Consolidation and Maintenance in Newly Diagnosed Symptomatic Multiple Myeloma

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Consolidation with VTD after ASCT

- Phase II/III, 39 patients

- ASCT conditioning regimens (x 2): Melphalan 200 mg/m^2 (n = 25) or 100 mg/m^2 (n = 14)

  39/39 in ≥ VGPR following ASCT

  → 4 cycles of VTD

- 22% of the patients: true molecular CR

Ladetto M, et al. J Clin Oncol. 2010;28:2077-2084.

Clinical outcome according to tumor burden by quantitative polymerase chain reaction

- Progression-free survival is superior with low vs high tumor burden
  - After 2 courses of VTD ($P = .018$)
  - At the end of consolidation ($P < .001$)
  - At 6-month follow-up ($P = .016$)

Ladetto M, et al. J Clin Oncol. 2010;28:2077-2084.

IMWG 2009, Washington

Stringent CR: The panel approved an update to the definition of stringent CR in the IMWG criteria to require negative clonal cells by multiparametric flow cytometry (with ≥4 colors). Stringent CR is defined as CR plus absence of phenotypically aberrant PC in bone marrow with a minimum of 3000 total PC analyzed by multiparametric flow cytometry ("immunophenotypic CR")

Rajkumar SV, et al. XII IMW. 2009.

IMWG 2009, Washington

Molecular CR: The panel approved a definition of molecular CR to be incorporated into the IMWG criteria. Molecular CR is defined as stringent CR plus negative ASO-PCR (sensitivity 10^{-5})

Rajkumar SV, et al. XII IMW. 2009.

Phase III Study: bortezomib consolidation versus no consolidation following ASCT

Induction + single or double ASCT (n=404)

↓

Randomization (3 months post-ASCT) (n=372)

Bortezomib (n=149)

1.3 mg/m^2

Days 1, 4, 8, 11 for two 3-week cycles

then Days 1, 8, 15 for four 4-week cycles

(total of 20 injections over 21 weeks)

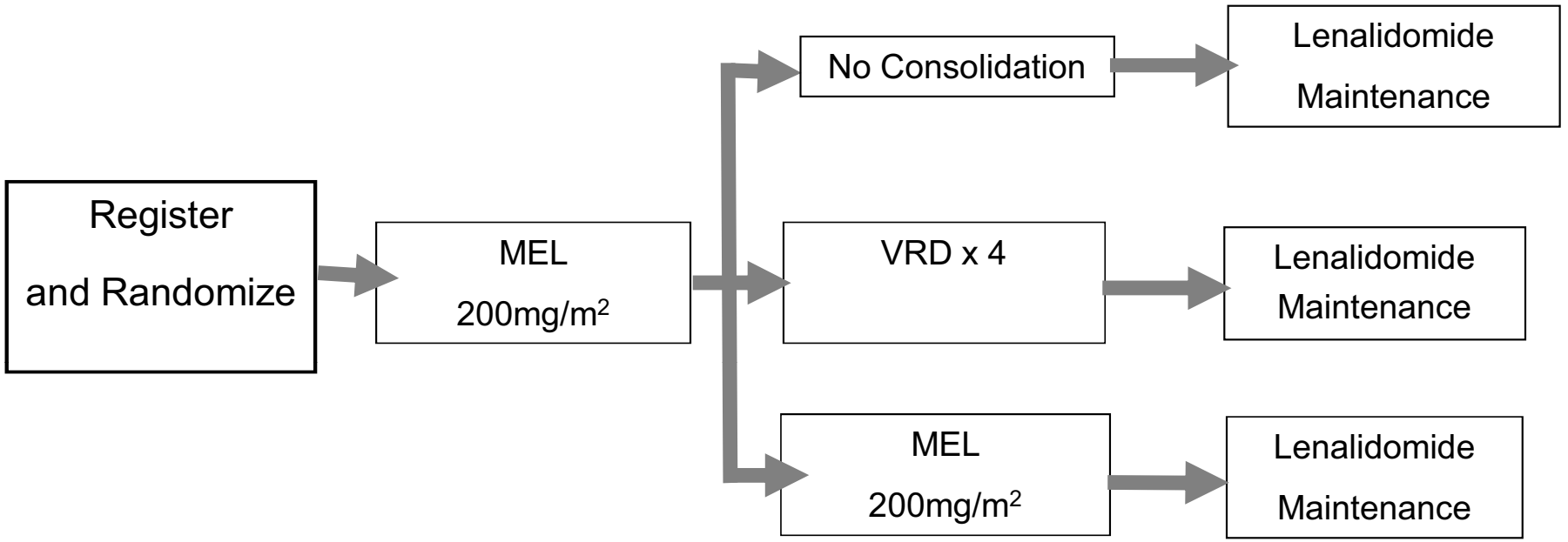
Observation (n=150)

Mellqvist U-H, et al. ASH 2009. Abstract 530.

What is the best consolidation after ASCT?

→ BMT-CTN study!

