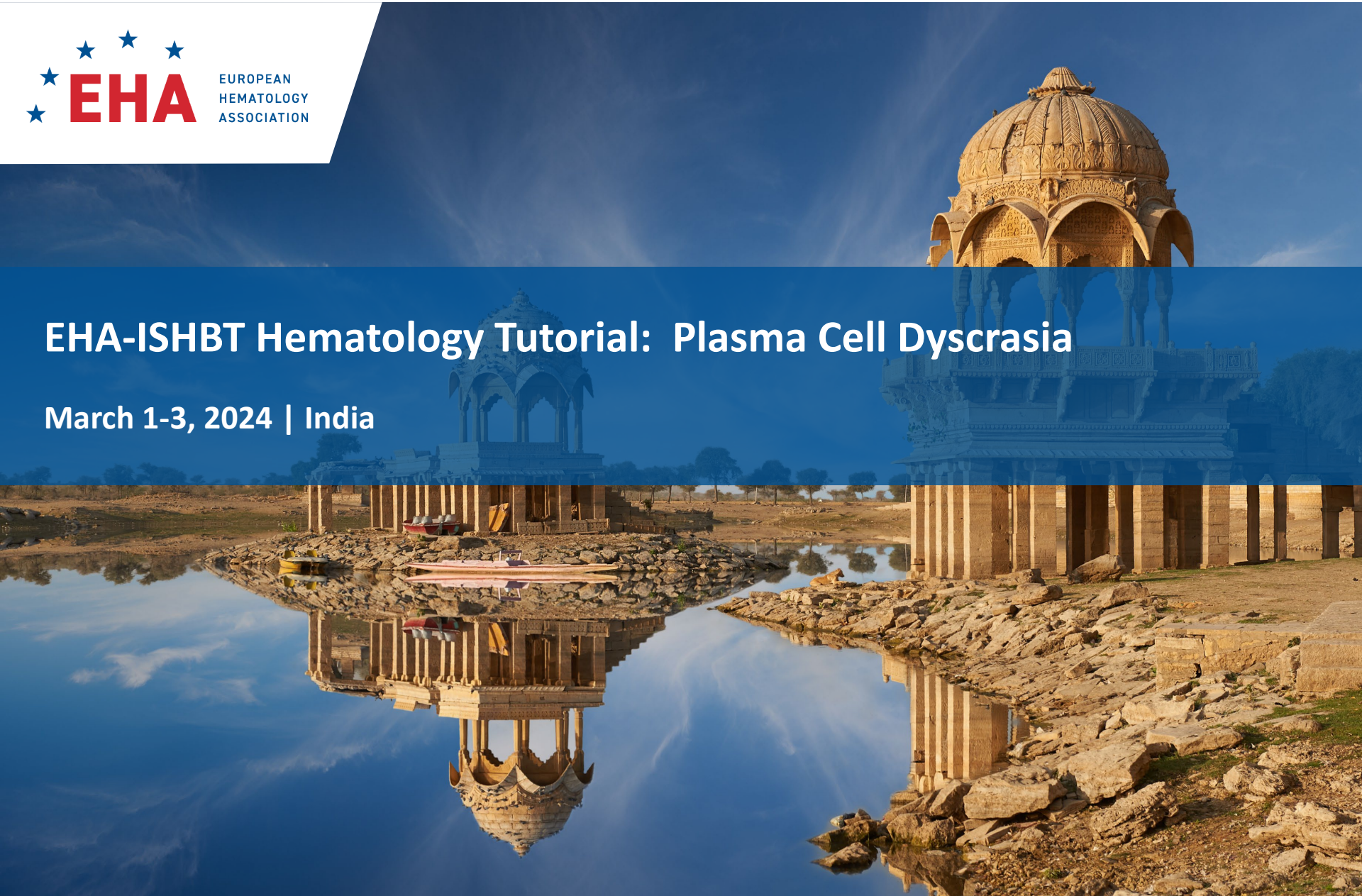


EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial: Plasma Cell Dyscrasia

March 1-3, 2024 | India

Plasma Cell Dyscrasia

Prof. Dr. Meral Beksaç
İstinye University
Ankara Liv Hospital

Learning objectives

- The spectrum of monoclonal gamopathies
- What is new in the staging of Multiple Myeloma
- Myeloma treatment at diagnosis and relapse: an uptodate overview
- AL Amyloidosis: differential diagnosis
- İmportance of staging
- Response assessment in AL amyloidosis
- Contemprorary treatment of AL Amyloidosis

disclosures

- Speakers bureau: Amgen, Janssen, Sanofi, BMS, Pfizer
- Advisory Board: Amgen, GSK, Janssen, Takeda, Menarini, Pfizer

Monoclonal gamopathies

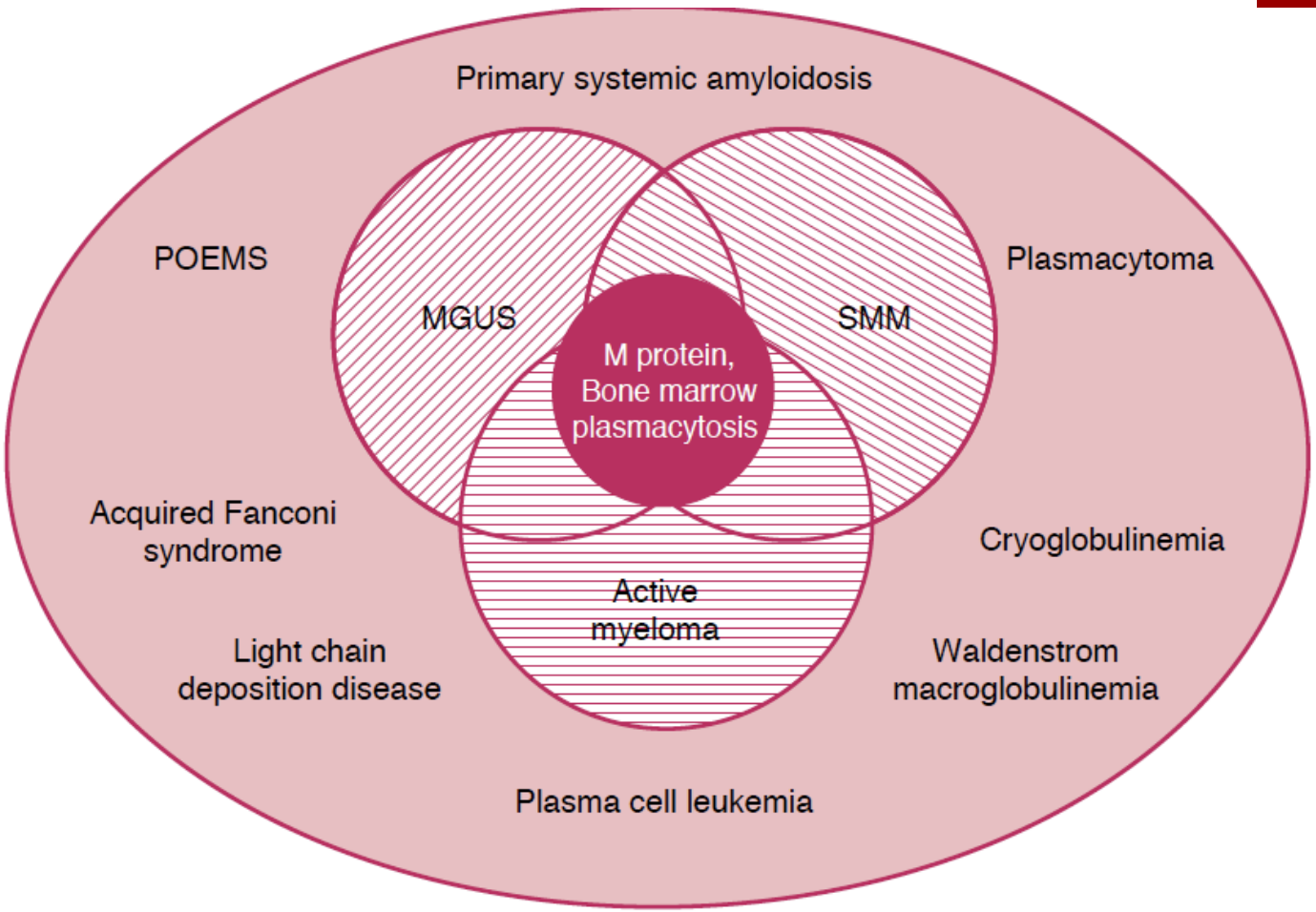
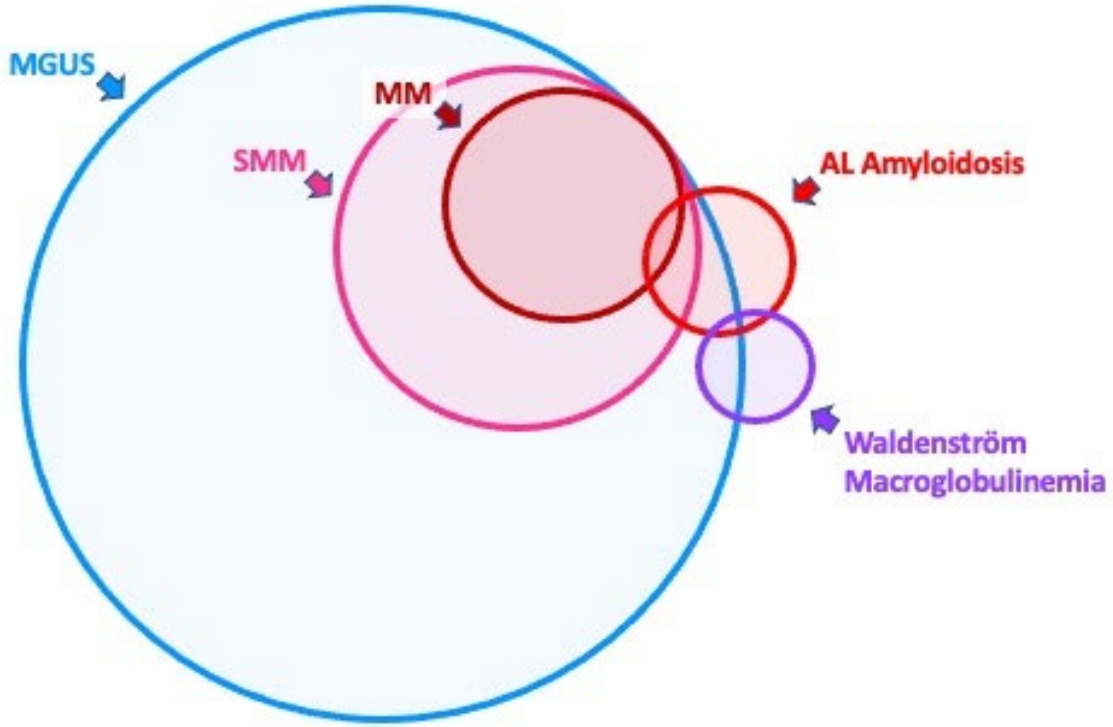


Figure 3. Differential diagnosis for multiple myeloma.

MONOCLONAL GAMMOPATHY OF SIGNIFICANCE

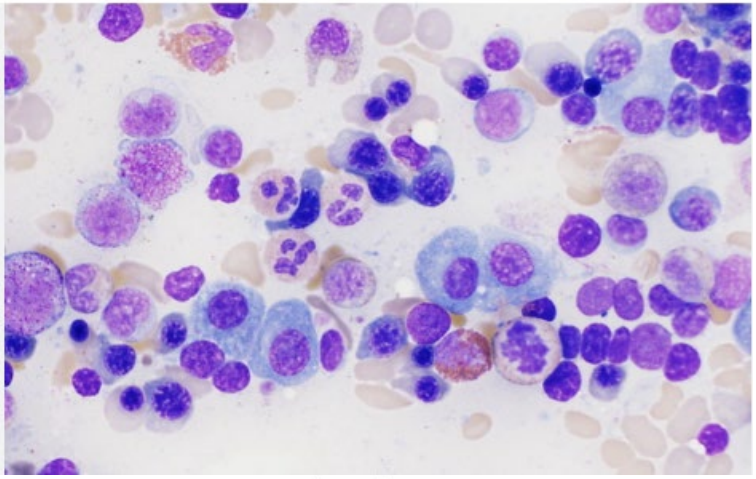


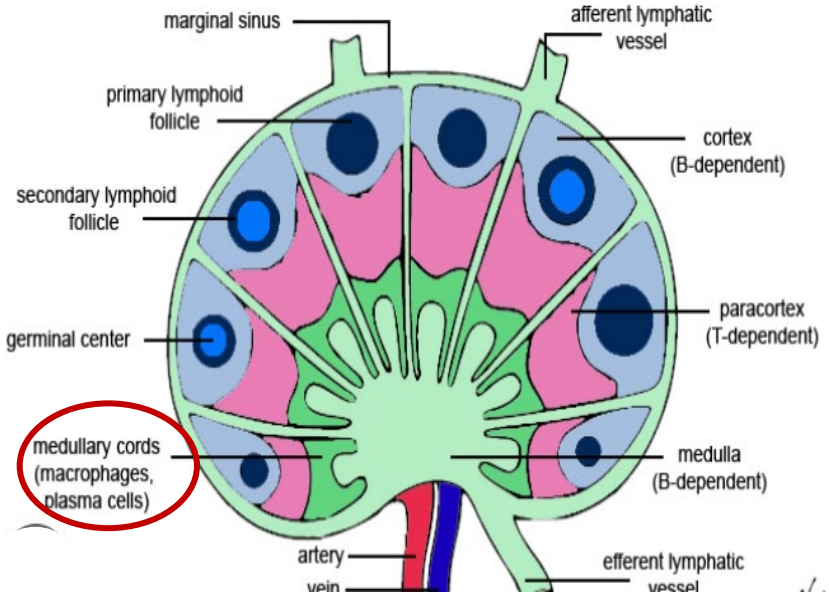
Incidence:

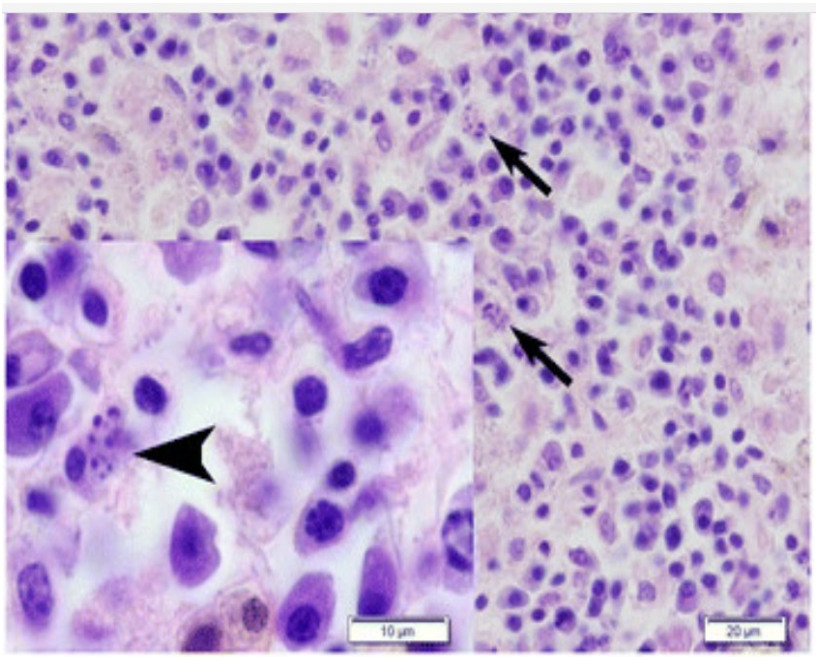
MGUS: 120 / 100 000 (above 50 years) [4]
MM: 4-7 / 100 000 [5]
AL Amyloidosis: 1-1.4 / 100 000 [6]
Waldenström Macroglobulinemia: 3-4 / 1 000 000 [7]
SMM : 0.9 / 100 000 [8]

Beksac et al ASCO 2022

Multiple Myeloma

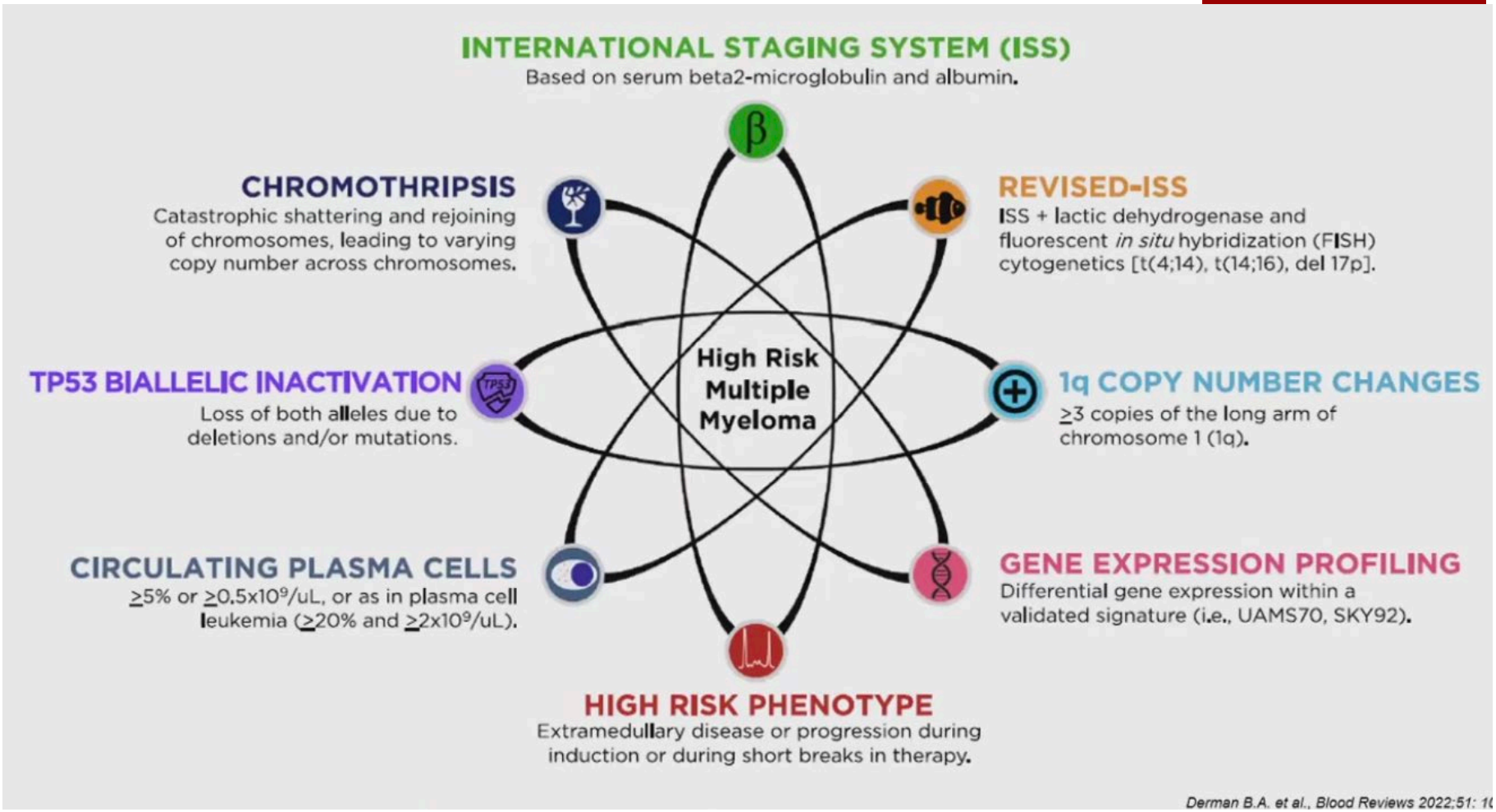






Histological section of a lymph node from female D. The medulla contained numerous plasma cells and

