Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

RRMM Lenalidomide-refractory

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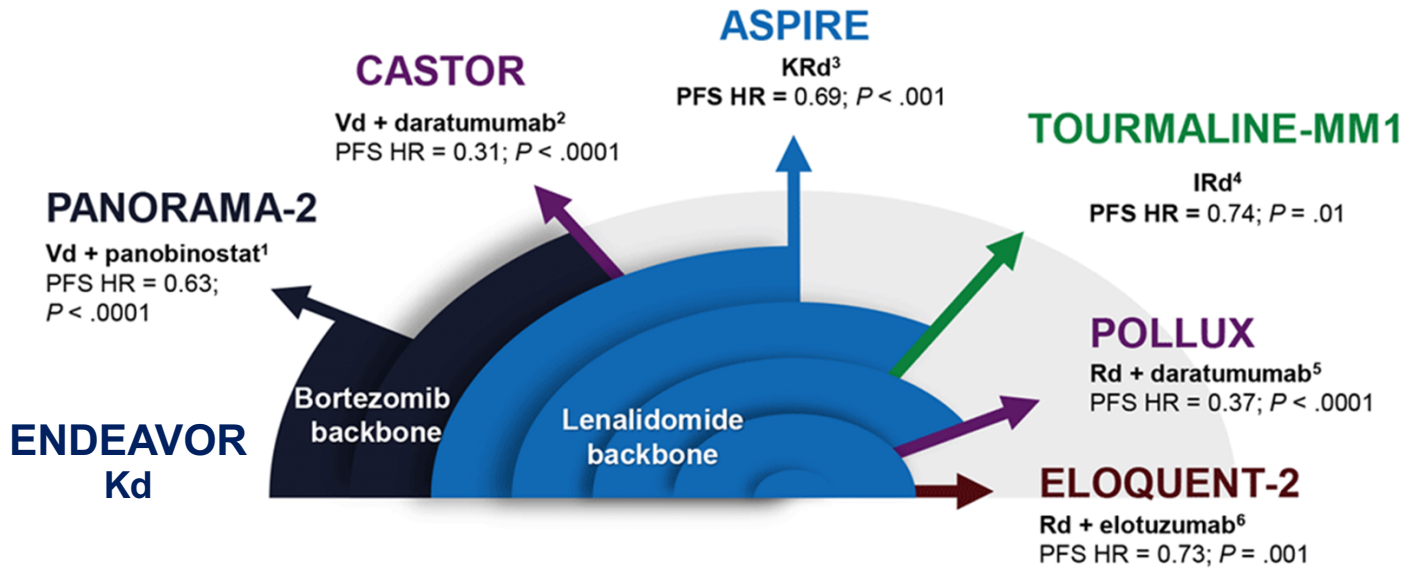
AOU Ospedali Riuniti di Ancona

Phase 3 trials in rrMM

Major Studies Have Validated Triplets in RRMM



1. San-Miguel JF et al. *Lancet Haematol*. 2016;3:e506-e5. 2. Spencer A et al. *Haematologica*. 2018 Sep 20 [Epub ahead of print].
3. Siegel DS et al. *J Clin Oncol*. 2018;10;36:728-734. 4. Avet-Loiseau H et al. *Blood*. 2017;130:2610-2618.
5. Dimopoulos MA et al. *N Engl J Med*. 2016;375:1319-1331. 6. Lonial S et al. ASCO 2017. Abstract 8028.

2014-2016

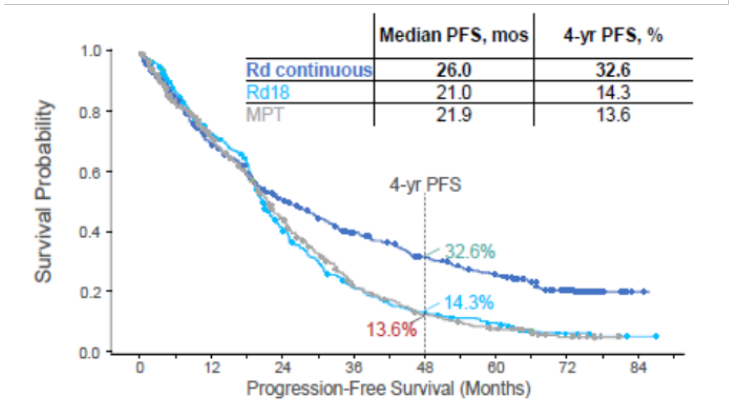
Lenalidomide-exposed-refractory

Trial	ASPIRE/KRd[2]	TOURMALINE/IRd[3]	ELOQUENT-2/ERd[4]	POLLUX/DRd[5]
Median prior lines	2	2	2	1
Rd-based trials	13% / 7% / 80%	12% / 88%	5% / 95%	18% / 82%

Trial	CASTOR/DVd[6]	ENDEAVOR/Kd[7]	PANORAMA/PANO-Vd[†8]
Median prior lines	2	2	1
PI-based trials	18% / 18% / 64%	14% / 24% / 62%	19% / 81%

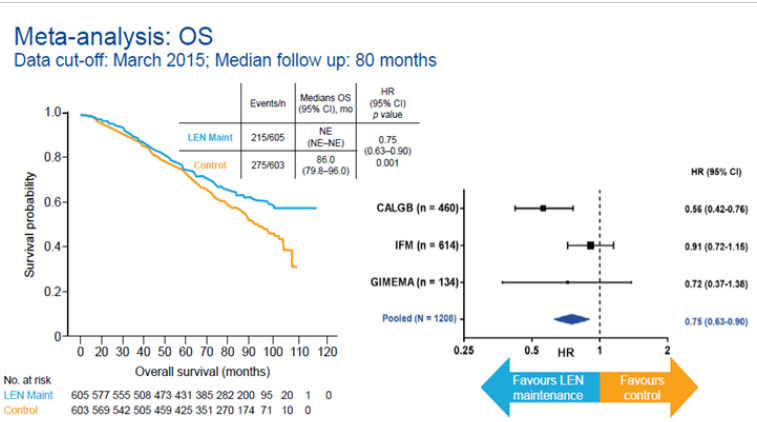
Epidemiology

Rd continuous

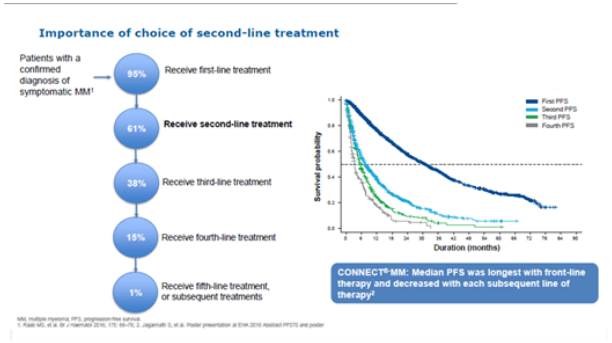


AIFA release: October, 2016
Relapse wave: Q3 2019

R maintenance



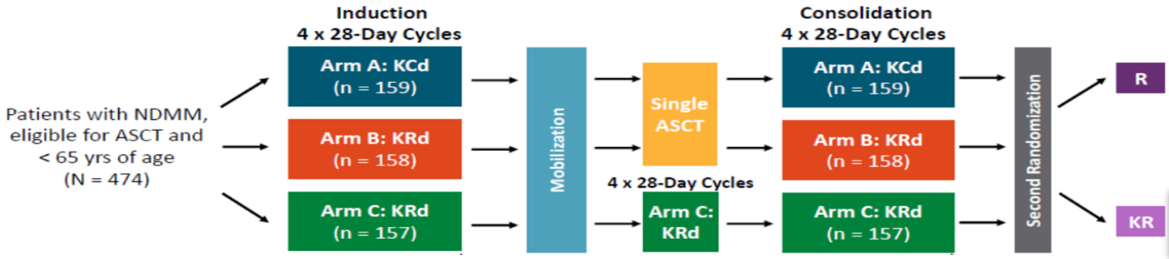
Improvement in median survival of approximately 2.5 years



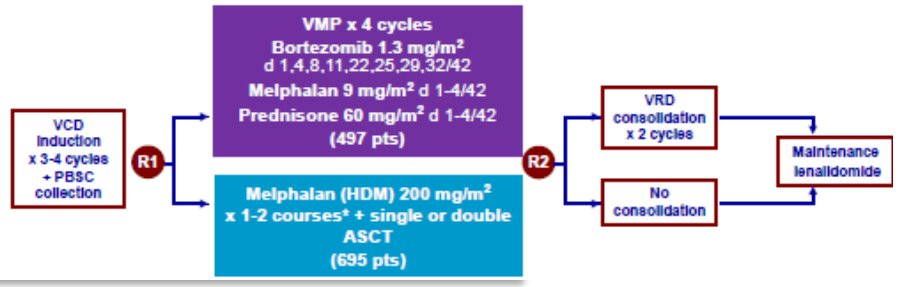
AIFA release: May, 2018
Relapse wave: Q3 2021

