The Role of Maintenance Therapy in Multiple Myeloma

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Providing Extraordinary Care

Why Maintenance Therapy?

- Can maintenance therapy:
  - prevent or delay disease progression?
  - convert partial responses to complete responses?
  - improve overall survival?

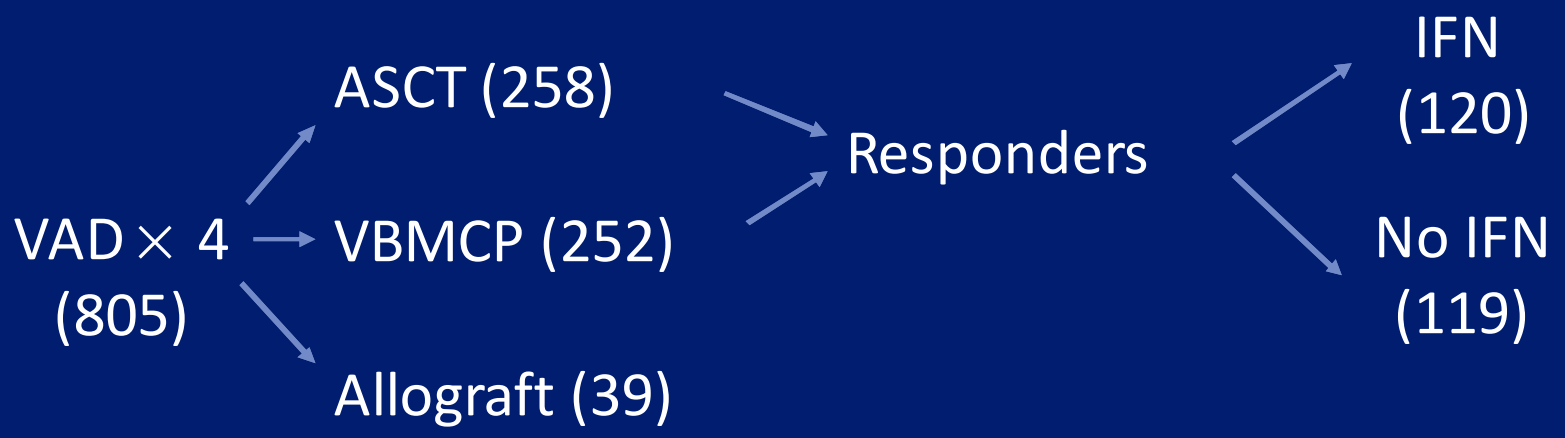
MAINTENANCE AFTER INDUCTION THERAPY

Interferon Maintenance Following Conventional Therapy

- Multiple Myeloma Trialists (Br J Haematol 2001;113:1020-34)
  - Marginal benefit for progression-free survival
- S9321 (Barlogie et al Blood 102: abstract 135, 2003)
  - No benefit in progression-free survival

Comparable Survival in MM

In study of 899 patients,
HDT (melphalan 140 mg/m2 + TBI 12 Gy) vs standard dose VBMCP



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

Comparable Survival in MM With or Without IFN

	CR	PR	PFS	OS	
ASCT	17%	93%	25 mo *P*=0.05	58 mo *P*=0.8	*P*=NS
VBMCP	15%	91%	21 mo	53 mo	
+ IFN			21 mo	58 mo	
– IFN			19 mo	79 mo	

Interferon maintenance therapy showed no benefit after conventional therapy or transplant

52% VBMCP patients had salvage ASCT→59% PR (OS 30 mo) vs 23 mo w/o ASCT(*P*=0.05)

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

Steroid Maintenance Is Beneficial Following Conventional Therapy

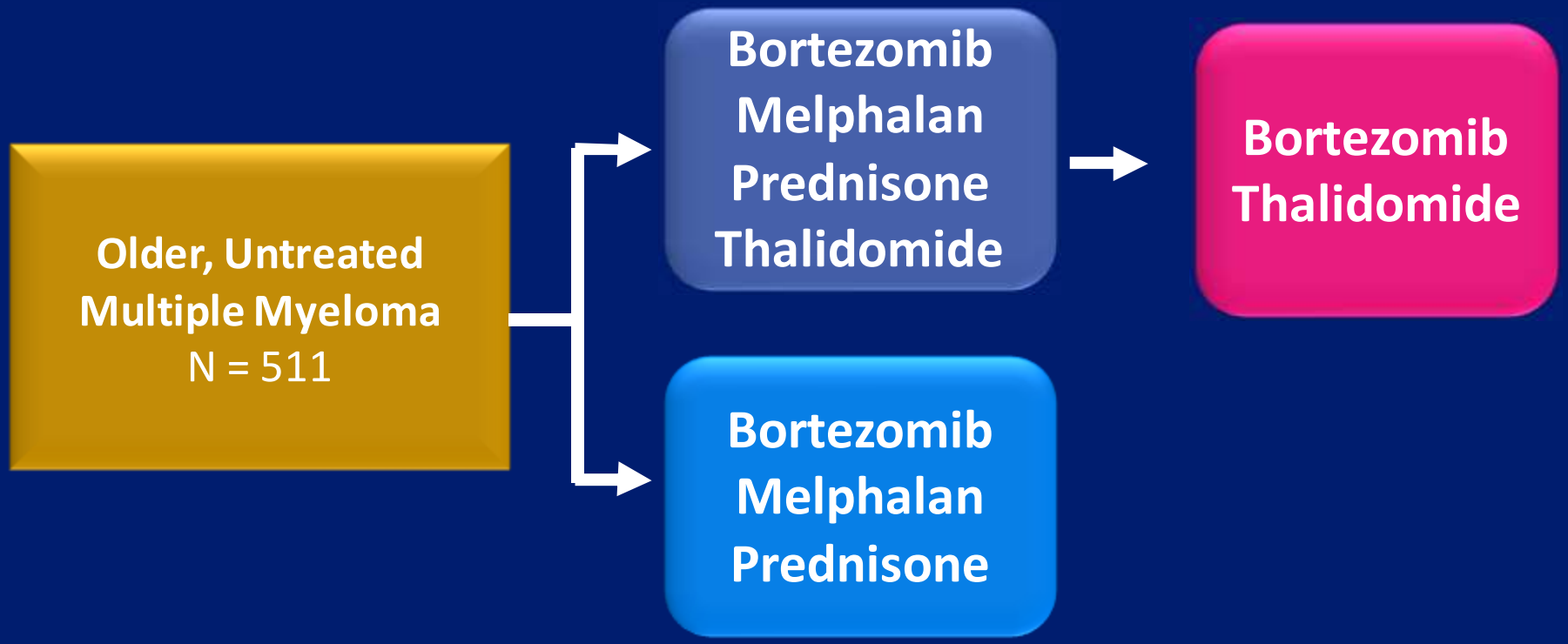
Berenson et al SWOG (Blood 99:3163-8, 2002)

- Prednisone 50 mg alternate days versus 10mg daily
- PFS 14 versus 5 months p=0.003
- OS 37 versus 26 months p=0.05

Shustik et al NCIC My7 (Br J Haematol 136:203-11, 2007.)

- Dex 40 mg x 4 days once monthly after M and P
- PFS 2.8 versus 2 years p=0.0001; no difference in OS

Phase III: VMPT versus VMP



Induction (5-wk cycle) x 9: Bortezomib 1.3 mg/m^2, d1, 8, 15, 22
Melphalan 9 mg/m^2, d1-4
Prednisone 60 mg/m^2, d1-4
Thalidomide 50 mg/d

Maintenance: Bortezomib 1.3 mg/m^2, d1, 8, 15, 22
Thalidomide 50 mg/day

Palumbo et al J Clin Oncol. 2010;28:5101-9

RESULTS

	VMP (N=253)	VMPT→VT (N=250)	P value
CR	24%	38%	0.0008
TTNT @ 3 years	60%	75%	0.0029
PFS @ 3 years	42%	60%	0.007
OS @ 3 years	89%	89%	0.96

Palumbo et al J Clin Oncol. 2010;28:5101-9

VMPT→VT vs VMP: Phase III in Previously Untreated Pts ≥65

Twice vs Once Weekly Dosing of Bortezomib

	VMP	
	2×/wk (n=63)	1×/wk (n=190)
Total planned dose	**67.6 mg/m^2**	**46.8 mg/m^2**
Total delivered dose	**41 mg/m^2**	**40 mg/m^2**
CR	**25%**	**23%**
2-year PFS	**56%**	**58%**
Any grade PN	**43%**	**21%**
Grade 3–4 PN	**14%**	**2%**
Discontinuation due to PN	**16%**	**4%**

- Safety:
  - VMPT→VT Gr 3–4 AE included (in order of higher to lower incidence) neutropenia, thrombocytopenia, infections, anemia, cardiologic, PN, DVT/PE
  - VMP Gr 3–4 AE included (in order of higher to lower incidence) neutropenia, thrombocytopenia, anemia, infections, cardiologic, PN, DVT/PE

Efficacy and Toxicity by Bortezomib schedule

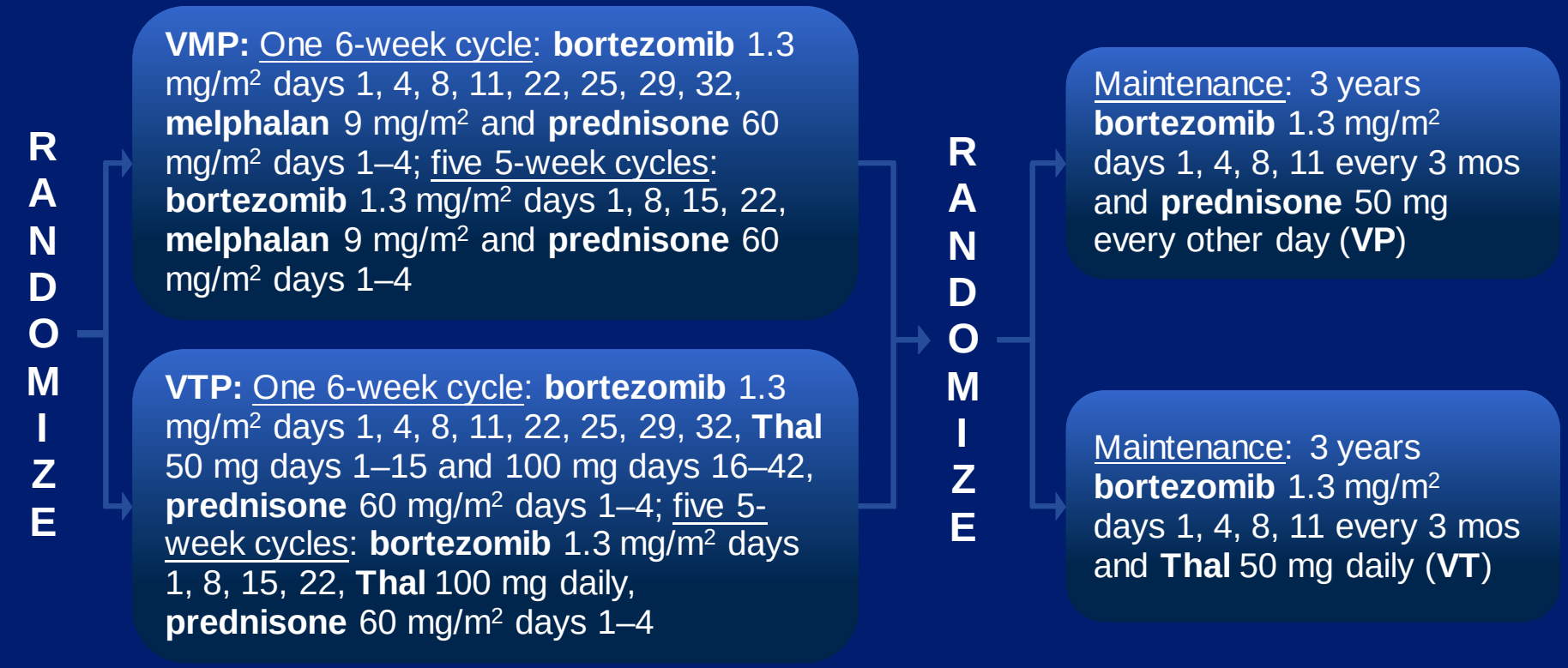
	VMP* (VISTA)	VMP twice weekly N=63°	VMP once weekly N=190°
CR	30%	25%	23%
PFS @ 2 years	48%	56%	58%
Sensory PN			
Any grade	44%	43%	21%
Grade 3-4	13%	14%	2%
PN discontinuation	NA	16%	4%
Total planned dose	67.6	67.6 mg/m^2	46.8 mg/m^2
Total delivered dose	NA	41 mg/m^2	40 mg/m^2

