ORUS
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HÔPITAUX SUD-LORRAINE
GROUPEMENT HOSPITALIER DE TERRITOIRE

CHRU NANCY

Traitement du myélome multiple en rechute/réfractaire : Actualités en 2024

IHE 2024

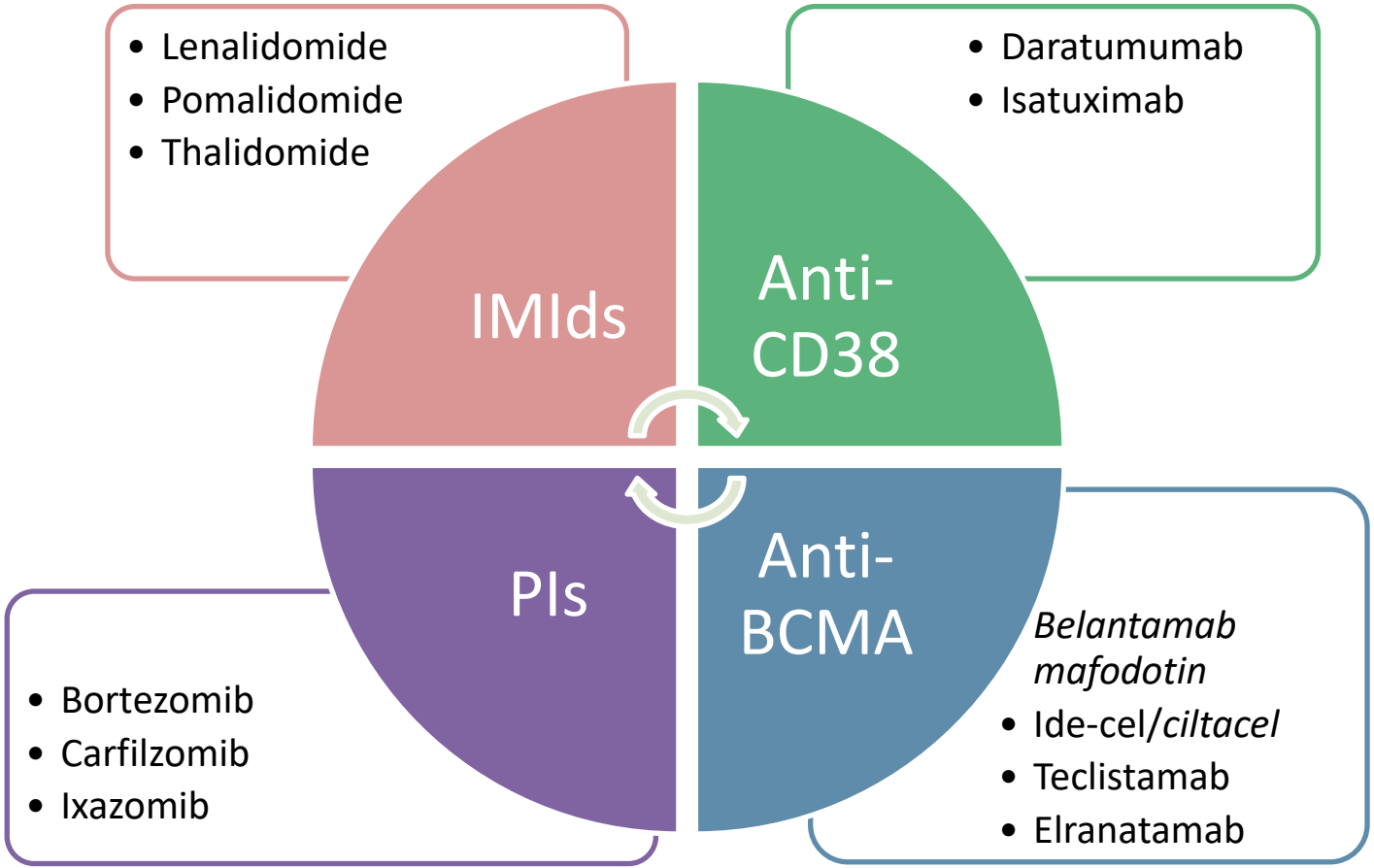
C.JACQUET – CHRU Nancy

Liens d’intérêts

Advisory board et invitation au congrès/réunion :

- Janssen
- Pfizer
- GSK
- Amgen
- Sanofi
- Menarini - Stemline

4 piliers dans traitement du MM en 2024



Autres molécules disponibles :

- *Selinexor*
- Melfufen
- *CELMoDs*
- Venetoclax
- *Elotuzumab*

Problématiques actuelles

- Résistance aux drogues majeures utilisées dès la 1ère ligne
  - IMiD, IP, Anti-CD38
  - Lenalidomide en continu => Len refractaire
  - Réfractaire précoce à l'anti-CD38

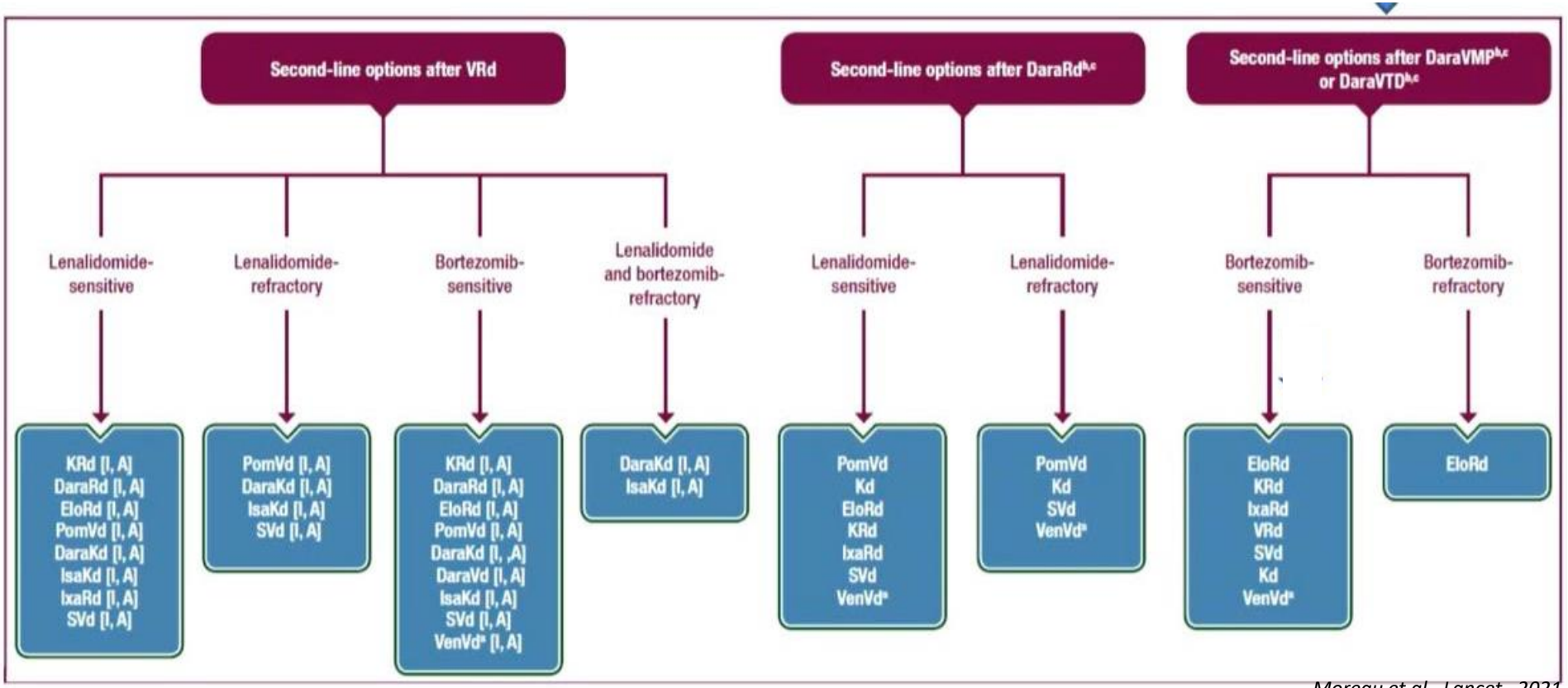
- Qui des patients qui sont :
  - Lenalidomide réfractaire
  - Anti-CD38 réfractaire
  - IP réfractaire

} **= Triple réfractaire**

- Utilisation d'une triplette = approche standard

- Quid de la tolérance et de la toxicité

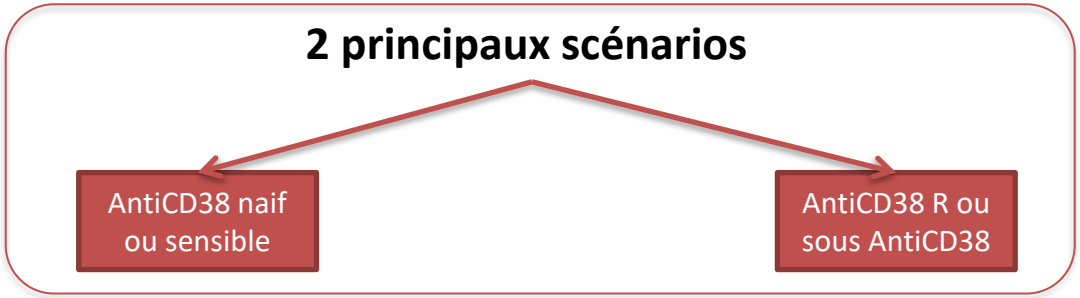
Options thérapeutiques à la 1ère rechute : recommandations EHA-ESMO



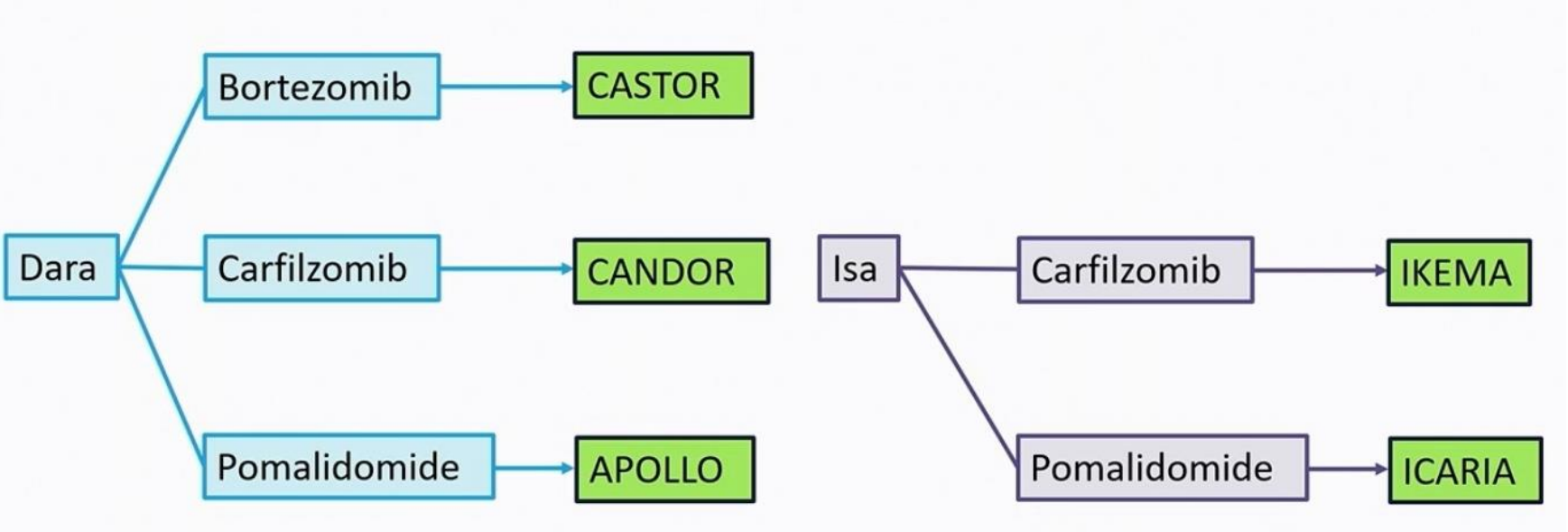
Moreau et al., Lancet, 2021

Lenalidomide réfractaire

- Utilisation en induction et maintenance chez les patients TE et NTE
- Mauvais pronostic chez les patients Len ref après 1-3 lignes de TTT – Médiane OS 21,5mois
- Principales stratégies utilisées (en dehors T-cell thérapie)
  - Utilisation d'une autre classe active
    - Anti-CD38
    - IP
    - Ac conjugué anti-BCMA
  - Utilisation d'un autre IMiD ou apparentés
    - Pomalidomide
    - CELMoDS (Iberdomide)



