ARC TALKS
WEBINAR SERIES

Navigating AL Amyloidosis:

A Guide to Care and Treatment

June 26 | 12pm - 1pm ET

Sascha Tuchman, MD, MHS

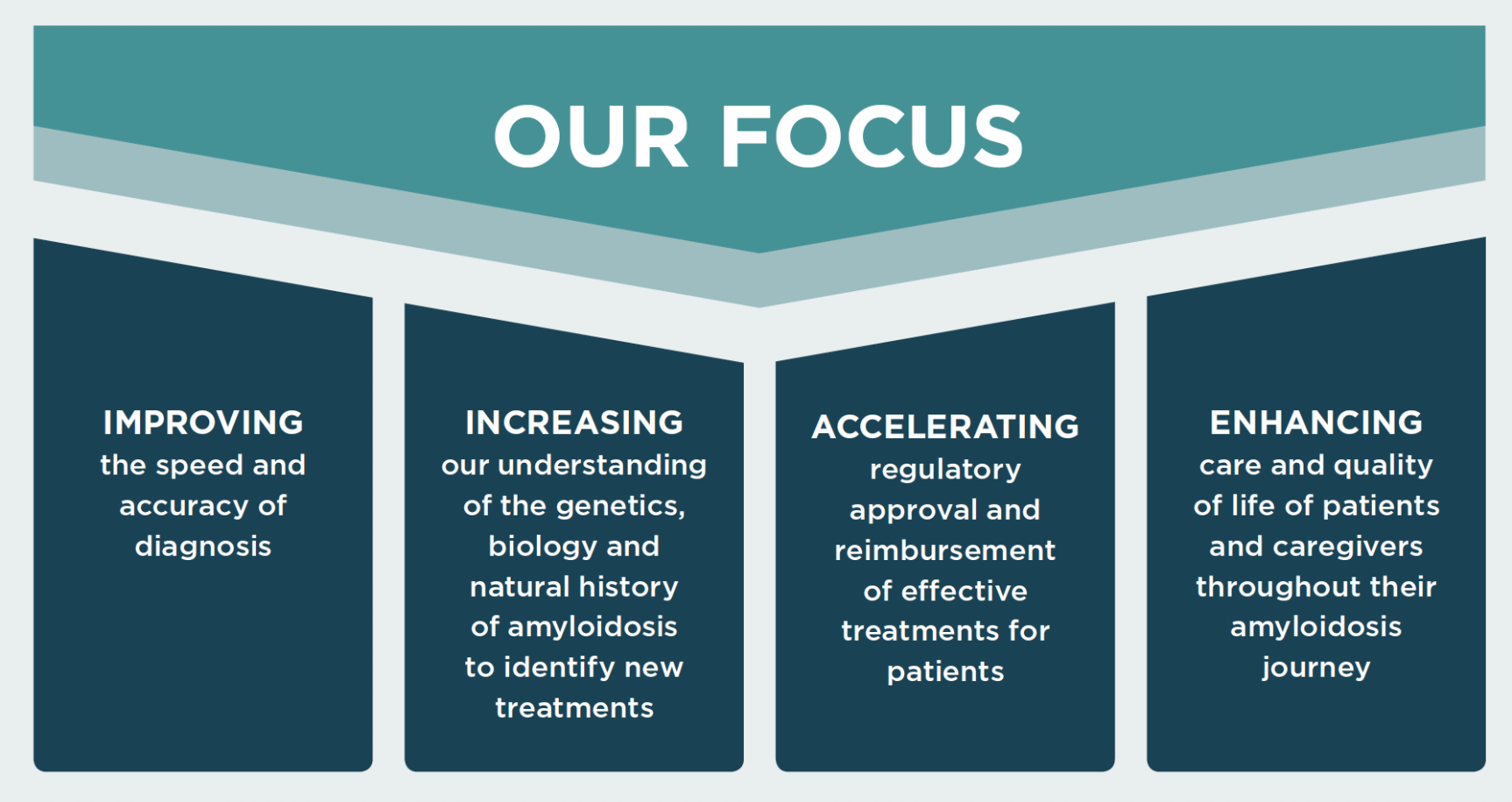
Director, Multiple Myeloma and Amyloidosis Program

UNC - Chapel Hill

About ARC

Amyloidosis Research Consortium

ARC's mission is to improve and extend the lives of those with amyloidosis



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Before We Begin

Amyloidosis Research Consortium

This webinar is recorded. We will post the webinar on our website so you can view it again later.

Submit your questions anytime via the Q&A box. We will try to answer them at the end.

If you are having trouble with the audio using your computer, you can dial in (check your email for info).

AL Amyloidosis Booklets

arci.org/booklets

Upcoming Webinars

Amyloidosis Research Consortium

Healthy Aging and Amyloidosis
August 27 | Noon ET

Jill Waldron, MSN
University of Utah

Orthopedic Issues in Amyloidosis
September 24 | Noon ET

Mazen Hanna, MD
Cleveland Clinic

William Seitz, MD
Cleveland Clinic

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Relevant Disclosures

- Research support: Sanofi, Caelum, Abbvie, BMS, Janssen

What is amyloidosis?

