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Treatment algorithm for multiple myeloma: where do we go from here?

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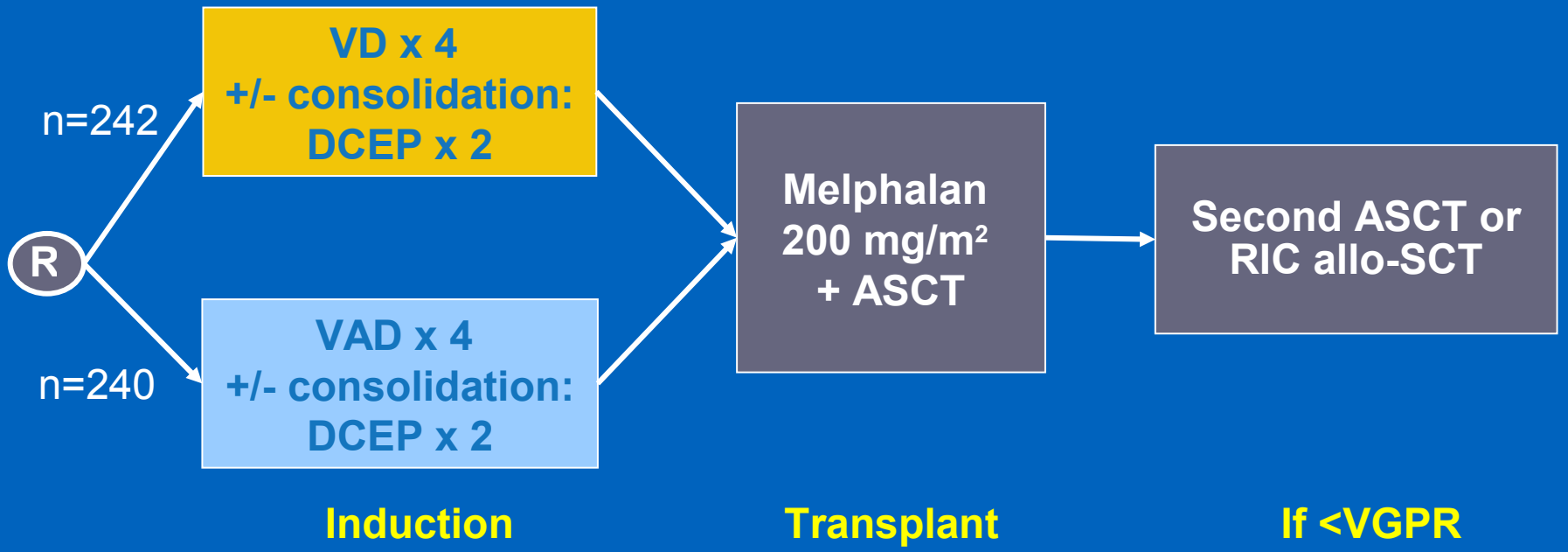
What are the treatment options for younger patients?

VD (bortezomib-dexamethasone) vs VAD induction therapy in younger transplant eligible patients

IFM2005/01 study

- Phase II study of newly diagnosed patients ≤65 years of age
- Primary analysis: post-induction response (CR + nCR) with VD vs VAD



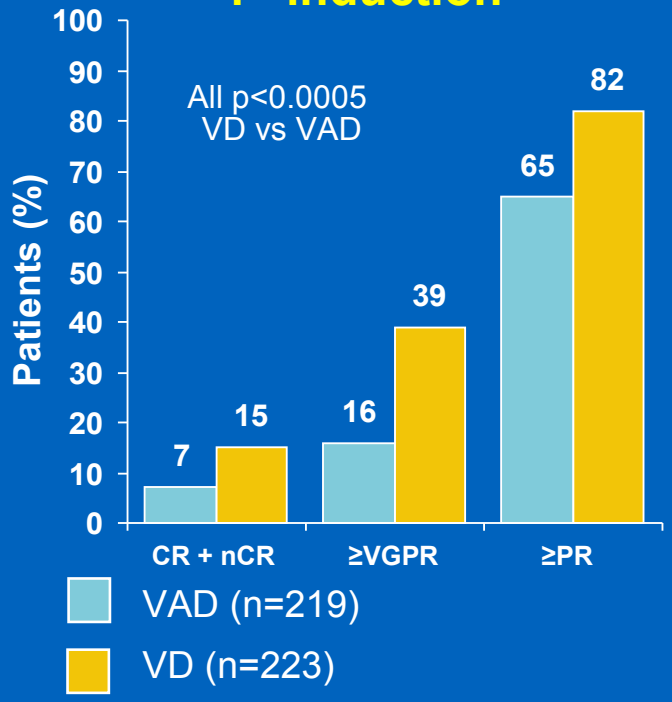
VAD, vincristine-doxorubicin-dexamethasone
CR + nCR, complete response + near complete response
DCEP, dexamethasone, cyclophosphamide, etoposide, platinum
ASCT, autologous stem cell transplantation
RIC allo, reduced intensity conditoning allogeneic
VGPR, very good partial response

Harousseau JL et al. *J Clin Oncol* 2008;26(15S):8505 and oral presentation

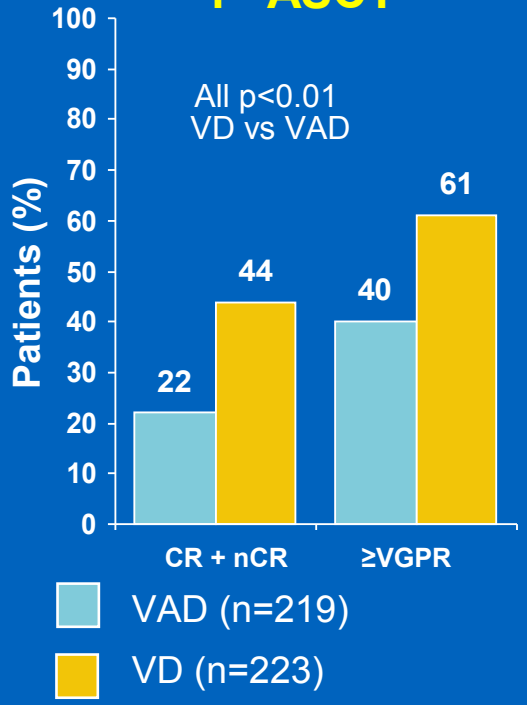
VD vs VAD induction therapy in younger transplant eligible patients

IFM2005/01 study

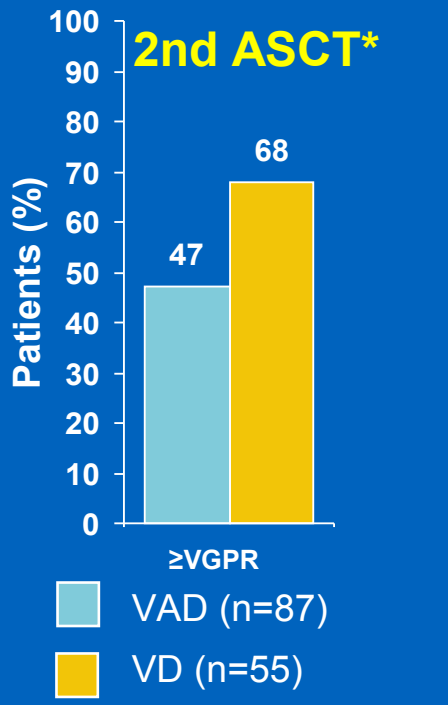
Response after 1st induction*



Response after 1st ASCT*



Response after 2nd ASCT*



*Response in evaluable patients

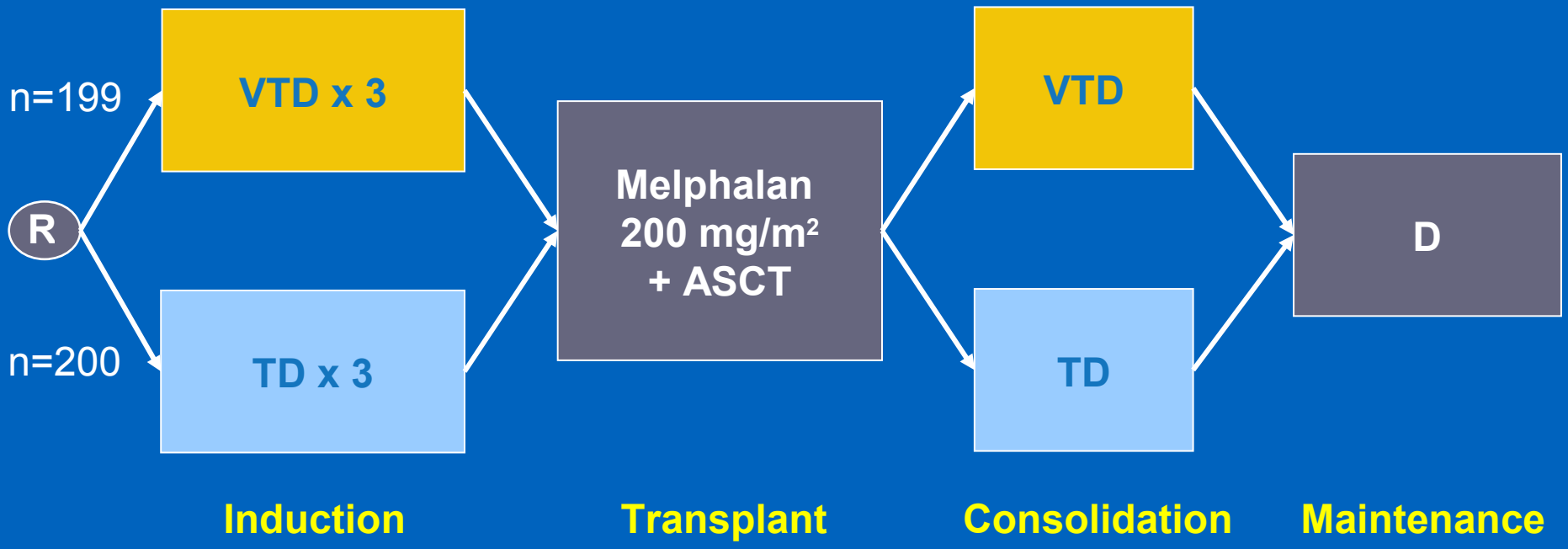
VD, bortezomib-dexamethasone
VAD, vincristine-doxorubicin-dexamethasone
PR: partial response

