

mSMART

Mayo Consensus on AL Amyloidosis: Diagnosis, Treatment and Prognosis

AL Amyloidosis Diagnosis

- The diagnosis of systemic amyloidosis requires the presence of all of the following:
 - Presence of amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract or peripheral nerve involvement)
 - Positive amyloid staining by Congo Red or EM in any tissue
 - Clear evidence that amyloid is immunoglobulin related by direct subtyping of amyloid deposits (Mass spectroscopy is standard approach at our institution)
 - Evidence of a monoclonal plasma cell proliferative disorder (any or all of the following: serum or urine M protein, abnormal free light chain ratio or clonal plasma cells in bone marrow)
- Localized forms of amyloidosis (such as tracheobronchial, genitourinary, isolated carpal tunnel and non-purpuric cutaneous lesions) do not require systemic therapy
- The recommendations presented herein are a general approach. However, [clinical trials are preferred](#) at every step.

Hematological response assessment

Response type	Criteria
<i>HEMATOLOGIC RESPONSE¹</i>	
Complete response (CR)	Negative serum and urine IFE and Normal serum immunoglobulin κ/λ FLC ratio or uninvolved FLC concentration greater than the involved FLC concentration, with or without an abnormal FLC ratio
Very good partial response (VGPR)	dFLC < 40 mg/L
Partial response (PR)	dFLC decrease of greater than 50%
No response (NR)	Less than a partial response
Response for those with baseline dFLC 20-50 mg/L	
CR	Negative serum and urine IFE and Normal serum immunoglobulin κ/λ FLC ratio or uninvolved FLC concentration greater than the involved FLC concentration, with or without an abnormal FLC ratio
dFLC PR	dFLC <10 mg/L

dFLC, difference between involved and uninvolved serum immunoglobulin free light chain

Organ response assessment

Organ response type	Criteria
<i>CARDIAC RESPONSE¹</i>	
Cardiac Complete <i>response</i> (CarCR)	Nadir NT-proBNP \leq 350 pg/mL or BNP \leq 80 pg/mL
Cardiac Very good partial response (CarVGPR)	>60% reduction in NT-proBNP/BNP from baseline level not meeting CarCR
Cardiac Partial response (CarPR)	31-60% reduction in NT-proBNP from baseline level not meeting CarCR
Cardiac No response (CarNR)	\leq 30% reduction in NT-proBNP from baseline level
<i>RENAL RESPONSE²</i>	
Renal Complete <i>response</i> (RenCR)	Nadir proteinuria \leq 200 mg/24-h
Renal Very good partial response (RenVGPR)	>60% reduction in proteinuria from baseline level not meeting renCR
Renal Partial response (RenPR)	31-60% reduction in proteinuria from baseline level not meeting renCR
Renal No response (RenNR)	\leq 30% reduction in proteinuria from baseline level
<i>Hepatic response³</i>	
Hepatic response	Decrease in Serum alkaline phosphatase from baseline value >50%
Hepatic no response	Decrease in Serum alkaline phosphatase from baseline value \leq 50%

