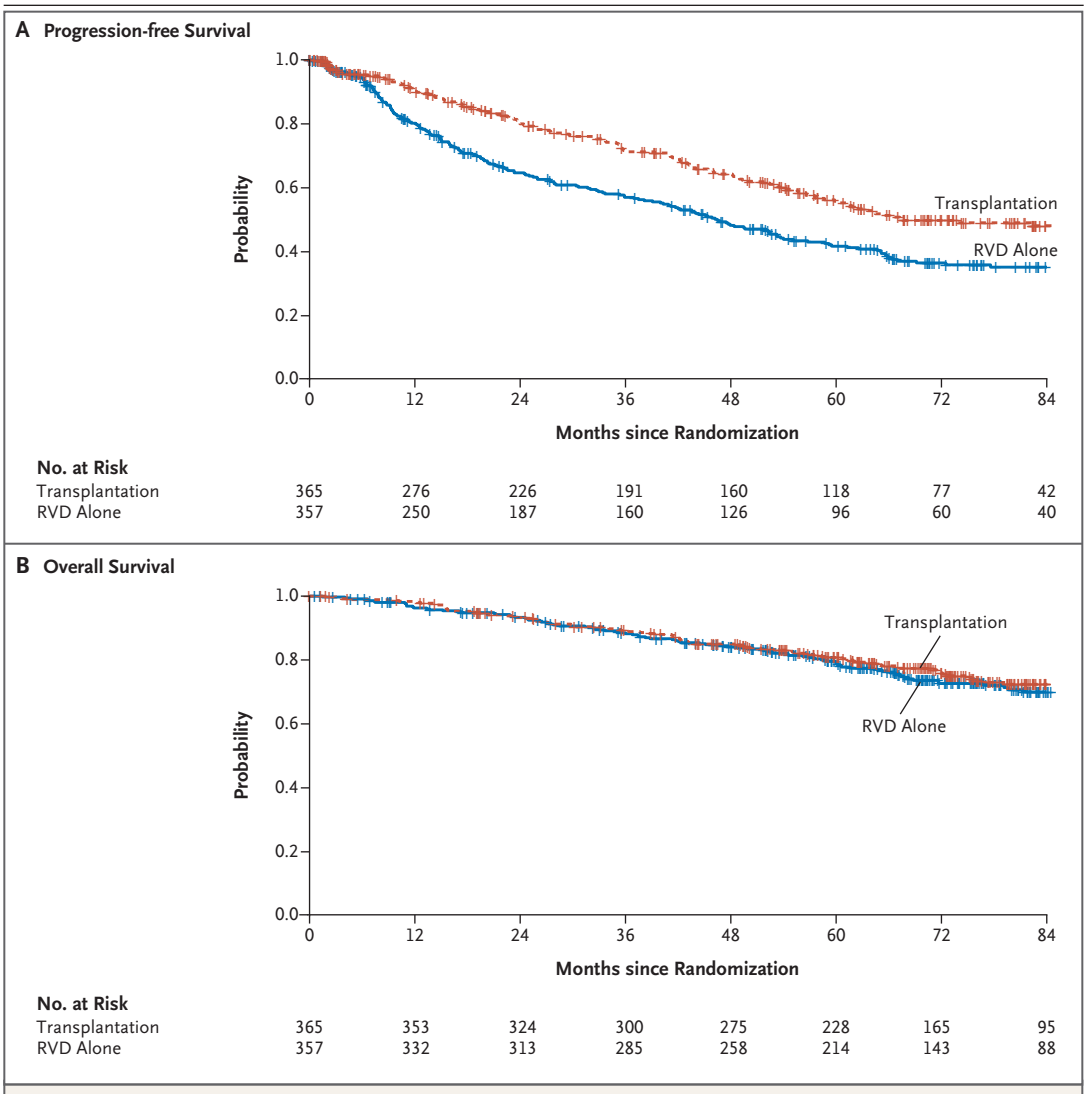

Figure 2. Kaplan–Meier Curves for Progression-free Survival and Overall Survival in the Intention-to-Treat Population.
Panel A shows progression-free survival among patients who received RVD alone and among those who received RVD plus transplantation. In the RVD-alone group, of 189 events of disease progression or death, 1 death occurred in the absence of disease progression. In the transplantation group, of 139 events, 11 deaths occurred in the absence of disease progression. Panel B shows the Kaplan–Meier analysis of overall survival in the two groups; there were 90 deaths in the RVD-alone group and 88 deaths in the transplantation group. In both panels, tick marks indicate censored data.