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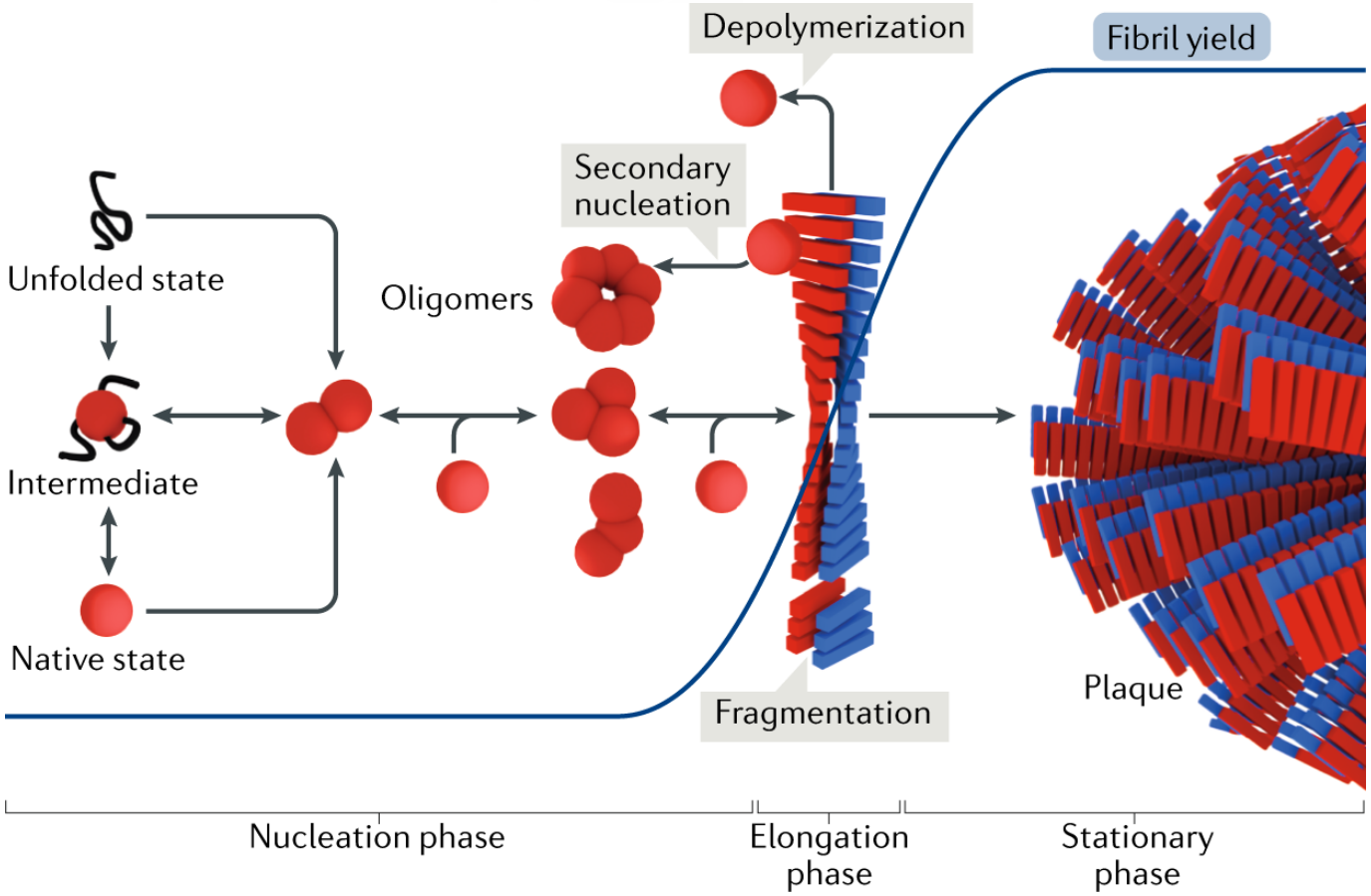
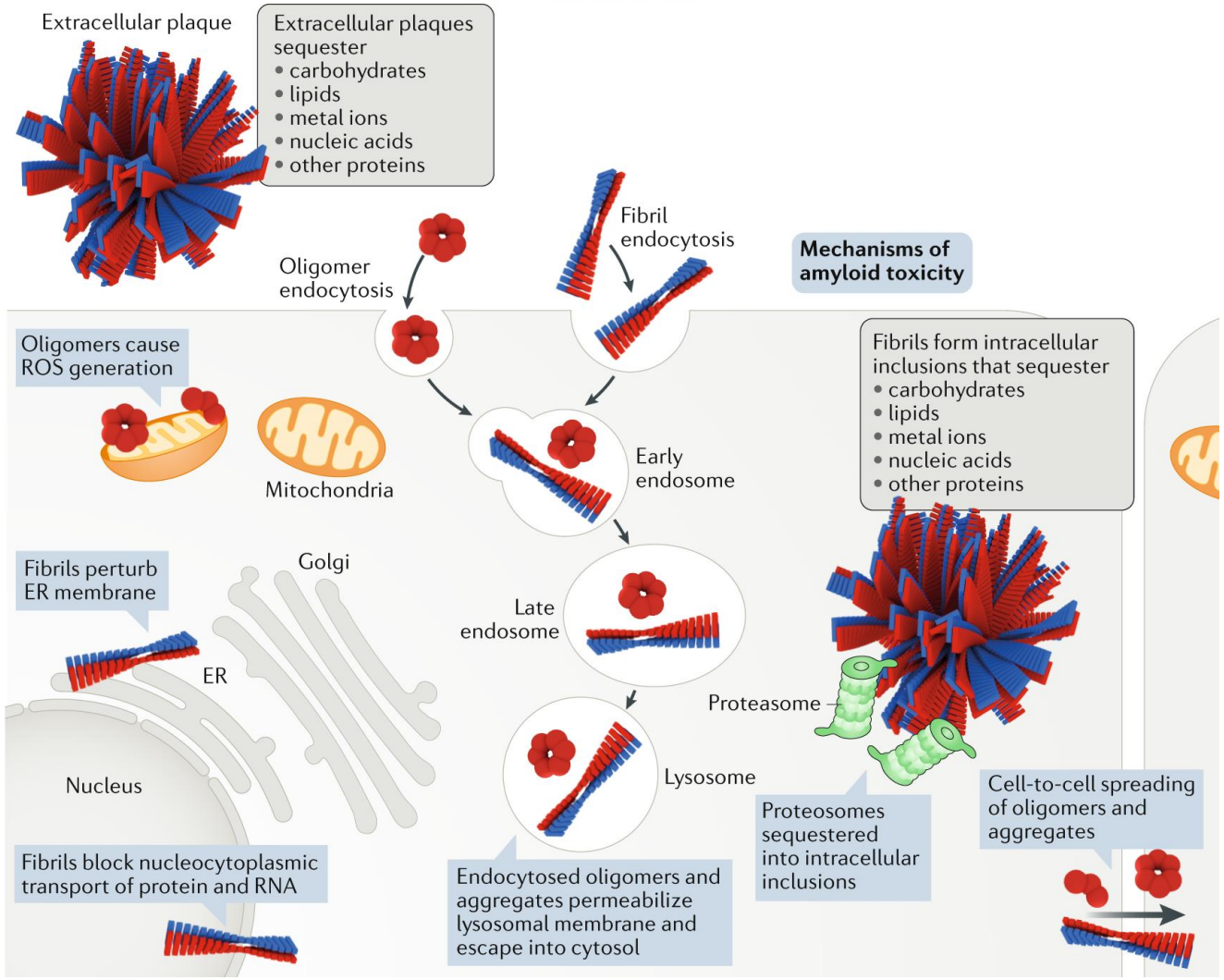
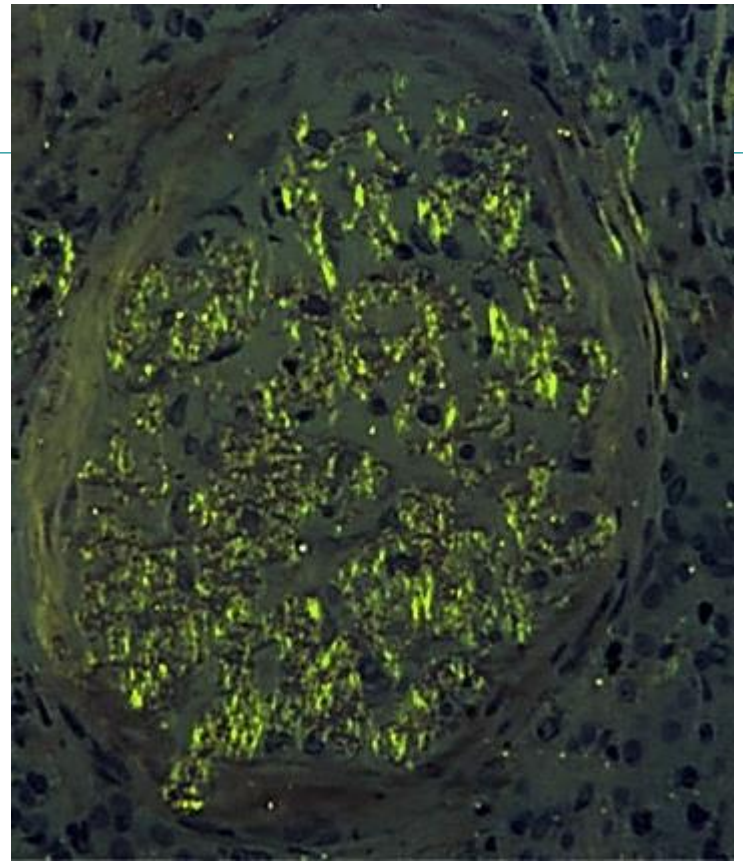


Idanza MG, *Nat Rev Cell Bio* 2018

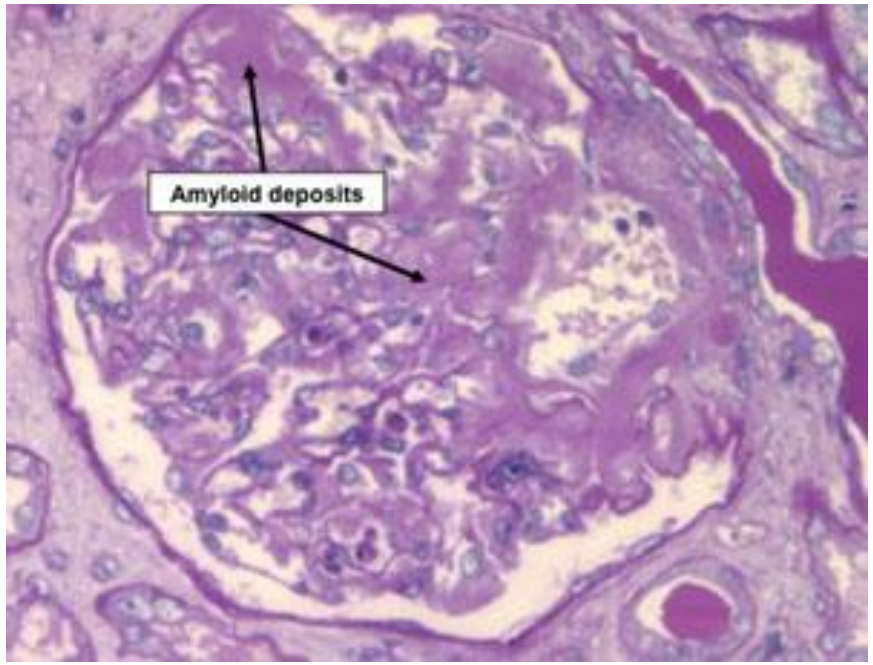
What is amyloidosis?



