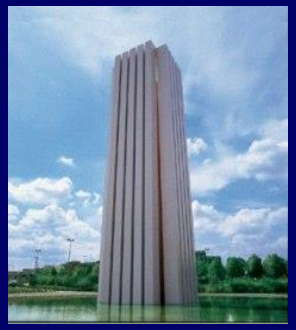


# Recent progress in first-line treatment of multiple myeloma

**Michel Delforge**
**University Hospital Leuven**
**Belgium**

**Tallinn, 19th October 2017**

# Goals of novel agent-based induction therapies

- Achieve a rapid and marked reduction in tumor burden, up to the VGPR and sometimes even CR level
- Reverse disease-related complications, such as hypercalcemia, renal failure and anemia
- Ameliorate symptoms
- Enable the successful collection of peripheral blood stem cells
- Minimize toxicities precluding subsequent autologous SCT

Cavo et al, Blood 2011; 117: 6063-73

# Outline of first-line treatment

# ESMO guidelines 2016

## Eligibility for ASCT

### Yes

Induction: 3-drug regimens
- VTD
- VCD
- RVD
- PAD

↓

200 mg/m² Melphalan followed by ASCT

↓

Maintenance
Lenalidomide

### No

First option: VMP, Rd, VRD

Second option: VCD, MPT

Other options : BP, CTD, MP

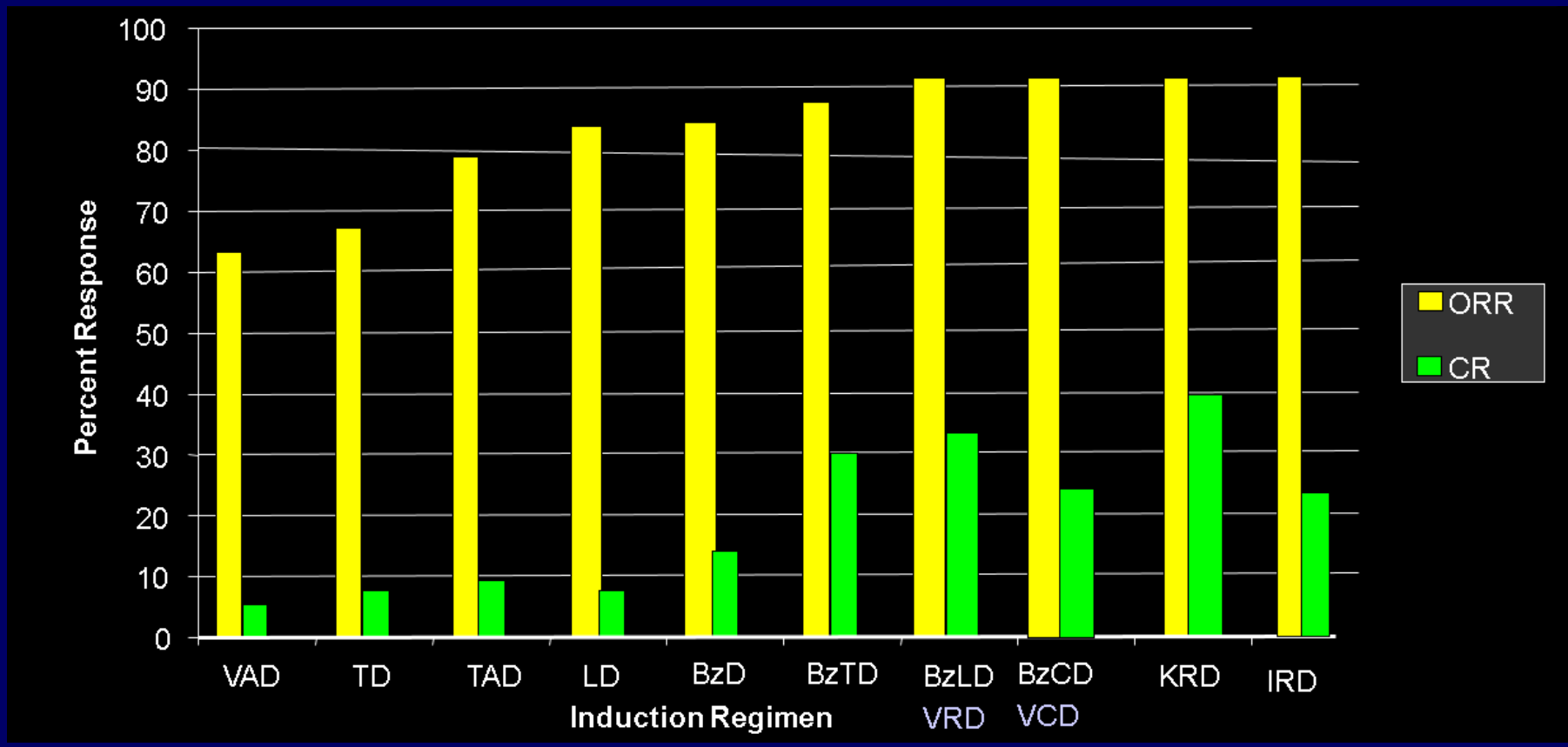
Moreau P, et al. Ann Oncol 2017

# What is the most optimal induction regimen ?

taking into consideration:

- published data
- drug availability
- toxicities

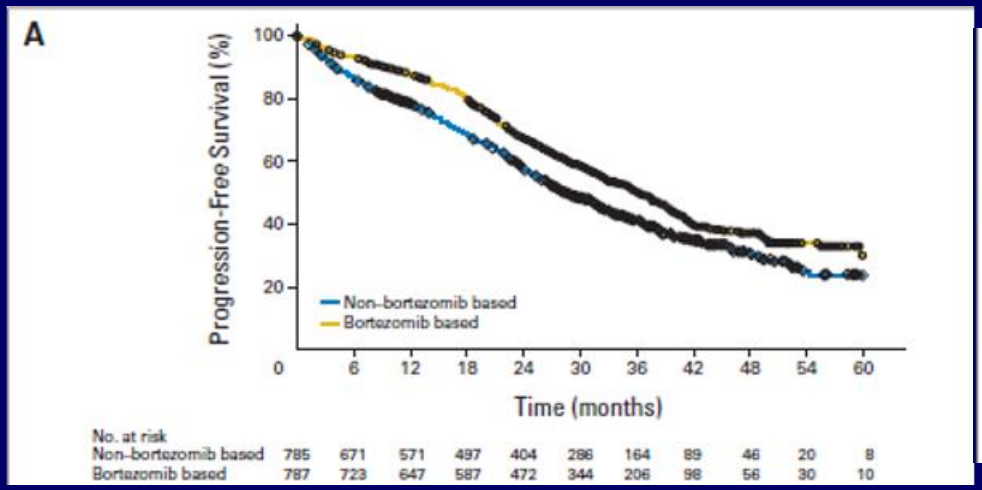
# Overview of induction regimens

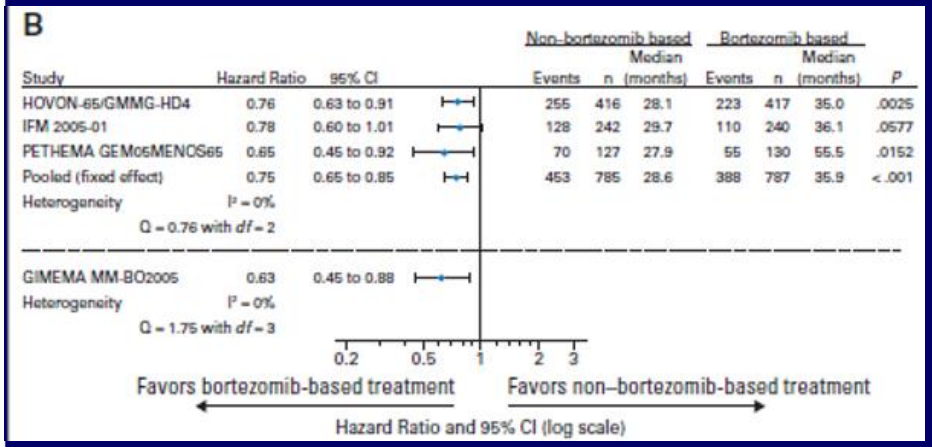



*Adapted from: How I treat MM in younger patients by Stewart K, Richardson P , San Miguel JF . Blood 2009; 114: 5436-43*

# Bortezomib-based induction regimens

## meta analysis




| | Bortezomib-based(n=775) | Non-bortezomib based (n=772) | P-value |
|---|---|---|---|
| CR+nCR post transplant | 38% | 24% | P<0.001 |
| Median PFS | 36 mo | 29 mo | P<0.001 |

Sonneveld et al. J Clin Oncol 2013;31:3279

# Bortezomib-based induction regimens

## VTD or VCD ?

- Multi-centre, randomized, open-label trial
- Patients: symptomatic de novo multiple myeloma, <66 years of age
- Treatment: VTD x 4 versus VCD x 4 as induction therapy prior to ASCT
  - Bortezomib 1.3 mg/m²/d, **SC** D1, 4, 8 and 11 in each arm

| | VTD<br>N = 169 | VCD<br>N = 169 | P value |
|---|---|---|---|
| ≥ CR | 13.0% | 8.9% | 0.22 |
| ≥ VGPR | 66.3% | 56.2% | 0.05 |
| ≥ PR | 92.3% | 83.4% | 0.01 |

Response: Centralised assessment (Dr Dejoie, Nantes) IMWG criteria 2011
Intent-to-treat population

Moreau, P et al. Blood 2016; 127:2569

# RVd for induction

## results from the phase II study

Table 4. Best response to treatment for the treated population and the phase 2 population

| | All patients (N = 66) | | | Phase 2 population (n = 35) | | |
|---|---|---|---|---|---|---|
| Response* | n | % | 90% CI | n | % | 90% CI |
| CR | 19 | 29 | 20-39 | 13 | 37 | 24-52 |
| nCR | 7 | 11 | 5-19 | 7 | 20 | 10-34 |
| VGPR | 18 | 27 | 18-38 | 6 | 17 | 8-31 |
| PR | 22 | 33 | 24-44 | 9 | 26 | 14-41 |
| CR + nCR | 26 | 39 | 29-50 | 20 | 57 | 42-71 |
| CR + nCR + VGPR | 44 | 67 | 56-76 | 26 | 74 | 59-86 |
| At least PR | 66 | 100 | 96-100 | 35 | 100 | 92-100 |

CI indicates confidence interval; CR, complete response; nCR, near-complete response; PR, partial response; VGPR, very good partial response.

*Per EBMT criteria,[23] all response categories, including VGPR, required a confirmatory assessment at 6 weeks.

n=8 cycles

Richardson et et al. Blood 2010;166:679

# Carfilzomib-lenalidomide-dexa (KRd)

## phase I/II study

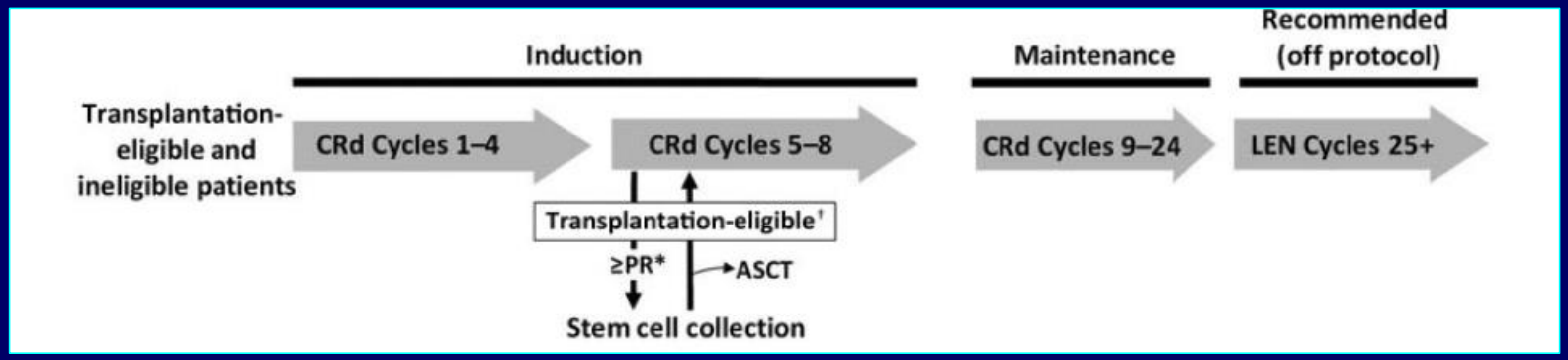



**Table 3. Best response to treatment in evaluable patients**

| | Response, n (%)* | | | |
|---|---|---|---|---|
| | ≥ PR | ≥ VGPR | ≥ nCR | sCR |
| All patients (N = 53) | 52 (98) | 43 (81) | 33 (62) | 22 (42) |
| **Treatment duration** | | | | |
| 4+ cycles (n = 49) | 49 (100) | 43 (88) | 33 (67) | 22 (45) |
| 8+ cycles (n = 36) | 36 (100) | 33 (92) | 28 (78) | 22 (61) |
| 12+ cycles (n = 29) | 29 (100) | 25 (86) | 21 (72) | 18 (62) |

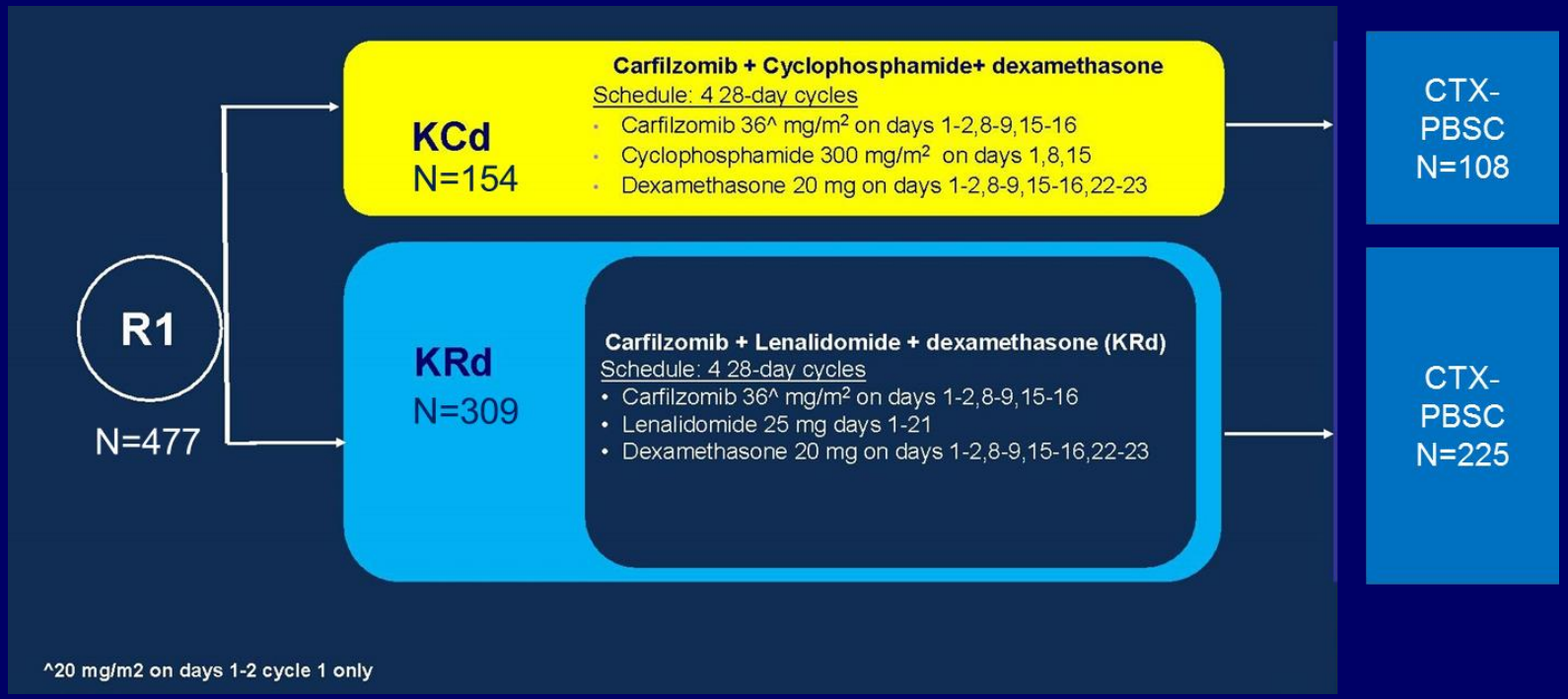
IMWG indicates International Myeloma Working Group; nCR, near-complete response; PR, partial response; sCR, stringent complete response; and VGPR, very good partial response.

*Assessed by Modified IMWG Uniform Criteria with the addition of nCR.