Harousseau JL et al. *J Clin Oncol* 2008;26(15S):8505 and oral presentation

VTD (bortezomib-thalidomide-dexamethasone) vs TD in younger transplant eligible patients

GIMEMA study

- Phase III study of patients ≤65 years of age with symptomatic MM
- Primary analysis: post-induction response (CR + nCR) with VTD vs TD



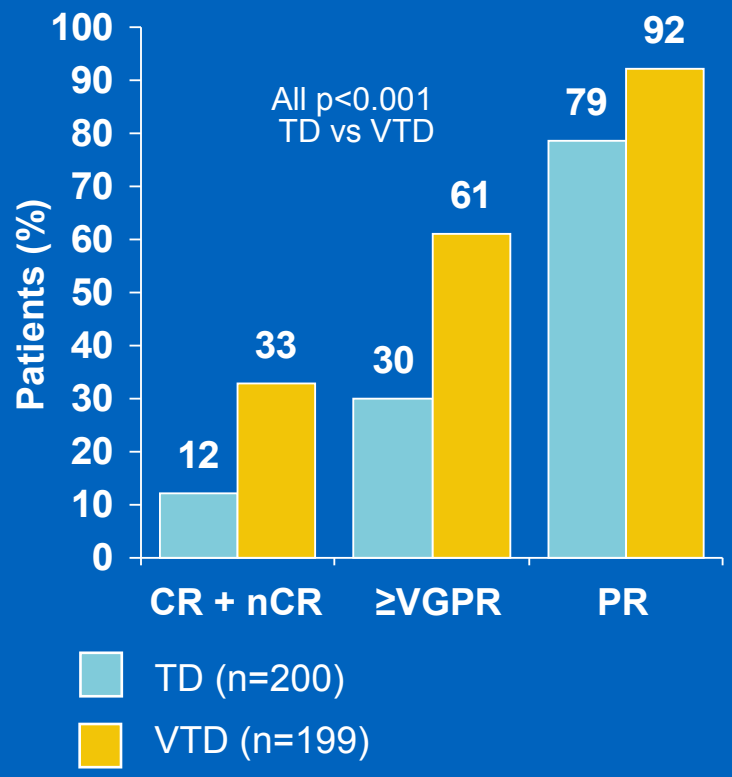
TD, thalidomide-dexamethasone
D, dexamethasone
MM, multiple myeloma

Cavo M et al. *Blood* 2007;110: Abstract 73

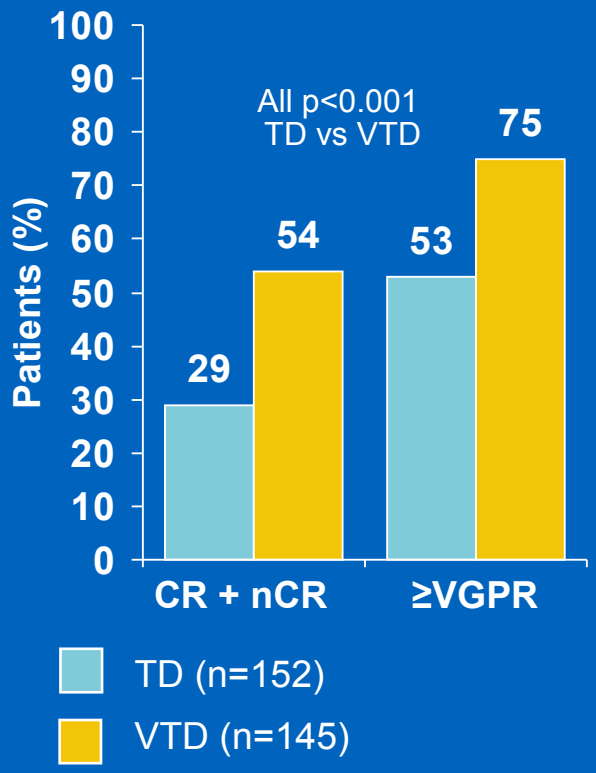
VTD vs TD therapy in younger transplant eligible patients

GIMEMA study

Response after induction



Response after ASCT



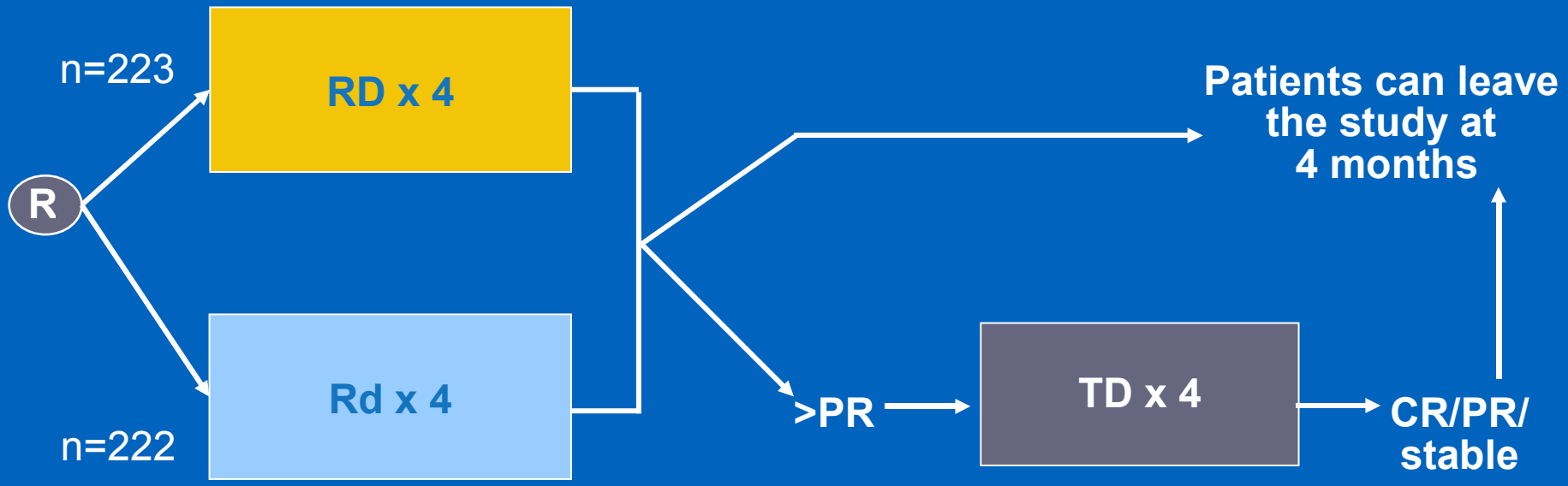
VTD, bortezomib-thalidomide-dexamethasone
TD, thalidomide-dexamethasone

Cavo M et al. *Blood* 2007;110: Abstract 73

Lenalidomide + high- vs low-dose dexamethasone (RD/Rd) in older transplant eligible patients

ECOG-E4A03

- Phase III study of untreated symptomatic patients (mean age 65 years)
- Primary analysis: response rate with high- vs low-dose dexamethasone at 4 months



RD, lenalidomide-high-dose dexamethasone
Rd, lenalidomide-low-dose dexamethasone
TD, thalidomide-dexamethasone

Rajkumar SV et al. *Blood* 2007;110: Abstract 74

RD vs Rd in older transplant eligible patients: response at 4 and 36 months

ECOG-E4A03

Response category	RD (%)	Rd (%)	p value
Within first 4 cycles			
≥PR	79	68	0.008
≥VGPR	42	24	<0.008
Best overall response at 36 months*			
≥PR	81	70	0.009
≥VGPR	51	40	0.040
CR (IF-)	17	14	0.428
PFS probability at 36 months*	39	43	0.08 (log-rank) 0.04 (Pepe-Fleming)
TTP probability at 36 months*	45	42	NS
Stem cell harvest (n=167)	97.6% successful		2.4% unsuccessful

*DMC closed study at median follow-up of 12.5 months, and immediate crossover to Rd was mandated. At median follow-up of 36 months, 404 patients (91%) are off study (197 were off study by 4 months; 253 were off study by 6 months)

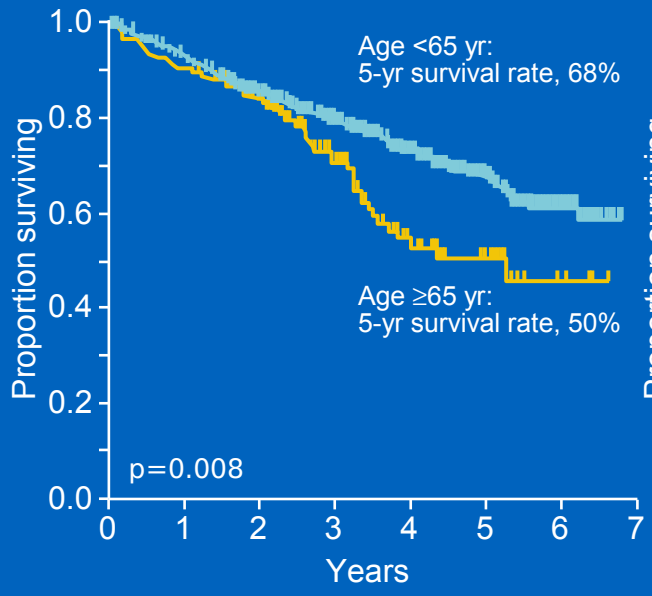
RD, lenalidomide-high-dose dexamethasone; Rd, lenalidomide-low-dose dexamethasone
TTP, time to progression; NS, not significant

Rajkumar SV et al. ASH 2008; San Francisco, CA

What are the treatment options for older patients eligible for transplant?