primary reasons for dose modifications were adverse events or illness (in 50.5% of the modifications in the RVD-alone group and 51.6% of the modifications in the transplantation group).

EFFICACY

At a median follow-up of 76.0 months, the risk of disease progression or death was 53% higher in the RVD-alone group than in the transplantation group (hazard ratio, 1.53; 95% CI, 1.23 to 1.91; P<0.001). Of the 328 patients with events of disease progression or death, 189 were in the the RVD-alone group (52.9% of the patients in that group) and 139 were in the transplantation group (38.1% of the patients in that group). The median duration of progression-free survival was 46.2 months (95% CI, 38.1 to 53.7) in the RVD-alone group and 67.5 months (95% CI, 58.6 to not reached) in the transplantation group (Fig. 2A). Progression-free survival in patient

Table 2. Response to Treatment.*

Variable	RVD-Alone Group (N=357)	Transplantation Group (N=365)	Hazard Ratio (95% CI)	Adjusted P Value†
Best response				
Partial response or better				0.55‡
No. with response	339	356		
Percentage with response (95% CI)	95.0 (91.0–97.5)	97.5 (94.5–99.2)		
Very good partial response or better				0.99‡
No. with response	284	302		
Percentage with response (95% CI)	79.6 (73.3–85.0)	82.7 (76.8–87.7)		
Complete response or better				0.99‡
No. with response	150	171		
Percentage with response (95% CI)	42.0 (35.0–49.3)	46.8 (39.8–54.0)		
Stringent complete response — no. (%)	99 (27.7)	120 (32.9)		
Complete response — no. (%)	51 (14.3)	51 (14.0)		
Very good partial response — no. (%)	134 (37.5)	131 (35.9)		
Partial response — no. (%)	55 (15.4)	54 (14.8)		
Stable disease — no. (%)	15 (4.2)	7 (1.9)		
Progressive disease — no. (%)	1 (0.3)	1 (0.3)		
Not evaluable — no. (%)	2 (0.6)	1 (0.3)		
Duration of response				
Median duration of partial response or better — mo	38.9	56.4		
Disease progression events — no./total no. (%)	194/339 (57.2)	164/356 (46.1)	1.45 (1.09–1.93)	0.003
Complete response or better at 5 yr — %	52.9	60.6		
Disease progression events — no./total no. (%)	61/150 (40.7)	57/171 (33.3)	1.35 (0.83–2.22)	0.70

* Responses were assessed according to the International Myeloma Working Group criteria by a central response review committee.
† P values were adjusted with the use of Bonferroni's correction to control the overall family-wise error rate for secondary outcomes.
‡ This P value was calculated with the use of Fisher's exact test.

subgroups that were defined according to stratification factors and key baseline characteristics is summarized in Figures S3 and S4. The median duration of progression-free survival among patients with a high-risk cytogenetic profile was 17.1 months in the RVD-alone group and 55.5 months in the transplantation group. For the secondary end point of disease progression in a time-to-event analysis, the percentage of patients who were alive without progression at 5 years was 41.6% and 58.4%, respectively (hazard ratio, 1.66; 95% CI, 1.21 to 2.27) (Fig. S5).

The percentage of patients with a partial response or better was 95.0% in the RVD-alone group and 97.5% in the transplantation group (P=0.55), and the percentage with a complete response or better was 42.0% and 46.8%, respectively (P=0.99). The median duration of response was 38.9 months in the RVD-alone group and 56.4 months in the transplantation group (hazard ratio, 1.45; 95% CI, 1.09 to 1.93). The percentage of patients with a complete response or better at 5 years was 52.9% and 60.6%, respectively (Table 2 and Fig. S6).

