webinar

HEALTH PROFESSIONALS

Thursdays Webinars

Update in the treatment of AL amyloidosis and Monoclonal gammopathies of clinical significance

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Paris, France

30 October 2025

ERN | EuroBloodNet

MGCS: Concept

Review in translational hematology

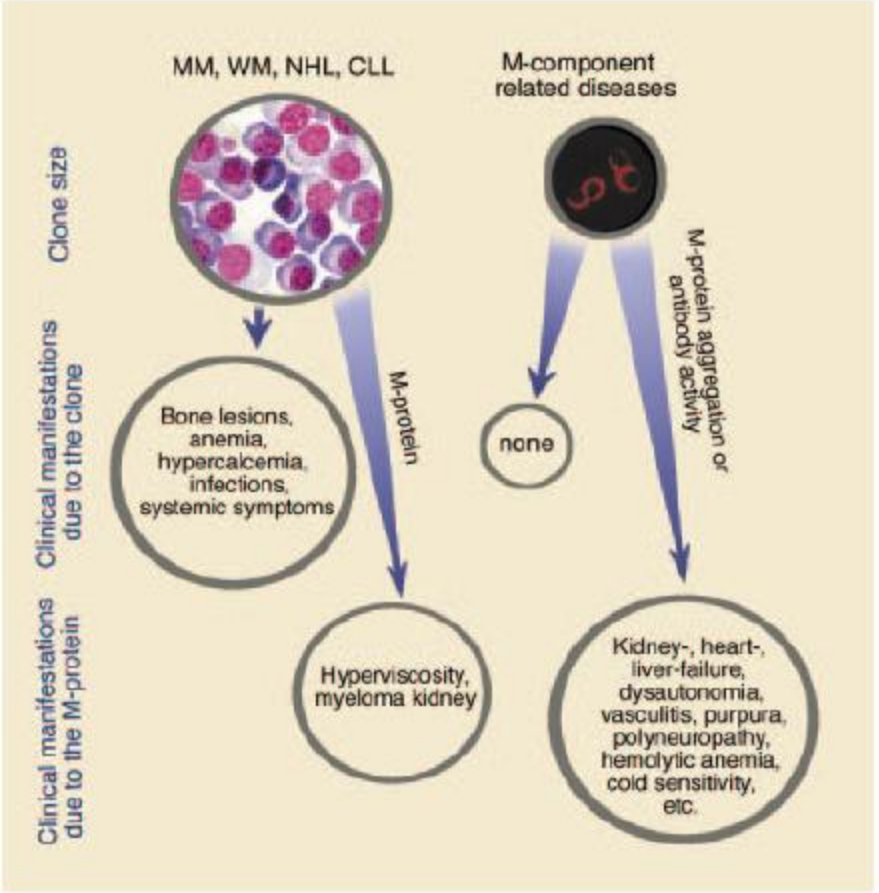
BLOOD, 15 OCTOBER 2006 • VOLUME 108, NUMBER 8

Dangerous small B-cell clones

Giampaolo Merlini and Marvin J. Stone

Table 1. Most common monoclonal component-related diseases

Diseases caused by M-protein aggregation
Light chain-cast nephropathy
AL amyloidosis
Light chain-deposition disease
Crystal-storing histiocytosis: adult Fanconi syndrome
Cryoglobulinemia type I
Diseases caused by M-protein antibody activity
Mixed cryoglobulinemia type II
Monoclonal cold agglutinins
Polyneuropathies



Monoclonal Gammopathies

MGUS

MGCS

MM

Non-IgM MGUS	1. <10% BMPC 2. Serum monoclonal protein (non-IgM) <3 g/dL 3. No SLiM-CRAB criteria[a]
IgM MGUS	1. <10% BMPC 2. Serum IgM monoclonal protein <3 g/dL 3. No symptoms attributable to underlying lymphoplasmacytic disorder (anemia, hyperviscosity, adenopathy, organomegaly, or constitutional symptoms)
Light chain MGUS	1. Abnormal FLC ratio (<0.26 or >1.65) 2. Increased level of the appropriate involved light chain (increased κ FLC in patients with ratio >1.65 and increased λ FLC in patients with ratio <0.26) 3. No immunoglobulin heavy chain expression on immunofixation 4. Urinary monoclonal protein <500 mg/24 h 5. <10% BMPC 6. No SLiM-CRAB criteria[a]
MGRS	1. Presence of monoclonal immunoglobulin or light chain 2. Kidney biopsy showing renal impairment related to the monoclonal protein[28,97] 3. Diagnostic criteria for MM or other lymphoplasmacytic disorder not met
MGCS[b]	1. Presence of monoclonal immunoglobulin or light chain 2. Symptoms or clinical manifestations attributable to the presence of monoclonal protein[31] 3. Diagnostic criteria for MM or other lymphoplasmacytic disorder not met
SMM	No SLiM-CRAB criteria[a] plus at least 1 of the following: 1. BMPC ≥10% 2. Serum M-spike ≥3 g/dL (or urine paraprotein ≥500 mg/24 h in the absence of a serum M-spike)
MM	1. BMPC ≥10%[c] 2. Presence of any SLiM-CRAB criteria[a]

Schmidt et al., J Natl Compr Canc Netw 2020
Glavey & Leung. Blood Reviews, 2016

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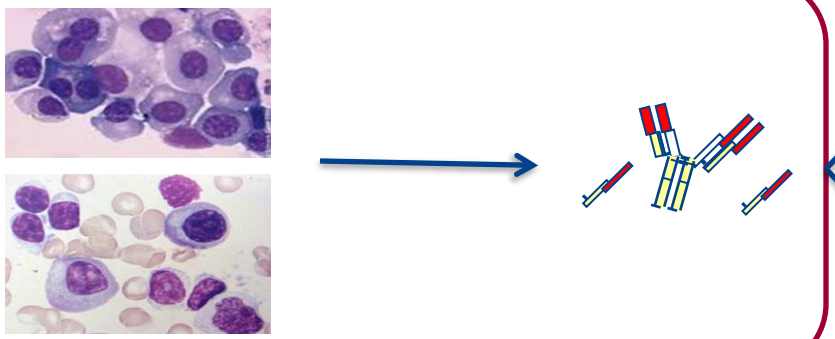
2018 132: 1478-1485
doi:10.1182/blood-2018-04-839480 originally published online July 16, 2018

Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications

Jean-Paul Fermand, Frank Bridoux, Angela Dispenzieri, Arnaud Jaccard, Robert A. Kyle, Nelson Leung and Giampaolo Merlini



Depositis/precipitation

Organized	**Non organized**
Fibrillar	MIDD
Microtubular	L/HCDD
Cristal	PGNMID

- Autoantibody activity
- Immune complex
- Complement (CAP) interference

Cytokine overproduction

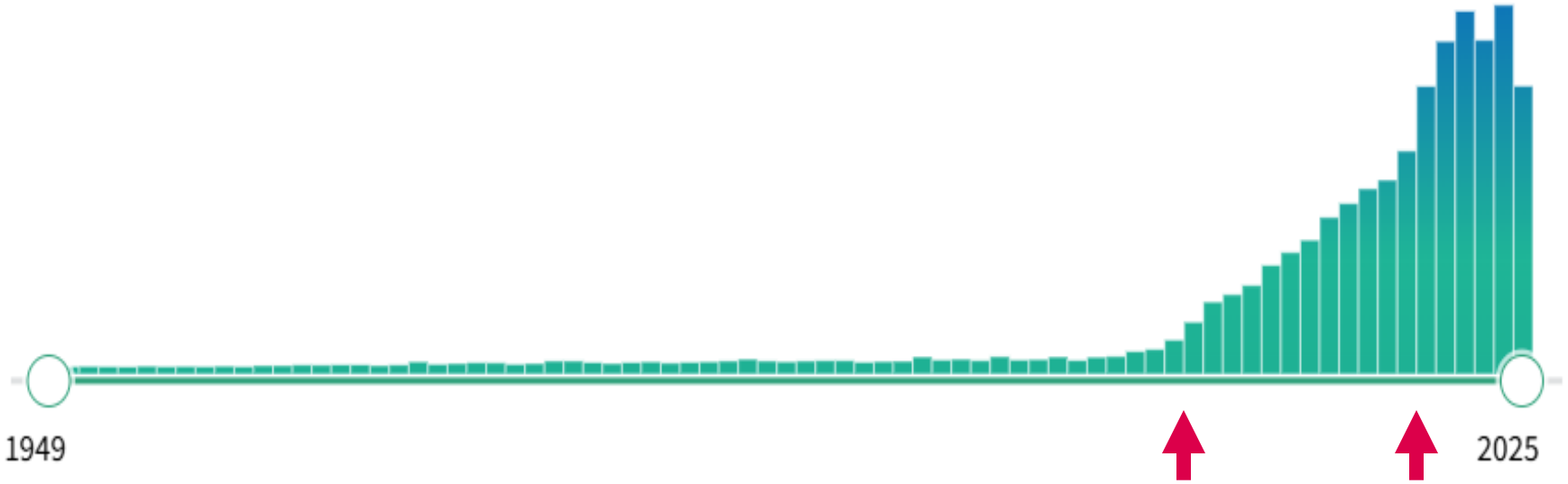
Unknown mechanisms

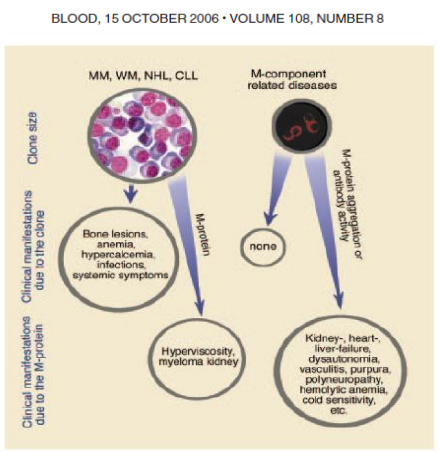
MGCS-related disorders: publication

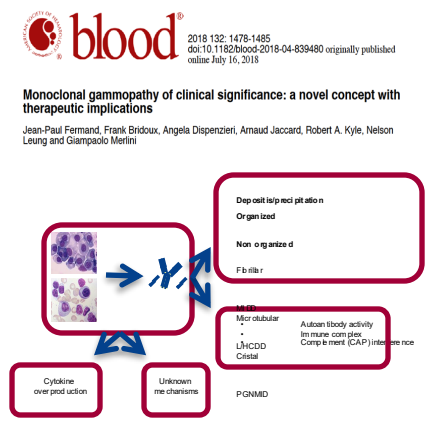
PMC PubMed Central®

monoclonal gammopathy of clinical significance

Search in PMC







MGCS: Diagnostic challenges

Early detection +++

Careful clinical work-up in baseline evaluation and follow-up of all monoclonal gammopathies,
looking at any renal and extra-renal manifestation (cardiac, cutaneous, neurologic….)

Prove B cell clone existence +++

Identification/Détection/quantification monoclonal Ig

SPEP, Freelite, Mass spec, IF….

Biopsy :Anatomopathology/immuno-histochemistry, Electronic Microscopie…

Search for and clone characterisation (lymphoplasmacytic or plasma cell)

Bone marrow (+/- BOM): cyto, phenotypage, FISH, (t(11;14), MYD88, NGS

Séquençing, protéomic, variables light and heavy chain region, cytokines….complement

PGNMID

Exclude fortuitous association

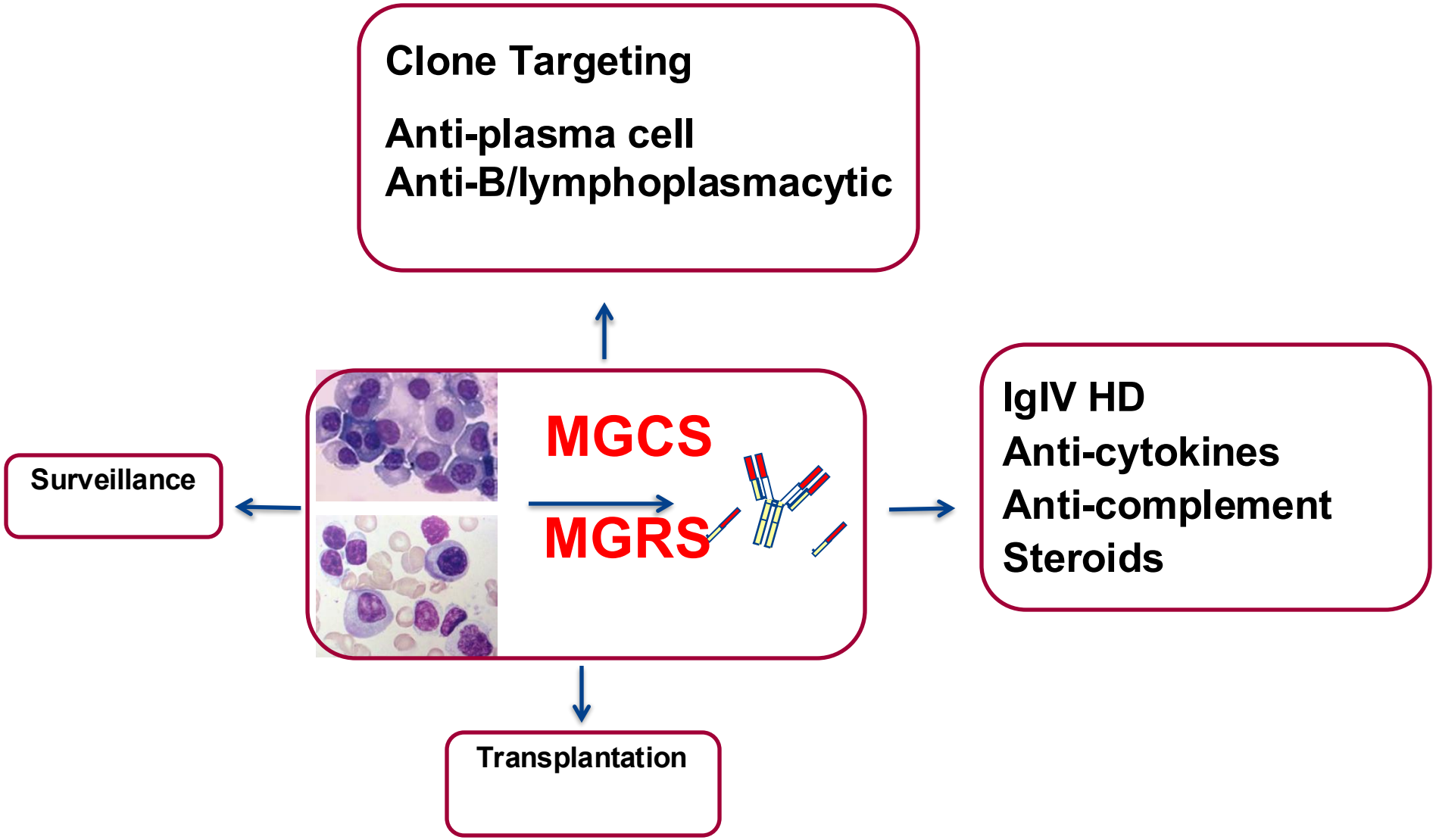
Epidemiologically related (if unknown pathophysiology)

Parallel evolution between symptoms and monoclonal Ig level

Increase frequency of MGUS in elederly

¼ of wild type TTR amyloidosis with MGUS

MGCS: therapeutic considerations



Anti-plasma cell therapy: Which one ?

Chemo « classical »

Immunomodulators/Celmod Imids

proteasome inhibitor

Ac Mo anti CD38

Immuno Therapies Anti-BCMA

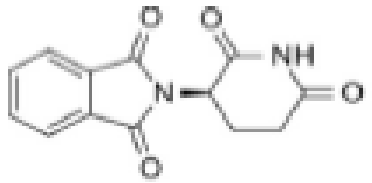
Alkylating

Melphalan
Endoxan
Bendamustine

Dexamethasone

Anthracyclines…

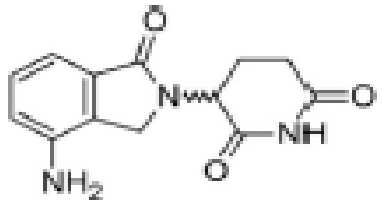
Thalidomide



(R)-thalidomide

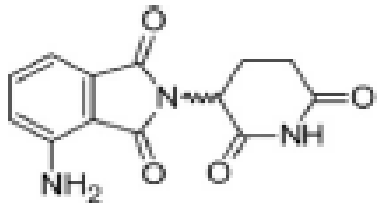
Lenalidomide

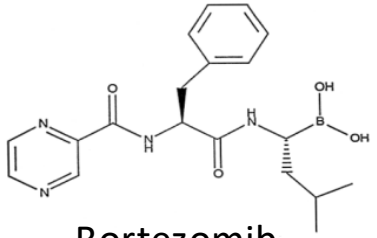
Revlimid °



Pomalidomide

Imnovid°





Bortezomib

Velcade° (sc)

Ixazomib

Ninlaro° (p.o)

Carfilzomib

Kyprolis° (IV)

Daratumumab

Darzalex°

Isatuximab

ADC Belantamab

CAR T Ide-cel Cilta-el

Ac Mo Bispe Tec., Elra.

