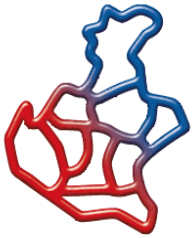
IL FUTURO DELLA
RETE EMATOLOGICA
NELLA REGIONE DEL VENETO



RETE
EMATOLOGICA
VENETA

SINERGIA PER CONDIVIDERE
ASSISTENZA
FORMAZIONE
RICERCA

PADOVA 6 GIUGNO 2017
AZIENDA OSPEDALIERA
AULA MAGNA PALAZZINA DEI SERVIZI - VIA GIUSTINIANI 2

La terapia del MM: stato dell'arte e analisi degli scenari

Renato Zambello, MD

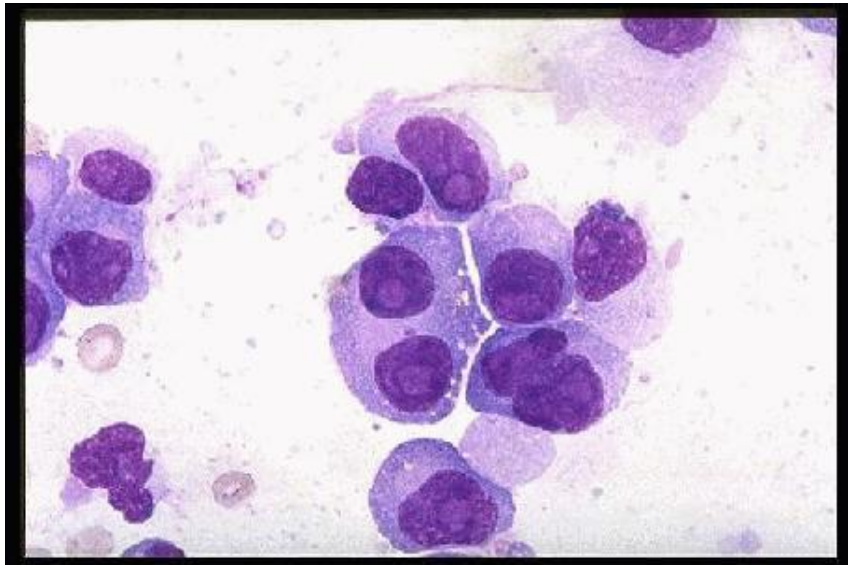
Dipartimento di Medicina

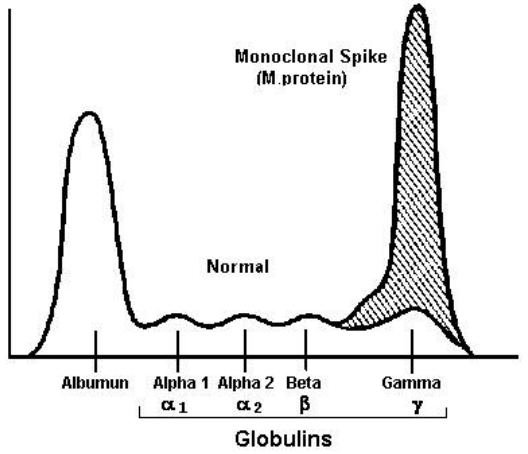
Università di Padova

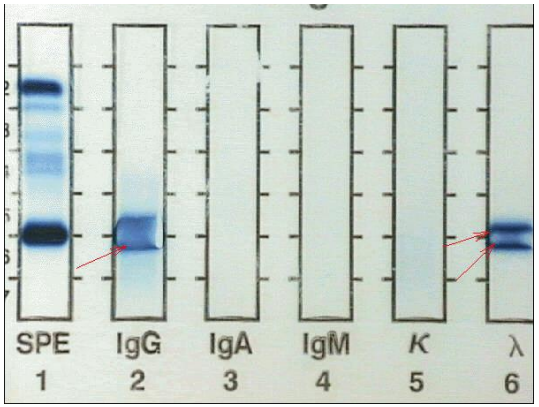
Ematologia e Immunologia Clinica

Mieloma Multiplo

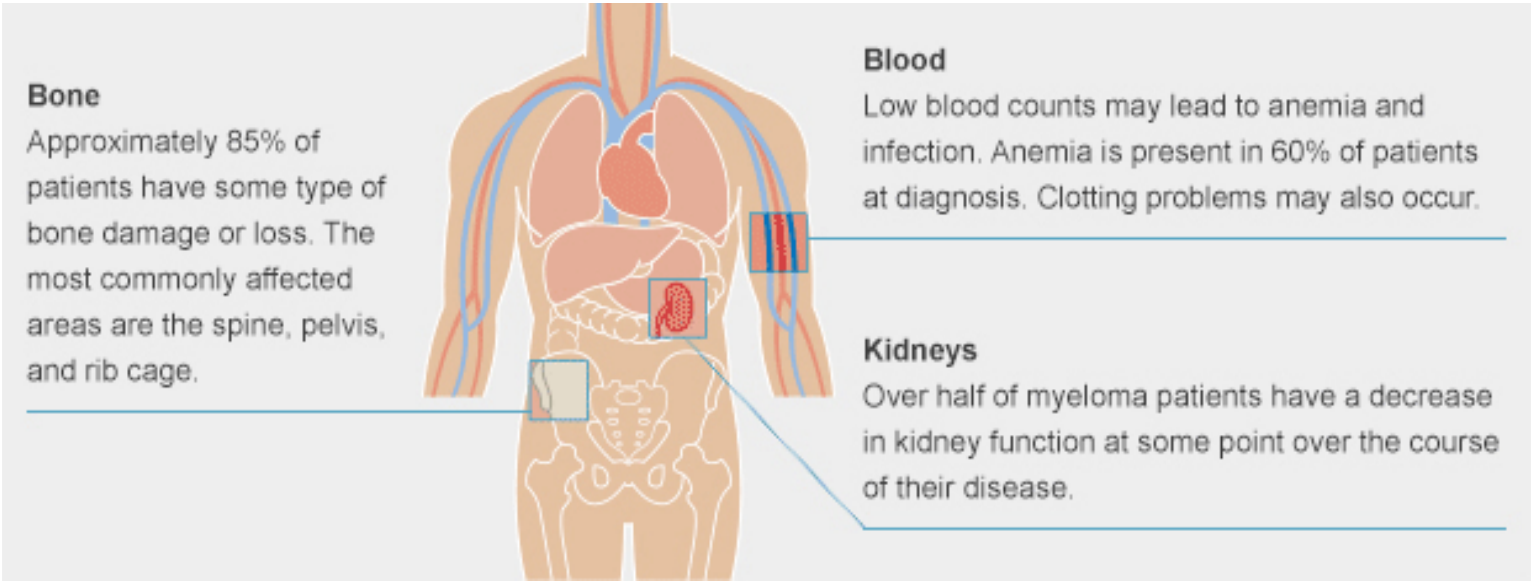
- Il mieloma multiplo è una neoplasia ematologica incurabile caratterizzata dall'accumulo di plasmacellule tumorali nel midollo osseo e di una componente monoclonale sierica e/o urinaria

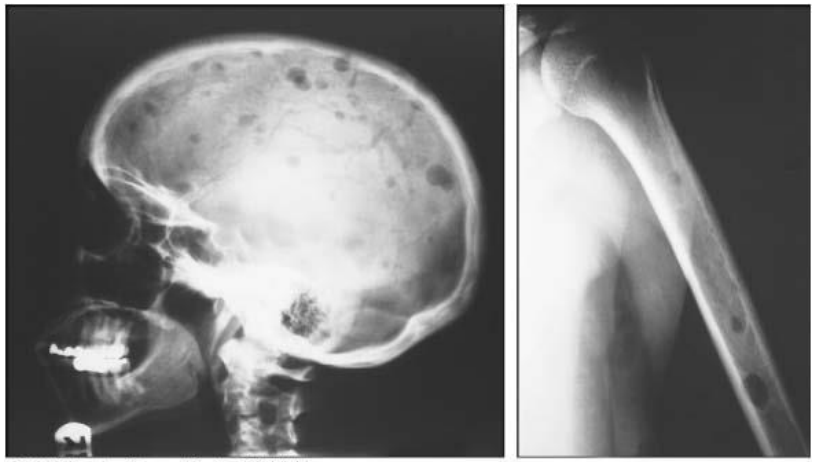


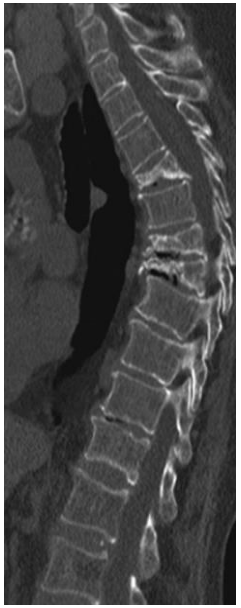




Multiple myeloma







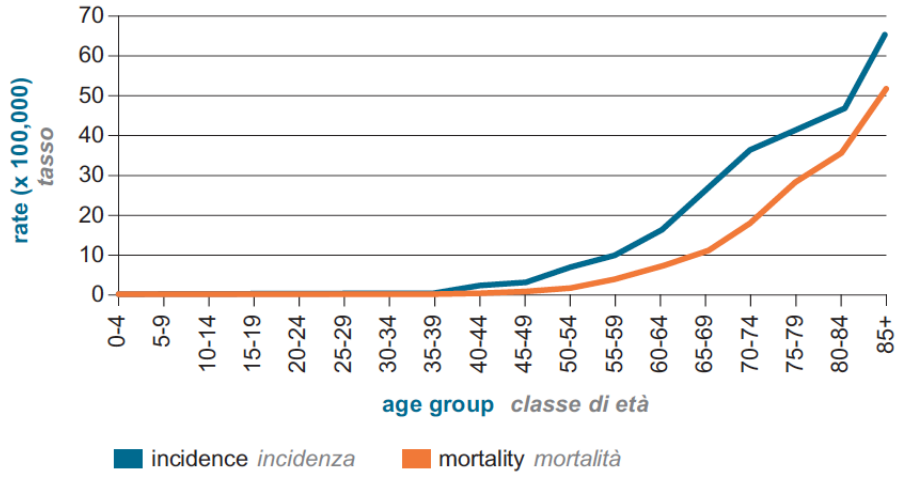
Mieloma Multiplo

- Rappresenta l'1.3% di tutti I tumori e il 15% delle neoplasia ematologiche.
- Le stime per l'Italia (2006) indicano un totale di 2.315 nuovi casi diagnosticati ogni anno fra i maschi e di 2.098 fra le femmine, mentre per quanto riguarda la mortalità si sono verificati, nel 2002, 1.268 decessi per mieloma fra i maschi e 1.357 fra le femmine.
- L'età mediana alla diagnosi è di 70 anni
- L'incidenza negli ultimi anni è stabile mentre la prevalenza è in aumento per l'allungamento della sopravvivenza dei pazienti con i nuovi farmaci

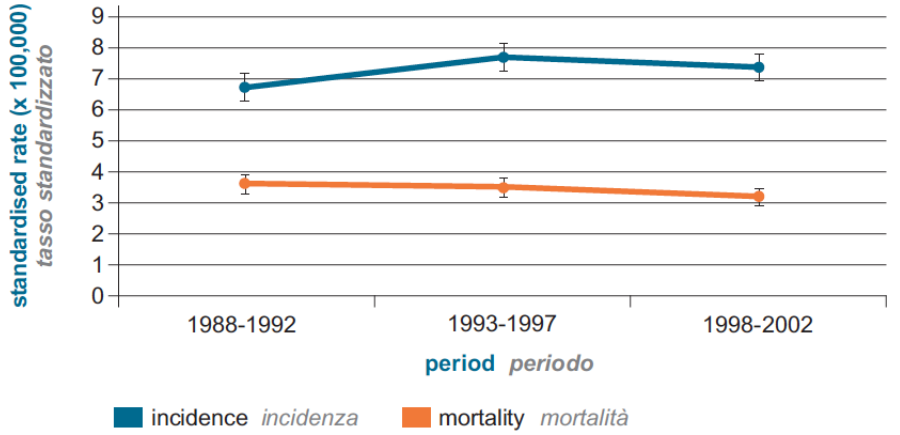
Sede	Maschi			Femmine		
	Nord	Centro	Sud/isole	Nord	Centro	Sud/isole
Linfoma di Hodgkin	3,6	4,7	3,8	3,2	4,0	3,4
Linfoma non-Hodgkin	18,2	17,3	15,8	13,0	13,1	10,4
Mieloma	6,6	6,6	5,7	4,6	3,5	4,1
Leucemie	12,0	13,3	12,6	7,6	8,4	8,1

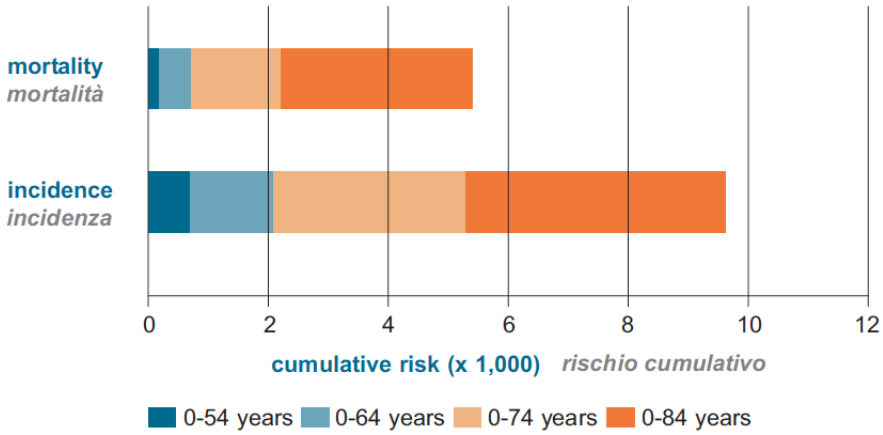
AIRTUM: AIRTUM 2007-2011. Tassi di incidenza standardizzati sulla popolazione europea per area geografica e sesso (x 100.000).

♂ Maschi Males

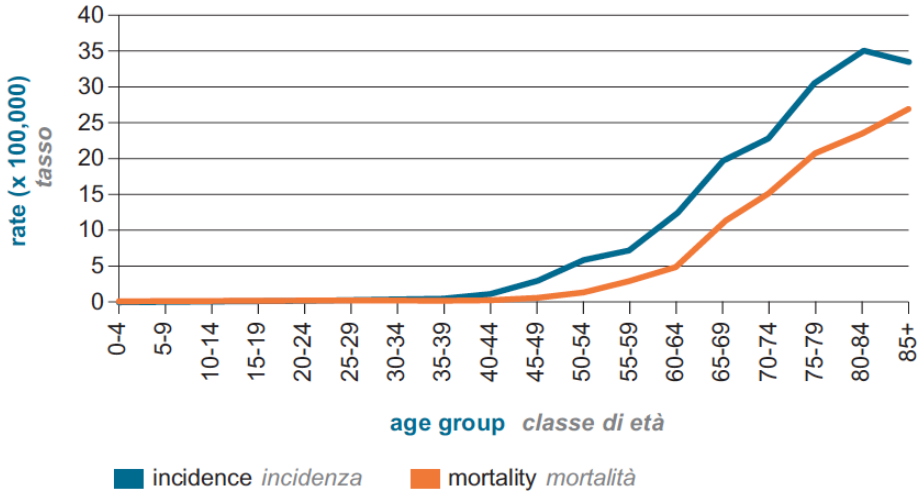


Basis of diagnosis *Modalità di diagnosi*	n. cases	%
histology *istologica*	1,578	65%
cytology *citologica*	554	23%
clinical *clinica*	270	11%
DCO *solo certificato di morte*	29	1%
	2,431	

