Evaluating the Impact of Cytogenetic Abnormalities on Treatment Outcomes in Patients With AL Amyloidosis: Subanalyses From the ANDROMEDA* Study

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Disclosures: Shaji Kumar

- Served as a consultant for Abbvie, Amgen, BMS, Janssen, Roche-Genentech, Takeda, Astra-Zeneca, Bluebird Bio, Epizyme, Secure Biotherapeutics, Oncopeptides, BeiGene, and Antengene
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Introduction

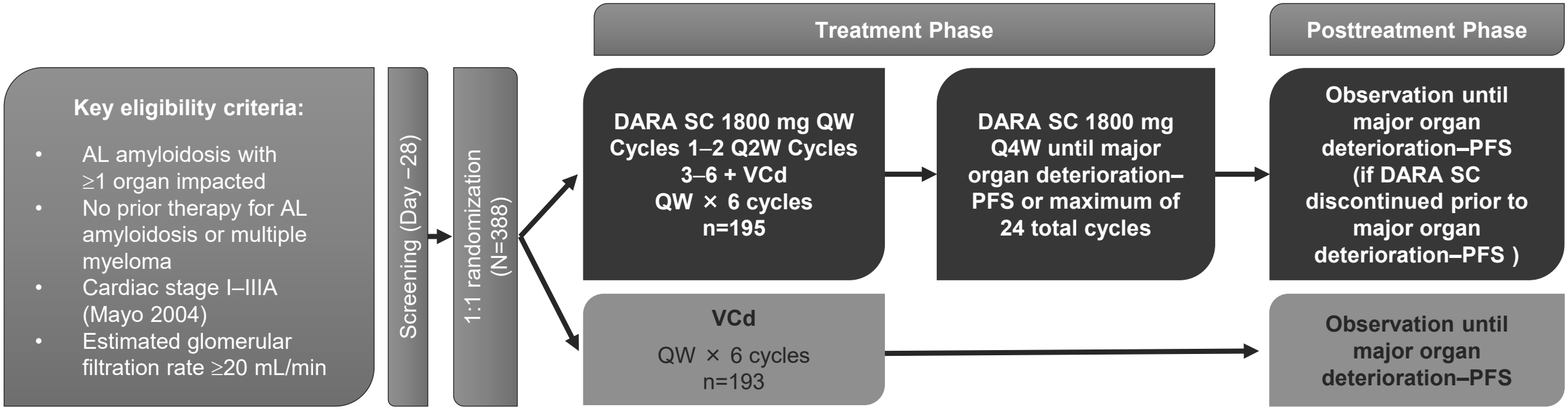
- Like MM, AL amyloidosis is associated with a high frequency of cytogenetic abnormalities; however, the distribution of these differs significantly[1]
  - In patients with AL amyloidosis, t(11;14) is the most common abnormality, occurring in 40–60% of patients, compared with <20% of patients with MM
- The prognostic roles of cytogenetic abnormalities are not as well understood in AL amyloidosis as in MM[1]
  - The prognostic effects of t(11;14) and amp1q21 remain to be elucidated and appear to be affected by treatment regimen
  - To date, no significant prognostic impact of del13q14 or del17p13 has been identified
- Based on the superior efficacy shown versus VCd alone in the ANDROMEDA study, D-VCd became the first approved therapy for the treatment of AL amyloidosis[2,3]
- In these post hoc analyses, we explore outcomes in patients with cytogenetic abnormalities in ANDROMEDA

AL, light chain; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; MM, multiple myeloma; VCd, bortezomib, cyclophosphamide, and dexamethasone.

1. Xu L, Su Y. *Exper Hematol Oncol.* 2021;10(1):43; 2. Kastritis E, et al. *N Engl J Med.* 2021;385(1):46-58; 3. Darzalex injection for subcutaneous use [prescribing information]. Horsham, PA: Janssen Biotech, Inc; Feb 2021.