FORTE trial

- Multicenter, randomized, open-label phase II study



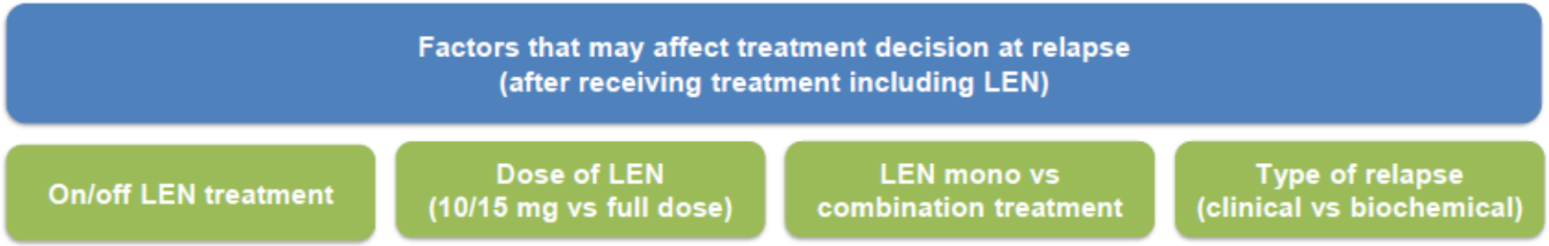
EMN-02/HO95



Epidemiology

Considerations for the treatment of lenalidomide-refractory patients

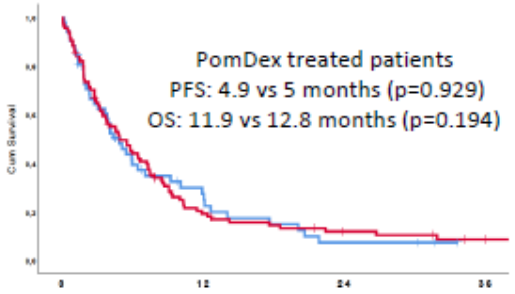
- A high proportion of patients with NDMM receive LEN as first-line therapy until progression; therefore, at the time of relapse, many patients are resistant to LEN
- LEN-refractory patients represent a clinically relevant population with an unmet need



LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma.
Moreau P, et al. Blood Cancer J 2019; 9: 38.

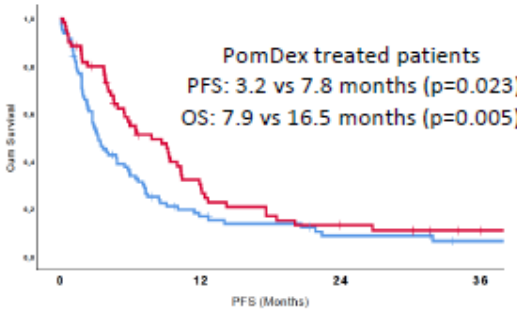
Lenalidomide dose and duration

PFS according to last Len dose (5-15 mg vs 25 mg)



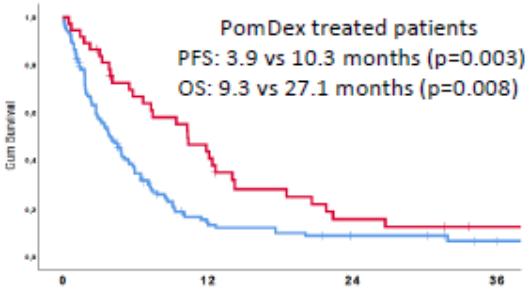
Len last dose 5-15 mg	52	11	3	
Len last dose 25 mg	95	17	8	4

PFS according to Duration on Len therapy <12 vs ≥12 months



Len duration <12 months	86	12	5	2
Len duration >12 months	61	16	6	2

PFS according to IMiD free interval (<18 months vs ≥18 months)



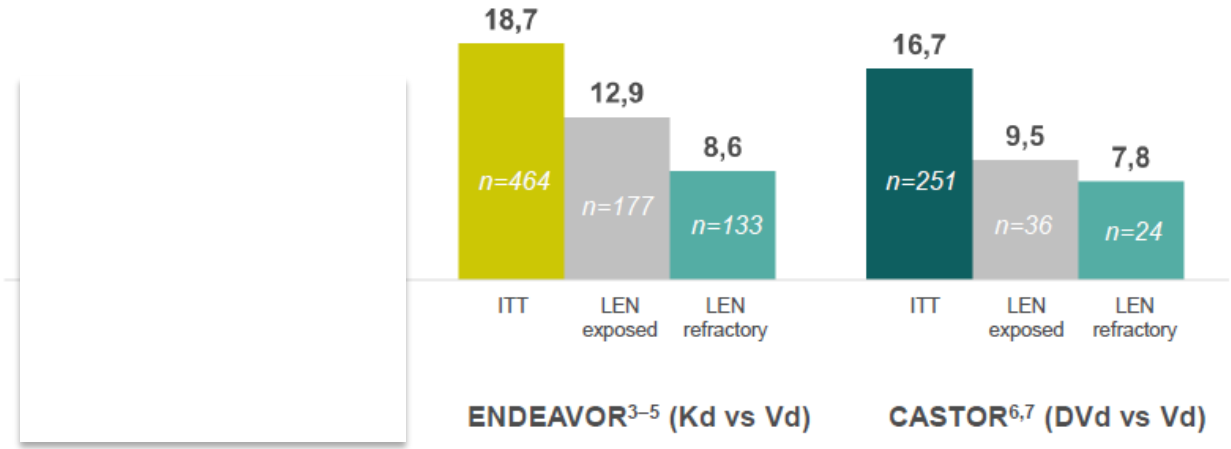
IMiD free interval <18 months	110	13	6	2
IMiD free interval >18 months	37	15	5	2

Kastritis E, et al. Blood Adv 2019; in press

Unmet need

PATIENTS WHO HAVE FULLY BENEFITTED FROM LEN NEED A CLINICALLY PROVEN TREATMENT OPTION

Median PFS for ITT, LEN-exposed and LEN-refractory populations (months)



At relapse, patients have worse prognosis, overall survival and QoL; this is particularly pronounced in patients who have become refractory to treatment

DVd, daratumumab, bortezomib and dexamethasone; ITT, intention to treat; Kd, carfilzomib and dexamethasone; LEN, lenalidomide; PFS, progression-free survival; PVd, pomalidomide, bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

1. Richardson P, et al. J Clin Oncol. 2018;36:(suppl, abstr 8001); 2. Dimopoulos MA, et al. Blood. 2018;132:(suppl, abstr 3278); 3. Dimopoulos MA et al. Lancet Oncol. 2016;17:27–38; 4. Dimopoulos MA, et al. Lancet Oncol. 2017;18:1327–1337; 5. Moreau P, et al. Leukemia. 2017;31:115–122; 6. Mateos MV, et al. Blood. 2018;132:(suppl, abstr 3270); 7. Usmani SZ, et al. Blood. 2018;132;(suppl, abstr 3288).

Dara-Vd: 1th relapse Len-refractory

F. 1 prior line (prior lenalidomide)

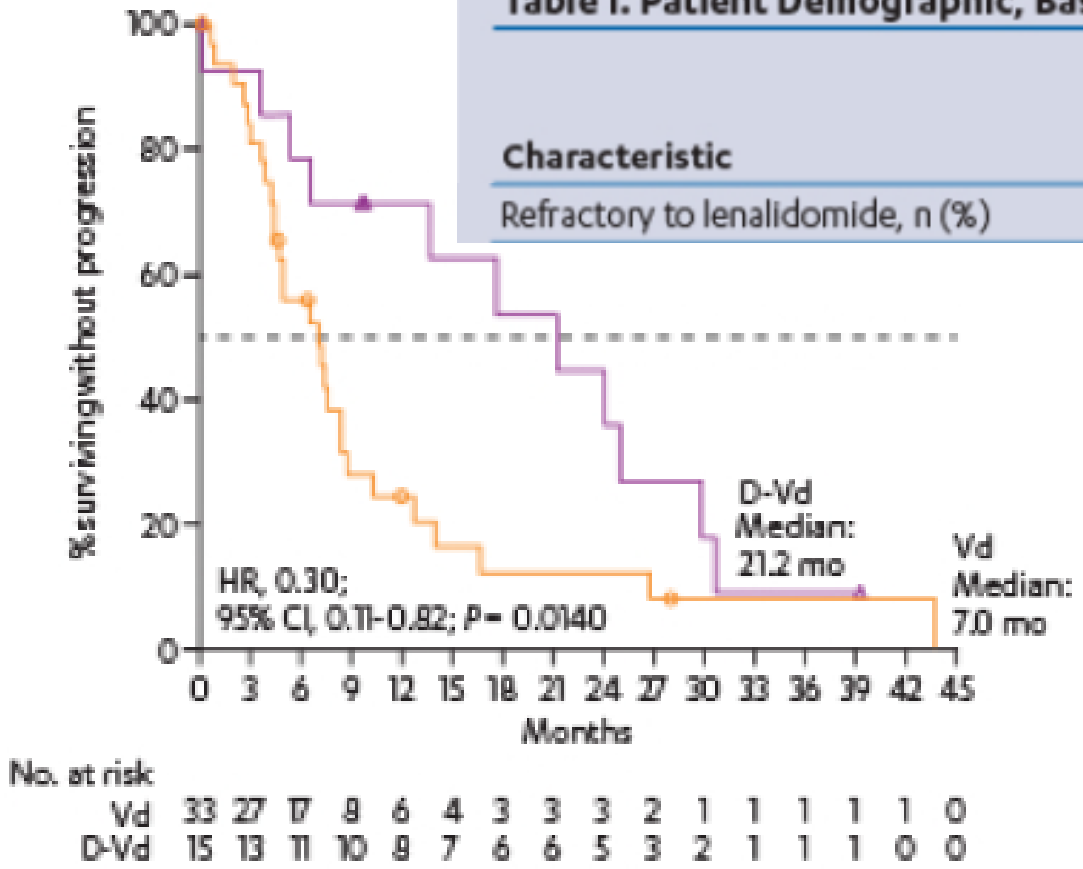


Table 1. Patient Demographic, Baseline Disease, and Clinical Characteristics

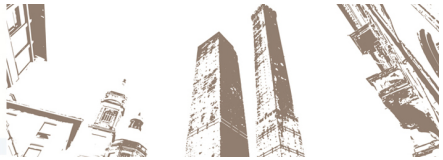
Characteristic	ITT population		1PL subgroup	
	D-Vd (n = 251)	Vd (n = 247)	D-Vd (n = 122)	Vd (n = 113)
Refractory to lenalidomide, n (%)	60 (24)	81 (33)	6 (5)	18 (16)

