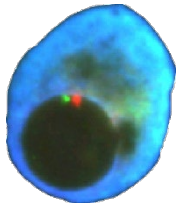
Morie Gertz MD MACP



Amyloidosis: Diagnosis, Risk Stratification and Treatment

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

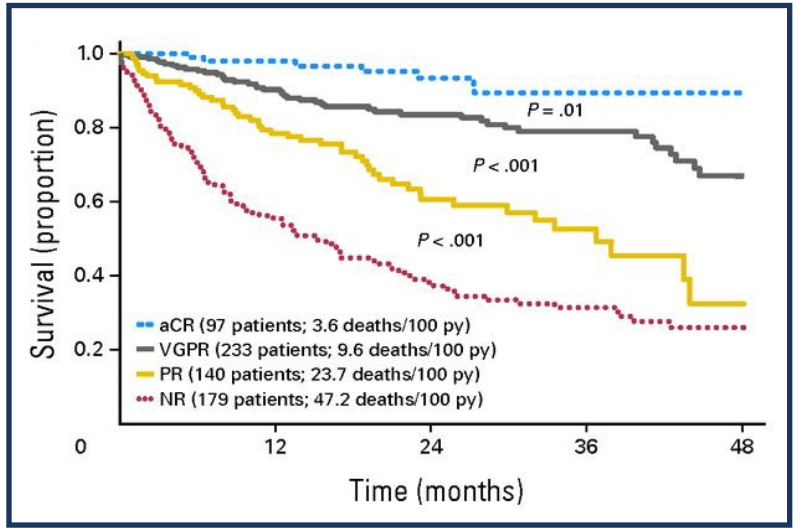
Learning Objectives

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

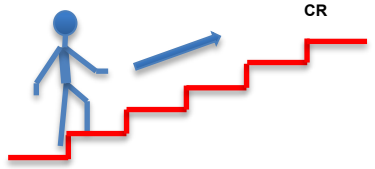
Hematological response criteria

Response category	Criteria
CR	Negative SPEP/IFE, UPEP/IFE, normal FLC ratio
VGPR	dFLC <40 mg/L
PR	dFLC decrease ≥50% (assessable in patients with baseline dFLC ≥50 mg/L)
NR	Less than PR

- Four levels of response
- Bone marrow biopsy is not needed for CR confirmation



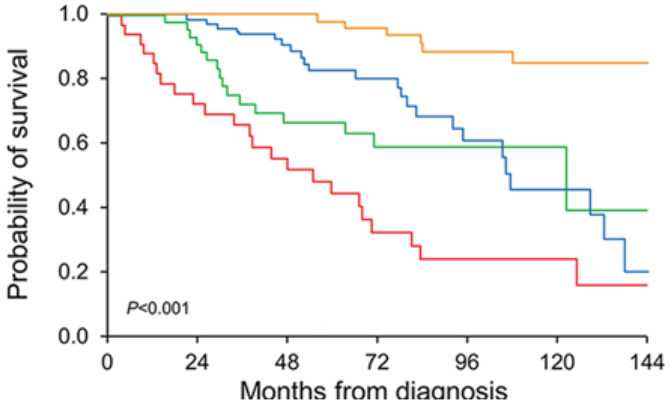
dFLC=Difference between involved to uninvolved light chains

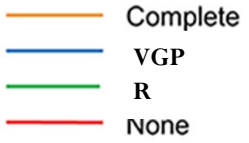


CR in the preferred response goal
VGPR is an acceptable alternative

Palladini G et al, J Clin Oncol. 2012

Graded cardiac response



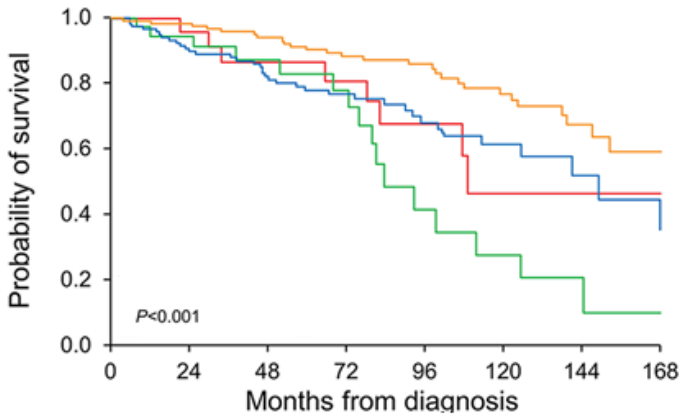


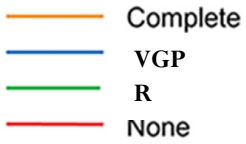
	5-year OS
CR	96%
VGPR	83%
PR	63%
No response	44%

- **Complete cardiac response:**
  Nadir NT-proBNP ≤400 pg/mL
- **Very good partial cardiac response:**
  >60% reduction in NT-proBNP not meeting complete cardiac response definition
- **Partial cardiac response**:
  31–60% reduction in NT-proBNP
- **No cardiac response**:
  ≤30% reduction in NT-proBNP

Muchtar E et al, Leukemia. 2018

Graded renal response





	5-year OS
CR	90%
VGPR	78%
PR	83%
No response	87%

- **Complete renal response:**

  Nadir proteinuria ≤200 mg per 24 h

- **Very good partial renal response:**

  >60% reduction in proteinuria not meeting complete renal response definition

- **Partial renal response**:

  31–60% reduction in proteinuria

- **No renal response**:

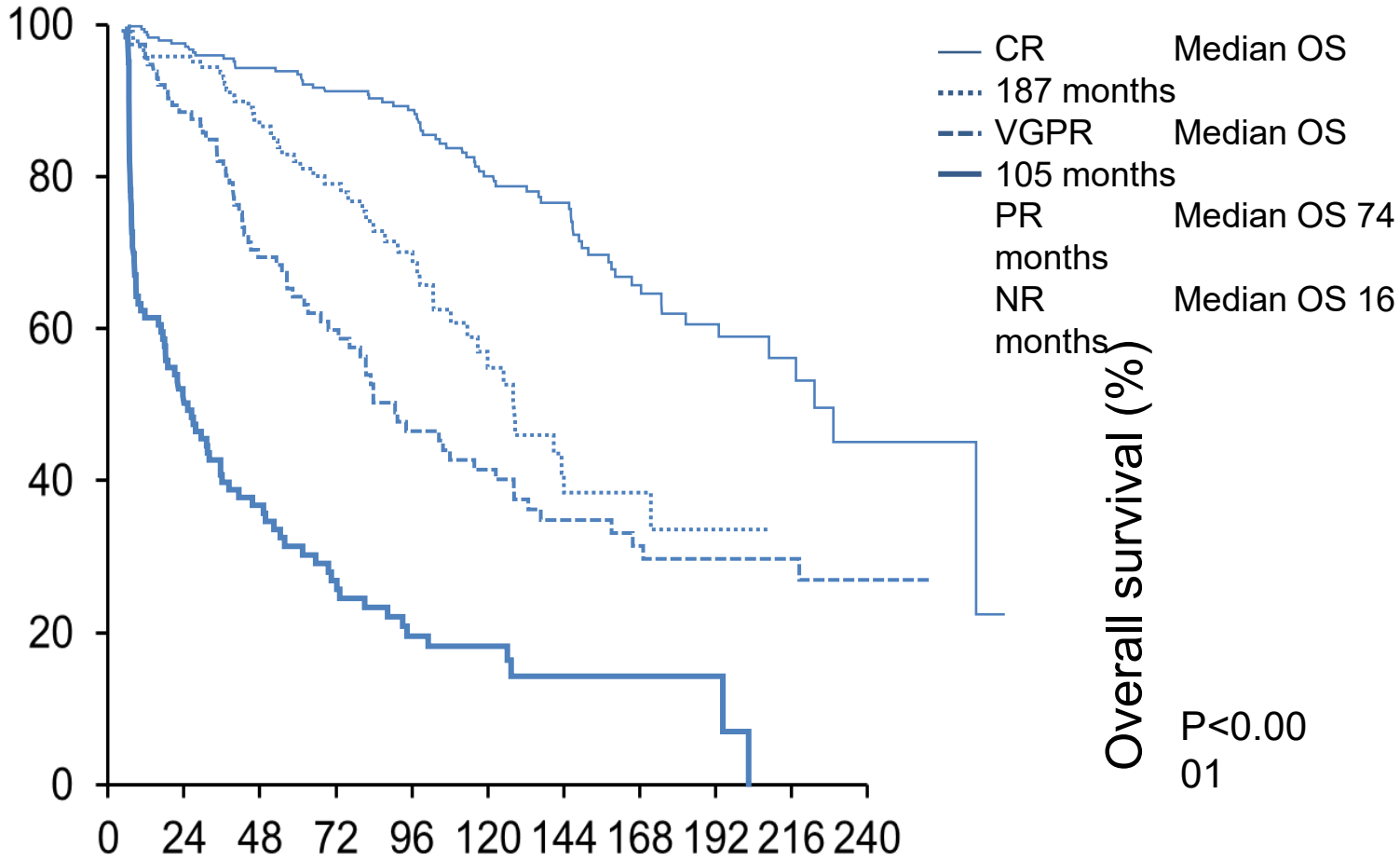
  ≤30% reduction in proteinuria

Muchtar E et al, Leukemia. 2018;32:2240-2249

Amyloidosis 2021

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

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.

