The evidence supporting continuous therapy in multiple myeloma

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Historical perspective

Study	Therapy	Years	Duration
SWOG 727	MP vs MPPro	68-70	To relapse
CALGB 7261	MP vs MCBP	71-72	To relapse
NCI MY-1	MP vs MCBVP	73-77	To relapse
CALGB 7761	MP vs MCBP	77-82	2 years
SWOG 7701	MP vs VMCP	77-79	2 years
MRC MYEL 4	MP vs VMP	80-82	Plateau – randomize
Harstad	MP vs VMCBP	81-82	12 months and randomize

Myeloma Trialist's Collaborative Group. J Clin Oncol. 1998;16:3832-42.

Philosophical perspective

Pros

- Increases remission duration
- Maintains minimal disease burden preventing end-organ damage
- Targets “tumour cells” that leave “dormancy phase”
- May further decrease tumour burden after primary therapy

Cons

- Exposes all patients to the side-effects of prolonged treatment
- Can result in resistant clones
- Late effects of long-term therapy
- Cost

Common wisdom dictates that PFS by itself may not justify continuous therapy for all patients with a specific disease. Either a survival or QoL benefit needs to be shown when comparing continuous therapy with therapy upon progression. The question is made even more difficult if the issue of pre-emptive (i.e. early) intervention is included

Rationale for continuous treatment in the era of IMiDs® and proteasome inhibitors

- Primary therapy even with high-dose treatment results in a CR in < 50% of patients
- Longer treatment can result in better disease control and may be associated with
  - prolonged duration of response
  - increased depth of response
    - survival benefit???
- Use of different mechanisms of action of novel agents
- Tolerability of novel agents allows for longer-term treatment

Potential risks of continuous treatment in the era of IMiDs® and proteasome inhibitors

- Adverse events related to long-term treatment
  - reduced QoL
  - impact on subsequent therapeutic options
  - second primary malignancies
- Reduced survival after relapse
  - selection of resistant clones
  - availability of non-cross-reacting agents

The facts… just the facts….

Historical perspective

- Long-term alkylator therapy is associated with a higher risk of secondary MDS/AML
- Maintenance therapy with IFN in multiple randomized trials showed marginal benefit in PFS and no survival benefit. Compliance was poor[1–3]
- Long-term steroid therapy is potentially beneficial[4]

1.Myeloma Trialist's Collaborative Group. Br J Haematol. 2001;113:1020-34. 2. Fritz E, Ludwig H. Ann Oncol. 2000;11:1427-36.
3. Barlogie B, et al. J Clin Oncol. 2006;24:929-36. 4. Berenson JR, et al. Blood. 2002;99:3163-8.

Maintenance with IFN after ASCT Comparable Survival in MM

In a study of 899 patients, HDT (melphalan 140 mg/m^2 + TBI 12 Gy) vs standard dose VBMCP therapy showed no benefit for IFN maintenance

Barlogie B, et al. J Clin Oncol. 2006;24:929-36.

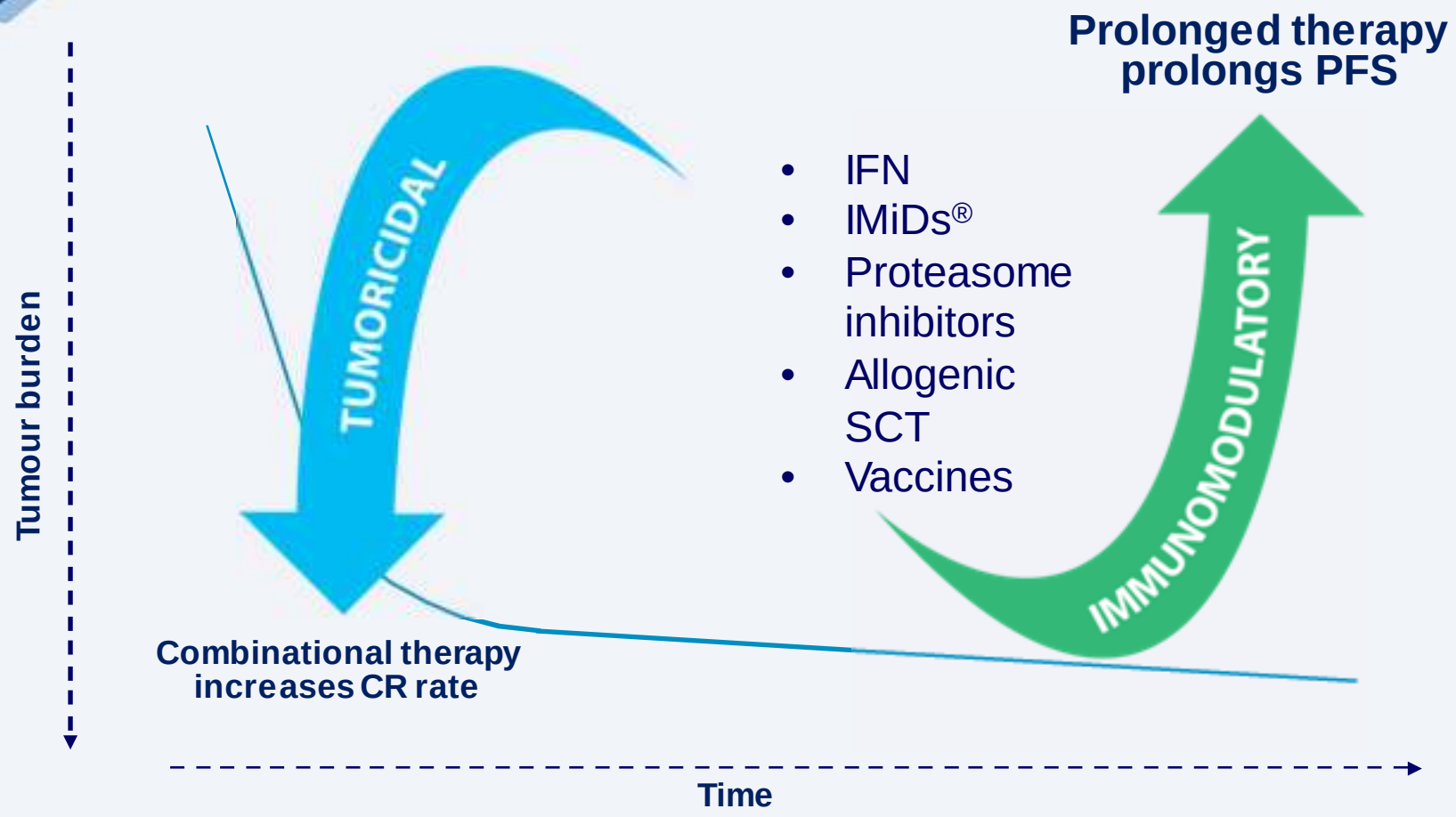
Comparable survival in MM with or without IFN

	CR (%)	PR (%)	PFS (months)	OS (months)
ASCT	17	93	25 p = 0.05	62 p = 0.8
VBCMP	15	91	21	53
+ IFN			23	59
− IFN			18	
				p = NS

- 52% of VBCMP patients had salvage ASCT → 59% of whom had a PR (median OS 30 months) vs 23 months in patients who received non-transplant salvage therapy (p = 0.13)

Barlogie B, et al. J Clin Oncol. 2006;24:929-36.

Treatment strategy



SCT = stem cell transplantation.

Palumbo A. Presented at ASH 2010 Educational Sessions.

Consolidation regimens post-ASCT improved response rates

Patients (N)	Consolidation	CR/nCR/sCR pre-consolidation (%)	CR/nCR/sCR post-consolidation (%)	Other outcome measures reported
330[1]	Bortezomib single agent x 6 cycles vs no consolidation	20 vs 19 (p = NS)	49 vs 33 (p = 0.01)	6% vs 12% progression between 3 and 9 months (p = 0.08)
45[2]	VD x 6 cycles	25	51	–
31[3]	VRD x 2 cycles	35	52	–
46[4]	VTD x 2 cycles	37	68	–
474[5]	VTD vs TD x 2 cycles	30 vs 10 (p < 0.001)	60 vs 44 (p = 0.001)	Median PFS: not reached vs 42 months (p = 0.006) OS: 84% vs 74% at 44 months (p = NS)

1. Mellqvist U-H, et al. Blood. 2009;114:[abstract 530]. 2. Sahebi F, et al. Blood. 2010;116:[abstract 2399]. 3. Roussel M, et al. Blood. 2010;116:[abstract 624]. 4. Roussel M, et al. Blood. 2010;116:[abstract 3041]. 5. Cavo M, et al. Blood. 2010;116:[abstract 42].

