Supplementary Appendix

Supplement to: Richardson PG, Jacobus SJ, Weller EA, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. N Engl J Med 2022;387:132-47. DOI: 10.1056/NEJMoa2204925

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix to:

Triplet Therapy, Transplantation, and Maintenance to Progression in Myeloma

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Supplementary Appendix

DFCI 10-106 DETERMINATION: accruing sites and principal investigators

Site	Enrolling Principal investigator(s)
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Massachusetts General Hospital	Noopur S. Raje Andrew J. Yee
Knight Cancer Institute, Oregon Health & Science University	Eva Medvedova Emma Scott
Roswell Park Comprehensive Cancer Center	Philip L. McCarthy Pallawi Torka
University of Washington, Fred Hutchinson Cancer Center	Edward N. Libby
University of North Carolina	Peter M. Voorhees Brandi Reeves
The University of Texas MD Anderson Cancer Center	Robert Z. Orlowski Michael Wang
Simmons Comprehensive Cancer Center, UT Southwestern Medical Center	Larry D. Anderson Jr
Barbara Ann Karmanos Cancer Institute / Wayne State University School of Medicine	Jeffrey A. Zonder
University of Mississippi Medical Center	Carter P. Milner Tondre Buck
Duke University Medical Center	Cristina Gasparetto Gwynn Long
UPMC (University of Pittsburgh Medical Center) Hillman Cancer Center	Mounzer Agha
The Ohio State University Comprehensive Cancer Center	Abdullah Khan Yvonne A. Efebera
Wake Forest University School of Medicine	David D. Hurd Cesar Rodriguez Valdes
University of Arizona, Department of Bone Marrow Transplant and Cellular Therapy	Krisstina Gowin Faiz Anwer Amit Agarwal
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Davenport-Mugar Cancer Center, Cape Cod Hospital	Thomas Openshaw Frank Basile
Cancer Center at Beth Israel Deaconess Medical Center	David Avigan
Ochsner Cancer Institute	Carter Davis
Moores Cancer Center at University of California San Diego	Caitlin Costello
Colorado Blood Cancer Institute	Jeffrey Matous
Mass General Cancer Center at Newton-Wellesley	Robb Friedman
UCSF Helen Diller Family Comprehensive Cancer Center	Jeffrey Wolf
Rush University Cancer Center	Sunita Nathan
St. Luke's Cancer Institute	William Kreislew
University of Chicago Comprehensive Cancer Center	Andrzej Jakubowiak
University of Florida Health Cancer Center	John Himenz
Fox Chase Comprehensive Cancer Center	Henry Fung
Solinsky Center for Cancer Care, New Hampshire Oncology and Hematology	Douglas Weckstein
Wilmot Cancer Institute – University of Rochester Medical Center	Michael Becker
Herbert Irving Comprehensive Cancer Center (HICCC) at Columbia University Medical Center	Suzanne Lentzsch
Gibbs Cancer Center & Research Institute – Spartanburg	Tondre Buck
Case Comprehensive Cancer Center	Hillard Lazarus

Supplementary Methods

Study oversight

The trial was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice, US Code of Federal Regulations governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki, US state laws, and Dana-Farber/Harvard Cancer Center research policies and procedures. An independent Data and Safety Monitoring Committee (DMC) and study Steering Committee regularly reviewed safety, study progress, and interim analyses of outcome data. A central response review committee reviewed all response and progression coding.

Concomitant medications

Thromboprophylaxis, herpes zoster prophylaxis, and concomitant bisphosphonates were required during cycles of RVd. Thromboprophylaxis was provided with aspirin, low-molecular-weight heparin, or enoxaparin based on the risk determined by the patient's treating physician. Herpes zoster prophylaxis comprised acyclovir or valaciclovir or equivalent.

Objectives, end points, and definitions

The primary objective was to compare progression-free survival (PFS) between the two arms. The primary endpoint of PFS was defined as time from randomization to the earlier of disease progression as determined by central review or death from any cause (events). Patients who started non-protocol therapy (NPT) were censored at the date of NPT initiation if available or date treatment ended if date of NPT was missing. Deaths occurring beyond 1 year from the date last known progression-free are not counted as events and censored at date of last disease evaluation. Patients who had not started NPT, progressed, or died were censored at the date of last disease evaluation. All patients were followed until disease progression and death. In a sensitivity analysis for PFS, patients who received NPT were not censored.

Secondary objectives were to compare response rates, duration of response (DOR), time to progression (TTP), overall survival (OS), safety, tolerability, and quality of life (QoL) between the two arms, to define genetic prognostic groups evaluated by gene expression profiling (GEP), and to examine the best treatment in each GEP-defined prognostic group. An additional secondary objective was to collect medical resource utilization (MRU) information for potential use in economic evaluation models (data not reported in this manuscript). Event-free survival (EFS) is also reported as a post-hoc sensitivity analysis to evaluate the impact of censoring for non-protocol therapy. In the primary endpoint of PFS, patients are censored at the time of non-

protocol therapy, and in the EFS analysis, patients are considered failures at the time of non-protocol therapy.

For the secondary end points of response rates and DOR, disease response was assessed using criteria based upon the International Myeloma Working Group (IMWG) uniform response criteria.[1,2] Patients with serum free light chain (FLC) level as their only measurable disease parameter were assessed according to FreeLite™ disease response criteria.[3] Disease response according to modified European Group for Blood and Marrow Transplantation (EBMT) response criteria was also collected as a secondary measure. Disease response was confirmed by two consecutive assessments made at any time before initiation of new therapy (IMWG criteria) or at a minimum of 6 weeks apart (EBMT criteria). Disease response assessments underwent central review, which was performed on the following disease response measures: M-protein quantification and immunofixation from serum, 24-hour urine collection, and serum FLC testing. DOR was defined as the time from documented best response to documented disease progression per IMWG criteria, and was estimated separately in patients achieving complete or partial response as best IMWG response.

TTP was defined as time from randomization to time of documented IMWG disease progression or censoring time (time of last disease evaluation for those alive, time to death among those who died). Similar to the PFS analysis, patients initiating non-protocol therapy prior to progression or death were censored at the date of non-protocol therapy in the TTP analysis. EFS was defined as the time from randomization to the earliest of IMWG disease progression, death, or initiation of non-protocol therapy (events); patients were censored date of last disease evaluation. OS was defined as time from randomization to death due to any cause; patients alive were censored at date last known alive.

For the QoL end points, QoL domains from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core-30 (QLQ-C30) module, the EORTC QLQ-MY20 multiple myeloma module, and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-NTX) side-effects questionnaire were compared between arms. These included the domains of health-related QoL, distress, psychological functioning, physical well-being, and functional well-being.

Safety end points comprised all serious adverse events, treatment-related adverse events, and laboratory data, categorized and graded, experienced from cycle 1 onwards and on maintenance only. Second primary malignancies (SPM) were evaluated separately, and the

cumulative incidence of SPMs was estimated with death as a competing risk overall and by class (invasive, hematologic, solid, non-melanoma skin). Tolerability end points included dose modifications on RVd, rates of mobilization failure, and estimates of treatment exposure on maintenance; data not reported in the present manuscript. Treatment duration (months) was also estimated from randomization and start of maintenance by Kaplan–Meier methods.

Bone marrow aspirate and peripheral blood sample collection

Bone marrow aspirate samples for response evaluation and correlative analyses, plus peripheral blood samples for correlative analyses, were planned to be collected at screening, at the time of response assessment or confirmation (for patients achieving a very good partial response or better) if clinically indicated, within 42 days of ASCT (RVd+ASCT arm), on day 1 of RVd cycle 4 (RVd+ASCT arm), prior to lenalidomide maintenance, and at the time of disease relapse or progression. Samples were also to be collected annually during maintenance from patients providing additional informed consent.

Assessment of quality of life and patient-reported outcomes

Patients were requested to complete the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core-30 (QLQ-C30) module, the EORTC QLQ-MY20 multiple myeloma module, and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-NTX) side-effects questionnaire at nine time points: at baseline, on day 1 of RVd cycle 2, prior to cyclophosphamide mobilization, post-ASCT and prior to RVd cycle 4 (RVd+ASCT arm only), on day 1 of RVd cycles 5 and 8 (RVd-alone arm only), on day 1 of cycle 6 of lenalidomide maintenance therapy, at 2 and 3 years post baseline, and at end of study treatment.

Evaluation of minimal residual disease

Bone marrow aspirate samples obtained from patients prior to the start of lenalidomide maintenance and after 1 year of maintenance were sent for central laboratory evaluation of minimal residual disease (MRD) using the validated, US Food and Drug Administration-approved clonoSEQ® next-generation sequencing platform (Adaptive Biotechnologies) with a minimum sensitivity of 1×10^{-5}. Patients with MRD levels of $<1 \times 10^{-5}$ were classified as MRD-negative, and those with levels of $\geq 1 \times 10^{-5}$ were classified as MRD-positive. PFS was evaluated by MRD status at the start of maintenance therapy and by treatment arm, with PFS time being from the start of maintenance.

Correlative studies

Proposed correlative studies were to conduct gene expression profiling (GEP) using whole genome sequencing (WGS) and correlate findings with clinical outcomes, and to investigate genomic changes at the time of progression or relapse and evaluate mechanisms underlying genomic instability. In order to identify genomic alterations and correlate with clinical outcome, the role of DNA copy number alterations (CNAs) by high throughput single nucleotide polymorphism (SNP) array analysis, as well as WGS and gene expression changes by expression array, were to be analyzed for response and survival. mRNA splicing by exon array and microRNA profiles in study participants were to be evaluated and correlated with clinical endpoints. Both the direct and indirect relationship between CNAs and gene expression changes were also to be investigated. To investigate genomic changes at the time of progression or relapse and evaluate mechanisms underlying genomic instability, genome-wide SNP analyses, expression profiling, and WGS on paired samples obtained at the time of diagnosis and at the time of progression or relapse were planned to be performed to identify genomic regions with amplifications, deletions, and changes in heterozygosity. It was planned to evaluate mutations in light of the known pattern of changes and identify those which may predict different clinical outcomes. Based on data showing that elevated homologous recombination (HR) activity plays a significant role in ongoing genomic instability in myeloma, HR activity in primary myeloma samples was to be measured to correlate with acquisition of new genomic changes as well as clinical outcome.

In the preliminary WGS analyses reported in this paper, we analyzed data from CD138+ myeloma cells purified from screening bone marrow samples from 140 patients. These patients were equally distributed between the RVd and RVd+ASCT arms. Data were evaluated to correlate best response achieved with genomic features, and with 140 patients the correlative analysis is not powered to detect genomic features associated with survival.

Interim analyses

Interim analyses were planned at 33% and 69% information and the final analysis at full information. These results were presented to the data monitoring committee. To preserve the overall type I error rate, critical values at the interim analyses were determined using the Lan-DeMets error spending rate function corresponding to the O'Brien-Fleming boundary. The O’Brien-Fleming upper boundary at 33%, 69%, and 100% information is 3.7334, 2.4670, and 1.9996, with corresponding nominal significance levels of 0.0000944467, 0.00681167, and 0.0227744, respectively. The study was also monitored for early stopping in favor of the null hypothesis using Jennison-Turnbull repeated confidence interval (CI) methodology. At each

interim analysis, the one-sided 97.5% repeated confidence upper limit on the HR was computed using the critical value from the error spending function. Data cut-off for this full-information analysis (328/329 progression-free survival events, 99.7%) was December 10, 2021.

Study design history

Originally this study was planned to be conducted together with the IFM 2009 study.[4,5] The primary endpoint of PFS was to have been compared between Arm A (RVd-only) and Arm B (transplantation), with patients stratified by country/region (United States vs Intergroupe Francophone du Myèlome [IFM]) as well as by cytogenetics risk category and International Staging System (ISS) disease stage. With a planned population size of 1000 patients (and full information of 658 events under the alternative hypothesis), the two studies combined had 92% power to detect a 23% reduction in the hazard of progression or death in Arm B versus Arm A, corresponding to a hazard ratio (HR) of 1.30 (Arm A vs Arm B), using a stratified two-sided log-rank test with an overall type I error rate of 0.05.

Based on evidence supporting the benefit of lenalidomide maintenance given until disease progression,[6] the protocol for this study, DFCI 10-106, was revised in October 2012 to extend duration of lenalidomide maintenance from 1 year to until disease progression. The IFM 2009 trial protocol retained the duration of lenalidomide maintenance as 1 year. At this time, the two trials were separated, and both trials were powered independently to detect a PFS benefit. Based on assumed hazard rates at the time, the sample size for the DFCI 10-106 study was 660 patients. Subsequently, results from a meta-analysis of the benefit of lenalidomide maintenance therapy[7] indicated a potentially lower-than-assumed hazard rate for PFS with lenalidomide maintenance. With a reduction in the failure rate, the time to the full information could be longer than expected. Therefore, the sample size was increased further, to 720 randomized patients, to account for potential reduction in hazard rates and reduce the time to full information of the primary endpoint of PFS by 5 months. All modifications to the study design were presented to the DMC and the Steering Committee for review and approval.

Additional statistical analyses

Patient characteristics were summarized using proportions for categorical data and median for continuous variables. Best response rates (complete response, very good partial response or better, and partial response or better) were compared between arms using Fisher's exact test, with at least 80% power to detect differences of at least 11 percentage points (two-sided significance level of 0.05). Duration of response was estimated using the Kaplan-Meier Method and compared between responding patients in each arm using a log-rank test. The estimated

odds ratio and the 95% CI are provided to evaluate the association of response and MRD. For treatment exposure, the mean (standard deviation) of the average lenalidomide dose across each 28-day cycle is reported by cycle. The proportion of cycles for which the average dose of lenalidomide was at least 10 mg is reported per patient. Maintenance treatment exposure information was missing for 8 and 7 patients on the RVd-alone and RVd+ASCT arms, respectively.

The incidence rates of grade 3 or higher adverse events were compared between groups using Fisher's exact test, with at least 80% power to detect differences between groups of at least 10 percentage points for more common (incidence rate >20%) toxicities or at least 5 percentage points for rate (incidence rate <10%) toxicities (two-sided significance level of 0.05). Changes in quality-of-life instrument domain scores from baseline were compared between groups using a two-sided t-test, with Bonferroni correction to adjust for seven multiple comparisons over the time points (this excluded the end of treatment). All quality-of-life analyses included only patients that submitted at least a baseline form and one or more follow-up forms, similar to data reported from the IFM 2009 study,[8] with similar results seen. With 400 or 700 subjects with QOL assessments complete, the effect size that can be detected with 80% power between the two arms in the change of QOL scores from time of randomization (two-sided t-test with a 0.05/8 significance level) are 0.36 and 0.25, respectively.

Figure S1: Study treatment schema.

Protocol-planned therapy on the RVd-alone (left) and RVd+ASCT (right) arms.

ASCT, autologous stem cell transplantation. GCSF, granulocyte colony-stimulating factor. IV, intravenously. PO, orally. RVd, lenalidomide, bortezomib, dexamethasone. SC, subcutaneously.

