Amyloidosis Research Consortium

Light Chain Amyloidosis (AL) Treatments

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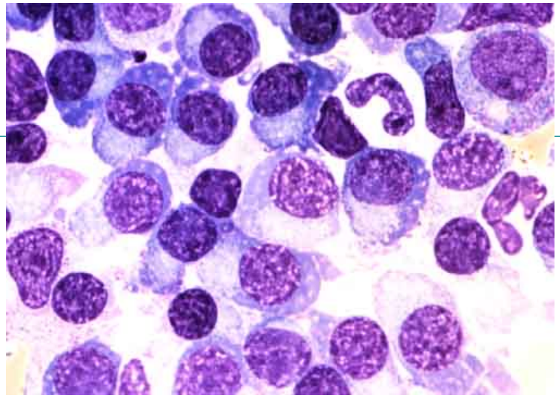
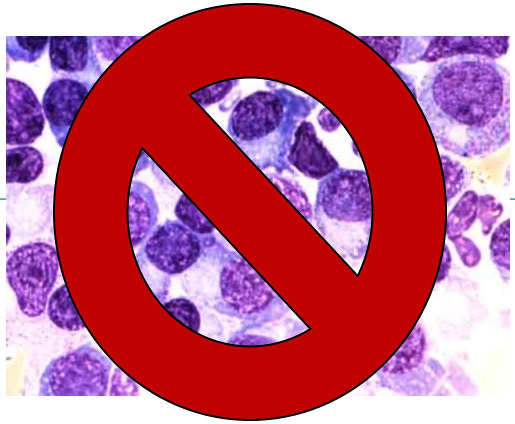
March 2025



toxic light chains in blood

Amyloid deposition in organs, causing damage



Chemotherapy
(standard)

toxic light chain in blood

New agents
(coming soon?)

clearance of amyloid
from organs?

The Usual Treatments Pre-ANDROMEDA

- Non-transplant treatment regimens: reasonably tolerable, but not adequately effective
  - Oral melphalan and dexamethasone
  - Oral melphalan, dexamethasone, and bortezomib (Velcade)
  - CyBorD = bortezomib (Velcade), cyclophosphamide + dexamethasone

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

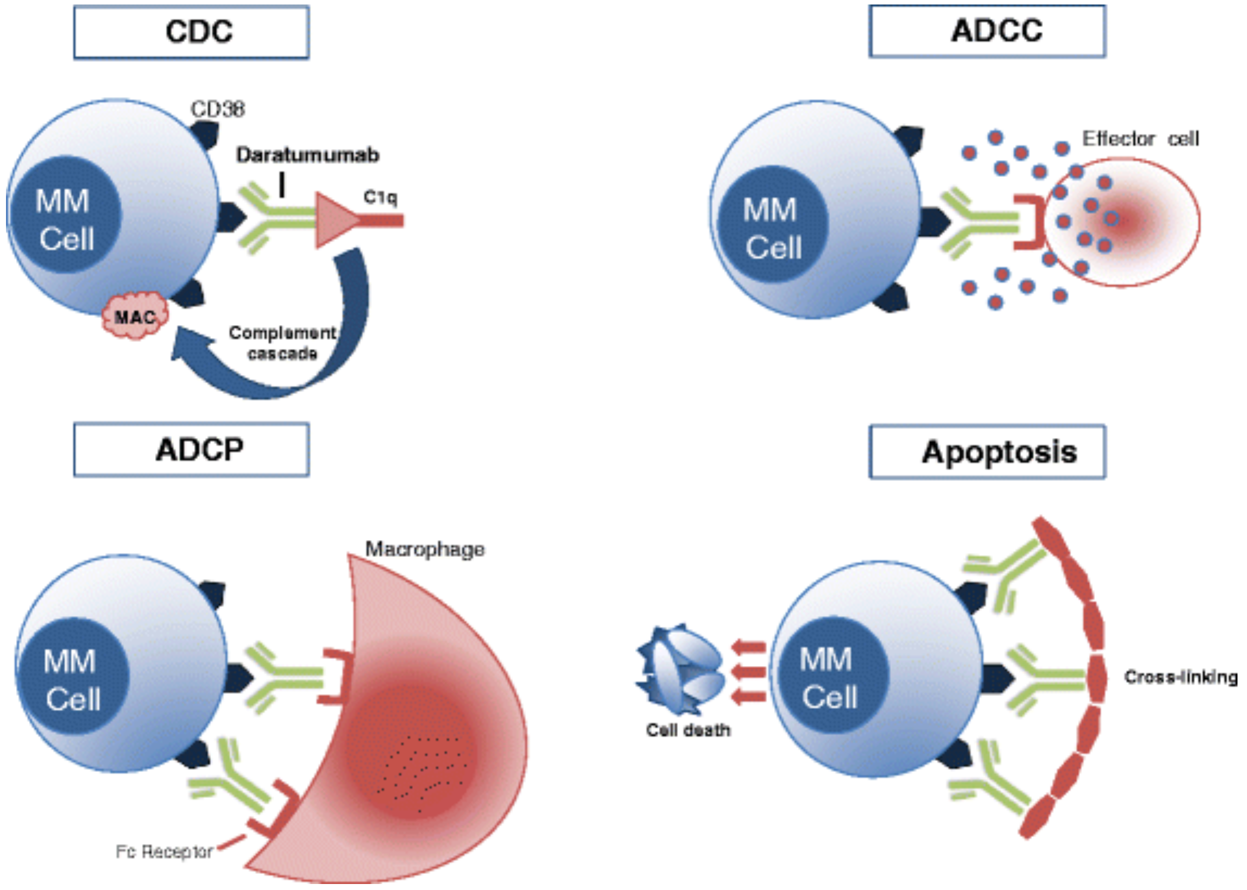
Initial pilot studies in AL showing good tolerability and effectiveness

