2022 ASCO® ANNUAL MEETING

ASCO Direct Highlights Multiple Myeloma

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Plasma Cell Malignancies

Disclosures

- Josh Epworth has no disclosures

2022 ASCO® ANNUAL MEETING

RVd ± ASCT and Lenalidomide Maintenance to Progression for NDMM

The Phase 3 DETERMINATION Trial

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Does ASCT improve outcomes for NDMM patients receiving triplet induction (RVd) and lenalidomide maintenance until disease progression?

- ASCT with HD melphalan is a standard of care for transplant-eligible NDMM patients [1,2]
- Optimal use of induction therapy, ASCT, maintenance in transplant-eligible NDMM patients continues to evolve
  - Triplet induction regimens are highly efficacious, with high response rates, high rates of MRD-negative responses, and prolonged clinical benefit [3–7]
  - Long-term maintenance therapy with lenalidomide also improves outcomes through prolonged disease control [8,9]
- In this context, how much does first-line ASCT enhance efficacy in NDMM, and can its use be delayed or kept in reserve in selected patients? [10]

ASCT, autologous stem cell transplantation; HD, high-dose; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; RVd, lenalidomide, bortezomib, dexamethasone.

1. Callander NS, et al. J Natl Compr Canc Netw 2022;20:8–19. 2. Dimopoulos MA, et al. Ann Oncol 2021;32:309–22.
3. Richardson PG, et al. Blood 2010;116:679–86. 4. Kumar SK, et al. Lancet Oncol 2020;21:1317–30.
5. Attal M, et al. N Engl J Med 2017;376:1311–20. 6. Perrot A, et al. Blood 2020;136:39.
7. Durie BGM, et al. Lancet 2017;389(10068):519–27. 8. McCarthy PL, et al. J Clin Oncol 2017;35:3279–89.
9. McCarthy PL, et al. N Engl J Med 2012;366(19):1770–81.
10. Richardson PG, et al. Hematology Am Soc Hematol Educ Program. 2014;1:255–61.

DETERMINATION: Key findings

Addition of ASCT to triplet induction and lenalidomide maintenance to progression results in:

- Highly significant increase in PFS, with improvement in median of over 21 months
- Similar OS after a median follow-up of 76 months
- Similar ORR and rates of ≥VGPR and ≥CR (IMWG criteria) by central response review committee
- Higher rate of MRD-negative responses at start of maintenance (preliminary data)
- Higher toxicity rates; transient, clinically meaningful decrease in QoL during transplant, then improvements from baseline throughout maintenance
- No difference in rate of second primary malignancies; higher incidence of AML/MDS

Practice-informing:

- Confirms overall PFS benefit with early ASCT in first line, esp. high-risk; reaffirms ASCT as a standard-of-care
- Demonstrates clinical benefit of maintenance until progression and confirms this as standard-of-care
- Supports personalized approaches, with no OS difference to date, and option of keeping ASCT in reserve for selected patients
- Endorses potential of MRD negativity to guide decision-making
- Outlines comparative toxicity, acute and long-term, as well as QoL findings to further inform patient choice, provider recommendations
- Provides context for emerging quadruplet regimens incorporating monoclonal antibodies and next-generation novel therapies

AML, acute myeloid leukemia; CR, complete response; IMWG, International Myeloma Working Group; MDS, myelodysplastic syndromes; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; VGPR, very good partial response.

Phase 3 DETERMINATION trial (NCT01208662; DFCI 10-106/BMT CTN 1304): Background

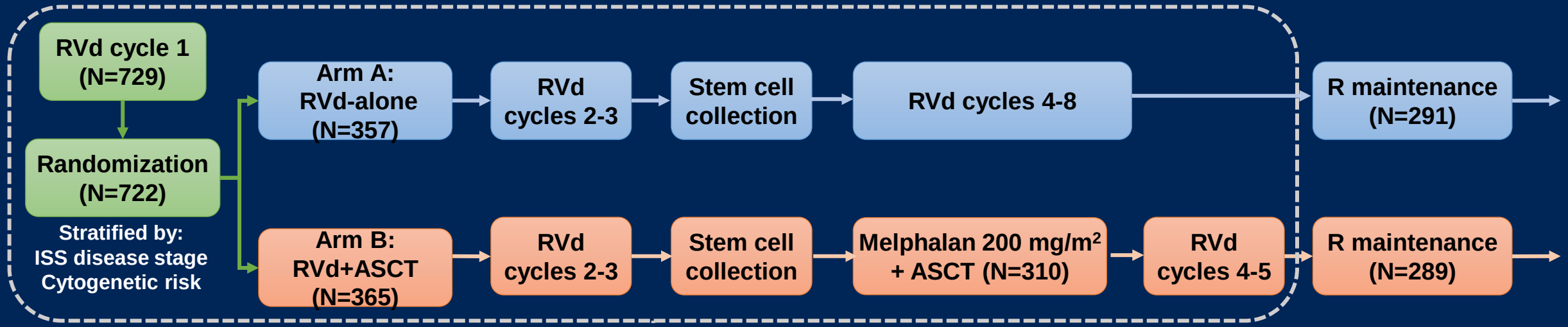
- RVd highly efficacious in phase 2 studies: ORR 93–100%; ≥VGPR 61–67% [1,2]
  - IFM phase 2 study of RVd-ASCT-RVd plus lenalidomide maintenance for 1 year: ORR 100%; ≥VGPR 84%; ≥CR 58%; MRD-neg 68%; 3-yr PFS 77% [3]
- DETERMINATION originally a parallel study to phase 3 IFM 2009 trial [4]
  - IFM 2009: lenalidomide maintenance for 1 year [4]
  - CALGB-100104 demonstrated benefit of lenalidomide maintenance to disease progression (median TTP 46 mos) [5]
  - DETERMINATION protocol amended: lenalidomide maintenance until disease progression in both arms
- IFM 2009 demonstrated significantly superior PFS with ASCT-based approach [4,6]
  - However, OS similar after median follow-up of 7.5 years [6]

CALGB, Cancer and Leukemia Group B; CR, complete response; IFM, Intergroupe Francophone du Myelome; ORR, overall response rate; TTP, time to progression; VGPR, very good partial response

1. Richardson PG, et al. Blood 2010;116(5):679–86. 2. Kumar S, et al. Blood 2012;119(19):4375–82. 3. Roussel M, et al. J Clin Oncol 2014;32(25):2712–7. 4. Attal M, et al. N Engl J Med 2017;376:1311-20. 5. McCarthy PL, et al. N Engl J Med 2012;366(19):1770–81. 6. Perrot A, et al. Blood 2020;136:39.

DETERMINATION: study design and patient disposition

DETERMINATION: Delayed vs Early Transplant with Revlimid Maintenance and Antimyeloma Triple Therapy



Each RVd cycle (21 days):
R 25 mg/day PO, days 1-14
V 1.3 mg/m² IV/SC, days 1, 4, 8, 11
Dex 20/10 mg PO, days 1, 2, 4, 5, 8, 9, 11, 12

Induction ± ASCT + consolidation treatment duration = ~6 months

Lenalidomide maintenance
Months 1-3: 10 mg/day
Month 4 onwards: 15 mg/day

Primary endpoint: PFS

Secondary endpoints: response rates; DOR; TTP; OS; QoL; safety

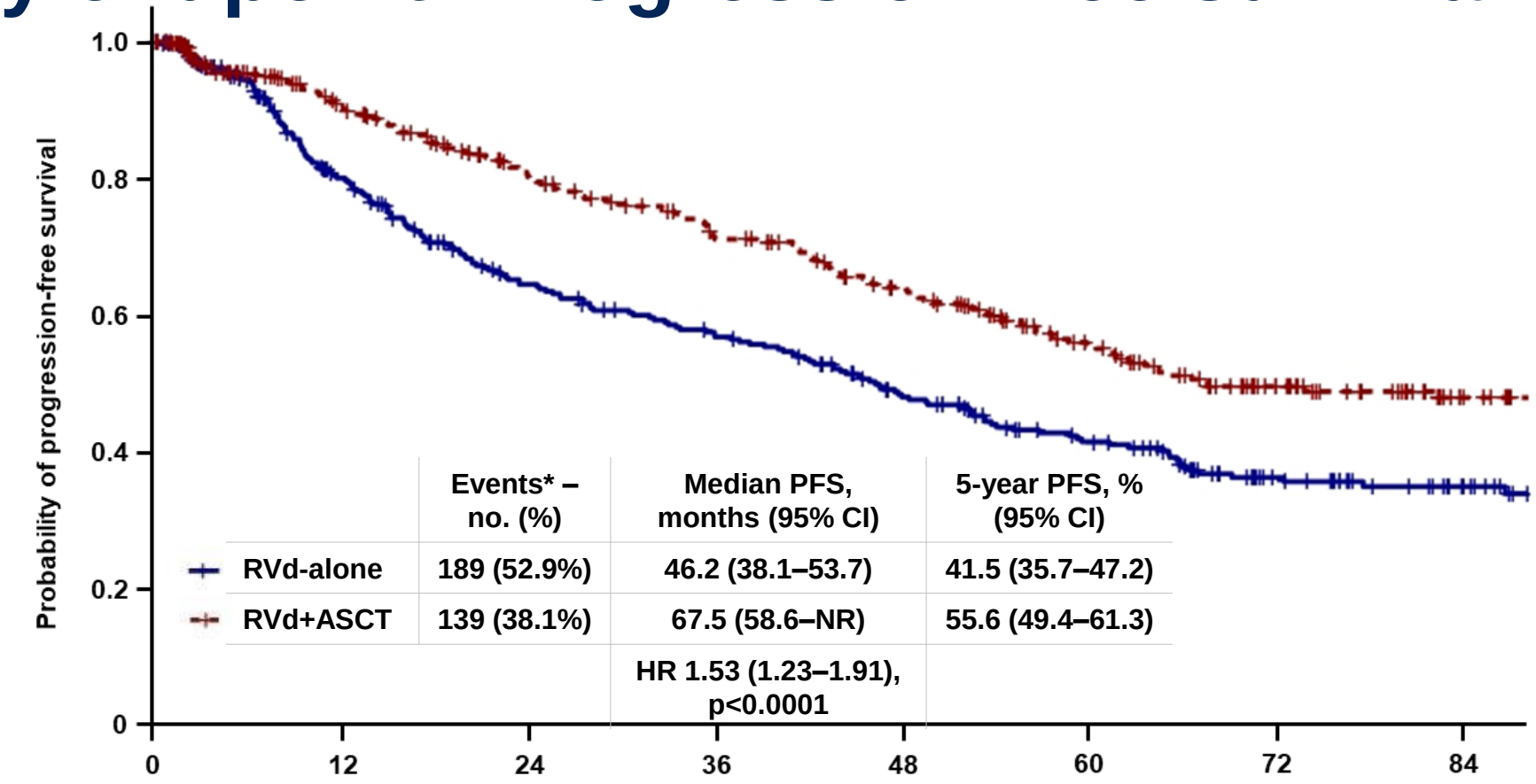
d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

Patient demographics and disease characteristics

Characteristic	RVd-alone (N=357)	RVd+ASCT (N=365)
Median age (interquartile range) – years	57 (25–66)	55 (30–65)
Male/female, %	56.6 / 43.4	58.9 / 41.1
Race: White, Caucasian / Black, African-American / Other, %	76.4 / 18.8 / 4.8	75.8 / 18.4 / 5.8
ECOG performance status: 0 / 1 / 2, %	42.9 / 49.6 / 7.6	45.1 / 44.2 / 10.7
BMI: <25 / 25 to <30 / ≥30, %	22.4 / 39.5 / 38.1	22.2 / 34.8 / 43.0
MM disease type: IgG / IgA / Light chain only / Other, %	66.7 / 21.8 / 10.3 / 1.2	59.3 / 28.2 / 12.2 / 0.3
ISS disease stage: I / II / III, %	49.9 / 36.4 / 13.7	50.4 / 36.7 / 12.9
Elevated lactate dehydrogenase (≥225 U/L), %	27.0	25.4
Cytogenetics: high-risk* / standard-risk, %	19.8 / 80.2	19.4 / 80.6
Cytogenetics: t(4;14) / t(14;16) / del 17p,† %	9.6 / 3.0 / 11.4	8.2 / 4.4 / 10.0
Revised-ISS disease stage:‡ I / II / III, %	30.9 / 60.7 / 8.4	31.2 / 62.6 / 6.2

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group. *High-risk includes t(4;14), t(14;16), and deletion 17p. †Cutoff threshold for positivity per institutional standards. ‡Classified using ≥225 U/L cutoff for elevated lactate dehydrogenase level. Patients registered between October 1, 2010, and January 30, 2018.

Primary endpoint: Progression-free survival (PFS)



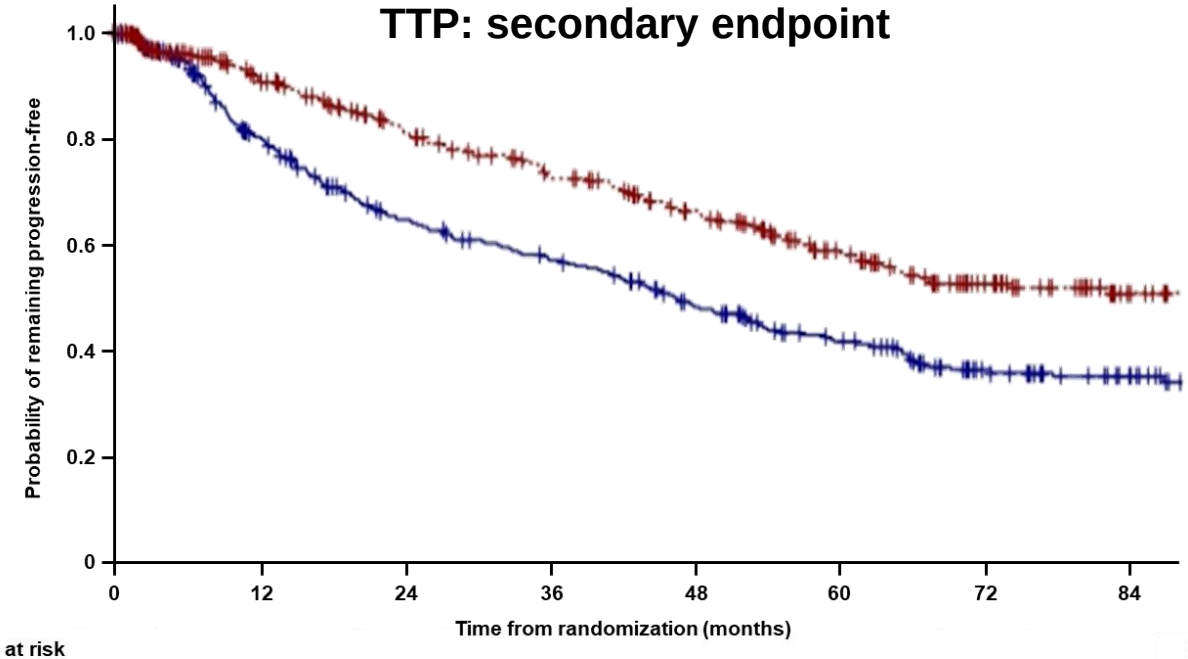
	Events* – no. (%)	Median PFS, months (95% CI)	5-year PFS, % (95% CI)
RVd-alone	189 (52.9%)	46.2 (38.1–53.7)	41.5 (35.7–47.2)
RVd+ASCT	139 (38.1%)	67.5 (58.6–NR)	55.6 (49.4–61.3)
		HR 1.53 (1.23–1.91), p<0.0001	

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

CI, confidence interval; HR, hazard ratio; Data cutoff: 12/10/21. *PFS events: disease progression or death.

