עדכונים מכנס ASH

AL amyloidosis

2024

ד"ר קרייניץ נטליה

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

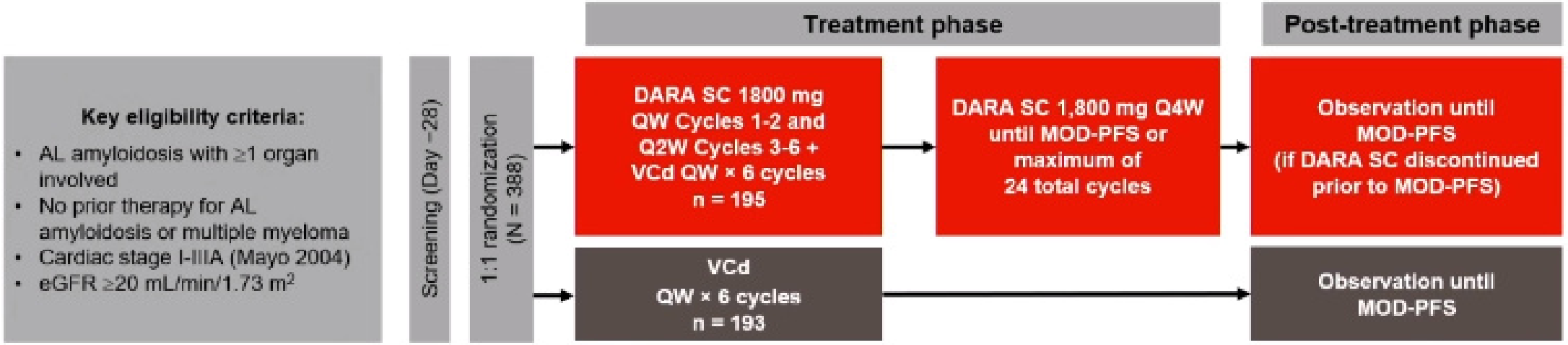
- Systemic AL amyloidosis is characterized by deposition of immunoglobulin light chains produced by clonal CD38$^+$ plasma cells as insoluble amyloid fibrils in vital organs, which often leads to poor prognosis[1-4]
  - 5-year survival rate reported as 48% overall and 35% for patients with cardiac involvement[5]
- 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 Engl 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.

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



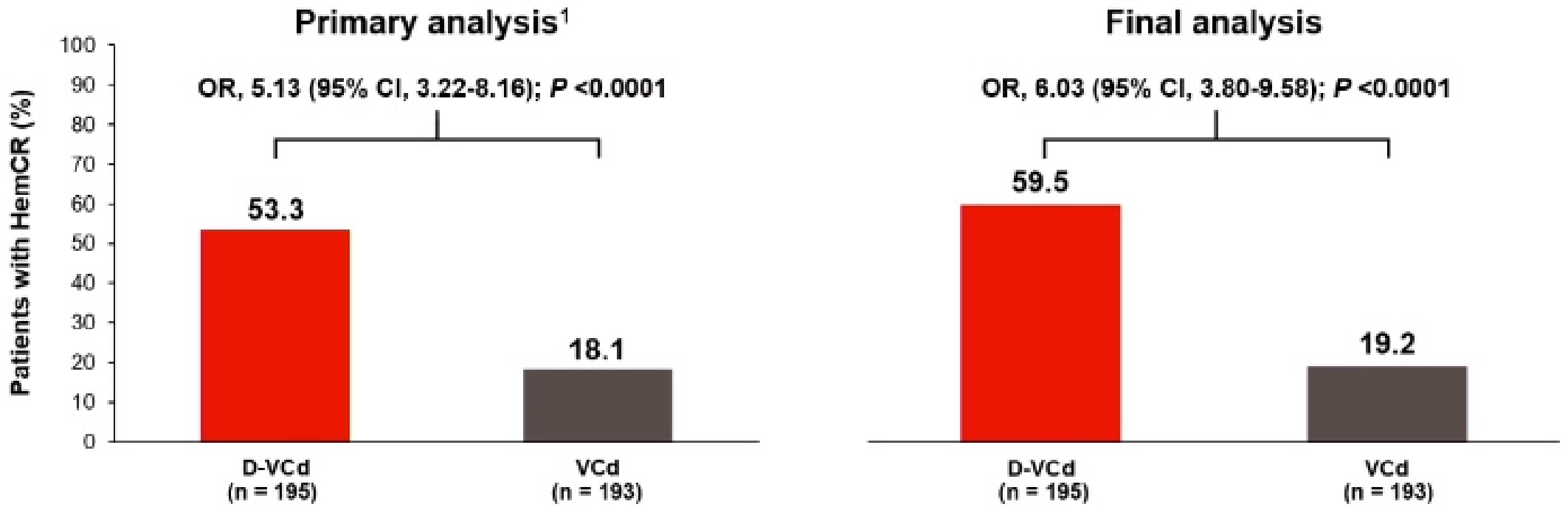
Stratification criteria:
- Cardiac stage (I vs II vs IIIA)
- Transplant typically offered in local country (yes vs no)
- Creatinine clearance (≥60 mL/min vs <60 mL/min)

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.

