Cardiac Risk Factors and Cardiac Events in Patients with Newly Diagnosed Amyloid Light Chain (AL) Amyloidosis from the Phase 2 AQUARIUS Study of Daratumumab (DARA) plus Bortezomib, Cyclophosphamide, and Dexamethasone (D-VCd)

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AQUARIUS: Introduction

- Systemic amyloid light chain (AL) amyloidosis is characterized by deposition of amyloid fibrils, derived from the immunoglobulin light chains produced by clonal CD38+ plasma cells in vital organs, leading to serious organ dysfunction
  - Cardiac involvement is a major risk factor for poor survival[1]
- Based on the phase 3 ANDROMEDA study, D-VCd was established as the only approved regimen for newly diagnosed AL amyloidosis. D-VCd significantly improved hematologic responses, organ responses, major organ deterioration progression-free survival (MOD-PFS), and OS vs VCd alone[2]
- The phase 2 AQUARIUS study (NCT05250973) evaluated the cardiac safety of 2 different D-VCd treatment schedules in patients with newly diagnosed systemic AL amyloidosis with cardiac involvement

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AL, amyloid light chain; D-VCd, daratumumab, bortezomib, cyclophosphamide, dexamethasone; MOD-PFS, major organ deterioration progression-free survival; VCd, bortezomib, cyclophosphamide, dexamethasone.

1. Staron A, et al. *Blood Cancer J* 2021;11(8):139. 2. Kastritis E, et al. *N Engl J Med* 2021;385(1):46-58.

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AQUARIUS: Study Design (Cardiac Safety Analysis Set)[1,2]

Cohort 1: (N = 119)[a]

Key eligibility criteria:

- Newly diagnosed AL amyloidosis
- No prior therapy for AL amyloidosis or MM
- Mayo cardiac stage II-IIIA ± other organs involved

Cohort 2: (N = 23)

Key eligibility criteria:

- Newly diagnosed AL amyloidosis with ≥1 impacted organ. Cardiac Safety Analysis includes only those participants with cardiac involvement
- No prior therapy for AL amyloidosis or MM
- Self-identified racial and ethnic minorities[b]

2:1 randomization

Follow-up: 12 cycles or 12 months from first dose

Cohort 1: Arm A — **Daratumumab + Immediate VCd (n = 80)**
- **Daratumumab[c]**
- **VCd:** QW Cycles 1-6

Cohort 1: Arm B — **Daratumumab + Deferred VCd (n = 39)**
- **Daratumumab[c]**
- **VCd:** QW Cycles 4-9

Cohort 2: Daratumumab + Immediate VCd (n = 23)
- **Daratumumab[c]**
- **VCd:** QW Cycles 1-6

28-day cycles

Primary endpoint:

- **Cohort 1**: Safety (Cardiac events)
- **Cohort 2**: Daratumumab maximum trough concentration (C3D1 pre-dose)

Key secondary endpoints:

- HemCR and ≥VGPR rates
- Time to HemCR and ≥VGPR
- Duration of HemCR and ≥VGPR
- Organ response
- Clinical signs and symptoms of cardiac AL amyloidosis

142 patients with cardiac involvement received ≥1 dose of D + Immediate VCd (n=103) or D + Deferred VCd (n=39)

[a]Stratification based on baseline cardiac stage (Mayo stage II-IIIA). [b]Minimum enrollment of ≥15 Black or African American participants. Minority participants could also be enrolled in Cohort 1 provided participants met eligibility criteria for Cohort 1. [c]Daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20) 1,800mg QW Cycles 1-2, Q2W Cycles 3-6, Q4W Cycles 7+.
Cardiac safety analysis set: all randomized patients from Cohort 1 who received ≥1 dose of any study treatment and all patients from Cohort 2 who had cardiac involvement and received ≥1 dose of any study treatment.
AL, amyloid light chain; HemCR, hematologic complete response; MM, multiple myeloma; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; VCd, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

1. Rosenzweig M, et al. Presented at: ASH Annual Meeting; 9-12 December 2023; San Diego, CA, USA. 2. ClinicalTrials.gov identifier: NCT05250973. Accessed 5 February 2025.

