Myelome Multiple
NDMM NTE

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Disclosures

- Merci au P Rousselot, je suis tres honore d'organiser cette journee pour vous qui etes l'avenir de l'Hematologie
- Merci au Pr Rousselot de venir aujourd'hui, j'ai failli etre le plus vieux… Quelle ----
- Merci a tous ceux et celles a qui j'ai emprunte des diapositives [Arthur (Poitiers), Laura (Brest) et Domitille (Nantes)
- Merci aux internes de Poitiers. Je vous rentre dedans et vous remonte les bretelles tout le temps, mais vous faites tous un boulot merveilleux
- Merci a mes collegues orateurs de ce jour. J'aime soigner le Myelome aussi parce que nous sommes un groupe genial, grace a vous.

Mon ordinateur etant US, merci de tolerer la langue Francaise sans les accents

Petit état des lieux avant de commencer...

Age médian au diagnostic ≈ 70 ans

Vieillissement de la population mondiale

≈ 1/3 des patients ≥ 75 ans
≈ 1/3 des patients *unfit* ou fragiles

≈ 60 % inéligibles à un traitement intensif (NTE)

- Âge (≥ 65ans/70ans)
- Comorbidités

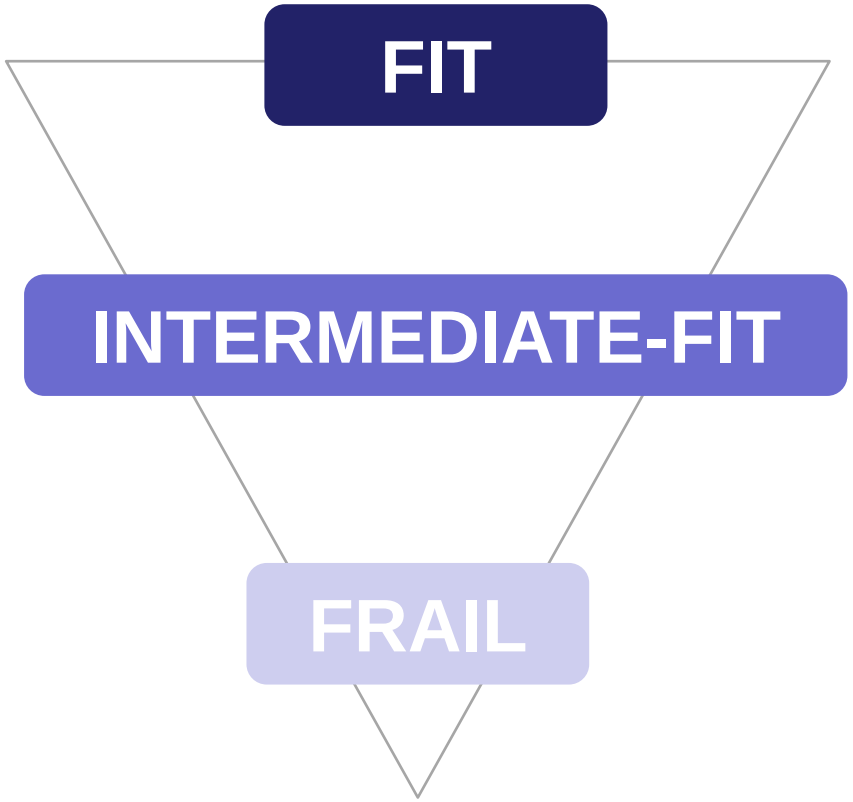
Taux d'incidence selon la classe d'âge en France en 2018

TABLEAU 2 | Nombre de cas par classe d'âge en France en 2018 - Myélome multiple et plasmocytome

Âge (années)	[0;14]	[15;19]	[20;24]	[25;29]	[30;34]	[35;39]	[40;44]	[45;49]	[50;54]	[55;59]	[60;64]	[65;69]	[70;74]	[75;79]	[80;84]	[85;89]	[90;94]	[95;+]
INCIDENCE																		
Homme	0	1	1	3	6	14	34	79	148	225	312	435	450	399	376	244	82	13
Femme	0	0	0	1	3	13	34	65	100	149	225	342	381	376	438	354	123	16

Palumbo et al, NEJM, 2011
Kristinsson et al, JCO, 2003
Seer.gov.fr
Santé publique France.fr

Les patients non éligibles à l'autogreffe : 3 sous-groupes



Facteurs de risques liés au patient :
- Âge biologique
- Comorbidités (Charlson)
- Score OMS/ECOG
- Echelles : ADL, IADL[ǂ]

➔ Evaluation onco-gériatrique

➔ Scores : R-MCI[*], IMWG[#] frailty index

+

Facteurs de risques liés au myélome :
- génomique
- ISS, R-ISS
- Lésions extra-medullaire (EMD)
- Plasmablastes
- Plasmocytes circulants

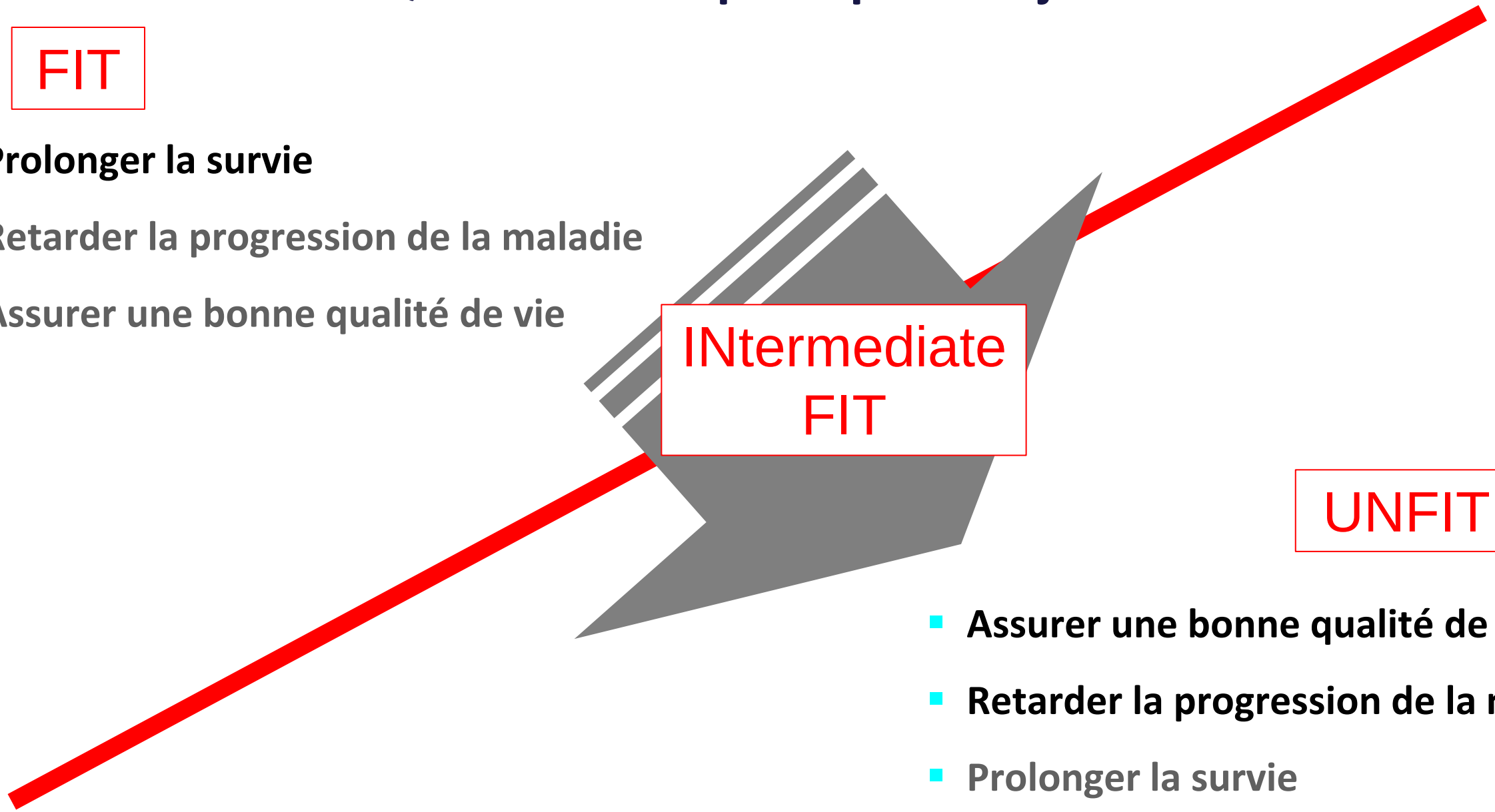
Les patients *frails* sont aujourd'hui traités à part

[ǂ]Instrumental Activities of Daily Living [#]*IMWG (International Myeloma Working Group)* [*]*R-MCI (Revised Myeloma Comorbidity Index*

Quels sont les principaux objectifs?

FIT

- **Prolonger la survie**
- **Retarder la progression de la maladie**
- **Assurer une bonne qualité de vie**

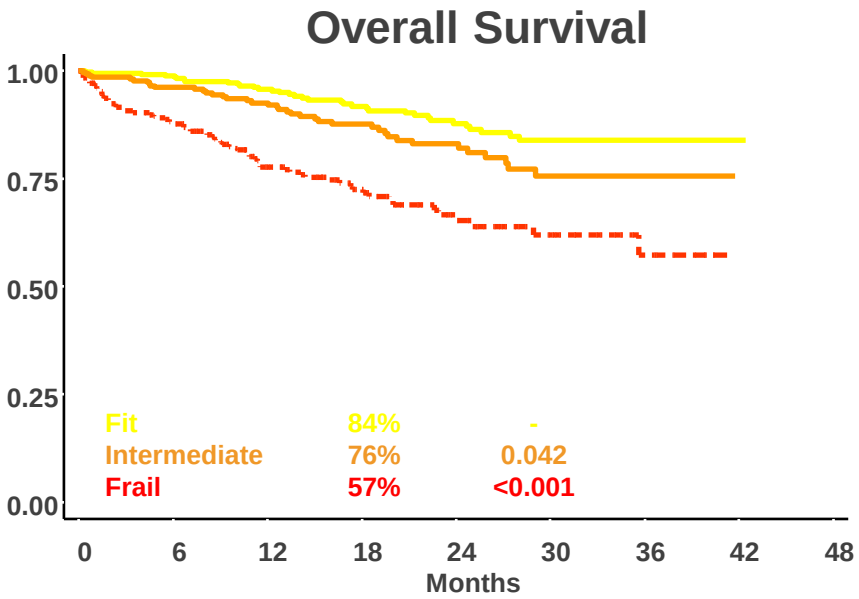


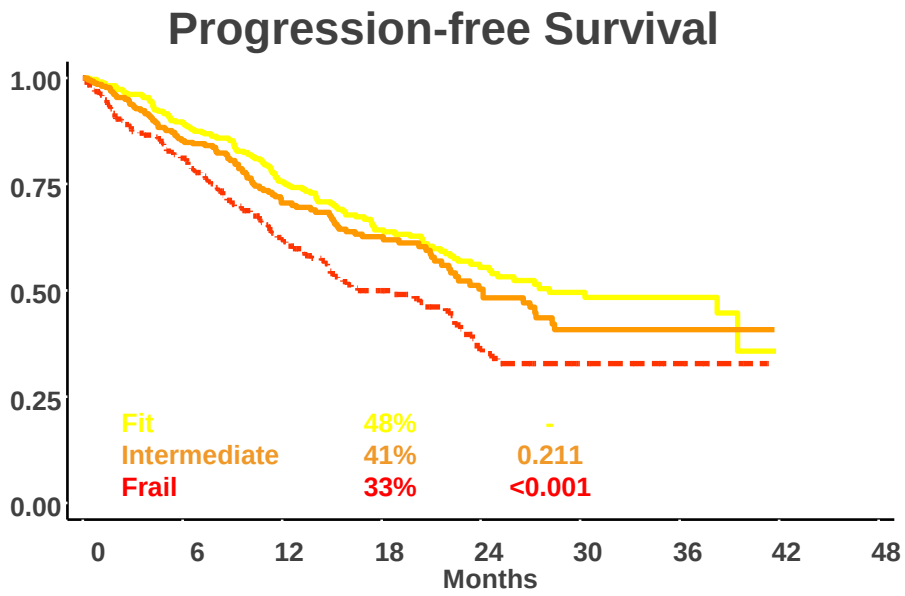
- **Assurer une bonne qualité de vie**
- **Retarder la progression de la maladie**
- **Prolonger la survie**

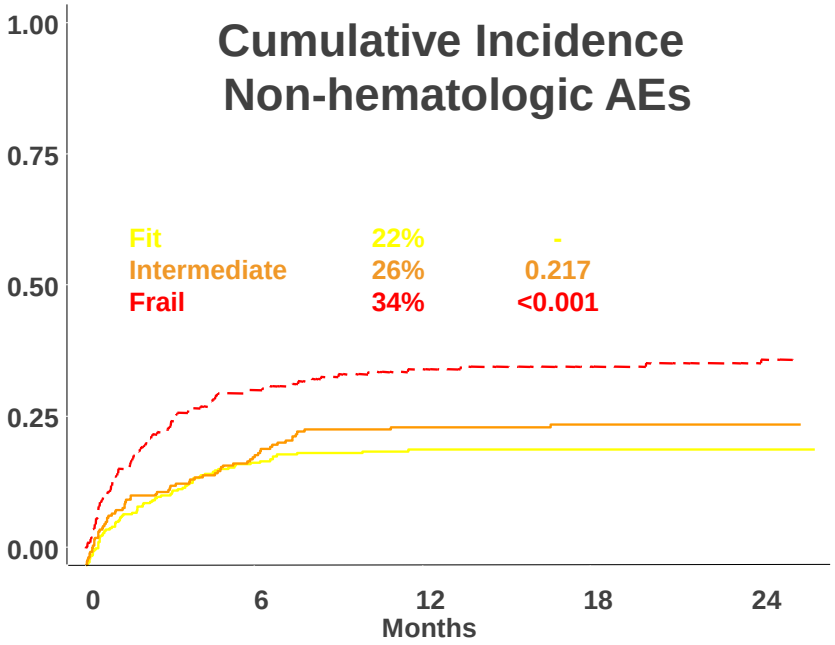
Discontinuation reduces dose-intensity

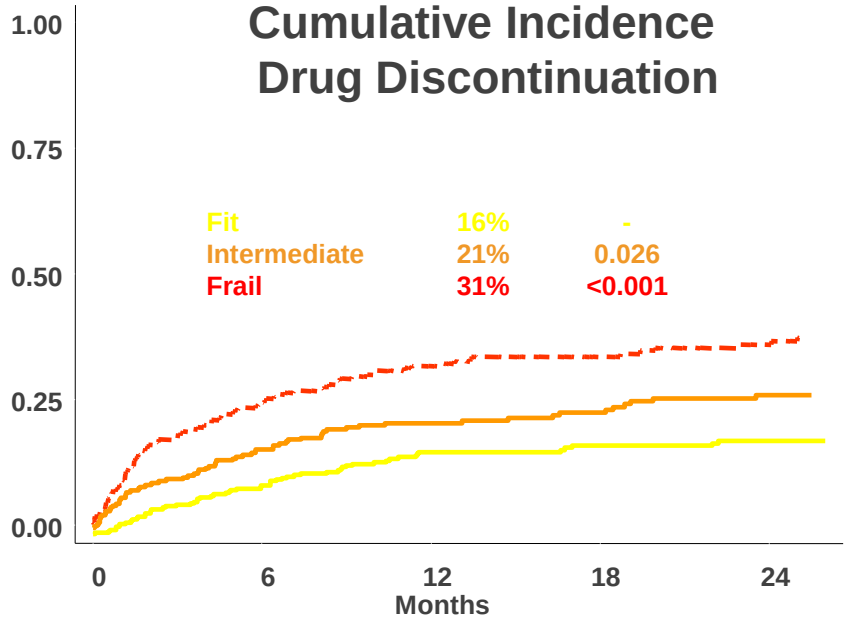
	3-drug	2-drug
Discontinuation %		
65 - 75 years	17	10
> 75 years	34	16
Cumulative dose intensity %		
65 - 75 years	88	97
> 75 years	56	97

MM Frailty Score: long-term outcome









Palumbo A et al, Blood 25(13):2068-74, 2015

MM Frailty Score

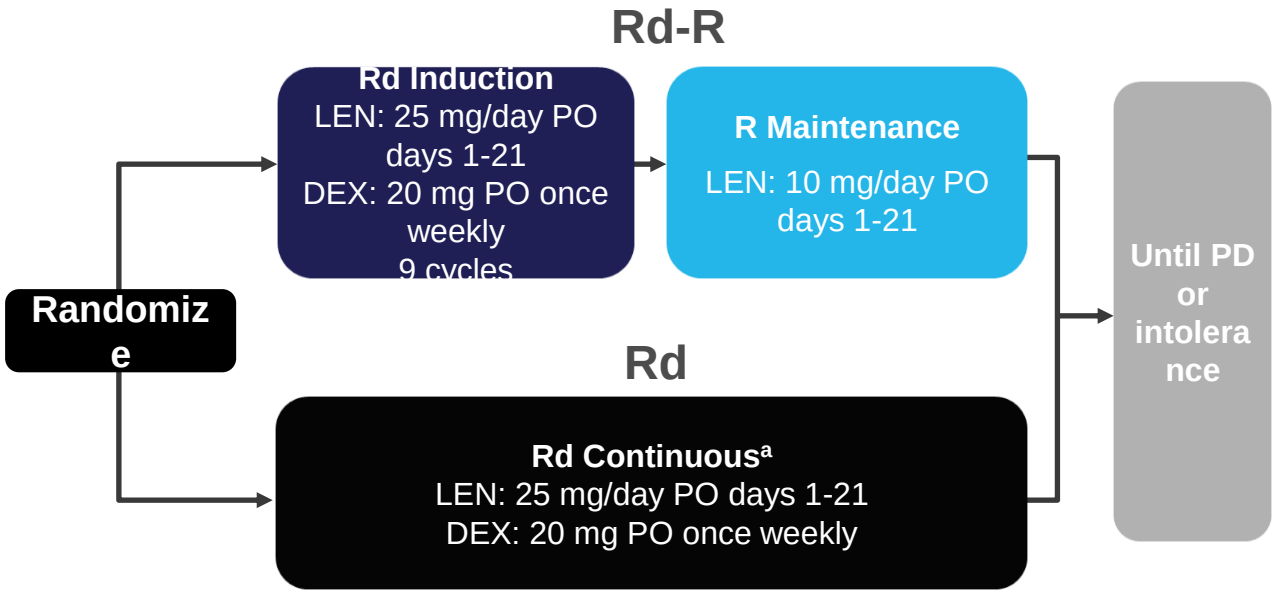
Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.13 (0.76-1.69)	0.549	1
	Age >80 years	2.40 (1.56-3.71)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.37 (0.92-2.05)	0.125	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.67 (1.08-2.56)	0.02	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.43 (0.96-2.14)	0.078	1

ADDITIVE TOTAL SCORE	PATIENT STATUS	%
0	**FIT**	**39%**
1	**INTERMEDIATE**	**31%**
≥2	**FRAIL**	**30%**

Efficacy and Feasibility of Dose/Schedule-Adjusted Rd-R Vs Continuous Rd in Elderly and Intermediate-Fit Newly Diagnosed Multiple Myeloma (NDMM) Patients: RV-MM-PI-0752 Phase 3 Randomized Study

Alessandra Larocca,[1] Marco Salvini,[1] Lorenzo De Paoli,[1] Nicola Cascavilla,[1] Giulia Benevolo,[1] Monica Galli,[1] Vittorio Montefusco,[1] Tommaso Caravita di Toritto,[1] Anna Baraldi,[1] Stefano Spada,[1] Nicola Giuliani,[1] Chiara Pautasso,[1] Stefano Pulini,[1] Sonia Ronconi,[1] Norbert Pescosta,[1] Anna Marina Liberati,[1] Francesca Patriarca,[1] Claudia Cellini,[1] Patrizia Tosi,[1] Massimo Offidani,[1] Michele Cavo,[1] Antonio Palumbo,[2] Mario Boccadoro,[1] Sara Bringhen[1]
on behalf of co-investigators

Study design[1]



- N=199 intermediate-fit patients
- **Primary endpoint:**
  - EFS
    - Hematologic grade 4 AEs
    - Non-hematologic grade 3/4 AEs, including SPMs
    - LEN therapy discontinuation
    - PD
    - Death due to any cause
- **Secondary endpoints:**
  - PFS
  - OS
  - Response rate
  - Incidence of dose reduction and discontinuation

[a] Dose and schedule adopted in the FIRST trial in patients > 75 years[2].