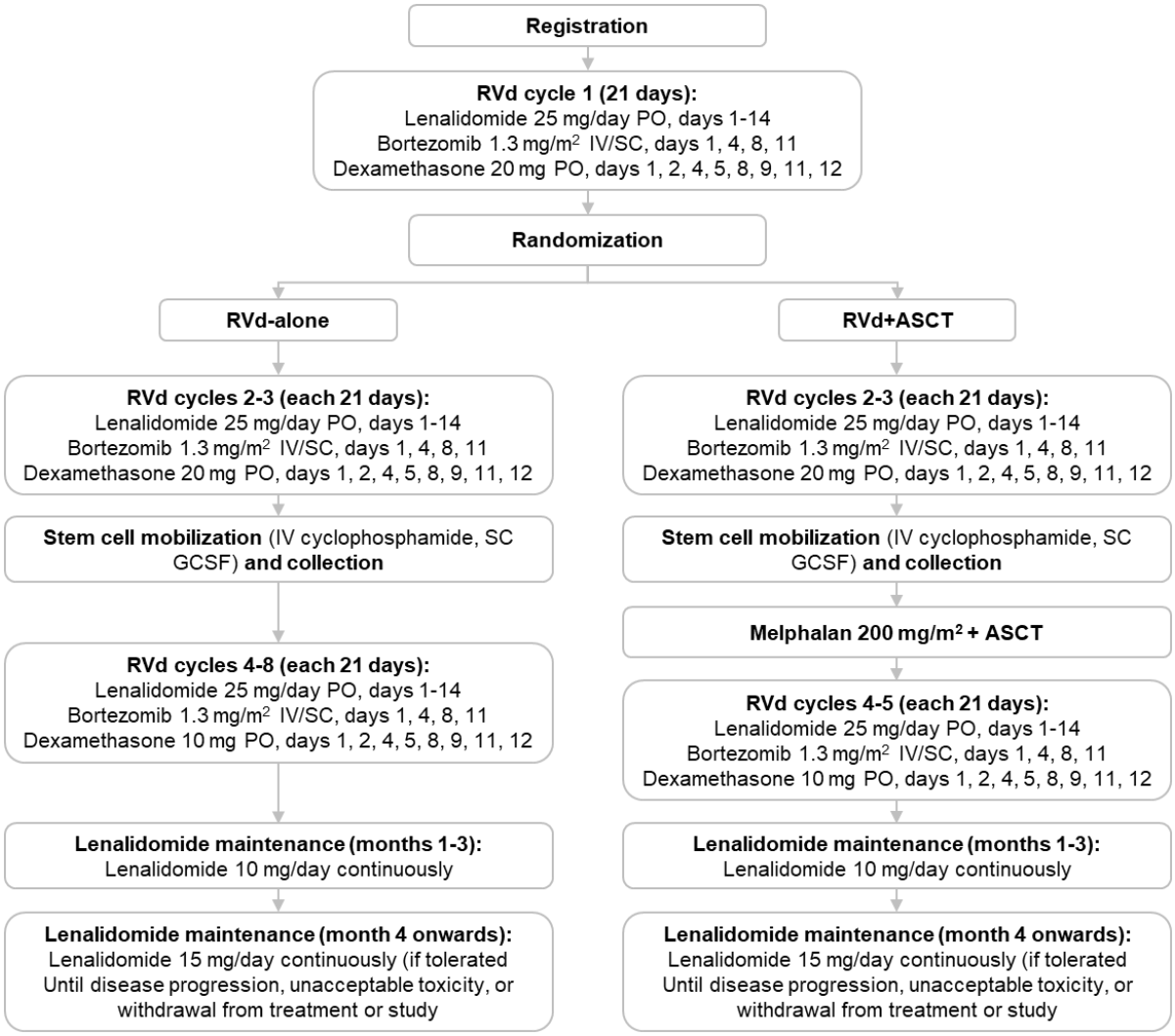
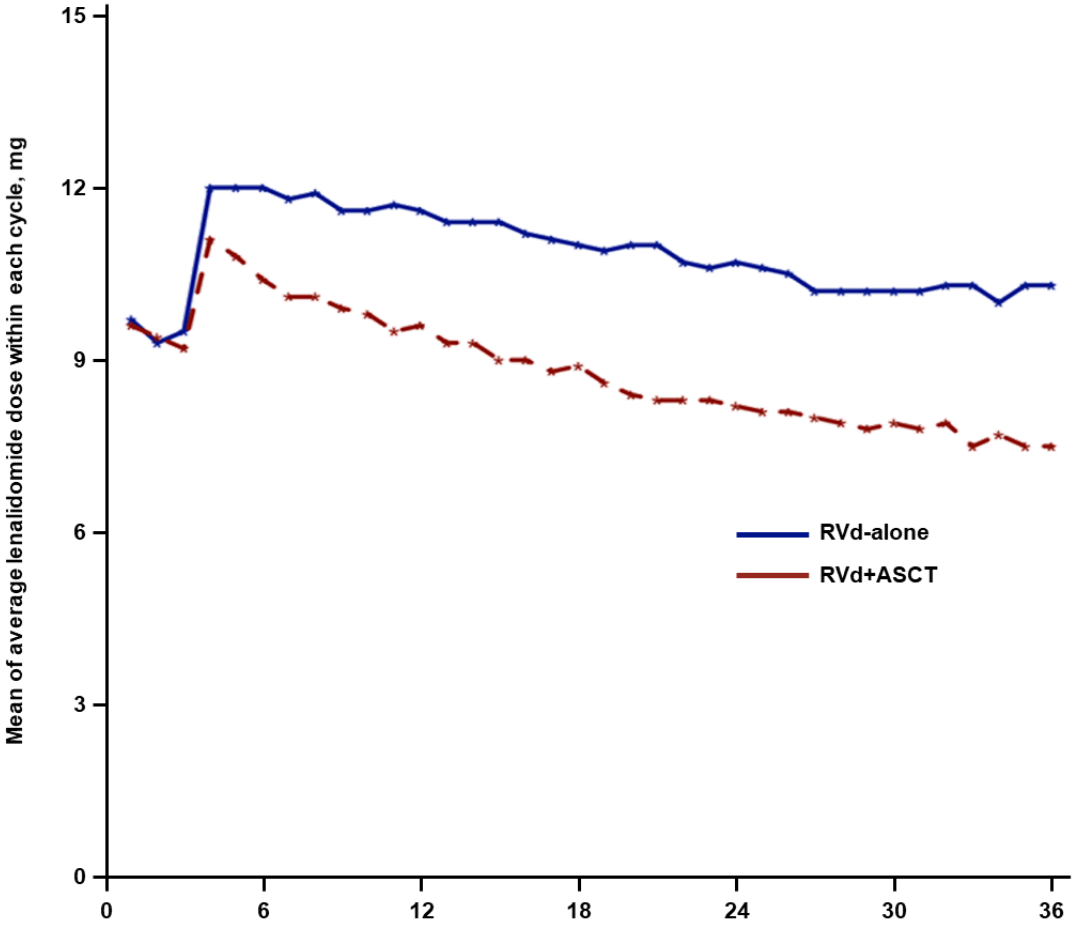


Figure S2: Exposure to lenalidomide maintenance treatment over time

Average lenalidomide dose was determined for each 28-day cycle; the mean of the average lenalidomide dose is shown by treatment cycle.



Patients							
RVd-alone	291	241	206	184	168	153	143
RVd+ASCT	289	258	230	208	187	170	159

Figure S3: Forest plot of progression-free survival, including subgroup analyses by stratification factors and other key baseline patient and disease characteristics.

Forest plot of progression-free survival, including subgroup analyses by stratification factors and other key baseline patient and disease characteristics. Subgroup data not shown for t(14;16) due to small event and patient numbers (5/10 vs 5/15, median 19.8 months vs not reached; HR 2.18, 95% CI: 0.57–8.31). The widths of the CIs have not been adjusted for multiplicity, and so the intervals should not be used in place of a hypothesis test. ASCT, autologous stem cell transplantation. CI, confidence interval. ECOG, Eastern Cooperative Oncology Group. ISS, International Staging System. ITT, intent-to-treat. HR, hazard ratio. RVd, lenalidomide, bortezomib, dexamethasone.

Subgroup analysis of progression-free survival	No. of events / total no. of patients		Median, months		HR	(95% CI)
	RVd-alone	RVd+ASCT	RVd-alone	RVd+ASCT		
All patients, ITT analysis	189/357	139/365	46.2	67.5	1.53	(1.23–1.91)
Age						
<60 years	122/235	100/263	46.2	73.8	1.49	(1.14–1.95)
≥60 years	67/122	39/102	46.5	66.5	1.59	(1.05–2.40)
Sex						
Male	107/202	81/215	47.4	66.5	1.50	(1.11–2.02)
Female	82/155	58/150	45.3	82.3	1.54	(1.09–2.17)
Race						
White/Caucasian	150/268	104/272	44.3	67.2	1.67	(1.29–2.15)
Black/African American	24/66	24/66	NR	61.4	1.07	(0.61–1.89)
Other	12/17	5/21	38.1	NR	3.40	(1.00–11.5)
ECOG performance status						
0	76/153	64/164	56.7	67.2	1.32	(0.94–1.86)
1–2	113/204	75/200	37.5	67.5	1.72	(1.28–2.32)
Body mass index						
<25	49/80	25/81	33.6	NR	2.60	(1.56–4.31)
25 to <30	71/141	53/127	52.3	64.3	1.24	(0.86–1.80)
≥30	69/136	61/157	45.8	64.4	1.41	(0.98–2.02)
Myeloma type						
IgG	108/220	80/200	53.3	67.2	1.25	(0.93–1.67)
IgA	43/72	33/95	46.5	NR	2.31	(1.43–3.74)
Light chain	21/34	16/41	23.3	57.5	2.33	(1.14–4.74)
ISS stage						
I	89/178	62/184	52.0	NR	1.83	(1.32–2.54)
II	69/130	56/134	46.2	62.5	1.38	(0.96–1.96)
III	31/49	21/47	40.3	35.9	1.14	(0.64–2.01)
Lactate dehydrogenase level						
Not elevated (<225 U/L)	132/260	106/270	47.7	67.2	1.45	(1.12–1.88)
Elevated (≥225 U/L)	56/96	31/92	41.1	NR	1.77	(1.09–2.88)
FISH cytogenetics						
High risk	37/66	28/66	17.1	55.5	1.99	(1.21–3.26)
t(4;14)	18/32	11/28	19.8	56.5	2.72	(1.19–6.24)
Del(17p)	22/38	18/34	16.3	41.3	1.44	(0.76–2.73)
Standard risk	135/268	103/274	53.2	82.3	1.38	(1.07–1.79)
Revised-ISS stage						
I	45/103	39/105	59.1	NR	1.38	(0.90–2.12)
II	109/202	78/211	40.9	67.5	1.63	(1.22–2.19)
III	17/28	11/21	22.2	32.5	0.96	(0.43–2.13)

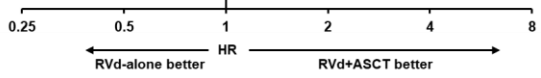
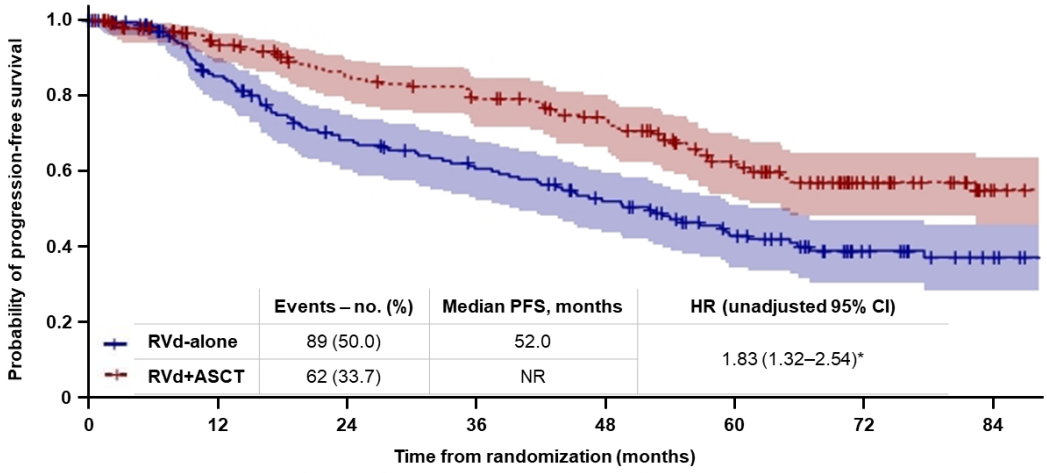


Figure S4: Kaplan–Meier analyses of progression-free survival according to randomization stratification factors.

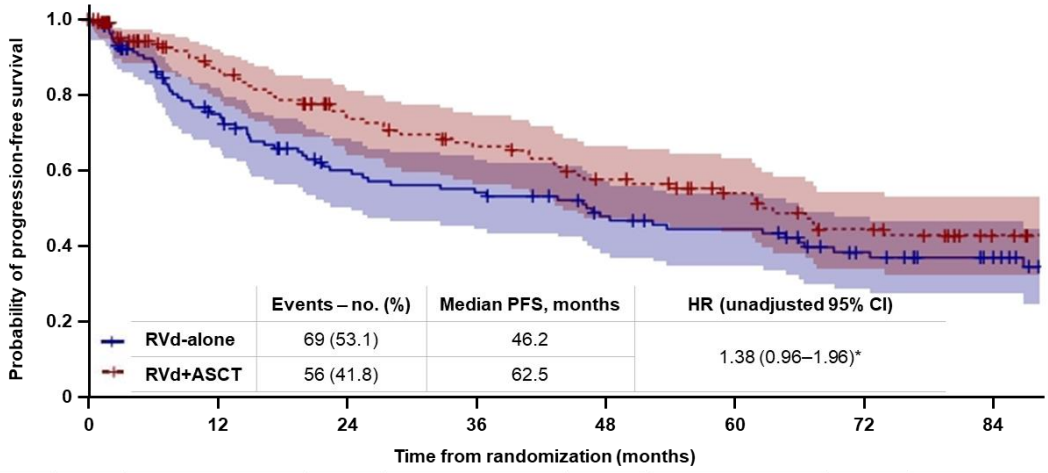
Progression-free survival with RVd-alone and RVd+ASCT in patients with ISS stage (A) I, (B) II, and (C) III disease, and in patients with (D) high-risk, (E) standard-risk, and (F) non-evaluable cytogenetics. Shaded areas indicate 95% CIs. ASCT, autologous stem cell transplantation. CI, confidence interval. ISS, International Staging System. PFS, progression-free survival. RVd, lenalidomide, bortezomib, dexamethasone. *The widths of the CIs have not been adjusted for multiplicity, and so the intervals should not be used in place of a hypothesis test.

