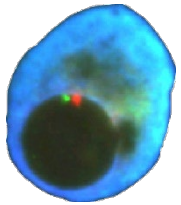
Morie Gertz MD MACP



Therapy in Amyloidosis 2024

Indianapolis Society of Hematology 2024

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

Financial Disclosures

- Dr. Morie Gertz – Honoraria:
  - Celgene
  - Proteo Tech, Inc.
  - Research To Practice
  - Medscape, LLC
  - Sanofi-Aventis
  - National Cancer Institute of Frederick
  - Sofinnova Ventures, Inc.
  - Novartis
  - Ionis
  - Prothena
  - Johnson & Johnson

Learning Objectives

- Weigh merits of conventional therapy as management
- Importance of insuring amyloid type

Amyloidosis 2023

- New Diagnostic Strategies
- New methods of monitoring
- New prognostic indicators
- New therapies

EHA-ISA Guidelines for Stem Cell Transplantation in AL Amyloidosis

Eligibility Criteria

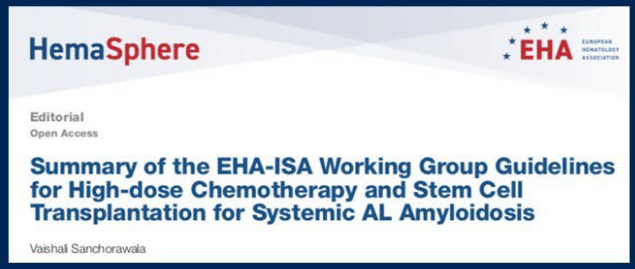
- Age >18 and <70 years
- At least one vital organ involvement
- Left ventricular ejection fraction ≥40% and NYHA class <III
- Oxygen saturation ≥95% on room air and DLCO >50%
- Supine systolic blood pressure ≥90 mm Hg
- ECOG performance status score ≤2
- Direct Bilirubin <2 mg/dL
- NTproBNP <5000 pg/mL
- Troponin I <0.1 ng/mL, Troponin T <0.06 ng/mL, hs-Troponin T <75 ng/mL

Induction Therapy

- Consider if bone marrow plasmacytosis >10%
- Bortezomib based regimen 2-4 cycles
- Defer SCT if hematologic CR achieved with induction therapy

Stem Cell Mobilization and Collection

- G-CSF at 10-16 mcg/kg/day (single or split dose)
- Plerixafor on demand or planned
- Avoid cyclophosphamide



Risk-Adapted Melphalan Dosing

	MEL 200[a]	MEL 200 vs non-SCT regimens[b]	MEL 140
Age (years)	≤65	66-70	
Cardiac stage	I	II	
eGFR (mL/min/m²)	>50	30-50	≤30[c]

[a] *must meet **all** criteria*
[b] *multidisciplinary discussion recommended*
[c] *increased risk of AKI and ESRD during the peri-SCT period; may consider if on a stable chronic dialysis schedule*

Sanchorawala V, Boccadoro M, Gertz MA, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. *Amyloid* 2021:1–7.

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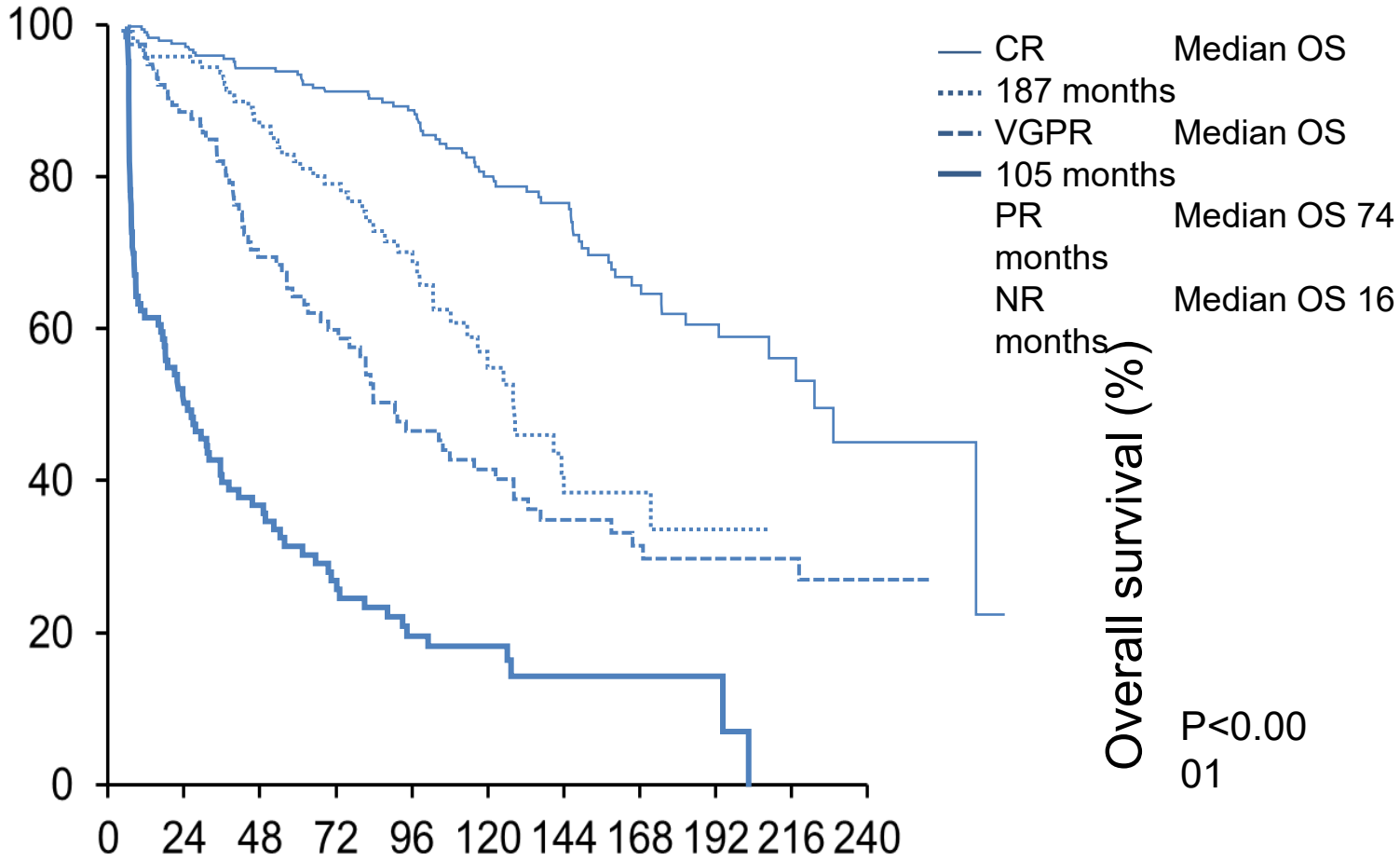
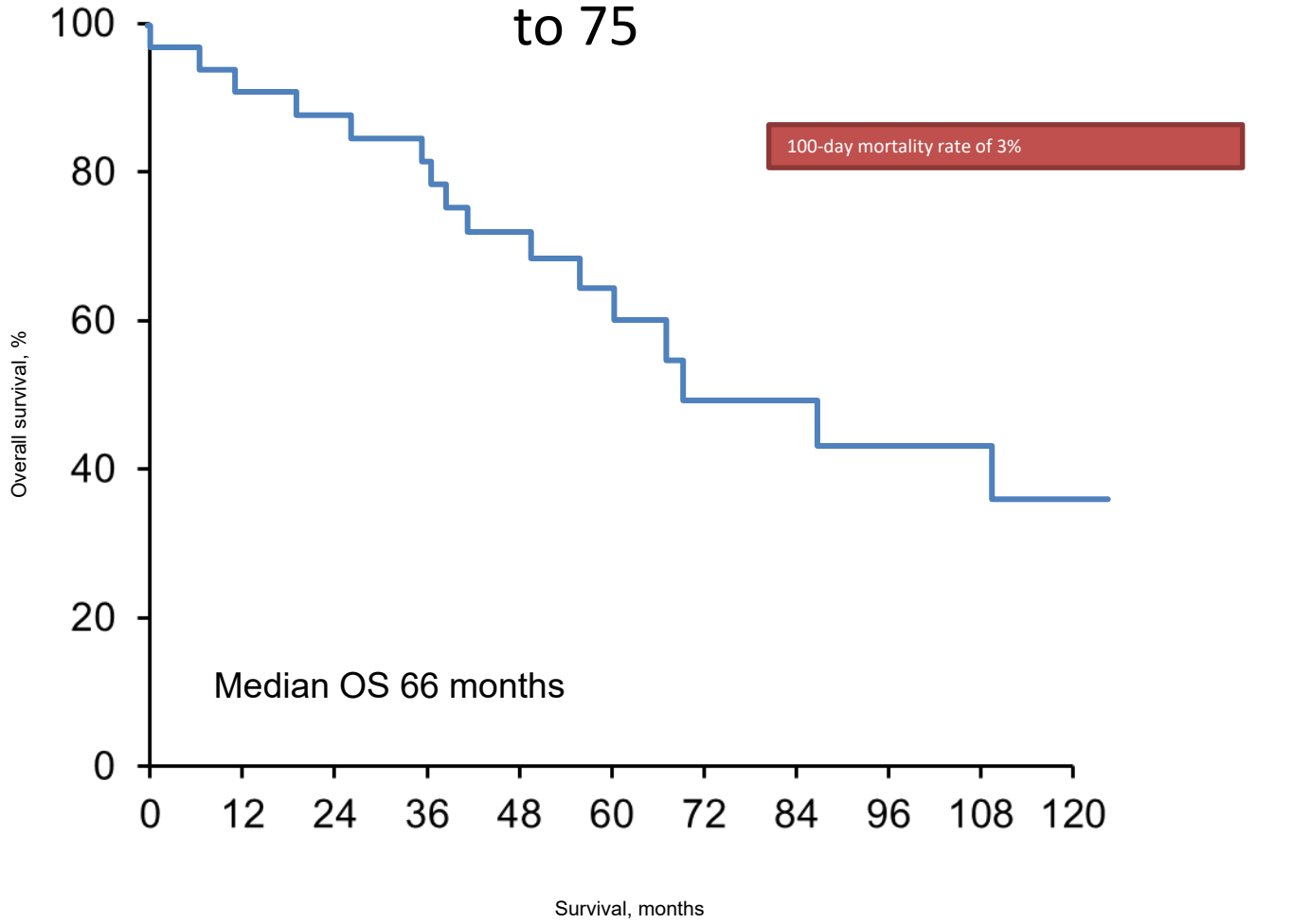
Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time



