Les Hôpitaux Universitaires de STRASBOURG

ICANS INSTITUT DE CANCÉROLOGIE STRASBOURG EUROPE
ALLIANCE CLCC-CHU

MYELOME
Traitement du Myélome en 1ère ligne
Changement de paradigme?

Dr Cécile SONNTAG

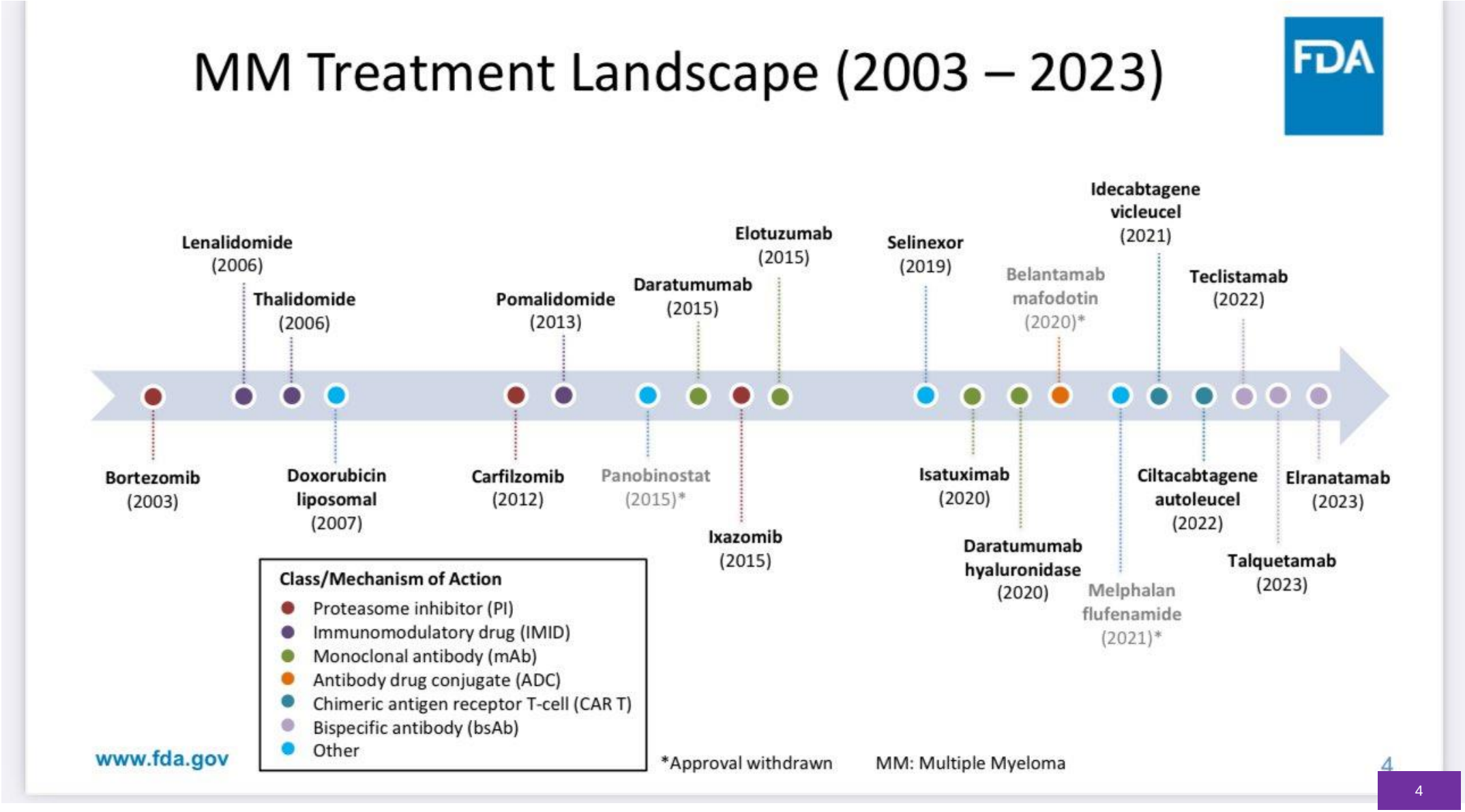
Liens d’interets

- Boards Janssen, BMS, Sanofi, Pfizer; Amgen, Takeda

Quelques rappels

- Au diagnostic :
  - Age médian : 69 ans
  - 1/3 des patients ont au moins 75 ans
  - Population très hétérogène : TE/NTE
  - Forte hausse de la prévalence

Timeline


MM Treatment Landscape (2003 – 2023)
FDA
Bortezomib (2003)
Lenalidomide (2006)
Thalidomide (2006)
Doxorubicin liposomal (2007)
Pomalidomide (2013)
Carfilzomib (2012)
Daratumumab (2015)
Panobinostat (2015)*
Elotuzumab (2015)
Ixazomib (2015)
Selinexor (2019)
Isatuximab (2020)
Belantamab mafodotin (2020)*
Daratumumab hyaluronidase (2020)
Idecabtagene vicleucel (2021)
Melphalan flufenamide (2021)*
Teclistamab (2022)
Ciltacabtagene autoleucel (2022)
Talquetamab (2023)
Elranatamab (2023)
Class/Mechanism of Action
Proteasome inhibitor (PI)
Immunomodulatory drug (IMID)
Monoclonal antibody (mAb)
Antibody drug conjugate (ADC)
Chimeric antigen receptor T-cell (CAR T)
Bispecific antibody (bsAb)
Other
www.fda.gov
*Approval withdrawn
MM: Multiple Myeloma
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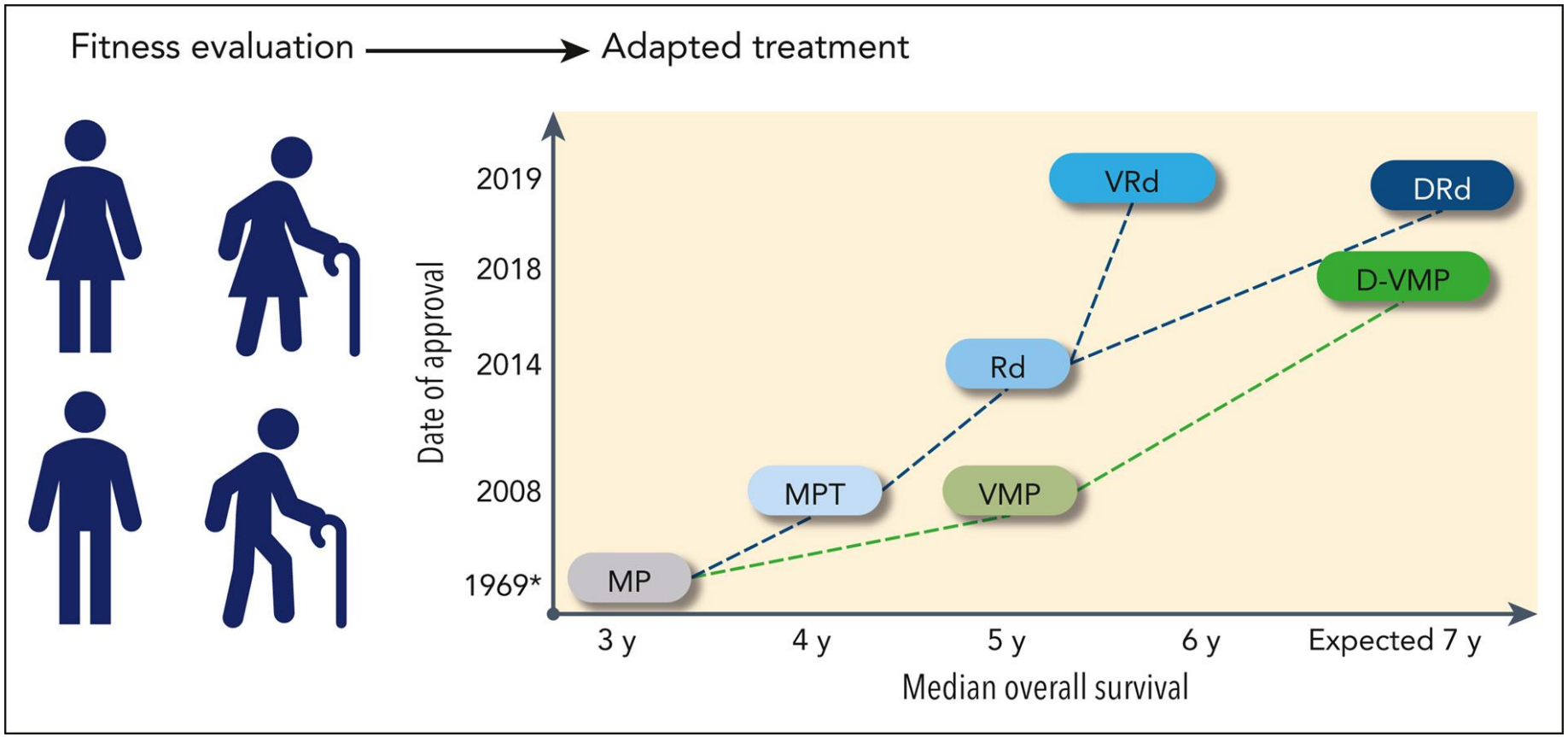
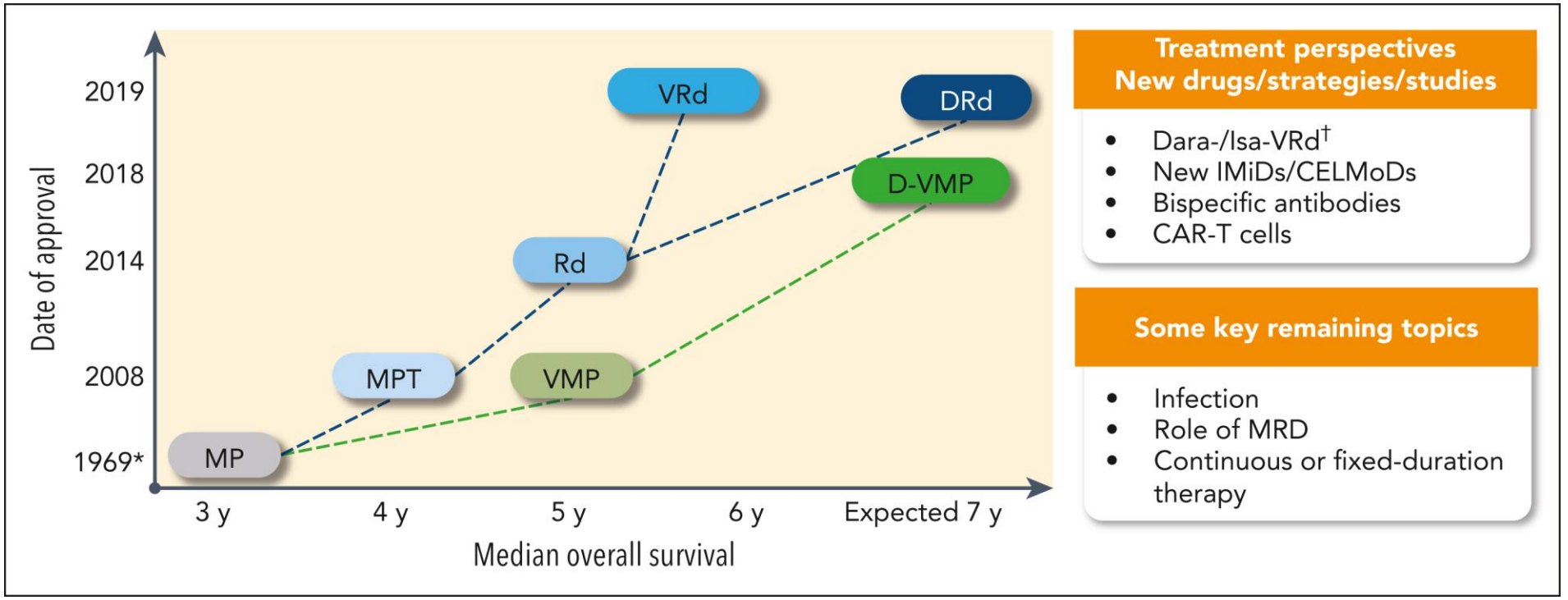
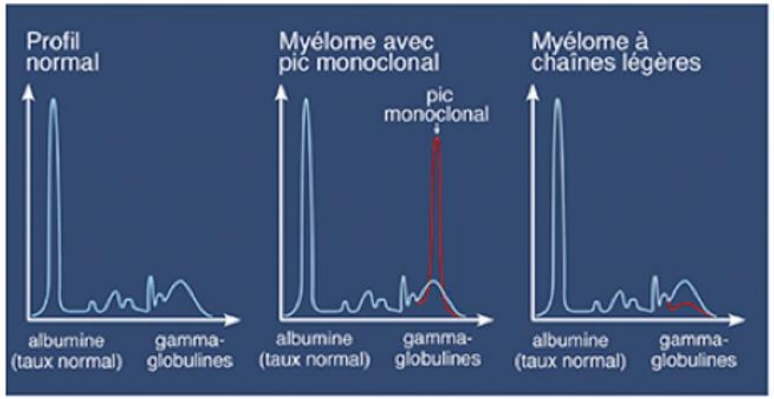


Thierry Facon,Xavier Leleu,Salomon Manier, How I treat multiple myeloma in geriatric patients, Blood, 2024,

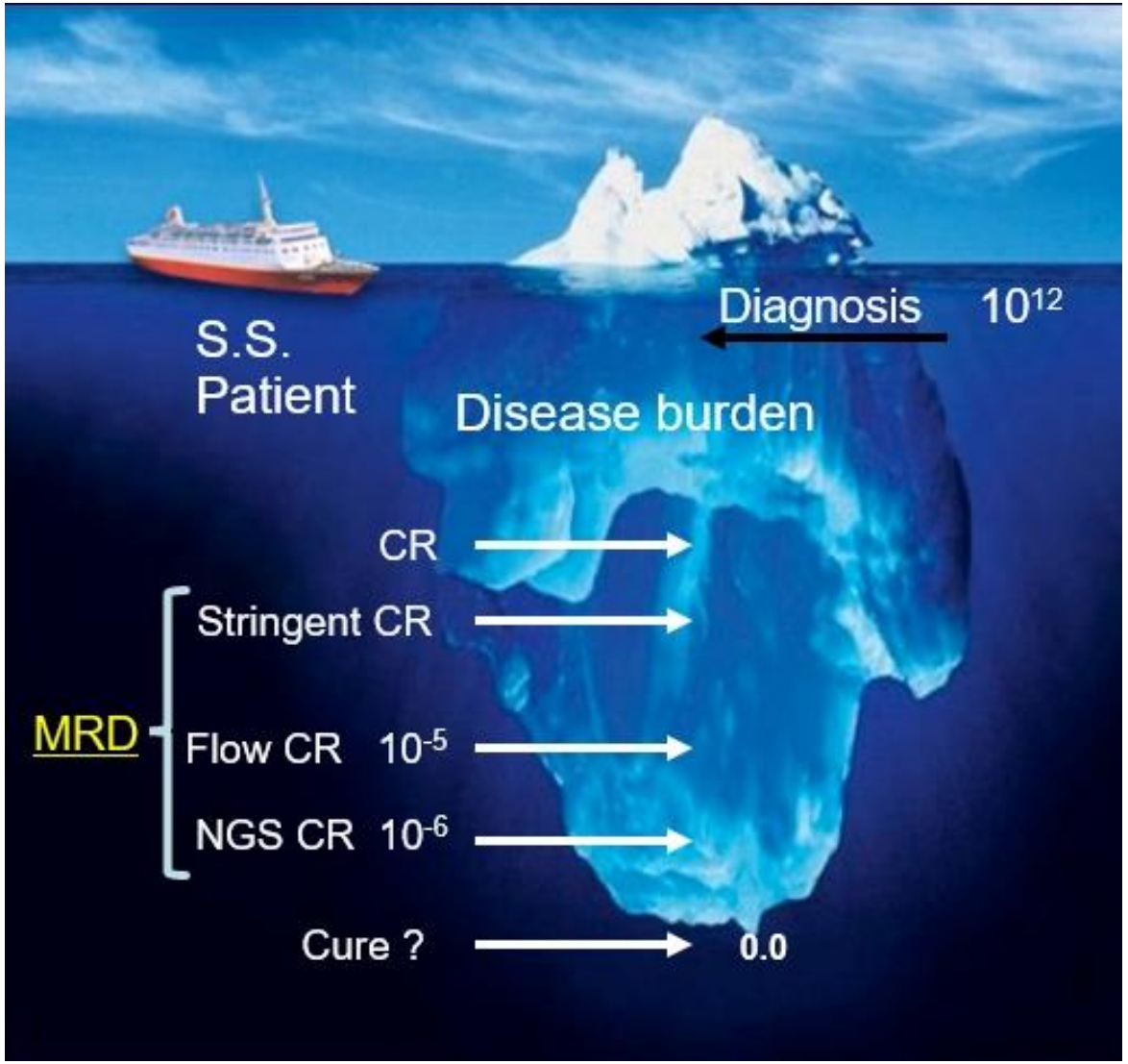
How I treat multiple myeloma in geriatric patients



Thierry Facon,Xavier Leleu,Salomon Manier, How I treat multiple myeloma in geriatric patients, Blood, 2024, Figure 1.



D'après Cancer Info. Comprendre le myélome. Octobre 2015



D'après Cancer info Comprendre le myélome 2015

Score de frailty :

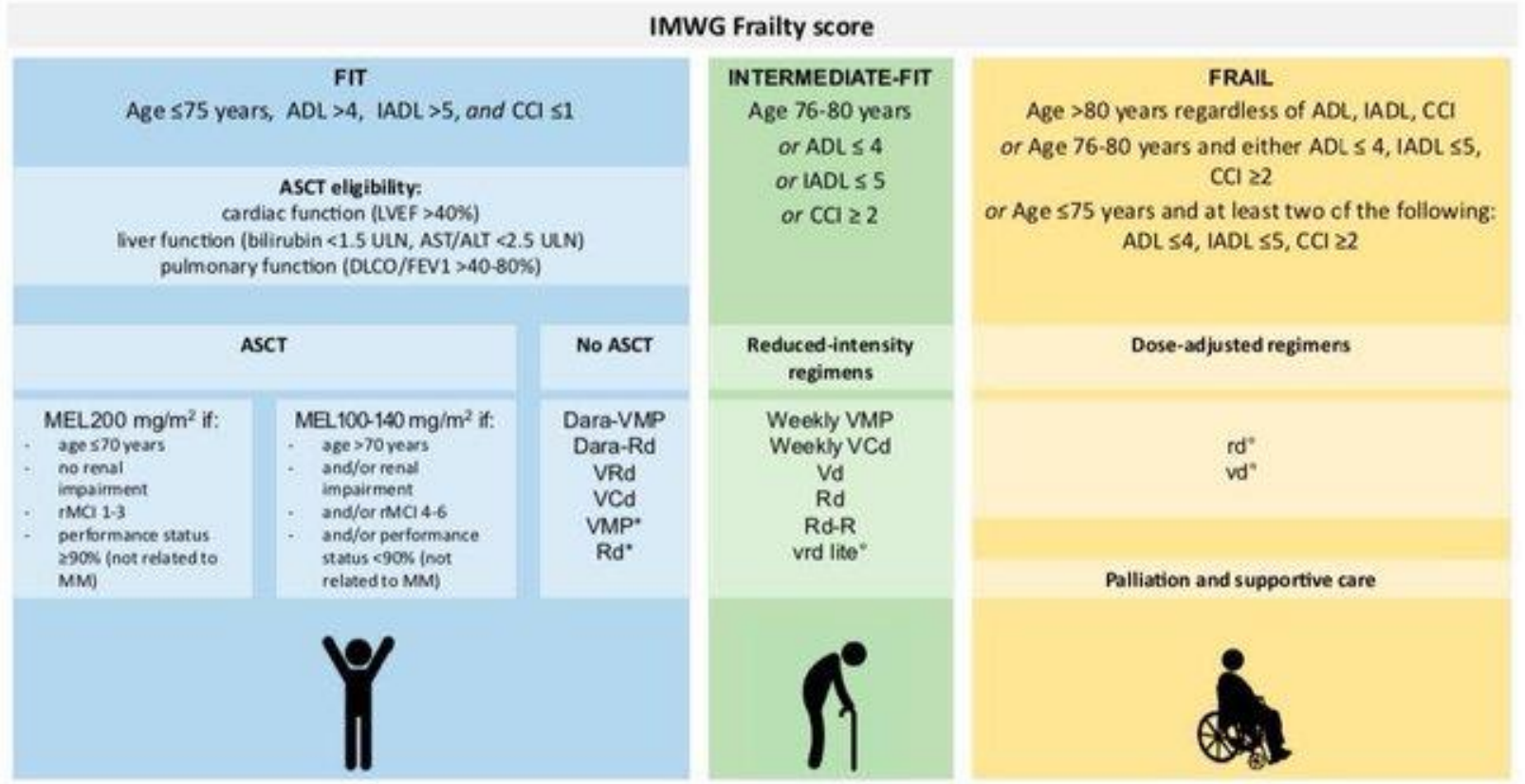
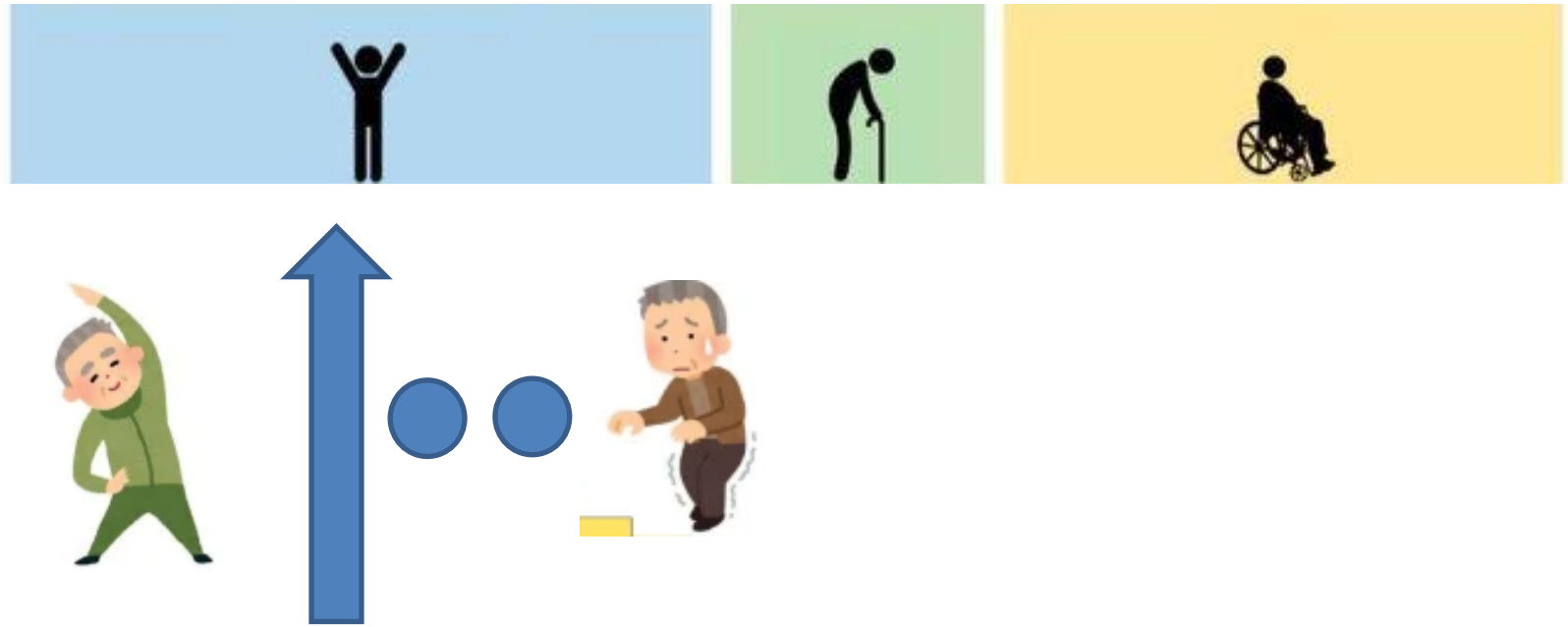


FIGURE 1. Newly Diagnosed Patients With MM: Approach to Treatment

Abbreviations: ADL, activities of daily living; ALT, alanine aminotransferase; ASCT, autologous stem cell transplantation; AST, aspartate aminotransferase; CCI, Charlson comorbidity index; Dara, daratumumab; DLCO, diffusion capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 second; IADL, instrumental ADLs; IMWG, International Myeloma Working Group; LVEF, left ventricular ejection fraction; MEL, melphalan (with dosages in mg/m^2); MM, multiple myeloma; Rd, lenalidomide and dexamethasone; Rd-R, lenalidomide and dexamethasone followed by lenalidomide maintenance; rMCI, revised myeloma comorbidity index; ULN, upper limit of normal; VCd, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRd/vrd, bortezomib, lenalidomide, and dexamethasone. (*) If daratumumab-based combinations or VRd are unavailable. (°) The lowercase letter indicates a reduced dose.

