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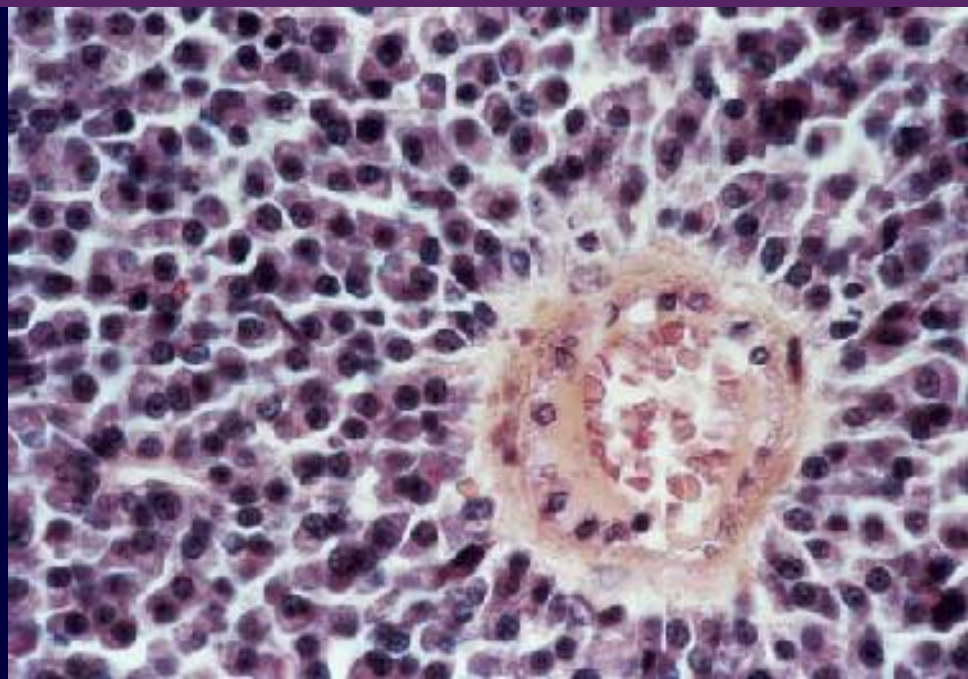
Novel Approaches and Implications for Transplantation: Understanding the Options for Frontline Multiple Myeloma



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Advances in the Frontline Treatment of Multiple Myeloma

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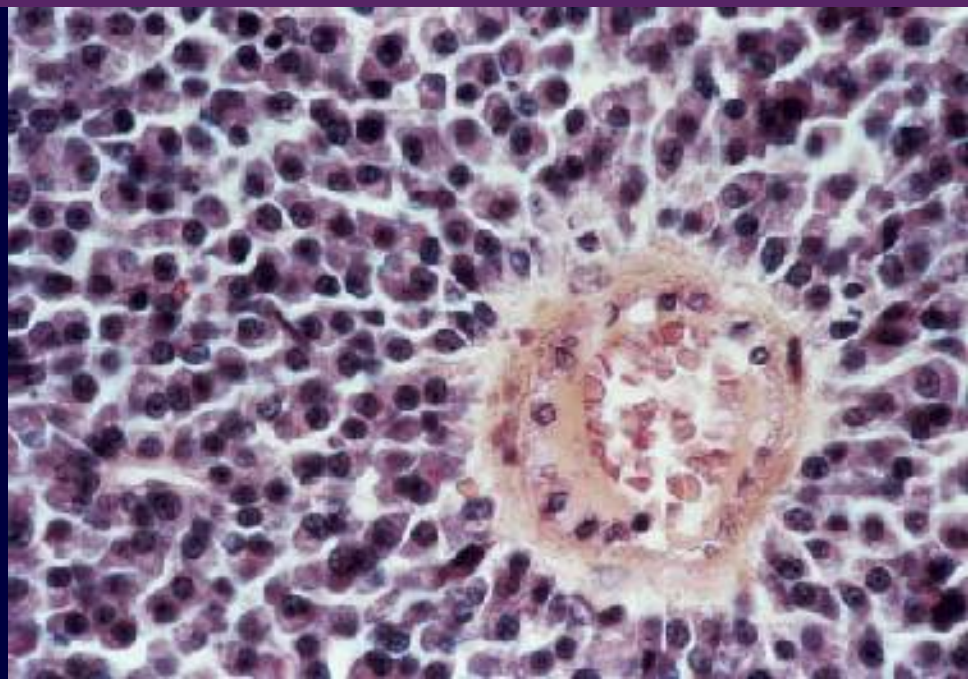

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- We are grateful to Amitabha Mazumder, MD, of St Vincent's Comprehensive Cancer Center, New York, New York, who aided in the content creation of these slides.

Multiple Myeloma: Summary of Disease Characteristics

- Malignant plasma cell disorder affecting the bone marrow
- Estimated yearly incidence: 19,900 cases
- Median age at diagnosis is older than 65 years (cutoff for transplantation)
  - Median survival: ~ 3 years
- Early-stage disease often asymptomatic; common symptoms include
  - Kidney dysfunction, pain, fatigue, recurrent infection, CNS dysfunction: subtly, neuropathy, CHF, dyspnea
  - Symptoms due to either the hyperviscosity or light chain

Diagnosis

- Confirmation of 1 major and 1 minor criterion or 3 minor criteria in symptomatic patients

Major Diagnostic Criteria	Minor Diagnostic Criteria
▪ Biopsy-proven plasmacytoma	▪ Bone marrow sample = 10% to 30% plasma cells
▪ Bone marrow sample = 30% plasma cells	▪ Minor monoclonal immunoglobulin levels in blood or urine (< 3 g/dL)
▪ Elevated monoclonal immunoglobulin levels in blood or urine	▪ Osteopenia/lytic bone lesions (confirmed through imaging studies)
	▪ Abnormally low antibody levels (not associated with malignant cells) in the blood

Multiple Myeloma Research Foundation. Available at: http://www.multiplemyeloma.org/about_myeloma/2.06.asp.

Myeloma Classification

<table>
<tr><th colspan="2">Monoclonal Gammopathy of Undetermined Significance</th></tr>
<tr><td colspan="2">▪Serum M-protein < 3 g/dL</td></tr>
<tr><td colspan="2">▪Bone marrow plasma cells < 10%</td></tr>
<tr><td colspan="2">▪ Absence of anemia, renal failure, hypercalcemia, lytic bone lesions</td></tr>
<tr><th colspan="2">Asymptomatic Multiple Myeloma</th></tr>
<tr><th>Smoldering Multiple Myeloma</th><th>Indolent Multiple Myeloma</th></tr>
<tr><td>▪ Serum M-protein > 3 g/dL and/or bone marrow plasma cells ≥ 10%</td><td>▪Bone marrow plasmacytosis</td></tr>
<tr><td>▪ No anemia, renal failure, hypercalcemia, lytic bone lesions</td><td>▪Mild anemia or few small lytic bone lesions</td></tr>
<tr><td rowspan="2">▪ Stable serum/urine M-protein</td><td>▪No symptoms</td></tr>
<tr><td>▪Presence of serum/urine M-protein</td></tr>
<tr><th colspan="2">Symptomatic Multiple Myeloma</th></tr>
<tr><td colspan="2">▪Bone marrow plasmacytosis (> 10%)</td></tr>
<tr><td colspan="2">▪Anemia, renal failure, hypercalcemia, or lytic bone lesions</td></tr>
</table>

Multiple Myeloma Research Foundation. Available at: http://www.multiplemyeloma.org/about_myeloma/2.06.asp.

Staging

- Durie-Salmon system: widely used since 1975
  - Stage based on M-protein levels, bone lesions, Hb values, serum calcium—many variables
- International Staging System
  - Simplified staging based on serum β_2-microglobulin

Stage	International Staging System Criteria
I	β_2-microglobulin < 3.5; albumin ≥ 3.5
II	Neither stage I nor stage III values
III	β_2-microglobulin > 5.5

Durie BG, et al. Cancer. 1975;36:842-854.
Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

Multiple Myeloma: High-Risk Features

- High-risk genetic factors
  - t(4;14) and t(14;16) translocations
  - del(13q) and del(17p) chromosomal abnormalities
  - Hypoploidy
- Other factors conferring high risk in myeloma
  - 75 years of age or older
  - Elevated β_2-microglobulin level
  - High plasma cell labeling index
  - Elevated creatinine level

Myeloma: Current Standards of Care

- Only symptomatic patients need treatment
- Initial treatment of patients younger than 65 years of age, good organ function
  - High-dose chemotherapy, autologous SCT; median OS: 54 months[1]
  - Older patients unlikely candidates for SCT
- Other active therapies in frontline setting
  - Alkylators: cyclophosphamide, melphalan
  - Corticosteroids: dexamethasone, prednisone
  - Immunomodulating agents: thal, lenalidomide
  - Proteasome inhibitors: bortezomib
  - Anthracyclines: doxorubicin, pegylated liposomal doxorubicin

1. Child JA, et al. N Engl J Med. 2003;348:1875-1883.

International Myeloma Working Group Uniform Response Criteria

- CR
  - Negative immunofixation (serum and urine), disappearance of soft tissue plasmacytomas, ≤ 5% plasma cells in bone marrow
  - Stringent CR: < 1% clonal plasma cells and normalization of free light chain ratio (serum free light chain assay)
- VGPR
  - > 90% reduction in serum M-protein
  - Urine M-protein level < 100 mg per 24 hours
- PR
  - ≥ 50% reduction in serum M-protein or plasma cells (if bone marrow plasma cell percentage ≥ 30%)
  - If present at baseline, ≥ 50% reduction in soft tissue plasmacytomas

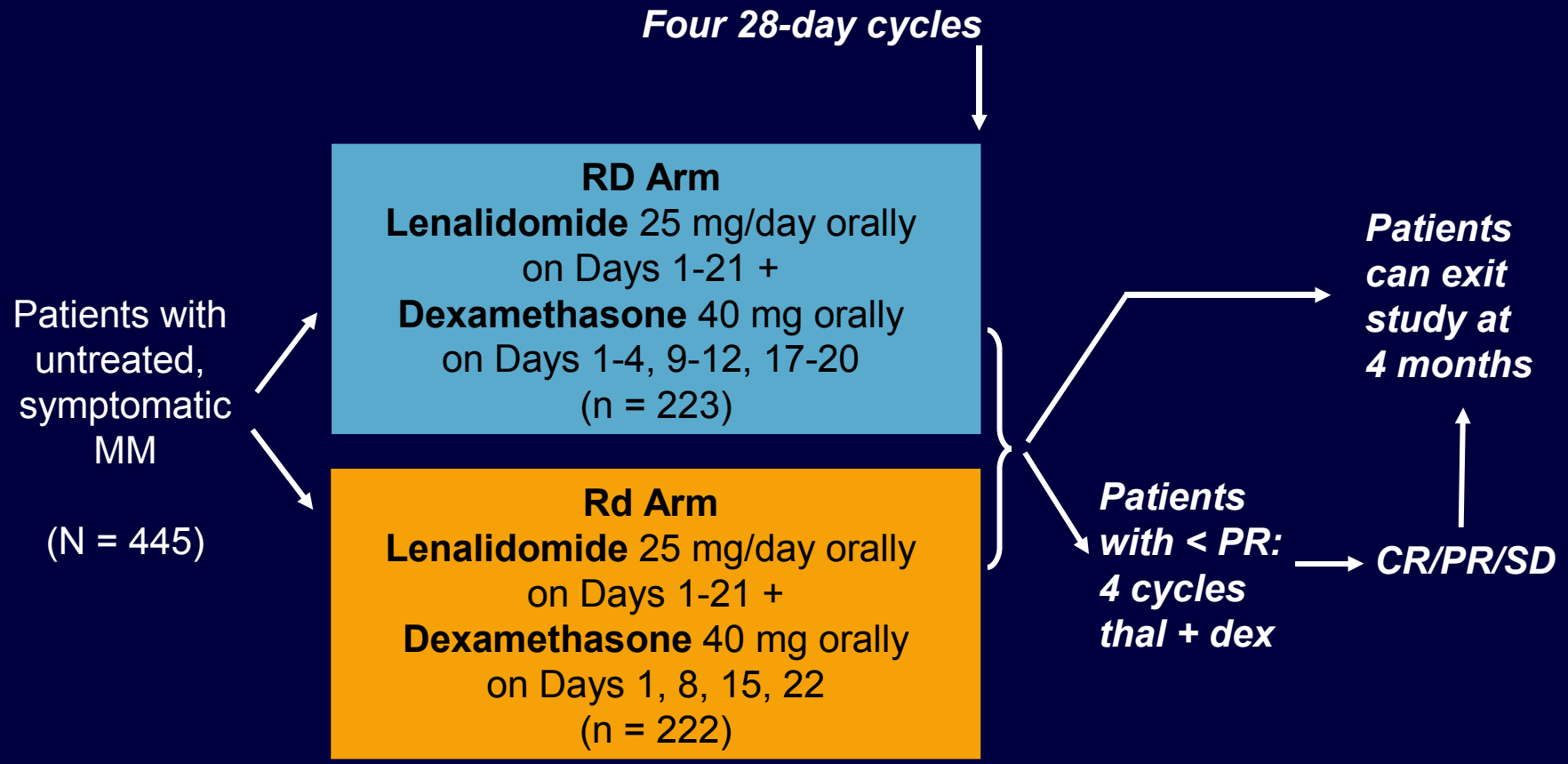
Durie BGM, et al. Leukemia. 2006;20:1467-1473.