*San Miguel JF et al. New Eng J Med 2008; 359: 906-17; °3 patients in twice weekly and 1 patient in once weekly group are not evaluable because they never start therapy
PN: peripheral neuropathy

Phase III: VMP vs VTP in MM

Pts ≥65 Yrs

- **Endpoint:** *Primary*: post-induction ORR, CR; post-maintenance CR, toxicity; OS, PFS
- **Patients:** 260 previously untreated MM pts



Mateos M et al. Lancet Oncol. 2010;11:934-41

Phase III: VMP vs VTP in MM Pts

Response to Induction Therapy

Response*	VMP (n=130)	VTP (n=130)
CR^{IF-}	20%	27%
CR^{IF+} (nCR)	12%	10%
PR	48%	46%
ORR	**80%**	**81%**

*EBMT criteria

Clinical outcome	VMP	VTP	
PFS	34 mos	23 mos	(HR 1.3; p=0.1)
3-yr OS	80%	64%	(HR 1.4; p=0.1)

Mateos M et al. Lancet Oncol. 2010;11:934-41

Phase III: VMP vs VTP in MM Pts

- **Response to Maintenance Therapy: (n=178)**

Response (EBMT criteria)	VT (n=91)	VP (n=87)
CR^{IF-}	**44%**	**39%**
CR^{IF+} (nCR)	**15%**	**16%**
PR	**39%**	**44%**
ORR	**98%**	**99%**

Clinical outcome	VMP→ VT	VMP→ VP	VMP→ HR	VTP→ VT	VTP→ VP	VTP→ HR
Med PFS*	**NR**	**32 mos**	**1.7** ***p =0.1***	**NR**	**27 mos**	**1.7** ***p=0.1***
2-yr OS	**88%**	**88%**		**84%**	**81%**	

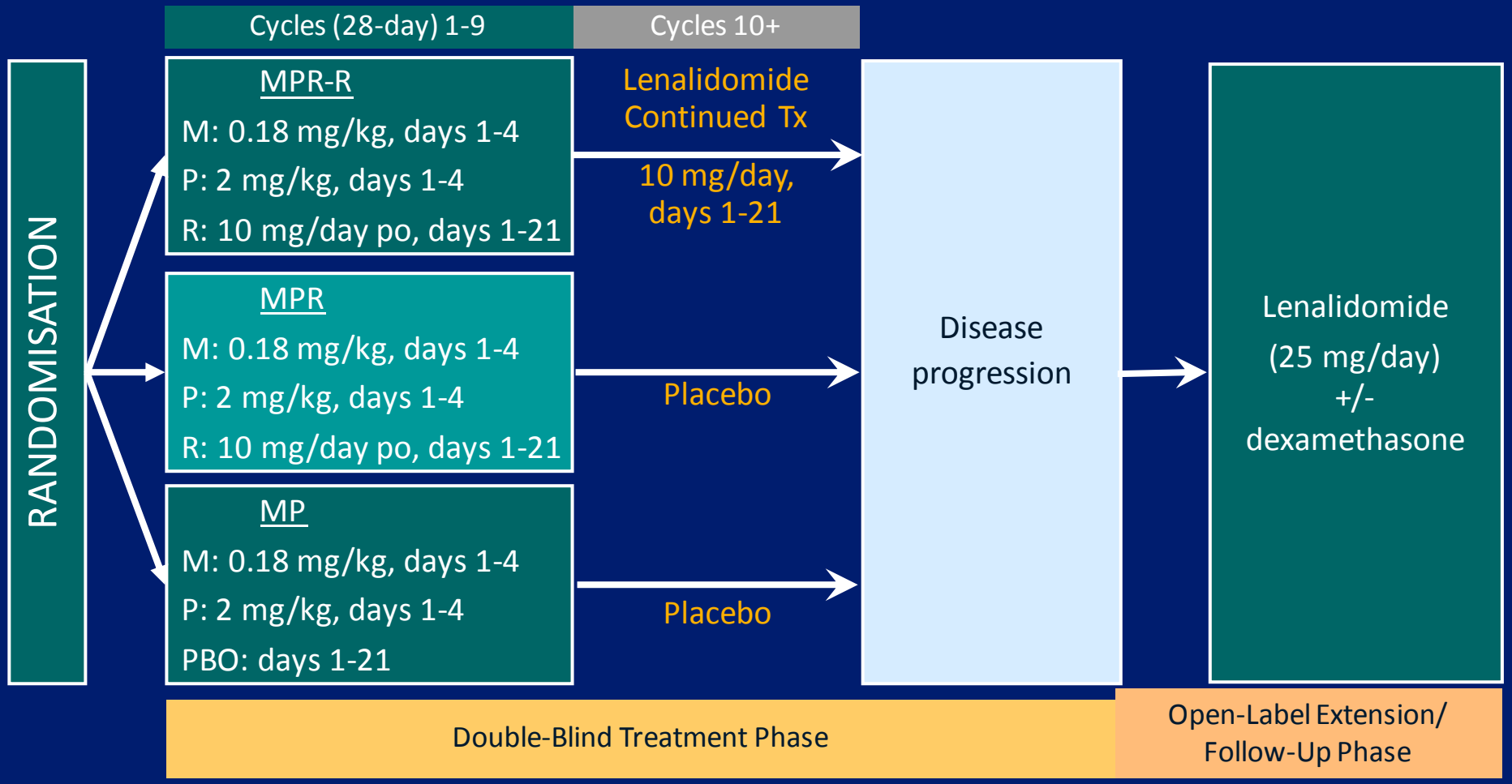
***** Median PFS for VTP → VP (27 mos) vs VMP → VT (NR): HR 1.6, p=0.008 (favoring VMP →VT)

- **Effect of Minimal Residual Disease (MRD) on Clinical Outcome:**
  - Pts without MRD (n=34) showed no progression at ~40 months follow-up vs pts with MRD (n=119) who had median TTP of 31 months (p<0.001)
  - Median OS for pts with or without MRD has not been reached; trend was significantly in favor of pts without MRD (p=0.07)

Mateos M et al. Lancet Oncol. 2010;11:934-41

Phase III Study Schema

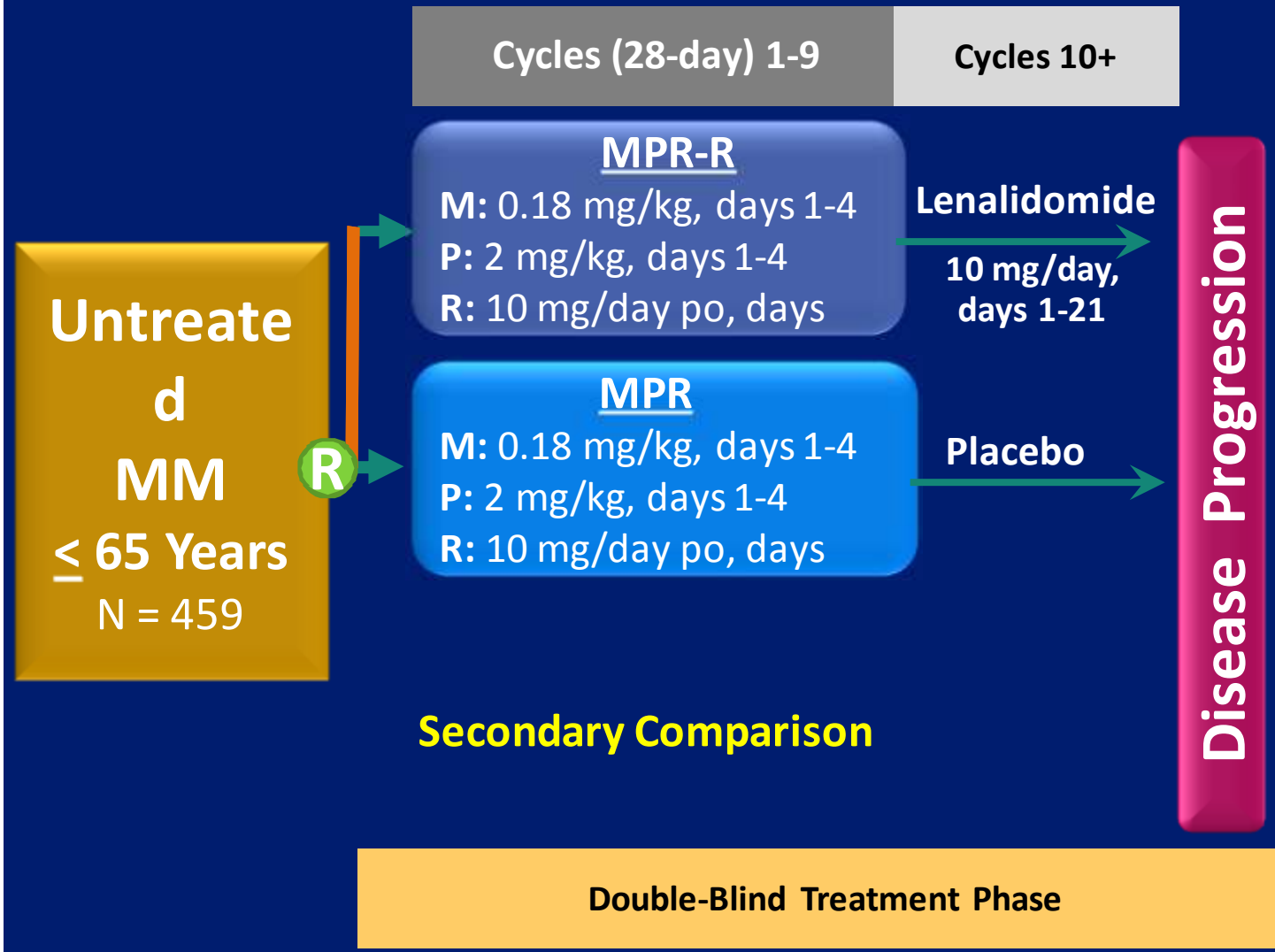
N=459, 82 centers in Europe, Australia and Israel



Stratified by age (≤ 75 vs. > 75 years) and stage (ISS 1,2 vs. 3)

M, melphalan; P, prednisone; R, lenalidomide; PBO, placebo.