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AQUARIUS: Disposition, Treatment Duration, and Deaths

	D + Immediate VCd	D + Deferred VCd
Disposition, n	103	39
Median treatment duration, months	10.4	10.4
Subjects completing ≥10 cycles, n (%)	81 (78.6)	33 (84.6)
Subjects discontinuing treatment, n (%)	14 (14.6)	7 (17.9)
Death	3 (2.9)	3 (7.7)
Adverse event	3 (2.9)	1 (2.6)
Other	9 (8.7)	3 (7.7)
Subjects discontinuing study, n (%)	8 (7.8)	4 (10.3)
Death	6 (5.8)	3 (7.7)
Withdrawal by subject	2 (1.9)	1 (2.6)

- 2/9 deaths occurred within 60 days of treatment start
- Both were in the immediate VCd group, cardiac-related, and unrelated to treatment

Median treatment duration and proportion completing ≥10 cycles were similar between groups

D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); VCd, bortezomib, cyclophosphamide, dexamethasone.

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AQUARIUS: Baseline Characteristics

Characteristic	D + Immediate VCd n = 103	D + Deferred VCd n = 39
Age, mean (SD)	63.9 (9.99)	65.6 (12.25)
Female, n (%)	46 (44.7)	19 (48.7)
Race, n (%)		
Asian	18 (17.5)	8 (20.5)
Black/African American	16 (15.5)	0
White	66 (64.1)	29 (74.4)
Not reported/Other	3 (2.9)	2 (5.1)
Ethnicity, n (%)		
Hispanic	12 (11.7)	2 (5.1)
Not Hispanic/not reported	91 (88.3)	37 (94.9)
Baseline NYHA class, n (%)		
I	29 (28.2)	7 (17.9)
II	65 (63.1)	27 (69.2)
IIIA	9 (8.7)	5 (12.8)

Characteristic	D + Immediate VCd n = 103	D + Deferred VCd n = 39
Organ involvement, n (%)		
Kidney	70 (68.0)	20 (51.3)
Soft tissue	18 (17.5)	10 (25.6)
Nerve	15 (14.6)	3 (7.7)
Liver	9 (8.7)	7 (17.9)
Mayo stage,[a] n (%)		
I	2 (1.9)	2 (5.1)
II	64 (62.1)	21 (53.8)
IIIa	36 (35.0)	14 (35.9)
IIIb	1 (1.0)	2 (5.1)
Renal stage,[b] n (%)		
I	47 (47.0)	21 (53.8)
II	42 (42.0)	14 (35.9)
III	11 (11.0)	4 (10.3)

Baseline characteristics were generally balanced between the two groups

[a]Per protocol, participants in Mayo I stage at screening were excluded from Cohort 1 and those in Mayo IIIb stage were excluded from the study. However, some improved from Mayo II to Mayo I or worsened from Mayo IIIa to Mayo IIIb prior to baseline. [b]Renal stage was evaluated in 100 participants in the D + Immediate VCd group.
D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); NYHA, New York Heart Association Functional Classification; VCd, bortezomib, cyclophosphamide, dexamethasone.