Mina R et al 2019 ASCO Educational Book

Score de frailty : de la salle d'attente au bureau de consultation



Mina R et al 2019 ASCO Educational Book

En première ligne de traitement TE NDMM

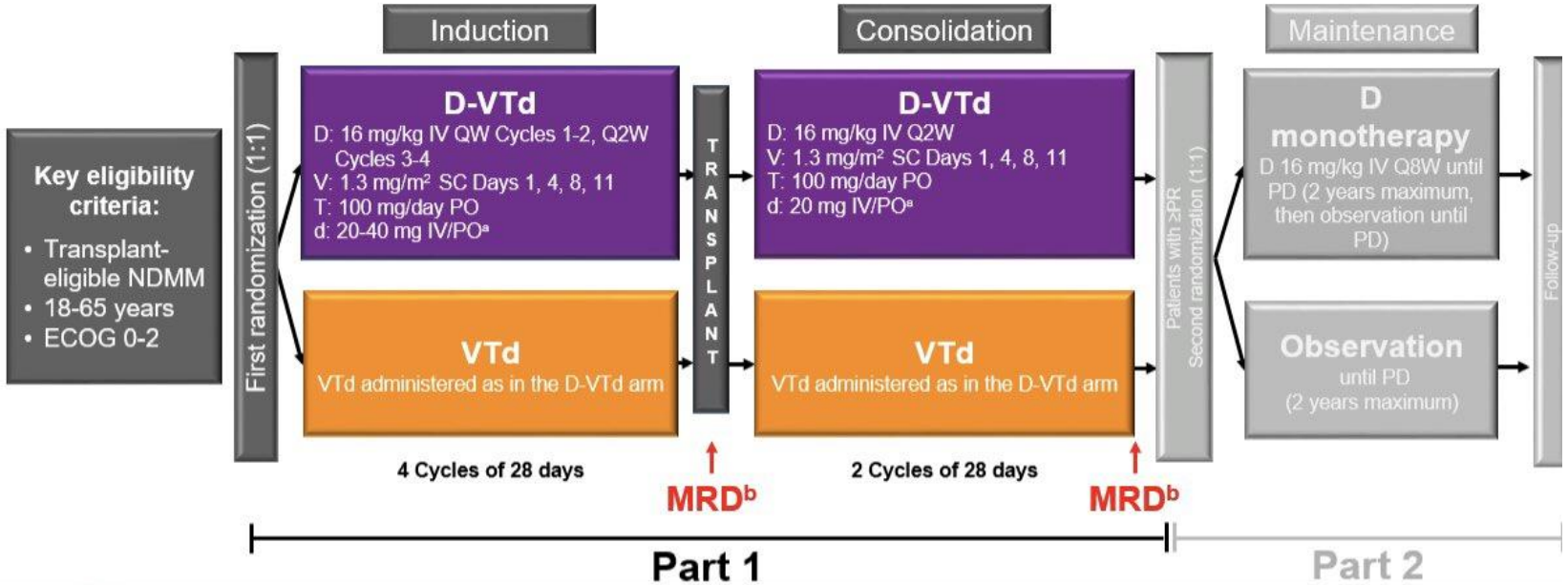
TE NDMM

Etude CASSIOPEA

EHA 2024 :
Suivi de plus de 6 ans
SSP 83 mois
bras Dara VTD
versus 53 mois pour bras VTD

CASSIOPEIA Study Design (Moreau et al. *Lancet* 2019)

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017



American Society of Hematology

ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease.
[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6. [b]MRD analyses were performed for all patients, regardless of response.

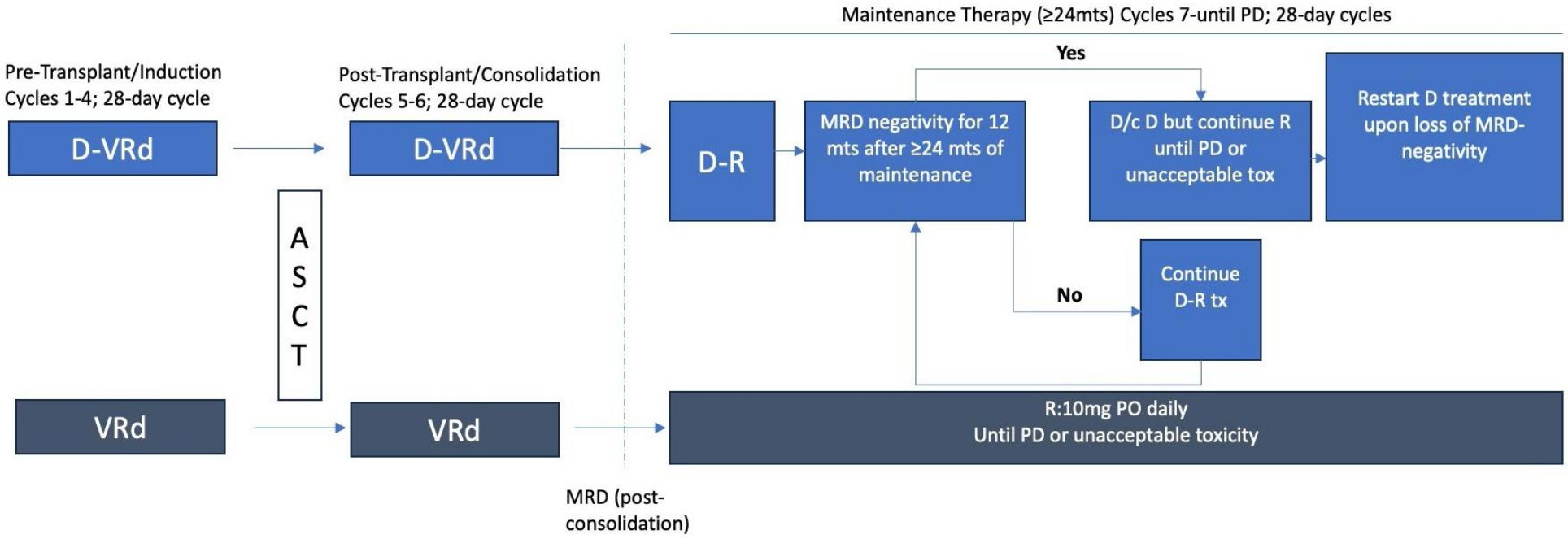
TE NDMM

Etude PERSEUS

EHA 2024 :

- 700 patients
- SSP à 4 ans

= 84% / 67%



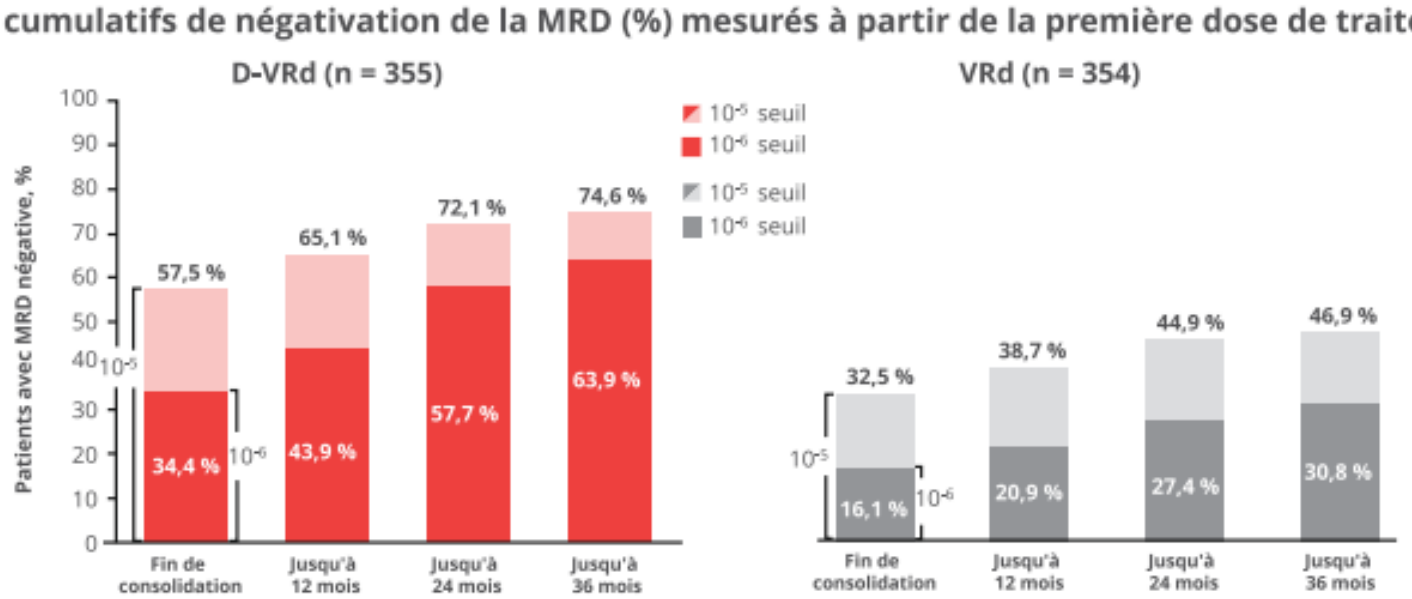
D-VRd (induction): D: 1800 mg SC QW at cycles 1-2 and Q2W at cycles 3-4; V: 1.3 mg/m2 SC on days 1,4,8 and 11; R: 25 mg PO on days 1-21 of each cycles; d: 40 mg PO on days 1-4 and 9-12
D-VRd(consolidation) D: 1800 mg SC Q2W at cycles 5-6; VRd same dose as induction
VRd: V: 1.3/m2 SC on days 1,4,8 and 11; R: 25 mg PO on days 1-21; d: 40 mg PO on days 1-4 and 9-12
D-R: D:1800 mg SC Q4W; R: 10 mg PO daily unilt PD or unacceptable tox

D'après communication orale Sonneveld P EHA 2024 abstract S201

TE NDMM

Etude PERSEUS

EHA 2024 :
Taux de MRD neg
qui augmentent ++
au fil du traitement



Abréviations : D : daratumumab ; d : dexaméthasone ; MRD : maladie résiduelle détectable ; R : lénalidomide ; V : bortézomib.

Figure 5 : Taux de MRD négative en fonction de la durée du traitement.

D'après communication orale Sonneveld P EHA 2024 abstract S201

EFFICACY AND SAFETY OF ISA-KRD INDUCTI BEFORE RESPONSE-ADAPTED CONSOLIDAT TRANSPLANT ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA: AN INTERIM ANALYSIS OF THE IFM2020-02 MIDAS STUDY

A Perrot, C Touzeau, J Lambert, C Hulin, D Caillot, L Karlin, B Arnulf, P Rey, L Garderet, M Macro, M Escoffre-Barbe, J Gay, T Chalopin, K Belhadj, JM Schiano, M Tiab, M Mohty, F Kuhnowski, J Fontan, S Manier, F Orsini-Piocelle, L Vincent, X Leleu, J Corre, P Moreau

On behalf the IFM group

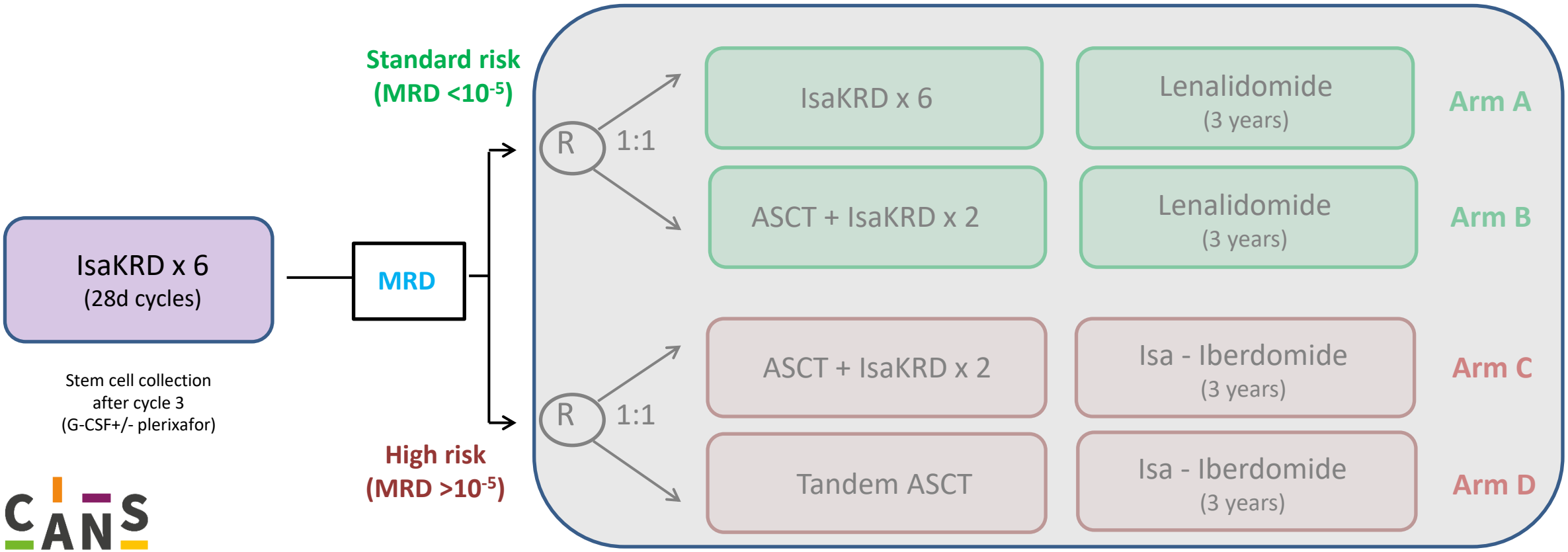
Background MIDAS

- **Les régimens à 4 drogues (quadruplettes) ont révolutionné le traitement de 1 ère ligne**
  - CASSIOPEIA (*Moreau P et al., Lancet 2019*; *Moreau P et al., Lancet Oncol 2024*)
  - PERSEUS (*Sonneveld P et al. N Engl J Med 2024*)

- **MIDAS = comparer en première ligne autogreffe versus pas d'autogreffe après une induction à 4 drogues. Adapter la stratégie après l'induction en fonction de la profondeur de réponse :**

Study design

MIDAS = MInimal residual Disease Adapted Strategy



Study design

MIDAS = MInimal residual Disease Adapted Strategy

Induction

IsaKRD x 6
(28d cycles)

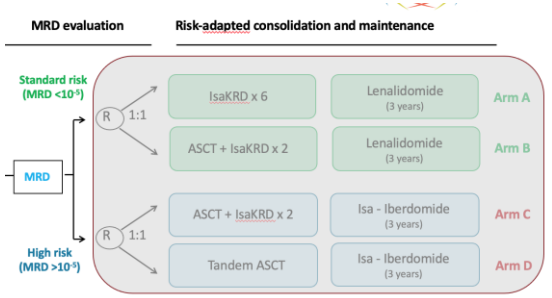
Stem cell collection
after cycle 3
(G-CSF+/- plerixafor)

Isatuximab 10 mg/kg C1: D1, D8, D15, D22
C2+: D1, D15

Carfilzomib C1: 20 mg/m^2 D1, then 56 mg/m^2 D8, D15
C2+: 56 mg/m^2 D1, D8, D15

Lenalidomide 25 mg/d, D1-D21

Dexamethasone 40 mg weekly



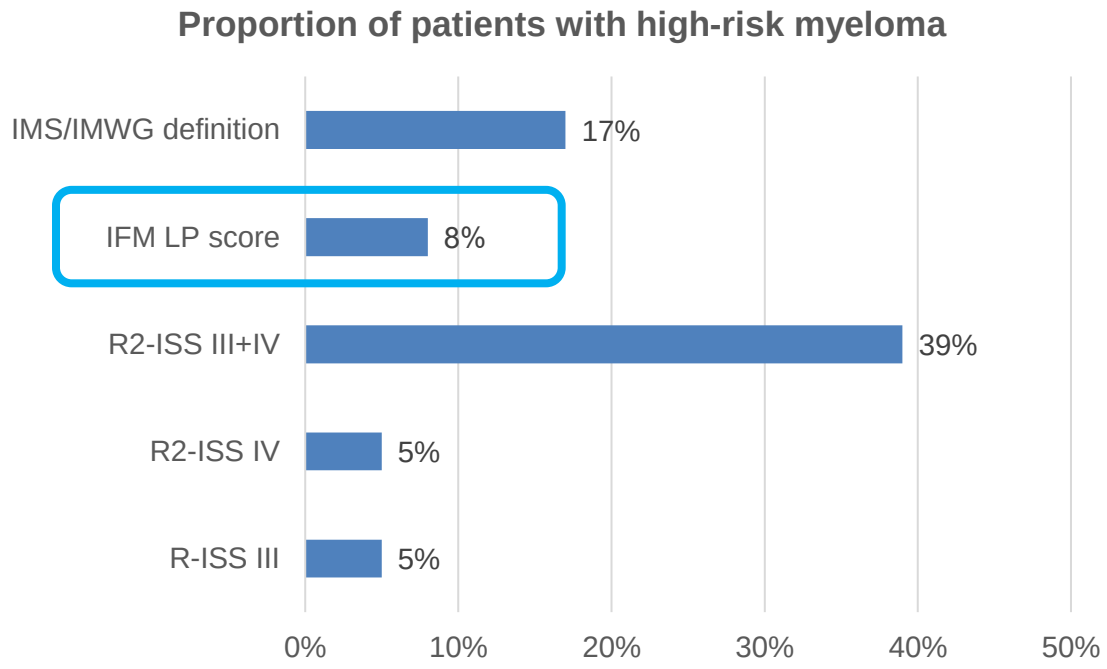
Caractéristiques des patients

791 patients ont été inclus dans 72 centres entre le 8 Dec 2021 et le 10 Juillet 2023

Characteristic		Whole cohort (N = 791) N (%)
Age (years), median [range]		58.7 [25.4-66]
>60 years		330 (42%)
Gender	Male	454 (57%)
	Female	337 (43%)
ECOG performance status	0	338 (43%)
	1	355 (45%)
	2	98 (12%)
Criteria for symptomatic MM		
CRAB		726 (92%)
Osteolytic lesions		595 (75%)
Anemia		206 (26%)
SLiM only		61 (8%)
ISS stage	I	346 (44%)
	II	346 (44%)
	III	99 (13%)
Elevated LDH		212 (27%)
Extramedullary disease		5 (1%)
Circulating plasma cells (by morphology)	Any	53 (7%)
	>5%	9 (1%)

Cytogenetics at diagnosis

Cytogenetics abnormalities/scores	Whole cohort (N = 791) N (%)
R-ISS stage I	236 (30%)
II	511 (65%)
III	43 (5%)
R2-ISS stage I	193 (25%)
II	273 (36%)
III	265 (34%)
IV	36 (5%)
Cytogenetic score LP >1	63 (8%)
IMS/IMWG consensus HRMM	135 (17%)
Detailed cytogenetic abnormalities	
t(4;14)	63 (8%)
t(14;16)	19 (3%)
t(14;20)	11 (1%)
t(11;14)	199 (26%)
1q gain	200 (26%)
monoallelic del(1p32)	55 (7%)
biallelic del(1p32)	8 (1%)
del(17p)*	46 (6%)
TP53 mutation	31 (4%)
trisomy 5	307 (41%)
trisomy 21	202 (27%)

