Subcutaneous Daratumumab (DARA) + Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) in Patients With Newly Diagnosed Light-Chain (AL) Amyloidosis: Overall Survival and Final Major Organ Deterioration–Progression-free Survival Results from the Phase 3 ANDROMEDA Study

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ANDROMEDA: Introduction

- Systemic AL amyloidosis is characterized by deposition of immunoglobulin light chains produced by clonal CD38^{+} plasma cells as insoluble amyloid fibrils in vital organs, which often leads to poor prognosis[1-4]
  - 5-year survival rate reported as 48% overall and 35% for patients with cardiac involvement[5]
- Phase 3 ANDROMEDA study primary analysis (median follow-up: 11.4 months)[6] showed the addition of subcutaneous daratumumab (DARA) to VCd (D-VCd) resulted in:
  - Significant increase in HemCR rate (53.3% vs 18.1%; *P* <0.0001)
  - Prolonged major organ deterioration (MOD)–PFS (HR, 0.58; 95% CI, 0.36-0.93; *P* = 0.02)
- D-VCd is the first and only approved therapy for AL amyloidosis and is considered SoC for newly diagnosed patients[7-9]

Here we report results from the final analysis for MOD-PFS and OS of ANDROMEDA with a median follow-up of 5 years

AL, light-chain; VCd, bortezomib/cyclophosphamide/dexamethasone; HemCR, hematologic complete response; MOD-PFS, major organ deterioration−progression-free survival; HR, hazard ratio; CI, confidence interval; SoC, standard of care; OS, overall survival. MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death.

1. Merlini G, et al. *Expert Rev Hematol*. 2014;7(1):143-156. 2. National Organization for Rare Disorders. Amyloidosis. Accessed October 22, 2024. https://rarediseases.org/rare-diseases/amyloidosis/#affectedpopulations. 3. Weiss BM, et al. *J Clin Oncol*. 2014;32(25):2699-2704. 4. Palladini G, et al. *J Clin Oncol*. 2012;30(36):4541-4549. 5. Staron A, et al. *Blood Cancer J*. 2021;11(8):139. 6. Kastritis E, et al. *N Eng J Med*. 2021;385(1):46-58. 7. DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) [package insert]: Janssen Biotech, Inc.; 2024. 8. European Medicines Agency. DARZALEX 20 mg/mL concentrate for solution for infusion [summary of product characteristics]. Accessed August 6, 2024. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf. 9. Wechalekar AD, et al. *Amyloid*. 2023;30(1):3-17.

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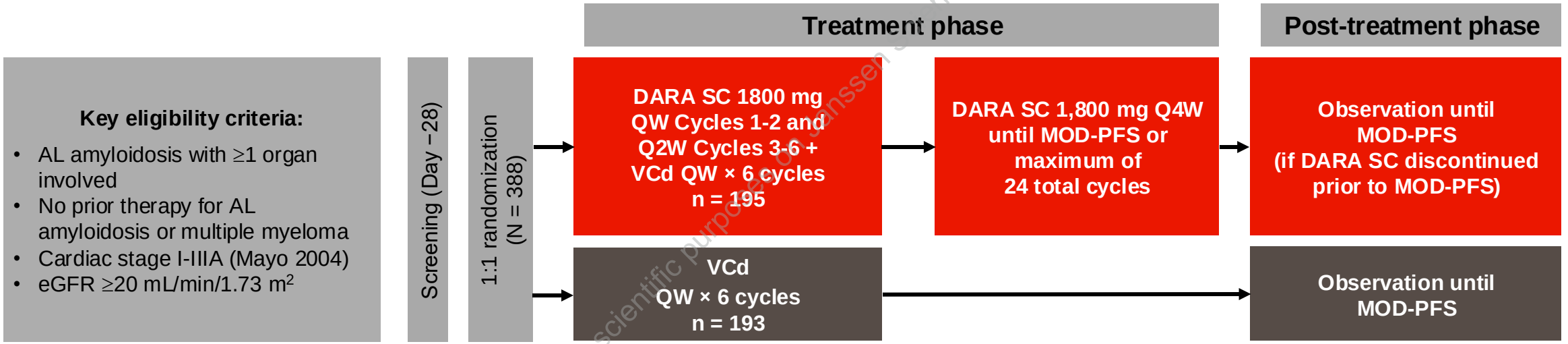
ANDROMEDA: Study Design

- ANDROMEDA is a randomized, open-label, phase 3 study of DARA plus VCd (D-VCd) versus VCd alone in patients with newly diagnosed AL amyloidosis



Stratification criteria:
- Cardiac stage (I vs II vs IIIA)
- Transplant typically offered in local country (yes vs no)
- Creatinine clearance (≥60 mL/min vs <60 mL/min)

Primary endpoint: Overall HemCR rate[a]

Secondary endpoints: MOD-PFS (end-stage cardiac or renal disease, hematologic progression, or death),[b] OS, organ response rate, time to hematologic response, safety

D-VCd, daratumumab 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA)] plus VCd; eGFR, estimated glomerular filtration rate; SC, subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks. [a]Defined here as normalization of free light-chain (FLC) levels and ratio (FLCr) and negative serum and urine immunofixation, confirmed at a subsequent visit; normalization of uninvolved FLC level and FLCr were not required if involved FLC was lower than the upper limit of normal; [b]A composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines,[1] or death. 1. Comenzo RL, et al. *Leukemia*. 2012;26(11):2317-2325.

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ANDROMEDA: Baseline Demographic and Clinical Characteristics

Characteristic	D-VCd (n = 195)	VCd (n = 193)
Age		
Median (range), years	62 (34-87)	64 (35-86)
≥65, n (%)	87 (44.6)	96 (49.7)
Male sex, n (%)	108 (55.4)	117 (60.6)
Race, n (%)[a]		
White	151 (77.4)	143 (74.1)
Black or African American	6 (3.1)	7 (3.6)
Not reported	7 (3.6)	5 (2.6)
ECOG PS score, n (%)[b]		
0	90 (46.2)	71 (36.8)
1	86 (44.1)	106 (54.9)
2	19 (9.7)	16 (8.3)
AL isotype, n (%)[c]		
Lambda	158 (81.0)	149 (77.2)
Kappa	37 (19.0)	44 (22.8)
Median time since amyloidosis diagnosis (range), days	48 (8-1,611)	43 (5-1,102)

Characteristic	D-VCd (n = 195)	VCd (n = 193)
Involved organs		
Median (range)	2 (1-5)	2 (1-6)
Distribution, n (%)		
Heart	140 (71.8)	137 (71.0)
Kidney	115 (59.0)	114 (59.1)
Liver	15 (7.7)	16 (8.3)
Other[d]	127 (65.1)	124 (64.2)
Cardiac stage, n (%)[e]		
I	47 (24.1)	43 (22.3)
II	76 (39.0)	80 (41.5)
IIIA	70 (35.9)	64 (33.2)
IIIB[f]	2 (1.0)	6 (3.1)
Renal stage, n/total n (%)[g]		
I	107/193 (55.4)	101/193 (52.3)
II	67/193 (34.7)	74/193 (38.3)
III	19/193 (9.8)	18/193 (9.3)

Demographic and baseline characteristics were well balanced between groups

ECOG PS, Eastern Cooperative Oncology Group performance status; NT-proBNP, N-terminal pro–B-type natriuretic peptide. [a]Race was reported by the patient. [b]ECOG PS is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. [c]Data are based on immunofixation and light-chain measurement. [d]Other includes gastrointestinal tract, lung, peripheral nervous system, autonomic nervous system, and soft tissue. [e]Cardiac stage was classified in accordance with the European modification of the staging system of the Mayo Clinic. [e]Cardiac stage was based on 2 biomarker risk factors—NT-proBNP and high-sensitivity cardiac troponin T—that were assessed at a central laboratory. [f]All the patients had a cardiac stage of I, II, or IIIA at screening; however, some converted to stage IIIB at Cycle 1, Day 1 (results determined by the central laboratory were made available only after Cycle 1, Day 1). [g]Renal stage is based on the combination of eGFR and urinary protein excretion.