ANDROMEDA Study Design

- ANDROMEDA is a randomized, open-label, active-controlled, phase 3 study of D-VCd vs 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 hematologic CR rate
- Negative serum and urine immunofixation, and
- Normalization of FLCs and FLCr (not required if iFLC <upper limit of normal)

Secondary endpoints: major organ deterioration–PFS[a], organ response rate, time to hematologic response, OS[b], safety

[a]End-stage cardiac disease, end-stage renal disease, hematologic progression per consensus guidelines, and death; [b]OS data are immature and were not analyzed here.
AL, light chain; CR, complete response; DARA, daratumumab; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; FLC, free light chain; FLCr, free light chain ratio; iFLC, involved free light chain; OS, overall survival; PFS, progression-free survival; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; VCd, bortezomib, cyclophosphamide, and dexamethasone.

Distribution of Cytogenetic Abnormalities

- Of the 388 patients in the ITT population, 321 (82.7%) underwent FISH and/or karyotyping

	D-VCd N=195	VCd N=193	Total N=388
FISH/karyotype test performed, n (%)	155 (79.5)	166 (86.0)	321 (82.7)
Cytogenetic abnormality, n/N (%)			
del17p13	9/134 (6.7)	9/148 (6.1)	18/282 (6.4)
t(11;14)	54/126 (42.9)	56/140 (40.0)	110/266 (41.4)
del13q14	18/111 (16.2)	28/127 (22.0)	46/238 (19.3)
amp1q21	32/126 (25.4)	28/138 (20.3)	60/264 (22.7)
Cytogenetic abnormality + 1 additional chromosome abnormality, n/N (%)			
del17p13	9/133 (6.8)	6/147 (4.1)	15/280 (5.4)
t(11;14)	27/124 (21.8)	30/137 (21.9)	57/261 (21.8)
del13q14	16/111 (14.4)	26/127 (20.5)	42/238 (17.6)
amp1q21	27/126 (21.4)	25/138 (18.1)	52/264 (19.7)

Primary data cut (CCO Feb 2020). Note: Percentages are calculated with the number of patients in each group if test was performed and results are available. For FISH/karyotype, numerator = abnormality of the specified gene plus 1 additional chromosomal abnormality, denominator = total number of patients with the specified chromosome tested plus ≥1 additional gene tested from FISH test and the number of patients who had whole bone marrow karyotype performed.

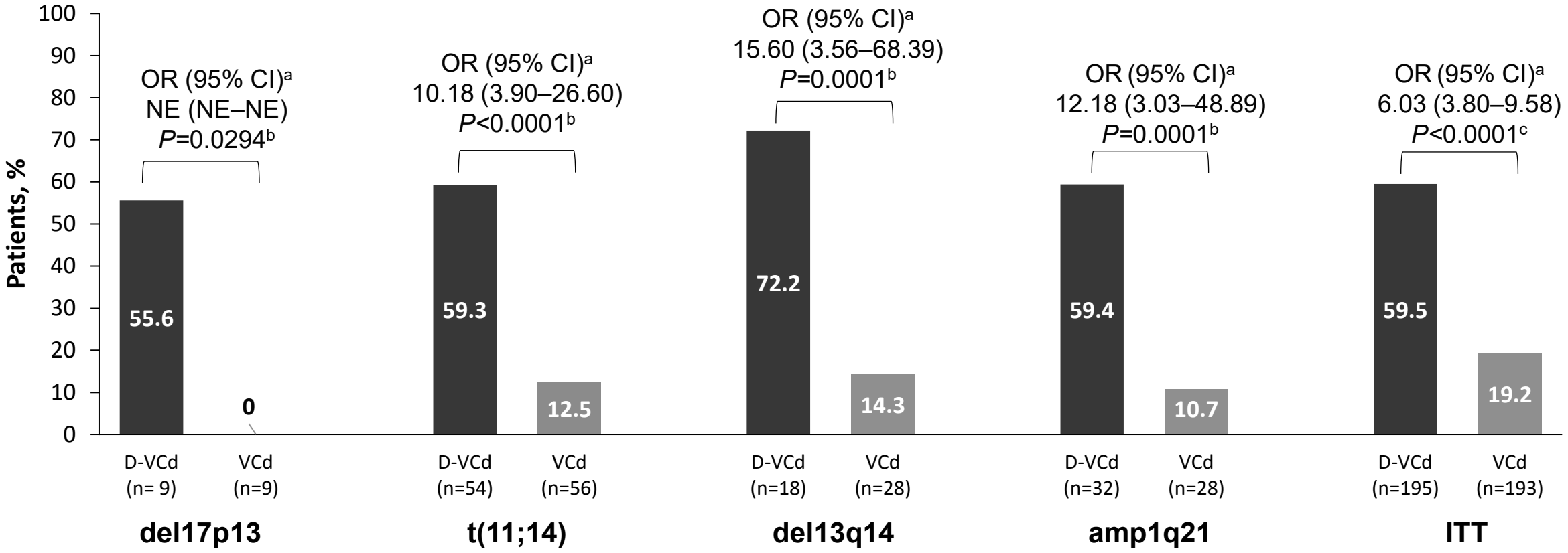
D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; FISH, fluorescence in situ hybridization; ITT, intention-to-treat; VCd, bortezomib, cyclophosphamide, and dexamethasone.