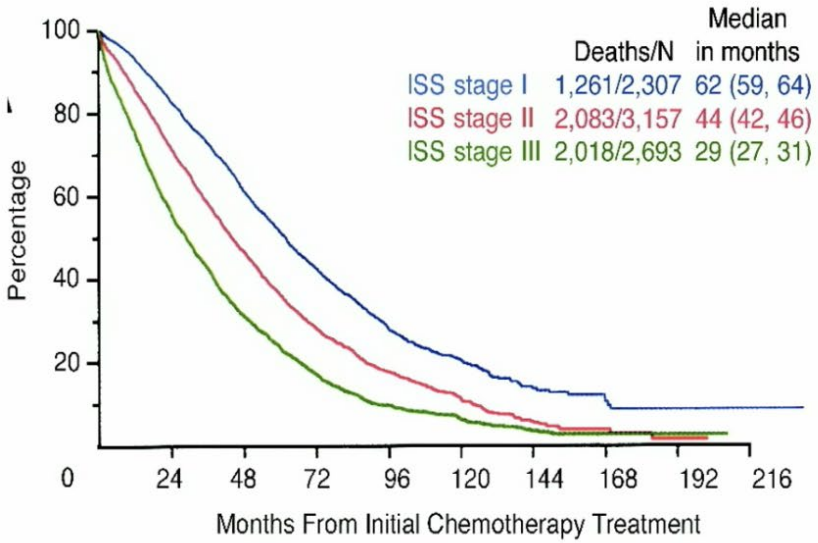
Not all myelomas are the same



Derman B.A. et al., Blood Reviews 2022;51: 1

International Staging System

Stage	Criteria
I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Not stage I or III*
III	Serum β_2-microglobulin ≥ 5.5 mg/L



Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

Cytogenetic risk in Myeloma

t(4;14)
t(14;16)

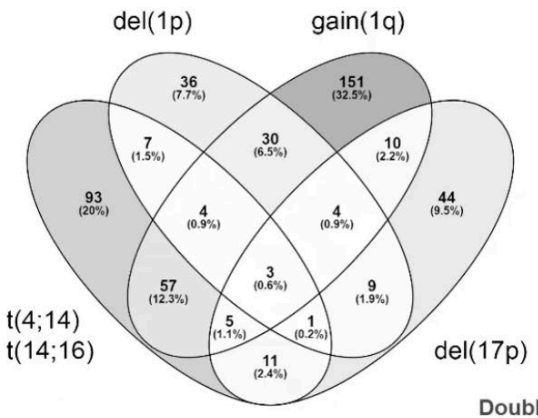
del(17p)

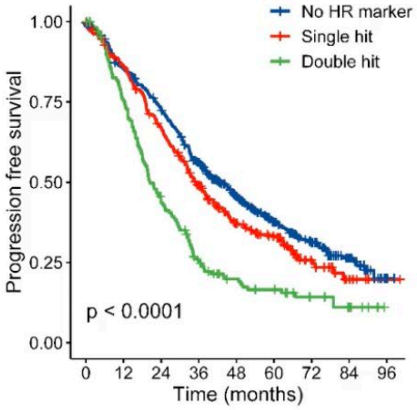
IMWG
(~15%)

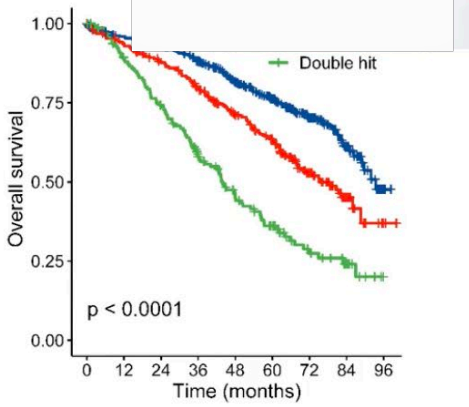
gain(1q)

del(1p)

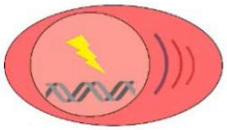
Validated risk
markers
(~15%)

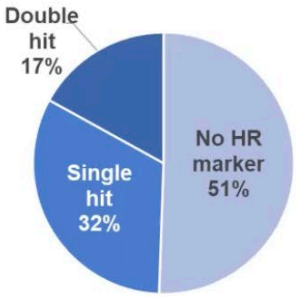






2 or more risk markers
= Double hit
= Genomic instability





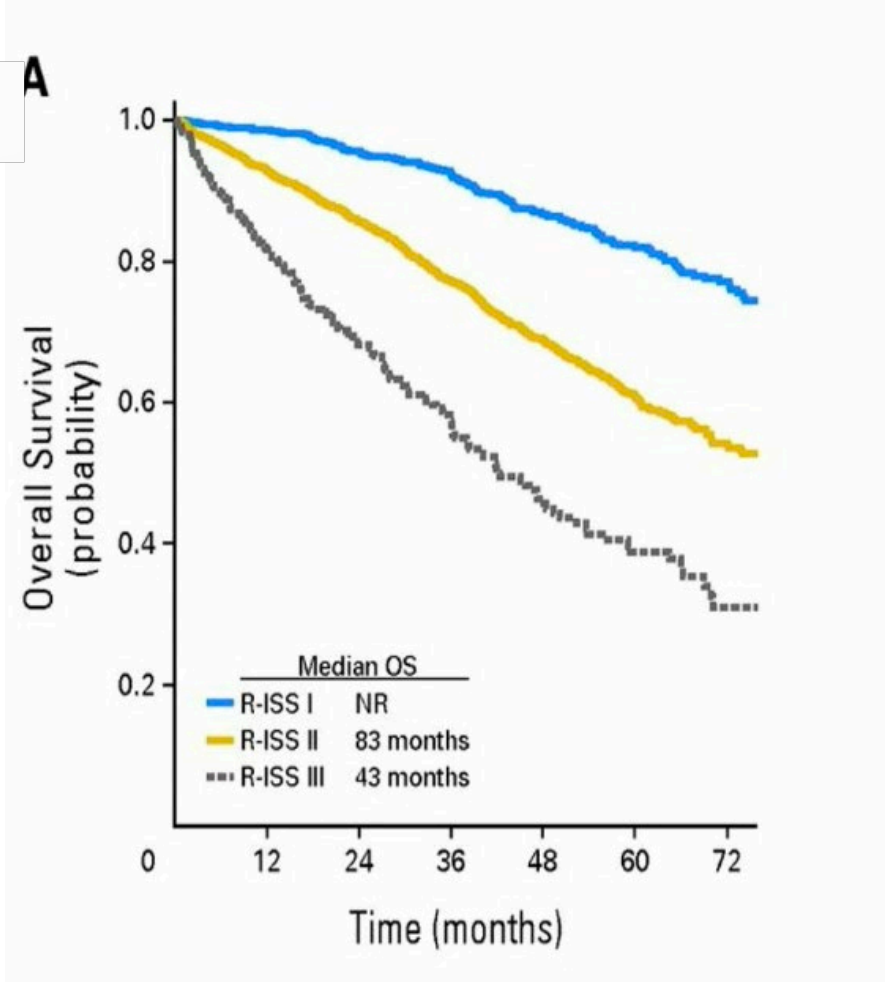
= Ultra high-risk MM (~15-20%)

Validated in multiple trials

Leukemia 2017;34:3091-96

Revised ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH



Palumbo JCO,2015:61;2267

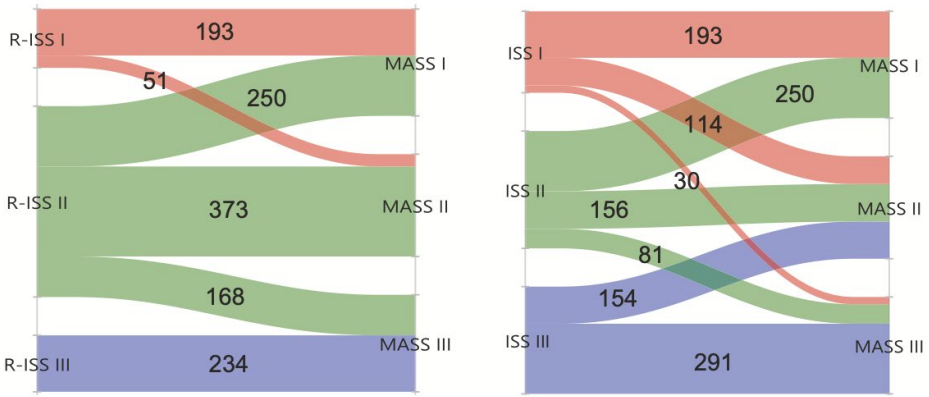
A simple additive staging system for newly diagnosed multiple myeloma

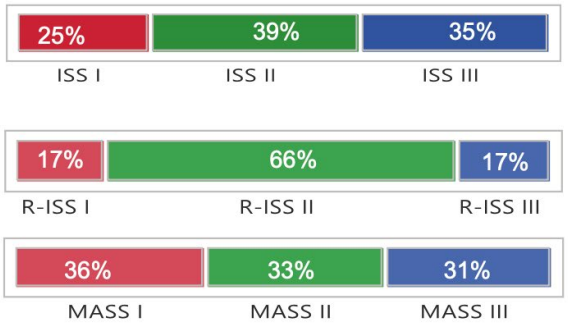
Nadine H. Abdallah[1], Moritz Binder[1], S. Vincent Rajkumar[1], Patricia T. Greipp[2], Prashant Kapoor[1], Angela Dispenzieri[1], Morie A. Gertz[1], Linda B. Baughn[2], Martha Q. Lacy[1], Suzanne R. Hayman[1], Francis K. Buadi[1], David Dingli[1], Ronald S. Go[1], Yi L. Hwa[1], Amie L. Fonder[1], Miriam A. Hobbs[1], Yi Lin[1], Nelson Leung[1,3], Taxiarchis Kourelis[1], Rahma Warsame[1], Mustaqeem A. Siddiqui[1], Robert A. Kyle[1], P. Leif Bergsagel[4], Rafael Fonseca[4], Rhett P. Ketterling[1] and Shaji K. Kumar[1]✉

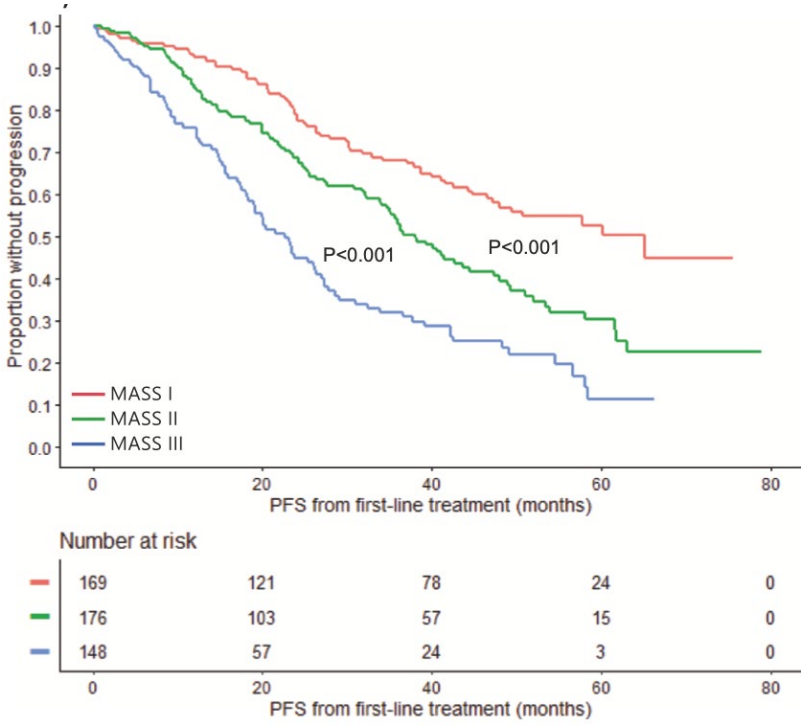
Risk	Score	Total score	stage	PFS (month)	OS (year)
high risk IGH translocation (t(4;14), t(14;16))	+1	0	MASS I	63,1	11,0
1q gain/amplification	+1				
chromosome 17 anomaly	+1	1	MASS II	44,0	7,0
ISS stage III	+1				
high LDH	+1	2+	MASS III	28,6	4,5

Blood Cancer Journal (2022)12:21

Mayo additive staging system(MASS)







Abdallah NH, BCJ 2021

Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project

Mattia D'Agostino, MD[1]; David A. Cairns, PhD[2]; Juan José Lahuerta, MD, PhD[3]; Ruth Wester, MD[4]; Uta Bertsch, MD[5]; Anders Waage, MD, PhD[6]; Elena Zamagni, MD, PhD[7,8]; María-Victoria Mateos, MD, PhD[9]; Daniele Dall'Olio, MSc[10]; Niels W.C.J. van de Donk, MD, PhD[11]; Graham Jackson, MD[12]; Serena Rocchi, MD[7,8]; Hans Salwender, MD[13]; Joan Bladé Creixenti, MD, PhD[14]; Bronno van der Holt, PhD[15]; Gastone Castellani, PhD[8]; Francesca Bonello, MD[1]; Andrea Capra, MScEng[1]; Elias K. Mai, MD[5]; Jan Dürig, MD[16]; Francesca Gay, MD, PhD[1]; Sonja Zweegman, MD, PhD[11]; Michele Cavo, MD[7,8]; Martin F. Kaiser, MD[17]; Hartmut Goldschmidt, MD[5]; Jesús María Hernández Rivas, MD, PhD[18]; Alessandra Larocca, MD, PhD[1]; Gordon Cook, MD, PhD[2]; Jesús F. San-Miguel, MD, PhD[19]; Mario Boccadoro, MD[1]; and Pieter Sonneveld, MD, PhD[4]

Risk Feature	OS HR (95% CI)	PFS HR (95% CI)	Score Value[a]
ISS II	1.75 (1.49 to 2.05)	1.43 (1.28 to 1.61)	1
ISS III	2.53 (2.13 to 3.01)	1.76 (1.54 to 2.01)	1.5
del(17p)	1.82 (1.53 to 2.17)	1.43 (1.23 to 1.65)	1
LDH high	1.60 (1.36 to 1.88)	1.37 (1.20 to 1.57)	1
t(4;14)	1.53 (1.29 to 1.81)	1.40 (1.21 to 1.62)	1
1q+	1.47 (1.29 to 1.68)	1.33 (1.20 to 1.48)	0.5

Group	No. (%)	Total Additive Score
Low (I)	428 (19)	0
Low-intermediate (II)	686 (31)	0.5-1
Intermediate-high (III)	917 (41)	1.5-2.5
High (IV)	195 (9)	3-5

JCO, 2022

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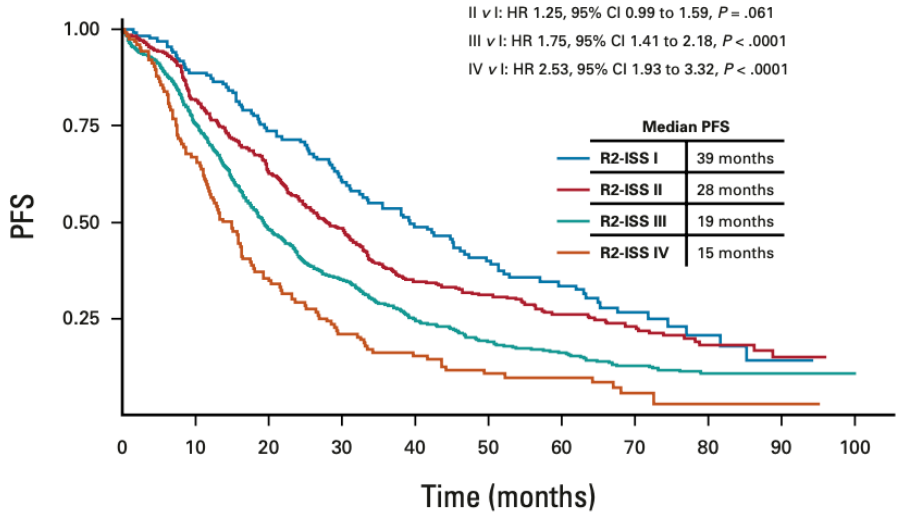
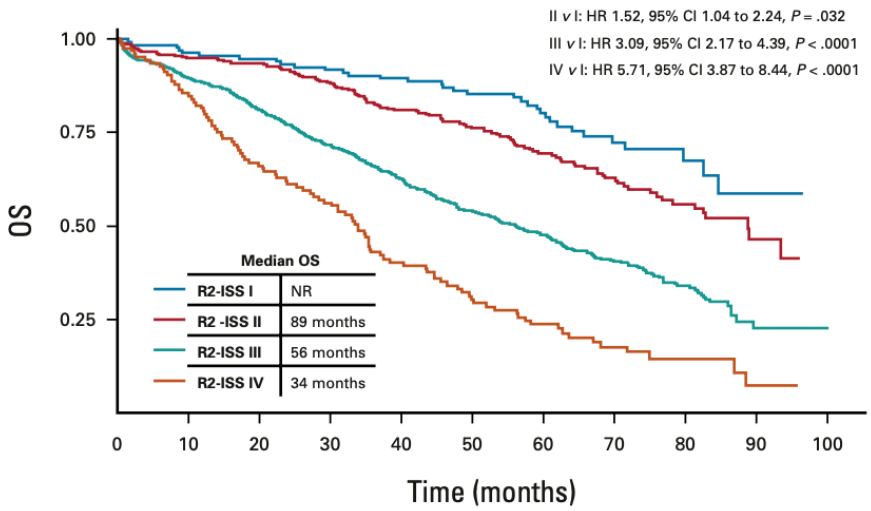


No. at risk (censored):

I	135 (0)	119 (1)	98 (2)	81 (2)	62 (5)	47 (9)	32 (17)	18 (25)	8 (32)	1 (37)	0 (38)
II	322 (0)	257 (8)	197 (9)	148 (13)	103 (16)	81 (28)	59 (38)	38 (53)	21 (63)	6 (76)	0 (82)
III	627 (1)	454 (25)	289 (26)	209 (27)	143 (31)	100 (44)	71 (58)	40 (76)	17 (94)	6 (105)	1 (110)
IV	130 (0)	83 (6)	44 (6)	26 (6)	18 (7)	11 (9)	9 (10)	3 (13)	1 (14)	1 (14)	0 (15)



No. at risk (censored):

I	135 (0)	129 (1)	126 (2)	122 (2)	113 (8)	94 (22)	75 (36)	44 (61)	21 (82)	6 (95)	0 (101)
II	322 (0)	297 (9)	290 (12)	266 (19)	233 (31)	181 (70)	136 (100)	92 (133)	50 (167)	12 (200)	0 (211)
III	627 (0)	540 (23)	485 (28)	424 (32)	351 (53)	271 (86)	205 (121)	139 (160)	70 (214)	12 (258)	1 (269)
IV	130 (0)	106 (6)	80 (8)	68 (8)	47 (10)	32 (14)	22 (17)	13 (21)	8 (24)	2 (28)	0 (30)

JCO, 2022

BOX 1: THE HIGH-RISK MULTIPLE MYELOMA DISEASE SEGMENT

The challenges of HR disease

- HR disease is seen in up to 30% of NDMM.
- The proportion of patients with HR disease increases with each successive relapse.
- HR disease is a significant cause of mortality in multiple myeloma.
- Current therapy has not significantly improved the outcome of HR.

