Bispecific antibodies: mechanisms, benefits, risks, interest in nephrology: “treatment paradigm shift”?

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Disclosures

- Advisory Boards and consulting :
  - Abbvie, AstraZeneca, Amgen, BMS, Pfizer, Sanofi, Menarini, GSK, JNJ

BCMA répond aux critères d'une cible thérapeutique idéale : BCMA est un régulateur majeur de la survie du plasmocyte

Expression tumorale élevée

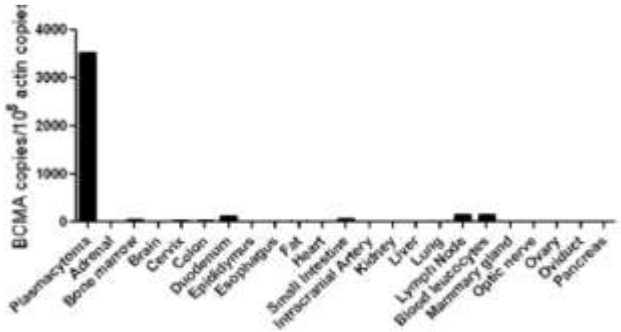
Expression limitée aux tissus sains

Rôle biologique dans la survie du clone

Cible validée par plusieurs plateformes
Trois approches thérapeutiques principales :

- **ADC**
  - Belantamab
- **Bispécifiques**
  - Teclistamab
  - Elranatamab
  - Linvoseltamab
- **CAR-T**
  - Idecel
  - Ciltacel

BCMA



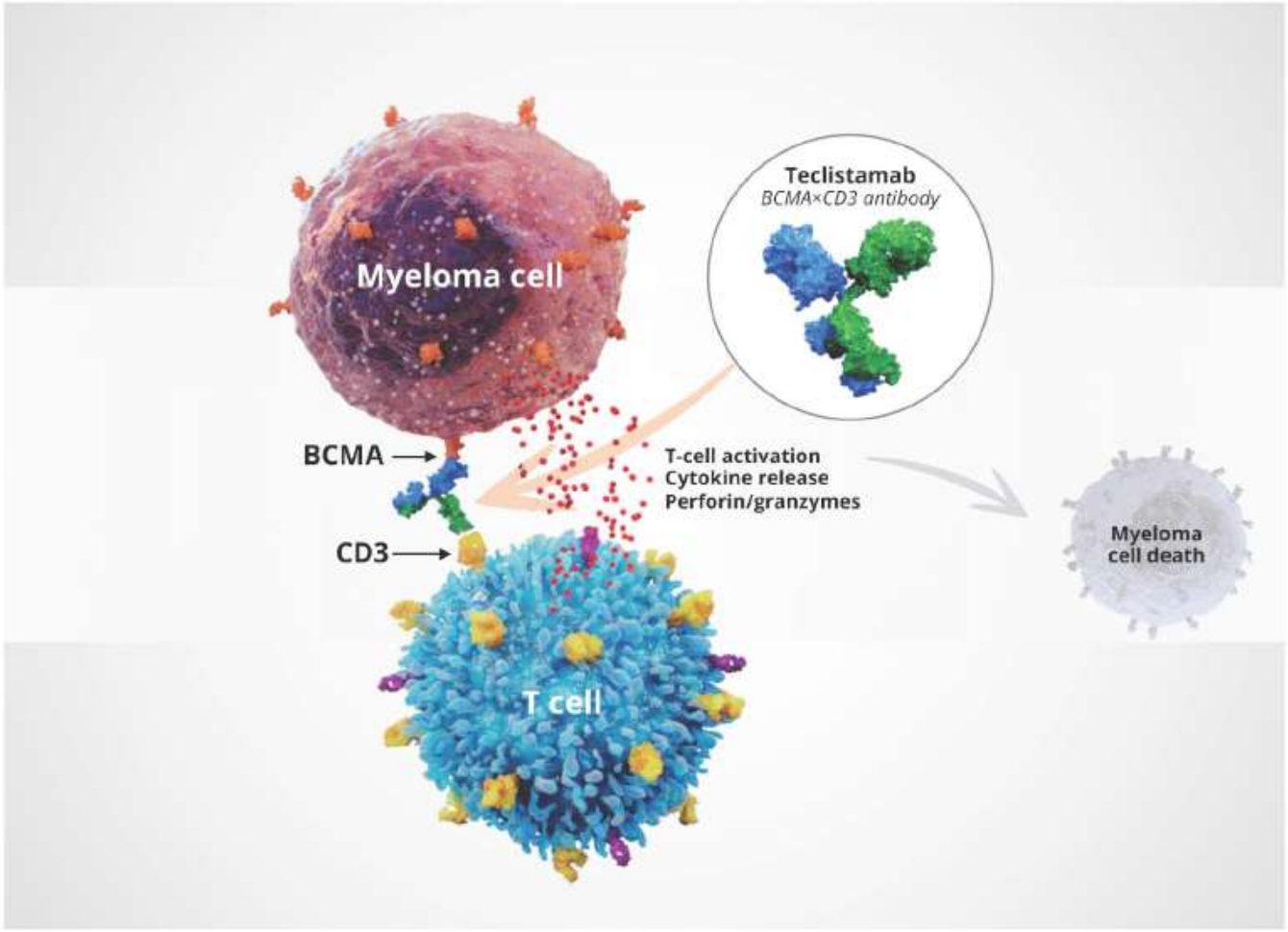
- **Dans le myélome multiple :**
- **• densité antigénique élevée**
- **• corrélation avec la masse tumorale**
- **Clivage par γ-secretase → BCMA soluble (sBCMA)**
- **Le sBCMA :**
- **• reflète la charge tumorale**
- **• diminue sous traitement efficace**

Lee et al., Blood 2018; Laurent et al., Nat Comm 2015

RECHUTES TARDIVES - MOLÉCULES DISPONIBLES ACTUELLEMENT

2 ANTICORPS BISPÉCIFIQUES ANTI-BCMA

Elranatamab : anticorps bispécifique IgG2 kappa dérivé de 2 anticorps monoclonaux dirigés contre l'antigène de maturation des lymphocytes B (BCMA) et le récepteur CD3 ; produit à partir de 2 lignées cellulaires recombinantes issues d'ovaires de hamster chinois[2]



Téclistamab : 1er anticorps bispécifique remboursé, humanisé de type immunoglobuline G4-proline, alanine, alanine (IgG4-PAA) dirigé contre l'antigène de maturation des lymphocytes B (BCMA) et le récepteur CD3 ; produit dans une lignée cellulaire de mammifère (ovaire de hamster chinois) à l'aide de la technologie de l'ADN recombinant[3]

1. D'après Guo Y, et al. Clin Transl Sci. 2024;17(1):e13717. 2. Résumé des Caractéristiques du Produit elranatamab. 3. Résumé des Caractéristiques du Produit teclistamab.

Les anticorps bispécifiques anti-BCMA

Structure :
- un bras anti-BCMA
- un bras anti-CD3

Mécanisme :
1. liaison plasmocyte tumoral
2. recrutement lymphocyte T
3. formation synapse immunologique
4. activation cytotoxique T

Effets :
- libération perforine / granzymes
- production cytokines
- destruction cellulaire tumorale

Anticorps IgG-like pleine longueur.

Caractéristiques PK :
- administration sous-cutanée
- absorption lente (lymphatique)
- demi-vie prolongée
- exposition plasmatique stable

Avantages administration SC :
- réduction du CRS
- meilleure tolérance
- pics plasmatiques plus faibles

Mode d’action

Activation lymphocytaire :
- CD69
- CD25
- expansion clonale T

Libération cytokines :
- IL-6
- IFN-γ
- TNF-α

Conséquences cliniques :
- syndrome de relargage cytokinique (CRS)
- cytotoxicité rapide
- réduction plasmocytes médullaires

Administration :
- sous-cutanée
- dose hebdomadaire initiale
- passage possible Q2W

Pharmacocinétique :
- demi-vie ≈ 22 jours

INDICATIONS

- Teclistamab est indiqué en monothérapie, pour le traitement des patients adultes atteints d'un myélome multiple en rechute et réfractaire
- Ayant reçu au moins trois traitements antérieurs, incluant
  - un agent immunomodulateur
  - un inhibiteur du protéasome
  - et un anticorps anti-CD38
- et dont la maladie a progressé pendant le dernier traitement.

Résumé des Caractéristiques Produits

MAJESTEC-1
OBJECTIFS ET DESIGN DE L'ÉTUDE

- **Etude de phase 1/2, en ouvert, multicentrique et à un seul bras, menée chez 165 patients atteints de myélome multiple**
- **Objectif de l'étude :** évaluer l'efficacité et la sécurité d'emploi de teclistamab chez des patients adultes atteints d'un myélome multiple en rechute et/ou réfractaire qui avaient déjà reçu au moins 3 lignes antérieures de traitement contre le myélome multiple.

SÉLECTION

Cohorte A
(exposés à 3 classes thérapeutiques)

Principaux critères d'éligibilité:
- MM mesurable
- MMRR, ≥3 lignes antérieures
- IP, IMiD, et anti-CD38 antérieurs
- Pas de traitement antérieur par anti-BCMA
- ECOG 0 ou 1

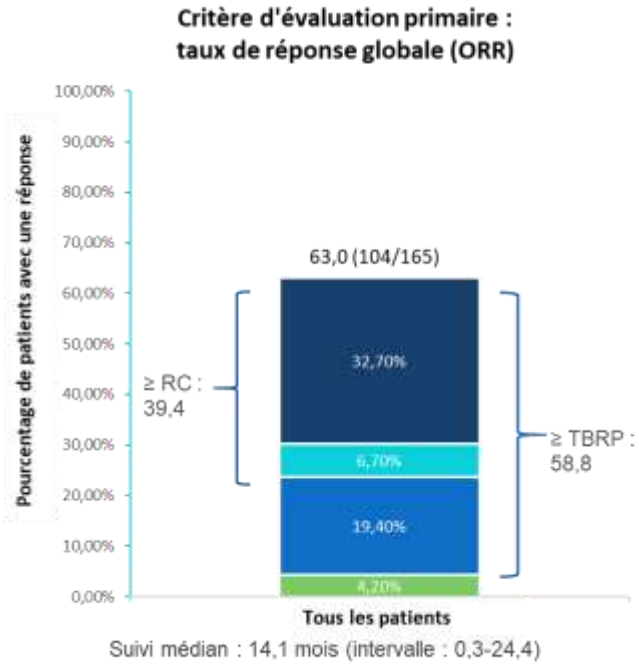
TRAITEMENT

Semaine 1
- Etapes de paliers de dose de teclistamab SC (0,06 et 0,3 mg/kg)

Cycles 1+
- Dose hebdomadaire de teclistamab[a] SC 1,5 mg/kg jusqu'à la progression

POST-TRAITEMENT

Suivi 2 ans après le dernier patient inclus



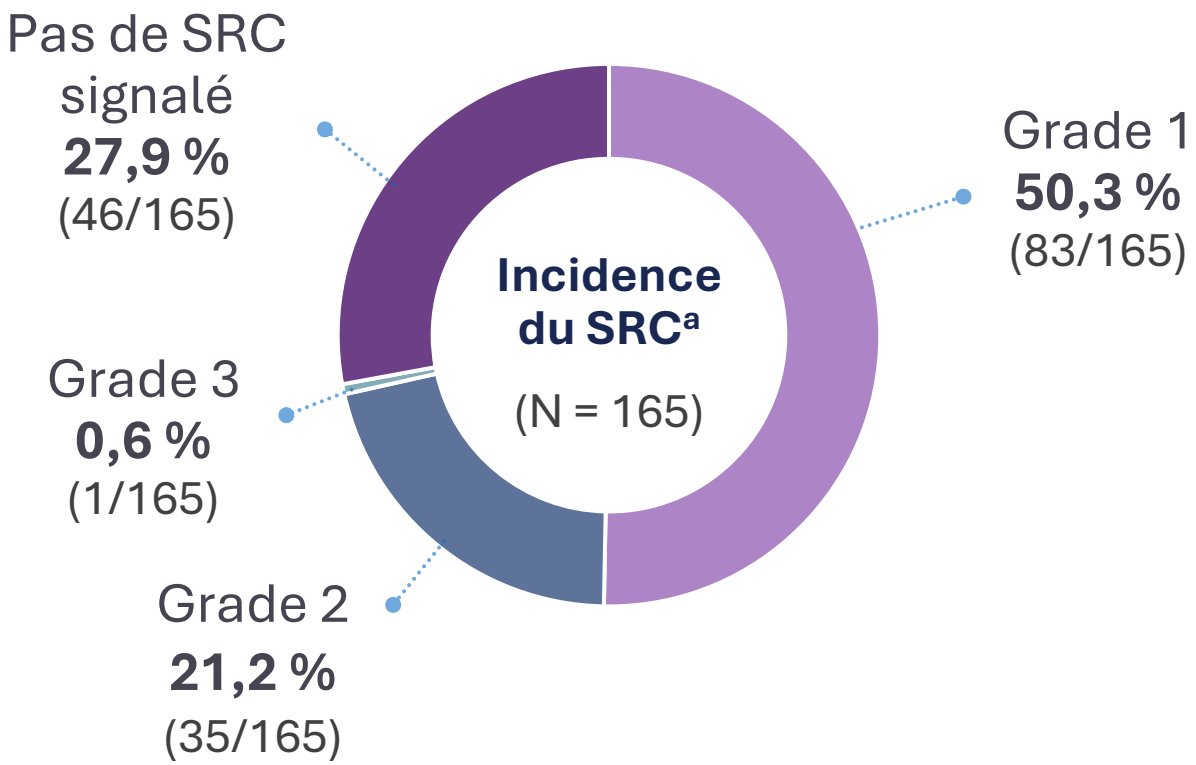
- **Critère d'évaluation principal** : ORR
- **Principaux critères d'évaluation secondaires** : Durée de réponse, ≥VGPR, ≥ R, sCR, TTR, statut de la MRD, PFS, OS, sécurité d'emploi, pharmacocinétique, immunogénicité, PRO

[a]*Le passage à une posologie toutes les deux semaines a été autorisé en fonction de la réponse obtenue.*

Moreau P, *et al.* N Engl J Med. 2022 Aug 11;387(6):495-505

SURVENUE DES SRC AVEC LE TÉCLISTAMAB[1-2]

Des SRC sont survenus chez 72,1 % des patients recevant le schéma posologique recommandé



- 50,3 % des patients (83/165) ont présenté un cas de grade 1
- Aucun événement de SRC de grade 4/5 n'a été observé
- La majorité des cas de SRC étaient de grade 1 ou 2
- Parmi les patients ayant développé un SRC, les symptômes associés comprenaient : fièvre (72 %), hypoxie (13%), frissons (12%), hypotension (12%), tachycardie sinusale (7%), céphalées (7%) et ASAT/ALAT élevés (3,6%)

- Pour prendre en charge le SRC, les patients présentant un événement de SRC (n = 110) ont reçu :
  - 36,4 % (60/110) ont reçu du tocilizumab
  - 8,5 % (14/110) des patients ont reçu des stéroïdes

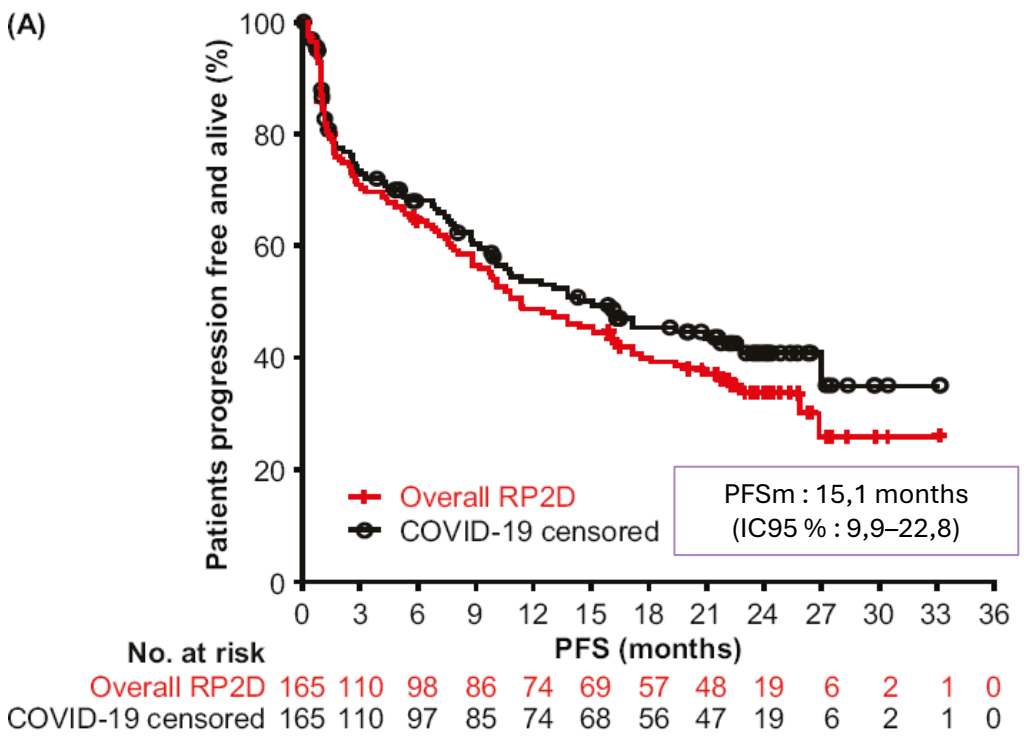
[a]Le SRC a été noté selon les critères de l'ASTCT 2019.