¹Muchtar et al, JCO 2023

²Muchtar et al ASH 2021

³Gertz et al, AJH 2005

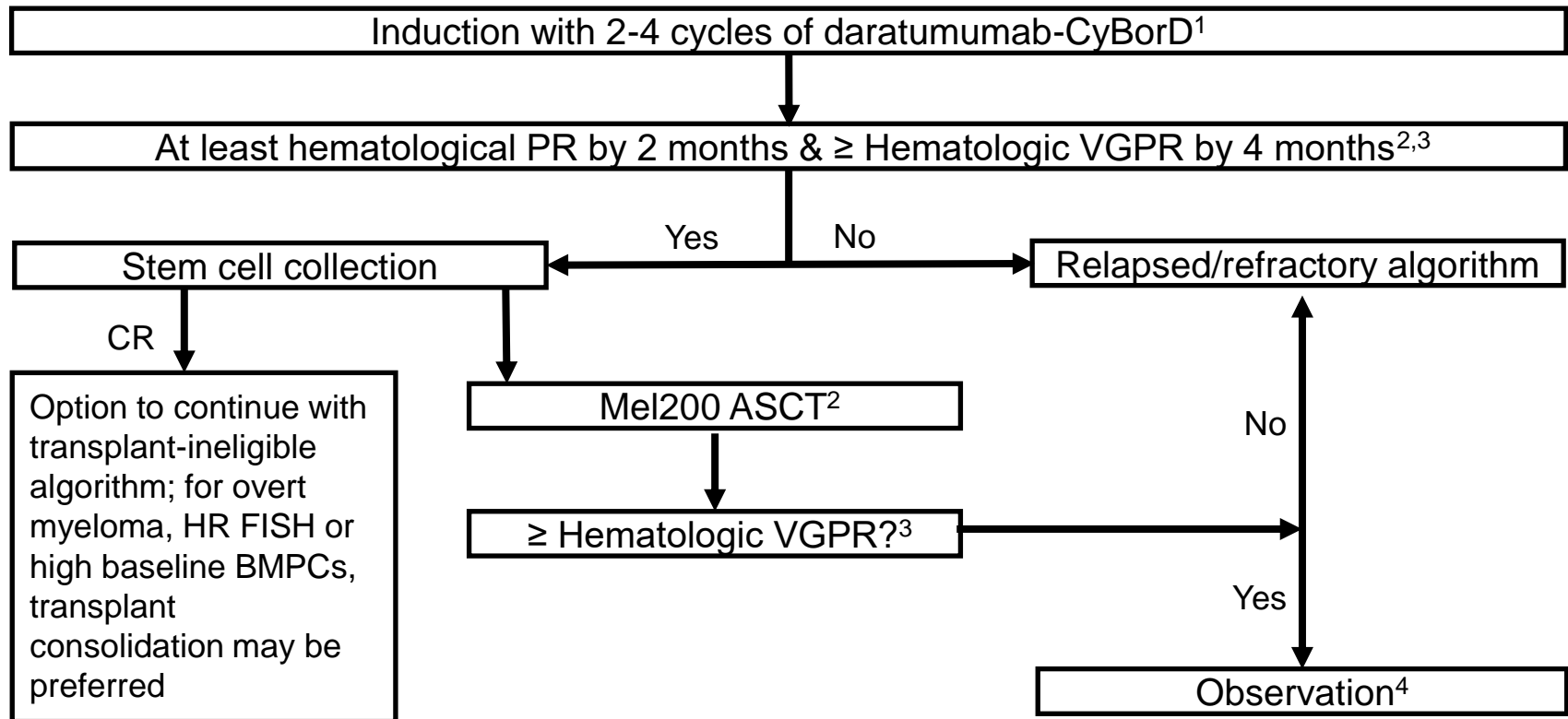
ASCT Transplant Eligibility Criteria

- **“Physiologic” Age \leq 70 years**
- **Performance Score \leq 2**
- **Systolic BP \geq 90 mmHg ^a**
- **TnT $<$ 0.06 ng/ml (or hs-TnT $<$ 75 ng/ml)**
- **CrCl \geq 30 ml/min ^b (unless on chronic dialysis)**
- **NYHA Class I/II**

^a Caution as well for patients with SBP $<$ 100 mmHg

^b Selected patients may become eligible for ASCT with cardiac and renal transplantation