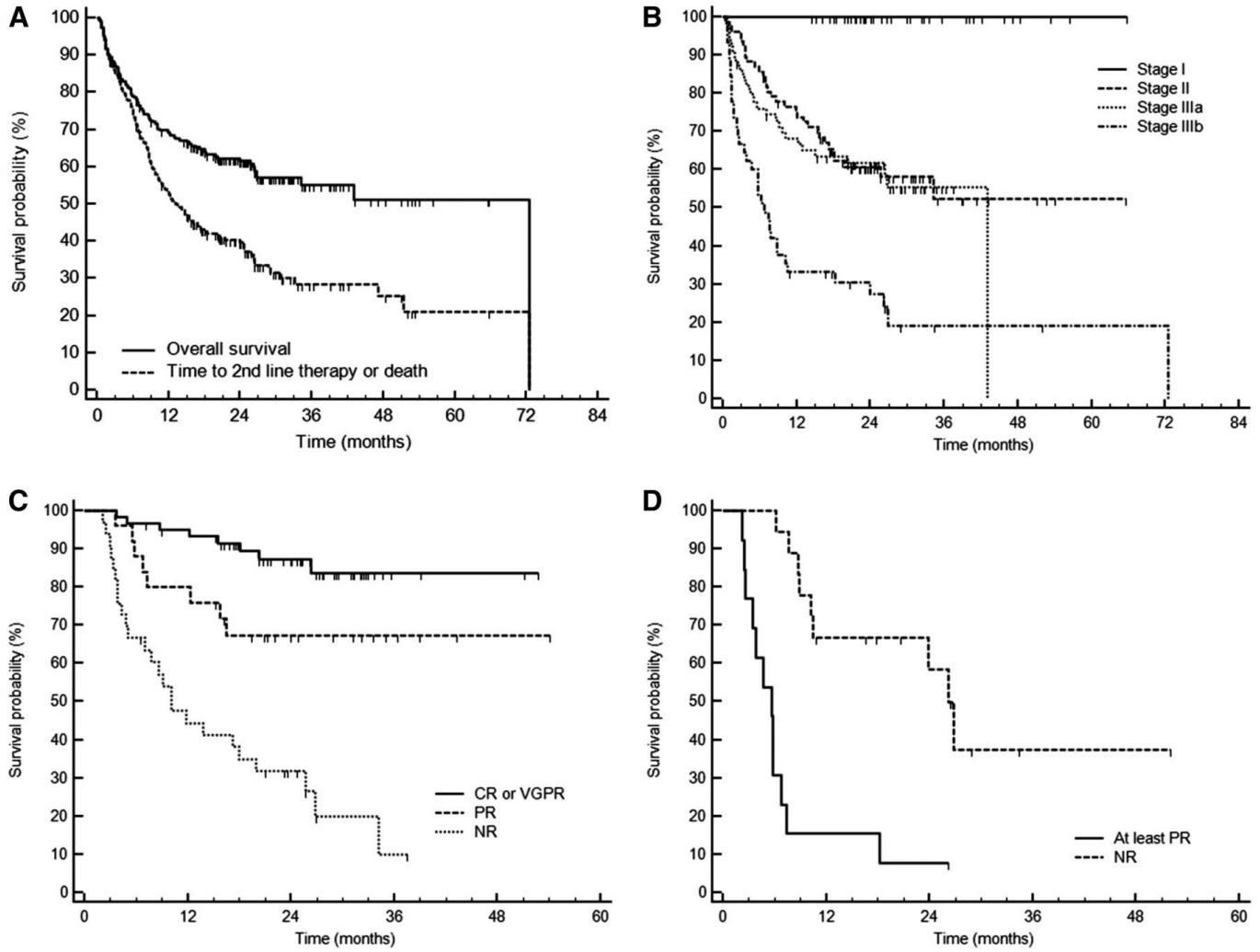
No. at risk							
CR	267	241	213	178	131	95	51
	29	13	4	1			
VGPR	150	131	84	52	30	15	
6	0	0	0	0			
PR	115	96	64	43			
35	26	18	16	8	2	0	
NR	107	45	27	18	12	5	

ASCT Transplant Eligibility Criteria

- "Physiologic" Age ≤ 70 years
- Performance Score ≤ 2
- Systolic BP ≥ 90 mmHg [a]
- TnT < 0.06 ng/ml (or hs-TnT < 75 ng/ml)
- CrCl ≥ 30 ml/min [b] (unless on chronic dialysis)
- NYHA Class I/II

[a] Caution as well for patients with BP <100 mmHg
[b] Selected patients may become eligible for ASCT with cardiac and renal transplantation

Survival of 230 patients with AL amyloidosis treated with CyBorD.



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

PI's other than bortezomib

- Ixazomib[1]:
  - Phase 1/2 study in 27 patients with R/R AL, 70% with prior Bortz
  - MTD* 4 mg, dex was allowed from cycle 4
  - ORR 52%, CR 10%, VGPR 33%. Responses were higher in PI-naïve patients
  - Median PFS 13.6 months.
  - Grade 3/4 AEs: fatigue, dyspnea 15% each

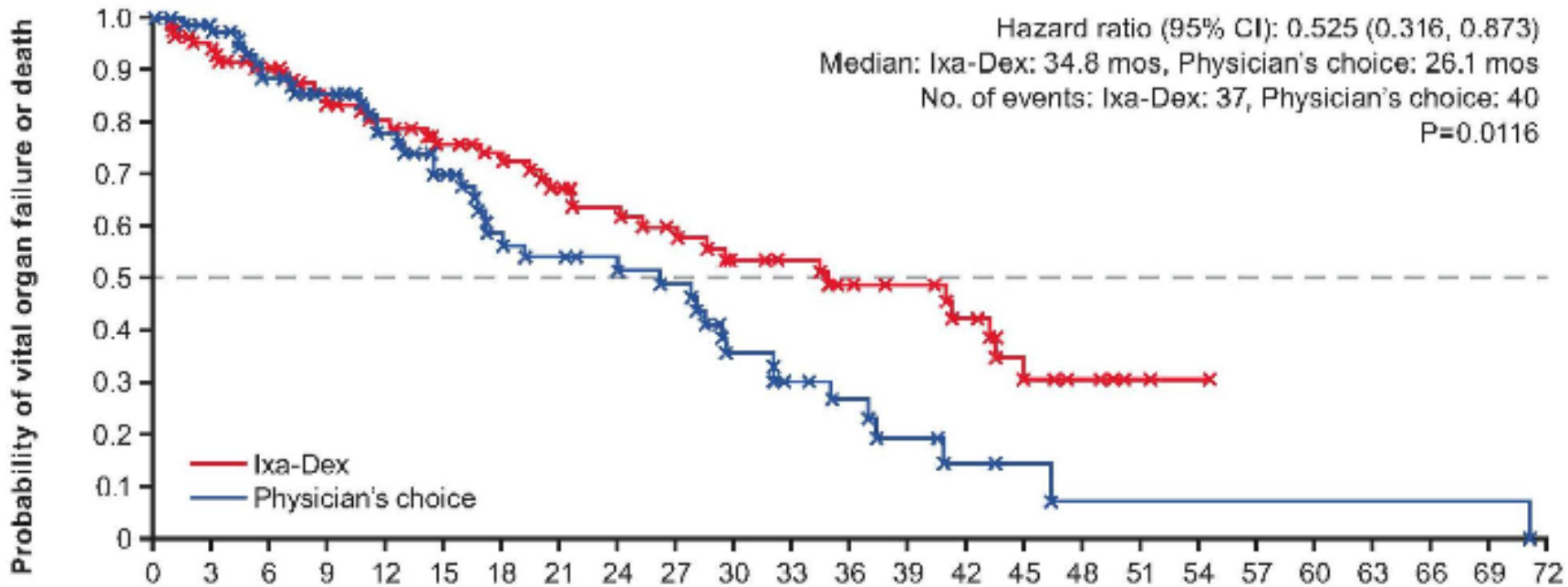
* MTD=Maximal tolerated dose

- Carfilzomib[2]:
  - Challenging use in AL amyloidosis: 10% cardiac toxicity in MM patients; IV infusion
  - Dose-escalating phase 1 (n=28). MTD* 20/36 mg/m^2
  - ORR 54%, ≥VGPR 39%
  - Cardiac toxicity 36% (VTs, decreased EF, hypoxemia…)