Idanza MG, *Nat Rev Cell Bio* 2018

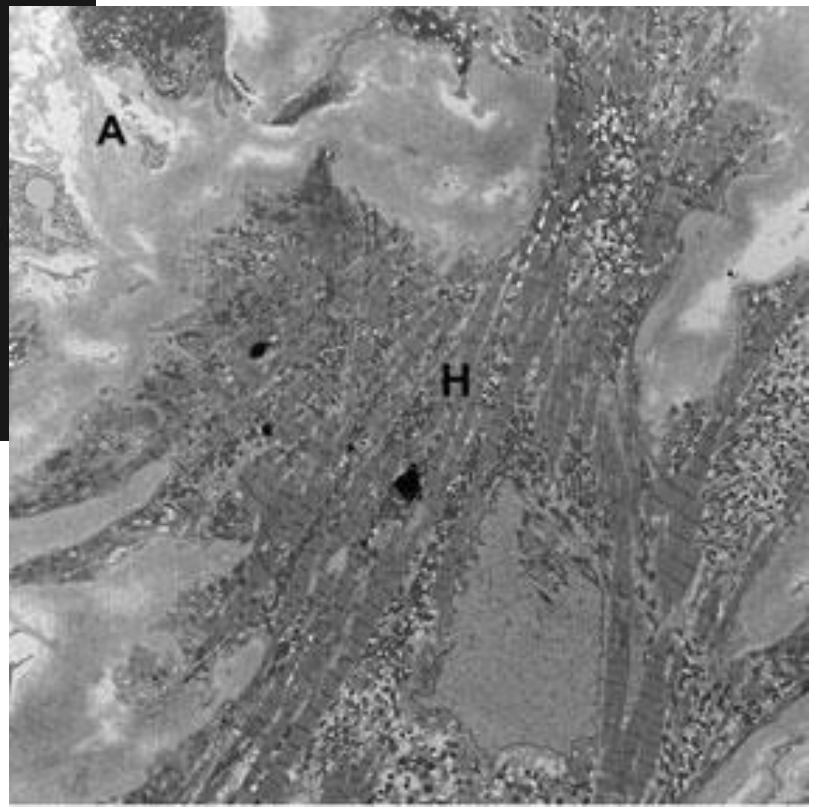


http://www.pathology.vcu.edu/education/PathLab/pages/renalpath/rpsr/images/amyloid_sr/



http://stanfordhospital.org/cardiovascularhealth/amyloid/al_primary_amyloidosis.html

www.med.uottawa.ca/patho/eng/public/cardio/amyloidgross.gif



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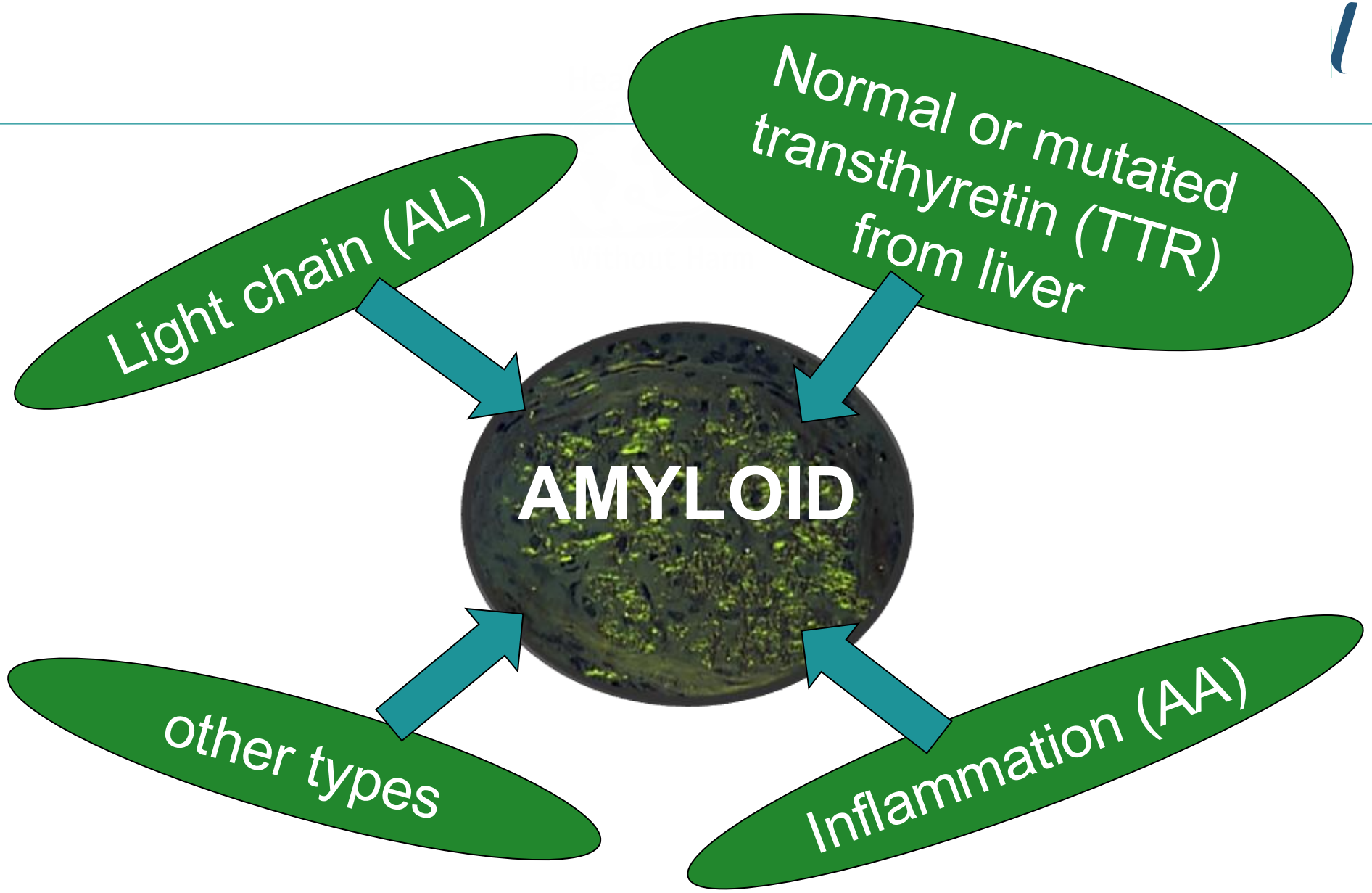
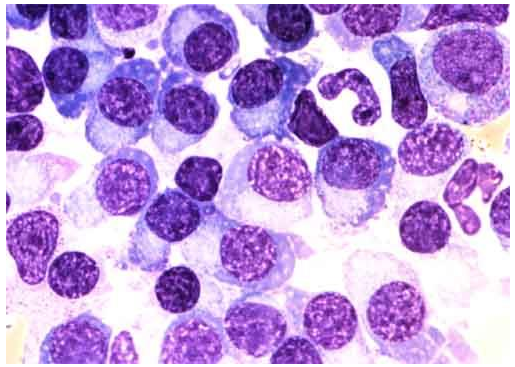

Light chain (AL)
Normal or mutated transthyretin (TTR) from liver
AMYLOID
other types
Inflammation (AA)

The type of damage amyloid causes depends on the source

Light chain (AL) amyloidosis can affect most organs of the body

- Most commonly kidneys / heart / nerves / GI tract
- Also can involve lungs, skin, tongue, muscles, joints, etc.