Kd pooled (Champion-1+ Endeavor): 1th relapse, Len-refractory

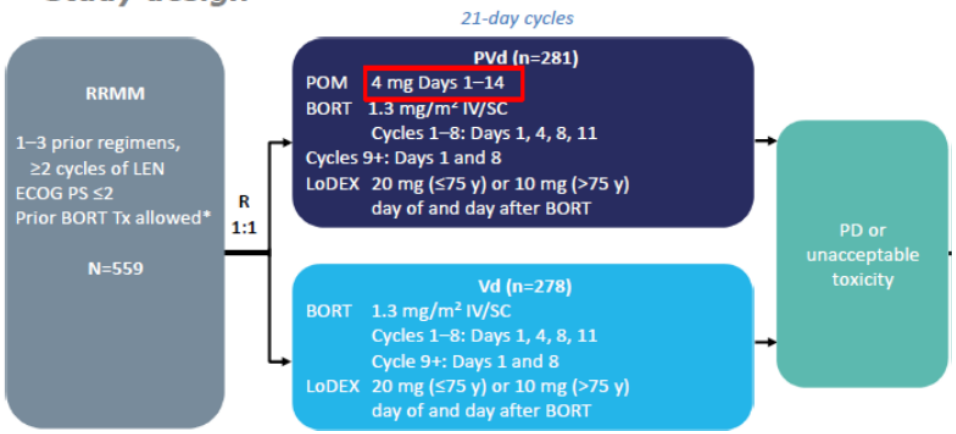
		PVd (Vd)[1]	Kd (Vd)[2]
LEN exposed, non-refractory, at 1st relapse[a]	N value	47 (50)	39
	PFS, months	22.0 (12.0)	18.3
	ORR, %	95.7 (60)	89.7
LEN refractory at 1st relapse	N value	64 (65)	32
	PFS, months	17.8 (9.5)	15.6
	ORR, %	85.9 (50.8)	81.3

Solely for the purpose of internal scientific education. This chart is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.
a Includes both LEN-refractory and LEN-sensitive patients.
ASH, American Society of Hematology; DVd, daratumumab, bortezomib and dexamethasone; Kd, carfilzomib and dexamethasone; LEN, lenalidomide; ORR, overall response rate; PFS, progression-free survival; PVd, pomalidomide, bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.
1. Dimopoulos MA et al. ASH 2018. Abstract 3278; 2. Mateos MV et al. ASH 2018. Abstract 1963.

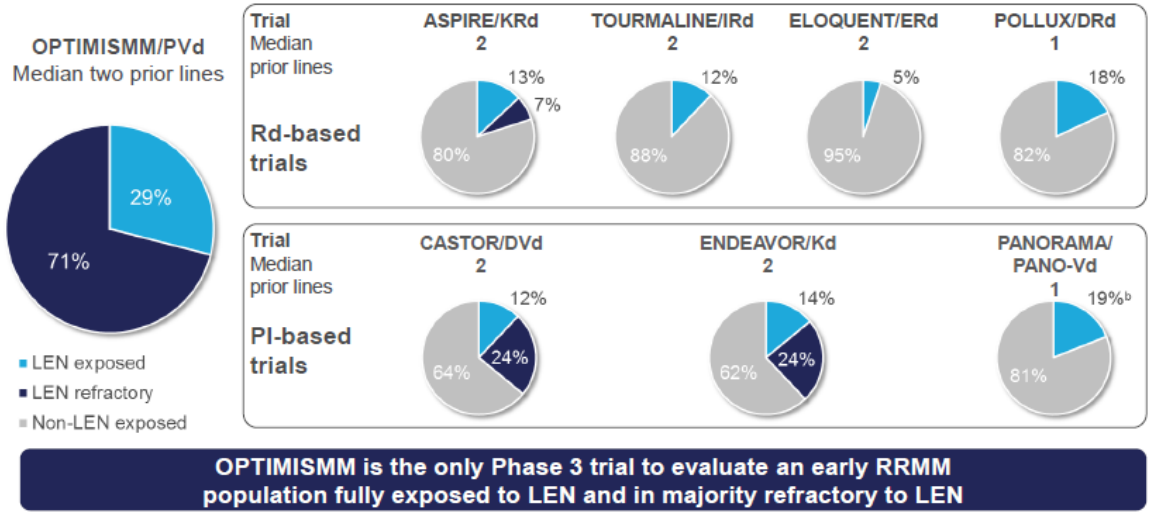
OPTIMISMM: PVd *vs* Vd



Study design



OPTIMISMM IS UNIQUE BECAUSE IT IS THE ONLY PUBLISHED PHASE 3 TRIPLET TRIAL THAT EXCLUSIVELY STUDIES THE POST-REVLIMID POPULATION IN L2+



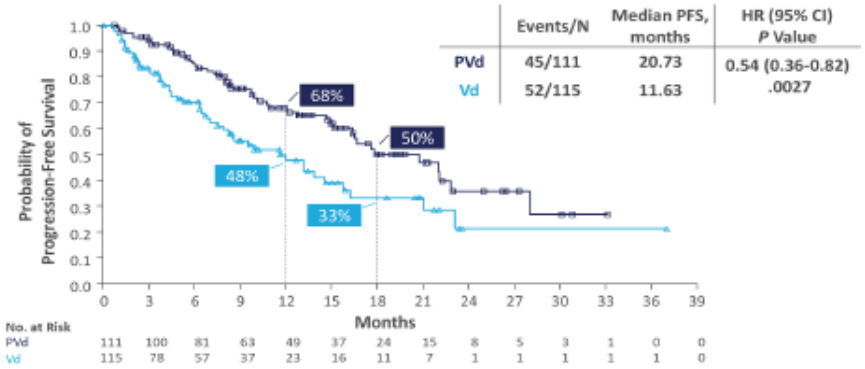
OPTIMISMM is the only Phase 3 trial to evaluate an early RRMM population fully exposed to LEN and in majority refractory to LEN

OPTIMISMM: PVd *vs* Vd

OPTIMISMM-IMW 2019 Update:
PFS in Patients with one prior line of therapy and LEN refractoriness

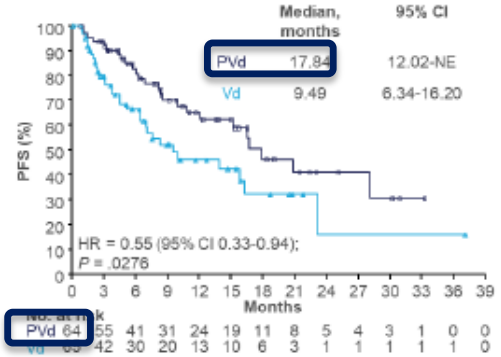
- PFS was significantly improved with PVd vs Vd in patients with 1 prior LOT, regardless of refractoriness to LEN

1 PRIOR LOT

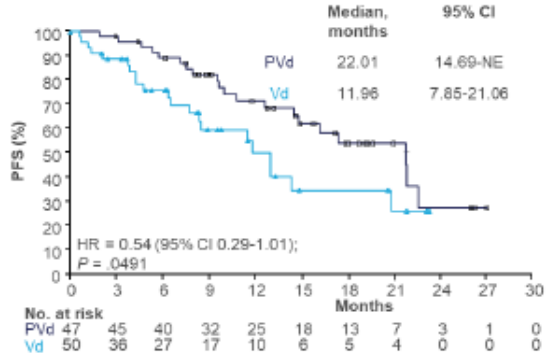


	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	45/111	20.73	0.54 (0.36-0.82)
Vd	52/115	11.63	.0027

1 PRIOR LOT: LEN REFRACTORY[a]



1 PRIOR LOT: LEN NONREFRACTORY



IMW 2019 OAB-047: OPTIMISMM—Meletios Dimopoulos, MD

OPTIMISMM: PVd *vs* Vd

HOW DO YOU DEFINE [redacted] REFRACTORY?

Refractory disease was defined as: failure to achieve minimal response or development of progressive disease during therapy, or progression within 60 days of last dose, inclusive.

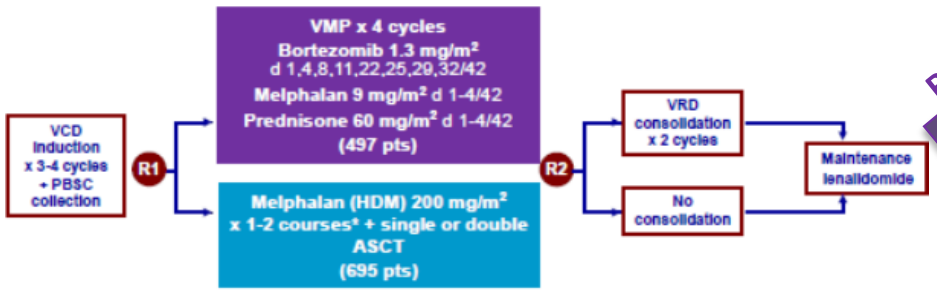
Patients on [redacted] maintenance that only achieved minimal response or developed progressive disease during therapy, or progressed within 60 days of last [redacted] dose, were considered [redacted] refractory.

There was a mix of [redacted] regimens used prior to PVd in OPTIMISMM with different dosing (10mg and/or 25mg). The data capture does not allow us to analyze these groups separately.