Time to progression (TTP) / Event-free survival (EFS)

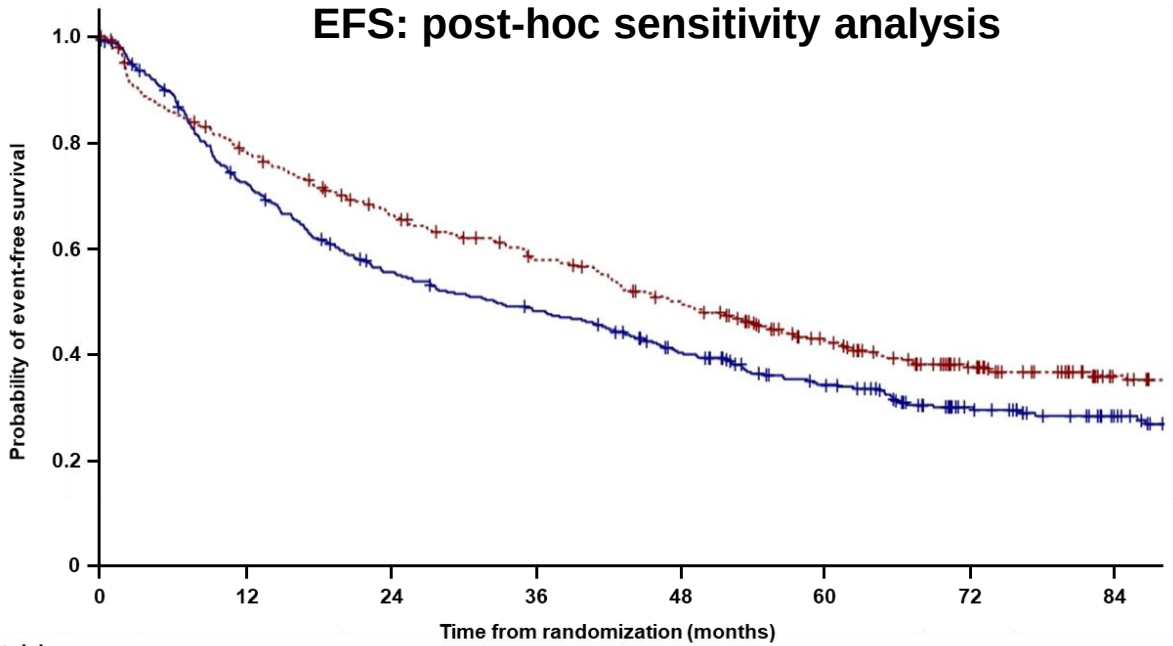
TTP: secondary endpoint



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

	Events* – no. (%)	5-year TTP, %	HR (adjusted CI†)
RVd-alone	188 (52.7)	41.6	1.66 (1.21–2.27) p<0.001†
RVd+ASCT	128 (35.1)	58.4	

EFS: post-hoc sensitivity analysis



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

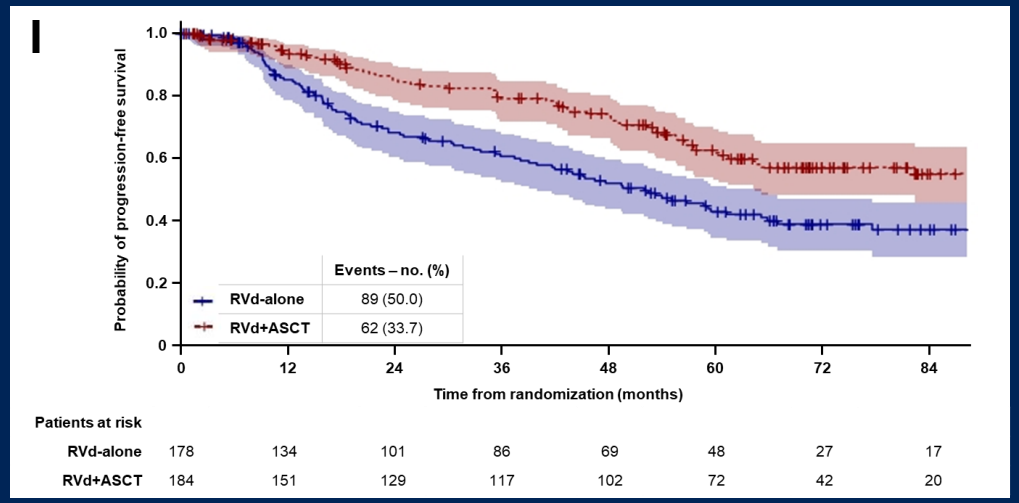
	Events* – no. (%)	Median EFS, months	HR (95% CI)
RVd-alone	242 (67.8)	32.0	1.23 (1.02–1.48)
RVd+ASCT	219 (60.0)	47.3	

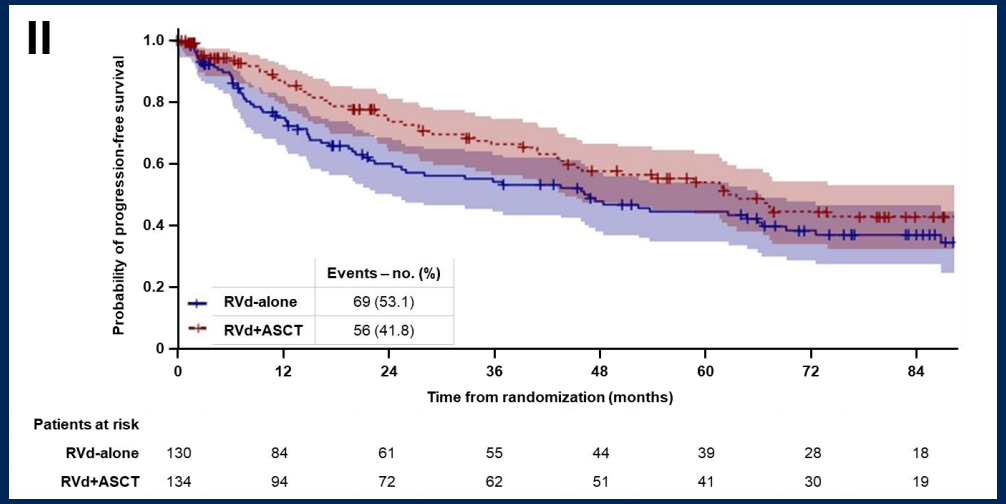
*TTP events: disease progression. EFS events: receipt of non-protocol therapy, progression, or death.

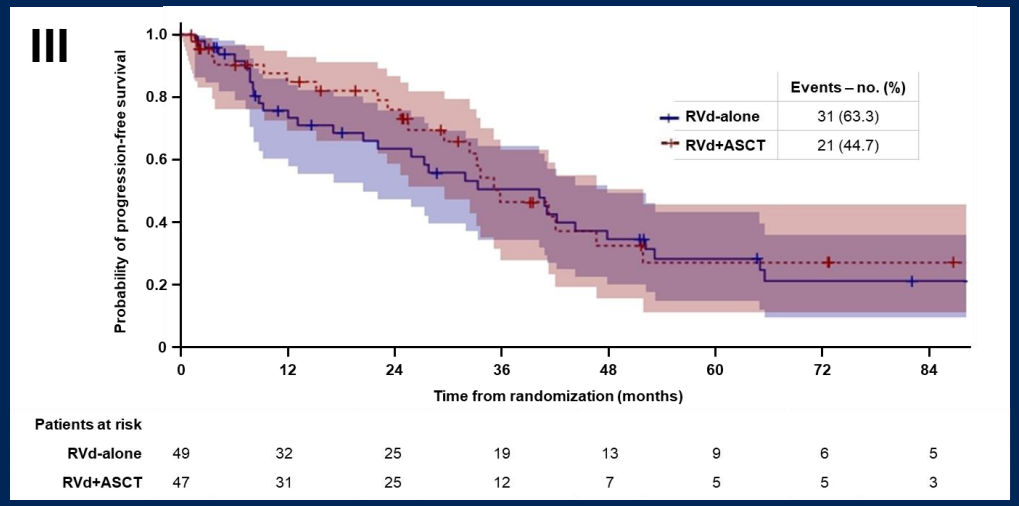
†CIs and p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes. Therefore, CIs use an α level of 0.05/7.

Data cutoff: 12/10/21

PFS by stratification factor – ISS disease stage



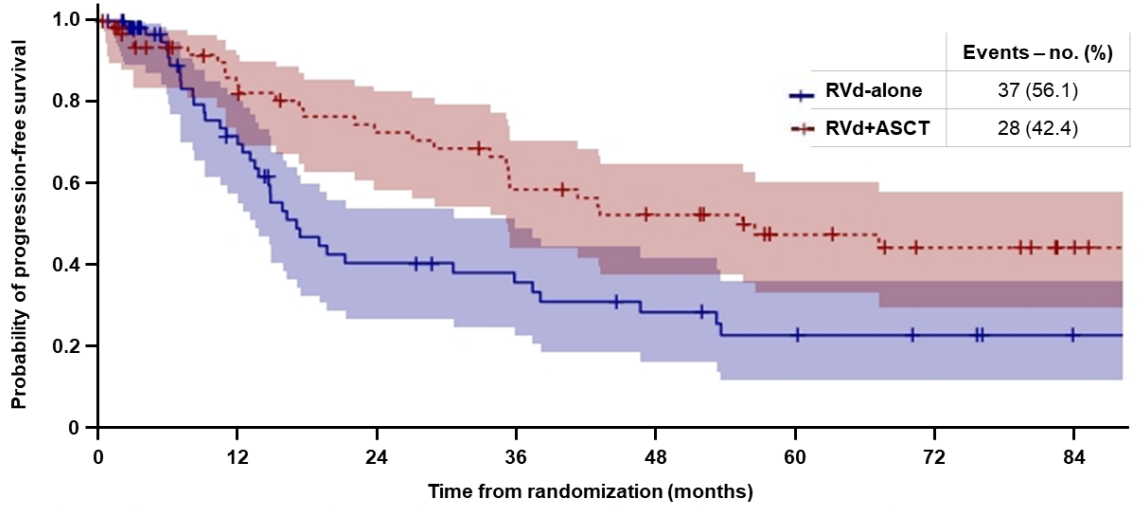




Shaded areas indicate 95% CIs

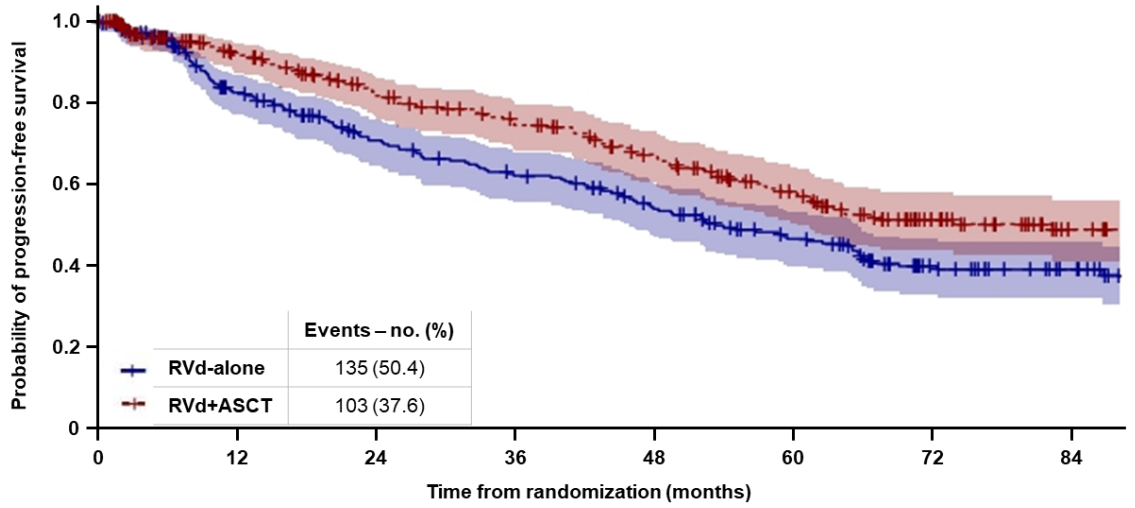
Median PFS, months	RVd-alone	RVd+ASCT
ISS I	52.0	Not reached
	HR 1.83 (95% CI 1.32–2.54)	
ISS II	46.2	62.5
	HR 1.38 (95% CI 0.96–1.96)	
ISS III	40.3	35.9
	HR 1.14 (95% CI 0.64–2.01)	

PFS by stratification factor – cytogenetic risk



Patients at risk

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



Patients at risk

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

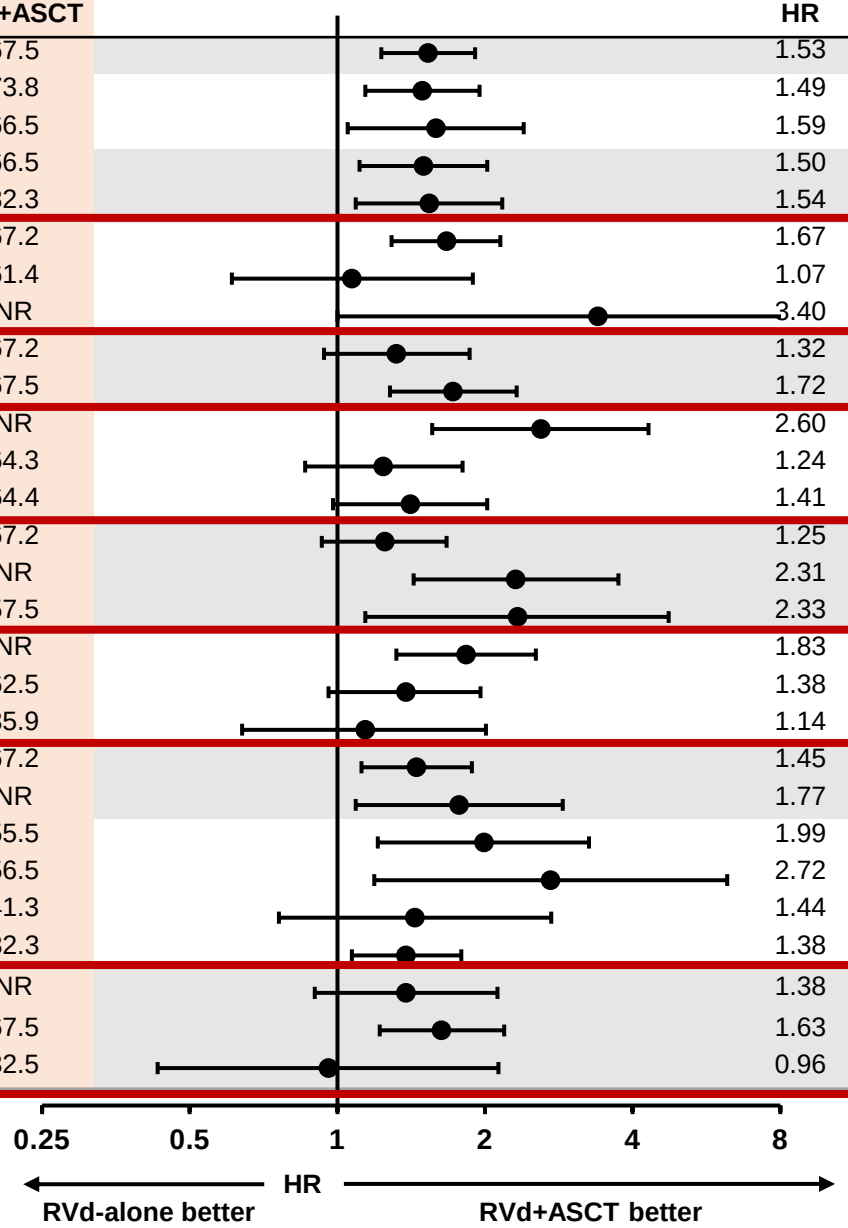
Shaded areas indicate 95% CIs

Median PFS, months	RVd-alone	RVd+ASCT
High-risk	17.1	55.5
	HR 1.99 (95% CI 1.21–3.26)	