Sidiqi MH, Aljama MA et al. J Clin Oncol. 2018;36(13):1323-9.

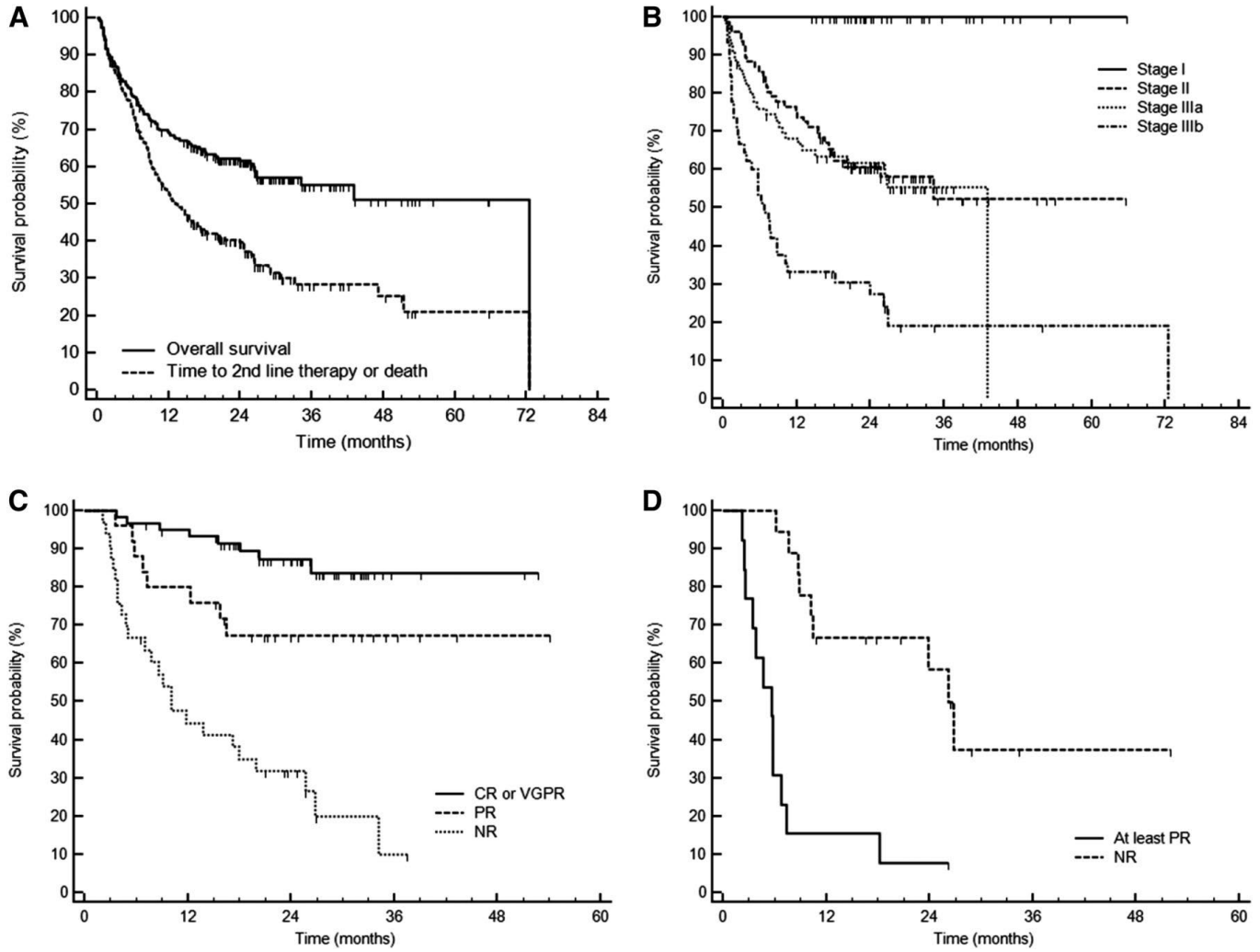
No. at risk							
CR	267	241	213	178	131	95	51
	29	13	4	1			
VGPR	150	131	84	52	30	15	
6	0	0	0	0			
PR	115	96	64	43			
35	26	18	16	8	2	0	
NR	107	45	27	18	12	5	

Autologous stem cell transplant for AL amyloidosis patients aged 70 to 75



Sidiqi MH, Aljama MA et al. Published online ahead of print; Biology of Bone Marrow Transplantation, June 2018.