In preliminary analyses involving patients with samples that could be evaluated from the start of

Table 3. Treatment-Related Adverse Events.*

Event	RVD-Alone Group (N=357)	Transplantation Group (N=365)
	number of patients (percent)	
Any event	279 (78.2)	344 (94.2)
Any hematologic event	216 (60.5)	328 (89.9)
Any grade 5 event†	1 (0.3)	5 (1.4)
Blood and lymphatic system disorders	221 (61.9)	328 (89.9)
Neutropenia	152 (42.6)	315 (86.3)
Thrombocytopenia	71 (19.9)	302 (82.7)
Leukopenia	70 (19.6)	145 (39.7)
Anemia	65 (18.2)	108 (29.6)
Lymphopenia	32 (9.0)	37 (10.1)
Febrile neutropenia	15 (4.2)	33 (9.0)
Gastrointestinal disorders	28 (7.8)	68 (18.6)
Diarrhea	14 (3.9)	18 (4.9)
Nausea	2 (0.6)	24 (6.6)
Oral mucositis	0	19 (5.2)
General disorders and administration-site conditions	29 (8.1)	54 (14.8)
Fatigue	10 (2.8)	22 (6.0)
Fever	7 (2.0)	19 (5.2)
Infections and infestations	34 (9.5)	67 (18.4)
Pneumonia	18 (5.0)	33 (9.0)
Investigations	16 (4.5)	14 (3.8)
Elevated liver-enzyme levels	8 (2.2)	8 (2.2)
Metabolism and nutrition disorders	65 (18.2)	59 (16.2)
Hypophosphatemia	34 (9.5)	30 (8.2)
Hyperglycemia	9 (2.5)	15 (4.1)
Hypokalemia	12 (3.4)	7 (1.9)
Nervous system disorders	32 (9.0)	41 (11.2)
Neuropathy‡	20 (5.6)	26 (7.1)
Sensory peripheral neuropathy	17 (4.8)	19 (5.2)
Syncope	8 (2.2)	7 (1.9)
Skin and subcutaneous tissue disorders	14 (3.9)	15 (4.1)
Maculopapular rash	10 (2.8)	13 (3.6)
Vascular disorders	18 (5.0)	32 (8.8)
All thromboembolic events§	10 (2.8)	15 (4.1)

* All adverse events were coded according to the system used in the *Medical Dictionary for Regulatory Activities*, version 24.0. Listed are adverse events of grade 3 or higher reported during the entire treatment period (induction through maintenance therapy) in at least 2% of the patients in either group. Adverse events of any grade that were determined by the investigators to be related to trial treatment are summarized in Table S2.

† After the data-cutoff date, all sites were contacted by the Dana–Farber Cancer Institute trial team and the contract research organization and were asked to review all deaths to confirm that no additional treatment-related deaths should be reported. Consequently, one additional grade 5 event in the transplantation group was identified as being treatment-related, so the total number of grade 5 events in that group was 6 (1.6%). Other than events related to disease progression, deaths from grade 5 treatment-related adverse events that occurred during the trial (within 30 days after the last dose of a trial treatment) were reported in 1 patient in the RVD-alone group (cardiac collapse that occurred during RVD cycle 2) and in 5 patients in the transplantation group (stroke during maintenance cycle 61 in 1 patient, endocarditis during maintenance cycle 5 in 1 patient, necrotizing fasciitis during maintenance cycle 20 in 1 patient, sepsis during maintenance cycle 5 in 1 patient, and sepsis, cardiomyopathy, and respiratory failure after ASCT in 1 patient).

‡ Neuropathy events include sensory peripheral neuropathy, sensory neuropathy, and neuropathy.

