2023 UPDATES IN LIGHT CHAIN (AL) AMYLOIDOSIS

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Disclosures

- Clinical Trial Support: Abbvie, Sanofi, Takeda, Janssen, Novartis, Regeneron, TeneoBio, CAELUM, Prothena
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Objectives

- AL amyloidosis staging and response assessment
- Treatment of newly diagnosed and relapsed/refractory AL
- Supportive care

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When you see a newly diagnosed AL amyloidosis

- Subtype the amyloid so you know what you are treating. Whenever possible refer to amyloid center
- Know affected organs and numbers to follow
- Treatment of AL amyloidosis
- Supportive care

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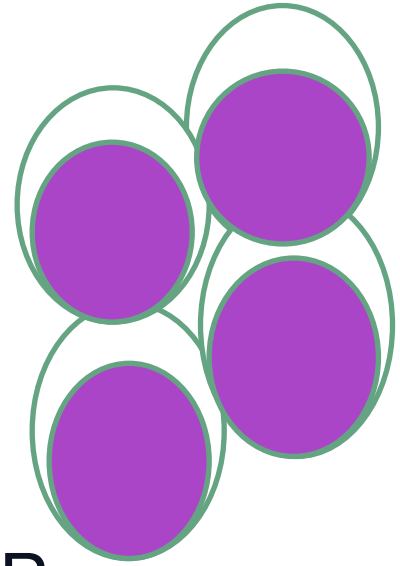
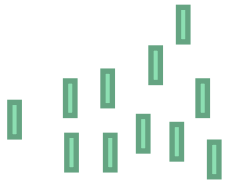
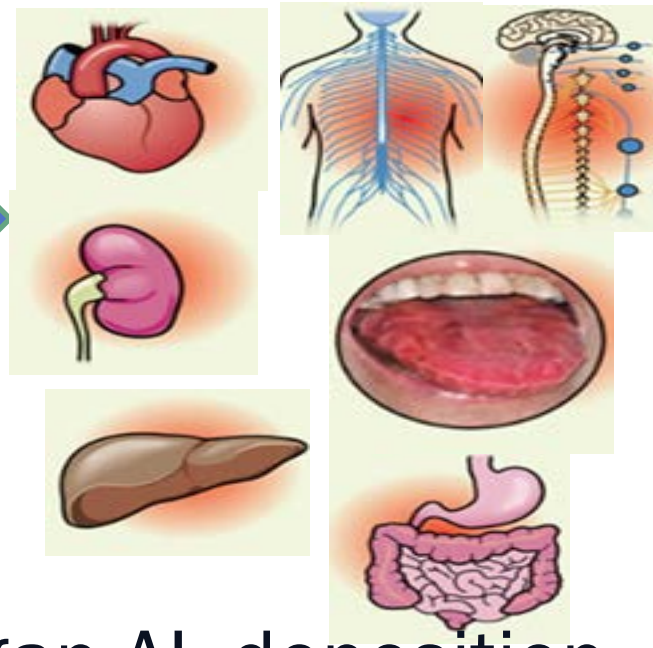


Bone marrow plasma cell clone



clonal free light chains

misfolded light chains (AL)



organ AL deposition leading to dysfuntion

Plasma cell-directed chemotherapy

No effective treatments
Needs time to improve
Chemotherapy adverse effects can worsen
e.g., fluid retention, cardiotoxicity, neuropathy

