EuroBloodNet

UMC Utrecht

5e Multidisciplinair Symposium Systemische Amyloïdose

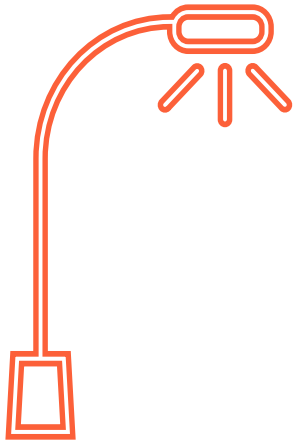
Innovatie in diagnostiek en behandeling

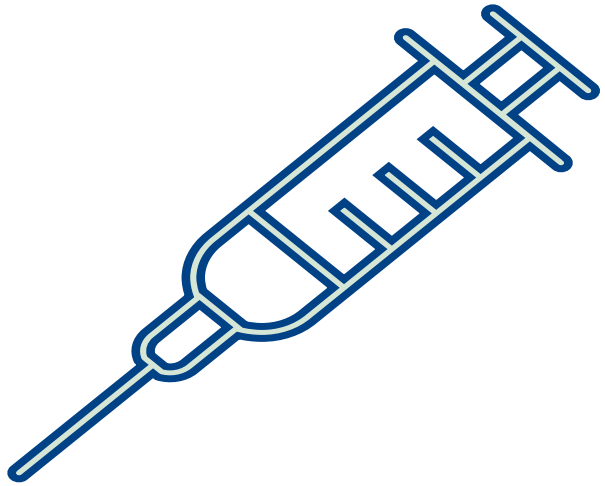
Monique Minnema, hematoloog, UMC Utrecht

Disclosures

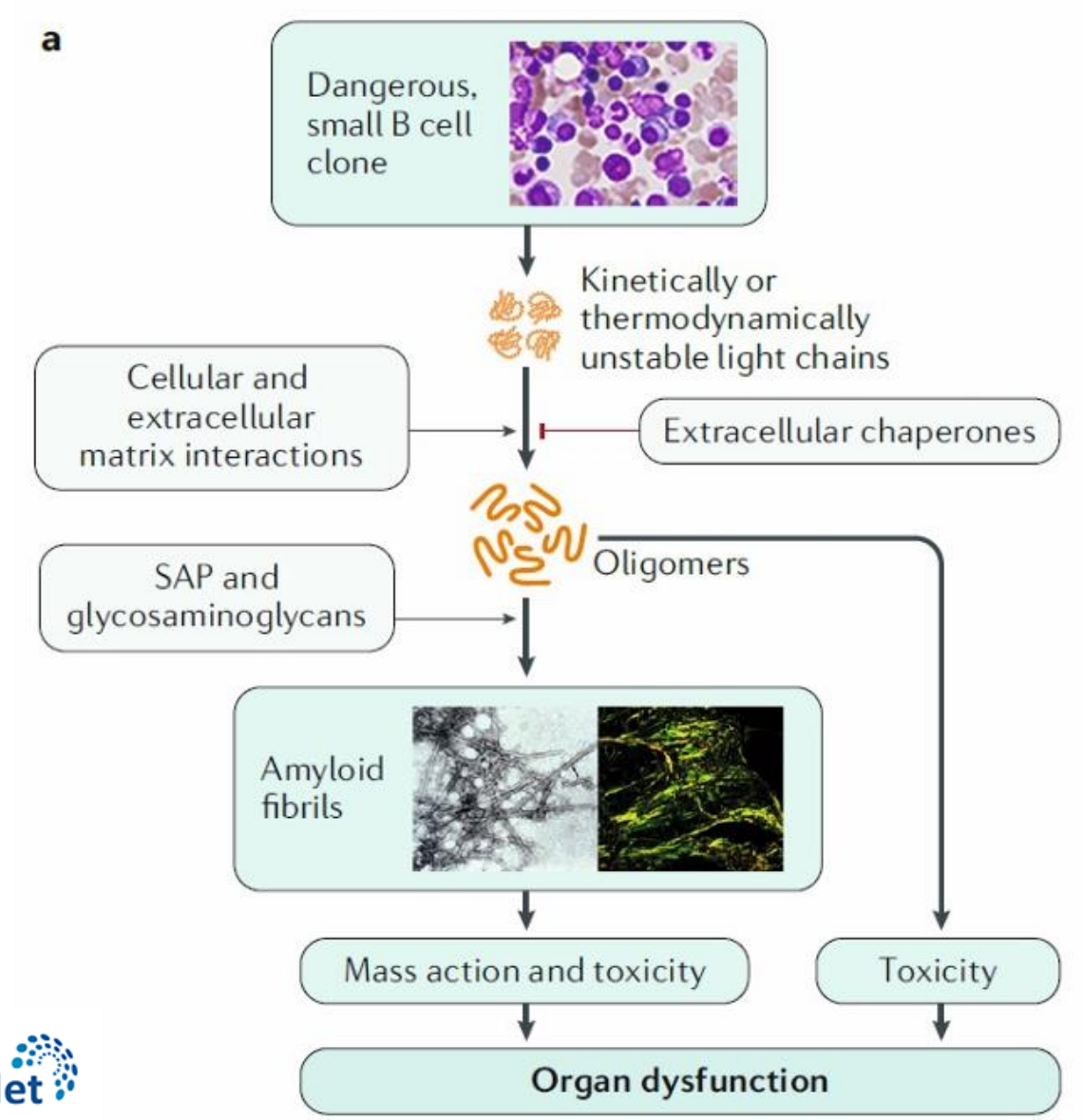
Type of affiliation / financial interest, paid to institution	**Name of commercial company**
Receipt of grants/research supports:	Beigene
Receipt of honoraria or consultation fees:	-
Participation in a company sponsored speaker's bureau:	Pfizer, Siemens, Janssen-Cilag
Stock shareholder:	-
Other support (please specify): Hospitality	Janssen Cilag, Beigene
Scientific advisory board	Janssen Cilag

