ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

L'IMMUNOTERAPIA SOLO NEL PAZIENTE REFRATTARIO/RESISTENTE?

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Disclosures – Michele Cavo

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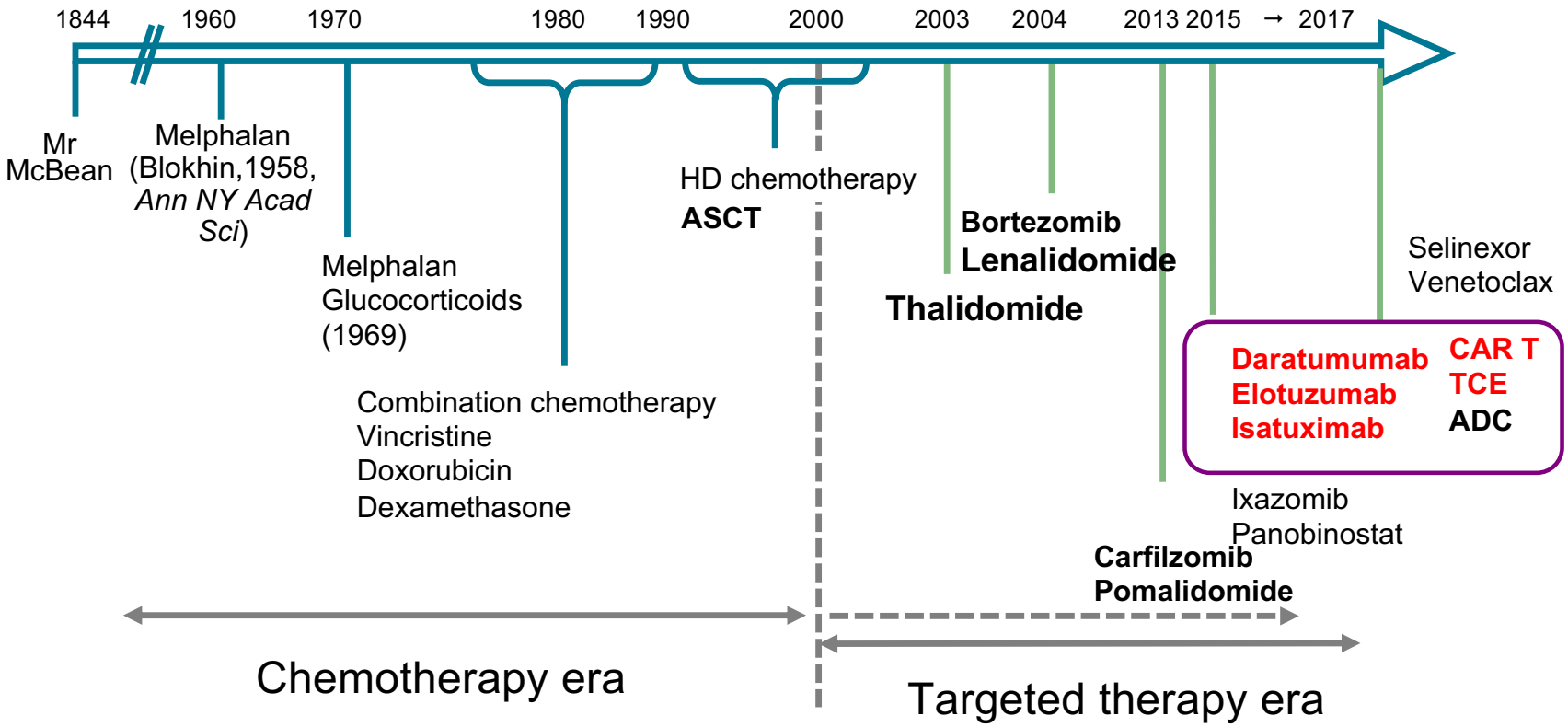
Honoraria	Janssen, Celgene, Bristol-Myers Squibb, Amgen, Takeda, Sanofi
Scientific Advisory Board	Janssen, Celgene, Takeda, Amgen, Bristol-Myers Squibb, Sanofi

Presentation includes discussion of the off-label use of a drug or drugs

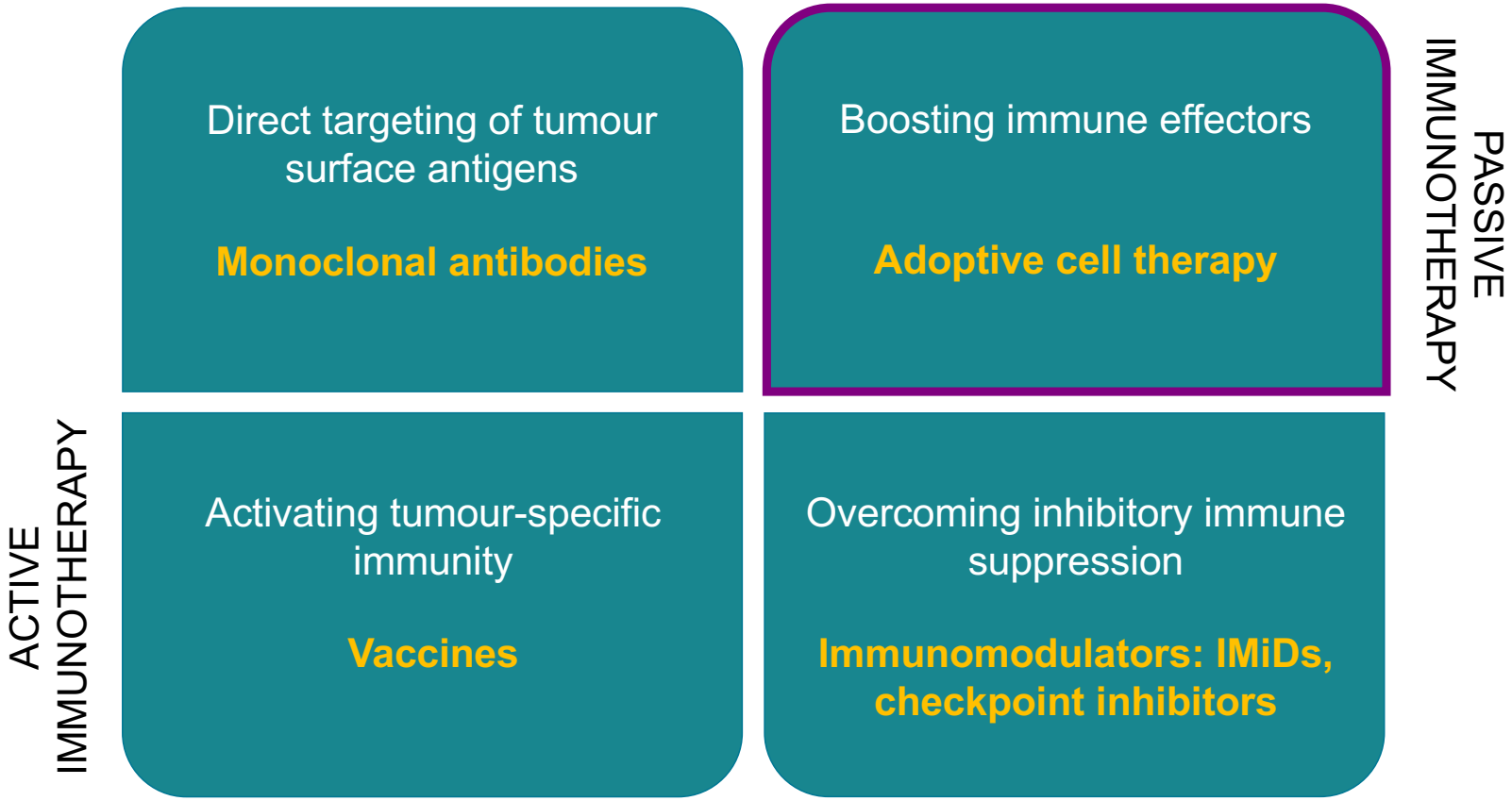
Do we need new treatments for MM?



ADC, antibody drug conjugate; ASCT, autologous stem cell transplantation; CAR T, chimeric antigen receptor T cell; HD, high-dose; MM, multiple myeloma; TCE, T-cell engager.

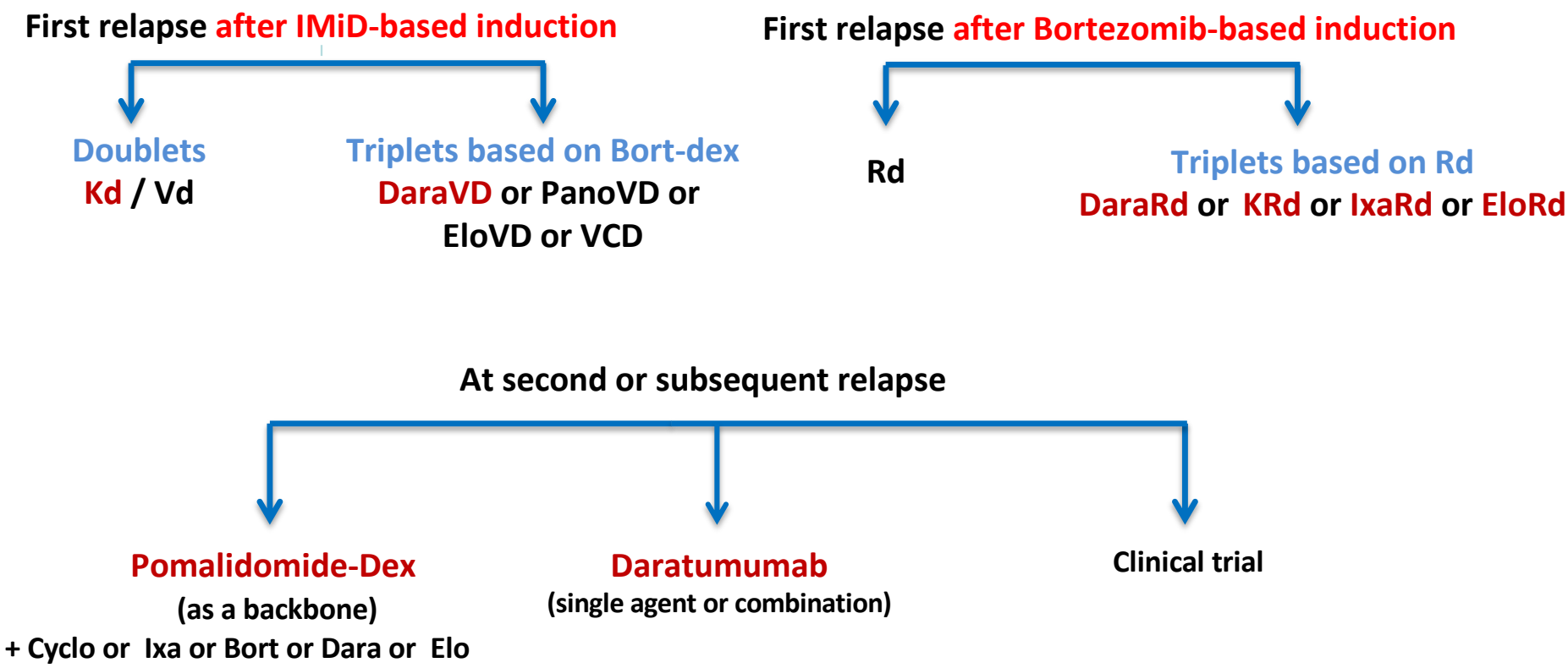
Cavo M, *personal communication*

The immunotherapy era of MM



Rodríguez Otero P, et al. Haematologica. 2017;102:423-32.