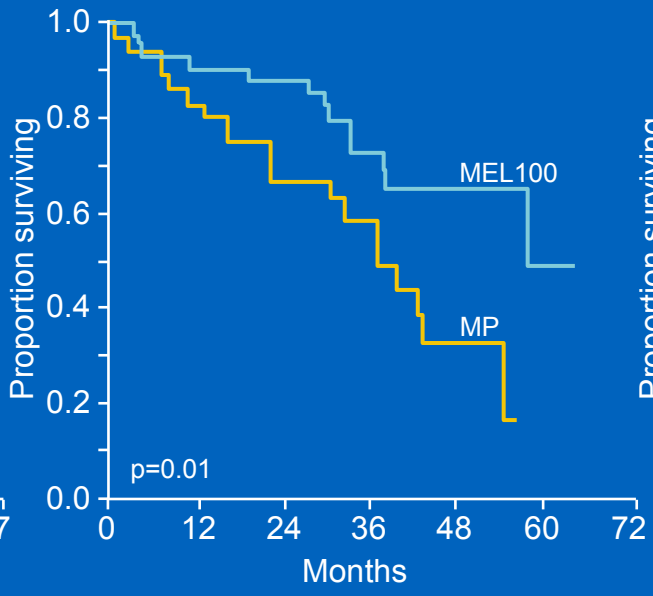
ASCT in older patients

Survival advantage Age <65 years[1]



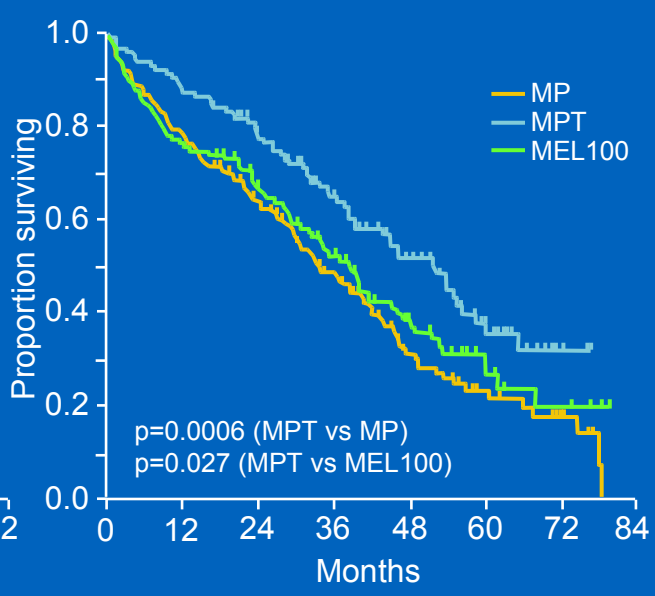
Tandem MEL200

Survival advantage Age 65–70 years[2]



Tandem MEL100

NO survival advantage Age 65–75 years[3]



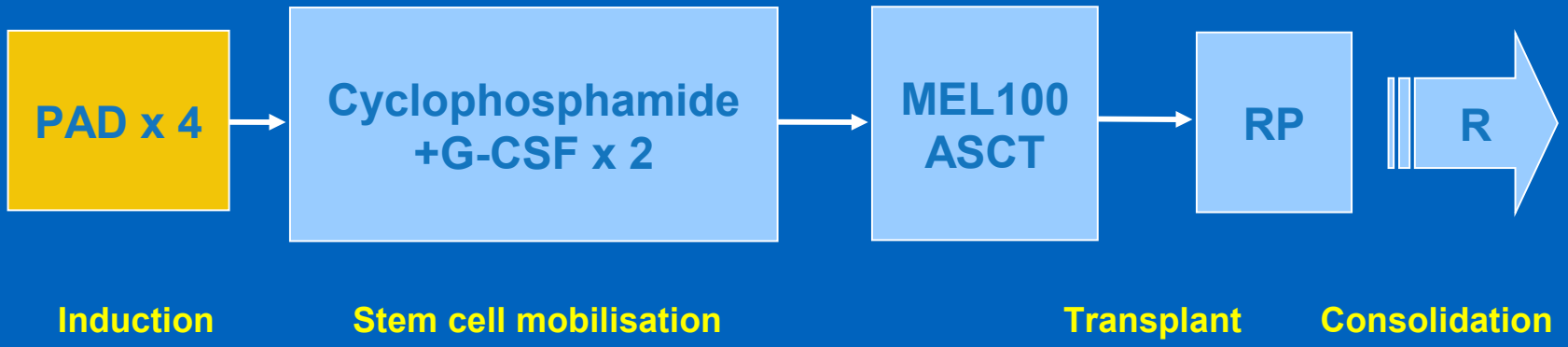
Tandem MEL100

MP, melphalan-prednisone
MPT, melphalan-prednisone-thalidomide
MEL100, melphalan 100 mg/m^2
MEL200, melphalan 200 mg/m^2

1. Barlogie B et al. *N Engl J Med* 2006;354:1021–1030;
2. Palumbo A et al. *Blood* 2004;104: 3052–3057;
3. Facon T et al. *Lancet* 2007;370:1209–1218.

PAD induction prior to reduced intensity ASCT and lenalidomide consolidation/maintenance in elderly patients

- Phase III study of newly diagnosed patients aged 65–75 years
- Primary objectives: safety (grade 3 non-haematological toxicity <30%) and efficacy (near CR rate >35%)

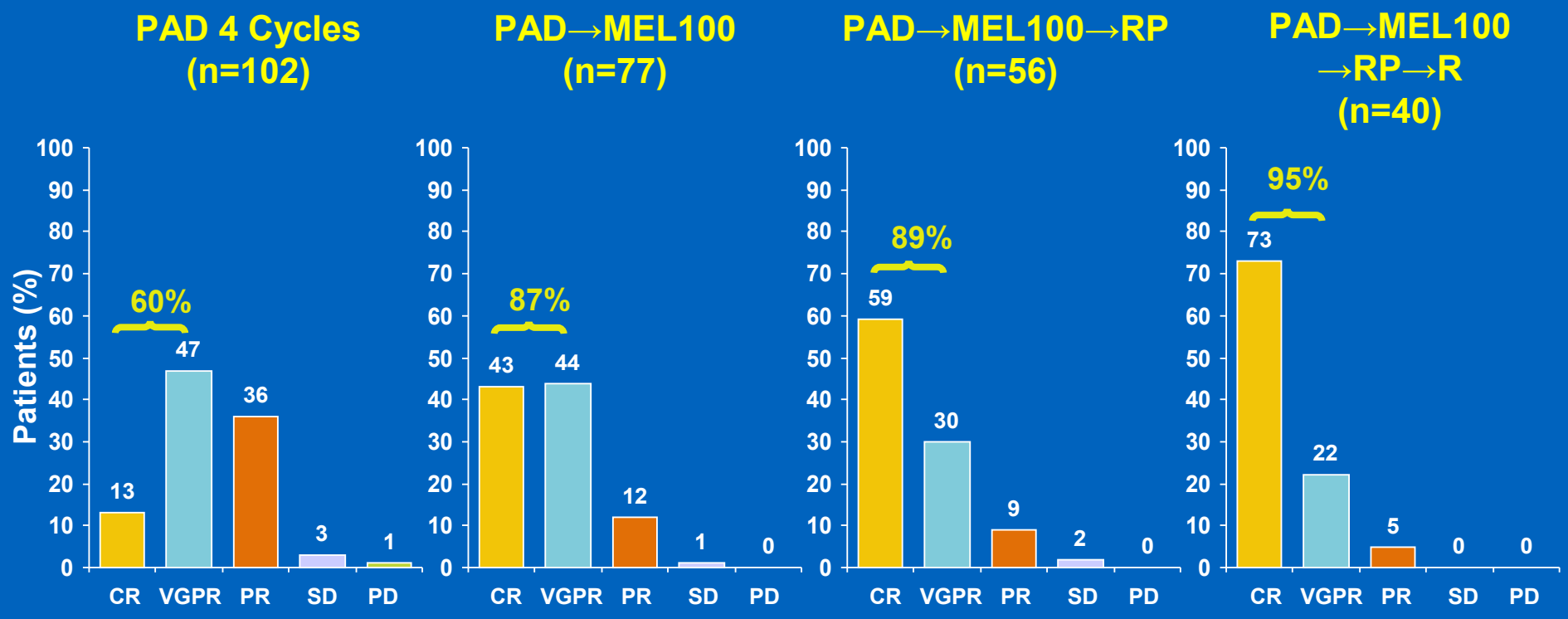


PAD, bortezomib-PEG doxorubicin-dexamethasone
MEL100, melphalan 100 mg/m^2
RP, lenalidomide-prednisone
R, lenalidomide

Palumbo A et al. *Blood* 2008;112: Abstract 159

PAD induction prior to reduced intensity ASCT and lenalidomide consolidation/maintenance in elderly patients

Response rates: per protocol



PAD, bortezomib-PEG doxorubicin-dexamethasone
MEL100, melphalan 100 mg/m^2
RP, lenalidomide-prednisone; R, lenalidomide
SD, stable disease; PD, progressive disease