Laatste ontwikkelingen AL amyloïdose

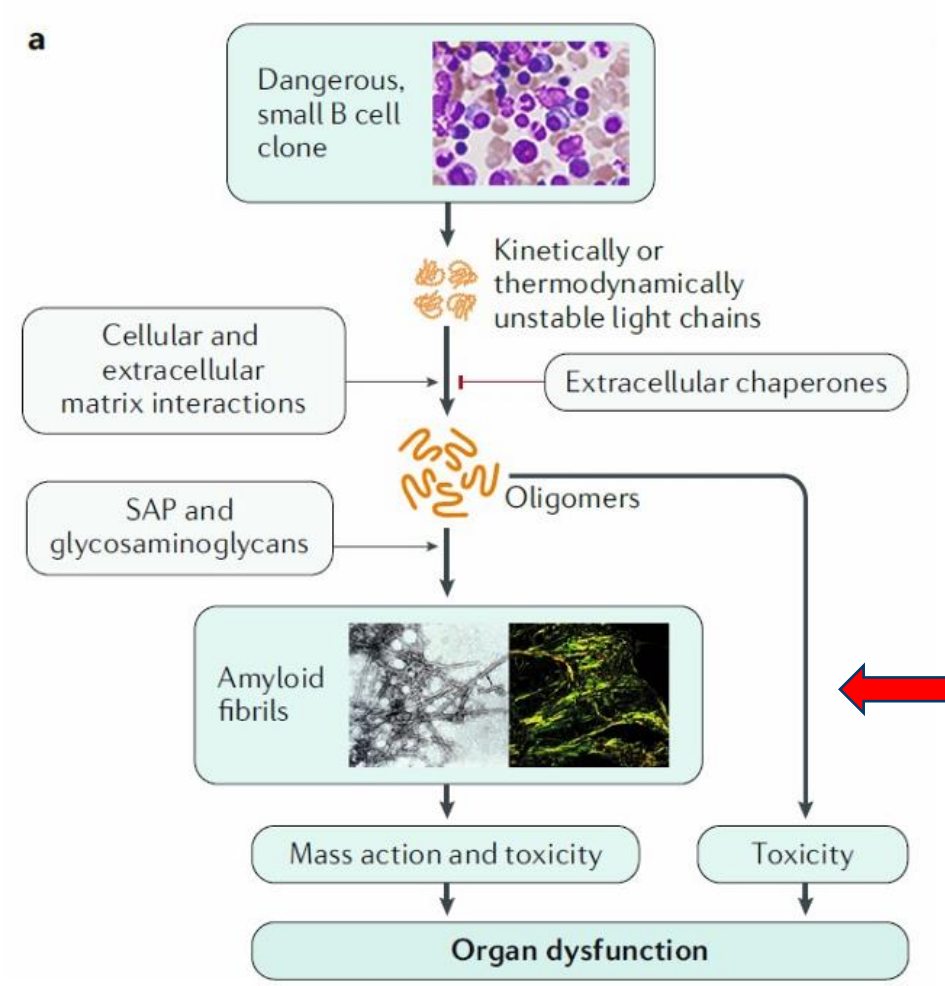


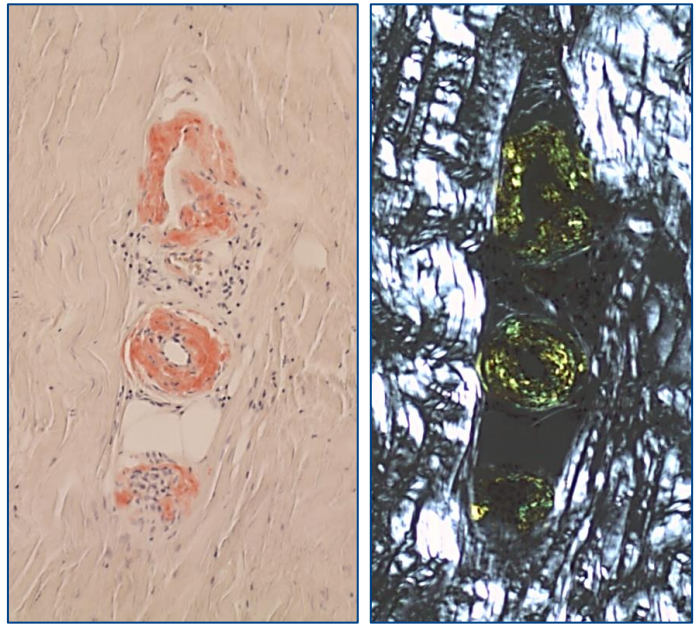


AL amyloidose

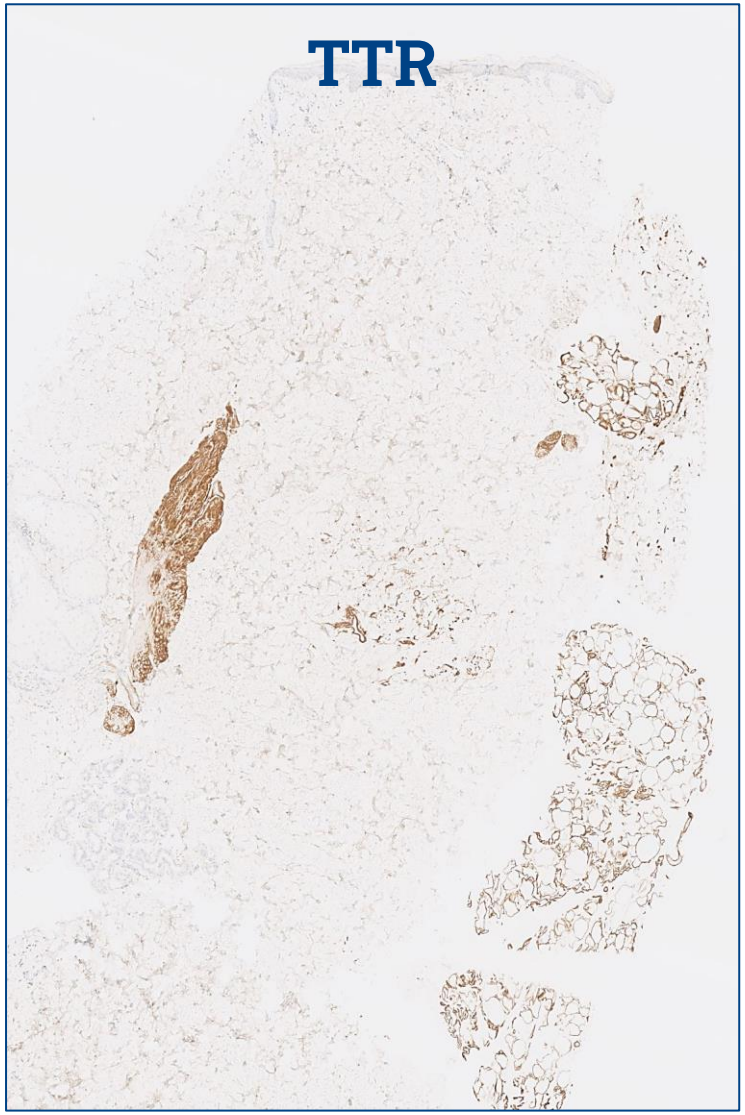


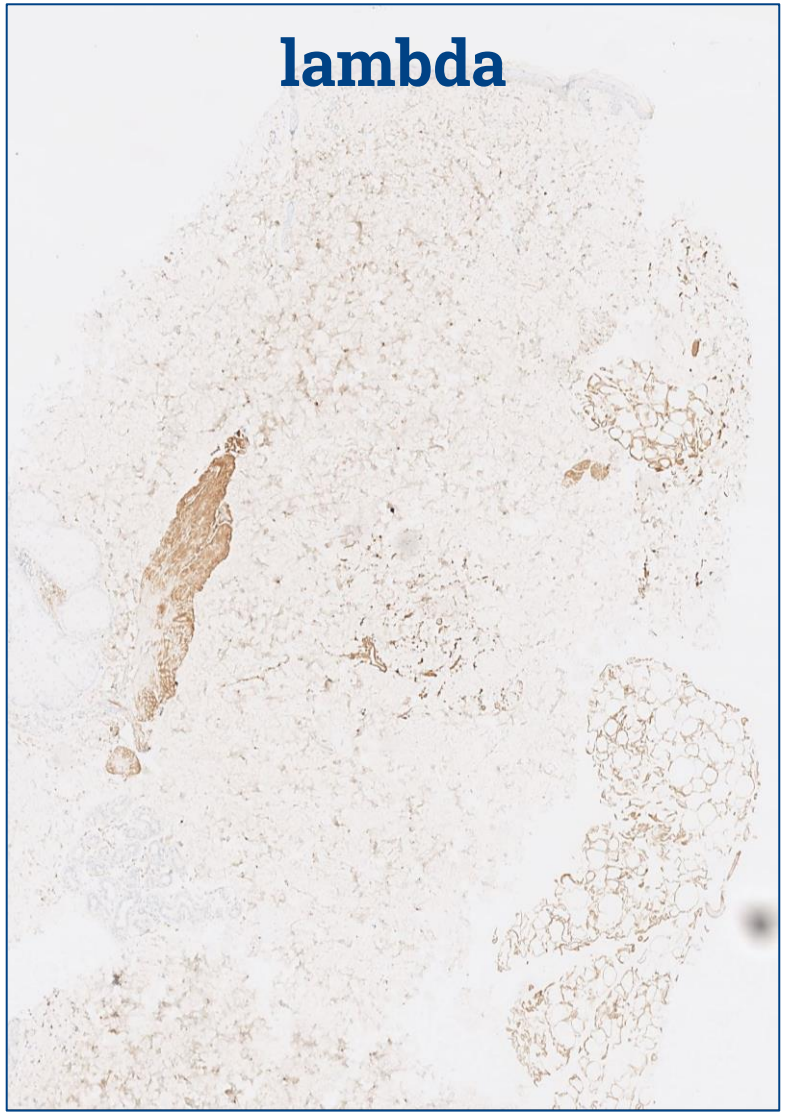
AL amyloidose

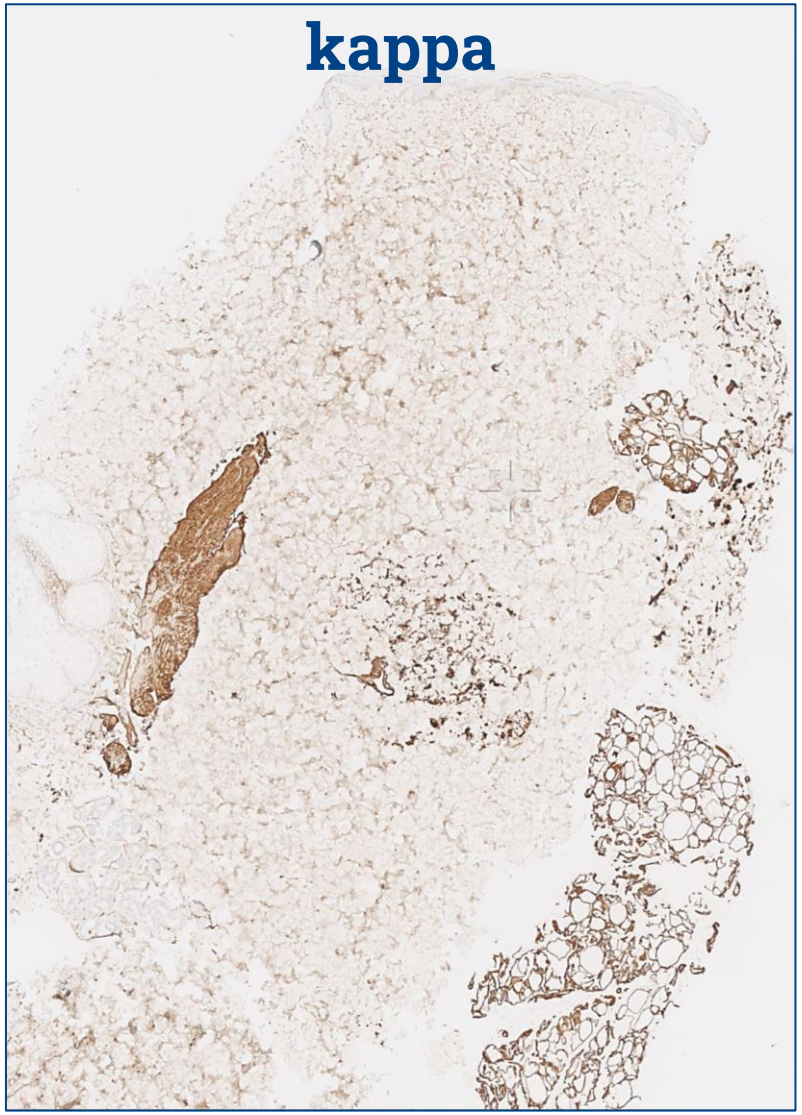




“Immuunhistochemie probleem”

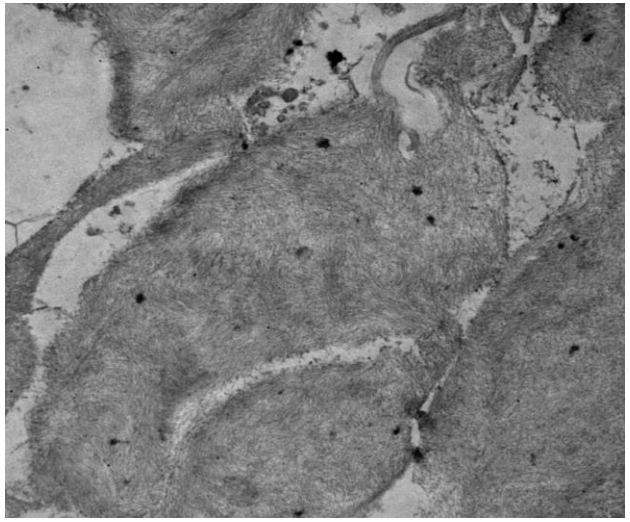




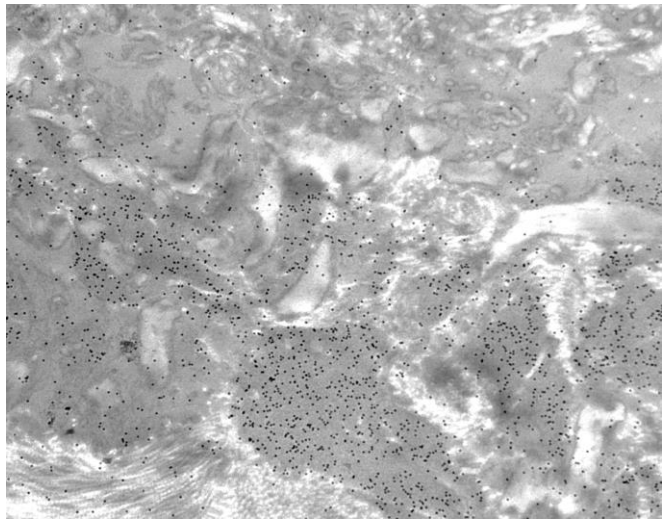


Immuno-electronenmicroscopie

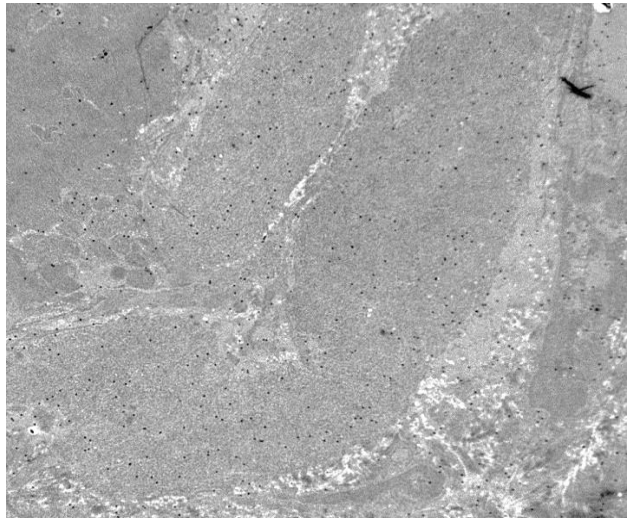
TTR



lambda



kappa



Roos Leguit, hemato-patholoog UMC Utrecht

- Immuun-fluorescentie Nier pathologie
- ELISA techniek buikvetaspiraten UMCG

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Diagnostiek PA

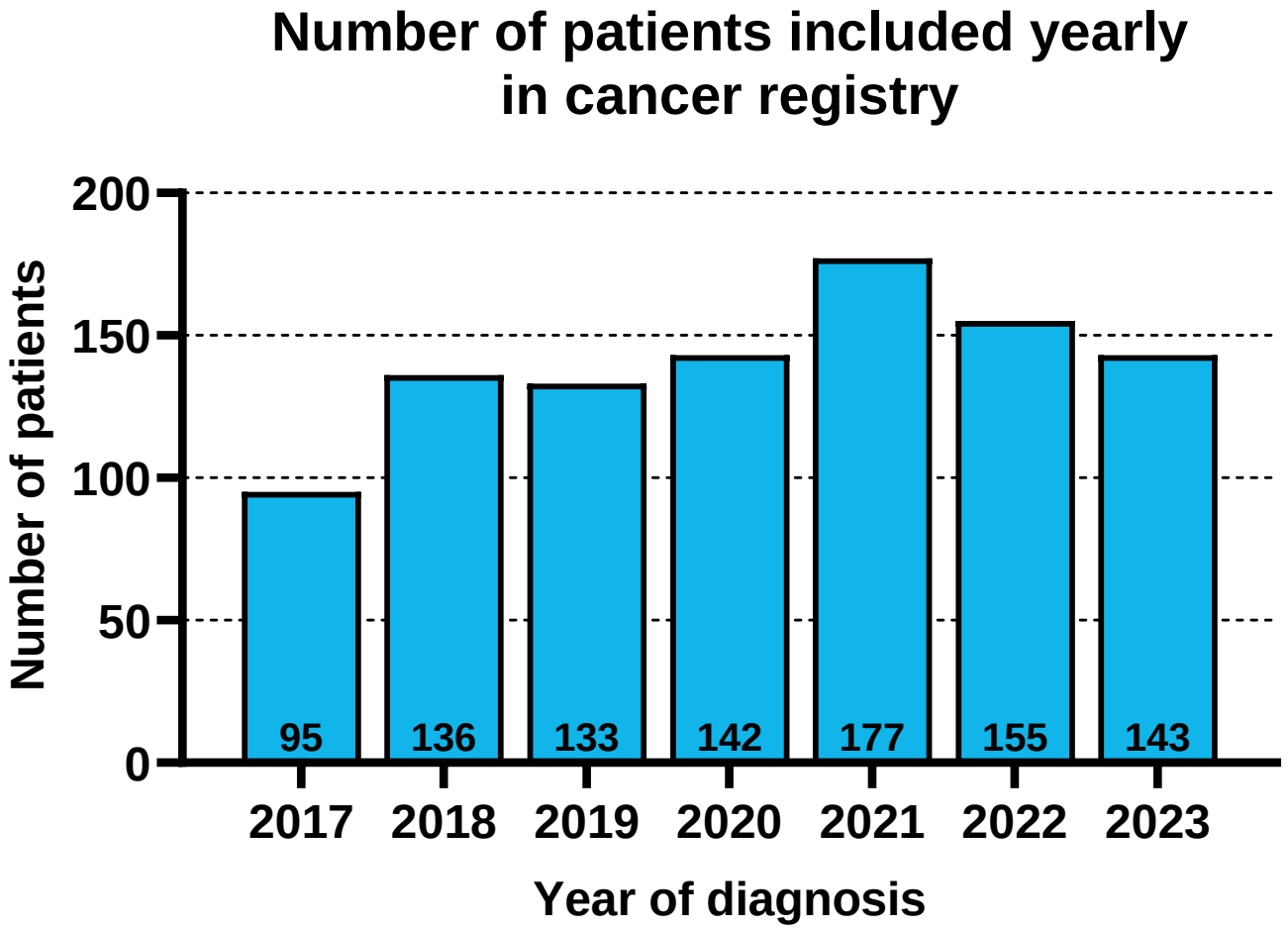
- 2de (expert) patholoog ziet soms meer; gebruik de expertise centra!
- Typering van het amyloïd moet altijd geprobeerd worden

<u>Plasmacel kloon beenmerg</u>

- Ook kleine (<10%) klonale plasmacel infiltratie in het beenmerg kan bij amyloïdose klinisch relevant zijn en dienen door de patholoog in de conclusie vermeld te worden
- >75% van de plasmacel klonen bij systemische AL amyloïdose zijn Cycline D1 positief