Treatment of RRMM: ESMO guidelines 2017



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

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

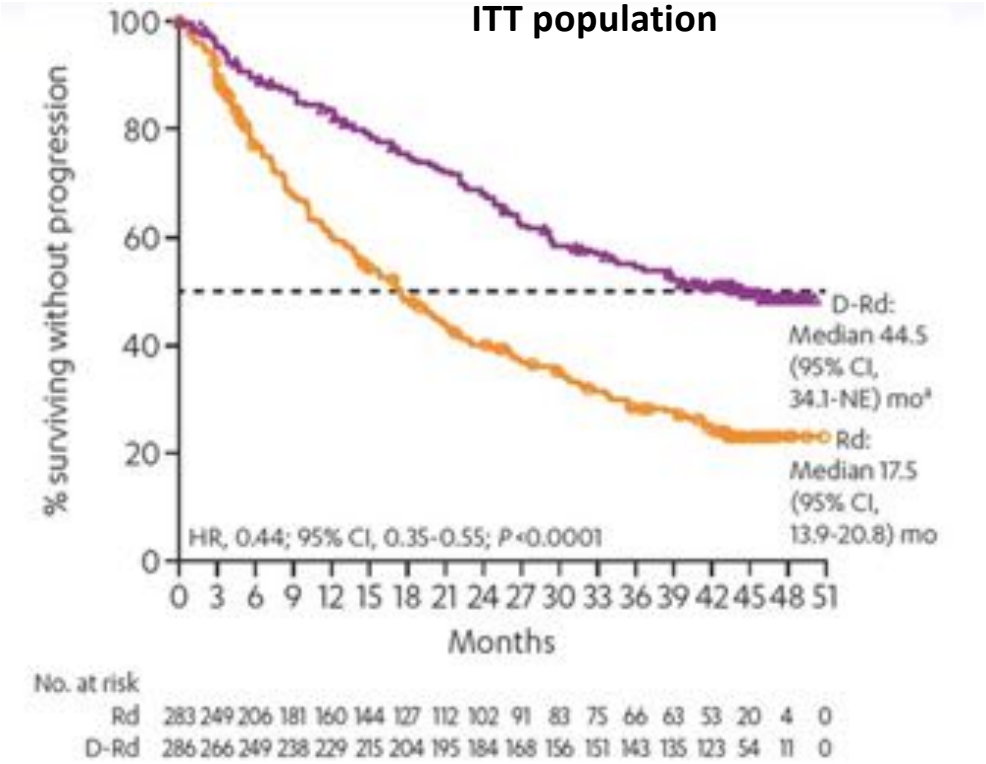
Lenalidomide-dex

Relapse

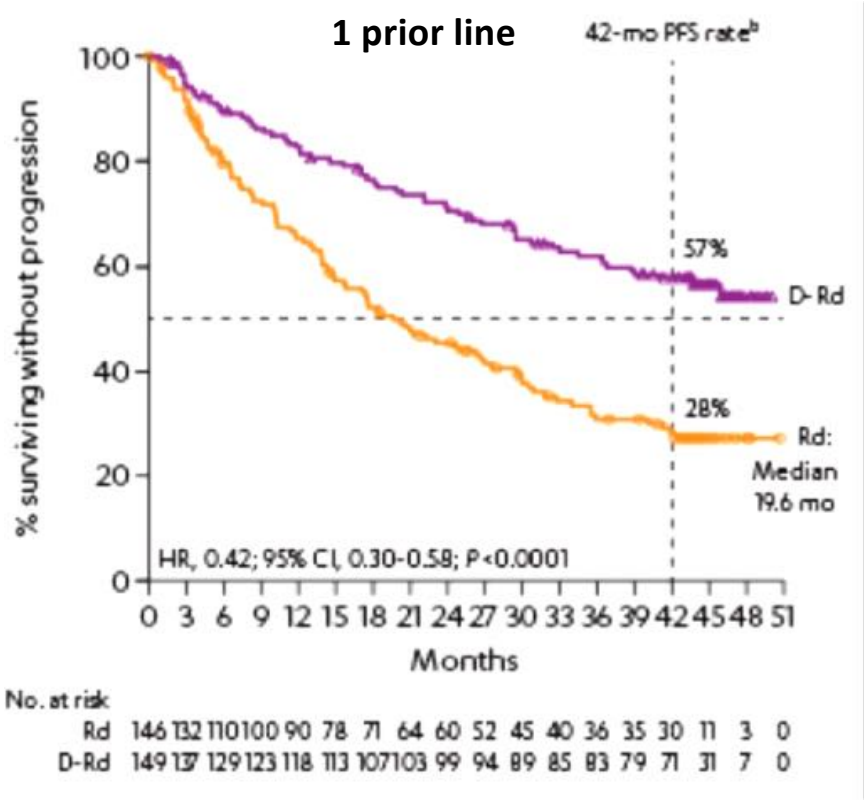
PIs based combinations		IMiDs based combinations	
Kd 18.7 m, HR:0.53 CR 13%	**DaraVD** PFS: 16.7 m, HR 0.32 CR 30%	**KRd** PFS: 26.3m, HR: 0.69 CR 32%	**DaraRd** PFS: 58%@30m,HR:0.44 CR 46%
		EloRd PFS: 19.4m, HR: 0.71 CR 5%	**IxaRd** PFS: 20.6m, HR: 0.74 CR 12%

Dimopoulos MA et al, Lancet Oncology 2016; Spencer at al, Haematologica 2018; Stewart AK et al, N Engl J Med 2015; Dimopoulos MA et al, Haematologica 2018; Dimopoulos MA et al, Br J Haematol 2017; Moreau P et al, NEJM 2016

POLLUX: PFS at median follow up of 44.3 months



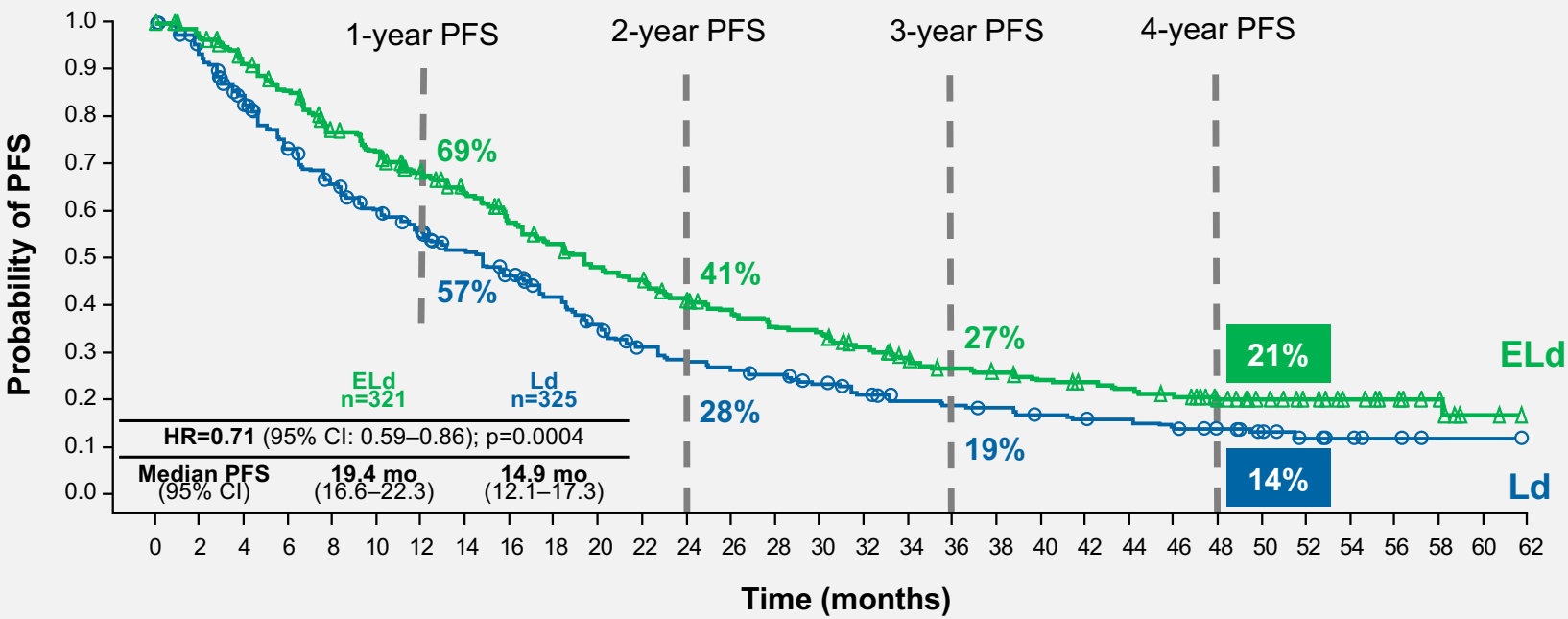
mPFS: **44.5 months** vs 17.5 months (HR:0.44; p < 0.0001)
56% reduction in the risk of progression or death in patients receiving D-Rd



mPFS : **NR** vs 19.6 months
@42 months: 57% vs 28% (HR:0.42; p < 0.0001)
58% reduction in the risk of progression or death in patients receiving D-Rd

Bahlis et al. Poster Presentation 1996 ASH 2018

ELOQUENT-2 trial: Elo-Rd vs Rd

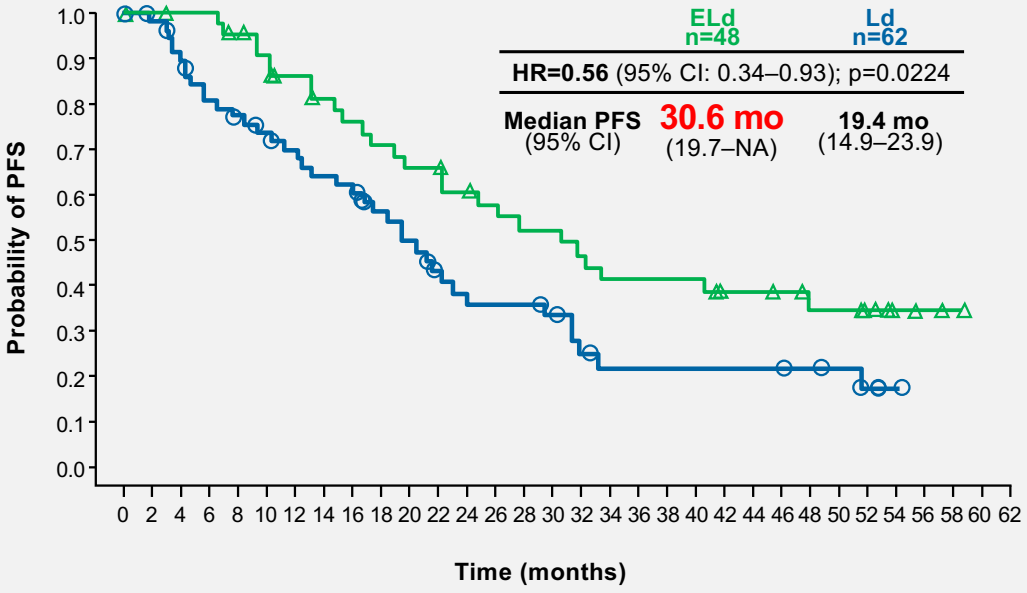


- At 4 years, ELOQUENT-2 has the longest follow-up for PFS in RRMM
- 29% reduction in the risk of progression or death (sustained over time)
- 50% relative improvement in the PFS rate at 4 years (21% vs 14%) in favor of ELd

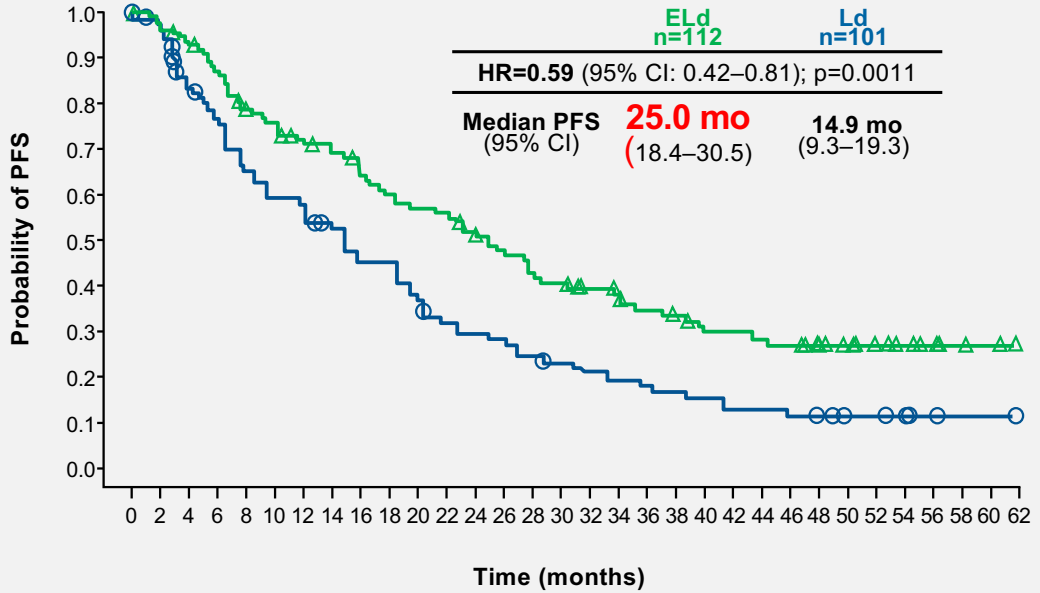
Progression-Free Survival – Median Time Since Diagnosis (3.5 years) and Prior Lines of Therapy