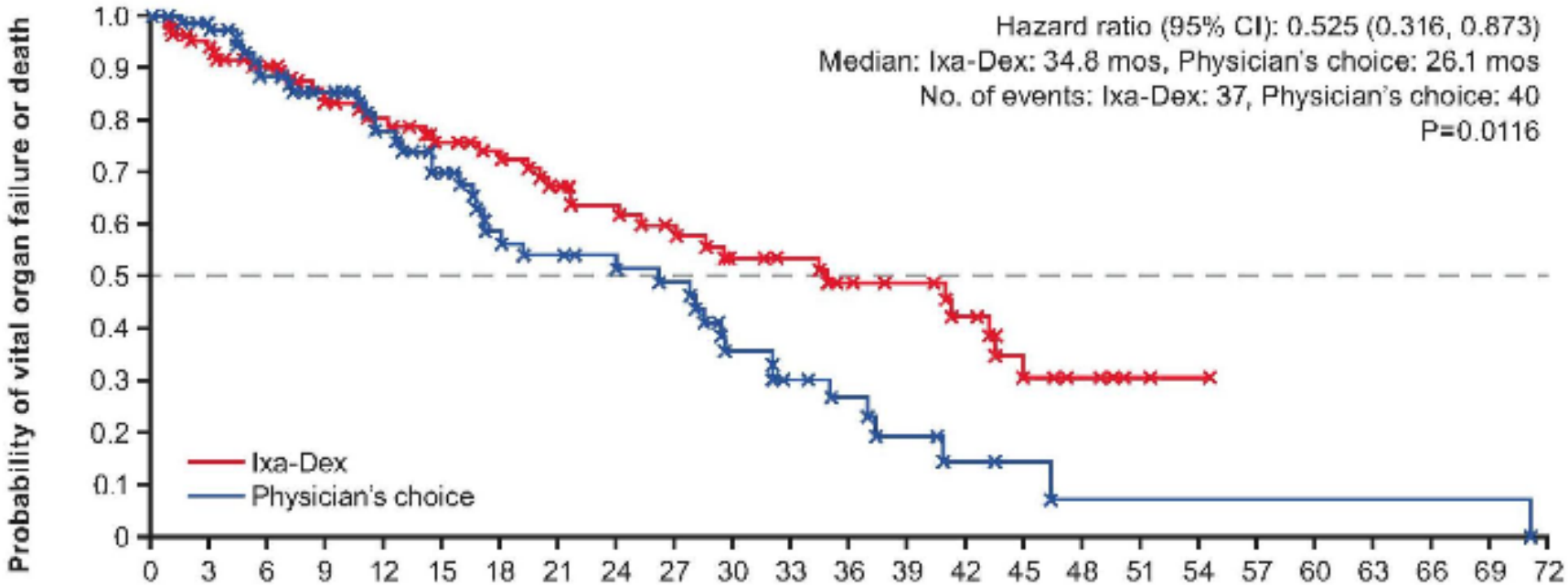
Survival of 230 patients with AL amyloidosis treated with CyBorD.



Giovanni Palladini et al. Blood 2015;126:612-615

Trial of Ixazomib-Dexamethasone Versus Physician's Choice of Therapy in Patients (Pts) with Relapsed/Refractory Primary Systemic AL Amyloidosis (RRAL)

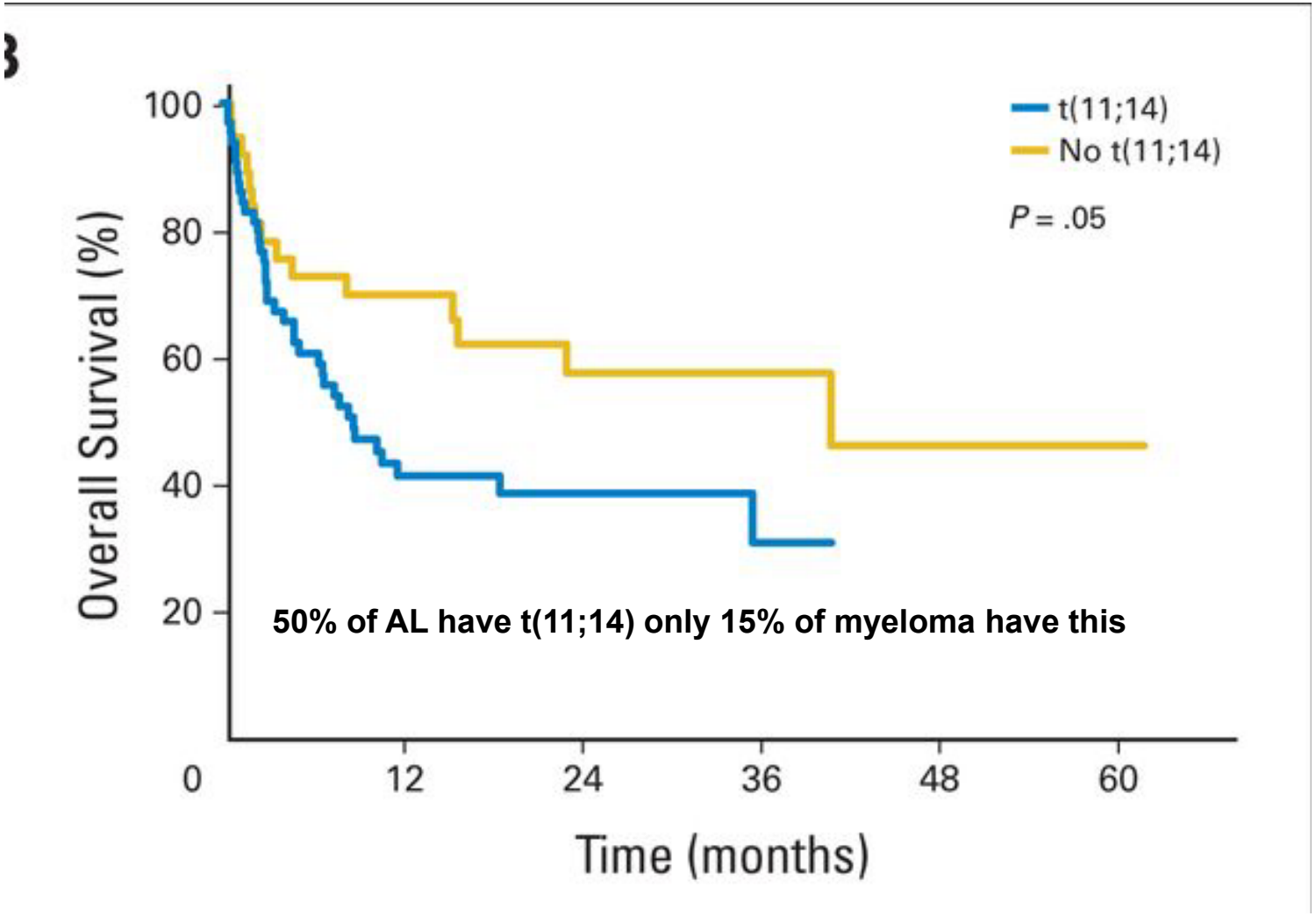
Figure. Time to vital organ deterioration/death and efficacy outcomes (PA)



Number of Patients at Risk

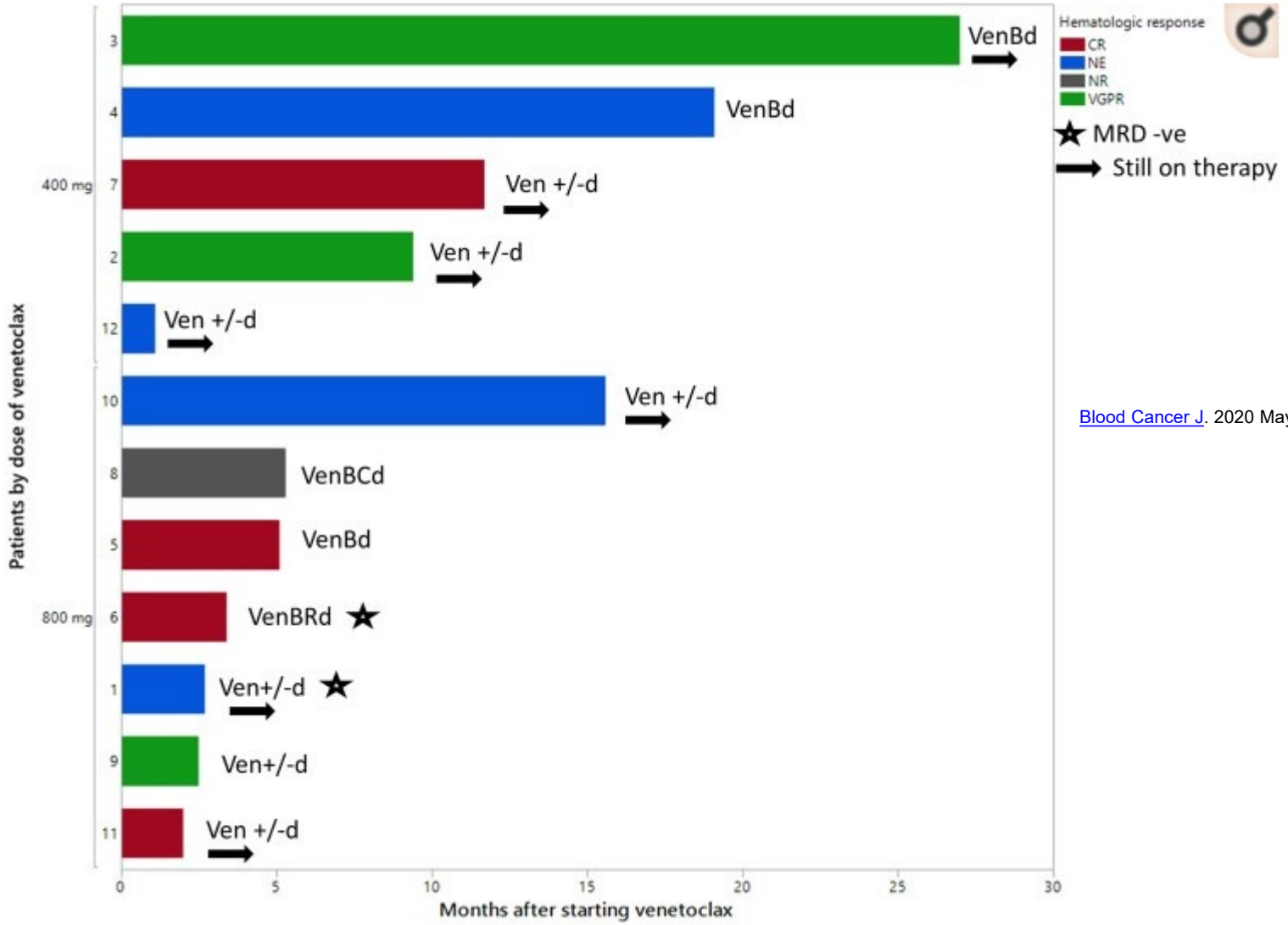
Ixa-Dex	85	78	68	58	55	49	42	39	34	29	25	22	18	16	13	7	5	2	1	0	0	0	0	0	0
Physician's choice	83	69	60	51	41	33	25	24	20	19	13	10	7	5	3	2	1	1	1	1	1	1	1	1	0