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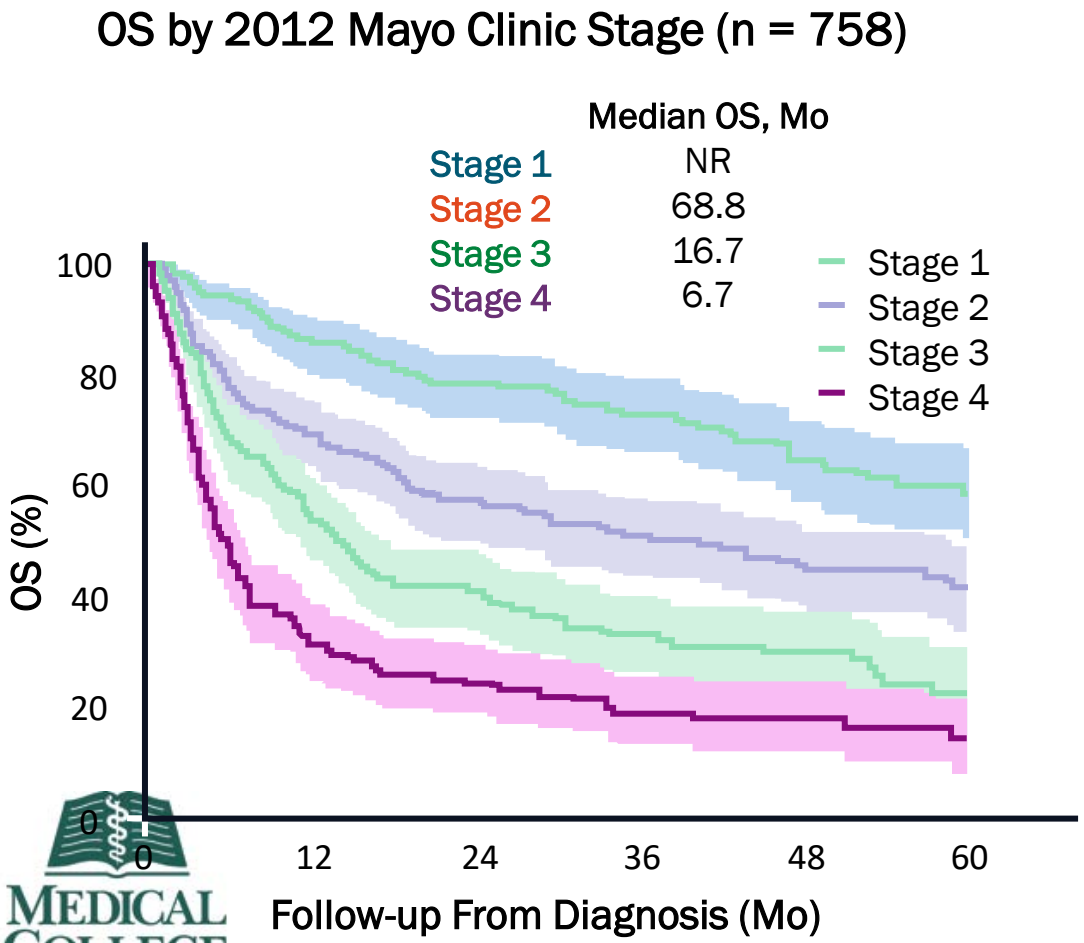
AL Amyloidosis: Overall Survival by Stage



Staging System	Markers/Thresholds	Stages
2004 Mayo Clinic Cardiac Staging System with 2015 European modification	NT-proBNP >332 ng/L cTnT >0.035 ng/mL (or cTnI >0.1 ng/mL)	I. 0 markers above cutoff II. 1 marker above cutoff IIIa. Both markers above cutoff and NT-proBNP <8500 ng/L IIIb. Both markers above cutoff and NT-proBNP ≥8500 ng/L
2012 Revised Mayo Clinic Staging System	NT-proBNP >1800 ng/L cTnT >0.025 ng/mL dFLC >180 mg/L	I. 0 markers above cutoff II. 1 marker above cutoff III. 2 markers above cutoff IV. 3 markers above cutoff
2014 Palladini Renal Staging System	eGFR <50 mL/min per 1.73 m^2 proteinuria >5 g per 24 hr	I. Both eGFR above and proteinuria below cutoffs II. Either eGFR below or proteinuria above cutoffs III. Both eGFR below and proteinuria above cutoffs

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Kumar et al. JCO. 2012;30:989. Milani et al. Mediterr J Hematol Infect Dis. 2018;10:e2018022.

AL Amyloidosis Goals for Therapy and Measuring Response

Goals for Therapy

- **Deep response:** normalization or near normalization of serum free light chain
- **Durable** response
- **Minimizing toxicity:** risk-adapted therapy that does not lead to mortality or decompensate patients
- **Supportive care**

Measuring Response in AL Amyloidosis

- **Hematologic response**
  - Reduction in M protein (SPEP, UPEP, dFLC)
- **Organ response**
  - **Cardiac:** NT-ProBNP
  - **Renal:** 24-hr urine protein, eGFR
  - **Liver:** liver span, alkaline phosphatase
- **Imaging**
  - **Echo:** Global longitudinal strain
  - **CMR:** Myocardial ECV tracking, T1 mapping, LGE
- **Functional outcomes**
  - **Six-minute walk test**
  - **NYHA Class**
  - **PROs/HRQL:** KCCQ, SF-36, and PROMIS

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Palladini et al. JCO. 2012;30:4541. Fotiou et al. Hemasphere. 2020;4:e454. Mutchar et al. Leukemia. 2018;32:2240.

Hematologic Response Criteria

Response	Definition
Complete response	*Both criteria must be met* ▪ Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) defined by negative IFE of both serum and urine + ▪ Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio
Very good partial response	dFLC concentration <40 mg/L or 4 mg/dl
Partial response	dFLC decrease >50% compared with baseline
No response	All other patients

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Palladini et al. Amyloid. 2021;28:1.

