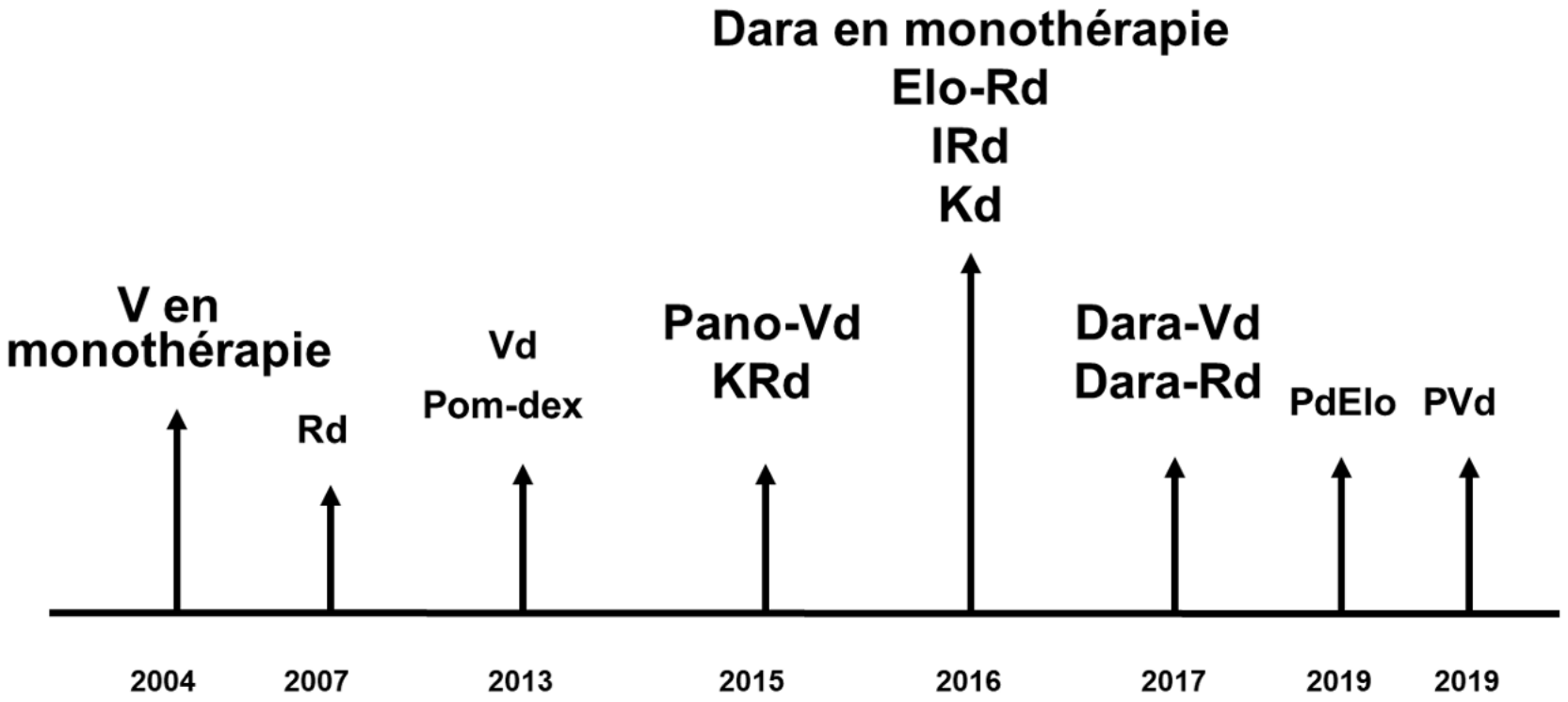
Le myélome multiple en rechute / réfractaire en France aujourd'hui

Dr Aurore Perrot

Liens d’intérêts

Honoraires et advisory boards : Abbvie, Amgen, BMS/Celgene, GSK, Janssen, Sanofi, Takeda.

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

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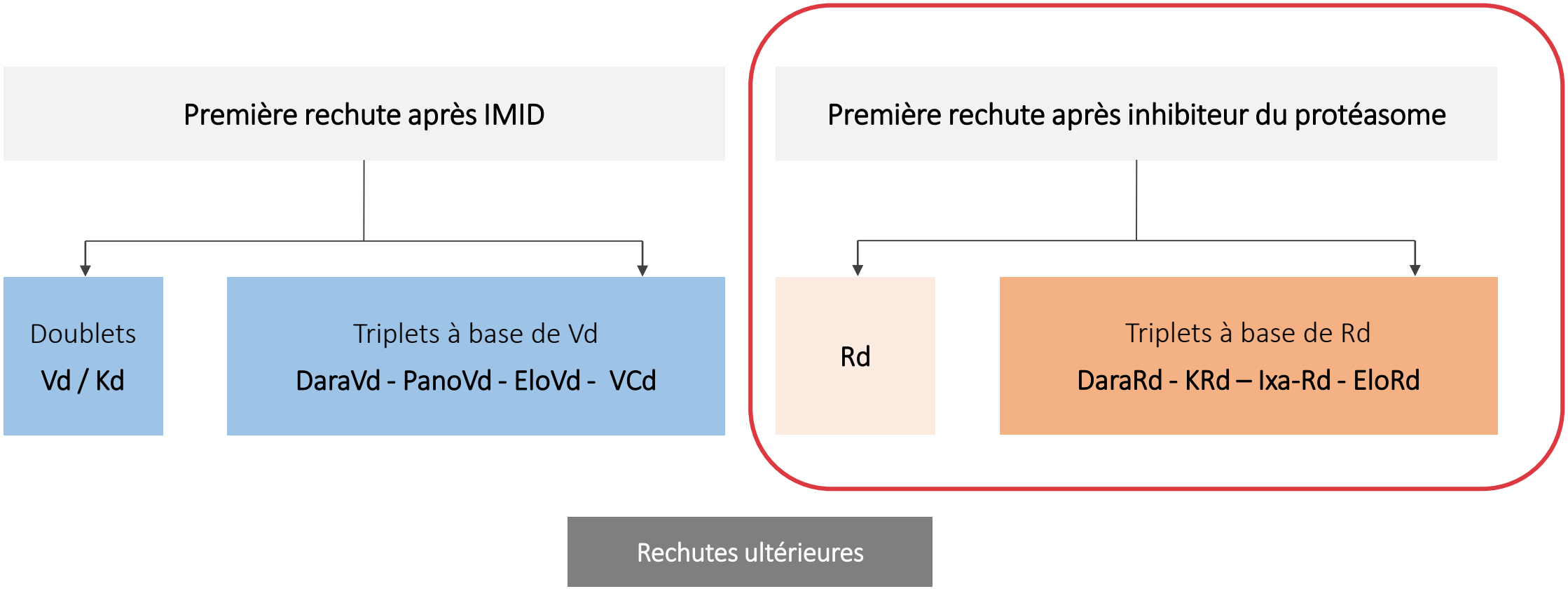
Recommandations ESMO

