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Mieloma Recidivo/Refrattario: Strategie terapeutiche e Anticorpi Monoclonali

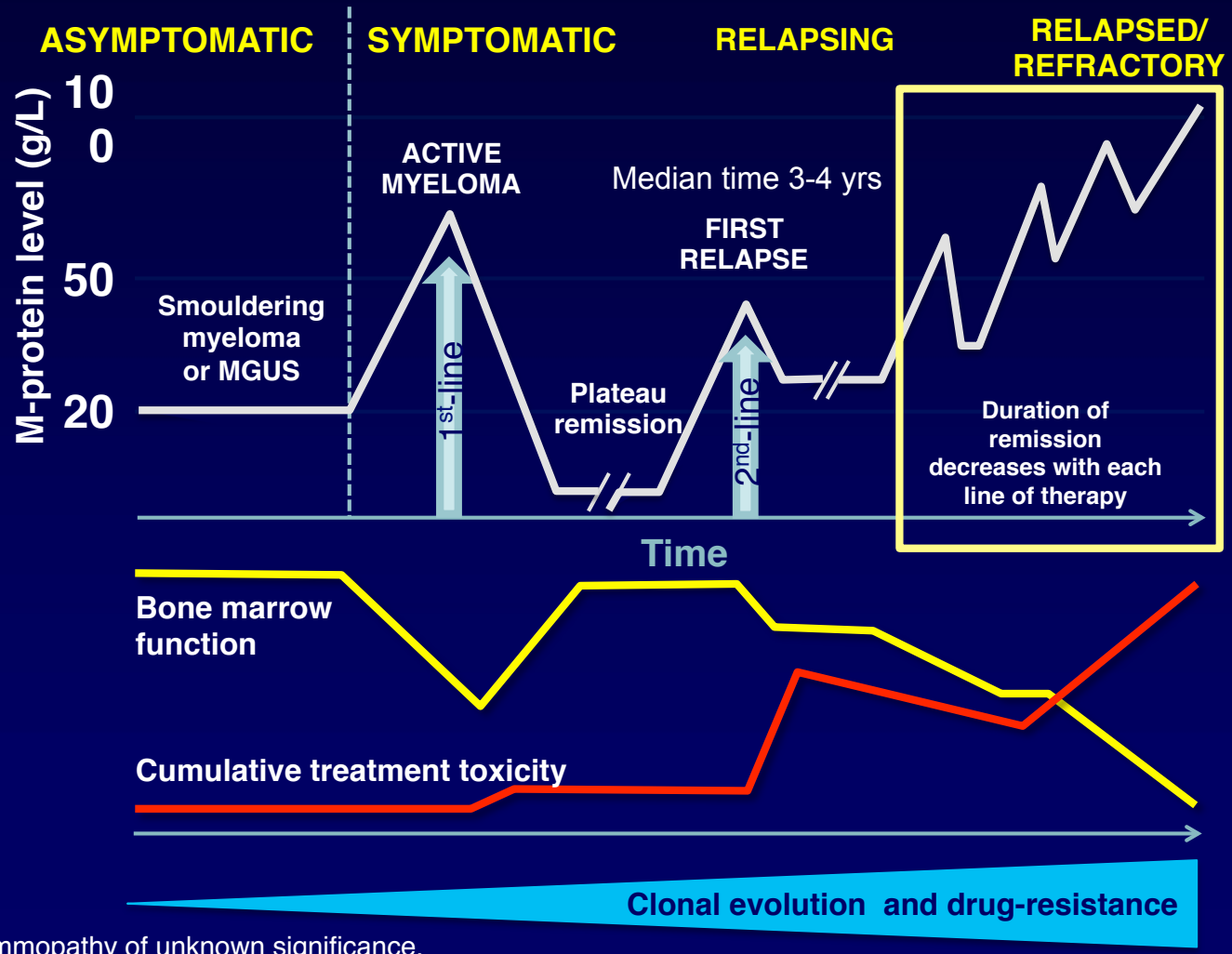
IL MIELOMA MULTIPLO

Nuove prospettive ed aspettative di vita

RESPONSABILI SCIENTIFICI
Felicetto Ferrara
Fabrizio Pane
Ugo Trama

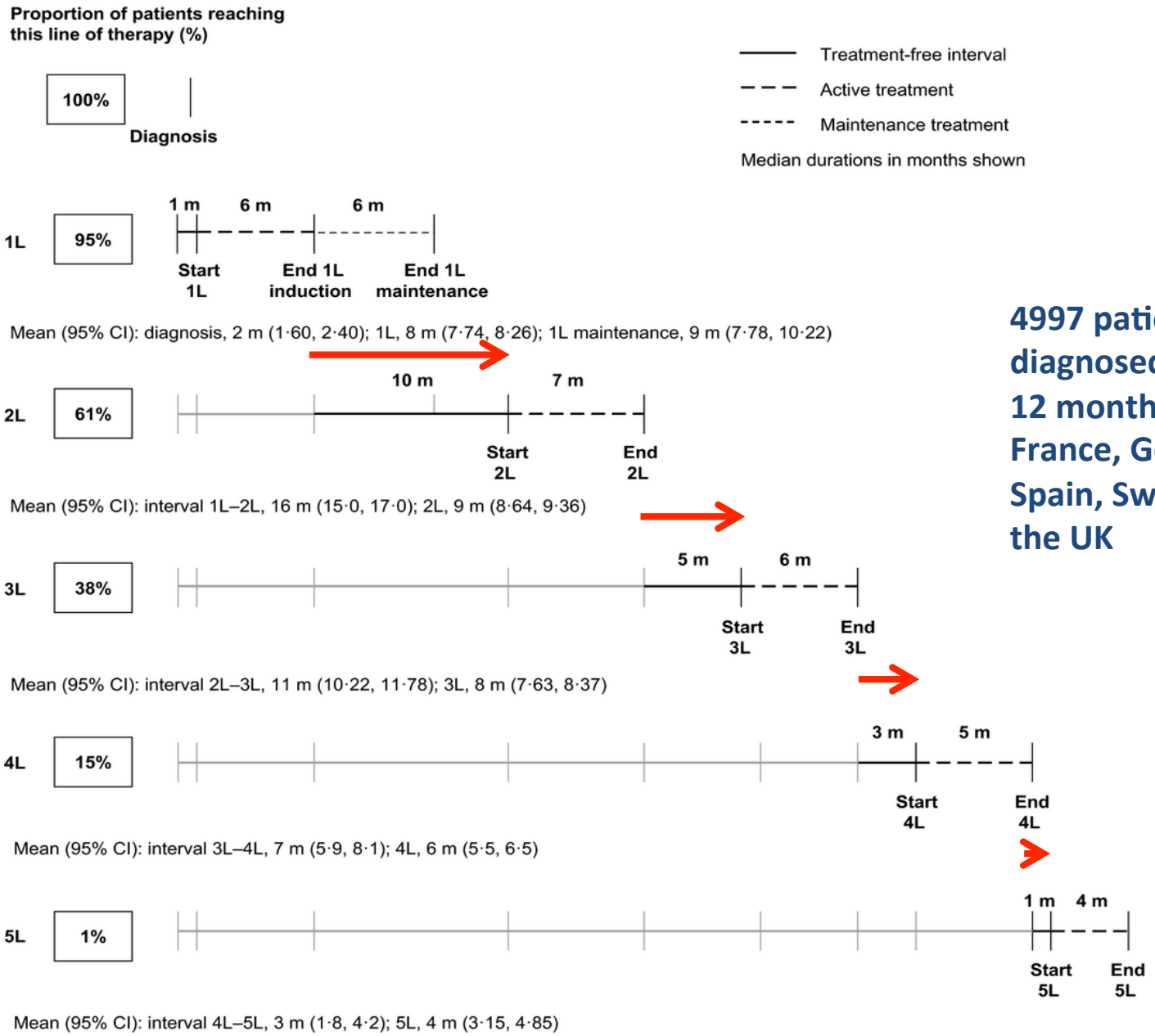
NAPOLI
31 ottobre 2017
HOTEL ROYAL CONTINENTAL

Pattern of remission and relapse defines natural course of multiple myeloma



MGUS, monoclonal gammopathy of unknown significance.
Figure adapted from Durie BGM. Concise review of the disease and treatment options; Edition 2016. http://myeloma.org/pdfs/ConciseReview.pdf [Accessed July 2016]; Chung DJ, et al. Cancer Immunol Res 2016;4:61-71; Boland E, et al. J Pain Symptom Manage 2013;46:671-80; Bolli N, et al. Nat Commun 2014;5:2997.

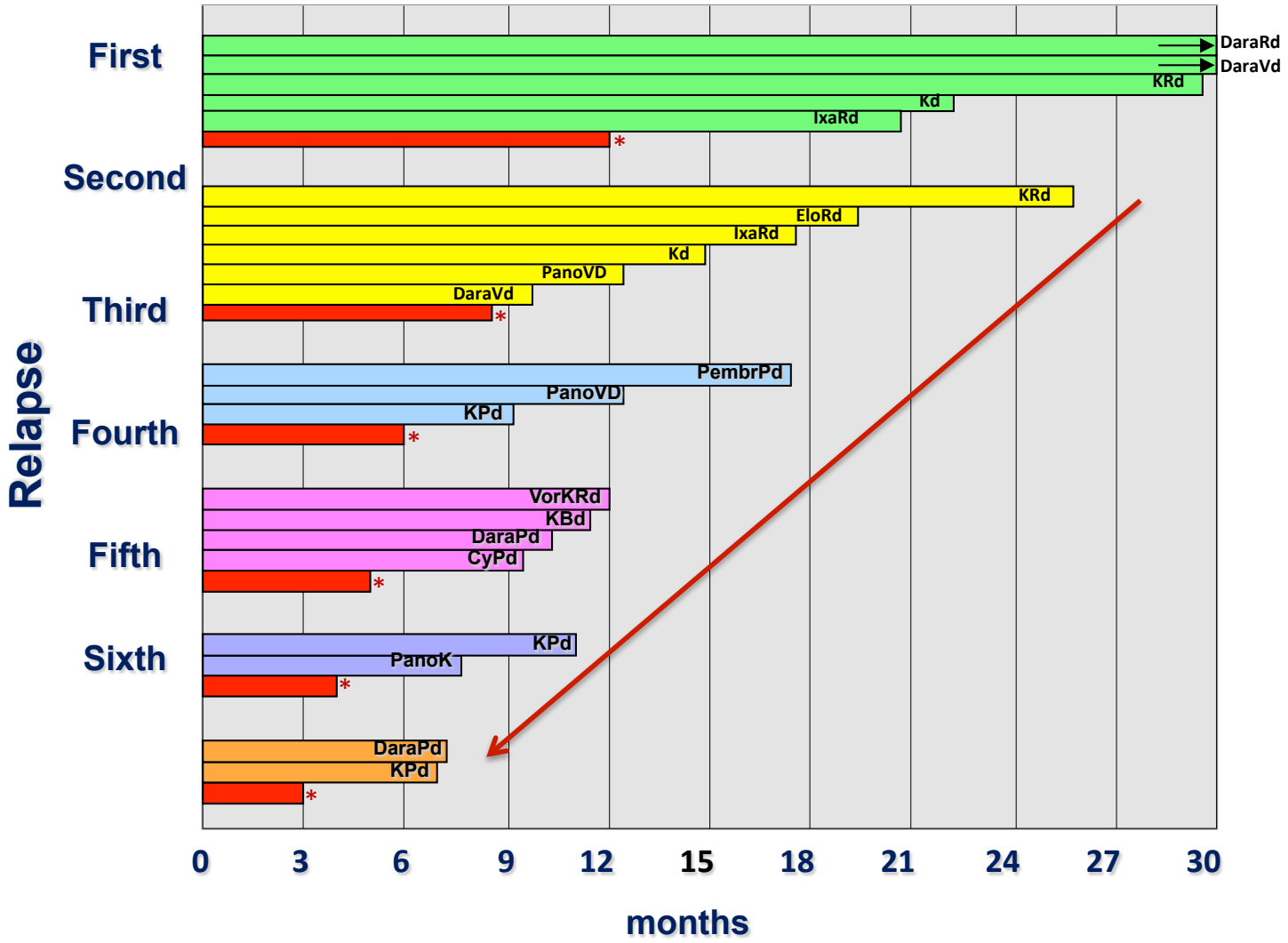
Patient outcome in real-word practice



4997 patients diagnosed during 12 months in Belgium, France, Germany, Italy, Spain, Switzerland and the UK

Yong et al. Br J Haematol, 2016

Expected *vs* current PFS by treatments and line of therapy at relapse



* Expected

FOCUS study

> 3 lines, refractory last line

R

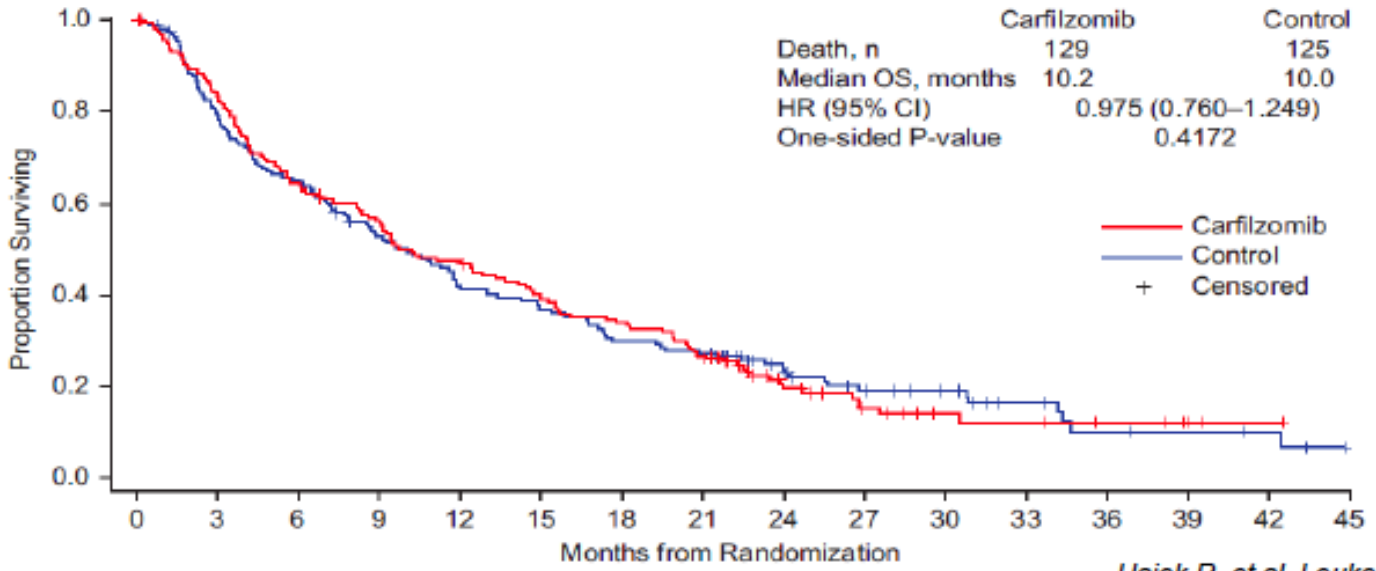
1:1

Carfilzomib (28-day cycles)

Cycle 1: 20 mg/m2 IV day 1, 2 in cycle 1, escalated to 27 mg/m2 on day 8, 9, 15, 16
Cycles 2-9: 27 mg/m2 on day 1, 2, 8, 9, 15, 16
Cycle >9: 27 mg/m2 on day 1, 2, 8, 9, 15, 16 and optional on day 8, 9

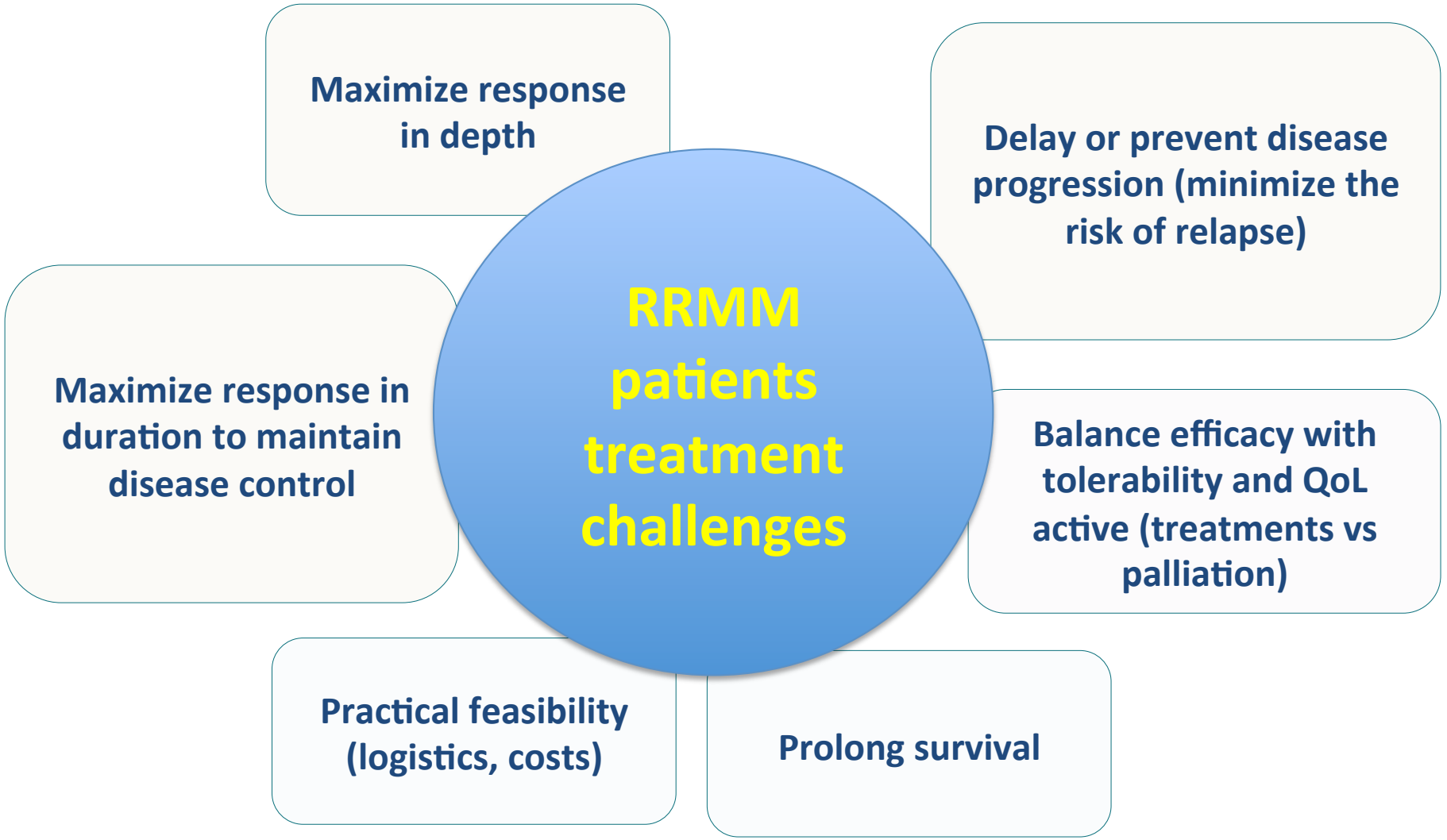
Control with corticosteroids

Prednisone 30 mg PO every other day or dexamethasone 6 mg PO every other day
+
Optional cyclophosphamide 50 mg PO

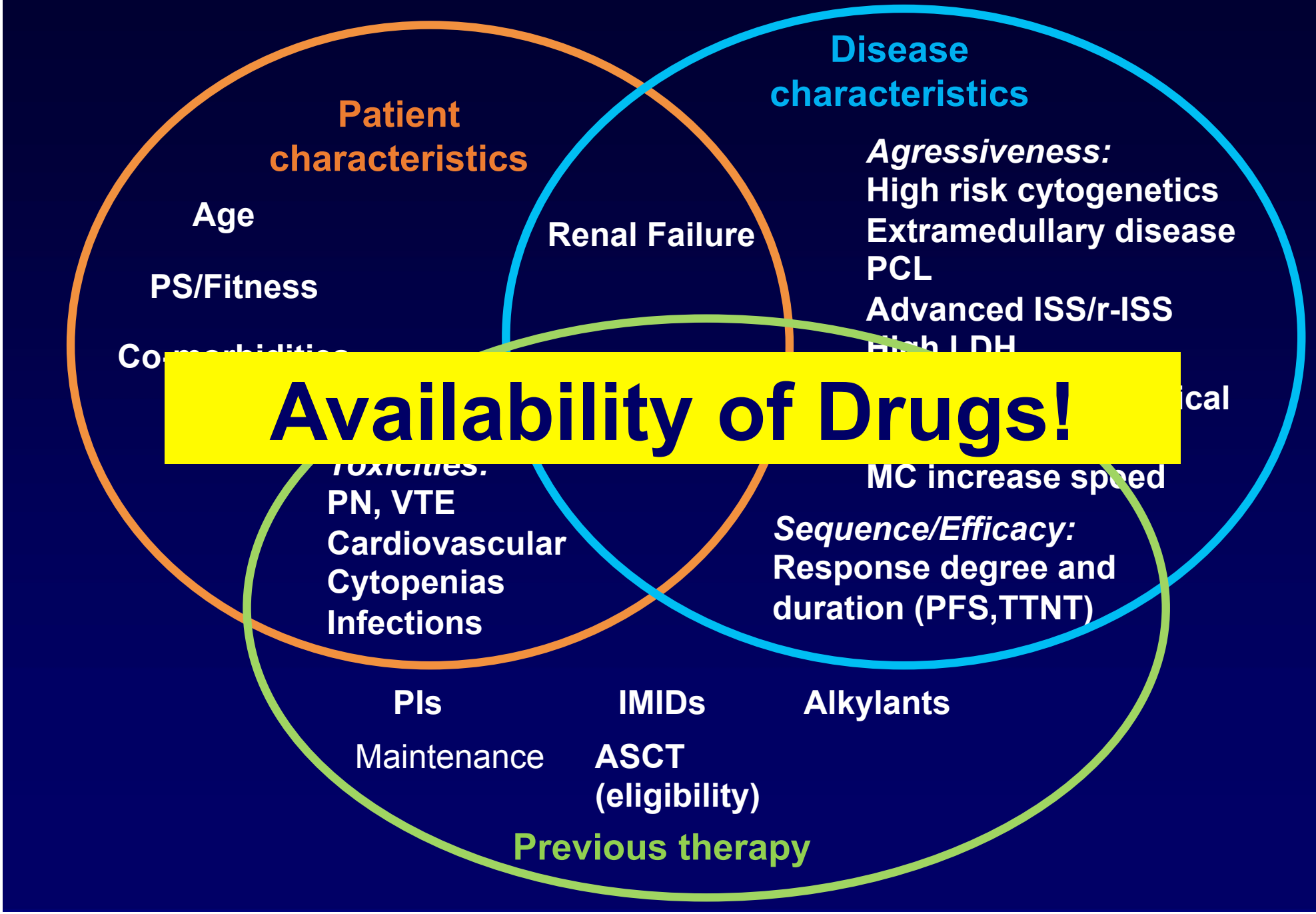


Hajek R, et al. Leukemia. 2017;31:107–114

Treatment challenges in patients with RRMM



General considerations for salvage therapy selections



Impatto sul paziente

- Impegno logistico:
  - Accessibilita' e numero di accessi in ospedale
  - Impegno del caregiver
- Effetti collaterali (citopenia, infezioni, PN, TVP, cuore)
- Terapie di supporto (profilassi antitrombotica, antibiotica, antivirale, ecc.)
- Terapia orale vs i.v.
- Durata della terapia
- Qualità della vita
- Possibilità di continuare a svolgere le proprie attività
- Preferenze

Relapses are associated with a high emotional and physical burden for patients, caregivers and physicians

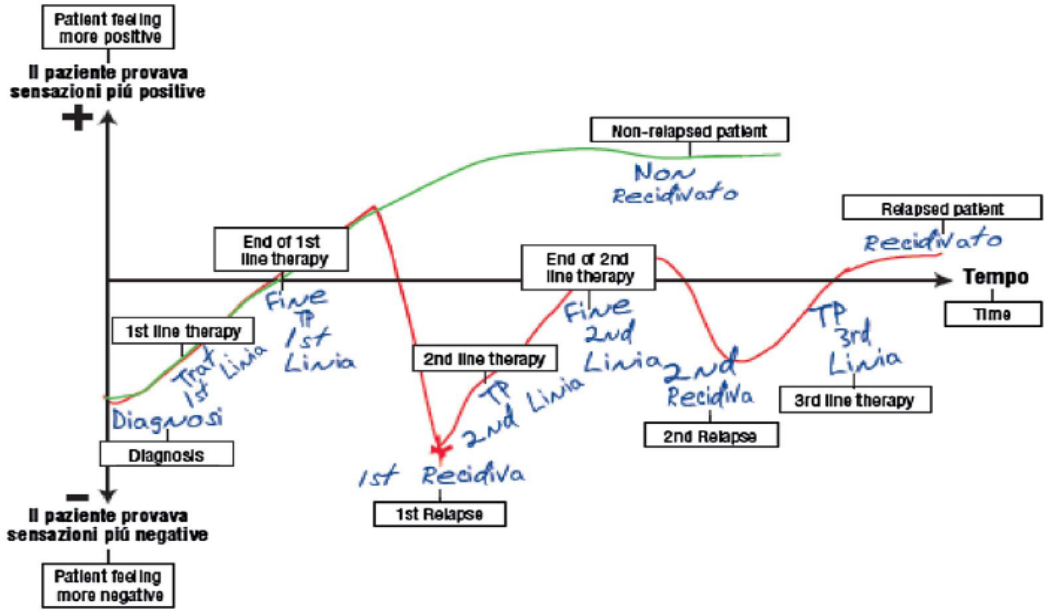


Illustration from a hematologist with 50 multiple myeloma patients per month, 90% of time spent in clinical care.