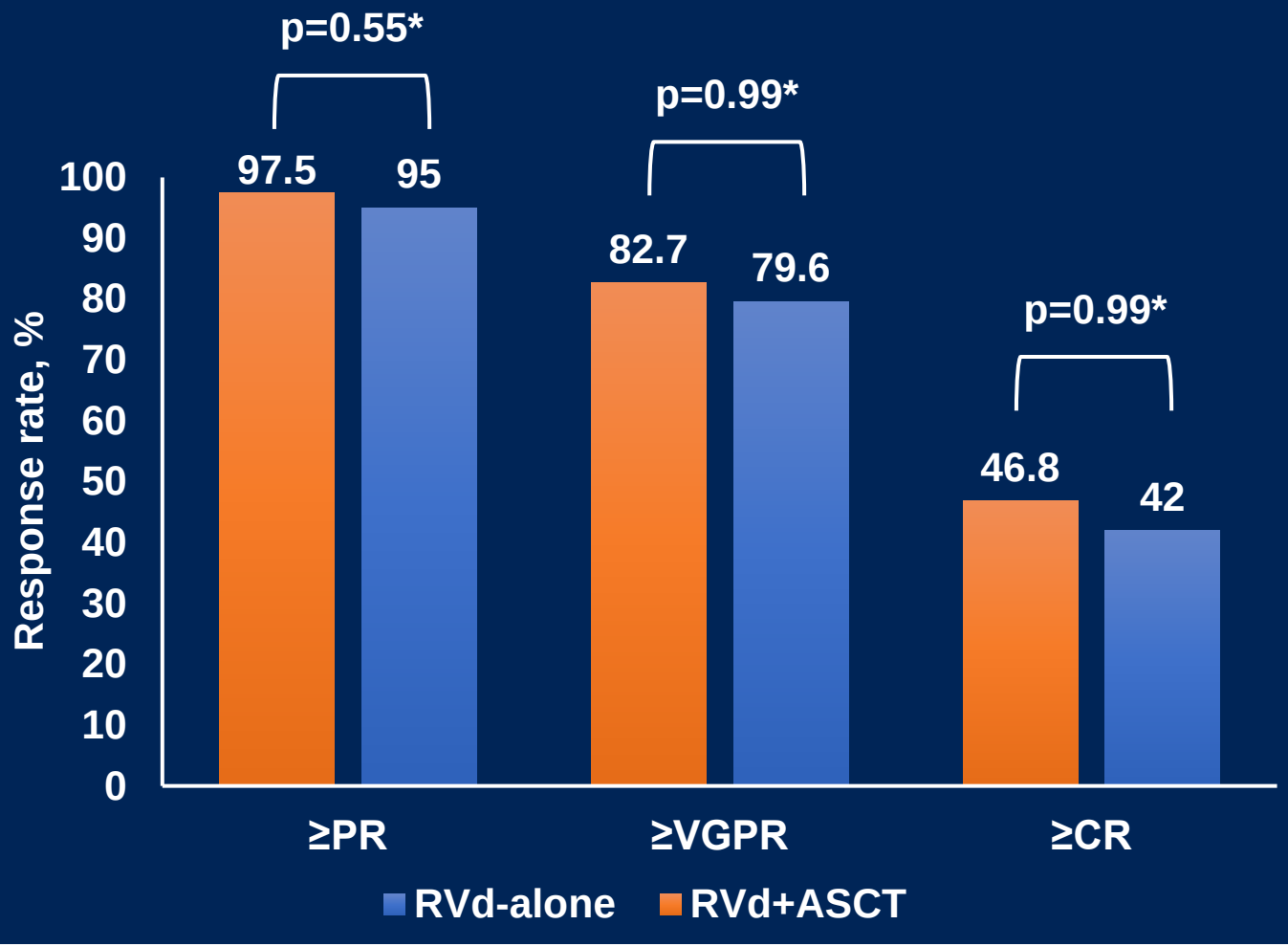
Median PFS, months	RVd-alone	RVd+ASCT
Standard-risk	53.2	82.3
	HR 1.38 (95% CI 1.07–1.79)	

PFS by subgroup

Subgroup		Events / patients		Median, months		HR	(95% CI)
		RVd-alone	RVd+ASCT	RVd-alone	RVd+ASCT		
All	**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	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)
BMI	<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)
MM	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	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)
LDH	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	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)
R-ISS	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)



Best response to treatment and duration of response



Duration of response	RVd-alone	RVd+ASCT
Median duration of ≥PR, months	38.9	56.4
	HR 1.45 (Adjusted CI* 1.09–1.93), p=0.003*	
5-year duration of ≥CR, %	52.9	60.6
	HR 1.35 (Adjusted CI* 0.83–2.22), p=0.698*	

*CIs and p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes. Therefore, CIs use an α level of 0.05/7.

MRD / PFS by MRD status

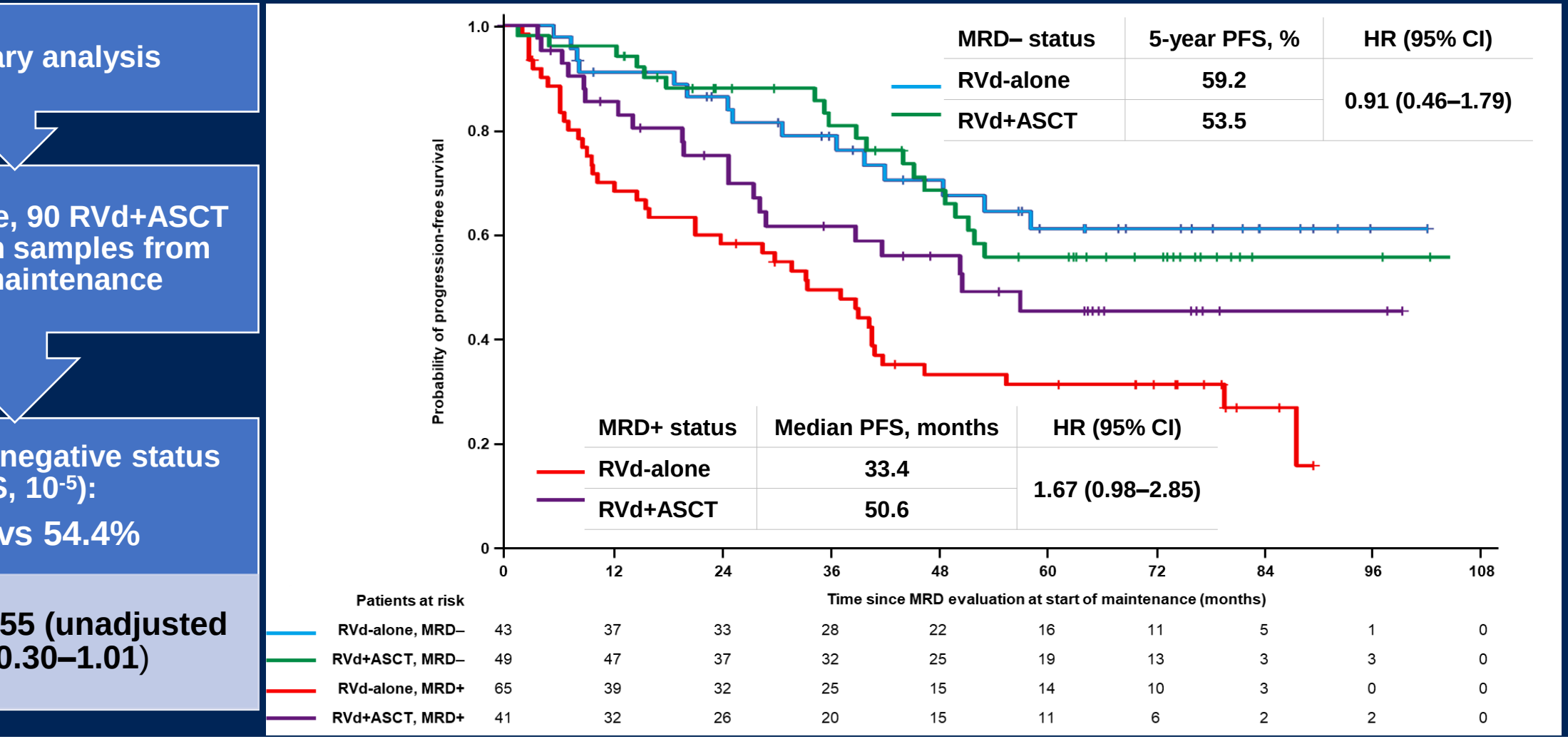
Preliminary analysis

108 RVd-alone, 90 RVd+ASCT patients with samples from start of maintenance

Rate of MRD-negative status (NGS, 10^{-5}):

39.8% vs 54.4%

Odds ratio 0.55 (unadjusted 95% CI 0.30–1.01)



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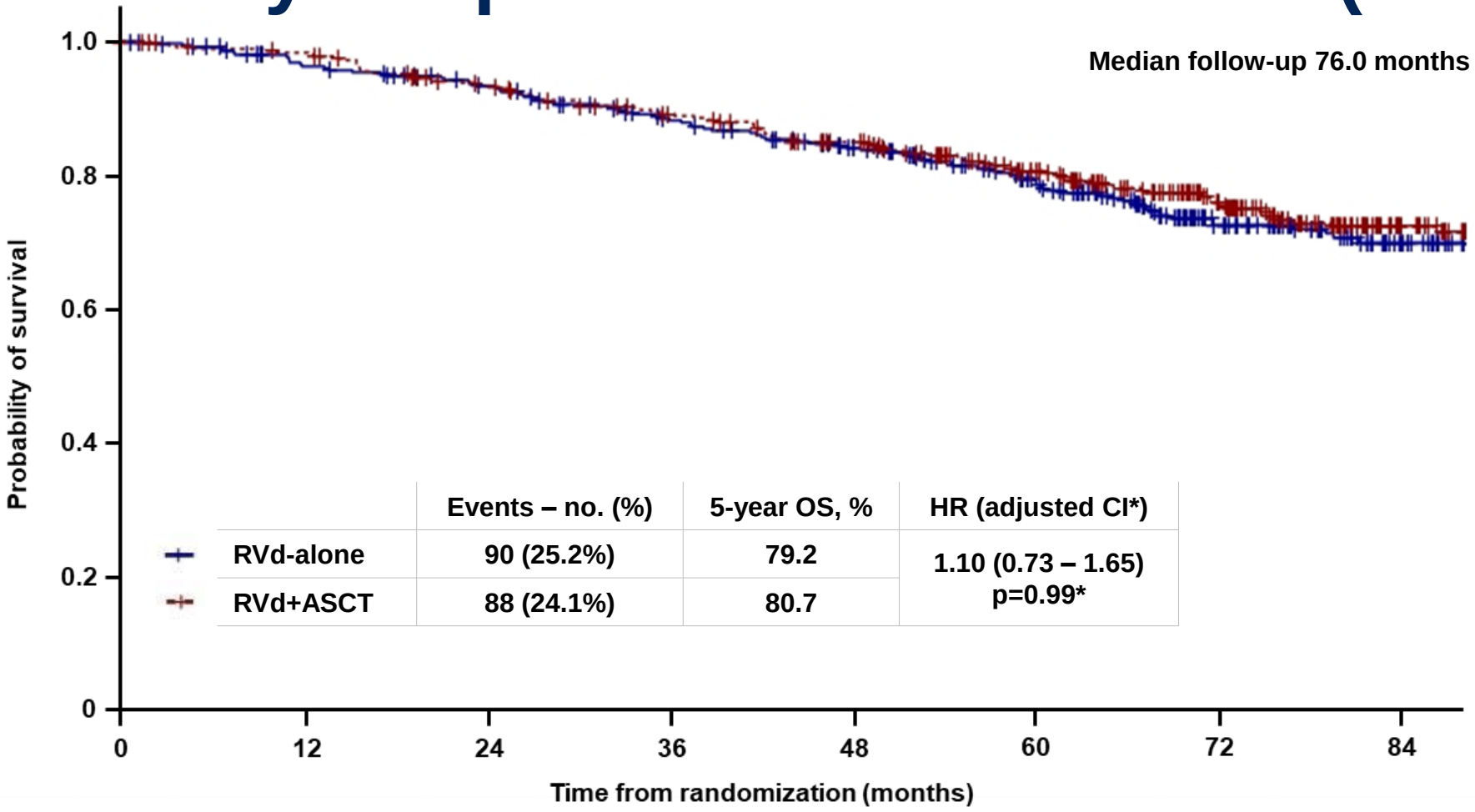
Key secondary endpoint: Overall survival (OS)



	Events – no. (%)	5-year OS, %	HR (adjusted CI*)
RVd-alone	90 (25.2%)	79.2	1.10 (0.73 – 1.65) p=0.99*
RVd+ASCT	88 (24.1%)	80.7	