Upgrade in MRD negativity with consolidation: GIMEMA study

- VTD compared with TD consolidation (x 2 cycles starting within 3 months post-ASCT) on MRD in MM patients treated in the phase 3 GIMEMA trial
- Results (VTD, n = 35; TD, n = 32)
  - upgrade in MRD negativity from 43% to 67% for VTD vs from 38% to 52% with TD (p = 0.05 for 67% vs 52%)
  - PCR bone marrow analysis showed a median 5 log reduction in tumour burden with VTD vs a 1 log reduction with TD (p = 0.05)

Terragna C, et al. Blood. 2010;116:[abstract 861].

Impact of thalidomide-based maintenance after ASCT

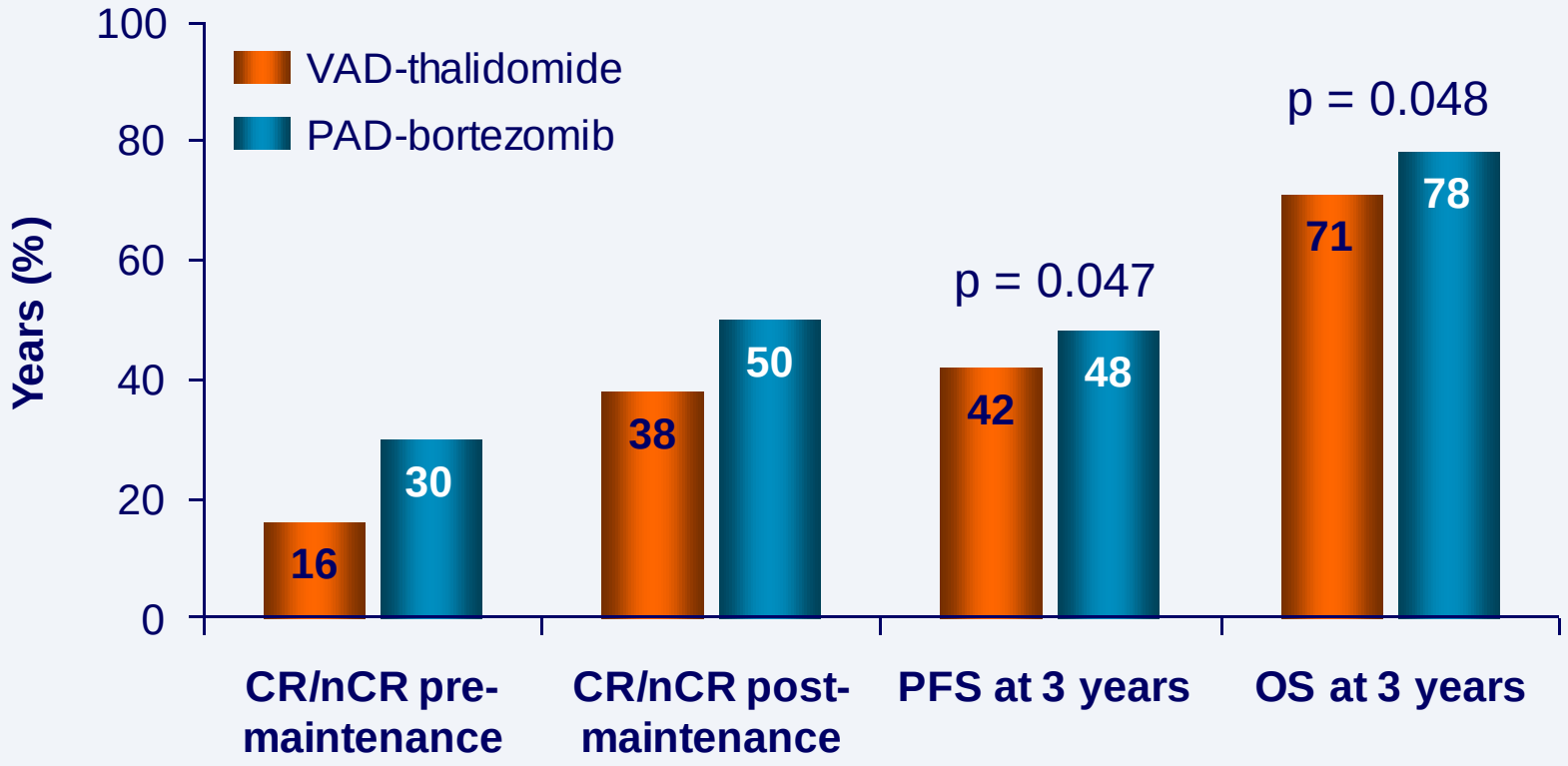
	Patients (N)	Duration of treatment	CR + VGPR (%)	EFS or PFS (%)	OS (%)
TT2[1,2]	668	Double ASCT Thal vs no maintenance until progression	**64** vs 43 (CR only) p < 0.001	**52** vs 41 (5 years) p = 0.0005	**57** vs 44 (8 year) p = 0.09 Sign in cyto abnormalities
IFM 99-02[3]	597	Double ASCT	**67** vs 57 vs 55	**52** vs 37 vs 36	**87** vs 74 vs 77
Spencer[4]					
Morgan[5]					
Lokhorst[6]	556	Double or single ASCT Thal vs alpha-IFN until progression	**66** vs 54 p = 0.005	**34** vs 22 p < 0.001	73 vs 60 p = 0.77
Stewart[7]	332	Single ASCT Thal + Pred vs observation until progression	Not reported	**28 months** vs 17 months p < 0.0001	Median not reached vs 5 years p = 0.18

- 6/6 trials showed a significant benefit on PFS
- 2/6 trials showed a significant benefit on OS + 1/6 showed a significant OS benefit in patients with cytogenetic abnormalities

1. Barlogie B, et al. Blood. 2008;112:3115-21. 2. Barlogie B, et al. J Clin Oncol. 2010;28:3023-7.
3. Attal M, et al. Blood. 2006;108:3289-94. 4. Spencer A, et al. J Clin Oncol. 2009;27:1788-93. 5. Morgan GJ, et al. Blood. 2010;116:[623].
6. Lokhorst HM, et al. Blood. 2010;115:1113-20. 7. Stewart AK, et al. Blood. 2010;116:[39].

Impact of bortezomib and thalidomide maintenance after ASCT

HOVON-65/GMMG-HD4 trial*

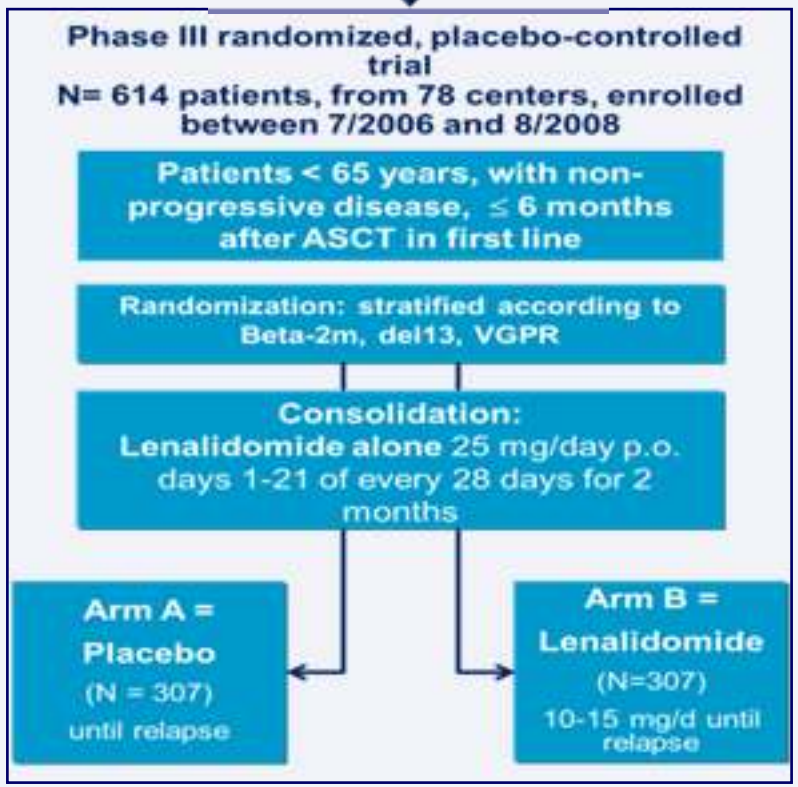


* Patients received one (HOVON) or two (GMMG) treatments with high-dose melphalan with ASCT.