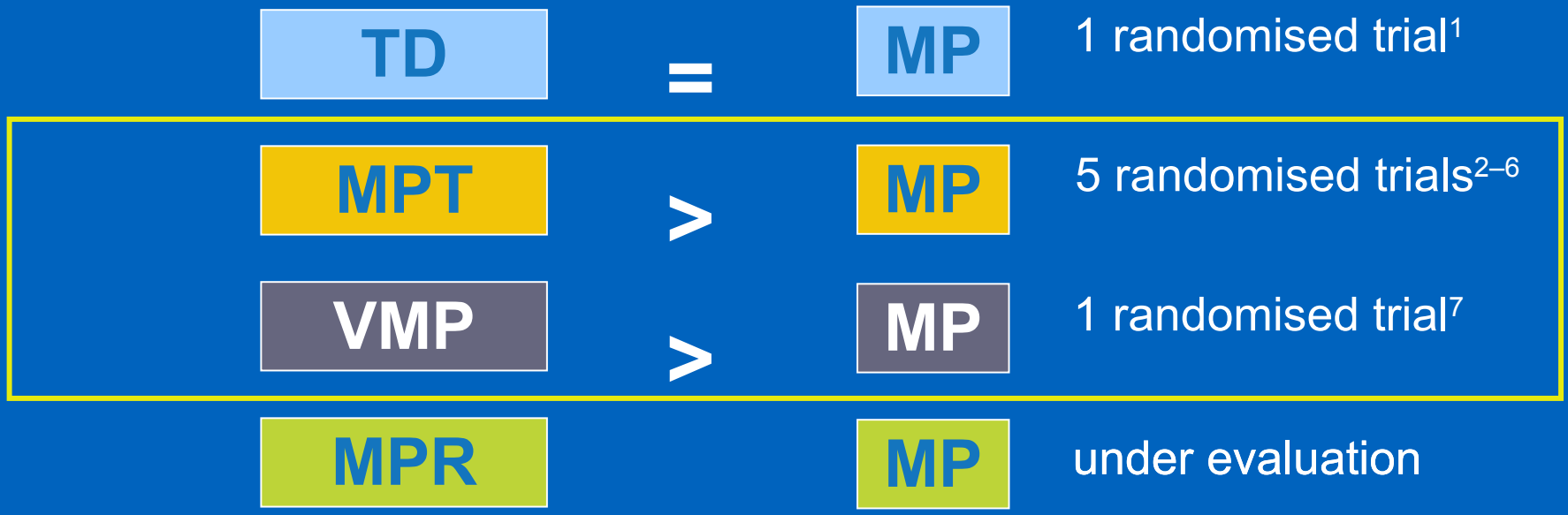
Palumbo A et al. *Blood* 2008;112: Abstract 159

What are the treatment options for elderly patients *not* eligible for transplant?

Novel agents plus chemotherapy improve outcomes in older transplant ineligible patients

Level of evidence 1b (≥ 1 randomised trial)

Diagnosis >65 years



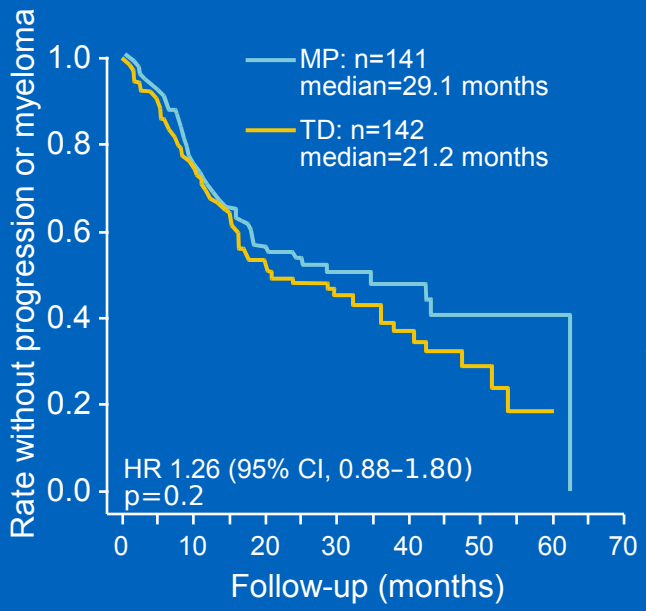
TD, thalidomide-dexamethasone
MP, melphalan-prednisone
MPT, melphalan-prednisone-thalidomide
VMP, bortezomib-melphalan-prednisone
MPR, melphalan-prednisone-lenalidomide

1. Ludwig H et al. *Blood* 2009;113:3435–3442; 2. Facon T et al. *Lancet* 2007;370:1209–1218; 3. Palumbo A et al. *Lancet* 2006;367:825–831; 4. Hulin C et al. *Blood* 2007;110: Abstract 75; 5. Waage A et al. *Blood* 2007;110: Abstract 78; 6. Wijermans P et al. *Haematologica* 2008;93: Abstract 0440; 7. San Miguel JF et al. *N Engl J Med* 2008;359:906–917

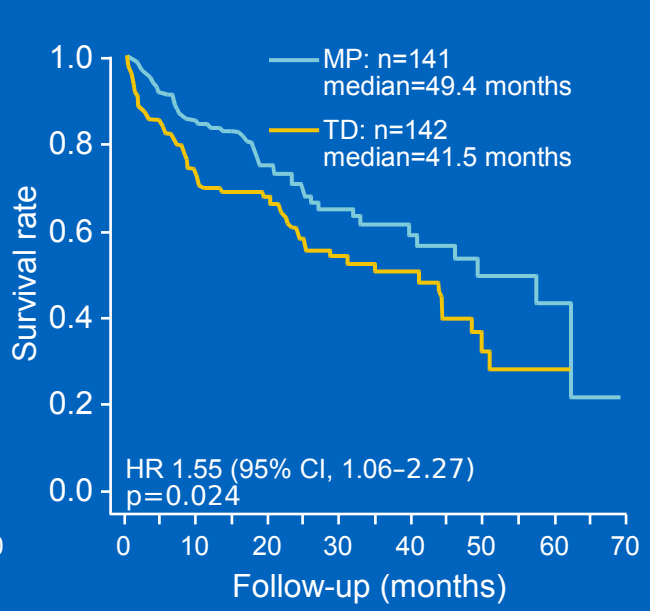
TD (thalidomide-dexamethasone) vs MP in newly diagnosed older transplant ineligible patients

- Phase III study of newly diagnosed patients aged >65 years or ≤65 years but ineligible for transplant
- Primary analysis: progression-free survival and tolerance

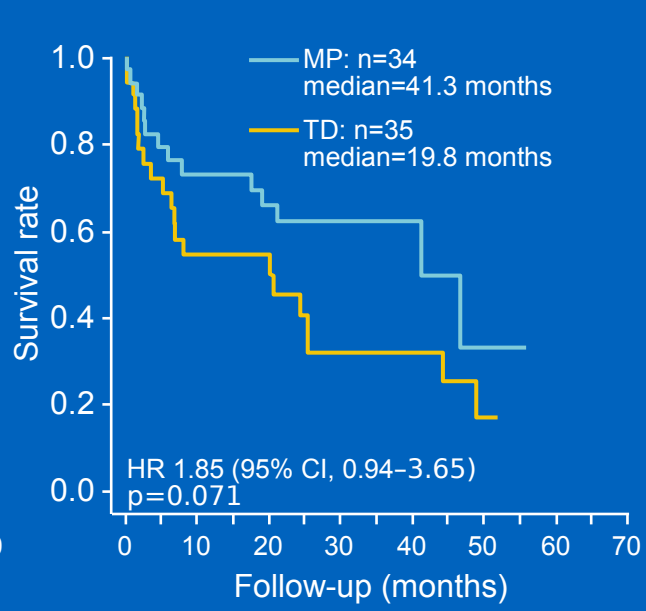
Time to progression



Overall survival



Survival: >75 years



MP, melphalan-prednisone

Ludwig H et al. *Blood* 2009;113:3435–3442

MPT (melphalan-prednisone-thalidomide): a standard of care in older transplant ineligible patients

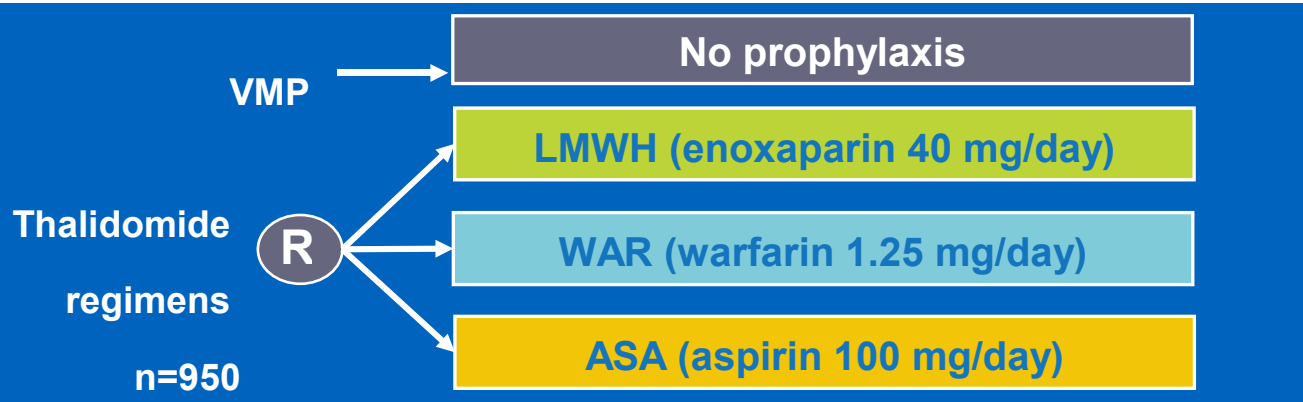
	Median PFS (months) MPT	MP	PFS p value	Median OS (months) MPT	MP	OS p value
IFM[1]	27.5	17.8	<0.0001	51.6	33.2	0.0006
GIMEMA[2]	N/A		0.0006	N/A		NS
IFM[3]	24.1	19	0.001	45.3	27.7	0.03
Nordic[4]	16	14	NS	29	33	NS
Hovon[5]	N/A		<0.001	N/A		NS