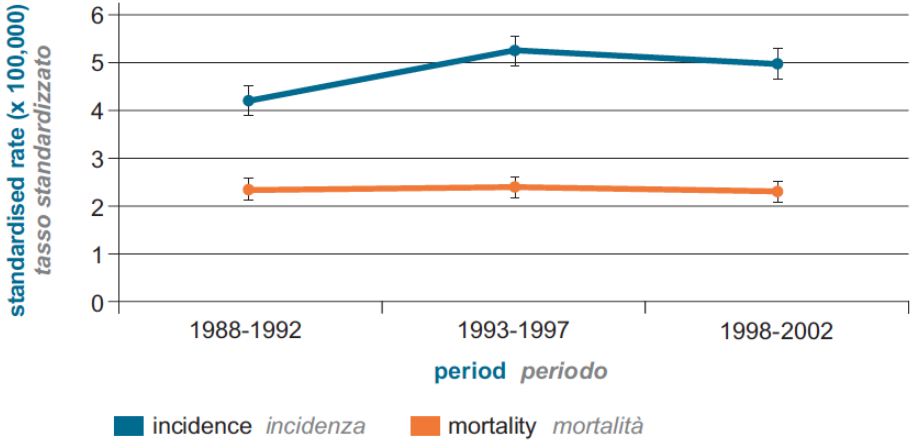


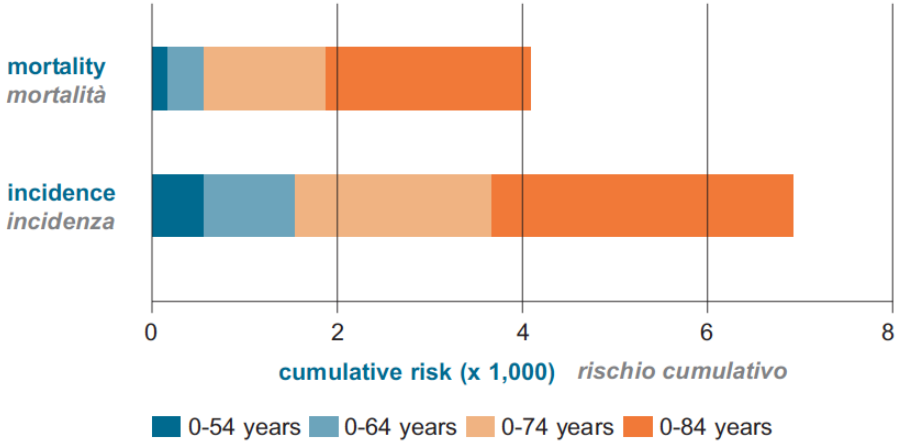


♀ Femmine Females

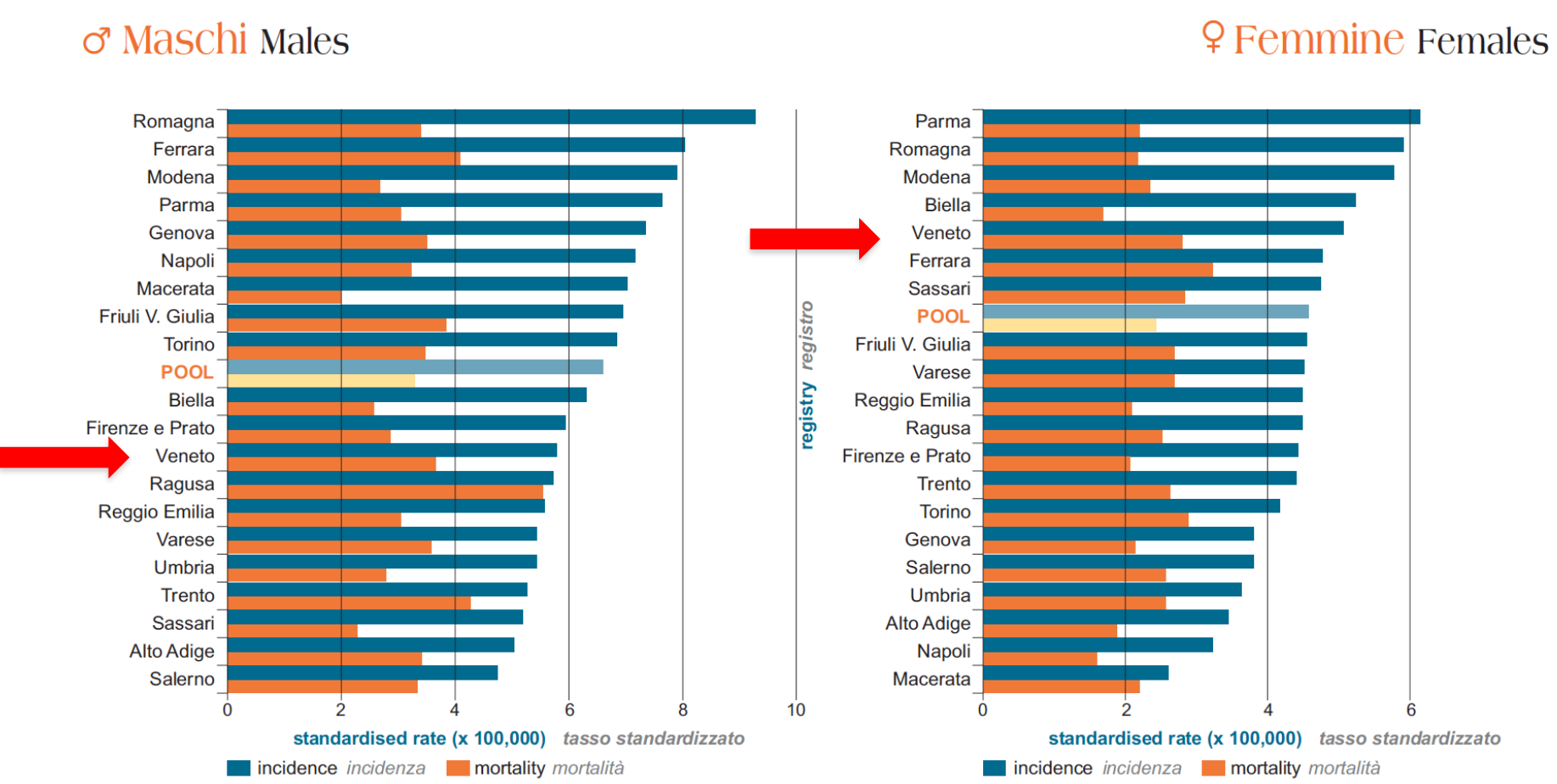


Basis of diagnosis *Modalità di diagnosi*	n. cases	%
histology *istologica*	1,455	63%
cytology *citologica*	568	24%
clinical *clinica*	267	12%
DCO *solo certificato di morte*	29	1%
	2,319	



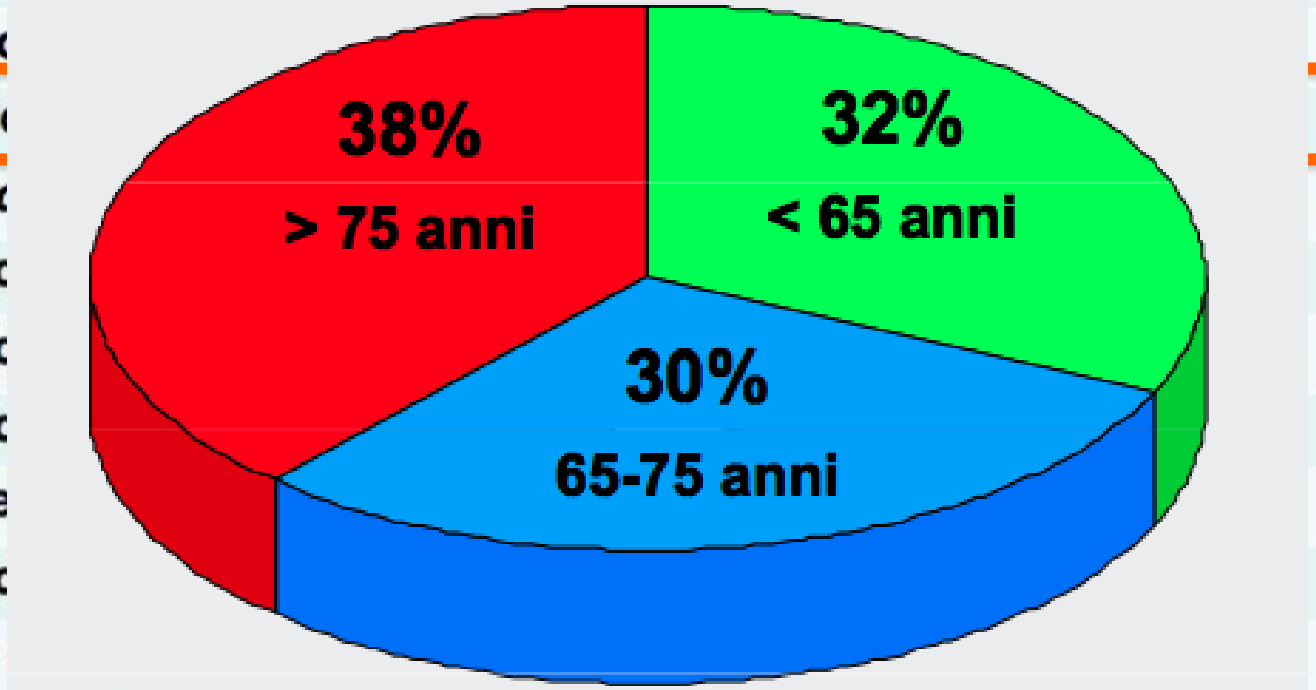


Incidenza e Mortalità per MM



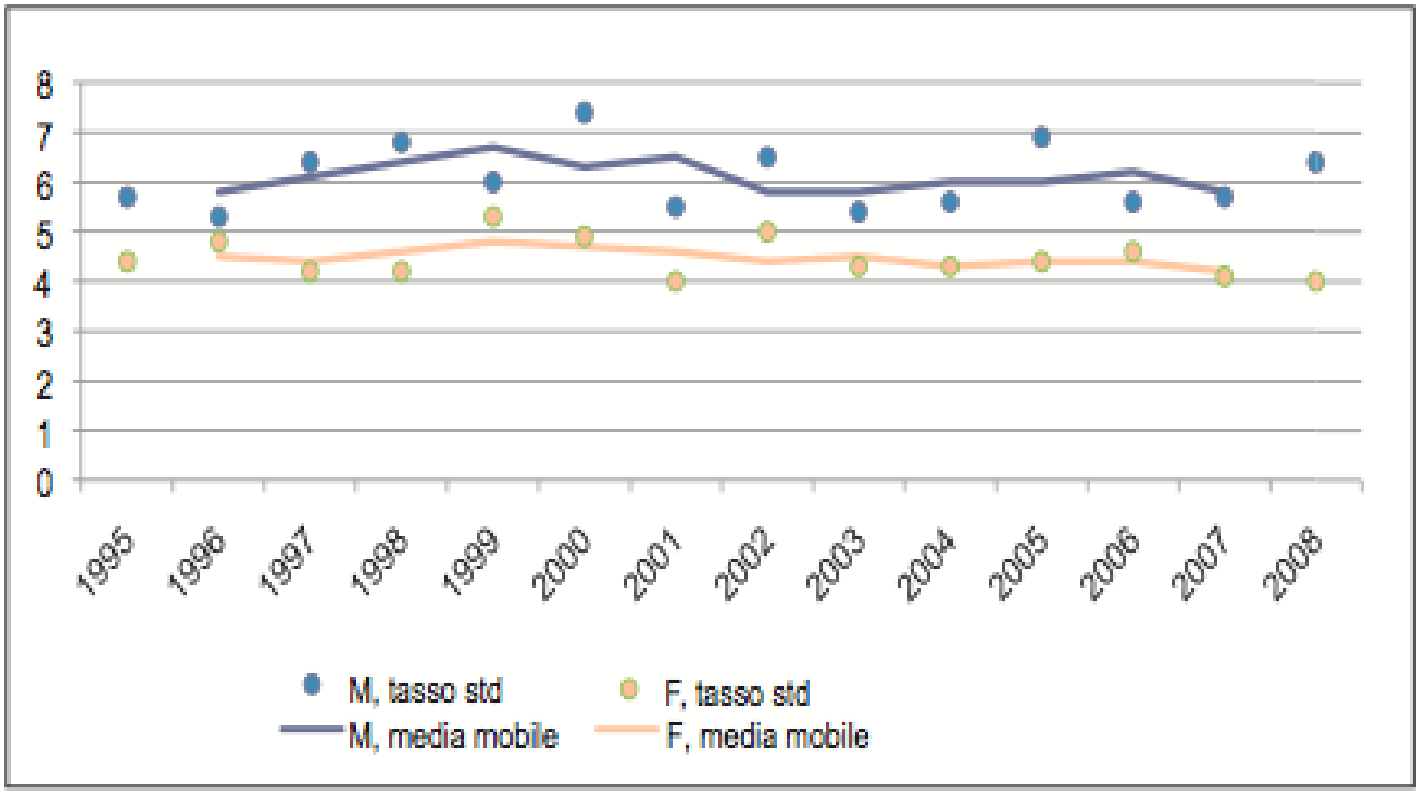
Neoplasie ematologiche
Incidenza -Veneto

Tasso grezzo (x100,000) anni 2007-2009, M + F



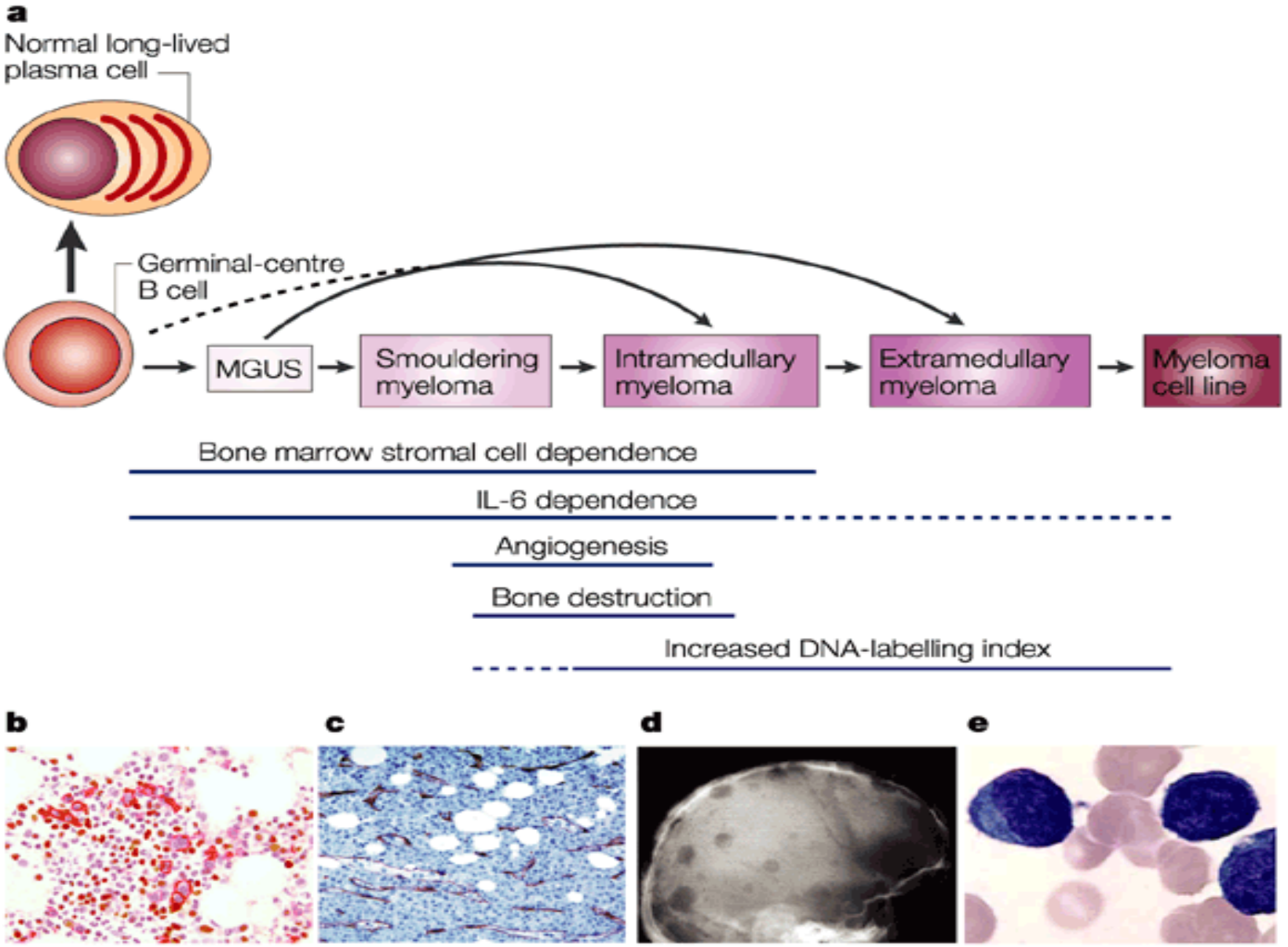
Fonte: Registro Tumori Veneto

Mortalità per mieloma multiplo (ICD9 203; ICD10 C90): tasso standardizzato (per 100.000; standard = popolazione regionale 2002), valori annuali e media mobile triennale. Veneto 1995-2008.



Estratto da IES, Bollettino informativo del Sistema Epidemiologico Regionale del Veneto - n.3, ottobre 2010 pp.3-5

Evolution of plasma cell disorders



Differential diagnosis

	Monoclonal gammopathy of undetermined significance (MGUS)	Asymptomatic (smoldering) myeloma	Symptomatic myeloma
Serum monoclonal protein	<3 g/dL	≥3 g/dL	Presence of serum and/or urinary monoclonal protein
Clonal BM plasma cells	<10%	And/or ≥10%	≥10%
End-organ damage	Absent	Absent	Present; Can be attributed to the underlying plasma cell proliferative disorder (CRAB symptoms)

C: Serum Calcium ≥11.5 mg/dL
R: Renal insufficiency: serum creatinine >2 mg/dL
A: Anemia: Hb <10 g/dL or 2 g/dL below normal
B: Bone lesions: lytic or pathologic fractures

Adapted from Dimopoulos M et al. *Blood*. 2011;117:4701-4705.