What is light chain (AL) amyloidosis?



toxic light chains in blood

Amyloid deposition in organs, causing damage

Plasma cell-directed treatments

to c ight hains in blood

New agents (coming soon?)

clearance of amyloid from organs?

Historical standard pre-ANDROMEDA

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Mel-dex: Oral melphalan and steroid (dexamethasone or prednisone)

MVD: Mel-dex plus subcutaneous or IV bortezomib (Velcade)

CyBorD = bortezomib (Velcade), cyclophosphamide + dexamethasone

High-dose chemotherapy with autologous stem cell transplant (“bone marrow transplant”)

- One of our most effective treatments but also the most toxic, with higher risk of severe morbidity or even mortality

ANDROMEDA: CyBorD with or without Daratumumab

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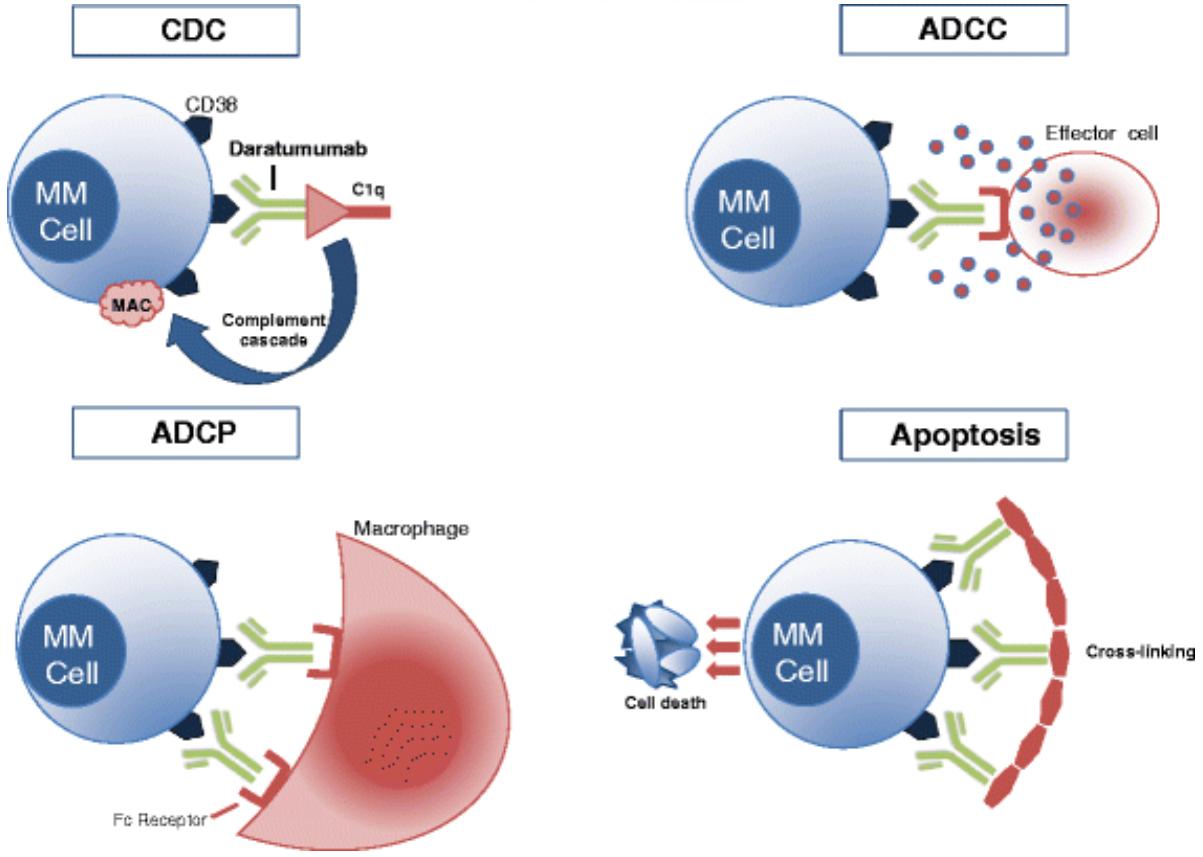
- Daratumumab: FDA-approved in multiple myeloma and borrowed for AL for years
- CD38 unconjugated monoclonal antibody, meaning no payload
- Initial pilot studies in AL showing good tolerability and effectiveness

- Footnote: Why does multiple myeloma (MM) always come up in these AL discussions?
  - They're "cousins" that both stem from plasma cells
  - MM is 10x more common, so many drugs are initially developed and get FDA approval in MM. They're then "borrowed" for treatment of AL without FDA approval.

How Daratumumab Kills Plasma Cells



Sanchez L, *J Hemat Oncol* 2016

ANDROMEDA: CyBorD with or without Daratumumab

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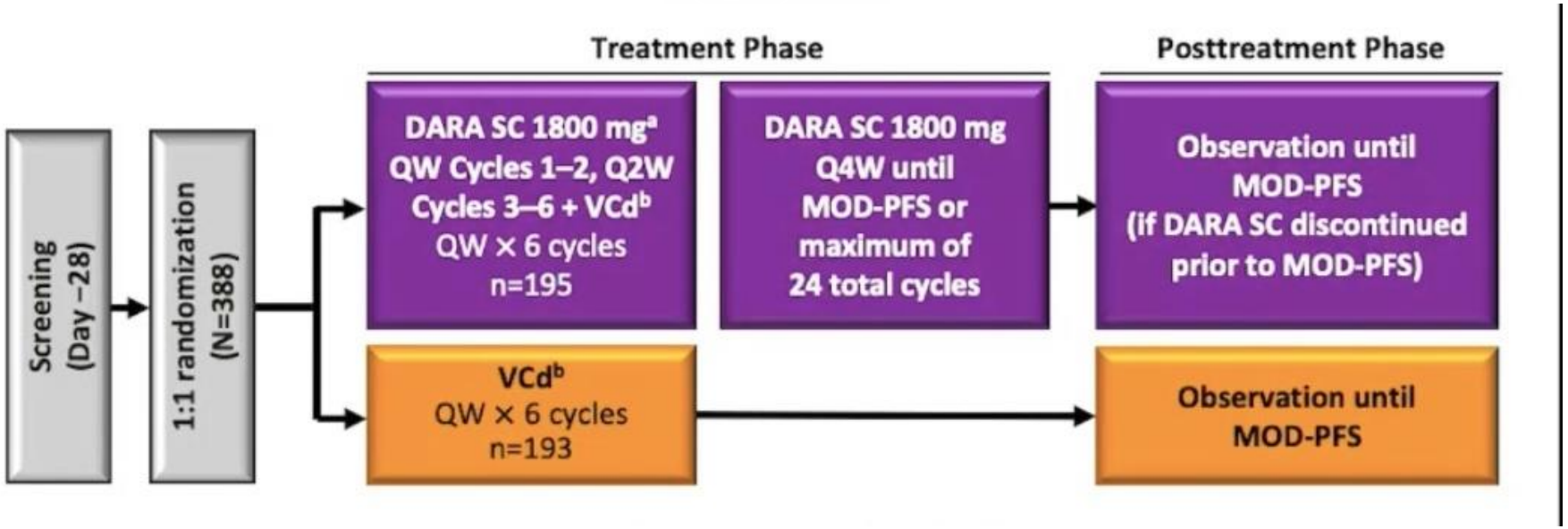
- Newly diagnosed AL with heart involvement
- Excluded patients with
  - NYHA class IIIb or IV CHF, Mayo stage 3b (NT-proBNP ≥8500 ng/L) (severe heart failure)
  - GFR ≤ 20 ml/min (severely reduced kidney function)
  - Unmeasurable disease hematologically (M-spike ≤0.5 g/dL and involved-uninvolved light chain of ≤ 5 mg/dL). (really low levels of amyloid protein in the blood)