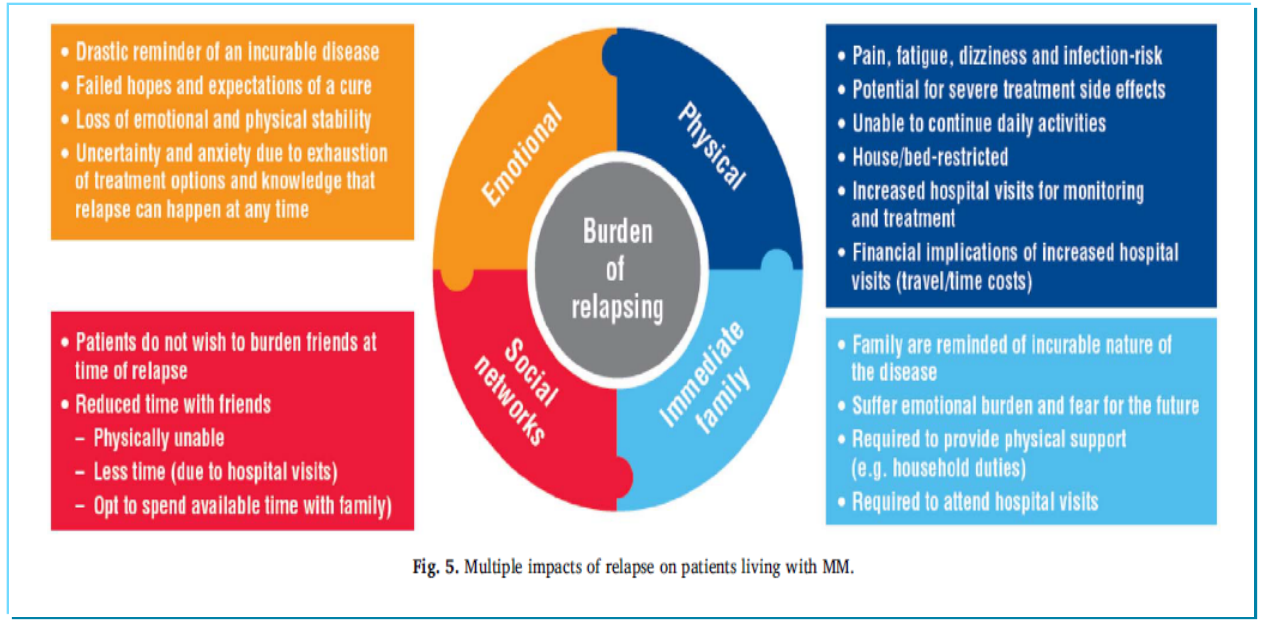
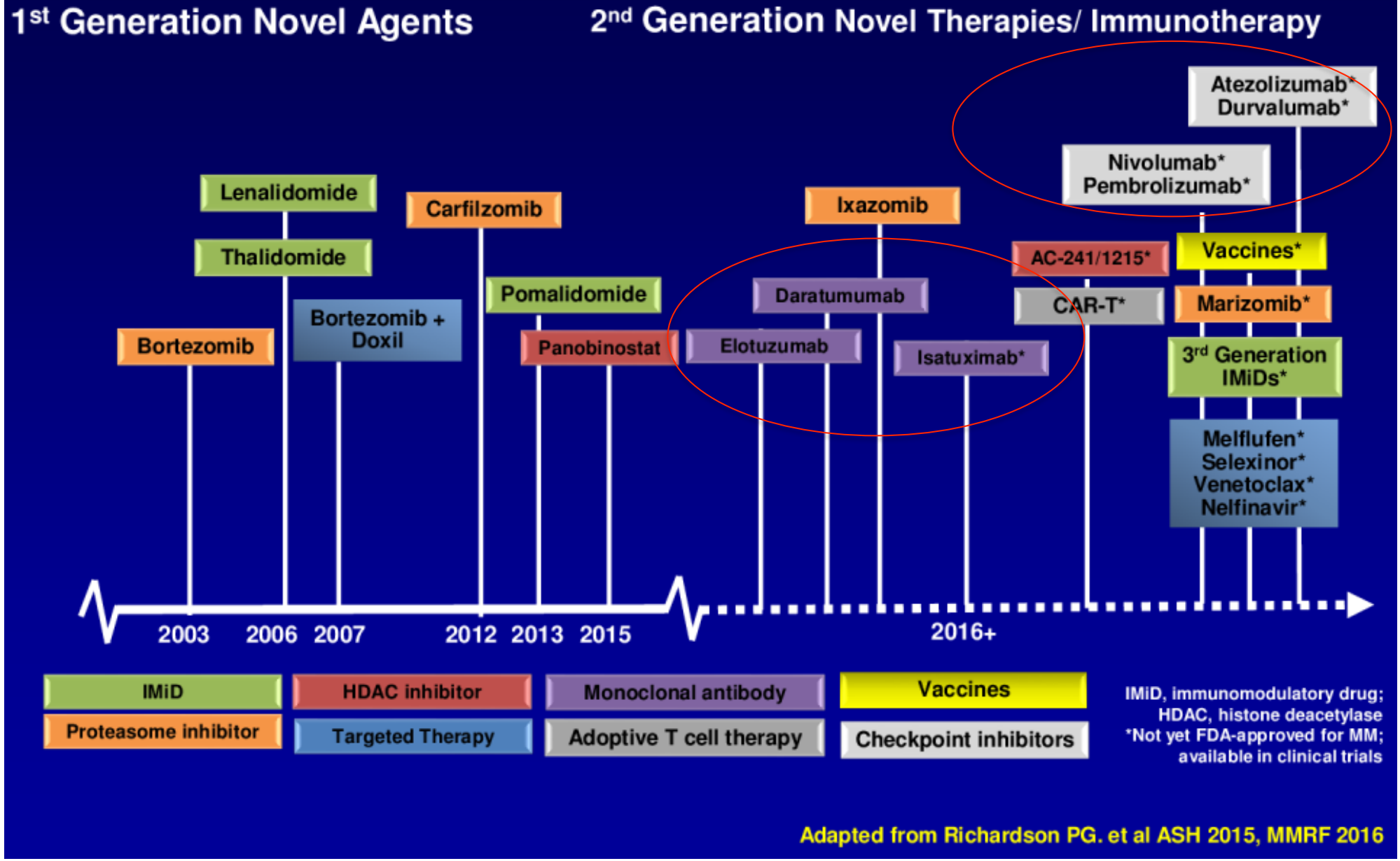


Fig. 5. Multiple impacts of relapse on patients living with MM.

Hulin et al. *Leukemia Research (2017)*

Continuing Evolution of Multiple Myeloma Treatment: Selected New Classes and Targets 2016- 2017



Adapted from Richardson PG. et al ASH 2015, MMRF 2016

EDITORIALS

Progress in Myeloma — A Monoclonal Breakthrough

S. Vincent Rajkumar, M.D., and Robert A. Kyle, M.D.

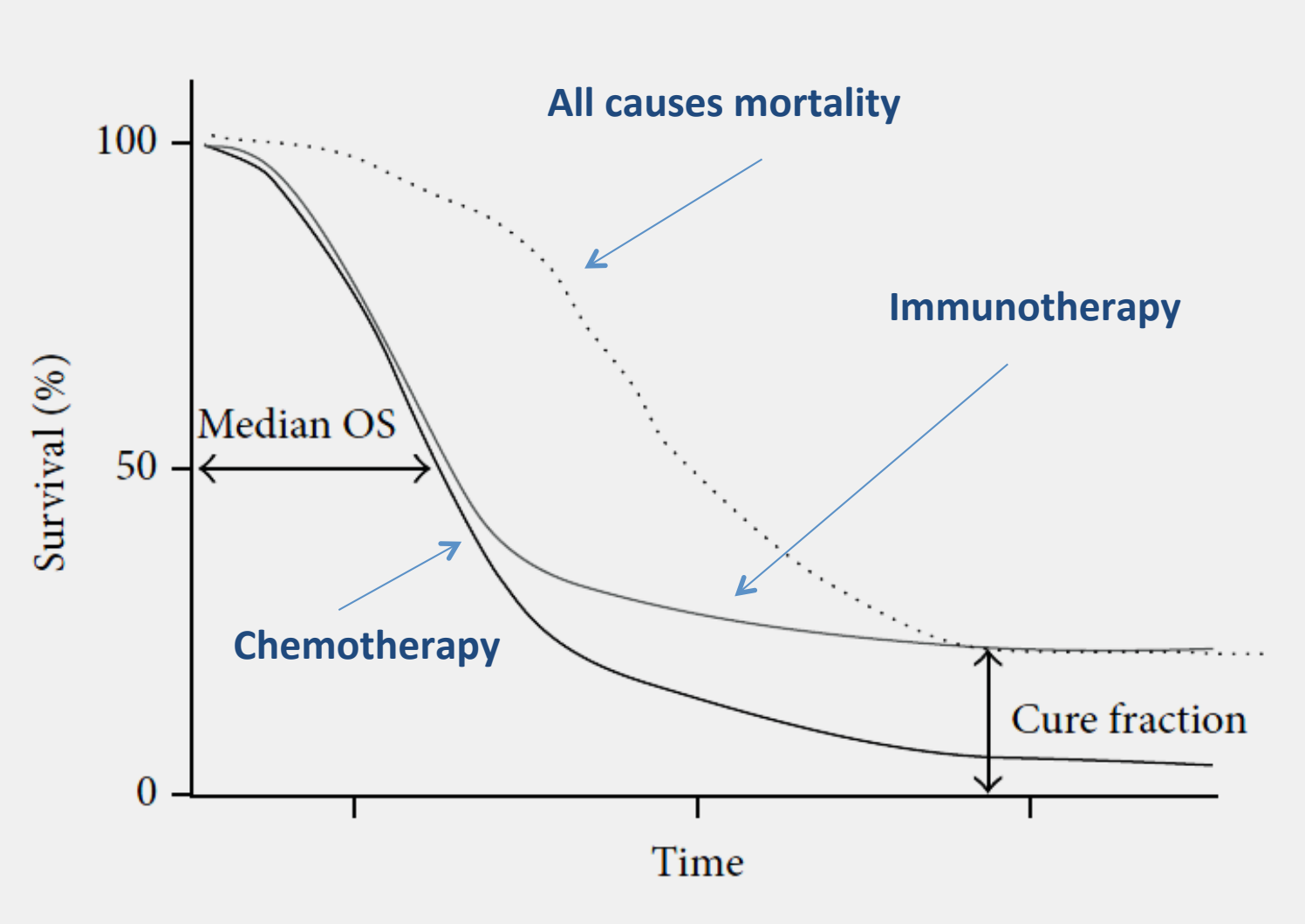
"In the past decade, we have witnessed more progress in the treatment of multiple myeloma than any other cancer."

Rajkumar SV, et al. *N Engl J Med.* 2016;375(14):1390-1392.

Monoclonal antibodies in MM

Target	mAb			Stage of development
Surface molecules				
SLAMF7 (CS1)	Elotuzumab	FDA & EMA approved	Humanized	Phase 1/2/3
CD38	Daratumumab	FDA & EMA approved	Fully human	Phase 1/2/3/4
	Isatuximab (SAR650984)		Chimeric	Phase 1/2/3
	MOR202		Fully human	Phase 1/2
CD138	Indatuximab ravtansine (BT062)			Phase 1/2
BCMA	J6M0-mcMMAF (GSK2857916)			Phase 1
Signaling molecules				
IL-6	Siltuximab			Phase 2
RANKL	Denosumab			Phase 3
VEGF	Bevacizumab			Phase 2
DKK1	BHQ880			Phase 2
Immune checkpoint inhibitors				
PD-1	Pembrolizumab			Phase 1/2/3
	Nivolumab			Phase 1/2
	Pidilizumab			Phase 1/2
PD-L1	Durvalumab			Phase 1
CTLA4	Ipilimumab			Phase 1/2
KIR	Lirilumab			Phase 1

Is the paradigm of survival evaluation changing also in myeloma?



- Median OS provides a measure of when 50% of patients will die, it does not provide a true reflection of the survival time that may be expected from the patients who are alive after the median OS is reached
- Median OS is considered less suitable for survival curves that are skewed to the right since it does not differentiate the proportion of patients alive or dead after 50% of the patients have died

RELAPSE / REFRACTORY MULTIPLE MYELOMA
ESMO guidelines 2017

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

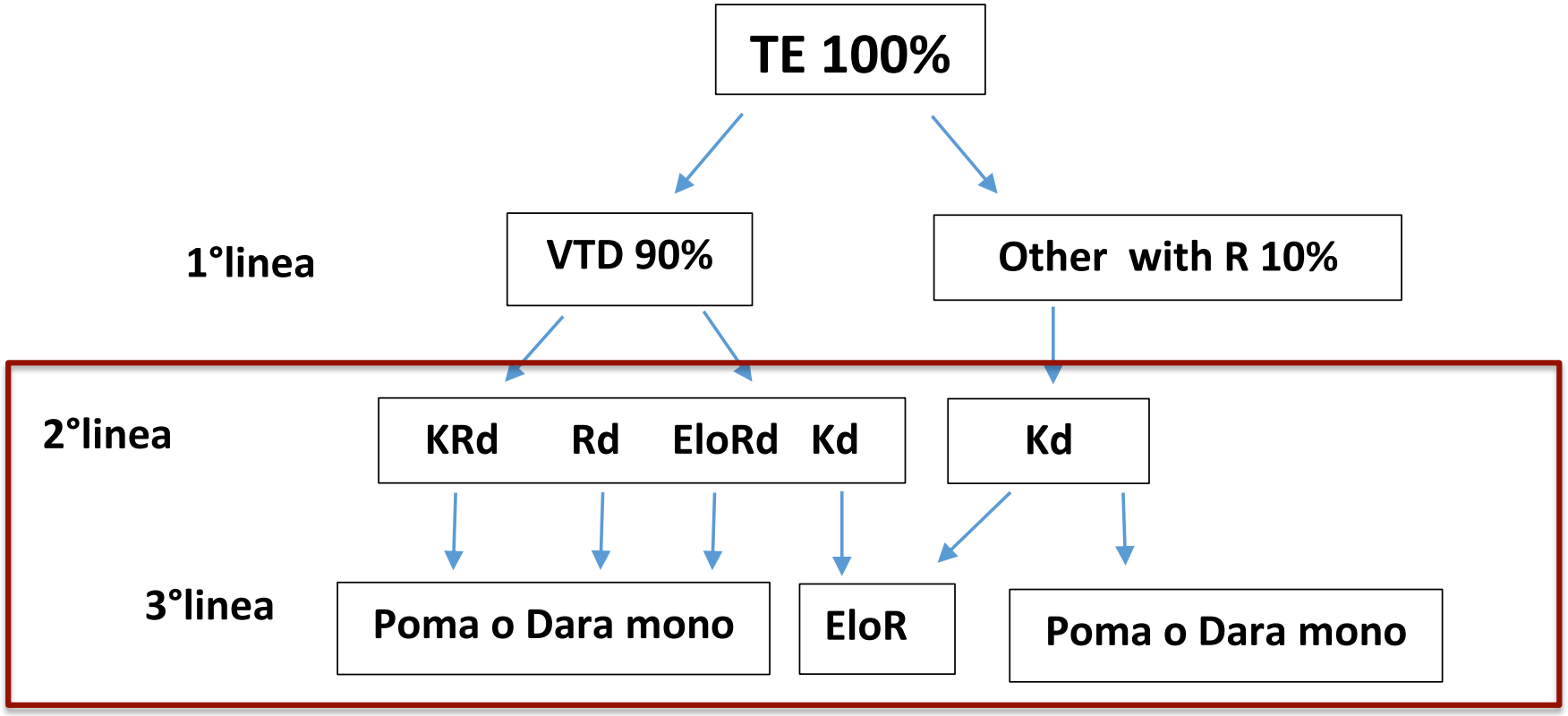
- Rd
- Triplets (with Rd as backbone): DaraRd or KRd or IxaRd or EloRD

At second or subsequent relapse

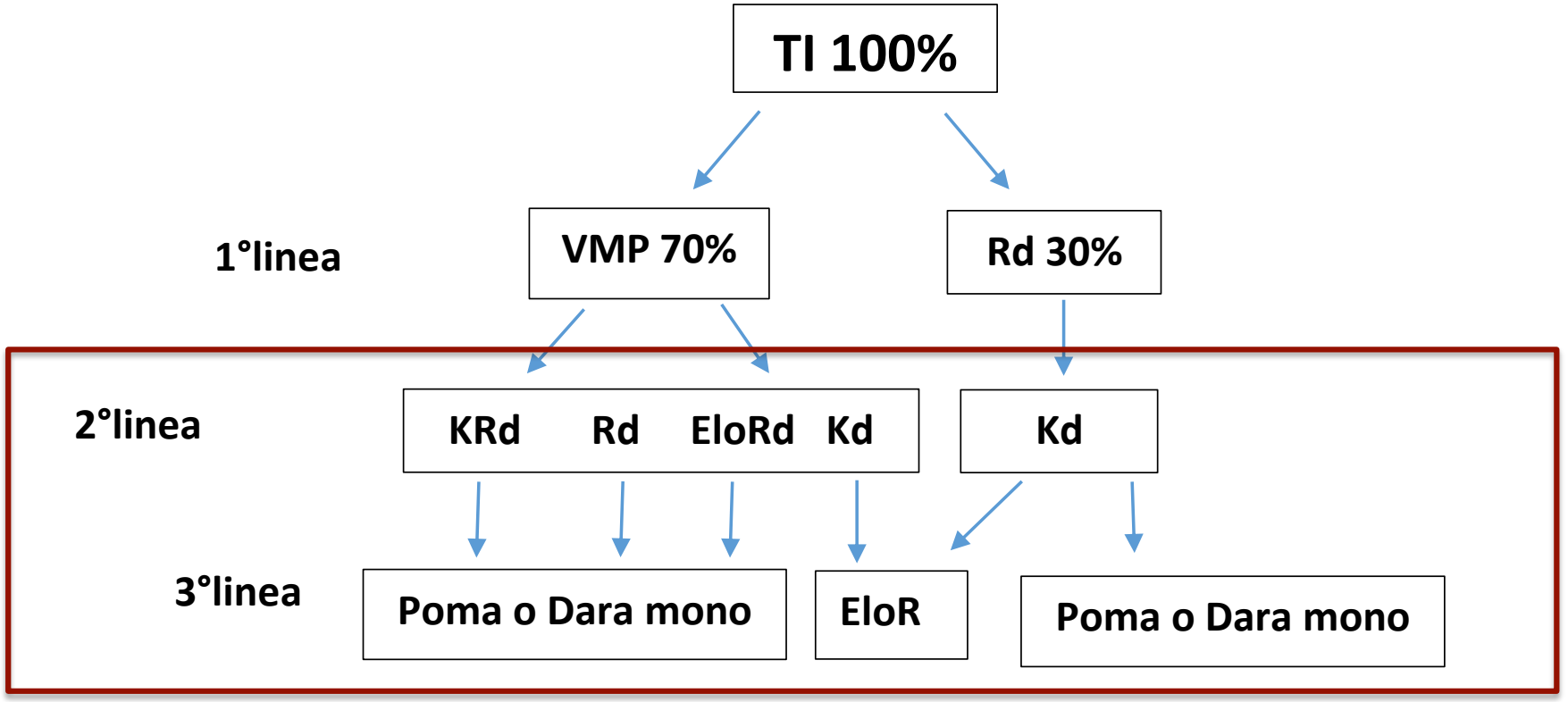
- Pomalidomide-Dex (as a backbone) + Cyclo or Ixa or Bort or Dara or Elo
- Daratumumab (single agent or combination)
- Clinical Trial

Moreau et al. Ann Oncol 2017, in press

Possibile algoritmo rimborsato da Ottobre 2017 nel paziente elegibile al trapianto



Possibile algoritmo rimborsato da Ottobre 2017 nel paziente inelegibile al trapianto



Strategies at Relapse: How to Make the Right Choice

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction VMP

Rd continuous

Early relapse (<1 year) 5-10%	Intermediate relapse (1-3 years) 80%	Late relapse (>3 years) 10%
"Overcome drug resistance"	*"Prolong survival until curative treatments are developed"*	*"Retreatments"* *Including ASCT*
Combinations of non-cross-resistant agents VTD-PACE ± Dox + Cyclo → RIC-Allo		

San Miguel J, et al. JCO 2013; 31:448-455

Strategies at Relapse: How to Make the Right Choice

Induction Bortezomib-based combination

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Early relapse (<1 year)	Intermediate relapse (1-3 years)	Late relapse (>3 years)
5-10%	80%	10%
"Overcome drug resistance"	*"Prolong survival until curative treatments are developed"*	*"Retreatments"*
Combinations of non-cross-resistant agents VTD-PACE ± Dox + Cyclo → RIC-Allo		

San Miguel J, et al. JCO 2013; 31:448-455

Treatment options in relapsed MM
The past

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction VMP

Rd continuous

Second transplant, Allo-RIC

(Re)treatment with bortezomib-based combinations *

Rd Continuous therapy

* Doxil, bendamustine

Treatment options in relapsed MM
The present

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction VMP

Rd continuous

Second transplant, Allo-RIC

Carfilzomib plus Dex[1]

Daratumumab plus Vd[6]

Retreatment with bortezomib-based combination

Rd Continuous therapy

Carfilzomib plus Rd[2]

Elotuzumab plus Rd[3]

Ixazomib plus Rd[5]

Daratumumab plus Rd[4]

1. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Lonial S et al. N Engl J Med 2015;373:621-31; 4. Dimopoulos MA, eta la. N Engl J Med. 2016;375(14):1319-1331; 5. Moreau P et al. NEJM 2016;374(17):1621-34; 6. Palumbo A, et al. N Engl J Med. 2016 Aug 25;375(8):754-66.