Len réfractaire + AntiCD38 naïf



Mateos M-V et al. *Clin Lymph Myeloma Leuk* 2019; 509; Sonneveld P et al. *JCO* 2022; 41:1600; Usmani S et al. *Lancet Oncol* 2022; 23:65; Usmani S et al. *Blood Advances* 2023: 7:3739; Palumbo P et al. *NEJM* 2016;375:754; Dimopoulos M et al. *Lancet* 2020; 396: 186; Dimopoulos M et al. *Lancet Haematol* 2023; 10: e813 ; Dimopoulos M et al. *Lancet Oncol* 2021;22:801; Martin T et al. *Blood Cancer J* 2023; 13:72; Dimopoulos M et al. *Am J Hematol* 2023;98: e15; Attal M et al. *Lancet* 2019; 394: 2096; Moreau P et al. *Lancet* 2021; 397: 2361; Richardson P et al. *Lancet Oncol* 2022; 23:416

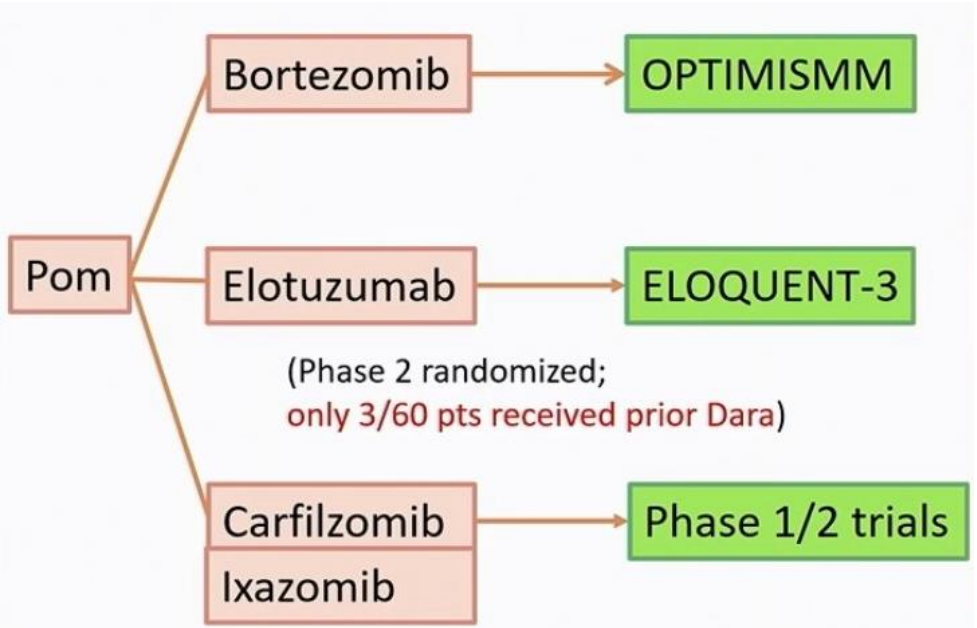
Etudes de phase III

Study	Regimen	Median prior lines	% Len-refractory/ number		PFS (m) Len refractory	PFS HR Len refractory	OS (m) Len refractory	OS HR Len refractory
CASTOR	Dara-Vd	2 (1-10)	24%	83	7.8	0.44*	28.9 (IMiD-R)	0.97 (IMiD-R)
	Vd				4.9		32.6	
CANDOR	Dara-Kd	2 (1-3)	32%	99	28.1	0.46*	NR	0.69
	Kd				11.1		38.2	(0.43-1.11)
IKEMA	Isa-Kd	2 (1-3)	32%	57	NR	0.60		not yet reported
	Kd				15.7			
APOLLO	Dara-Pd	2 (1-5)	79%	120	9.9	0.66	34.4 (all pts)	0.82 (all pts)
	Pd				6.5		23.7 (all pts)	(0.61-1.11)
ICARIA	Isa-Pd	3 (2-11)	94%	144	11.4	0.59	22.7	0.79
	Pd				5.6		17.5	(0.59-1.05)

*Statistically significant; NR: not reached

Mateos M-V et al. *Clin Lymph Myeloma Leuk* 2019; 509; Sonneveld P et al. *JCO* 2022; 41:1600; Usmani S et al. *Lancet Oncol* 2022; 23:65; Usmani S et al. *Blood Advances* 2023: 7:3739; Palumbo P et al. *NEJM* 2016;375:754; Dimopoulos M et al. *Lancet* 2020; 396: 186; Dimopoulos M et al. *Lancet Haematol* 2023; 10: e813 ; Dimopoulos M et al. *Lancet Oncol* 2021;22:801; Martin T et al. *Blood Cancer J* 2023; 13:72; Dimopoulos M et al. *Am J Hematol* 2023;98: e15; Attal M et al. *Lancet* 2019; 394: 2096; Moreau P et al. *Lancet* 2021; 397: 2361; Richardson P et al. *Lancet Oncol* 2022; 23:416

Utilisation du Pomalidomide - Len réfractaire (et Anti-CD38 exposés/réfractaires)



	Median prior lines	% Len-R	PFS (m) for Len-R	PFS HR for Len-R	OS (m) Len-R	OS HR Len-R
PVd	2 (1-3)	71%	9.5	0.65*	[35.6] all pts	0.94 all pts
Vd			5.6		[31.6] all pts	
EloPd	3 (2-8)	98%	10.2[a]	0.56[a]	[29.8] all pts	0.60
Pd			4.7[a]		[17.4] all pts	
KPd	6 (2-12)	100%	7.2	-	20.6	
IxaPd	3 (2-5)	100%	4.4		34.3	

a: Len+PI refractory; *Statistically significant

Richardson P et al. *Lancet Oncol* 2019; 20: 781-94; Dimopoulos M et al. *J Clin Oncol* 2022; 41:568-78; Dimopoulos M et al. *NEJM* 2018; 379:1811-22; Gentile M et al. *Haematologica* 2024 109:245-55; Shah J et al. *Blood* 2015;126:2284-90; Sonneveld P et al. *HemaSphere* 2022; 6:e786; Voorhees P et al. *Am J Hematol* 2021; 96: 1595-1603

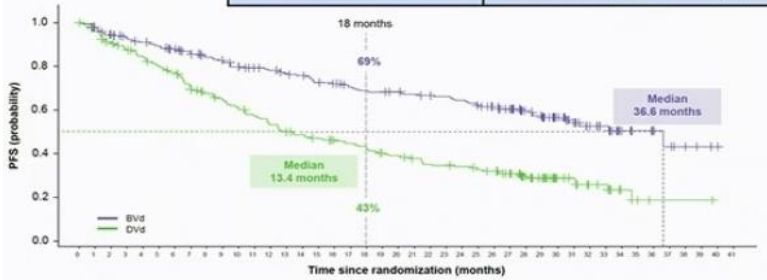
Len réfractaire + Anti-CD38 réfractaire

- Utilisation T-cell thérapie

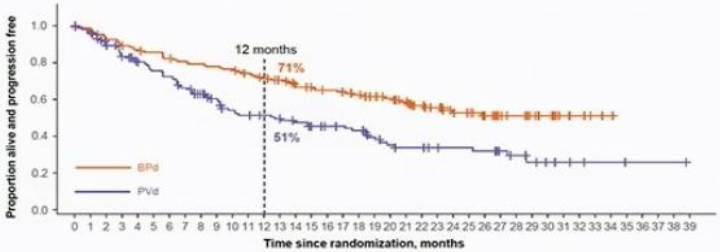
- Thérapie non antiCD38 – non Len/Pom
  - Belantamab
  - CELMoDs

Retour du Belantamab

DREAMM-7	BVd (n=243)	DVd (n=251)
PFS (mo)(95% CI)	36.6 (28.4-NR)	13.4 (11.1-17.5)
HR	0.41 (0.31-0.53) p<0.001	



DREAMM-8	BPd (n=155)	PVd (n=147)
PFS (mo)(95% CI)	NR (20.6-NR)	12.7 (9.1-18.5)
HR	0.52 (0.37-0.73) p<0.001	



Prior Tx/refractoriness	No previous Dara exposure (1-2% exposed, in fact)	23-24% anti-CD38 refractory
	86-90% PI exposed	24-26% PI refractory
	34% Len refractory	76-81% Len refractory
	81-86% iMid exposed	100% iMid exposed
Prior lines	51% had 1 prior line	52-53% had 1 prior line
PFS (m); HR-Len refractory	25.0 (18.1-NR); HR 0.37 (0.24-0.56)	HR 0.45 (0.31-0.65)
PFS (m); HR – anti-CD38 refractory	N/A	HR 0.65 (0.36-1.18)

Hungria V et al. *NEJM* 2024; 391:393-407; Dimopoulos MA et al. *NEJM* 2024; 391:408-21

Retour du Belantamab

Bilateral Worsening in Best Corrected Visual Acuity

20/20

20/50

20/200

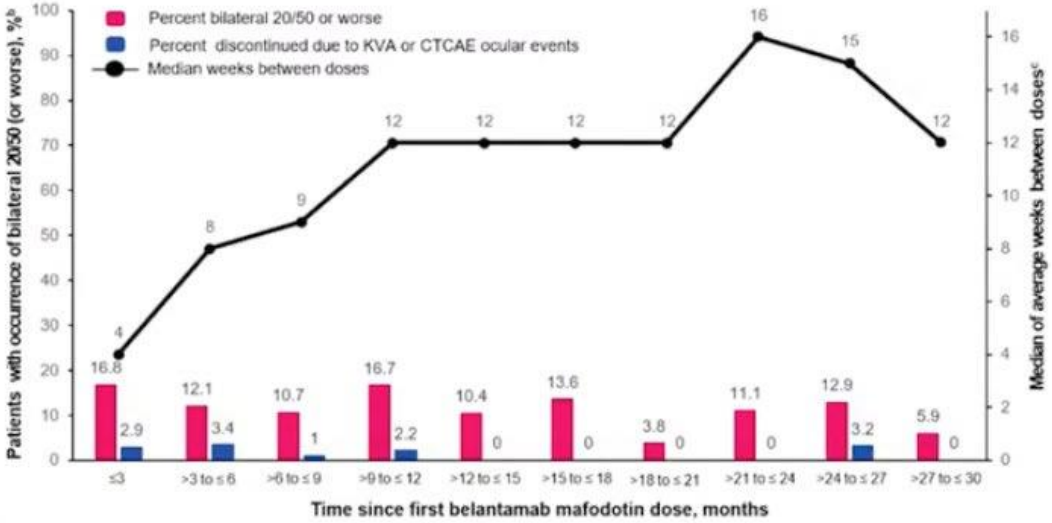
BPd	Bilateral worsening of BCVA in patients with normal baseline (20/25 or better in ≥1 eye)	
	20/50 or worse[a]	20/200 or worse[a]
Patients, n/N (%)	51/150 (34)	2/150 (1)
Time to onset of first event, median (range), days	112 (28-761)	351 (29-673)
Time to resolution of first event to normal baseline, median (range), days[b,c]	57 (14-451)	NA[d]
First event resolved to normal baseline, n/N (%)[c]	43/51 (84)	1/2 (50)
Follow-up ended with event ongoing, n/N (%)[c,e]	4/51 (8)	1/2 (50)

Visual acuity changes that could affect activities of daily living were reversible in most patients

Dimopoulos M al., EHA 2024

Retour du Belantamab

Dose Modifications Optimize Efficacy vs Ocular Safety[a]



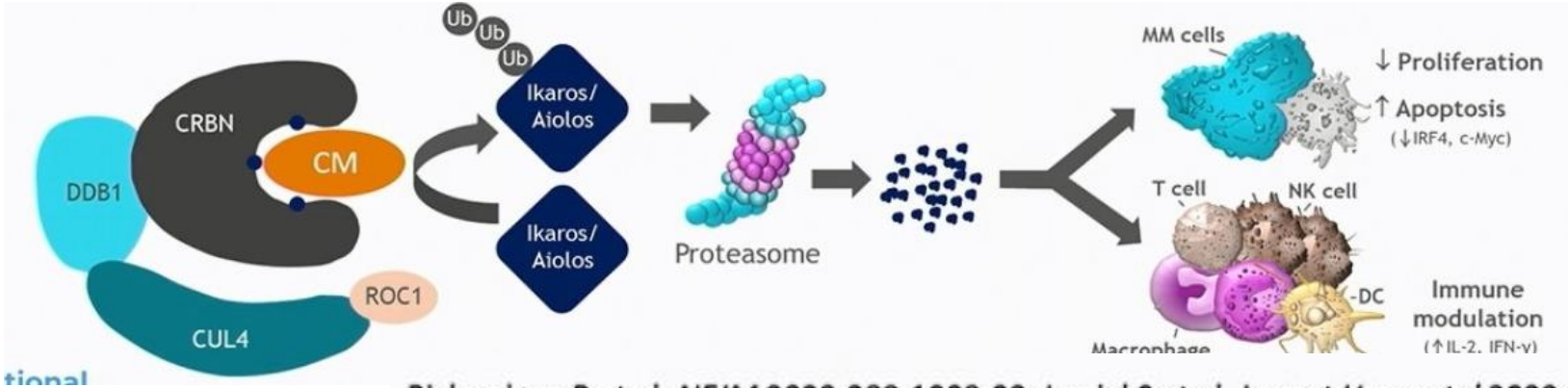
	≤3	>3 to ≤6	>6 to ≤9	>9 to ≤12	>12 to ≤15	>15 to ≤18	>18 to ≤21	>21 to ≤24	>24 to ≤27	>27 to ≤30
No. of patients on treatment[b]	137	116	103	90	77	59	52	45	31	17
No. of patients with bilateral 20/50 or worse[b]	23	14	11	15	8	8	2	5	4	1
Median days between doses[b]	28.5	56	63.5	84	84	86	84	111	106	84
No. of patients who discontinued due to KVA or ocular CTCAE event[b]	4	4	1	2	0	0	0	0	1	0

- Median time between doses increased the longer patients were on therapy
- Longer dosing intervals did not impact PFS[d]
  - Median PFS was not reached in BPd-treated patients (N=93) with ≥1 dose delay of ≥12 weeks
- 16.8% of patients experienced BCVA 20/50 or worse within the first 3 months of treatment; prevalence remained low thereafter, generally decreasing with time
- Treatment discontinuations due to ocular events were low

Dimopoulos M al., EHA 2024

CELMoDs – Mezigdomide et Iberdomide

- Modulateurs de la ligase E3 de Cereblon de nouvelle génération avec une capacité de liaison augmentée à la cible de 10 à 20 fois > lenalidomide – pomalidomide
- **MEZI + DXM** : mediane 6 lignes ant – 100% de triple-refracatire
  - 30% ayant eu un TTT antiBCMA (BsA – CART)
  - OR 41%, PFS 4,4 mois (Médiane suivie 7,5mois)
- **IBER + DXM** : mediane 6 lignes ant – 97% de triple-réfractaire
  - OR 26%, PFS 3mois (Médiane suivie 5,8mois)



Richardson P et al. *NEJM* 2023;389:1009-22; Lonial S et al. *Lancet Haematol* 2022; 9:e822-31.