Kastritis E, *New Eng J Med* 2021

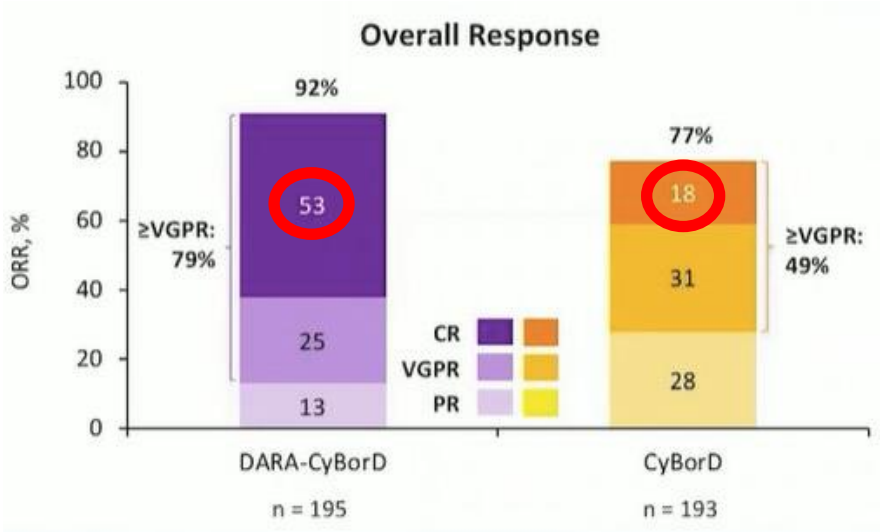
6 months 18 months



Footnote: VCd = CyBorD

Adapted from Kastritis E, *New Eng J Med* 2021

Adding dara suppresses light chains in the blood more deeply and more quickly



Primary endpoint – hematological complete response

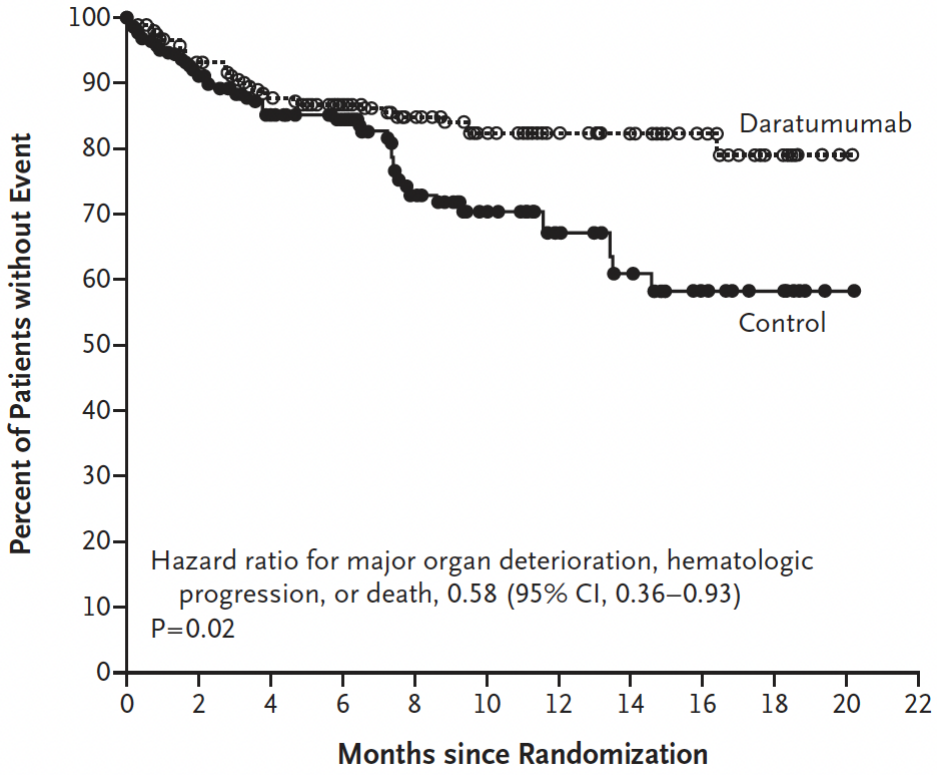
(suppression of light chain proteins below detectable levels)

Median time to best response: 60 days for dara-CyBorD vs 90 days for CyBorD

Subgroup analysis: Benefit present irrespective of baseline variables

Kastritis, *EHA* 2020, abstract #LB2604

Adding dara prolongs time until amyloid proteins again rise in blood, end-stage organ failure, or death



- MOD-PFS defined as haematologic progression (IRC assessed), end-stage cardiac or renal disease, or death
- At a median follow-up of 11.4 months, MOD-PFS was improved with DARA-CyBorD[a]

Kastritis, *EHA* 2020, abstract #LB2604; Kastritis, *New Eng J Med* 2021

Adding dara facilitates heart and kidney recovery

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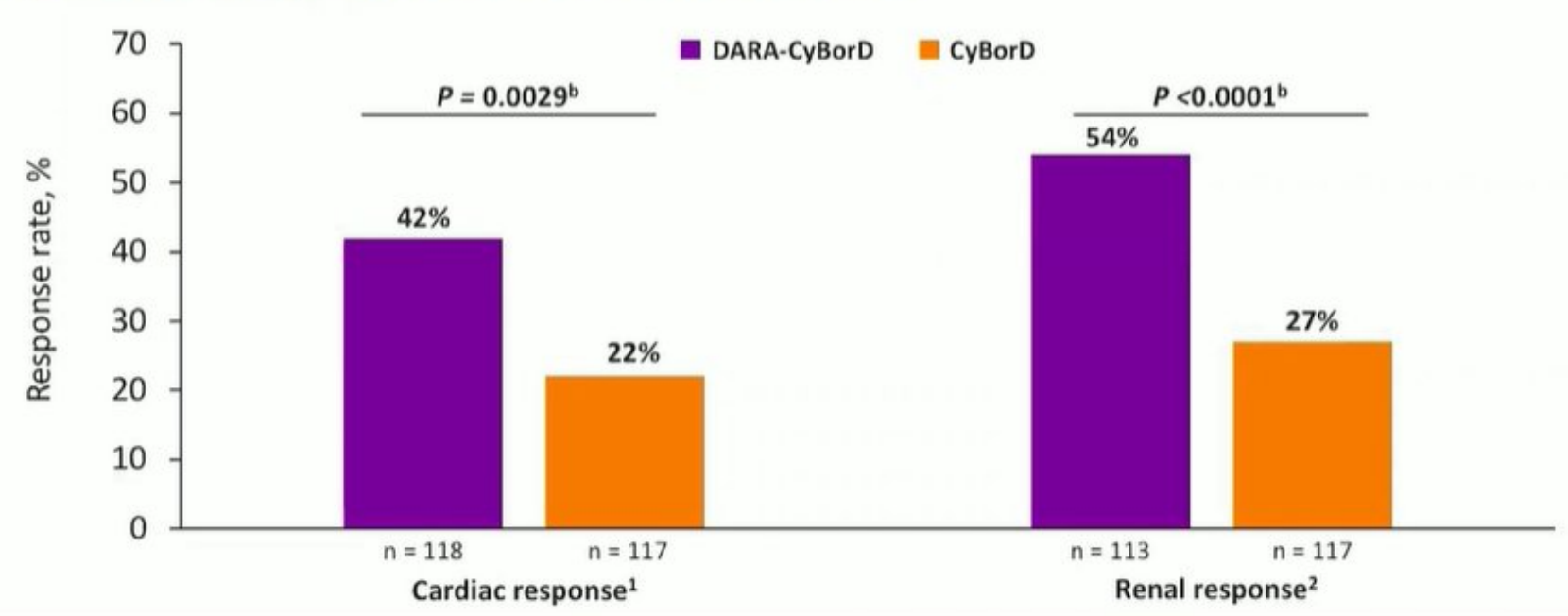
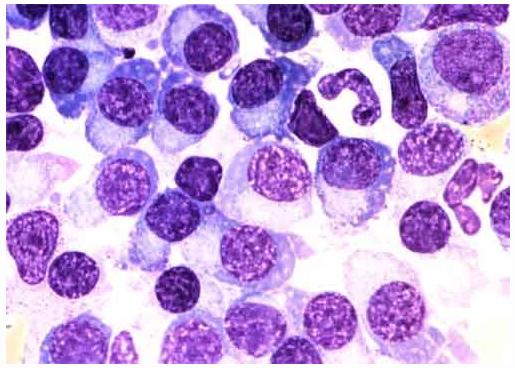
6 month organ response by arm