≥Median time from diagnosis

1 prior line of therapy



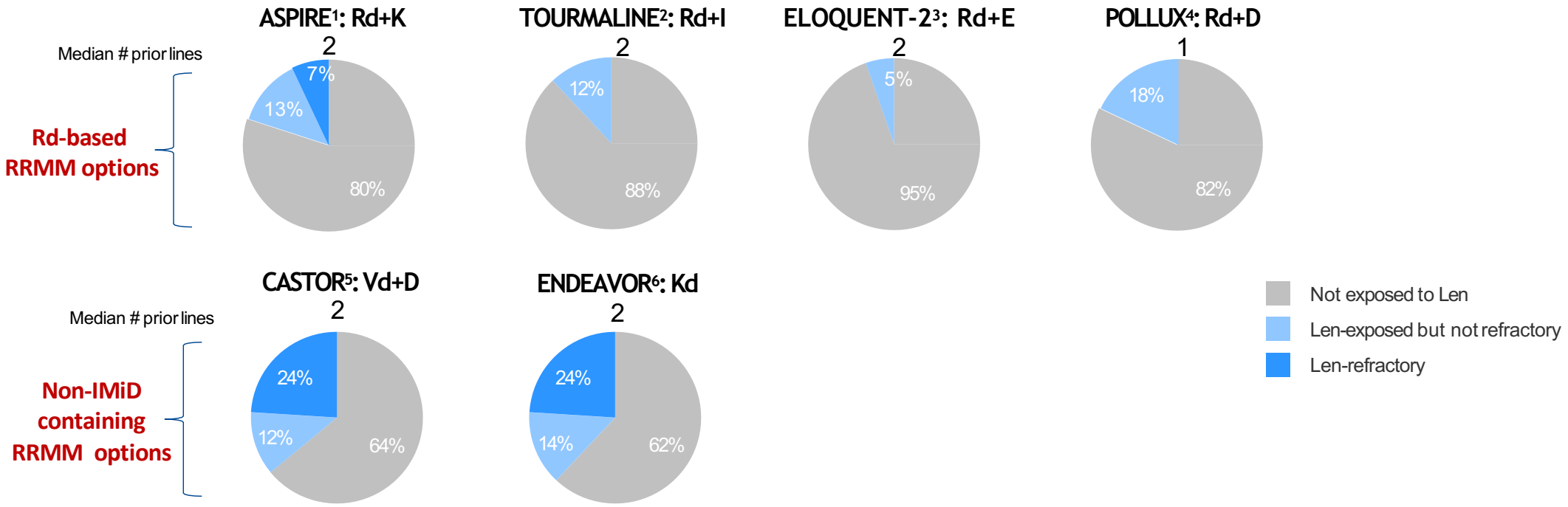
>1 prior line of therapy



- Greatest benefit in patients with ≥3.5 years (median time) since diagnosis and 1 prior line of therapy
- 44% reduction in the risk of progression or death

Len-refractory patients are growing and have been underrepresented in previous clinical trials

% Len-exposed, Len-refractory and non-Len exposed patients in early-RRMM* combination trials



*Median 1-2 prior lines. † Includes Kd patients in both study arms.
D, daratumumab; d, dexamethasone; E, elotuzumab; I, isatuximab; IMiD, immunomodulatory drug; K, carfilzomib; P, pomalidomide; R/Len, lenalidomide; RRMM, relapsed/refractory multiple myeloma; V, bortezomib.
1. Siegel D et al. *JClin Oncol*. 2018;36:728-37; 2. Moreau P et al. *N Engl JMed.* 2016;374:1621-1634; 3. Lonial S et al. *N Engl JMed*. 2015;373:621-631; 4. Dimopoulos M et al. *N Engl JMed* 2016;375:1319-1331;
5 Palumbo A et al. *N Engl JMed*. 2016;375:754-766. 6. Dimopoulos MA et al. *Lancet Oncol*. 2017; 18:1327-37;

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(VRd)

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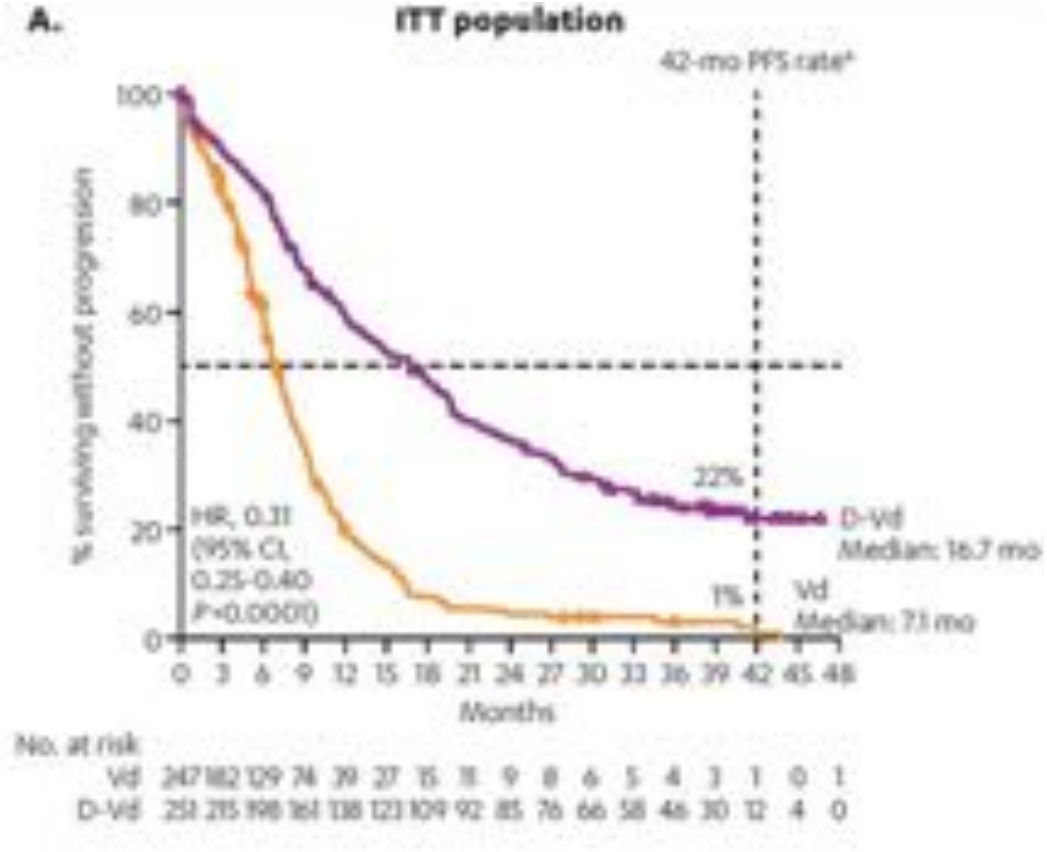
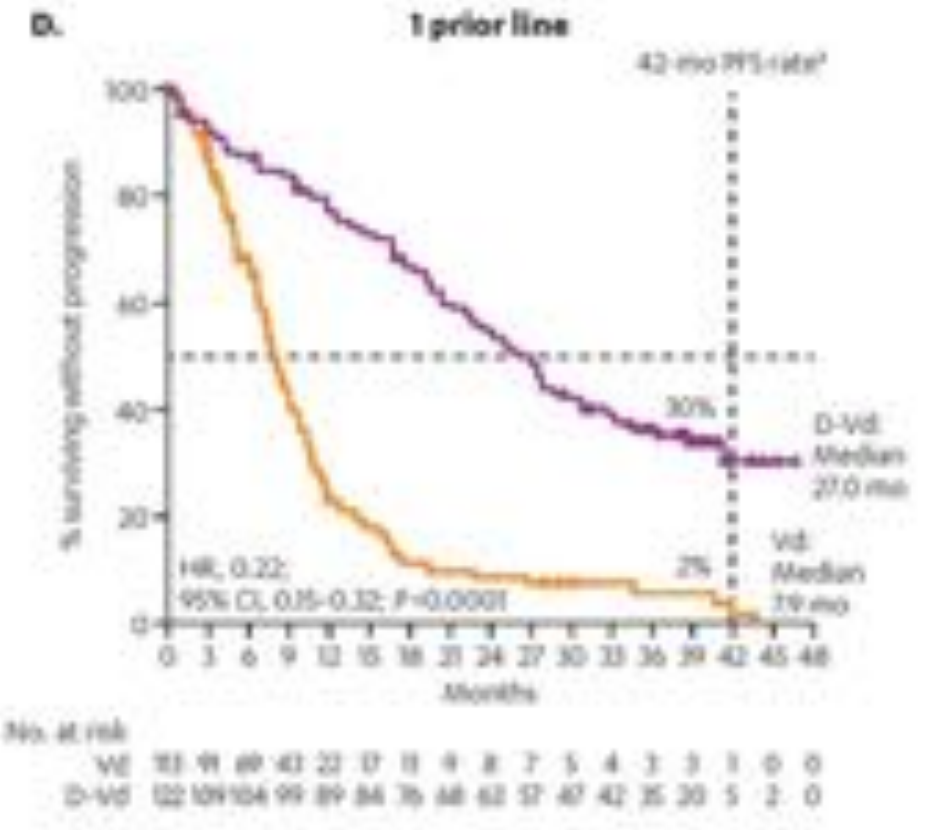
CASTOR: PFS at median follow up 40 months



mPFS: **16.7** months vs 7.1 months (HR: 0.31; p<0.0001)

69% reduction in the risk of progression or death in patients receiving D-Vd



mPFS: **27** mesi vs 7.9 mesi (HR: 0.22; p<0.0001)

78% reduction in the risk of progression or death in patients receiving D-Vd

Mateos et al. Poster Presentation 3270 ASH 2018

Patients refractory to frontline lenalidomide

	Endeavor[1]		Castor[2]	
	Kd	Vd	DaraVd	Vd
Len-refractory to any prior line, n=	113	122	60	81
Median PFS, months	**8.6**	**6.6**	**7.8**	**4.9**
Len-refractory 1 prior line, n=	UK	UK	UK	UK
Median PFS, months	UK	UK	UK	UK

1. Moreau P et al. Leukemia 2017; 31(1):115-122 2. Usmani SZ et al. ASH 2018;132:3288

CLINICAL TRIALS AND OBSERVATIONS

Comment on Mikhael et al, page 123

Facing lenalidomide-refractory myeloma

Michele Cavo | Bologna University School of Medicine

In this issue of *Blood*, Mikhael et al report the results of a phase 1b study of isatuximab combined with standard-dose pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM) who had received ≥2 prior lines of treatment that included lenalidomide and a proteasome inhibitor (PI).[1]

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Treatment of relapse: the changing landscape….

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 refractoriness to lenalidomide

- Poma-dex + Bort (OPTIMISMM)
- Poma-dex + Cyclo
- Poma-dex + Dara (APOLLO)
- Poma-dex + Isa (ICARIA)
- Poma-dex + Elo (ELOQUENT-3)
- Poma-dex + K

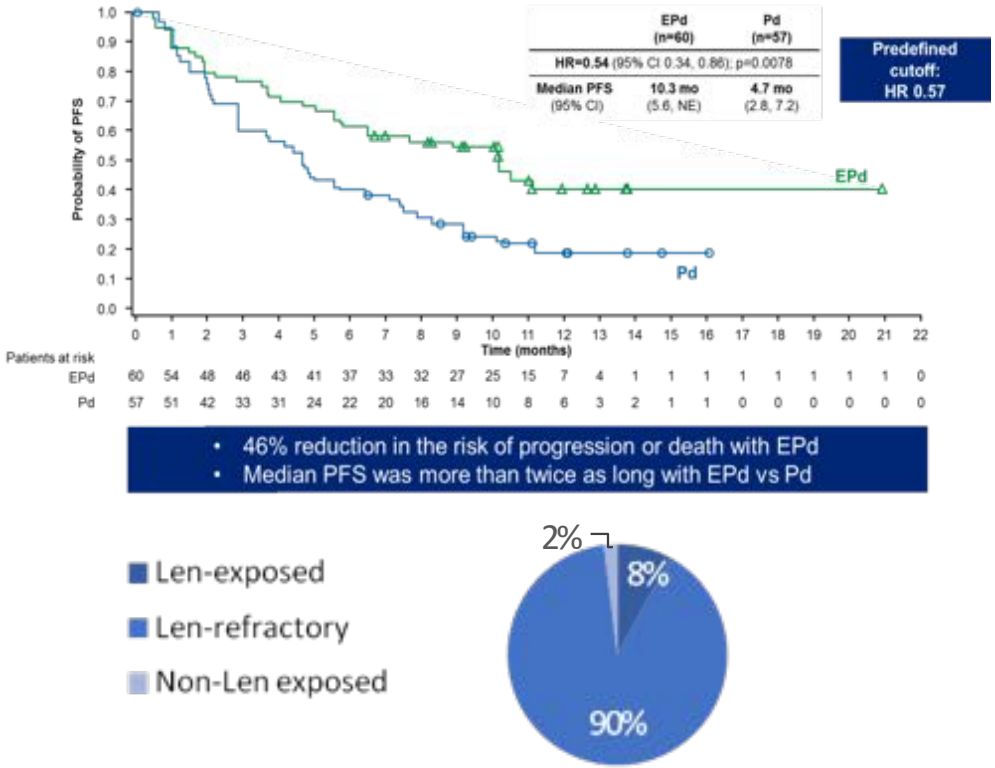
- Kd + Dara (CANDOR)
- Kd + Isatuximab (IKEMA)
- Kd + Cyclo
- Kd + Venetoclax