[1]Sanchorawala V et al , Blood. 2017;130(5):597-605
[2]Cohen AD et al, Blood. 2016;128:645–645

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

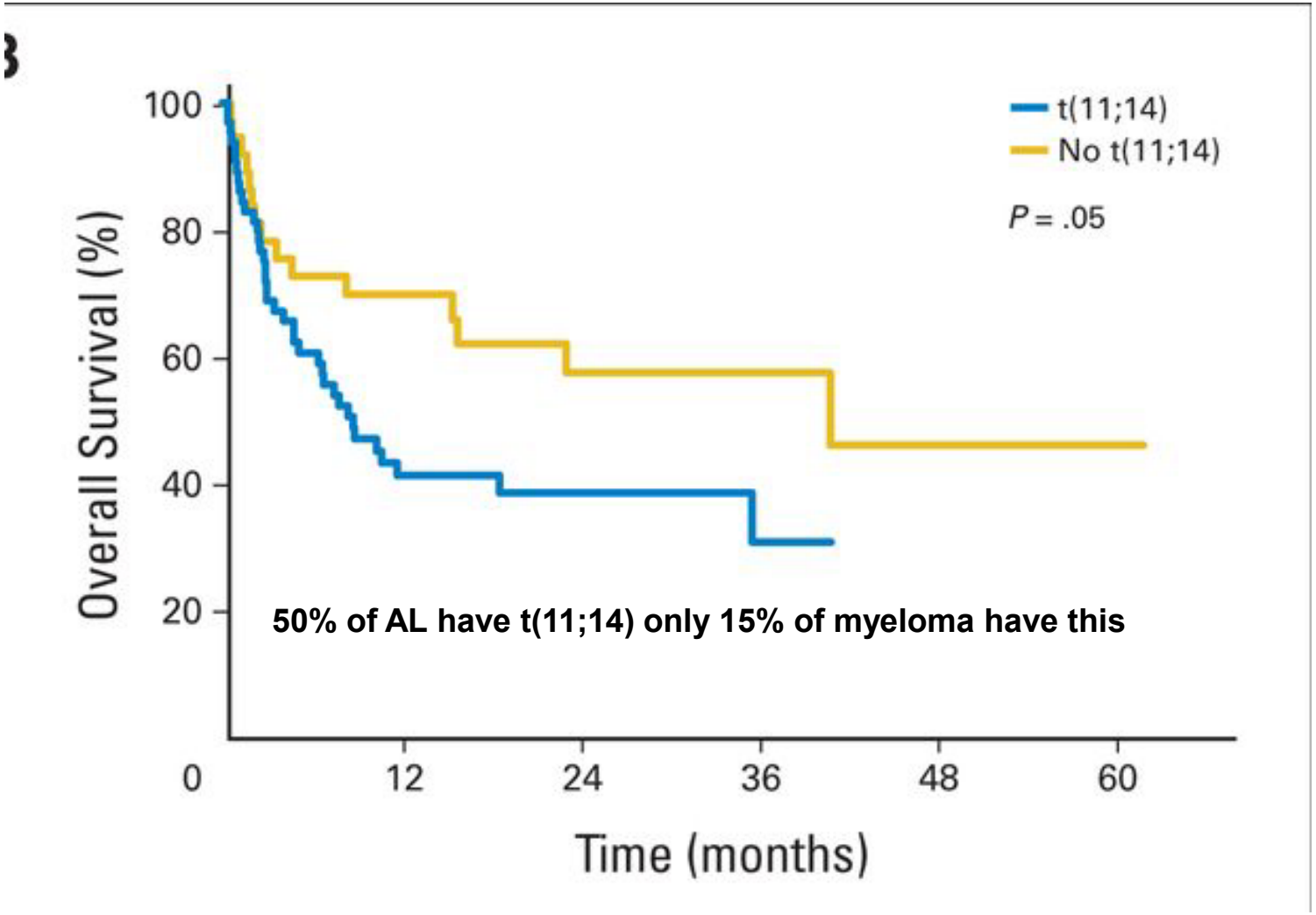
Figure. Time to vital organ deterioration/death and efficacy outcomes (PA)



Number of Patients at Risk

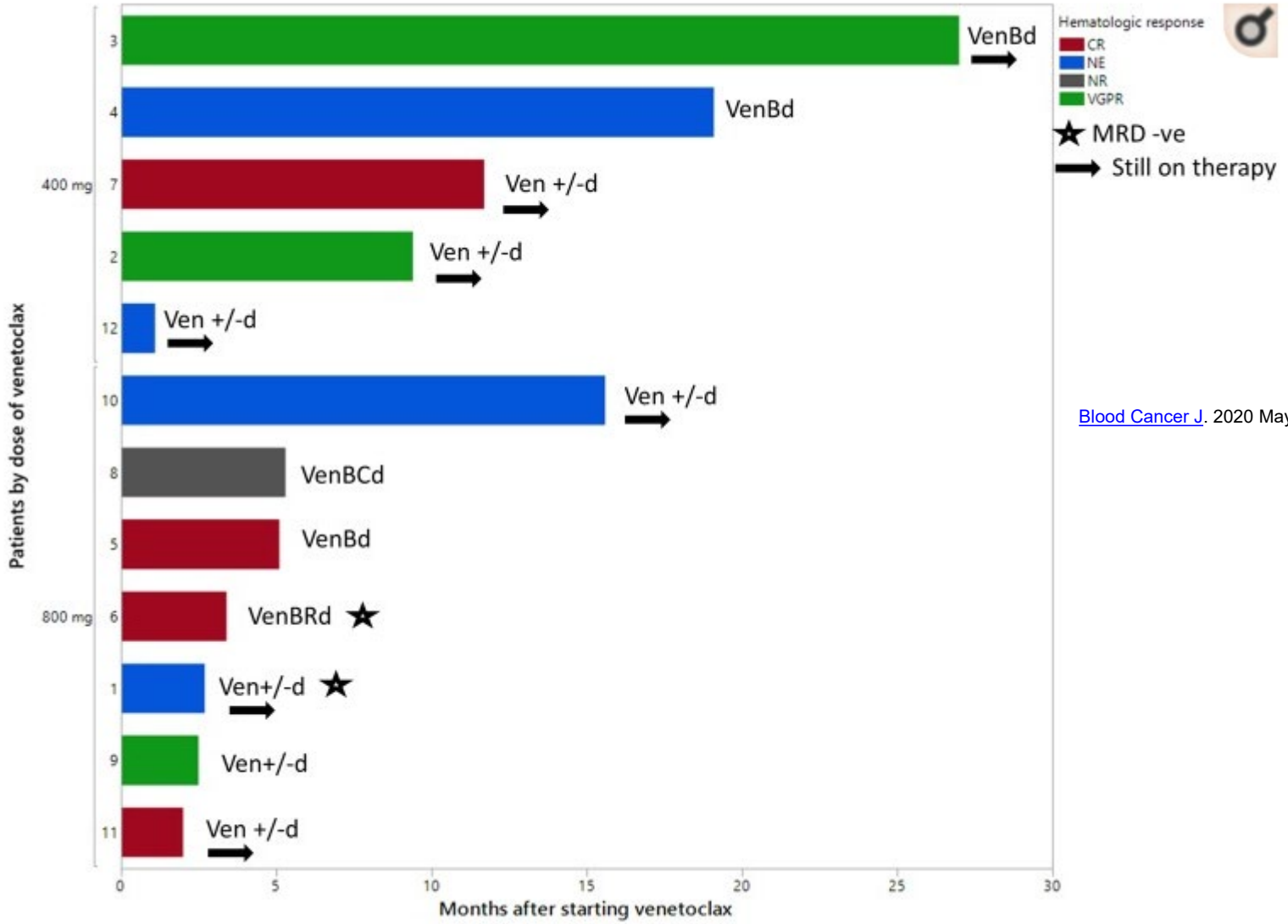
Ixa-Dex	85	78	68	58	55	49	42	39	34	29	25	22	18	16	13	7	5	2	1	0	0	0	0	0	0
Physician's choice	83	69	60	51	41	33	25	24	20	19	13	10	7	5	3	2	1	1	1	1	1	1	1	1	0