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ANDROMEDA: Treatment Exposure and Subsequent Therapy

	D-VCd (n = 193)	VCd (n = 188)
Median duration of study treatment (range), months	21.3 (0.03-26.7)	5.3 (0.03-7.3)
Median number of cycles received (range)	24.0 (1.0-25.0)	6.0 (1.0-6.0)
Received 6 cycles of treatment per protocol, n (%)[a]	159 (82.4)	121 (64.4)
Completed 2 years of DARA maintenance, n (%)[a]	124 (64.2)	–
Most common reason for DARA discontinuation, n		
Death	23	–
ASCT	12	–
Adverse event	11	–

Subsequent therapy

- Median duration of follow-up: 61.4 months
- 25.9% (50/193) and 61.2% (115/188) of patients randomized to D-VCd and VCd, respectively, received subsequent therapy[b]
- 71.3% (82/115) of patients in the VCd arm who received subsequent therapy received DARA-based treatment

>70% of VCd patients who received subsequent therapy received DARA-based treatment

ASCT, autologous stem cell transplant.
[a]Patients in the VCd arm received a maximum number of 6 cycles of treatment, whereas the maximum treatment duration was 2 years for patients in the D-VCd arm.
[b]Non–cross-resistant subsequent therapy, which was defined as any anti–plasma cell agent not included in the original protocol-assigned treatment.

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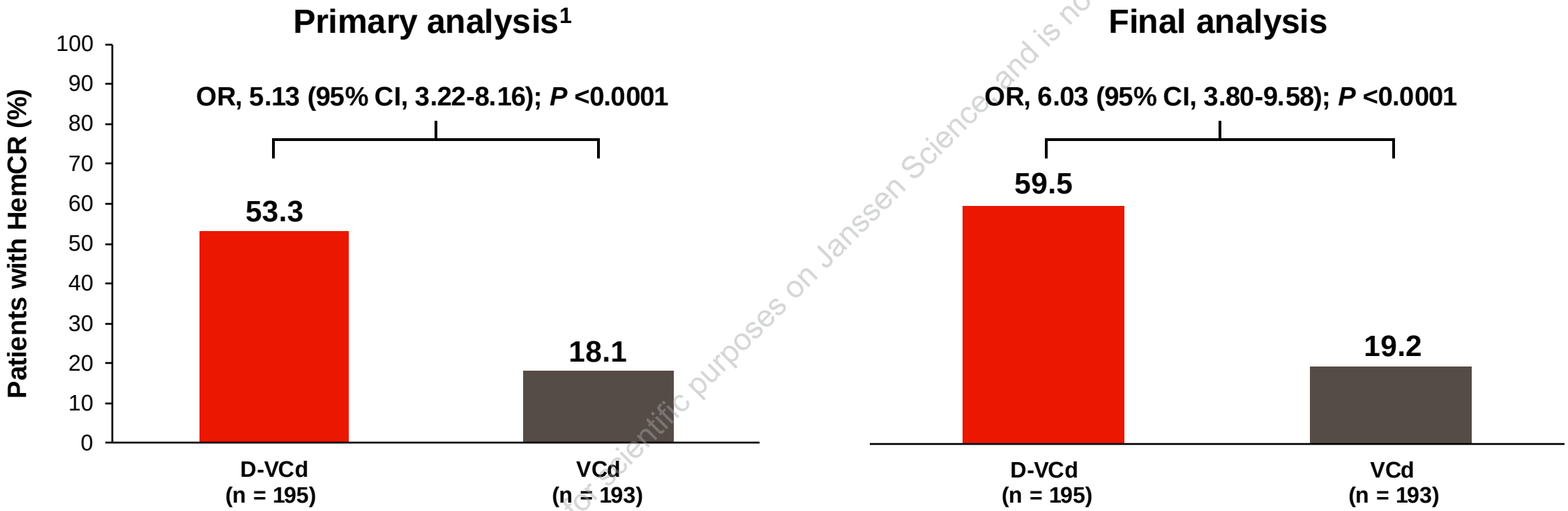
ANDROMEDA: Overall Hematologic Complete Response Rate (Primary Endpoint)



- Median time to HemCR was 67.5 days for D-VCd versus 85.0 days for VCd

The final analysis confirms that the addition of DARA to VCd substantially increased HemCR versus VCd alone

OR, odds ratio. 1. Kastritis E, et al. *N Engl J Med*. 2021;385(1):46-58.

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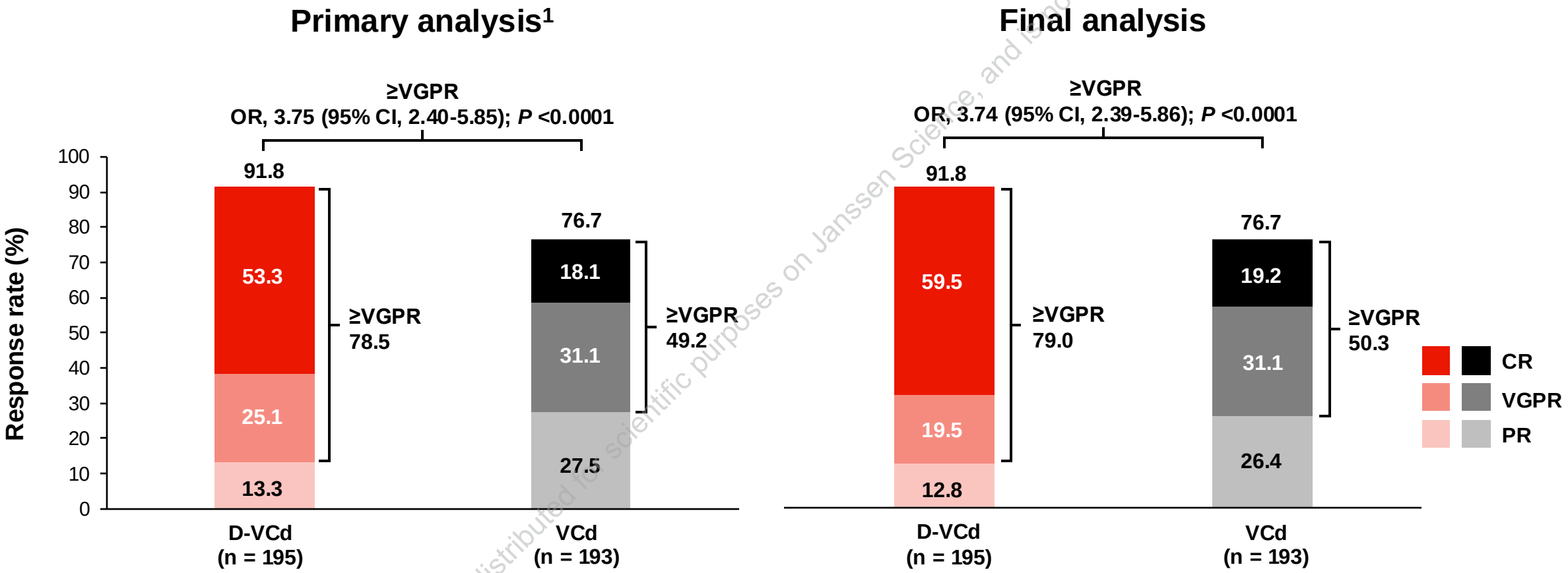
ANDROMEDA: Overall Hematologic Response at the Final Analysis