In the OPTIMISMM study, 100% of patients were [redacted] exposed to at least 2 cycles and 71% were [redacted] refractory. This evidence supports the PVd regimen as a proven choice in 2L post-[redacted]

EMN011 trial

EMN-02/HO95



Relapse

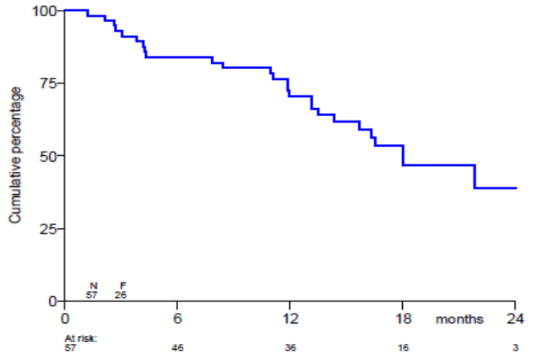
EMN011/HO114 MM trial

28-days cycles
Pomalidomide 4 mg, days 1-21
Carfilzomib 20/36mg/m² twice weekly
Dexamethasone 40 mg/w

R
- Pomalidomide 21 days until PD
- Pomalidomide plus Dexamethasone 21 days until PD

Patients who had not received HDM/ASCT during 1st line in EMN02 were offered this after 4 cycles

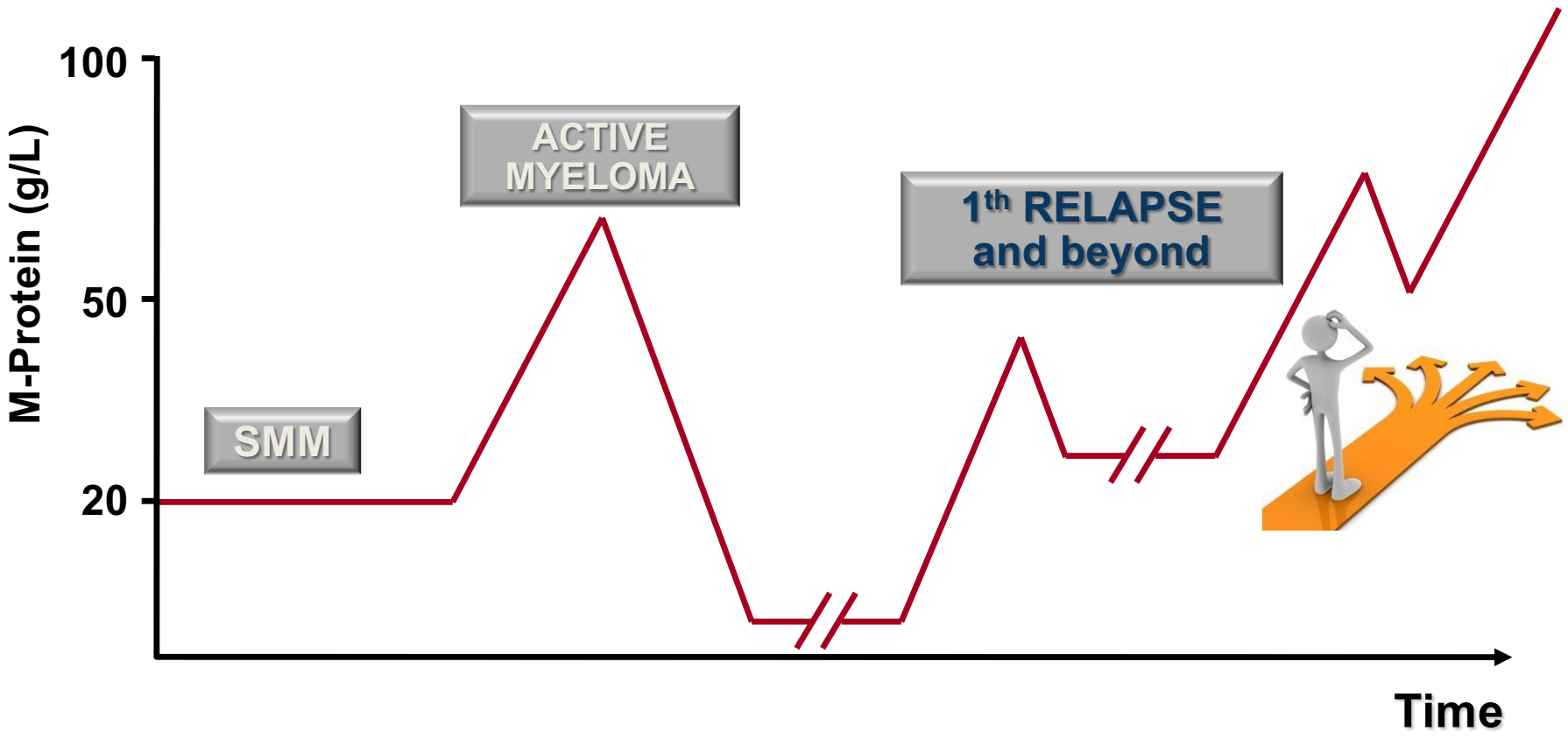
PD during Len maintenance 57/60 (95 %)



Median PFS 18 months

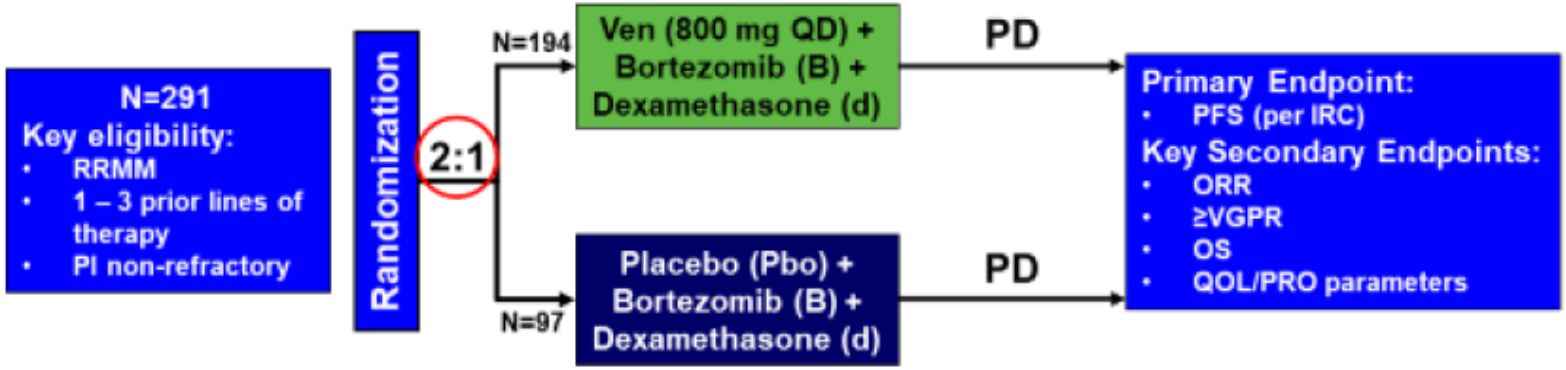
Sonneveld P et al, ASH 2018

1th relapse and beyond



Bellini: Venetoclax-Vd *vs* Vd

Venetoclax May Be Another Option for This Population
BELLINI trial: Update from IMW 2019



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

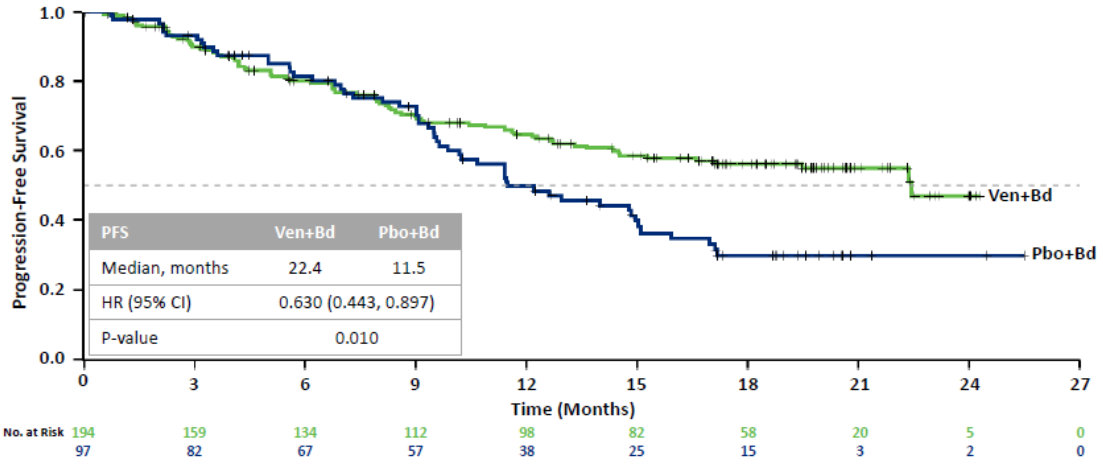
Cycles 9+: 35-day, Bortezomib 1.3 mg/m^2 Days 1, 8, 15, 22 and dexamethasone 20 mg Days 1, 2, 8, 9, 15, 16, 22, 23

Stratification factors	• Bortezomib sensitive vs naïve • Prior lines of therapy: 1 vs 2–3
Non-ranked secondary endpoints	PFS in BCL-2^{high} (IHC), DOR, TTP, MRD negativity rate, other PROs (GHS, fatigue)
Key subgroup analyses	t(11;14), high/standard-risk cytogenetics, and *BCL2* expression (gene expression)

