MRD dans le myélome multiple : Aspects cliniques

Dr Julien Depaus – LJBM – 16/10/2025

EpiCURA mon hôpital

CHU UCL NAMUR Dinant Godinne Sainte-Eli

Conflits d’intérêts

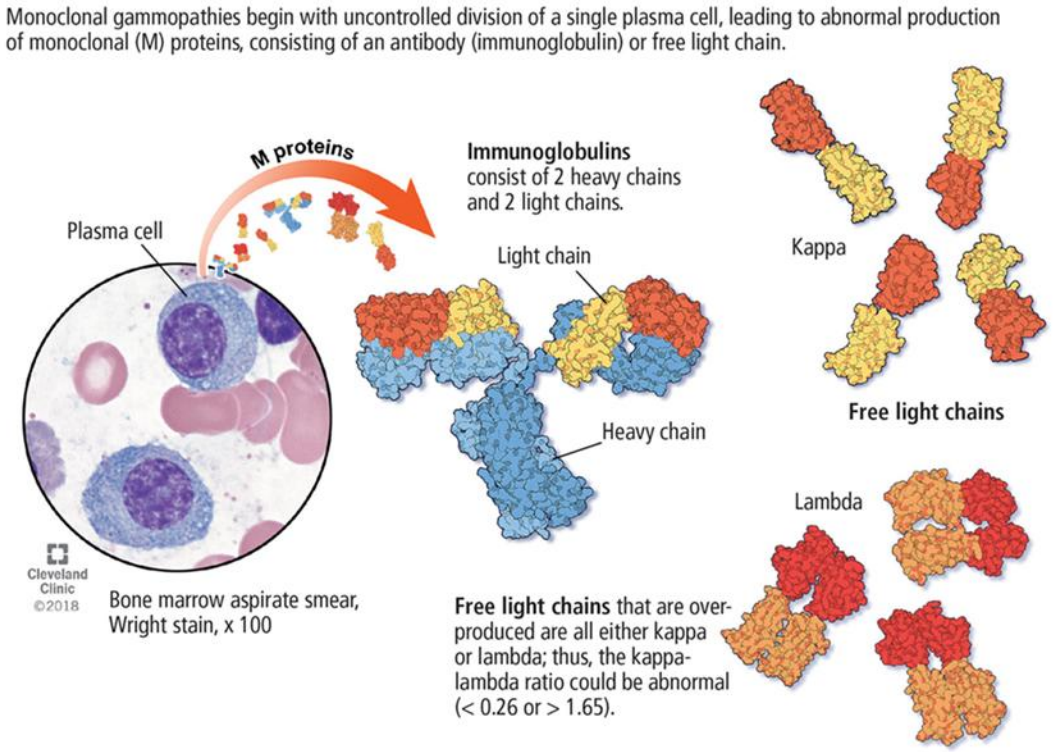
- Consultance : Pfizer
- Advisory Board : Sanofi, Amgen, Pfizer, BMS, Johnson & Johnson
- Speaker fees : GSK, Johnson & Johnson, Amgen, Binding Site
- Frais de congrès : Sanofi, Johnson & Johnson, Amgen, Pfizer, BMS
- Etudes cliniques : Pfizer, GSK, Johnson & Johnson, Sanofi

Plan de l’exposé

- Introduction
- MRD : aspect pronostique
- Données récentes études de 1ère ligne
- Traitement guidé par la MRD
- Intérêts économiques potentiels MRD
- Pistes futures
- Conclusion

Introduction

- Pathologie cancéreuse
- Présence de plasmocytes clonaux
- Production protéine monoclonale détectable dans le sang et/ou urines (plus rarement non sécrétant)

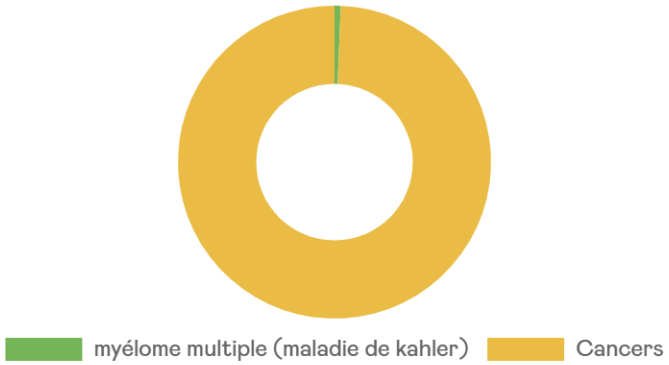


Khoury, Cleveland Clinic Journal of Medicine, 2019

Introduction

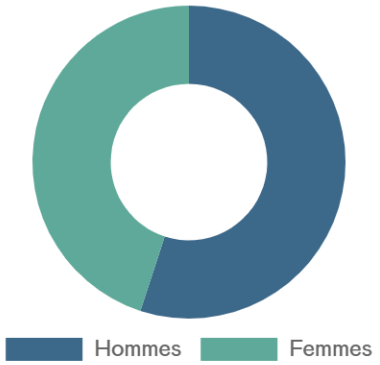
Le myélome multiple (maladie de kahler) est le 15e cancer le plus fréquent en Belgique.
En 2021, 482 personnes sont décédées de ce cancer en Belgique.

Nombre de cancers en Belgique



En 2022, **76220** cas de cancers, dont* **1043** myélomes multiple (maladie de kahler) **(1,37%)**

Nombre de myélomes multiple (maladie de kahler) en 2022



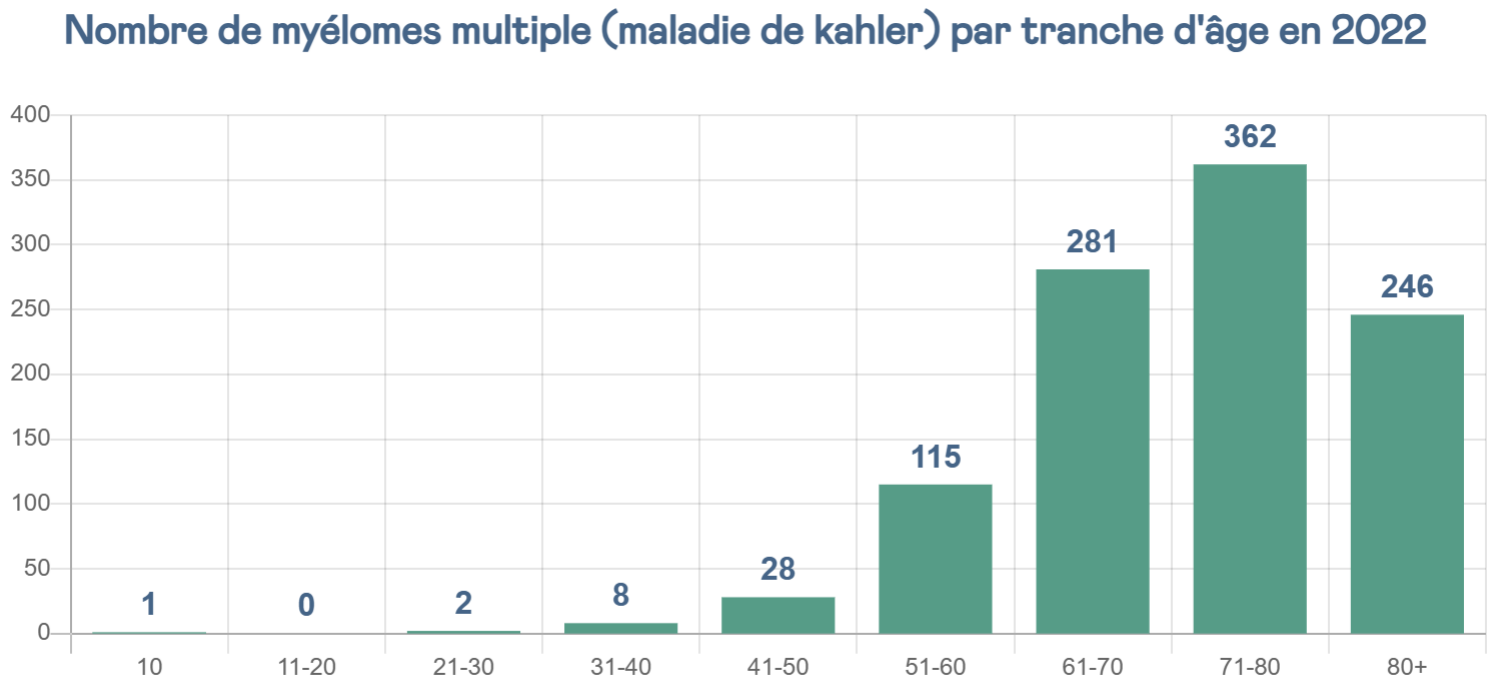
469 femmes pour **574** hommes

10 à 15% des hémopathies malignes
1 à 2% de l'ensemble des cancers

https://cancer.be/cancer/myelome-multiple-maladie-de-kahler/

Introduction

Age médian au diagnostic : 69 ans



https://cancer.be/cancer/myelome-multiple-maladie-de-kahler/

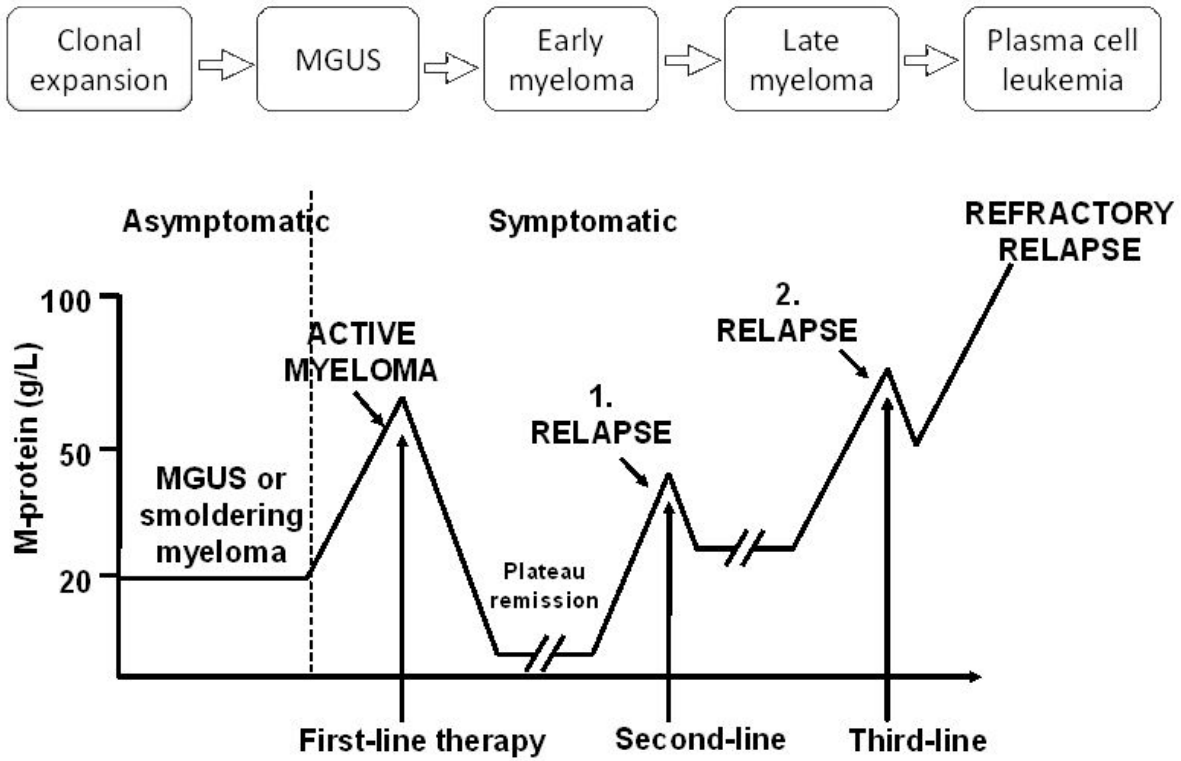
Introduction

Incidence projections

Figure 7 Plasma cell neoplasms: Observed and projected incidence (WSR) by sex, Belgium 2004-2025

Belgian Cancer Registry – Haematological malignancies Belgium 2004 -2018

Introduction



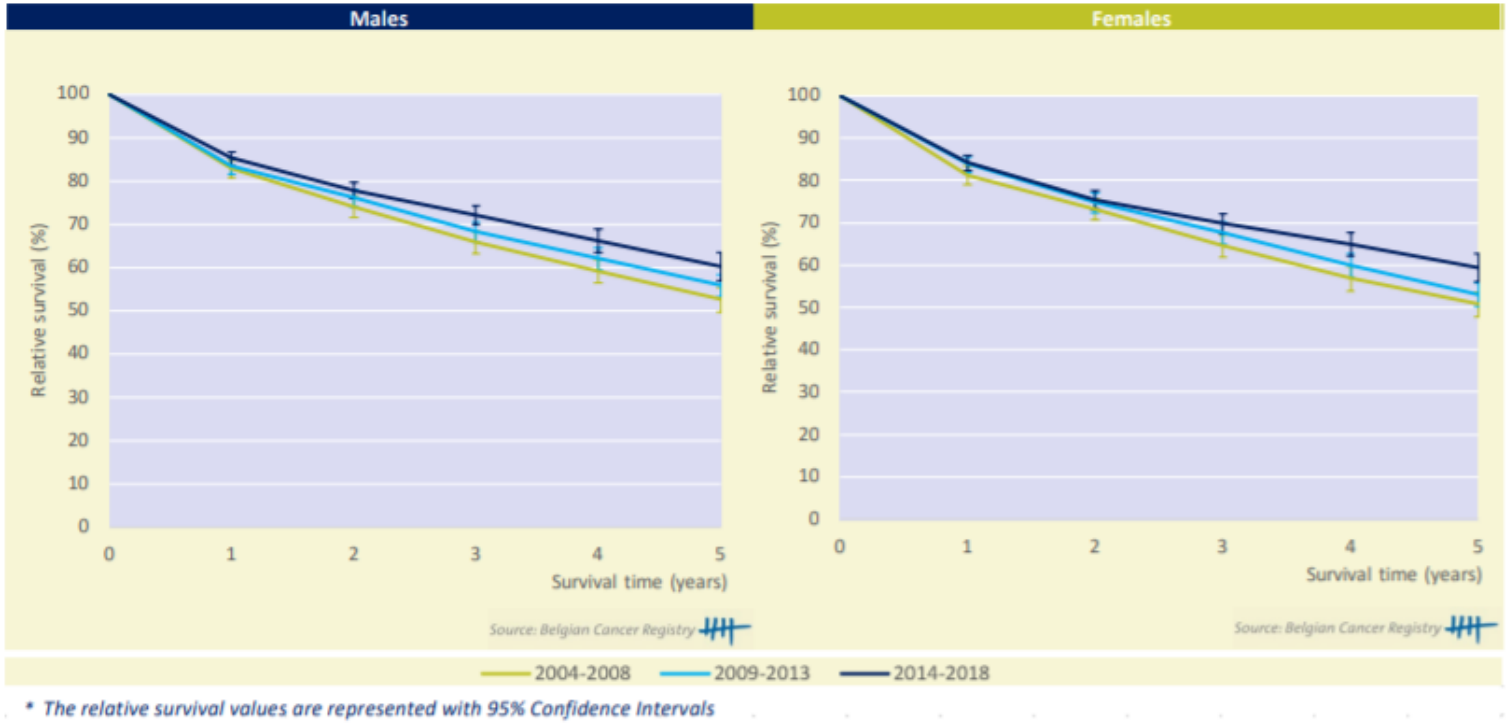
Maladie incurable en 2025

Hajek R. Multiple Myeloma - A Quick Reflection on the Fast Progress, 2013

Introduction

Survival trends

Figure 11 Plasma cell neoplasms: Relative survival* by cohort and sex, Belgium 2004-2018