Melflufen

NewCelmods: (Iberdomide,mezigdomide)

….Venetoclax

Selinexor

Traitements anti-plasmocyte: effets indésirables ?

Chimiothérapie « classique »

Immunomodulateurs Imids

Inhibiteur Protéasome

Ac Mo anti CD38

Immuno Thérapies Anti-BCMA

Alk

Cytopenia
Myélodysplasia

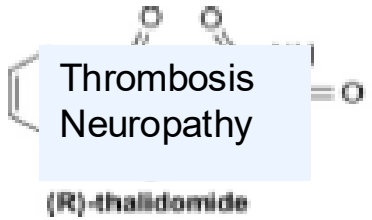
Melphalan
Endoxan
Bendamust

Dexamethasone

Anthracyclines…

Cytopenia
Cardiotoxicity

Thalidomide



(R)-thalidomide

Thrombosis
Neuropathy

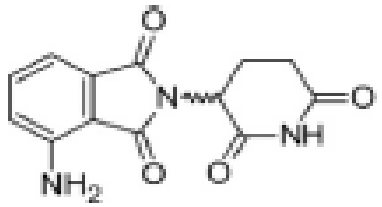
Lenalidomide

Revlimid °

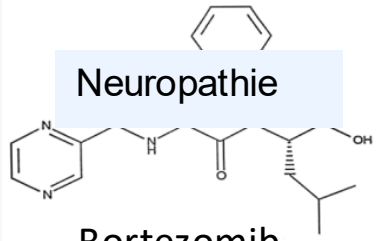
Thrombosis
Cytopenia
Renal concern

Pomalidomide

Imnovid°



Neuropathie



Bortezomib

Velcade° (sc)

Ixazomib

Ninlaro° (p.o)

Carfilzomib

Cytopenia
Cardiotoxicity

Daratumumab

Darzalex°

Infections

Isatuximab

ADC

Ocular
Thrombo
penia

CAR T anti BCMA

CRS
ICAN

Ac Mo Bispé

Infections

CRS
ICAN

Melflufen

Nouveaux Imids (Celmods: Iberdomide)

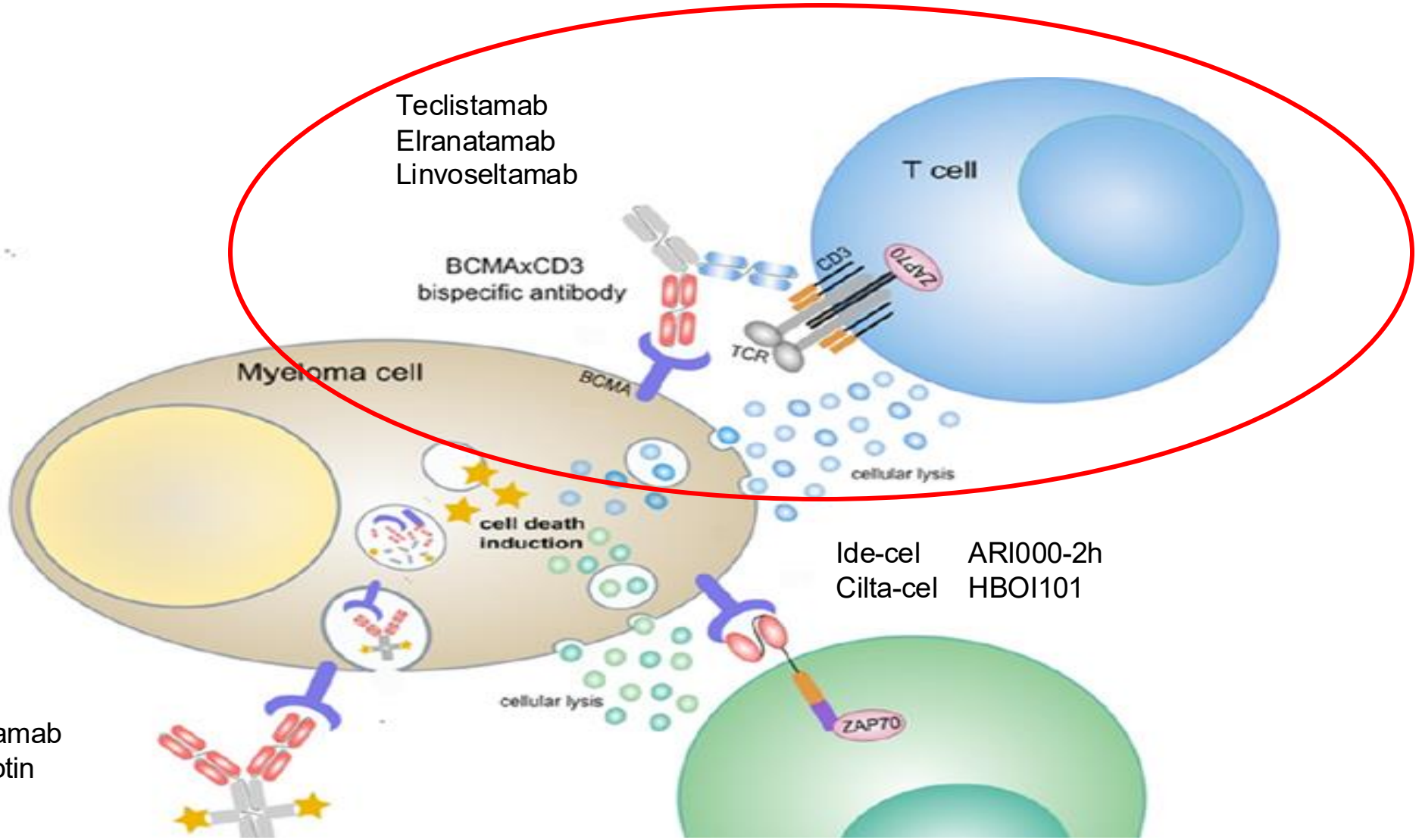
….Venetoclax

Cytopenia

Selinexor

BCMA directed anti-plasma cell mmunotherapy

Teclistamab
Elranatamab
Linvoseltamab

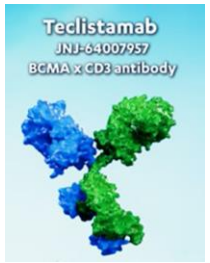


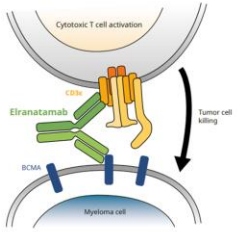
Ide-cel ARI000-2h
Cilta-cel HBOI101

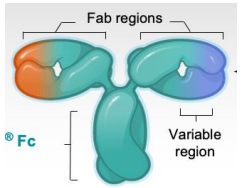
Belantamab
Mafodotin

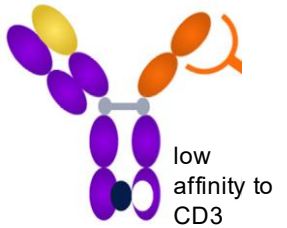
BCMA-targeting bispecific antibodies

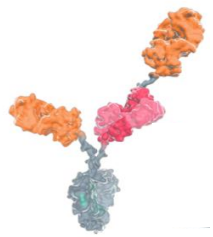
	Approved BsAb		2:1 binding	IV infusion		Trispecifics
	Teclistamab MajesTEC-1[1] (n=165)	Elranatamab Magnetismm3[2] (n=123)	Alnuctamab[5] CC-93269 (n=68)	ABBV-383[3] (n=118)	Linvoseltamab LINKER-MM1[4] (n=117)	HPN217[7] (n=62)
Phase	I/II	I/II	I/II	I	II	I
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3-Albumin
scFv	Humanized	Humanized	Humanized	Human	Human	Humanized
Ig	IgG4	IgG2a	IgG1-based	IgG4	IgG4	Small globular protein
Administration	SC	SC	SC	IV	IV	IV
# prior lines	5 (2-14)	5 (2-12)	4 (3-11)	5 (1-15)	5 (2-14)	6 (2-19)
Age	64 (33-84)	69 (44-89)	64 (36-79)	68 (35-88)	70 (37-91)	69 (38 – 85)

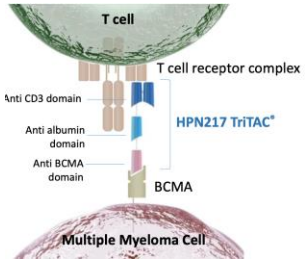












[1]Nooka et al. ASCO 2022; [2]Bahlis et al. ASH 2022; [3]Voorhees et al. IMS 2022; [4]Hans L. et al. ASCO 2023; [5]Wong et al. ASH 2019; [6]Suvannasankha et al. AACR 2023; [7]Abdallah et al. ASH 2022

anti-BCMA Bispecific antibodies in Multiple Myeloma

Teclistamab BCMA x CD3

Phase 1-2 study R/R myeloma (MajesTec-1)

n=165

ORR 63%

26.7% MRD negativity

Median PFS 11.3 months

Elranatamb BCMAxCD3

Phase 2 study R/R MM (MagnetisMM-3)

n=123

ORR 61%

35% ≧ CR

17 months PFS

Linvoseltamab BCMA x CD3

LINKER Phase 2 RRMM

N=117

ORR 48%

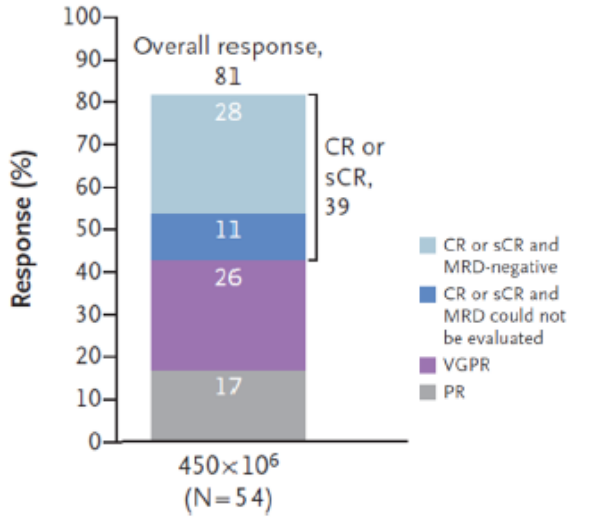
CR 21%

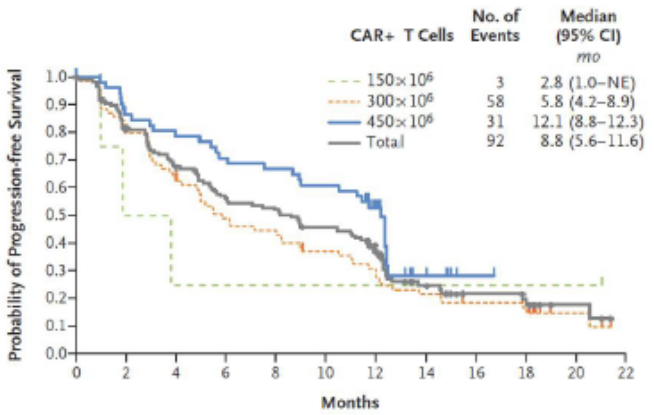
Median DOR # 28 m

+ ABBV 383……

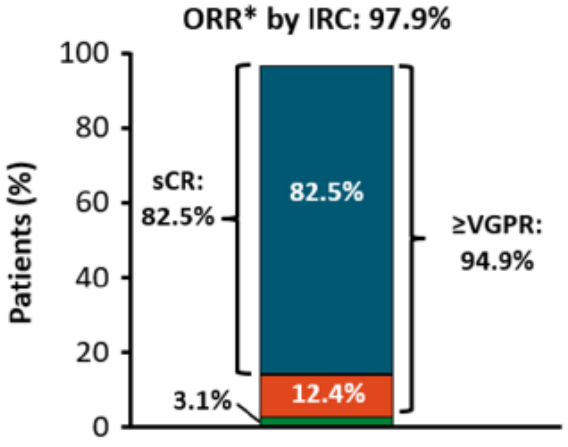
CAR-T cells in Multiple Myeloma

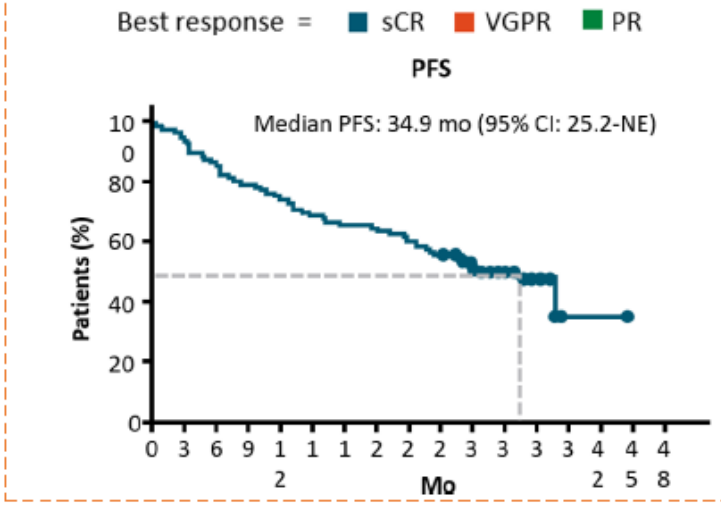
Ide-cel
Refractory: 19%
mPFS: 12 months



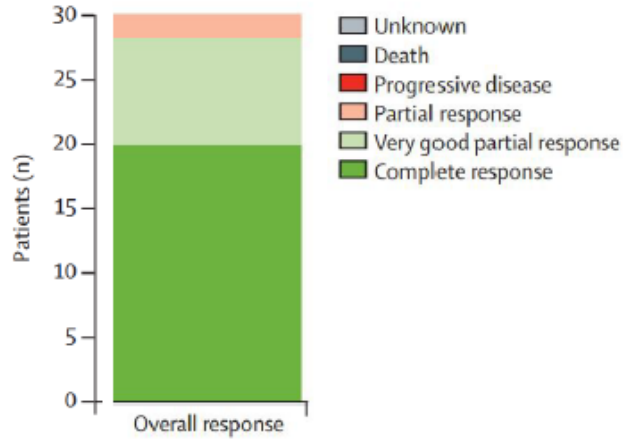


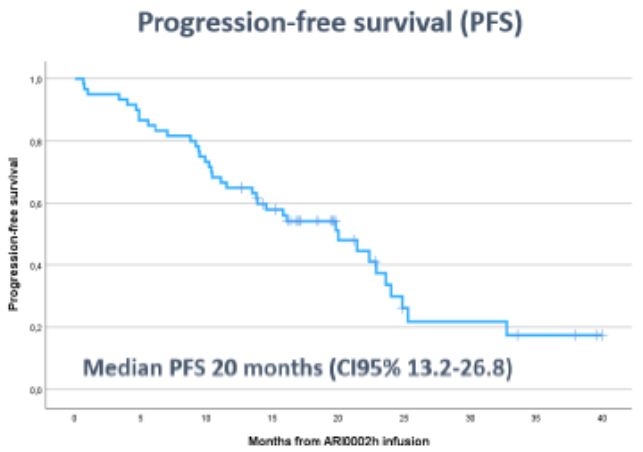
Cilta-cel
Refractory: 2%
mPFS: 35 months





ARI0002h
Refractory: 5%
mPFS: 20 months





From C. De Larrea, IKMG 2025

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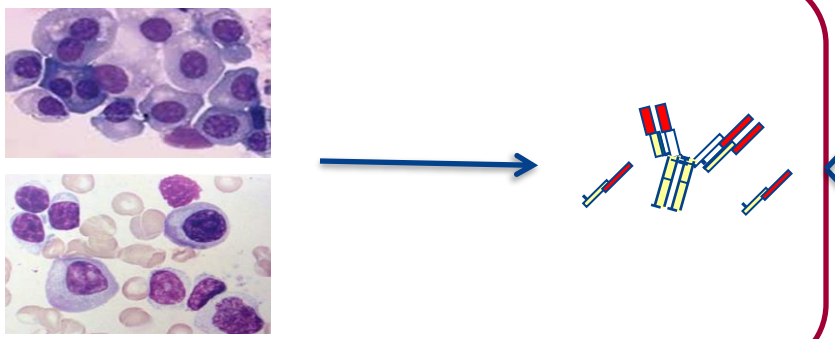
Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications

Jean-Paul Fermand, Frank Bridoux, Angela Dispenzieri, Arnaud Jaccard, Robert A. Kyle, Nelson Leung and Giampaolo Merlini



