Myélome multiple en rechute réfractaire

(hors immunothérapie moderne)

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Cours de DES national_26 novembre 2021

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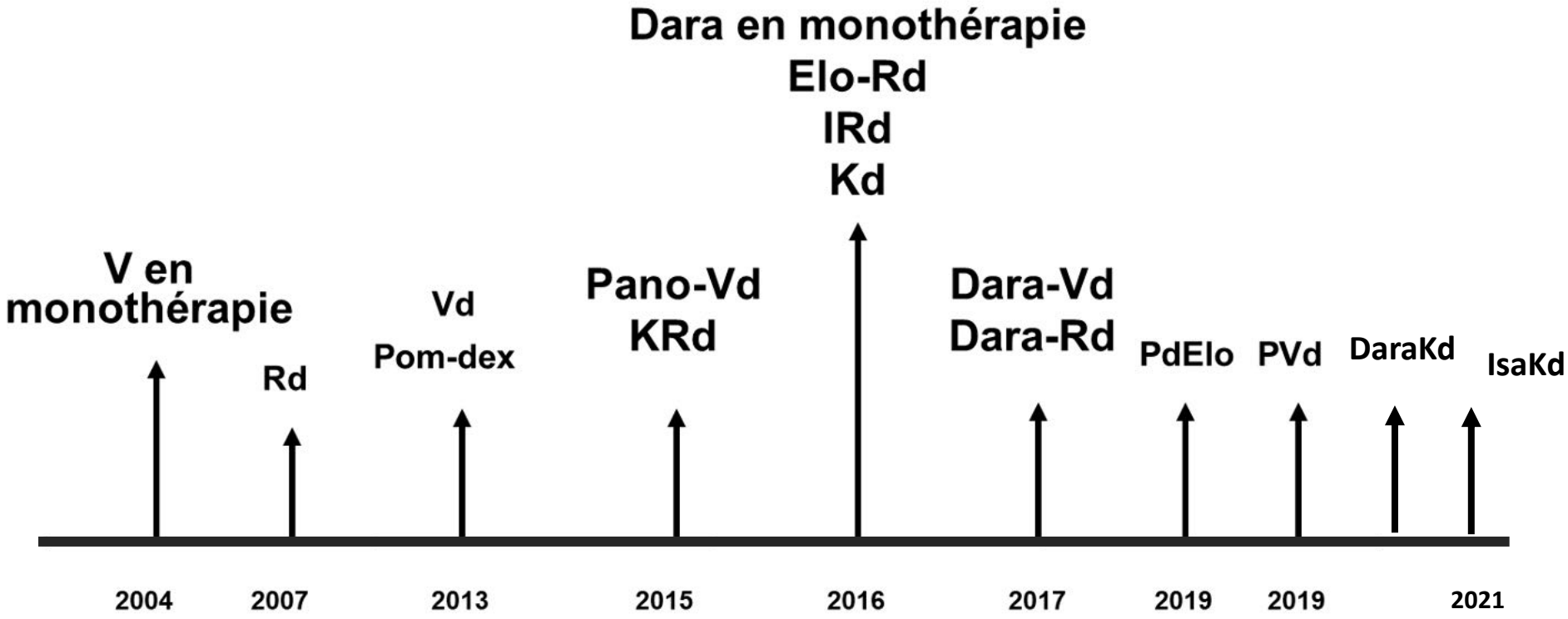
ifm

Combinaisons approuvées par l'EMA dans le MM RR



V : bortézomib ; R : lénalidomide ; Pom : pomalidomide ; dex : dexaméthasone ; Pano : panobinostat ; K : carfilzomib ;
Dara : daratumumab ; Elo : élotuzumab; I : ixazomib

www.ema.europa.eu

Qu’est-ce qu’une rechute ?

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

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

MM Ig complète : augmentation du pic de plus de 25 % par rapport au nadir, et au moins de 5 g/L
MM à CLS : augmentation du composant urinaire de plus de 25 %, et au moins de 200 mg/24h
MM non mesurable dans les urines : dFLC

S Kumar et al, Lancet Oncol 2016

Rechute biologique ou clinique

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcaemia (>11 mg/dL); Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein

Augmentation d'un plasmocytome ou de lésions osseuses de 50 % (somme des produits des diamètres) et plus d'1 cm
Hypercalcémie
Anémie (non reliée au traitement ou à une autre cause)
Majoration de la créatinine attribuable au myélome

S Kumar et al, Lancet Oncol 2016

Définition d'une progression dans un essai clinique

Maladie mesurable		Définition	Suivi
Maladie mesurable	Sérique et urinaire	PM sérique ≥ 10 g/L et PM urinaire ≥ 200 mg/24h	Suivi sérique et urinaire
	Sérique seule	PM sérique ≥ 10 g/L et PM urinaire < 200 mg/24h	Suivi sérique
	Urinaire seule	PM sérique < 10 g/L et PM urinaire ≥ 200 mg/24h	Suivi urinaire
Maladie non mesurable	PM sérique < 10 g/L et PM urinaire < 200 mg/24h		Suivi sur le dosage des CLS si > 100 mg/L

Progression de la maladie mesurable !

Ou atteinte osseuse..

B Durie et al, Leukemia 2006

Faut-il traiter une rechute ?

Leukemia (2016) **30,** 1005–1017

www.nature.com/leu

REVIEW

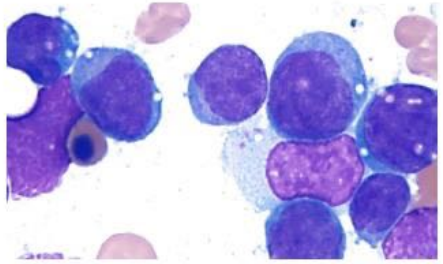
Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group

GENERAL TREATMENT PRINCIPLES IN THE MANAGEMENT OF RELAPSED MM

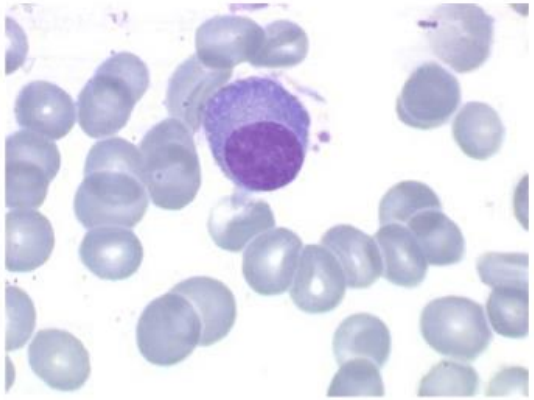
When to treat?

Treatment is indicated when patients develop symptomatic relapse, a rapidly rising paraprotein level or extramedullary disease. Patients experiencing biological relapse alone do not necessarily need to be treated immediately. In this case, the speed of increase of the monoclonal peak, such as a doubling time of 3 months or shorter, would suggest initiating treatment. For asymptomatic biochemical relapse and a slow rise in the paraprotein level, restaging with a stringent wait and watch approach and follow up at least every 3 months can be recommended. Some patients develop oligoclonal reconstitution post-ASCT, which can occur in up to 37% of patients in this setting.[19] This is transient, can be observed and should not be treated.

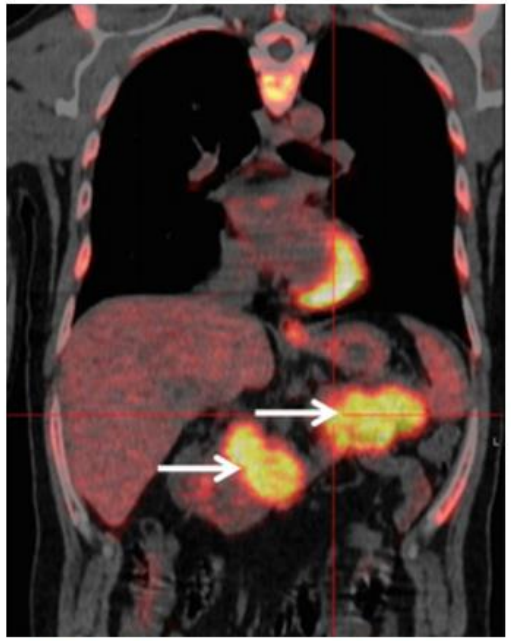
Définir le risque à la rechute



Cytologie plasmablastique



Leucémie à plasmocytes



Maladie extramédullaire

TP53 del17p

trisomy 21

t(4;14) del1p32

trisomy 5

gain1q DIS3

Rechute précoce

Pour préparer son dossier RCP…

MM Ig/FLC
CRAB / SlimCRAB

TP53 del17p
t(4;14) trisomy 21 del1p32
trisomy 5 gain1q DIS3

t(11;14) ?

Patient et Maladie
Cytogénétique ?
Traitements antérieurs ?

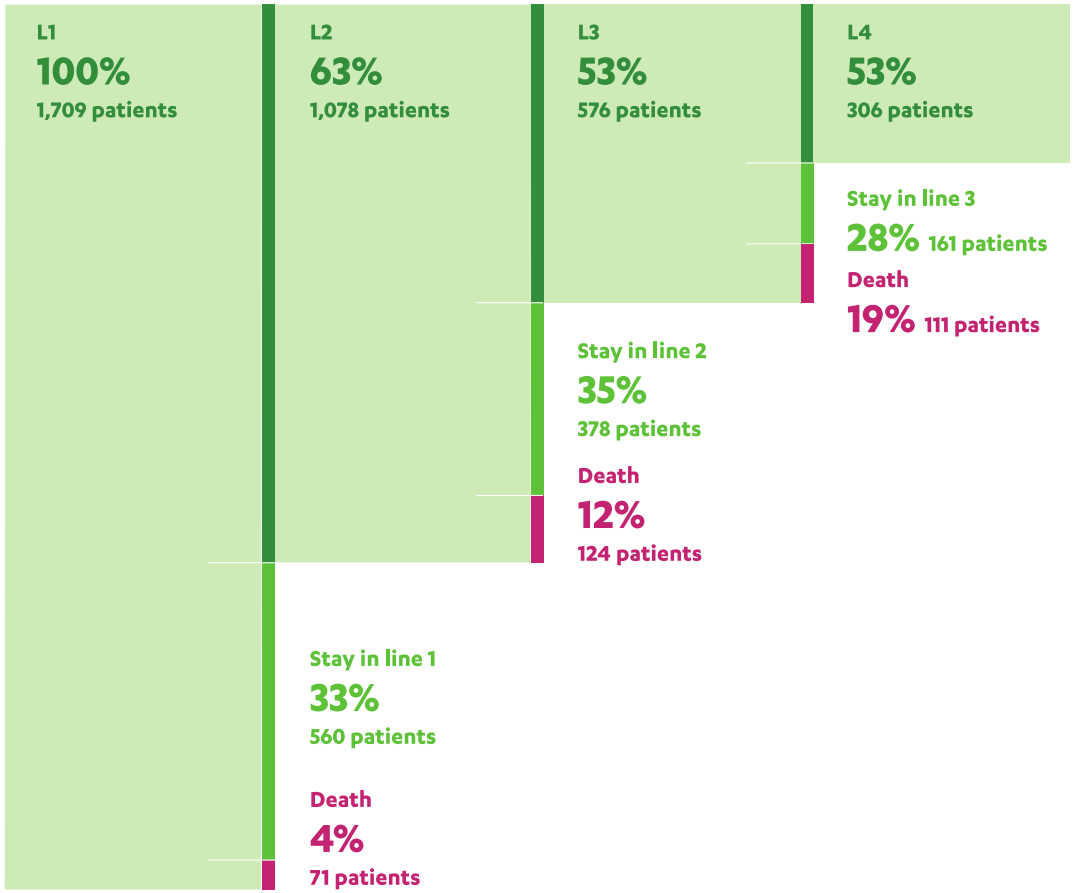
Comorbidités
Lignes reçues
1)
Meilleure réponse + date
Complications / séquelles
2)

Efficacité
Réponse
PFS
OS

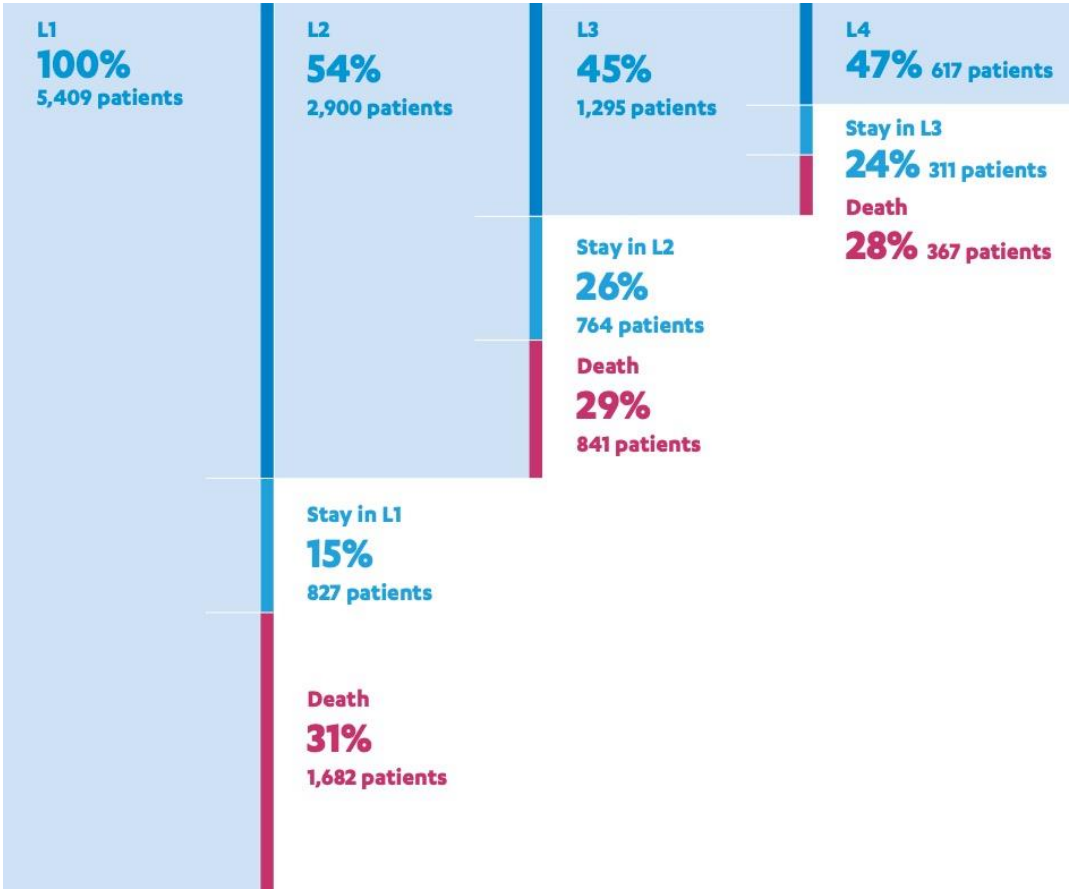
Toxicité / QoL
Toxicité
IV vs oral
Contraintes

Stratégie en vie réelle : faut-il se garder des cartouches ?

Patients greffés en L1



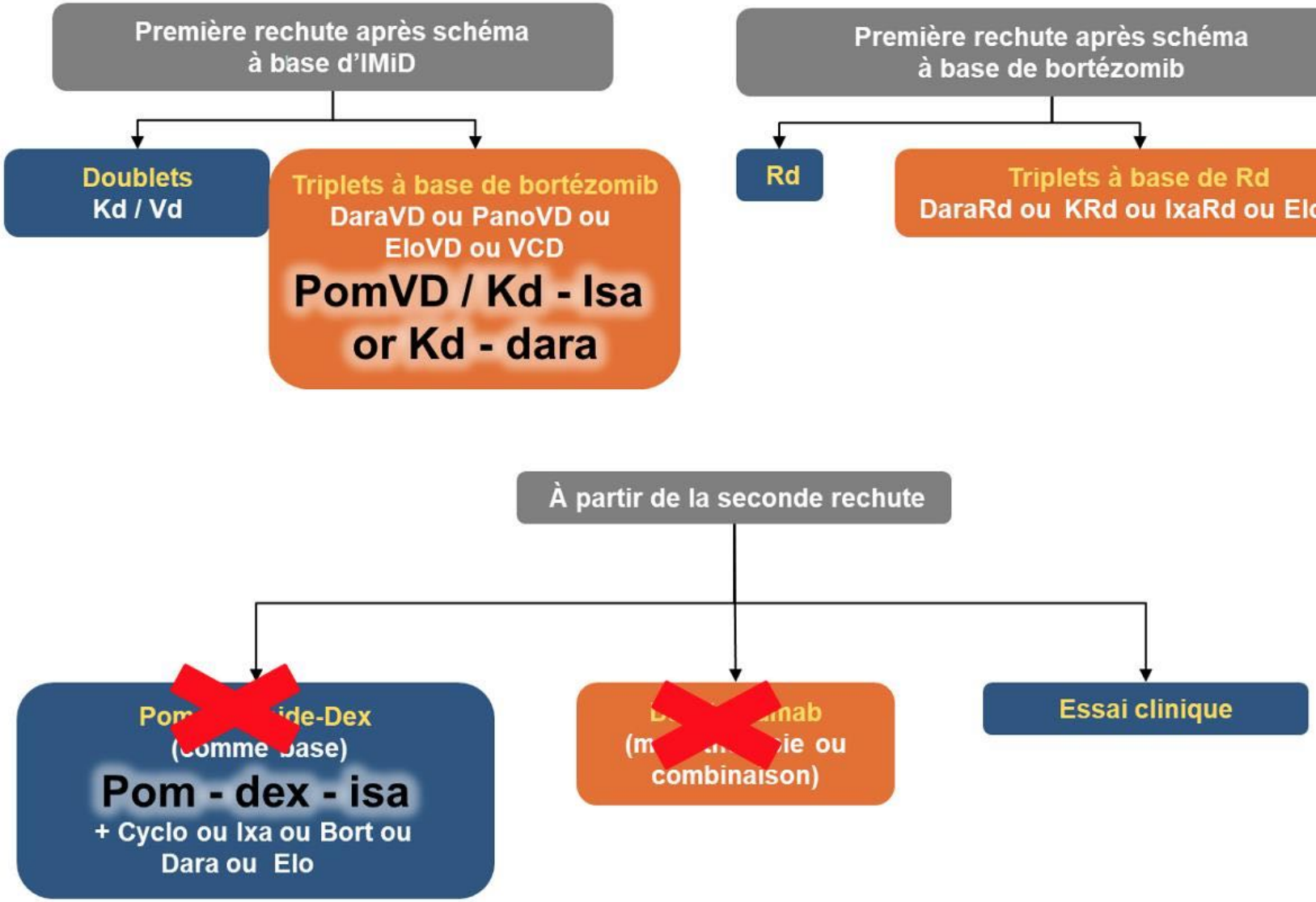
Patients non greffés en L1



All-cause of deaths are considered in this study

A Perrot, .., C Touzeau, IMW 2021

Stratégies actualisées d'après les recommandations de l'ESMO



D'après les recommandations de l'ESMO 2021

Rechute Len exposé non réfractaire

Patient de 69 ans

Myélome IgG kappa sans t(4;14) ni del(17p)

Traitement de 1ère ligne en 2017 par 4 VTD / Mel 200 + ASCT / 2 VTD et entretien par Revlimid pendant 2 ans jusque octobre 2019

Rechute biochimique (pic 15 g/L) et osseuse (nouvelles lésions ostéolytiques du bassin)

Rechute Len exposé non réfractaire

Quel traitement proposez-vous ?

1. VRD
2. KRD
3. DaraRD
4. IxaRD
5. Nouvelle autogreffe

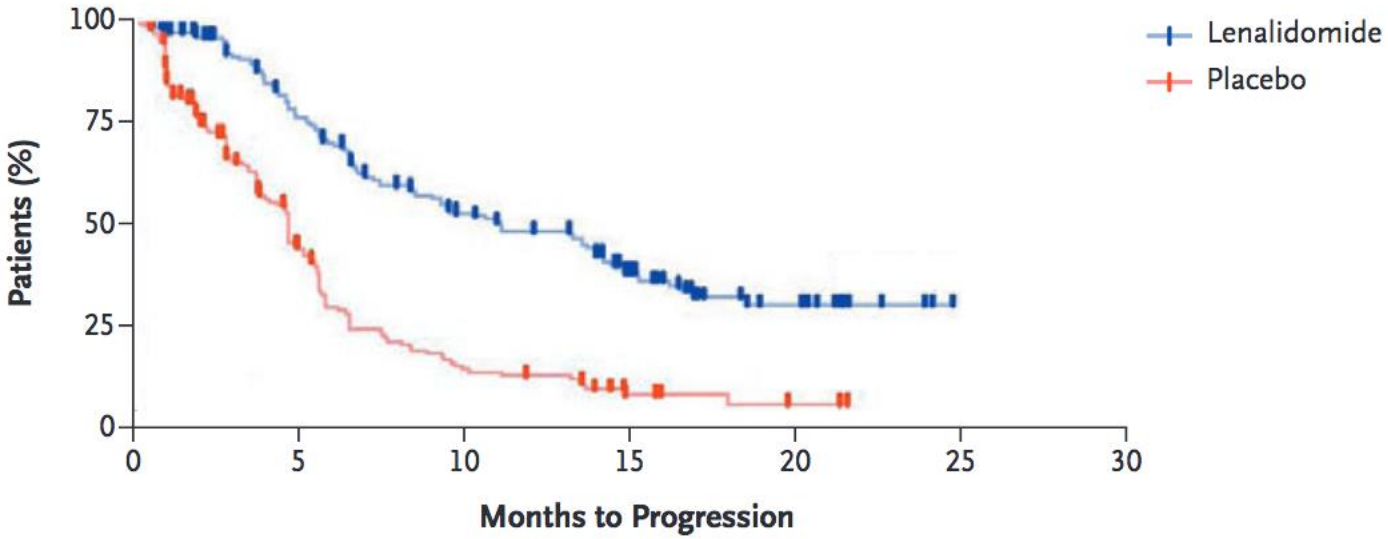
Rd versus d

Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America

Donna M. Weber, M.D., Christine Chen, M.D., Ruben Niesvizky, M.D., Michael Wang, M.D., Andrew Belch, M.D., Edward A. Stadtmauer, M.D., David Siegel, M.D., Ivan Borrello, M.D., S. Vincent Rajkumar, M.D., Asher Alban Chanan-Khan, M.D., Sagar Lonial, M.D., Zhinuan Yu, Ph.D., John Patin, M.S., Marta Olesnyckyj, R.N., Jerome B. Zeldis, M.D., Ph.D., and Robert D. Knight, M.D., for the Multiple Myeloma (009) Study Investigators*

MM-009

PFS médiane : 11,1 vs 4,7 mois
OS médiane : 29,6 vs 20,2 mois



DM Weber et al, N Engl J Med 2007

Rd versus d

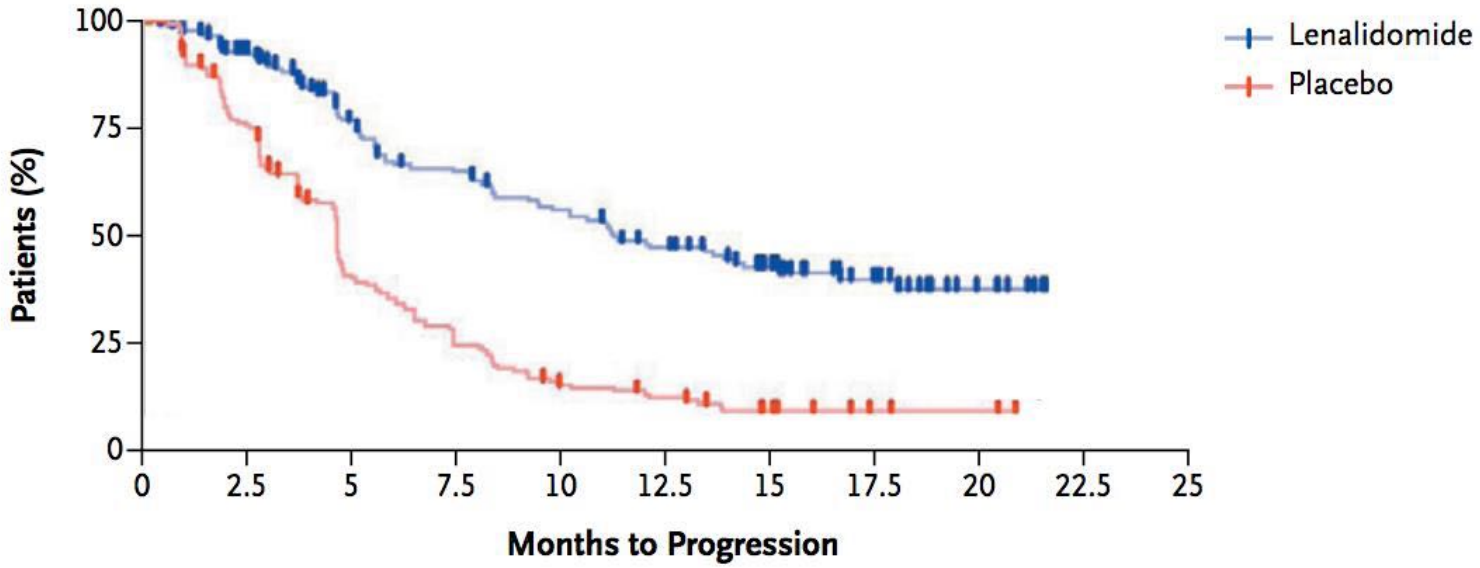
Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma

Meletios Dimopoulos, M.D., Andrew Spencer, M.D., Michael Attal, M.D., H. Miles Prince, M.D., Jean-Luc Harousseau, M.D., Anna Dmoszynska, M.D., Jesus San Miguel, M.D., Andrzej Hellmann, M.D., Thierry Facon, M.D., Robin Foà, M.D., Alessandro Corso, M.D., Zvenyslava Masliak, M.D., Marta Olesnyckyj, R.N., Zhinuan Yu, Ph.D., John Patin, M.S., Jerome B. Zeldis, M.D., Ph.D., and Robert D. Knight, M.D., for the Multiple Myeloma (010) Study Investigators*

MM-010

PFS médiane : 11,3 vs 4,7 mois

OS médiane : NA vs 20,6 mois



M Dimopoulos et al, N Engl J Med 2007

KRd versus Rd

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

A. Keith Stewart, M.B., Ch.B., S. Vincent Rajkumar, M.D., Meletios A. Dimopoulos, M.D., Tamás Masszi, M.D., Ph.D., Ivan Špička, M.D., Ph.D., Albert Oriol, M.D., Roman Hájek, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., David S. Siegel, M.D., Ph.D., Georgi G. Mihaylov, M.D., Ph.D., Vesselina Goranova-Marinova, M.D., Ph.D., Péter Rajnics, M.D., Ph.D., Aleksandr Suvorov, M.D., Ruben Niesvizky, M.D., Andrzej J. Jakubowiak, M.D., Ph.D., Jesus F. San-Miguel, M.D., Ph.D., Heinz Ludwig, M.D., Michael Wang, M.D., Vladimír Maisnar, M.D., Ph.D., Jiri Minarik, M.D., Ph.D., William I. Bensinger, M.D., Maria-Victoria Mateos, M.D., Ph.D., Dina Ben-Yehuda, M.D., Vishal Kukreti, M.D., Naseem Zojwalla, M.D., Margaret E. Tonda, Pharm.D., Xinqun Yang, Ph.D., Biao Xing, Ph.D., Philippe Moreau, M.D., and Antonio Palumbo, M.D., for the ASPIRE Investigators*

ASPIRE

Randomization

N=792

Stratification:

- **β_2-microglobulin**
- **Prior bortezomib**
- **Prior lenalidomide**

KRd

Carfilzomib 27 mg/m^2 IV (10 min)

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

After cycle 12, carfilzomib given on days 1, 2, 15, 16

After cycle 18, carfilzomib discontinued

Rd

Lenalidomide 25 mg *Days 1–21*

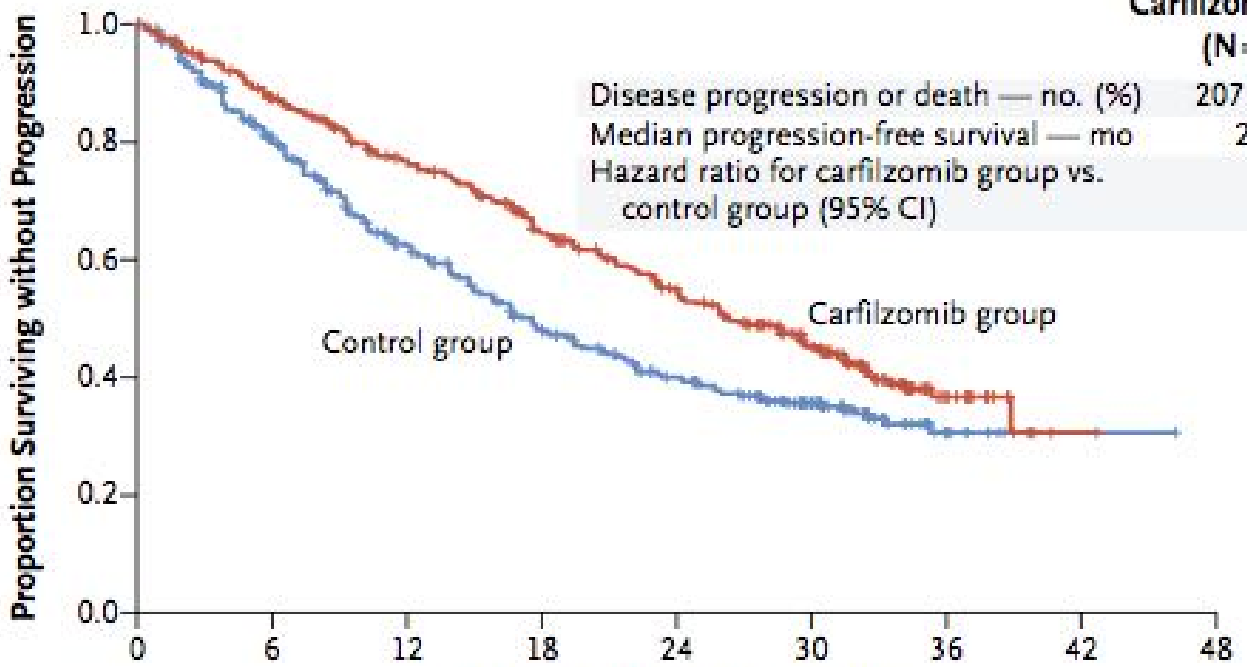
Dexamethasone 40 mg *Days 1, 8, 15, 22*

AK Stewart et al, N Engl J Med 2015

Etude ASPIRE : approbation de KRd

PFS médiane : 26,3 vs 17,6 mois

n = 792



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	
	P=0.0001	

No. at Risk

Carfilzomib group	396	332	279	222	179	112	24	1
Control group	396	287	206	151	117	72	18	1