Mezigdomide en association

	MEZI-Vd (expansion) N=49	MEZI-Kd N=27	MEZI-Dara-d N=59 (3 dose cohorts)	MEZI-Elo-d N=20
Median prior lines	1 (1-3)	2 (2-4)	3 (2-5)	3 (2-5)
IMiD refractory	63%	89%		
Len ref			71%	70%
Pom ref			31%	30%
Anti-CD38 refractory	35%	74%	0	80%
TCR	2%	37%	0	30%
OR	84-91%	78-89%	78%	45%
≥VGPR	63-82%	33-55%	28*-74%	15%
OR Len+ αCD38 ref	75%	82%	N/A	Not reported but activity seen
DOR (months)	NR (12.1-NR)	12.3	9.5 to NR	5.0
F/up (months)	12.7	12.5	3.1-22.6	7.1

Oriol A et al. *Clin Lymph Myeloma Leuk* 2023; 23 (Suppl 2): S31
Richardson P et al. *Blood* 2023; 142 (Suppl 1): 1013

Iberdomide en association

- IBER + Dara / Bz /Cfz + DXM
- Médiane de suivi 4,2- 5mois

	IBER-Dd (n=43)	IBER-Vd (n=25)	IBER-Kd (n=9)
No. Prior lines	4 (2-13)	5 (1-4)	6 (2-8)
IMiD-refractory	95%	80%	89%
Anti-CD38 refractory	37%	80%	78%
TCR	33%	48%	56%
OR (≥VGPR)	46% (22%)	56% (28%)	50% (38%)
DOR	NR	9 mo	NR

Etude IFM 2022-01 : I2D

- Age > 70ans,
- Frailty score de fragilité > 2 dans 50%

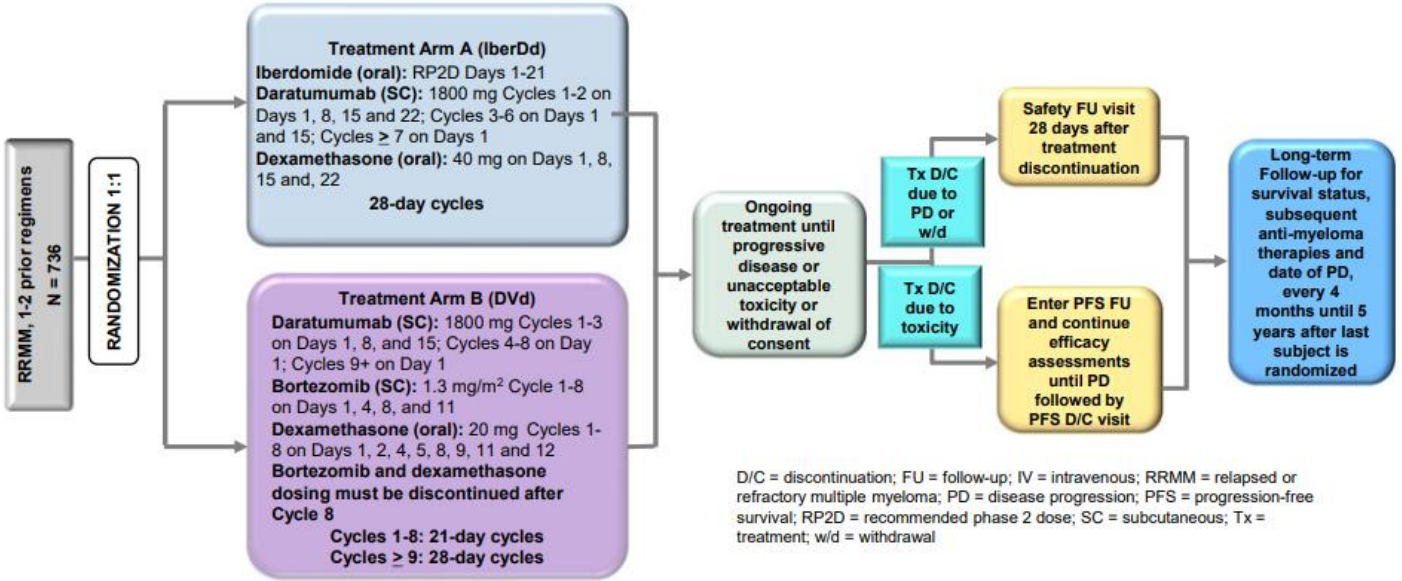
	IBER-Ixa-d (n=70)
No. Prior lines	1
Len-refractory	74%
Anti-CD38 refractory	37%
OR (≥VGPR)	64% (33%)
PFS (Len+αCD38 ref)	10 mths
PFS (all pts)	13 mths
12 month OS (all pts)	85%

Lonial S et al., Clin Lymph Myeloma 2021 ; Touzeau C et al., JCO 2024

Iberdomide en association

Etude en cours

- Autre phase 2 combinaison avce cyclophosphamide et Carfilzomide + Dara
- Phase 3 : Iber-Dara-d vs Dara-VD : EXCALIBER



Autres régimes

- **Inhibiteurs du Bcl-2** : t(11;14) et expression élevée de Bcl-2 : Venetoclax, Sonrotoclax
- **SELINEXOR**

	Sd[1] (n=122)	SVd[2] (n=195)	SKd[3] (n=23)	SPd[3] (n=23)	SDaraVd[4] (n=24) (part 1)
Prior LOT	7 (3-18)	2 (1-2)	4 (2-8)	4 (2-10)	3 (2-3)
IMiD ref	100%	26%	83%	91%	96%
αCD38 ref	100%	NR	96%	91%	0
TCR	100%	NR	52%	74%	IMid/PI ref 70%
PFS (mths)	3.7 (TCR)	10.2 (Len-ref)	15 (all pts) 23.7 (TCR)*	8.9 (TCR)	7.2 (all pts)**
OS (mths)	8.6 (TCR)	26.7 (Len-ref)	33 (all pts)	9.6 (all pts) – mF/up 12mths	28.5 (all pts)

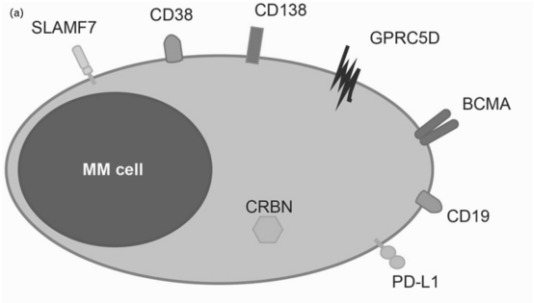
- Combinations with Ixazomib, Pom+Elo, Belantamab, Dara+Pom ongoing

1. Chari A et al. *NEJM* 2019; 381:727-38; 2. Mateos MV et al. *Eur J Haematol*. 2024;113:242–252. 3. Schiller GJ et al. *Clin Lymph Myeloma Leuk* 2023; 23:e286–e296; 4. Gonzalez-Calle, V. et al. *Hematologica* 2024; 109:2220-8.

Cible redirecting T-cells

BCMA

- Récepteur transmembranaire membre de la famille des récepteurs TNF
- APRIL et BAFF 2 ligands connus activant la voie NFκB
- BCMA favorise la survie des plasmocytes, croissance, résistance à l'apoptose, adhésion et angiogenèse
- Le clivage de la γ-secretase provoque excrétion de BCMA soluble
- BCMA est exprimé sur les PCs malins, à faible niveau sur PCs normaux



GPRC5D

- Membre de la famille des récepteur couplé à la protéine G avec une fonction inconnue
- Expression limités au PCs dans la MO avec une faible expression dans les tissus normaux

FcRH5

- protéine de surface de la superfamille des Ig
- Expression uniquement sur la lignée B avec augmentation de l'expression sur B mature et PC
- Rôle dans la prolifération d'isotype

Verkleij et al. Curr Opin Oncol. 2020 ; Rees and Kumar, Leukemia and Lymphoma, 202 4 ; Pillarisetti et al., Blood 2020 ; Rodriguez-Otero et al. Blood Cancer Journal, 2024 ; Elkins et al., Molecular Cancer Therapeutics, 2012

CART Cell : cible anti-BCMA

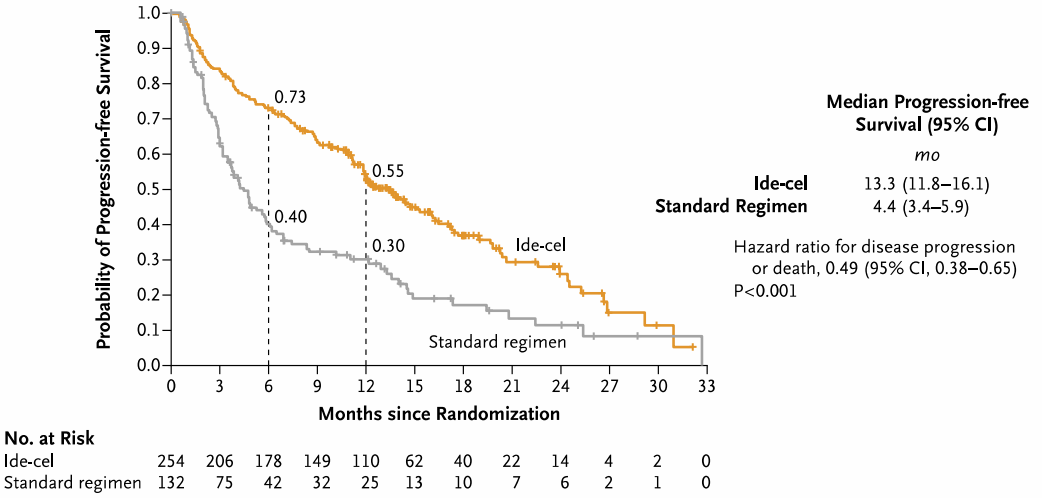
Essai	KarMMa (n = 128) (Munshi et al., 2021)	CARTITUDE-1 (n = 97) (Usmani et al., 2021)	EVOLVE (n = 62) (Mailankody et al., 2020)	CRB-402 (n = 38) (Alsina et al., 2020)
Nom du CAR-T	idecabtagene vicleucel (ide-cel) ou bb2121	ciltacabtagene autoleucel (cilta-cel), ou JNJ-4528	orva-cel (JCAR125)	bb21217: bb2121 + bb007 (inhibiteur de PI3K)
Domaine de reconnaissance de l'antigène	scFv murin	2 V_HH lama en tandem, contre deux épitopes différents	scFv humain	scFv murin
Nombre de CAR-T réinjectées	150 à 450 $\times$ 10^6 (dose autorisée)	0,75 $\times$ 10^6/ kg	300 à 600 $\times$ 10^6	450 $\times$ 10^6
Médiane de lignes de traitements antérieurs	6	6	6	6
HR/ atteinte extra-médullaire (%)	35/ 39	24/ 13	41/ 23	34/ NC
Triple-/ Penta-réfractaires (%)	84/ 26	88/ 42	94/ 48	63/ NC
Réponse : toute profondeur/ réponse complète (%)	global : 73/ 33 450 $\times$ 10^6 : 81/ 39	98/ 80	92/ 36	83/ 33
MRD négative (%)	global : 26 450 $\times$ 10^6 : 28	58	NC	NC
SSP médiane/ SG médiane (mois)	global : 8,8/ 19,4 450 $\times$ 10^6 : 12,1/ non atteinte	Non atteintes SSP à 18 mois : 66 % Survie globale à 18 mois : 81 %	Non atteintes à 6 mois	Non atteintes SSP à 12 mois : 58 %
CRS : total/ $\geq$G3 (%)	84/ 5	95/ 5	89/ 3	66/ 6
CRS : délai apparition/ durée (j)	1/ 5	7/ 4	2/ 4	3/ 4
ICANS : total/ $\geq$G3 (%)	18/ 3	17/ 2	13/ 3	24/ 8
Infections : total/ $\geq$G3, %	69/ NC	NC	40/ 13	NC/ 18

NC : non communiqué ; HR : haut risque cytogénétique : del(17p), t(4;14), et t(14;16) ; MRD : minimal residual disease, au seuil 10^{-5} ; SSP : survie sans progression ; SG : survie globale ; $\geq$G3 : grade supérieur ou égal à 3 selon les classifications internationales de référence ; CRS : cytokine release syndrome (selon Lee et al., 2014) ; ICANS : immune effector cell-associated neurotoxicity syndrome (selon NCI CTCAE).