Treatment options in relapsed MM
The present

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction VMP

Rd continuous

Retreatment with bortezomib-based combination

Rd Continuous therapy

Second transplant, Allo-RIC

Rd Continuous therapy as backbone

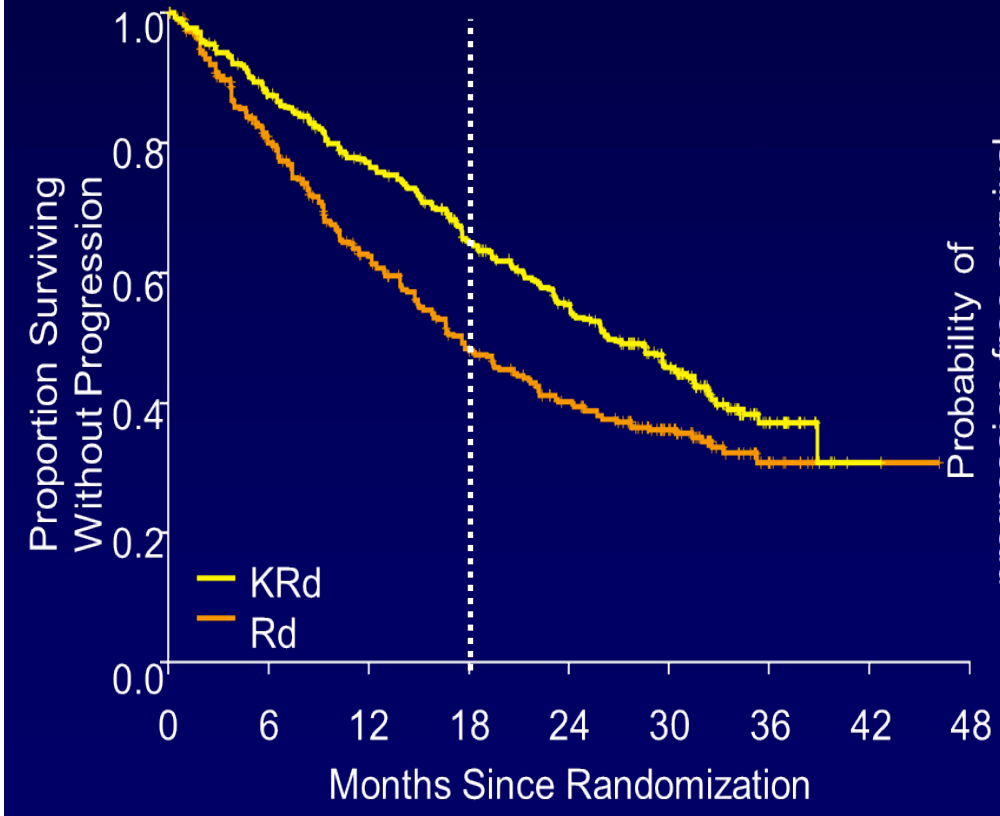
- Carfilzomib plus Dex[1]
- Vd[6]
- Carfilzomib plus Rd[2]
- Elotuzumab plus Rd[3]
- Ixazomib plus Rd[5]
- Daratumumab plus Rd[4]

1. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Lonial S et al. N Engl J Med 2015;373:621-31; 4. Dimopoulos MA, eta la. N Engl J Med. 2016;375(14):1319-1331; 5. Moreau P et al. NEJM 2016;374(17):1621-34; 6. Palumbo A, et al. N Engl J Med. 2016 Aug 25;375(8):754-66.

Rd *versus* Rd + Proteasome Inhibitors
Progression-Free Survival

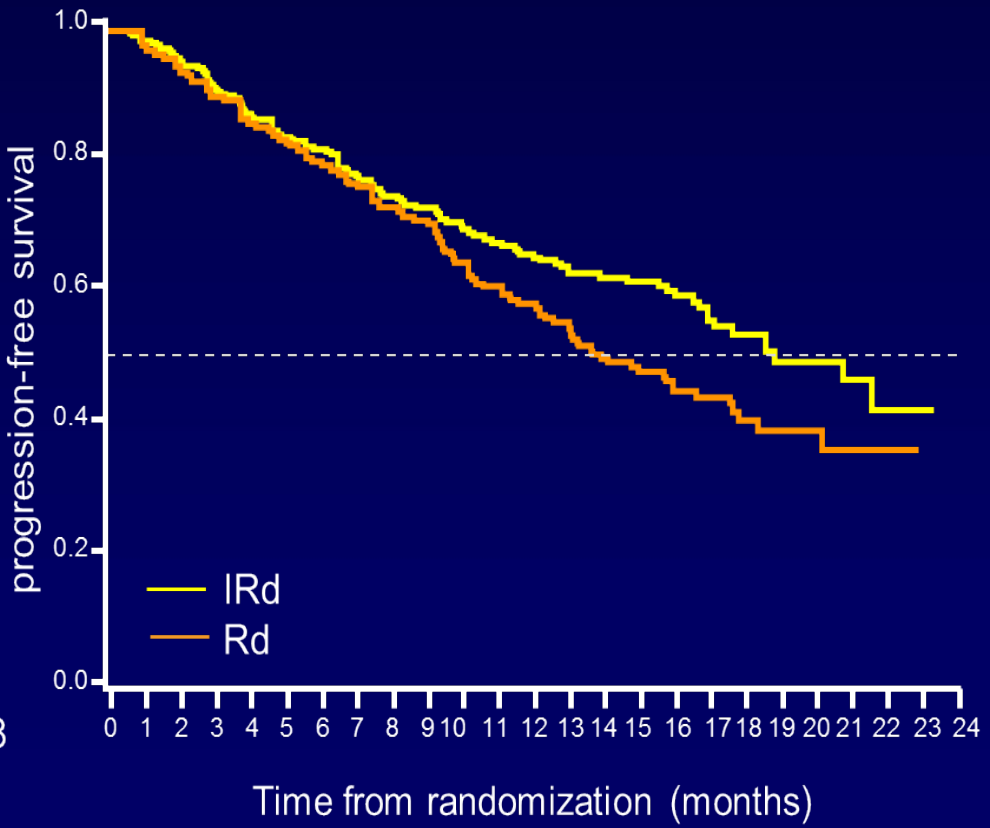
Carfilzomib

	KRd (n=396)	Rd (n=396)
Median PFS, mo	26.3	17.6
HR (Rd/KRd) (95% CI)	0.69 (0.57–0.83)	
P value	0.0001	



Ixazomib

	IRd (n=360)	Rd (n=362)
Median PFS, mo	20.6	14.7
HR (Rd/IRd) (95% CI)	0.74 (0.59–0.94)	
P value	0.01	

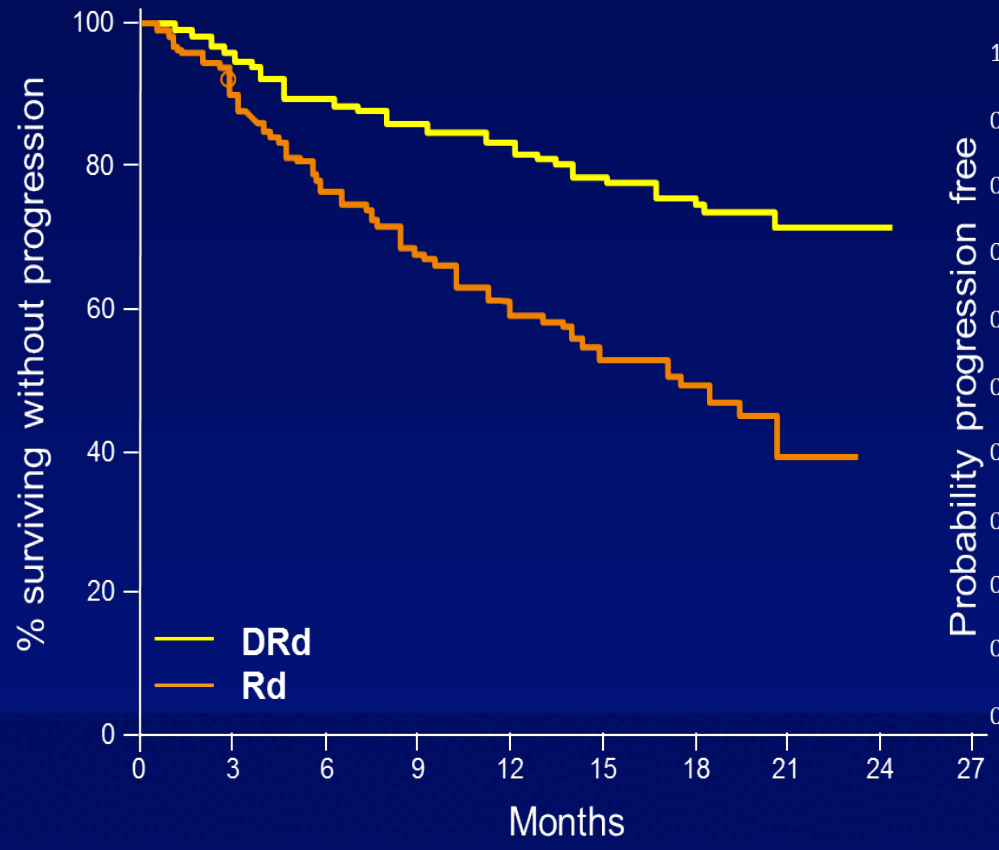


Stewart AK, et al. N Engl J Med 2015;372:142-52; Moreau P et al. NEJM 2016;374(17):1621-34

Rd *versus* Rd + Monoclonal antibodies
Progression-Free Survival

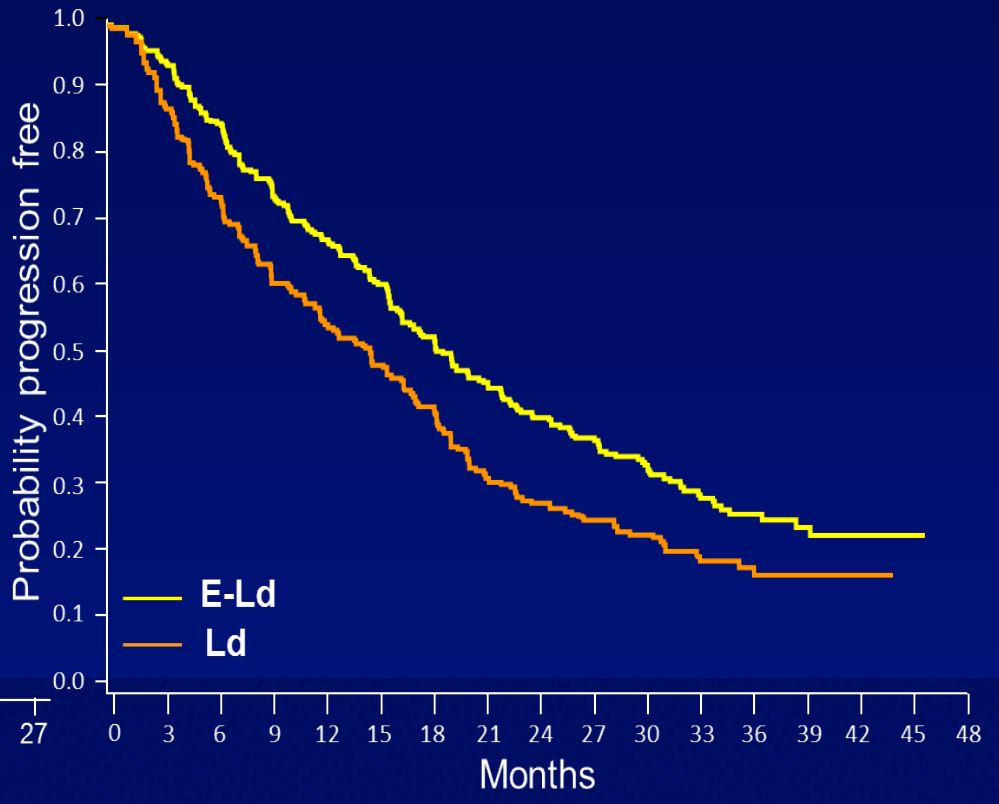
Daratumumab

	DRd (n=286)	Rd (n=283)
Median PFS, mo	NR	17.5
HR (Rd/DRd) (95% CI)	0.37 (0.28–0.50)	
P value	<0.0001	



Elotuzumab

	ERd (n=321)	Rd (n=325)
Median PFS, mo	19.4	14.9
HR (Rd/DRd) (95% CI)	0.73 (0.60–0.89)	
P value	0.0014	



Dimopoulos MA, eta la. N Engl J Med. 2016;375(14):1319-1331; Lonial S, et al. N Engl J Med 2015; 373(7):621–31

Dara-Rd vs Lenalidomide-based Studies

	POLLUX DRd vs Rd	ASPIRE KRd vs Rd[1]	ELOQUENT-2 ERd vs Rd[2,3]	TOURMALINE-MM1 IRd vs Rd[4]
PFS HR (95% CI)	**0.37 (0.27-0.52)**	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
ORR	**93%**	87%	79%	78%
≥VGPR	**76%**	70%	33%	48%
≥CR	**43%**	32%	4%	14%
Duration of response, mo	**NE**	28.6	20.7	20.5
OS HR (95% CI)	**0.64 (0.40-1.01)**	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

1. Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152.
2. Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631.
3. Dimopoulos MA, et al. *Blood*. 2015;126(23):Abstract 28.
4. Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634.

K, carfilzomib; E, elotuzumab; N, ixazomib.

Dimopoulos er al. N Engl J Med 2016;375:1319-31

Treatment options in relapsed MM
The present

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction VMP

Rd continuous

Retreatment with bortezomib-based combination

Rd Continuous therapy

PI as backbone

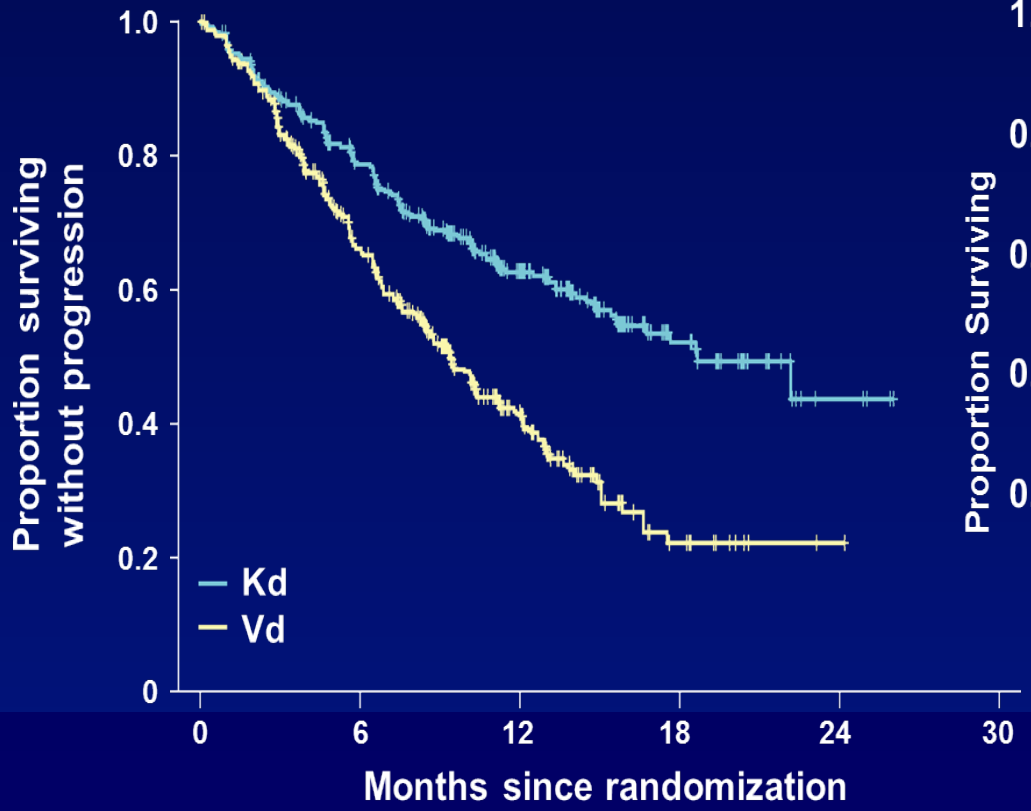
- Carfilzomib plus Dex[1]
- Daratumumab plus Vd[6]
- Carfilzomib plus Rd[2]
- Elotuzumab plus Rd[3]
- Daratumumab plus Rd[5]
- Ixazomib plus Rd[4]

1. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Lonial S et al. N Engl J Med 2015;373:621-31; 4. Dimopoulos MA, eta la. N Engl J Med. 2016;375(14):1319-1331; 5. Moreau P et al. NEJM 2016;374(17):1621-34; 6. Palumbo A, et al. N Engl J Med. 2016 Aug 25;375(8):754-66.

Kd *versus* Vd
Progression-free and Overall Survival

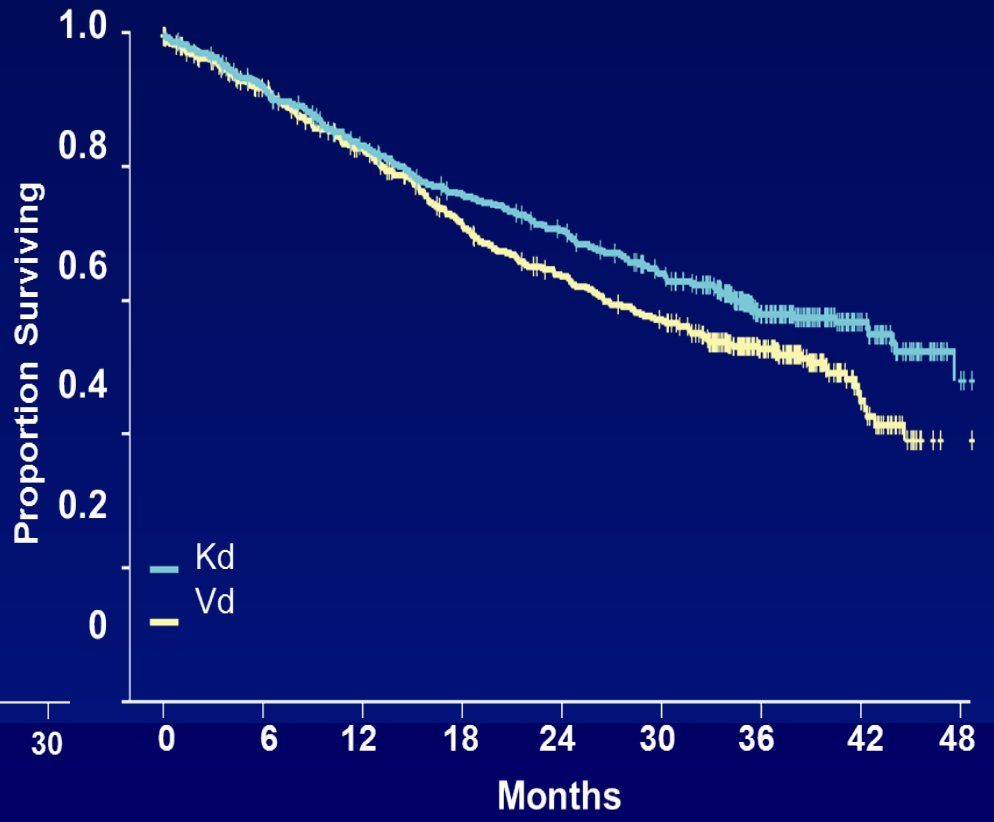
Progression-free survival

	Kd (n=396)	Vd (n=396)
Median PFS, mo	18.7	9.4
HR (Vd/Kd) (95% CI)	0.53 (0.44–0.65)	
P value	<0.0001	



Overall Survival

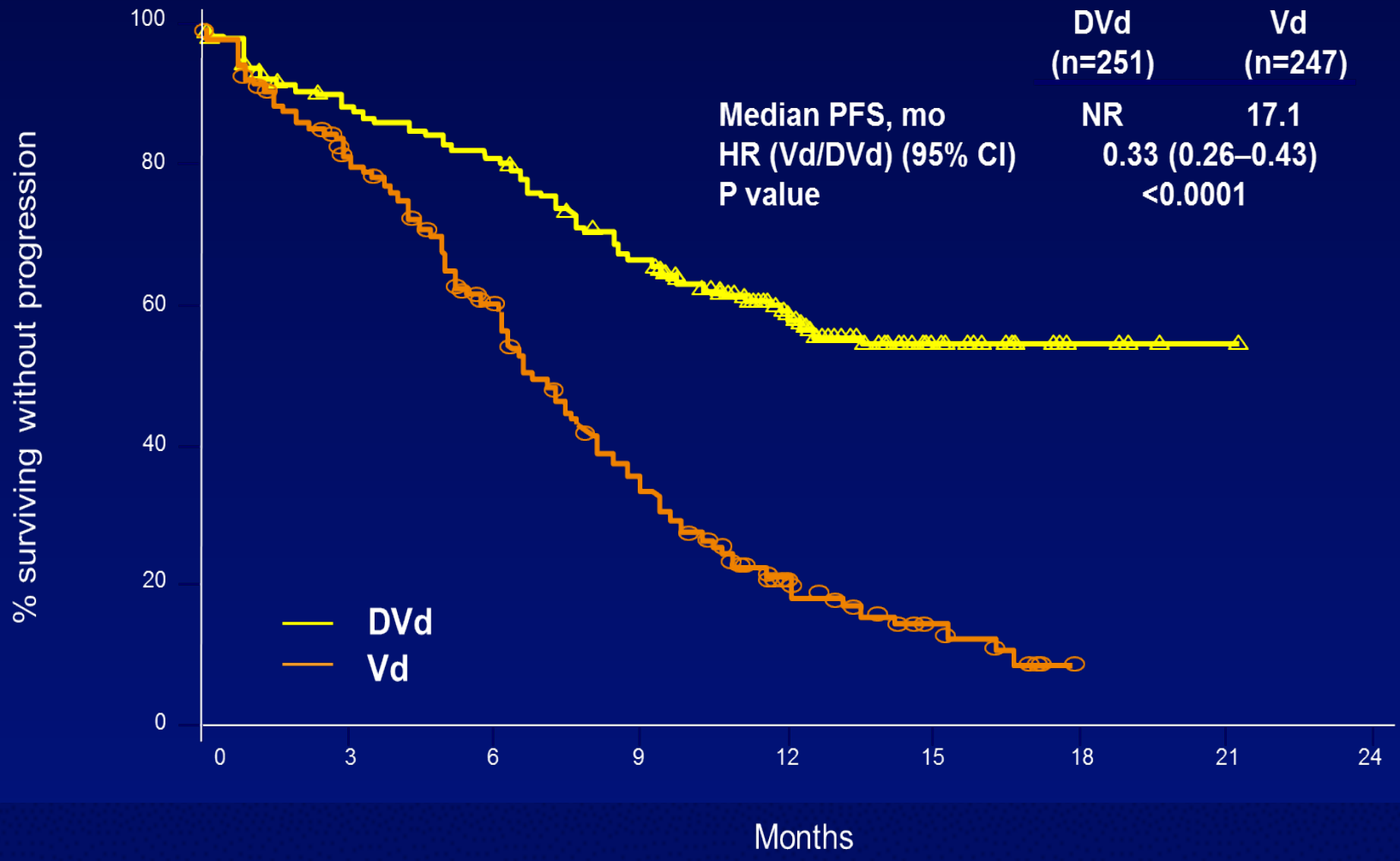
	Kd (n=396)	Vd (n=396)
Median PFS, mo	47.6	40.0
HR (Vd/Kd) (95% CI)	0.79 (0.65–0.96)	
P value	0.01	



Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; Dimopoulos MA, et al. 16th IMW; March 1-4, 2017; New Delhi, India.