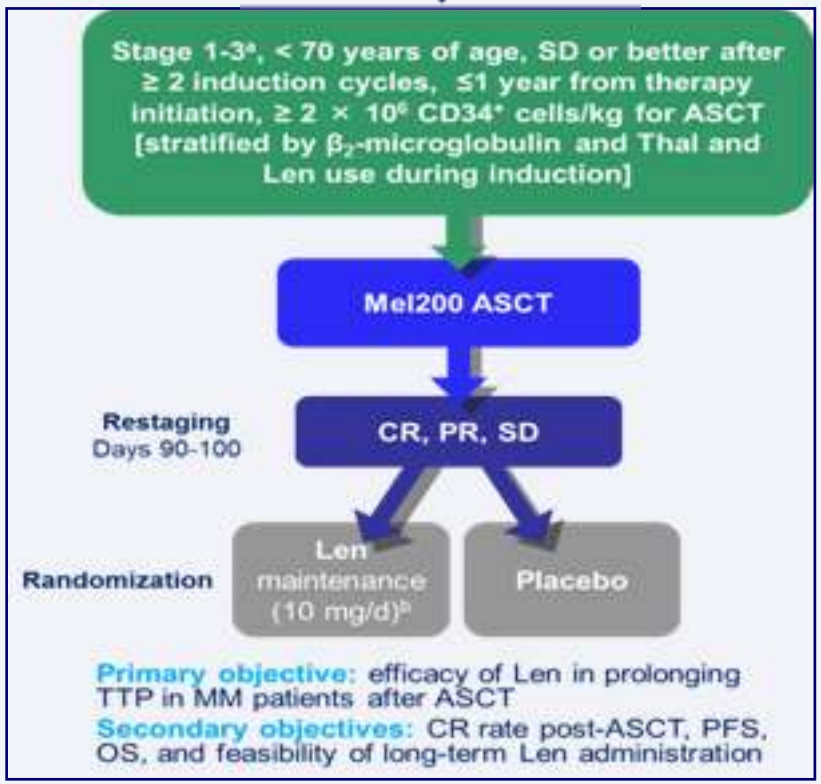
Sonneveld P, et al. Blood. 2010;116:[abstract 40].