IMWG UPDATED CRITERIA FOR THE DIAGNOSIS OF MM

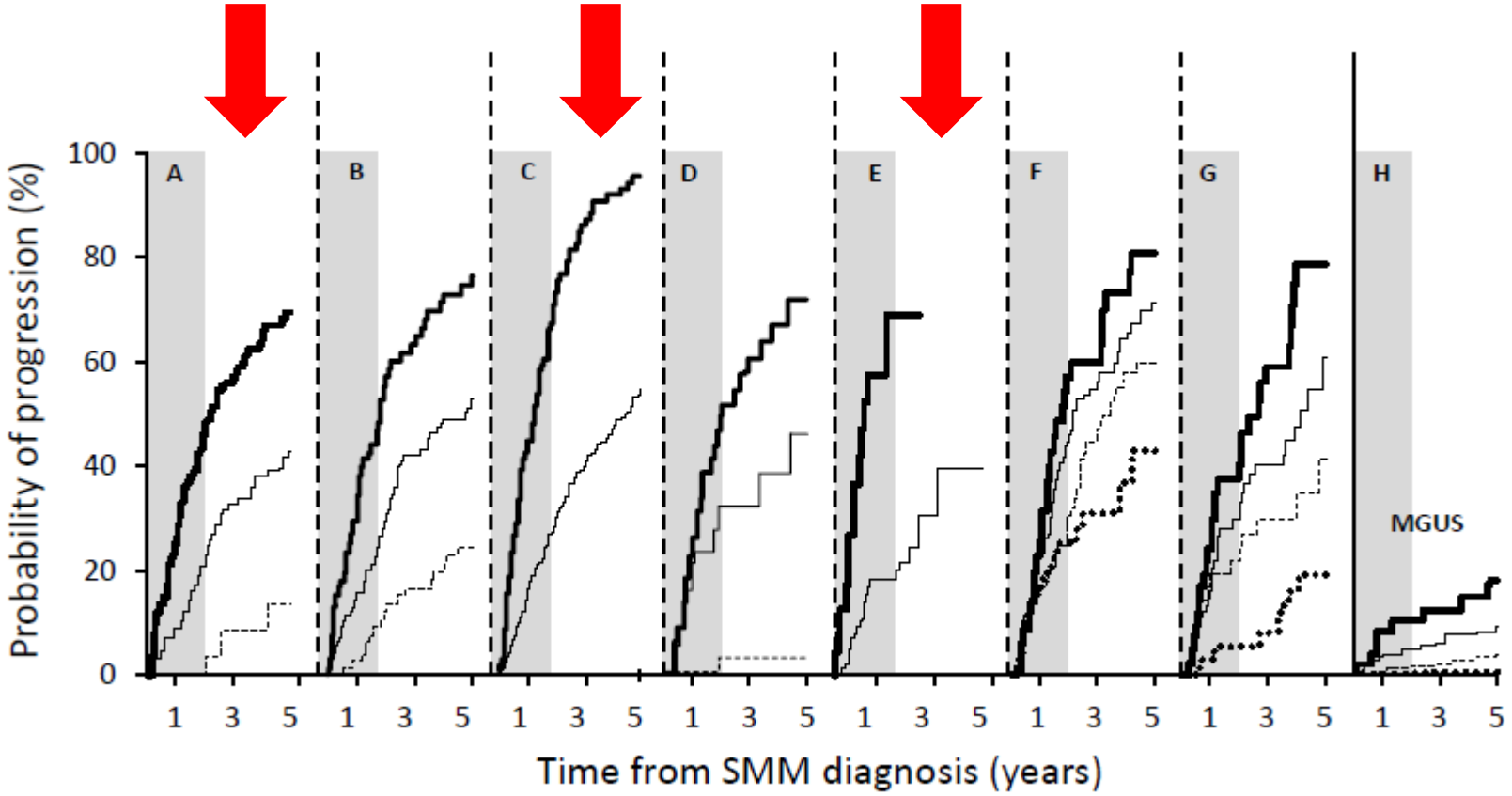
Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Rajkumar V. et al., Lancet Oncology 2014

Risk of SMM progression to active MM according to different prognostic



A. SMM risk based on BMPC>=10%, M-protein >=30 g/L21

B. SMM risk based on BMPC ≥10, M-protein ≥30 g/L, and involved FLC / uninvolved FLC ≥82

C. SMM risk based on involved FLC / uninvolved FLC ≥100

D. SMM risk based on (absence of CD19 and/or CD45 expression, over expression of CD56, or weak expression of CD38) and immunoparesis of either of the uninvolved immunoglobulins

E. SMM risk based on presence (bold solid) or absence (solid) of 1 or more focal lesion on whole body MRI

F. SMM risk based on FISH

G. SMM risk based on high risk iFISH (del 17p, t(4;14), +1q21, or hyperdiploidy) and high tumor burden (M-protein >=20 g/L)

Angela Dispenzieri Blood 2013 Prepublished online October 21, 2013

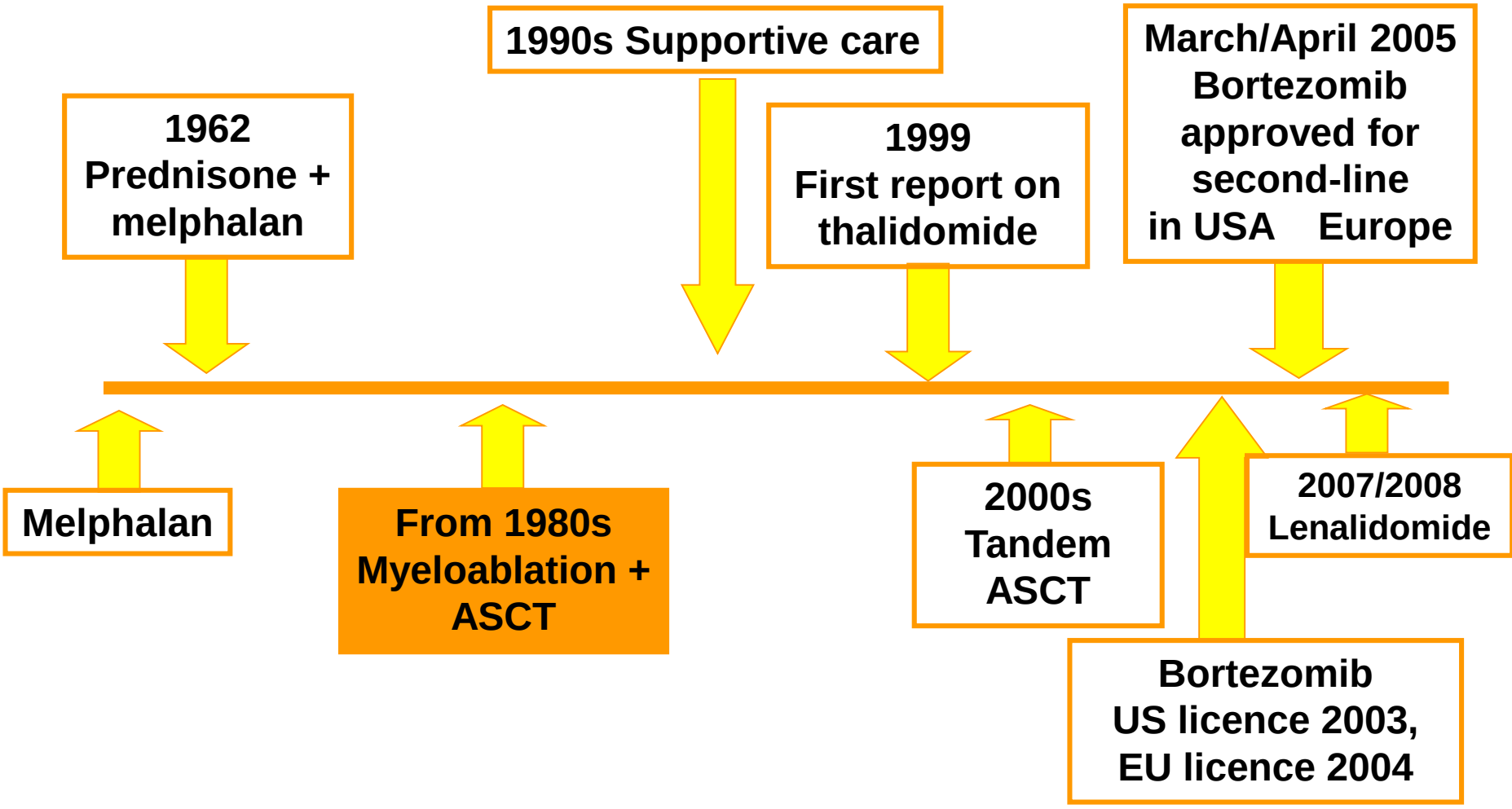
Active Myeloma

Not CRAB but now SLiM CRAB

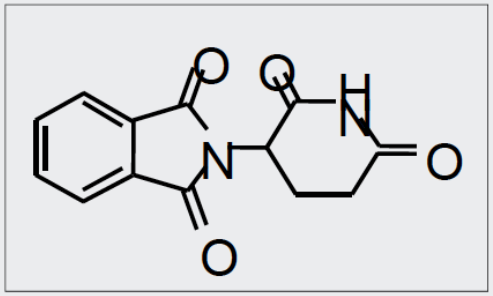
- S (60% Plasmacytosis)
- Li (Light chains I/U >100)
- M (MRI 1 or more focal lesion)
- C (Calcium elevation)
- R (Renal insufficiency)
- A (Anemia)
- B (Bone disease)

Rajkumar et al. IMWG updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15:e538-e548

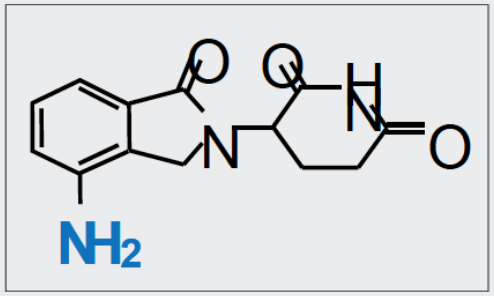
Progressi nel trattamento del Mieloma Multiplo negli ultimi 40 anni



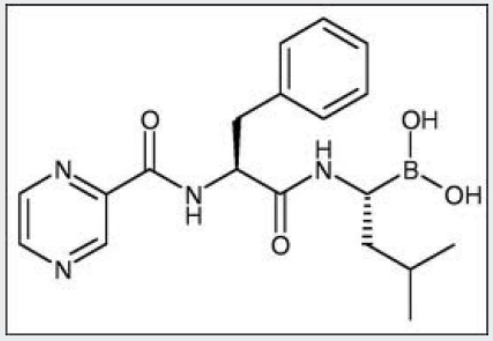
Nuovi farmaci disponibili



THALIDOMIDE

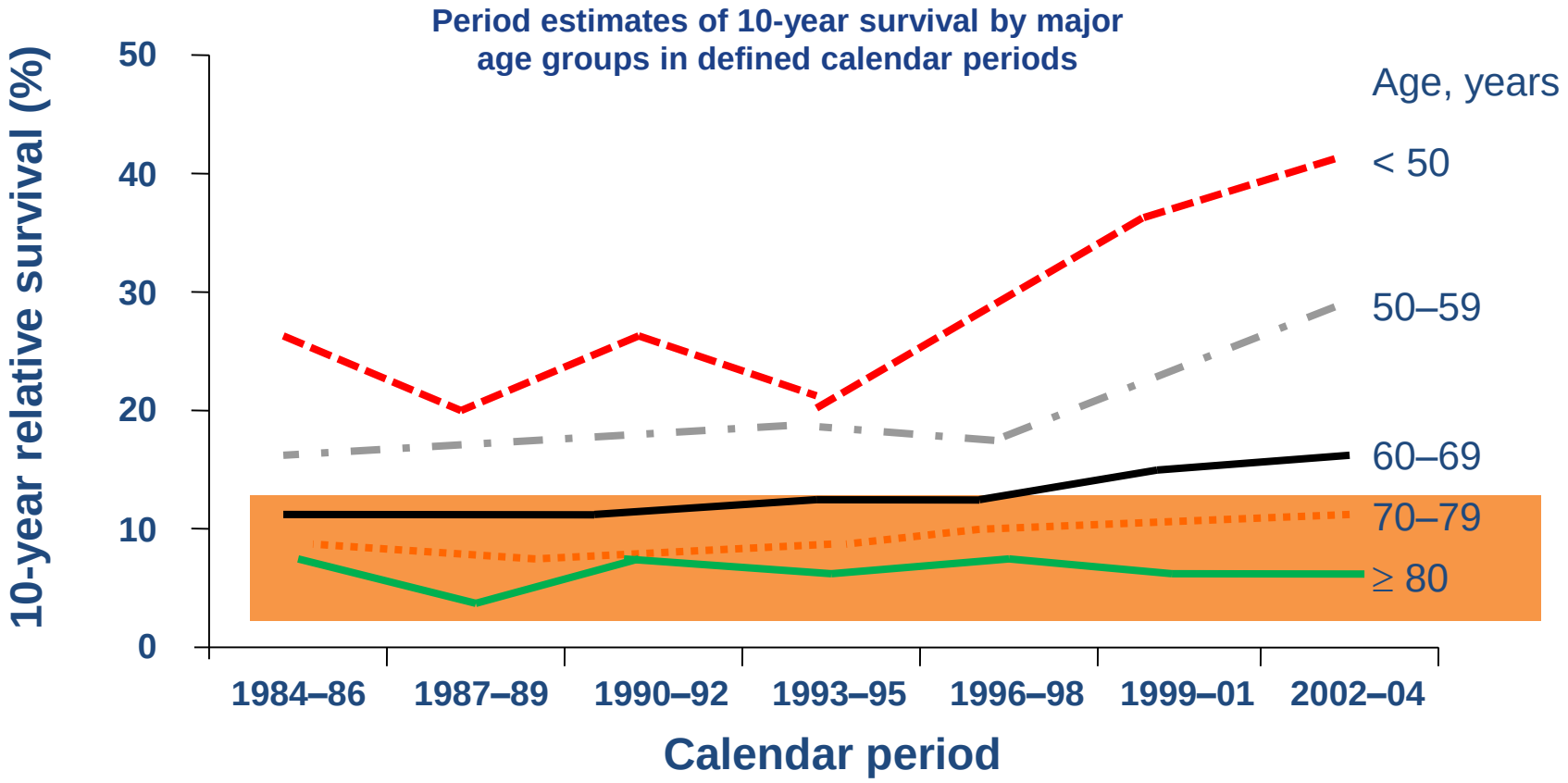


LENALIDOMIDE



BORTEZOMIB

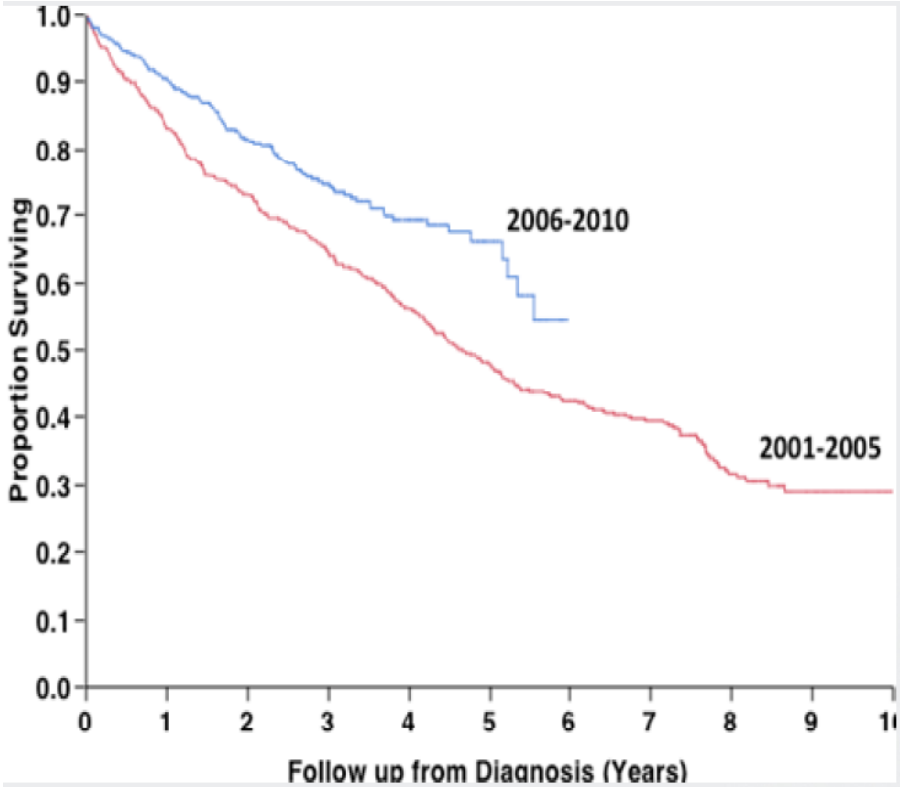
Survival of Myeloma patients according to age



Brenner H, et al. Blood. 2008;111:2521-26.

