9th EDITION

Highlights from EHA


ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

# Multiple Myeloma


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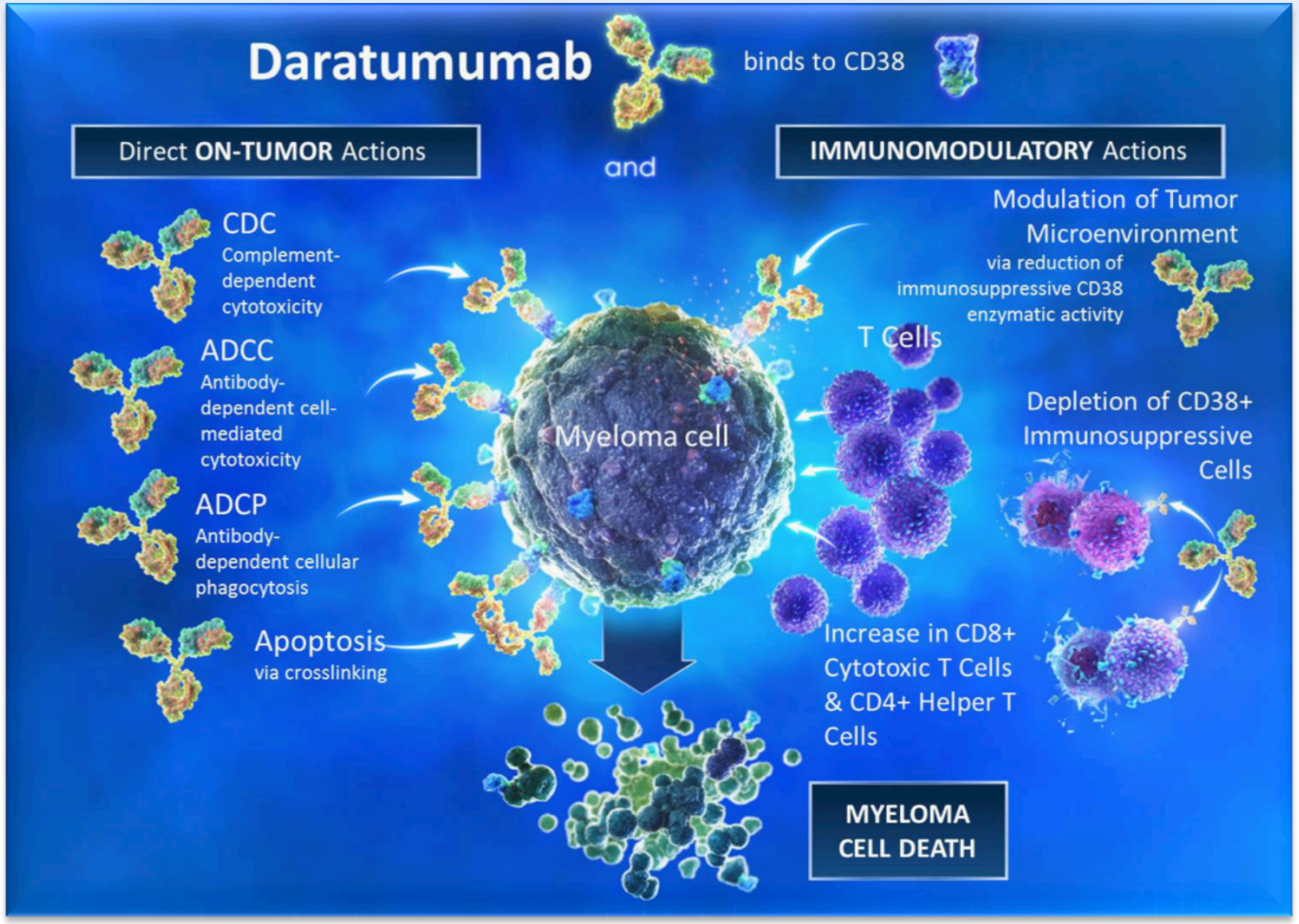
# Daratumumab: Mechanism of Action

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]

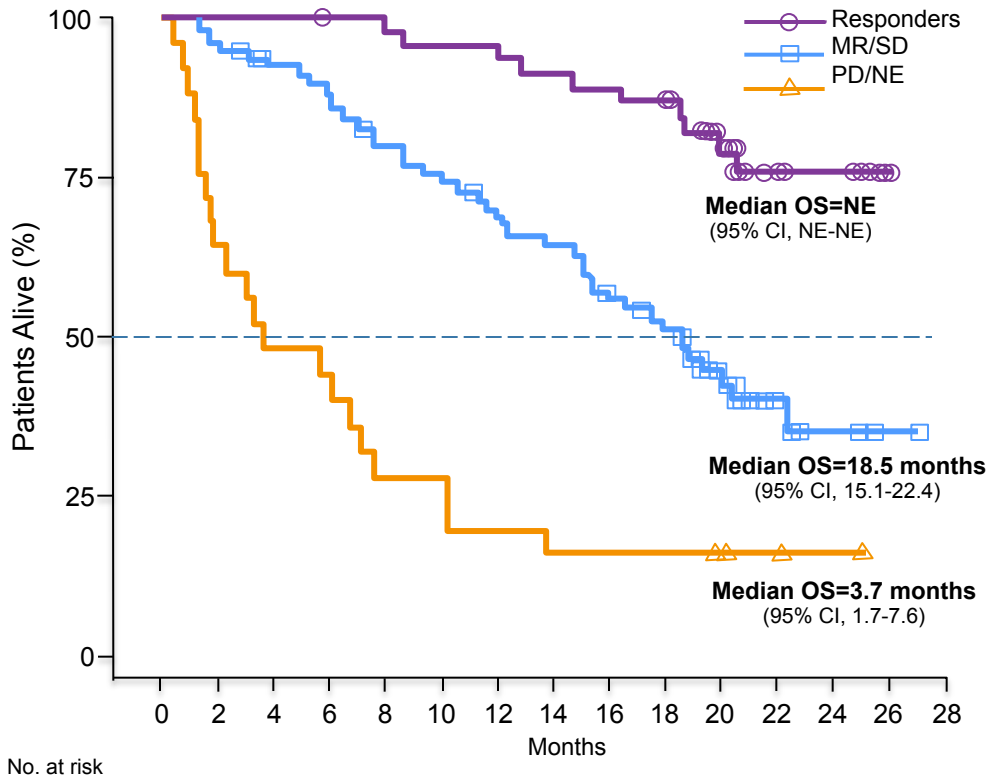




1. Lammerts van Bueren J, et al. *Blood*. 2014;124:Abstract 3474.
2. Jansen JMH, et al. *Blood*. 2012;120:Abstract 2974.
3. de Weers M, et al. *J Immunol*. 2011;186:1840-8.
4. Overdijk MB, et al. *MAbs*. 2015;7:311-21.
5. Krejcik J, et al. *Blood*. 2016. Epub ahead of print.

# Daratumumab: Single-agent Activity

- **Daratumumab as a single agent[1,2]**
  - Approved by FDA and conditionally approved by EMA in relapsed/refractory multiple myeloma
- **Patients received a median of 5 prior lines of therapy**
  - 86.5% of patients were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD)[3]
- **Combined overall response rate (ORR):31%[3]**
- **Median overall survival (OS) of 20.1 months[3]**
  - 2-year OS was ~75% in responders
  - Median OS was 18.5 months in MR/SD patients




MR, minimal response; SD, stable disease; PD, progressive disease; OS, overall survival; CI, confidence interval; NE, not evaluable.


1. Lokhorst HM, et al. *N Engl J Med*. 2015;373:1207-19.
2. Lonial S, et al. *Lancet*. 2016;387:1551-60.
3. Usmani SZ, et al. *Blood*. 2016. Epub ahead of print.

# POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

**Key eligibility criteria**

- RRMM
- ≥1 prior line of therapy
- **Prior lenalidomide exposure, but not refractory**
- Patients with creatinine clearance ≥30 mL/min

RANDOMIZE

1:1

**DRd (n = 286)**

Daratumumab 16 mg/kg IV
- Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

**Rd (n = 283)**

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Cycles: 28 days

**Primary endpoint**
- PFS

**Secondary endpoints**
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

**Stratification factors**
- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

**Statistical analyses**
- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

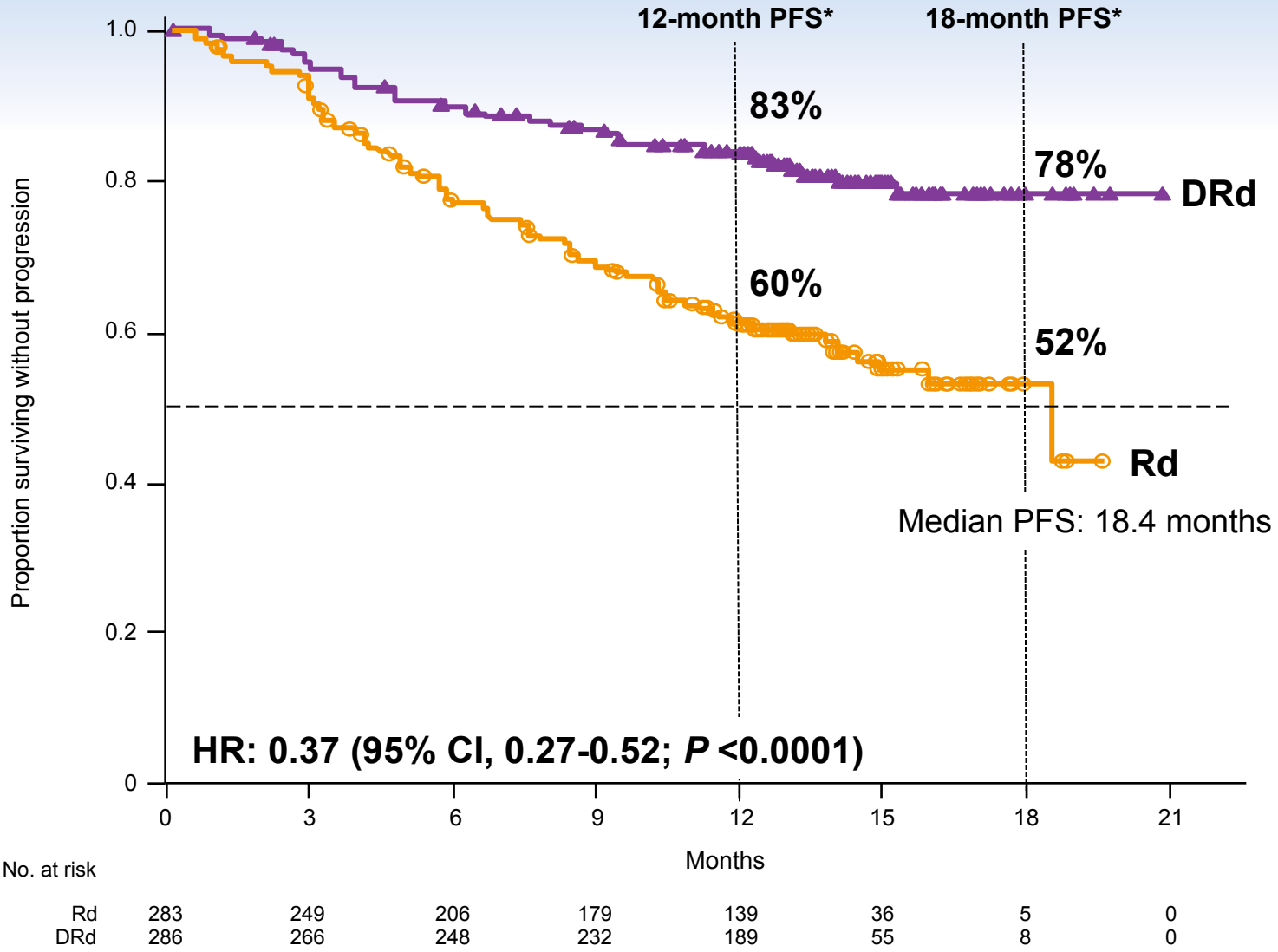
[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.