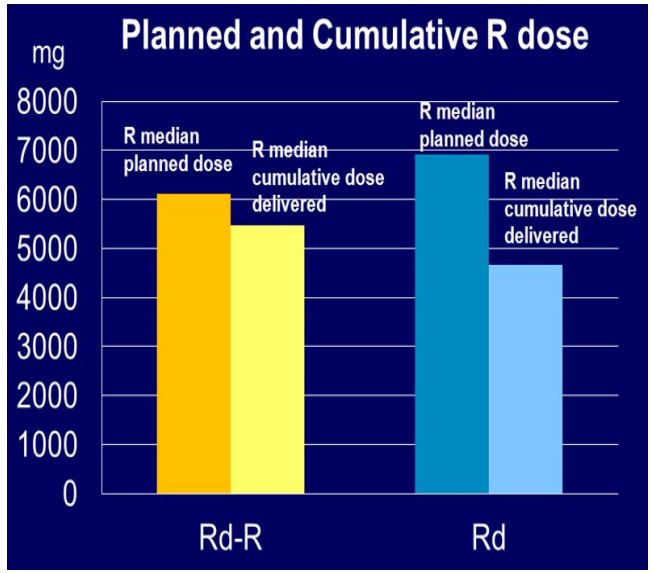
1. Larocca A, et al. ASH 2018 [abstract 1305]. 2. Hulin C, et al. *J Clin Oncol.* 2016;34:3609-3617

Adverse Events and dose modifications

Grade ≥ 3 Toxicity, %	Rd-R	Rd
Neutropenia	17	14
Thrombocytopenia	2	2
≥ 1 non-hematologic toxicity	31	39
Central Nervous	0	6
Diarrhea	2	2
Infections	9	11
Dermatologic	3	7
Cardiac	1	2
Vascular	2	3
SPM	2	1
G-CSF	17	15
LEN discontinuation due to AEs[a]	19	23
LEN dose reduction due to AEs[a]	33	43

Parameter, %	Rd-R	Rd
Patients with LEN dose reduction due to AEs	33	43
Patients with LEN first dose reduction after induction	14	21
LEN median relative dose intensity	100	90
P value[b]	.009	

?



[a] All grade [b] Kruskal Wallis test.

AUTHORs Conclusions

	Rd-R	Rd	Rd FIRST >75 Years
Age > 75 years	48%	57%	35%
EFS *(toxicity, discontinuation, PD, death)*	9.3 months	6.6 months	NA
At least 1 non-hematologic grade ≥3 tox	**31%**	**39%**	**NA**
R discontinuation	**19%**	**23%**	**26%**
R dose reduction	**33%**	**43%**	**44%**
R dose reduction after induction	**14%**	**21%**	**NA**
R Median Relative Dose Intensity	**100%**	**90%**	**NA**
20-month PFS	43%	42%	≈50%
20-month OS	84%	79%	≈80%

Comparable Efficacy Rd = Rd-R

Improved Tolerance/Feasibility Rd-R > Rd

Hulin C, et al JCO 2016. Benboubker L et al N Engl J Med 2014.

La prise en charge des patients non éligibles à la greffe :

D'où part-on ?

PI-based

VMP

VISTA trial

PFS: 21 months

OS: 56 months

San Miguel. J Clin Oncol. 2013; 31: 448-55

IMiD-based

Len-dex (Rd)

FIRST trial

PFS: 26 months

OS: 59 months

Benboubker L, et al. NEJM 2014; 371: 906-17

IMiD + PI

VRd/ VRd lite

SWOG S0777 : mFS 43 months, mOS 75

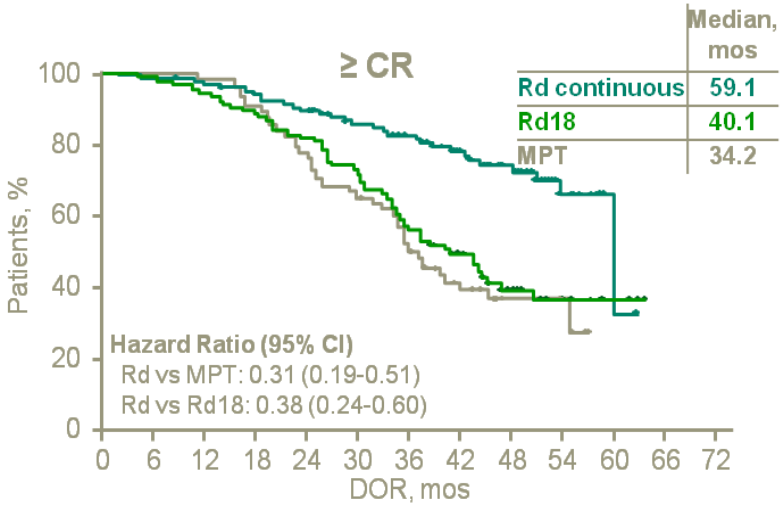
VRd Lite : mPFS: 35 months,

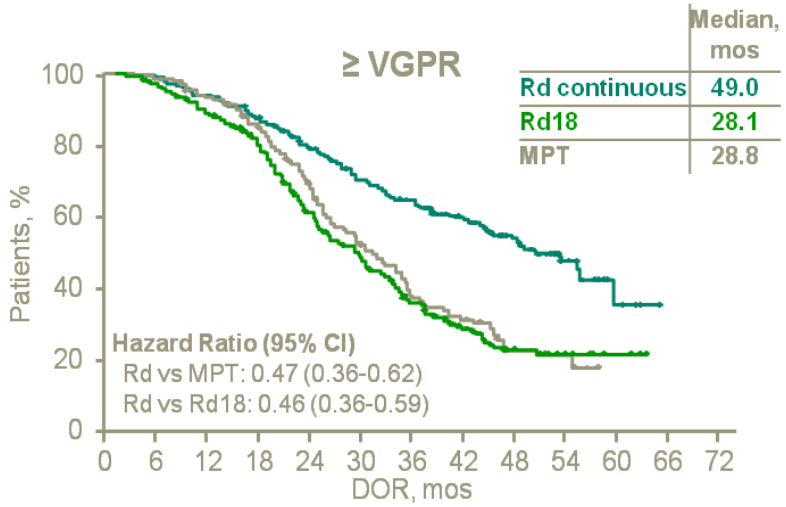
OS: 65 months

Durie B. Lancet 2017

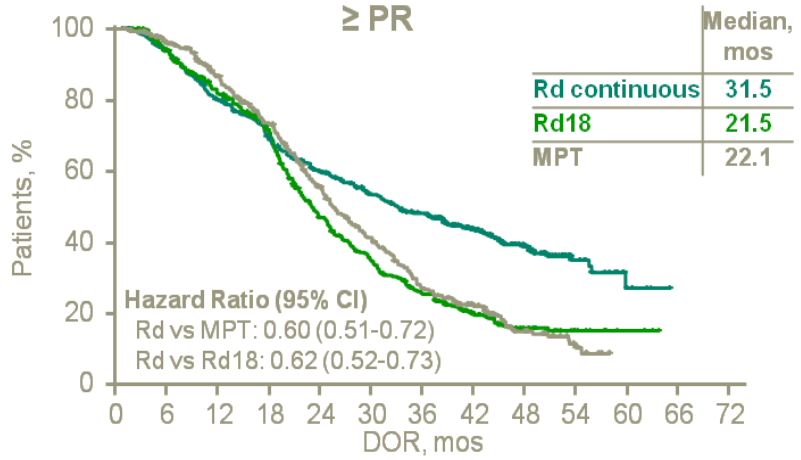
O'Donnell E. Br J Haematol 2018

Rd (FIRST): Impact of depth of response on duration of response





Doublets …



Median DOR was prolonged with Rd continuous vs Rd18 or MPT

CR, complete response; DOR, duration of response; MPT, melphalan-prednisone-thalidomide; PR, partial response; Rd, lenalidomide and low-dose dexamethasone; Rd18, Rd for 18 cycles; VGPR, very good partial response.

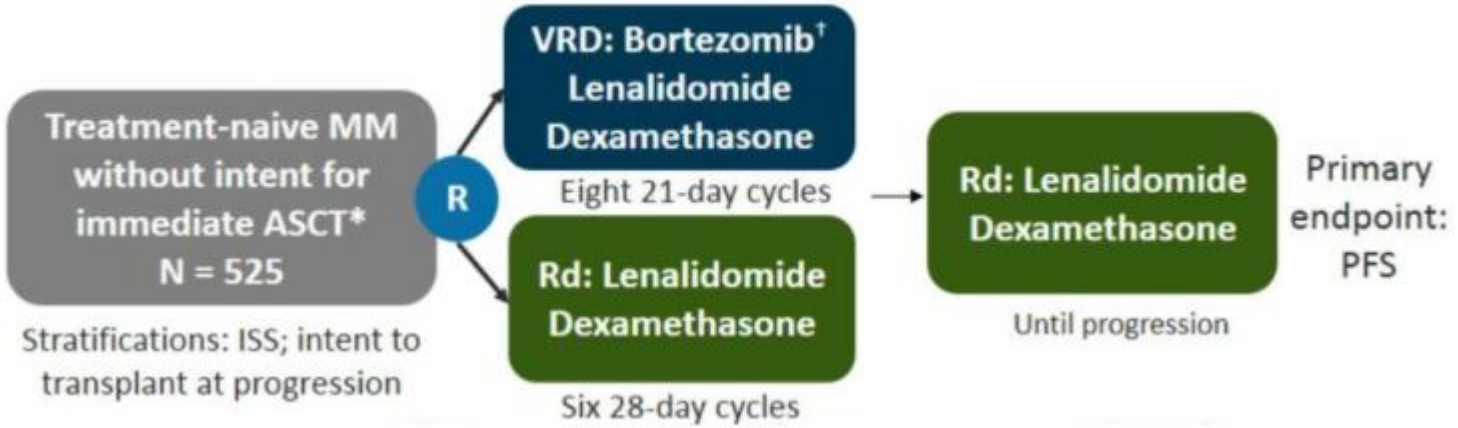
Bahlis N et al. Presented at EHA 2015

La meilleure efficacité : VRD, DRD ou LES DEUX ?

VRd : SWOG S0777 trial

Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial

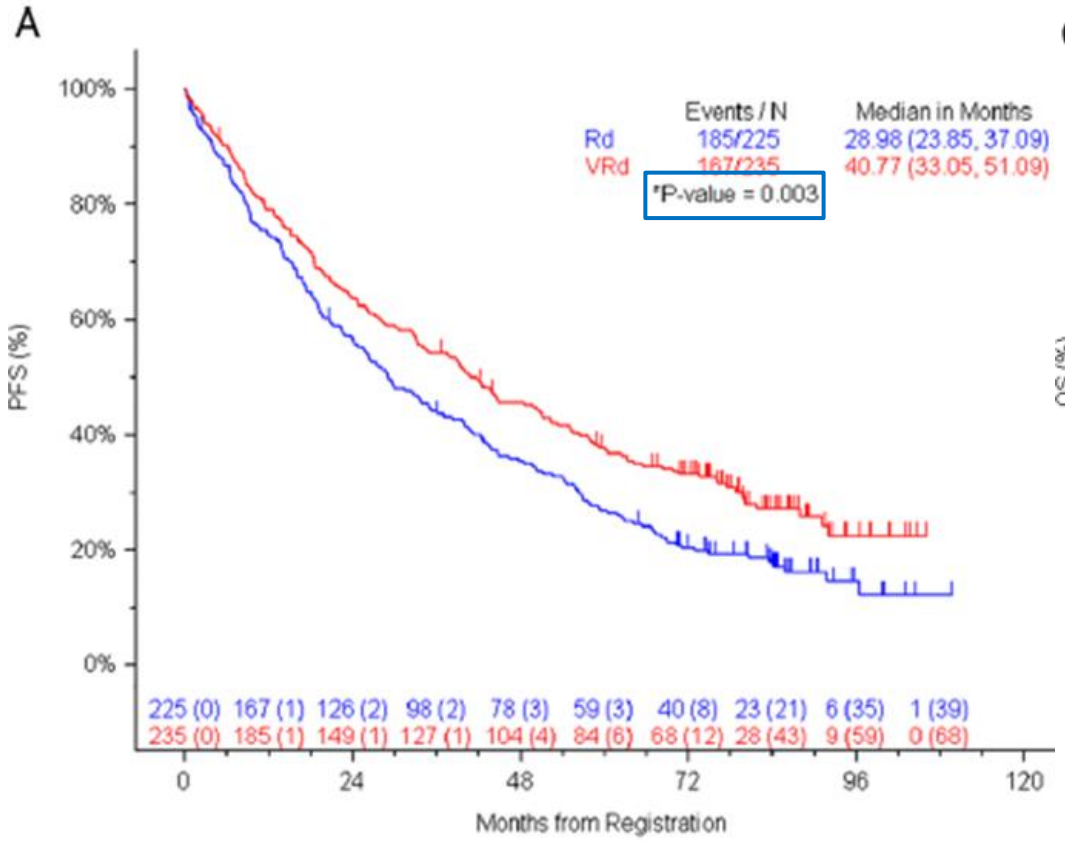
Brian G M Durie, Antje Hoering, Muneer H Abidi, S Vincent Rajkumar, Joshua Epstein, Stephen P Kahanic, Mohan Thakuri, Frederic Reu, Christopher M Reynolds, Rachael Sexton, Robert Z Orlowski, Bart Barlogie, Angela Dispenzieri

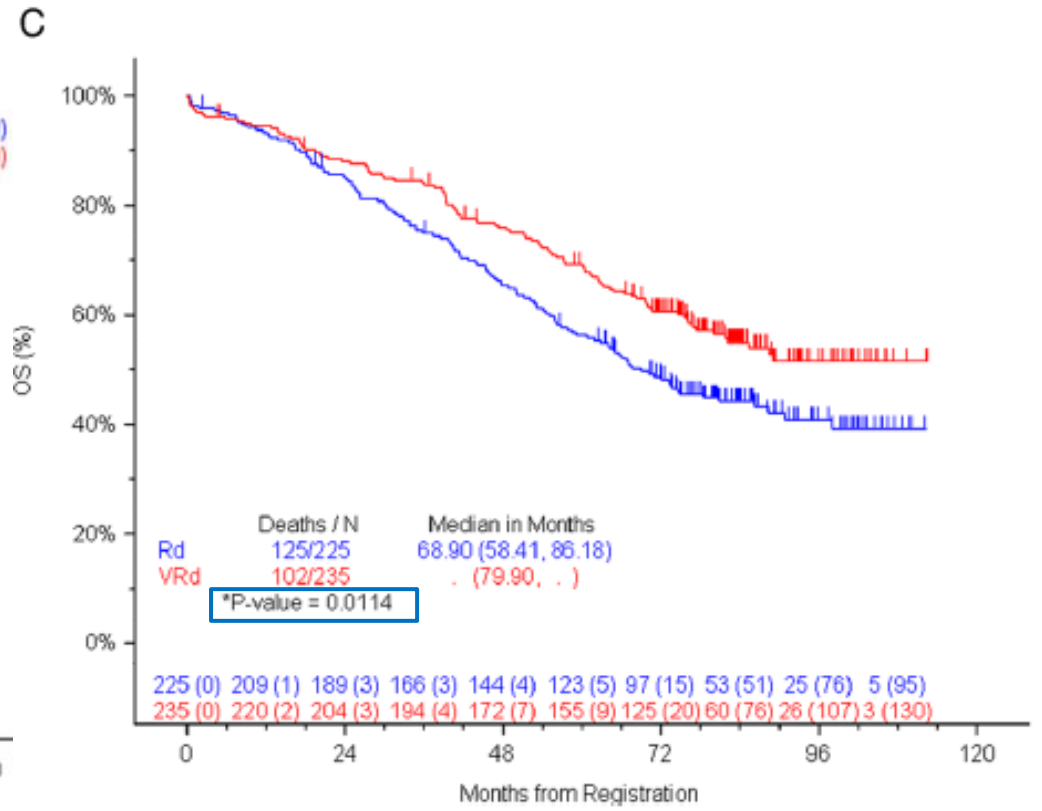


Durie et al, Lancet, 2017
Durie et al, Blood Cancer Journal, 2020

La meilleure efficacité : VRd, DRd ou les deux ?

VRd : SWOG S0777 trial





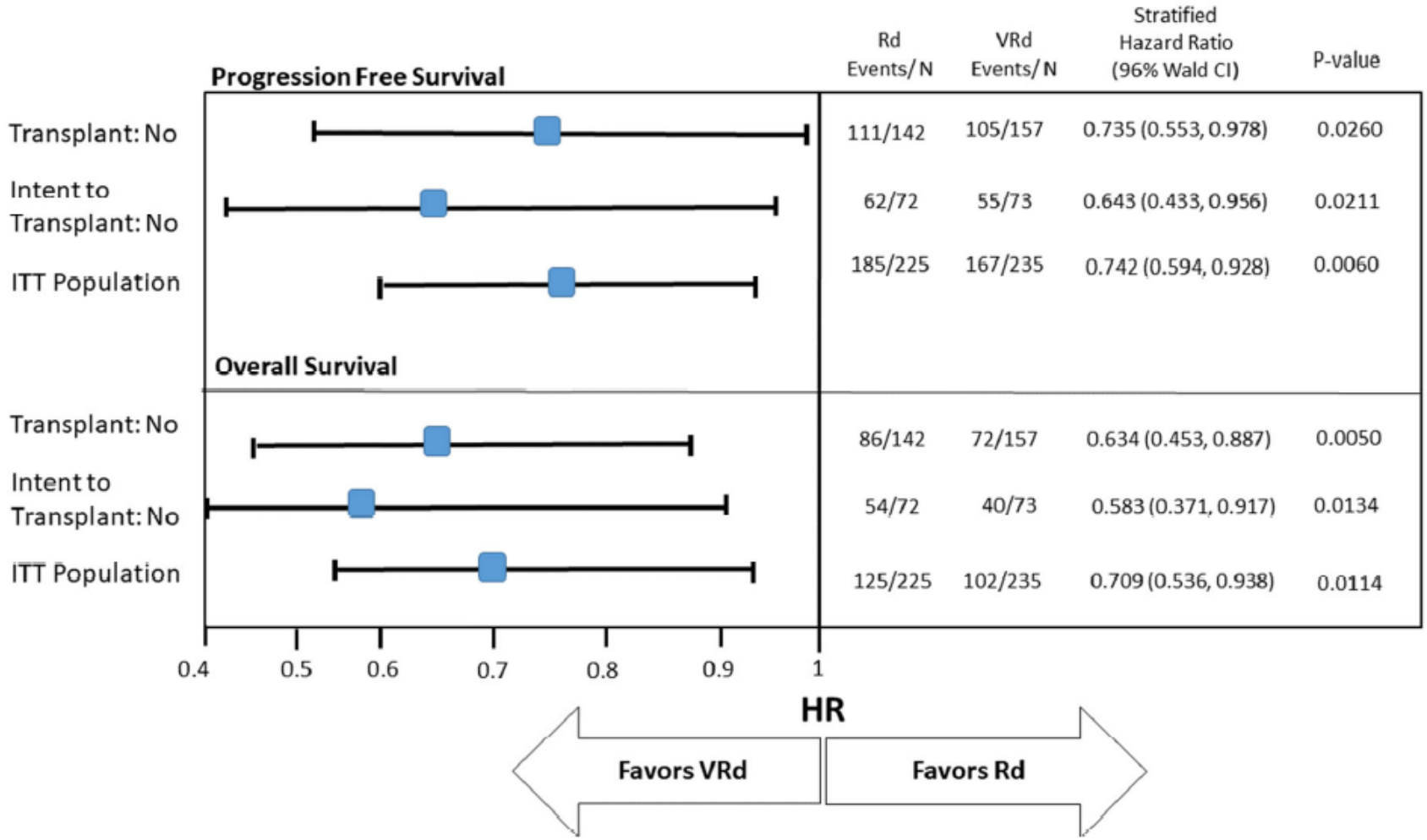
✓ **PFS : 29 mois vs 41 mois, p=0.003**

✓ **Bénéfice également en OS !**

Durie et al, Lancet, 2017
Durie et al, Blood Cancer Journal, 2020

La meilleure efficacité : VRD, DRD ou LES DEUX ?