Organ Response Criteria in AL Amyloidosis

Organ	Response	Progression
Heart	*NT-proBNP response*: >30% and ↓ >300 ng/L in patients w/baseline NT-proBNP ≥650 ng/L or *NYHA class response*: ↓ ≥2 class in patients w/baseline NYHA class 3-4	*NT-proBNP progression*: >30% and ↑ >300 ng/L or *cTn progression*: ↑ ≥33% or *Ejection fraction progression*: ↓ ≥10%
Kidney	↓ 50% (≥0.5 g/d) of 24-hr urine protein (required: >0.5 g/d pretreatment); creatinine and creatinine clearance must not worsen by 25% above BL	50% ↑ (≥1 g/d) of 24-hr urine protein to >1 g/d or 25% worsening of creatinine or creatinine clearance
Liver	50% ↓ in abnormal AP and ↓ ≥2 cm in liver size (radiographic)	50% ↑ of AP above lowest value

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Comenzo et al. Leukemia. 2012;26:2317.

Conversion/Cross-Reference by Biomarkers

	cTnT, µg/L	cTnI, µg/L	Hs-cTnT, ng/L	NT-proBNP, ng/L	BNP, ng/L
2004 Mayo Stage	≥0.035	≥0.1	≥50	≥332	81
2015 European modification of Mayo 2004	≥0.035	≥0.1	≥50	≥332	81
				>8,500	>700
2012 Mayo Stage	≥0.025	ND	>40	≥1800	≥400

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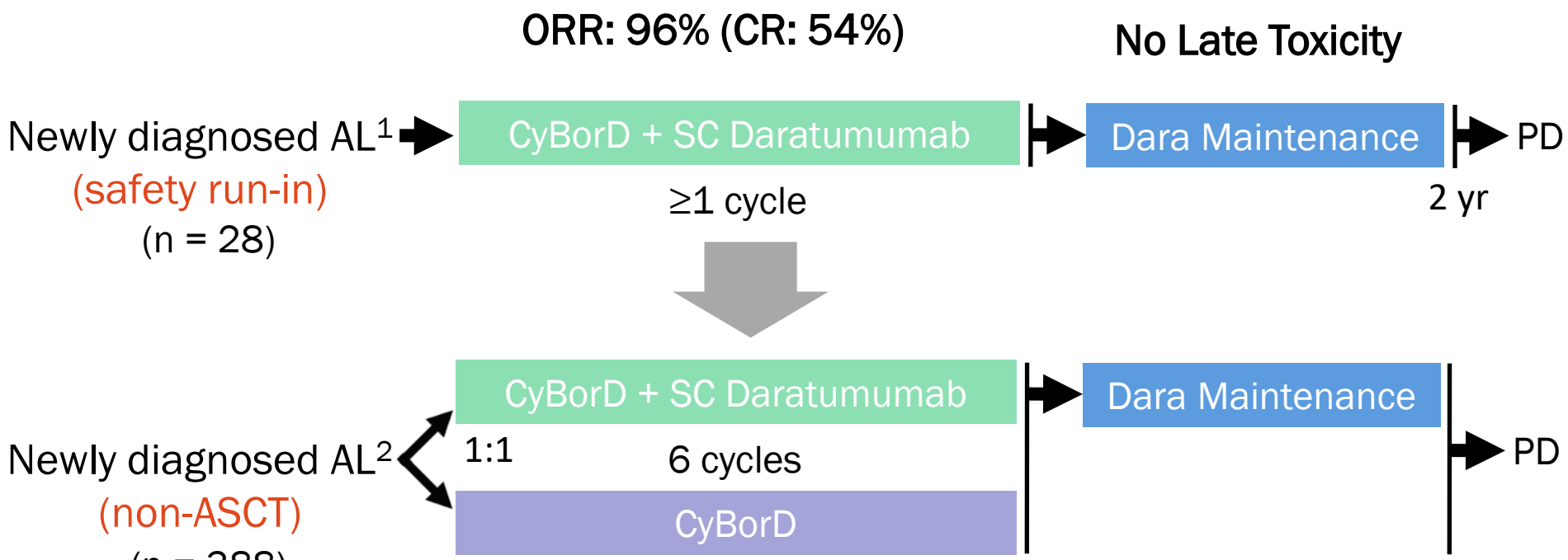
Muchtar et al. Blood. 2019;133:763.

ANDROMEDA: VCD vs Daratumumab/VCD for AL



Stratification:

- Mayo stage I/II/IIIa
- ASCT availability
- CrCl ≥60 or <60 mL/min

Patients enrolled at 109 sites in 22 countries from May 2018 through August 2019

1. Palladini et al. Blood. 2020;136:71. 2. Kastritis et al. NEJM. 2021;385:46.

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Slide credit: clinicaloptions.com