Overall survival in the bortezomib-dexamethasone cohort according to t(11;14)



Tilmann Bochtler et al. JCO 2015;33:1371-1378

Venetoclax for the treatment of translocation (11;14) AL amyloidosis



Blood Cancer J. 2020 May; 10(5): 55.

Daratumumab: Summary of data

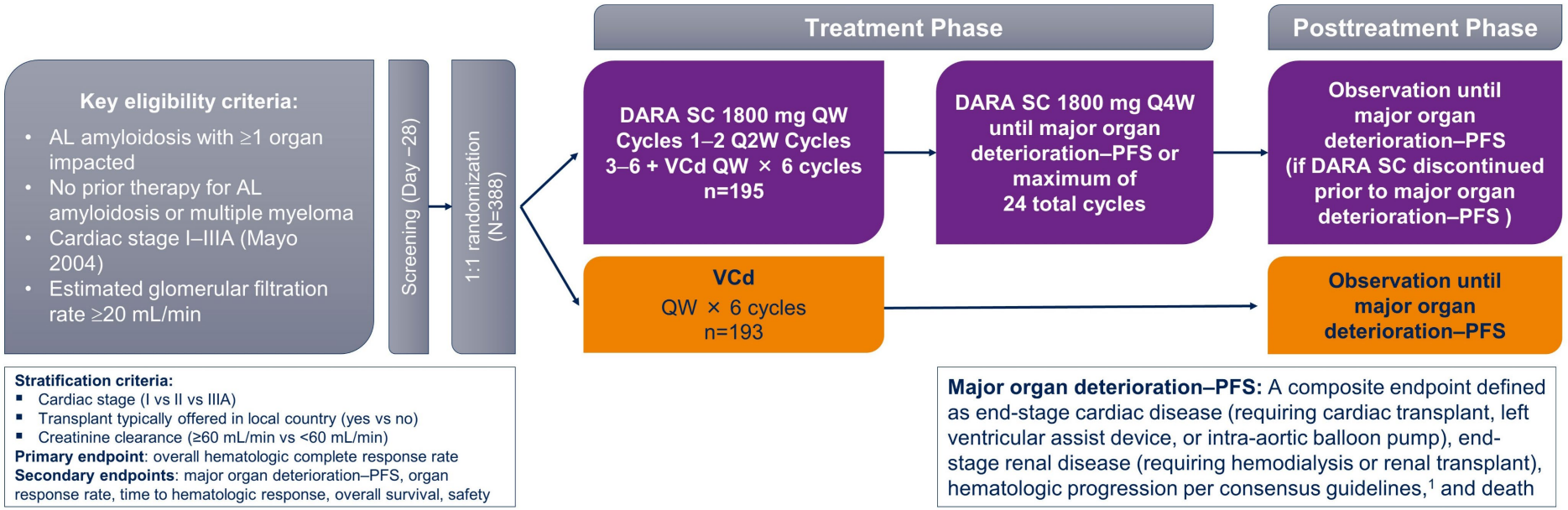
Ref	Design	Prior lines, med	N	Median time to response	ORR (%)	≥VGPR/CR (%)	Median FU
1	Retrospective	3	25	1.0 month	76%	60%/36%	NR
2	Retrospective	3	44; 50% in combination	2.2 months	83%	80%/17%	10.2 months
3	Retrospective	3	20	4 weeks	86%	86%/33%	10 months
4	Phase II	2	21	Fast	100%	84.2% at 3mo	NR
5	Phase II	3	32	1.0 month	63%	46%/17%	NR

1 Kaufman GP et al, Blood. 2017 130(7):900-902
2 Abeykoon JP et al, Leukemia. 2018
3 khouri J et al, Br J Haematol 2018
4 Sanchorawala V et al, *Blood*. 2017;130(Suppl 1):507.
5 Roussel M et al, *Blood*. 2017;130(Suppl 1):508

ORR=Overall response rate
VGPR=Very good partial response
CR-Complete response

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**

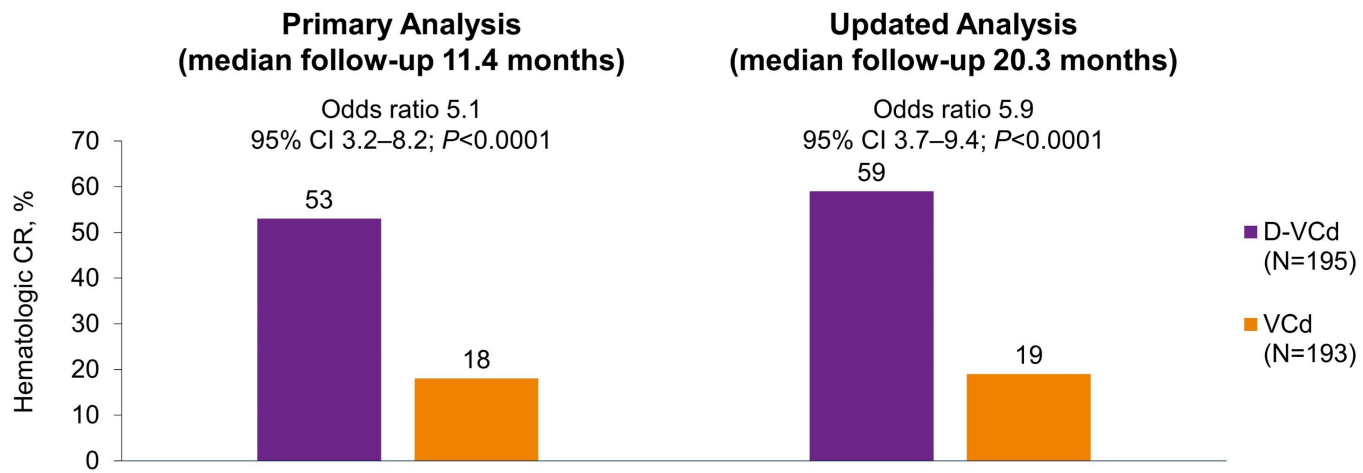


AL, light chain; DARA, daratumumab; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; PFS, progression-free survival; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous.