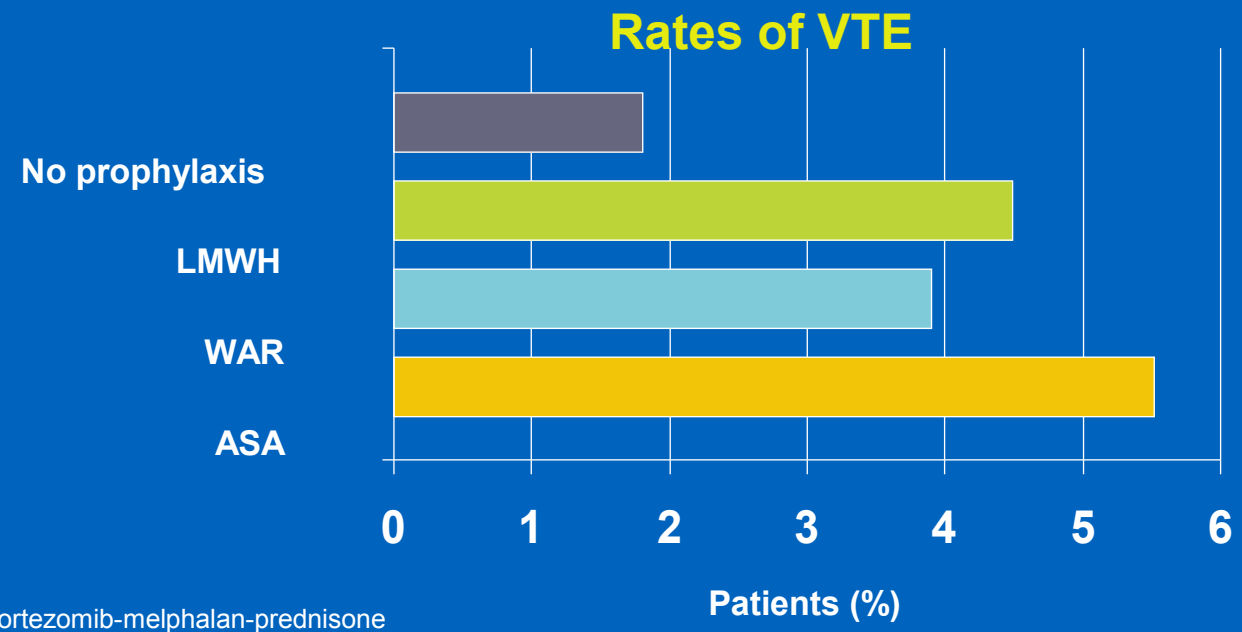
N/A, not available; NS, not significant

MP, melphalan-prednisone

1. Facon T et al. *Lancet* 2007;370:1209–1218; 2. Palumbo A et al. *Lancet* 2006;367:825–831;
3. Hulin C et al. *Blood* 2007;110: Abstract 75; 4. Waage A et al. *Blood* 2007;110: Abstract 78;
5. Wijermans P et al. *Haematologica* 2008;93: Abstract 0440

Low molecular weight heparin vs warfarin vs aspirin prophylaxis for thalidomide regimens





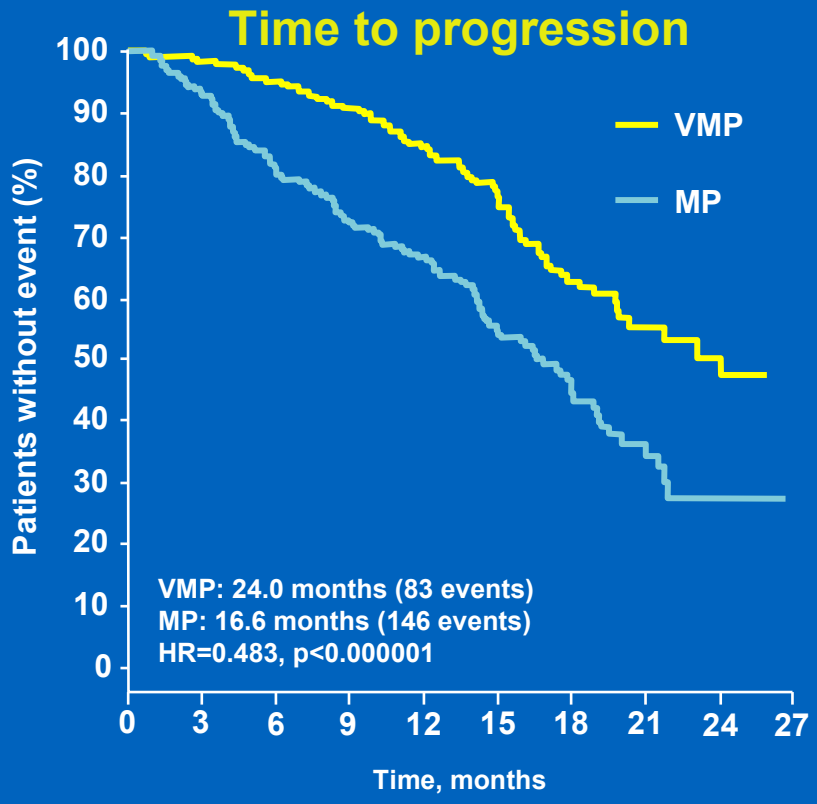
VMP, bortezomib-melphalan-prednisone
LMWH, low molecular weight heparin
VTE, venous thromboembolism

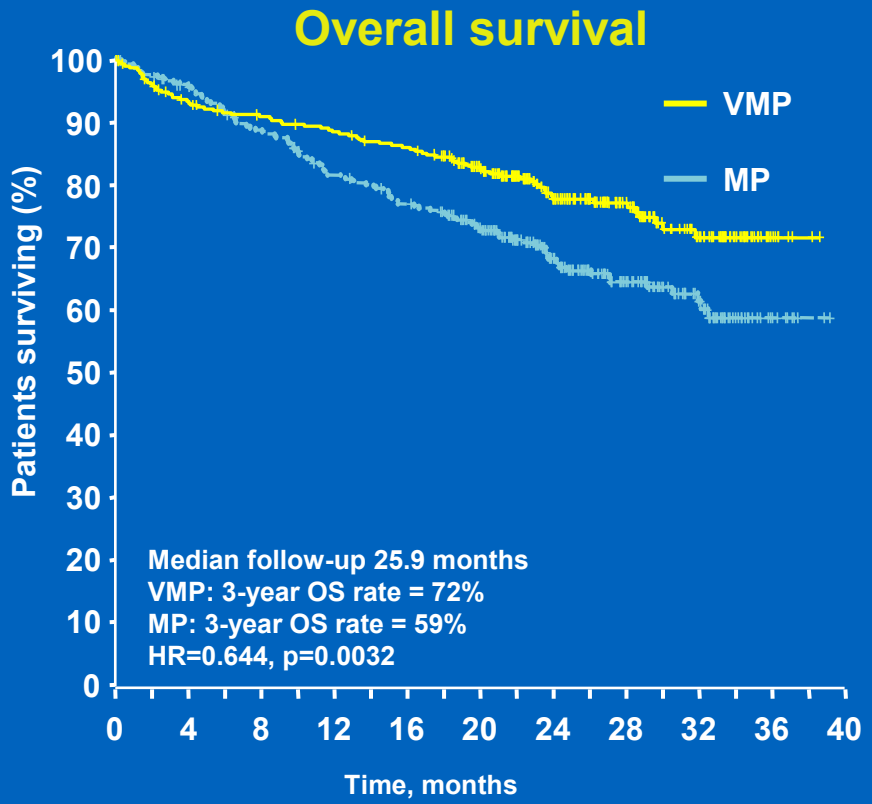
Cavo M et al. *Blood* 2008;112: Abstract 3017

VMP (bortezomib-melphalan-prednisone): a standard of care in older transplant ineligible patients

52% reduced risk of progression

~36% reduced risk of death





MP, melphalan-prednisone
HR, hazard ratio

San Miguel JF et al. *N Engl J Med* 2008;359:906–917

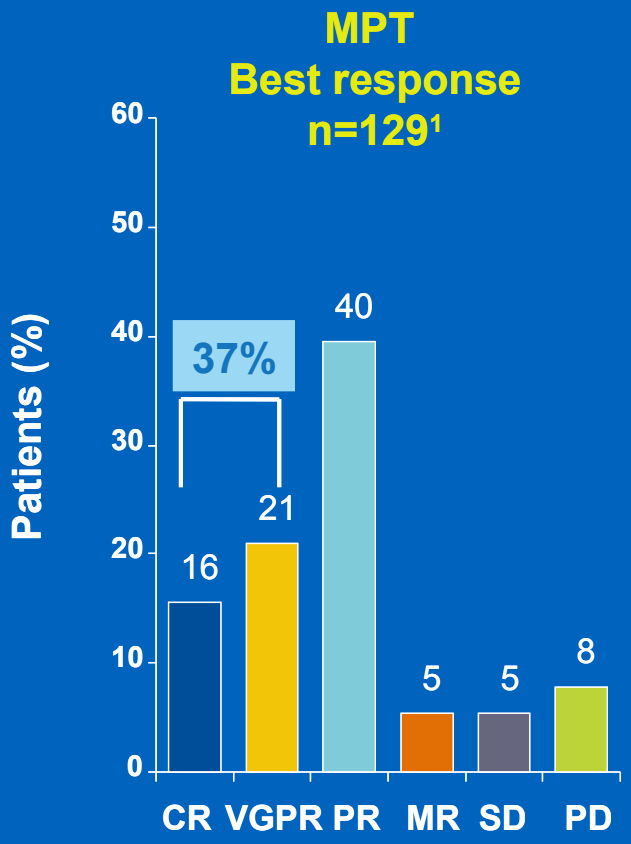
VMP: biweekly or weekly infusion?