Newly Diagnosed AL Amyloidosis - Transplant eligible



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

²For CrCl <30, use Mel 140 mg/m²

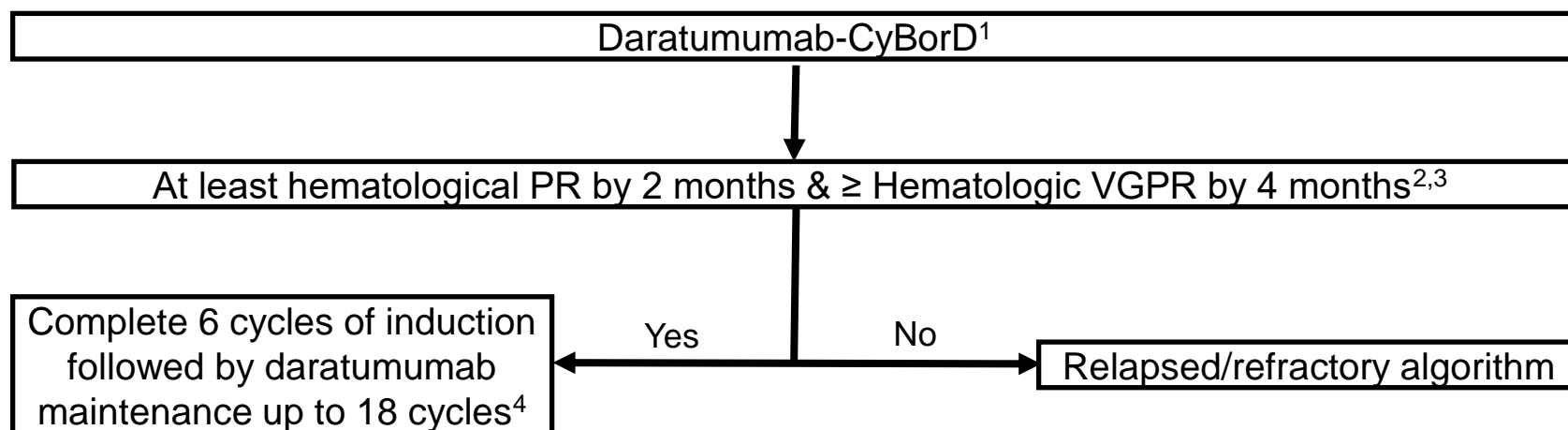
³Decision to change therapy if in VGPR but < CR is based on a number clinical factors. Re-refer to amyloid center of excellence

⁴For 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[#]

<http://msmart.org>

V10 April 2023



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

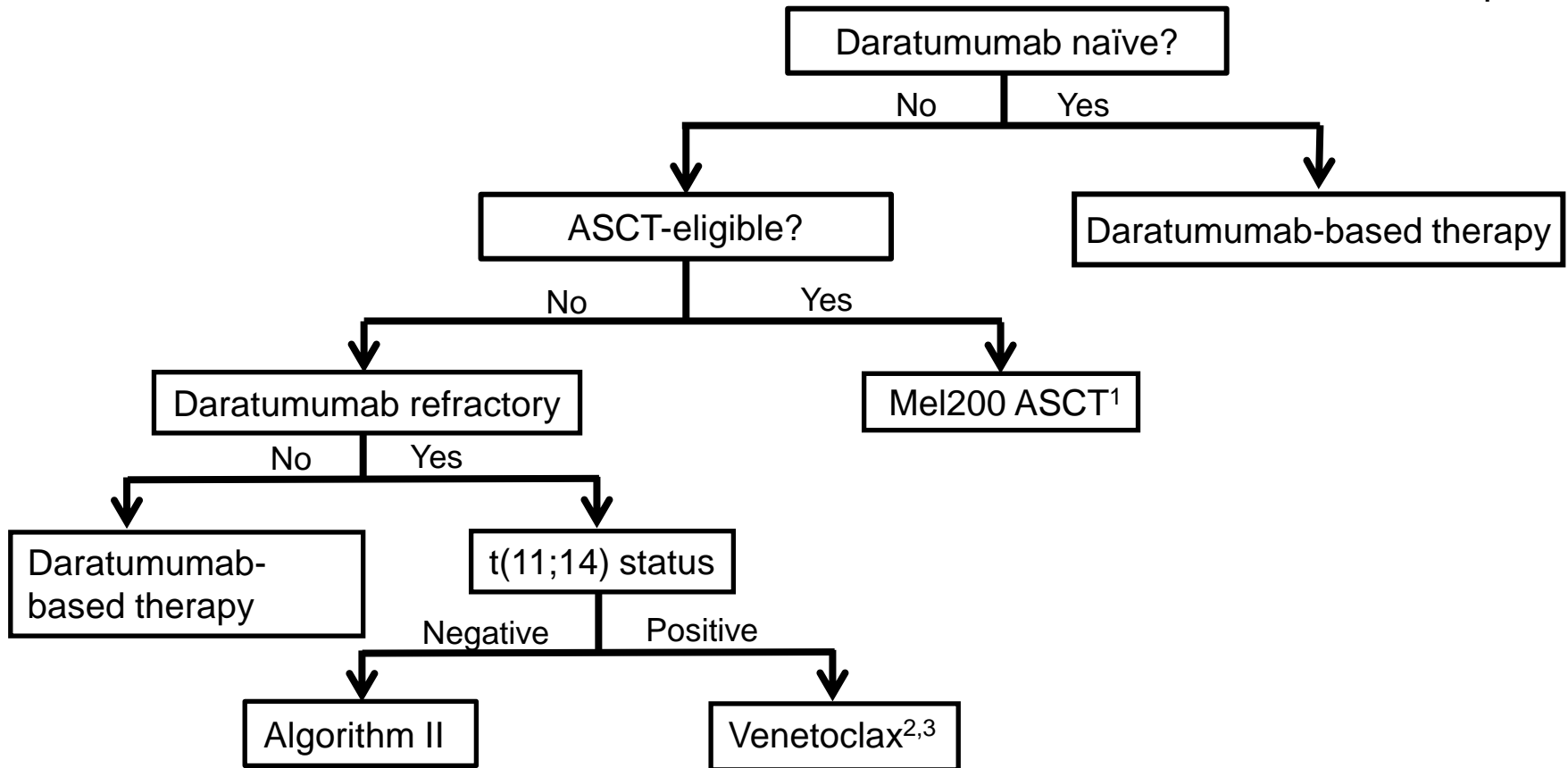
¹If daratumumab-CyBorD, 6 cycles followed by daratumumab monotherapy, completing up to 24 cycles. If daratumumab is not accessible, CyBorD or BMDex for 6-12 cycles are acceptable alternative regimens (weekly bortezomib)