A



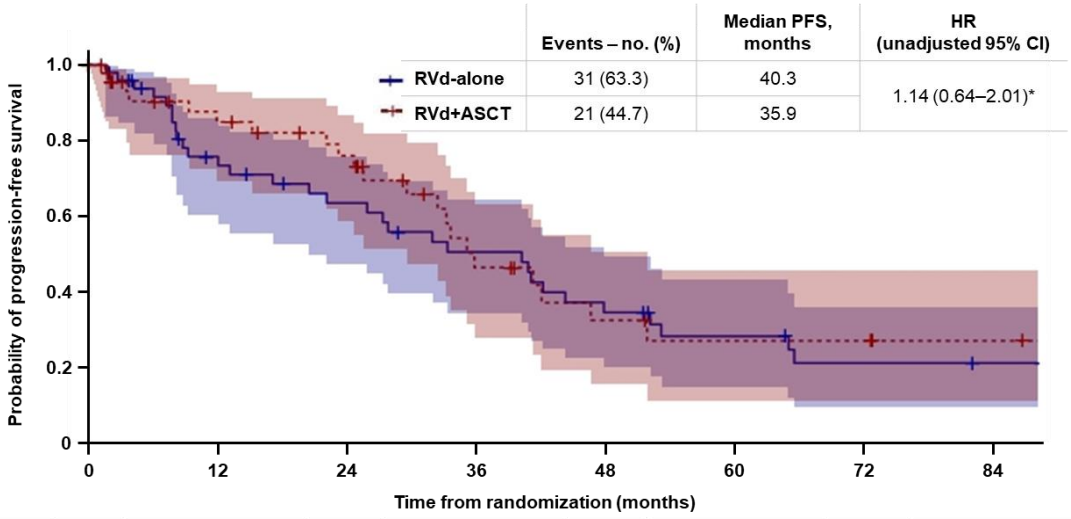
Patients at risk								
RVd-alone	178	134	101	86	69	48	27	17
RVd+ASCT	184	151	129	117	102	72	42	20

B



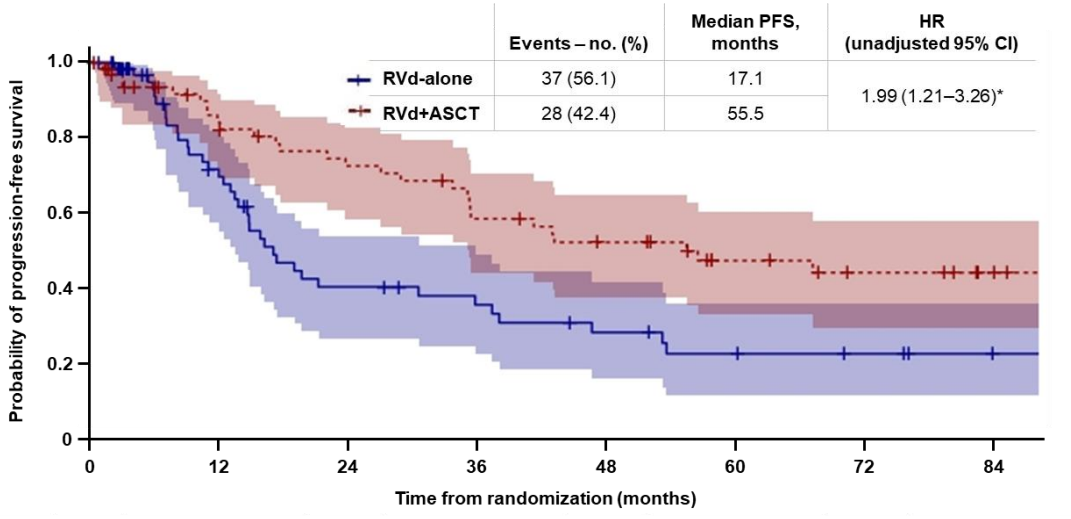
Patients at risk								
RVd-alone	130	84	61	55	44	39	28	18
RVd+ASCT	134	94	72	62	51	41	30	19

C



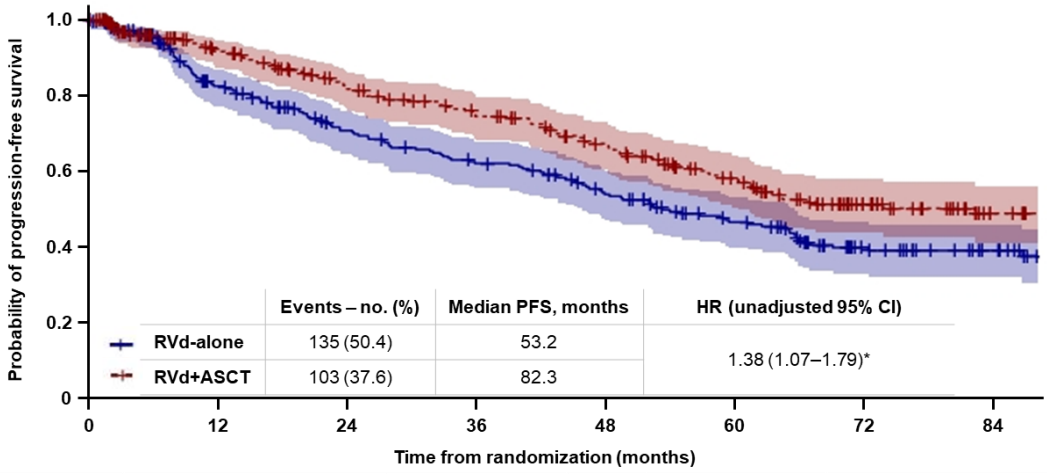
Patients at risk								
RVd-alone	49	32	25	19	13	9	6	5
RVd+ASCT	47	31	25	12	7	5	5	3

D



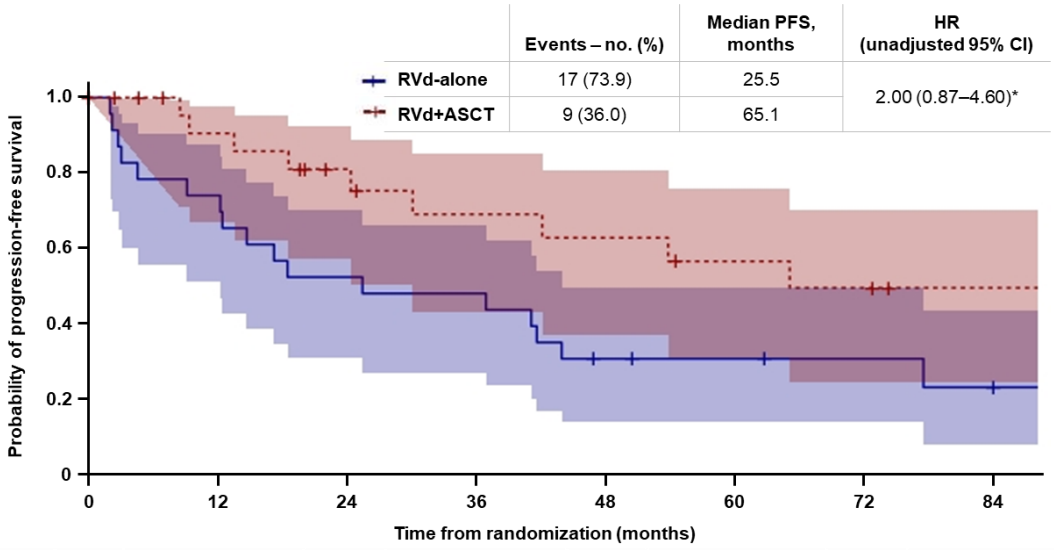
Patients at risk								
RVd-alone	66	36	19	16	11	8	6	3
RVd+ASCT	66	45	37	29	24	16	12	8

E



Patients at risk								
RVd-alone	268	197	156	134	109	83	50	34
RVd+ASCT	274	212	175	151	126	94	58	29

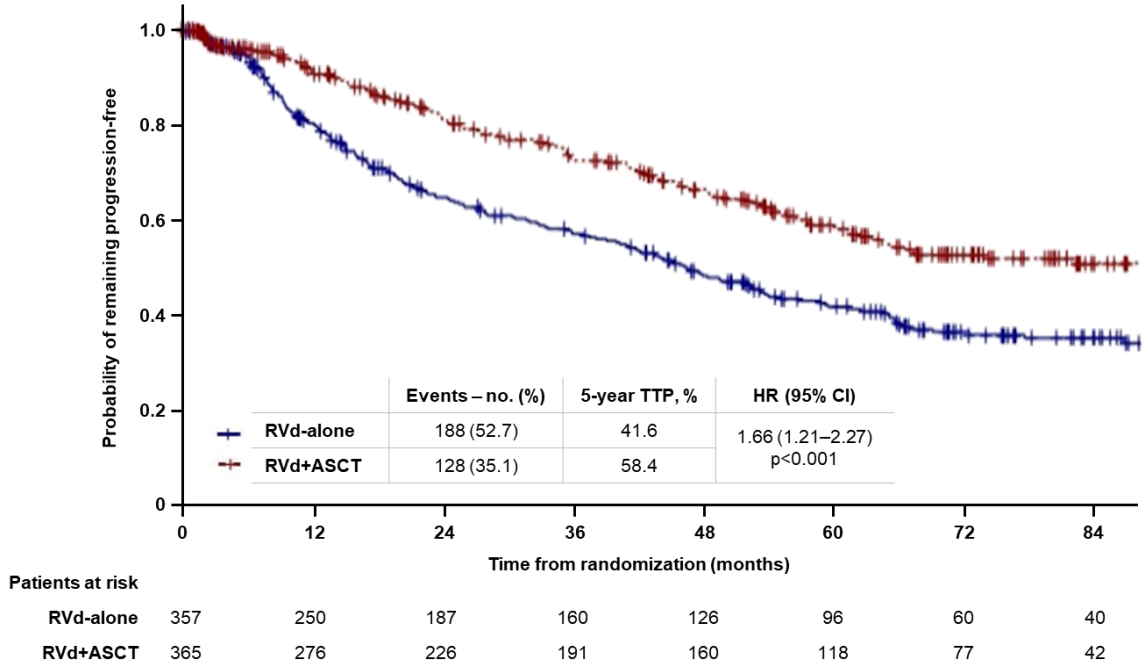
F



Patients at risk								
RVd-alone	23	17	12	11	6	5	4	3
RVd+ASCT	25	19	14	11	10	8	7	5

Figure S5: Kaplan–Meier analysis of time to progression in the intent-to-treat population

There were 188 and 128 events of disease progression on the RVd-alone and RVd+ASCT arms, respectively, at data cut-off. ASCT, autologous stem cell transplantation. CI, confidence interval. HR, hazard ratio. RVd, lenalidomide, bortezomib, dexamethasone.

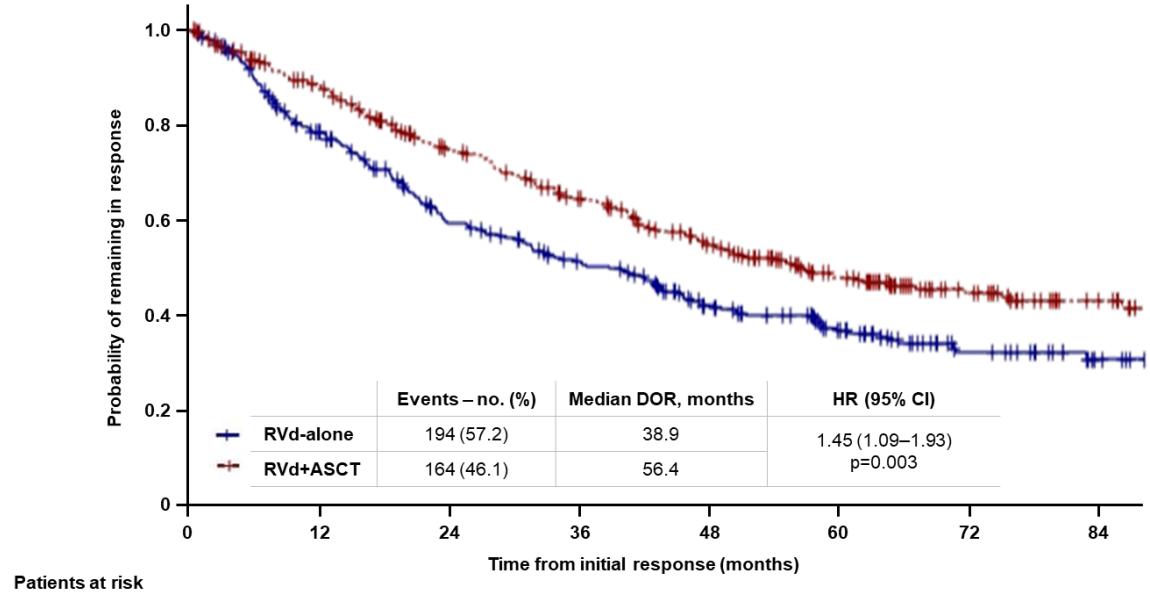


Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

Figure S6: Kaplan–Meier analysis of duration of response in responding patients

(A) Duration of partial response or better. (B) Duration of complete response or better. ASCT, autologous stem cell transplantation. CI, confidence interval. CR, complete response. DOR, duration of response. HR, hazard ratio. NR, not reached. PR, partial response. RVd, lenalidomide, bortezomib, dexamethasone.

A



Patients at risk								
RVd-alone	339	249	175	140	99	64	34	17
RVd+ASCT	356	292	228	184	140	95	58	31

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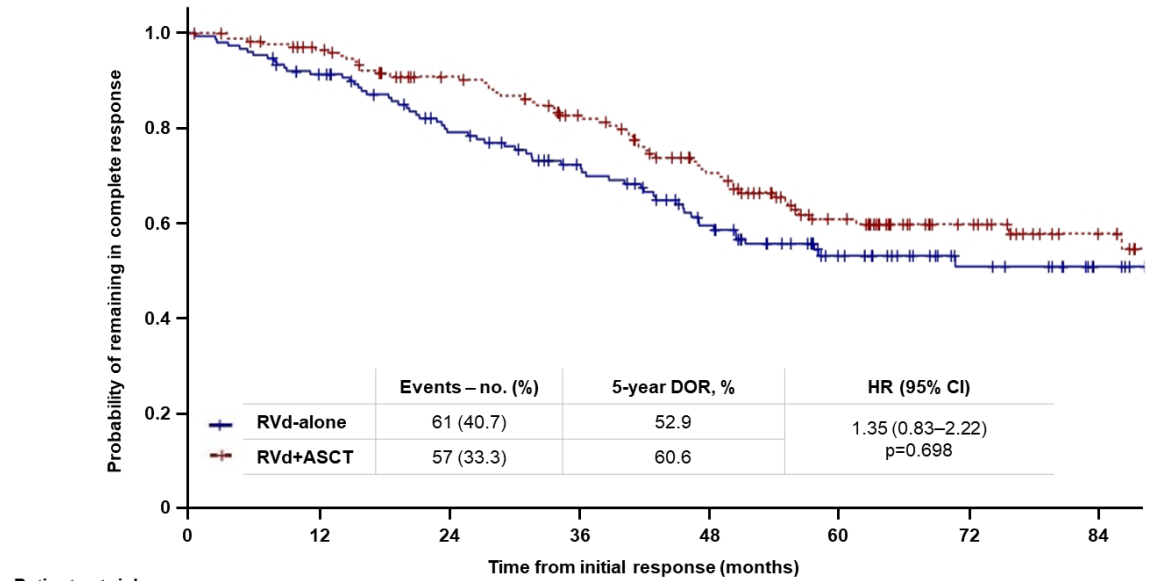


Patients at risk								
RVd-alone	150	133	107	88	65	38	22	12
RVd+ASCT	171	157	135	114	87	59	36	20

Figure S7: Kaplan–Meier analysis of progression-free survival by MRD status from start of maintenance therapy

ASCT, autologous stem cell transplantation. CI, confidence interval. HR, hazard ratio. MRD, minimal residual disease. PFS, progression-free survival. RVd, lenalidomide, bortezomib, dexamethasone. *The widths of the CIs have not been adjusted for multiplicity, and so the intervals should not be used in place of a hypothesis test.