- Vd + Selinexor
- Vd + Venetoclax

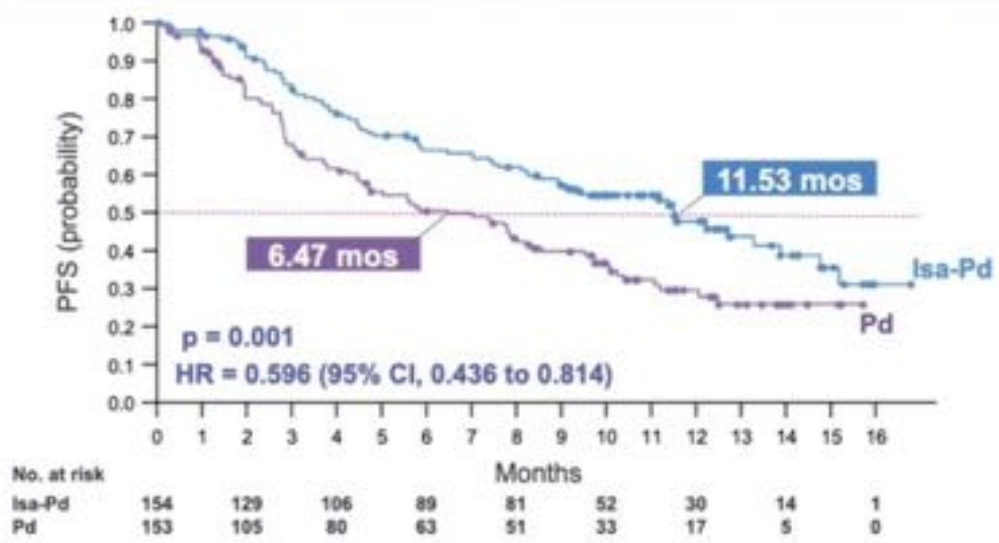
Moreau P et al. Ann Oncol 2017;28(suppl_4):iv52-iv61
Facon T EHA 2019

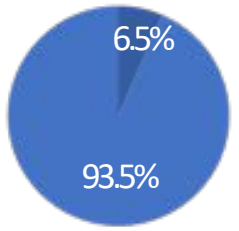
POM-DEX-based triplets (+ELOTUZUMAB or ISATUXIMAB) in LEN-refractoy RRMM patients with median 3 prior therapy

Phase 2 ELOQUENT-3 Trial: EloPd vs Pd



Phase 3 ICARIA Trial: IsaPd vs Pd





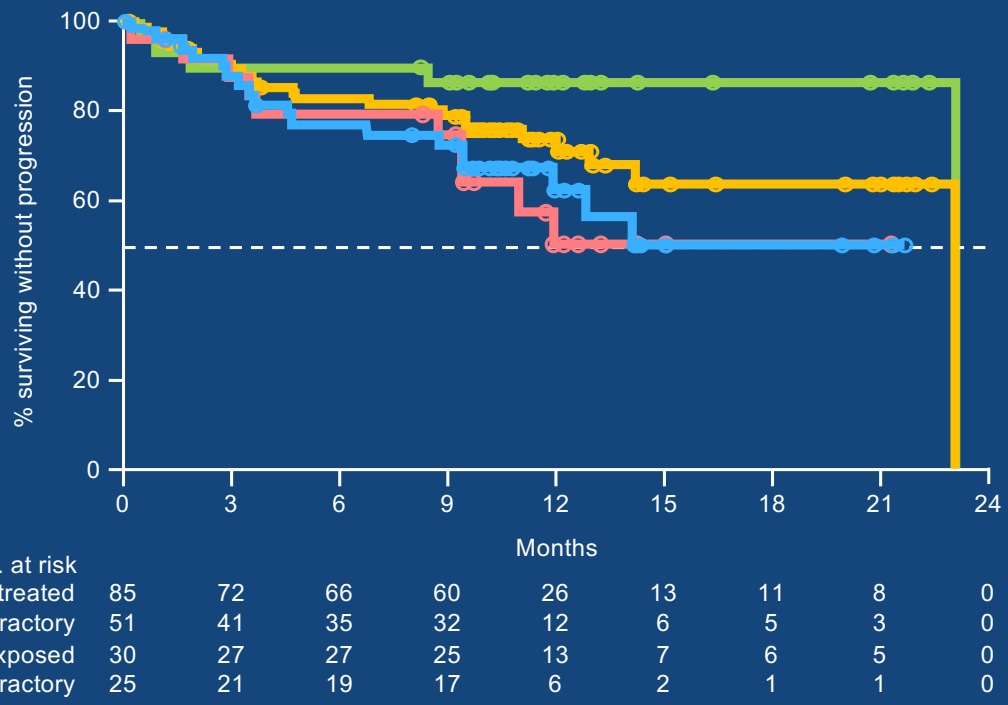
Dimopoulos A et al. NEJM 2018;379(19):1811-1822

Richardson P et al. Presented at EHA 2019 (Abstract S824), oral presentation

Dara-Kd: PFS Across Subgroups

- Median follow-up: 12.0 months

	Median PFS, mo	12-month PFS, %
All-treated	NE	71%
Len-exposed but not refractory	NE	87%
Len-refractory	14.1 (95% CI, 12.0-NE)	62%
PI/IMiD-refractory	NE (95% CI, 9.4-NE)	51%

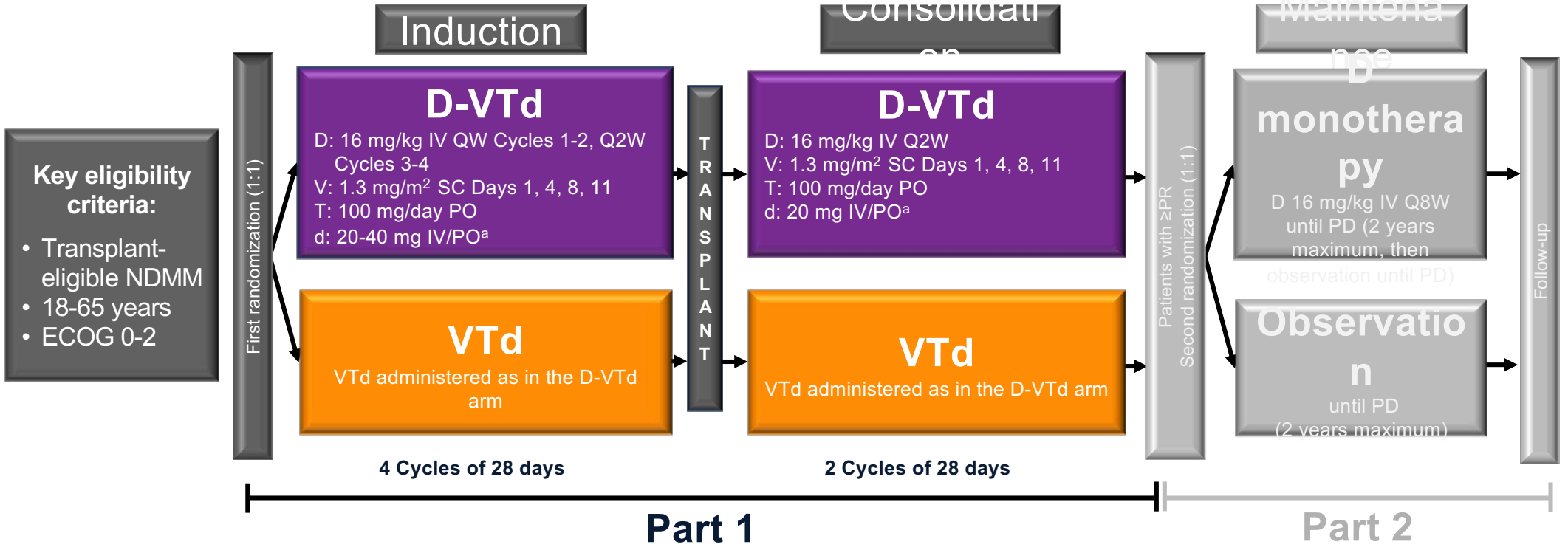


Encouraging PFS observed in lenalidomide- and PI/IMiD-refractory patients

NE, not estimable.

Phase 3 *CASSIOPEIA* Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), [illegible] sites from the 9/2015 to 8/2017

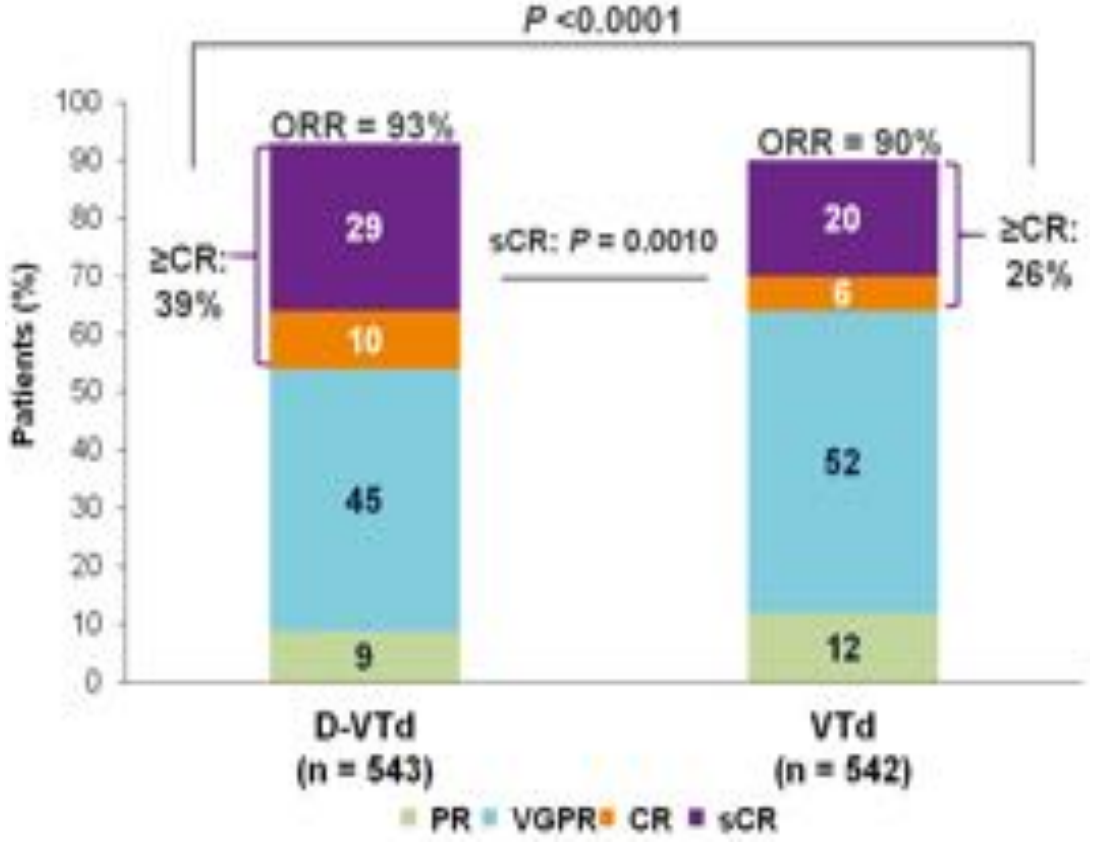


D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease; sCR, stringent complete response; PFS, progression-free survival; MRD, minimal residual disease; CR, complete response; OS, overall survival.
[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

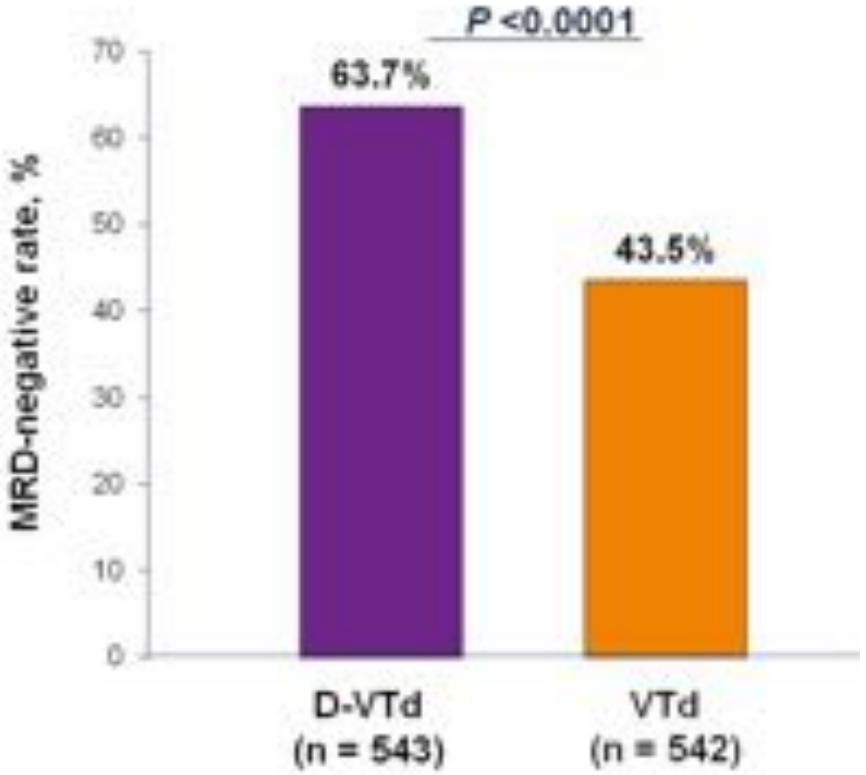
Moreau P, et al. Lancet. 2019; S0140-6736(19)31240-1.