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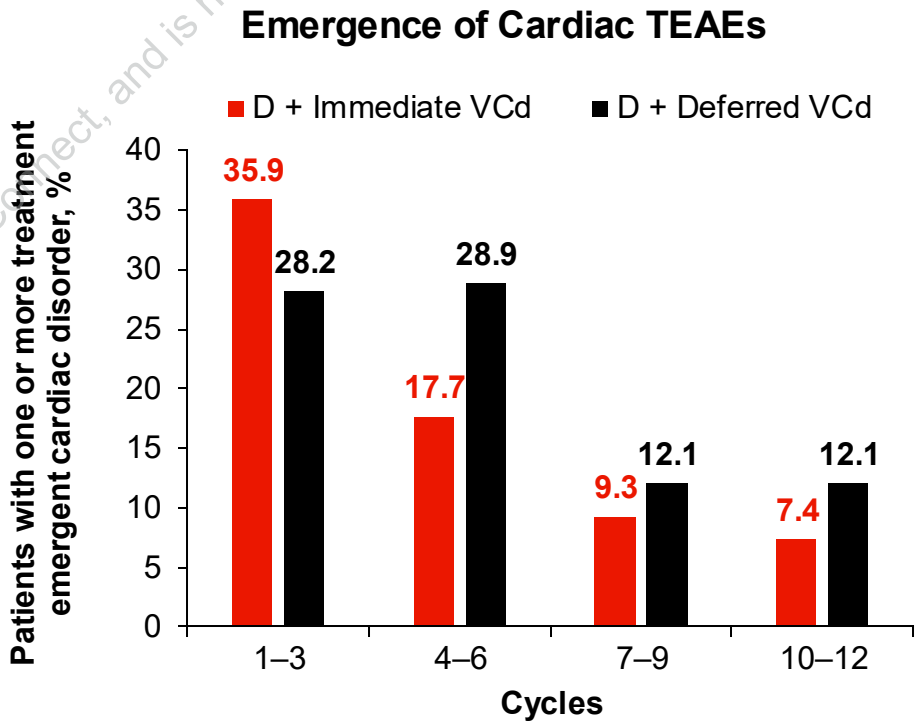
AQUARIUS: Cardiac Events (Primary Endpoint)

Subjects, n (%)	D + Immediate VCd n = 103	D + Deferred VCd n = 39
Subjects with ≥1 cardiac TEAE	50 (48.5)	24 (61.5)
Cardiac TEAEs of any grade (≥5% rates)		
Cardiac failure	28 (27.2)	7 (17.9)
Atrial fibrillation	7 (6.8)	2 (5.1)
Sinus tachycardia	3 (2.9)	2 (5.1)
Restrictive cardiomyopathy	11 (10.7)	4 (10.3)
Palpitations	9 (8.7)	3 (7.7)
Right ventricular dysfunction	5 (4.9)	3 (7.7)
Serious cardiac TEAEs	**8 (7.8)**	**3 (7.7)**
Cardiac failure	6 (5.8)	1 (2.6)
Atrial fibrillation	1 (1.0)	0
Cardiac arrest	1 (1.0)	0
Myocardial infarction	1 (1.0)	0
Myocardial injury	1 (1.0)	0
Tricuspid valve incompetence	0	1 (2.6)
Ventricular extrasystoles	0	1 (2.6)



There were similar rates of serious cardiac TEAEs in both groups. Higher rates correlate with the start of VCd. Cardiac TEAE rates were low for both groups in cycles 7–9 and 10–12

D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); TEAE, treatment-emergent adverse event; VCd, bortezomib, cyclophosphamide, dexamethasone.

