AZIENDA ULSS N. 6 - VICENZA
DIVISIONE DI EMATOLOGIA

FONDAZIONE PROGETTO EMATOLOGIA

GIORNATE EMATOLOGICHE VICENTINE

VII edizione

10-11-12 Ottobre 2016
Palazzo Bonin Longare
Vicenza

La terapia del mieloma multiplo
Prima linea: come e quando trattare

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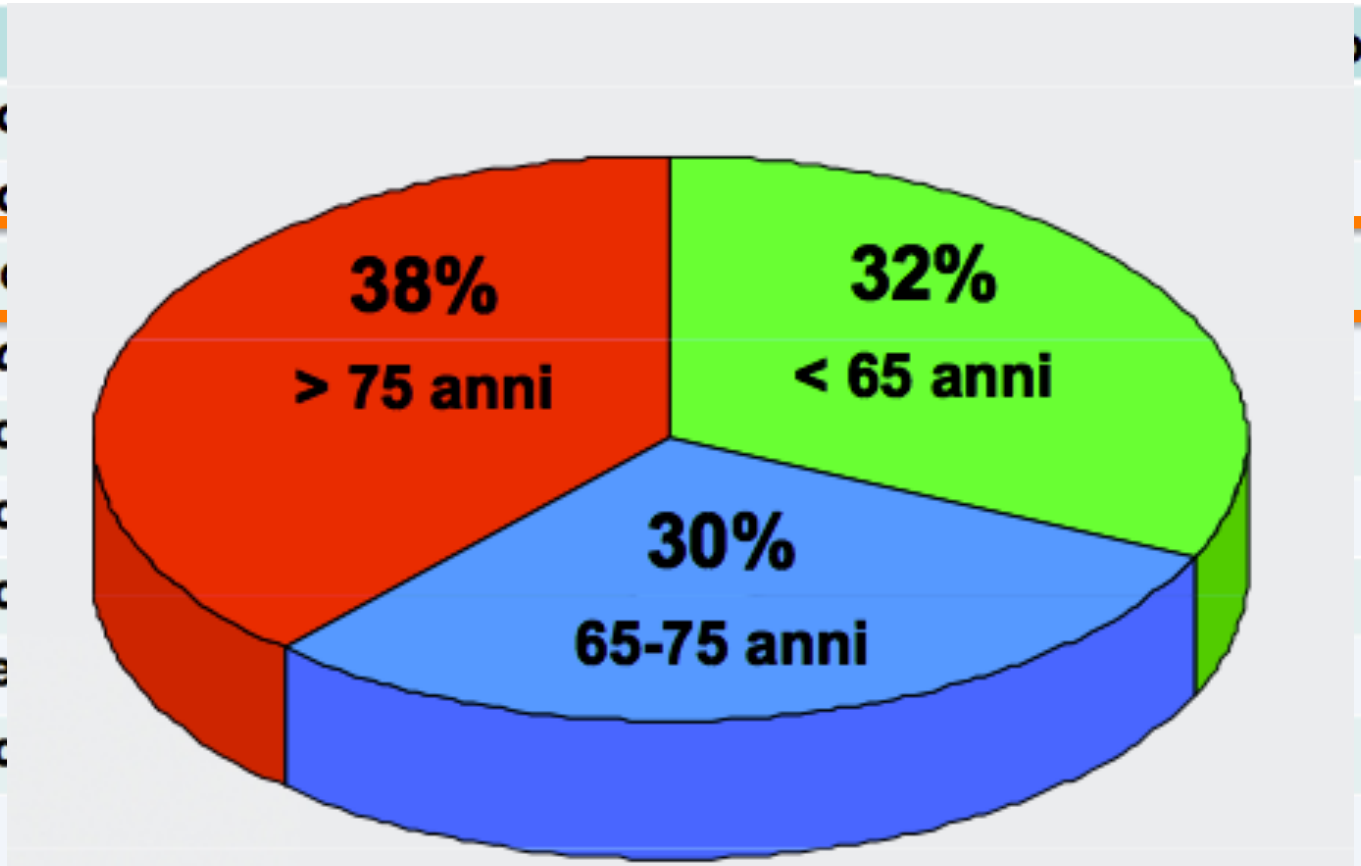
Ematologia e Immunologia Clinica

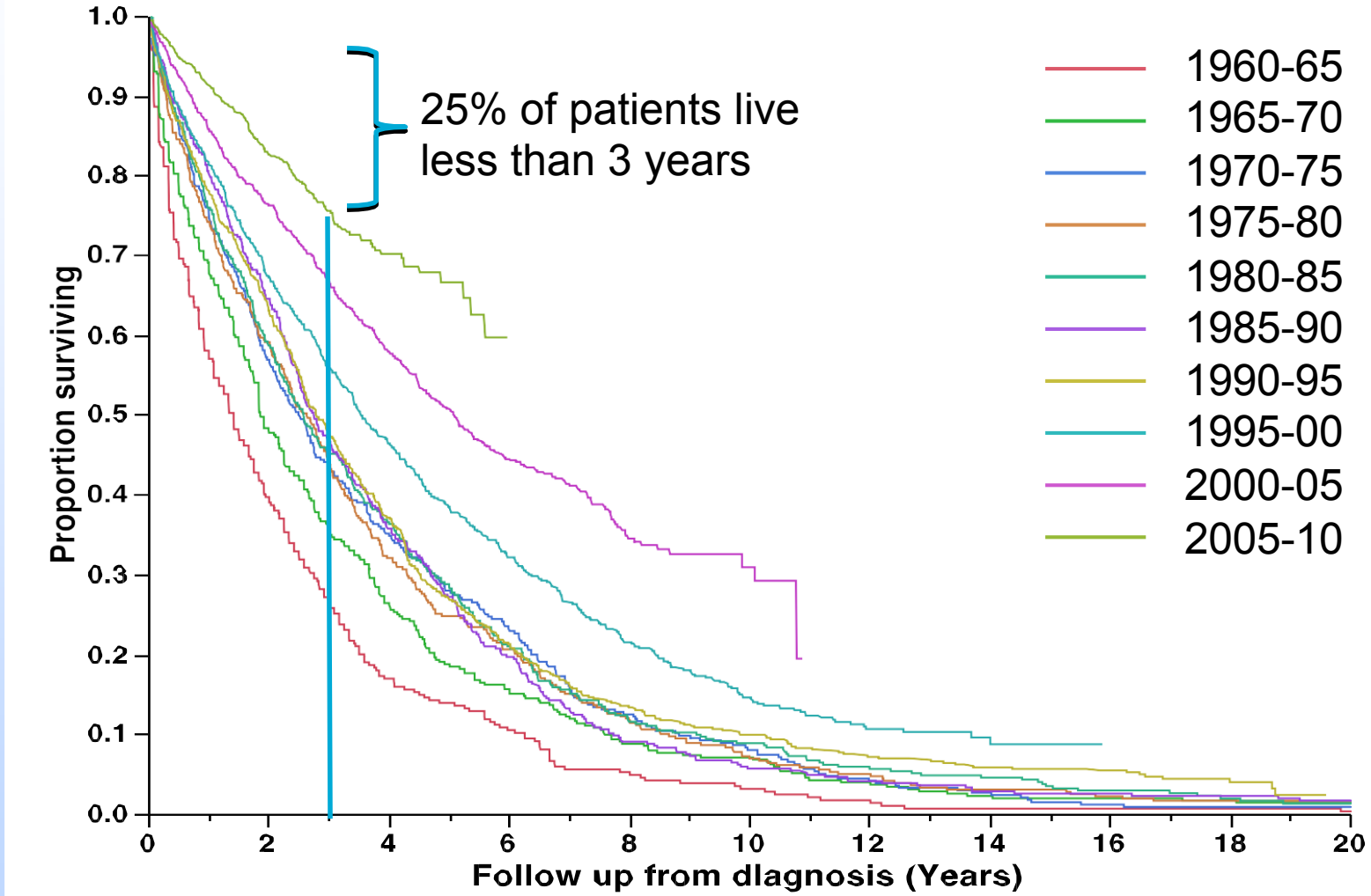
Neoplasie ematologiche
Incidenza -Veneto

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



Fonte: Registro Tumori Veneto

Improving Survival in MM



MAYO CLINIC

Quando trattare

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 osteopenic, or pathologic fractures

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

IMWG UPDATED CRITERIA FOR THE DIAGNOSIS OF MM

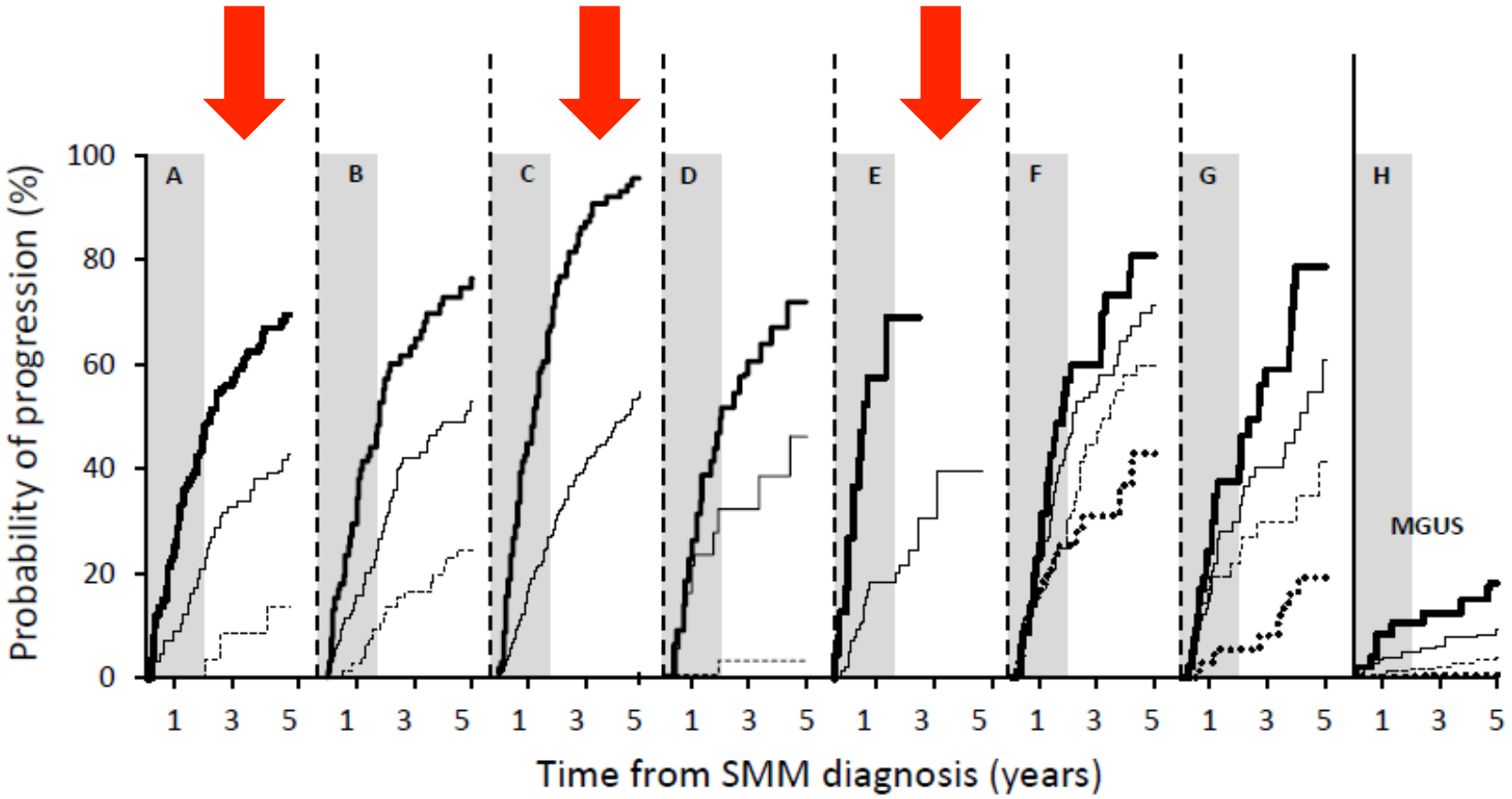
Definition of multiple myeloma

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

IMWG UPDATED CRITERIA FOR THE DIAGNOSIS OF MM

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Rajkumar V. et al., Lancet Oncology 2014

bjh research paper

Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review

COMPARISON OF PET, PET/CT, MRI OR CT vs WBXR AT STAGING

- 32 directly comparison studies, prospective and retrospective, 1661 patients
- All index tests had sensitivity above 0,9 as compared to WBXR (low false negative). Fewer additional lesions detected by PET/CT and MRI as compared to WBLDCT
- WBLDCT can replace WBXR
- Modern imaging techniques detected fewer lesions in the skull and ribs ⟶ «We therefore recommend additional X-ray of the ribs and the skull if clinically relevant»

Regelink J. et al., BJH 2013

The Role of Imaging in the Treatment of Patients With Multiple Myeloma in 2016

Evangelos Terpos, MD, PhD, Meletios A. Dimopoulos, MD, and Lia A. Moulopoulos, MD

- Whole-body LDCT seems to be most suitable for the detection of osteolytic bone disease in patients with multiple myeloma at diagnosis, replacing whole-body x-ray.