Depositis/precipitation

Organized	**Non organized**
Fibrillar	MIDD
Microtubular	L/HCDD
Cristal	PGNMID

- Autoantibody activity
- Immune complex
- Complement (CAP) interference

Cytokine overproduction

Unknown mechanisms

Pathophysiological classification of the main MGCS-related disorders

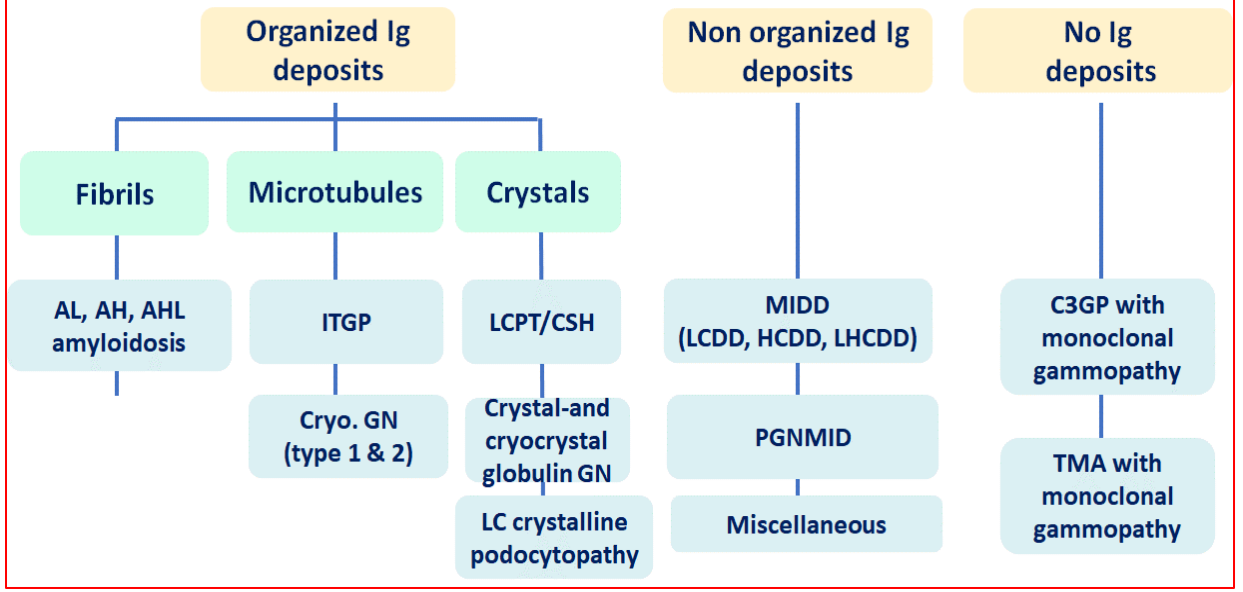
Depositis/precipitation

- Organized
  - Fibrillar: AL Amyloidosis
  - Microtubular :
    - Cryoglobulinemia
    - GOMMID
- Non organized
  - MIDD
  - PGNMID

Complement Interference

– C3 glomerulopathy

IKMG classification of MGRS-related renal diseases



How I Treat

2013

How I treat monoclonal gammopathy of renal significance (MGRS)

Jean-Paul Fermand,[1] Frank Bridoux,[2] Robert A. Kyle,[3] Efstathios Kastritis,[4] Brendan M. Weiss,[5] Mark A. Cook,[6] Mark T. Drayson,[7] Angela Dispenzieri,[3] and Nelson Leung,[3,8,9] on behalf of the International Kidney and Monoclonal Gammopathy Research Group

[1]University Hospital Center St. Louis, Paris, Ile de France, France; [2]Department of Nephrology and Transplantation, University Hospital Center Poitiers, Poitiers, France; [3]Division of Hematology, Mayo Clinic, Rochester, MN; [4]Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, School of Medicine and F... of Neph...

« the... ...ex in the abse... ...eferred to melp... [53,54] Ar... refer...

- **Clone targeted therapy :**

Plasma cell clone : bortezomib/anti-CD38 mAb-based regimens/ Venclyxto

Lymphoma clone: rituximab-based

Not identified : empiric strategy

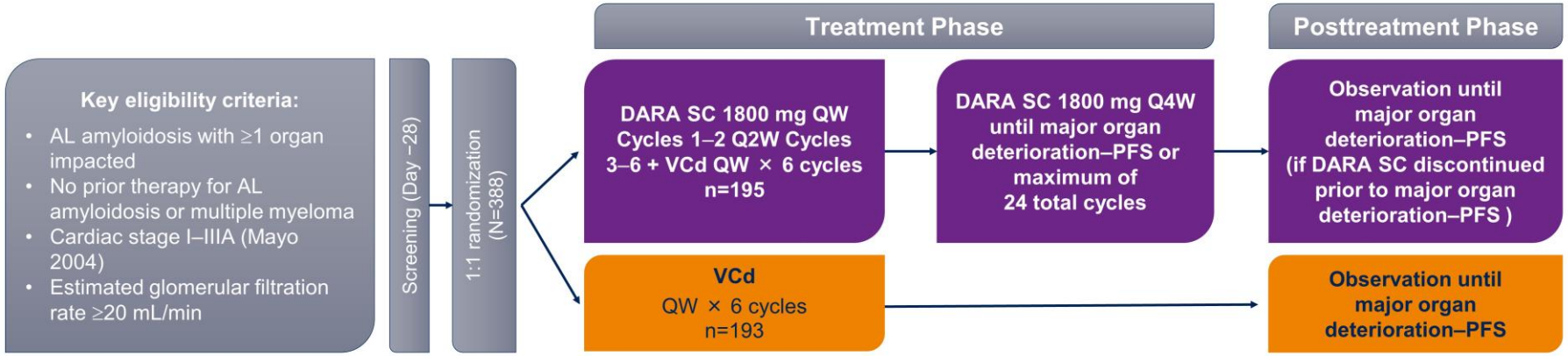
 # IgG, IgA or LC only : anti-myeloma agents

 # IgM : rituximab-based

Traitement de premiere ligne: VCD +/- Daratumumab

ANDROMEDA Study Design

- **ANDROMEDA is a randomized, open-label, active-controlled, phase 3 study of D-VCd vs VCd alone in patients with newly diagnosed AL amyloidosis**



AL, light chain; DARA, daratumumab; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; PFS, progression-free survival; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous.

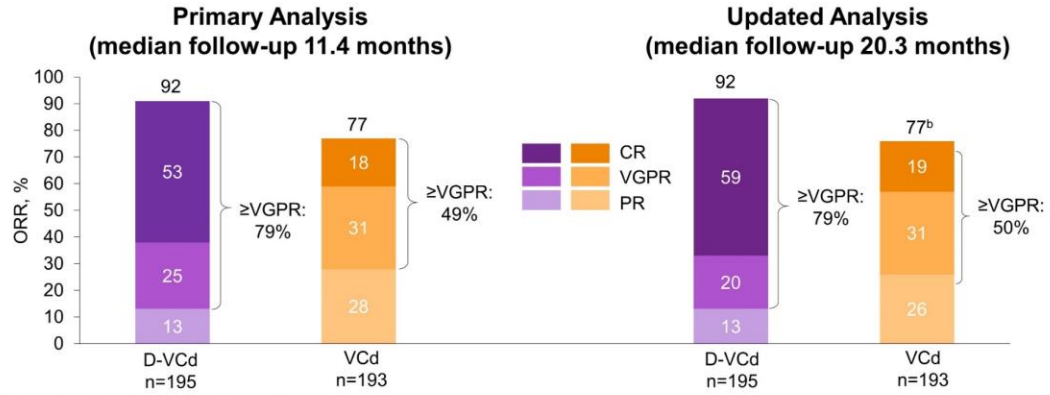
1. Comenzo RL, et al. *Leukemia* 2012;26:2317-25.

Kastritis et al., ASCO 2021

Andromeda study

Hematologic Overall Response

- **Longer follow-up confirmed the significantly higher rate of hematologic overall response (92% vs 77%) and ≥VGPR (79% vs 50%) with D-VCd vs VCd**
  - ≥VGPR: odds ratio 3.7, 95% CI 2.4–5.9, *P*<0.0001
  - Median time to ≥VGPR[a] was 0.56 months for D-VCd and 0.82 months for VCd

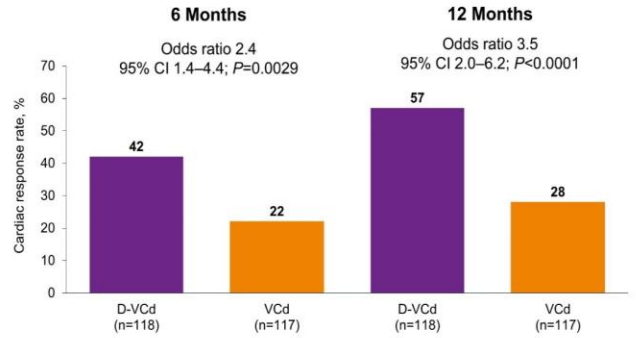


[a]Among ≥VGPR responders (D-VCd, n=154; VCd, n=97); [b]Numbers have been rounded.
CI, confidence interval; CR, complete response; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

Infections: 13% vs 9%
TAE Gr >3:
38% (1-6) + 20% (>6) vs 36%

Cardiac Response Rate at 6 and 12 Months

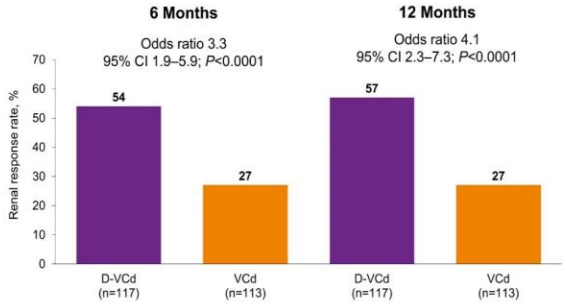
- **Cardiac response rates improved with longer follow-up, with a doubling of response when adding DARA to VCd at 12 months**



CI, confidence interval; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; DARA, daratumumab.

Renal Response Rate at 6 and 12 Months

- **Renal response rates improved with longer follow-up, with a doubling of response when adding DARA to VCd at 12 months**



CI, confidence interval; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; DARA, daratumumab.

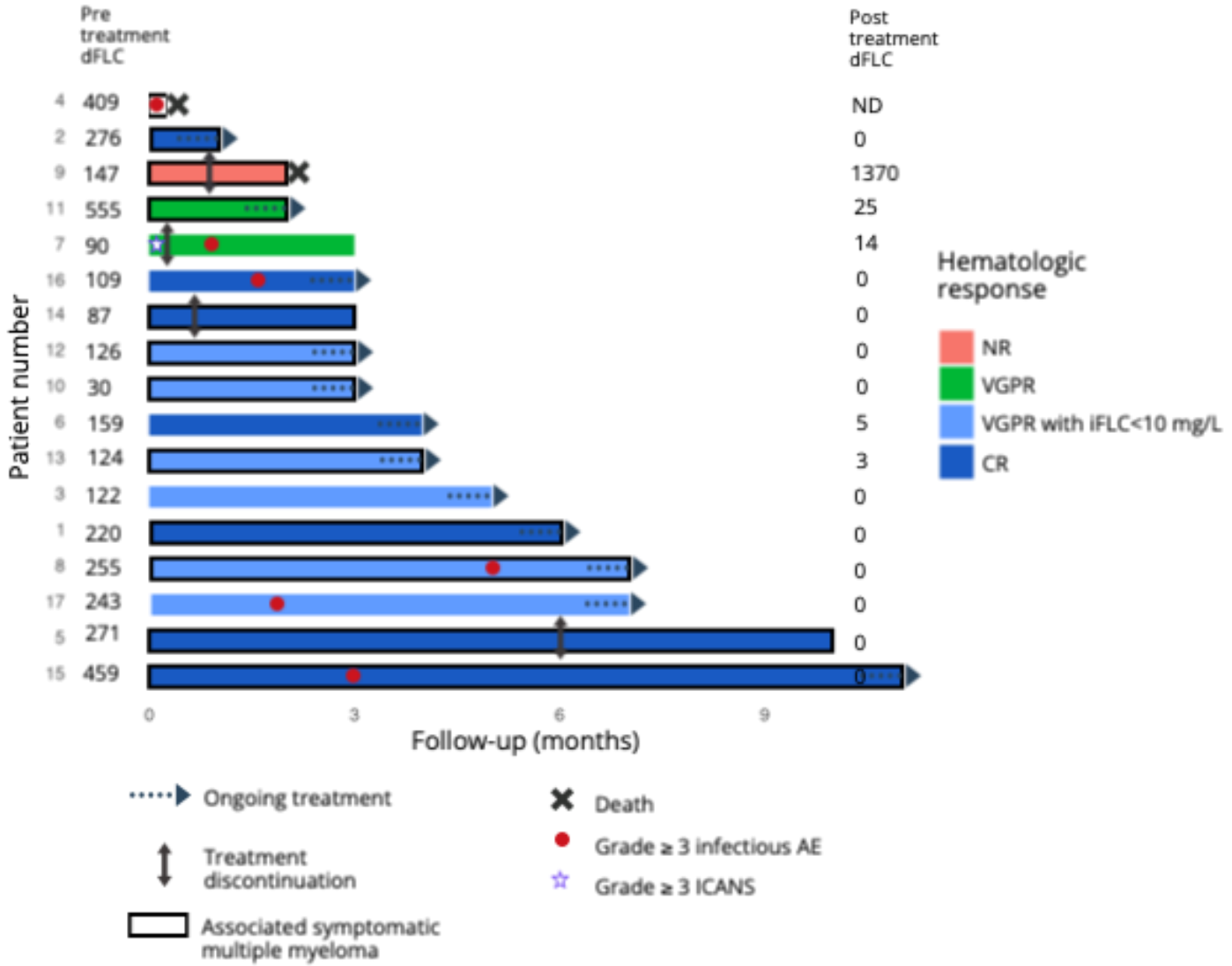
Guidelines for non-transplant chemotherapy for treatment of systemicAL amyloidosis: EHA-ISA working group

Ashutosh D. Wechalekar a , M. Teresa Cibeira b , Simon D. Gibbsc , Arnaud Jaccardd , Shaji Kumare ,Giampaolo Merlinif , Giovanni Palladini f , Vaishali Sanchorawala g , Stefan Sch€onlandh , Christopher Venneri ,Mario Boccadoro j and Efstathios Kastritis

Status	Patient		Risk assessment	Recommended treatments: First choice	Recommended treatments: Alternative
Newly diagnosed	Patients without significant neuropathy		Cardiac stage I–IIIa	Dara-CyBorD[A]	CyBorD[B] VMDex[A]
			Cardiac stage IIIb	Dose modified Dara-CyBorD[C] Single agent daratumumab[C]	Dose modified CyBorD[B] Or VMDex[B]
	Patients with significant neuropathy		All stages*	Single agent daratumumab[C] Lenalidomide-Dexamethasone[B]	MelDex[B] Carfilzomib-Dex[C] Venetoclax[C]
Relapsed	Proteasome inhibitor Naïve or prolonged response to 1st line PI		All stages*	CyBorD/VMDex[B] Ixazomib-Dex[A]	Dara-V(C)D[C]
	Proteasome Inhibitor Exposed	Daratumumab Naïve	All stages*	Single agent daratumumab[B] Dara-V(C)D [C]	Dara-RD[B] Isatuximab[C]
		IMiD Naïve	All stages*	Lenalidomide-Dexamethasone (±cyclophosphamide)[B]	IRD[B]
		Lenalidomide refractory	All stages*	Pomalidomide-Dexamethasone[B]	Bendamustine[B]
		t(11;14)	All stages*	Venetoclax[C]	Venetoclax-Bortezomib-Dexamethasone[C] MelDex[C]
IgM related AL (With lymphoid component in the marrow)			All stages*	Rituximab-Bendamustine[C] ASCT [C]	Rituximab-bort-Dex[C] Rituximab-Cyclo-Dex[C] CyBorD[C] Ibrutinib (±Ritux)[C]