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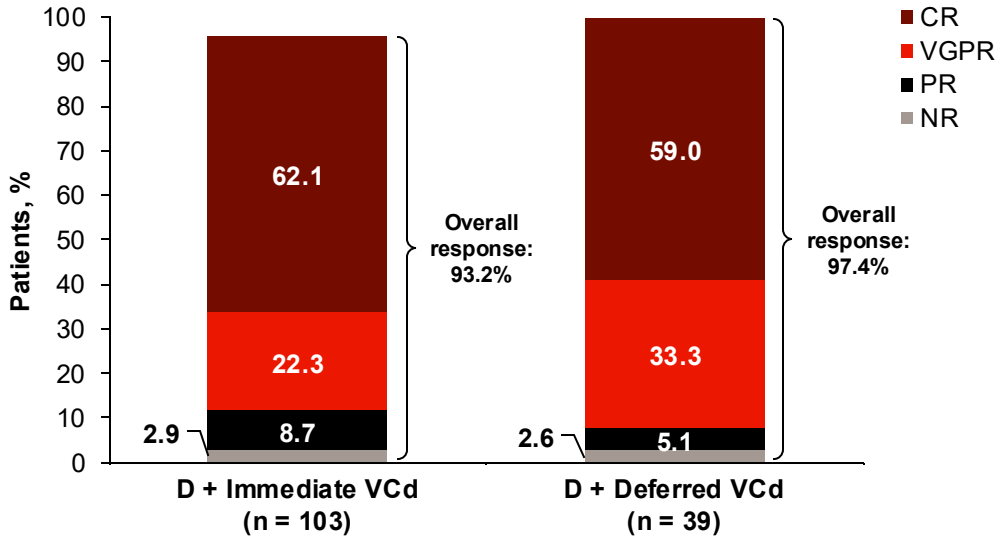
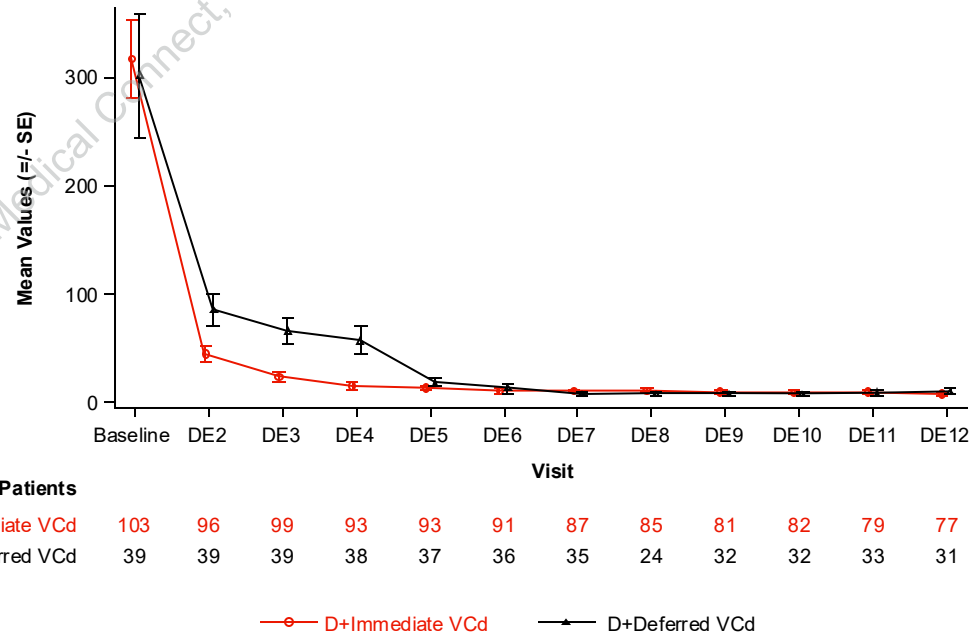
AQUARIUS: Hematologic Response

Best Hematologic Response



Time to response	D + Immediate VCd	D + Deferred VCd
Patients with CR, n	64	23
Median time to CR, days[a]	63.5	113.0
Patients with VGPR or CR, n	87	36
Median time to VGPR, days[b]	29.0	72.5

dFLC Over Time



CR rates were similar in both groups. Median time to CR was 64 days for the immediate VCd group and 113 days for the deferred VCd group

[a]Time from first dose date up to the first response of complete hematologic response is summarized. [b]Time from first dose date up to the first response of complete hematologic response or VGPR, whichever is earlier, is summarized.
[c]n (%) is displayed as number of subjects who achieved cardiac response at 6 months / number of subjects who are cardiac response evaluable and have at least one NYHA or central lab NT-proBNP assessment at 6 months).
Note: Per protocol, DEs were done on or around Day 1 of each cycle.
CR, complete response; D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); DE, disease evaluation; dFLC, difference in free light chains; NR, no response; PR, partial response; VCd, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

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AQUARIUS: Cardiac Response

Summary of Cardiac Response Rate at 6 Months Based on Investigator Assessment

	D + Immediate VCd		D + Deferred VCd	
	n (%)	95% CI[a] for %	n (%)	95% CI[a] for %
Cardiac response-evaluable patients	85		34	
Cardiac response at 6 months[b]	47 (55.3)	(44.1–66.1)	20 (58.8)	(40.7–75.4)

Cardiac response rates were similar between the immediate VCd group and the deferred VCd group

[a]95% CIs are based on Clopper-Pearson exact test. [b]n (%) is displayed as number of subjects who achieved cardiac response at 6 months / number of subjects who are cardiac response-evaluable and have at least one NYHA or central lab NT-proBNP assessment at 6 months).
D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); VCd, bortezomib, cyclophosphamide, dexamethasone.