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

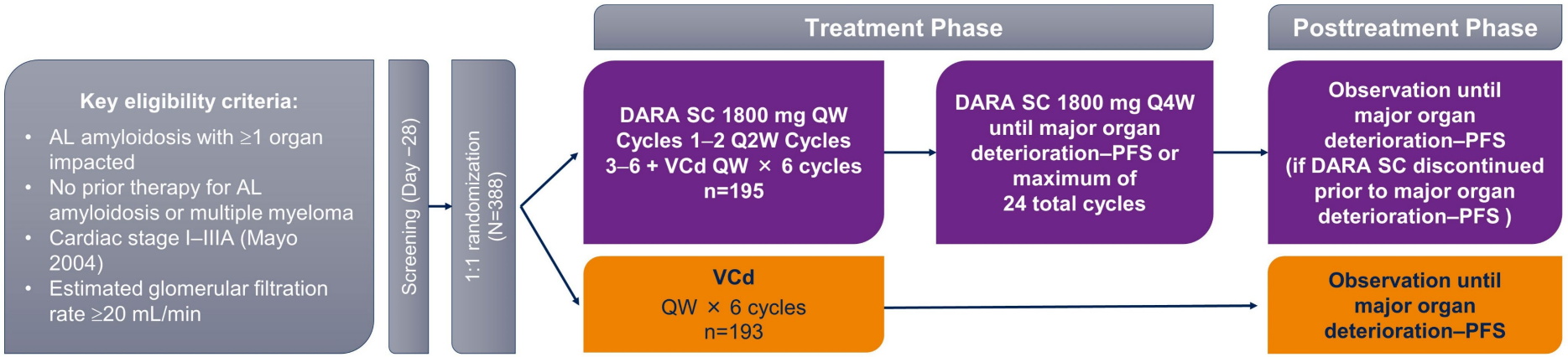
Ref	Design	Prior lines, med	N	Median time to response	ORR (%)	≥VGPR/CR (%)	Median FU
1	Retrospective	3	25	1.0 month	76%	60%/36%	NR
2	Retrospective	3	44; 50% in combination	2.2 months	83%	80%/17%	10.2 months
3	Retrospective	3	20	4 weeks	86%	86%/33%	10 months
4	Phase II	2	21	Fast	100%	84.2% at 3mo	NR
5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

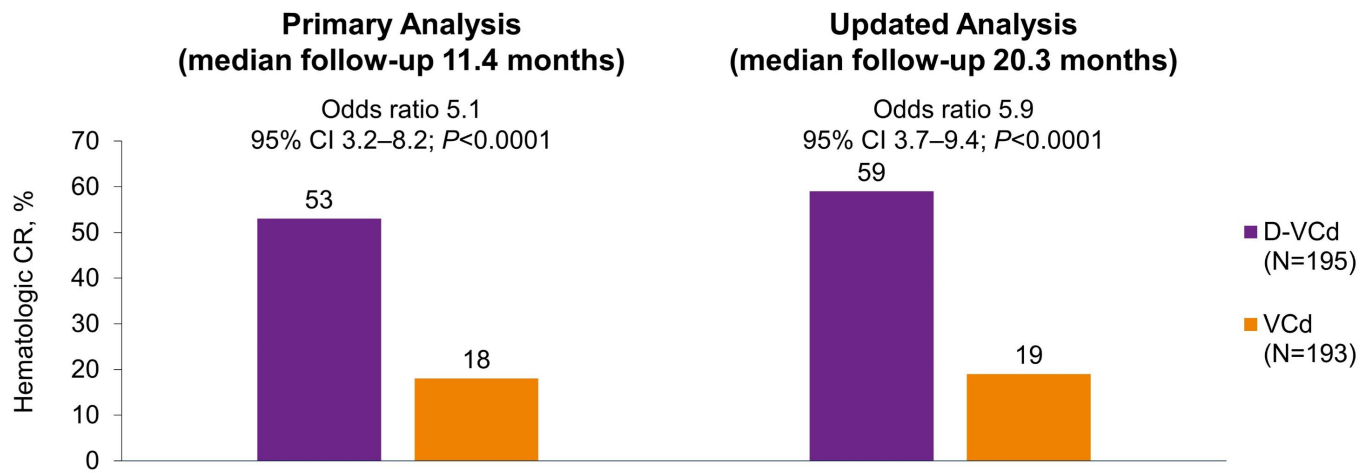


AL, light chain; DARA, daratumumab; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; PFS, progression-free survival; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous.

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

Hematologic CR: Primary Endpoint

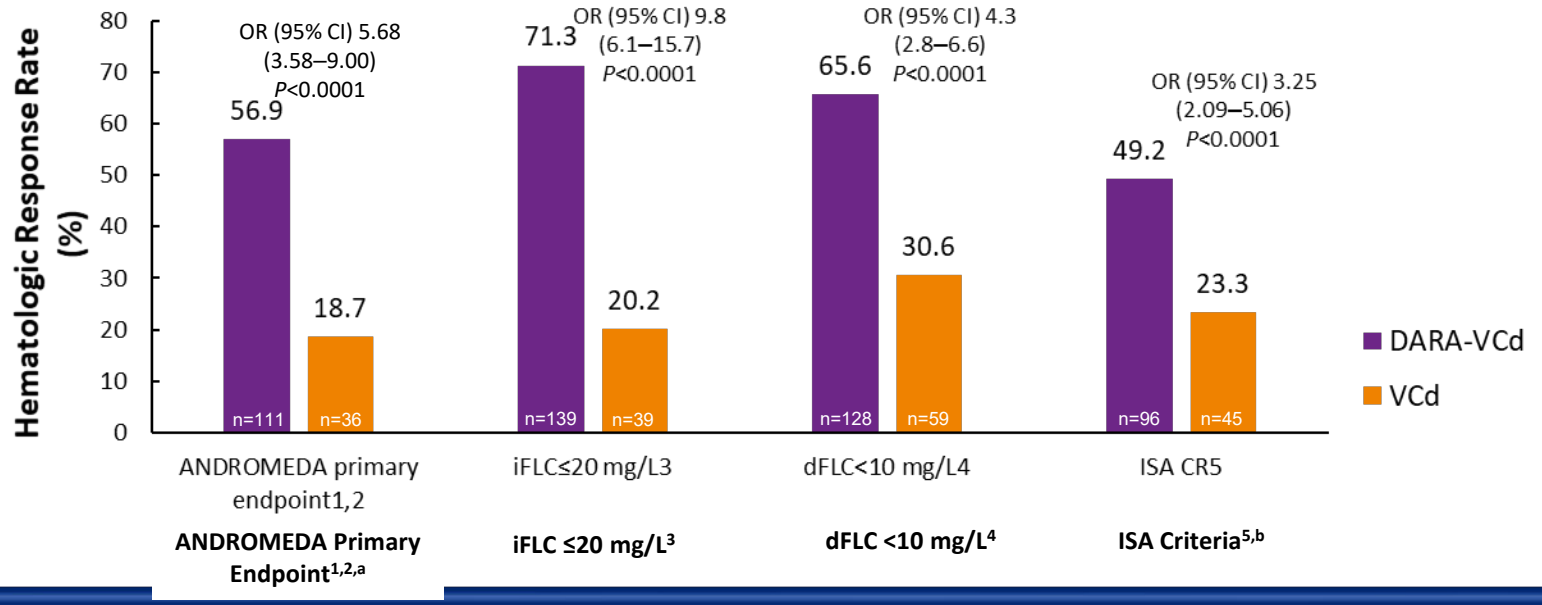
- **Hematologic CR was defined as normalization of FLC levels and FLC ratio and negative serum and urine immunofixation**
  - If iFLC < upper limit of normal, normalization of the uninvolved FLC and FLC ratio were not required
- **Rates of hematologic CR remained significantly higher with D-VCd than 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.