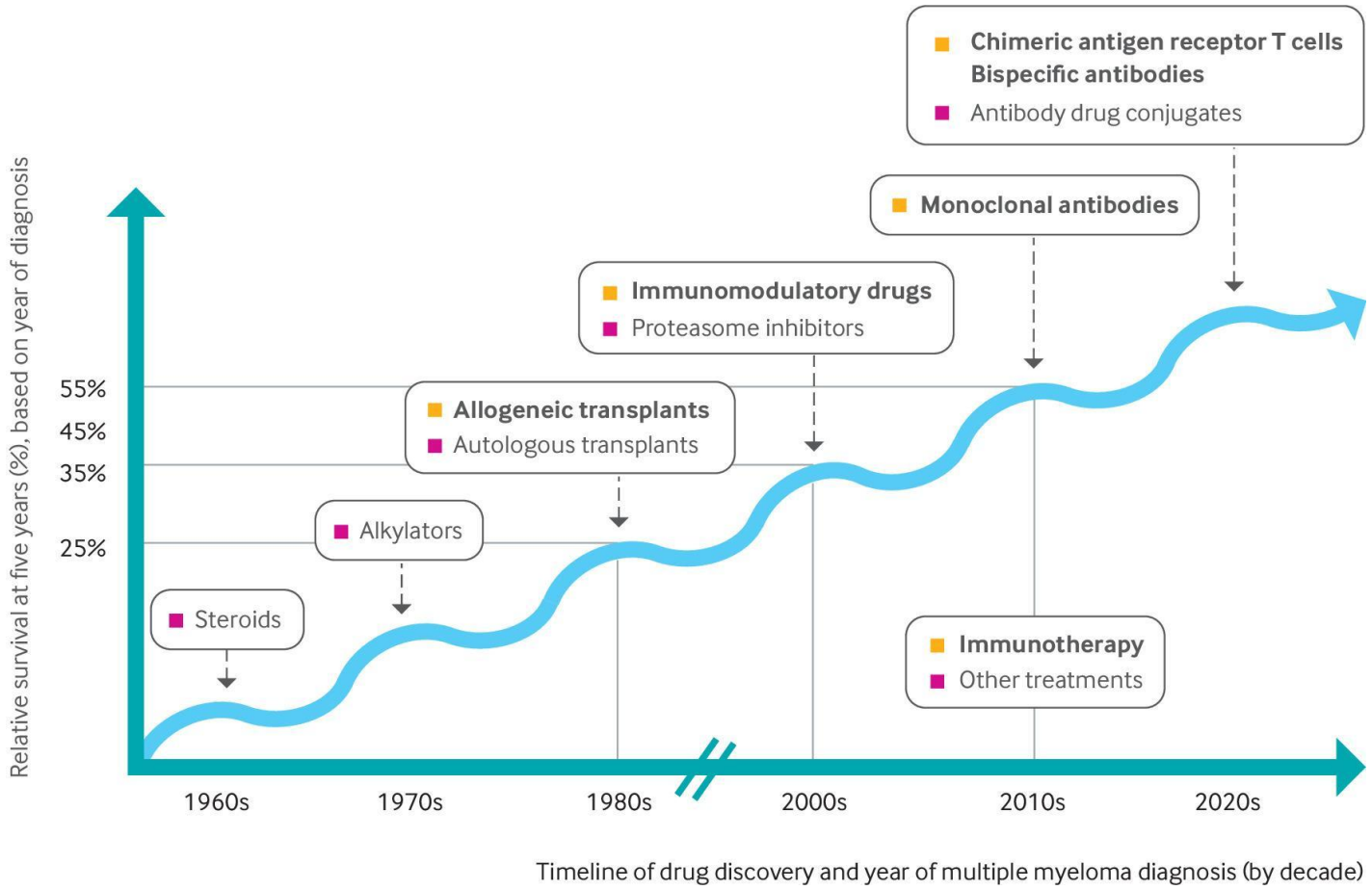


* The relative survival values are represented with 95% Confidence Intervals

!! Avancées thérapeutiques récentes !!

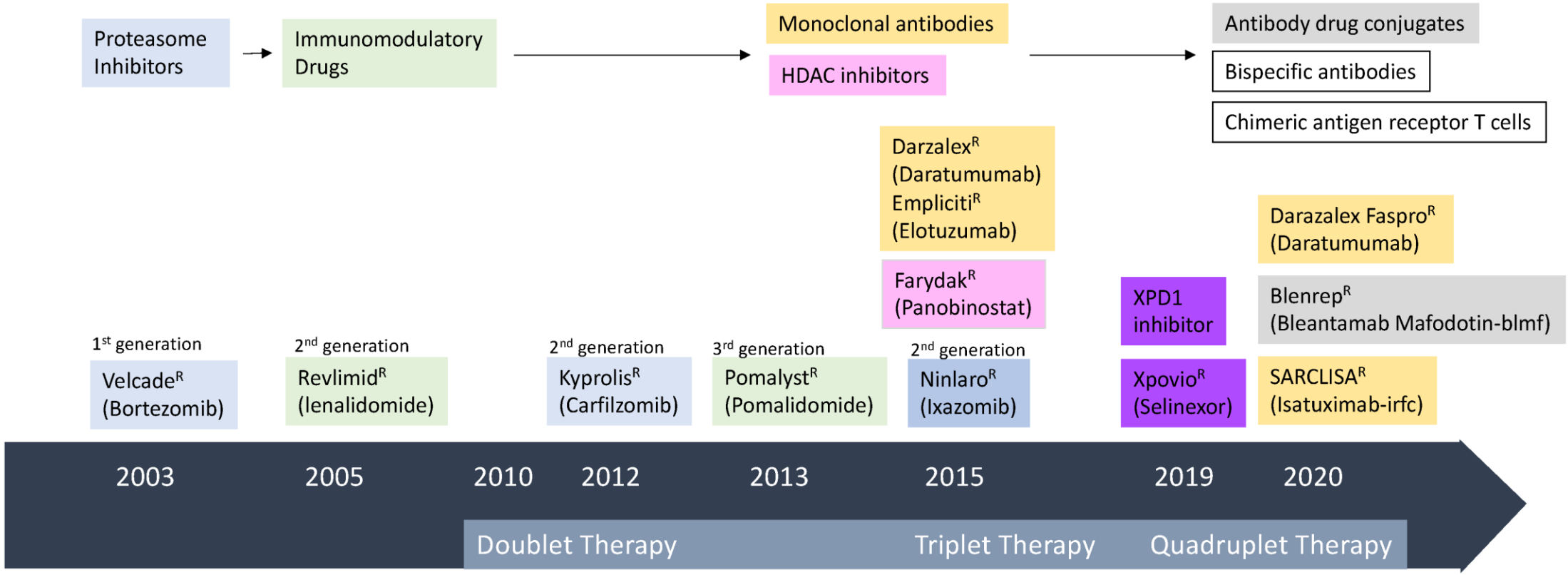
Belgian Cancer Registry – Haematological malignancies Belgium 2004 -2018

Introduction



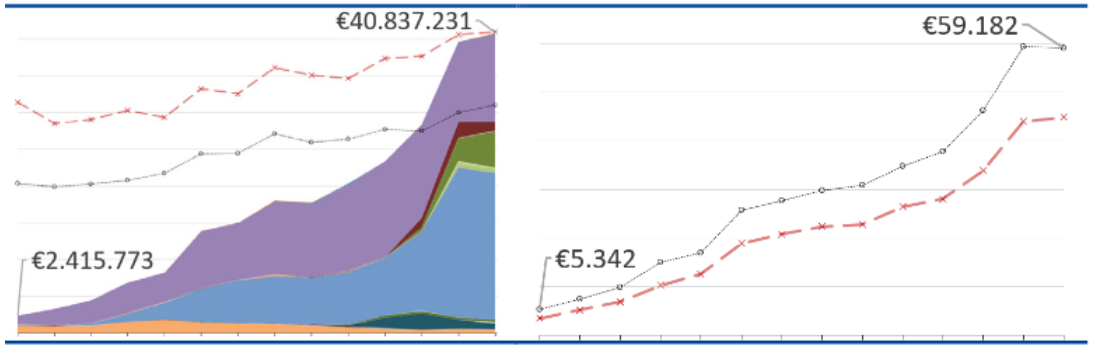
Shah U et al, BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m3176

Introduction



Nishida H, Cancers 2021, 13(11), 2712; https://doi.org/10.3390/cancers13112712

Introduction



Myélome multiple : la survie est restée stable entre 2004 et 2013, et tend à augmenter dans la dernière période d'incidence 2014-2017. Les dépenses globales et les coûts moyens par patient ont augmenté régulièrement au fil du temps, passant respectivement de moins de 2,5 millions € en 2004 à plus de 40 millions € en 2017, et de 5300 € en 2004 à 59 200 € en 2017.

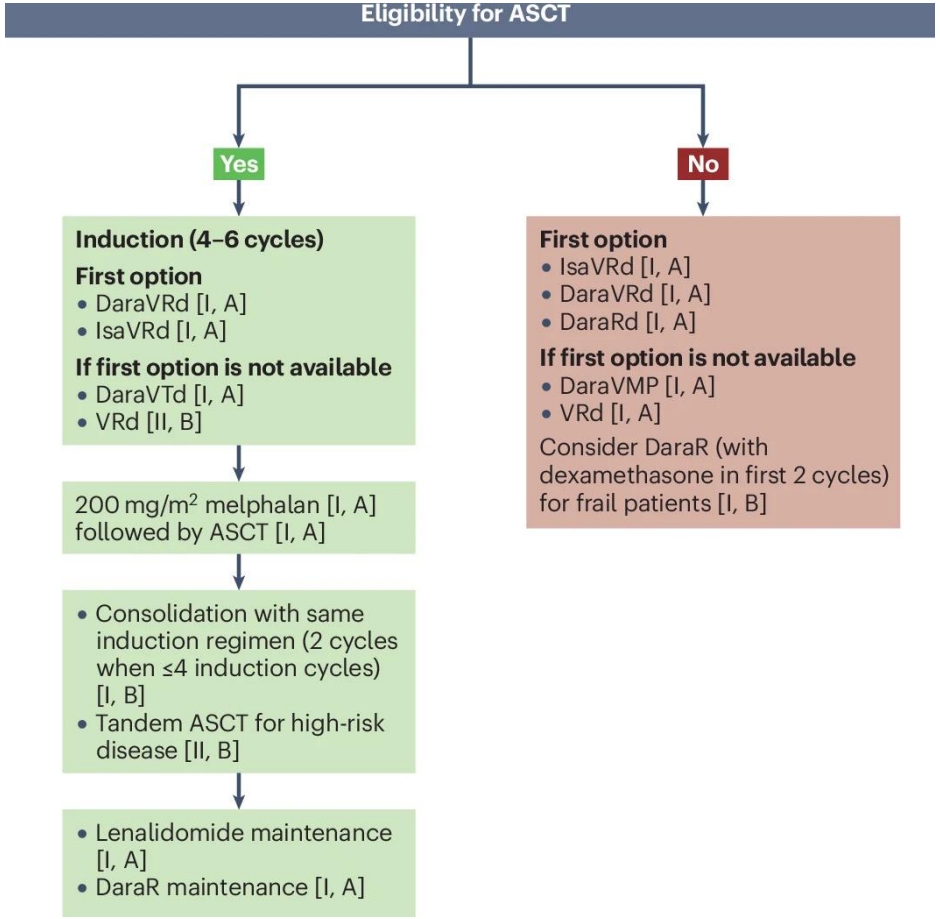
KCE 2021

!! Explosion des coûts !!

Introduction

Traitement de 1ère ligne

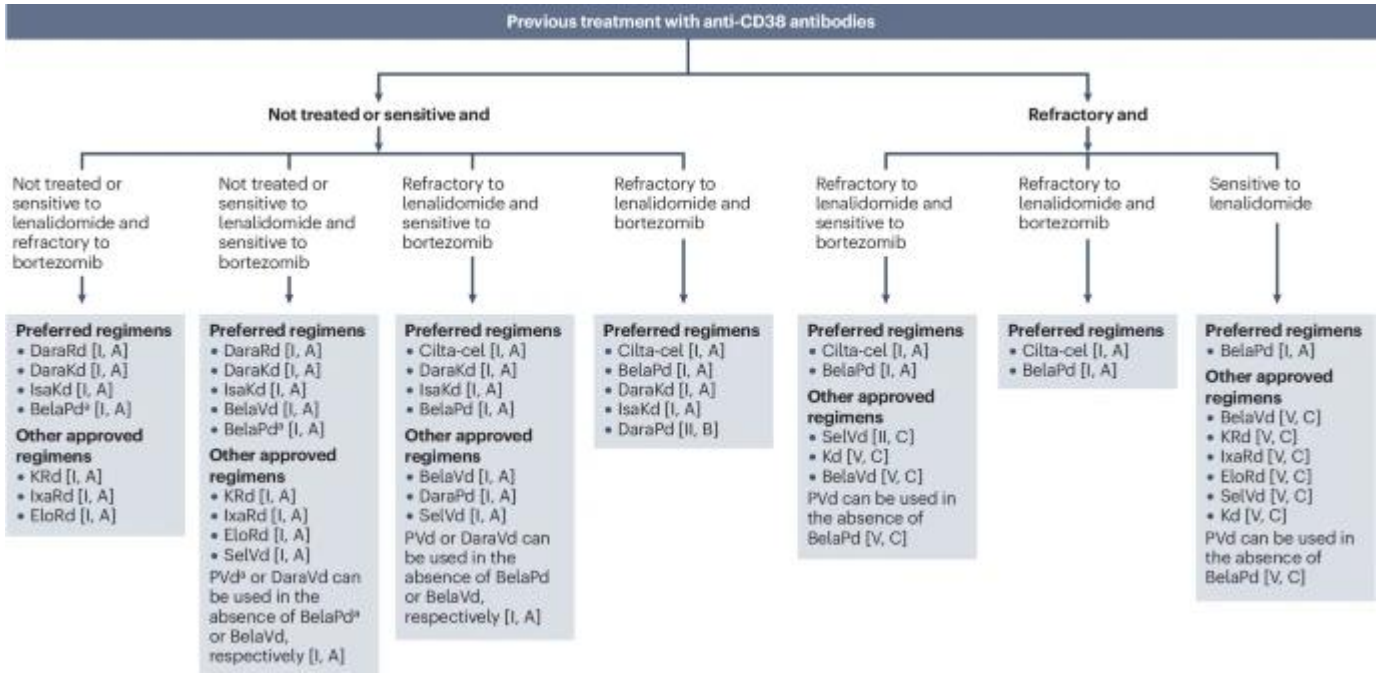
Indiqué en cas de myélome multiple symptomatique (au moins 1 critère SLiM-CRAB présent)