The addition of DARA to VCd consistently led to higher rates of hematologic response

VGPR, very good partial response; CR, complete response; PR, partial response. 1. Kastritis E, et al. *N Engl J Med*. 2021;385(1):46-58.

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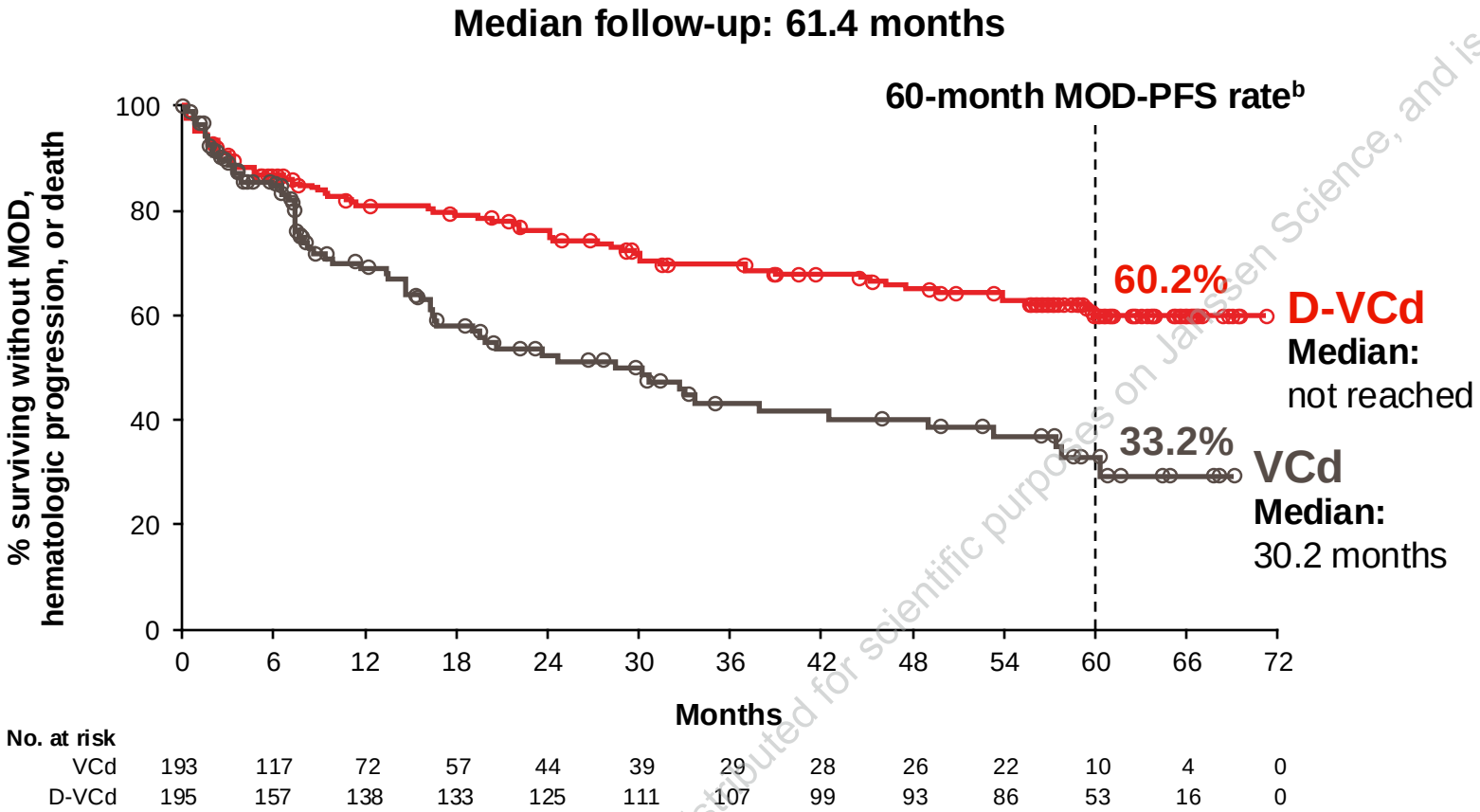
ANDROMEDA: Major Organ Deterioration (MOD)–PFS[a]



- **HR, 0.44 (95% CI, 0.31-0.63); *P* <0.0001[c,d]**

	D-VCd (n = 195)	VCd (n = 193)
MOD-PFS event, n	79	118
Hematologic progression	41	63
MOD	3	11
Death	35	44

The addition of DARA to VCd significantly improved MOD-PFS versus VCd

[a]MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death. [b]Kaplan–Meier estimates. [c]MOD-PFS was analyzed by employing the inverse probability of censoring weight method. [d]Crossing the prespecified significance boundary of 0.0495.

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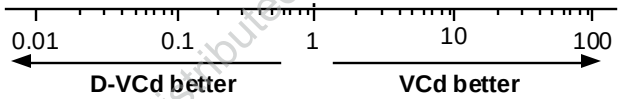
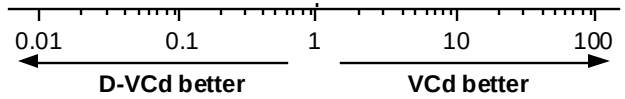
ANDROMEDA: Prespecified Subgroup Analysis of Major Organ Deterioration (MOD)–PFS

Subgroup	MOD-PFS, n/N D-VCd	MOD-PFS, n/N VCd	Median MOD-PFS, months D-VCd	Median MOD-PFS, months VCd	HR (95% CI)
Sex					
Male	45/108	76/117	NE	22.14	0.46 (0.32-0.66)
Female	34/87	42/76	NE	33.61	0.49 (0.31-0.78)
Age					
<65 years	38/108	52/97	NE	31.11	0.44 (0.29-0.67)
≥65 years	41/87	66/96	59.66	20.86	0.51 (0.34-0.75)
Baseline weight					
≤65 kg	23/62	49/74	NE	20.40	0.35 (0.21-0.57)
>65-85 kg	42/96	41/74	NE	23.66	0.58 (0.38-0.89)
>85 kg	14/37	28/45	NE	38.21	0.47 (0.25-0.89)
Race					
White	64/151	87/143	NE	31.11	0.50 (0.36-0.69)
Asian	7/30	21/34	NE	16.33	0.25 (0.11-0.59)
Other	8/14	10/16	53.59	24.05	0.83 (0.32-2.12)
Baseline cardiac stage					
I	18/47	22/43	NE	48.59	0.56 (0.30-1.04)
II	27/76	50/80	NE	24.64	0.39 (0.24-0.62)
IIIA/IIIB	34/72	46/70	59.66	20.86	0.51 (0.33-0.80)
Residence in a country that typically offers transplantation for patients with AL amyloidosis					
Yes	58/147	90/146	NE	26.74	0.45 (0.32-0.63)
No	21/48	28/47	NE	31.11	0.53 (0.30-0.94)