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AQUARIUS: Cardiac Events Characterization

- **Cardiac TEAEs (any grade) were more frequent in Mayo Stage III patients, independent of treatment schedule**

Cardiac TEAEs (any grade), stratified by Mayo Stage

Cardiac stage	D + Immediate VCd	D + Deferred VCd
Mayo Stage II	35.9%	57.1%
Mayo Stage III	73.0%	68.8%

- **Major cardiac TEAEs[a] (Grade >3/Serious): 30 events in 20 patients**
  - 28 events attributed to underlying cardiac amyloid disease, per independent committee.
  - Patients with major cardiac TEAEs had worse baseline characteristics vs the rest:

Baseline characteristics	Patients with major cardiac TEAEs n = 20	Patients without major cardiac TEAEs n = 122
Mayo Stage IIIa, n (%)	14 (70.0)	36 (29.5)
NT-ProBNP (ng/L), median	4862	1723
6-minute walk test (m),[b] median	318.8	363.0
Overall cardiac signs & symptoms score, mean (SD)	7.7 (4.4)	4.7 (3.6)
GLS %,[c] median (greater absolute value = better function)	–8.8	–13.7
E Prime Lateral,[d] median (greater value = better function)	4.4	6.1

Cardiac events occurred more frequently among patients with more advanced cardiac disease at baseline

[a]Major cardiac TEAEs included all clinically relevant Grade 3-5 or Serious Cardiac AEs (except for solitary lab findings). All Major cardiac TEAEs were reviewed by an independent committee to assess causality. [b]116 patients without major cardiac TEAEs. [c]19 patients with major cardiac TEAEs; 121 patients without major cardiac TEAEs. [d]17 patients with major cardiac TEAEs; 115 patients without major cardiac TEAEs.
D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); GLS, global longitudinal strain; HS, high sensitivity; NT-proBNP, N-terminal pro-brain natriuretic peptide; TEAE, treatment-emergent adverse event; VCd, bortezomib, cyclophosphamide, dexamethasone.

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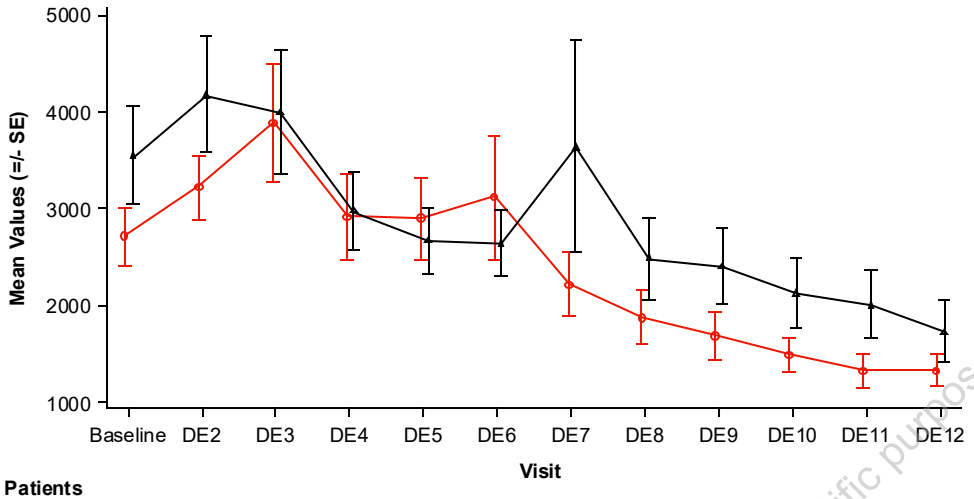
AQUARIUS: Cardiac Biomarkers Over Time