Demographics and Clinical Characteristics

	del17p13 (N=18)	t(11;14) (N=110)	del3q14 (N=46)	amp1q21 (N=60)	ITT (N=388)
Median (range) age, years	66.5 (45–79)	63.0 (41–87)	64.0 (43–79)	65.0 (44–83)	64.0 (34–87)
Male sex, n (%)	7 (38.9)	80 (72.7)	27 (58.7)	30 (50)	225 (58.0)
ECOG performance status					
0	2 (11.1)	46 (41.8)	22 (47.8)	31 (51.7)	161 (41.5)
1	12 (66.7)	53 (48.2)	23 (50.0)	26 (43.3)	192 (49.5)
2	4 (22.2)	11 (10.0)	1 (2.2)	3 (5)	35 (9.0)
Median (range) organs involved	2 (1–6)	2 (1–5)	2 (1–6)	2 (1–6)	2 (1–6)
Organ involvement, n (%)					
Heart	14 (77.8)	85 (77.3)	34 (73.9)	46 (76.7)	277 (71.4)
Kidney	12 (66.7)	65 (59.1)	30 (65.2)	42 (70.0)	229 (59.0)
Cardiac stage					
I	2 (11.1)	19 (17.3)	10 (21.7)	8 (13.3)	90 (23.2)
II	6 (33.3)	45 (40.9)	17 (37.0)	26 (43.3)	156 (40.2)
IIIa	38 (44.4)	44 (40.0)	17 (37.0)	25 (41.7)	134 (34.5)
IIIb	2 (11.1)	2 (1.8)	2 (4.3)	1 (1.7)	8 (2.1)