Nederlandse kanker registratie

Flores Weverling, PhD



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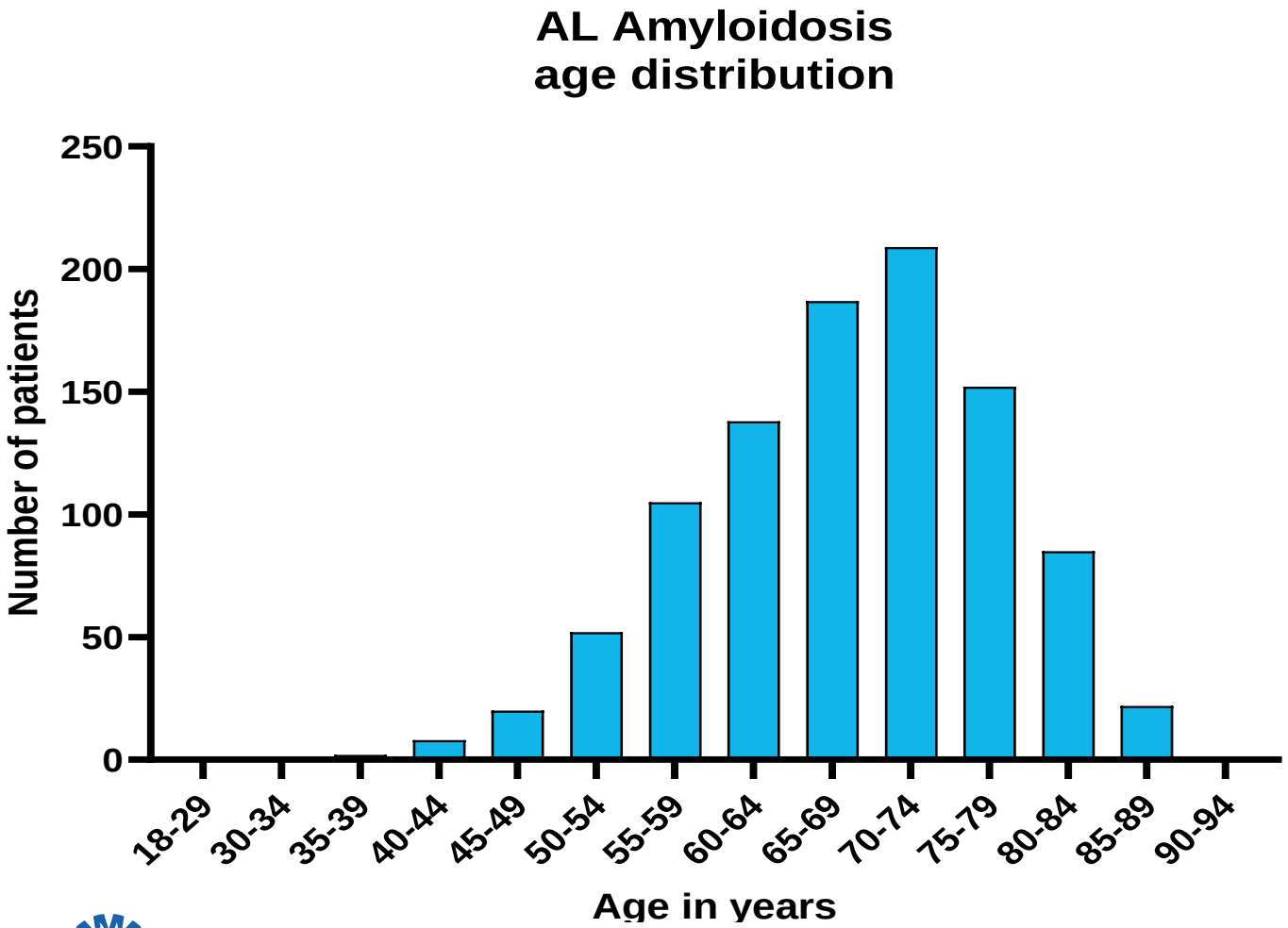
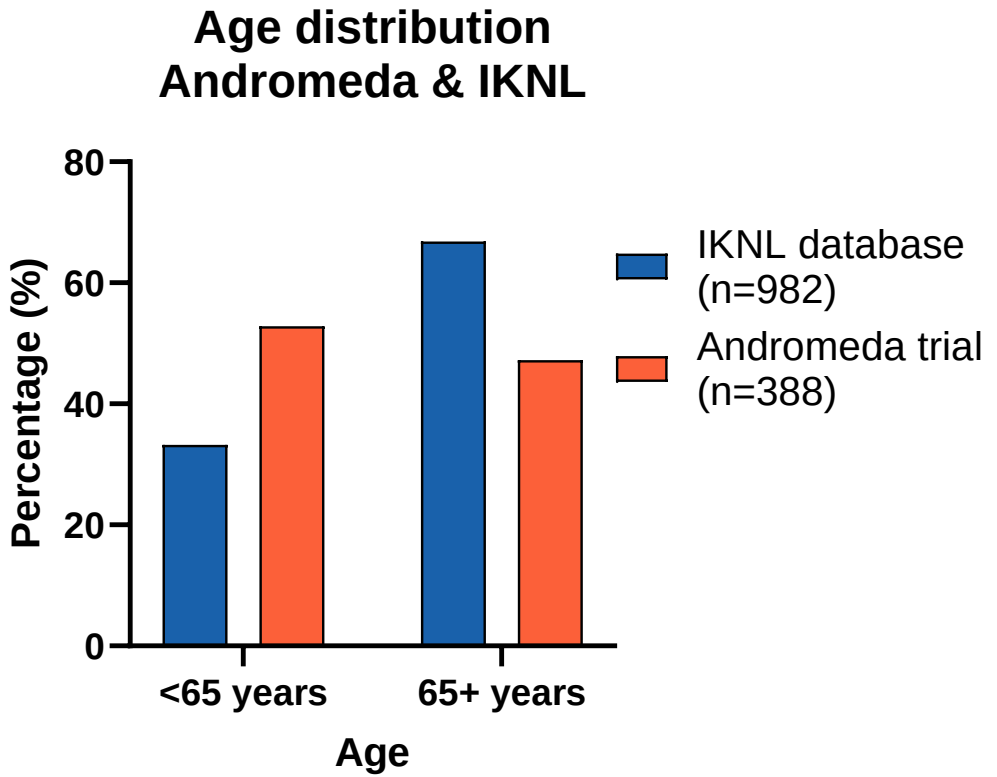
Nederlandse kanker registratie





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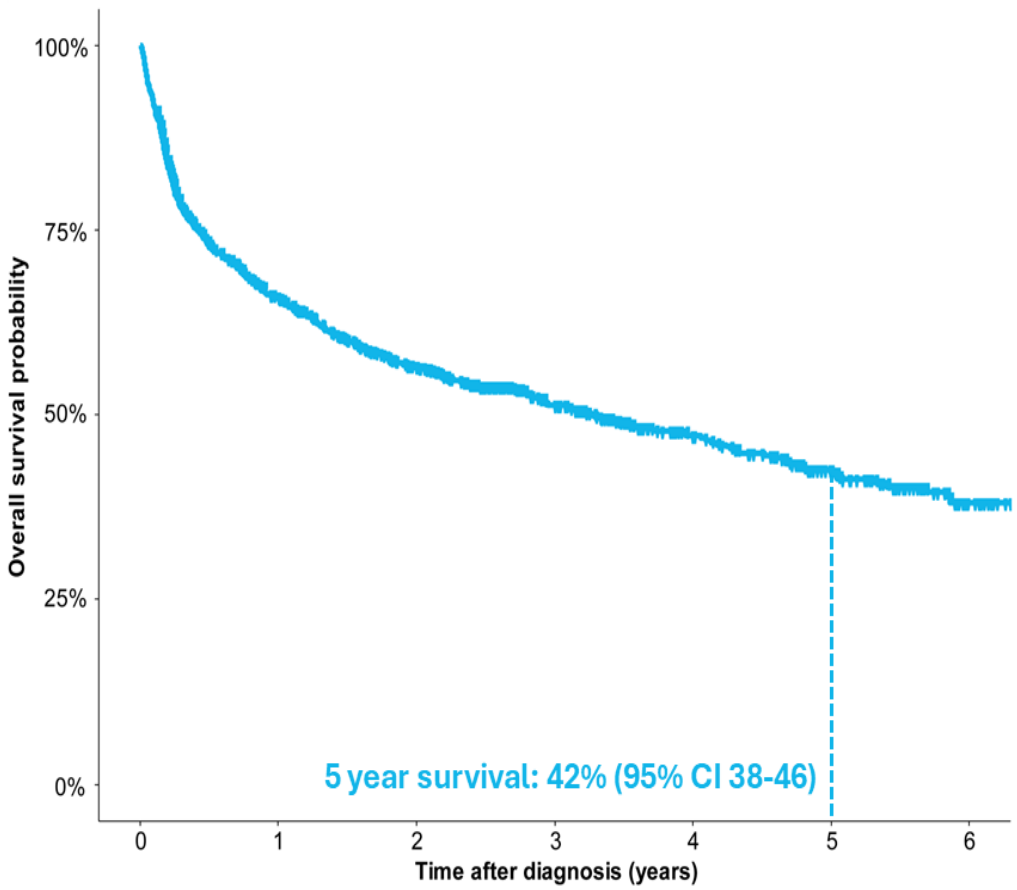
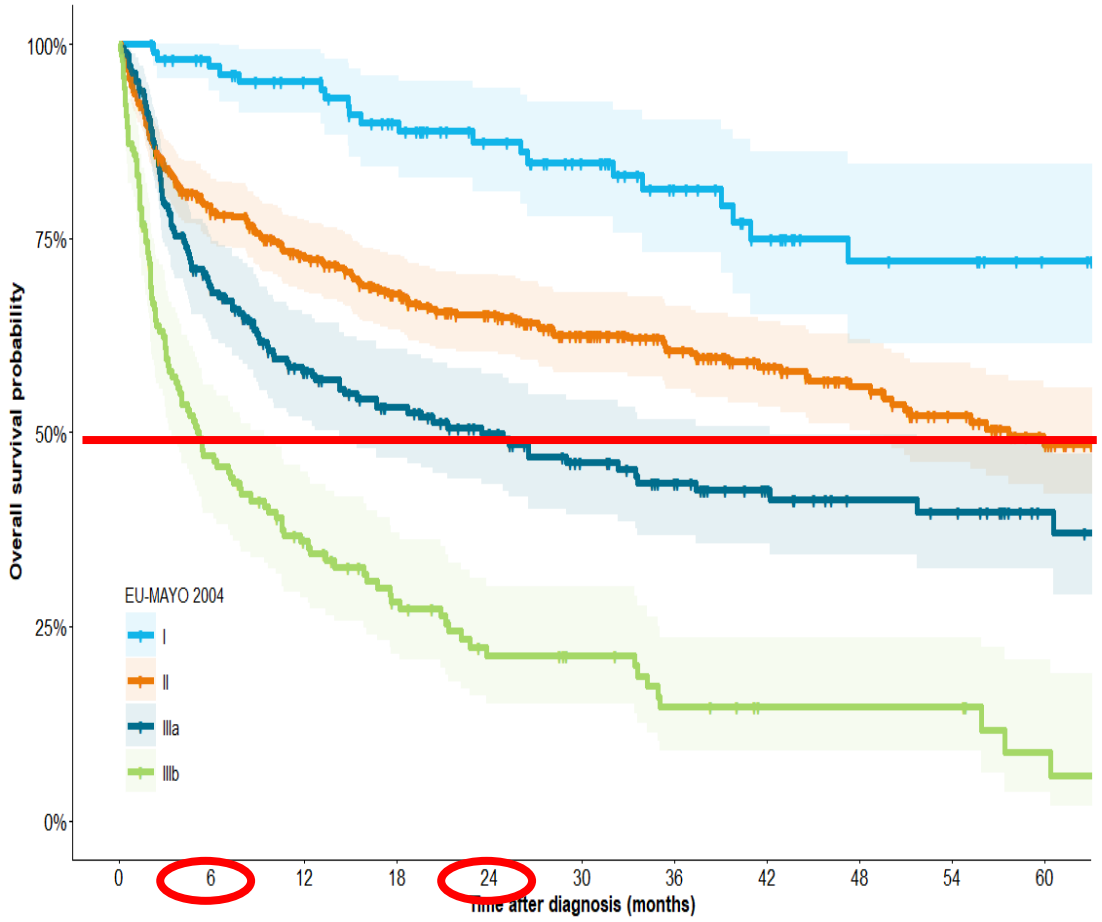
AL amyloidose pt NL overleving