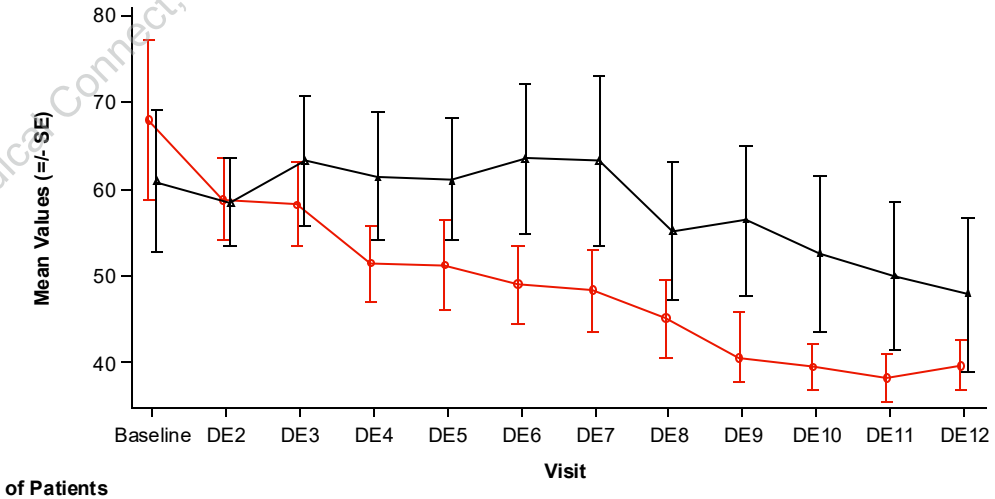
Mean (+/- SE) Values for NT-proBNP (ng/L) Over Time



No. of Patients												
D+immediate VCd	103	96	99	92	93	91	86	85	82	82	78	77
D+deferred VCd	39	39	39	37	36	36	35	34	32	31	33	31

D+immediate VCd D+deferred VCd

Mean (+/- SE) Values for High-Sensitivity Troponin T (ng/L) Over Time



No. of Patients												
D+immediate VCd	103	91	99	92	93	89	86	85	82	82	77	77
D+deferred VCd	39	39	39	38	37	35	34	34	33	31	32	31

D+immediate VCd D+deferred VCd

NT-proBNP and HS troponin T levels improved with both daratumumab + immediate and deferred VCd

Note: Per protocol, DEs were done on or around Day 1 of each cycle.
D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); DE, disease evaluation; HS, high sensitivity; NT-proBNP, N-terminal pro-brain natriuretic peptide; VCd, cyclophosphamide-bortezomib-dexamethasone.

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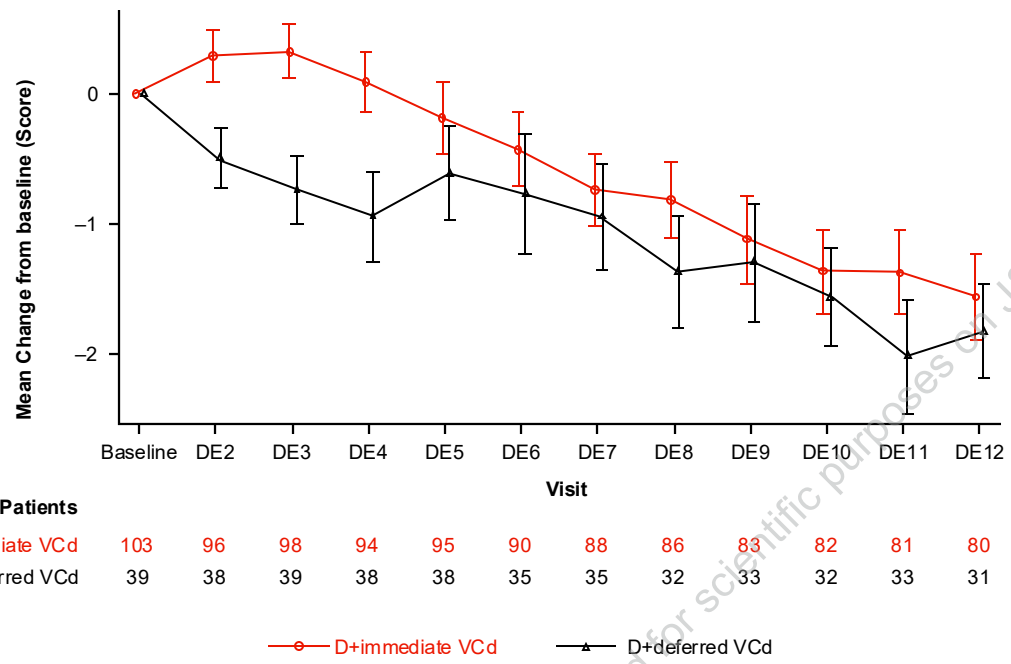
AQUARIUS: Cardiac Signs & Symptoms Over Time