VRd : SWOG S0777 trial



	Rd Events/N	VRd Events/N	Stratified Hazard Ratio (96% Wald CI)	P-value
Progression Free Survival				
Transplant: No	111/142	105/157	0.735 (0.553, 0.978)	0.0260
Intent to Transplant: No	62/72	55/73	0.643 (0.433, 0.956)	0.0211
ITT Population	185/225	167/235	0.742 (0.594, 0.928)	0.0060
Overall Survival				
Transplant: No	86/142	72/157	0.634 (0.453, 0.887)	0.0050
Intent to Transplant: No	54/72	40/73	0.583 (0.371, 0.917)	0.0134
ITT Population	125/225	102/235	0.709 (0.536, 0.938)	0.0114

Durie et al, Lancet, 2017
Durie et al, Blood Cancer Journal, 2020

La meilleure efficacité : VRD, DRD ou LES DEUX ?

VRd lite :

A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma

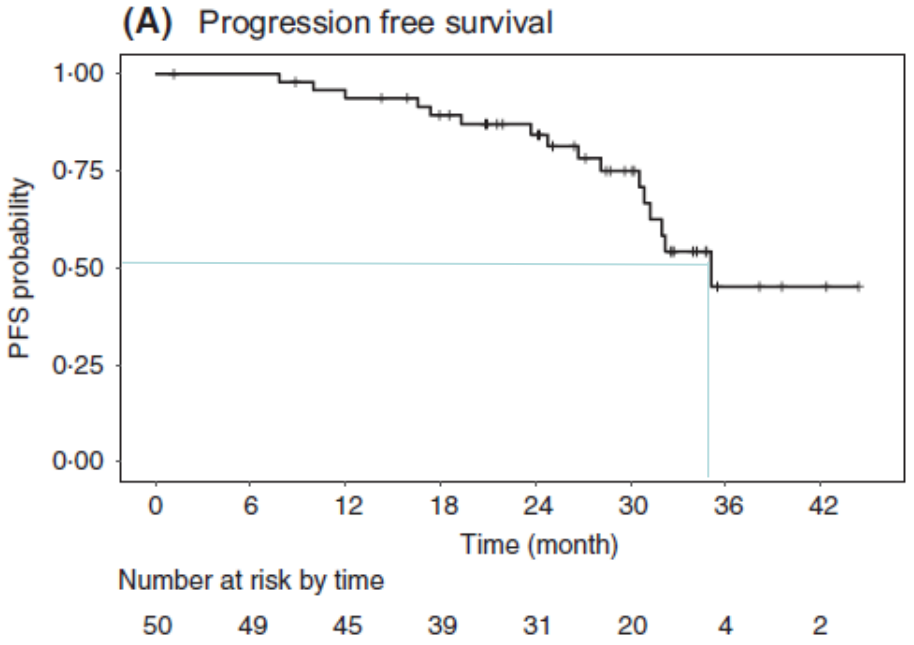
Induction (cycles 1–9)
Repeat q35 days × 9 cycles

Lenalidomide 15 mg po days 1–21
Bortezomib 1·3 mg/m² sc* days 1, 8, 15, 22
Dexamethasone 20 mg po days 1, 2, 8, 9, 15, 16, 22, 23 (patients ≤75 years)
Dexamethasone 20 mg po days 1, 8, 15, 22 (patients >75 years)

↓

Consolidation (cycles 10–15)
Repeat q28 days × 6 cycles

Lenalidomide 15 mg po days 1–21 (or last tolerated dose as of cycle 9)
Bortezomib 1·3 mg/m² sc on days 1, 15 (or last tolerated dose as of cycle 9)



- ✓ 50 patients
- ✓ Âge médian=73 ans
- ✓ 14% ECOG=2
- ✓ 12% de haut risque cytogénétique

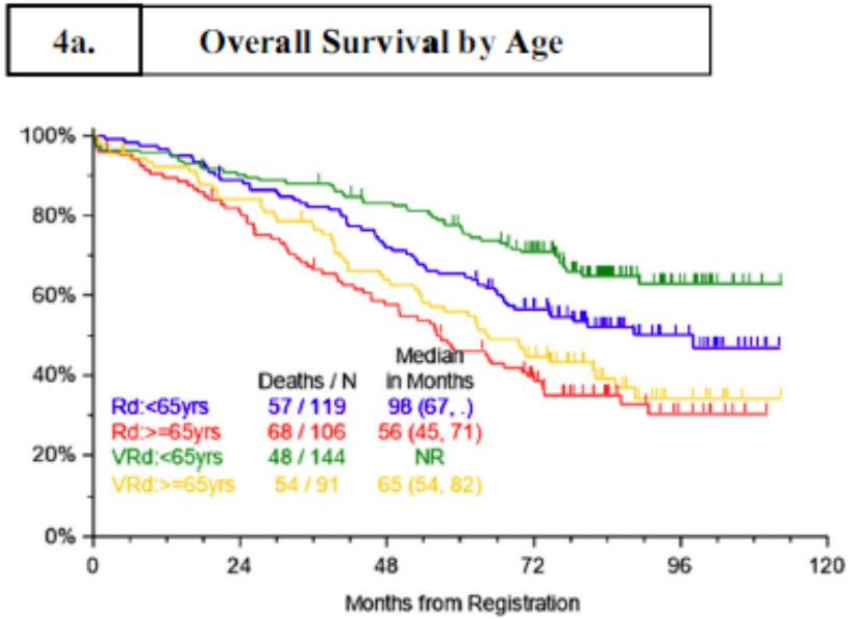
O'Donnell et al, BJH, 2018

Sous-groupe patients ≥ 75ans / fragiles :

VRd, DRd ou LES DEUX ?

VRd SWOG S0777 :

- ✓ Age médian 63 ans avec seulement 43% ≥ 65 ans
- ✓ 14% de patients ECOG>1



Cohorte EMMY :

- ✓ Augmentation prescription VRd
- ✓ Avantage modeste VRd patients ≤ 75 ans

Age < 65 years: HR= 0.640 (0.421,0.973);
stratified, two-sided p= 0.028
Age ≥ 65 years: HR= 0.769 (0.520,1.138);
stratified, two-sided p= 0.168

Durie et al, Lancet, 2017 *Facon et al, NEJM, 2019* *SFH 2021*
Durie et al, Blood Cancer J, 2020 *Stege et al, Blood, 2019*

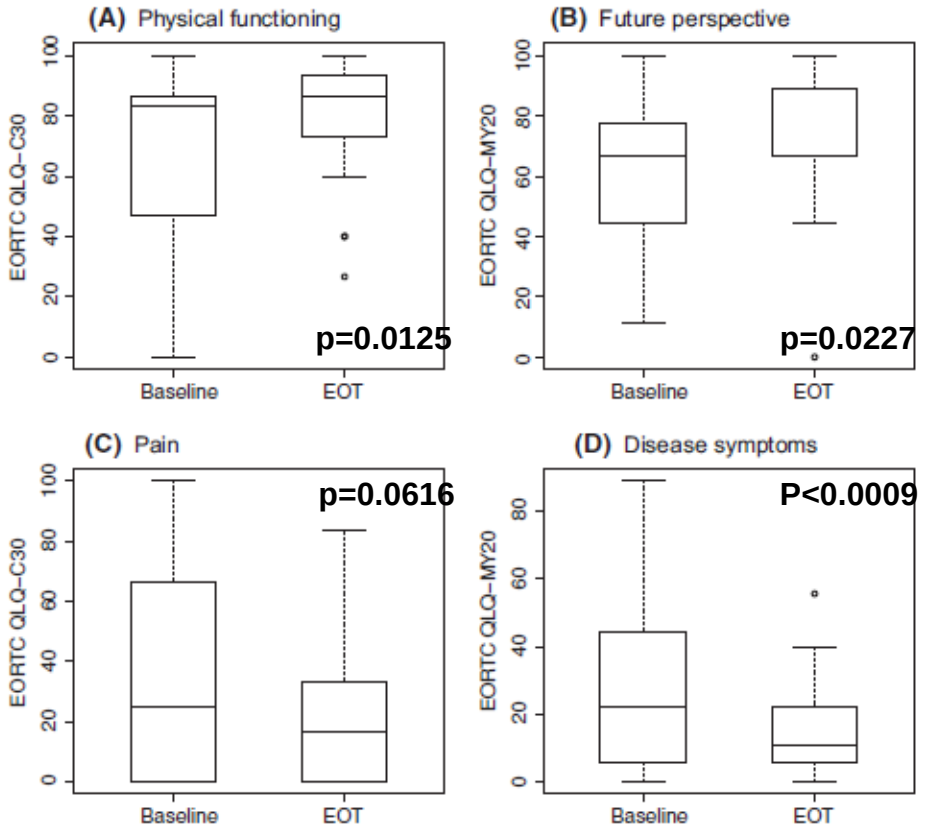
La meilleure qualité de vie : VRD, DRD ou LES DEUX ?

VRd lite :

- ✓ Amélioration QoL au cours du traitement : capacité physique, santé globale, douleur, symptômes liés à la maladie
- ✓ Schéma simple, pas de perfusion IV
- ✓ Durée fixe

MAIS :

- ✓ Effets secondaires : neuropathie
- ✓ HAD ou HDJ pour SC 2 fois/semaine, 2se
- ✓ Rd jusqu'à progression dans le SWOG S(



O'Donnell et al, BJH, 2018

La meilleure tolérance : VRd, DRd ou les deux ?

VRd : SWOG S0777 trial

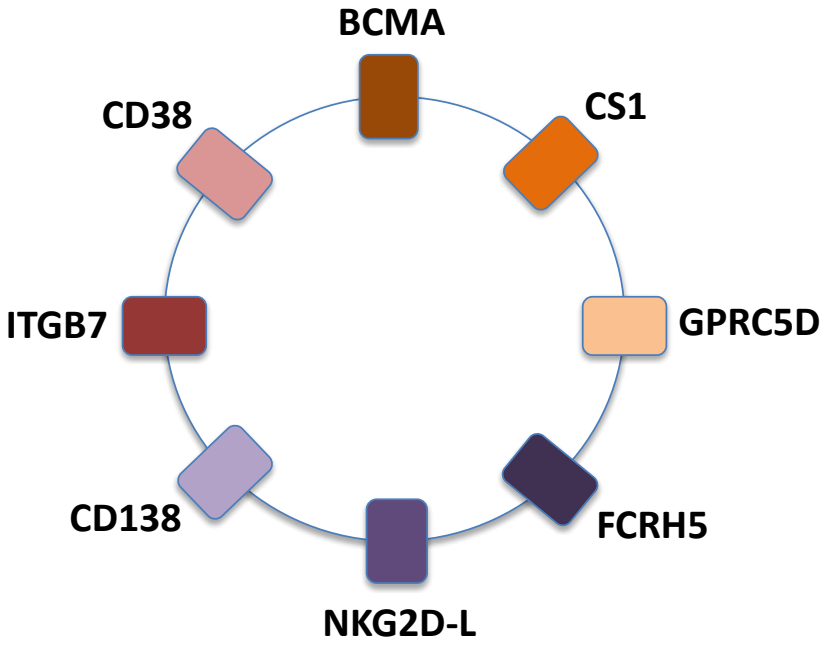
Table 5 Adverse events at least possibly attributable to study drug by category.

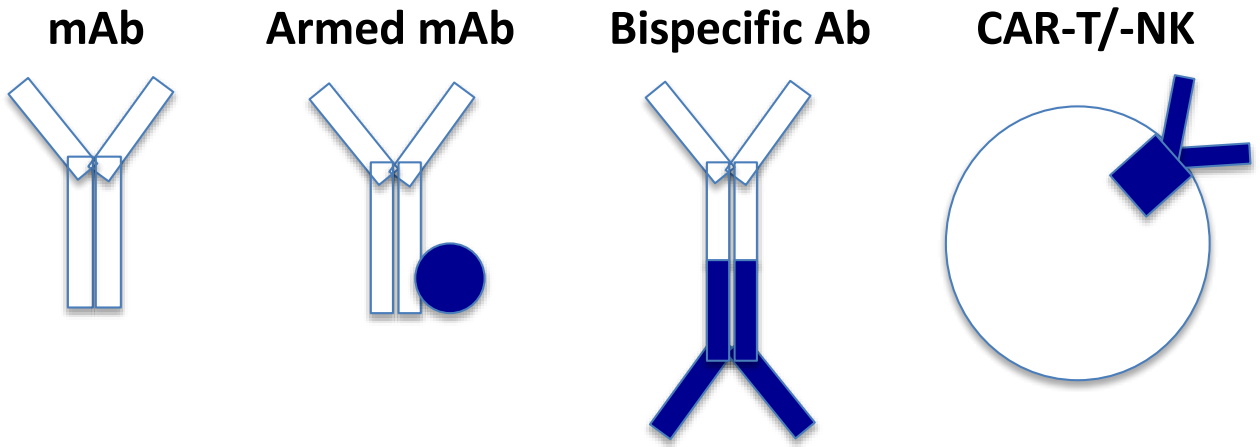
Adverse event description	Revlimid/dexamethasone (*N* = 222)					Velcade/Revlimid/dexamethasone (*N* = 234)				
	1	2	3	4	5	1	2	3	4	5
Blood/bone marrow	22 (10%)	53 (24%)	68 (31%)	39 (18%)		27 (12%)	52 (22%)	70 (30%)	44 (19%)	
Infection	1 (<1%)	31 (14%)	27 (12%)	4 (2%)		1 (<1%)	33 (14%)	34 (15%)	7 (3%)	1 (<1%)
Gastrointestinal	77 (35%)	71 (32%)	19 (9%)			64 (27%)	79 (34%)	51 (22%)	2 (<1%)	1 (<1%)
Neurology	78 (35%)	44 (20%)	21 (9%)	3 (1%)	1 (<1%)	42 (18%)	70 (30%)	77 (33%)	4 (2%)	
Secondary malignancy			5 (2%)	1 (<1%)				5 (2%)	2 (<1%)	

- ✓ Cytopénies
- ✓ Infections
- ✓ Symptômes digestifs
- ✓ Toxicité neurologique ++ (mais IV)
- ✓ Même taux de cancers secondaires

Durie et al, Lancet, 2017
Durie et al, Blood Cancer Journal, 2020

Immunotherapies in MM





- **CAR-T cells:** Ide-cel, Cilta-cel*, Orva-cel*, bb21217*
- **BsAb*:** Teclistamab, CC93269, AMG701, REGN5428, PF-3135, Talquetamab, BCFR4350A
- **ADC:** Belantamab mafodotin, MEDI2228*

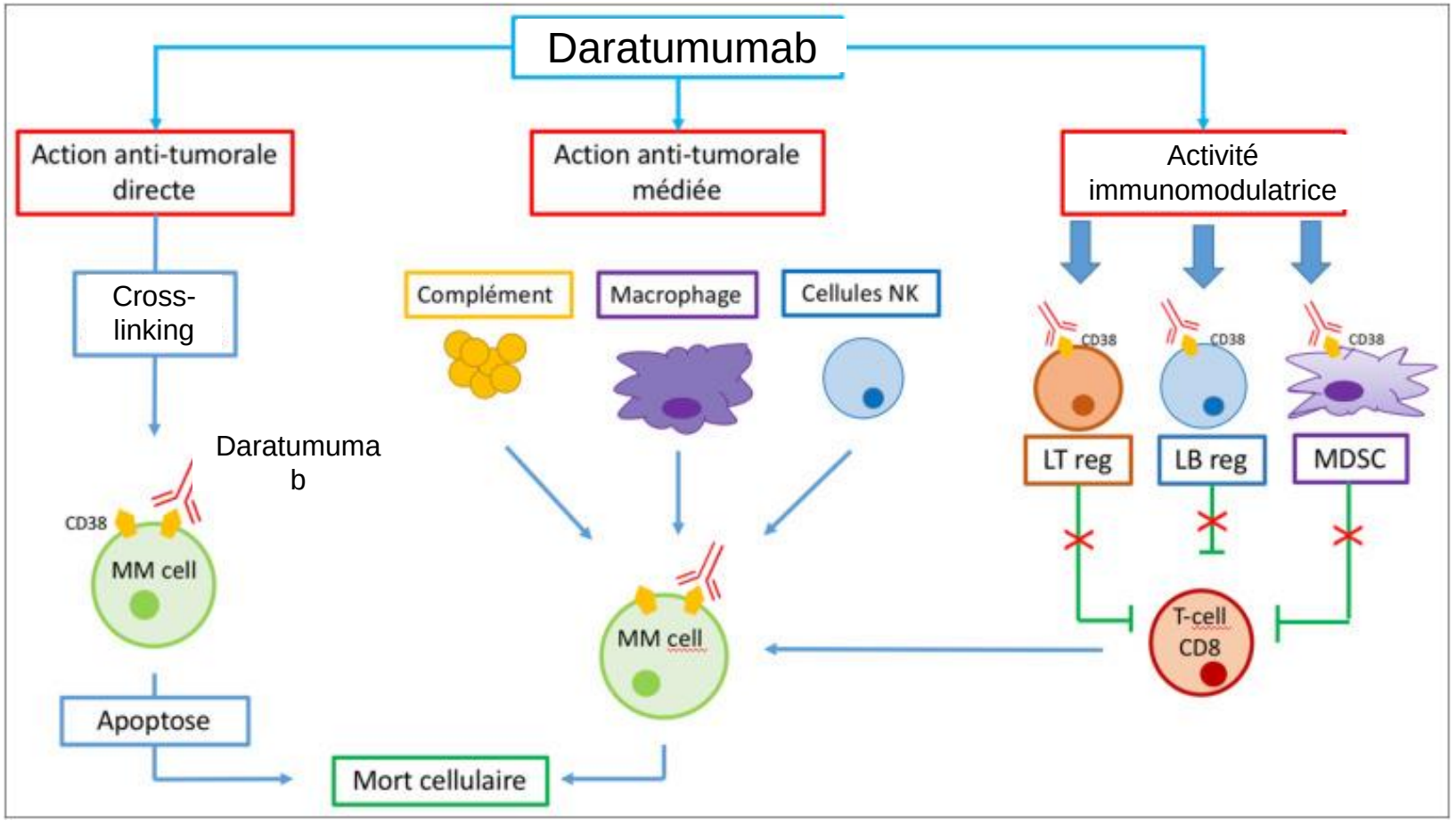
US FDA has approved ide-cel for the treatment of multiple myeloma. Ide-cel is not approved by EMA in Europe; FDA and EMA has approved belantamab mafodotin for the treatment of multiple myeloma.
* not approved by any regulatory agency;.
ADC: antibody-drug conjugate; BsAb: Bispecific antibody

Personal communication

Mécanisme d'action le plus prometteur :

VRD, DRD ou LES DEUX ?

DRd !