# Baseline Demographics and Clinical Characteristics

| Characteristic | DRd (n = 286) | Rd (n = 283) |
|---|---|---|
| Age, yr | | |
| Median (range) | 65 (34-89) | 65 (42-87) |
| ≥75, % | 10 | 12 |
| ISS stage, %[a] | | |
| I | 48 | 50 |
| II | 33 | 30 |
| III | 20 | 20 |
| Median (range) time from diagnosis, yr | 3.48 (0.4-27.0) | 3.95 (0.4-21.7) |
| Creatinine clearance (mL/min) | | |
| N | 279 | 281 |
| >30-60 | 28 | 23 |
| >60 | 71 | 77 |
| Prior lines of therapy, % | | |
| **Median (range)** | **1** (1-11) | **1** (1-8) |
| 1 | 52 | 52 |
| 2 | 30 | 28 |
| 3 | 13 | 13 |
| >3 | 5 | 7 |

[a]ISS stage is derived based on the combination of serum β2-microglobulin and albumin.

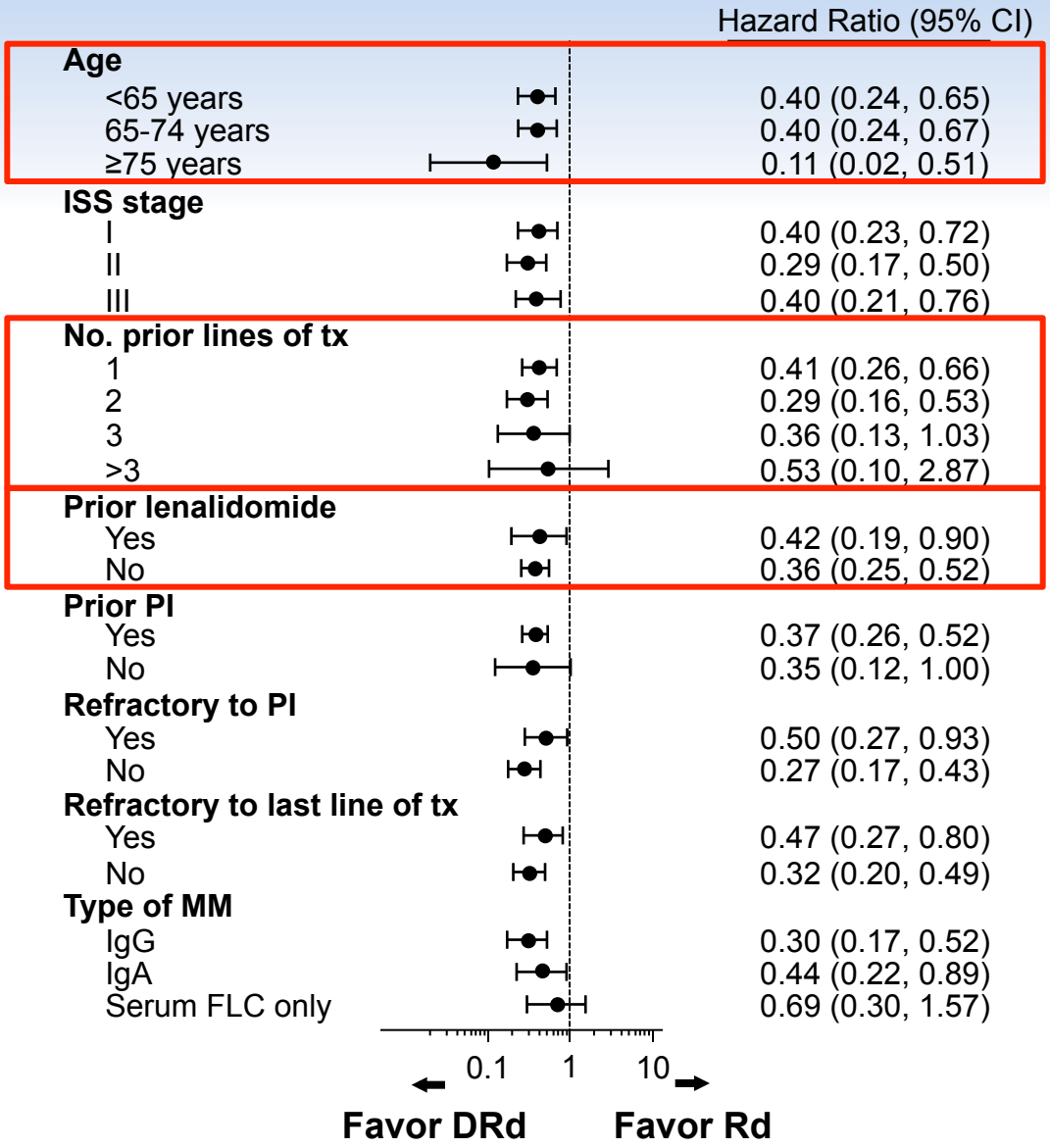
# Progression-free Survival




63% reduction in the risk of disease progression or death for DRd vs Rd

*KM estimate; HR, hazard ratio.

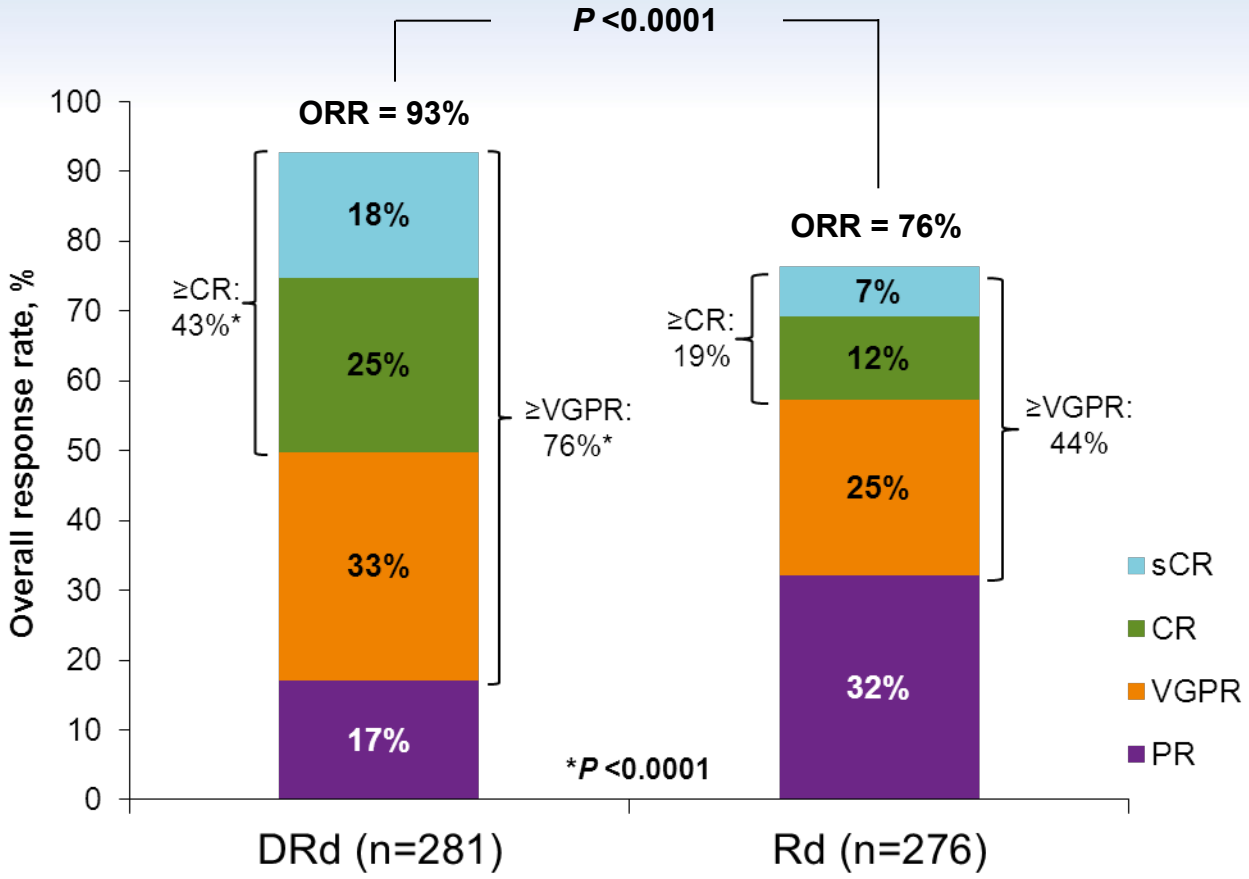
# PFS: Subgroup Analysis




Higher efficacy was observed for DRd versus Rd across all subgroups

Tx, treatment; MM, multiple myeloma; IgG, immunoglobulin G; IgA, immunoglobulin A; FLC, free light chain.