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

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

⁴Only 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



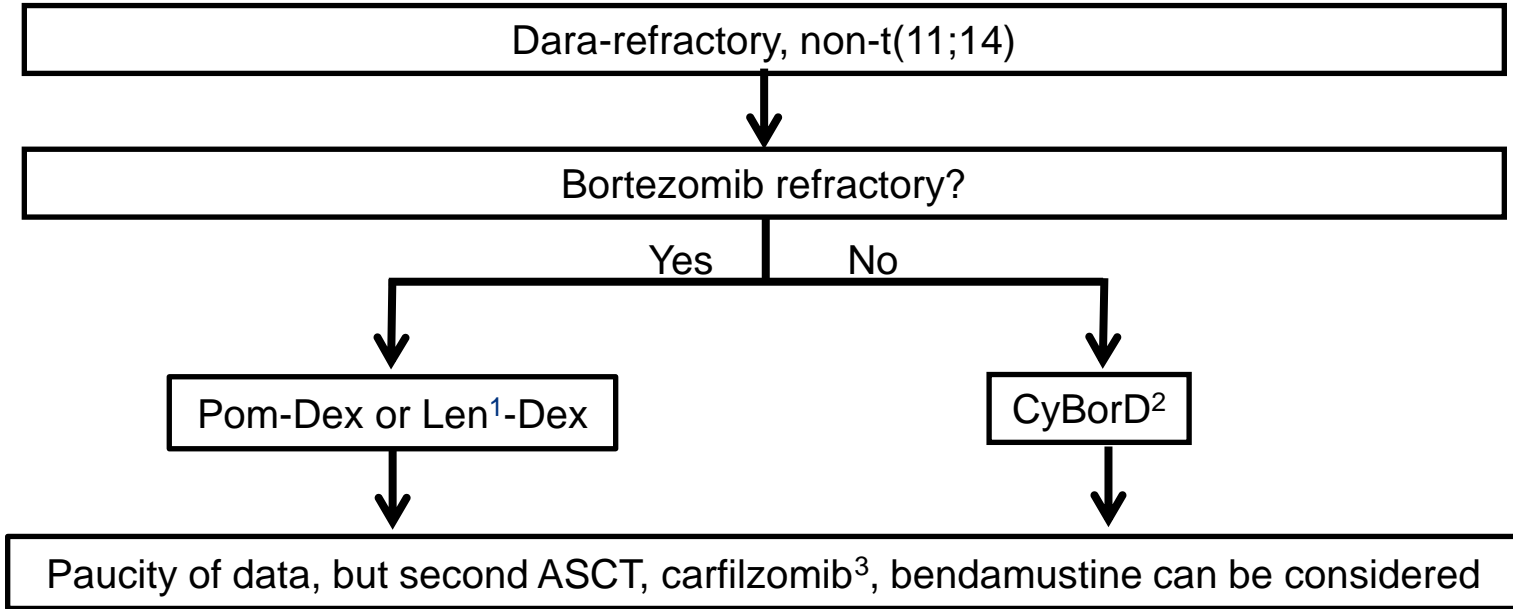
ASCT, autologous stem cell transplant

¹Induction should be considered in high-burden disease; For CrCl <30, use Mel 140 mg/m²