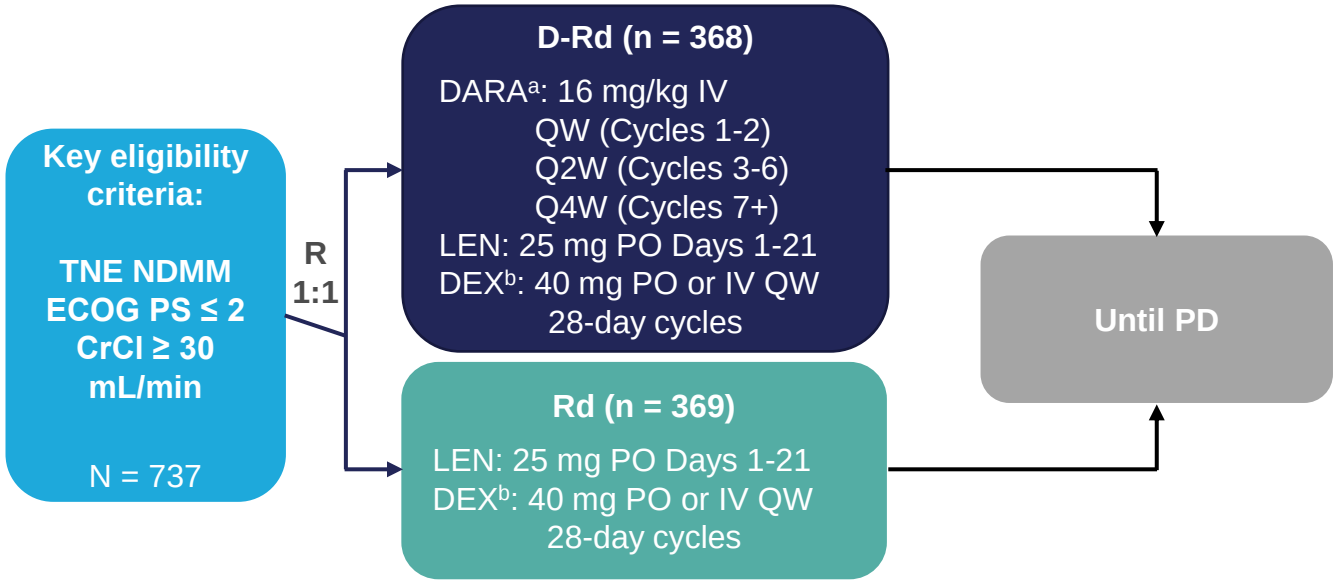
Croizier et al, Elsevier, 2018
Romano et al, Future Medicine, 2017

Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone Versus Lenalidomide and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma Ineligible for Transplant (MAIA)

Thierry Facon[1], Shaji Kumar[2], Torben Plesner[3], Robert Z. Orlowski[4], Philippe Moreau[5], Nizar Bahlis[6], Supratik Basu[7], Hareth Nahi[8], Cyrille Hulin[9], Hang Quach[10], Hartmut Goldschmidt[11], Michael O'Dwyer[12], Aurore Perrot[13], Christopher P Venner[14], Katja Weisel[15], Joseph R Mace[16], Tahamtan Ahmadi[17], Christopher Chiu[18], Jianping Wang[19], Rian Van Rampelbergh[20], Clarissa M Uhlar[18], Rachel Kobos[19], Ming Qi[18], and Saad Z Usmani[21]

[1]Service des Maladies du Sang, Hôpital Claude Huriez, Lille, France; [2]Department of Hematology, Mayo Clinic, Rochester, MN, USA; [3]Vejle Hospital and University of Southern Denmark, Vejle, Denmark; [4]Department of Lymphoma-Myeloma, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [5]Hematology, University Hospital Hôtel-Dieu, Nantes, France; [6]University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada; [7]Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, United Kingdom; [8]Karolinska Institute, Department of Medicine, Division of Hematology, Karolinska University Hospital at Huddinge, Stockholm, Sweden; [9]Department of Hematology, Hospital Haut Leveque, University Hospital, Pessac, France; [10]St. Vincent's Hospital, University of Melbourne, Melbourne, Australia; [11]University Hospital Heidelberg and National Center of Tumor Diseases (NCT), Heidelberg, Germany; [12]Dept. of Medicine/Haematology, NUI, Galway, Ireland; [13]Hematology Department, University Hospital, Vandoeuvre Les Nancy, France; [14]Division of Medical Oncology University of Alberta, Edmonton, AB, Canada; [15]Universitaetsklinikum Tuebingen der Eberhard-Karls-Universitaet, Abteilung fuer Innere Medizin II, Tuebingen, Germany; [16]Florida Cancer Specialists & Research Institute, St. Petersburg, FL, USA; [17]Genmab US, Inc., Princeton, NJ, USA; [18]Janssen Research & Development, LLC, Spring House, PA, USA; [19]Janssen Research & Development, Raritan, NJ, USA; [20]Janssen Research & Development, Beerse, Belgium; [21]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA

MAIA - Study design



- **Stratification:**
  - ISS stage (I vs II vs III)
  - Region (North America vs other)
  - Age (< 75 vs ≥ 75 years)
- **Clinical trial identifier:** NCT02252172

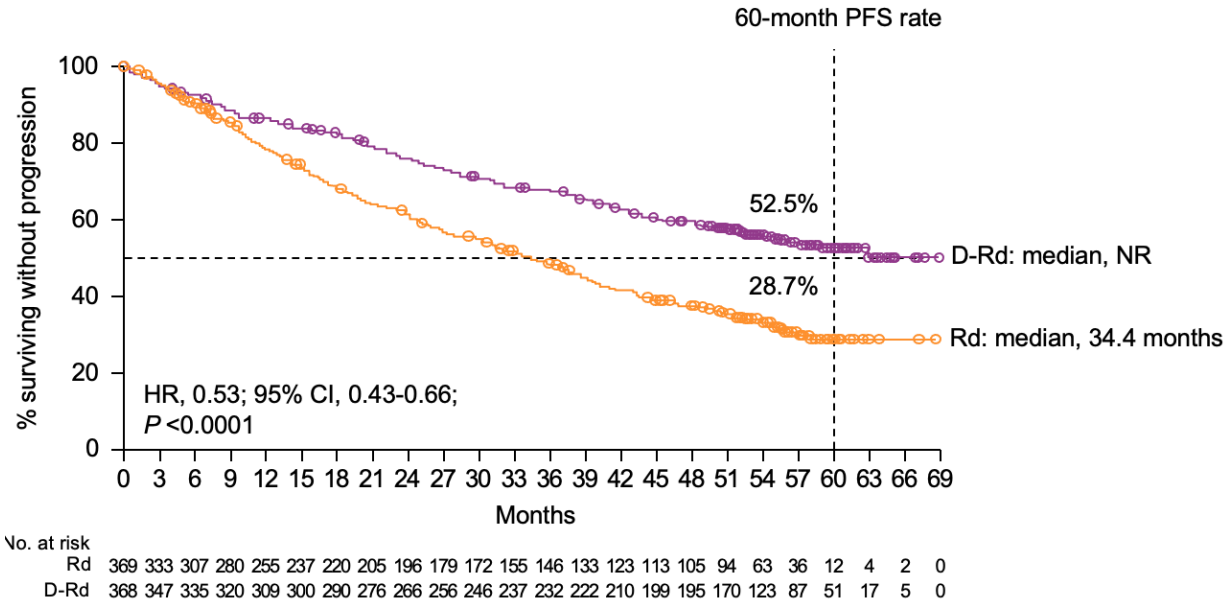
- **Primary endpoint:**
  - PFS
- **Key secondary endpoints[c]:**
  - ≥ CR rate
  - ≥ VGPR rate
  - MRD-negativity rate (NGS; 10^{-5})
  - ORR
  - OS
  - Safety

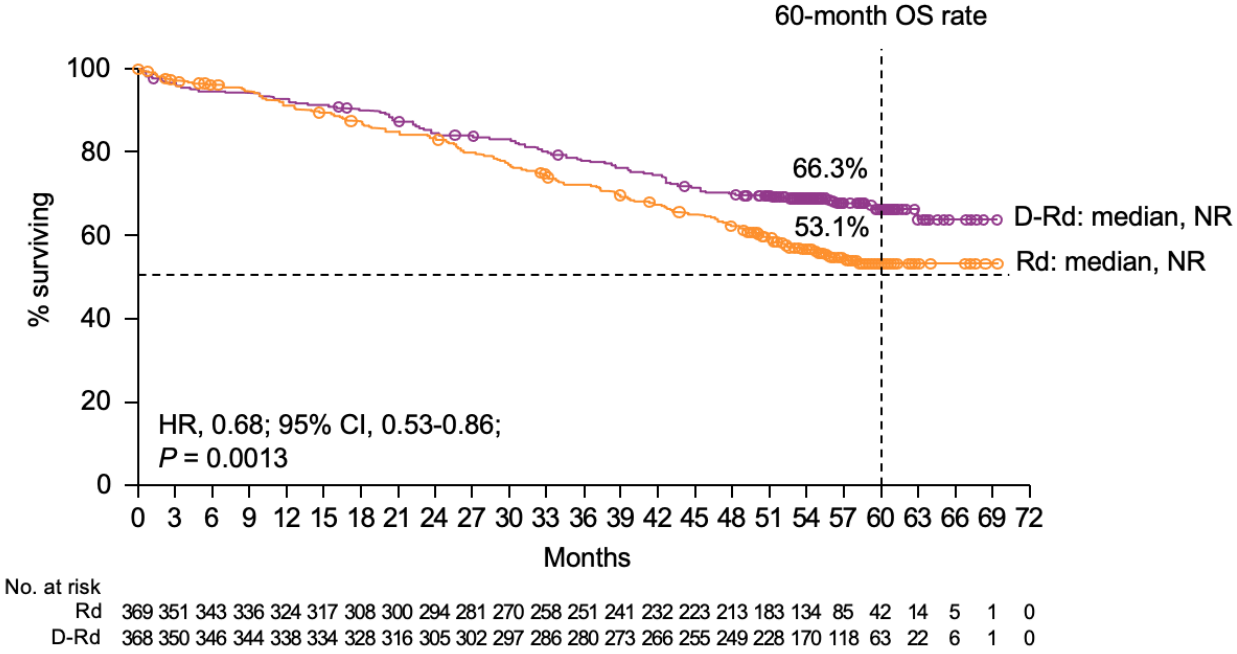
[a] On DARA days, DEX was administered as the treatment dose of steroid for that day and as the required pre-infusion modification. [b] DEX was administered at a 20 mg weekly dose in patients aged > 75 years or with a BMI < 18.5. [c] Efficacy endpoints were sequentially tested in the indicated order.

Facon T, et al. ASH 2018 [abstract LBA-2].

Approbation et remboursement D-Rd

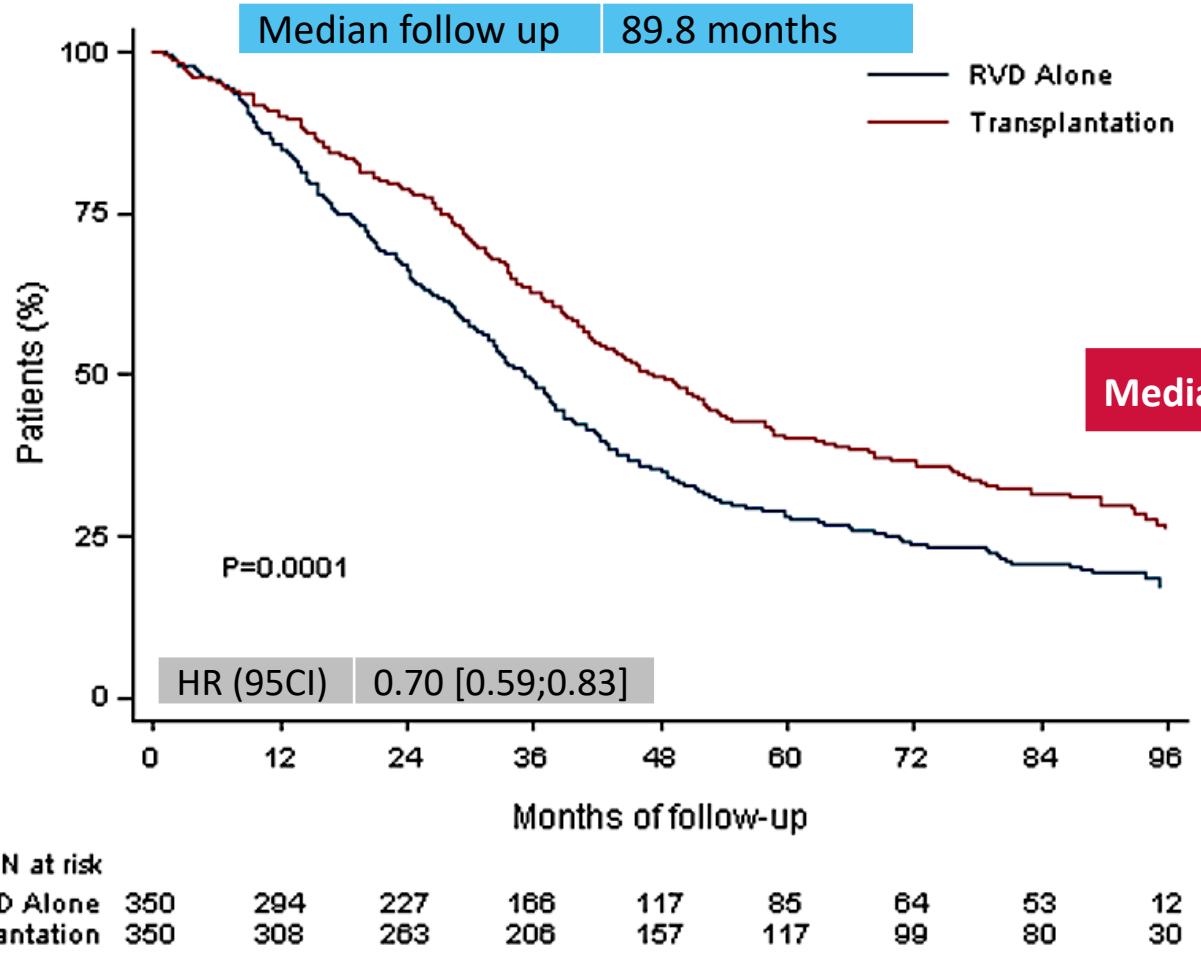
Réduction de 57 % du risque de progression et décès par rapport à Rd
Réduction de 32 % du risque de décès par rapport à Rd





T Facon et al, N Engl J Med 2019
T Facon et al, EHA LBA 2021

IFM 2009 : PFS actualisée



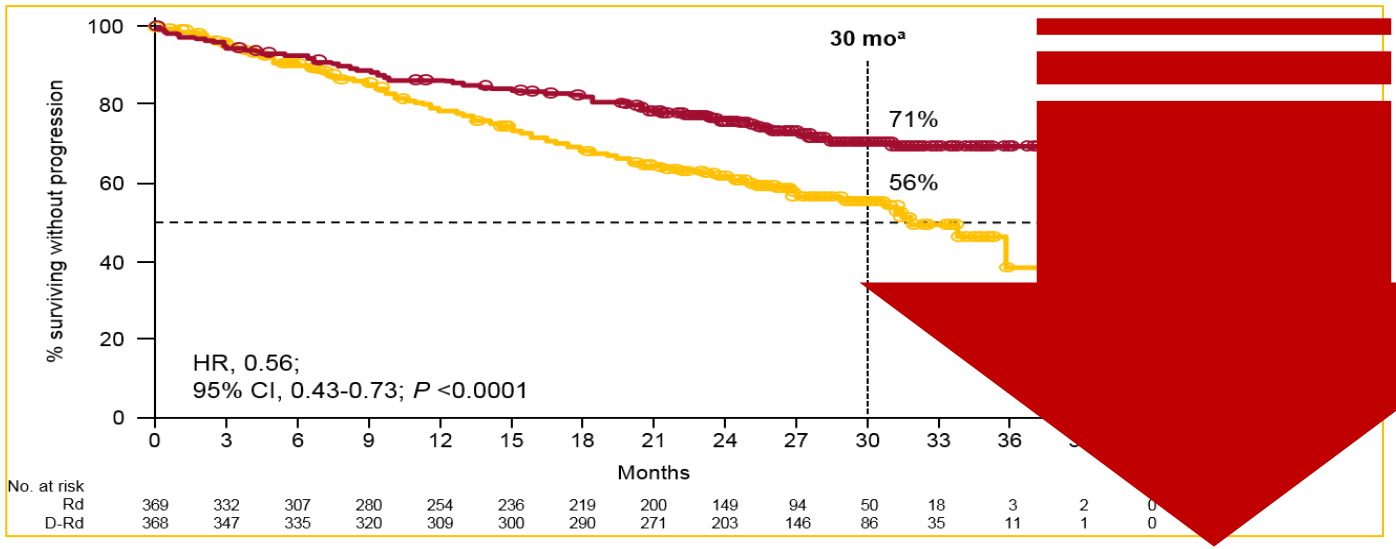
Median PFS 47.3 months (Transplantation, arm B)

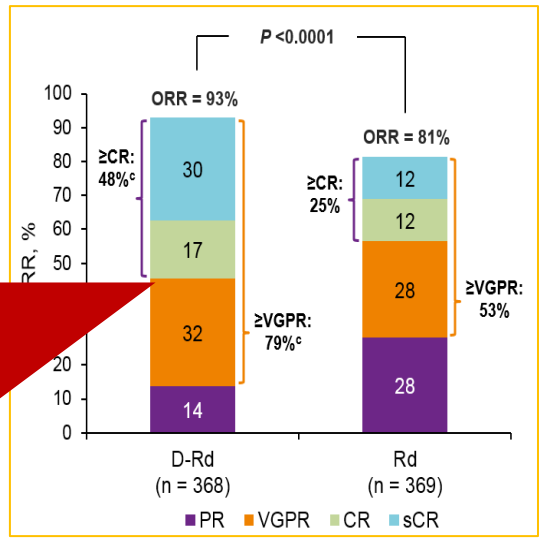
Median PFS 35 months (RVD alone, arm A)

30% reduction in the risk of progression or death in patients receiving transplant

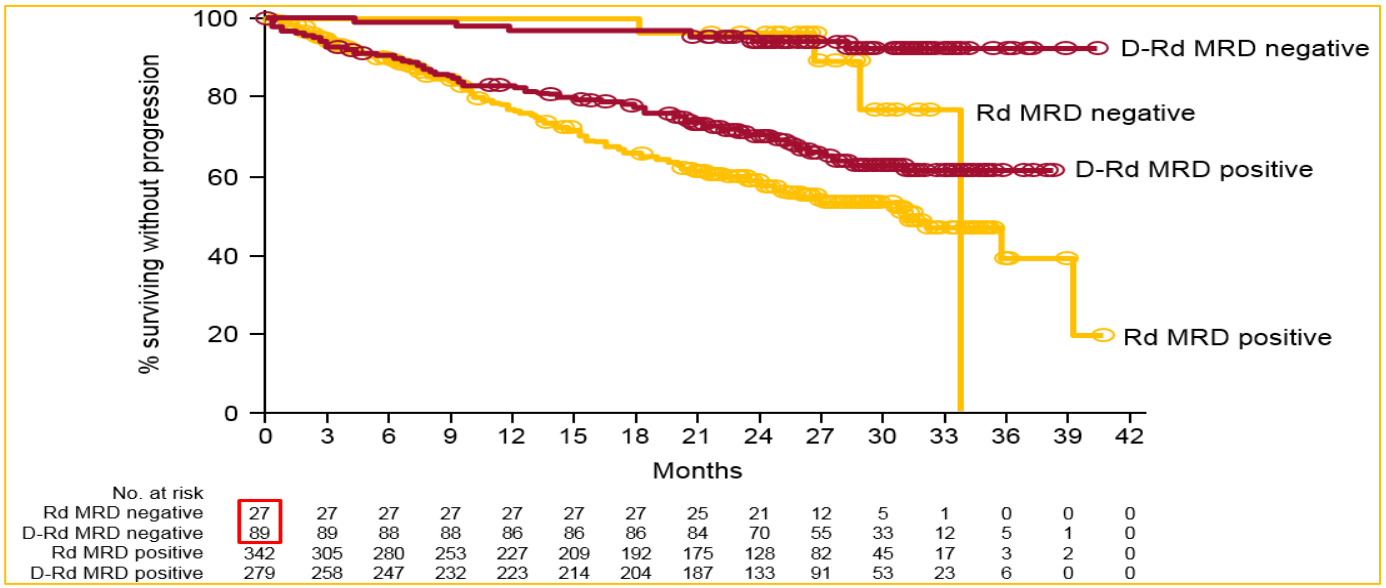
A Perrot et al, ASH 2020

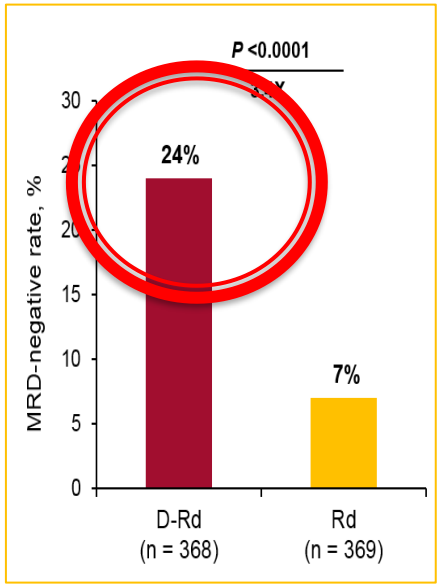
Efficacy: ORR and PFS





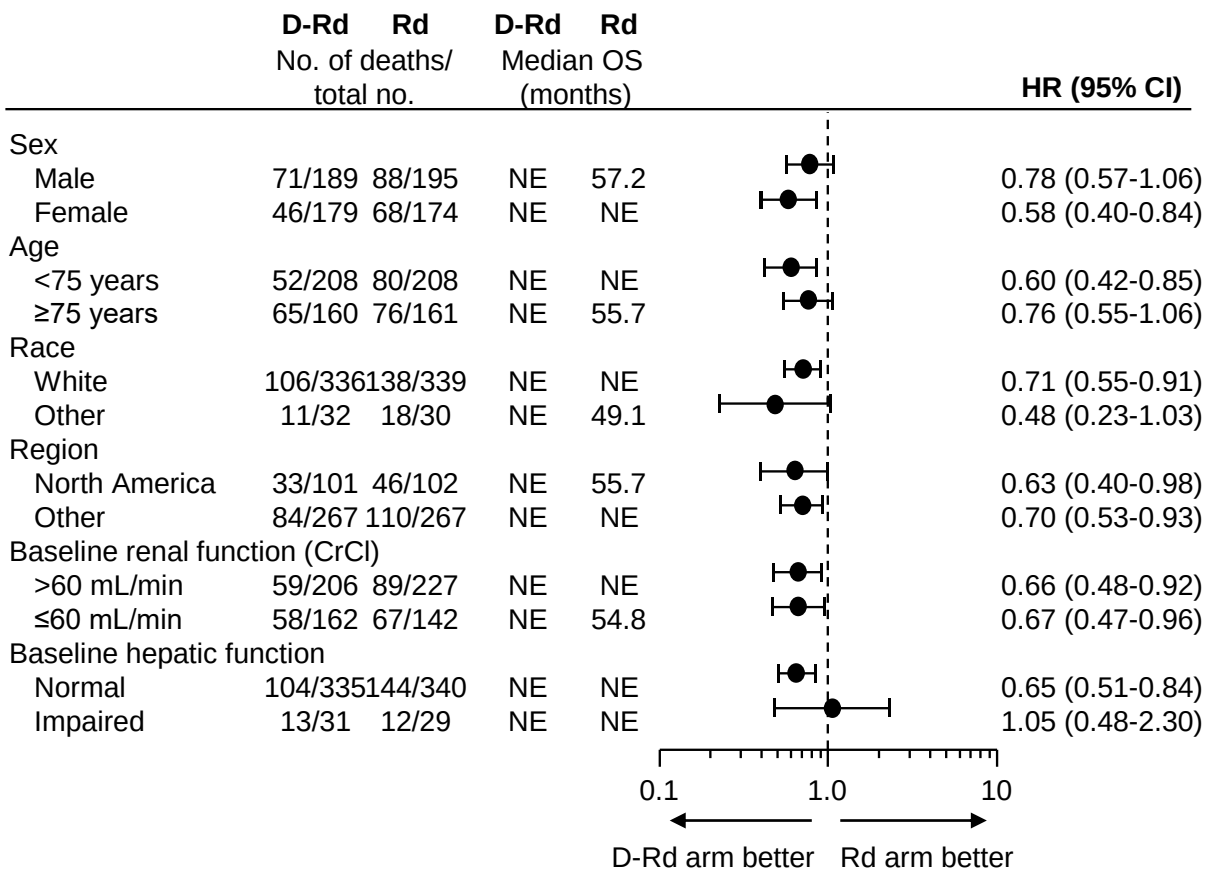
Median follow-up: 28 months (range: 0.0-41.4)