Phase III trials: maintenance therapy post-ASCT with Lenalidomide versus placebo

IFM 2005-02: Study design

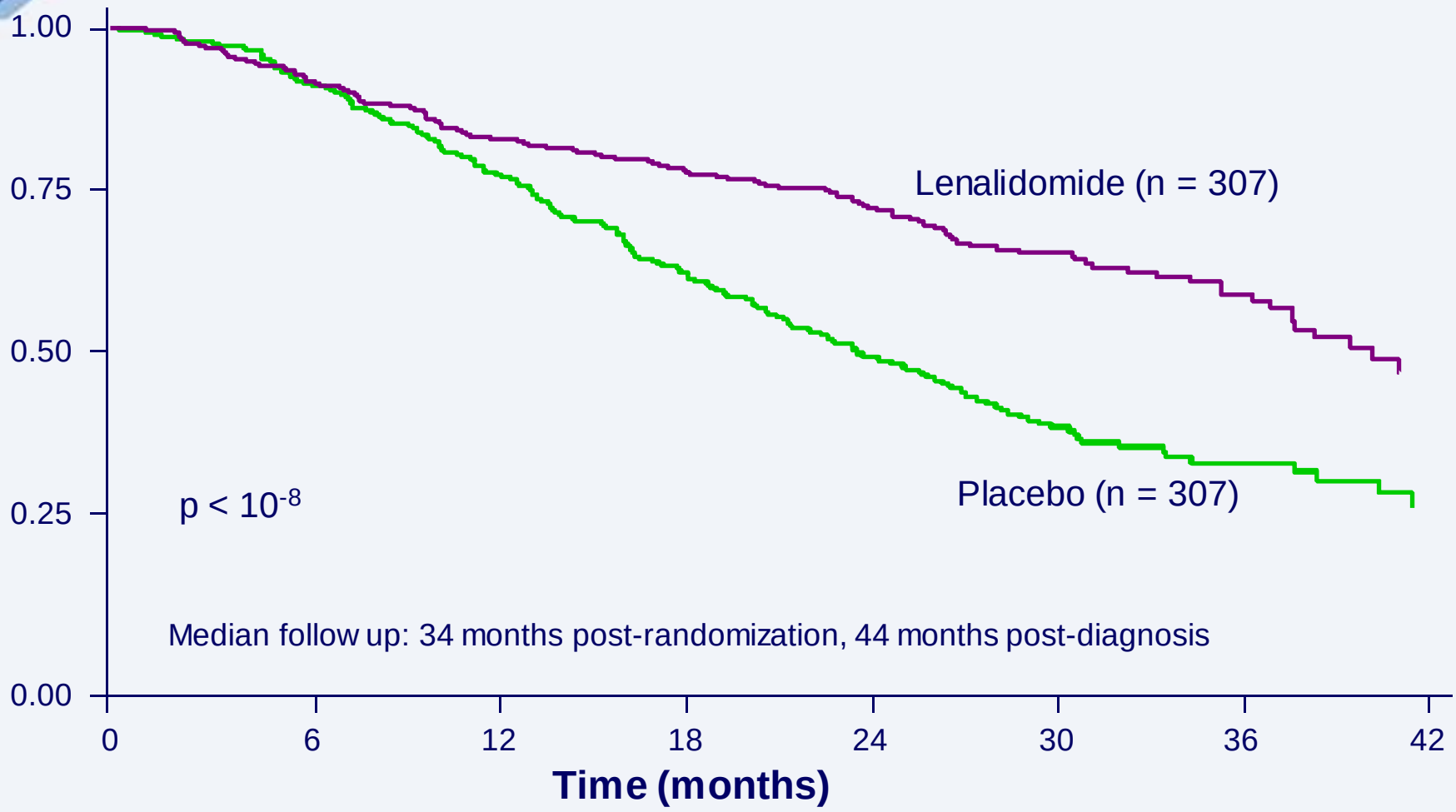


CALGB 100104: Study design



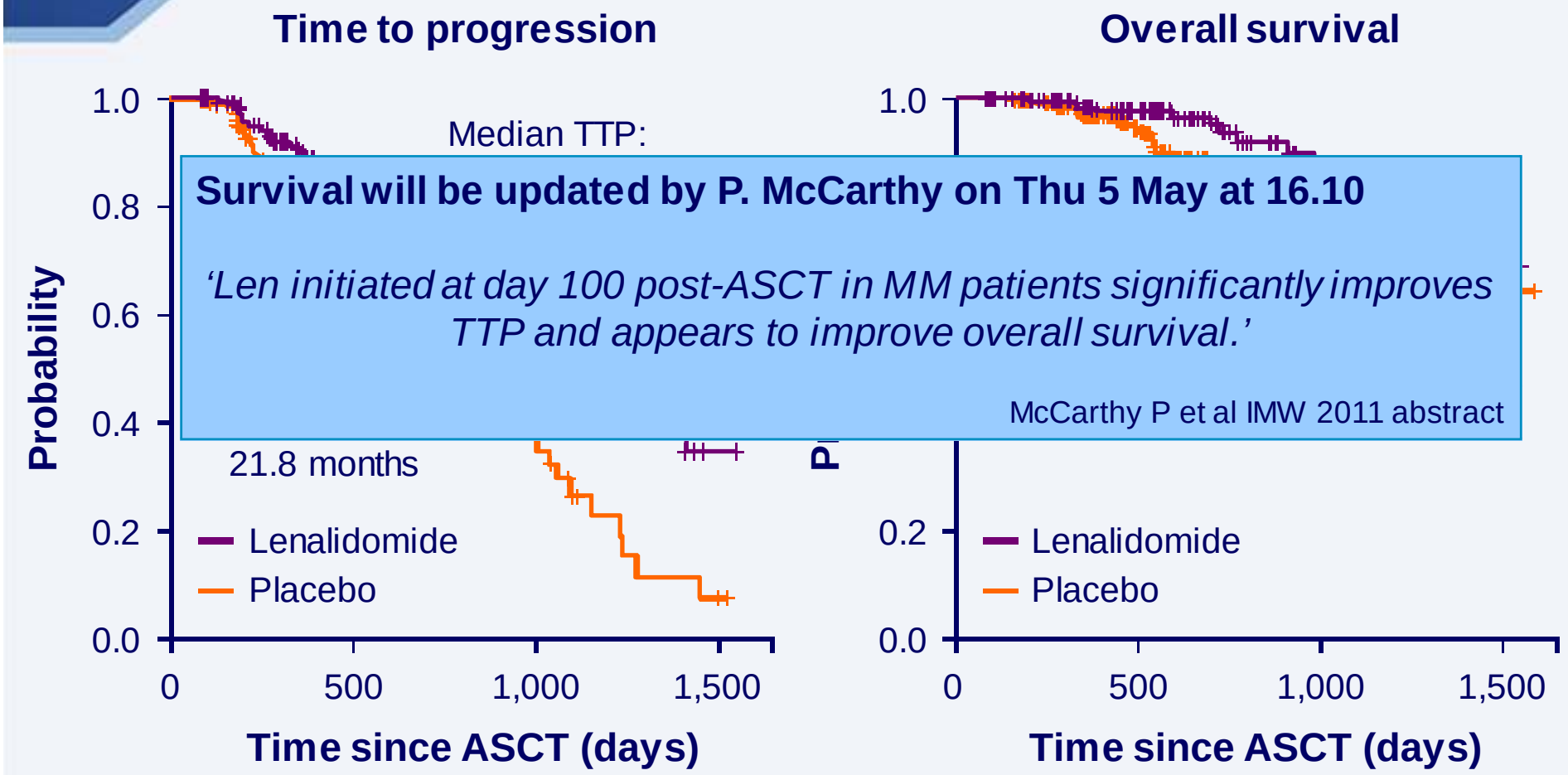
Attal M, et al. Blood. 2010;116:[abstract 310]. Updated data presented at ASH 2010.
McCarthy PL, et al. Blood. 2010;28:[abstract 37]. Updated data presented at ASH 2010.

IFM 2005-02: PFS significantly improved with lenalidomide maintenance



Attal M, et al. Blood. 2010;116:[abstract 310]. Updated data presented at ASH 2010.

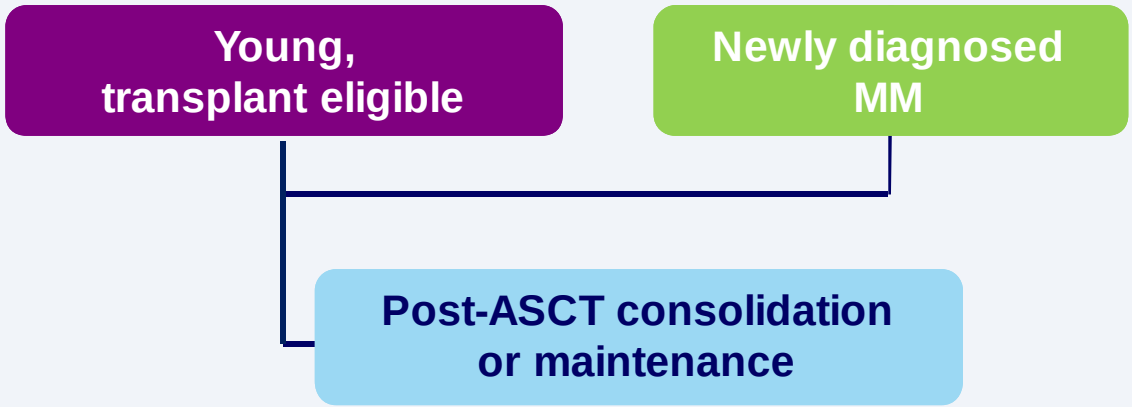
CALGB 100104: maintenance therapy with lenalidomide prolongs TTP



Data cut-off November 2009, median follow-up 12 months

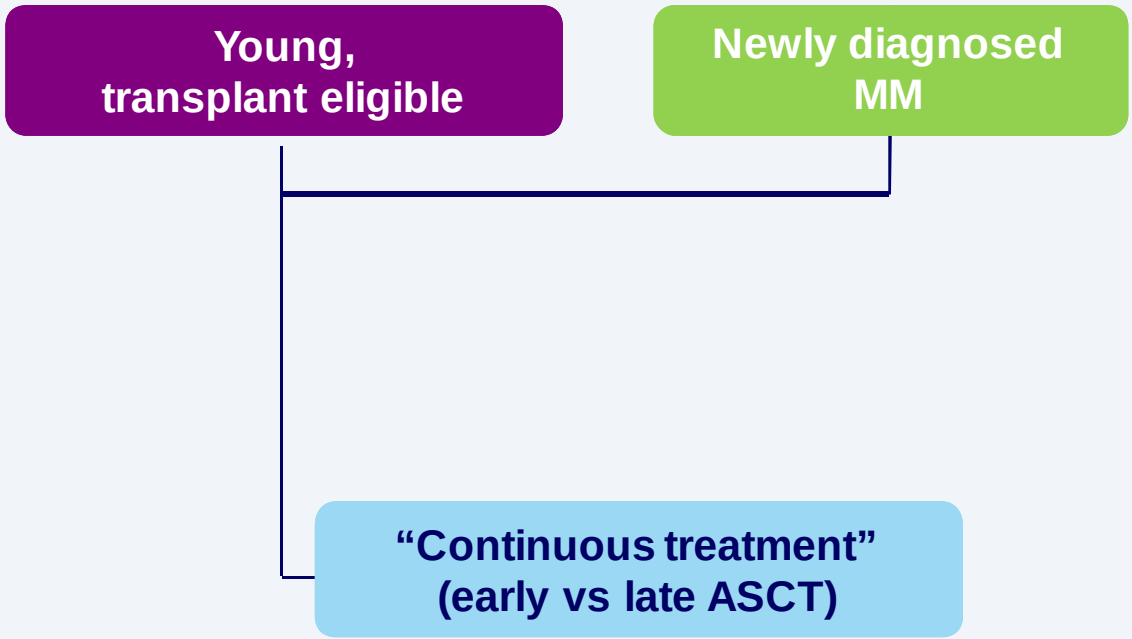
McCarthy PL, et al. Blood. 2010;28:[abstract 37] . Updated data presented at ASH 2010.

Post-ASCT consolidation or maintenance for patients with MM



- Post-ASCT consolidation strategies appear to increase depth of response, which may lead to improved long-term outcomes
- Post-ASCT maintenance strategies improve PFS/TTP
  The full impact on OS is not yet known and requires further follow-up

What continuous-treatment data are available?



ECOG-E4A03: survival probability of early transplant or continued therapy

Post-hoc analysis of a phase 3 trial where patients could choose to have ASCT or remain on continued therapy

		Survival probability (%)		
	Subgroup	**< 65 years**	**> 65 years**	**> 70 years**
No early transplant	All patients	78	69	70
	Rd	78	67	74
	RD	79	70	66
Early transplant	All patients	94	83	–
	Rd	94	75	–
	RD	95	92	–

Siegel DS, et al. Blood. 2010;116:[abstract 38].