EHA–EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma, Nature Reviews Clinical Oncology | Volume 22 | September 2025 | 680–700

Introduction

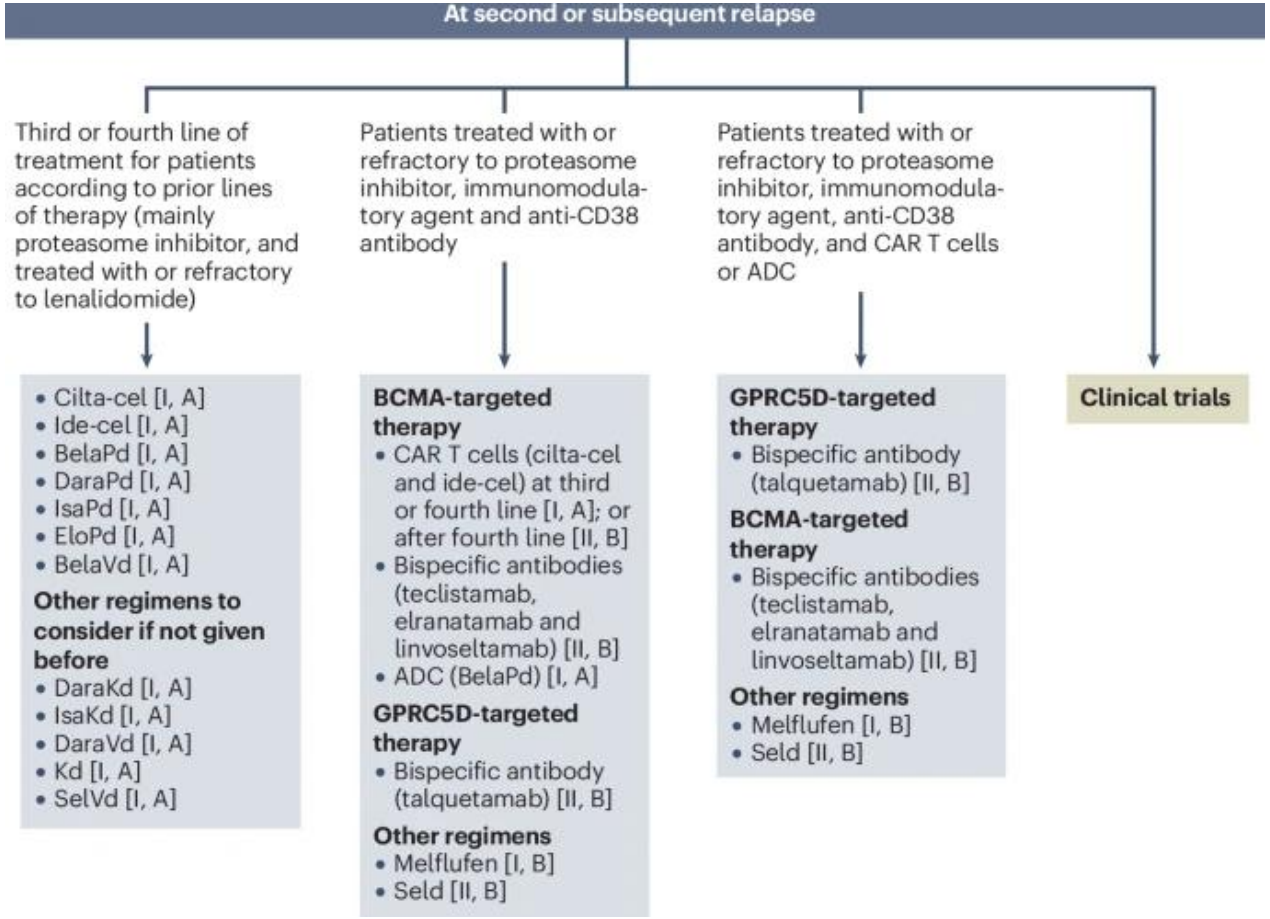
Traitement de 2ème ligne



EHA–EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma, Nature Reviews Clinical Oncology | Volume 22 | September 2025 | 680–700

Introduction

Traitement de 3ème ligne et au-delà



EHA–EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma, Nature Reviews Clinical Oncology | Volume 22 | September 2025 | 680–700

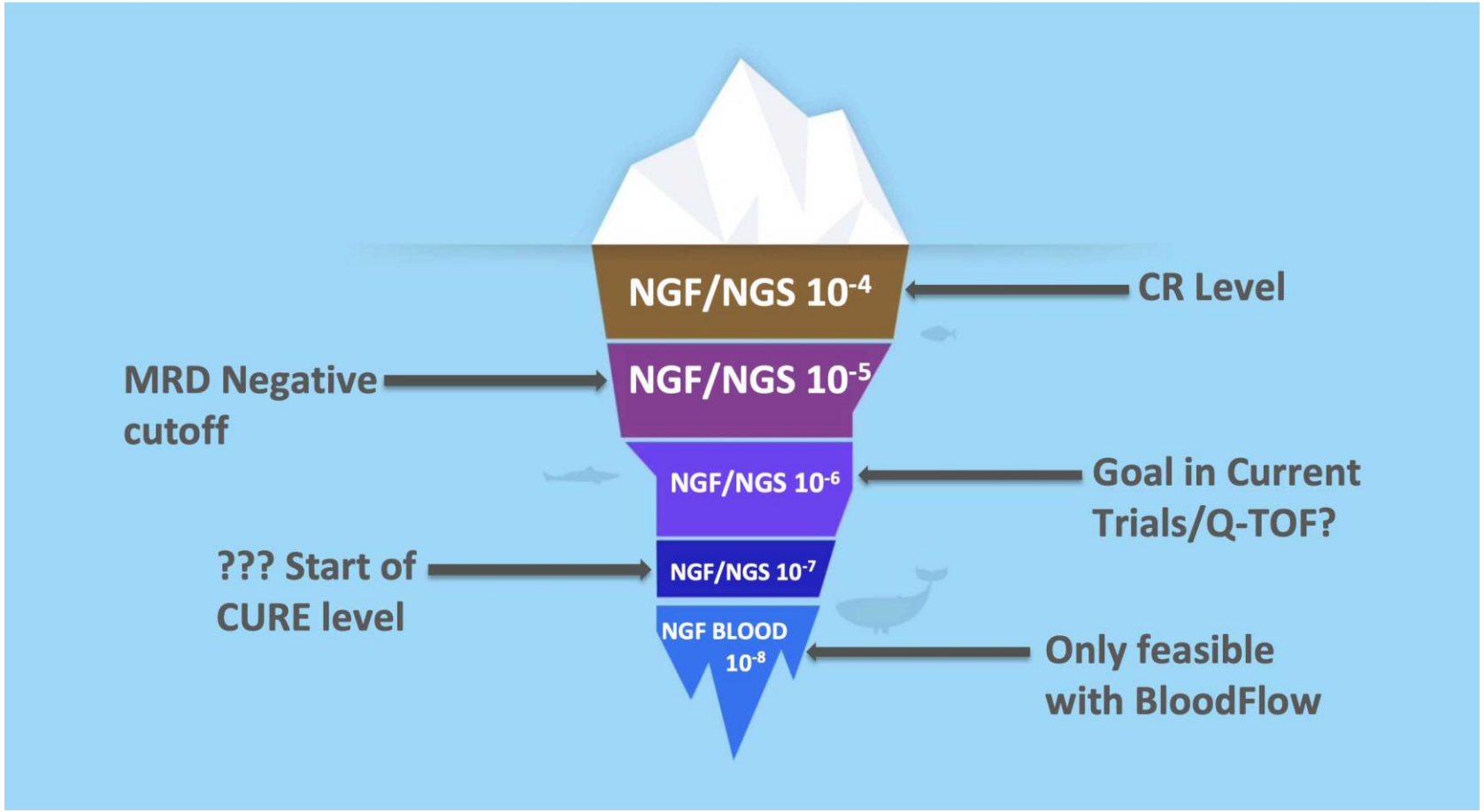
Introduction

	Response criteria*
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

(Table 4 and footnotes continue on the next page)

Kumar S; et al, The Lancet Oncology, Volume 17, Issue 9, September 2016,

Introduction



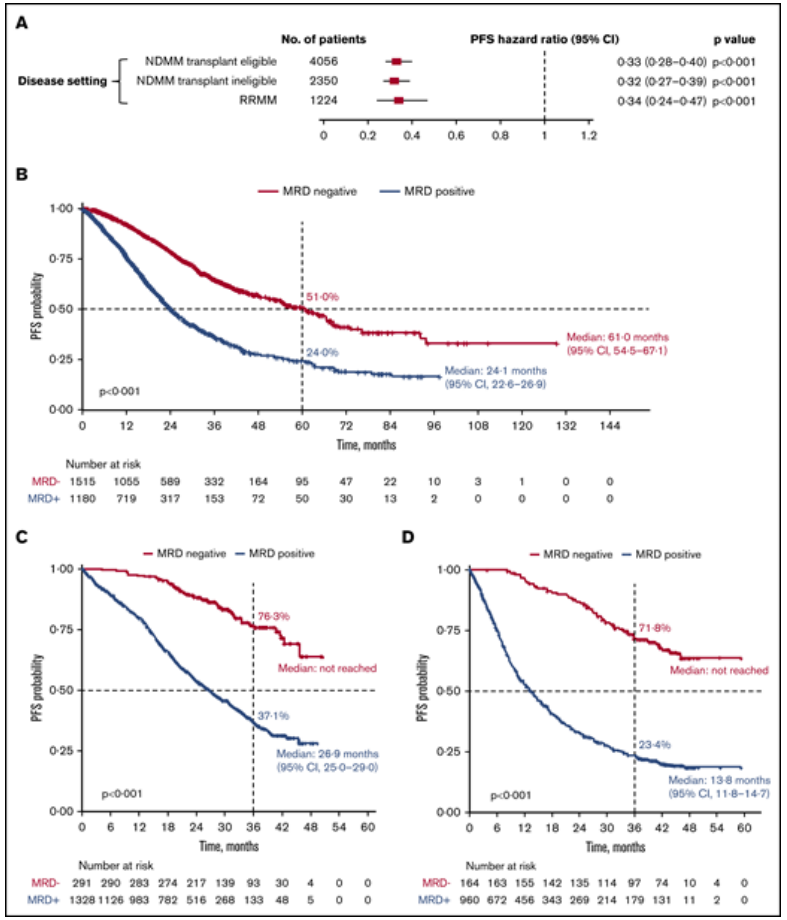
https://www.myeloma.org/blog/dr-duries/next-generation-testing-and-decision-making

MRD : aspect pronostique

- Corrélation entre la profondeur de la réponse et la survie sans progression (PFS)
- MRD indétectable : meilleur pronostic que MRD détectable

MRD : aspect pronostique

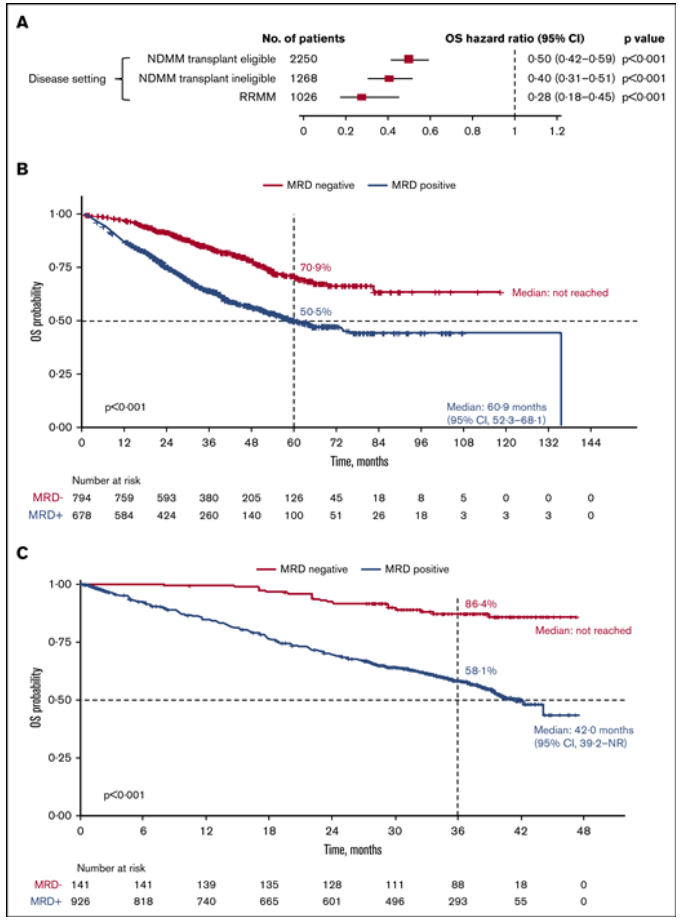
Méta-Analyse, données issues de 44 études avec 8098 patients (3111 MRD neg, 4987 MRD pos)