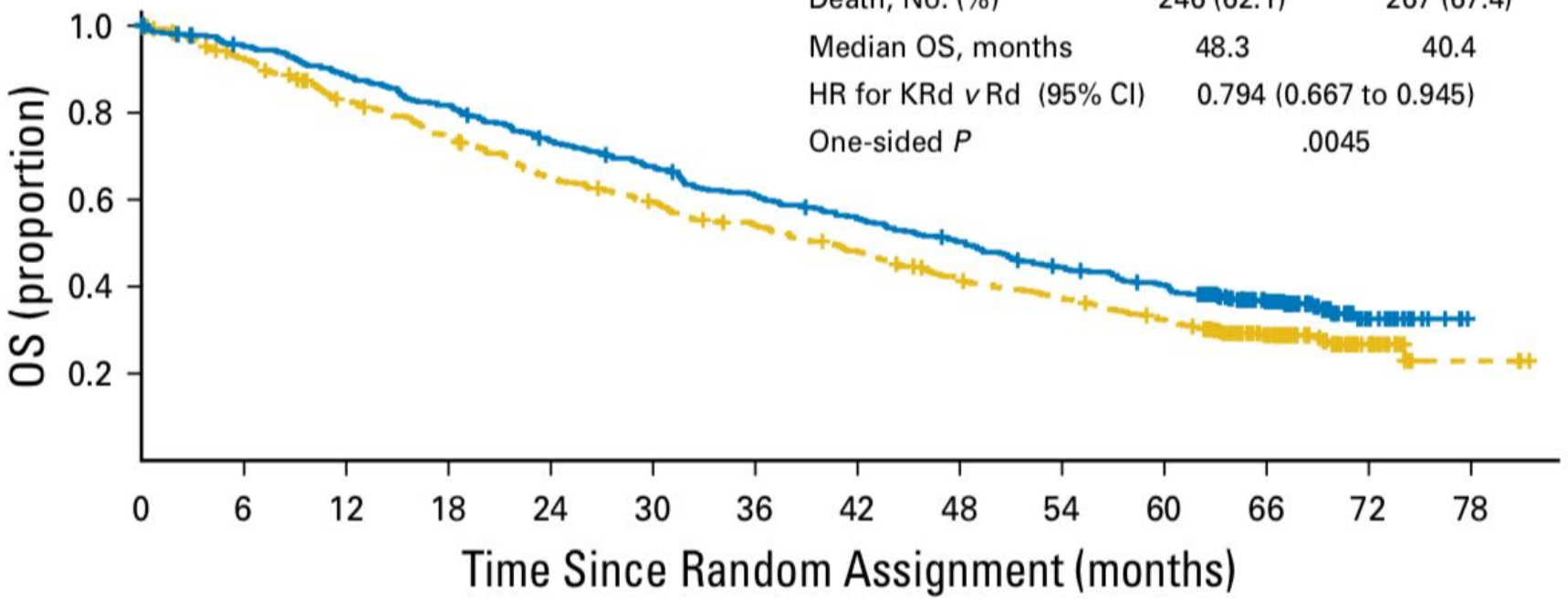
AK Stewart et al, N Engl J Med 2015

Etude ASPIRE : approbation de KRd

OS médiane : 48,3 vs 40,4 mois

Suivi médian : 67,1 mois

	KRd (n = 396)	Rd (n = 396)
Death, No. (%)	246 (62.1)	267 (67.4)
Median OS, months	48.3	40.4
HR for KRd *v* Rd (95% CI)	0.794 (0.667 to 0.945)	
One-sided *P*	.0045	



No. at risk:

KRd	396	369	343	316	282	259	232	211	190	166	149	88	22	0
Rd	396	356	313	281	243	220	199	176	149	133	113	69	20	3

DS Siegel et al, J Clin Oncol 2018

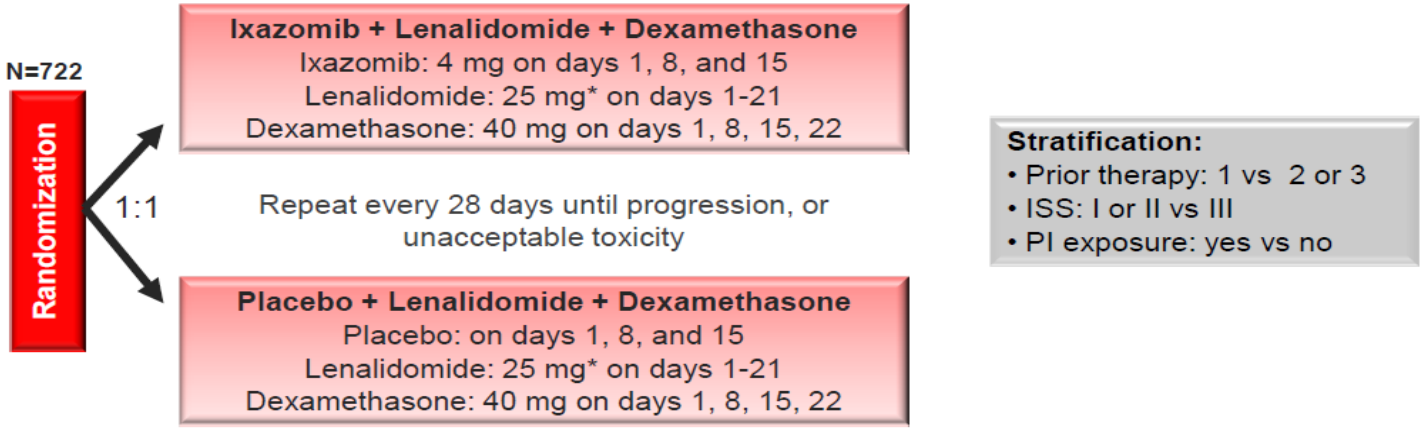
IRd versus (placebo)Rd

Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

P. Moreau, T. Masszi, N. Grzasko, N.J. Bahlis, M. Hansson, L. Pour, I. Sandhu, P. Ganly, B.W. Baker, S.R. Jackson, A.-M. Stoppa, D.R. Simpson, P. Gimsing, A. Palumbo, L. Garderet, M. Cavo, S. Kumar, C. Touzeau, F.K. Buadi, J.P. Laubach, D.T. Berg, J. Lin, A. Di Bacco, A.-M. Hui, H. van de Velde, and P.G. Richardson, for the TOURMALINE-MM1 Study Group*

TOURMALINE-MM1

Global, double-blind, randomized, placebo-controlled study design



Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria[1]) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

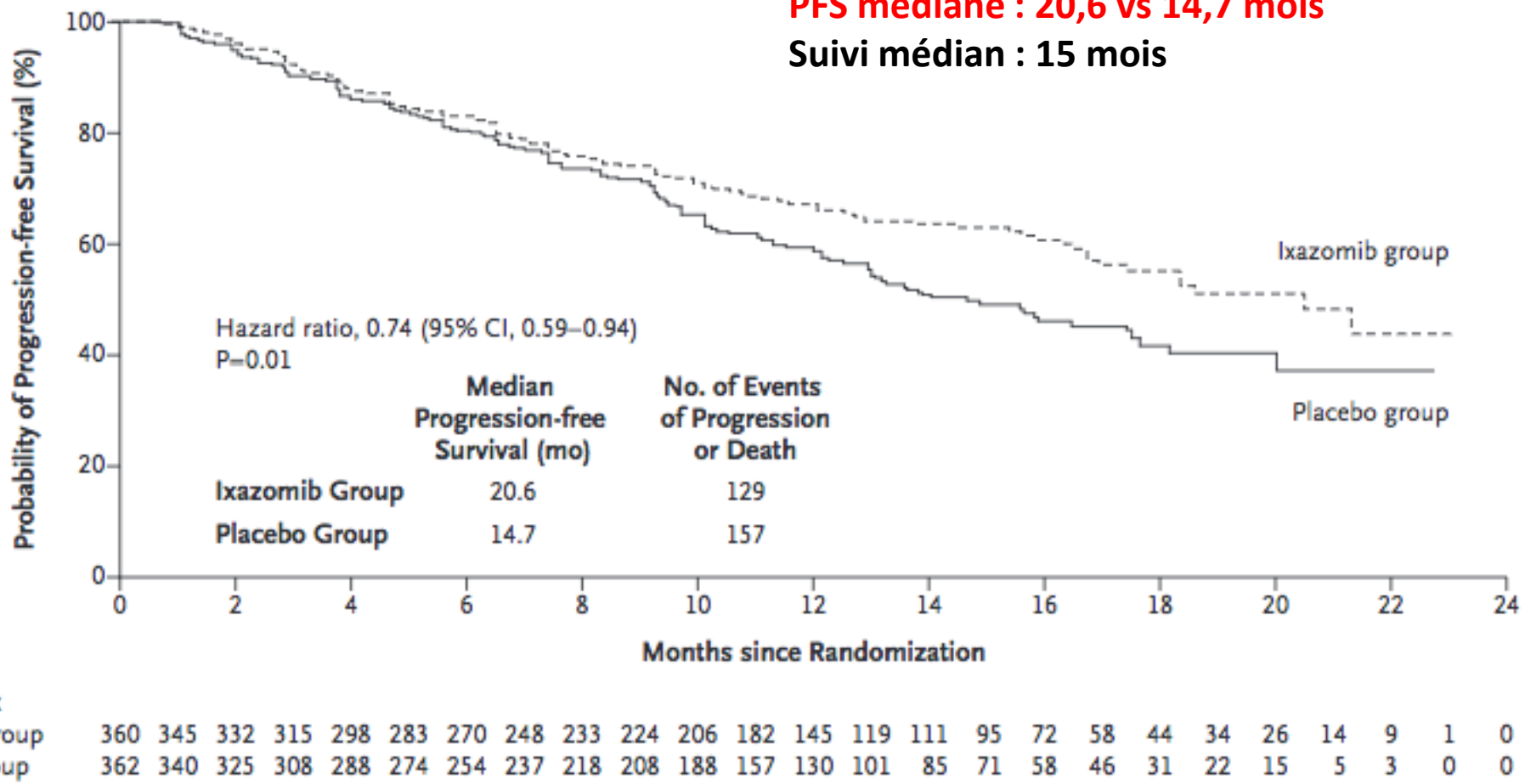
P Moreau et al, N Engl J Med 2016

Etude TOURMALINE-MM1 : approbation d'IxaRd

PFS médiane : 20,6 vs 14,7 mois

Suivi médian : 15 mois

n = 722



P Moreau et al, N Engl J Med 2016

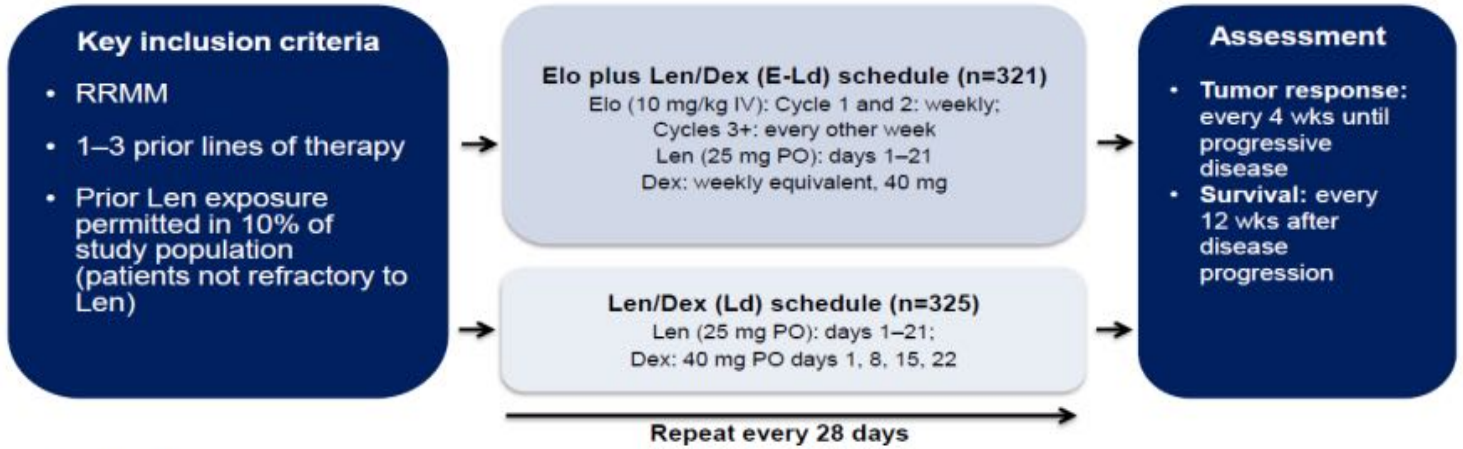
Elo-Rd versus Rd

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

ELOQUENT-2

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)

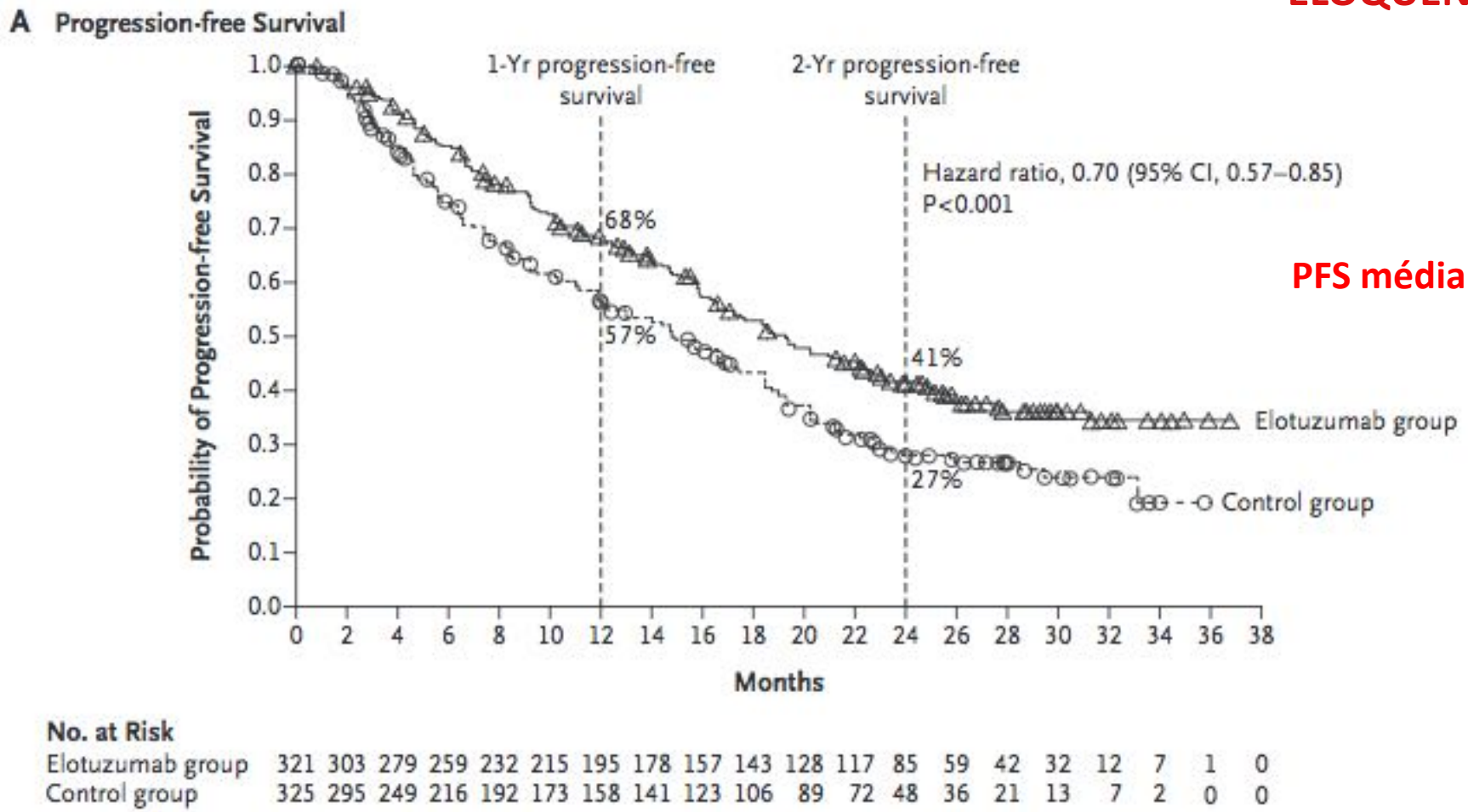


- Endpoints:
  - Co-primary: PFS and ORR
  - Other: overall survival (data not yet mature); duration of response, quality of life, safety
- All patients received premedication to mitigate infusion reactions prior to Elo administration

S Lonial et al, N Engl J Med 2015

Etude ELOQUENT-2 : approbation d'Elo-Rd

ELOQUENT-2



PFS médiane : 19,4 vs 14,9 mois

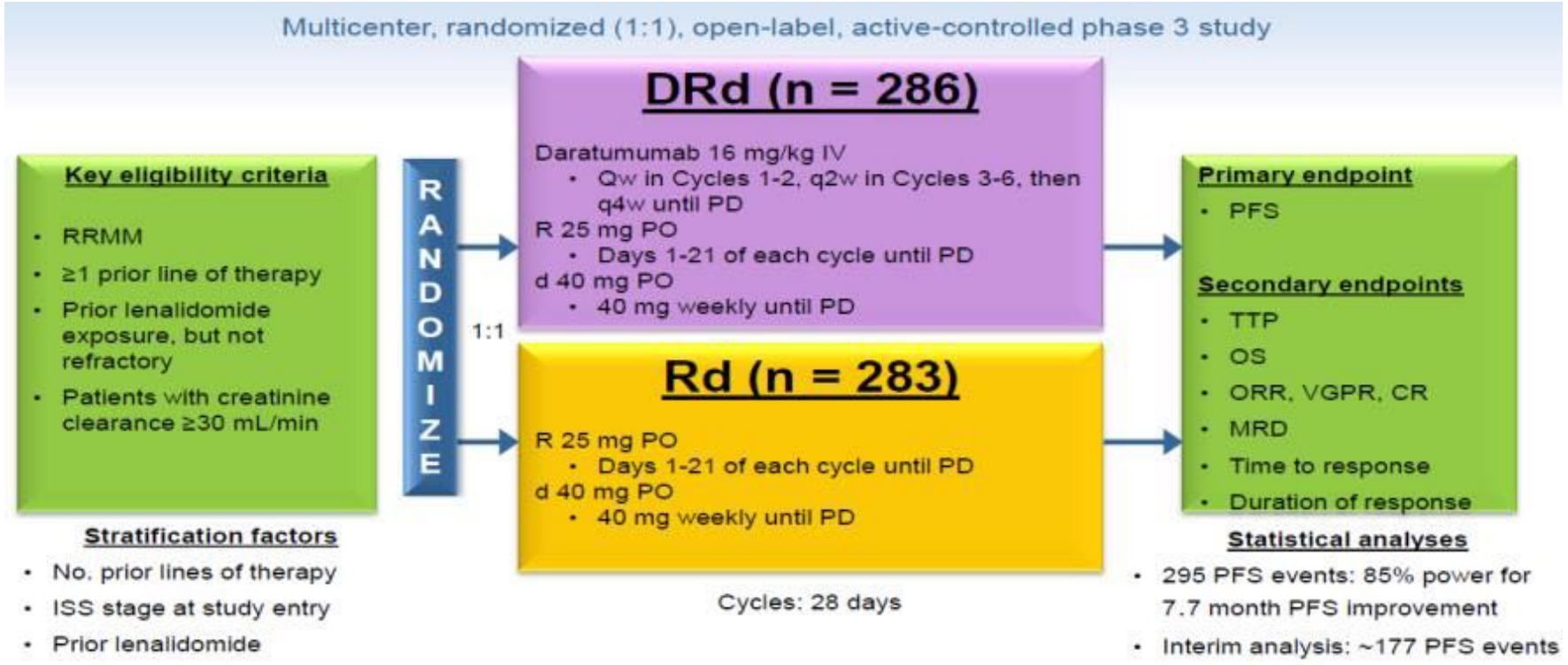
S Lonial et al, N Engl J Med 2015

Dara-Rd versus Rd

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

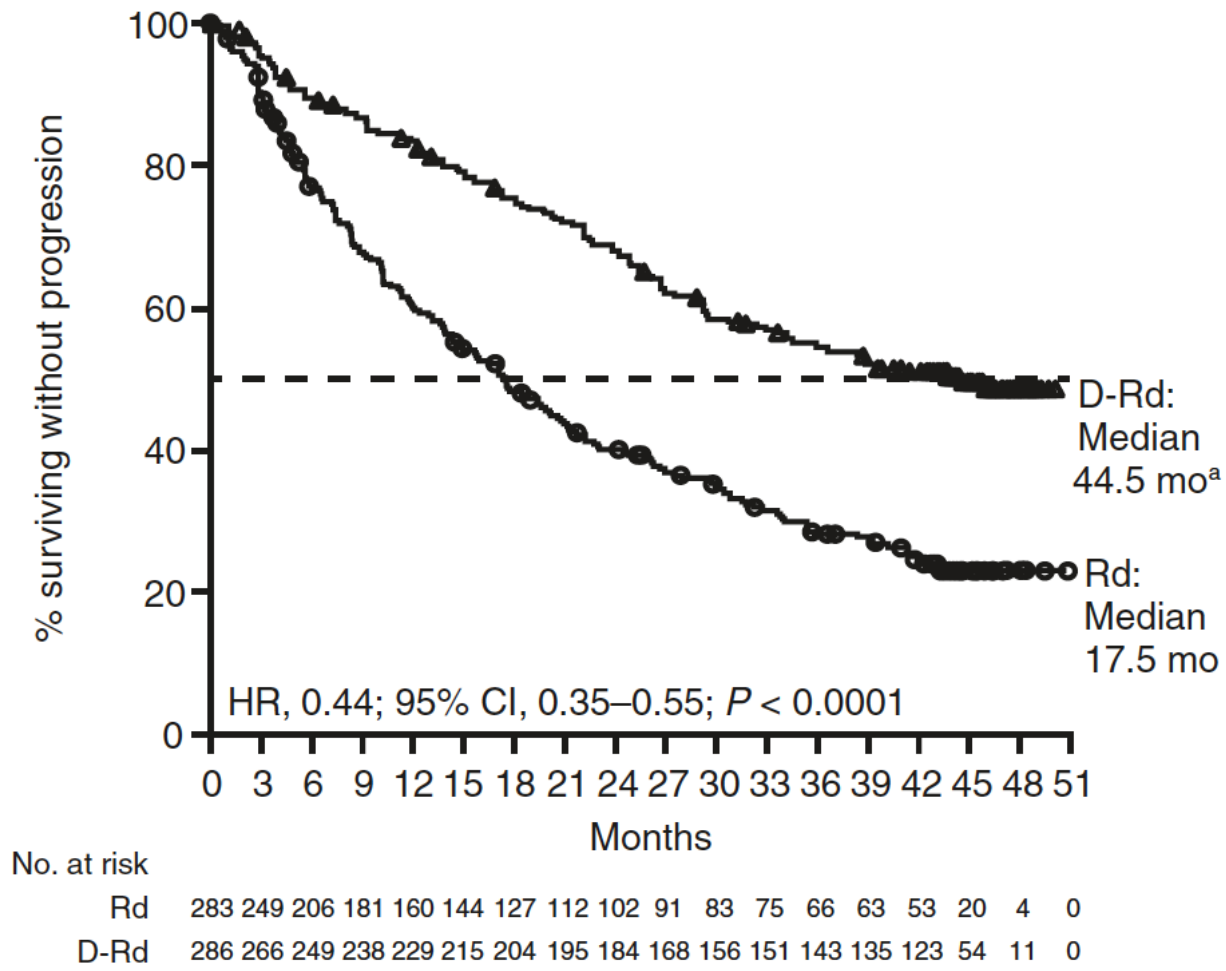
POLLUX



M Dimopoulos, N Engl J Med 2016

Etude POLLUX : approbation de Dara-Rd

n = 569



M Dimopoulos et al, N Engl J Med 2016
NJ Bahlis et al, Leukemia 2020

Rechute Len exposé non réfractaire

	Intention-to-treat population			One previous line of therapy		
	n	Median PFS, months (95% CI)	HR (95% CI);* p value	n	Median PFS, months (95% CI)	HR (95% CI);* p value
ASPIRE[11]	..	..	0·69 (0·57–0·83); <0·0001	..	..	0·69 (0·52–0·94); 0·012
Rd group	396	17·6 (15·0–20·6)	..	157	17·6 (15·0–22·2)	..
KRd group	396	26·3 (23·3–30·0)	..	184	29·6 (23·2–33·5)	..
TOURMALINE[12]	..	..	0·74 (0·59–0·94); 0·012	..	..	0·83 (0·63–1·20); NA
Rd group	362	14·7, NA	..	217	NA	..
IRd group	360	20·6, NA	..	224	NA	..
POLLUX[14,38]	..	..	0·44 (0·35–0·54); <0·0001	..	..	0·42 (0·30–0·57); <0·0001
Rd group	283	17·5 (13·9–20·8)	..	146	19·6, NA	..
DRd group	286	44·5 (34·1–NE)	..	149	53·3, NA	..
ELOQUENT-2[13]	..	..	0·70 (0·57–0·85); 0·0004	..	..	0·75 (0·56–1·00); NA
Rd group	325	14·9 (12·1–17·2)	..	159	NA	..
Elo–Rd group	321	19·4 (16·6–22·2)	..	151	NA	..

Rechute Len réfractaire

Patient de 57 ans

Myélome IgA lambda avec t(4;14) sans del(17p)

Traitement de 1ère ligne en 2020 par 4 VRD / Mel 200 + ASCT / 2 VRD et entretien par Revlimid en cours

Meilleure réponse : TBRP (pic 0 g/L, IF positive)

Rechute biochimique (pic 12 g/L en octobre 2019 versus 2 g/L en août 2021) sans atteinte osseuse

Rechute Len réfractaire

Quel traitement proposez-vous ?

1. IsaPomDex
2. DaraKD
3. IsaKD
4. PVD
5. KD
6. Autre ?

Nouvelles combinaisons à base de Vd / Kd ou Pd

Première rechute après IMID

Doublets
Vd / Kd

Triplets à base de Vd/Kd
DaraVd - PanoVd - EloVd - VCd
PVd – DaraKd – IsaKd – IsaPd – SelVd – VenVd

OPTIMISMM

CANDOR

IKEMA

BOSTON

BELLINI

HORIZON

ICARIA

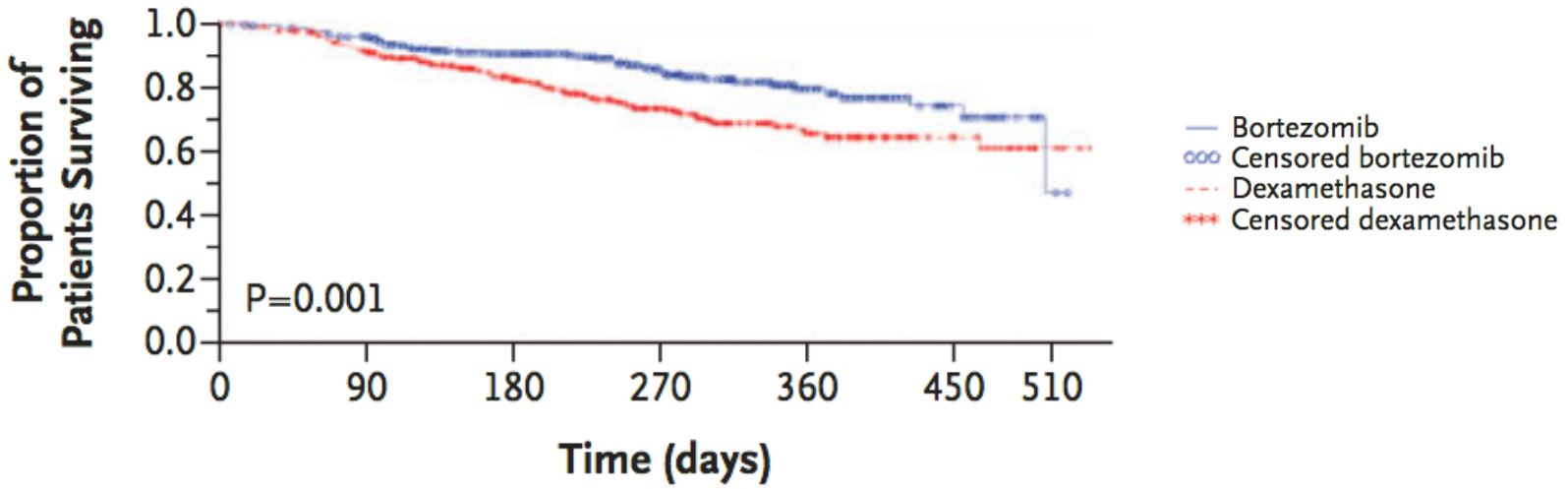
V versus d

Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma

Paul G. Richardson, M.D., Pieter Sonneveld, M.D., Michael W. Schuster, M.D., David Irwin, M.D., Edward A. Stadtmauer, M.D., Thierry Facon, M.D., Jean-Luc Harousseau, M.D., Dina Ben-Yehuda, M.D., Sagar Lonial, M.D., Hartmut Goldschmidt, M.D., Donna Reece, M.D., Jesus F. San-Miguel, M.D., Joan Bladé, M.D., Mario Boccadoro, M.D., Jamie Cavenagh, M.D., William S. Dalton, M.D., Anthony L. Boral, M.D., Ph.D., Dixie L. Esseltine, M.D., Jane B. Porter, M.S., David Schenkein, M.D., and Kenneth C. Anderson, M.D., for the Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators*

APEX

PFS médiane : 6,2 vs 3,5 mois
OS à 1 an : 80 % vs 66 %



No. at Risk						
Bortezomib	310	219	138	62	21	2
Dexamethasone	292	201	118	59	20	4

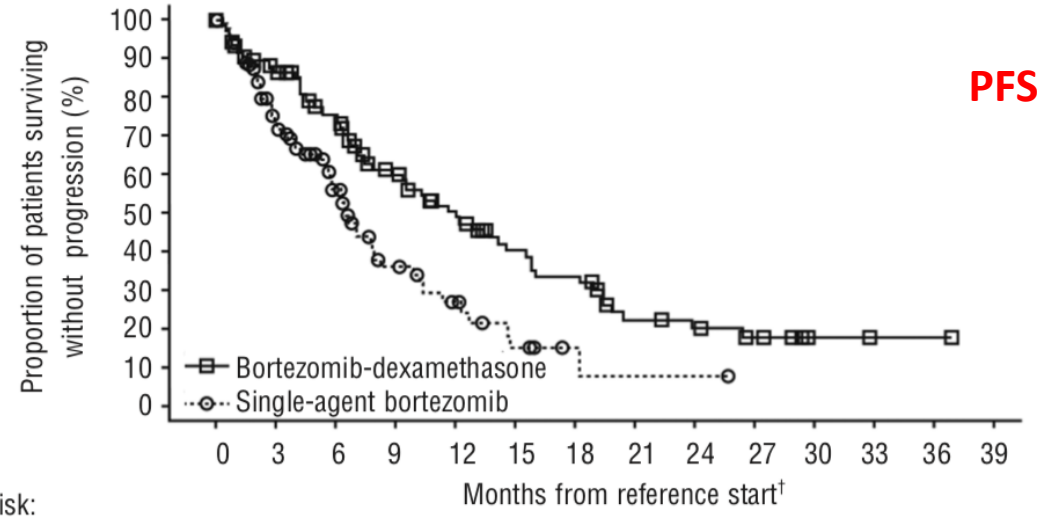
PG Richardson et al, N Engl J Med 2005

Vd versus V

Retrospective matched-pairs analysis of bortezomib plus dexamethasone versus bortezomib monotherapy in relapsed multiple myeloma