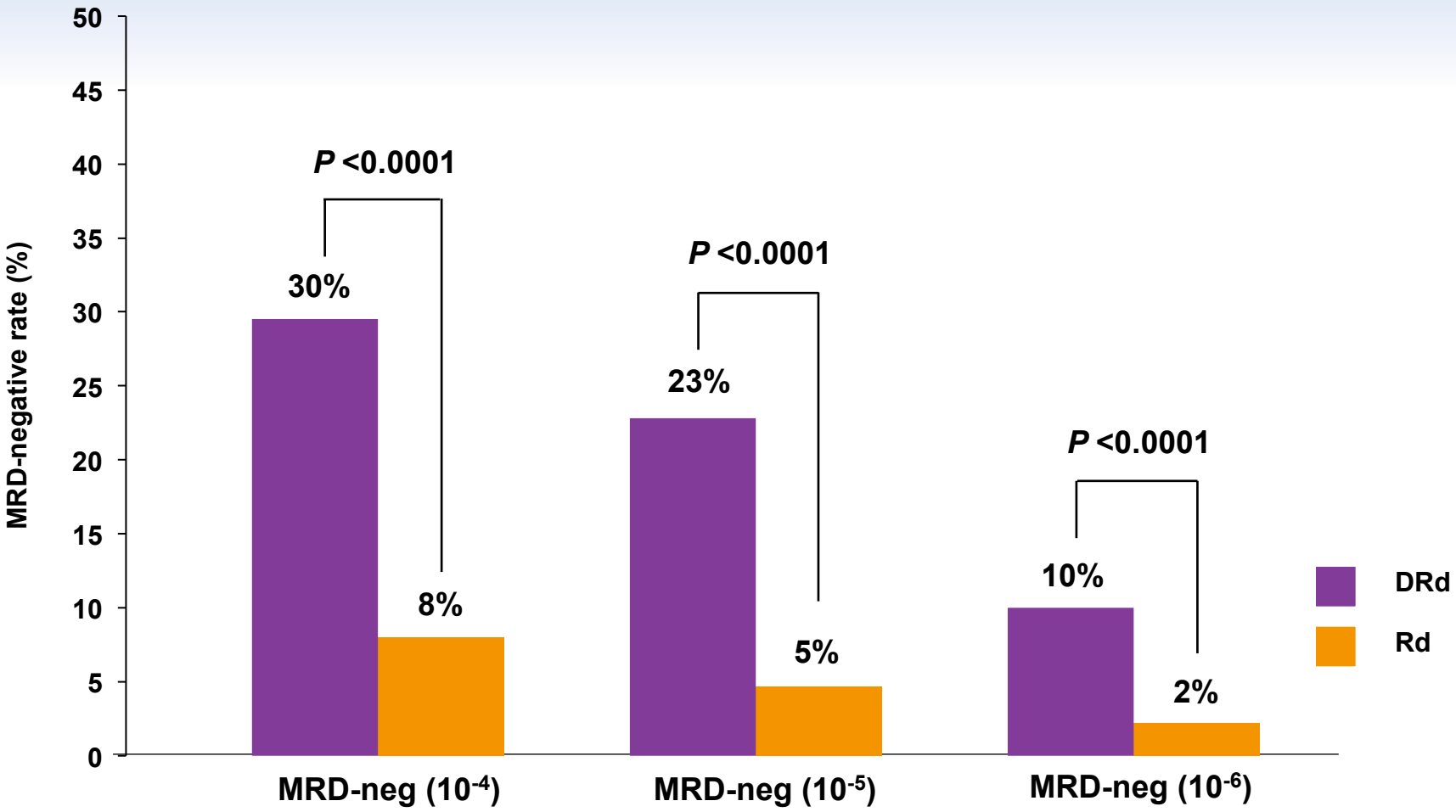
# Overall Response Rate[a]




- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd

[a]When serum interference was suspected, CR was confirmed using the daratumumab interference reflex assay.

# MRD-negative Rate




Significantly higher MRD-negative rates for DRd vs Rd

Response-evaluable set. Assessed by next generation sequencing in bone marrow.

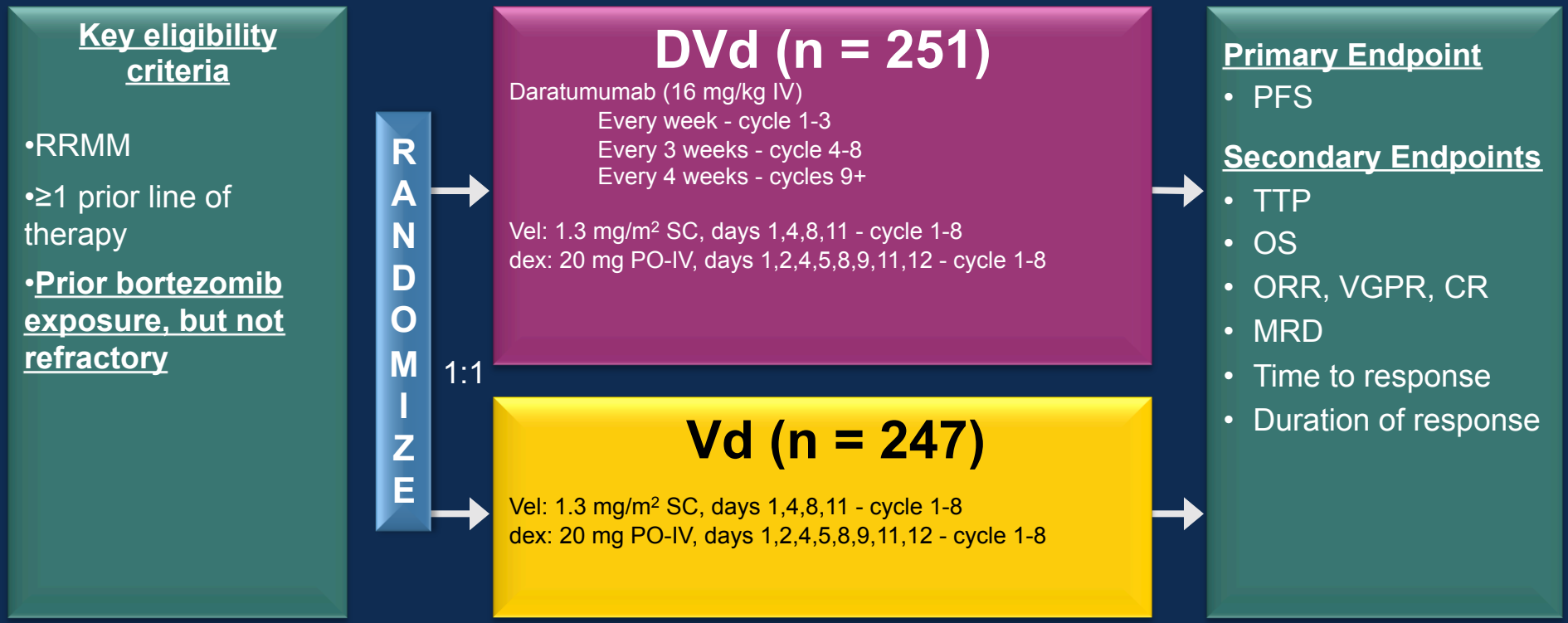
# Infusion-related Reactions (IRRs)

| IRRs ≥2% | Safety Analysis Set (n = 283) | |
|---|---|---|
| | All grades (%) | Grade 3 (%) |
| Patients with IRRs | 48 | 5 |
| Cough | 9 | 0 |
| Dyspnea | 9 | 0.7 |
| Vomiting | 6 | 0.4 |
| Nausea | 5 | 0 |
| Chills | 5 | 0.4 |
| Bronchospasm | 5 | 0.4 |
| Pruritus | 3 | 0.4 |
| Throat irritation | 3 | 0 |
| Headache | 3 | 0 |
| Nasal congestion | 3 | 0 |
| Wheezing | 2 | 0.7 |
| Laryngeal edema | 2 | 0.4 |
| Rhinorrhea | 2 | 0 |
| Pyrexia | 2 | 0 |

- No grade 4 or 5 IRRs were reported
- 92% of all IRRs occurred during the first infusion
- 1 patient discontinued daratumumab due to an IRR

