HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

University of Salamanca

Current Management of Relapsed/Refractory MM

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Conflicts of Interest

Honoraria derived from lectures and participation in advisory boards from Janssen, Celgene, Takeda, Amgen, GSK, AbbVie, EDO, Pharmamar

Case Presentation: Dr Brenner

68-year-old man

- 2015: Plasmablastic R-ISS Stage I multiple myeloma, with multiple metaphase cytogenetic abnormalities
- RVd → ASCT → lenalidomide maintenance x 2.5 years
  - Biochemical relapse

Questions regarding management of relapsed MM

Dr Morganstein

Dr Peswani

Outline

- What is the goal of treatment at the moment of relapse?
- Which options do we have to rescue our MM patients at 1st relapse?
- How to proceed in the clinical practice? How to make the right choice?

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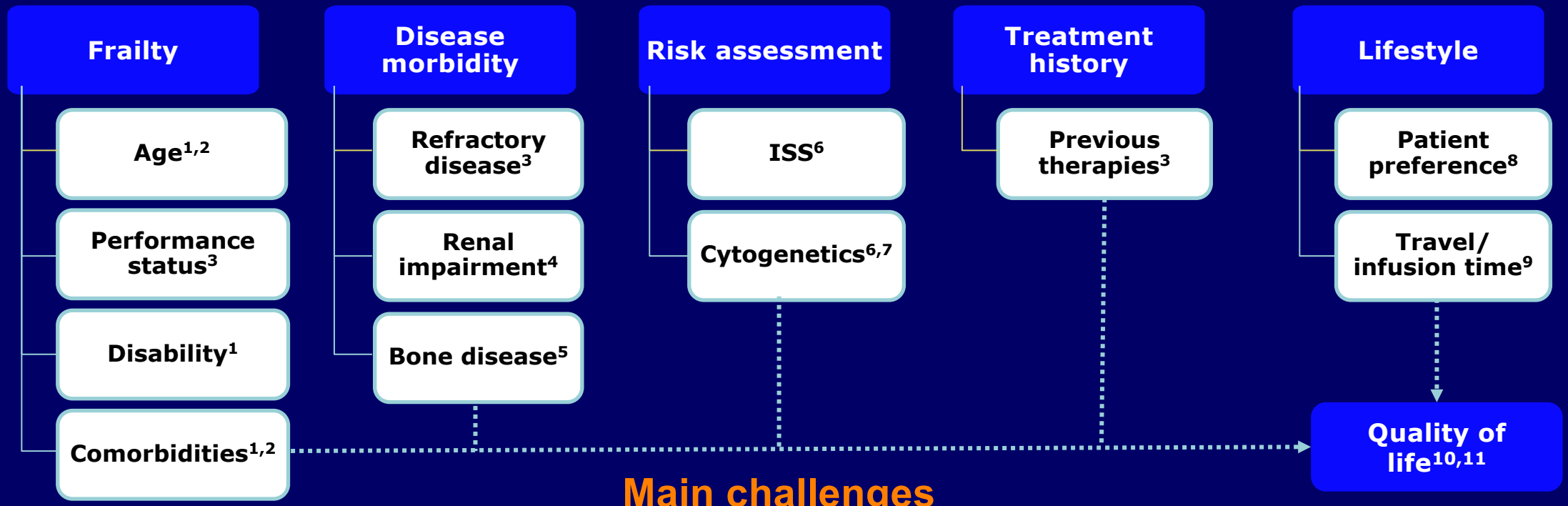
- How to proceed in the clinical practice? How to make the right choice?

Factors to take into account to make the right choice



Main challenges

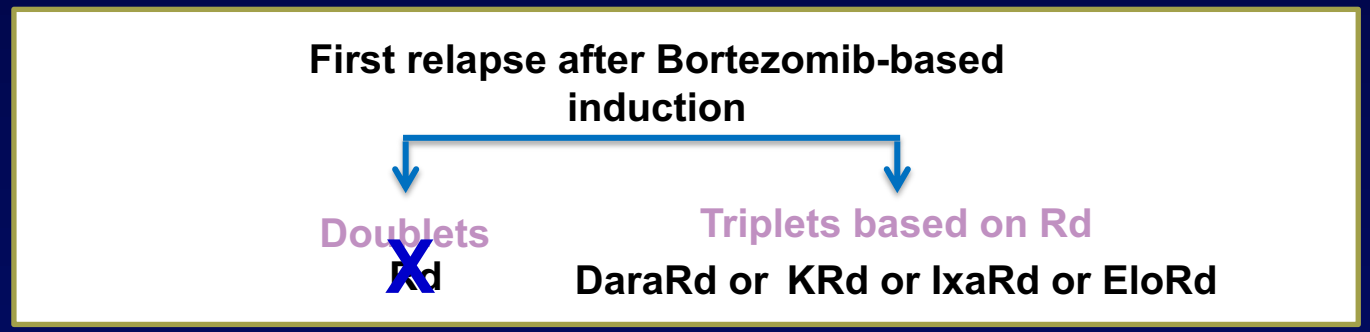
- The selection of rescue therapy is mainly influenced by the first line of therapy
- The first line of therapy is rapidly evolving towards new standards of care

1. Clegg A, *et al*. *Lancet* 2013;381:752–762; 2. Handforth C, *et al*. *Ann Oncol* 2015;26:1091–1101; 3. Dimopoulos MA, *et al*. *Cancer Treat Rev* 2015;41:827–835; 4. Faiman BM, *et al*. *Clin J Oncol Nurs* 2011;15 suppl:66–76; 5. Miceli TS, *et al*. *Clin J Oncol Nurs* 2011;15:9–23; 6. Greipp PR, *et al*. *J Clin Oncol* 2005;23:3412–3420; 7. Chng WJ, *et al*. *Leukemia* 2016;30:1071–1078; 8. Tariman JD, *et al*. *Cancer Treat Commun* 2014;2:34–47; 9. Barbee MS, *et al*. *Ann Pharmacother* 2013;47:1136–1142; 10. Sonneveld P, *et al*. *Leukemia* 2013;27:1959–69;
11. Ramsenthaler C, *et al*. *BMC Cancer* 2016;16:427.