BMT/CTN Phase III Study



- **Active Myeloma within 12 months of initial treatment**
- **Age ≤ 70 yrs**
- **Pts with progressive disease will be excluded**
- **All pts will have enough PBPC collected for two transplants**
- **Stratify by B2M, response to initial therapy and cytogenetics**
- **Intent-to-treat analysis. Randomization prior to first ASCT**
- **New IWG criteria will be used for response assessment**

Clinical Trials.gov. NCT01109004.

IFM 2005-02: lenalidomide maintenance after ASCT

Phase III prospective randomised, versus placebo

Patients < 65 y, non-progressive or stable,
≤ 6 months post-ASCT

Randomisation

Consolidation
Lenalidomide 25 mg/d, D1-21, 28-day cycle, during 2 cycles

Lenalidomide
10 -15 mg/d

Until progression

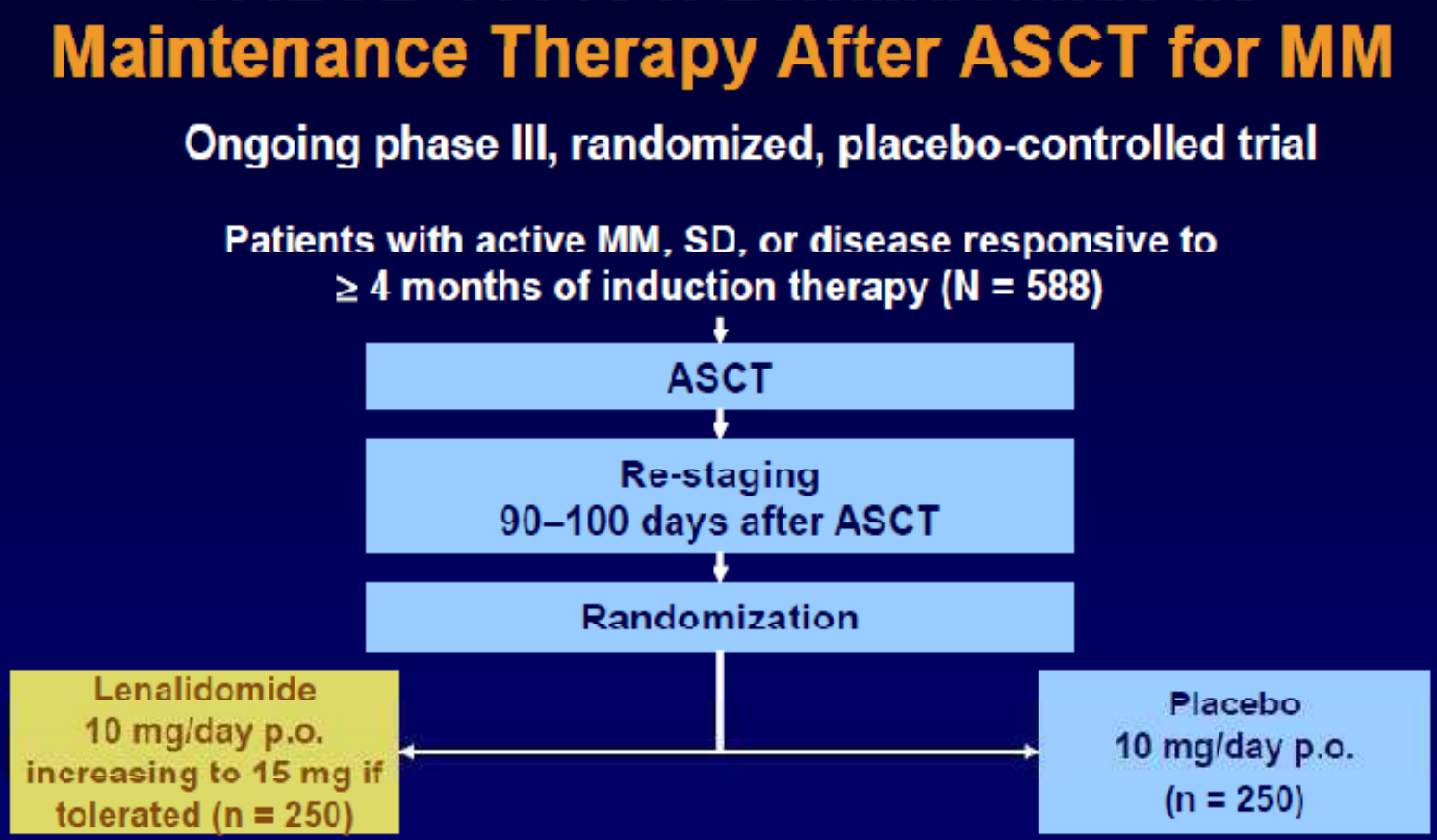
Placebo
until progression

Primary end-point : TTP
Secondary end-points: CR, PFS, OS, feasibility-toxicity

Clinical Trials.gov. NCT00430365.
Attal M, et al. ASCO 2010. Abstract 8018.