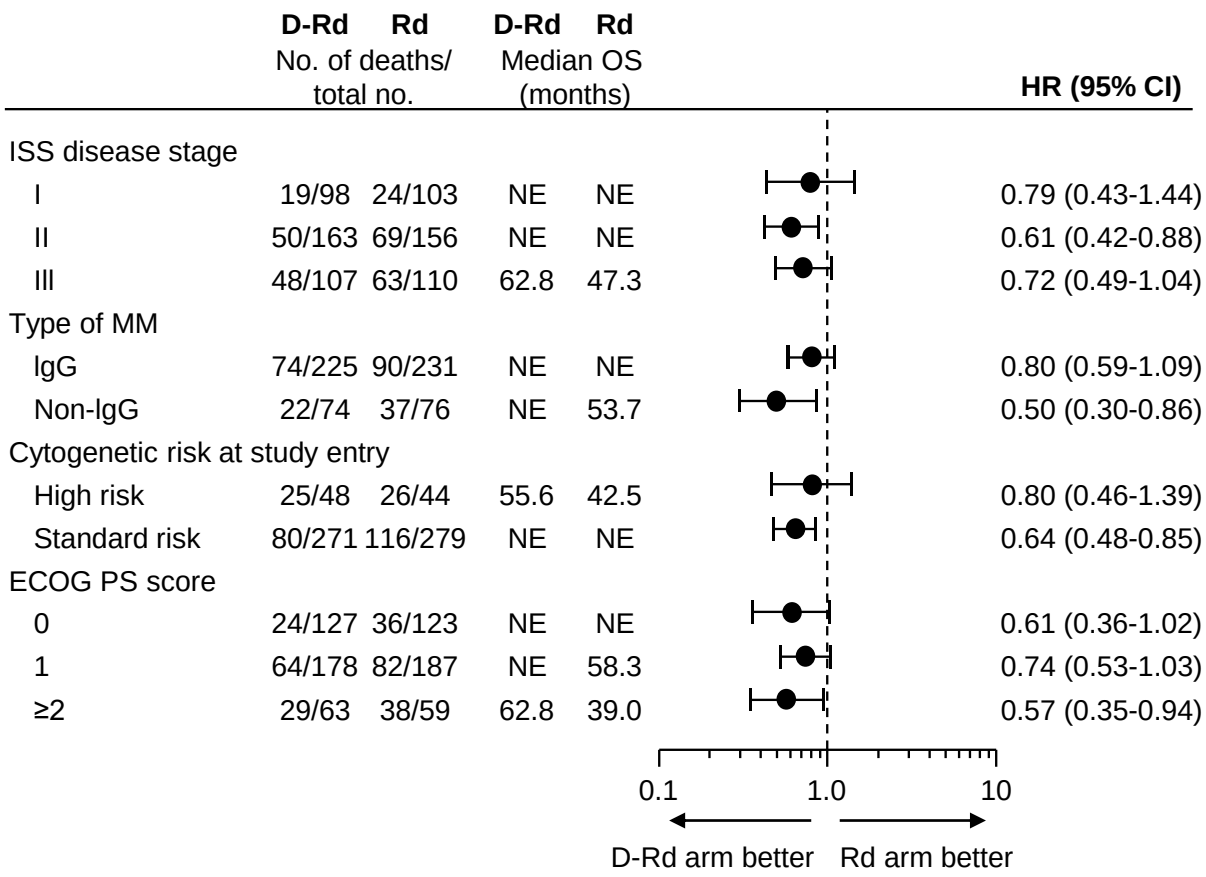




Facon T, et al. ASH 2018 [abstract LBA-2].

Subgroup Analysis of OS





OS benefit with D-Rd was generally consistent across patient subgroups

NE, not estimable; CrCl, creatinine clearance.

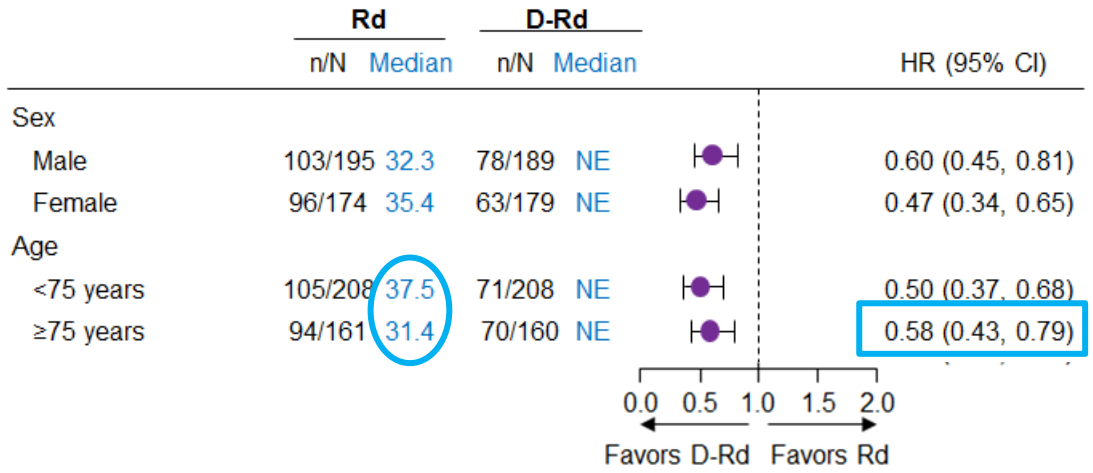
T Facon et al, N Engl J Med 2019
T Facon et al, EHA LBA 2021

Sous-groupe patients ≥ 75ans / fragiles :

DRd MAIA :

- ✓ Age médian 73 ans
- ✓ 17% patients ECOG>1

PFS



Median PFS (months)
SWOG

Age (years)	VRd	Rd
<65	48	34
≥65	34	24
>75	34	17

PFS VRd SWOG <=> PFS Rd MAIA

Durie et al, Lancet, 2017
Durie et al, Blood Cancer J, 2020
Facon et al, NEJM, 2019
Stege et al, Blood, 2019
SFH 2021

Summary of Relative Dose Intensity (Safety Population)

	Non-frail						Frail	
	Fit (n=145)		Intermediate (n=250)		Total Non-frail (n=395)		Frail (n=334)	
	D-Rd (n=68)	Rd (n=77)	D-Rd (n=128)	Rd (n=122)	D-Rd (n=196)	Rd (n=199)	D-Rd (n=168)	Rd (n=166)
Lenalidomide RDI, %								
N	66	75	125	120	191	195	148	153
Median (range)	70.4 (20.9-235.7)	84.7 (24.9-100.0)	79.7 (7.9-241.2)	86.6 (20.6-238.6)	77.2 (7.9-241.2)	86.4 (20.6-238.6)	65.4 (9.5-175.0)	92.9 (4.8-238.1)
Dexamethasone RDI, %								
Median (range)	71.5 (30.8-100.0)	83.3 (29.9-100.8)	77.5 (22.9-100.0)	85.8 (27.2-100.0)	75.0 (22.9-100.0)	84.8 (27.2-100.8)	85.8 (28.0-110.7)	90.3 (18.9-154.5)
Daratumumab RDI, %								
Median (range)	98.4 (61.5-104.7)	–	98.2 (38.5-107.0)	–	98.2 (38.5-107.0)	–	98.0 (3.2-107.0)	–

- **Median RDI of daratumumab was similar across frailty subgroups**
- **Median RDI of lenalidomide was higher in the total non-frail vs frail subgroup with D-Rd but lower in the total non-frail vs frail subgroup with Rd**

RDI, relative dose intensity.

La meilleure tolérance : VRD, DRD ou LES DEUX ?

DRd : MAIA trial

Groupe DRd:
+ de neutropénie
+ d'infections (pneumopathies++)
≈ 40 % de réactions tout grade à la perfusion

MAIS :
- ✓ Pas de surmortalité
- ✓ Pas + d'arrêt de traitement
- ✓ Réaction uniquement (>98%) à la 1ère IV
- ✓ AMM du Daratumumab SC

DRd ?

Table 3. Most Common Adverse Events and Second Primary Cancers Reported during Treatment in the Safety Population.*

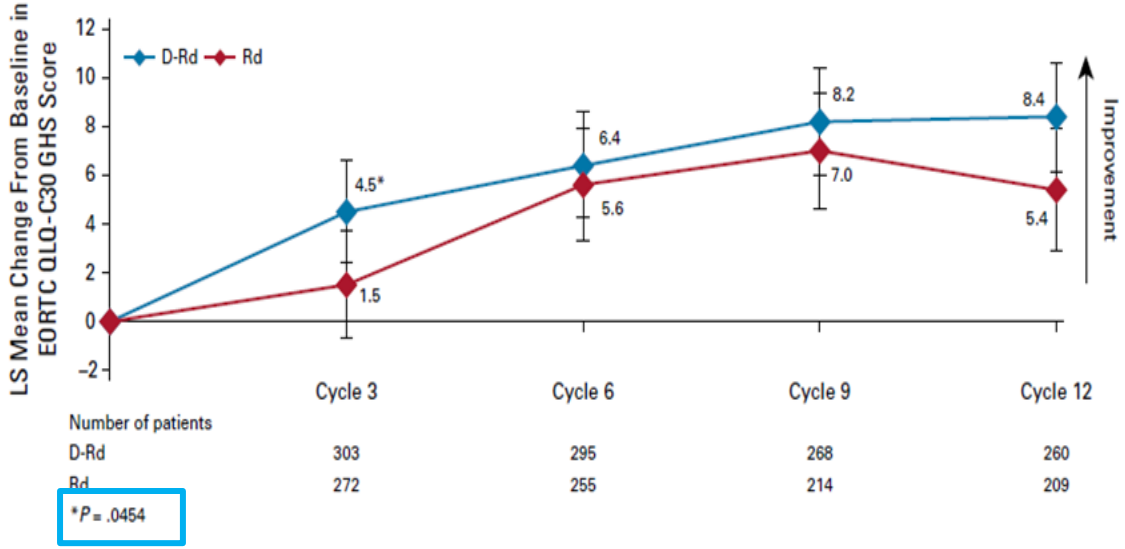
Event	Daratumumab Group (N=364)		Control Group (N=365)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Hematologic adverse events				
Neutropenia	207 (56.9)	182 (50.0)	154 (42.2)	129 (35.3)
Anemia	126 (34.6)	43 (11.8)	138 (37.8)	72 (19.7)
Leukopenia	68 (18.7)	40 (11.0)	34 (9.3)	18 (4.9)
Lymphopenia	66 (18.1)	55 (15.1)	45 (12.3)	39 (10.7)
Nonhematologic adverse events				
Infections	314 (86.3)	117 (32.1)	268 (73.4)	85 (23.3)
Pneumonia	82 (22.5)	50 (13.7)	46 (12.6)	29 (7.9)
Diarrhea	207 (56.9)	24 (6.6)	168 (46.0)	15 (4.1)
Constipation	149 (40.9)	6 (1.6)	130 (35.6)	1 (0.3)
Fatigue	147 (40.4)	29 (8.0)	104 (28.5)	14 (3.8)
Peripheral edema	140 (38.5)	7 (1.9)	107 (29.3)	2 (0.5)
Back pain	123 (33.8)	11 (3.0)	96 (26.3)	11 (3.0)
Asthenia	117 (32.1)	16 (4.4)	90 (24.7)	13 (3.6)
Nausea	115 (31.6)	5 (1.4)	84 (23.0)	2 (0.5)
Second primary cancer†	32 (8.8)	NA	26 (7.1)	NA
Invasive second primary cancer	12 (3.3)	NA	13 (3.6)	NA
Any infusion-related reaction	149 (40.9)	10 (2.7)	NA	NA

Facon et al, NEJM, 2019

La meilleure qualité de vie : VRD, DRD ou LES DEUX ?

DRd (MAIA) :

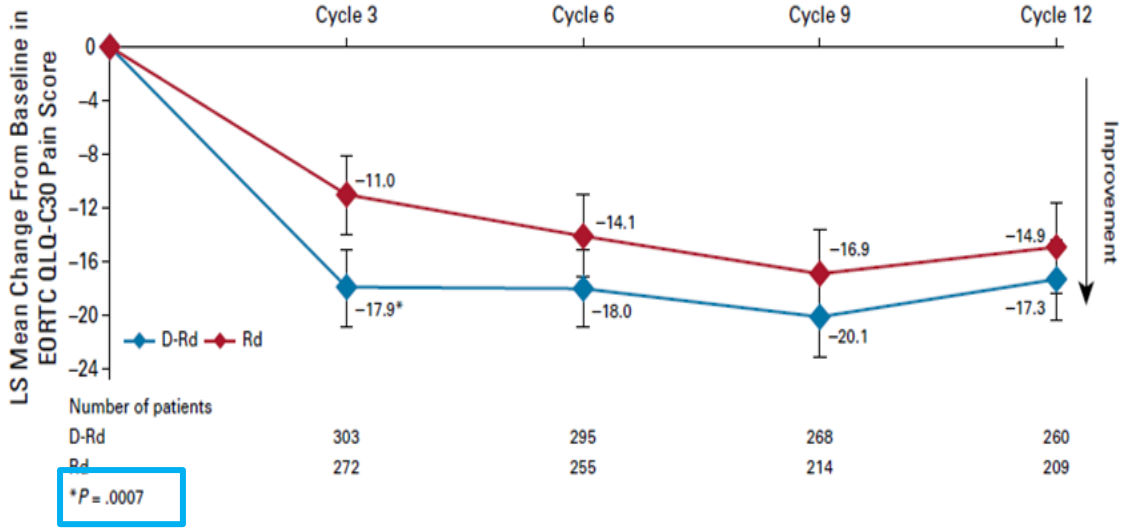
- ✓ Amélioration QoL : santé globale, douleur…
- ✓ Surtout si âge ≥ 75 ans ou ECOG 1-2



MAIS :

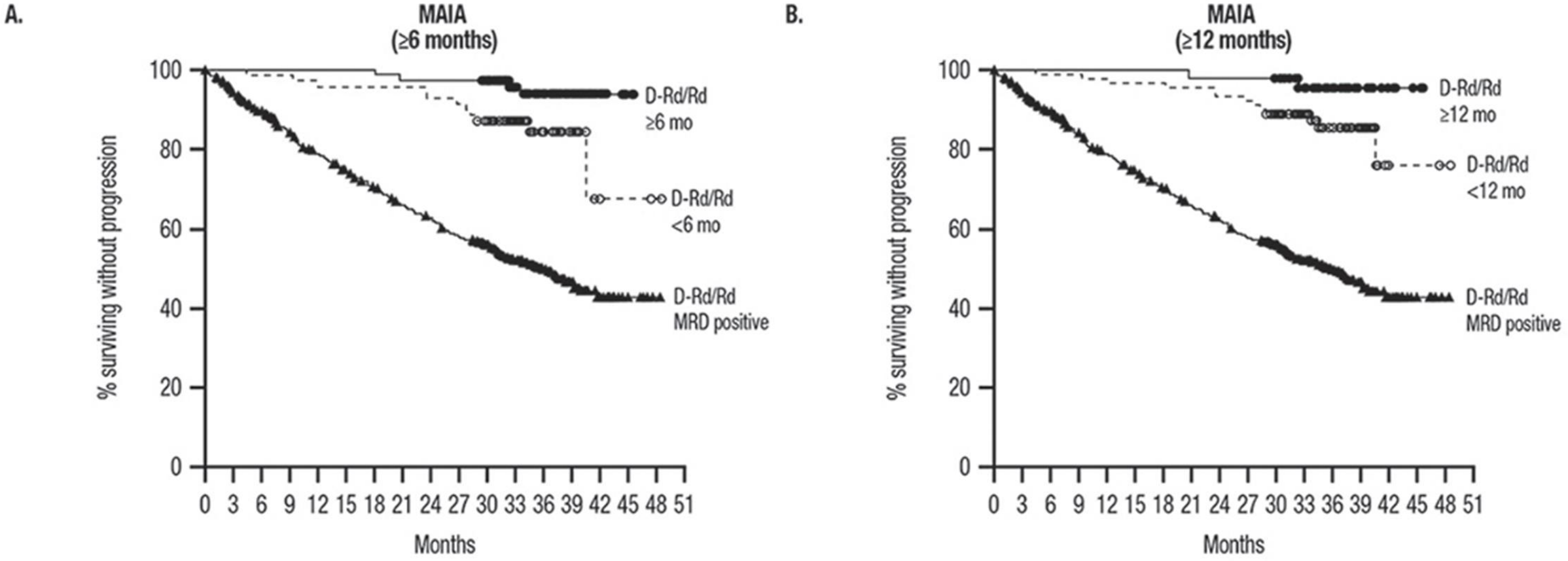
- ✓ Daratumumab IV
- ✓ DRd jusqu'à progression

⇒ Impact de la qualité de vie et impact financier



Perrot et al, JCO, 2021

MRD négative (10^{-5}) *sustained* : MAIA



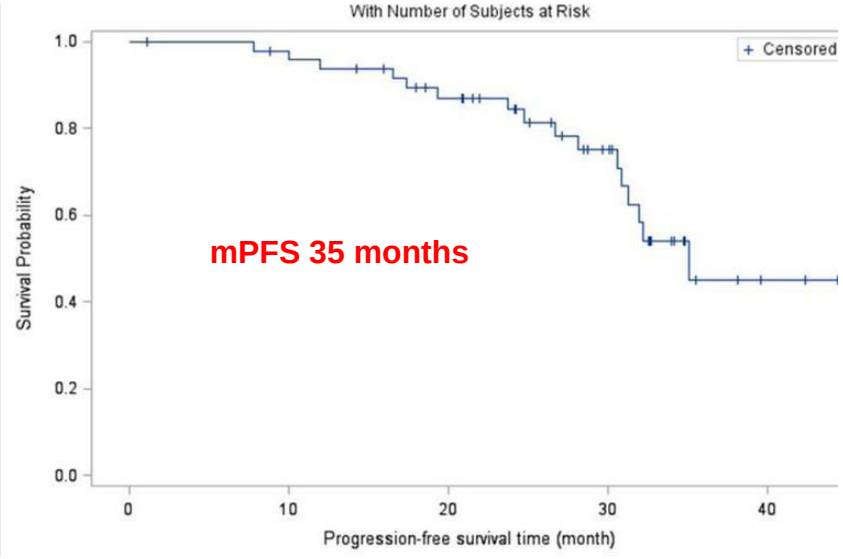
La PFS est prolongée chez les patients ayant une MRD *sustained de* ≥6-mois et ≥12-mois, quelque soit le bras de traitement