Munshi N. et al, Blood Advances, (2020) 4 (23): 5988–5999

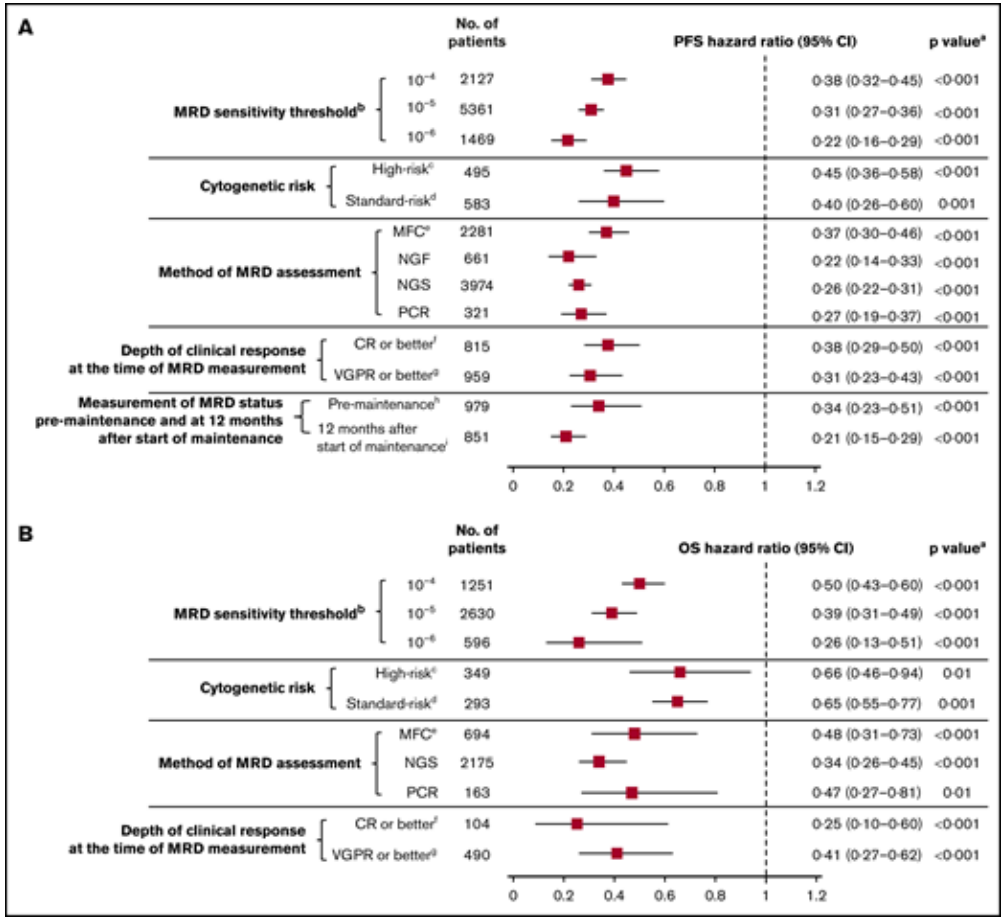
MRD : aspect pronostique

Méta-Analyse, données issues de 23 études avec 4297 patients (1605 MRD neg, 2692 MRD pos)



Munshi N. et al, Blood Advances, (2020) 4 (23): 5988–5999

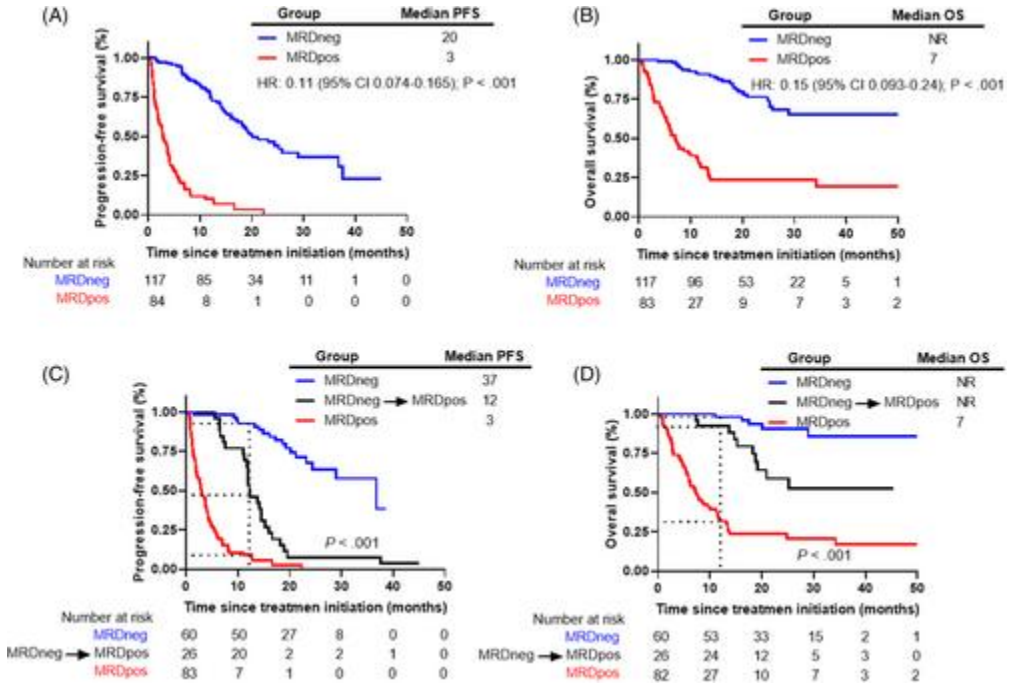
MRD : aspect pronostique



Munshi N. et al, Blood Advances, (2020) 4 (23): 5988–5999

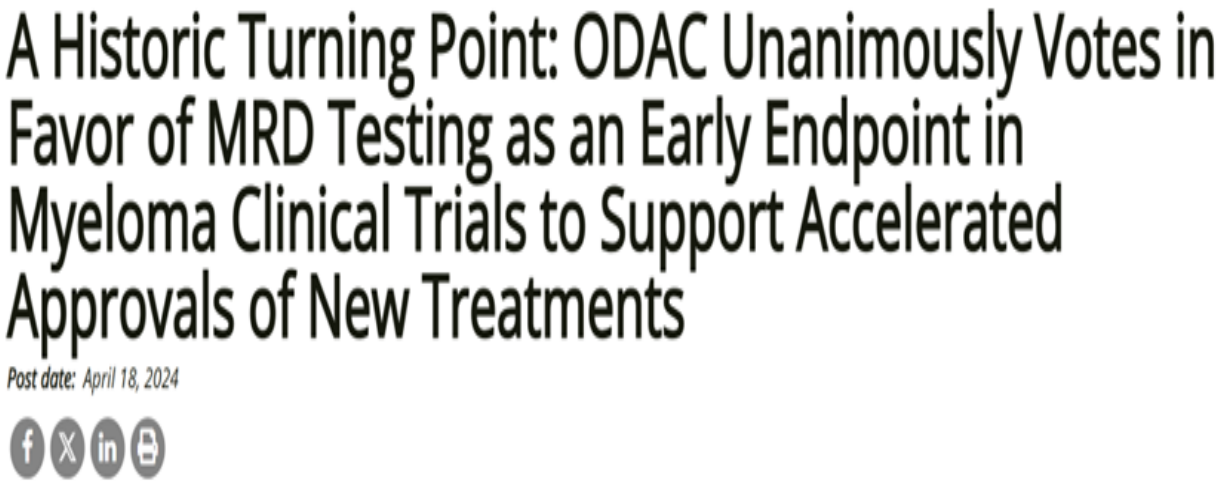
MRD : Aspect pronostique

Analyse de 201 patients espagnols inclus dans des essais CART ou Ac bispécifiques avec RRMM



Zabaleta A. et al, American Journal of Hematology, Jan 2025

MRD : Aspect pronostique



A Historic Turning Point: ODAC Unanimously Votes in Favor of MRD Testing as an Early Endpoint in Myeloma Clinical Trials to Support Accelerated Approvals of New Treatments

Post date: April 18, 2024

La FDA approuve la MRD comme endpoint primaire des essais cliniques myélome (avril 2024)

MRD : Aspect pronostique

Intérêt MRD combinée Moelle Osseuse/PET

CASSIOPET Study: Prognostic Value of Pre-Maintenance (PM) FDG-PET/CT in Newly Diagnosed Multiple Myeloma (NDMM) Patients Treated With Daratumumab

Context of Research

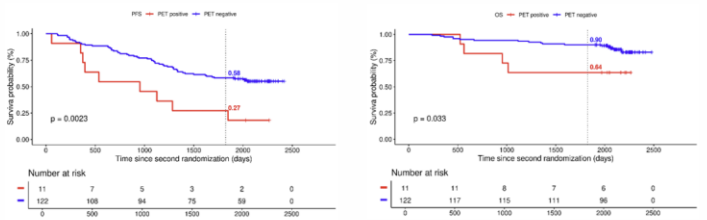
- **FDG-PET/CT** is a reliable imaging technique for the initial workup and therapy assessment with prognostic impact for NDMM patients
- Further work is needed to assess the prognostic value of pre-maintenance standardized FDG-PET/CT negativity in the era of anti-CD38 monoclonal antibodies

Patients and Methods

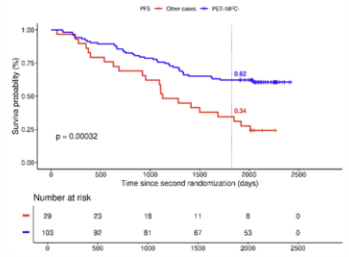
- 225 patients randomized in the trial **CASSIOPEIA part 2 (NCT02541383)**
  - 112 patients treated by daratumumab (D)
  - 113 set to observation
- 175 (77.8%) with a baseline positive FDG-PET/CT
- Standardized PM FDG-PET/CT response analyzed according to the **Deauville scale**
- Bone marrow (BM) minimal residual disease assessed by **multiparameter flow cytometry (MFC)** at 10^{-5} sensitivity threshold

Main Findings

- **Pre-maintenance FDG-PET/CT results were associated with both PFS and OS in daratumumab-treated patients**



- **Achieving PET and MFC double negativity after therapy was associated with better PFS**



Conclusions: For patients with NDMM undergoing daratumumab-based intensive therapy, pre-maintenance PET/CT findings based on the Deauville scale demonstrated prognostic significance. Attaining PET and MFC double negativity at the pre-maintenance stage could serve as a criterion for determining the intensity of maintenance therapy.

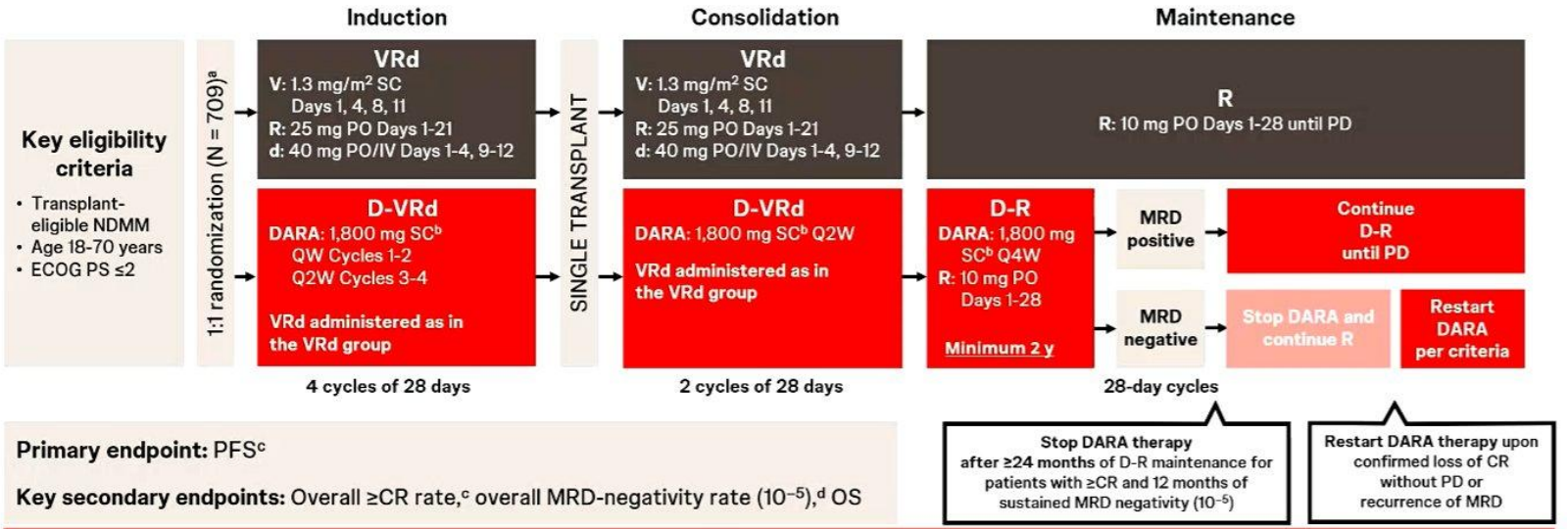
*Kraeber-Bodere et al. DOI: xxx/**blood**.2025XXX*

blood Visual Abstract

PET-CT : maladie extramédullaire, infiltration hétérogène de la moelle osseuse

Données récentes études de 1ère ligne

PERSEUS: Study Design

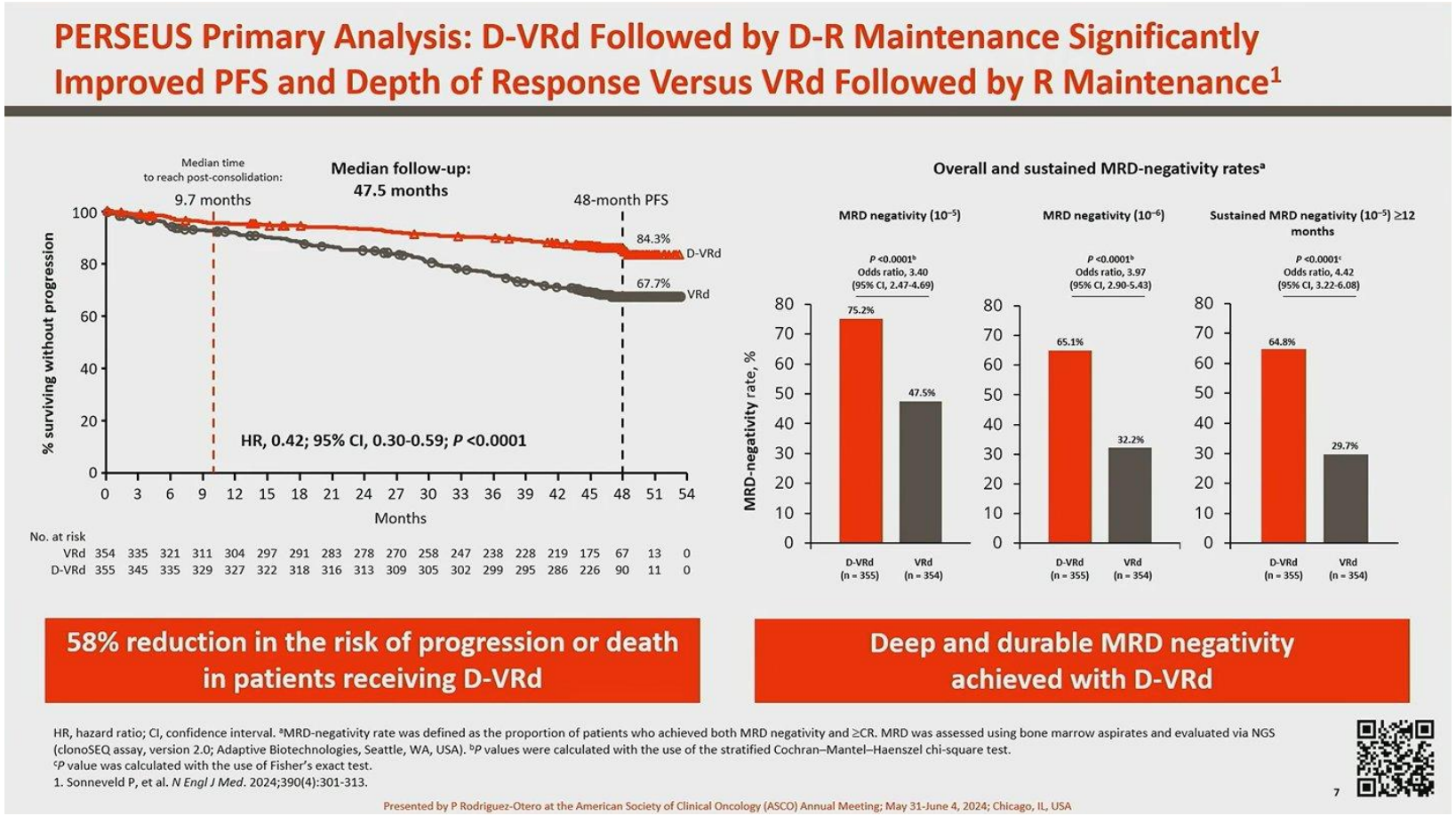


MRD response-adapted approach in maintenance:
MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive.