MPR vs ASCT + MEL200: similar outcomes with MPR vs transplant

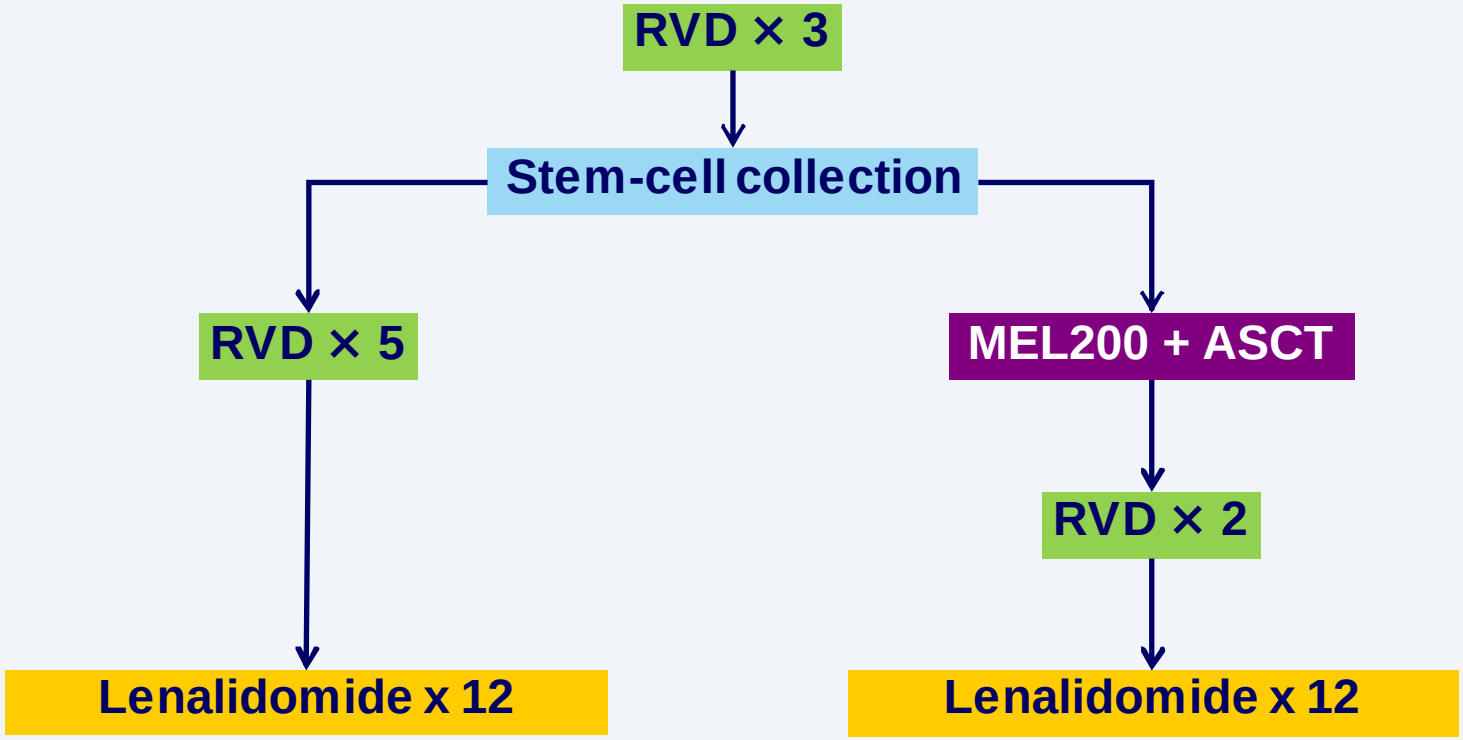
Phase 3 trial of Lenalidomide + Dex induction followed by MPR vs ASCT + MEL200 consolidation in younger patients

Outcome (%)	MPR (n = 117)	ASCT + MEL200 (n = 122)	p value
≥ VGPR	60	58	NS
CR	20	25	NS
2-Year PFS	73	78	NS
2-Year OS	95	97	NS

Palumbo A, et al. Blood. 2010;116:[abstract 3573]. Updated data presented at ASH 2010.

RVD + Lenalidomide continuous treatment vs ASCT + Lenalidomide maintenance

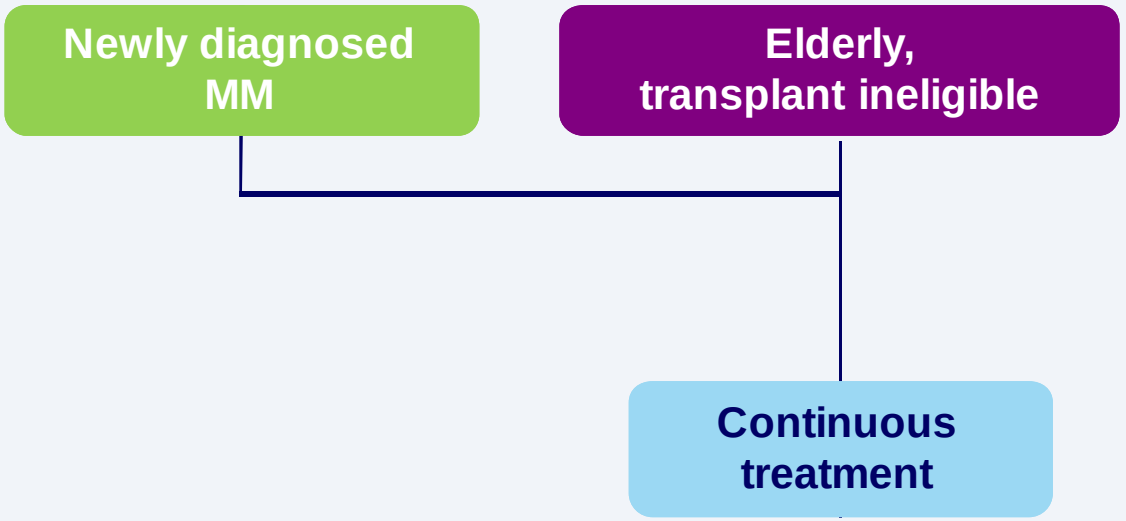
IFM/DFCI2009: phase 3 trial in younger patients



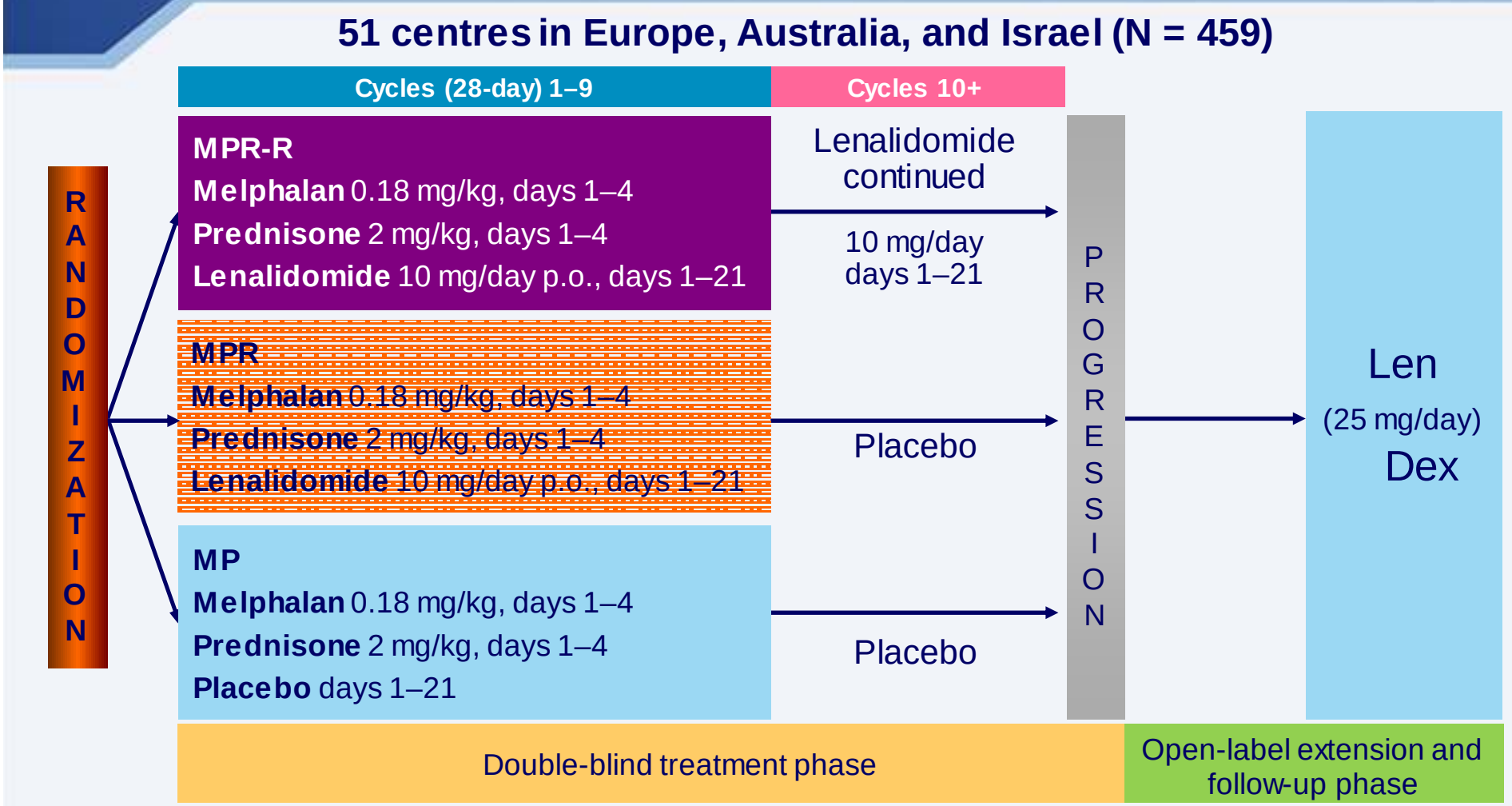
Can early SCT prolong EFS by at least 9 months?