Sustained MRD negativity was defined as the maintenance of MRD negativity confirmed ≥6 or ≥12 months apart

San-Miguel JF.. Blood, 2020

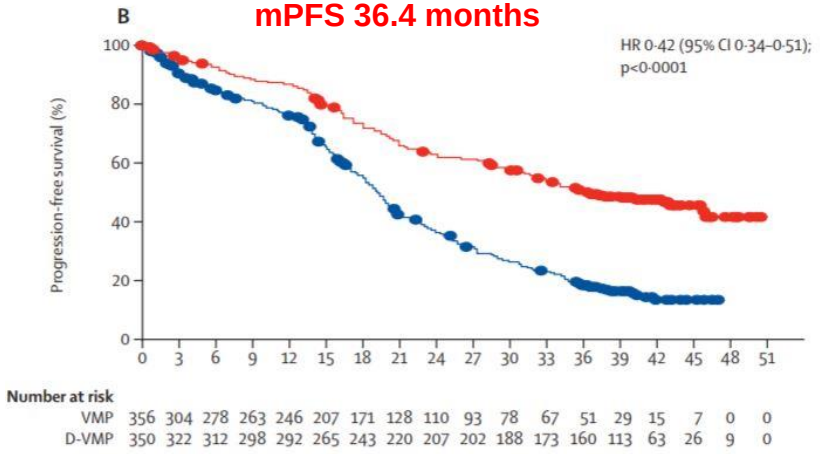
Les 3 nouveaux standards de traitement des patients NTE

	VRd (lite)	DaraVMP	DaraRd
ORR/CR	86%/32%	91%/46%	93%/50%
MRD- negative	NA	28%	29%

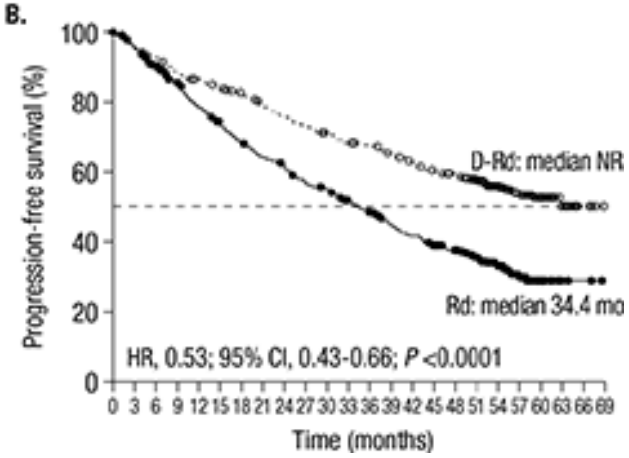


mPFS 35 months

mPFS 36.4 months

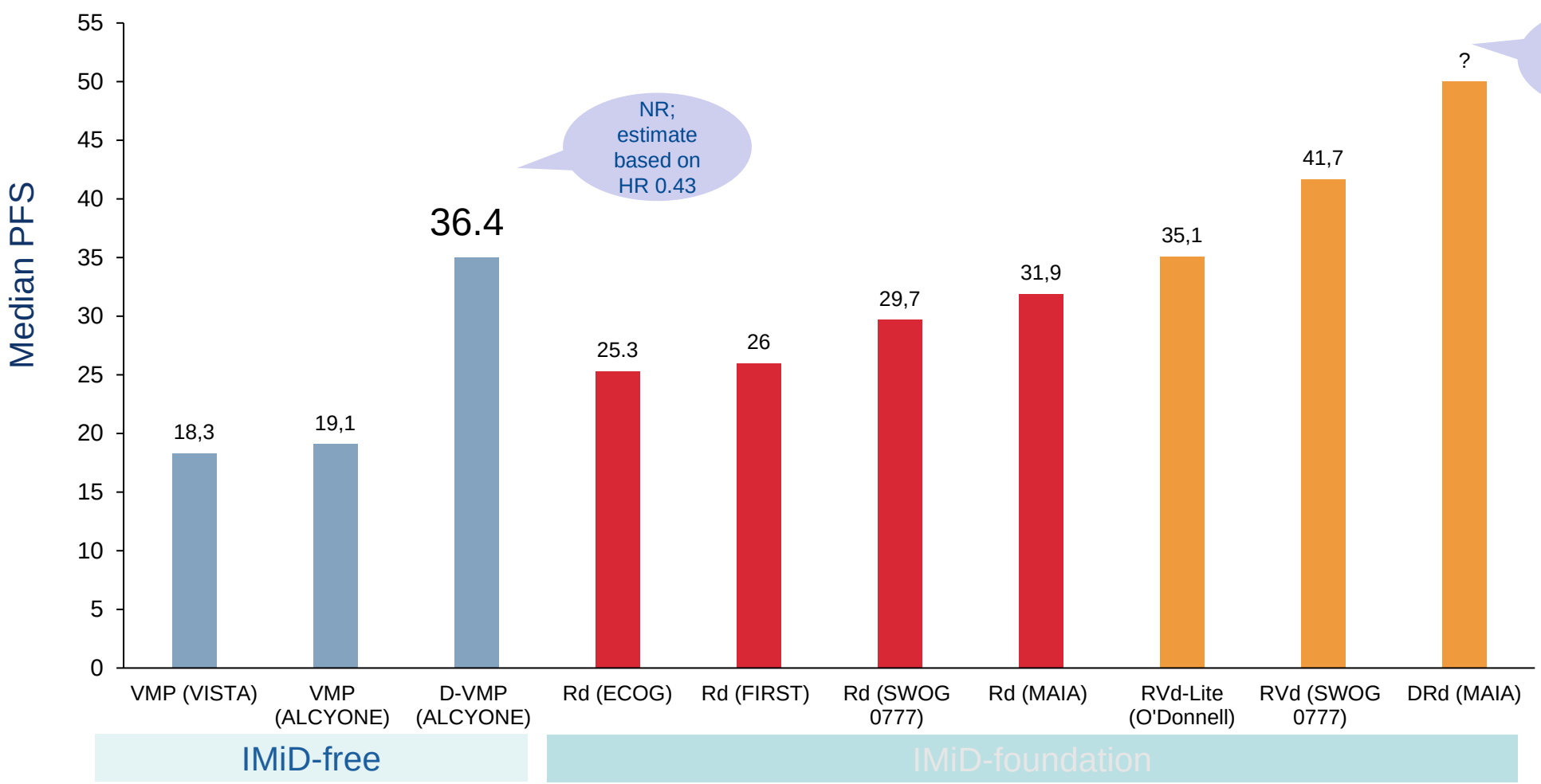


mPFS not reached, 5-year PFS 52.5%



Mateos MV NEJM 2018 *Facon T, NEJM 2019*

Vue globale des médianes de PFS des essais de phase 3 pour les NTE



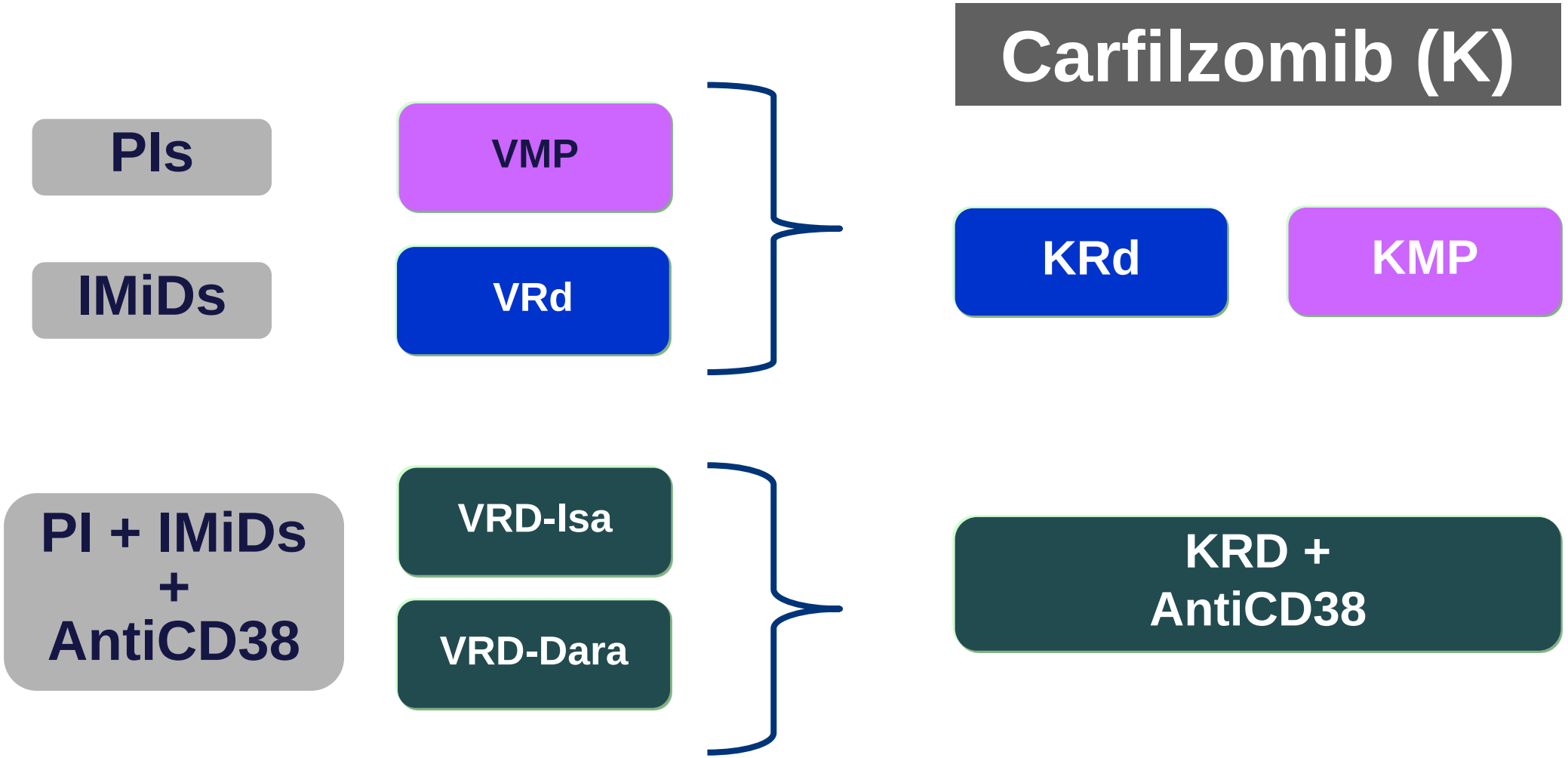
Median PFS estimates calculated by dividing the median PFS of the comparator by the HR

Direct comparison between trials is not intended and should not be inferred.

1. Velcade [SmPC]. Beerse, Belgium. Janssen-Cilag International; 2014.
2. Dimopoulos M, et al. Blood. 2018;132:156. Presented at ASH 2018. 3. Rajkumar SV, et al. Lancet Oncol. 2010;11:29-37.
4. Facon T, et al. Blood. 2018;131:301-10. 5. REVLIMID [SmPC]. Utrecht, Netherlands. Celgene Europe BV; 2019.
6. Facon T, et al. Blood. 2018;132:LBA-2. Presented at ASH 2018. 7. O'Donnell EK, et al. Br J Haematol. 2018;182:222-30.

Peut-on améliorer ces résultats?

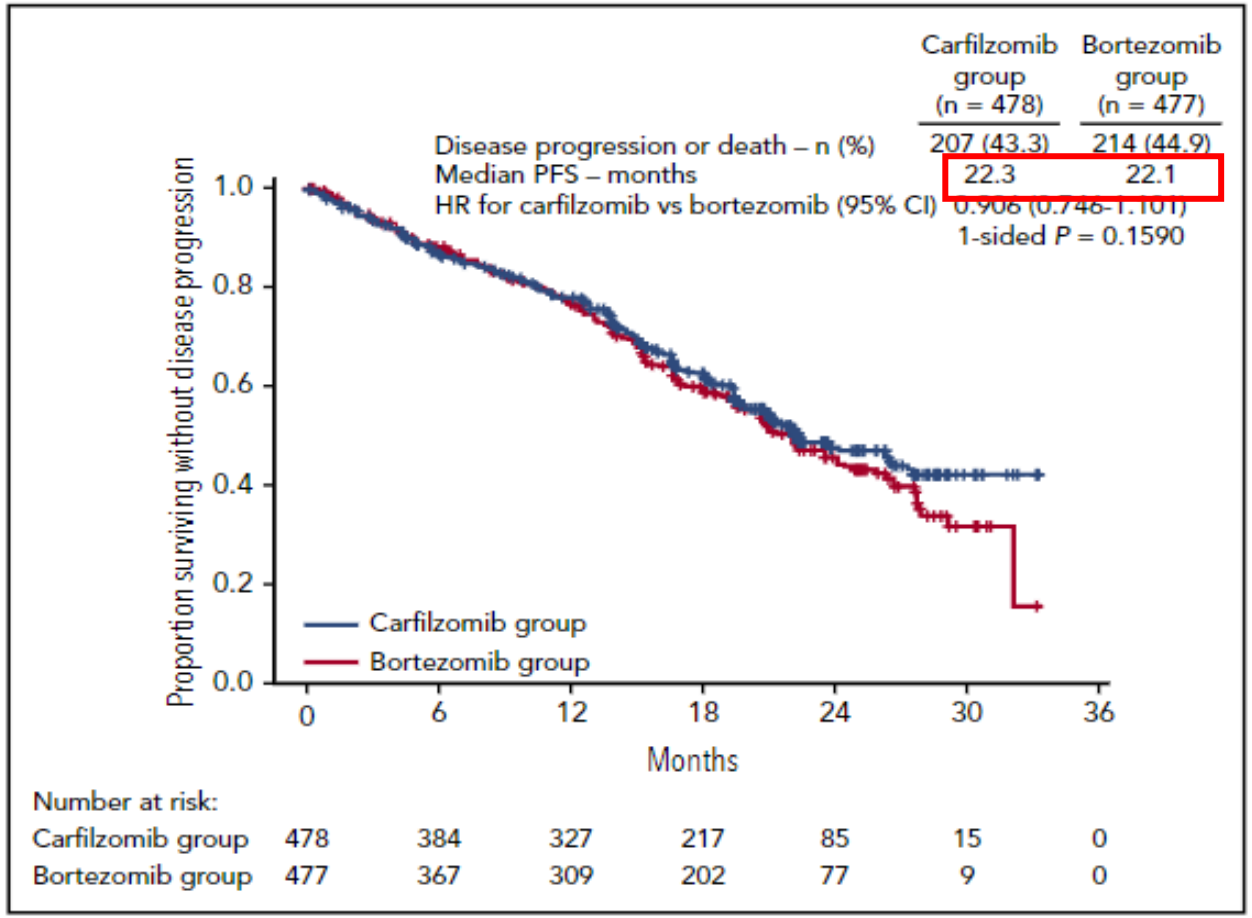
Faut-il utiliser du carfilzomib chez ces patients pour améliorer la survie/réponse ?



CLARION (phase 3): KMP vs VMP pour les NTE NDMM

VMP ou KMP x 9 cycles
955 patients
Age médian 72 ans
KMP 31.6% ≥ 75, and 30.4% pour VMP
Haut risques: 12.7%

Survie sans progression



T Facon et al., Blood 2019

ENDURANCE (phase 3) : KRd vs VRd pour les NDMM

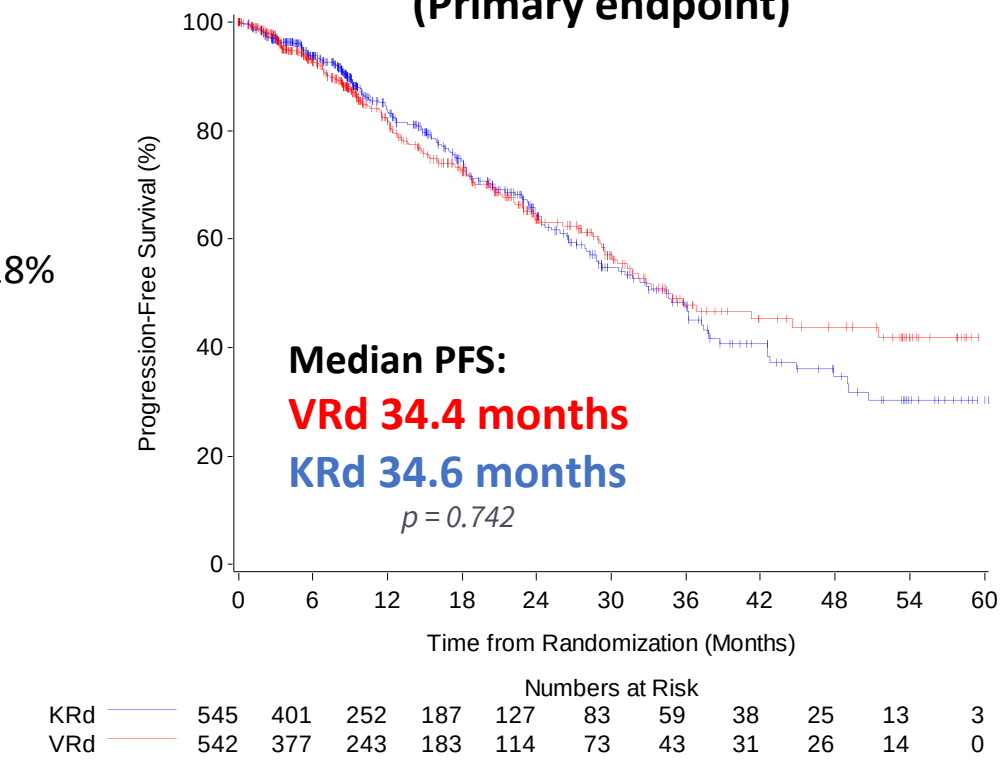
KRd (x9 cycles) **vs VRd** (x12 cycles)
Suivi d'une maintenance jusqu'à progression vs 24 mois

Age médian : 65 ans

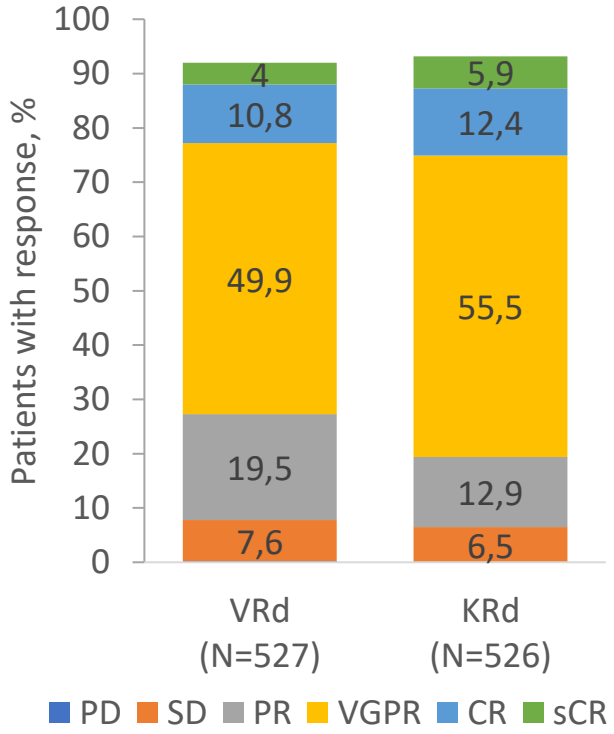
Cytogénétique anormale : 28%

Suivi médian : 15 mois

PFS from Induction Randomization (Primary endpoint)



Response to Induction

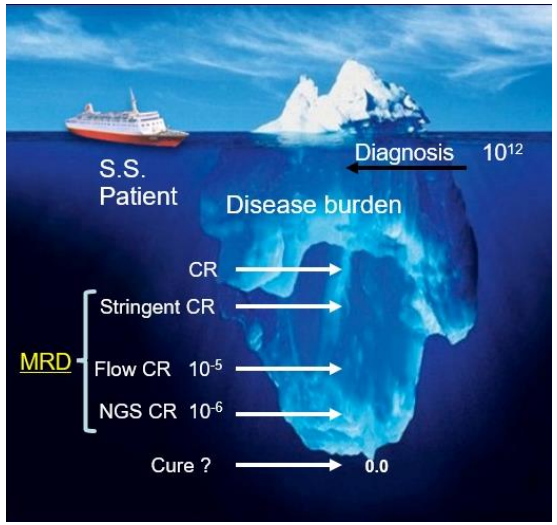


Kumar S, et al. ASCO 2020; abstract LBA3

Peut-on encore approfondir la réponse ?