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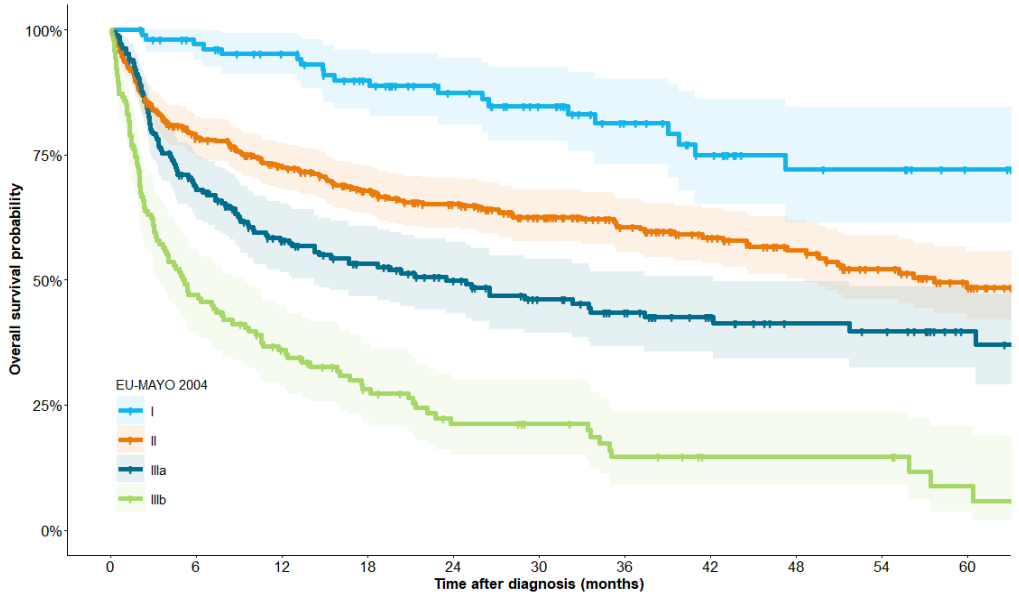
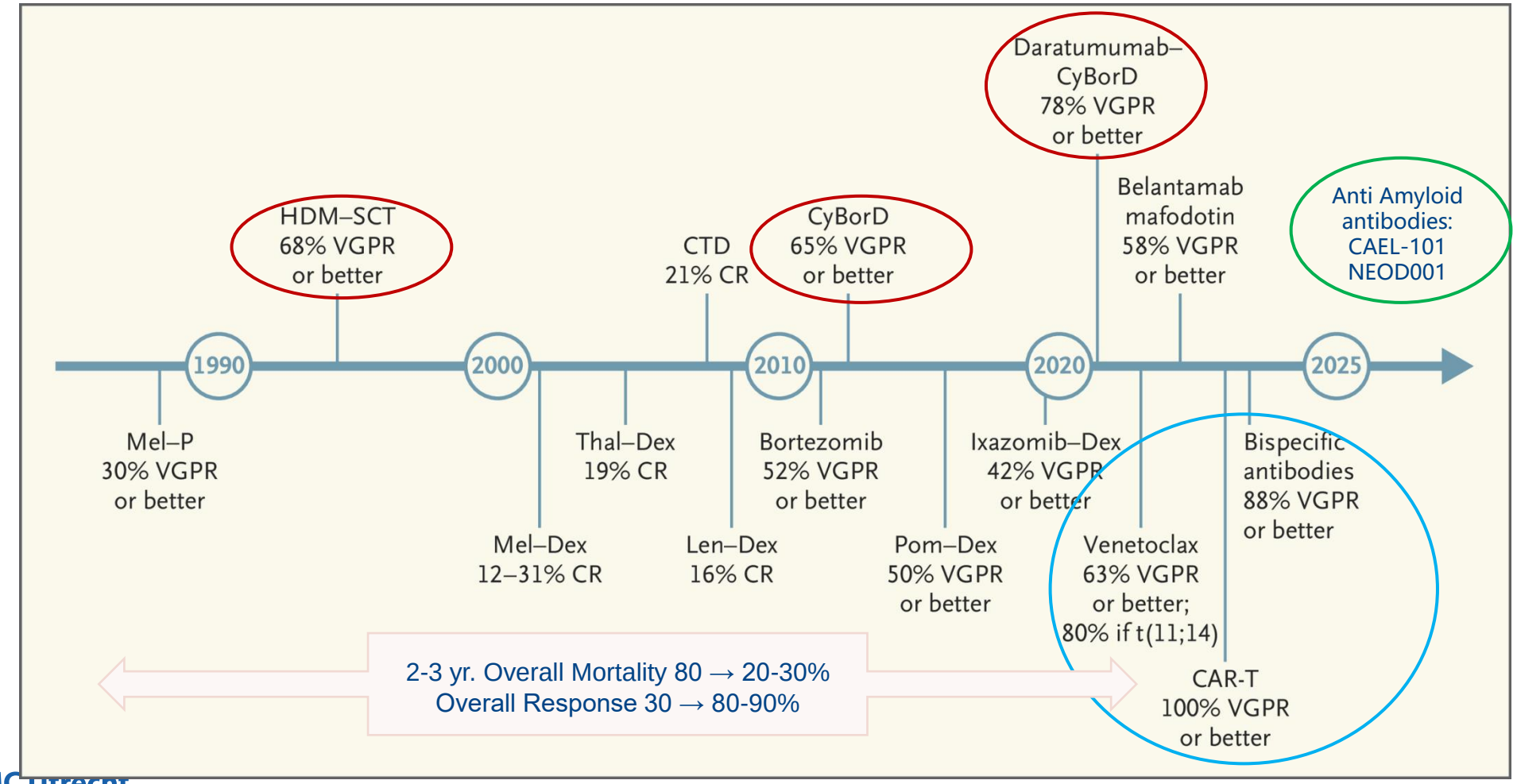
Behandeling; Goals of therapy

- Red levens; AL amyloidosis is een zeer dodelijke ziekte
- Behoud/verbeter orgaanfunctie en QoL
- **Hematological goals:**



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**

Hoe hematologische respons bereiken?



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Sanchorawala et al, NEJM 2024

HOVON 104 FU

Received: 15 April 2024 | Accepted: 15 April 2024

DOI: 10.1002/jha2.918

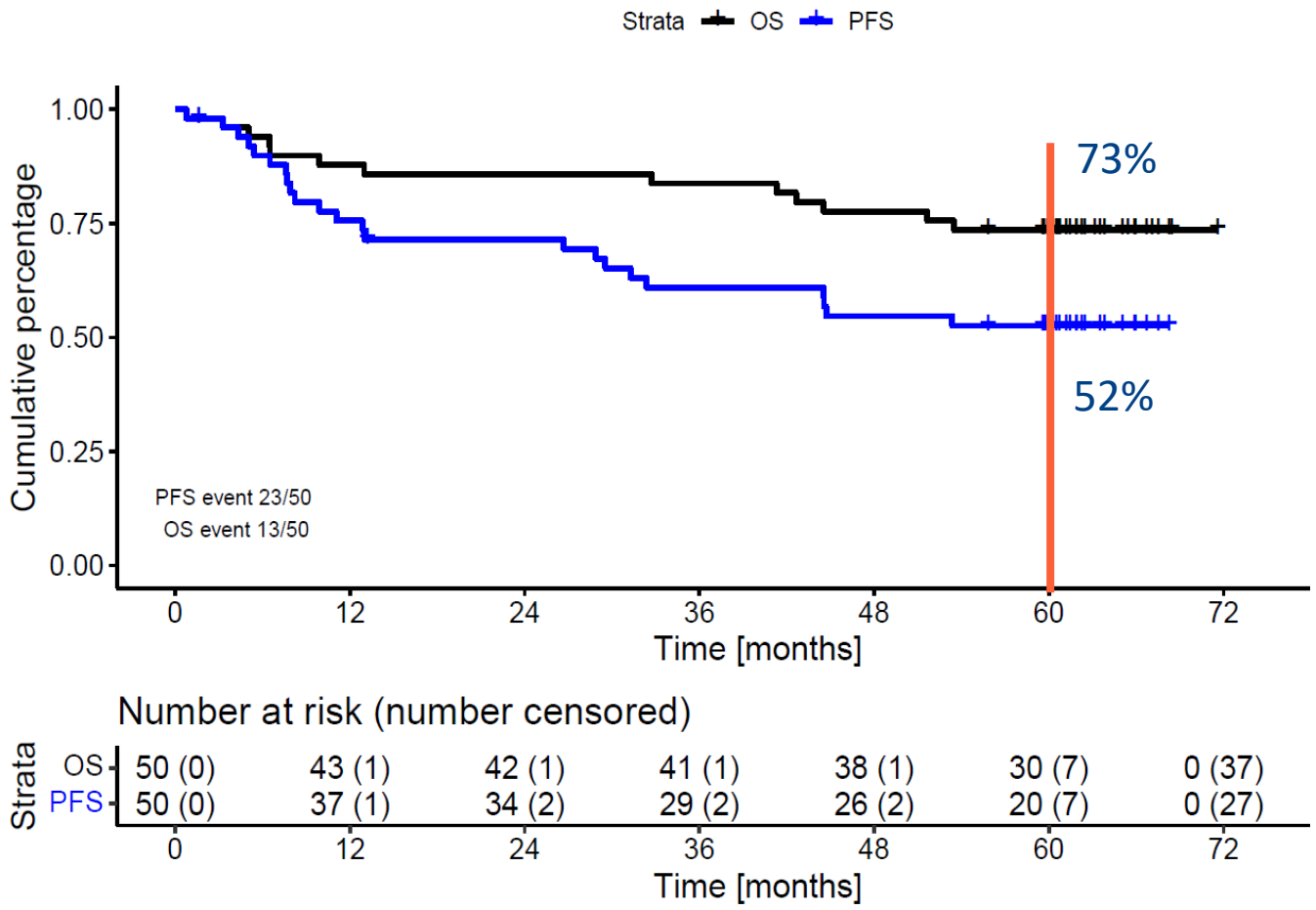
eJHaem

British Society for Haematology

SHORT REPORT

HOVON 104, long-term follow-up of bortezomib-dexamethasone induction therapy followed by autologous stem cell transplantation in newly diagnosed AL amyloidosis patients

HOVON 104 FU



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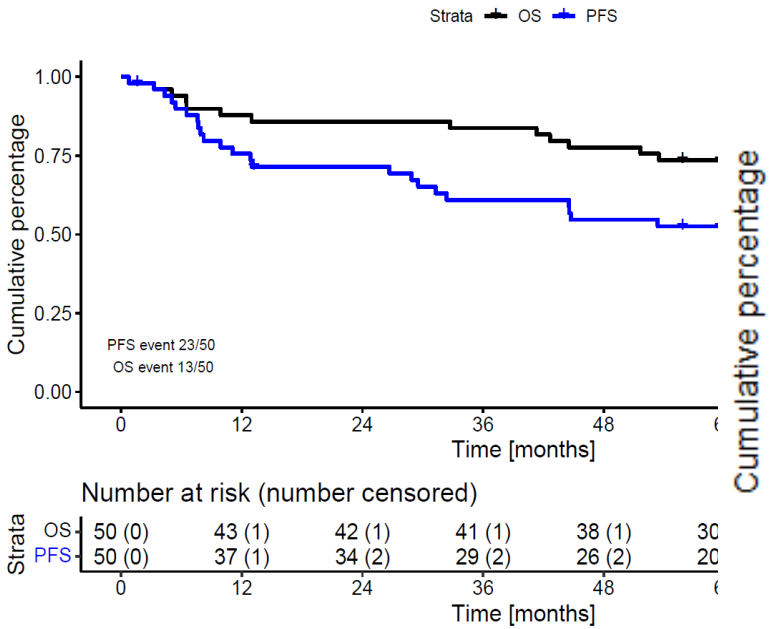
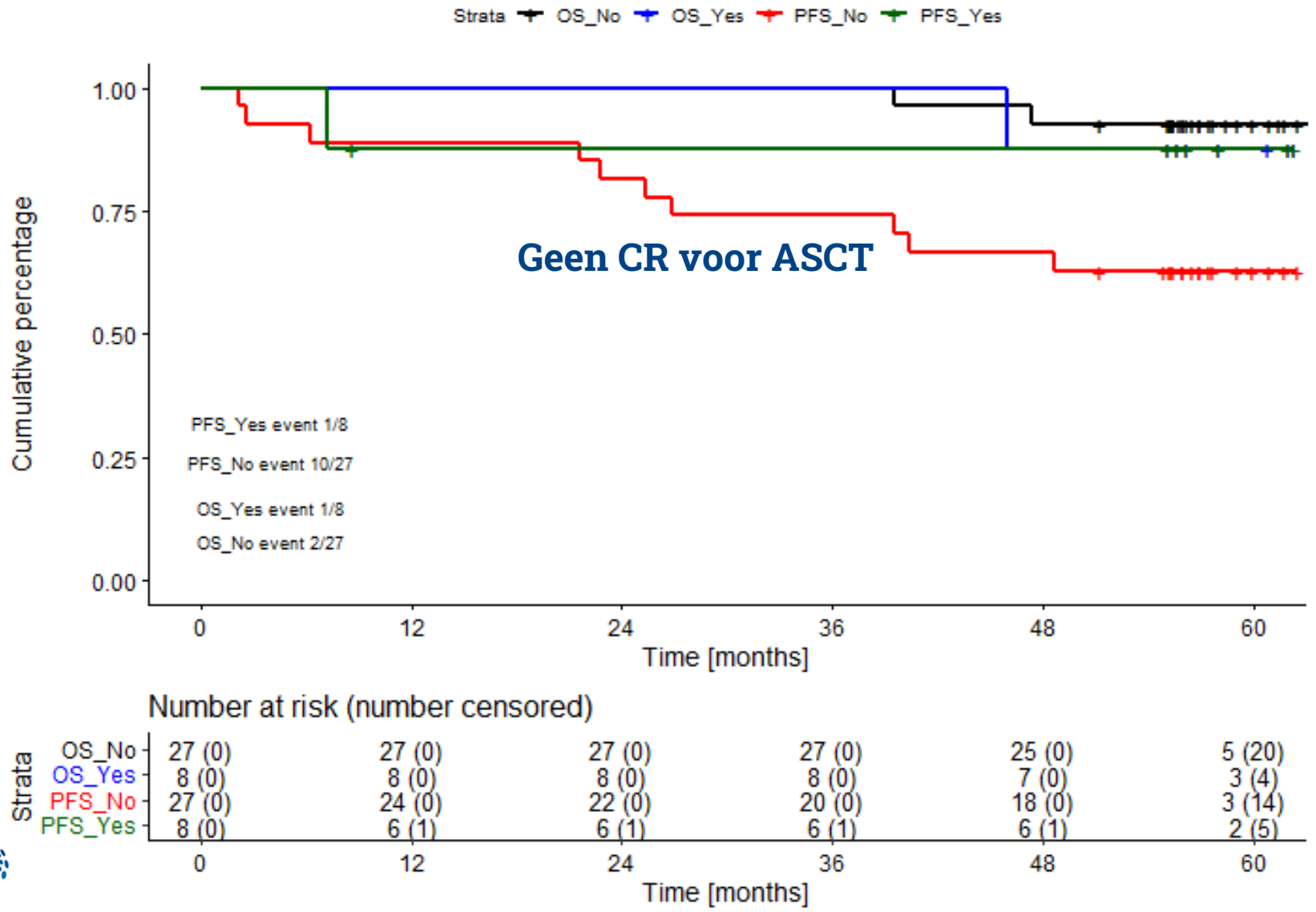
HOVON 104 FU