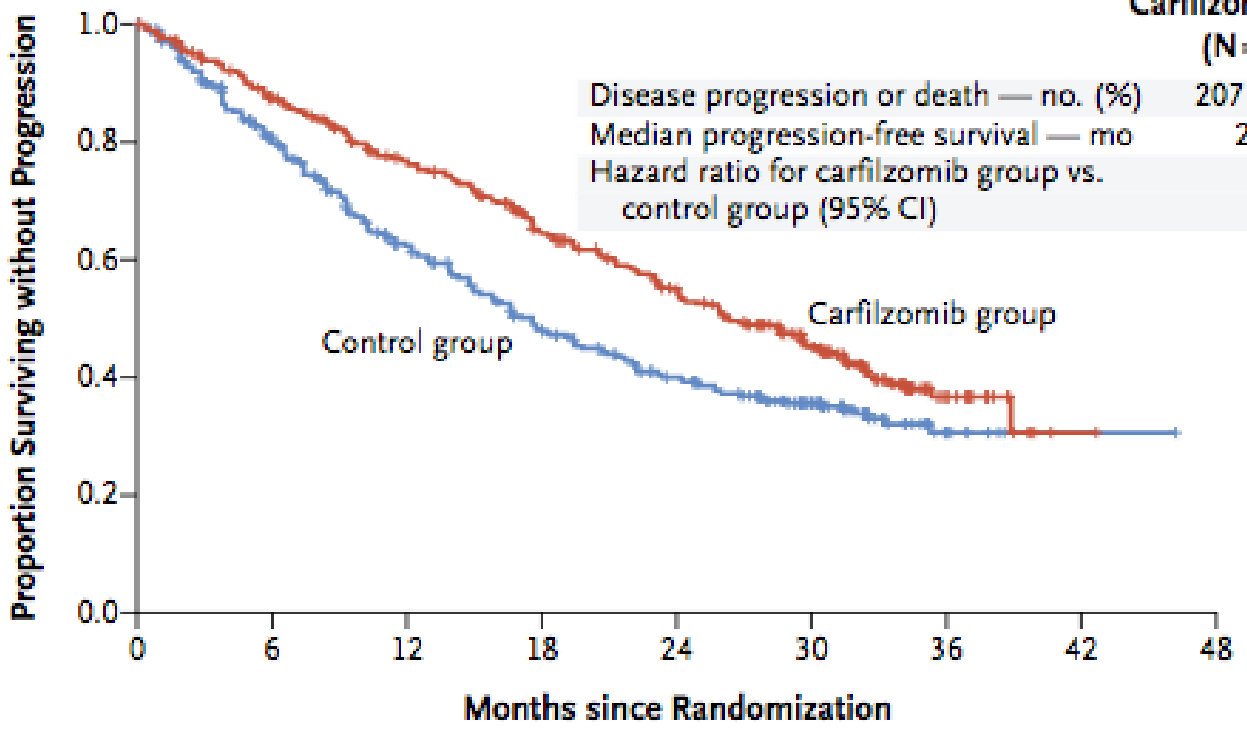


P Moreau et al, Ann Oncol 2017

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

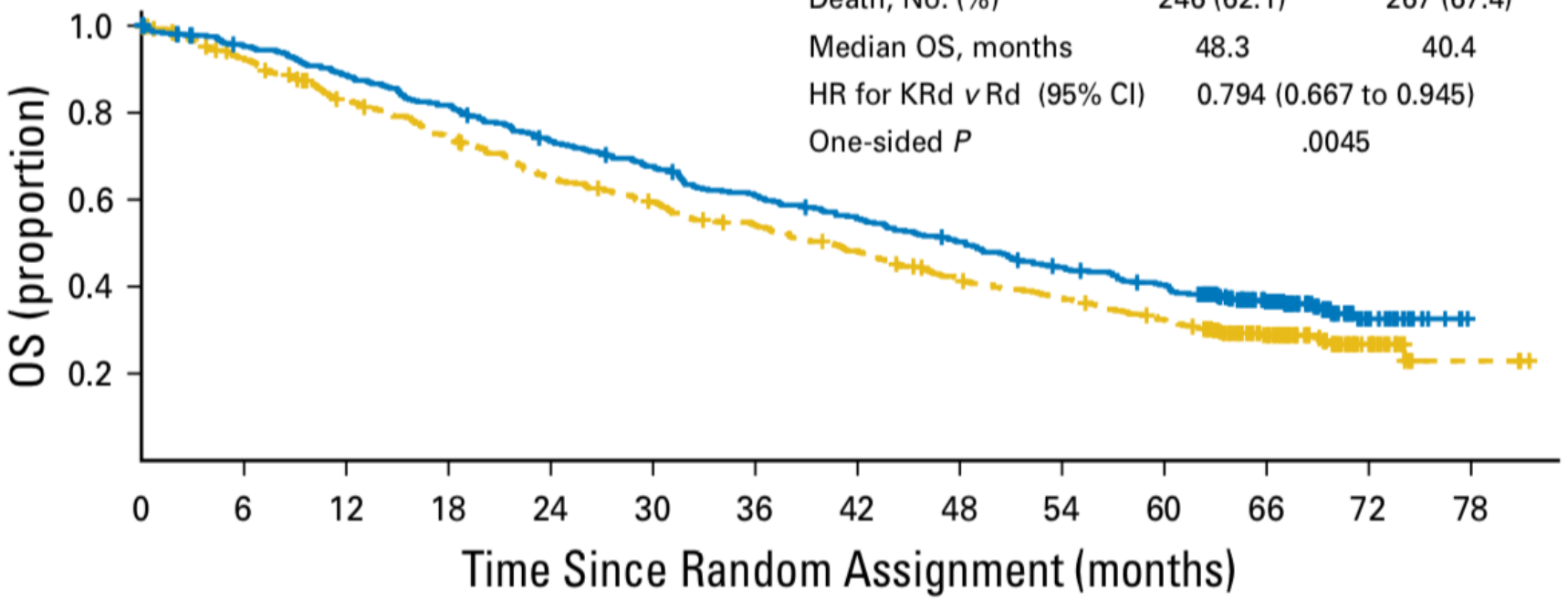
AK Stewart et al, N Engl J Med 2015

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

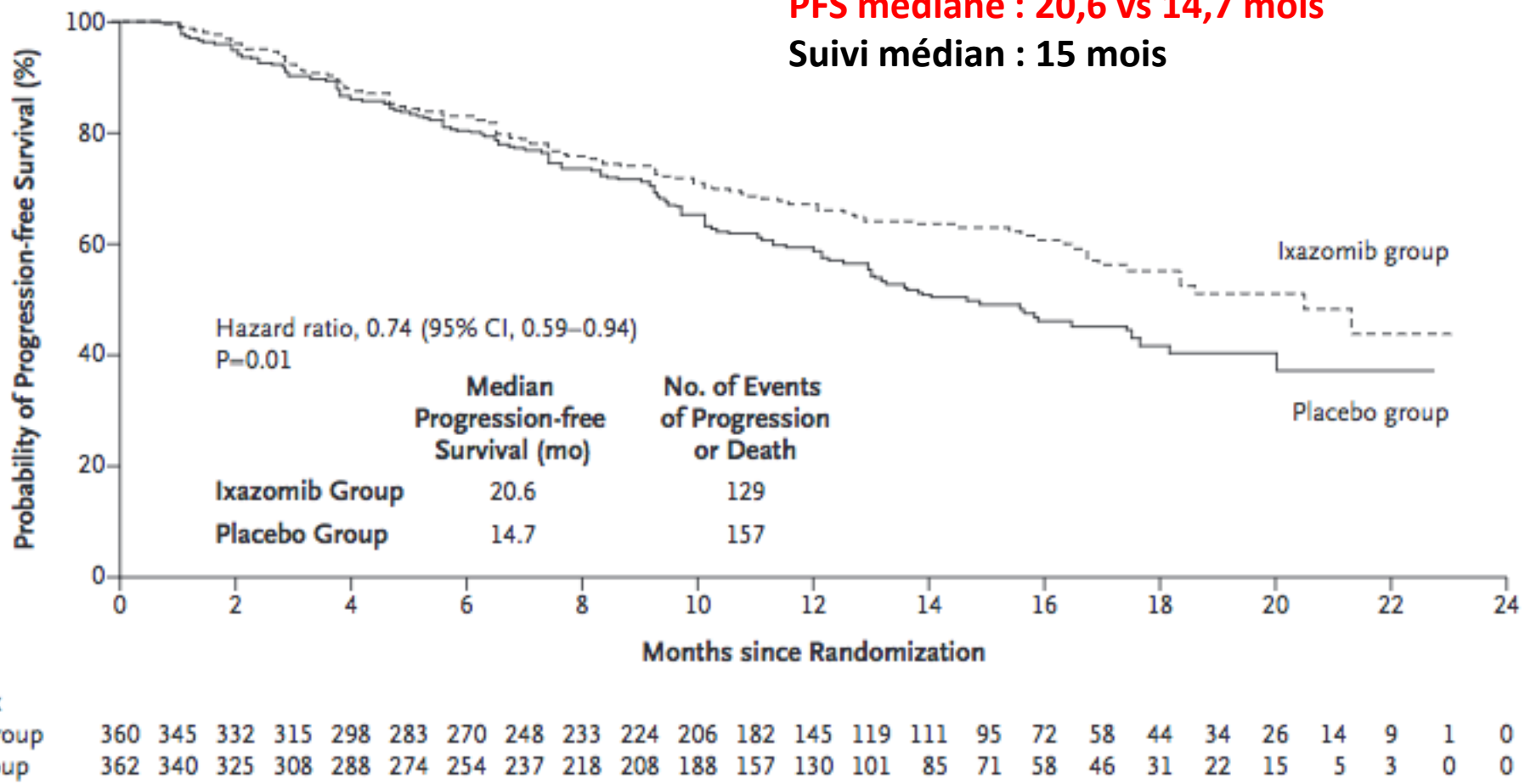
DS Siegel et al, J Clin Oncol 2018

Etude TOURMALINE-MM1 : approbation d'IxaRd

n = 722

PFS médiane : 20,6 vs 14,7 mois

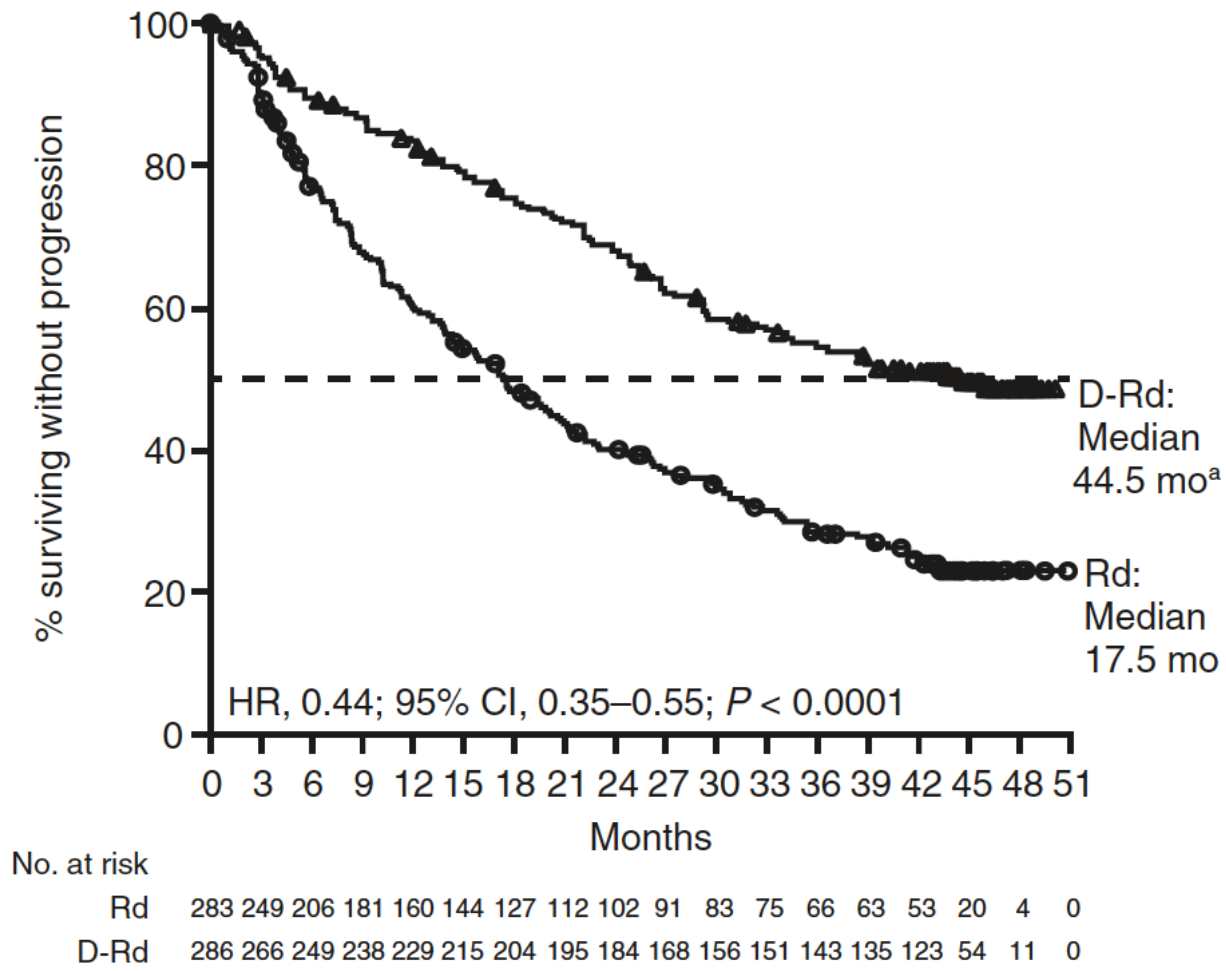
Suivi médian : 15 mois



P Moreau et al, N Engl J Med 2016

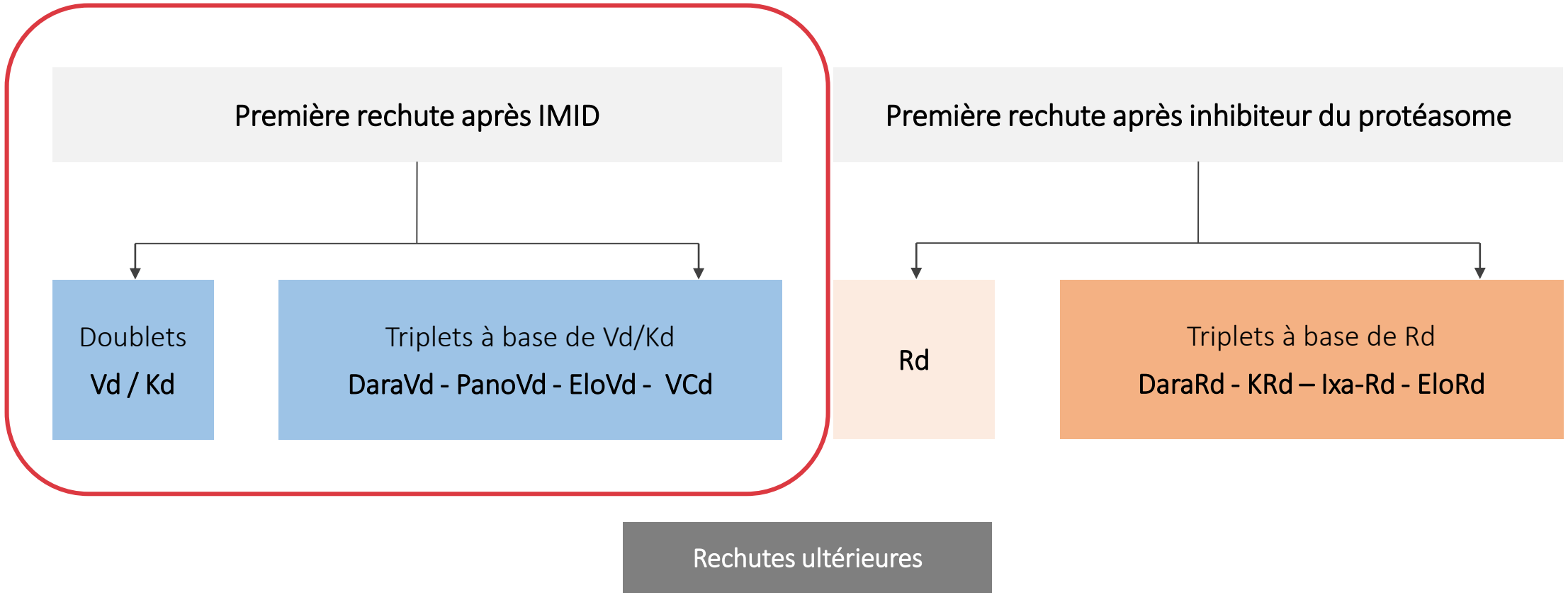
Etude POLLUX : approbation de Dara-Rd

n = 569



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

Recommandations ESMO



P Moreau et al, Ann Oncol 2017

Etude ENDEAVOR : approbation de Kd

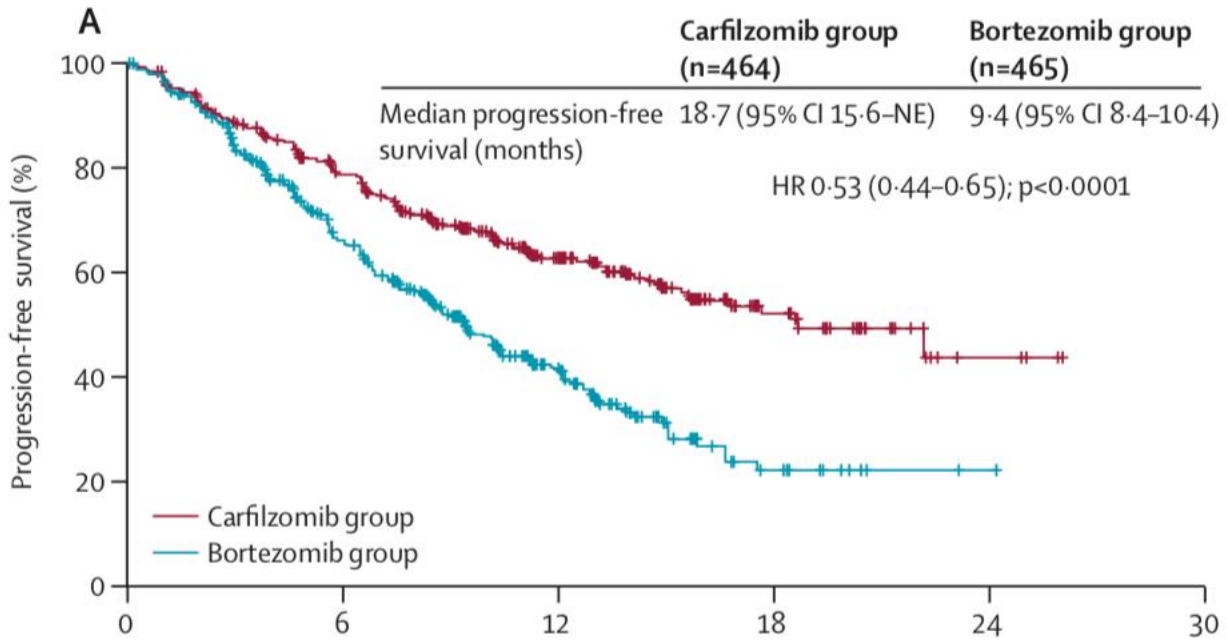
Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study