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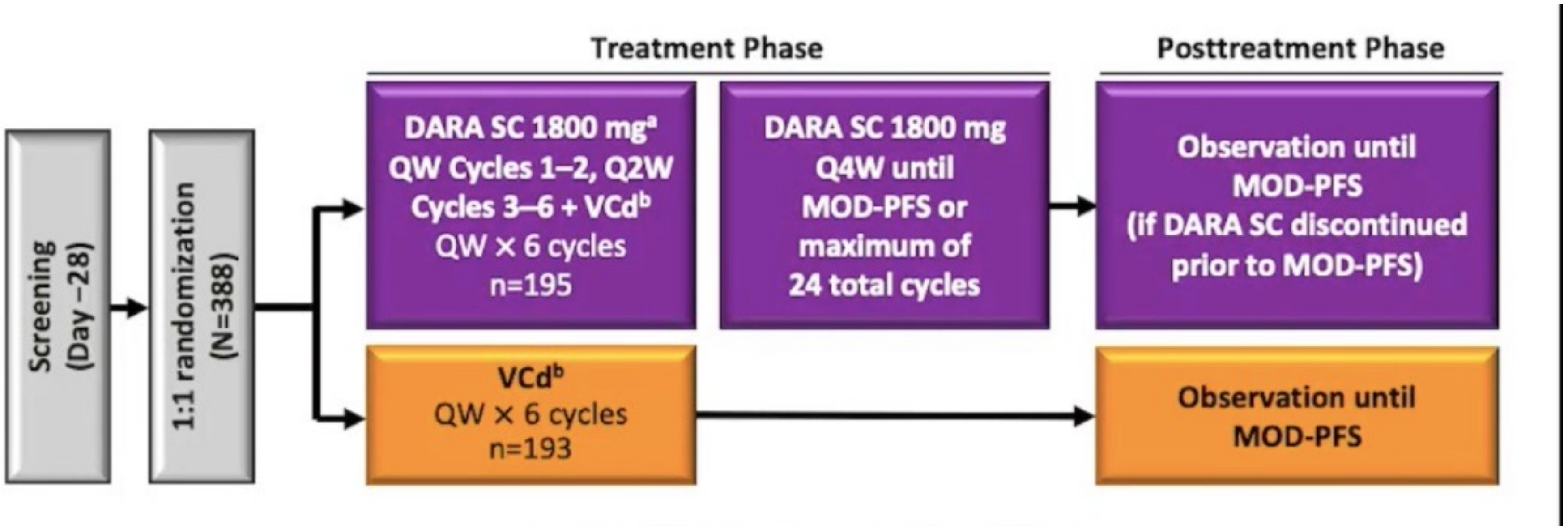
- Newly diagnosed AL with heart involvement
- Excluded patients with
  - NYHA class IIIb or IV CHF, Mayo stage 3b (NT-proBNP ≥8500 ng/L) (severe heart failure)
  - GFR ≤ 20 ml/min (severely reduced kidney function)
  - Unmeasurable disease hematologically (M-spike ≤0.5 g/dL and involved-uninvolved light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