The biology of HR disease

- HRMM is an acquired biological trait that is characterized by a phenotype of:
  - increased proliferation rate
  - resistance to apoptosis
  - focal growth
  - bone marrow–independent growth
  - more than one type of biology
  - intraclonal heterogeneity
- HR subclones may be selected for by treatment.
- Treatment needs to address intraclonal heterogeneity.

Features of HR disease

- Clinical features
  - extra-medullary disease
  - large focal lesions
  - plasma cell leukemia
  - primary refractoriness to treatment
- Laboratory and genetic features
  - R-ISS
  - cytogenetic features
    - t(4;14)
    - t(14;16)
    - t(14;20)
    - gain(1q)
    - deletion and mutation of TP53
  - HR gene expression profiles
- Functional features
  - Initial response to therapy with relapse within 12–18 months.
- Novel features
  - Microenvironment features identified by single-cell analysis and advanced imaging.

Induction Treatment for Newly Diagnosed Multiple Myeloma

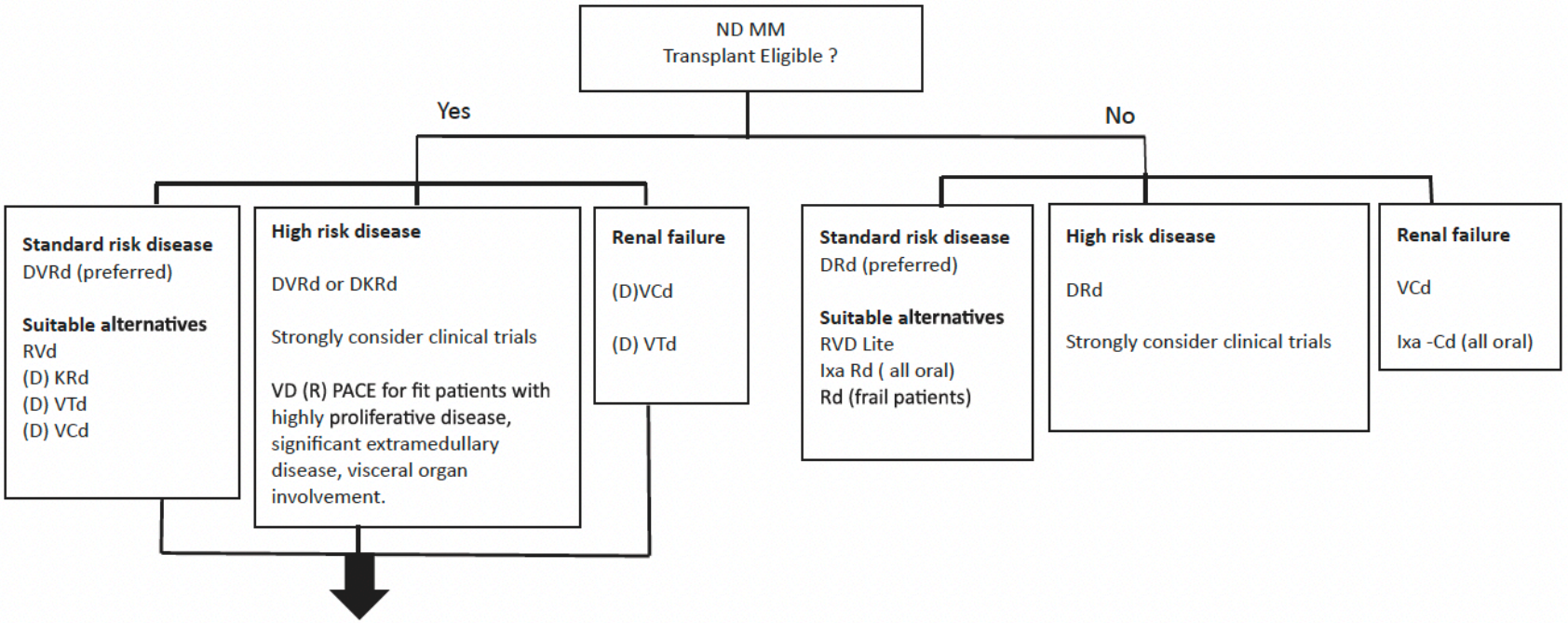
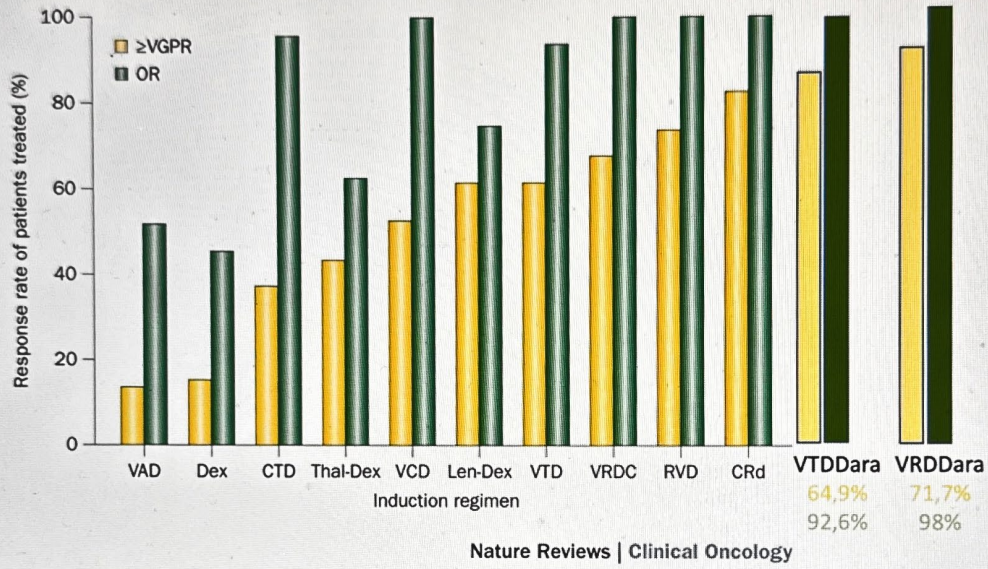


Fig.1. Currentinductionapproachesfornewlydiagnosedmultiplemyeloma.

Devasia et al Hem Oncol Clin North Am 2024

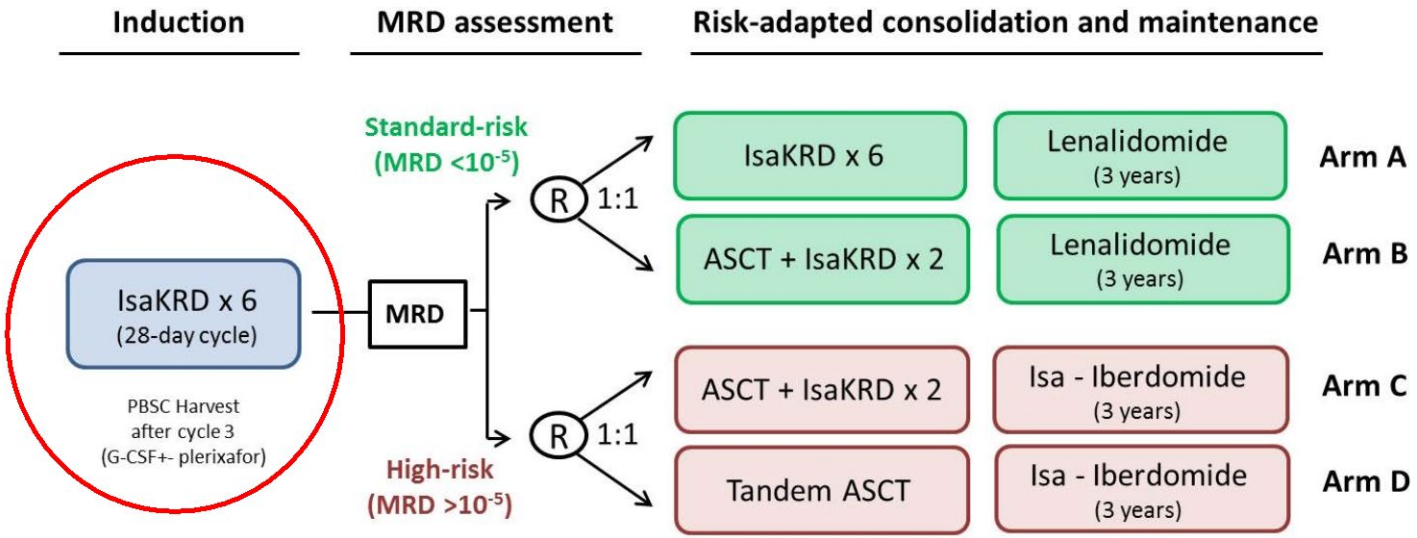
Treatment response with induction regimens in MM



Modified with permission from Springer Science+Business Media © Kumar, S. *Med. Oncol.* **27** (Suppl. 1), S14–S24 (2010)

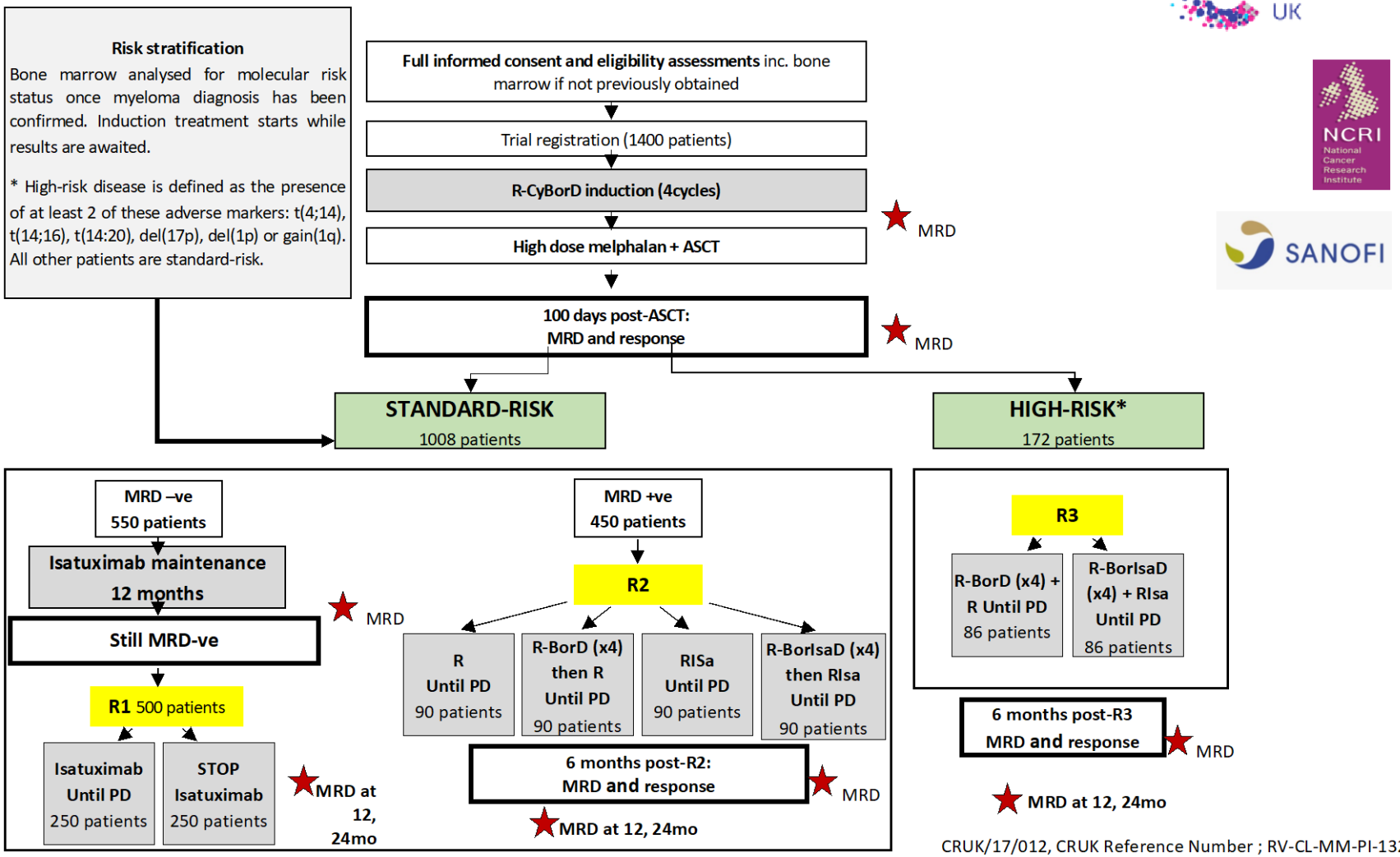
Mailankody, S. *et al.* (2015) Minimal residual disease in multiple myeloma: bringing the bench to the bedside
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2014.239

PIs : A Perrot, C Touzeau



338 / 700 patients recruited !

Myeloma XV (RADAR) study design



CRUK/17/012, CRUK Reference Number ; RV-CL-MM-PI-13264.

TREATMENT OF RELAPSE/REFRACTORY MYELOMA

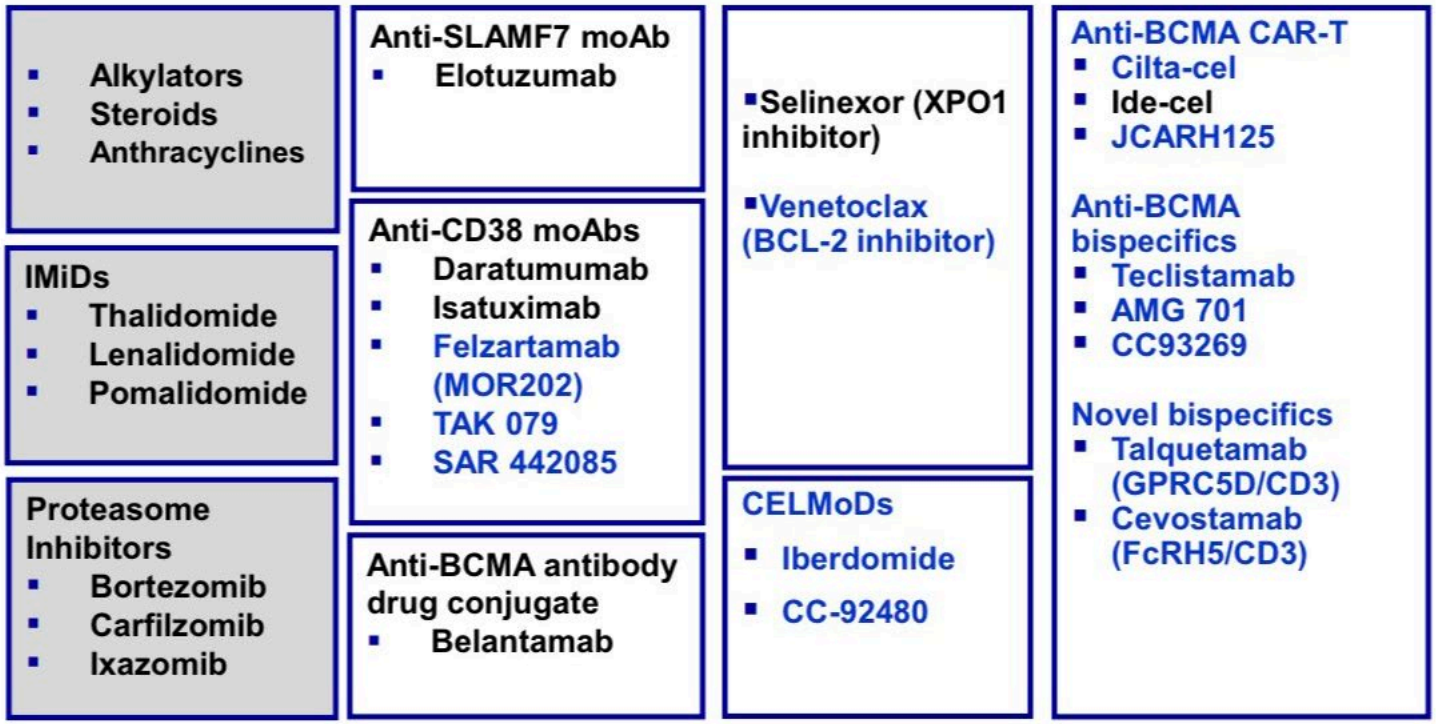
first relapse

After VRd	R-sensitive	KRd, DaraRd, PVd, DaraKd, IsaKd, IsaPd, IxaRd, Seli-Vd, KCd, KPd, PCd, EloRd
	R-refractory	PVd, DaraKd, IsaKd, IsaPd, Sel-Vd, KCd, KPd, PCd
	V-sensitive	KRd, DaraRd, EloRd, PVd, DaraKd, DaraVd, IsaKd, IsaPd, Seli-Vd, VenVd, KCd, KPd, PCd
	R/V-refractory	DaraKd, IsaKd, IsaPd, KCd, KPd, PCd
after DaraRd	R-sensitive	PVd, Kd, EloRd, KRd, KCd, KPd, PCd, IxaRd, Seli-Vd, Seli-Pd, VenVd, VenKd
	R-refractory	PVd, Kd, Seli-Vd, Seli-Pd, VenVd, VenKd, KCd, KPd, PCd
after DaraVMP or DaraVTD	V-sensitive	EloRd, KRd, IxaRd, VRd, Seli-Vd, Seli-Pd, Kd, VenVd, VenKd, PVd
	V-refractory	EloRd, KCd, KPd, PCd, Seli-Pd, VenKd

Second or more relapses

R/V-refractory	DaraKd, IsaPd, EloPd, IsaKd, DaraPd, Seli-Pd, VenKd
R-refractory, PI-sensitive	DaraKd, EloPd, IsaKd, IsaPd, DaraPd, DaraVd, Seli-Vd, Seli-Pd, VenVd, VenKd
Alternative (not optimal) options	PCd, daratumumab, panobinostat-tabanlı rejimler
tripple class refractory	Clinical trials, Seli-d, belamaf, melflufen-dex, venetoclax t(11;14) (+), elranatamab, teclistamab, talquetamab, CAR-T