Meletios A Dimopoulos, Philippe Moreau*, Antonio Palumbo, Douglas Joshua, Ludek Pour, Roman Hájek, Thierry Facon, Heinz Ludwig, Albert Oriol, Hartmut Goldschmidt, Laura Rosiñol, Jan Straub, Aleksandr Suvorov, Carla Araujo, Elena Rimashevskaya, Tomas Pika, Gianluca Gaidano, Katja Weisel, Vesselina Goranova-Marinova, Anthony Schwarer, Leonard Minuk, Tamás Masszi, Ievgenii Karamanesht, Massimo Offidani, Vania Hungria, Andrew Spencer, Robert Z Orlowski, Heidi H Gillenwater, Nehal Mohamed, Shibao Feng, Wee-Joo Chng, for the ENDEAVOR investigators*

PFS médiane : 18,7 vs 9,4 mois

Suivi médian : 11,2 mois

n = 929



MA Dimopoulos et al, Lancet Oncol 2016

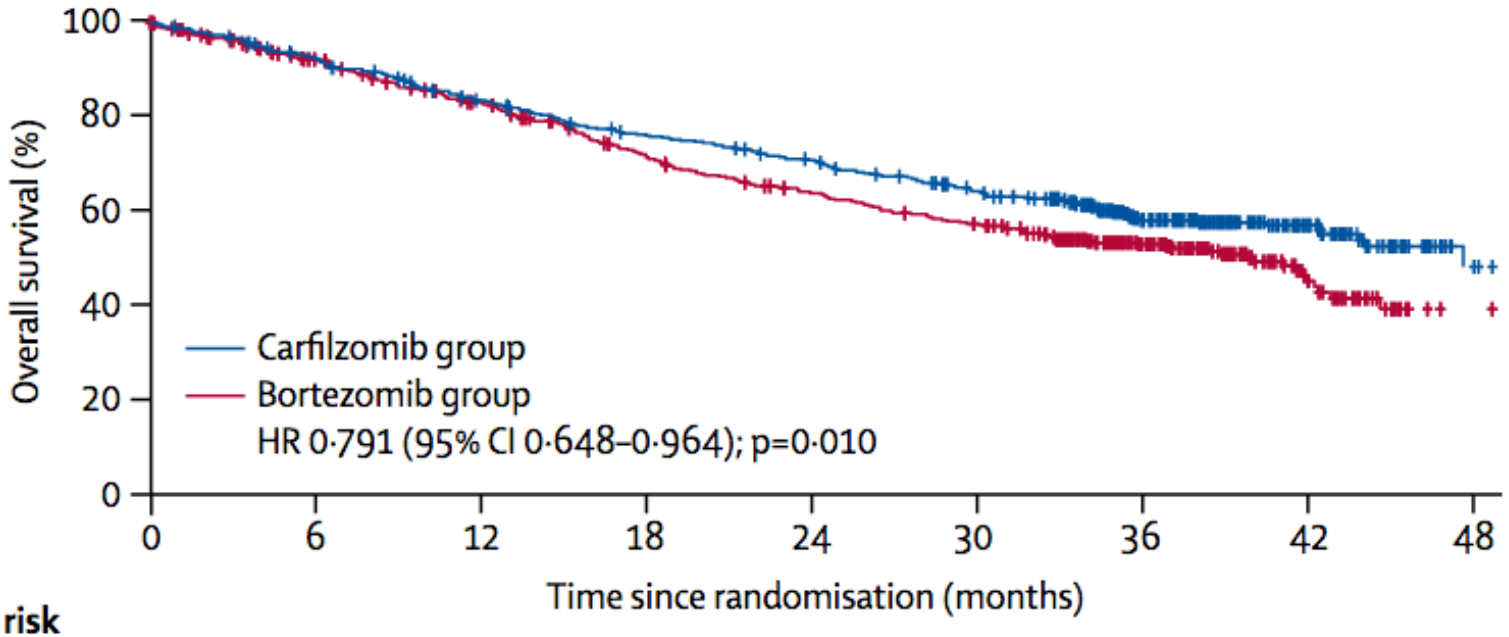
Etude ENDEAVOR : approbation de Kd

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

OS médiane : 47,6 vs 40 mois

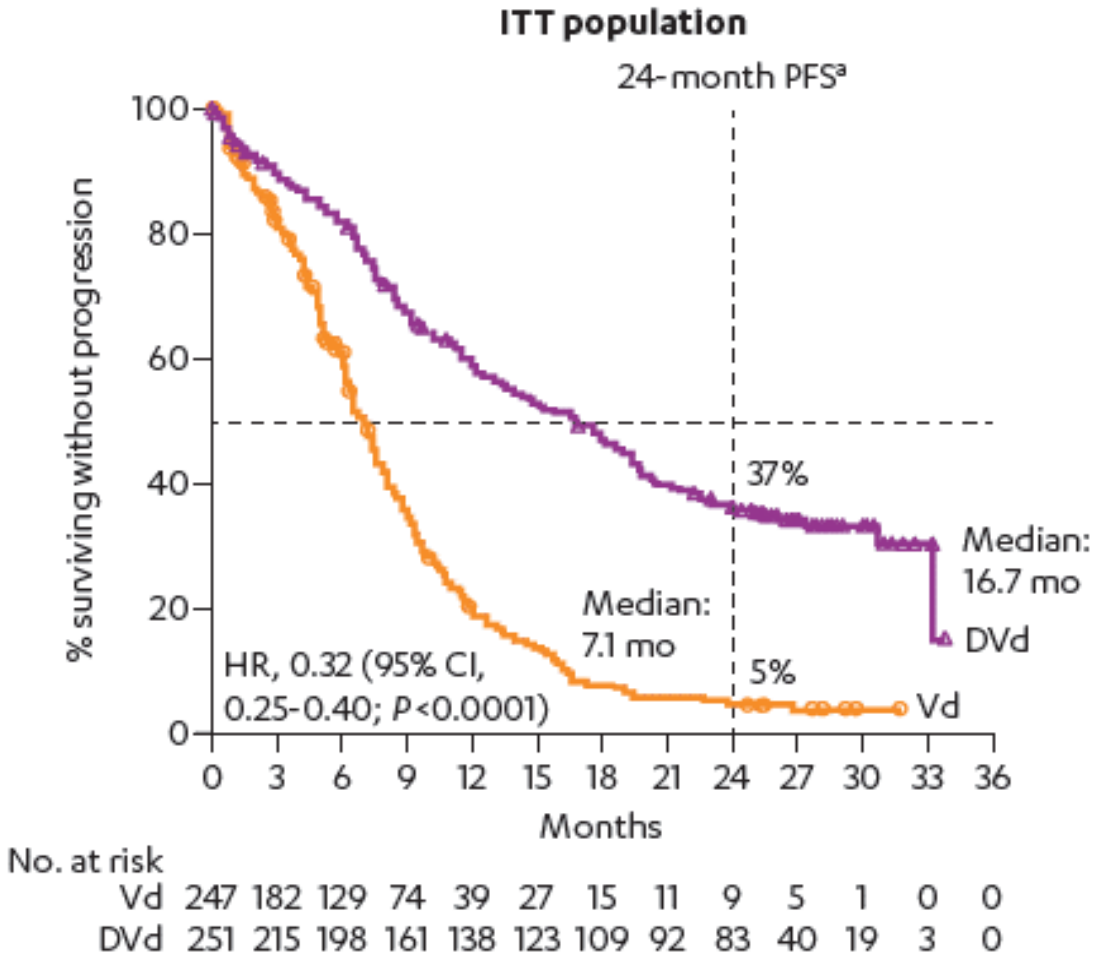
Suivi médian : 37 mois



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

Etude CASTOR : approbation de DaraVd



Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

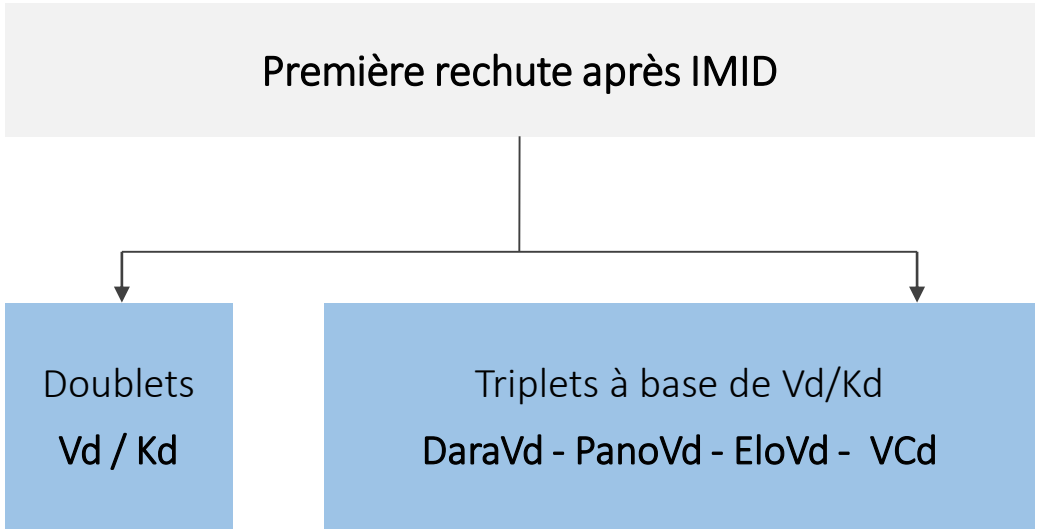
Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, 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

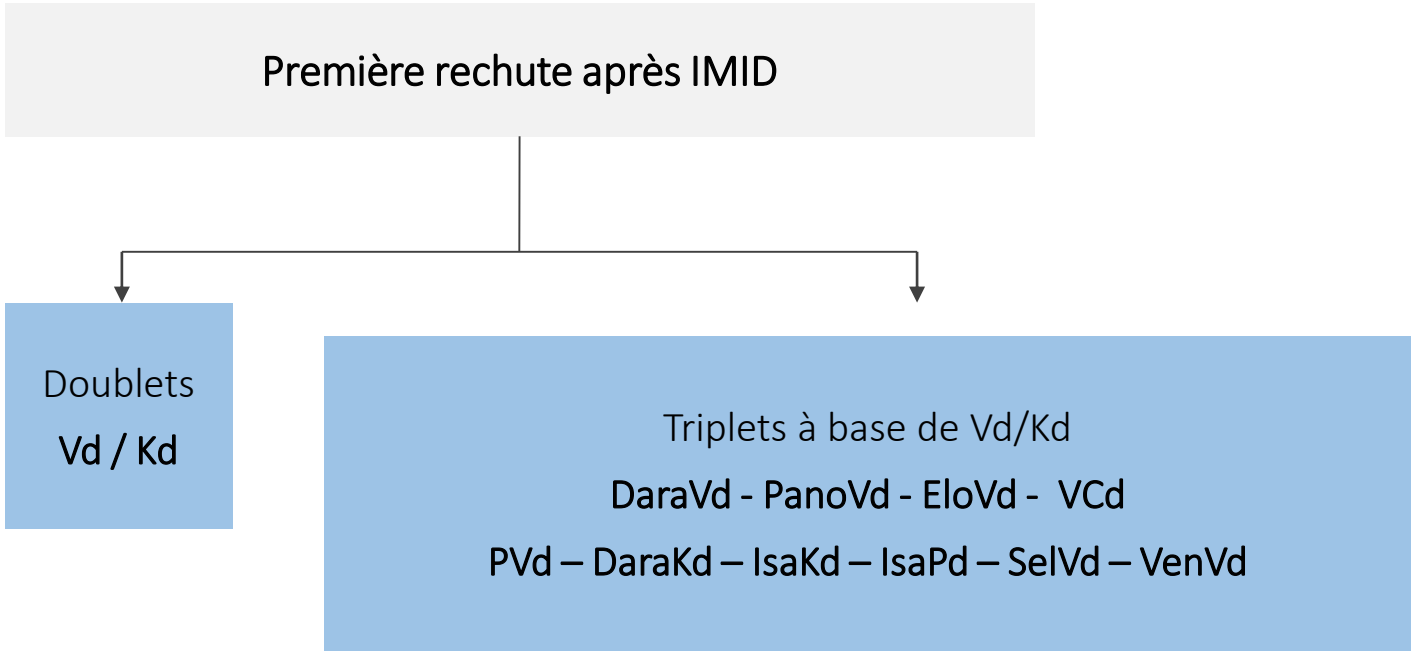
A Palumbo et al, N Engl J Med 2016
A Spencer et al, Haematologica 2018