1. Résumé des Caractéristiques du Produit teclistamab ; 2. Moreau P, et al. NEJM. 2022;387:495-505.

RECHUTES TARDIVES - MOLÉCULES DISPONIBLES ACTUELLEMENT

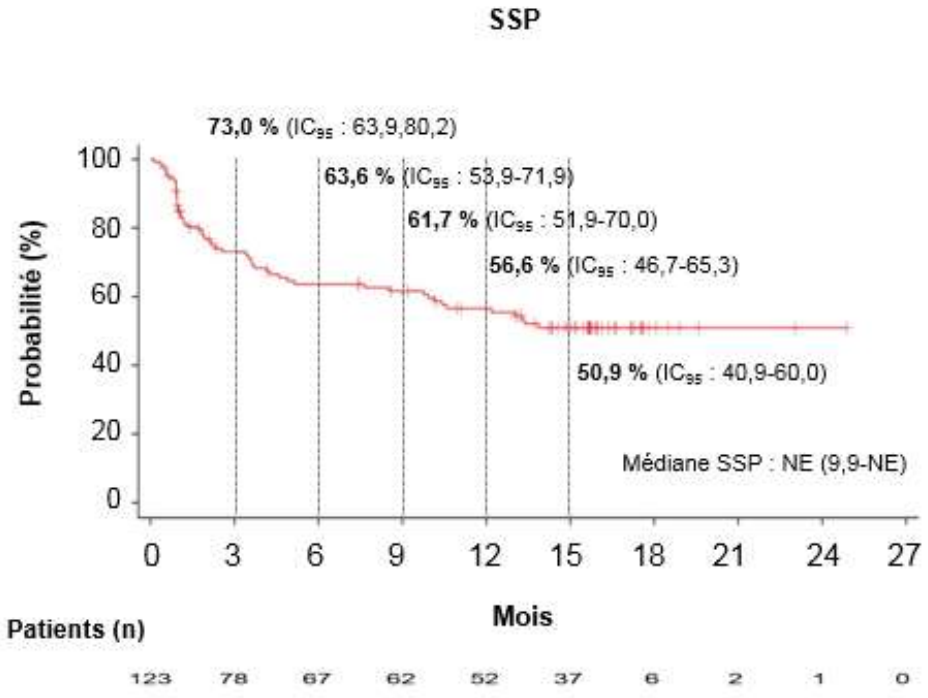
2 ANTICORPS BISPÉCIFIQUES ANTI-BCMA

- **Téclistamab** (MajesTEC- 1)



Moreau et al. NEJM 2022 ;
Van de Donk N, et al. Blood Cancer J. 2024;14:186

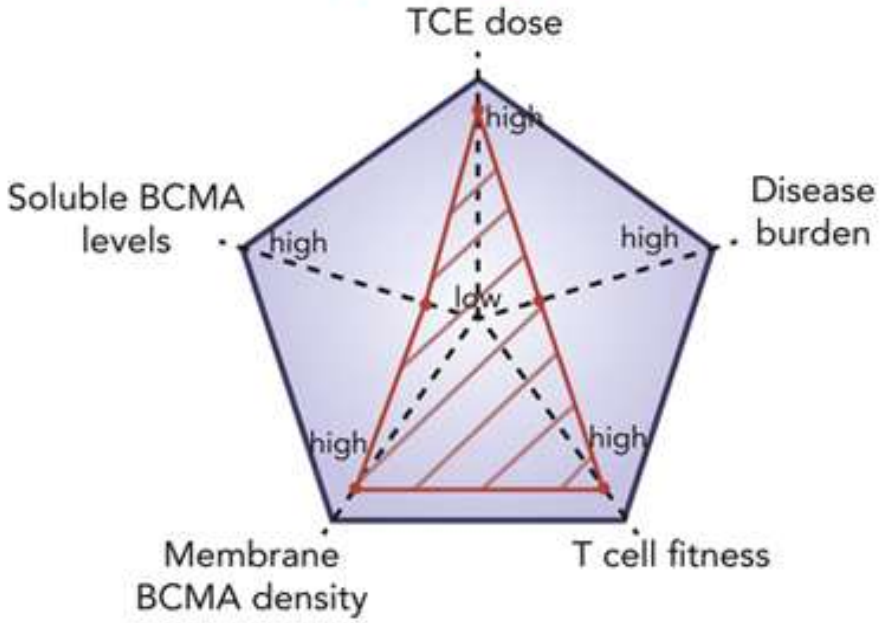
- **Elranatamab** (MagnetisMM-3)



Mothy et al. ASCO 2023

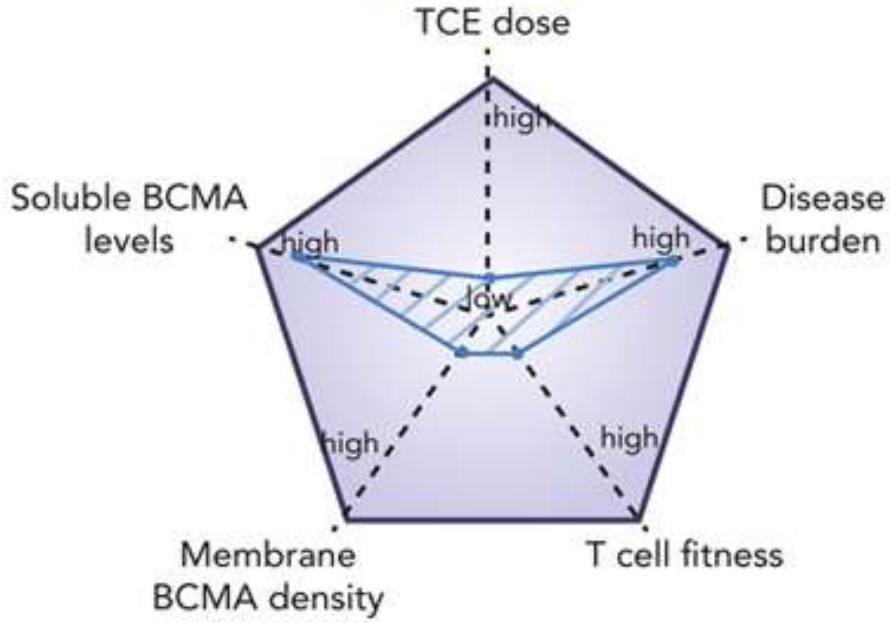
Les paramètres influent la réponse aux anticorps bispécifiques anti-BCMA dans le myélome multiple

Responding patients:



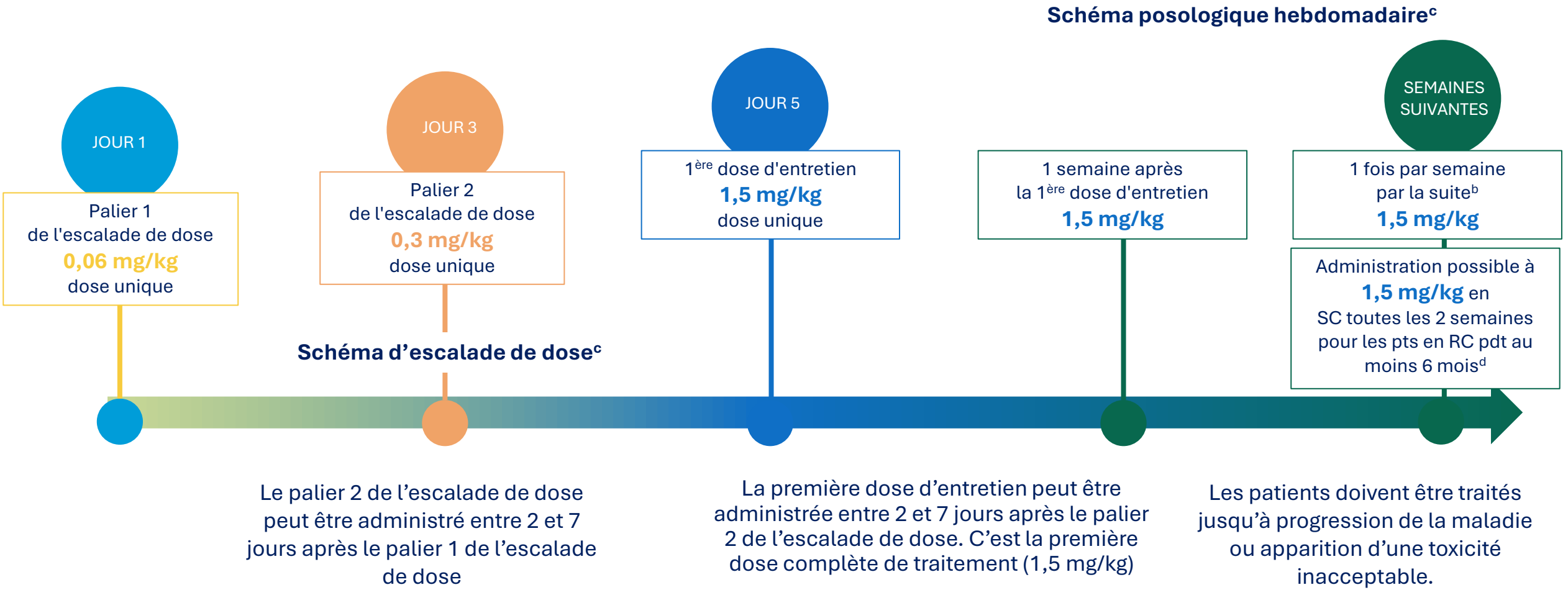
- Therapeutic TCE dosing
- Normal T-cell absolute count/fitness
- Low disease burden
- Low soluble BCMA (<400 ng/mL)
- High membrane bound BCMA

Nonresponding patients:



- Sub-therapeutic TCE dosing
- Low T-cell absolute count/fitness
- High disease burden
- High soluble BCMA (>400 ng/mL)
- Low membrane bound BCMA

ADMINISTRATION DU TÉCLISTAMAB



[a] La dose est basée sur le poids corporel réel et doit être administrée par voie sous-cutanée.[b] Maintenir un minimum de cinq jours entre les doses d'entretien hebdomadaires. [c] Voir le tableau des recommandations de reprise du teclistamab après un report de dose. [d]Résumé des Caractéristiques du Produit teclistamab

PRÉMÉDICATION ET SURVEILLANCE AVEC LE TÉCLISTAMAB[1]

- La prémédication doit être administrée **1 à 3 heures** avant chaque dose du schéma d'escalade de dose de teclistamab afin de réduire le risque de syndrome de relargage de cytokines :

- **corticoïdes** (dexaméthasone 16 mg par voie orale ou intraveineuse)

- **anti-histaminique** (diphénhydramine 50 mg ou équivalent par voie orale ou intraveineuse)

- **anti-pyrétiques** (paracétamol 500 à 1 000 mg ou équivalent par voie orale ou intraveineuse)

- L'administration d'une prémédication peut également être nécessaire **avant l'administration des doses ultérieures** de teclistamab chez les patients suivants :

- patients dont les doses sont répétées durant le schéma d'escalade de dose de teclistamab en raison de reports de dose,

- ou patients qui ont présenté un SRC suite à la dose précédente.

- Dans les cas suivants, il convient de demander aux patients de rester à proximité d'un établissement de santé et d'être surveillés quotidiennement pendant **48 heures** :

- si le patient a reçu 1 **dose du schéma d'escalade de dose** de teclistamab (pour un SRC)

- si le patient a reçu teclistamab après avoir présenté un SRC de grade 2 ou plus

PRISE EN CHARGE DES CRS :GRADES ET SYMPTÔMES

	Paramètre	Grade 1	Grade 2	Grade 3	Grade 4
Grade et Symptomes	Température	≥ 38°C[b]	≥ 38°C[b]	≥ 38°C	≥ 38°C
	avec				
	Hypotension	Non	répondant aux solutés de remplissage et ne nécessitant pas de vasopresseurs	nécessitant un vasopresseur avec ou sans vasopressine	nécessitant plusieurs vasopresseurs (à l'exclusion de la vasopressine)
	et/ou				
	Hypoxie	Non	Besoin en oxygène par canule nasale à faible débit[c] ou insufflateur	Besoin en oxygène par canule nasale à haut débit[c], masque facial simple, masque sans réinhalation ou masque Venturi	Besoin en oxygène par pression positive (par ex., ventilation par pression positive continue, pression positive à deux niveaux, intubation et ventilation mécanique)

PRISE EN CHARGE DES CRS: RECOMMANDATIONS EMN

Grade 1
- Supportive care including analgesics and antipyretics
- If fever is present, treat for neutropenic infections protocol
- Consider tocilizumab for persistent (i.e., >3 days) and refractory fever

Grade 2
- IV fluid bolus 500–1000 mL to maintain SBF >90 mm Hg
- Administer tocilizumab* (8 mg/kg infused over 1 hour) early if persistent fever of ≥39 °C, hypotension after initial fluid bolus, or initiation of oxygen supplementation
- If persistent hypotension after two fluid bolus and tocilizumab, consider low-dose vasopressor therapy
- Add dexaméthasone 10 mg IV every 6 hours if hypotension persists after anti-IL-6 therapy, high risk for severe CRS, worsening hypoxia, or clinical concern

Grade 3
- Admission to ICU should be considered
- Administer tocilizumab
- Continue within 24hours, dexamethasone 10 mg IV every 6 hours
- If refractory, increase to 20 mg IV every 6 hours
- If condition is unresponsive, add anakinra 2 mg/kg daily for 3–5 days
- Consider anti-TNF antibodies† as clinically appropriate
- Perform ECG if persistent hypotension is present

Grade 4
- **Should be treated in ICU**
- **Administer tocilizumab**
- **High-dose methylprednisolone 1 g/day IV**
- **If condition is unresponsive, add anakinra**
- **If condition is unresponsive, consider alternative agents such as anti-TNF, and other agents as appropriate**

Guidance based on bispecific antibody and CAR T cell management

*Total single dose not to exceed 800 mg; repeat dose if no response within 6–12 hours and consider corticosteroids as indicated. †Etanercept. CAR T = chimeric antigen receptor cell therapy; CRS = cytokine release syndrome; ECG = echocardiogram; EMN = European Myeloma Network; ICU = intensive care unit; Hg = hemoglobin; IL = interleukin; IV = intravenous; SBP = systolic blood pressure; TNF = tumor necrosis factor.

Ludwig H et al. Lancet Oncol 2023;24:e255–69.

PRISE EN CHARGE DES ICANS : RECOMMANDATIONS EMN

- EMN recommendations can be used to guide the management and treatment of ICANS

Grade 1
- Management: observation
- Withhold oral food, medicine, fluid intake, switch to IV intake
- If patient is agitated, haloperidol 0–5 mg or lorazepam 0.25–0.5 mg every 8 hours
- Consider early dexamethasone in patients at high risk
- Start non-sedating AEDs, if not on already
- MRI of brain, lumbar puncture, funduscopic exam, EEG

Grade 2
- Management: dexamethasone 10 mg every 12 hours
- If no improvement after 48 hours, consider high-dose dexamethasone (20 mg ever 6 hours) and alternative agents such as anakinra or tocilizumab if concomitant CRS
- Start non-sedating AEDs if not on already
- Consider EEG and CT-MRI

Grade 3
- Management: dexamethasone 10 mg every 6 hours
- If no improvement after 24 hours, consider high-dose dexamethasone (20 mg every 6 hours), high dose methylprednisolone (1–2 g/day), or alternative agents such as anakinra
- Start non-sedating AEDs, if not on already
- Consider EEG and CT-MRI
- Check CSF pressure; if increased use acetazolamide, mannitol or hypertonic saline

Grade 4
- Management: dexamethasone 20 mg every 6 hours
- If dexamethasone refractory, consider high-dose methylprednisolone 2 mg/kg every 12 hours
- If refractory, consider alternative therapies including lymphodepletion with cyclophosphamide or other drugs
- Consider mechanical ventilation, EEG, and CT-MRI
- If CSF pressure >20 mm Hg Ommaya reservoir or cranial or lumbar catheter

Ludwig H et al. *Lancet Oncol* 2023;24:e255–69.