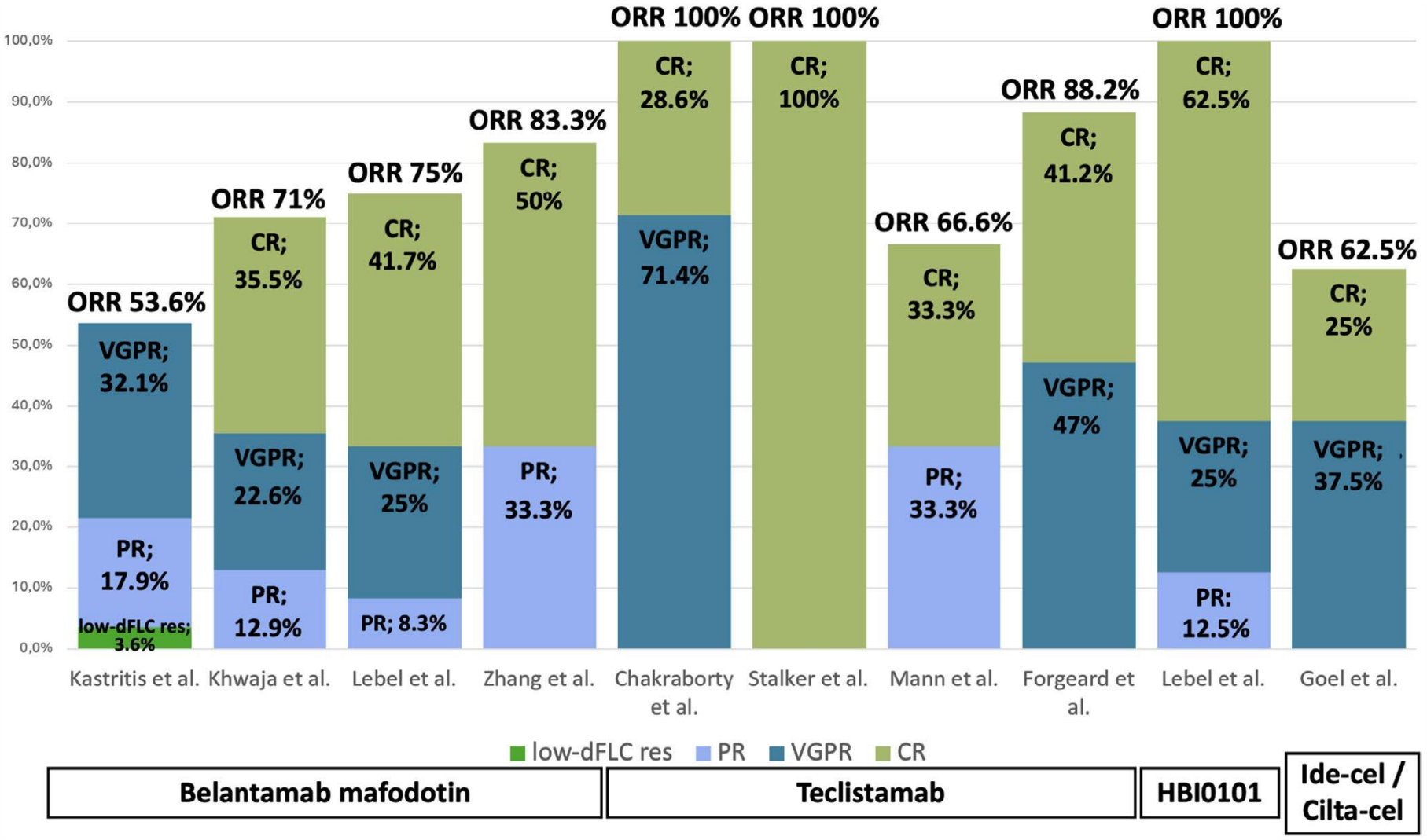
anti-BCMA Bispecific antibodies in AL amyloidosis

	n=17
Demographics	
Median age, yrs	67
Associated multiple myeloma, n(%)	10 (59)
Heart involvement, n(%)	16 (94)
Kidney involvement, n(%)	10 (59)
Median nb of prior lines of therapy	4
Prior anti-BCMA exposure, n(%)	2 (12)
Safety	
CRS, n(%)	9 (53)
ICANS, n(%)	1 (6)
Grade 3+ infections, n(%)	6 (35)



Forgeard et al, Teclistamab in relapsed or refractory AL amyloidosis, a multinational retrospective case series, Blood 202

anti-BCMA immunotherapies in AL amyloidosis



Jamroziac et al., BJH 2024

Anti-BCMA Bispecific antibodies in AL amyloidosis (Teclistamab)

	Study Type	NCT Number	Status	Conditions	Interventions	sponsor
	A Phase II Trial of Teclistamab in Participants With Previously Treated Immunoglobulin Light-chain (AL) Amyloidosis	NCT06649695	Recruiting	•AL Amyloidosis	•Drug: Teclistamab	European Myeloma Network B.V.
Teclistamab	Prospective Study of Teclistamab in the Treatment of Systemic AL Amyloidosis	NCT06699394	Recruiting	•AL Amyloidosis	•Drug: Teclistamab (Tec)	Peking University People's Hospital
	Teclistamab in Previously Treated AL Amyloidosis	NCT06935162	Recruiting	•AL Amyloidosis	•Drug: Teclistamab (Tec)	Peking Union Medical College Hospital
	Teclistamab in Newly Diagnosed Mayo Stage IIIB AL AmyloidosisNew	NCT07079423	Recruiting	•AL Amyloidosis	•Drug: Teclistamab (Tec)	Peking Union Medical College Hospital
	Teclistamab-Daratumumab in AL AmyloidosisNew	NCT07110844	Not yet recruiting	•Amyloid Light-chain Amyloidosis	•Drug: Teclistamab •Drug: Daratumumab and Hyaluronidase-fihj	Suzanne Lentzsch, MD
	The Norwegian Immunotherapy in Multiple Myeloma Study	NCT06855121	Recruiting	•Myeloma Multiple •Plasma Cell Leukemia •AL Amyloidosis	•Drug: Teclistamab •Drug: Elranatamab •Biological: Ciltacabtagene Autoleucel •2 more	St. Olavs Hospital

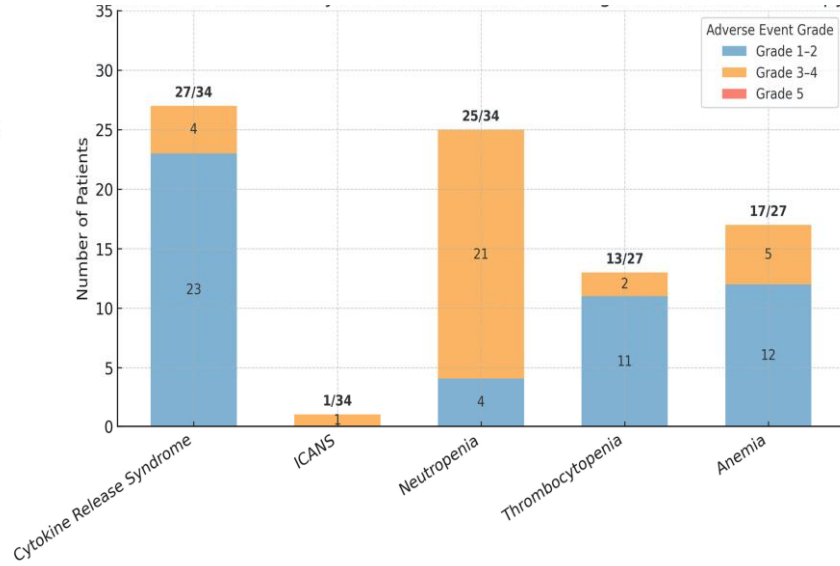
international, multicenter, open-label, single-arm phase 2 study
10 sites across 6 countries
AL pts with At least one prior line of ttt including PI and anti-CD38
Cl creatinine ≥20 mL/min
Teclistamab step up
C1 1.5 mg/Kg weekly
C2-C6 3 mg/Kg monthly (max 12 cycle)

Endpoint: hematologic complete response rate after 3 cycles.

Secondary endpoints include ORR, VGPR, duration of response, time to response, organe response
PFS, MOD-EFS…
Safety, quality of life

Anti-BCMA CAR -T cells in AL amyloidosis

Data Source	Oliver-Caldes et al., 2021 [53]	Das et al., 2023 [56]	Goel et al., 2024 [54]	Lebel et al., 2024 [55] NexiCART-1	Landau et al., 2025 [57] ** NexiCART-2 Trial Ongoing **
BCMA CAR-T Product	*ARI0002h*	Ide-cel (1) and Cilta-cel (1)	Ide-cel (6) and Cilta-cel (2)	NCX-201 (Formerly *HBI010*)	NCX-201
Number of Patient(s)	n = 1	n = 2	n = 8	n = 16	n = 7
Patient(s) Age Mean (range)	Early 60s	Patient 1 (Ide-cel)—62 Patient 2 (Cilta-cel)—33	70.5 (range 56–75)	64 (range 55–82)	66 (range 56–82)
Diagnosis and Stage	Mayo stage II AL amyloidosis with concurrent R-ISS stage II IgA-lambda MM	Patient 1—Mayo stage II Kappa AL amyloid with concurrent R-ISS stage II MM Patient 2—Mayo stage IV Lambda AL amyloidosis with concurrent MM	AL amyloidosis with concurrent MM Mayo AL amyloidosis stage I (n = 1) II (n = 3) n/a (n = 4) R-ISS stage I (n = 2) II (n = 5) III (n = 0) n/a (n = 1)	AL amyloidosis (n = 14). AL amyloidosis with concurrent MM (n = 2) Mayo staging I-II (n = 11) IIIa (n = 4) IIIb (n = 1)	AL amyloidosis Mayo staging I (n = 2) II (n = 4) IIIa (n = 1)



Lewis, Jimenez-Zepeda. Curr Oncol. 2025

Pathophysiological classification of the main MGCS-related disorders

Depositis/precipitation

- Organized
  - Fibrillar AL Amyloidosis
  - Microtubular :
    - Cryoglobulinemia
    - GOMMID
- Non organized
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  - PGNMID
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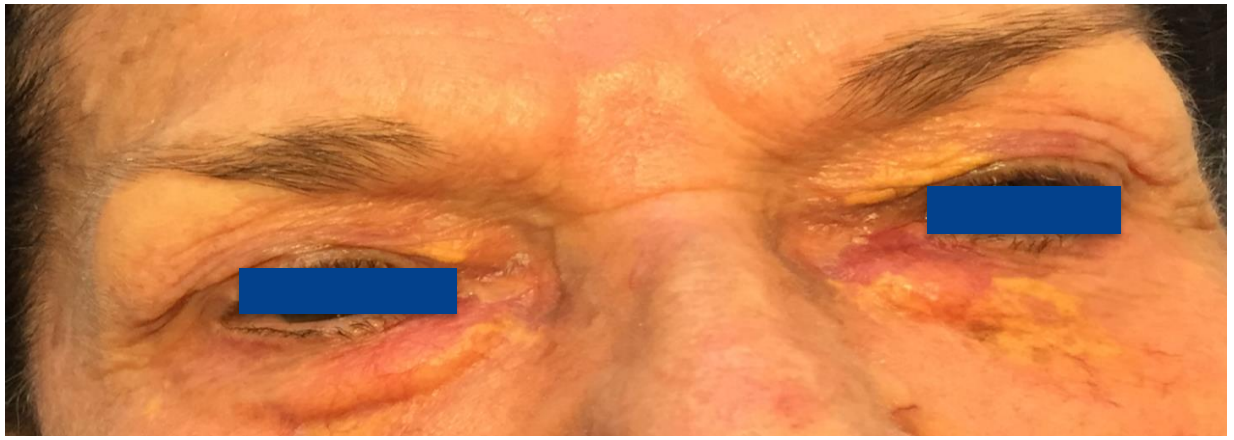
Complement Interference

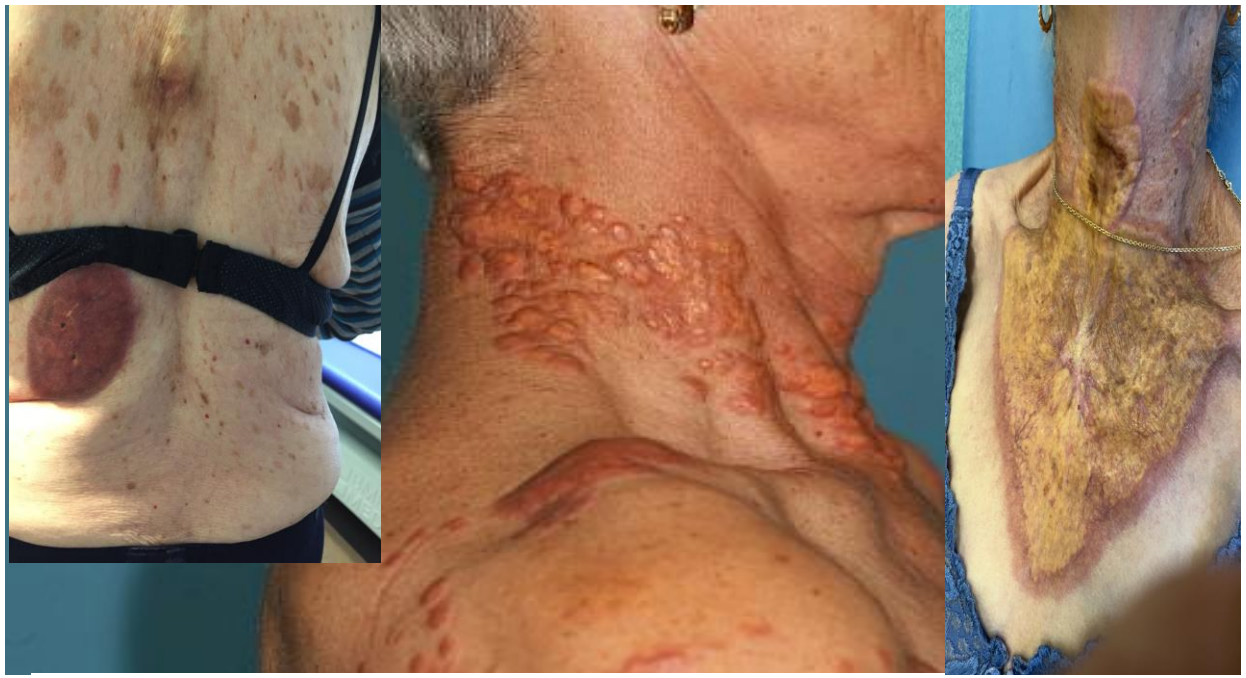
- C3 nephropathy

Auto antibody activity/Immune Complex

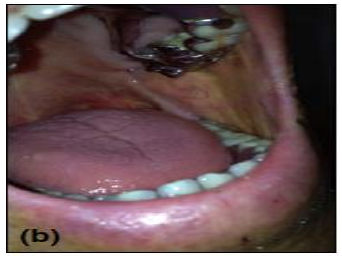
- Xanthomas, Necrobiotic xanthogranulomas
- Bullous Dermatosis
- type II Cryoglobulinemia
- Angioneurotic Œdema
- Anti-MAG neuropathy
- Cold agglutinin disease

Immune complex- related MGCS: Xanthoma/Xanthogranuloma





Normal Cholesterolemia
Hypocomplementemia +++
Frequent neutropenia



Enhanced lipid accumulation in macrophages due to antigen-antibody interaction between the MIg and various lipoproteins

Necrobiotic Xanthogranuloma

HD IVIg partially efficient

Szalat et al. Blood, 2011

Necrobiotic Xanthogranuloma: diagnosis and Treatment

Major Criteria

1.Cutaneous papules, plaques, and/or nodules, most often yellow or orange; and

2.Histopathological features demonstrating palisading granulomas with lymphoplasmacytic infiltrate and zones of necrobiosis.