§ All thromboembolic events include pulmonary embolism, thromboembolic event, stroke, and deep-vein thrombosis.

lenalidomide maintenance therapy (108 patients in the RVD-alone group and 90 patients in the transplantation group), the percentage of those with minimal residual disease that could not be detected by next-generation sequencing was 40% in the RVD-alone group (43 patients) and 54% in the transplantation group (49 patients) (odds ratio, 0.55; unadjusted 95% CI, 0.30 to 1.01). Sequencing was performed at a sensitivity level of 10^{-5}, indicating detection of 1 malignant plasma cell within 100,000 bone marrow cells. In patients in whom minimal residual disease was not detected, 5-year progression-free survival after the evaluation for minimal residual disease was 59.2% in the RVD-alone group and 53.5% in the transplantation group (hazard ratio for disease progression or death, 0.91; unadjusted 95% CI, 0.46 to 1.79); in patients in whom minimal residual disease was detected, median progression-free survival was 33.4 months and 50.6 months, respectively (hazard ratio, 1.67; unadjusted 95% CI, 0.98 to 2.85) (Fig. S7). Preliminary correlative analyses of genetic mutations in 140 patients did not reveal associations with status regarding minimal residual disease or progression-free survival; the presence of a 17p deletion (odds ratio, 0.24; unadjusted 95% CI, 0.07 to 0.72) or *TP53* mutations (odds ratio, 0.12; unadjusted 95% CI, 0.002 to 1.19) was associated with a lower response rate.

With 90 deaths in the RVD-alone group and 88 deaths in the transplantation group, the estimated 5-year survival was 79.2% and 80.7%, respectively (hazard ratio for death, 1.10; 95% CI, 0.73 to 1.65; P>0.99) (Fig. 2B). Overall survival in patient subgroups that were defined according to stratification factors and key baseline characteristics is summarized in Figure S8. The 5-year overall survival among patients with a high-risk cytogenetic profile was 54.3% in the RVD-alone group and 63.4% in the transplantation group. Kaplan–Meier analyses of overall survival according to stratification factors are shown in Figure S9.

SAFETY

The most common treatment-related adverse events that occurred during the entire trial treatment period are summarized in Table S2. Treatment-related events of grade 3 or higher occurred in 279 patients (78.2%) in the RVD-alone group and 344 patients (94.2%) in the transplantation group; 60.5% and 89.9%, respectively, reported treatment-related hematologic adverse events of grade 3 or higher (P<0.001) (Table 3). Adverse events that occurred during lenalidomide maintenance therapy are summarized in Table S3. Serious RVD-related adverse events were reported in 144 patients in the RVD-alone group (40.3%) and 172 patients in the transplantation group (47.1%), and treatment-related serious infections were reported during maintenance therapy in 33 of 291 patients (11.3%) and 48 of 289 patients (16.6%), respectively (Table S4).

Second primary cancers were reported in 37 patients (10.4%) in the RVD-alone group and 39 patients (10.7%) in the transplantation group (5-year cumulative incidence, 9.7% and 10.8%; P=0.90) (Table S5 and Fig. S10). Second primary hematologic cancers occurred in 9 patients in the RVD-alone group (2.5%) and 13 patients in the transplantation group (3.6%) (5-year cumulative incidence, 1.6% and 3.5%; P=0.32), with acute myeloid leukemia or myelodysplastic syndromes reported in none of the patients in the RVD-alone group, as compared with 10 patients in the transplantation group (2.7%) (P=0.002). The 5-year cumulative incidence of invasive second primary cancers was similar in the two groups (RVD-alone group, 4.9%; transplantation group, 6.5%).