Meletios A. Dimopoulos,[1] Robert Z. Orlowski,[2] Thierry Facon,[3] Pieter Sonneveld,[4] Kenneth C. Anderson,[5] Meral Beksac,[6] Lotfi Benboubker,[7] Huw Roddie,[8] Anna Potamianou,[9] Catherine Couturier,[10] Huaibao Feng,[11] Ozlem Ataman,[12] Helgi van de Velde,[13] and Paul G. Richardson[5]

	Bortezomib-dexamethasone (n=109)	Single-agent bortezomib (n=109)	HR (95% CI)	*P*
PFS				
Events n(%)	62 (57)	58 (53)		
Median PFS, months	11.9	6.4	0.595 (0.351-1.008)	0.051*



Patients at risk:														
Bortezomib-dexamethasone	109	85	68	46	33	24	19	11	8	6	2	1	1	0
Single-agent bortezomib	109	62	35	18	10	5	1	1	1	0	0	0	0	0

PFS médiane : 11,9 vs 6,4 mois

MA Dimopoulos, Haematologica 2015

Vd versus Kd

Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial

Meletios A Dimopoulos, Hartmut Goldschmidt, Ruben Niesvizky, Douglas Joshua, Wee-Joo Chng, Albert Oriol, Robert Z Orlowski, Heinz Ludwig, Thierry Facon, Roman Hajek, Katja Weisel, Vania Hungria, Leonard Minuk, Shibao Feng, Anita Zahlten-Kumeli, Amy S Kimball, Philippe Moreau

ENDEAVOR

Randomization 1:1

N=929

Stratification:

- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of V administration

Kd

Carfilzomib 56 mg/m² IV
Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)
Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg
Days 1, 2, 8, 9, 15, 16, 22, 23
28-day cycles until PD or unacceptable toxicity

Vd

Bortezomib 1.3 mg/m² (IV bolus or subcutaneous injection)
Days 1, 4, 8, 11

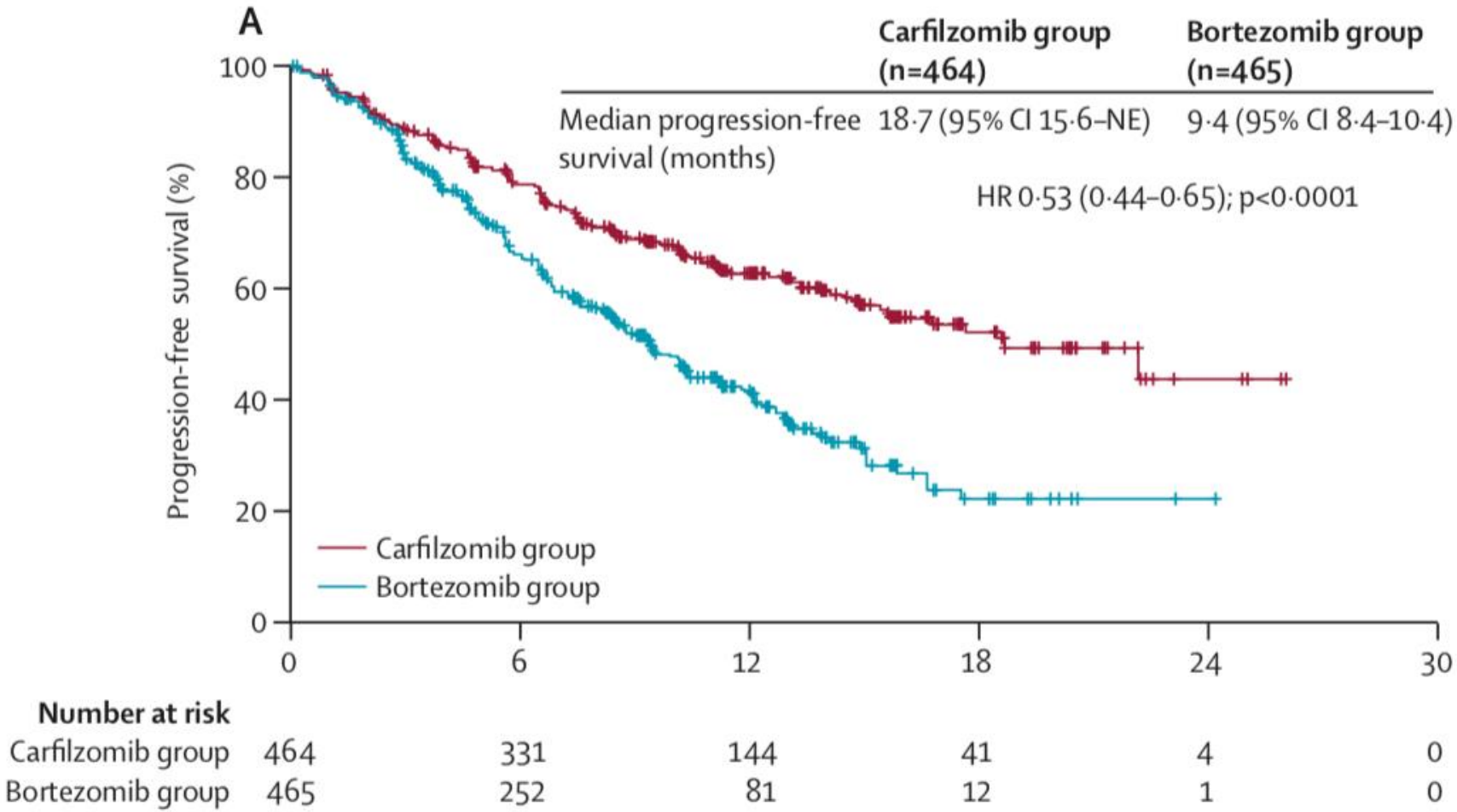
Dexamethasone 20 mg
Days 1, 2, 4, 5, 8, 9, 11, 12
21-day cycles until PD or unacceptable toxicity

ISS, International Staging System; IV, intravenous; PD, progressive disease
Kd, carfilzomib and dexamethasone
Vd, bortezomib and dexamethasone; V, bortezomib.

MA Dimopoulos et al, Lancet Oncol 2017

Etude ENDEAVOR : approbation de Kd

n = 929



PFS médiane : 18,7 vs 9,4 mois

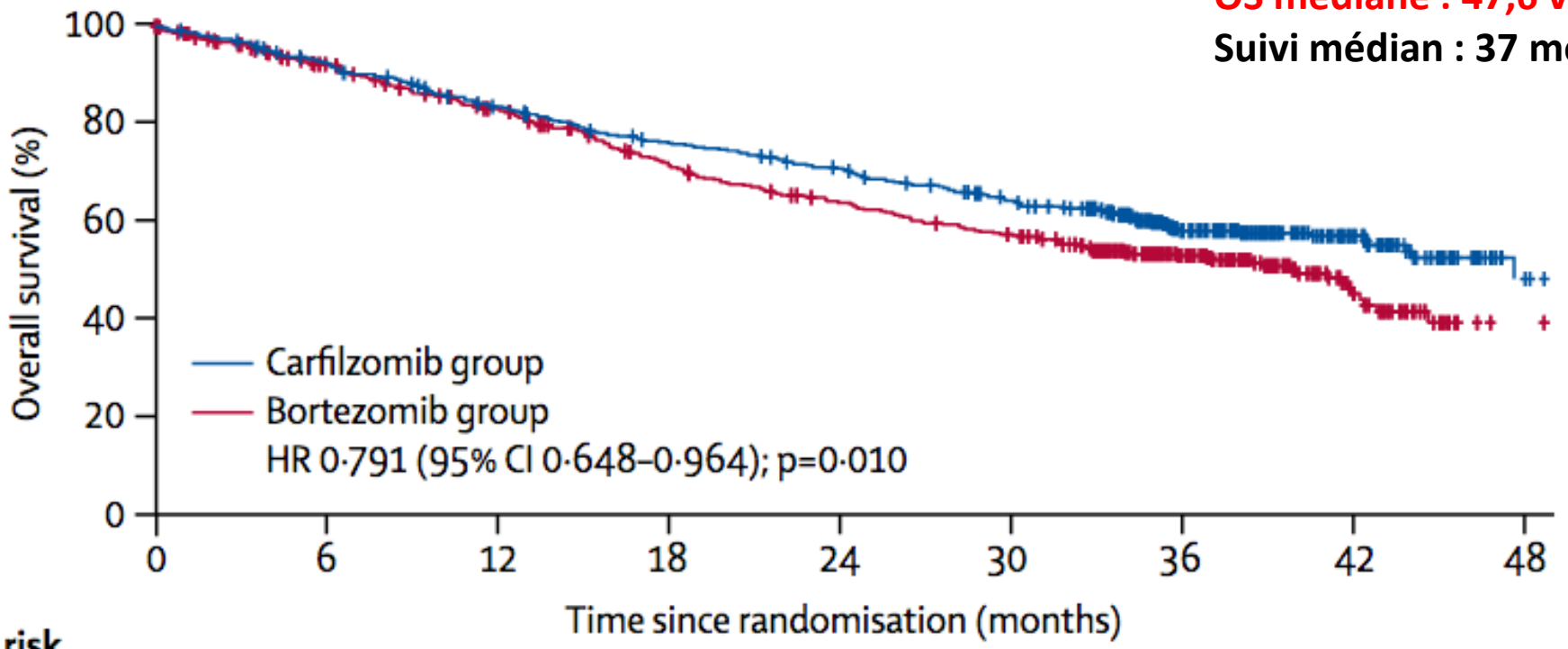
Suivi médian : 11,2 mois

MA Dimopoulos et al, Lancet Oncol 2016

Etude ENDEAVOR : approbation de Kd

OS médiane : 47,6 vs 40 mois

Suivi médian : 37 mois



Number at risk (number censored)									
Carfilzomib group	464 (0)	423 (7)	373 (16)	335 (21)	308 (25)	270 (35)	162 (121)	66 (215)	10 (266)
Bortezomib group	465 (0)	402 (28)	351 (40)	293 (50)	256 (56)	228 (58)	140 (130)	39 (221)	5 (251)

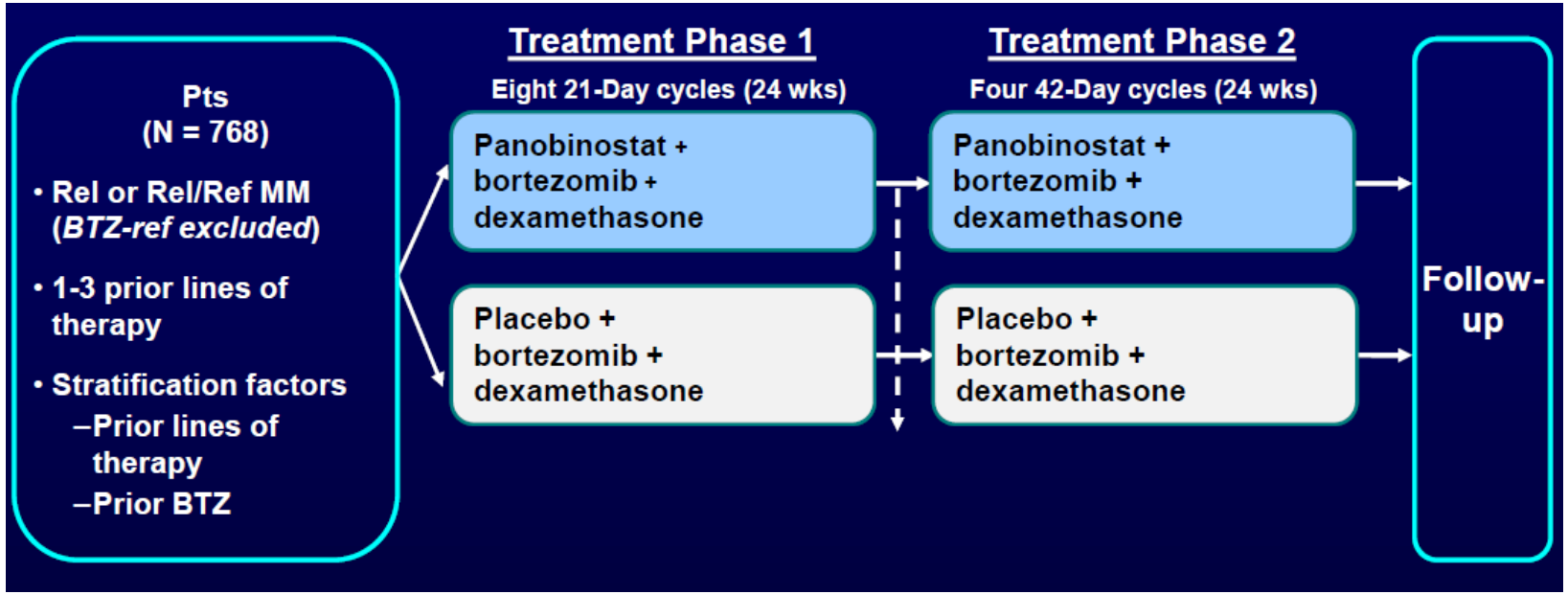
MA Dimopoulos et al, Lancet Oncol 2017

Vd versus Vd+Panobinostat

Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial

Jesús F San-Miguel, Vânia T M Hungria, Sung-Soo Yoon, Meral Beksac, Meletios Athanasios Dimopoulos, Ashraf Elghandour, Wieslaw Wiktor Jedrzejczak, Andreas Günther, Thanyaphong Na Nakorn, Noppadol Siritanaratkul, Paolo Corradini, Suporn Chuncharunee, Je-Jung Lee, Robert L Schlossman, Tatiana Shelekhova, Kwee Yong, Daryl Tan, Tontanai Numbenjapon, Jamie D Cavenagh, Jian Hou, Richard LeBlanc, Hareth Nahi, Lugui Qiu, Hans Salwender, Stefano Pulini, Philippe Moreau, Krzysztof Warzocha, Darrell White, Joan Bladé, WenMing Chen, Javier de la Rubia, Peter Gimsing, Sagar Lonial, Jonathan L Kaufman, Enrique M Ocio, Ljupco Veskovski, Sang Kyun Sohn, Ming-Chung Wang, Jae Hoon Lee, Hermann Einsele, Monika Sopala, Claudia Corrado, Bourras-Rezki Bengoudifa, Florence Binlich, Paul G Richardson

PANORAMA 1



Panobinostat 20 mg/day d1, 3, 5, 8, 10, 12
(d1 = d21)

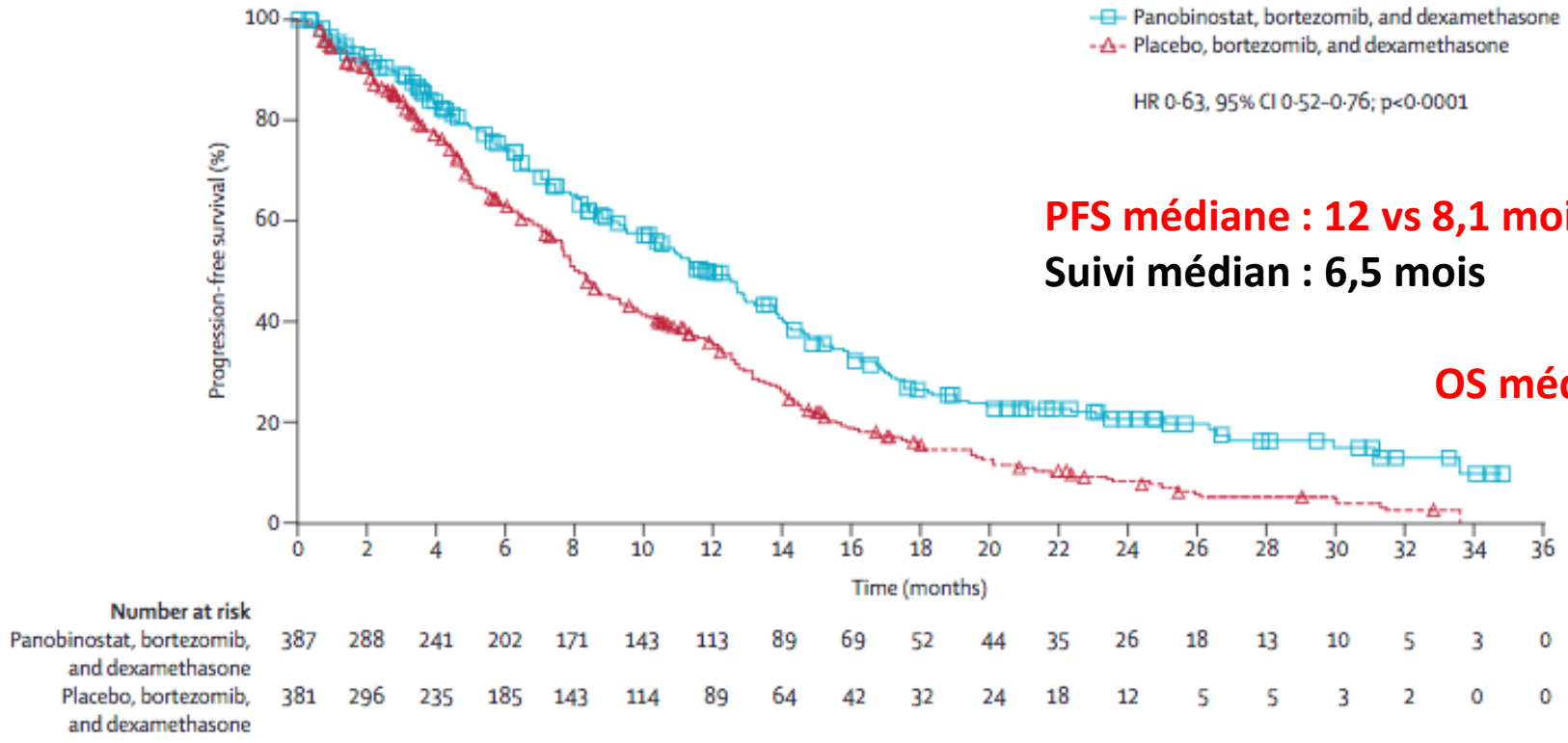
J San Miguel et al, Lancet Oncol 2014

Vd versus Vd+Panobinostat

Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial

Jesús F San-Miguel, Vânia T M Hungria, Sung-Soo Yoon, Meral Beksac, Meletios Athanasios Dimopoulos, Ashraf Elghandour, Wieslaw Wiktor Jedrzejczak, Andreas Günther, Thanyaphong Na Nakorn, Noppadol Siritanaratkul, Paolo Corradini, Suporn Chuncharunee, Je-Jung Lee, Robert L Schlossman, Tatiana Shelekhova, Kwee Yong, Daryl Tan, Tontanai Numbenjapon, Jamie D Cavenagh, Jian Hou, Richard LeBlanc, Hareth Nahi, Lugui Qiu, Hans Salwender, Stefano Pulini, Philippe Moreau, Krzysztof Warzocha, Darrell White, Joan Bladé, WenMing Chen, Javier de la Rubia, Peter Gimsing, Sagar Lonial, Jonathan L Kaufman, Enrique M Ocio, Ljupco Veskovski, Sang Kyun Sohn, Ming-Chung Wang, Jae Hoon Lee, Hermann Einsele, Monika Sopala, Claudia Corrado, Bourras-Rezki Bengoudifa, Florence Binlich, Paul G Richardson

PANORAMA 1



PFS médiane : 12 vs 8,1 mois

Suivi médian : 6,5 mois

OS médiane : 40,3 vs 35,8 mois (NS)

J San Miguel et al, Lancet Oncol 2014

Vd versus Vd+Daratumumab

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*

CASTOR

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior bortezomib exposure, but not refractory

RANDOMIZE 1:1

DVd (n = 251)

Daratumumab (16 mg/kg IV)
Every week - cycle 1-3
Every 3 weeks - cycle 4-8
Every 4 weeks - cycles 9+

Vel: 1.3 mg/m^2 SC, days 1,4,8,11 - cycle 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycle 1-8

Vd (n = 247)

Vel: 1.3 mg/m^2 SC, days 1,4,8,11 - cycle 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycle 1-8

- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

Primary Endpoint

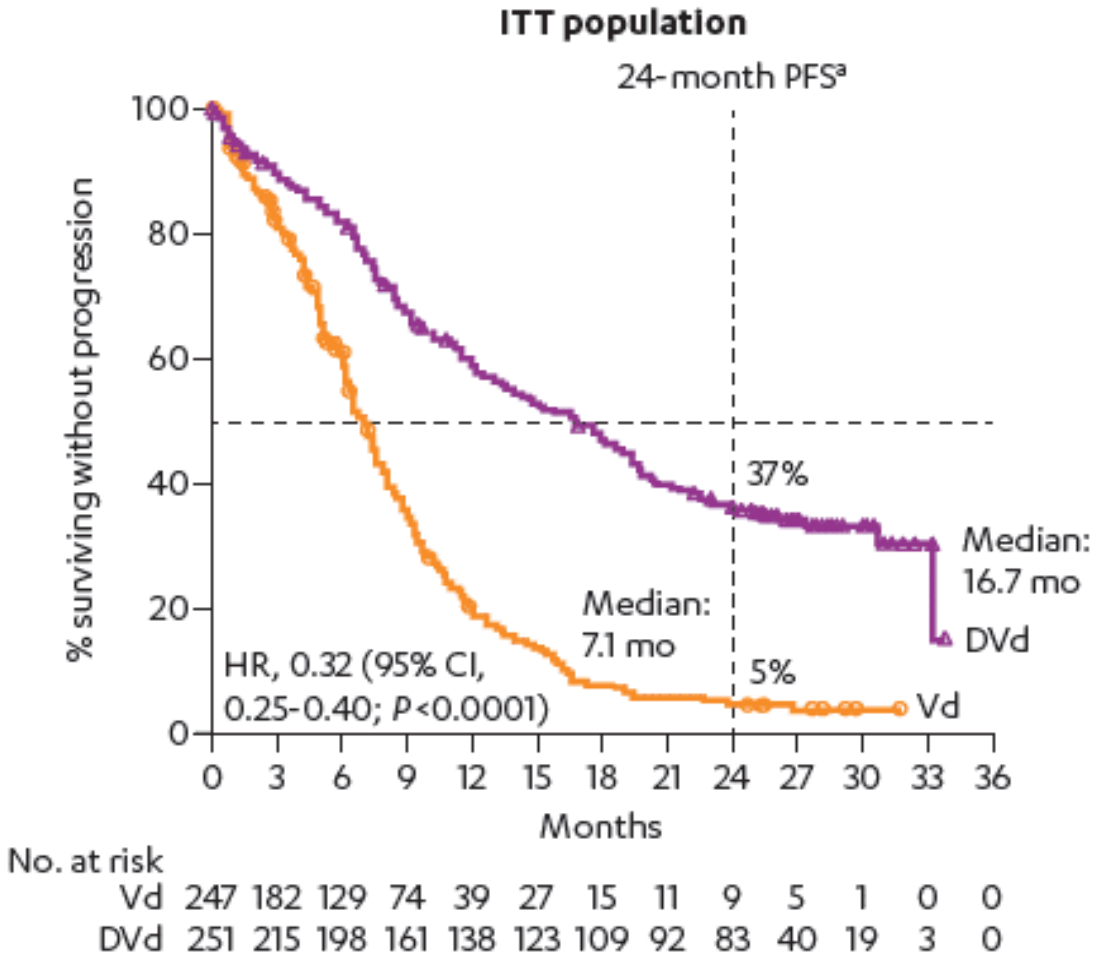
- PFS

Secondary Endpoints

- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

A Palumbo et al, N Engl J Med 2016

Etude CASTOR : approbation de DaraVd



Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*

PFS médiane : 16,7 vs 7,1 mois

Suivi médian : 26,9 mois

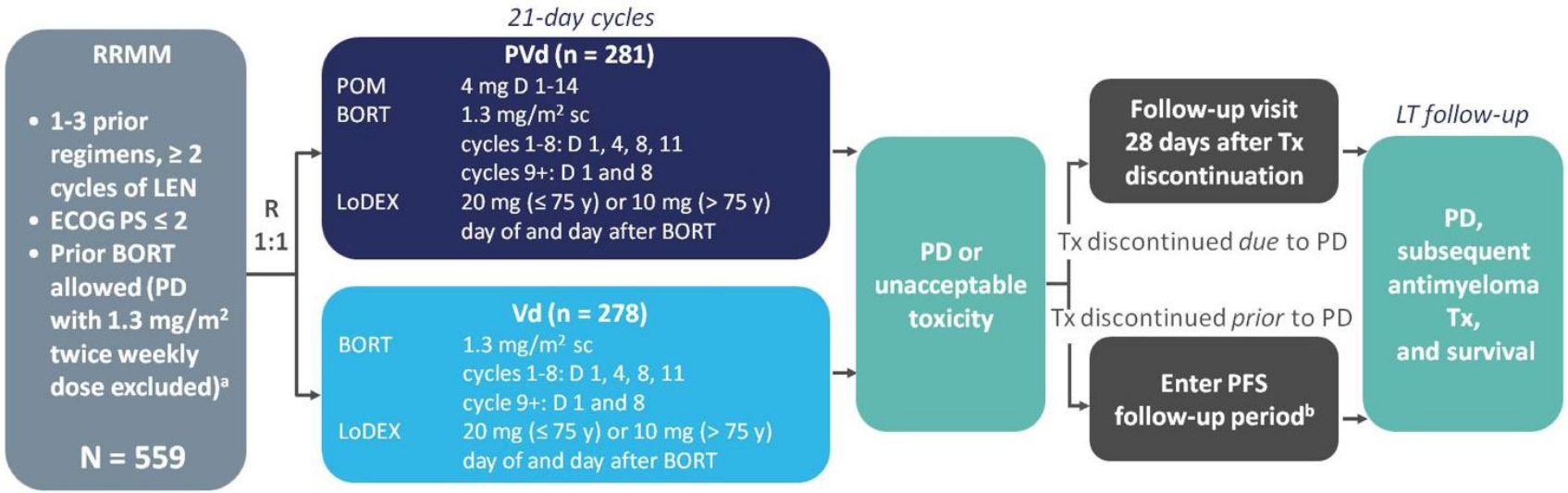
A Palumbo et al, N Engl J Med 2016
A Spencer et al, Haematologica 2018

Vd versus Vd+Pomalidomide

Pomalidomide, Bortezomib, and Low-Dose Dexamethasone (PVd) vs Bortezomib and Low-Dose Dexamethasone (Vd) in Lenalidomide-Exposed Patients With Relapsed or Refractory Multiple Myeloma: Phase 3 OPTIMISMM Trial

Paul Richardson,[1] Albert Oriol,[2] Meral Beksac,[3] Anna Marina Liberati,[4] Monica Galli,[5] Fredrik Schjesvold,[6] Jindriska Lindsay,[7] Katja Weisel,[8] Darrell White,[9] Thierry Facon,[10] Jesus San Miguel,[11] Kazutaka Sunami,[12] Peter O'Gorman,[13] Pieter Sonneveld,[14] Xin Yu,[15] Thomas Doerr,[15] Amine Bensmaine,[15] Mohamed Zaki,[15] Kenneth Anderson,[1] Meletios Dimopoulos[16] *on behalf of the OPTIMISMM trial investigators*

OPTIMISMM



- **Stratification**
  - Age (≤ 75 y vs > 75 y)
  - Prior regimens (1 vs > 1)
  - β2-microglobulin at screening (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L)

- **Study endpoints**
  - Primary: PFS
  - Secondary: OS, ORR by IMWG criteria, DOR, safety
  - Key exploratory: TTR, PFS2, efficacy analysis in subgroups
- **Data cutoff:** October 26, 2017

[a]Patients with PD during therapy or within 60 days of the last dose of a BORT-containing therapy under the approved dosing schedule of 1.3 mg/m² twice weekly were excluded. [b]Efficacy evaluated every 21 days (± 3 days) until PD.

DOR, duration of response; LT, long-term; PFS2, progression-free survival after next line of therapy; TTR, time to response.

NCT01734928

P Richardson et al, ASCO 2018

Etude OPTIMISMM : approbation de PVd

PRIOR THERAPY (ITT)

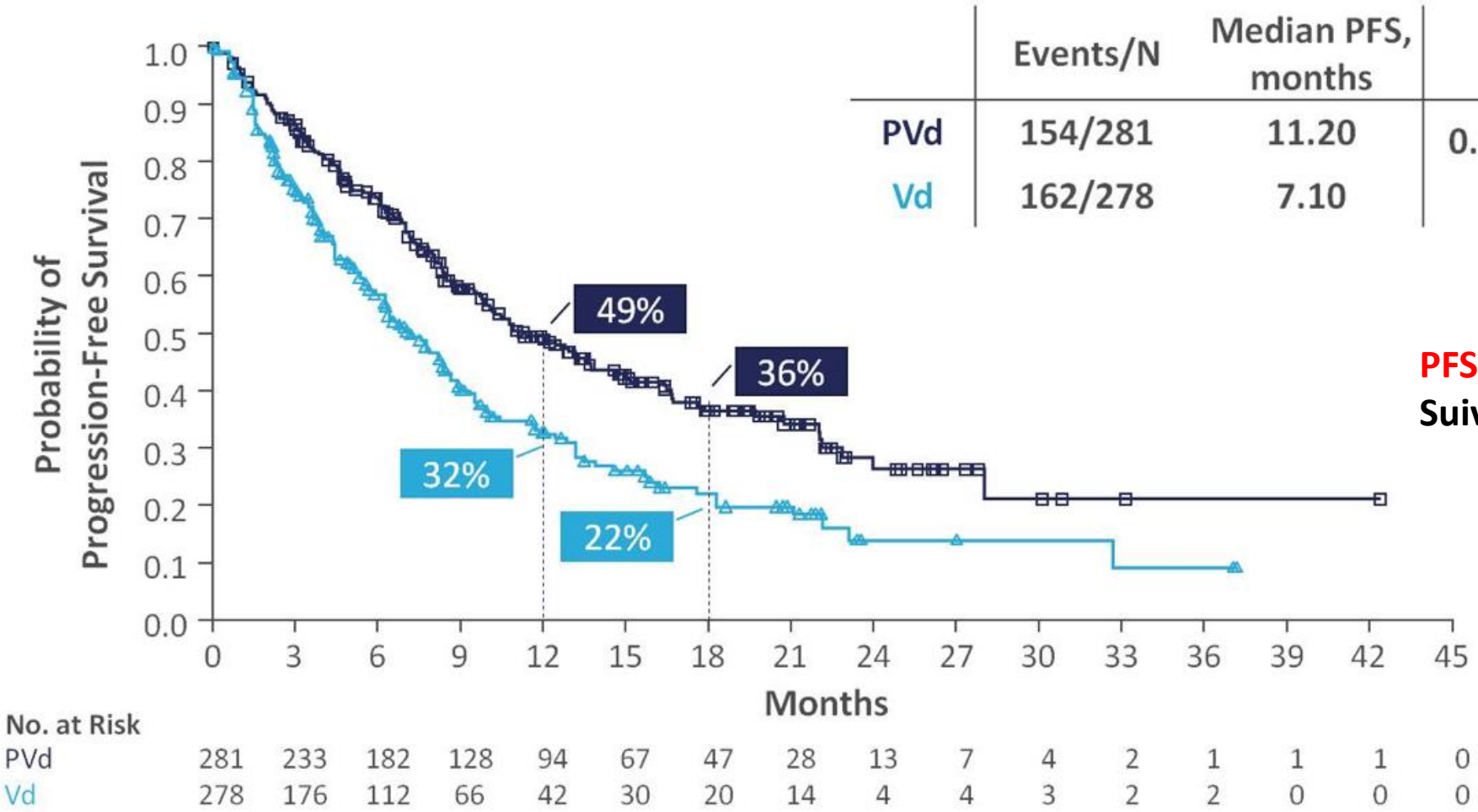
- As per protocol, 100% of patients received prior treatment with LEN

Characteristic	PVd (n = 281)	Vd (n = 278)
Median no. of prior lines of therapy (range)	2 (1-3)	2 (1-4)[a]
1 prior line, %	40	41
2 prior lines, %	42	37
≥ 3 prior lines, %	19	21
Prior SCT, %	57	59
Prior LEN, %	100	100
LEN-refractory, %	71	69
Refractory to LEN in last prior regimen, %	63	60
Prior PI, %	75	77
PI-refractory, %	13	13
Prior BORT, %	72	73
BORT-refractory, %	9	12
Refractory to last prior regimen, %	70	66

[a] One patient in the Vd arm received > 3 prior lines of therapy.