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA). [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

Presented by P Sonneveld at the European Hematology Association (EHA) Hybrid Congress; June 13-16, 2024; Madrid, Spain

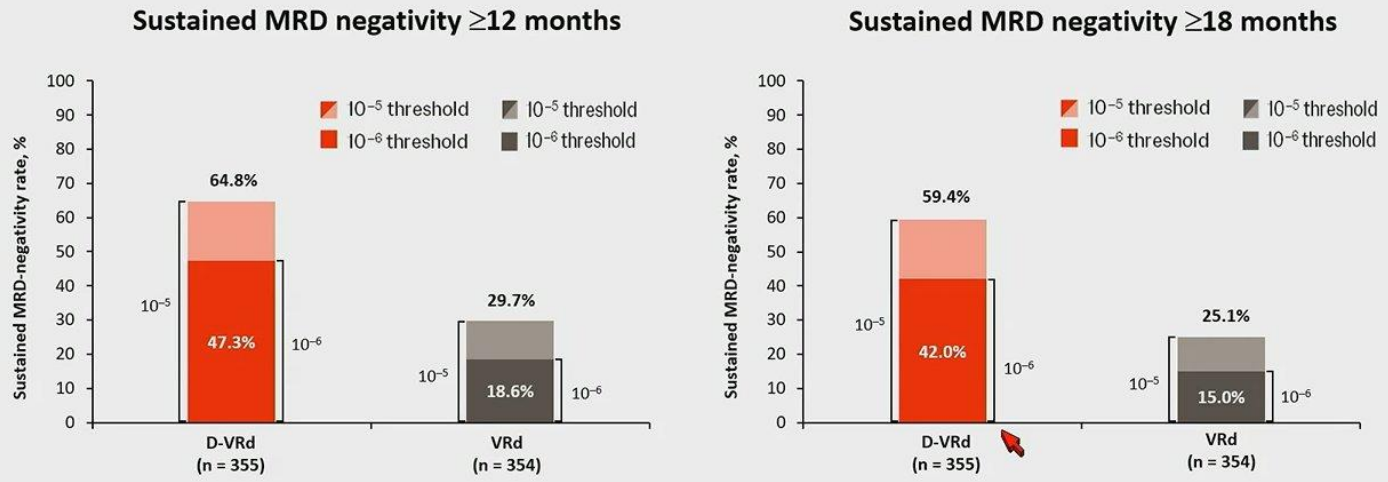
Données récentes études de 1ère ligne



mPFS estimée de 17,1 ans bras expérimental versus 7,3 ans pour le bras standard

Données récentes études de 1ère ligne

PERSEUS: Sustained MRD-negativity Rates (10^{-5} and 10^{-6}; ITT)



- Rates of sustained MRD negativity at 10^{-6} were 2.5-fold higher for D-VRd + D-R versus VRd + R
- More than 40% of patients had sustained MRD negativity at 10^{-6} for ≥18 months with D-VRd + D-R

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive. *P* values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test. *P* <0.0001 for all comparisons of D-VRd versus VRd.

Presented by P Rodriguez-Otero at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA

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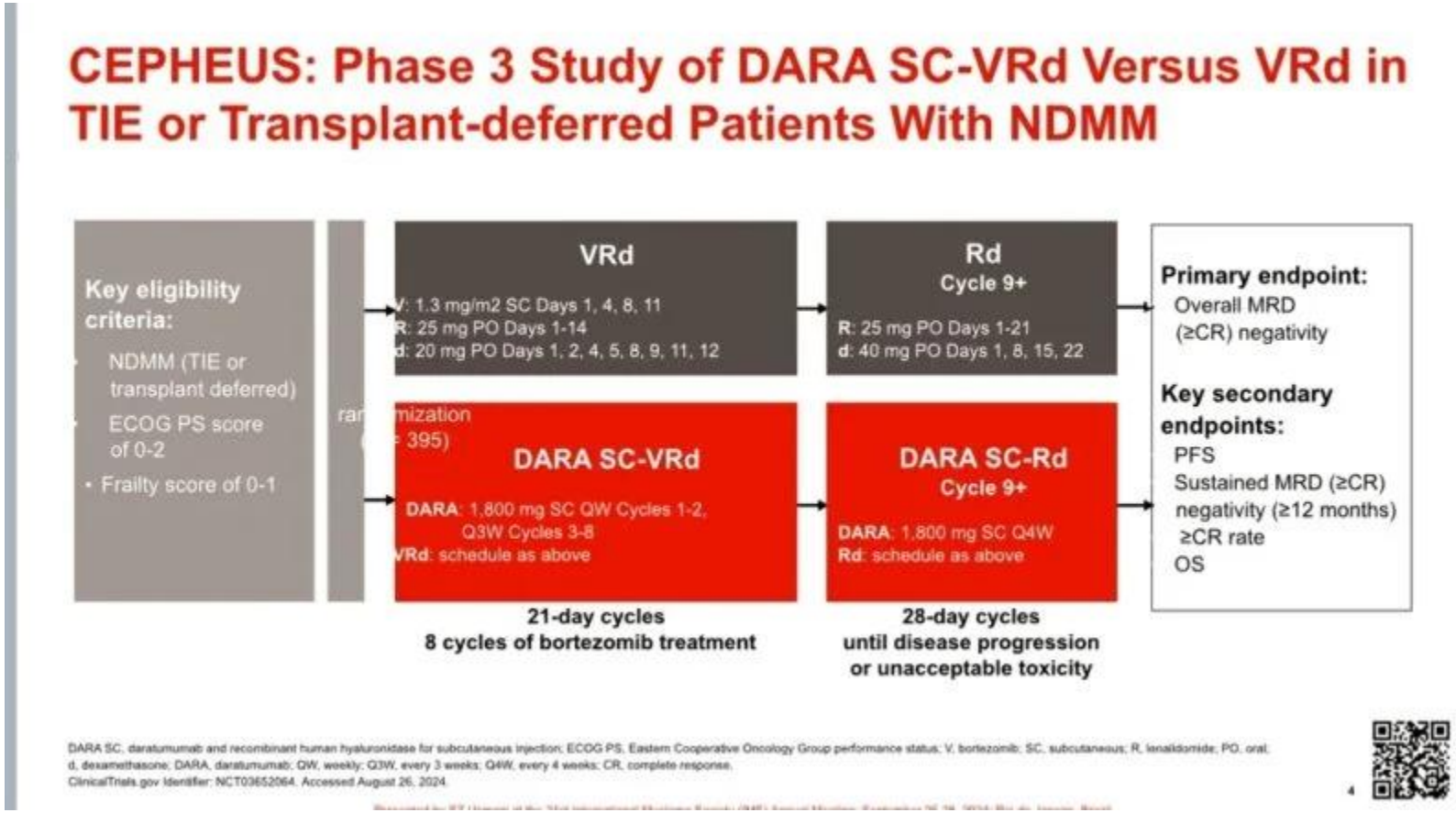
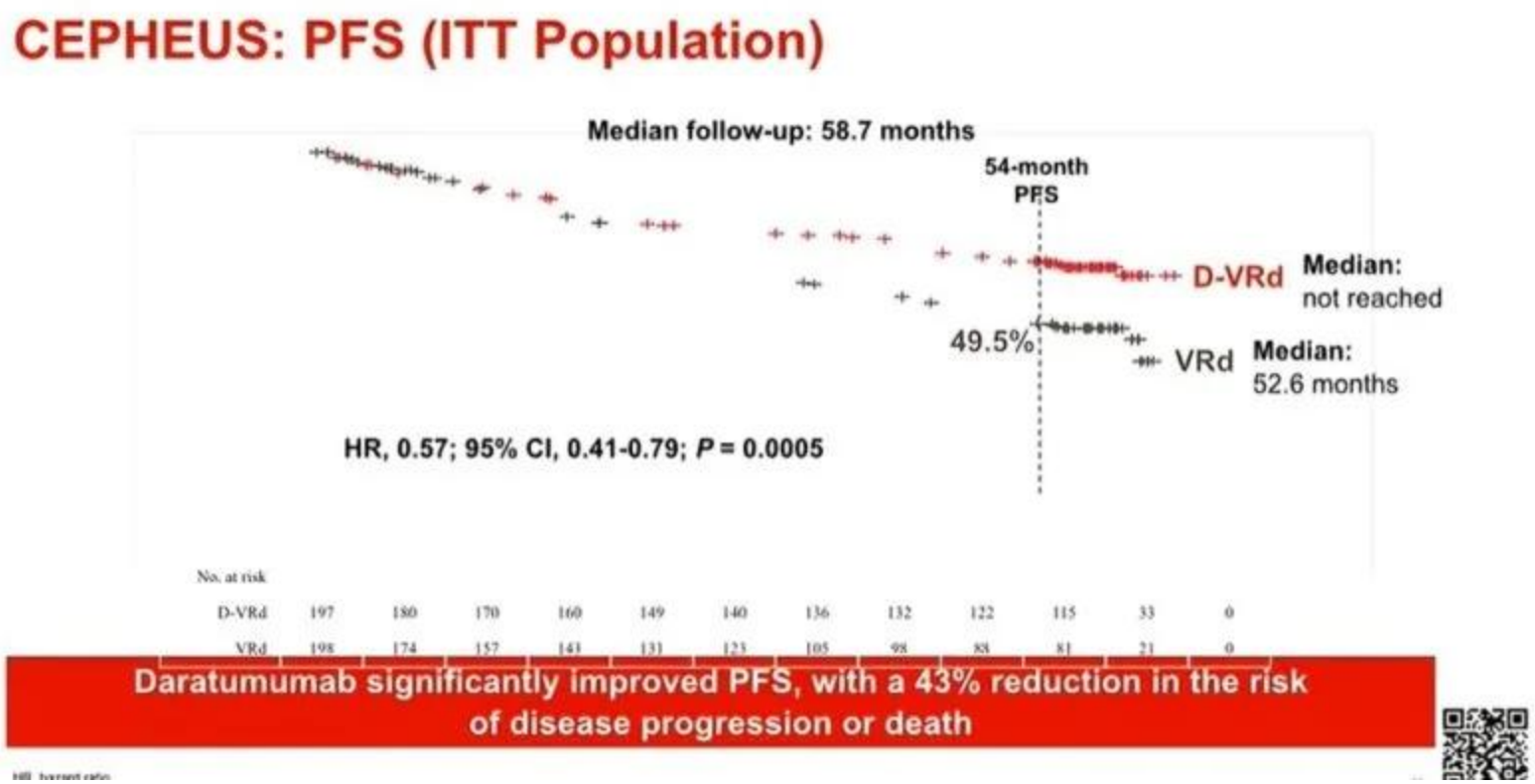
Données récentes études de 1ère ligne