Jakubowiak et al. Blood 2012;120:1801

# KCd vs KRd

## carfilzomib, lenalidomide, and dexamethasone versus carfilzomib, cyclophosphamide, and dexamethasone

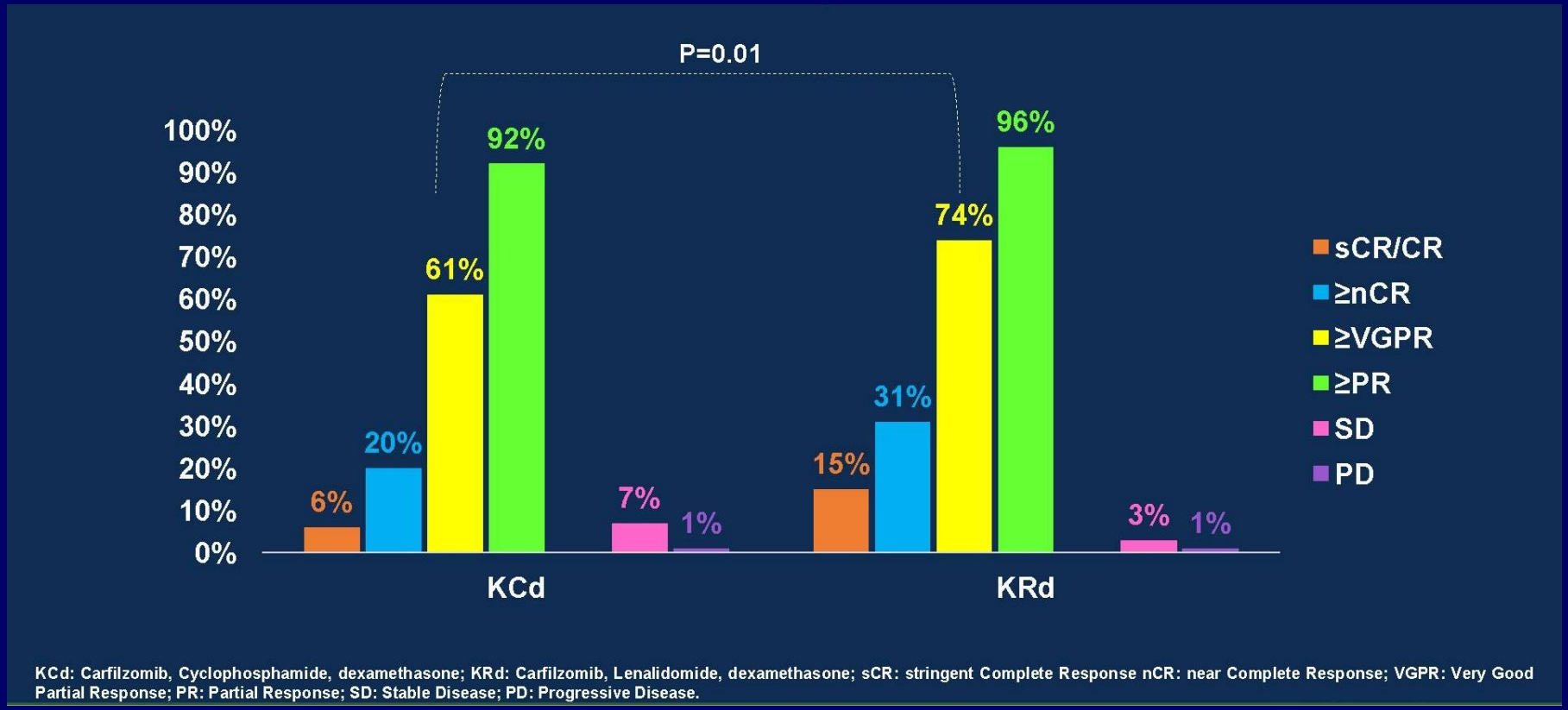



- Newly-diagnosed MM
- Median age: 57 years

Gay F, et al. Presented at ASCO 2017 (Abstract 8003), oral presentation; Gay F, et al. Presented at EHA 2017 (Abstract S410), oral presentation.

# KCd vs KRd

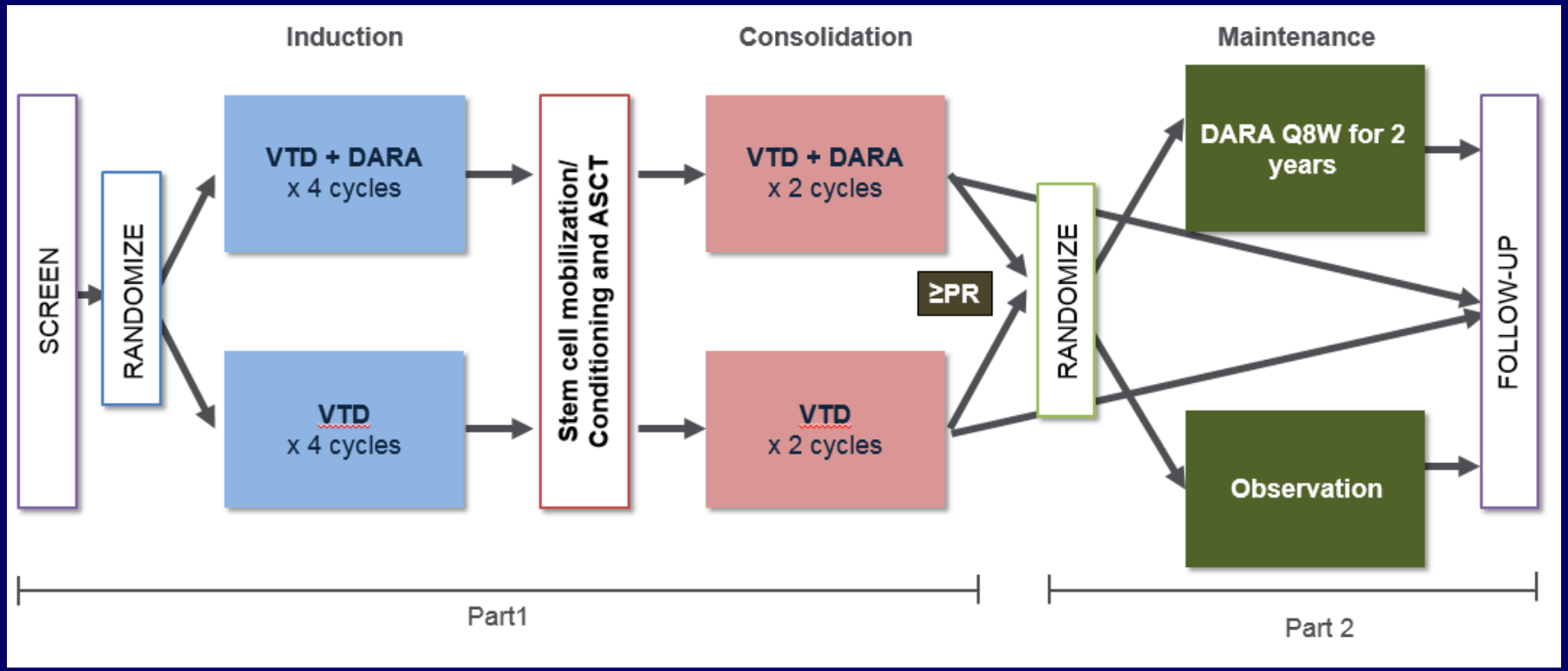
## best response




KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; sCR: stringent Complete Response nCR: near Complete Response; VGPR: Very Good Partial Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.


Gay F, et al. Presented at ASCO 2017 (Abstract 8003), oral presentation;
Gay F, et al. Presented at EHA 2017 (Abstract S410), oral presentation.

# VTD vs VTD + daratumumab:
## study design

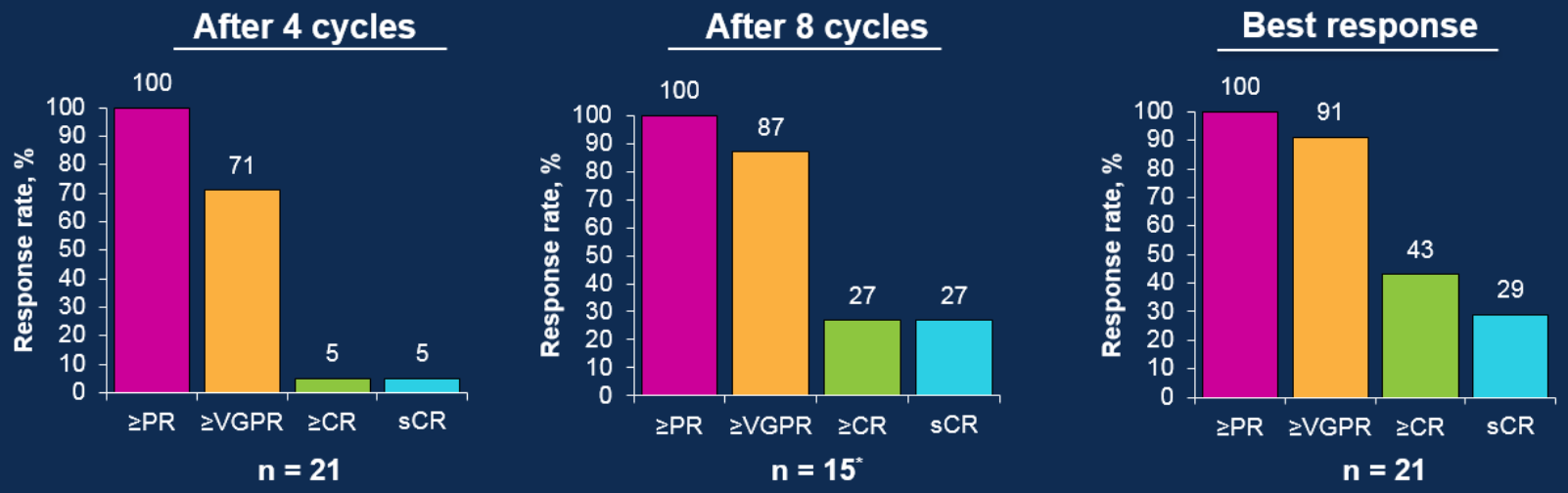


# KRd plus daratumumab

## phase I-II study

### Response Rate[a,b]

- Median number of treatment cycles: 11.5 (range, 1.0-13.0)




**Depth of response improved with duration of treatment**

*5 patients who proceeded to ASCT before C8 and 1 patient who discontinued due to PD at C7 were excluded.

PR, partial response; CR, complete response.
[a]Response-evaluable population. [b]Response rate (≥PR) evaluated by IMWG criteria; M-protein measurements by central lab assessment.

Usmani SZ, et al. Presented at EHA 2017 (Abstract P676), poster presentation.

# Conclusions for induction

- Induction regimen: a combination of a proteasome inhibitor seems to offer the best responses (e.g. VTD, VRD; future: KRd, IxaRd)
- number of cycles: usually 4 cycles are administered. For regimens like VTD this is mainly driven by neurotoxicity. Regimens like KRd give better responses with prolonged administration
- the added value of a monoclonal antibody like an anti-CD38 or elotuzumab is under investigations
- no significant impact of any regimen on stem cell mobilization efficiency

# Is there currently still a role for high-dose chemotherapy ?

# Historical data:

## ASCT is superior to conventional chemo

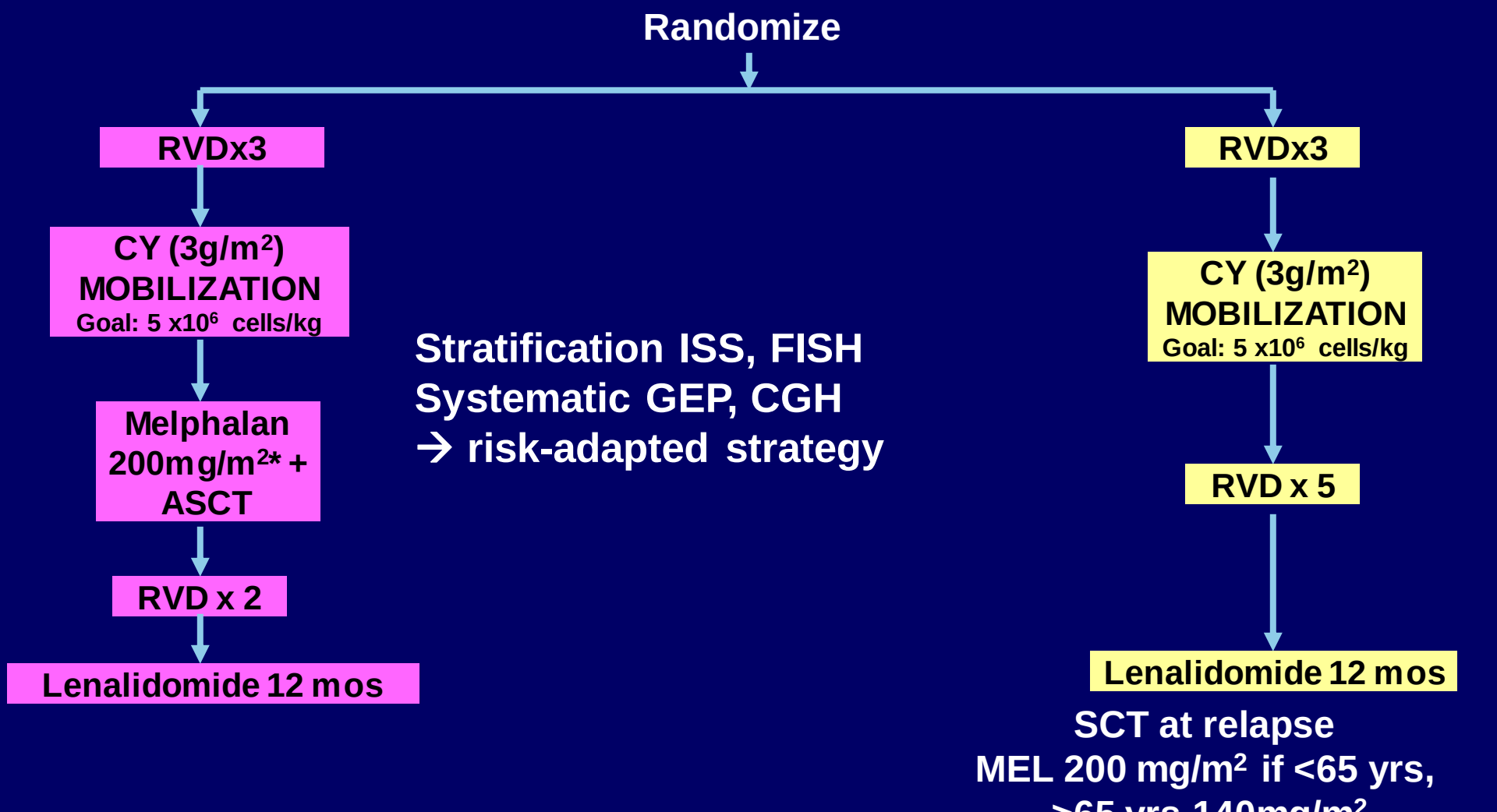
**Table 2. Randomized trials: single ASCT versus conventional chemotherapy**

| Reference | CR, % | Median PFS, mo | Median OS, mo |
|---|---|---|---|
| Attal et al[23] (1996) | 22 vs 5 | 28 vs 18 | 57 vs 42 |
| Child et al[24] (2003) | 44 vs 9 | 32 vs 20 | 55 vs 42 |
| Bladé et al[25] (2005) | 30 vs 11 | 42 vs 34 | 67 vs 65 |
| Fermand et al[26] (2005) | 8.5 vs 7 | 25 vs 19 | 47.8 vs 47.6 |
| Barlogie et al[27] (2006) | 17 vs 15 | 25 vs 21 | 58 vs 53 |

Attal et al. New Engl J Med 1996; 335: 91
Child et al. New Engl J Med 2003;348: 1875
Bladé et al. Blood 2005; 106: 3755
Fermand et al. J Clin Oncol 2005; 23: 9227
Barlogie et al. J Clini Oncol 2006;24: 929

# IFM/DFCI 2009 Study

## Newly Diagnosed MM Pts (SCT candidates)



# IFM 2009 trial:

## response rates

**Table 2. Response to Treatment.***

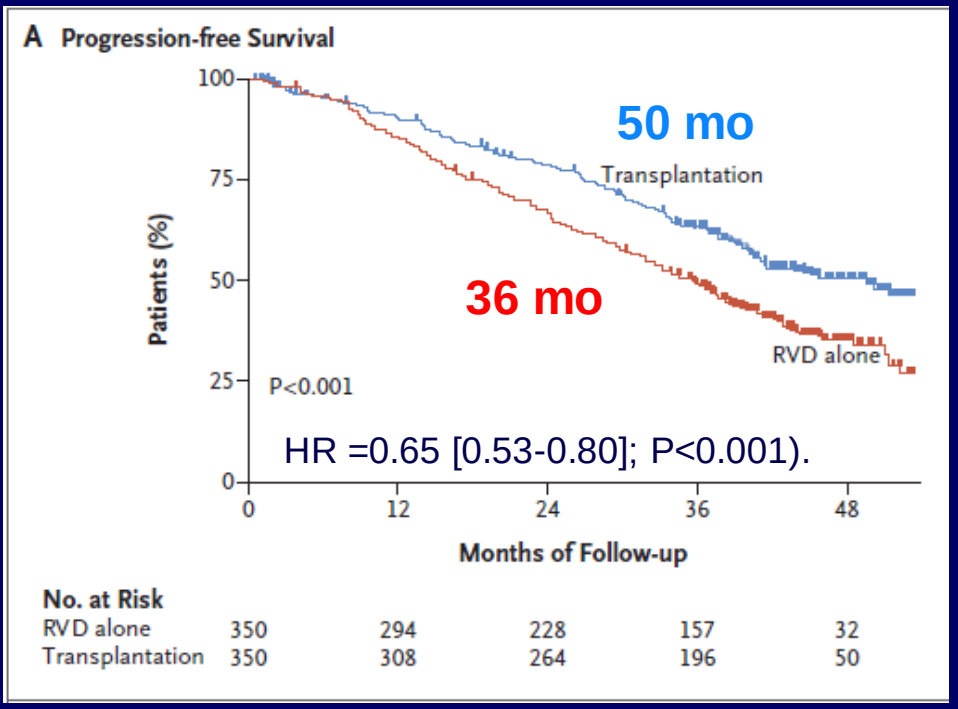
| Outcome | RVD-Alone Group (N=350) | Transplantation Group (N=350) | Adjusted P Value† |
|---|---|---|---|
| Best response during the study — no. (%) | | | 0.02 |
| Complete response | 169 (48) | 205 (59) | |
| Very good partial response | 101 (29) | 102 (29) | |
| Partial response | 70 (20) | 37 (11) | |
| Stable disease | 10 (3) | 6 (2) | |
| Complete response — no. (%) | 169 (48) | 205 (59) | 0.03 |
| Complete response or very good partial response — no. (%) | 270 (77) | 307 (88) | 0.001 |
| Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡ | 171/265 (65) | 220/278 (79 | <0.001 |

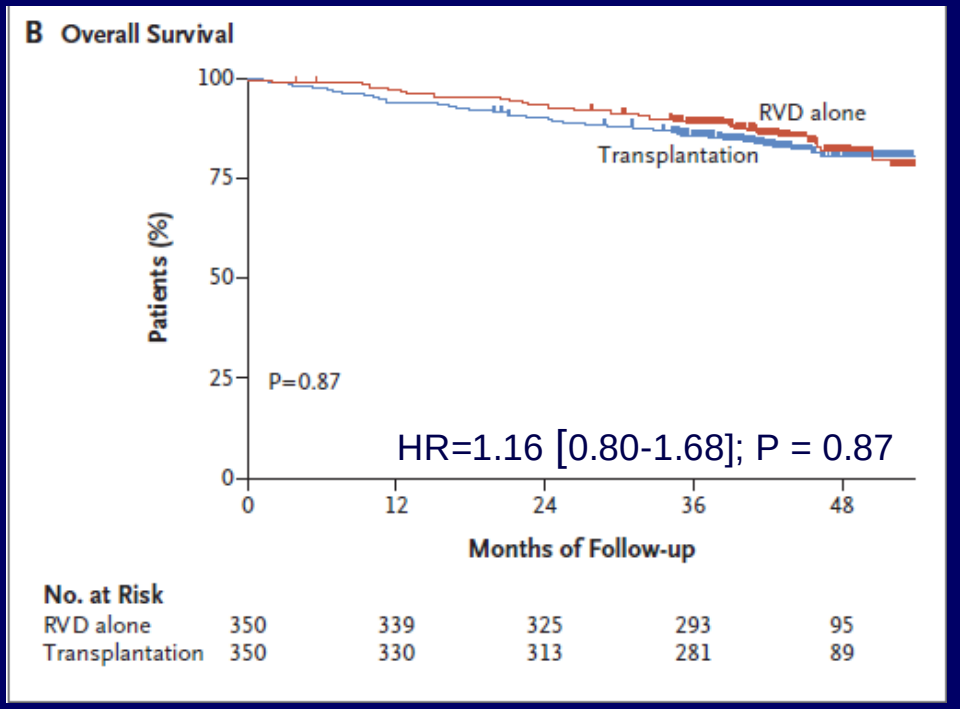
* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.
† P values were adjusted for multiplicity with the use of the Holm procedure to control the family-wise error rate at 0.05.
‡ Minimal residual disease was detected by means of flow cytometry. As a result of decisions made by the patient or the investigator, 5 patients in the RVD-alone group and 29 patients in the transplantation group were not tested.