Treatment of Multiple Myeloma: Unanswered Questions

- Optimal induction regimen
  - Combinations of active therapies
  - Bortezomib plus dexamethasone or pegylated liposomal doxorubicin
  - Lenalidomide plus dexamethasone or MP
- The emerging role of maintenance
- Transplantation issues: Is delayed second transplantation feasible? Is transplantation necessary for patients in CR?
- Relapsed and/or refractory disease: combinations of various active therapies being investigated
- Evolving role of free light chain

Frontline Therapy: Transplantation Candidates

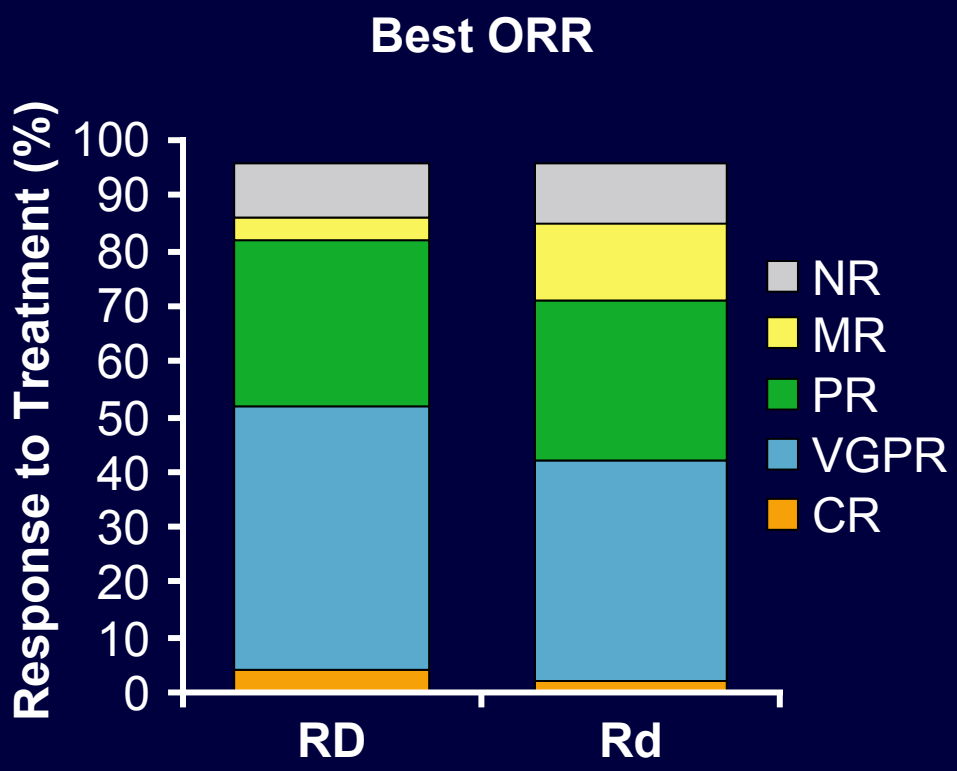
ECOG (E4A03): Lenalidomide + High- or Low-Dose Dex in Newly Diagnosed MM



Rajkumar SV, et al. ASH 2007. Abstract 74.

ECOG (E4A03): Response

- Not designed to evaluate long-term outcomes
  - Primary endpoint: rate of response at 4 months
- Lower RR in Rd arm vs RD arm, but within 15% limit of clinical equivalence
  - CR + VGPR rate 52% f or Rd vs 42% for RD (P = .06)



Rajkumar SV, et al. ASH 2007. Abstract 74.

ECOG (E4A03): Survival, RD vs Rd

- OS superior in Rd arm

Parameter, %	RD (n = 214)	Rd (n = 207)	*P* Value
12-mo OS			
▪ All patients	88	96	.005
▪ < 65 yrs old	97	92	.13
▪ ≥ 65 yrs old	95	84	.01
24-mo OS			
▪ All patients	78	88	.007

- RD associated with more deaths < 4 months: 5.0% vs 0.5% (*P* = .01)
  - Primarily in those older than 65 years of age
  - Due to both disease progression and toxicity

Rajkumar SV, et al. ASH 2007. Abstract 74.
Rajkumar SV, et al. ASCO 2008. Abstract 8504

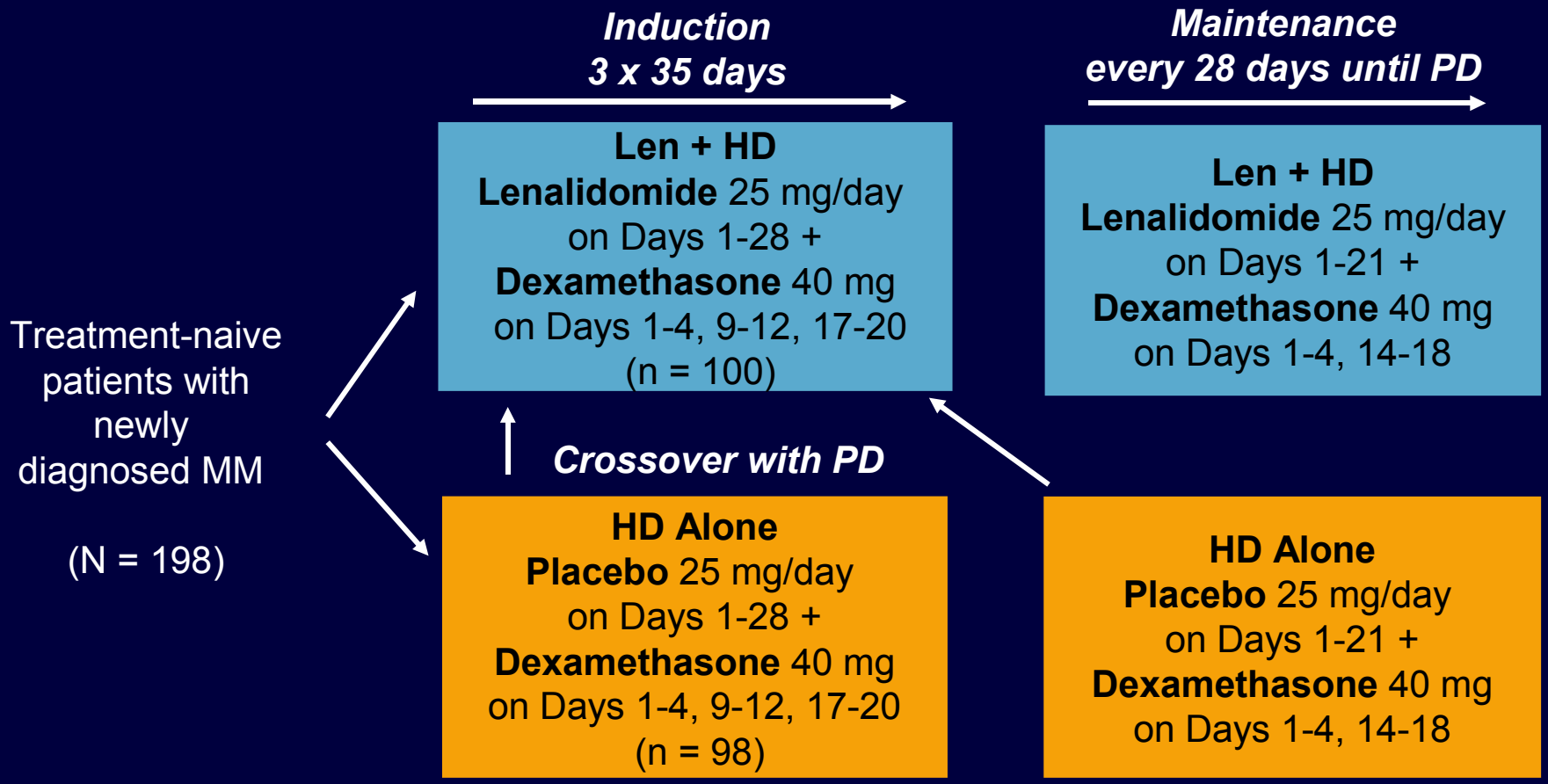
ECOG (E4A03): Landmark Analysis

- SCT after primary therapy dramatically improved OS compared with no therapy
- Continued Rd achieved similar OS to ASCT

2-Yr OS, %	RD	Rd
Off chemotherapy after primary study		
▪ No SCT	72	69
▪ SCT	94	92
Continued chemotherapy after primary study		
▪ RD	82	--
▪ Rd	--	93