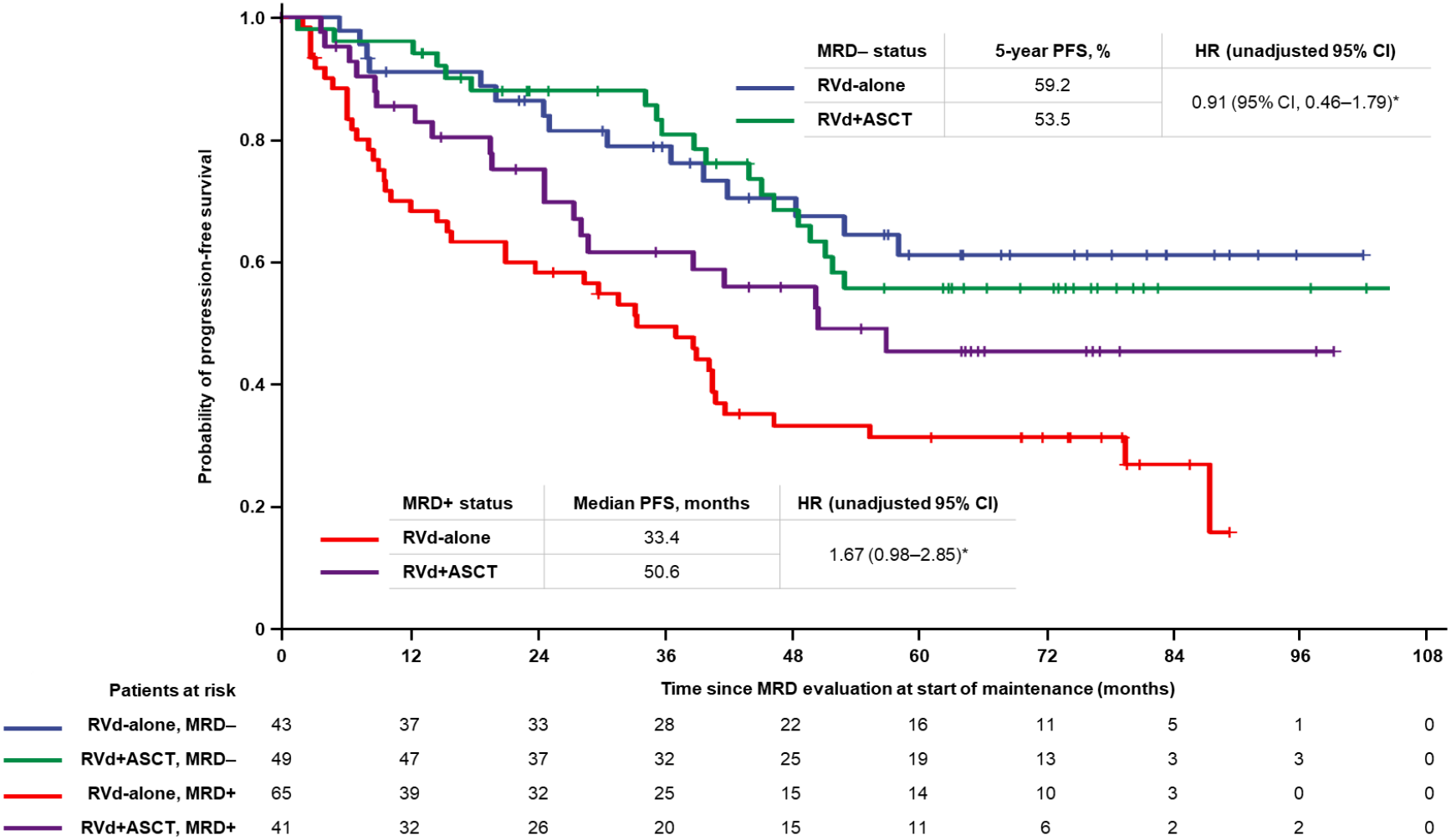


Figure S8: Forest plot of overall survival, including subgroup analyses by stratification factors and other key baseline patient and disease characteristics.

Overall survival with RVd-alone and RVd+ASCT in all patient subgroups analyzed. Subgroup data not shown for t(14;16) due to small event and patient numbers (3/10 vs 4/15, 5-year OS: 64.3% vs 71.4% ; HR 0.67, 95% CI: 0.11–4.07). The widths of the CIs have not been adjusted for multiplicity, and so the intervals should not be used in place of a hypothesis test. ASCT, autologous stem cell transplantation. CI, confidence interval. ECOG, Eastern Cooperative Oncology Group. HR, hazard ratio. Ig, immunoglobulin. ISS, International Staging System. ITT, intent-to-treat. NR, not reached. RVd, lenalidomide, bortezomib, dexamethasone.

Subgroup analysis of overall survival	No. of events / total no. of patients		5-year rate, %		HR	(95% CI)
	RVd-alone	RVd+ASCT	RVd-alone	RVd+ASCT		
All patients, ITT analysis	90/357	88/365	79.2	80.7	1.10	(0.81–1.47)
Age						
<60 years	56/235	57/263	79.4	82.8	1.11	(0.76–1.62)
≥60 years	34/122	31/102	78.9	75.2	1.08	(0.65–1.80)
Sex						
Male	54/202	46/215	79.2	83.0	1.33	(0.89–1.99)
Female	36/155	42/150	79.3	77.6	0.88	(0.55–1.39)
Race						
White/Caucasian	72/268	69/272	77.1	80.3	1.08	(0.78–1.51)
Black/African American	14/66	14/66	83.2	78.7	0.99	(0.45–2.16)
Other	3/17	3/21	92.3	95.0	1.68	(0.28–10.3)
ECOG performance status						
0	34/153	34/164	84.4	83.8	1.03	(0.63–1.68)
1–2	56/204	54/200	75.2	78.0	1.11	(0.75–1.63)
Body mass index						
<25	21/80	17/81	74.9	83.7	1.36	(0.68–2.72)
25 to <30	31/141	34/127	82.3	77.8	0.86	(0.52–1.43)
≥30	38/136	37/157	78.6	81.4	1.17	(0.74–1.86)
Myeloma type						
IgG	48/220	44/200	81.3	82.6	0.94	(0.62–1.42)
IgA	25/72	25/95	72.7	78.4	1.79	(0.98–3.24)
Light chain	7/34	15/41	83.0	71.4	0.55	(0.21–1.45)
ISS stage						
I	38/178	32/184	82.9	87.7	1.42	(0.88–2.27)
II	36/130	37/134	76.4	76.3	0.98	(0.62–1.55)
III	16/49	19/47	73.8	65.1	0.82	(0.41–1.62)
Lactate dehydrogenase level						
Not elevated (<225 U/L)	59/260	59/270	80.4	82.7	1.09	(0.76–1.58)
Elevated (≥225 U/L)	31/96	28/92	75.9	75.2	1.06	(0.61–1.84)
FISH cytogenetics						
High risk	32/66	29/66	54.3	63.4	1.25	(0.75–2.08)
t(4;14)	12/32	10/28	64.0	65.3	1.39	(0.58–3.36)
Del(17p)	21/38	20/34	53.8	55.3	1.03	(0.54–1.97)
Standard risk	48/268	50/274	86.2	86.0	0.98	(0.66–1.46)
Revised-ISS stage						
I	13/103	14/105	90.1	91.0	1.08	(0.50–2.29)
II	56/202	51/211	77.0	80.0	1.14	(0.78–1.68)
III	11/28	13/21	64.4	51.0	0.67	(0.29–1.55)

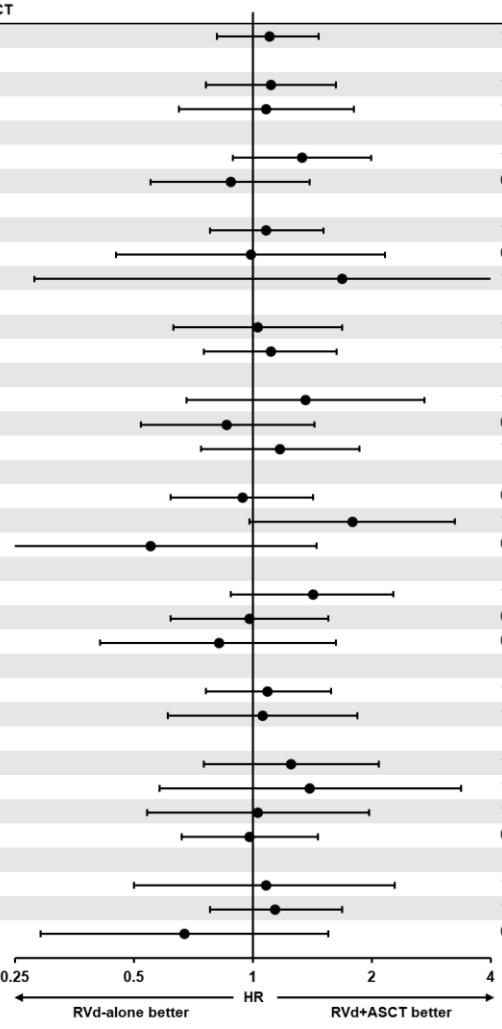
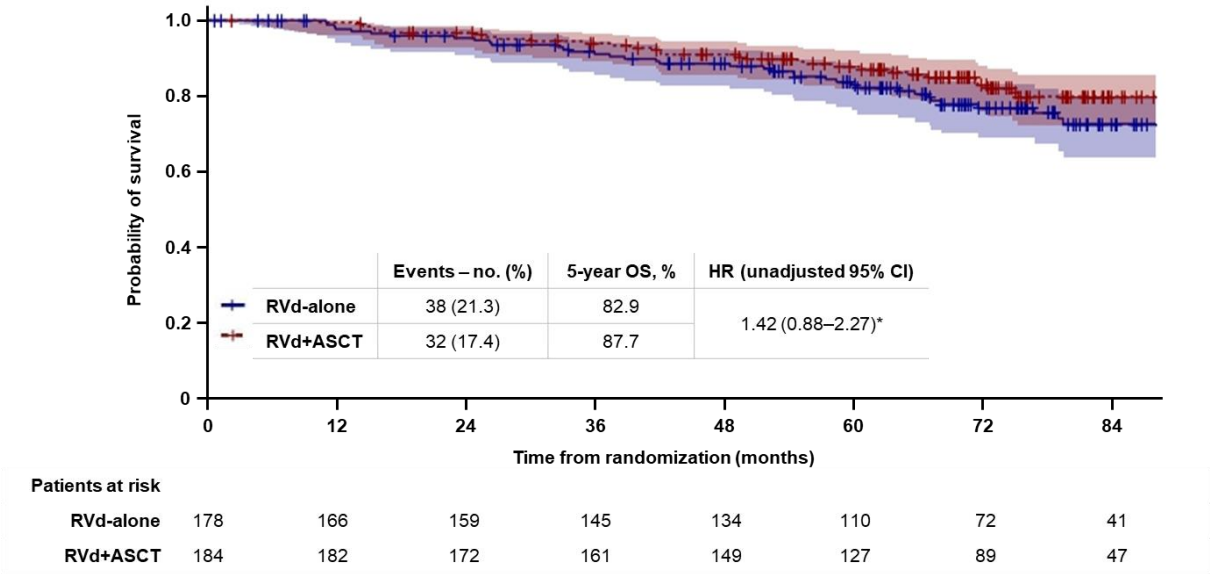


Figure S9: Kaplan–Meier analyses of overall survival according to randomization stratification factors.

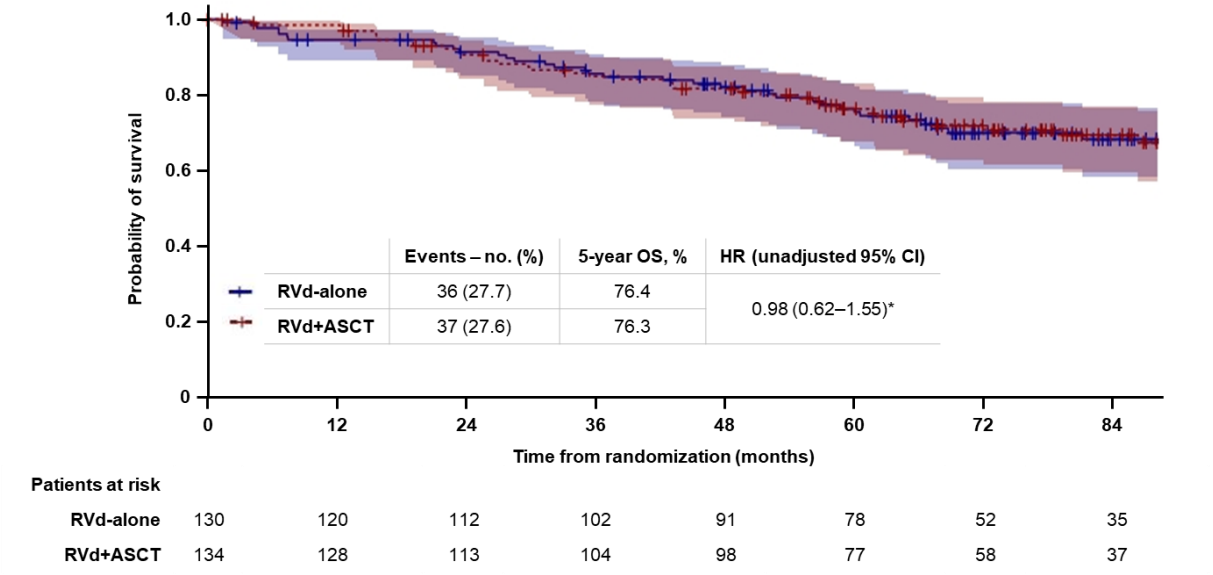
Overall survival with RVd-alone and RVd+ASCT in patients with ISS stage (A) I, (B) II, and (C) III disease, and in patients with (D) high-risk, (E) standard-risk, and (F) non-evaluable cytogenetics. Shaded areas indicate 95% CIs. ASCT, autologous stem cell transplantation. CI, confidence interval. ISS, International Staging System. OS, overall survival. RVd, lenalidomide, bortezomib, dexamethasone. *The widths of the CIs have not been adjusted for multiplicity, and so the intervals should not be used in place of a hypothesis test.