MPR vs MPR + Maintenance Lenalidomide

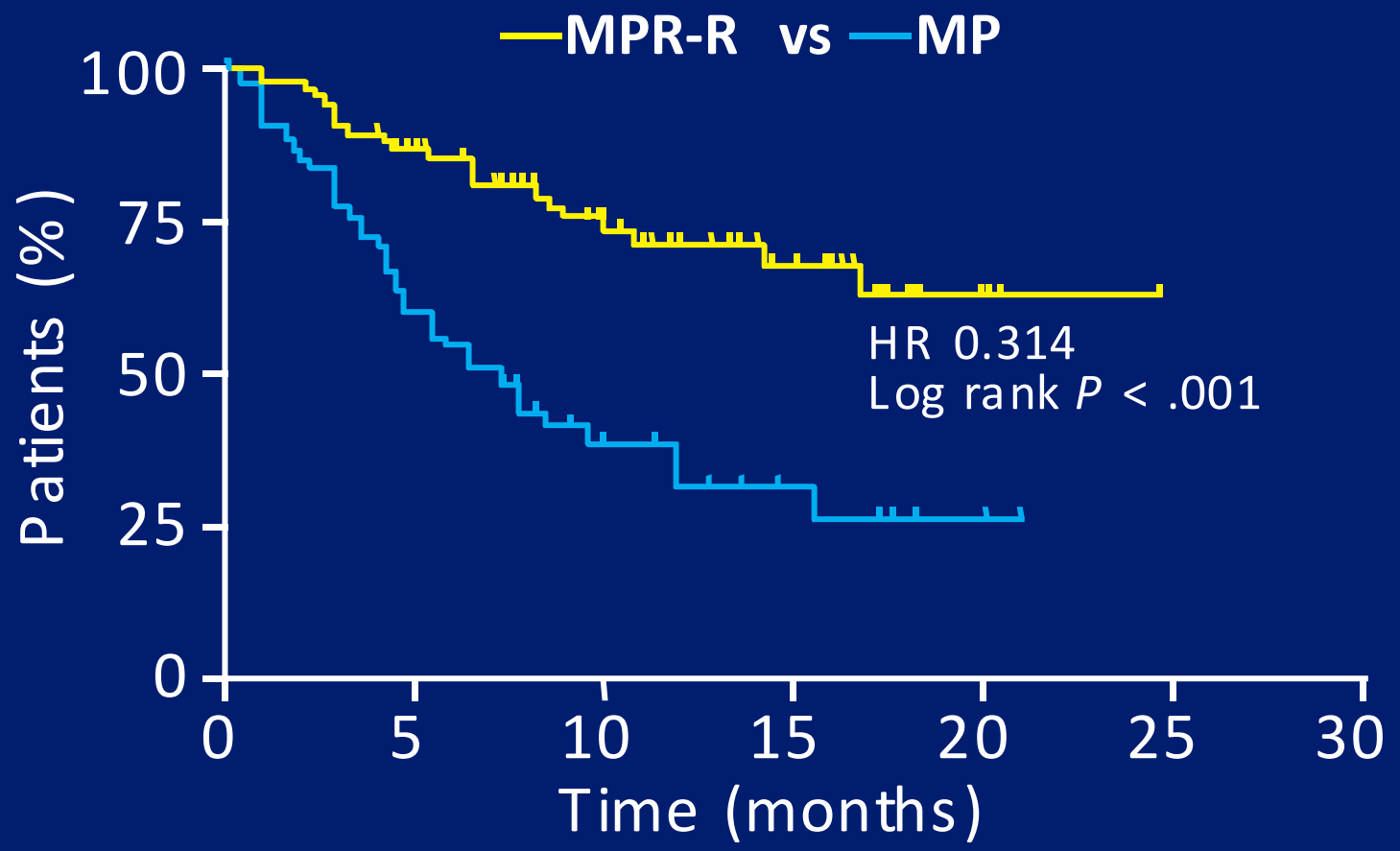


Palumbo A, et al. *Blood.* 2009;114(22). Abstract 613.

Palumbo A, et al. European Hematology Association 15th Congress. 2010. Abstract 566.

MP vs MPR-R, PFS Landmark Analysis

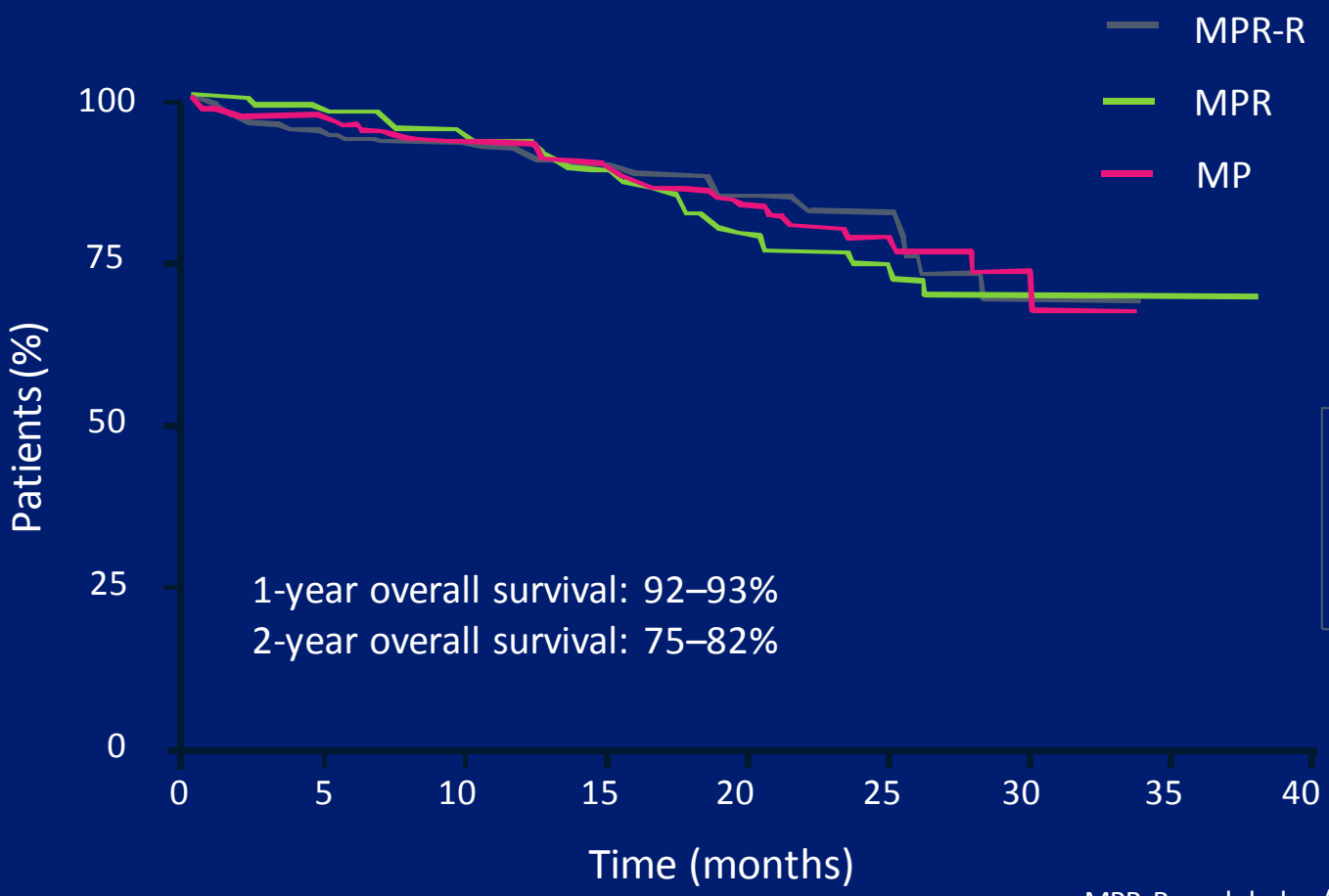
Landmark Analysis: PFS After Cycle 9



Median follow-up: 21 months

Palumbo A, et al. *Blood*. 2009;114(22). Abstract 613.
Palumbo A, et al. European Hematology Association 15th Congress. 2010. Abstract 566.

Overall Survival Is Similar After Treatment With MPR-R or MP



- Small number of events
- Median follow-up of 21 months

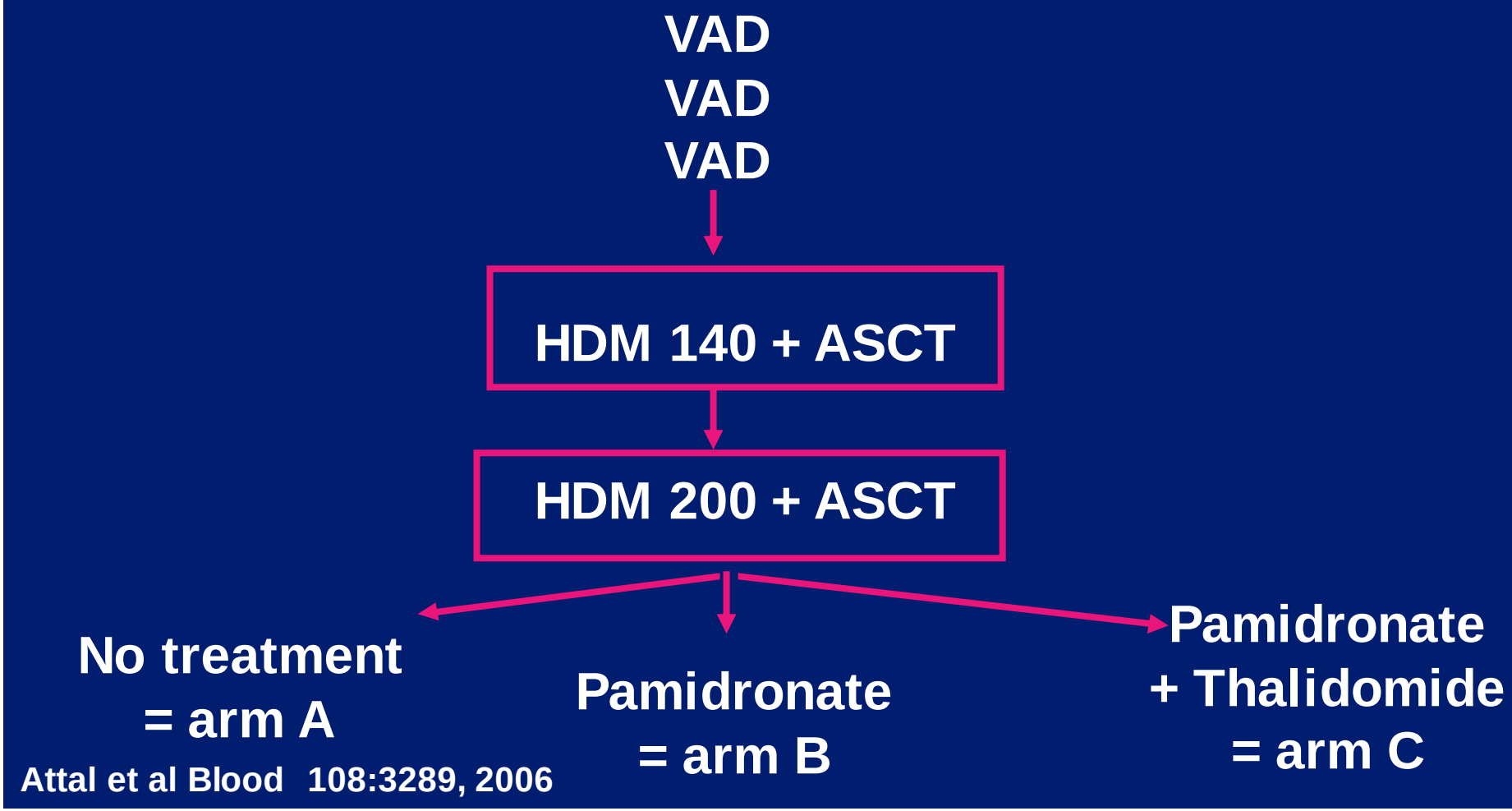
MPR-R=melphalan/prednisone/lenalidomide followed by continuous lenalidomide.
MPR=melphalan/prednisone/lenalidomide.
MP=melphalan/prednisone.

Palumbo A, et al. Blood. 2009;114(22). Abstract 613.
Palumbo A, et al. European Hematology Association 15th Congress. 2010. Abstract 566.