- Whole-body MRI (or at least MRI of the spine and pelvis if whole-body MRI is not available) should be performed for all patients with smoldering multiple myeloma with no lytic lesions to look for occult disease, which may justify treatment.

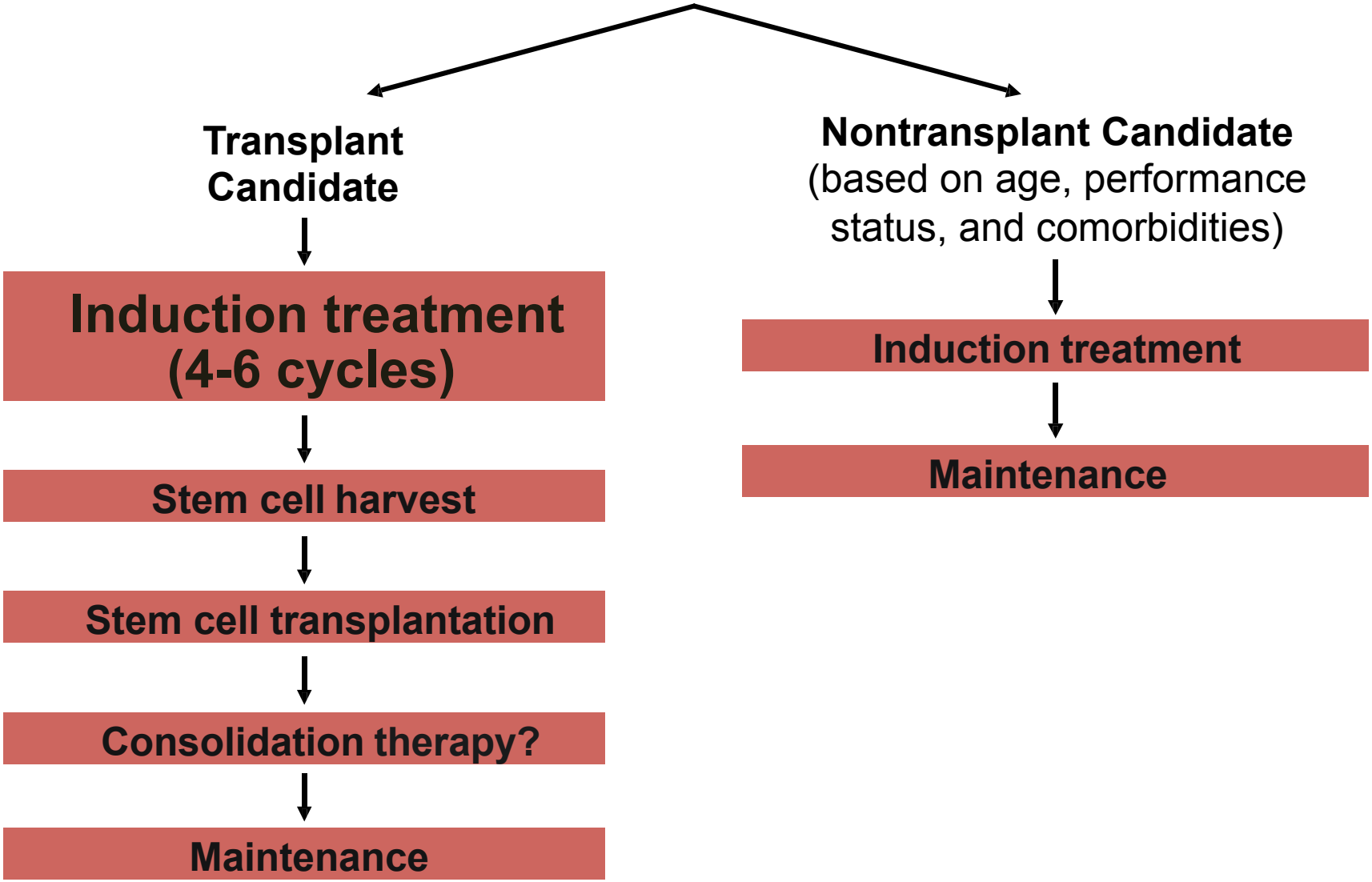
- PET/CT seems to be inferior to MRI regarding the detection of marrow involvement in multiple myeloma, but it is probably the best technique for optimal definition of CR and follow-up of patients with myeloma.

Problemi nella «real life»

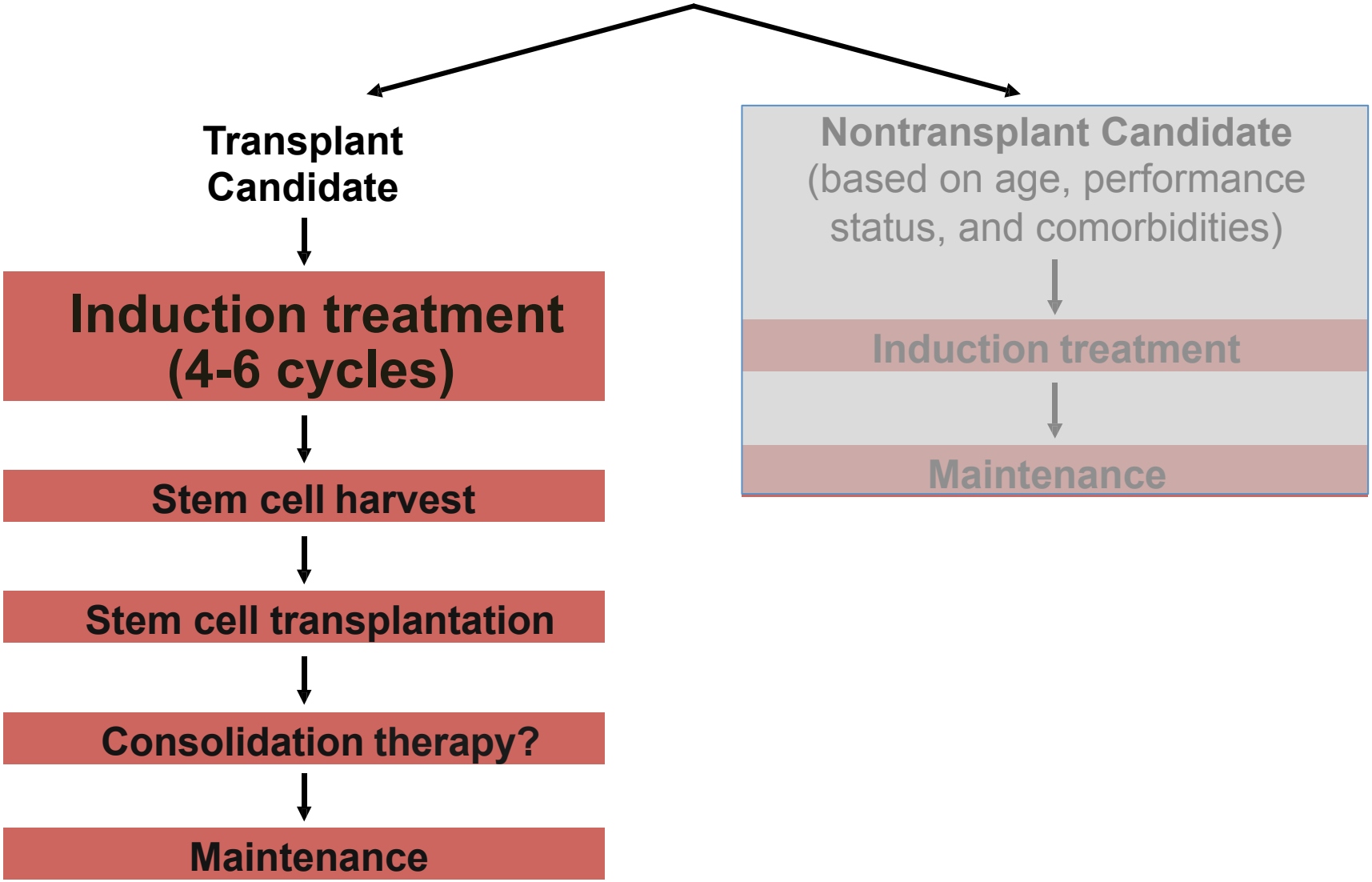
- Accessibilità del dosaggio delle FLC
- Accessibilità, costi e tempistiche delle indagini radiologiche /nucleari: accentramento delle indagini in centri di secondo o terzo livello
- Tempistiche di follow-up in relazione a dose di radiazioni, accessibilità e costi

Come trattare

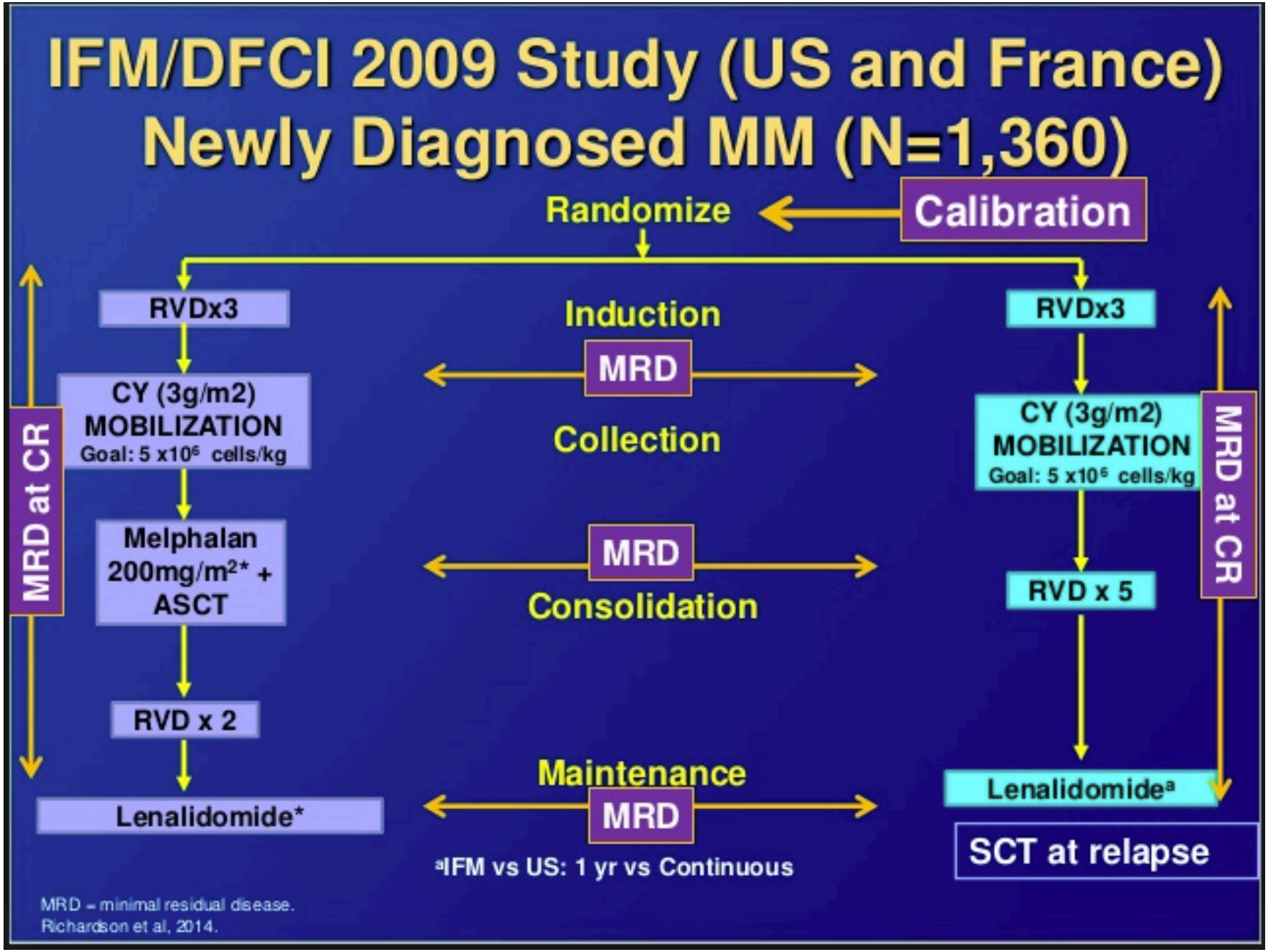
Initial Approach to Treatment of Myeloma