CALGB 100104: Lenalidomide as Maintenance Therapy After ASCT for MM

Ongoing phase III, randomized, placebo-controlled trial



Primary end-point: time to disease progression after autologous ASCT
Secondary end-points: CR rate, PFS, OS, and feasibility of long-term lenalidomide

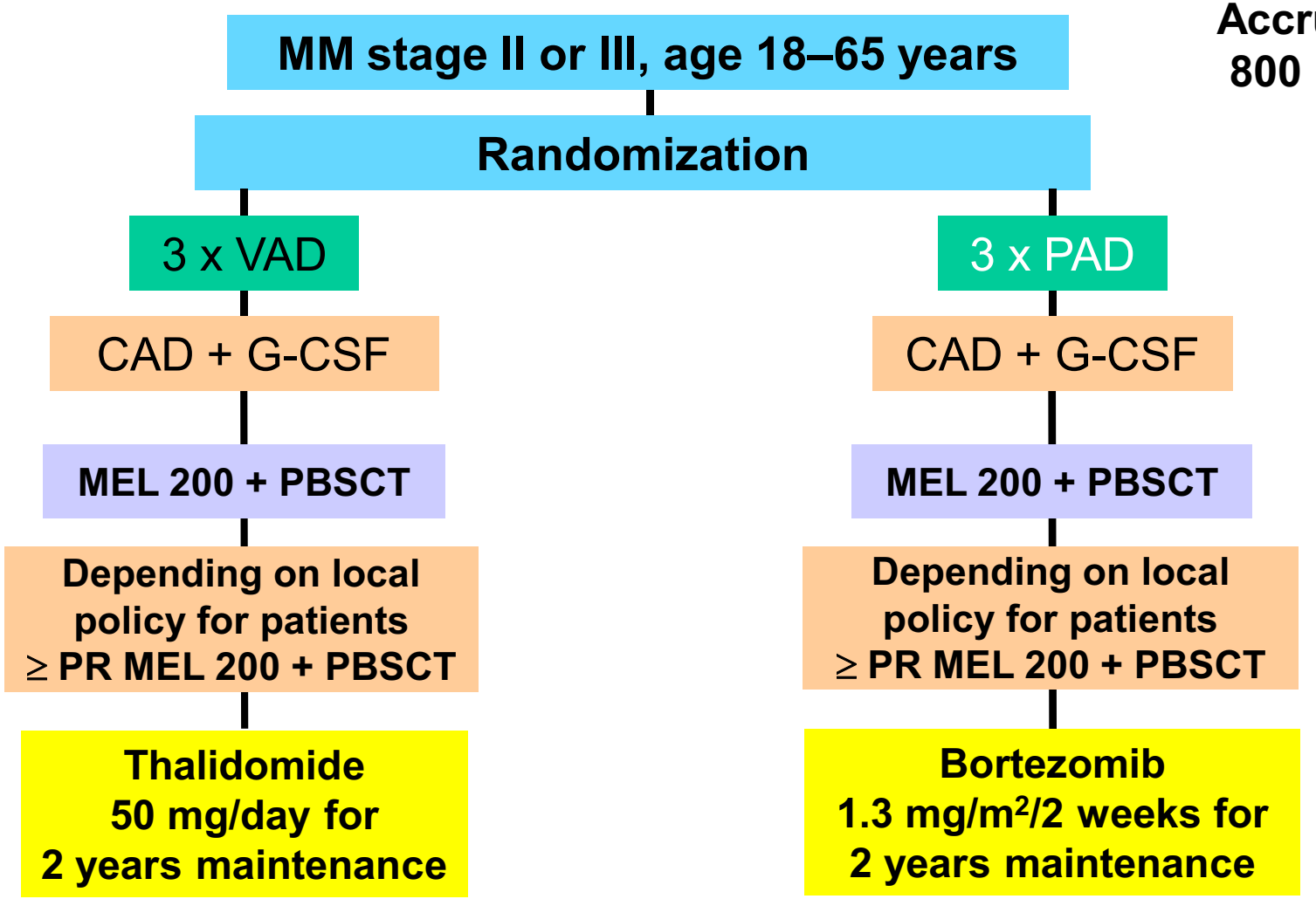
Trial NCT00114101. Available from: www.ClinicalTrials.gov.

CALGB 100104

- CALGB 100104: lenalidomide vs placebo as maintenance therapy following ASCT in myeloma
  - Phase III study
  - N = 418 patients
- Time to progression
  - Lenalidomide: median not yet reached
  - Placebo: median 25.5 months
- Overall survival
  - Follow-up not long enough to determine if there is a difference in OS
    - 11 deaths in lenalidomide arm vs 17 in placebo arm ($P < .20$)

McCarthy PL, et al. ASCO 2010. Abstract 8017.