ÉTUDE MBISPID - ÉTUDE DE VRAIE VIE
CARACTÉRISTIQUES PRINCIPALES DES INFECTIONS

- Accès précoce français téclistamab
- n = 303 patients
- 46,2 % de patients non éligibles à MajesTEC-1

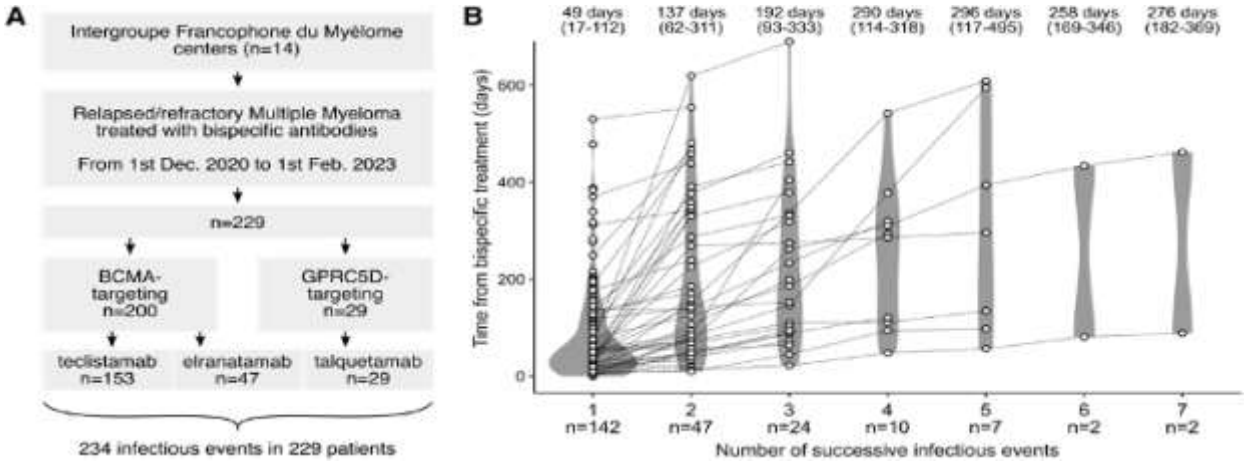
- Suivi médian : 11,9 mois [95 % CI, 9,2- 14,8]
- Taux de réponse globale : 6,8 % dont 61,4 % de très bonne réponse partielle ou mieux
- Survie sans progression médiane :
  - 11,3 mois [95 % CI, 8,9 - 14.9]
  - 17 mois [95 % CI, 16,4 - NA] chez les 175 répondeurs
- Survie globale médiane : 17 mois [95 % CI, 13,8 - NA]

Subgroups (N)	Median PFS	
Age < 75	9.1 months (6.3-13)	p = 0.007
Age 75 or more - 90 (29,7%)	16.4 months (10.7-NR)	
Extra medullary disease – 34 (11,8%)	3.7 months (2-NR)	
No extra medullary disease	11.3 months (8.8-16.2)	p = 0.057
Paramedullar disease – 70 (25,5%)	16.2 months (9.3-NR)	
No paramedullar disease	9.2 months (7.3-13.3)	p = 0.103
Circulating plasmacytosis – 39 (13,8%)	4.7 months (1.7-10.5)	
No circulating plasmacytosis	12.6 months (9.7-16.4)	p = 0.001
del(17p) or TP53 mutation - 54/179 (30.2%)	5.2 months (2.9-9.1)	
No del(17p), no mutation TP53	16.4 months (4.1-NR)	p = 0.009
Ineligibility to MAJESTEC-1 - 86 (28.4%)	3.9 months (2.3-7.9)	
Eligibility to MAJESTEC-1	14.9 months (11.3-NR)	p < 0.001
No previous Auto Transplant	12.5 months (9.7-NR)	
Previous Auto Transplant - 171 (56.4%)	9.1 months (6.3-16.2)	p = 0.357

Perrot A, et al. poster ASH 2023 ; Lebreton et al. Br J Haematol 2024 Nov;205(5):2077-2079

ÉTUDE MBISPID - ÉTUDE DE VRAIE VIE

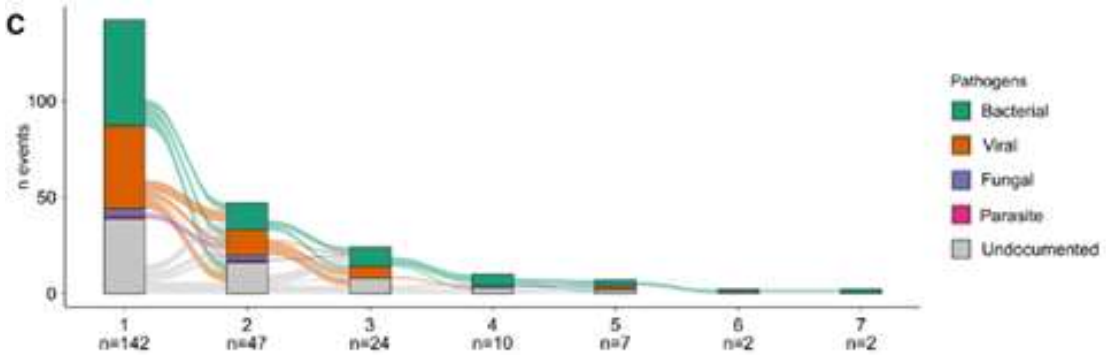
CARACTÉRISTIQUES PRINCIPALES DES INFECTIONS



- Survenue d'au moins 1 épisode infectieux : 142 patients (62 %)
- 234 épisodes infectieux au total :
  - 131 (56 %) ayant nécessité une hospitalisation dont 30 (13 %) en réanimation
  - 70 (30 %) ayant conduit à une pause du traitement
  - 31 (13 %) à un arrêt du traitement par anticorps bispécifique

Incidence cumulative du 1ère épisode infectieux : 70 %

- 73 % dans le groupe anti-BCMA
- 51 % dans le groupe anti-GPRCD

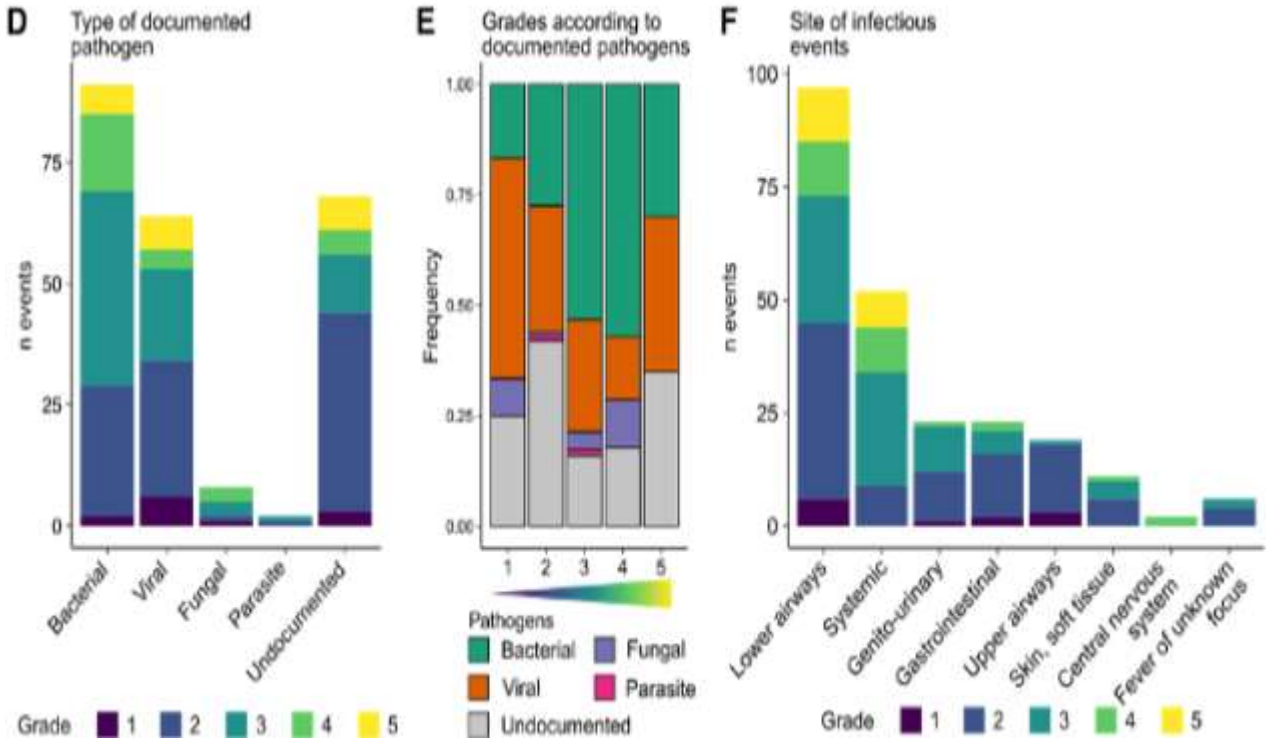


Jourdes A, et al. Clin Microbiol Infect. 2024 Jun;30(6):764-771.

ÉTUDE MBISPID - ÉTUDE DE VRAIE VIE

CARACTÉRISTIQUES PRINCIPALES DES INFECTIONS

- Toutes les infections de grade 4-5 sont survenues dans le groupe anti-BCMA
- Facteur de risque infectieux : corticoïdes



Jourdes A, et al. Clin Microbiol Infect. 2024 Jun;30(6):764-771.

	Infections bactériennes	Infections virales saisonnières	Infections opportunistes
	40-50 %	35-40 %	5 %
	Sites : Pneumopathie +++ **Germes :** • Pyocyanique • Pneumocoque • Coli • CG+…	**Sites :** Bronchite/pneumopathie +++ **Virus :** • COVID • Grippe • VRS • Rhinovirus/entérovirus	**Germes/virus :** • Pneumocytose • CMV (réactivation et maladie) • HSV/VZV • BK/JC virus dont LEMP • Parvovirus B19
Prévention	▪ **Substitution en IgIV ou SC systématique +++** ▪ AB prophylaxie discuté ▪ Ab thérapie rapide en cas de fièvre	▪ Vaccination systématique ▪ Si possible avant ttt ▪ Vaccination entourage ++ ▪ Dépistage précoce grippe et COVID et ttt anti viral	▪ Prévention antiPCP systématique si possible par cotrimoxazole ▪ Valaciclovir systématique ▪ Pas de monitoring CMV systématique ▪ Mais bilan d'infection opportuniste rapide en cas de fièvre ou point d'appel

- Espacer les injections au moins tous les 15 jours
- Stopper rapidement les corticoïdes en prémédication
- Ne pas réinjecter si fièvre

Harel S. Présentation Journées scientifiques de l'IFM. Synthèse des données de la littérature

IMPORTANCE DE LA SUBSTITUTION EN IGIV SOUS ANTICORPS BISPÉCIFIQUES ANTI-BCMA

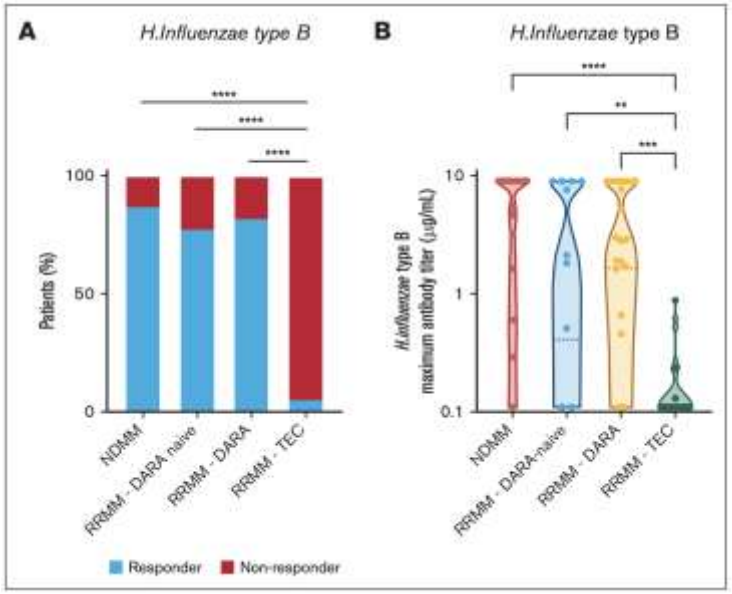
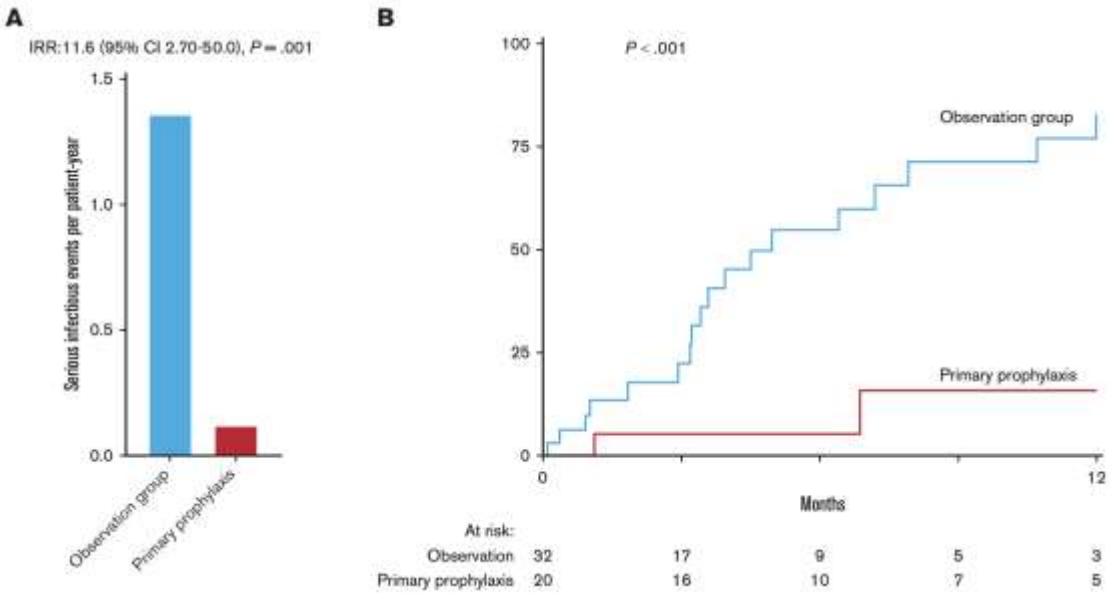


Figure 3. Teclistamab impairs vaccine response to *H. influenzae*. (A) Response after vaccination against *H. influenzae* type B in patients treated with teclistamab (n = 17). Control groups were patients with NNMM on maintenance therapy after autologous stem cell transplantation (n = 22), patients with daratumumab-naive RRMM (n = 11), and patients with RRMM treated with a daratumumab-containing regimen (n = 20). Response rates were compared using Pearson χ^2 test or Fisher exact test. (B) Peak specific IgG titers (µg/mL), assessed by enzyme-linked immunosorbent assay, after *H. influenzae* type B vaccination in the teclistamab-treated and control groups. Data are depicted as violin plots, indicating the distribution, including the median and interquartile range. Groups were compared using Kruskal-Wallis test with Dunns correction for multiple comparisons. RRMM-DARA naive, patients with daratumumab-naive RRMM; RRMM-DARA, patients with RRMM treated with a daratumumab-containing regimen; RRMM-TEC, patients with RRMM treated with teclistamab; $^{**}P < .01$; $^{***}P < .001$; and $^{****}P < .0001$.