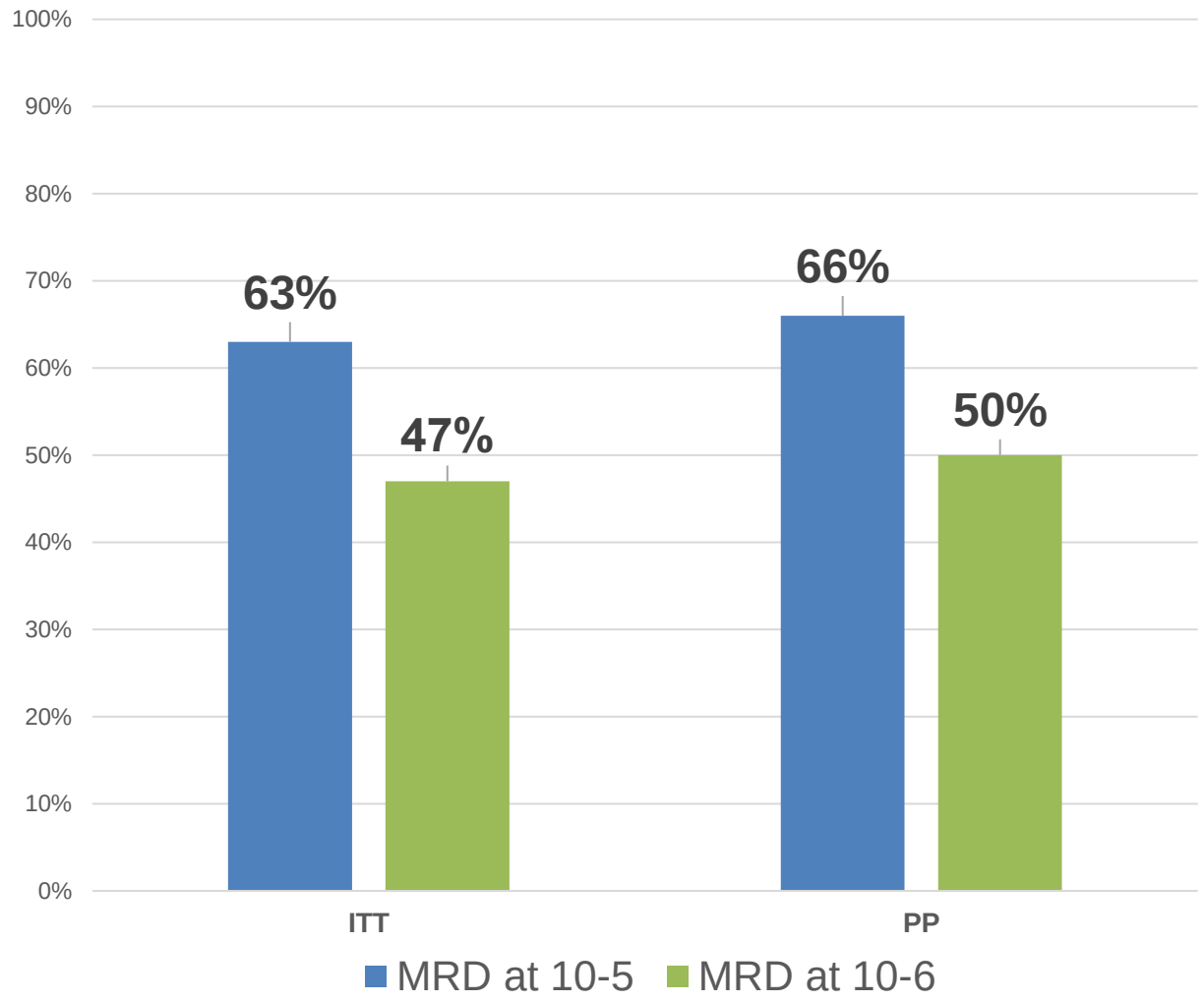


* cut-off 55%

Taux de MRD neg après induction

MRD évaluée après 6 cycles
- NGS

Taux MRD-neg = 63% at 10^{-5}

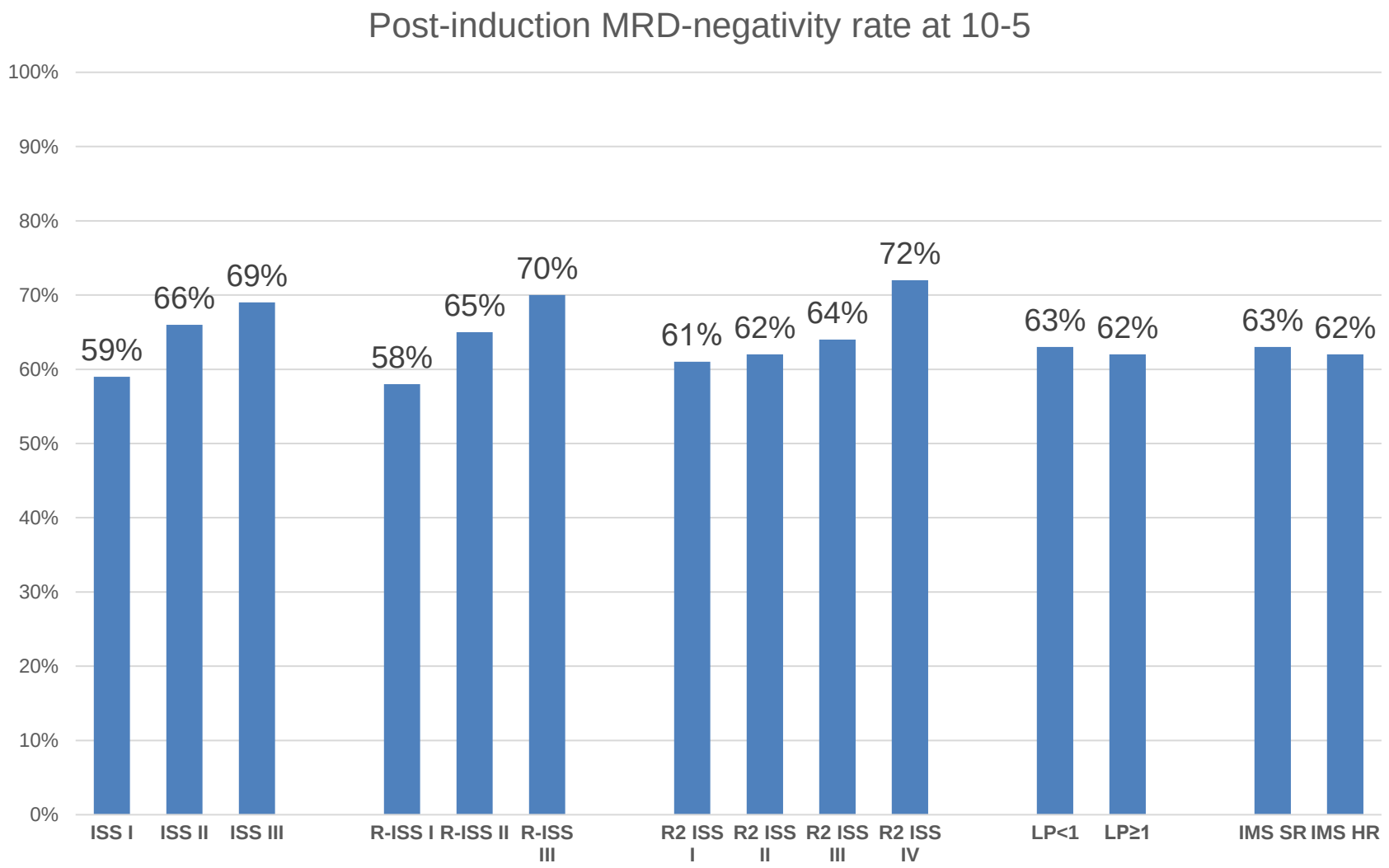


Myeloma

Subgroup analyses of MRD-negativity

No significant differences according to:

- ISS stage
- R-ISS stage
- R2-ISS stage
- IFM LP score
- IMS/IMWG consensus definition



Safety

Evenements indesirables

	Any grade, N (%)	Grade >2, N (%)
Hematologic		
Anemia	134 (17%)	52 (7%)
Thrombocytopenia	100 (13%)	42 (5%)
Neutropenia	229 (29%)	204 (25%)
Non hematologic		
Gastrointestinal disorders	441 (56%)	22 (3%)
Infections	364 (46%)	54 (7%)
Hepatobiliary disorders	104 (13%)	46 (6%)
Cardiac disorders	49 (6%)	9 (1%)
Peripheral neuropathies	103 (13%)	3 (<1%)
Thrombotic microangiopathy	1 (<1%)	1 (<1%)

Taux de mortalité <1% avec IsaKRD

Elements apportés par la première analyse de MIDAS

- **Essai MIDAS =**
- **adapter le traitement en fonction de la MRD après une induction par Isa KRD**

- **Après Isa KRD : MRD 10-5= 63 % (35% dans Cassiopéa);taux de RC 66%**
- **Facteurs pronostics initiaux « effacés » par cette induction**

Quid maintenance ?

AURIGA: Study Design

- Objective: To determine the impact of adding DARA to R maintenance on MRD-negative conversion

Key eligibility criteria
- 18-79 years of age
- NDMM with ≥4 cycles of induction therapy and underwent ASCT within 12 months of the start of induction
- ≥VGPR at screening[a]
- MRD[b] positive (10^{-5}) post-ASCT
- No prior anti-CD38
- Randomization within 6 months of ASCT date

Stratification factor
- Cytogenetic risk[c] (standard risk/unknown vs high risk)

1:1 RANDOMIZATION (N = 200)

Maintenance: up to 36 cycles[d] (28-day cycles)

D-R

D: 1,800 mg SC[e] QW Cycles 1-2, Q2W Cycles 3-6, Q4W Cycles 7+

R: 10 mg PO daily Days 1-28 (after Cycle 3, 15 mg PO daily if tolerated)

R

R: 10 mg PO daily Days 1-28 (after Cycle 3, 15 mg PO daily if tolerated)

Primary endpoint
- MRD-negative (10^{-5}) conversion rate from baseline to 12 months after maintenance treatment
  - N = 214 planned to achieve ≥85% power to detect 20% improvement

Secondary endpoints
- PFS, overall MRD-negative conversion rate, sustained MRD-negative rate, response rates, duration of ≥CR, OS, safety

MRD[b] obtained after 12, 18, 24, and 36 cycles

VGPR, very good partial response; D, daratumumab; SC, subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PO, orally; CR, complete response. [a]As assessed by International Myeloma Working Group 2016 criteria. [b]MRD based upon NGS (clonoSEQ®; Adaptive Biotechnologies). [c]For stratification, cytogenetic risk was evaluated per investigator assessment, in which high risk was defined as the presence of ≥1 of the following cytogenetic abnormalities: del[17p], t[4;14], or t[14;16]. [d]Study treatment continued for a planned maximum duration of 36 cycles or until progressive disease, unacceptable toxicity, or withdrawal of consent. After the end of the study treatment period of 36 months and after the end of the study, patients benefiting from treatment with DARA and/or R could continue receiving treatment per the investigator's discretion. [e]DARA SC (DARA 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA]).

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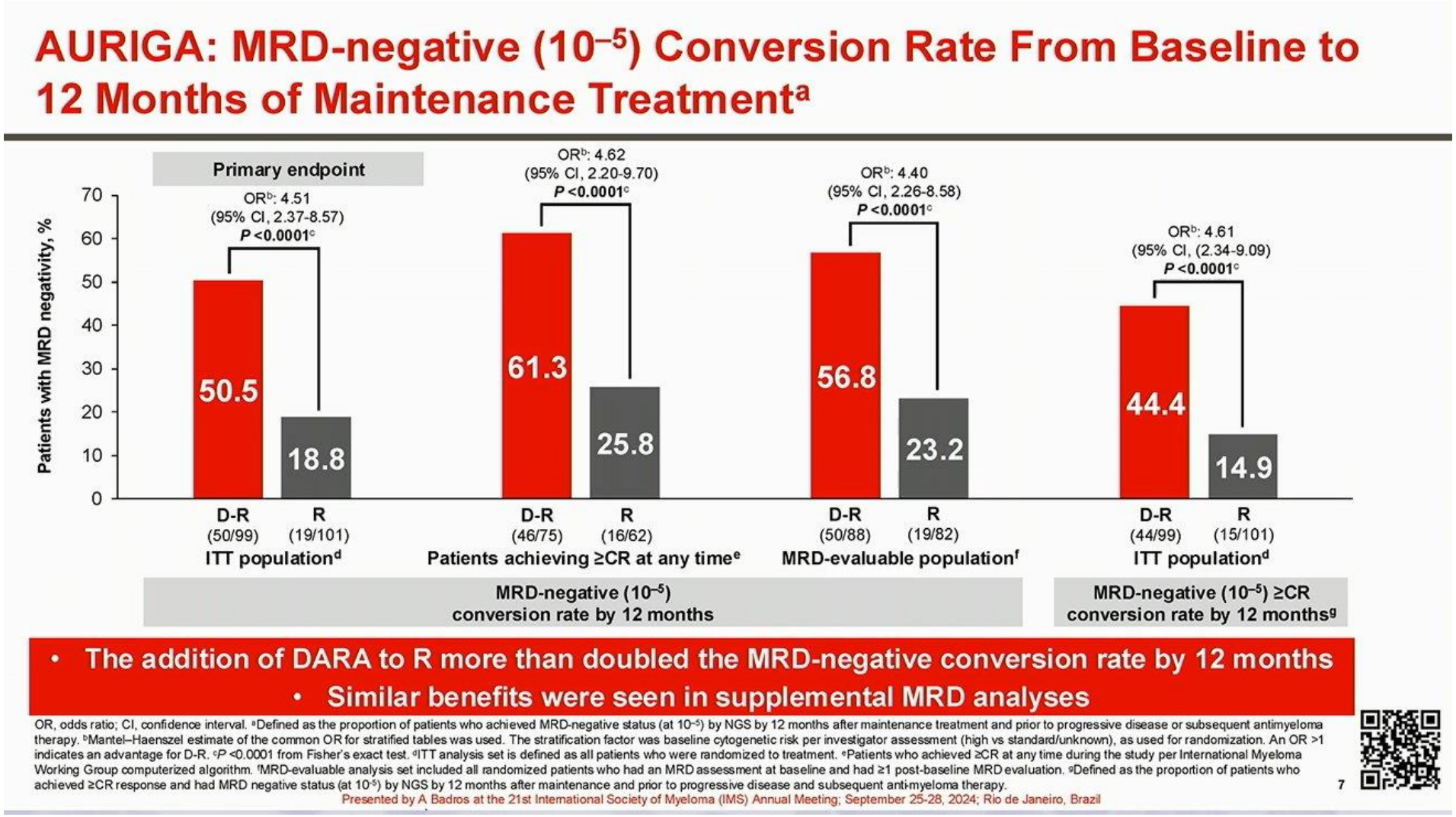
Presented by A Badros at the 21st International Society of Myeloma (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil

Quid maintenance ?



Quid maintenance ?

AURIGA : Chez les patients TE NDMM naïfs de daratumumab et en MRD + post autogreffe -> Maintenance par Dara Rev permet de doubler le taux de MRD neg à 12 mois

PERSEUS : Chez les patients TE NDMM non naîfs de daratumumab et autogreffés -> Maintenance par Dara Rev permet également d'augmenter significativement la réponse

EMA : Autorisation de Dara rev en maintenance

En première ligne de traitement TE NDMM

Induction AntiCD38 + VRD
Recueil de CSP
Autogreffe (s)
Consolidation AntiCD38 + VRD
Maintenance Lenalidomide (+ Ac anti CD38) autorisation en attente)

En première ligne de traitement NTE NDMM

– 1 ere ligne pour patients non éligibles à l’autogreffe NTE NDMM

2024 ASCO ANNUAL MEETING

EHA 2024 , Abstract #S100

Isatuximab plus lenalidomide and dexamethasone with weekly bortezomib versus isatuximab plus lenalidomide and dexamethasone in newly diagnosed transplant ineligible Multiple Myeloma. The BENEFIT (IFM 2020-05) study

ICANS

Contexte

- Faire mieux de dara Revdex de MAIA

- Question posée BENEFIT : Améliorer MRD negative en rajoutant Bortezomib (30% dans MAIA)

- Question posée IMROZ : Est ce que le rajout d'un Ac anti CD 38 améliore les resultats de l'étude du SWOG VRD

- POPULATION
  - BENEFIT 270 patients age median 73 ans
  - IMROZ 446 patients randomisés 3:2dans bras Isa VRD ; age median 72 ans

d, dexamethasone; Dara, daratumumab; Isa, isatuximab; NDMM, newly diagnosed multiple myeloma; ODAC, Oncologic Drugs Advisory Committee; R, lenalidomide; SOC, Standard of care; Ti, transplant ineligible; V, bortezomib.

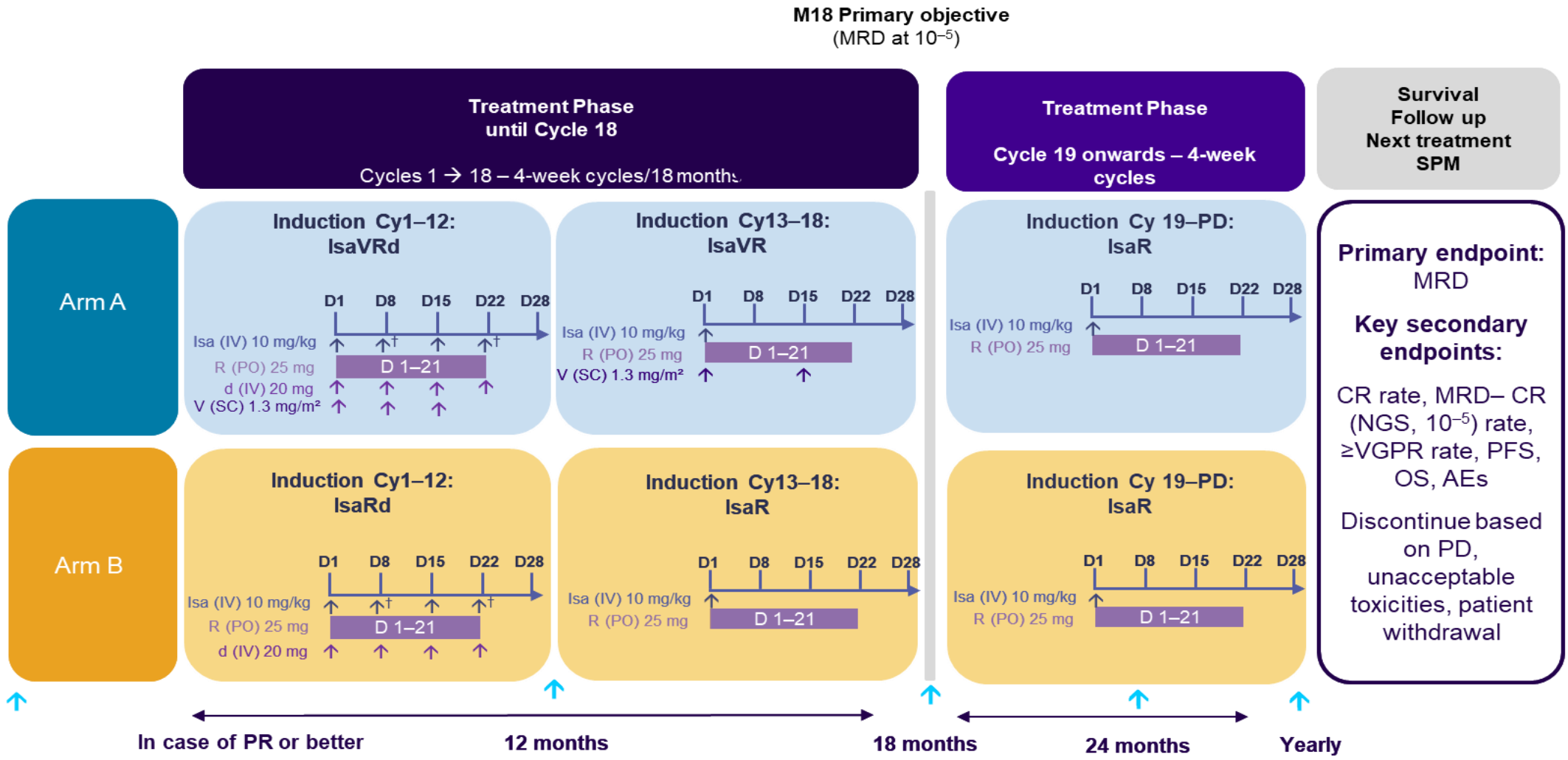
1. ClinicalTrials.gov; NCT03319667; 2. Facon T, et al. *N Engl J Med* 2019;380:2104–15; 3. Dimopoulos MA, et al. *Ann Oncol* 2021;32:309–22; 4. Rajkumar SV, Kumar S. *Blood Cancer J* 2020;10:94; 5. O'Donnell EK, et al. *Br J Haematol* 2018;182:222–30; 6. Mateos MV, et al. *Haematologica* 2014;99:1114–22; 7. Hoff F, et al. *Blood Cancer J* 2024;14:52; 8. Durie BGM, et al. *Lancet* 2017;289:519–27; 9. U.S. Food & Drug Administration. Last updated April 17, 2024. Accessed April 22, 2024. https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024.