Nouvelles combinaisons à base de Vd / Kd



A Perrot, personnal communication

Nouvelles combinaisons à base de Vd / Kd ou Pd



OPTIMISMM

CANDOR

IKEMA

BOSTON

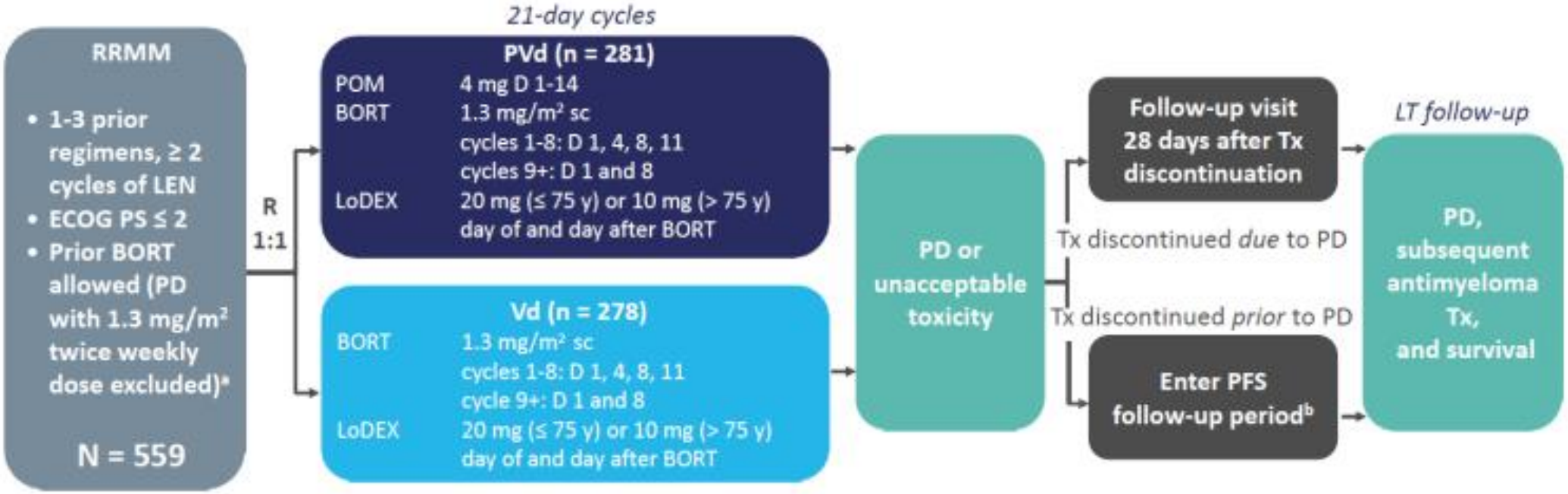
BELLINI

HORIZON

ICARIA

A Perrot, personnal communication

Etude OPTIMISMM : approbation de PVd



- **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

* 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

4

P Richardson et al, ASCO 2018

Etude OPTIMISMM : approbation de PVd

PRIOR THERAPY (ITT)

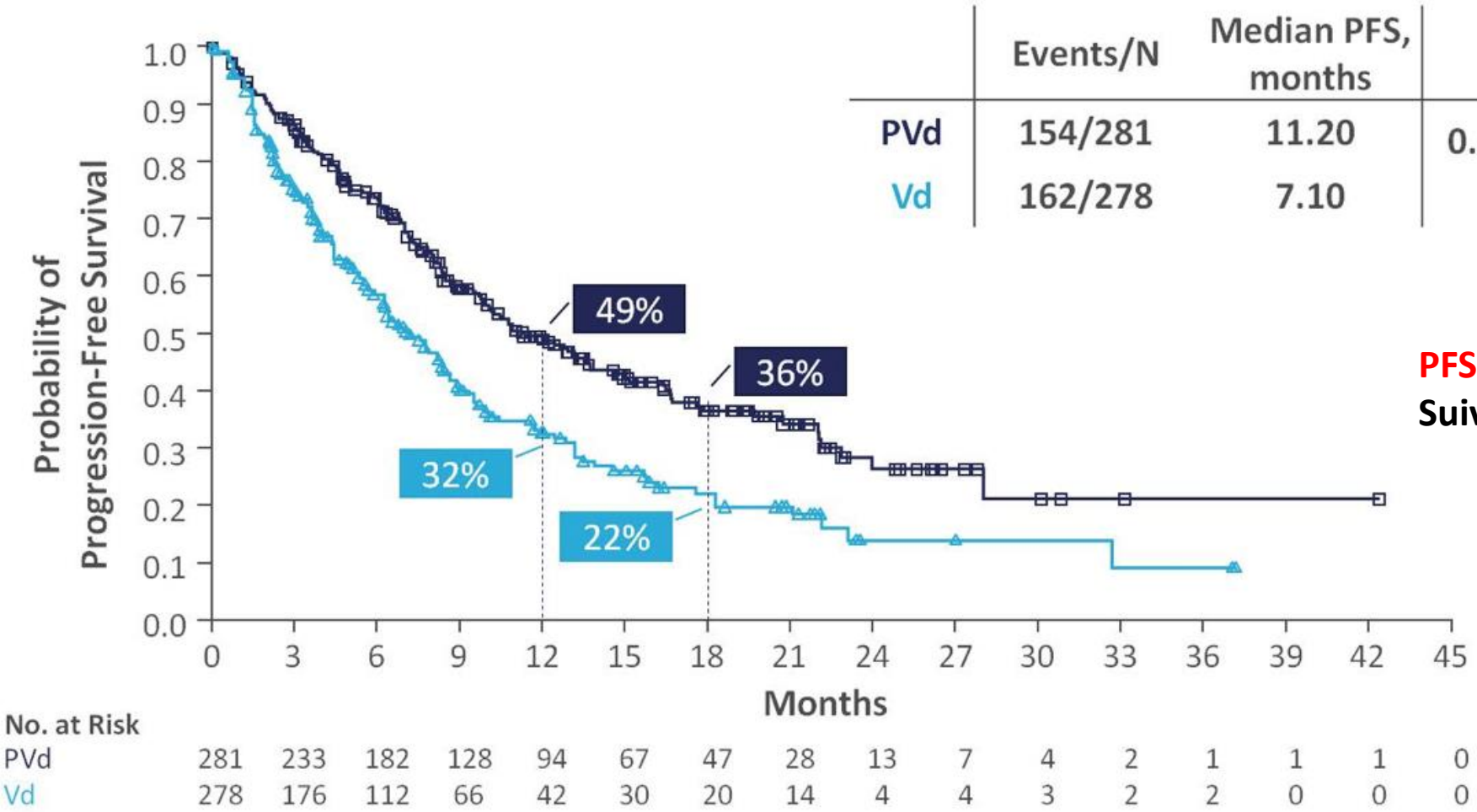
- As per protocol, 100% of patients received prior treatment with LEN

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

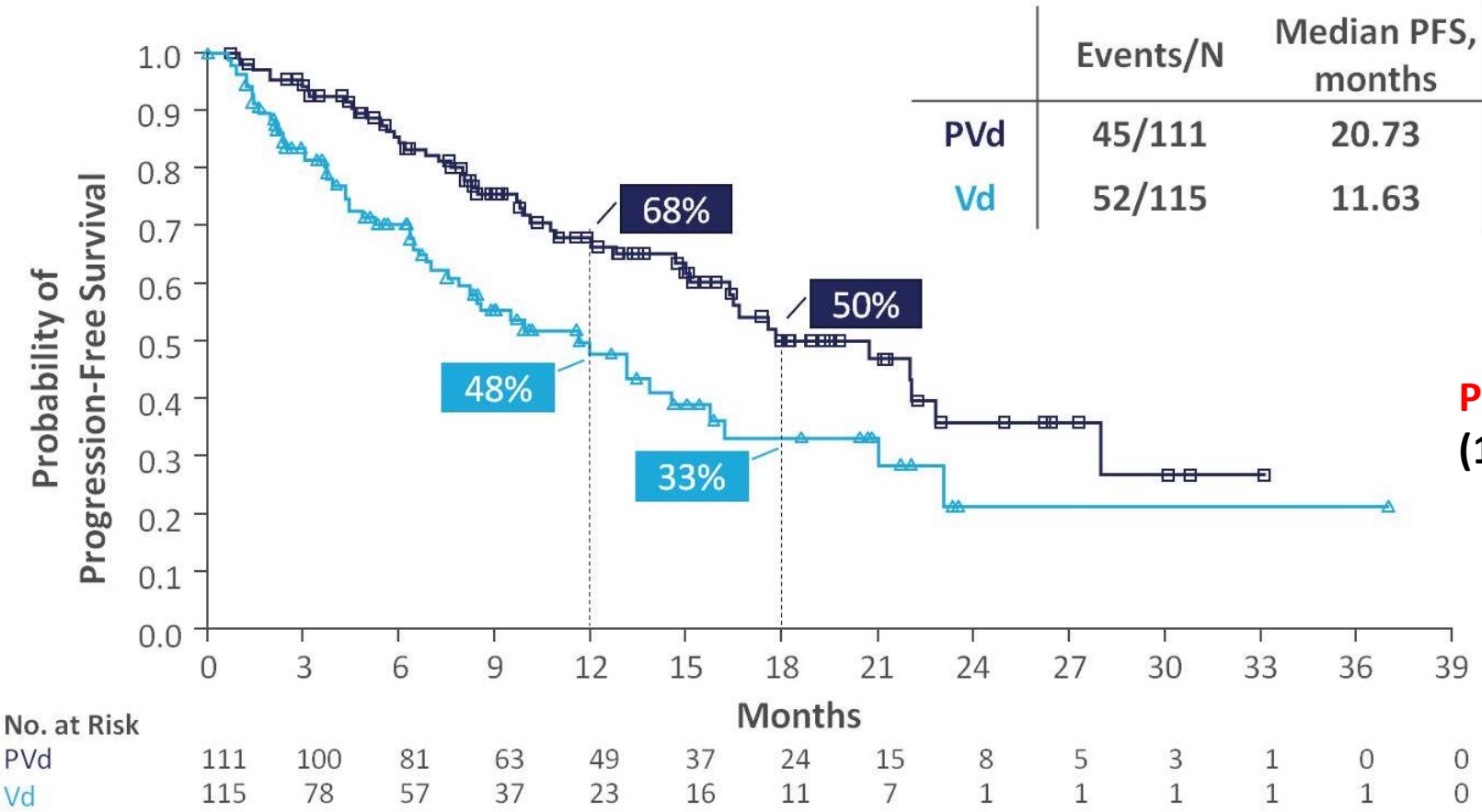
PFS médiane : 11,2 vs 7,1 mois

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

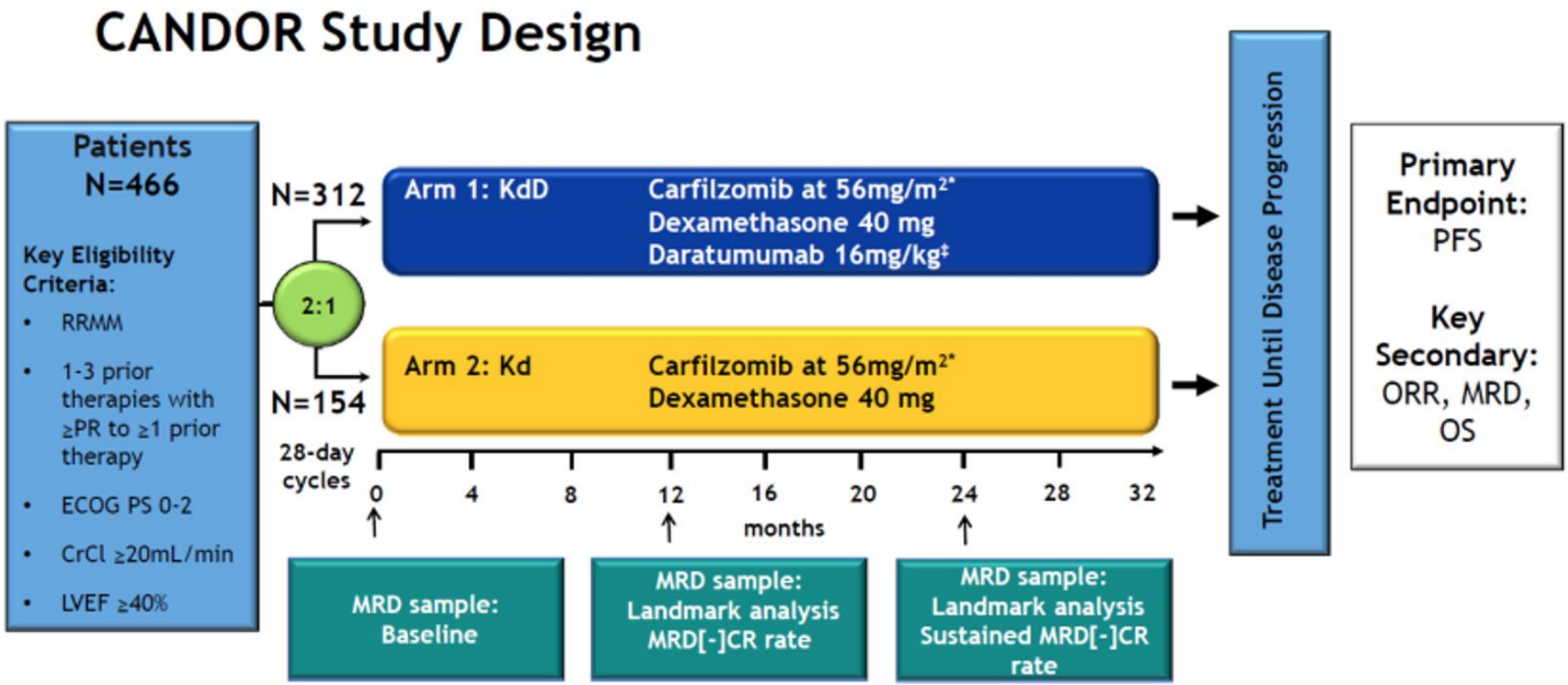
PFS médiane : 20,7 vs 11,6 mois
(1ère rechute)

[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

P Richardson et al, ASCO 2018

Etude CANDOR : approbation de DaraKd ?