Subgroup	MOD-PFS, n/N D-VCd	MOD-PFS, n/N VCd	Median MOD-PFS, months D-VCd	Median MOD-PFS, months VCd	HR (95% CI)
Baseline creatinine clearance					
≥60 mL/min	49/126	74/131	NE	28.42	0.46 (0.32-0.67)
<60 mL/min	30/69	44/62	NE	29.90	0.47 (0.29-0.74)
Baseline cardiac involvement					
Yes	57/140	87/137	NE	21.88	0.44 (0.31-0.61)
No	22/55	31/56	NE	42.41	0.55 (0.32-0.96)
Baseline renal stage					
I	13/39	22/36	NE	20.57	0.30 (0.15-0.60)
II	20/56	35/60	NE	33.02	0.40 (0.23-0.70)
III	7/19	13/18	59.33	45.50	0.49 (0.19-1.24)
Baseline alkaline phosphatase					
Abnormal	4/11	12/15	NE	17.74	0.20 (0.06-0.66)
Normal	75/184	106/178	NE	30.23	0.50 (0.37-0.67)
Baseline ECOG PS score					
0	34/90	40/71	NE	43.96	0.47 (0.30-0.75)
1 or 2	45/105	78/122	NE	20.83	0.49 (0.34-0.70)
Cytogenetic risk at study entry					
High risk	6/17	15/19	NE	16.39	0.24 (0.09-0.62)
Standard risk	55/138	90/147	NE	28.42	0.46 (0.33-0.65)
FISH t(11;14)					
Abnormal	18/51	30/55	NE	34.10	0.41 (0.23-0.75)
Normal	13/44	32/52	NE	20.27	0.33 (0.17-0.63)



The addition of DARA to VCd provided MOD-PFS benefit across preplanned relevant subgroups

NE, not estimable; FISH, fluorescence in situ hybridization. MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death.

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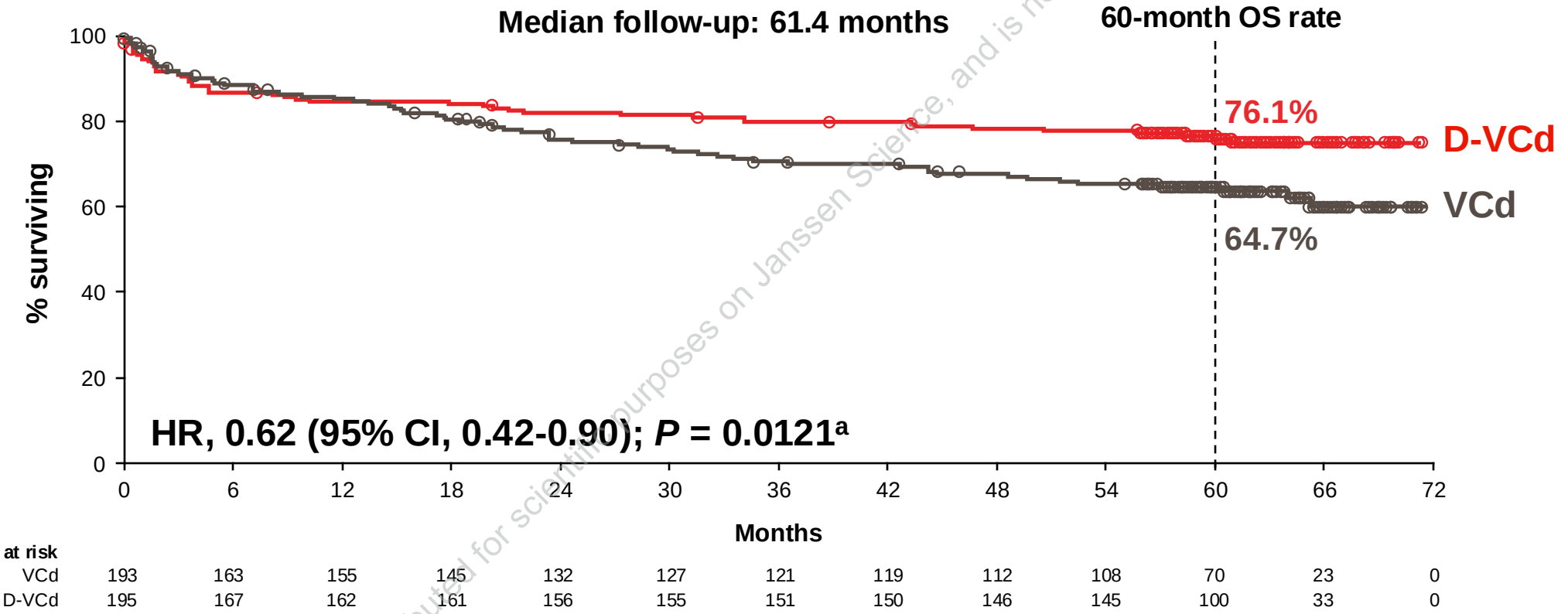
ANDROMEDA: Overall Survival



The addition of DARA to VCd significantly improved OS versus VCd despite cross-over in >70% of VCd patients who received DARA as subsequent therapy, highlighting the importance of DARA use in frontline treatment

[a]Crossing the prespecified stopping boundary of 0.0163.