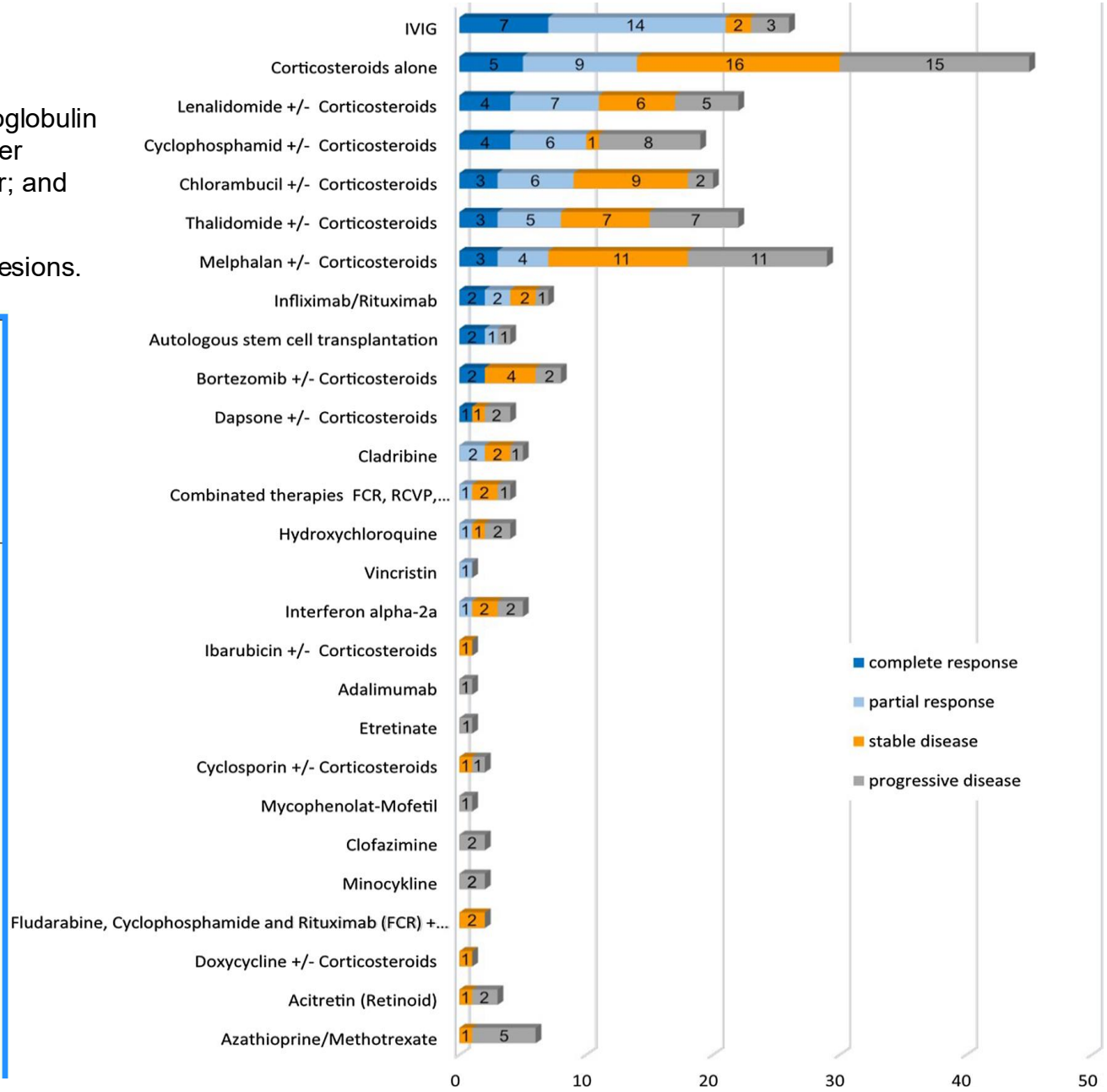
Minor Criteria

1.Paraproteinemia, most often immunoglobulin G–κ, plasma-cell dyscrasia, and/or other associated lymphoproliferative disorder; and

2.Periorbital distribution of cutaneous lesions.

Diagnostic criteria	Cases fulfilling criteria, No. (%)				
	NXG (n = 164)	Erdheim-Chester disease (n = 96)	Granuloma annulare (n = 417)	Necrobiosis lipoidica (n = 182)	Overall (N = 859)
Clinical features	161 (98.1)	91 (94.7)	397 (95.2)	165 (90.6)	814 (94.7)
Histopathologic features	164 (100)	2 (2.1)	153 (36.7)	85 (46.7)	404 (47.0)
Paraproteinemia and/or other associated lymphoproliferative disorder	129 (78.6)	3 (3.1)	25 (6.0)	3 (1.6)	160 (18.6)
Periorbital distribution of cutaneous lesions	80 (48.7)	68 (70.8)	17 (4.1)	4 (2.2)	169 (19.7)
Overall criteria	148 (90.2)	1 (1.0)	21 (5.0)	4 (2.2)	174 (20.3)

Validation of the Delphi Consensus Diagnostic Criteria for Necrobiotic Xanthogranuloma
Bassir et al., Jama dermatol., 2024



Steinhelfer et al., Orphanet Journal of Rare Diseases (2022)

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Bassir et al., Jama dermatol., 2024

•Periorbital **necrobiotic xanthogranuloma** resolved with three years of systemic lenalidomide treatment.Hofer LK, Buckley KA, Foster JA.
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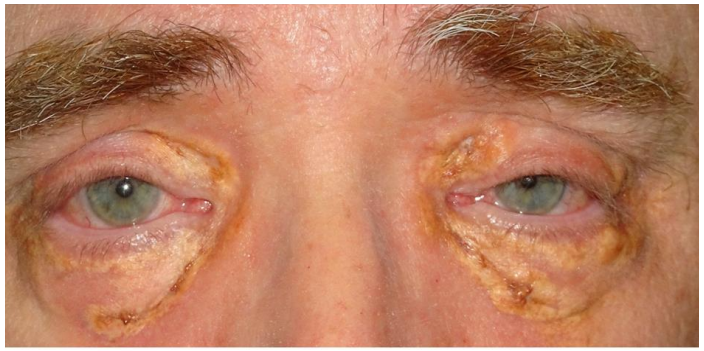
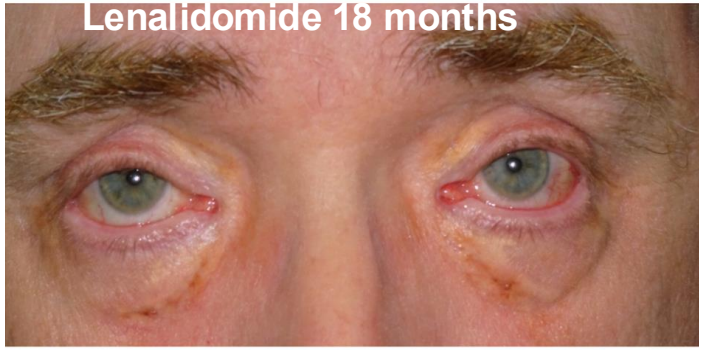
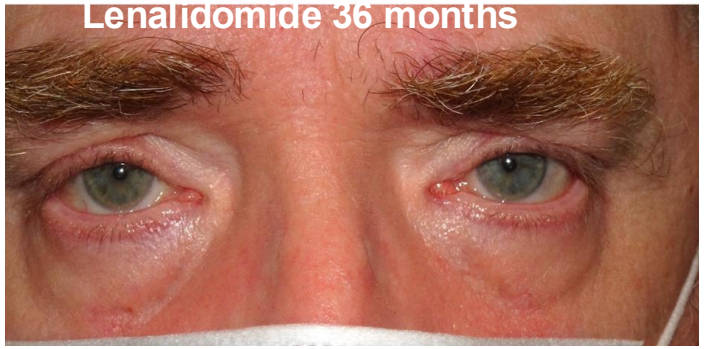
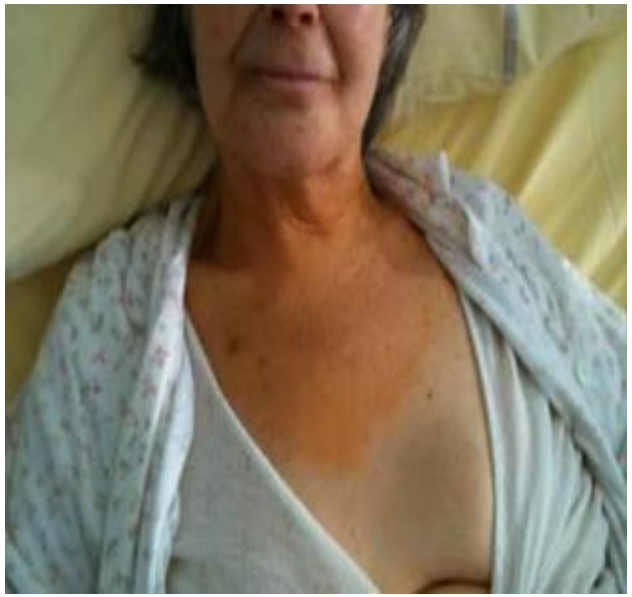
Parallele outcome between clonal proliferation and lipids depositis in xanthomas and necrobiotic xanthogranulomas associated with monoclonal Ig

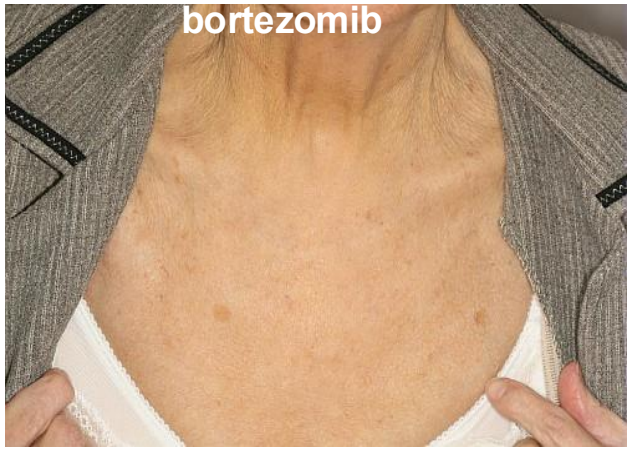
IGIV partially efficient ➔ anti-plasma cell treatment ?

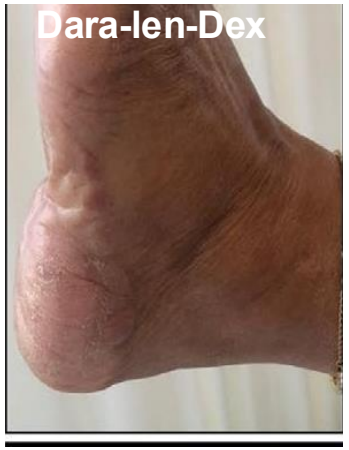












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- Angioneurotic Œdema
- Anti-MAG neuropathy
- Cold agglutinin disease

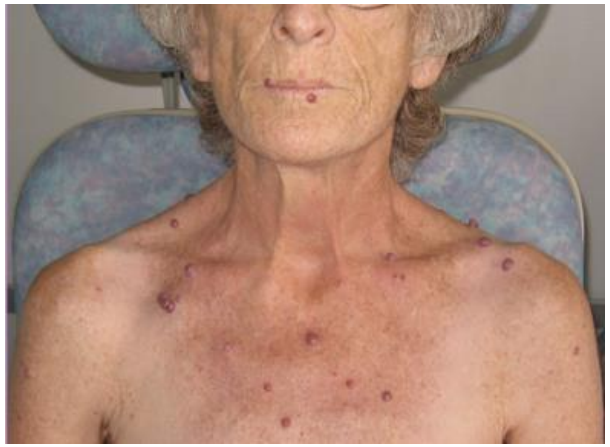
Cytokine mediated

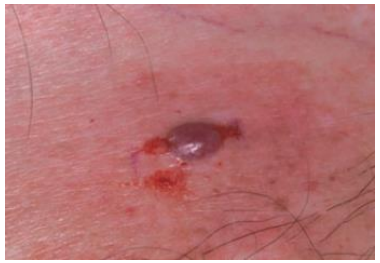
- POEMS
- AESOP
- TEMPI
- Schnitzler

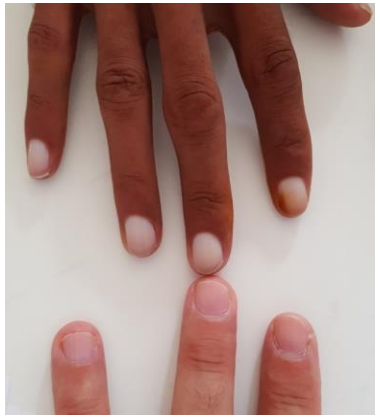
Polyneuropathy **O**rganomegaly **E**ndocrinopathy **M**onoclonal component **S**kin changes

Major Criteria	**1. Polyneuropathy (demyelinisating)** **2. Plasma cell proliferation (almost always lambda)**
Other major criteria inconstant (1)	1. Castleman 2. Osteosclerotic bone lesion **3. Increased VEGF**
Minor criteria (1)	1. Organomégaly (hepatosplenic, adénopathies) 2. œdema, pleural effusion, ascitis) 3. Endocrinopathies (surenal, thyroïd, gonade, parathyroïds, pancréatic) 4. Skin changes hyperpigmentation, hypertrichositis, glomériuloïd angioma, acrocyanosis, white nails) 5. Papillary oedema 6. Thrombocytosis/polycythemia
Others	Hippocratisme digital, weight loss, pulmonary

about 50 new cases a year in France (# 1/100 myeloma)

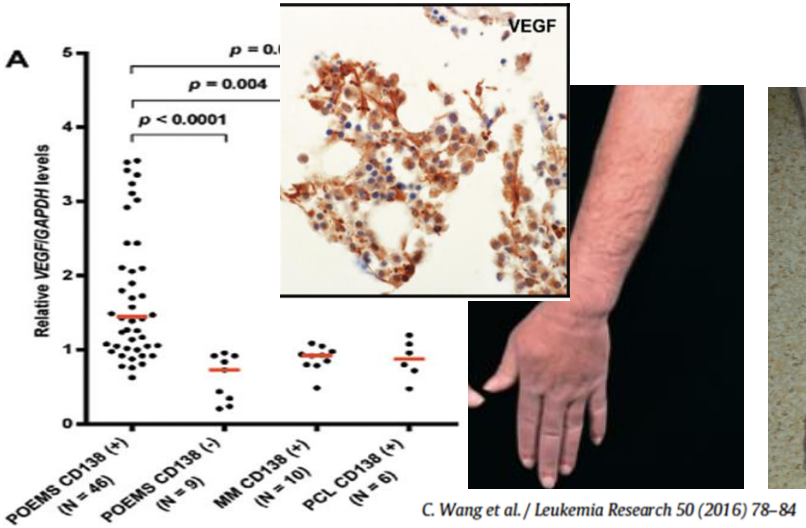


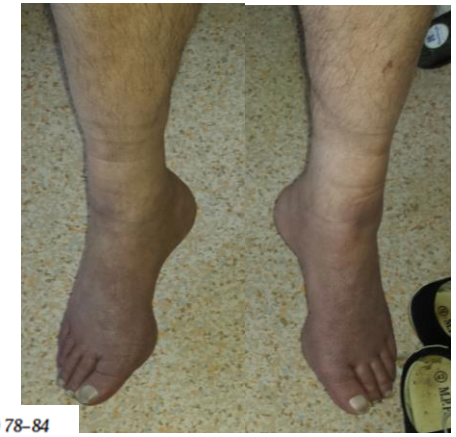




Light chain « toujours » lambda
(VI1 40*01 or VI1 44*01)

Consistant VEGF Hypersecretion





POEMS Syndrome: 2019 Update on diagnosis, risk-stratification, and management

Angela Dispenzieri

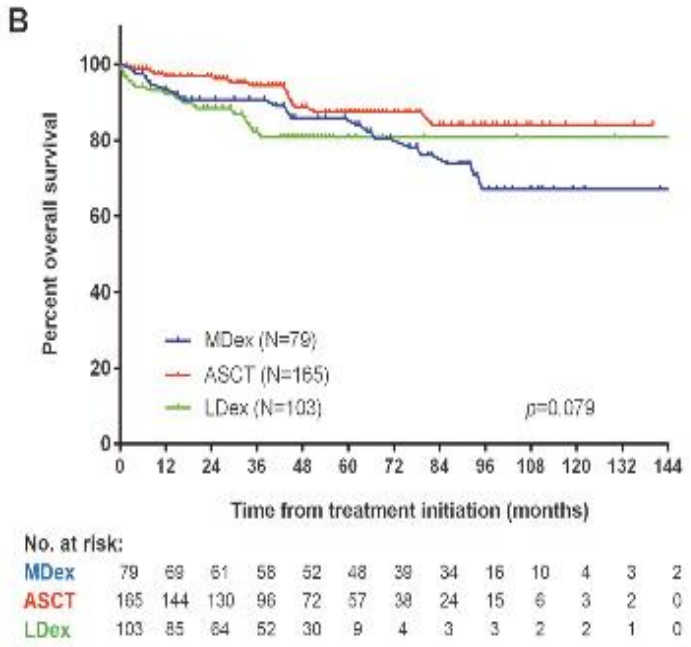
International Journal of Dermatology 2013, **52**, 1349–1356 *Bender et al., Blood 2020*

POEMS: New therapeutic stratégies

What is the best first-line treatment for POEMS syndrome: autologous transplantation, melphalan and dexamethasone, or lenalidomide and dexamethasone?