Ferment et Arnulf, Blucan,, 2021

KarMMa-3 : ide-cel versus régime standard dans MM en rechute

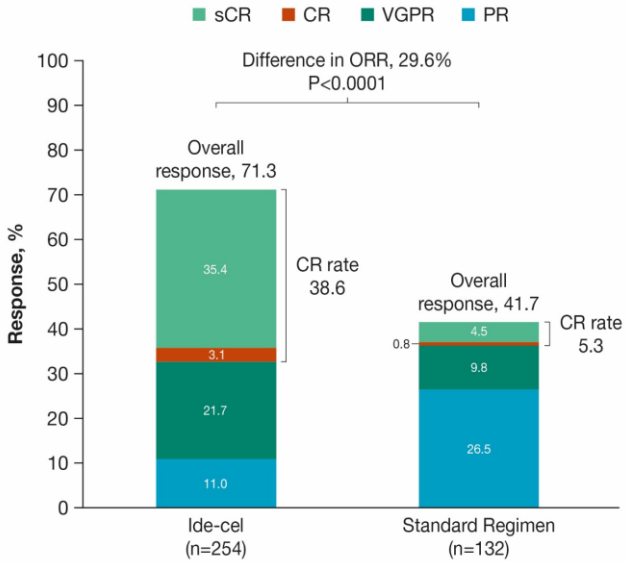
Ide-cel versus régime standard (Dara-Vd/DaraPd/Ird/Kd/Elo-Pd)
2 à 4 lignes de traitement antérieures – Triples exposés



Median Progression-free Survival (95% CI)

	mo
Ide-cel	13.3 (11.8–16.1)
Standard Regimen	4.4 (3.4–5.9)

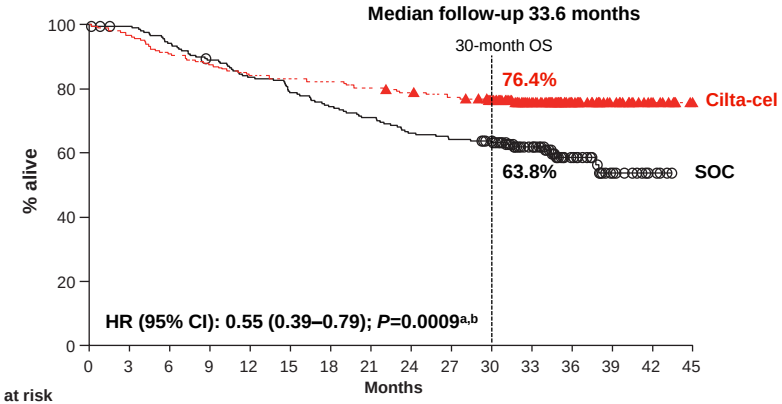
Hazard ratio for disease progression or death, 0.49 (95% CI, 0.38–0.65)
P<0.001



Rodriguez-Otero et al., NEJM, 2023

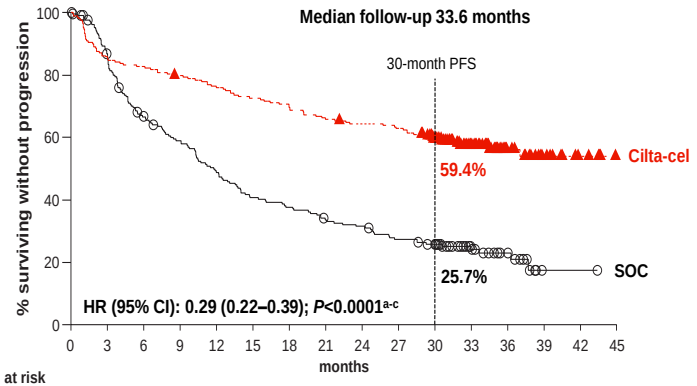
CARTITUDE-4 : cilta-cel versus régime standard dans MM en rechute

Cilta-cel versus régime standard (PVd/DaraPd)
1 à 3 lignes de traitement antérieures – Lenalidomide réfractaire



No. at risk																
Cilta-cel	208	201	190	183	175	173	171	167	163	159	146	93	44	24	9	0
SOC	211	207	196	184	173	163	154	147	137	133	127	71	35	13	4	0

First CAR-T to demonstrate overall survival benefit in multiple myeloma



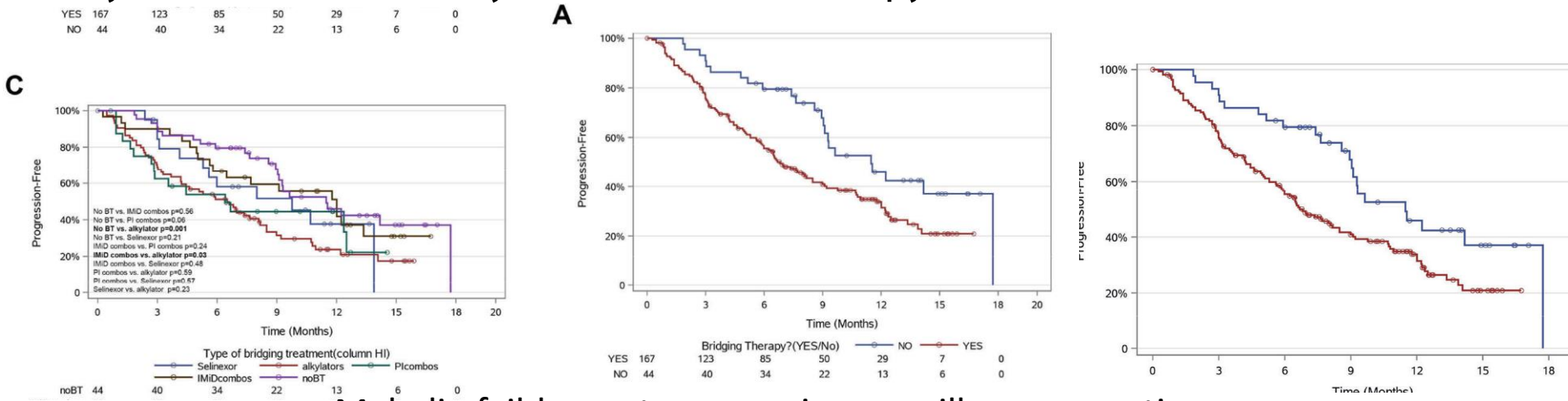
No. at risk																
Cilta-cel	208	177	172	165	157	150	145	136	132	129	111	65	29	13	5	0
SOC	211	176	133	116	96	80	74	65	61	52	47	25	12	1	1	0

~70% reduction in the risk of progression or death in patients who received cilta-cel and mPFS has not been reached

Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

Impact du bridging sur l'efficacité des CART

Real-world impact of bridging therapy on outcomes of ide-cel for myeloma in the U.S. Myeloma Immunotherapy Consortium



Maladie faiblement progressive = meilleur pronostic

Moins option pour un bridging optimal

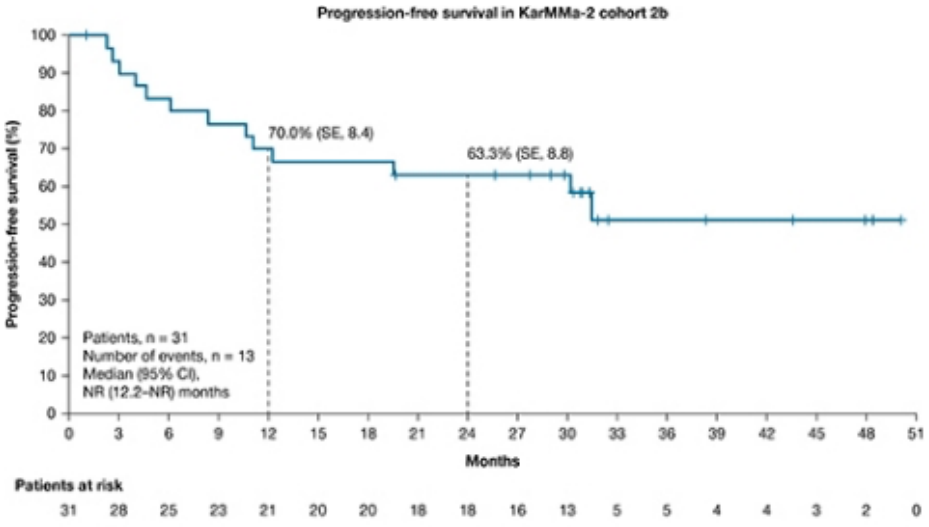
Patients haut risques = bridging plus intensif

Afrough et al., Blood Cancer J 2024

KARMMA-2 Cohorte 2-B

Etude de phase 2

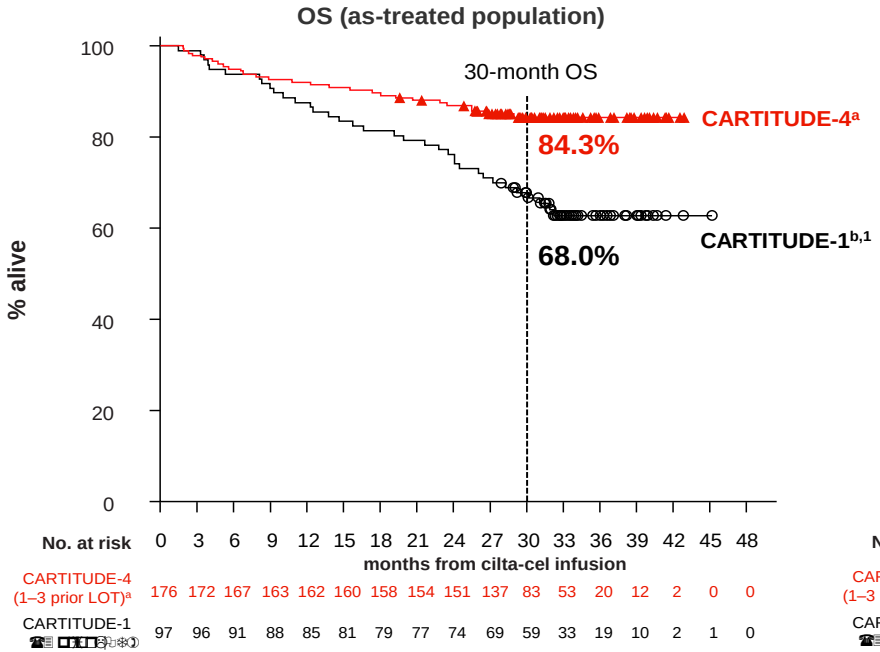
- MM en rechute précoce (< 18mois) après 1L
  - ayant ASCT (2a)
  - excluant ASCT (2b)
  - Réponse inadéquate après 1L ASCT (2c)

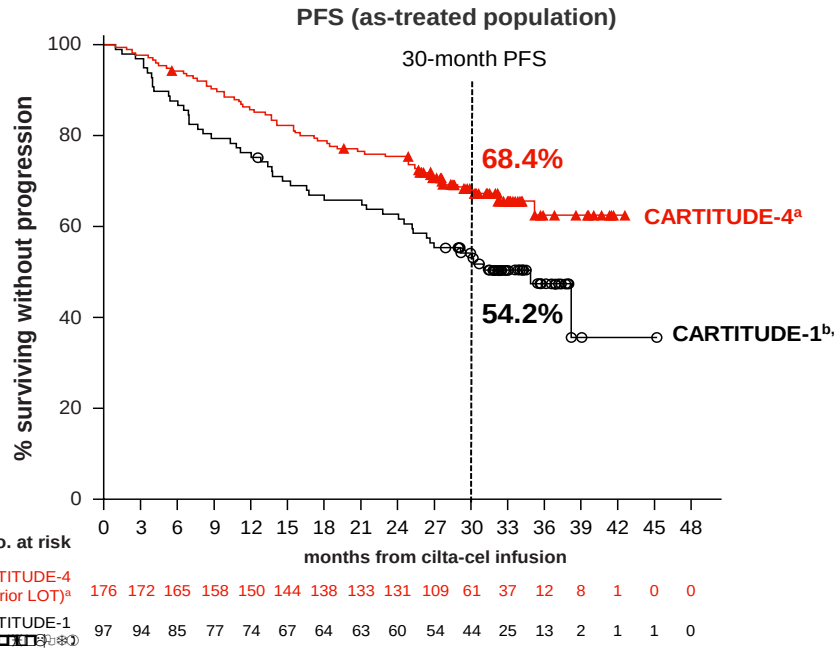


35 patient inclus – 31 réinjections
Age median 60ans – HR cytogénétique 39%
Suivi médian 30mois
RC 71% - SSP à 12mois 70%

X. Leleu, EHA 2024

Cilta-cel : CARTITUDE-4 versus CARTITUDE-1





Cilta-cel use in earlier lines demonstrated numerically higher rates of overall and progression-free survival

[a]Re-baselined to begin at time of cilta-cel infusion for patients who received cilta-cel as study treatment, with median follow-up of 30.5 months. [b]33.4-month median follow-up.
Cilta-cel, ciltacabtagene autoleucel; LOT, line of therapy; OS, overall survival; PFS, progression-free survival; SOC, standard of care.
1. Lin et al. Abstract 8009, presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual.