# CASTOR: Study Design

Multicenter, randomized, open-label, active-controlled phase 3 study

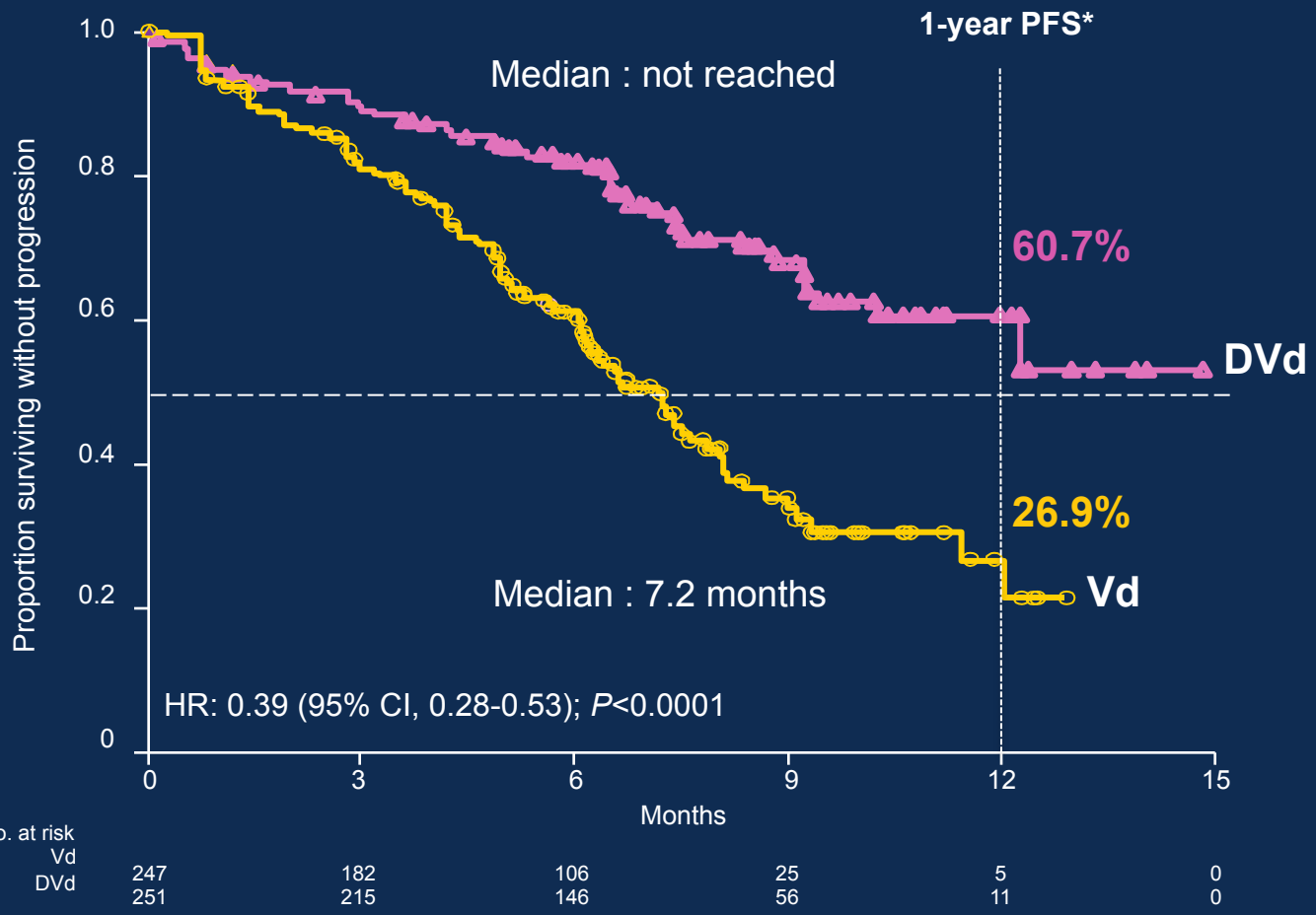



- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

**Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted**

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

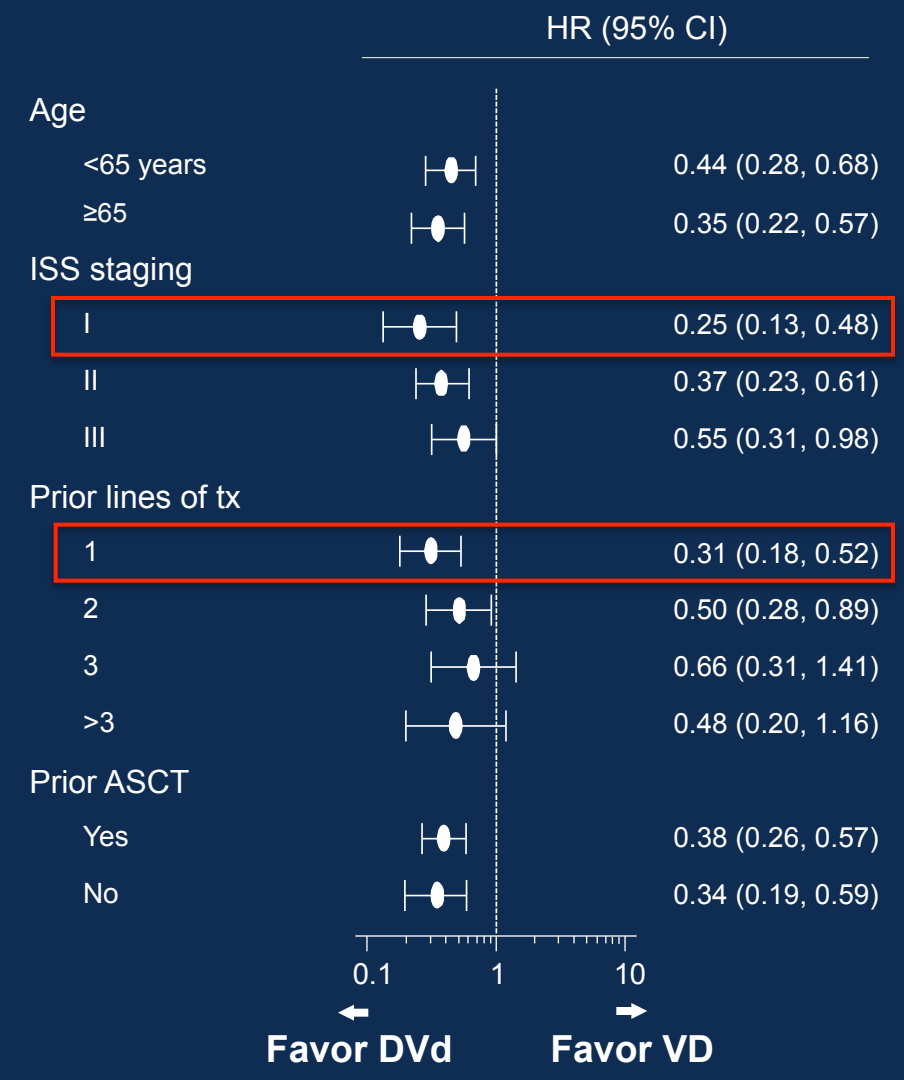
# Progression-free Survival

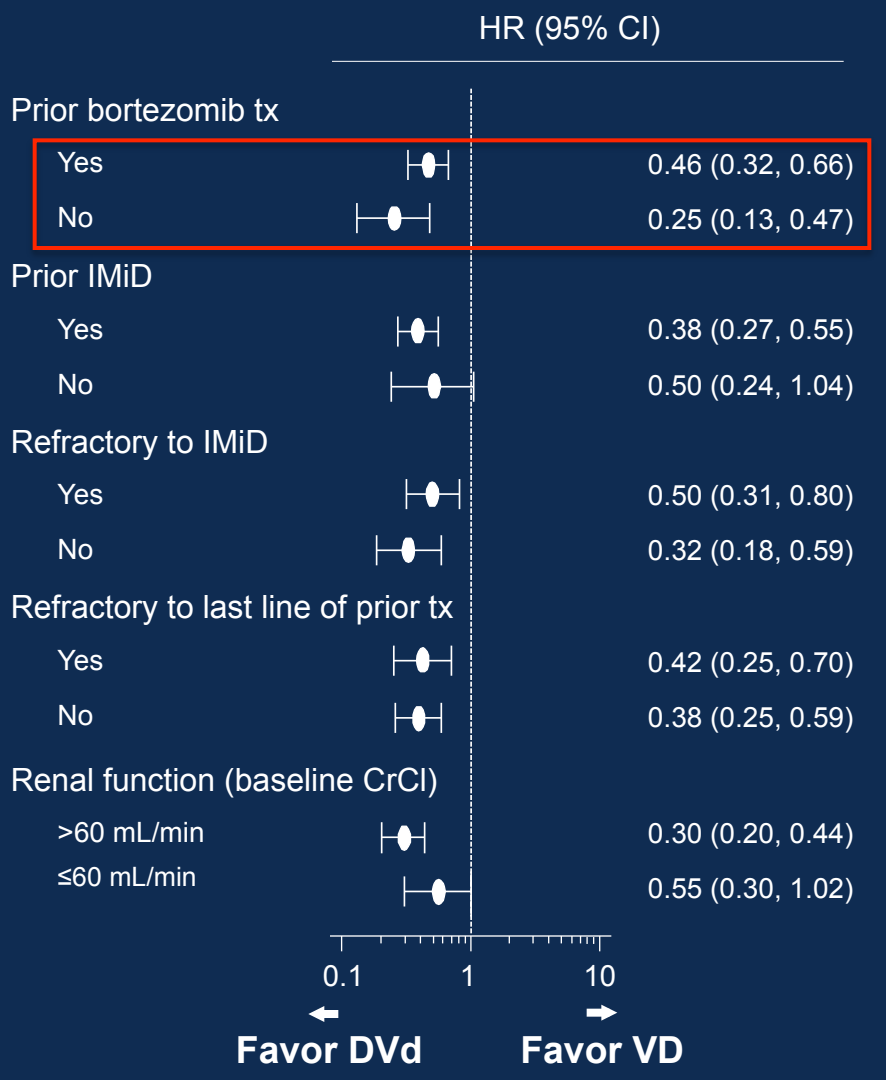



61% reduction in the risk of disease progression or death for DVd vs Vd

*KM estimate; HR, hazard ratio.

# PFS: Subgroup Analysis




Tx, treatment; CrCl, creatinine clearance.

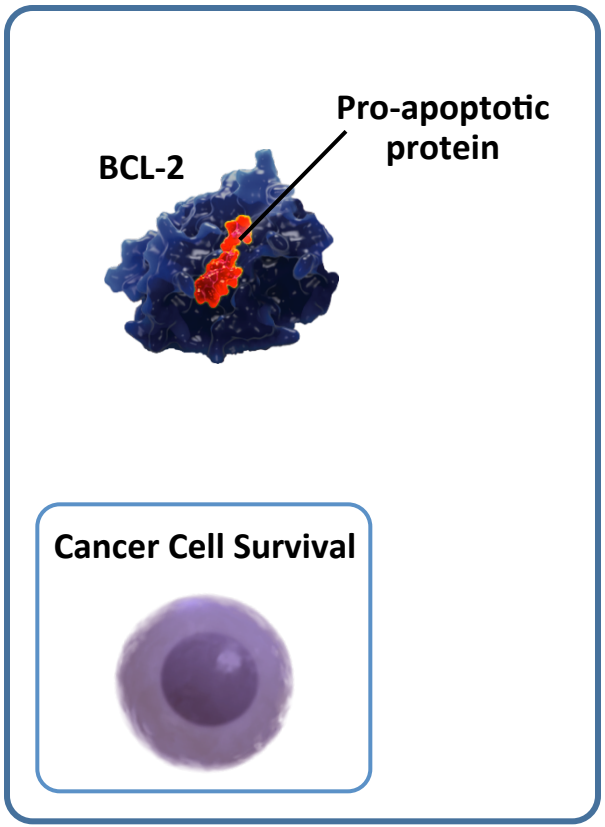
# Background

- BCL-2, an anti-apoptotic protein, is highly expressed in a subset of myeloma cells and can promote cell survival[1]
- Venetoclax is a potent, selective, orally available small molecule BCL-2 inhibitor[2]
- Venetoclax induces cell death in multiple myeloma (MM) cell lines and primary samples in vitro[1]
- Most MM cells harboring the t(11;14) translocation have a high level of BCL-2 and low level of MCL-1, which increases sensitivity to venetoclax monotherapy[1]