Best Hematologic Response Rates at Any Time by Treatment Group



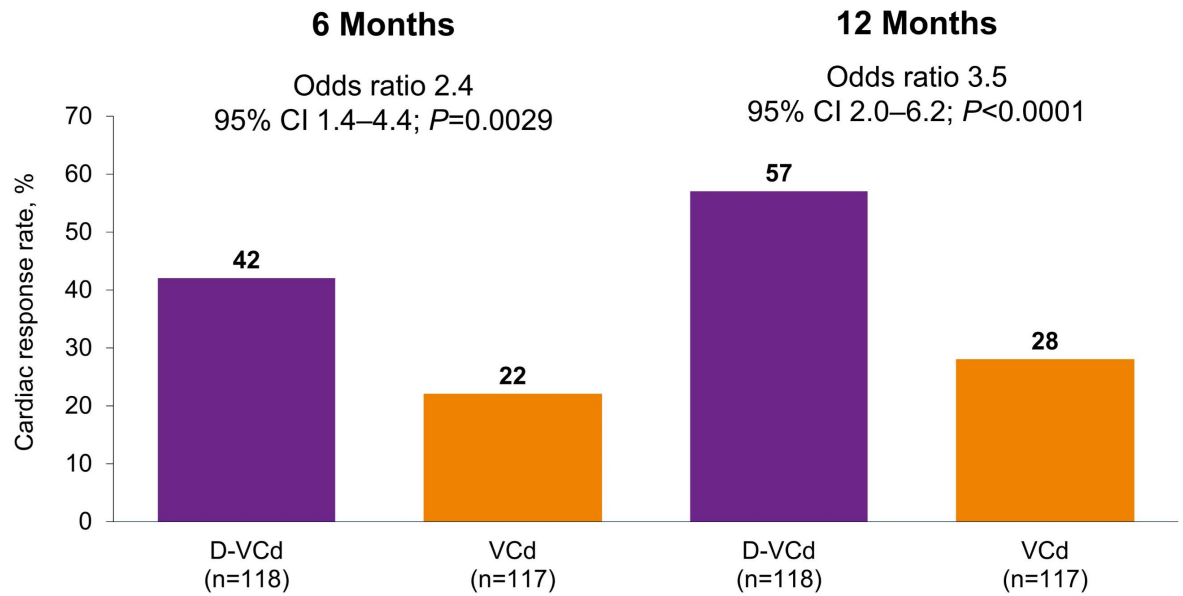
Higher rates of hematologic response were observed with Dara-VCd across all criteria

DARA, daratumumab; dFLC, difference between involved and uninvolved free light chain; FLCr, free light chain ratio; iFLC, involved free light chain; ISA, International Society of Amyloidosis; OR, odds ratio; ULN, upper limit of normal; VCd, bortezomib, cyclophosphamide, and dexamethasone.

Data cutoff: 15Jun20. [a]Defined as negative serum and urine immunofixation and iFLC<ULN regardless of FLCr. [b]Defined as normal FLCr and negative serum and urine immunofixation. 1. Comenzo RL, et al. *Leukemia* 2012;26(11):2317-25. 2. Sidana S, et al. *Leukemia* 2019;34(5):1472-5. 3. Muchtar E, et al. *Leukemia* 2019;33(3):790-4. 4. Manwani R, et al. *Blood* 2019;134(25):2271-80. 5. Palladini G, et al. *J Clin Oncol* 2012;30:4541-9.

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**

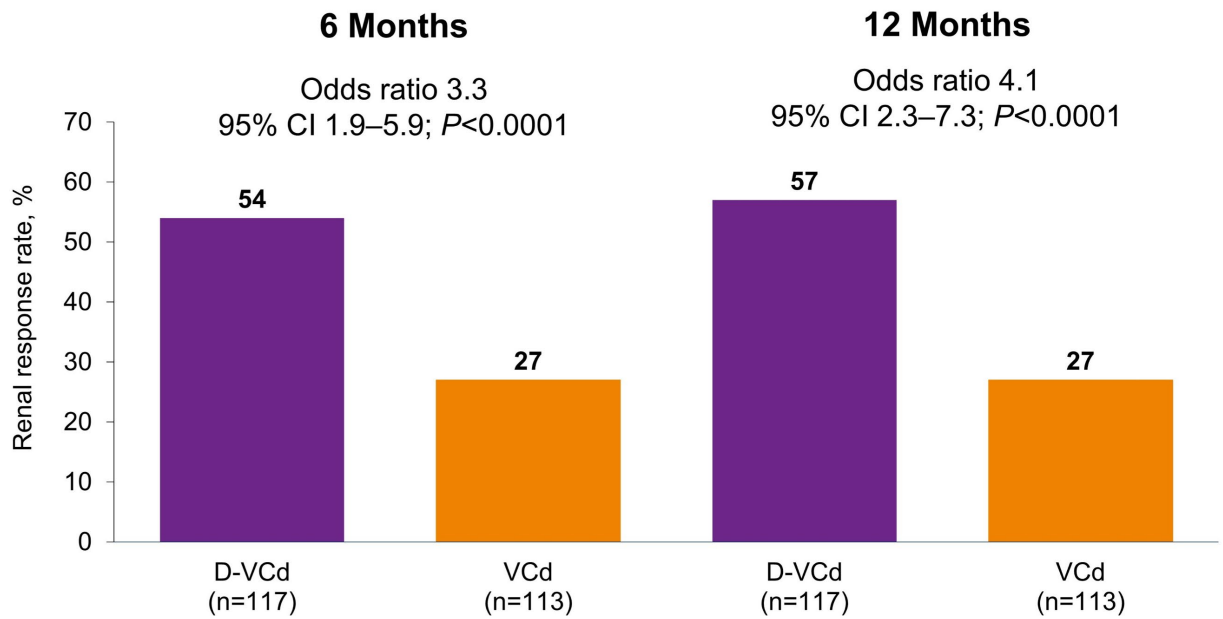


CI, confidence interval; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; DARA, daratumumab.

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

Renal Response Rate at 6 and 12 Months

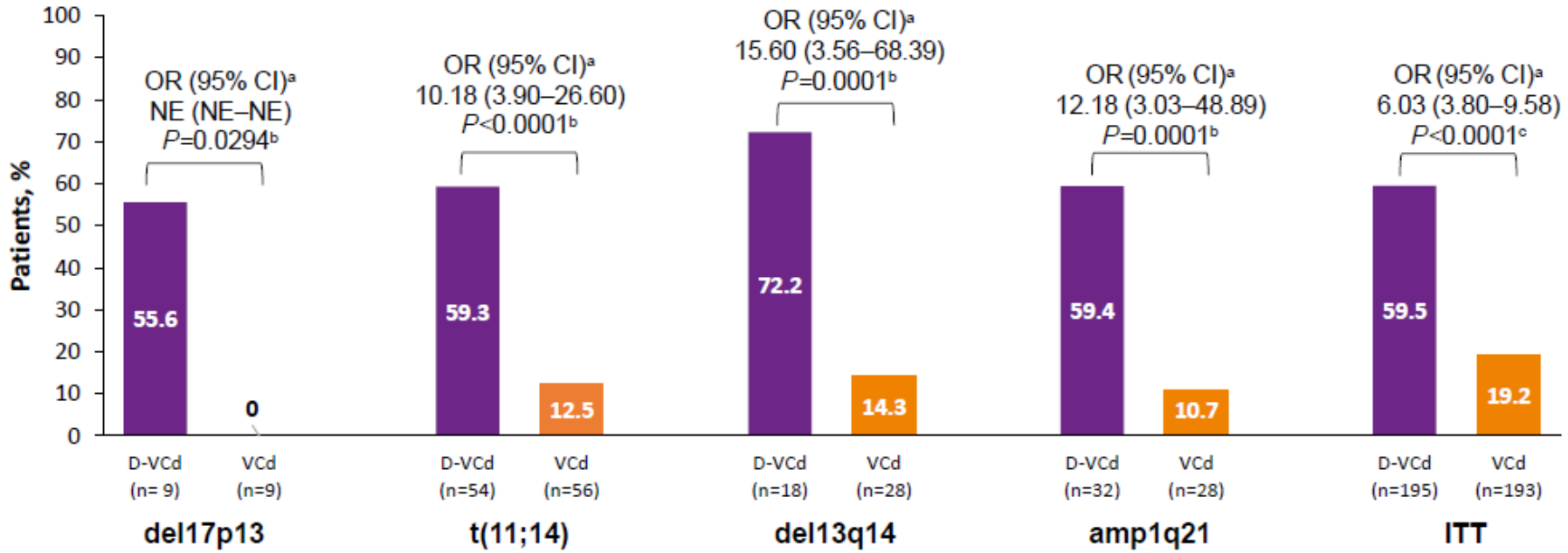
- **Renal response rates improved with longer follow-up, with a doubling of response when adding DARA to VCd at 12 months**