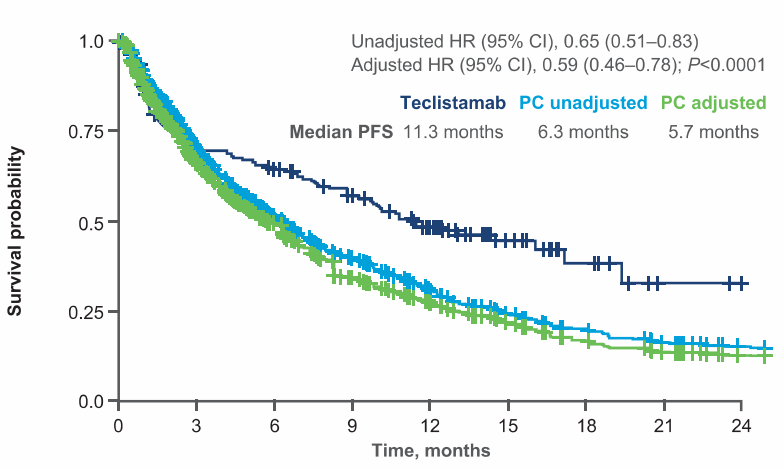
Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

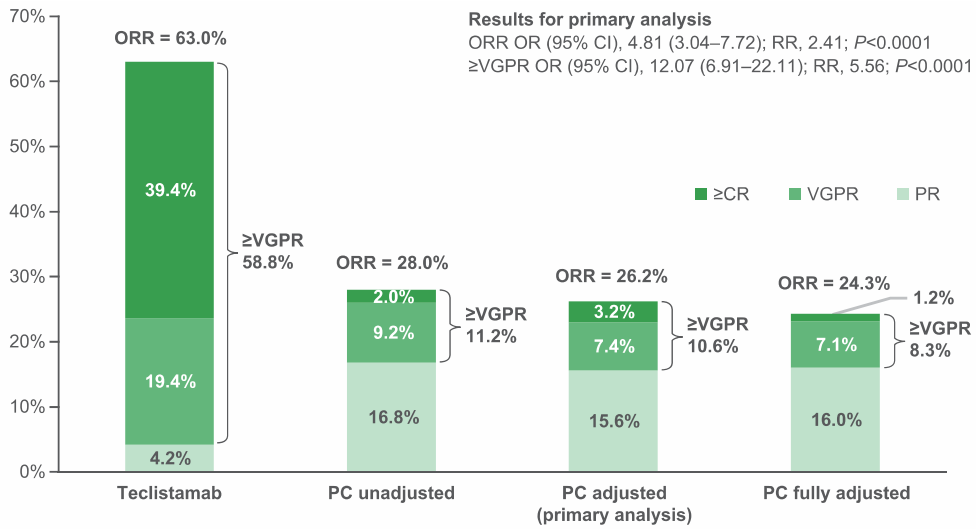
Anticorps bispécifique anti BCMA

	Teclistamab	Elranatamab	Linvoseltamab	Alnuctamab	ABBV-38
Patients (n)	165	123	117	73	124
Dosing	W/Q2W SC	W/Q2W IV	W/Q2 or 4W IV	W/Q2-4W IV/SC	Q3W IV
Med Prior LOT	5	5	5	4	5
ISS3 / PC (%)	12,3/11,2	15,4/21,1	18,2/22,2	16/-	31/-
HT /EMD (%)	25,7/17	25,2/31,7	35,9/13,7	26/21	18/-
TCR (%)	77,6	100	73,5	63	82
ORR / ≥CR (%)	63/45,5	61/35	71/30	69/43	57/17
mDOR	24mo	69% @18mo	-	-	72,2% @12mo
mPFS	12,5mo	17,2mo	72,7% @6mo	53% @12mo	10,4mo 57,9% @12mo
mOS	21,9mo	56,3%@15mo	-	-	-
CRS (%)	72,1	56,3	45,3	56	57
Infections (%)	80	69,9	59,8	62	41

Teclistamab versus régime standard dans MM en rechute

Teclistamab versus régime standard (DVd/DRd/DaraPd)
≥ 3 lignes de traitement antérieures – Triple exposé

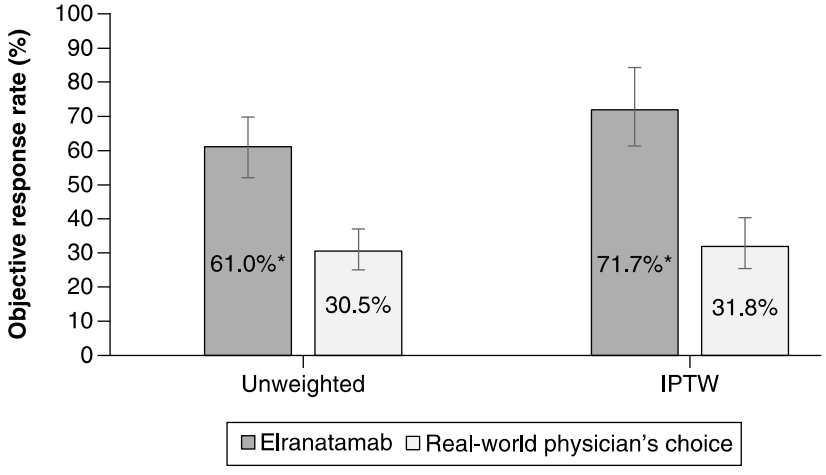


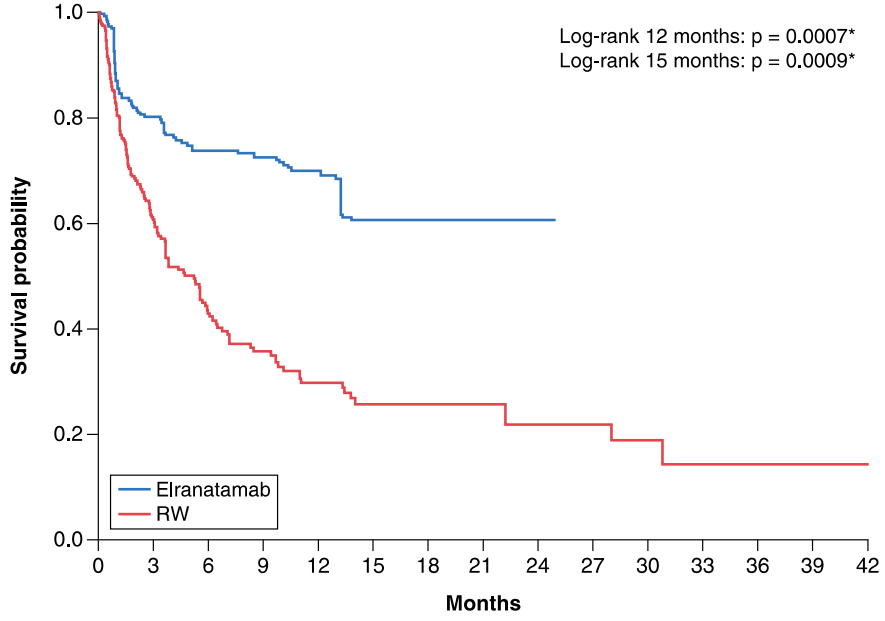


Mateos et al., Clinical Lymphoma, Myeloma and Leukemia, 2023

Elranatamab versus régime standard dans MM en rechute

Elranatamab versus régime standard
≥ 3 lignes de traitement antérieures –
Triple exposé



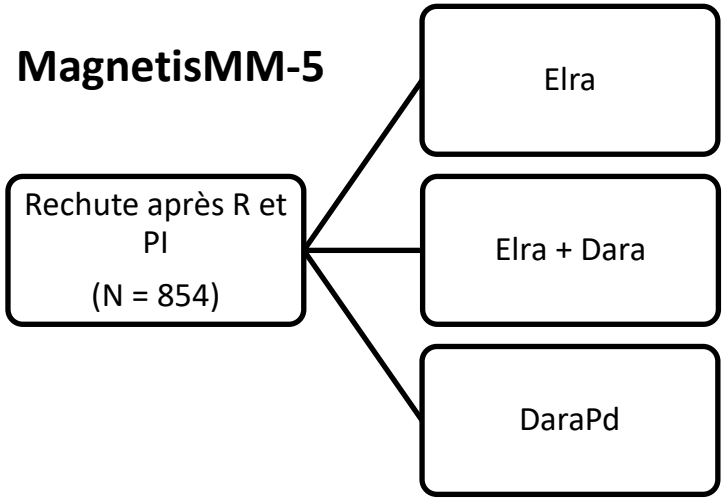


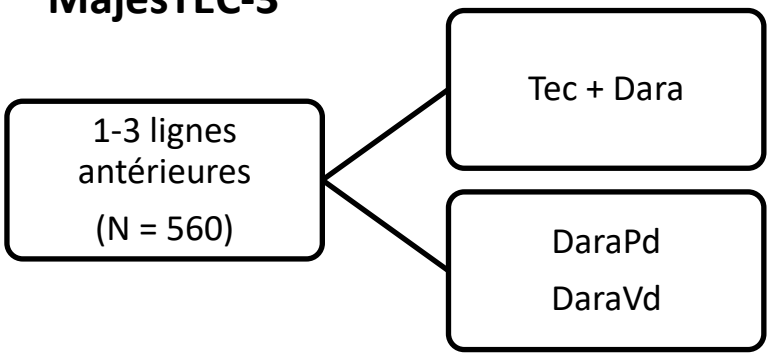
No. at risk

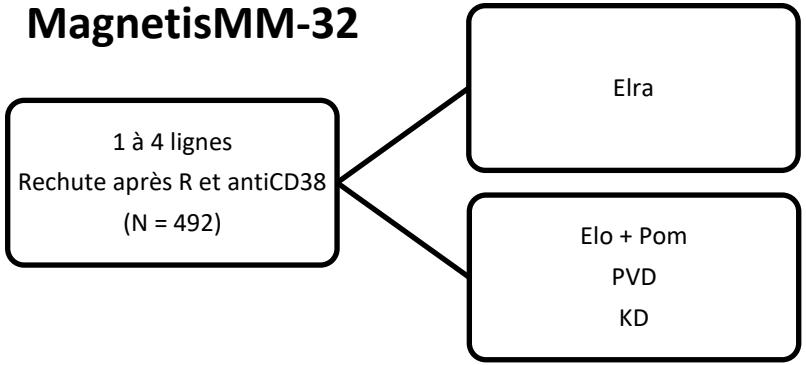
Elranatamab	113	83	71	66	59	45	4	2	1	0	0	0	0	0	0
Real-world physician's choice	235	91	54	40	24	18	11	10	8	5	4	1	1	1	1

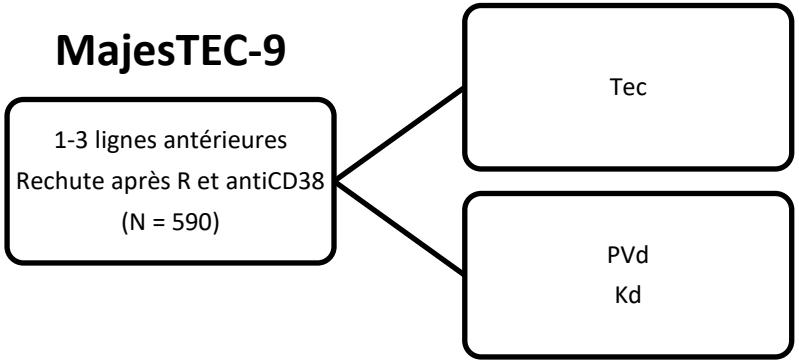
Costa et al., Future Oncol. 2024

Bispécifique en rechute précoce : essai en cours







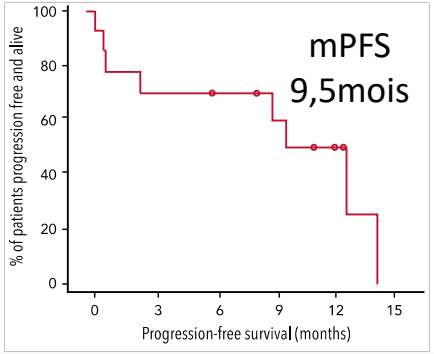


Comment choisir entre CART et BsAB ?