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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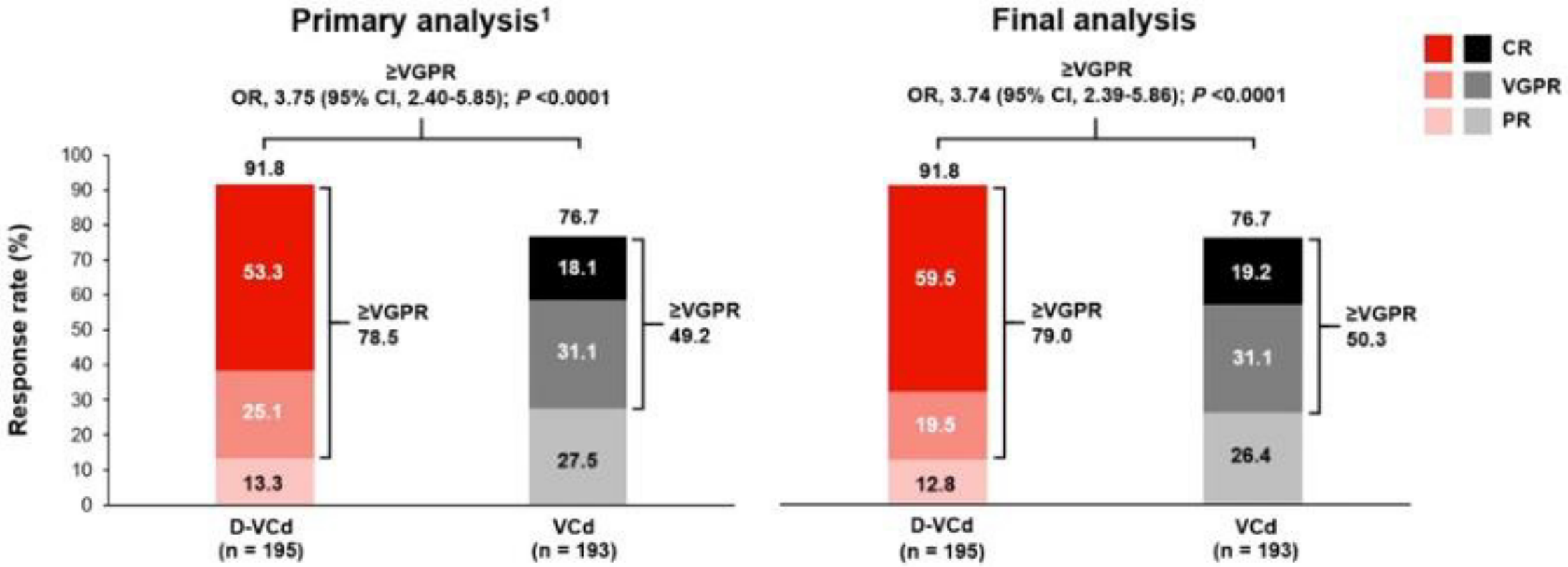
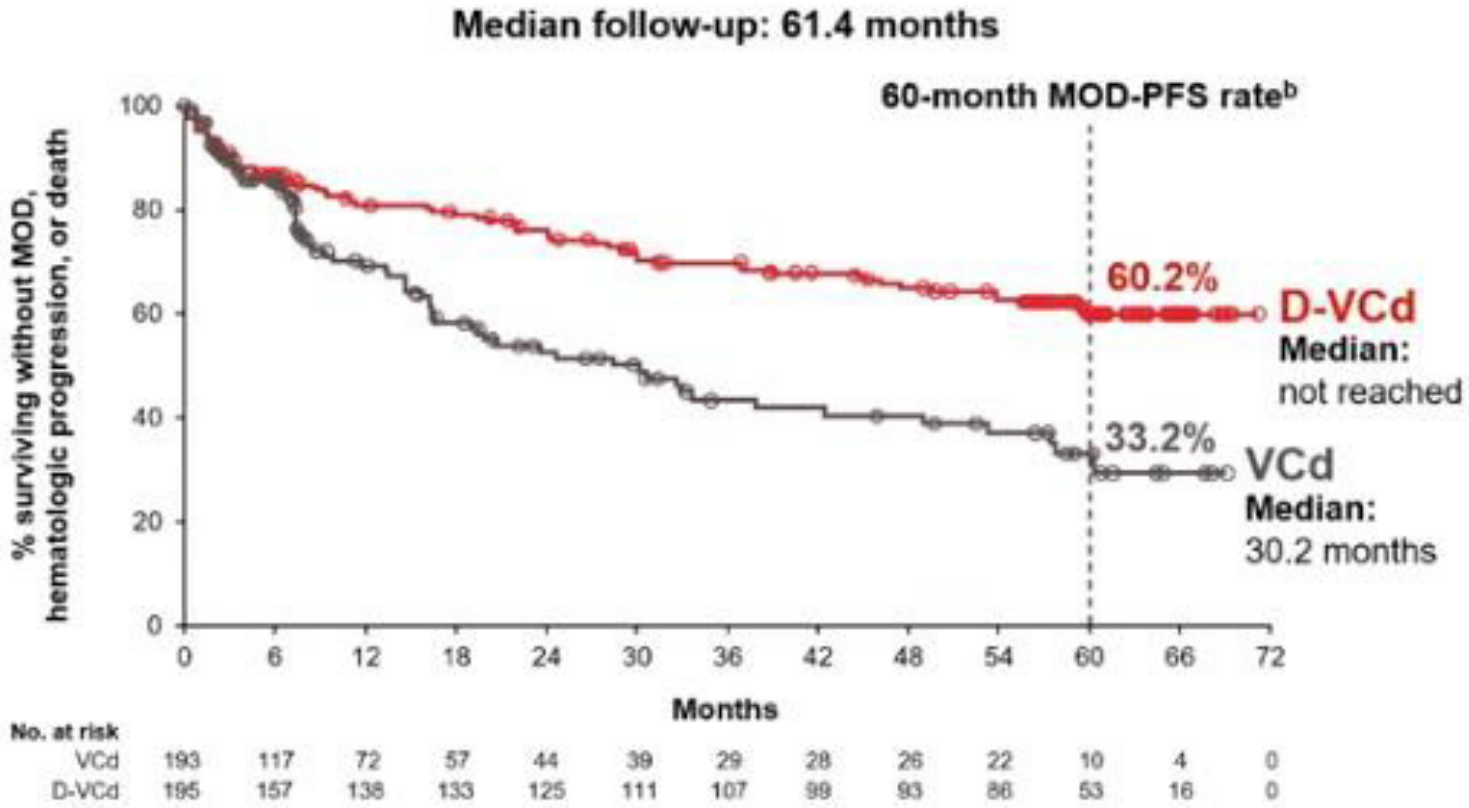
Final Analysis



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.

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



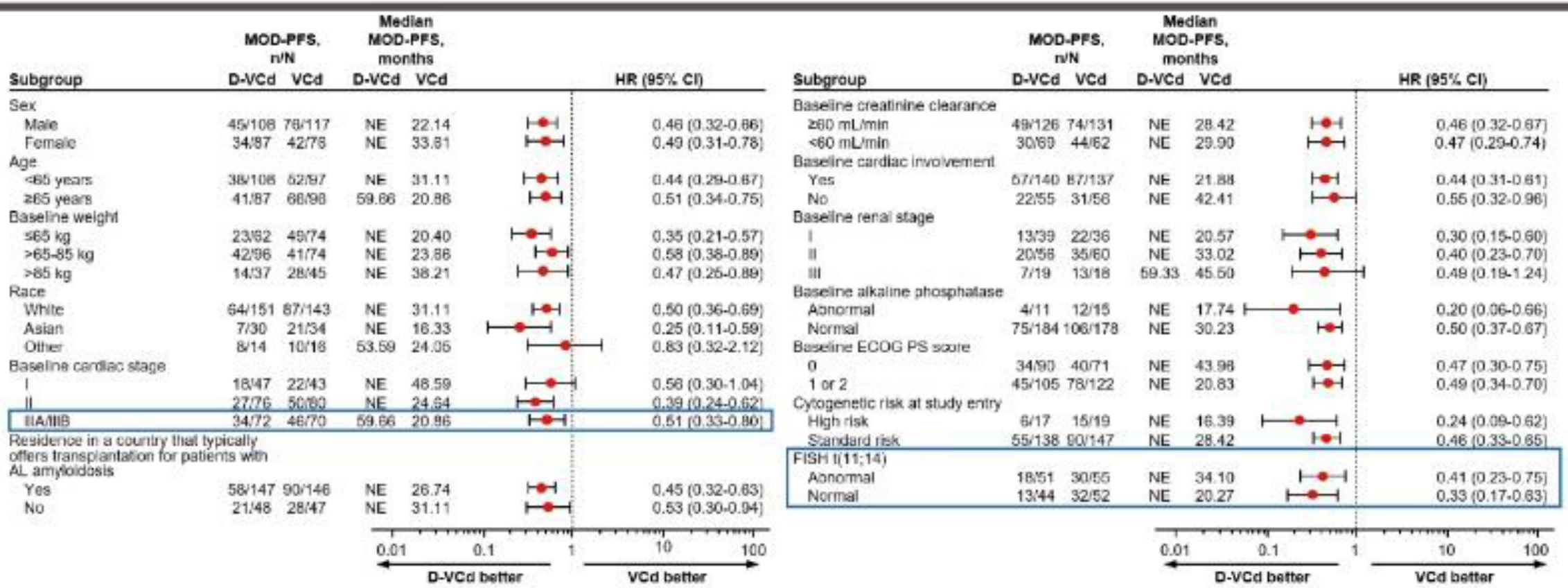
- **HR, 0.44 (95% CI, 0.31-0.63); *P* <0.0001[c,d]**

	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.