ClinicalTrials.gov: NCT01208662.

What continuous-treatment data are available?

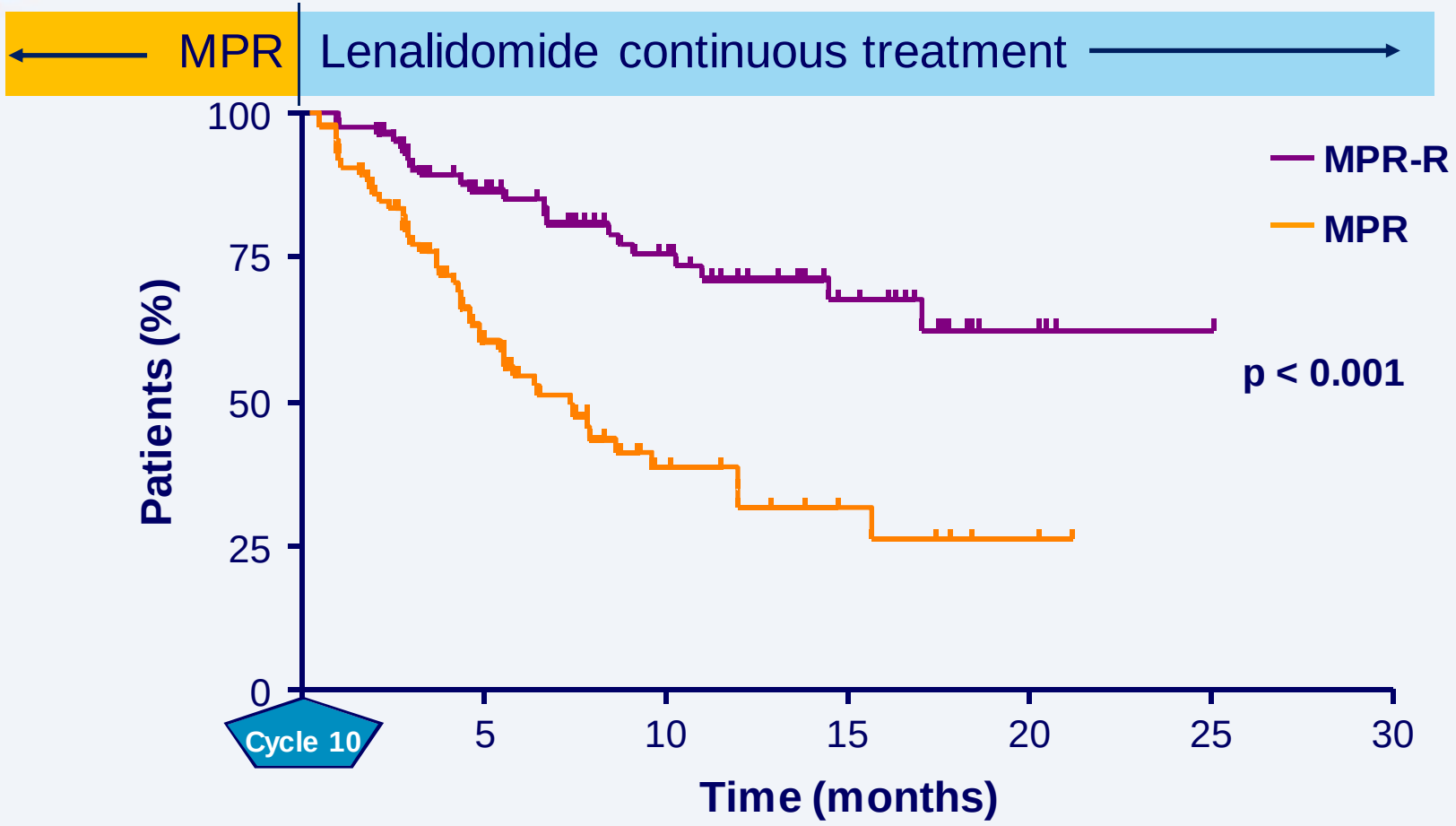


MM-015: phase 3 trial of MPR vs MP for long-term control in newly diagnosed MM



Palumbo A, et al. Blood. 2010;116:[abstract 622]. Updated data presented at ASH 2010.

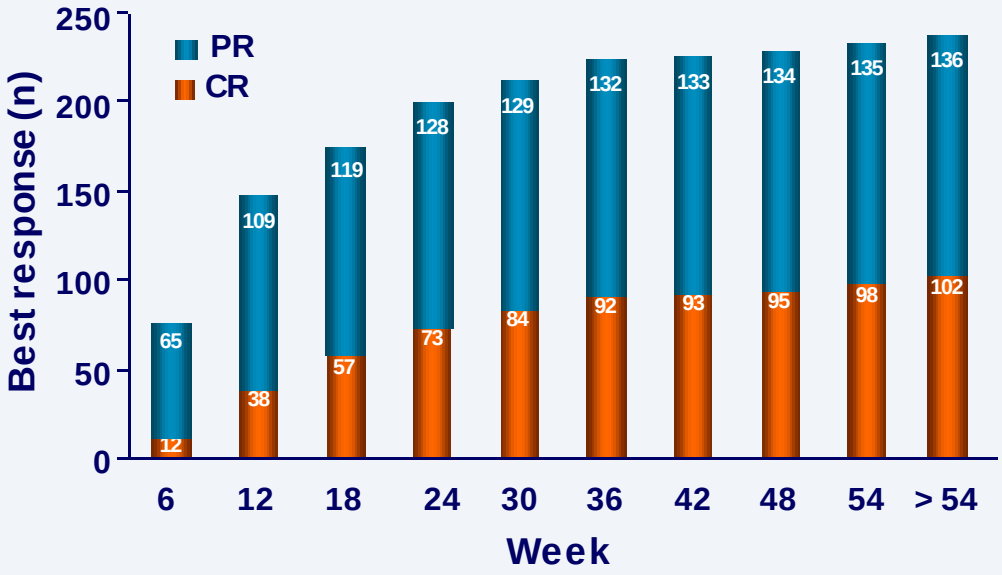
MM-015: landmark analysis
69% reduced risk of progression