MAINTENANCE AFTER TRANSPLANT THERAPY

IFM 99-02

- Patients ≤ 65 years, de novo
- 0 or 1 adverse prognostic factors (chr 13 (FISH), β2M)



Attal et al Blood 108:3289, 2006

Thalidomide as Post-transplantation Maintenance Therapy

- Thalidomide is effective as maintenance therapy
  - Longer progression-free survival (PFS)
  - Significant benefits only in patients with
    - < 90% response at randomization
    - No Chr 13 deletion
    - Either β2M > 3 mg/L or < 3 mg/L

Response	No Maintenance	Pamidronate	Pamidronate + Thalidomide	*P* Value
CR or VGPR, %	55	57	67	0.001
3-year EFS, %	36	37	52	0.009
OS at 4-year, %	77	74	87	<0.04
Bone events, %	24	21	18	0.4

Attal et al. Blood. 108:3289, 2006

Thalidomide Maintenance

- Pamidronate vs Thal/Pam vs no maintenance
  - Pamidronate vs no maintenance: no difference
  - At 4 years: thalidomide improved EFS (*P* = 0.002), RFS (*P* = 0.003), OS (*P* = 0.04)
  - At 7 years: no OS advantage (*P* = 0.39)
- Total Therapy 2
  - Improved EFS, 8 year OS difference NS (*P* = 0.09)
- Myeloma IX Maintenance, Thal vs no maintenance
  - Maintenance thalidomide improved PFS in patients < VGPR
  - Non-significant trend toward improved PFS
  - No benefit in overall survival
  - Survival of patients progressing after a PR was worse with thalidomide (*P* = 0.002)
  - Patients with del(17p) had worse survival (HR = 4.55, *P* = 0.02)
    - Small cohort
- Positive thalidomide + prednisolone (Australian Study)

Attal M, et al. *Blood*. 2006;108:3290-3294. Barlogie B, et al. *J Clin Oncol*. 2009;27(15S): Abstract 8519; Morgan GJ, et al. *Blood*. 2008;112. Abstract 656. Spencer et al J Clin Oncol. 2009 ;27:1788-93

Post-Autologous Stem Cell Transplant (ASCT) Maintenance Regimens

	n	Thalidomide	CR Rate	PFS (Year)	OS (Year)
Barlogie	**668**	**400 mg Taper**	**62% vs 43%**	**5-year 56% vs 44%**	**5-year NS**
Attal	**597**	**400 mg Until progression or adverse event**	**67% vs 55%**	**4-year 52% vs 36%**	**4-year 87% vs 77%**
Abdelkefi	**195**	**100 mg 6 months**	**After 6-months 68% vs 54%**	**3-year 85% vs 57%**	**3-year 85% vs 65%**
Spencer	**243**	**200 mg 12 months**	**1-year maintenance 63% vs 40%**	**3-year 63% vs 36%**	**3-year 90% vs 81%**

- IMiDs as maintenance drugs improve progression-free survival (PFS) and overall survival (OS)

Barlogie, Tricot, et al. 2006.
Attal, et al. 2003.
Abdelkefi, et al. 2008.
Spencer, et al. 2009.

Lenalidomide Maintenance vs Placebo

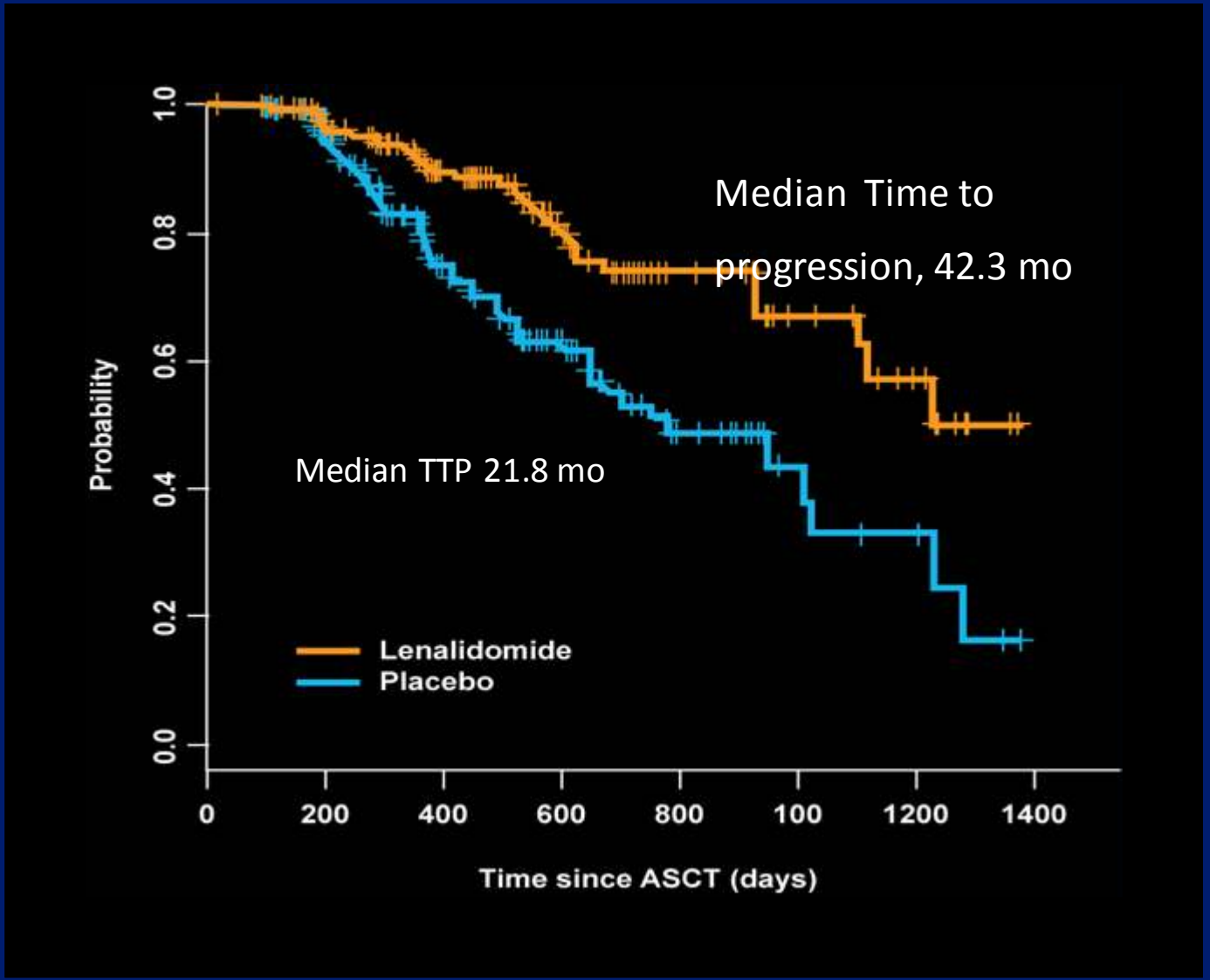
CALGB 100104

*Increased to 15 mg daily after 3 months if no toxicity.

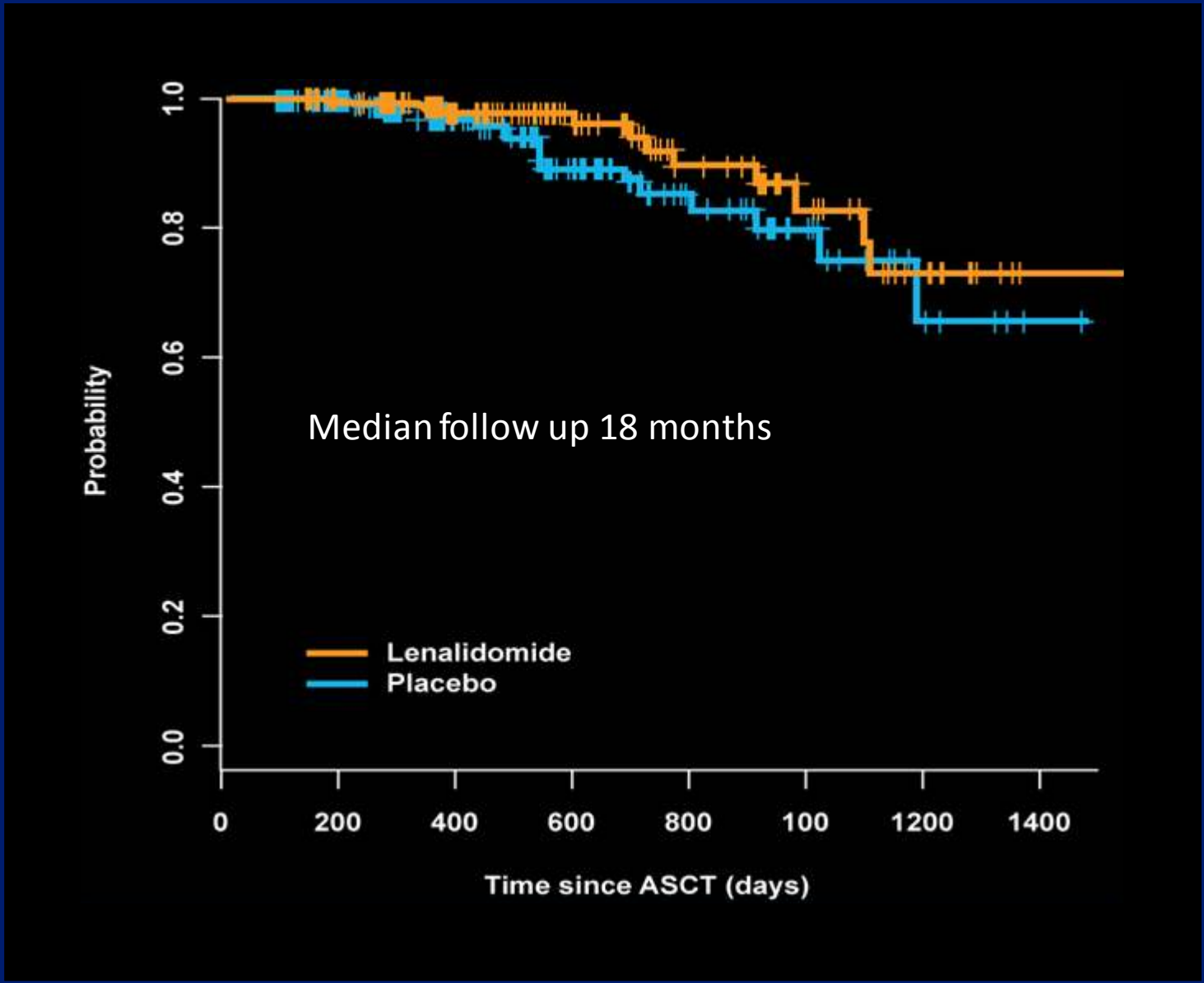
Median follow-up = 1 year

McCarthy PH, et al. *J Clin Oncol.* 2010;(15S). Abstract 8017.