P Richardson et al, ASCO 2018

Etude OPTIMISMM : approbation de PVd



	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	154/281	11.20	0.61 (0.49-0.77)
Vd	162/278	7.10	< .0001

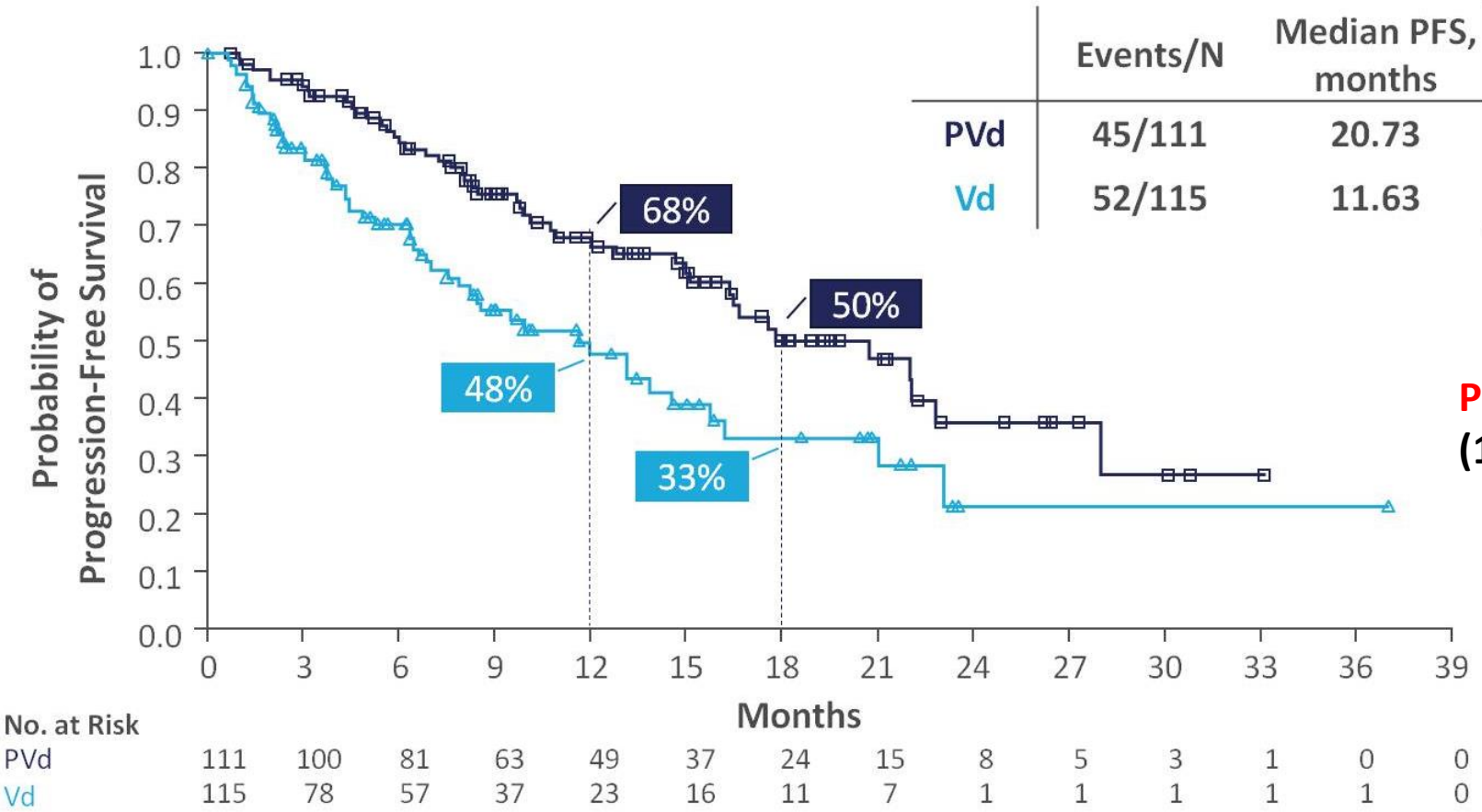
PFS médiane : 11,2 vs 7,1 mois

Suivi médian : 6,5 mois

P Richardson et al, ASCO 2018

Etude OPTIMISMM : approbation de PVd

- In patients with 1 prior line, PVd reduced the risk of progression and death by 46% compared with Vd



	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	45/111	20.73	0.54 (0.36-0.82)
Vd	52/115	11.63	.0027

No. at Risk														
PVd	111	100	81	63	49	37	24	15	8	5	3	1	0	0
Vd	115	78	57	37	23	16	11	7	1	1	1	1	1	0

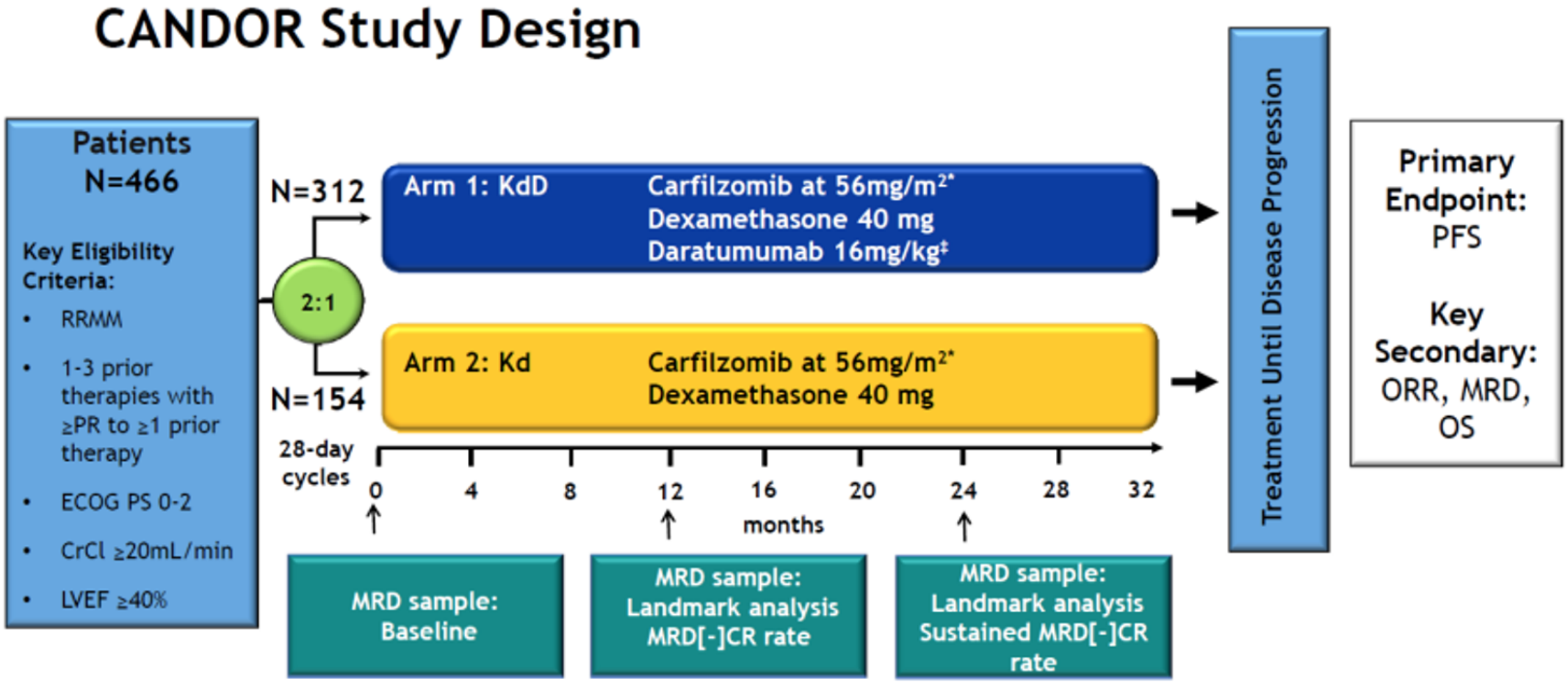
[a] 57.7% of patients treated with PVd and 56.5% treated with Vd were refractory to LEN.

ASCO 2018 Abstract 8001: OPTIMISMM—Paul Richardson, MD

PFS médiane : 20,7 vs 11,6 mois
(1ère rechute)

P Richardson et al, ASCO 2018

Etude CANDOR : Kd versus DaraKd



Usmani et al, ASH 2019

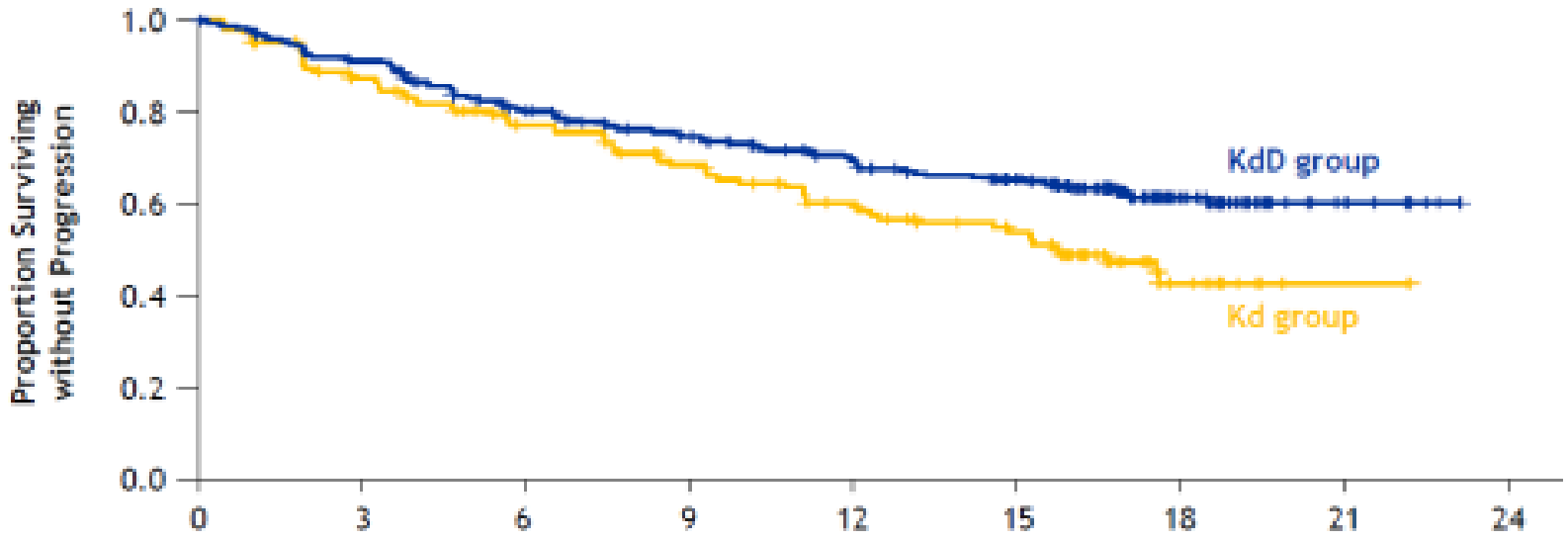
Etude CANDOR : approbation de DaraKd

Characteristic	KdD (n=312)	Kd (n=154)
Median age, years (range)	64 (29-84)	65 (35-84)
≤64, n (%)	163 (52.2)	77 (50.0)
65-74, n (%)	121 (38.8)	55 (35.7)
≥75, n (%)	28 (9.0)	22 (14.3)
ECOG PS, %		
0 or 1	295 (94.6)	147 (95.5)
2	15 (4.8)	7 (4.5)
ISS stage at baseline, %		
I	147 (47.1)	79 (51.3)
II	103 (33.0)	48 (31.2)
III	61 (19.6)	27 (17.5)
Cytogenetic risk category by FISH, %		
High*	48 (15.4)	26 (16.9)
Standard†	104 (33.3)	52 (33.8)
Unknown‡	160 (51.3)	76 (49.4)
Number of prior therapies, %		
1	144 (46.2)	70 (45.5)
≥2	168 (53.8)	83 (53.9)
Prior therapies, %		
Bortezomib	287 (92.0)	134 (87.0)
Lenalidomide	123 (39.4)	74 (48.1)
Refractory to prior bortezomib, %	88 (28.2)	47 (30.5)
Refractory to prior lenalidomide, %	99 (31.7)	55 (35.7)

*Consists of genetic subtypes t(4;14), t(14;16), or del(17p); †Consists of patients without t(4;14), t(14;16), and del(17p). ‡Includes samples that failed or were cancelled

P Usmani et al, ASH 2019

Etude CANDOR : approbation de DaraKd



No. at Risk									
KdD group	312	279	236	211	189	165	57	14	0
Kd group	154	122	100	85	70	55	13	2	0

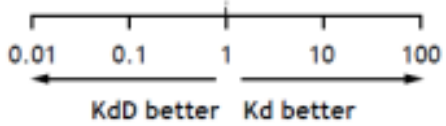
	KdD (n=312)	Kd (n=154)
Median follow-up time, months	16.9	16.3
Progression/Death, n (%)	110 (35%)	68 (44%)
Median PFS, months	NE	15.8
HR (KdD/Kd) (95% CI)	0.63 (0.46-0.85)	
p-value (1-sided)	0.0014	

P Usmani et al, ASH 2019

Étude CANDOR : analyse en sous-groupes

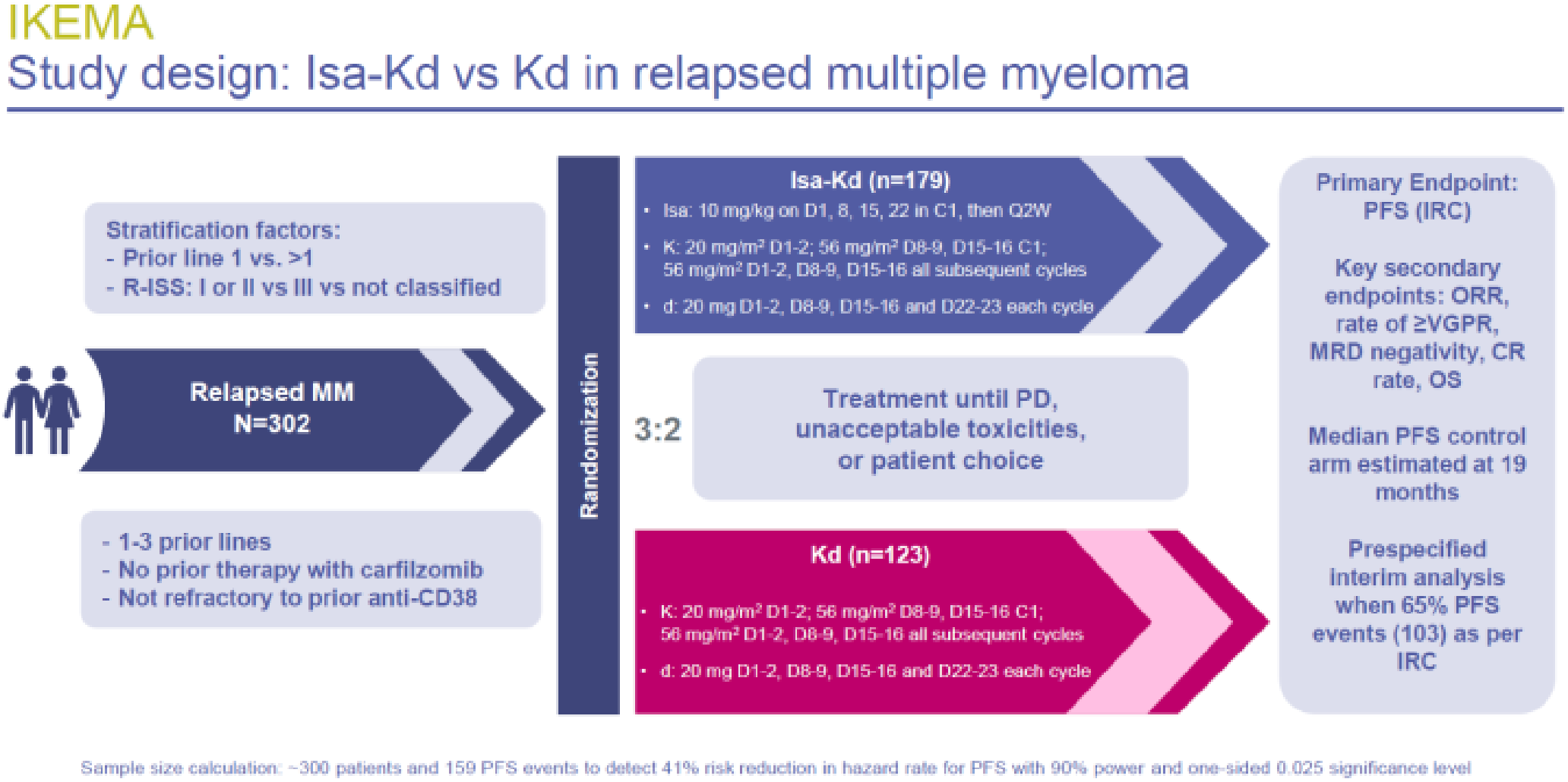
PFS Hazard-Ratios Across Prespecified Subgroups (continued)

Subgroup	KdD group (n=312) No. of subjects	Kd group (n=154) No. of subjects	Hazard ratio for KdD group vs. Kd group (95% CI)
Number of prior lines of therapy			
1	133	67	0.70 (0.42-1.17)
≥2	179	87	0.63 (0.44-0.92)
Prior lenalidomide exposure			
No	189	80	0.87 (0.56-1.35)
Yes	123	74	0.52 (0.34-0.80)
Refractory to lenalidomide			
No	213	99	0.85 (0.57-1.27)
Yes	99	55	0.45 (0.28-0.74)
Prior proteasome inhibitor exposure			
No	33	15	0.93 (0.29-3.02)
Yes	279	139	0.64 (0.47-0.88)
Refractory to bortezomib			
No	224	107	0.59 (0.40-0.85)
Yes	88	47	0.83 (0.49-1.41)



Dimopoulos MA *et al. Lancet* 2020; 396(10245):186-97
Usmani s MA *et al. Blood.* 2019;134(Suppl 2):LBA6 (ASH)

Etude IKEMA : Kd versus IsaKd



P Moreau et al, EHA 2020

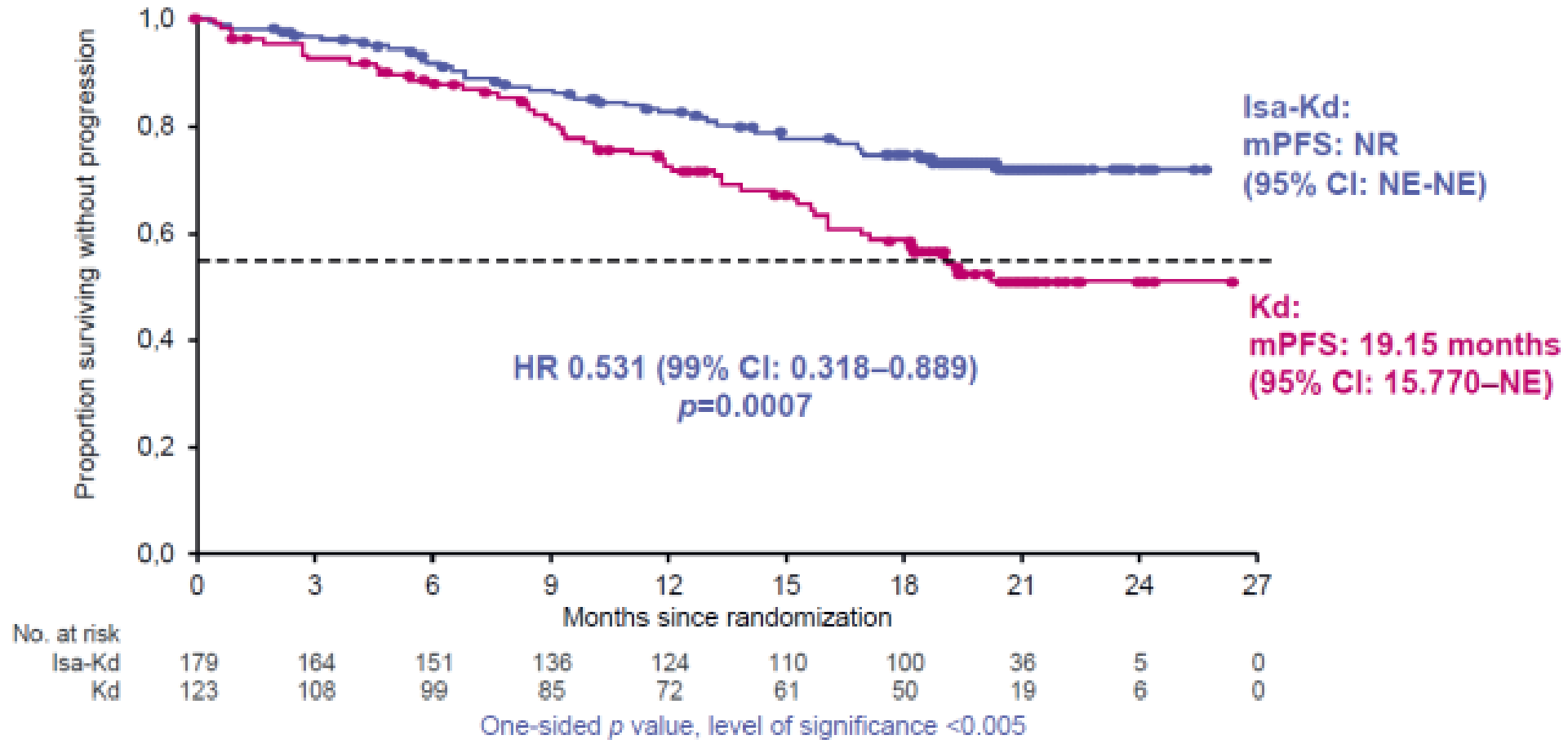
Etude IKEMA : caractéristiques

ITT population	Isa-Kd (n=179)	Kd (n=123)
Age in years, median (range)	65.0 (37–86)	63.0 (33–90)
Age in years, by category, n (%)		
<65	88 (49.2)	66 (53.7)
65 – <75	74 (41.3)	47 (38.2)
≥75	17 (9.5)	10 (8.1)
CrCl <60 mL/min/1.73 m² (MDRD)*, n (%)	43 (26.1)	18 (16.2)
ISS stage at baseline, n (%)		
Stage I	89 (48.7)	71 (57.7)
Stage II	63 (35.2)	31 (25.2)
Stage III	26 (14.5)	20 (16.3)
Cytogenetic risk at baseline†, %		
High	42 (23.5)	31 (25.2)
Standard	114 (63.7)	78 (63.4)
Missing	23 (12.8)	14 (11.4)

ITT population	Isa-Kd (n=179)	Kd (n=123)
Prior lines of therapy, median (range)‡	2 (1–4)	2 (1–4)
1, n (%)	79 (44.1)	55 (44.7)
2, n (%)	64 (35.8)	36 (29.3)
3, n (%)	33 (18.4)	30 (24.4)
Prior proteasome inhibitors	166 (92.7)	105 (85.4)
Prior IMiDs	136 (76.0)	100 (81.3)
Patients refractory to, n (%)		
IMiD	78 (43.6)	58 (47.2)
Lenalidomide	57 (31.8)	42 (34.1)
PI	56 (31.3)	44 (35.8)
Last regimen	89 (49.7)	73 (59.3)

P Moreau et al, EHA 2020

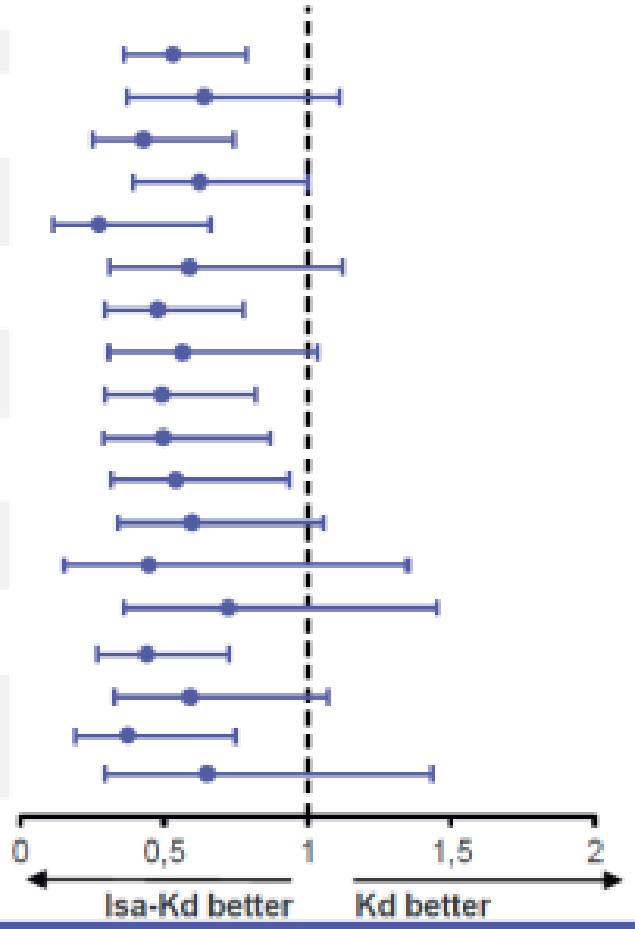
Etude IKEMA : approbation de IsaKd



P Moreau et al, EHA 2020

Etude IKEMA : analyse de sous-groupes

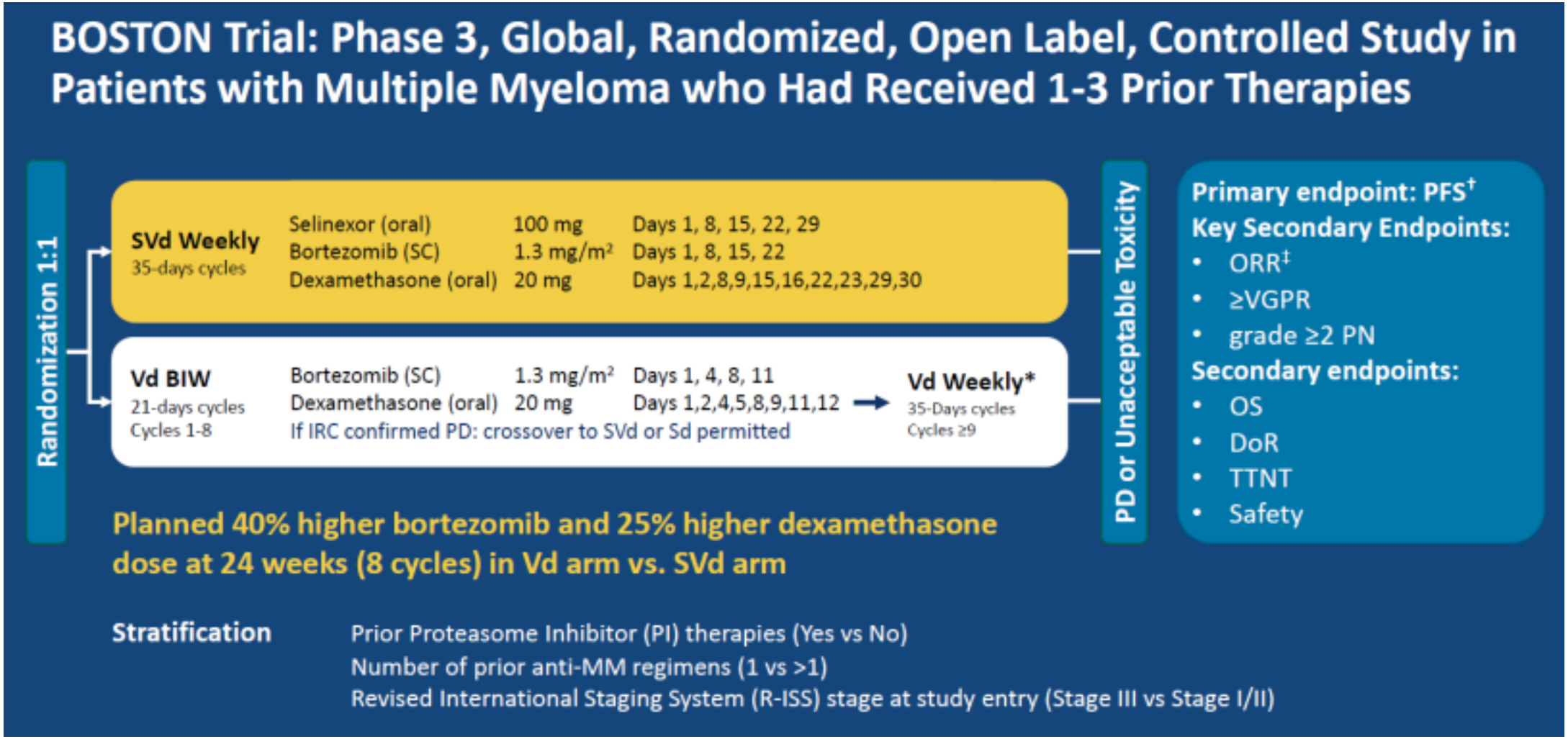
Subgroup		Isa-Kd No. of events/total no.	Kd No. of events/total no.	Hazard ratio (95% CI)
All patients		48/179	55/123	0.531 (0.359–0.786)
Age	<65 years	25/88	26/66	0.640 (0.370–1.109)
	≥65 years	23/91	29/57	0.429 (0.248–0.742)
Baseline eGFR (MDRD)	≥60 mL/min/1.73 m²	32/122	38/93	0.625 (0.391–1.001)
	<60 mL/min/1.73 m²	10/43	10/18	0.273 (0.113–0.660)
Number of prior lines of therapy	1	18/80	19/55	0.589 (0.309–1.123)
	>1	30/99	36/68	0.479 (0.294–0.778)
Prior PI treatment*	Yes	22/81	20/47	0.565 (0.308–1.036)
	No	26/98	35/76	0.493 (0.296–0.819)
Prior IMiD treatment*	Yes	22/81	29/62	0.498 (0.286–0.869)
	No	26/98	26/61	0.542 (0.314–0.933)
Refractory to Len	Yes	23/57	25/42	0.598 (0.339–1.055)
	No	5/15	9/17	0.448 (0.149–1.349)
High-risk cytogenetic status	Yes	17/42	15/31	0.724 (0.361–1.451)
	No	27/114	35/77	0.440 (0.266–0.728)
ISS staging at study entry	I	20/89	24/71	0.592 (0.327–1.071)
	II	17/63	16/31	0.375 (0.188–0.748)
	III	11/26	14/20	0.650 (0.295–1.434)