Scenario 1

1st line

- Bortezomib-based combinations
- Lenalidomide-free



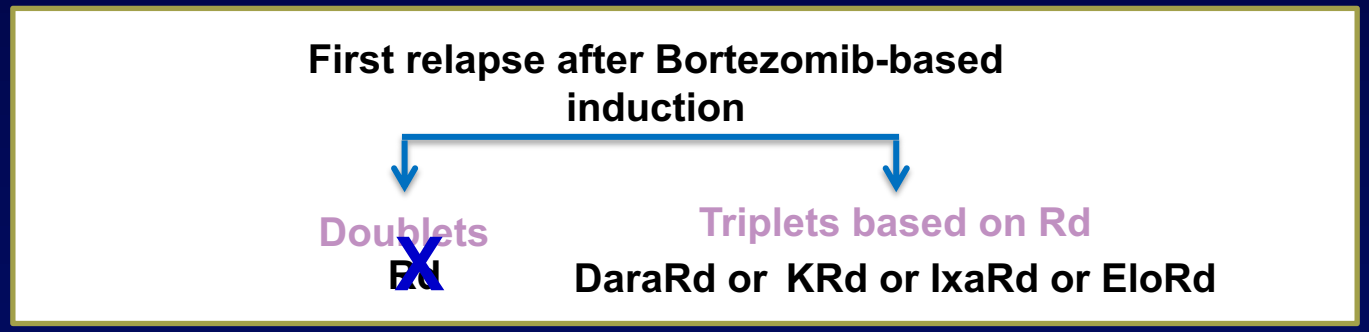
Efficacy	POLLUX DaraRd vs Rd[1-3]	ASPIRE KRd vs Rd[4,5]	ELOQUENT-2 ERd vs Rd[6]	TOURMALINE-MM1 IRd vs Rd[7]
PFS HR (95% CI)	0.44 (0.35–0.55) 44.5 m vs 17.5 m	0.670 (0.558–0.803) 26.3 vs 17.6 m	0.71 (0.59–0.86) 19.4 vs 14.9 m	0.74 (0.59–0.94) 20.6 vs. 14.7 m
ORR, %	93	87	79	78
≥ CR, %	57 (MRDneg 30%)	32	5	14
DOR, months	NE	28.6	21.2	20.5
OS HR (95% CI)	0.63 (0.42–0.95)	0.79 (0.63–0.99) 48 vs. 40 m	0.78 (0.63–0.96) 43.7 vs 39.6 m	NE

Moreau P, et al. Ann Oncol 2017;00:1–11, 2017.

Scenario 2

1st line

- Bortezomib-based combinations
- Exposed to lenalidomide but not progressing under lenalidomide therapy



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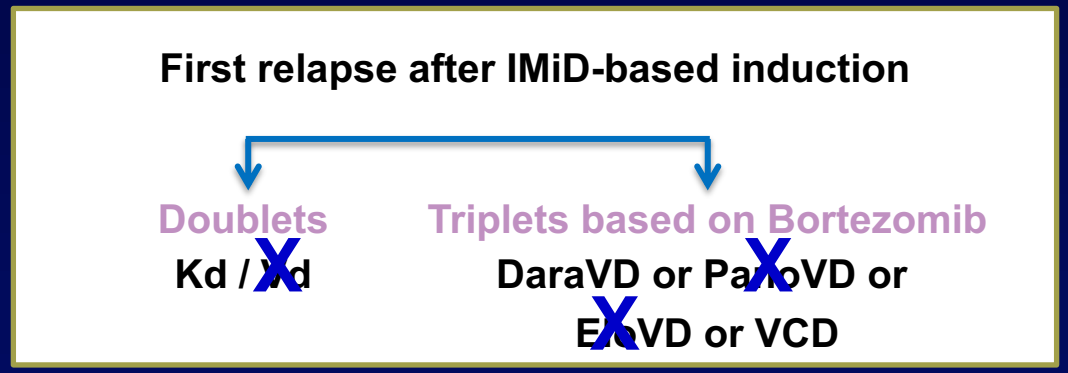
PFS HR (95% CI), median In len-exposed	0.38 (0.21–0.66) 38.8 m vs 18.6 m	0.796 (0.522–1.215) 19.4 m vs 13.9 m	Only 5 pts	0.58 NR vs 17.5 m

Moreau P, et al. Ann Oncol 2017;00:1–11, 2017.

Scenario 3

1st line

- Bortezomib-based combinations followed by TFI
- Exposed to lenalidomide and progressing under lenalidomide therapy



Efficacy	ENDEAVOR (n=929) Kd vs Vd[2]	CASTOR (n=499) DaraVd vs Vd[1]
PFS HR (95% CI)	0.53 (0.44 – 0.63) 18.7 vs 9.4 m	0.31 (0.25 – 0.40) 16.7 vs 7.1 m
ORR, %	77	92
≥ CR, %	13	43 (MRD neg 20%) (sustMRD 7%)
OS HR (95% CI)	0.79 (0.65–0.96) 47.6 vs 40 m	—

How many patients included in both ENDEAVOR and CASTOR trials were treated with lenalidomide and refractory to it?

Moreau P, et al. Ann Oncol 2017;00:1–11, 2017.