Rajkumar SV, et al. ASCO 2008. Abstract 8504

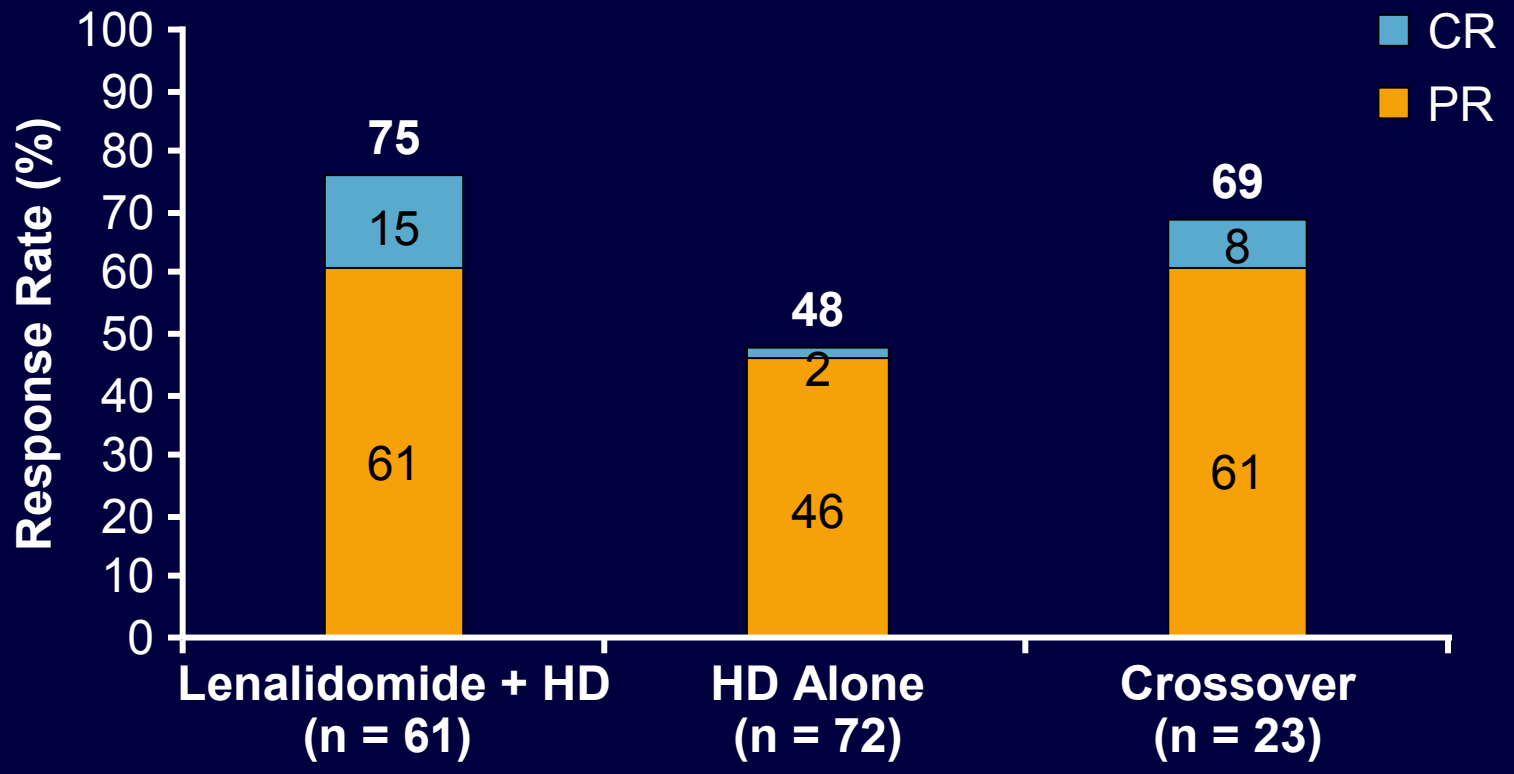
Lenalidomide + HD vs HD Alone in Newly Diagnosed MM (SWOG S0232)



Zonder JA, et al. ASH 2007. Abstract 77.

Lenalidomide + HD vs HD (SWOG S0232): Response by IMWG Criteria

- ORR higher in lenalidomide + HD arm (*P* = .001)



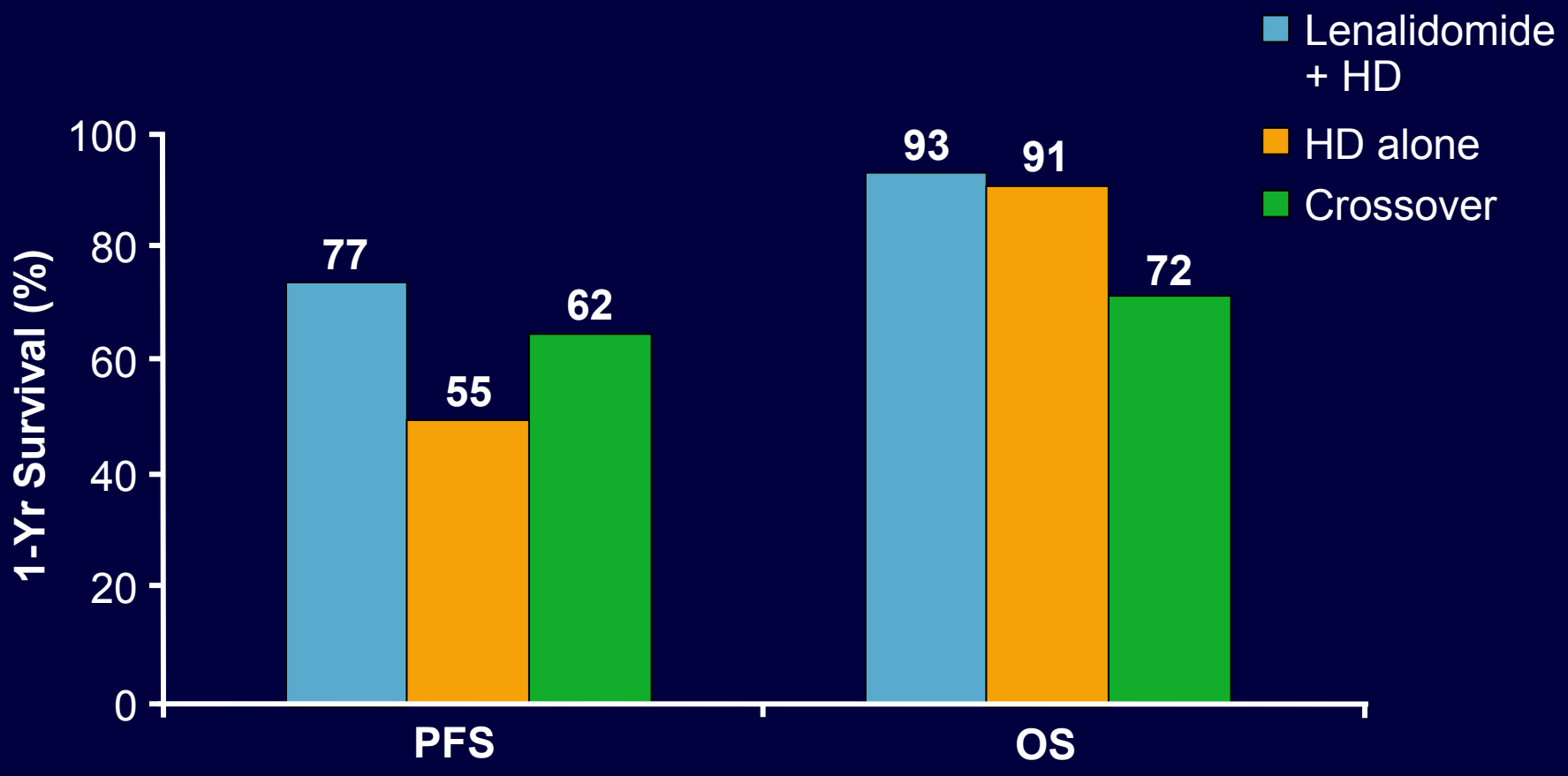
Zonder JA, et al. ASCO 2008. Abstract 8521.

Lenalidomide + HD vs HD (SWOG S0232): Response and Toxicity

- Lenalidomide + HD more active
  - Higher ORR
  - Higher CR
- Toxicity “manageable but not trivial”
  - Increased grade 3/4 neutropenia
- High rates of thrombosis on ASA

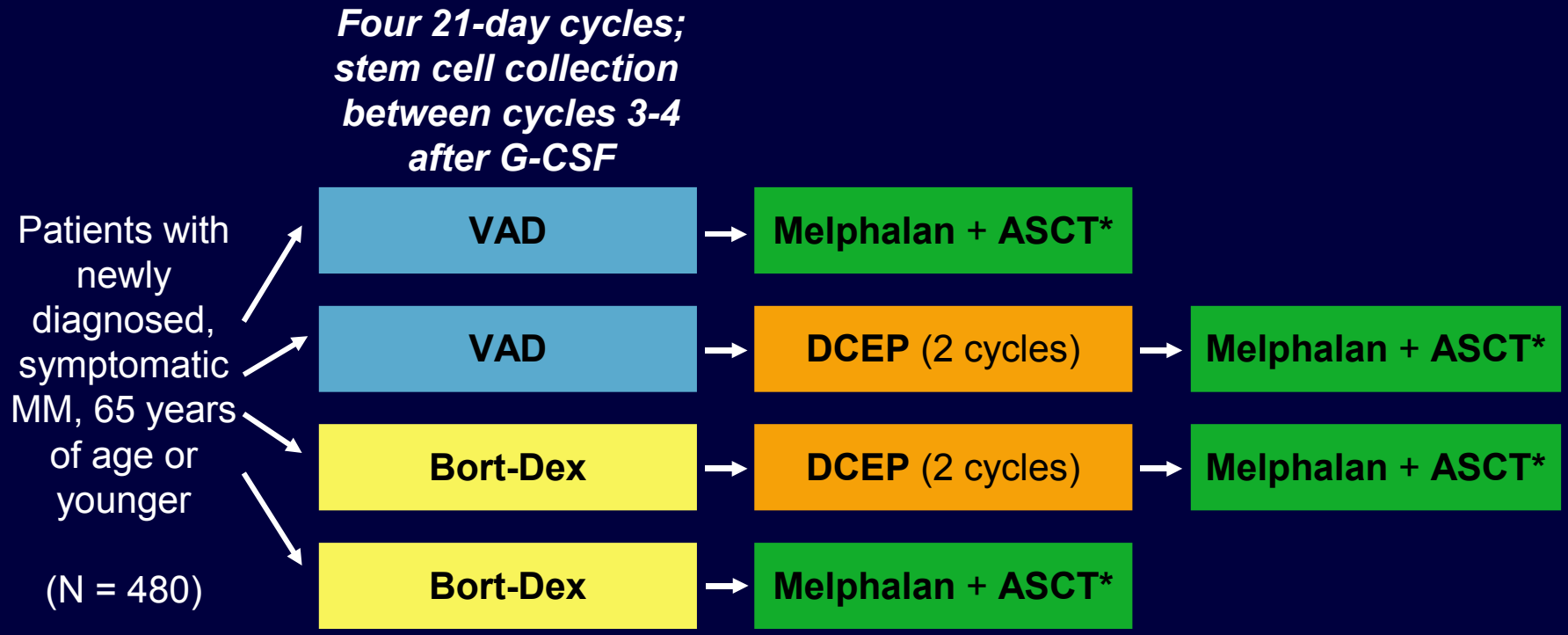
Zonder JA, et al. ASH 2007. Abstract 77.

Lenalidomide + HD vs HD (SWOG S0232): Survival Data (12-Mo Estimate)



Zonder JA, et al. ASH 2007. Abstract 77.

Bort-Dex vs VAD Pre-ASCT in Newly Diagnosed MM (IFM 2005/01)



Stratified by cytogenetics, β_2-microglobulin level

*Second ASCT or reduced-intensity conditioning allogeneic transplantation if < VGPR.

Harousseau JL, et al. ASH 2007. Abstract 450.