Initial Approach to Treatment of Myeloma



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

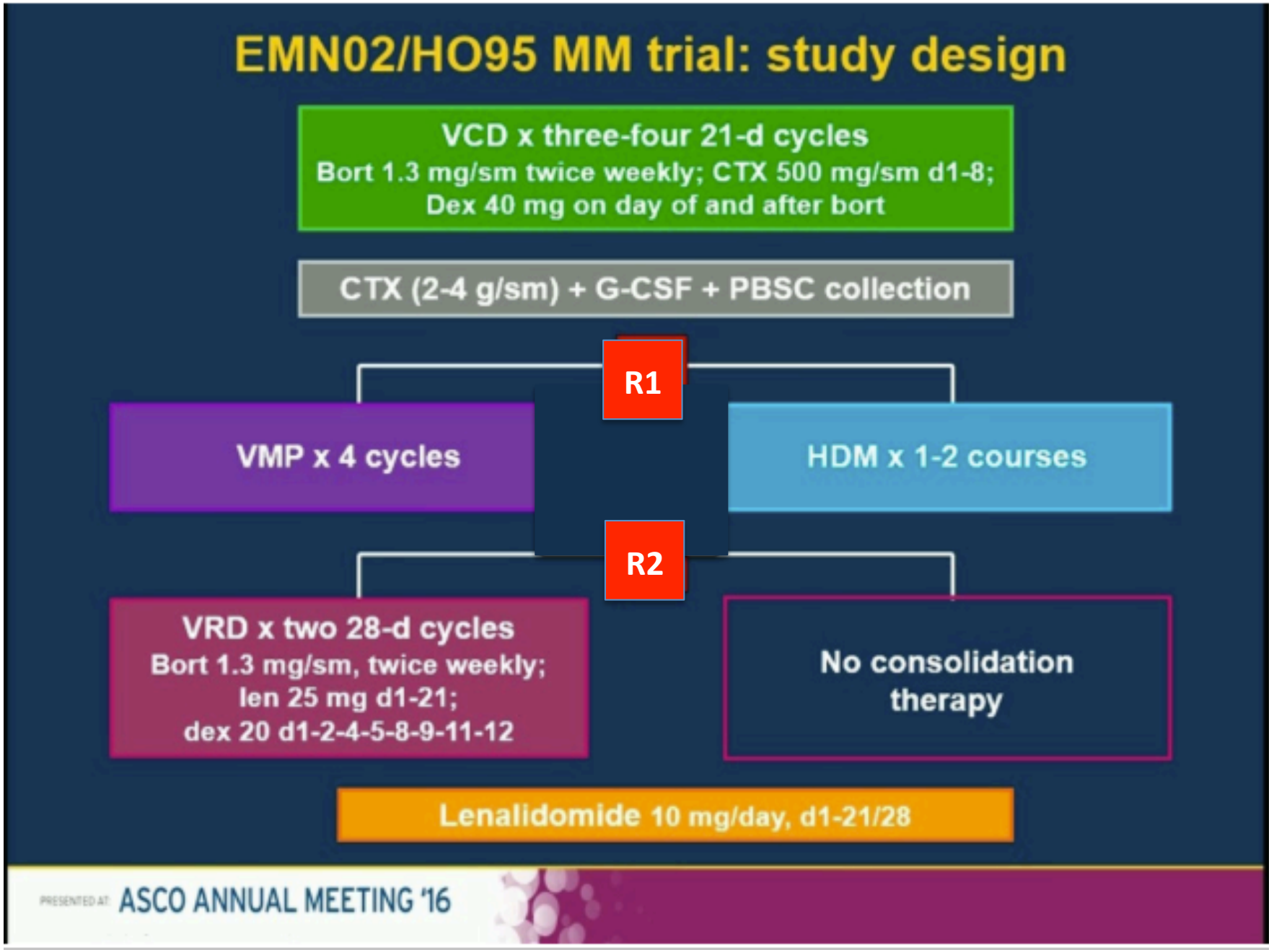


Attal M et al ASH 2015 abstr 391

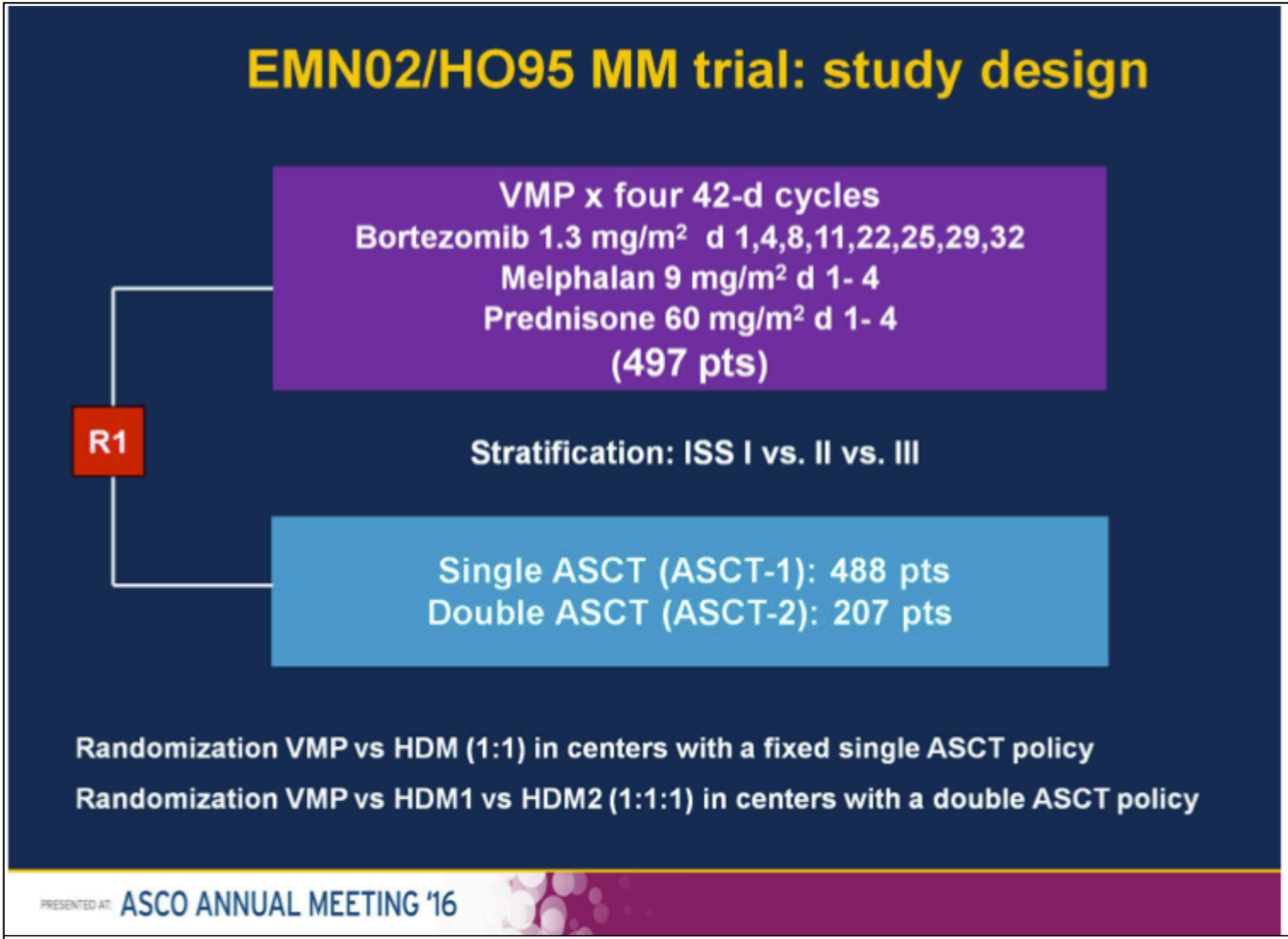
Results

- 700 patients randomized in France and Belgium (American contribution not reported at this time)
- Median follow-up 39mo
- ASCT improved PFS ($p < 0.0002$; HR= 1.5, 95% CI= 1.2-1.9).
  - 3-year PFS 61% vs 48%
  - benefit observed in: age (≤ or > 60 years), sex, Ig isotype, ISS stage, cytogenetics, and response after the 3 first cycles of RVD (CR vs no-CR).
- The 3-year OS was extremely high (88%) and similar between the groups (p=0.25).
- CR rate was higher in the transplant arm compared to the RVD arm: 58% versus 46%, respectively (p<0.01).

Attal M et al ASH 2015 abstr 391

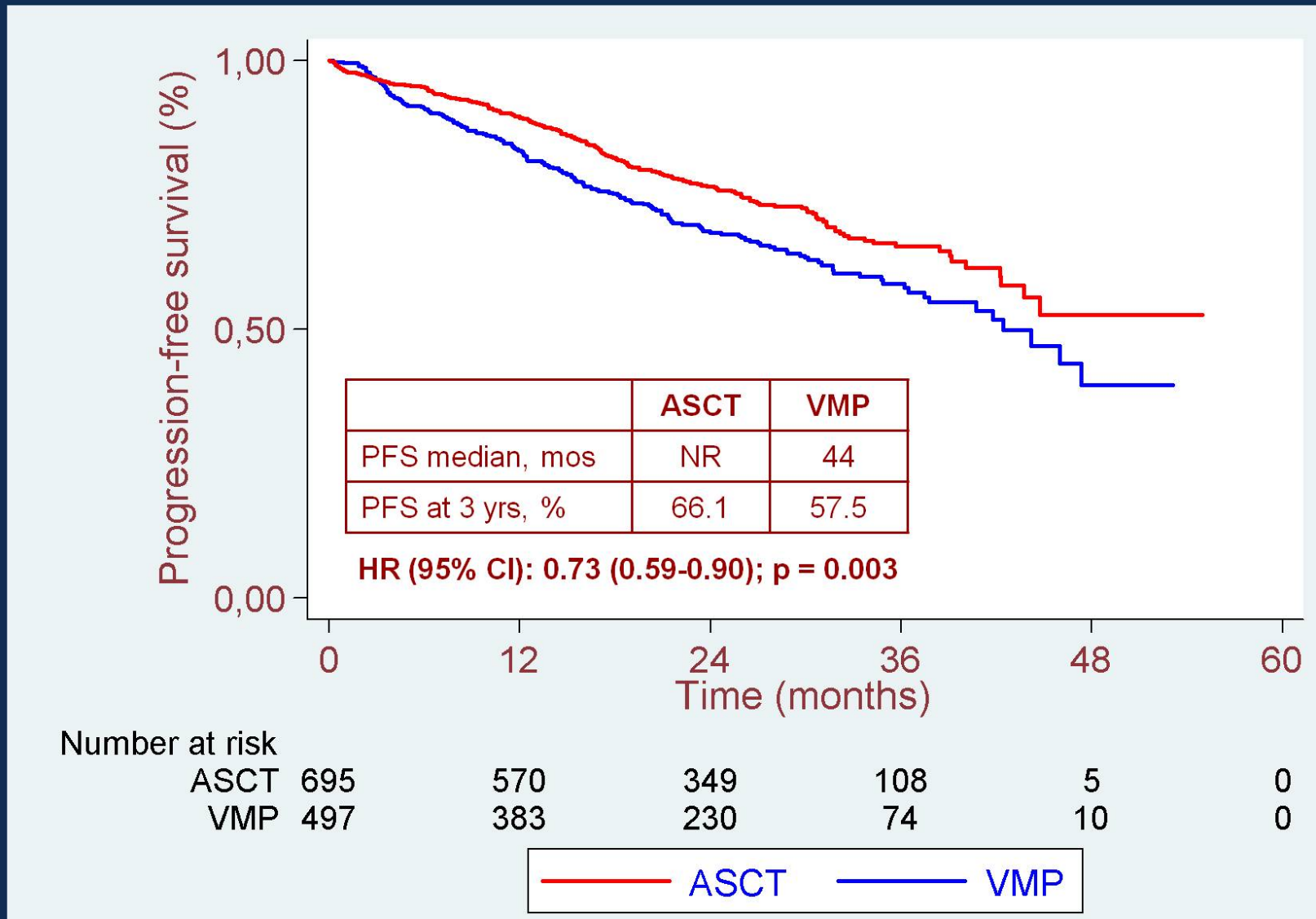


Presented By Michele Cavo at 2016 ASCO Annual Meeting



Presented By Michele Cavo at 2016 ASCO Annual Meeting

PFS by Randomization



Presented By Michele Cavo at 2016 ASCO Annual Meeting

Prospective randomized clinical trials comparing new drug induction and consolidation to ASCT in NDMM patients