CASTOR and ENDEAVOR trials: Lenalidomide-refractory patients

	CASTOR[1,2]		ENDEAVOR[3,4] + CHAMPION-1[5]	
	D-Vd	Vd	Kd	Vd
mPFS, months in the whole population	16.7	7.1	18.7	9.4
mPFS, months In Len exposed patients	9.5	6.1	12.9	7.3
mPFS, months In Len refractory to any prior line	7.8 (60 pts)	4.9 (81 pts)	8.6 (113 pts)	6.6 (103 pts)
Number of pts refractory to Len in 1st line	—	—	32 (ENDEAVOR plus CHAMPION-1)	—
mPFS, months In Len refractory to 1st line	—	—	15.6	—

Do we need new combinations for these patients?
Do we have any information?

1. Mateos MV et al. ASH 2018, abstract 3270; 2. Usmani SZ, et al. ASH 2018, abstract 3288; 3. Dimopoulos MA, et al. Lancet Oncology 2016;17:27-38; 4. Moreau P et al., Leukemia 2017;31(1):115-122; 5. Mateos MV et al. ASH 2018, abstract 1963.

Relapsed/Refractory MM patients
Future guidelines

First relapse after IMiD-based induction

- **Doublets**
  - Kd / Vd
- **Triplets based on Bortezomib**
  - DaraVD or PanoVD or EloVD or VCD

First relapse after Bortezomib-based induction

- **Rd**
- **Triplets based on Rd**
  - DaraRd or KRd or IxaRd or EloRd

First relapse after PI and/or IMiD-based induction and len-refractory

Vd + Selinexor: ??
Vd + Venetoclax: t(11;!4)

Kd + Dara: preliminary data
Kd + Cyclo:??

Pomalidomide +Vd
Pom+Cy+Dex
Pom-dex-Dara
Pom-dex + K

The strongest data we have for first relapse after PI and IMiD exposure are from PVd

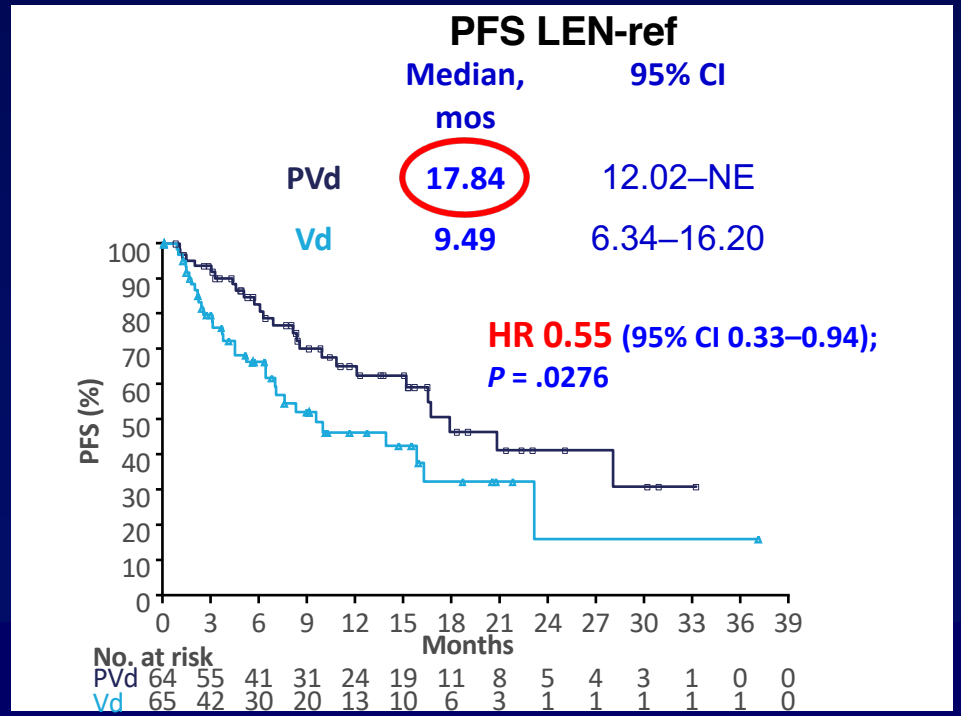
Moreau P et al. Ann Oncol 2017;28(suppl_4):iv52-iv61; Costa et al., ASH 2018; abstract 303; Mateos, personal communication

OPTIMISMM Ph3 trial: PVd versus Vd in RRMM patients

559 pts. Median 2 prior lines of therapy; 100% LEN-exposed; 70% LEN-refractory and 63% LEN-refractory as part of the last line of therapy

Subgroup	PFS	PVd	Vd
LEN-refractory[a]	n/N	120/200	118/191
	Median, months	9.53	5.59
	HR (95% CI) *P* Value	0.65 (0.50-0.84) < .001	

Number of pts refractory to Len in 1st line (PVd vs Vd)	64	65



In the CASTOR and ENDEAVOR trials, the median PFS in Len-refractory were 7.8 and 8.6 months, respectively

Richardson PG et al. Lancet Oncol. 2019 Jun;20(6):781-794

Cross-trial comparisons: Lenalidomide-refractory patients

	CASTOR[1,2]		MMY1001[2]		MM-014[3]	ENDEAVOR[4,5] + CHAMPION-1[6]		OPTIMISMM[7,8]		EMN011[9]
	D-Vd	Vd	D-Kd*	D-Pd	D-Pd	Kd	Vd	PVd	Vd	KPd
mFU, months[c]	40.0		16.6	35.6	5.6	11.9	11.1	15.9		18
mPFS, months in the whole population	16.7	7.1	NR	9.9	NR	18.7	9.4	11.20	7.10	18
mPFS, months in Len refractory to any prior line	7.8	4.9	25.7	10.1	86% at 9 m	8.6	6.6	9.5	5.6	18
Number of pts refractory to Len in 1st line	-	-	-	-	-	32 (ENDEAVOR + CHAMPION-1)	-	64	65	60 (100%) to len 10mg
mPFS, months in Len refractory to 1st line	-	-	-	-	-	15.6	-	17.8	9.5	18