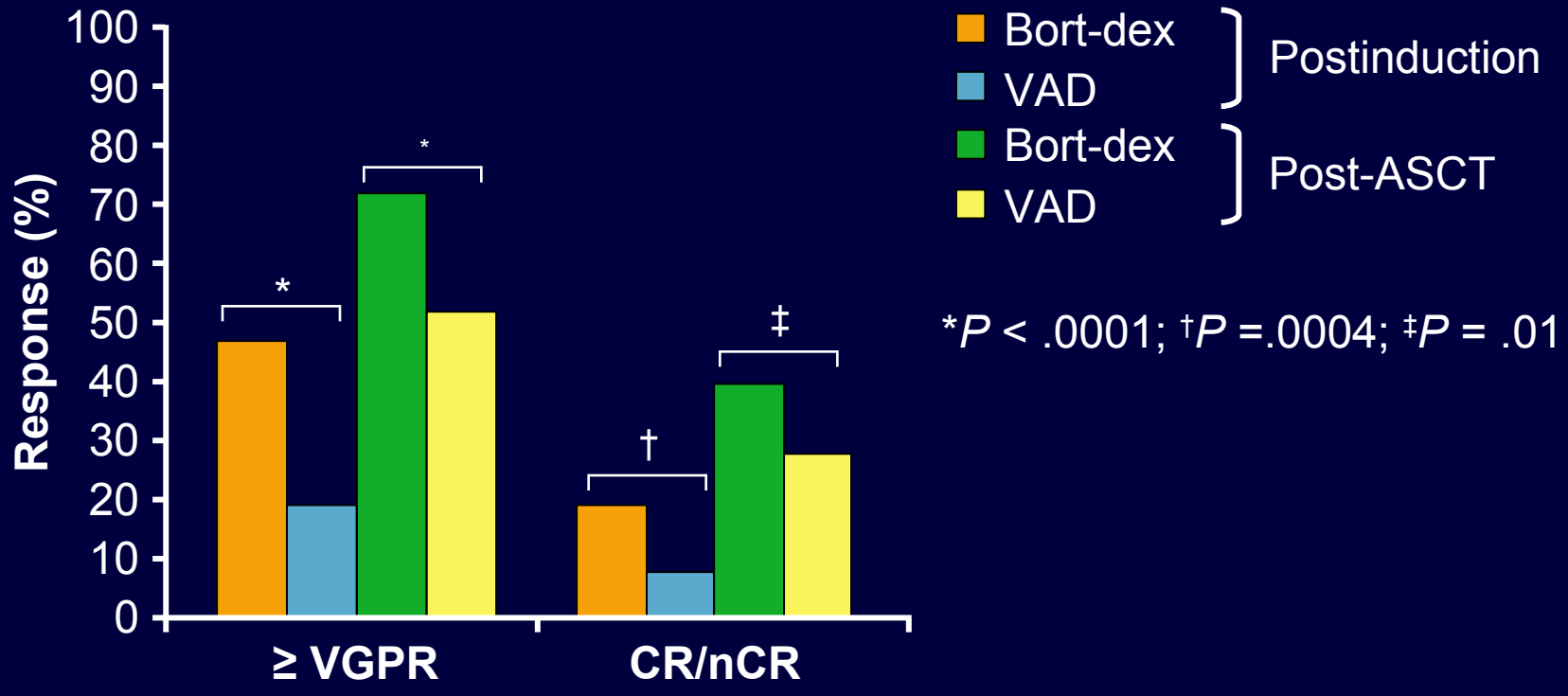
IFM 2005/01: Preliminary Results

- Primary objective: CR/nCR
- ASH 2006 (161 patients): higher CR/nCR with bort-dex
  - Bort-dex: 20%; VAD: 9%
  - Patients with del(13q), β_2-microglobulin > 3 mg/L have higher CR/nCR rates with bort-dex
- Grade 3/4 adverse events, bort-dex vs VAD: 30% vs 36%
- High postinduction CR/nCR may eliminate need for second ASCT and possibly for initial transplantation

Harousseau JL, et al. ASH 2006. Abstract 56.

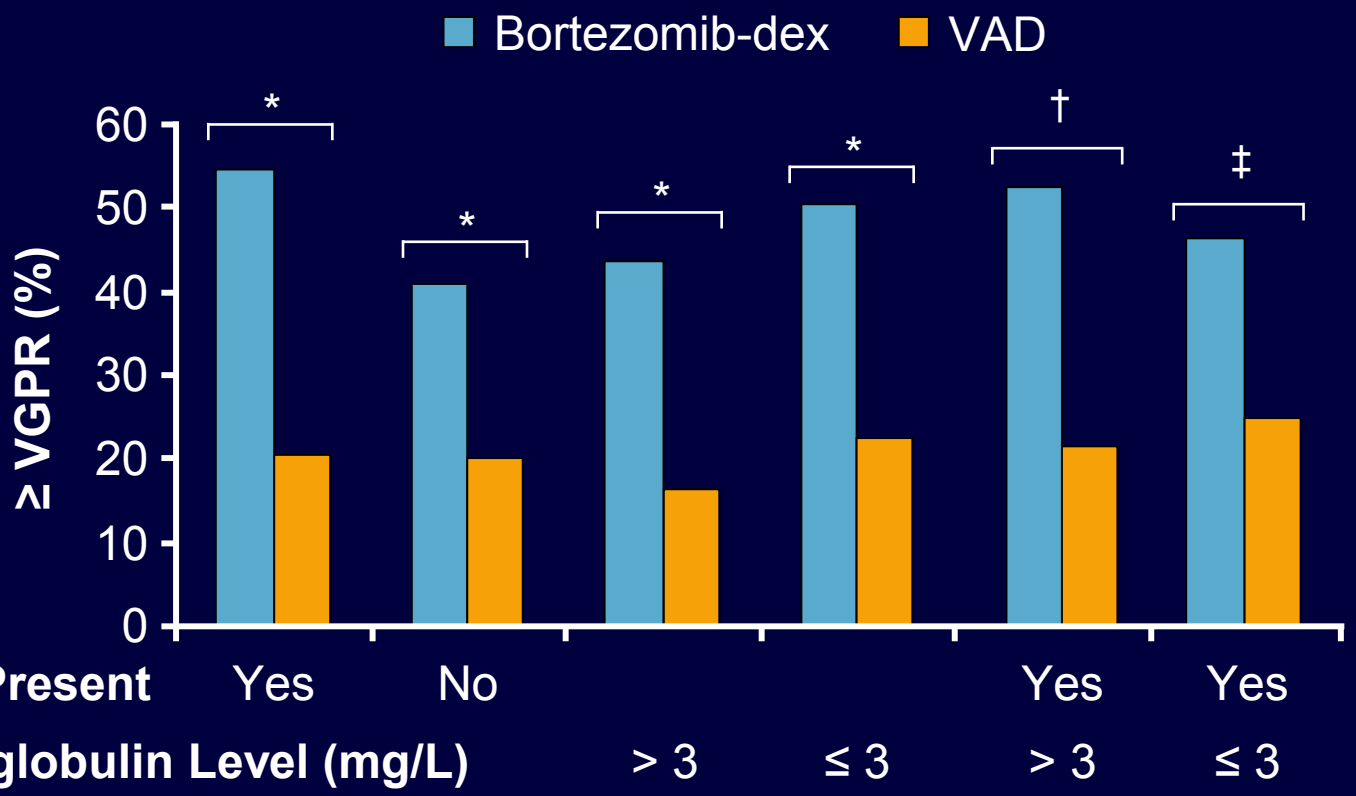
IFM 2005/01: Update

- Response rates postinduction and post-ASCT



*P < .0001; †P =.0004; ‡P = .01

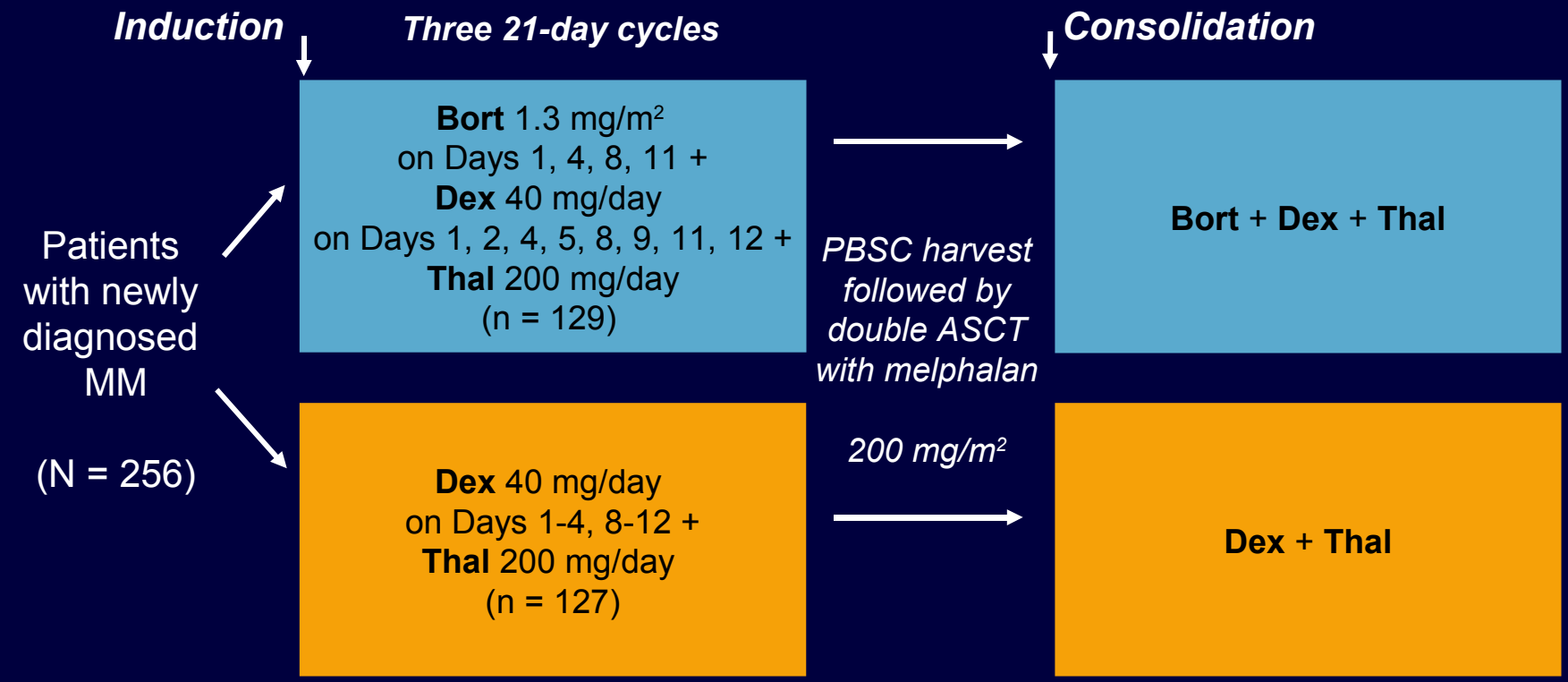
IFM 2005/01: Postinduction Response by β_2-Microglobulin and Del(13)



*P < .0001; †P =.0003; ‡P =.01

Harousseau JL, et al. ASCO 2008. Abstract 8505.

VTD vs TD Pre-ASCT in Newly Diagnosed MM



Patients also randomized to DVT prophylaxis with enoxaparin 40 mg/day, aspirin 100 mg/day, or warfarin 1.25 mg/day

Cavo M, et al. ASH 2007. Abstract 73.