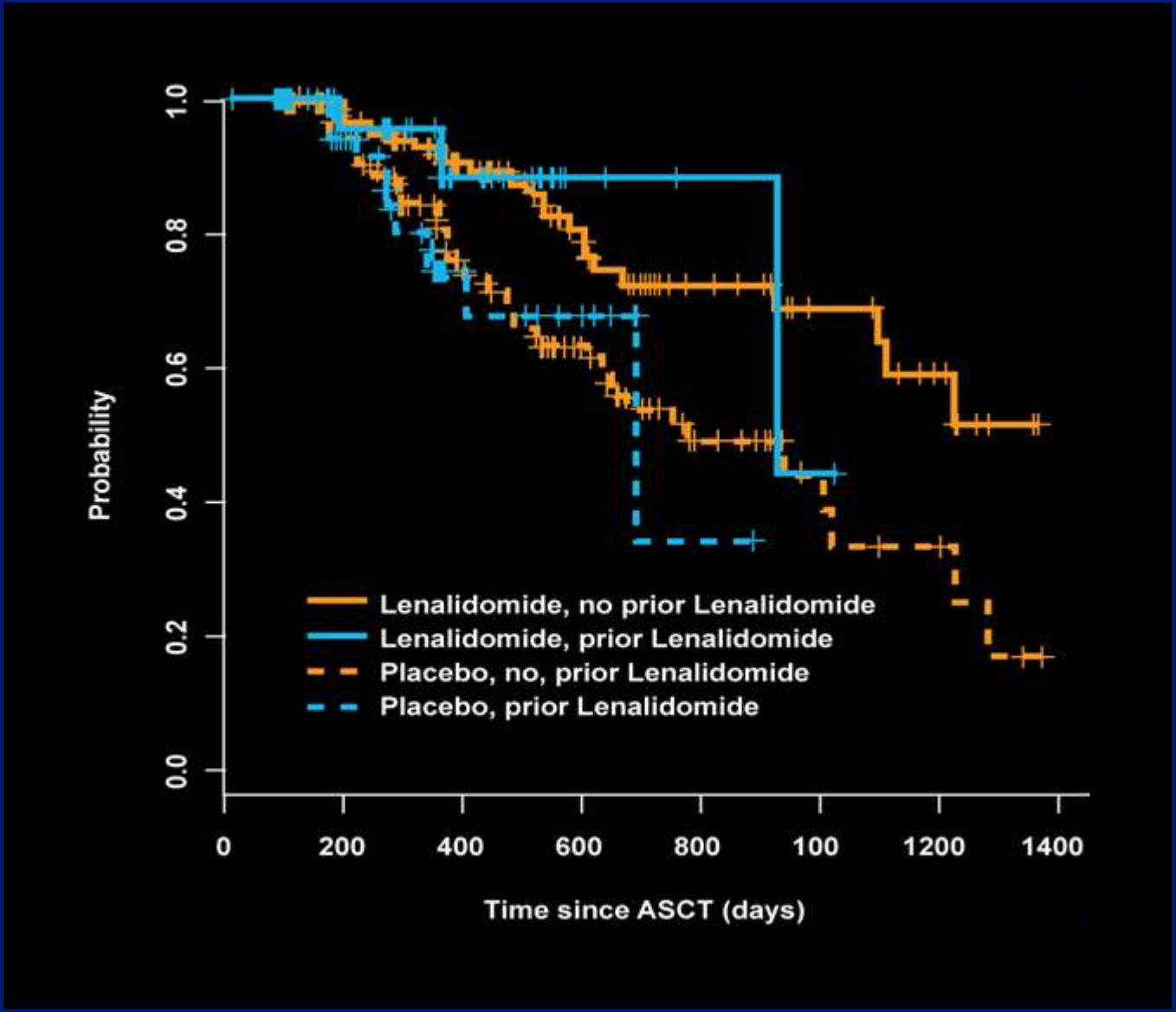
Time to Progression



Overall Survival



Time to Progression
Stratified by Arm & Prior Lenalidomide



Conclusions

- Maintenance therapy with lenalidomide when compared to placebo will significantly prolong time to disease progression
- Currently, there is no difference in OS
- Lenalidomide prolonged TTP within patient stratification by high and low β2-microglobulin, and prior thalidomide or lenalidomide induction therapy
- Lenalidomide maintenance produced some hematologic toxicity, but this was not severe with dropouts due to all AEs at 13%

IFM 2005-02: Study design

Phase III randomized, placebo-controlled trial
N= 614 patients

Patients < 65 years, with non-progressive disease, ≤6 months after ASCT in first line

Randomization: stratified according to Beta-2m, del13, VGPR

Consolidation:
Lenalidomide alone 25 mg/day p.o.
days 1-21 of every 28 days for 2 months

Arm A=
Placebo
(N=307)
until relapse

Arm B=
Lenalidomide
(N=307)
10-15 mg/d until relapse

Primary end-point: PFS.
Secondary end-points: CR rate, TTP, OS, feasibility of long-term lenalidomide….

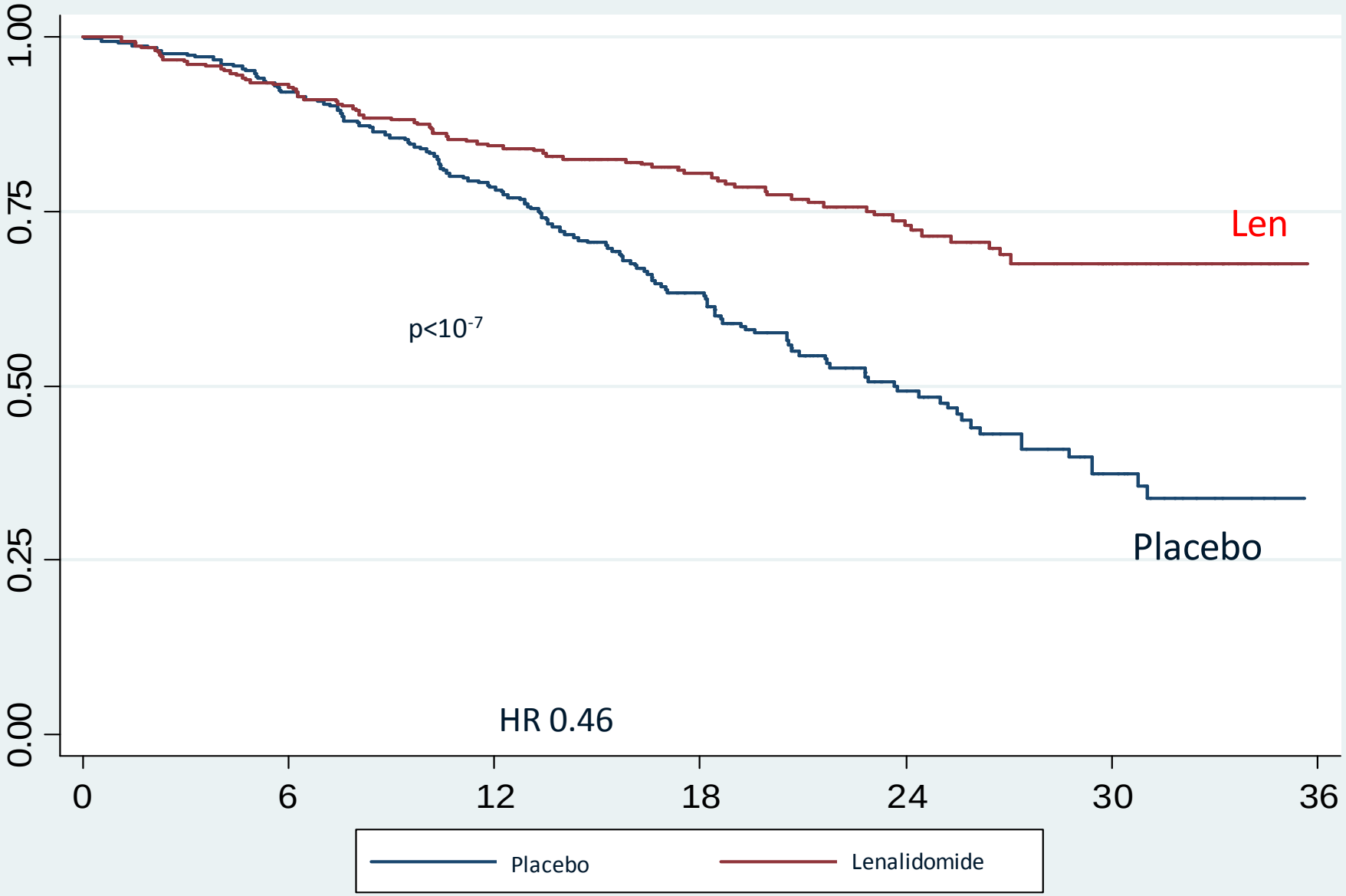
ASCT = autologous stem cell transplant. IFM = Intergroupe Francophone du Myelome.

IFM 2005 02 : Response[a] during consolidation (n= 572)

	PRE	POST	p value [b]
CR (IF -)	13 %	19 %	<0.0001
≥ VGPR	58 %	68 %	<0.0001

[a] IMW Criteria
[b] Mc Nemar test

IFM 2005-02 : PFS from randomization



IFM 2005 02 : Best Response[a] (N=614)

	Arm A (N= 307)	Arm B (N=307)	p value
CR (IF -)	22 %	25 %	0.4
≥ VGPR	70 %	77 %	0.08

[a] *IMW Criteria*

Efficacy Data from Newly Diagnosed Multiple Myeloma Studies

	Median PFS/TTP Lenalidomide Arm vs Control	Disease Progression Risk Reduction
MM-015[1]	31 vs 13 months	60% (p<0.001)
IFM 2005/02[2]	42 vs 24 months	50% (p<0.00000001)
CALGB 100104[3]	42 vs 22 months	61% (p<0.0001)

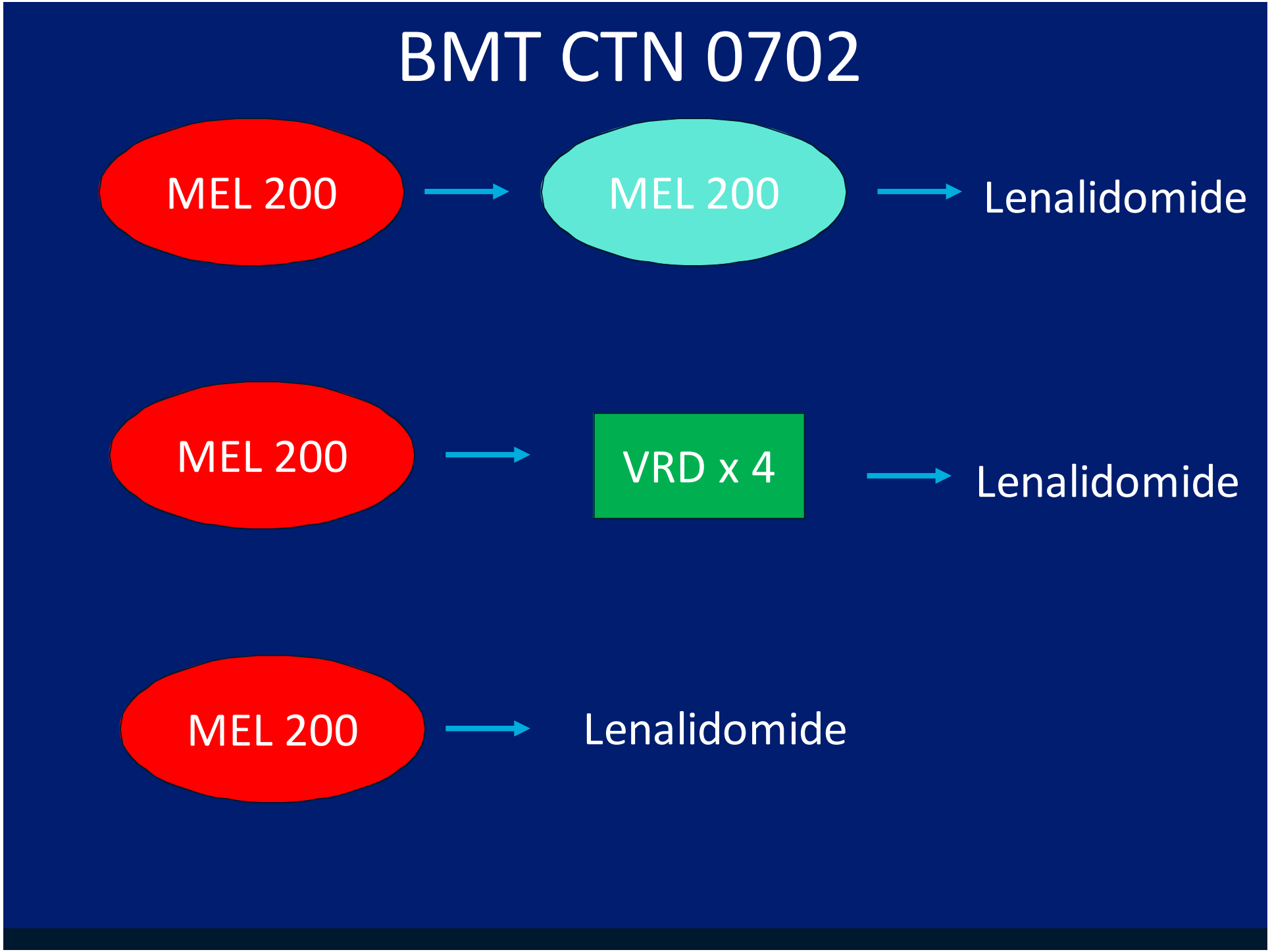
1. Palumbo et al. ASH 2010
2. Attal et al. ASH 2010
3. McCarthy et al. ASH 2010