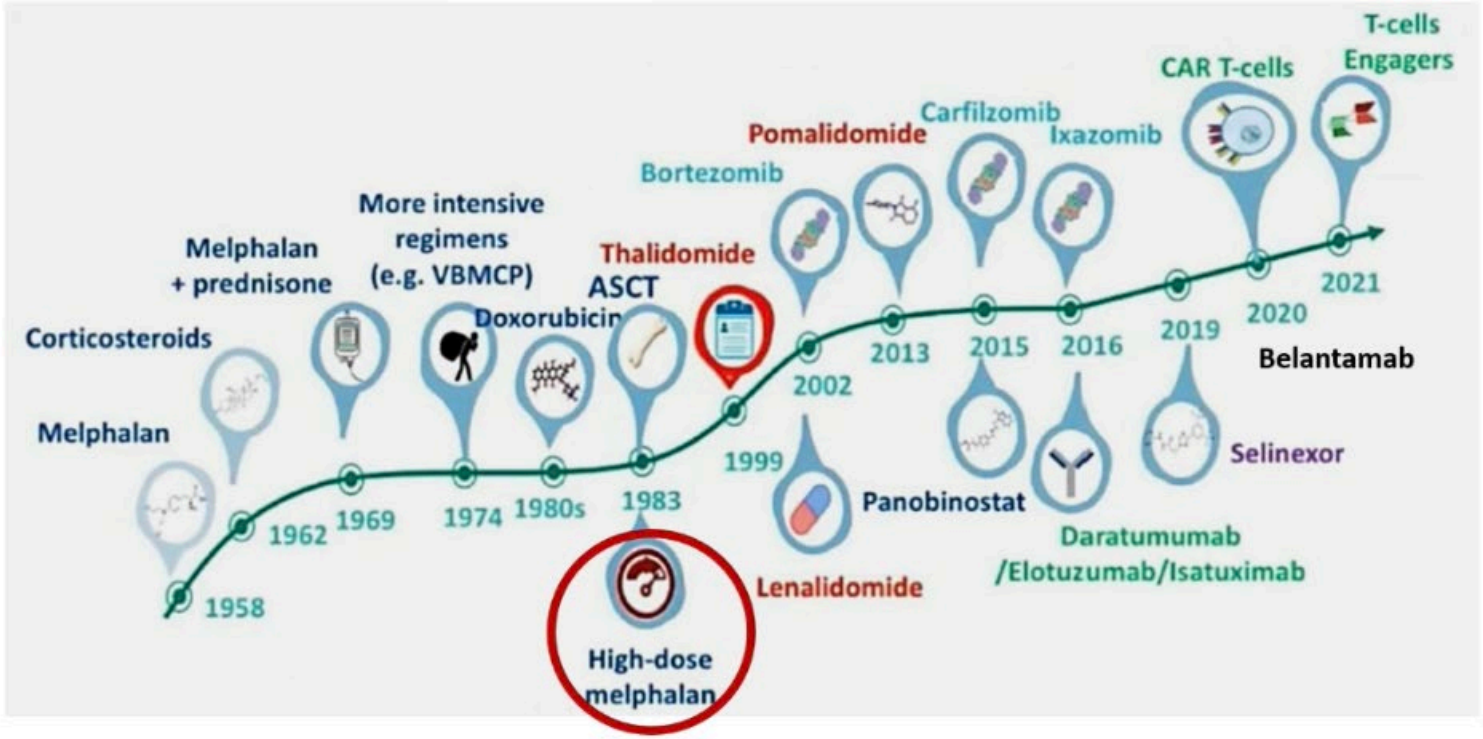
Adapted from M.V. Mateos



moAB: monoclonal antibody

Rajkumar SV. 2022

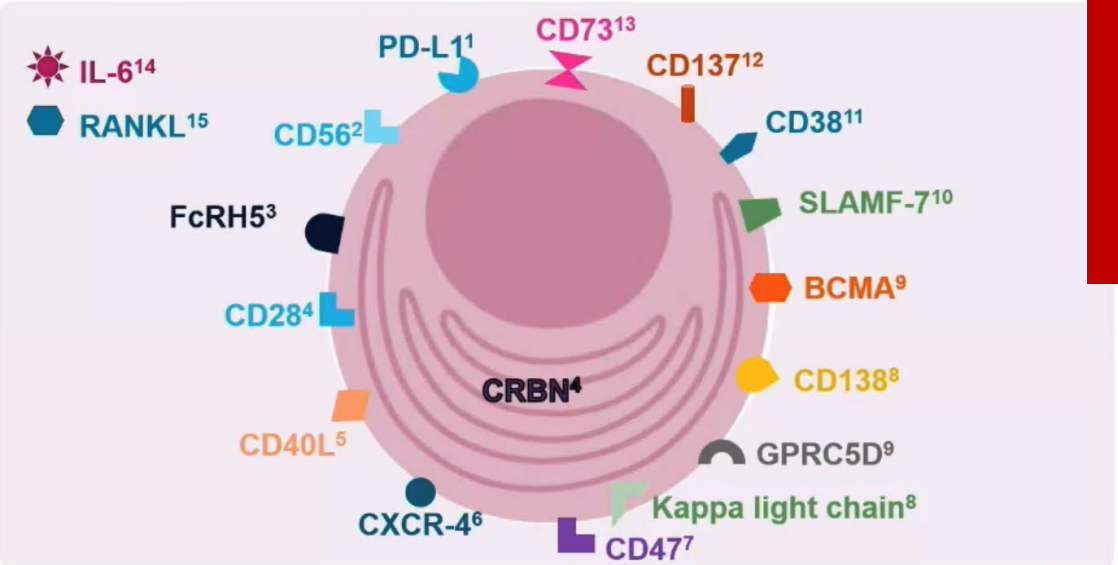
Treatment algorithm during the last two decades



Kyle R et al. Blood 2008;111:2962–2972; Alexanian R et al. JAMA 1969;208:1680–1685; Shah JJ et al. Ther Clin Risk Manag 2009;5:151–159; McElwain TJ et al. Lancet 1983;2:822–824; Garfell AL et al. N Engl J Med 2015;373:1040–1047; Bahlis N et al. Blood 2016;128:977; Kumar S et al. Blood 2017;130:2401–2409; https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio; https://www.ema.europa.eu/en/medicines/human/EPAR/abecma; https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti; https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep; https://www.ema.europa.eu/en/medicines/human/EPAR/tecvayli

CAR, chimeric antigen receptor; VBMCP, vincristine, bcnu, melphalan, cyclophosphamide, prednisone

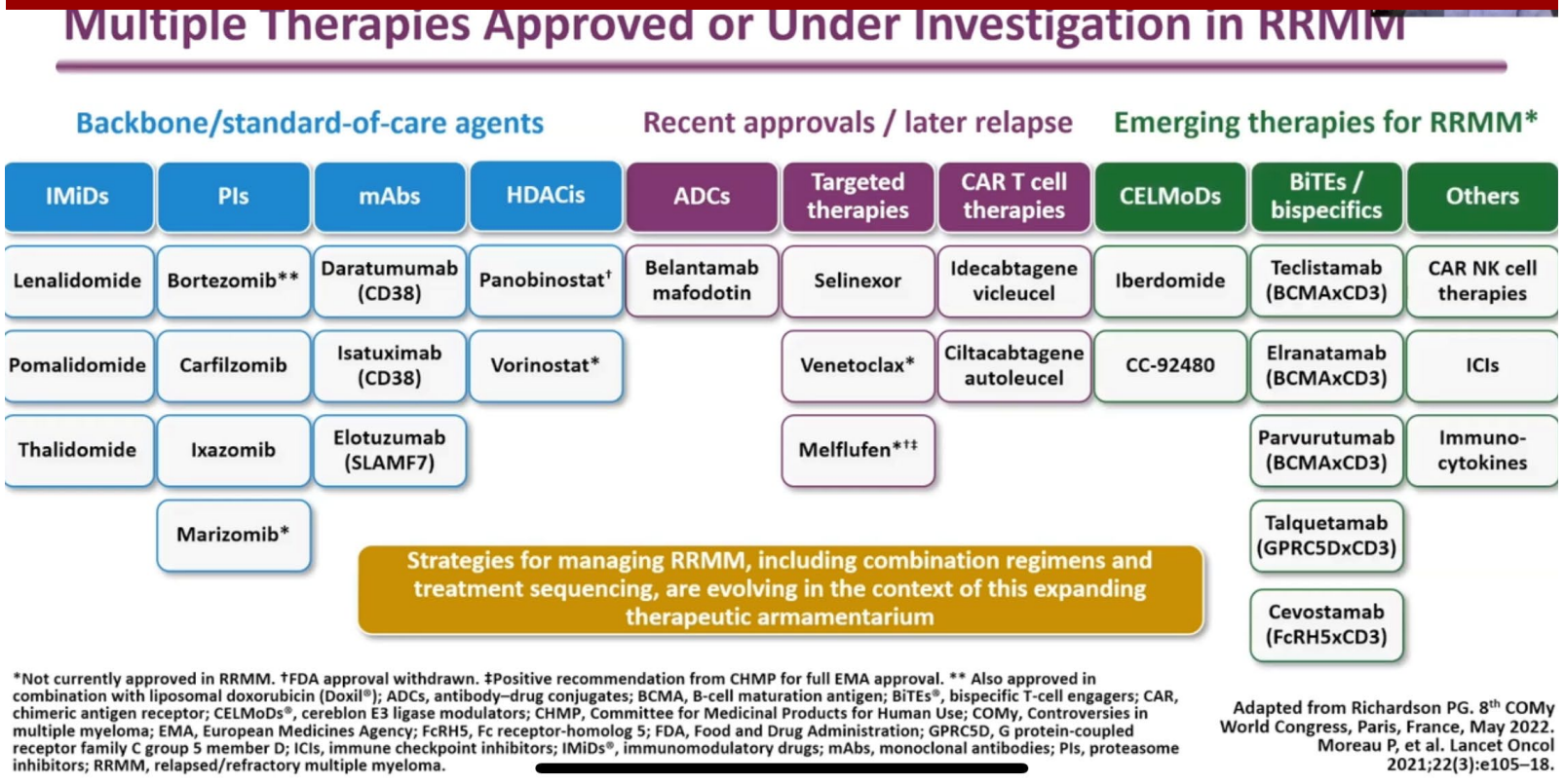
Novel targets for MM treatment



Target	Expression by myeloma cells	Expression by normal hematopoietic cells	Expression on other tissues	Clinical development of treatment options	Critical issues during development
CD38	Increased and uniform expression. Downregulated after Mab treatment	Myeloid and lymphoid cells, progenitor cells, NK and T cells, neutrophils and dendritic cells	Epithelial cells (prostate), pancreatic islet cells, pulmonary cells, Purkinje neurons (cerebellum)	Mabs (FDA, EMA approved) CAR T (clinical trials)	Mab treatment well tolerated Expression on normal tissues can hamper the development of more potent therapies
BCMA	60–100%	Plasmocytes and plasmoblasts	Absent (controversial expression on basal ganglia (brain)	Antibody–drug conjugate (FDA, EMA approved) CAR T (FDA, EMA approved) Bispecific antibodies (BITE and IgG format)	Duration of response for some of the CAR T constructs Potential neurotoxicity
SLAMF7/CS1	Increased and uniform expression	NK, T and B cells, monocytes, macrophages, dendritic cells and plasmacytes	Absent	Mabs (FDA, EMA approved) CAR T (clinical trials)	Fratricide on NK cells
FcRL5	Expression on > 80% of patients	B cells and plasmocytes	Absent	Bispecific antibodies (BiTE format)	IV formulation
GPRC5D	High expression in > 60% patients	B cells and plasma cells	Epithelial cells of skin and of filiform papillae (tongue)	Bispecific antibodies (IgG format) and CAR T, both in clinical trials	Skin and nail toxicity, dysgeusia
CD138	High expression	Plasmocytes	Epithelial cells of GI tract, hepatocytes	CAR T (clinical trials)	Currently in early development
CD19	Weak expression	B cell lineage cells	Absent	CAR T (clinical trials)	Weak expression on tumor cells
CD56	High expression in 80% of patients	NK and T cells, monocytes	Neural expression	CAR T (clinical trials)	Currently in early development

Kegyes et al Journal of Hematology & Oncology (2022) 15:78

WHAT ARE OPTIONS FOR PATIENTS EXPOSED AND REFRACTORY TO PI+ IMID+ ANTI-CD38



*Not currently approved in RRMM. †FDA approval withdrawn. ‡Positive recommendation from CHMP for full EMA approval. ** Also approved in combination with liposomal doxorubicin (Doxil®); ADCs, antibody–drug conjugates; BCMA, B-cell maturation antigen; BiTEs®, bispecific T-cell engagers; CAR, chimeric antigen receptor; CELMoDs®, cereblon E3 ligase modulators; CHMP, Committee for Medicinal Products for Human Use; COMy, Controversies in multiple myeloma; EMA, European Medicines Agency; FcRH5, Fc receptor-homolog 5; FDA, Food and Drug Administration; GPRC5D, G protein-coupled receptor family C group 5 member D; ICIs, immune checkpoint inhibitors; IMiDs®, immunomodulatory drugs; mAbs, monoclonal antibodies; PIs, proteasome inhibitors; RRMM, relapsed/refractory multiple myeloma.

Adapted from Richardson PG. 8th COMy World Congress, Paris, France, May 2022. Moreau P, et al. Lancet Oncol 2021;22(3):e105–18.

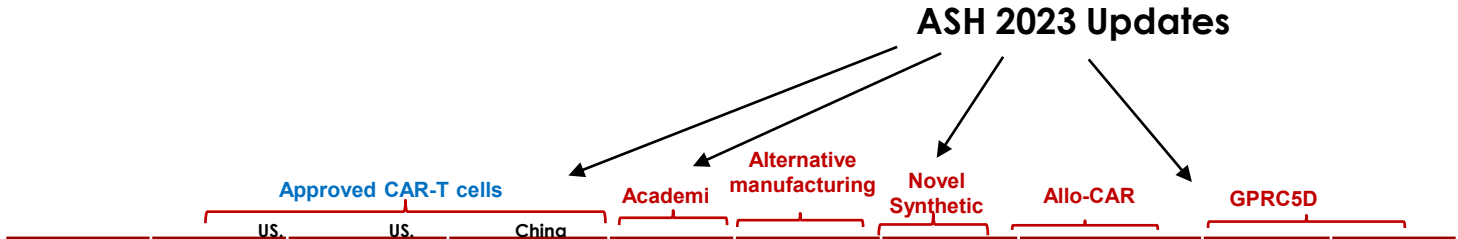
CAR-T studies in Myeloma

	2nd generation CAR T-cells[1]		Academic[2]	Human scFv[3,4]		Allogeneic CAR[5-7]			GPRC5D[8]
	Ide-cel[a] KarMMa (n=128)[9-13]	Cilta-cel[a] CARTITUDE-1 (n=97)[11,14-16]	ARI0002h[b] (n=30)[2,17]	CT053[b] LUMMICAR (n=20)[3,18,19]	CT103A[b] (n=71)[4,18,21]	ALLO-715[b] UNIVERSAL (n=43)[5,20,22]	ALLO-605[b] IGNITE (n=136[c])[6,23]	P-BCMA-ALLO1[b] (n=135[c])[7,24,25,26]	MCARH109[b] (n=17)[8,27,28]
Phase	2	1b/2	1/2	1b/2	1/2	1	1/2	1	1
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D
scFv	Chimeric mouse	Chimeric llama	Humanized	Human	Human	Human	Human	Humanized anti-BCMA VH-based	Human
Co-stimulatory	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous	Autologous	Autologous	Allogeneic CD52 and TCRα KO	Allogeneic TRAC/CD52	Allogeneic MHC I and TCR KOs	Autologous

[a]Approved in the EU and US for the treatment of RRMM.[12,15,29,30] [b]These therapies are not approved for the treatment of MM but are under clinical investigation in MM.[2,4,5,7,8,19,22] [c]Estimated enrolment.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; cilta-cel, ciltacabtagene autoleucel; GPRC5D, G-protein coupled receptor family C group 5 member D; ide-cel, idecabtagene vicleucel; KO, knockout; MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma; scFv, single-chain variable fragment; TCR, T-cell receptor; VH, variable heavy chain.

1. Du Z, et al. *Cancers*. 2023;15:567. 2. https://clinicaltrials.gov/ct2/show/NCT04309981. Accessed March 31, 2023. 3. Kumar S, et al. ASH 2020; Abstract 133 (oral presentation). 4. https://clinicaltrials.gov/ct2/show/NCT05066646. Accessed March 31, 2023. 5. Mailankody S, et al. *Nat Med*. 2023 Feb;29(2):422-429. 6. https://clinicaltrials.gov/ct2/show/NCT05000450. Accessed March 31, 2023. 7. https://clinicaltrials.gov/ct2/show/NCT04960579. Accessed March 31, 2023. 8. https://clinicaltrials.gov/ct2/show/NCT04555551. Accessed March 31, 2023. 9. Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716. 10. https://clinicaltrials.gov/ct2/show/NCT03361748. Accessed March 31, 2023. 11. van de Donk NWCJ, et al. *Blood cancer discov*. 2021;2(4):302-318. 12. Idecabtagene Vicleucel Summary of Product Characteristics, 2022. 13. Abebe EC, et al. *Front Immunol*. 2022;13:991092. 14. Martin T, et al. *J clin Oncol*. 2023;41(6):1265-1274. 15. https://clinicaltrials.gov/ct2/show/study/NCT03548207. Accessed March 31, 2023. 16. Ciltacabtagene Autoleucel Summary of Product Characteristics, 2023. 17. Fernandez de Larrea, et al. EHA 2022; Abstract S103 (oral presentation). 18. Zhang L, et al. *Ann Med*. 2021;53(1):1547-1559. 19. https://clinicaltrials.gov/ct2/show/NCT03915184. Accessed April 26, 2023. 20. Rafiq S, et al. *Nat Rev Clin Oncol*. 2020;17(3):147-167. 21. Li C, et al. *Blood*. 2021;138:547-548. 22. https://clinicaltrials.gov/ct2/show/NCT04093596. Accessed March 31, 2023. 23. Parikh RH, et al. *Cancer J Clin*. 2023. doi:10.3322/caac.21771. 24. Kocoglu MH, et al. *ESMO-IO*. 2022;16(S1):100152. doi:10.1016/j.iotech.2022.100152. 25. Cranert SA, et al. *Blood*. 2019;134(S1):4445. 26. Feng D, et al. *Scand J Immunol*. 2020;92(2):e12910. 27. Mailankody S, et al. *N Engl J Med*. 2022;387:1196-1206. 28. NCI. NCI Drug Dictionary. https://www.cancer.gov/publications/dictionaries/cancer-drug/def/autologous-anti-gprc5d-car-4-1bb-expressing-t-cells-mcarh109. Accessed March 31, 2023. 29. Idecabtagene Vicleucel Prescribing Information, 2021. 30. Ciltacabtagene Autoleucel Prescribing Information, 2023.