*D-Kd vs Kd in RRMM pts; HR=0.63 (LBA)

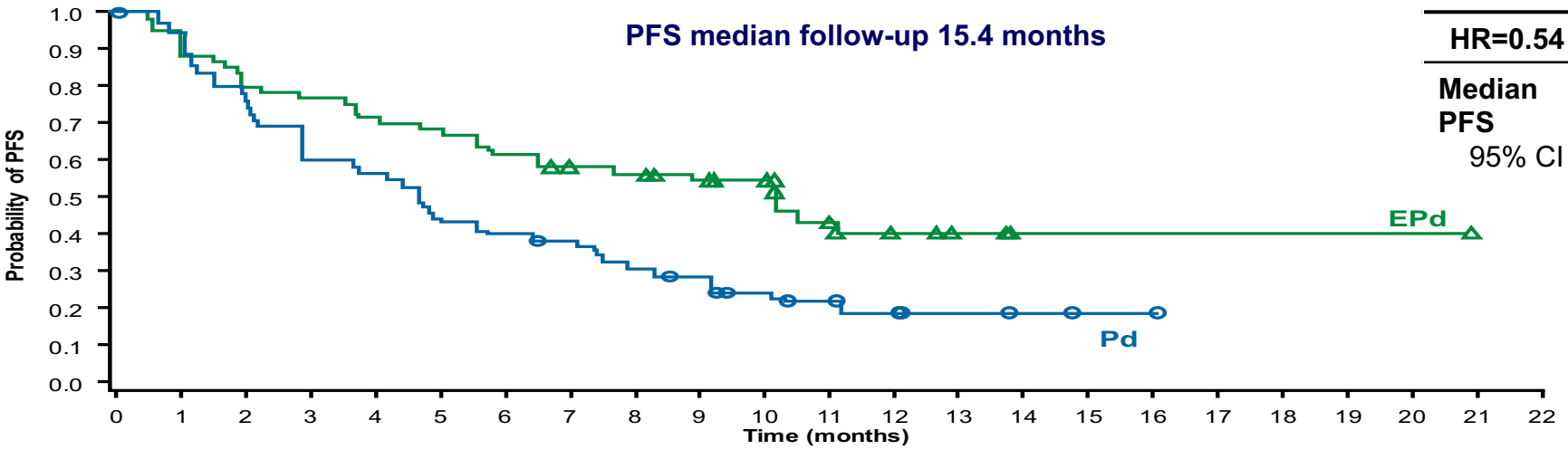
1. Mateos MV et al. ASH 2018, abstract 3270; 2. Usmani SZ, et al. ASH 2018, abstract 3288; 3. Siegel DS, et al. ASH 2018, abstract 3271; 4. Dimopoulos MA, et al. Lancet Oncology 2016;17:27-38; 5. Moreau P et al., Leukemia 2017;31(1):115-122; 6. Mateos MV et al. ASH 2018, abstract 1963; 7. Richardson PG et al., EHA 2018, abstract S847; 8. Dimopoulos MA et al. ASH 2018, abstract 3278; 9. Sonneveld P et al. ASH 2018, abstract 801.

But……

Is there any role for pom-dex based combinations in 3L and beyond?

Phase 2: Pomalidomide + low-dose dex plus/minus elotuzumab

Analysis of 117 pts, 70% of them double refractory to PI and lenalidomide after a median number of 3 lines



	EPd n=60	Pd n=57
HR=0.54 (95% CI 0.34, 0.86); p=0.0078		
Median PFS	**10.3 mo**	**4.7 mo**
95% CI	5.6, NE	2.8, 7.2