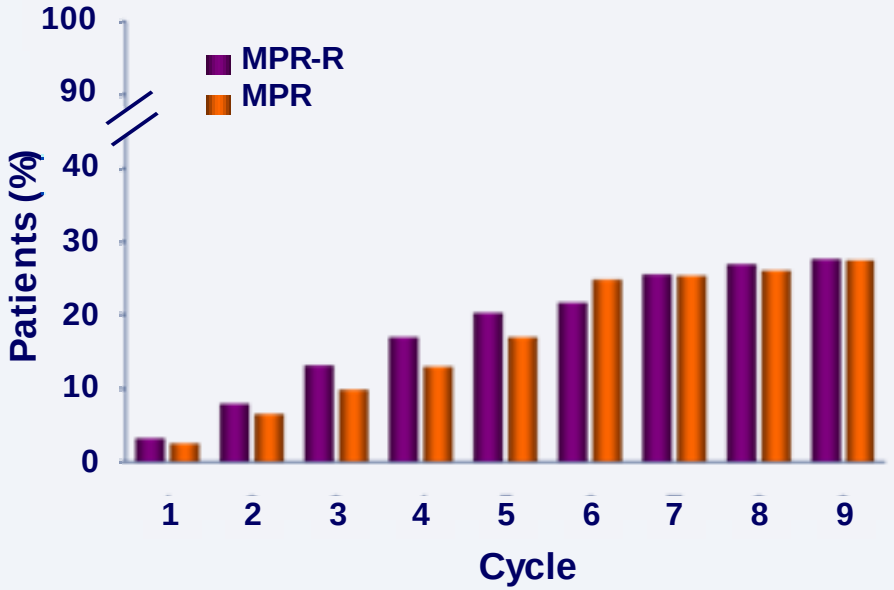
Palumbo A, et al. Blood. 2010;116:[abstract 622]. Updated data presented at ASH 2010.

Depth of response improved over time with continued therapy

VISTA: 28% (29/102) of CRs occurred after cycles 1–4 of bortezomib



MM-015: continued therapy with lenalidomide improved response (≥ VGPR) over time



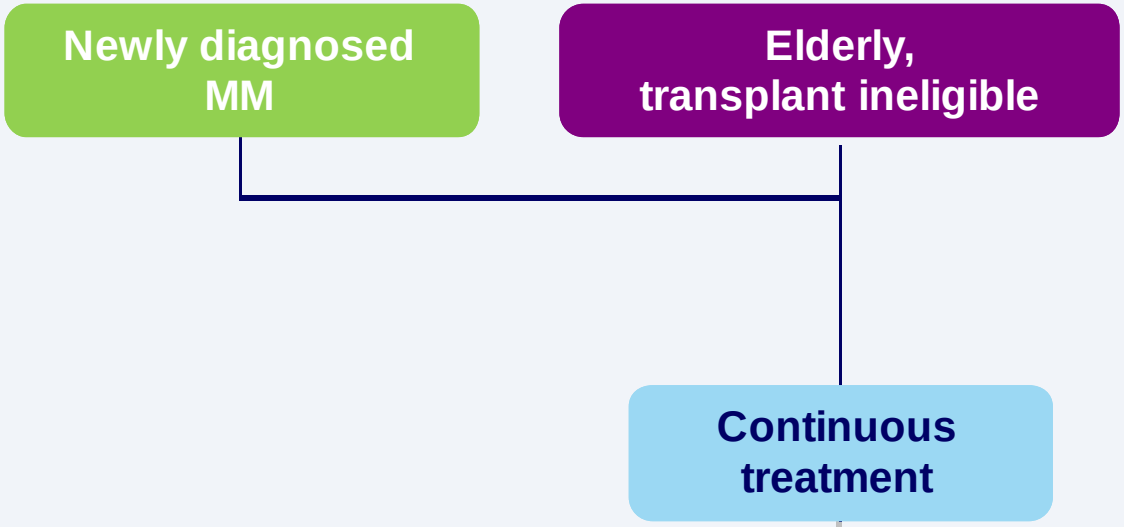
Harousseau JL, et al. Blood. 2010;116:3743-50.
Palumbo A, et al. Blood. 116;[abstract 622]. Data presented at ASH 2010.

Continuous therapy in non-transplant-eligible patients

Patients (N)	Duration of therapy	Median PFS (months)	OS
149[1]	VT vs observation until progression	37 vs 27 ($p < 0.0001$)	85 vs 80% at 3 years p = NS
178[2]	VT vs VP up to 3 years	32 vs 24 (p = NS)	p = NS
459[3]	Lenalidomide vs placebo until progression	31 vs 14 ($p < 10^{-7}$)	75–82% at 2 years p = NS

1. Palumbo A, et al. Blood. 2010;116:[abstract 620]. Updated data presented at ASH 2010.
2. Mateos MV, et al. Lancet Oncology. 2010;11:934-41. 3. Palumbo A, et al. Blood. 2010;116;[abstract 622]. Updated data presented at ASH 2010.

Continuous treatment in non-transplant-eligible patients with MM



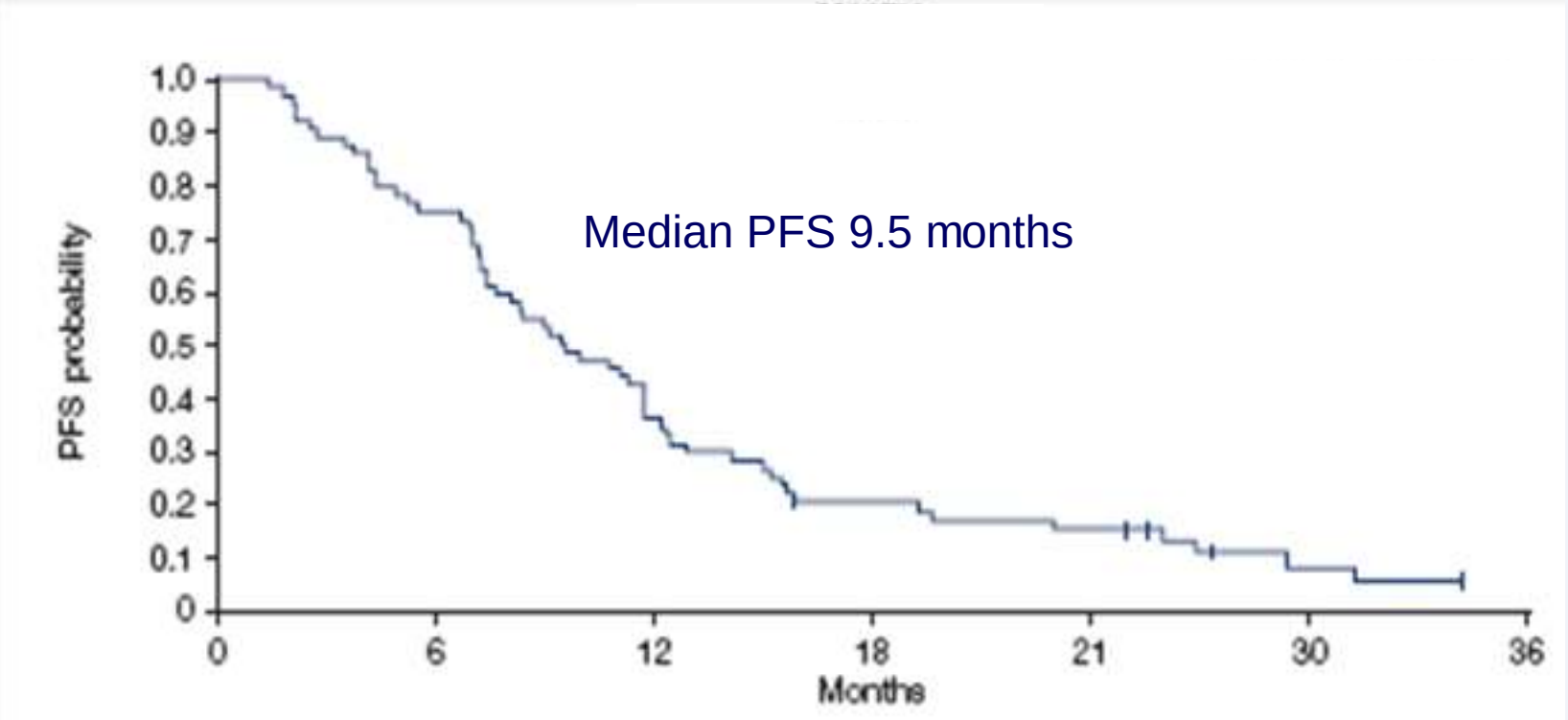
- Continuous treatment strategies using novel agents in non-transplant-eligible patients
  - increased depth of response
  - improved PFS, impact on OS to be determined
  - had manageable adverse event profiles

What continuous-treatment data are available?