Attal et al. N Engl J Med 2017;376:1311

# IFM 2009 trial:

## PFS and OS

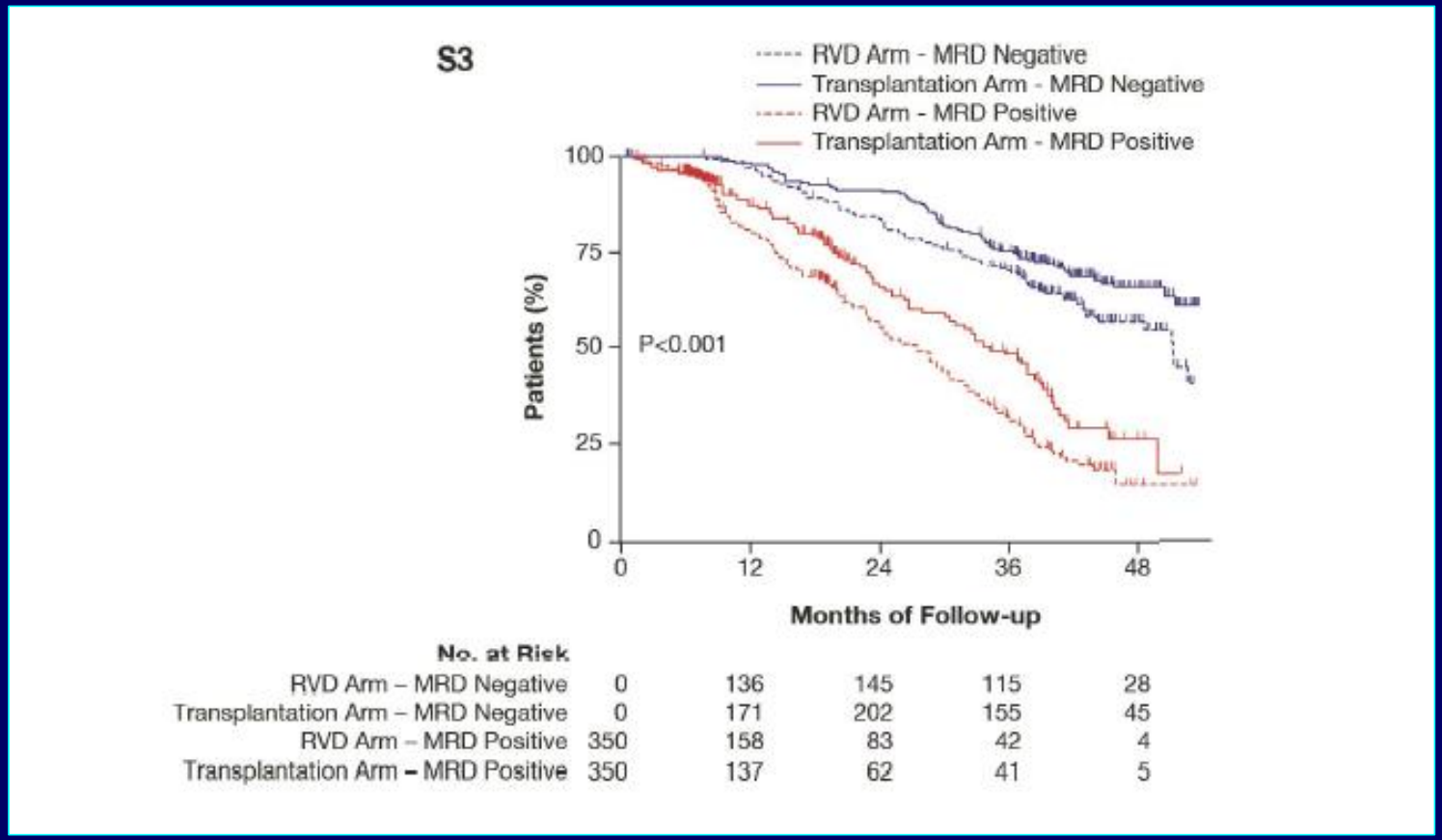



Attal et al. N Engl J Med 2017;376:1311

# IFM 2009 trial:

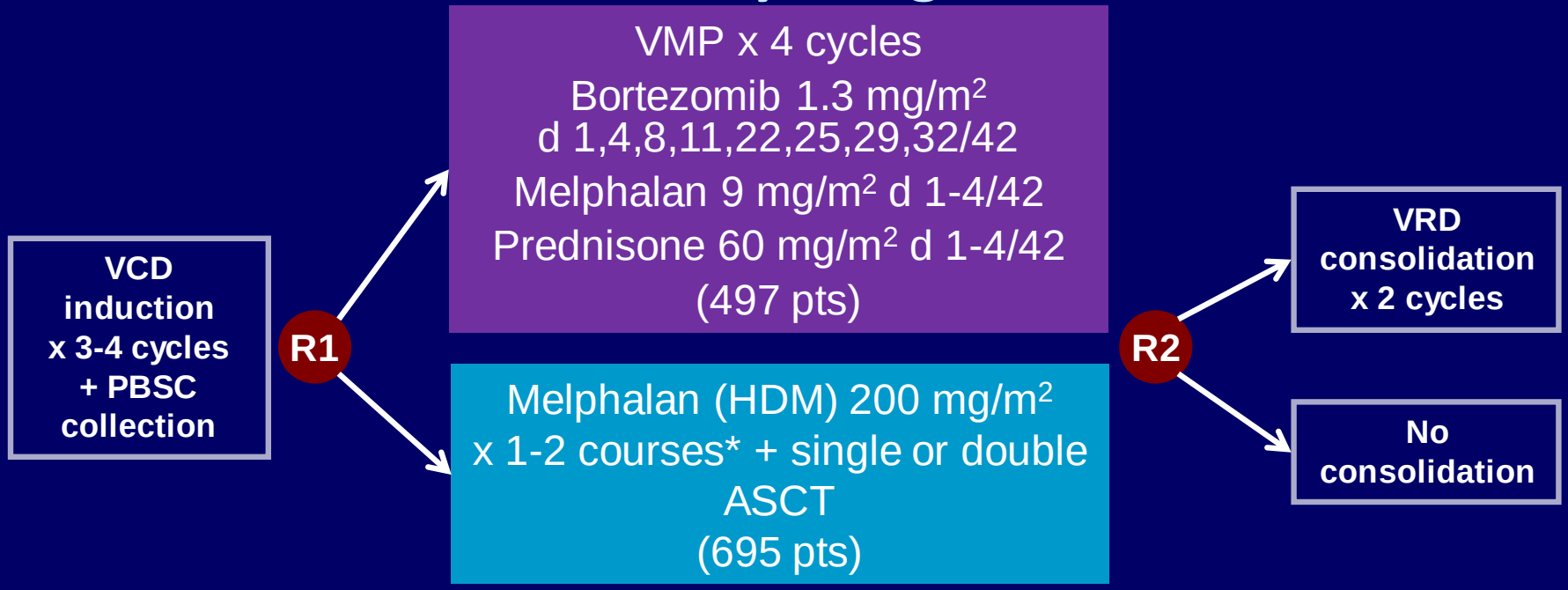
## Progression-free survival according to MRD status




Attal et al. N Engl J Med 2017;376:1311

# EMN02/HO95 MM trial:

## study design




**All pts received lenalidomide maintenance until R/P**

**Stratification: ISS I vs. II vs. III**

**Randomization to VMP *vs* HDM (1:1) in centers with a fixed single ASCT policy**

**Randomization to VMP *vs* HDM-1 vs HDM-2 (1:1:1) in centers with a double ASCT policy**

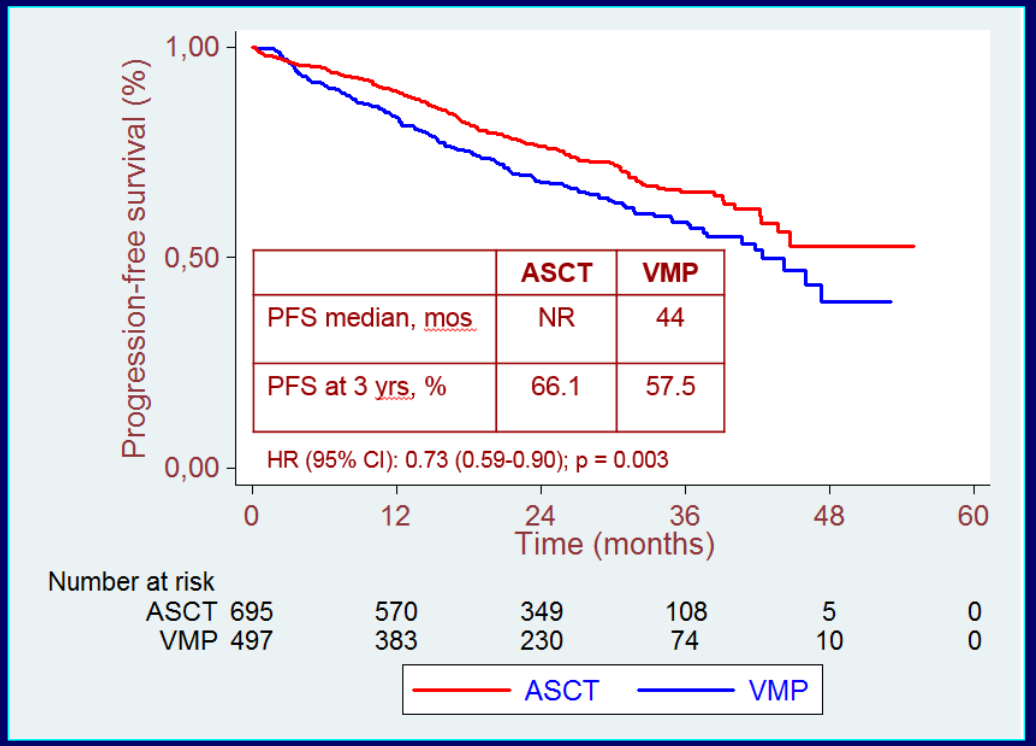
# EMN02/HO95 MM trial:

## First interim analysis

### Best response

| | ASCT (N=641) | VMP (N=451) | P-value |
|---|---|---|---|
| sCR, % | 17.0 | 18.2 | |
| CR, % | 25.3 | 25.3 | |
| VGPR, % | 43.2 | 30.4 | |
| PR, % | 11.2 | 14.9 | |
| <PR, % | 3.3 | 11.2 | |
| At least VGPR, % | **85.5** | **73.8** | <.0001 |

### PFS by randomization




Cavo et al. Presented at ASCO 2016 (Abstract 8000), oral presentation

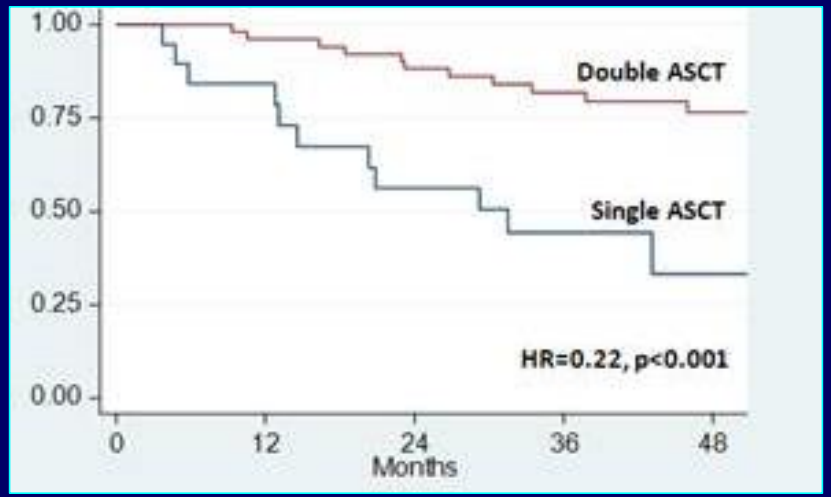
# Autologous SCT

## is one enough?

| | |
|---|---|
| **After first autologous stem-cell transplantation** | |
| Complete response | 89 (38%, 31·5–43·9) |
| Complete or near complete response* | 123 (52%, 45·7–58·5) |
| Very good partial response or better | 186 (79%, 73·6–84·0) |
| Partial response or better | 220 (93%, 90·0–96·4) |
| Minimal response or stable disease | 15 (6%, 3·2–9·5) |
| Progressive disease | 1 (<1%, 0·0–1·3) |
| **After second autologous stem-cell transplantation** | |
| Complete response | 98 (42%, 35·2–47·8) |
| Complete or near complete response* | 130 (55%, 48·7–61·4) |
| Very good partial response or better | 193 (82%, 76·9–86·7) |
| Partial response or better | 220 (93%, 90·0–96·4) |
| Minimal response or stable disease | 14 (6%, 2·9–8·9) |
| Progressive disease | 2 (1%, 0·0–2·0) |

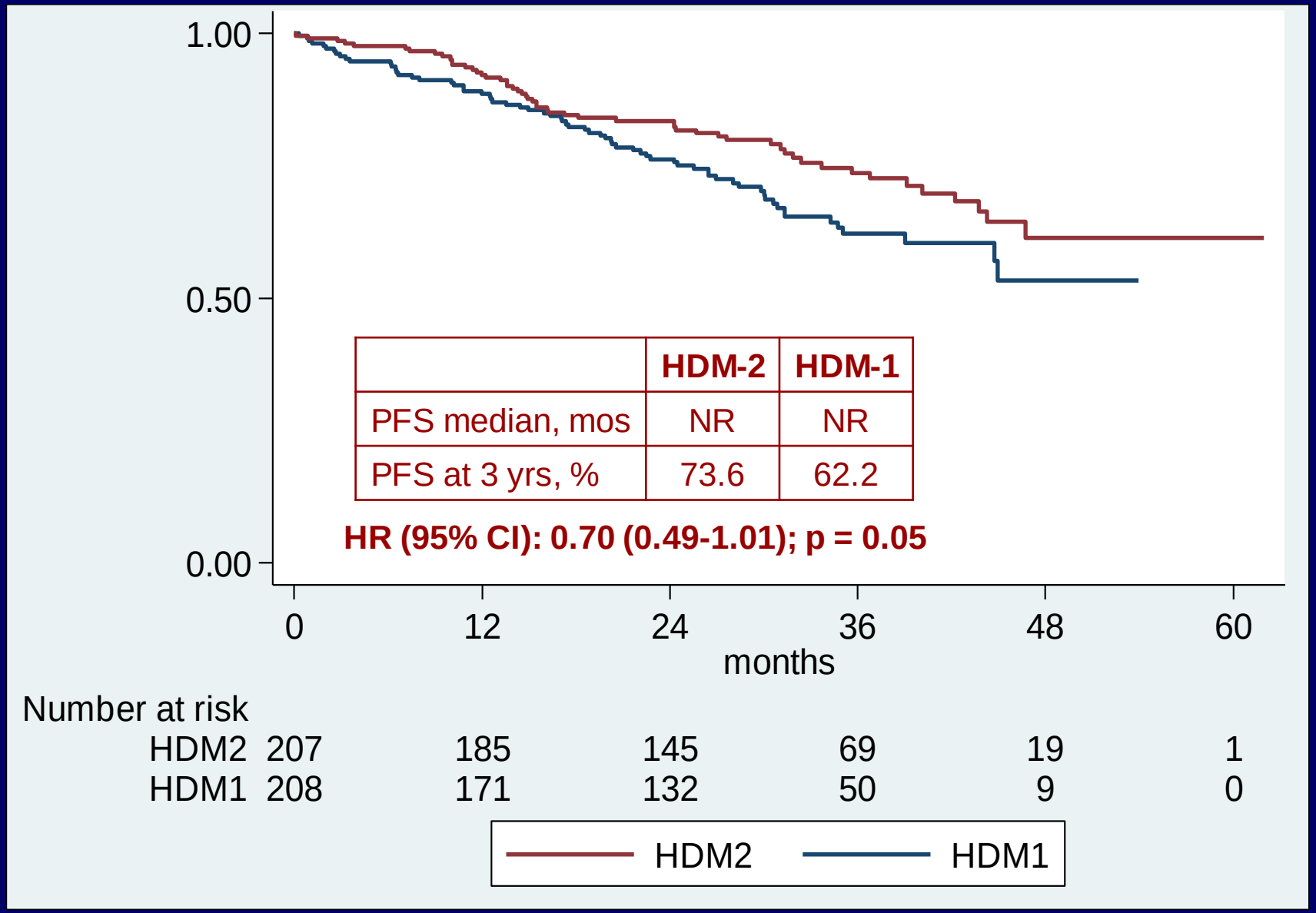
Cavo et al. Lancet 201;376:2075

**OS benefit with double ASCT particularly relevant for pts who failed CR after bortezomib-based induction therapies and who had high-risk cytogenetics or ISS 3**