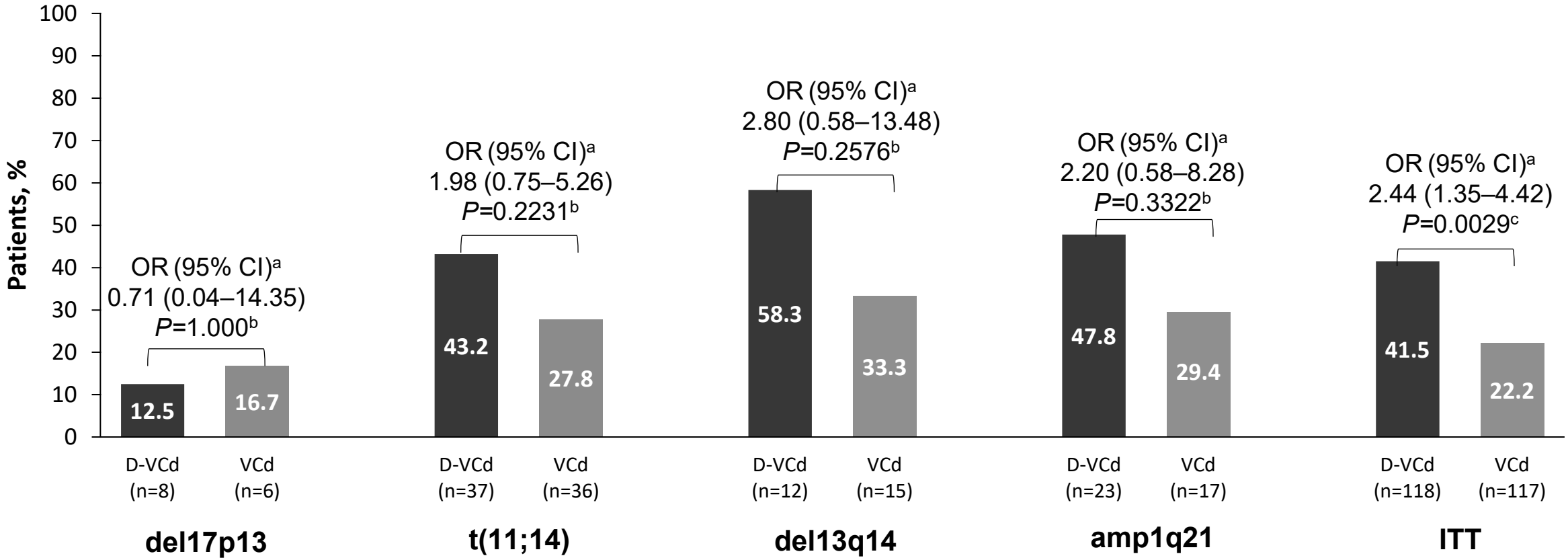
Primary data cut (CCO Feb 2020).
ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat.

At a Median Follow-up of 20.3 Months, Hematologic CR Rate Was Higher With D-VCd Than VCd in all Subgroups



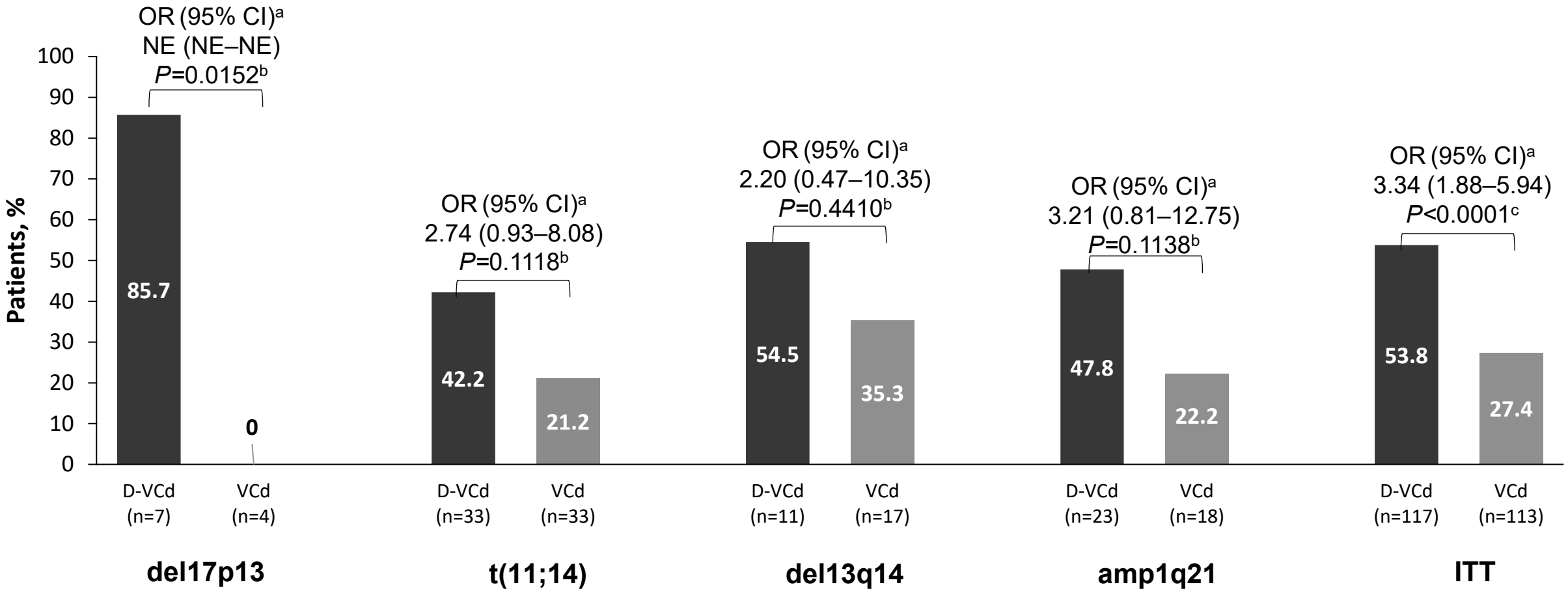
[a]ORs and 95% CI were calculated using Mantel-Haenszel estimates; [b]nominal p-values were calculated from Fisher's exact test; [c]p-value was calculated from Cochran Mantel-Haenszel Chi-Squared test.
12-month landmark data cut (CCO November 2020).
CI, confidence interval; CR, complete response; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; ITT, intention-to-treat; NE, not evaluable; OR, odds ratio; VCd, bortezomib, cyclophosphamide, and dexamethasone.