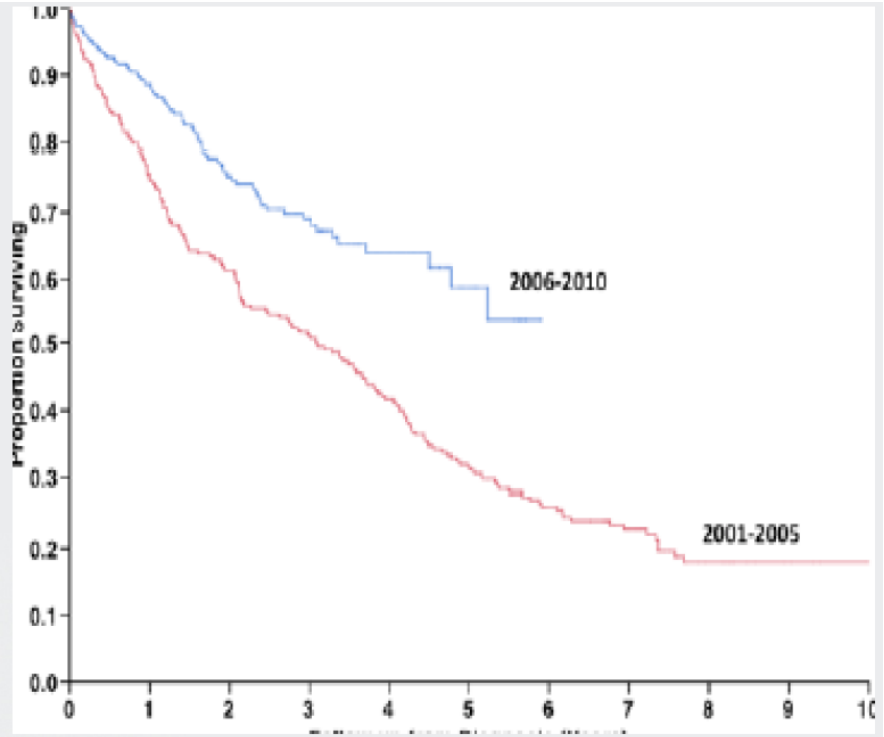
Sopravvivenza nei pazienti diagnosticati nel periodo 2001-2005 e nel periodo 2006-2010 in relazione alla popolazione totale di pazienti (A) e i pazienti con più di 65 anni (B)

A



Sopravvivenza globale suddivisa per data della diagnosi

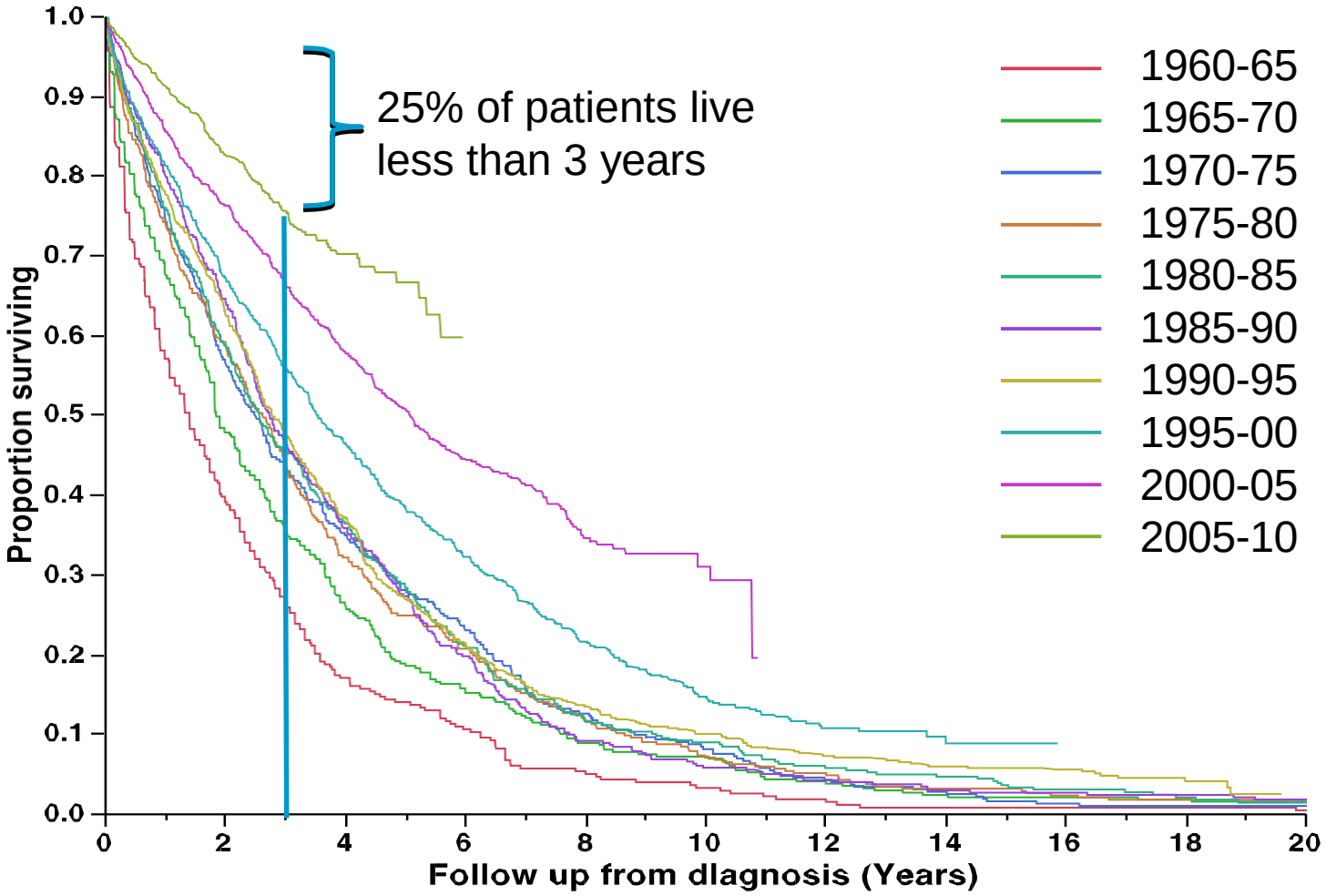
B



Sopravvivenza globale suddivisa per data della diagnosi
nei pazienti > 65 anni

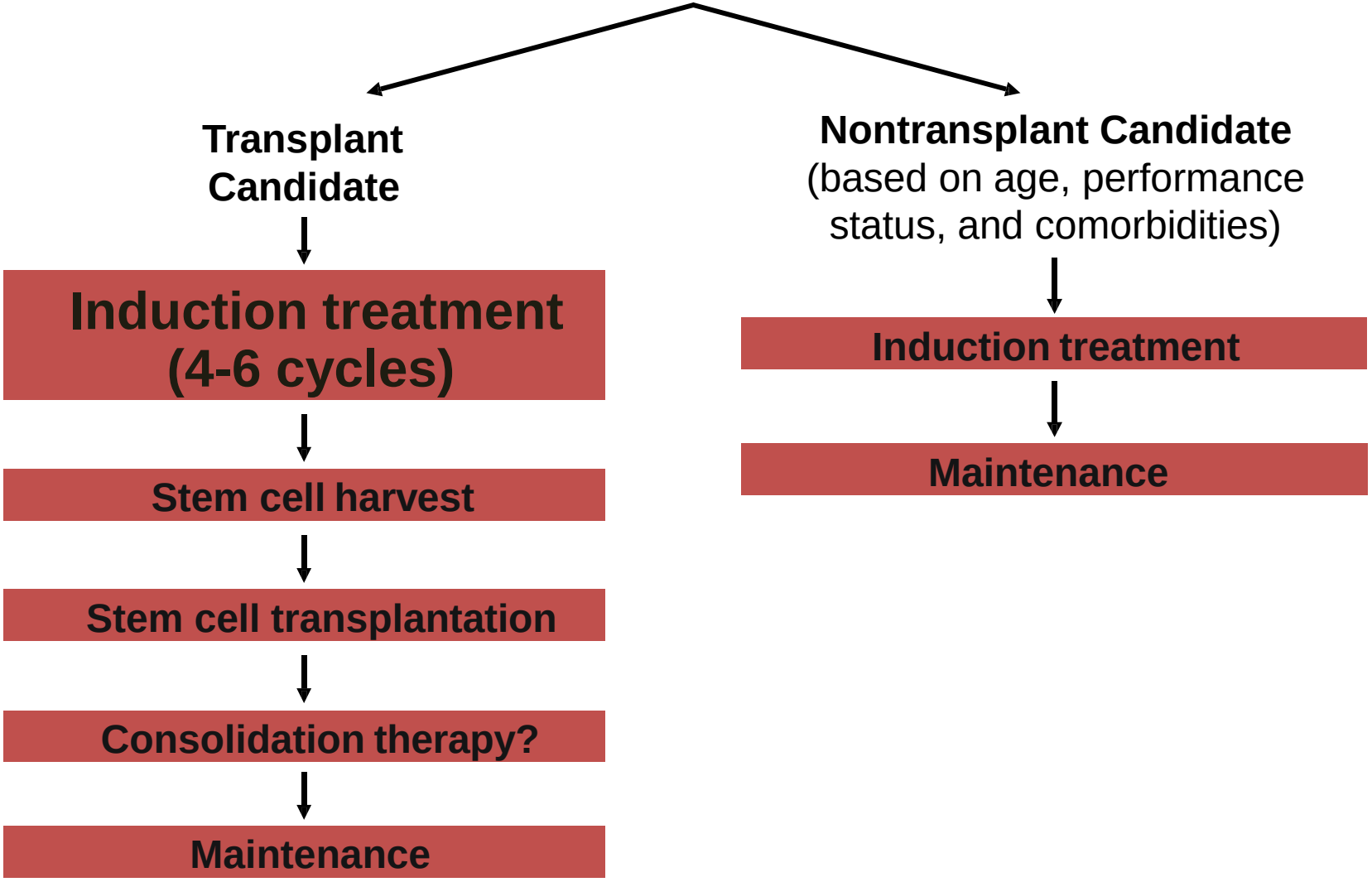
S K Kumar, Leukemia 2013

Improving Survival in MM

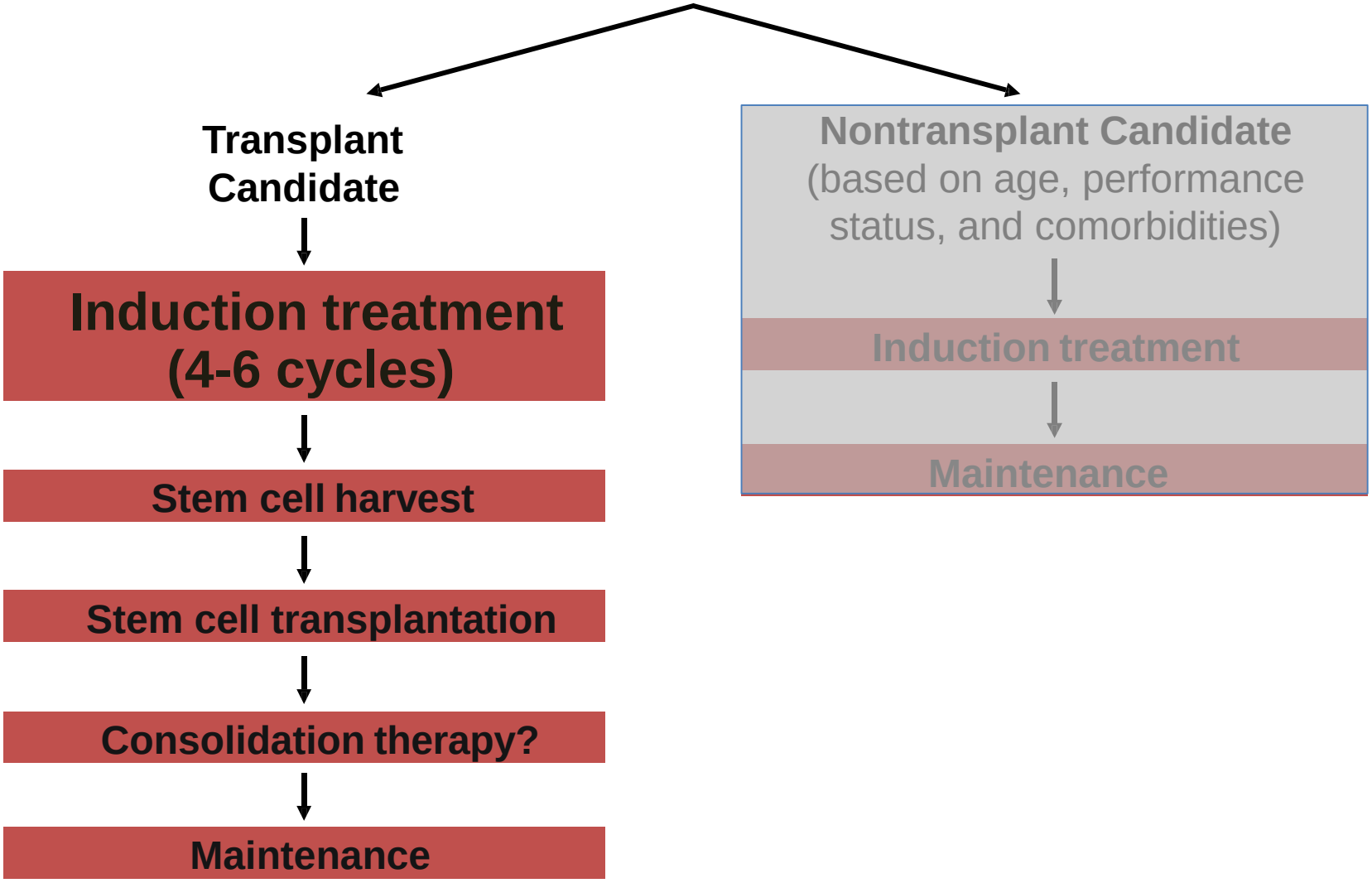


MAYO CLINIC

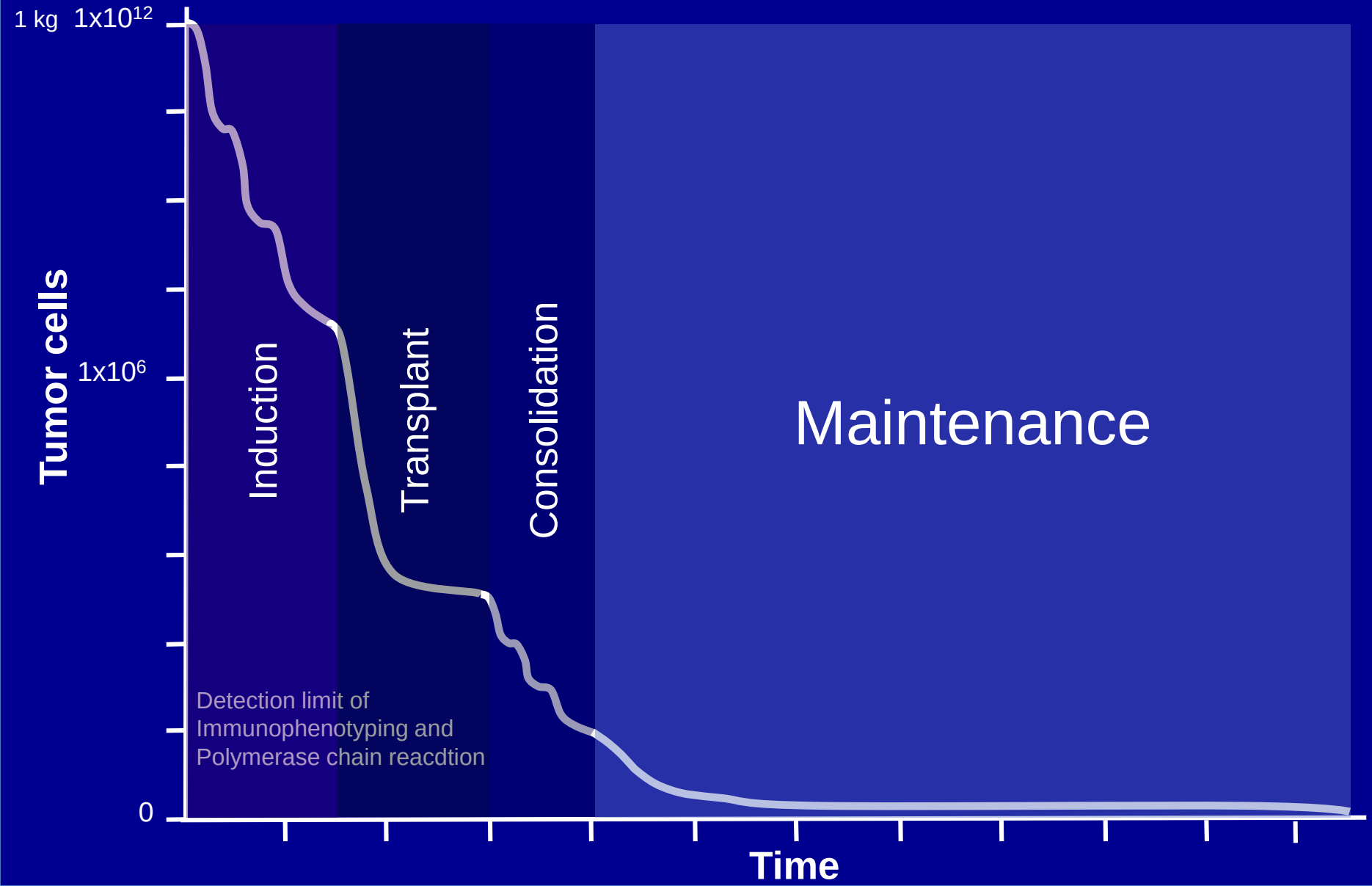
Initial Approach to Treatment of Myeloma



Initial Approach to Treatment of Myeloma



Progressive reduction in tumor cell mass throughout induction, ASCT, consolidation and maintenance therapy



Paradigma nella terapia del mieloma

Profondità della risposta (negatività MRD)

Rischio citogenetico:

t(4;14); t (14;16)

del 17 amp1q

What is the best induction regimen with transplant ?

Regimens for induction therapy before high-dose therapy and stem cell transplantation

Main components	Preferred option–3 drug, bortezomib-based regimens	2-drug regimens	4-drug regimens
Bortezomib-based	PAD, VCD	VD	
Bortezomib + IMID based	VRD, VTD		VRDC, VDTC
Lenalidomide -based		LD, Ld	
Talidomide - based	TAD, CTD	Td	
If none of the novel drugs available	VAD		

Abbreviations: **CTD**, cyclophosphamide with thalidomide plus dexamethasone; **LD**, lenalidomide with high-dose dexamethasone; **Ld**, lenalidomide with low- dose dexamethasone; **PAD**, bortezomib with adriamycin plus dexamethasone; **TD**, thalidomide with dexamethasone; **TAD**, thalidomide with adriamycin plus dexamethasone; **VCD**, bortezomib with cyclophosphamide plus dexamethasone; **VD**, bortezomib with dexamethasone; **VRD**, bortezomib with lenalidomide plus dexamethasone; **VTD**, bortezomib with thalidomide plus dexamethasone; **VRDC**, bortezomib with lenalidomide plus dexamethasone plus cyclophosphamide; **VDTC**, bortezomib with dexamethasone plus thalidomide plus cyclophosphamide; **VAD**, vincristine with adriamycin plus dexamethasone.