Consistent treatment effect was seen for Isa-Kd across subgroups

P Moreau et al, EHA 2020

Etude BOSTON : Vd versus Vd + Selinexor



M Dimopoulos et al, ASCO 2020

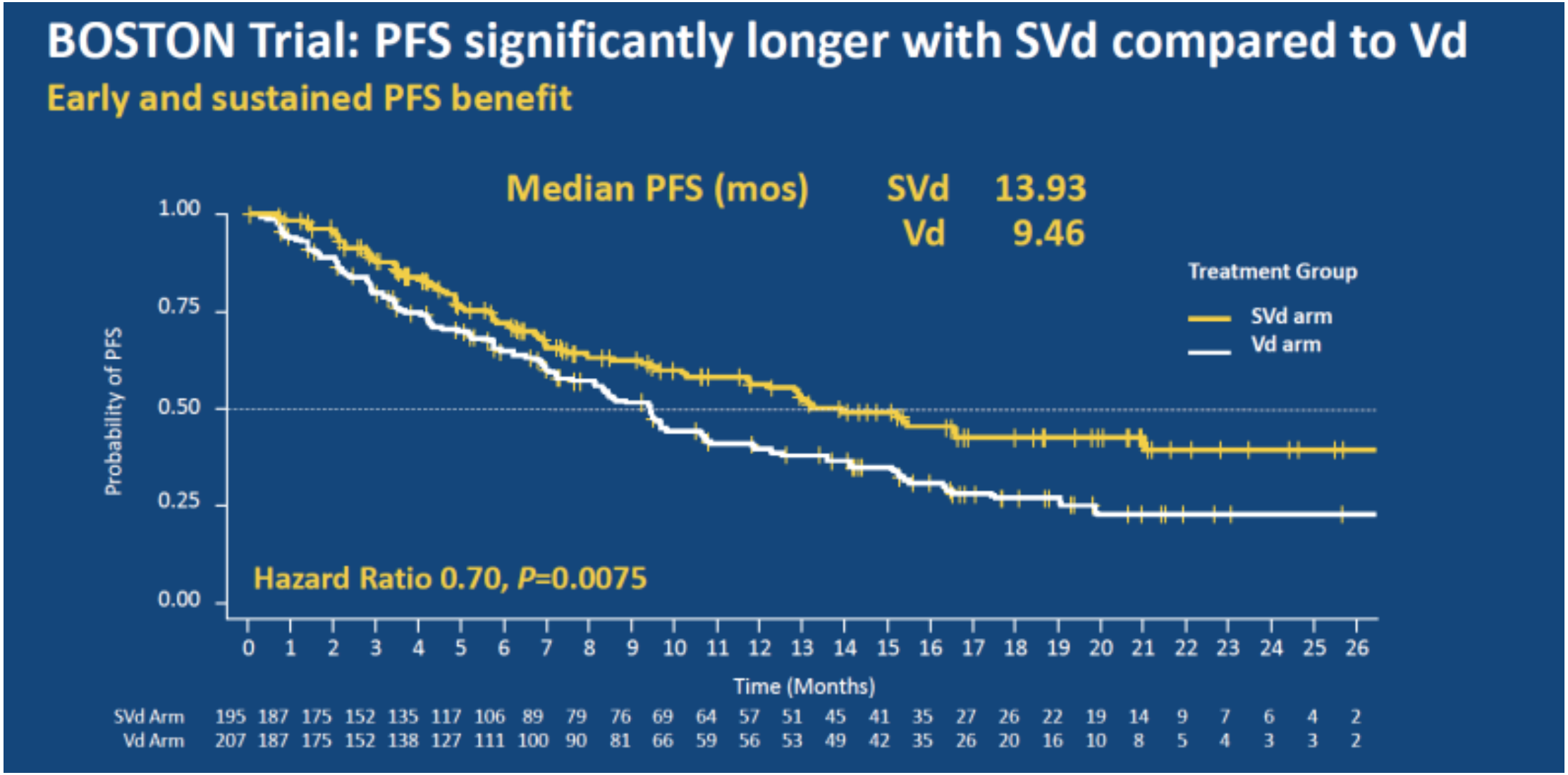
Etude BOSTON : caractéristiques

Patient and Disease Characteristics Well Balanced Between Treatment Arms

Characteristic	SVd arm (n=195)	Vd arm (n=207)
Media Age, years (range)	66 (40, 87)	67 (38, 90)
≥75 years, n (%)	34 (17)	47 (23)
Male, n (%)	115 (59)	115 (56)
Creatinine Clearance 30-60 mL/min, n (%)	53 (27)	60 (29)
Time since initial diagnosis, years, (range)	3.8 (0.4, 23.0)	3.6 (0.4, 22.0)
High Risk Cytogenetic, [del (17p) or t (14;16) or t (4;14) or amp 1q21] n (%)*	97 (50)	95 (46)
R-ISS disease stage at screening, n (%)		
I or II	173 (89)	177 (86)
III	12 (6)	16 (8)
Unknown	10 (5)	14 (7)
Number of prior lines of therapy, n (%)		
1	99 (51)	99 (48)
2	65 (33)	64 (31)
3	31 (16)	44 (21)
Prior Therapies, n (%)		
Bortezomib	134 (68.7)	145 (70.0)
Carfilzomib	20 (10.3)	21 (10.1)
Daratumumab	11 (5.6)	6 (2.9)
Lenalidomide	77 (39.5)	77 (37.2)

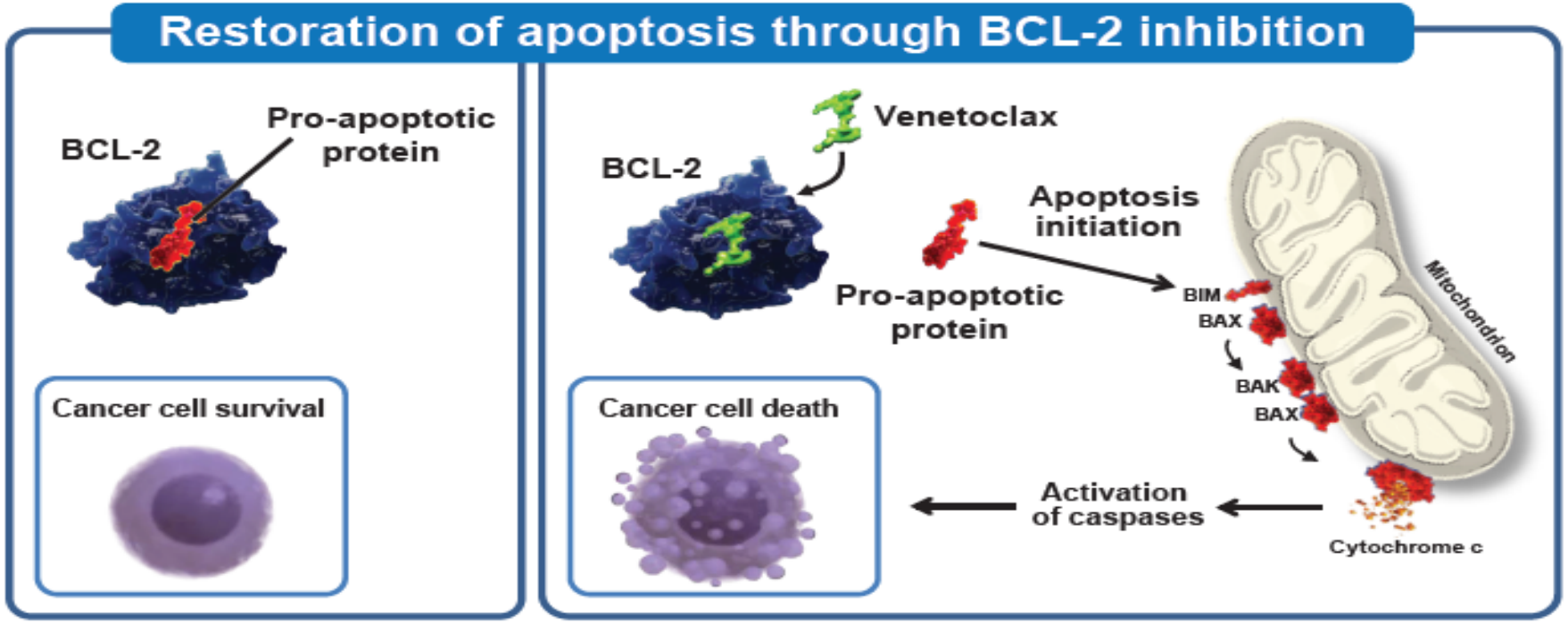
M Dimopoulos et al, ASCO 2020

Etude BOSTON : approbation SVd ?



M Dimopoulos et al, ASCO 2020

Venetoclax : the first-in-class oral Bcl-2 specific BH3 mimetic

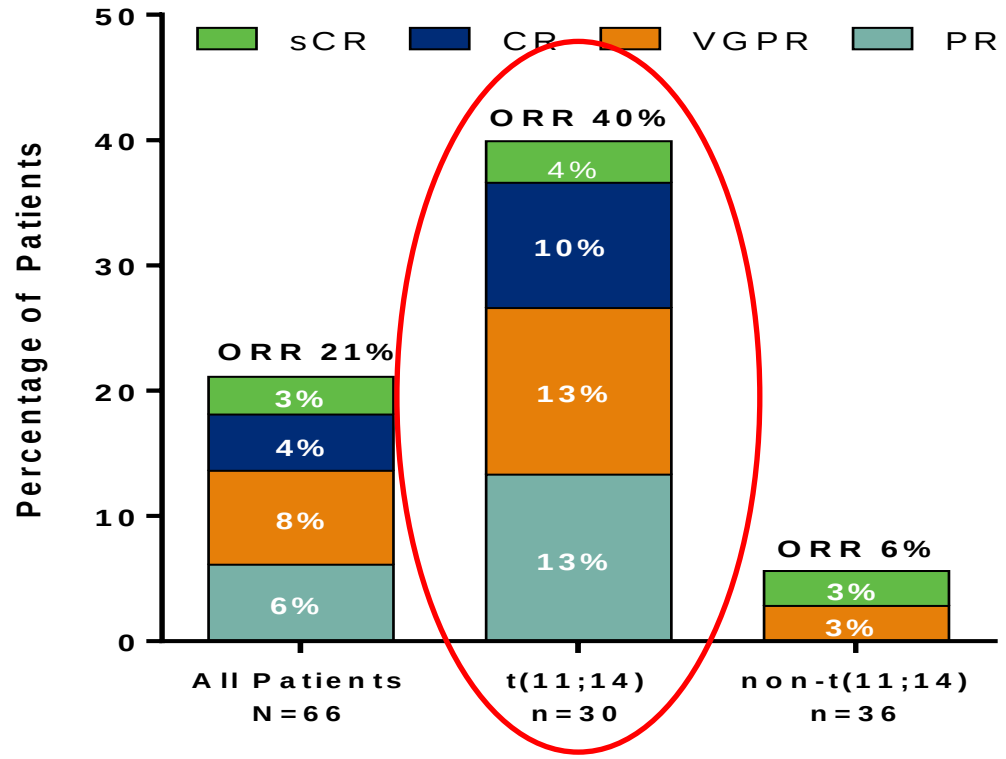


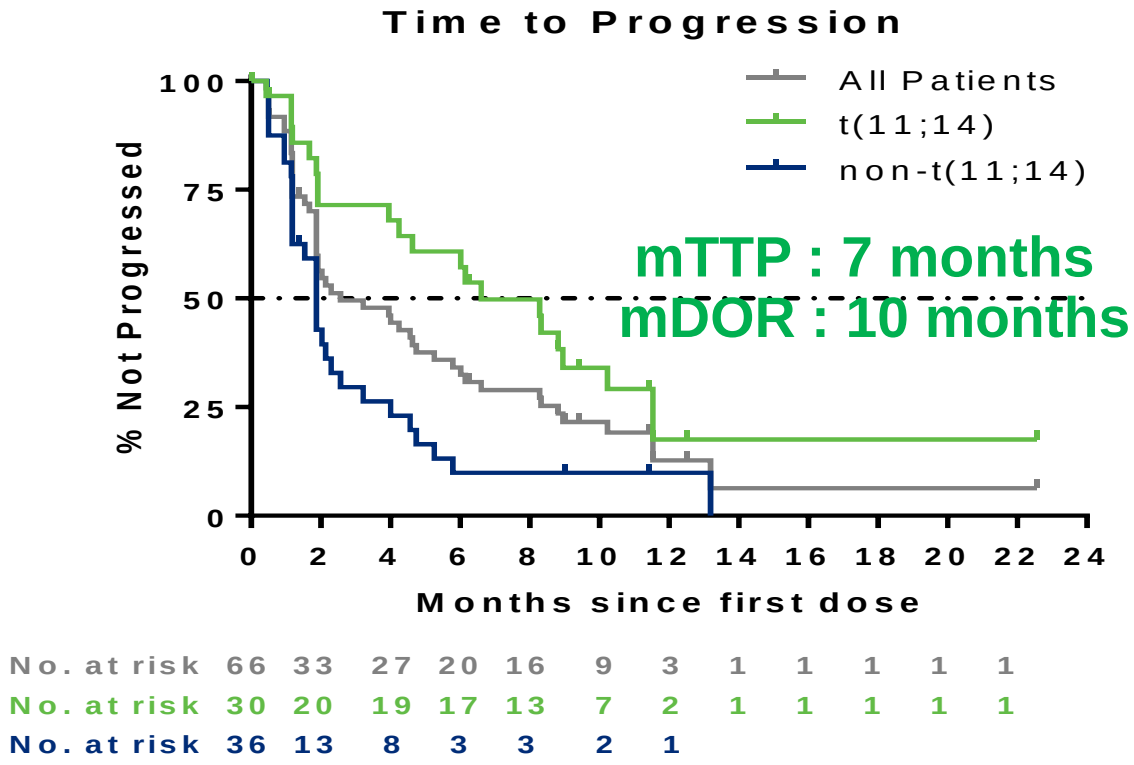
BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).

t(11;14) as biomarker of response to venetoclax

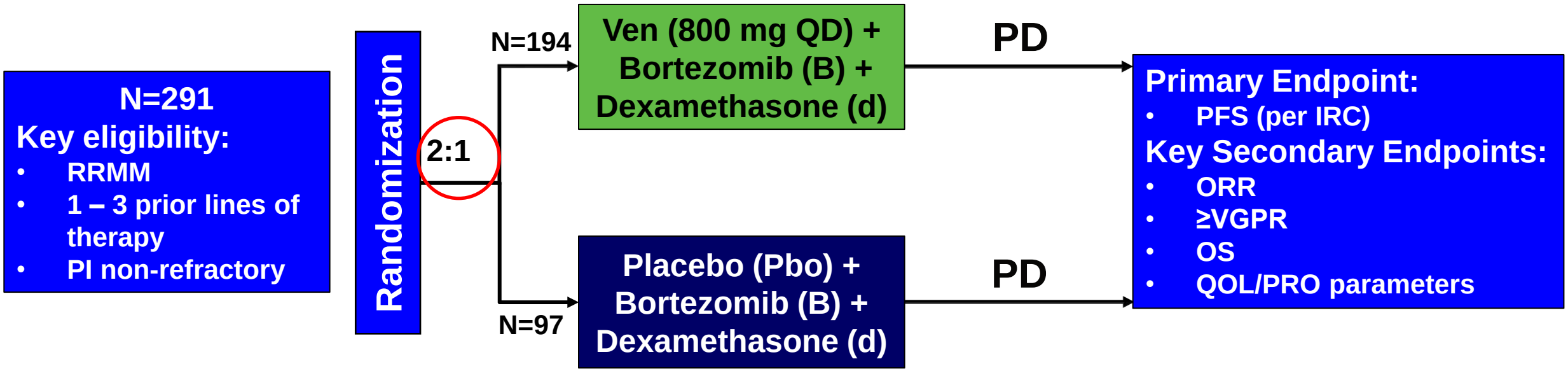
Phase 1-2 dose-escalating study, n=66
Advanced RRMM patients (median of 5 prior lines, 61% refractory PI + IMID)
Venetoclax single agent (300 to 1200 mg daily)





Kumar et al. Blood 2018

VD vs Venetoclax VD : étude BELLINI

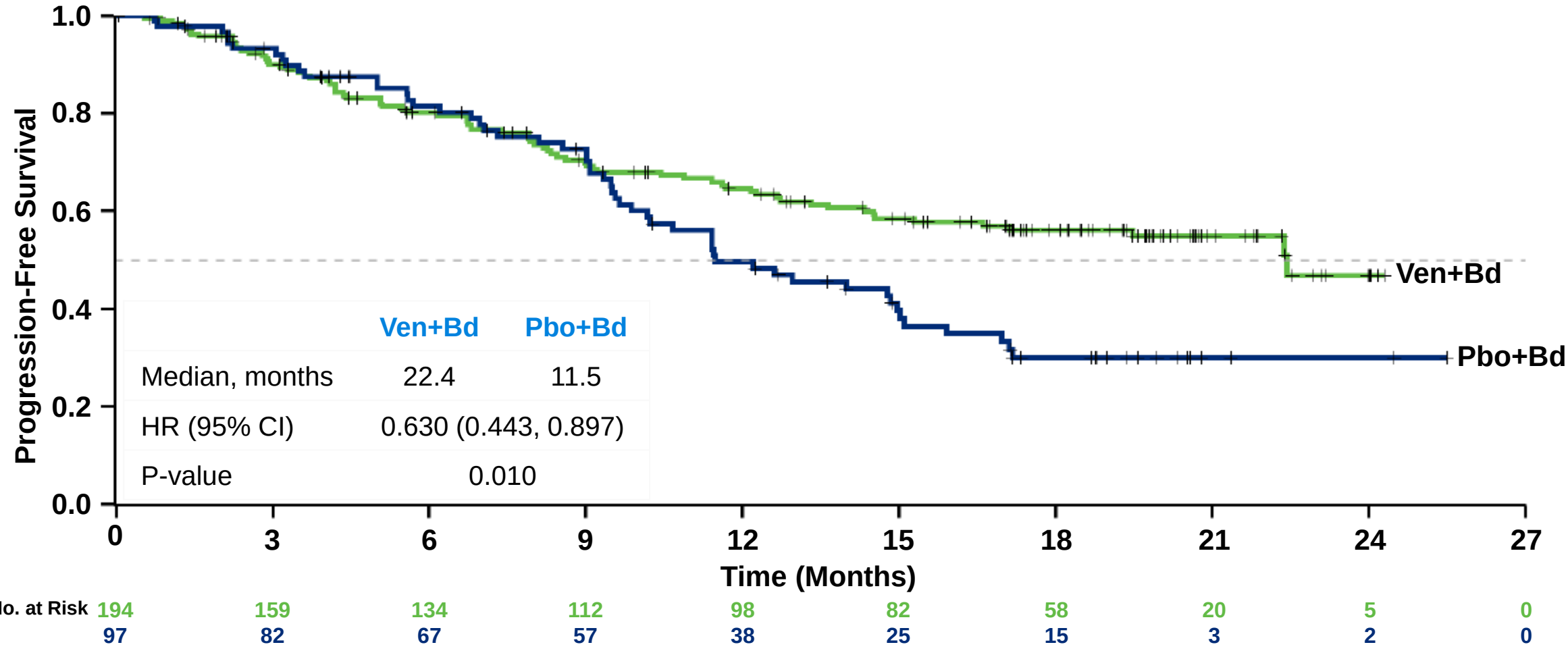


Cycles 1 – 8: 21-day, Bortezomib 1.3 mg/m^2 Days 1, 4, 8, 11 and dexamethasone 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12

Cycles 9+: 35-day, Bortezomib 1.3 mg/m^2 Days 1, 8, 15, 22 and dexamethasone 20 mg Days 1, 2, 8, 9, 15, 16, 22, 23

Kumar et al. IMW 2019

VD vs Venetoclax VD : étude BELLINI



The BELLINI study met its primary endpoint with superior median PFS in the Ven+Bd arm versus Pbo+Bd

Kumar et al. IMW 2019

Etude BELLINI : tolérance

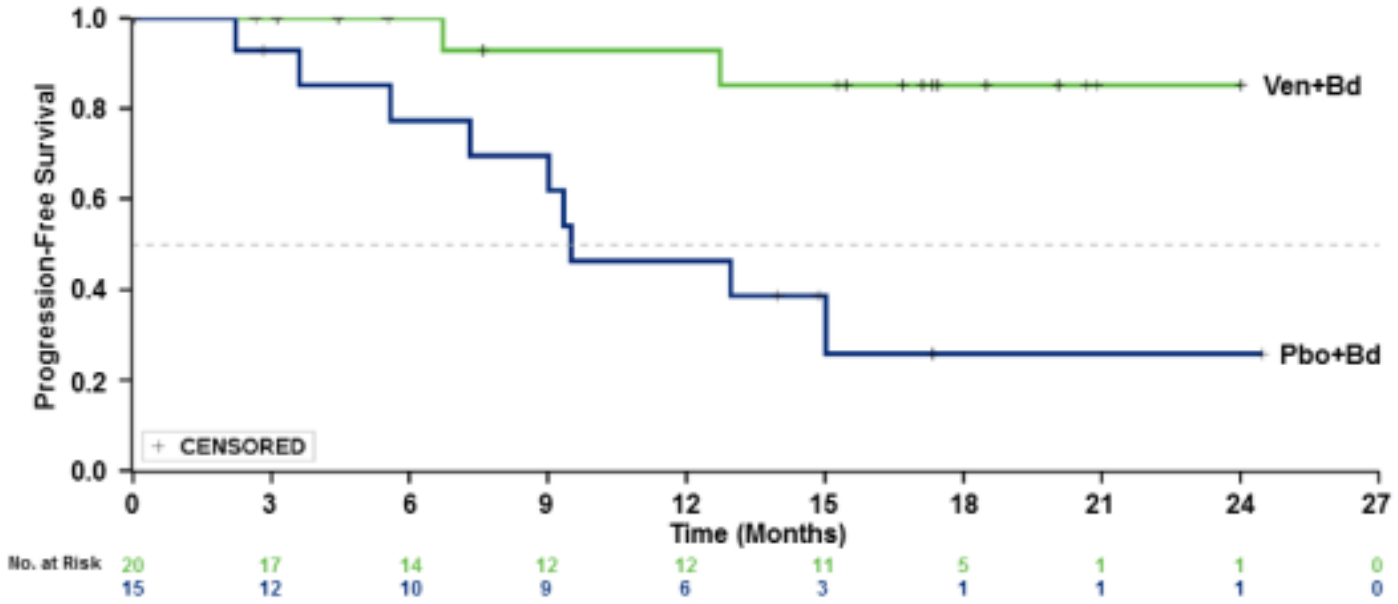
	Ven+Bd (N = 193) n (%)	Pbo+Bd (N = 96) n (%)
All deaths	**40 (21)**	**11 (11)**
Infection	14 (7)	2 (2)
Progressive disease	17 (9)	8 (8)
Other*	9 (5)	1 (1)
Deaths occurring within 30 days of last dose	**13 (7)**	**1 (1)**
Infection	8 (4)	0
Progressive disease	2 (1)	1 (1)
Other	3 (2)	0
Deaths occurring after 30 days of last dose	**27 (14)**	**10 (10)**
Infection	6 (3)	2 (2)
Progressive disease	15 (8)	7 (7)
Other	6 (3)	1 (1)

*Includes: cardiac/cardiopulmonary arrest (n = 4), congestive heart failure (n = 1), pancreatic cancer (n = 1), and unknown cause (n = 4).

More deaths were observed in the Ven+Bd arm, with a more prominent imbalance in the treatment-emergent deaths attributed to infectious causes

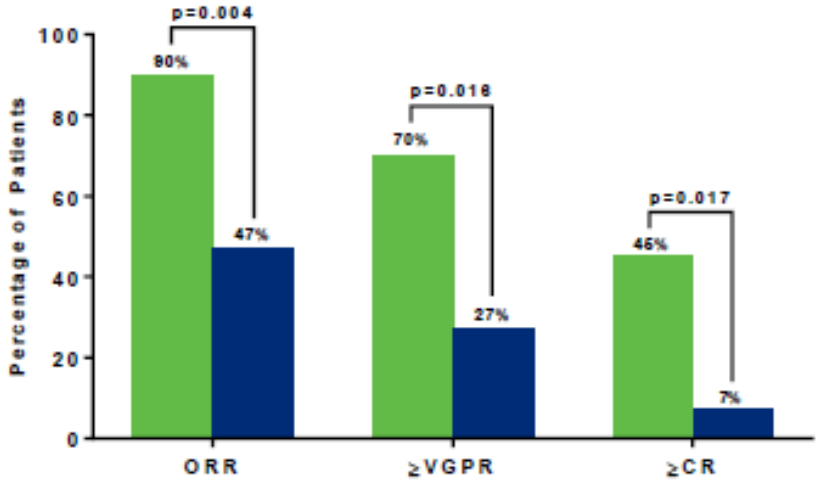
Kumar et al. IMW 2019

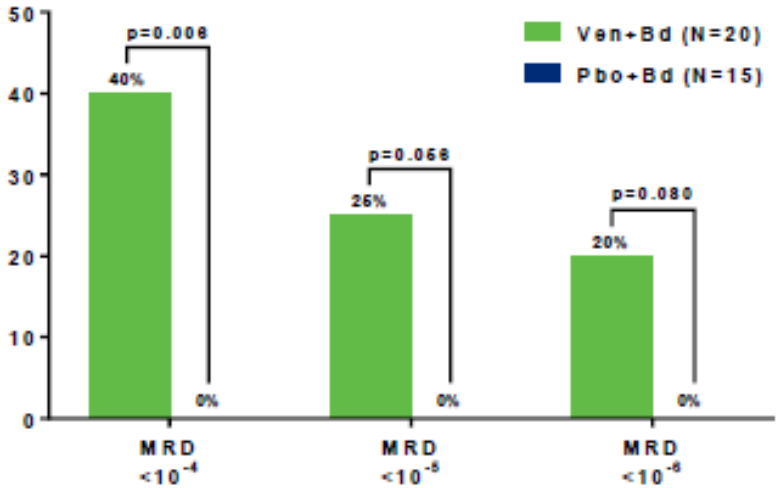
Etude BELLINI : sous-groupe t(11;14)



	Ven+Bd	Pbo+Bd
Median, months	Not reached	9.5
HR (95% CI)	0.110 (0.022, 0.560)	
P-value	0.002	

Efficacité remarquable
Pour les patients t(11;14)