Group	No	Induction	Comparator	RR	PFS	OS
GIMEMA NEJM 2014	402	RD x4	MPR x6 ASCT x2	>VGPR 63 59	22mo 43mo*	65% 4y 81%*
MultiCentr LancetOncol 2015	389	RD x4	CDR x6 ASCT x2	>VGPR 50 54	29mo 43mo*	68% 4y 77%*
IFM 2009 ASH 2015	700	VRD x3	VRD x5 ASCT + VRD x2	>VGPR 78 88*	34mo 43mo*	83% 4y 81%
EMN ASCO 2016	1192	VCD x3-4	VMP x4 ASCT 1 or 2	>VGPR 74 85*	44mo NR HR 0.73*	NS (short fu)

* $p < 0.01$

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 CC 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

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

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IMWG recommendations, Leukemia (2013) 1 – 12

What is the best induction regimen with or without transplant ?

Leukemia (19 March 2015) | doi:10.1038/leu.2015.80

Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma

E K Mai, U Bertsch, J Dürig, C Kunz, M Haenel, I W Blau, M Munder, A Jauch, B Schurich, T Hielscher, M Merz, B Huegle-Doerr, A Seckinger, D Hose, J Hillengass, M S Raab, K Neben, H-W Lindemann, M Zeis, C Gerecke, I G H Schmidt-Wolf, K Weisel, C Scheid, H Salwender and H Goldschmidt

504 patients in the MM5 prospective trial

PAD and VCD were equally effective: VGPR rates 34.3% vs 37% p=0.5

VCD is less toxic: Serious Adverse Events 24% vs 32.7%, p=0.04

VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial

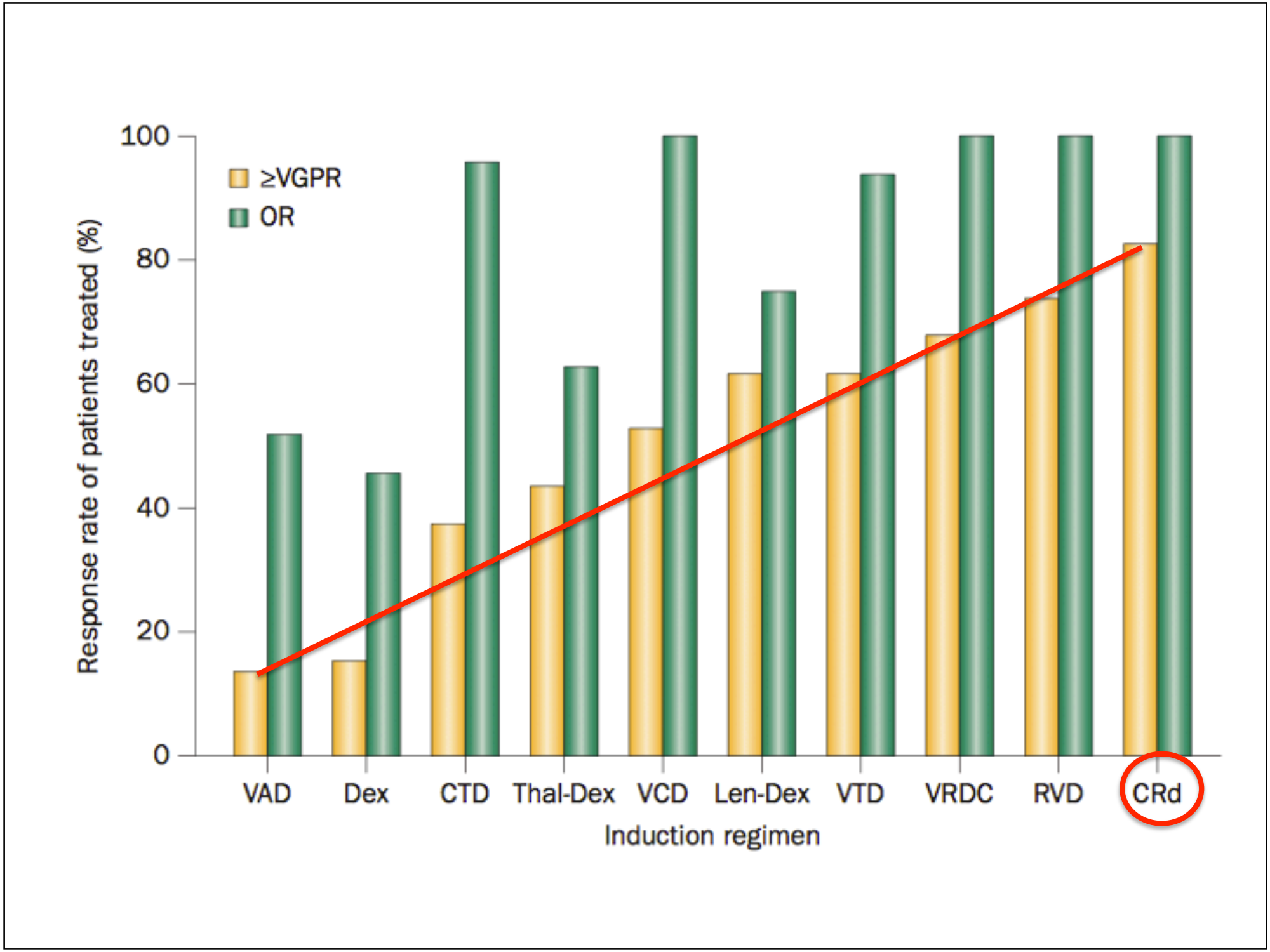
Philippe Moreau,[1] Cyrille Hulin,[2] Margaret Macro,[3] Denis Caillot,[4] Carine Chaleteix,[5] Murielle Roussel,[6] Laurent Garderet,[7] Bruno Royer,[8] Sabine Brechignac,[9] Mourad Tiab,[10] Mathieu Puyade,[11] Martine Escoffre,[12] Anne-Marie Stoppa,[13] Thierry Facon,[14] Brigitte Pegourie,[15] Driss Chaoui,[16] Arnaud Jaccard,[17] Borhane Slama,[18] Gerald Marit,[2] Karim Laribi,[19] Pascal Godmer,[20] Odile Luycx,[21] Jean-Claude Eisenmann,[22] Olivier Allangba,[23] Mamoun Dib,[24] Carla Araujo,[25] Jean Fontan,[26] Karim Belhadj,[27] Marc Wetterwald,[28] Véronique Dorvaux,[29] Jean-Paul Fermand,[30] Philippe Rodon,[31] Brigitte Kolb,[32] Sylvie Glaisner,[33] Jean-Valere Malfuson,[34] Pascal Lenain,[35] Laetitia Biron,[1] Lucie Planche,[1] Helene Caillon,[1] Herve Avet-Loiseau,[6] Thomas Dejoie,[1] and Michel Attal[6]

- Significantly higher rates of VGPR (primary endpoint) and PR with 4 cycles VTD vs VCD induction therapy

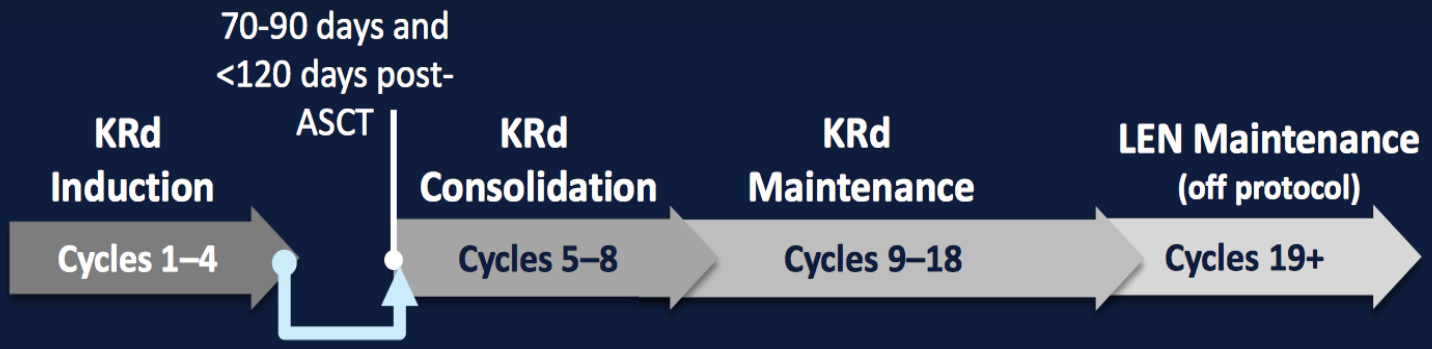
Response,*† %	VTD (n = 169)	VCD (n = 169)	*P* Value
≥ CR	13.0	8.9	.22
≥ VGPR	66.3	56.2	.05
≥ PR	92.3	83.4	.01

*Centralized assessment by IMWG criteria 2011. †Intent-to-treat analysis.