IMWG recommendations, Leukemia (2013) 1 – 12

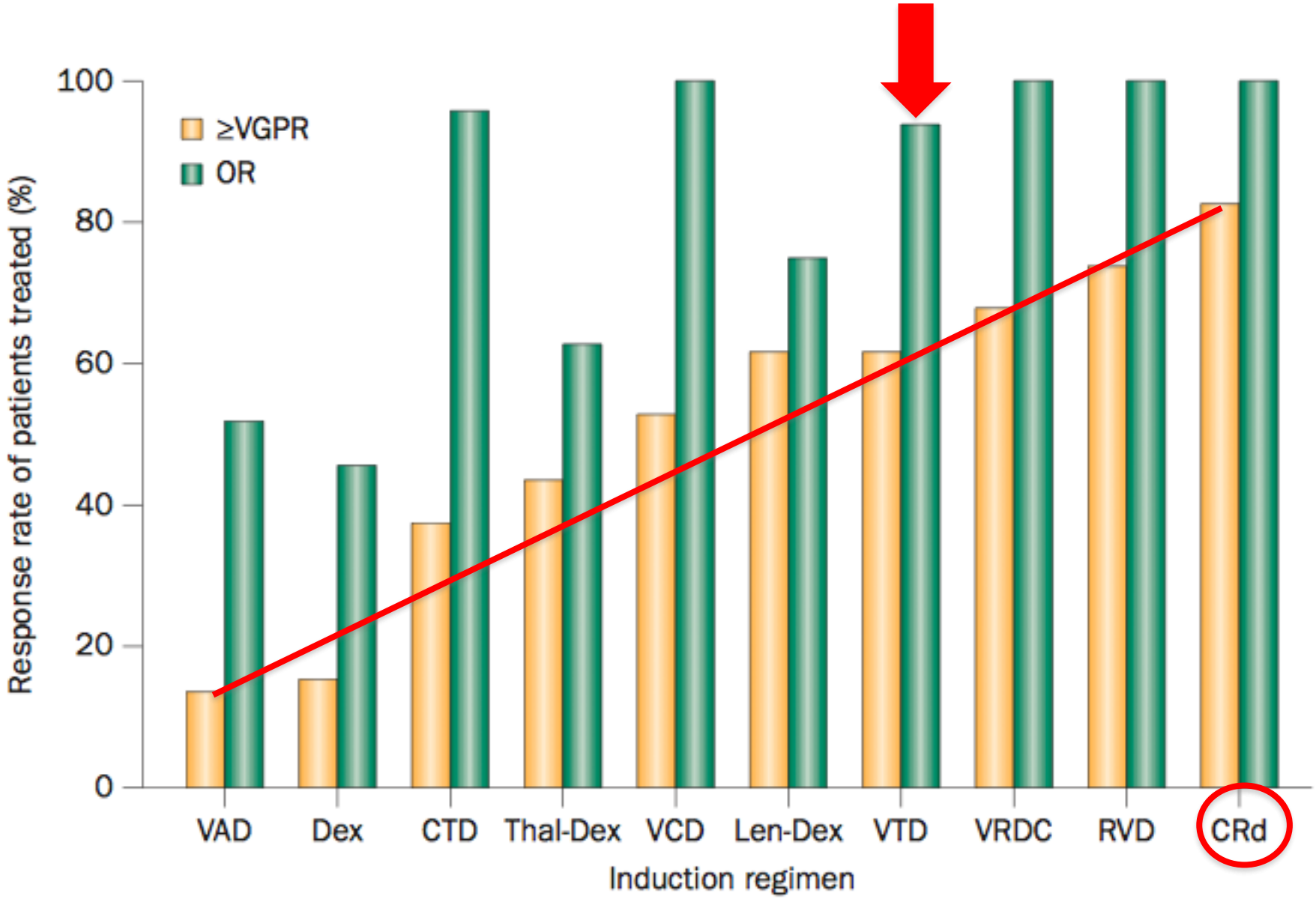
Regimens for induction therapy before high-dose therapy and stem cell transplantation

Main components	Preferred option–3 drug, bortezomib-based regimens	2-drug regimens	4-drug regimens
Bortezomib-based	PAD, VCD	VD	
Bortezomib + IMID based	VRD, VTD		VRDC, VDTC
Lenalidomide -based		LD, Ld	
Talidomide - based	TAD, CTD	Td	
If none of the novel drugs available	VAD		

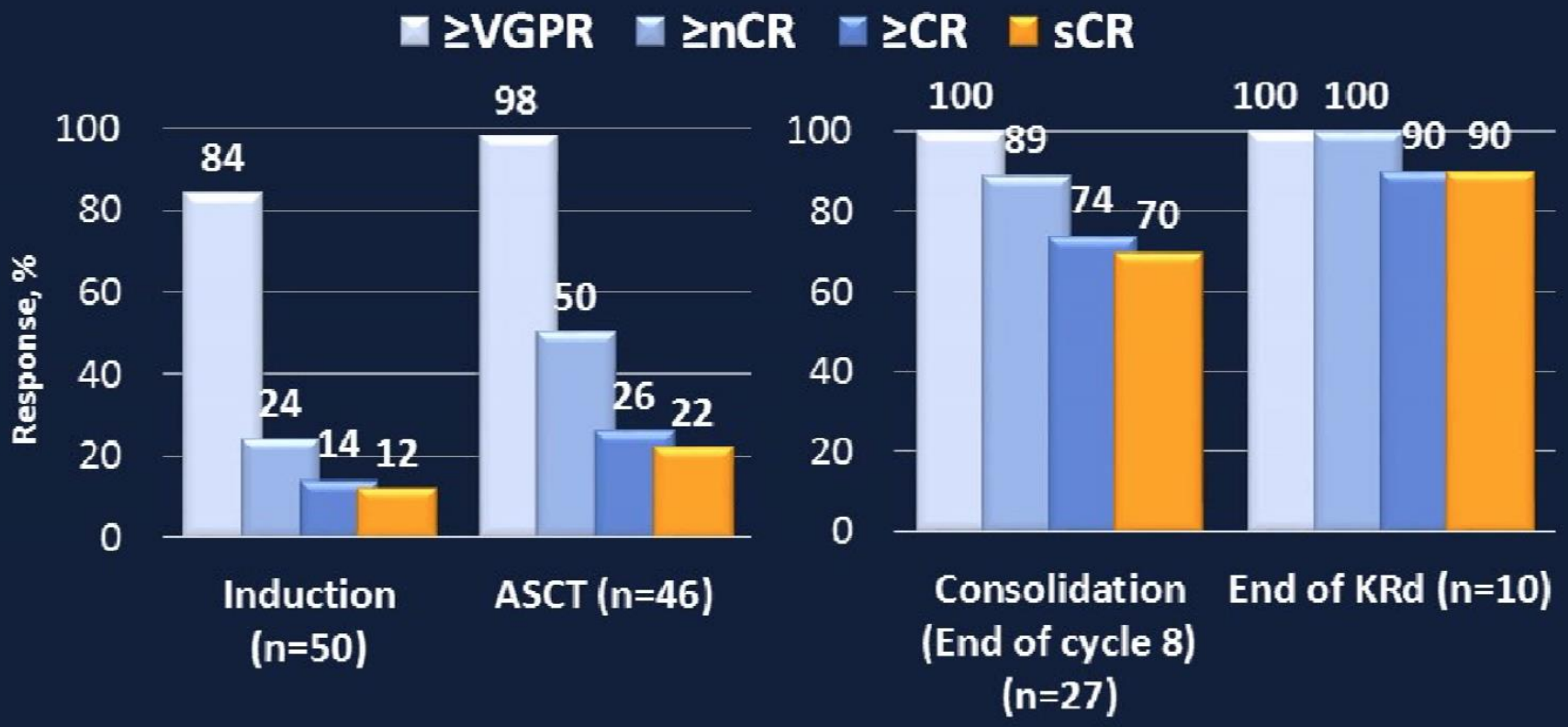
Abbreviations: **CTD**, cyclophosphamide with thalidomide plus dexamethasone; **LD**, lenalidomide with high-dose dexamethasone; **Ld**, lenalidomide with low- dose dexamethasone; **PAD**, bortezomib with adriamycin plus dexamethasone; **TD**, thalidomide with dexamethasone; **TAD**, thalidomide with adriamycin plus dexamethasone; **VCD**, bortezomib with cyclophosphamide plus dexamethasone; **VD**, bortezomib with dexamethasone; **VRD**, bortezomib with lenalidomide plus dexamethasone; **VTD**, bortezomib with thalidomide plus dexamethasone; **VRDC**, bortezomib with lenalidomide plus dexamethasone plus cyclophosphamide; **VDTC**, bortezomib with dexamethasone plus thalidomide plus cyclophosphamide; **VAD**, vincristine with adriamycin plus dexamethasone.

IMWG recommendations, Leukemia (2013) 1 – 12

Induction regimens in MM patients candidate to Transplant

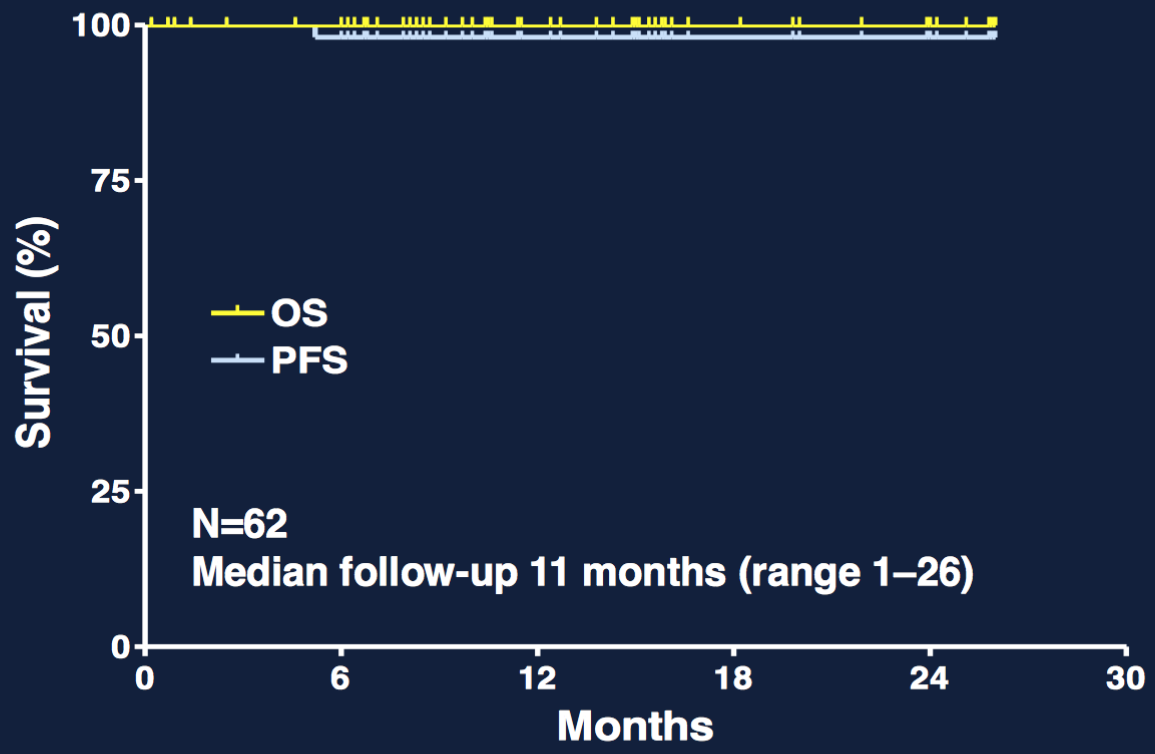


Induzione con Carfilzomib-lenalidomide-desametasone (KRD) + ASCT + KRD consolidamento



Jakuboviak EHA 2016

Treatment Outcomes



All patients were alive and 61/62 were progression free

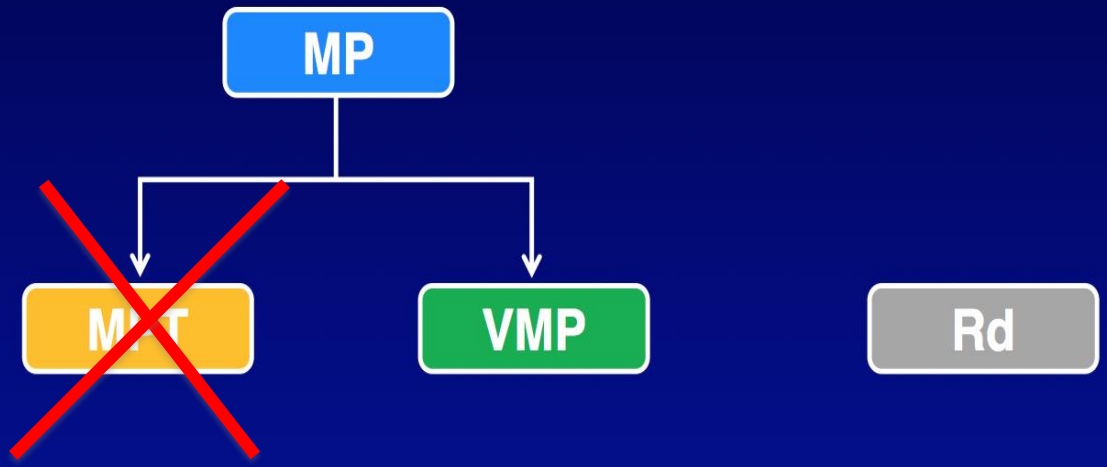
Jakuboviak EHA 2016

Is autologous stem cell transplant a useful consolidation treatment in the era of new drugs ?

Autologous stem cell trapiantation in the era of new drug

- ASCT improves the depth of response, regardless of induction therapy
- Four trials comparing different induction and consolidation to 1 or more ASCT show significant improved PFS
- Two trials with more than 36 mo follow up show improved OS
- ASCT remains an important consolidation therapy after novel drug induction

Standards of care for elderly patients



MP, melphalan-prednisone; MPT, melphalan-prednisone-thalidomide; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide plus low-dose dexamethasone; PFS, progression-free survival; OS, overall survival.

1. Moreau P, et al. *Blood.* 2015;125:3076-84.
2. Fayers PM, et al. *Blood.* 2011;118:1239-47.
3. San Miguel JF, et al. *N Engl J Med.* 2008;359:906-17.
4. San Miguel JF, et al. *J Clin Oncol.* 2013;31:448-55.
5. Benboubker L, et al. *N Engl J Med.* 2014;371:906-17.