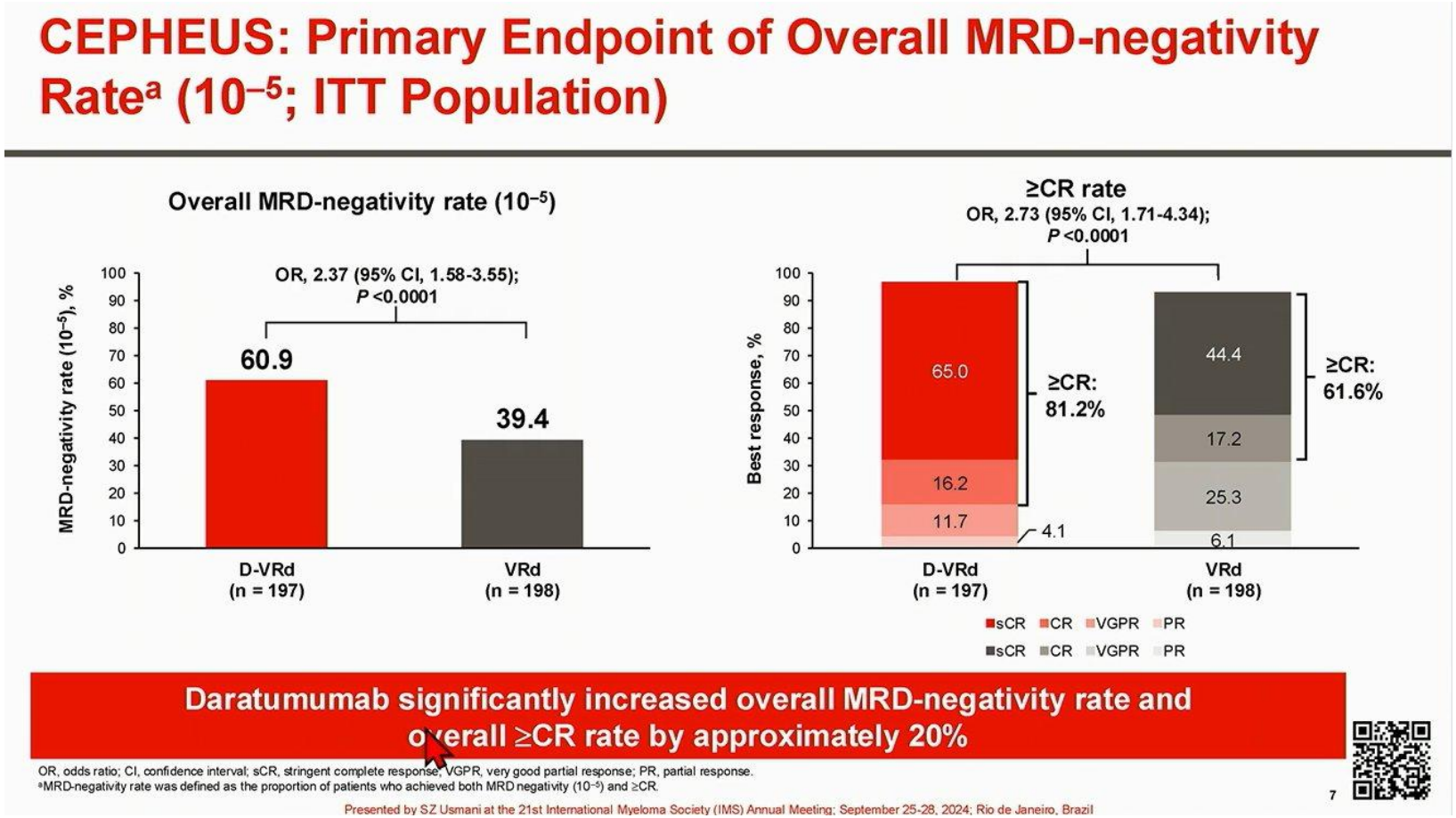


Données récentes études de 1ère ligne



mPFS estimée de 8,3 ans pour le bras expérimental

Données récentes études de 1ère ligne



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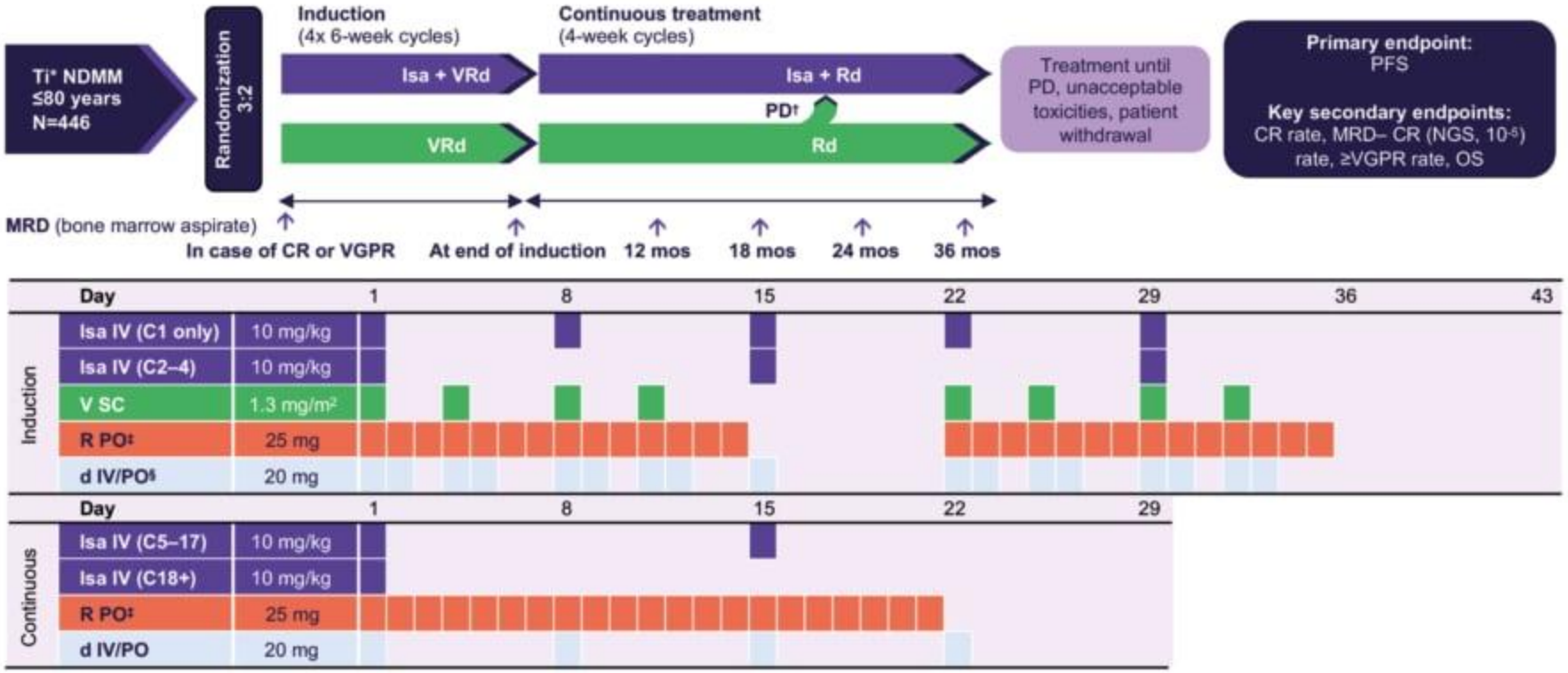
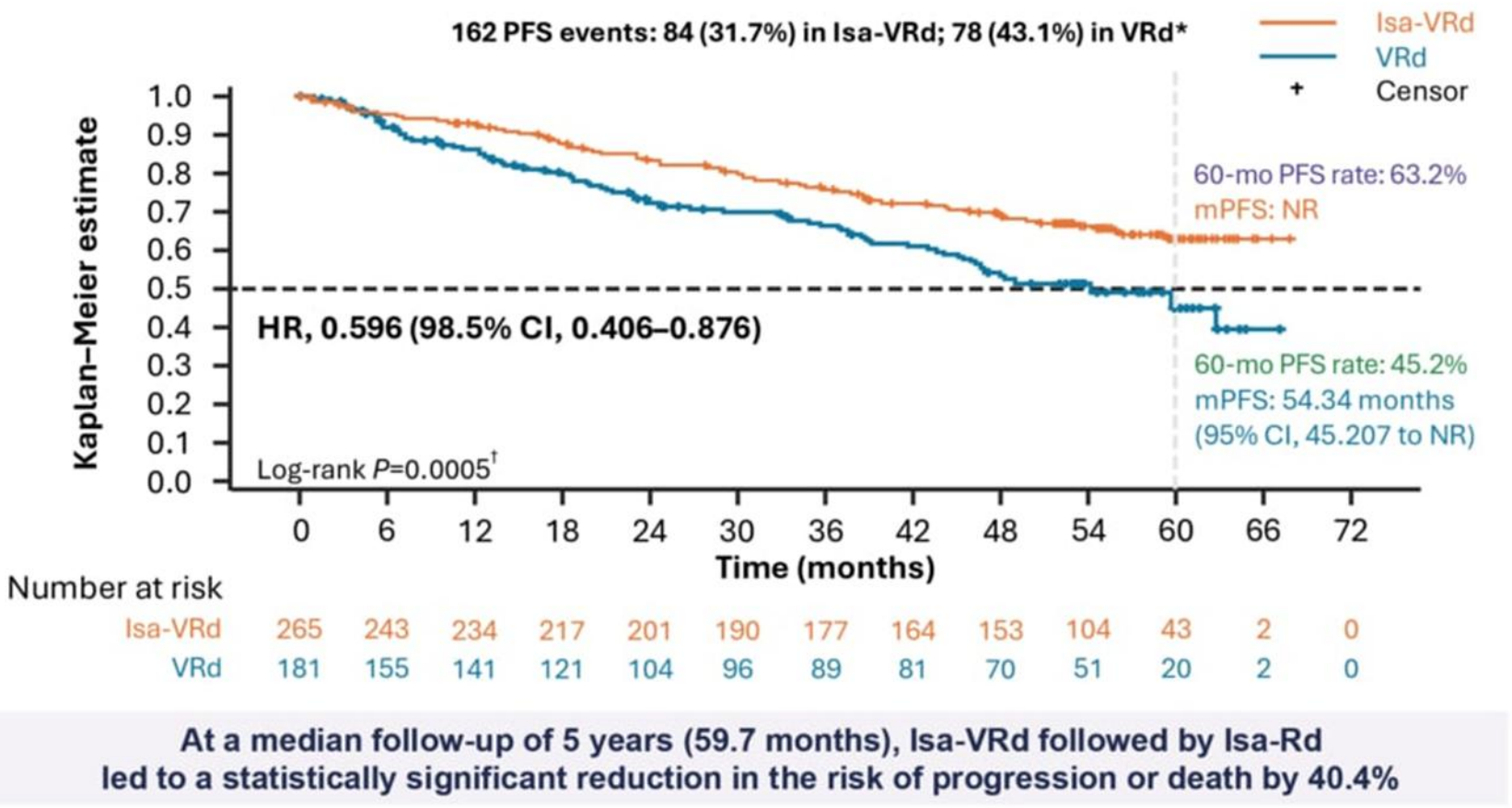


Essai IMROZ (*Facon et al, ASCO 2024)*

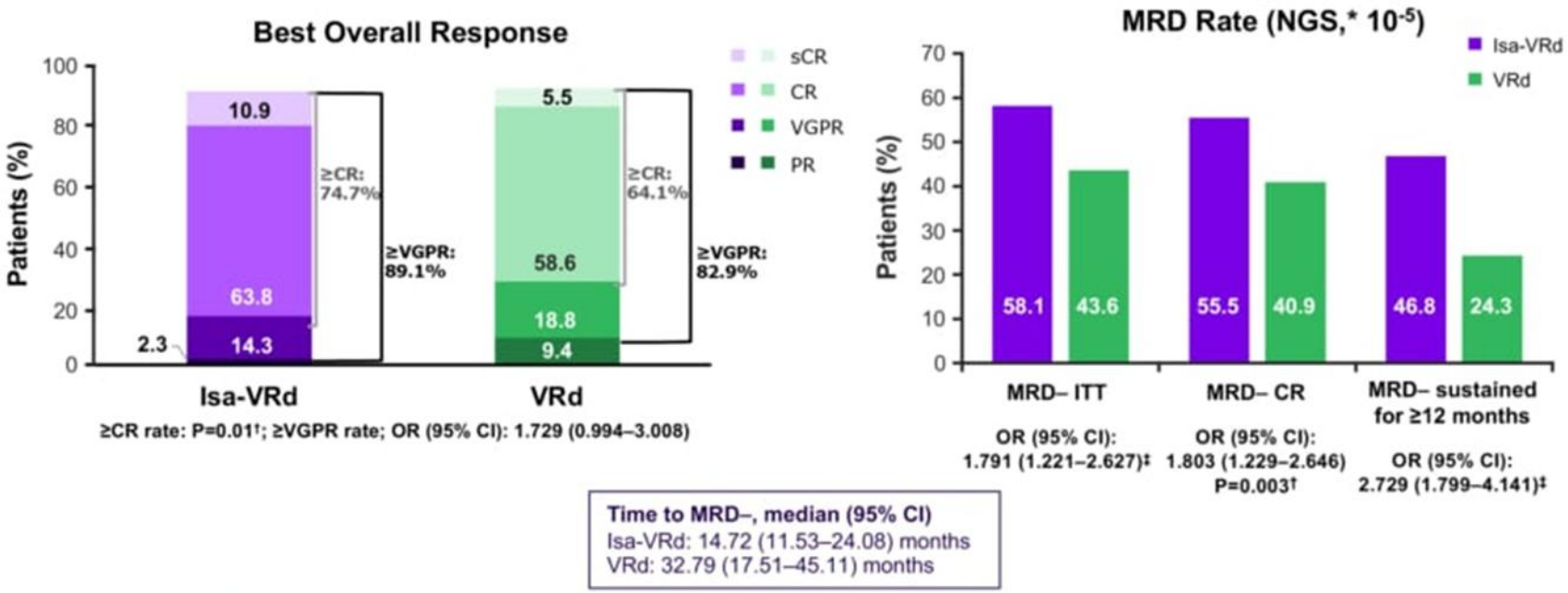
Données récentes études de 1ère ligne



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%

Essai IMROZ (*Facon et al, ASCO 2024)*

Données récentes études de 1ère ligne

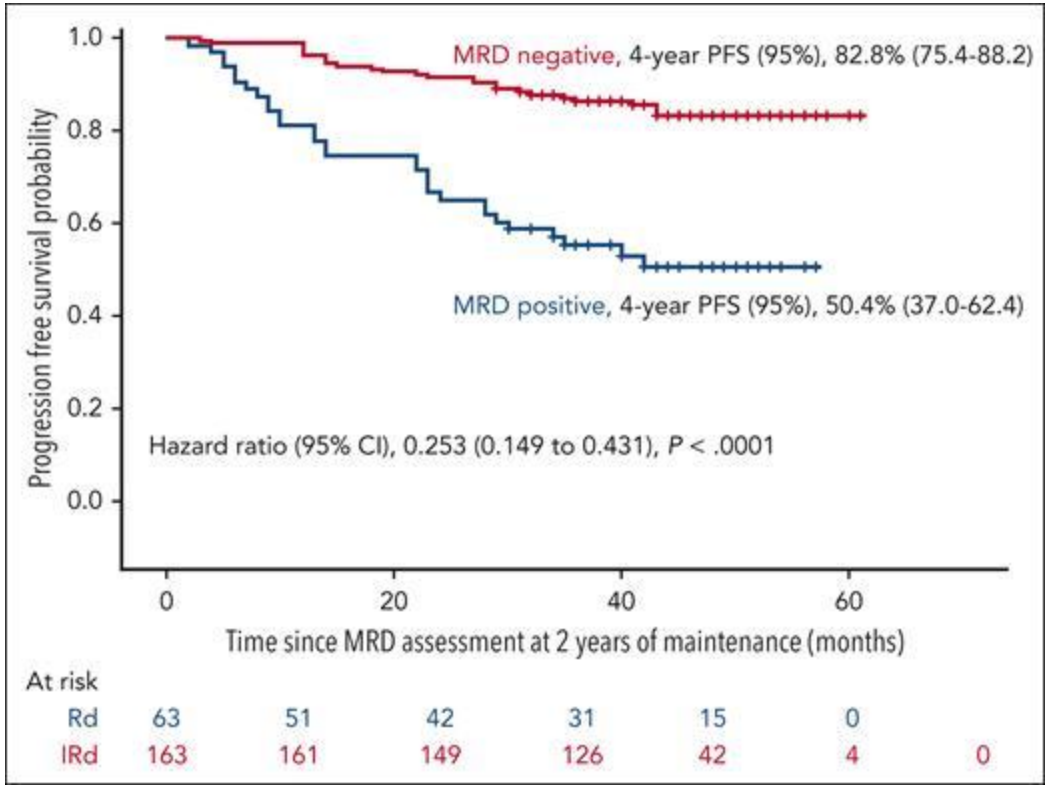


Isa-VRd followed by Isa-Rd resulted in deep response rates, with a significant improvement in the MRD– CR rate, as well as higher rates of MRD– and sustained MRD– for ≥12 months at any point in the ITT population