CASSIOPEIA study: depth of response

Post-consolidation rates of response



MRD (Flow Cytometry; 10^{-5})

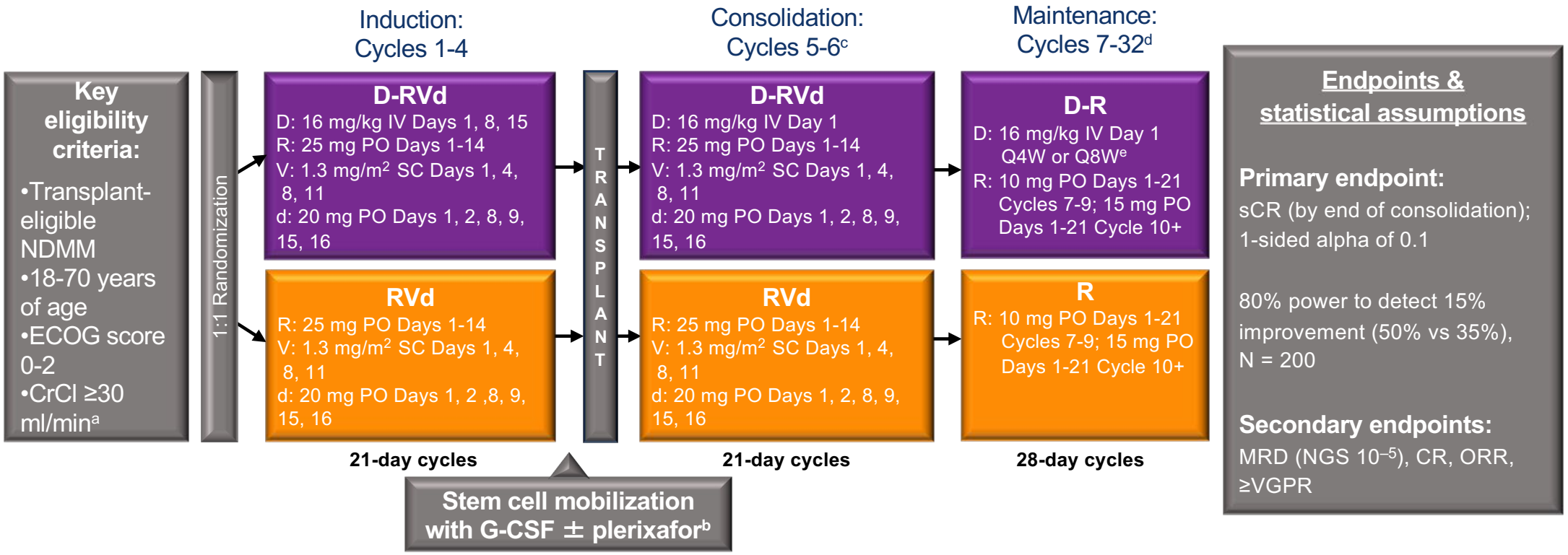


D-VTd improved the rate of sCR (primary study endpoint), ≥CR and MRD negativity

Moreau P. et al, Lancet. 2019; S0140-6736(19)31240-1.

GRIFFIN (NCT02874742): Dara-VRD vs VRD

- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018



D-RVd, daratumumab-lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; US, United States; ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab-lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; CR, complete response; ORR, overall response rate; VGPR, very good partial response.

[a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60-100 days post transplant. [d]Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).

Post-Consolidation MRD Negativity

MRD-Negative Status (10^{-5}),[a] n (%)	D-RVd	RVd	Odds Ratio (95% CI)	*P* value[b]
In ITT population				
MRD negative regardless of response	46/104 (**44.2**)	15/103 (**14.6**)	4.70 (2.38-9.28)	<0.0001
MRD negative with CR or better	30/104 (**28.8**)	10/103 (**9.7**)	3.73 (1.71-8.16)	0.0007
In patients achieving CR or better	30/51 (**58.8**)	10/41 (**24.4**)	4.65 (1.76-12.28)	0.0014
In patients who received ASCT	45/94 (**47.9**)	14/78 (**17.9**)	4.31 (2.10-8.85)	<0.0001

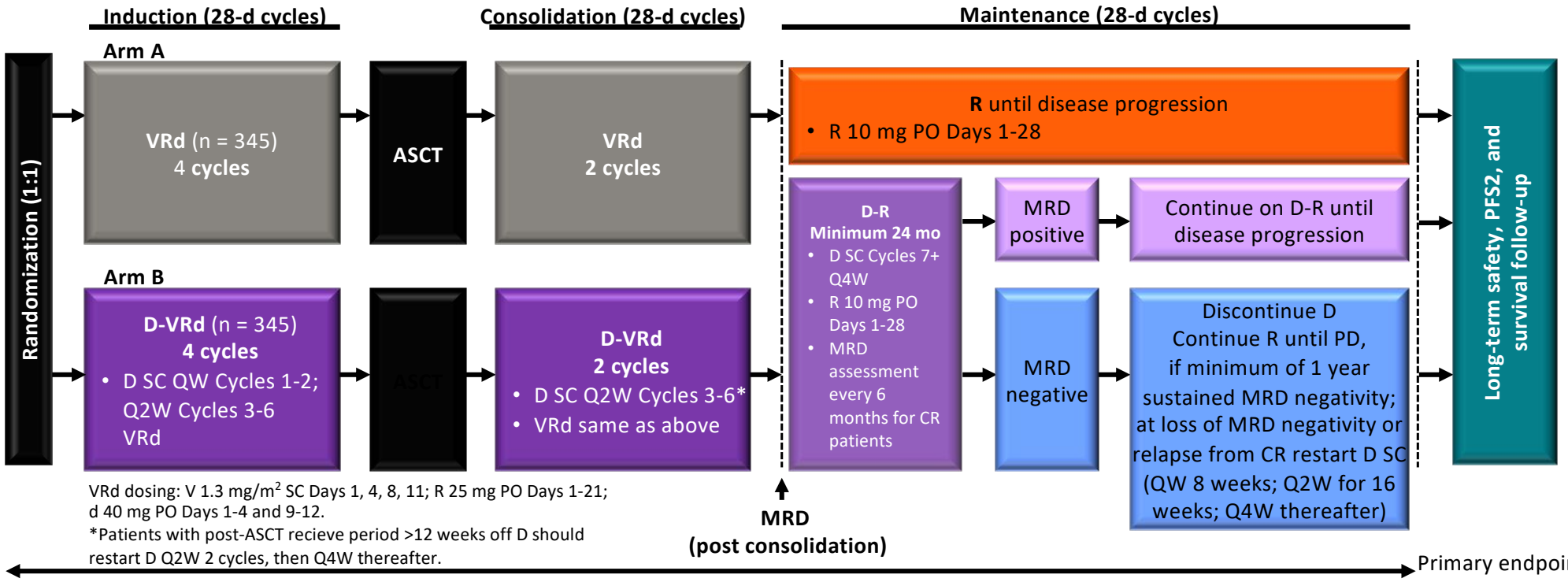
D-RVd improved MRD-negativity (10^{-5}) rates at the end of consolidation

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on assessment of bone marrow aspirates by next-generation sequencing in accordance with International Myeloma Working Group criteria. MRD assessments occurred in patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken (D-RVd, n = 71; RVd, n = 55). Patients with a missing or inconclusive assessment were considered MRD positive. [b]*P* values were calculated from the Fisher's exact test.

Daratumumab-VRd vs VRd

PERSEUS phase 3 trial: Design

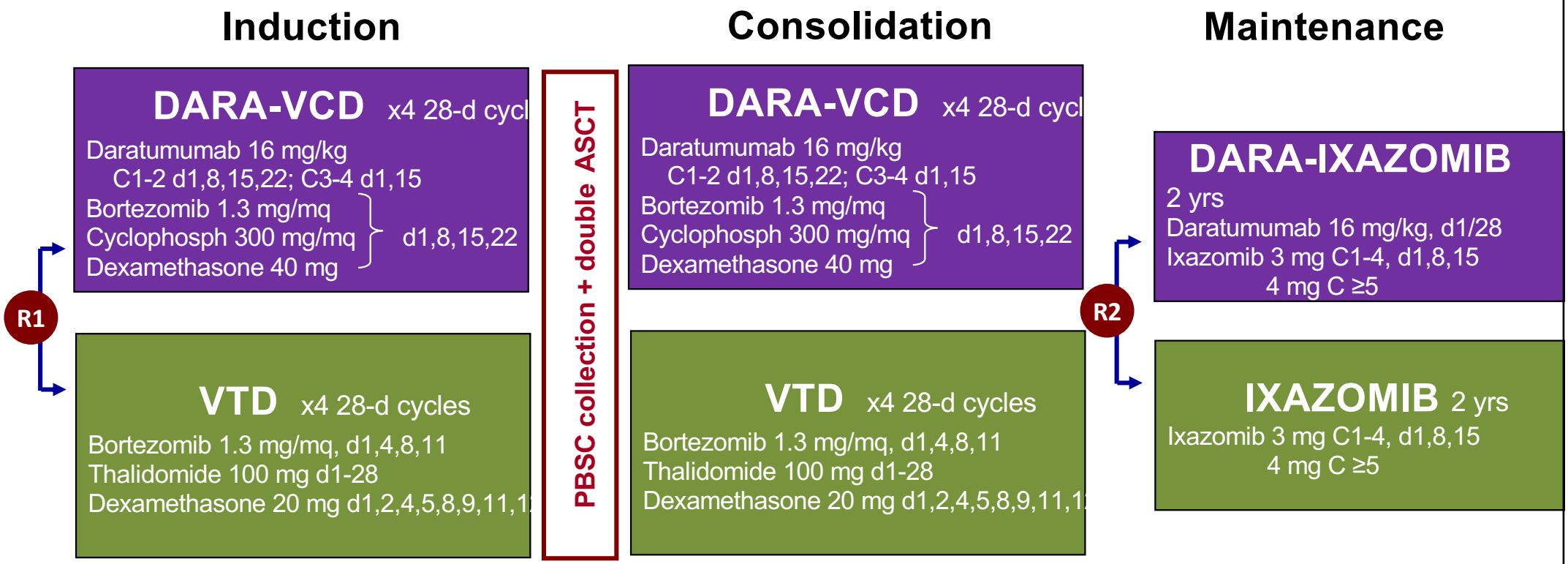
- Collaborative study with European Myeloma Network (EMN)
- Phase 3 study of DARA in combination with VRd versus VRd for newly diagnosed transplant-eligible patients; N ≈ 690



DSC, daratumumab subcutaneous; RVd, lenalidomide/bortezomib/dexamethasone; ASCT, autologous stem cell transplant; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; MRD, minimal residual disease; PO, by mouth; PFS2, progression-free survival on next line of therapy.
Protocol EMN17/54767414MMY3014.