Blood. 2016 May 26;127(21):2569-74


100
80
60
40
20
0
Response rate of patients treated (%)
≥VGPR
OR
VAD
Dex
CTD
Thal-Dex
VCD
Len-Dex
VTD
VRDC
RVD
CRd
Induction regimen

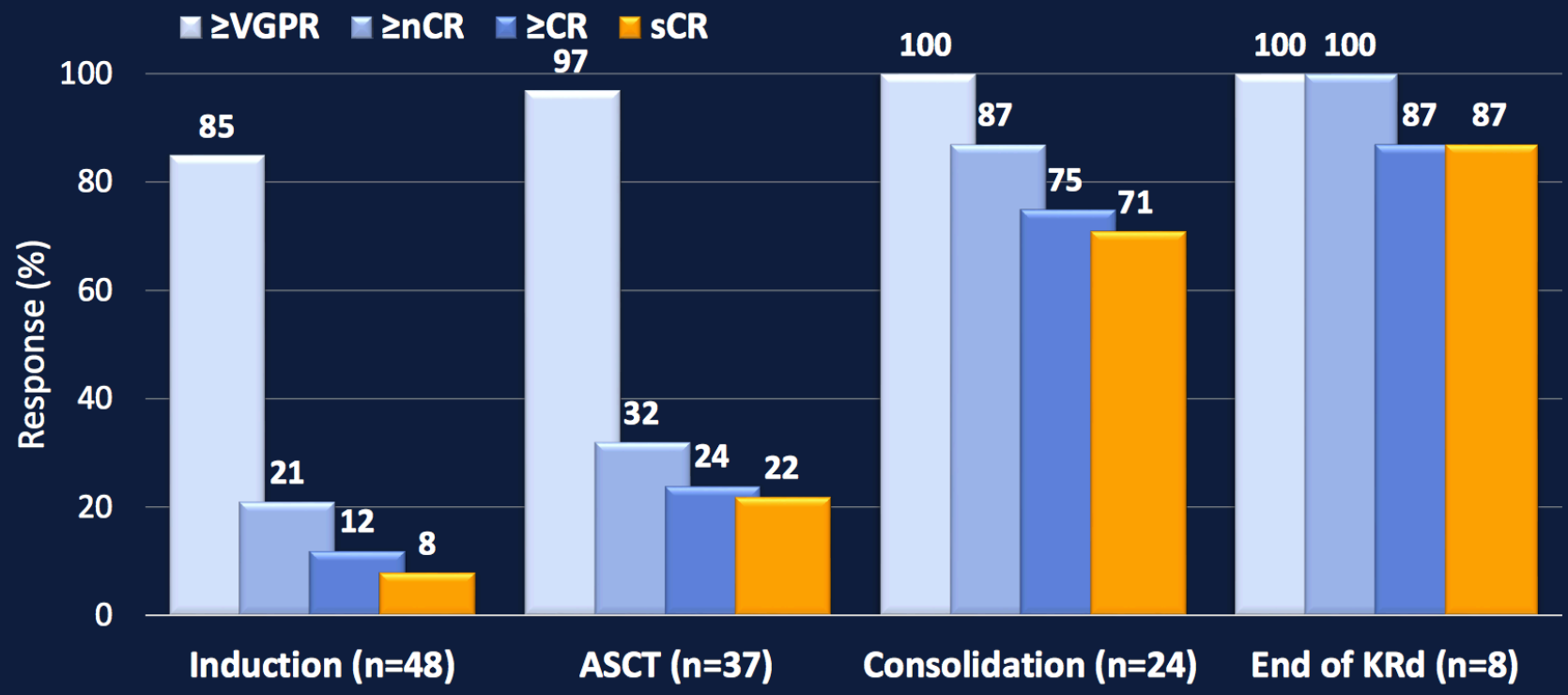
Treatment Schema – 28-day Cycle



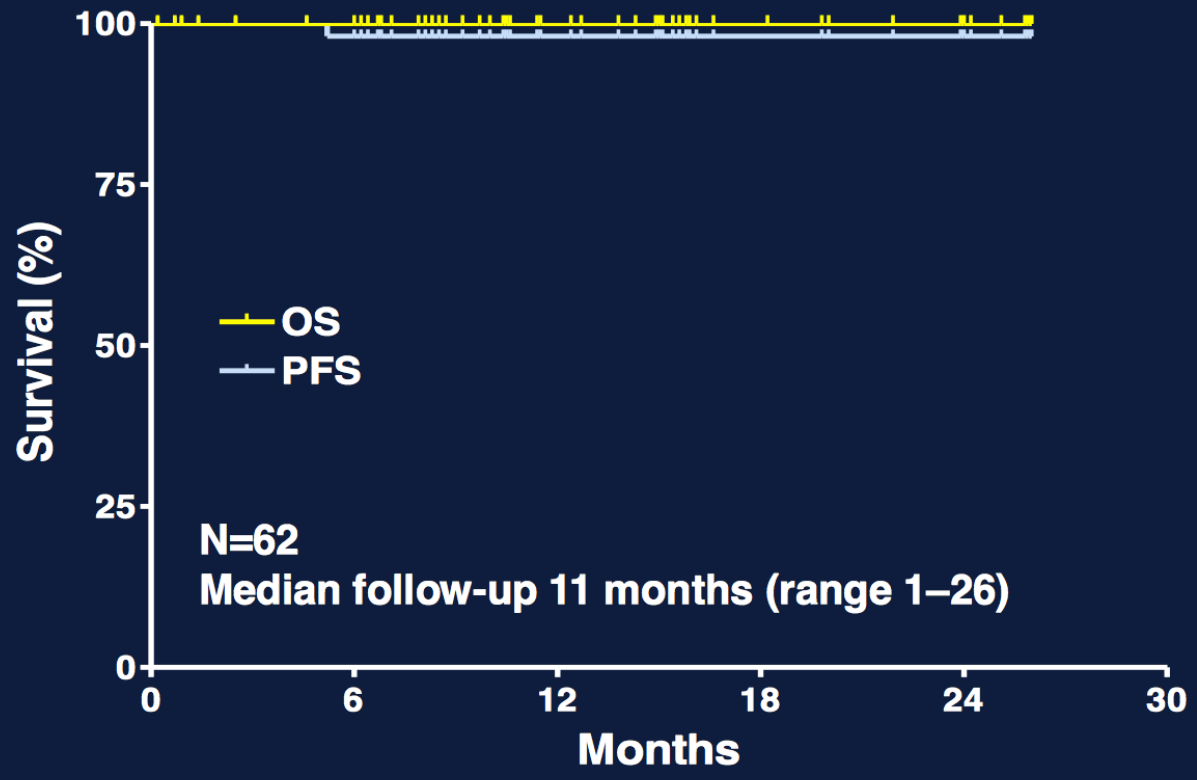
CFZ	Days 1-2, 8-9, 15-16 20 mg/m²*→36 mg/m²	Days 1-2, 8-9, 15-16 LTD	Days 1-2, 15-16 LTD	
LEN	Days 1-21 25 mg	Days 1-21 15 mg Cycle 5→LTD	Days 1-21 LTD	Days 1-21 LTD
dex	Weekly 40 mg	Weekly 20 mg or LTD	Weekly LTD	

KRd+ASCT considered promising: improvement of ***sCR at the end of 8 cycles***
from historical rate of ***30% for KRd without transplant*** to ***50% for KRd+ASCT***

Response Rates Over the Course of Treatment

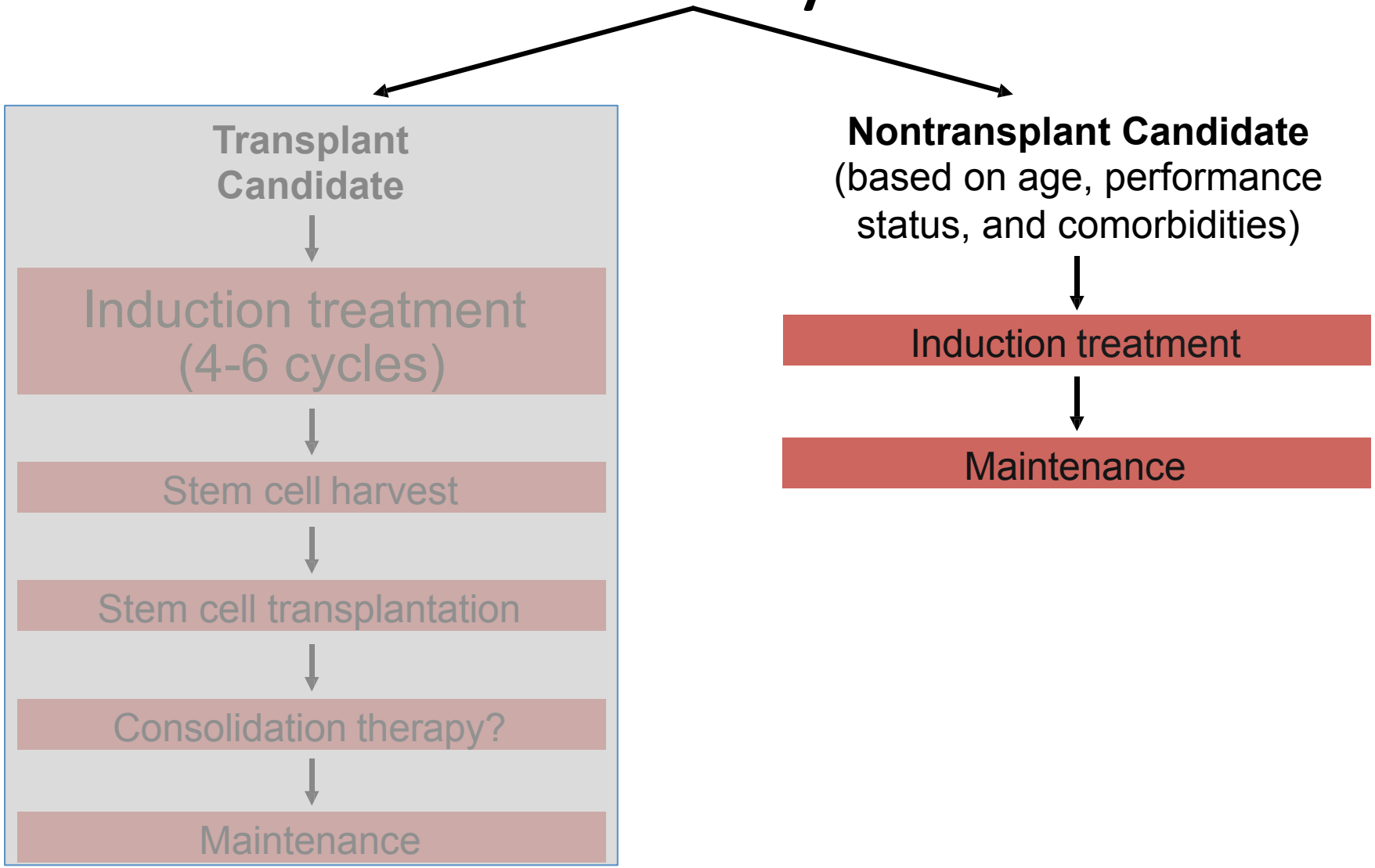


Treatment Outcomes



All patients were alive and 61/62 were progression free

Initial Approach to Treatment of Myeloma



Regimens for induction therapy for patients not eligible for high-dose therapy and stem cell transplantation

Main components	Preferred option–3 drug, melphalan-or cyclophosphamide-based regimens	2-drug regimens	4-drug regimens
Thalidomide	MPT, CTD	TD	
Bortezomib	MPV, VCD	VD, vD	
Thalidomide and bortezomib	VTD		VMPT
Lenalidomide		LD, Ld	
If none of the novel drugs available		MP, BP	

Abbreviations: **BP**, bendamustine plus prednisone; **CTD**, cyclophosphamide with thalidomide plus dexamethasone; **LD**, lenalidomide with high-dose dexamethasone; **Ld**, lenalidomide with low-dose dexamethasone; **MPT**, melphalan with prednisone plus thalidomide; **MPV**, melphalan with prednisone plus bortezomib; **MP**, melphalan with prednisone; **TD**, thalidomide with dexamethasone; **VCD**, bortezomib with cyclophosphamide plus dexamethasone; **VD**, bortezomib with dexamethasone; **vD**, reduced-dose bortezomib with dexamethasone; **VMPT**, bortezomib with melphalan plus prednisone plus thalidomide; **VTD**, bortezomib with thalidomide plus dexamethasone.