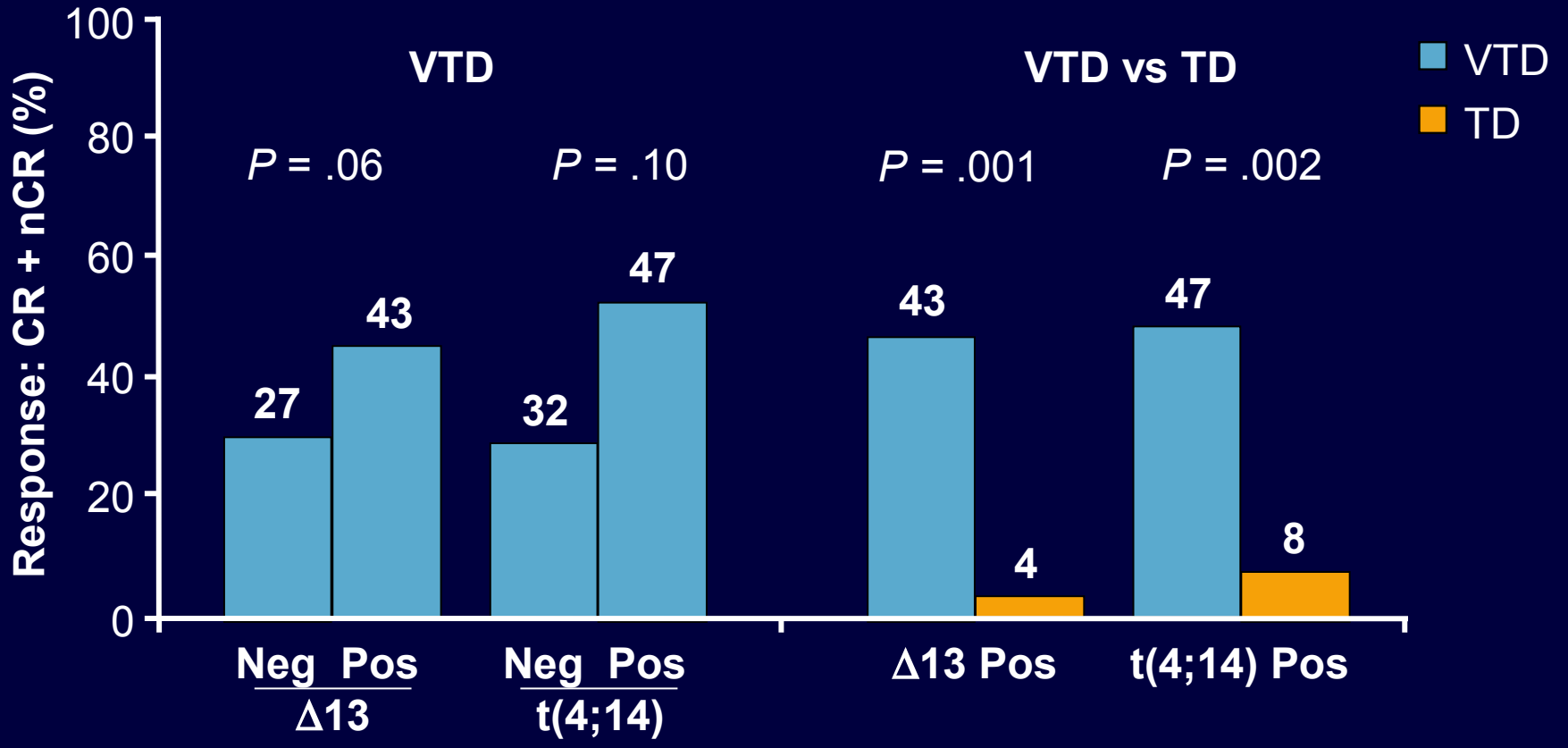
VTD vs TD in Newly Diagnosed MM: Response to Primary Therapy

- VTD: no adverse impact on PBSC harvest

Patients, %			
Response	**VTD (n = 129)**	**TD (n = 127)**	***P* Value**
CR + nCR	36	9	< .001
≥ VGPR	60	27	< .001
< PR	7	20	.003
Progression	0	5.5	.008

Cavo M, et al. ASH 2007. Abstract 73.

VTD vs TD, Primary Therapy: Response by Genetic Abnormalities



VTD vs TD: Response to First ASCT

- Superior in VTD arm

Patients, %			
Response	**VTD (n = 74)**	**TD (n = 79)**	***P* Value**
CR + nCR	57	28	< .001
CR	45	19	< .001
≥ VGPR	77	54	.003

Cavo M, et al. ASH 2007. Abstract 73.

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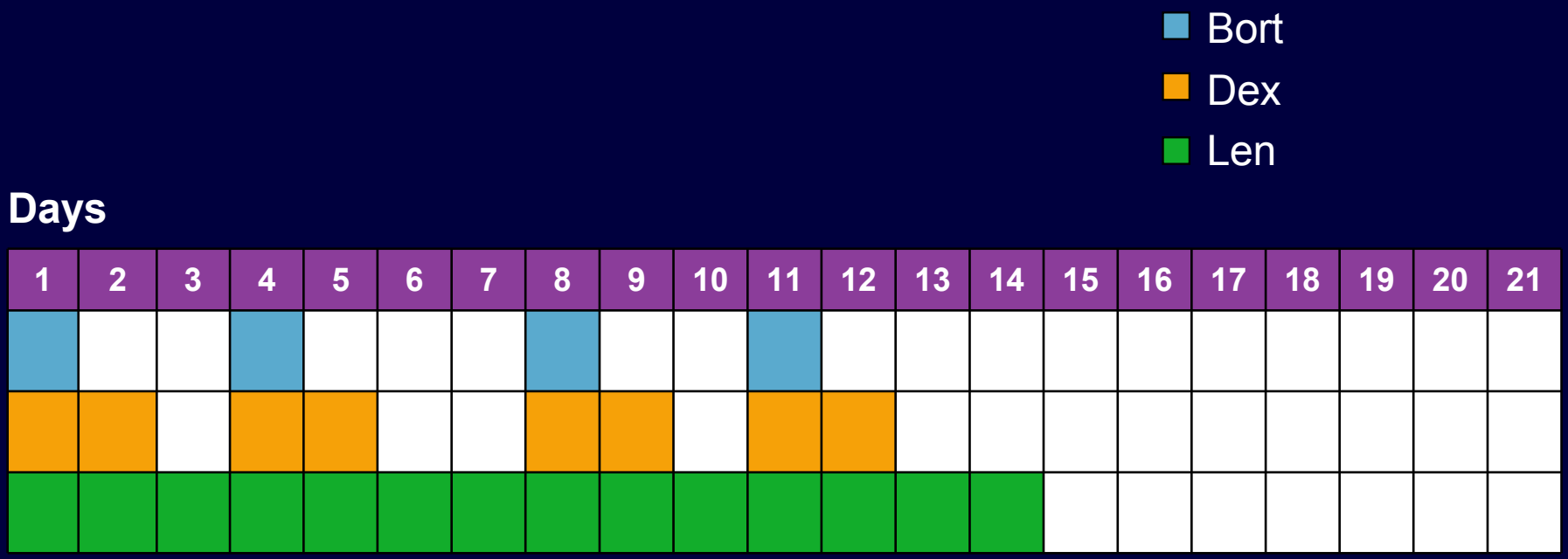
Len-Bort-Dex as Frontline MM Therapy: Phase I-II Study (Preliminary Results)



Up to eight 21-day cycles

Richardson P, et al. ASH 2007. Abstract 187.

Len-Bort-Dex as Frontline MM Therapy: Response by Phase and Cohort

- Median of 8 cycles (range: 2-28) among responders

Dose Level, n (%)	N (Evaluable)	CR	nCR	VGPR	PR	MR
Phase I	31	8 (26)	0 (0)	14 (45)	8 (26)	1 (3)
Phase II	35	9 (25)	7(20)	9 (26)	10 (29)	
Total	66	17 (26)	7 (11)	23 (35)	18 (27)	1 (2)

Richardson P, et al. ASCO 2008. Abstract 8520.

Doxorubicin Combination Regimens as Frontline MM Therapy: Phase II Results

Outcome, %	Bort + PLD[1] (n = 29)	Bort + PLD + Thal [2] (n = 26)	Bort + PLD + Dex[3] (n = 40)
CR	52	17.6	43
Grade 3/4 hematologic toxicity	43	42	10[4]
Grade 3/4 nonhematologic toxicity	67	15	43[4]

1. Orlowski RZ, et al. ASH 2006. Abstract 797.
2. Chanan-Khan AA, et al. ASH 2007. Abstract 3614.
3. Jakubowiak A, et al. IMW 2007. Abstract PO-721
4. Jakubowiak, A, et al ASH 2006. Abstract 3093.

Role of Transplantation With Novel Drugs

- No randomized trials of novel agents ± transplantation
- Novel drugs and transplantation may be complementary (rather than alternative) approaches
  - CR rate improved after transplantation when bort was used as induction[1]
  - Survival with transplantation poor in high-risk patients
    - No data that these patients do not benefit from transplantation
  - New wave of studies examining whether novel drugs (eg, bort) can be interwoven with the high-dose melphalan used in transplantation

1. Cavo M, et al. ASH 2007. Abstract 73.

Role of Transplantation With Novel Drugs (cont'd)

- Timing of transplantation
  - Later transplantation does not affect survival; early transplantation affords a longer time without systemic therapy
- Number of transplantations
  - Double transplantation strategy: only studied formally in the upfront setting[1]
  - Consensus is to perform the second transplantation only in those patients who have not achieved a VGPR after first transplantation
  - A major role for novel agents in post-ASCT consolidation or as maintenance therapy for increasing the duration of response

1. Harousseau JL, et al. ASH 2007. Abstract 450.

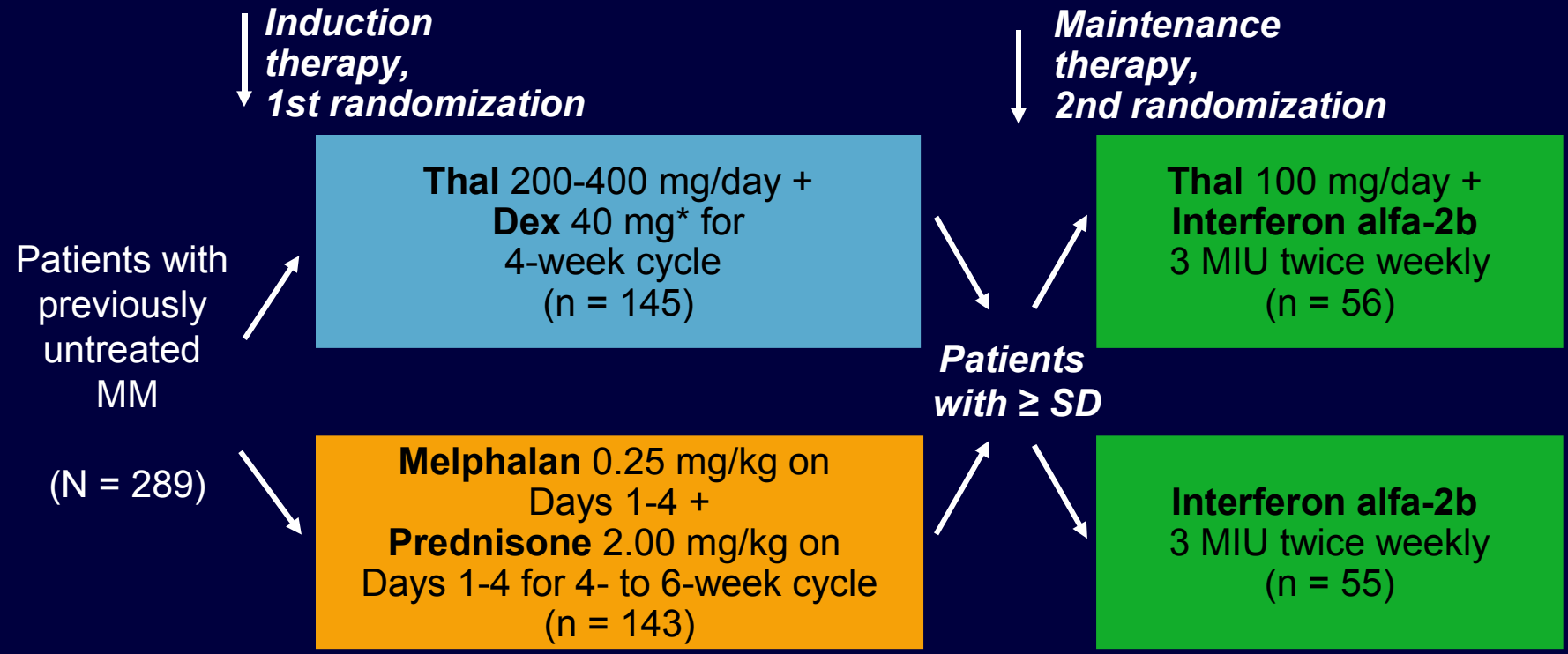
Role of Transplantation With Novel Drugs (cont'd)

- Outcome after transplantation
  - Worse in patients with truly progressive disease vs in patients with nonresponding, nonprogressing disease (survival similar to responding patients)
- Allogeneic transplantation: role still unclear
  - PETHEMA/GEM study: Patients received nonmyeloablative allogeneic transplantation after autologous transplantation
  - Significantly higher CR rate vs second autologous transplantation (33% vs 11%; *P* = .02) but no difference in survival[1]

1. Blade J, et al. ASCO 2007. Abstract 8021.

Frontline Therapy: Nontransplantation Candidates/Elderly

Thal-Dex vs MP in Elderly Patients With MM (CEMSG Study)



All patients received zoledronate 4 mg every 4 weeks
*Odd cycle: treatment on Days 1-4, 15-18; even cycle: treatment on Days 1-4.