P Usmani et al, ASH 2019

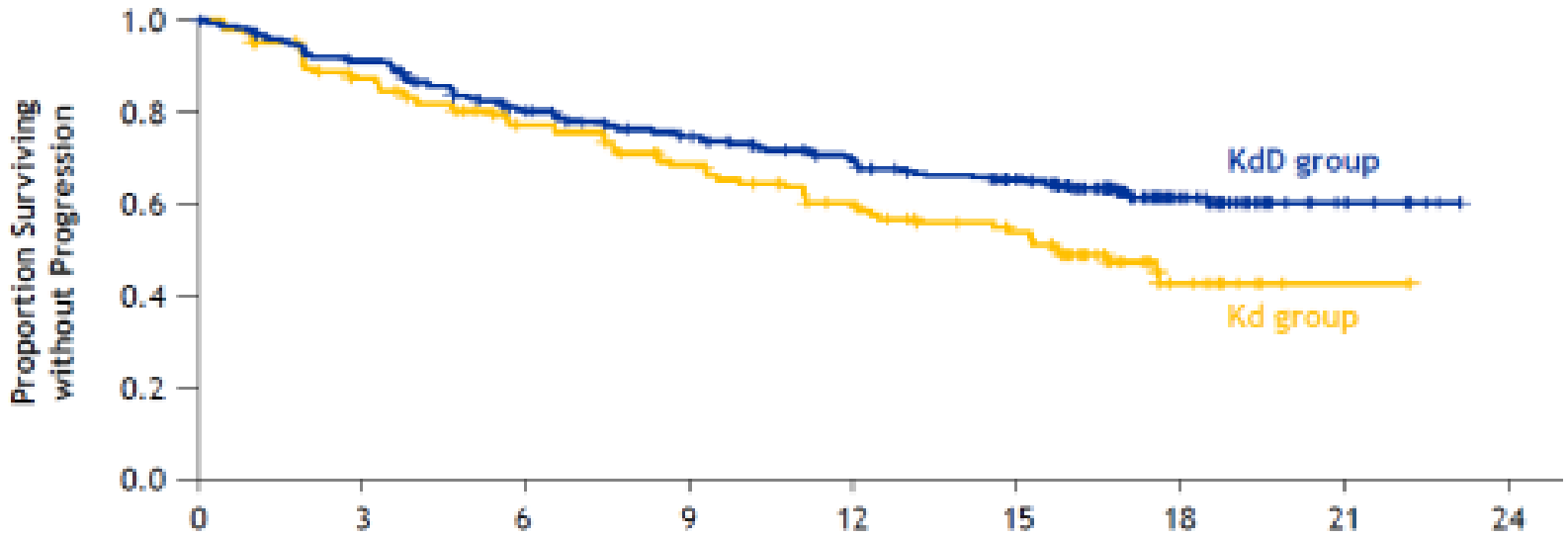
Etude CANDOR : approbation de DaraKd ?

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 ?

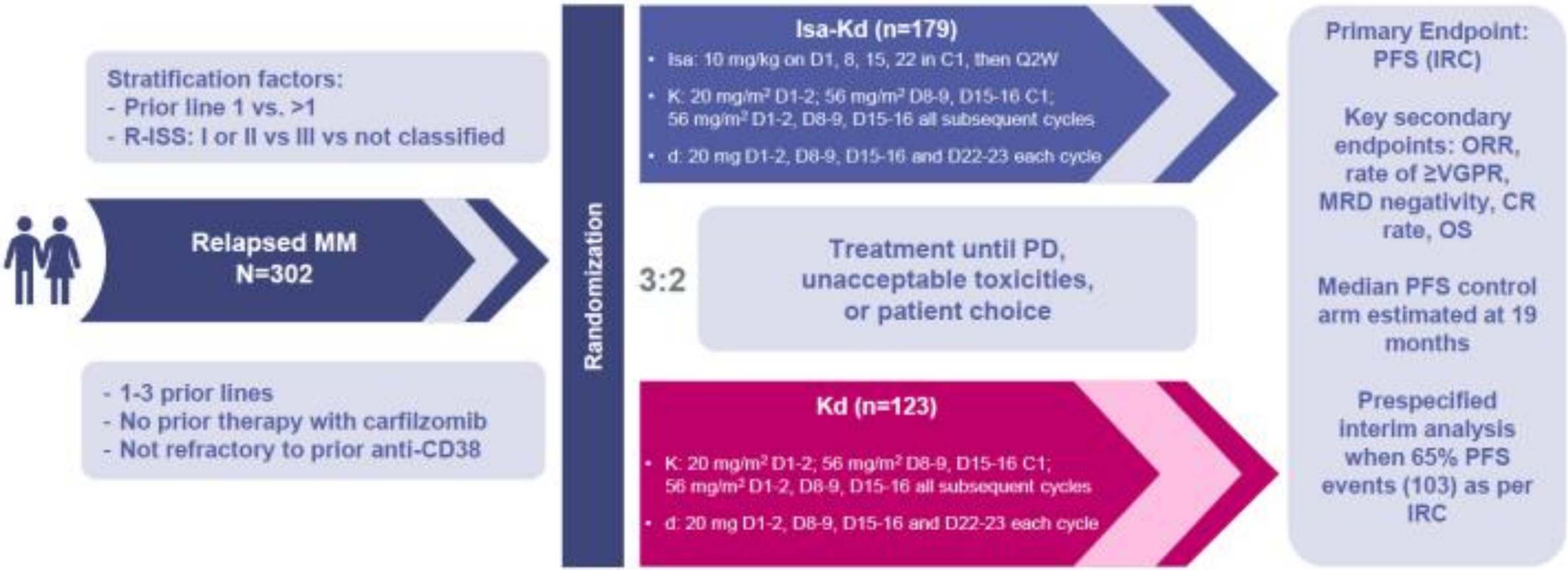


No. at Risk									
KdD group	312	279	236	211	189	165	57	14	0
Kd group	154	122	100	85	70	55	13	2	0

	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

Etude IKEMA : approbation de IsaKd ?



P Moreau et al, EHA 2020

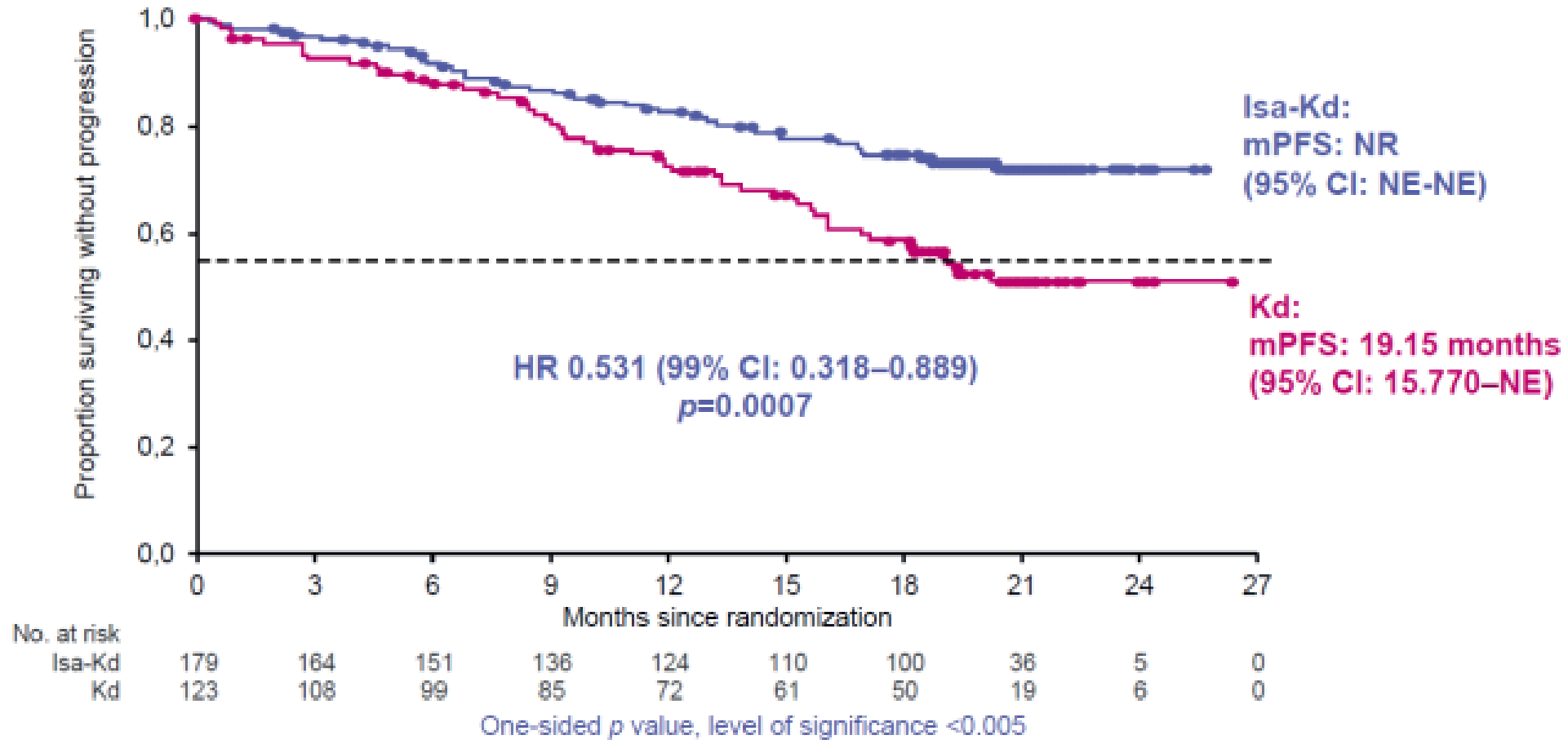
Etude IKEMA : approbation de IsaKd ?

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)

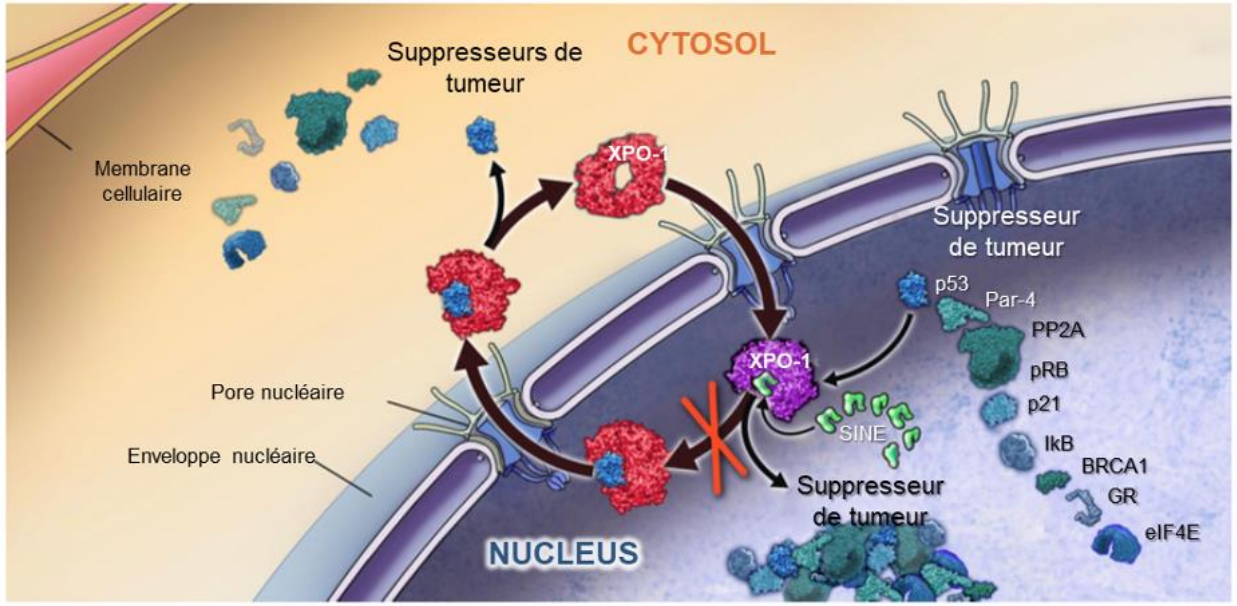
P Moreau et al, EHA 2020

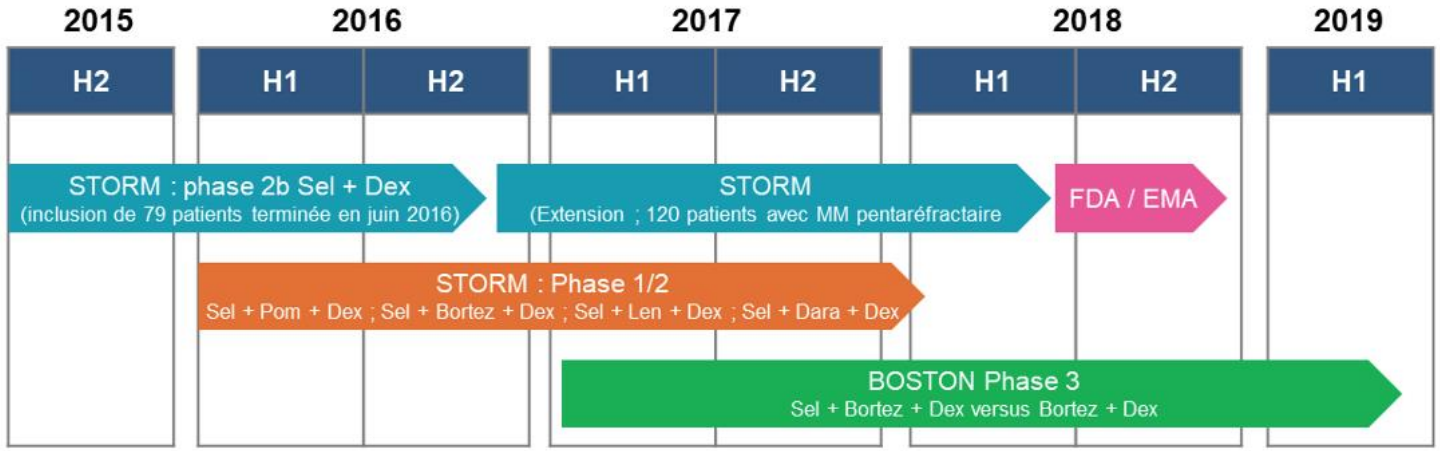
Etude IKEMA : approbation de IsaKd ?