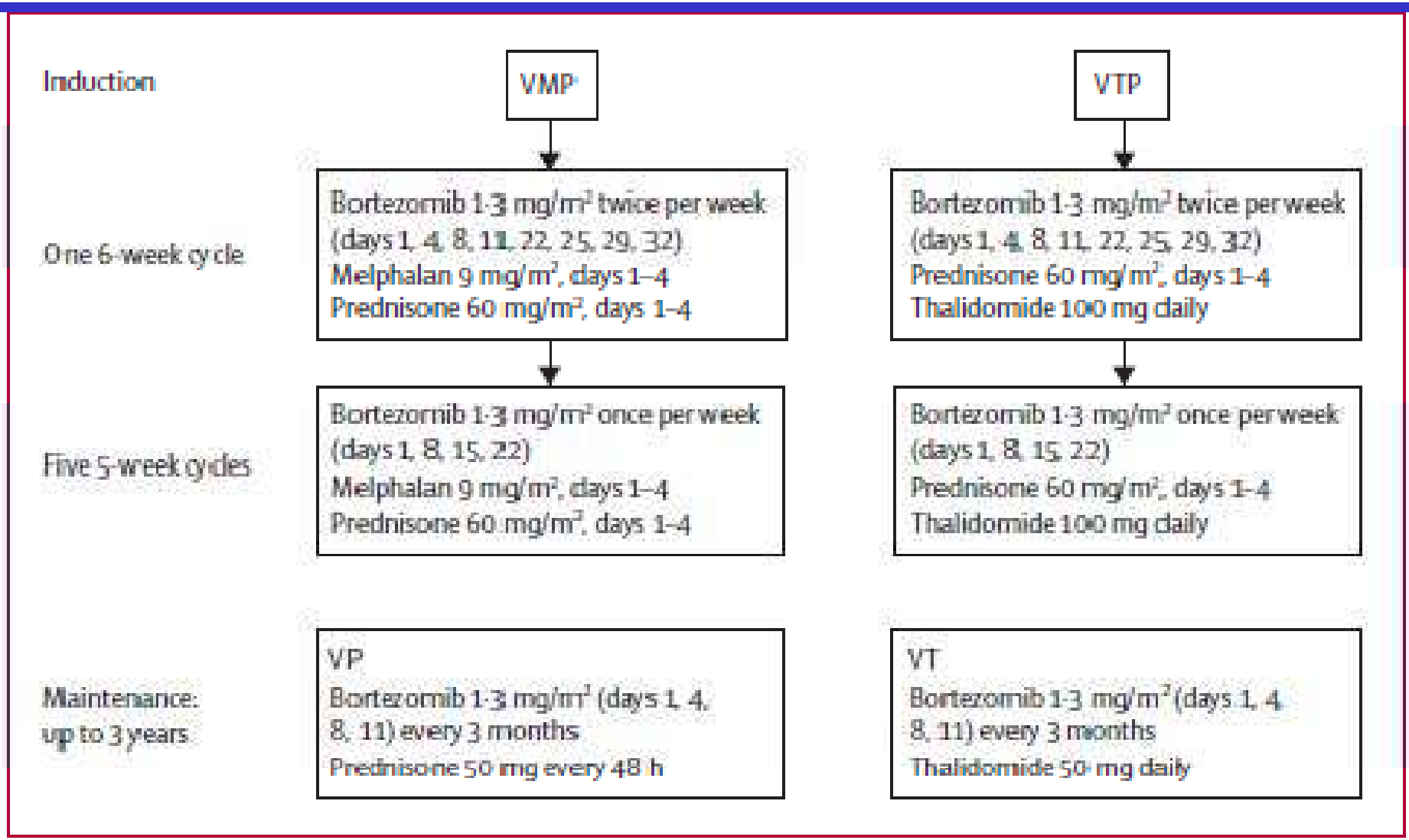
HOVON-65/GMMG-HD4 phase III trial



Accrual goal: 800 patients

Sonneveld P, et al. ASH 2008. Abstract 653.

Maintenance in elderly patients



Mateos MV, et al. Lancet Oncol. 2010;11:934-941.

Toxicity Profile During Maintenance Therapy

- VP: n = 87 / VT: n = 91)
- Hematologic toxicity (grades 1-2)
  - Anemia, neutropenia, thrombocytopenia in < 5% of patients receiving either VP or VT (*P* = .8)
- Nonhematologic toxicity (grades 3-4)
  - Discontinuations due to AEs: 8% with VT vs 5% with VP (*P* = .60)
  - Peripheral neuropathy: 7% with VT vs 2% with VP (*P* = .60)
  - GI toxicity: 4% with VT vs 1% with VP (*P* = .60)

Mateos MV, et al. Lancet Oncol. 2010;11:934-941.

VMP vs VTP

- Median PFS
  - VMP: 34 months
  - VTP: 25 months
- 3-year OS
  - VMP: 74%
  - VTP: 65%

Mateos MV, et al.
Lancet Oncol. 2010;11:934-941.