Etude BENEFIT : Isa-VRd vs Isa-Rd pour patients NTE NDMM

N=270

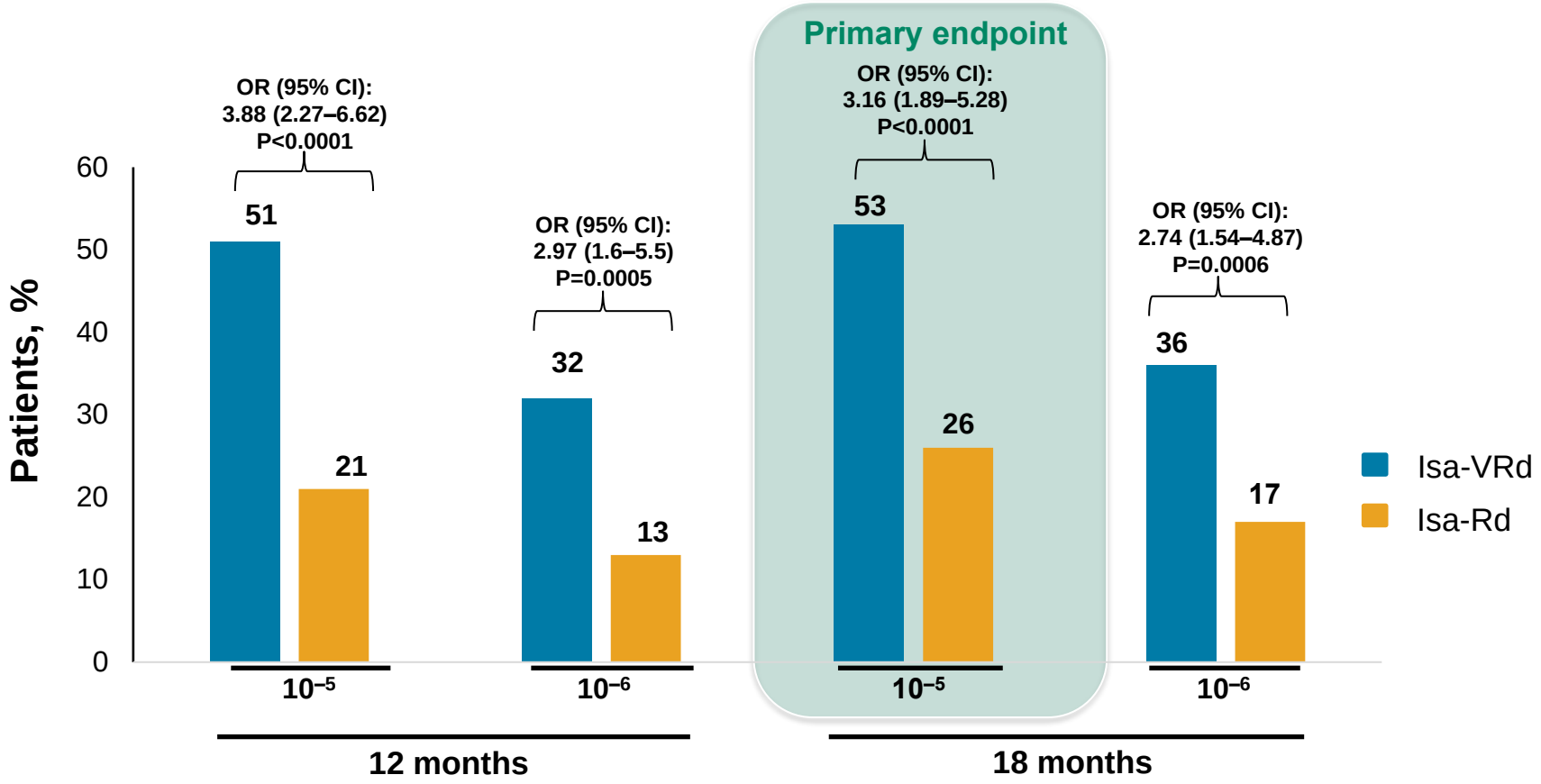
- **Randomization1:1**
- **Stratified by:**

- Age: <75 and ≥ 75yrs
- Cytogenetic result by FISH (Modified Perrot score)
- Center



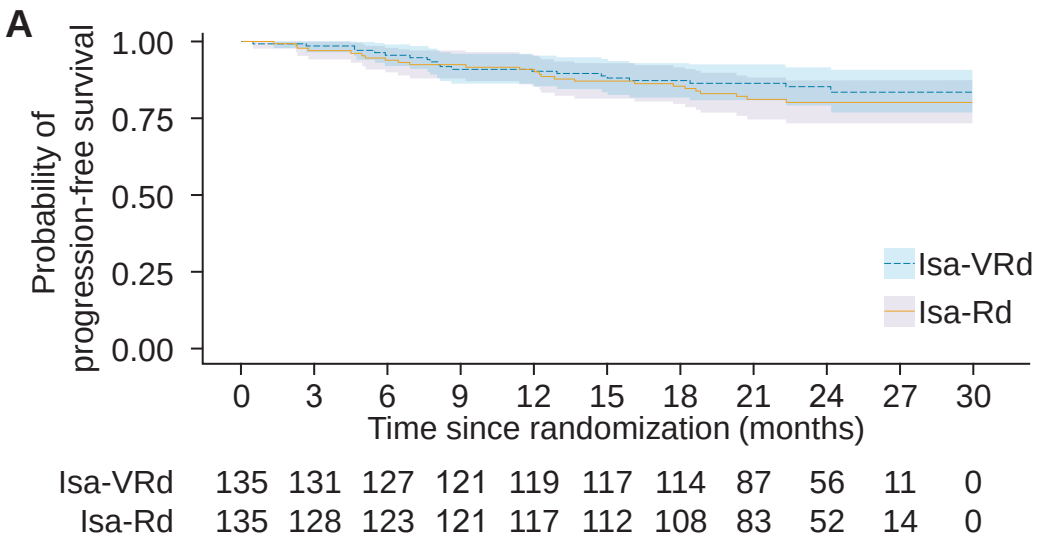
†Cycle 1 only. CR, complete response; Cy, cycle; d, dexamethasone; D, day; Isa, isatuximab; M, month; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, lenalidomide; SPM, second primary malignancy; Ti, transplant-ineligible; V, bortezomib; VGPR, very good partial response.

ETUDE BENEFIT EFFICACITE : MRD



*MRD was assessed on the basis of IMWG recommendations.[1]
CI, confidence interval; Isa, isatuximab; ITT, intent-to-treat; MRD–, minimal residual disease negativity; NGS, next generation sequencing; OR, odd ratio; R, lenalidomide; V, bortezomib.
1. Kumar S, et al. *Lancet Oncol* 2016;17:e328–e346.

BENEFIT : analyse de la survie immature



Estimated 24 months PFS
85.2% (95%CI 79.2–91.7) for Isa-VRd
80.0% (95% CI 73.3–87.4) for Isa-Rd

d, dexamethasone; Isa, isatuximab; IRC, independent review committee; ITT, intent-to-treat; CI, confidence interval; OS, overall survival; PFS, progression-free survival; R, lenalidomide; V, bortezomib.

Effets indesirables BENEFIT

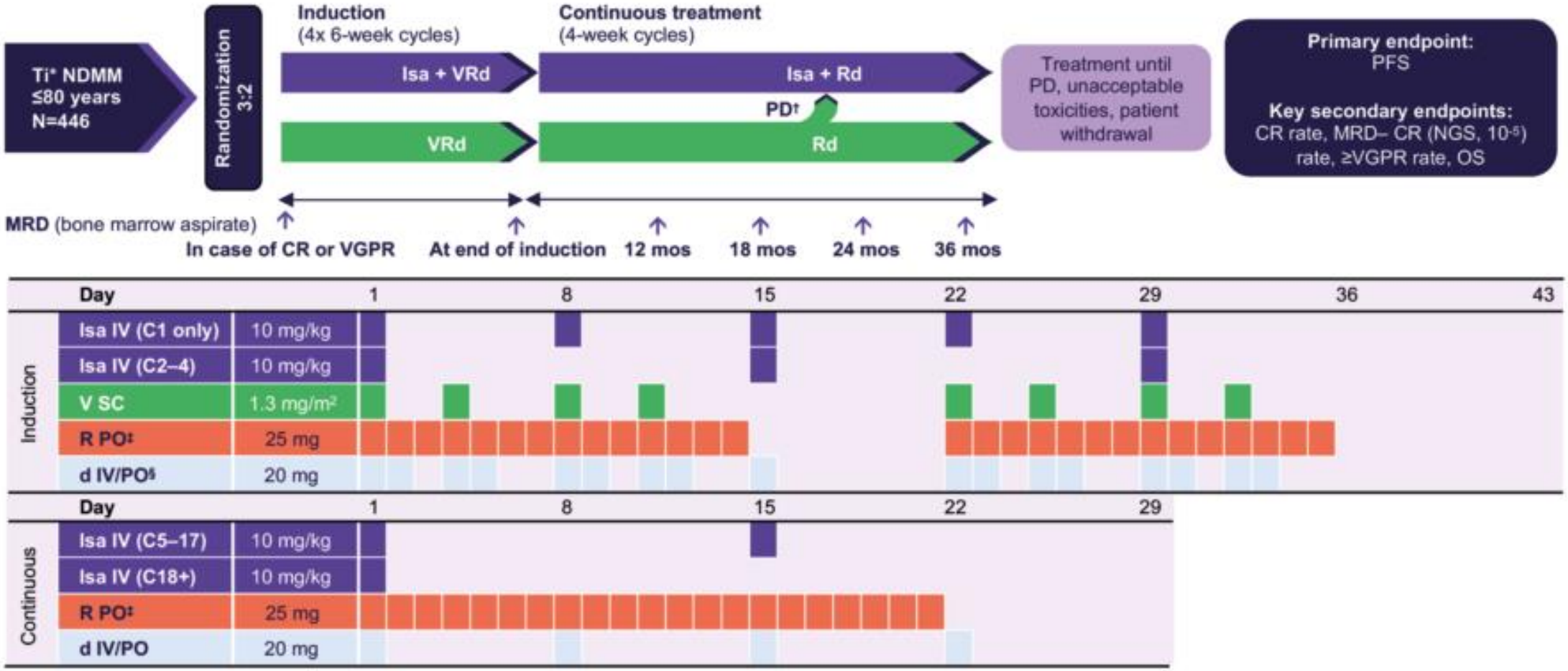
Event, no. of patients (%)	Isa-VRd (n=135)		Isa-Rd (n=135)	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Hematologic adverse events				
Neutropenia	77 (57)	53 (40)	82 (61)	61 (45)
Lymphopenia	53 (39)	44 (33)	38 (28)	33 (24)
Anemia	30 (22)	13 (10)	27 (20)	7 (5)
Thrombocytopenia	37 (27)	16 (12)	19 (14)	8 (5)
Event, no. of patients (%)	**Any Grade**	**≥Grade 2**	**Any Grade**	**≥Grade 2**
Nonhematologic adverse events				
Diarrhea	66 (49)	39 (29)	65 (48)	30 (22)
Constipation	52 (39)	30 (22)	41 (30)	19 (14)
Rash	21 (16)	12 (9)	16 (12)	9 (7)
Asthenia	41 (30)	24 (18)	48 (36)	18 (14)
Peripheral Oedema	48 (36)	18 (14)	27 (20)	10 (7)
Muscle spasms	27 (20)	7 (5)	28 (21)	9 (7)
Psychiatric disorders	33 (24)	22 (16)	32 (24)	17 (13)
Vascular disorders	36 (27)	21 (15)	34 (25)	23 (17)

Event, no. of patients (%)	Isa-VRd (n=135)		Isa-Rd (n=135)	
	Any Grade	≥Grade 2	Any Grade	≥Grade 2
Nonhematologic adverse events (cont'd)				
Eye disorders	20 (15)	10 (7)	19 (14)	12 (8)
SPMs	6 (4)	6 (4)	6 (4)	6 (4)
Infections and infestations				
Infection of other types	61 (45)	48 (36)	48 (36)	35 (28)
Infection of the respiratory system	65 (48)	47 (35)	64 (47)	54 (40)
Covid-19	55 (41)	34 (24)	59 (44)	31 (23)
Nervous system disorders				
Peripheral neuropathy	70 (52)	37 (27)†	38 (28)	13 (10)‡
Other	38 (28)	19 (14)	41 (30)	17 (13)

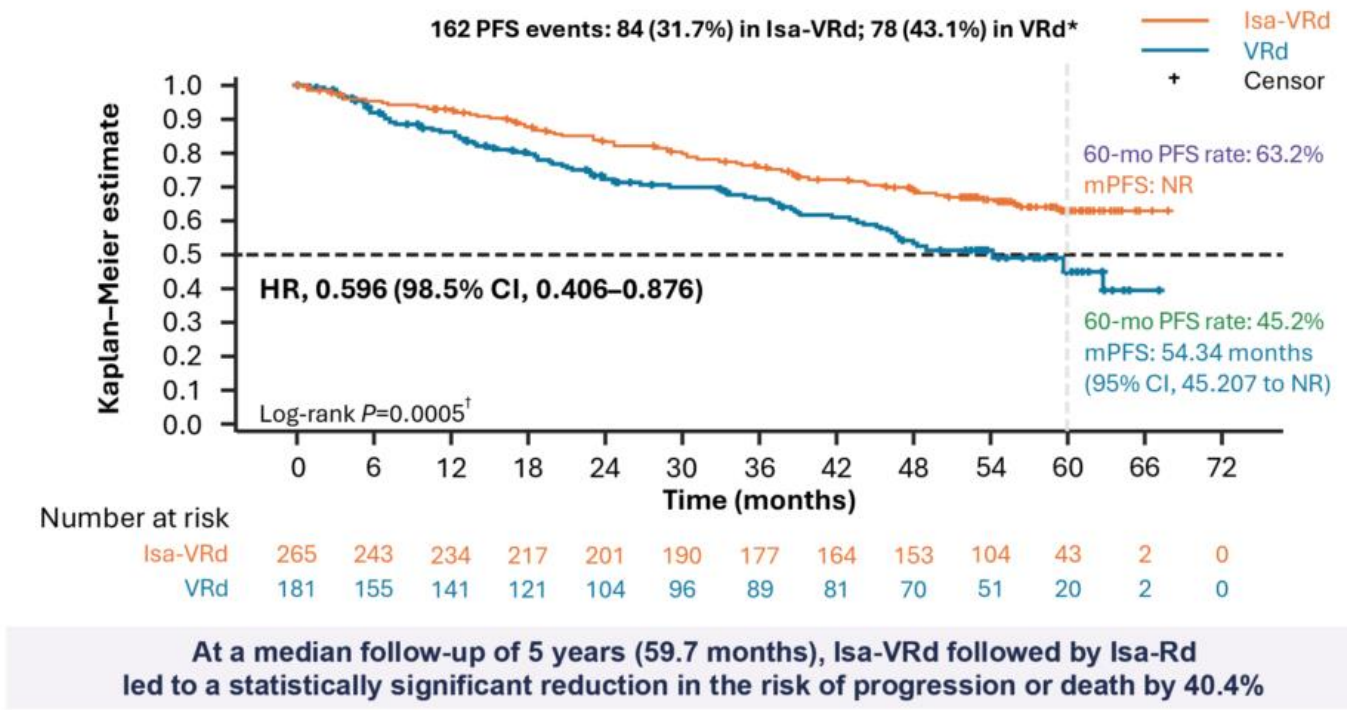
NEUROTOXICITE non negligeable

*The safety population included all patients who received at least one dose of study treatment; †Four patients had a Grade 3 event in Isa-VRd arm; ‡One patient had a Grade 3 event in the Isa-Rd.
d, dexamethasone; Isa, isatuximab; R, lenalidomide; SPM, second primary malignancies; V, bortezomib.

Etude IMROZ : Isa-VRd vs VRD pour patients NTE NDMM



EFFICACITE IMROZ : SSP

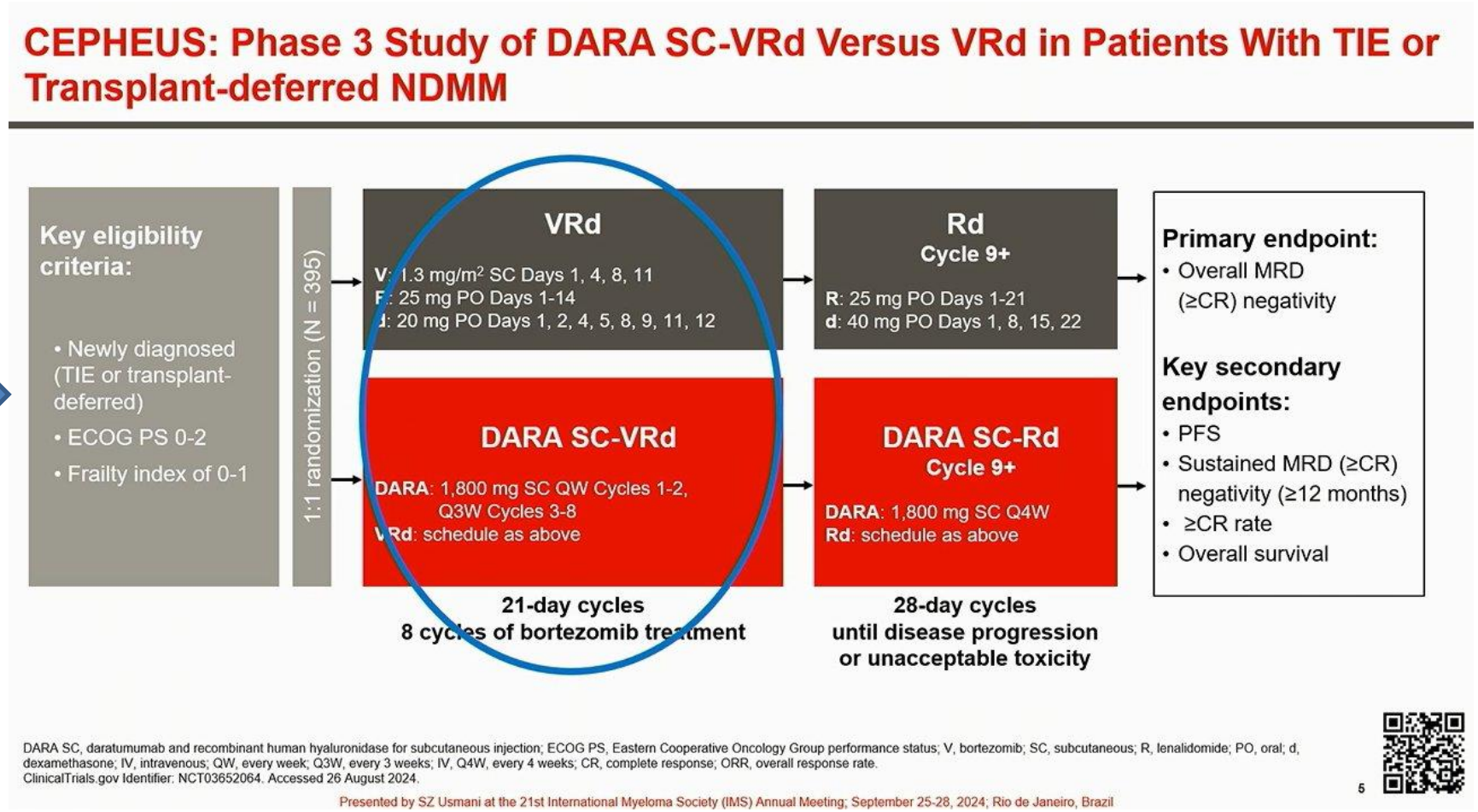


At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

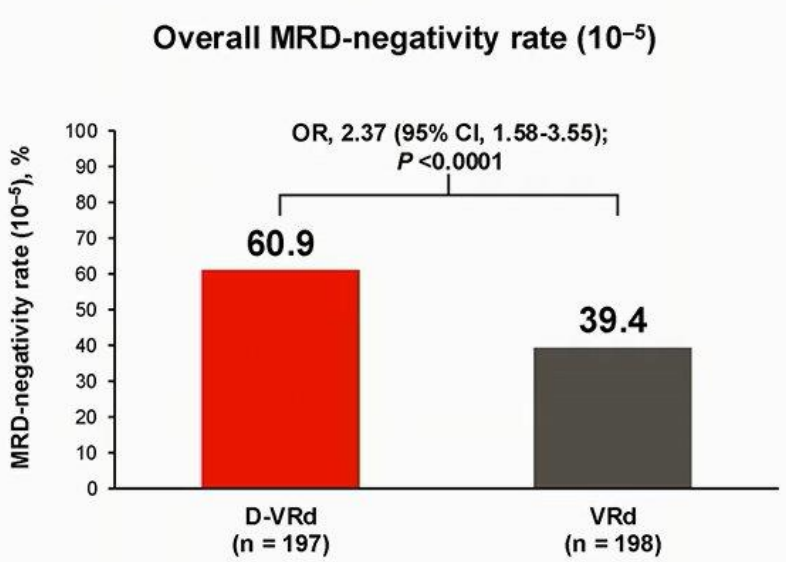
MRD neg à 10-5 à 18 mois = 58 % (bras Isa VRD) versus 43% (bras VRD)

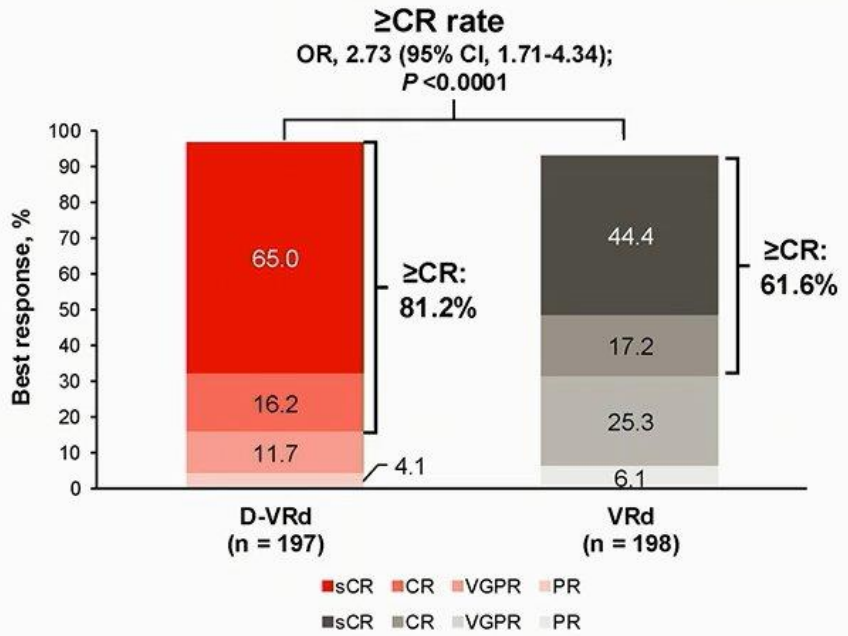
MRD neg à 10-5 à 12 mois = 47% (bras Isa VRD) versus 24% (bras VRD)

Etude miroir /IMROZ



CEPHEUS: Primary Endpoint of Overall MRD-negativity Rate[a] (10^{-5}; ITT Population)



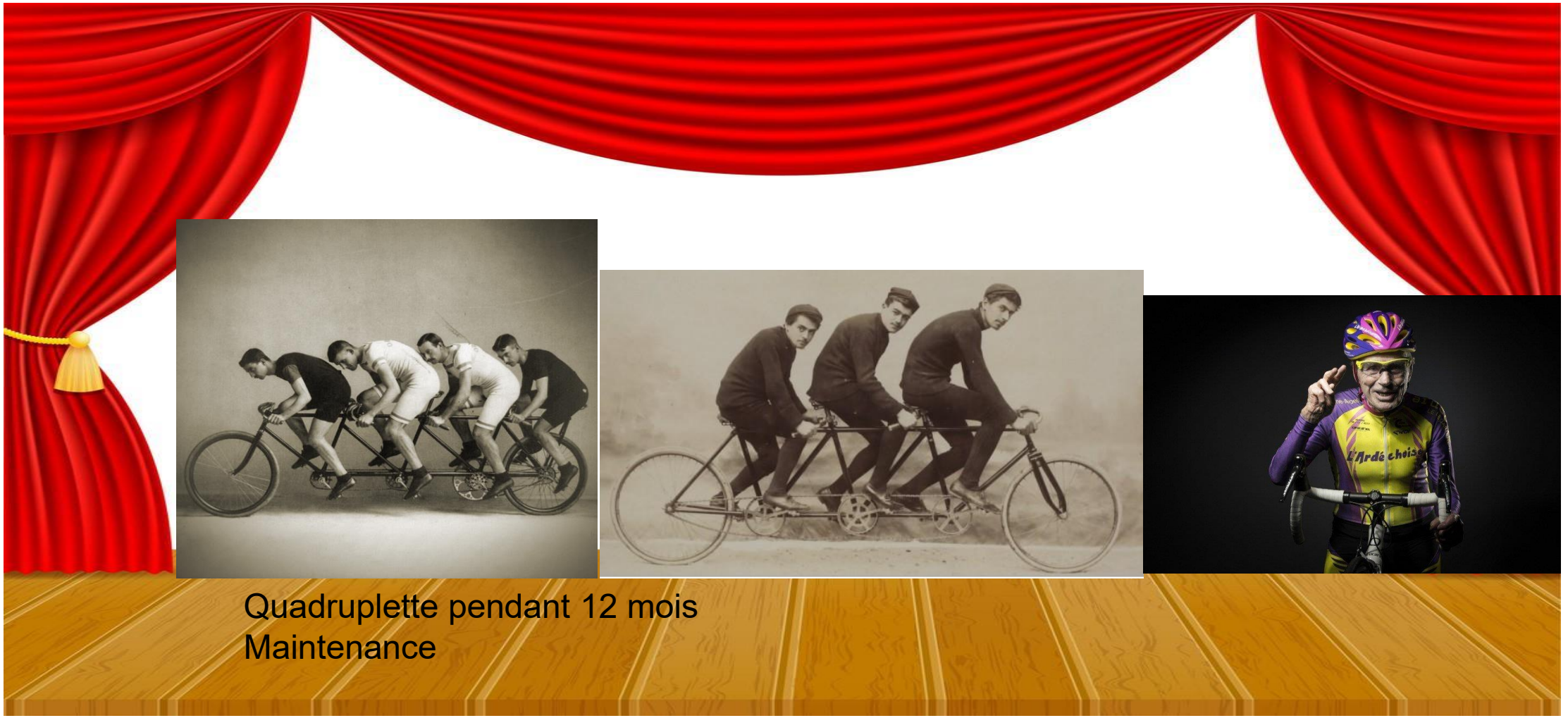


Daratumumab significantly increased overall MRD-negativity rate and overall ≥CR rate by approximately 20%

OR, odds ratio; CI, confidence interval; sCR, stringent complete response; VGPR, very good partial response; PR, partial response.
[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5}) and ≥CR.