A



Patients at risk								
RVd-alone	178	166	159	145	134	110	72	41
RVd+ASCT	184	182	172	161	149	127	89	47

B



Patients at risk								
RVd-alone	130	120	112	102	91	78	52	35
RVd+ASCT	134	128	113	104	98	77	58	37

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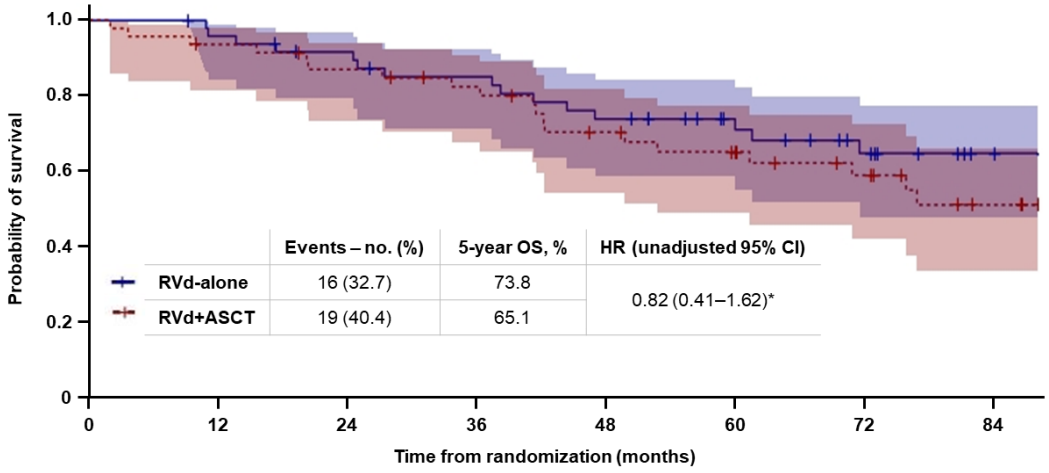
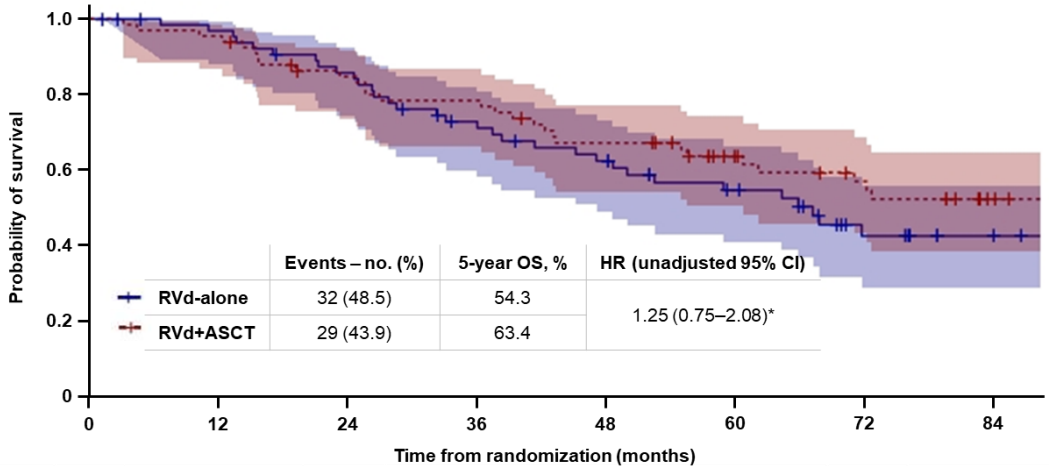


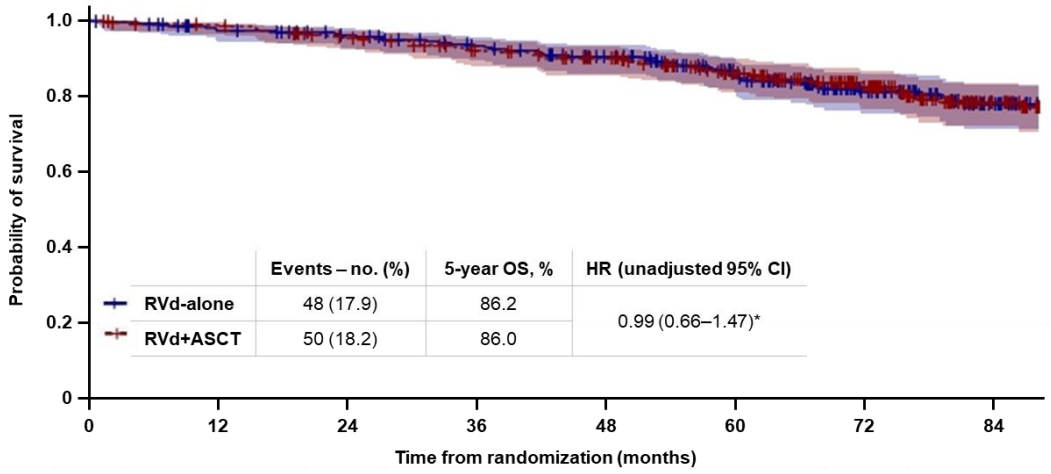
Patients at risk								
RVd-alone	49	46	42	38	33	26	19	12
RVd+ASCT	47	43	39	35	28	24	18	11

D



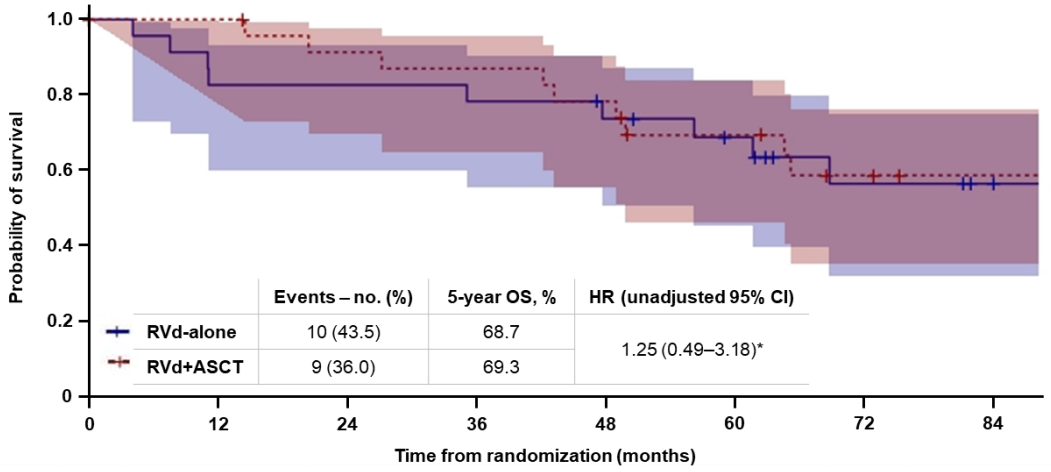
Patients at risk								
RVd-alone	66	61	53	41	35	26	14	8
RVd+ASCT	66	63	53	49	41	30	24	16

E



Patients at risk								
RVd-alone	268	252	241	226	207	175	121	74
RVd+ASCT	274	266	250	231	216	184	131	71

F

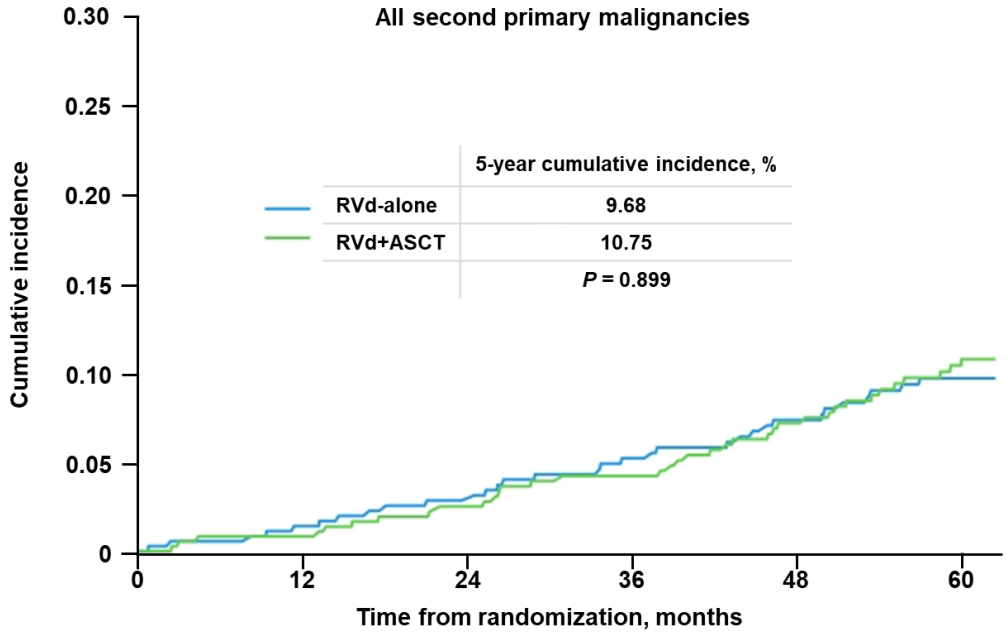


Patients at risk								
RVd-alone	23	19	19	18	16	13	8	6
RVd+ASCT	25	24	21	20	18	14	10	8

Figure S10: Cumulative incidence of second primary malignancies in DETERMINATION, with comparison of 5-year cumulative incidence vs IFM 2009

Cumulative incidence analysis with death as a competing risk for (A) any second primary malignancy, (B) any invasive second primary malignancy, (C) any second primary hematologic malignancy, (D) any second primary solid tumor, and (E) any non-melanoma skin second primary malignancy in the RVd-alone (blue lines) and RVd+ASCT (green lines) arms. ASCT, autologous stem cell transplantation. RVd, lenalidomide, bortezomib, dexamethasone. In the IFM 2009 study (N=350 in both arms),[4,5] after median follow-up of 93.0 months on the RVd-alone arm and 93.6 months on RVd+ASCT arm, the 5-year cumulative incidence of invasive second primary malignancies was 5.56% vs 6.91%, and the 5-year cumulative incidence of second primary hematologic malignancies was 0.58% vs 1.44%, respectively [Perrot A, personal communication].

A



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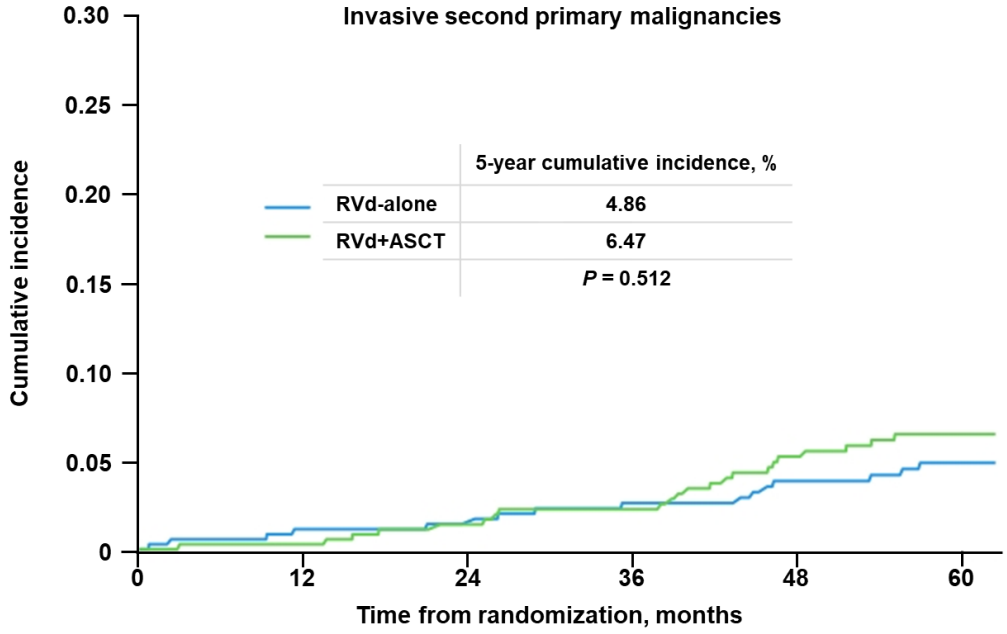

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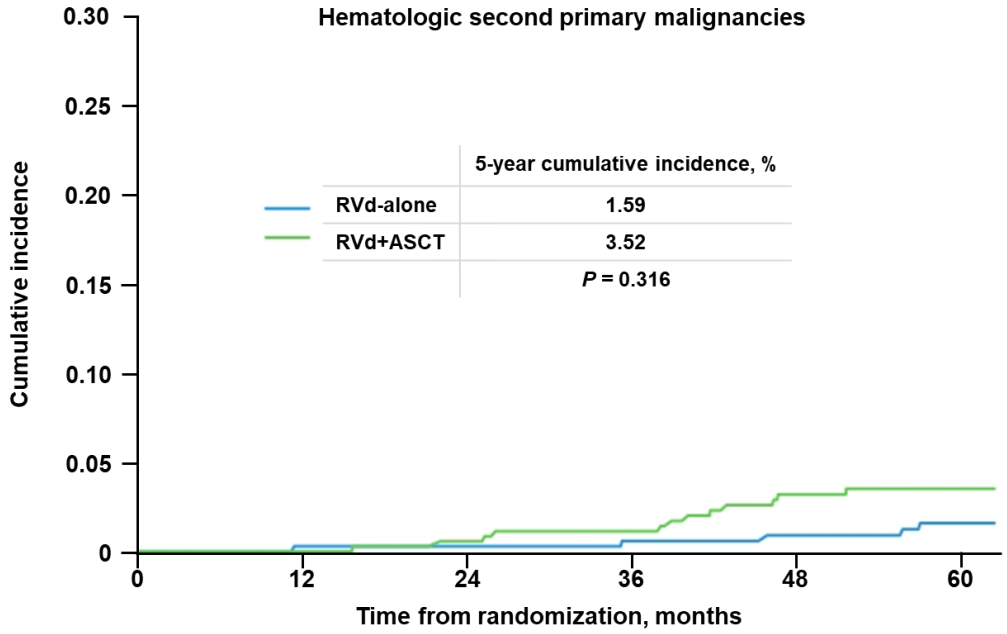
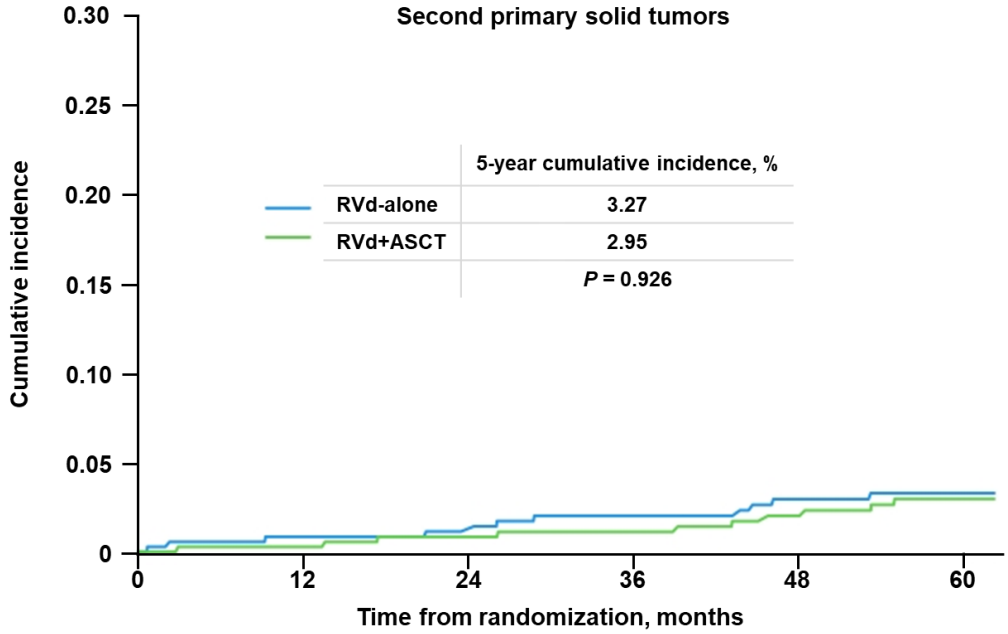