Riepilogo studi prima linea pazienti No-ASCT

	VISTA (VMP arm) San Miguel	VMP (OW) Palumbo	FIRST (Continuous Rd) Facon
CR	30%	24%	15.1%
PFS	21.7m	24.8m	26m
OS	Median: 56.4m	Median: 60.6m	Median: 59m

Facon et al. EHA 2015
Palumbo et al. N Engl J Med 2012;366(19):1759-69
San Miguel et al. N Engl J Med 2008; 359: 906-917

Bortezomib: Once Weekly

	VMP twice-weekly	VMP once-weekly
CR	27%	23%
2-year PFS	56%	58%
Sensory PN		
Any grade	44%	22%
Grade 3/4	14%	2%
Discontinuation due to PN	16%	4%
Total planned dose	67.6 mg/m^2	46.8 mg/m^2
Total delivered dose	40.1 mg/m^2	39.4 mg/m^2

Bringhen S, et al. Blood. 2010;116:4745-53

Bortezomib IV vs SC

222 relapsed refractory MM patients. BZ is given at conventional dose and scheme

Bortezomib IV (pz 73)	Bortezomib SC (pz 145)
Primary endpoint: response after 4/8 cycles (single agent BZ ± dexa)	
ORR **42/52%**	**42/52%**
CR **8/12%**	**6/10%**
TTP **9.4 m**	**10.4 m**

	Bortezomib IV		Bortezomib SC	
	all pz	grade 2/3	all pz	grade 2/3
Peripheral neurophaty	53%	16%	30%	6%
		p<004		p<0.03

Moreau P et al Lancet Oncol 2011; 12(5):431-440

FIRST Trial: tossicità grado 3-4

	Rd Continuo (n=532)	Rd x 18 cicli (n=540)	MPT x 12 cicli (n=541)
Hematological (%)			
Anemia	18.2	15.7	18.9
Neutropenia	27.8	26.5	44.9
Piastrinopenia	8.3	8.0	11.1
Febbre e neutropenia	1.1	3.0	2.6
Non-hematological (%)			
Infezioni	28.9	21.9	17.2
Polmoniti	8.1	8.3	5.7
Diarrea	3.9	3.3	1.5
Stipsi	2.3	1.9	5.4
Neuropatia periferica	1.1	0.4	9.4
Trombosi/EP	7.9	5.6	5.4
Cataratta	5.8	2.6	0.6

Severity of AEs graded according to NCI CTCAE v3.0

L’età è importante ma non può essere l’unico parametro da considerare

Gli anziani non sono tutti uguali

Valutazione Geriatrica Multidimensionale

Frailty score

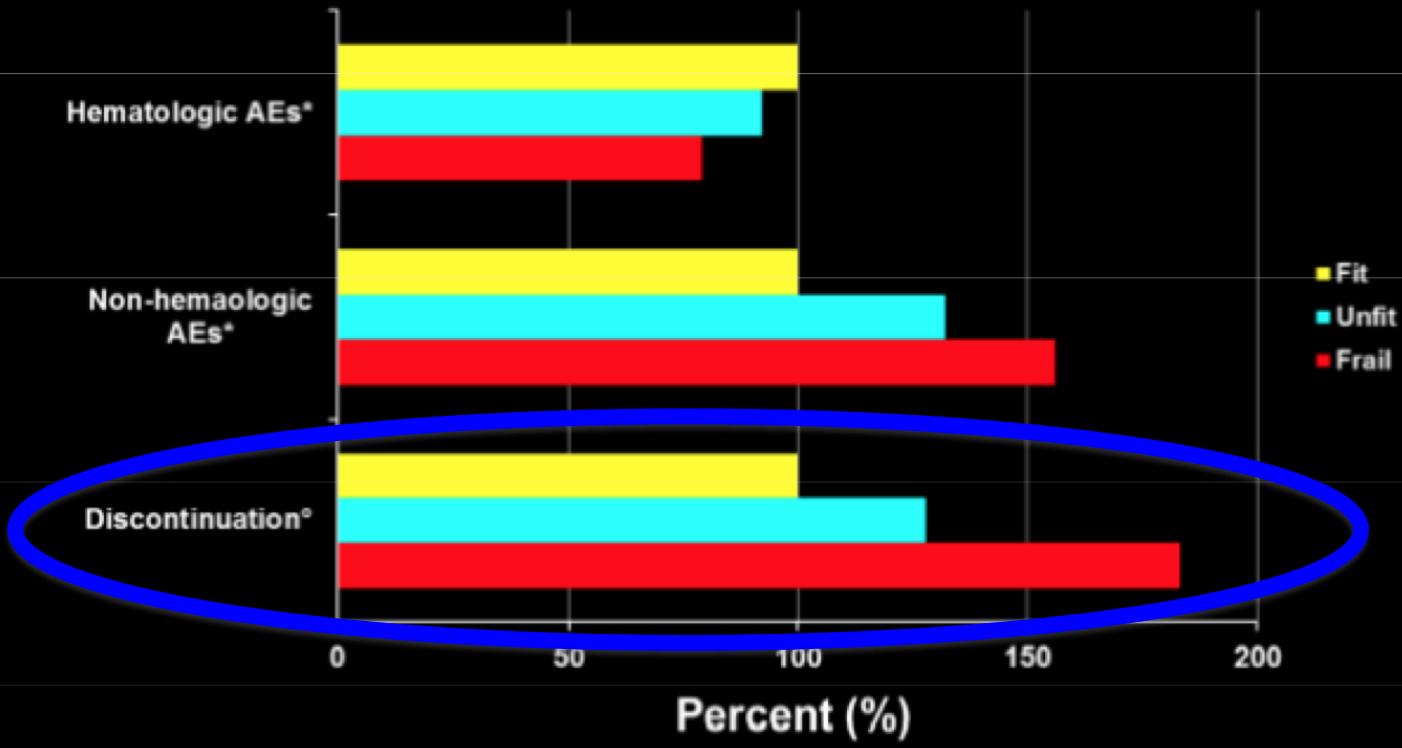
Patients (n=869) received dose-adjusted bortezomib- or lenalidomide-based combinations

Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.37 (0.93-2.03)	0.114	1
	Age >80 years	2.75 (1.81-4.18)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.6 (1.07-2.39)	0.021	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.76 (1.14-2.71)	0.01	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.53 (1.03-2.27)	0.036	1

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

Larocca et al. ASH 2013 (Abstract 687), oral presentation

All grade 3-5 Adverse Events
Risk ratio

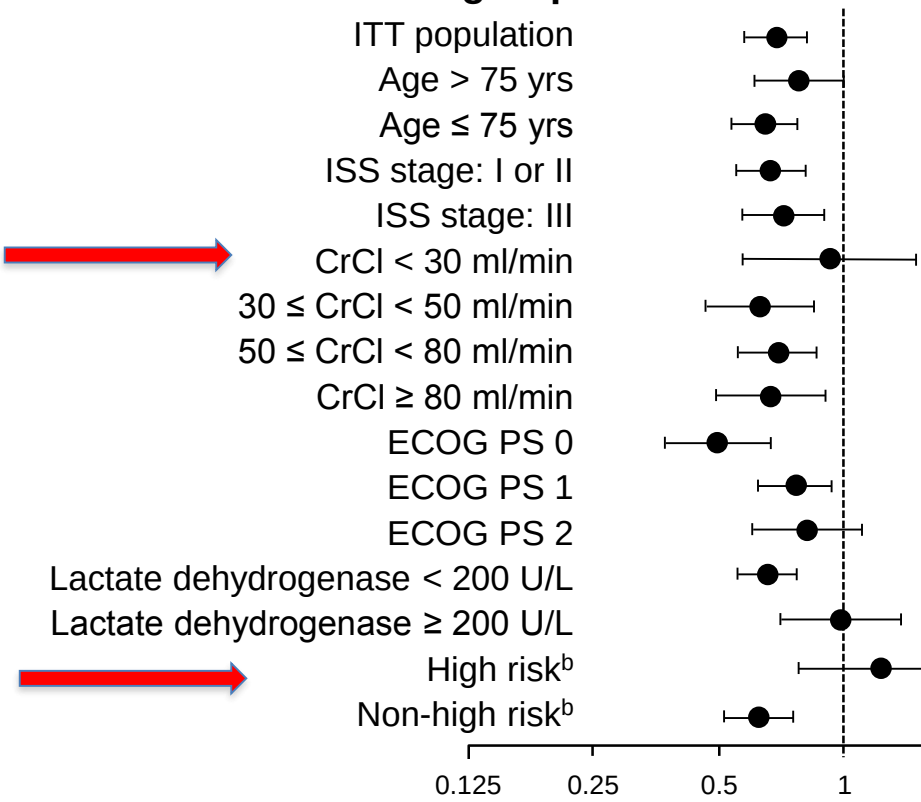


*At least 1 adverse event (AE); °Due to AEs, withdrawal of consent, patient compliance, unknown; progressive disease was excluded.

Larocca et al. ASH 2013 (Abstract 687), oral presentation

FIRST (MM-020): *Effect of Subgroup on PFS*

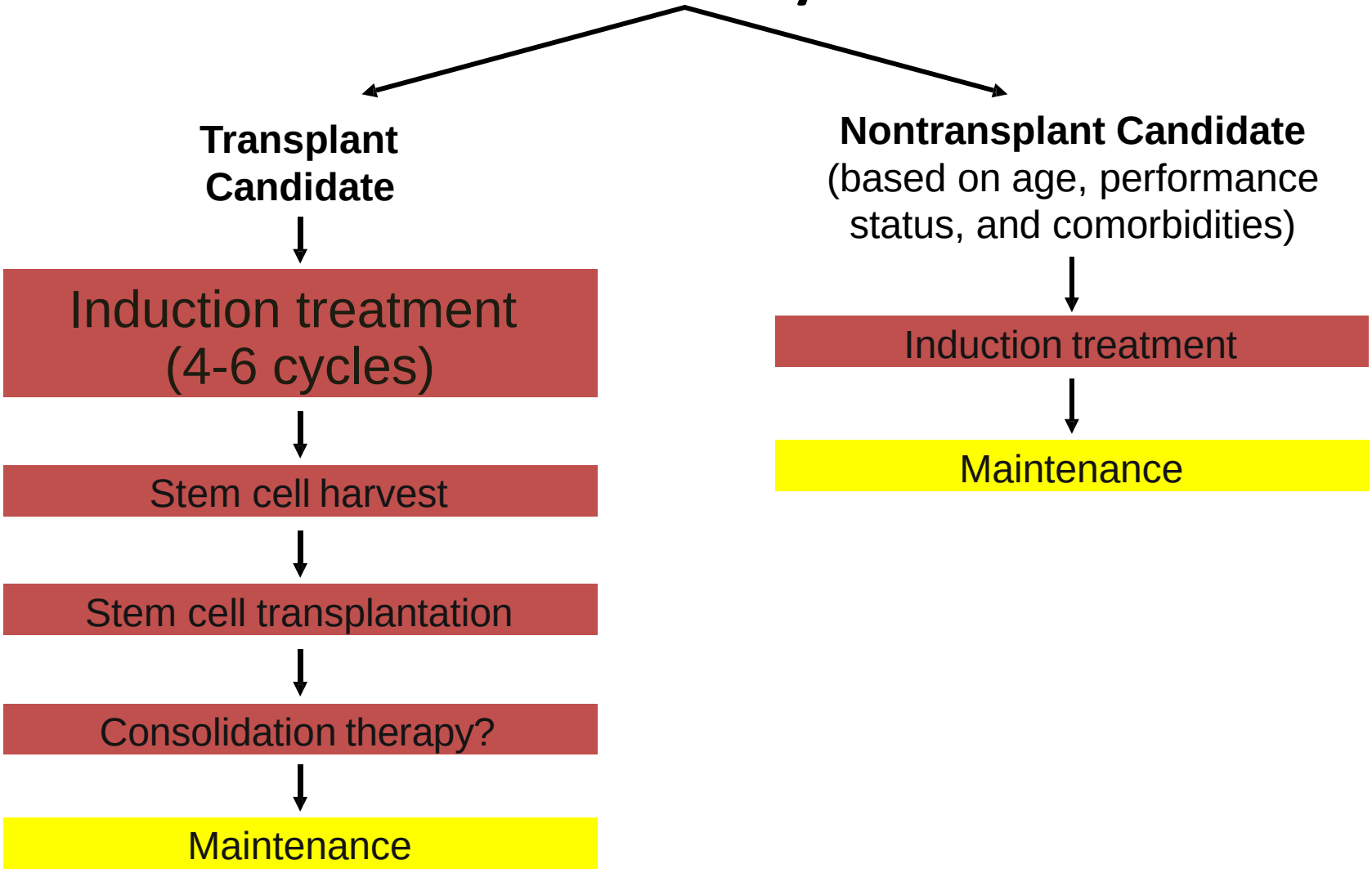
- PFS favored Rd continuous over MPT in the majority of subgroups analyzed



Subgroup	Rd Cont[a]	MPT[a]	HR (95% CI)
ITT population	343/535	387/547	0.69 (0.59, 0.79)
Age > 75 yrs	124/186	127/188	0.78 (0.60, 0.99)
Age ≤ 75 yrs	219/349	260/359	0.64 (0.54, 0.77)
ISS stage: I or II	201/319	228/323	0.67 (0.55, 0.81)
ISS stage: III	142/216	159/224	0.71 (0.57, 0.90)
CrCl < 30 ml/min	29/45	40/55	0.93 (0.57, 1.51)
30 ≤ CrCl < 50 ml/min	83/126	91/126	0.63 (0.47, 0.85)
50 ≤ CrCl < 80 ml/min	158/241	158/222	0.69 (0.55, 0.87)
CrCl ≥ 80 ml/min	73/123	98/144	0.67 (0.49, 0.91)
ECOG PS 0	86/155	104/156	0.50 (0.37, 0.66)
ECOG PS 1	171/257	197/275	0.76 (0.62, 0.94)
ECOG PS 2	84/119	82/111	0.82 (0.60, 1.11)
Lactate dehydrogenase < 200 U/L	282/448	309/434	0.65 (0.55, 0.77)
Lactate dehydrogenase ≥ 200 U/L	60/86	77/112	0.98 (0.70, 1.38)
High risk[b]	39/43	37/47	1.27 (0.81, 2.01)
Non-high risk[b]	125/205	147/206	0.66 (0.52, 0.84)

[a] Number of events/number of patients.
[b] Complete cytogenetics profile for 501 patients (248 in Rd continuous and 253 in MPT); high-risk cytogenetics included t(4;14), t(14;16), and del(17p).
CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; HR, hazard ratio; ISS, International Staging System; ITT, intent to treat; MPT, melphalan, prednisone, thalidomide; PFS, progression-free survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression.
Facon T, et al. Final Analysis of Overall Survival From the FIRST Trial. *ASH 2016, abstract 241*.