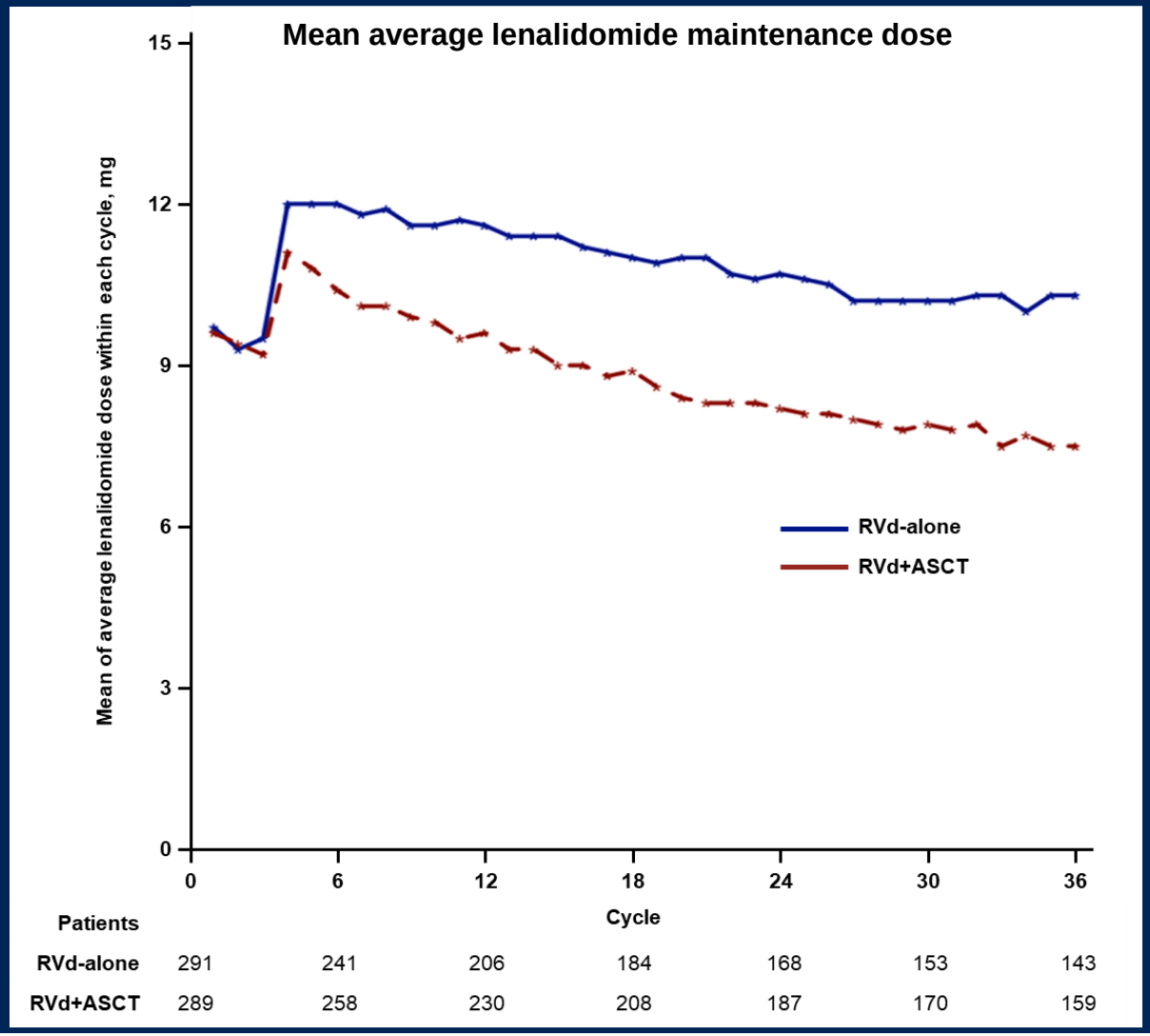
Patients at risk								
RVd-alone	357	332	313	285	258	214	143	88
RVd+ASCT	365	353	324	300	275	228	165	95

*CIs and p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes. Therefore, CIs use an α level of 0.05/7.

Data cutoff:12/10/21

Treatment exposure (RVd-alone vs RVd+ASCT)

Median duration of all treatment from randomization (n=357 vs n=365)	• 28.2 vs 36.1 months
Median duration of lenalidomide maintenance (n=291 vs n=289)	• 36.4 vs 41.5 months
Median proportion of maintenance cycles with average lenalidomide dose ≥10 mg	• 87% vs 60%



Grade ≥3 treatment-related AEs (all treatment)

AE, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	78.2	94.2
Any hematologic	60.5	89.9
Any grade 5 (fatal) AE	0.3	1.6 *
Neutropenia	42.6	86.3
Thrombocytopenia	19.9	82.7
Leukopenia	19.6	39.7
Anemia	18.2	29.6
Lymphopenia	9.0	10.1
Febrile neutropenia	4.2	9.0
Diarrhea	3.9	4.9
Nausea	0.6	6.6
Mucositis oral	0	5.2
Fatigue	2.8	6.0
Fever	2.0	5.2
Pneumonia	5.0	9.0
Hypophosphatemia	9.5	8.2
Neuropathy	5.6	7.1

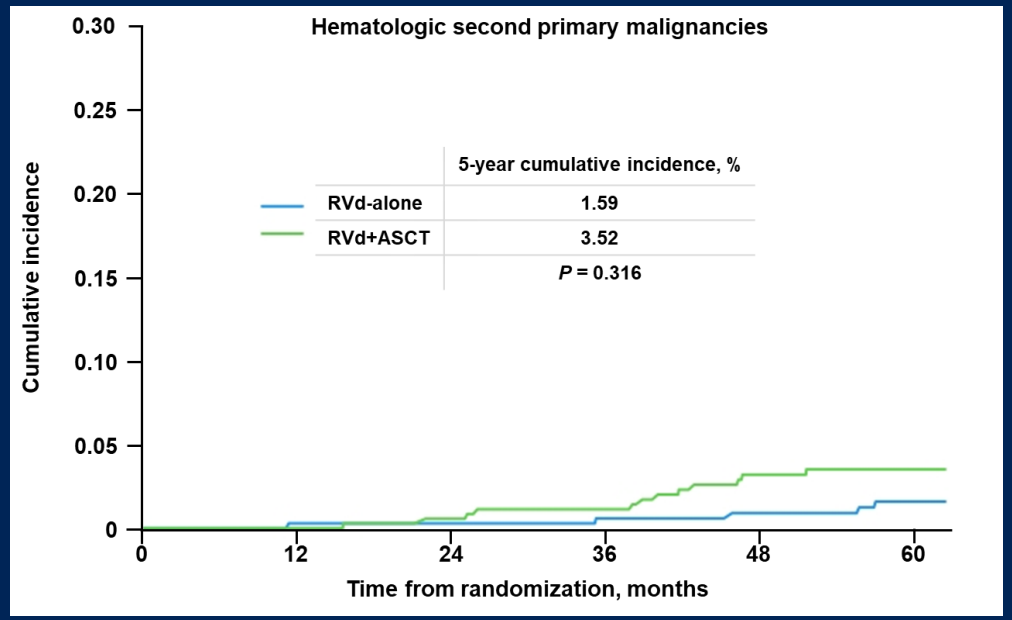
(S)AE, (serious) adverse event

- Rates of all grade ≥3 and of hematologic grade ≥3 treatment-related AEs during all treatment significantly higher with RVd + ASCT (both p<0.001)
  - Rates hematologic grade ≥3 treatment-related AEs during maintenance: 26.1% vs 41.9%
- Related SAEs:
  - Prior to maintenance: 40.3% vs 47.1%
  - During maintenance: 11.3% vs 16.6%

* Includes 1 death related to ASCT on Arm B identified after data cutoff; p=0.12

Second primary malignancies

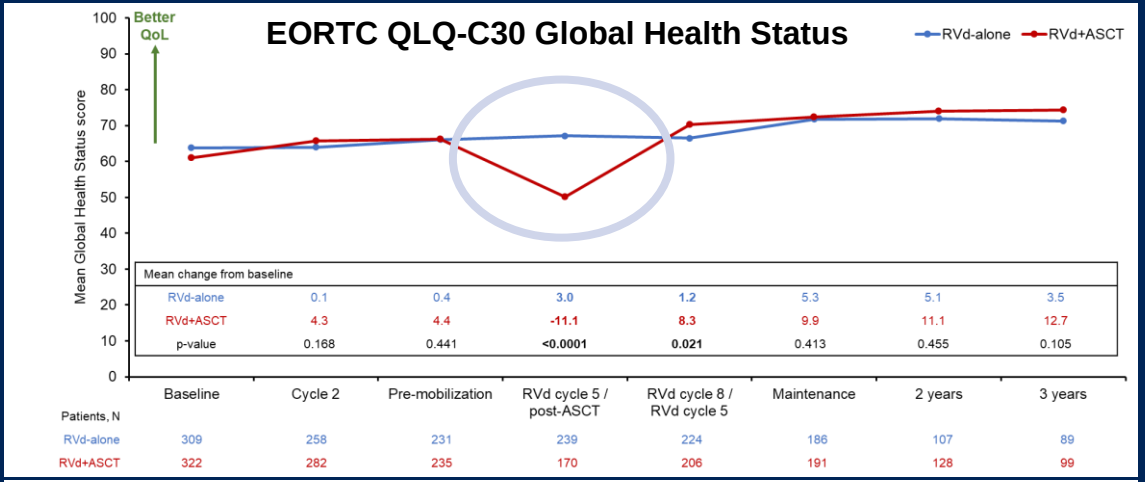
- 5-year cumulative incidence of SPMs (RVd-alone vs RVd+ASCT):
  - All : 9.7% vs 10.8%
  - Invasive: 4.9% vs 6.5%
  - Hematologic: 1.59% vs 3.52%

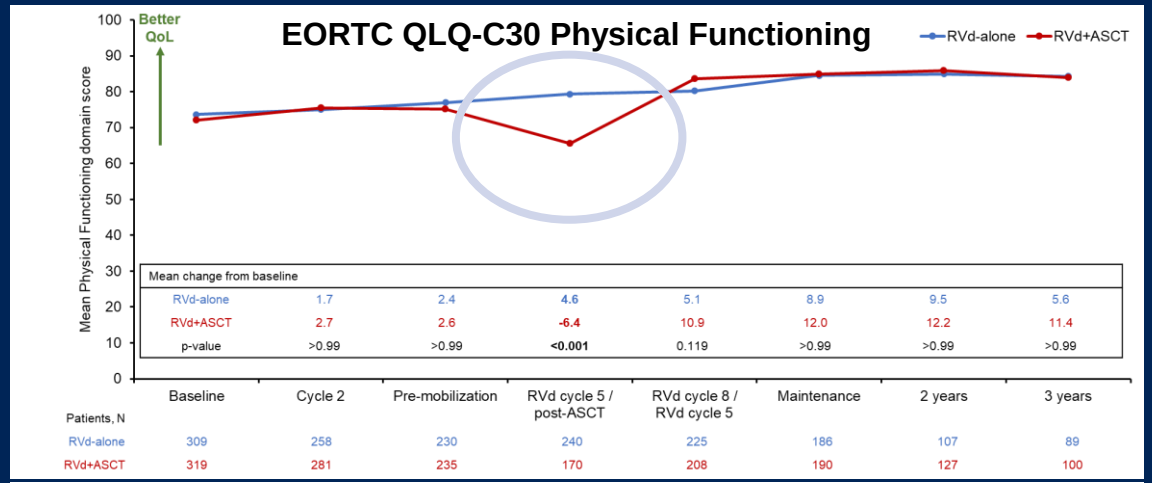


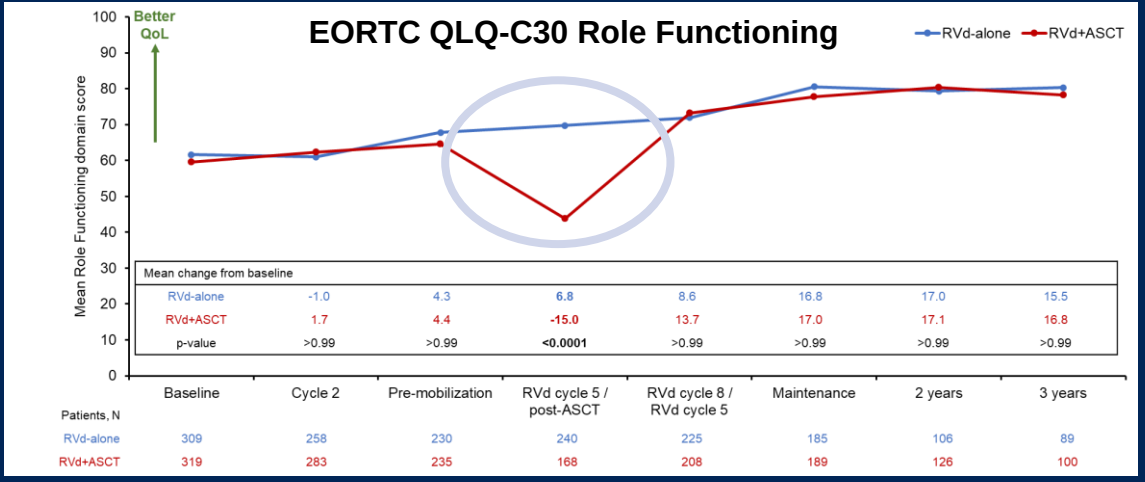
SPMs, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	10.4	10.7
Any invasive SPM	5.3	6.8
Any hematologic SPM	2.5	3.6
ALL, n	7	3
AML/MDS, n	0*	10*
CLL/CML, n	2	0
Any solid tumor SPM	3.4	3.3
Any non-invasive solid tumor SPM	0	0.5
Any non-melanoma skin cancer	5.9	4.1

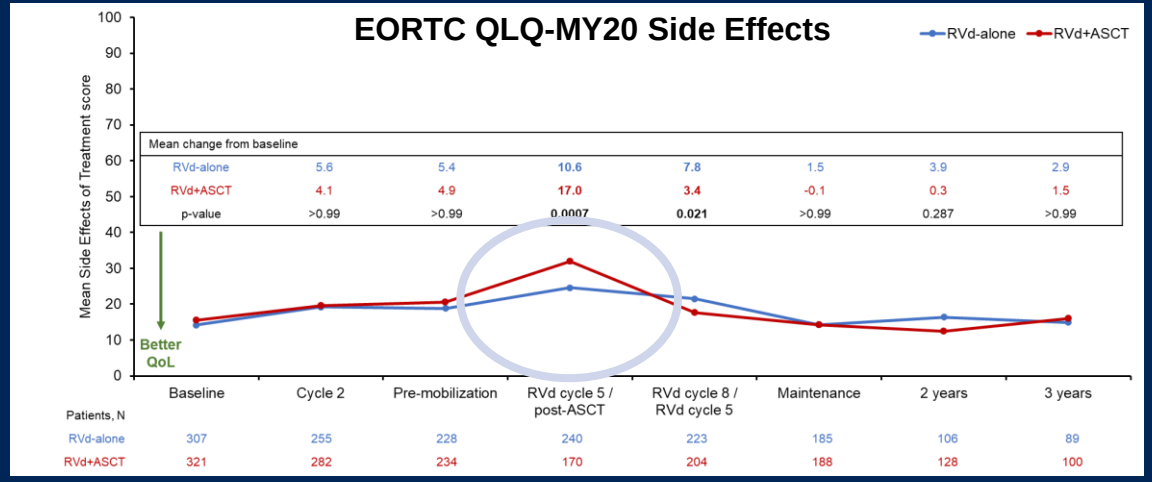
* p=0.002

QoL over the course of treatment with RVd-alone vs RVd+ASCT (baseline N >300 patients per arm)









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Subsequent therapy and rate of ASCT in RVD-alone arm (delayed ASCT)

279 RVd-alone and 276 RVd+ASCT patients were off protocol therapy

- 222 (79.6%) and 192 (69.6%) had received subsequent therapy (table)

Only 78 (28.0%) of 279 RVd-alone patients had received ASCT at any time following end of study treatment

Subsequent therapy in patients off protocol therapy, %	RVd-alone (N=279)	RVd+ASCT (N=276)
Any treatment *	79.6	69.6
Subsequent therapy	n=222	n=192
Any immunomodulatory drug	55.9	58.3
Pomalidomide	30.2	29.2
Lenalidomide	25.7	29.2
Any proteasome inhibitor	55.9	50.0
Bortezomib	27.5	25.5
Carfilzomib	21.2	16.7
Ixazomib	8.1	7.8
Marizomib	0	0.5
Any monoclonal antibody	16.2	27.6
Daratumumab	11.3	21.4
Elotuzumab	4.5	6.3
Isatuximab	0.5	0

*Including IMiDs, PIs, mAbs, HDACi (panobinostat), ASCT, chemotherapy, RT, steroids, other