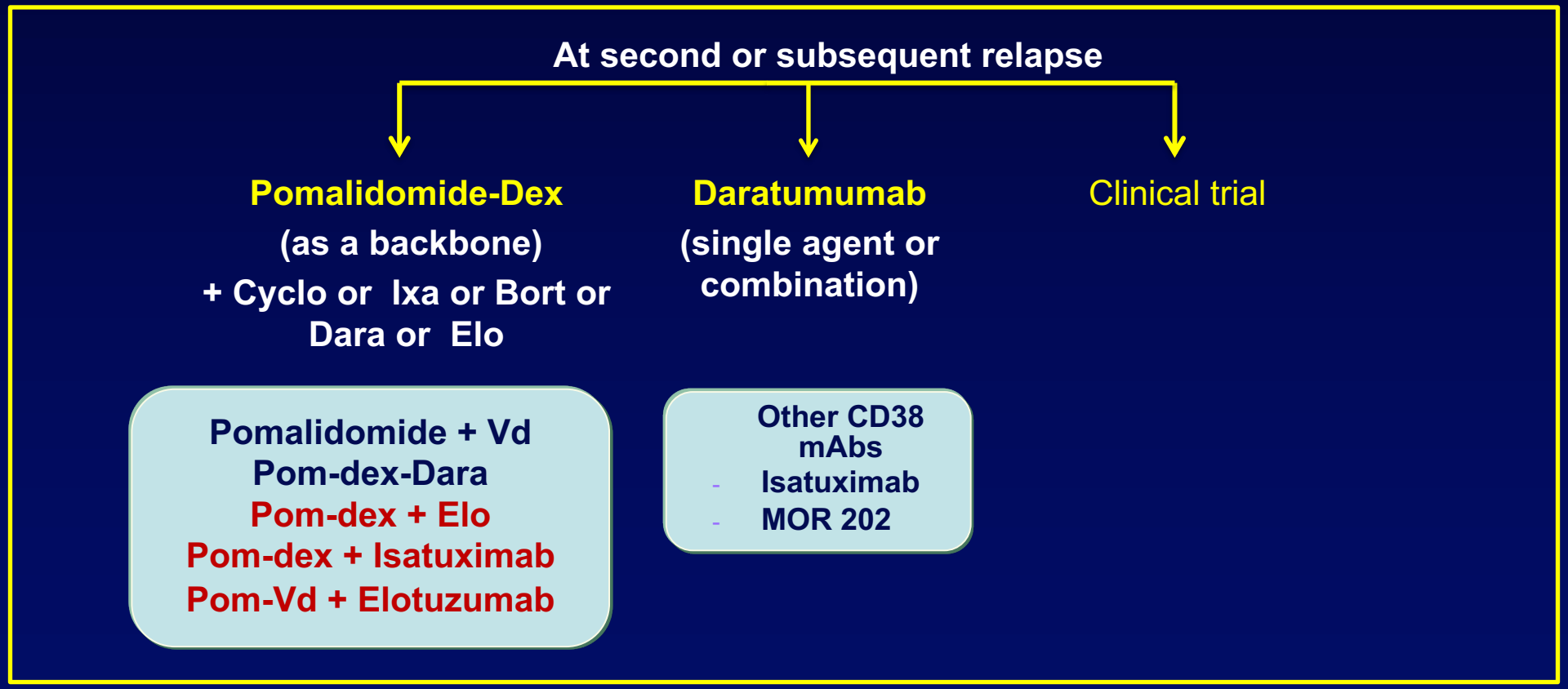
- 46% reduction in the risk of progression or death with EPd
- Median PFS was more than twice as long with EPd vs Pd

Benefit sustained across the different subgroups of patients, including high-risk CA, or double refractoriness

The label will be for RRMM after at least 2 prior lines of therapy

Dimopoulos MA, et al., N Engl J Med 2018;379(19):1811-1822

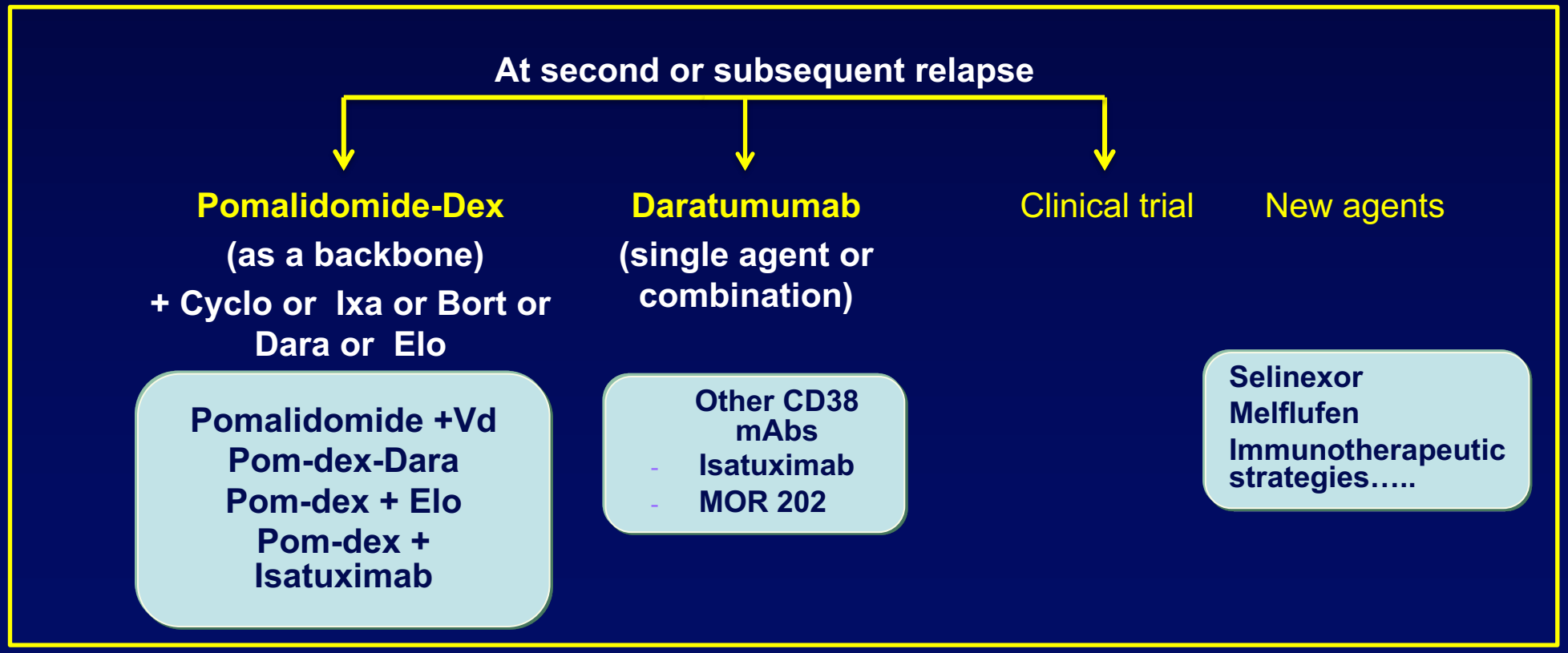
Relapsed/Refractory MM patients



- These new Pom-dex based combinations should be moved to the second line but the label in EU will be restricted to 3L and beyond....