Kastritis, *EHA* 2020, abstract #LB2604

As a result of ANDROMEDA, most patients with newly diagnosed AL amyloidosis get some form of daratumumab + CyBorD

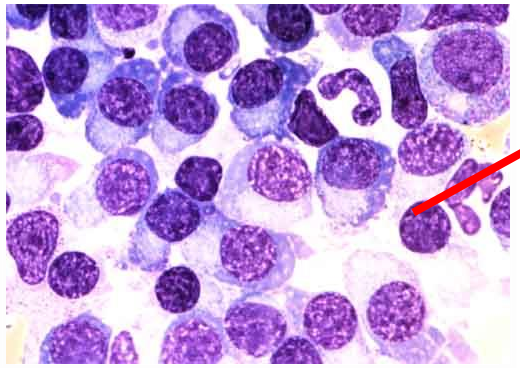
Relapsing amyloidosis: How it presents



toxic light chains in blood

Amyloid deposition in organs, causing damage

Relapsing amyloidosis: How it presents



Cells grow first, but we don't see that because they're in the bone marrow

toxic light chains in blood – usually this is what we see first, on blood work

Amyloid deposition in organs, causing damage, if levels get high enough

Relapsing amyloidosis: How it presents

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Recurrent amyloidosis organ damage is often a matter of AL "picking up where it left off," meaning organs affected before can start taking damage again.

New organs can also be impacted.

What’s the role for stem cell transplant in 2026?

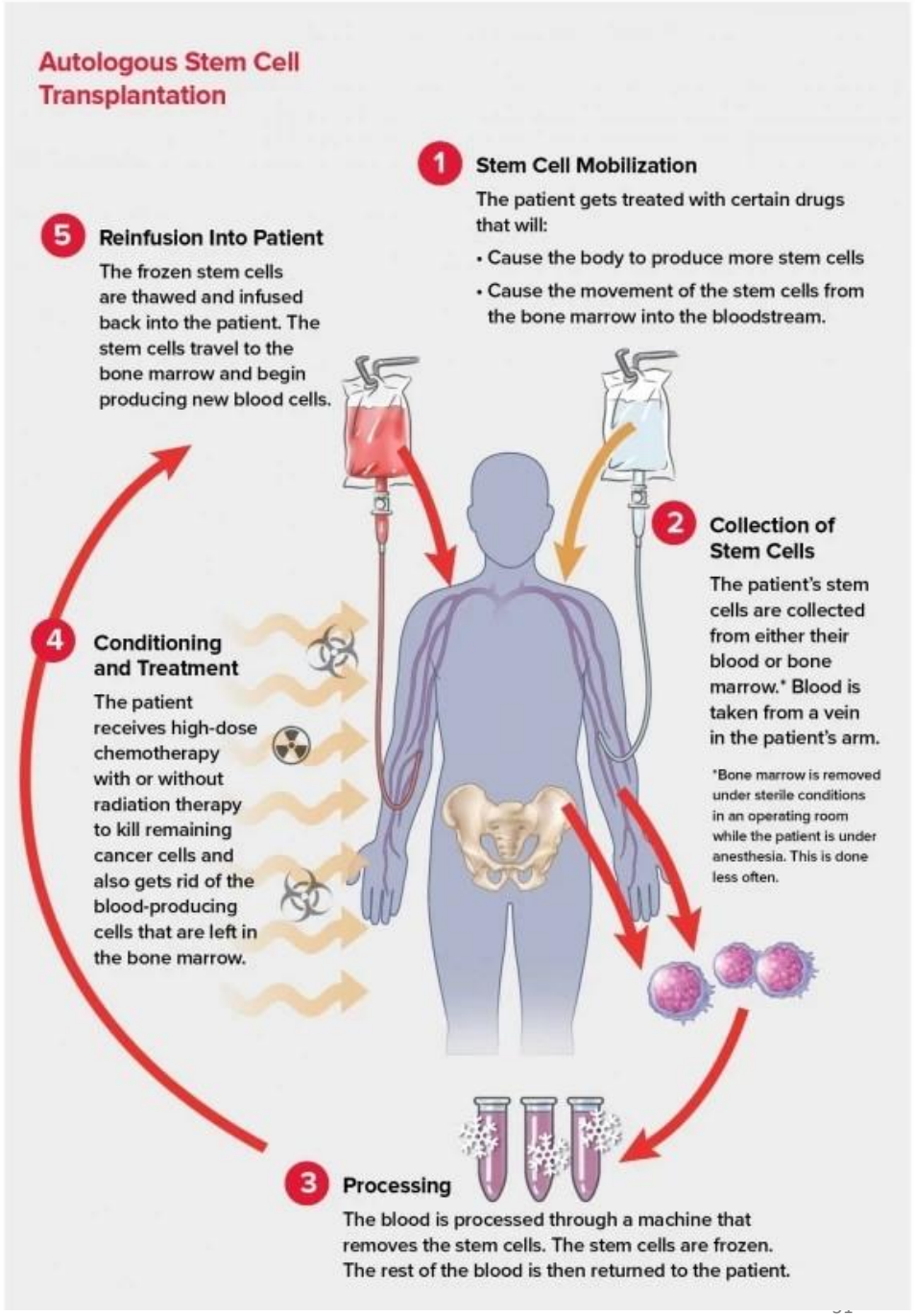
Amyloidosis Research Consortium

What's the role for stem cell transplant

The stem cells do nothing for AL. They're purely for bone marrow recovery.

It's the chemotherapy that treats amyloidosis by killing stem cells.

Stem cell transplant is really just very intensive plasma cell-directed therapy.



https://bloodcancerunited.org/blood-cancer-care/adults/types-blood-cancer-treatment/stem-cell-transplantation/autologous

What's the role for stem cell transplant in 2026?

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- Stem cell transplant was arguably the gold standard for treating many people with newly diagnosed AL until ANDROMEDA
- Daratumumab-CyBorD is highly effective and certainly less toxic than transplant. Is it as effective?
- That's unknown. What happens most often currently, is that we often start with dara-CyBorD, and if response is inadequate, plan B is sometimes transplant

How do we treat relapsed AL?

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- No clear gold standard, but many options
- For AL with t(11;14), we often use venetoclax
- Can recycle what we did before, if first remission was long enough (repeat daraCyBorD, etc.)
- Borrow agents from myeloma: lenalidomide, pomalidomide, carfilzomib, etc.