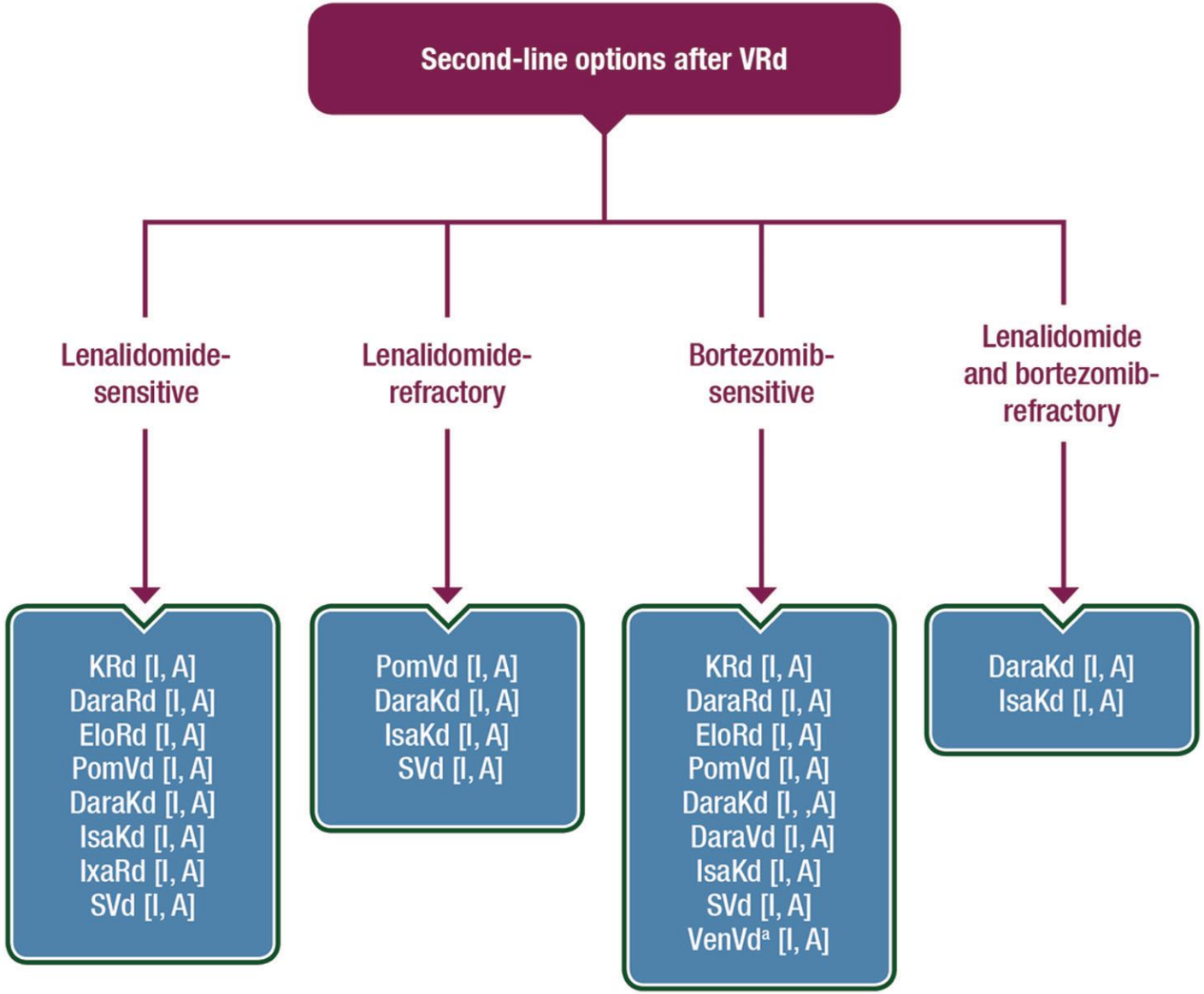


Kumar et al. IMW 2019

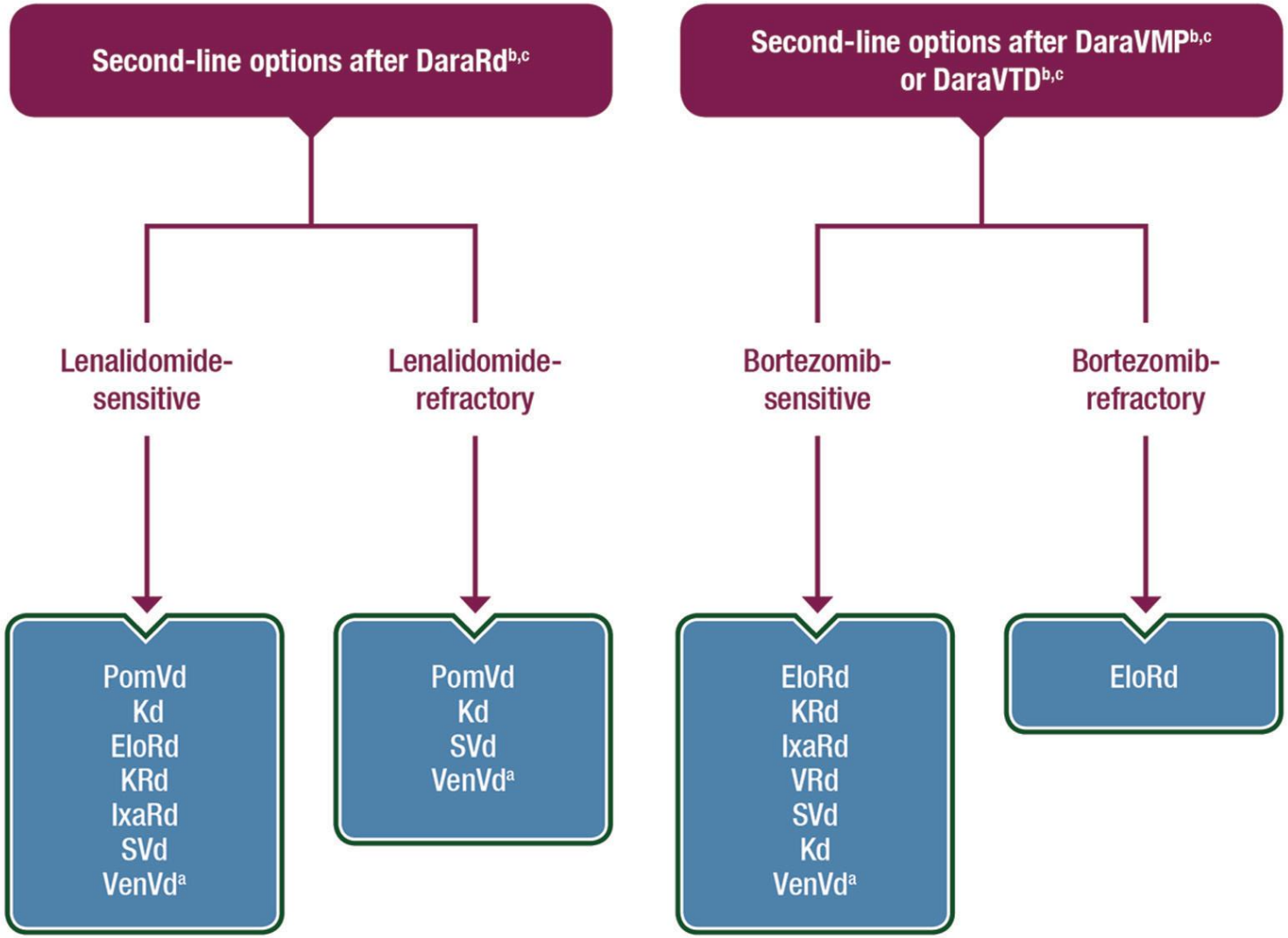
Rechute Len exposé non réfractaire

ENDEAVOR[17,19]	..	..	0·53 (0·44–0·65); <0·0001
Vd group	465	9·4 (8·4–10·4)	..
Kd group	464	18·7 (15·6–NE)	..
CASTOR[21,22]	..	..	0·31 (0·25–0·39); <0·0001
Vd group	247	7·1 (6·2–7·9)	..
DVd group	251	16·7 (12·3 to NE)	..
OPTIMISMM[26]	..	..	0·61 (0·49–0·77); <0·0001
Vd group	278	7·1 (5·9–8·5)	..
PVd group	281	11·2 (9·7–13·7)	..
BOSTON[39]	..	..	0·70 (0·53–0·93); 0·0075
Vd group	207	9·4 (8·1–10·8)	..
SVd group	195	13·9 (11·7–NE)	..
CANDOR[28]	..	..	0·63 (0·46–0·85); 0·0027
Kd group	154	15·8 (12·1–NE)	..
DKd group	312	NR (NE) > 24	..
IKEMA[29]	..	..	0·53 (0·32–0·89); 0·0007
Kd group	123	19·1 (15·8–NE)	..
Isa–Kd group†	179	NR (NE) 30 ?	..
BELLINI[40]	..	..	0·63 (0·44–0·90); 0·010
Vd group	97	11·5 (9·6–15·0)	..
Vd plus venetoclax group	194	22·4 (15·3–NE)	..

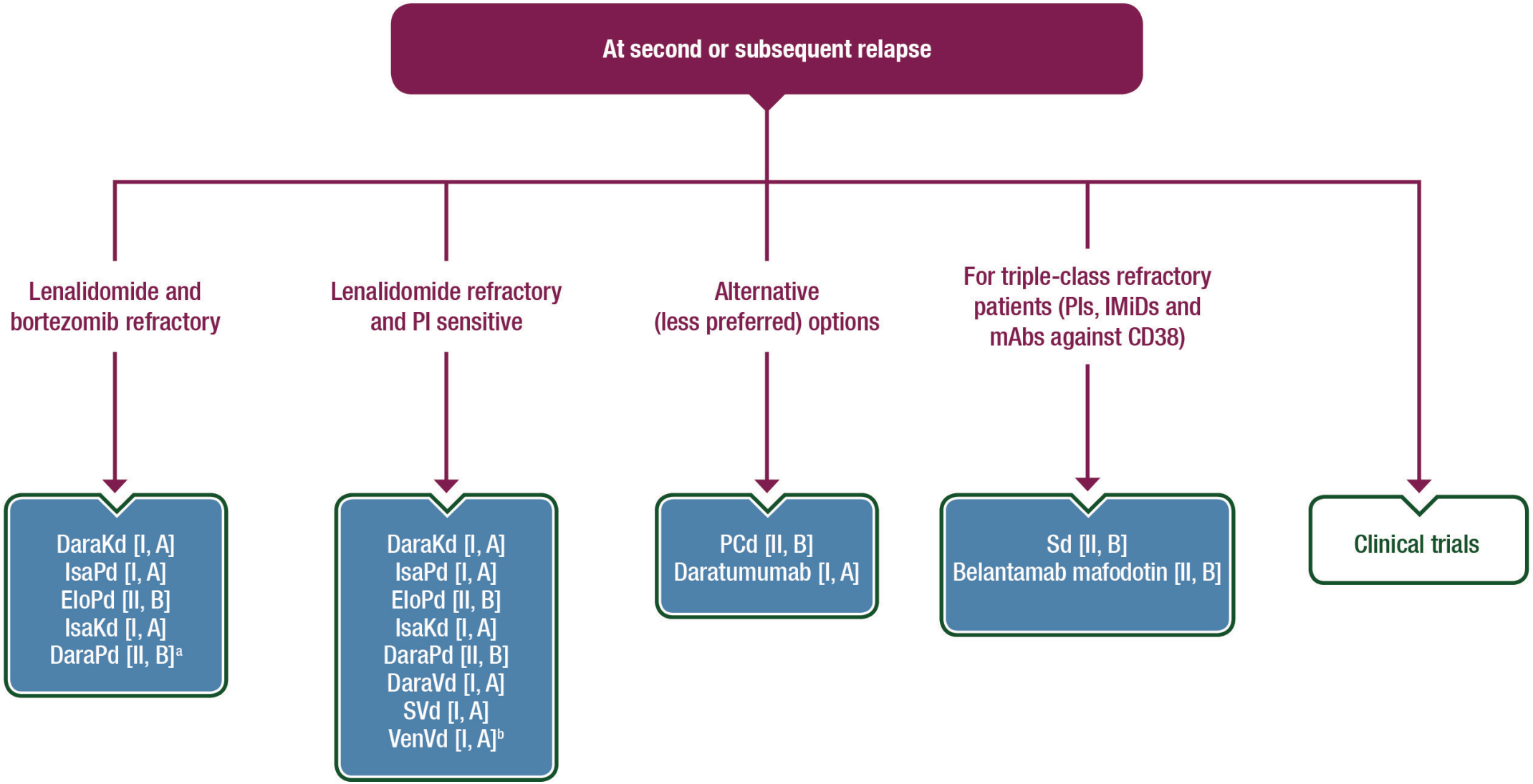
Options en première rechute après IP / IMiDs



Options en première rechute après 2021…



Options à partir de la deuxième rechute

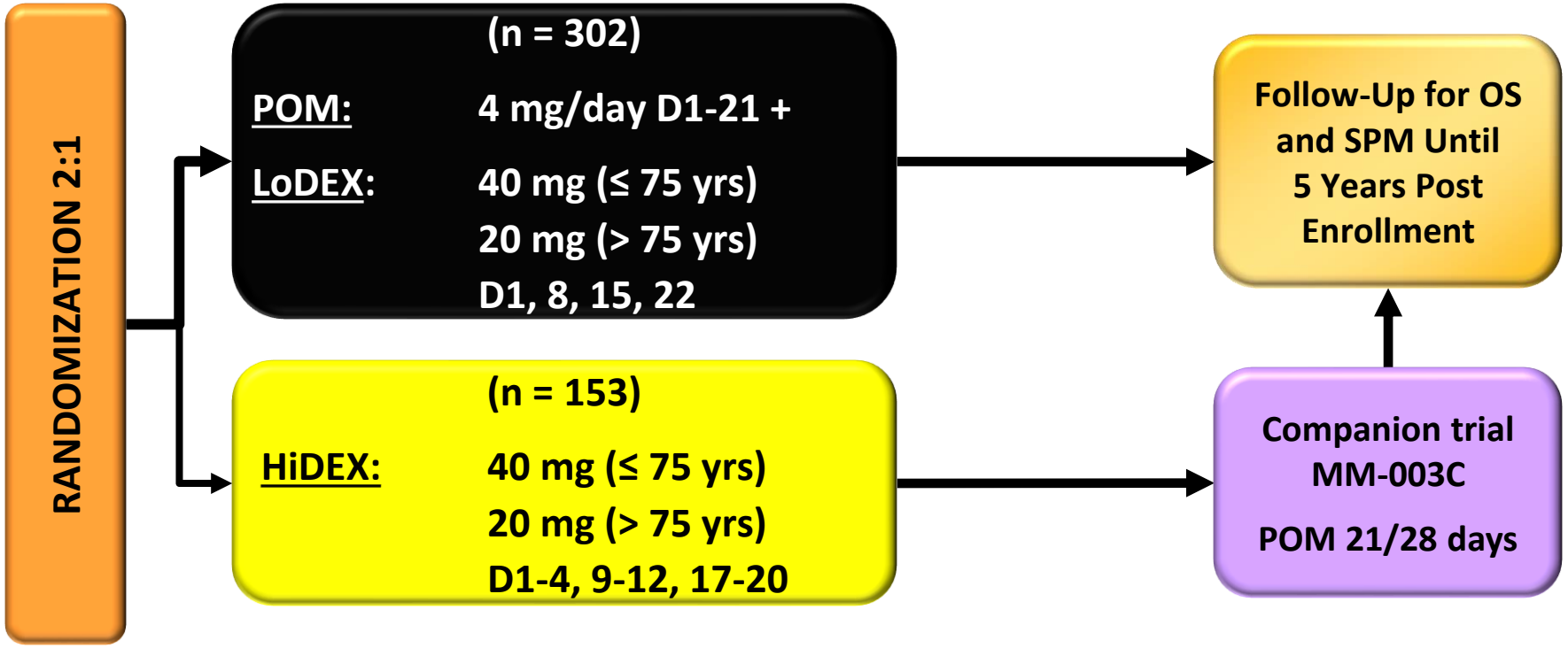


Pd versus D

Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial

Jesus San Miguel, Katja Weisel, Philippe Moreau, Martha Lacy, Kevin Song, Michel Delforge, Lionel Karlin, Hartmut Goldschmidt, Anne Banos, Albert Oriol, Adrian Alegre, Christine Chen, Michele Cavo, Laurent Garderet, Valentina Ivanova, Joaquin Martinez-Lopez, Andrew Belch, Antonio Palumbo, Stephen Schey, Pieter Sonneveld, Xin Yu, Lars Sternas, Christian Jacques, Mohamed Zaki, Meletios Dimopoulos

MM-003



J San Miguel, Lancet Oncol 2013

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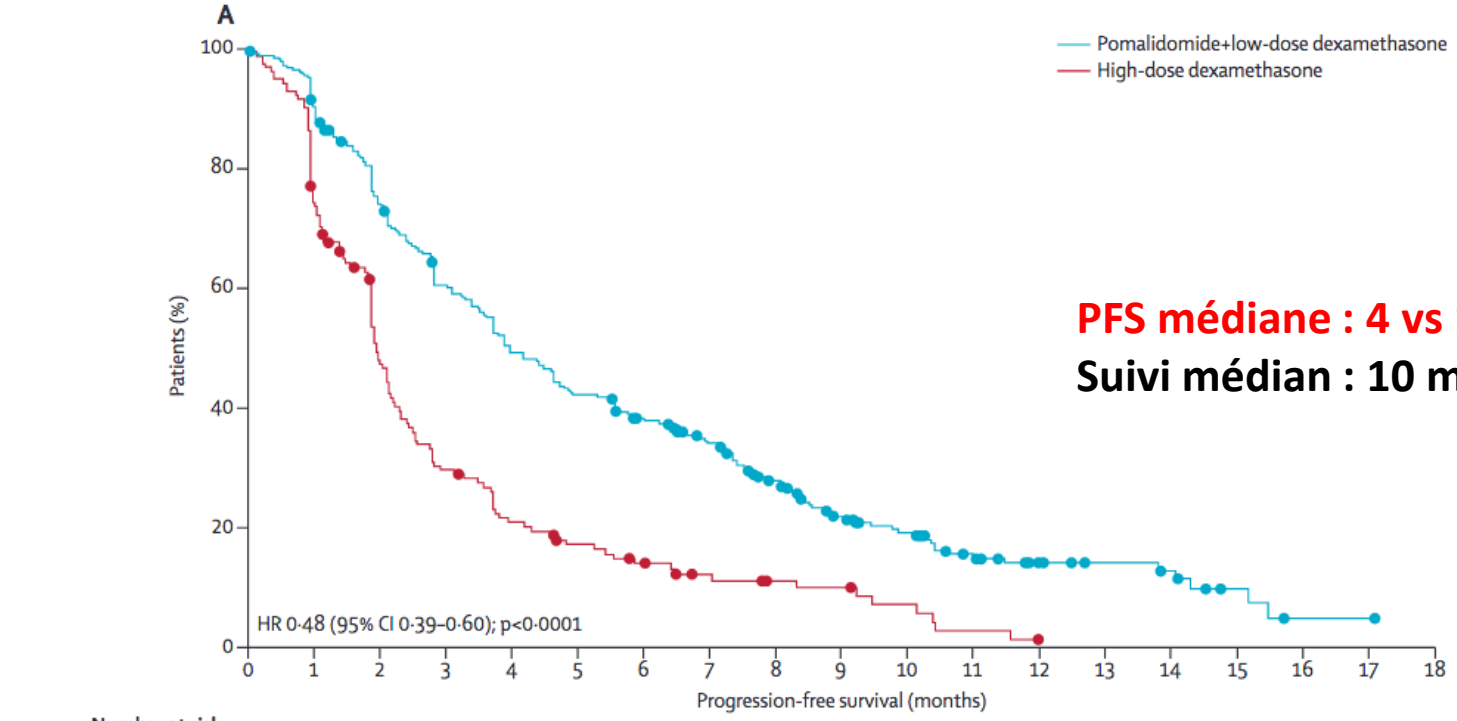
MM-003



PFS médiane : 4 vs 1,9 mois

Suivi médian : 10 mois

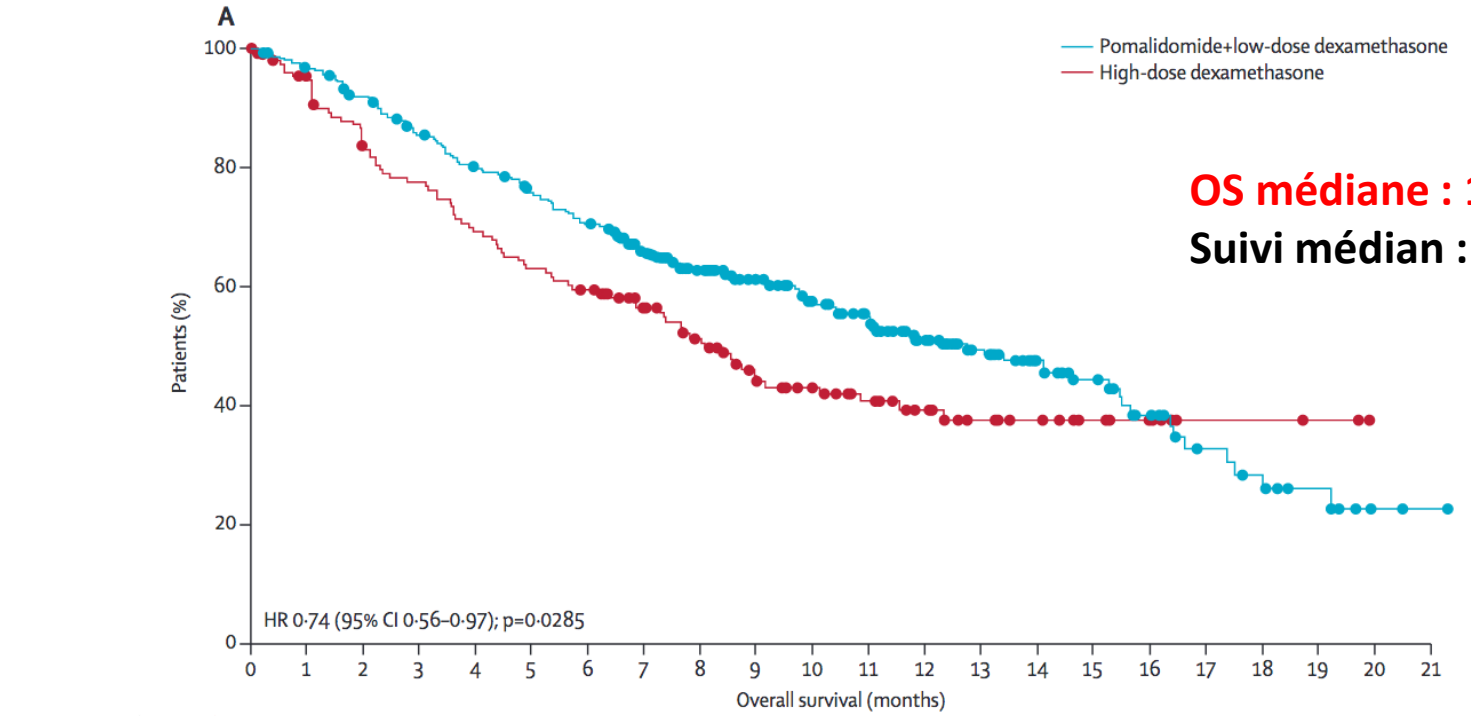
J San Miguel, Lancet Oncol 2013

Pd versus D

Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial

Jesus San Miguel, Katja Weisel, Philippe Moreau, Martha Lacy, Kevin Song, Michel Delforge, Lionel Karlin, Hartmut Goldschmidt, Anne Banos, Albert Oriol, Adrian Alegre, Christine Chen, Michele Cavo, Laurent Garderet, Valentina Ivanova, Joaquin Martinez-Lopez, Andrew Belch, Antonio Palumbo, Stephen Schey, Pieter Sonneveld, Xin Yu, Lars Sternas, Christian Jacques, Mohamed Zaki, Meletios Dimopoulos

MM-003



OS médiane : 12,7 vs 8,1 mois

Suivi médian : 10 mois

J San Miguel, Lancet Oncol 2013

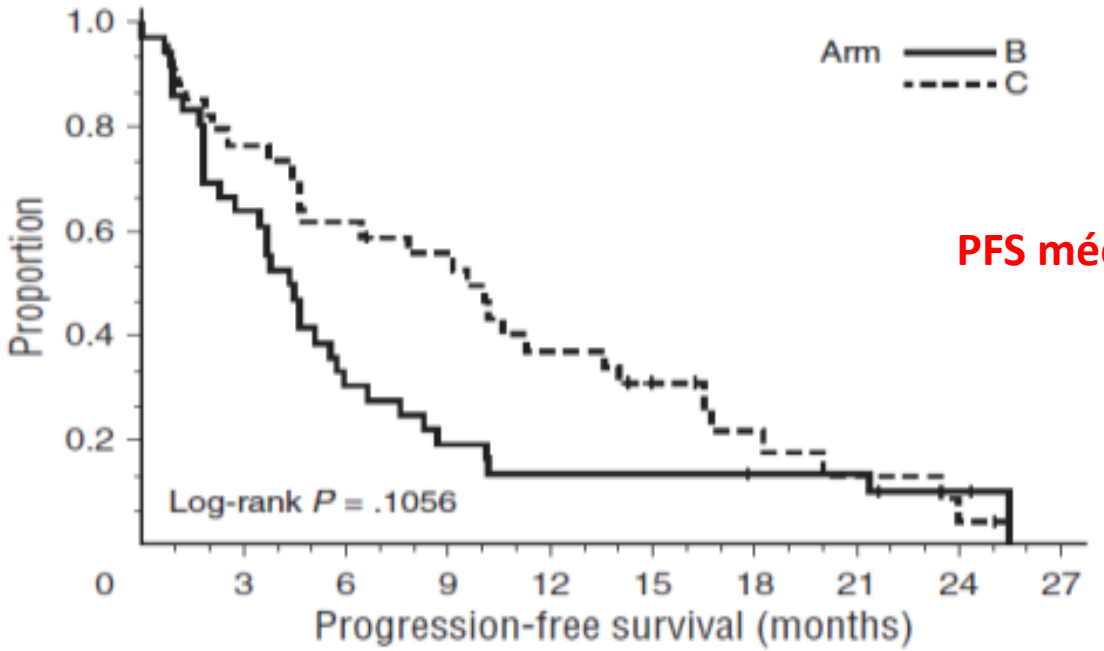
PCd versus Pd

Randomized multicenter phase 2 study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma

Rachid C. Baz,[1] Thomas G. Martin III,[2] Hui-Yi Lin,[3] Xiuhua Zhao,[3] Kenneth H. Shain,[1] Hearn J. Cho,[4] Jeffrey L. Wolf,[2] Anuj Mahindra,[2] Ajai Chari,[4] Daniel M. Sullivan,[5] Lisa A. Nardelli,[1] Kenneth Lau,[4] Melissa Alsina,[5] and Sundar Jagannath[4]

[1]Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [2]Myeloma Program, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [3]Department of Biostatistics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [4]Multiple Myeloma Program, Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY; and [5]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Cy : 400 mg J1, J8, J15

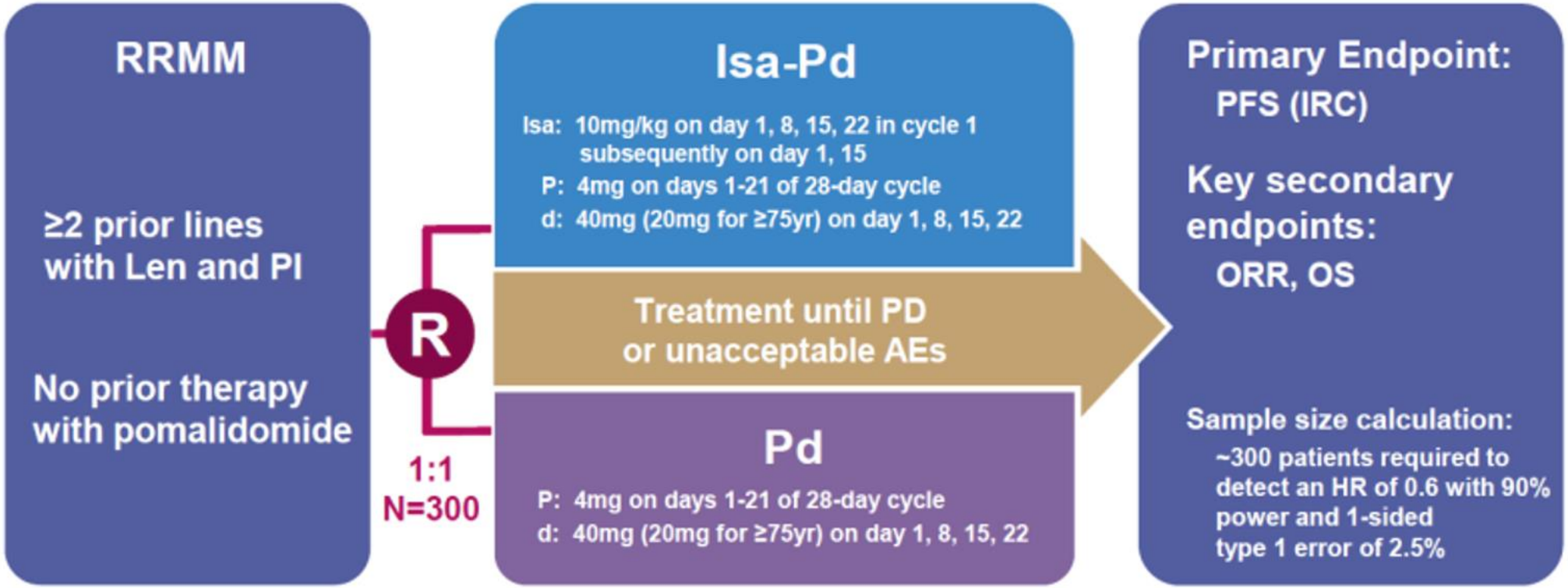


Arm	N	Event	Censored	Median (95% CI)
B	36	33 (92%)	3 (8%)	4.4(2.3, 5.7)
C	34	29 (85%)	5 (15%)	9.5(4.6, 14.0)

PFS médiane : 9,5 vs 4,4 mois

RC Baz, Blood 2016

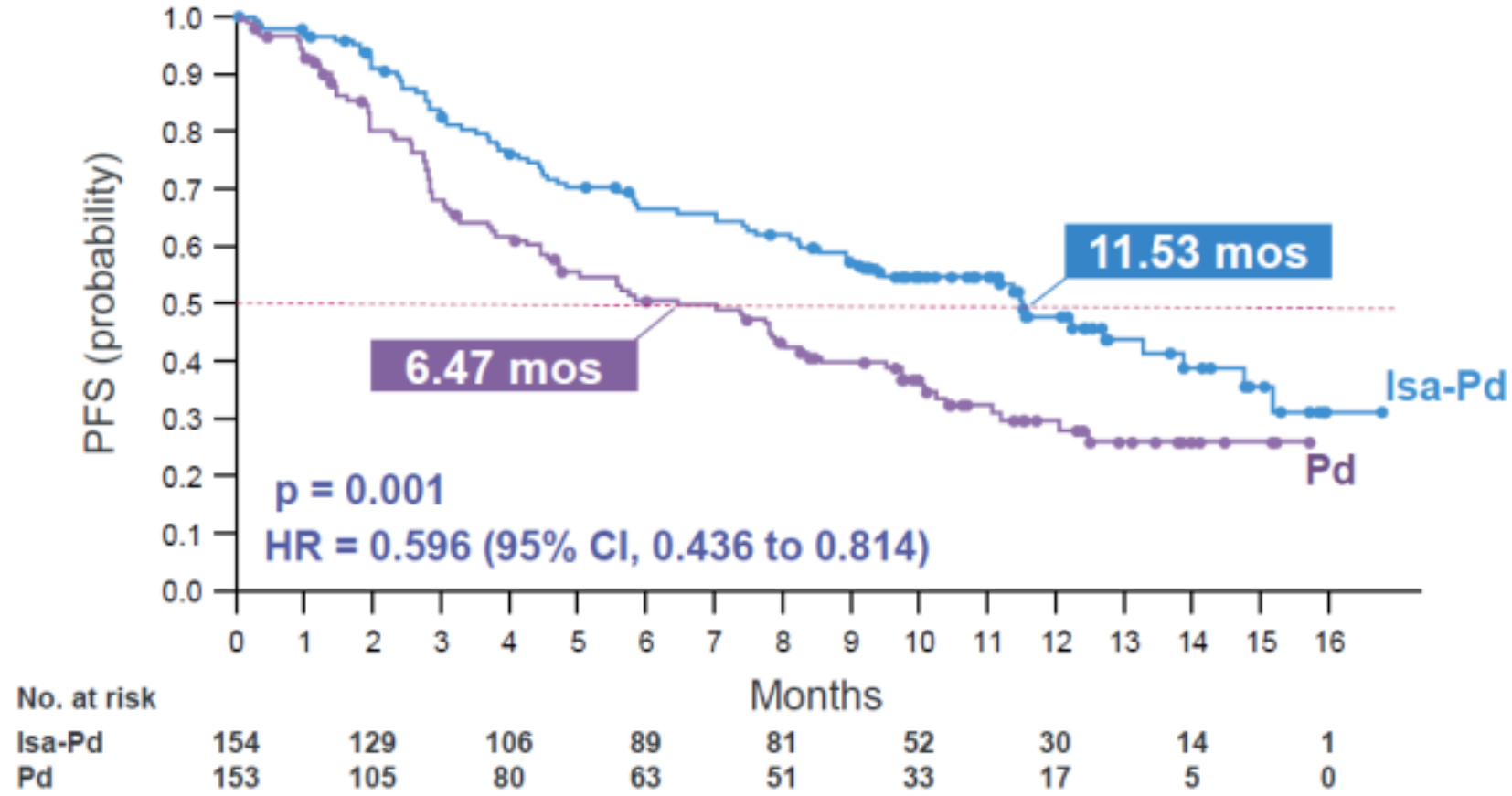
Etude ICARIA



ICARIA-MM is the 1st randomized phase 3 trial adding a CD38 antibody to the Pd backbone