Conclusions

- RVd + ASCT offers significantly superior PFS vs RVd-alone
  - 67.5 vs 46.2 months – longest seen to date with RVd-based approaches
  - Demonstrates tolerability and clinical benefit of long-term lenalidomide maintenance in both arms; compared to median PFS 47.3 vs 35.0 months in IFM 2009, with 1 year of maintenance
- No OS benefit after median follow-up of >6 yrs: 5-yr OS 80.7% vs 79.2% (IFM 2009:[1] 8-yr OS 62.2% vs 60.2%)
  - In context of low rate (28.0%) of ASCT in RVd-alone arm (delayed ASCT; as compared with IFM 2009:[1] 76.7%) and impact of other novel therapies at first relapse (including monoclonal antibodies)
- Similar ORR (97.5% vs 95.0%) and rates of ≥VGPR (82.7% vs 79.6%) and ≥CR (46.9% vs 42.0%) per IMWG criteria with RVd + ASCT vs RVd-alone (by central response review committee)
- Higher rate of MRD-negative responses with RVd + ASCT: 54.4% vs 39.8% at start of maintenance (preliminary data)
  - MRD-negative response associated with better outcome vs MRD-positive response in both arms
    - 5-year PFS in MRD-negative patients similar with RVd + ASCT vs RVd-alone: 53.5% vs 59.2%
- RVd + ASCT associated with generally manageable but significantly higher rates of toxicity, plus a low overall rate of grade 5 (fatal) AEs (1.6% vs 0.3% with RVd-alone)
  - Evidence of hematologic SPM signal, specifically AML/MDS
  - Transient, clinically meaningful decrease in QoL associated with transplant, followed by improvement from baseline throughout maintenance

1. Perrot A, et al. Blood 2020;136:39.

Next Steps and Future Directions

- Additional analyses of MRD, including longitudinal data
- Evaluation of patient- and disease-related factors, including Race and BMI, cytogenetics and (R) ISS
  - PFS HR (magnitude of PFS benefit) ranged from 0.96 to 3.40 in preplanned subgroup analyses
- Whole-genome sequencing analyses:
  - Associations with response and outcomes: preliminary data show presence of del17p (OR 0.24) and TP53 mutations (OR 0.12) associated with lower response rates
  - Evaluation of change in mutational burden at progression/relapse and impact on outcome [1–4]
  - Investigate mechanisms underlying genomic instability [5,6]
- Additional analyses of QoL; applications to real world practice,[7] and HRU – economics/costs of treatment
- Future directions in NDMM
  - MRD-directed studies with next-generation agents ± ASCT (e.g. MIDAS by IFM; DETERMINATION 2 in development)
  - Impact of quadruplet therapies (RVd + DARA, KRd + DARA) ± ASCT – e.g. GRIFFIN,[8] MASTER,[9] MANHATTAN [10] studies, as well as cellular therapies (CAR T), bispecifics, antibody-drug conjugates, and CELMoDs [11–13]
  - Evaluation of del17p-targeting treatment for high-risk disease (e.g. selinexor & other approaches, inc. cellular therapies) [11,14]
  - Novel agents targeting "stemness" with potentially less toxicity/improved therapeutic index vs melphalan (e.g. melflufen)[15,16]

HRU, healthcare resource utilization; OR, odds ratio

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14. Grosicki S, et al. Lancet 2020;396(10262):1563–73. 15. Richardson PG, et al. J Clin Oncol 2021;39(7):757–67. 16. Schjesvold FH, et al. Lancet Haematol 2022;9(2):e98–110.

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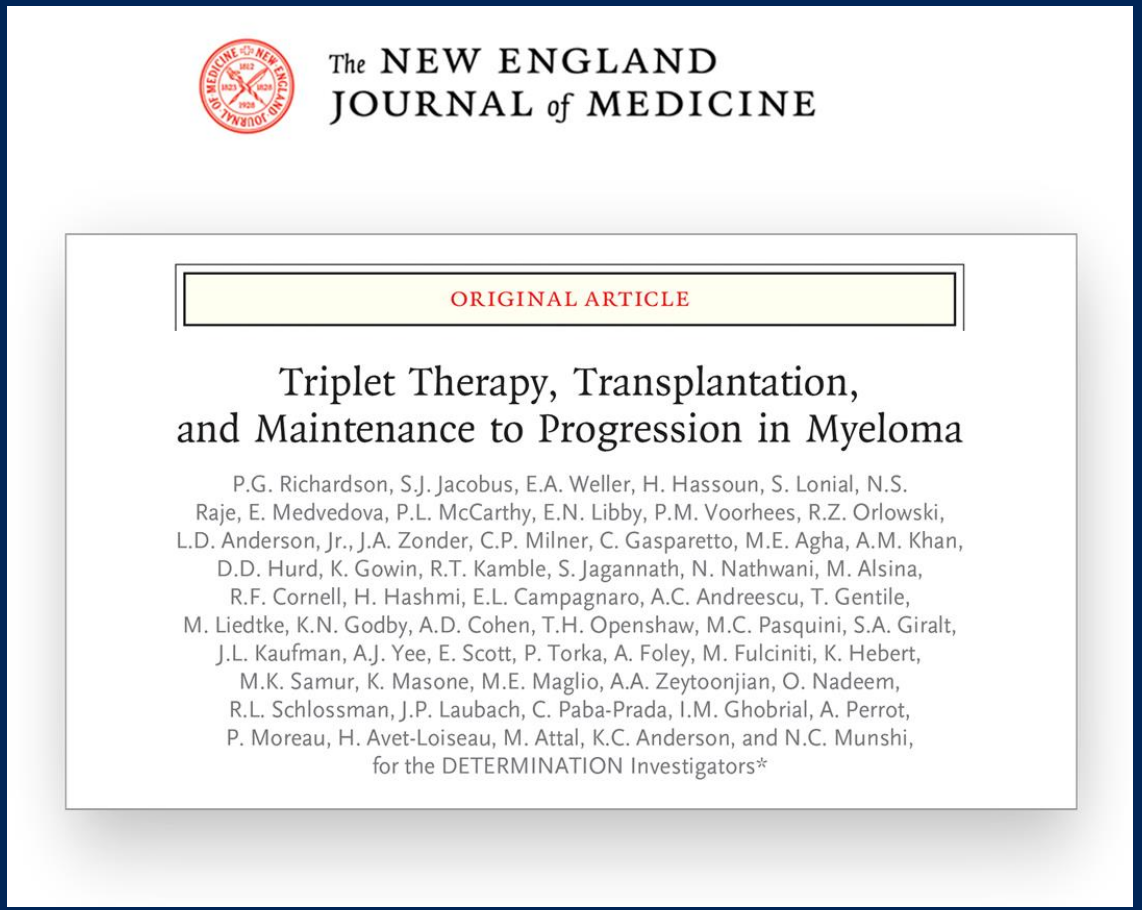


DOI: 10.1056/NEJMoa2204925

Phase 1b/2 Study of Ciltacabtagene Autoleucel, a BCMA-Directed CAR-T Cell Therapy, in Patients With Relapsed/Refractory Multiple Myeloma (CARTITUDE-1): 2 Years Post LPI

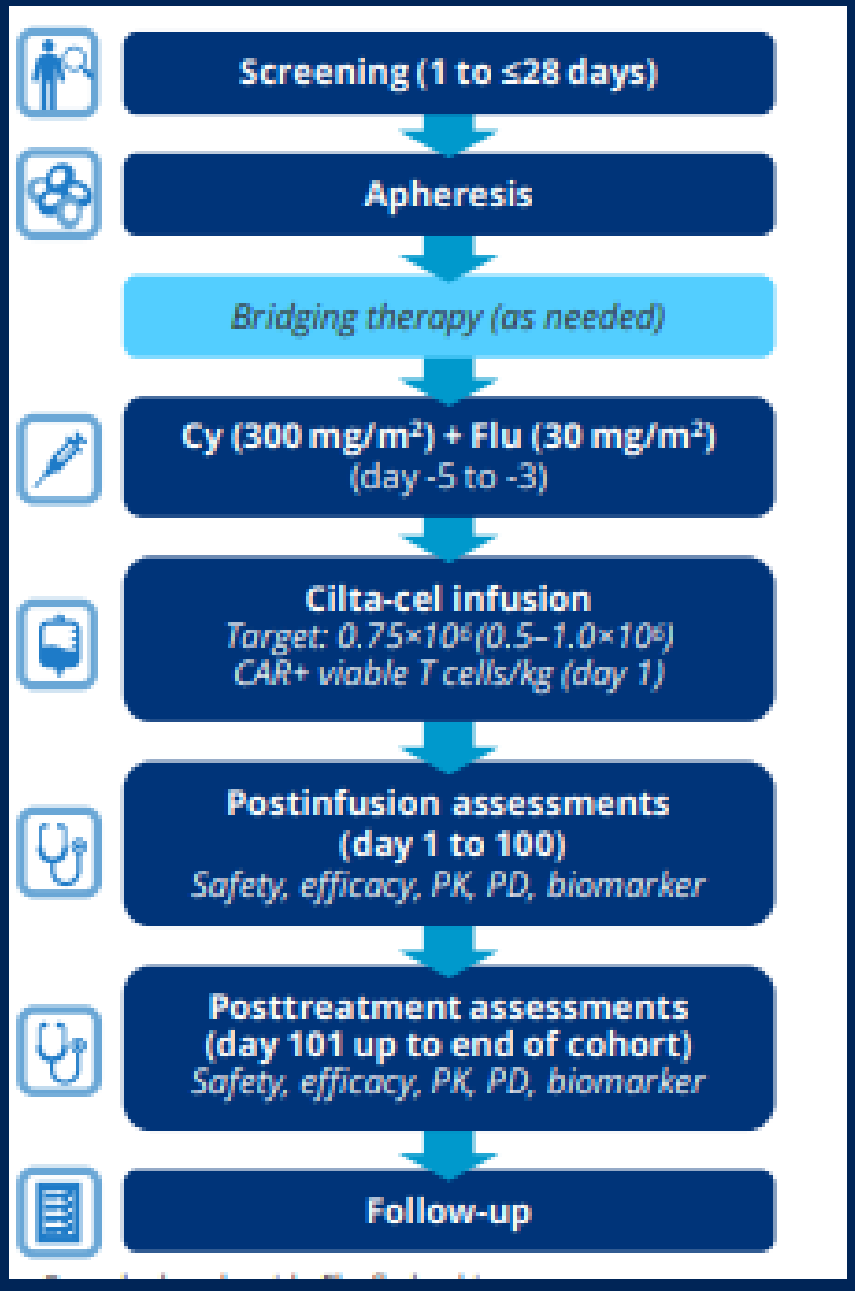
- Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor (CAR)-T cell therapy for the treatment of patients with relapsed/refractory multiple myeloma (RRMM)[1]
- In the phase 1b/2 CARTITUDE-1 study, early, deep, and durable responses were observed with a single cilta-cel infusion in heavily treated patients with RRMM[1]
  - At a median follow-up of 21.7 months, responses were deepening and durable, with an overall response rate (ORR) of 98% and 82.5% of patients reaching stringent complete response (sCR)[2]
  - Median progression-free survival (PFS) and overall survival (OS) were not reached
- Cilta-cel was recently approved by the US Food and Drug Administration for the treatment of adult patients with RRMM after ≥4 prior lines of therapy (LOT), including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody (mAb)[3]
- The Committee for Medicinal Products for Human Use of the European Medicines Agency has recommended cilta-cel for authorization in patients with ≥3 prior LOT[4]
- Here, we report landmark 2 years post last-patient-in results from the CARTITUDE-1 study with a longer duration of follow-up of 27.7 months

Primary endpoints

- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel

Key eligibility criteria

- Progressive MM per International Myeloma Working Group criteria
- Eastern Cooperative Oncology Group performance status ≤1
- Measurable disease
- ≥3 prior LOT or double refractory
- Prior PI, IMiD, and anti-CD38 mAb exposure



Study population

- As of January 11, 2022, 97 patients were treated with cilta-cel with a median follow-up of 27.7 months
- Patients had received a median of 6.0 (range, 3–18) prior LOT
- Patient demographics and baseline characteristics have been previously described[1,2]

Efficacy response

- ORR was 97.9% (95% CI, 92.7–99.7; **Figure 2**)
  - 82.5% (95% CI, 73.4–89.4) achieved sCR
- Responses deepened over time from the 12-month follow-up[1]

- Median duration of response (DOR) was not estimable (95% CI, 23.3 months–NE)
- Most patients in high-risk subgroups responded (ORR range 95.1–100%), including those with high-risk cytogenetics, high tumor burden (≥60% bone marrow plasma cells), and baseline plasmacytomas
- DOR, PFS, and/or OS were shorter in subgroups with high-risk cytogenetic, ISS stage III, high tumor burden, and presence of plasmacytomas
- High efficacy response rates were achieved despite a lack of detectable CAR-T cell persistence in peripheral blood following infusion among patients with 6 months of follow-up[1]
- Of 61 patients evaluable for minimal residual disease (MRD), 91.8% were MRD negative (10^{-5}) at a median follow-up of 27.7 months
- Patients with sustained MRD negativity (10^{-5}) for ≥6 and ≥12 months had improved PFS compared with the overall population (**Figure 3**)