Hematologic second primary malignancies
5-year cumulative incidence, %
RVd-alone
1.59
RVd+ASCT
3.52
P = 0.316
Cumulative incidence
0.30
0.25
0.20
0.15
0.10
0.05
0
0
12
24
36
48
60
Time from randomization, months

D


Second primary solid tumors
5-year cumulative incidence, %
RVd-alone
3.27
RVd+ASCT
2.95
P = 0.926
Cumulative incidence
0.30
0.25
0.20
0.15
0.10
0.05
0
0
12
24
36
48
60
Time from randomization, months

E

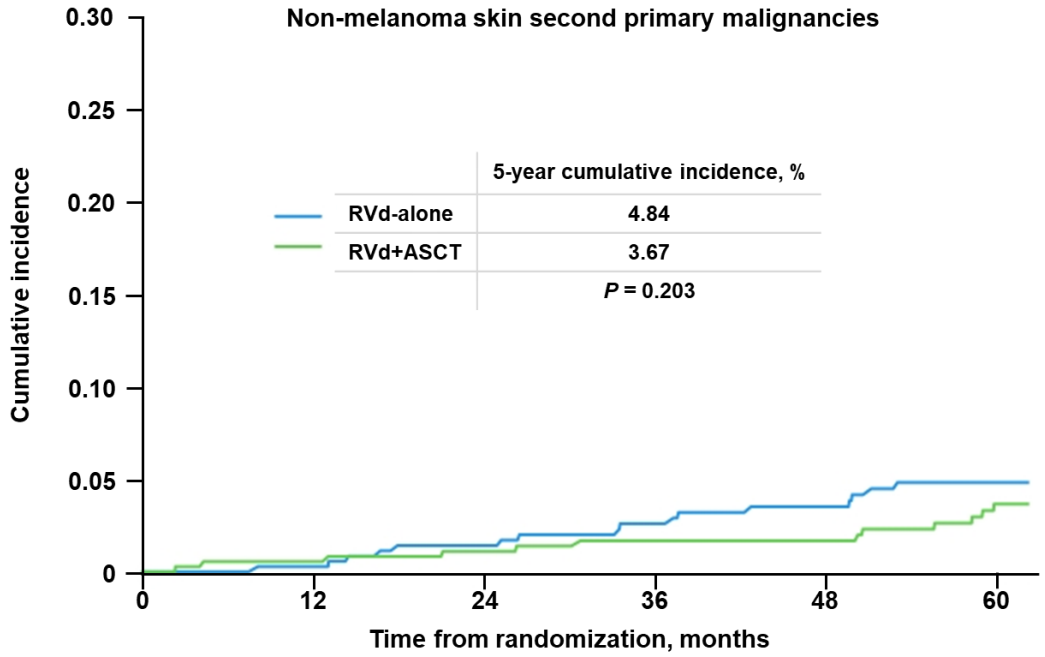
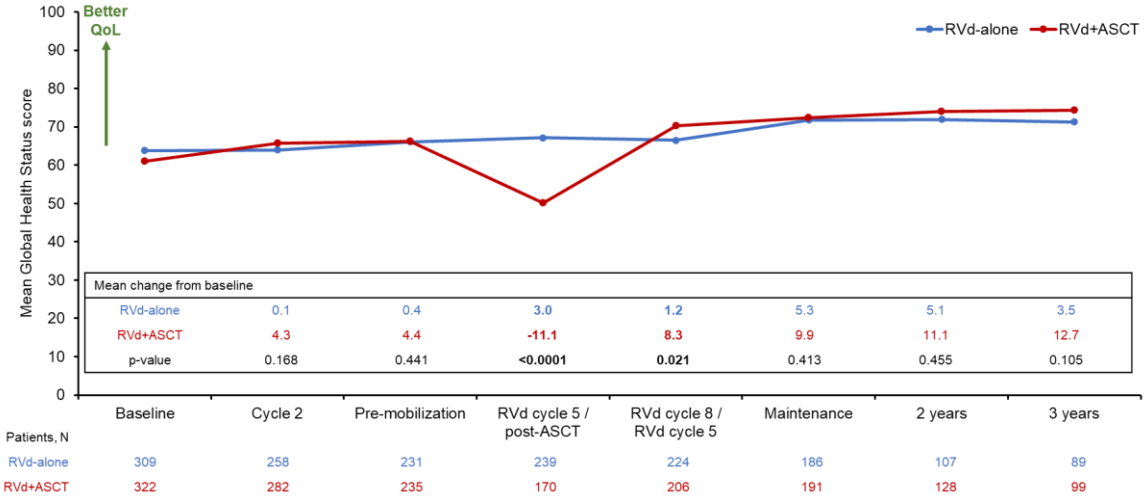

Non-melanoma skin second primary malignancies
5-year cumulative incidence, %
RVd-alone
4.84
RVd+ASCT
3.67
P = 0.203
Cumulative incidence
0.30
0.25
0.20
0.15
0.10
0.05
0
0
12
24
36
48
60
Time from randomization, months

Figure S11: Mean quality of life domain scores at baseline and on-treatment assessment timepoints

Panels show the mean domain scores among patients completing the respective instruments at each timepoint for the (A) Global Health Status/QoL, (B) Physical Functioning, and (C) Role Functioning domains of the EORTC QLQ-C30 instrument, the (D) Disease Symptoms and (E) Side Effects scores of the EORTC QLQ-MY20 instrument, and (F) the FACT/GOG-NTx instrument neurotoxicity score. Changes in domain scores from baseline were compared between groups using a two-sided t-test, with Bonferroni correction to adjust for seven multiple comparisons over the time points. ASCT, autologous stem cell transplantation. C30, core 30 module. EORTC, European Organization for the Research and Treatment of Cancer. FACT, Functional Assessment of Cancer Therapy. GOG, Gynecologic Oncology Group. MY20, myeloma-specific module. Ntx, neurotoxicity. QLQ, quality of life questionnaire. QoL, quality of life. RVd, lenalidomide, bortezomib, dexamethasone.

A



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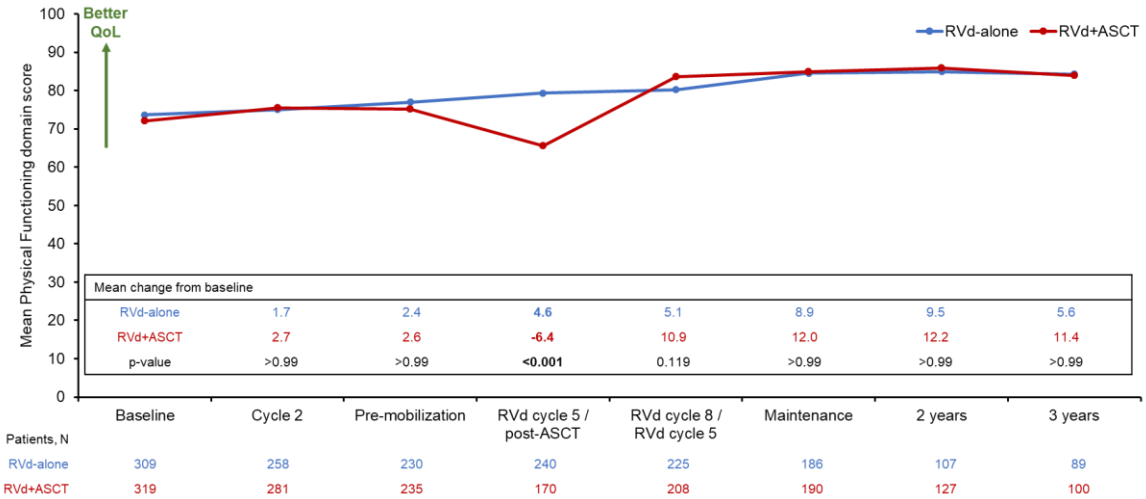

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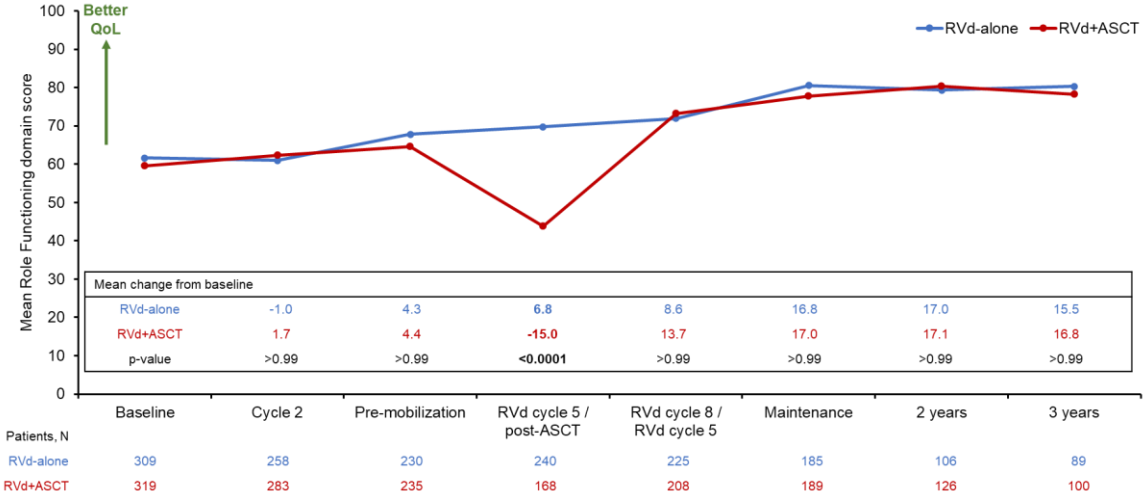
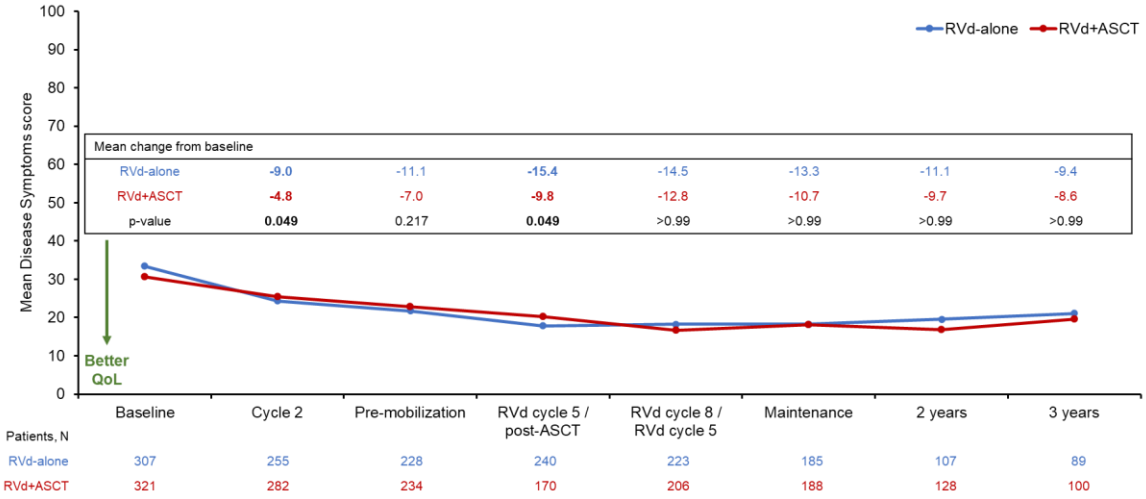


Mean change from baseline	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	-1.0	4.3	**6.8**	8.6	16.8	17.0	15.5
RVd+ASCT	1.7	4.4	**-15.0**	13.7	17.0	17.1	16.8
p-value	>0.99	>0.99	**<0.0001**	>0.99	>0.99	>0.99	>0.99

Patients, N	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	309	258	230	240	225	185	106	89
RVd+ASCT	319	283	235	168	208	189	126	100

D



Mean change from baseline	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	**-9.0**	-11.1	**-15.4**	-14.5	-13.3	-11.1	-9.4
RVd+ASCT	**-4.8**	-7.0	**-9.8**	-12.8	-10.7	-9.7	-8.6
p-value	**0.049**	0.217	**0.049**	>0.99	>0.99	>0.99	>0.99

Patients, N	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	307	255	228	240	223	185	107	89
RVd+ASCT	321	282	234	170	206	188	128	100