Vd *versus* Vd + Monoclonal antibodies

Progression-Free Survival



Palumbo A, et al. N Engl J Med. 2016 Aug 25;375(8):754-66.

Dara-Vd vs PI-based Studies

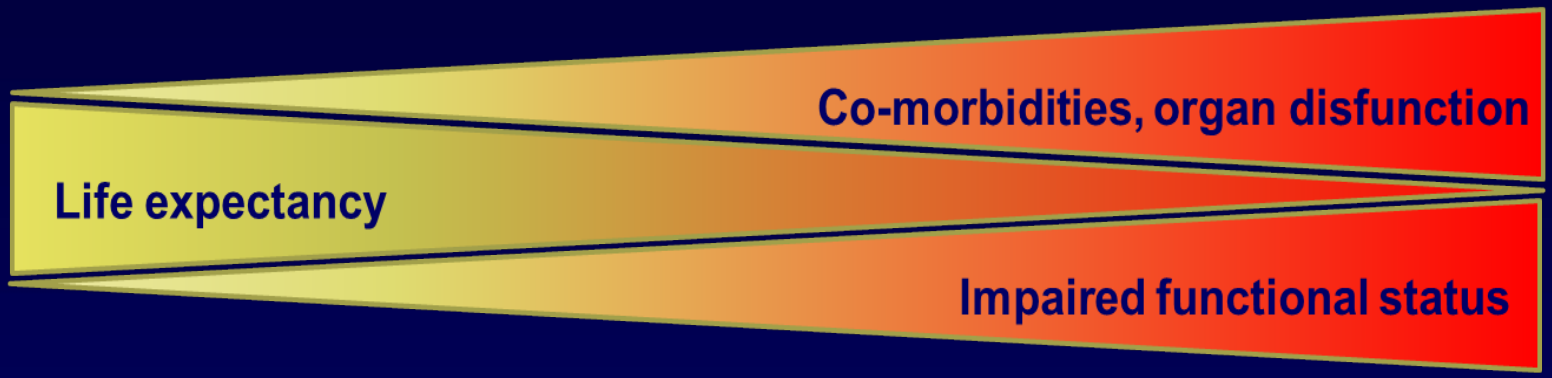
	Daratumumab DVd vs Vd	Carfilzomib Kd vs Vd[1]	Panobinostat PVd vs Vd[2,3]	Elotuzumab EVd vs Vd[4]
PFS HR (95% CI)	**0.39 (0.28-0.53)**	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
PFS, median mo	**NE**	18.7	12.0	9.7
≥VGPR	**59%**	54%	28%	36%
≥CR	**19%**	13%	11%	4%
Duration of response, mo	**NE**	21.3	13.1	11.4
OS HR (95% CI)	**0.77 (0.47-1.26)**	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

1. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
2. San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
3. San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
4. Jakubowiak A, et al. *Blood*. 2016. Epub ahead of print.

Palumbo et al. N Engl J Med 2016;375:754-66

Treatment goals in elderly MM patients

FIT	INTERMEDIATE	FRAIL



	Deep remission	Balance efficacy/safety	Do not harm
Goal	CR/MRD-negativity	Good response	QoL
Priority	Efficacy	Combination of efficacy/safety	Low toxicity

How can we choose the right treatment?

1. Bortezomib or Lenalidomide refractory
2. N. of prior lines
3. High vs standard risk
4. Safety profile
5. Frailty
6. Bortezomib AND Lenalidomide refractory

How can we choose the right treatment?

1. Bortezomib or Lenalidomide refractory
2. N. of prior lines
3. High vs standard risk
4. Safety profile
5. Frailty
6. Bortezomib AND Lenalidomide refractory

Role of refractoriness to Bor or Len
Eligibility criteria of the studies

	Included if refractory to Len	Included if refractory to Bort
KRd vs Rd[1]	No	No
IRd vs Rd[2]	No	No
ERd vs Rd[3]	No	Yes
DaraRd vs Rd[4]	No	Yes
Kd vs Vd[5]	Yes	No
DaraVd vs Vd[6]	Yes	No

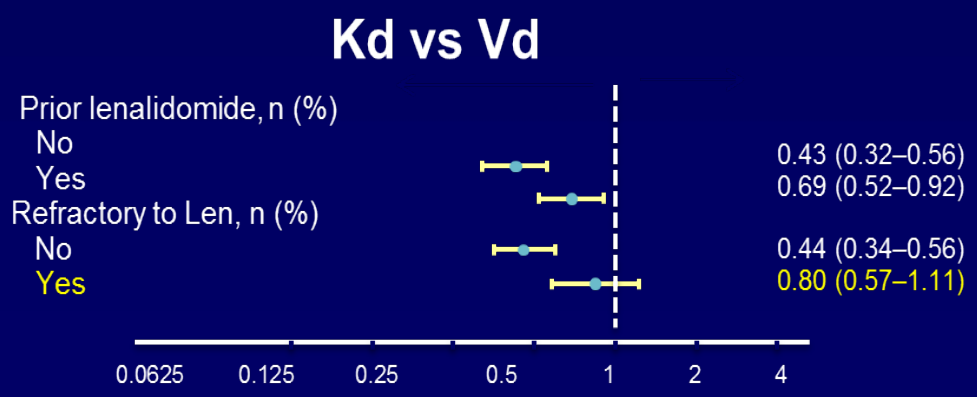
1. Stewart AK, et al. N Engl J Med 2015;372:142-52; 2. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; 3. Lonial S et al. N Engl J Med 2015;373:621-31; 4. Dimopoulos MA, eta la. N Engl J Med. 2016;375(14):1319-1331; 5. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; 6. Palumbo A, et al. N Engl J Med. 2016 Aug 25;375(8):754-66.

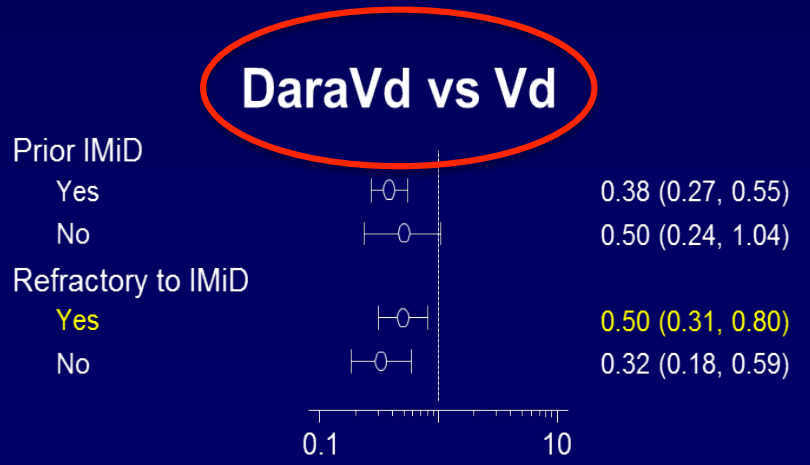
Eligibility criteria of the studies
Role of refractoriness to Bor or Len

	Enrolment if refractory to	
	Len	Bort
KRd vs Rd[1]	No	No
DaraRd vs Rd[4]	No	Yes

Len-refractory: Kd or DaraVd

Kd vs Vd[5]	Yes	No
DaraVd vs Vd[6]	Yes	No



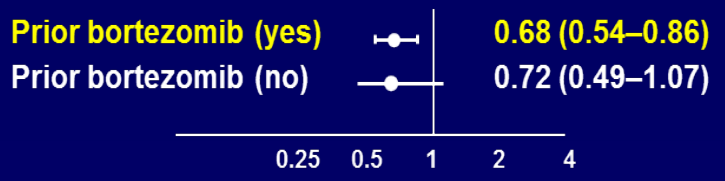


Eligibility criteria of the studies
Role of refractoriness to Bor or Len

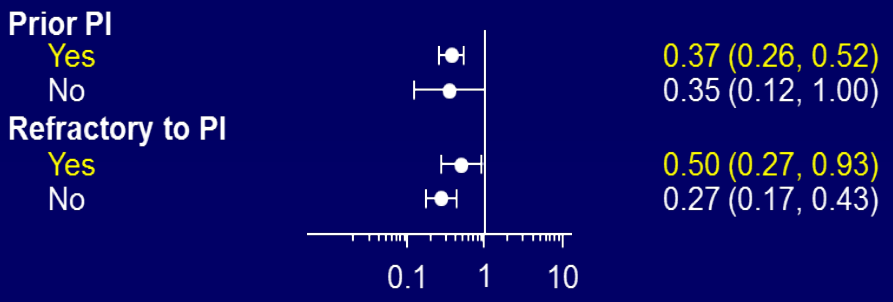
	Enrolment if refractory to	
	Len	Bort
KRd vs Rd[1]	No	No
IRd vs Rd[2]	No	No
Erd vs Rd[3]	No	Yes
DaraRd vs Rd[4]	No	Yes
Kd vs Vd[5]	[illegible]	No

Bort-refractory: ERd or DaraRd

ERd vs Rd



DaraRd vs Rd

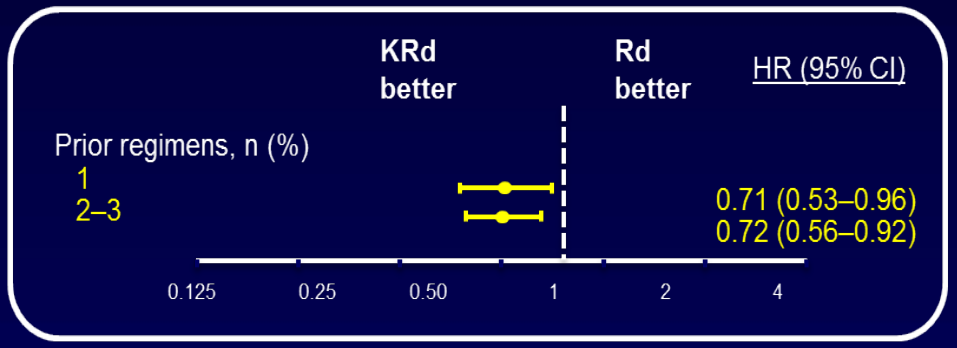


How can we choose the right treatment?

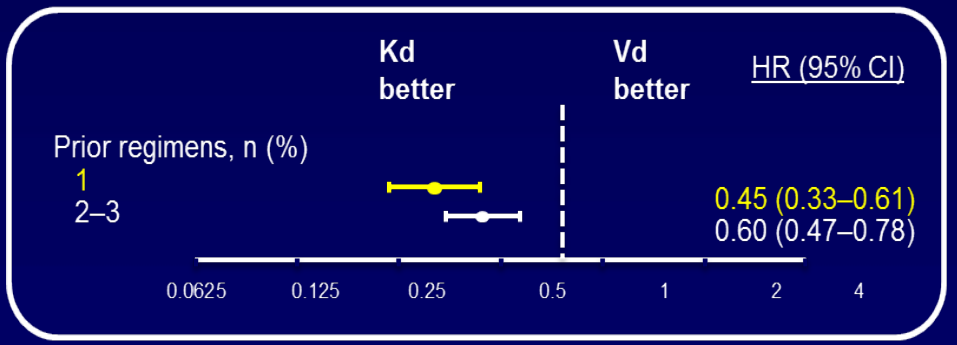
1. Bortezomib or Lenalidomide refractory
2. N. of prior lines
3. High vs standard risk
4. Safety profile
5. Frailty
6. Bortezomib AND Lenalidomide refractory

Number of prior lines of therapy

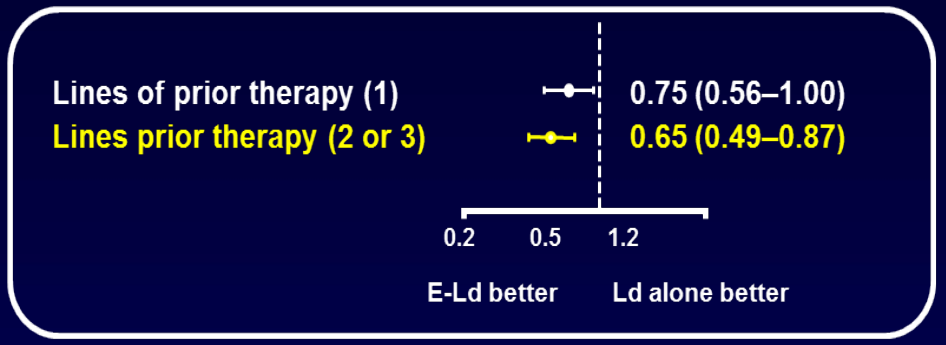
KRd vs Rd



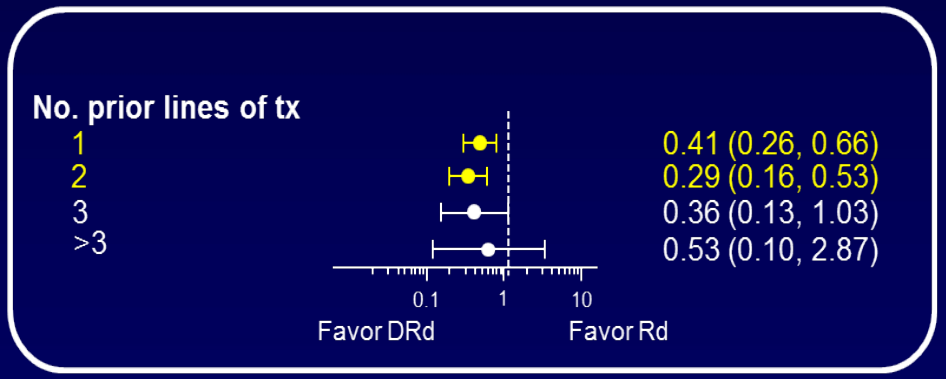
Kd vs Vd



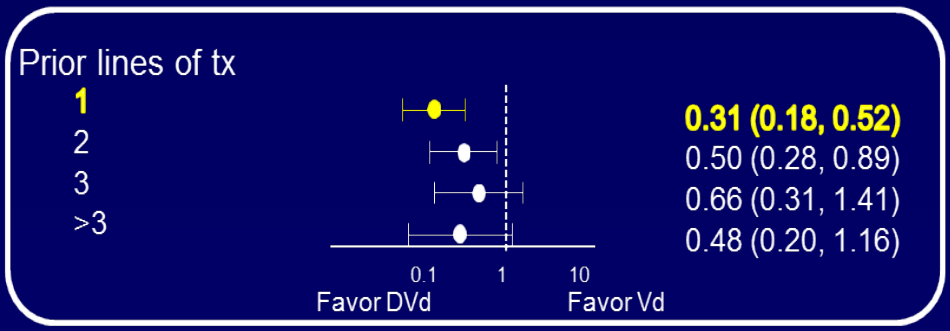
ERd vs Rd



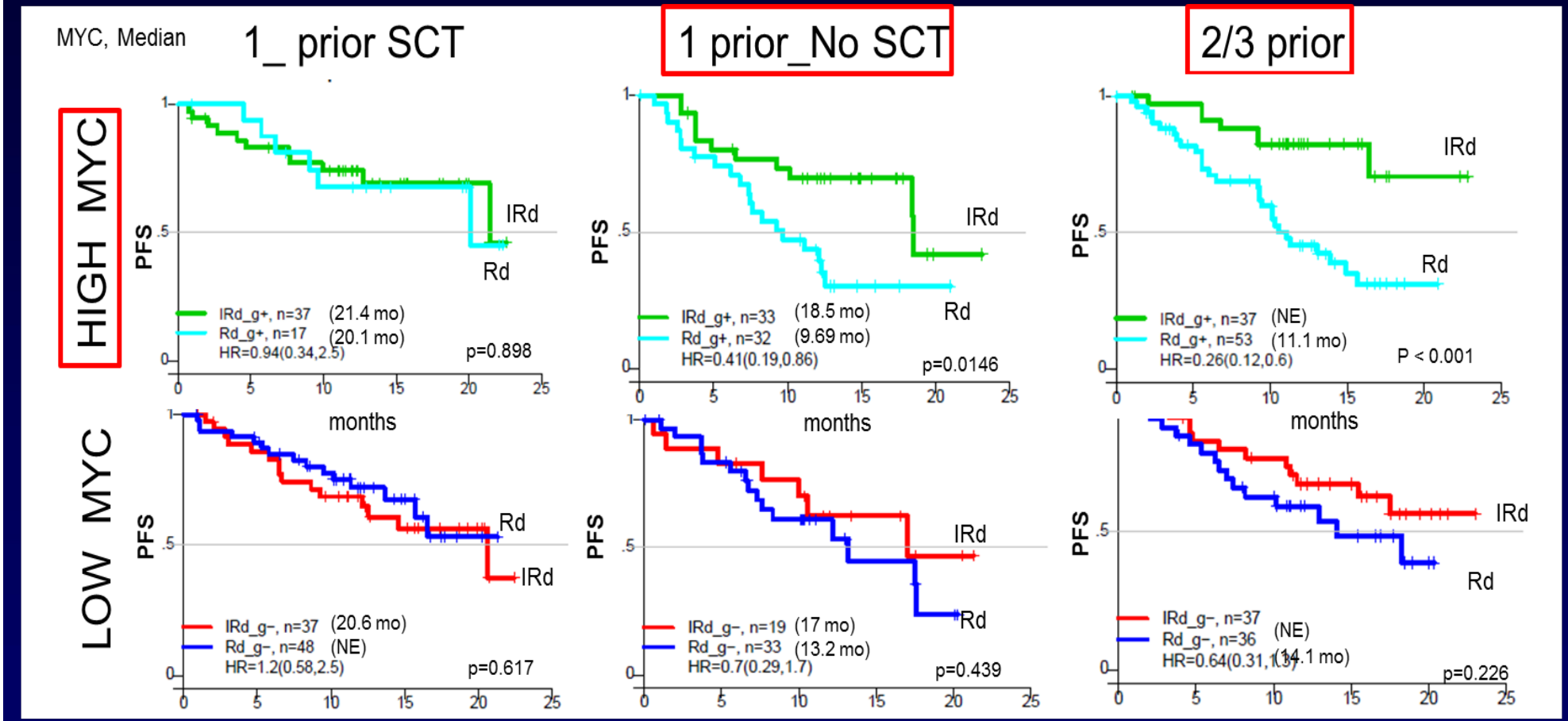
DaraRd vs Rd



DaraVd vs Vd



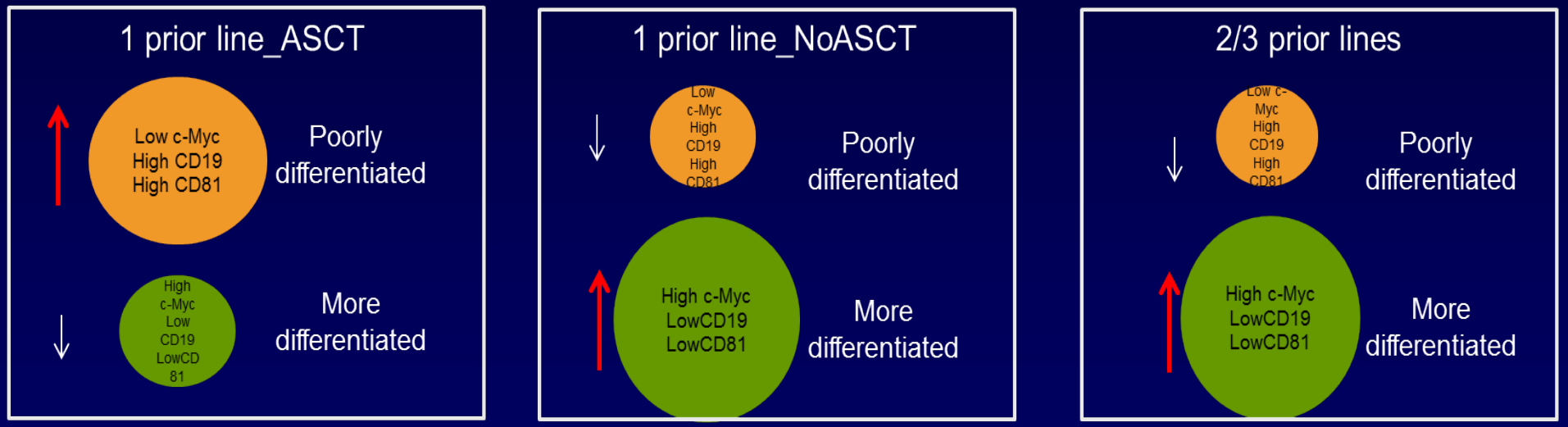
Number of prior lines of therapy
Ixa-Rd



Di Bacco A et al. ASH 2016: abstract 243

Number of prior lines of therapy
Ixa-Rd

- PC differentiation is characterized by the acquisition of secretory capacity, cell-cycle exit and changes in both surface phenotype and gene expression (1)



Sample tumors from patients relapsing after 1 prior line/no ASCT and 2/3 prior lines, have higher levels of c-MYC expression, while tumors relapsing post-ASCT tend to have lower levels

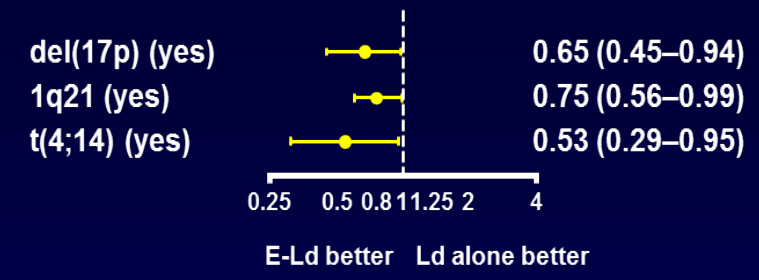
(1) Shapiro-Shelef M., Calame K. Nat Rev Immunol 2005

How can we choose the right treatment?