²can be used with dexamethasone or as a single agent; No need for dose ramp up; dose can be capped at 400 mg/d

³infectious disease prophylaxis is recommended

Treatment of relapsed/refractory AL amyloidosis - II



ASCT, autologous stem cell transplant

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

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

³Not recommended in patients with cardiac involvement



MAYO CLINIC

mSMART

Mayo Consensus on AL Amyloidosis: Prognosis

Mayo AL amyloidosis prognostic system (2012) ¹

Mayo System	Troponin T	NT-proBNP, ng/L	dFLC, mg/L	Stage
2012	< 0.025 mcg/L, or if high sensitivity, < 40 pg/L ^{2,3}	< 1800	< 180	I = all low; II = one elevated; III = two elevated; IV = all three elevated

<http://msmart.org>
V10 April 2023

¹ Kumar *J Clin Oncol.* 2012;30:989-995.

² Kumar <https://www.ncbi.nlm.nih.gov/pubmed/30433848>

³ Muchtar <https://www.ncbi.nlm.nih.gov/pubmed/30545829>

AL amyloid Staging Systems Conversion:

use one troponin threshold and one BNP threshold except where indicated

Model	cTnT	cTnI	Hs-cTnT	NT-proBNP	BNP
Mayo 2004 model ^a	≥ 0.035 mcg/L	≥ 0.1 mcg/L	≥ 50 ng/L ^e	≥ 332 ng/L	≥81 ng/L
Modification of Mayo 2004 model ^b	≥ 0.035 mcg/L	≥ 0.1 mcg/L ^f	≥ 50 ng/L ^{e,f}	≥ 332 ng/L ≥ 8500 ng/L	≥ 81 ng/L ≥ 700 ng/L
Mayo 2012 model ^c	≥ 0.025 mcg/L	ND	≥ 40 ng/L ^f	≥ 1800 ng/L	≥ 400 ng/L ^g
Mayo ASCT troponin risk marker ^d	≥ 0.06 mcg/L	ND	≥ 75 ng/L ^f	--	--

Abbreviations: ASCT, Autologous stem cell transplantation; NA, not applicable; ND, no data.

^a Original 3 stage model using cTnT and NT-proBNP cut-points as listed. cTnI also tested in same paper

^b Original 3 stage model using cTnT and NT-proBNP cut-points as listed, but separate stage III into IIIa and IIIb based on whether or not NT-proBNP is higher than 8500 ng/L.

^c 4 stage model using cTnT and NT-proBNP cut-points as listed along with difference of involved free light chain ≥ 18 mg/dL.

^d Simple binary troponin T threshold predicting for transplant-related mortality 25% versus 4%

^e In separate study, hs-cTnT 54 found to be comparable to cTnT cut-point of 0.035, but re-analysis using quartic formula yielded 51 ng/L

^f Extrapolated numbers are based on quartic formula applied to a dataset of 224 newly diagnosed AL amyloidosis patients.¹⁰

^g In original study, BNP threshold was found to be comparable NT-proBNP

ATTR amyloid staging systems conversion:

*use one troponin threshold and one BNP threshold
except where indicated*

Model	cTnT	cTnl	Hs-cTnT	NT-proBNP	BNP
Mayo ATTRwt	≥ 0.05 mcg/L	ND	≥ 65 ng/L ^a	3000 ng/L	ND
NAC ATTR ^b	NA	NA	NA	3000 ng/L	NA

Abbreviations: ASCT, Autologous stem cell transplantation; ATTRwt, Wild-type Transthyretin amyloidosis; NA, not applicable; NAC, National amyloidosis center (UK); ND, no data.

^a Extrapolated numbers are based on quartic formula applied to a dataset of 224 newly diagnosed AL amyloidosis patients.¹⁰

^b eGFR threshold of <45 ml/min/1.73m² is used in addition to the NT-proBNP.