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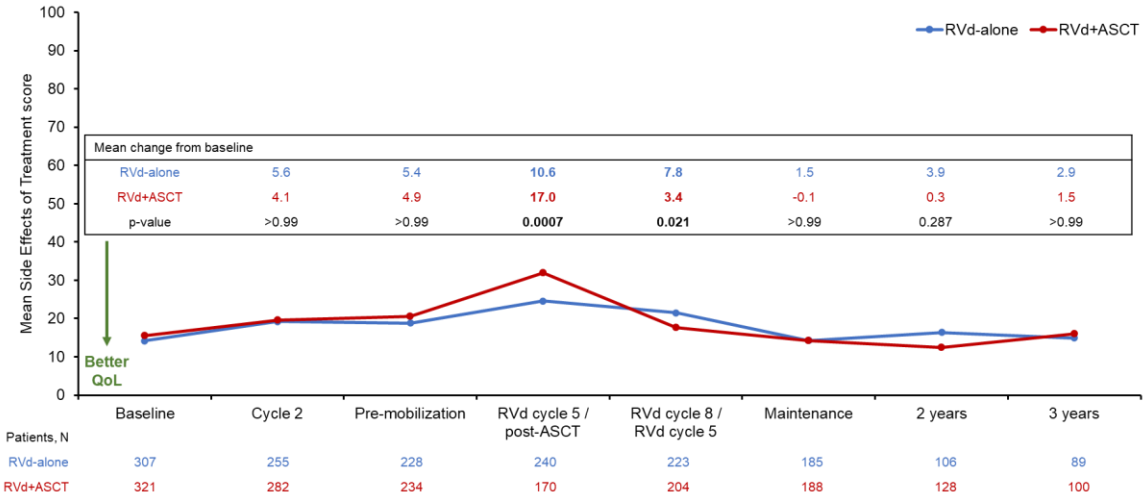
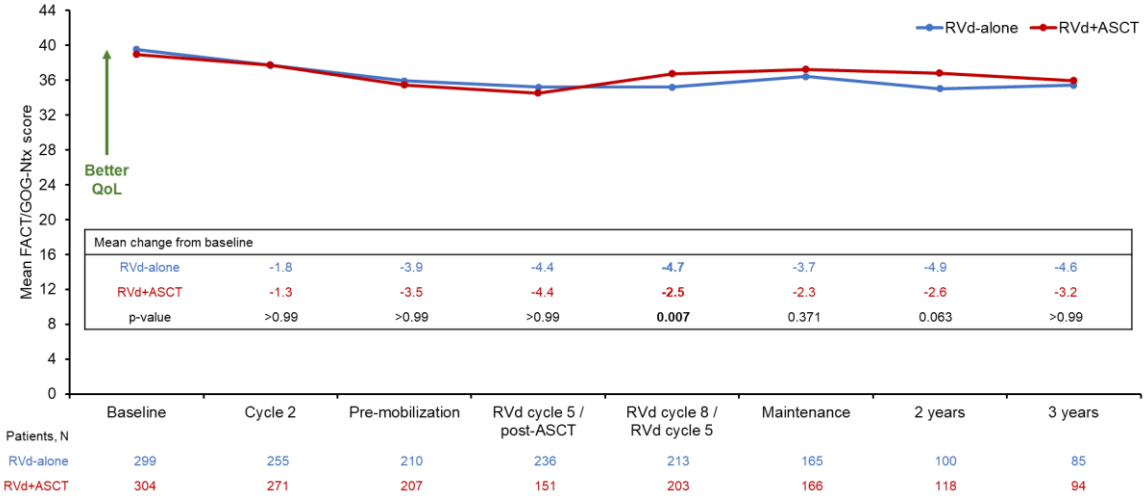


Mean change from baseline	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	5.6	5.4	**10.6**	**7.8**	1.5	3.9	2.9
RVd+ASCT	4.1	4.9	**17.0**	**3.4**	-0.1	0.3	1.5
p-value	>0.99	>0.99	**0.0007**	**0.021**	>0.99	0.287	>0.99

Patients, N	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	307	255	228	240	223	185	106	89
RVd+ASCT	321	282	234	170	204	188	128	100

F

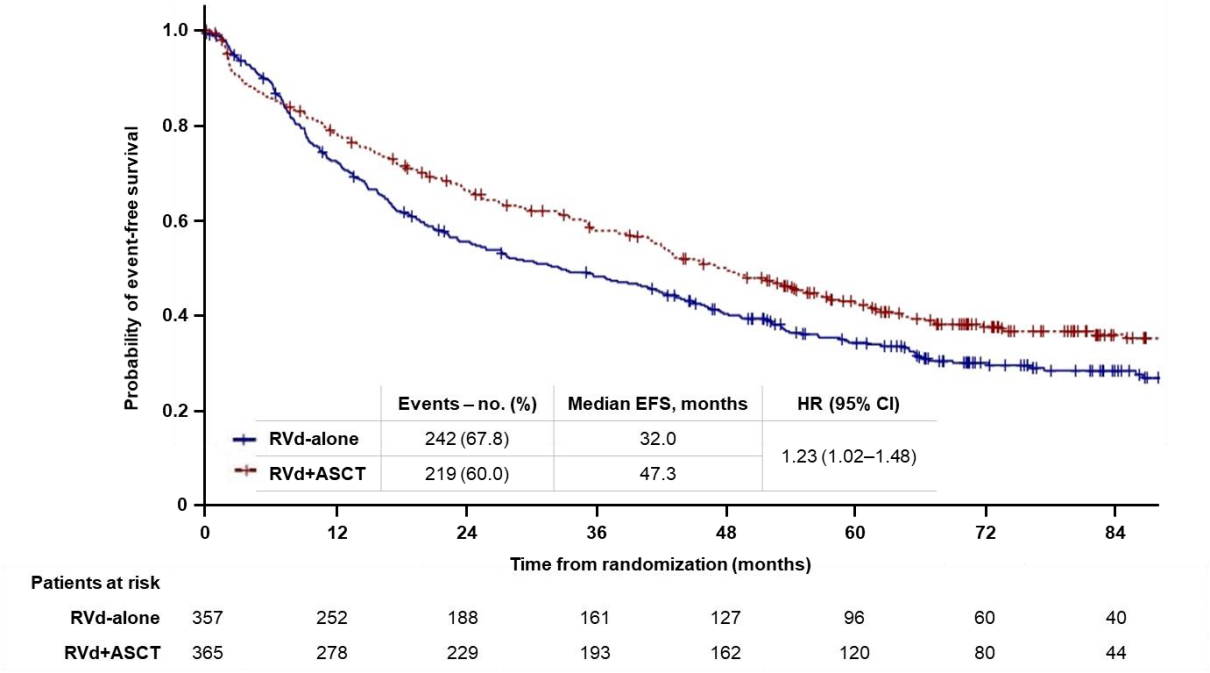


Mean change from baseline	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	-1.8	-3.9	-4.4	**-4.7**	-3.7	-4.9	-4.6
RVd+ASCT	-1.3	-3.5	-4.4	**-2.5**	-2.3	-2.6	-3.2
p-value	>0.99	>0.99	>0.99	**0.007**	0.371	0.063	>0.99

Patients, N	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	299	255	210	236	213	165	100	85
RVd+ASCT	304	271	207	151	203	166	118	94

Figure S12: Kaplan–Meier analysis of event-free survival in the intent-to-treat population

Event-free survival included receipt of non-protocol therapy, disease progression, and death as events. ASCT, autologous stem cell transplantation. This post-hoc sensitivity analysis was conducted to evaluate the impact of censoring for non-protocol therapy in the PFS analysis. CI, confidence interval. EFS, event-free survival. HR, hazard ratio. RVd, lenalidomide, bortezomib, dexamethasone.



Patients at risk								
RVd-alone	357	252	188	161	127	96	60	40
RVd+ASCT	365	278	229	193	162	120	80	44

Table S1: Eligibility criteria – hematologic, hepatic, renal, and cardiac parameters.

All laboratory assessments were required to be performed within 21 days of initiating protocol therapy

Organ/system	Parameter	Exclusion criterion
Hematologic	Platelet count	<50,000/mm^3 for patients in whom <50% of bone marrow nucleated cells are plasma cells
		<30,000/mm^3 for patients in whom >50% of bone marrow nucleated cells are plasma cells
	Absolute neutrophil count	<1000/mm^3
	Hemoglobin	<8 g/dL
Hepatic	Total bilirubin	>1.5 x ULN
	AST	≥2 x ULN
	ALT	≥2 x ULN
	Alkaline phosphatase	≥2 x ULN
Renal	Serum creatinine	>2.0 mg/dL within 7 days of initiating protocol therapy
	Creatinine clearance	<50 mL/min (actual or calculated) within 7 days of initiating protocol therapy
Cardiac	LVEF	<40%
	–	Clinical signs of heart or coronary failure Myocardial infarction within prior 6 months NYHA Class III or IV heart failure Uncontrolled angina Severe uncontrolled ventricular arrhythmias Electrocardiographic evidence of acute ischemia or active conductive system abnormalities

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ULN, institutional upper limit of normal

Table S2: Treatment-related adverse events of any grade reported during treatment (induction through maintenance) in at least 2% of RVd-alone or RVd+ASCT patients

Event – no. (%)	RVd-alone (N = 357)	RVd+ASCT (N = 365)
Any event	344 (96.4)	359 (98.4)
Any hematologic event	230 (64.4)	331 (90.7)
Blood and lymphatic system disorders	234 (65.5)	331 (90.7)
Neutropenia	162 (45.4)	316 (86.6)
Thrombocytopenia	90 (25.2)	305 (83.6)
Leukopenia	94 (26.3)	171 (46.8)
Anemia	90 (25.2)	137 (37.5)
Lymphopenia	41 (11.5)	47 (12.9)
Febrile neutropenia	15 (4.2)	37 (10.1)
Cardiac disorders	44 (12.3)	60 (16.4)
Bradycardia	20 (5.6)	17 (4.7)
Sinus bradycardia	11 (3.1)	10 (2.7)
Tachycardia	5 (1.4)	16 (4.4)
Ear and labyrinth disorders	21 (5.9)	19 (5.2)
Tinnitus	8 (2.2)	9 (2.5)
Eye disorders	79 (22.1)	49 (13.4)
Blurred vision	51 (14.3)	25 (6.8)
Dry eyes	18 (5.0)	13 (3.6)
Gastrointestinal disorders	262 (73.4)	293 (80.3)
Diarrhea	169 (47.3)	225 (61.6)
Nausea	123 (34.5)	191 (52.3)
Constipation	143 (40.1)	142 (38.9)
Vomiting	31 (8.7)	99 (27.1)
Mucositis	12 (3.4)	73 (20.0)
Stomach pain	31 (8.7)	50 (13.7)
Dyspepsia	25 (7.0)	32 (8.8)
Abdominal distension	23 (6.4)	21 (5.8)
Dry mouth	18 (5.0)	22 (6.0)
Esophagitis	2 (0.6)	27 (7.4)
Loose stools	8 (2.2)	19 (5.2)
Heartburn	13 (3.6)	11 (3.0)
Flatulence	8 (2.2)	15 (4.1)
Abdominal discomfort	3 (0.8)	14 (3.8)
Acid reflux	9 (2.5)	6 (1.6)
Gastroesophageal reflux disease	2 (0.6)	13 (3.6)
General disorders and administration site conditions	267 (74.8)	280 (76.7)
Fatigue	203 (56.9)	218 (59.7)
Edema	123 (34.5)	109 (29.9)
Fever	46 (12.9)	85 (23.3)
Pain	35 (9.8)	36 (9.9)

Event – no. (%)	RVd-alone (N = 357)	RVd+ASCT (N = 365)
Flu like symptoms	16 (4.5)	19 (5.2)
Malaise	17 (4.8)	15 (4.1)
Chest pain	10 (2.8)	19 (5.2)
Chills	8 (2.2)	21 (5.8)
Mucositis	2 (0.6)	21 (5.8)
Weakness	8 (2.2)	13 (3.6)
Irritability	11 (3.1)	5 (1.4)
Infections and infestations	170 (47.6)	185 (50.7)
Upper respiratory infection	108 (30.3)	118 (32.3)
Pneumonia	37 (10.4)	61 (16.7)
Cold	23 (6.4)	29 (7.9)
Sinusitis	17 (4.8)	19 (5.2)
Stye	17 (4.8)	9 (2.5)
Urinary tract infection	13 (3.6)	12 (3.3)
Herpes zoster	7 (2.0)	13 (3.6)
Influenza	8 (2.2)	10 (2.7)
Cellulitis	5 (1.4)	10 (2.7)
Thrush	3 (0.8)	12 (3.3)
Injury, poisoning and procedural complications	16 (4.5)	25 (6.8)
Bruising	6 (1.7)	13 (3.6)
Investigations	93 (26.1)	92 (25.2)
Elevated liver enzymes	33 (9.2)	38 (10.4)
Weight loss	18 (5.0)	15 (4.1)
Weight gain	22 (6.2)	7 (1.9)
Creatinine increased	13 (3.6)	13 (3.6)
Blood bilirubin increased	10 (2.8)	8 (2.2)
Metabolism and nutrition disorders	166 (46.5)	185 (50.7)
Hypokalemia	55 (15.4)	62 (17.0)
Anorexia	43 (12.0)	65 (17.8)
Hypophosphatemia	48 (13.4)	50 (13.7)
Hyperglycemia	38 (10.6)	33 (9.0)
Hypocalcemia	25 (7.0)	30 (8.2)
Hypomagnesemia	22 (6.2)	26 (7.1)
Hyponatremia	19 (5.3)	25 (6.8)
Dehydration	11 (3.1)	16 (4.4)
Decreased appetite	12 (3.4)	14 (3.8)
Hypoalbuminemia	8 (2.2)	10 (2.7)
Musculoskeletal and connective tissue disorders	154 (43.1)	169 (46.3)
Cramps	34 (9.5)	34 (9.3)
Myalgia	33 (9.2)	29 (7.9)
Muscle cramps	31 (8.7)	29 (7.9)
Bone pain	25 (7.0)	29 (7.9)

Event – no. (%)	RVd-alone (N = 357)	RVd+ASCT (N = 365)
Arthralgia	16 (4.5)	30 (8.2)
Back pain	19 (5.3)	23 (6.3)
Muscle weakness	8 (2.2)	17 (4.7)
Pain in extremity	17 (4.8)	6 (1.6)
Pain in legs	6 (1.7)	15 (4.1)
Leg cramps	7 (2.0)	10 (2.7)
Muscle spasm	6 (1.7)	10 (2.7)
Pain in shoulder	8 (2.2)	8 (2.2)
Nervous system disorders	291 (81.5)	273 (74.8)
Neuropathy†	261 (73.1)	241 (66.0)
Sensory peripheral neuropathy	236 (66.1)	219 (60.0)
Dizziness	55 (15.4)	58 (15.9)
Headache	44 (12.3)	52 (14.2)
Neuropathy	49 (13.7)	37 (10.1)
Dysgeusia	43 (12.0)	42 (11.5)
Paresthesia	41 (11.5)	33 (9.0)
Tremor	27 (7.6)	23 (6.3)
Memory impairment	22 (6.2)	23 (6.3)
Light headedness	14 (3.9)	12 (3.3)
Syncope	10 (2.8)	10 (2.7)
Numbness of extremities	7 (2.0)	8 (2.2)
Respiratory, thoracic and mediastinal disorders	122 (34.2)	130 (35.6)
Dyspnea	57 (16.0)	59 (16.2)
Cough	52 (14.6)	54 (14.8)
Nasal congestion	18 (5.0)	20 (5.5)
Sore throat	13 (3.6)	20 (5.5)
Hiccups	11 (3.1)	14 (3.8)
Skin and subcutaneous tissue disorders	157 (44.0)	175 (47.9)
Maculo-papular rash	87 (24.4)	96 (26.3)
Dry skin	36 (10.1)	34 (9.3)
Alopecia	48 (13.4)	17 (4.7)
Pruritis	15 (4.2)	26 (7.1)
Rash pruritic	5 (1.4)	12 (3.3)
Night sweats	6 (1.7)	10 (2.7)
Vascular disorders	75 (21.0)	109 (29.9)
All thromboembolic events‡	25 (7.0)	40 (11.0)
Thromboembolic event	12 (3.4)	23 (6.3)
Deep vein thrombosis	9 (2.5)	9 (2.5)
Hypertension	25 (7.0)	24 (6.6)
Hypotension	15 (4.2)	33 (9.0)
Hot flashes	12 (3.4)	15 (4.1)

†Neuropathy events include sensory peripheral neuropathy, sensory neuropathy, and neuropathy. ‡All thromboembolic events include pulmonary embolism, thromboembolic event, stroke, and deep vein thrombosis. ASCT, autologous stem cell transplantation. RVd, lenalidomide, bortezomib, dexamethasone.