Table 1. Second Primary Malignancies in Lenalidomide Studies in NDMM Patients

SPM	MM-015			MM-020		IFM 2005-02		CALGB 100104		TOTAL	
	MPR-R (N = 150) n (%)	MPR (N = 152) n (%)	MP (N = 153) n (%)	Len (N = 1015) n (%)	MPT (N = 511) n (%)	Len (N = 306) n (%)	PBO (N = 302) n (%)	Len (N = 231) n (%)	PBO (N = 229) n (%)	Len (N = 1854) n (%)	Control (N = 1195) n (%)
Median follow-up	2.5 years			32 weeks		3.1 years		1.6 years			
Hematologic Malignancies											
AML	4 (2.7)	2 (1.3)	0	0	1 (0.2)	2 (0.7)	2 (0.7)	4 (1.7)	0	13 (0.7)	3 (0.3)
AML from MDS	0	1 (0.7)	0	0	0	0	0	1 (0.4)	0	1 (0.05)	0
MDS	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.1)	0	3 (1.0)	0	3 (1.3)	1 (0.4)	10 (0.5)	2 (0.2)
CMML	1 (0.7)	0	0	0	0	0	0	0	0	1 (0.05)	0
T-ALL	1 (0.7)	0	0	0	0	0	0	0	0	1 (0.05)	0
B-ALL	0	0	0	0	0	2 (0.7)	0	1 (0.4)	0	3 (0.2)	0
Hodgkin's Disease	0	0	0	0	0	4 (1.3)	0	1 (0.4)	0	5 (0.3)	0
Total Hematologic Malignancies	7 (4.7)	5 (3.3)	1 (0.7)	1 (0.1)	1 (0.2)	11 (3.4)	2 (0.7)	10 (4.3)	1 (0.4)	34 (1.8)	5 (0.4)
Solid tumors	5 (3.3)	4 (2.6)	3 (2.0)	12 (1.2)	7 (1.4)	6 (2.0)	1 (0.3)	8 (3.5)	4 (1.7)	35 (1.9)	15 (1.3)
Total SPMs	**12 (8.0)**	**9 (5.9)**	**4 (2.6)**	**13 (1.3)**	**8 (1.6)**	**17 (5.6)**	**3 (1.0)**	**18 (7.8)**	**5 (2.2)**	**69 (3.7)**	**20 (1.7)**

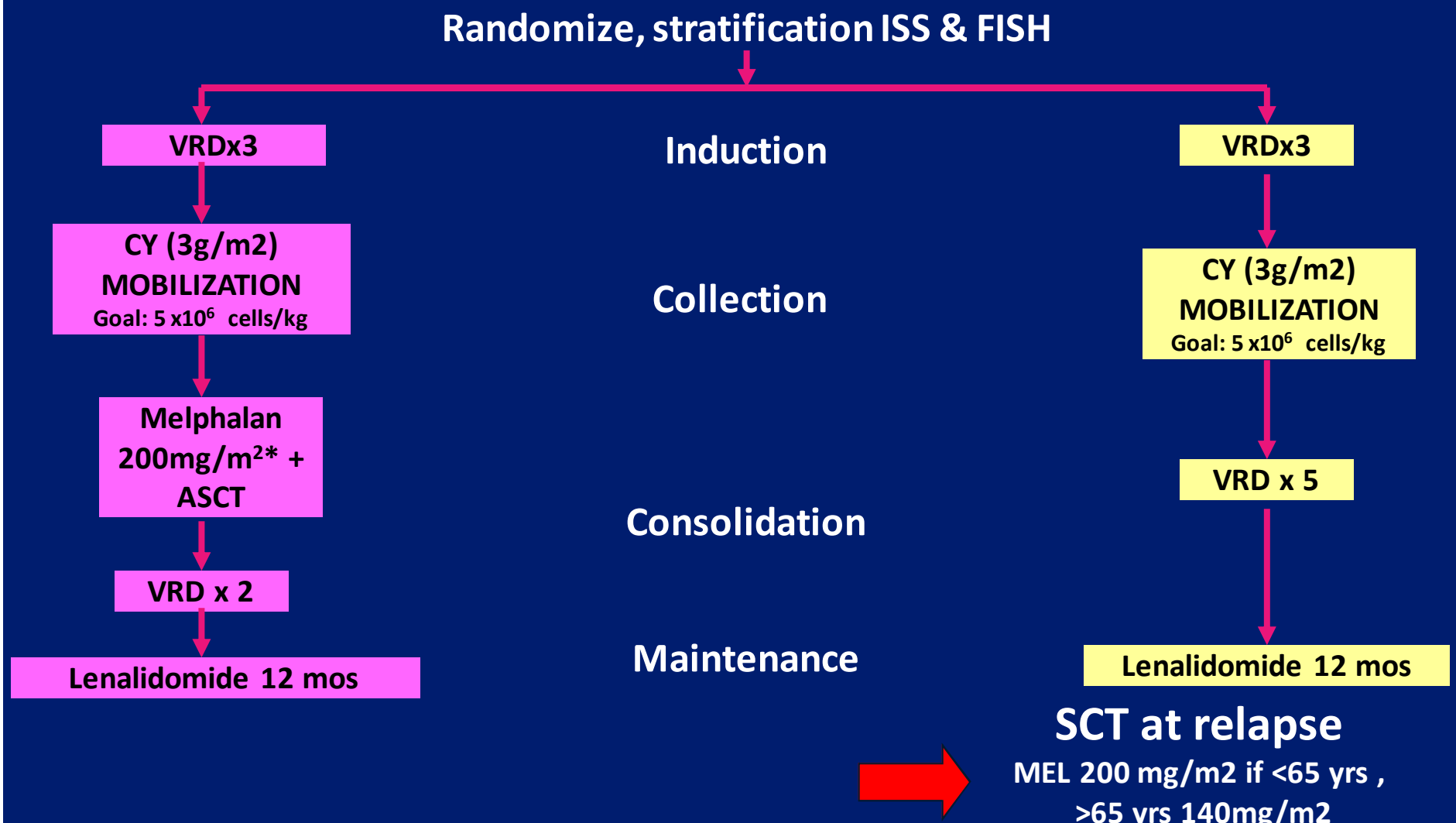
ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CALGB = Cancer and Leukemia Group B; IFM = Intergroupe Francophone du Myélome; Len = lenalidomide; MDS = myelodysplastic syndromes; MP = melphalan, prednisone; MPR = melphalan, prednisone, lenalidomide; MPR-R = melphalan, prednisone, lenalidomide followed by continuous lenalidomide until progression; MPT = melphalan, prednisone, thalidomide; NDMM = newly diagnosed multiple myeloma; PBO = placebo; SPM = second primary malignancy.

BMT CTN 0702


MEL 200
MEL 200
Lenalidomide
MEL 200
VRD x 4
Lenalidomide
MEL 200
Lenalidomide

DANA-FARBER CANCER INSTITUTE

IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)



NMSG 15/05:
Bortezomib Consolidation Post-ASCT

Initial TX
OPTIONAL

ASCT + 3 months

Eligibility: no bortezomib
Stratification: age < 60 years vs. ≥ 65 years;
single/double ASCT

Consolidation

Bortezomib 1.3 mg/m²;
Cycles 1-2: days, 1 4, 8, 11; q3 weeks
Cycles 3-6: days, 1 8, 15; q4 weeks

No Consolidation

Primary endpoint: EFS

Mellqvist et al., ASH 09; abstract 530

Bortezomib Consolidation After ASCT

- Bortezomib-naïve patients were randomized 3 months post-ASCT to 21 weeks of bortezomib or control

	Bortezomib n = 149	**Control n = 150**	***P***
CR / nCR month 3	20%	19%	0.9
CR / nCR month 9	49.3%	33.3%	0.01
Progression	6%	11.7%	0.08

- Toxicity
  - ≥ grade 3 neutropenia (22%), thrombocytopenia (9%), neurological pain (5%), sensory neuropathy (3%)

Mellqvist U, et al. *Blood*. 2009:114(22). Abstract 530.

vTD consolidation after novel agent induction

Prospective mono-center study

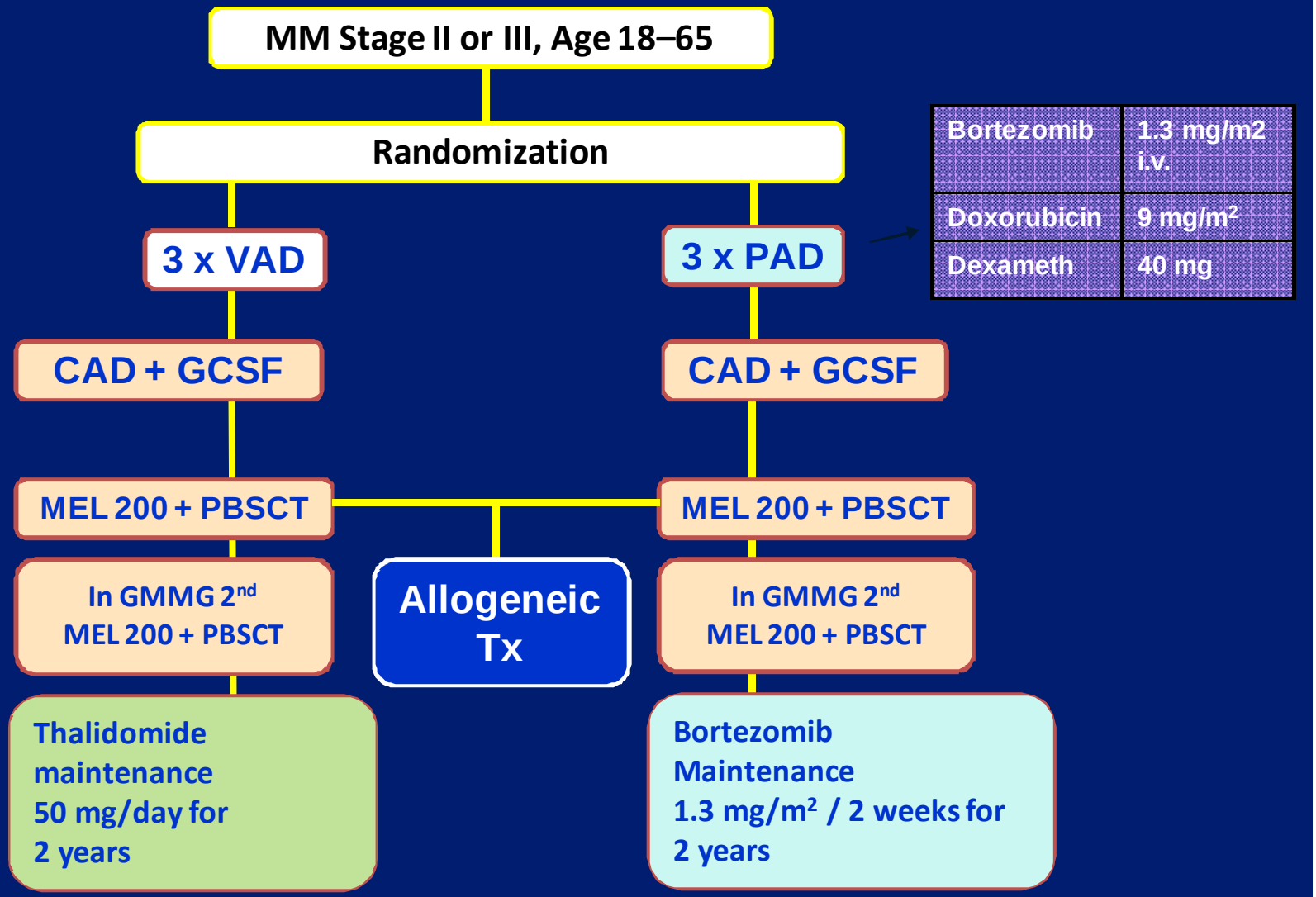
- Patients (n=46)
  - ≥PR after HDM (induction with Vel/dex [82%] or vTD [11%])
  - no ≥ grade 2 PN
- Treatment (2 cycles, started within 3 months from ASCT)
  - Bortezomib 1mg/m^2 twice weekly, Thal 100 mg/day, Dex 40 mg/day once a week
  - Results: Improvement of response in 39%