www.clinicaltrials.gov identifier: NCT03710603, accessed March 2019

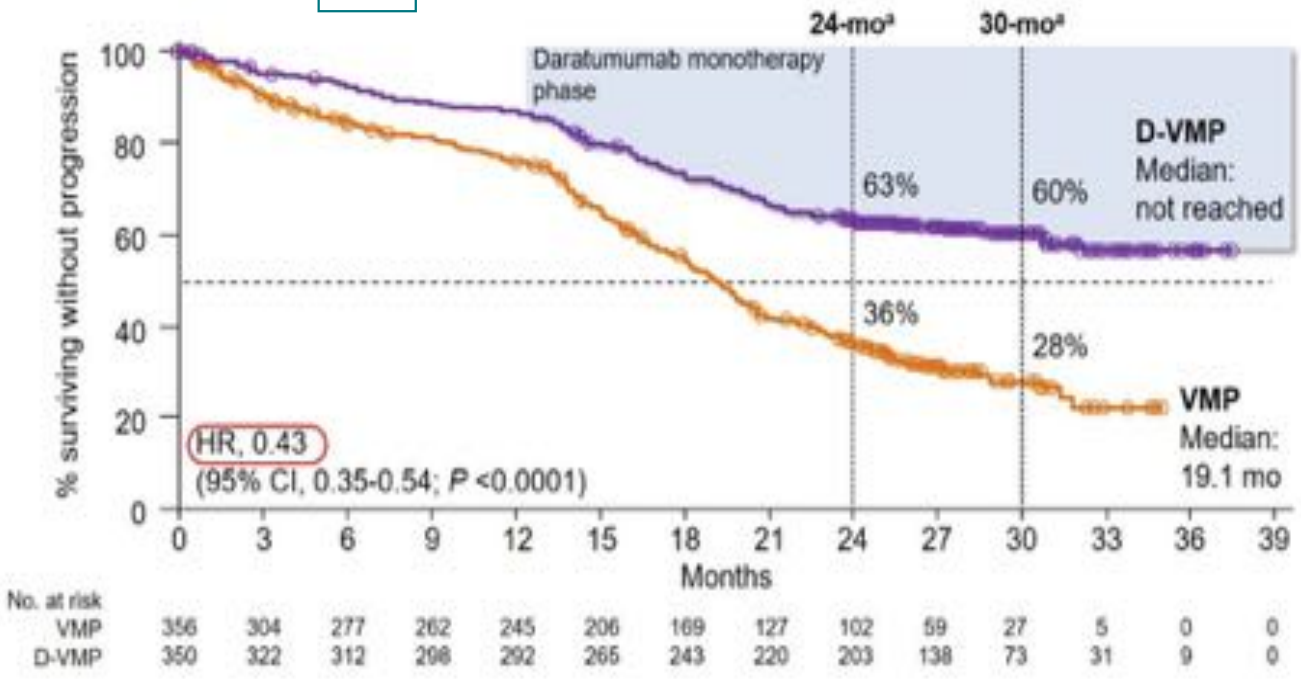
EMN18 phase III study design



Daratumumab + VMP vs VMP: ALCYONE study

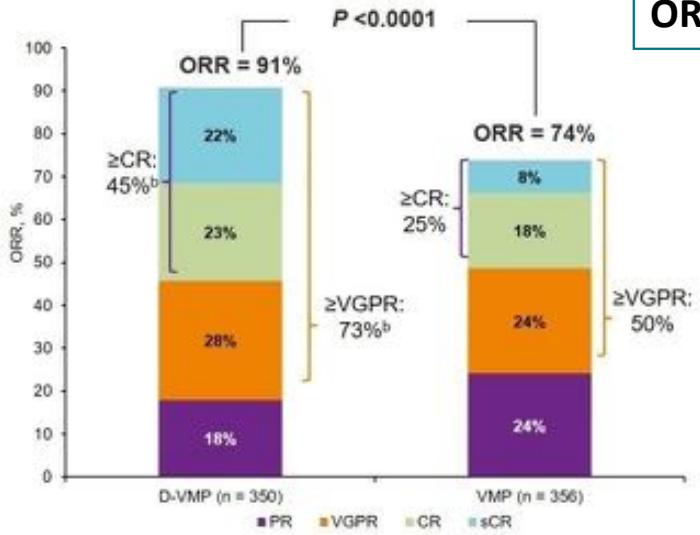
PFS

Median follow-up: 27.8 (0-39.2) months

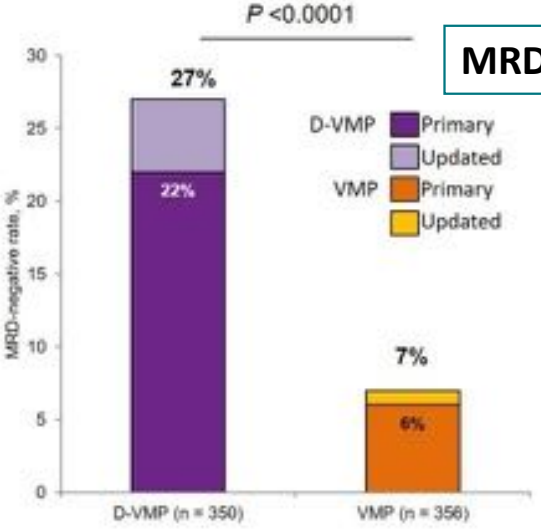


- 57% reduction in the risk of progression or death in patients receiving D-VMP vs VMP
- Significantly higher ORR, ≥VGPR rate, and ≥CR rate with D-VMP; >2-fold increase in sCR rate with D-VMP
- Deepening MRD-negative rate with longer follow-up for D-VMP

ORR



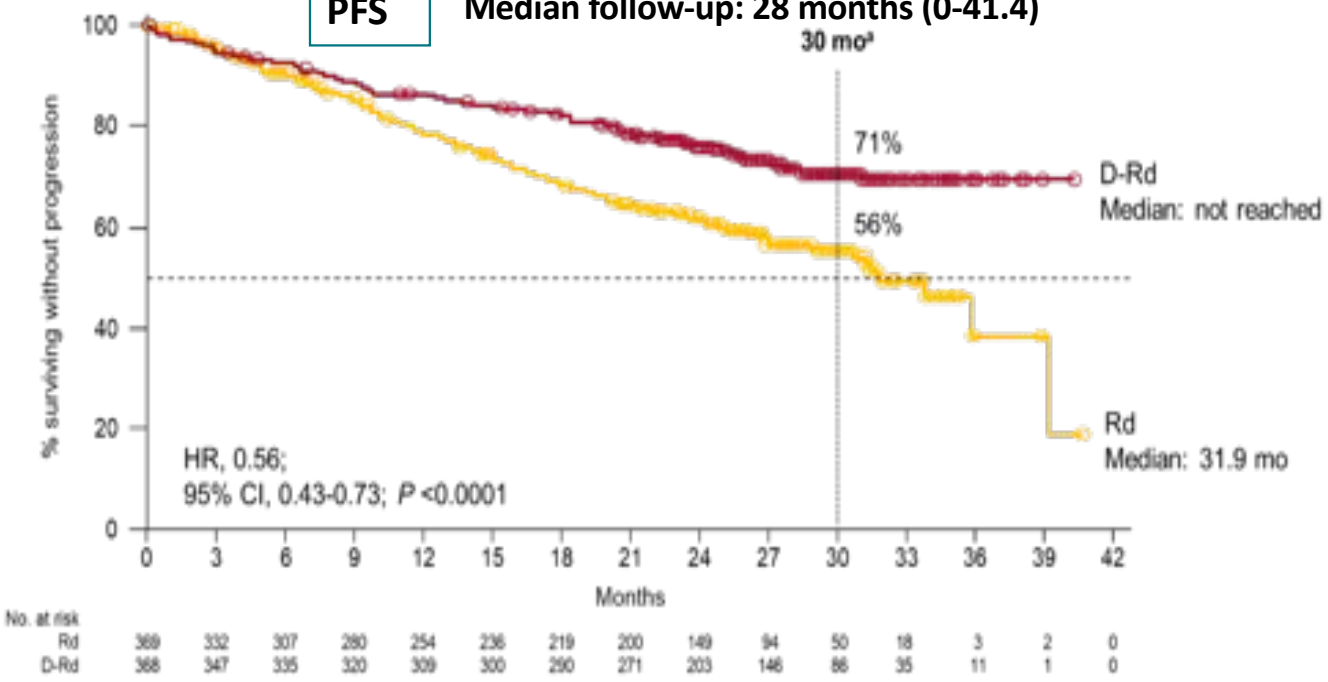
MRD (NGS 10^{-5})



Dimopoulos et al., ASH 2018; abstract 156

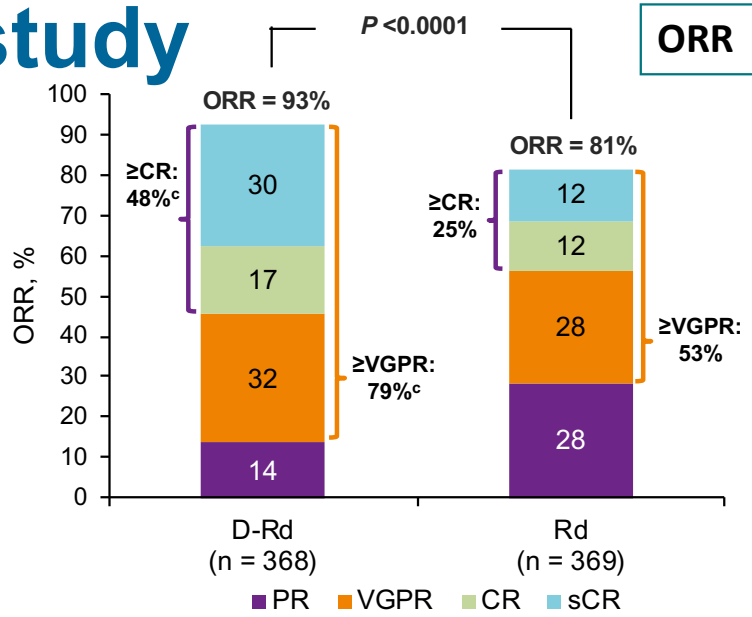
Daratumumab + Rd vs Rd: MAIA study

PFS **Median follow-up: 28 months (0-41.4)**



- 44% reduction in the risk of progression or death in patients receiving D-Rd vs Rd
- Significantly higher ORR, ≥CR rate, ≥VGPR rate, and MRD-negative rate with D-Rd than Rd
- Safety profile is consistent with findings from POLLUX for D-Rd and the population evaluated in ALCYONE

ORR



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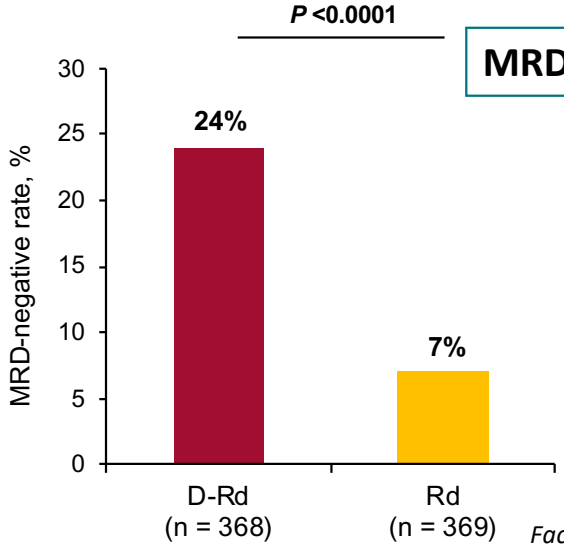
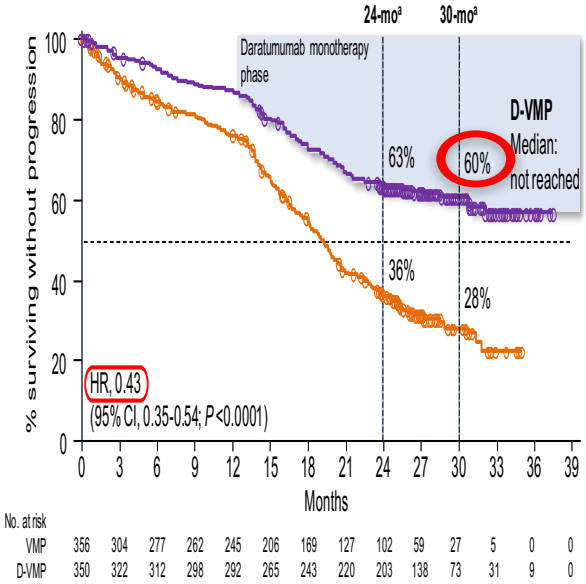
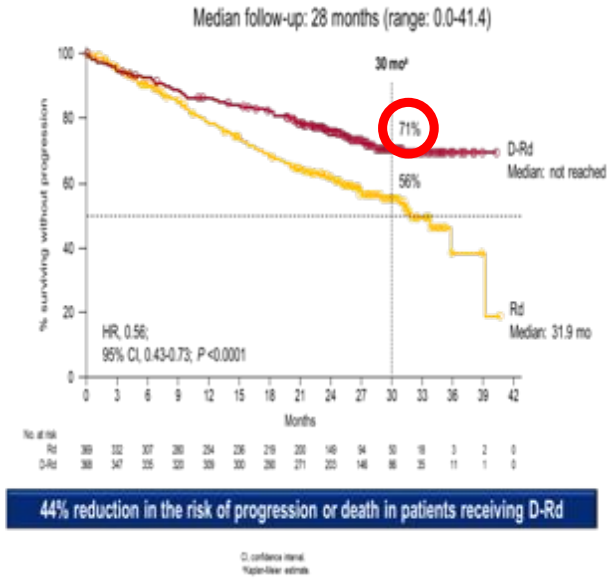