Cavo et al. ASH 2013 (Abstract 767), oral presentation

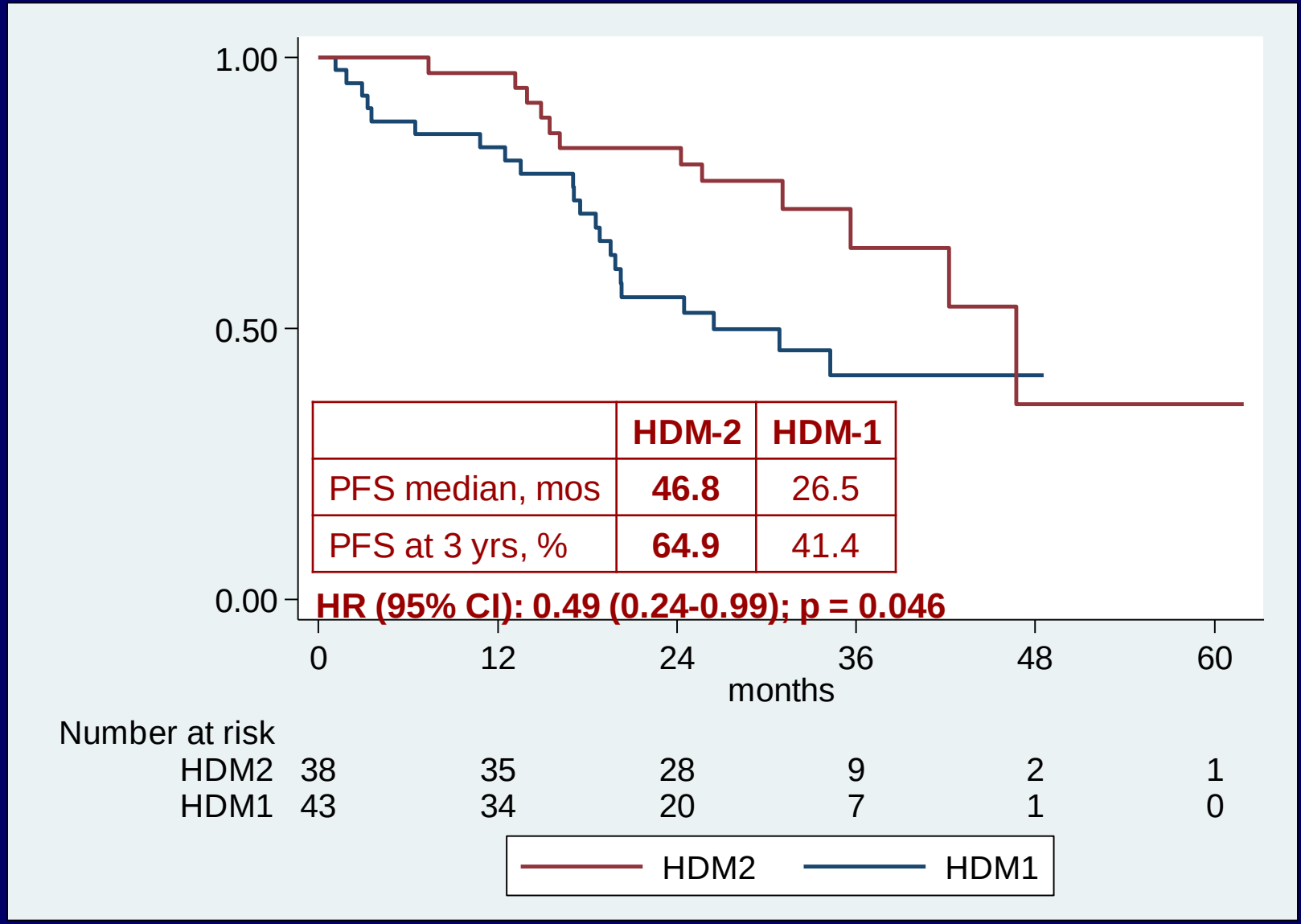
# EMN02: Single or tandem ASCT for all patients




Median follow-up: 32 months (IQR 26-41)

Cavo et al. ASH 2016; session 731

# EMN02: Single or tandem ASCT for high-risk cytogenetics




Cavo et al. ASH 2016; session 731

# Time to further improve the conditioning regimen ?

## Combination of melphalan with bortezomib

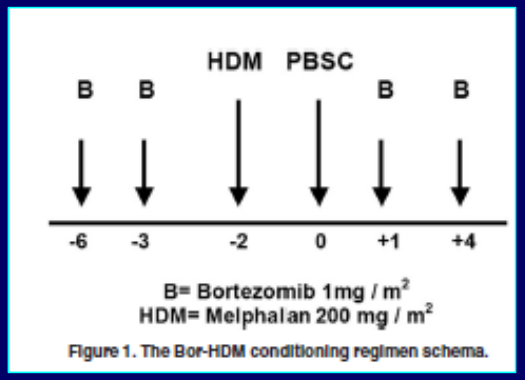
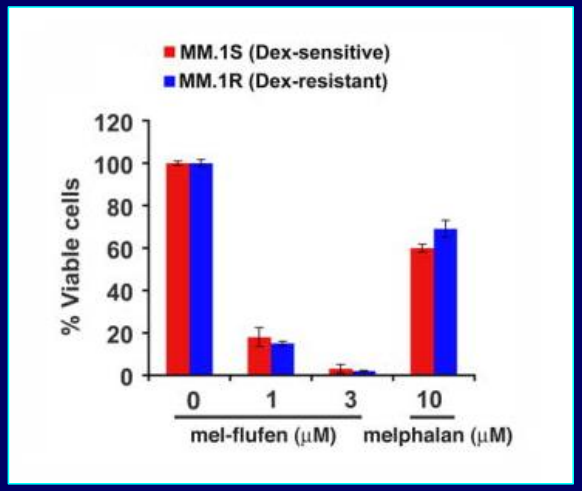


Figure 1. The Bor-HDM conditioning regimen schema.

| | All patients | | |
|---|---|---|---|
| Response, n (%) | IFM 2005-01 (n = 115) | Bor-HDM (n = 46) | *P* |
| CR | 13 (11) | 16 (35) | .001 |
| VGPR* | 49 (43) | 16 (35) | |
| PR | 50 (43) | 12 (26) | |
| SD | 3 (3) | 2 (4) | |
| CR + VGPR | 62 (54) | 32 (70) | .078 |

Roussel et al. Blood 2010;115:32

## New drug formulations: mel-flufen




Chauhan et al. Clin Cancer Res 2013;11:3019

blood

Prepublished online October 7, 2014;
doi:10.1182/blood-2014-07-552059

**Curing myeloma at last: defining criteria and providing the evidence**

Bart Barlogie, Alan Mitchell, Frits van Rhee, Joshua Epstein, Gareth J. Morgan and John Crowley

# What are the treatment goals ?

# =

- **full eradication of the disease (cfr acute leukemia) ?**
- **continuous suppression of minimal residual disease (cfr CML) ?**
- **bringing the disease back to an indolent phase (cfr some forms of indolent lymphoma ?)**

# Aims of consolidation and maintenance therapy

## Consolidation

- Improve response/induce deeper response following therapy
  - by administration of treatment for a limited period

## Maintenance

- Maintain response achieved following therapy
  - by administration of treatment for a prolonged period

**Reduce the risk of relapse**
**extend progression-free and overall survival**

# Phase 3: VTD vs TD (GIMEMA study)

## impact of VTD consolidation

**Per-protocol analysis: n=321, received entire treatment program**

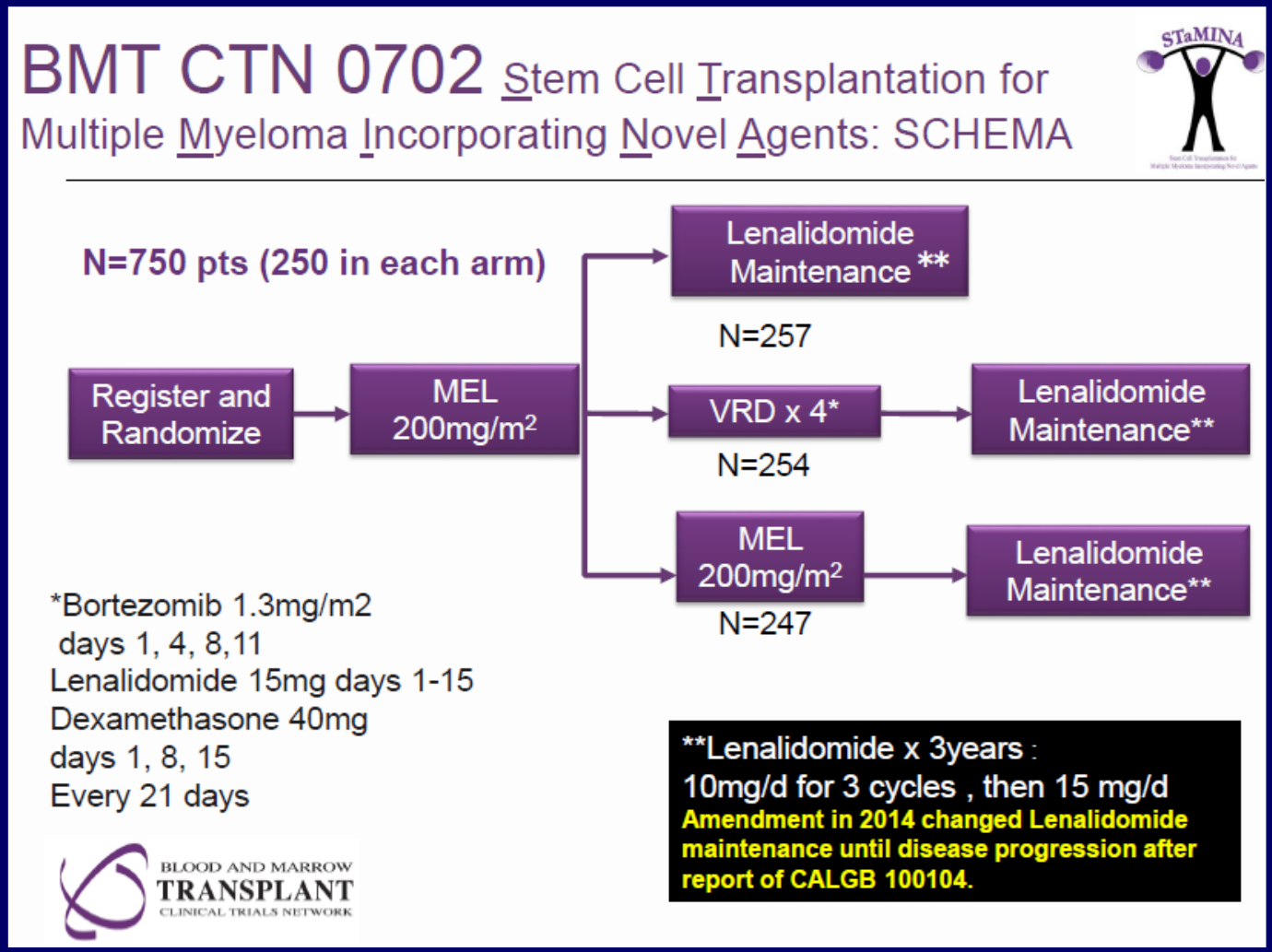
| | VTD | TD | p |
|---|---|---|---|
| CR post-consolidation | 61% | 47% | 0.012 |
| Upgrade to CR post-consolidation | 30.4% | 16.6% | 0.030 |
| Landmark analysis from start of consolidation (30 months median follow up) | | | |
| 3-yr PFS | 60% | 48% | 0.025 |

- Frequency of grade 2/3 PN
  - 8,1% VTD, 2,4% TD
- VTD arm: patients received 93% of planned doses of bortezomib and thal

Cavo et al. Blood 2012;120:9

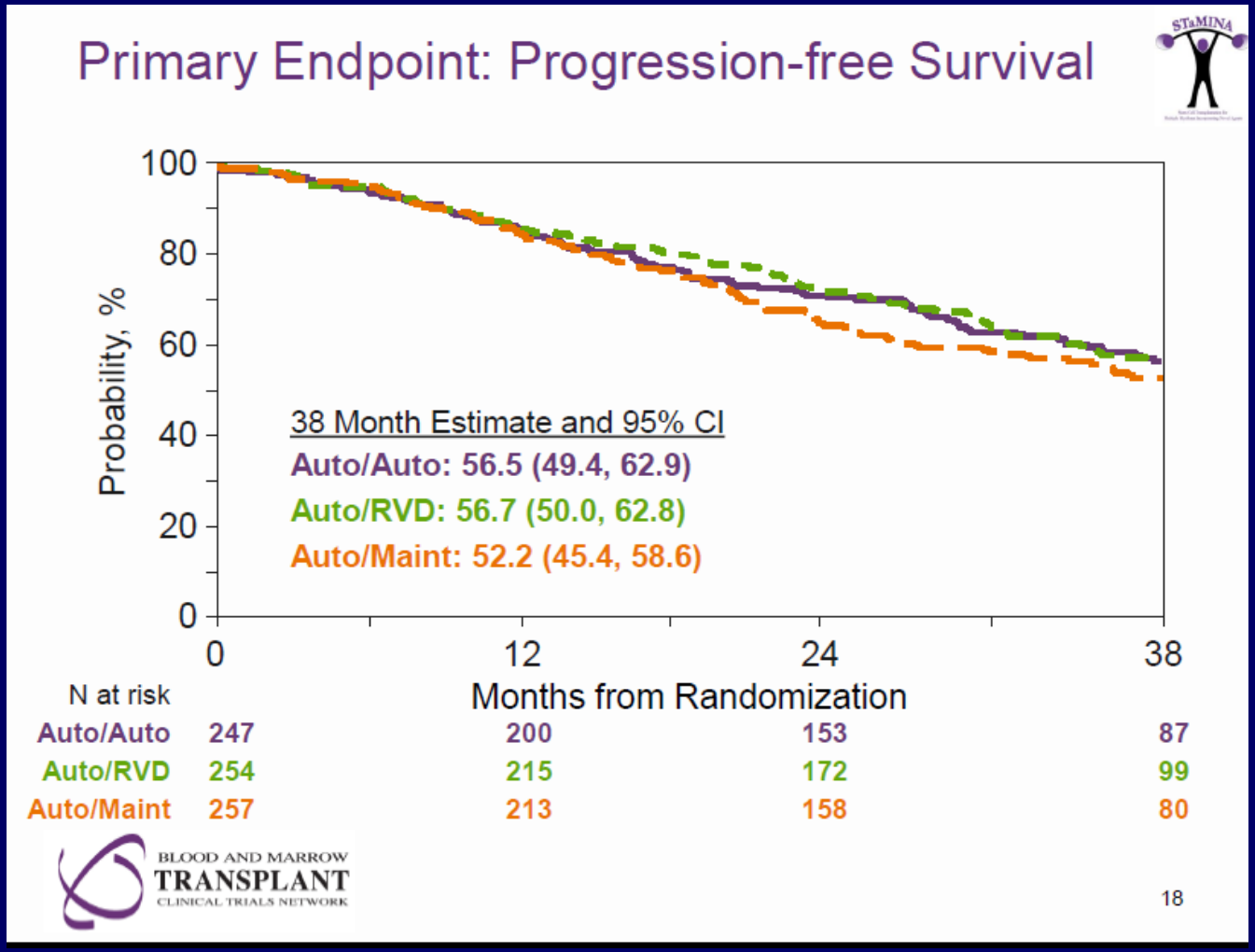
# Consolidation vs maintenance:

## the STAMINA trial




Stadtmauer et al. ASH 2016; LBA-1

# The STAMINA trial:
## progression-free survival




Stadtmauer et al. ASH 2016; LBA-1

# The STAMINA trial:

## delivered treatment vs intention to treat

### Compliance with each intervention

| | Auto/Auto (N=247) | | Auto/RVD (N=254) | | Auto/Maint (N=257) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Received 2nd Intervention | | | | | | |
| No | 79 | 32.0 | 30 | 11.8 | - | - |
| Yes | 168 | 68.0 | 224 | 88.2 | - | - |
| Started maintenance | | | | | | |
| No | 41 | 16.6 | 43 | 16.9 | 14 | 5.4 |
| Yes | 206 | 83.4 | 211 | 83.1 | 243 | 94.6 |

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

17

Stadtmauer et al. ASH 2016; LBA-1

# Key Questions for Maintenance

- Which drug at which dose ?
  - ~~Chemotherapy~~
  - ~~Steroids~~
  - Interferon-α
  - Immunomodulatory agents:
    - thalidomide
    - lenalidomide
  - Proteasome inhibitors: bortezomib, ixazomib
- Which patients benefit most from maintenance ?
- How long should maintenance treatment be given ?
  - Based on response
  - Based on treatment duration:
    - for a fixed duration (eg, 1 or 2 y)?
    - until progression ?