QUALITY OF LIFE

On the EORTC QLQ-C30, the mean score for global health status was similar in the two groups throughout treatment (Fig. S11), except at the following two evaluation points in the trial. First, patients in the RVD-alone group had better mean changes in scores during RVD cycle 5 than those in the transplantation group at the corresponding time point after ASCT, with an increase from baseline of 3.0 points and a decrease of 11.1 points, respectively (P<0.001), and with 83.1% and 59.2% of the patients in the respective groups having completed the questionnaire at that time point (Table S6). Second, patients in the RVD-alone group had lower mean changes in scores during RVD cycle 8 than those in the transplantation group at the corresponding time point during RVD cycle 5, with increases from baseline of 1.2 points and 8.3 points, respectively (P=0.02), and with 79.9% and 77.3% of the patients in the respective groups having completed the questionnaire at that time point. Similar trends in between-group differences and changes from baseline were seen in the physical and

role functioning domains of EORTC QLQ-C30 and in the domain of side effects of treatment of EORTC QLQ-MY20.

THERAPY OUTSIDE THE TRIAL PROTOCOL

Among the patients who had discontinued trial treatment, subsequent therapy outside the trial protocol was administered to 222 of 279 patients (79.6%) in the RVD-alone group and 192 of 276 patients (69.6%) in the transplantation group (Table S7). Of the 279 patients in the RVD-alone group who discontinued trial treatment, 78 (28.0%) underwent ASCT (35.1% of those who received subsequent post-protocol therapy). A post hoc sensitivity analysis of event-free survival was conducted to evaluate the effect of censoring for therapy outside the trial protocol. Median event-free survival (for which events included receipt of therapy outside the trial protocol, disease progression, and death) was 32.0 months in the RVD-alone group and 47.3 months in the transplantation group (hazard ratio, 1.23; 95% CI, 1.02 to 1.48) (Fig. S12).

DISCUSSION

The phase 3 DETERMINATION trial showed the superiority of ASCT-based first-line therapy with respect to progression-free survival among eligible patients with newly diagnosed myeloma, findings that confirm those of the IFM 2009 trial.[1,9] We found a significant 21.3-month benefit in median progression-free survival and a 35% lower risk of disease progression or death with RVD plus ASCT than with RVD alone.

Our results also highlight the value of long-term lenalidomide maintenance therapy until disease progression in both groups. In our trial, the median progression-free survival among patients who received RVD alone was 11.2 months longer than that in the IFM 2009 trial (46.2 vs. 35.0 months); in the latter trial, patients received the same treatment as in the current trial except with only 1 year of maintenance therapy.[9] The median progression-free survival among patients who received RVD plus ASCT was 20.2 months longer in our trial than in the IFM 2009 trial (67.5 vs. 47.3 months). These findings confirm previous observations of increased progression-free survival with a greater duration of lenalidomide maintenance therapy.[10,14,15] However, despite a median follow-up of more than 6 years in our trial, approximately one quarter of the patients had died, and given the lengthy median overall survival among patients in this population in general,[16] we did not observe an overall survival advantage of RVD plus ASCT over RVD alone.

The lack of an overall survival benefit of RVD plus ASCT is probably associated with the multiple, highly efficacious options available after first-line therapy that have emerged over the past 10 years.[11,12,17] Similarly, in the IFM 2009 trial,[1] 8-year survival rates were approximately 60% with both approaches after a median follow-up of nearly 7.5 years; 76.7% of the patients in the RVD-alone group who had disease relapse received ASCT as part of second-line therapy.[9] In contrast, in the DETERMINATION trial, only 28.0% of the patients in the RVD-alone group who had discontinued trial treatment (35.1% of those who received post-protocol therapy) had received subsequent ASCT at the data-cutoff date; this proportion may increase with longer follow-up. Post-protocol treatment was selected according to patient and physician decision; an explanation of the reason why ASCT was not selected was not formally required. Possible drivers may have included the perception of need for ASCT (on the basis of the overall survival data in the IFM 2009 trial and other studies involving a similar patient population), patient choice, the patient's condition at the time of relapse, and increasing availability of other therapeutic options. The effect of this limited crossover on long-term outcomes warrants longer follow-up.