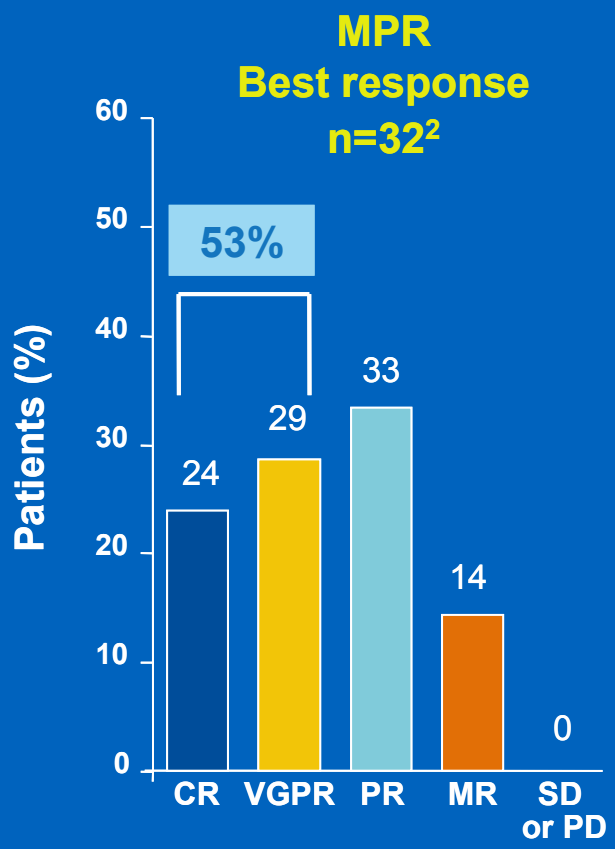
	VMP Twice weekly (n=42)	VMP Mix (n=19)	VMP Weekly (n=116)
CR	27%	23%	20%
Grade 3-4 peripheral sensory neuropathy	14%	16%	2%
Neuralgia	12%	10%	3%
Discontinuation	24%	22%	10%

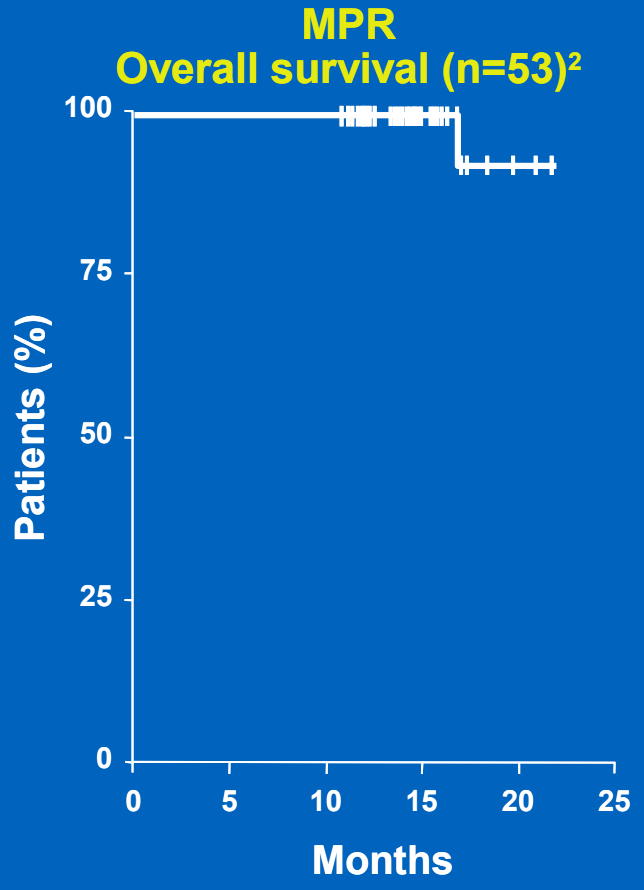
VMP, bortezomib-melphalan-prednisone
CR, complete response

Palumbo A et al. *Blood* 2008;112: Abstract 652 and oral presentation

Indirect comparison of response: MPT vs MPR







MPT, melphalan-prednisone-thalidomide
MPR, melphalan-prednisone-lenalidomide

1. Palumbo A, et al. *Lancet* 2006;367:825–831
2. Palumbo A, et al. *J Clin Oncol* 2007;25:4459–4465

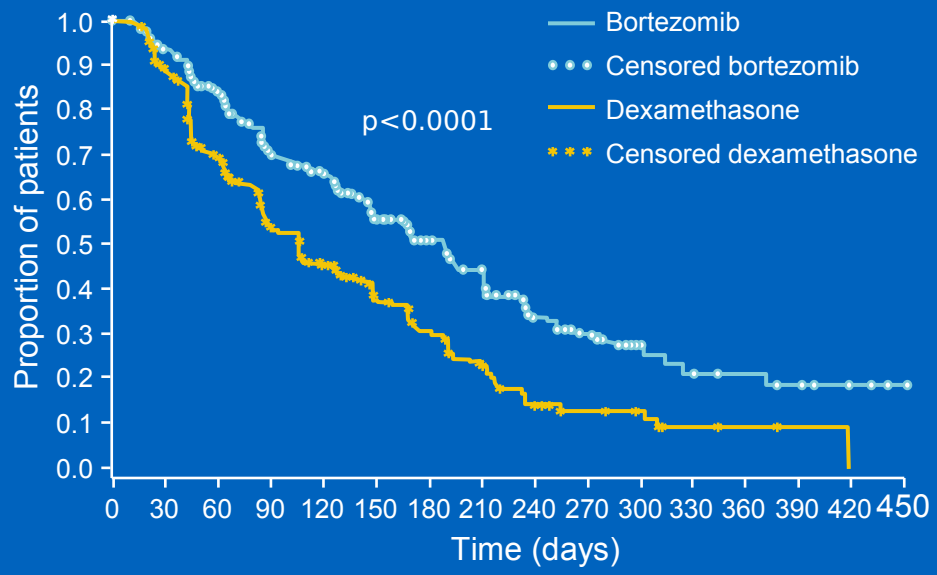
What are the treatment options for patients with relapsed/refractory disease?

Bortezomib vs dexamethasone in relapsed MM

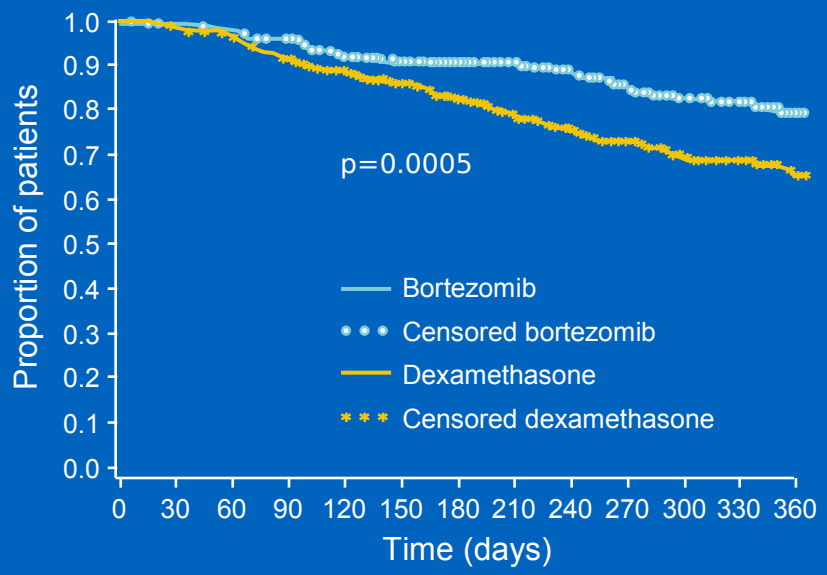
- Bortezomib 1.3 mg/m^2 IV push
- Days 1, 4, 8, 11 Q3W cycle, 8 cycles

Time to progression (n=669)

78% improvement in median TTP with bortezomib



1-year survival (n=669)



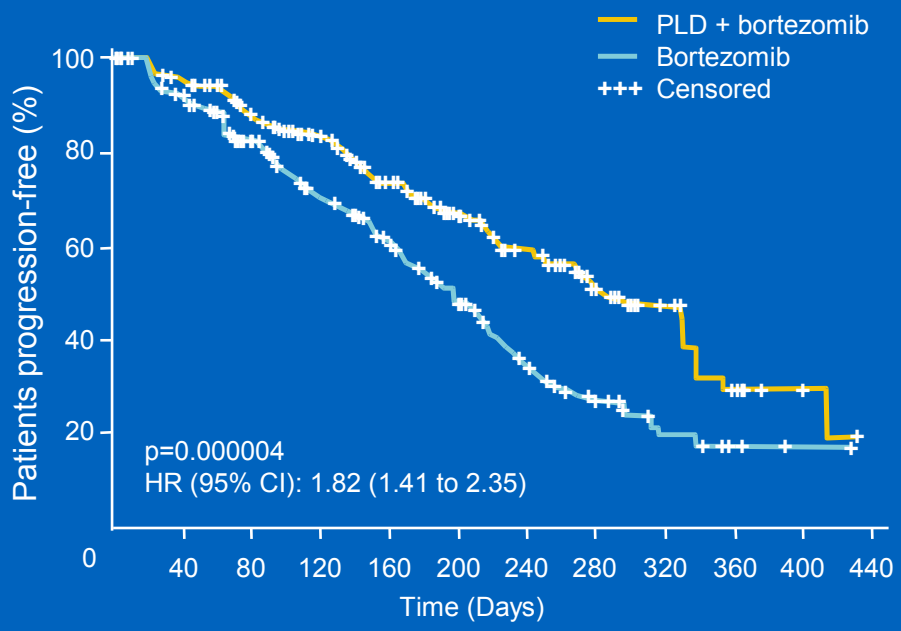
IV, intravenous

Richardson P et al. *N Engl J Med* 2005;352:2487–2498

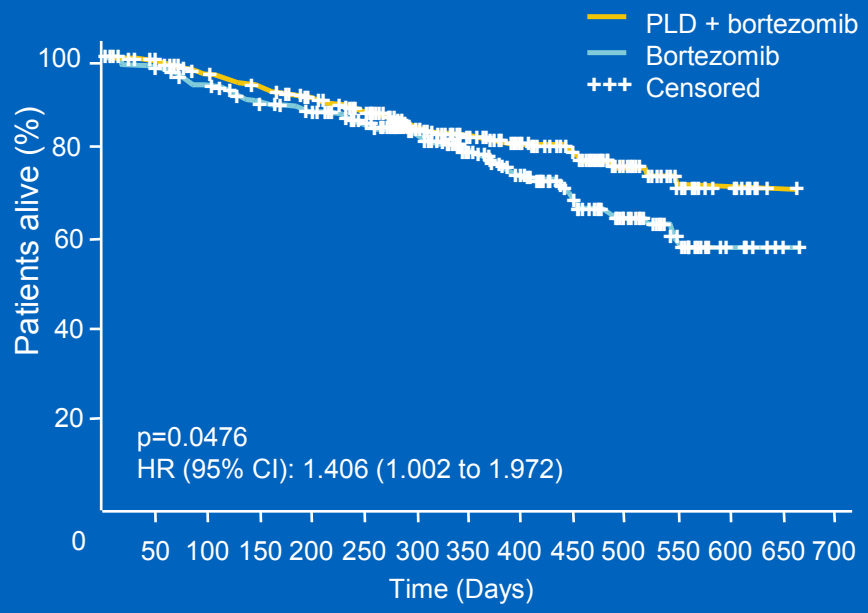
Pegylated liposomal doxorubicin + bortezomib vs bortezomib in relapsed/refractory myeloma