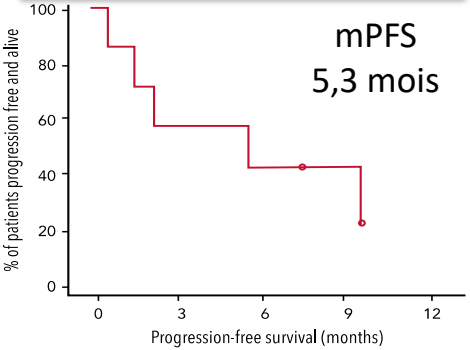
	CART	Anticorps Bispécifique	
Cible	BCMA	BCMA	GPRC5D
Réponse	ORR : 73-98% CR : 33-83%	ORR : 61-74% CR : 32,4-45,5%	
Tolérance	CRS, ICANS, tox neuro tardive, cytopénies, infections	CRS, ICANS, cytopénies, infections	CRS, ICANS, cytopénies, infections, troubles cutané muqueux
Dose	1 dose	QW/Q2W/Q4W jusqu'à progression ?	
Administration	Hospitalisation	Hospitalisation step up dose puis ambulatoire	
Accessibilité	Délai de fabrication	Immédiatement	
Autres	Fitness du patient, comorbidités Séquence de traitement antérieures		

Quelle stratégie : Bispécifique antiBCMA puis CART Cell ?

Cilta-cel après ADC



Cilta-cel après bsAb



CARTITUDE-2 : cohorte C

	Full cohort N = 20	ADC exposed* N = 13	Bispecific exposed* N = 7
Overall response rate,† % (95% CI)	60.0 (36.1-80.9)	61.5 (31.6-86.1)	57.1 (18.4-90.1)
Best response, rate, n (%)			
Stringent complete response	1 (5.0)	1 (7.7)	0
Complete response	5 (25.0)	4 (30.8)	1 (14.3)
Very good partial response	5 (25.0)	3 (23.1)	2 (28.6)
Partial response	1 (5.0)	0	1 (14.3)
Minimal response‡	1 (5.0)	0	1 (14.3)
Stable disease	3 (15.0)	2 (15.4)	1 (14.3)
Progressive disease	3 (15.0)	3 (23.1)	0
Not evaluable‡,§	1 (5.0)	0	1 (14.3)
≥VGPR	11 (55.0)	8 (61.5)	3 (42.9)
Median duration of response (95% CI), mo	11.5 (7.9-NE)	11.5 (7.9-NE)	8.2 (4.4-NE)
Median time to first response (range), mo	0.95 (0.9-6.0)	0.97 (0.9-5.1)	0.92 (0.9-6.0)
Median time to best response (range), mo	2.22 (0.9-9.9)	2.58 (0.9-9.9)	1.41 (0.9-7.0)
MRD negativity, n (%)			
No. of patients evaluable at 10^{-5}	10	7	3
Rate, n (%)	7 (70.0)	5 (71.4)	2 (66.7)

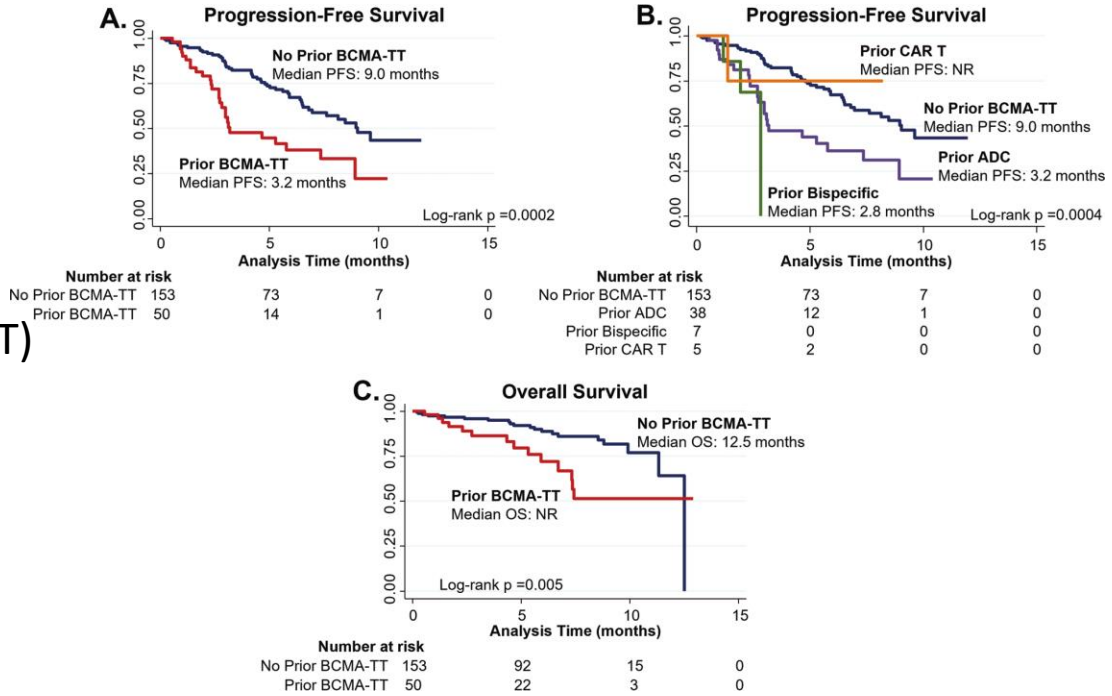
Cohen et al., Blood, 2023

Quelle stratégie : Bispécifique antiBCMA puis CART Cell ?

Real-world experience of patients with multiple myeloma receiving ide-cel after a prior BCMA-targeted therapy

Etude rétrospective – 11 centres US
Avril 2021 – Mai 2022
Ide-cel

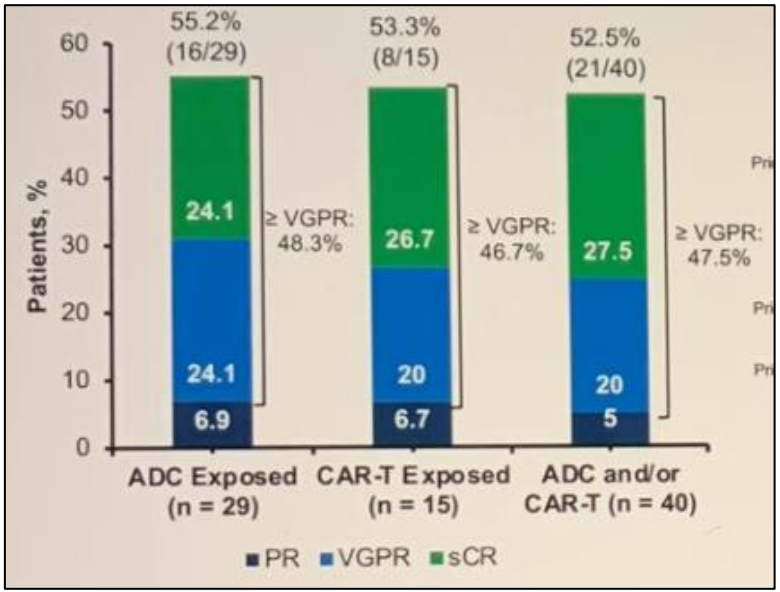
- 56 patients ayant eu un TTT antiBCMA (38 ADC, 7 BsA, 5 CART)
- 153 patients sans TTT antiBCMA



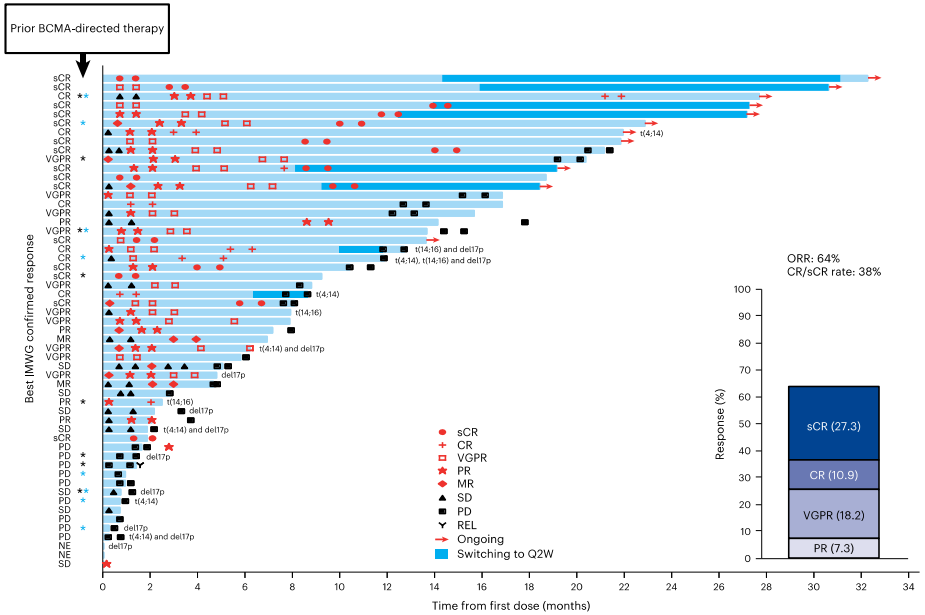
Ferreri et al. Blood Cancer J 2024

Quelle stratégie : CART Cell puis Bispécifique antiBCMA ?

Teclistamab, MajesTEC-1, Cohort C



Elranatamab, MagnetisMM-1

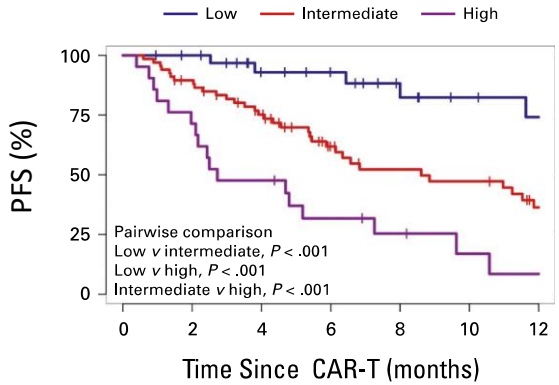


Touzeau et al., ASCO 2022, Abstract 8013 ; Bahlis etal., Nature Medicine, 2023

Comment choisir entre CART et BsAB ?

- Plutôt pas CART Cell
  - EMD
  - Cytogénétique de haut risque
  - B2 microglobuline élevée
  - Cinétique de progression rapide
  - Ferritine élevée

Factor	HR	95% CI	*P*	Score
EMD or PCL present	1.92	1.30 to 2.82	<.001	1
High-risk cytogenetics	1.95	1.31 to 2.92	.001	1
Ferritin > NL (sex-/age-adjusted)	1.59	1.07 to 2.37	.02	1
Lenalidomide refractoriness	1.69	1.02 to 2.82	.04	1
MyCARe risk				
Low (score 0-1)	Ref			
Intermediate (score 2-3)	3.27	1.87 to 5.72	<.001	
High (score 4)	7.89	4.21 to 14.79	<.001	



Gagelmann et al. JCO 2024

Anticorps bispécifique anti GPRC5D et anti FcRH5

	Anti-GPRC5D		Anti-FcRH5
	Talquetemab	Forimtamig	Cevostamab
Patients (n)	143	57	161
Dosing	405mi/kg SC QW	1200-7200mi SC Q2-3W	20-198mg IV Q3W
Med Prior LOT	5	4	6
ISS3 / PC (%)	19,6/12,3	-	-
HR /EMD (%)	31,1/23,1	47,7/31,6	39,8/21,1
TCR (%)	74,1	71,9	84,5
ORR /≥CR (%)	74,1/33,6	63,6/25,5	56,7/8,4
mDOR	9,5 mo	12,5 mo	11,5mo
12months PFS (%)	34,9	-	-
12months OS (%)	76,4	-	-
CRS (%)	79	78,9	79,5
Infections (%)	58,7	45,6	43
Dysgeusia/Skin/Nail (%)	72/55,9/54,5	77,2/28,1	NA

Association de 2 BsA ?