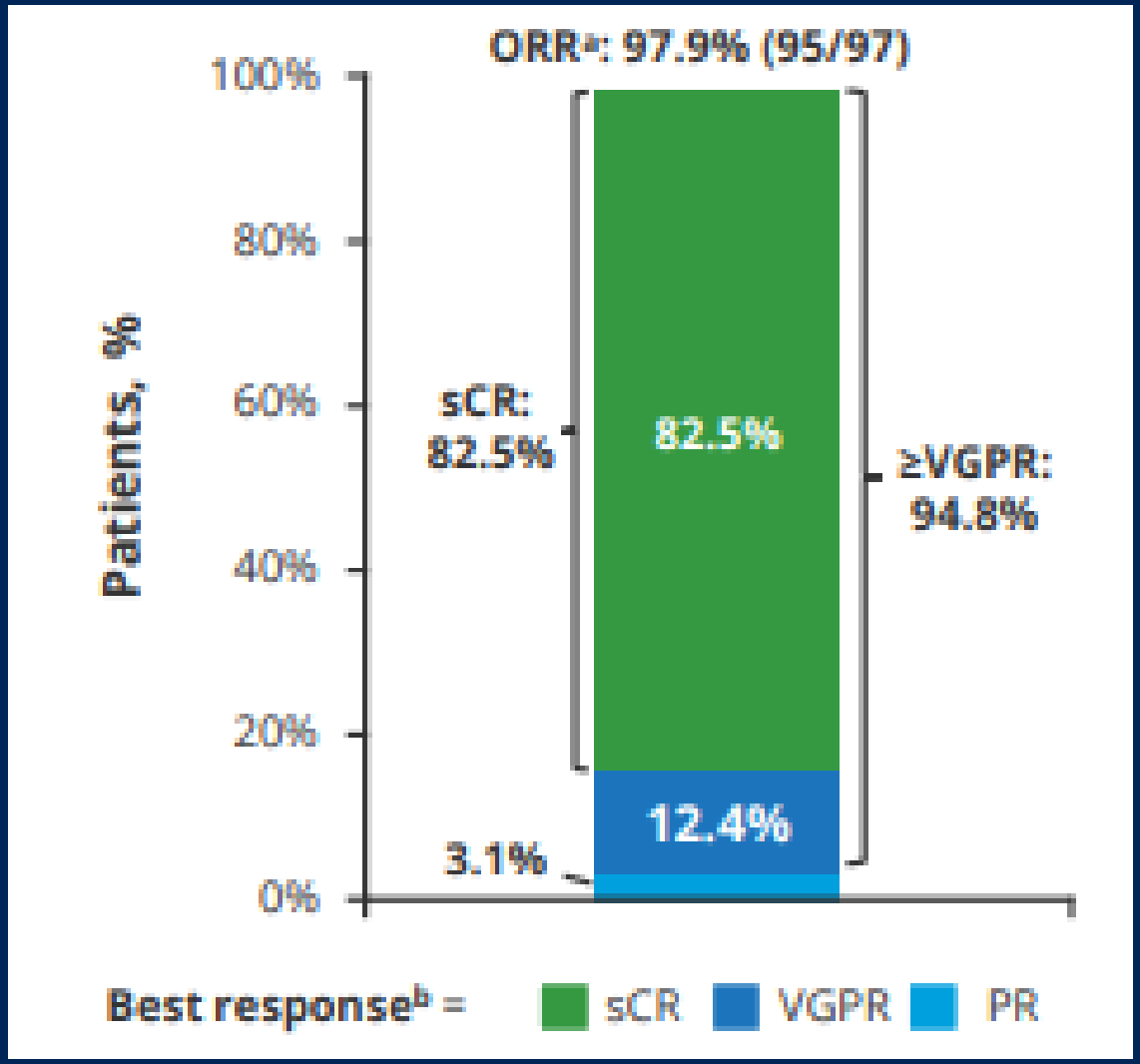


FIGURE 3: Progression-free survival

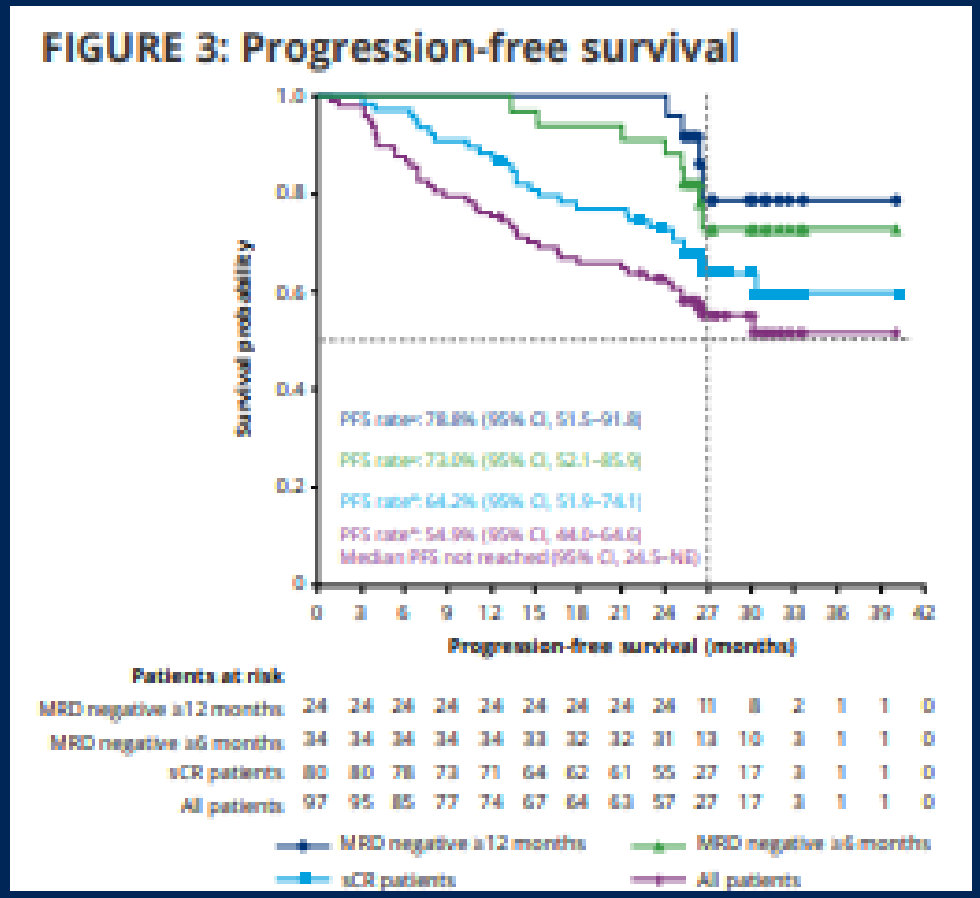
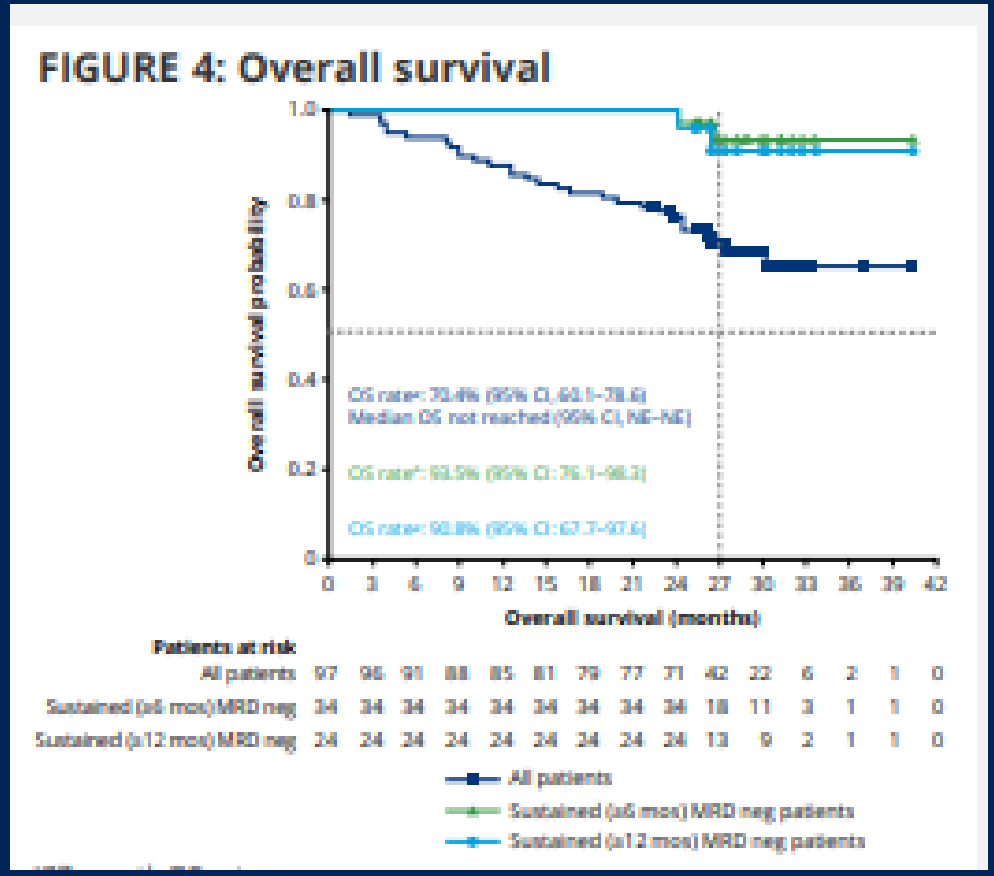


FIGURE 4: Overall survival



	Total (N=97)	Time of death post cilta-cel infusion (days)
Total deaths during the study	30	45–917
Due to progressive disease	14	253–746
AEs unrelated to treatment (n=10)		
Pneumonia	1	109
Acute myeloid leukemia[a]	3	418, 582, 718
Ascites[b]	1	445
Myelodysplastic syndrome	1	803
Respiratory failure	3	733, 793, 829
Septic shock	1	917
AEs related to treatment (n=6)		
Sepsis and/or septic shock	2	45, 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

Safety

- The safety profile was manageable
- There were no new treatment-related deaths (**Table 1**)
  - A total of 30 deaths occurred during the study after cilta-cel infusion
  - No deaths occurred within the first 30 days, 2 occurred within 100 days, and 28 occurred >100 days post infusion

A total of 20 secondary primary malignancies were reported in 16 patients

- Nine patients with hematologic malignancies (1 low-grade B-cell lymphoma, 6 MDS, 3 fatal AML [one patient had both MDS and fatal AML])
- One patient each with malignant melanoma, adenocarcinoma, myxofibrosarcoma, and prostate cancer
- Six non-melanoma skin cancers

- One new case of signs and symptoms of parkinsonism (previously termed movement and neurocognitive treatment-emergent AEs) (total n=6)
  - On day 914, patient experienced cognitive slowing, gait instability, and neuropathy (all grade 1), and tremor (grade 3); he is currently stable and functioning and remains in sCR
  - Had 2 risk factors for parkinsonism (grade 2 CRS and grade 3 immune effector cell-associated neurotoxicity syndrome) after cilta-cel[5,6]
- Following implementation of patient management strategies, the incidence of parkinsonism has decreased from 6% in CARTITUDE-1 to <0.5% across the CARTITUDE program[6]
- Three of the 6 total patients with parkinsonism have died (two from other underlying causes [sepsis and lung abscess] and 1 related to parkinsonism)
- Of the other two who are living, one has recovered, and one is recovering (ongoing grade 2 symptoms) at the time of the data cut

At a median follow-up of 28 months, patients treated with cilta-cel showed durable and deepening responses, with median PFS and OS not yet reached and a manageable safety profile

The ORR to cilta-cel remained at 98%, with 83% of patients achieving sCR with longer follow-up

The safety profile was manageable with a favorable risk-benefit profile and one new case of parkinsonism (day 914 after cilta-cel) since the last report

Cilta-cel is currently under further investigation in patients with MM in earlier-line settings in CARTITUDE-2, CARTITUDE-4, CARTITUDE-5, *EM*agine/CARTITUDE-6[7]

Cilta-cel (CARVYKTI™) has been approved in the US for patients with ≥4 prior LOT[3] and will help fill an unmet need in this difficult-to-treat population

Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Results From MajesTEC-1

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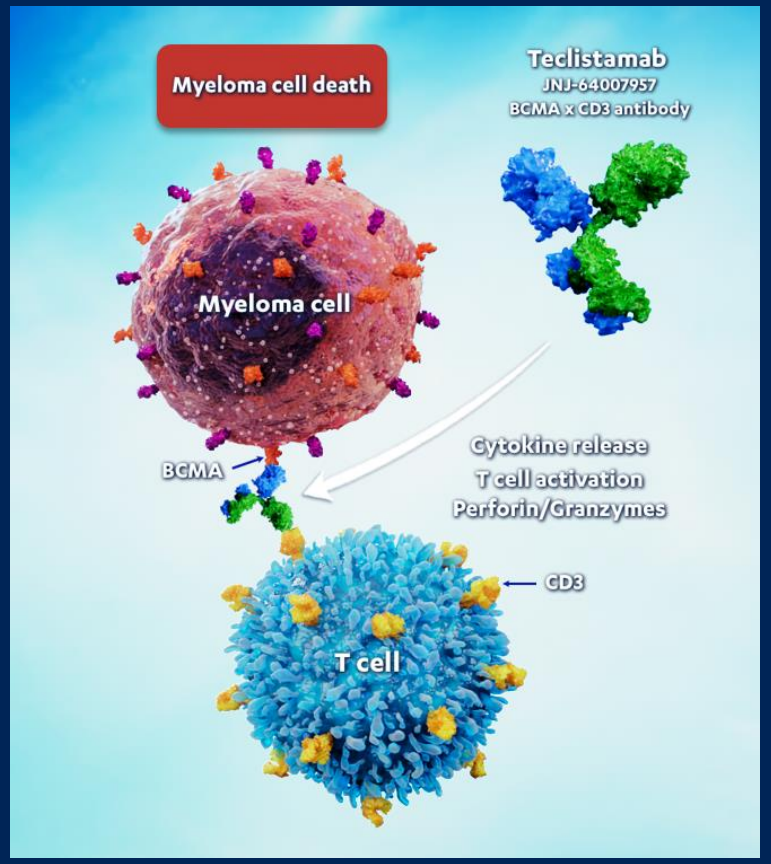
ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

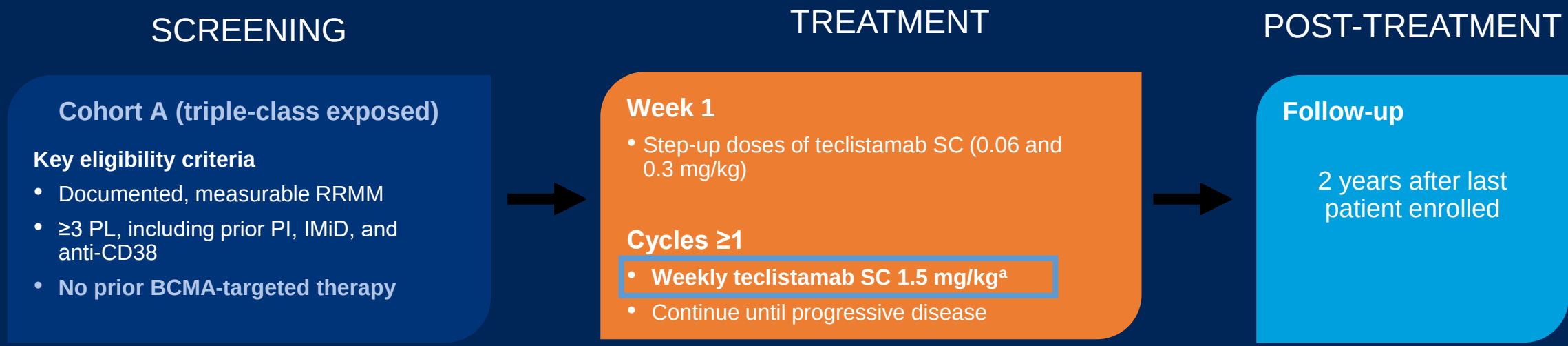
Teclistamab: A Novel BCMA × CD3 T-Cell Redirecting Bispecific Antibody

- Despite newly approved therapies for patients with triple-class exposed RRMM, unmet medical need remains high[1,2]
- Teclistamab is an off-the-shelf fully humanized IgG4 BCMA x CD3 bispecific antibody based on a validated platform
- Teclistamab redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells[3,4]
- The multicohort, phase 1/2 MajesTEC-1 study is investigating the safety and efficacy of teclistamab in patients with RRMM who previously received ≥3 lines of therapy[5]
  - Initial results demonstrated that weekly teclistamab 1.5 mg/kg[a] was well tolerated with a high response rate
- Here we present updated results from the all-treated patient population[b] with longer follow-up