# of Major Organ Deterioration (MOD)–PFS



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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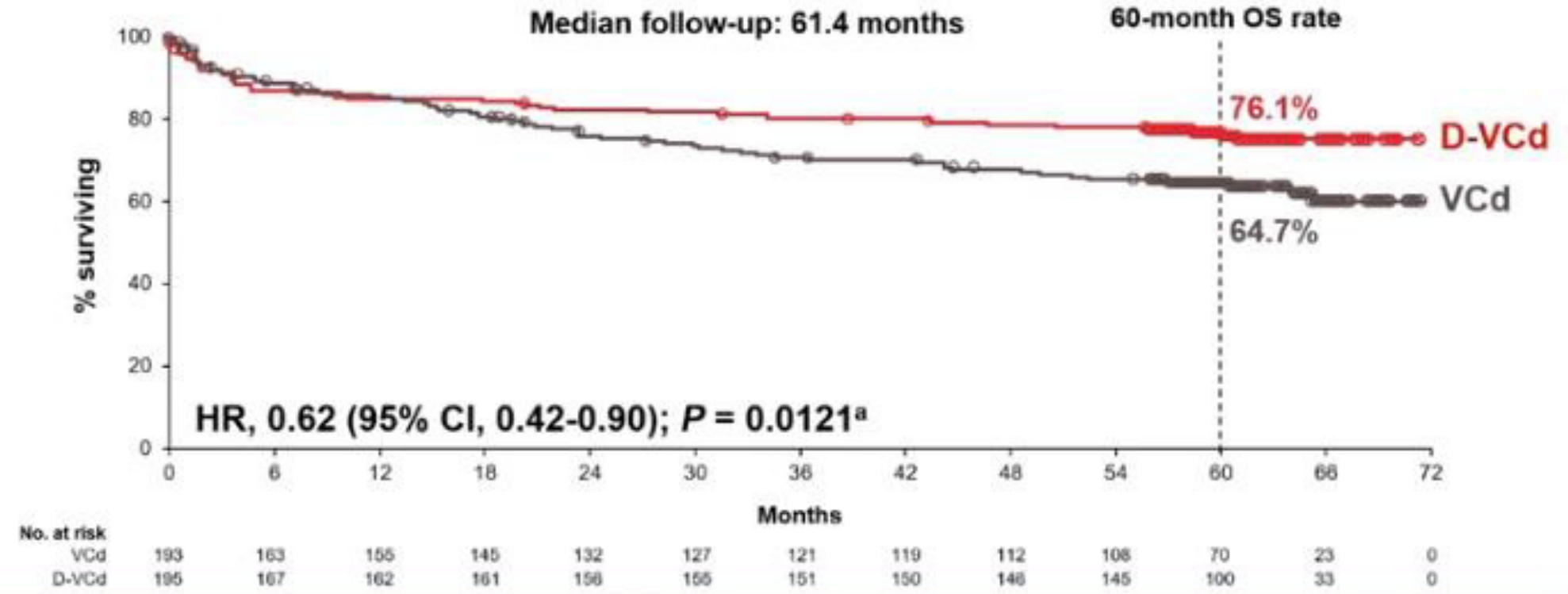
ANDROMEDA: Overall Survival



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

aCrossing the prespecified stopping boundary of 0.0163

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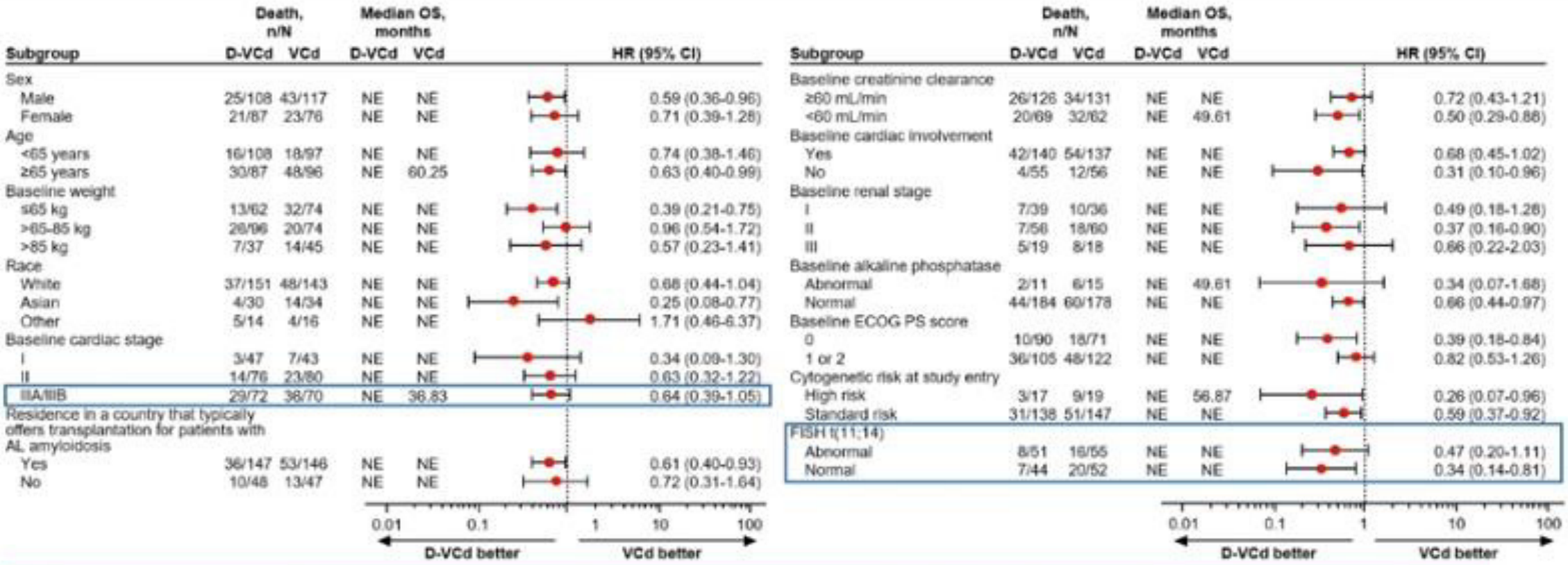
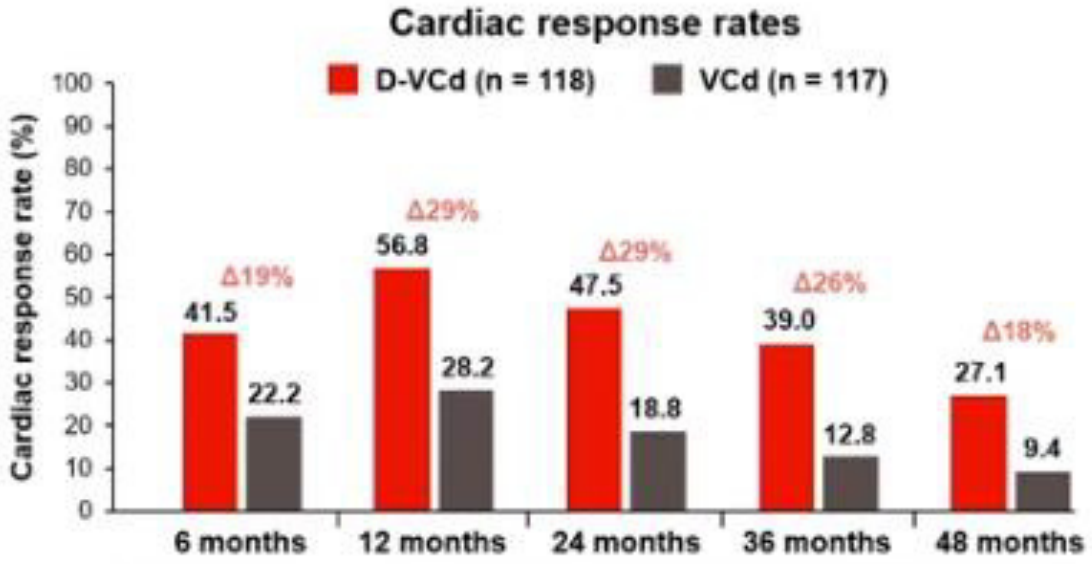
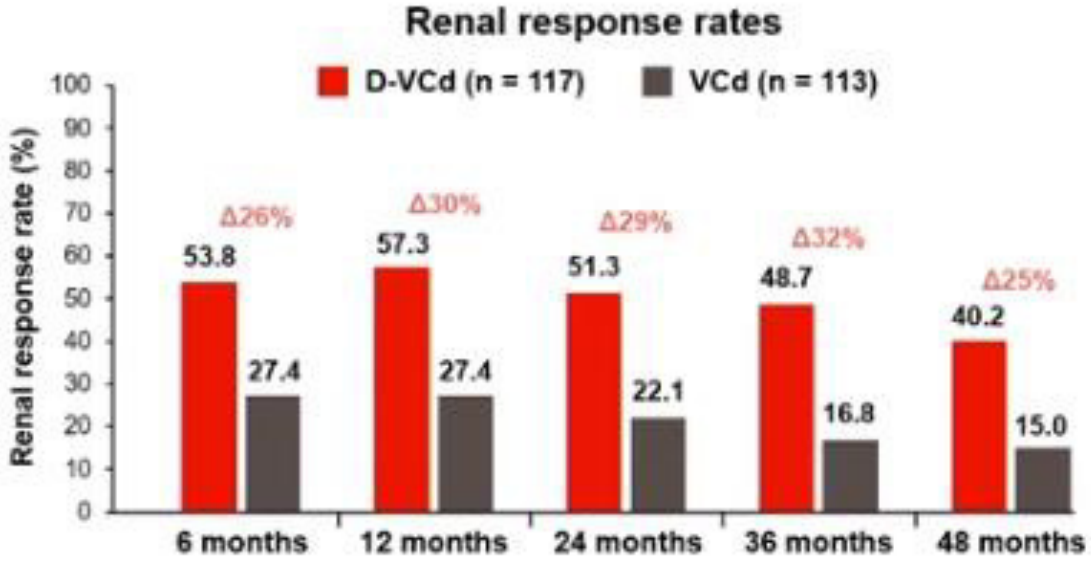
ANDROMEDA: Prespecified Subgroup Analysis of Overall Survival