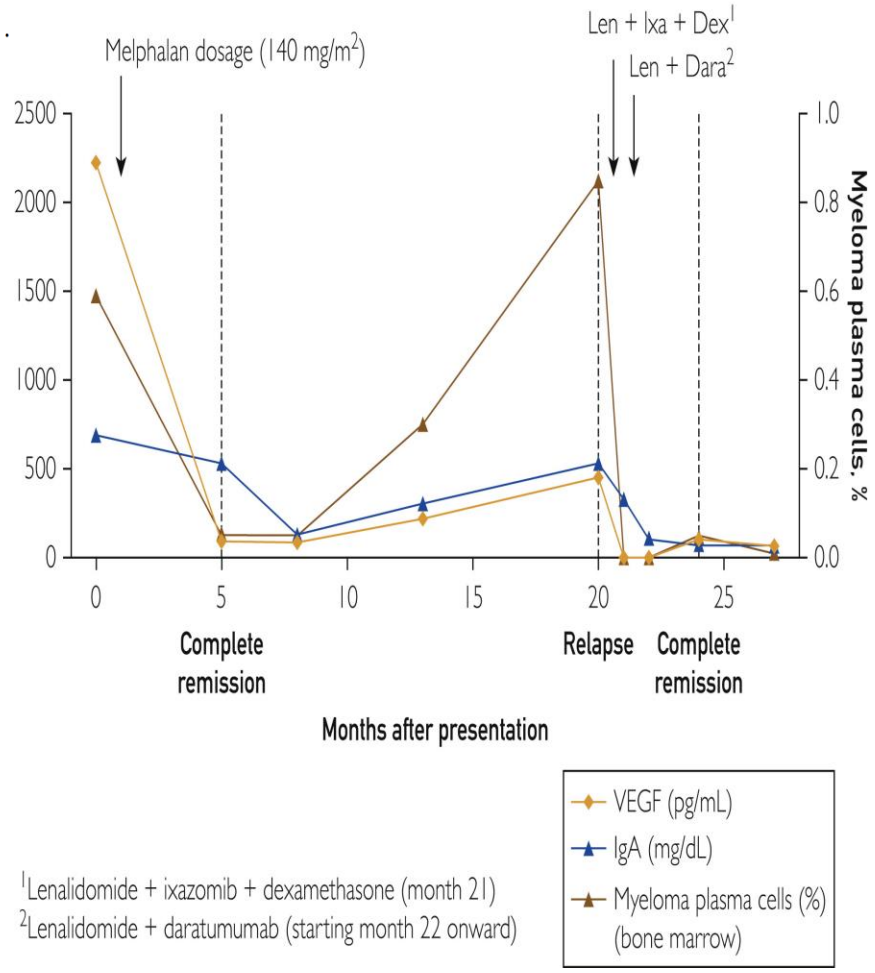
Hao Zhao[1] · Xu-fei Huang[1] · Xue-min Gao[1] · Hao Cai[1] · Lu Zhang[1] · Jun Feng[1] · Xin-xin Cao[1] · Dao-bin Zhou[1] · Jian Li[1]

- 347 patients (jan 2000-oct 2017)
- ASCT, n=165 / M-Dex, n=79 / Rev-Dex, n=103
- Median follow up: 45 m



Leukemia (2019) 33:1023–1029

Daratumumab for POEMS Syndrom

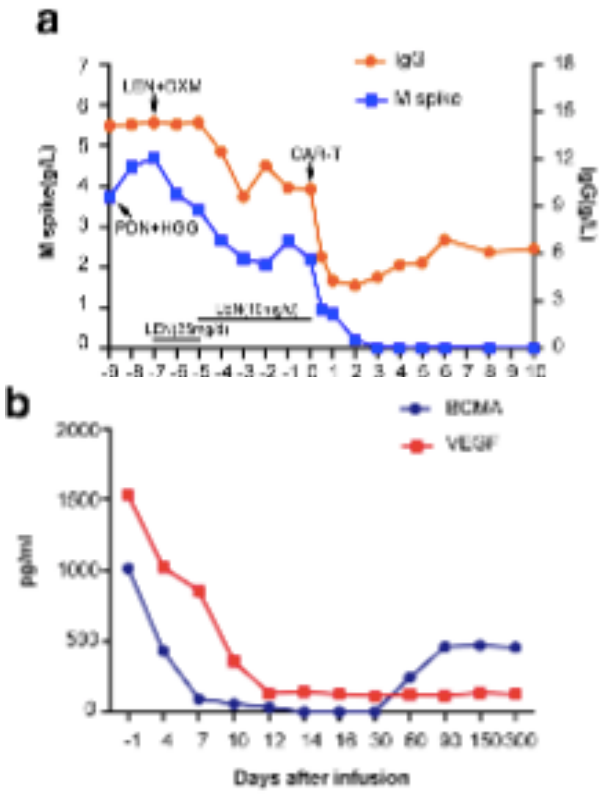


[1]Lenalidomide + ixazomib + dexamethasone (month 21)
[2]Lenalidomide + daratumumab (starting month 22 onward)

Khan et al., Mayo Clinic Proceedings 2018

CASE REPORT Open Access

Anti-BCMA CAR-T cells for treatment of plasma cell dyscrasia: case report on POEMS syndrome and multiple myeloma



Xu et al. Journal of Hematology & Oncology

Teclistamab in R/R POEMS

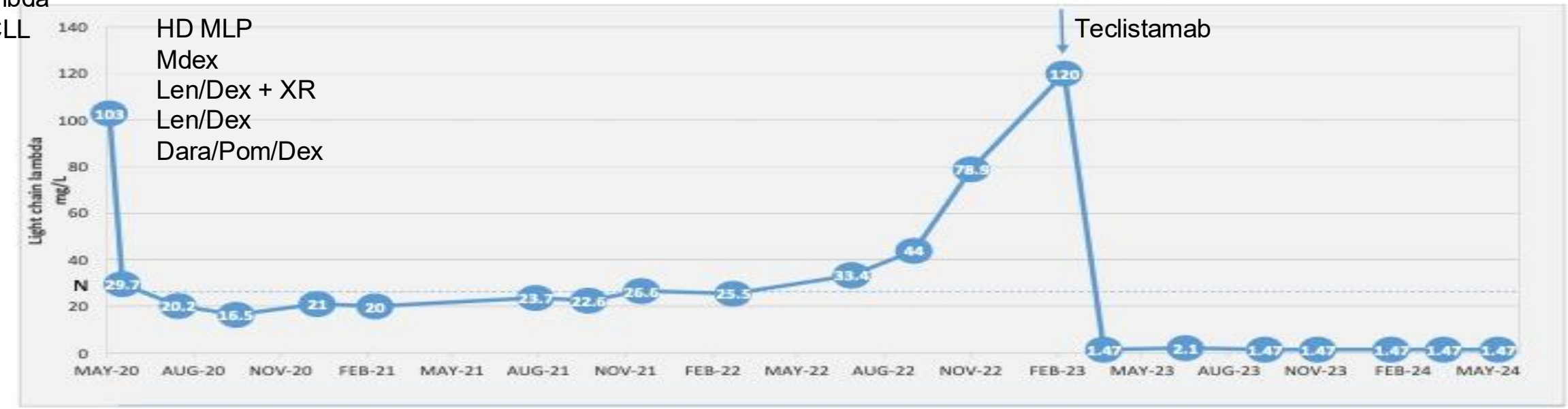
haematologica
Journal of the Ferrata Storti Foundation

From myeloma to POEMS: extending the potential of T-cell redirecting therapies

by Joselle Cook and Angela Dispenzieri

Talbot et al., Haematologica, 2025

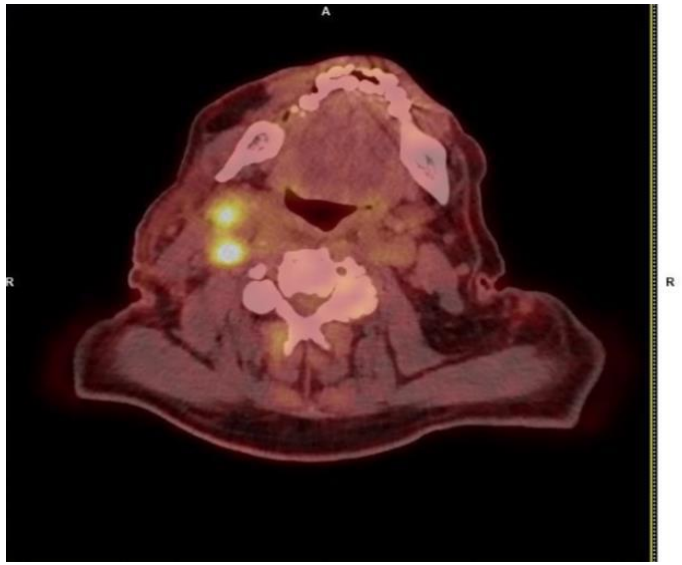
Lambda CLL

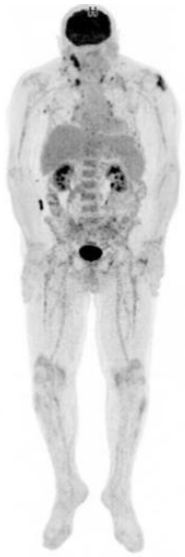


VEGF

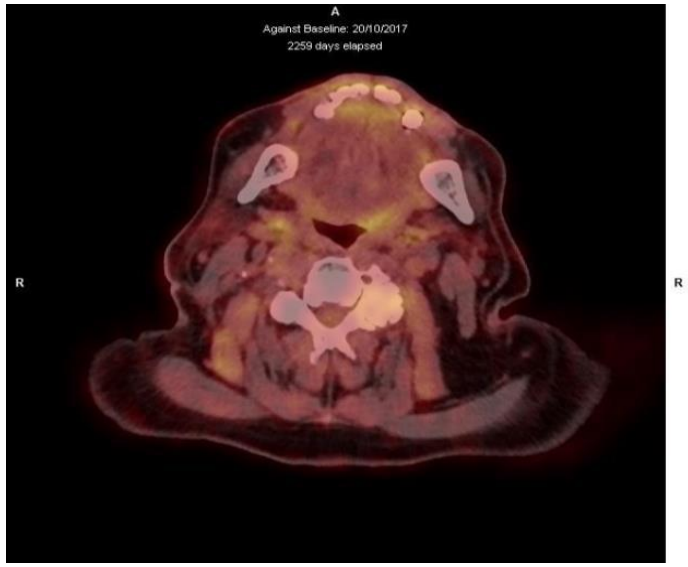
Teclistamab in R/R POEMS

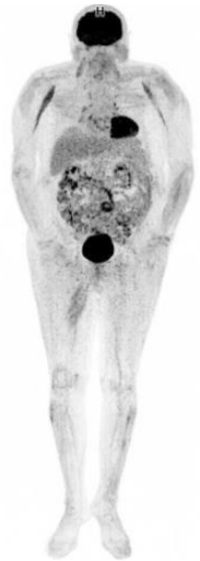
Before





After



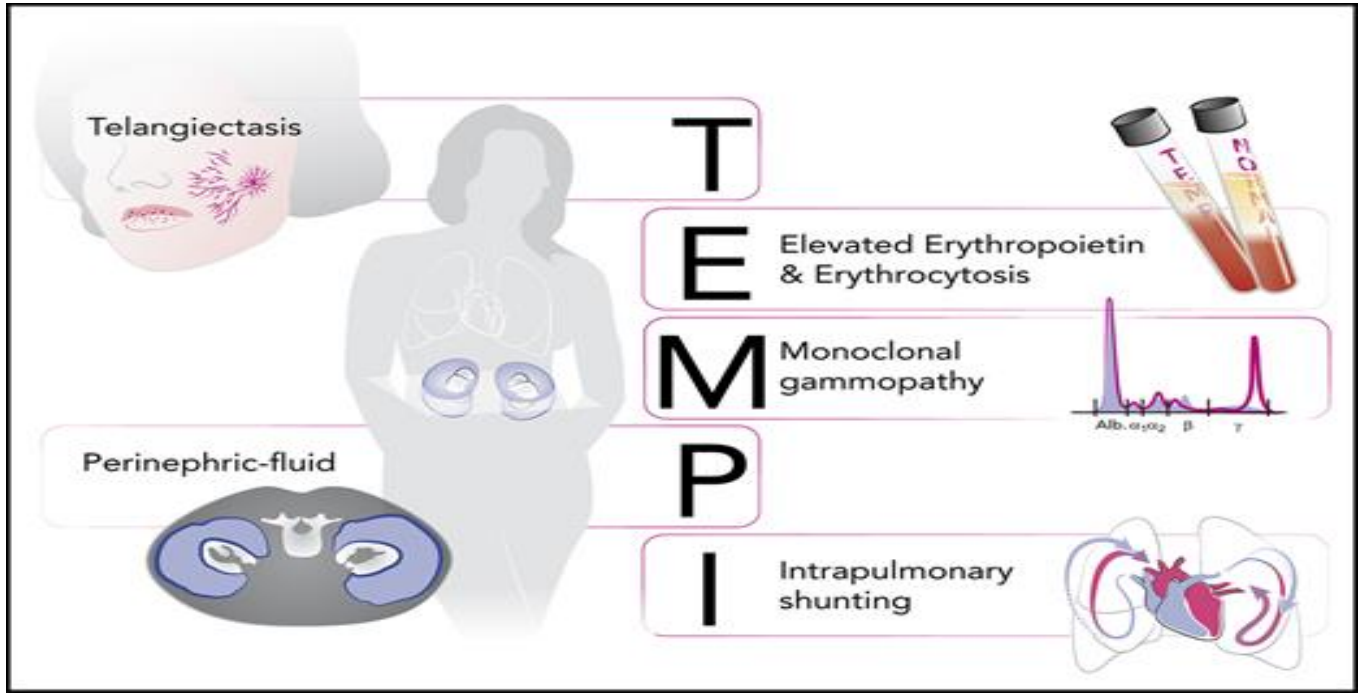


Talbot et al., Haematologica, 2025

2011:: Telangiectasie Erythrocytosis Monoclonal gammopathy Perineprehretic fluid and Intrapulmonary shu

Gender	Age	T	Etythrocytosis	EPO	M (g/dL)	P	I	BM-PCs	Others
Male	42	Yes	Yes	>5000	IgGκ (0.7)	Yes	Yes	<10%	Venous thrombosis; Ascites; Plew-effusion; Hepatic hemangioma
Female	36	Yes	Yes	>5000	IgGκ (0.7)	Yes	Yes	<10%	Venous thrombosis; Spontaneous intracranial hemorrhage
Female	39	Yes	Yes	>5000	IgGκ (0.7)	Yes	Yes	<10%	Venous thrombosis; Spontaneous intracranial hemorrhage
Male	35	NR	Yes	>500	NR	Yes	NR	NR	Hypertension; Iatrogenic iron-deficient anemia
Male	56	Yes	Yes	Increased	IgG(l)	NR	Yes	<10%	Iatrogenic iron-deficient anemia; Hemanigioma
Male	36	NR	Yes	38-86	NR	Yes	NR	NR	Ascites
Female	49	Yes	Yes	>8000	IgGκ	NR	Yes	NR	NR
Female	58	Yes	Yes	134	IgAλ (1.4)	Yes	No	10%	Hepatic hemangioma; Hypothyroidism; Hypertension; Diarrhea
Female	56	Yes	Yes	100	IgGλ (3.6)	Yes	NR	10%-15%	Diffuse pains
Male	49	Yes	Yes	78	IgAλ (0.2)	Yes	NR	NR	Ascites: Pleural effusion
Male	50	Yes	Yes	433	IgGκ	Yes	Yes	<10%	Glomerulosclerosis
Male	49	NR	Yes	5236	IgGκ (0.89)	Yes	Yes	7%-18%	Iatrogenic iron-deficient anemia; Venous thrombosis
Female	49	Yes	Yes	8144	IgGκ (1.8)	Yes	Yes	5%-10%	Iatrogenic iron-deficient anemia
Female	54	Yes	Yes	5000	IgGκ (0.8)	Yes	Yes	NR	Iatrogenic iron-deficient anemia Ascites; Bilateral pleural effusions
Female	65	Yes	Yes	>5000	IgGκ (2.3)	No	Yes	10.50%	Rheumatoid arthritis
NR	67	Yes	Yes	NR	NR	Yes	Yes	NR	Atrophie blanche
Male	46	NR	Yes	142	igAκ (1.23)	Yes	NR	40.60%	NR
Male	47	Yes	Yes	4468.3	IgGκ	Yes	NR	3.10%	Ascites
Female	65	Yes	Yes	NR	NR	Yes	Yes	NR	Tachycardia
Female	56	Yes	Yes	3656-5728	IgGκ (0.98)	Yes	Yes	20%	Right pleural effusion; Retroperitoneal fibrosis; Deep telangiectasia
Male	50	Yes	Yes	NR	IgGκ (0.91)	Yes	Yes	NR	NR
Female	70	Yes	Yes	302	IgGκ	Yes	Yes	2%	Hypertension; Pericardial effusion
Female	75	Yes	Yes	>750	IgAλ	Yes	Yes	<10%	NR
Male	47	Yes	Yes	279.76	IgGκ (3.175)	Yes	NR	16%	Hypertension
Female	52	Yes	Yes	106	IgGκ (0.71)	Yes	Yes	7%	Left pleural effusion; Abdominal effusion; Cyanosis
Male	60	Yes	Yes	676.16	igAκ (0.51)	Yes	Yes	3%	Pleural effusion: Ascites; Pelvic effusion
Male	57	Yes	Yes	741	IgGκ (0.96)	Yes	Yes	2.50%	Right pleural effusion; Ascites; Pelvic effusion: Retroperitoneal effusion
Male	66	Yes	Yes	537	IgGκ (0.983)	NR	NR	10%	Cutaneous ulcers: Polyneuropathy; Venous thrombosis: Nail clubbing
Female	63	Yes	Yes	2265	IgMλ (1.28)	Yes	Yes	15%	NR

Sykes, NEJM, 2011



Major Criteria :

Telangiectasias, elevated erythropoietin and erythrocytosis, and monoclonal gammopathy