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

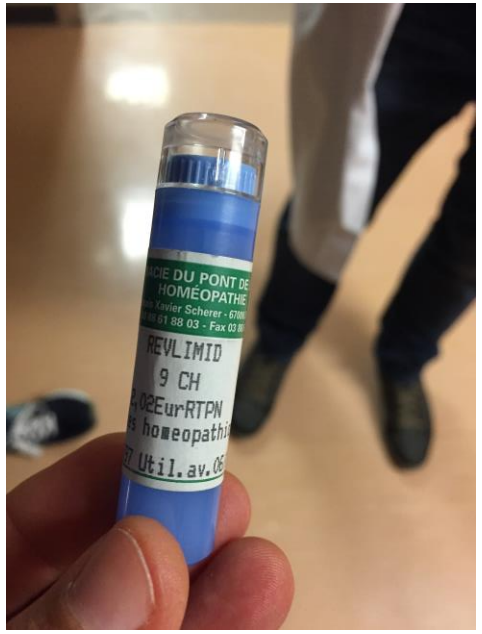
En première ligne de traitement NTE NDMM



Et après ….

- Prévalence de patients myélome en nette augmentation
- Graal de la guérison du myélome
- Maladie incurable

Et après : l'activité physique plutôt que les Fake med?

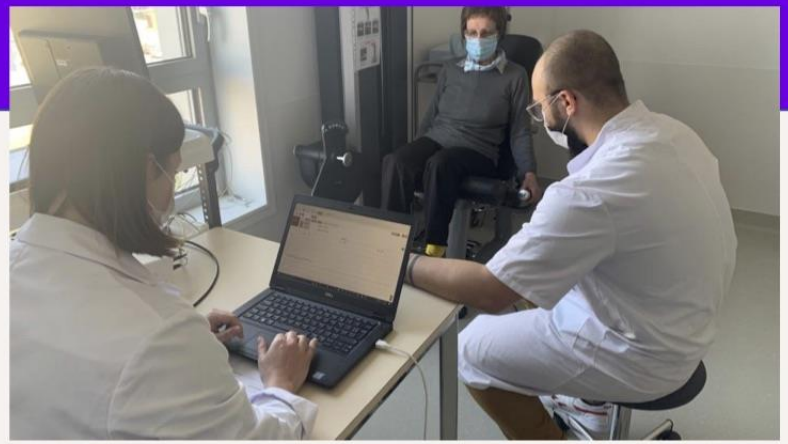


Améliorer Connaissances/Etude PROTECT

- Unité d'APA
- 2 chercheurs en physiologie de l'exercice (Elyse HUCTEAU et Joris Mallard)

- Caractériser la condition physique des patients atteints de myélome au décours de leur prise en charge
  - Diagnostic
  - 8 semaines après début des traitements
  - Avant autogreffe
  - Avant le traitement de maintenance
  - A distance de la fin des traitements

- Etude en cours 21 patients



17

RS_2023-11_Paris_RS2H_Bénéfice de l'APA_C Sonntag

Activité physique ADAPTEE et MYELOME

A chacun son Hohneck

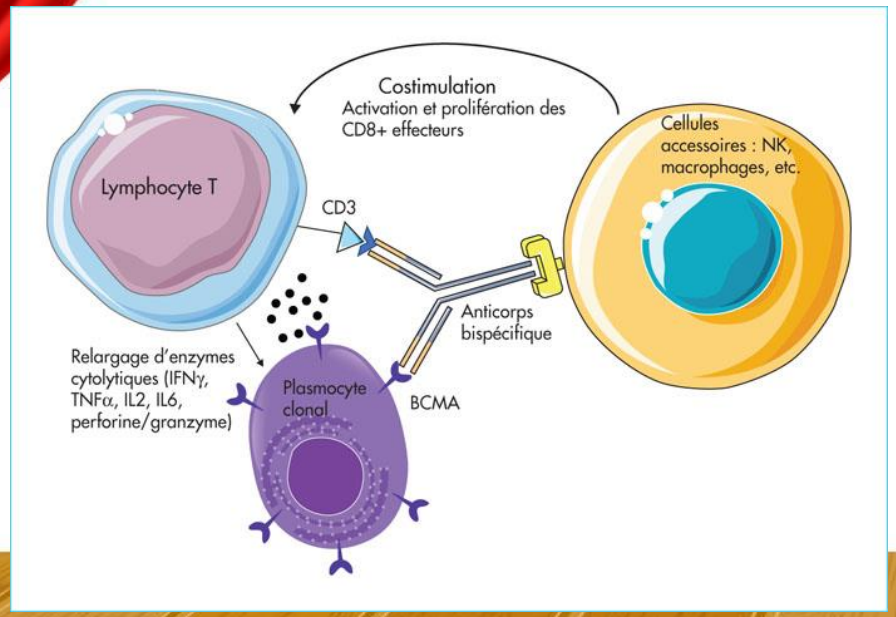
CONCLUSION

TE NDMM : Induction -Autogreffe-Consolidation –Maintenance
Quid Maintenance par Ac anti CD38 –lenalidomide

NTE NDMM : Quadruplette si réalisable?
Veiller à la Qualité de vie

Des questions ??

Bispécifiques

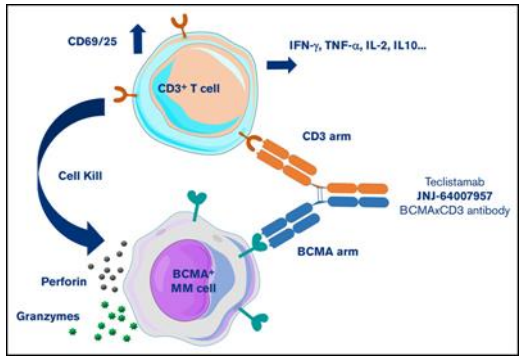


TECLISTAMAB : Majestec-1
ELRANATAMAB : MAGNETISMM 3
TALQUETAMAB : MonumenTAL-1
ASSOCIATION Bispectifique + Ac anti CD38
ASSOCIATION 2 Ac bispecifiques

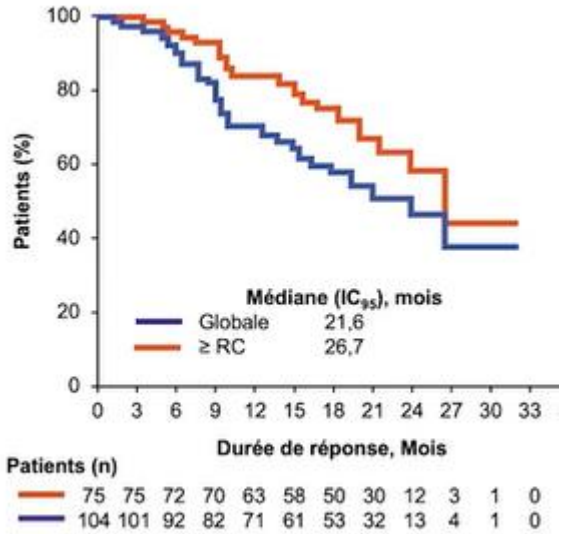
Le Grand S, Perrot A. Les anticorps bispécifiques. Hématologie 2021 ; 27(supplément 3) : 19-25. doi : 10.1684/hma.2021.1650

Des questions ??

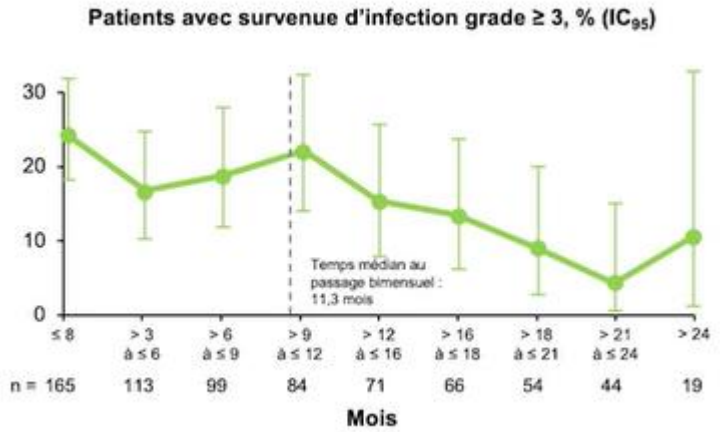
TECLISTAMAB



MajesTEC-1



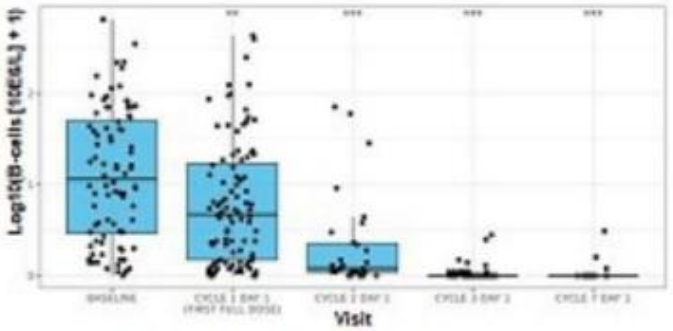
Mise à jour des données Majestec -1 : 2 ans de recul
France : Ac bispécifique disponible en accès précoce
>600 patients
Patients lourdement traités >5 lignes
Taux de réponse 63%
PFS médiane 11,3 mois
Durée de réponse chez les patients répondeurs : 21 mois
Meilleure gestion des infections au fil du temps



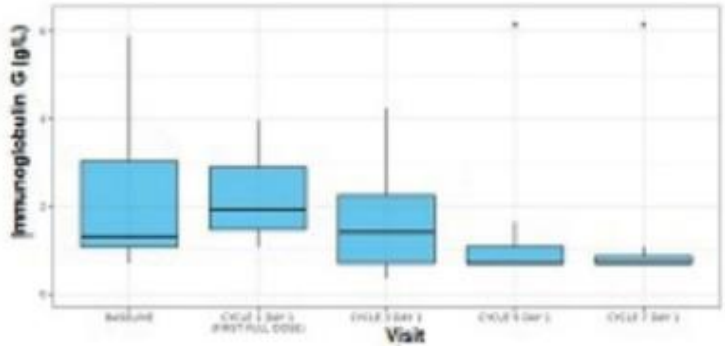
EHA 2023 Van de Donck abstract 8011/ Usmani et al abstr 8034 actualisés

TECLISTAMAB

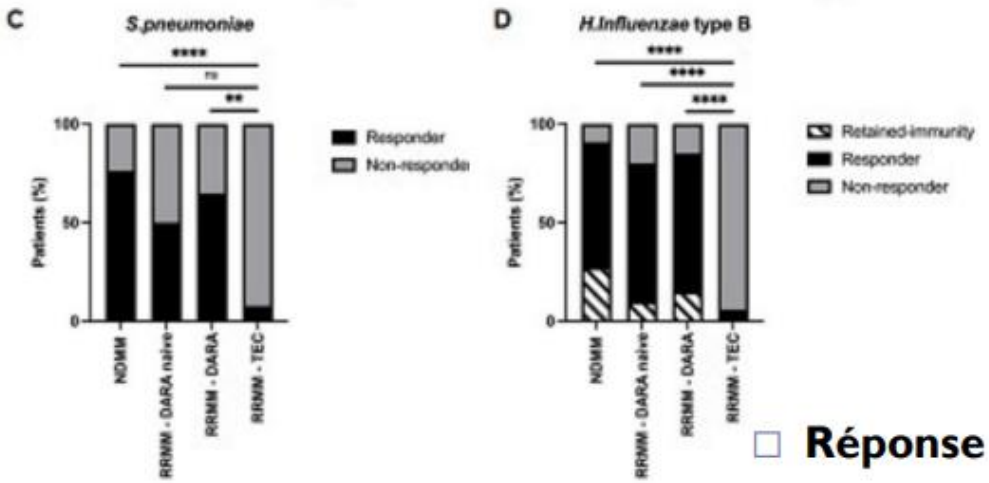
Données biologiques de Majestec 1(teclistamab)



- **A. Diminution rapide et durable des LB circulants**
  - C1J1 : 10,6x10^6
  - C2J1 : 0,2x10^6
  - C7J1 : 0



- **B. Diminution rapide et durable des IgG polyclonales**
  - C1J1 : 1,4g/L
  - C5J1 : 0,8g/L
- **Mais aussi des IgA et des IgM**



- **Réponse vaccinale quasi nulle**

- **Substitution en Ig :**
- Diminution du risque d'infections de grade 3/4 de 45 à 16% à 6 mois (p=0,002)

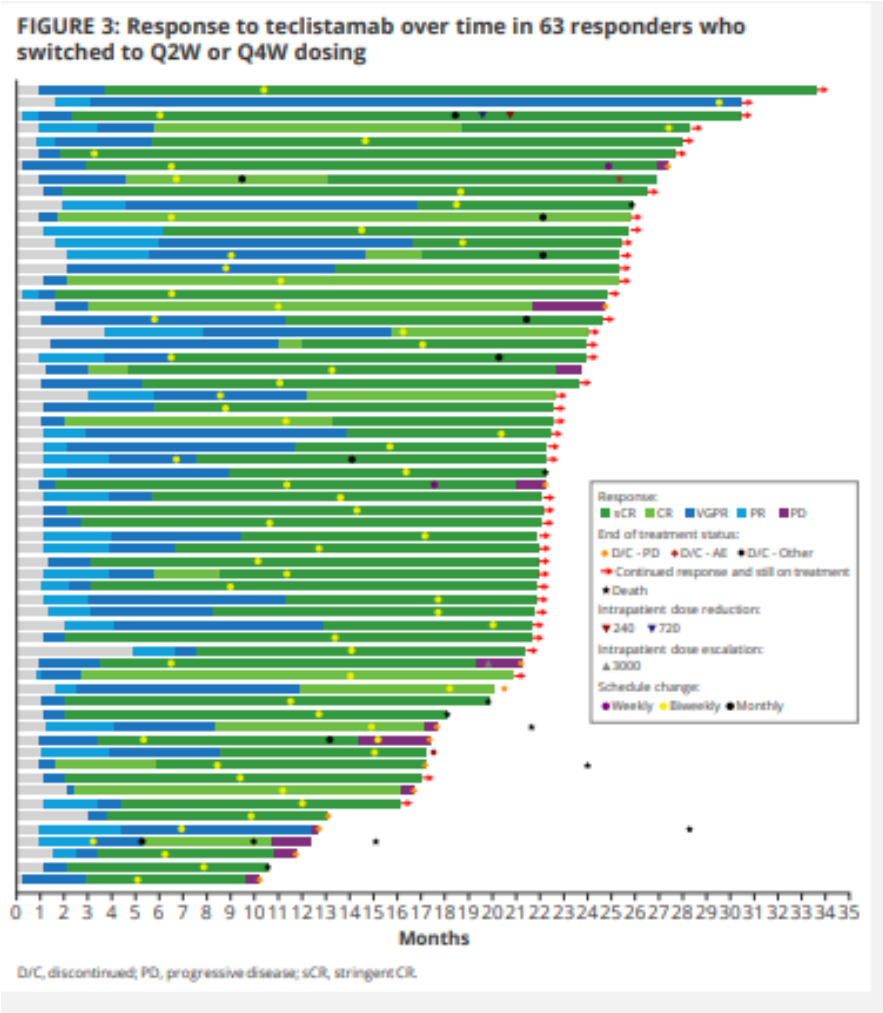
Frerichs et al, EHA 2023. Abstract P1506

TECLISTAMAB

MajesTEC-1

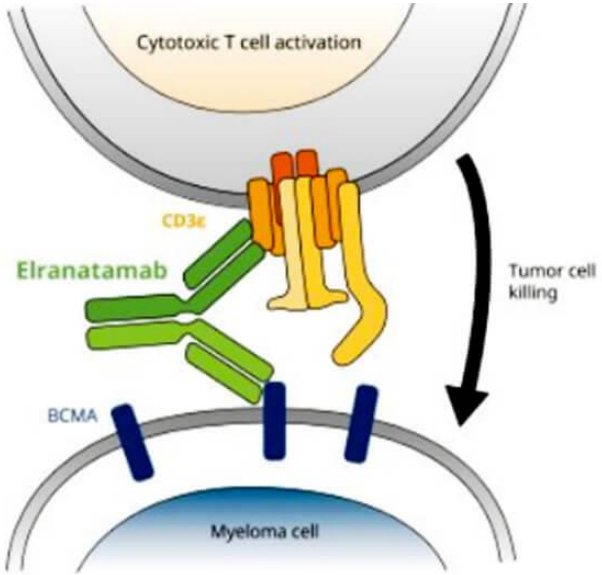
Réponse durable avec espacement des doses
Durée médiane de réponse non atteinte :
68 % des patients qui switchent restent en réponse >= 2 ans

Diminution de moitié des infections de grade 3



Poster EHA :Manisha Bhutan
Durability of Responses With Biweekly Dosing of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma Achieving a Clinical Response in the MajesTEC-1 Study

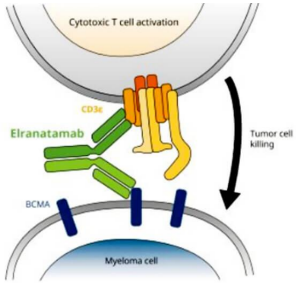
ELRANATAMAB



Ac bispecifique ciblant BCMA et CD3
Disponible en accès précoce

ELRANATAMAB

MagnetisMM-3



MagnetisMM-3 Study

- MagnetisMM-3 is an open-label, multicenter, non-randomized, phase 2 study

Patients with RRMM

Key inclusion criteria:
- Refractory to ≥1 each of the following: proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody[a]
- ECOG performance status ≤2
- Creatinine clearance ≥30 mL/min
- Platelets ≥25 × 10^9/L
- ANC ≥1.0 × 10^9/L
- Hemoglobin ≥8 g/dL

Cohort A (n=123)
No prior BCMA-directed treatment

Cohort B (n=64)
Prior BCMA-directed ADC or CAR-T

- Patients will be followed for ~2 y from enrollment

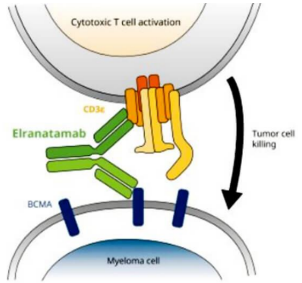
Elranatamab 76 mg SC QW on a 28-d cycle

Primary endpoint
- ORR by BICR[b]

Secondary endpoints
- Duration of response[b,c]
- CR rate[b,c]
- ORR[c]
- ORR by baseline extramedullary disease status[b]
- Duration of CR[b,c]
- Time-to-response[b,c]
- PFS[b,c]
- MRD-negativity rate
- OS
- Safety
- Pharmacokinetics

ELRANATAMAB

MagnetisMM-3



MagnetisMM-3: Elranatamab Dosing Schedule

Cycle 1				Cycles ≥2				Cycles ≥7			
Step-up doses of 12 mg and 32 mg SC	76 mg SC QW			76 mg SC QW				76 mg SC Q2W			
Wk 1 (D 1 and 4)	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4
Elranatamab											

For patients receiving ≥6 cycles and achieving partial response or better with responses persisting for ≥2 mo, the dosing interval will be changed to Q2W

Premedication:

60 min (±15 min) prior to the first 3 doses of elranatamab

- Acetaminophen 650 mg (or paracetamol 500 mg)
- Diphenhydramine 25 mg (or equivalent), oral or IV
- Dexamethasone 20 mg (or equivalent), oral or IV

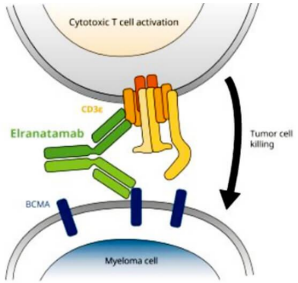
Protocol-required hospitalization:

- Dose 1: 48 hr
- Dose 2: 24 hr

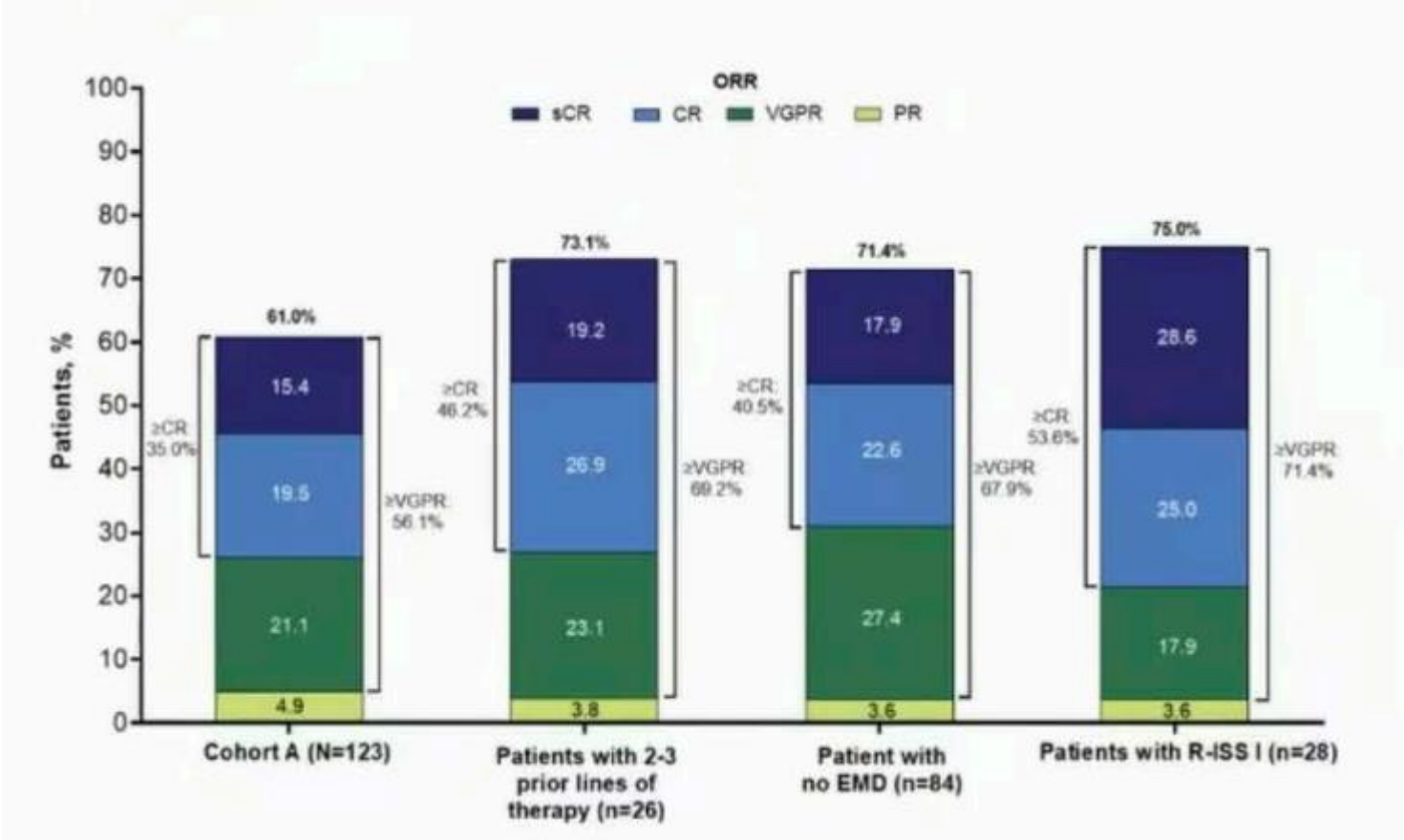
IV=intravenous; QW=once weekly; Q2W=once every 2 weeks; SC=subcutaneous