Kumar S, et al. IMW 2019

Bellini: Venetoclax-Vd *vs* Vd

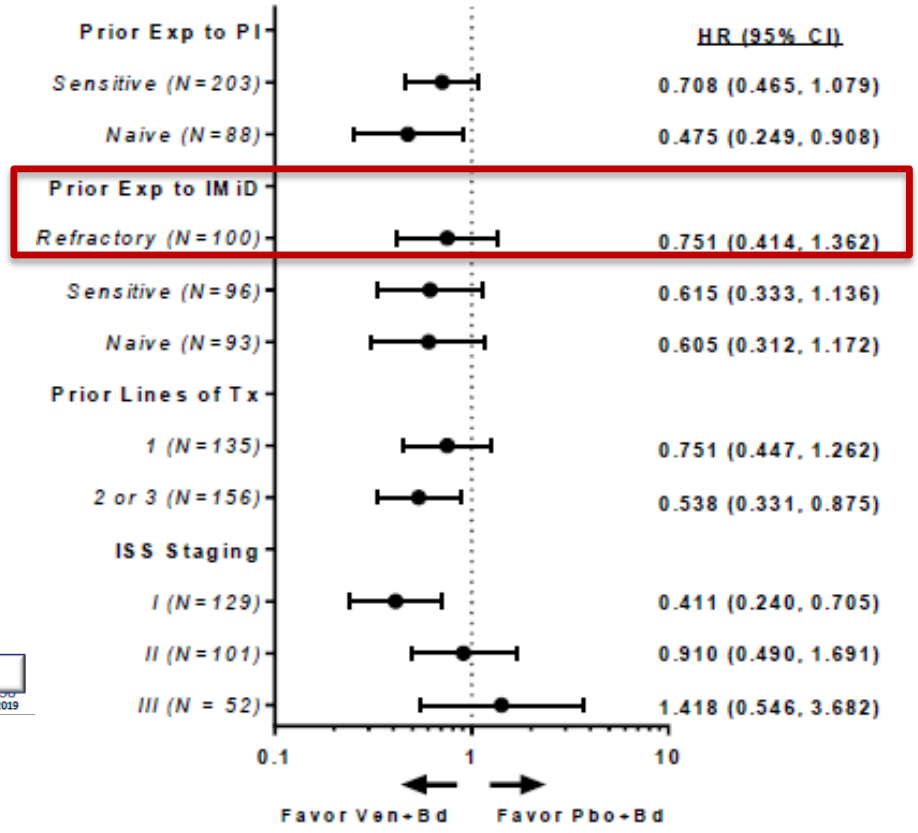
BELLINI - Primary Endpoint Analysis: Progression-Free Survival



PFS	Ven+Bd	Pbo+Bd
Median, months	22.4	11.5
HR (95% CI)	0.630 (0.443, 0.897)	
P-value	0.010	

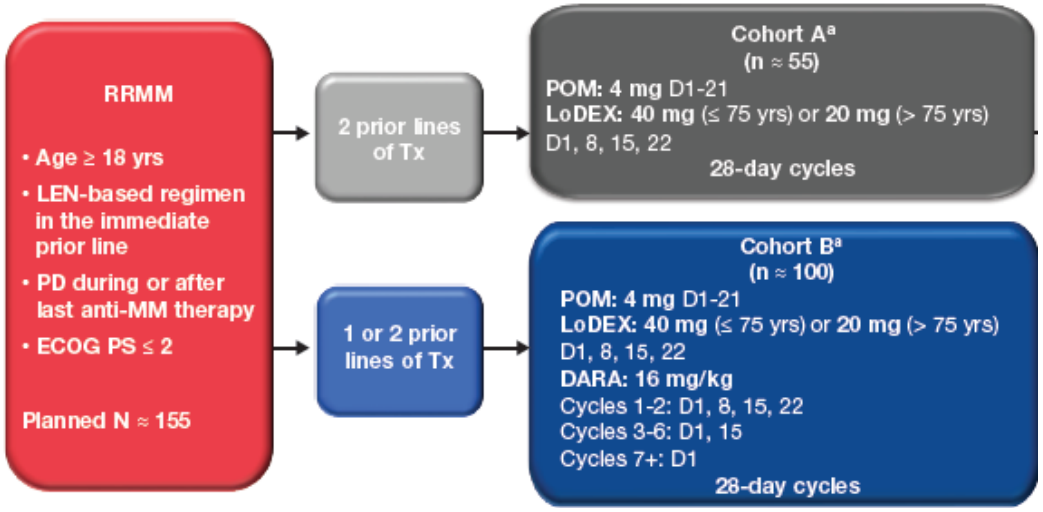
The BELLINI study met its primary endpoint with superior median PFS in the **Ven+Bd arm versus Pbo+Bd**

Kumar S, et al. IMW 2019



MM-014 trial (phase 2): cohort B (Dara-Pd)

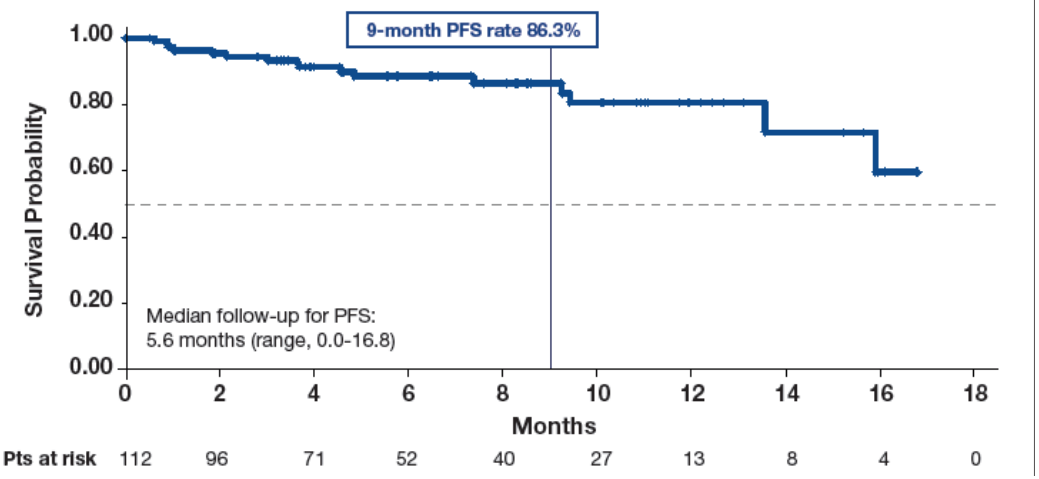
MM-014 Trial Design



Characteristics	ITT Population (N = 112)
No. of prior regimens, median (range)	2 (1-5)
One prior line of therapy, n (%)	70 (62.5)
Two prior lines of therapy, n (%)	42 (37.5)
Refractory to LEN, n (%)	84 (75.0)

Progression-Free Survival (ITT population)

Events, N	Median PFS, mos	95% CI
16	NE	13.6-NE

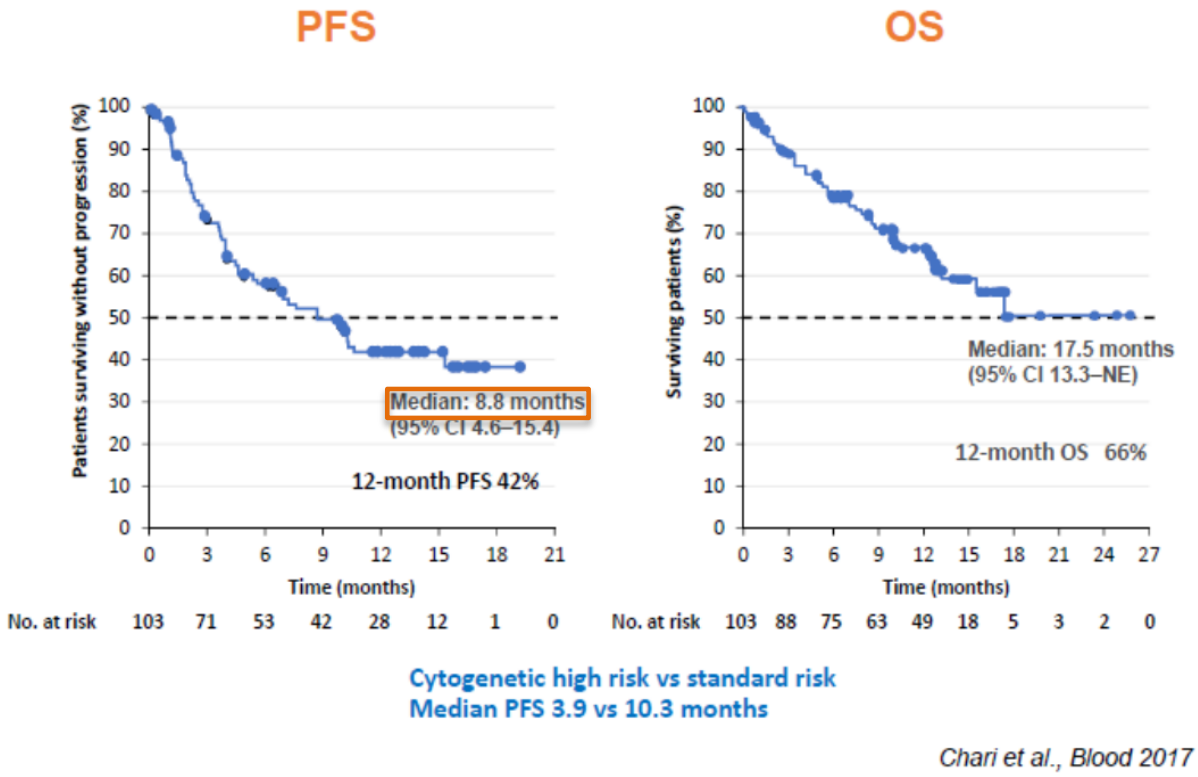


Siegel DS et al, ASH 2018

EQUULEUS (phase 1b): Dara-Pd (Phase 3 Apollo)