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

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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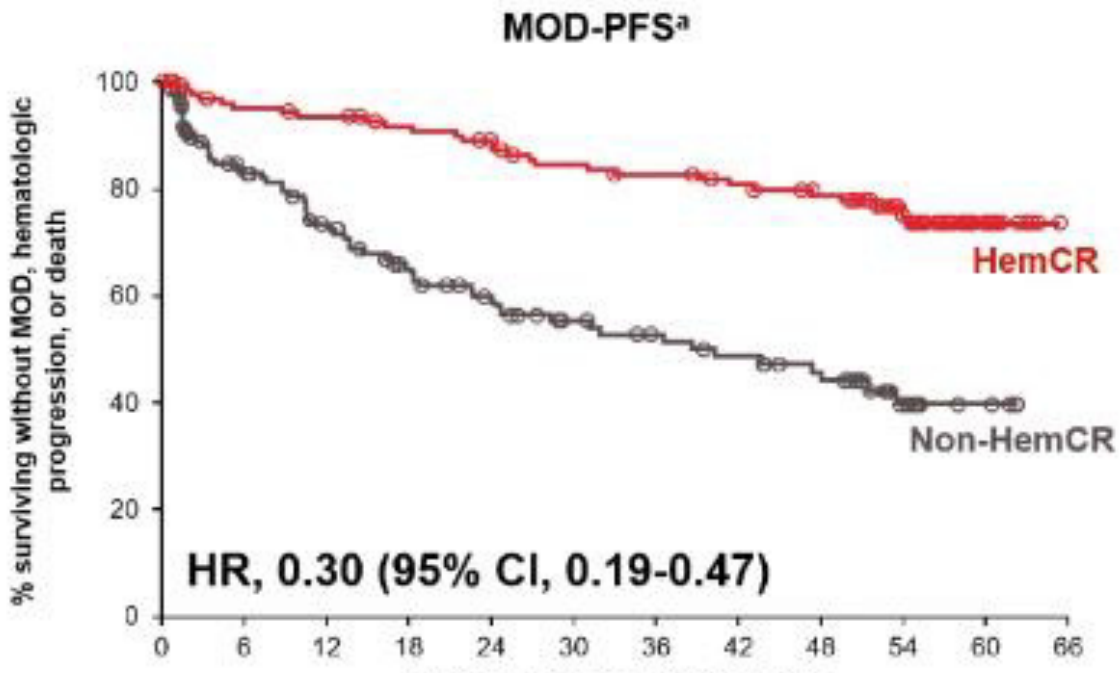
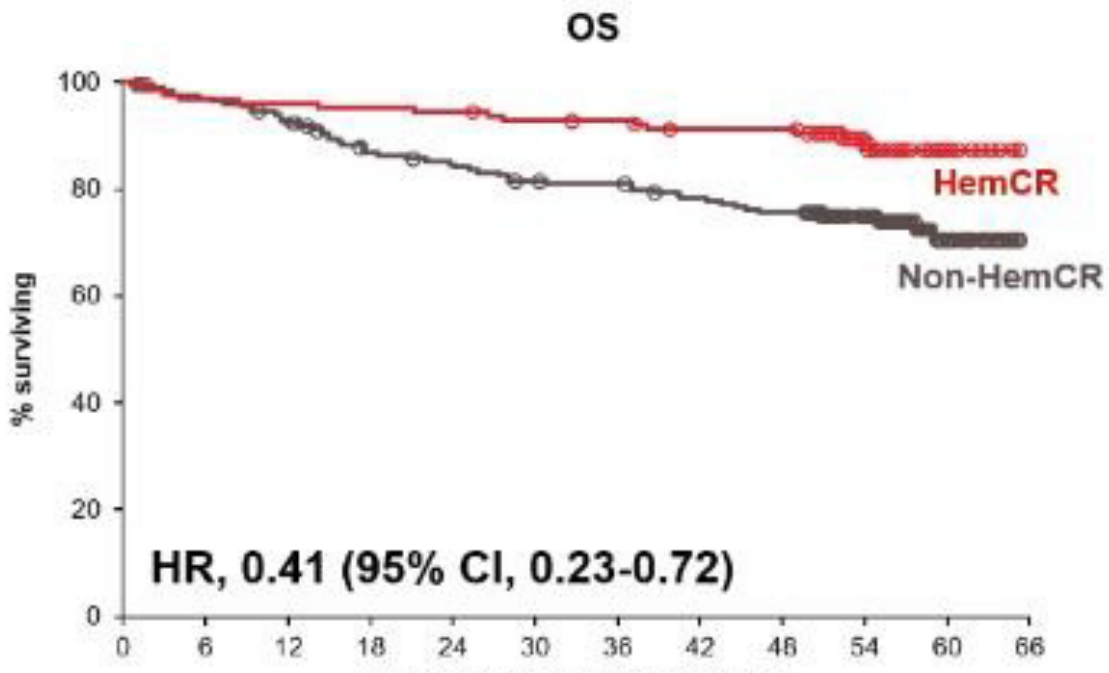
Overall Survival by Hematologic Complete Response