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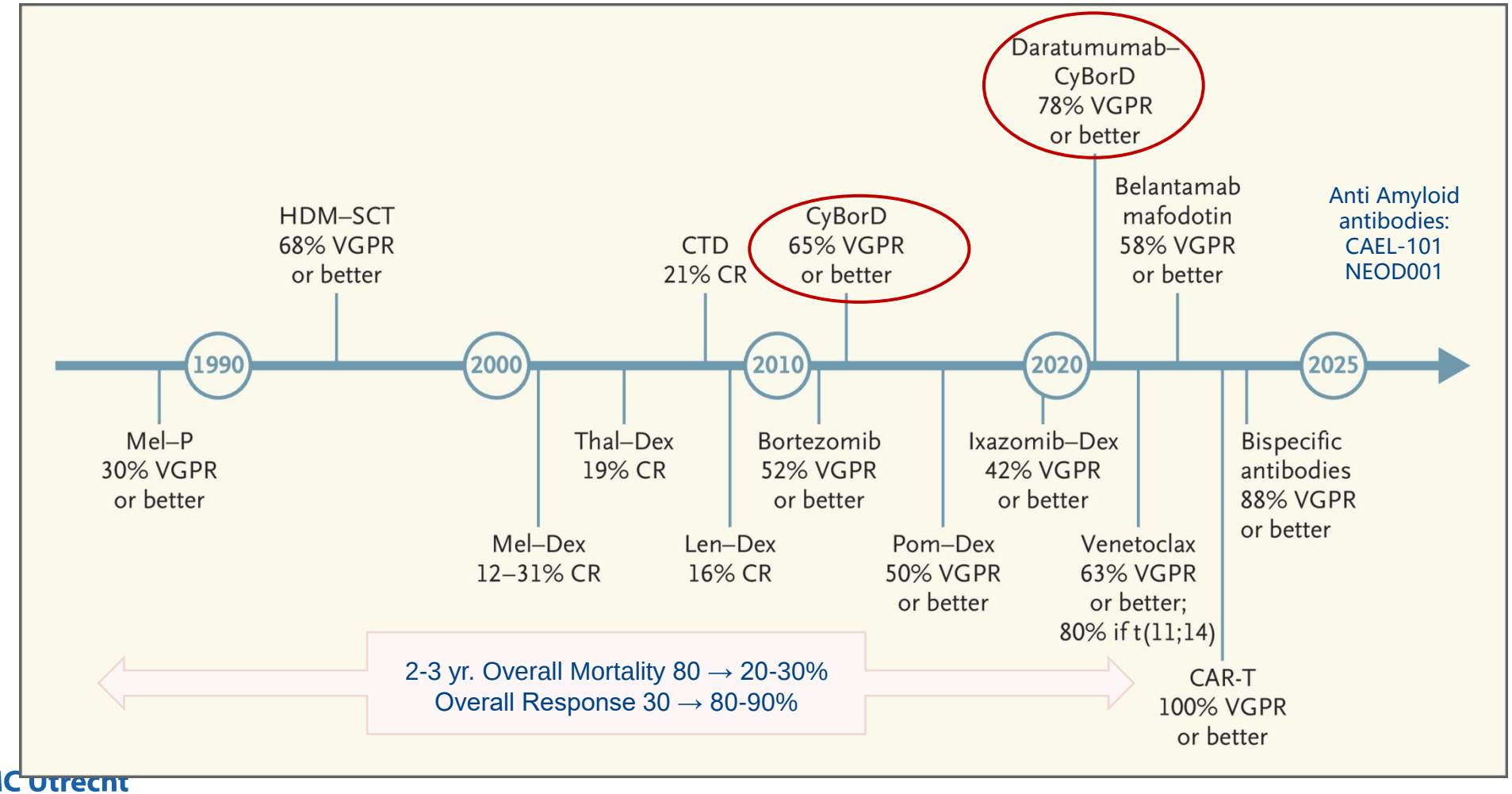
Hoe hematologische respons bereiken?



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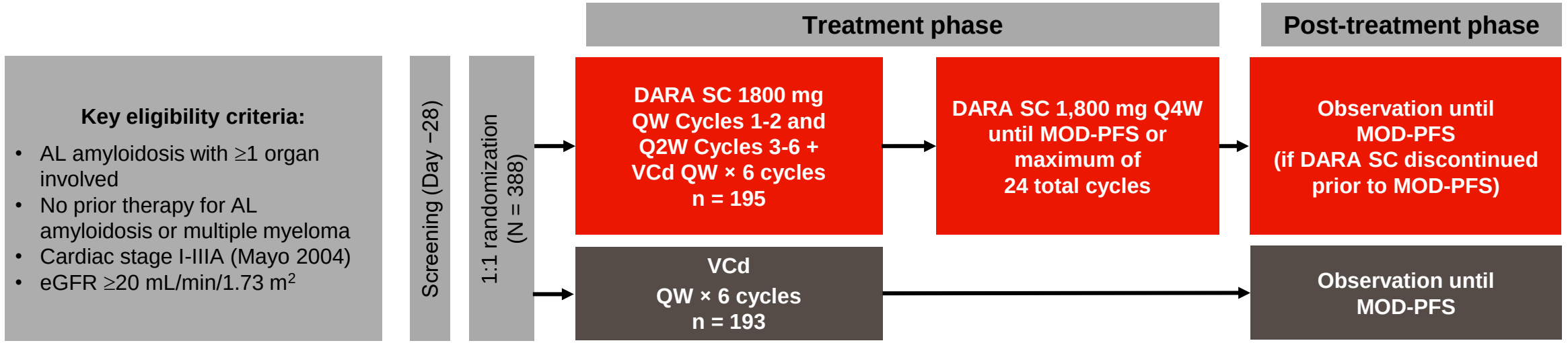
Sanchorawala et al, NEJM 2024

ANDROMEDA: Study Design

- ANDROMEDA is a randomized, open-label, phase 3 study of DARA plus VCd (D-VCd) versus VCd alone in patients with newly diagnosed AL amyloidosis



Stratification criteria:
- Cardiac stage (I vs II vs IIIA)
- Transplant typically offered in local country (yes vs no)
- Creatinine clearance (≥60 mL/min vs <60 mL/min)

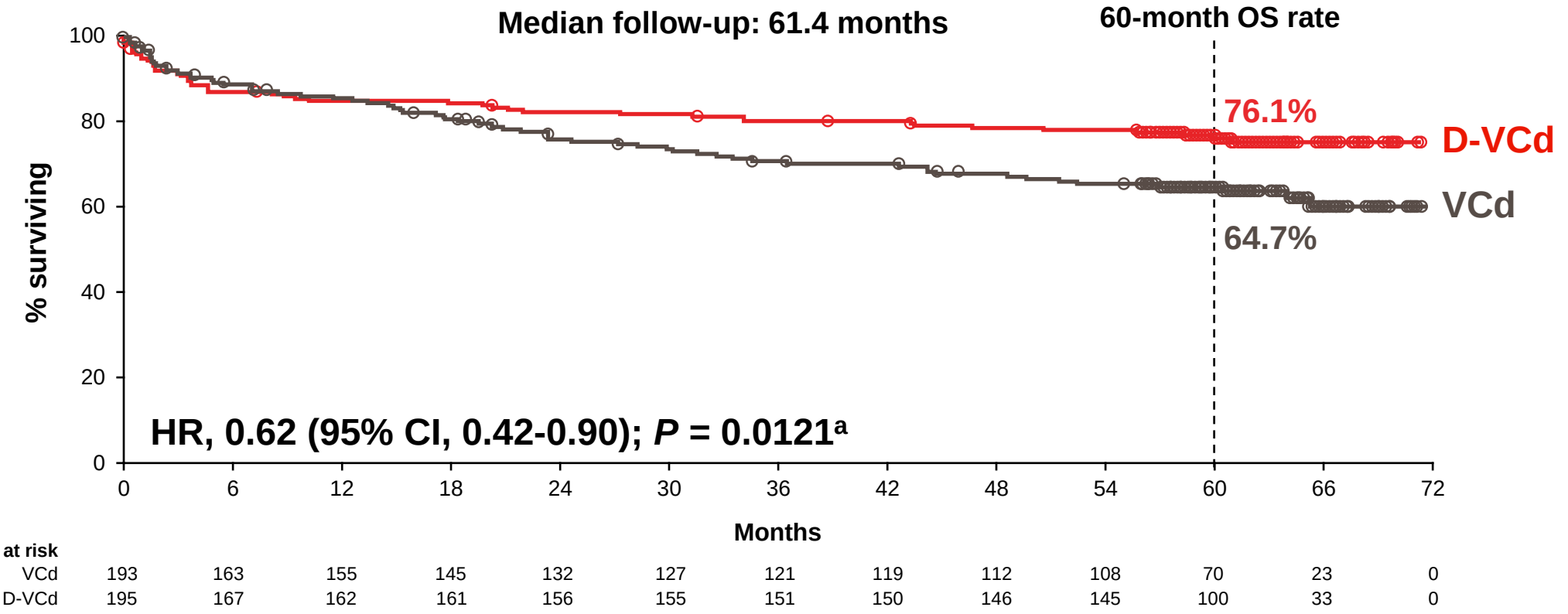
Primary endpoint: Overall HemCR rate[a]

Secondary endpoints: MOD-PFS (end-stage cardiac or renal disease, hematologic progression, or death),[b] OS, organ response rate, time to hematologic response, safety

D-VCd, daratumumab 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA)] plus VCd; eGFR, estimated glomerular filtration rate; SC, subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks. [a]Defined here as normalization of free light-chain (FLC) levels and ratio (FLCr) and negative serum and urine immunofixation, confirmed at a subsequent visit; normalization of uninvolved FLC level and FLCr were not required if involved FLC was lower than the upper limit of normal; [b]A composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines,[1] or death. 1. Comenzo RL, et al. *Leukemia*. 2012;26(11):2317-2325.

Presented by E Kastritis at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

ANDROMEDA: Overall Survival



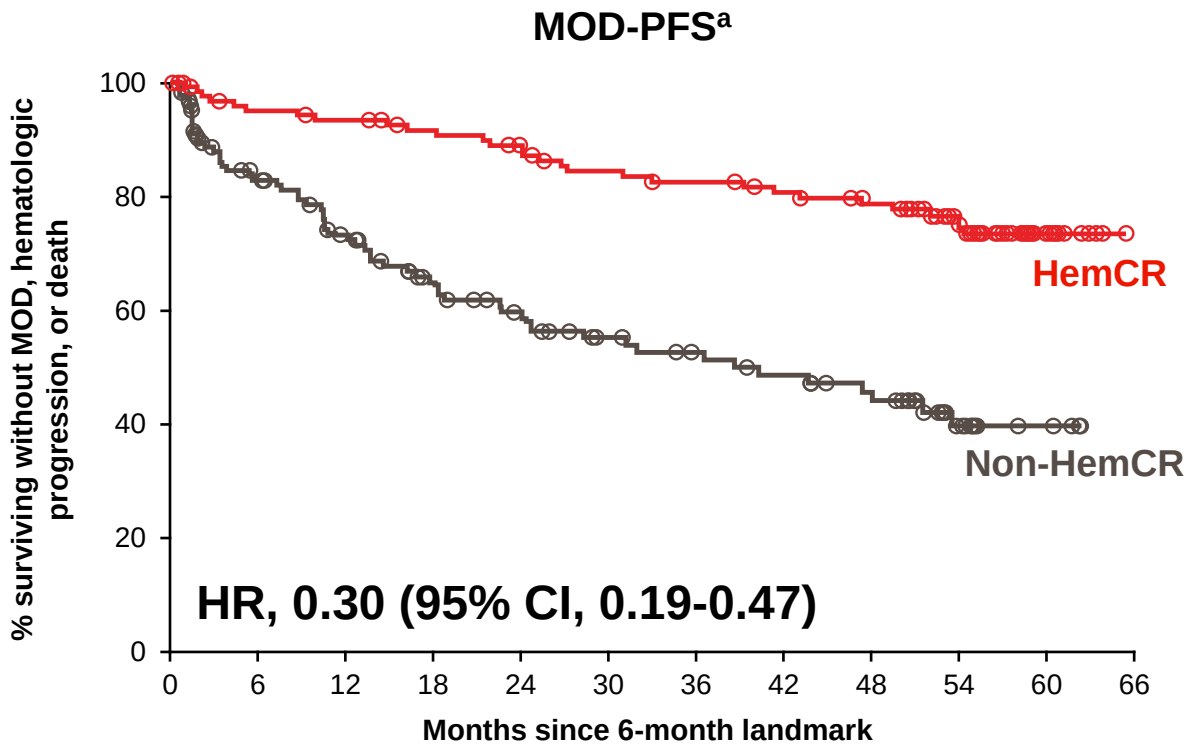
No. at risk													
VCd	193	163	155	145	132	127	121	119	112	108	70	23	0
D-VCd	195	167	162	161	156	155	151	150	146	145	100	33	0

The addition of DARA to VCd significantly improved OS versus VCd despite cross-over in >70% of VCd patients who received DARA as subsequent therapy, highlighting the importance of DARA use in frontline treatment

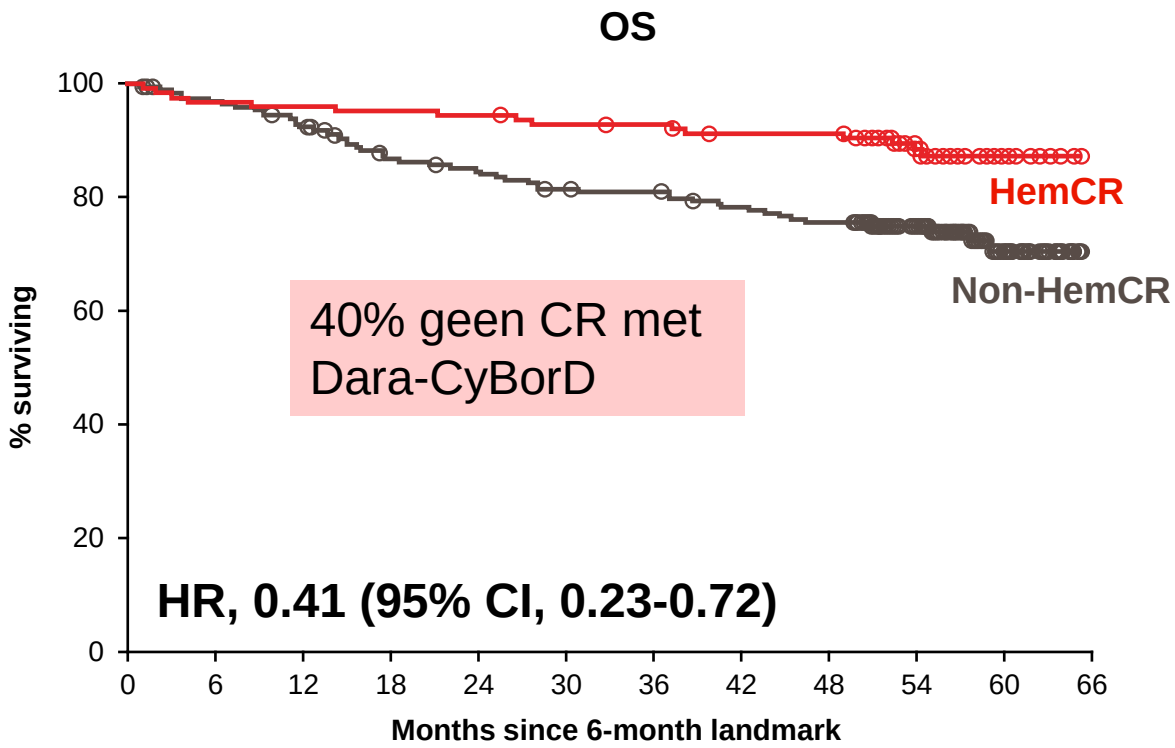
[a]Crossing the prespecified stopping boundary of 0.0163.