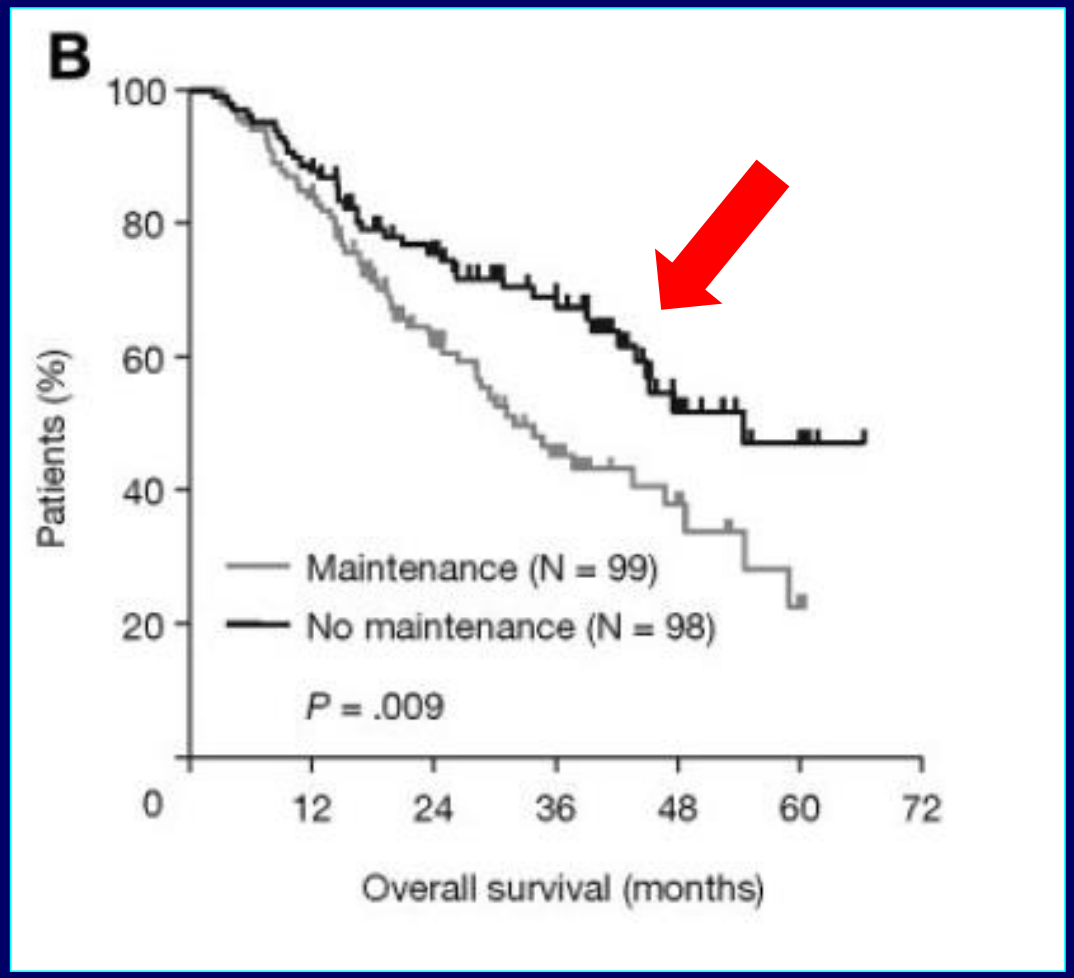
# Thalidomide maintenance therapy

| | Significant improvement in PFS with maintenance therapy | Significant improvement in OS with maintenance therapy | Survival after relapse |
|---|---|---|---|
| Spencer | Yes | Yes (3 years follow up) | Similar in all groups |
| Attal | Yes | Yes (@ 39 m), but OS advantage disappeared with longer follow-up (5.7 years) | Similar in all groups |
| Barlogie | Yes | Yes (7.2 years follow-up) | Reduced OS after thal exposure |
| Lokhorst | Yes | No | Reduced OS after thal exposure |
| Morgan | Yes | No | Reduced OS after thal exposure |
| Stewart | Yes | No | Reduced OS after thal exposure |

Spencer et al. J Clin Oncol 2009; 27: 1788-1793; Attal et al. Blood 2006; 108: 3289-3294; Barlogie et al. N Engl J Med 2006; 354: 1021-1030; Blood 2008; 112: 3115-3121; J Clin Oncol 2010; 28: 1209-1214 & Data Suppl; Lokhorst et al. Blood 2010; 115: 1113-20; Morgan et al. ASH 2011 (abstract 993), oral presentation; Stewart et al. ASH 2010 (Abstract 39), oral presentation