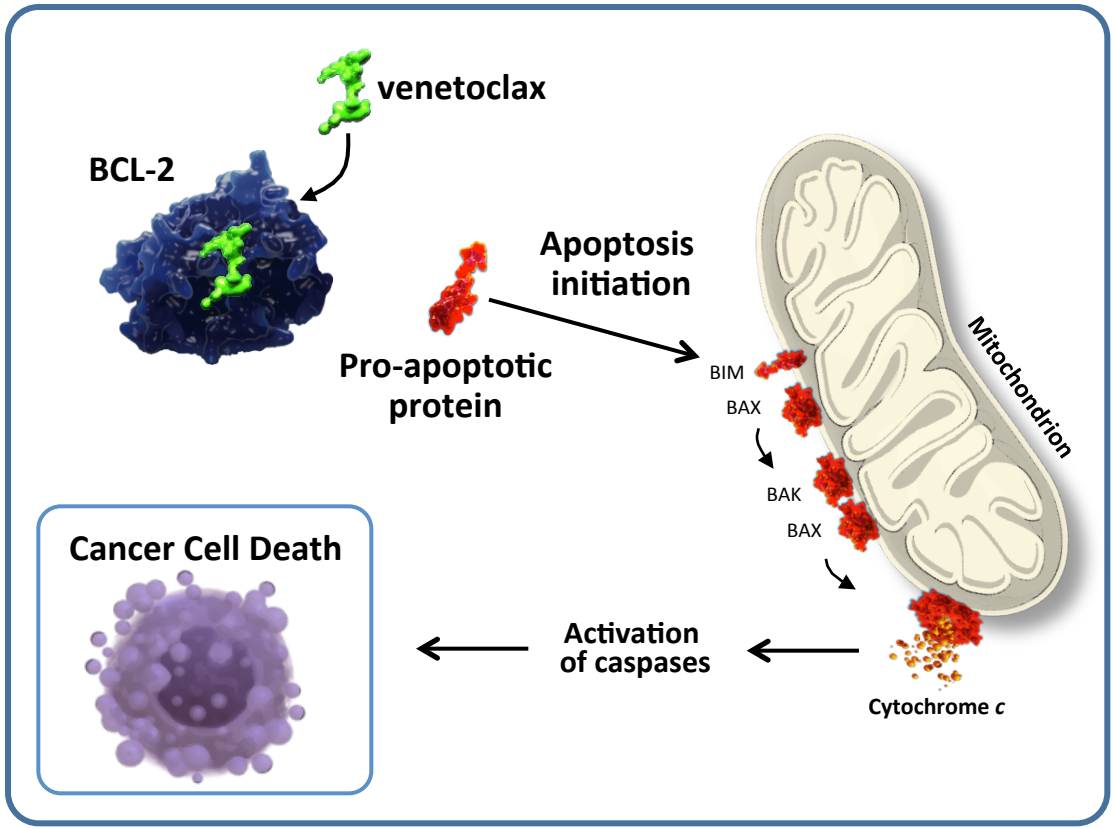
*1. Touzeau C, et al. Leukemia 2014. 2. Roberts AW, et al. N Eng J Med 2016.*

# Background

## Restoration of apoptosis through BCL-2 inhibition




BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.




Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).

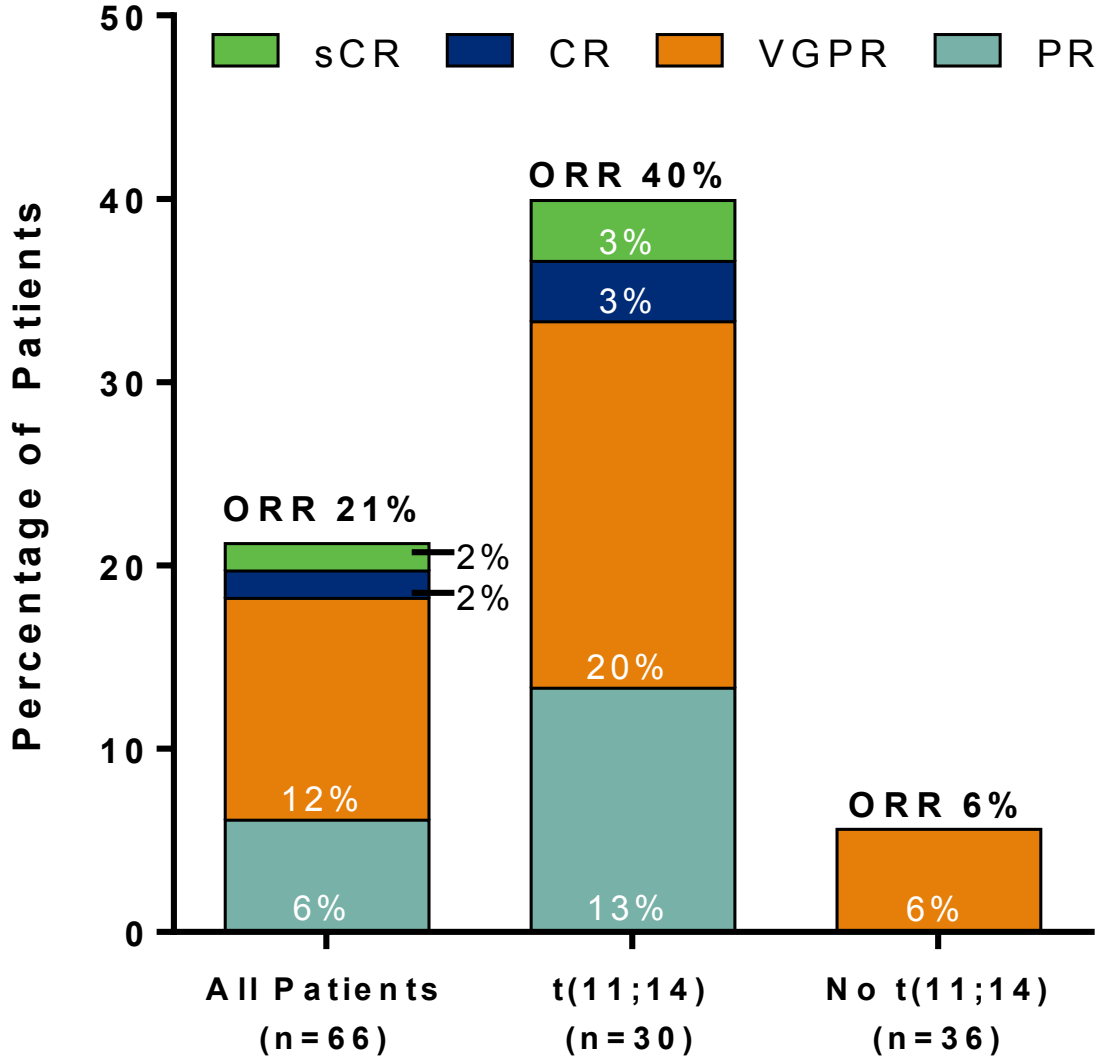
# Patient Characteristics

| | N=66 |
|---|---|
| Age, median (range), years | 63 (31 – 79) |
| Male, n (%) | 30 (46) |
| White, n (%) | 59 (94) |
| ISS stage, n (%) | |
| Stage I | 24 (38) |
| Stage II/III | 39 (62) |
| Unknown | 3 |
| Cytogenetic abnormalities, n (%) | |
| t(11;14) | 30 (46) |
| t(4;14) | 6 (9) |
| del(17p) | 12 (18) |
| del(13q) | 32 (48) |
| Hyperdiploid | 27 (41) |
| **No. of prior lines of therapy, median**[a] (range) | **5** (1 – 15) |
| Stem cell transplant,[a] n (%) | 50 (76) |
| Bortezomib/refractory,[a] n (%) | 62 (94)/46 (70) |
| Lenalidomide/refractory,[a] n (%) | 62 (94)/51 (77) |
| Bortezomib and lenalidomide refractory,[a] n (%) | 40 (61) |

[a]Percentages based on total study population.

As of 10Feb2016

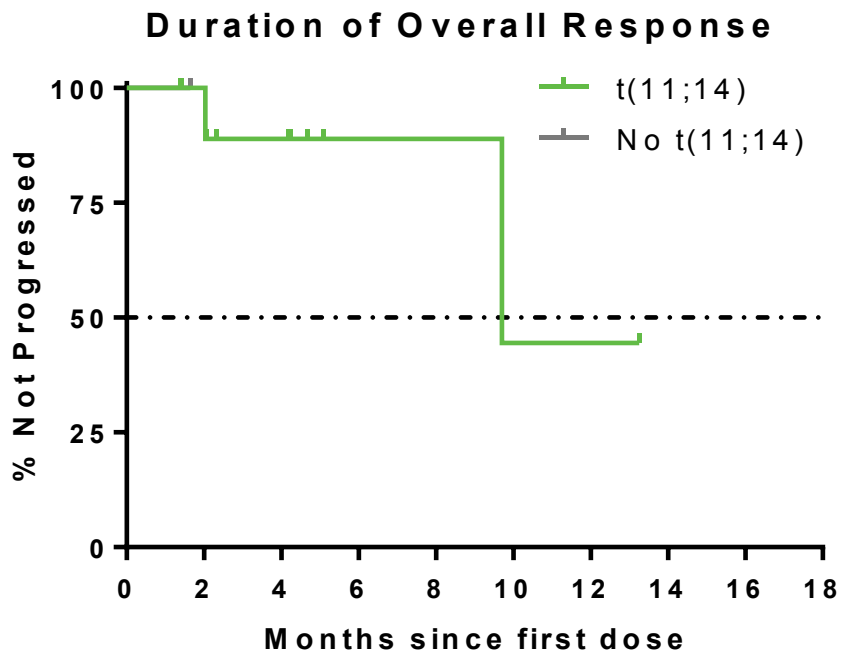
# Objective Response Rates by t(11;14) Status

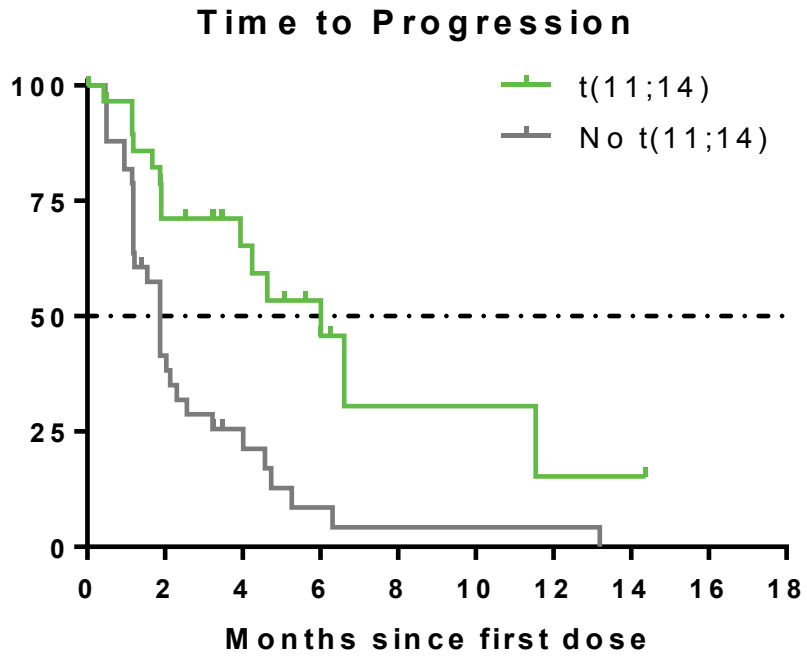



ORR, PR or better.