Kastritis E, *New Eng J Med* 2021

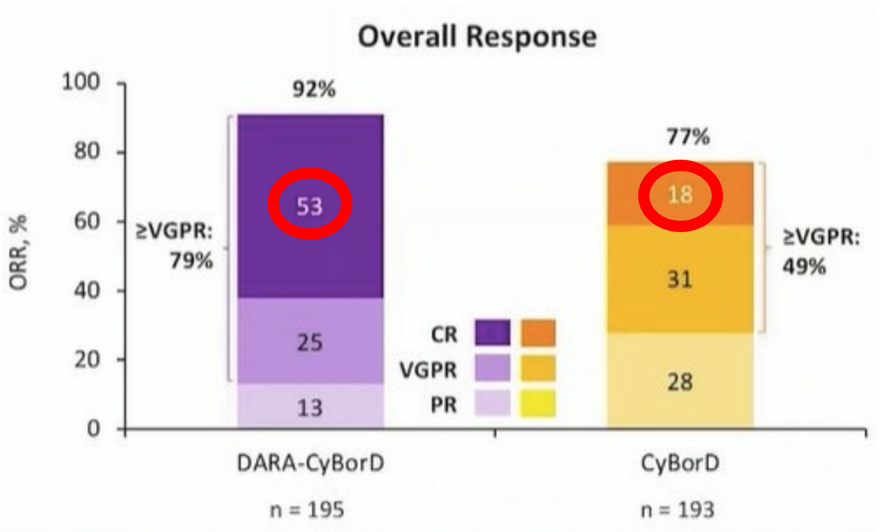
6 months 18 months



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

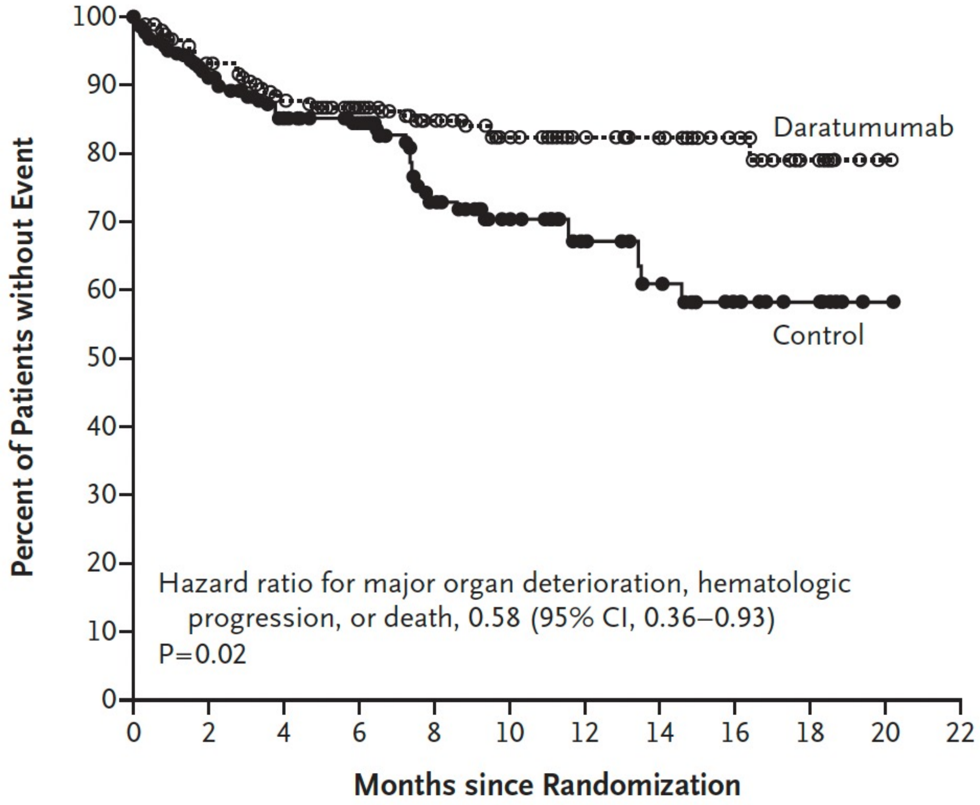
(suppression of light chain proteins below detectable levels)