RedirecTT-1 : TAL + TEC

Phase 1b

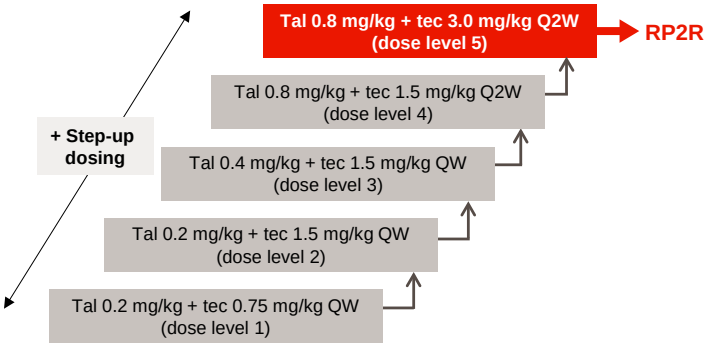
Key eligibility criteria

- Measurable MM
- [illegible]
- RR or intolerant to established therapies, including last LOT
- Triple-class exposed (prior PI, IMiD, anti-CD38)

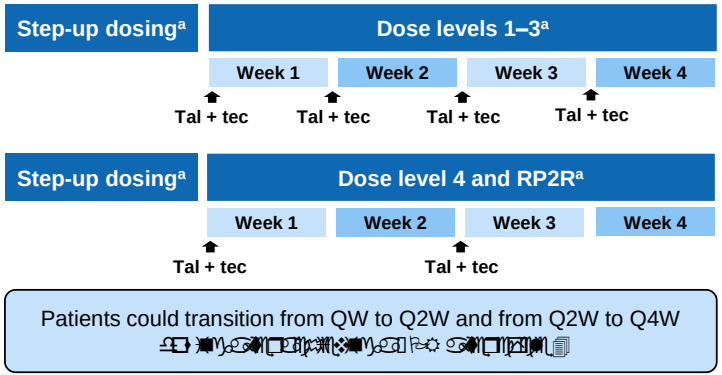
Key objectives

- Safety, including DLTs
- Identify RP2R(s)
- ORR, DOR, time to response, PK, immunogenicity
- PFS

Phase 1 dose escalation

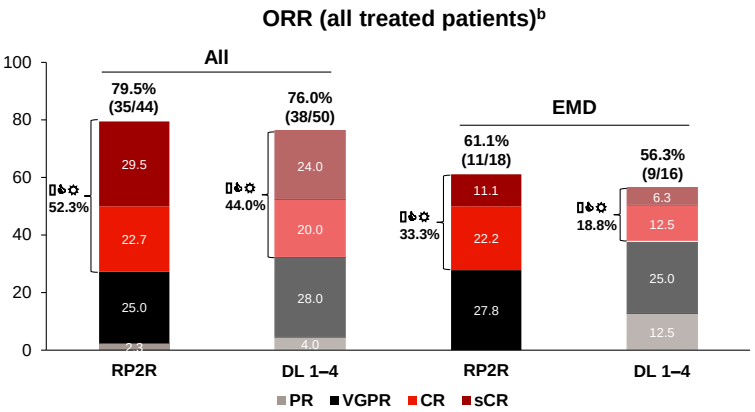


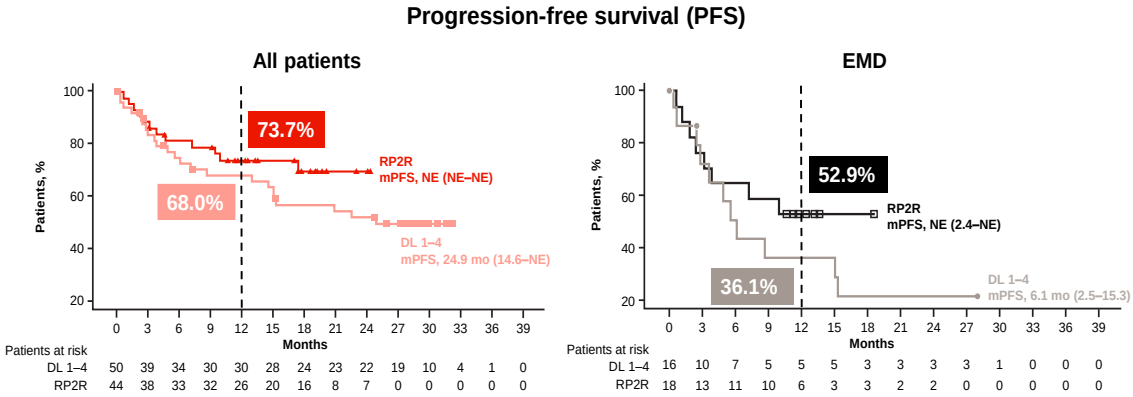
Dosing schedule

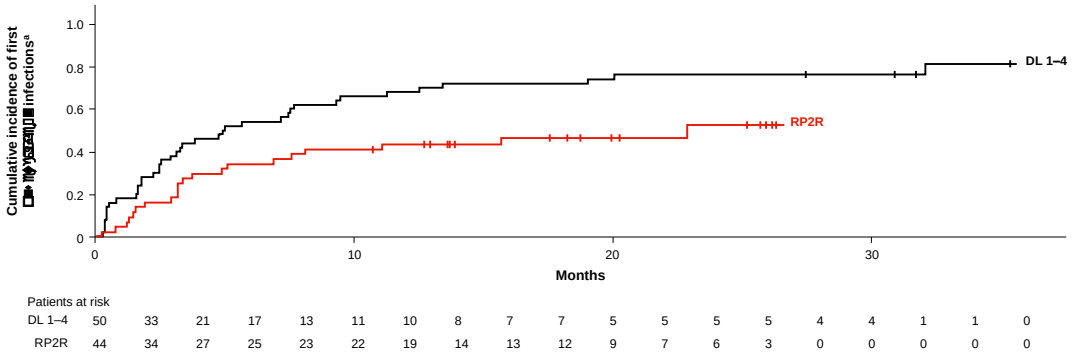


Presented by YC Cohen at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

RedirecTT-1 Tal + Tec

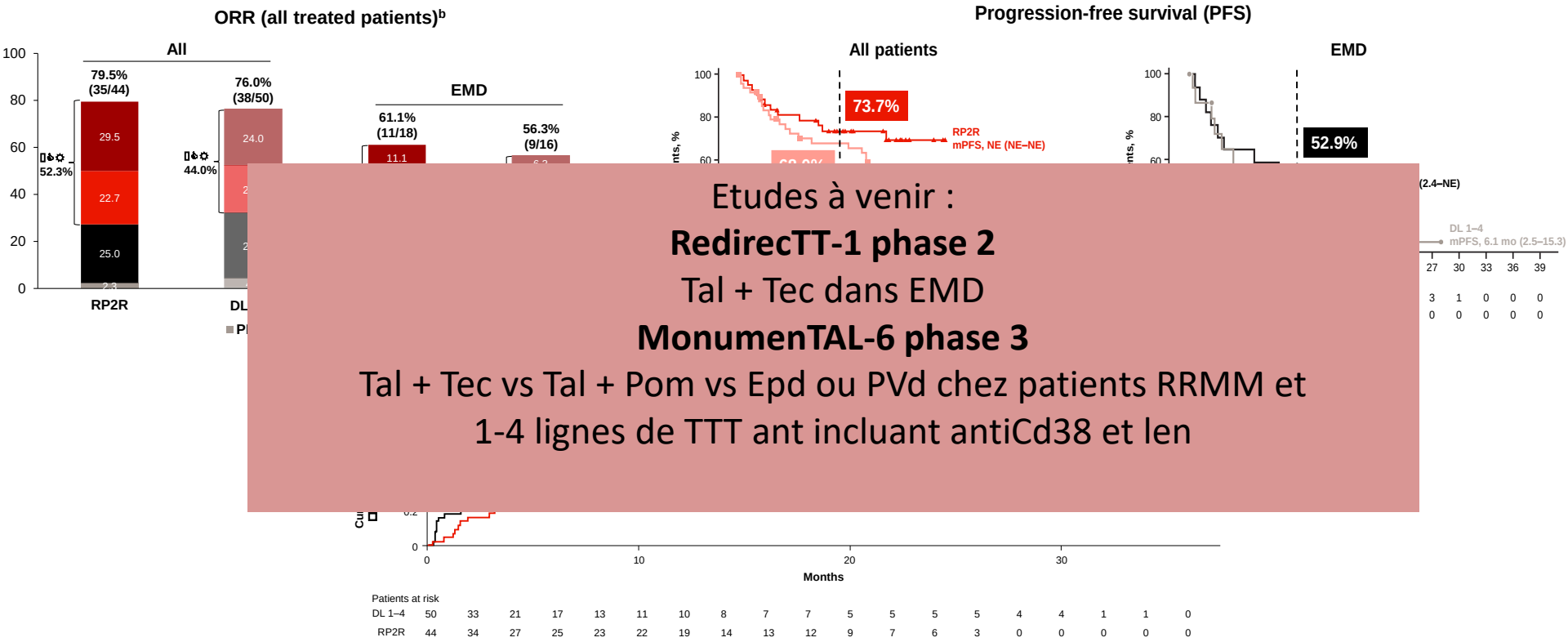






Presented by YC Cohen at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

RedirecTT-1 Tal + Tec



Etudes à venir :

RedirecTT-1 phase 2

Tal + Tec dans EMD

MonumenTAL-6 phase 3

Tal + Tec vs Tal + Pom vs Epd ou PVd chez patients RRMM et 1-4 lignes de TTT ant incluant antiCd38 et len

Presented by YC Cohen at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

Quid de la rechute post BCMA ?

Essai TRIMM-2

Key eligibility criteria

- MM per IMWG
- ≥3 prior LOT[a] or double refractory to PI and IMiD
- Permitted:
  - Anti-CD38 mAb >90 days and IMiD >7 days prior
  - Refractory to anti-CD38 mAb
  - Prior bispecific antibody or CAR-T exposure

Tal[b] + **Dara[c] 1800 mg SC** + **Pom 2 mg PO**

Tal[b]	Dara[c] 1800 mg SC	Pom 2 mg PO
SUD followed by 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W	QW cycles 1–2 Q2W cycles 3–6 Q4W cycles ≥7	Starting cycle 2
May change schedule from QW to Q2W after cycle 4 if in PR and from Q2W to Q4W after cycle 8 if in VGPR		*May be reduced in response to hematologic AEs*

Key objectives

- Safety and antitumor activity

Presented by N Bahlis at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

TRIMM-2 : Caractéristiques des patients

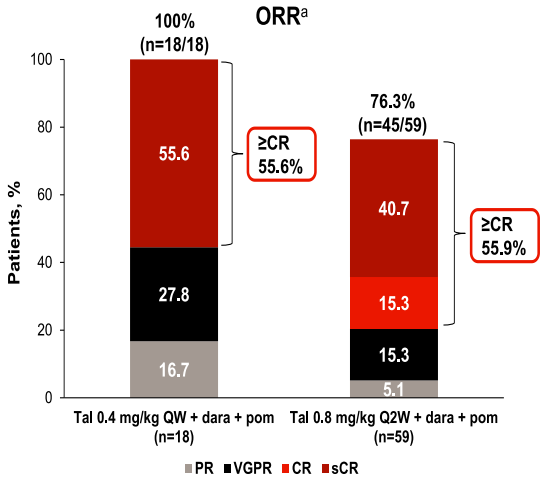
Characteristic	Tal 0.4 mg/kg QW + dara + pom (n=18)	Tal 0.8 mg/kg Q2W + dara + pom (n=59)
Age (years), median (range)	62 (42–75)	64 (33–81)
Male, n (%)	12 (66.7)	31 (52.5)
Race, n (%)		
White	12 (66.7)	51 (86.4)
Black/African American	4 (22.2)	4 (6.8)
Asian	1 (5.6)	1 (1.7)
American Indian/Alaska Native	0 (0)	1 (1.7)
Not reported	1 (5.6)	2 (3.4)
Soft tissue plasmacytoma(s),[a] n (%)	4 (22.2)	14 (23.7)
High cytogenetic risk,[b] n (%)	4 (22.2)	13 (27.7)
ISS stage,[c] n (%)		
I	8 (50.0)	29 (52.7)
II	3 (18.8)	15 (27.3)
III	5 (31.3)	11 (20.0)
Time since diagnosis (years), median (range)	5.7 (0.3–18.3)	7.2 (0.7–17.5)