M Attal et al, Lancet 2019

Etude ICARIA : approbation de IsaPomDex

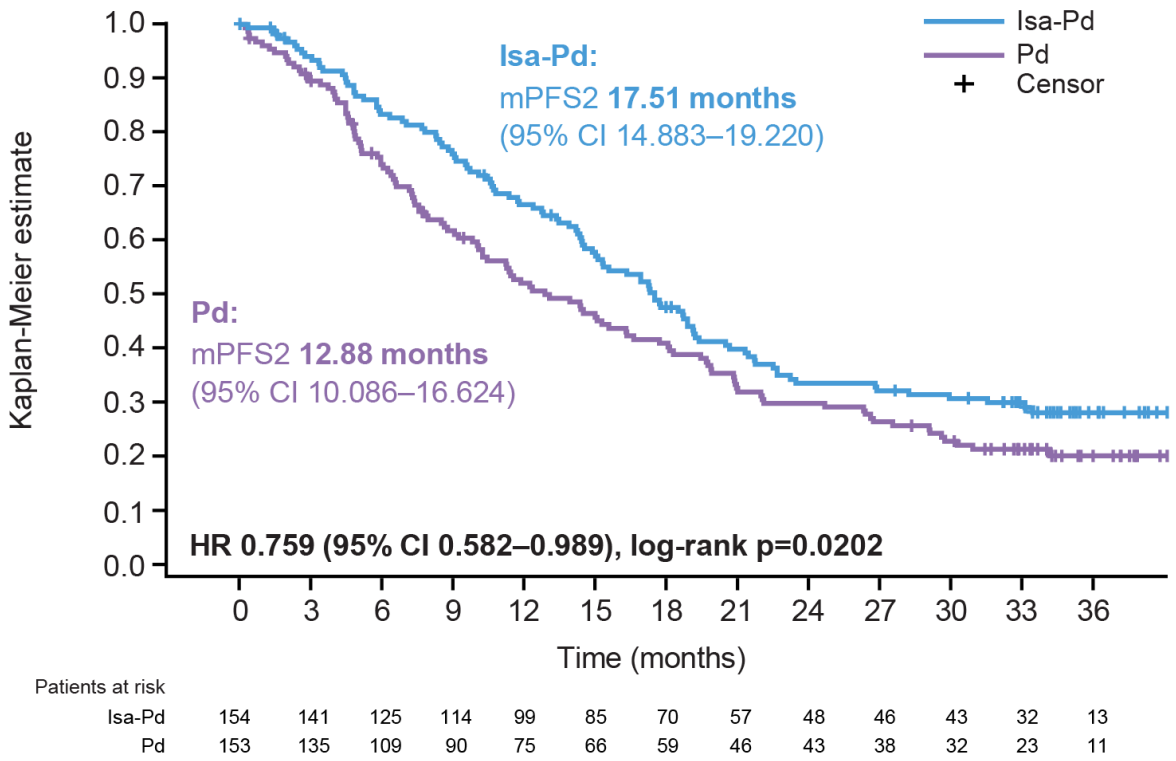


Statistically significant and clinically meaningful improvement in PFS

M Attal et al, Lancet 2019

Etude ICARIA : approbation de IsaPomDex

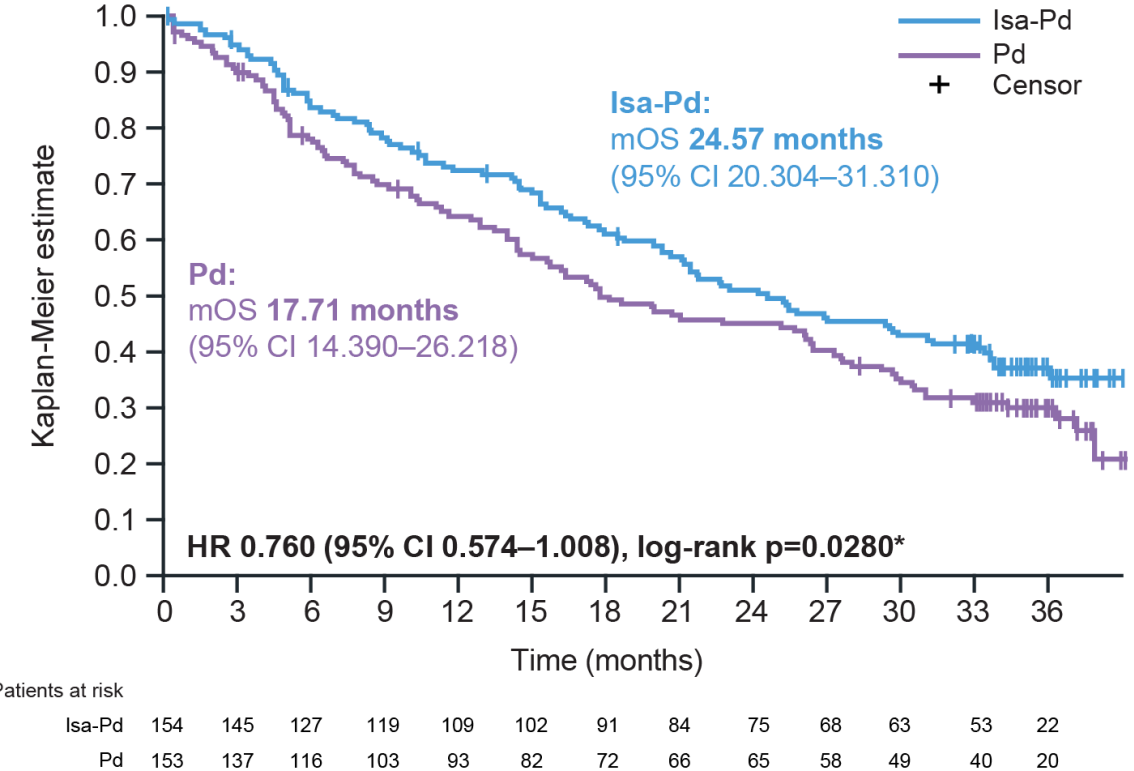
PFS2



Patients at risk

Isa-Pd	154	141	125	114	99	85	70	57	48	46	43	32	13
Pd	153	135	109	90	75	66	59	46	43	38	32	23	11

OS[a]



Patients at risk

Isa-Pd	154	145	127	119	109	102	91	84	75	68	63	53	22
Pd	153	137	116	103	93	82	72	66	65	58	49	40	20

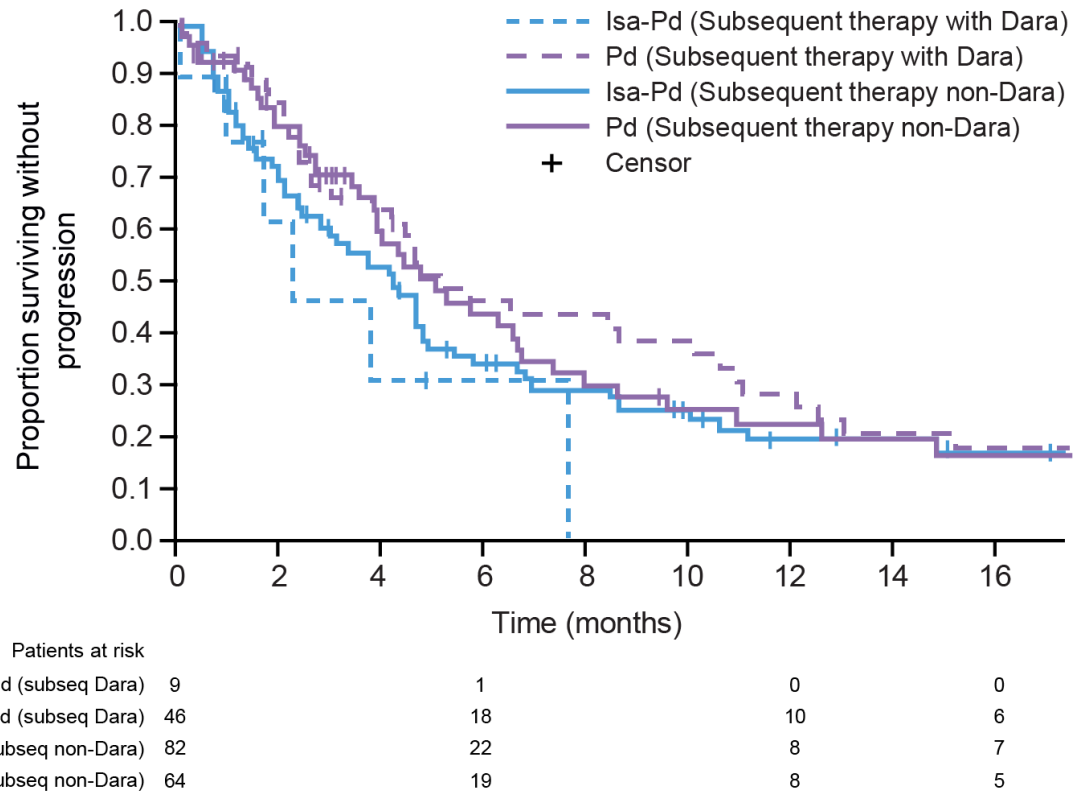
Etude ICARIA : traitements ultérieurs

First subsequent therapy	mPFS	
	Isa-Pd (n=82)	Pd (n=64)
Non-daratumumab	4.2 months	5.0 months
First subsequent therapy	**Isa-Pd (n=9)**	**Pd (n=46)**
Daratumumab	2.2 months	5.1 months

ORR in patients who received subsequent daratumumab therapy

Daratumumab regimen	Isa-Pd (n=22)	
Monotherapy or combined with steroids	14.3%	37.9%
Combined with a PI, IMiD, or alkylating agent	30.8%	31.8%

PFS on first subsequent therapy



Daratumumab en monothérapie

Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

SIRIUS

Sagar Lonial, Brendan M Weiss, Saad Z Usmani, Seema Singhal, Ajai Chari, Nizar J Bahlis, Andrew Belch, Amrita Krishnan, Robert A Vescio, Maria Victoria Mateos, Amitabha Mazumder, Robert Z Orlowski, Heather J Sutherland, Joan Bladé, Emma C Scott, Albert Oriol, Jesus Berdeja, Mecide Gharibo, Don A Stevens, Richard LeBlanc, Michael Sebag, Natalie Callander, Andrzej Jakubowiak, Darrell White, Javier de la Rubia, Paul G Richardson, Steen Lisby, Huaibao Feng, Clarissa M Uhlar, Imran Khan, Tahamtan Ahmadi, Peter M Voorhees

Demographics (n = 106)			
Median (range) age, y	63.5 (31–84)	Renal function (CrCl), n %	
Age ≥75 y, n (%)	12 (11)	≥60 mL/min	60 (57)
		<60 mL/min	46 (43)
ISS staging, n (%)			
I	26 (25)	ECOG score	
II	40 (38)	0	29 (27)
III	40 (38)	1	69 (65)
		2	8 (8)
High risk cytogenetics, n (%)	20 (19)		
Prior therapies (n = 106)			
Median (range) number of prior therapies	5 (2–14)	>3 lines of prior therapy, n (%)	87 (82)
Prior chemotherapy	106 (100)	Prior IMiD, n (%)	106 (100)
Alkylating agents, n (%)	106 (100)	LEN	105 (99)
Anthracyclines	55 (52)	POM	67 (63)
		THAL	47 (44)
Prior ASCT, n (%)	85 (80)	Prior PI, n (%)	106 (100)
		BORT	105 (99)
		CARF	53 (50)

CrCl, creatinine clearance; ISS, International Staging System; LEN, lenalidomide; POM, pomalidomide; THAL, thalidomide; ASCT, autologous stem cell transplantation; BORT, bortezomib; CARF, carfilzomib.

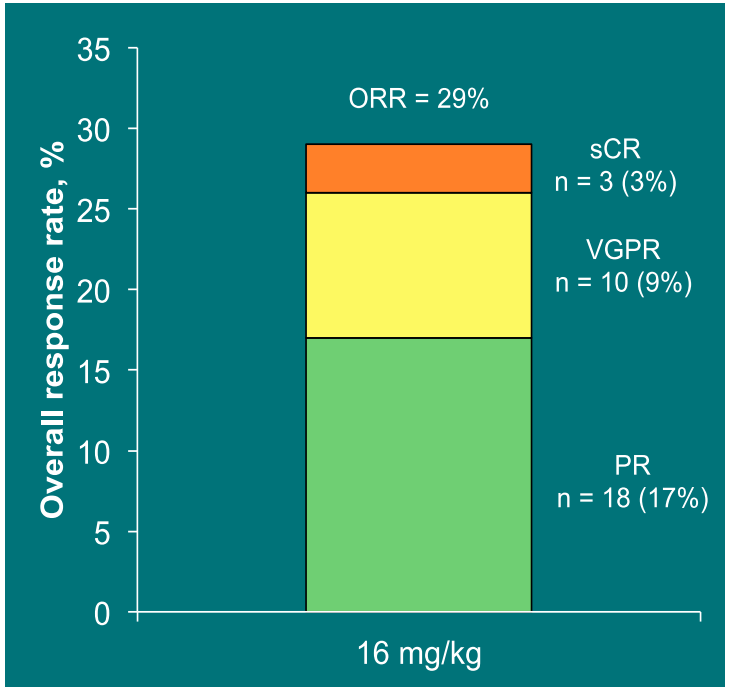
S Lonial, Lancet 2016

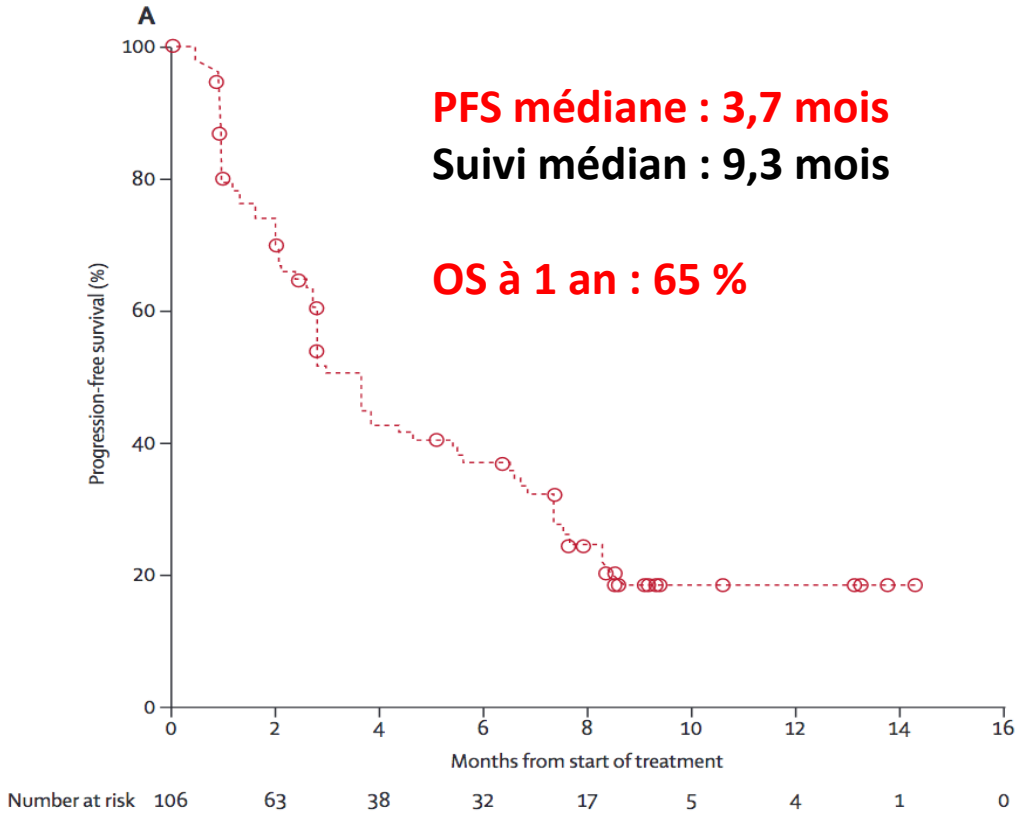
Daratumumab en monothérapie

Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

Sagar Lonial, Brendan M Weiss, Saad Z Usmani, Seema Singhal, Ajai Chari, Nizar J Bahlis, Andrew Belch, Amrita Krishnan, Robert A Vescio, Maria Victoria Mateos, Amitabha Mazumder, Robert Z Orlowski, Heather J Sutherland, Joan Bladé, Emma C Scott, Albert Oriol, Jesus Berdeja, Mecide Gharibo, Don A Stevens, Richard LeBlanc, Michael Sebag, Natalie Callander, Andrzej Jakubowiak, Darrell White, Javier de la Rubia, Paul G Richardson, Steen Lisby, Huaibao Feng, Clarissa M Uhlar, Imran Khan, Tahamtan Ahmadi, Peter M Voorhees

SIRIUS (MMY2002)





PFS médiane : 3,7 mois

Suivi médian : 9,3 mois

OS à 1 an : 65 %

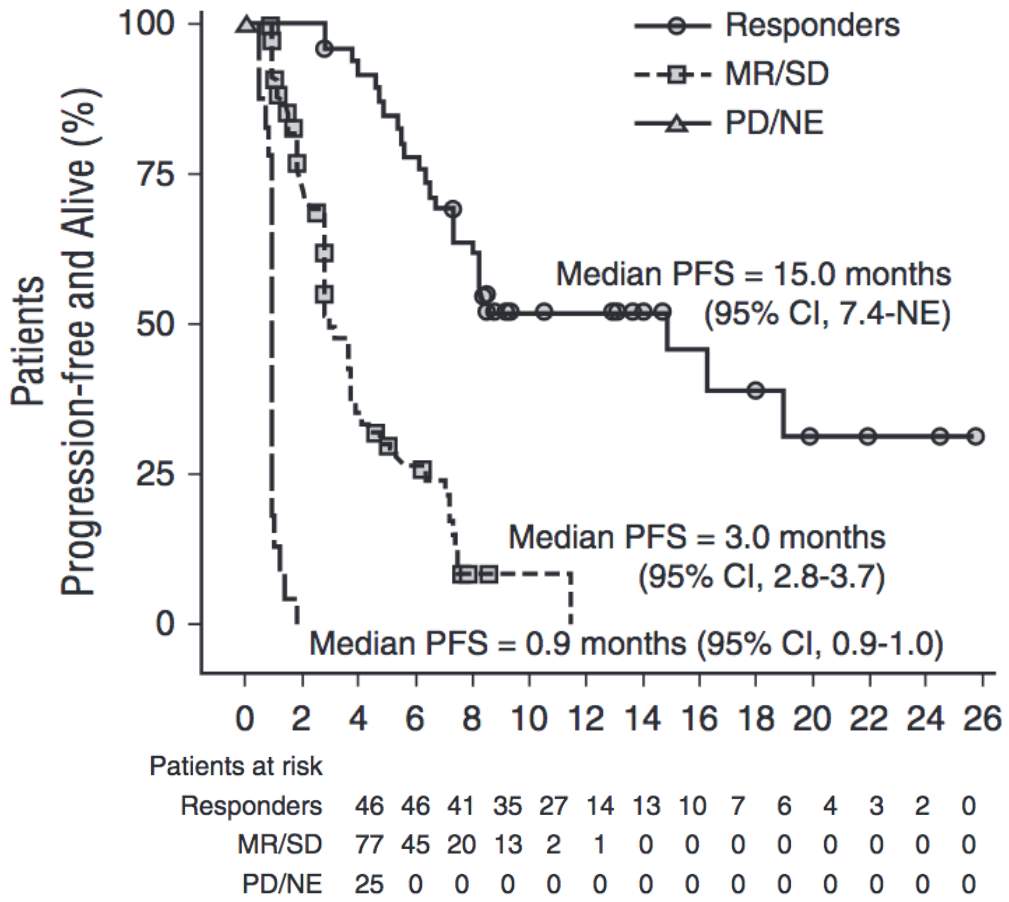
S Lonial, Lancet 2016

Daratumumab en monothérapie

Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma

Saad Z. Usmani,[1] Brendan M. Weiss,[2] Torben Plesner,[3] Nizar J. Bahlis,[4] Andrew Belch,[5] Sagar Lonial,[6] Henk M. Lokhorst,[7] Peter M. Voorhees,[8] Paul G. Richardson,[9] Ajai Chari,[10] A. Kate Sasser,[11] Amy Axel,[11] Huaibao Feng,[12] Clarissa M. Uhlar,[11] Jianping Wang,[11] Imran Khan,[12] Tahamtan Ahmadi,[11] and Hareth Nahi[13]

SIRIUS + GEN 501 part 2



PFS médiane : 4 mois

PFS médiane chez les répondeurs : 15 mois

OS médiane : 20 mois

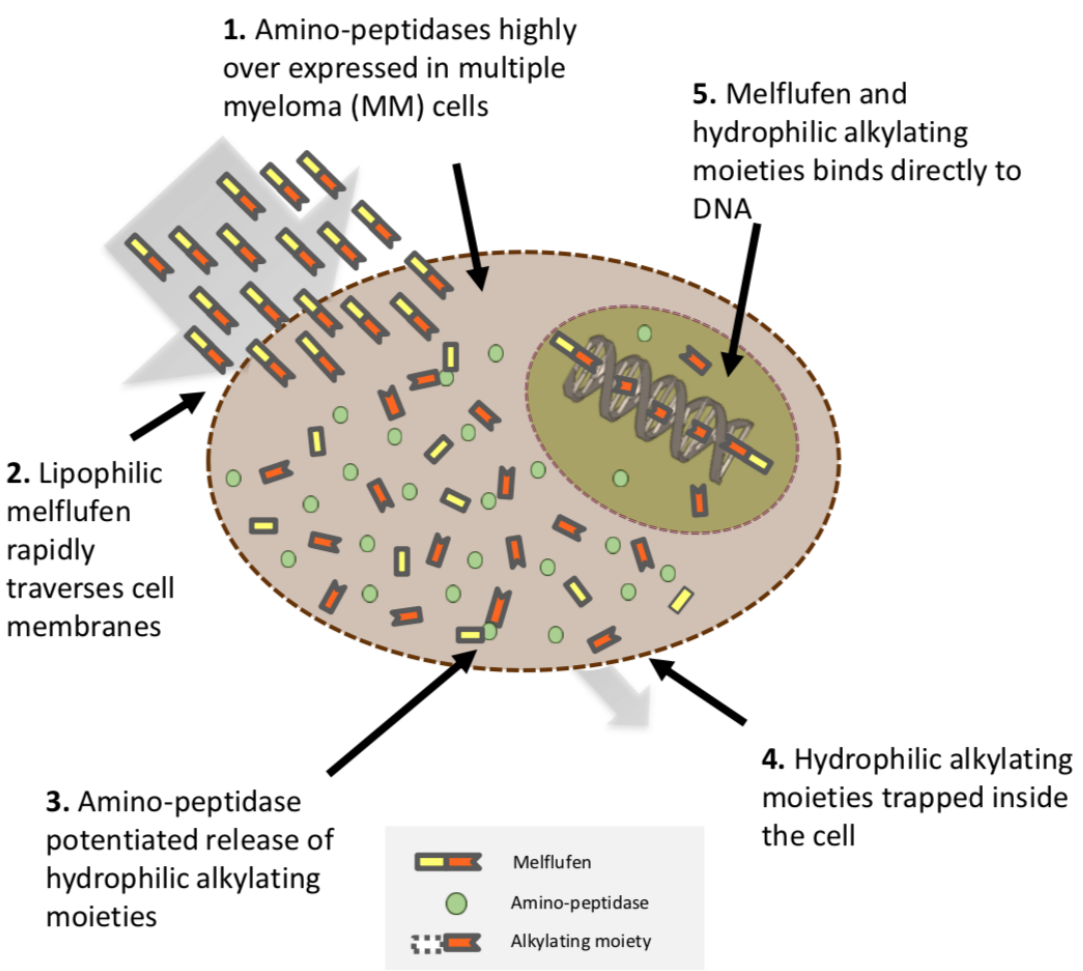
OS médiane NA si réponse

OS médiane : 18 mois si maladie stable

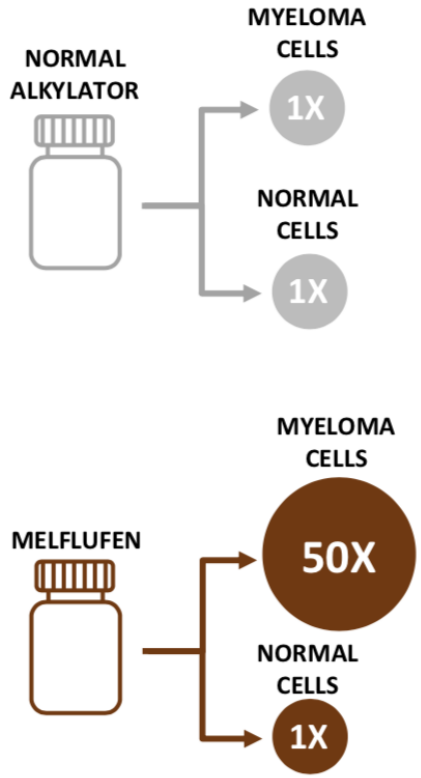
SZ Usmani, Blood 2016

Melflufen = Melphalan flufenamide
First-in-class peptide conjugated alkylator

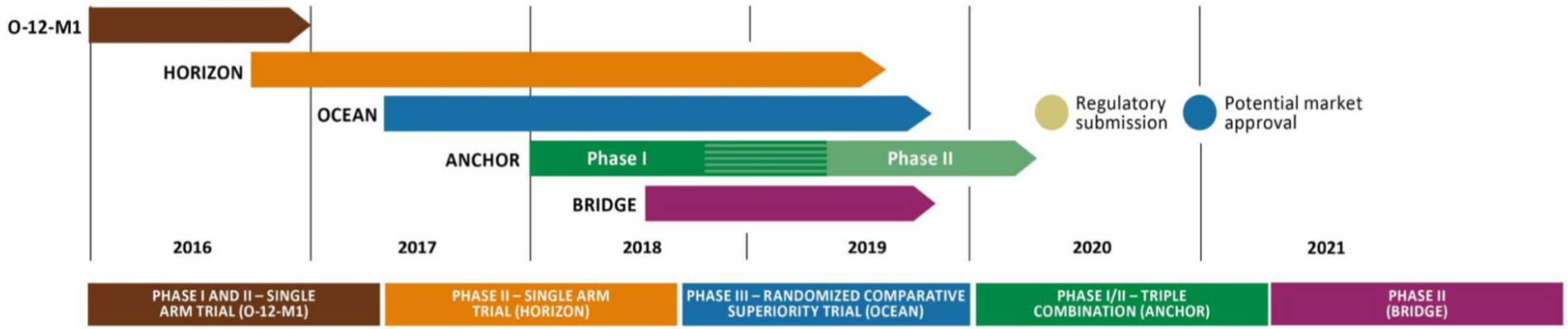
Peptidase enhanced activity in Multiple Myeloma cells



Results in 50-fold higher potency



Place à venir du Melflufen ?

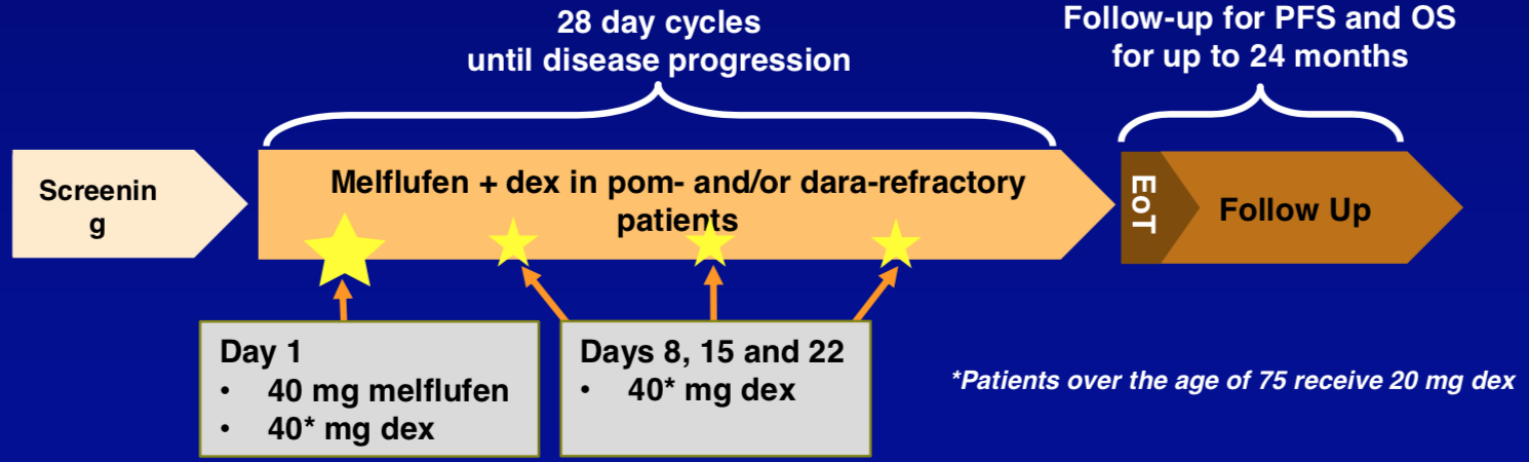


O-12-M1	HORIZON	OCEAN	ANCHOR	BRIDGE
Show single-agent activity in RRMM	Show single-agent activity in RRMM	Show single-agent superiority over SoC backbone in RRMM (pomalidomide)	Show combination synergy and tolerability with daratumumab and bortezomib	Show that melflufen can be used in patients with renal impairment

HORIZON : phase 2

OP-106 HORIZON: Phase 2 of Safety and Efficacy of Melflufen in Pomalidomide- and/or Daratumumab-refractory RRMM Patients

Background	HORIZON Design	Potential Outcomes
• Patients who are daratumumab (dara) and/or pomalidomide (pom) refractory have limited options • Introducing a class change with an effective compound may represent a new best treatment strategy • Data suggests patients could derive clinical benefit if administered Melflufen in this setting	• Single arm, open-label, phase II multicenter study • ≥2 lines of prior therapy and pts are refractory to pomalidomide and/or daratumumab • Primary endpoint: ORR • Secondary endpoints: PFS, DOR, OS, CBR, TTR, TTP, safety and tolerability	• Supports OCEAN to receive regulatory approval



P Richardson et al, ASH 2018

HORIZON : phase 2

Patient Characteristics at Study Entry (n=83)