Essai IMROZ (*Facon et al, ASCO 2024)*

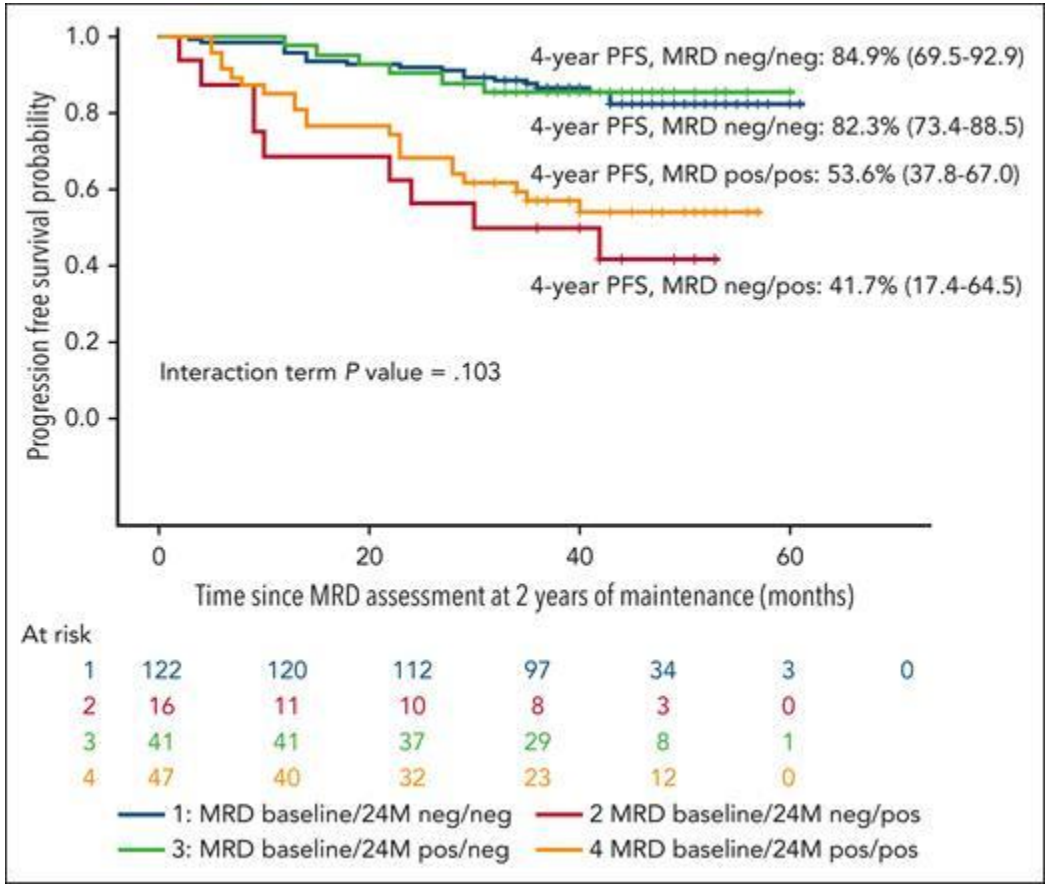
Traitement guidé par la MRD

- Essai GEM12MENOS65
- Induction VRD x6 puis Mel200 mg/m^2 + ASCT puis consolidation VRD x2
- Maintenance Lenalidomide versus Lenalidomide – Ixazomib
- MRD par CMF
- Arrêt la maintenance après 24 mois en cas de MRD indétectable



Rosinol L et al, Blood (2023) 142 (18): 1518–1528

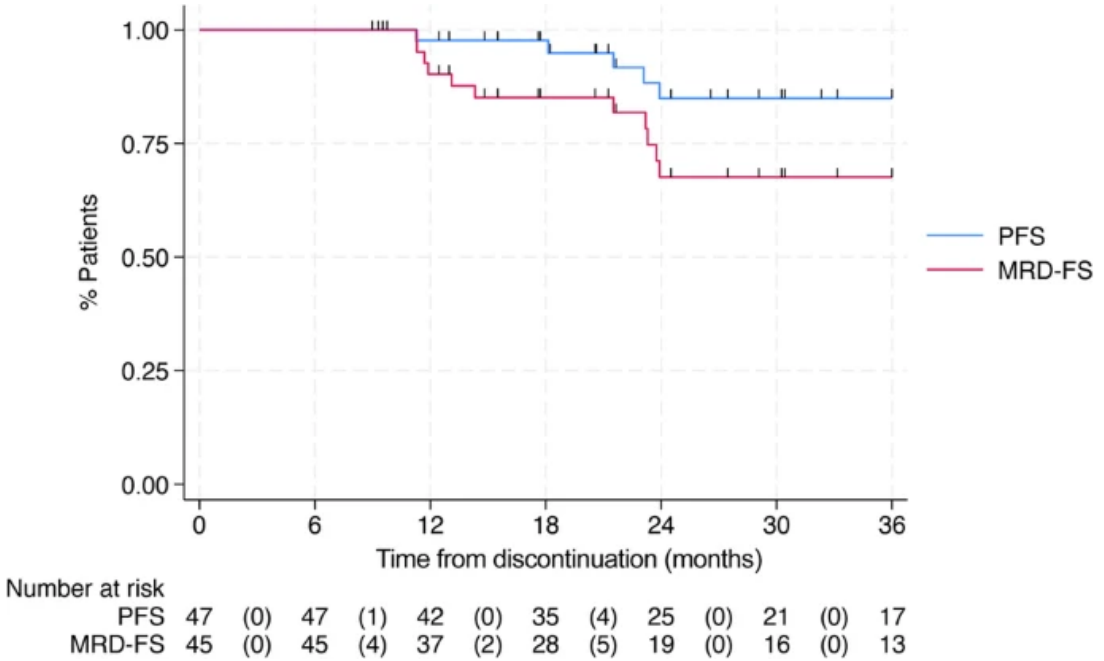
Traitement guidé par la MRD



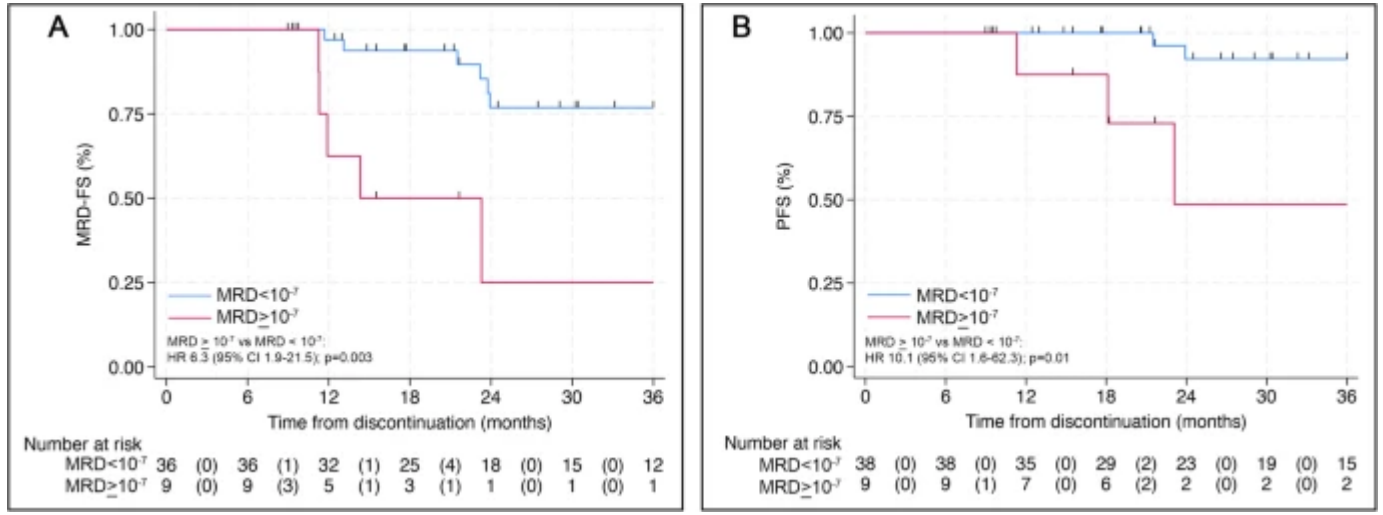
Rosinol L et al, Blood (2023) 142 (18): 1518–1528

Traitement guidé par la MRD

- Etude MRD2STOP
- ≥1 an de maintenance
- MRD indétectable confirmée par PET-CT et CMF sur la moelle (limite detection 10−5) et clonoSEQ sur la moelle (Limite détection 10−6)
- 47 patients évaluables

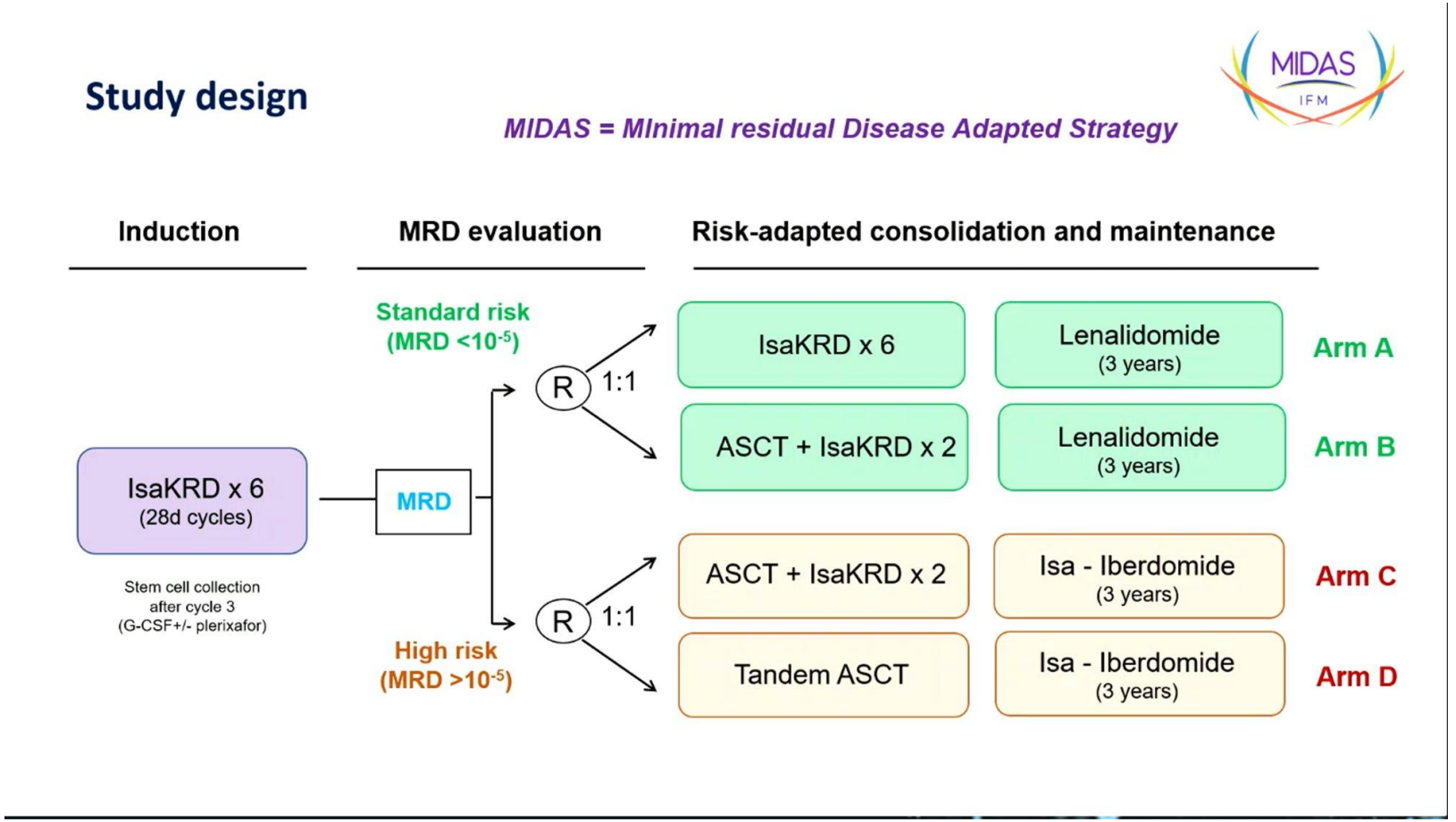


Traitement guidé par la MRD



Traitement guidé par la MRD

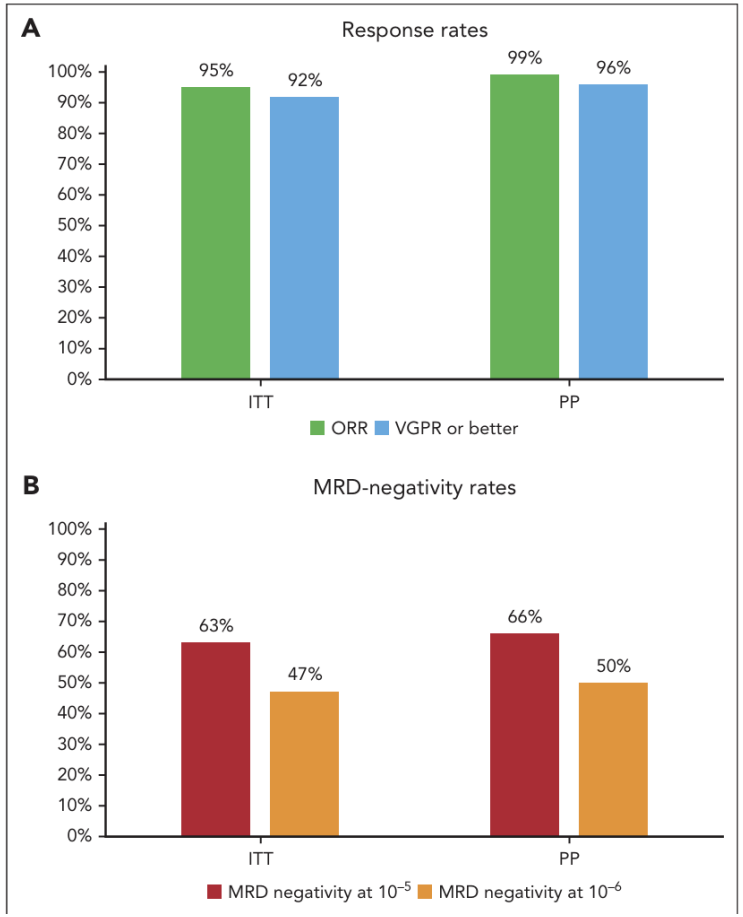
Essai MIDAS



Traitement guidé par la MRD

Essai MIDAS

Résultats fin induction

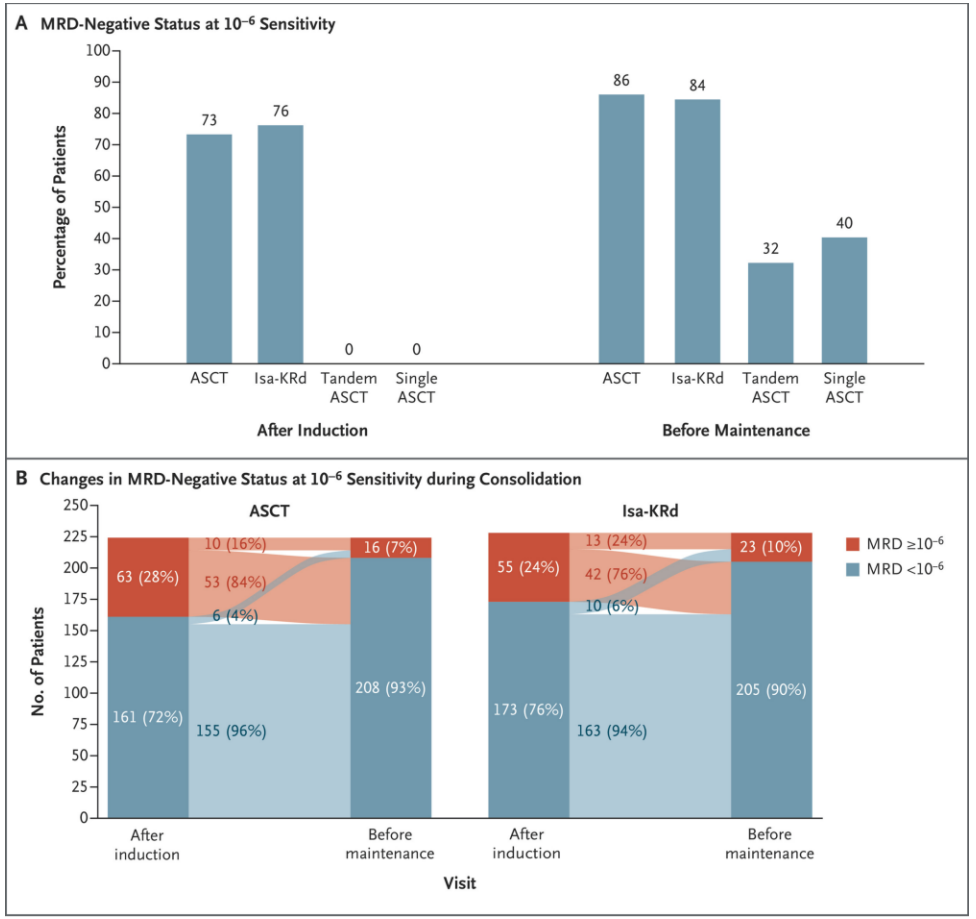


Perrot A. et al, Blood,3 july 2025, vol 146, number 1

Traitement guidé par la MRD

Essai MIDAS

Pas d'impact de l'autogreffe en cas de MRD indétectable en fin d'induction



Perot A. et al, N Engl J Med 2025;393:425-437

Intérêts économiques potentiels MRD

- Gains potentiels :

➢ Diminution des procédures d'intensification/autogreffe ?