Presented by E Kastritis at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

ANDROMEDA: Major Organ Deterioration (MOD)–PFS and Overall Survival by Hematologic Complete Response



No. at risk												
HemCR	125	112	109	104	97	92	88	84	79	48	16	0
Non-HemCR	149	98	81	65	53	44	39	35	29	15	4	0



No. at risk												
HemCR	127	123	122	121	120	117	116	112	112	80	29	0
Non-HemCR	203	194	184	167	162	155	153	146	141	90	27	0

Achieving HemCR was associated with improved MOD-PFS and OS from the 6-month landmark analysis and beyond

[a]MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death. Kaplan–Meier estimates in those patients who achieved HemCR versus those who did not achieve HemCR.

Presented by E Kastritis at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

ANDROMEDA: The Unanswered Questions

- Randomized, open-label phase III trial of Dara-VCd vs VCd alone in patients with newly diagnosed AL amyloidosis

Stratified by cardiac stage (I vs
(yes vs no), CrCl (≥60 mL/min vs <60 mL/min)

1st new unmet need:
No CR – 40%

Adults with AL amyloidosis with ≥1 organ affected; no prior tx for MM or AL amyloidosis; cardiac stage I-IIIa; eGFR ≥20 mL/min (N = 388)

Screening at Day 28

Dara SC 1800 mg QW cycles 1-2; Q2W cycles 3-6 + **VCd*** QW for 6 cycles (n = 195)

Dara SC 1800 mg Q4W until MOD-PFS* or max 24 cycles (n = 195)

Observed until MOD-PFS (if Dara SC d/c before MOD-PFS)

VCd* QW for 6 cycles (n = 193)

Observed until MOD-PFS†

*SC bortezomib (1.3 mg/m^2), cyclophosp
(300 mg/m^2 orally), or IV (500 mg max w
and dexamethasone (40 mg orally or IV)
for six 28-day cycles.

The unanswered question:
- Benefit of Dara maintenance in those in a CR

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stage ren
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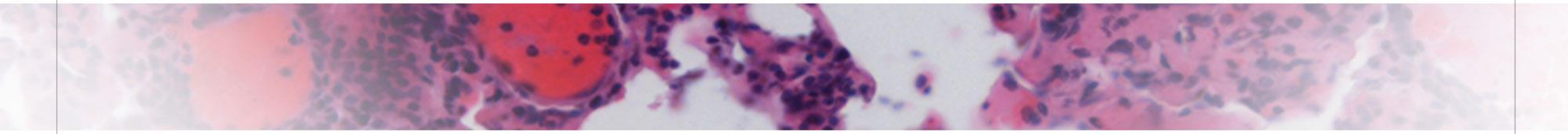
2nd new unmet need
How to treat PD on Dara

1. Wide eligibility criteria
2. Excluded
   - Stage IIIB
   - Advanced renal
   - Sensory or peripheral neuropathy

Slide Courtesy of A. Wechalekar. University College London.

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

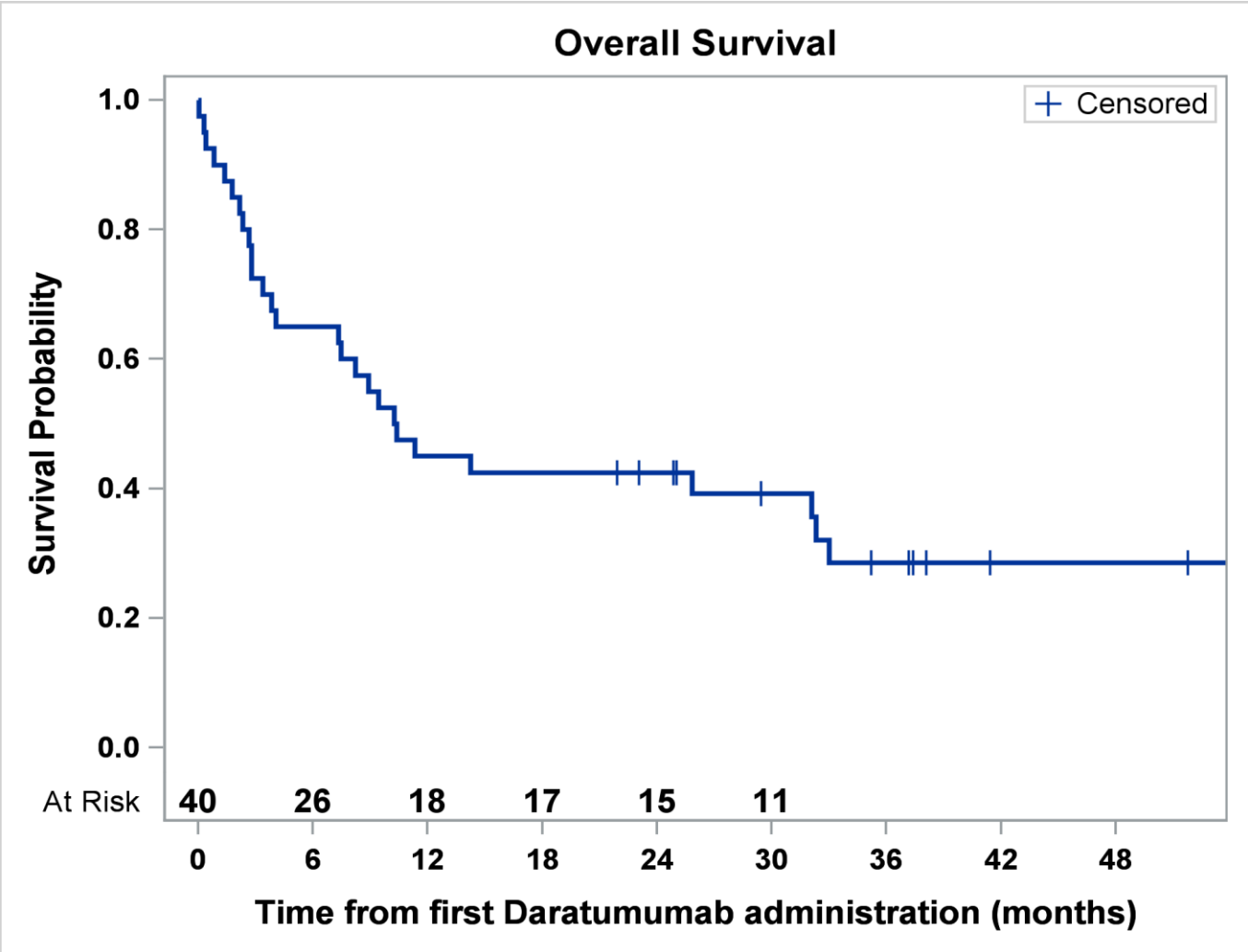


Efficacy and Safety of Daratumumab Monotherapy in Newly Diagnosed Patients with Stage 3B Light-Chain Amyloidosis: A Phase 2 Study by the European Myeloma Network

E. KASTRITIS[1], M. C. MINNEMA[2], M. A. DIMOPOULOS[1], G. MERLINI[3], F. THEODORAKAKOU[1], D.FOTIOU[1], A. HUART[4], K. BELHADJ[5], S. GKOLFINOPOULOS[6], N. ANTONIOU[6], G. PSARROS[6], P. SONNEVELD[7], G. PALLADINI[3]

[1]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece,
[2]Department of Hematology, University Medical Center Utrecht, Utrecht, Netherlands,
[3]Amyloidosis Research and Treatment Center, University of Pavia, Pavia, Italy,
[4]Department of Nephrology and Transplantation, Rangueil University Hospital, Toulouse, France,
[5]Lymphoid Malignancies Unit, Henri Mondor Hospital, Créteil, France,
[6]Health Data Specialists, Dublin, Ireland,
[7]Erasmus MC Cancer Institute, Rotterdam, Netherlands

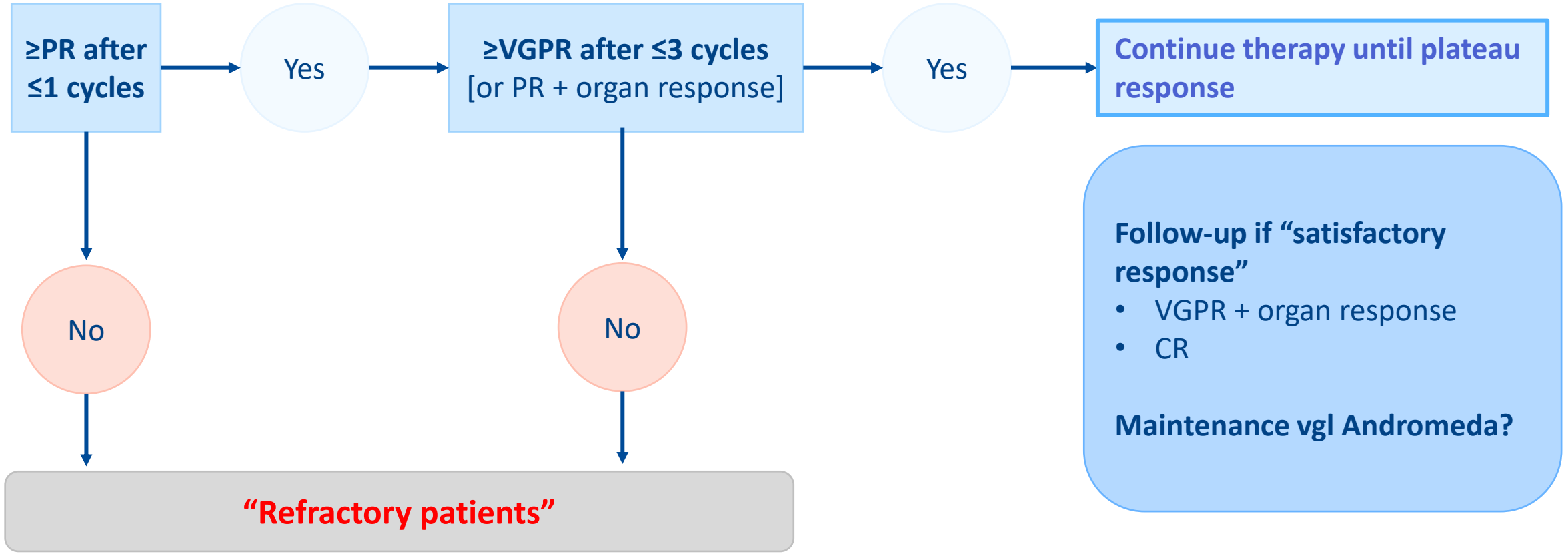
Overall survival IIIb patients



- **No of Dara infusions**: 18 (1-36)
- **Duration of therapy**: 6.6 (<0.1-25.3) mos
- **Follow up**: 10.3 (<0.1-55.6) mos

- **Median OS (months): 10.3 (95% CI: 4.1-32.3)**
- Early mortality rates
  - 15 days following C1D1: 7.5% (3 deaths)
  - 1 month following C1D1: 10.0% (4 deaths)

Follow up tijdens therapie



Follow-up if "satisfactory response"

- VGPR + organ response
- CR

Maintenance vgl Andromeda?