Rate of Cardiac Response at 6 Months Was Numerically Higher With D-VCd Than With VCd in 3 of 4 Subgroups



[a]ORs and 95% CI were calculated using Mantel-Haenszel estimates; [b]nominal p-values were calculated from Fisher's exact test; [c]p-value was calculated from Cochran Mantel-Haenszel Chi-Squared test.
12-month landmark data cut (CCO November 2020).
12-month landmark data cut (CCO November 2020).
CI, confidence interval; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; ITT, intention-to-treat; OR, odds ratio; VCd, bortezomib, cyclophosphamide, and dexamethasone.

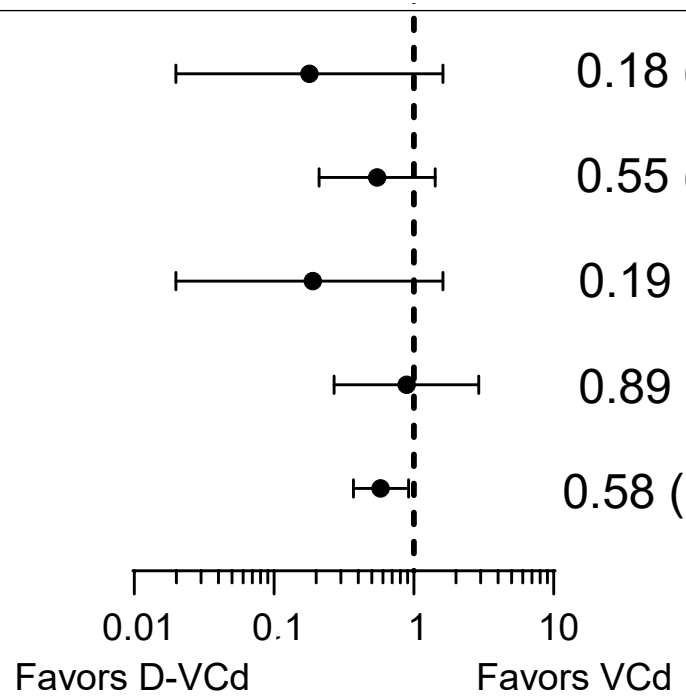
Rate of Renal Response at 6 Months Was Numerically Higher With D-VCd Than With VCd Across All Subgroups



[a]ORs and 95% CI were calculated using Mantel-Haenszel estimates; [b]nominal p-values were calculated from Fisher's exact test; [c]p-value was calculated from Cochran Mantel-Haenszel Chi-Squared test.
12-month landmark data cut (CCO November 2020).
CI, confidence interval; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; ITT, intention-to-treat; NE, not evaluable; OR, odds ratio; VCd, bortezomib, cyclophosphamide, and dexamethasone.