Initial Approach to Treatment of Myeloma

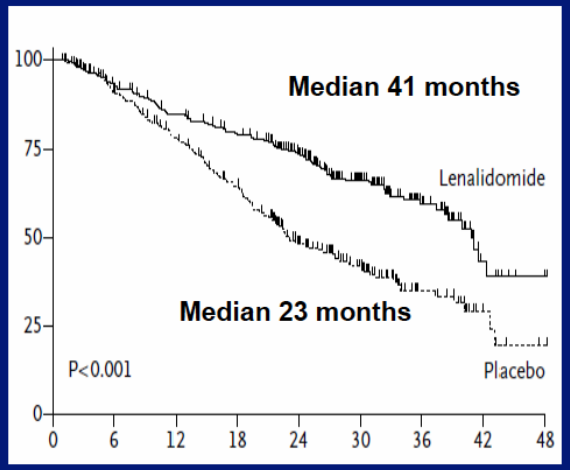


Lenalidomide maintenance

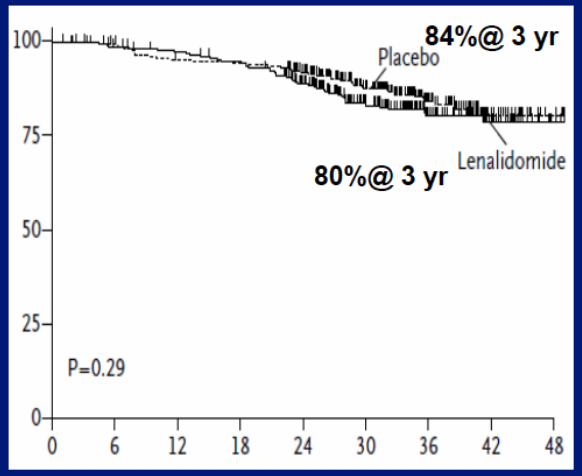
IFM 05-02

Median follow-up 45 months

PFS



OS

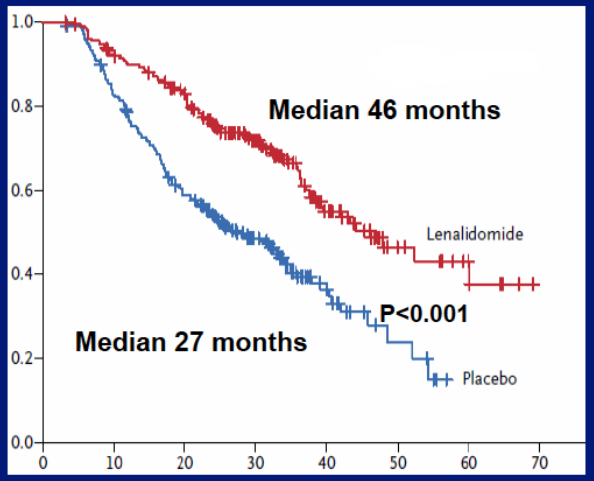


Attal M, et al. NEJM 2012;366:1782

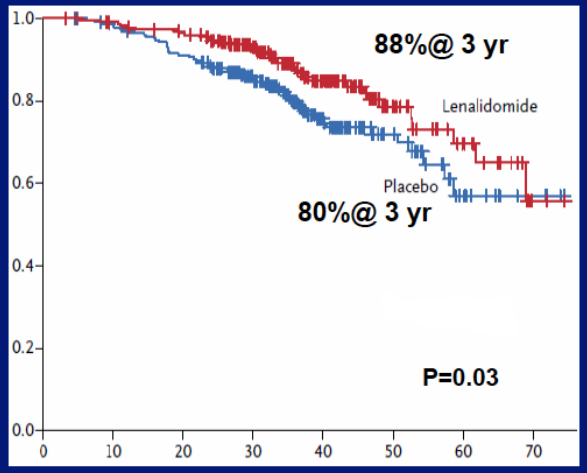
CALGB 100104

Median follow-up 34 months

PFS



OS

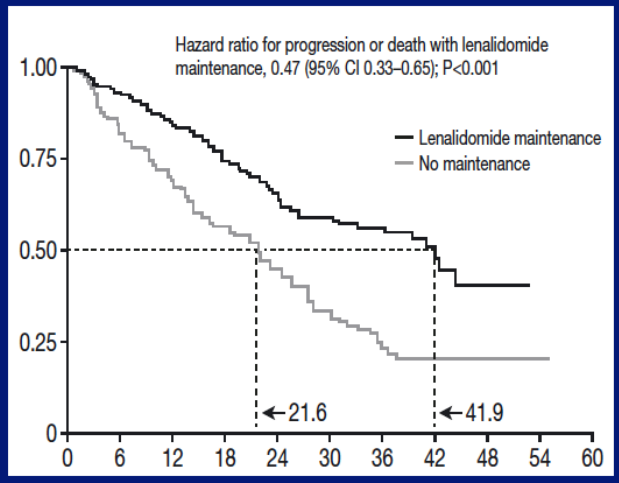


McCarthy PL, et al. NEJM. 2012;366:1770

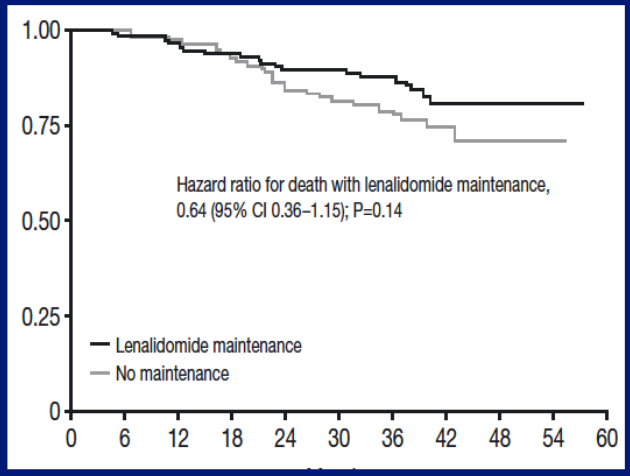
GIMEMA MM RV 209

Median follow-up 51 months

PFS



OS

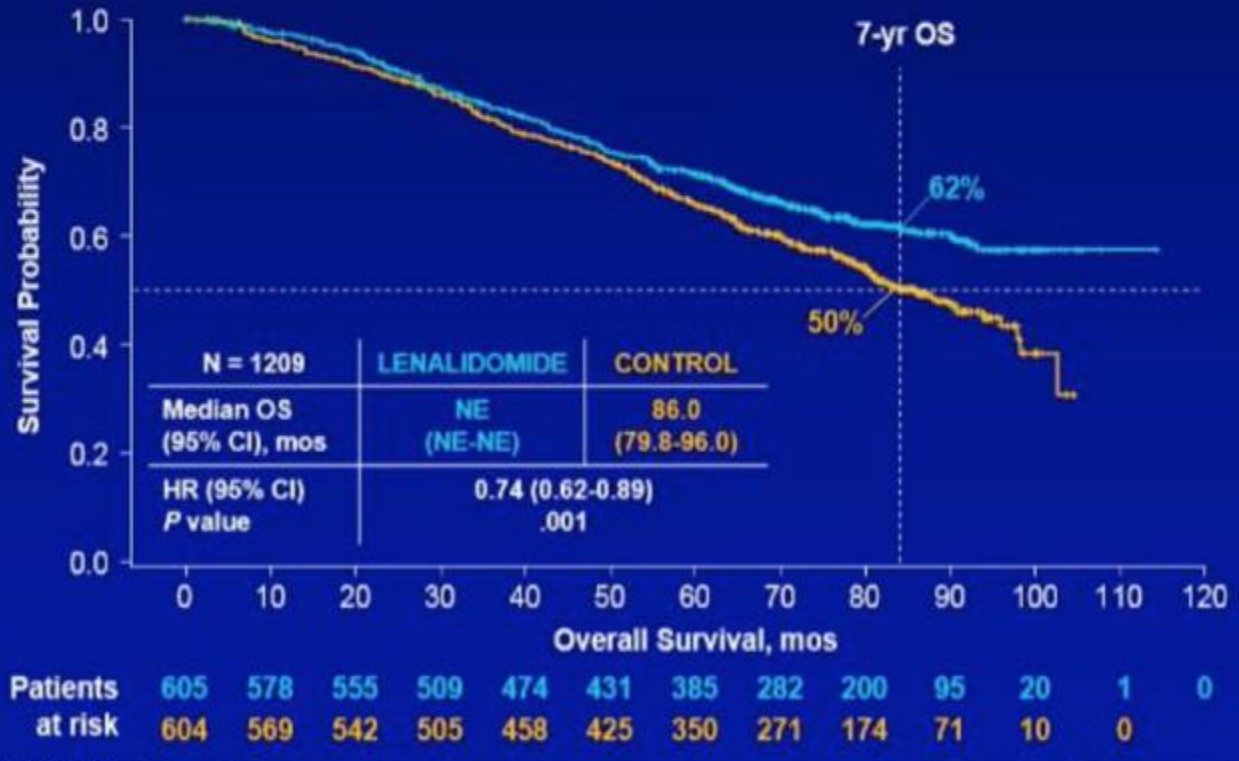


Palumbo A, et al. NEJM 2014;371:10

Maintenance lenalidomide: a meta-analysis

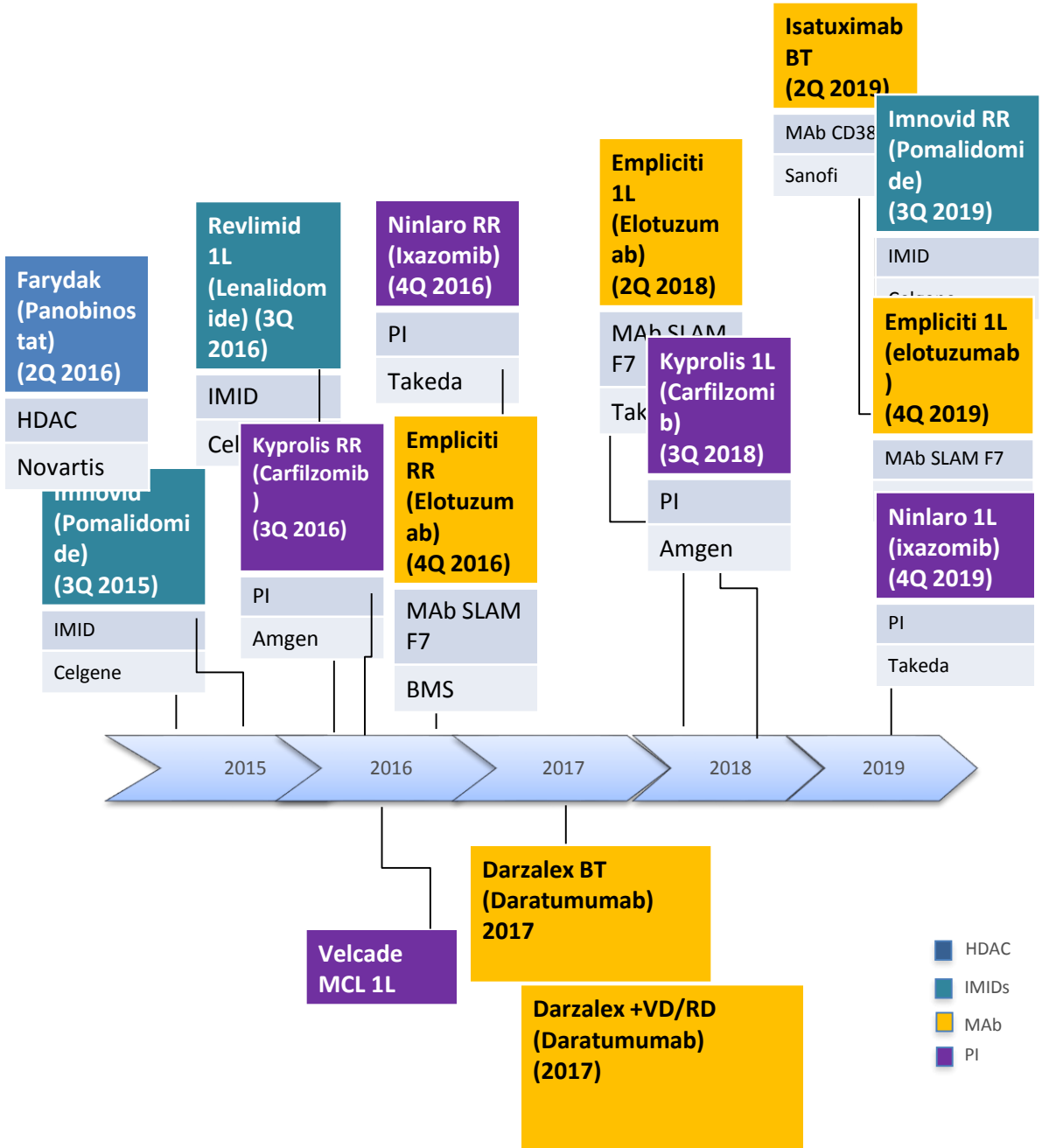
Overall Survival: Median Follow-Up of 80 Months

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival[a]



1. Attal et al, ASCO *2016*

Mieloma Multiplo scenario 2015-2019



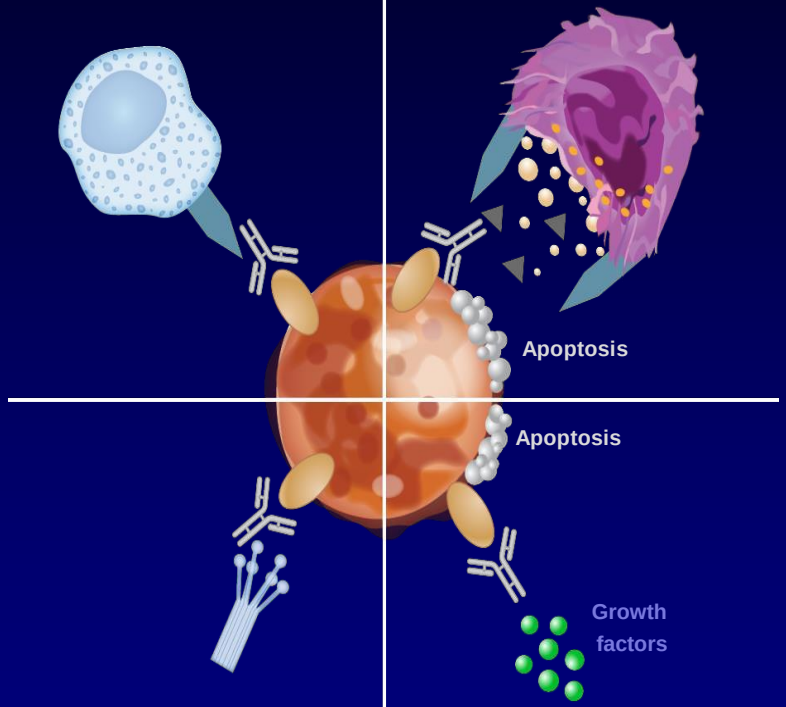
Tumor-directed mAb: Passive immunotherapy

Macrophage-mediated ADCP[1]

- Macrophages recruited to engulf tumor cells

NK cell–mediated ADCC[2]

- Target cell death induced via release of cytotoxic granules or expression of cell death–inducing molecules



Complement protein-mediated CDC[2]

- Complement proteins recruited to initiate complement cascade, resulting in cell death via plasma membrane pore formation

Direct induction of myeloma cell apoptosis[3,4]

- Antibodies block proteins required for tumor survival/ induce apoptotic signaling cascades

Adapted from Brody J et al. 2011[5] and Bakema JE et al. 2014.[1]

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity, NK=natural killer.

1. Bakema JE, van Egmond M. Curr Top Microbiol Immunol. 2014;382:373-392. 2. Wang SY, Weiner G. Expert Opin Biol Ther. 2008;8:759-768.

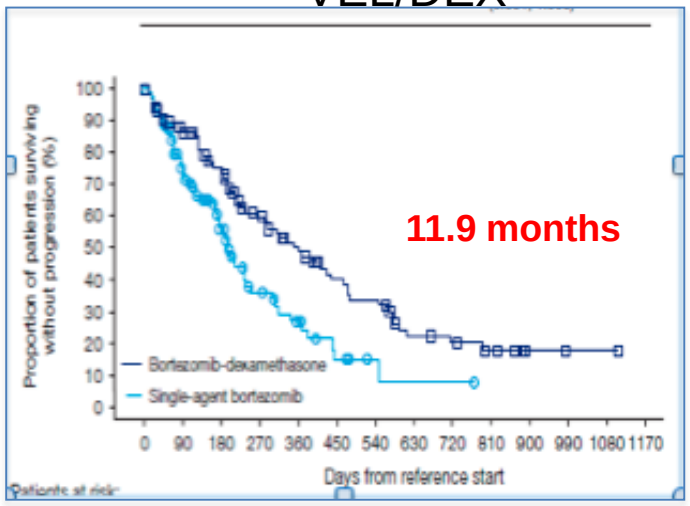
3. Metzger-Filho O et al. Clin Cancer Res. 2013;19:5552-5556. 4. Weiner GJ. Semin Hematol. 2010:47:115-123. 5. Brody J et al. J Clin Oncol. 2011;29:1864-1875.

AGENTS RECENTLY AUTHORIZED FOR THE TREATMENT OF RRMM (5/2017)

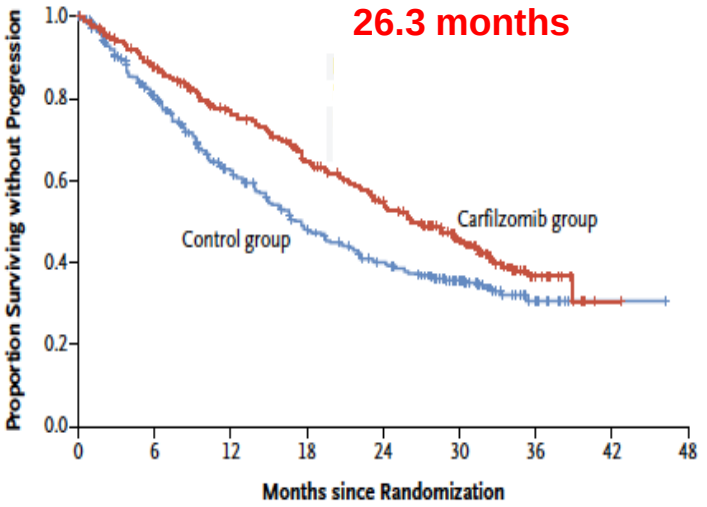
AGENT	TRADE NAME	MECHANISM OF ACTION	INDICATION	DATE OF AUTHORIZATION
POMALIDOMIDE	Imnovid®	IMiD	Treatment of patients with relapsed and refractory MM who have received *≥2 prior regimens* including bortezomib and lenalidomide and have demonstrated disease progression on the last therapy; in combination with dexamethasone.	05 August 2013 (EMA) 05 August 2015 (AIFA)
CARFILZOMIB	Kyprolis®	Proteasome inhibitor	Treatment of patients with MM who have received *≥ 1 prior therapy*; in combinations with lenalidomide and dexamethasone.	19 November 2015 (EMA) 3 October 2016 (AIFA)
ELOTUZUMAB	Empliciti™	Anti-SLAMF7 monoclonal antibody	Treatment of patients with MM who have received *≥ 1 prior therapy*; in combinations with lenalidomide and dexamethasone.	11 May 2016 (EMA) 15 March 2017 (AIFA)
DARATUMUMAB	Darzalex™	Anti-CD38 monoclonal antibody	Treatment of patients with RRMM *whose prior therapy included a PI and an IMiD* and who have demonstrate disease progression on the last therapy; monotherapy.	20 May 2016 (EMA) 10 May 2017 (AIFA)

MM patients: Therapy at Relapse (PFS)

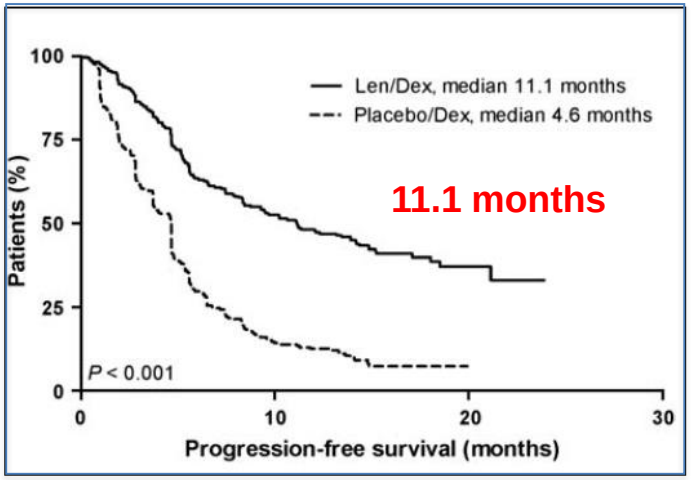
VEL/DEX



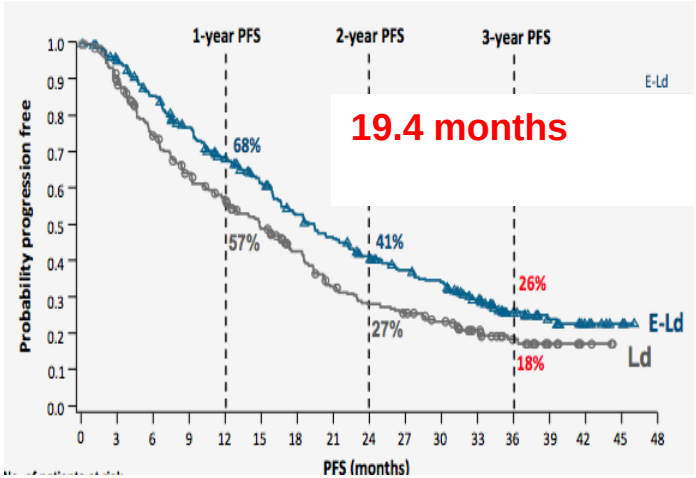
KRD



LEN/DEX



EloRD



Dimopoulos et al., Haematologica 2014

Dimopoulos et. Al, Leukemia 2009

PLACE IN THERAPY IN RELAPSED MM

- Bilancio tra indicazioni, confronto con altre terapie disponibili, individuazione di gruppi di pazienti candidati al trattamento, sostenibilità
- Sinonimo di appropriatezza

CARFILZOMIB FOR THE TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Regimen	Trial	Phase	N	Population	Prior Lines median	ORR. %	PFS/TTP HR	OS, mo HR
CFZ 20/27 mg/m^2 CFZ vs DEXA+/- CTX	PX-171-003-A1 Focus trial	2	266	Relapsed/refractory prior BTZ 99.6% BTZ & LEN refractory or intolerant 80%	5	23.7%	3.7 Median OS 10 months in both arms	15,4 months
CFZ 20/27 mg/m^2- LEN-Dex vs LEN-Dex	ASPIRE	3	792	Relapsed MM with 1-3 prior lines BTZ and LEN not refractory** - prior LEN 19.8% LEN refractory 7.3% - prior BTZ 65.8% BTZ non responsive 15.2%	2	87 vs 67 P < 0.001	26.3 VS 17.6 P = 0.001 HR: 0.69 1 prior line: 29.6 vs 17.6 HR 0.69 ≥ 2 prior lines 25.8 vs 16.7 HR 0.69	2- year OS: 73% vs 65% P = 0.04 HR: 0.79 (n.s.)
CFZ 56 mg/m^2 - Dex vs BTZ-dex	ENDEAVOR	3	929	Relapsed or progressing MM with 1-3 prior lines - prior LEN 38% - prior BTZ 54% BTZ refractory 3.7%	2	77 vs 63 P < 0.001	18.7 vs 9.4 P < 0.001 HR 0.53 1 prior line: 22.2 vs 10.1 HR. 0.45 ⩾2 prior lines: 14.9 vs 8.4 HR. 0.60	Interim analysis HR 0.79 (n.s.)