CAR-T cells in RRMM



	Ide-cel KarMMa[1] (n = 128)	Cilta-cel CARTITUDE-1 (n = 97) [2,3]	CT103A[7] (n= 79)	ARI0002h[4] (n = 60)	P-BCMA-101 PRIME[5,6] (n = 53)	ddBCMA[7] (n= 40)	ALLO-715 UNIVERSAL[8] (n = 43)	CC-95266[9] (n= 70)	OriCAR -017[90] (n= 13)
Phase	II	Ib/II	I/II	I/II	I/II	I	I	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	**GPRC5D**	**GPRC5D**
scFv	**Chimeric mouse**	**Chimeric Llama**	Human	**Humanized**	**Chimeric mouse**	Synthetic	Human	Human	**Humanized Bi-epitopic**
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Specificity	Auto	Auto	Auto	Auto	Auto-**piggyBac**	Auto	**Allo CD52 & TCR KO**	Auto	Auto
Age, (range)	61 (33-78)	61 (56-68)	57 (39-70)	61 (36-74)	60 (42-74)	66 (44-76)	64 (46-77)	60 (38-76)	64 (58-68)
# of lines	6	6	5	3	8	4	5	NR	5.5
HR cytog, %	35	24	34	28	NA	29	37	46	60
EMD, %	39	13	13	18	NA	34	21	43	40
Triple-R, %	84	88	17	67(?)	60	100/68(pent)	91	34(penta)	15
ORR, %	81	98	95	95	67	100	71	86	100
CR/sCR, %	39	82	68	58	NA	76	25	38	60
PFS	12.2 m	34.9 m	NR	15.8 m	NR	67%, 18m	NR	NR	NR

*There, are no head-to-head comparisons of these data and naïve comparison should be conducted with caution
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMD, extramedullary disease; HR cytog, high-risk cytogenetics; NA, not available; NR, not reached/not reported; ScFv, single-chain variable fragment; TCR, T-cell receptor; triple-R, triple-class refractory

1. Anderson L et al. ASCO 2021;abstract;8016 (poster presentation); 2. Berdeja J et al. Lancet 2021;398;314-24; 3. Lin Y et al. EHA 2022;abstract P961 (poster presentation); 4. Fernández de Larrea C, et al. EHA 2022;abstract S103 (oral presentation); 5. Costello C, et al. ASH 2020;abstract 134; 6. Mohyuddin GR et al. Blood Adv 2021;5(4):1097-1101; 7. Li C et al. EHA 2022;abstract S187 (oral presentation); 7. Li C, et al. ASH 2021;abstract 143; 8. Mailankody S, et al. ASH 2021;abstract 651; 9. Mailankody S, et al NEJM 2022. 10. Zhang et al Lancet Hematology 2023

Caldes AO, et al. ASH 2023
Frigault, M, et al. ASH2023.
Bal S et al. ASH 23

Du J, et al ASH 2023: Abstract 1022: FasT

Table 5. Comparison of novel immunotherapy approaches in multiple myeloma

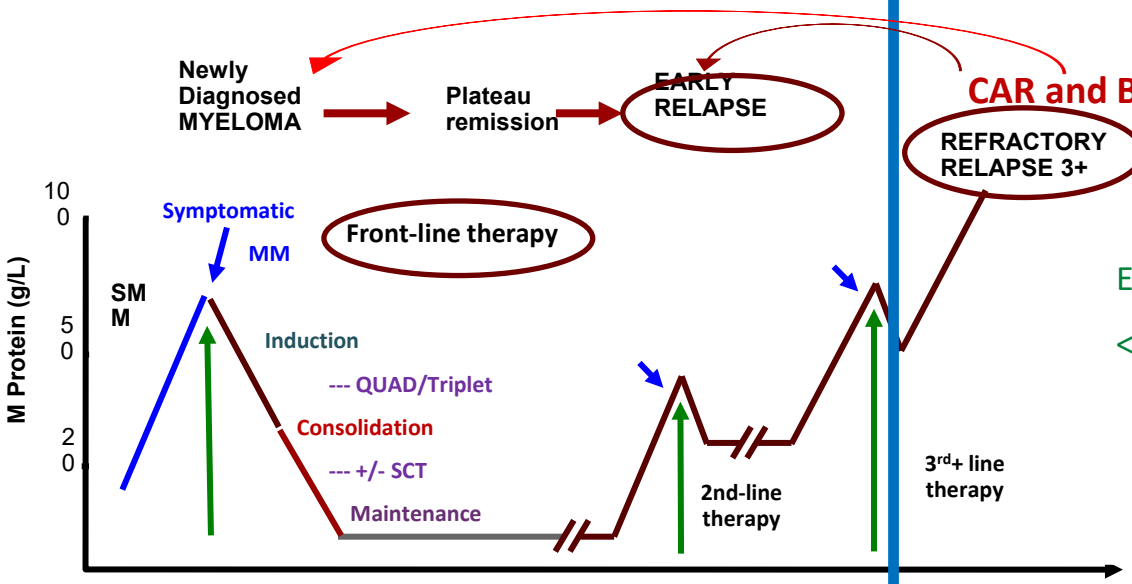
	Antibody drug conjugates	Bispecific T-cell engagers	CAR T-cell therapy
Advantages	Off-the-shelf therapy	Off-the-shelf therapy	-
	Immune and nonimmune mechanisms of action	-	-
	Infrequent dosing (every 3 wk-12 wk)	-	One-time therapy
	Encouraging response rates	Deep responses	Deep responses
	No CRS/ICANS	Mostly grade 1–2 CRS/ICANS	-
	Outpatient administration	Only initial dosing as inpatient	Vacation from continuous therapy
Disadvantages	Continuous therapy until progression	Continuous therapy until progression	-
	Frequent dose interruptions	Weekly or biweekly dosing	Administration delays due to manufacturing time
	Ocular toxicity	Significant immunosuppression	Potential for severe CRS/ICANS; prolonged cytopenias
	Ophthalmic exams prior to dosing	Specialized centers required	Complex infrastructure required
	Cost ($$)	Cost ($$)	Cost ($$$)

ICANS, immune effector cell-associated neurotoxicity syndrome; wk, week.

New targeted immunotherapies at earlier stages of Myeloma under development

Evolving MM Treatment Paradigm:

Where will Immunotherapies make the biggest impact?



SMM
Risk assessment

Frontline
Triplet/QUAD: +/- CAR

Early Relapse (1-3 Prior Lines)
CAR +/- CELMoD
TCE +/- CELMoD

Late Relapse
BCMA - CAR
~~*Belantamab*~~
Selinexor

Clinical Trial: BsAb, GPRC5D, etc.

Tom Martin

Conclusions: MM can be CURED? CARs and BsAbs) are the way !!!

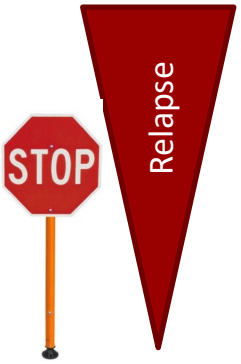
Future treatment paradigms…….

SCT eligible

QUAD Induction (4-6 cycles) → **CAR-T cell** → BsAb Maintenance (1, 2 yr)

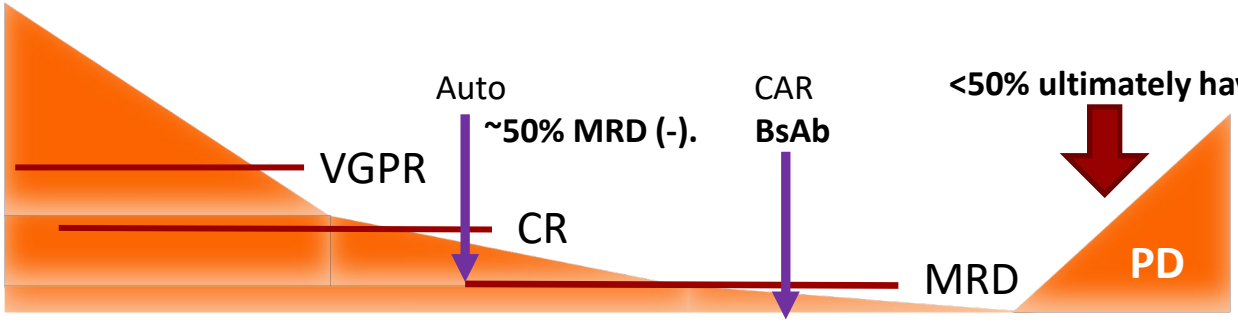
CAR eligible

Quad Induction (4-6 cycles) → CAR T-cell → Iber/BsAb Maintenance (1, 2 yr)



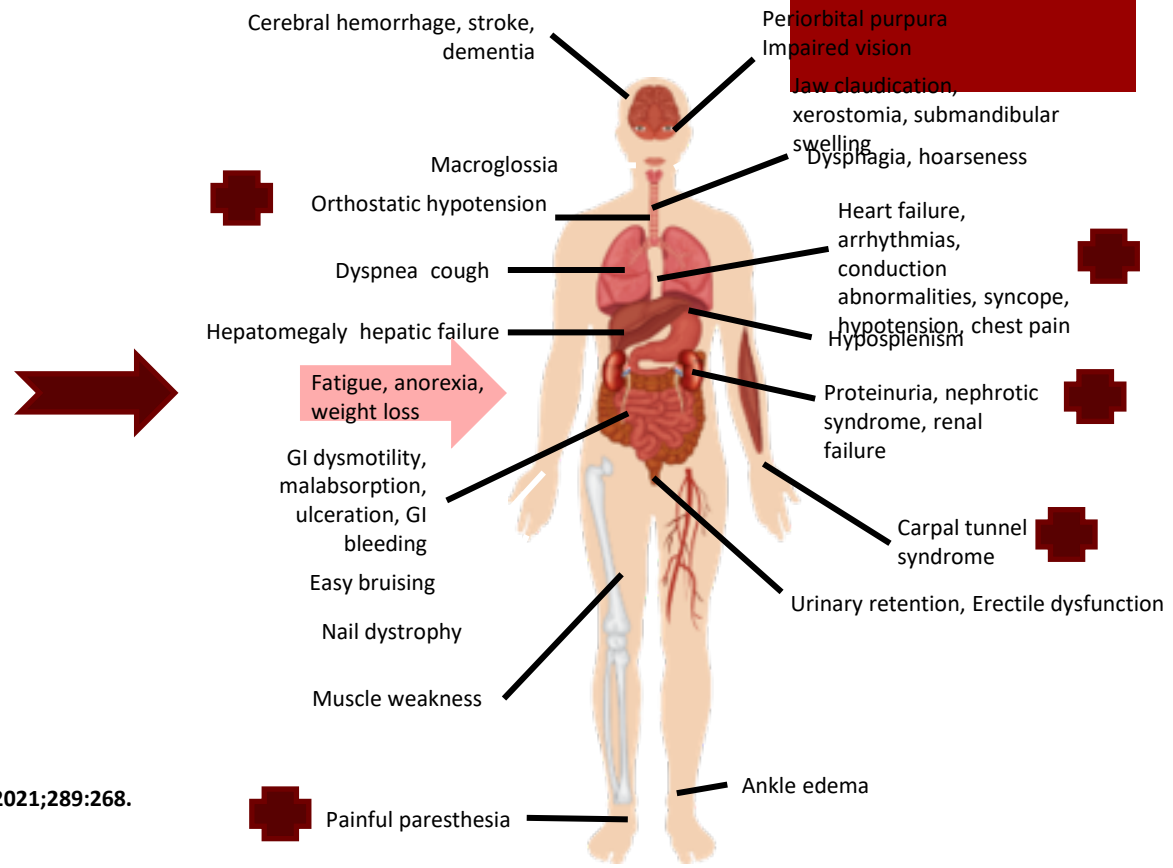
Frail

BsAb +/- partner(CD38) → **BsAb (different target)**



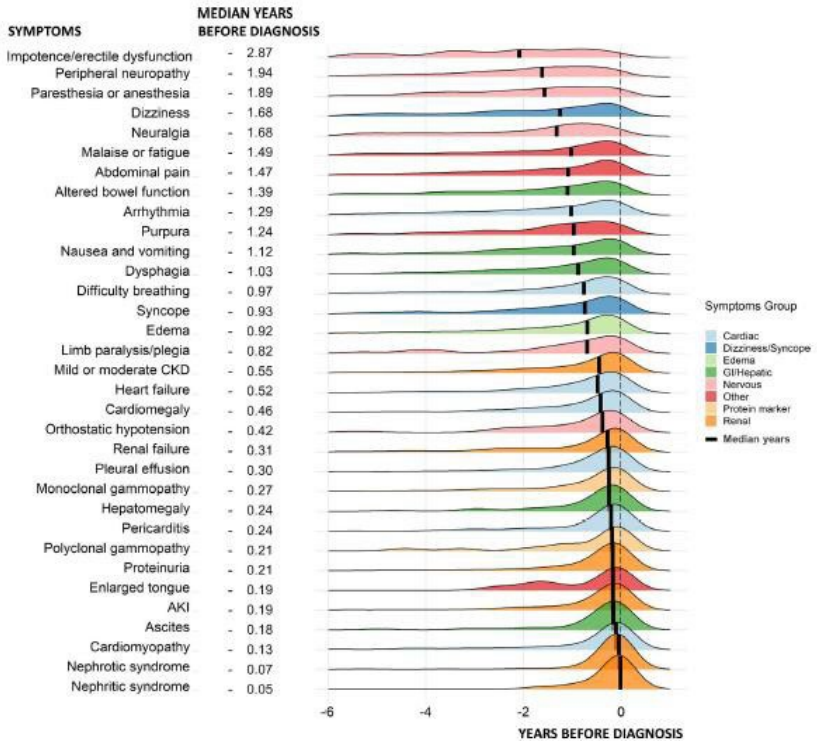
AL Amyloidosis

Amyloidosis: Clinical Presentation



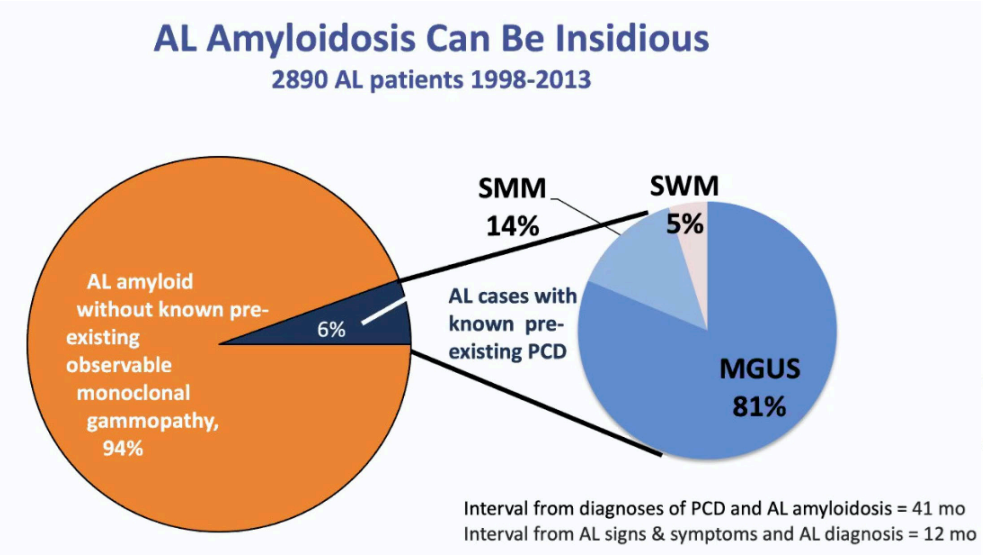
Gertz. JAMA. 2020;324:79. Adapted from Muchtar. J Intern Med. 2021;289:268.

AL Amyloidosis Diagnostic Prodrome

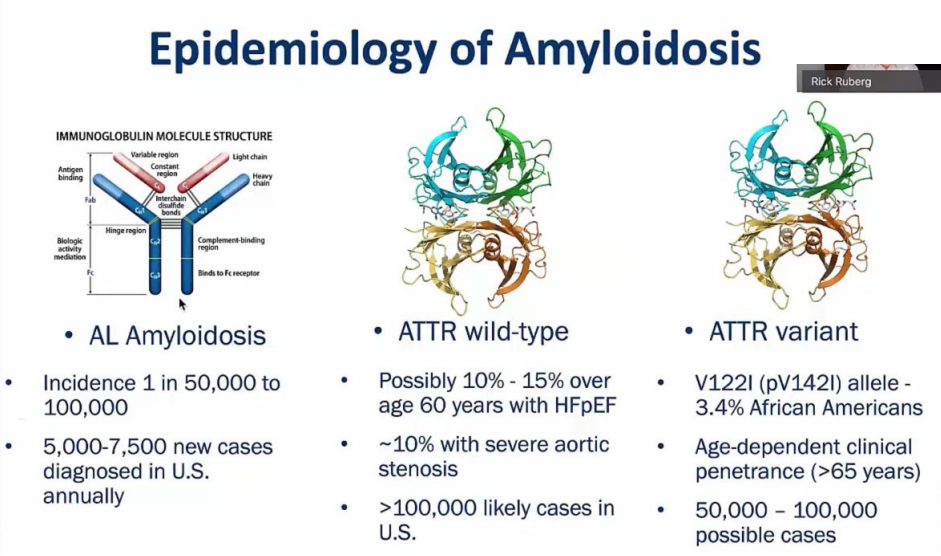


- 1523 patients with new diagnosed light-chain amyloidosis between 2001 and 2019
- Median time from symptom onset to diagnosis is **2.7 years**
- 50% of patients visited **≥5 physician specialties prior to diagnosis**

Amyloidosis Conundrum



Courtesy Dr Shaji Kumar

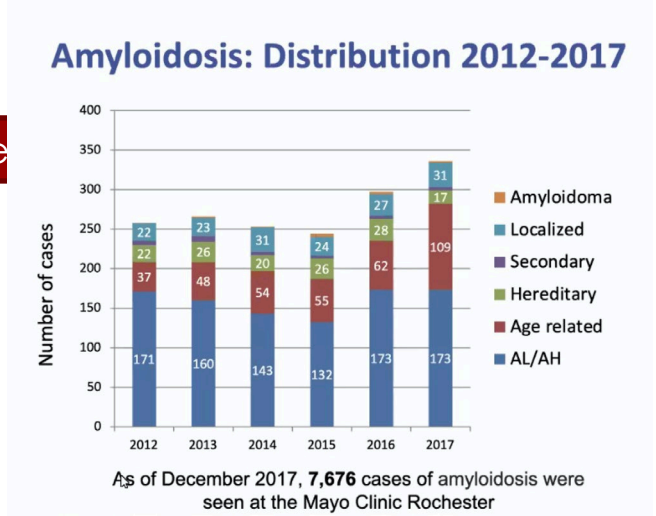


Courtesy Dr Rick Ruberg

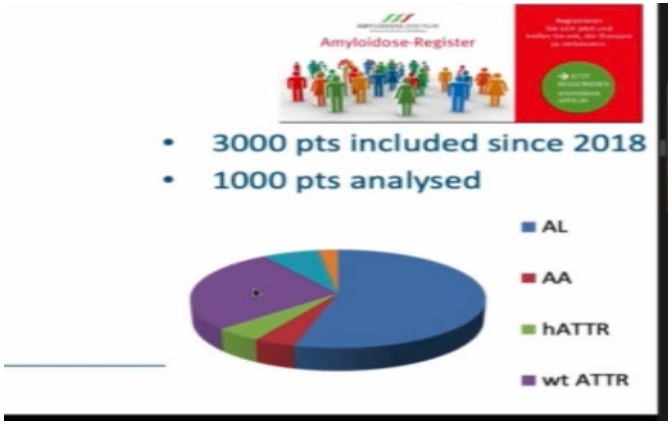
Incidence of Amyloidosis

*: among 5100 patients seen at UK-National Amyloidosis Cente

	Relative İncidence*
AA	12 %
AL	6.8 %
ATTR wt	3.2 %
ATTR mut	6.6 %



*: among 3000 patients seen at Heidelberg Amyloidosis Center



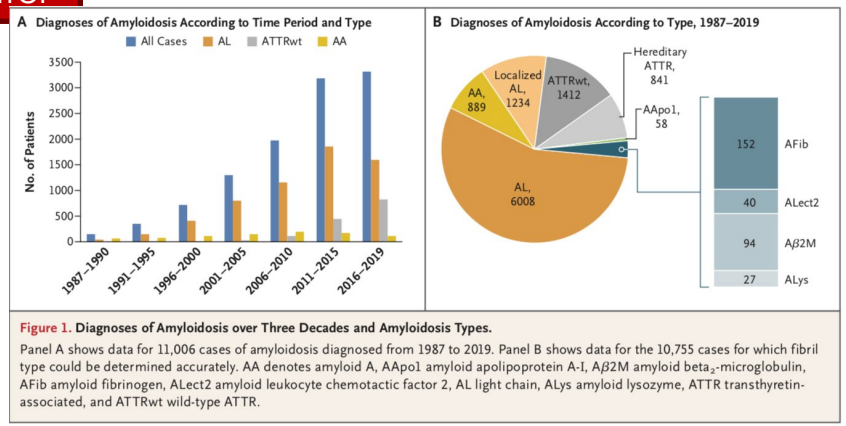


Figure 1. Diagnoses of Amyloidosis over Three Decades and Amyloidosis Types.