IMWG recommendations, Leukemia (2013) 1 – 12

Regimens for induction therapy for patients not eligible for high-dose therapy and stem cell transplantation

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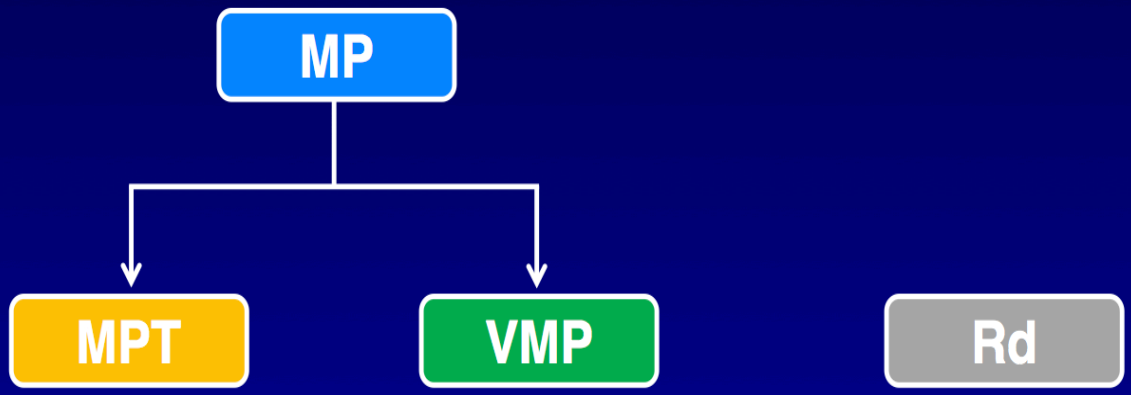
Bortezomib	**MPV**, VCD	VD, vD	
Thalidomide and bortezomib	VTD		VMPT
Lenalidomide		LD, Ld	
If none of the novel drugs available		**MP, BP**	

Abbreviations: **BP**, bendamustine plus prednisone; **CTD**, cyclophosphamide with thalidomide plus dexamethasone; **LD**, lenalidomide with high-dose dexamethasone; **Ld**, lenalidomide with low-dose dexamethasone; **MPT**, melphalan with prednisone plus thalidomide; **MPV**, melphalan with prednisone plus bortezomib; **MP**, melphalan with prednisone; **TD**, thalidomide with dexamethasone; **VCD**, bortezomib with cyclophosphamide plus dexamethasone; **VD**, bortezomib with dexamethasone; **vD**, reduced-dose bortezomib with dexamethasone; **VMPT**, bortezomib with melphalan plus prednisone plus thalidomide; **VTD**, bortezomib with thalidomide plus dexamethasone.

IMWG recommendations, Leukemia (2013) 1 – 12

Standards of care for elderly patients



Six randomized trials[2]
Benefit in
PFS & OS
vs MP

One randomized trial[3,4]
Benefit in
PFS & OS
vs MP

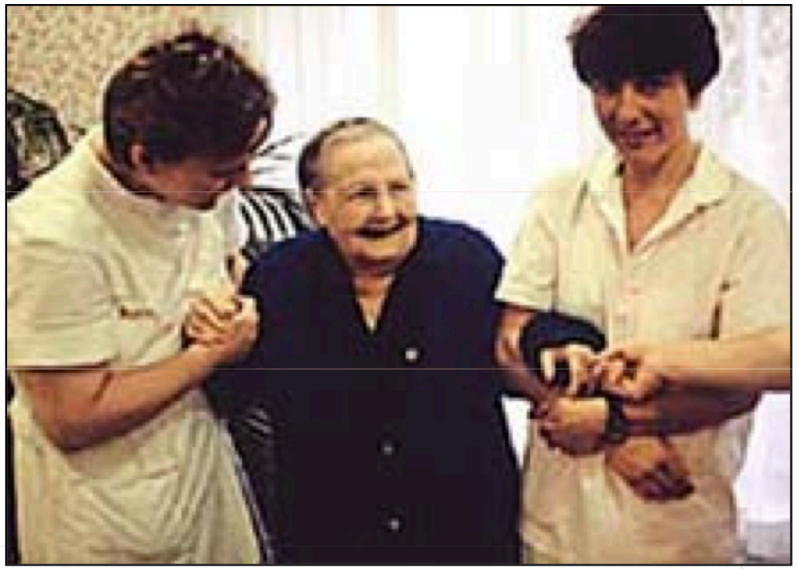
One randomized trial[5]
Benefit in
PFS & OS
vs MPT

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.

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

Gli anziani non sono tutti uguali



Valutazione Geriatrica Multidimensionale

Frailty score

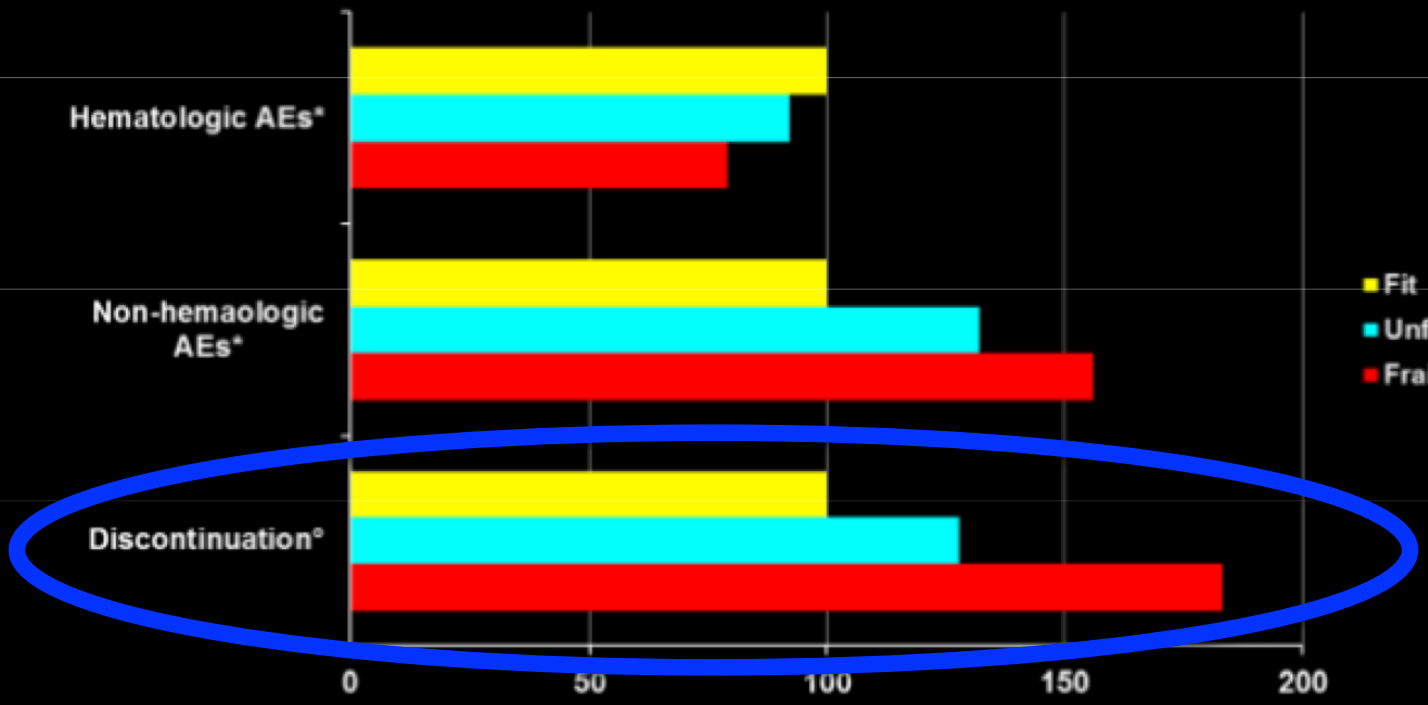
Patients (n=869) received dose-adjusted bortezomib- or lenalidomide-based combinations

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

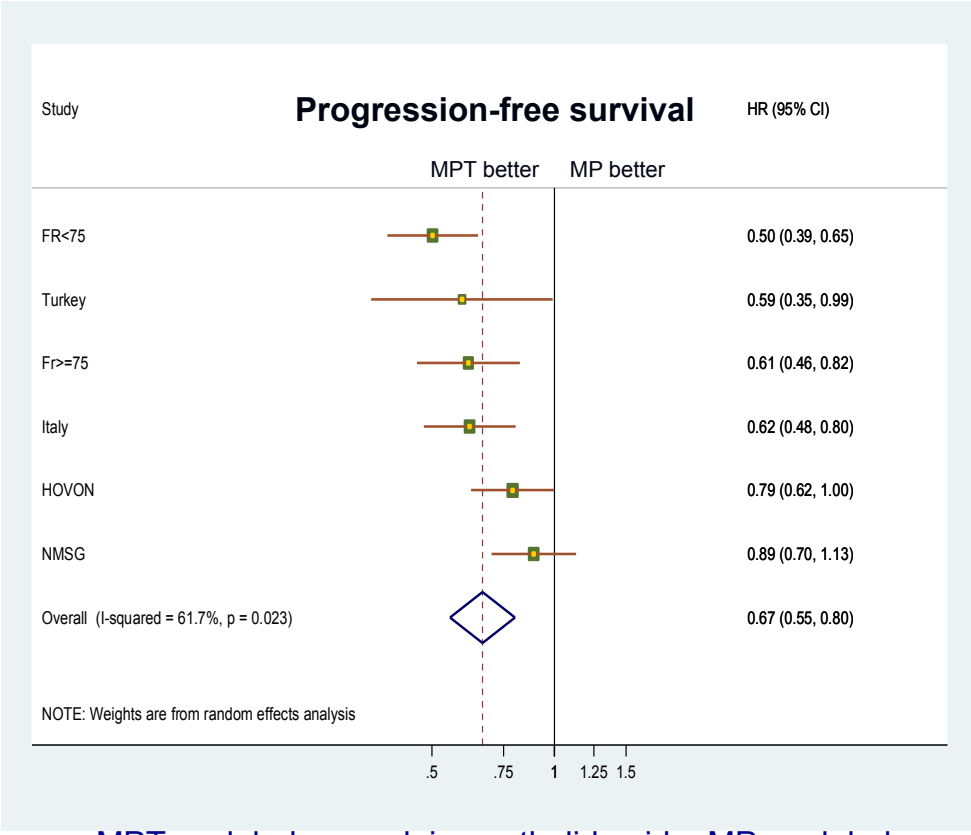
All grade 3-5 Adverse Events
Risk ratio

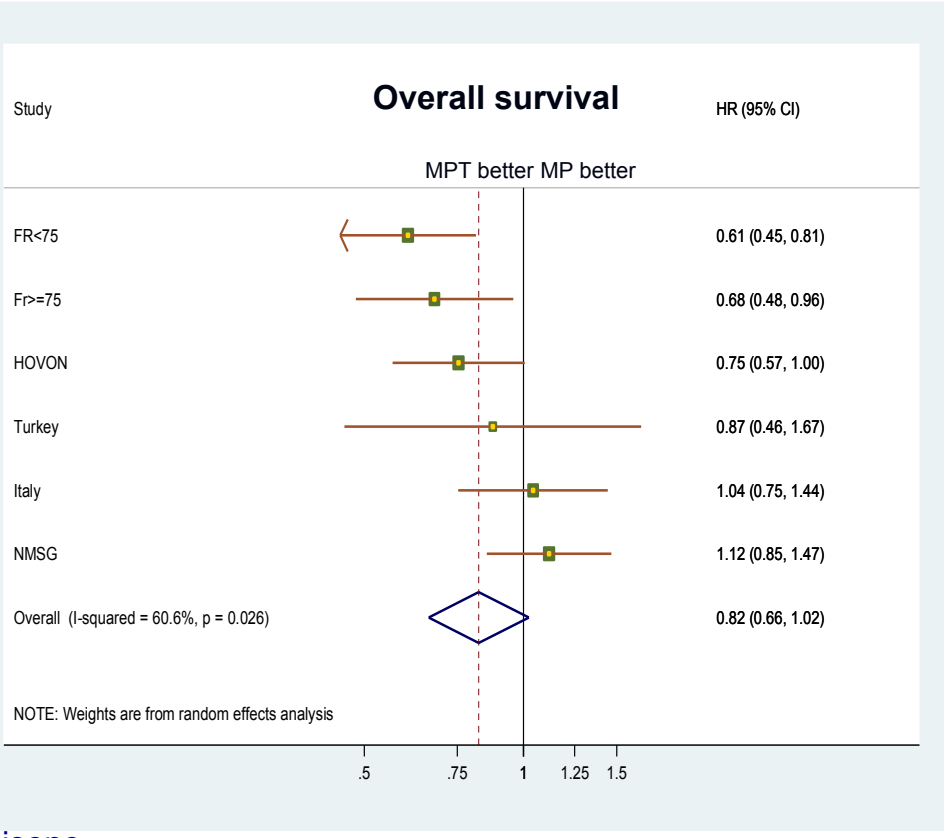


*At least 1 adverse event (AE); °Due to AEs, withdrawal of consent, patient compliance, unknown; progressive disease was excluded.