	Prior to consolidation	After vTD consolidation
CR	**23%**	**36%**
≥ nCR	**37%**	**68%**
≥ VGPR	**85%**	**91%**

  - Adverse events
    - no toxic death, no grade 3/4 hematological toxicity
    - Non-hematological toxicities: fatigue 18%, PN (all grades) 9%, pneumonia 7%, vertigo 7%, constipation 6%, DVT 4.5%

Roussel et al. ASH 2010 (Abstract 3041)

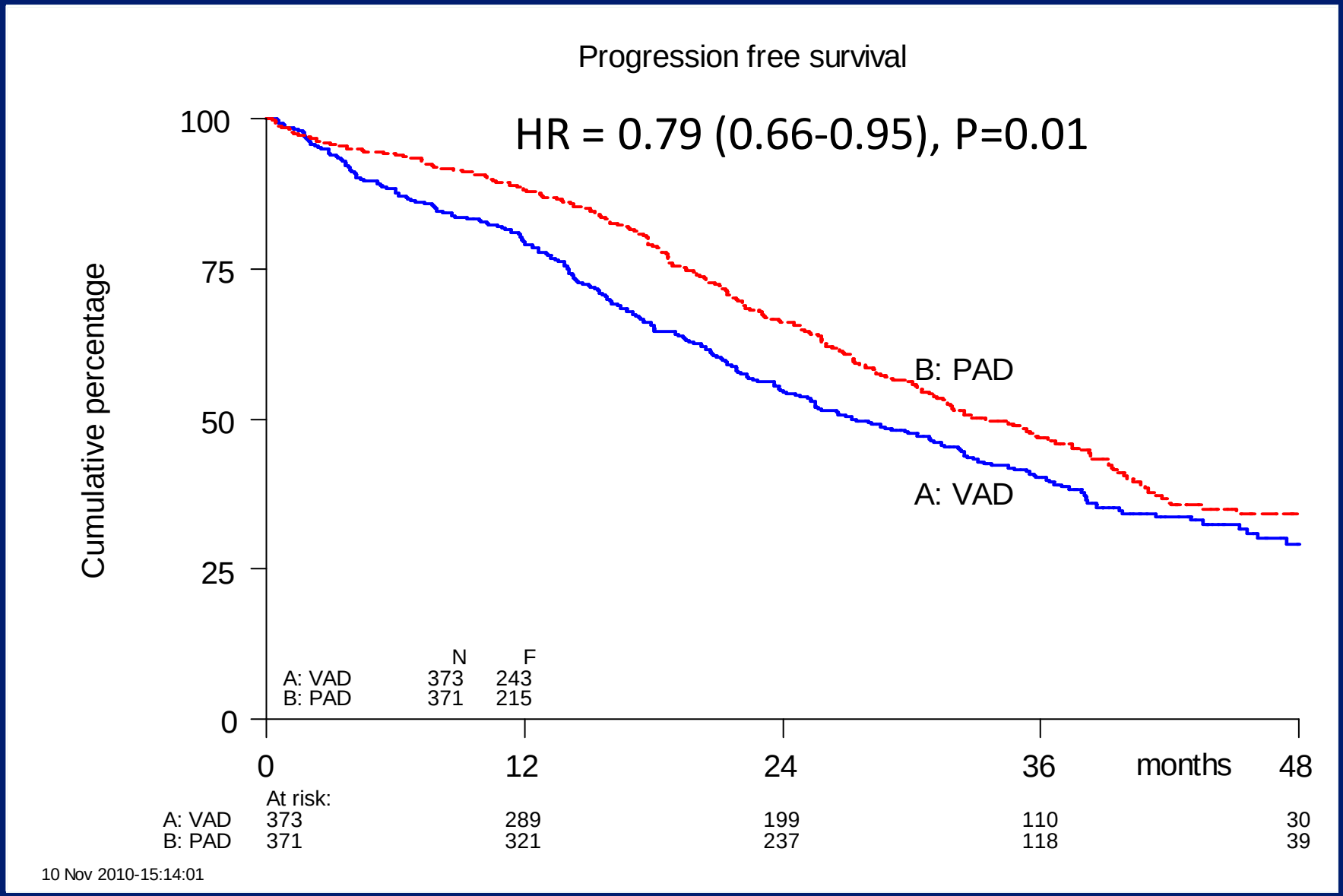
Treatment Schedule



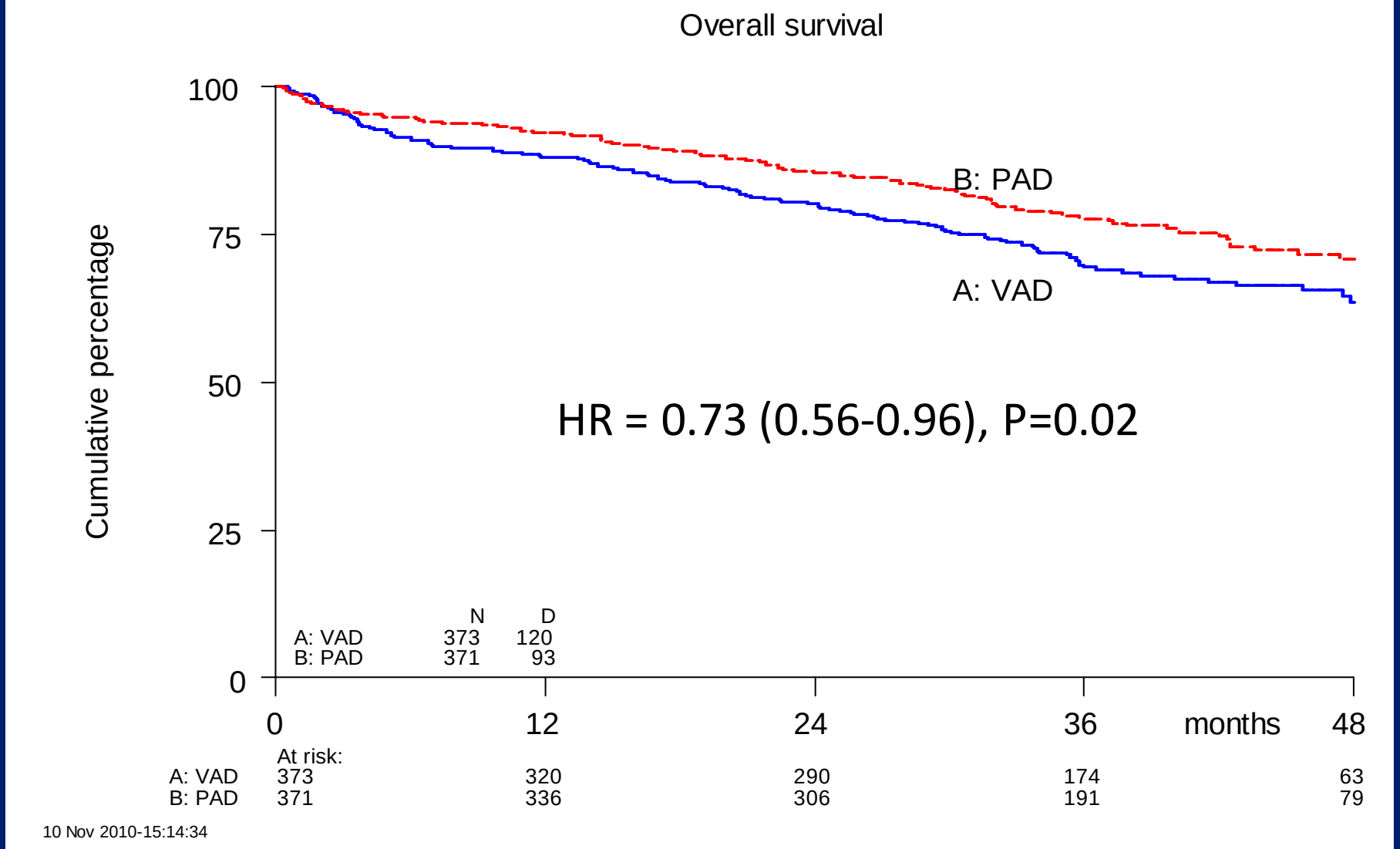
Response

	VAD arm %	PAD arm %	*P-value*
After induction			
CR/nCR	5	11	0.002
≥VGPR	15	42	<0.001
≥PR	55	78	< 0.001
After HDM 1			
CR/nCR	15	30	< 0.001
≥VGPR	36	61	<0.001
≥PR	77	88	< 0.001
On protocol			
CR/nCR	34	49	<0.001
≥VGPR	55	76	0.001
≥PR	83	91	0.003

Progression-free survival: all patients



Overall survival



Total Therapy (TT) Trials: Treatment Schema

Phase	TT1	TT2	TT3
Randomization	–	±Thal (400 mg/day)	–
Induction	VAD × 3 ↓ HDCTX ↓ EDAP	VAD ↓ DCEP ↓ CAD ↓ DCEP	VDT-DPACE ↓ VDT-DPACE
ASCT 1	MEL200	MEL200	MEL200
ASCT 2	MEL200 MEL140 + TBI if <PR	MEL200 BEAM if <PR	MEL200
Consolidation	None	DCEP/CAD	VDT-PACE
Maintenance	IFN-α	IFN-α (+ D in 1st yr)	1st yr with VTD 2nd yr with T+D

Barlogie B et al. *Blood*. 1999;93:55; Shaughnessy J Jr et al. *Br J Haematol*. 2003;120:44;
Barlogie B et al. *Blood*. 2005;106:337a [abstract 1154]

Comparison of Total Therapy Regimens

	TT1 N = 231	TT2 N = 668	TT3 N = 303
Regimen	Phase II High-dose CT w/ IFN maintenance	Phase III High-dose CT ± thalidomide w/ post-SCT consolidation	Phase II bortezomib + thalidomide throughout therapy
Median FU	15.6 years	7.2 years	3.9 years
CR rate	40%	50%	60%
Median CR duration	2.5 years	5 years	3-year estimate 90%
Median EFS	2.6 years	4.8 years	3-year estimate 80%
Median OS	5.7 years	9 years	3-year estimate 85%
Projected cure fraction	9.0%	8.5%	74% (low-risk)

Barlogie B, et al. *J Clin Oncol*. 2009;27(15S). Abstract 8519.
Barlogie B, et al. *J Clin Oncol.* 2008;26(15S). Abstract 8516.