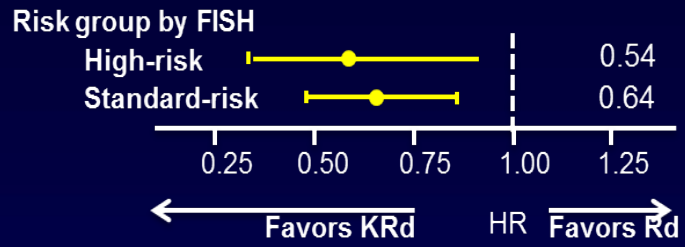
1. Bortezomib or Lenalidomide refractory
2. N. of prior lines
3. High vs standard risk
4. Safety profile
5. Frailty
6. Bortezomib AND Lenalidomide refractory

High risk *versus* standard risk

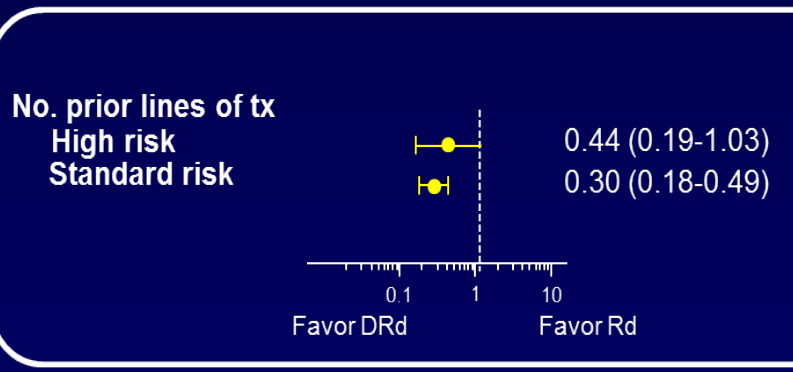
ERd vs Rd



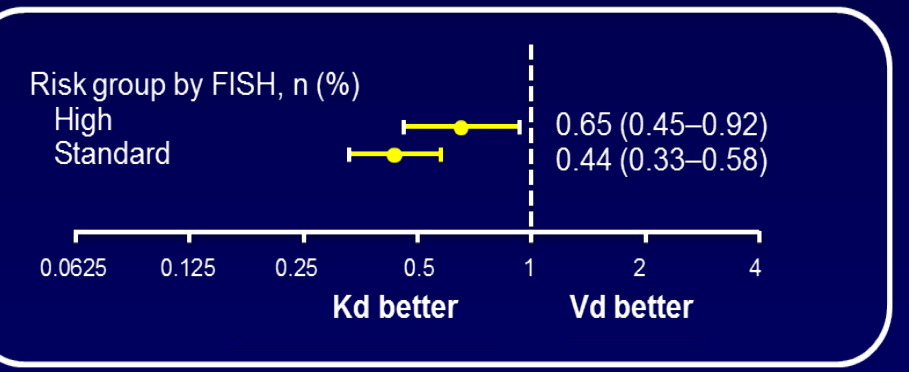
IRd vs Rd



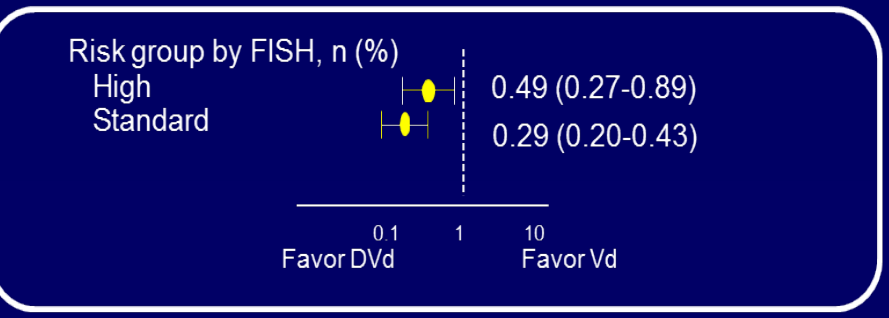
DaraRd vs Rd



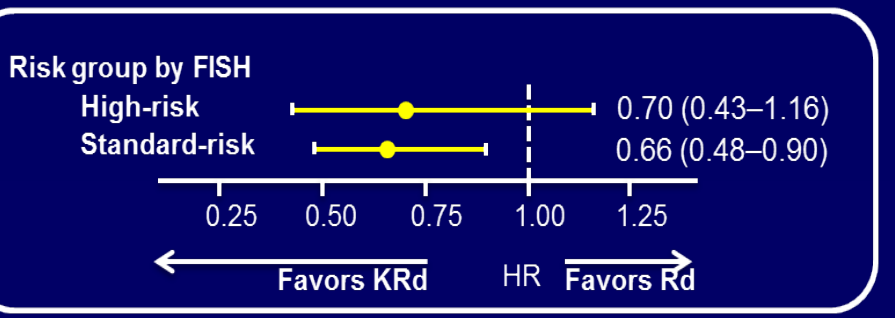
Kd vs Vd



DaraVd vs Vd



KRd vs Rd



High risk *versus* standard risk

But these results should be compared with caution because the cut off value of plasma cells with cytogenetic abnormalities is very different among the trials

Trials	PLCs %
IRd	<5%
KRd	60%
Kd	20%
DaraRd	-
ERd	60%
DaraVd	-

How can we choose the right treatment?

1. Bortezomib or Lenalidomide refractory
2. N. of prior lines
3. High vs standard risk
4. **Safety profile**
5. **Frailty**
6. Bortezomib AND Lenalidomide refractory

MM Frailty Score

Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.13 (0.76-1.69)	0.549	1
	Age >80 years	2.40 (1.56-3.71)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.37 (0.92-2.05)	0.125	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.67 (1.08-2.56)	0.02	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.43 (0.96-2.14)	0.078	1

ADDITIVE TOTAL SCORE	PATIENT STATUS
0	FIT
1	INTERMEDIATE
≥2	FRAIL

Suggested Empiric Age-Adjusted Dose Reduction in Pts With Myeloma

Agent	Younger Than 65 Yrs	65-75 Yrs	Older Than 75 Yrs
Dexamethasone	40 mg/day Days 1-4, 15-18 q4w ***or*** Days 1, 8, 15, 22 q4w	40 mg/day Days 1, 8,1 5, 22 q4w	20 mg/day Days 1, 8, 15, 22 q4w
Melphalan	0.25 mg/kg Days 1-4 q6w	0.25 mg/kg Days 1-4 q6w ***or*** 0.18 mg/kg Days 1-4 q4w	0.18 mg/kg Days 1-4 q6w ***or*** 0.13 mg/kg Days 1-4 q4w
Cyclophosphamide	300 mg/day Days 1, 8, 15, 22 q4w	300 mg/day Days 1, 8, 15 q4w ***or*** 50 mg/day Days 1-21 q4w	50 mg/day Days 1-21 q4w ***or*** 50 mg/day QOD Days 1-21 q4w
Thalidomide	200 mg/day	100 mg/day ***or*** 200 mg/day	50 mg/day to 100 mg/day
Lenalidomide	25 mg/day Days 1-21 q4w	15-25 mg/day Days 1-21 q4w	10-25 mg/day Days 1-21 q4w
Bortezomib	1.3 mg/m^2 bolus Days 1, 4, 8, 11 q3w	1.3 mg/m^2 bolus Days 1, 4, 8, 11 q3w ***or*** Days 1, 8, 15, 22 q5w	1.0- 1.3 mg/m^2 bolus Days 1, 8, 15, 22 q5w

Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.

Novel Combinations: Safety

	Rd as a backbone				PI as a backbone	
	POLLUX DRd vs Rd	ELOQUENT-2 ERd vs Rd	ASPIRE KRd vs Rd	TOURMALINE-1 IRd vs Rd	CASTOR DVd vs Vd	ENDEAVOR Kd vs VD
Discontinuation for AEs Deaths	NO INCREASE					
Renal Funtion: Creat clearence	>30 ml/min				>20 ml/min	>15ml/min
Hematologic toxicity						
G3-4 Neutropenia	52% vs 37%	34% vs 44%	30% vs 26%	23% vs 24%	13% vs 4%	-
G3-4 Thrombocytopenia	13% vs 13%	19% vs 20%	17% vs 12%	19% vs 9%	45% vs 32%	9% vs 9%
G3-4 Non hematologic	Diarrhea Infusion react	Fatigue Diarrhea Infusion react	Fatigue cardiovascular	Diarrhea Nausea rash	Infusion React hypertension PN	cardiovascular

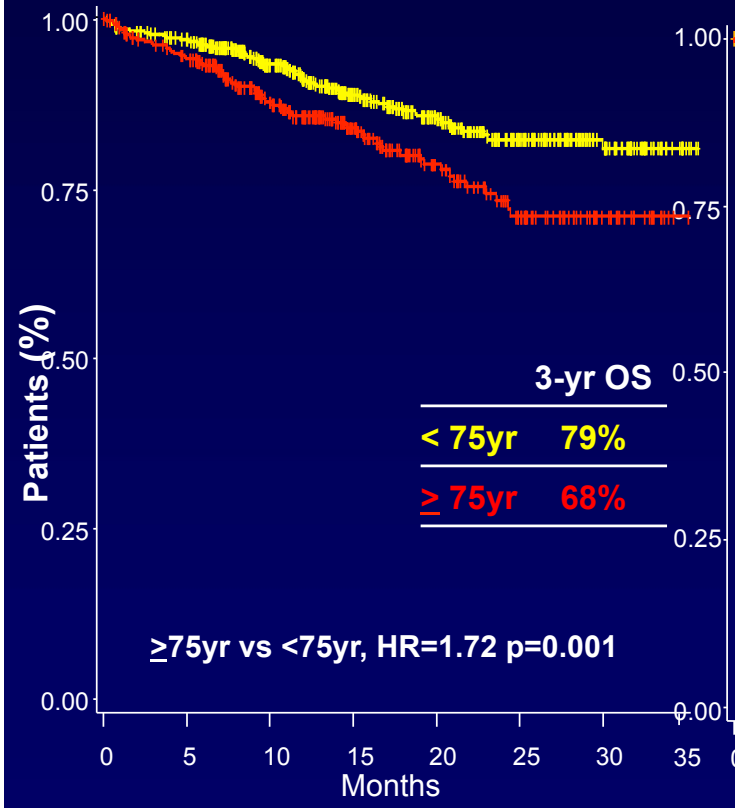
- **Triplets/second generation: no increase in treatment discontinuation or toxicity**
- **Different treatment emergent AEs**

1. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Lonial S et al. N Engl J Med 2015;373:621-31; 4. Dimopoulos MA, eta la. N Engl J Med. 2016;375(14):1319-1331; 5. Moreau P et al. NEJM 2016;374(17):1621-34; 6. Palumbo A, et al. N Engl J Med. 2016 Aug 25;375(8):754-66.

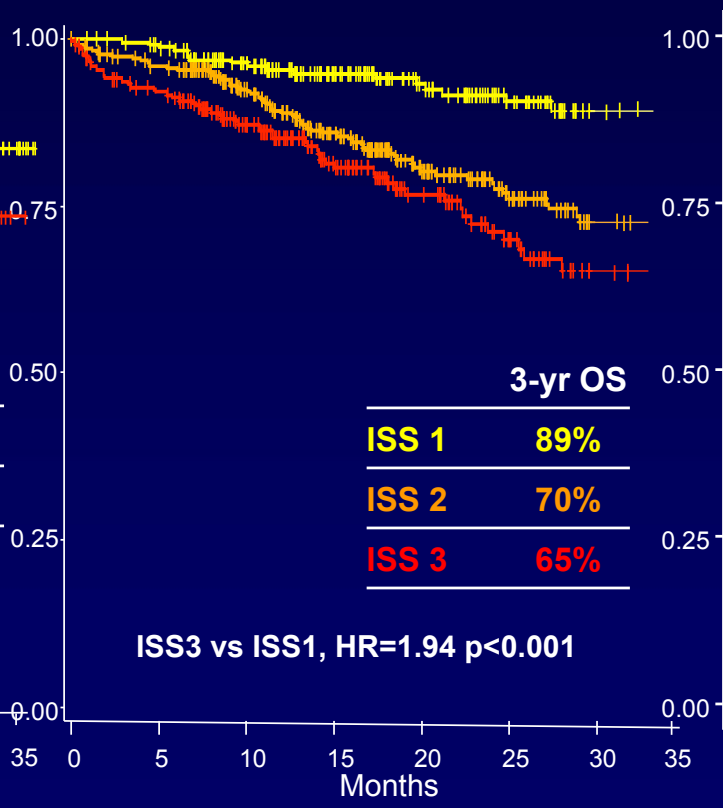
Overall Survival

Subgroup analysis in all patients

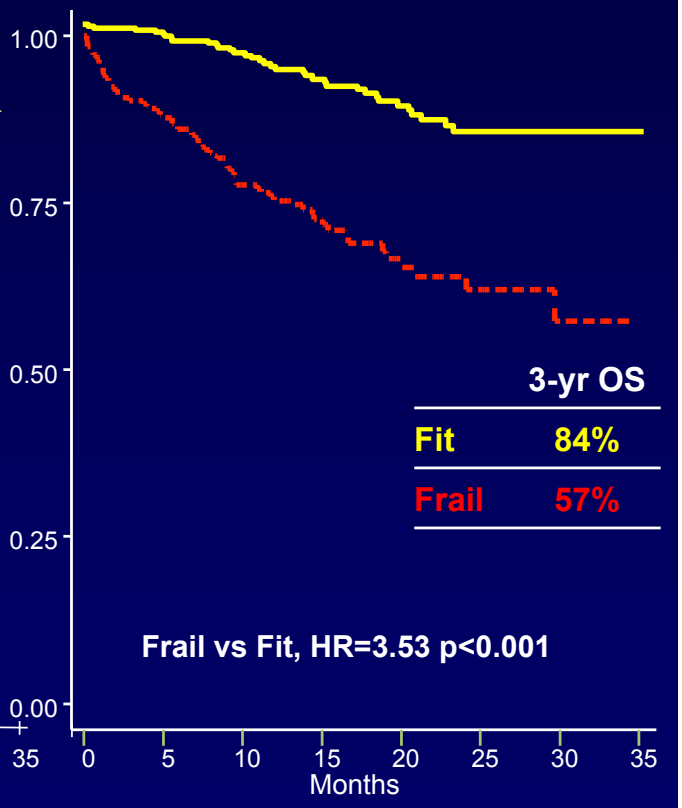
Age



ISS Stage



Frailty

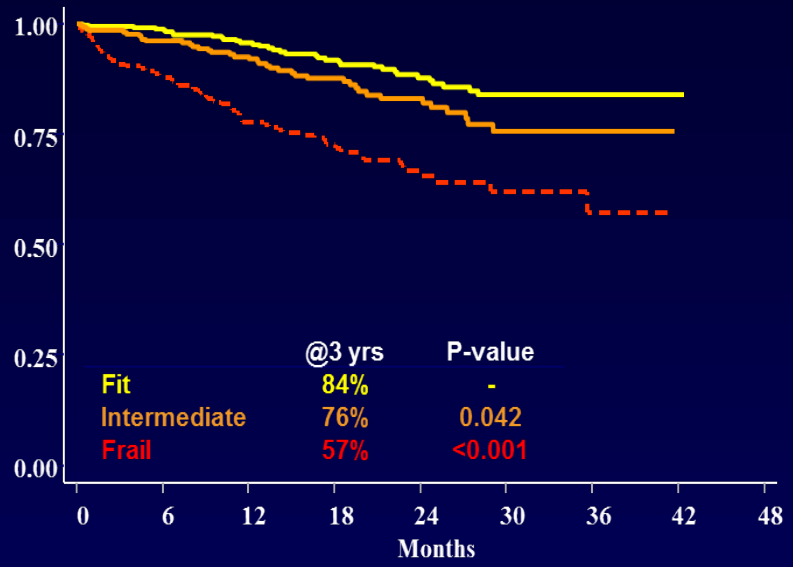


Fit defined as: score=0 Frail defined as: score≥2
HR Fish: presence of t(4;14) or t(14;16) or del 17q13

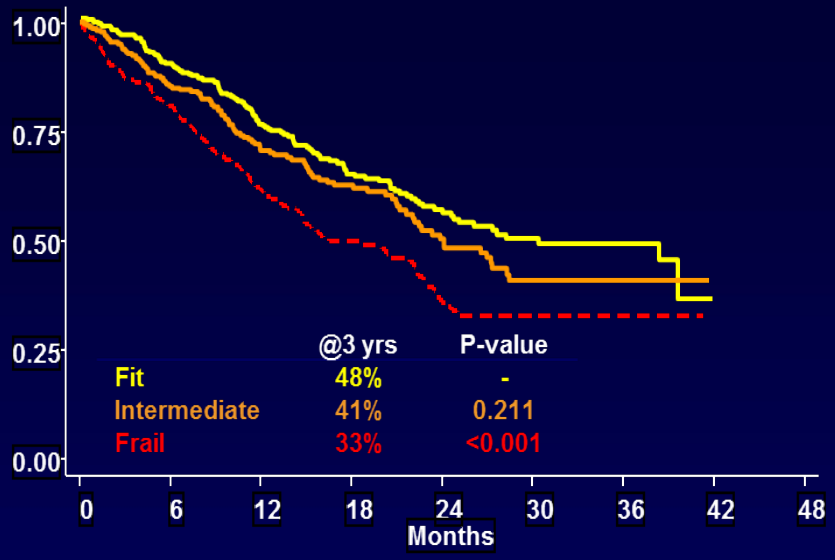
Palumbo A et al, Blood 25(13):2068-74, 2015

IMWG Frailty Score: long-term outcome

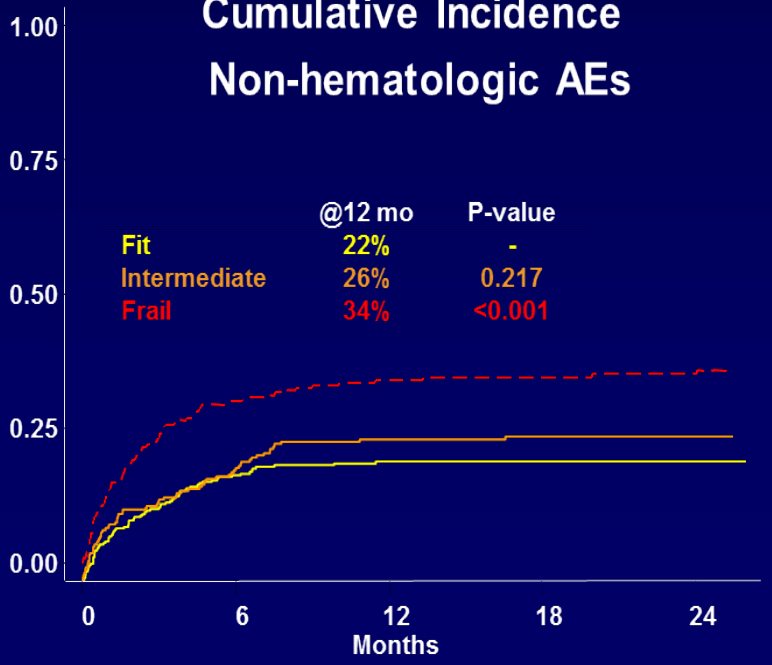
Overall Survival



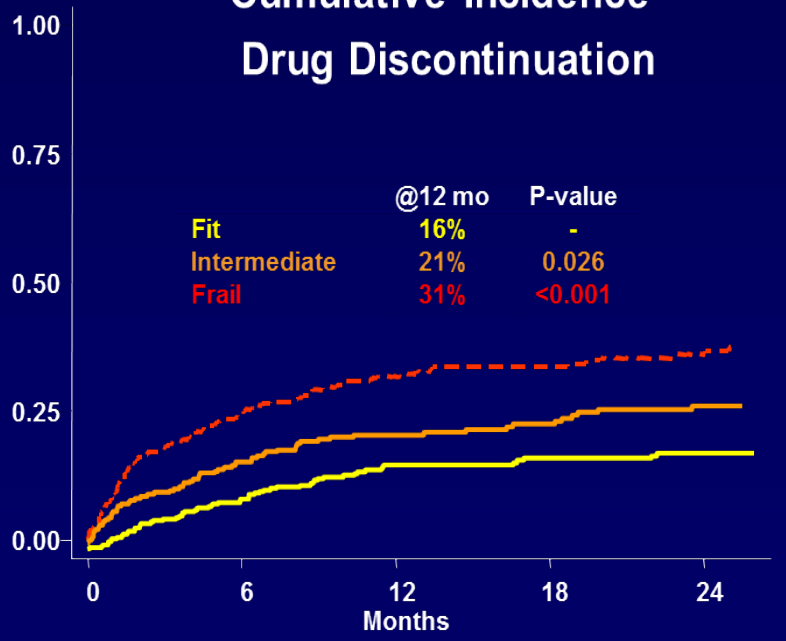
Progression-free Survival



Cumulative Incidence Non-hematologic AEs



Cumulative Incidence Drug Discontinuation



Palumbo A et al, Blood 25(13):2068-74, 2015

Novel combinations: Age

	Rd as a backbone				Vd as a backbone	
	POLLUX DRd vs Rd	ELOQUENT-2 ERd vs Rd	ASPIRE KRd vs Rd	TOURMALINE-1 IRd vs Rd	CASTOR DVd vs Vd	ENDEAVOR Kd vs VD
Median PFS (m)	NR vs 17.1	19.4 vs 14.9	26.3 vs 17.6	20.6 vs 14.7	NR vs 7.1	18.7 vs 9.4
HR	HR 0.37	HR 0.70	HR 0.69	HR 0.74	HR 0.39	HR 0.53
P value	P<0.001	P<0.001	P=0.0001	P=0.01	P<0.001	P<0.0001
Age (years)						
Median	65	66	64	66	64	65
range	(34-89)	(37-91)	(31-91)	(30-91)	(30-85)	(30-89)
65-75 years						
% pts	41%	57%°	50%°	37%	53%	38%
HR	0.4	0.65°	0.85°*	0.83	0.35	0.53
≥75						
% pts	11%	20%		15%	12%	15%
HR	0.11	0.56		0.87	0.27	0.38

- **Triplets/second generation always better than old standards**
- **All effective over 65**
- **Few data over 75**

1. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Lonial S et al. N Engl J Med 2015;373:621-31; 4. Dimopoulos MA, eta la. N Engl J Med. 2016;375(14):1319-1331; 5. Moreau P et al. NEJM 2016;374(17):1621-34; 6. Palumbo A, et al. N Engl J Med. 2016 Aug 25;375(8):754-66.

Carfilzomib: cardiovascular AEs
subgroup analysis

	All patients All grades heart failure n/N (%)
ASPIRE[1]	
KRd	27/392 (6.9)
Rd	16/389 (4.1)
ENDEAVOR[2]	
Kd	38/463 (8.2)
Vd	13/456 (2.9)
FORTE[3]	
KCyd	(3)
KRd	(5)
POOLED ANALYSIS[4]	
KCyd	17/154 (11)

1.Dimopoulos M, et al; Lancet 2015. 2.Stewart K, et al; NEJM 2015. 3.Gay F, et al. ASCO 2017. 4.Mina R, at al. IMW 2017

Carfilzomib: cardiovascular AEs
subgroup analysis

	All patients All grades heart failure n/N (%)	
ASPIRE[1]		
KRd	27/392 (6.9)	**56% resolved**
Rd	16/389 (4.1)	
ENDEAVOR[2]		
Kd	38/463 (8.2)	**37% resolved**
Vd	13/456 (2.9)	
FORTE[3]		
KCyd	(3)	
KRd	(5)	
POOLED ANALYSIS[4]		
KCyd	17/154 (11)	**67% resolved**

1.Dimopoulos M, et al; Lancet 2015. 2.Stewart K, et al; NEJM 2015. 3.Gay F, et al. ASCO 2017. 4.Mina R, at al. IMW 2017

Cardiovascular AEs according to age: subgroup analysis

	All patients All grades heart failure n/N (%)	**< 65 years** All grades heart failure n/N (%)	**65-74 years** All grades heart failure n/N (%)	**≥ 75 years** All grades heart failure n/N (%)
ASPIRE[1]				
KRd	27/392 (6.9)	7/207 (3.4)	7/142 (4.9)	**11/43 (25.6)**
Rd	16/389 (4.1)	6/184 (3.3)	7/155 (4.5)	3/50 (6)
ENDEAVOR[2]				
Kd	38/463 (8.2)	10/223 (4.5)	12/163 (7.4)	**16/77 (20.8)**
Vd	13/456 (2.9)	5/208 (2.4)	5/183 (2.7)	3/65 (4.6)
FORTE[3]				
KCyd	(3)	(3)	-	-
KRd	(5)	(5)	-	-
POOLED ANALYSIS[4]				
KCyd	17/154 (11)	-	9/117 (7.7)	**8/37 (21.6)**

1.Dimopoulos M, et al; Lancet 2015. 2.Stewart K, et al; NEJM 2015. 3.Gay F, et al. ASCO 2017. 4.Mina R, at al. IMW 2017

MoAb-related Adverse-Events

The majority (95%) of IRRs occurred at the first infusion. Most events occurred within the first few hours after the start of the infusion.