ANDROMEDA: Endpoints and Results

Primary Endpoint

Complete heme response

cHR 53.3% vs 18.1%

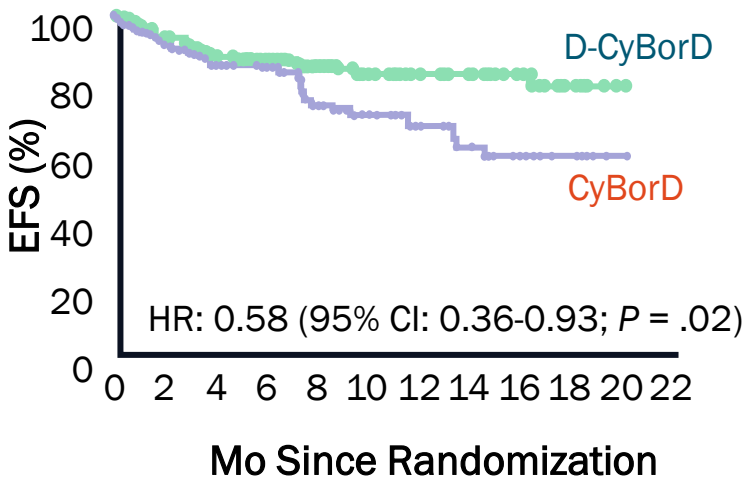
Patients, n	D-CyBorD (n = 195)	CyBorD (n = 193)
Heme progression	8	25
Deaths	27	29
Deaths by Day 60	13	13
Treatment change	19	79

Key Secondary Endpoints

MOD-PFS*

Overall survival

MOD-PFS



Other Endpoints

Organ response/progression

VGPR+

cHR at 6 mo

Time to heme response

Duration of heme response

Time to next therapy

*MOD-PFS: death, heme progression, cardiac transplant, LVAD, IABP, ESRD requiring HD, or renal transplant.

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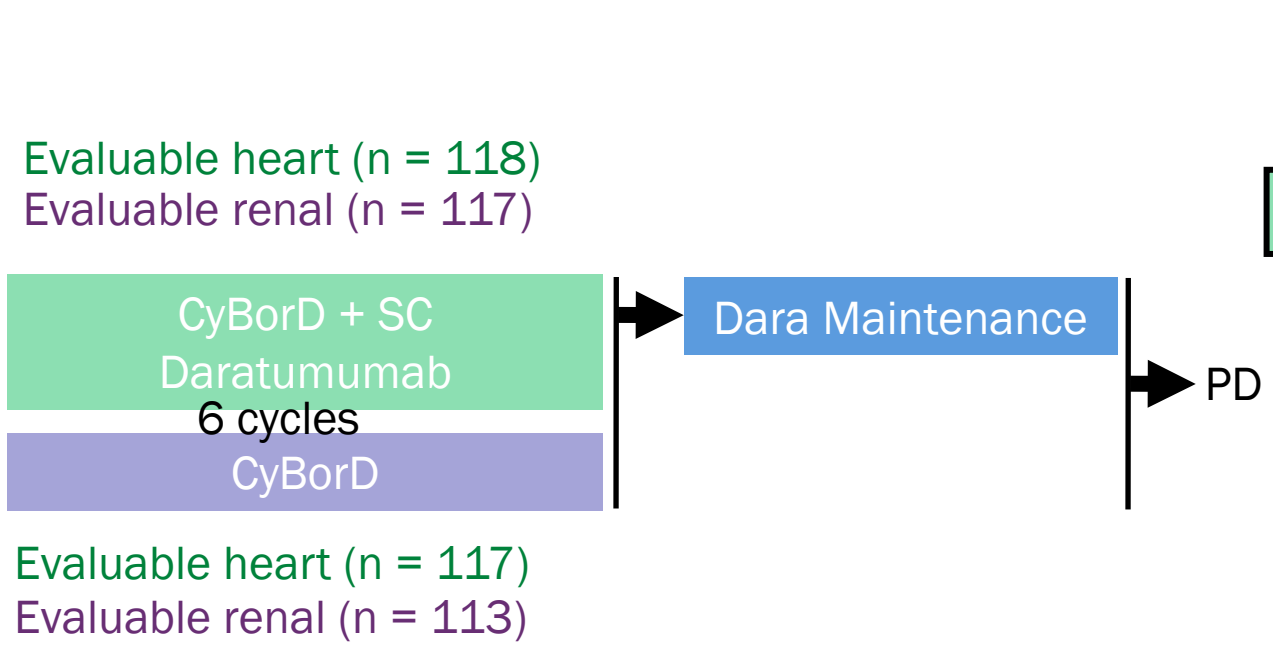
Kastritis. NEJM. 2021;385:46.

ANDROMEDA: Key Organ Status at 6 months



Heart Response	Heart Progress	Renal Response	Renal Progress
44%	2.5%	53%	4%
22%	8%	24%	11.5%

Cardiac and renal response rates doubled

Organ progression reduced by approximately two thirds

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- Kastritis. NEJM. 2021;385:46.

What we learned and what we didn't

- What we learned
  - Adding daratumumab to CyBorD improved complete HR rate and doubled cardiac and renal response at 6 months
  - Daratumumab does not improve early (cardiac) mortality
- What we did not learn
  - Is there any role for ASCT consolidation in transplant-eligible patients?
  - Is daratumumab maintenance needed for those in cHR?
  - Will long-term survival be improved with addition of daratumumab?
  - Can daratumumab be safely used in patients with advanced cardiac stage?