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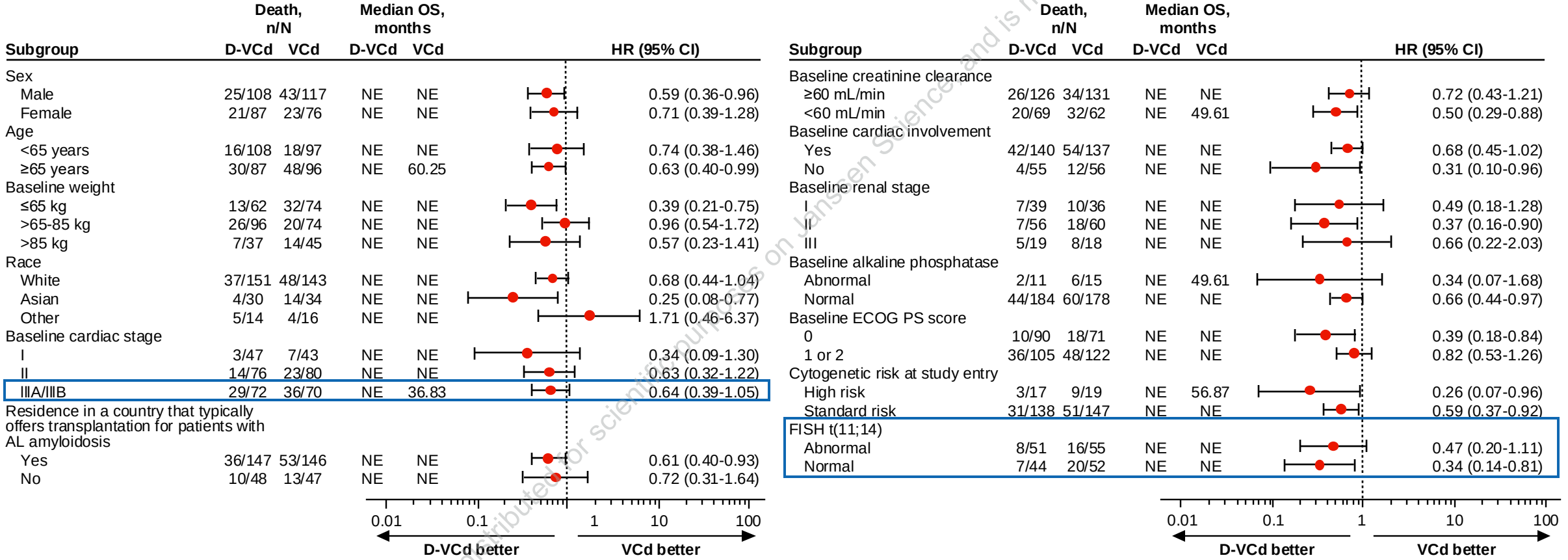
ANDROMEDA: Prespecified Subgroup Analysis of Overall Survival



The addition of DARA to VCd provided OS benefit across preplanned relevant subgroups

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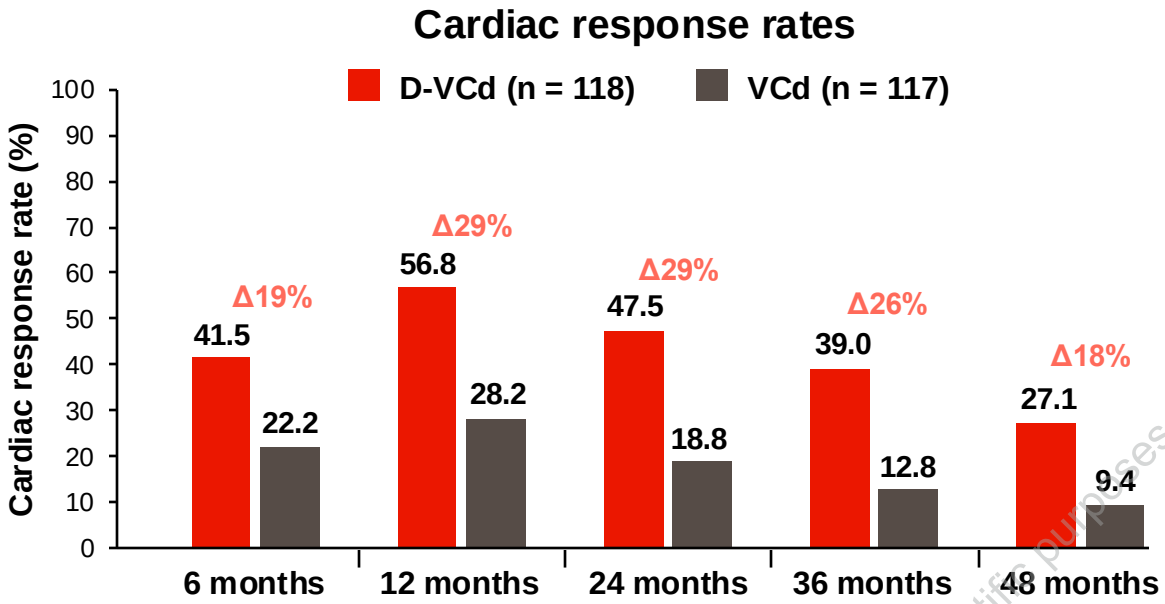
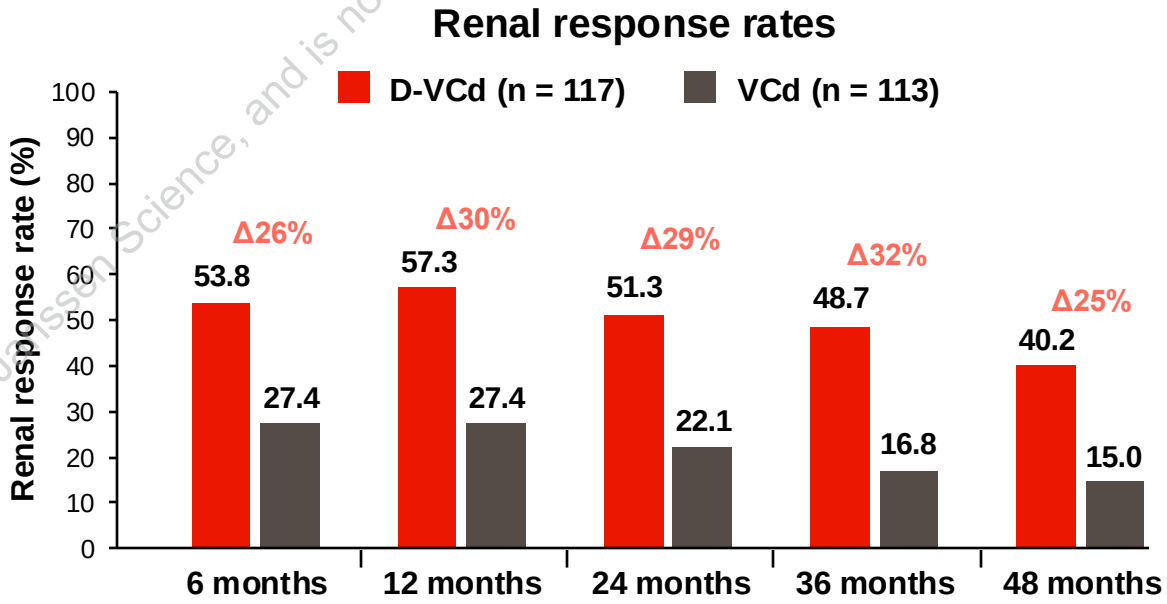
ANDROMEDA: Cardiac and Renal Response Rates





Graded response, %	D-VCd	VCd
Cardiac CR	40.7	13.7
Cardiac ≥VGPR	64.4	31.6

The addition of DARA to VCd led to 2 to 3 times higher cardiac and renal response rates versus VCd across study time points

CarCR, cardiac complete response. Both cardiac and renal response rates were determined by independent review committee assessment. Cardiac and renal response rates at a specific time point were calculated as the number of patients who had cardiac/renal response at the specific time point within a 1-month window; the denominator remained unchanged at each time point and represents the response-evaluable population. The cardiac/renal response rates displayed here are results without censoring non–cross-resistant anti–plasma therapy.