Across All 4 Subgroups, Point Estimates for Major Organ Deterioration–PFS Favored D-VCd Over VCd, Although 95% CIs Were Wide and Crossed 1

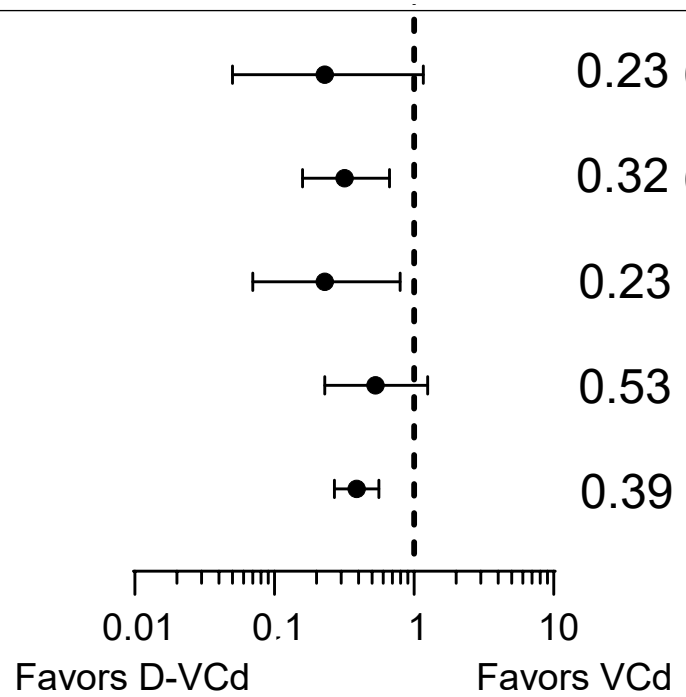
	D-VCd		VCd		
Subgroup	EVT/N (%)	Median, months	EVT/N (%)	Median, months	**HR (95% CI)[a]**
del17p13	1/9 (11.1)	NE	4/9 (44.4)	7.5	0.18 (0.02–1.62)
t(11;14)	7/54 (13.0)	NE	11/56 (19.6)	NE	0.55 (0.21–1.43)
del13q14	1/18 (5.6)	NE	6/28 (21.4)	NE	0.19 (0.02–1.62)
amp1q21	6/32 (18.8)	NE	5/28 (17.9)	NE	0.89 (0.27–2.93)
ITT	34/195 (17.4)	NE	53/193 (27.5)	NE	0.58 (0.36–0.93)[b]



[a]HR and 95% CI were evaluated using a Cox proportional hazards model with treatment as the sole explanatory variable; [b]Hazard ratio and 95% CI are from unstratified weighted Cox proportional hazards model including treatment group as the sole explanatory variable by using IPCW method. Primary data cut (CCO Feb 2020).
CI, confidence interval; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; EVT, event; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; PFS, progression-free survival; VCd, bortezomib, cyclophosphamide, and dexamethasone.

Across All 4 Subgroups, Point Estimates for Major Organ Deterioration–EFS Favored D-VCd Over VCd, Although 95% CIs Were Wide and Some Crossed 1

	D-VCd		VCd		
Subgroup	EVT/N (%)	Median, months	EVT/N (%)	Median, months	**HR (95% CI)[a]**
del17p13	2/9 (22.2)	NE	6/9 (66.7)	7.0	0.23 (0.05–1.17)
t(11;14)	10/54 (18.5)	NE	27/56 (48.2)	8.6	0.32 (0.16–0.67)
del13q14	3/18 (16.7)	NE	14/28 (50.0)	9.4	0.23 (0.07–0.80)
amp1q21	9/32 (28.1)	NE	13/28 (46.4)	13.44	0.53 (0.23–1.25)
ITT	46/195 (23.6)	NE	92/193 (47.7)	8.8	0.39 (0.27–0.56)



[a]HR and 95% CI were evaluated using a Cox proportional hazards model with treatment as the sole explanatory variable; [b]Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl >=60 mL/min or CrCl <60 mL/min) as randomized. Primary data cut (CCO Feb 2020).