Facon et al., ASH 2018

Three new SOC for NDMM patients non-eligible for ASCT

	Dara VMP	Dara Rd	VRd
ORR/CR	91%/45%	93%/48%	81%/16%
MRD-ve	27%	24%	NA



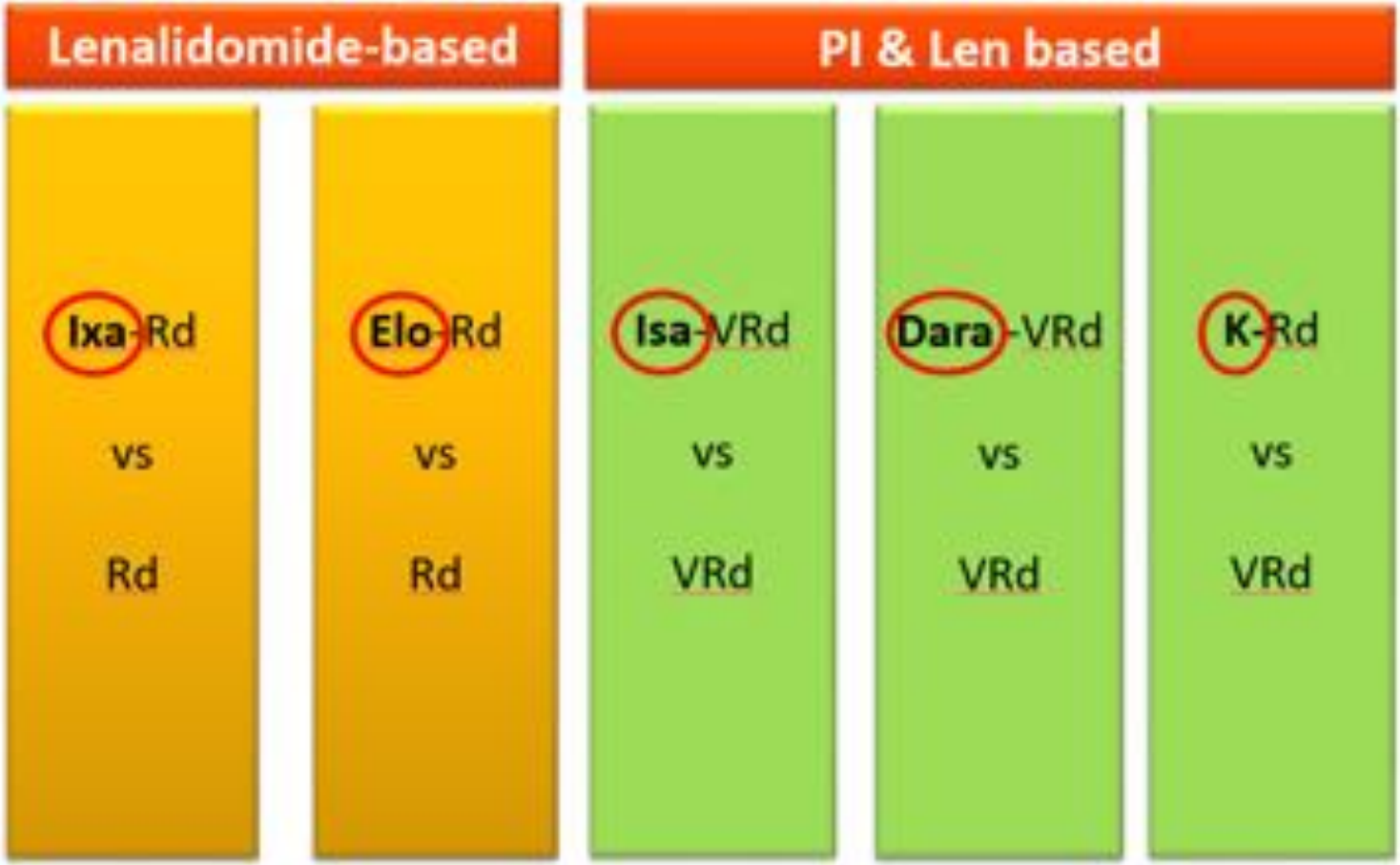


Median PFS (months)

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

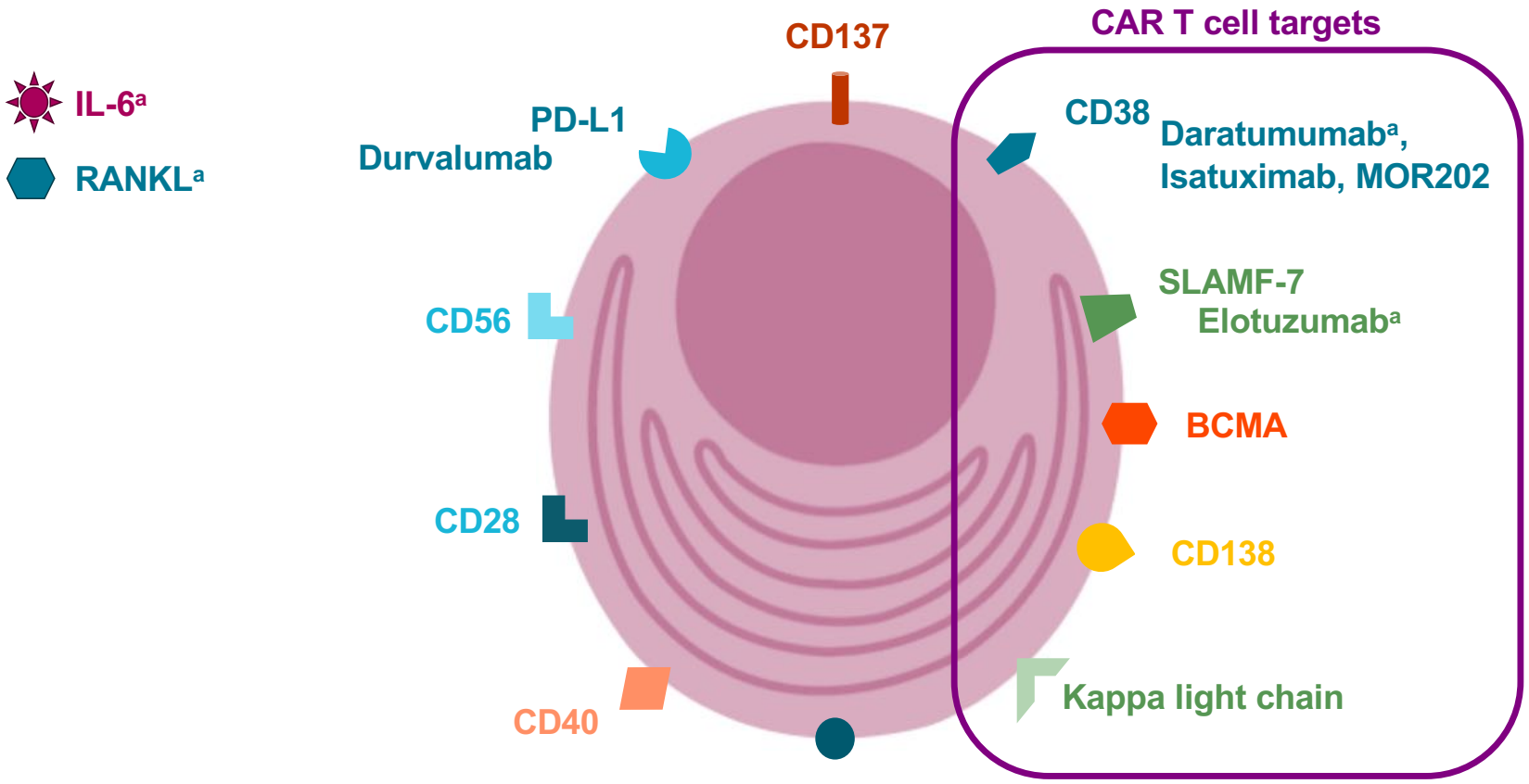
- VRd as SWOG will not be used but as VRd lite (few pts)
- DRd is better than DVMP in PFS but similar ORR, CR rate and MRD-ve
- DVMP might be optimized with V extended in combination with Dara ?
- High-risk CA pts remain a challenge

Future first line therapy in non-transplant eligible patients



clinicaltrials.gov identifiers: NCT02195479; NCT02252172; NCT01335399; NCT01850524; NCT03319667; NCT01863550

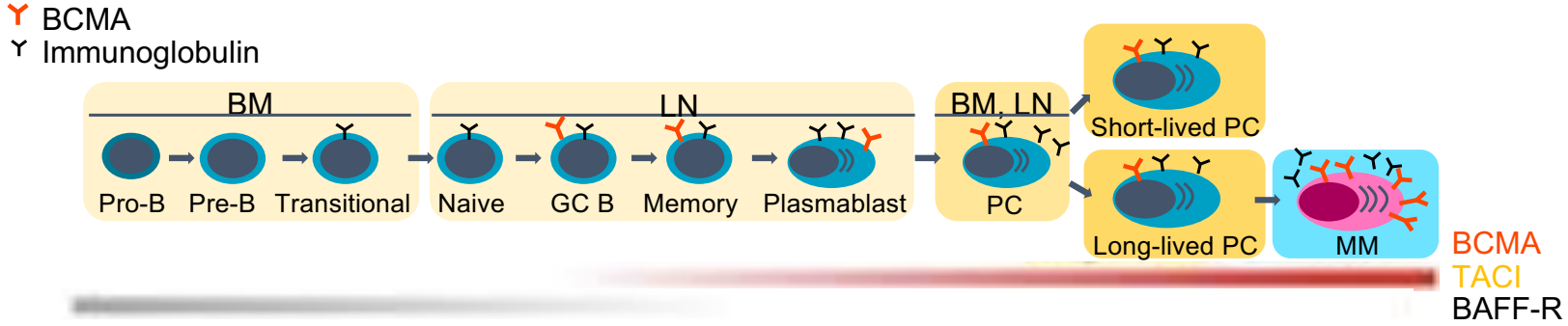
Surface antigens on clonal plasma cells

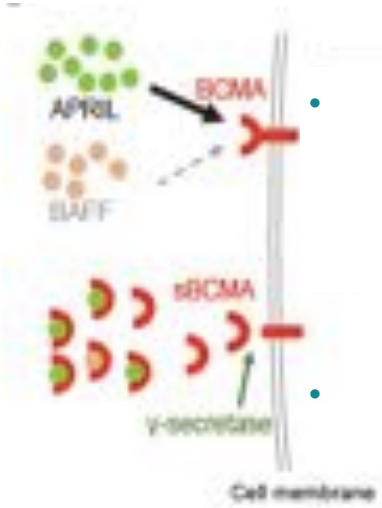


[a] Approved by the FDA and EMA.
BCMA, B-cell maturation antigen; IL-6, interleukin-6; PD-L1, programmed cell death-ligand; RANKL, receptor activator of nuclear factor kappa-B ligand.

Bhatnagar V, et al. Oncologist. 2017;22:1347-53. Gormley NJ, et al. Clin Cancer Res. 2017;23:6759-63. Jelinek T, et al. Front Immunol. 2018;9:2431. Moreno L, et al. Clin Cancer Res. 2019;25:3176-87. Raab MS, et al. Blood. 2016;128:1152. Rawstron AC, et al. Haematologica. 2008;93:431-8.

BCMA: an ideal target for immunotherapy





- BCMA is an antigen expressed specifically on PCs and myeloma cells
  - higher expression in myeloma cells than normal PCs
  - key role in B-cell maturation and differentiation
  - promotes myeloma cell growth, chemoresistance, and immunosuppression in the BM microenvironment
- Expression of BCMA increases as the disease progresses from MGUS to advanced myeloma

APRIL, a proliferation-inducing ligand; BAFF-R, B-cell activating factor receptor; GC, germinal centre; LN, lymph node; MGUS, monoclonal gammopathy of unknown significance; sBCMA, soluble BCMA; TACI, transmembrane activator and CAML interactor.

Cho SF, et al. Front Immunol. 2018;9:1821. Moreaux J, et al. Blood. 2004;103:3148-57. Sanchez E, et al. Br J Haematol. 2012;158:727-38.

CAR-T therapies targeting BCMA: intense field of clinical research

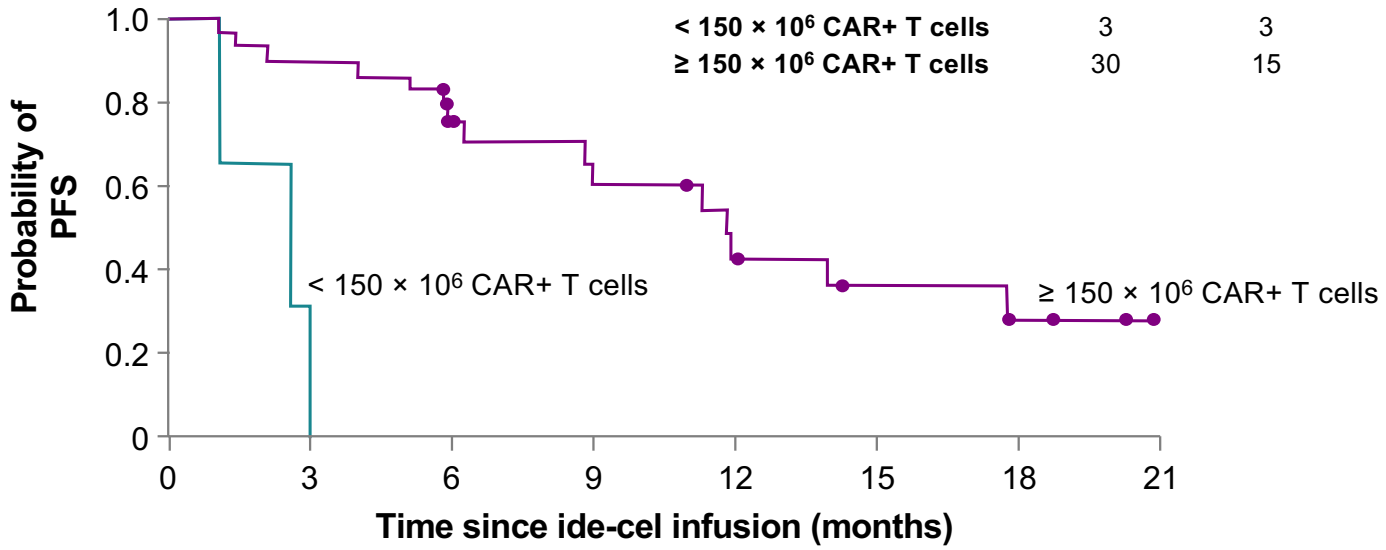
Agent	Target	Clinical Trial ID (Phase)	Recent Clinical Efficacy Data
CAR T Therapies in RRMM			
bb2121	BCMA	NCT02658929 (I)	• n = 43[1] (n = 18 efficacy evaluable patients) • ORR: 94% at ≥150 × 10^6 CAR T cells dose • CR/unconfirmed CR: 56% • mPFS: NR (6-month: 81%; 9-month: 71%)
bb21217	BCMA	NCT03274219 (I)	• n = approximately 50[2] (n = 7 efficacy evaluable patients) • ORR: 86% at 150 × 10^6 CAR T cells dose • ≥CR: 71%
JCARH125	BCMA	NCT03430011 (I/II)	• n = 10[3] (n = 8 efficacy evaluable) • ≥CR: 67% (2/3 confirmed responses)
KITE-585	BCMA	NCT03318861 (I)	NA
LCAR-B38M	BCMA (biepitope)	NCT03090659 (I)	• n = 57[4] • ORR: 88% • ≥CR: 74% • mPFS: 15 months • mOS: NR
MCARH171	BCMA	NA (I)	• n = 11[5] • ORR: 64%
P-BCMA-101	BCMA	NCT03288493 (I)	• n = 12[6] (n = 6 efficacy evaluable patients) • ORR: 83% • ≥CR: 17%