Dara-PD: Survival

Median Follow-up 13.1 months (0.2-25.8)



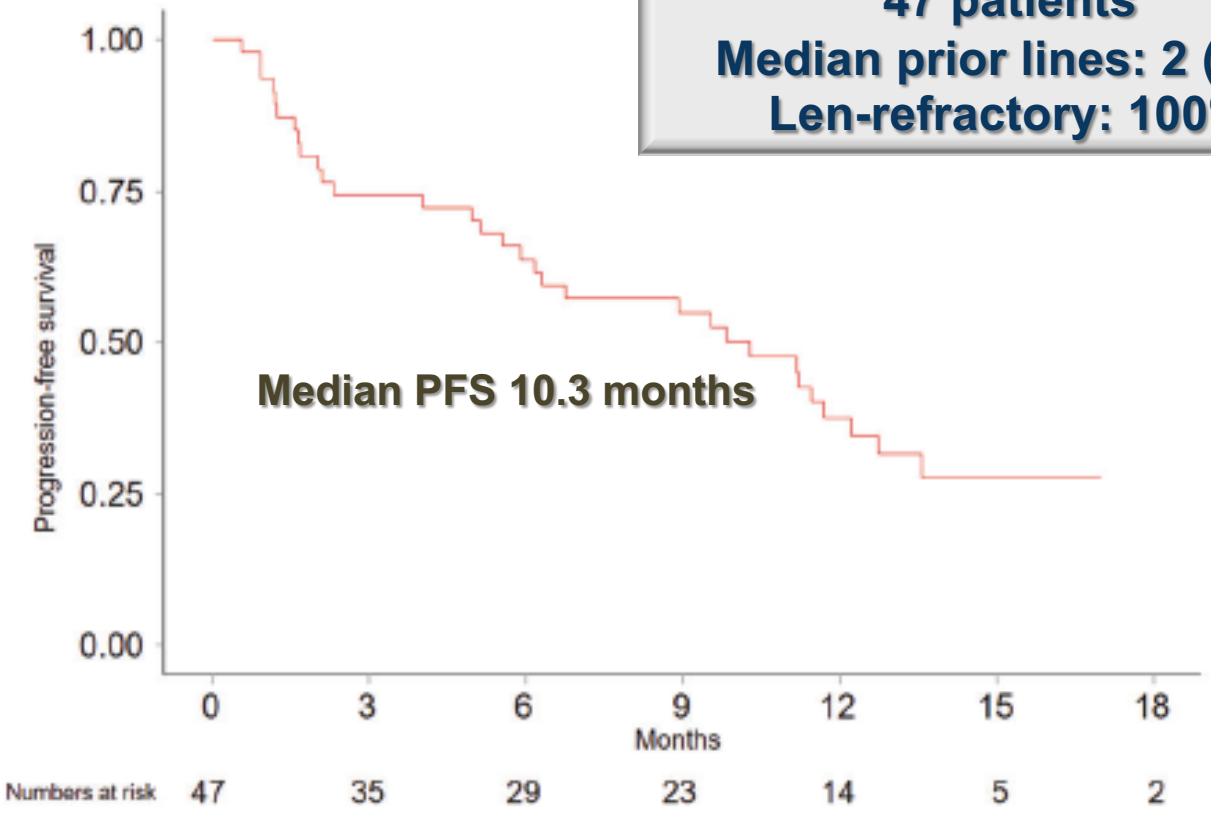
Cytogenetic high risk vs standard risk
Median PFS 3.9 vs 10.3 months

Chari et al., Blood 2017

103 patients
Median prior lines: 4 (1-13)
Len-refractory: 89%

wKPd: phase 1/2 study

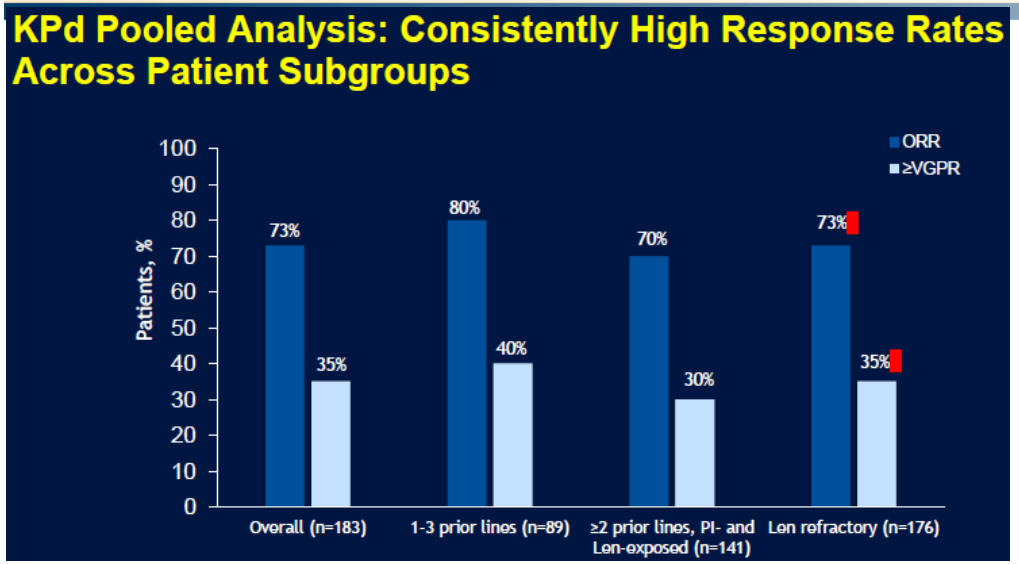
47 patients
Median prior lines: 2 (1-3)
Len-refractory: 100%



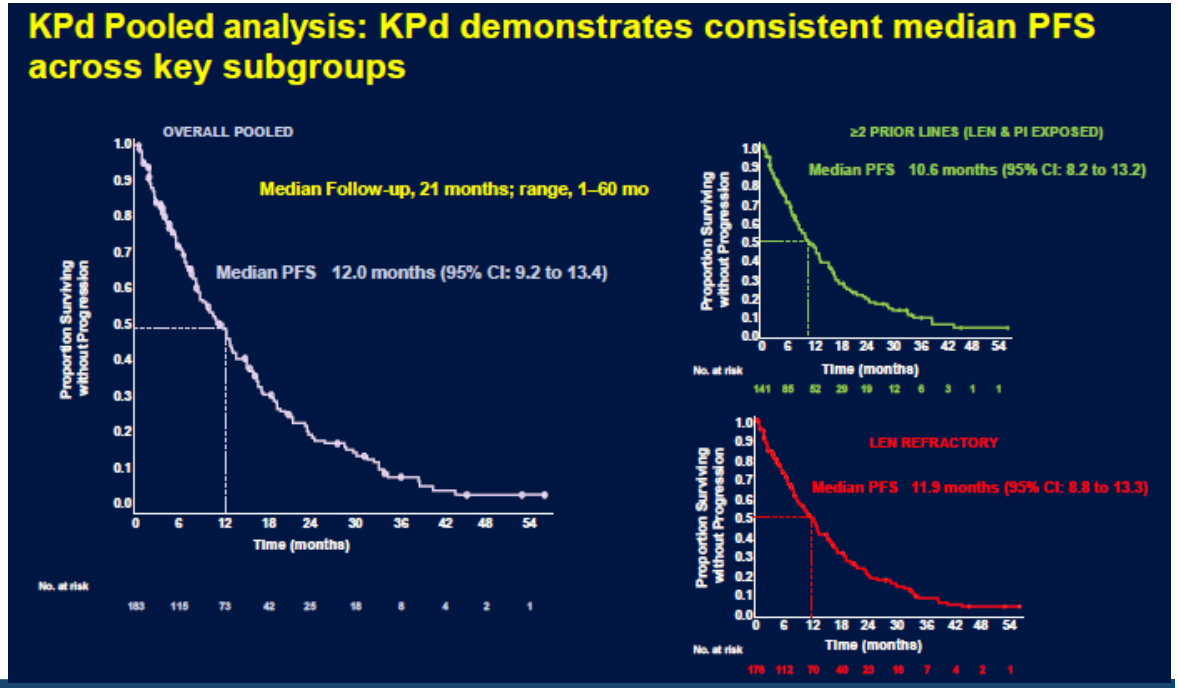
Five DLTs were observed: 2 with carfilzomib at the dose of 45 mg/ m^2 (1 grade 3 hypertension and 1 sudden death) and 3 with carfilzomib at the dose of 36 mg/ m^2 (1 grade 3 atrial fibrillation, 1 grade 3 hypertension, and 1 grade 5 heart failure). Four of 5 DLTs in the first nine patients were considered related to hypertension.