Frerichs KA, et al. Blood Adv. 2024

LES INFECTIONS SOUS ANTICORPS BISPÉCIFIQUES ANTI-BCMA

ÉTUDE FRANÇAISE IFM

Table 2
Characteristics and grades of infections impacting patient management

Variables	Total (n = 234)
Site of infection, n (%)	
Systemic	52 (22)
Upper respiratory tract	19 (8)
Lower respiratory tract	97 (41)
Gastrointestinal tract	23 (10)
Genitourinary tract	23 (10)
Skin and soft tissue	11 (5)
CNS	2 (1)
Pathogens isolated[a], n (%)	n = 165
Bacterial	92/165 (56)
Enterobacteriaceae	48/165 (29)
Pseudomonas aeruginosa and other non-fermentative gram-negative bacteria	13/165 (7)
Anaerobic bacteria	11/165 (6)
Enterococci	6/165 (4)
Staphylococci	5/165 (3)
Streptococci[b]	4/165 (2)
Haemophilus influenzae	4/165 (2)
Neisseria	1/165 (1)
Viral	63/165 (38)
Respiratory viruses[c]	40/165 (24)
CMV	8/165 (5)
Enterovirus	3/165 (2)
HSV	2/165 (1)
VZV	2/165 (1)
Parvovirus B19	2/165 (1)
HBV	2/165 (1)
JC virus	2/165 (1)
Sapovirus	1/165 (1)
Adenovirus	1/165 (1)
Fungi	8/165 (5)
Aspergillus spp	6/165 (4)
Scedosporium spp	1/165 (1)
Pneumocystis jirovecii	1/165 (1)
Parasites	2/165 (1)
Toxoplasmosis	1/165 (1)
Giardiasis	1/165 (1)
Undocumented	69 (29)
Grade of infection[a], n (%)	
1	12/234 (5)
2	98/234 (41)
3	75/234 (32)
4	28/234 (12)
5	20/234 (9)

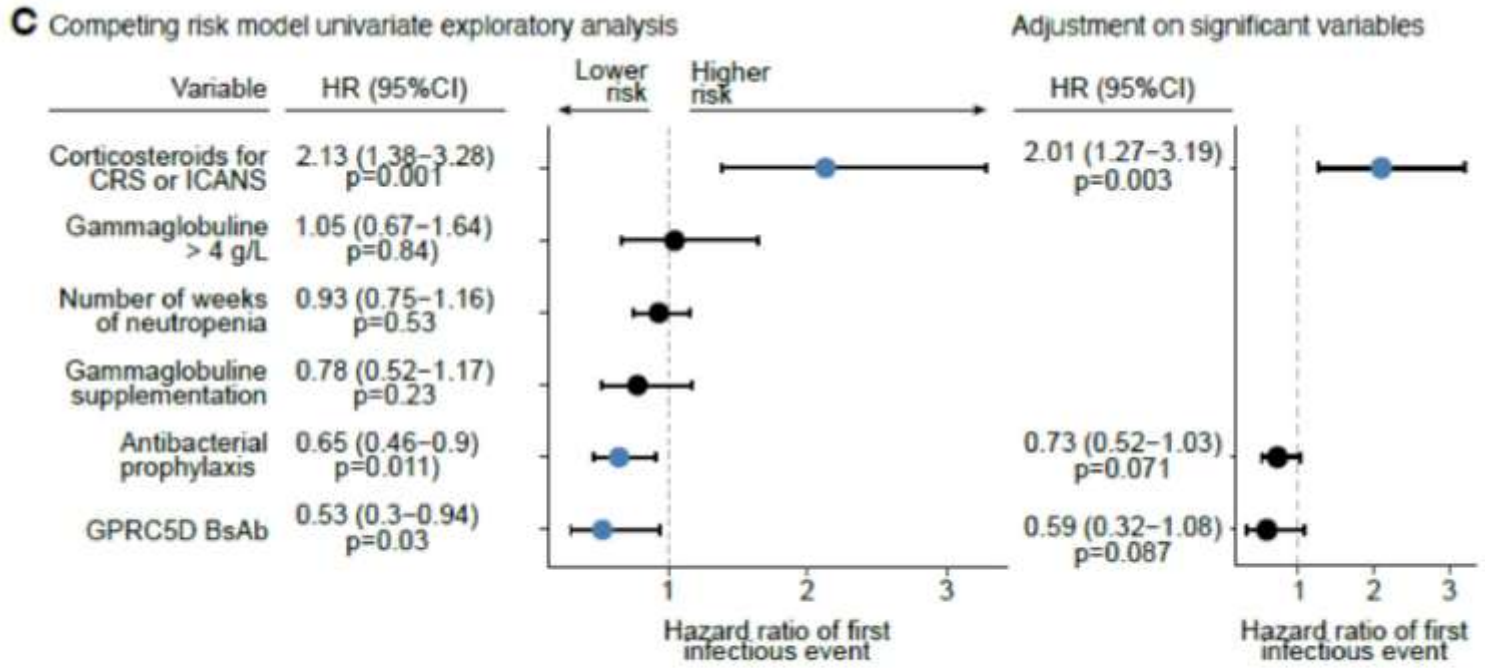
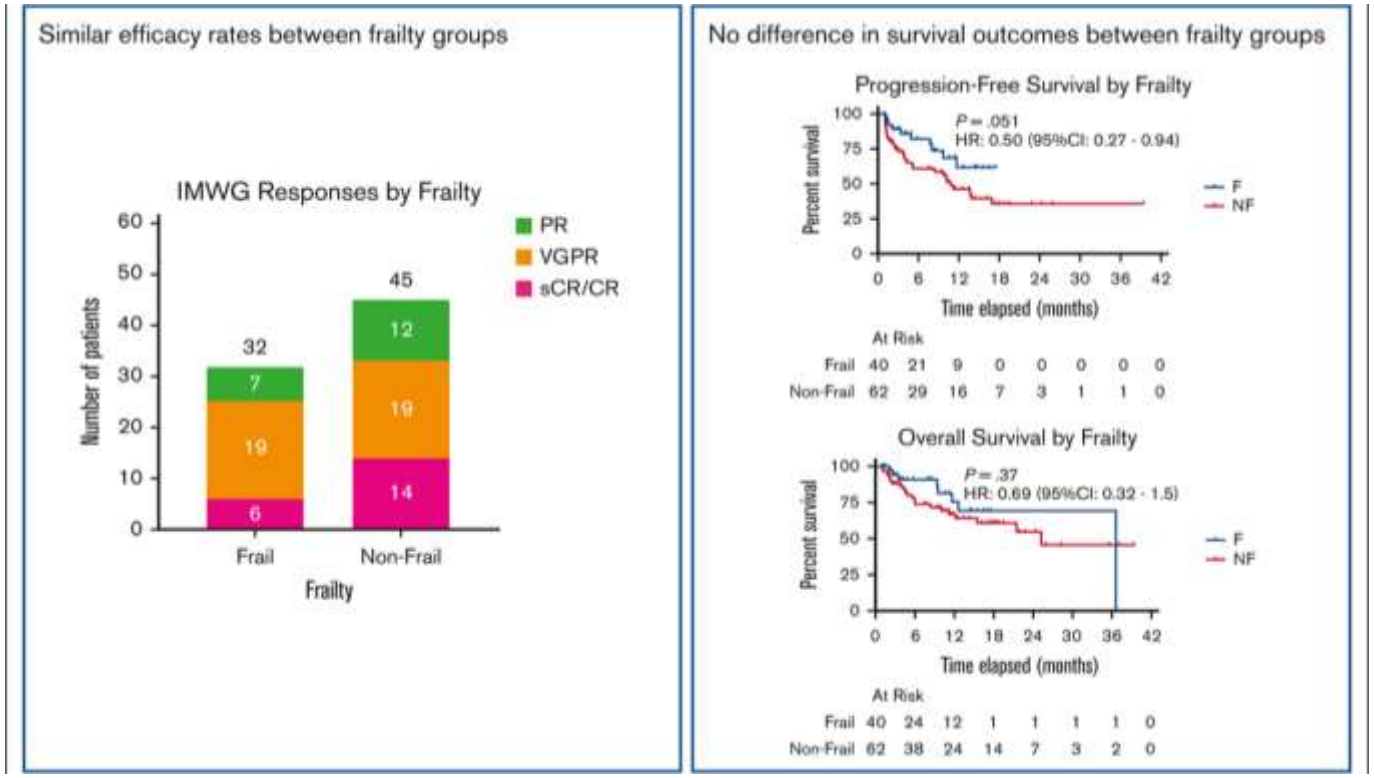


Fig. 2. Cumulative incidence of first infection. (A) Cumulative incidence function (CIF) of first infection. Death before first infection was used as a competing risk event. (B) The CIF of the first infection according to pathogen. Death was also used as a competing risk event. (C) Forest plot summarizing competing risk univariate exploratory analysis and multivariate adjustment of variables associated with first infection with death defined as a competing risk. Fine and Gray models were used to compute hazard ratios (HR), 95% CI and p-values.

Jourdes A et al. Clinical microbiology and infection. 2024

ANTICORPS BISPÉCIFIQUES CHEZ LES PATIENTS FRAGILES



- Les anticorps bispécifiques sont sûrs et efficaces chez les patients fragiles et âgés atteints de myélome multiple en rechute.
- Il n'existe pas de différences significatives en termes de survie selon l'âge, l'état général ou la charge de comorbidités dans cette Etudes rétrospective du MSKCC.

Adegbite B, et al. Blood Adv. 2025 Aug 12;9(15):4016-4022.

L'INSUFFISANCE RÉNALE NE DOIT PAS ÊTRE UN FREIN À L'UTILISATION DE BISPÉCIFIQUES

- Téclistamab chez des patients en rechute, lourdement prétraités et présentant une insuffisance rénale

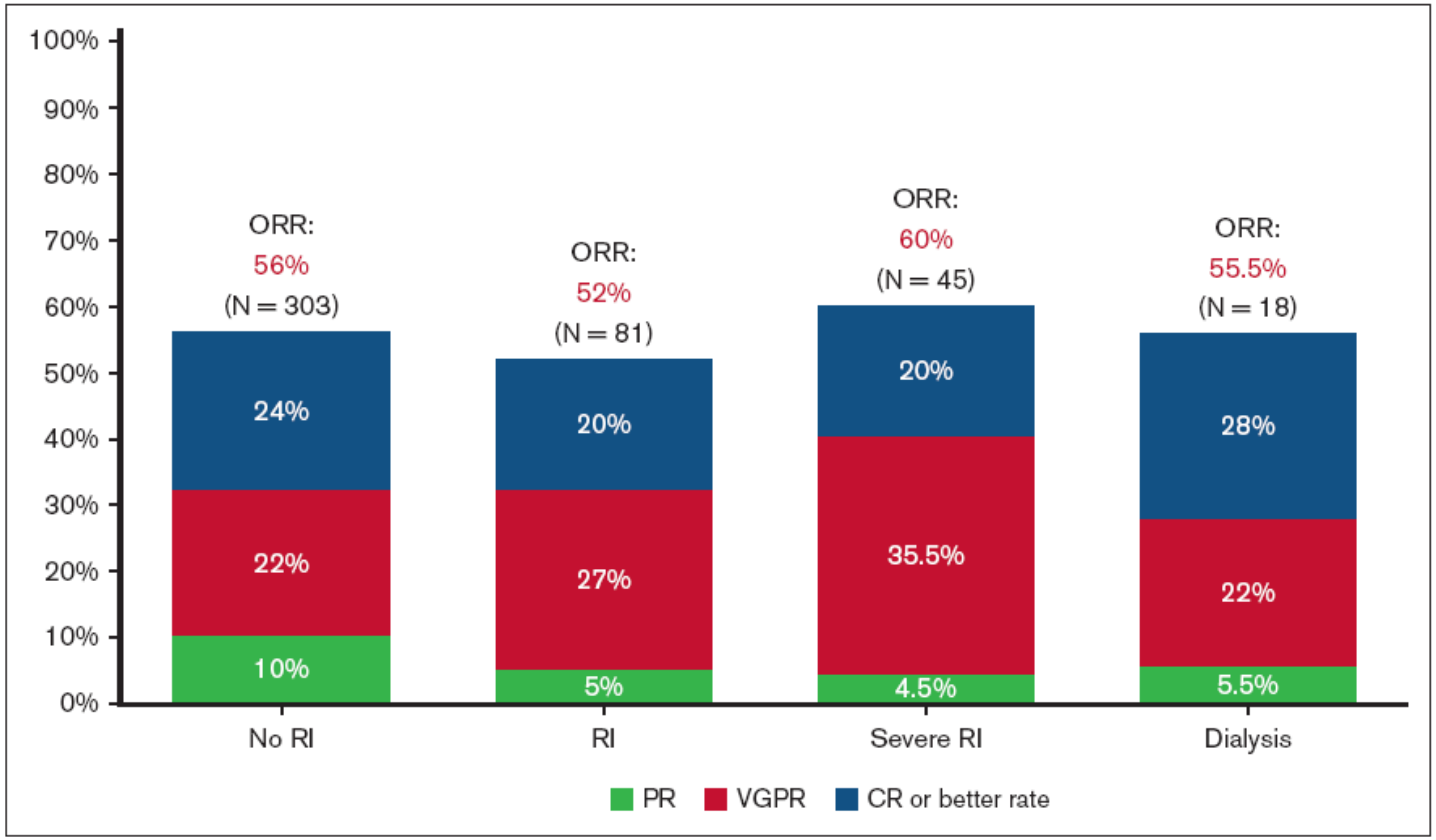


Figure 1. ORR and depth of response outcomes. PR, partial response; VGPR, very good partial response.

Dima D, et al. Blood Adv. 2025 Jul 22;9(14):3408-3417.

POPULATION DE PATIENTS DIALYSÉS

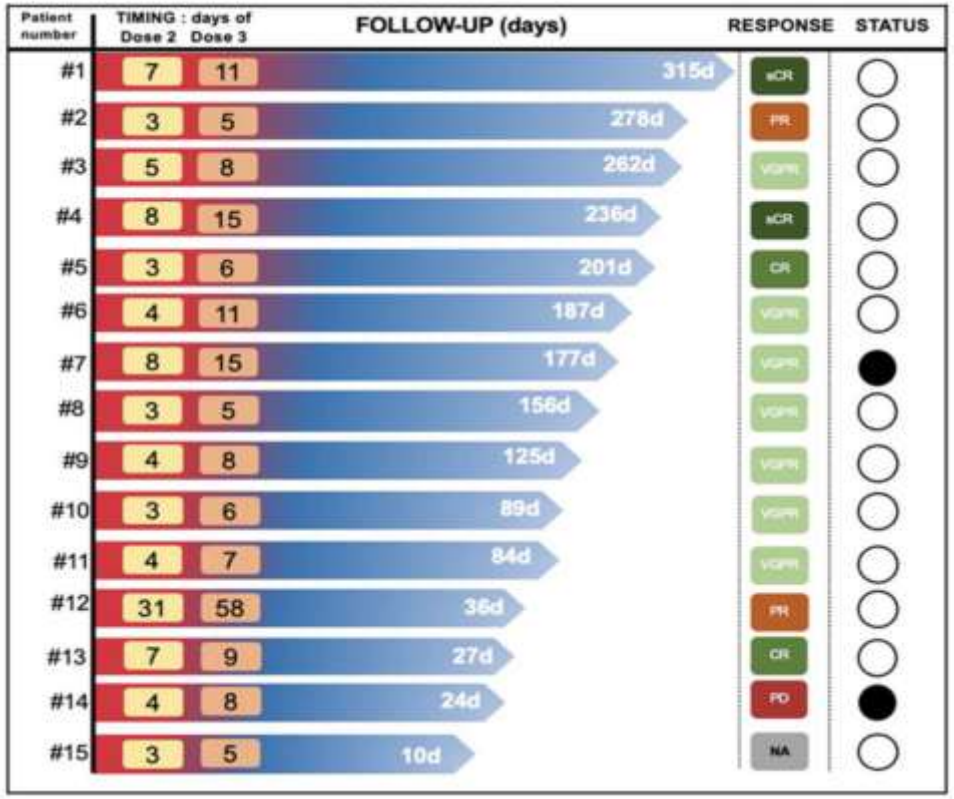
Teclistamab in Relapsed Refractory Multiple Myeloma patients on Dialysis: a French experience

F LACHENAL[1*], P. LEBRETON [2*], S. BOUILLIE[3], GM PICA[4], H. AFTISSE[5], L. PASCAL[6] , L. MONTES[7], M. MACRO[8], N. JOHNSON[9], S. HAREL[10], M FERNANDEZ[11], B. DE RENZIS[12], B. LIOURE[13], A. LAZARETH[14], M. JAVELOT[3], C LOUNI[15], A. HUART[16], A. PERROT [17]

1 CH Nord Dauphiné, Bourgoin Jallieu, 2. CH J. Venot, Montpellier, 3. Janssen, Issy les Moulineaux, 4. CH Chambery, 5. CH Saint Quentin, 6. Hôpital Saint Vincent de Paul, Lille, 7. CHU Amiens, 8. CHU Caen, 9. Hôpital Cochin, Paris, 10. Hôpital Saint Louis, Paris, 11. Janssen, USA, 12. CHU Clermont Ferrand, 13. ICANS, Strasbourg, 14. CHU Lyon, 15. IPM, Paris, 16. CHU Rangueil Toulouse, 17. CHU Oncopole, Toulouse.

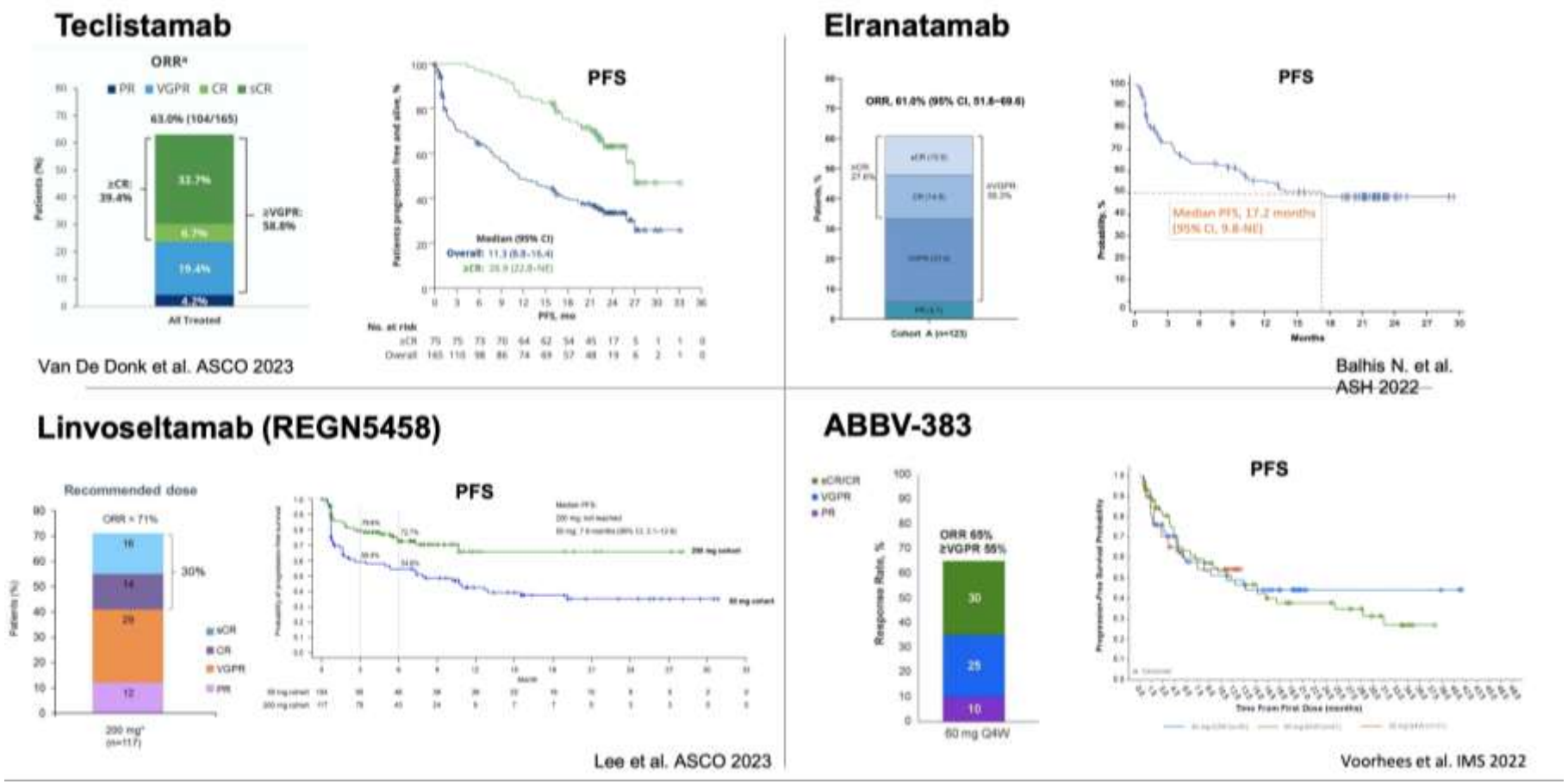
TABLE 1 Patients' characteristics.