As of 10Feb2016

# Duration of Response and Time to Progression



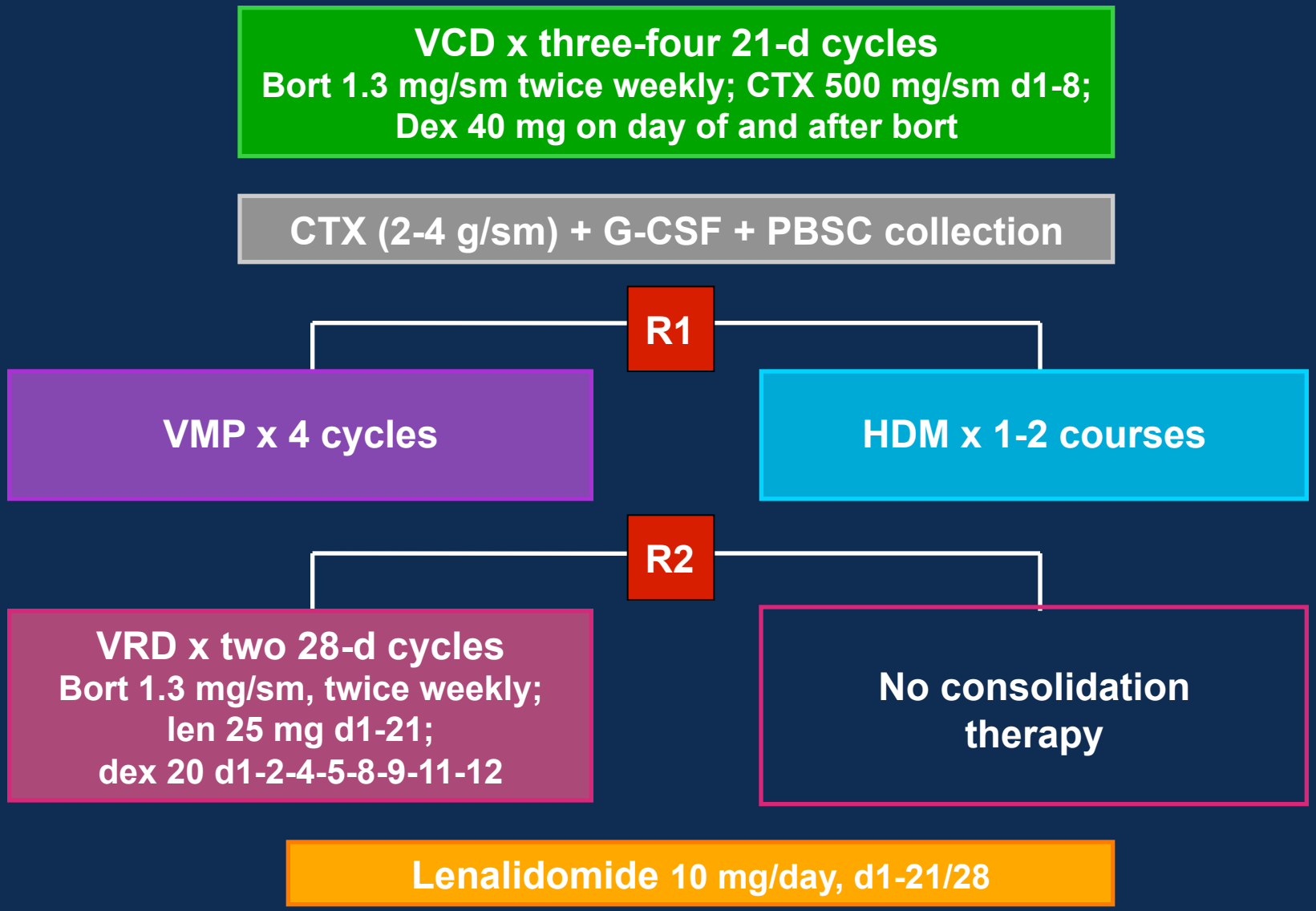




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pts at risk | 12 | 9 | 6 | 2 | 2 | 1 | 1 | |
| Pts at risk | 2 | | | | | | | |

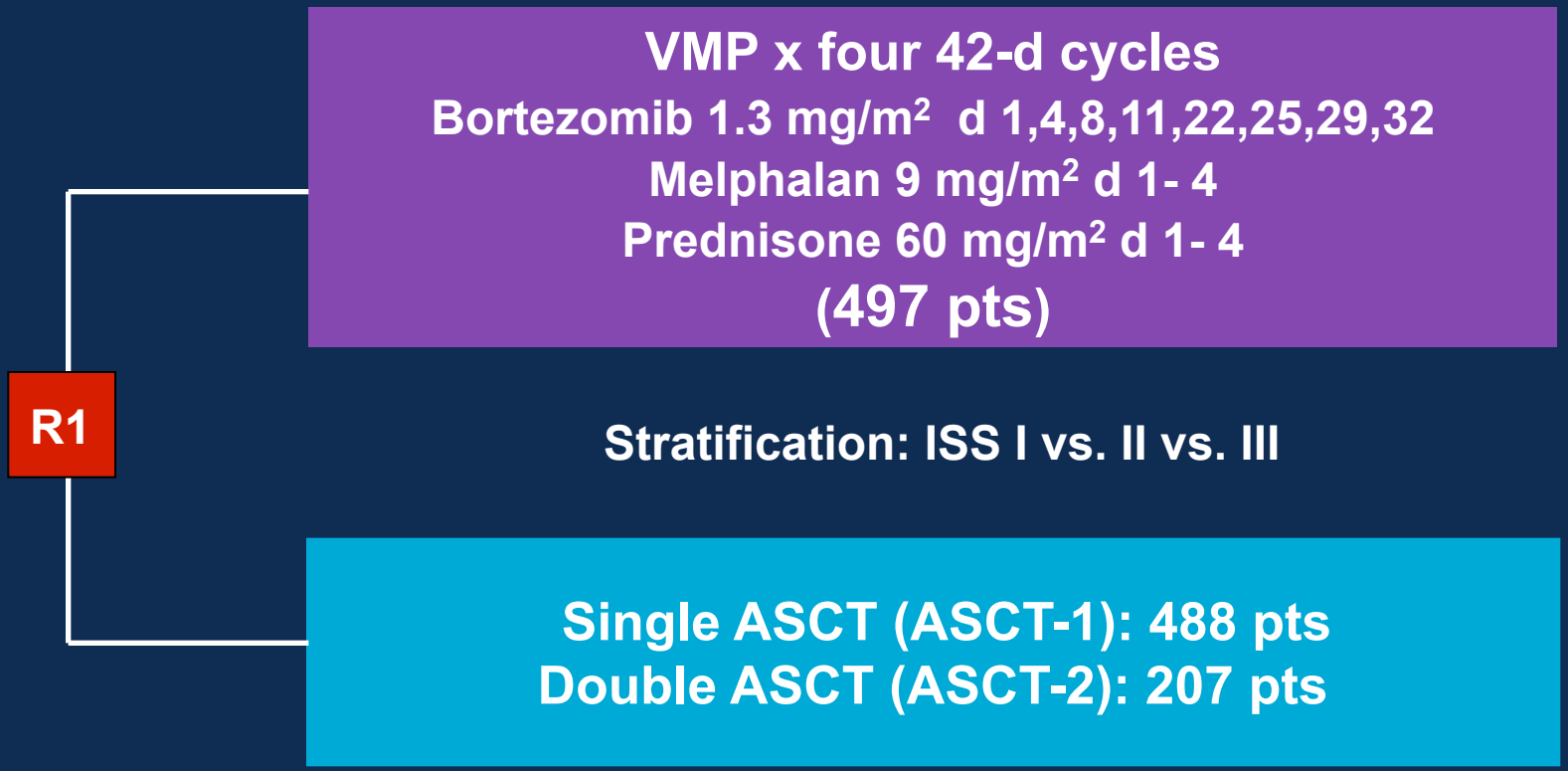
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 30 | 19 | 11 | 7 | 2 | 2 | 1 | 1 |
| | 36 | 13 | 6 | 2 | 1 | 1 | 1 | |