Minor Criteria

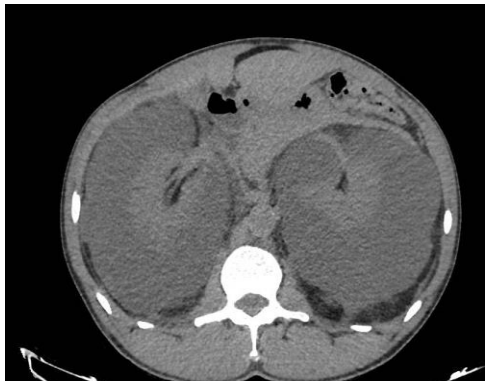
Shunt intrapulmonary, effusion

Other: thrombosis, cerebral bleeding, ascitis….PAHT, Hypothyroidy, HSF

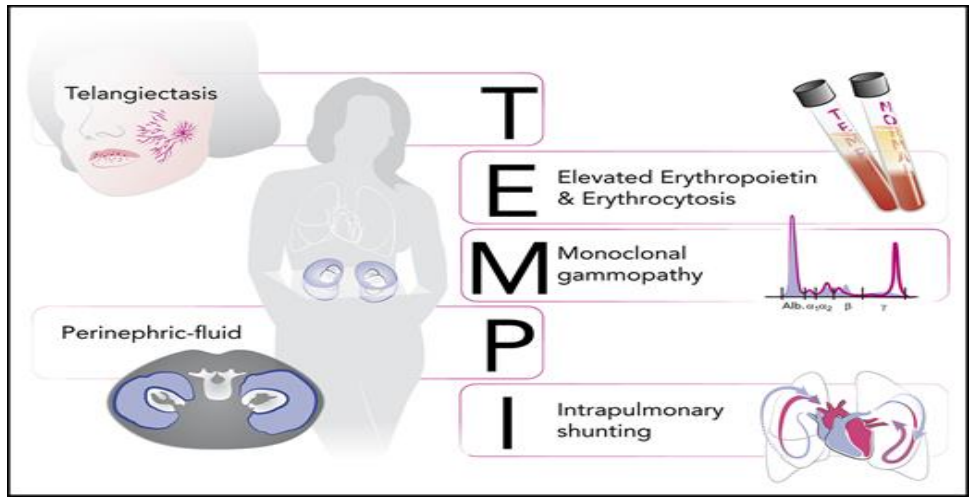
EPO: 78 to 8144 mIU/mL

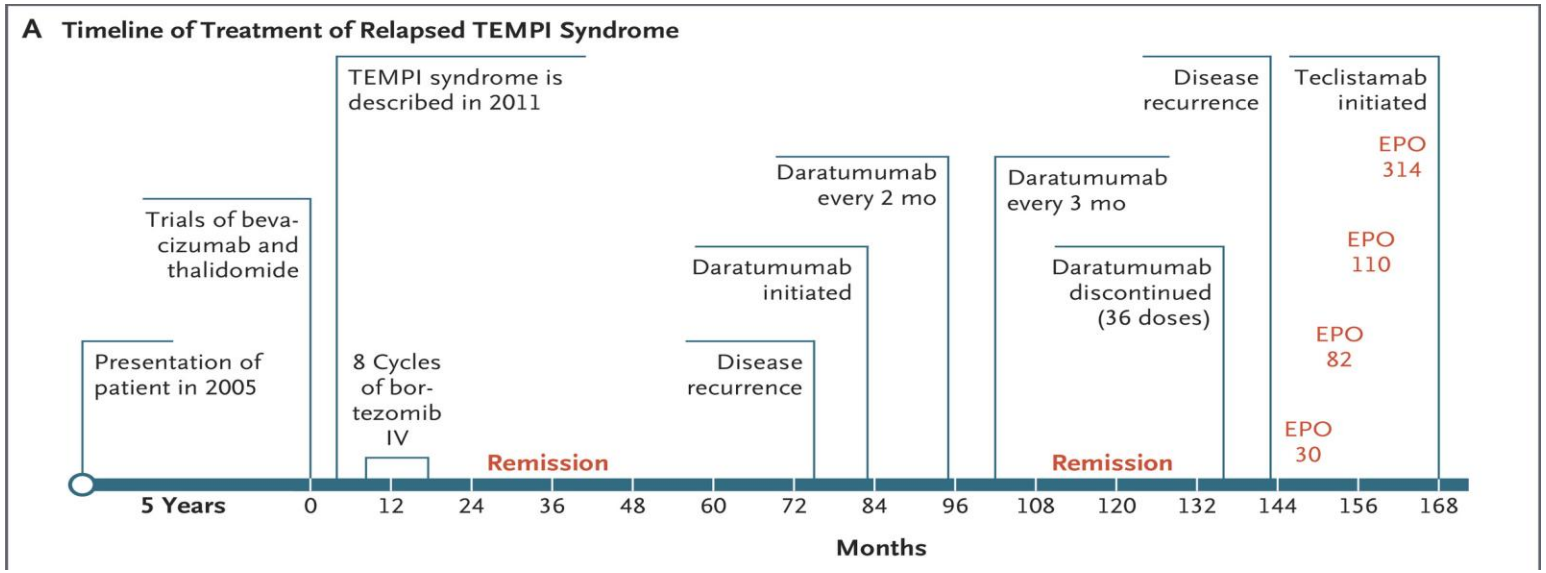
VEGF usually normal

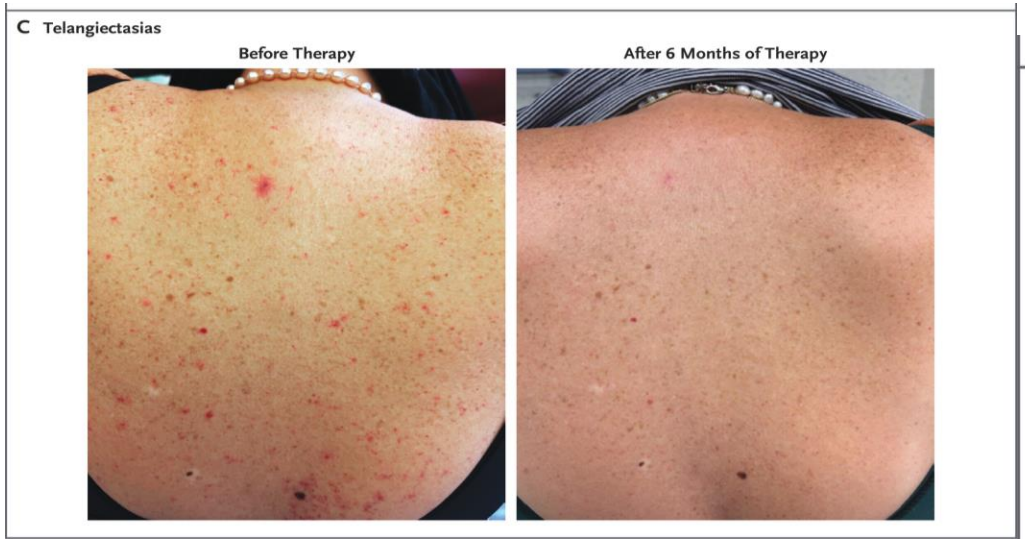
Xu et al., Frontiers Endocrinol., 2022

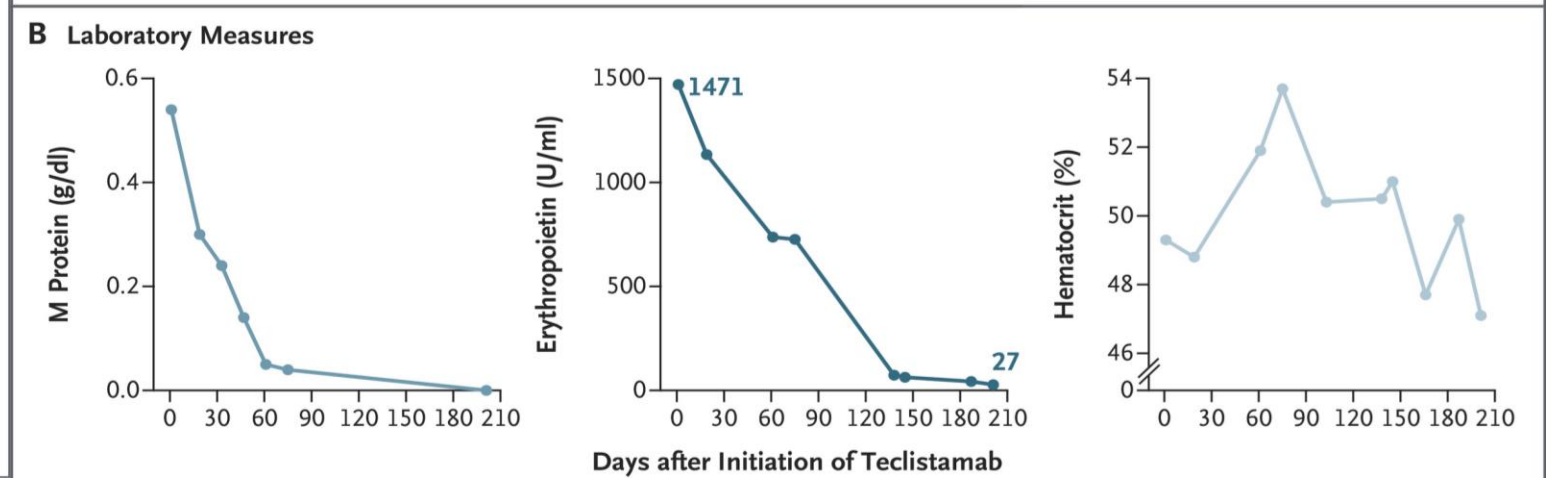


TEMPI treatment: anti-BCMA Bispecific Antibody









Sykes et al., NEJM 2024

Pathophysiological classification of the main MGCS-related disorders

Deposits/precipitation

- Organized
  - Fibrillar AL Amyloidosis
  - Microtubular :
    - Cryoglobulinemia
    - GOMMID
- Non organized
  - MIDD
  - PGNMID
- Vascular/Interstitial

Cytokine mediated

- POEMS
- TEMPI ?
- Schnitzler

Complement (CAP) Interference

- C3 nephropathy

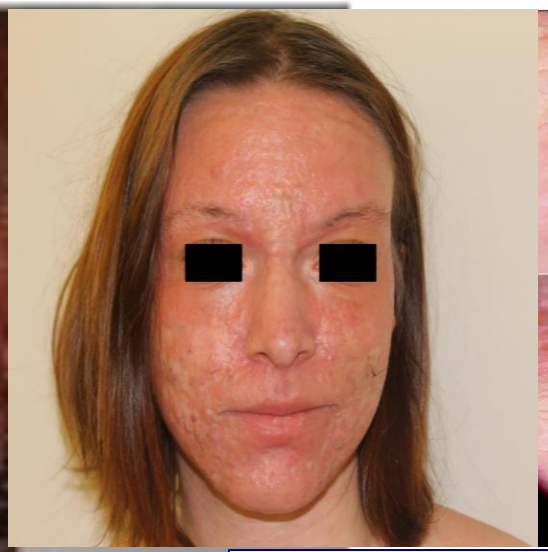
Auto antibody activity/Immune Complex

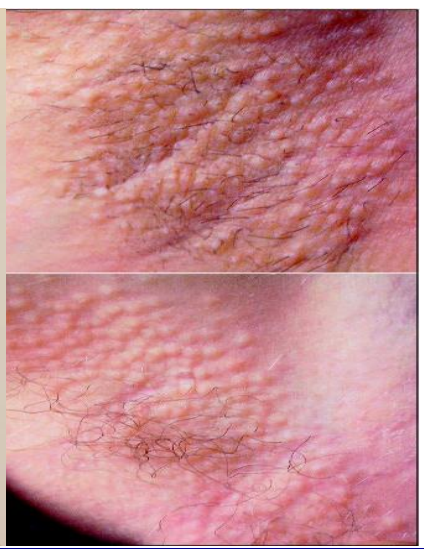
- Xanthomas, Necrobiotic xanthogranulomas
- Bullous Dermatosis
- type II Cryoglobulinemia
- Angioneurotic Œdema
- Anti-MAG neuropathy
- Cold agglutinin disease

Unknown Mechanisms

- Mucinosis, scleroedema, scleromyxoedema
- Neutrophilic Dermatosis
- Acquired Cutis Laxa
- Capillary leak syndrome

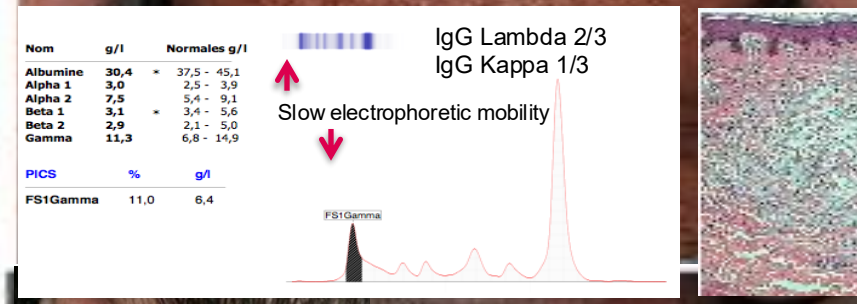
MGCS with unknow pathophysiology: Papular mucinosis and Scleromyxoedema

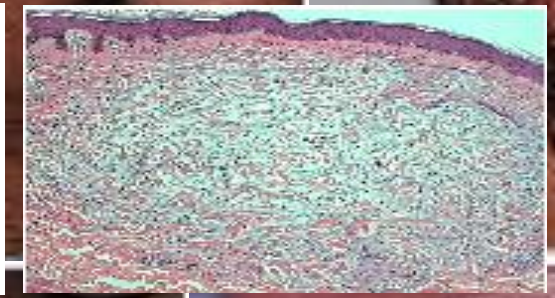


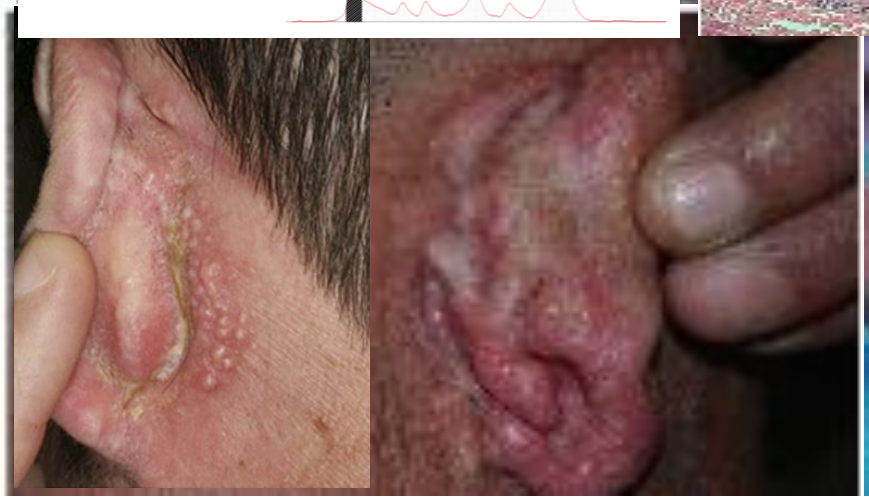


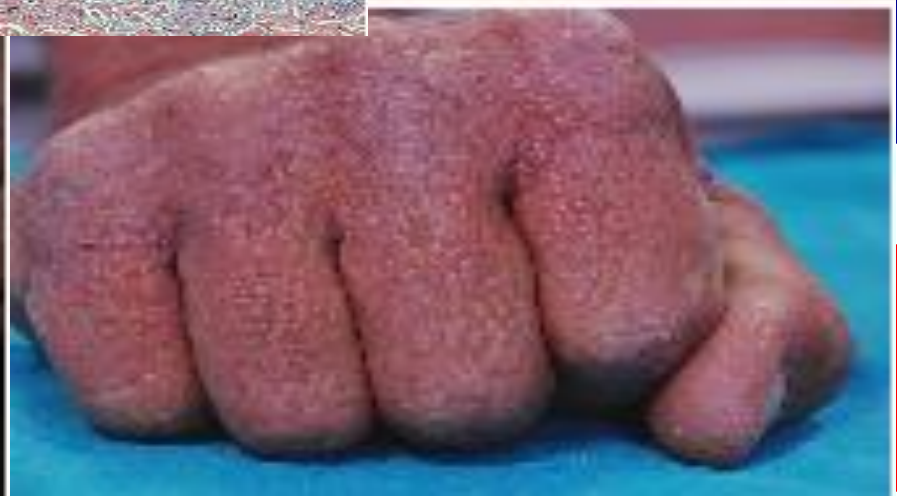
Nom	g/l		Normales g/l
Albumine	30,4	*	37,5 - 45,1
Alpha 1	3,0		2,5 - 3,9
Alpha 2	7,5		5,4 - 9,1
Beta 1	3,1	*	3,4 - 5,6
Beta 2	2,9		2,1 - 5,0
Gamma	11,3		6,8 - 14,9

PICS	%	g/l
FS1Gamma	11,0	6,4









Extra cutaneous Severe Involvement:

- Dermato Neurosyndrom (DNS)
➔ Flu-like fever, Seizure, coma….