Phase III: VMPT + VT vs VMP in elderly patients with newly diagnosed MM – GIMEMA study

Patients (n=511): >65 years old; median age 71 years

Treatment

VMPT

9 x 5-week cycles

Bortezomib

Melphalan

Prednisone

Thalidomide

Maintenance:
Bortezomib +
Thalidomide

VMP

9 x 5-week cycles
Bortezomib
Melphalan
Prednisone

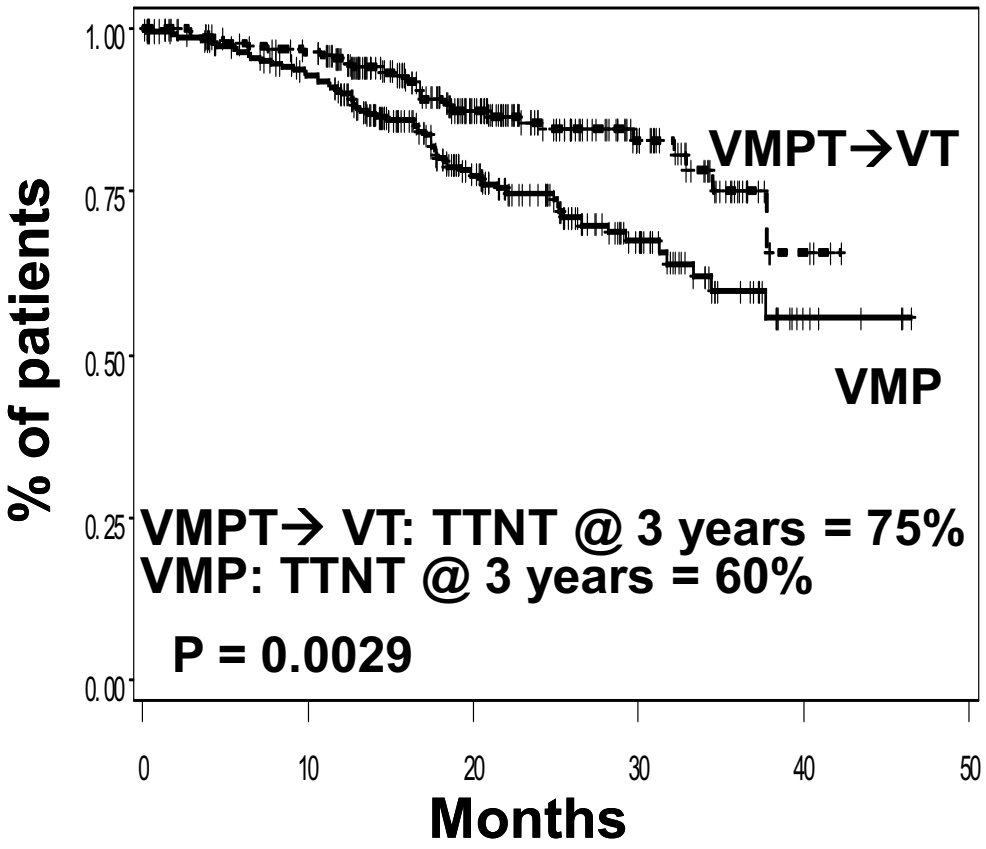
No maintenance

Bringhen S, et al. Blood. 2010;Aug. 31:[E-pub ahead of print]
Palumbo A, et al. ASH 2009. Abstract 128.

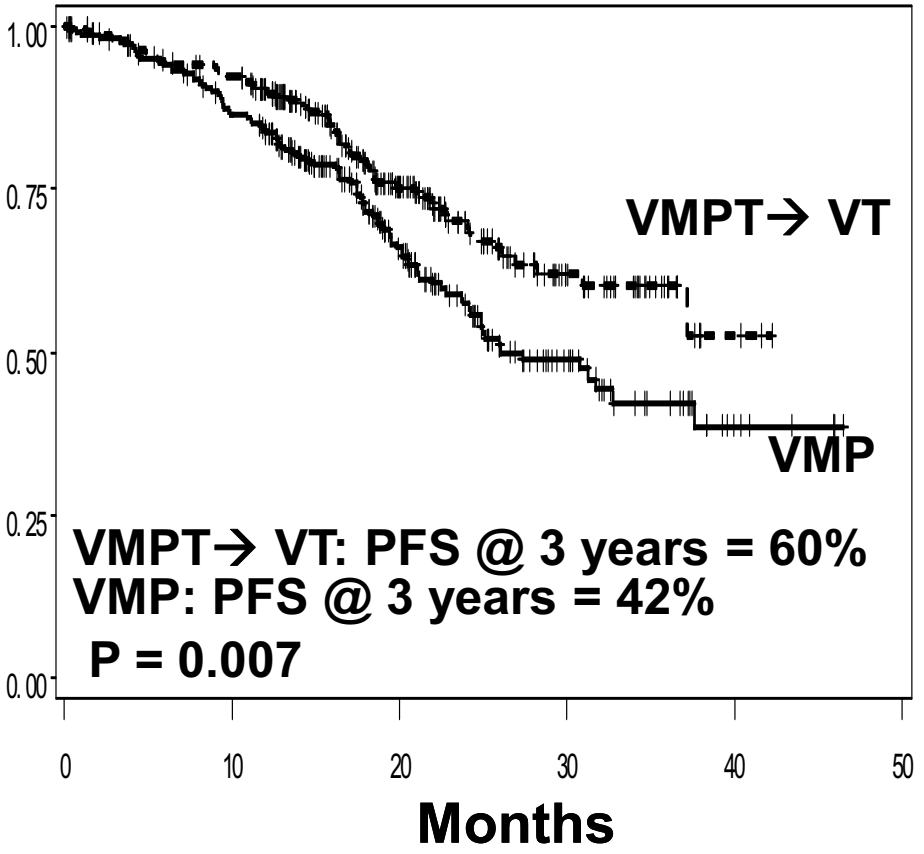
Phase III: VMPT + VT vs VMP

Median follow-up 21.6 months

Time to next therapy



Progression free survival



PFS comparable in patients with and without t(4;14) or t(14;16) or del17

Palumbo A, et al. ASH 2009. Abstract 128.