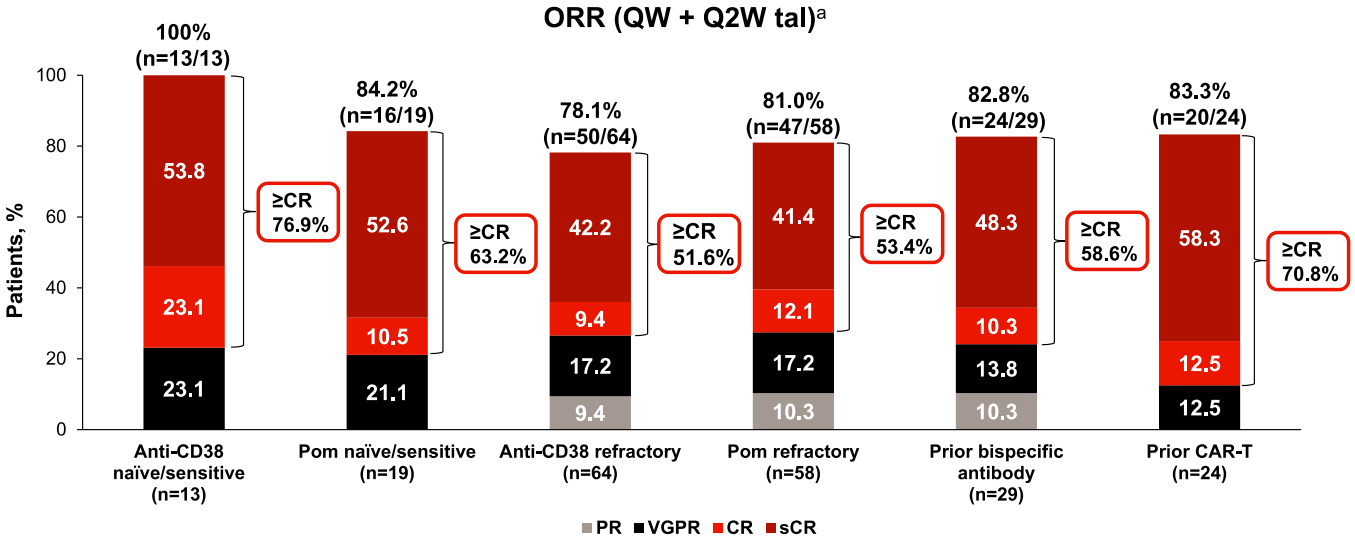
Characteristic	Tal 0.4 mg/kg QW + dara + pom (n=18)	Tal 0.8 mg/kg Q2W + dara + pom (n=59)
Prior LOT (n), median (range)	6 (3–11)	6 (1–17)
Prior stem cell transplantation, n (%)	16 (88.9)	50 (84.7)
Prior therapies, n (%)		
Anti-CD38	17 (94.4)	55 (93.2)
IMiD	18 (100.0)	59 (100.0)
Triple class[d]	17 (94.4)	55 (93.2)
Penta drug[e]	12 (66.7)	41 (69.5)
BCMA-targeted therapy	13 (72.2)	40 (67.8)
CAR-T	5 (27.8)	19 (32.2)
Bispecific antibody[f]	6 (33.3)	17 (28.8)
ADC	3 (16.7)	12 (20.3)
Refractory status, n (%)		
Anti-CD38[g]	15 (83.3)	49 (83.1)
Pom	13 (72.2)	45 (76.3)
Triple class[d]	15 (83.3)	45 (76.3)
Penta drug[e]	4 (22.2)	20 (33.9)
Any prior bispecific antibody	7 (38.9)	22 (37.3)
To last line of therapy	17 (94.4)	53 (89.8)

Data cut-off: July 29, 2024. [a]Soft tissue plasmacytomas not associated with the bone were included. [b]del(17p), t(4;14), and/or t(14;16); percentages calculated from n=18 for tal QW and n=47 for tal Q2W. [c]Percentages calculated from n=16 for tal QW and n=55 for tal Q2W. [d]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [e]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb. [f]6 patients received non-BCMA–directed bispecific antibodies. [g]All patients in the tal QW cohort received dara; in the tal Q2W cohort, 89.8% received dara, 13.6% received isatuximab, and 1.7% received other anti-CD38 therapies. ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; dara, daratumumab; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; mAb, monoclonal antibody; PI, proteasome inhibitor; pom, pomalidomide; Q2W, every other week; QW, weekly; tal, talquetamab.

Presented by N Bahlis at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

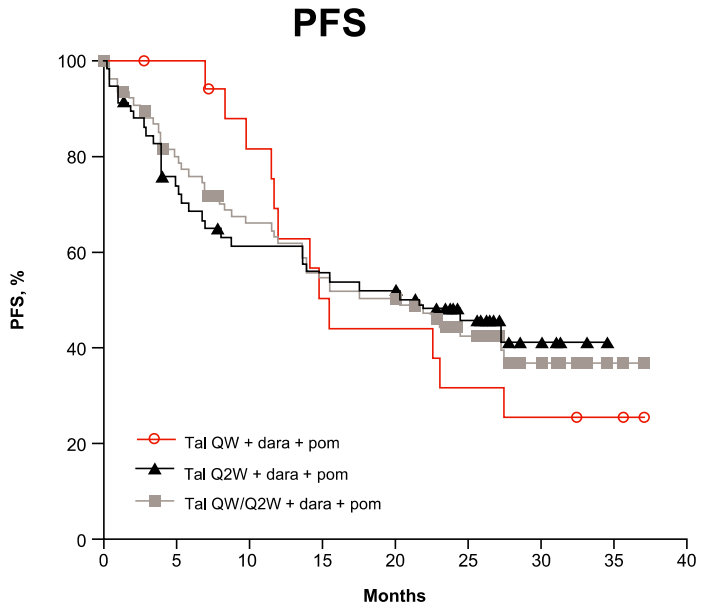
TRIMM-2 : Taux de réponse





Presented by N Bahlis at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

TRIMM-2 : PFS



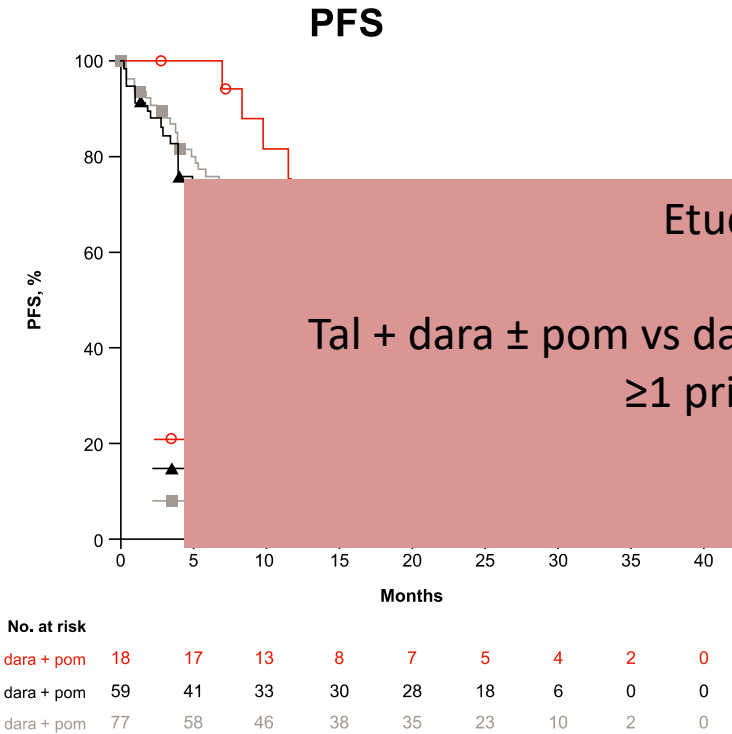
Parameter	Tal 0.4 mg/kg QW + dara + pom (n=18)	Tal 0.8 mg/kg Q2W + dara + pom (n=59)
Median (range) follow-up, months	15.8 (3.2–37.9)	17.5 (0.2–37.7)
Median PFS, months (95% CI)	15.4 (11.5–27.5)	20.3 (7.9–NE)
12-month PFS, % (95% CI)	62.7 (35.1–81.3)	61.1 (47.1–72.4)

12-month PFS (QW + Q2W tal)

- Anti-CD38 naïve/sensitive (n=13): 84.6%
- Pom naïve/sensitive (n=19): 68.4%
- Anti-CD38 refractory (n=64): 56.9%
- Pom refractory (n=58): 59.4%
- Prior bispecific antibody (n=29): 69.2%
- Prior CAR-T (n=24): 73.9%

Presented by N Bahlis at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

TRIMM-2 : PFS



Parameter	Tal 0.4 mg/kg QW + dara + pom (n=18)	Tal 0.8 mg/kg Q2W + dara + pom (n=59)
Median (range)	15.8	17.5 (2–37.7)
		20.3 (9–NE)
		61.1 (1–72.4)

Etude phase 3 en cours :

MonumenTAL-3

Tal + dara ± pom vs dara + pom + dex chez patients RRMM et ≥1 prior LOT (NCT05455320)

- Anti-CD38 refractory (n=64): 56.9%
- Pom refractory (n=58): 59.4%
- Prior bispecific antibody (n=29): 69.2%
- Prior CAR-T (n=24): 73.9%

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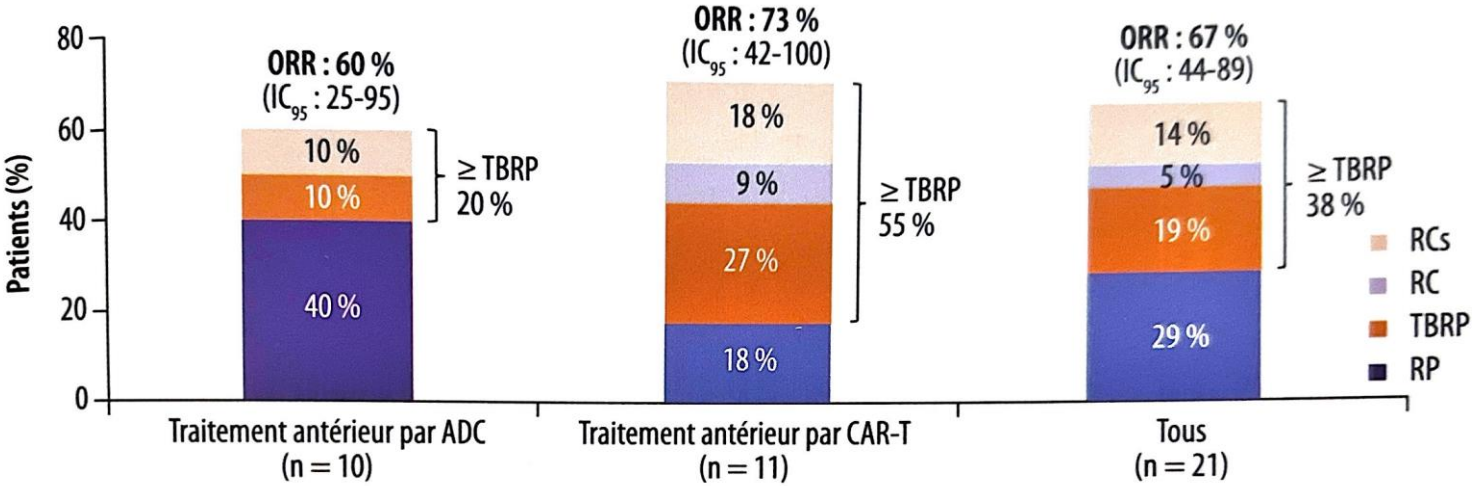
Cevostamab : Etude CAMMA-2



21 patients en rechute/réfractaire + exposés à antiBCMA (CART ou ADC)
Taux de réponse 67%
Bonne tolérance : CRS plus fréquent mais grade 1-2
Pas EI cutanéomuqueux

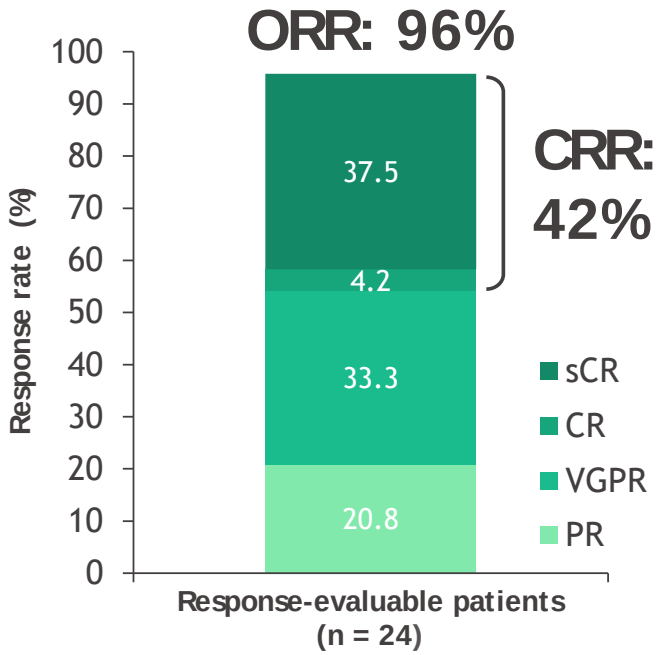
S. Kumar, EHA 2024

CART anti-GPRC5D : BMS-986393

Etude phase 1

Part B Dose Expansion
Cohort C: key eligibility criteria

- [illegible] 12 months of the most recent regimen per IMWG criteria[a]
- 1-3 prior antimyeloma regimens including a PI and an IMiD, and ASCT[b]
- Prior BCMA-directed therapies allowed, including CAR T cell therapies
- ECOG PS 0-1



Tolérance correcte

- CRS grade ½
- Atteintes cutané muqueuses - faible grade

Myo Htut et al., Prsentation number OA-08, IMS 2024

Conclusion

- Le caractère réfractaire précoce à plusieurs classes est de + en + courant
- Place antiCD38 – IP – DXM chez le Len refractaire
- Place importante des T-Cell thérapies dans le TTT de la rechute
  - CART puis BsA
- Discussion avec le patient essentielle dans le choix
- Nécessité d'améliorer connaissances sur mécanismes de résistance à l'immunothérapie
- Quid des associations avec Bispécifique ?
- Quid de la rechute post anti-BCMA ?
- Place des autres molécules en rechute post T-Cell thérapie

Merci de votre attention