ELRANATAMAB

MagnetisMM-3

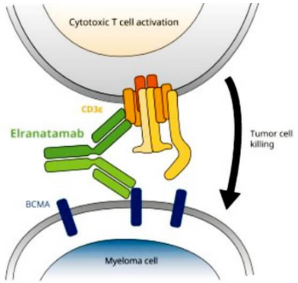


Taux de RC 35 %
chez des patients lourdement traités

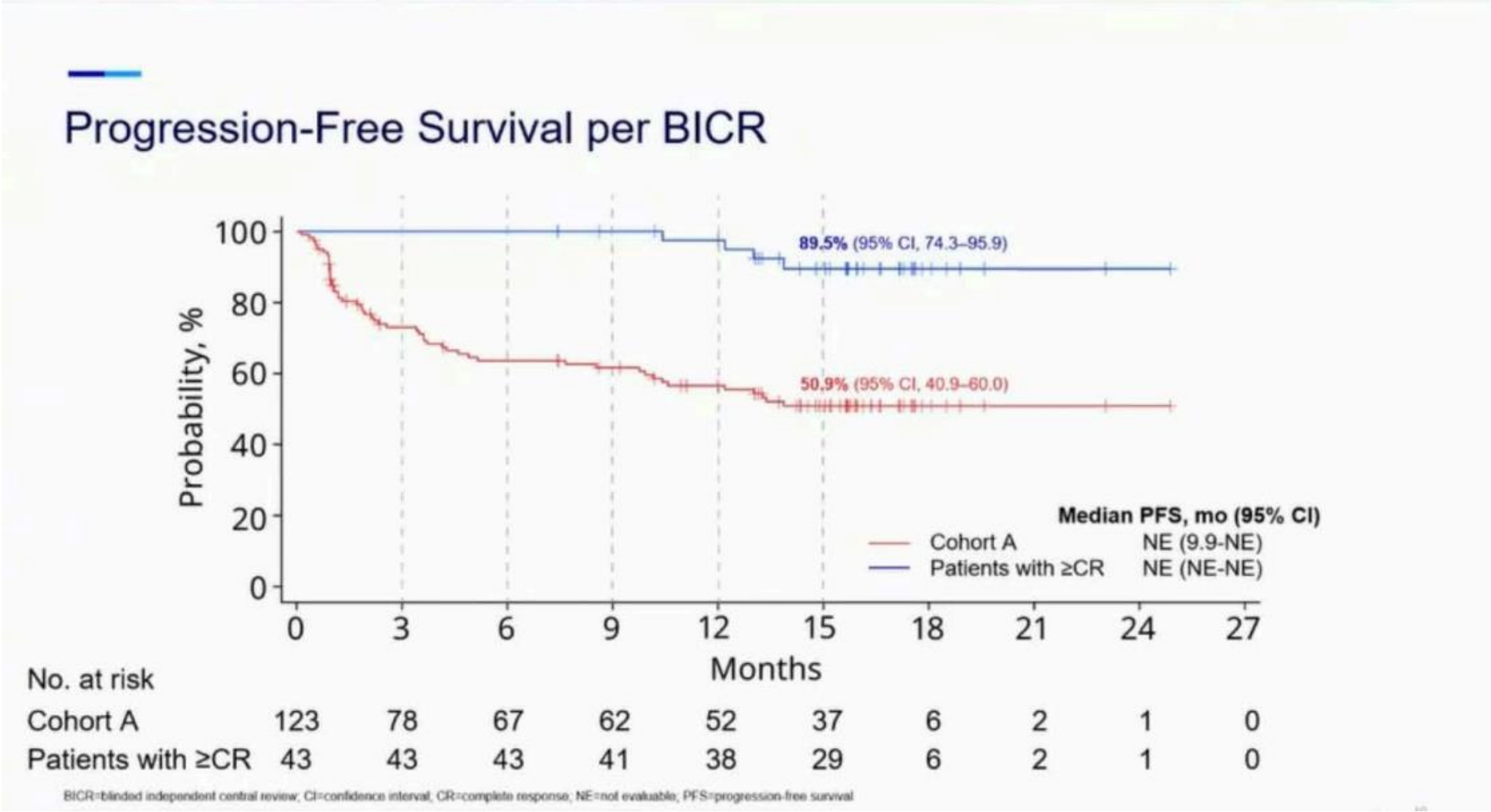


ELRANATAMAB

MagnetisMM-3

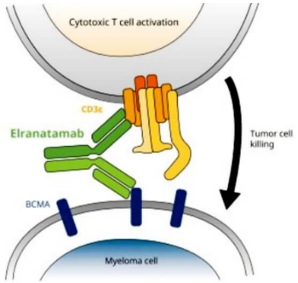


PFS médiane non atteinte

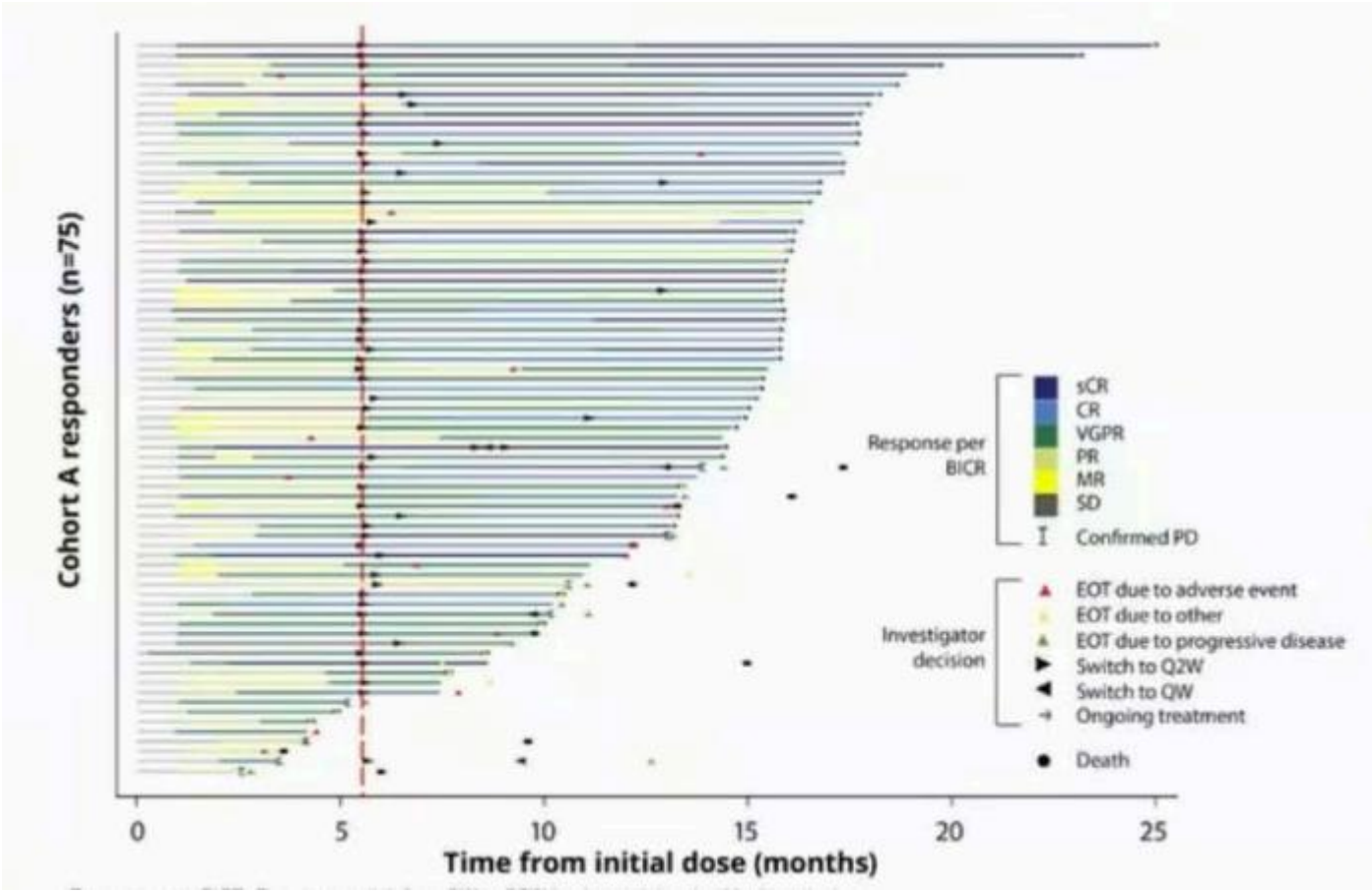


ELRANATAMAB

MagnetisMM-3

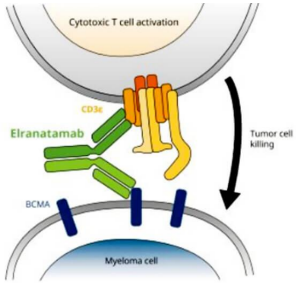


50 patients en RC ont pu switcher à une administration bi-mensuelle

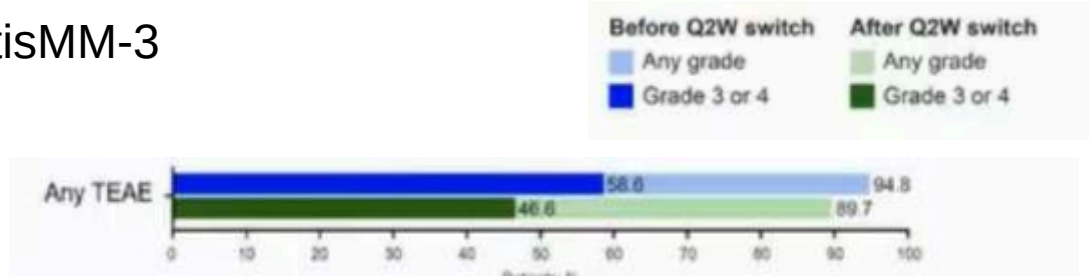


ELRANATAMAB

MagnetisMM-3



TEAEs in ≥20 of patients, n (%)	Cohort A (N=123) Any grade	Grade 3/4
Hematologic		
Anemia	60 (48.8)	46 (37.4)
Neutropenia	60 (48.8)	60 (48.8)
Thrombocytopenia	38 (30.9)	29 (23.6)
Lymphopenia	33 (26.8)	31 (25.2)
Non-hematologic		
CRS	71 (57.7)	0
Diarrhea	52 (42.3)	2 (1.6)
Fatigue	45 (36.6)	4 (3.3)
Decreased appetite	41 (33.3)	1 (0.8)
Pyrexia	37 (30.1)	5 (4.1)
COVID-19–related[a]	36 (29.3)	19 (15.4)
Injection site reaction	33 (26.8)	0
Nausea	33 (26.8)	0
Hypokalemia	32 (26.0)	13 (10.6)
Cough	31 (25.2)	0
Headache	29 (23.6)	0



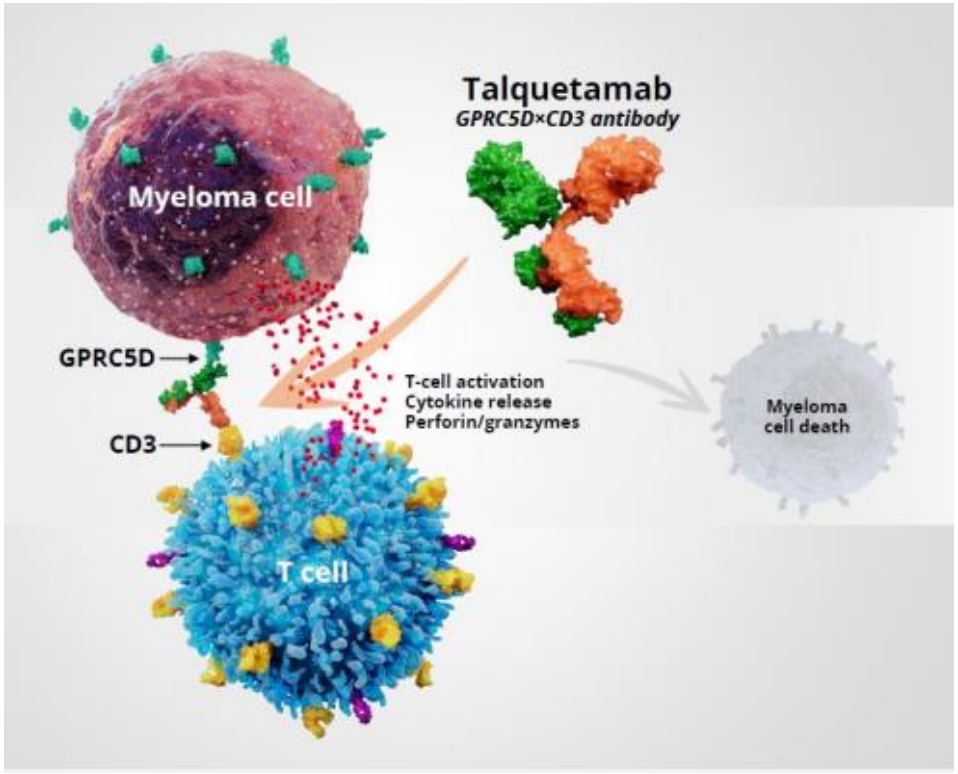
Patients, n (%)	Cohort A (N=123) Any grade	Grade 3/4	Grade 5
Infection TEAEs in ≥5% of patients			
COVID-19–related[a]	36 (29.3)	19 (15.4)	2 (1.6)
Upper respiratory tract infection	20 (16.3)	0	0
Pneumonia	20 (16.3)	10 (8.1)	0
Sinusitis	13 (10.6)	2 (1.6)	0
Urinary tract infection	12 (9.8)	4 (3.3)	0
Sepsis	8 (6.5)	8 (6.5)	0
Bacteremia	7 (5.7)	2 (1.6)	0
CMV reactivation	7 (5.7)	2 (1.6)	0
Key infections occurring in <5% of patients[b]			
Pneumocystis jirovecii pneumonia	6 (4.9)	5 (4.1)	0
CMV infection	4 (3.3)	0	0
Adenoviral hepatitis	1 (0.8)	0	1 (0.8)
Adenovirus infection	1 (0.8)[c]	0	1 (0.8)[c]
Hepatitis B reactivation	1 (0.8)	0	0
Pneumonia adenoviral	1 (0.8)[c]	0	1 (0.8)[c]
Pneumonia cytomegaloviral	1 (0.8)	1 (0.8)	0
Pneumonia pseudomonal	1 (0.8)	0	1 (0.8)

Safety
69,9 % d'infections reportées
39,8 % de grade ¾
Diminution de l'incidence des AE de grade 3-4 >10% après le switch en administration bi mensuelle

CRS essentiellement de grade 1-2

TALQUETAMAB

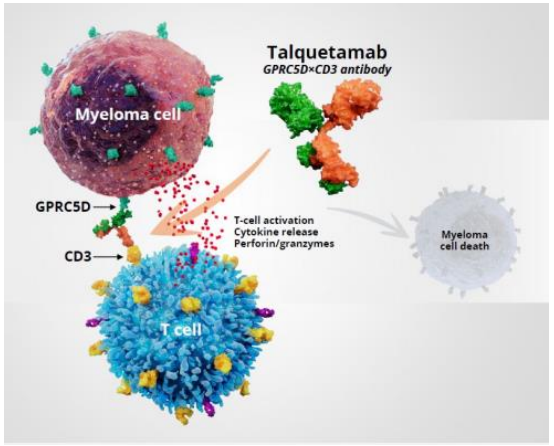
MonumenTAL -1



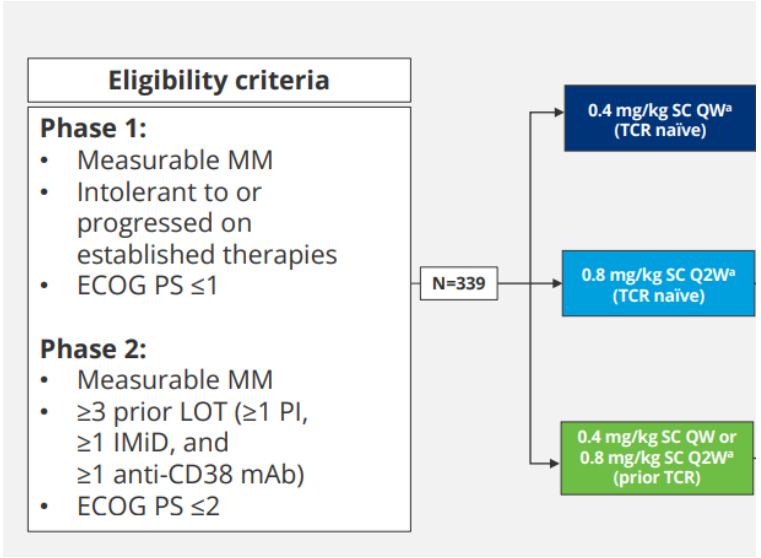
TALQUETAMAB : Ac bispécifique ciblant GPRCD et CD3
Administration sous cutanée

TALQUETAMAB

MonumenTAL -1



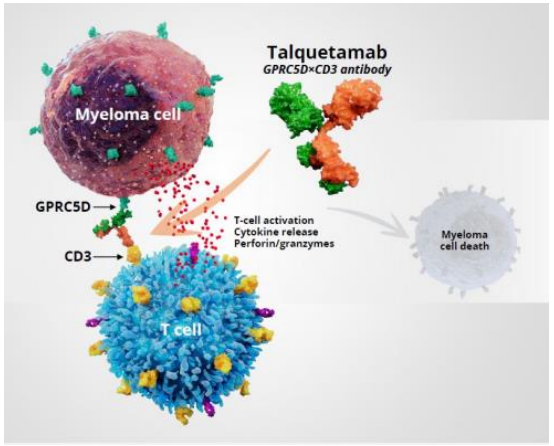
Essai de phase 1/2 chez 339 patients avec RRMM
(>=3 lignes de traitement dont un anticorps anti-CD38, IPP et IMID)



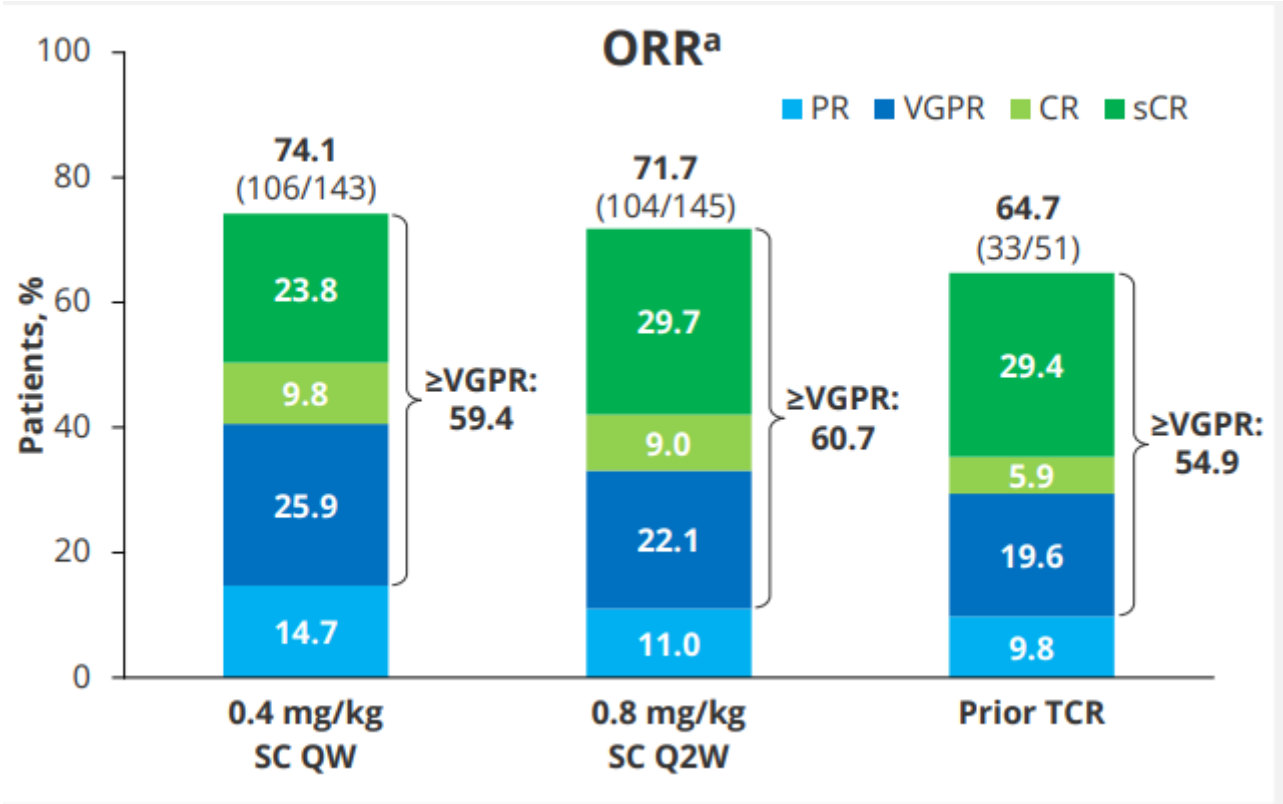
Characteristic	0.4 mg/kg SC QW n=143	0.8 mg/kg SC Q2W n=145	Prior TCR n=51
Exposure status, n (%)			
Triple-class[e]	143 (100)	145 (100)	51 (100)
Penta-drug[f]	105 (73.4)	101 (69.7)	40 (78.4)
Prior BCMA			
Belantamab	22 (15.4)	16 (11.0)	6 (11.8)
BsAb	NA	NA	16 (31.4)[g]
CAR-T therapy	NA	NA	34 (66.7)[h]
Refractory status, n (%)			
PI[i]	114 (79.7)	120 (82.8)	46 (90.2)
IMiD[i]	133 (93.0)	130 (89.7)	49 (96.1)
Anti-CD38 mAb[k]	133 (93.0)	134 (92.4)	49 (96.1)
Belantamab	18 (12.6)	13 (9.0)	4 (7.8)
Triple-class[e]	106 (74.1)	100 (69.0)	43 (84.3)
Penta-drug[f]	42 (29.4)	34 (23.4)	21 (41.2)
To last line of therapy	134 (93.7)	137 (94.5)	31 (60.8)