No. at risk												
HemCR	125	112	109	104	97	82	66	64	79	48	16	0
Non-HemCR	149	98	81	65	53	44	39	35	29	15	4	0



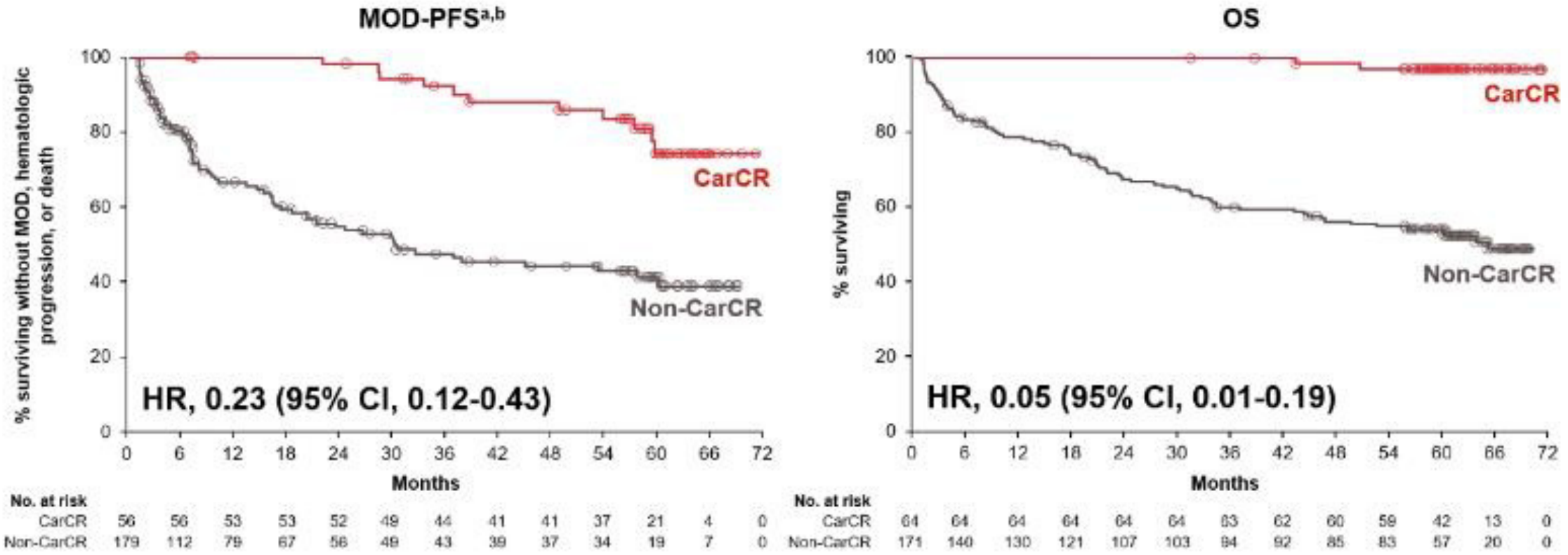
No. at risk												
HemCR	127	123	122	121	120	117	116	112	112	80	29	0
Non-HemCR	203	194	184	167	162	155	153	146	141	90	27	0

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.

Presented by E. Kastritis at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

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



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.

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.

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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EFFICACY AND SAFETY OF ISATUXIMAB, POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED AL AMYLOIDOSIS: INTERIM RESULTS OF THE ISAMYP PHASE 2 JOINT STUDY FROM THE IFM AND ALLG

Peter Mollee, Antoine Huart, Olga Mortona, Kentin Queru, Cecile Leyronnas, Stéphanie Harel, Hasib Sidiqi, Estelle Desport, Laure Vincent, Margaret Macro, Salomon Manier, Caroline Jacquet, Pierre Morel, Noemi Horvath, Sébastien Bender, Guillaume Olombel, Virginie Pascal, Jill Corre, Frank Bridoux, Arnaud Jaccard, and Murielle Roussel, on behalf the IFM and the ALLG

IFM 2020-01

MM24-IsAMYP

Centre national de référence Amylose AL

CHU

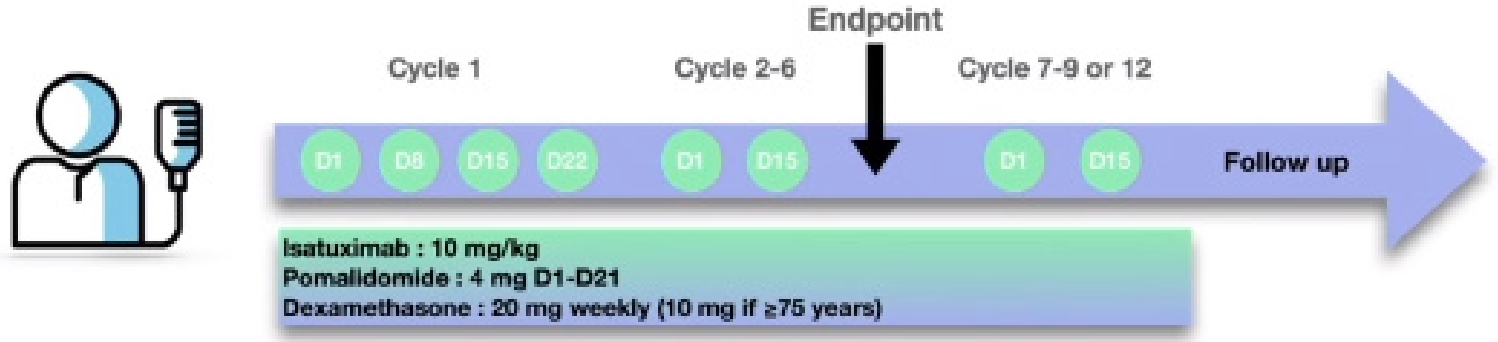
CHU Poitiers

Hôpital Saint-Louis AP-HP

ALLG

STUDY DESIGN: PHASE II, OPEN-LABEL, MULTICENTER, INTERNATIONAL STUDY

- 46 patients planned, in 22 centers (France and Australia)