Characteristic	Cohort ($n=15$)
Median age (years, range)	68 [58–83]
Sex: male/female	11/4
Median time since diagnosis (years, range)	6 [2–9]
Isotype of myeloma: full Ig/Light chain	4/11
High-risk cytogenetics[a]	7
Extramedullary disease	1
Number of prior lines of therapy (median, range)	4 [3–6]
Type of dialysis: haemodialysis/peritoneal dialysis	14/1
CRS grade >2 incidence	0
ICANS >2 incidence	0



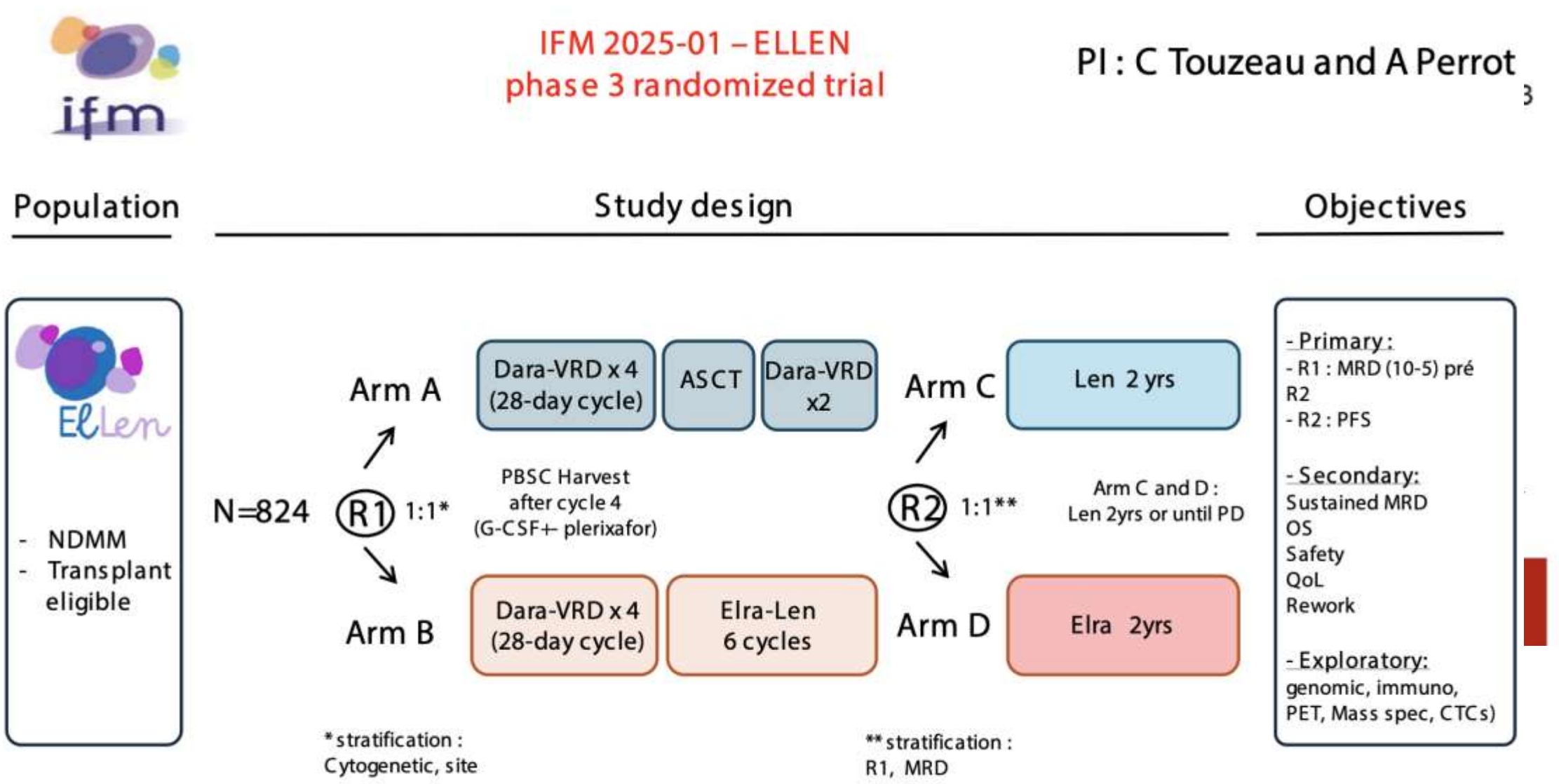
Lebreton et al. Br J Haematol 2024 Nov;205(5):2077-2079

BCMA/CD3 bispecific antibodies



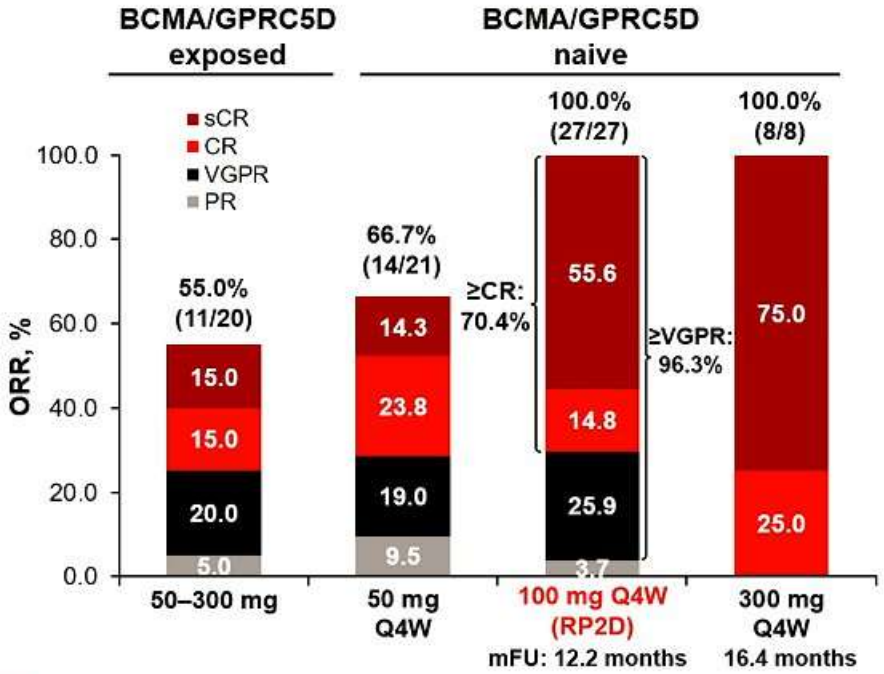
- **Mechanism:** off-the-shelf T-cell engagers (BCMA, GPRC5D, FcRH5).
- **Key trials:** *Teclistamab (MajesTEC-1)* – ORR ~63%, mPFS ~11 mo. *Elranatamab (MagnetisMM-3)* – ORR ~61%, mPFS ~17 mo. GPRC5D (Talquetamab), FcRH5 (Cevostamab) expanding options.
- **Advantages:** ready-to-use, repeat dosing, outpatient feasibility.
- **Limitations:** infections, long-term immune exhaustion, indefinite therapy.

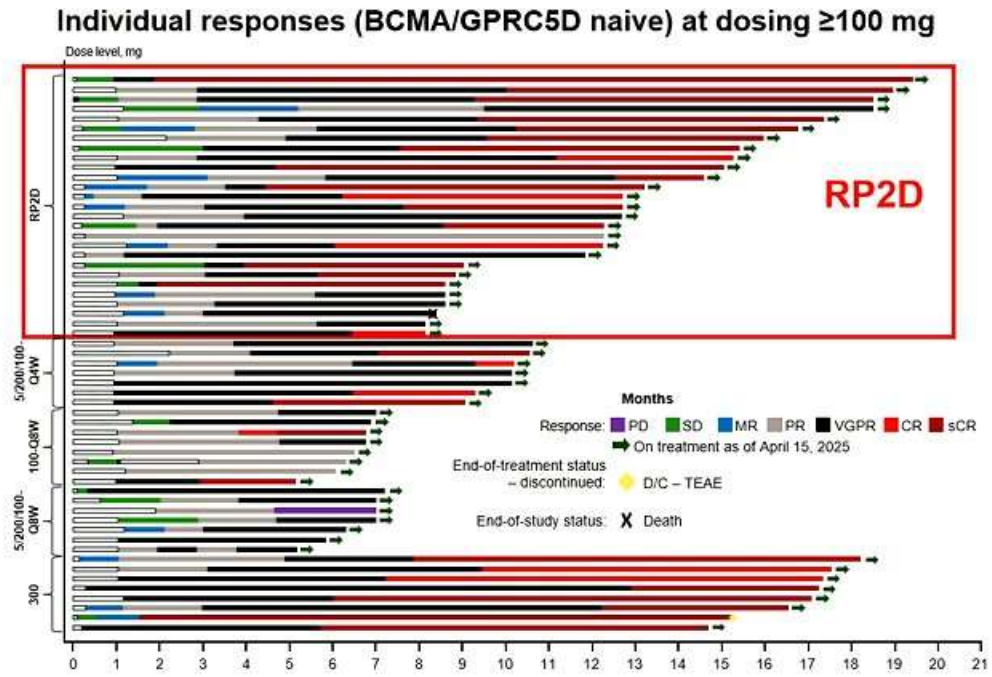
GMMG-HD10/DSMM-XX (MajesTEC-5) : induction and maintenance therapy



Trispecific anti CD3/BCMA/GPRC5D

JNJ-5322 Trispecific: ORR and Individual Responses in Patients Naive or Exposed to BCMA/GPRC5D Therapies





- At the RP2D in patients naive to BCMA/GPRC5D (n=27)
  - Median follow-up, months (range) is 12.2 (7.4–18.6)
  - Median time to first response, months (range) is 1.2 (0.3–5.2)
  - Median time to best response, months (range) is 5.9 (0.3–11.1)

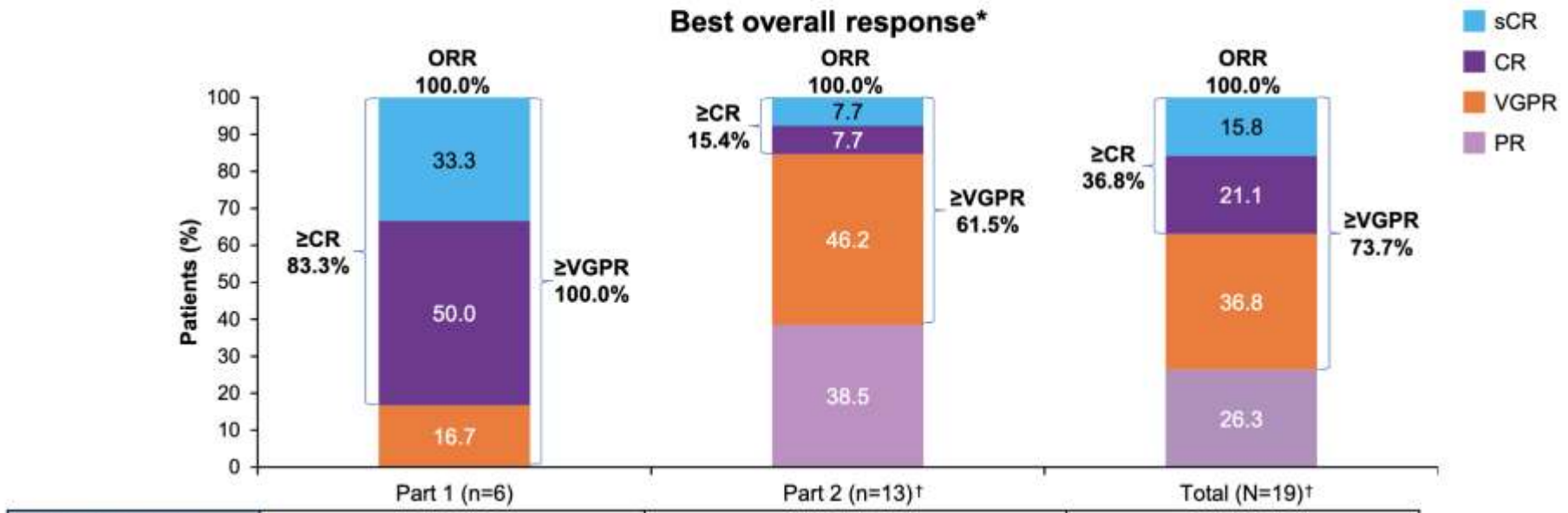
Almost all patients remain in response with 12 months of follow-up[a]

Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with 1 5-mg SUD. [a]One patient was in response at time of death. CR, complete response; D/C, discontinued; mFU, median follow-up; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; Q4W, every 4 weeks; sCR, stringent complete response; SD, stable disease; TEAE, treatment-emergent adverse event; VGPR, very good partial response.

Presented by H Lee at the Society of Hematologic Oncology (SOHO) Annual Meeting, September 3–6, 2025; Houston, TX, USA

Bispecific for Smoldering HR Myeloma

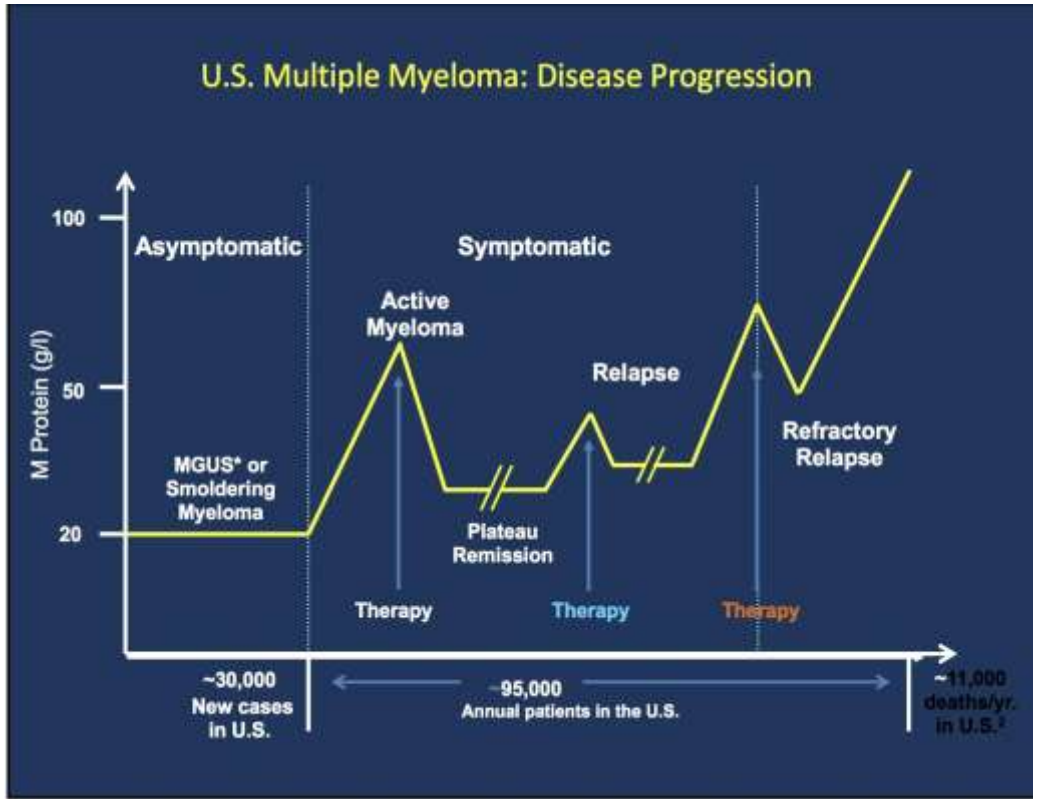
Preliminary efficacy: ORR



	Part 1 (n=6)	Part 2 (n=13)†	Total (N=19)†
Median follow-up, months (range)	12.7 (11–13)	3.3‡ (0–7)	3.9‡ (0–13)

- Among efficacy-evaluable patients who received ≥1 cycle of full-dose linvoseltamab (N=19)†, investigator-assessed ≥CR per IMWG criteria was 37% (ORR 100%; ≥VGPR 74%)

Data cut-off date: May 28, 2025.
*Response-evaluable population included patients who received at least one cycle of linvoseltamab 200 mg. Percentages may not total 100 due to rounding; †Not included: n=5 not evaluable; ‡Median follow-up is for all patients in full analysis set (N=24; Part 1, n=6; Part 2, n=18).
CR, complete response; IMWG, International Myeloma Working Group; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.