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

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

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

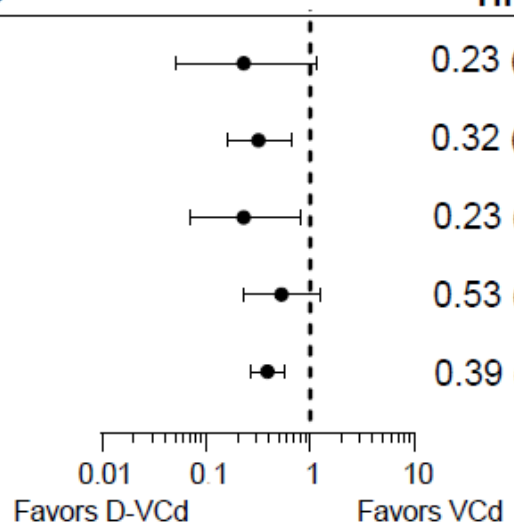


[a]ORs and 95% CI were calculated using Mantel-Haenszel estimates; [b]nominal p-values were calculated from Fisher's exact test; [c]p-value was calculated from Cochran Mantel-Haenszel Chi-Squared test.
12-month landmark data cut (CCO November 2020).
CI, confidence interval; CR, complete response; D-VCd,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

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

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

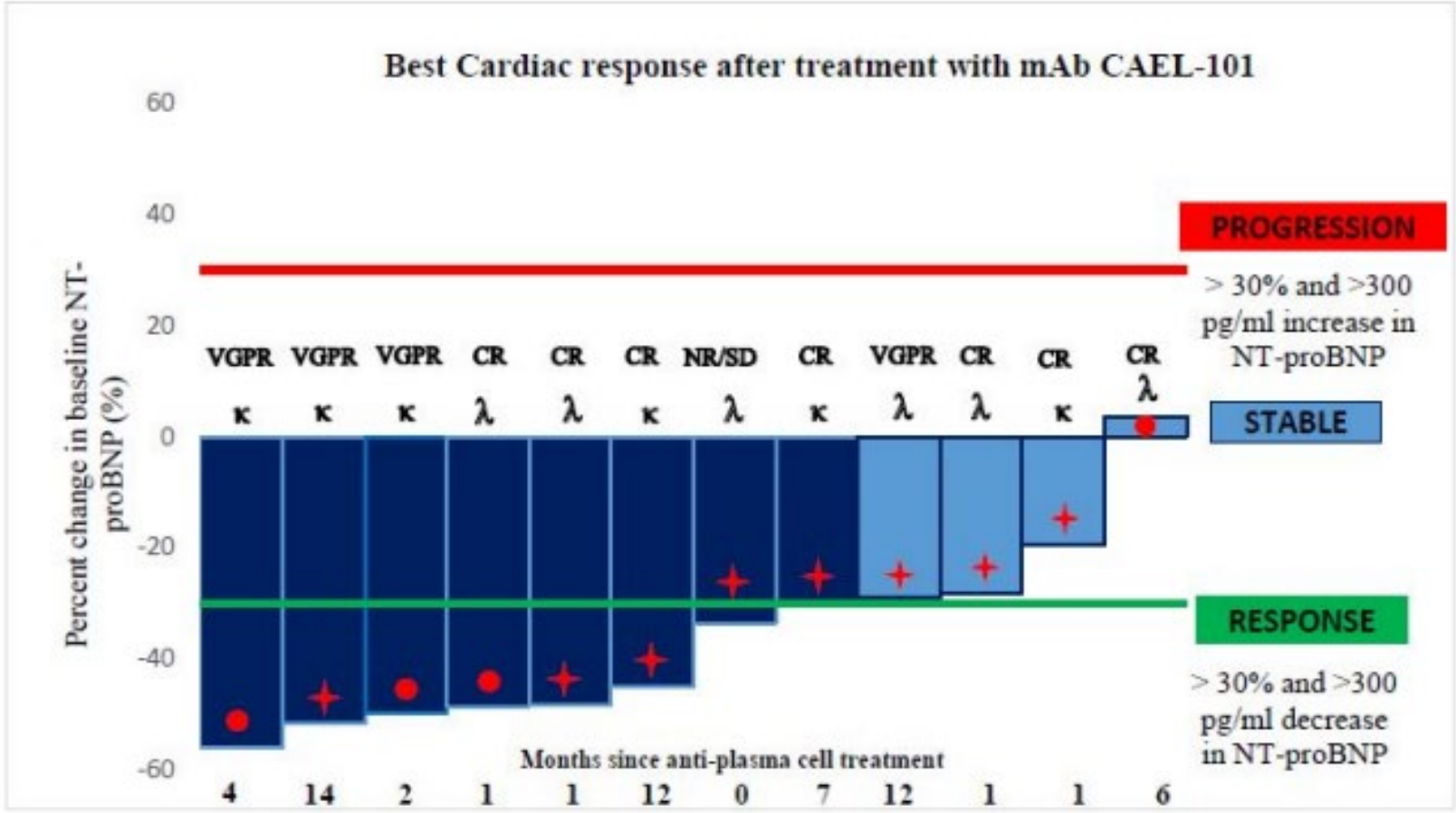
- **Dose reduction:** 48%[1], NR[2], 32%[3]
- **Grade 3/4 toxicities:**
  - Myelosuppression 26%-45%
  - Fatigue 18%
  - Pneumonia 11%-21%
  - Renal failure 3%-7.5%
  - Arrhythmias 0-21%