Ludwig H, et al. ASH 2007. Abstract 529.

Thal-Dex vs MP (CEMSG Study): Response

- Higher RR with thal-dex
- More rapid response
  - Time to response: 6 vs 10 weeks ($P < .0001$)
  - Time to best response: 16 vs 23 weeks ($P < .0002$)

Parameter, %	TD (n = 145)	MP (n = 143)
CR	15	7
nCR	15	7
VGPR	18	15
PR	21	21
MR	12	21
SD	4	18
PD	15	10

Ludwig H, et al. ASH 2007. Abstract 529.

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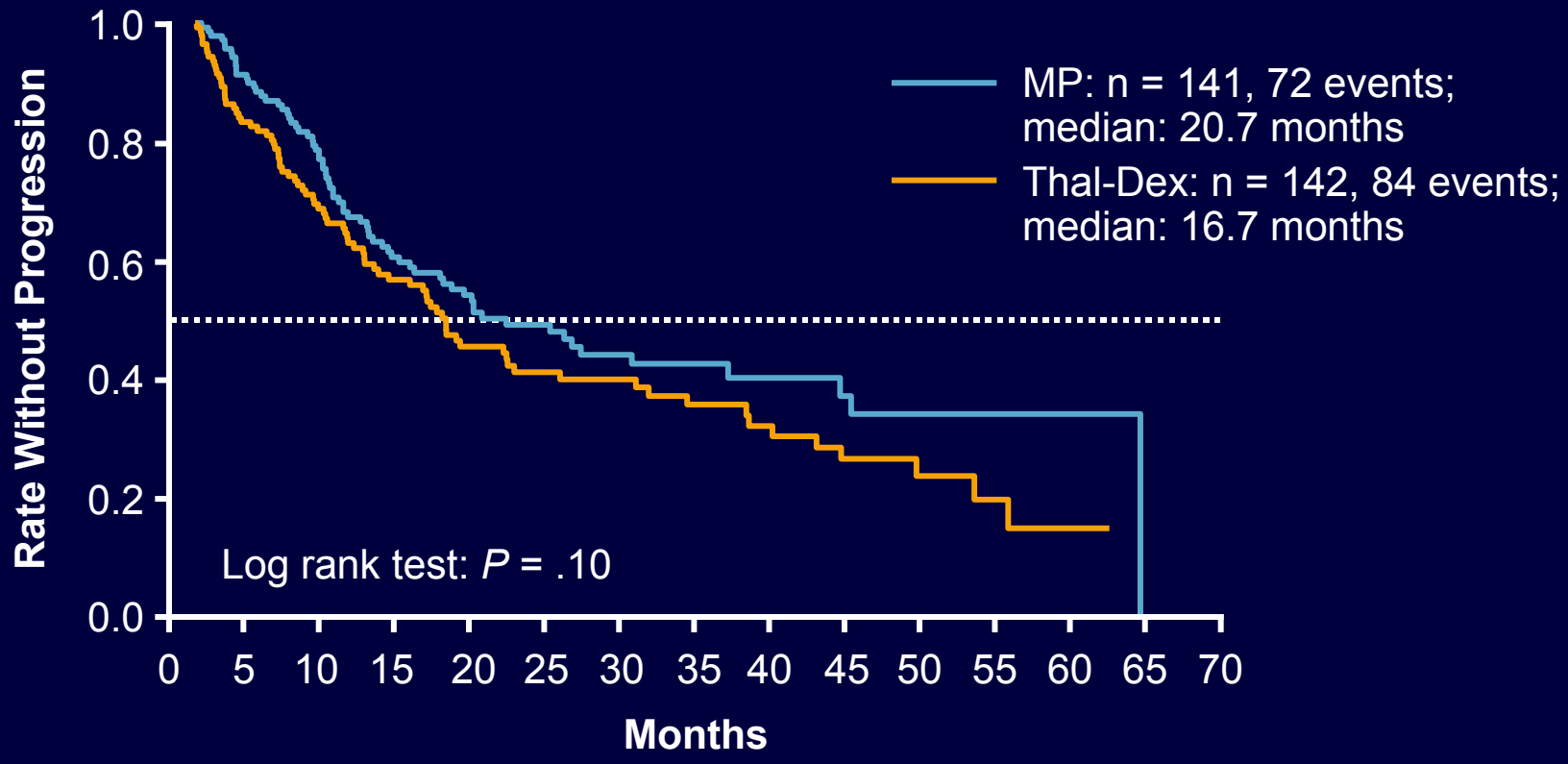
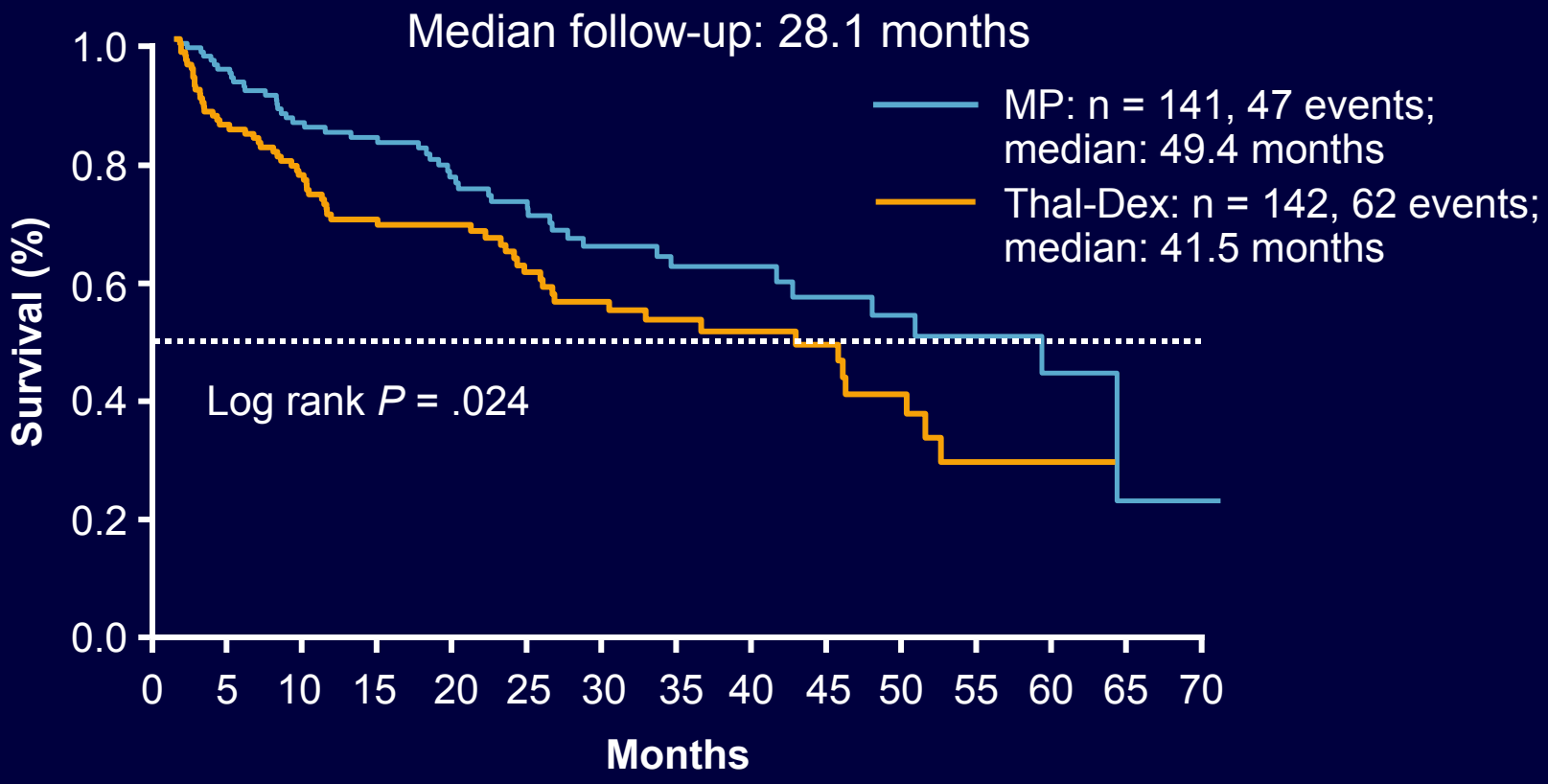
Thal-Dex vs MP (CEMSG Study): PFS



Ludwig H, et al. ASH 2007. Abstract 529.

Thal-Dex vs MP (CEMSG Study): OS



Ludwig H, et al. ASH 2007. Abstract 529.

Thal-Dex vs MP (CEMSG Study): Survival, Toxicity, and Maintenance

- Thal-dex associated with
  - Shorter OS at median follow-up of 28.1 months (41.5 vs 49.4 months for MP; *P* = .024)
    - Similar PFS of thal-dex vs MP (16.7 vs 20.7 months, respectively; *P* = .10)
  - More grade 2-4 neuropathy, constipation, psychological events (but fewer grade 3/4 leukopenia and thrombocytopenia)
  - Higher death rate in first year (31 vs 17 deaths)
- No survival benefit with addition of thal to maintenance interferon alfa-2b
- Results highlight importance of individualizing therapy and of toxicity of higher doses of thal-dex

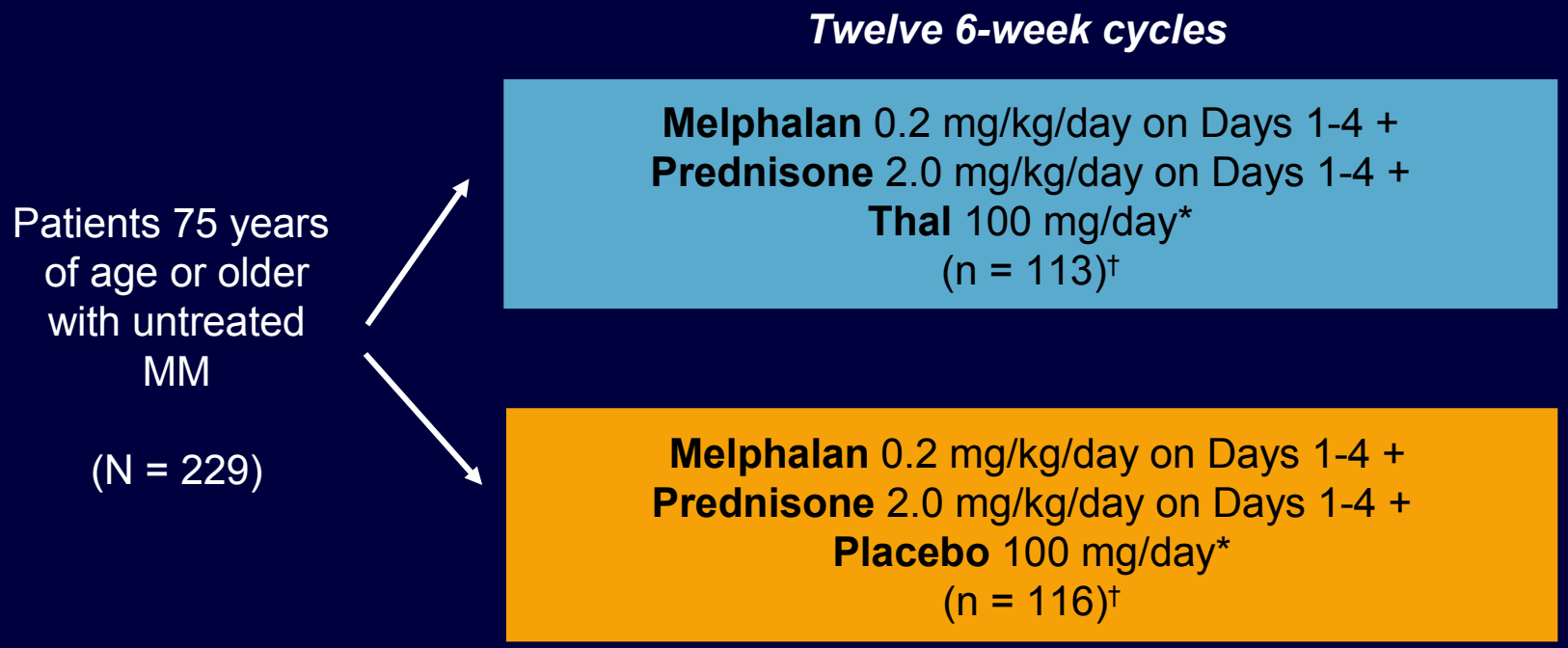
Ludwig H, et al. ASH 2007. Abstract 529.