CI, confidence interval; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; EFS, event-free survival; EVT, event; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; VCd, bortezomib, cyclophosphamide, and dexamethasone.

In All Subgroups, More Patients in the VCd Group Than the D-VCd Group Went on to Receive ≥1 Subsequent Line of Therapy

	del17p13		t(11;14)		del13q14		amp1q21	
	D-VCd	VCd	D-VCd	VCd	D-VCd	VCd	D-VCd	VCd
Patients with ≥1 subsequent LOT, n/N (%)	1/9 (11.1)	4/9 (44.4)	6/54 (11.1)	35/56 (62.5)	2/18 (11.1)	13/28 (46.4)	5/32 (15.6)	20/28 (71.4)
1 subsequent LOT	0	3/4 (75.0)	5/6 (83.3)	25/35 (71.4)	1/2 (50.0)	9/13 (69.2)	3/5 (60.0)	13/20 (65.0)
>1 subsequent LOT	1 /1 (100.0)	1/4 (25.0)	1/6 (16.7)	10/35 (28.6)	1/2 (50.0)	4/13 (30.8)	2/5 (40.0)	7/20 (35.0)

12-month landmark data cut (CCO November 2020)
D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; LOT, line of therapy; VCd, bortezomib, cyclophosphamide, and dexamethasone.

Impact of t(11;14) on Depth of Response by Treatment

	D-VCd			VCd		
Patients, n (%)	**With t(11;14) N=54**	**Without t(11;14) N=72**	**P-value[a]**	**With t(11;14) N=56**	**Without t(11;14) N=84**	**P-value[a]**
Hematologic CR	32 (59.3)	44 (61.1)	0.8558	7 (12.5)	20 (23.8)	0.1264
≥VGPR	42 (77.8)	58 (80.6)	0.8245	26 (46.4)	47 (56.0)	0.3027

[a]nominal p-values were calculated from Fisher's exact test.
12-month landmark data cut (CCO November 2020).
CR, complete response; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; ≥VGPR, very good partial response or better.

Impact of amp1q21 on Depth of Response by Treatment

	D-VCd			VCd		
Patients, n (%)	**With amp1q21 N=32**	**Without amp1q21 N=94**	**P-value[a]**	**With amp1q21 N=28**	**Without amp1q21 N=110**	**P-value[a]**
Hematologic CR	19 (59.4)	56 (59.6)	1.000	3 (10.7)	21 (19.1)	0.4068
≥VGPR	26 (81.3)	76 (80.9)	1.000	15 (53.6)	55 (50.0)	0.8333

[a]nominal p-values were calculated from Fisher's exact test.
12-month landmark data cut (CCO November 2020).
CR, complete response; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; ≥VGPR, very good partial response or better.

Conclusions

- These post hoc subgroup analyses were generally consistent with primary results from ANDROMEDA and add to the body of evidence regarding cytogenetics in patients with AL amyloidosis
  - Rates of overall hematologic CR and cardiac and renal response at 6 months were numerically higher with D-VCd than VCd
  - Major organ deterioration–PFS and –EFS favored D-VCd over VCd
- The presence of t(11;14) and amp1q21 appeared to impact rates of deep hematologic response in the VCd group but not in the D-VCd group
- These findings should be interpreted with caution due to small sample sizes, but appear to support the use of D-VCd in patients with newly diagnosed AL amyloidosis, regardless of cytogenetic abnormalities

AL, light chain; CR, complete response; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; EFS, event-free survival; PFS, progression-free survival; VCd, bortezomib, cyclophosphamide, and dexamethasone.

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