Moreau P et al. Ann Oncol 2017;28(suppl_4):iv52-iv61

Relapsed/Refractory MM patients ESMO guidelines 2017

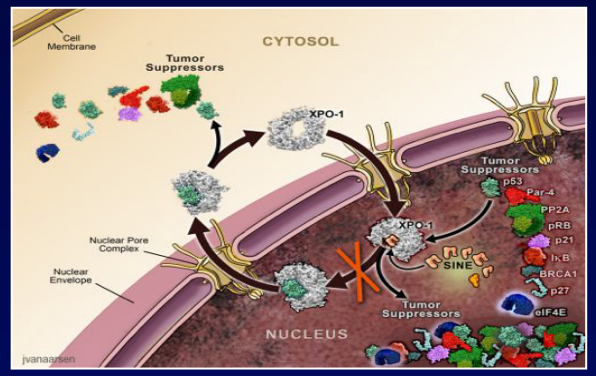


- What about patients already exposed to Pis and IMiD's (first and/or second generation) and antiCD38 mAbs?
- Does this population represent an unmet medical need?

Moreau P et al. Ann Oncol 2017;28(suppl_4):iv52-iv61

XPO1 Inhibitor Selinexor in RRMM

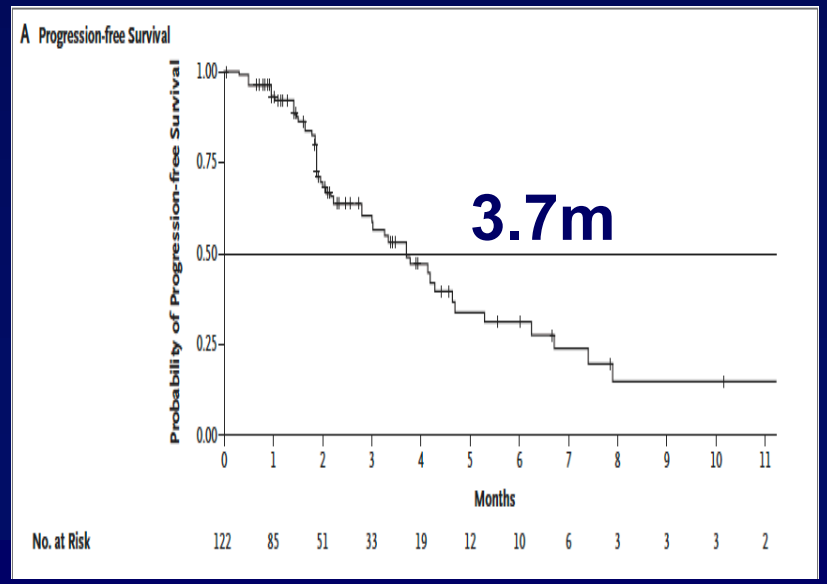
First-in-class, oral Selective Inhibitor of Nuclear Export (SINE) that inhibits XPO1 and activates Tumor Suppressor Proteins & reduces Oncoproteins

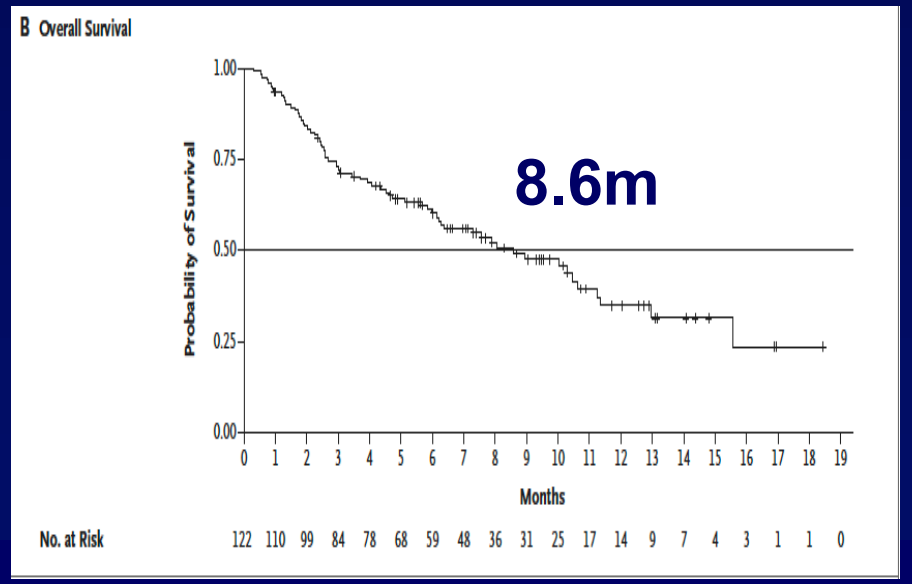


- STORM study: 122 patients with RRMM after a median of 7PL of therapy previously exposed to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and an alkylating agent and had disease refractory to at least one proteasome inhibitor, one immunomodulatory agent, and daratumumab **(triple-class refractory)**

ORR 26%, including two pts in sCR and MR observed in 39% → sustained across the different subgroups of patients