MP-T in Elderly Patients With Newly Diagnosed MM

- Patients 65-75 years of age
  - MP-T now standard
  - Superior survival vs MP and vs reduced-intensity SCT using melphalan 100 mg/m^2 (MEL100)
- Patients older than 75 years of age
  - Substantial proportion of patients with MM
  - Frequently excluded from major clinical trials
  - No treatment recommendations regarding MP-T in this group

Facon T, et al. Lancet. 2007;370:1209-1218.

MP-T vs MP in Older Patients Older Than 75 Years With MM: IFM 01/01

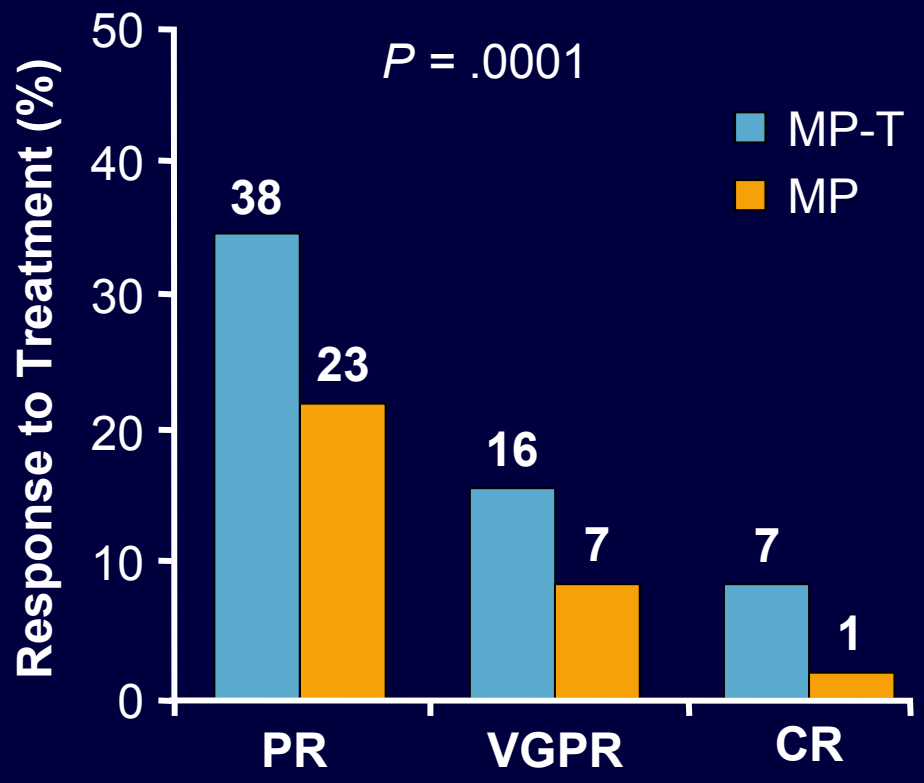


*Administered continuously for 18 months.
†All patients received clodronate.

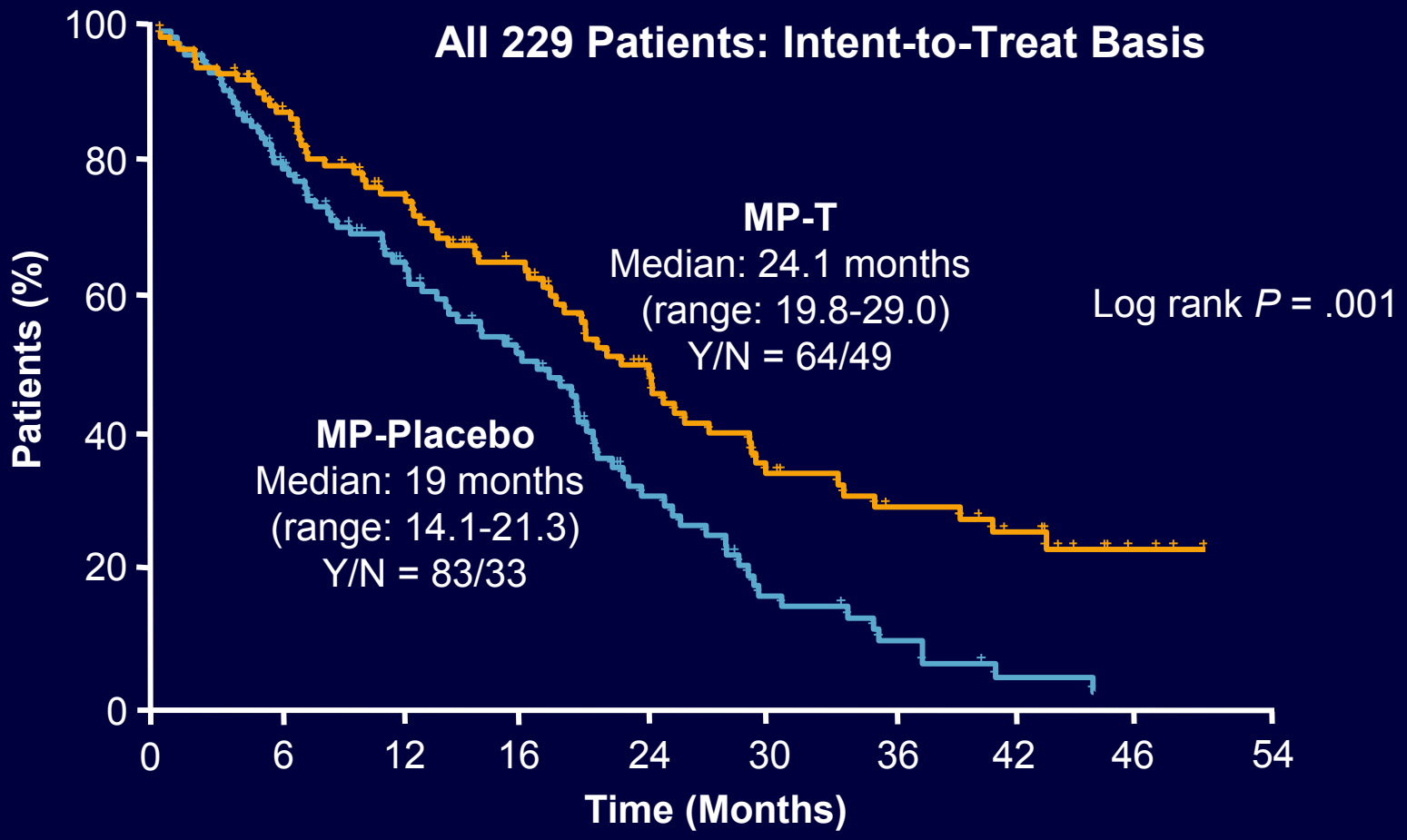
Hulin C, et al. ASH 2007. Abstract 75.

IFM 01/01: Response and Survival Data

- Superior survival with MP-T vs MP
  - Median OS: 45.3 vs 27.7 months (*P* = .033)
  - Median PFS: 24.1 vs 19 months (*P* = .001)
- Acceptable toxicity
  - Less neurotoxicity with shorter T duration?