MajesTEC-1: Study Design

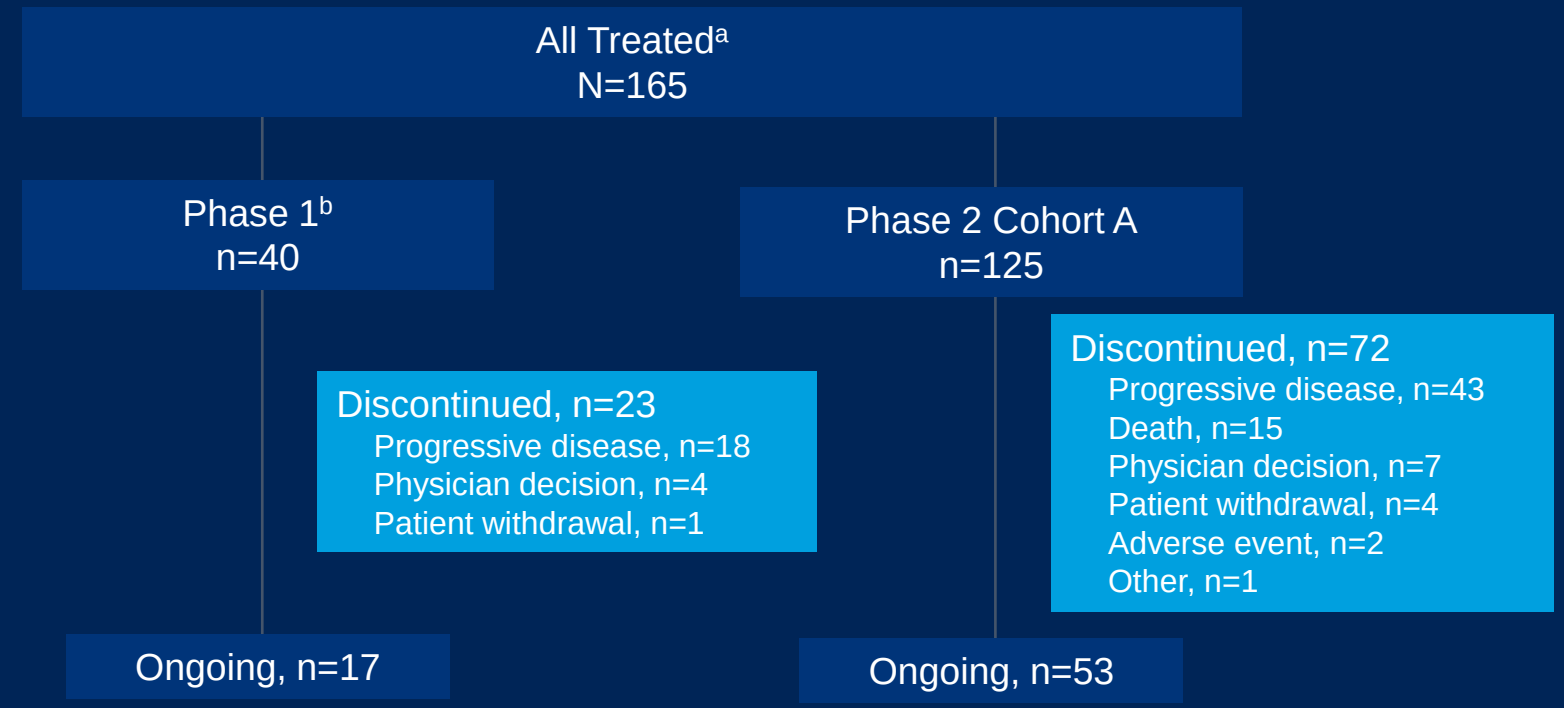
- **First-in-human, phase 1/2, open-label, multicohort, multicenter, dose-escalation study evaluating teclistamab in patients with RRMM who previously received ≥3 lines of therapy (triple-class exposed)**



- **Primary endpoint:** ORR
- **Key secondary endpoints:** DOR, ≥VGPR, ≥CR, sCR, TTR, MRD status, PFS, OS, safety, PK, immunogenicity, PROs

[a]Schedule change to biweekly (every other week) dosing was permitted based on response.
BCMA, B-cell maturation antigen; CR, complete response; DOR, duration of response; IMiD, immunomodulatory drug; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PL, prior line; PRO, patient-reported outcome; RRMM, relapsed/refractory multiple myeloma; sCR, stringent CR; SC, subcutaneous; TTR, time to response; VGPR, very good partial response

MajesTEC-1: Treatment Disposition and Exposure



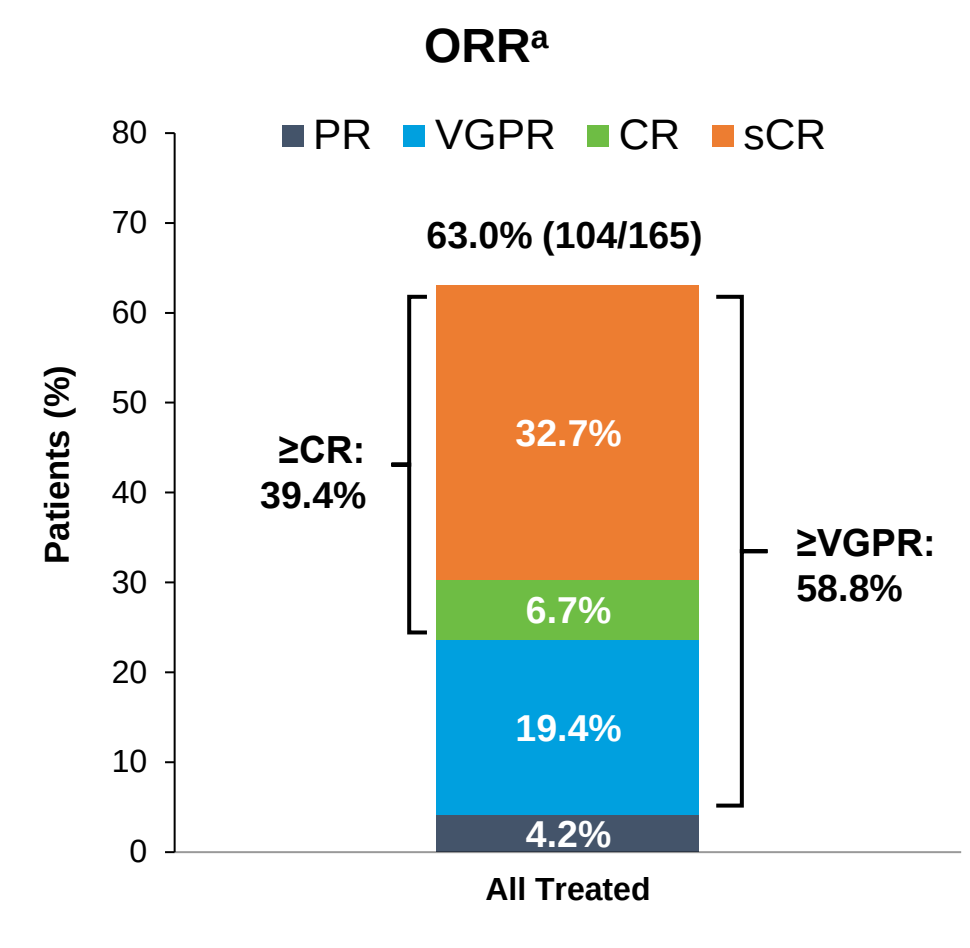
Median follow-up, months (range)	14.1 (0.26[+]–24.4)
Median treatment duration, months (range)	8.5 (0.2–24.4)
Median relative dose intensity[c], %	93.7

MajesTEC-1: Patient Demographics and Baseline Characteristics

Characteristic	N=165
Age (years), median (range)	**64.0 (33–84)**
Age ≥75 years, n (%)	**24 (14.5)**
Male, n (%)	**96 (58.2)**
Race, n (%)	
White	**134 (81.2)**
Black/African American	**21 (12.7)**
Other[a]	**10 (6.1)**
Bone marrow plasma cells ≥60%[b], n (%)	**18 (11.3)**
Extramedullary plasmacytomas ≥1[c], n (%)	**28 (17.0)**
High-risk cytogenetics[d], n (%)	**38 (25.7)**
ISS stage[e], n (%)	
I	**85 (52.5)**
II	**57 (35.2)**
III	**20 (12.3)**

Characteristic	N=165
Baseline renal function, n (%)	
<60 mL/min/1.73m^2	**44 (26.7)**
≥60 mL/min/1.73m^2	**121 (73.3)**
Time since diagnosis (years), median (range)	**6.0 (0.8–22.7)**
Prior lines of therapy, median (range)	**5.0 (2–14)**
≥4 prior lines, n (%)	**122 (73.9)**
Autologous transplantation, n (%)	**135 (81.8)**
Allogeneic transplantation, n (%)	**8 (4.8)**
Exposure status, n (%)	
Triple-class[f]	**165 (100)**
Penta-drug exposed[g]	**116 (70.3)**
Refractory status, n (%)	
Triple-class[f]	**128 (77.6)**
Penta-drug[g]	**50 (30.3)**
To last line of therapy	**148 (89.7)**

MajesTEC-1: Overall Response to Teclistamab

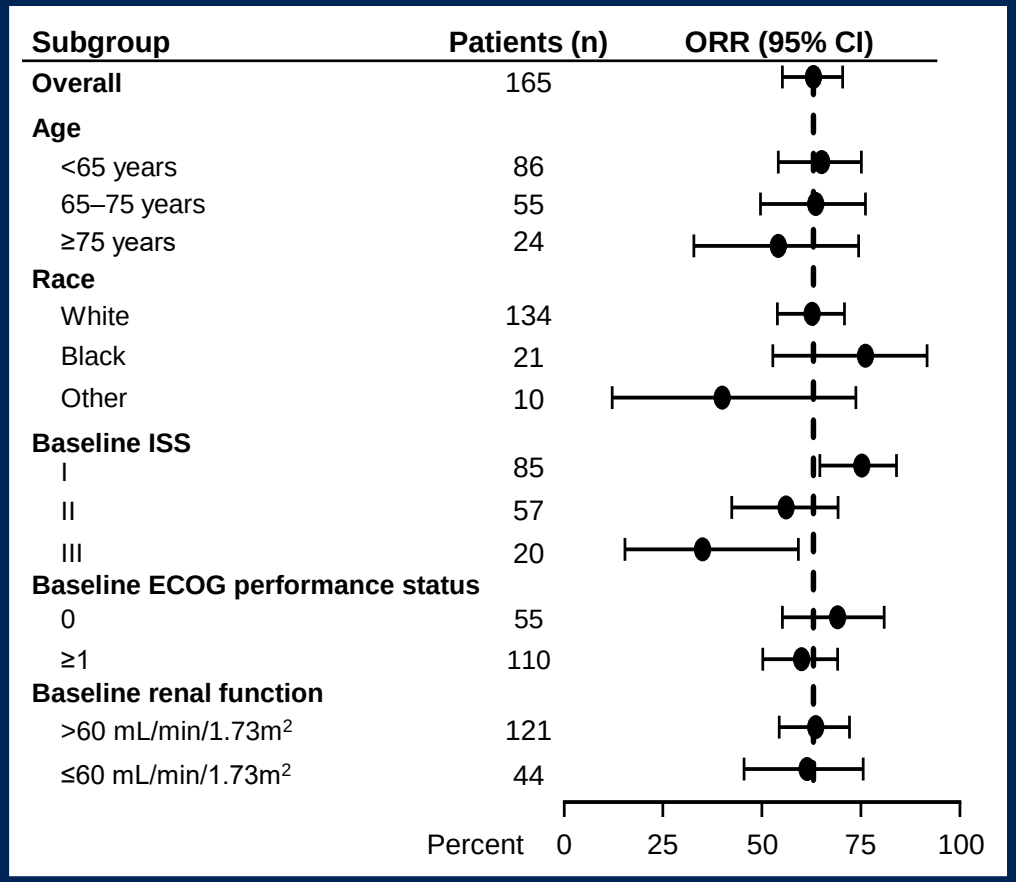


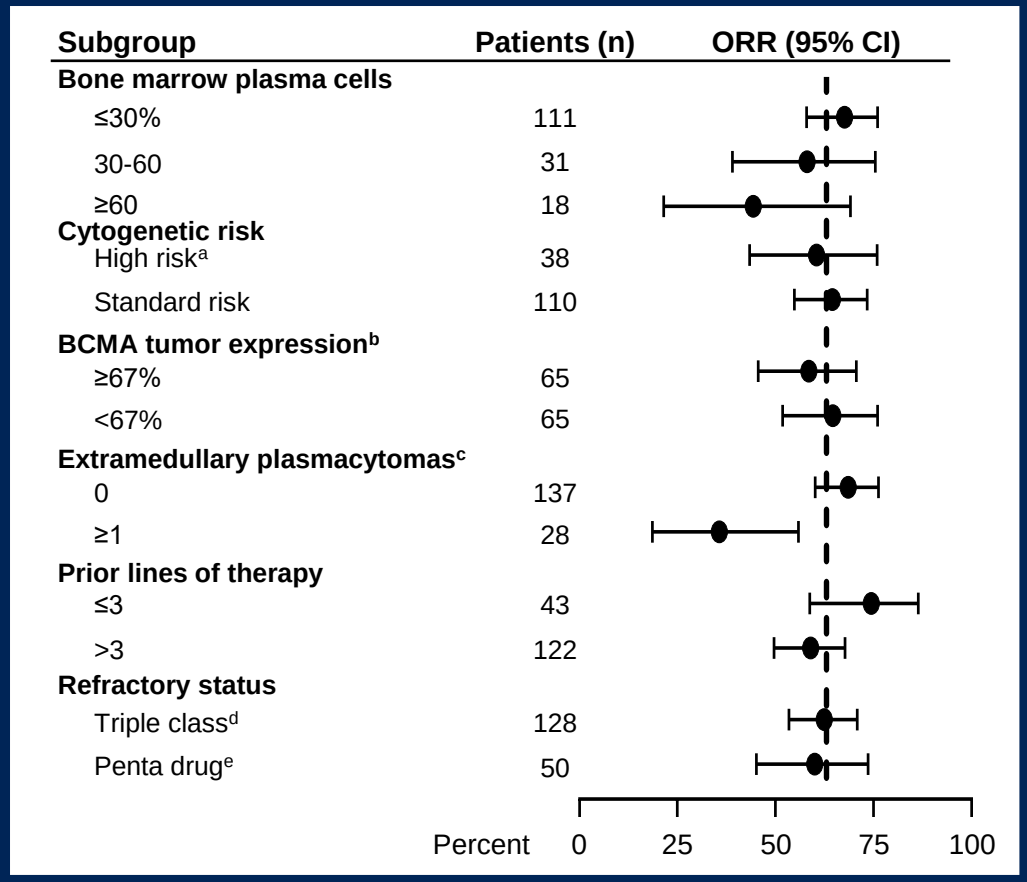
ORR of 63.0% (95% CI: 55.2–70.4) represents a substantial benefit for patients with triple-class exposed disease

- Median time to response (n=104)
  - First response: 1.2 months (range: 0.2–5.5)
  - Best response: 3.8 months (range: 1.1–16.8)
- MRD negativity rate at 10^{-5}[b]
  - 26.7% in the all-treated (N=165) patient population
    - 81.5% of MRD-evaluable patients (44 of 54) were MRD negative
  - Almost half (46.2%) of patients with ≥CR were MRD negative