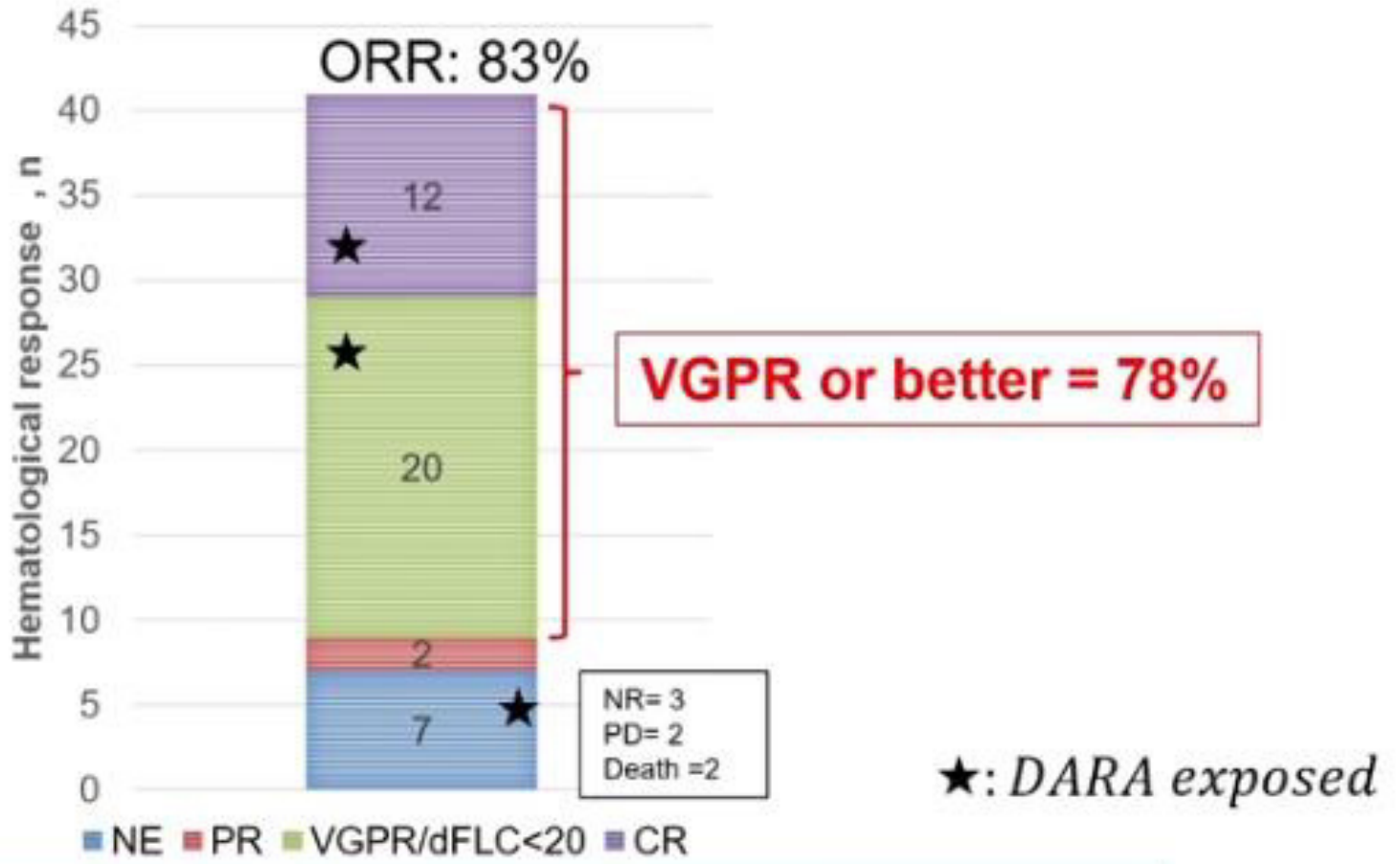


At least 6 cycles, 9 to 12 according to Hem Response

- Central lab for SPEP, UPEP, FLC (Binding Site), IFIX and NT-proBNP

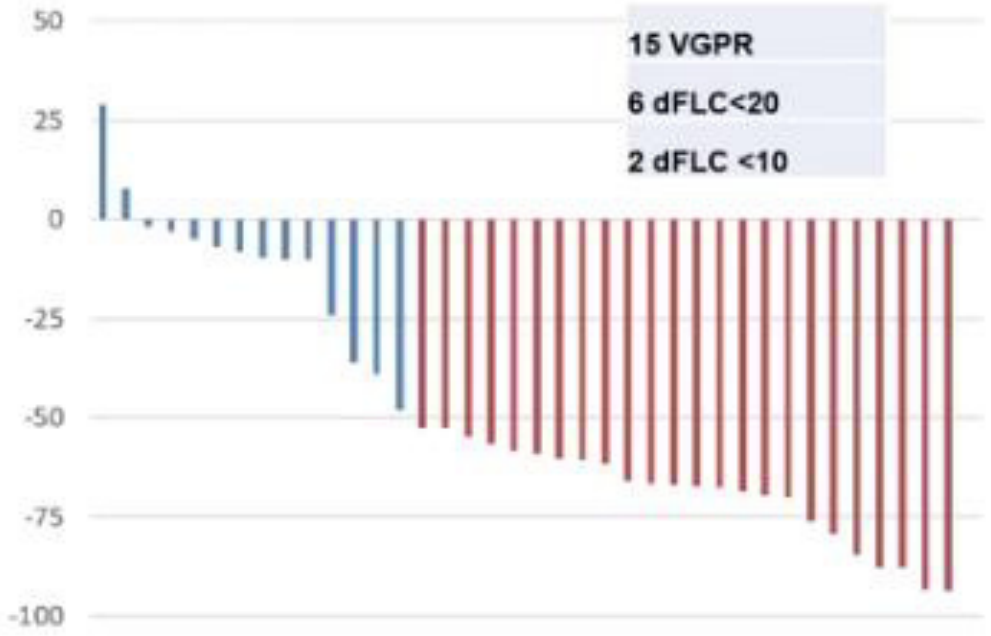
FLC/NT-proBNP: day 1 and 8 cycle 1, day 1 cycle 2 to 6, end of treatment and every 3 months for 1 year

HEMATOLOGICAL RESPONSES AT THE COMPLETION OF 6 CYCLES OF ISATUXIMAB POMALIDOMIDE AND DEXAMETHASONE



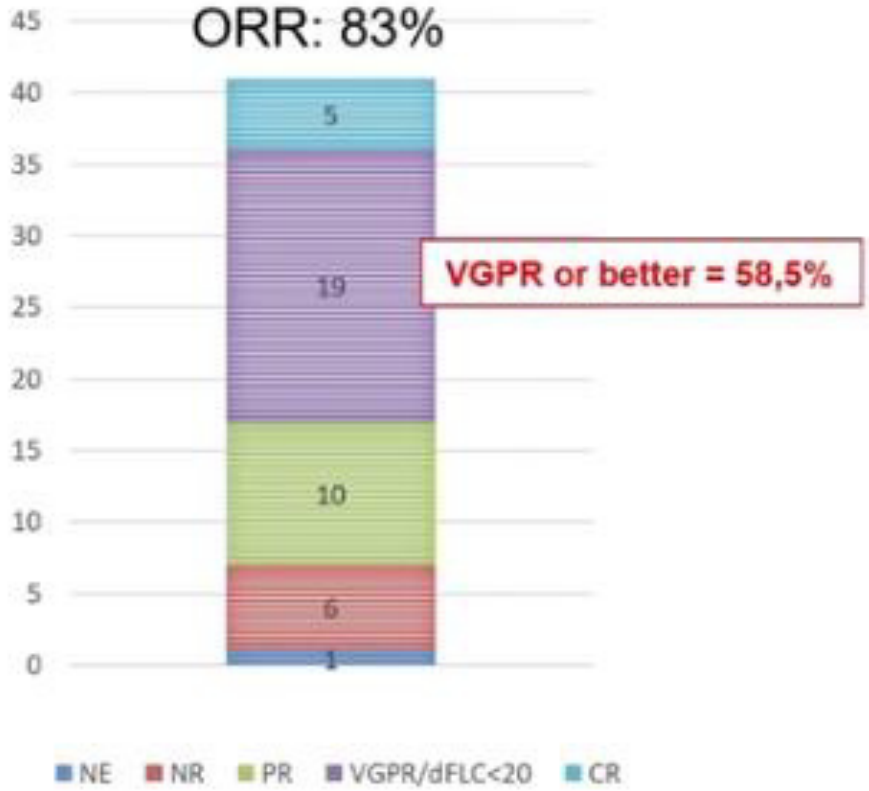
AMYDARA Overall response rate: 59.5%, VGPR or better: 47.5%