De la MRD négative à …

MRD négative à 10^{-5}*

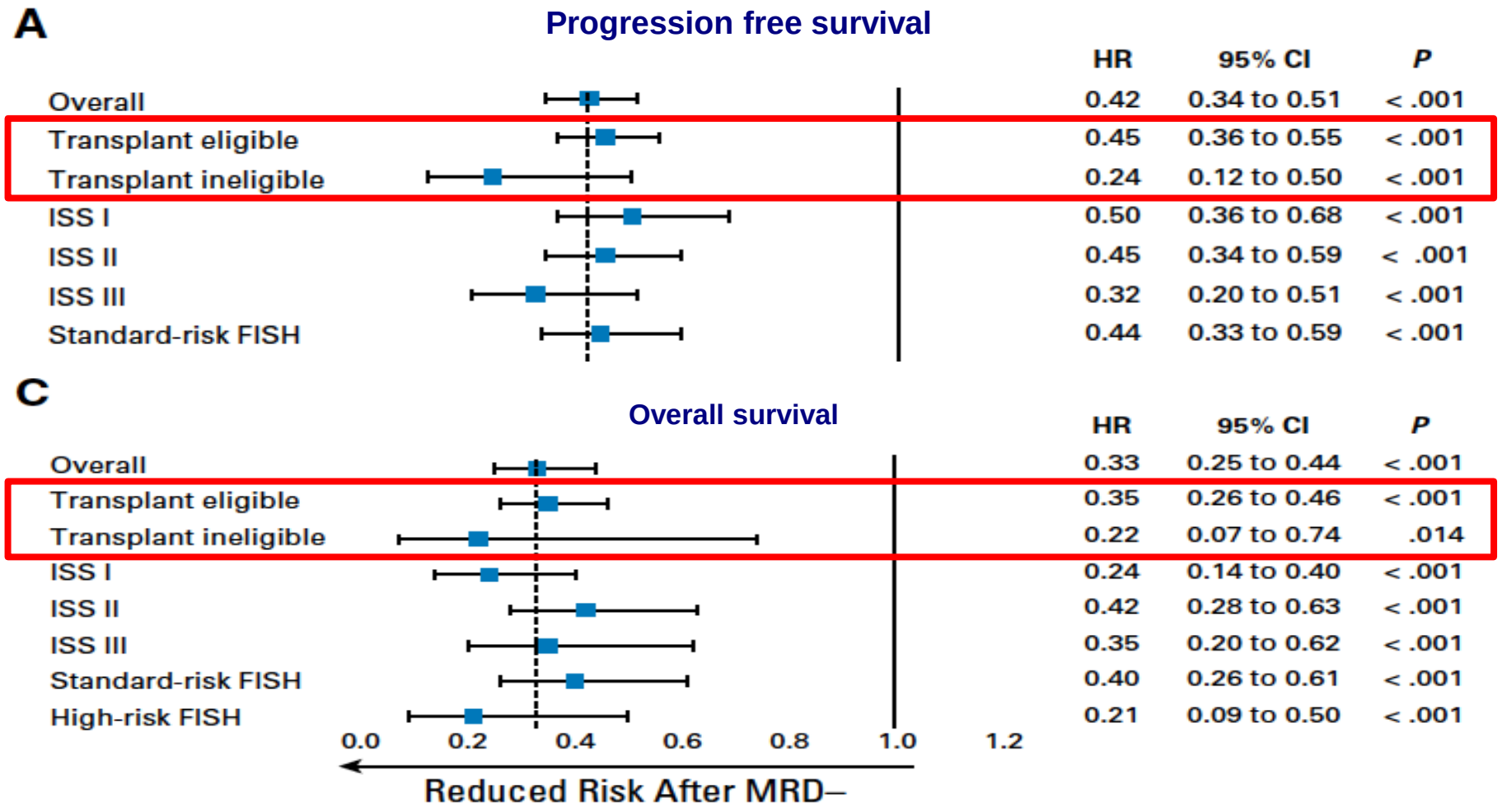


La MRD *sustained* (maintenue)

MRD 10^{-5} pendant ≥12 mois*

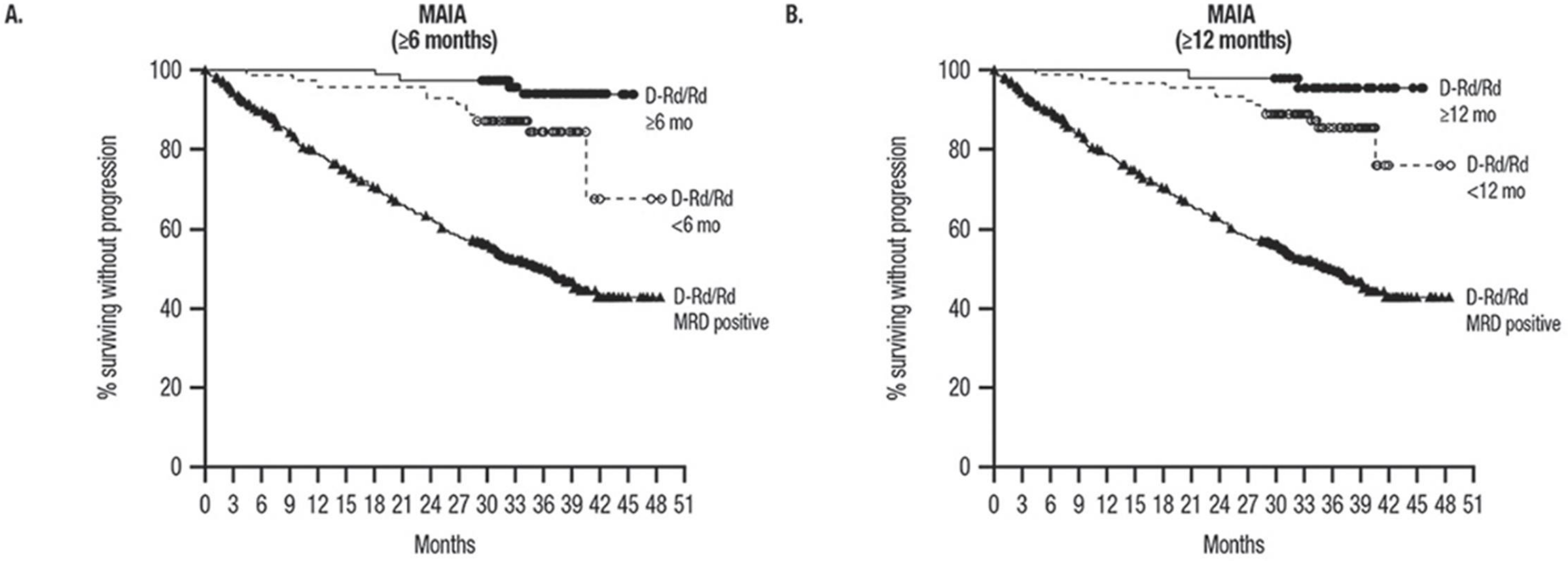
*S. Kumar et al. IMWG consensus criteria for response and MRD. Lancet, 2016

Le taux de MRD négative est prédictif de la survie pour tous les sous-groupes de patients



Lahuerta JJ et al. JCO 2017: Epub ahead of print

MRD négative (10^{-5}) *sustained* : MAIA



La PFS est prolongée chez les patients ayant une MRD *sustained de* ≥6-mois et ≥12-mois, quelque soit le bras de traitement

Sustained MRD negativity was defined as the maintenance of MRD negativity confirmed ≥6 or ≥12 months apart

San-Miguel JF.. Blood, 2020

La prise en charge des sujets non éligibles à l'autogreffe

« la situation actuelle »

- Le traitement de en 1ère ligne qui permet la meilleure PFS est DRd
- La médiane de PFS n'est toujours pas atteinte avec un suivi de près de 5 ans
- Le taux de MRD négative est de 24%

- **MAIS, le taux de MRD *sustained* est <15%**

➡ **Peut-on encore faire mieux ?**

Plus de drogues pour de meilleurs résultats ?
Vers l'ère des "quadruplettes"

PIs — **VMP** → **VMP - Dara**

Essai ALCYONE

IMiDs — **VRd** + **DRd** → **VRd + anti-CD38**

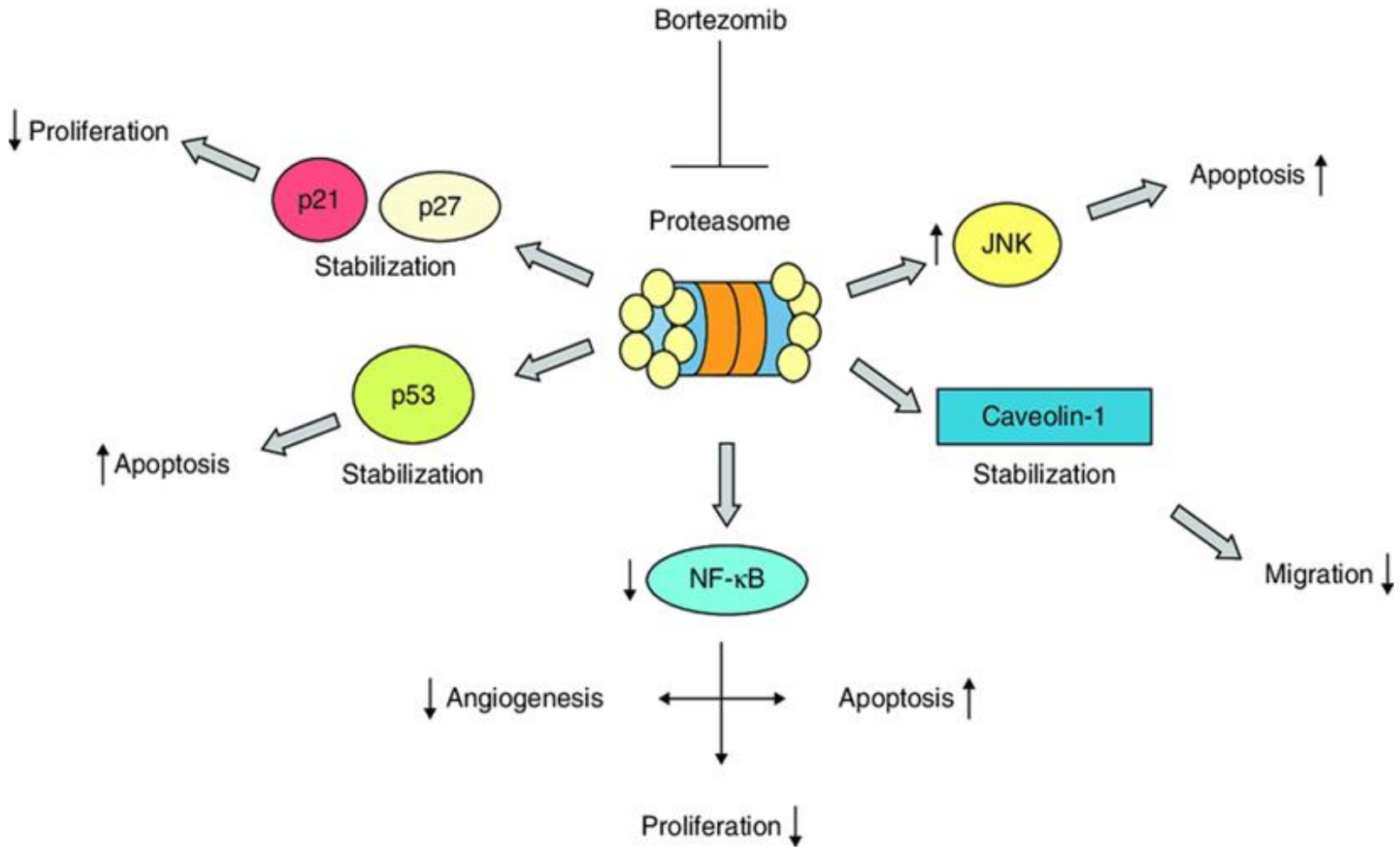
VRD-Isa | **VRD-Dara**

Mateos MV NEJM 2018 *Facon T, NEJM 2019*

Mécanisme d'action le plus prometteur :

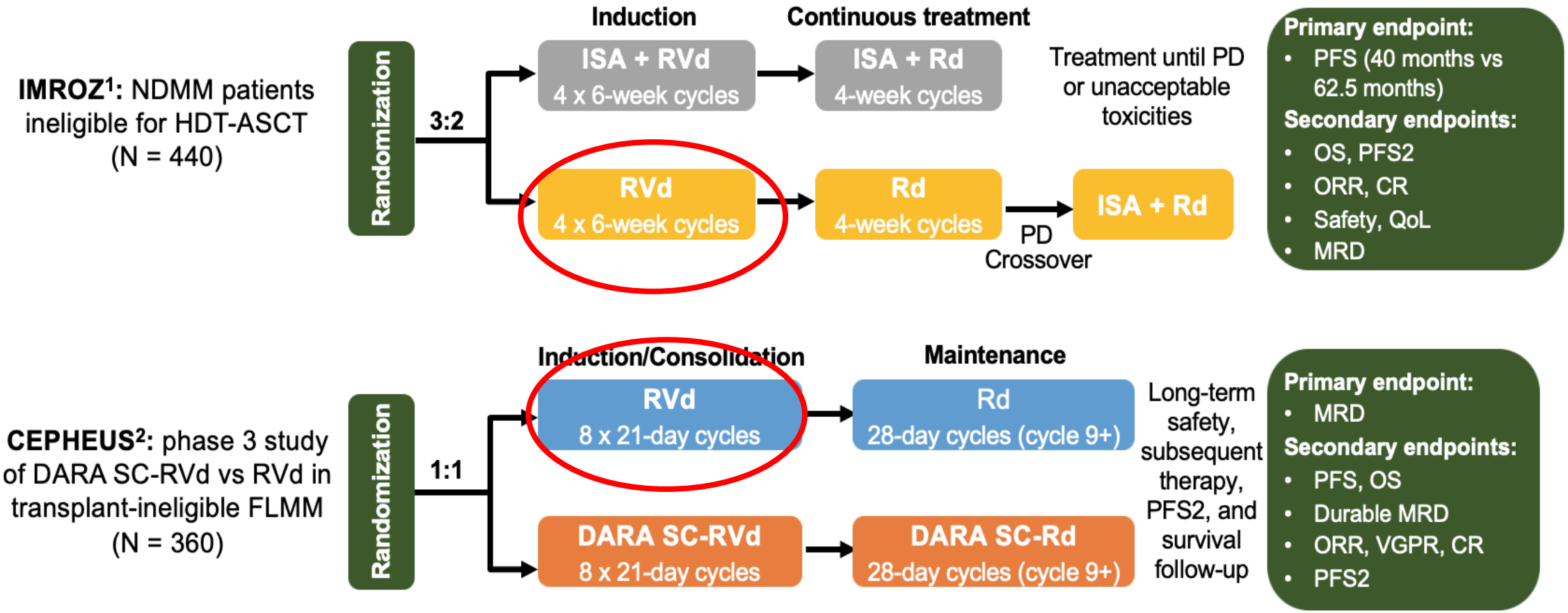
VRD, DRD ou LES DEUX ?

VRd ?



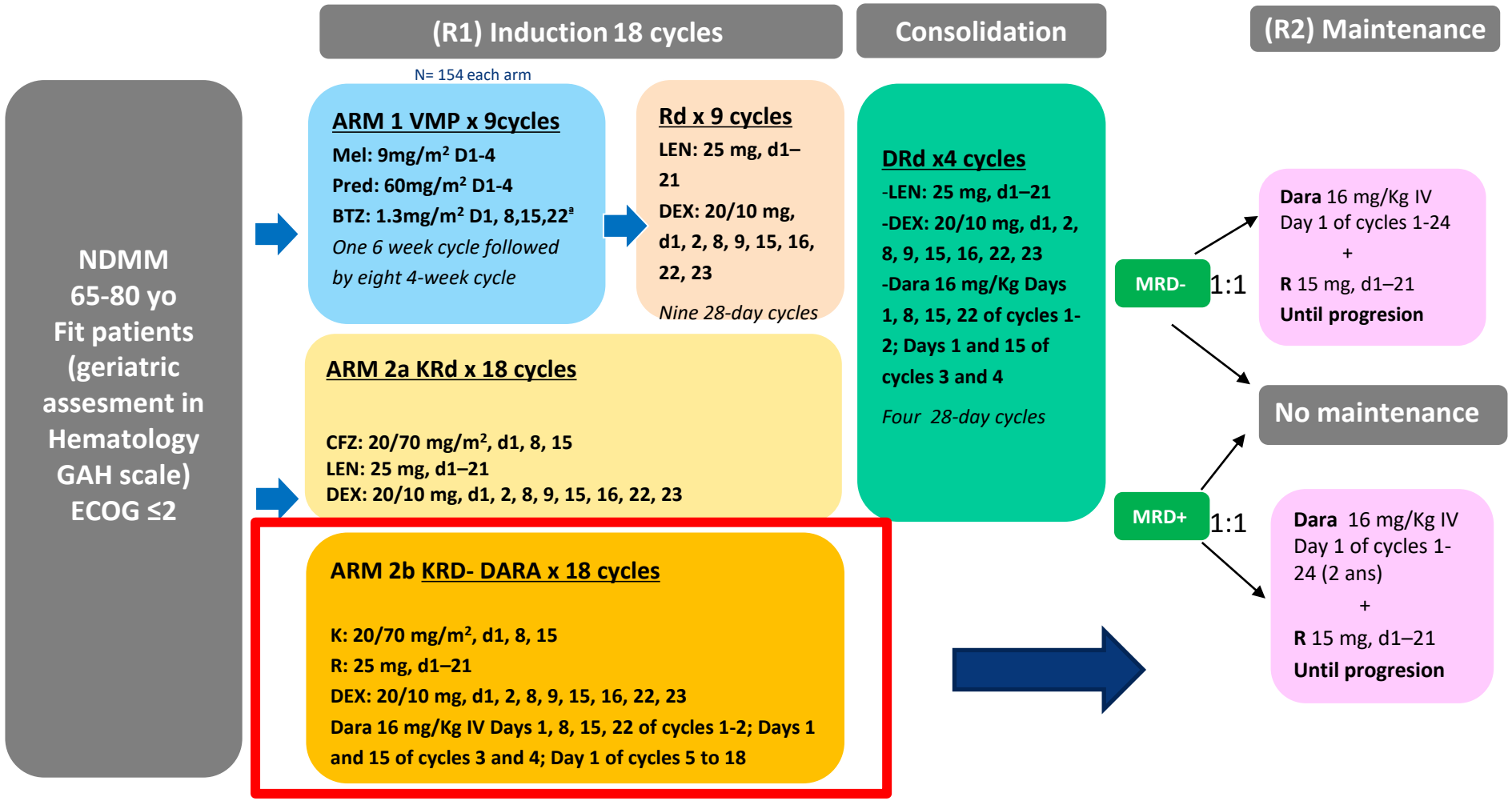
Russo et al, Expert Opin. Ther. Targets, 2008

Les quadruplettes chez les NDMM NTE non *frails*



/!\ Dans les 2 essais, le bras control est VRd et non anti-CD38 + Rd (cf MAIA)

GEM2017FIT pour les NTE NDMM fit (phase 3) : dara-KRd



NCT03742297

BENEFIT - IFM 2020-05 (NDMM NTE [65-79] non *frail*)