Where we go from here…

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- We’re getting better with treatments, but we’re not quite there yet
- Persistent problems we’re working on:
  - “Heme responses” are sometimes inadequate, meaning light chains are insufficiently suppressed, and daraCyBorD is not benign
  - Organ damage takes months to years to improve, if it improves at all
    - Existing AL therapies suppress light chains in blood but do nothing to remove amyloid that’s in organs already

Improving plasma cell-directed therapies

- Bispecifics
- CAR-T
- Both being investigated for both newly diagnosed and relapsed AL

Removing amyloid from tissues

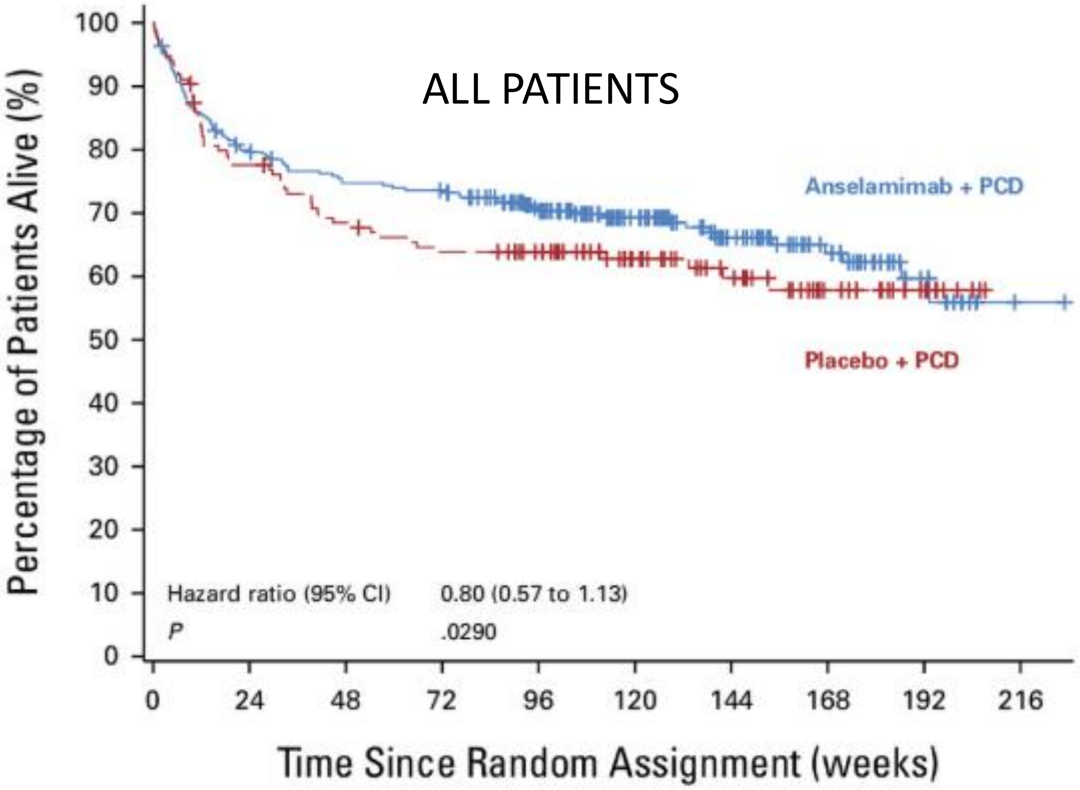
- NEOD-001
- CAEL-101 (anselamimab)

Plasma cell-directed treatments

to [illegible]ight [illegible]hains in blood

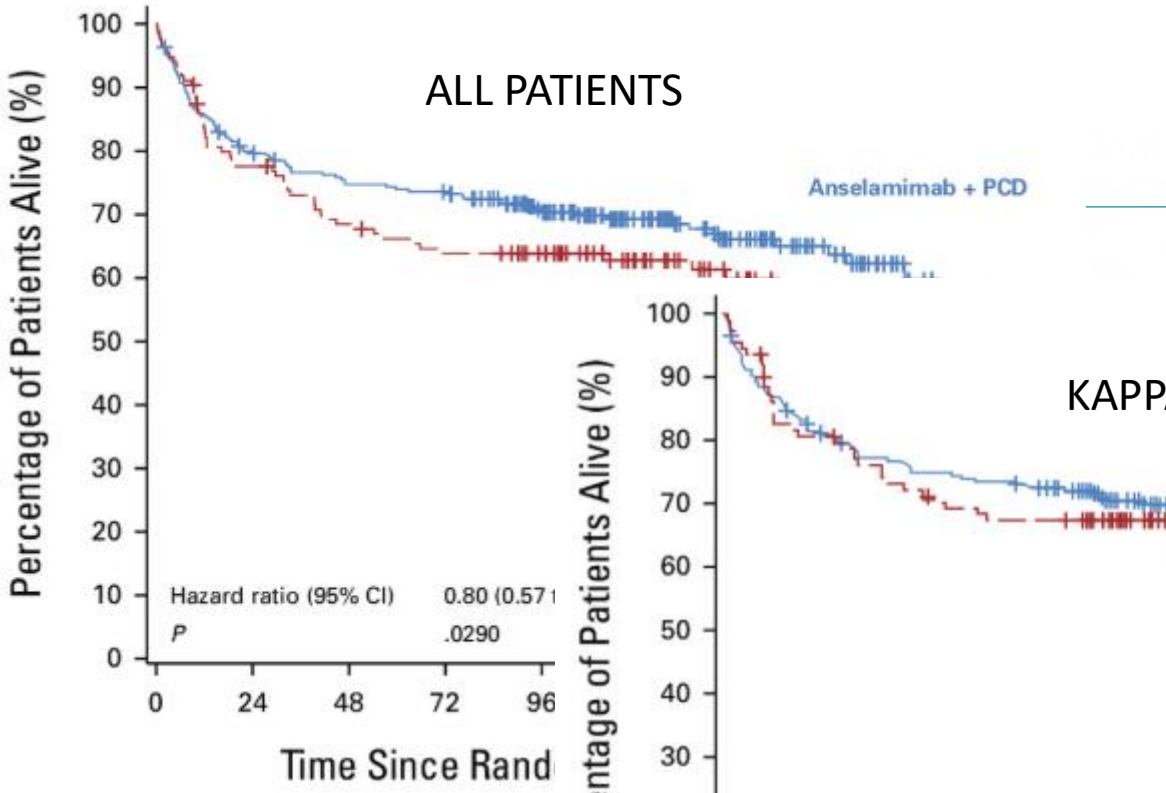
New agents (coming soon?) → clearance of amyloid from organs?