Ghobrial I et al. Clinical Lymphoma, Myeloma & Leukemia 2019

Ide-cel CRB-401 phase 1 trial: PFS

PFS at < 150 × 10^6 and ≥ 150 × 10^6 CAR T cells

	No. of patients	No. of events	Median PFS (95% CI), months
< 150 × 10^6 CAR+ T cells	3	3	2.6 (1.1–2.9)
≥ 150 × 10^6 CAR+ T cells	30	15	11.8 (6.2–NE)



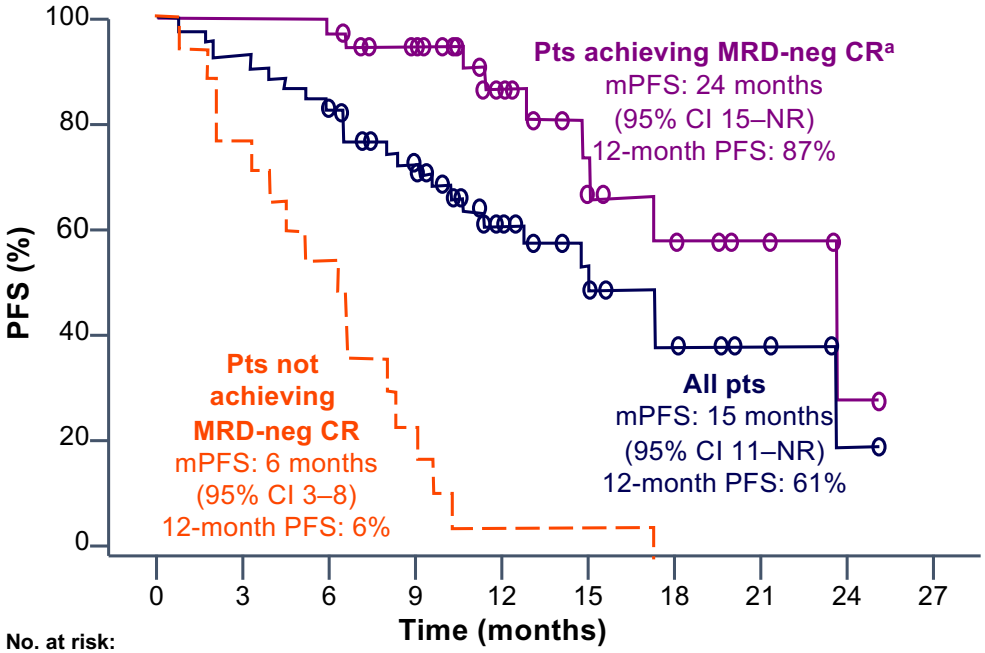
No. at risk

< 150 × 10^6 CAR+ T cells	3	3	2	0																	
≥ 150 × 10^6 CAR+ T cells	30	30	28	27	26	26	17	14	14	12	12	11	8	7	6	5	5	5	3	2	2	0

Raje N, et al. N Engl Med. 2019;380:1726-37.

LCAR-B38M: Legend Biotech phase 1 trial - updated single-centre experience (LEGEND 2)

ORR = 88% 74% CR and 68% MRD-neg CR



No. at risk:										
All pts:	57	53	48	37	21	11	7	4	1	0
Pts achieving MRD-neg CR:	39	39	38	33	20	10	7	4	1	0
Pts not achieving MRD-neg CR:	18	14	10	4	1	1	0	0	0	0

- **CAR T cells**: 0.07–2.1 × 10^6
  Median dose: 0.5 × 10^6 cells/kg
- **Split infusion:** Day 1 20%, Day 3 30%, Day 7 50%
- **Conditioning**: Cyclophosphamide 300 mg/m^2

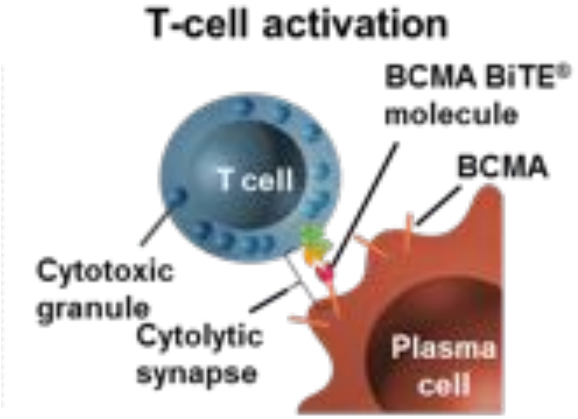
- mDOR = 16 months (95% CI 12–NR)
- mDOR for MRD-neg CR: 22 months (95% CI 14–NR)
- 12-month OS: 75%; 94% for patients achieving MRD-neg CR
- Patients not achieving MRD-neg CR had poor outcome: mPFS 6 months, mOS 8 months, 12-month OS 29%

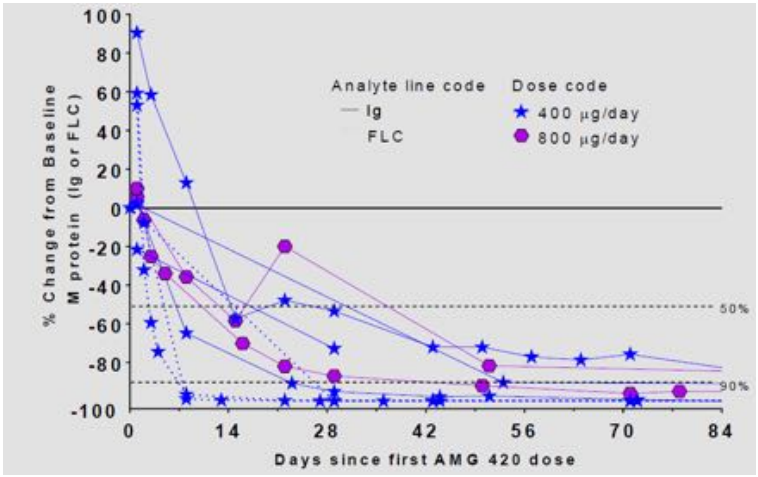
Toxicity profile
- 35% grade 2 CRS; 7% grade 3; no grade 4
- TOZ use: 46%

Zhao WH, et al. Presented at ASH 2018;abstract 955.

New mAbs (bispecific and drug conjugate) targeting BCMA

- **BiTEs: AMG 420,** binds BCMA on tumor cells and plasma cells and CD3 on T cells





Phase 1
dose escalation study

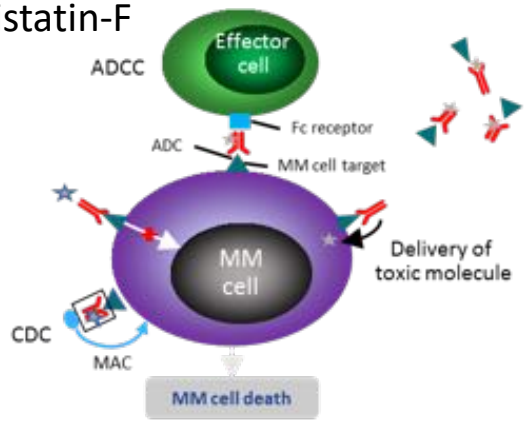
N° of pts: 42

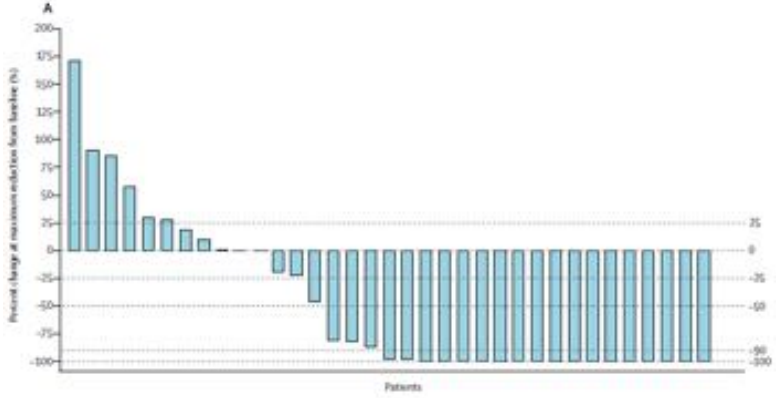
Median prior lines of therapy: 4 (2-13)

At MTD, 7/10 pts responded, 5/7 achieving MRD- CR

Einsele H et al, Presented at IMW 2019; Abstract OAB-025

- **BCMA-antibody drug conjugate: GSK2857916,** humanized, IgG1 anti-BCMA antibody conjugated to monomethyl Auristatin-F





DREAMM-1 Phase 1
dose escalation study

N° of pts: PART 2 35 pts

Prior lines of therapy: 57% pts received ≥ 5 lines

ORR 60%

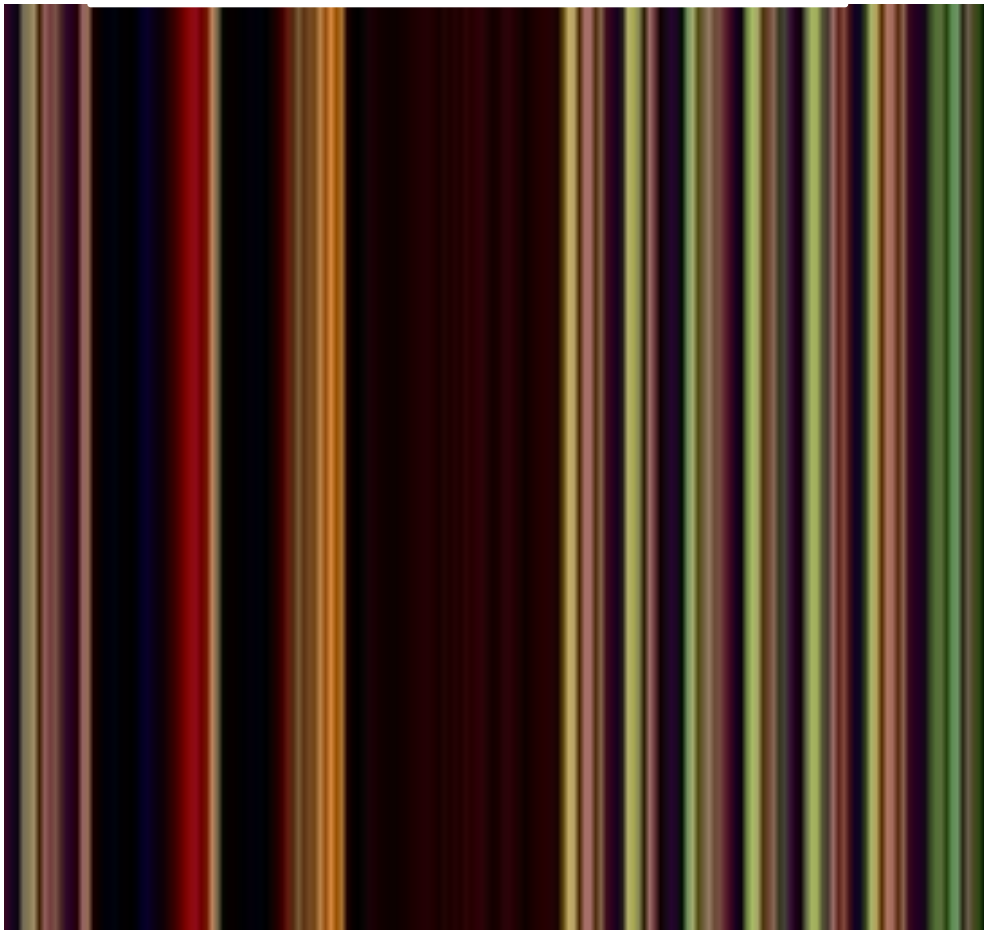
Trudel S et al, Lancet Oncology 2018;19(12):1641-1653

Conclusions

- First line therapy influences treatment options at subsequent relapse
- Switch of class is a paradigm in treatment sequencing for RRMM
- Patients at first relapse will be more frequently len-refractory and dara-refractory, and this is a challenge
- Novel pom-based and carf-based triplets incorporating an anti-CD38 mAb are under evaluation and will be available very soon
- Triplets and quadruplets incorporating an anti-CD38 mAb will become the new SoC for NDMM
- CAR-T and BiTes, actually explored in advanced phases of the disease, will move in earlier phases and in adequately selected patients

Acknowledgements

Seràgnoli Institute of Hematology



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