- Assessed at baseline and monthly
- Prespecified list of signs and symptoms, including the categories of cardiac arrhythmia, heart failure, coronary artery disorders, and other cardiac signs and symptoms
- Score is weighted according to severity of signs and symptoms

Cardiac signs & symptoms improved with both daratumumab + immediate and deferred VCd

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Note: Per protocol, DEs were done on or around Day 1 of each cycle.
AL, amyloid light chain; D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); DE, disease evaluation; VCd, cyclophosphamide-bortezomib-dexamethasone.

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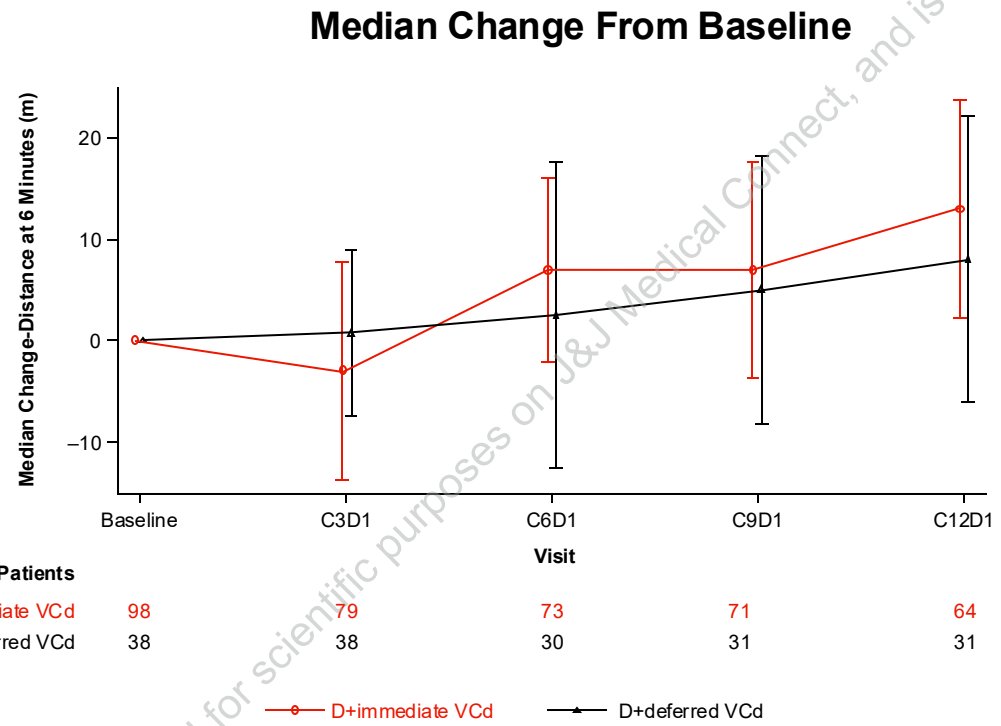
AQUARIUS: 6-Minute Walk Test Total Distance Over Time



6-minute walk distance improved with both daratumumab + immediate and deferred VCd

Note: Per protocol, DEs were done on or around Day 1 of each cycle.
D, daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); DE, disease evaluation; VCd, cyclophosphamide-bortezomib-dexamethasone.