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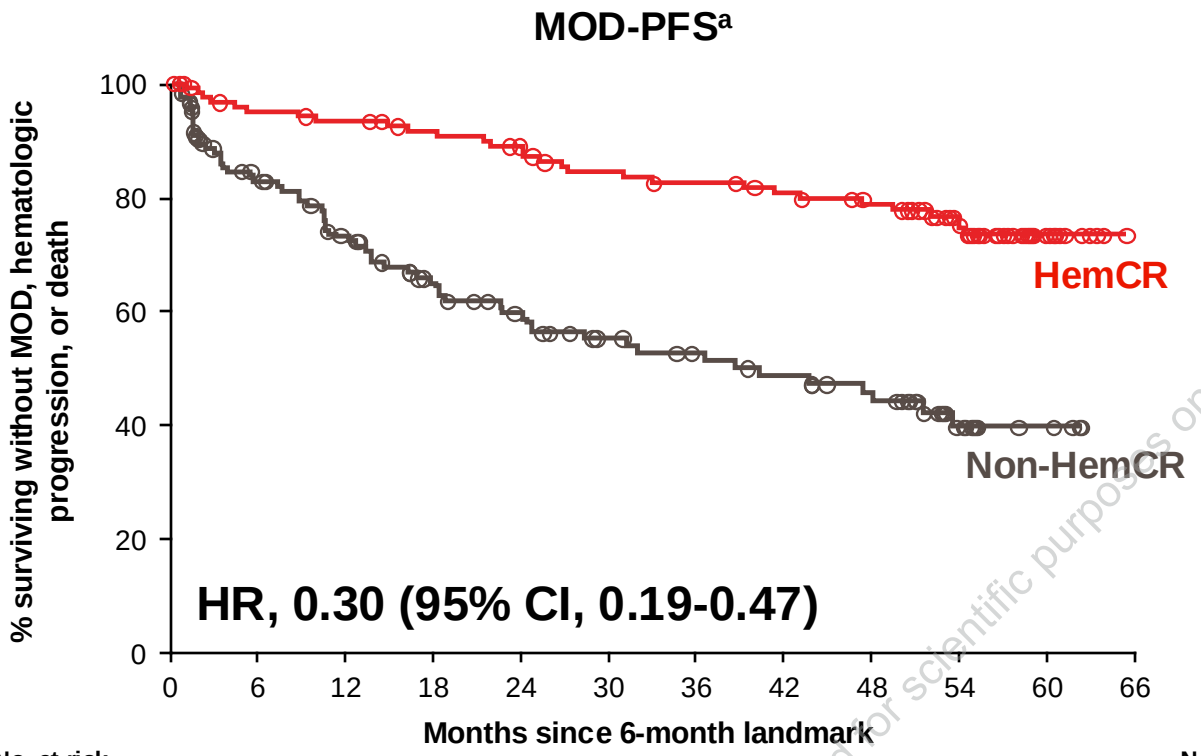
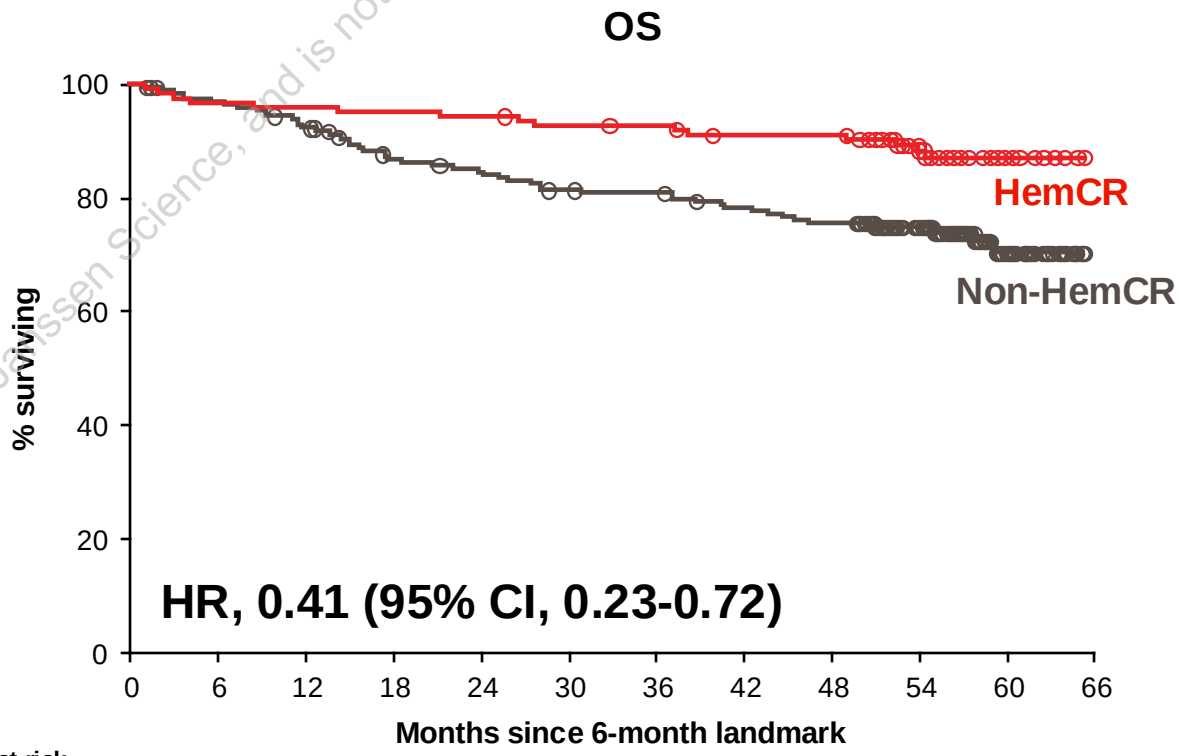
ANDROMEDA: Major Organ Deterioration (MOD)–PFS and Overall Survival by Hematologic Complete Response



No. at risk												
HemCR	125	112	109	104	97	92	88	84	79	48	16	0
Non-HemCR	149	98	81	65	53	44	39	35	29	15	4	0



No. at risk												
HemCR	127	123	122	121	120	117	116	112	112	80	29	0
Non-HemCR	203	194	184	167	162	155	153	146	141	90	27	0

Achieving HemCR was associated with improved MOD-PFS and OS from the 6-month landmark analysis and beyond

[a]MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death. Kaplan–Meier estimates in those patients who achieved HemCR versus those who did not achieve HemCR.