P Moreau et al, EHA 2020

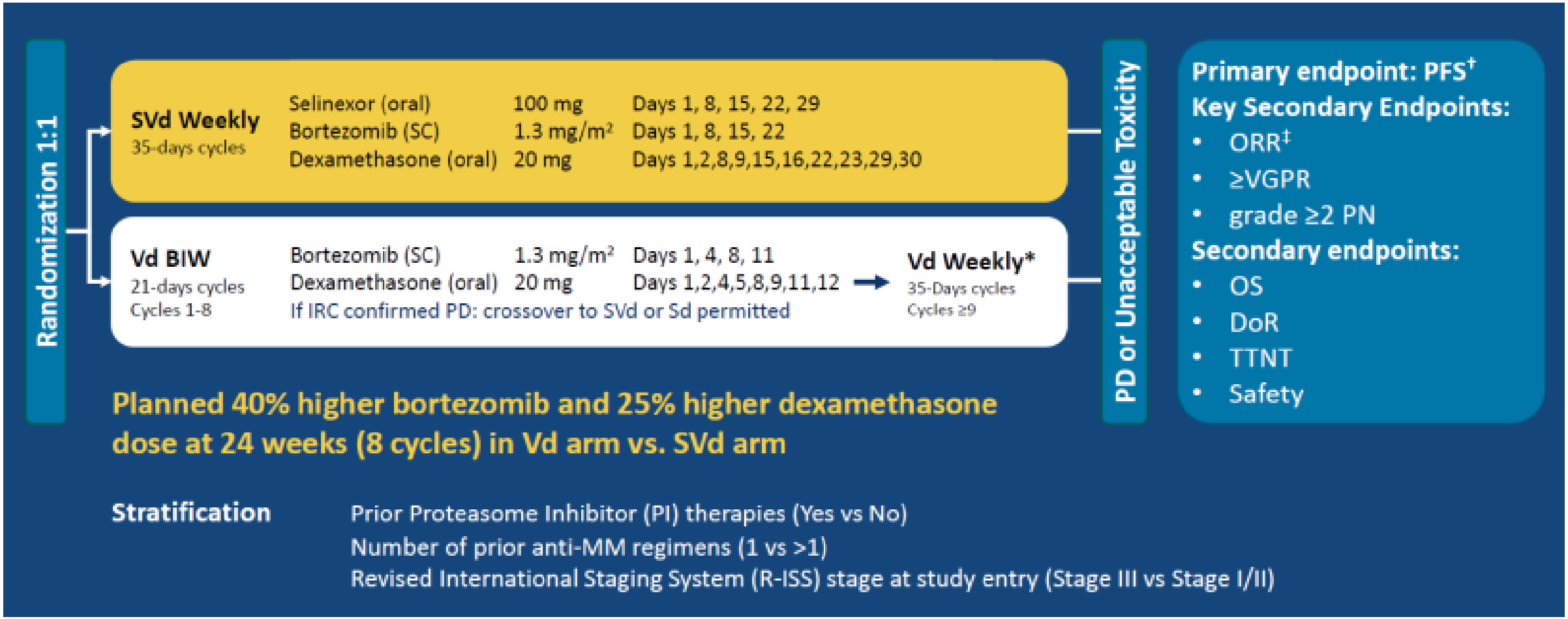
Etude BOSTON : approbation de Sel-Vd ?





Dimopoulos et al, ASCO 2020

Etude BOSTON : approbation de Sel-Vd ?



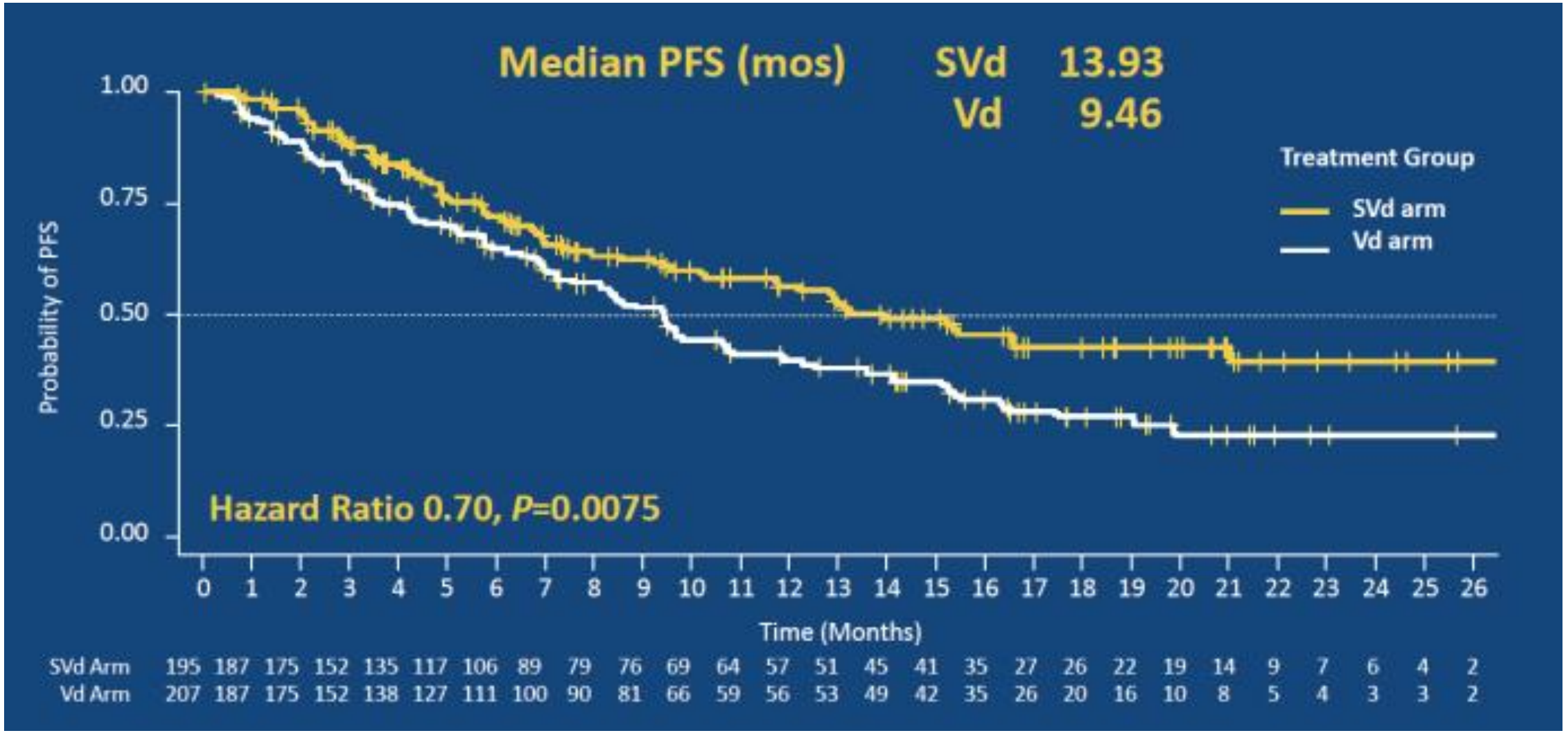
Dimopoulos et al, ASCO 2020

Etude BOSTON : approbation de Sel-Vd ?

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)

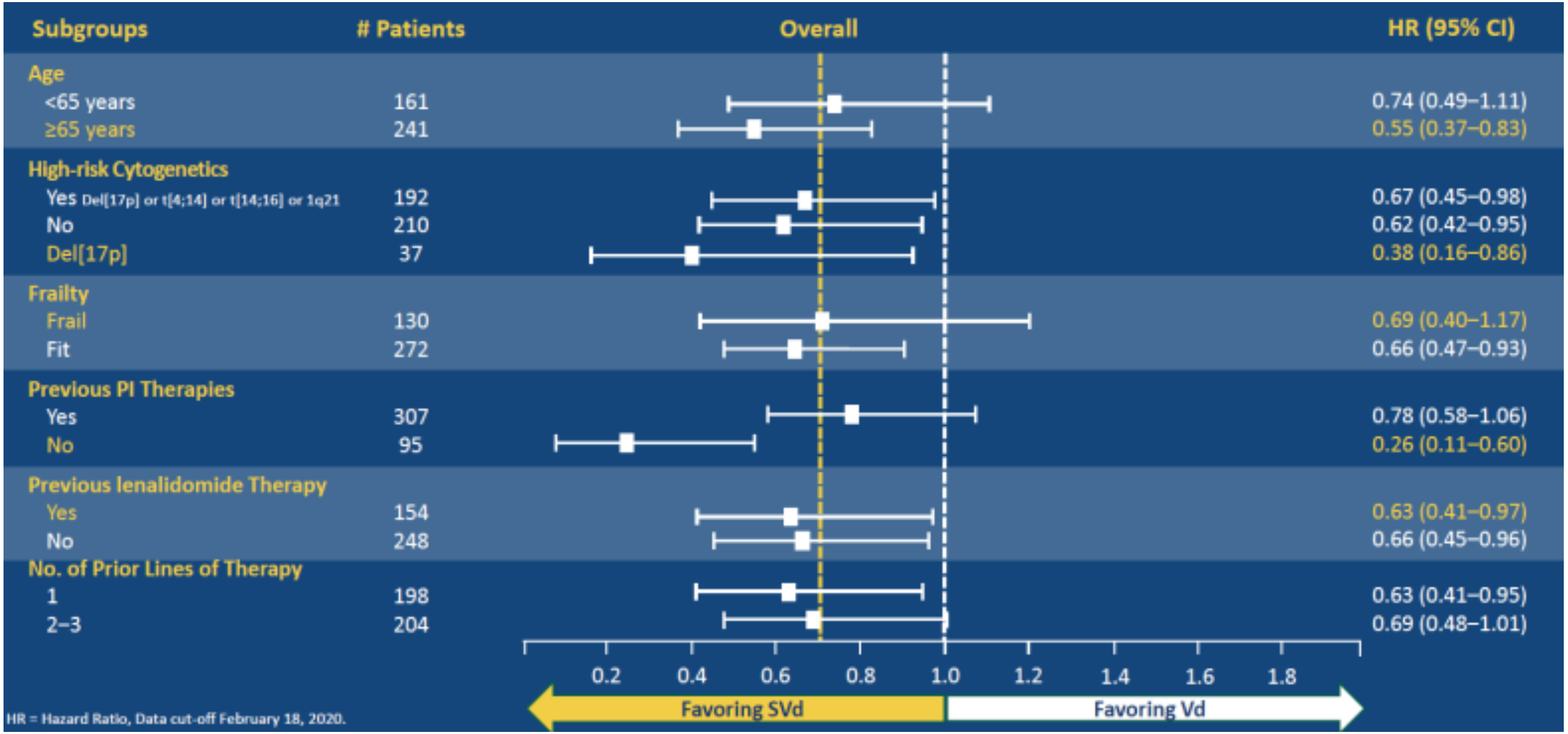
Dimopoulos et al, ASCO 2020

Etude BOSTON : approbation de Sel-Vd ?



Dimopoulos et al, ASCO 2020

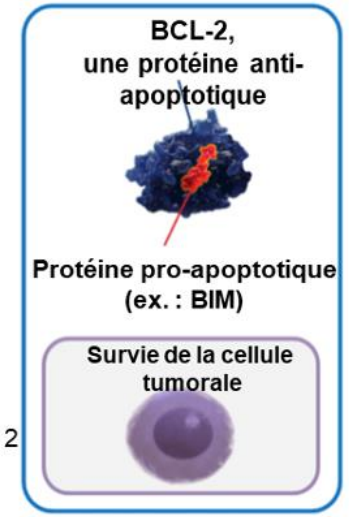
Etude BOSTON : approbation de Sel-Vd ?