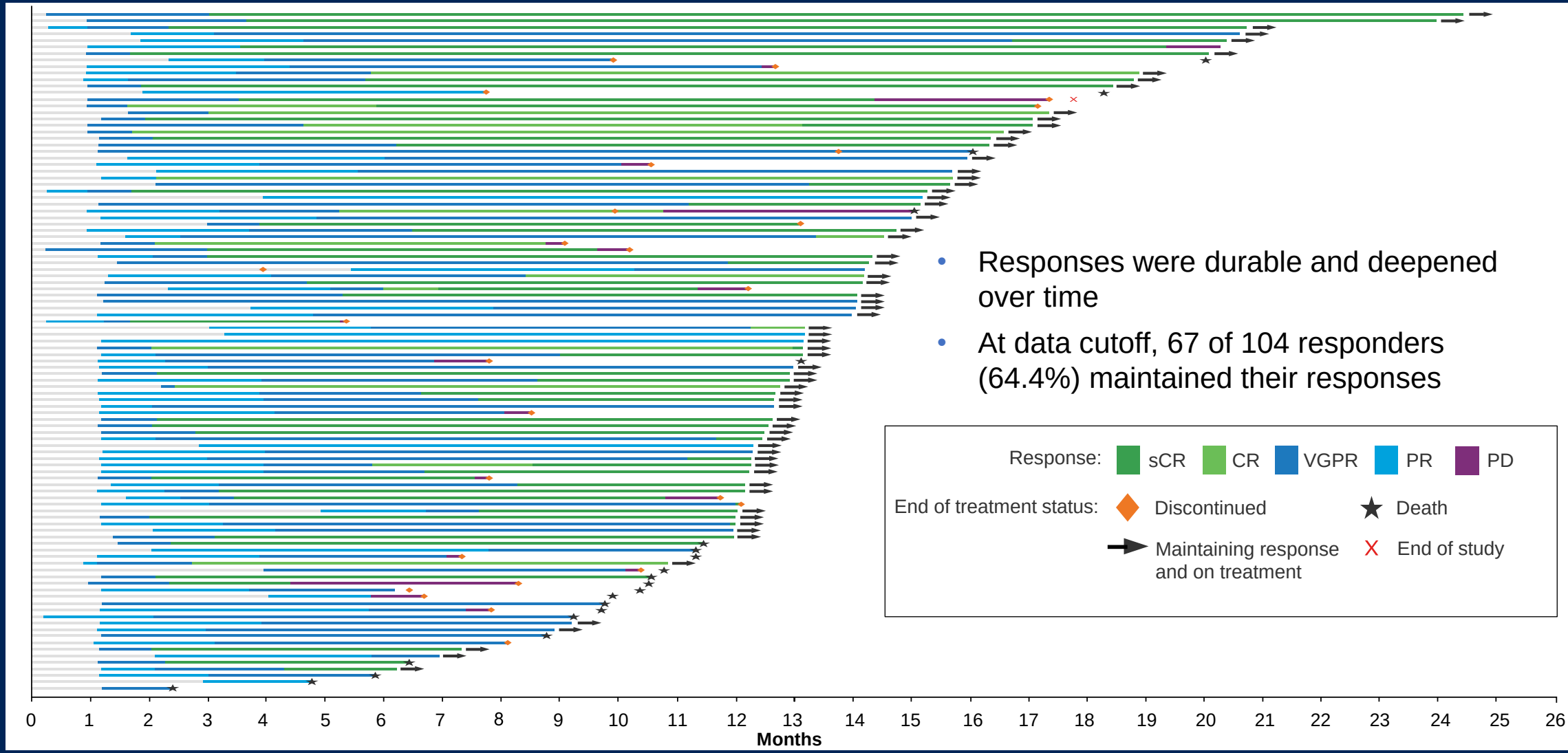
MajesTEC-1: ORR Across Subgroups

- **ORR was consistent across clinically relevant subgroups, including high cytogenetic risk and penta-drug refractory subgroups**



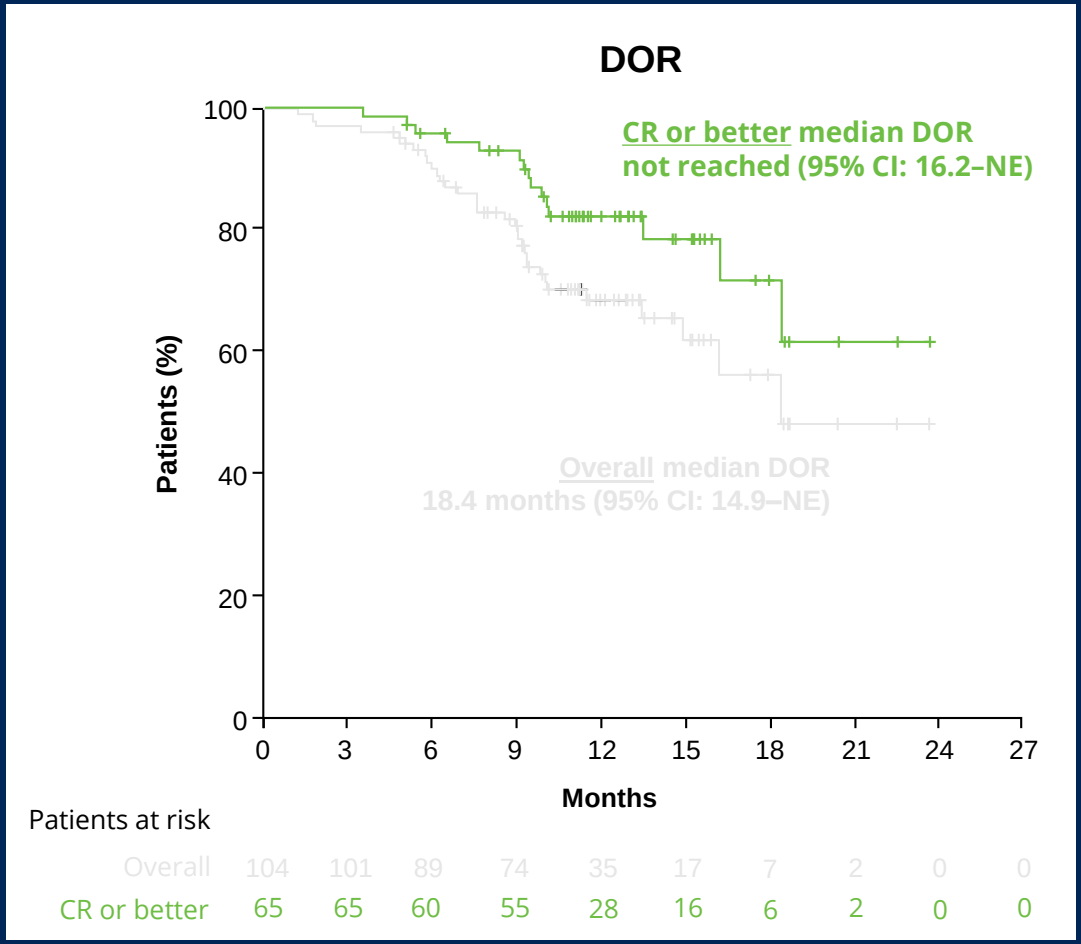


MajesTEC-1: Durability of Response



Analysis cutoff date: March 16, 2022. CR, complete response; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response

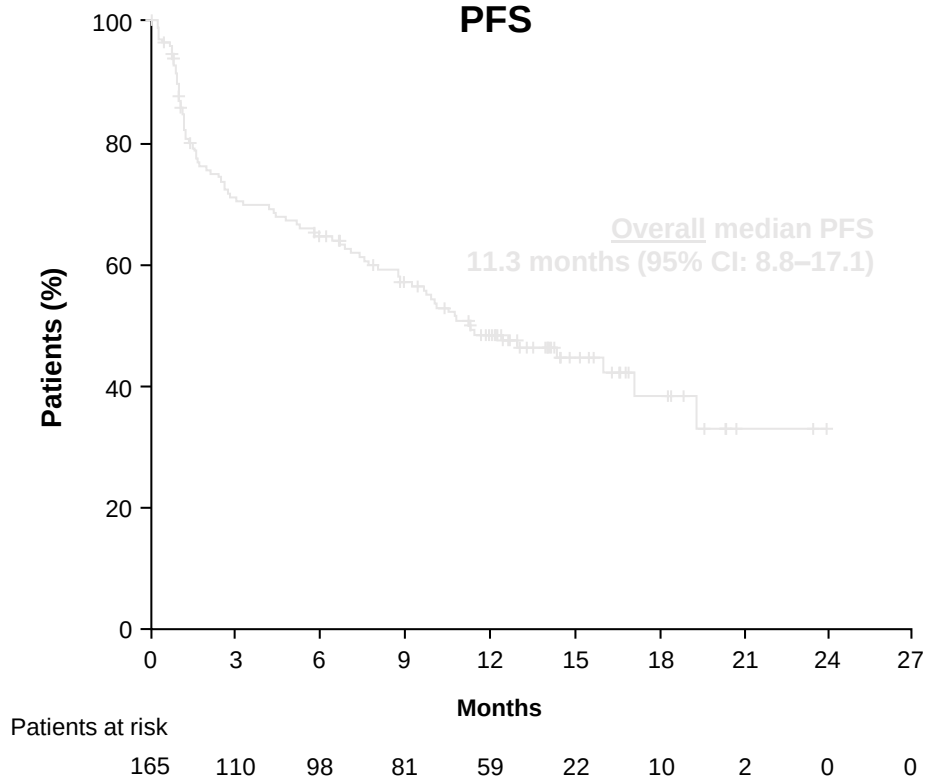
MajesTEC-1: Duration of Response



- Overall median DOR of **18.4 months (95% CI: 14.9–NE),** and was not yet mature with data from 71 patients (68.3%) censored

- **12-month event-free rate:**
- **Overall:** 68.5% (95% CI: 57.7–77.1)
- **Patients with CR or better:** 80.1% (95% CI: 67.6–88.2)

MajesTEC-1: Progression-Free Survival



- **With a median follow-up of 14.1 months, median PFS was 11.3 months (95% CI: 8.8–17.1)**
- Median OS was 18.3 months (95% CI: 15.1–NE) and was not yet mature, with data from 97 patients (58.8%) censored

Analysis cutoff date: March 16, 2022.
NE, not estimable; OS, overall survival; PFS, progression-free survival

MajesTEC-1: Overall Safety Profile

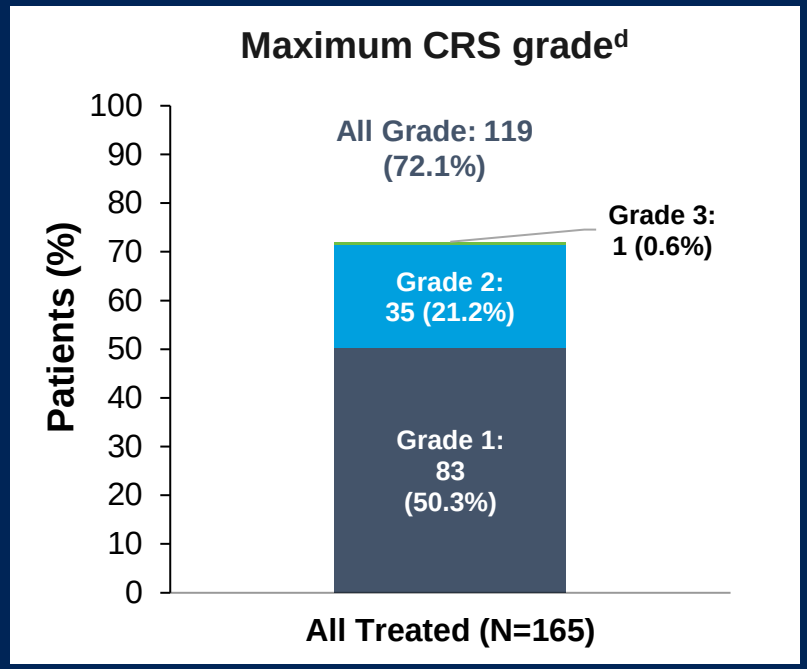
AEs ≥20%, n (%)	Any Grade	Grade 3/4
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Nonhematologic		
CRS	119 (72.1)	1 (0.6)
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Pyrexia	45 (27.3)	1 (0.6)
Injection site erythema	43 (26.1)	0 (0)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0 (0)
Cough	33 (20.0)	0 (0)

Teclistamab was well tolerated; discontinuations and dose reductions were infrequent

- 2 patients (1.2%) discontinued due to AEs (grade 3 adenoviral pneumonia; grade 4 PML)
- 1 patient had dose reduction at cycle 21
- The most common AEs were CRS and cytopenias
- Infections occurred in 126 (76.4%) patients (grade 3/4: 44.8%)
- 123 patients (74.5%) had evidence of hypogammaglobulinemia[a]
- There were 19 deaths due to AEs, including 12 COVID-19 deaths
  - 5 deaths due to teclistamab-related AEs:
    - COVID-19 (n=2)
    - Pneumonia (n=1)
    - Hepatic failure (n=1)
    - PML (n=1)

MajesTEC-1: Cytokine Release Syndrome

Parameter	N=165
Patients with CRS, n (%)	**119 (72.1)**
Patients with ≥2 CRS events	**55 (33.3)**
Time to onset[a] (days), median (range)	**2 (1–6)**
Duration (days), median (range)	**2 (1–9)**
Received supportive measures[a] for CRS, n (%)	**110 (66.7)**
Tocilizumab[b]	**60 (36.4)**
Low-flow oxygen by nasal cannula[c]	**21 (12.7)**
Corticosteroids	**14 (8.5)**
Single vasopressor	**1 (0.6)**



- Most CRS events were confined to step-up and first full treatment doses
- All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that occurred in the context of concurrent pneumonia (resolved in 2 days)
- All CRS events fully resolved without treatment discontinuation or dose reduction

Analysis cutoff date: March 16, 2022.
[a]A patient could receive >1 supportive therapy. [b]Tocilizumab was administered at physician discretion. [c]≤6 L/min. [d]CRS was graded using Lee et al *Blood* 2014 in the phase 1 portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al *Blood* 2014 criteria were mapped to ASTCT criteria for patients in the phase 1 portion.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome

MajesTEC-1: Neurotoxic Events

Parameter	N=165
Neurotoxic event[a], n (%)	**24 (14.5)**
Headache	**14 (8.5)**
ICANS[b]	**5 (3.0)**
Dysgeusia	**2 (1.2)**
Lethargy	**2 (1.2)**
Tremor	**2 (1.2)**
Grade ≥3 events, n (%)	**1 (0.6)**
Time to onset, median (range) days	**3.0 (1–13)**
Duration, median (range) days	**7.0 (1–291)**
Received supportive measures for neurotoxic events[c], n (%)	**14 (8.5)**
Tocilizumab	**3 (1.8)**
Dexamethasone	**3 (1.8)**
Levetiracetam	**2 (1.2)**
Gabapentin	**1 (0.6)**

- The overall incidence of neurotoxic events was low
- All neurotoxic events were grade 1/2, except for 1 grade 4 seizure (in the context of bacterial meningitis during cycle 7)
- 5 patients (3.0%) had a total of 9 ICANS events
  - 7 events were concurrent with CRS
  - All ICANS events were grade 1/2 and fully resolved
- There were no treatment discontinuations or dose reductions due to neurotoxic events, including ICANS

MajesTEC-1: Conclusions

- **After a median follow-up of 14 months, teclistamab yields deep and durable responses in patients with highly refractory MM**
- Response rate remained high (63.0%) with CR or better achieved in 39.4% of patients
- Median DOR of 18.4 months and in those achieving a CR or better event-free rate was 80.1% at 12 months
- Median PFS of 11.3 months
- **Teclistamab toxicities were manageable**
- CRS was predominantly grade 1/2 and incidence of neurotoxic events was low
- Cytopenias and infections were common but consistent with heavily pretreated RRMM
- **These data support teclistamab as a promising new, off-the-shelf, T-cell redirecting therapy targeting BCMA for patients with RRMM**
- Phase 3 studies are ongoing and early access programs are underway
- Data in patients with prior BCMA exposure was presented by Dr. Touzeau (presentation #8013)

Thank You