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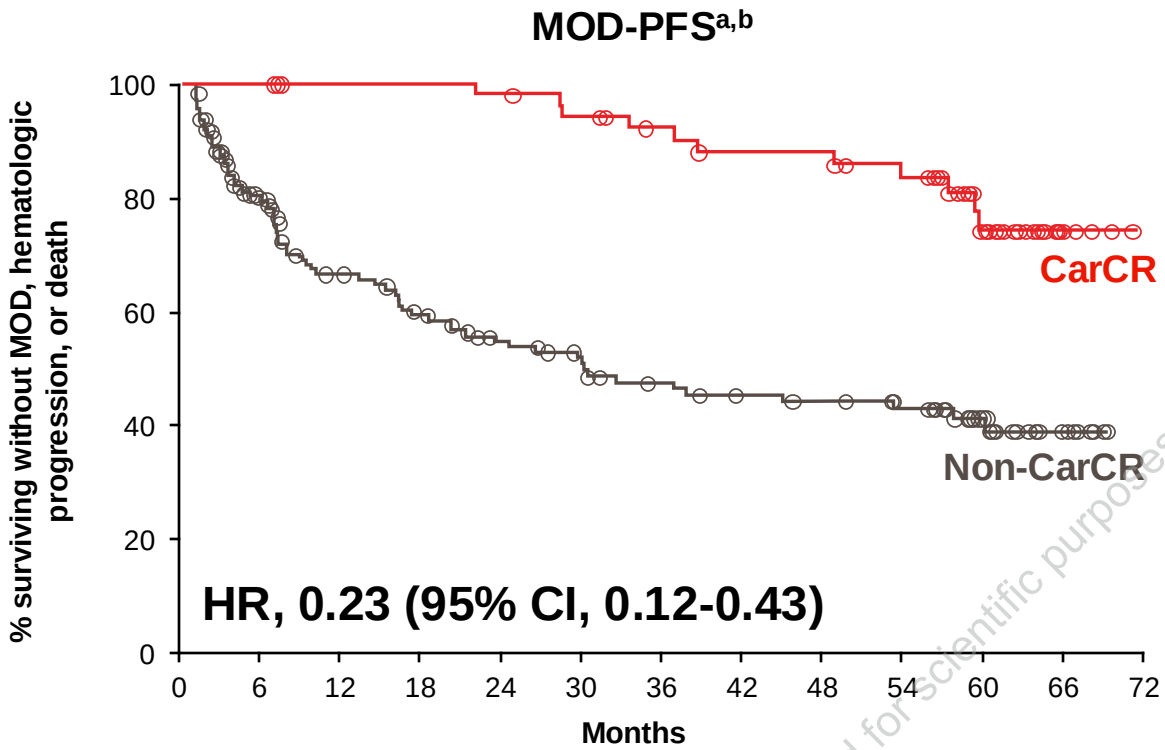
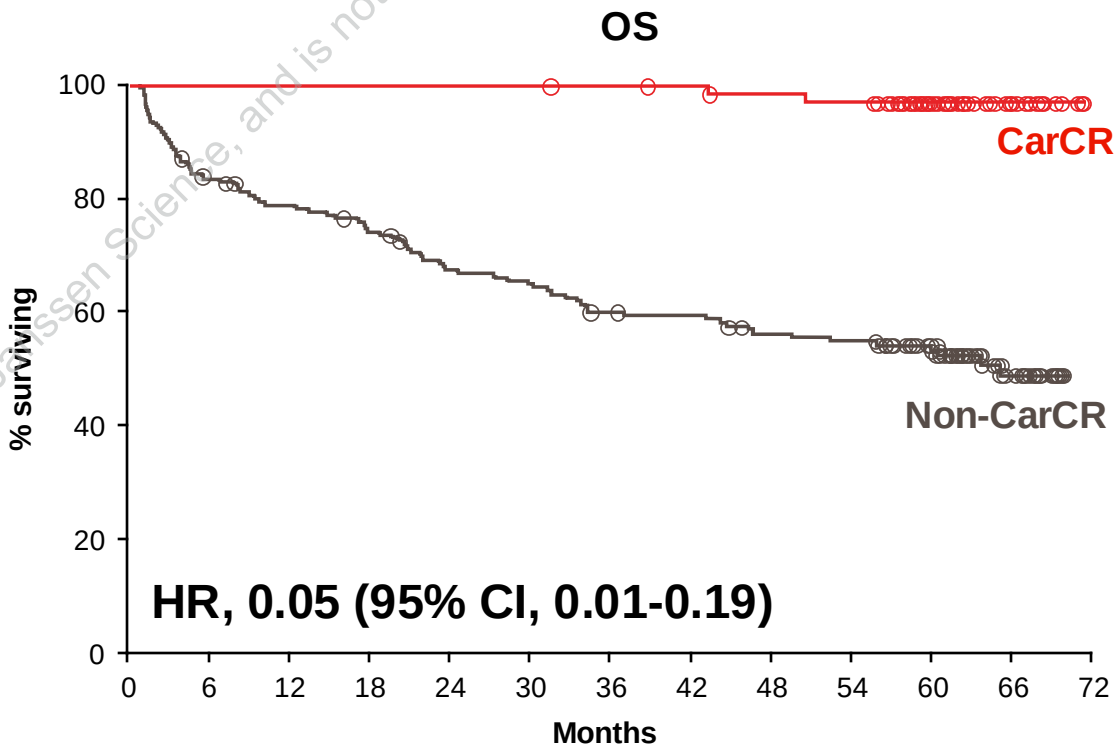
ANDROMEDA: Major Organ Deterioration (MOD)–PFS and Overall Survival by Cardiac Complete Response



No. at risk													
CarCR	56	56	53	53	52	49	44	41	41	37	21	4	0
Non-CarCR	179	112	79	67	56	49	43	39	37	34	19	7	0



No. at risk													
CarCR	64	64	64	64	64	64	63	62	60	59	42	13	0
Non-CarCR	171	140	130	121	107	103	94	92	85	83	57	20	0

Achieving CarCR was associated with improved MOD-PFS and OS

[a]MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death. [b]When assessing the correlation between MOD-PFS and CarCR, MOD-PFS was censored for non–cross-resistant subsequent therapy. There were 8 patients who achieved CarCR after receiving non–cross-resistant subsequent therapy; these 8 patients were treated as non-CarCR for the evaluation of MOD-PFS.