Table S3: Treatment-related adverse events (any grade and grade 3 or higher) reported during maintenance in at least 2% of patients receiving maintenance in either arm

Event – no. (%)	RVd-alone (N = 291)	RVd+ASCT (N = 289)
Any-grade events		
Any event	244 (83.8)	242 (83.7)
Any hematologic event	110 (37.8)	149 (51.6)
Blood and lymphatic system disorders	110 (37.8)	150 (51.9)
Neutropenia	88 (30.2)	124 (42.9)
Leukopenia	37 (12.7)	57 (19.7)
Thrombocytopenia	15 (5.2)	53 (18.3)
Anemia	21 (7.2)	28 (9.7)
Cardiac disorders	27 (9.3)	29 (10.0)
Bradycardia	19 (6.5)	16 (5.5)
Sinus bradycardia	6 (2.1)	9 (3.1)
Eye disorders	23 (7.9)	15 (5.2)
Blurred vision	9 (3.1)	5 (1.7)
Gastrointestinal disorders	161 (55.3)	160 (55.4)
Diarrhea	121 (41.6)	126 (43.6)
Nausea	39 (13.4)	42 (14.5)
Constipation	44 (15.1)	34 (11.8)
Vomiting	15 (5.2)	25 (8.7)
Stomach pain	18 (6.2)	14 (4.8)
Dyspepsia	8 (2.7)	10 (3.5)
Abdominal distension	6 (2.1)	9 (3.1)
Dry mouth	10 (3.4)	5 (1.7)
Flatulence	5 (1.7)	7 (2.4)
General disorders and administration site conditions	132 (45.4)	140 (48.4)
Fatigue	94 (32.3)	104 (36.0)
Edema	35 (12.0)	28 (9.7)
Fever	16 (5.5)	26 (9.0)
Flu like symptoms	9 (3.1)	10 (3.5)
Pain	10 (3.4)	5 (1.7)
Malaise	8 (2.7)	6 (2.1)
Chest pain	4 (1.4)	8 (2.8)
Infections and infestations	118 (40.5)	128 (44.3)
Upper respiratory infection	73 (25.1)	88 (30.4)
Pneumonia	27 (9.3)	42 (14.5)
Cold	21 (7.2)	20 (6.9)
Sinusitis	15 (5.2)	15 (5.2)
Herpes zoster	6 (2.1)	10 (3.5)
Influenza	6 (2.1)	8 (2.8)

Event – no. (%)	RVd-alone (N = 291)	RVd+ASCT (N = 289)
Investigations	46 (15.8)	47 (16.3)
Elevated liver enzymes	15 (5.2)	23 (8.0)
Creatinine increased	6 (2.1)	10 (3.5)
Blood bilirubin increased	8 (2.7)	4 (1.4)
Metabolism and nutrition disorders	79 (27.1)	60 (20.8)
Hypophosphatemia	28 (9.6)	25 (8.7)
Hypokalemia	29 (10.0)	15 (5.2)
Anorexia	18 (6.2)	11 (3.8)
Hypomagnesemia	11 (3.8)	7 (2.4)
Hypocalcemia	13 (4.5)	3 (1.0)
Hyperglycemia	7 (2.4)	6 (2.1)
Musculoskeletal and connective tissue disorders	79 (27.1)	86 (29.8)
Myalgia	20 (6.9)	17 (5.9)
Cramps	16 (5.5)	20 (6.9)
Muscle cramps	11 (3.8)	15 (5.2)
Arthralgia	9 (3.1)	16 (5.5)
Back pain	7 (2.4)	10 (3.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (6.2)	21 (7.3)
Squamous cell carcinoma	9 (3.1)	4 (1.4)
Nervous system disorders	140 (48.1)	118 (40.8)
Neuropathy†	102 (35.1)	88 (30.4)
Sensory peripheral neuropathy	89 (30.6)	77 (26.6)
Paresthesia	19 (6.5)	13 (4.5)
Headache	17 (5.8)	14 (4.8)
Neuropathy	17 (5.8)	14 (4.8)
Memory impairment	9 (3.1)	16 (5.5)
Dizziness	14 (4.8)	7 (2.4)
Dysgeusia	13 (4.5)	7 (2.4)
Tremor	5 (1.7)	8 (2.8)
Psychiatric disorders	26 (8.9)	24 (8.3)
Insomnia	20 (6.9)	15 (5.2)
Depression	5 (1.7)	8 (2.8)
Respiratory, thoracic and mediastinal disorders	60 (20.6)	55 (19.0)
Dyspnea	29 (10.0)	33 (11.4)
Cough	20 (6.9)	16 (5.5)
Nasal congestion	14 (4.8)	16 (5.5)
Sore throat	9 (3.1)	8 (2.8)
Skin and subcutaneous tissue disorders	64 (22.0)	80 (27.7)
Maculo-papular rash	29 (10.0)	34 (11.8)
Dry skin	25 (8.6)	22 (7.6)
Pruritis	7 (2.4)	8 (2.8)

Event – no. (%)	RVd-alone (N = 291)	RVd+ASCT (N = 289)
Vascular disorders	27 (9.3)	38 (13.1)
Hypertension	14 (4.8)	19 (6.6)
Hot flashes	6 (2.1)	6 (2.1)
All thromboembolic events‡	7 (2.4)	14 (4.8)
Thromboembolic event	5 (1.7)	7 (2.4)
Grade 3 or higher events		
Any event	129 (44.3)	177 (61.2)
Any hematologic event	76 (26.1)	121 (41.9)
Blood and lymphatic system disorders	76 (26.1)	122 (42.2)
Neutropenia	68 (23.4)	107 (37.0)
Leukopenia	14 (4.8)	26 (9.0)
Thrombocytopenia	3 (1.0)	27 (9.3)
Lymphopenia	9 (3.1)	9 (3.1)
Gastrointestinal disorders	11 (3.8)	12 (4.2)
Diarrhea	9 (3.1)	5 (1.7)
General disorders and administration site conditions	12 (4.1)	20 (6.9)
Fatigue	9 (3.1)	13 (4.5)
Infections and infestations	22 (7.6)	36 (12.5)
Pneumonia	13 (4.5)	20 (6.9)
Investigations	8 (2.7)	7 (2.4)
Elevated liver enzymes	15 (5.2)	23 (8.0)
Creatinine increased	6 (2.1)	10 (3.5)
Blood bilirubin increased	8 (2.7)	4 (1.4)
Metabolism and nutrition disorders	27 (9.3)	17 (5.9)
Hypophosphatemia	20 (6.9)	13 (4.5)
Nervous system disorders	4 (1.4)	17 (5.9)
Neuropathy†	4 (1.4)	10 (3.5)

†Neuropathy events include sensory peripheral neuropathy, sensory neuropathy, and neuropathy. ‡All thromboembolic events include pulmonary embolism, thromboembolic event, stroke, and deep vein thrombosis. ASCT, autologous stem cell transplantation. RVd, lenalidomide, bortezomib, dexamethasone.

Table S4: Serious adverse events reported in the RVd-alone and RVd+ASCT arms

SAE – no. (%)	RVd-alone (N = 357)	RVd+ASCT (N = 365)
Any SAE	176 (49.3)	235 (64.4)
Any RVd-related SAE	144 (40.3)	172 (47.1)
Infections		
Any SAE	47 (13.2)	77 (21.1)
Any RVd-related SAE	42 (11.8)	58 (15.9)
Thromboembolic events*		
Any SAE	13 (3.6)	21 (5.8)
Any RVd-related SAE	11 (3.1)	14 (3.8)
SAEs occurring during maintenance	n = 291	n = 289
Any SAE	35 (12.0)	54 (18.7)
Any lenalidomide-related SAE	33 (11.3)	48 (16.6)

*Thromboembolic events include pulmonary embolism, thromboembolic event, stroke, and deep vein thrombosis. ASCT, autologous stem cell transplantation. RVd, lenalidomide, bortezomib, dexamethasone. SAE, serious adverse event.

Table S5: Second primary malignancies reported in the RVd-alone and RVd+ASCT arms

Patients – no. (%)	**RVd-alone (N = 357)**	**RVd+ASCT (N = 365)**
Patients with any second primary malignancy*	37 (10.4)	39 (10.7)
Number of second primary malignancies	44	44
Median time to second primary malignancy events from randomization (range), months	44.3 (0.6–123.2)	44.5 (2.3–85.5)
Patients with any invasive second primary malignancy†	19 (5.3)	25 (6.8)
Patients with any second primary hematologic malignancy	9 (2.5)	13 (3.6)
Acute lymphoblastic leukemia‡	7	3
Acute myeloid leukemia	0	4
Myelodysplastic syndromes§	0	6
Chronic lymphocytic leukemia	1	0
Chronic myelogenous leukemia	1	0
Patients with any second primary solid tumor	12 (3.4)	12 (3.3)
Anal cancer	2	0
Bladder cancer	0	1
Breast cancer	2	2
GIST	0	1
Kidney cancer	1	0
Lung cancer	0	2
Melanoma	5	4
Nerve sheath tumor	0	1
Prostate cancer	2	0
Rectal cancer	0	1
Patients with any non-invasive second primary solid tumor	0	2 (0.5)
Breast cancer (DCIS)	0	1
Melanoma in situ	0	1
Patients with any second primary non-melanoma skin cancer¶	21 (5.9)	15 (4.1)
Basal cell carcinoma	6	8
Squamous cell carcinoma	15	7

*Patients could have multiple second primary malignancies at different specific sites; reports of duplicate specific sites are excluded. †'Invasive' includes all second primary malignancies except for non-melanoma skin cancer and non-invasive second primary malignancies. ‡Includes the reported terms of acute lymphoblastic leukemia, acute lymphocytic leukemia, and lymphoblastic lymphoma. §One patient on the RVd+ASCT arm was reported as having myelodysplastic syndrome and then acute myeloid leukemia; they are counted only once – as a case of myelodysplastic syndrome – in the data on second primary hematologic malignancies. ¶One patient on the RVd-alone arm was reported as having basal cell carcinoma and squamous cell carcinoma in the same cycle; they are counted only once, as basal cell carcinoma. Two patients, one on each arm, were reported as having squamous cell carcinoma and then basal cell carcinoma; they are counted only once as squamous cell carcinoma.
ASCT, autologous stem cell transplantation. DCIS, ductal carcinoma *in situ*. GIST, gastrointestinal stromal tumor. RVd, lenalidomide, bortezomib, dexamethasone.

Table S6: Compliance with patient-reported quality-of-life assessments among patients in the RVd-alone and RVd+ASCT populations

Instrument / time-point – no. / total no. (%)	RVd-alone (N = 357)	RVd+ASCT (N = 365)
EORTC QLQ-C30		
Cycle 1 (Baseline)	326/357 (91.3)	332/364 (91.2)
Cycle 2	270/348 (77.6)	300/363 (82.6)
Pre-mobilization	250/317 (78.9)	254/292 (87.0)
Cycle 5 (RVd-alone) / post-ASCT (RVd+ASCT)	260/313 (83.1)	183/309 (59.2)
Cycle 8 (RVd-alone) / cycle 5 (RVd+ASCT)	238/298 (79.9)	225/291 (77.3)
Maintenance	203/243 (83.5)	207/261 (79.3)
2 years	122/186 (65.6)	143/221 (64.7)
3 years	102/160 (63.8)	109/185 (58.9)
End of treatment	161/278 (57.9)	160/276 (58.0)
EORTC QLQ-MY20		
Cycle 1 (Baseline)	326/357 (91.3)	332/364 (91.2)
Cycle 2	270/348 (77.6)	300/363 (82.6)
Pre-mobilization	250/317 (78.9)	254/292 (87.0)
Cycle 5 (RVd-alone) / post-ASCT (RVd+ASCT)	260/313 (83.1)	183/309 (59.2)
Cycle 8 (RVd-alone) / cycle 5 (RVd+ASCT)	238/298 (79.9)	225/291 (77.3)
Maintenance	203/243 (83.5)	207/261 (79.3)
2 years	122/186 (65.6)	143/221 (64.7)
3 years	102/160 (63.8)	109/185 (58.9)
End of treatment	161/278 (57.9)	160/276 (58.0)
FACT/GOG-NTx		
Cycle 1 (Baseline)	312/357 (87.4)	316/364 (86.8)
Cycle 2	282/348 (81.0)	302/363 (83.2)
Pre-mobilization	231/317 (72.9)	233/292 (79.8)
Cycle 5 (RVd-alone) / post-ASCT (RVd+ASCT)	265/313 (84.7)	171/309 (55.3)
Cycle 8 (RVd-alone) / cycle 5 (RVd+ASCT)	238/298 (79.9)	229/291 (78.7)
Maintenance	190/243 (78.2)	194/261 (74.3)
2 years	116/186 (62.4)	139/221 (62.9)
3 years	102/160 (63.8)	111/185 (60.0)
End of treatment	154/278 (55.4)	154/276 (55.8)

ASCT, autologous stem cell transplantation. C30, core 30 module. EORTC, European Organization for the Research and Treatment of Cancer. FACT, Functional Assessment of Cancer Therapy. GOG, Gynecologic Oncology Group. MY20, myeloma-specific module. Ntx, neurotoxicity. QLQ, quality of life questionnaire. RVd, lenalidomide, bortezomib, dexamethasone.

Table S7: Summary of subsequent therapies received

Subsequent therapies received by patients off study protocol therapy	RVd-alone (N = 279)	RVd+ASCT (N = 276)
Any subsequent therapy – no. (%)	222 (79.6)	192 (69.6)
Received subsequent therapy prior to disease progression	5	15
No recorded disease progression prior to death	9	11
Subsequent therapy	n = 222	n = 192
Any immunomodulatory drug within subsequent therapy	124 (55.9)	112 (58.3)
Pomalidomide	67 (30.2)	56 (29.2)
Lenalidomide	57 (25.7)	56 (29.2)
Any proteasome inhibitor within subsequent therapy	124 (55.9)	96 (50.0)
Bortezomib	61 (27.5)	49 (25.5)
Carfilzomib	47 (21.2)	32 (16.7)
Ixazomib	18 (8.1)	15 (7.8)
Marizomib	0 (0)	1 (0.5)
Any monoclonal antibody within subsequent therapy	36 (16.2)	53 (27.6)
Daratumumab	25 (11.3)	41 (21.4)
Elotuzumab	10 (4.5)	12 (6.3)
Isatuximab	1 (0.5)	0 (0.0)
Corticosteroid	137 (61.7)	125 (65.1)
Chemotherapy	20 (9.0)	11 (5.7)
Panobinostat	2 (0.9)	4 (2.1)
Other therapy	8 (3.6)	14 (7.3)
Radiation	15 (6.8)	6 (3.1)
ASCT within next therapy	29 (13.1)	11 (5.7)
ASCT received at any time following end of study treatment – no. (%)*	78 / 279 (28.0)	26 / 55 (47.3)

*RVd-alone group includes all patients no longer receiving study protocol therapy. RVd+ASCT group shows data only for patients who discontinued study protocol therapy prior to undergoing on-study ASCT.

ASCT, autologous stem cell transplantation. RVd, lenalidomide, bortezomib, dexamethasone.

Supplementary References

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