MM-015: MPR vs MP for long-term control in newly diagnosed MM

51 centres in Europe, Australia, and Israel (N = 459)

Double-blind treatment phase

Up to 9 courses in the absence of PD or unacceptable adverse events

Patients with newly diagnosed, untreated MM who are not eligible for a transplant

RANDOMIZATION

Melphalan 0.18 mg/kg, days 1–4
Prednisone 2 mg/kg, days 1–4
Lenalidomide 10 mg/day p.o. days 1–21 → **Lenalidomide**

Melphalan 0.18 mg/kg, days 1–4
Prednisone 2 mg/kg, days 1–4
Lenalidomide 10 mg/day p.o. days 1–21 → **Placebo**

Melphalan 0.18 mg/kg, days 1–4
Prednisone 2 mg/kg, days 1–4
Placebo days 1–21 → **Placebo**

Primary end-point: progression-free survival

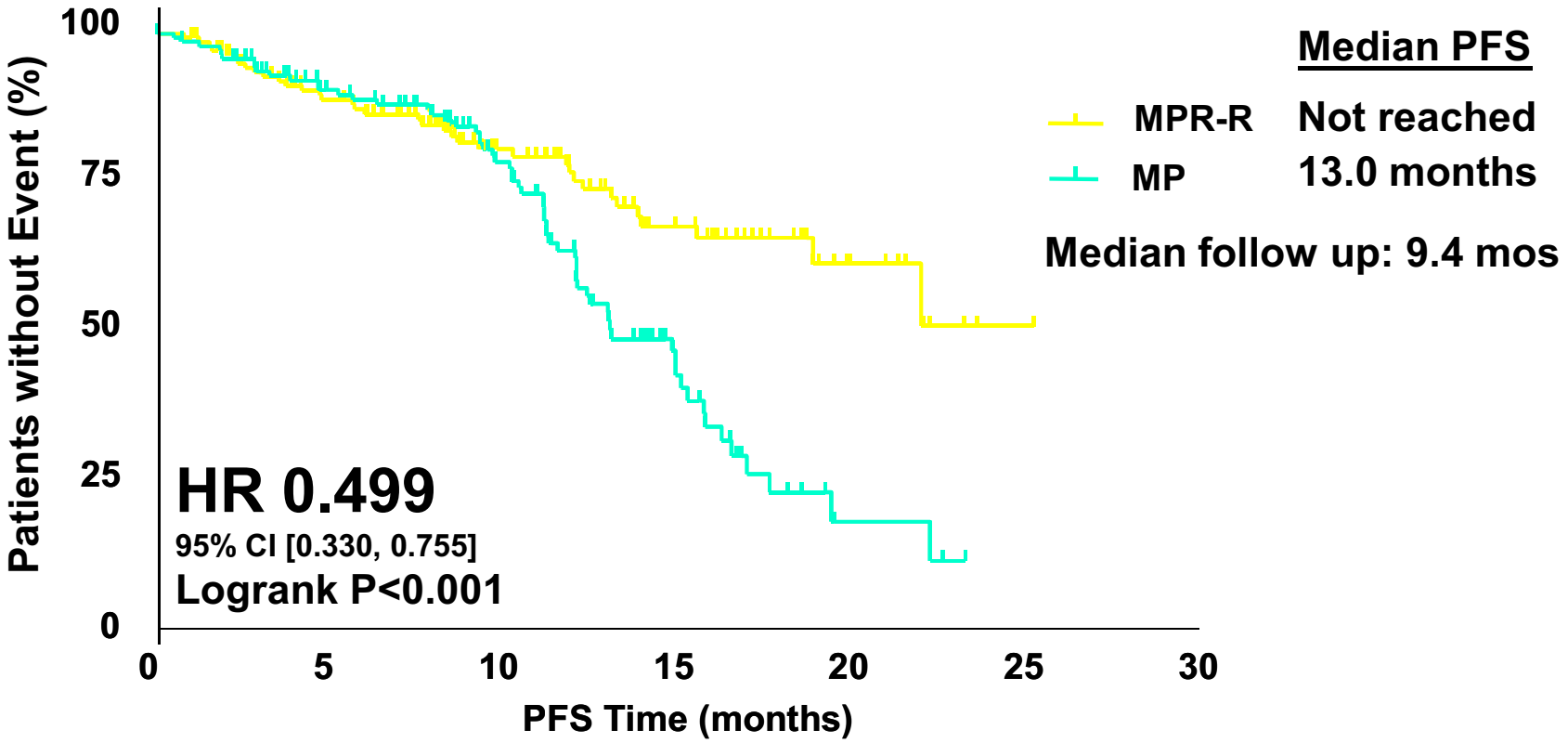
Secondary end-points: OS, TTP, ORR, TTR, duration of response, and quality of life

All patients will receive aspirin prophylaxis (75-100 mg/day)

TTR = time to response.