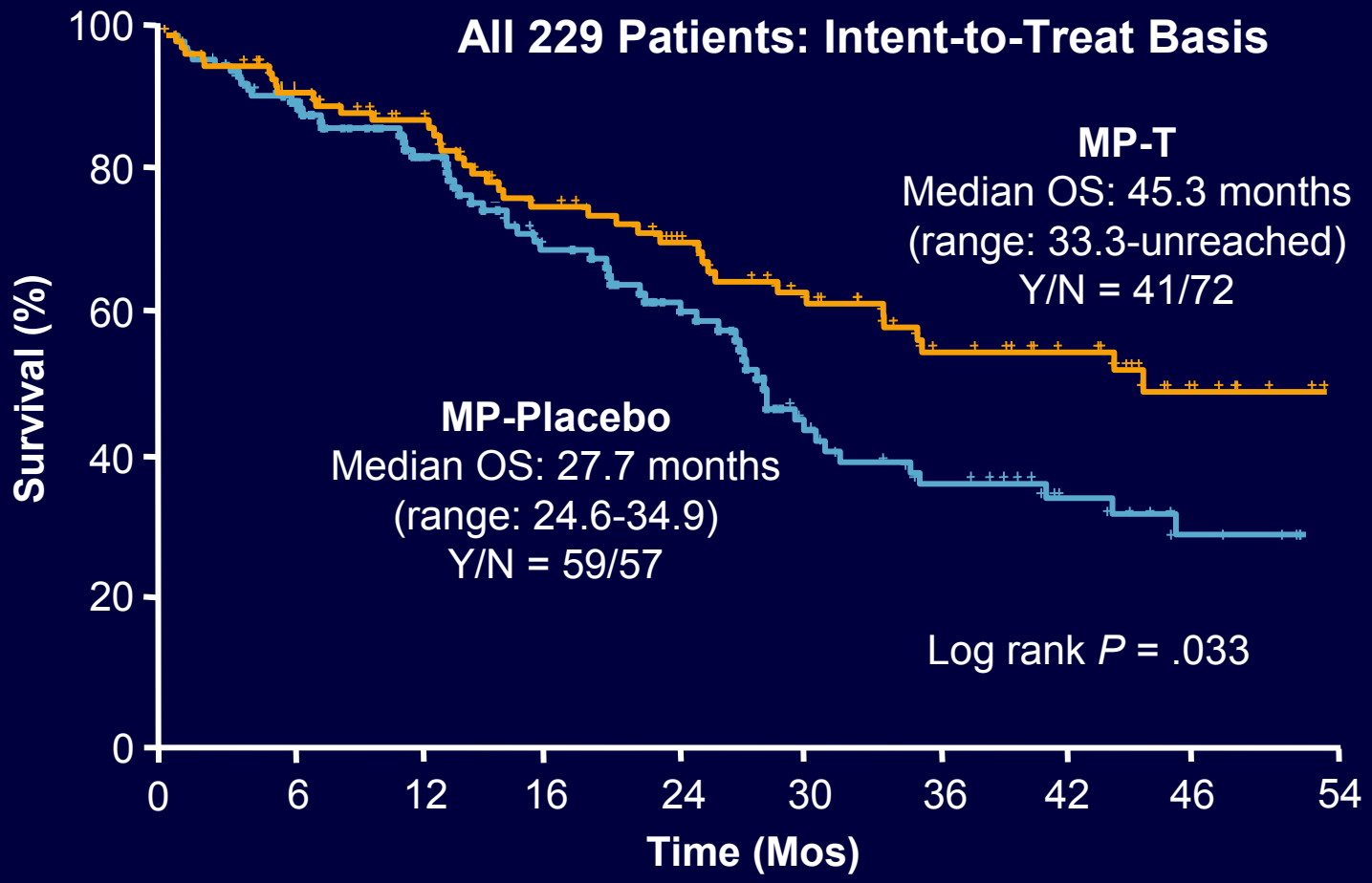


IFM 01/01: PFS by Treatment



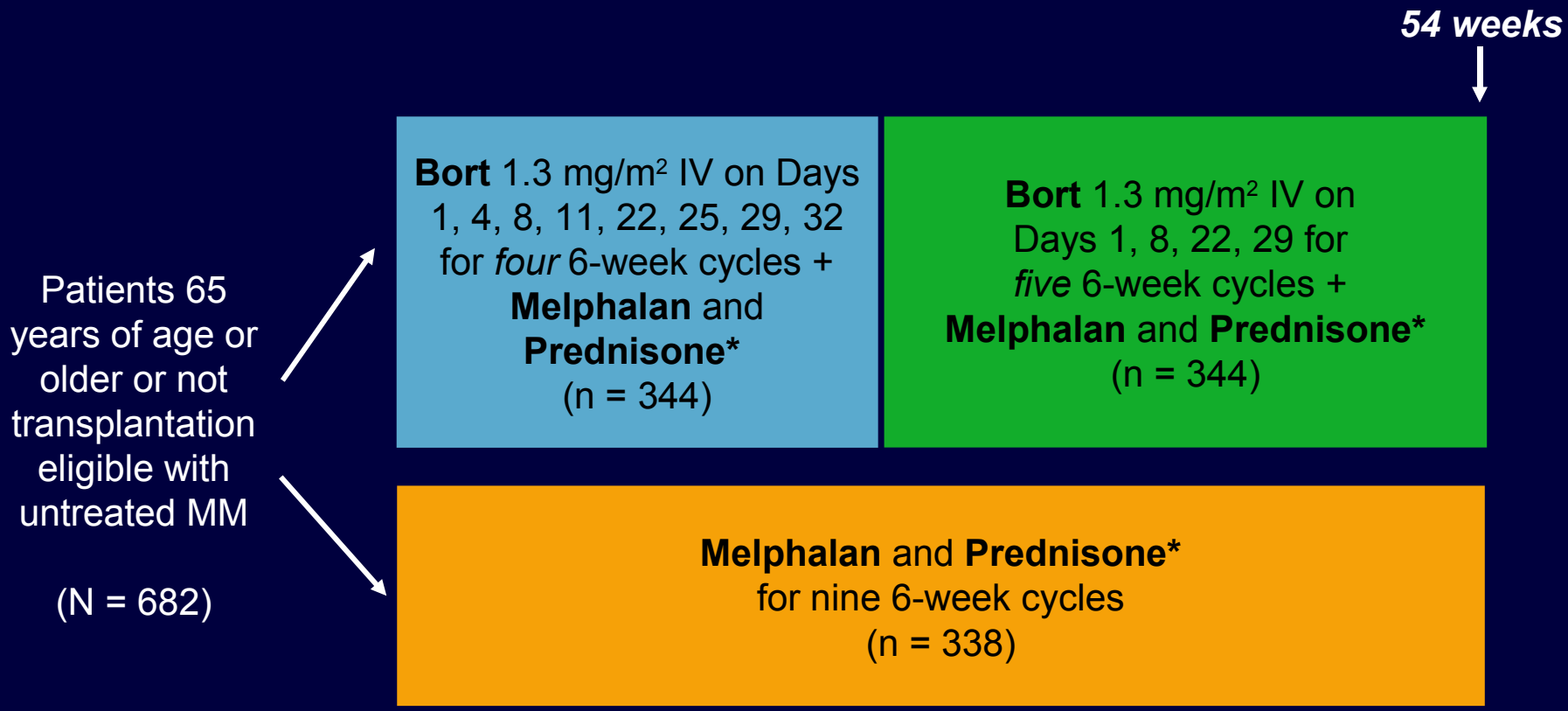
Hulin C, et al. ASH 2007. Abstract 75.

IFM 01/01: OS by Treatment



Hulin C, et al. ASH 2007. Abstract 75.

VMP vs MP in Newly Diagnosed MM (MMY-3002; VISTA)



*Melphalan 9 mg/m² orally QD and prednisone 60 mg/m² on Days 1-4 each cycle.

San Miguel JF, et al. ASH 2007. Abstract 76.

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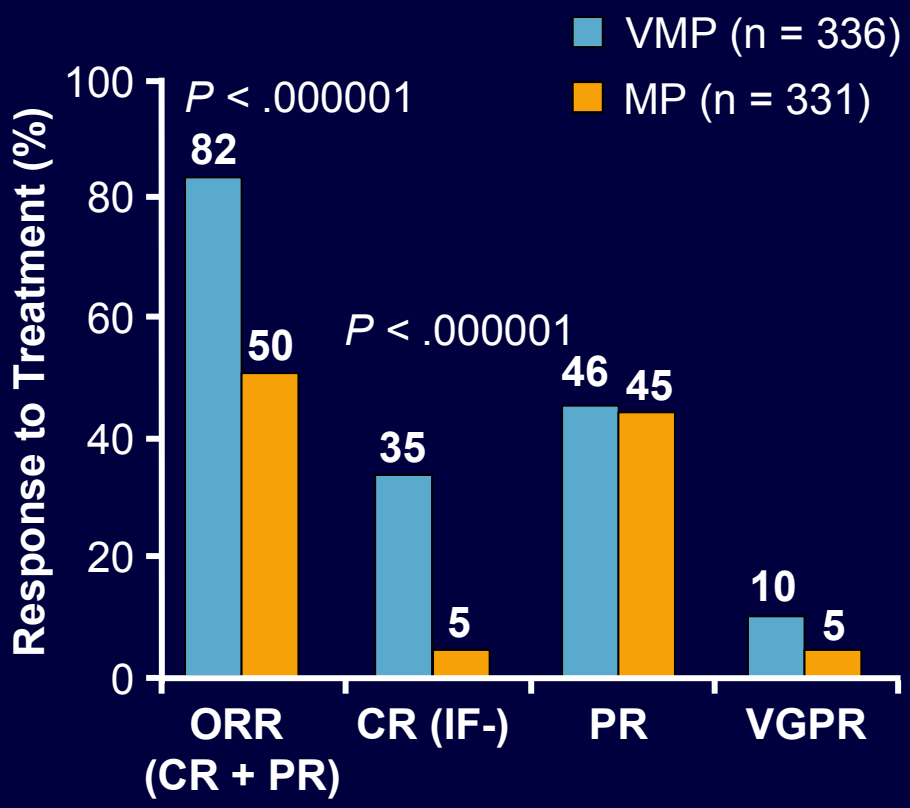
VMP vs MP (MMY-3002; VISTA): Response to Treatment

- Responses with VMP rapid and durable
  - Time to response, all responders: 1.4 vs 4.2 months ($P < 10^{-10}$)
  - Response duration in patients with CR: 24.0 vs 12.8 months



San Miguel JF, et al. ASH 2007. Abstract 76.

VMP vs MP (MMY-3002; VISTA): Time to Progression

- Time to progression was significantly longer with the addition of bort to MP
  - VMP: 24 months (83 events)
  - MP: 16.6 months (146 events)
  - HR: 0.483; *P* < .000001

San Miguel JF, et al. ASH 2007. Abstract 76.

VMP vs MP (MMY-3002; VISTA): OS

- OS at 2 years improved with the addition of bort to MP, although median not reached for either arm
  - VMP: 82.6% (45 deaths; 1% treatment related)
    - Younger than 75 years of age: 84%
    - Older than 75 years of age: 79%
  - MP: 69.5% (76 deaths)
    - Younger than 75 years of age: 74%
    - Older than 75 years of age: 60%
  - HR: 0.607; *P* = .0078

San Miguel JF, et al. ASH 2007. Abstract 76.

VMP vs MP (MMY-3002; VISTA): Time to Next Treatment

- Time to next treatment not reached for VMP vs 20.8 months for MP (HR: 0.522; *P* =.000009)
  - Patients on VMP 48% less likely to start second-line therapy
  - For VMP vs MP patients, at 2 years 35% vs 57% started second-line therapy
- Median treatment-free interval not reached for VMP vs 9.4 months for MP (*P* = .0001)

San Miguel JF, et al. ASH 2007. Abstract 76.

VMP vs MP in Newly Diagnosed MM (MMY-3002; VISTA): More Results

- ~ 52% reduction in risk of progression
- ~ 40% reduction in risk of death
  - At 16.3-week median follow-up, median OS not reached
  - VMP: 45 deaths; MP: 76 deaths; HR: 0.607; *P* = .0078
- No impact on efficacy: age, creatinine clearance, cytogenetics (FISH)
- VMP patients 48% less likely to start a second-line therapy
- Serious AEs: 46% for VMP; 36% for MP
  - 1% DVT in both arms

San Miguel JF, et al. ASH 2007. Abstract 76.

VMP vs MP in Newly Diagnosed MM (MMY-3002; VISTA): Update

- 3-year survival: 72% for VMP vs 59% for MP
  - Median survival not reached; HR: 0.664; *P* = .0032
  - Median follow-up: 25.9 months
- VMP continues to yield higher response rates than MP

Parameter, %	MP (n = 331)	VMP (n = 337)	*P* Value
ORR	35	70	< .00001
CR	4	30	< .000001
PR	31	40	< .0001

San Miguel JF, et al. EHA 2008. Abstract 473.

PLD + Bort + Dex Induction for ASCT in Elderly Patients

- PAD induction followed by MEL100/ASCT, LP consolidation, and lenalidomide maintenance
  - 65-75 years of age, newly diagnosed multiple myeloma
- PAD/MEL100 compared with historical control group of VAD/MEL200

Outcome, %	PAD MEL100[1] (n = 86)	VAD MEL200[2] (n = 337)
CR	53	15
≥ VGPR	88	36
2-yr EFS	83	62
2-yr OS	92	85

1. Palumbo A, et al. ASCO 2008 Abstract 8518.
2. Palumbo A, et al ASH 2007. Abstract 727.

Conclusions

- Significantly longer 12- and 24-month OS with Rd than with RD in ECOG E4A03 study
- RD produced significantly higher response rates in SWOG S0232 vs high-dose dex alone
- Bort plus dex improved response rates vs VAD in IFM 2005/01
  - Including high-risk patients with del(13q) or high β_2-microglobulin
- Addition of bort to thal/dex increased the CR/nCR rate
  - Including high-risk patients with del(13q) or t(4;14)
- Bort combined with PLD ± thal or dex produces excellent response rates as frontline therapy

Conclusions (cont'd)

- Transplantation with novel drugs produces worse outcomes in patients with progressive disease
  - Allogeneic transplantation following autologous transplantation improves CR rate but not survival
- In elderly patients, response rates were higher and responses were faster with thal/dex vs MP
  - Thal/dex associated with shorter survival but similar PFS to MP
- The addition of thal to MP in IFM 01/01 improved OS and PFS and increased response rates
- Addition of bort to MP in the VISTA study improved response rates, time to progression, and the 2-year OS rate

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