Relapsed/refractory MM with RVD

Phase II Trial of RVD in RRMM for up to eight treatment cycles.

- Patients ≥ SD continue treatment beyond 8 cycles
- Primary end point: PFS at 6 months in 74% of patients

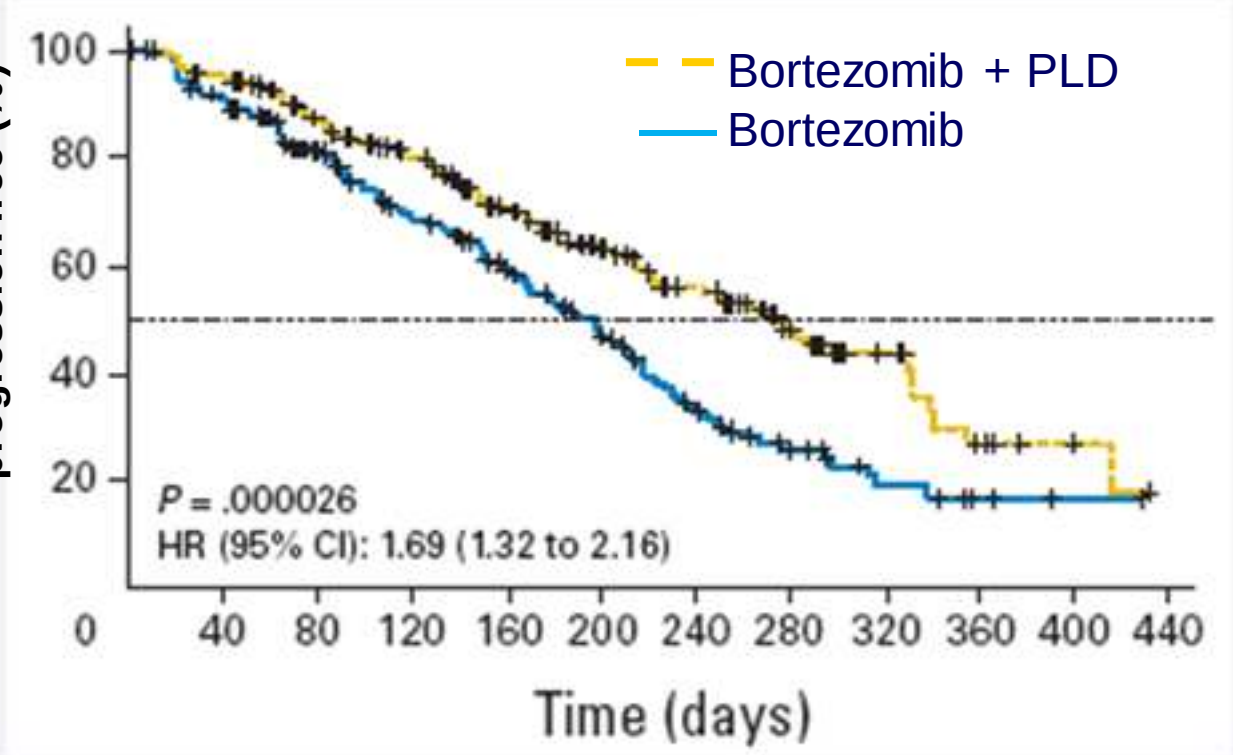


Richardson PG, et al. Blood. 2010; 2010;116:[abstract 3049]. Updated data presented at ASH 2010

Relapsed/refractory MM with bortezomib + PLD

Phase III Trial of combination of bortezomib + PLD vs bortezomib in RRMM

- Treatment 8 cycles or until disease progression or unacceptable treatment-related toxicity
- Patients ≥ SD continue treatment beyond 8 cycles



Median PFS
9.0 vs 6.5 months
(p< 0.000026)

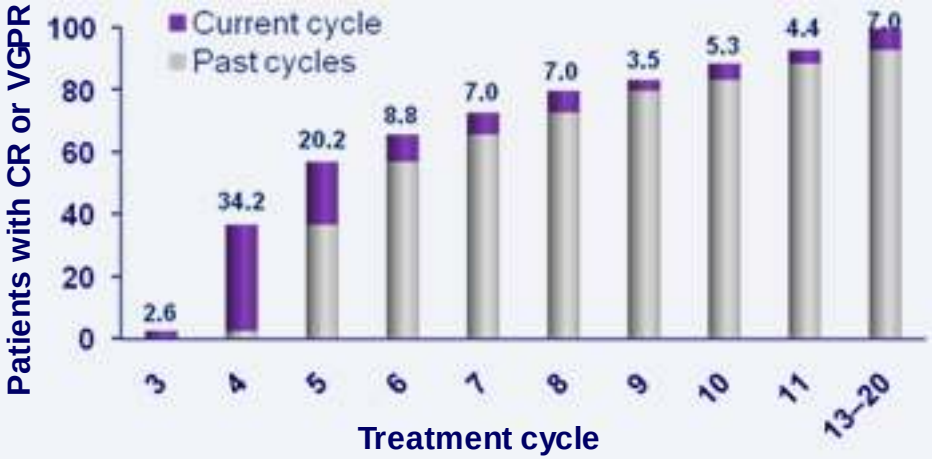
PLD = Pegylated liposomal doxorubicin

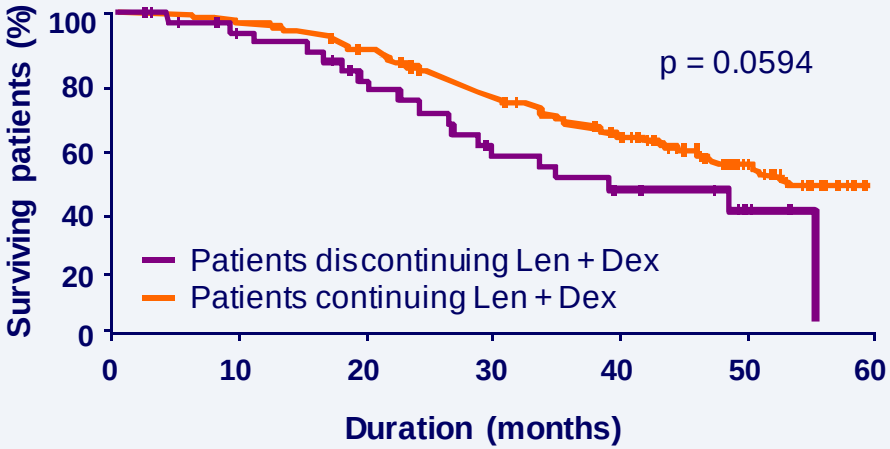
Orlowski RZ, et al. J Clin Oncol. 2007;25:3892-901.

Long-term treatment with Lenalidomide + Dex improved depth of response and prolonged OS

MM-009 and MM-010: subgroup analysis, Lenalidomide + Dex in relapsed/refractory patients

CR or VGPR achieved in 114 of 353 patients treated with Lenalidomide + Dex





Continuing Lenalidomide + Dex treatment resulted in additional late CR or VGPR

Continuous treatment with Lenalidomide + Dex beyond best response (≥ PR) prolongs OS

Harousseau JL, et al. Haematologica. 2010;95:1738-44.
San Miguel JF, et al. Clin Lymphoma, Myeloma Leuk. 2011;11:38-43.

Relapsed/refractory MM

- Long-term treatment using Lenalidomide improved response in relapsed/refractory patients
- Fixed number of cycles followed by watchful waiting also reasonable for patients with good response to salvage and “indolent relapses”
- Prolonged therapy seems to be associated with improved PFS
  New agents and combinations may change this

Conclusions

- Continuous treatment strategies are being evaluated in all phases of myeloma disease, from smouldering myeloma to relapsed/refractory myeloma
- Continuous therapy appeared to
  - improve response rates
  - prolong PFS/EFS; the impact on OS remains to be determined
- All novel agents appear to have benefits with longer-term use. Management of adverse events is crucial

The Continuum of Care for the Multiple Myeloma Patient

Wednesday 4 May 2011
10:30–12:30
Paris, France

13th IMW 2011 PARIS
www.myeloma-paris2011.com

A Celgene-sponsored satellite symposium
at the 13th International Myeloma Workshop

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