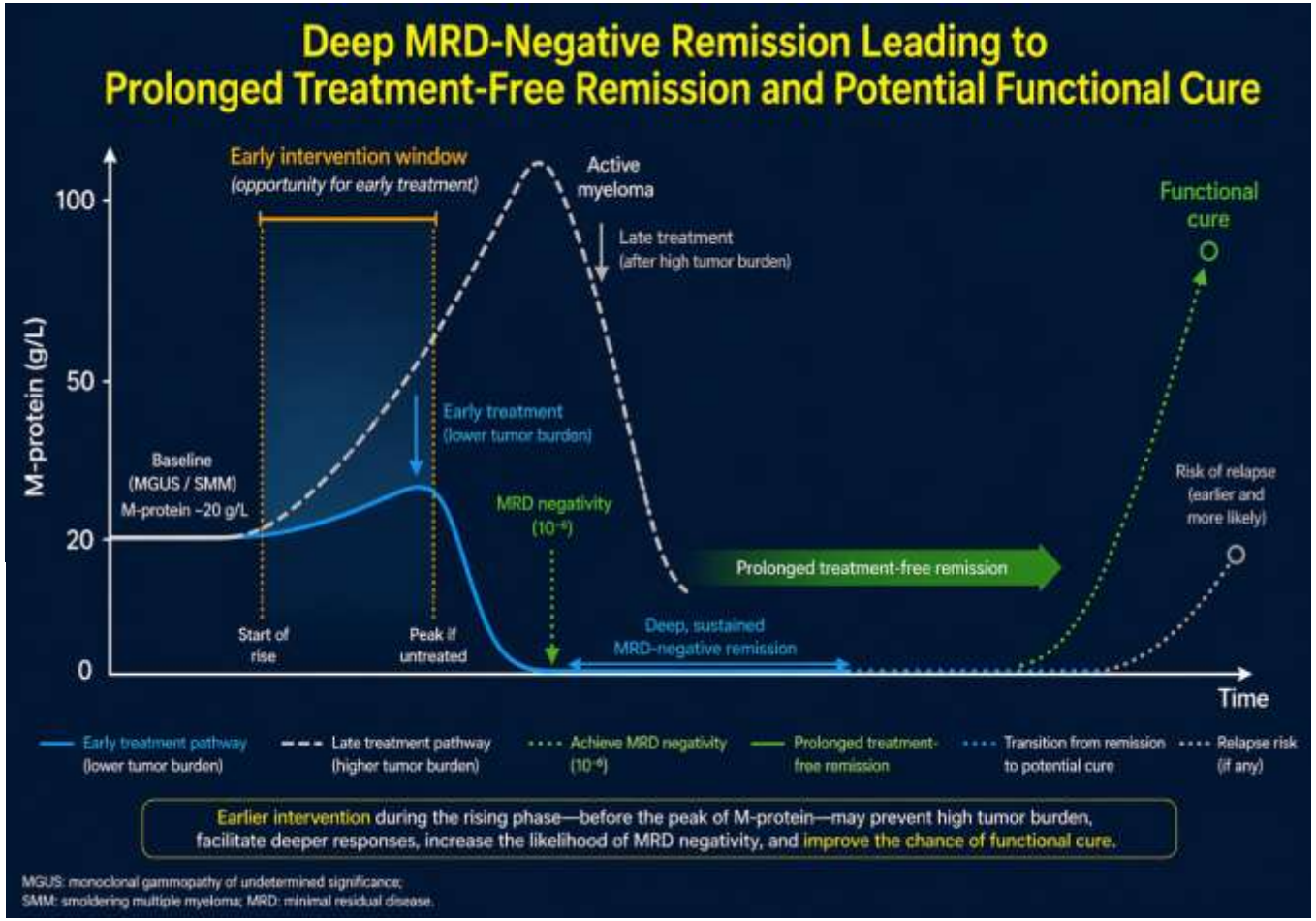


Table 1. Five transformative concepts in multiple myeloma

Concept	Trial	Phase	NCT	Key Question
Immune consolidation	CARTITUDE-6 ELlen	Phase 3	NCT05257083 NCT06918002	Can TCE (BCMA CAR T/BsAb) replace transplantation in frontline therapy?
MRD-guided therapy	MASTER2 MIDAS	Phase 2/3	NCT05231629 NCT04934475	Can MRD guide treatment?
Finite therapy	CARTITUDE-5 iMMagine-3	Phase 3 Phase 3	NCT04923893 NCT06413498	Can early therapy induce durable remission?
Multi-antigen targeting	Trilogy program Trignite program	Phase 1	NCT05652335 NCT05862012	Can multi-antigen targeting prevent immune escape?
Early immune interception	LINKER-SMM1 LINKER-MGUS	Phase 2	NCT05955508 NCT06140524	Can early immune intervention prevent progression to overt MM?

Talbot A et al., Med 2026, accepted

Current available TCE

Currently available T-cell engagers and their route of administration, dosing regimen, and approved indications.

TCE	Target(s)	Route	Usual regimen	Approved indication(s)	Year of first approval*
Blinatumomab	CD19 × CD3	Continuous IV infusion	Continuous infusion in 28-day cycles	ALL	2014
Mosunetuzumab	CD20 × CD3	IV or SC	Step-up dosing, then fixed-duration 21-day cycles	R/R FL	2022
Glofitamab	CD20 × CD3	IV infusion	Obinutuzumab pretreatment, then step-up dosing and fixed-duration treatment	R/R DLBCL	2023
Epcoritamab	CD20 × CD3	SC injection	Step-up dosing, then continued treatment until progression or unacceptable toxicity	R/R DLBCL; R/R FL	2023 (DLBCL); 2024 (FL)
Teclistamab	BCMA × CD3	SC injection	Step-up dosing, then weekly dosing; may be reduced in selected responders	R/R MM	2022
Elranatamab	BCMA × CD3	SC injection	Step-up dosing, then weekly dosing; may transition to every 2 weeks in responders	R/R MM	2023
Talquetamab	GPRC5D × CD3	SC injection	Step-up dosing, then weekly or every-2-week dosing	R/R MM	2023
Linvoseltamab	BCMA × CD3	IV infusion	Step-up dosing, then weekly maintenance dosing	R/R MM	2025

ALL: B-cell precursor acute lymphoblastic leukemia; **BCMA**: B-cell maturation antigen; **DLBCL**: diffuse large B-cell lymphoma; **FL**: follicular lymphoma; **GPRC5D**: G protein–coupled receptor class C group 5 member D; **IV**: intravenous; **MM**: multiple myeloma; **R/R**: relapsed/refractory; **SC**: subcutaneous.

* For products with region- or indication-specific expansion, the year refers to the first major regulatory approval (FDA or EMA), with indication-specific nuance added where needed.

Larue M. et al., Autoimmunity reviews, 2026

anti-BCMA are no longer myeloma drugs

- **Why nephrologists should care?”**
  - HLA sensitization
  - lupus nephritis
  - MGCS: AL amyloidosis, cryoglobulinemia
- **Immunology beyond oncology**
- **Plasma-cell depletion is becoming a platform immunotherapy**

Hôpital Bichat Claude-Bernard AP-HP

Université Paris Cité

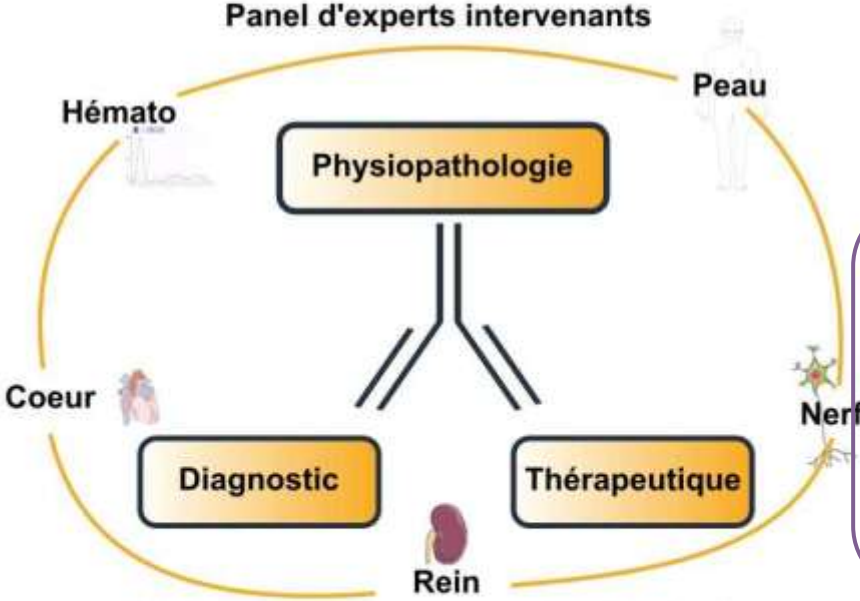
Hôpital Saint-Louis AP-HP



Formation Qualifiante MGCS
Gammapathie Monoclonales de signification clinique
9-10-11 avril 2024

Première formation entièrement dédiée aux gammapathies monoclonales de signification clinique

Panel d'experts intervenants



Pré-inscriptions : camille.cohen@aphp.fr

Distanciel possible pour les non-parisiens

Centre national de référence Amylose AL & autres maladies par dépôts d'immunoglobulines monoclonales

CHU

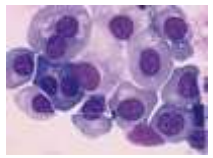
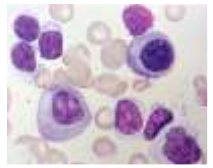
CHU

Nep HémA

blood®
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

Dépôts/précipitation

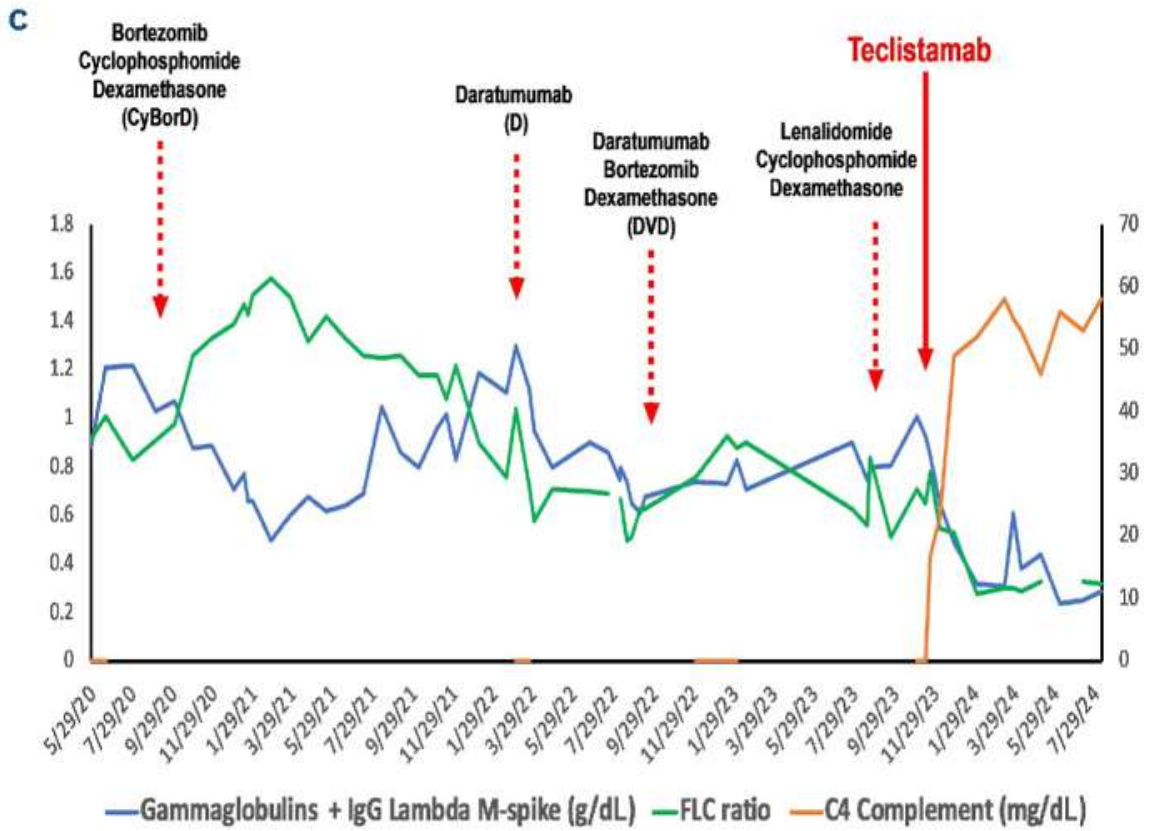
Organisés	**Non organisés**
Amylose AL	**L/HCDD**

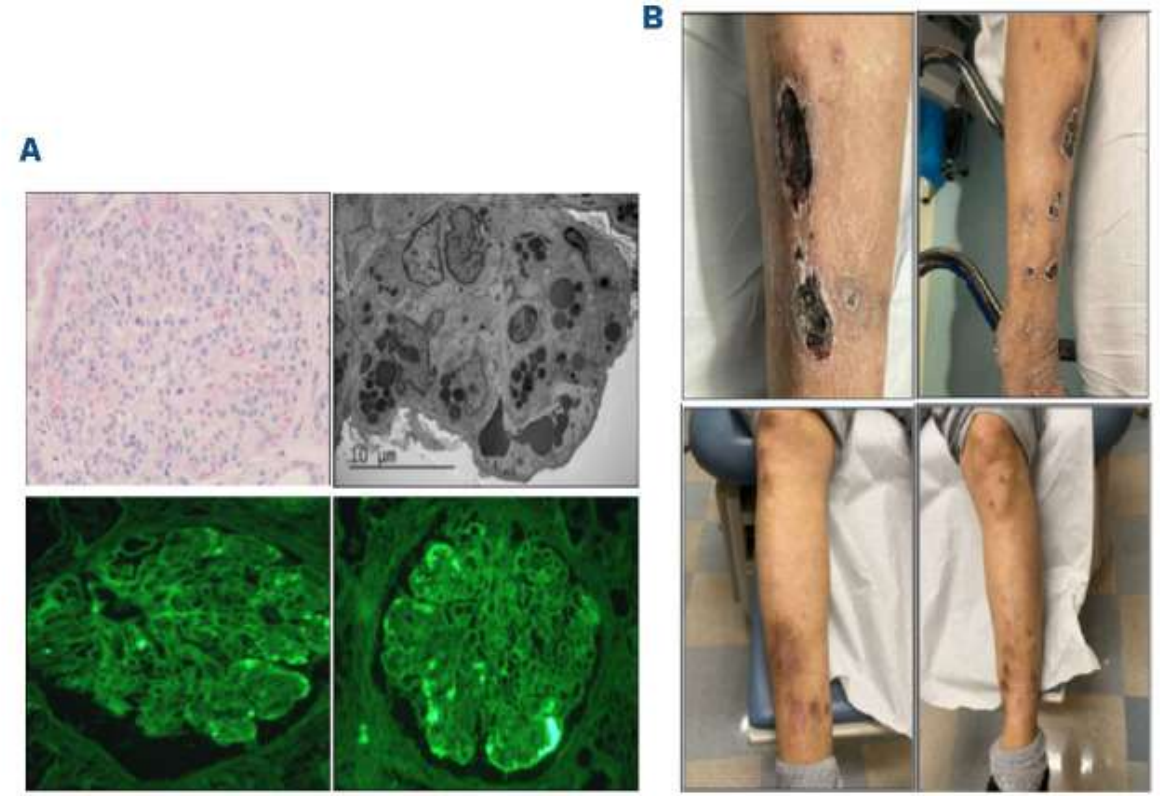
Activité auto-anticorps : **anti-MAG, MAF**
Complexes Immuns : **cryoglobuline**