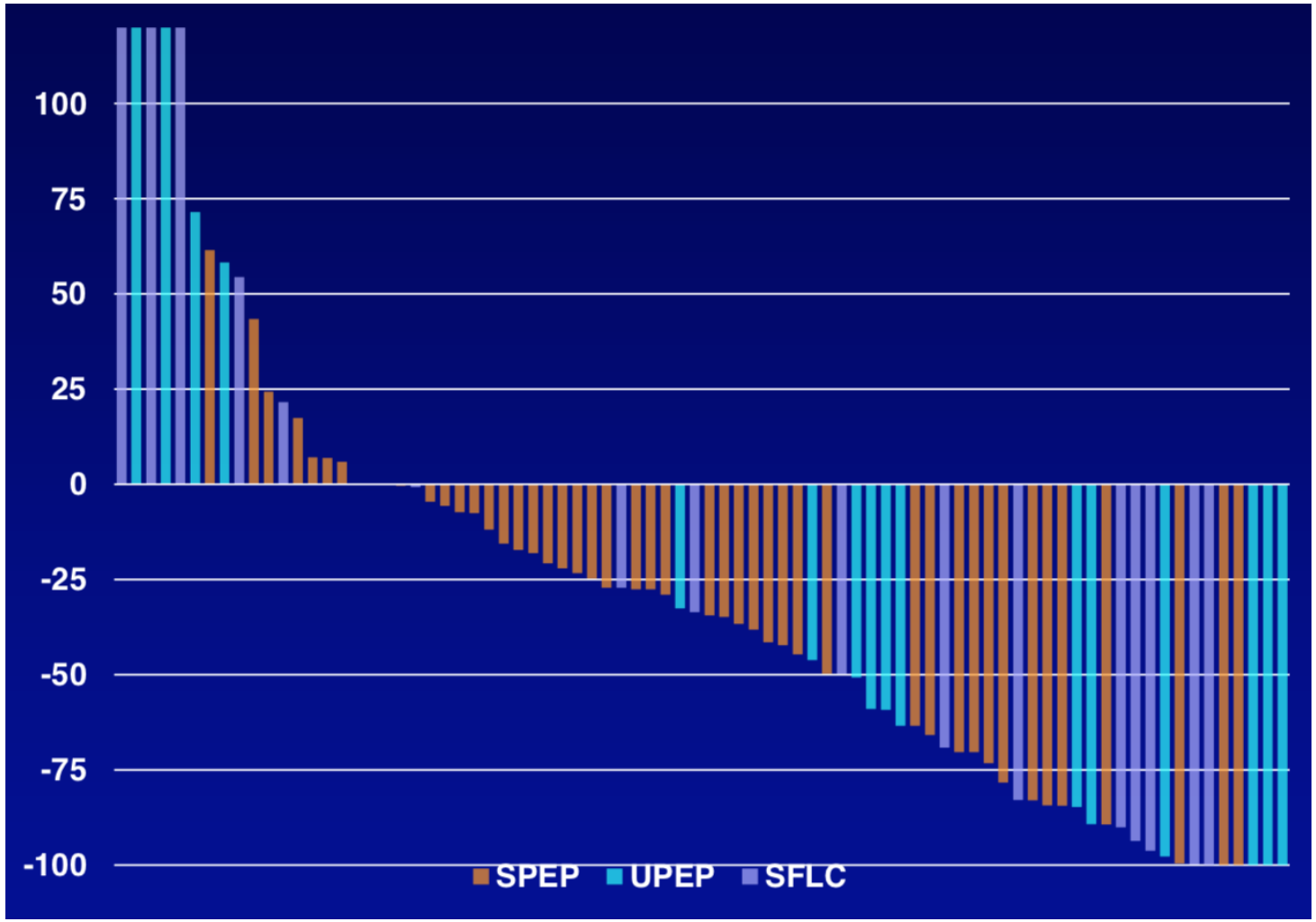
		Range
Age (median)	63 yrs	(35-86)
Male / Female	59 / 41 %	
Median time since diagnosis	6.5 yrs	(0.7-25)
Median prior lines of therapy	5	(2-13)
ISS stage I / II / III*	33 / 29 / 36 %	
ECOG 0 / 1 / 2	27 / 58 / 16 %	
High-risk cytogenetics** / 2 or more high risk abnormalities	61 / 20 %	
Received ASCT (%) / Relapsed within 1 year after ASCT (%)	69 / 17 %	
Albumin < 3.5 g/dl	35 %	
Baseline β_2 microglobulin ≥ 3.5 mg/l	50 %	

*ISS at study entry unknown for 3 pts **HR status data pending/missing in 23 pts

Refractory to	%
Pom or dara	100
Pom and dara	60
Double refractory (PI+IMiD)	86
Double + anti-CD38 refractory	60
Monoclonal antibody (MoAb)	80
Alkylator exposed	84
Alkylator refractory	55
Received 1 ASCT / 2 ASCT	69 / 25
Refractory in last line	93

P Richardson et al, ASH 2018

HORIZON : phase 2

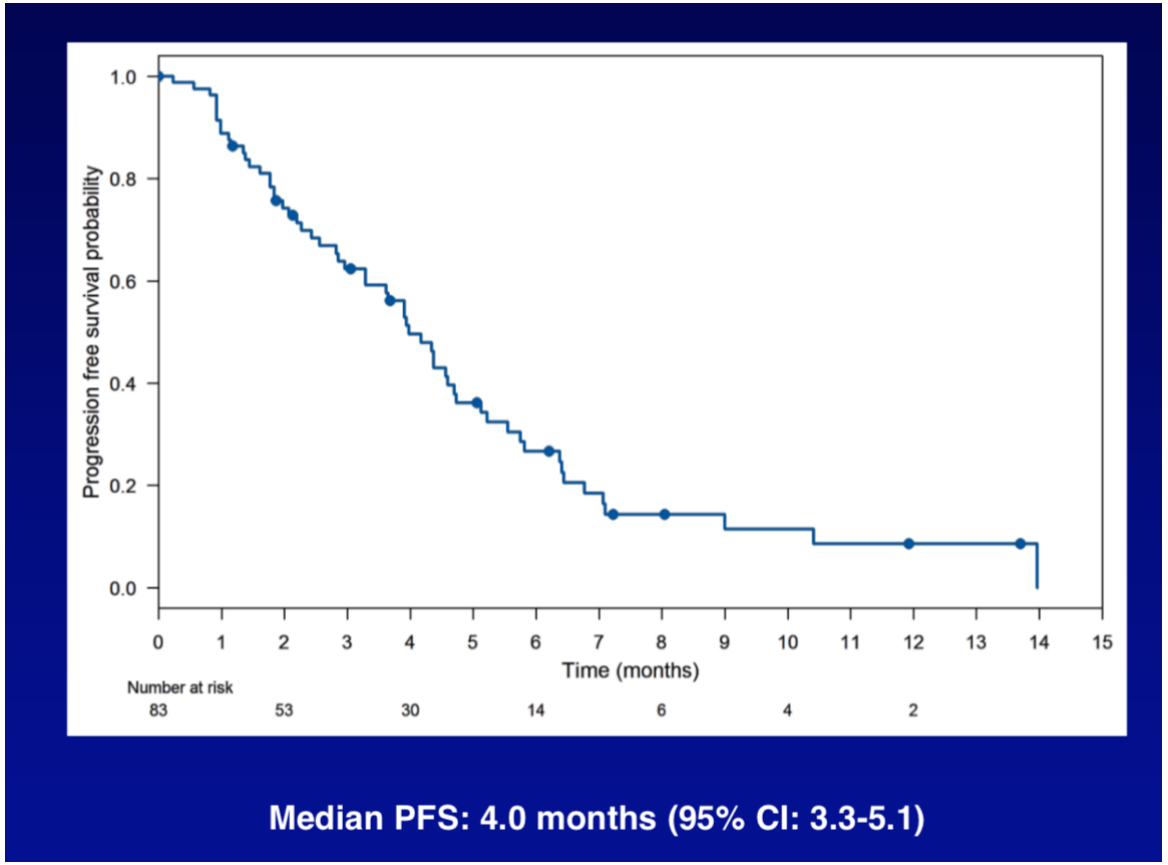


P Richardson et al, ASH 2018

HORIZON : phase 2

Taux de réponse

	N	%
Réponse globale	27	33
RCs	1	1
RC	0	0
TBRP	9	11
RP	17	21



P Richardson et al, ASH 2018

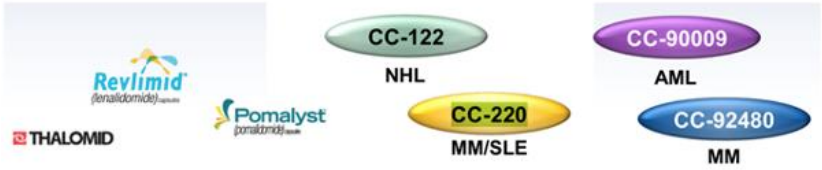
HORIZON : tolérance

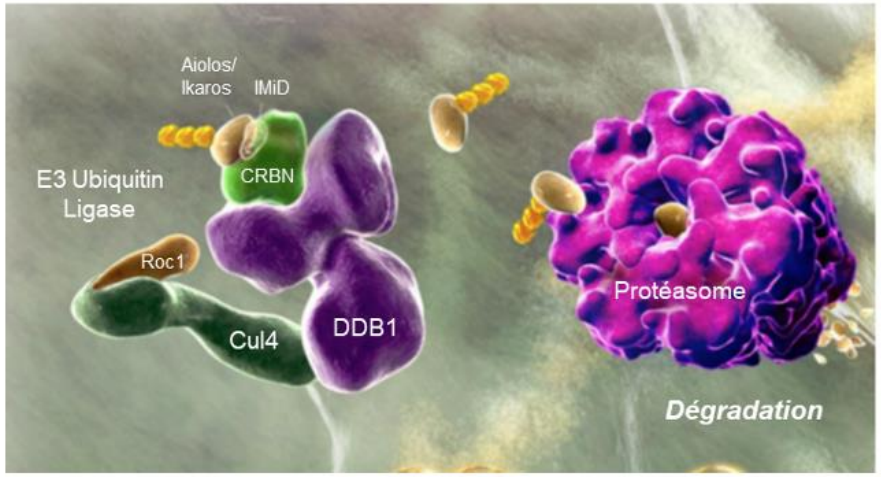
AE

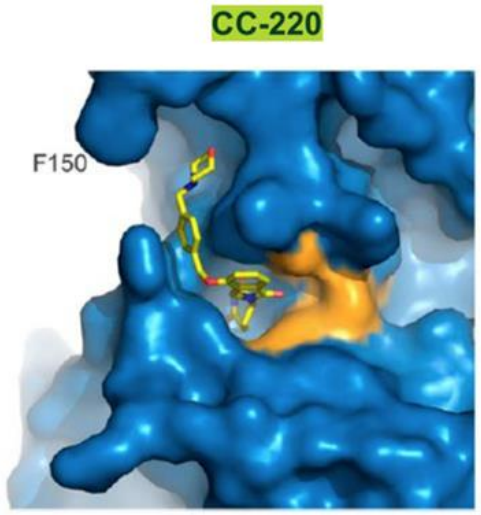
	G3/G4 n (%)	G4 n (%)
Any treatment-related grade 3-4 AEs in ≥2 pts	62 (75)	42 (51)
Blood and lymphatic system disorders	61 (73)	41 (49)
Neutropenia	51 (61)	29 (35)
Thrombocytopenia	49 (59)	30 (36)
Anaemia	21 (25)	1 (1)
Febrile neutropenia	5 (6)	2 (2)
Leukopenia	4 (5)	3 (4)
Lymphopenia	4 (5)	1 (1)
Infections and infestations	6 (7)	0 (0)
Pneumonia	2 (2)	0 (0)
Treatment-related SAEs	14 (16)*	5 (6)

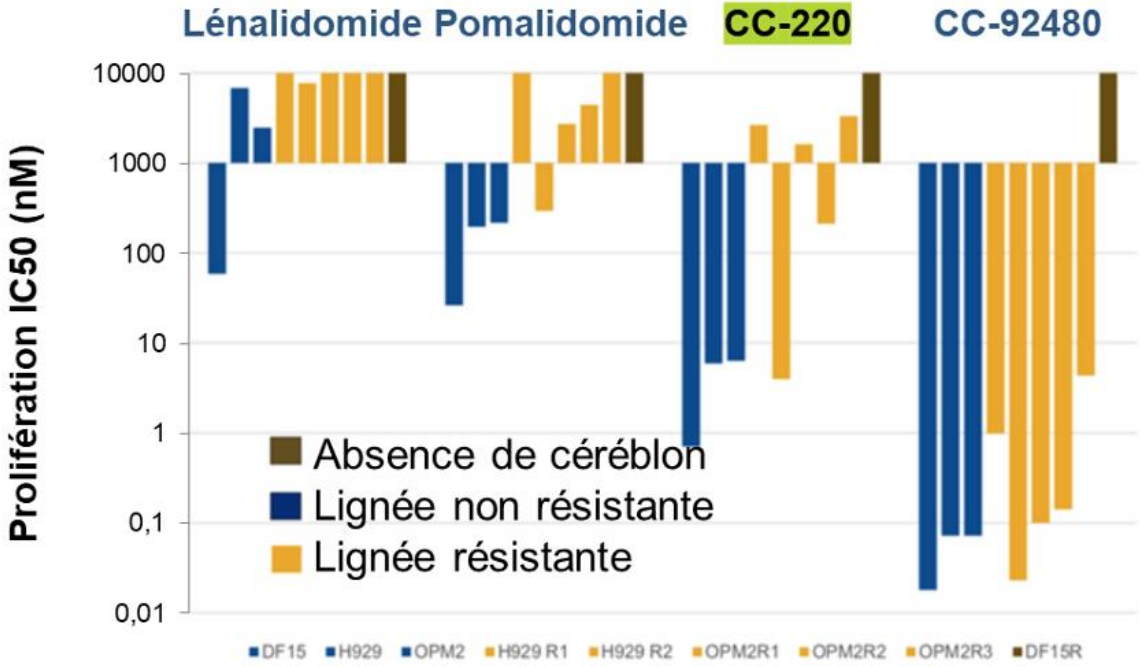
P Richardson et al, ASH 2018

Place à venir des CelMods ?









Et donc en RCP…

MM Ig/FLC
CRAB / SlimCRAB

TP53 del17p
t(4;14) trisomy 21
del1p32
trisomy 5
gain1q DIS3

t(11;14) ?

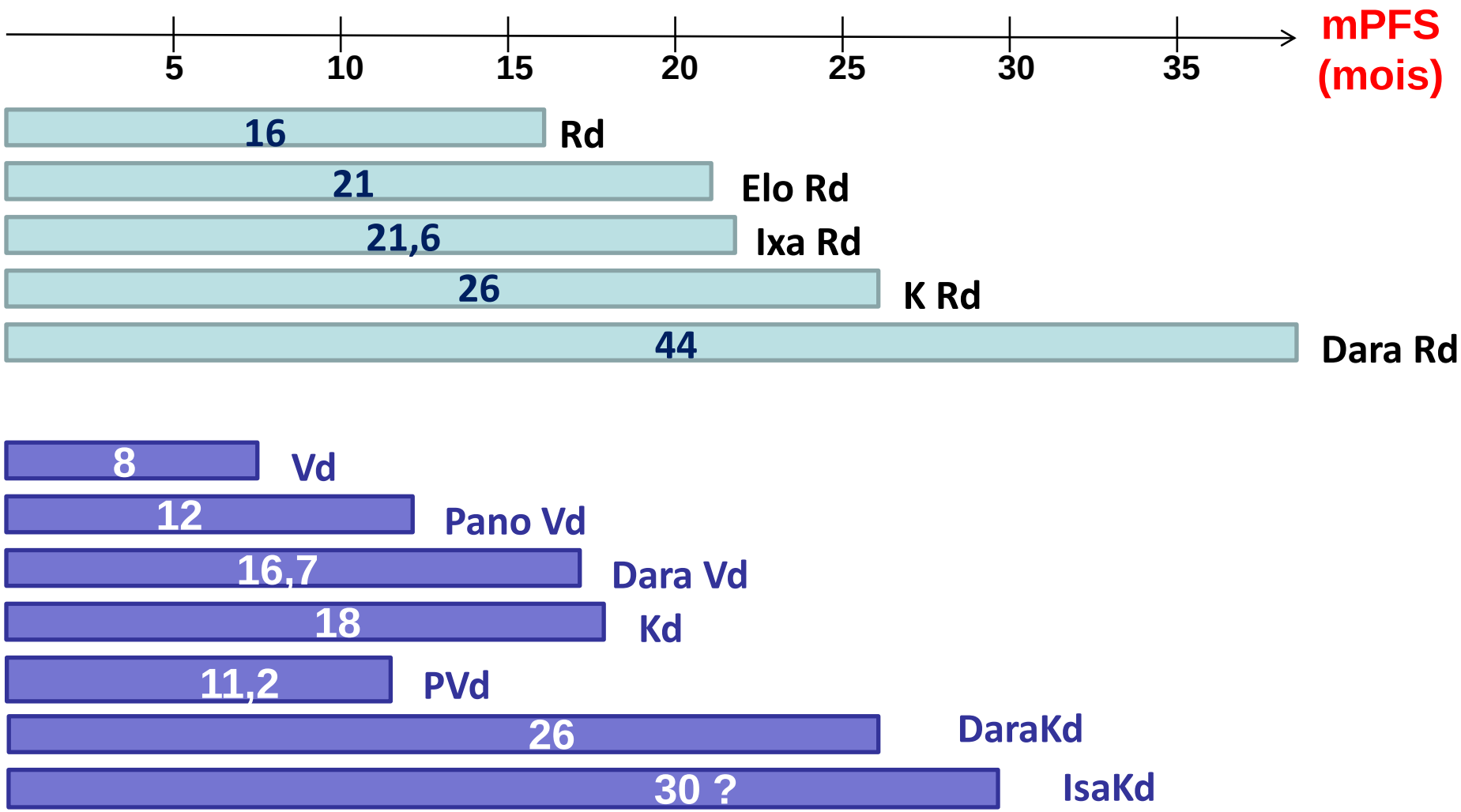
Patient et Maladie
Cytogénétique ?
Traitements antérieurs ?

Comorbidités
Lignes reçues
1)
Meilleure réponse + date
Complications / séquelles
2)

Efficacité
Réponse
PFS
OS

Toxicité / QoL
Toxicité
IV vs oral
Contraintes

Comparaisons indirectes de PFS ?

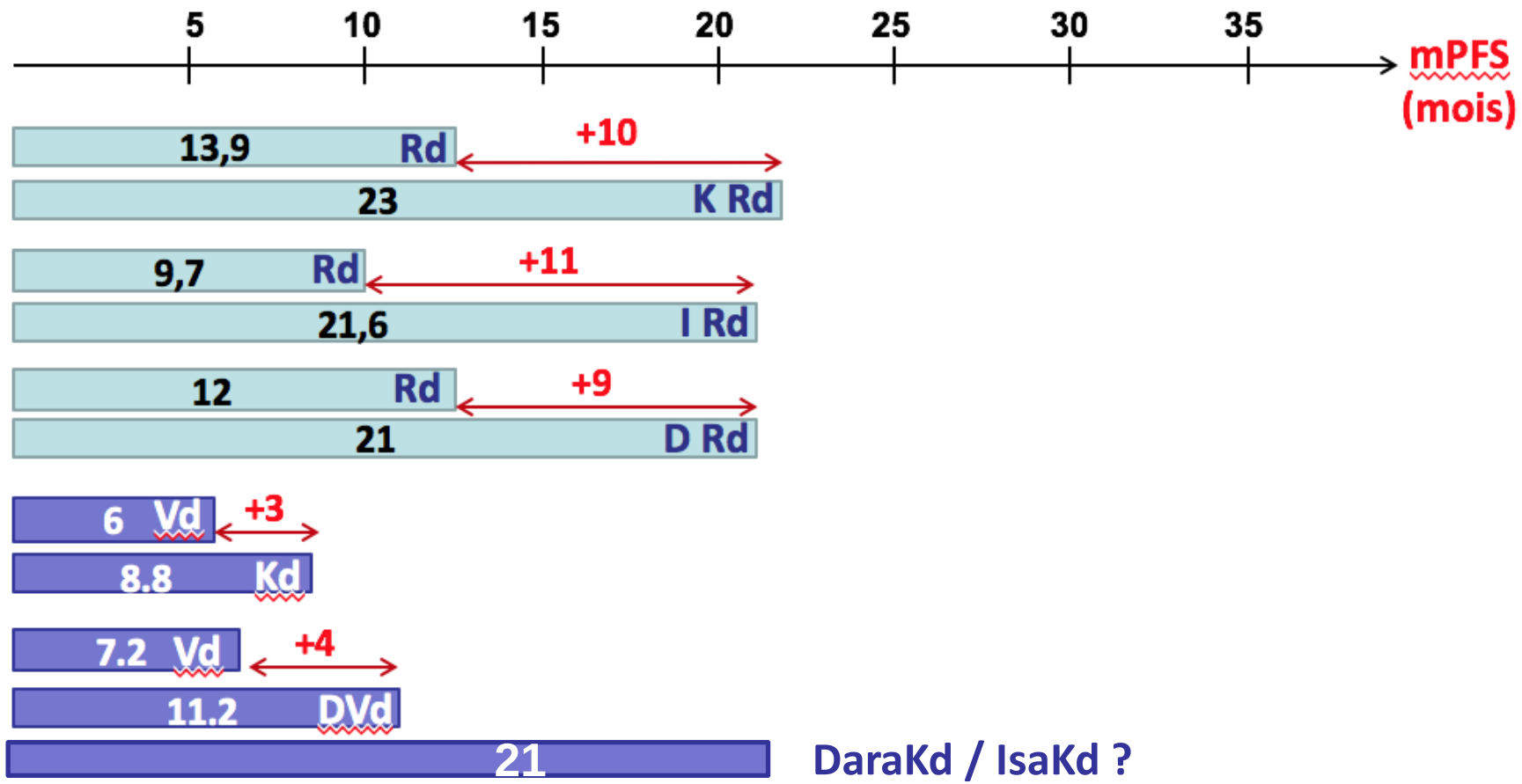


Focus sur les patients réfractaires au Lénalidomide

	ENDEAVOR Kd 56x2	CASTOR Dara Vd	OPTIMISMM PVd	ARROW Kd 70x1	CANDOR Dara Kd	IKEMA Isa Kd	ICARIA IsaPd
Exposés / réfractaires au Lénalidomide (%)							
Exposés	38	36	100	86	42	76	100
Réfractaires	**24**	**24**	**70**	**75**	**33**	**32**	**93**
PFS de la population globale (mois)							
PFS médiane	18,7	16,7	11,2	11,1	*≈ 25*	*≈ 30 ?*	*11,5*
PFS si réfractaire au Lénalidomide (mois)							
PFS médiane	8,6	7,8	9,5		*≈ 25*	*≈ 28*	

Choix selon risque cytogénétique

PFS chez les haut risque



DaraKd / IsaKd ?

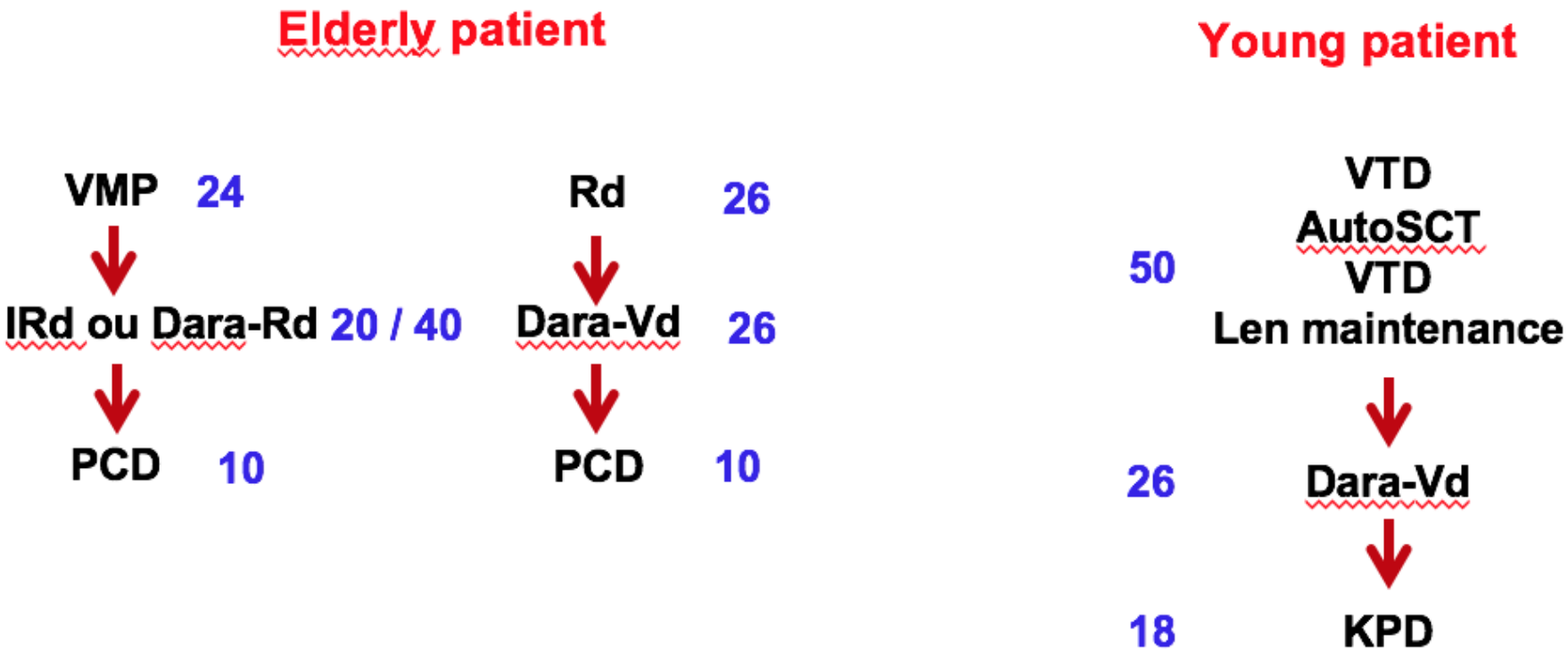
Choix selon le profil de toxicité

DRUG	AE	Grade ¾ (%)
CARFILZOMIB	CARDIAC FAILURE/ISCHEMIC DISEASE	7
	HYPERTENSION	4
	RENAL FAILURE	3
IXAZOMIB	RASH	5
	THROMBOCYTOPENIA	19
DARATUMUMAB	INFUSION REACTION	5%
ELOTUZUMAB	INFUSION REACTION	1%
PANOBINOSTAT	DIARRHEA	25%
	FATIGUE	24%
	THROMBOCYTOPENIA / NEUTROPENIA	68% / 35%

Prise en compte de la qualité de vie du patient

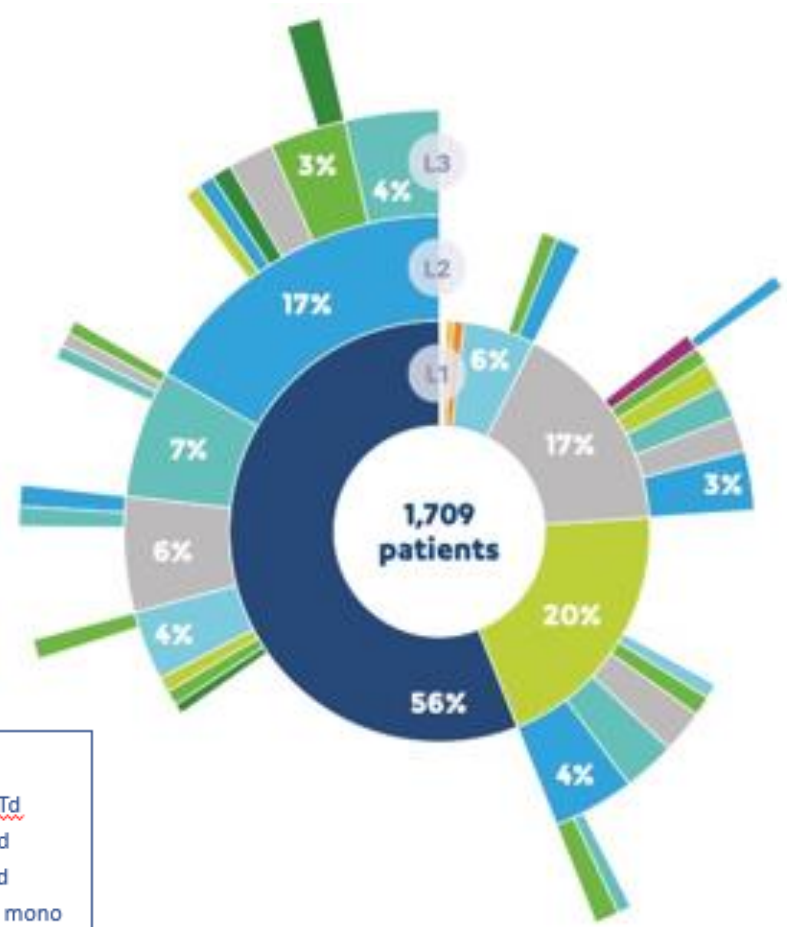
	Ixa-Rd	Dara-Rd	Carf-Rd
Administration	PO	IV (Dara)	IV (carfilzomib)
Fréquence des venues	Mensuelle	Hebdo 2 mois Bimensuelle 4 mois puis mensuelle	Bi-hebdo
Durée des visites	20 mn	4 h	2 h
Nombre de visites (18 cycles)	18	26	108
Temps passé à l'hôpital (18 cycles)	6 h	104 h	216 h

Séquences thérapeutiques et somme des PFS



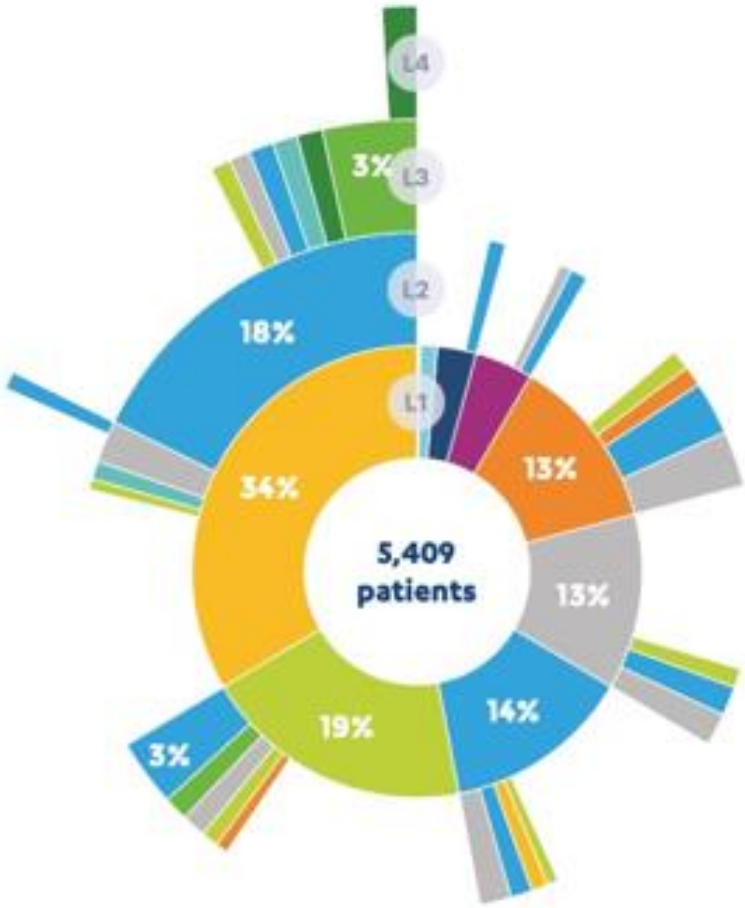
Séquences de traitement (cohorte 2014-2015 MYLORD)

Patients greffés en L1



Main course:
- L1: VTd
- L2: Rd
- L3: Pd
- L4: D mono

Patients non greffés en L1



Main course:
- L1: VMP
- L2: Rd
- L3: Pd
- L4: D mono

- BP, BVd
- MP, MPT
- VMP
- V
- Pd
- D mono
- VTd
- Rd
- VRd
- Triplets
- Others

Triplets: IRd; KRd; DRd; DVd; PVd; DPd; VRd

En attendant les anti-BCMA…

Questions ?