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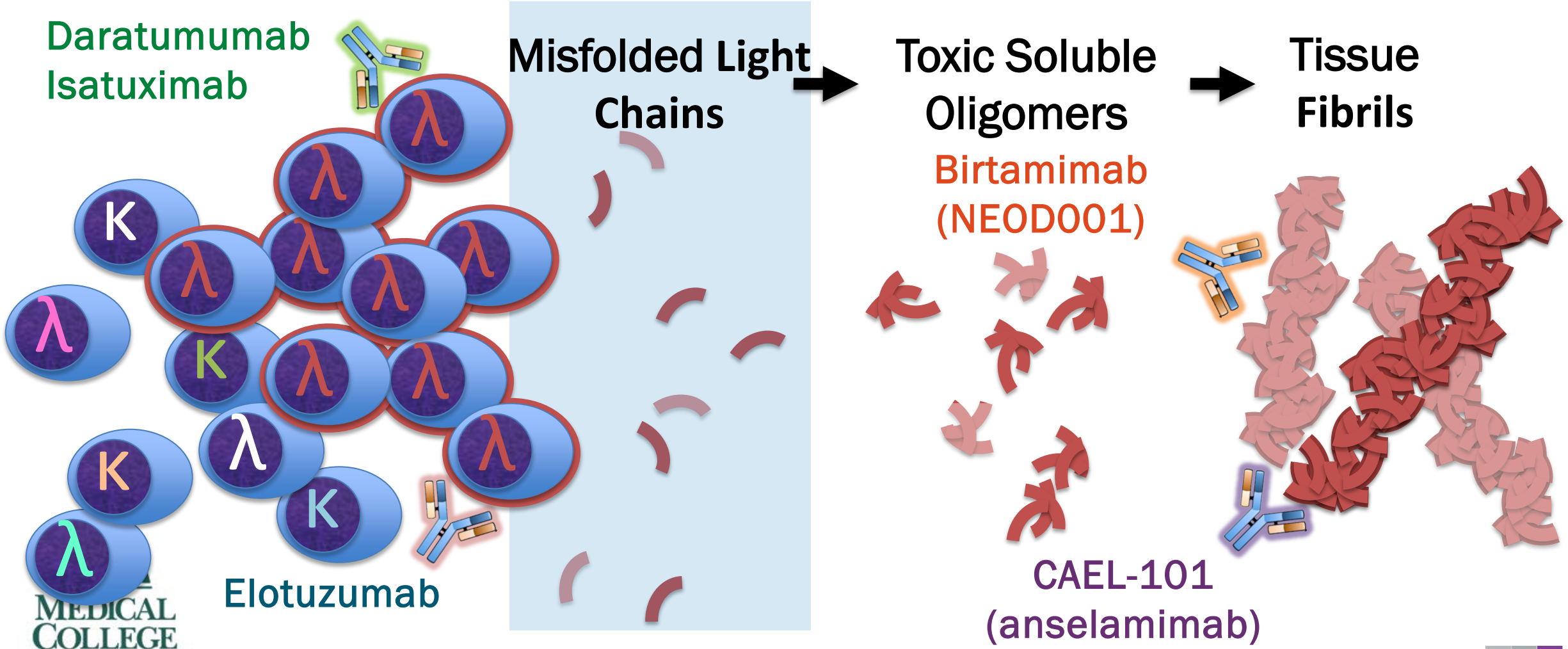
Monoclonal antibodies in AL Amyloidosis



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Slide credit: clinicaloptions.com

Birtamimab and CAEL 101 phase 3 trials- similarities and differences

	Birtamimab (NEOD001)	Anselamimab (CAEL-101)
Dosing	Every 4 weeks, 1-hour infusion	Weekly for 4 weeks, then bi-weekly, 2-hour infusion
Ongoing Trials	AFFIRM-AL • Newly diagnosed, treatment naïve Mayo Stage IV patients with cardiac involvement	CAEL-101 301 and 302 studies • Newly diagnosed, treatment naïve Mayo Stage IIIA & IIIb patients with cardiac involvement
Endpoints	• Primary Endpoint: All-cause mortality • Secondary Endpoints: SF-36v2 PCS, 6MWT • Exploratory Endpoints: GLS, hospitalizations	• Primary Endpoint: All-cause mortality • Secondary Endpoints: 6MWT, KCCQ-OS, SF-36v2 PCS, GLS
Key criteria	• 2:1 randomization • Mayo 2012 stage 4, excludes IIIb stage • NT-proBNP 1800-8500/BNP 400, cTNT 0.025/hsTNT 40, dFLC 180 • Allows daratumumab-based treatment, no intent for ASCT • No prior chemotherapy	• 2:1 randomization • Mayo 2004 stage III with European modification • NT-proBNP >=650, cTNT 0.035/hsTNT 50/cTnI 0.1, measurable hematologic disease • Allows daratumumab-based treatment, no intent for ASCT • Up to 2 weeks of chemotherapy prior to randomization

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Clinicaltrials.gov

When to move to Second-line Therapy?