Surproduction Cytokine
POEMS

Mécanismes inconnus

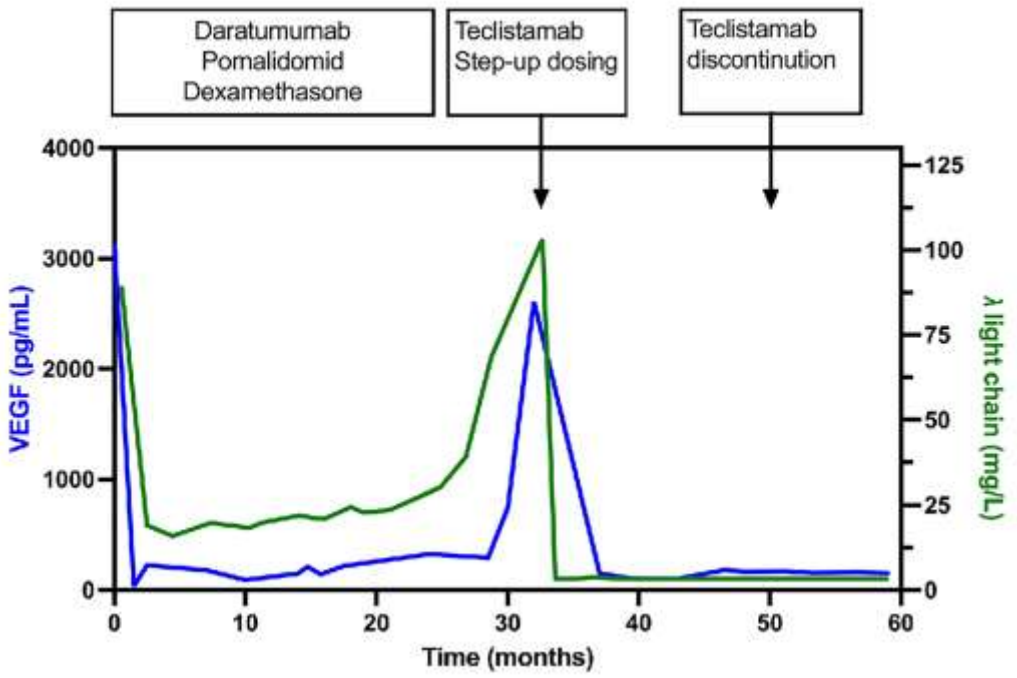
Teclistamab therapy for refractory type 1 cryoglobulinemia

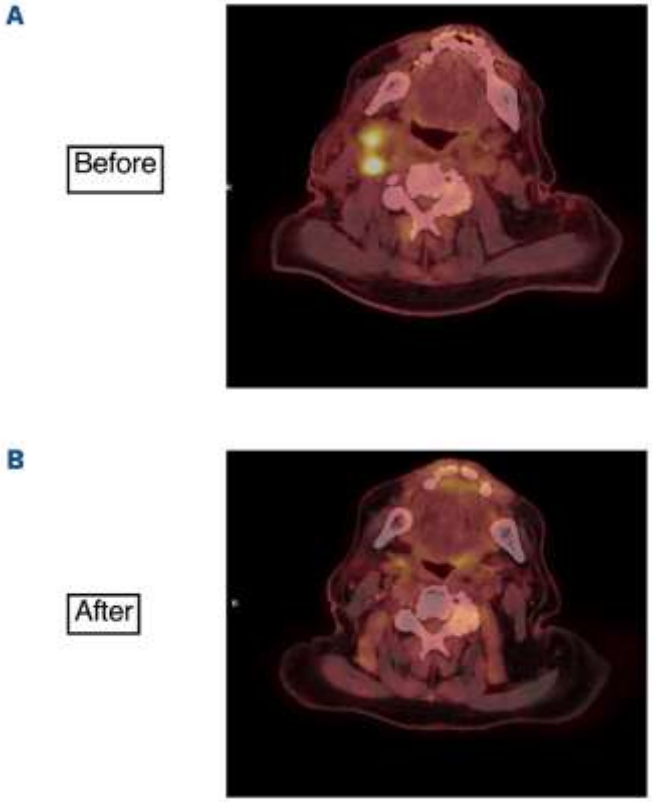




Battaglini. Ju et al. *Haematologica,* 2025

Teclistamab for heavily pretreated relapsed/refractory POEMS syndrome.





Talbot A. et al. *Haematologica,* 2025

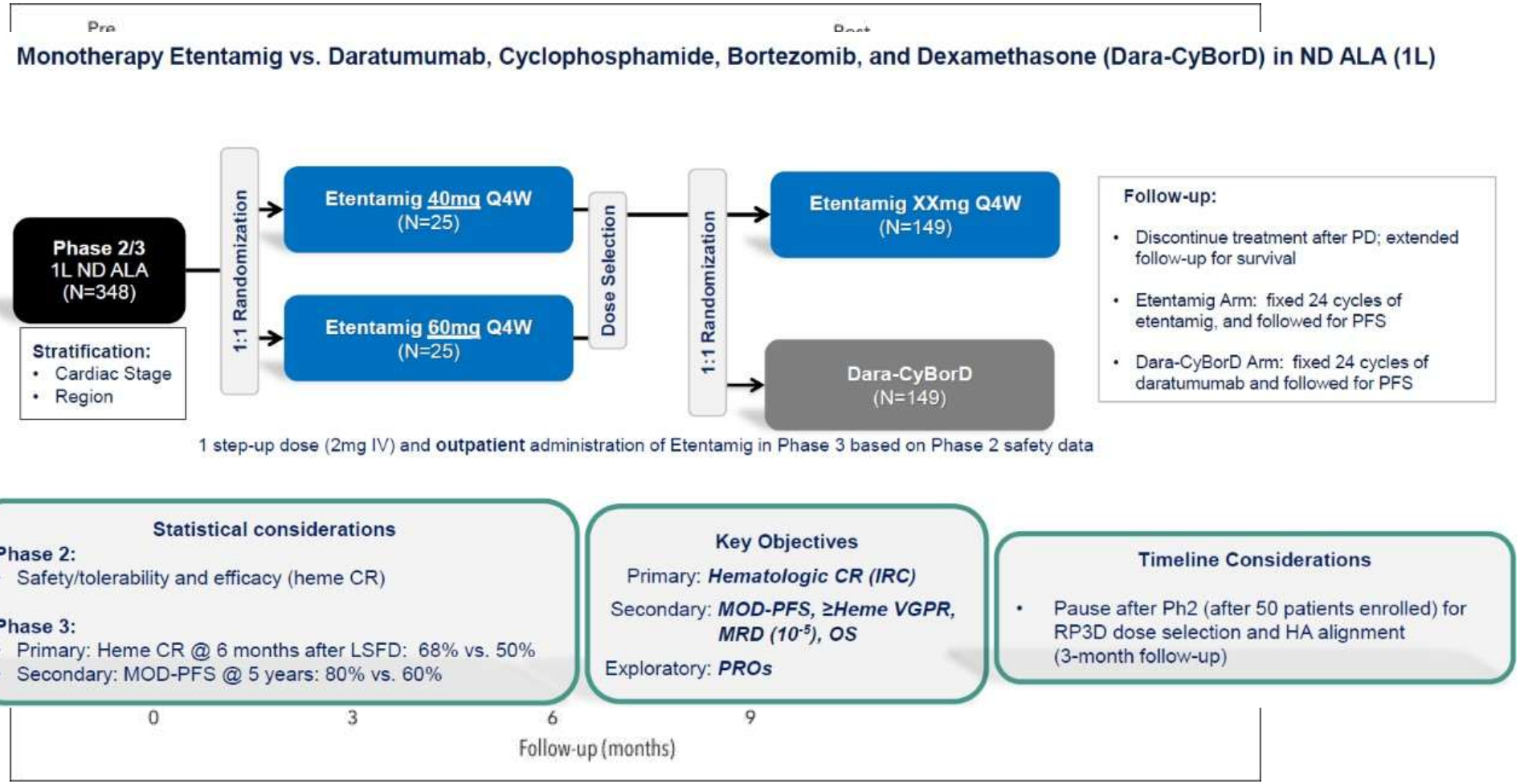
Teclistamab in relapse RR AL amyloidosis: a multinational retrospective case series

Variables	n = 17
Males/females, n (%)	10 (59)/7 (41)
Age at teclistamab initiation, median (range), y	67 (48-83)
Bone marrow plasma cells at diagnosis, median (range), %	21 (5-90)
Involved light chain, κ/λ, n(%)	8 (47)/9 (53)
dFLC at teclistamab initiation, median (range), mg/L	159 (30-555)
Involved organs	
Heart, n (%)	16 (94)
Mayo stage 1	2
2	4
3a	6
3b	4
NT-proBNP, median (range), ng/L	1924 (219-60 887)
Kidney	10 (59)
eGFR, median (range)	44 (7-103)
Serum albumin, median (range), g/L	36 (28-44)
Chronic hemodialysis, n (%)	2 (11)
Liver	2 (11)
Peripheral nerve system	1 (6)
Gastrointestinal tract	1 (6)
t(11;14)	3 (18)
Associated symptomatic MM	10 (59)
Number of prior lines of therapy, median (range)	4 (2-8)
Time between last treatment and teclistamab, median (range), mo	1.25 (0.07-11)
Triple-exposed* patients, n (%)	16 (94)
Triple-refractory patients, n (%)	12 (71)
Penta-exposed† patients, n (%)	3 (18)
Penta-refractory patients, n (%)	3 (18)
Non-IgG M-spike (IgA), n (%)	1 (6)
Time from diagnosis to teclistamab initiation, median (range), y	4 (0.4-23)
Gammaglobulin level at teclistamab initiation, median (range), g/dL	0.37 (0.11-1.3)
Lymphocyte count at teclistamab initiation, median (range), $\times 10^9$/L	1.0 (0.2-6)
Platelets count at teclistamab initiation, median (range), $\times 10^9$/L	243 (146-312)

eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; NT-proBNP, N-terminal pro-brain natriuretic peptide type B.

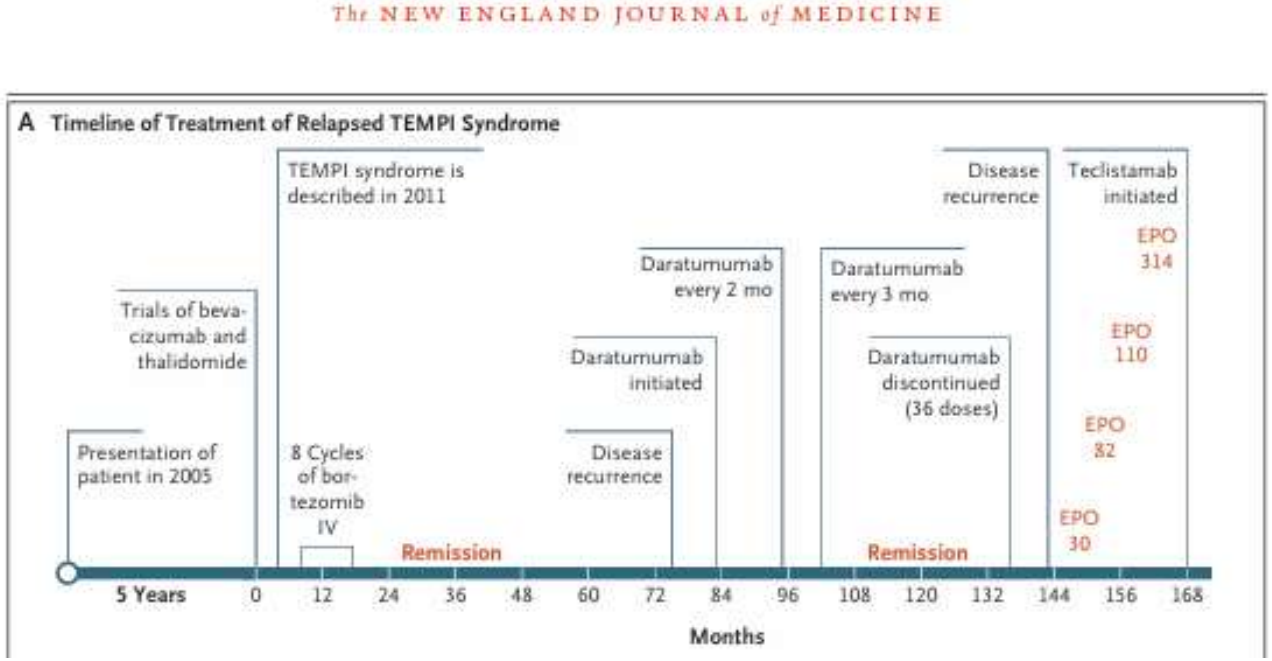
*≥1 proteasome inhibitor (PI), 1 immunomodulatory drug (IMiD), and anti-CD8 monoclonal antibody (mAb)

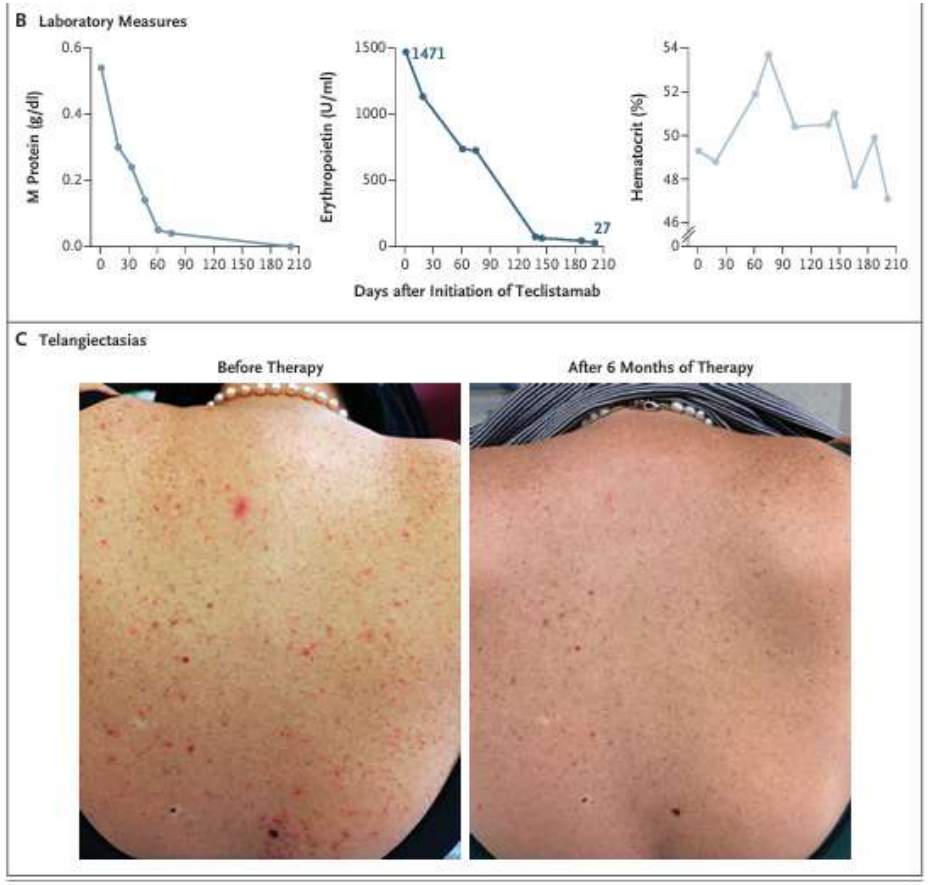
†≥2 PI, 2 IMiDs, anti-CD38 mAb



Forgeard N. et al. *Blood,* 2025

TEMPI Teclistamab





NEJM, 2025

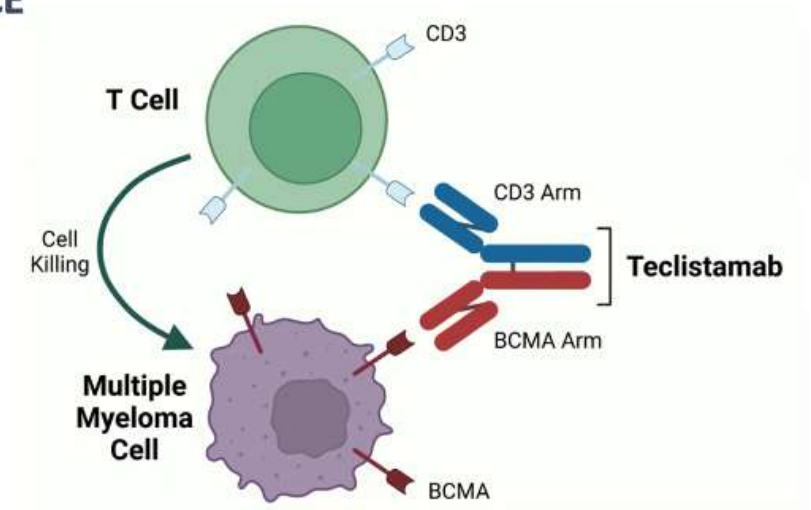
TCE in autoimmune diseases

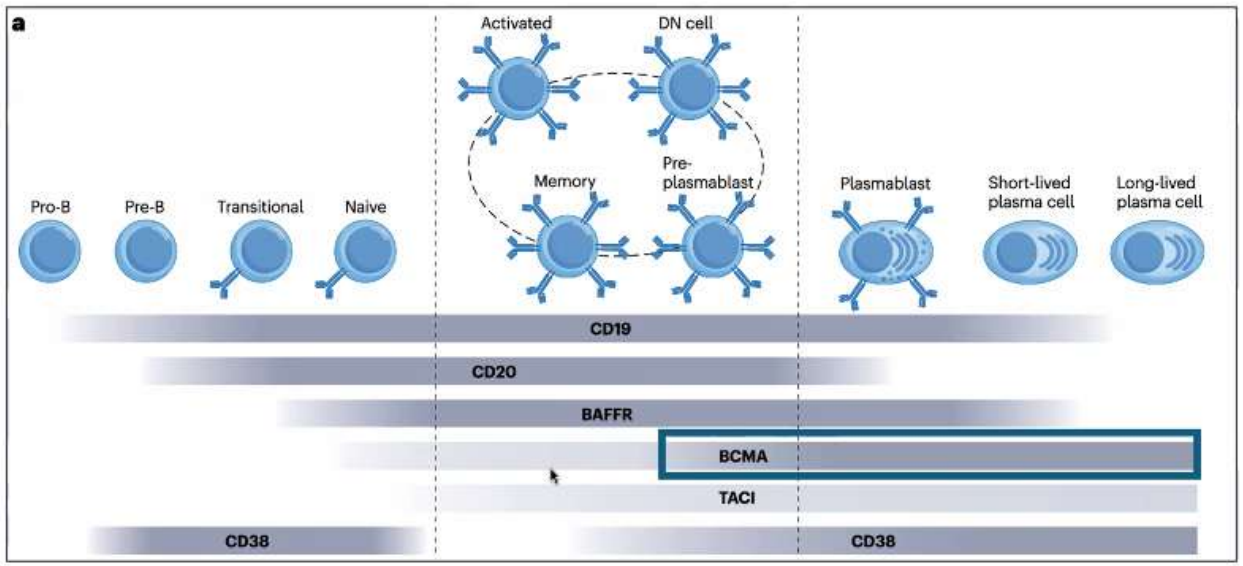
Research on bispecific antibodies in autoimmune diseases.