1. Comenzo RL, et al. *Leukemia* 2012;26:2317-25.

Hematologic CR: Primary Endpoint

- **Hematologic CR was defined as normalization of FLC levels and FLC ratio and negative serum and urine immunofixation**
  - If iFLC < upper limit of normal, normalization of the uninvolved FLC and FLC ratio were not required
- **Rates of hematologic CR remained significantly higher with D-VCd than VCd**
- **Median time to hematologic CR[a] was 2.0 months with D-VCd vs 2.8 months with VCd**

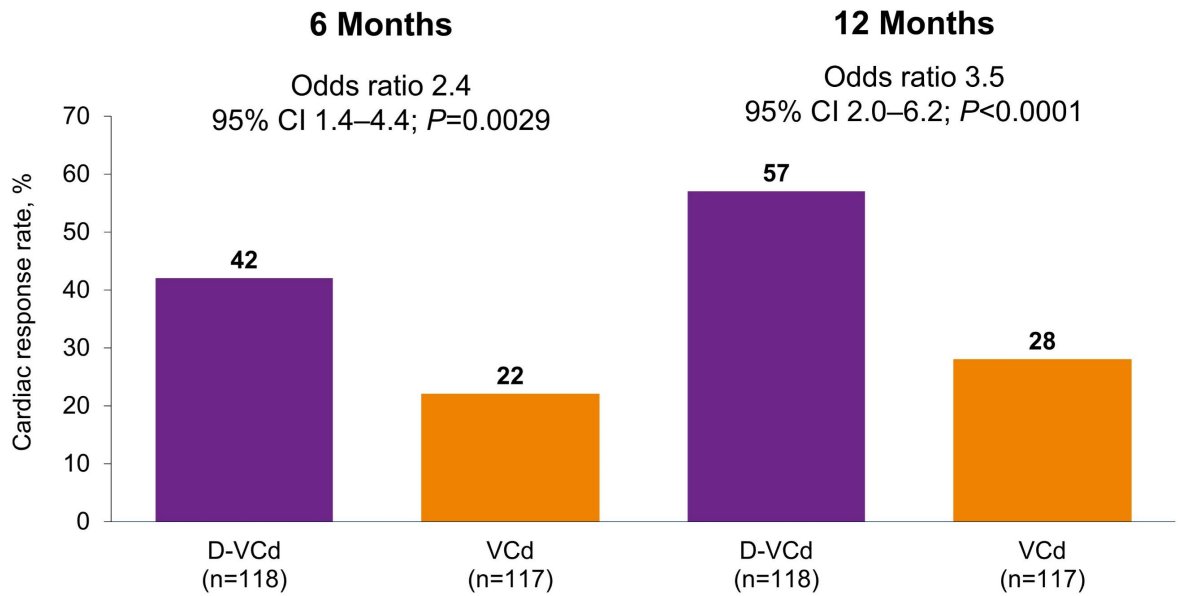


[a]Among CR responders (D-VCd, n=115; VCd, n=37).
CI, confidence interval; CR, complete response; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; FLC, free light chain; iFLC, involved free light chain.

Kastritis E., et al. Oral Presentation, ASCO 2021.

Cardiac Response Rate at 6 and 12 Months

- **Cardiac response rates improved with longer follow-up, with a doubling of response when adding DARA to VCd at 12 months**

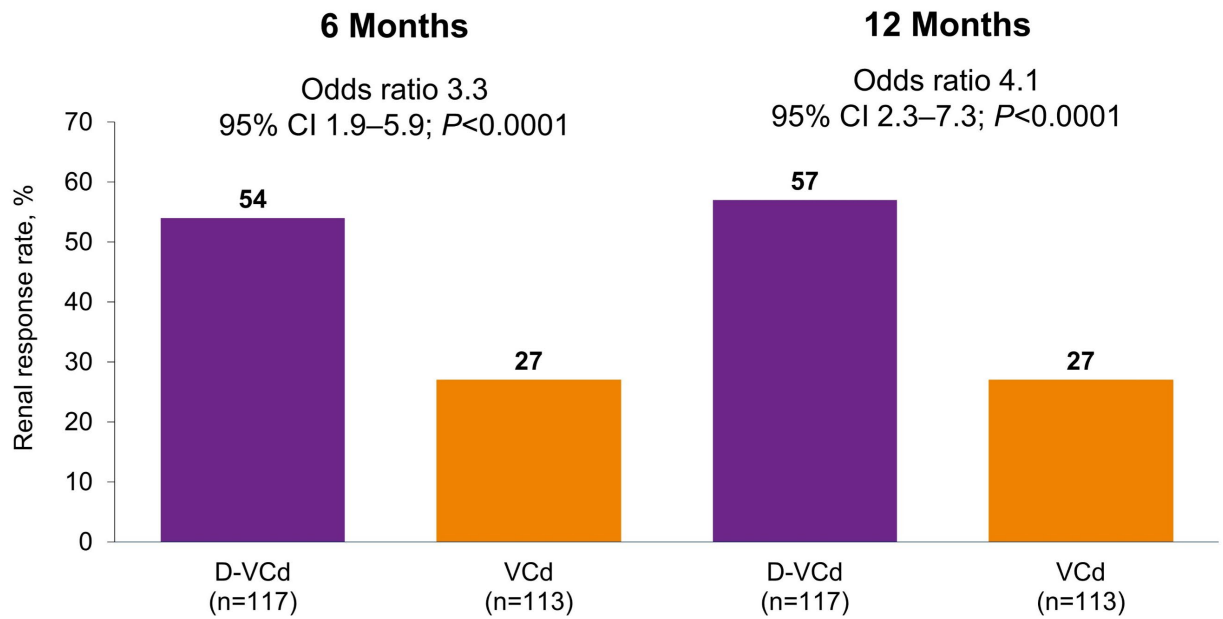


CI, confidence interval; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; DARA, daratumumab.

Kastritis E., et al. Oral Presentation, ASCO 2021.

Renal Response Rate at 6 and 12 Months

- **Renal response rates improved with longer follow-up, with a doubling of response when adding DARA to VCd at 12 months**

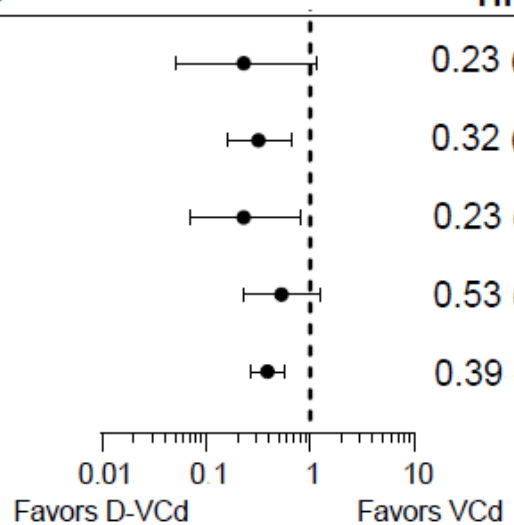


CI, confidence interval; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; DARA, daratumumab.

Kastritis E., et al. Oral Presentation, ASCO 2021.

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.

Presented at the International Myeloma Workshop (IMW); September 8–11, 2021 in Vienna, Austria

Pomalidomide in AL amyloidosis

Ref	Prior lines	N	Dosing	Median time to response	ORR/ ≥ VGPR	PFS	FU
1	2 (1-8)	33	2 mg daily Dex 40 mg/W	1.9 months	48%/18%	14 months	28 months
2	2 (1-6)	27	2/3 mg/d (n=15) 4 mg/d for 21 days (n=12) Dex 20 mg/W	3 months	50%/37.5%	18 months	17 months
3	2 (1-7)	28	2 mg/d (n=3) 4 mg/d daily (n=25) Dex 20/40 mg/W	1 month	68%/29%	16 months	44 months