1. Issues with toxicity that cannot be corrected by dose modifications or supportive care

2. Refractory or inadequate response

3. Relapsing or progressive disease

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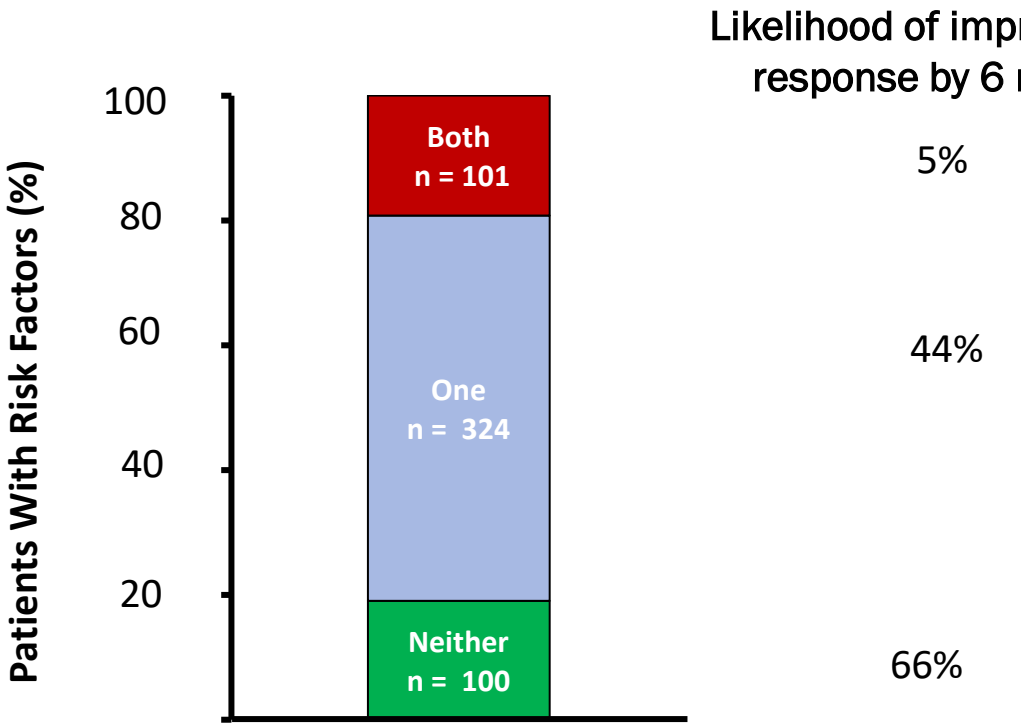
What is an Inadequate Hematologic Response?



Newly diagnosed AL amyloidosis with <VGPR at 1 mo
2 risk factors predicted for lack of deepening response by 6 months

- Baseline dFLC >400 mg/L
- < PR at 1 month

- **Recommendation:** At 1 month, change therapy for patients with **both** risk factors (<PR and baseline dFLC > 400 mg/L)
- At 3 mo, among intermediate- and low-risk patients:
  - Only 23% of patients with < VGPR at 3 mo had an improved response at 6 mo
- **Recommendation:** At 3 months, change therapy in patients not achieving VGPR

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Ravichandran et al. Br J Haematol. 2022;198:328.

Definition of Hematologic Relapse/Progression

2005 ISA Criteria[1]	Pavia Criteria for High-Risk dFLC Progression[2]
From CR ▪ Any detectable monoclonal protein *or* ▪ Abnormal FLC ratio (& doubled light chain)	Requires all 3 ▪ dFLC >20 mg/L (absolute value) ▪ dFLC >20% of baseline (diagnostic) ▪ dFLC ↑ >50% above nadir of best response
From PR ▪ iFLC ↑ 50% (absolute value >100 mg/L) *or* ▪ Serum M protein ↑ 50% to 0.5 g/dL, *or* ▪ 24-hr urine M protein ↑ 50% to >0.2 g/day	