Safety profile: thrombocytopenia and some GI events, manageable

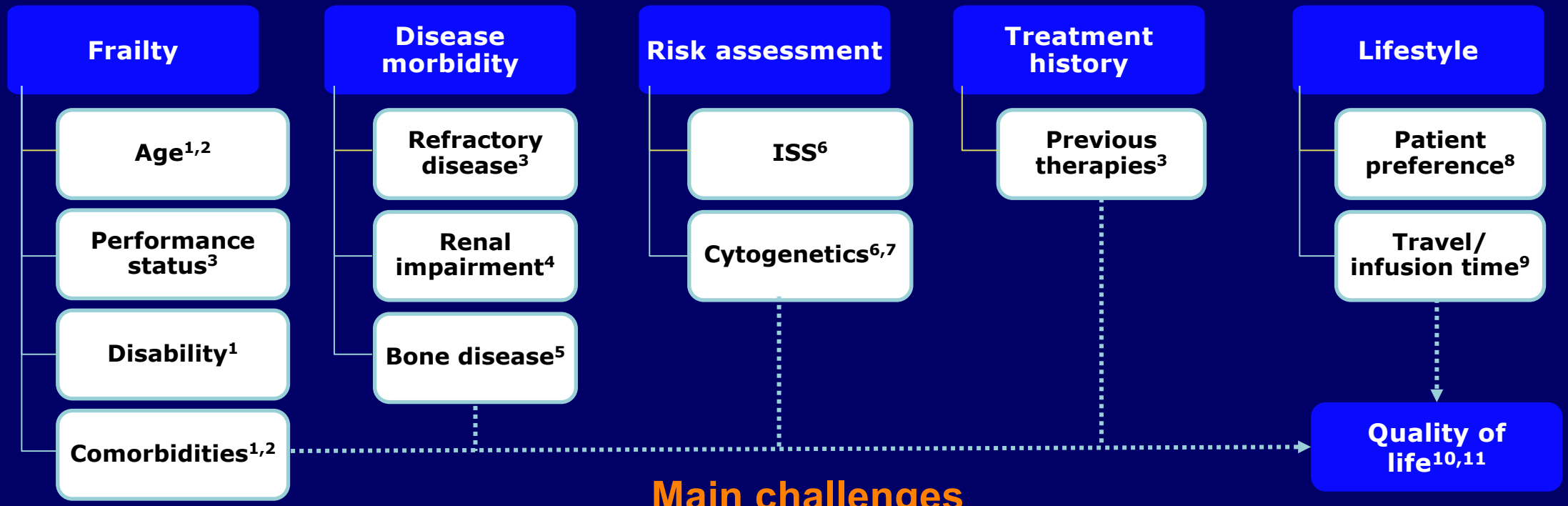




Selinexor-Pom-dex in RRMM (4PL): 58% ORR in pom naïve and median PFS of 12 m
31% ORR in pom/len refractory and median PFS of 4 m

1. Chari et al. NEJM 2019

Patient-based factors are highly influential in treatment decision making



Main challenges

- The selection of rescue therapy is mainly influenced by the first line of therapy
- The first line of therapy is rapidly evolving towards new standards of care

1. Clegg A, *et al*. *Lancet* 2013;381:752–762; 2. Handforth C, *et al*. *Ann Oncol* 2015;26:1091–1101; 3. Dimopoulos MA, *et al*. *Cancer Treat Rev* 2015;41:827–835; 4. Faiman BM, *et al*. *Clin J Oncol Nurs* 2011;15 suppl:66–76; 5. Miceli TS, *et al*. *Clin J Oncol Nurs* 2011;15:9–23; 6. Greipp PR, *et al*. *J Clin Oncol* 2005;23:3412–3420; 7. Chng WJ, *et al*. *Leukemia* 2016;30:1071–1078; 8. Tariman JD, *et al*. *Cancer Treat Commun* 2014;2:34–47; 9. Barbee MS, *et al*. *Ann Pharmacother* 2013;47:1136–1142; 10. Sonneveld P, *et al*. *Leukemia* 2013;27:1959–69; 11. Ramsenthaler C, *et al*. *BMC Cancer* 2016;16:427.

Is it possible to optimize the use of Carfilzomib?

1:1 Randomization

N = 478

- Relapsed and Refractory MM
- 2-3 prior lines
- Prior exposure to IMiD & PI (except carfilzomib or oprozomib)

Arm A: Once-weekly carfilzomib + dex

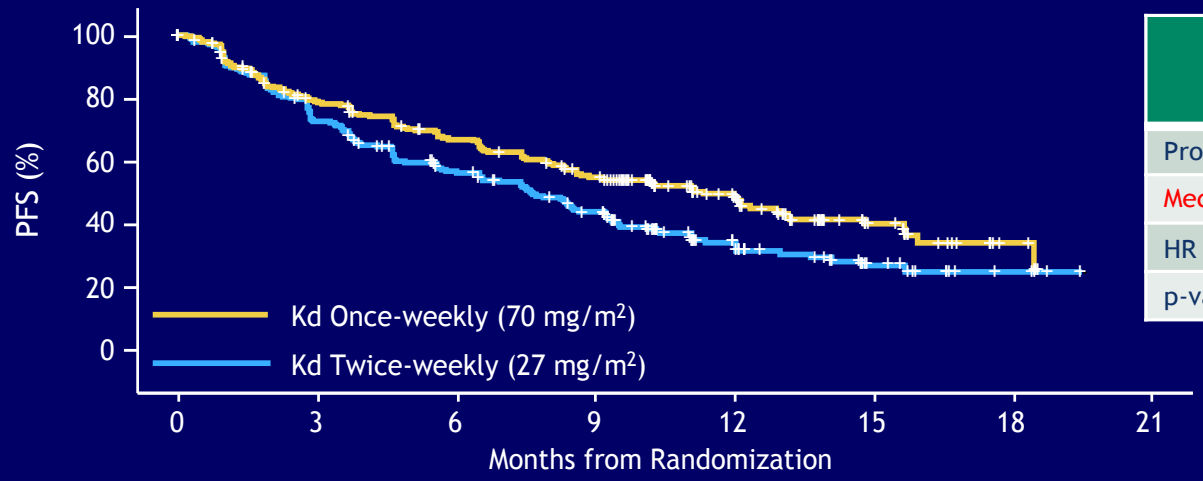
(30 min infusion of K)