As of 10Feb2016

# EMN02/HO95 MM trial: study design



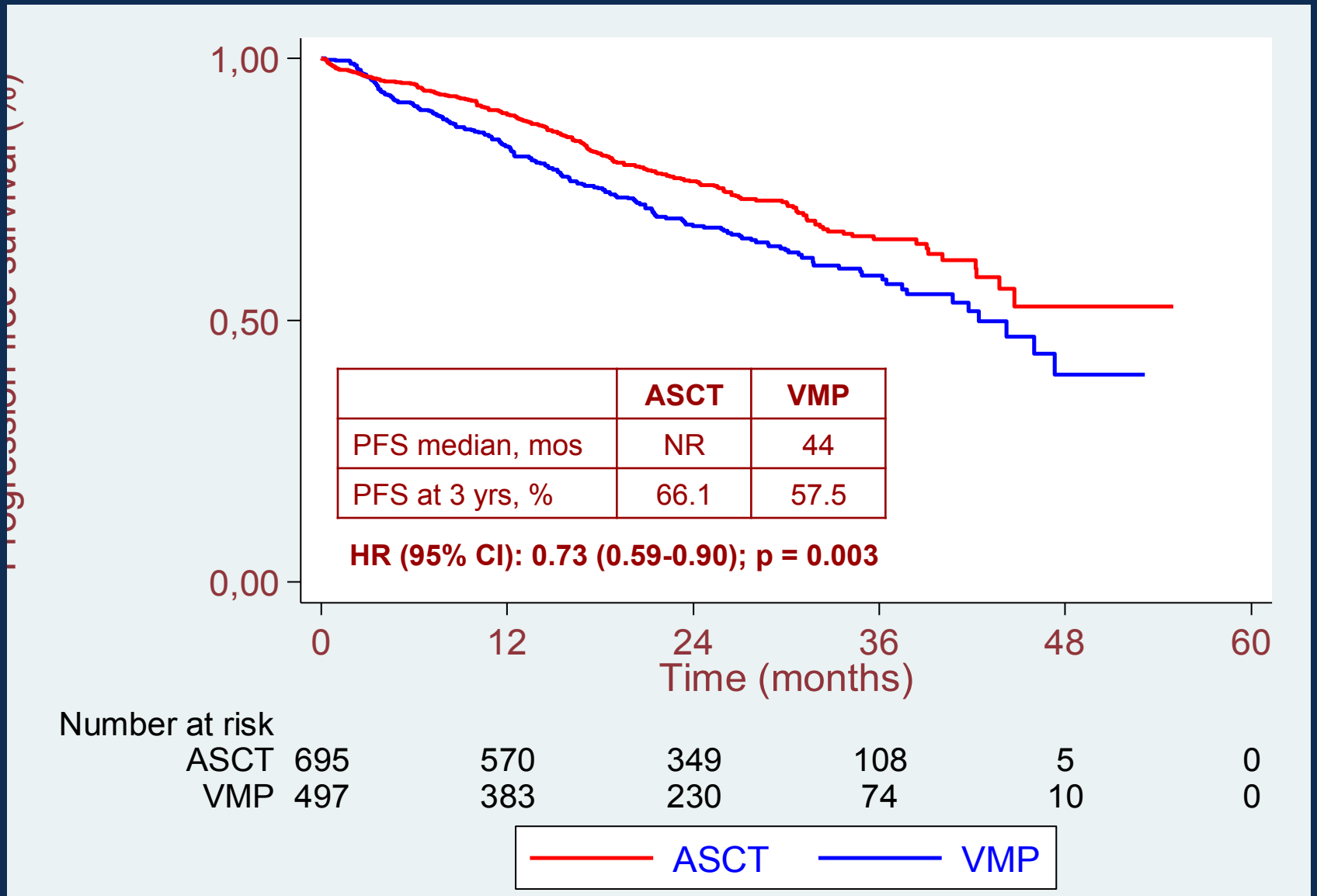
# EMN02/HO95 MM trial: study design




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

Randomization VMP vs HDM1 vs HDM2 (1:1:1) in centers with a double ASCT policy

# PFS by Randomization



# Results

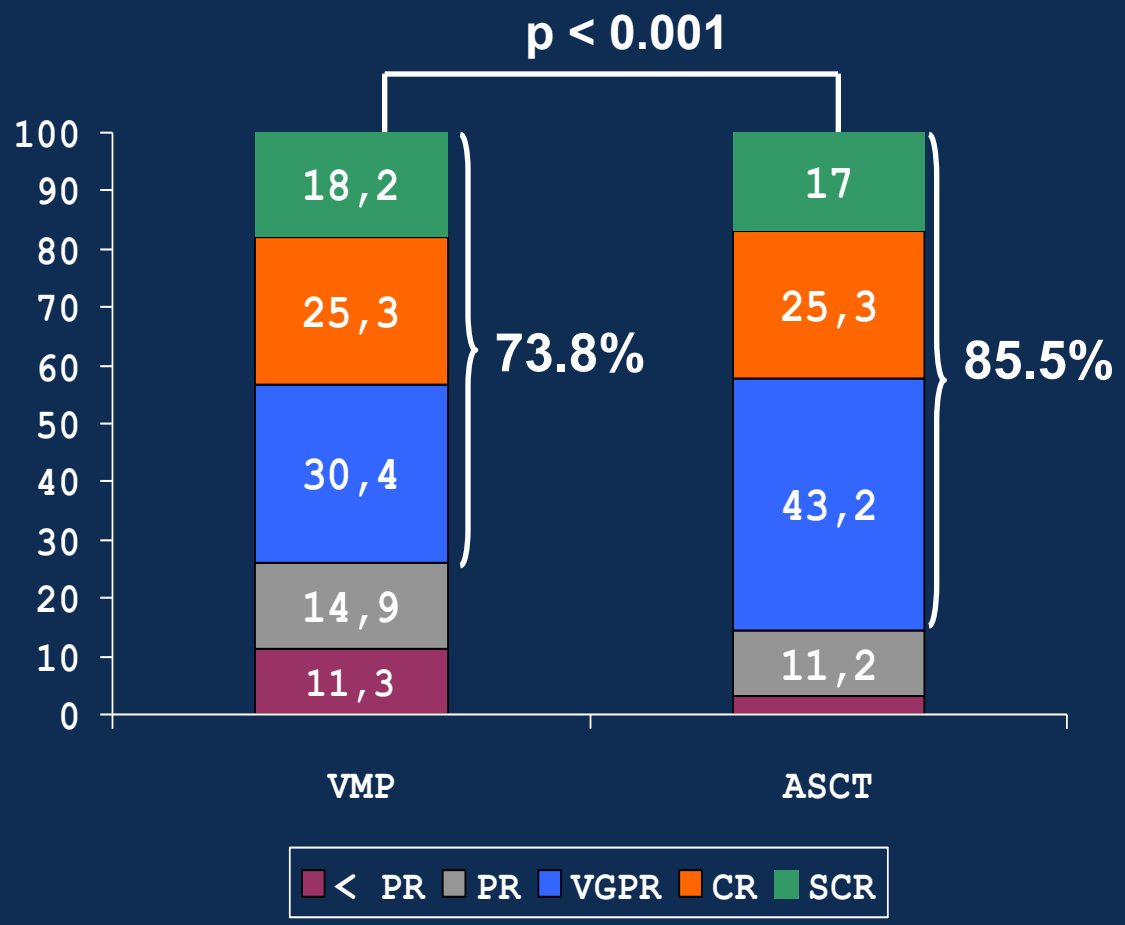
| | VMP | ASCT | PFS @ 36 months | | |
|---|---|---|---|---|---|
| **Patient subgroups** | **n° pts** | **n° pts** | **HR** | **95% CI** | **P value** |
| Overall population | 497 | 695 | 0.73 | 0.59-0.90 | 0.003 |
| ISS I | 206 | 289 | 0.69 | 0.48-0.98 | 0.037 |
| ISS II | 188 | 270 | 0.78 | 0.56-1.07 | 0.123 |
| ISS III | 103 | 136 | 0.72 | 0.48-1.08 | 0.112 |
| Revised-ISS I | 70 | 85 | 0.60 | 0.29-1.26 | 0.176 |
| Revised-ISS II | 235 | 352 | 0.71 | 0.54-0.95 | 0.020 |
| Revised-ISS III | 64 | 91 | 0.59 | 0.56-0.97 | 0.036 |
| HR cytogenetics | 181 | 292 | 0.69 | 0.52-0.92 | 0.010 |
| SR cytogenetics | 220 | 290 | 0.68 | 0.47-0.98 | 0.034 |

# Results. 2

| MULTIVARIATE ANALYSIS | | | |
|---|---|---|---|
| **Variables affecting PFS** | **HR** | **95% CI** | ***P*-value** |
| Best CR+sCR | 0.22 | 0.16-0.30 | <0.001 |
| Standard Risk cytogenetics | 0.44 | 0.34-0.57 | <0.001 |
| Randomization to ASCT | 0.54 | 0.42–0.68 | <0.001 |
| ISS I | 0.60 | 0.43-0.83 | 0.002 |

# Results. 3

| | VMP (n = 451) | ASCT (n = 641) |
|---|---|---|
| Response | (%) | (%) |
| sCR | 18.2 | 17.0 |
| CR | 25.3 | 25.3 |
| VGPR | 30.4 | 43.2 |
| PR | 14.9 | 11.2 |
| < PR | 11.2 | 3.3 |