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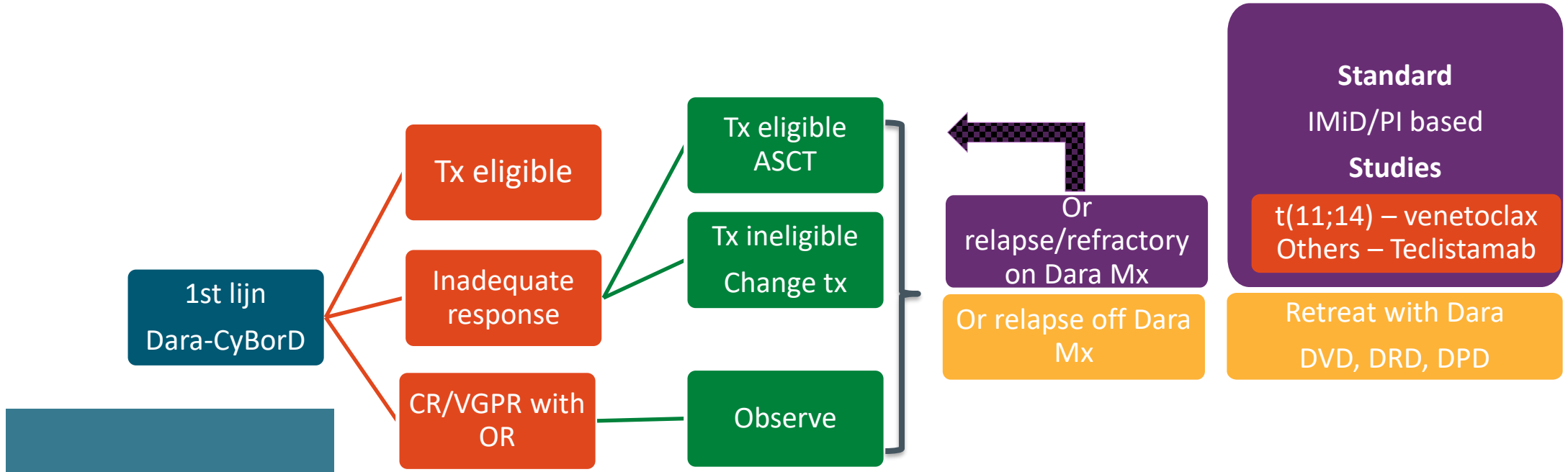
Behandelings strategie



Alternatief:
DRD
(CyBorD)

ASCT 1ste lijn: niet tenzij
Risk/benefit gunstig lijkt :
Jong, “mono” orgaanfalen zoals nier,
IgM amyloidose

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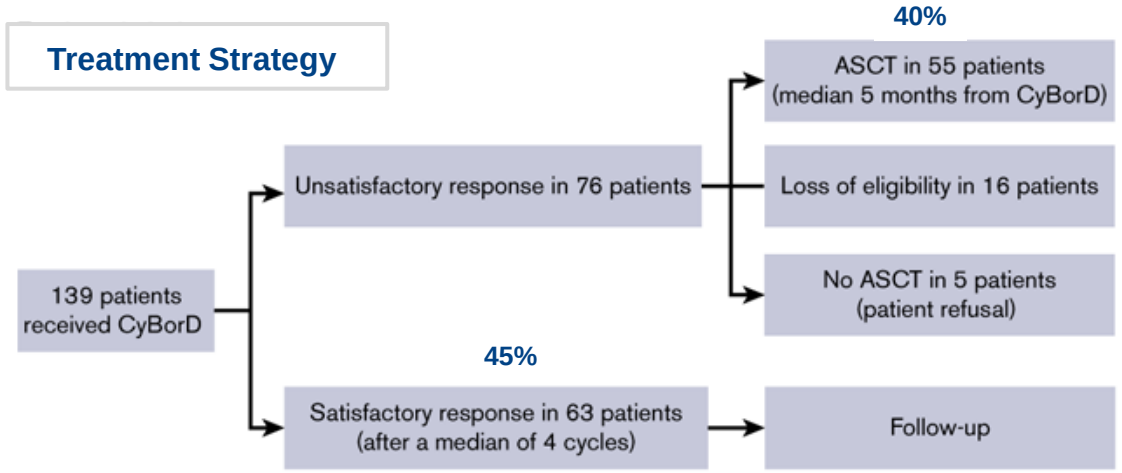
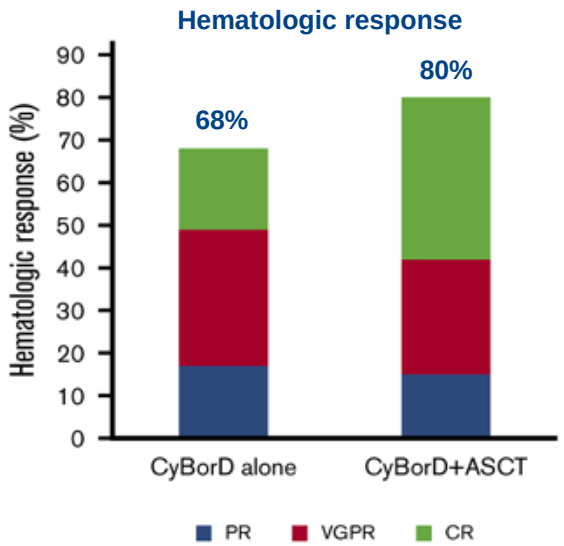
Hematologische respons gedreven therapie; alleen ASCT bij onvoldoende respons op CyBorD



Definitions

Satisfactory response:
PR+OR, VGPR + OR, CR

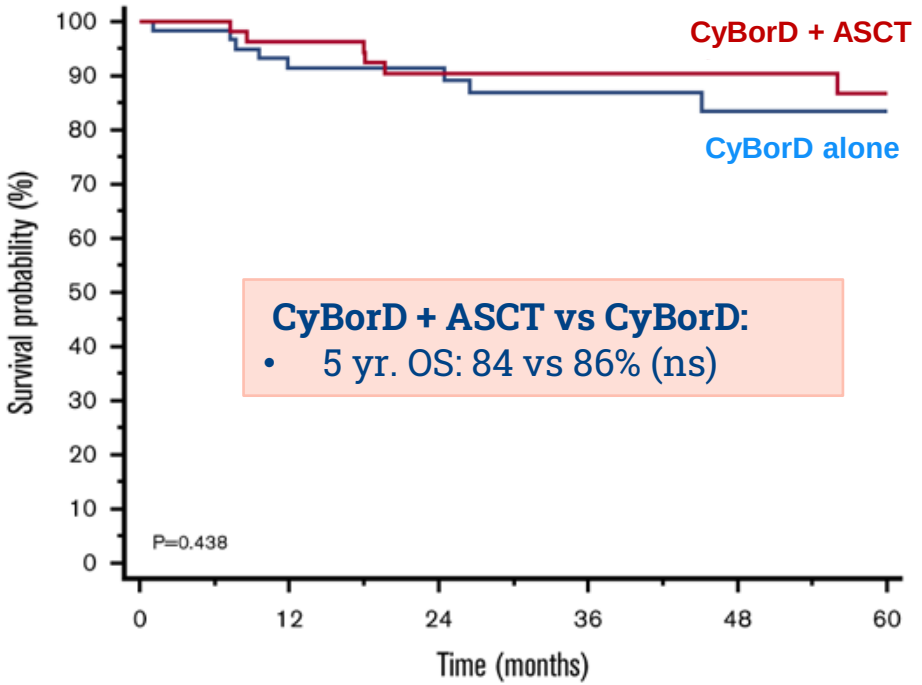
Unsatisfactory response:
NR, PR without OR,VGPR without OR



Treatment related mortality

One patient (cardiac stage IIIa) died during induction with CyBorD. No patients died within 100 days from ASCT.

Overall survival

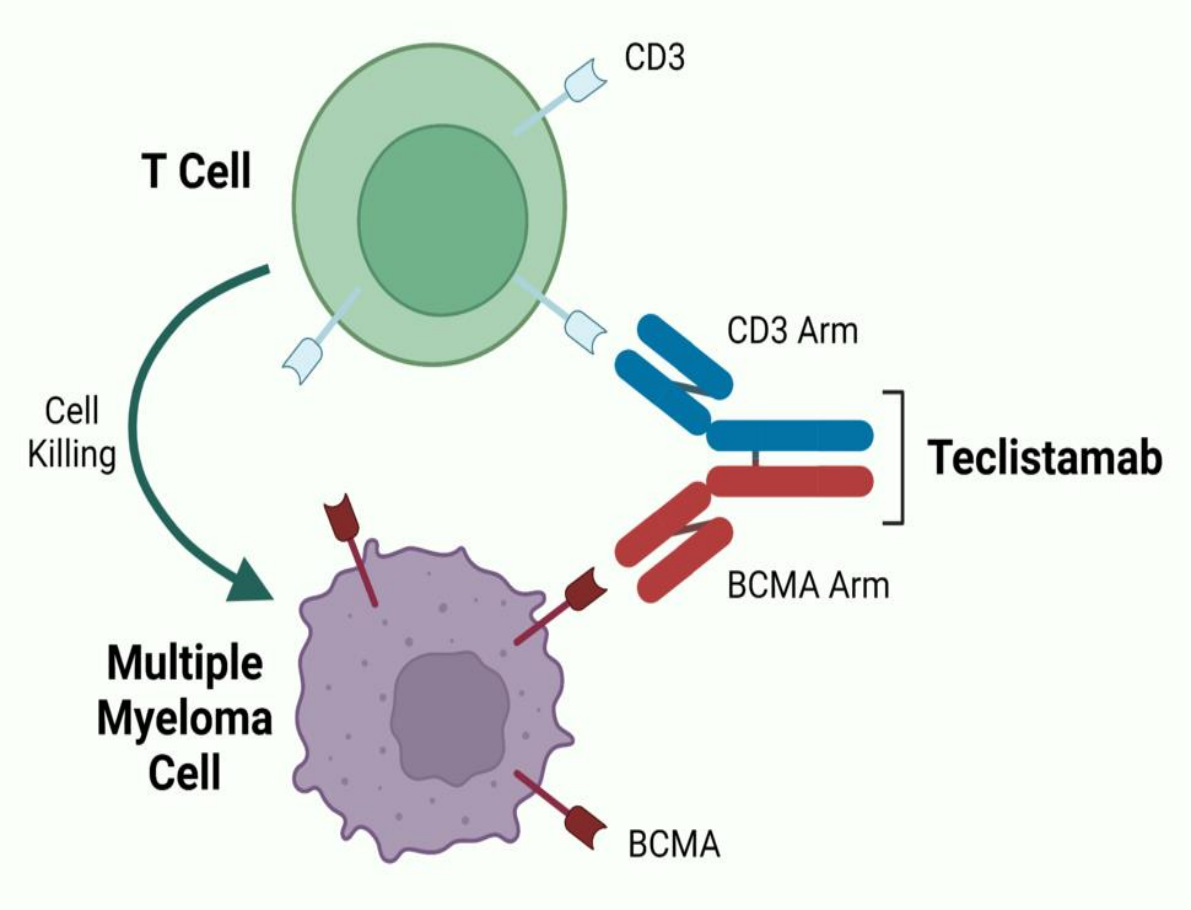


CyBorD + ASCT vs CyBorD:
- 5 yr. OS: 84 vs 86% (ns)

Basset M et al. Blood Adv. 2020

Studies & de toekomst van immuuntherapie

- Monoklonale antistoffen
- Bispecifieke antistoffen
  - Teclistamab
  - Elranatamab
  - Talquetamab
- Trispecifieke Ab
- CAR-T cellen