- Bortezomib 1.3 mg/m^2 days 1, 4, 8, 11
- Pegylated liposomal doxorubicin (PLD) 30 mg/m^2 day 4, 8 cycles

Time to progression



Overall survival

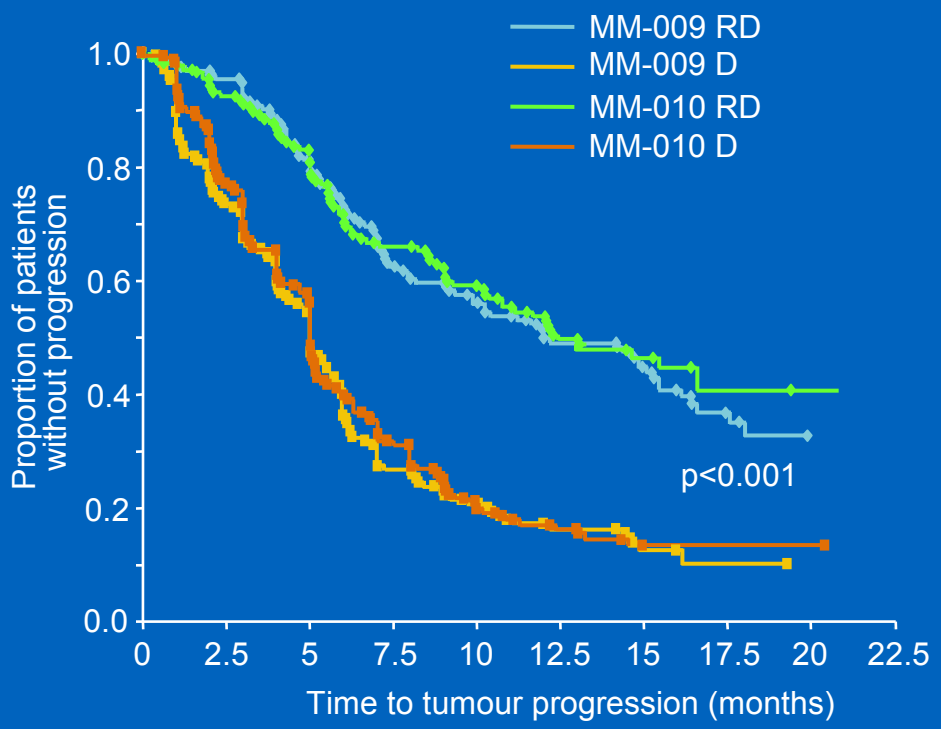


Orlowski RZ et al. *J Clin Oncol* 2007;25:3892−3901

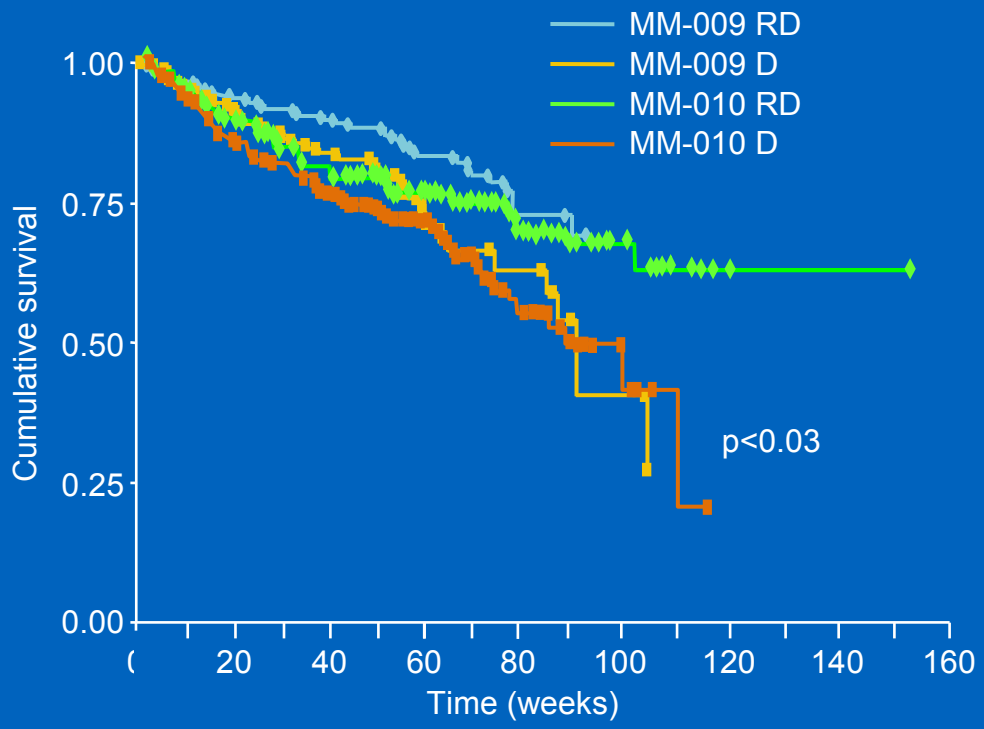
Lenalidomide/dexamethasone (RD) vs dexamethasone (D) in relapsed MM (MM09-MM010)

- Lenalidomide 25 mg, days 1–21
- Dexamethasone 40 mg, days 1–4, 9–12, 17–20

Time to progression



Survival



Dimopoulos MA et al. *Blood* 2005;106: Abstract 6;
Weber DM et al. *J Clin Oncol* 2006;24 Suppl 18S:427s; Abstract 7521

Longer treatment duration is associated with prolonged overall survival

- Subgroup analysis of MM-009 and MM-010: lenalidomide + dex. (RD)

Effect of longer duration of RD in responding patients

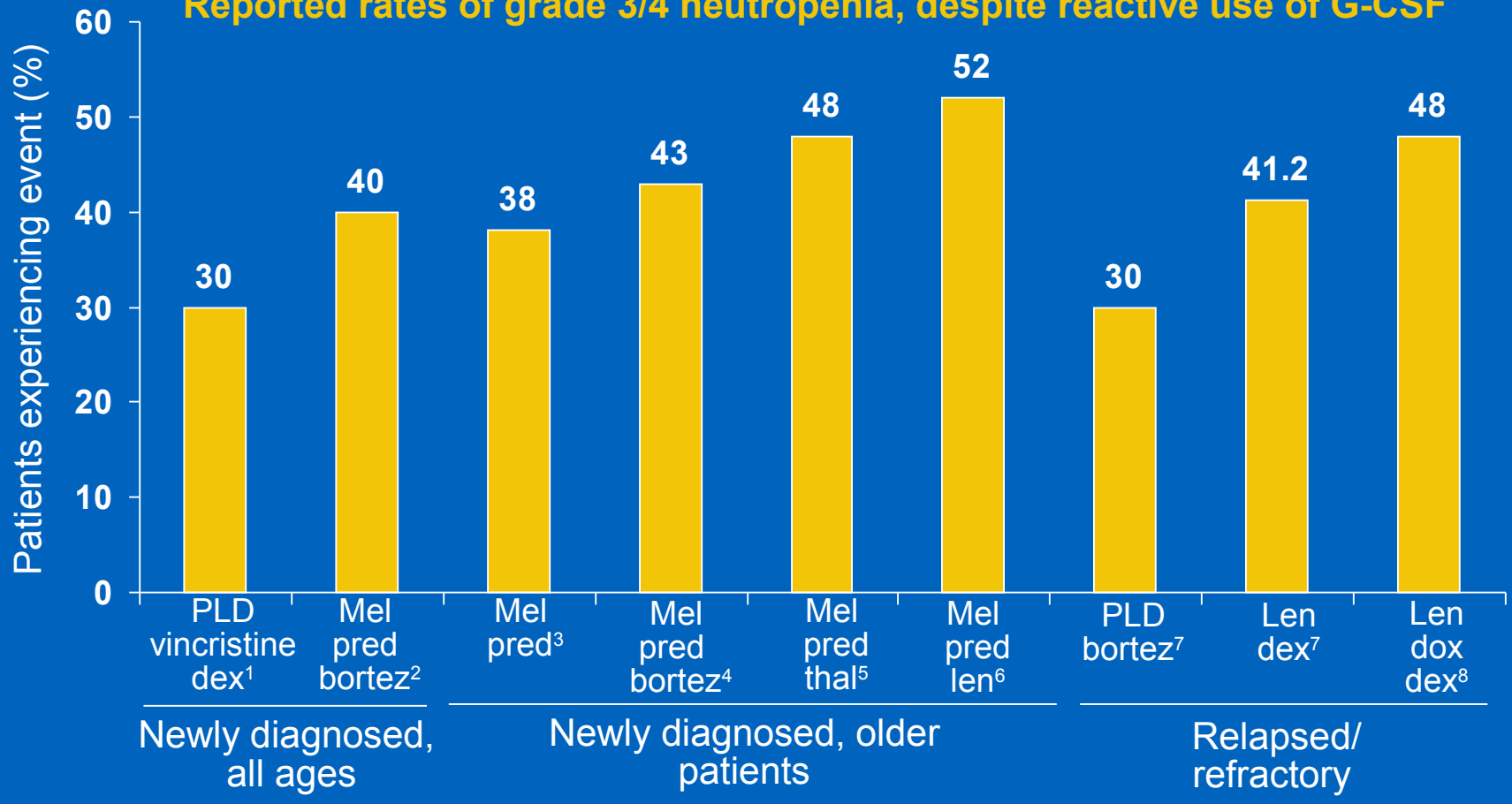
	≤10 months (n=223)	>10 months (n=98)	p value
Mean treatment duration (range), months	6.6 (0.2−25.0)	17.6 (12.3−25.6)	
Median OS, months	23.4	NR (>31.6 months)	<0.0001
2-year survival rate (%)	48.4	93.8	<0.0001

- Every effort should be made to manage adverse events so that patients can remain on treatment
- Neutropenia is a major dose-limiting side effect of lenalidomide treatment

San Miguel JF et al. *Blood* 2008;112: Abstract 3702 and oral presentation

How to manage neutropenia?