# Thalidomide maintenance:

## adverse prognosis in high-risk cytogenetics

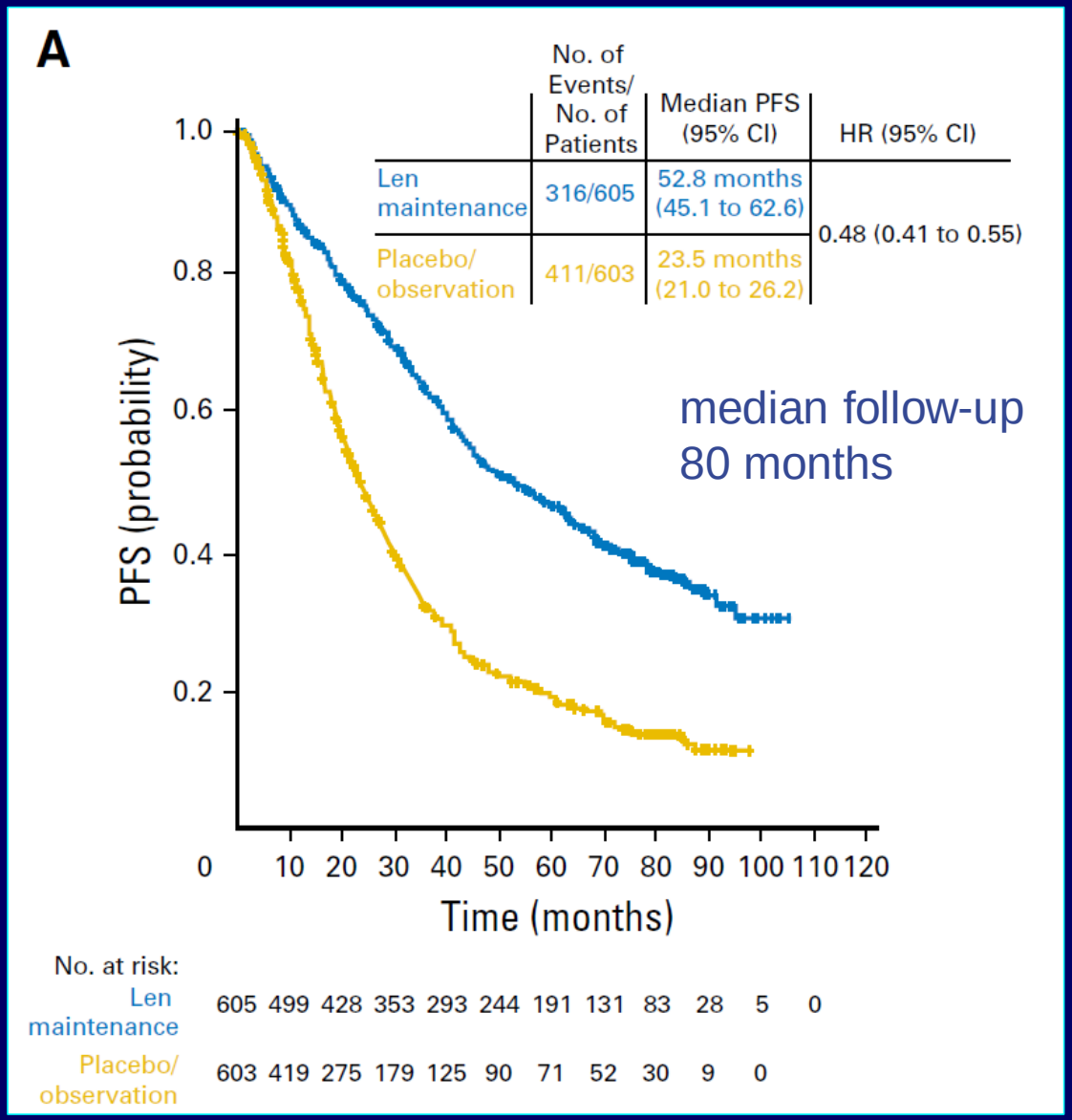



**Adverse cytogenetics defined as:**

- **amp (1q)**
- **t(4;14)**
- **t(14;16)**
- **t(14;20)**
- **del(17p)**

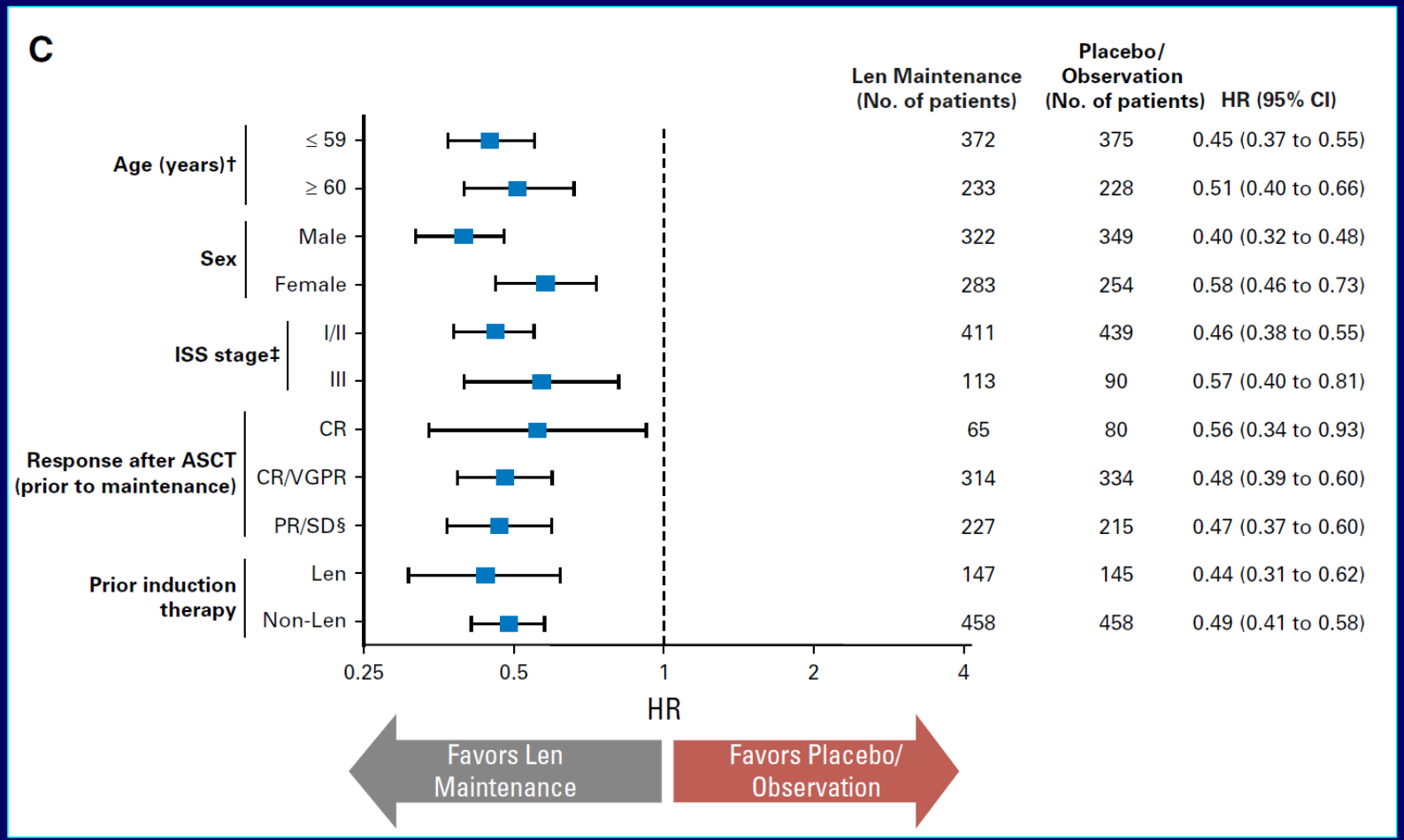
Morgan et al. Blood 2012;119:7

# Lenalidomide maintenance: PFS



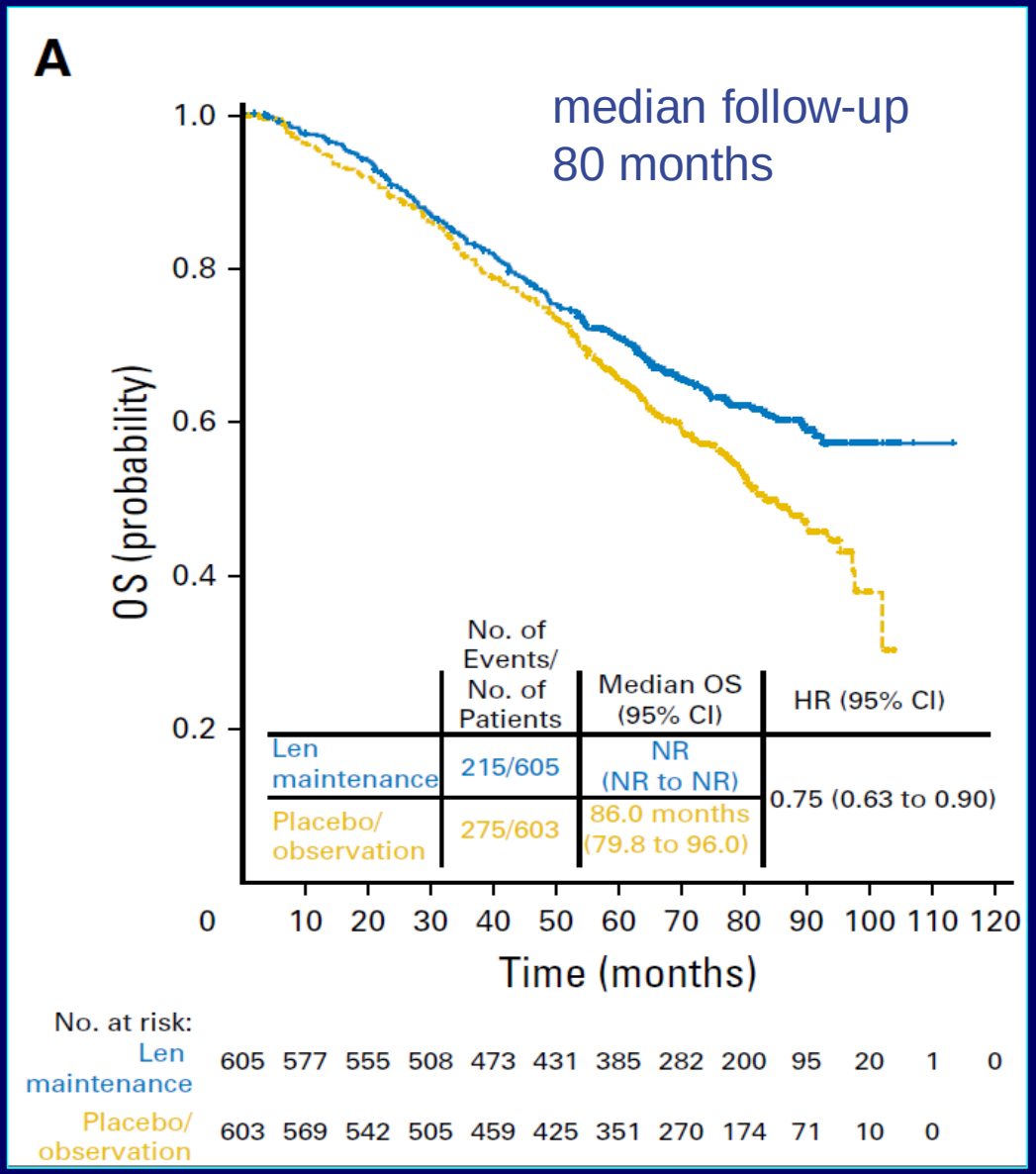

McCarthy et al. J Clin Oncol 2017; Epub Jul 25

# Lenalidomide maintenance:
## subgroup analysis



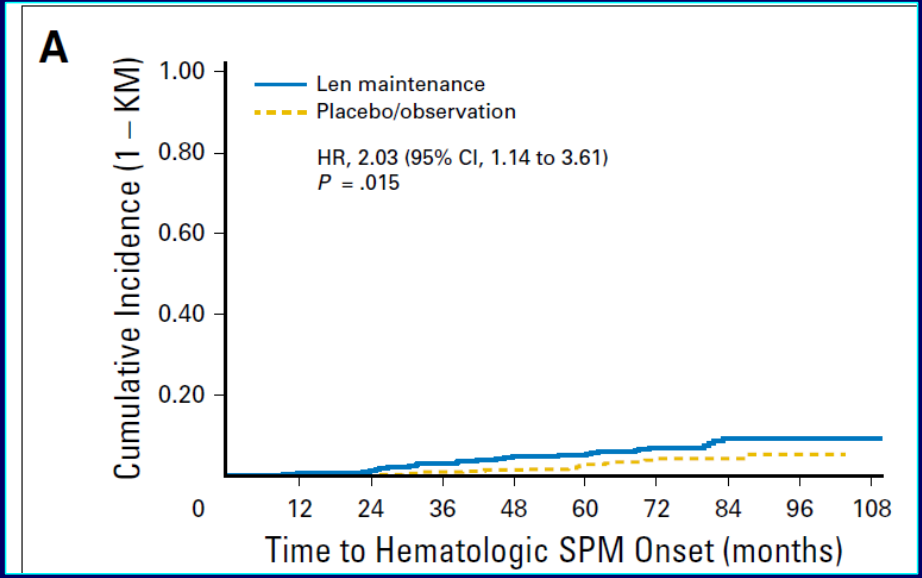

McCarthy et al. J Clin Oncol 2017; Epub Jul 25

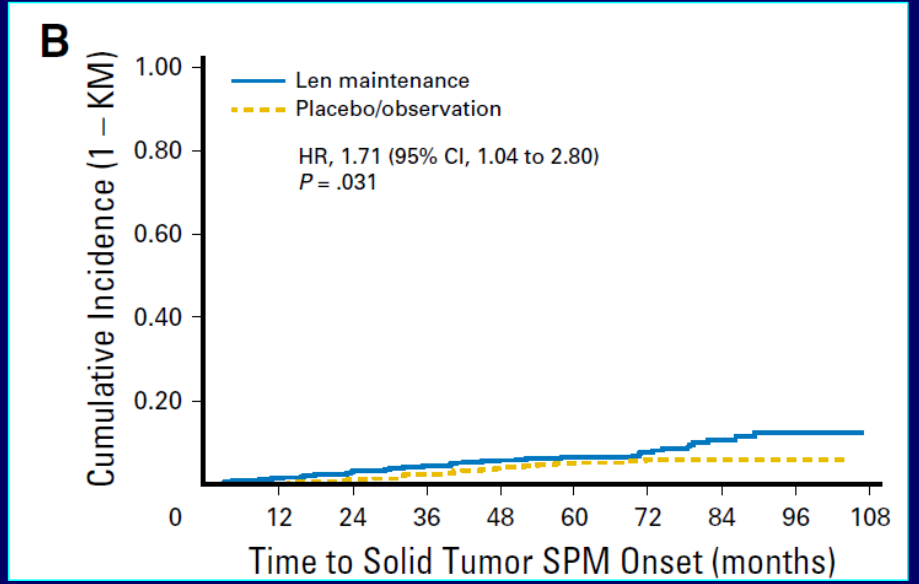
# Lenalidomide maintenance: OS




McCarthy et al. J Clin Oncol 2017; Epub Jul 25

# Second primary malignancies (SPM) with lenalidomide maintenance




McCarthy et al. J Clin Oncol 2017; Epub Jul 25

# Maintenance with proteasome inhibitors

## Bortezomib

| Study details* | n | Treatment | PFS | OS |
|---|---|---|---|---|
| HOVON 65 MM / GMMG-HD4[1]<br>Median follow-up: 91.4 months<br>(Overall trial) | 413<br><br>414 | PAD x 3 → HDM → Bortezomib every 2 weeks for 2 years<br><br>VAD x 3 → HDM → Thalidomide daily for 2 years | 34 m<br><br>28 m; p=0.001 | 48%<br><br>45%; p=0.22<br><br>bortezomib plus tandem ASCT abrogates neg impact of del 17p |
| PETHEMA/GEM[2]<br>Median follow-up: 34.9 months<br>(From maintenance start) | 89<br><br>87<br><br>90 | VT (1 cycle bortezomib every 3 m, thal daily) for 3 years<br><br>Thal (daily for 3 years)<br><br>Interferon-$\alpha$2b (3 x week for 3 years) | Significant benefit for VT<br>P=0.0009 | Not significantly diffferent between arms |

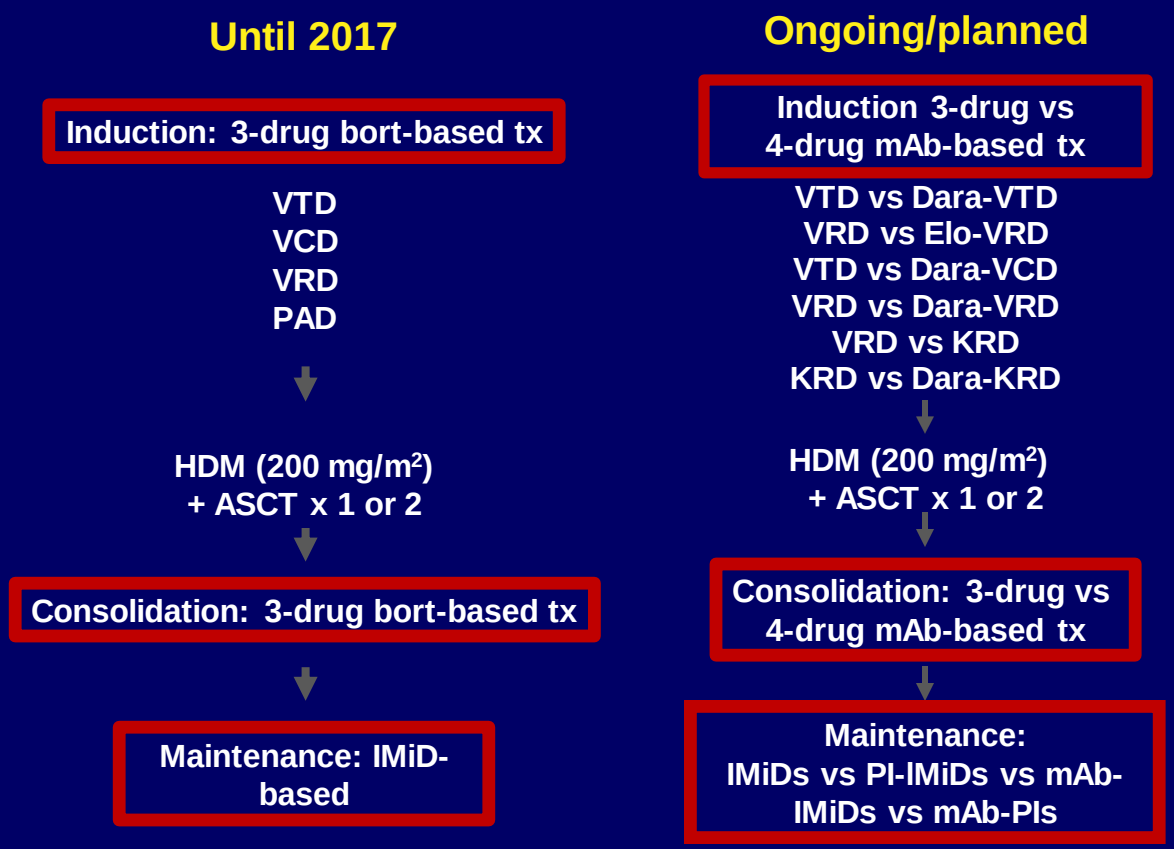
## Ixazomib

| Study details | n | Treatment | PFS |
|---|---|---|---|
| MLN9708[3]<br>Median follow-up: 31.2 months (Overall trial) | 21 | Ixazomib + Rd → ASCT (eligible patients) → ixazomib maintenance | Not reached |

*Bortezomib administered at 1.3mg/m2 IV in both studies

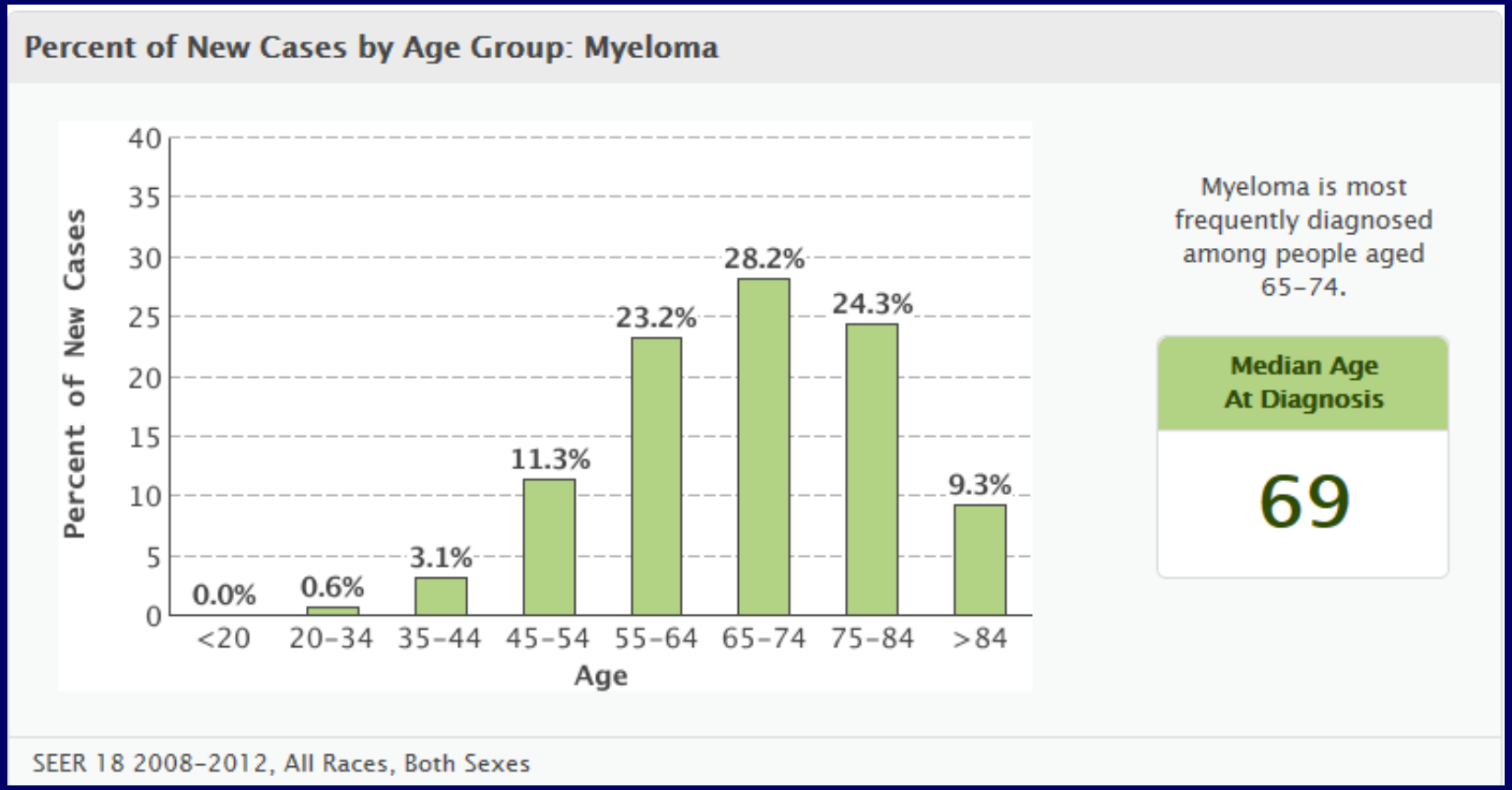

1. Sonneveld et al. ASH 2015 (Abstract 27), oral presentation;
2. Rosinol et al. ASH 2012 (Abstract 334), oral presentation;
3. Kumar et al. ASH 2014 (Abstract 82), oral presentation

# Current and future treatment algorithm for transplant-eligible MM patients




Moreau P, et al. Ann Oncol 2017;00:1–11; Cavo, personal communication; clinicaltrials.gov identifiers: NCT02874742; NCT02541383; NCT02495922; NCT01863550

# Myeloma is primarily a disease of elderly patients

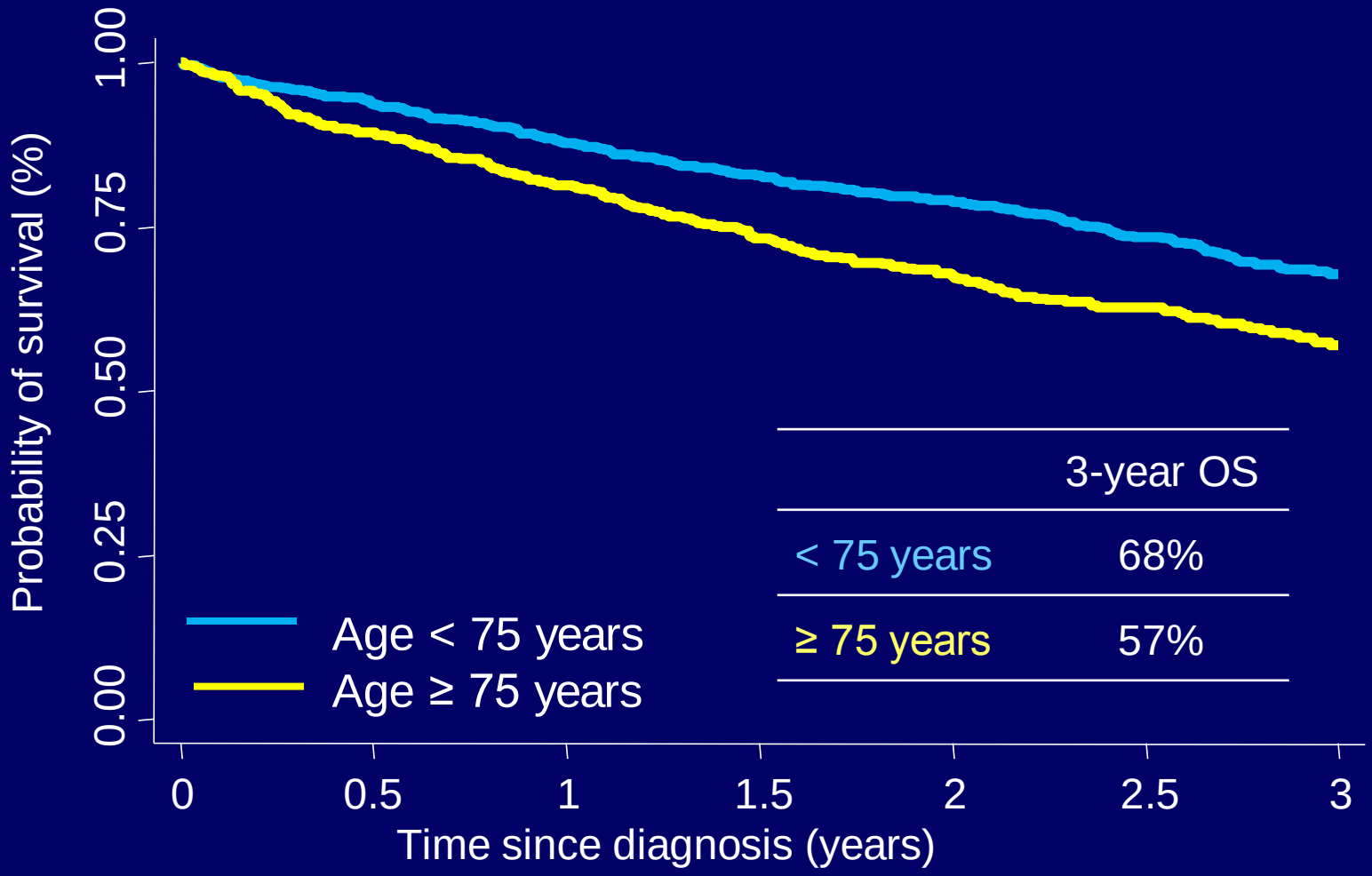



incidence in patients > 75y = 50/100.000/y

SEER database, accessed november 2015

# Survival in newly diagnosed elderly MM patients
## negative impact of age

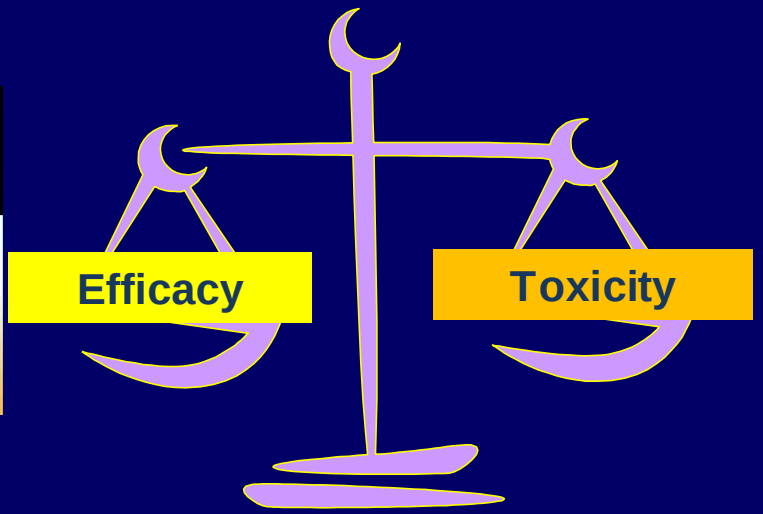
Meta-analysis of European trials (MP vs MPT, VMP vs VTP, VMP vs VMPT-VT); 1435 newly diagnosed MM patients




Bringhen et al. Haematologica 2013;98(6):980-987

# Treatment optimization in the elderly

- **Aim: to deliver effective treatment without excessive toxicity**

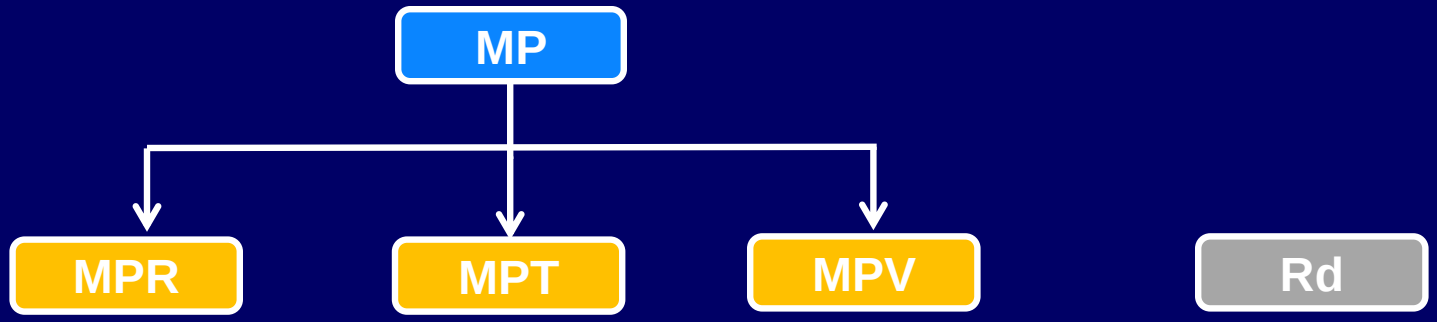




- **Risk of undertreatment: early relapse**
- **Risk of overtreatment: early treatment discontinuation**