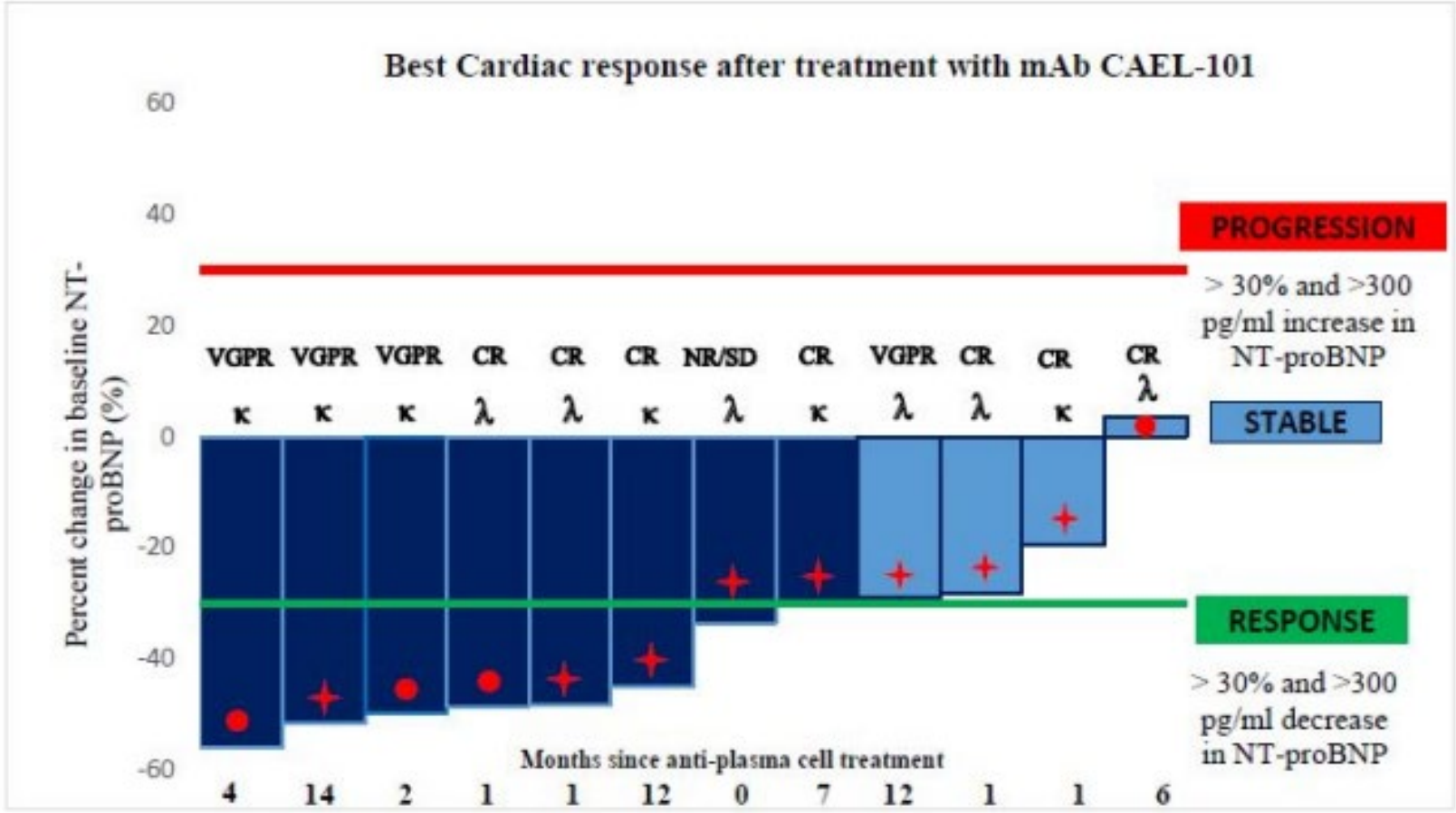
- **Dose reduction:** 48%[1], NR[2], 32%[3]
- **Grade 3/4 toxicities:**
  - Myelosuppression 26%-45%
  - Fatigue 18%
  - Pneumonia 11%-21%
  - Renal failure 3%-7.5%
  - Arrhythmias 0-21%

Rise in NT-proBNP was frequently seen, in most cases w/o clinical CHF

[1]Dispenzieri A et al, Blood. 2012;119(23):5397-404
[2]Sanchorawala V et al, Blood. 2016;128(8):1059-62
[3]Palladini G et al, Blood. 2017;129(15):2120-2123

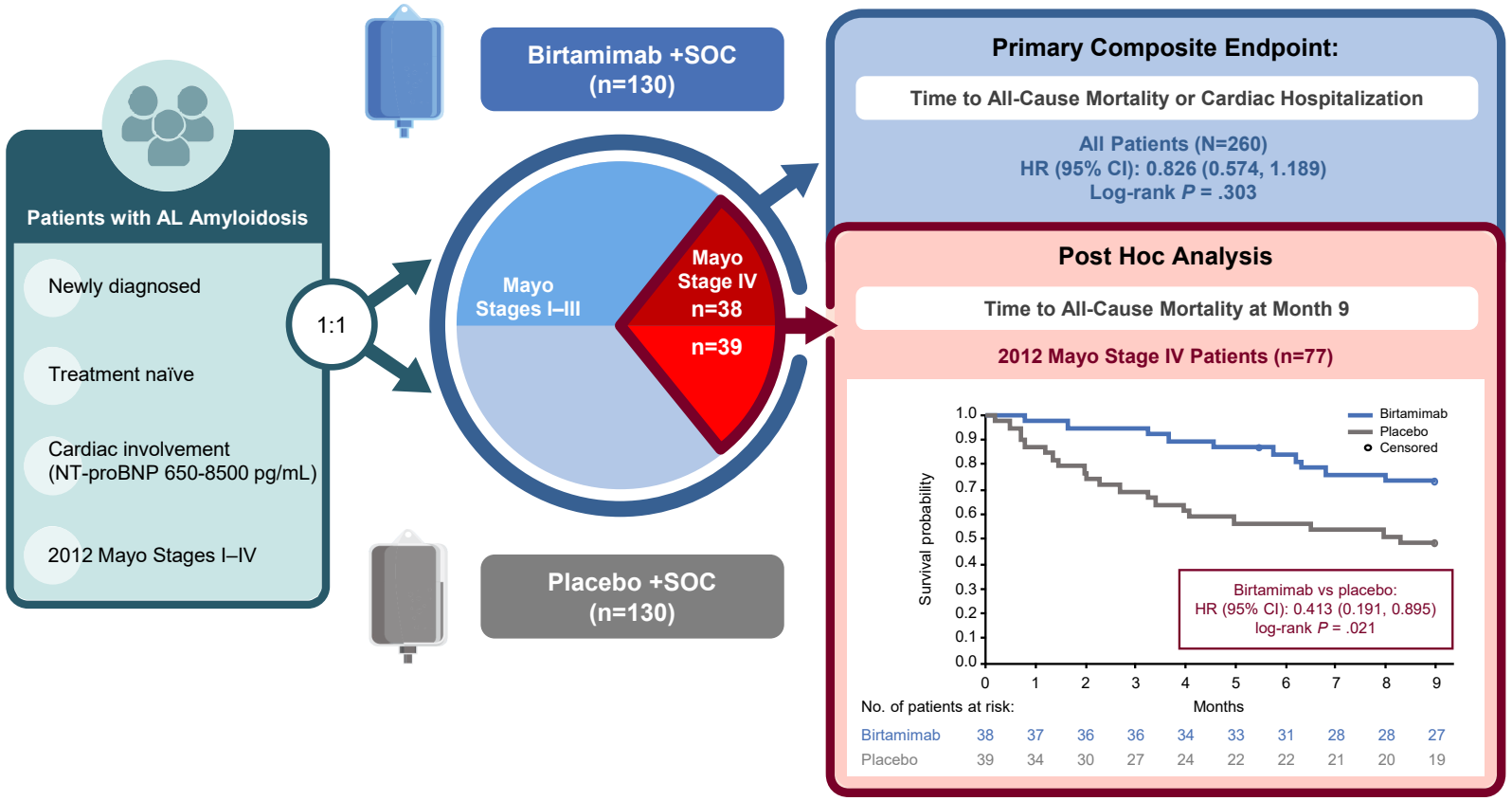
CAEL101 in cardiac AL

Phase 1a/b Study of Monoclonal Antibody CAEL-101 (11-1F4) in Patients with AL Amyloidosis
Blood Available online 16 September 2021