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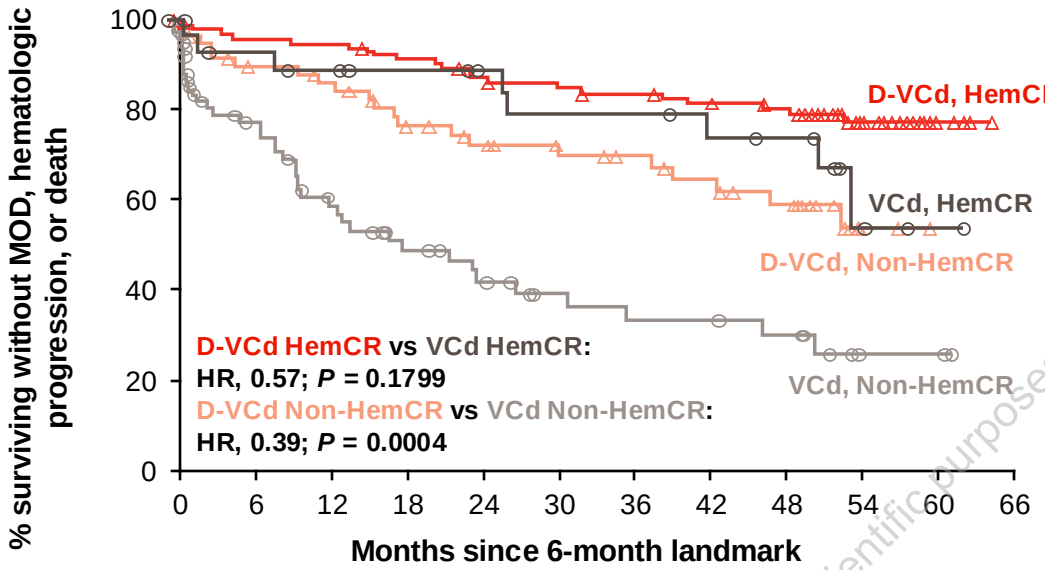
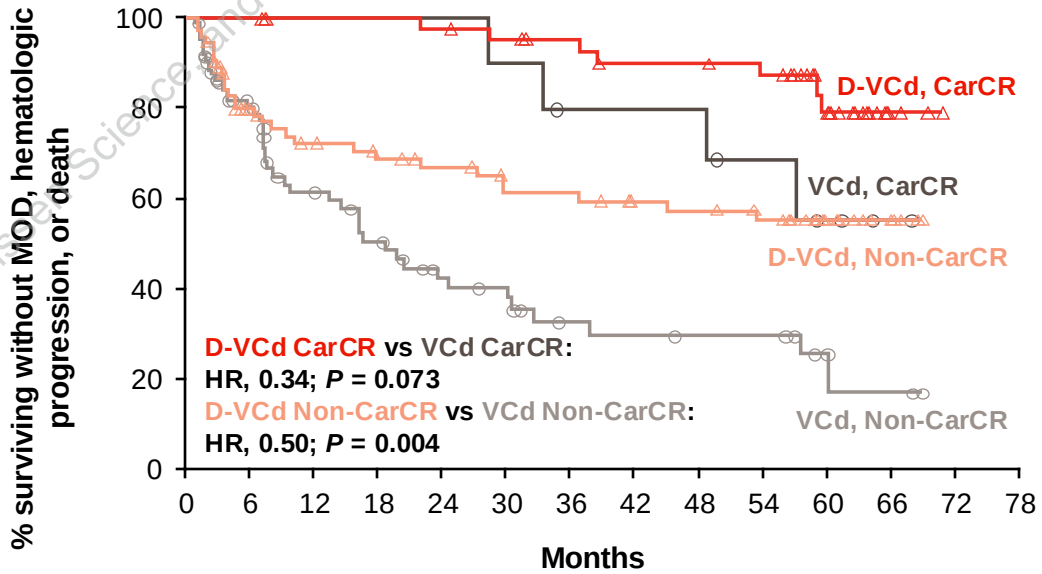
ANDROMEDA: Major Organ Deterioration (MOD)–PFS by Hematologic and Cardiac Complete Response

MOD-PFS[a] by HemCR[b]



No. at risk												
VCd, HemCR	29	24	22	20	19	16	16	15	13	5	1	0
VCd, Non-HemCR	88	48	35	24	20	13	12	11	9	5	3	0
D-VCd, HemCR	96	88	87	84	78	76	72	69	66	43	15	0
D-VCd, Non-HemCR	61	50	46	41	33	31	27	24	20	10	1	0

MOD-PFS[a] by CarCR[c]



No. at risk														
VCd, CarCR	11	11	10	10	10	9	7	7	7	5	3	1	0	0
VCd, Non-CarCR	106	61	35	27	19	17	11	10	9	9	4	2	0	0
D-VCd, CarCR	45	45	43	43	42	40	37	34	34	32	18	3	0	0
D-VCd, Non-CarCR	73	51	44	40	37	32	32	29	28	25	15	5	0	0

- **Achieving HemCR or CarCR was associated with improved MOD-PFS**
- **DARA treatment effect was demonstrated in both Hem/Car CR and non-CR patients**

[a]MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death. [b]6-month landmark analysis. [c]When assessing the correlation between MOD-PFS and CarCR, MOD-PFS was censored for non–cross-resistant subsequent therapy. There were 8 patients who achieved CarCR after receiving non–cross-resistant subsequent therapy; these 8 patients were treated as non-CarCR for the evaluation of MOD-PFS.

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ANDROMEDA: Safety[a]

Event, n (%)	D-VCd (n = 193)		VCd (n = 188)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Peripheral edema	71 (36.8)	6 (3.1)	68 (36.2)	11 (5.9)
Diarrhea	70 (36.3)	11 (5.7)	57 (30.3)	7 (3.7)
Constipation	70 (36.3)	3 (1.6)	54 (28.7)	0
Peripheral sensory neuropathy	65 (33.7)	5 (2.6)	37 (19.7)	4 (2.1)
Fatigue	55 (28.5)	10 (5.2)	53 (28.2)	6 (3.2)
Nausea	55 (28.5)	3 (1.6)	52 (27.7)	0
Upper respiratory tract infection	**50 (25.9)**	**1 (0.5)**	**21 (11.2)**	**1 (0.5)**
Anemia	49 (25.4)	8 (4.1)	44 (23.4)	9 (4.8)
Insomnia	49 (25.4)	0	47 (25.0)	2 (1.1)
Dyspnea	49 (25.4)	5 (2.6)	32 (17.0)	6 (3.2)
Lymphopenia	37 (19.2)	25 (13.0)	28 (14.9)	19 (10.1)
Hypokalemia	26 (13.5)	4 (2.1)	28 (14.9)	10 (5.3)
Pneumonia	**24 (12.4)**	**16 (8.3)**	**12 (6.4)**	**8 (4.3)**
Neutropenia	21 (10.9)	10 (5.2)	12 (6.4)	5 (2.7)
Cardiac failure	**18 (9.3)**	**12 (6.2)**	**10 (5.3)**	**5 (2.7)**
Syncope	16 (8.3)	12 (6.2)	12 (6.4)	12 (6.4)

Safety data were consistent with the known safety profiles for VCd and DARA

[a]The safety population included patients who received ≥1 dose of study treatment.
Adverse events of any grade that were reported in >25% of patients in either treatment group and grade 3 or 4 adverse events that were reported in ≥5% of patients in either treatment group are listed.

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ANDROMEDA: Conclusions

- With 5 years of follow-up, D-VCd was superior to VCd and had a manageable safety profile:
  - Substantially deeper HemCR rates (59.5% vs 19.2%) and more rapid responses (67.5 vs 85.0 days)
  - Cardiac and renal response rates were 2 to 3 times higher, translating into better MOD-PFS (HR, 0.44) and OS (HR, 0.62)
  - Improvement in MOD-PFS and OS was generally consistent across preplanned relevant subgroups
  - Achievement of HemCR (MOD-PFS: HR, 0.30; OS: HR, 0.41) or CarCR (MOD-PFS: HR, 0.23; OS: HR, 0.05) correlated with favorable long-term outcomes
  - DARA treatment effect on MOD-PFS was demonstrated in both Hem/Car CR and non-CR patients
- The addition of DARA to VCd significantly improved OS versus VCd despite DARA cross-over in >70% of VCd patients who received subsequent therapy, highlighting the importance of frontline D-VCd

ANDROMEDA shows that the addition of DARA to VCd improves survival for patients with newly diagnosed AL amyloidosis and reaffirms frontline D-VCd as the SoC in this difficult-to-treat disease

MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death.

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ANDROMEDA: Acknowledgments

- Patients who participated in this study
- Investigators and staff members at the study sites
- Members of the independent data monitoring committee
- Members of the independent review committee
- Staff members involved in data collection and analyses

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