# Current standards of care for newly diagnosed elderly myeloma patients

**Fixed duration/ Alkylator-based regimens[1]**

**Continuous treatment/ Alkylator-free regimens[1]**




One randomized trial[5]
Benefit in
PFS vs MP

Six randomized trials[2]
Benefit in
PFS & OS
vs MP

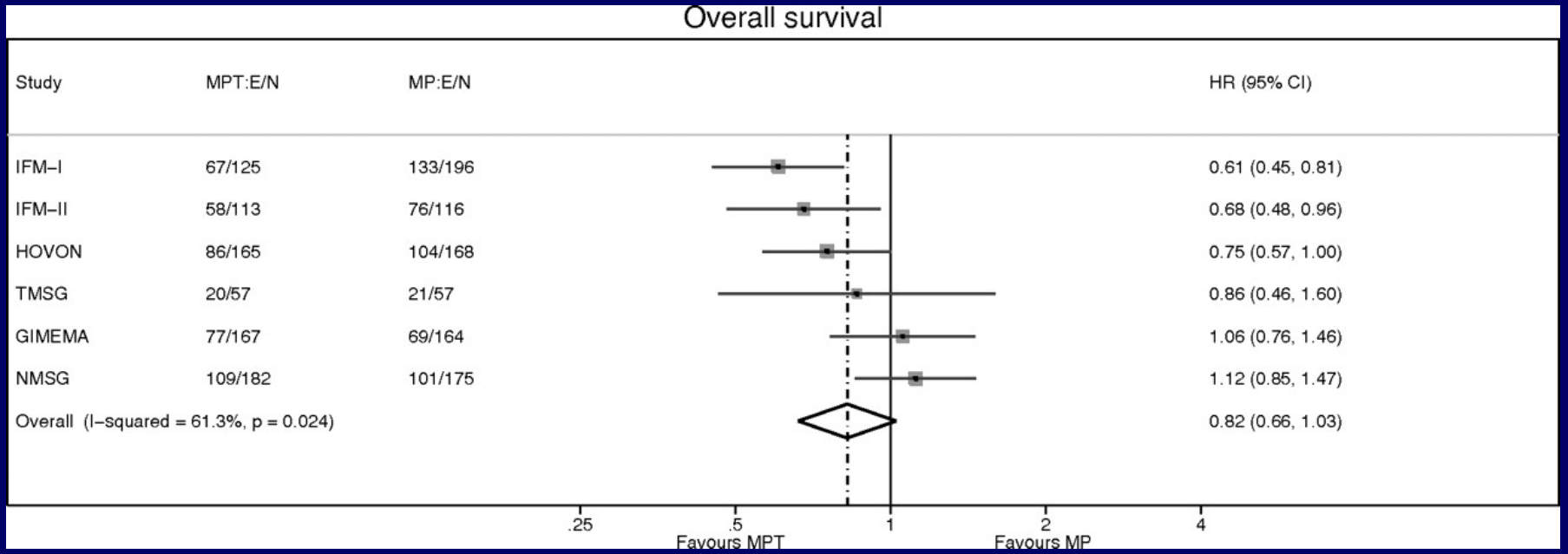
One randomized trial[3,4]
Benefit in
PFS & OS
vs MP

One randomized trial[5]
Benefit in
PFS & OS
vs MPT

MP, melphalan-prednisone; MPT, melphalan-prednisone-thalidomide; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide plus low-dose dexamethasone; PFS, progression-free survival; OS, overall survival.


1. Moreau P, et al. Blood. 2015;125:3076-84.
2. Fayers PM, et al. Blood. 2011;118:1239-47.
3. San Miguel JF, et al. N Engl J Med. 2008;359:906-17.
4. San Miguel JF, et al. J Clin Oncol. 2013;31:448-55
5. Palumbo et al. New Engl J Med 2012;366:1759
6. Benboubker L, et al. N Engl J Med. 2014;371:906-17.

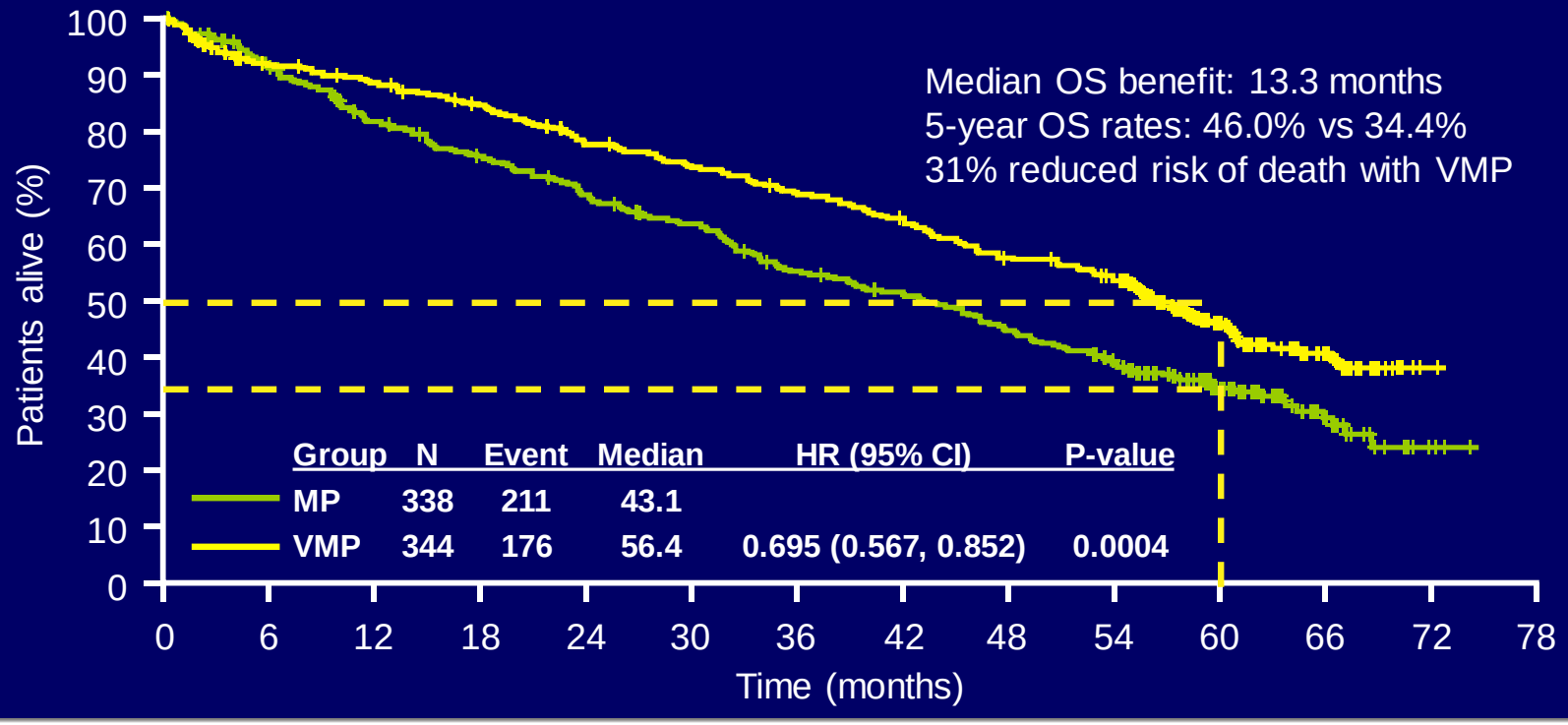
# Melphalan-prednisone-thalidomide (MPT)




- **n = 1685 patients**
- **better 1-y response rates with MPT (PR or better: 59% vs 37%)**
- **median OS time increased from 32.7 mo to 39.3 mo (p = 0.004); increase with 6.6 mo**

Fayers et al. Blood 2011;118:4519

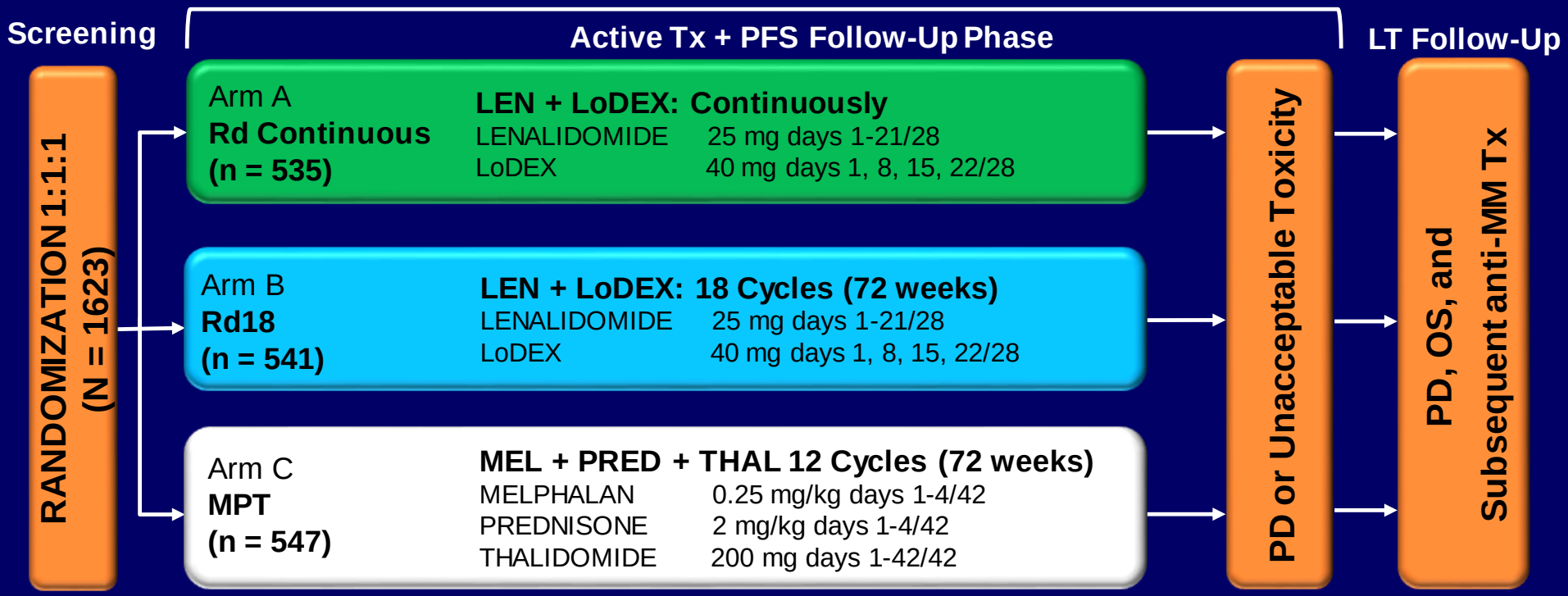
# Melphalan-prednisone-bortezomib (VMP)




| Group | Estimate | 95% CI | MP Events/n | MP Median | VMP Events/n | VMP Median |
|---|---|---|---|---|---|---|
| Age, years | | | | | | |
| < 75 | 0.69 | 0.53 to 0.89 | 136/237 | 47.7 | 113/237 | 58.6 |
| ≥ 75 | 0.70 | 0.49 to 1.01 | 75/101 | 32.9 | 63/107 | 50.7 |

San Miguel J. et al. J Clin Oncol. 2013:448-55

# FIRST (MM-020): Study Design




*Pts > 75 y: LoDEX 20 mg days 1, 8, 15, 22/28; THAL 100 mg days 1-42/42; MEL 0.2 mg/kg days 1-4*

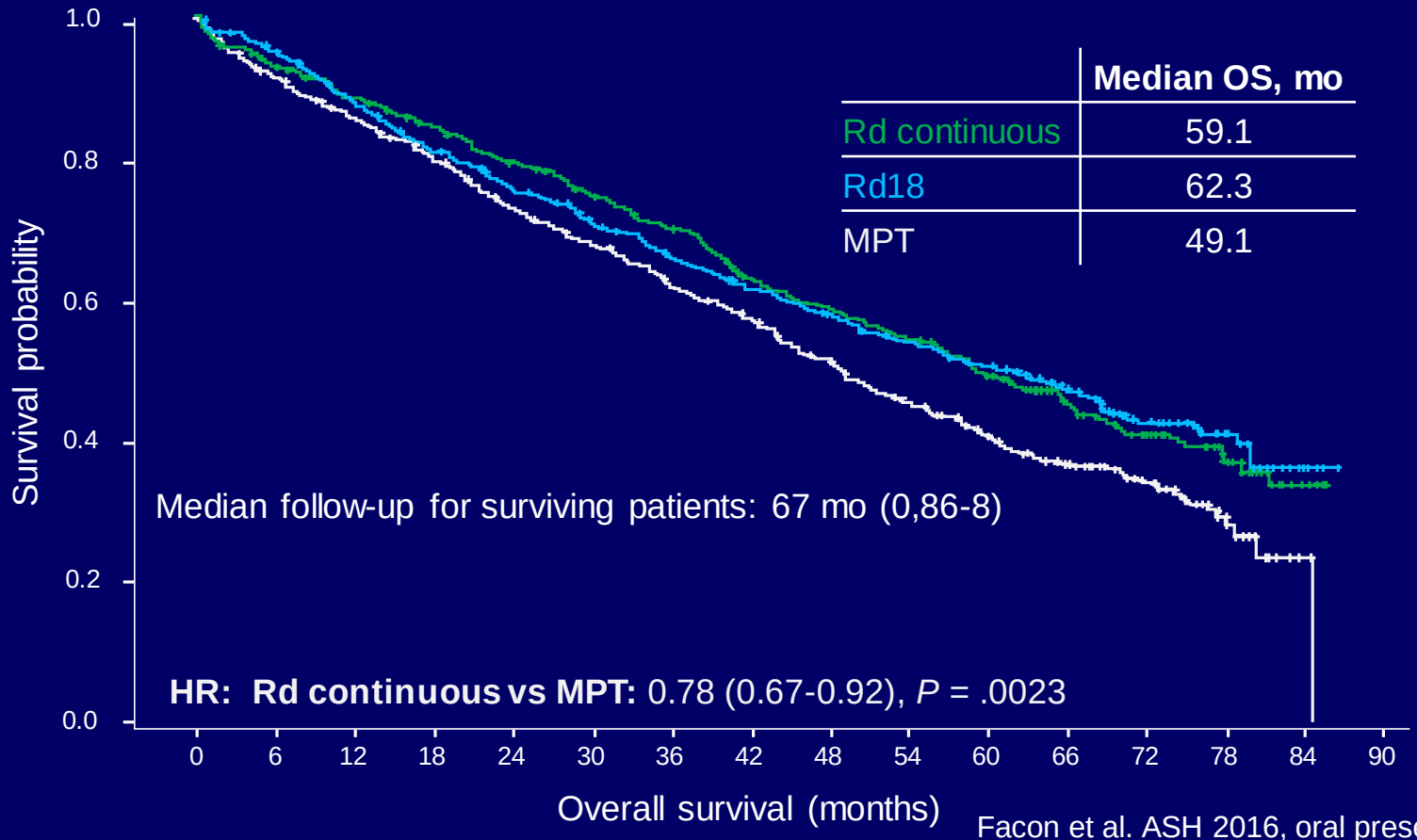
- Stratification: Age (≤ 75 y vs > 75 y), country, and ISS stage (I/II vs III)
- Thromboprophylaxis was mandatory
- Data cutoff: January 21, 2016

ISS, International Staging System; LoDex, low-dose dexamethasone; LT, long-term; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pts, patients; Tx, treatment.

Benboubker L, et al. *N Engl J Med*. 2014;371:906-917.