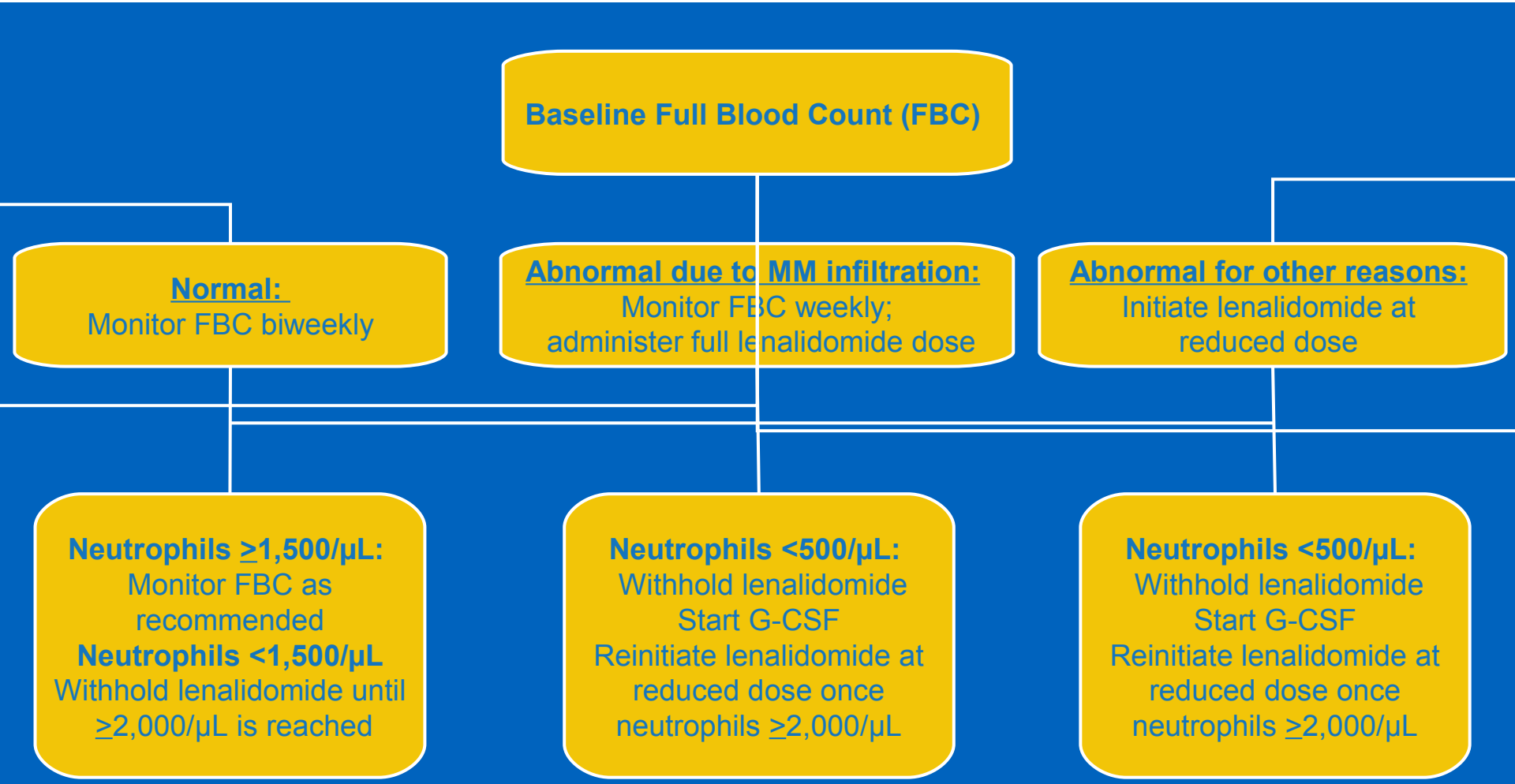
At what threshold does severe neutropenia impact outcome?



PLD, pegylated liposomal doxorubicin
red dex, reduced dose dexamethasone
mel, melphalan
pred, prednisone
len, lenalidomide
dox, doxorubicin

1. Hussein M et al. *Cancer* 2002;95:2160–2168; 2. San Miguel et al. *N Engl J Med* 2008;359:906–917;
3. Velcade Prescribing Information; 4. Mateos MV et al. *Haematologica* 2008;93:560-565;
5. Facon T et al. *Lancet* 2007;370:1209–1218; 6. Palumbo A et al. *J Clin Oncol* 2007;25:4450–4465;
7. Weber D et al. *N Eng J Med* 2007;357:2133–2142; 8. Knop S et al. *Blood* 2009;113:4137−4143

Management of neutropenia is critical to ensuring optimal outcomes

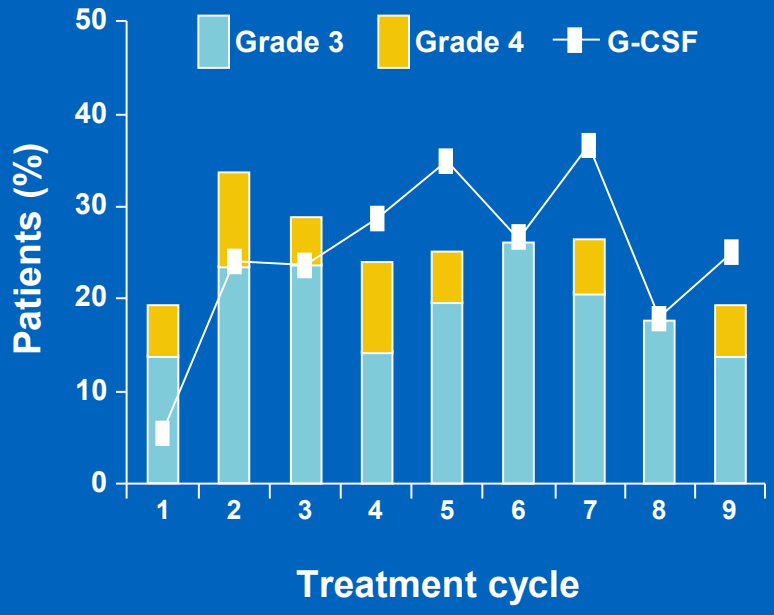


Palumbo et al. *Blood Reviews* 2009;23:87–93

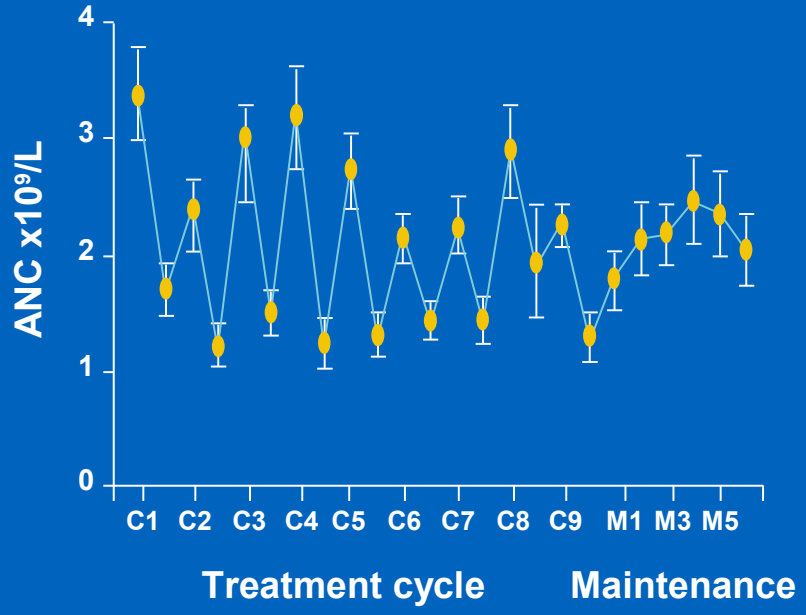
G-CSF required by 43% of patients receiving MPR (melphalan-prednisone-lenalidomide)

- Phase I/II study in newly diagnosed patients, median age 69 years (n=21)
- G-CSF prophylaxis recommended in case of prior cycle severe neutropenia

Grade 3 and 4 neutropenia: incidence and percentage of patients treated with G-CSF



Mean ANC during treatment cycles



ANC, absolute neutrophil count

Palumbo A et al. *Blood* 2008;112: Abstract 2768

Pegfilgrastim allows delivery of lenalidomide, doxorubicin and dexamethasone (RAD) in relapsed/refractory MM

Dose level	n	Lenalidomide	Doxorubicin	Dexamethasone	Pegfilgrastim
1	3	10 mg d1-21	4 mg/m² d1-4	40 mg d1-4, d17-20	
2	3	10 mg d1-21	6 mg/m² d1-4	40 mg d1-4, d17-20	
3	3	10 mg d1-21	9 mg/m² d1-4	40 mg d1-4, d17-20	
4	6	15 mg d1-21	9 mg/m² d1-4	40 mg d1-4, d17-20	
4-G	3	15 mg d1-21	9 mg/m² d1-4	40 mg d1-4, d17-20	6 mg; d 6
5-G	6	25 mg d1-21	9 mg/m² d1-4	40 mg d1-4, d17-20	6 mg; d 6

- Grade 4 febrile neutropenia at dose level 4 in 2/6 patients (30%)
- The addition of pegfilgrastim on day 6 allowed continued dose escalation
- Overall response rate 84% (n=37)

Knop S et al. *Blood* 2009;113:4137−4143

Summary

- In younger patients, novel agents and autologous transplantation are the standard[2]
- In elderly patients, MP + novel agents are the standard
- Combination of novel agents with chemotherapy is frequently associated with neutropenia[3–9]
- G-CSF is recommended for grade 4 neutropenia or febrile neutropenia and pegfilgrastim is an effective agent[10–12]

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PS, performance status

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