Patients with underlying pulmonary disease such as COPD or asthma are at increased risk for bronchospasms.

Infusion Related Reactions (IRRs)

STUDY	Grade 1-2	Grade 3-4	Discontinuation
Elotuzumab + Rd[1]	9%	1%	<1%
Elotuzumab + Vd[2]	7%	0	0
Daratumumab + Rd[3]	43%	5%	<1%
Daratumumab + Vd[4]	36%	9%	<1%

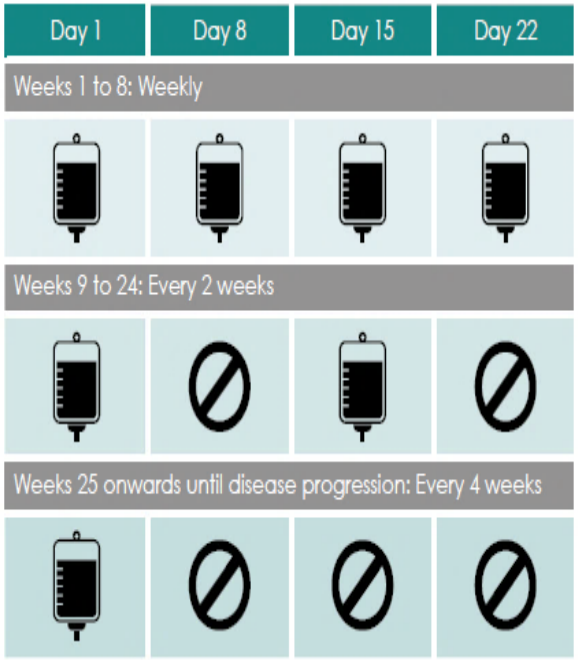
MoAb, monoclonal antibody; Rd, lenalidomide-dexamethasone; Vd, bortezomib-dexamethasone

≥ 5% of pts:
- nasal congestion,
- cough,
- chills,
- allergic rhinitis,
- throat irritation,
- dyspnoea,
- nausea.

Bronchospasm (2.6%)
Hypertension (1.3%)
Hypoxia (1.3%).

Lonial S, et al. NEJM 2015; Jakubowiak A, et al. Blood 2016; Dimopoulos MA, et al. NEJM 2016; Palumbo A, et al. NEJM 2016

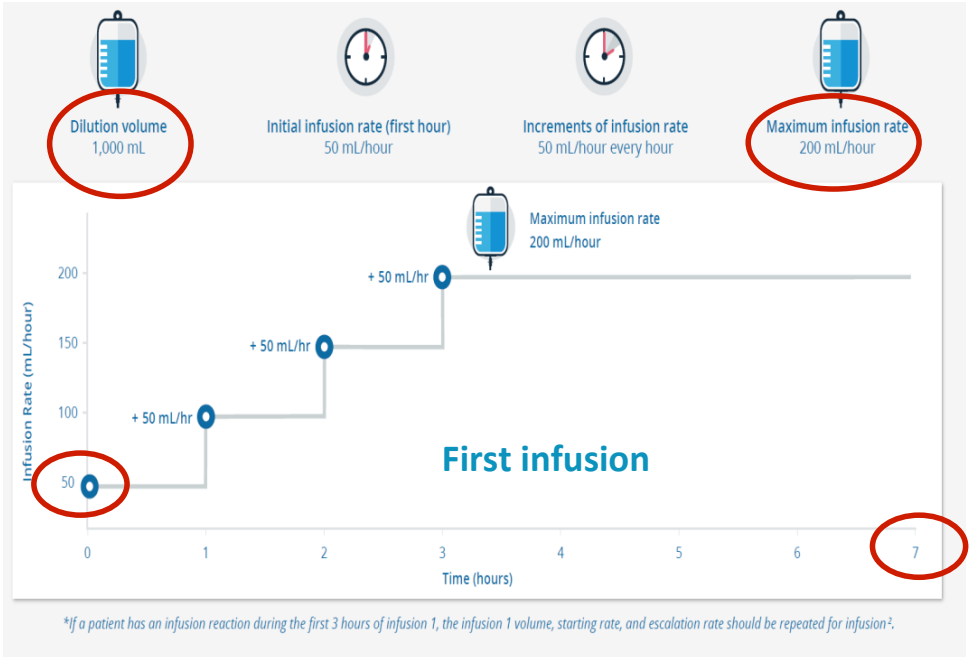
Daratumumab infusion



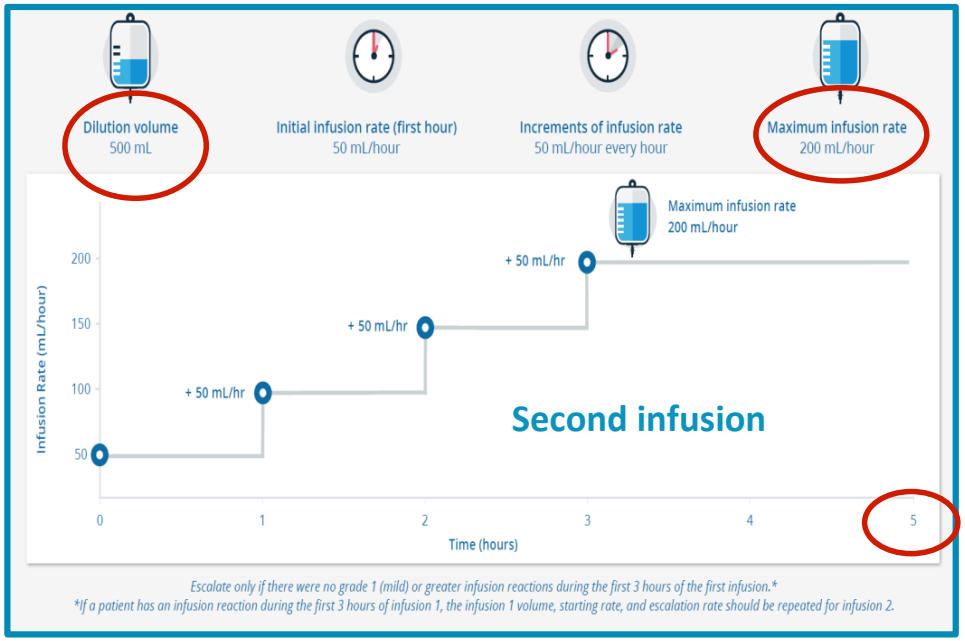
Infusion flow control
Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator

Pre-medications
1 hour prior to every daratumumab infusion

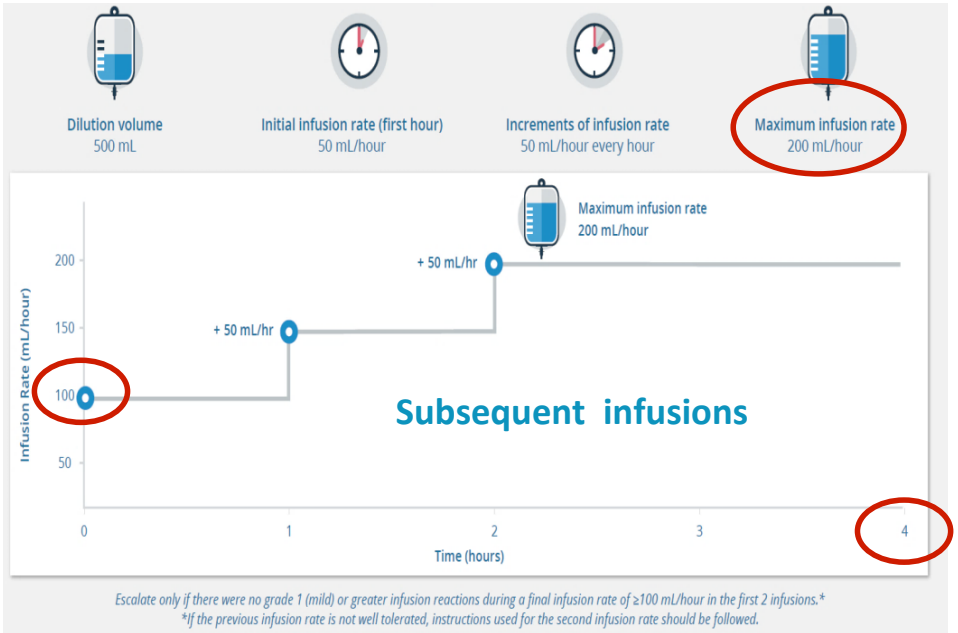
Post-medications
On each of the two days following all infusions (beginning the day after the infusion)



*If a patient has an infusion reaction during the first 3 hours of infusion 1, the infusion 1 volume, starting rate, and escalation rate should be repeated for infusion[2].



*Escalate only if there were no grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.**
**If a patient has an infusion reaction during the first 3 hours of infusion 1, the infusion 1 volume, starting rate, and escalation rate should be repeated for infusion 2.*



*Escalate only if there were no grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hour in the first 2 infusions.**
**If the previous infusion rate is not well tolerated, instructions used for the second infusion rate should be followed.*

Prevention of IRRs

- Administer **pre-medication** to reduce the risk of IRRs (approximately 1 hour prior to every daratumumab infusion)
  - intravenous corticosteroid (methylprednisolone 100 mg or equivalent)
  - oral antipyretic (paracetamol at 650-1000 mg)
  - oral or intravenous antihistamine (diphenhydramide 25-50 mg or equivalent)

- **Post-medication** corticosteroids on 1st and 2nd day after all infusions

- **In case of occurrence of IRRs**
  - React early to mild signs of symptoms and **immediately stop the infusion**
  - Manage symptoms appropriately, consider e.g. antihistamines, corticosteroids
  - Once symptoms have resolved, treatment resumed at half the infusion rate
  - In case of grade 4 IRRs permanently discontinue treatment.

Adapted from: Protocol for: Lokhorst et al. N Engl J Med 2015 Aug 26 [Epub]
EMA SmPC Nov 2016

Daratumumab in specific populations

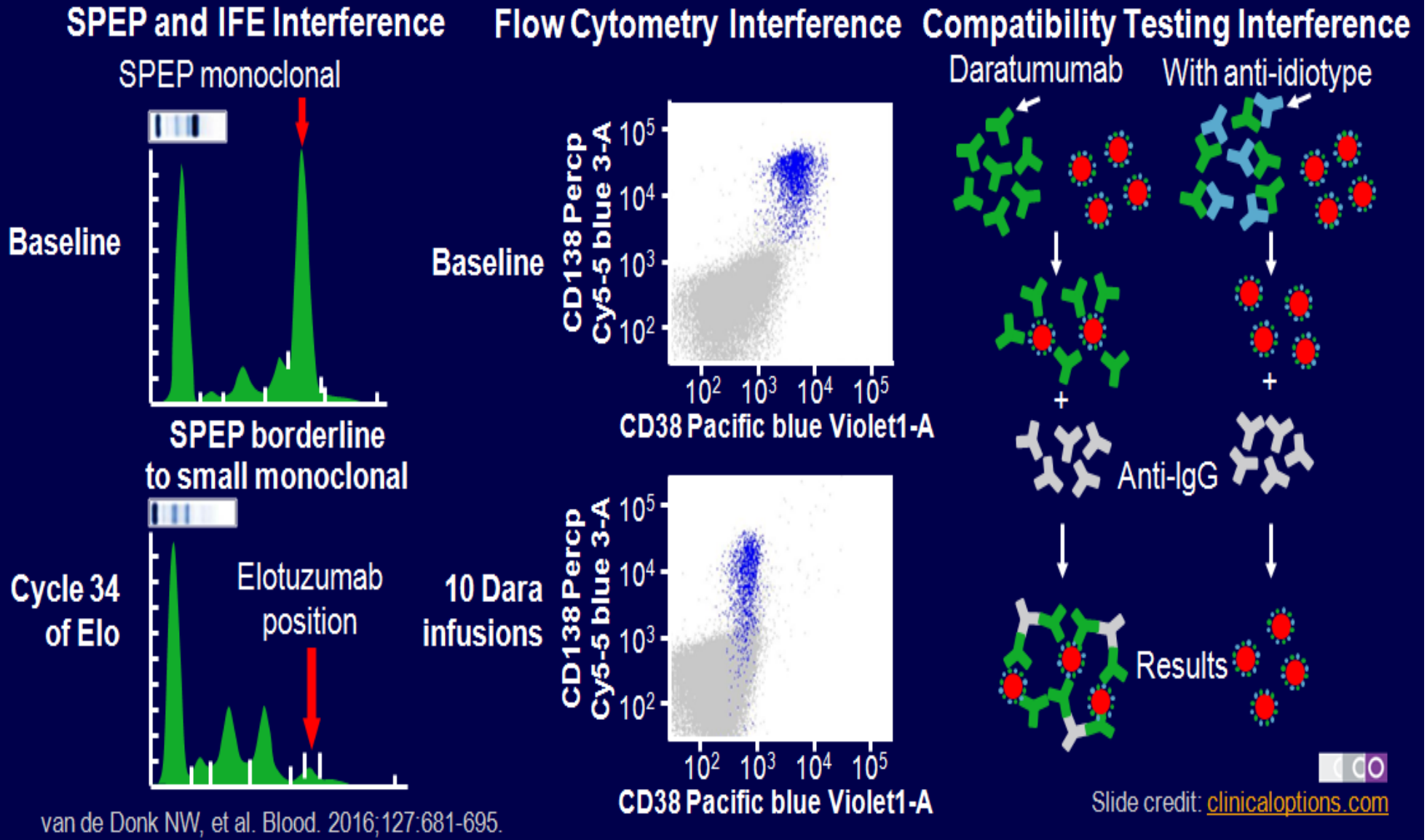
Liver dysfunction. No dose modifications are necessary for patients with mild hepatic impairment based on population pharmacokinetic analysis. No data are available for moderate or severe hepatic impairment (accessed 19 July 2016).

Renal dysfunction. DARA is not metabolized by the kidney; such that renal failure is not a contraindication for treatment. The GEN501 and SIRIUS trials each included patients with mild-to-moderate renal failure, creatinine clearance 30–60 ml/min and the ORR in these patients was 26.2%. [Lonial *et al.* 2016b]. No data are available to provide guidance on patients with severe renal impairment.

Advanced age. The GEN501 was administered to 16 patients aged 65–74 years, 56% of whom responded [Lokhorst *et al.* 2015], while none of the 4 patients over age 75 responded. In the SIRIUS trial, 36 patients were aged 65–74 years, and 12 patients were 75 years or older. The ORR in these subgroups of patients was 25% and 33.3%, respectively, suggesting that the efficacy of DARA is equivalent in all age groups.

Costello C, Ther Adv Hematol 2017

Laboratory Interference Associated With mAbs



van de Donk NW, et al. Blood. 2016;127:681-695.

Slide credit: clinicaloptions.com

Strategies at Relapse : How to Make the Right Choice

EARLY RELAPSE

No refractory to LENALIDOMIDE

KRd | DRd | ERd | IRd | Rd

FIT
All the options, no IRd if ASCT

INTERMEDIATE
DRd or Erd or Ird

FRAIL
Ird or Rd

HIGH RISK/ AGGRESSIVE
KRd or DRd

STANDARD RISK
All the options

No refractory to BORTEZOMIB

Kd | DVd | PVd | Vd

FIT
All the options

INTERMEDIATE
DVd or Vd

FRAIL
Vd

HIGH RISK/ AGGRESSIVE
Kd or DVd

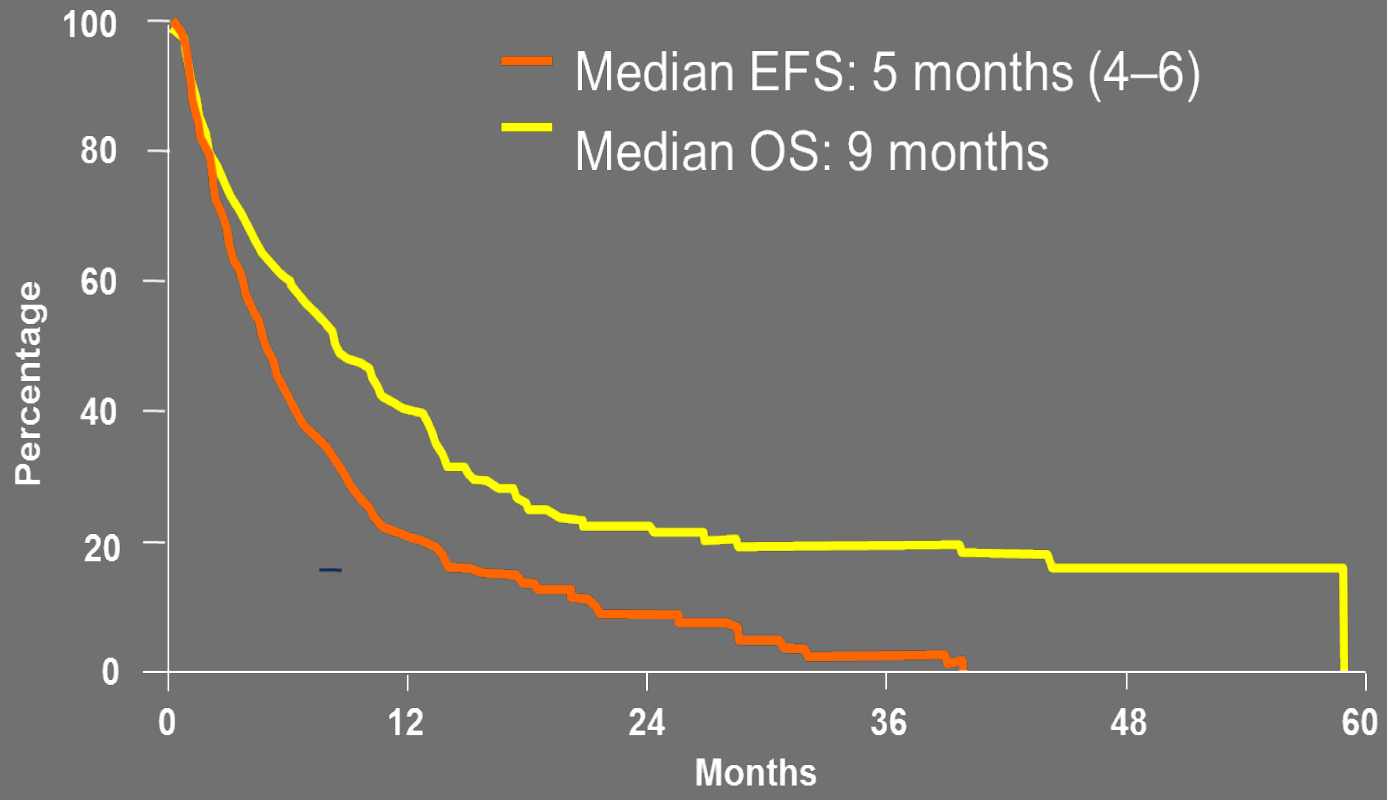
STANDARD RISK
All the options

How can we choose the right treatment?

1. Bortezomib or Lenalidomide refractory
2. N. of prior lines
3. High vs standard risk
4. Safety profile
5. Frailty
6. **Bortezomib AND Lenalidomide refractory**

Outcome from relapse

Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib

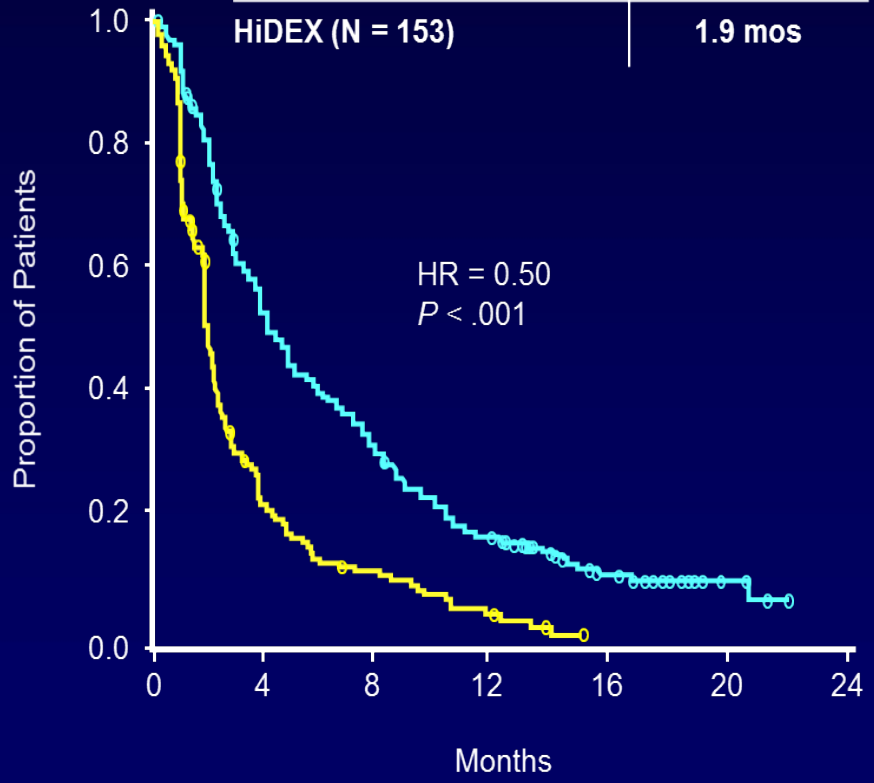


Kumar SG et al, Leukemia 2012

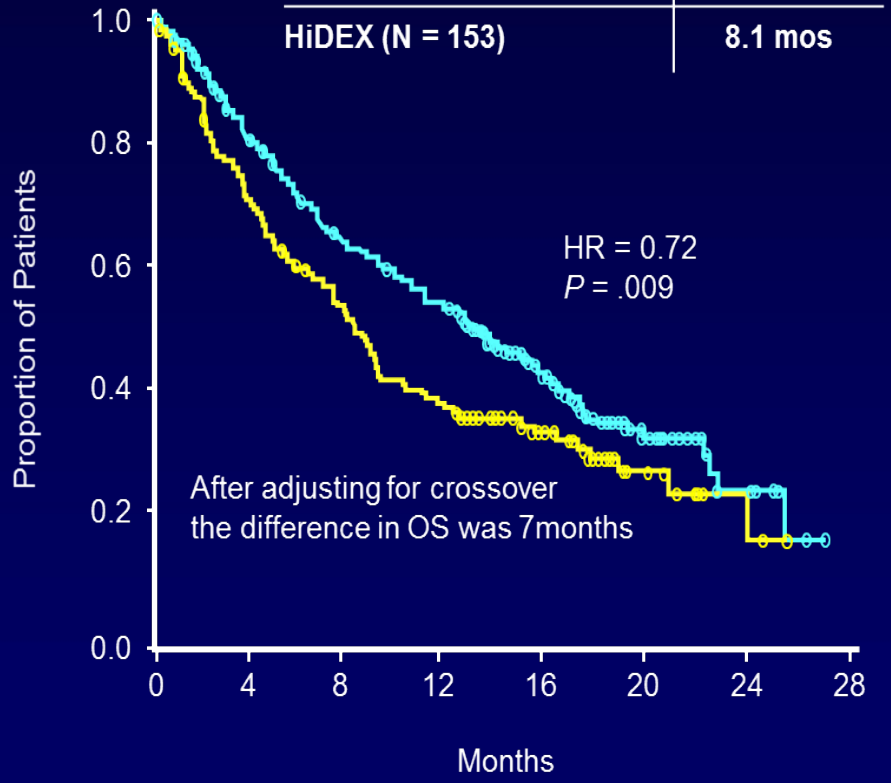
Pomalidomide and low dose Dex

Superior PFS and OS independently of double refractory disease

	Median PFS
POM + LoDEX (N = 302)	4.0 mos
HiDEX (N = 153)	1.9 mos



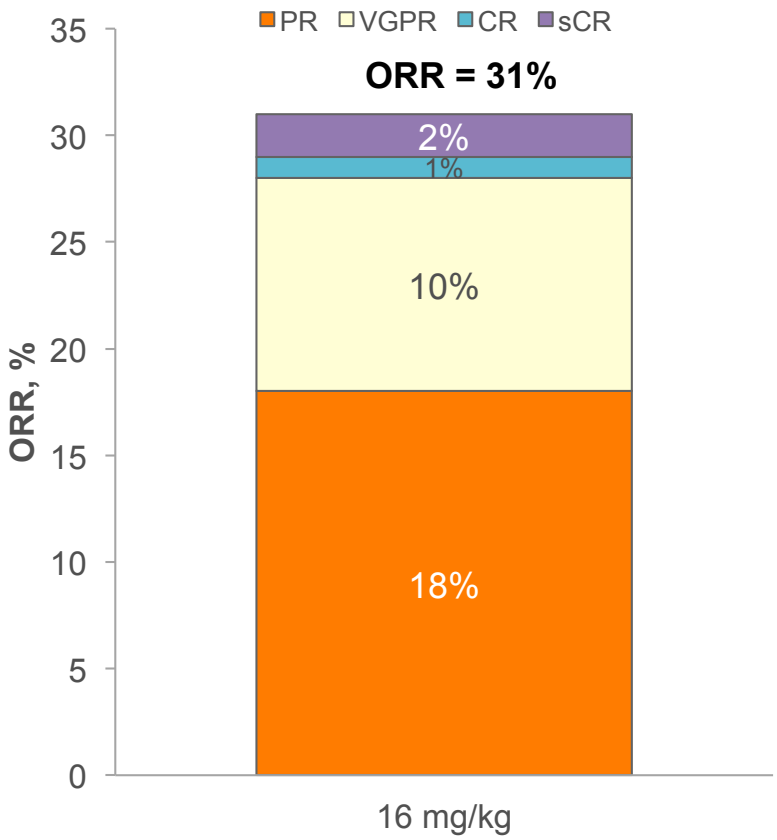
	Median OS
POM + LoDEX (N = 302)	13.1 mos
HiDEX (N = 153)	8.1 mos