Maintenance Therapy: Conclusions

- Improvement in PFS
  - After conventional therapy with lenalidomide and bortezomib-based therapies (Palumbo; Mateos)
  - After transplant with lenalidomide (Attal; McCarthy)
- No data on OS in any trial!
- Development of resistant clones
  - Short survival after relapse (Arkansas)
- Increase in second primary cancers after melphalan-based treatment
- COST to health care system

Lenalidomide Maintenance vs Placebo

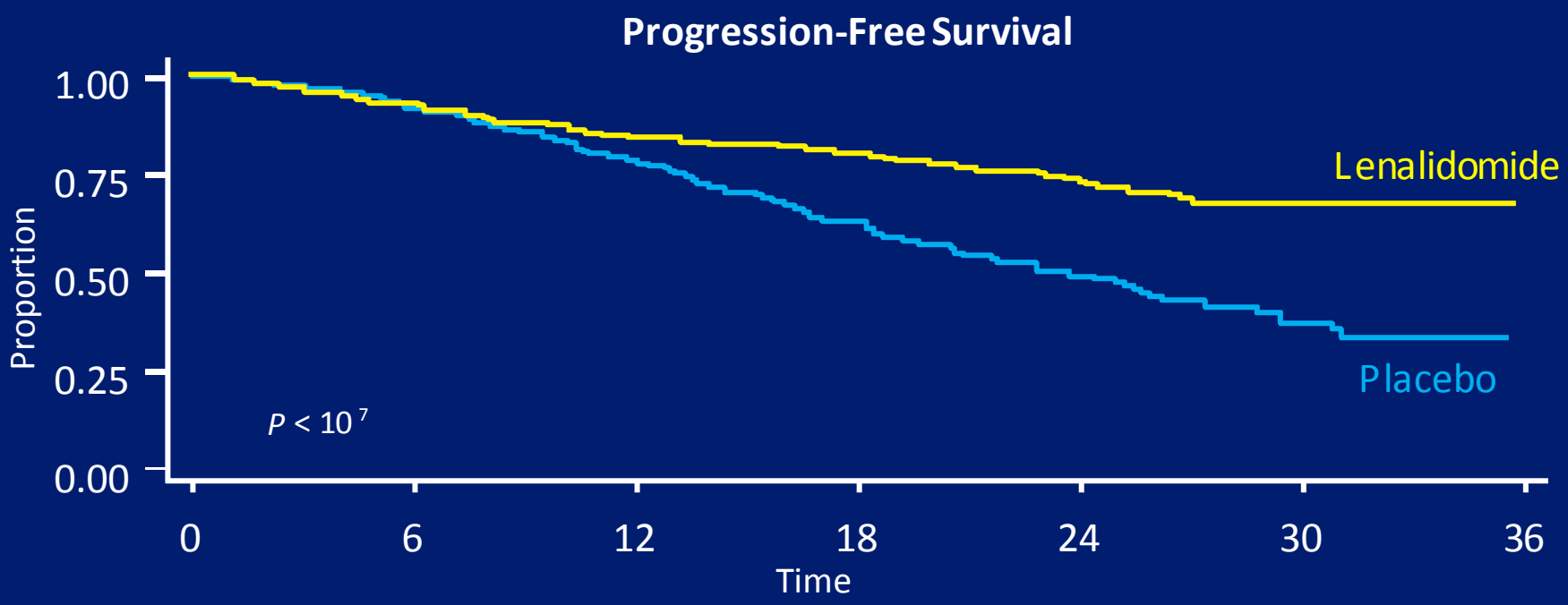
IFM 2005-02 Schema

MM
< 65 years Mp
≥ SD
≤ 6 months post ASCT
N = 614

Lenalidomide Consolidation
25 mg/d, d1-21
q 28 days x 2
N = 572

Placebo
N = 307

Lenalidomide
10 - 15 mg/day
N = 307



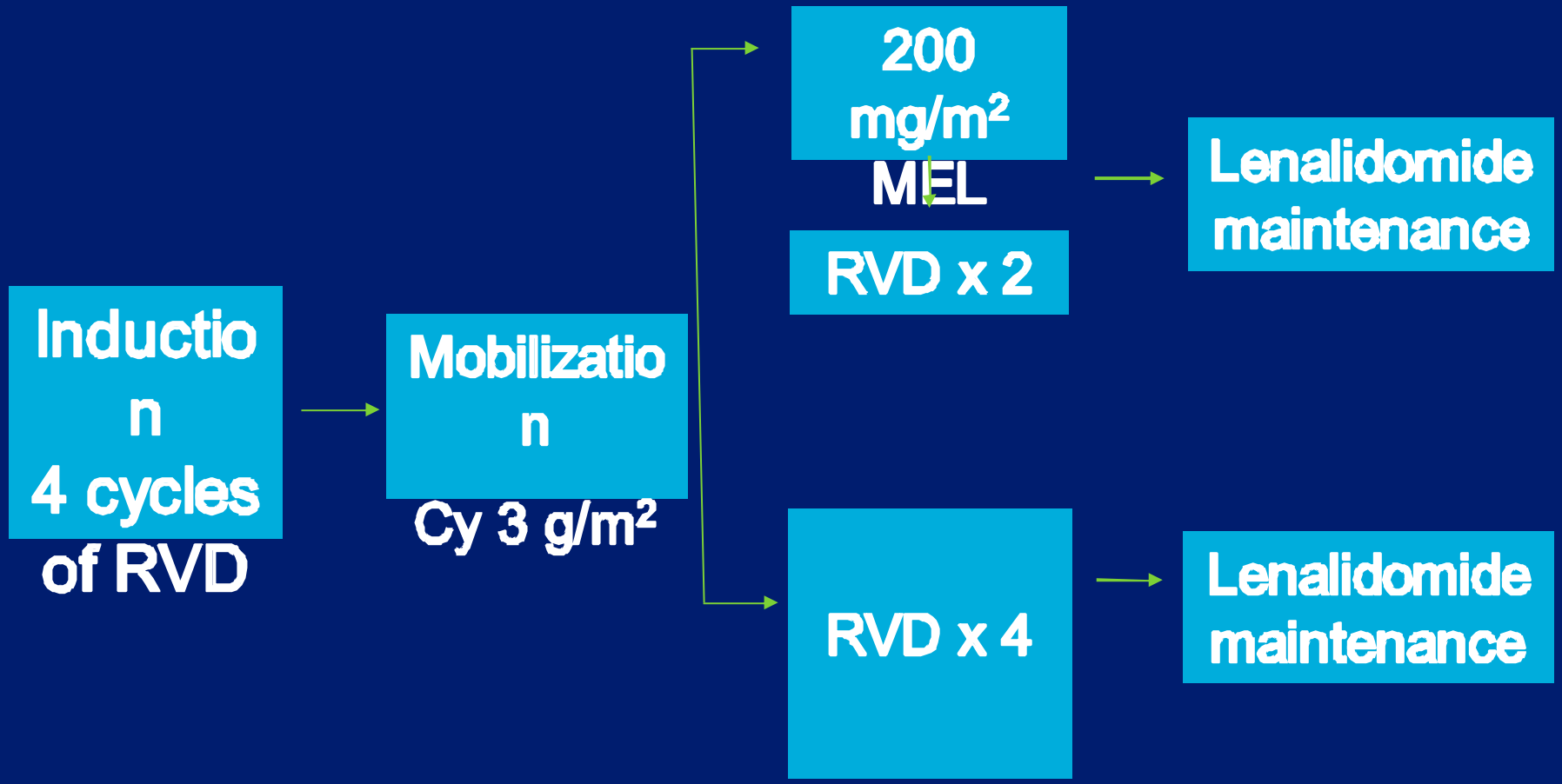
Median follow-up: 34 months post-randomization

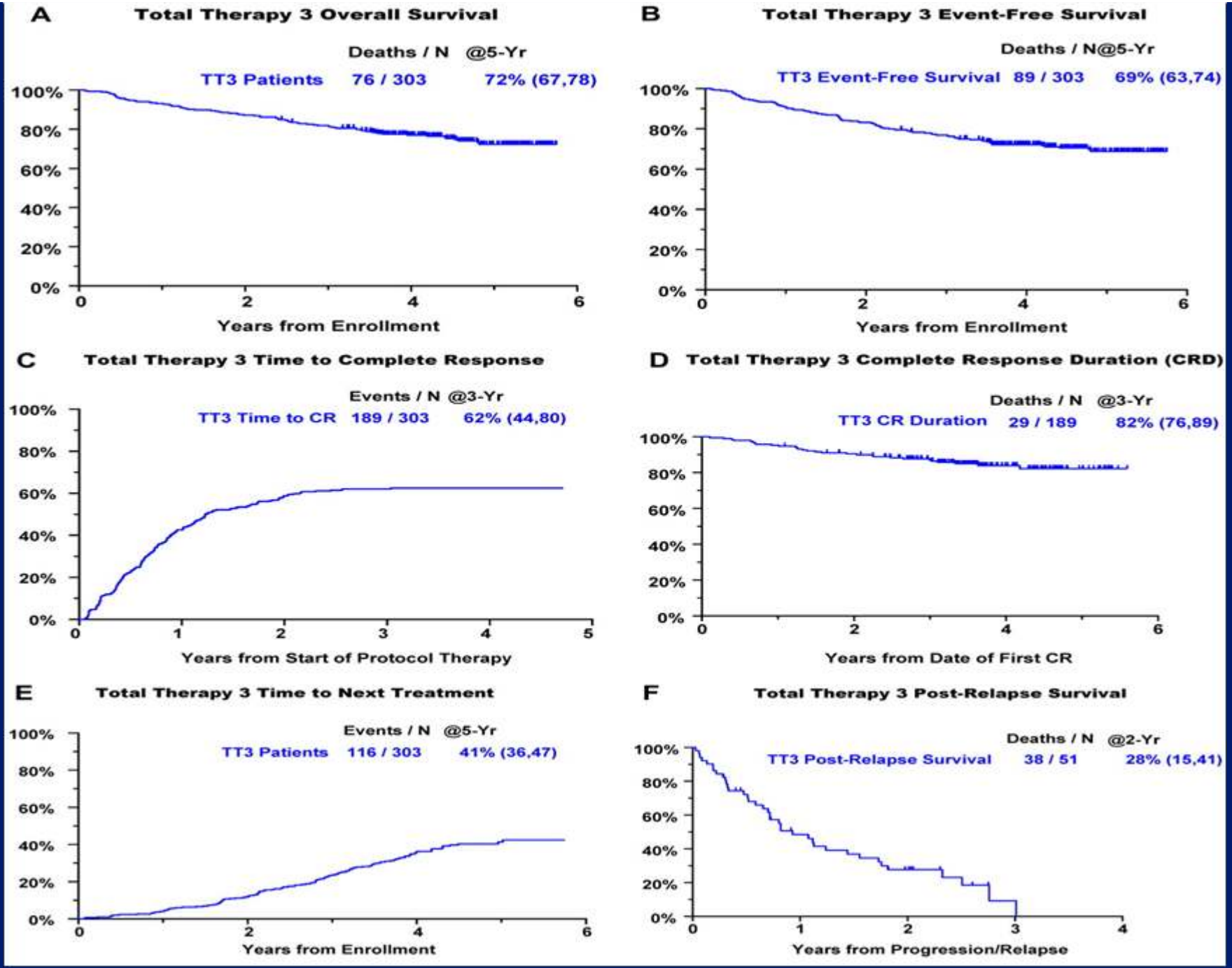
Attal M, et al. *J Clin Oncol.* 2010;(15S). Abstract 8018.

IFM 2005-02: First Interim Analysis
(Cut off date 4th September 2009)

- Maintenance therapy with Lenalidomide:
  - Is well tolerated:
    - ✓ Low discontinuation rate due to SAE (A=4%vs B=6%, NS)
    - ✓ No increased incidence of DVT or peripheral neuropathy
  - Is superior to placebo:
    - ✓ 54% reduction risk of progression ($p < 10^{-7}$)
    - ✓ In all stratified subgroups (VGPR, ß2m, del 13)
- A longer follow-up is required to appreciate the impact of Lenalidomide on OS (Final analysis: 8/2010)

IFM/DFCI Trial





van Rhee, F. et al. Blood 2010;116:1220-1227