ClinicalTrials.gov. NCT00405756.

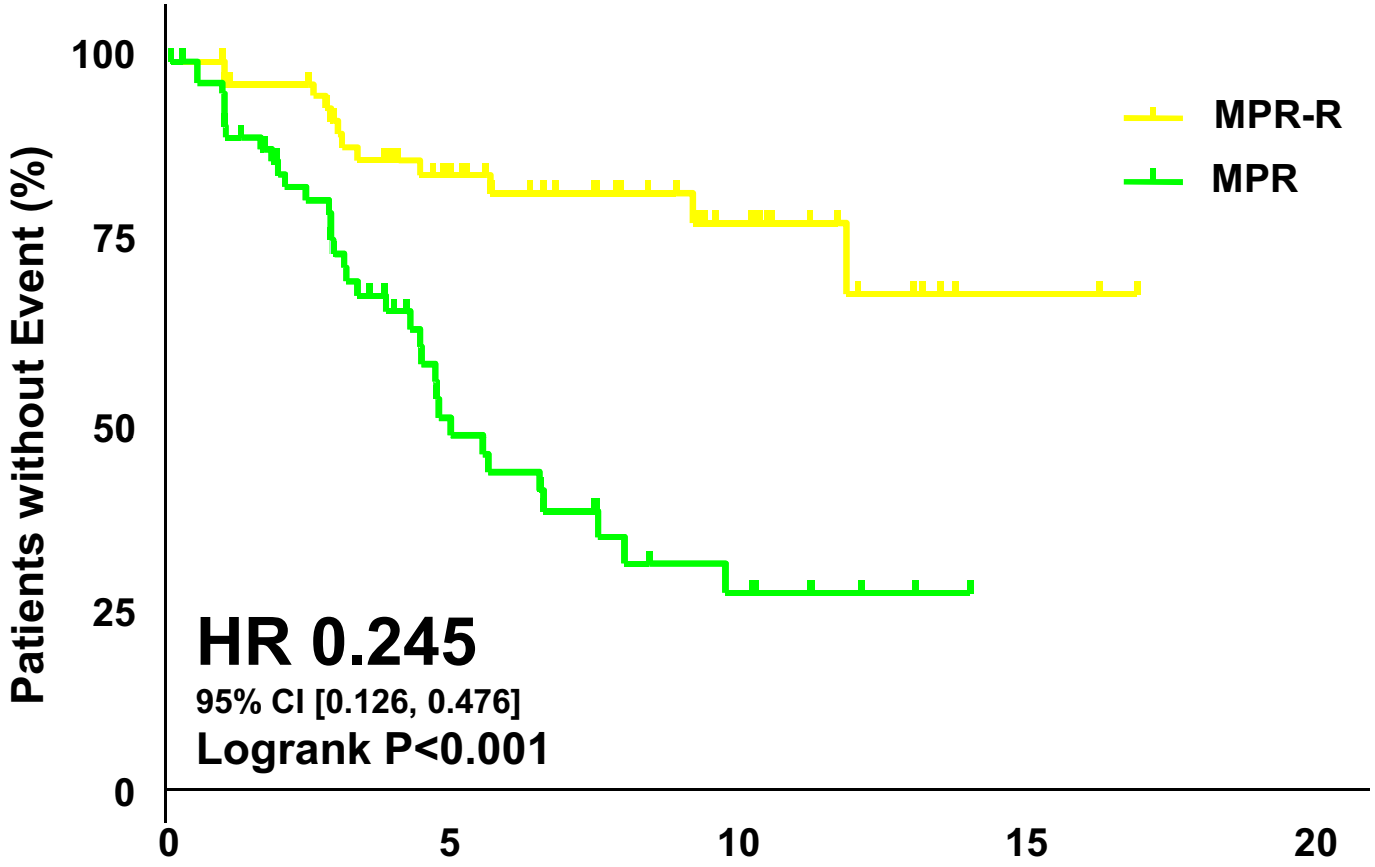
Progression-Free Survival
First Interim Analysis
50% Reduced Risk in PFS



Palumbo A, et al. ASH 2009. Abstract 613.