San-Miguel et al Lancet Oncology 2013;14(11):1055-66

Efficacy of Daratumumab as single agent: Combined Analysis

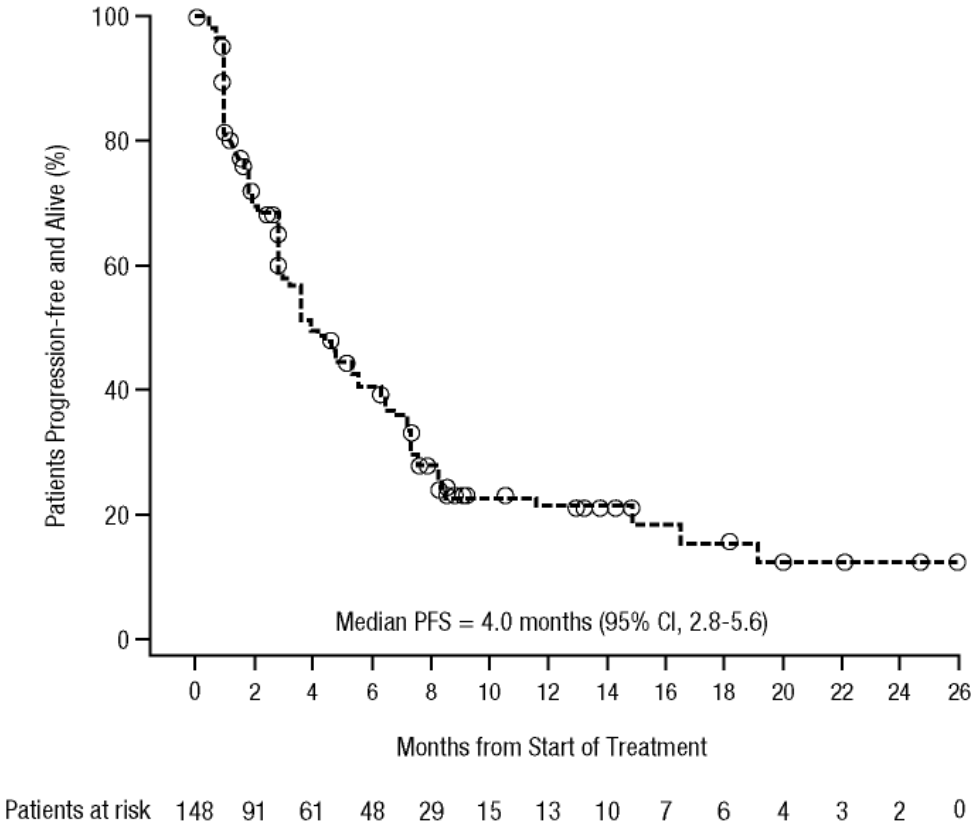
	16 mg/kg (N = 148)	
	n (%)	**95% CI**
ORR (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR+VGPR)	19 (13)	7.9-19.3
CR or better (sCR+CR)	5 (3)	1.1-7.7

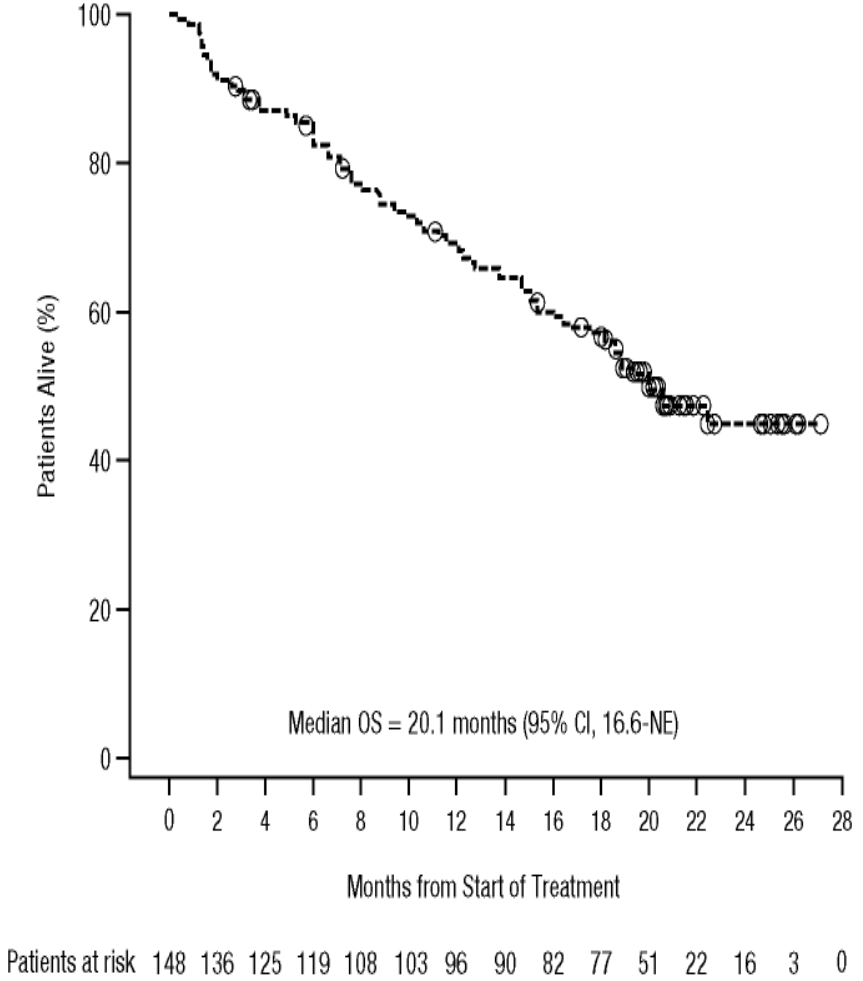


- **ORR = 31%**
- **CBR = 83% → OS benefit observed also in SD/MR pts**
- Median (range) **TTR: 0.95** (0.5-5.6) months
- Median **DOR = 7.6** (95% CI, 5.6-NE) months; responses deepened with continued treatment (7/10 PR → VGPR; 3 PR → CR - 1 patient - sCR - 2 patients)

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

Daratumumab Monotherapy – PFS/OS





Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

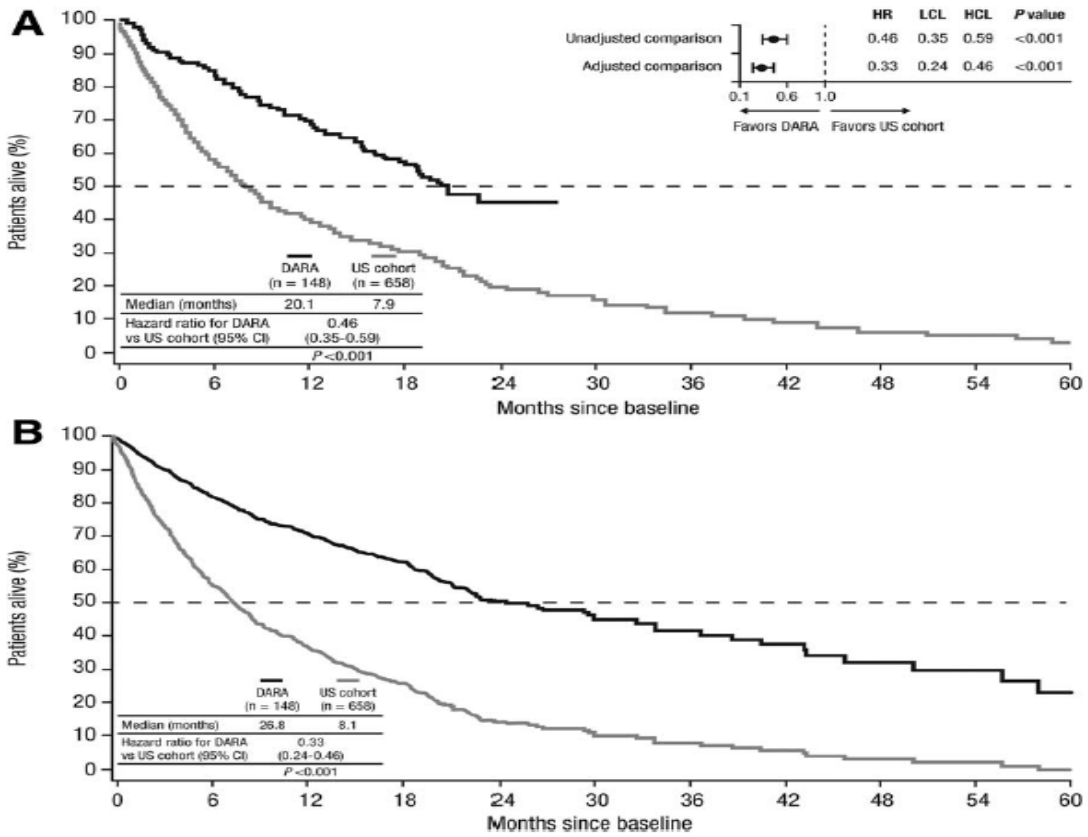
Received: 18 October 2016 | Revised: 28 April 2017 | Accepted: 1 May 2017
DOI: 10.1002/ajh.24781

RESEARCH ARTICLE

WILEY AJH

Daratumumab monotherapy compared with historical control data in heavily pretreated and highly refractory patients with multiple myeloma: An adjusted treatment comparison

Saad Z. Usmani[1] | Joris Diels[2] | Tetsuro Ito[3] | Maneesha Mehra[4] | Imran Khan[5] | Annette Lam[4]



OS

FIGURE 1 Unadjusted (A) and adjusted (B) overall survival in daratumumab-treated patients versus historical controls from US claims databases. Adjusted and unadjusted HRs are also shown in the forest plot (A). HR, hazard ratio; LCL, lower confidence level; HCL, higher confidence level; DARA, daratumumab; CI, confidence interval

Received: 28 July 2017 | Revised: 7 August 2017 | Accepted: 8 August 2017
DOI: 10.1002/ajh.24883

RESEARCH ARTICLE

WILEY AJH

Efficacy of daratumumab-based therapies in patients with relapsed, refractory multiple myeloma treated outside of clinical trials

Arjun Lakshman[1] | Jithma P. Abeykoon[2] | Shaji K. Kumar[1] | S. Vincent Rajkumar[1] | David Dingli[1] | Francis K. Buadi[1] | Wilson I. Gonsalves[1] | Nelson Leung[1] | Angela Dispenzieri[1] | Taxiarchis V. Kourelis[1] | Ronald S. Go[1] | Martha Q. Lacy[1] | Miriam A. Hobbs[1] | Yi Lin[1] | Rahma Warsame[1] | John Lust[1] | Amie L. Fonder[1] | Yi L. Hwa[1] | Suzanne R. Hayman[1] | Stephen J. Russell[1] | Robert A. Kyle[1] | Morie A. Gertz[1] | Prashant Kapoor[1]

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Abstract

Outside of clinical trials, experience with daratumumab-based combination therapies (DCTs) using bortezomib (V)/lenalidomide (R)/pomalidomide (P), and dexamethasone (d) in relapsed/refractory multiple myeloma (RRMM) is limited. We reviewed the outcomes of 126 patients who received ≥ 1 cycle of any DCT. Median age at DCT initiation was 67 (range, 43-93) years. High-risk cytogenetics was present in 33% patients. Median number of prior therapies was 4 (range, 1-14) and time to first DCT from diagnosis was 4.3 years (range, 0.4-13.0). Seventeen (13%) patients were refractory to single agent daratumumab. Fifty-two (41%), 34 (27%), 23 (18%), and 17 (14%) received DPd, DRd, DVd and "other" DCTs, respectively. Overall response rate was 47%. Median follow-up was 5.5 months (95% CI, 4.2-6.1). Median progression-free survival (PFS) was 5.5 months (95% CI, 4.2-7.8). Median overall survival was not reached (NR) with any regimen. Median PFS (months) was worst for penta-refractory MM ($n = 8$) vs quadruple refractory MM ($n = 18$) and others ($n = 100$) (2.2 [95% CI, 1-2.4] vs 3.1 [95% CI, 2.1-NR] vs 5.9 [95% CI, 5.0-NR]; $P < .001$); those who were refractory to ≥1 agents used in the DCT vs others (4.9 [95% CI, 3.1-6.0] vs 8.2 [95% CI, 4.6-NR]; $P = .02$); and those who received >2 prior therapies vs others (5.0 months [95% CI, 3.7-5.9] vs NR [95% CI, NR-NR]; $P = .002$). Non-hematologic toxicities included infections (38%), fatigue (32%), and infusion reactions (18%). Grade 3 or higher hematological toxicities were seen in 41% of patients. DCTs are effective in RRMM. ORR and PFS in heavily pretreated patients are lower than those reported in clinical trials.

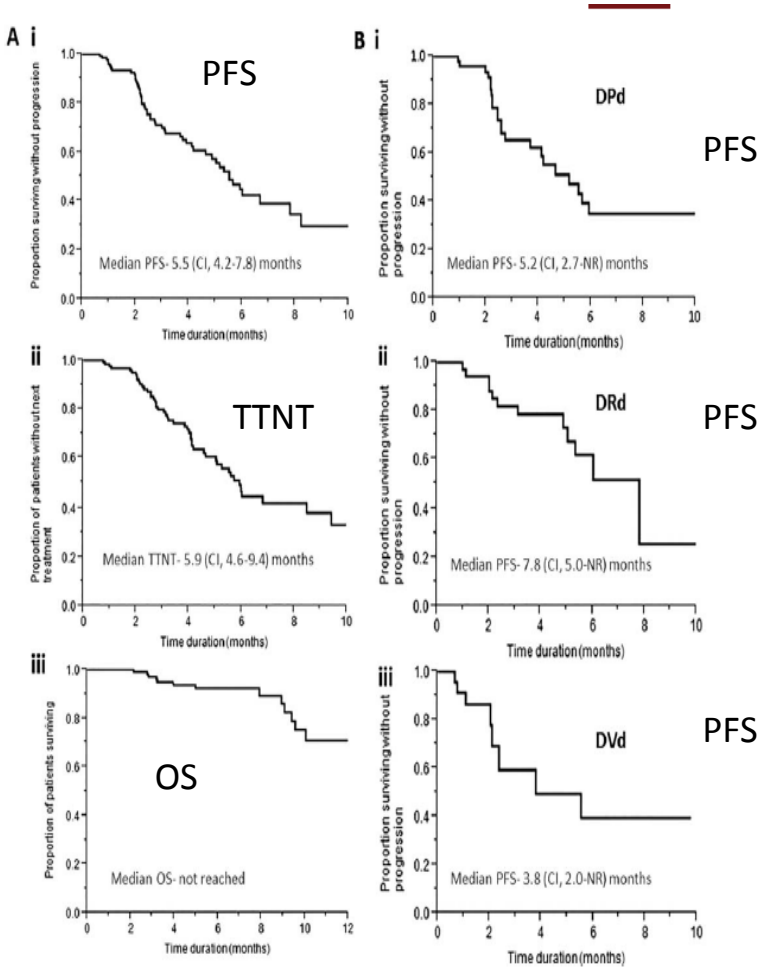
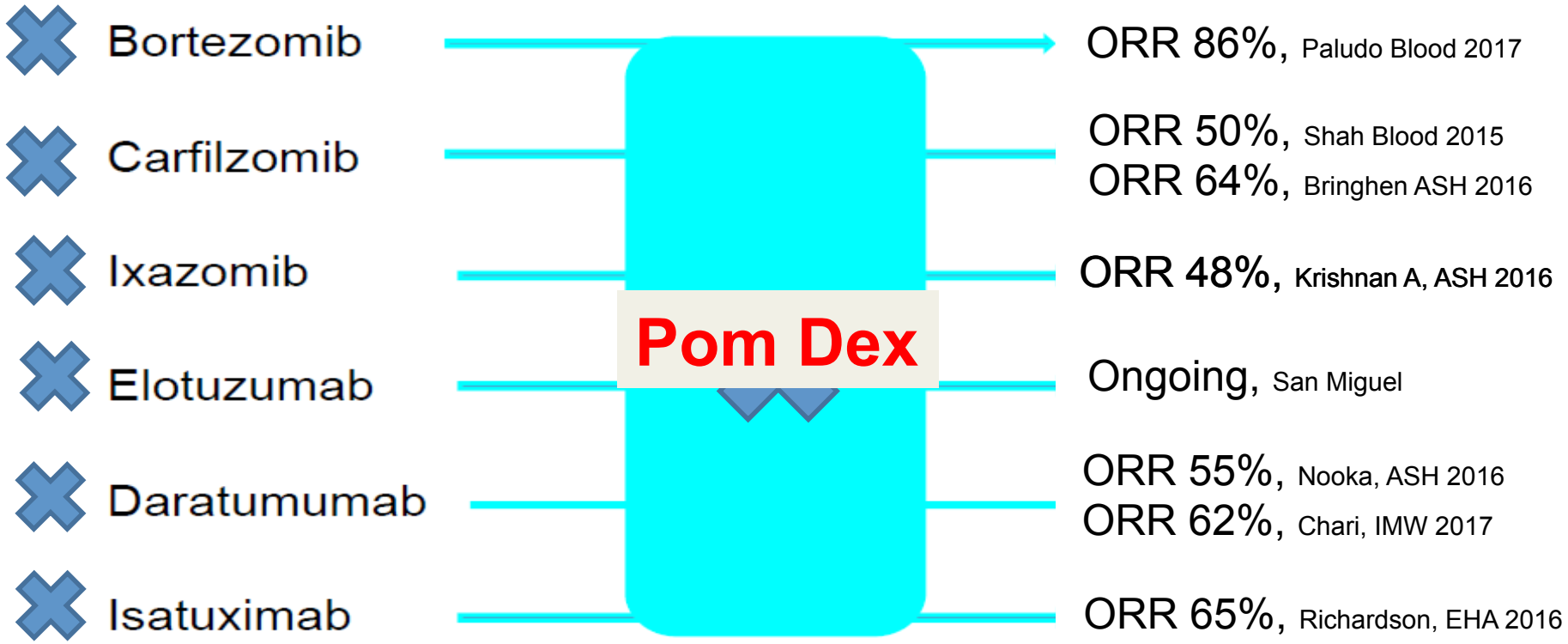


FIGURE 1 (A) Outcomes for patients receiving daratumumab-based therapies. Kaplan-Meier curves for patients receiving daratumumab-based therapies showing, (i) progression-free survival (PFS), (ii) time to next treatment (TTNT) and (iii) overall survival (OS). (B) PFS in patients receiving daratumumab-based therapies stratified by treatment regimens- Kaplan Meier curves showing progression-free survival (PFS) for patients receiving, (i) daratumumab with pomalidomide and dexamethasone (DPd) (ii) daratumumab with lenalidomide and dexamethasone (DRd) and (iii) daratumumab with bortezomib and dexamethasone (DVd).

How to improve long term outcome in double refractory: the case of Pomalidomide-based triplets in RRMM



Strategies at Relapse : How to Make the Right Choice

EARLY RELAPSE

No refractory to LENALIDOMIDE

KRd | DRd | ERd | IRd | Rd

FIT
All the options, no IRd if ASCT

INTERMEDIATE
DRd or Erd or Ird

FRAIL
Ird or Rd

HIGH RISK/ AGGRESSIVE
KRd or DRd

STANDARD RISK
All the options

No refractory to BORTEZOMIB

Kd | DVd | PVd | Vd

FIT
All the options

INTERMEDIATE
DVd or Vd

FRAIL
Vd

HIGH RISK/ AGGRESSIVE
Kd or DVd

STANDARD RISK
All the options

LATE RELAPSE

Pomalidomide and dexamethasone

Daratumamab

Clinical Trial

K, Carfilzomib; R, lenalidomide; d, low-dose dexamethasone; D, daratumumab; E, elotuzumab; I, Ixazomib; V, bortezomib; P, Panobinostat.

Fitness defined as Internatioanl Myeloma Frailty Score (Palumbo A, et al. Blood 2015). High-risk defined as cytogenetic high risk (presence of Del(17p), t(4;14), and t(14;16)) and/or aggressive disease (extramedullary disease, acute renal failure, monoclonal component doubling in 2 months).