TALQUETAMAB

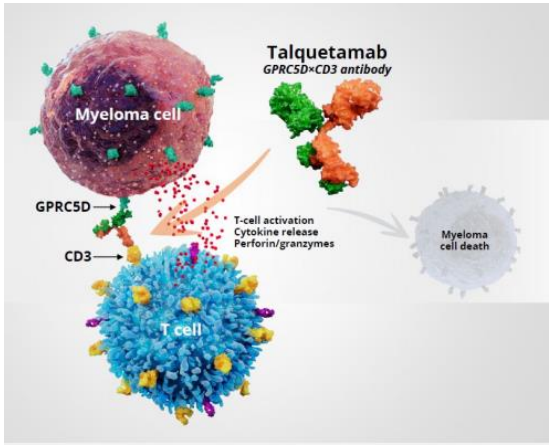
MonumenTAL -1



Taux de réponse profonde
Durée moyenne de réponse : 1 an



TALQUETAMAB



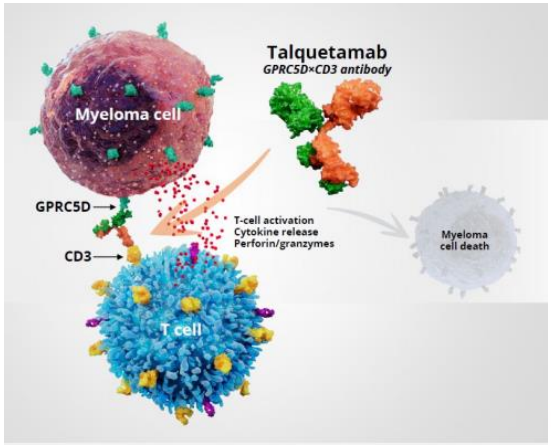
Toxicité différente :
dysgueusie et atteinte des phanères
Moins d'infections sévères
Cytopénies gérables

MonumenTAL -1

AEs (≥30% in any cohort), n (%)	0.4 mg/kg SC QW (n=143)		0.8 mg/kg SC Q2W (n=145)		Prior TCR (n=51)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nonhematologic AEs						
CRS[b]	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Dysgeusia[c]	103 (72.0)	NA	103 (71.0)	NA	39 (76.5)	NA
Infections[d]	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
Skin related[e]	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
Nail related[f]	78 (54.5)	0	78 (53.8)	0	32 (62.7)	0
Weight decreased	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)	15 (29.4)	0
Rash related[g]	57 (39.9)	2 (1.4)	43 (29.7)	8 (5.5)	18 (35.3)	2 (3.9)
Pyrexia	56 (39.2)	4 (2.8)	40 (27.6)	2 (1.4)	16 (31.4)	0
Dry mouth	38 (26.6)	0	58 (40.0)	0	26 (51.0)	0
Fatigue	35 (24.5)	5 (3.5)	40 (27.6)	1 (0.7)	23 (45.1)	1 (2.0)

AEs (≥30% in any cohort), n (%)	0.4 mg/kg SC QW (n=143)		0.8 mg/kg SC Q2W (n=145)		Prior TCR (n=51)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic AEs						
Anemia	64 (44.8)	45 (31.5)	66 (45.5)	40 (27.6)	25 (49.0)	14 (27.5)
Neutropenia	50 (35.0)	44 (30.8)	41 (28.3)	32 (22.1)	28 (54.9)	27 (52.9)
Thrombocytopenia	39 (27.3)	29 (20.3)	43 (29.7)	27 (18.6)	19 (37.3)	15 (29.4)

TALQUETAMAB + DARATUMUMAB



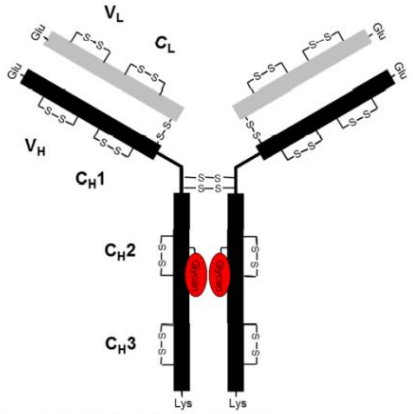
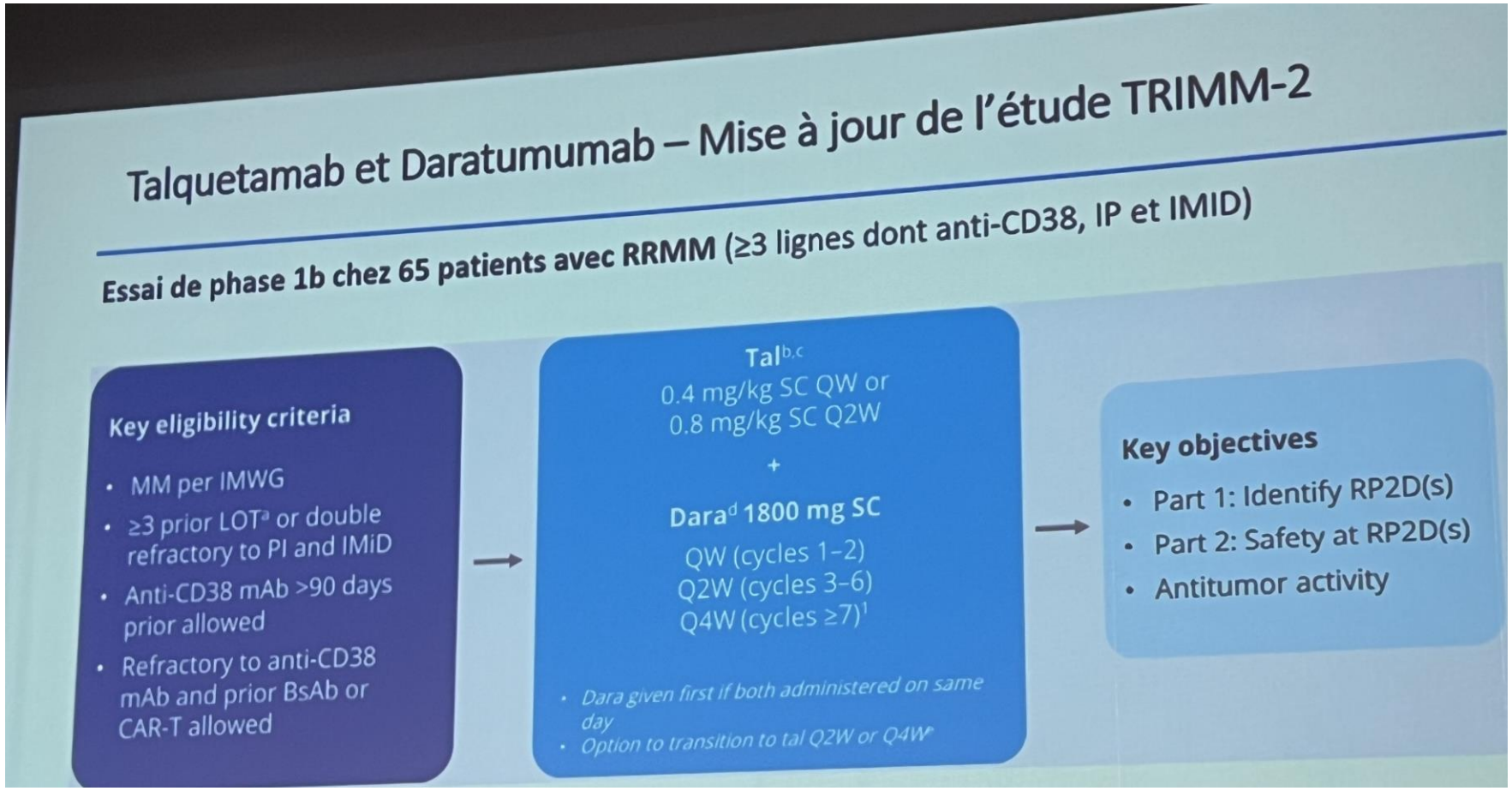


Figure 1 General structure of daratumumab

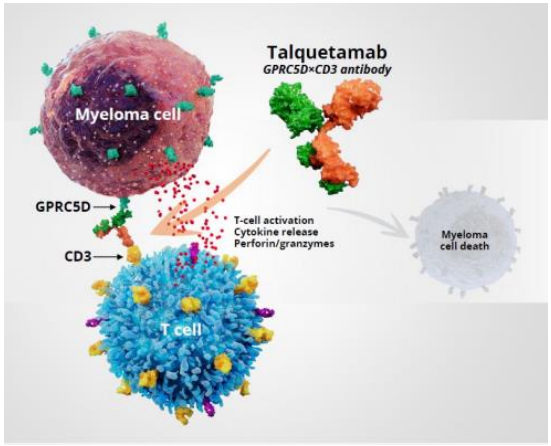
Etude TRIMM-2

Update ASCO EHA

- Talquetamab
  + DARA



TALQUETAMAB + DARATUMUMAB



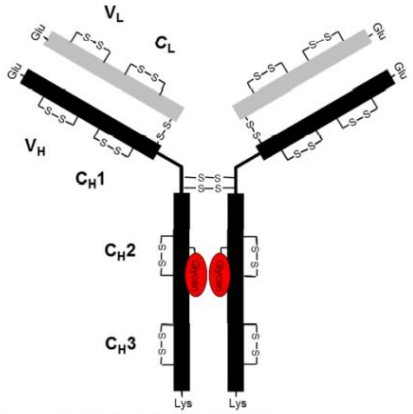


Figure 1 General structure of daratumumab

Réponse >60%

Toxicité hématologique : 30% anémie 30% de neutropénie30% de thrombopénie

CRS grade 1-2 (aucun CRS 3-4)

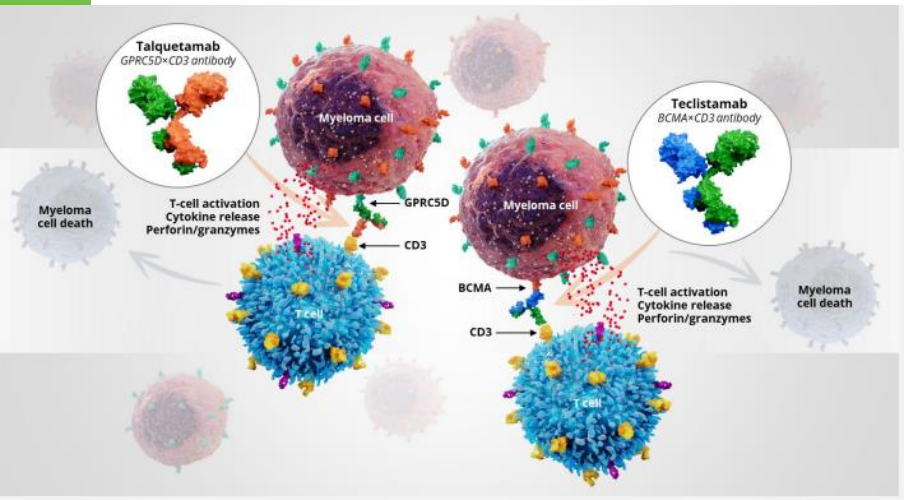
ICANS 4%

Toxicité cutanéo muqueuse (85% dysgeusie, 70% d'attiente cutanée , 70% d'atteinte unguéale

INFECTIONS : 70% avec 20% de grade 3-4

D'après Bahlis et Al ASCO 2023

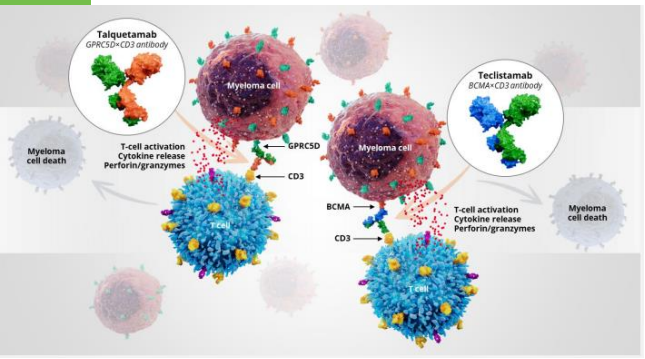
TALQUETAMAB + TECLISTAMAB



Etude REDIRECT -1

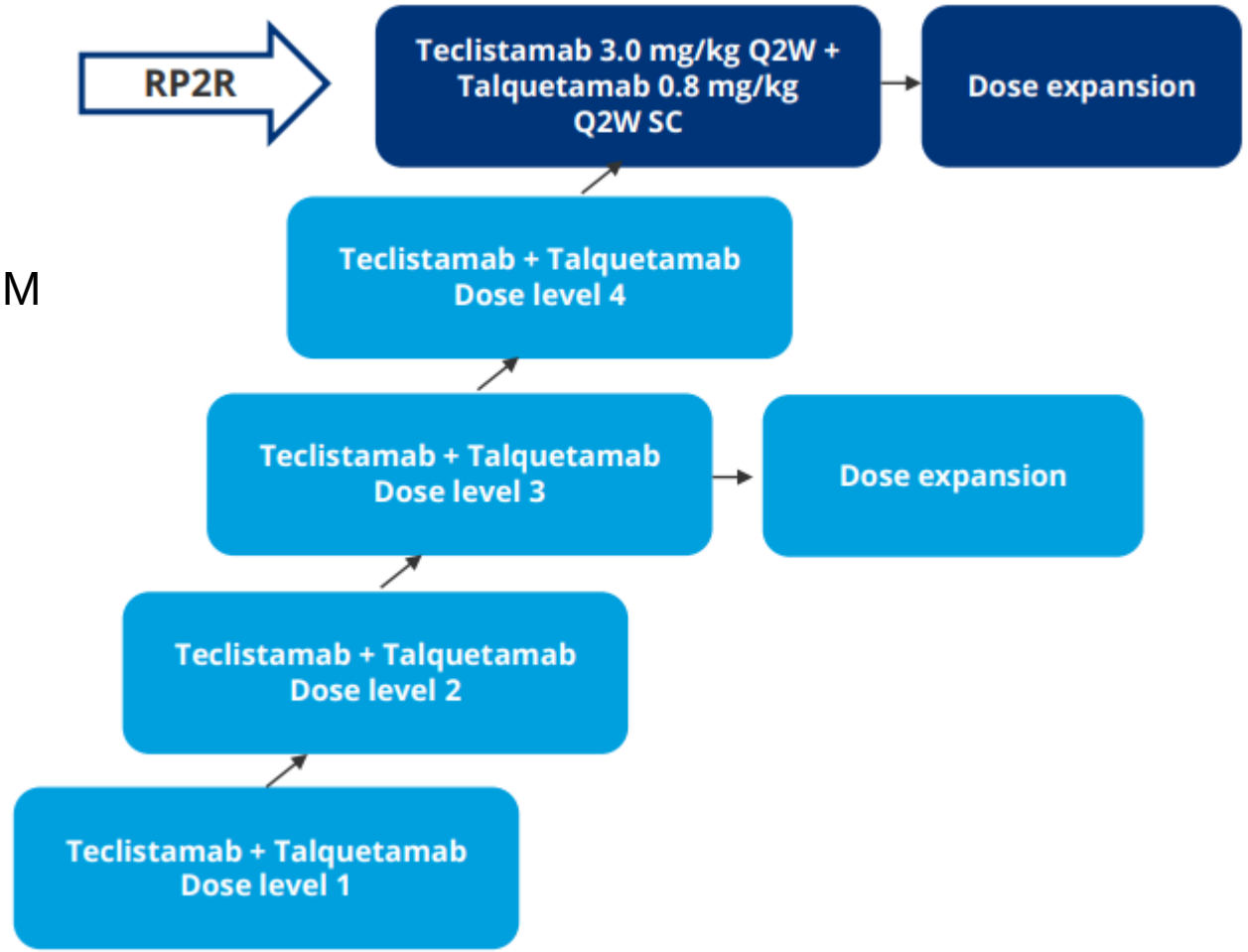
Cibler 2 molécules sur le plasmocyte
pour contourner les résistances : BCMA et GPRC5D

TALQUETAMAB + TECLISTAMAB



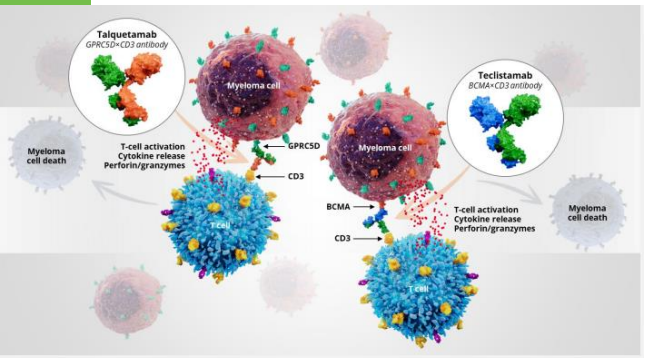
Etude REDIRECT -1

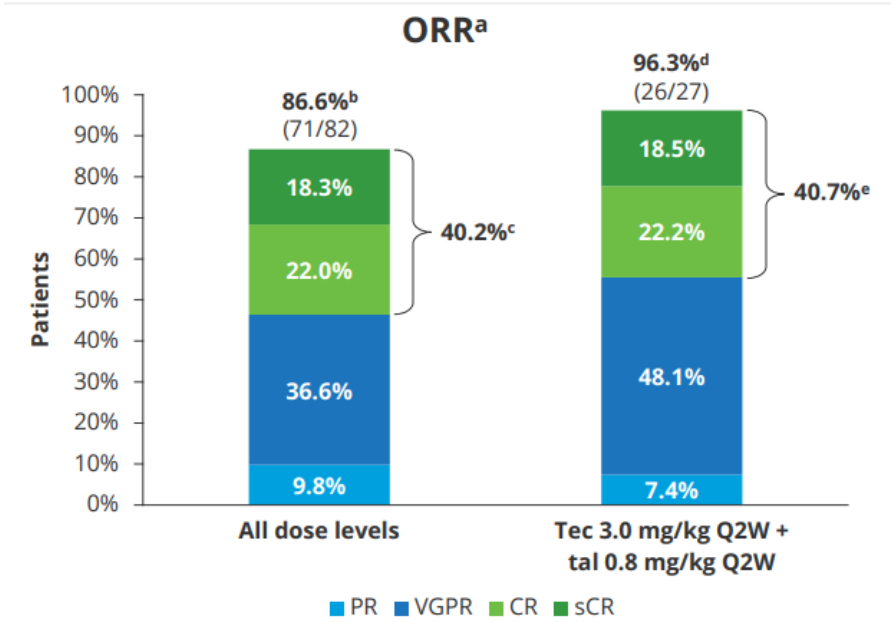
65 patients avec un myélome réfractaire RRMM
Essai phase 1b
>=1 lignes dont anti CD38 IMID et IP
35% d'atteinte extra médullaire



D'après EHA 2023Mateos M Jun 8,2023;387890;S190

TALQUETAMAB + TECLISTAMAB



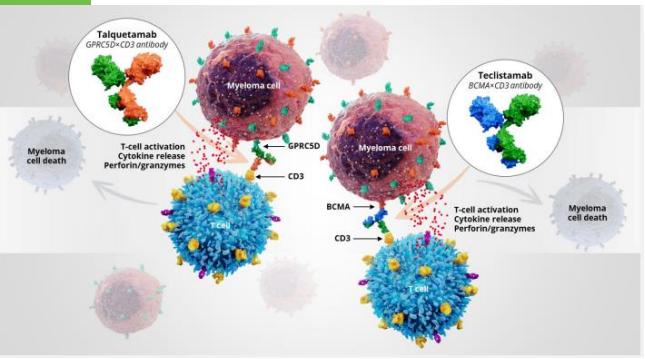


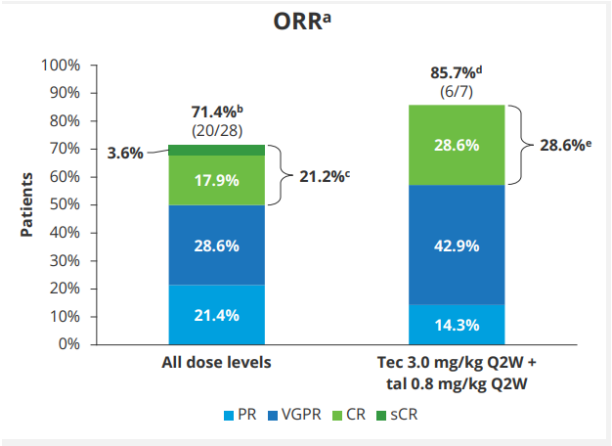
Etude REDIRECT -1

	All dose levels (N=93)	Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)
Median follow-up, months (range)	13.4 (0.3–25.6)	8.1 (0.7–15.0)
Median DOR,[f] months (95% CI)	NE (NE–NE)	NE (NE–NE)
Median time to first response,[f] months (range)	1.97 (0–7.7)	1.48 (0–4.0)
Median time to best response,[f] months (range)	3.98 (1.1–15.7)	3.22 (1.4–10.7)
Median PFS,[g] months (95% CI)	20.9 (13.0–NE)	NE (9.9–NE)
9-month PFS rate[g] (95% CI)	70.1 (58.0–79.4)	77.1 (50.8–90.5)

D'après EHA 2023Mateos M Jun 8,2023;387890;S190

TALQUETAMAB + TECLISTAMAB





Etude REDIRECT -1

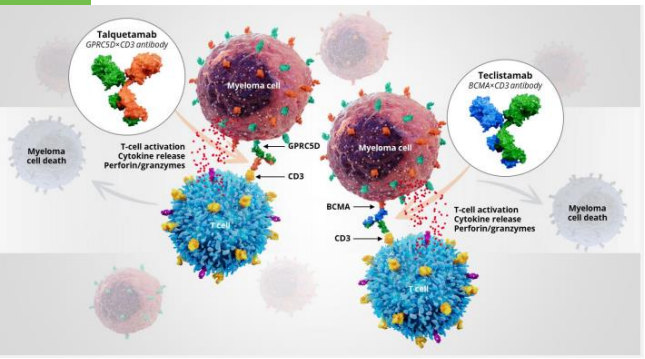
- 74-year-old male, penta refractory, 6 prior LOT including ASCT, belantamab mafodotin, and prior RT to humerus

ASCT, autologous stem cell transplant; LOT, line of therapy; RT, radiotherapy.