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

MPT vs MP: Efficacy in Newly Diagnosed Elderly Myeloma patients





MPT: melphalan-prednisone-thalidomide; MP: melphalan-prednisone

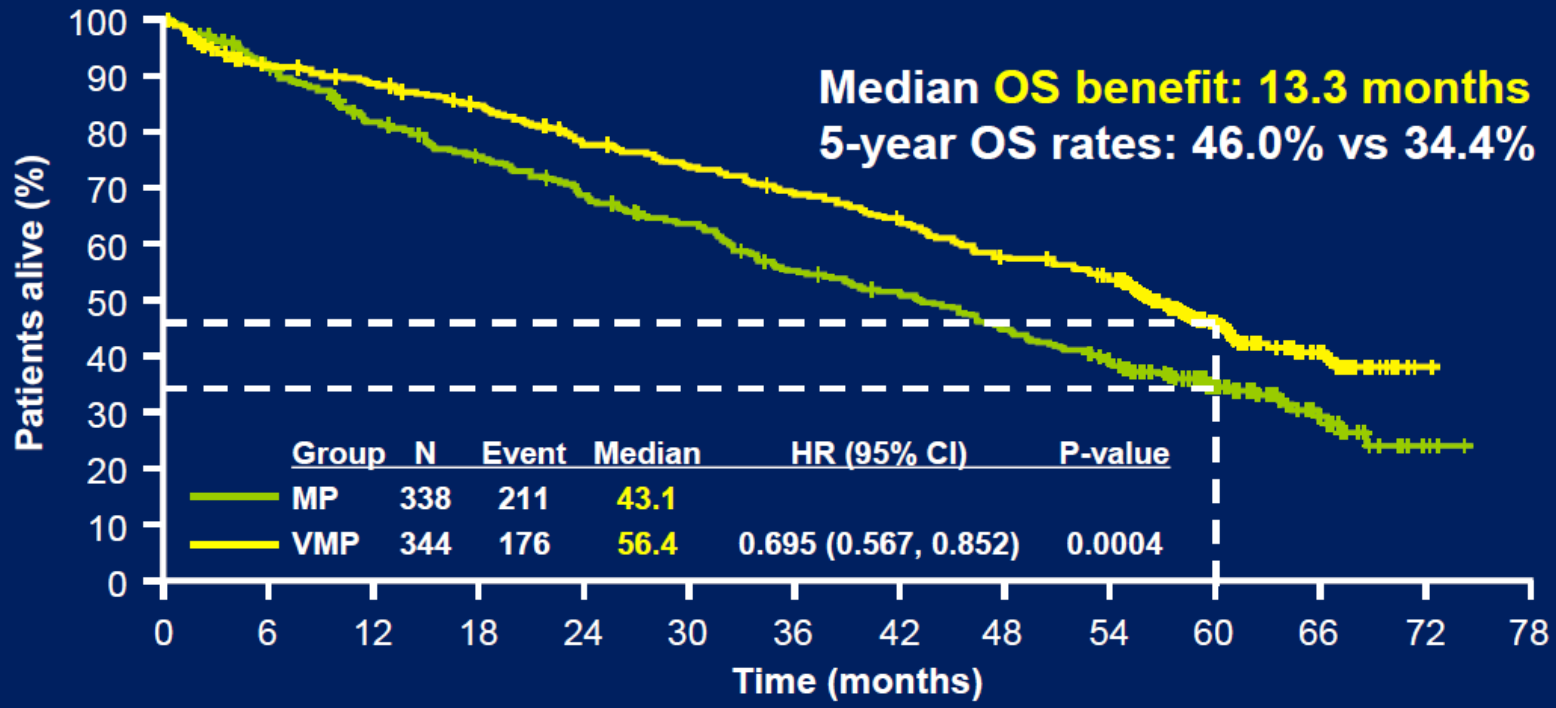
- **Meta-analysis of six phase 3 trials of thalidomide–MP (MPT) vs MP:[1]**
  - **Median OS: 39.3 vs 32.7 months (6.6-month benefit), HR 0.83, 17% reduced risk of death**

Fayers P et al Blood 2011,118:1239-1247

VISTA: Final updated OS analysis

31% reduced risk of death with VMP

Median follow-up 60.1 months



San Miguel ASH 2011

Bortezomib: Once Weekly

	VMP (VISTA)	VMP twice-weekly	VMP once-weekly
CR	30%	27%	23%
2-year PFS	48%	56%	58%
Sensory PN			
Any grade	44%	44%	22%
Grade 3/4	13%	14%	2%
Discontinuation due to PN	na	16%	4%
Total planned dose	67.6 mg/m^2	67.6 mg/m^2	46.8 mg/m^2
Total delivered dose	38.6 mg/m^2	40.1 mg/m^2	39.4 mg/m^2

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

Bortezomib IV vs SC

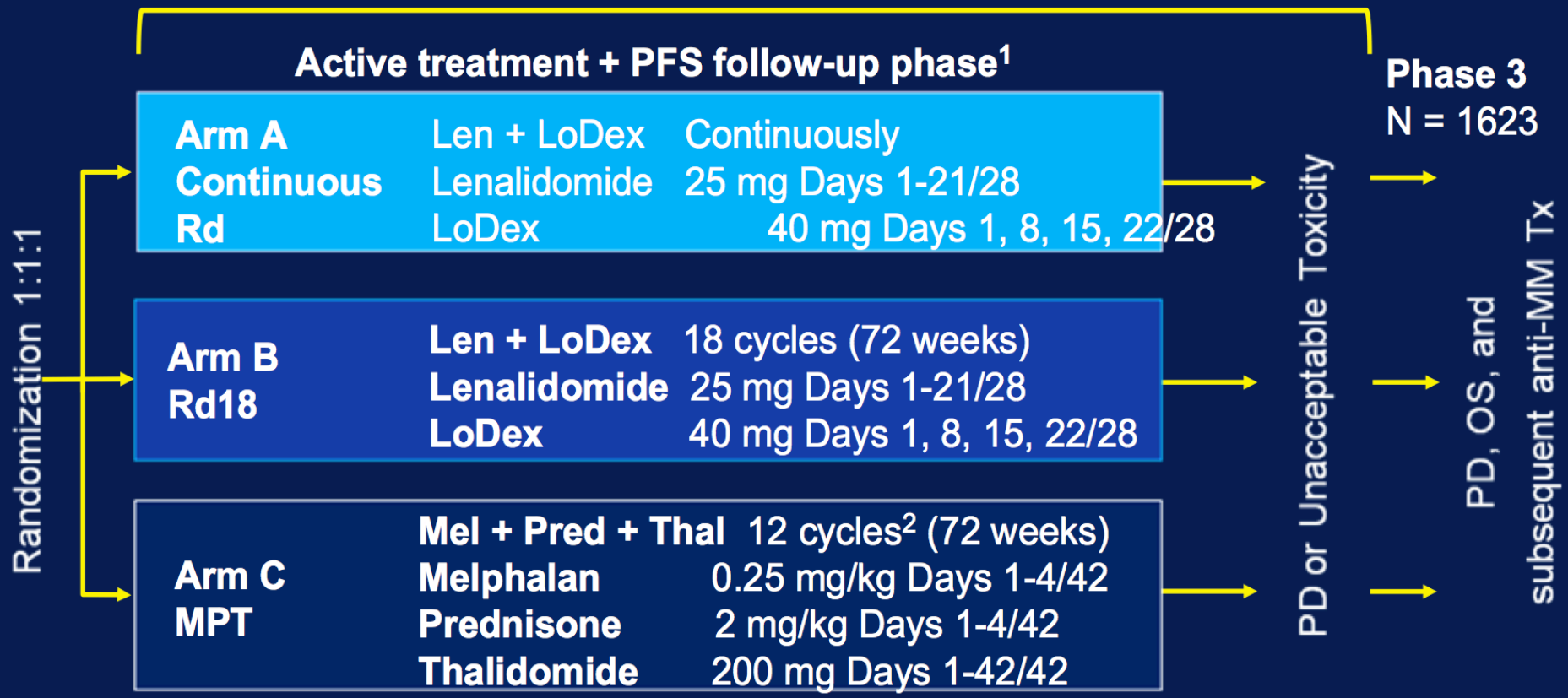
222 relapsed refractory MM patients. BZ is given at conventional dose and scheme

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: Lenalidomide/Dexamethasone vs MPT in NDMM SCT-Ineligible Patients



Patients >75 years: LoDex 20 mg Days 1, 8, 15, 22/28; Thal[3] 100 mg Days 1-42/42; Mel[3] 0.2 mg/kg Days 1-4
Stratification: age, country, and ISS stage

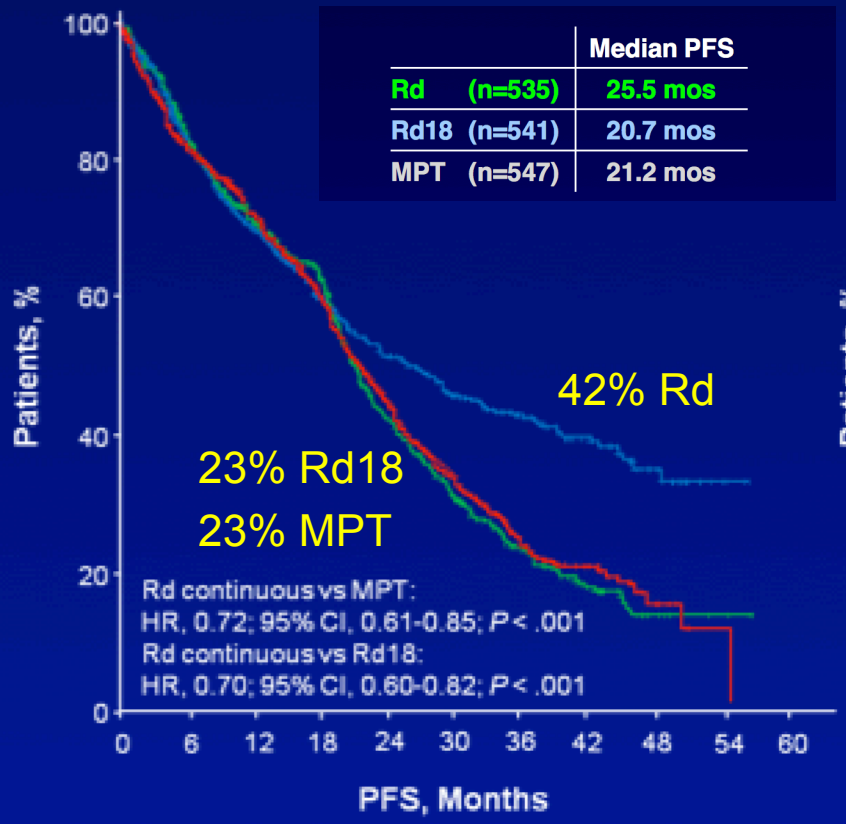
NDMM = newly diagnosed MM; SCT = stem cell transplant.

1. Facon T et al. ASH 2013 Annual Meeting. Abstract 2; 2. Facon T et al. *Lancet*. 2007;370:1209-1218;
3. Hulin C et al. *J Clin Oncol*. 2009;27:3664-3670.