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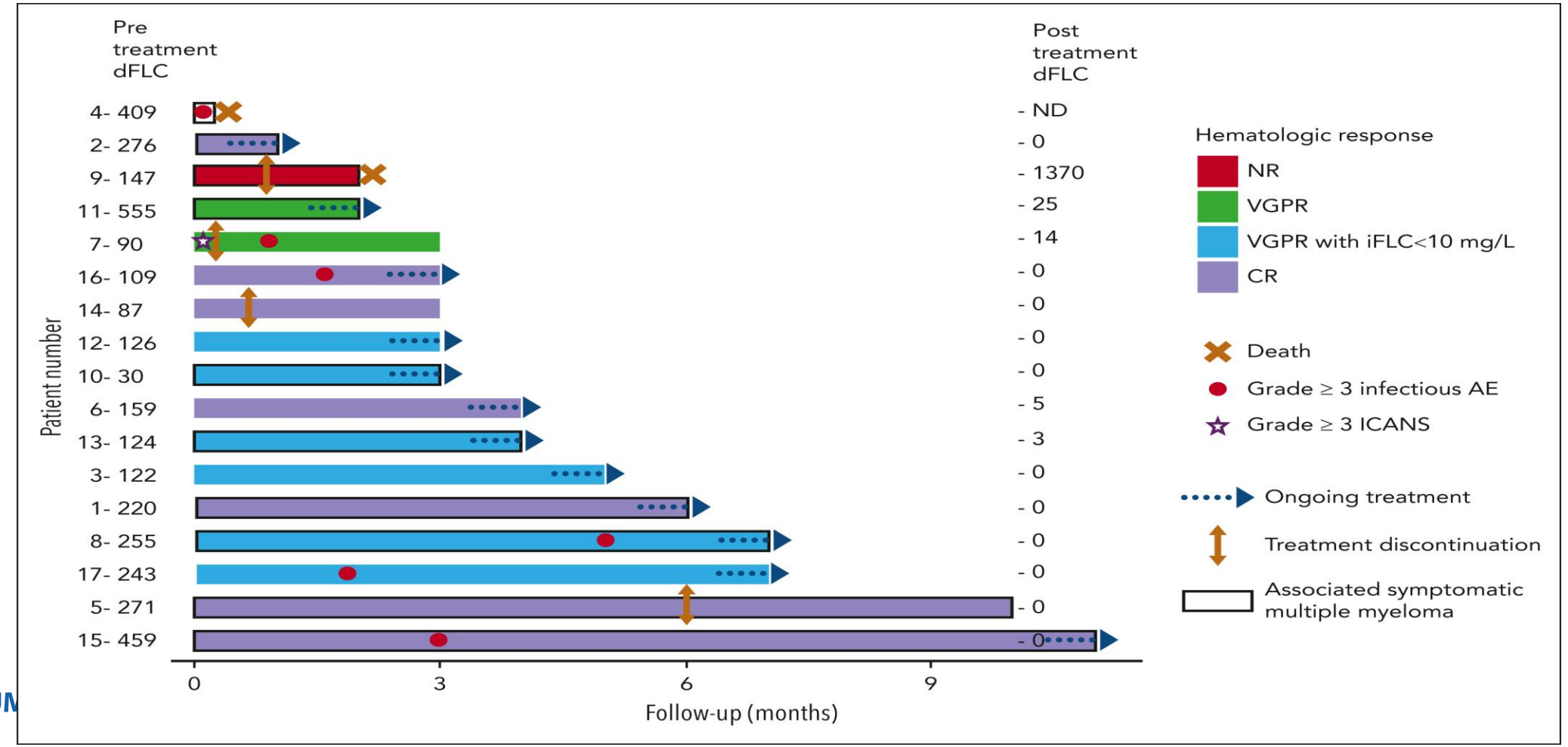
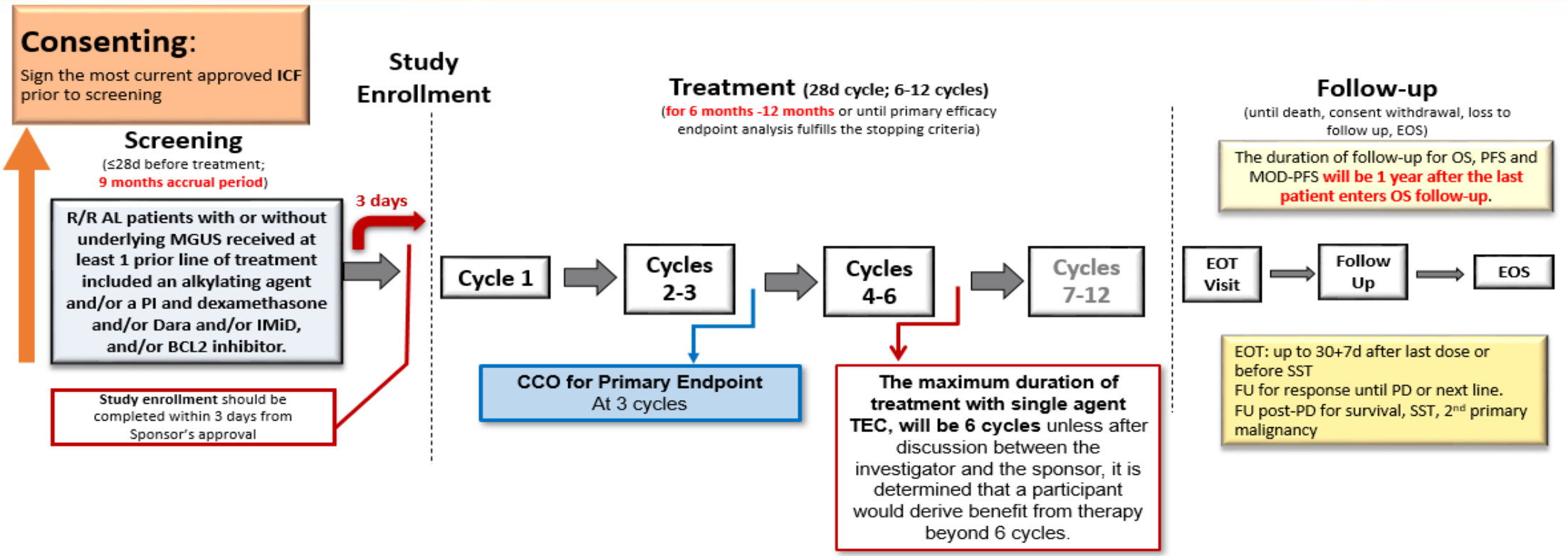
Bispecifieke ab

Teclistamab in relapsed or refractory AL amyloidosis: a multinational retrospective case series

Nathalie Forgeard,[1,2] Dikélélé Elessa,[1,2] Alexander Carpinteiro,[3] Karim Belhadj,[4] Monique Minnema,[5] Murielle Roussel,[6] Antoine Huart,[7] Vincent Javaugue,[8] Laurent Pascal,[9] Bruno Royer,[1] Alexis Talbot,[1,2] Romain Gounot,[4] Ute Hegenbart,[10] Stefan Schonland,[10] Lionel Karlin,[11] Stéphanie Harel,[1] Efstathios Kastritis,[12] Frank Bridoux,[8] Arnaud Jaccard,[6] and Bertrand Arnulf[1,2]

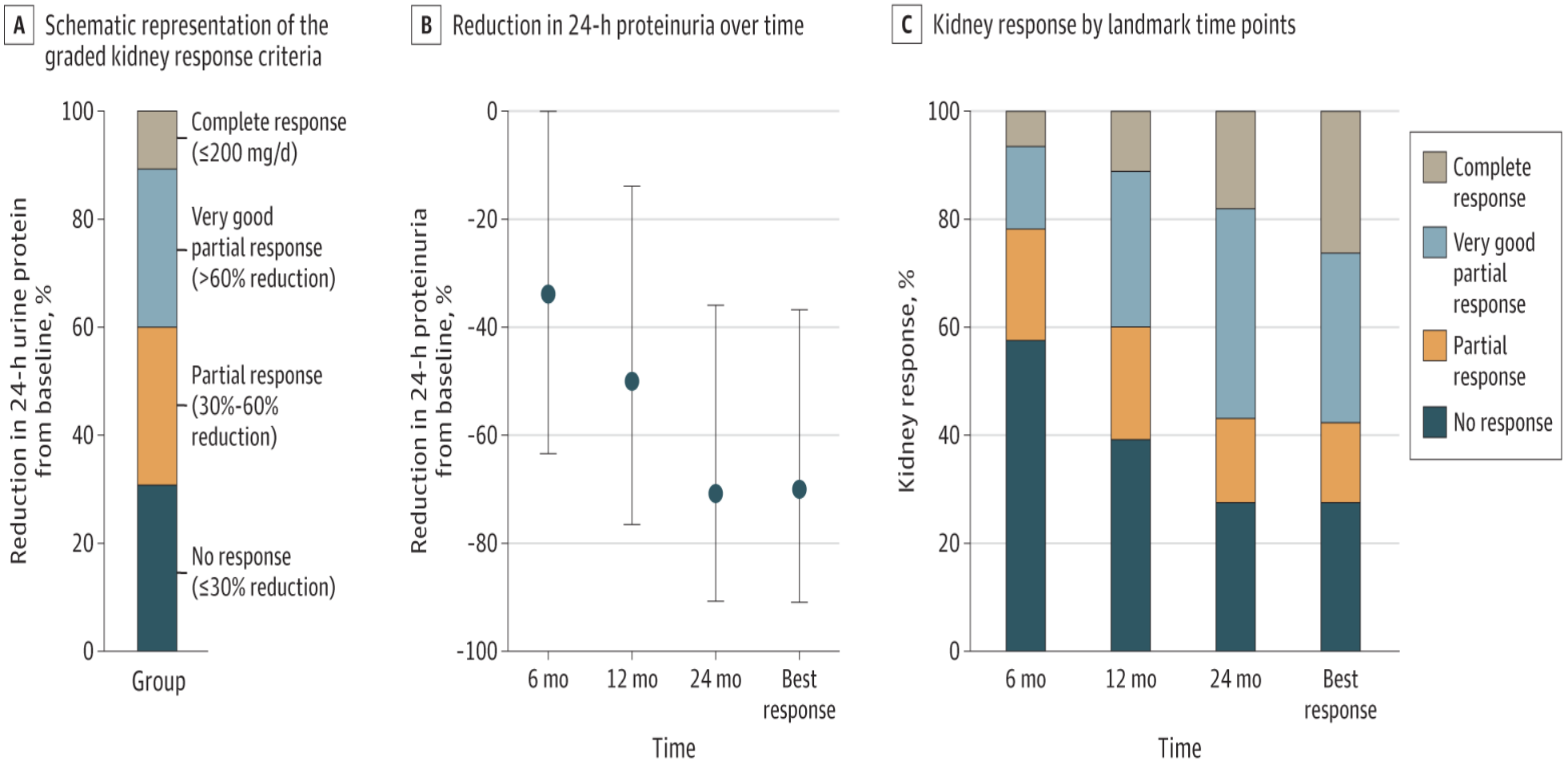


EMN40; Q2 2025 UMC Utrecht



A Phase II Trial of Teclistamab in participants with previously treated AL Amyloidosis, 30 pt
Primary Objective: To assess the hematologic CR rate after 3 cycles of teclistamab

“graded” renale respons



Muchtar et al, JAMA Oncol. 2024;10(10):1362-1369.

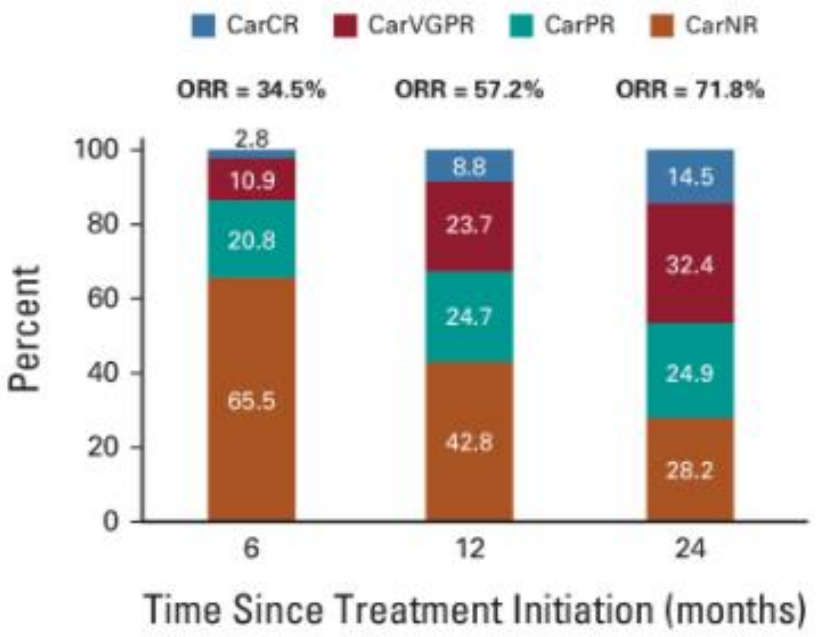
“graded” cardiale respons

TABLE 1. Cardiac Response and Progression Criteria

Category	Definition[a]
Cardiac response criteria	
CarCR	Nadir NT-proBNP ≤ 350 pg/mL (≤ 41.39 pmol/L) or BNP ≤ 80 pg/mL (≤ 9.46 pmol/L)
CarVGPR	> 60% reduction in NT-proBNP/BNP from baseline level not meeting CarCR
CarPR	31%-60% reduction in NT-proBNP from baseline level not meeting CarCR
CarNR	≤ 30% reduction in NT-proBNP from baseline level
Cardiac progression criteria (adopted from Palladini et al[3])	
Any of the following	NT-proBNP/BNP progression: > 30% and > 300 pg/mL (> 35.48 pmol/L) increase or rise in BNP > 30% and > 70 pg/mL (> 8.28 pmol/L) increase from nadir not precipitated by infection, elevated creatinine, or cardiac arrhythmia
	Troponin T/I progression: ≥ 33% increase from nadir
	EF progression: ≥ 10% decrease from best value

Abbreviations: BNP, brain natriuretic peptide; CarCR, cardiac complete response; CarNR, cardiac no response; CarPR, cardiac partial response; CarVGPR, cardiac very good partial response; EF, ejection fraction; NT-proBNP, N-terminal of prohormone brain natriuretic peptide.

[a]Best response by either natriuretic peptide should be considered if both are measured simultaneously.



UMC Utrecht

EuroBloodNet

Muchtar et al; JCO 2022 10-10, American Society of Clinical Oncology

Orgaan responsen verder verbeteren.....

Anselamimab

CARES trials: 2 placebo-controlled, double-blind, randomized, Phase 3 trials assessing CAEL-101 in patients with M**ayo stages IIIA/IIIB**

11-1F4 /CAEL-101 is a chimeric monoclonal IgG1 antibody isotype which binds to a cryptic epitope at the N-terminal of both κ and λ light chain proteins that adopt a non-native structure.

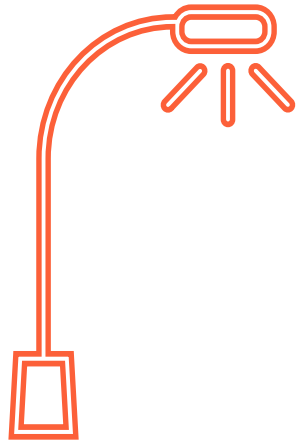
Birtamimab

AFFIRM-AL STUDY

The AFFIRM-AL study is a placebo-controlled, double-blind, randomized, Phase 3 trial evaluating Birtamimab **Mayo Stage IV** patients

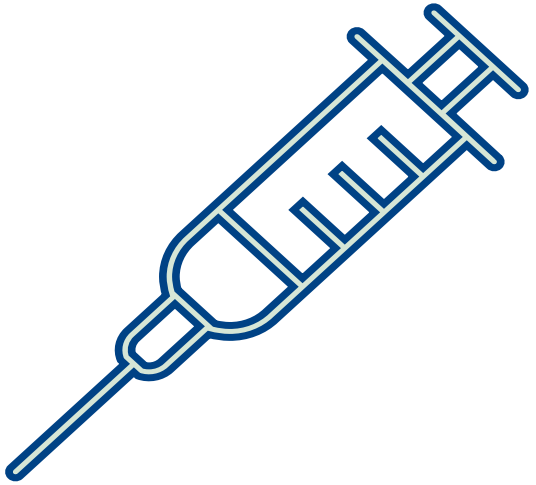
NEOD001/ has been shown to react with a cryptic epitope that is exposed on misfolded kappa and lambda light chains that misfold and form amyloid

Conclusie



Diagnostiek is complex: gebruik de expertise centra!

NKR is uniek en datasets klaar voor analyse



Immuuntherapie is toekomst (met nog een beetje ASCT)

Anti Amyloid therapie data nog even wachten…..

UMC Utrecht

EuroBloodNet

Dank voor uw aandacht!

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