HEMATOLOGICAL RESPONSES ARE FAST



n=39

median dFLC decrease 60%
at 1 week



at cycle 2

SAFETY SUMMARY

54 Serious AEs were reported in 22 (53.5%) patients,

- 24 infectious events in 18 patients
  - SARS COV 2 in 3 patients
  - Pneumonia in 7 patients
- 7 cardiac in 4 patients
  - Cardiac Failure in 3 patients (mainly related to AL)
  - Dysrythmia in 3 patients (DXM)

501 AEs were reported in 41(100%) patients mostly grade 1-2,

- 127 AEs grade ≥3 in 34 patients: hematological (n=22, 53.5%) and infectious (n=18, 44%)

+ fatigue, diarrhea, edema

8 infusion related reactions: 1 grade 3 at first injection that resumed at each infusions

CONCLUSIONS

Isatuximab, pomalidomide and dexamethasone regimen in previously-treated patients with AL Amyloidosis showed :

- ✓ Encouraging efficacy results after 6 cycles
  - Good Response rates with 78% VGPR or better and 29% CR
  - Deep and rapid clonal responses, within the first weeks
- ✓ A transient rise in NT-proBNP is a pomalidomide related effect that does not preclude cardiac deterioration
- ✓ Frequent Hematologic and infectious adverse events (grade ¾ in 50-60% of patients)
- ✓ Data must be confirmed in DARA exposed patients (2/3 in VGPR or better)

The IsaPomDex regimen must be optimized in AL patients to decrease hematological and infectious toxicities:

pomalidomide 3 mg, dexamethasone 10 mg weekly (only for 2 cycles?)

Trial is ongoing, data on organ responses and outcomes will be further evaluated for all patients.

Venetoclax Plus Dexamethasone as First-line Treatment for t(11; 14) Light-chain Amyloidosis: Preliminary Result of a Phase II Prospective, Multicenter, Single-arm Study

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Methods

Phase II Prospective, Multicenter, Single-arm Study

Key eligibility criteria:

- ≥ 18 years
- Newly diagnosed AL
- FISH t(11;14) ≥ 10%
- Baseline dFLC > 50 mg/L

N = 39

Screening (Day-28)

1-6 cycles

Venetoclax: 400 mg qd

Dexamethasone: 20-40 mg qw

7-12 cycles

Venetoclax: 400 mg qd

Dexamethasone: 10-20 mg qw

Primary endpoint:

CR+VGPR at 3 months

Secondary endpoints:

- Best hematologic response
- Organ response
- Time to next treatment
- Overall survival
- Adverse events

Results

Hematologic Response

	3 months N = 39	6 months N = 31	12 months N = 21	Best hematologic response N = 39
CR	15 (38.5)	9 (29.0)	6 (28.6)	19 (48.7)
VGPR	10 (25.6)	8 (25.8)	4 (19.0)	8 (20.5)
CR+VGPR	**25 (64.1)**	17 (54.8)	10 (47.6)	**27 (69.2)**
PR	11 (28.2)	7 (22.6)	1 (4.8)	10 (25.6)
ORR	36 (92.3)	24 (77.4)	11 (52.4)	**37 (94.9)**

- Data were presented as number (percent)
- Patients who died or discontinued treatment before response assessment were categorized under the NR group
- the rate of MRD negativity was 50.0% (3/6)

Results

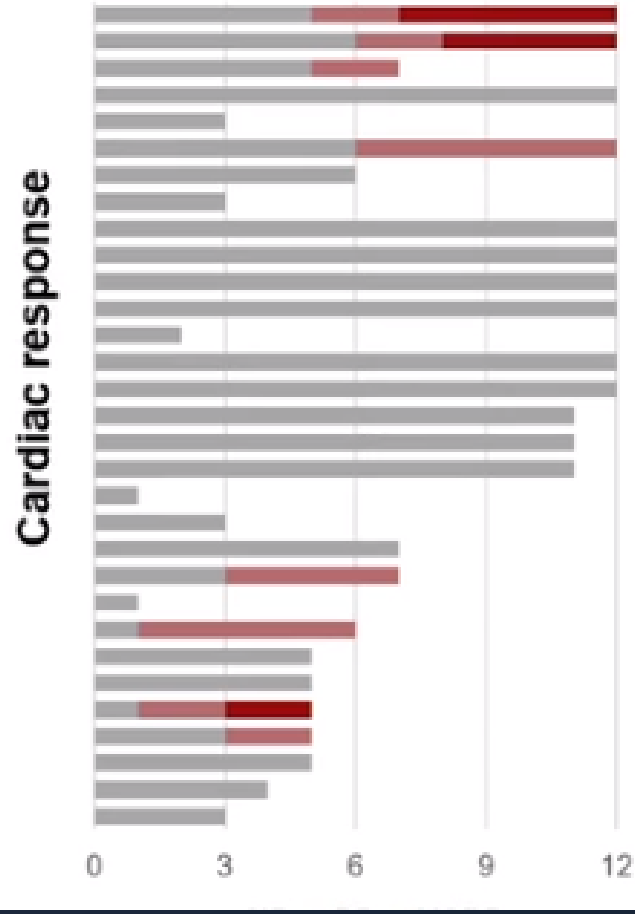
Organ Response at 6 Months

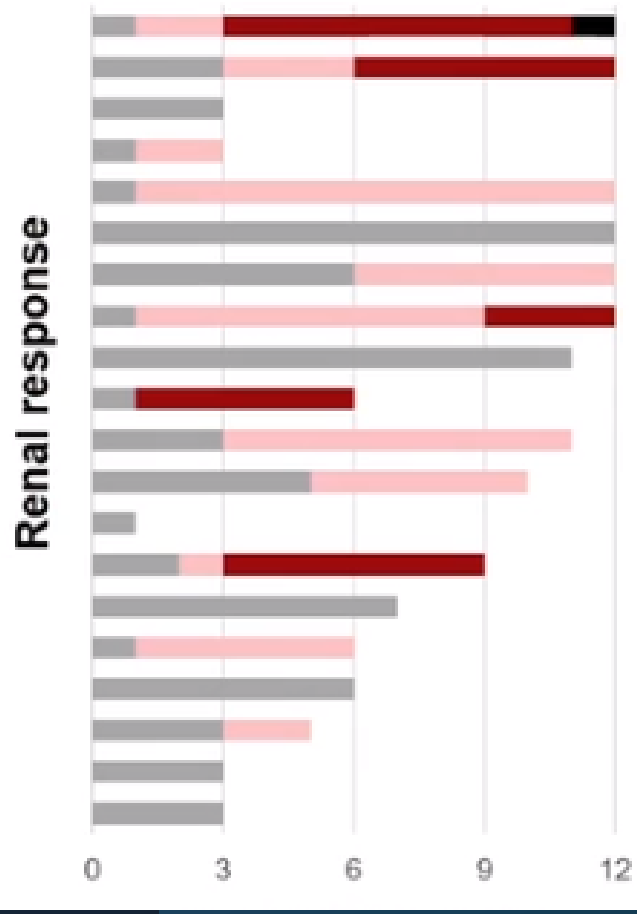
ORR: 39.1% (9/23)