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AQUARIUS: Conclusions

- In patients with newly diagnosed systemic AL amyloidosis and cardiac involvement:
  - The D-VCd regimen (immediate or deferred) had a manageable safety profile with a comparable incidence of cardiac TEAEs between schedules that correlated with the initiation of VCd
  - Cardiac TEAEs occurred more frequently in patients with higher Mayo stage at baseline, and major cardiac TEAEs were correlated with cardiac risk factors at baseline, warranting close clinical surveillance
  - Hematologic response rates were high and generally consistent in both the daratumumab + immediate (93%) and deferred (97%) VCd groups. Time to hematologic response was delayed for the deferred VCd arm
  - Patients' functional outcomes improved over time (6-minute walk test and AL amyloidosis-related cardiac signs & symptoms overall score)

Hematologic response rates were high and D-VCd had a manageable cardiac-related safety profile consistent with previous studies, further supporting its efficacy and safe use in this population

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AL, amyloid light chain; CR, complete response; D-VCd, daratumumab, bortezomib, cyclophosphamide, dexamethasone; TEAE, treatment-emergent adverse event; VCd, bortezomib, cyclophosphamide, dexamethasone.

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AQUARIUS: Acknowledgments

- Patients who participated in this study and their families
- Staff members at the study sites
- Data and safety monitoring committee
- Johnson & Johnson
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- AQUARIUS and this analysis were sponsored by Johnson & Johnson

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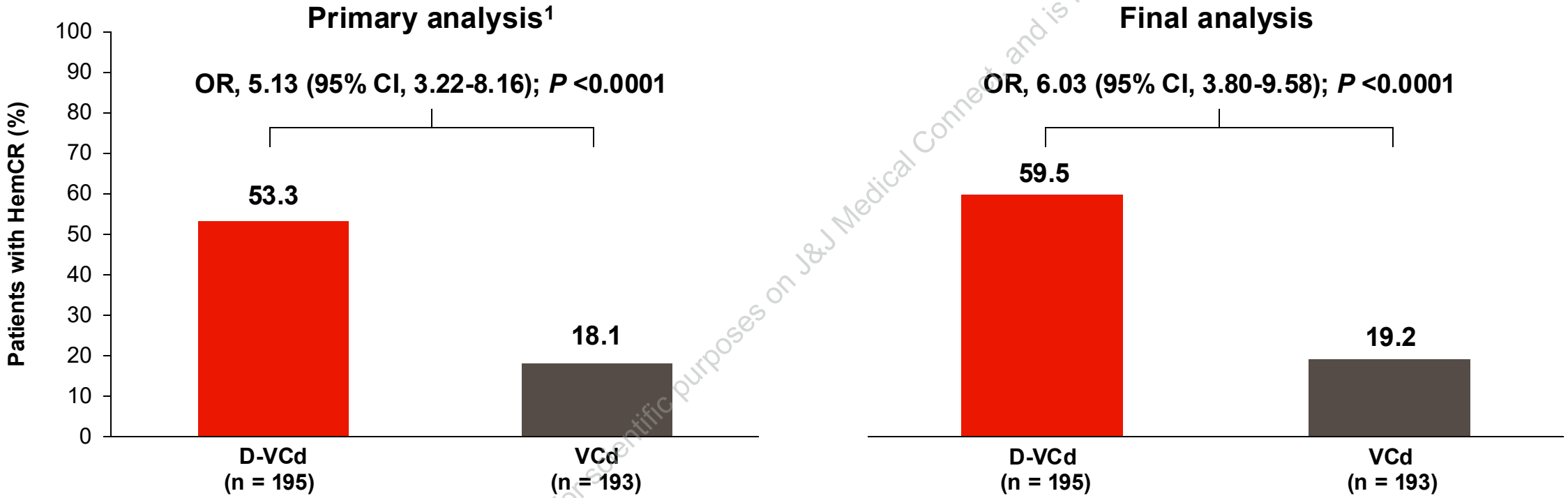
ANDROMEDA: Overall Hematologic Complete Response Rate (Primary Endpoint)



- 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 daratumumab to VCd substantially increased HemCR versus VCd alone

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

HemCR, hematologic complete response; D-VCd, daratumumab, bortezomib, cyclophosphamide, dexamethasone; VCd, bortezomib, cyclophosphamide, dexamethasone.

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