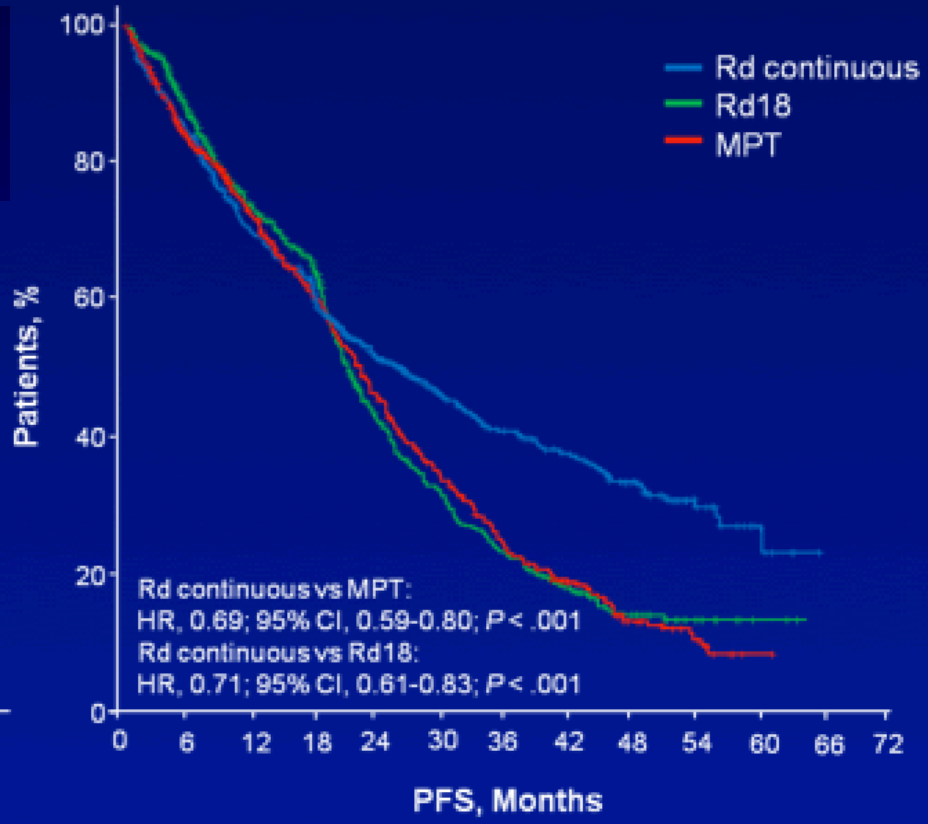
FIRST: Updated PFS

May 24, 2013 Data Cutoff[1,a]

	Median PFS
Rd (n=535)	25.5 mos
Rd18 (n=541)	20.7 mos
MPT (n=547)	21.2 mos



March 3, 2014 Data Cutoff[b]



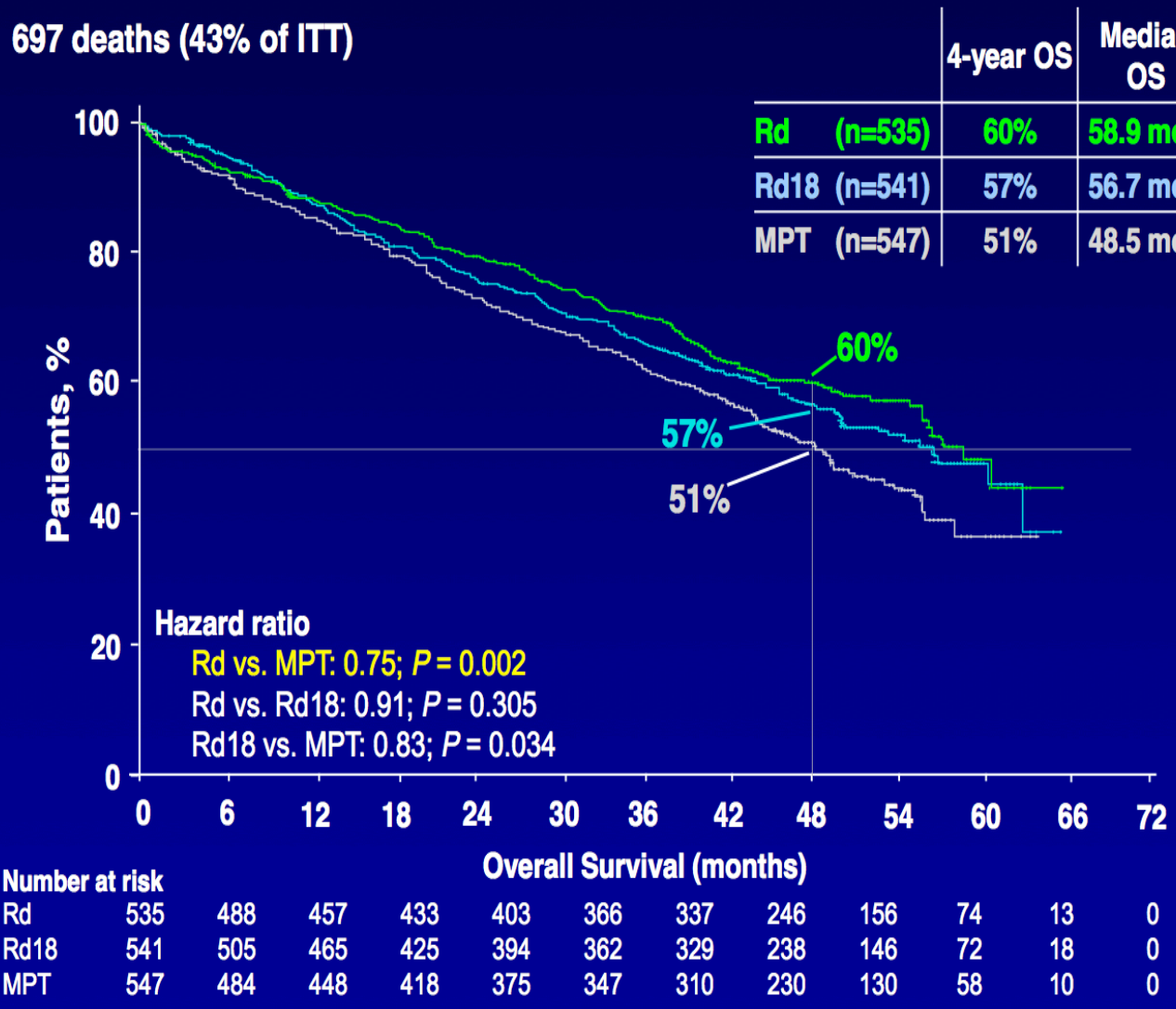
- A > 2-fold increase in 4-year PFS was observed with Rd continuous (33%) vs Rd18 (14%) and MPT (13%)

[a] IRAC assessed; [b] Investigator assessed.
HR, hazard ratio; IRAC, independent response adjudication committee; MPT, melphalan-prednisone-thalidomide; PFS, progression-free survival; Rd, lenalidomide + low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

1. Benboubker L, et al. *N Engl J Med*. 2014;371:906-917.
Facon T, et al. FIRST Study: Updated Overall Survival in Stem Cell Transplant-ineligible Newly Diagnosed Multiple Myeloma Patients Treated With Continuous Lenalidomide Plus Low-dose Dexamethasone vs Melphalan, Prednisone, and Thalidomide. *ASCO 2015, abstract #8524*.

FIRST Trial – Overall Survival

Median follow-up of 45.5 months as of 03 March, 2014



	4-year OS	Median OS
Rd (n=535)	60%	58.9 mos
Rd18 (n=541)	57%	56.7 mos
MPT (n=547)	51%	48.5 mos

Number at risk

Rd	535	488	457	433	403	366	337	246	156	74	13	0
Rd18	541	505	465	425	394	362	329	238	146	72	18	0
MPT	547	484	448	418	375	347	310	230	130	58	10	0

FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; MPT, melphalan, prednisone, thalidomide. Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Facon T, et al. *ASCO* 2015: Abstract 8524.

FIRST Trial: tossicità grado 3-4

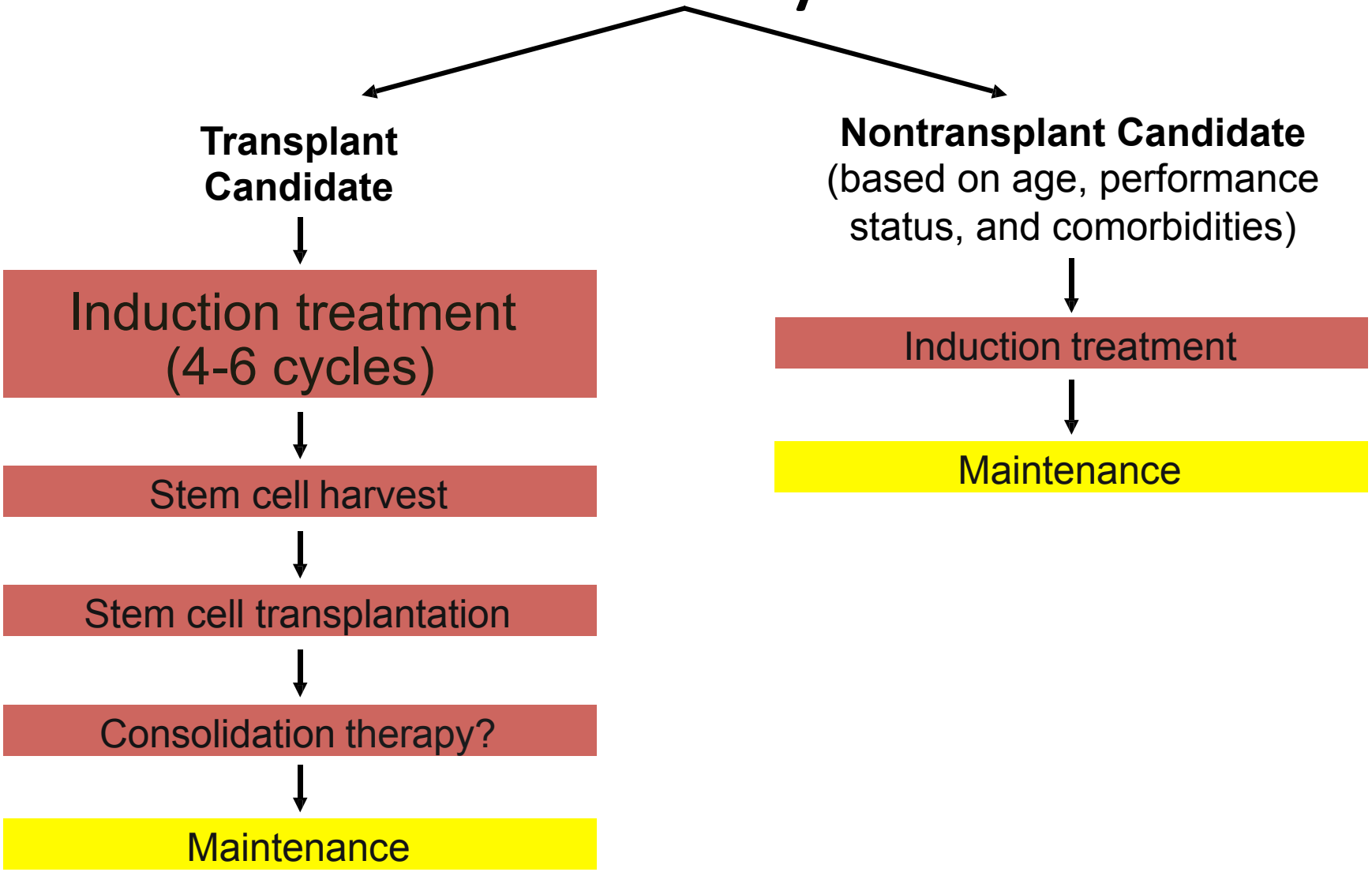
	Rd Continuo (n=532)	Rd x 18 cicli (n=540)	MPT x 12 cicli (n=541)
Hematological (%)			
Anemia	18.2	15.7	18.9
Neutropenia	27.8	26.5	44.9
Piastrinopenia	8.3	8.0	11.1
Febbre e neutropenia	1.1	3.0	2.6
Non-hematological (%)			
Infezioni	28.9	21.9	17.2
Polmoniti	8.1	8.3	5.7
Diarrea	3.9	3.3	1.5
Stipsi	2.3	1.9	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

Initial therapy for multiple myeloma

- **Triplet comparisons**
  - VCD = PAD
  - VTD better than VCD
- **Triplets vs RD?**
  - MPT better than MP, MPR better that MP
  - VMP better than MP, VTD better than TD
  - RD continous better than RD (18 months) and MPT

Initial Approach to Treatment of Myeloma



Take home message

- **I nuovi farmaci hanno modificato lo scenario terapeutico del paziente con MM**
- **Sebbene i nuovi farmaci siano diventati lo standard of care per i pazienti con NDMM, le alte dosi di melphalan -> ASCT migliorano la profondità della remissione indipendentemente dal regime di induzione, e questo si traduce in miglioramento di PFS e OS con i nuovi agenti**
- **VMP e MPT (e RD) sono attualmente lo standard of care per la terapia del paziente con MM non candidato ad autotrapianto**
- **L'aggiustamento della dose va considerato sulla base dell'età e delle comorbilità per poter ottimizzare la terapia nel modo più efficace**