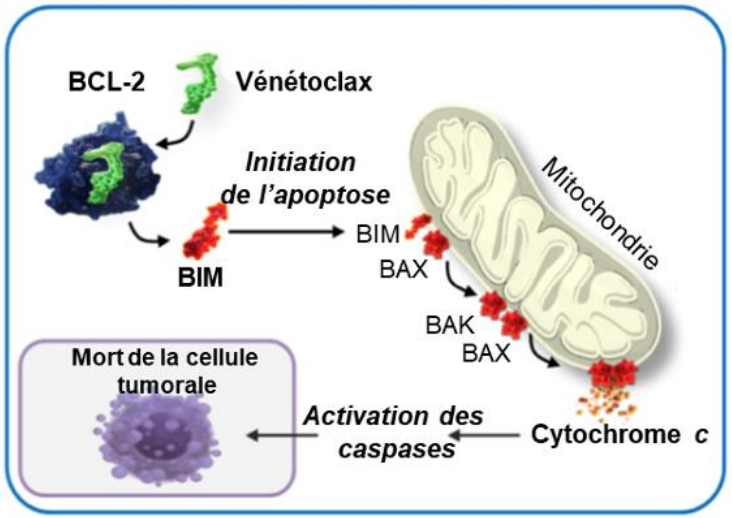
Dimopoulos et al, ASCO 2020

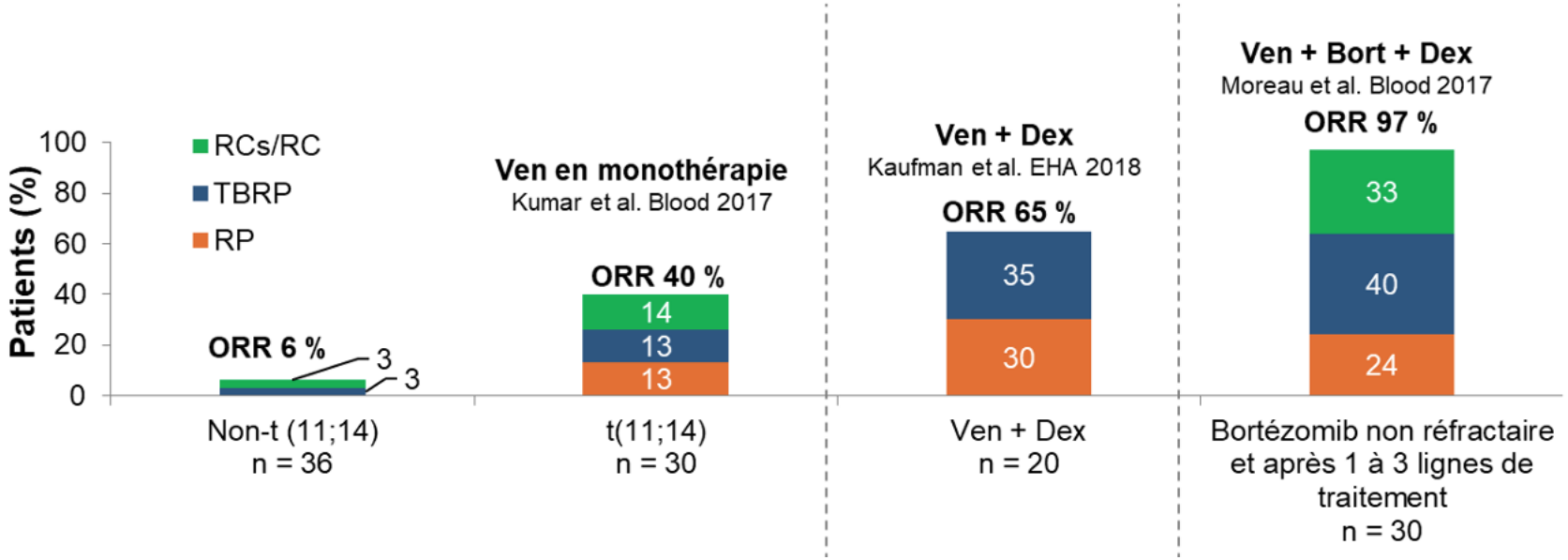
Etude BELLINI : approbation de Vd + Ven si t(11;14) ?

Venetoclax : BH3 mimétique ciblant BCL2



BCL-2 : B-cell lymphoma 2





P Moreau et al, Blood 2017

Etude BELLINI : approbation de Vd + Ven si t(11;14) ?

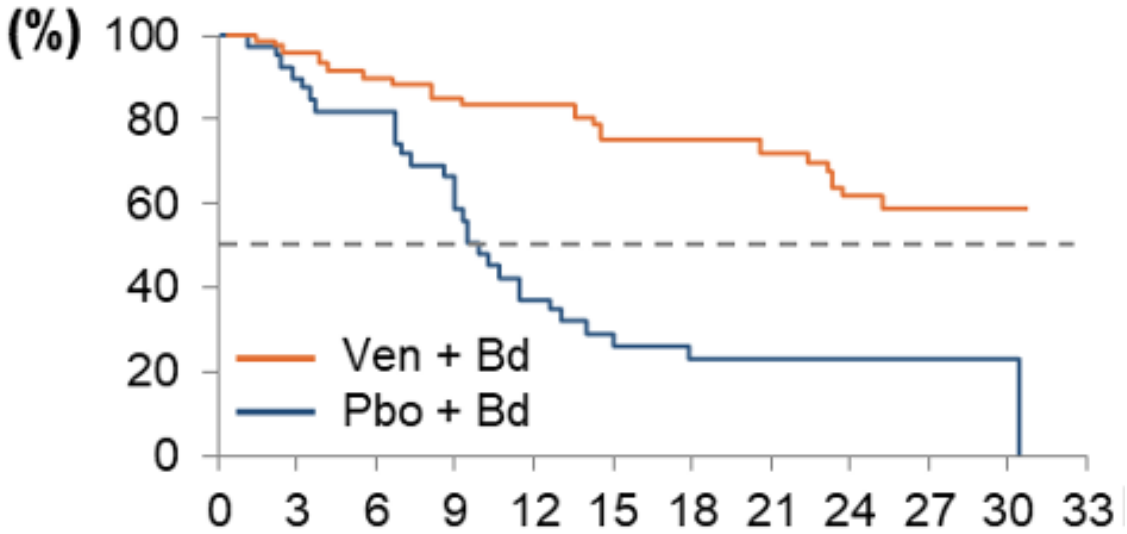
Critères d'inclusion
- Myélome en rechute
- 1-3 lignes antérieures
- Non réfractaire aux inhibiteurs du protéasome

R 2:1

n = 194 → Ven (800 mg QD) + bortézomib (B) + dexaméthasone (d)

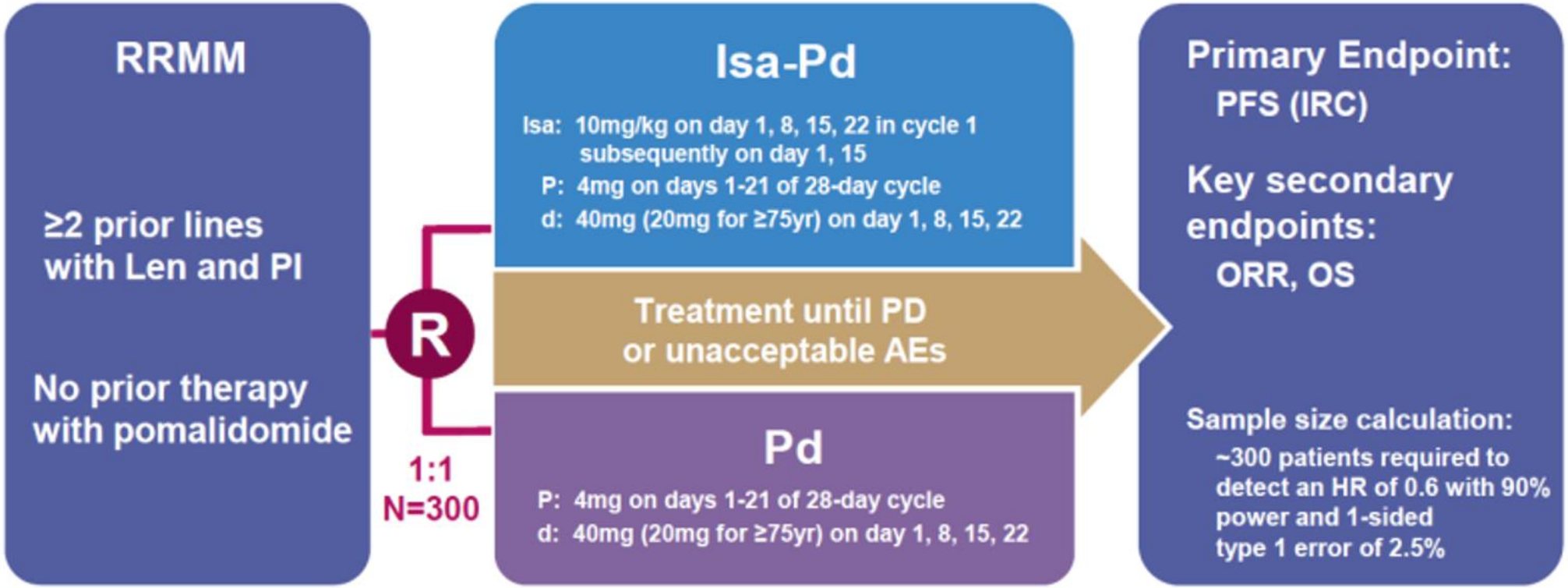
n = 97 → Ven (800 mg QD) + bortézomib (B) + dexaméthasone (d)

t(11;14) ou *BCL2*^{high}



S Harrison et al, ASH 2019

Etude ICARIA : approbation de IsaPomDex (dès L2 ?)



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

M Attal et al, Lancet 2019

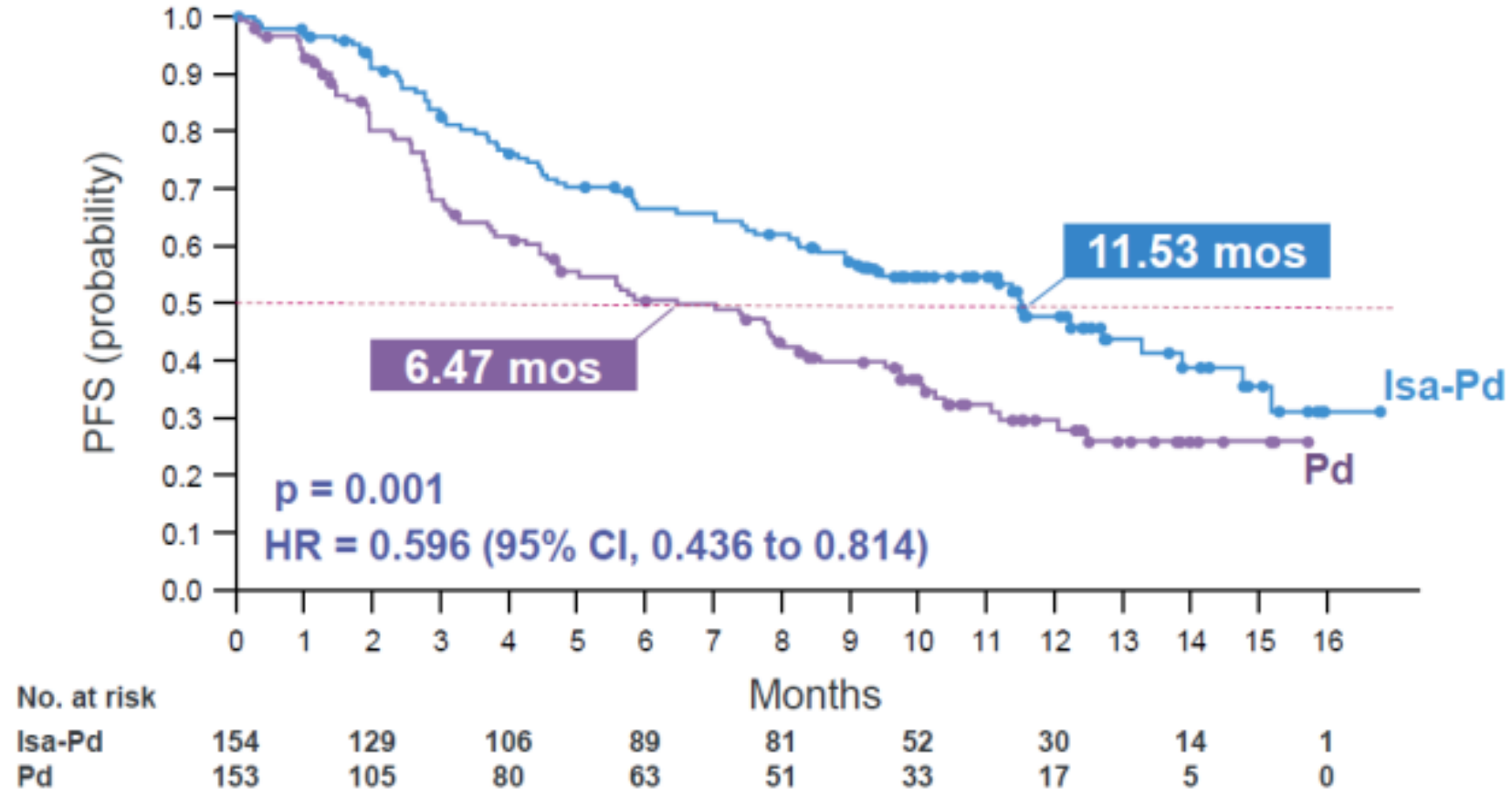
Etude ICARIA : approbation de IsaPomDex (dès L2 ?)

Baseline characteristics	Isa-Pd (n=154)	Pd (n=153)
Median number prior lines of therapy (range)	3 (2–11)	3 (2–10)
Prior PI, %	100	100
Prior IMiD, %	100	100
Prior alkylating agent, %	90.3	96.7
Prior ASCT, %	53.9	58.8
Refractory status, %		
IMiD-refractory	95.5	94.1
Len-refractory	93.5	91.5
PI-refractory	76.6	75.2
IMiD- + PI-refractory	73.4	71.9
Refractory to last line	97.4	98.7
Refractory to Len at last line	60.4	57.5

Isa-Pd: 93.5% of patients refractory to lenalidomide and 73.4% double refractory

M Attal et al, Lancet 2019

Etude ICARIA : approbation de IsaPomDex (dès L2 ?)