Upfront versus delayed ASCT

autore	terapia	Median PFS	4 y OS
Palumbo et al, NEJM 2014	Induzione: RD Consolidamento: MRP vs Mel 200	MRP: 22 mesi Mel 200:42 mesi	MPR : 79% Mel 200: 88%
Gay et al, Lancet Oncology 2015	Induzione RD Consolidamento: CRD vs Mel 200	CRD: 28 mesi Mel 200:43 mesi	CRD : 73% Mel 200: 86%
Attal et al, ASH 2015	Induzione RVD Consolidamento: RVD vs Mel 200	RVD: 34 mesi Mel 200:43 mesi	MPR : 81% Mel 200: 83%
Cavo et al, ASCO 2016	Induzione VCD Consolidamento: VMP vs Mel 200	PFS prolungata nel gruppo Mel 200 (HR 0.52)	data not mature

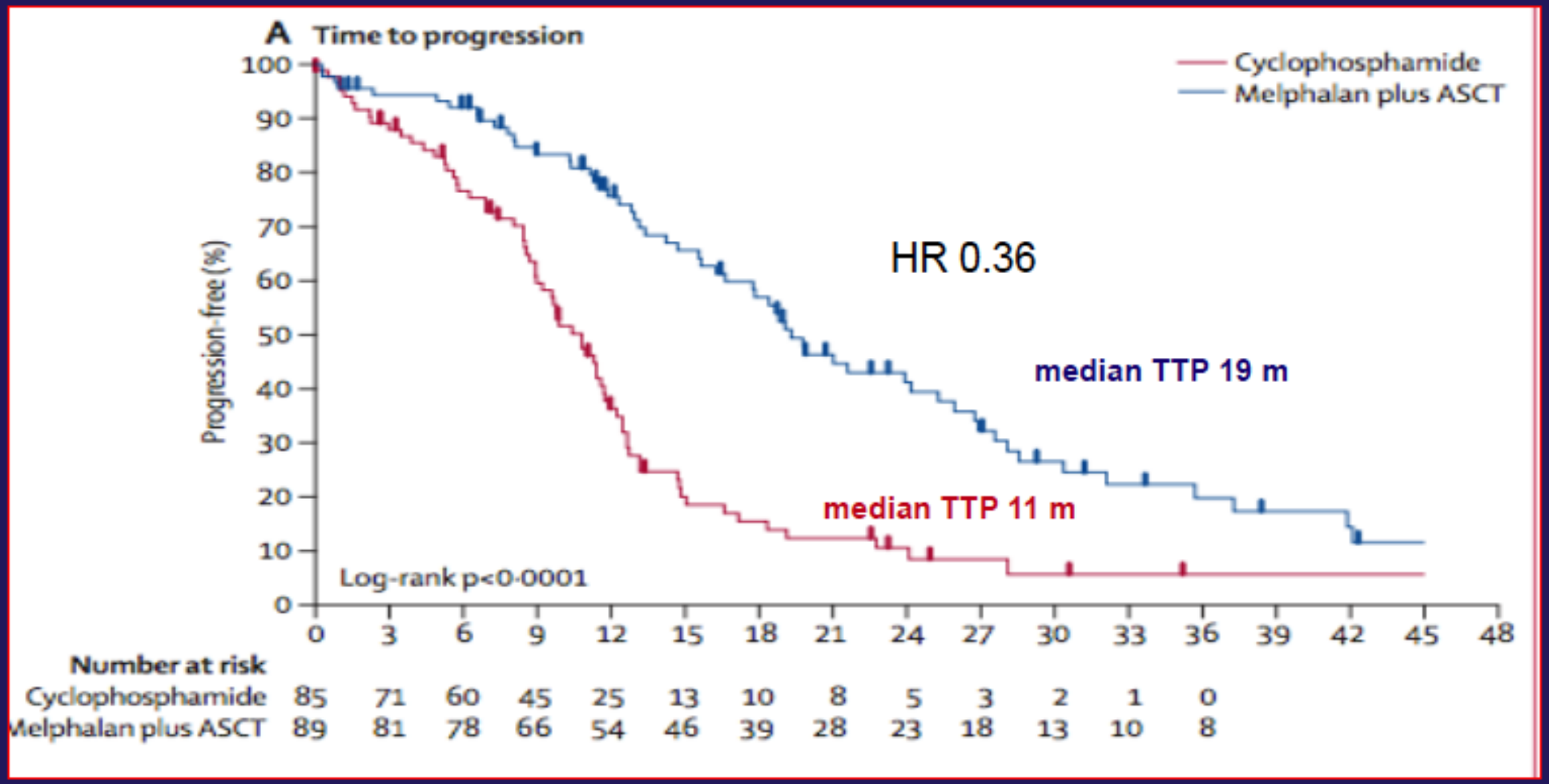
Secondo Trapianto in salvataggio

	N° pz	N° linee precedenti	Response rate	PFS (months)	OS (months)
Gonsalves *et al.* 2013	98	3	87% (CR 31%)	10	33
Lemieux *et al.* 2013	81	n.r.	93% (CR n.r.)	8	48
Sellner *et al.* 2013	200	n.r.	68% (CR 25%)	12	34
Auner *et al.* 2013	83	n.r.	n.r.	15	32
Jimenez *et al.* 2012	81	1	96% (CR 8%)	10 * 17	28 * 71
Michaelis *et al.* 2011	187	n.r.	80% (CR 25%)	15	42

* PFS e OS separati in base alla durata di risposta del primo AutoSCT > o < 2 anni

Il numero di linee precedenti e l'intervallo tra primo autologo ed autologo di salvataggio sono i fattori determinanti dell'outcome

Fase 3 autologo di salvataggio vs terapia convenzionale



Cook G et al, Lancet Oncology 2014

Aggiornamento dello studio

	Mel 200	CTX	HR
TTP1 mediana	19	11	0.45
OS mediana	67	52	0.56
TTP2 mediana	52	35	0.37
Secondi tumori	7/89 (8%)	5/85 (6%)	ns

Cook G et al, Lancet Haematology 2016

Trapianto autologo nel MM refrattario

126 pts nel registro inglese <PR prima del trapianto autologo , 47% dopo autologo di salvataggio
Condizionamento: melphalan 100-200 mg/mq
CR 21%, PR 74% al giorno + 100
PFS mediana 28 mesi, OS mediana 51 mesi

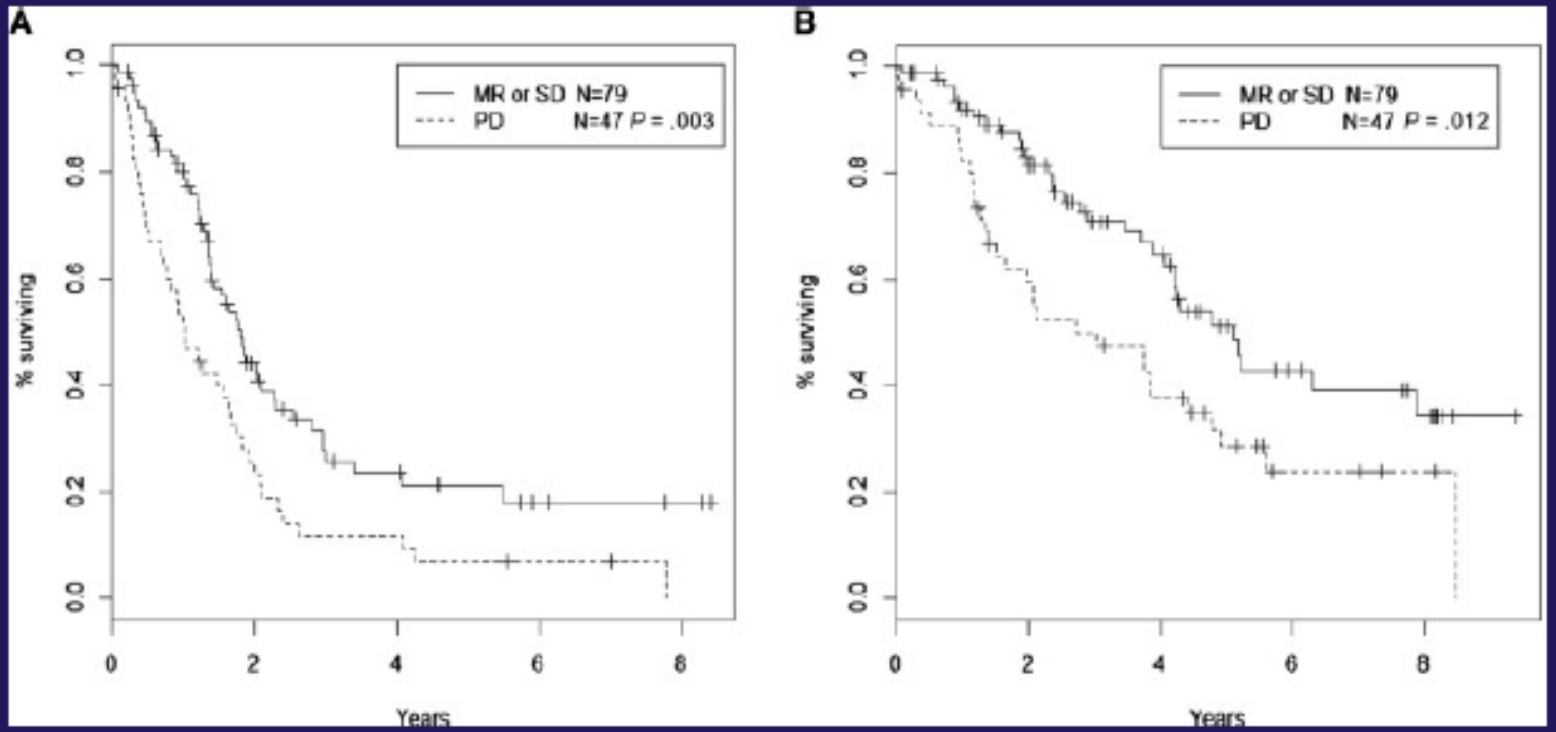
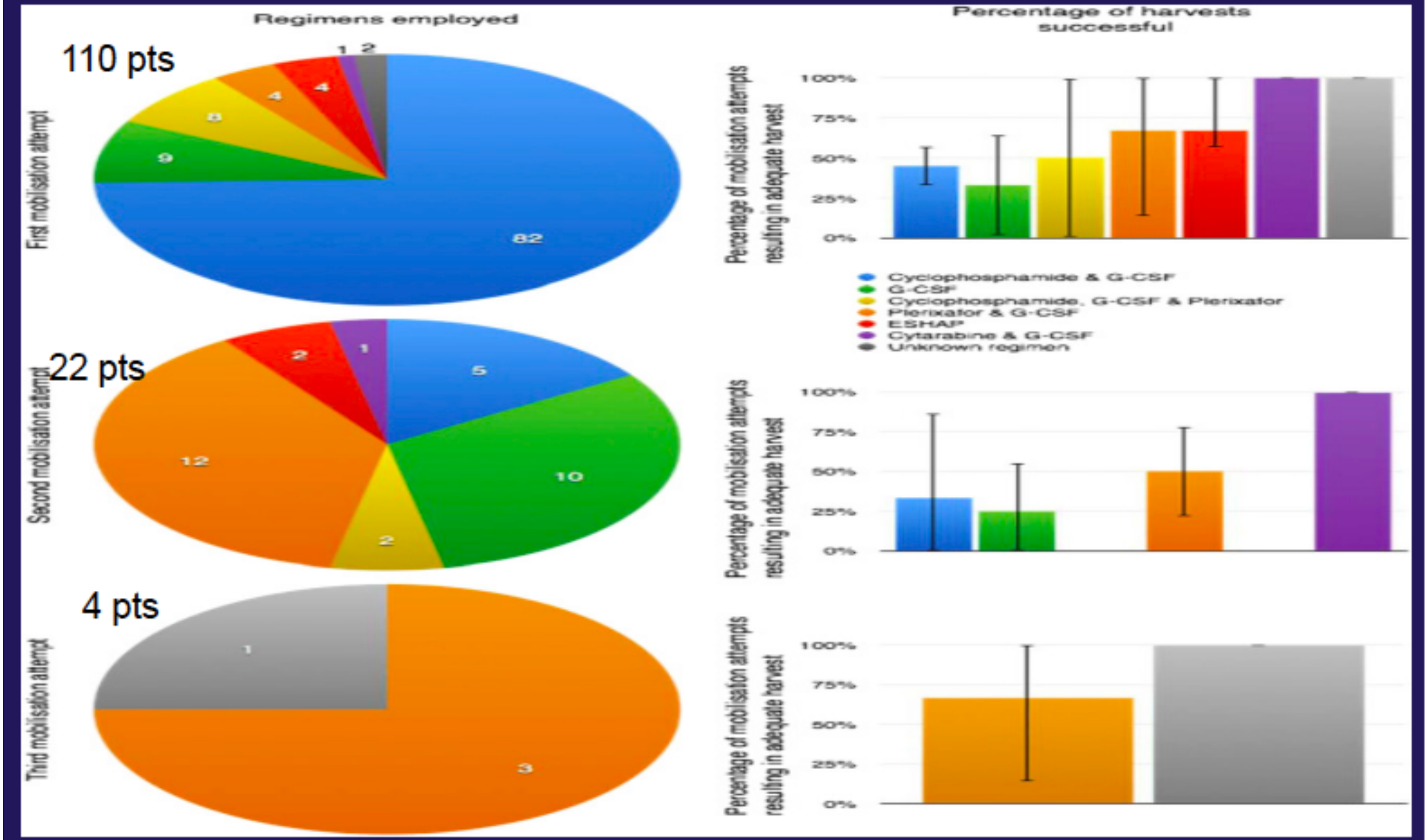


Figure 1. Kaplan-Meier estimates. (A) Shows PFS by disease status at transplantation and (B) shows OS by disease status at transplantation.

Parrish C et al, BBMT 2015

Risultati della rimobilizzazione in 110 pazienti



64% dei pts senza cellule congelate adeguate rimobilizzano PBSC

Parrish C et al, BBMT 2016

CONCLUSIONI E PROSPETTIVE

- Il trapianto autologo di salvataggio dopo terapia di prima linea che NON include alte dosi di chemioterapia è inferiore ad un autologo up-front.

- L' autologo di salvataggio dopo terapia di prima linea che include alte dosi di chemioterapia è fattibile in una proporzione di pazienti (16-59%) ed è efficiente se la durata PFS1 è > di 18- 24 mesi.

- Il trapianto autologo di salvataggio dovrebbe far parte di nuove piattaforme di trattamento della prima ricaduta , che includono nuovi condizionamenti (melphalan + bendamustina o bortezomib) e terapie post-trapianto.

Treatment Strategy: general principles

Multifactorial decision process

Benefit of three drug regimens in early phases of the disease

- Many combo available
- Possibility to choose the most suitable mainly (but not only!) according to pt fitness and previous treatments

At present, no triplets available in late phases of the disease

- In late phases, tolerability can become even more relevant than in early phases

Generally better to switch to a different class of agent

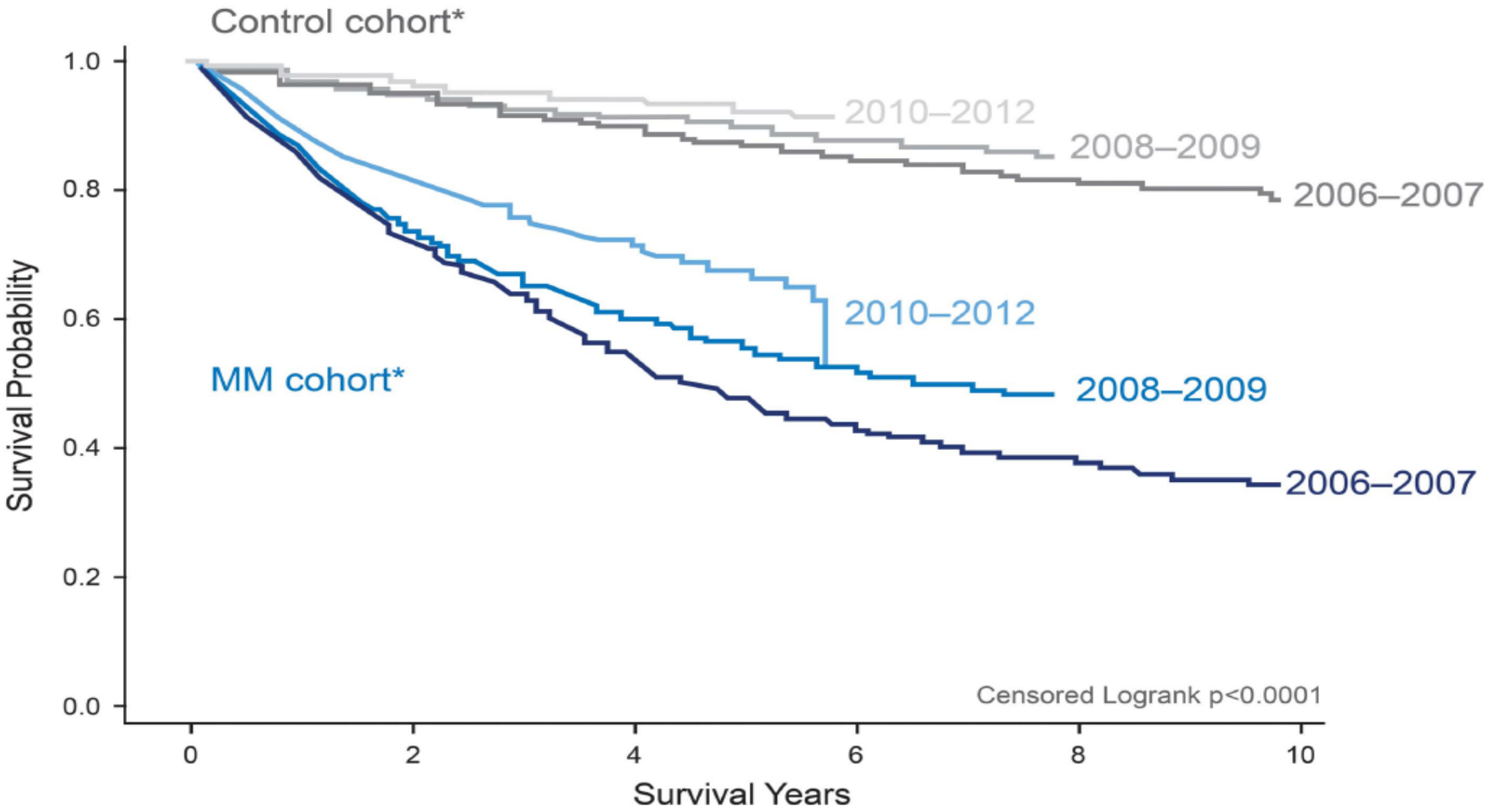
- At least one drug from a non-refractory class

Aggressiveness

But consider re-treatment in specific cases

- Duration of previous remission
- Clinical presentation defines agressiveness

Survival estimates of matched MM patients and controls



Fonseca R, Leukemia 2017

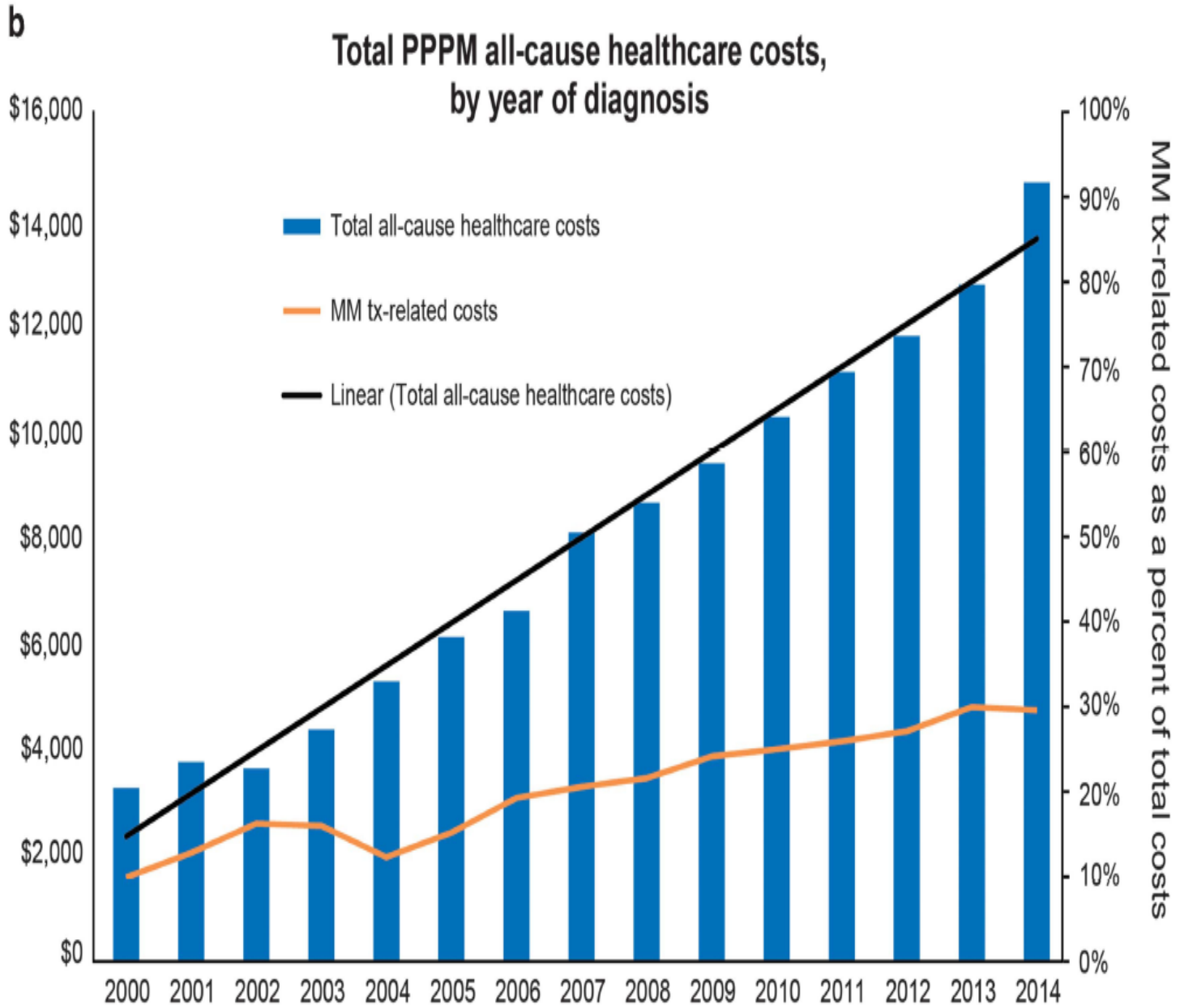
www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 20), pp: 34001-34017

Review

Systematic review and meta-analysis of the efficacy and safety of novel monoclonal antibodies for treatment of relapsed/ refractory multiple myeloma

Tiantian Zhang[1,*], Sen Wang[1,*], Tengfei Lin[2], Jingmei Xie[1], Lina Zhao[1], Zhuoru Liang[1], Yangqiu Li[3,4] and Jie Jiang[1,5]

- Thirteen clinical trials with 2,402 patients participating.
- ORR was 57% (95% confidence interval [CI]: 38-76%).
- VGPR was 32% (95% CI: 19- 46%).
- mAb-based regimens prolonged PFS (hazard ratio: 0.52, 95% CI: 0.36-0.75) compared to non-mAb-based regimens.
- The efficacy of triplet regimens was superior to that of single or doublet regimens for both daratumumab and elotuzumab, with acceptable toxicity
- The most common grade 3/4 adverse events: anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, pneumonia, and fatigue.
- Elotuzumab and daratumumab improved the ORR, at least VGPR, and PFS compared to non-mAb-based regimens.
- Daratumumab triplet therapy (daratumumab, lenalidomide, and dexamethasone) was superior to other triplet regimens.
- Daratumumab monotherapy was more effective than either single agent.



Fonseca R, Leukemia 2017