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

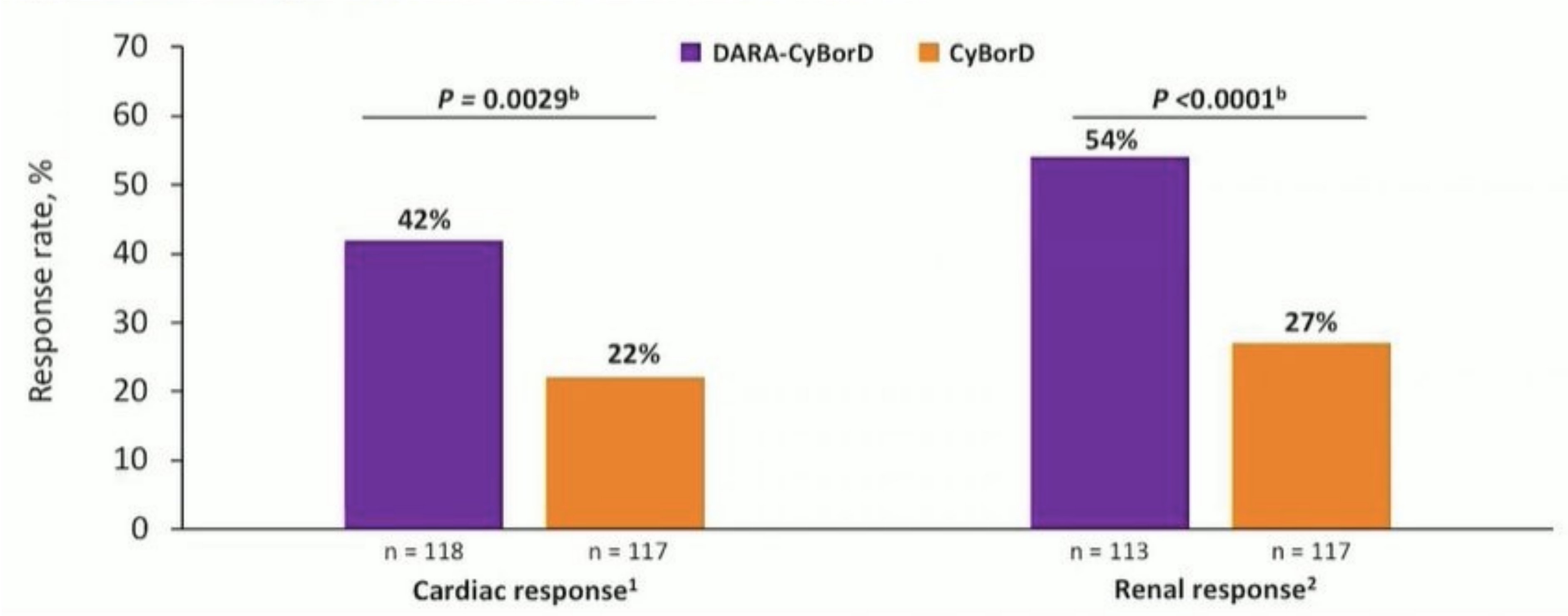


- MOD-PFS defined as haematologic progression (IRC assessed), end-stage cardiac or renal disease, or death
- At a median follow-up of 11.4 months, MOD-PFS was improved with DARA-CyBorD[a]

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

Adding dara facilitates heart and kidney recovery

6 month organ response by arm



Kastritis, *EHA* 2020, abstract #LB2604

ANDROMEDA: CyBorD with or without Daratumumab

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- Safety profile fit what was known for both CyBorD and SC daratumumab

➢ DaraCyBorD approved for use by FDA, EMA, and in other countries for newly diagnosed AL

Kastritis, *EHA* 2020, abstract #LB2604

Some unanswered, post-ANDROMEDA questions:

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How does stem cell transplant fit in, in the era of Dara-CyBorD?	Studies ongoing, but most often now used for patients who attain inadequate response with Dara-CyBorD
What's the role for newer agents?	Venetoclax Bispecific antibodies
How do we better break down amyloid proteins that are deposited in organs already	Studies ongoing: CAEL-101 (ansilamemab) and NEOD001 (birtamimab)