Statistically significant and clinically meaningful improvement in PFS

M Attal et al, Lancet 2019

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*	*≈ 36*	*11,5*
PFS si réfractaire au Lénalidomide (mois)							
PFS médiane	8,6	7,8	9,5		*≈ 25*		

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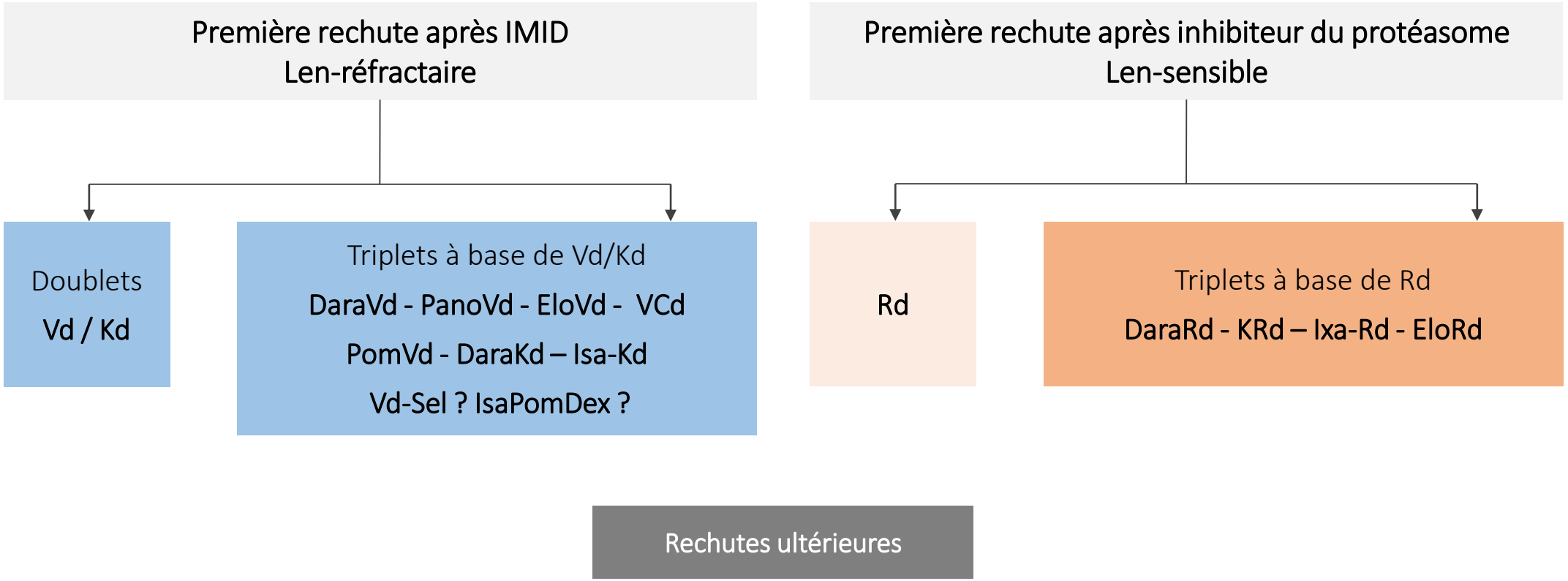
Recommandations ESMO (actualisation 2021)



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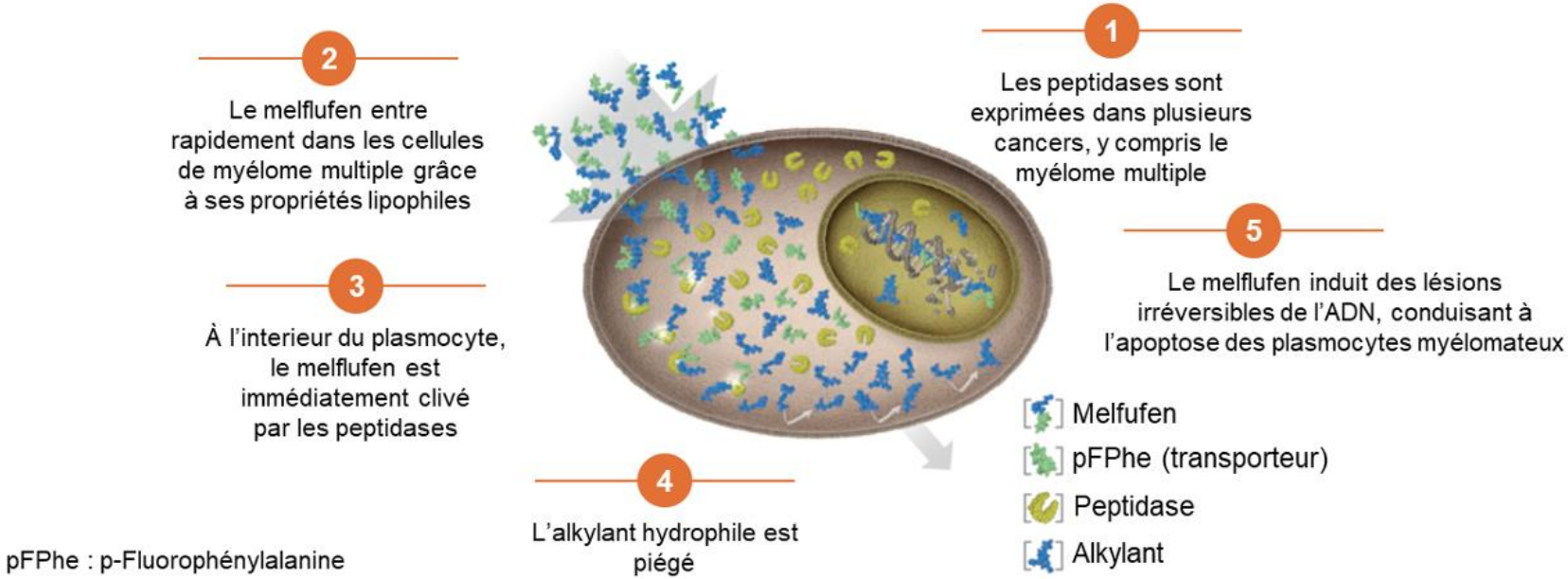
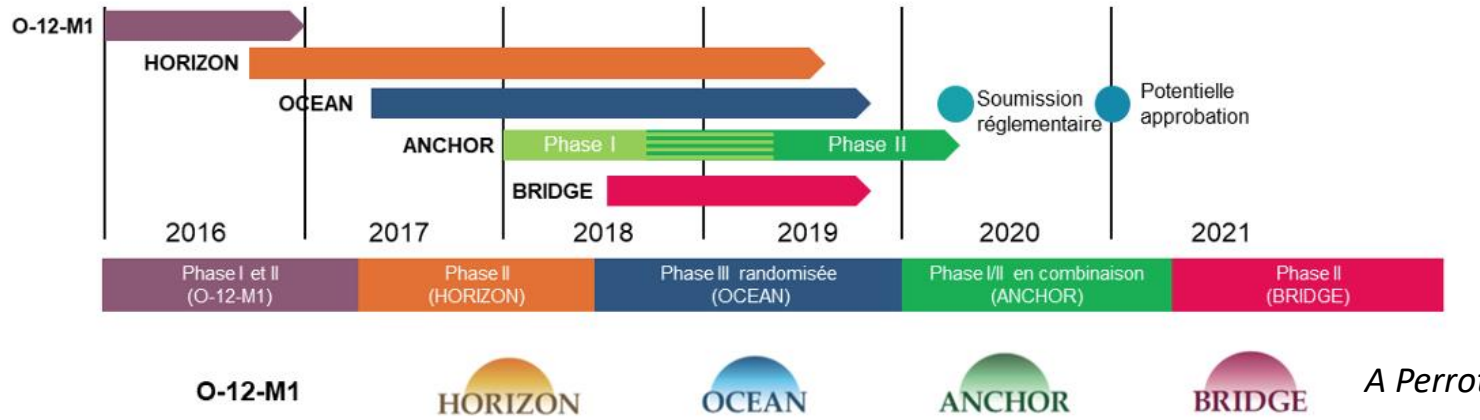
Place du Melflufen ?



pFPhe : p-Fluorophénylalanine



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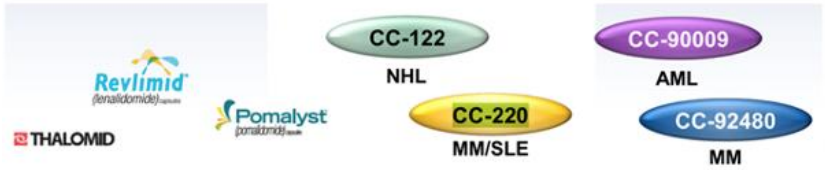
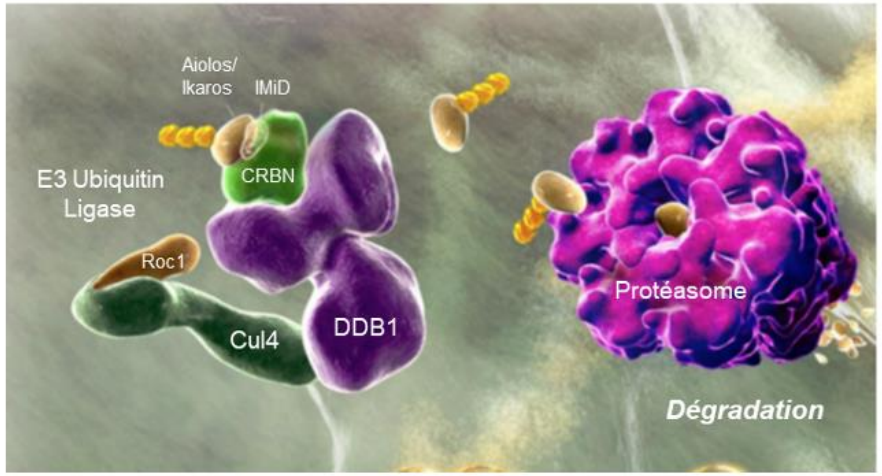
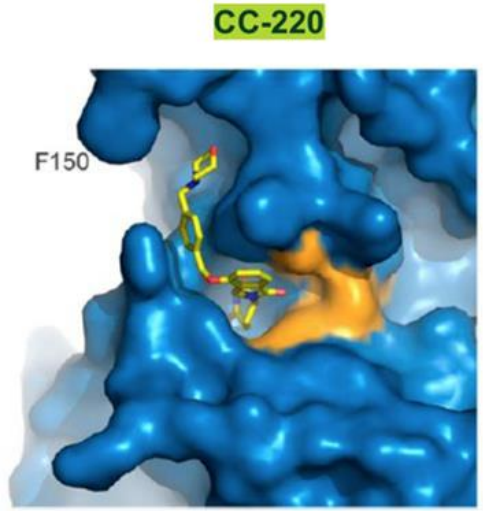
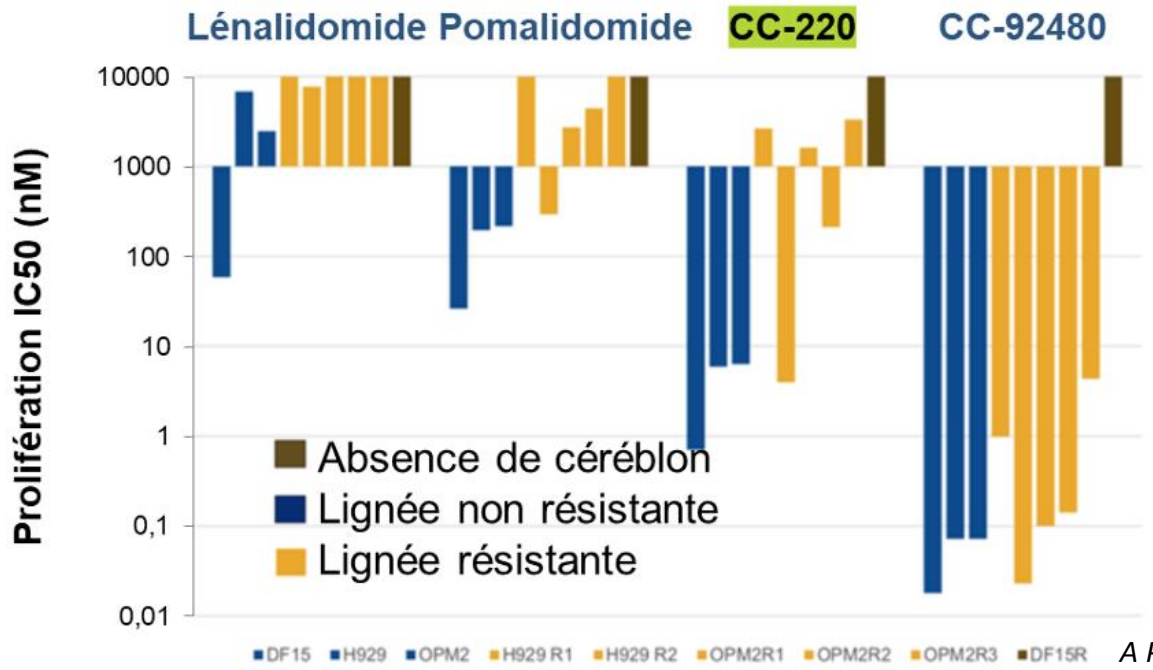
Place des CelMods ?









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Jusqu’à l’arrivée des anti-BCMA…

Electronic Certificate

Version: 1 . 0

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Product: BLENREP

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Role	Signature
Christophe Tessier - Medical Affairs (christophe.8.tessier@gsk.com)	It is approved that this material has been examined and is believed to be in accordance with the relevant Code of Practice and any other relevant regulations, policies and SOPs. Date: 11-Sep-2020 08:58:24 GMT+0000