VGPR/PR/NR: 4.3%/34.8%/60.9%

ORR: 73.3% (11/15)

VGPR/PR/NR: 26.7%/46.7%/26.7%

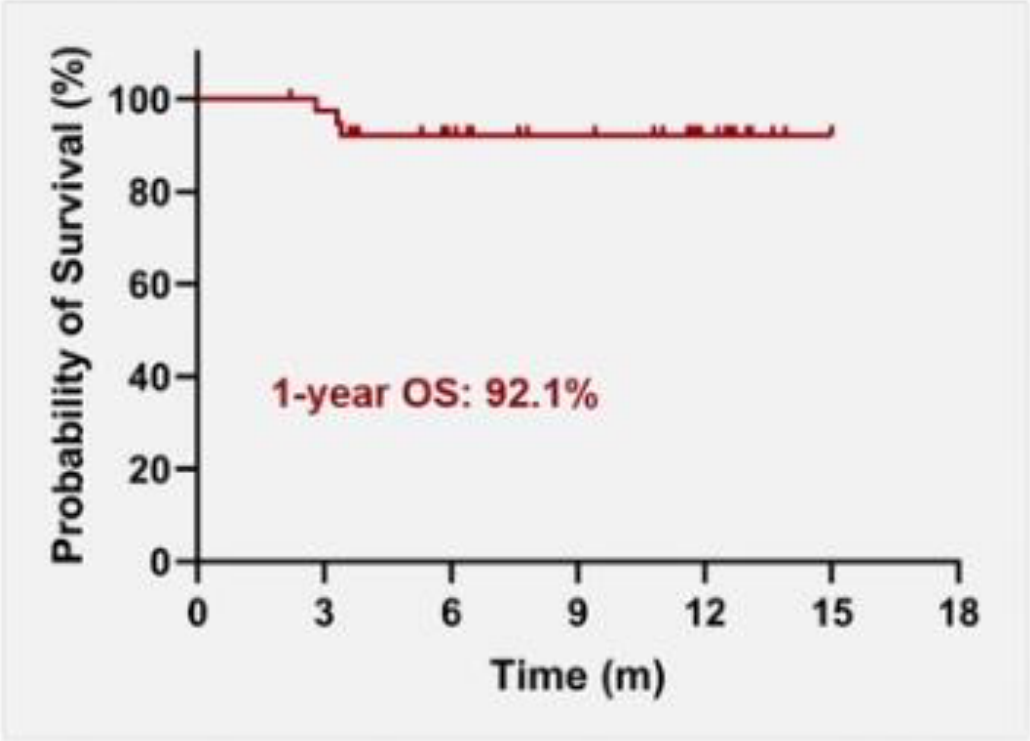


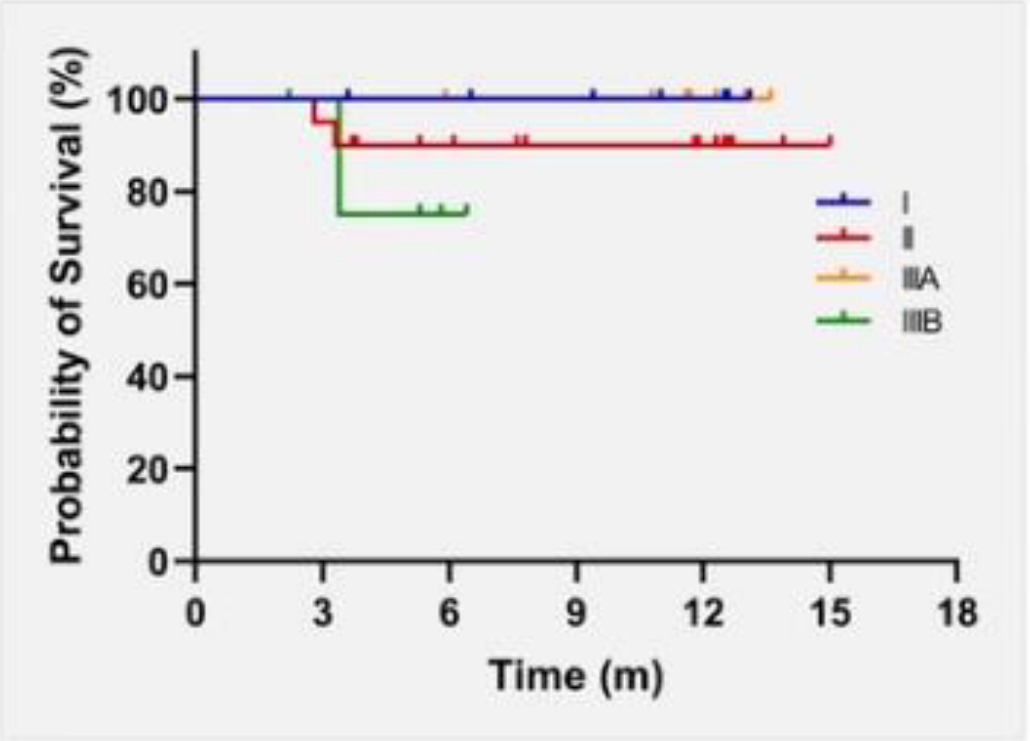


Results

Survival

Median follow-up duration: 11.0 months (range, 2.2-15.0 months)





Results

Adverse Events

Event	Any Grade	Grade 3-4
Hematologic		
Lymphopenia	9 (25.0)	**2 (5.6)**
Anemia	6 (16.7)	0 (0.0)
Neutropenia	3 (8.3)	**1 (2.8)**
Non-hematologic		
Fatigue	11 (30.6)	0 (0.0)
Edema	9 (25.0)	**1 (2.8)**
Nausea	9 (25.0)	**1 (2.8)**
Increased transaminase	8 (22.2)	**1 (2.8)**
Increased bilirubin	8 (22.2)	**1 (2.8)**
Constipation	6 (16.7)	0 (0.0)
Diarrhea	6 (16.7)	0 (0.0)
Weight loss	4 (11.1)	0 (0.0)

Event	Any Grade	Grade 3-4
Non-hematologic		
Hyponatremia	4 (11.1)	0 (0.0)
Upper respiratory tract infection	3 (8.3)	0 (0.0)
Emesis	2 (5.6)	0 (0.0)
Hypokalemia	2 (5.6)	0 (0.0)
Hyperkalemia	2 (5.6)	0 (0.0)
Syncope	1 (2.8)	**1 (2.8)**
Pneumonia	1 (2.8)	**1 (2.8)**
Dizziness	1 (2.8)	0 (0.0)
Insomnia	1 (2.8)	0 (0.0)
Herpes zoster	1 (2.8)	0 (0.0)
Increased creatinine	1 (2.8)	0 (0.0)
Hypernatremia	1 (2.8)	0 (0.0)

- Data were presented as number (percent)

Conclusion

- The combination of Ven-D as an initial treatment for t(11;14) AL amyloidosis demonstrates **rapid induction of high hematologic responses** with a **favorable tolerability profile**.
- The overall efficacy of the Ven-D regimen is comparable to Dara-based treatment, although the CR rate is slightly lower than the latter.
- The cardiac response rate is relatively low, and the potential for drug-related cardiotoxicity warrants attention. The **renal response rate** is particularly encouraging.
- An **all-oral regimen** avoids side effects such as diarrhea and peripheral neuropathy, making it a significant advantage of the Ven-D regimen.

Thank you!