12

Chez patients ayant atteinte extramédullaire
Taux de réponse satisfaisante

TALQUETAMAB + TECLISTAMAB



Etude REDIRECT -1

Toxicité hématologique : 30% anémie 45-60% de neutropénie 30% de thrombopénie

CRS 75%grade 1-2 (3%CRS 3-4)

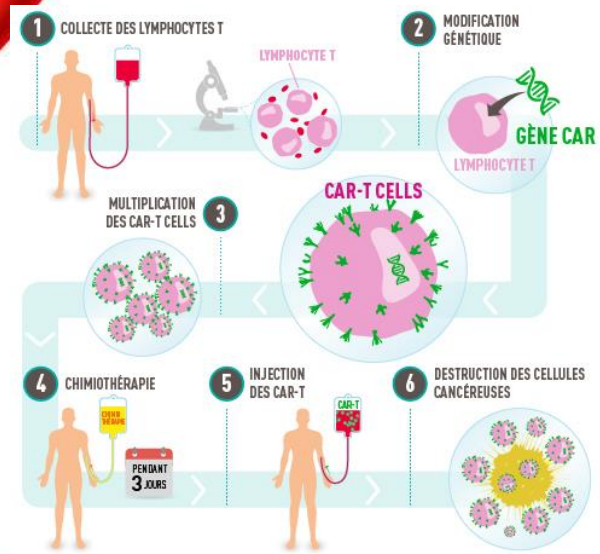
ICANS 3%

Toxicité cutanéo muqueuse (60% dysgeusie, 50% d'attiente cutanée , 40-45% d'atteinte unguéale

INFECTIONS : 80% avec 40-50% de grade 3-4

D'après EHA 2023Mateos M Jun 8,2023;387890;S190

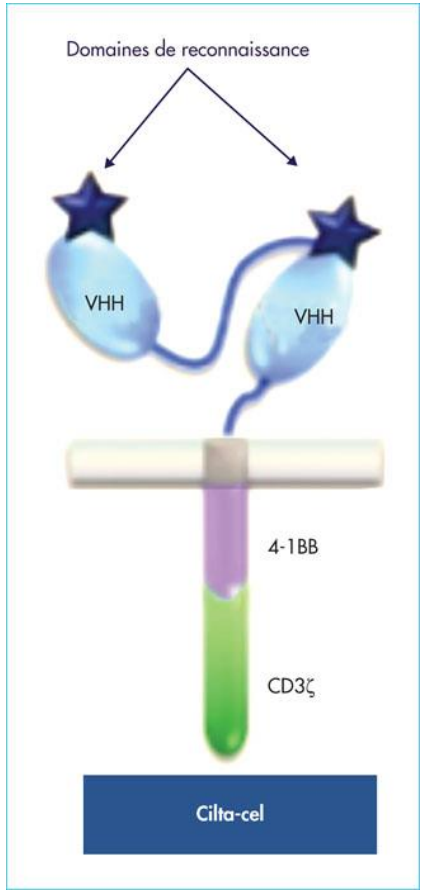
CarT cell



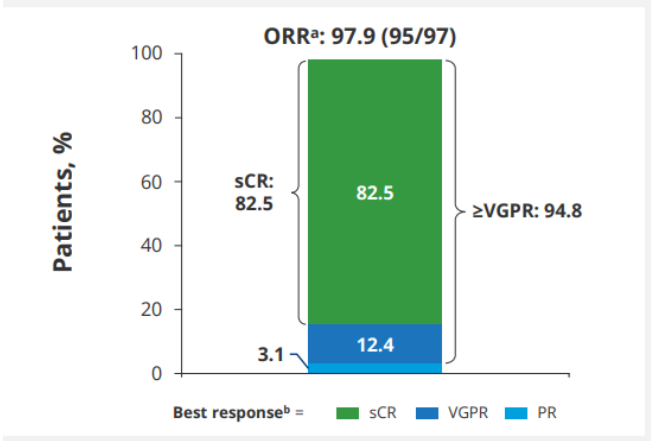
CILTA-CEL Cartitude 1 et 4

IDE-CEL

CILTACEL

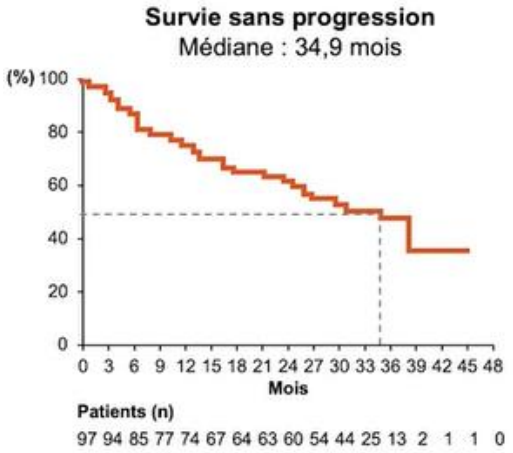


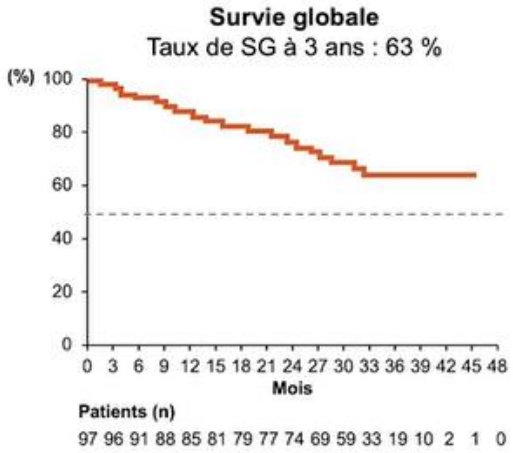
Mise à jour de l'essai CARTITUDE -1
Essai phase 1-2 :
97 patients
3 ans de suivi



CARTITUDE-1, étude de phase II (n = 97)		
Nbre médian de lignes antérieures : 6 (3-18)	88 % des patients étaient réfractaires à 3 classes thérapeutiques	Chimiothérapie de transition *(bridge)* autorisée Lymphodéplétion par Flu-Cy

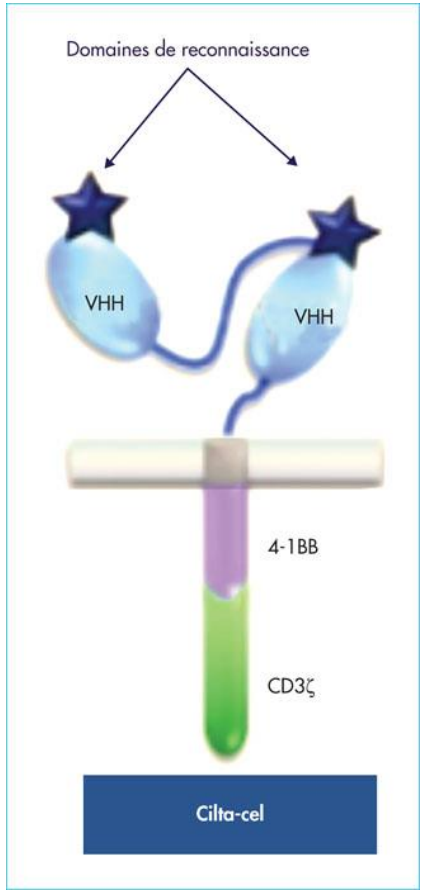
Approbation FDA en 2022
Approbation EMA en 2022



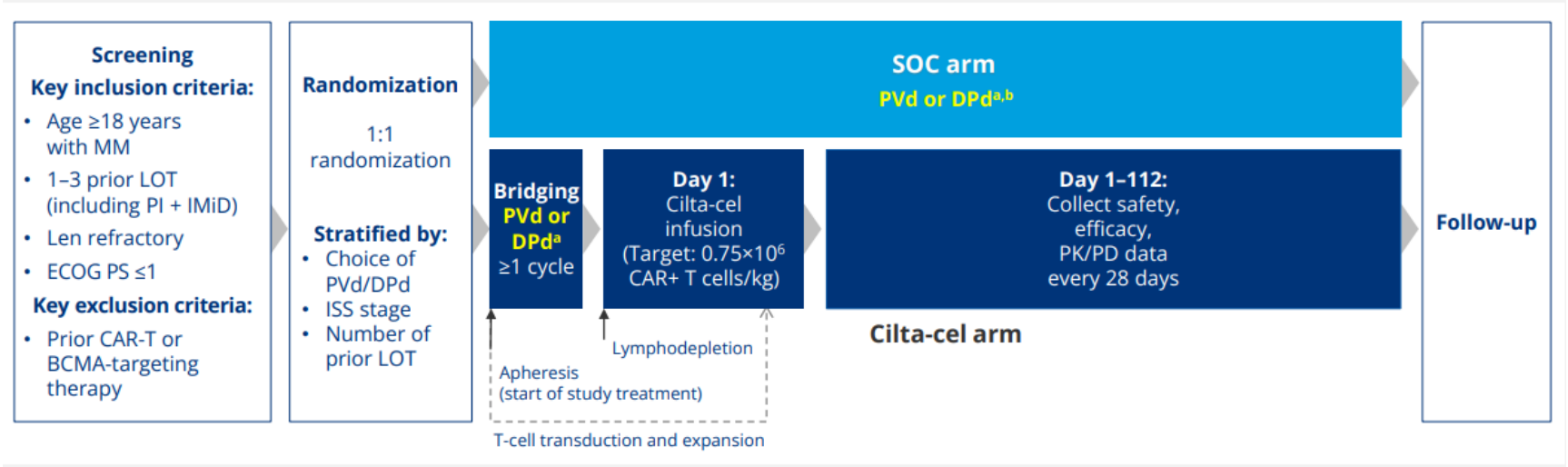


D'après Abstract 100 EHA Nikhil C Munshi

CILTACEL

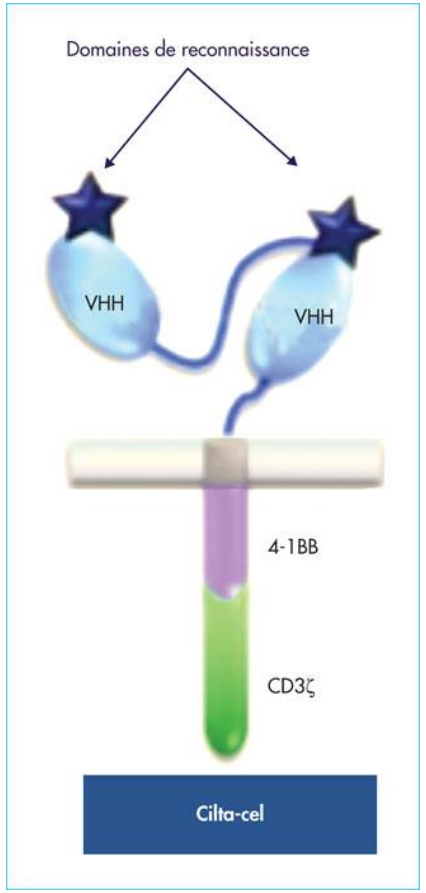


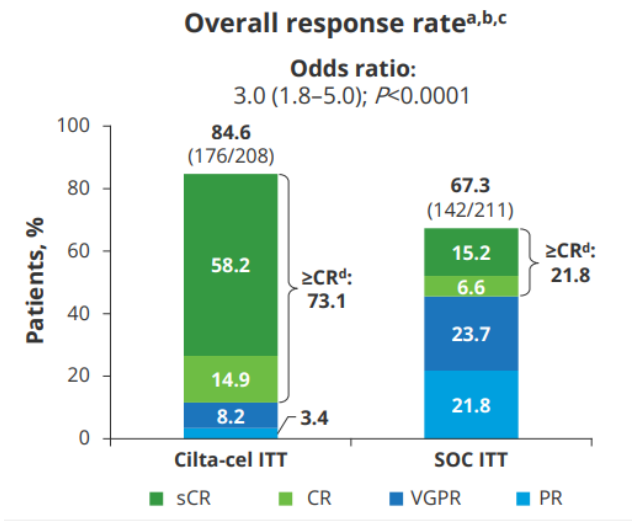
Resultats de l'essai de phase III CARTITUDE -4 :
CILTACEL versus Standard of care (PVD ou DPD)
Patient myélome Len refractaire
200 patients dans chaque bras
Temps médian aphérèse – Infusion : 79 jours

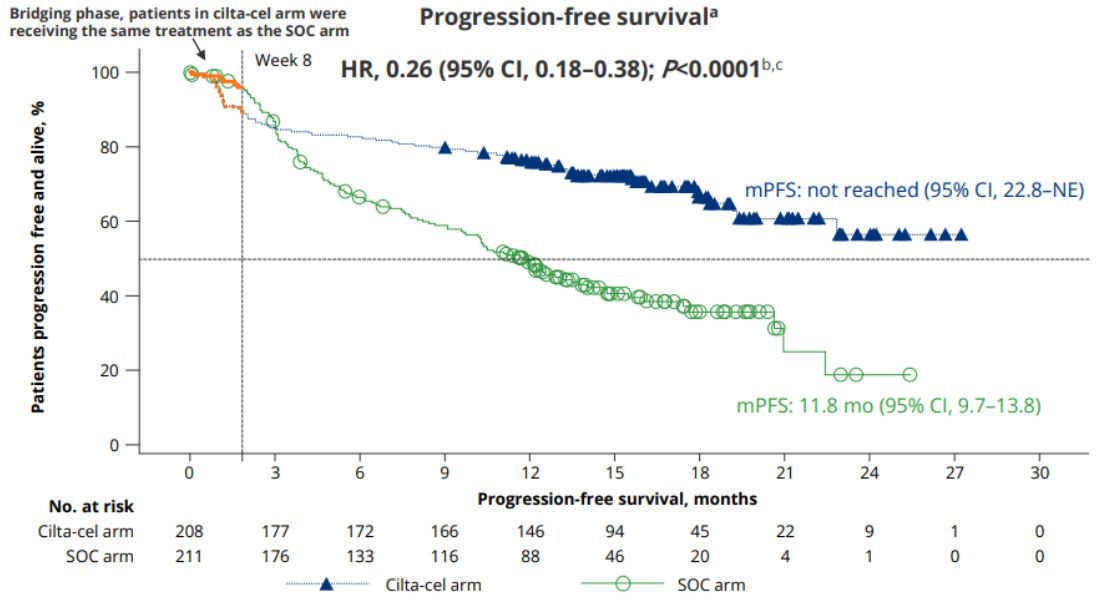


D'après Abstract 100 EHA 2023 Hermann Einsele Plenary abstrat session

CILTACEL



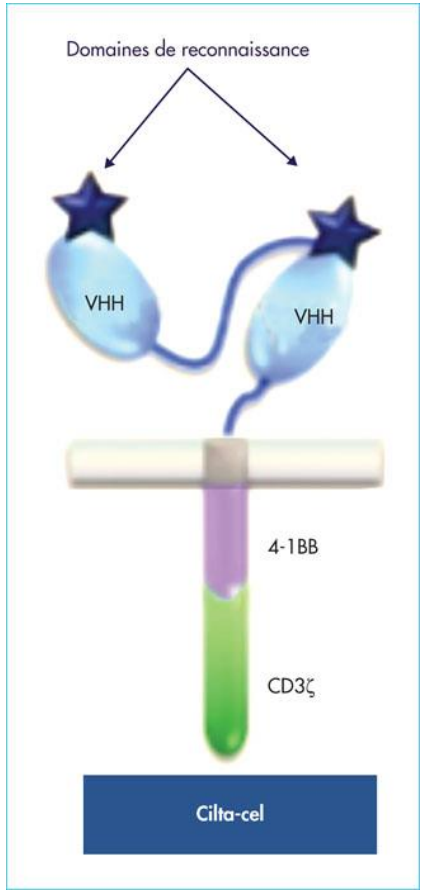




PFS médiane non atteinte à16 mois de suivi
>70 % de RC
Hasard Ratio ++

D'après Abstract 100 EHA 2023 Hermann Einsele Plenary abstrat session

CILTACEL

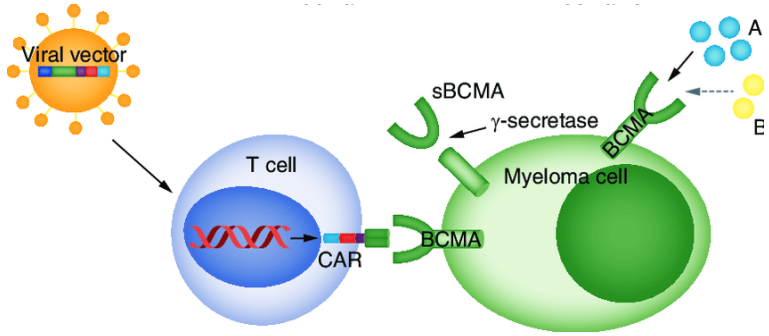


Resultats de l'essai de phase III CARTITUDE -4 : CILTACEL versus Standard of care (PVD ou DPD)

Événements indésirables, n (%)	Patients traités (n = 176)				
	Tout grade	Grade 3-4	Temps médian de survenue (jours)	Durée médiane (jours)	Résolus, n
SRC	134 (76,1)	2 (1,1)	8	3	134
Neurotoxicité	36 (20,5)	5 (2,8)			
ICANS	8 (4,5)	0	10	2	8
Autre	30 (17,0)	4 (2,3)			
Paralysie des nerfs crâniens	16 (9,1)	2 (1,1)	21	77	14
Neuropathie périphérique	5 (2,8)	1 (0,6)	63	201	3
Troubles du mouvement ou neurocognitifs (•)	1 (0,6)	0	85	–	0

D'après Abstract 100 EHA 2023 Hermann Einsele Plenary abstrat session

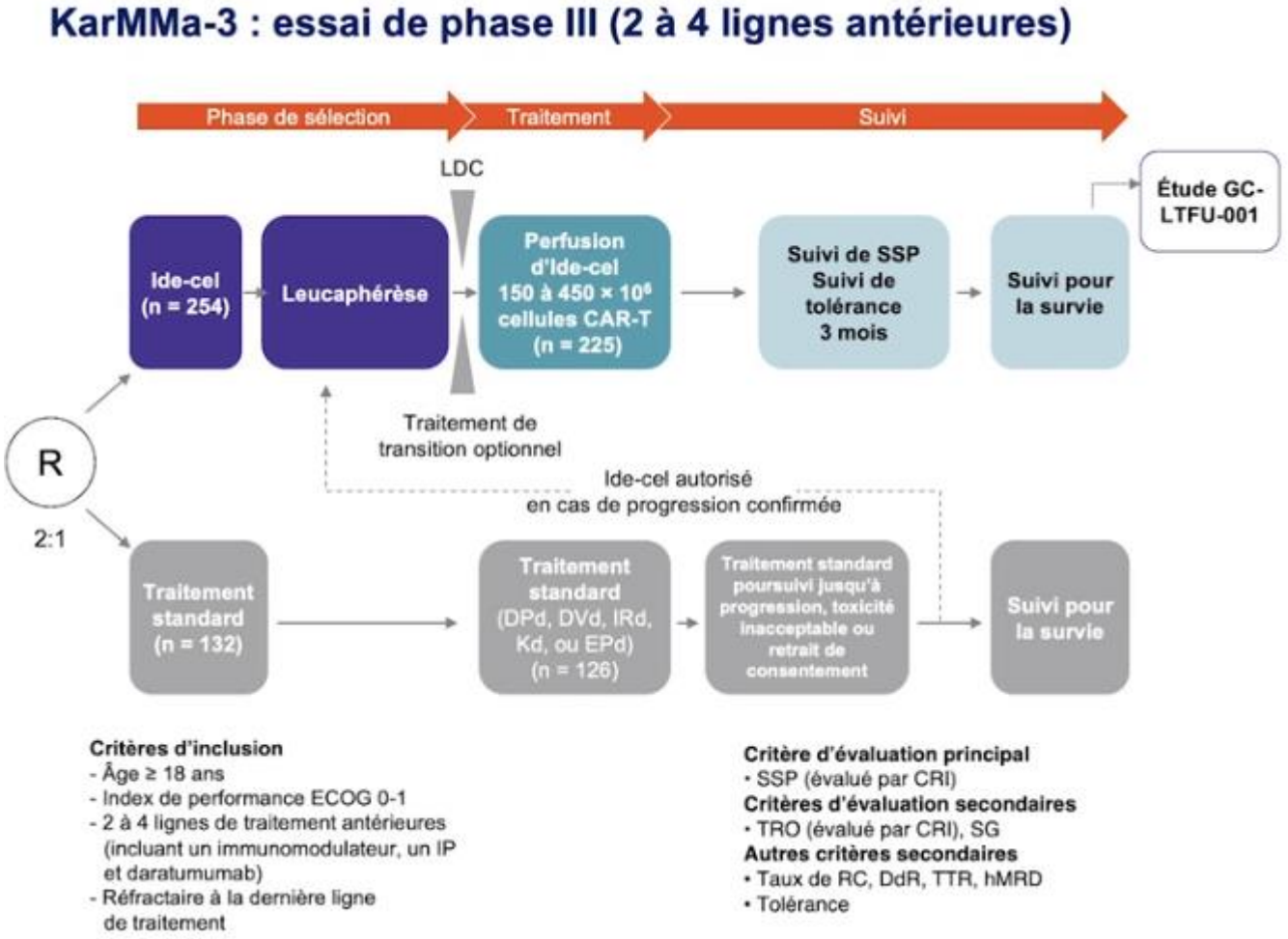
IDE-CEL



SSP 13 mois versus 4 mois

Analyse de sous groupe
- Cytogénétique défavorable :

Resultats en sous groupe de l'essai de phase III KArMMa-3: Ide-cel versus Standard of care



D'après Rodriguez Otero et al N Engl 2023

Update ASCO EHA

- CILTA CEL
  - Cartitude 4
  - Population rechutes précoces
  - RC 73%
  - CRS bas grade

  - MRD neg 60%
- CARITUDE 1
  - Pop
  - MRD sustained à 12 mois : 75%

Update ASCO EHA

- AMYLOSE
  - Belantamab
  - Tous les 2 mois
  - Tox : oculaire chez 96% dont 48% grade 3-4 ans malgré administration/ 2 mois

  - CAEL 101 : ac monoclonal chimérique
  - 25 patients
  - Peu de tox
  - Reponse 5 réponses cardiaques