ALL PATIENTS

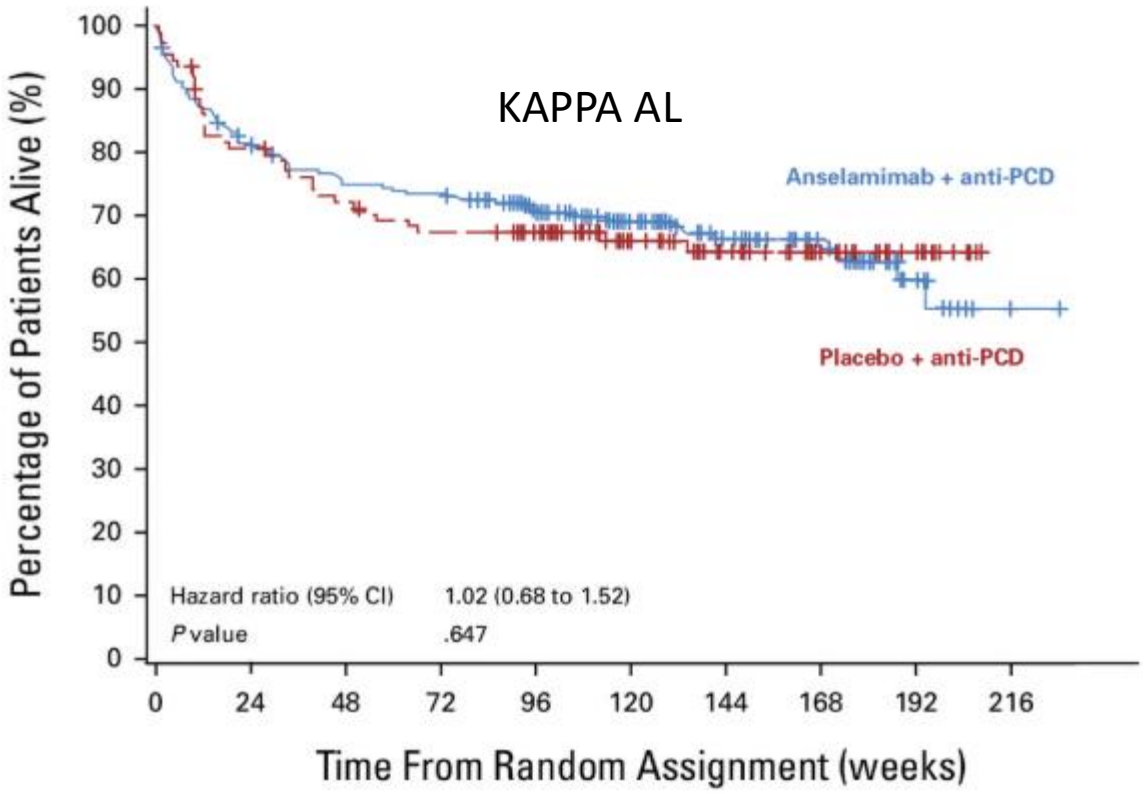


Adapted from Wechalekar, J Clin Oncol 2026

ALL PATIENTS



KAPPA AL



Adapted from Wechalekar, J Clin Oncol 2026

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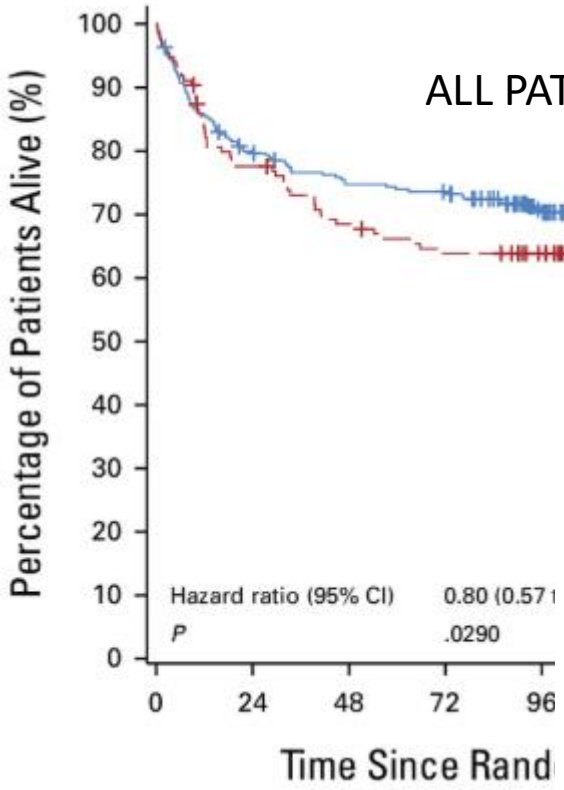
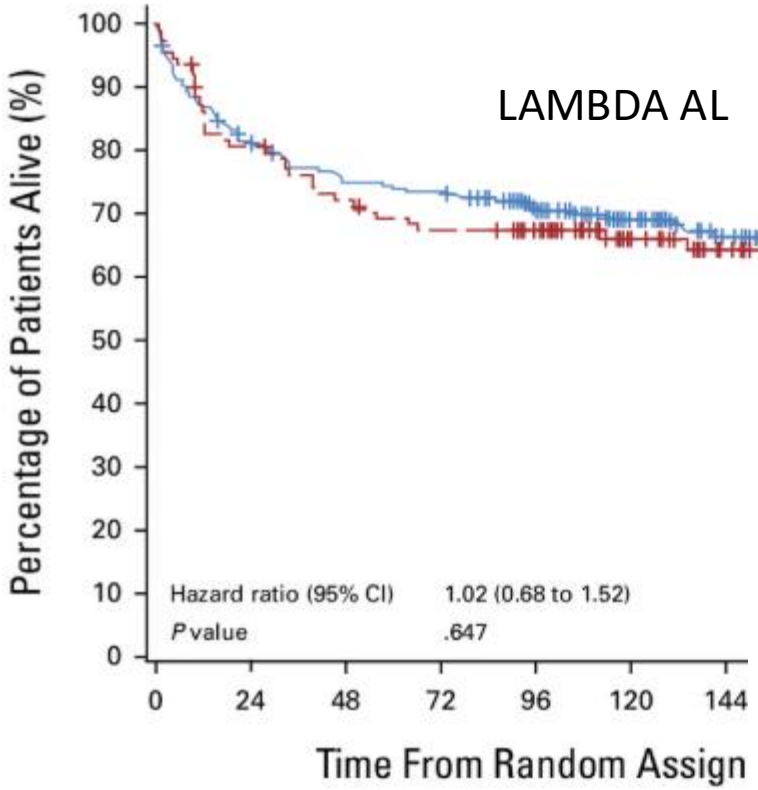
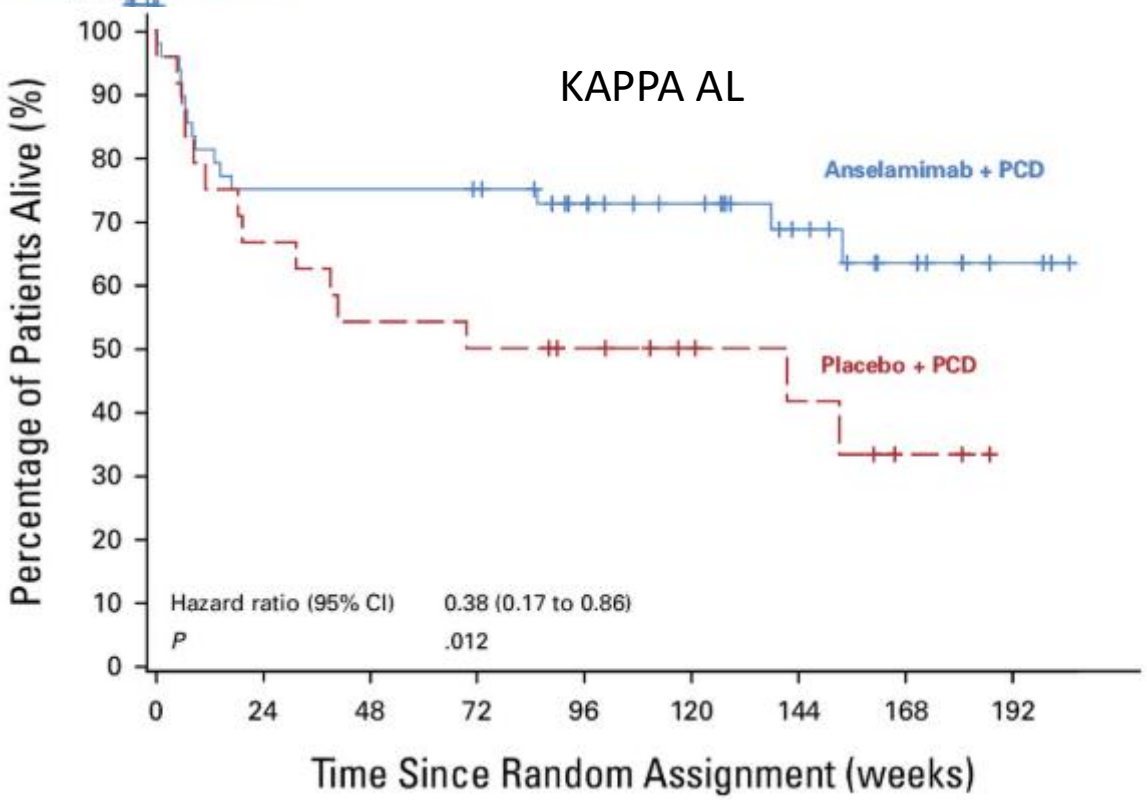
ALL PATIENTS



LAMBDA AL



KAPPA AL



Adapted from Wechalekar, J Clin Oncol 2026

Wrap-up

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- Daratumumab-CyBorD is standard for most patients with newly diagnosed light chain AL
- Heme responses are typically excellent, but still not perfect
- Stem cell transplant is probably fading out but not gone yet
- Newer approaches are extremely promising
  - Anselimumab for kappa AL
  - Venetoclax for t(11;14)
  - Bispecifics / CAR-T are coming