Bringhen S et al, Leukemia 2018

KPd: Phase 1/2 pooled analysis*



***183 patients**
(from Shah Blood 2015 and Jakuboviak EHA 2017)
Median prior lines: 4 (1-15)
Len-refractory: 95%

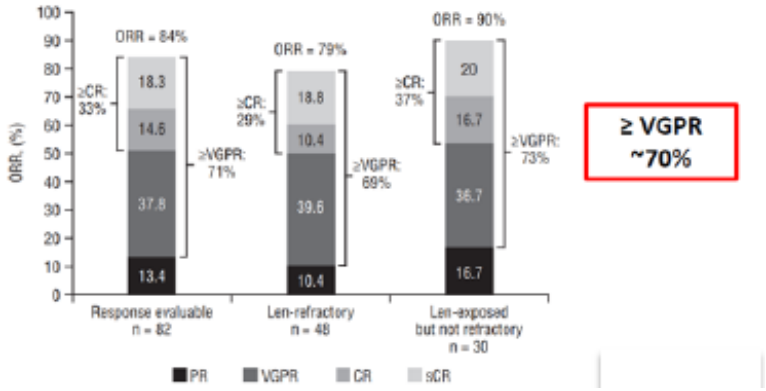


Jakuboviak et al, IMW 2019

MMY1001 (phase 1b): Dara-Kd

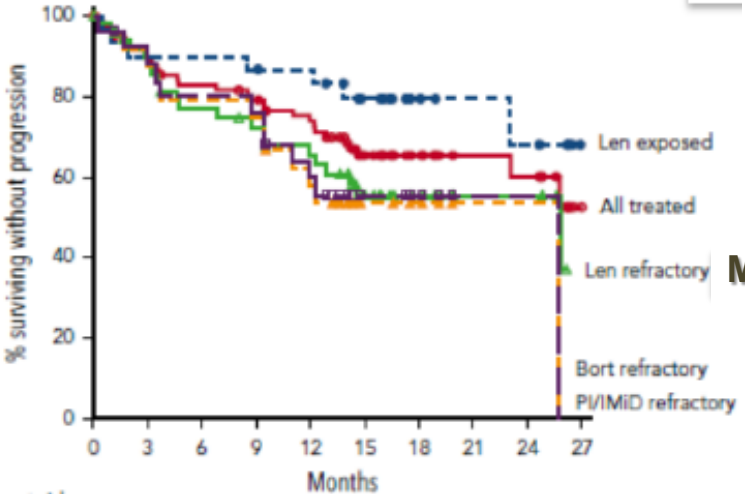
Daratumumab Plus Carfilzomib and Dexamethasone

Chari A et al, Blood 2019



≥ VGPR ~70%

85 patients
Median prior lines: 2 (1-4)
Len-refractory: 60%



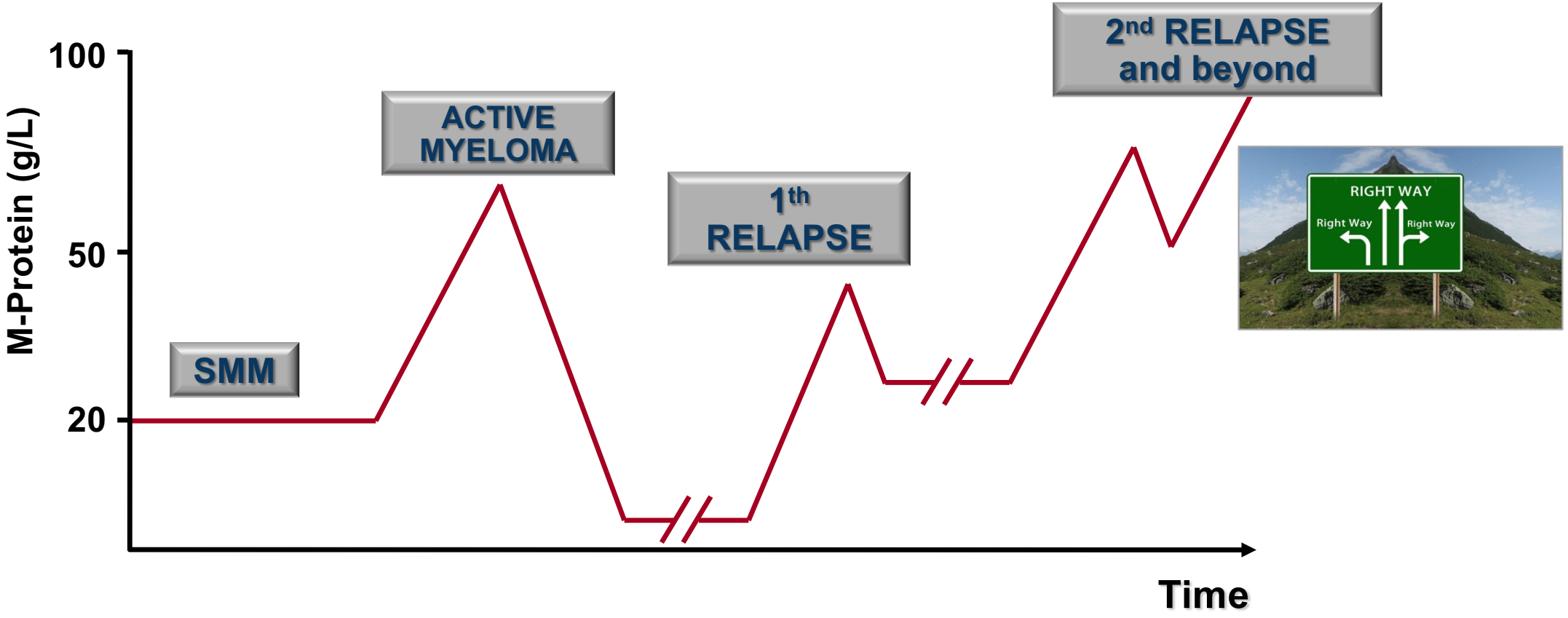
Median PFS: 25.7 mo

CANDOR (phase 3): Dara-Kd *vs* Kd

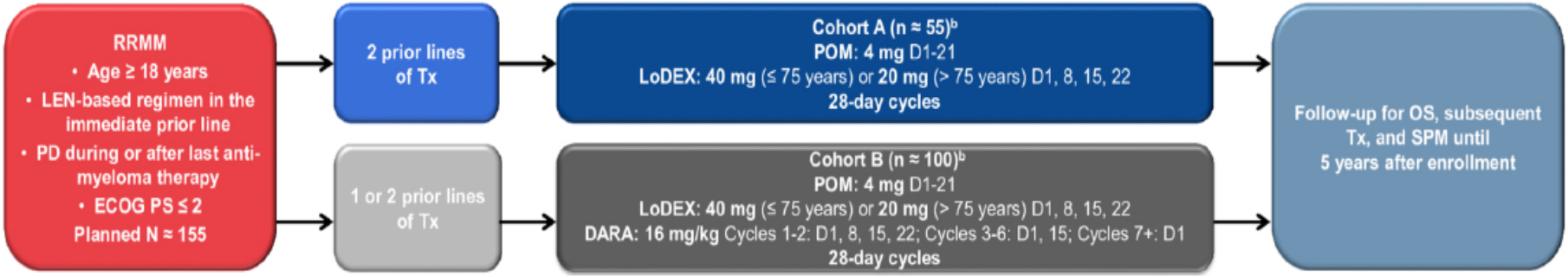
THOUSAND OAKS, Calif., Sept. 13, 2019

[redacted] today announced the **Phase 3 CANDOR** study evaluating Karfilzomib in combination with dexamethasone and daratumumab **(KdD)** compared to Carfilzomib and dexamethasone alone **(Kd)** met its primary endpoint of PFS. The median PFS for patients with relapsed or refractory (1-3 prior lines) multiple myeloma treated with **Kd** alone was **15.8 months** ***vs*** **NR** for **KdD** (HR=0.630; 95% CI: 0.464, 0.854; *p*=0.0014).