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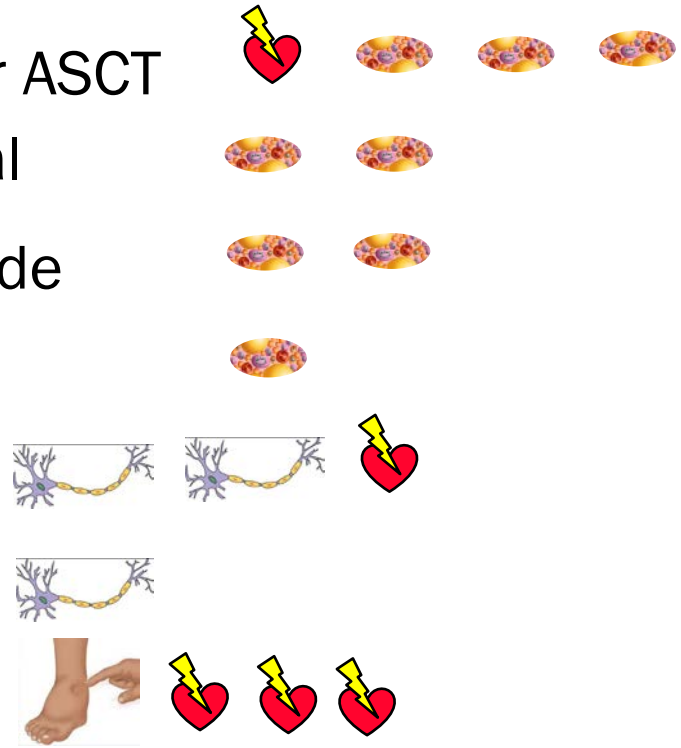
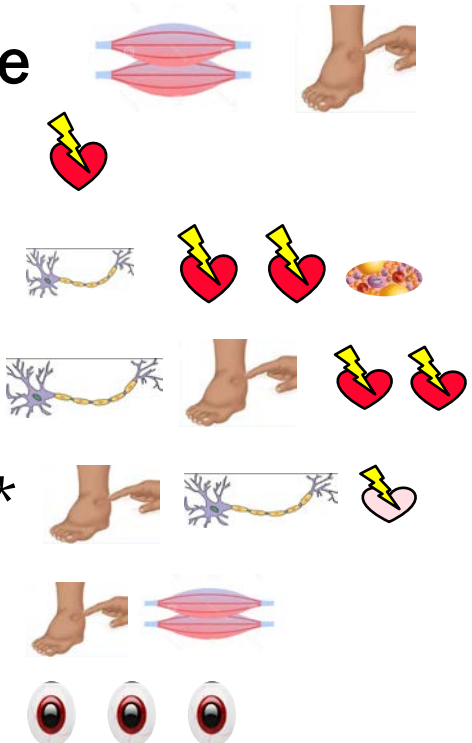
1. Gertz et al. Am J Hematol. 2005;79:319. 2. Palladini et al. Blood. 2018;131:525.

AL Amyloidosis Therapies: Off-Target Toxicities

- **Melphalan**
  - High dose for ASCT
  - Low dose oral
- Cyclophosphamide
- Bendamustine
- **Bortezomib**
- Ixazomib
- Carfilzomib



- **Dexamethasone**
- Pomalidomide
- Lenalidomide
- Thalidomide
- **Daratumumab***
- Venetoclax
- Belantamab†



Cardiotoxic | Neurotoxic | Myopathic | Edema | Myelotoxic | Ocular toxic

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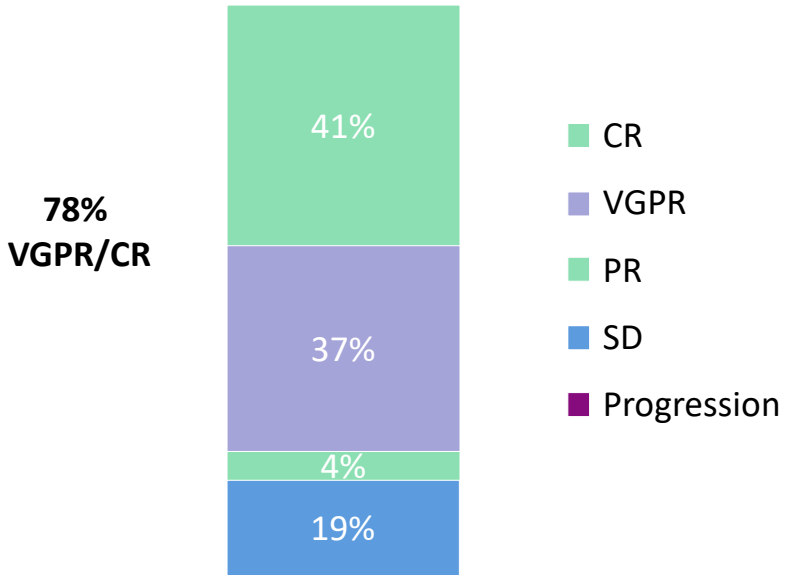
*Also, isatuximab