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

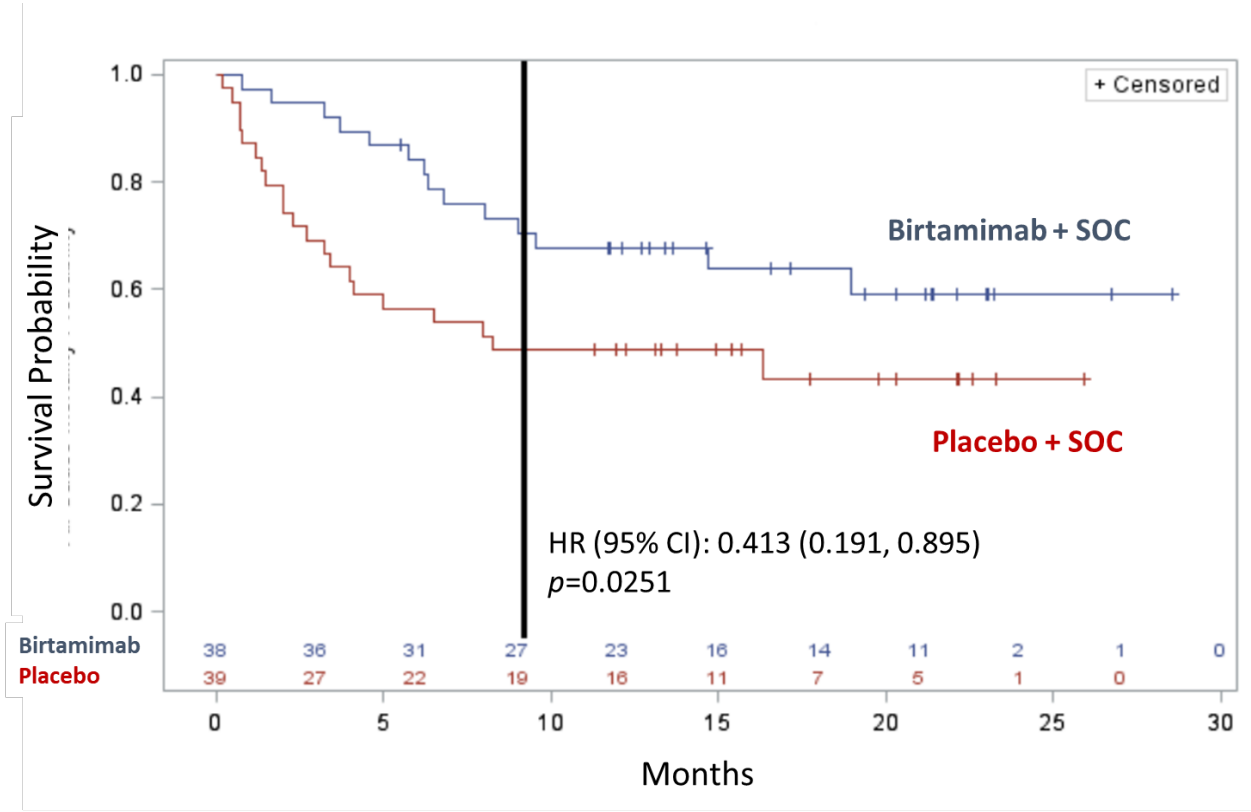
CAEL101 in cardiac AL

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



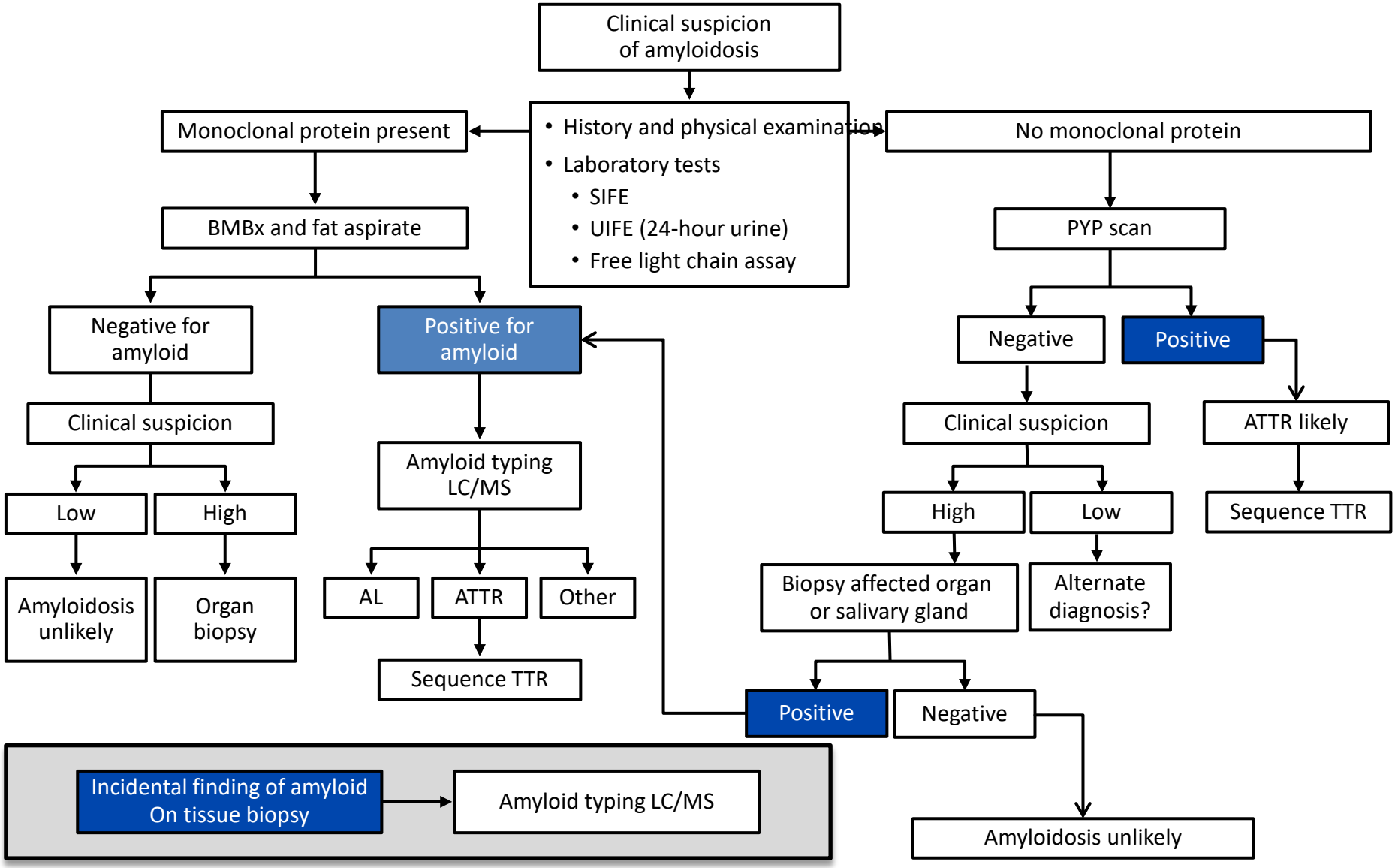
Antibody Therapy Directed at Deposits

ACM in VITAL for the Mayo Stage IV Subgroup of Patients with AL Amyloidosis



Author's slide submitted to ASH 2021

AMYLOIDOSIS DIAGNOSTIC ALGORITHM

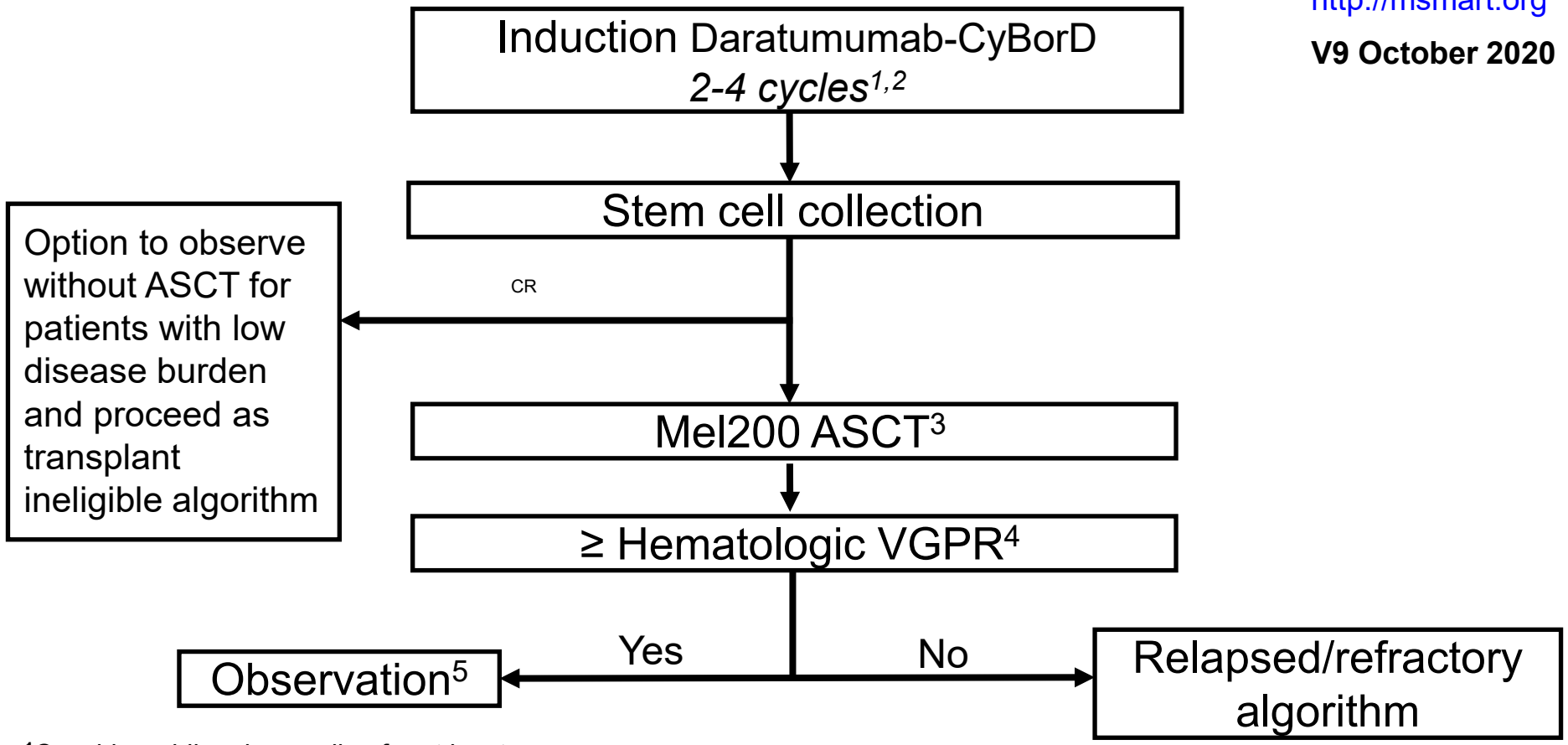


Author's slide

Newly Diagnosed AL Amyloidosis - Transplant eligible

http://msmart.org

V9 October 2020



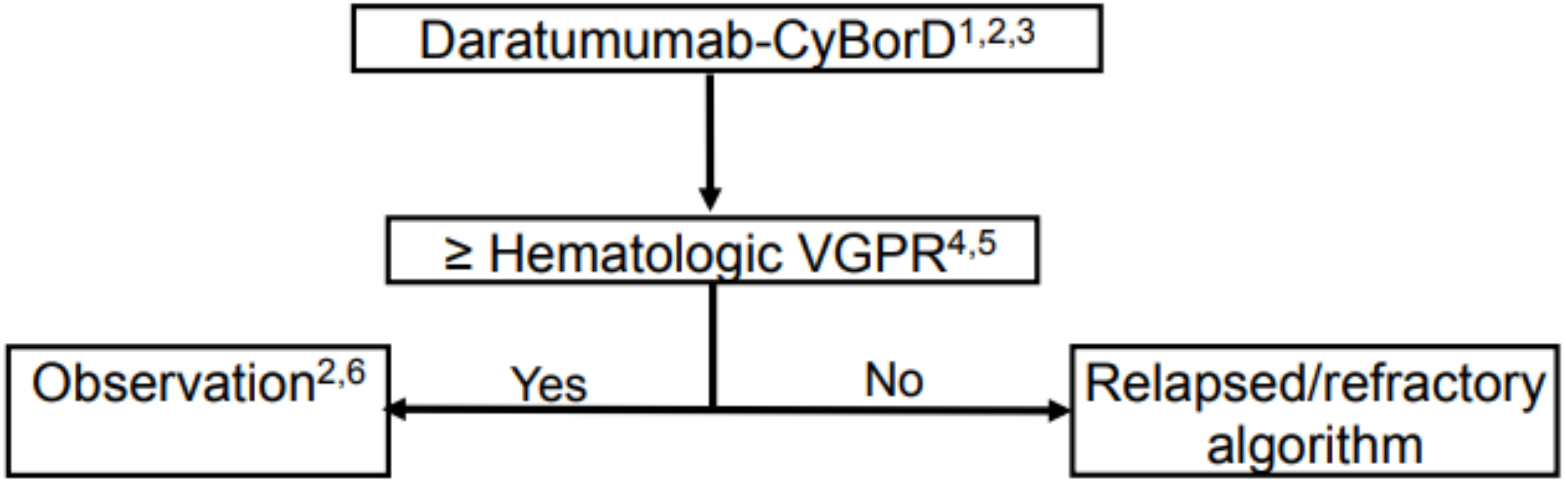
[1]Consider adding doxycycline for at least a year
[2]If daratumumab is not accessible, CyBorD is an acceptable alternative regimen (weekly bortezomib only)
[3]For CrCl <30, use Mel 140 mg/m2
[4]Decision to change therapy if in VGPR but < CR is based on a number clinical factors. Re-refer to amyloid center of excellence
[5]For patients with overt multiple, use myeloma-type maintenance; consider for BMPCs ≥20% and high-risk FISH (del 17p, t(4;14), t(14;16) and t(14;20)). Please refer for myeloma mSMART guidelines for choice of maintenance

MAYO CLINIC

Newly Diagnosed AL Amyloidosis - Transplant ineligible#