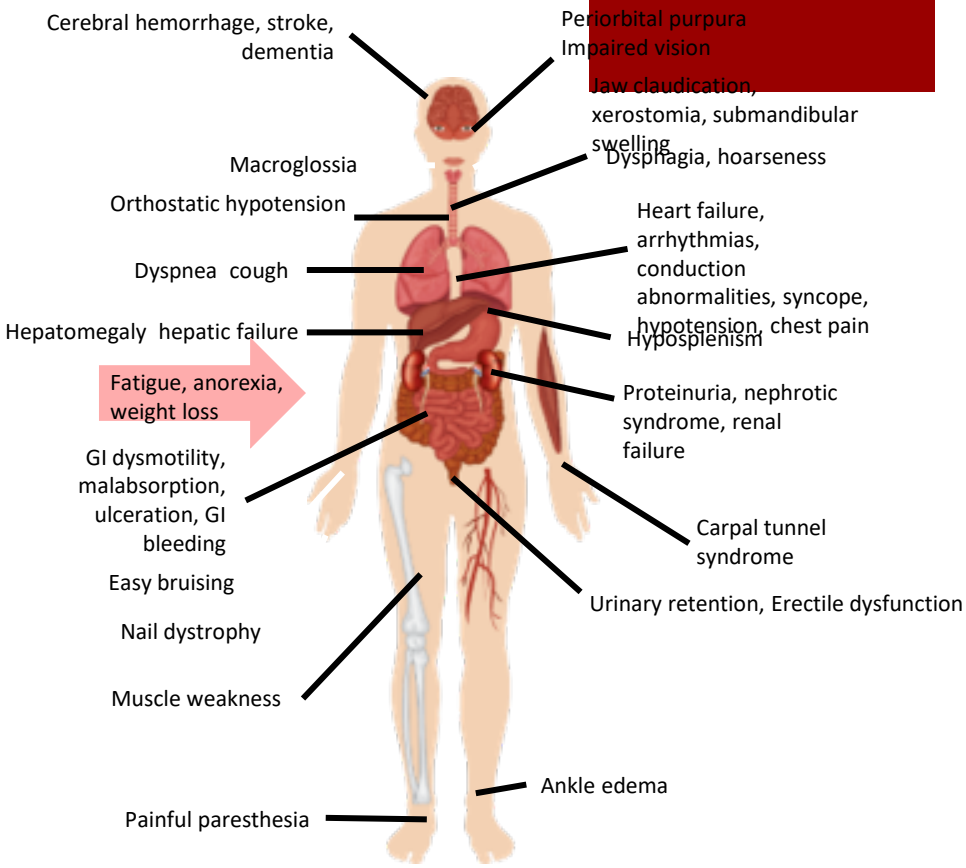
Panel A shows data for 11,006 cases of amyloidosis diagnosed from 1987 to 2019. Panel B shows data for the 10,755 cases for which fibril type could be determined accurately. AA denotes amyloid A, AApo1 amyloid apolipoprotein A-I, Aβ2M amyloid beta$_2$-microglobulin, AFib amyloid fibrinogen, ALect2 amyloid leukocyte chemotactic factor 2, AL light chain, ALys amyloid lysozyme, ATTR transthyretin-associated, and ATTRwt wild-type ATTR.

Ravichandran et al N Engl J Med 2020; 382;16 : 1567-8

DIFFERENTIAL DIAGNOSIS

Amyloidosis: Clinical Presentation

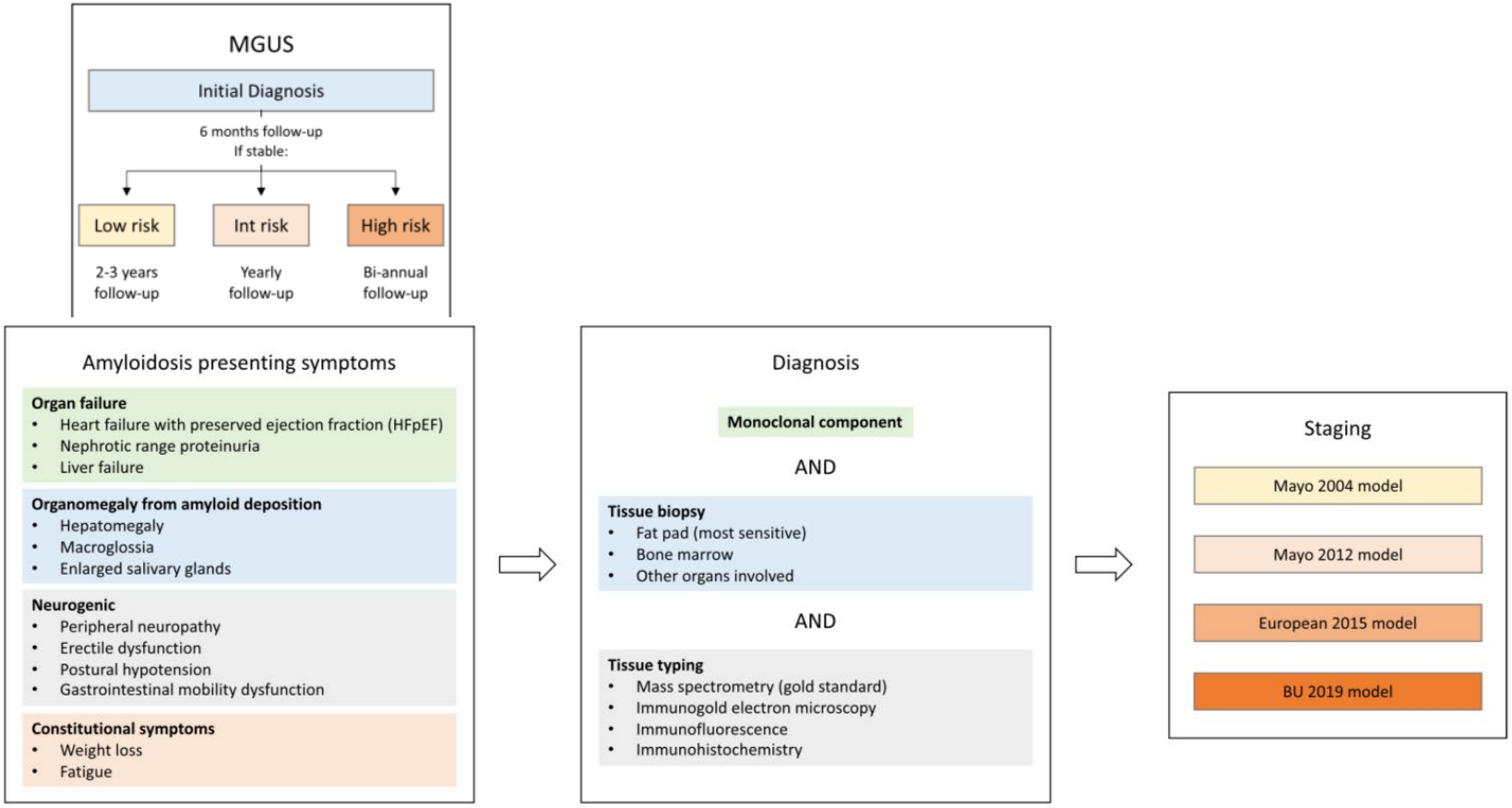
Symptom	AL	ATTRwt	ATTRv
Atypical MGUS or smoldering myeloma	X	--	--
Diastolic dysfunction, HFpEF	X	X	X
Proteinuria, nondiabetic	X	--	--
Small-fiber neuropathy	X	--	X
Autonomic dysfunction	X	--	X
Hepatomegaly, no imaging defects	X	--	--
Purpura on face and/or neck	X	--	--
Macroglossia	X	--	--
Bilateral carpal tunnel	X	X	X
Spinal stenosis/ pseudoclaudication	X	X	X
Biceps rupture	--	X	--



Gertz.

Comprehensive Review of AL amyloidosis: some practical recommendations

Hamed et al. Blood Cancer Journal (2021)11:97



STAGING

BIOMARKERS

Table 1. Staging systems for AL amyloidosis

Staging system	Markers and thresholds	Stages	Outcomes*
Cardiac (NT-proBNP based)	NT-proBNP >332 ng/L cTnT >0.035 ng/mL (or cTnI >0.01 ng/mL)	I. No markers above the cutoff II. One marker above the cutoff IIIa. Both markers above the cutoff and NT-proBNP <8500 ng/L IIIb. Both markers above the cutoff and NT-proBNP ≥8500 ng/L	I. Median survival not reached, 57% with 10-y survival II. Median survival 67 mo IIIa. Median survival 15 mo IIIb. Median survival 4 mo
Cardiac (BNP based)	BNP >81 ng/L cTnI >0.1 ng/mL	I. No markers above the cutoff II. One marker above the cutoff IIIa. Both markers above the cutoff and BNP <700 ng/L IIIb. Both markers above the cutoff and BNP ≥700 ng/L	I. Median survival 151 mo, 57% with 10-y survival II. Median survival 53 mo III. Median survival 13 mo IV. Median survival 4 mo
Revised Mayo Clinic	NT-proBNP >1800 ng/L cTnT >0.025 ng/mL dFLC >180 mg/L	I. 0 markers above the cutoff II. 1 marker above the cutoff III. 2 markers above the cutoff IV. 3 markers above the cutoff	I. Median survival not reached, 57% with 10-y survival II. Median survival 69 mo III. Median survival 16 mo IV. Median survival 6 mo
Renal	eGFR <50 mL/min per 1.73 m^2 proteinuria >5 g per 24 h	I. Both eGFR above and proteinuria below the cutoffs II. Either eGFR below or proteinuria above the cutoffs III. Both eGFR below and proteinuria above the cutoffs	I. 1% risk of dialysis at 2 y II. 12% risk of dialysis at 2 y III. 48% risk of dialysis at 2 y

Palladini et al Blood. 2020;136(23):2620-2627

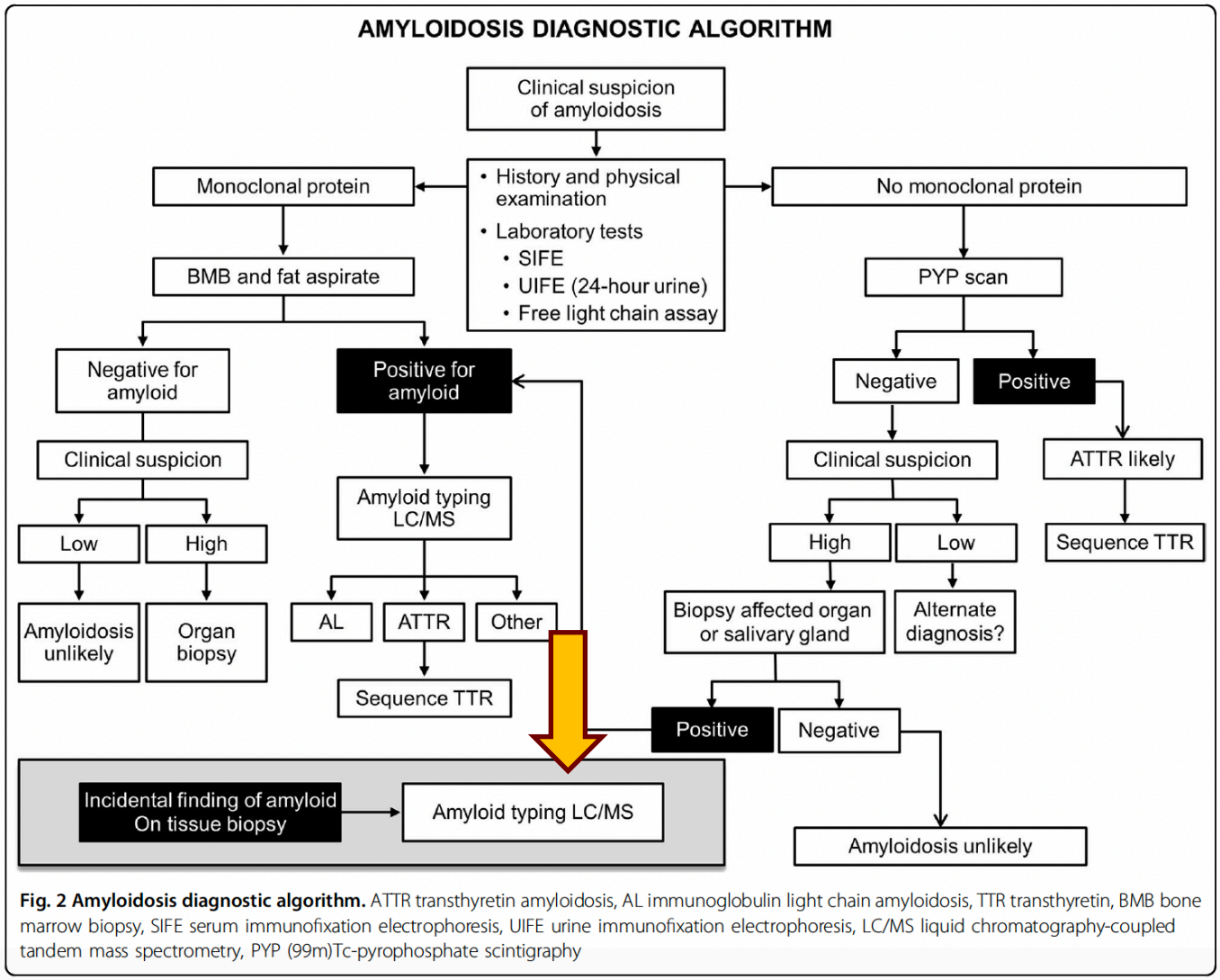


Fig. 2 Amyloidosis diagnostic algorithm. ATTR transthyretin amyloidosis, AL immunoglobulin light chain amyloidosis, TTR transthyretin, BMB bone marrow biopsy, SIFE serum immunofixation electrophoresis, UIFE urine immunofixation electrophoresis, LC/MS liquid chromatography-coupled tandem mass spectrometry, PYP (99m)Tc-pyrophosphate scintigraphy

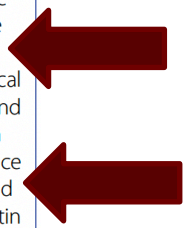
ARTICLE Open Access

Two types of amyloidosis presenting in a single patient: a case series

M. Hasib Sidiqi[1], Ellen D. McPhail[2], Jason D. Theis[2], Surendra Dasari[3], Julie A. Vrana[2], Maria Eleni Drosou[4], Nelson Leung[1,4], Suzanne Hayman[1], S. Vincent Rajkumar[1], Rahma Warsame[1], Stephen M. Ansell[1], Morie A. Gertz[1], Martha Grogan[5] and Angela Dispenzieri[1]

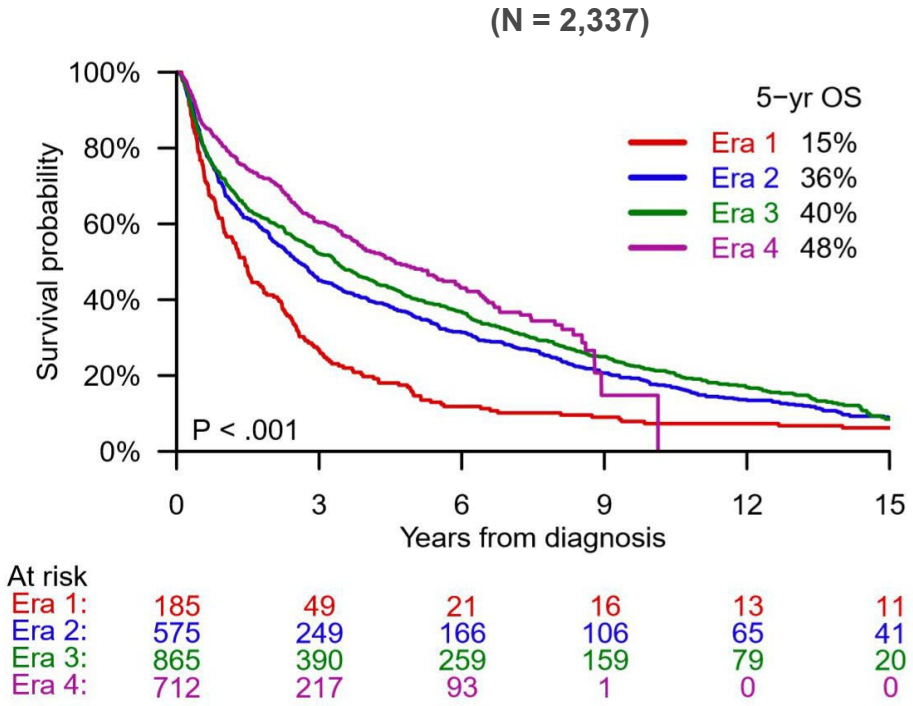
Abstract

The amyloidoses are a group of disorders with overlapping clinical presentations, characterized by aggregation and tissue deposition of misfolded proteins. The nature and source of the amyloidogenic protein determines therapy, therefore correct subtyping is critical to patient management. We report the clinicopathologic features of nine patients diagnosed with two amyloid types confirmed by liquid chromatography-coupled tandem mass spectrometry. The most common types were transthyrethin ($n = 9$) and immunoglobulin-derived ($n = 7$). Two patients did not have immunoglobulin-derived amyloidosis despite the presence of a monoclonal gammopathy. Eight patients were diagnosed with two types concurrently, and one patient had an 11-year interval between diagnoses. Histopathological distribution of amyloid was variable with vascular, interstitial, and periosteal deposits seen. Identification of a second type was incidental in seven patients, but led to genetic counselling in one patient and therapy directed at both amyloid subtypes in another. With longer survival of myeloma and AL amyloidosis patients and increasing prevalence of patients with wild-type transthyretin amyloidosis due to an aging population, the phenomenon of two amyloid types in a single patient will be encountered more frequently. In light of revolutionary new therapies for transthyretin amyloidosis (patisiran, tafamidis, and inotersen), recognition of dual amyloid types is highly clinically relevant.