MPR-R vs. MPR
Landmark PFS Analysis After Cycle 9

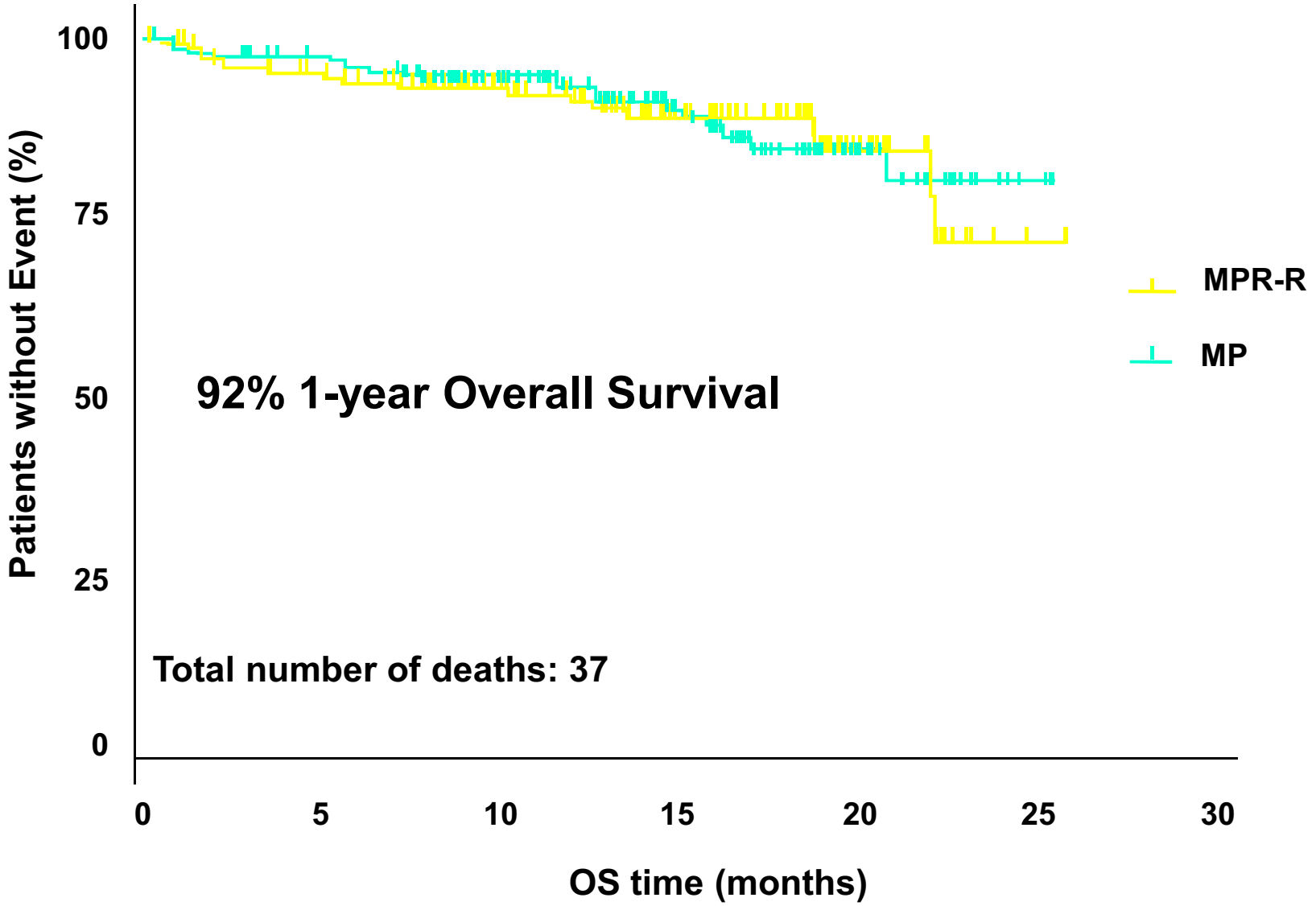
75% Reduced Risk in PFS



No. at Risk					
MPR-R	75	40	17	3	1
MPR	81	21	8	1	1

Palumbo A, et al. EHA 2010. Abstract 0566.

Overall Survival



Palumbo A, et al. ASH 2009. Abstract 613.

FIRST: lenalidomide + low-dose Dex vs MPT (IFM 07-01)

Inclusion criteria

- Previously untreated MM
- Age ≥ 65 years or not a candidate for transplantation
- No neuropathy of grade > 2
- CL_{Cr} > 30 ml/min

N = 1,590

Centres in EU, Switzerland, USA, and Canada

Lenalidomide 25 mg/day, days 1–21; every 28 days
Dexamethasone* 40 mg/day, days 1, 8, 15, 22; every 28 days
→ Until PD

Lenalidomide 25 mg/day, days 1–21; every 28 days
Dexamethasone* 40 mg/day, days 1, 8, 15, 22; every 28 days
→ Eighteen 4-week cycles

Melphalan* 0.25 mg/kg/day, days 1–4, every 42 days
Prednisone 2.0 mg/kg/day, days 1–4, every 42 days
Thalidomide* 200 mg/day, daily through 42-day cycle
→ Twelve 6-week cycles

* In patients older than 75 years: dexamethasone 20 mg/day, melphalan 0.20 mg/kg/day, thalidomide 100 mg/day.

Primary end-point: progression-free survival

Conclusions

- **Consolidation therapy following ASCT is under evaluation in clinical trials. Possible to achieve molecular CR.**
- **Maintenance therapy following ASCT is feasible and prolongs PFS. Impact on overall survival?**
- **Maintenance therapy following combination chemotherapy in elderly patients is feasible and prolongs PFS. Impact on overall survival?**