Carfilzomib 20 mg/m² IV D1 (Cycle 1)
Carfilzomib 70 mg/m² IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Arm B: Twice-weekly carfilzomib + dex

(10 min infusion of K)

Carfilzomib 20 mg/m² IV D1, 2 (Cycle 1)
Carfilzomib 27 mg/m² IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)



Number of Patients at Risk:

Kd 20/70	240	178	145	114	69	24	5	0
Kd 20/27	238	164	119	86	41	15	4	0

	Once-weekly Kd 20/70 mg/m² (n=240)	Twice-weekly Kd 20/27 mg/m² (n=238)
Progression/Death, n (%)	126 (53%)	148 (62%)
Median PFS, months	11.2	7.6
HR (Kd 20/70/Kd 20/27) (95% CI)	0.693 (0.544, 0.883)	
p-value (2-sided)	0.0029	

The weekly administration at dose of 70 mg/m2 is more convenient with a significant benefit from the patient care point of view

Moreau P , Mateos MV et al. Lancet Oncology 2018

Is it possible to optimize the use of Daratumumab?

Key eligibility criteria:

- RRMM
- ≥3 prior lines including a PI and an IMiD *or*
- Refractory to both a PI and an IMiD

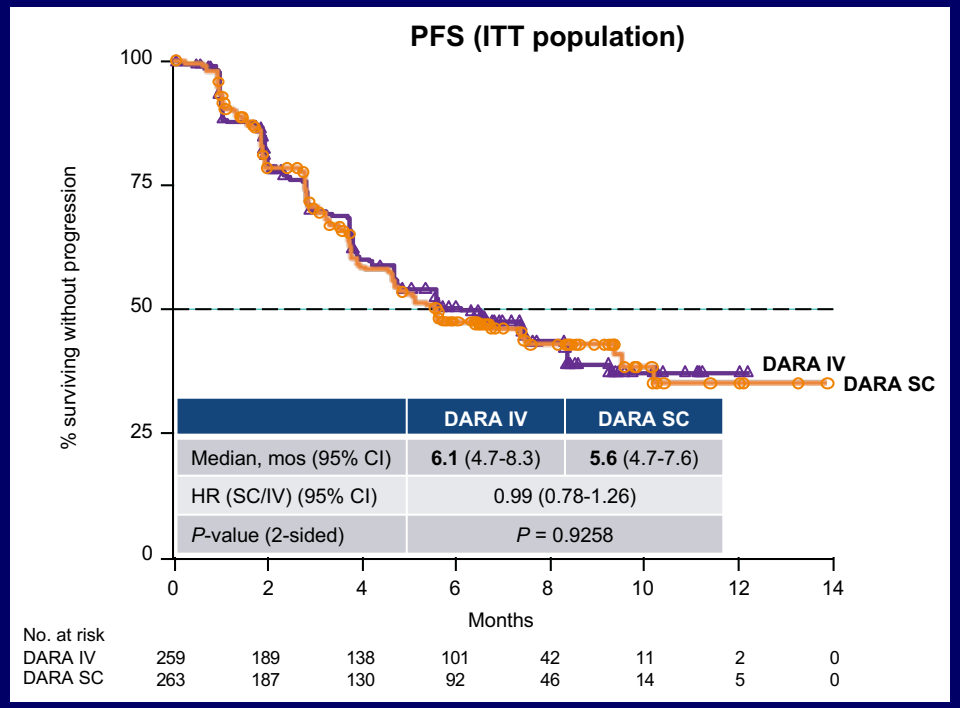
1:1 Randomization

DARA SC 1,800 mg (n = 263)
QW Cycles 1-2, Q2W Cycles 3-6, Q4W Cycles 7+ until PD

DARA IV 16 mg/kg (n = 259)
QW Cycles 1-2, Q2W Cycles 3-6, Q4W Cycles 7+ until PD

Co-primary endpoints:
- ORR
- Maximum C_{trough}[a]

Key secondary endpoints:
- IRR rate
- PFS
- ≥VGPR, ≥CR
- Time to next therapy
- OS
- PROs



	DARA IV (n = 258)	DARA SC (n = 260)	Odds ratio[a] (95% CI)	*P*- value[b]
IRR rate	**34.5%**	**12.7%**	0.28 (0.18-0.44)	<0.0001

Time of infusion: 3-5 minutes

The SC administration at flat dose of 1800 mg is not inferior to the IV, safer and more convenient

Mateos MV et al. EHA 2019

Is it possible to optimize the use of Daratumumab?

PLEIADES Phase 2 study of DARA SC combined with standard treatment regimens (N = 199)

Primary Endpoints: ORR for D-VMP and D-Rd and ≥VGPR for D-VRd

	D-VMP (n = 67)	D-Rd (n = 65)	D-VRd (n = 67)
ORR	88.1%	90.8%	97.0%
≥VGPR	64.2%	64.6%	71.6%
Median duration of follow-up	7 months	7 months	4 months

Median time of infusion: 5 minutes

Primary endpoints met for all cohorts

Rates of any grade IRRs and injection-site reactions were each 7.5% across all cohorts

Safety profiles in all cohorts were consistent with DARA IV in combination with the backbone regimens

Chari A et al. IMW 2019; Abstract OAB-022

Summary

- The landscape of treatment for RRMM patients is changing
- The first line of therapy will influence the choice at relapse
- The first line is rapidly evolving
- There is space for novel agents, especially if they have a different MoA
- The future landscape will be driven by:
  - First line of therapy
  - Response achieved
  - Molecular markers
  - Time at which the relapse occurs
  - ……..