➢ Arrêt de la maintenance en cas de MRD indétectable ?

➢ Meilleure qualité de vie ? Reprise activités professionnelles des patients ?

Intérêts économiques potentiels MRD

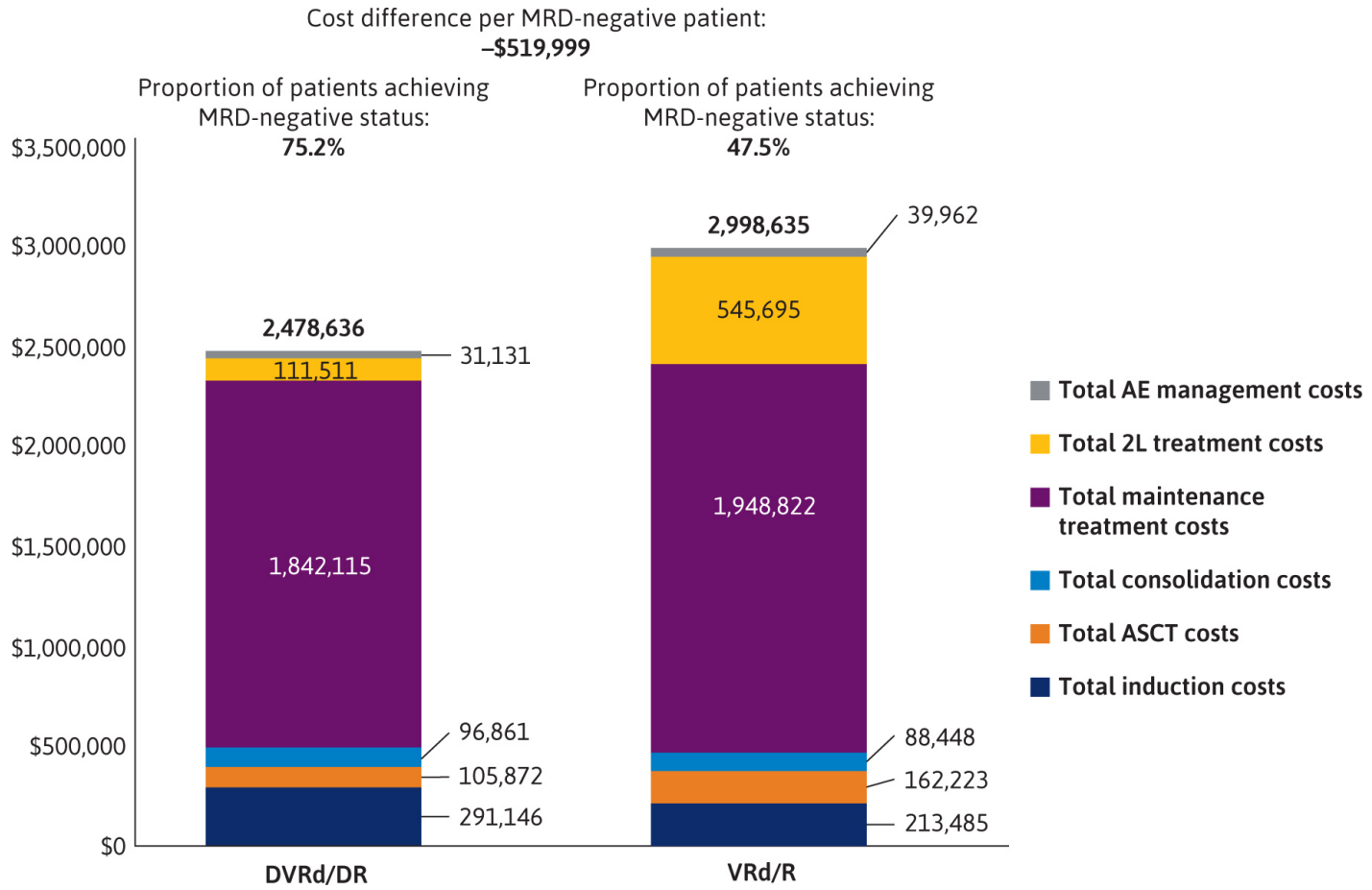
Cost-per-responder analysis of daratumumab, bortezomib, lenalidomide, and dexamethasone vs bortezomib, lenalidomide, and dexamethasone among transplant-eligible patients with newly diagnosed multiple myeloma

Santosh Gautam, PhD; Laura Morrison, MPH; Philippe Thompson-Leduc, MSc; Bronwyn Moore, BA; Gordon Wong, BA; Brian Macomson, PharmD; Vipin Khare, MD; Niodita Gupta-Werner, MD, MPH, PhD; Rohan Medhekar, PhD

Analyse des coûts/patient étude PERSEUS

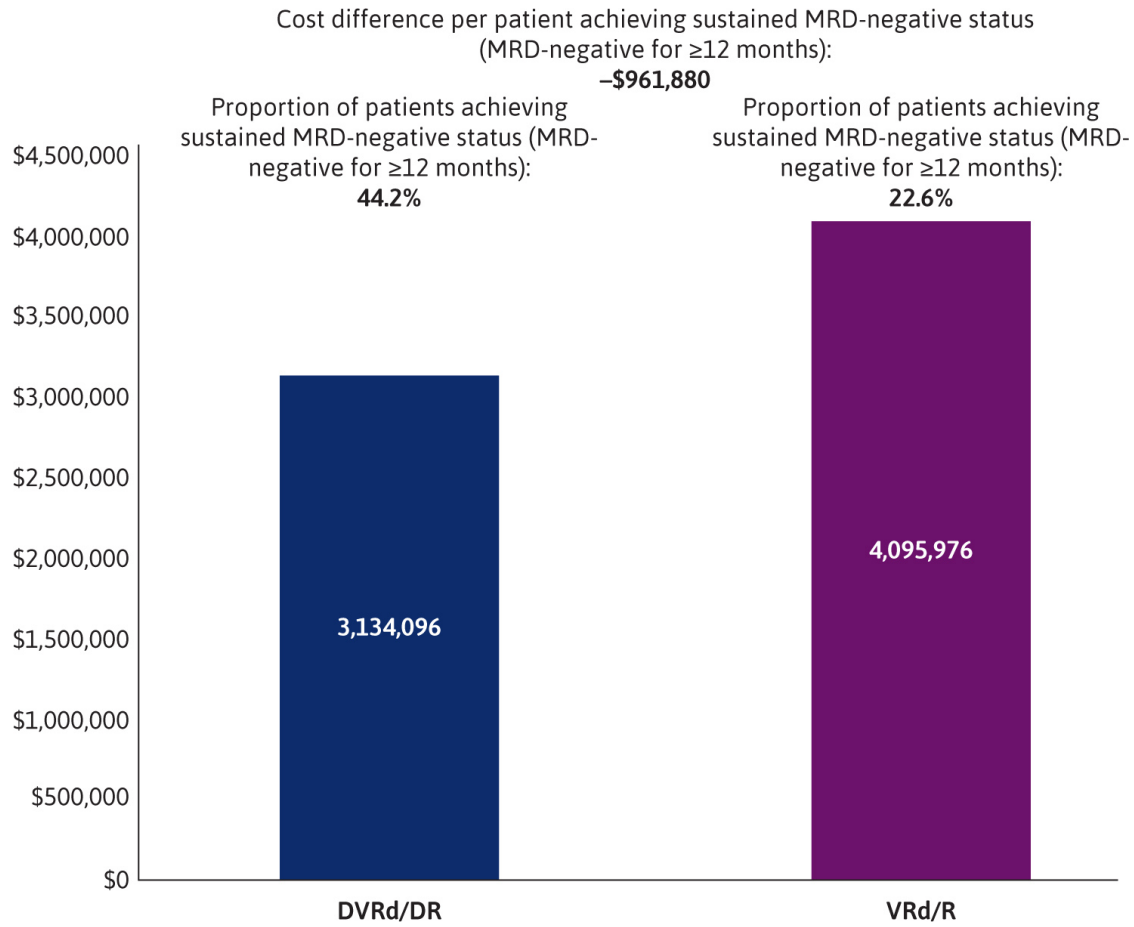
Gautham S; et al, J Manag Care Spec Pharm. 2025;31(10):1-1

Intérêts économiques potentiels MRD



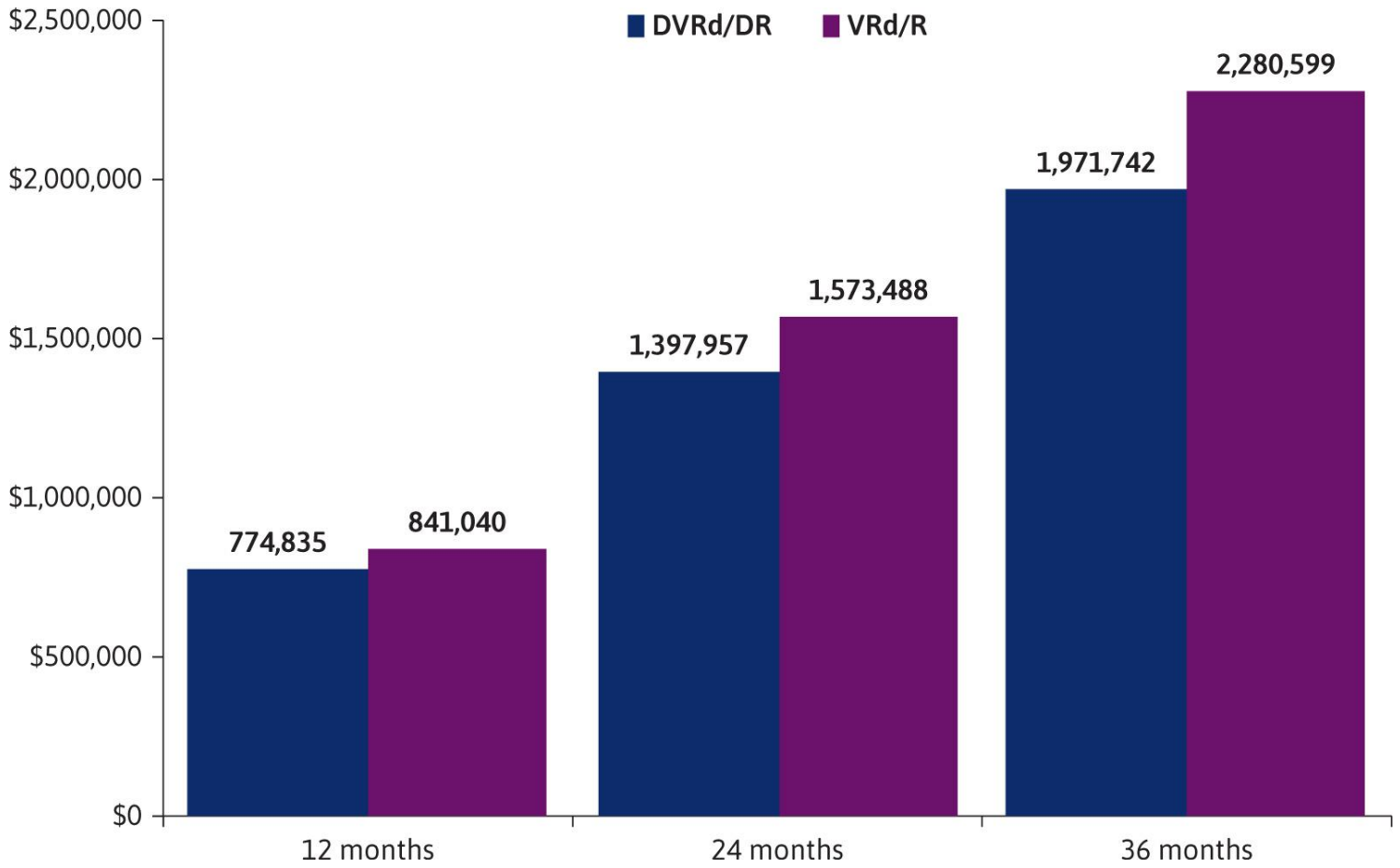
Gautham S; et al, J Manag Care Spec Pharm. 2025;31(10):1-1

Intérêts économiques potentiels MRD



Gautham S; et al, J Manag Care Spec Pharm. 2025;31(10):1-1

Intérêts économiques potentiels MRD



Gautham S; et al, J Manag Care Spec Pharm. 2025;31(10):1-1

Pistes futures

- Actuellement, MRD validée sur un prélèvement de moelle osseuse (acte invasif chez le patient)
- MRD évaluable sur le sang périphérique ?

Conclusions

- Myélome multiple toujours incurable en 2025 mais grandes avancées thérapeutiques
- Traitements efficaces avec réponses profondes
- Intérêt pronostique de la MRD clairement démontré
- Intégration future de la MRD dans le suivi/arrêt de traitement, adaptation du traitement ?
- Développement des techniques de MRD sur le sang périphérique