- Cardiac failure

HD IVIg initially efficient
incomplete response, Temporary effect…
Consider anti-plasma cell Therapy +++ (lenalidomide based)

Proposed algorithm for the therapeutic management of MG associated scleromyxedema

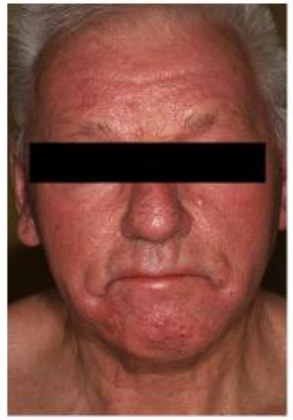
MG associated scleromyxedema

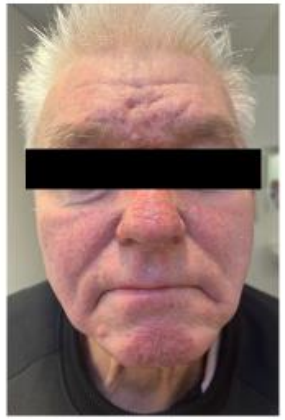
Severe/Complicated forms
(DNS, cardiac involvement)

HDIVIg
Plasma exchange
High dose steroids

HDIVIg
+
Anti plasma-cell
Therapy*

HDIVIg +/- anti plasma-cell*
maintenance





Non severe/complicated forms
(cutaneous only)

HDIVIg
+/- steroids

Clinical response

< PR
Relapse/Refractory

Anti plasma-cell
therapy*

PR
Or CR

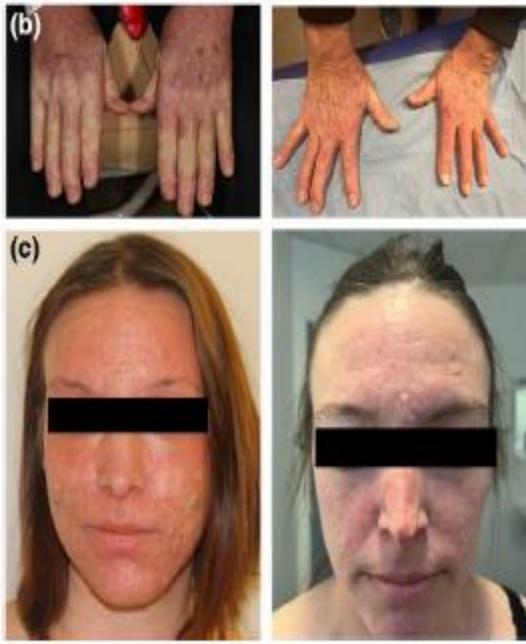
HDIVIg
maintenance

PR: partial response; CR: complete response; * Imids or Bortezomib based regimen

Mahevas T, Arnulf B et al., Blood 2021

Scleromyxoedema: anti plasma cell therapy (lenalidomide-based)

	Sex age (years)	Bone marrow (%plasma cell)	SPEP (g/L)	Extra cutaneous involvement	Previous treatments	Clinical response	Duration of remission of last treatment (months)	Anti-plasma cell treatment	Clinical response	Hematologic best response	Duration of treatment (months)	Duration of remission (months)	Stop HDIVIg	Relapse	Follow-up (months)
#1	F 76	1%	4.3 IgG lambda	Arthralgia and neurologic (DNS)	HDIVIg	CR	19	Lenalidomide dexamethasone	CR PGA = 2	VGPR	30	32	Yes	Yes	72
#2	M 79	1%	2 IgG kappa	-	HDIVIg	CR	1[illegible]	Lenalidomide dexamethasone	CR PGA = 2	CR	38	42 (on going)	Yes	No	141
#3	F 34	20%	4.6 IgG kappa	neurologic (DNS)	HDIVIg	PR	8	Lenalidomide dexamethasone	CR PGA = 2	CR	5[illegible]	63 (on going)	Yes	No	73
#4	F 34	5%	5.3 IgG lambda	Cardiac and neurologic (DNS)	HDIVIg	PR	11	Lenalidomide dexamethasone	PR PGA = 1	RP	15	15	No	Yes	77
#5	M 49	10%	6 IgG lambda	neurologic (DNS)	HDIVIg	CR	62	Lenalidomide dexamethasone	CR PGA = 2	VGPR	88	88	Yes	Yes	158
#6	F 69	6%	12 IgG kappa	hepatomegaly	MTX, cellcept, plaquenil HDIVIg	SD PR	45	VCD	PR PGA = 1	PR	5	21	No	Yes	29
#7	F 60	2%	6.4 IgG Lambda	-	HDIVIg	PR	6	Daratumumab lenalidomide dexamethasone	CR PGA = 2	VGPR	9 (on going)	9 (on going)	No	No	92
#8	F 40	1%	- IgG lambda	DNS	HDIVIg, thalidomide	CR SD	4	Daratumumab lenalidomide dexamethasone	CR PGA = 2	VGPR	4 (on going)	4 (on going)	No	No	37



Theves et al., JEADV, 2024

MGCS: Therapeutic considerations

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MGRS/other organ damage, severe/life threatning complication
Adapted to the nature of the clone and renal failure

- **Plasmacytic**: Bort-based (MGRS), Len-based, local irradiation, high dose MLP, anti-CD38 ? T cell engager ?

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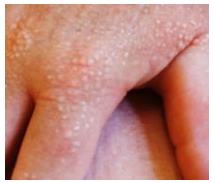
Cutaneous only, pauci symptomatic MGCS
No treatment of the B cell clone if no clear link with the Mig (reference center, MDM)

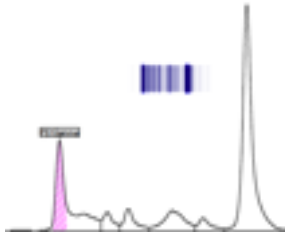
blood®
Regular Article

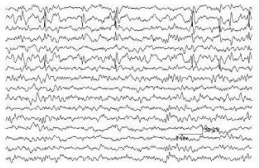
CLINICAL TRIALS AND OBSERVATIONS

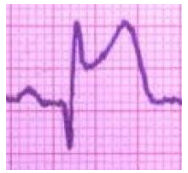
Plasma cell–directed therapies in monoclonal gammopathy–associated scleromyxedema

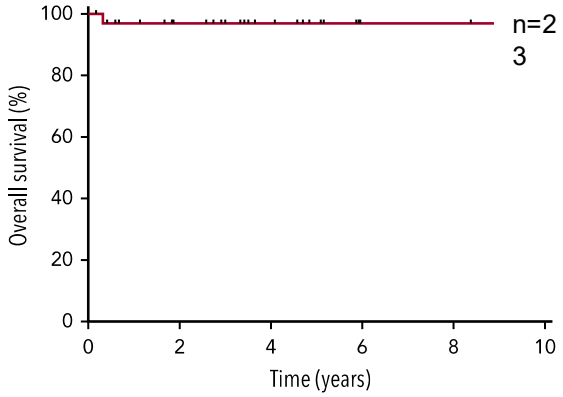
Thibault Mahévas,[1] Bertrand Arnulf,[2] Jean-David Bouaziz,[3] Cristina Bulai Livideanu,[4] Amélie Osio,[5] Amandine Servy,[6-8] Bernard Cribier,[9] Bruno Sassolas,[10] Marie Jachiet,[3] Laurence Michel,[11] Pierre Aucouturier,[12] Dan Lipsker,[9] Camille Frances,[13] Emilie Sbidian,[6-8] Michel Rybojad,[3] Vincent Descamps,[14] Michel D'Incan,[15] Philippe Humbert,[16] Marie Beylot-Barry,[17] Thierry Passeron,[18,19] Claire de Moreuil,[10,20] Ruba Y. Taha,[21] Olivier Hermine,[22] Alain Dupuy,[23] Sébastien Barbarot,[24] Sébastien Debarbieux,[25] Olivier Carpentier,[26] Fanny Brault,[27] Jean-Luc Schmutz,[27] Domitille Thomas-Beaulieu,[28] Philippe Modiano,[29] Charles Zarnitsky,[30] François Lifermann,[31] Emilie Baubion,[32] Nicolas Limal,[33] Fabien Le Bras,[34] Marie Le Moigne,[35] Marie Tauber,[4] Alexis Talbot,[2] Romain Prud'homme,[36] Sandy Peltier,[11] Adèle De Masson,[3] Maxime Battistella,[5,11] Martine Bagot,[3] Arsène Mékinian,[1] and Olivier Fain,[1] on behalf of Etude des Maladies Systémiques en Dermatologie, Société Nationale de Médecine Interne, French Network of Dysimmune Disorders Associated with Hemopathies, and Groupe d'Etude des Dermatoses Associées à Une Immunoglobuline Monoclonale

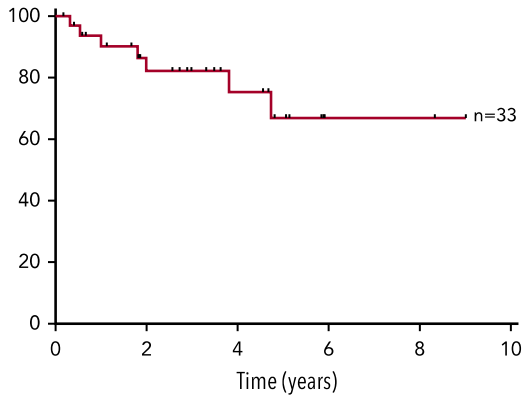












	Results
Patients	
Sex ratio (M/F)	1.06 (17/16)
Age, mean ± SD, y	55.4 ± 13.6
Follow-up, mean ± SD, y	4.3 ± 2.39
Death	1 (3)
Cutaneous manifestations	33 (100)
Papular eruption/pruritus	33 (100)/18 (54)
Sclerodermoid eruption/leonine facies	30 (90)/13 (39)
Depilation/alopecia	10/22 (45)/4 (12)
Purpura/livedo racemosa/cutis laxa–like syndrome/skin necrosis	1 (3)/3 (9)/3 (9)/1 (3)
Extracutaneous manifestations	22 (67)
Hematological involvement	33 (100)
MG/MGUS/hematologic malignancy	33 (100)/30 (91)/4 (12)
Neurological involvement	18 (54)
Central nervous system involvement/DNS	9 (27)/6 (18)
Carpal tunnel syndrome	12 (36)
Sensitive polyneuropathy	1 (3)
Cardiac and vascular involvement	5 (15)
Ischemic/mucinous cardiopathy	3 (9)/2 (6)
Arterial hypertension	11 (33)
Pulmonary involvement	3 (9)
Obstructive syndrome	3 (9)
Interstitial pneumopathy	1 (3)
Musculoskeletal involvement	9 (27)
Myositis/myalgia	2 (6)/2 (6)
Arthralgia/arthritis	9 (27)/1 (3)
Gastrointestinal involvement (dysphagia)	2 (6)
Head and neck involvement (dysphonia)	1 (3)
Ophthalmic (retrobulbar optic neuritis)	1 (3)
Laboratory findings	
MG/biclonal gammopathy	33 (100)/1 (3)
Serum IgG level, g/L	4.5 ± 3
κ or λ light chain in monoclonal Ig	10/33 (29) or 24/33 (73)
Skin histological findings	33 (100)
Dermal mucinosis/fibroblast proliferation/fibrosis	33 (100)
Granuloma annulare form: histiocytic infiltrate (CD68⁺ and CD163⁺)	10 (27)

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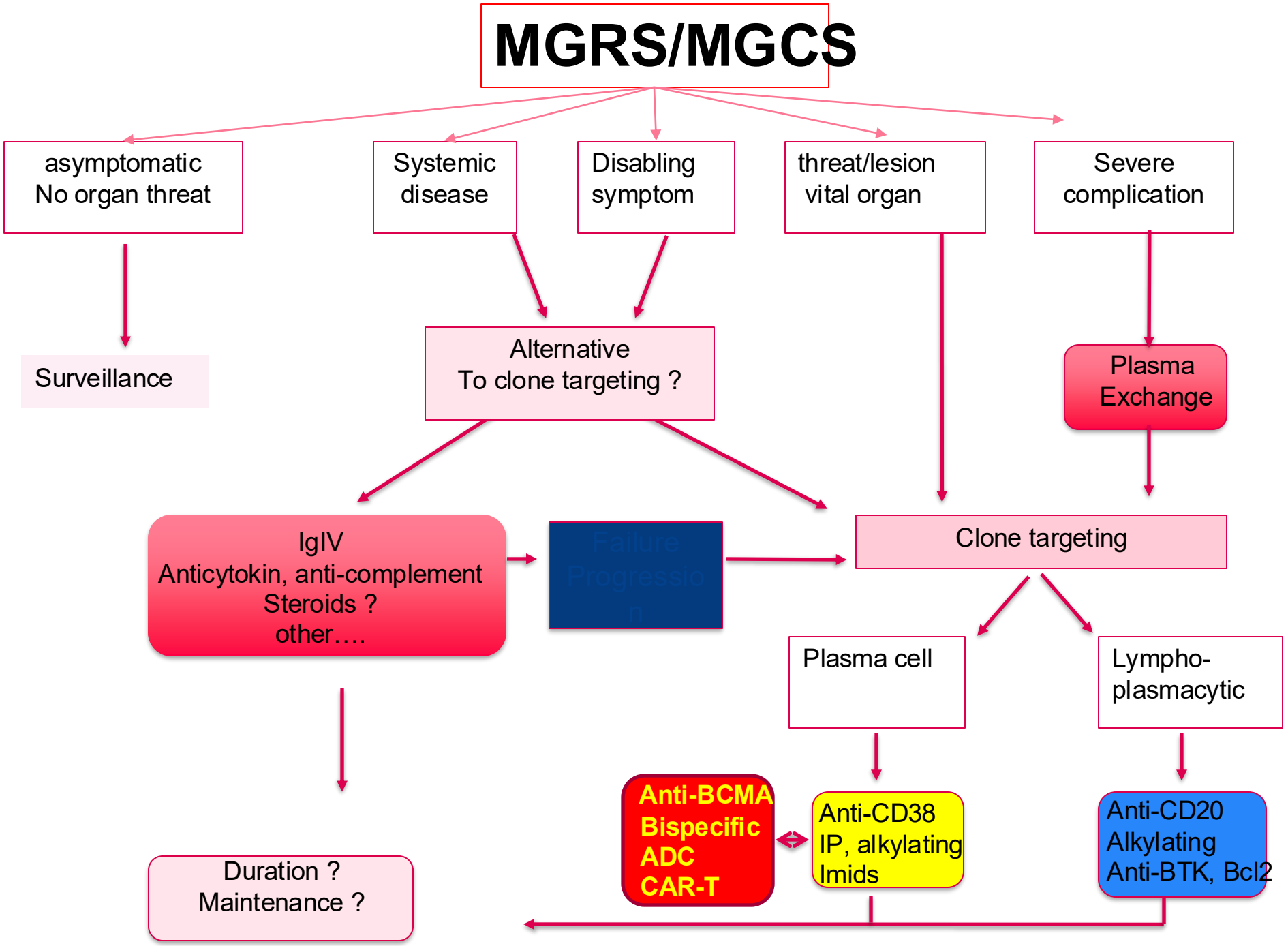
MGRS/MGCS
asymptomatic
No organ threat
Systemic
disease
Disabling
symptom
threat/lesion
vital organ
Severe
complication
Surveillance
Alternative
To clone targeting ?
Plasma
Exchange
IgIV
Anticytokin, anti-complement
Steroids ?
other….
Failure
Progressio
n
Clone targeting
Plasma cell
Lympho-
plasmacytic
Anti-BCMA
Bispecific
ADC
CAR-T
Anti-CD38
IP, alkylating
Imids
Anti-CD20
Alkylating
Anti-BTK, Bcl2
Duration ?
Maintenance ?

New immuno-therapeutic approach in AL Amyloidosis/MGRS/MGCS: Conclusion

Bispecifics:

- Unprecedented rapidity, rate and depth of response in healily pré-treated patients
- Off the shelf and easy to manage especially in patient with renal failure
- Fixed duration, short period of treatment, and dose spacing to mitigate infection and EI
- More Bispecific targeting GPRC5D, FcRH5….
- Trispecific (GPRC5D/BCMA/CD3, CD38/BCMA/CD3)
- Should be tested in frontline of MGRS/MGCS with indicated treatment

CAR-T cells/CAR-Macorphages:

- One shot
- More toxicity especially in patients with cardiac involvement
- New target, Dual targeting, new construct
- CAR Macrophages: improve AL depositis resorption ?
- In vivo approach…

THANK YOU

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