Personalizing decision making regarding treatment is important for patients with multiple myeloma, a heterogeneous population with heterogeneous disease who have differing treatment preferences and needs. RVD plus ASCT may lead to longer progression-free survival, and our findings illustrate how the ongoing improvement of treatment approaches[1-9,18-20] is providing clinical benefit for patients. However, the elimination of minimal residual disease is of increasing importance in tailoring treatment, in informing clinical care, and as a treatment goal,[21,22] given its prognostic value for better outcomes.[23-26] Increasingly high rates of elimination of minimal residual disease are associated with new four-drug induction regimens incorporating highly efficacious monoclonal antibodies.[6,8,20,21,27] Our

preliminary data are supportive in this regard. Despite similar rates of conventional responses between the two groups, RVD plus ASCT resulted in a higher percentage of patients in whom minimal residual disease was not detected. This suggests a benefit from high-dose melphalan coupled with long-term lenalidomide in driving deep and durable responses, enhancing cytoreduction,[24,26] and improving the antitumor immune microenvironment and tumor-specific immunity after cellular reconstitution.[28] However, no difference in progression-free survival was detected in patients who had no minimal residual disease, regardless of treatment. This finding and similar findings from recent trials suggest that treatment adaptation based on a sustained absence of minimal residual disease may be a feasible alternative to the standard use of ASCT[27] as well as maintenance therapy until disease progression.[21,25,26] However, data for the latter are limited pending additional study.

Such personalized approaches are important when considering toxic effects and the effect of treatment on quality of life. As in the IFM 2009 trial,[1,9] RVD plus ASCT in this trial was associated with a significantly higher incidence of toxic effects than RVD alone and a transient but clinically meaningful decrease in quality of life associated with ASCT, specifically with respect to overall global health status and physical and role functioning. Nevertheless, mean quality-of-life scores subsequently recovered, with mean improvements from baseline remaining numerically higher after RVD plus ASCT than after RVD alone throughout maintenance therapy; these findings suggest a rebound effect. The 5-year cumulative incidence of invasive second primary cancers was similar in the two groups (RVD-alone group, 4.9%; transplantation group, 6.5%); however, the between-group differences in the development of acute myeloid leukemia and myelodysplasia are in keeping with the well-established mutagenic effect of high-dose melphalan on stem cells and myeloma in such patients.[29-32] With longer-term use of lenalidomide in the DETERMINATION trial, the 5-year cumulative incidence of second primary hematologic cancers was 1.6% with RVD alone, as compared with 3.5% with RVD plus ASCT; the respective incidences in the IFM 2009 trial were 0.6% and 1.4% (Fig. S10).

Numerous patient-related and myeloma-related factors can affect treatment outcomes. We conducted preplanned subgroup analyses that showed hazard ratios for disease progression or death ranging from 0.96 to 3.40 for the comparison of RVD alone with RVD plus ASCT (Fig. S3); however, our trial was not powered to evaluate progression-free survival in patient subgroups, and no definitive interactions were identified for any subgroup category. Further investigations are under way to evaluate outcomes according to cytogenetic risk and specific genetic abnormalities, given preliminary whole-genome–sequencing analyses suggesting lower response rates associated with the presence of 17p deletion and *TP53* mutations and the known association of 17p deletion with impairment of the tumor suppressor p53, an impairment that confers resistance to chemotherapy.[33] An evaluation of the trial findings in Black patients, who composed almost 20% of the trial population, and other racial subgroups is under way to understand any differences that may mediate differential outcomes. Recent data have indicated improved responses[34] and better survival[35,36] among Black patients than among White patients who have received similar treatments, including ASCT. Evaluations of the trial findings according to body-mass index are also under way, given the effect of obesity on the pathobiologic features of myeloma and the side-effect profile of intensive therapy.[37]

In adults with multiple myeloma, progression-free survival was significantly longer among those who were assigned to the transplantation group than among those who were assigned to the RVD-alone group. In the absence of a demonstrated overall survival benefit, however, and in the context of considerations regarding real-world factors such as treatment burden, acute and long-term toxic effects, patient preference, and quality of life,[38] these findings may be taken into account when making treatment decisions.

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APPENDIX

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