TREATMENT

Overall Survival of Patients with AL Amyloidosis

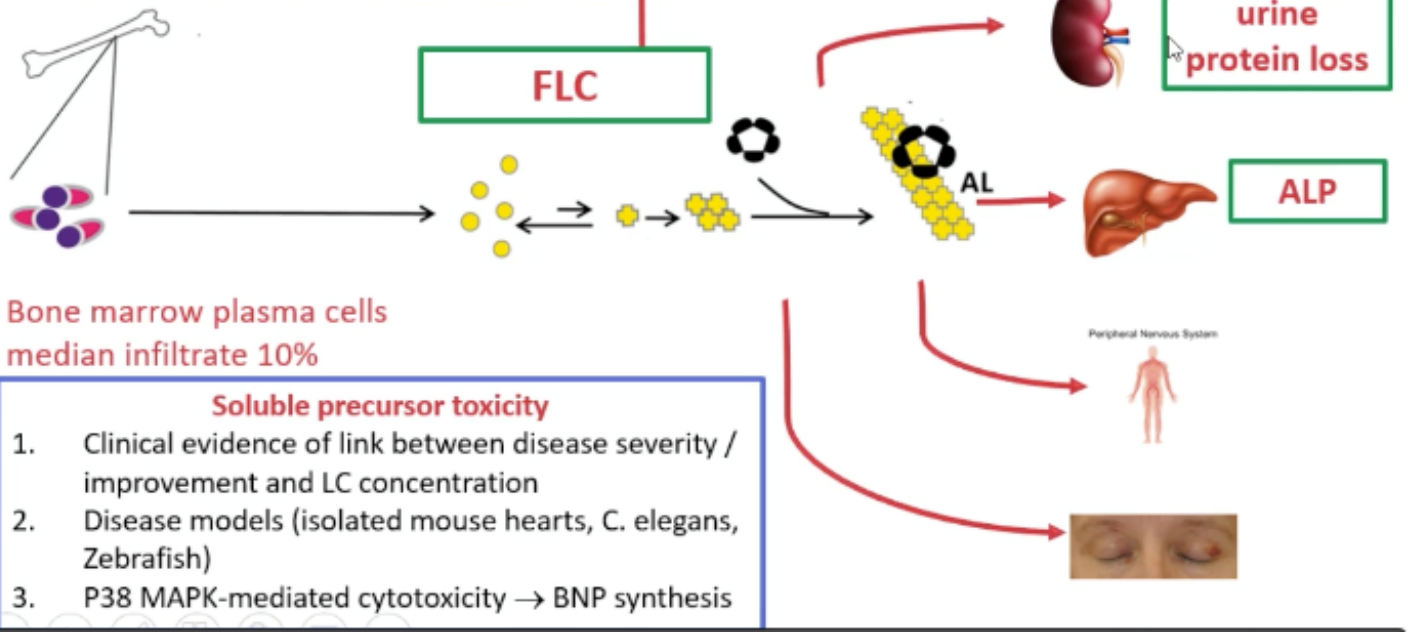


Stratum	Median OS, years
Era 1 1980–1989	1.4
Era 2 1990–1999	2.6
Era 3 2000–2010	3.3
Era 4 2010–2019	4.6

A dangerous small clone that causes multiple organ dysfunction

Amyloid deposits

1. Impaired molecule diffusion
2. Fibril cytotoxicity / interaction with cell membrane
3. Fibrils catalyze LC misfolding



Bone marrow plasma cells
median infiltrate 10%

Soluble precursor toxicity

1. Clinical evidence of link between disease severity / improvement and LC concentration
2. Disease models (isolated mouse hearts, C. elegans, Zebrafish)
3. P38 MAPK-mediated cytotoxicity → BNP synthesis

Al Hamed et al. Blood Cancer Journal (2021)11:97

ASCT Eligible

Eligibility Criteria
- Age <70 years
- ECOG performance status <2
- NYHA Class <III
- LVEF >45%
- SBP ≥100mmHg
- TnT <0.06 ng/mL or high-sensitivity (hs)-TnT <75 ng/mL
- NT-proBNP <5000 ng/L
- CrCl >50 ml/min (unless on chronic dialysis)
- Bilirubin <2 mg/dL
- DLCO >50%
- No more than 2 organs significantly involved

Induction
- Consider if high tumor burden (BMPC > 10%)
- Bortezomib-based regimens considered first line and confer deeper hematologic response
- IMiD/PI-based regimens emerging option, possibly positive predictor of improved OS

Stem Cell Mobilization
- G-CSF 10–16 µg/kg/day split into 2 doses
- Plerixafor if mobilization fails
- Avoid cyclophosphamide use to limit cardiac toxicity

High-dose Melphalan and ASCT
- 200 mg/m2
- Consider deferring ASCT if patient with low-risk disease achieves CR during induction therapy

Common adverse events
- Arrhythmias
- Worsening heart failure
- Progression to ESRD

ASCT Ineligible

Daratumumab-based regimen
- Daratumumab-CyBorD vs CyBorD
- Higher hematologic, cardiac, cardiac and renal response with prolonged PFS

Bortezomib-based regimen
- If daratumumab not available or contraindicated
- Avoid in the setting of pre-existing neuropathy (consider carfilzomib or attenuated dose)
- Weekly subcutaneous dosing is recommended
- Lower dose (0.7-1.0 mg/m2) initiation and up-titration as tolerable useful to limit cardiac burden

BMDex
- Considered first line
- Significantly improved hematologic response compared to Mdex translating to improved PFS and OS.

CyBorD
- Also considered first line, however reports suggest no benefit from cyclophosphamide addition. (Kastritis et al. Blood Cancer Journal. 2017)
- Less effective than BMDex in t(11;14) disease (Bochtler et al. J Clin Oncol. 2015.)

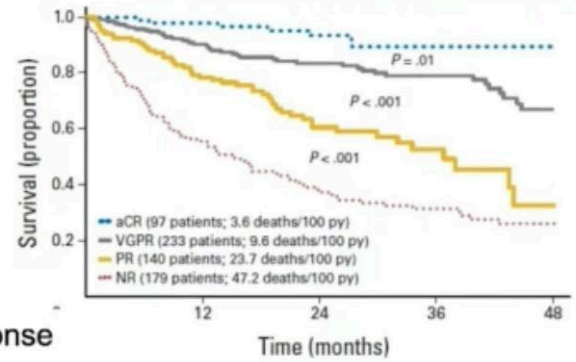
Vd
- Also an option, triplet-regimens preferred when possible.

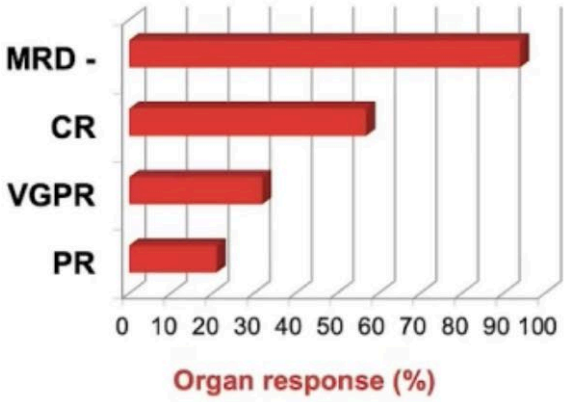
Mdex
- Effective when bortezomib unavailable or contraindicated
- First standard-intensity regimen with meaningful hematological response
- Low-dose dex should be considered in elderly patients with severe renal or cardiac involvement

Future therapies
- CAEL-101 for clearing amyloid deposits
- Carfilzomib when significant neuropathy present
- Low-dose IMiD addition (Lenalidomide/Pomalidomide)
- Venetoclax in t(11;14)

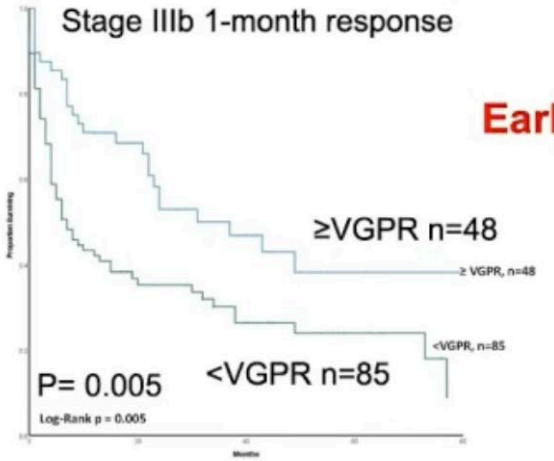
AL amyloidosis – response assessment based on graded FLC reduction

Criteria	Definition	HR (95%CI)	P
CR	Negative s & u IFE + normal. FLCR	reference	-
VGPR	dFLC <40 mg/L	2.67 (1.26-5.66)	0.01
PR	dFLC decrease >50%	6.24 (2.96-16.15)	<0.001
NR	All other patients	12.34 (6.03-25.35)	<0.001





Palladini et al, *BCJ 2021*



Ravichandran et al, *BCJ 2021*

Early and deep HR is vital

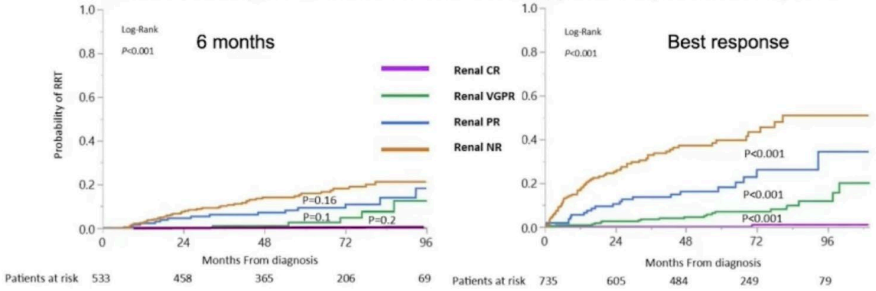
aim at:
PR by 1 month
VGPR by 2 months
OR by 3/6 months
MRD- if CR & no OR

ORGAN RESPONSE ASSESSMENT

Graded renal response assessment

- **Renal complete response (renCR):** 24-h proteinuria ≤200 mg/24-h
- **Renal very good partial response (renVGPR):** >60% reduction in 24-h proteinuria
- **Renal PR (renPR):** 31-60% reduction
- **Renal NR (renNR):** ≤30% reduction.

- Response was assessed compared to baseline at:
  - Fixed time points (6, 12 and 24 months from therapy initiation) and best response



Muchtar et al, *ASH 2021 abstr. # 2721*

Graded cardiac response assessment

- **Cardiac complete response (carCR):** nadir NT-proBNP≤350 pg/mL or BNP≤80 pg/mL)
- **Cardiac very good partial response (carVGPR):** >60% reduction in NT-proBNP/BNP from baseline)
- **Cardiac PR (carPR):** 31-60% reduction
- **Cardiac NR:** ≤30% reduction

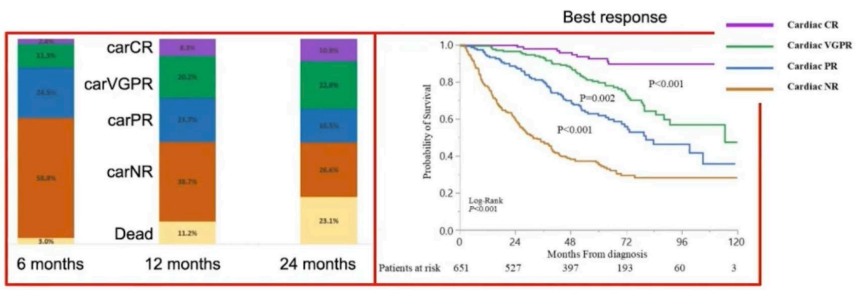
Response was assessed compared to baseline at:

- Fixed time points (6, 12 and 24 months from therapy initiation) and best response

The primary outcome was overall survival based on depth of cardiac response

Muchtar et al, *ASH 2021 abstr. #2720*

Graded cardiac response assessment



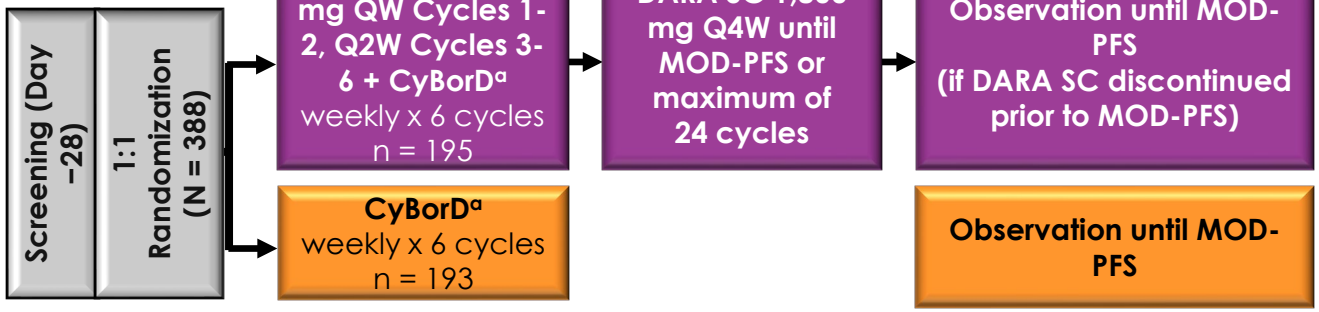
Muchtar et al, *ASH 2021 abstr. #2720*

ANDROMEDA is a randomized, open-label, active-controlled, phase 3 study of DARA SC plus CyBorD versus CyBorD alone in newly diagnosed AL amyloidosis

Kastritis et al N Engl J Med 2021;385(1):46-58.

Key eligibility criteria:

- AL amyloidosis with ≥1 organ impacted
- No prior therapy for AL amyloidosis or MM
- Cardiac stage I-IIIA (Mayo 2004)
- eGFR ≥20 mL/min



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 hematologic CR rate

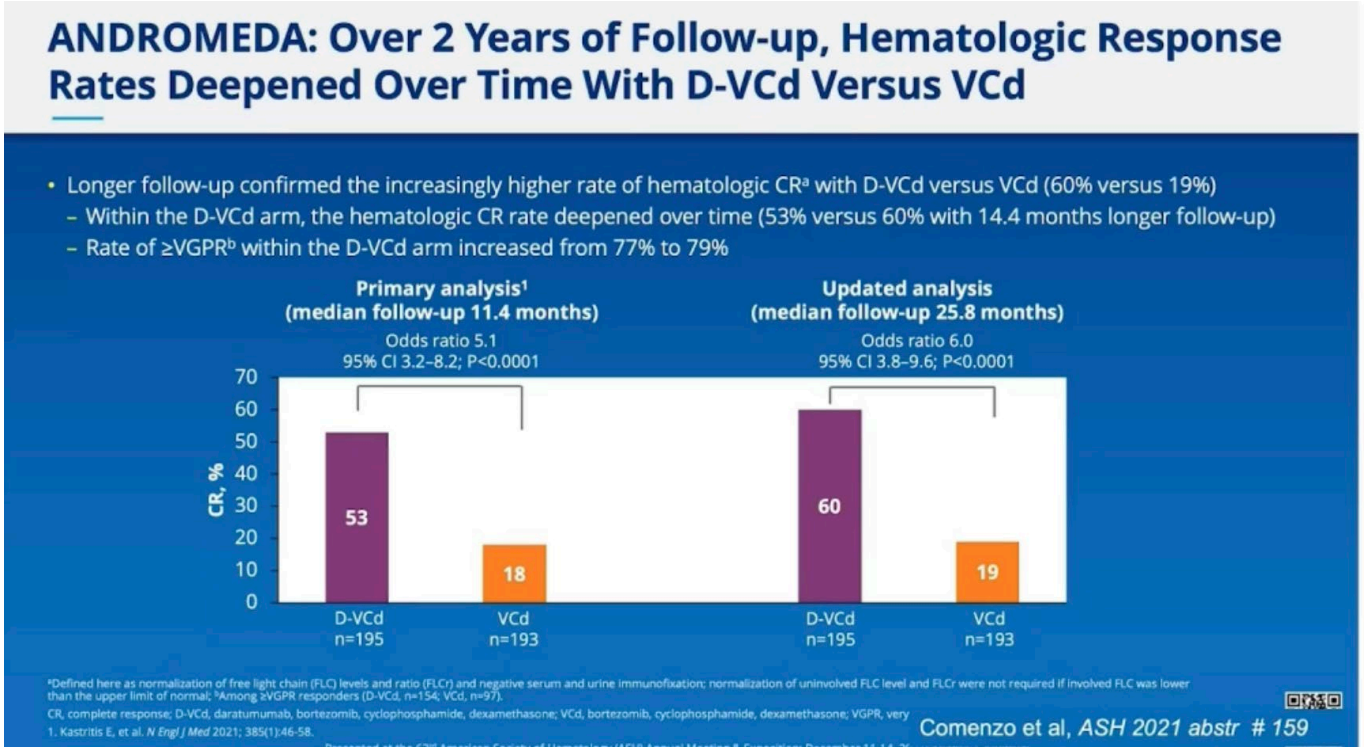
Secondary endpoints: MOD-PFS, organ response rate, time to hematologic response, overall survival, safety

DARA, daratumumab; SC, subcutaneous; CyBorD, cyclophosphamide/bortezomib/dexamethasone; AL, amyloid light chain; eGFR, estimated glomerular filtration rate; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; ECOG, Eastern Cooperative Oncology Group; CR, complete response; MOD-PFS, major organ deterioration progression-free survival; OS, overall survival.

[a]Dexamethasone 40 mg IV or PO, followed by cyclophosphamide 300 mg/m^2 IV or PO, followed by bortezomib 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 in every 28-day cycle for a maximum of 6 cycles. Patients will receive dexamethasone 20 mg on the day of DARA SC dosing and 20 mg on the day after DARA SC dosing.

Hematologic Overall Response

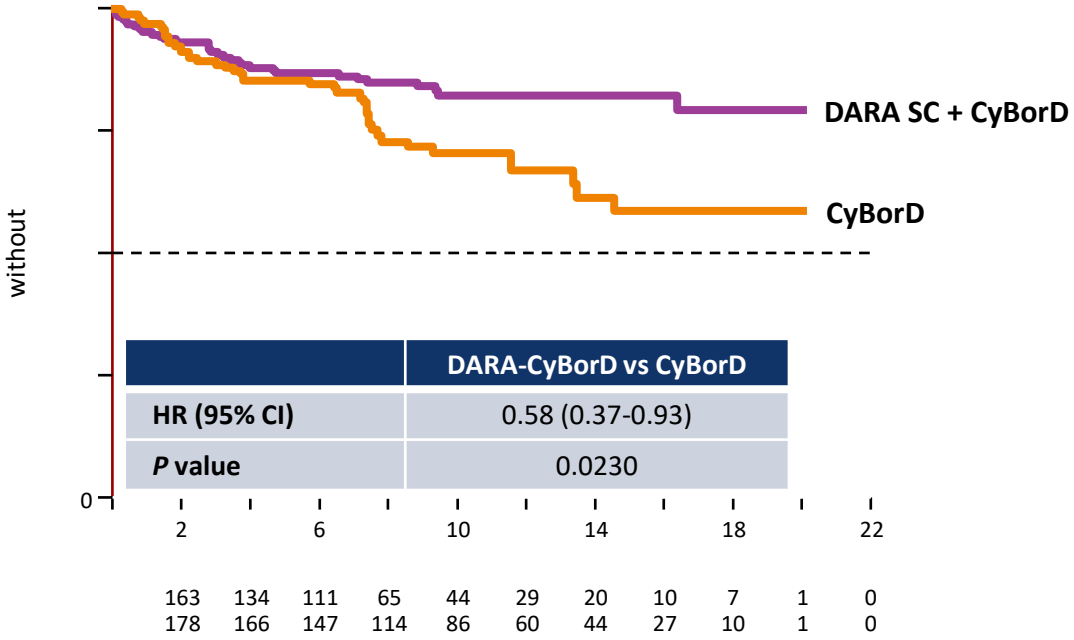
ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; DARA, daratumumab; CyBorD, cyclophosphamide/bortezomib/dexamethasone.
[a]Among responders (DARA-CyBorD, n = 179; CyBorD, n = 148).