# Overall Survival

- The pre-specified final OS analysis for the primary comparison shows Rd continuous significantly extended OS compared with MPT



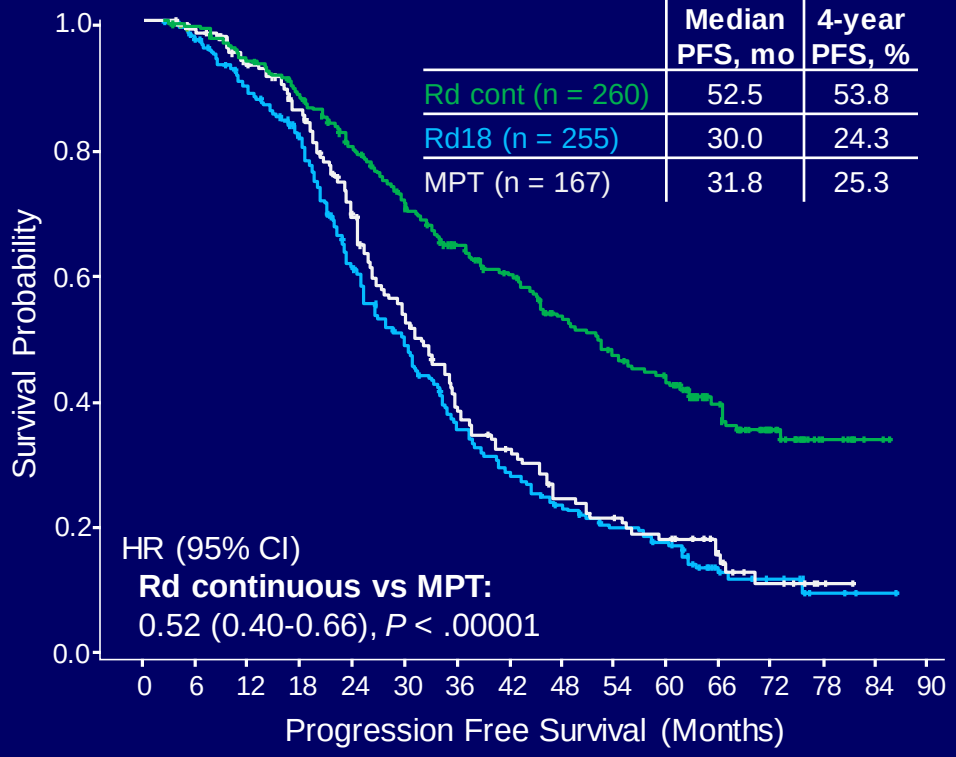

Facon et al. ASH 2016, oral presentation

HR, hazard ratio; MPT, melphalan, prednisone, thalidomide; OS, overall survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

# Progression-Free Survival by Response

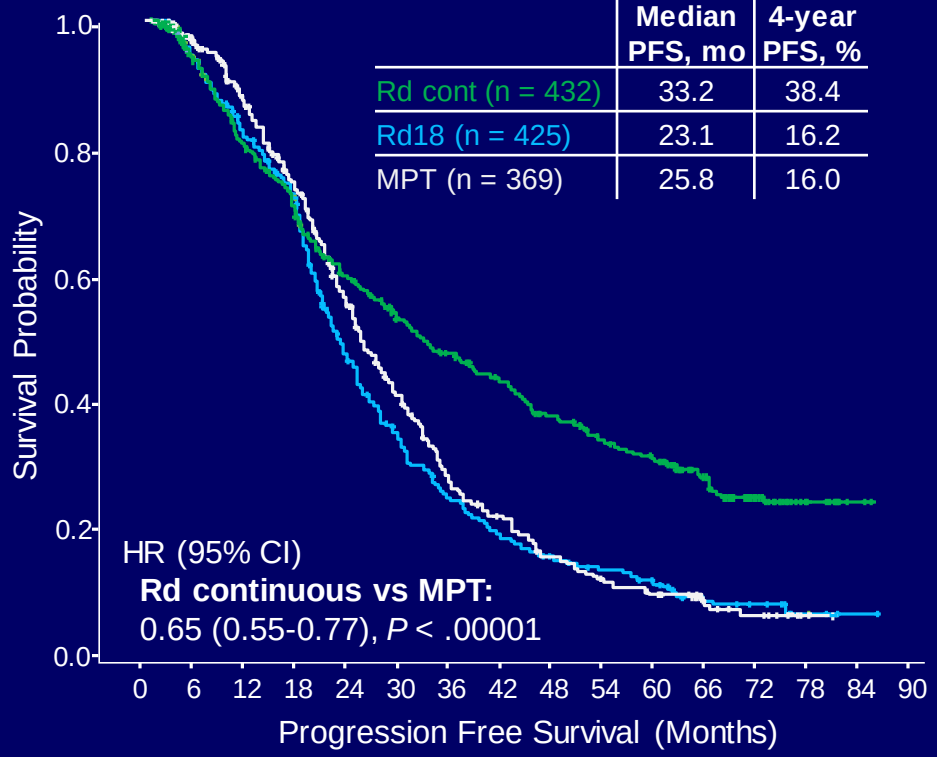
- Median PFS was prolonged in patients who responded to Rd continuous vs MPT, particularly in those who achieved a deeper response (CR/VGPR)

## PFS (CR/VGPR)




| | Median PFS, mo | 4-year PFS, % |
|---|---|---|
| Rd cont (n = 260) | 52.5 | 53.8 |
| Rd18 (n = 255) | 30.0 | 24.3 |
| MPT (n = 167) | 31.8 | 25.3 |

## PFS (≥ PR)




| | Median PFS, mo | 4-year PFS, % |
|---|---|---|
| Rd cont (n = 432) | 33.2 | 38.4 |
| Rd18 (n = 425) | 23.1 | 16.2 |
| MPT (n = 369) | 25.8 | 16.0 |

CR, complete response; HR, hazard ratio; MPT, melphalan, prednisone, thalidomide; PFS, progression-free survival; PR, partial response; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; VGPR, very good partial response.

Facon et al. ASH 2016, oral presentation

# VRd vs Rd: SWOG S0777 trial

**VRd**
**(n = 264)**

**8 x VRd (21 days)**
**V: bortezomib 1,3 mg/sm IV d1,4,8,11**
**R: lenalidomide 25 mg/d d1-14**
**d: dexamethasone 20 mg/d d 1,2,4,5,8,9,11,12**

**Rd maintenance**

**Rd**
**(n = 261)**

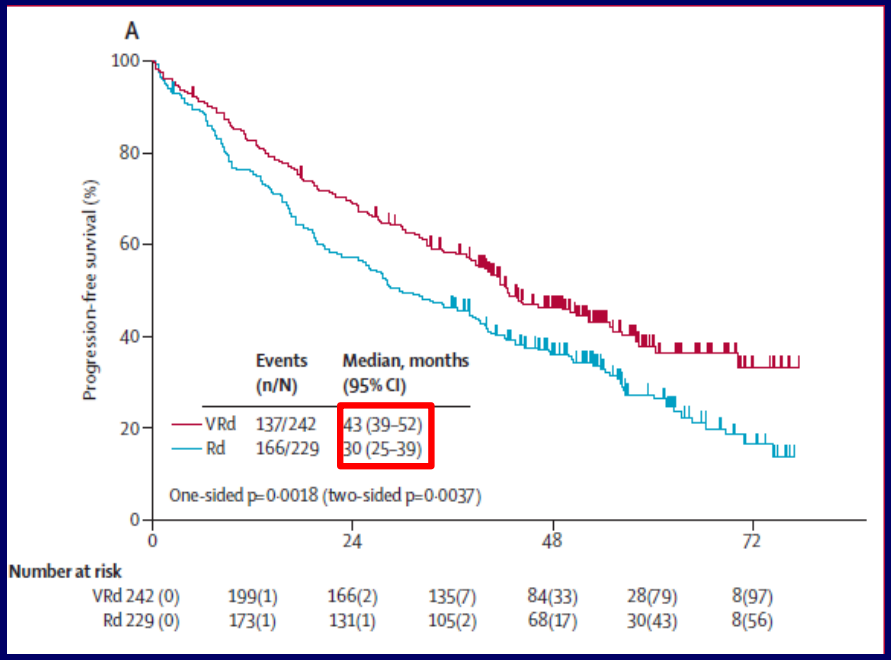
**6 x Rd (28 days)**
**R: lenalidomide 25 mg/d d1-21**
**d: dexamethasone 40 mg/d d 1,8,15,22**

**Rd maintenance**

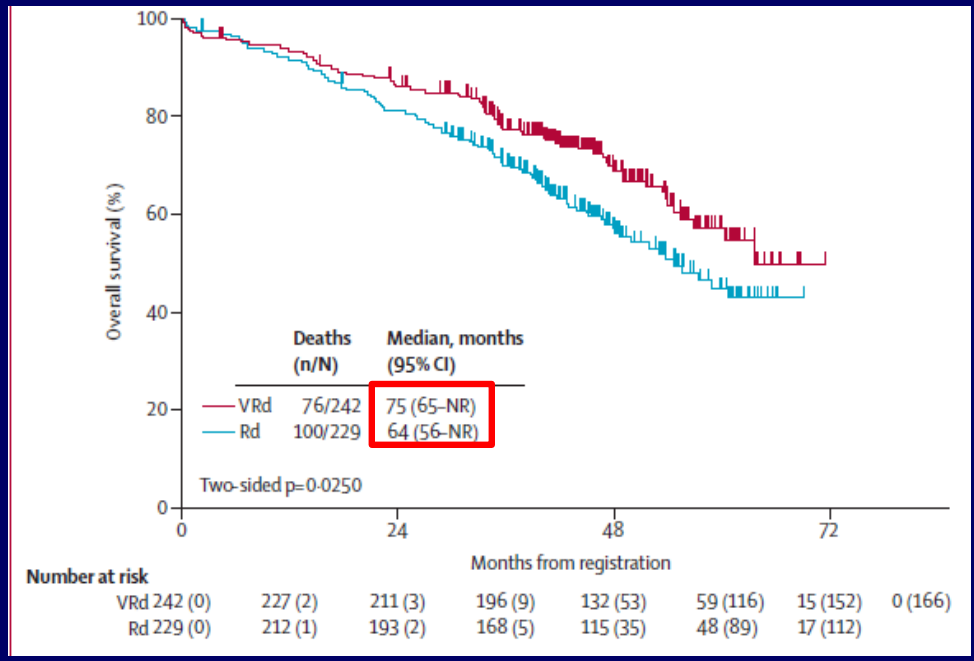
Durie et al. Lancet 2017;389:519

# VRd vs Rd: SWOG S0777 trial
## Results for PFS and OS

### Progression-free survival




### Overall survival




- **43% of patients were > 65 y**
- **For high-risk cytogenetics: median PFS: 38 mo vs 16 mo**

Durie et al. Lancet 2017;389:519

# Aiming too high in the very elderly:
## the MPR story

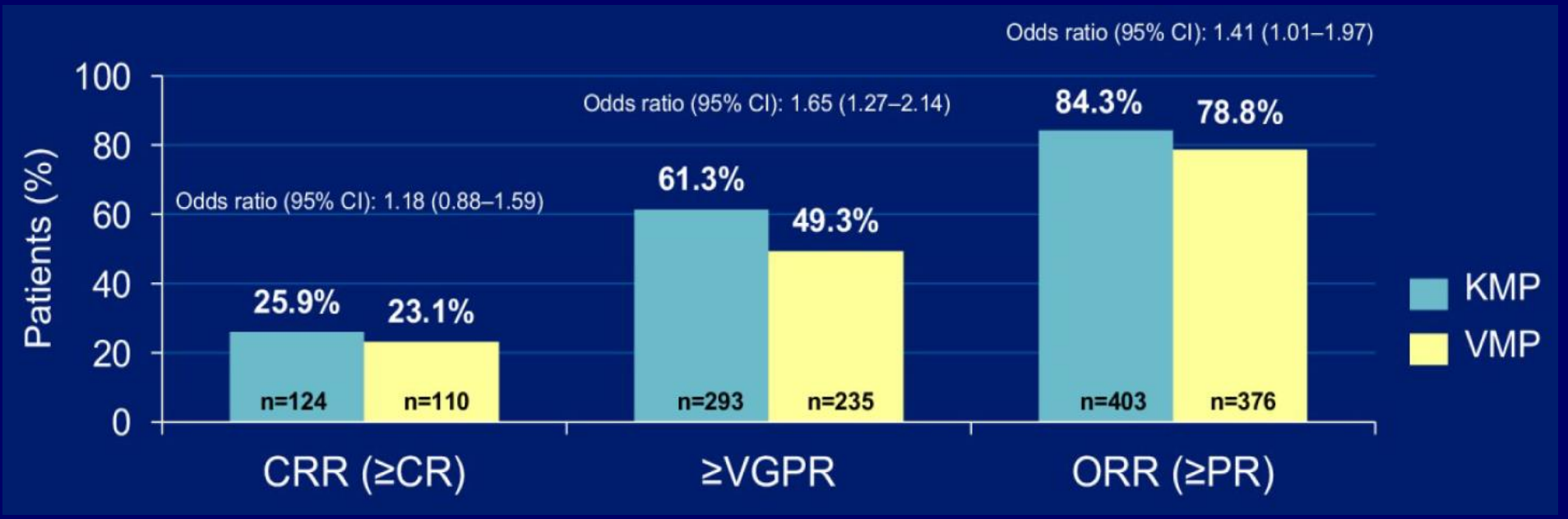
| | MPR[a] | MP |
|---|---|---|
| **Discontinuation rate[b]** | | |
| 65 - 75 years of age | 17% | 10% |
| > 75 years of age | 34% | 16% |
| **Cumulative dose intensity[c]** | | |
| 65 - 75 years of age | 88% | 97% |
| > 75 years of age | 56% | 97% |

[a] MPR includes MPR-R and MPR for the initial 9 cycles. [b] Discontinuation due to AEs or withdrawal of consent
[c] Cumulative dose intensity of melphalan and lenalidomide/placebo

Palumbo et al. New Engl J Med 2012;366:1759
Palumbo A, et al. Blood. 2010;116: Abstract 622.

# Carfilzomib-melphalan-prednisone (KMP) vs bortezomib-melphalan-prednisone (VMP)

## Responses and toxicities




- Grade ≥3 hypertension, dyspnea, acute renal failure, and cardiac failure were higher with KMP than VMP
- Grade ≥2 peripheral neuropathy rates were lower with KMP (2.5%) than VMP (35.1%)
  - 69% of patients in VMP group received subcutaneous bortezomib throughout their treatment

Facon T, et al. IMW 2017 (Abstract OP-044)

# Frail patients with comorbidities are underrepresented in clinical trials

**Table 2.** Frequencies of exclusion criteria that might negatively affect the inclusion of older individuals in ongoing clinical trials regarding hematologic malignancies. (n = 85 clinical trials)

| Exclusion criterion | Frequency, N. (%) |
|---|---|
| Upper age limit | 35 (41.18) |
| Reduced life expectancy | 23 (27.06) |
| Drug therapy (at least one drug) | 53 (62.35) |
| Abnormal laboratory result (at least one) | 69 (81.18) |
| Cognitive impairment | 5 (5.88) |
| Physical disability | 62 (72.94) |
| Inability to give informed consent | 32 (37.65) |
| Inability to attend follow-up visit | 5 (5.88) |
| Physician's judgement | 23 (27.06) |
| Reduced compliance | 28 (32.94) |
| Comorbidity (at least one disease) | 77 (90.59) |
| **Specific disease** | |
| Renal failure | 60 (70.6) |
| Cardiovascular | 56 (65.9) |
| Infectious | 47 (56.6) |
| Hematologic | 39 (45.9) |
| Lung | 33 (38.3) |
| Psychiatric | 31 (36.5) |
| Previous cancer | 18 (21.2) |
| Gastrointestinal | 17 (20) |
| Neurological | 15 (17.6) |
| Liver | 8 (9.6) |

"The main finding from our study is that older patients are still commonly excluded from clinical trials on hematologic malignancies"

Cherubini et al. Haematologica 2013;98:997

# The IMWG frailty scoring system

- Patients are categorized into 3 severity groups: fit, intermediate or frail

| IMWG Frailty Scale[1] | | Score |
|---|---|---|
| Age | | |
| ≤ 75 yrs | | 0 |
| 76–80 yrs | | 1 |
| > 80 yrs | | 2 |
| Activity of Daily Living score | | |
| > 4 | | 0 |
| ≤ 4 | | 1 |
| Instrumental Activity of Daily Living score | | |
| > 5 | | 0 |
| ≤ 5 | | 1 |
| Charlson Comorbidity Index score | | |
| ≤ 1 | **Total score:** | 0 |
| ≥ 2 | | 1 |

IMWG, International Myeloma Working Group.

**0: Fit**

**1: Intermediate**

**≥ 2: Frail**

Palumbo A, et al. *Blood.* 2015;125:2068-74.

# An intuitive approach for ‘vulnerable’ MM patiens

**Risk factors**

- **age over 75 y**
- **mild, moderate or severe frailty**
- **comorbidities: cardiac/pulmonary/hepatic/renal dysfunction**

**GO-GO**

no risk factors

**Dose level 0**

**MODERATE-GO**

at least one risk factor

**Dose level - 1**

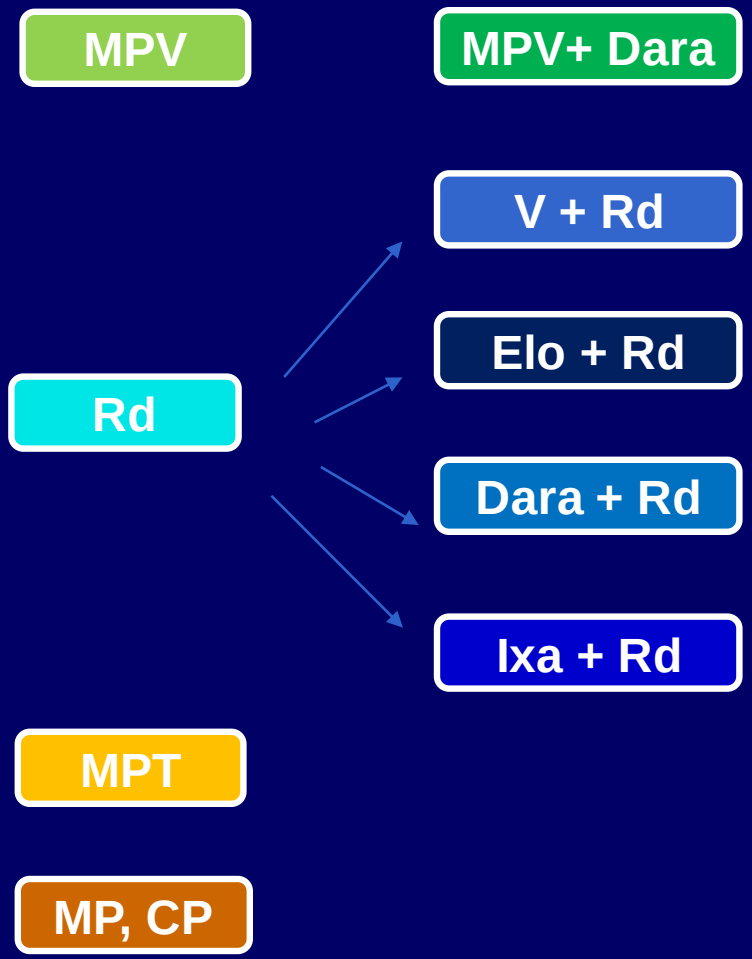
**SLOW-GO**

at least one risk factor plus occurence of grade 3-4 non-hematol. AE

**Dose level - 2**

Palumbo et al, Blood 2011;118(17):4519-29

# Future standards of care for newly diagnosed elderly myeloma patients




MP: melphalan, prednisone
MPV: melphalan, prednisone, bortezomib
Dara: daratumumab
Rd: lenalidomide, dexamethasone
Elo: elotuzumab
Ixa: ixazomib
MPT: melphalan, prednisone, thalidomide
CP: cyclophosphamide, prednisone