SCHEDA AIFA CARFILZOMIB

**Per la definizione di refrattarietà fare riferimento ai criteri utilizzati nello studio registrativo ASPIRE.*

Caratteristiche del paziente e aspetti rilevanti all'eleggibilità			
O	Precedente trattamenti con bortezomib?	*Si*	*campo compilato in automatico se tra le terapie precedenti è stato selezionato bortezomib*
		No	
E	*Se sì,* il paziente è progredito durante il trattamento con bortezomib?	Si	*blocca*
		No	

O	Precedente trattamenti con lenalidomide	*Si*	*campo compilato in automatico se tra le terapie precedenti è stato selezionato lenalidomide*
		No	
Se si indicare:			
E	Il paziente è progredito nei primi 3 mesi di terapia oppure in qualsiasi momento se il trattamento con lenalidomide è quello immediatamente precedente?	Si	*blocca*
		No	
E	*Se no alla riga sopra,* indicare se il paziente ha sospeso lenalidomide per intolleranza	Si	*blocca*
		No	

O	Anamnesi positiva per insufficienza cardiaca congestizia, aritmia, angina non controllata o recente infarto miocardico (negli ultimi 4 mesi) (vd paragrafo 4.4 RCP)	Si
		No
O	Anamnesi positiva per eventi tromboembolici	Si
		No
O	Anamnesi positiva per reazioni allergiche a talidomide e/o lenalidomide	Si
		No

6- Scheda Rivalutazione (RV)
Il trattamento può proseguire fino alla progressione della malattia o fino allo sviluppo di tossicità non tollerabile.
La valutazione clinica di continuare il trattamento con KYPROLIS in associazione con lenalidomide e desametasone per più di 18 cicli si deve basare sulla valutazione del rapporto rischio/beneficio individuale poichè i dati di tollerabilità e tossicità di carfilzomib oltre i 18 cicli sono limitati (vd paragrafo 5.1 RCP).
Rivalutazione obbligatoria dopo i primi 2 cicli, poi ogni 3 cicli

TOXICITY PROFILE

Table 3. Adverse Events in the Safety Population.*

Event	Carfilzomib Group (N = 392)		Control Group (N = 389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	number of patients (percent)			
Most common nonhematologic adverse events				
Diarrhea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
Fatigue	129 (32.9)	30 (7.7)	119 (30.6)	25 (6.4)
Cough	113 (28.8)	1 (0.3)	67 (17.2)	0
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	75 (19.3)	4 (1.0)
Hypokalemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
Other adverse events of interest				
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure†	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure‡	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease§	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

Steward K, NEJM 2015

Profilo del paziente candidato a KRD

- **prima ricaduta**

- < 75 anni

- ricaduta clinicamente aggressiva

- assenza di severe pregresse problematiche cardiologiche

-ipertensione ben controllata

ELOTUZUMAB FOR THE TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Regimen	Trial	Phase	*N*	Population	Prior lines Median	ORR. %	PFS/TTP mo HR	OS,mo HR
Elo-btz-dex vs btz-dex	Nct01478048	2	152	Relapsed/refractory MM with 1-3 prior therapies Btz refractory 22%	1	66 vs 63	9.7 vs 6.9 *P* = 0.09	Na Hr 0.61
Elo-len-dex vs len-dex	**Eloquent-2**	**3**	**646**	**Relapsed or refractory MM with 1-3 prior therapies** **- Prior len 5%** **Prior len permitted in 10% of patients (if sensitive)** **- Prior btz 70%** **BTZ refractory 22%**	**2**	**79 vs 66** ***P* < 0.001**	**19.4 vs 14.9** ***P* < 0.001** **Hr 0.73** **TnT 33 ns 21** **Se durata malattia>3.5 a e 1 recidiva HR 0.47**	**Interim analysis** **Hr 0.77 (n.S.)**

SCHEDA AIFA ELOTUZUMAB

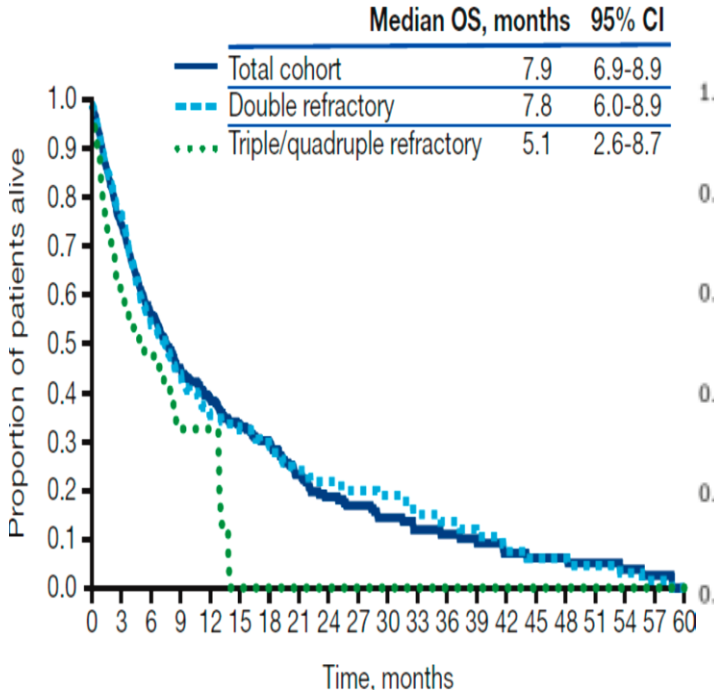
O	Data d'inizio linea n° (prima dispensazione)	../.... (mese/anno uniformando la data)	*Dato compilato in automatico se tali trattamenti sono monitorati tramite Registro*
O	Data fine linea n° (ultima dispensazione)	../.... (mese/anno uniformando la data)	
O	Migliore risposta ottenuta in corso di trattamento	Risposta Completa stringente (sRC)	
		Risposta Completa (RC)	
		Very good Partial Remission (VGPR)	
		Risposta Parziale (PR)	
		Risposta minima (MR)	
		Malattia stabile (SD)	
		Progressione (PD)	
		Non valutata (NV)	
E	Causa di fine trattamento	Intolleranza	
		Refrattarietà	
		Progressione	
		Fine regolare del trattamento	
		Causa non dipendente dal farmaco	
Per ciascuna linea di trattamento già effettuata successiva alla prima indicare i trattamenti impiegati. Questa finestra e la successiva devono essere ripetute tante volte quante sono le N linee di terapia ricevute, indicando la N linea a cui ci si riferisce (2^, 3^, ecc.)			

	Caratteristiche del paziente e aspetti rilevanti all'eleggibilità		
O	Precedente trattamento con **Lenalidomide**	*Si*	*Campo compilato in automatico se selezionata lenalidomide tra le terapie precedenti*
		No	
Se si indicare:			
E	Il paziente è refrattario alla lenalidomide? *Per la definizione di refrattarietà fare riferimento alla Consensus dell'International Myeloma Workshop (Rajkumar SV et al, Blood 2011)*	Si	*blocca*
		No	
E	*Se no alla riga sopra,* Il paziente ha sospeso lenalidomide per intolleranza	Si	*blocca*
		No	

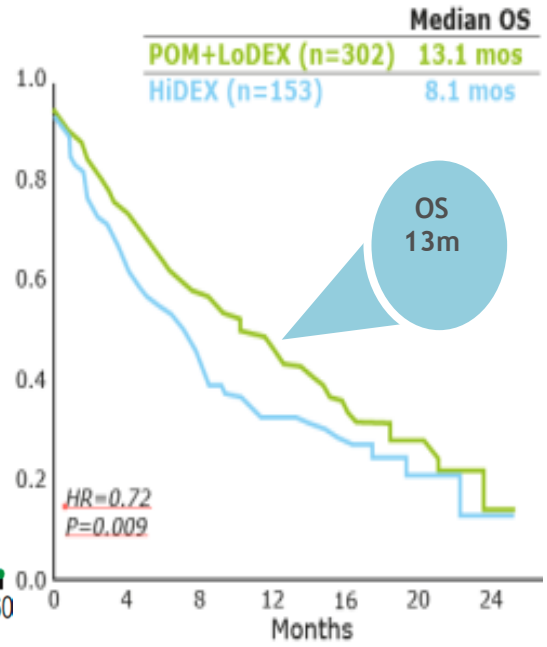
Profilo del paziente candidato a EloRD

- **prima ricaduta**
- **anche pazienti anziani e con comorbilità cardiovascolari**
- **ricaduta clinicamente non aggressiva**
- **anche cariotipo sfavorevole, p.e. t(4;14)**
- **disponibilità a terapia continuativa in regime di DH**

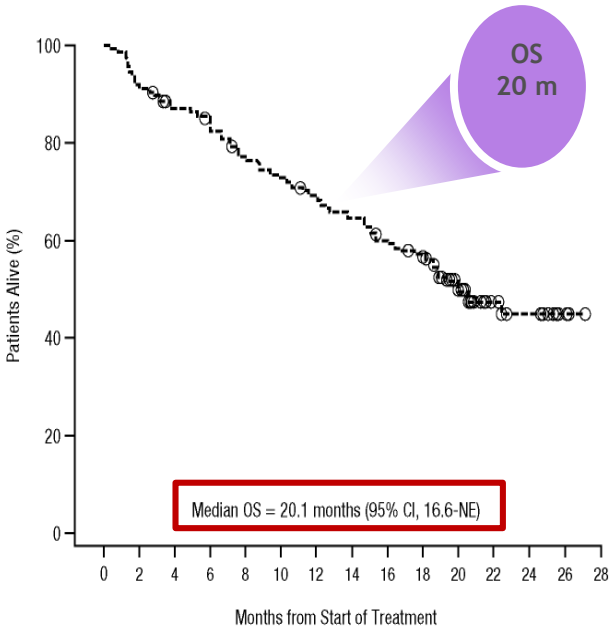
The Breakthrough (BT) population outcome



mOS 5-8 months in patients relapsed or refractory MM after ≥3 prior lines of therapy, including IMID and PI



PomDex: mOS 13,1months in patients relapsed or refractory MM after ≥2 prior lines of therapy, including IMID and PI



Daratumumab: mOS of 20 months in patients with relapsed or refractory, double refractory or relapsed after ≥3 L, including pomalidomide and carfilzomib

Usmani et al., Oncologist 2016; ***doi:10.1634/theoncologist.2016-0104***

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

Jesus San Miguel et.al, Lancet 2013

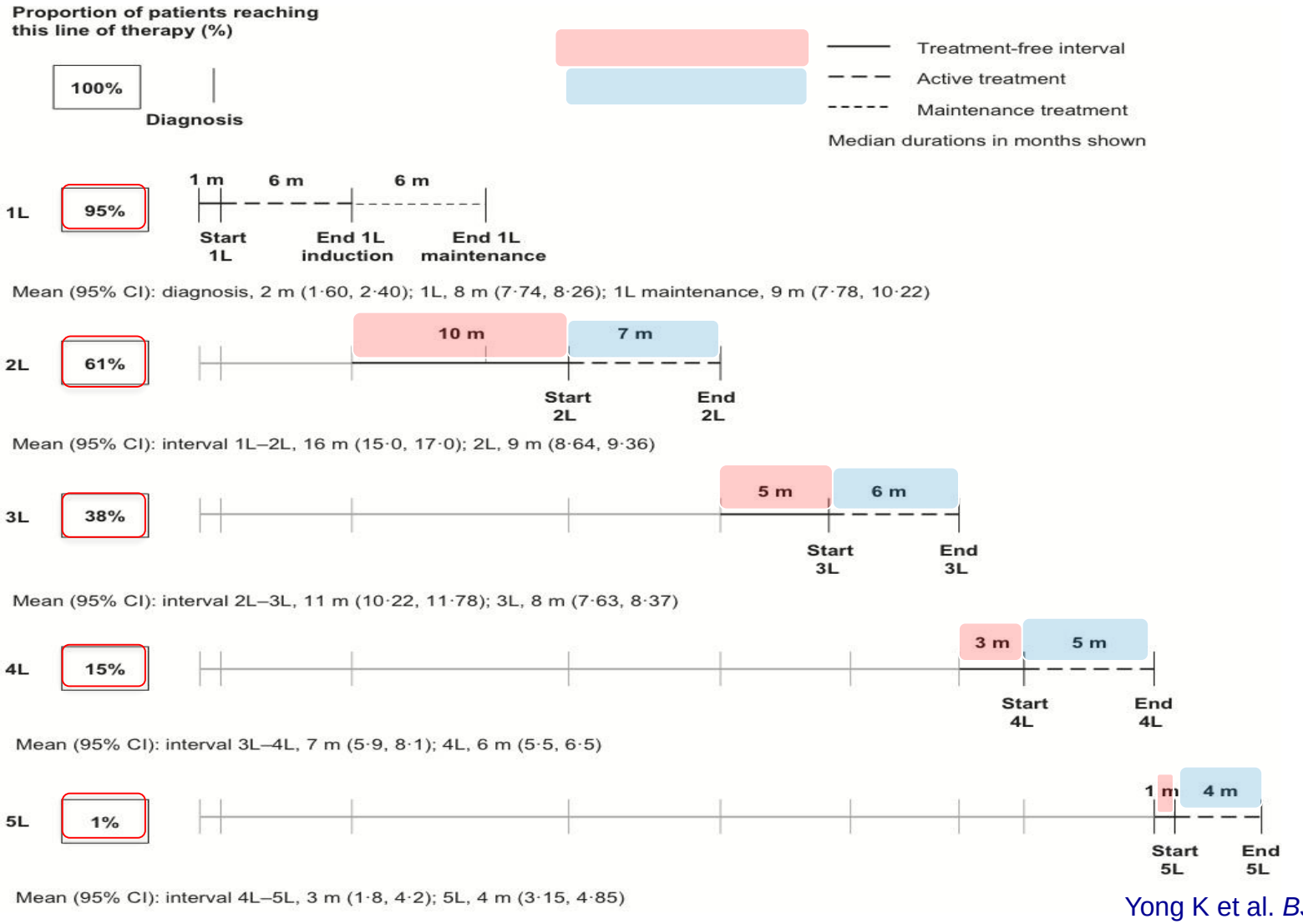
Profilo del paziente ricaduto/refrattario già esposto a bortezomib/lenalidomide

- **>2 ricaduta**
- **caratteristiche cliniche della ricaduta: aggressiva (Daratumumab) vs indolente (Pomalidomide)**
- **Malattia extramidollare (SNC)**
- **preferenze/esigenze del paziente (terapia orale vs terapia infusiva in DH)**

REAL-WORLD PRACTICE

TREATMENT DURATION AND TREATMENT-FREE INTERVALS

A total of 435 physicians retrospectively reviewed 4997 patient charts. In the 6 months before inclusion in the study, 1802 of the patients had been treated up to the end of first line, 1380 up to the end of second line and 1815 up to the end of third line or later.



Yong K et al. *BJH 2016*

Sostenibilità e diritto alle cure

La continua **evoluzione** della ricerca in ambito ematologico e oncologico rischia di mettere in difficoltà i sistemi sanitari nel mondo.

Discrepanza fra aspettative dei pazienti e l'evoluzione della ricerca da una parte e la paura degli enti pagatori di un tracollo finanziario dall'altra

Situazione paradossale in cui la **ricerca** in qualche modo rappresenta un problema per coloro che devono organizzare un sistema sanitario la cui missione è la cura dei propri utenti

Conclusioni

- Nell'ultima decade la storia del mieloma è cambiata completamente. Le possibilità terapeutiche sono aumentate in modo esponenziale raddoppiando la sopravvivenza non solo dei più giovani ma anche di quelli non candidati a terapie ad alte dosi
- La disponibilità di nuovi farmaci e la prospettiva di averne molti altri nel giro di pochi anni, non solo in ambito ematologico, rischiano di mettere in crisi il sistema sanitario portando alla ribalta i concetti di sostenibilità e appropriatezza
- In questa nuova dimensione il medico deve avere un ruolo centrale in quanto primo interlocutore del paziente e principale attore nella definizione del suo percorso diagnostico terapeutico