Significantly higher rates of response were observed with DARA-CyBorD

- Median time to ≥VGPR:[a]
  - DARA-CyBorD: 17 days
  - CyBorD: 25 days

Major Organ Deterioration (MOD)-PFS[a]



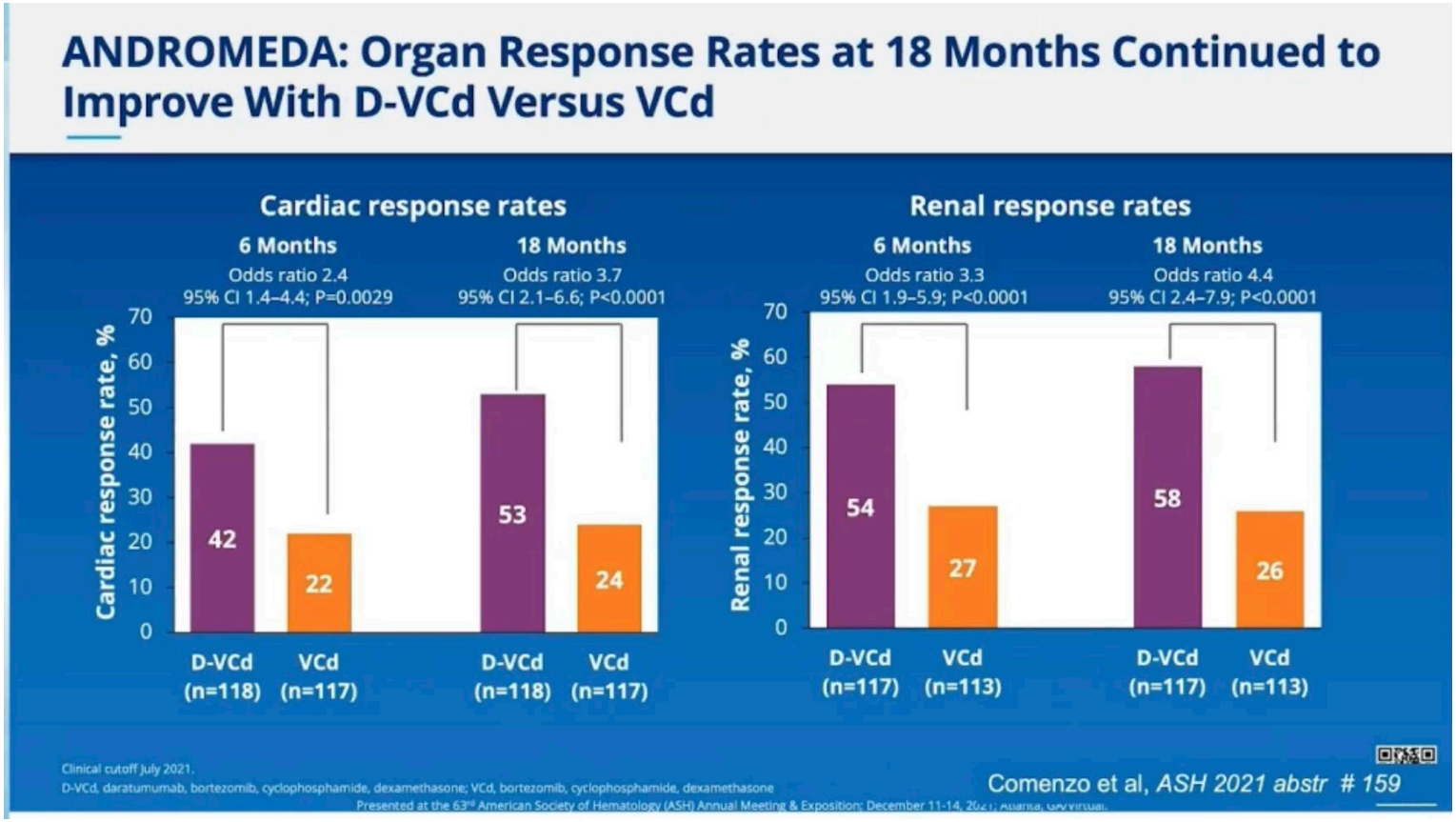
	DARA-CyBorD vs CyBorD
HR (95% CI)	0.58 (0.37-0.93)
P value	0.0230

- At a median follow-up of 11.4 months, MOD-PFS[a] was improved with DARA-CyBorD[b]
  - Results were consistent when not censored for subsequent therapy
- Median time to next treatment:
  - DARA-CyBorD: not reached
  - CyBorD: 10.4 months

Treatment with DARA-CyBorD substantially delayed major organ deterioration

Organ Response at 6 months[a]

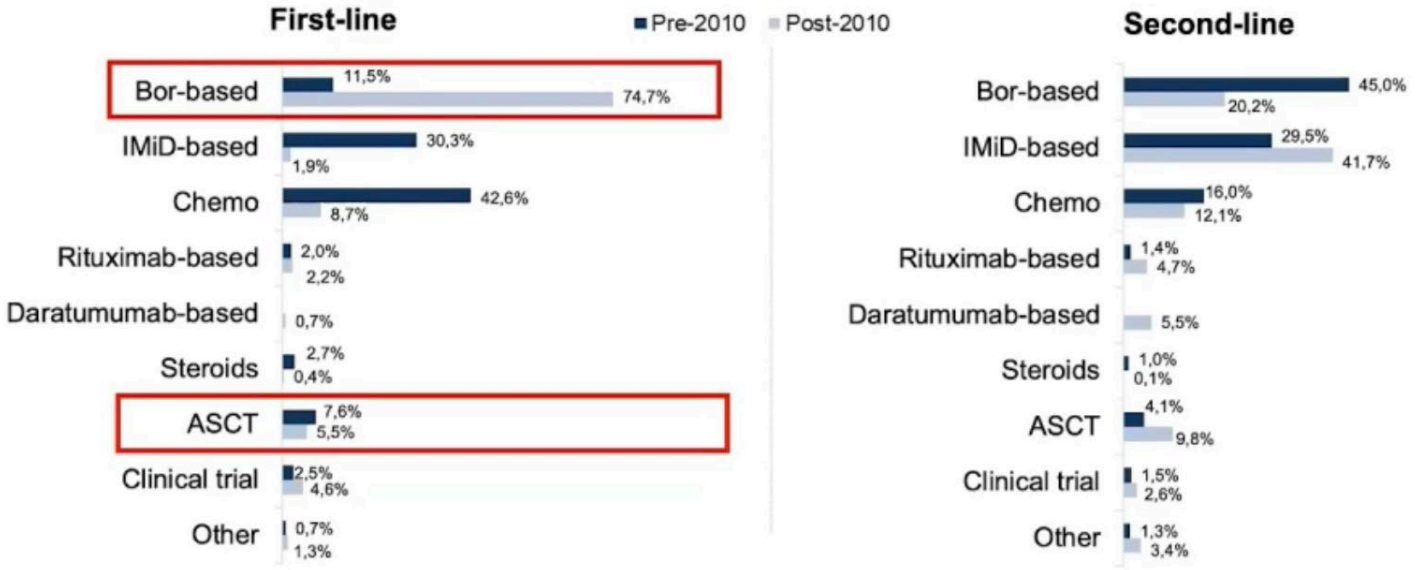
Cardiac and renal response rates were doubled with DARA-CyBorD versus CyBorD



[a]Organ response evaluable set (patients with organ involvement).
[b]Nominal P value.

Prevalence of regimen groups by line of treatment in Europe (4500 patients)

After 2010, Bortezomib-based regimens became the most widely used treatment at first line by far, and IMiDs became the primary salvage option.



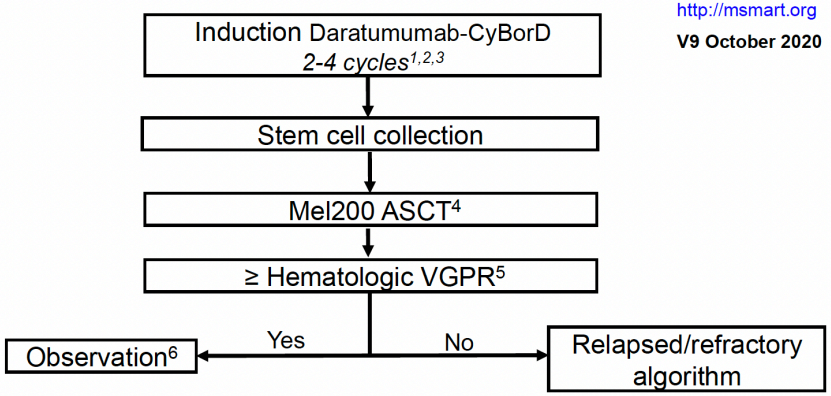
Palladini et al, *ASH 2021 a*bstr # 153

MAYO CLINIC

Newly Diagnosed AL Amyloidosis - Transplant eligible

http://msmart.org

V9 October 2020



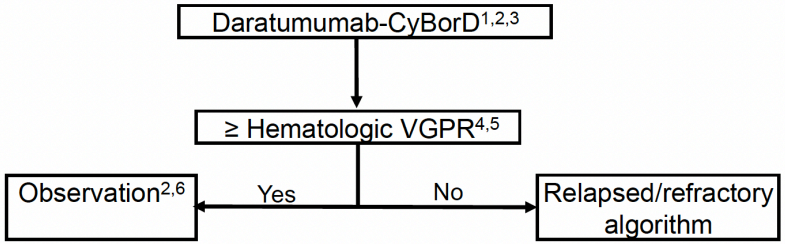
[1]Consider adding doxycycline for at least a year
[2]If daratumumab is not accessible, CyBorD is an acceptable alternative regimen (weekly bortezomib only)
[3]If CR, option to observe without ASCT for patients with low disease burden and proceed as transplant ineligible algorithm
[4]For CrCl <30, use Mel 140 mg/m2
[5]Decision to change therapy if in VGPR but < CR is based on a number clinical factors. Re-refer to amyloid center of excellence
[6]For patients with overt multiple, use myeloma-type maintenance; consider for BMPCs ≥20% and high-risk FISH (del 17p, t(4;14), t(14;16) and t(14;20)). Please refer for myeloma mSMART guidelines for choice of maintenance

MAYO CLINIC

Newly Diagnosed AL Amyloidosis - Transplant ineligible[#]

http://msmart.org

V9 October 2020



[1]Consider adding doxycycline for at least a year
[2]If 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)
[3]If young, consider stem cell collection for eventual ASCT if eligibility for transplant is foreseeable
[4]If < PR at 2 months or < VGPR within 4 cycles change therapy, unless signs of organ response are seen
[5]Decision to change therapy if in VGPR but < CR is based on a number clinical factors. Re-refer to amyloid center of excellence
[6]Only for patients with overt multiple myeloma, BMPCs ≥20% or high-risk FISH and who are not receiving extended duration daratumumab, consider maintenance. Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement

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

EHA-ISA Guidelines for Stem Cell Transplantation in AL Amyloidosis

Eligibility Criteria

- Age >18 and <70 years
- At least one vital organ involvement
- Left ventricular ejection fraction ≥40% and NYHA class <III
- Oxygen saturation ≥95% on room air and DLCO >50%
- Supine systolic blood pressure ≥90 mm Hg
- ECOG performance status score ≤2
- Direct Bilirubin <2 mg/dL
- NTproBNP <5000 pg/mL
- Troponin I <0.1 ng/mL, Troponin T <0.06 ng/mL, hs-Troponin T <75 ng/mL

Induction Therapy

- Consider if bone marrow plasmacytosis >10%
- Bortezomib based regimen 2-4 cycles
- Defer SCT if hematologic CR achieved with induction therapy

Stem Cell Mobilization and Collection

- G-CSF at 10-16 mcg/kg/day (single or split dose)
- Plerixafor on demand or planned
- Avoid cyclophosphamide

HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Editorial
Open Access

Summary of the EHA-ISA Working Group Guidelines for High-dose Chemotherapy and Stem Cell Transplantation for Systemic AL Amyloidosis

Vaishali Sanchorawala

Risk-Adapted Melphalan Dosing

	MEL 200[a]	MEL 200 vs non-SCT regimens[b]	MEL 140
Age (years)	≤65	66-70	
Cardiac stage	I	II	
eGFR (mL/min/m²)	>50	30-50	≤30[c]

[a] *must meet **all** criteria*

[b] *multidisciplinary discussion recommended*

[c] *increased risk of AKI and ESRD during the peri-SCT period; may consider if on a stable chronic dialysis schedule*

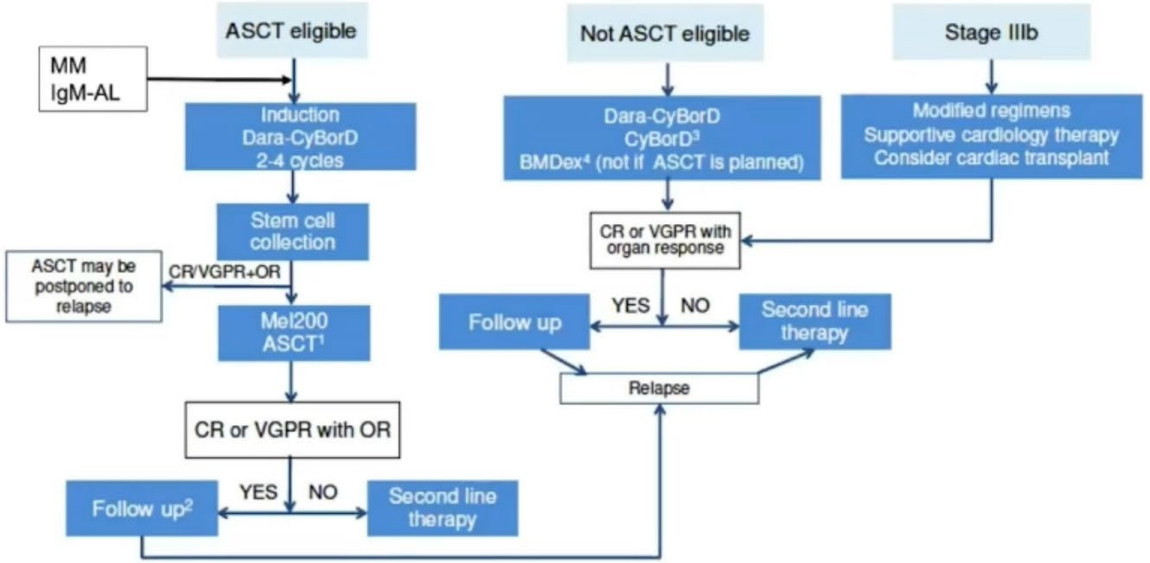
COMy

The 8th World Congress on

CONTROVERSIES IN MULTIPLE MYELOMA

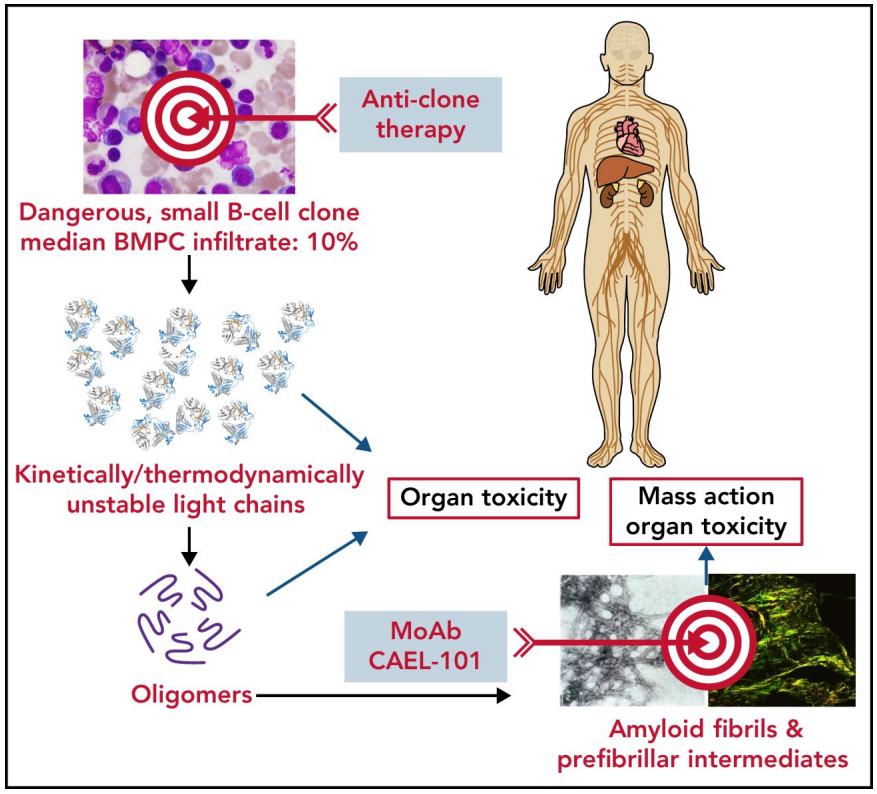
Giampaolo Merlini

New standards of care in AL amyloidosis



1. For patients with eGFR <30mL/min, Mel140 may be considered
2. For patients with multiple myeloma, consider maintenance
3. If daratumumab is not available
4. For patients with severe neuropathy, MDex can be considered

Palladini & Merlini, *Blood 2021*



Relapsed/Refractory

Hematological relapse ≥2 years since the last therapy
- Repeat original therapy

2nd line therapy: Daratumumab-based regimen
- Excellent ORR ranging from 63-100%
- 2-year OS rate of 74%

High-dose Melphalan and ASCT
- Transplantation is always an option for relapsed/refractory disease either as first transplant or repeat transplant.
- Evaluate eligibility and availability of alternative novel agents.

Bortezomib-sensitive
- CyBorD, BMDex, or Vd

Bortezomib-resistant: IMiDs-based regimen
- IMiDs generally not well tolerated by AL amyloidosis patients

Len-Dex
- Low starting dose of lenalidomide 5-15mg/day and uptitrate as tolerated.
- Monitor for fluid retention, cardiac biomarkers and kidney function.

Pom-Dex
- Slightly better tolerated, consider when available.
- Can increases proBNP/BNP without clinical congestive heart failure.

Second-generation PI

Ixazomib
- Ixa-Dex, Ixa-Cy-Dex
- Oral regimen, usually very effective and well tolerated.

Carfilzomib
- Challenging given cardiotoxicity profile
- Lower maximum tolerated dose compared to multiple myeloma (36mg/m²)

Other agents
- Venetoclax especially in t(11;14) disease
- Bendamustine especially in combination with rituximab in IgM-amyloidosis.
- Isatuximab

Table 3. Ongoing studies of novel therapies in AL amyloidosis

Drug	Mechanism of action	Trial identifier	Phase	Population	Enrollment target
Cael-101	Fibril-directed therapy Anti–light chain antibody	NCT04304144	2 (part A with VCD; part B with DVCD)	NDAL	25
Cael-101	Fibril-directed therapy Anti–light chain antibody	NCT04512235	3 (randomized, double blind)	NDAL (IIIA)	267
Cael-101	Fibril-directed therapy Anti–light chain antibody	NCT04504825	3 (randomized, double blind)	NDAL (IIIB)	111
Doxycycline	Fibril-directed therapy Fibril stabilizer	NCT03474458	2/3	NDAL	120
Isatuximab	Plasma cell–directed therapy Anti-CD38 monoclonal antibody	NCT04754945	1	NDAL (high risk=Mayo 2012 stage IV, Mayo 2004 IIIB BUMC 2019 3B)	25
Isatuximab	Plasma cell–directed therapy	NCT03499808	2	R/R	43
Venetoclax	Plasma cell–directed therapy BCL2 inhibitor	NCT02994784	1	R/R	24
Belantamab	Plasma cell–directed therapy Anti-BCMA antibody drug conjugate	NCT04617925	2	R/R	35
Melflufen	Plasma cell–directed therapy Alkylating agent	NCT04115956	1/2	R/R (after 1L)	46
STI-6129	Plasma cell–directed therapy Anti-CD38 antibody drug conjugate	NCT04316442	1	R/R (≥2)	60

DVCD, daratumumab, bortezomib, cyclophosphamide, dexamethasone; NDAL, newly diagnosed AL amyloidosis; R/R, relapsed/refractory; 1L, first line.

Bal & Landau ASH education

THANKS

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