http://msmart.org

V9 October 2020



[1]Consider adding doxycycline for at least a year

[2]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)

[3]If young, consider stem cell collection for eventual ASCT if eligibility for transplant is foreseeable

[4]If < PR at 2 months or < VGPR within 4 cycles change therapy, unless signs of organ response are seen

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

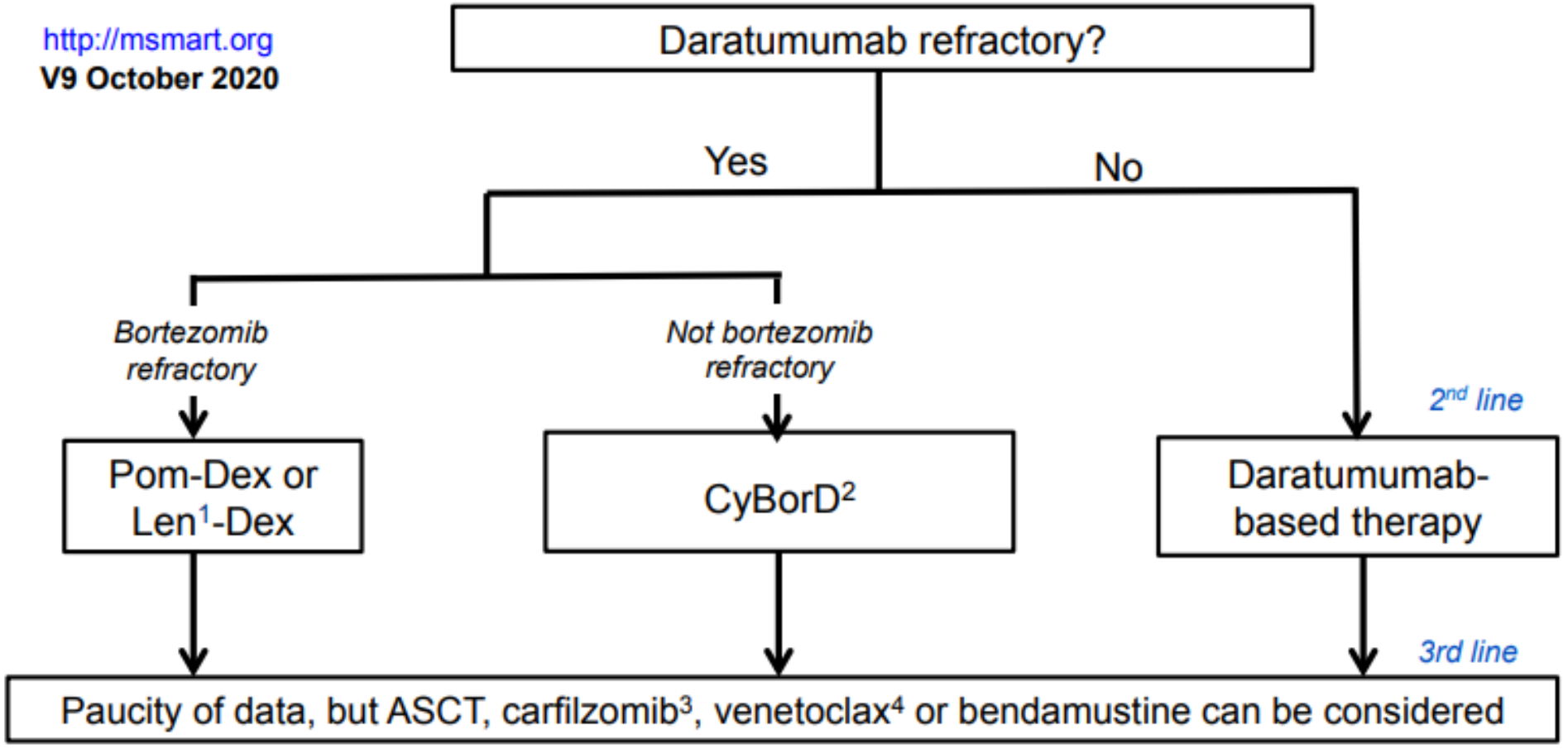
[6]Only for patients with overt multiple myeloma, BMPCs ≥20% or high-risk FISH and who are not receiving extended duration daratumumab, consider maintenance. Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement

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

MAYO CLINIC

Treatment of relapsed/refractory AL amyloidosis

http://msmart.org
V9 October 2020



[1]Starting dose of lenalidomide should be no higher than 15 mg/d
[2]Melphalan-dexamethaone or Ixazomib-dexamethasone are appropriate if patient has significant neuropathy
[3]Not recommended in patients with cardiac involvement
[4]For patients with t(11;14). Be cautious of infection risk.

ASCT, autologous stem cell transplant; Len, lenalidomide; Pom, pomalidomide; Dex, dexamethasone

GERTM@MAYO.EDU