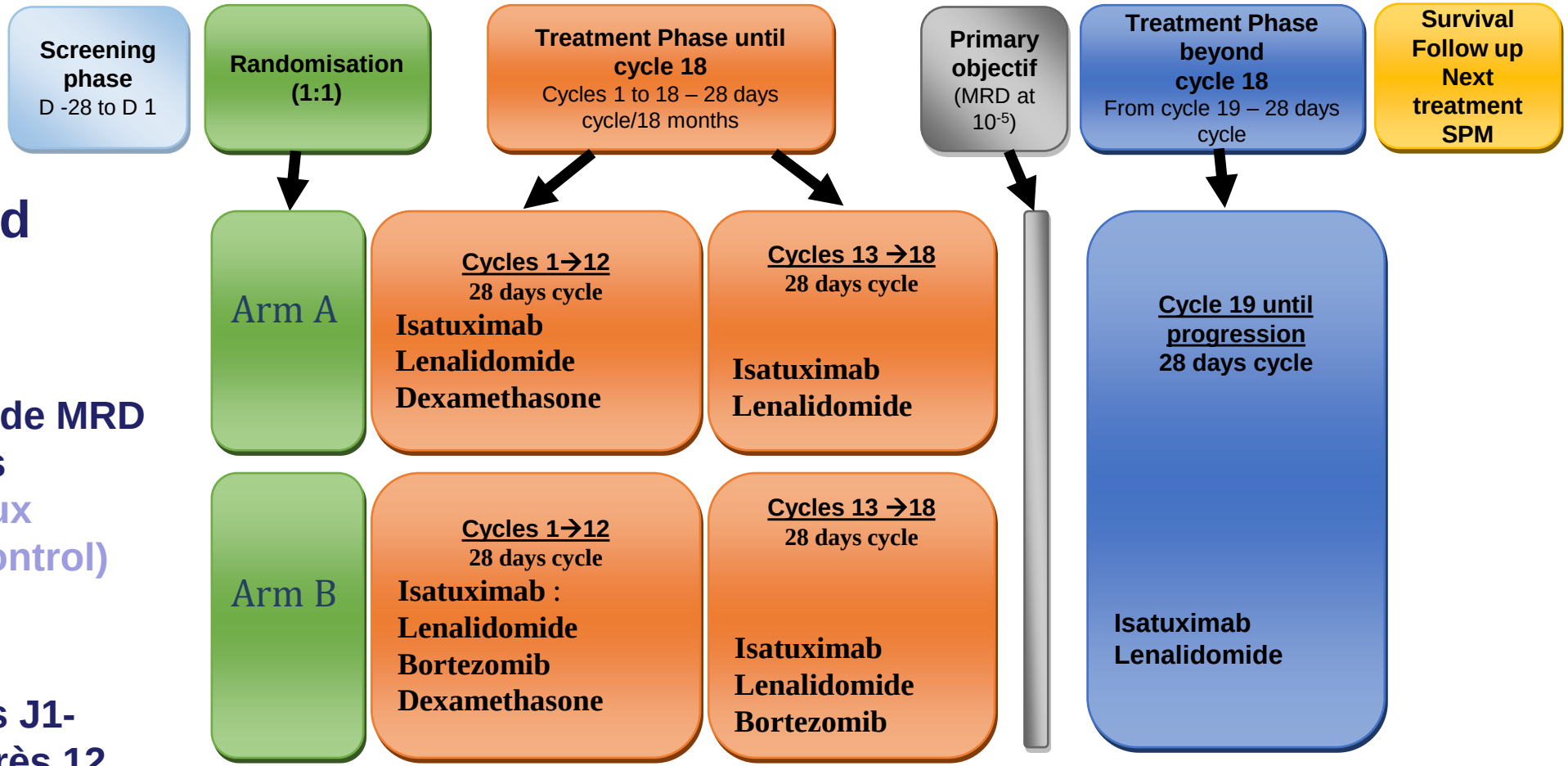
isa-VRD vs isa-Rd

Randomisation 1:1

Critère principal: taux de MRD négative 10^{-5} à 18 mois

Estimation des taux attendus : 15% (control) vs 30% (exp)

V Hebdo de C1-12 puis J1-J15, arrêt de la dex après 12 cycles



NCT04751877

Immunotherapie cellulaire Car t CILTA -CEL – CARTITUDE 5
NDMM NTE Non frail

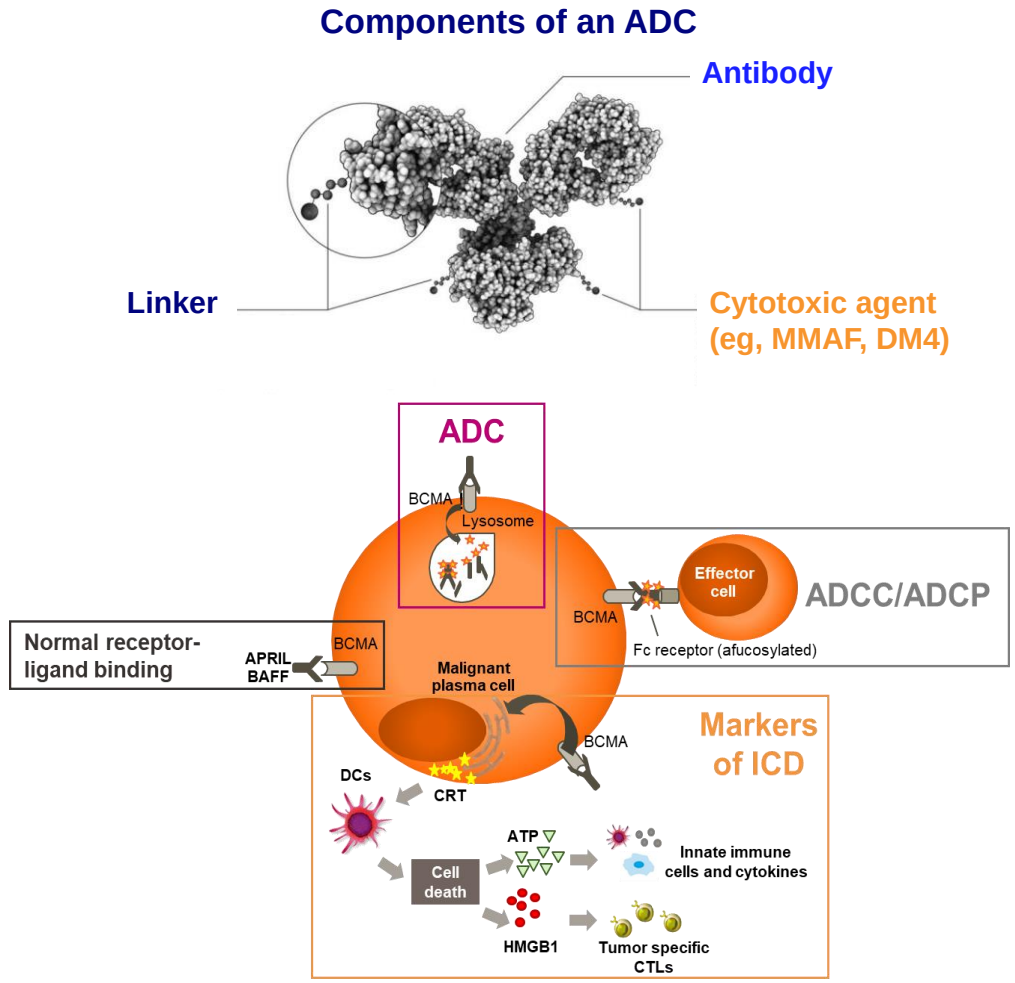
- VRd

versus

- Versus CAR T cilta cel

Antibody-drug conjugates in MM

Belantamab mafodotin, DREAMM2



Independent Review Committee-assessed Response*	Belantamab Mafodotin 2.5 mg/kg (N = 97)
Overall response rate,† n (%) (97.5% CI)	31 (32) (21.7-43.6)
Best response, n (%)	
Stringent complete response	2 (2)
Complete response	5 (5)
Very good partial response	11 (11)
Partial response	13 (13)
Minimal response	4 (4)
Stable disease	27 (28)
Median DoR, months (95% CI)	11 (4.2-NR)
Median PFS, months (95% CI)	2.8 (1.6-3.6)
Median OS, months (95% CI)	13.7 (9.9-NR)

AEs ≥Grade 3 occurring in ≥5% of patients in either group, n (%)*	Belantamab Mafodotin 2.5 mg/kg (N = 97)
Any event	80 (84)
Keratopathy	44 (46)
Anemia	20 (21)
Thrombocytopenia	21 (22)
Lymphocyte count decreased	12 (13)
Neutropenia	10 (11)

Lonial et al. *Lancet* 2020

EN 2021, TOUS LES PATIENTS ÂGÉS DOIVENT-ILS RECEVOIR LA MÊME 1ÈRE LIGNE DE TRAITEMENT ?

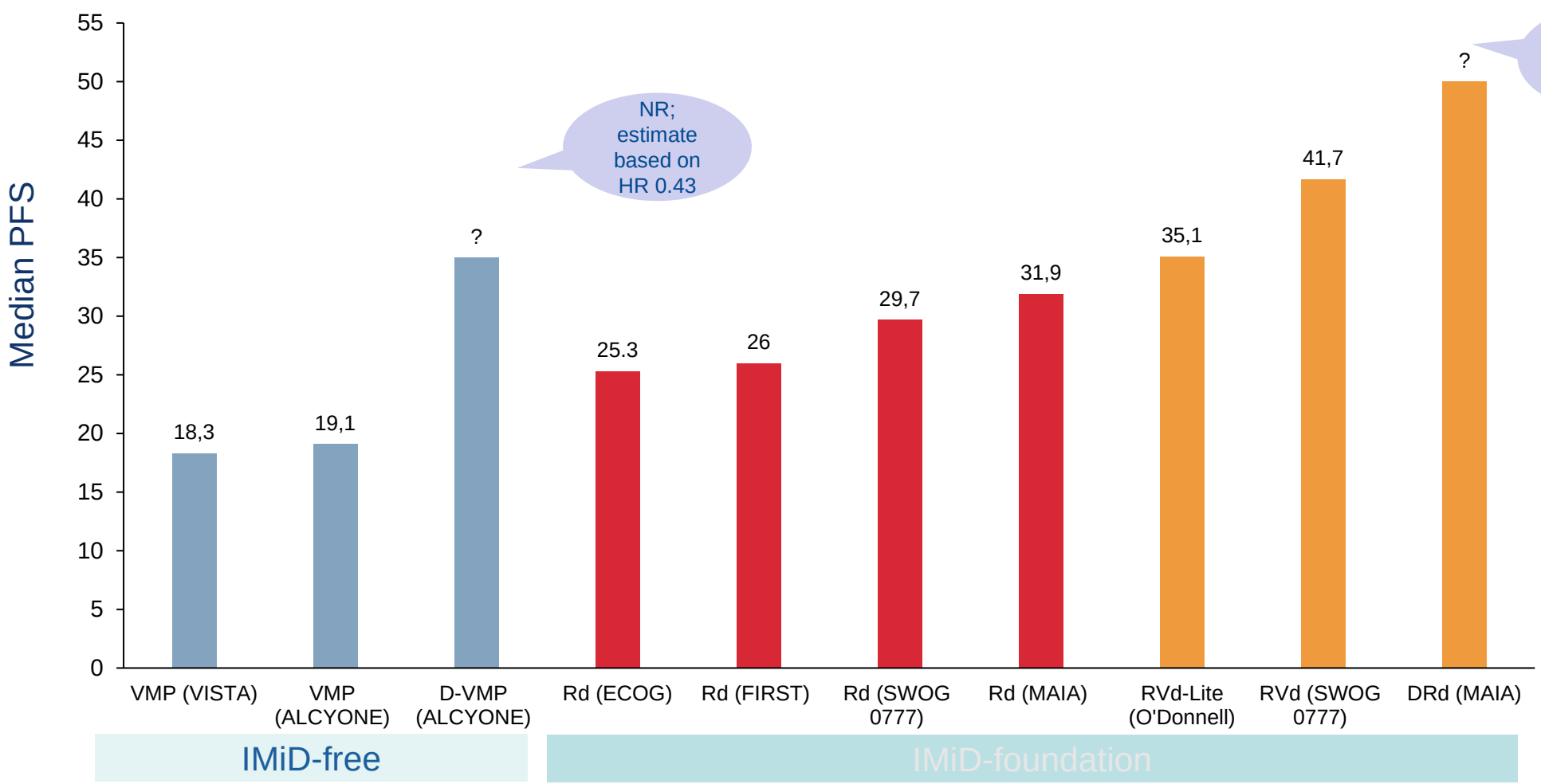
UH13
E-NSEMBLE AU CŒUR DE L'HÉMATOLOGIE

OUI

3 CONDITIONS pour un traitement « UNIVERSEL»

- EFFICACITE
- TOLERANCE
- FAISABILITE

Overview of mPFS in recent phase 3 trials in transplant-ineligible NDMM



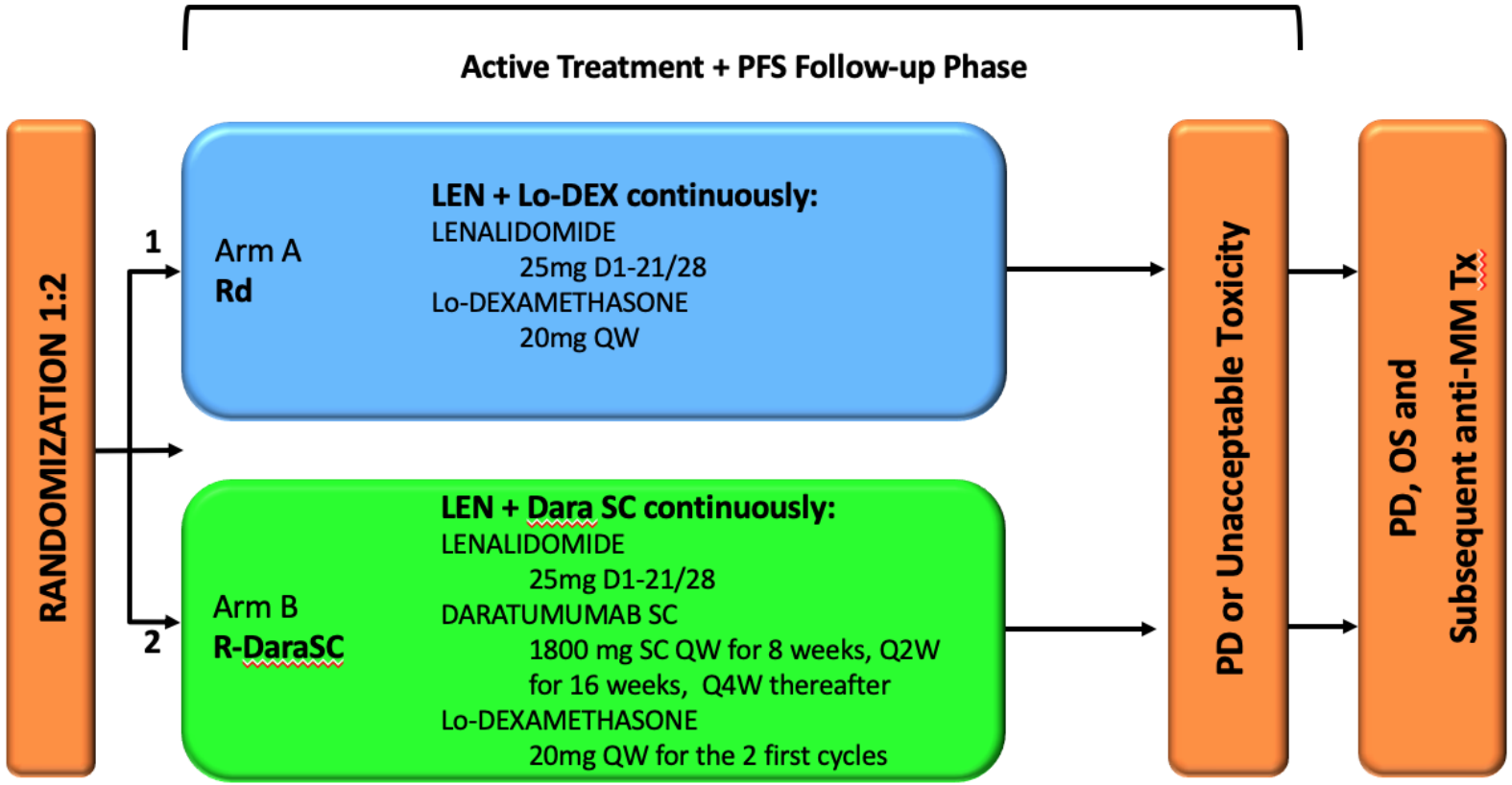
Median PFS estimates calculated by dividing the median PFS of the comparator by the HR

Direct comparison between trials is not intended and should not be inferred.

1. Velcade [SmPC]. Beerse, Belgium. Janssen-Cilag International; 2014.
2. Dimopoulos M, et al. Blood. 2018;132:156. Presented at ASH 2018. 3. Rajkumar SV, et al. Lancet Oncol. 2010;11:29-37.
4. Facon T, et al. Blood. 2018;131:301-10. 5. REVLIMID [SmPC]. Utrecht, Netherlands. Celgene Europe BV; 2019.
6. Facon T, et al. Blood. 2018;132:LBA-2. Presented at ASH 2018. 7. O'Donnell EK, et al. Br J Haematol. 2018;182:222-30.

IFM Perspective

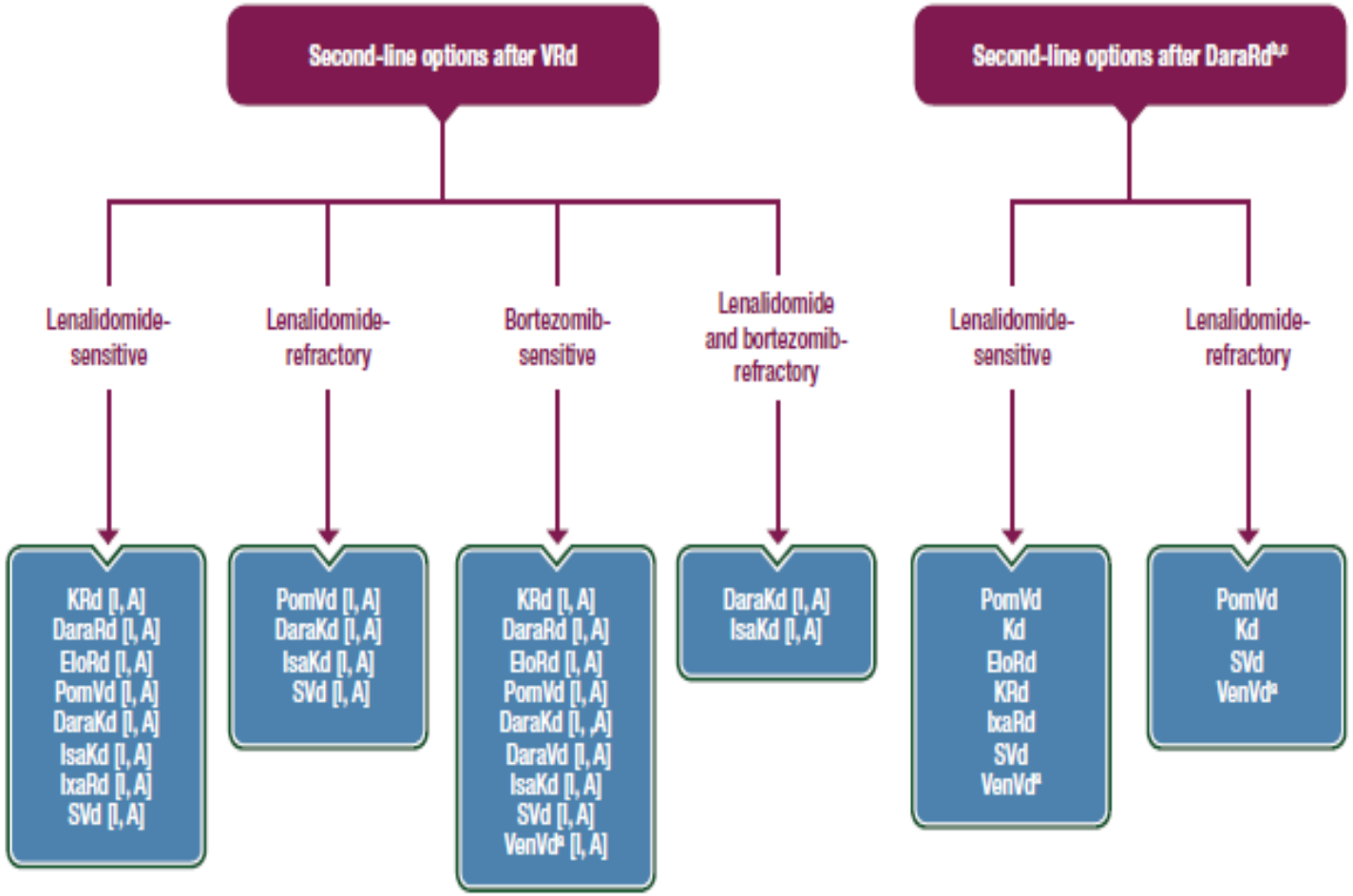
IFM 2017-03



Randomization will be stratified by International Staging System (I and II vs III) and age (<80 vs ≥80)

Le plus d'options si RRMM: VRD, DRD ou LES DEUX ?

VRd !



Mais émergence de nouvelles thérapies !

ESMO Guidelines

2020-2030

Merci!