†Belantamab was pulled from US market in November 2022

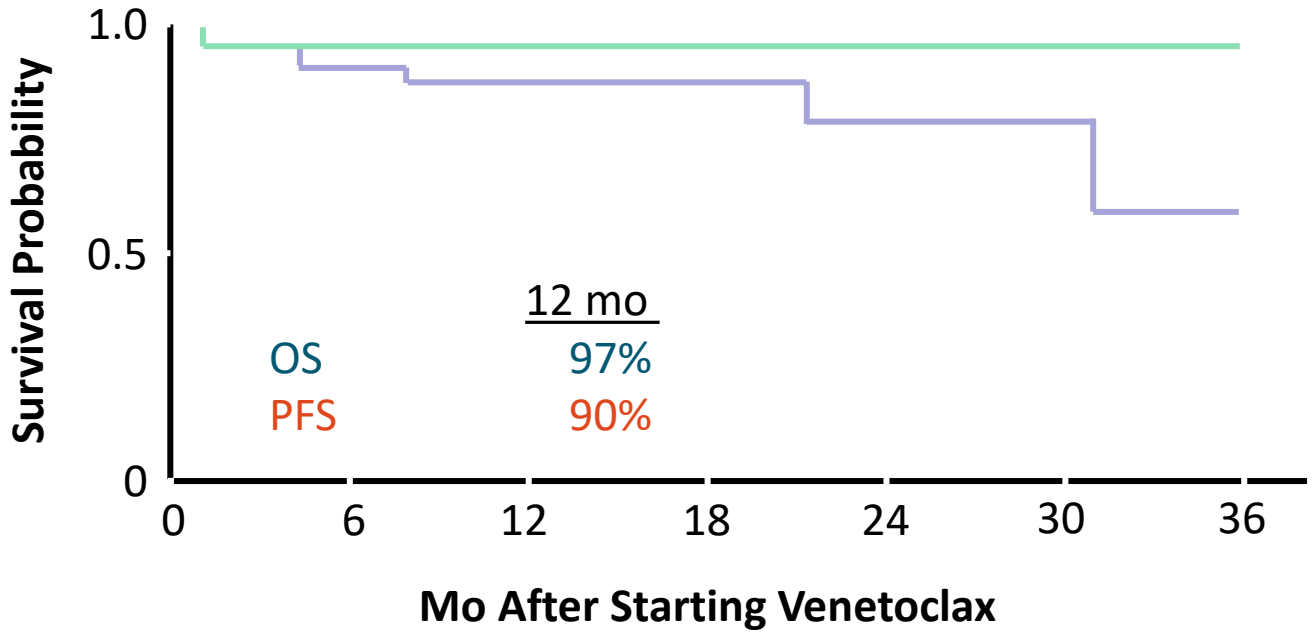
Slide courtesy: CCO

Venetoclax for AL Amyloidosis with t(11;14)

Best Response in Evaluable t(11;14) patients
(n = 27)



OS and PFS in Patients With t(11;14)



Median follow-up: 14.5 mo

Premkumar. Blood Cancer J. 2021;11:10.

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Hematology-Specific Supportive Care

Medications	Counteract
• Antivirals (acyclovir)	• Risk of shingles
• Antinausea	• Bortezomib, cyclophosphamide
• Acid blockers	• Dexamethasone
• Sleep aids	• Dexamethasone
• Diuretics	• Dexamethasone
• Laxatives	• Bortezomib

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Supportive Care for Organ Amyloidosis

CARDIAC AND RENAL

- ✓ Diuretics
  - Loop
  - Spironolactone
  - Albumin diuresis
- ✓ Daily weight & BP
- ✓ Sodium restriction
- ✓ Compression stockings
- ✓ Avoid nephrotoxic drugs (NSAIDs)
- ✓ Avoid typical heart failure drugs e.g., beta-blockers, Calcium channel blockers
- ✓ Atrial fibrillation- amiodarone or digoxin
- ✓ Anticoagulation as appropriate

NEUROLOGIC

Peripheral neuropathy

- ✓ Medications- gabapentin, pregabalin, duloxetine, nortriptyline, amitriptyline, topicals- lidocaine, ketamine
- ✓ Scrambler therapy
- ✓ Acupuncture
- ✓ Gait aids, PT/OT

Autonomic neuropathy- LOW BP

- ✓ Compression stockings
- ✓ Raise bed head
- ✓ Avoid standing too quickly
- ✓ Exercise (avoid heat, hot tubs)
- ✓ Medications- midodrine, droxidopa, pyridostigmine
- ✓ If no cardiac/renal restriction- salt tablets, fludrocortisone

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Take home points

- Heterogeneous disease with protean manifestations
  - Appropriate staging and measuring response to treatments using biomarkers
- Early treatment goals- rapid and deep hematologic response, fibril-directed agents on clinical trials
  - DaraVCD is the only FDA approved treatment and SOC for newly diagnosed AL
    - Role of daraVCD in advanced cardiac stage
    - Role of ASCT in newly diagnosed AL
- Multiple hematologic treatments are available for relapsed AL amyloidosis
  - When to start treatment
  - Unique toxicities of various treatments
- Supportive care is essential in the management of AL amyloidosis
  - Treating the underlying disease (e.g., chemotherapy) is only half the job

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Cardiac Imaging: J Rubenstein, MD
Electrophysiology: M Berger, MD, J Rubenstein, MD
Neurology: M Collins, MD, J Figueroa, MD, N Adaguntla, MD

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Available Clinical Trials at Froedtert & MCW CC

Newly diagnosed AL
- -CAEL-101 301 and 302
- -NEOD001

Relapsed AL
- -DaraPomDex
- -STI-6129
- -Venetoclax

Imaging
- -Florbetapir scan

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