VITAL Trial: Birtamimab In Light Chain (AL) Amyloidosis With Cardiac Involvement

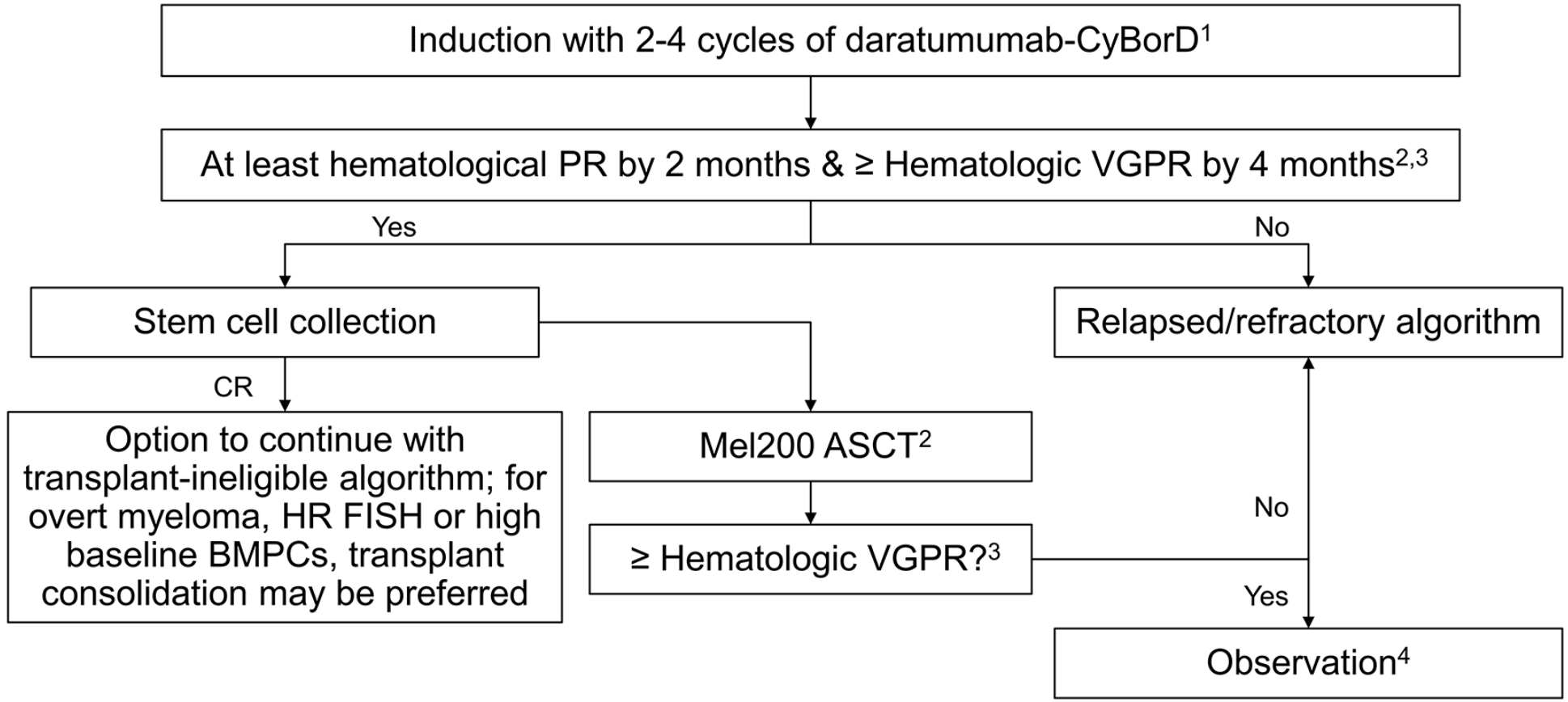
Phase 3 trial of amyloid-depleter birtamimab with standard of care (SOC) versus SOC alone



- **Birtamimab + SOC improved survival in patients with advanced AL amyloidosis in post hoc analysis**
- **The AFFIRM-AL trial is ongoing in Mayo Stage IV patients to confirm VITAL results**

Gertz et al. Blood, 2023

Newly Diagnosed AL Amyloidosis – Transplant eligible



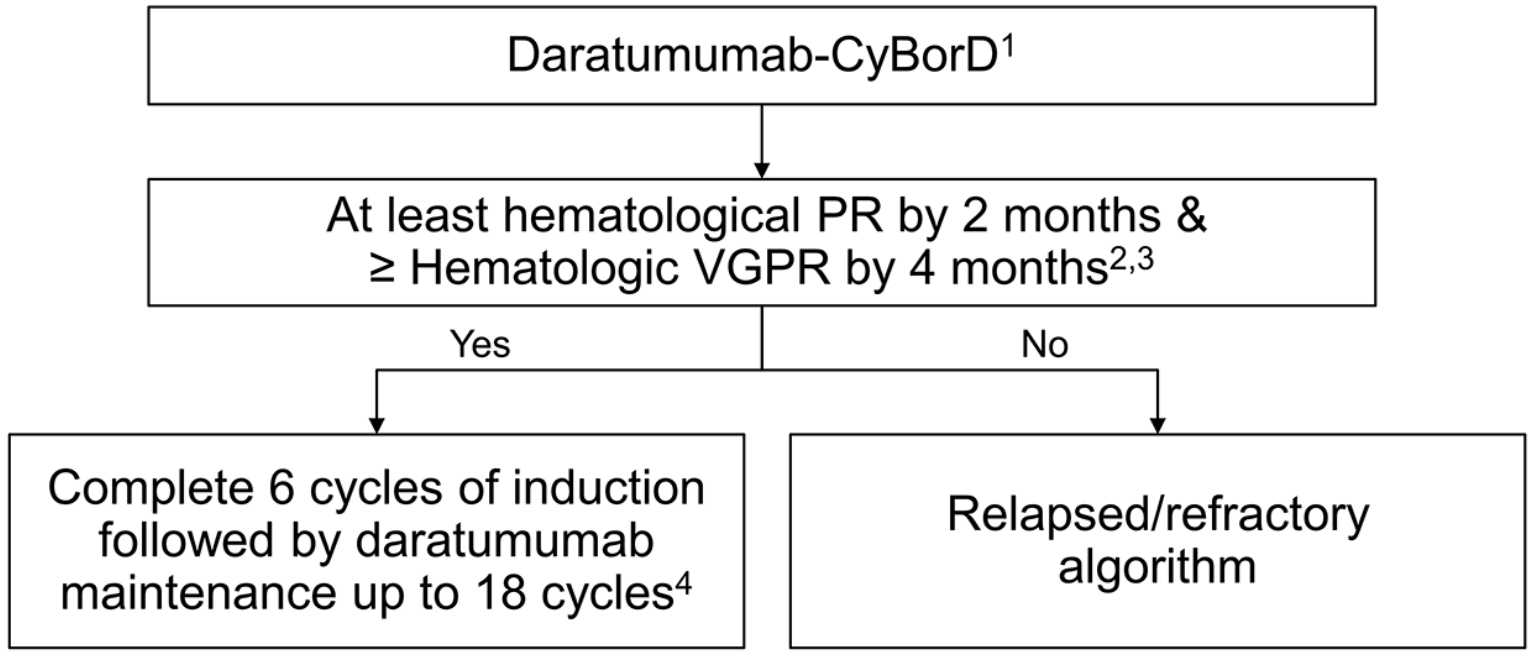
[1] If daratumumab is not accessible, CyBorD is an acceptable alternative regimen (weekly bortezomib only)

[2] For CrCl <30, use Mel 140 mg/m2

[3] Decision to change therapy if in VGPR but < CR is based on a number clinical factors. Re-refer to amyloid center of excellence

[4] For patients with overt multiple, BMPCs ≥20%, and high-risk FISH (del 17p, t(4;14), t(14;16) and t(14;20)), use myeloma-type maintenance; refer to myeloma mSMART guidelines for choice of maintenance

Newly Diagnosed AL Amyloidosis - Transplant ineligible#



For IgM AL amyloidosis consider referral to amyloidosis center due to a more challenging management