2nd relapse and beyond

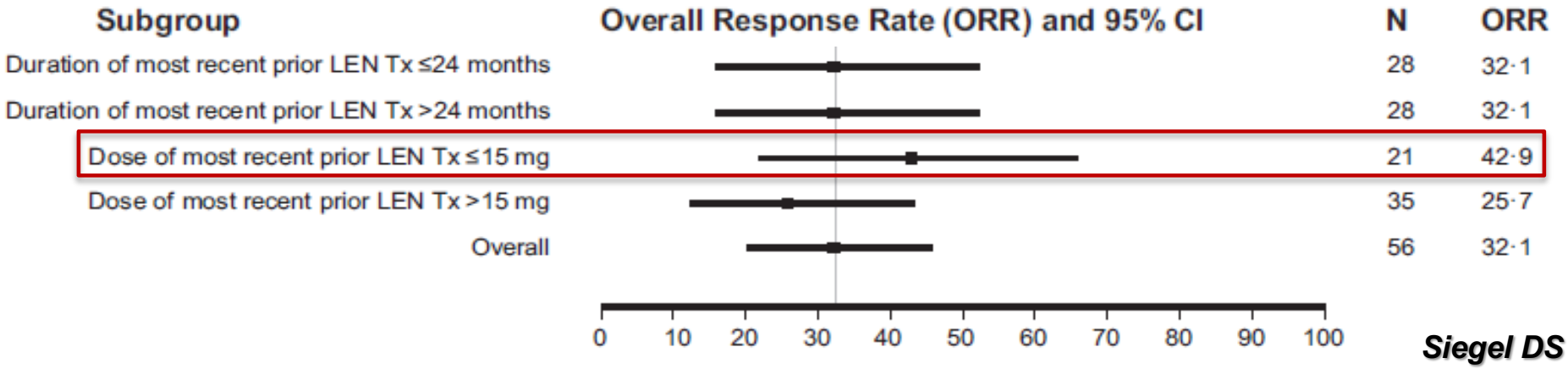


MM-014 (phase 2): Pd cohort



56 patients; median prior lines: 2 (2-5), lenalidomide refractory: 87.5%

Median PFS was 12.2 months



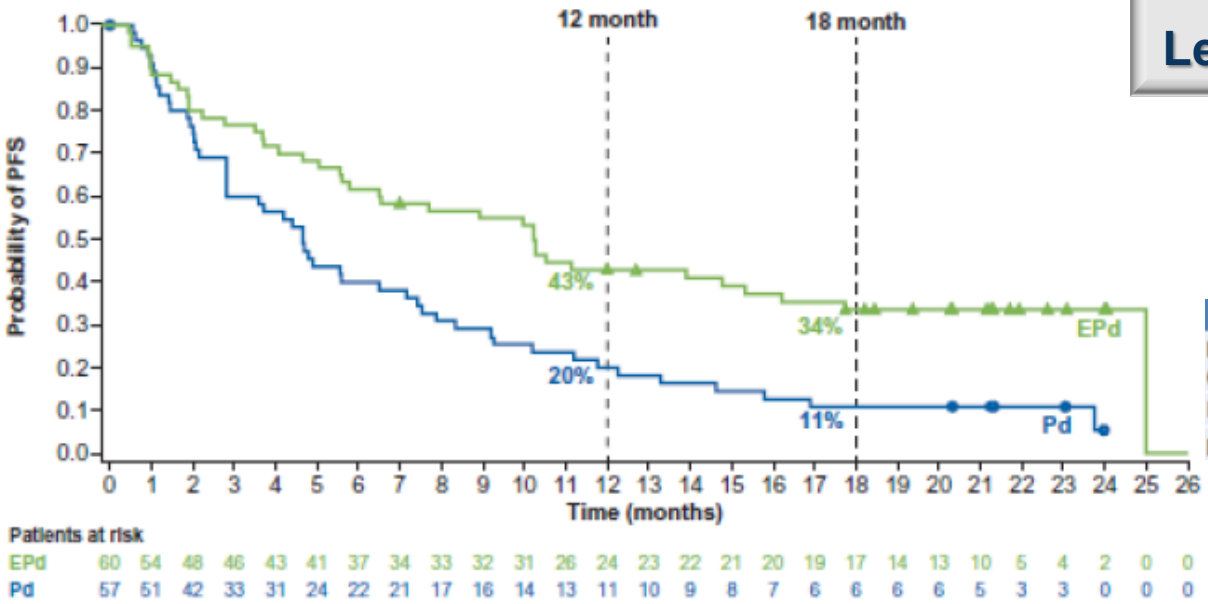
Siegel DS et al, BJH 2019

Eloquent-3 (phase 2): Elo-Pd *vs* Pd

ELOQUENT-3 Study: EloPomDex (n=60) vs PomDex (n=57)

IMW 2019 Update: PFS (minimum follow-up 18.3 months)

Median prior lines: 3 (2-8)
Lenalidomide refractory: 98%



	EPd	Pd
Median, month (95%CI)	10.3 (5.6–NR)	4.7 (2.8–7.2)
HR (95% CI)	0.54 (0.34 to 0.86)	
p-value	0.008	

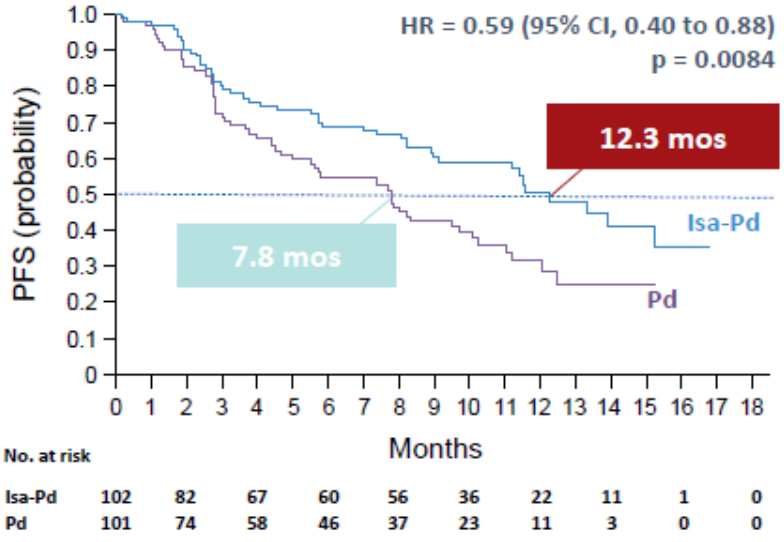
Dimopoulos MA et al, IMW 2019;abstract FP190

ICARIA (phase 3): Isatuximab-Pd *vs* Pd

ICARIA: PFS by prior lines of treatment

Median prior lines: 3 (2-11)
Lenalidomide refractory: 93.5%

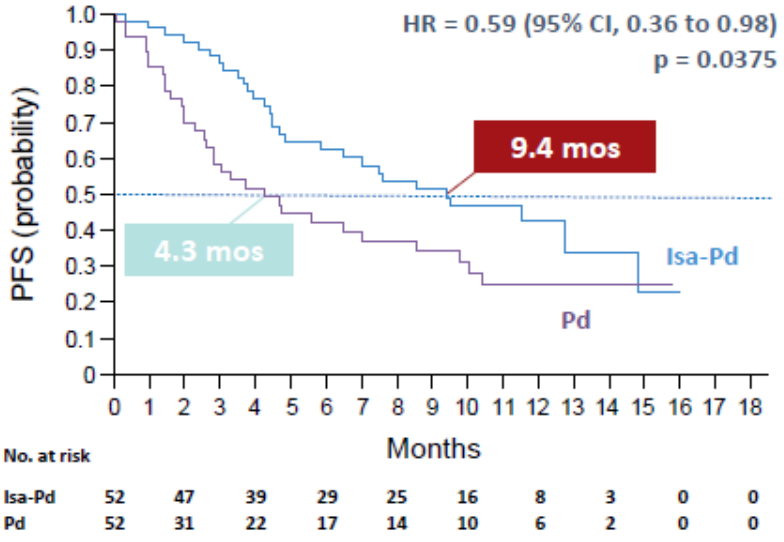
2–3 prior lines of therapy



No. at risk

Isa-Pd	102	82	67	60	56	36	22	11	1	0
Pd	101	74	58	46	37	23	11	3	0	0

>3 prior lines of therapy



No. at risk

Isa-Pd	52	47	39	29	25	16	8	3	0	0
Pd	52	31	22	17	14	10	6	2	0	0

Consistent improvement in PFS across lines of therapy

Data cut-off 11 Oct, 2018
CI, confidence interval; d, dexamethasone; HR, Hazard ratio; Isa, Isatuximab; mos, months; PFS, progression-free survival; P, pomalidomide

Richardson P, et al. EHA 2019 Abstract Code: S824

Summary

Studies in RRMM including patients in first relapse refractory to lenalidomide: results by subanalyses* or preliminary data°

Study	Phase	Treatment	No pts Len-refr 1th line	ORR (%)	mPFS (months)
ENDEAVOR, ARROW*	III	Kd	32	81	15.6
CASTOR*	III	Dara-VD	5	81	?
OPTIMISMM*	III	PVd	64	86	17.8
EMN011°	II	KPd	57	92	18

Mateos M- V et al, ASH 2018 abstract 1963; Mateos M-V et al, abstract 3270; Dimopoulos M et al, IMW 2019; Sonneveld P et al, ASH 2018 abstract 801

Summary

Studies in RRMM after ≥ 1 prior line

Study	Phase	Treatment	Median prior LoT (range)	Len refractory/No (%)	PFS (median, mo)
ENDEAVOR[1]	III	Kd	2 (1-3)	113 (24)	8.6*
wKPd[2]	I/II	KPd	2 (1-3)	47 (100)	10.3*
OPTIMISMM[3]	III	PVd	2 (1-3)	200 (71)	9.5*
BELLINI[4]	III	Ven-Vd	2 (1-3)	66 (34)	22.4
MMY1001[5]	Ib	Dara-Kd	2 (1-4)	85 (60)	25.7*
MM-014[6]	II	Dara-Pd	2 (1-5)	84 (75)	1 yr 77%
IxaPd[7]	I/II	Ixa-Pd	2 (1-5)	32 (100)	8.6*
CASTOR[8]	III	Dara-VD	2 (1-9)	60 (24)	7.8*
MMY1001 (EQ)[9]	Ib	Dara-Pd	4 (1-13)	92 (89)	8.8
KPd (pooled)[10]	I/II	KPd	4 (1-15)	173 (95)	11.9*

*Len refractory any line

[1]Moreau P et al, Leukemia 2016; [2]Bringhen S et al, Leukemia 2018; [3]Dimopoulos M et al, IMW 2019; [4]Kumar S et al, IMW 2019; [5]Chari A et al, Blood 2019; [6]Siegel DS et al, ASH 2018; [7]Krishnan A et al, Leukemia 2018; [8]Usmani SZ et al, ASH 2018; [9]Chari A et al, Blood 2017; [10]Jakuboviak A et al, IMW 2019

Summary

Studies in RRMM after ≥ 2 prior lines

Study	Phase	Treatment	Median prior LoT (range)	Len refractory/No (%)	PFS (median, mo)
MM-014[1]	II	Pd	2 (2-5)	49 (87)	12.2
ELOQUENT-3[2]	II	Elo-Pd	3 (2-8)	59 (98)	10.3
ICARIA[3]	III	Isa-Pd	3 (2-11)	144 (94)	11.5
STOMP[4]	Ib/II	Sel-Kd	4 (2-8)	14 (67)	3.7

[1]Siegel DS et al, Br J Haematol 2019; [2]Dimopoulos M et al, N Engl J Med 2019; [3]Richardson PG et al, IMW 2019; [4]Jakuboviak AJ et al, Br J Haematol 2019

Ongoing phase III trials

Trial	Patient Population	Investigational Regimen	Primary Endpoint
CANDOR	RRMM 1-3 lines of Tx	Dara-Kd *vs* Kd	PFS*
APOLLO	RRMM ≥ 1 line of Tx	Dara-Pd *vs* Pd	PFS°
IKEMA	RRMM 1-3 lines of Tx	Isa-Kd *vs* Kd	PFS°
BOSTON	RRMM 1-3 lines of Tx	Selinexor-Vd *vs* Vd	PFS°
OCEAN	RRMM 2-4 lines of Tx	Melfuflen-d *vs* Pd	PFS

*Just met; °Enrollment completed