Bispecific antibody (targets)	Indication	Study phase	Administration	Observed effects
A-319 (CD19 × CD3)	Severe and refractory SLE	Proof of concept	IV (dose escalation)	Rapid depletion of CD19+ B cells, improvement in SLEDAI-2 K, good tolerance
Mosunetuzumab (CD20 × CD3)	Active SLE (SLEDAI-2 K ≥ 4) with ANA ≥1:160 or anti-dsDNA/Sm positive, ≥ 12 weeks and ≥ 2 prior treatments	Phase I (NCT05155345)	SC (fractionated on days 1 and 8)	Prolonged LB depletion, decrease in anti-DNA antibodies, good tolerance
Imvotamab (CD20 × CD3)	Severe LES and moderate to severe RP with positive antibodies and active disease despite ≥2 prior treatments	Phase I (NCT06041568 / NCT06087406)	IV (dose escalation)	High affinity for CD20, depletion of switched and activated LB, efficacy and tolerance currently being evaluated
YK012 (CD19 × CD3)	Moderate to severe LES	Phase Ib/II (NCT07010835)	Not specified	Safety, efficacy, serum markers, quality of life monitored

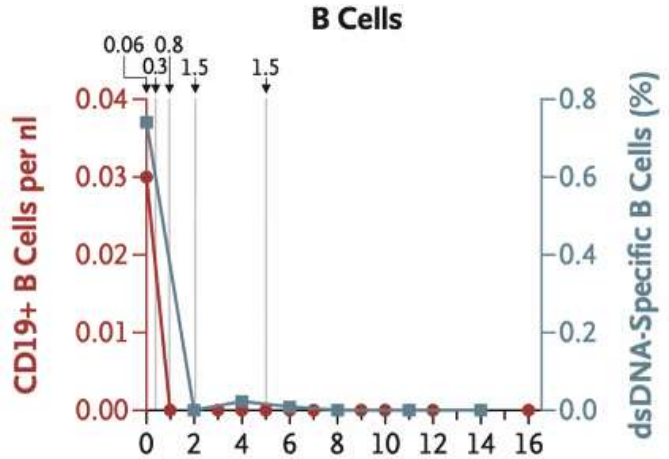
Larue M. et al., Autoimmunity reviews, 2026

CD3xBCMA TCE
Teclistamab

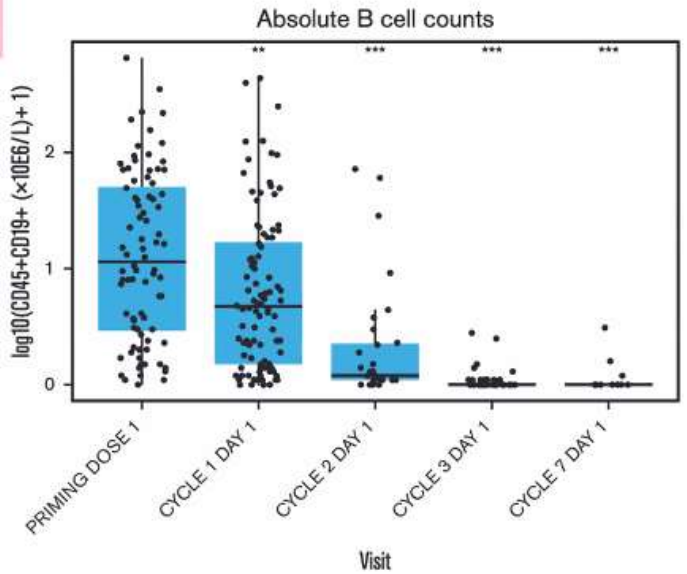




Lupus



Multiple myeloma



Junt, Nat Rev Immunol, 2025 ;
Alexander, NEJM 2024 ; Hagen, NEJM 2024, Frerichs, Blood Adv, 2024

Extreme HLA Sensitization: An Unmet Need in Kidney Transplantation

BACKGROUND

- Preformed anti-HLA antibodies remain a major barrier to successful kidney transplantation
- Highly sensitized patients are exposed to:
  - prolonged dialysis
  - increased rejection risk
  - early graft loss
- **Limitations of Current Desensitization**
- Conventional strategies often fail in extreme sensitization:
- plasmapheresis / imlifidase / ,IVIG
- anti-CD38 monoclonal antibodies
- Main limitation: persistence of:
  - long-lived plasma cells
  - memory B cells

INDEX CASE

- 37-year-old woman
- ESRD secondary to NPHS2 nephrotic syndrome
- Previous graft failure
- cPRA >99.9% despite >20 years on waiting list
- Failure of prior daratumumab-based desensitization

Obinutuzumab + Elranatamab: Profound Immunologic Response

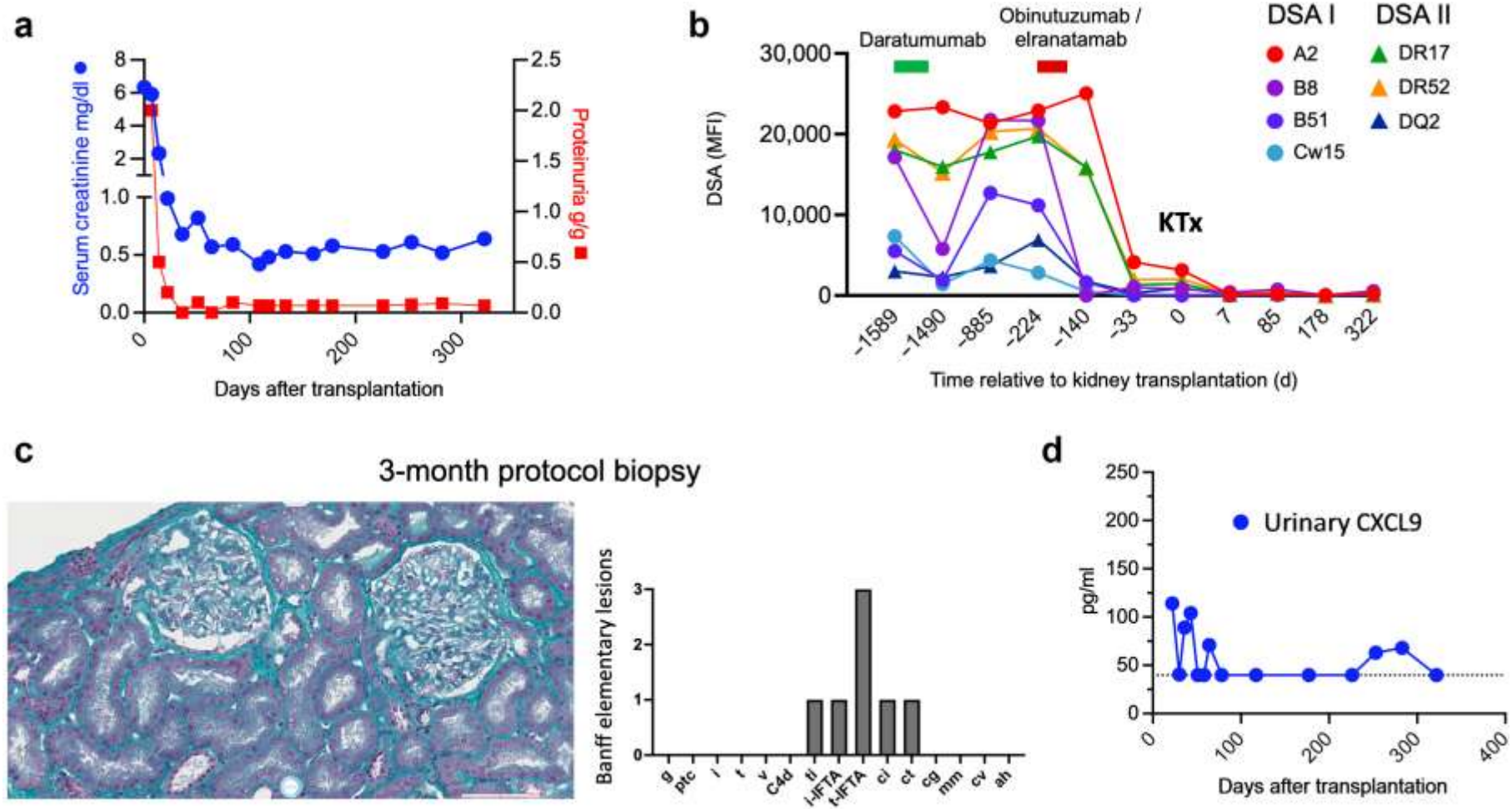
TREATMENT STRATEGY

- **Obinutuzumab**
- **Elranatamab**
- Step-up dosing:
  - 12 mg
  - 32 mg
  - 76 mg
- Then weekly administration

OUTCOMES

- **Safety**
  - No clinical CRS
  - No ICANS
  - No severe infectious complications
  - IVIG replacement maintained antiviral immunity
- **Key Immunologic Results**
- Sustained depletion of circulating CD19+ B cells
- Major reduction of anti-HLA class I and II antibodies
- cPRA evolution:
  - Baseline: 99.96%
  - 6 months: 0%

Leon J. et al. *Kidney international*, 2026



Leon J. et al. *Kidney international*, 2026

Successful Kidney Transplantation: A New Therapeutic Paradigm

TRANSPLANTATION OUTCOME

- Successful deceased donor kidney transplantation
- Markedly reduced donor-specific antibodies before transplant
- No post-transplant plasmapheresis required
- Excellent graft function
- No antibody-mediated rejection
- No DSA rebound
- Negative BK and CMV viremia
- Low urinary CXCL9 levels

PERSPECTIVES

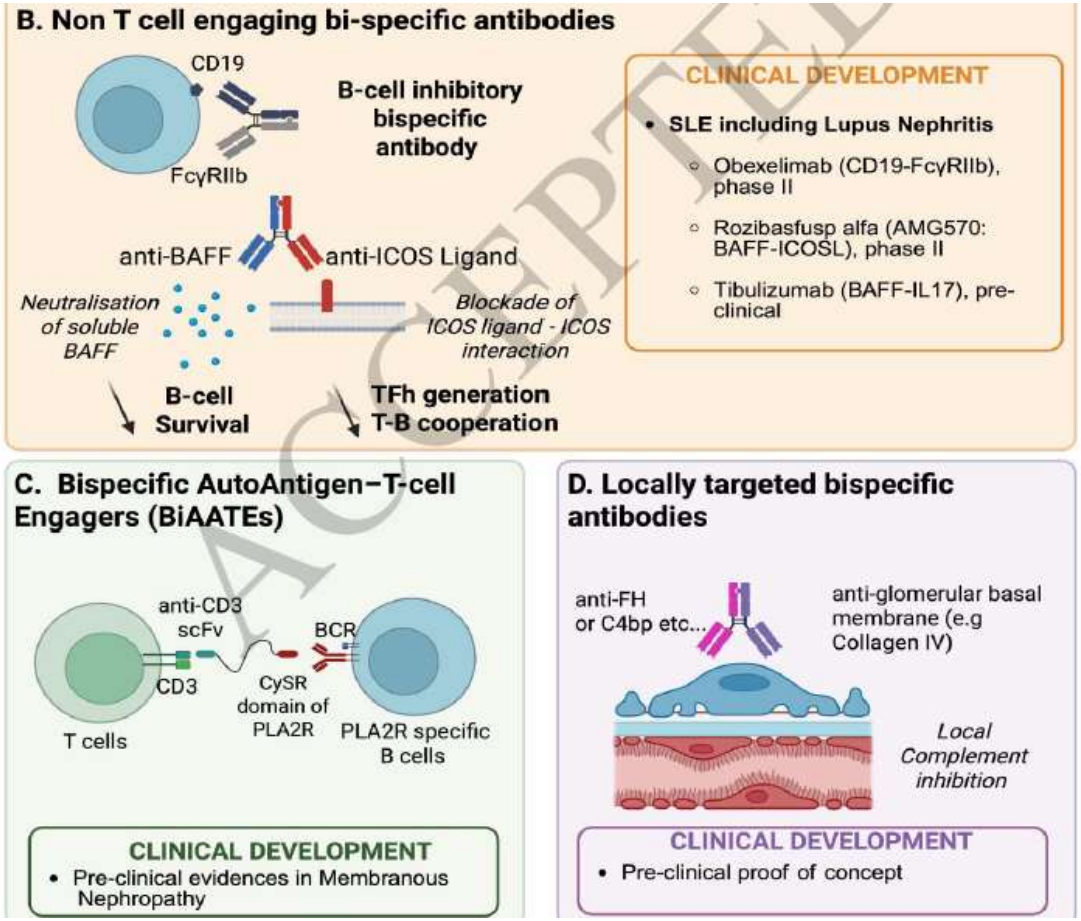
- First successful use of:
- anti-BCMA bispecific antibody
- combined with profound B-cell depletion for extreme HLA desensitization
- Proof-of-concept that BCMA-targeted immunotherapy may:
- transform transplant desensitization
- enable transplantation in previously “untransplantable” patients
- expand plasma cell–targeted therapies beyond myeloma

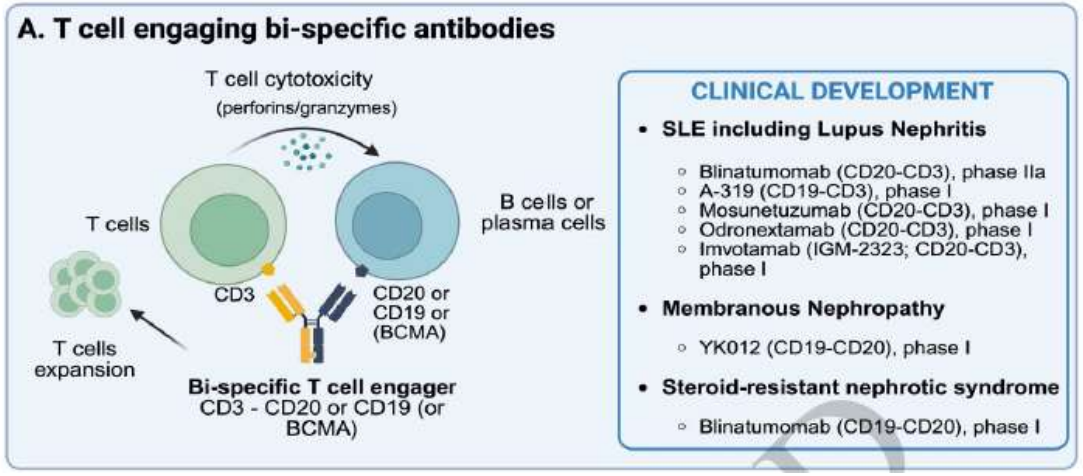
Leon J. et al. *Kidney international*, 2026

Major unresolved questions

- Duration of immune suppression?
- Optimal dosing?
- T-cell exhaustion?
- Infections?
- Cost?
- Fixed duration vs continuous?

Bispecific Antibodies for Glomerular Diseases: Are We Ready for Prime Time?





Karam S, Boudhabhay I, Jhaveri KD. J Am Soc Nephrol. 2026

Paradigm shift: conclusion

Both are **disruptive innovations** in myeloma.

CAR-T → most transformative biologically.

CAR-T = "curative potential" → one-time, deep remission, changing long-term outcomes.

Bispecifics → most transformative practically.

BsAb = "practical paradigm" → widespread accessibility, scalable, real-world impact.

Autoimmune diseases and MGCS +++

Patient profile: frail/unfit → BsAb; young/high-risk → CAR-T.

Safety profile: both have CRS/ICANS; infections more pronounced with BsAb.

Future positioning:

sequential or combinational use? CAR-T upfront, BsAb at relapse? Or BsAb as bridge to CAR-T?

earlier lines, combinations, off-the-shelf allogeneic CAR-T

Likely **both will shape the new paradigm** but in **complementary ways**.

Must be available everywhere