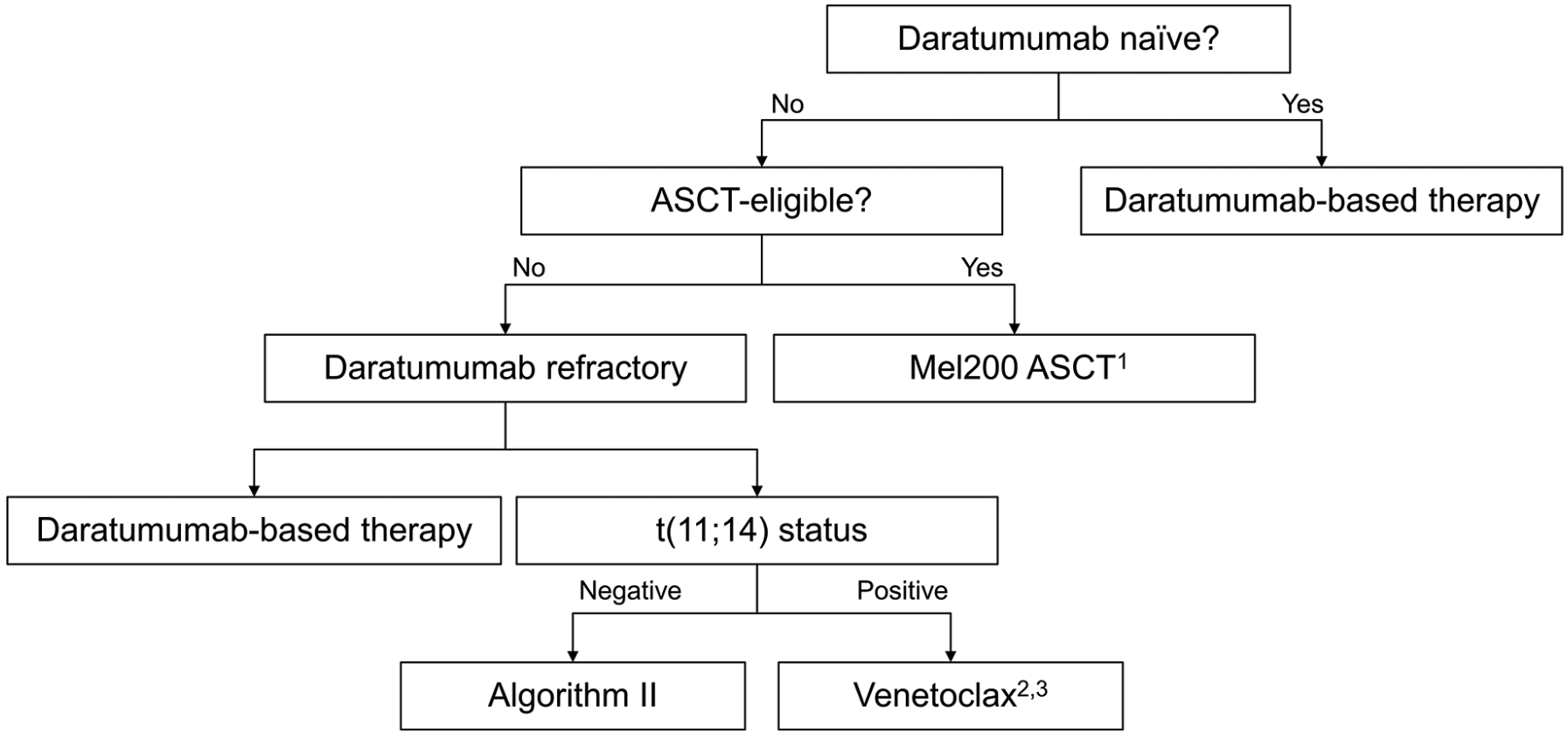
1 If daratumumab-CyBorD, 6 cycles followed by daratumumab monotherapy, completing up to 24 cycles. If daratumumab is not accessible, CyBorD or BMDex for 6-12 cycles are acceptable alternative regimens (weekly bortezomib)

2 If young, consider stem cell collection for eventual ASCT if eligibility for transplant is foreseeable

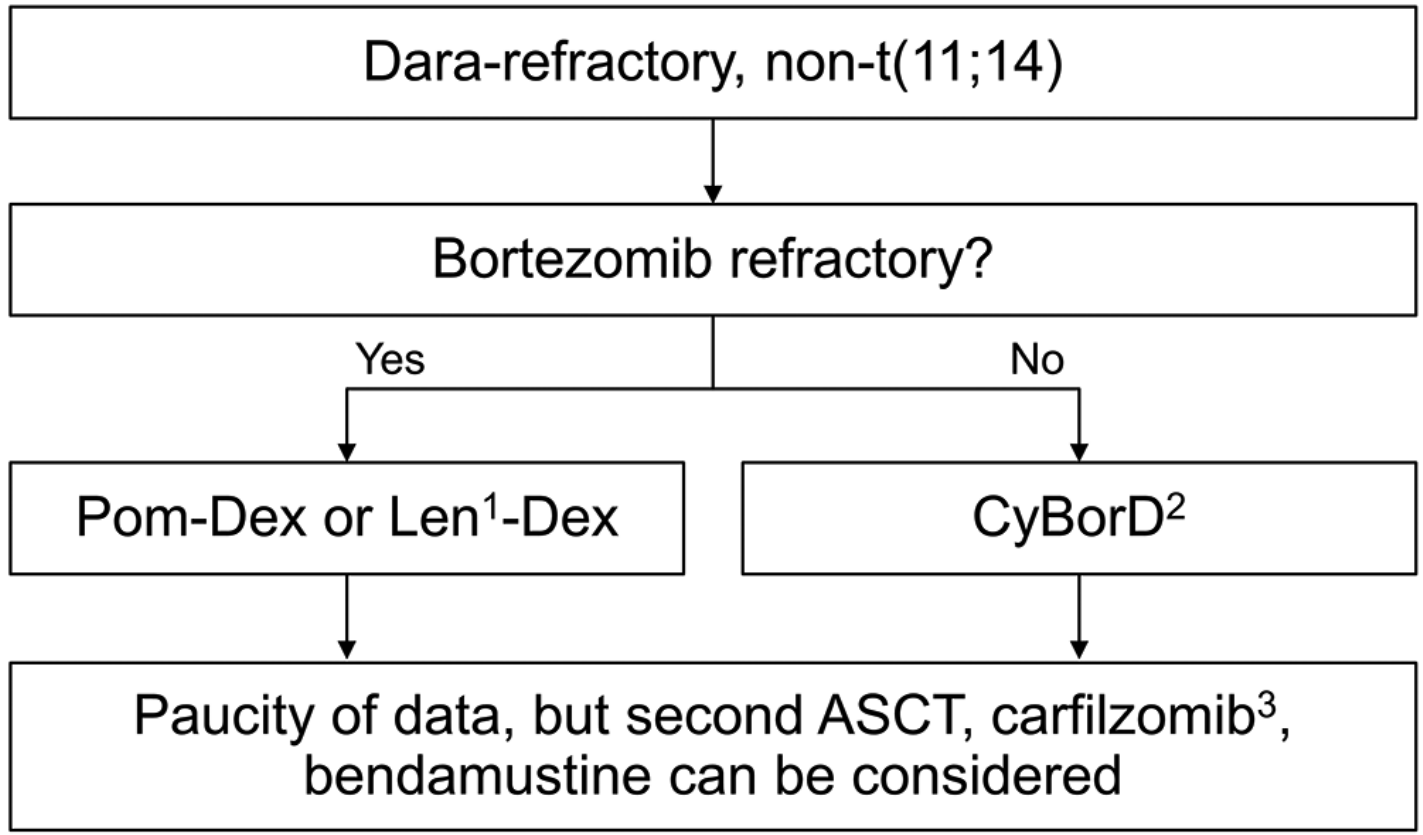
3 Decision to change therapy if in VGPR but < CR is based on a number clinical factors. Re-refer to amyloid center of excellence

4 Only for patients with overt multiple myeloma, BMPCs ≥20% or high-risk FISH consider extended duration daratumumab maintenance or other forms of maintenance used in myeloma. Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement

Treatment of relapsed/refractory AL amyloidosis – I



Treatment of relapsed/refractory AL amyloidosis – II



ASCT, autologous stem cell transplant

[1] Starting dose of lenalidomide should be no higher than 15 mg/d

[2] Melphalan-dexamethasone, bortezomib-melphalan-dexamethasone or Ixazomib-dexamethasone are appropriate if the patient has significant neuropathy

[3] Not recommended in patients with cardiac involvement

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