# ASCT vs CC+lenalidomide

## GIMEMA MM-RV-209[1]

**Rd***
***four 28-day courses***
R: 25 mg/d, days 1-21
d: 40 mg/d, days 1,8,15,22

1° RANDOMIZATION

**MEL200**
***two courses***
M: 200 mg/m2 day -2
Stem cell support day 0

**MPR**
***six 28-day courses***
M: 0.18 mg/Kg/d, days 1-4
P: 2 mg/Kg/d, days 1-4
R: 10 mg/d, days 1-21

Recommended ASCT at first relapse

## EMN MM-RV-441[2]

**Rd**
***four 28-day courses***
R: 25 mg/d, days 1 - 21
d: 40 mg/d, days 1,8,15,22

1° RANDOMIZATION

**MEL200**
***two courses***
M: 200 mg/m2 day -2
Stem cell support day 0

**CRD**
***six 28-day courses***
C: 300 mg/sqm, days 1,8,15
R: 25 mg/d, days 1-21
D: 40 mg days 1,8,15,22

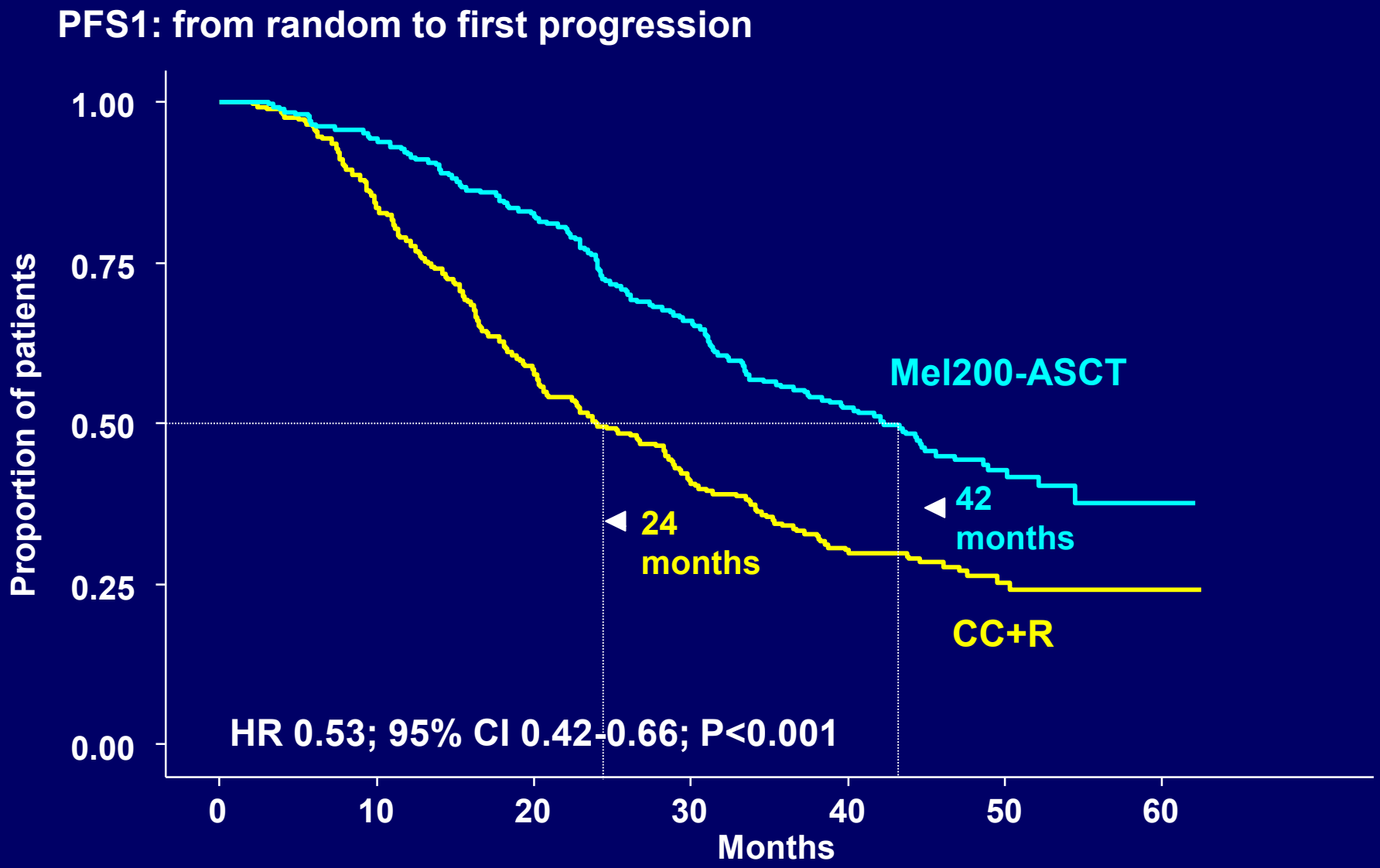
Recommended ASCT at first relapse

ASCT, autologous stem-cell transplantation; CC, conventional chemotherapy; Rd, lenalidomide plus low-dose dexamethasone; Mel200, melphalan 200 mg/m2; MPR, melphalan-prednisone-lenalidomide; CRD, cyclophosphamide-lenalidomide-dexamethasone; R, lenalidomide; P, prednisone

1. Palumbo A et al, N Engl J Med 2014 371(10):895-905; 2. Gay F et al. Lancet Oncol 2016; 1617-29.

# Mel200-ASCT vs CC+R: PFS1

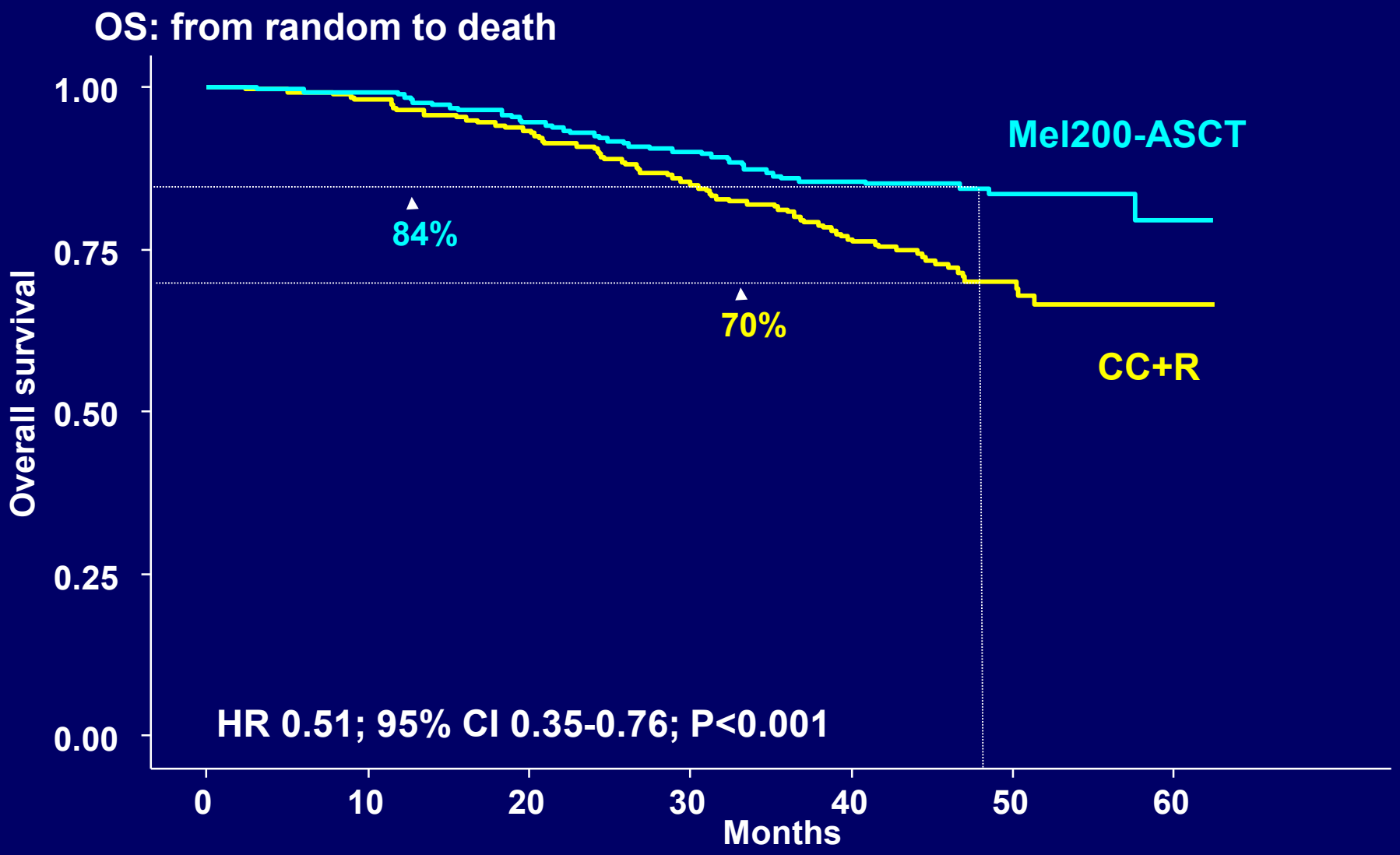
## Median progression-free survival1




Mel200–ASCT, melphalan 200 mg/m2 followed by autologous stem cell transplantation; CC+R, conventional chemotherapy + lenalidomide; PFS, progression-free survival.

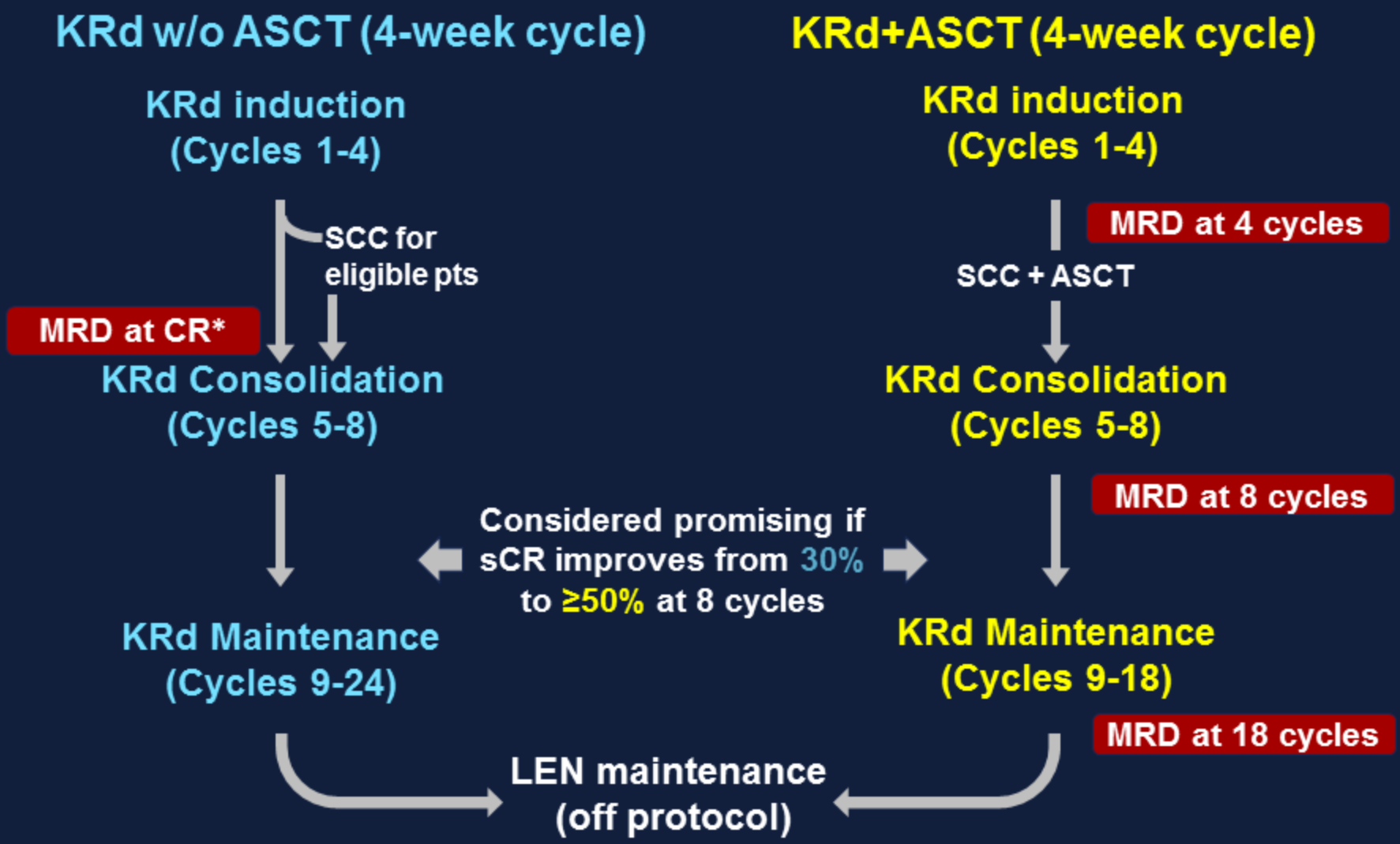
# Mel200-ASCT vs CC+R: OS

## 4-year overall survival



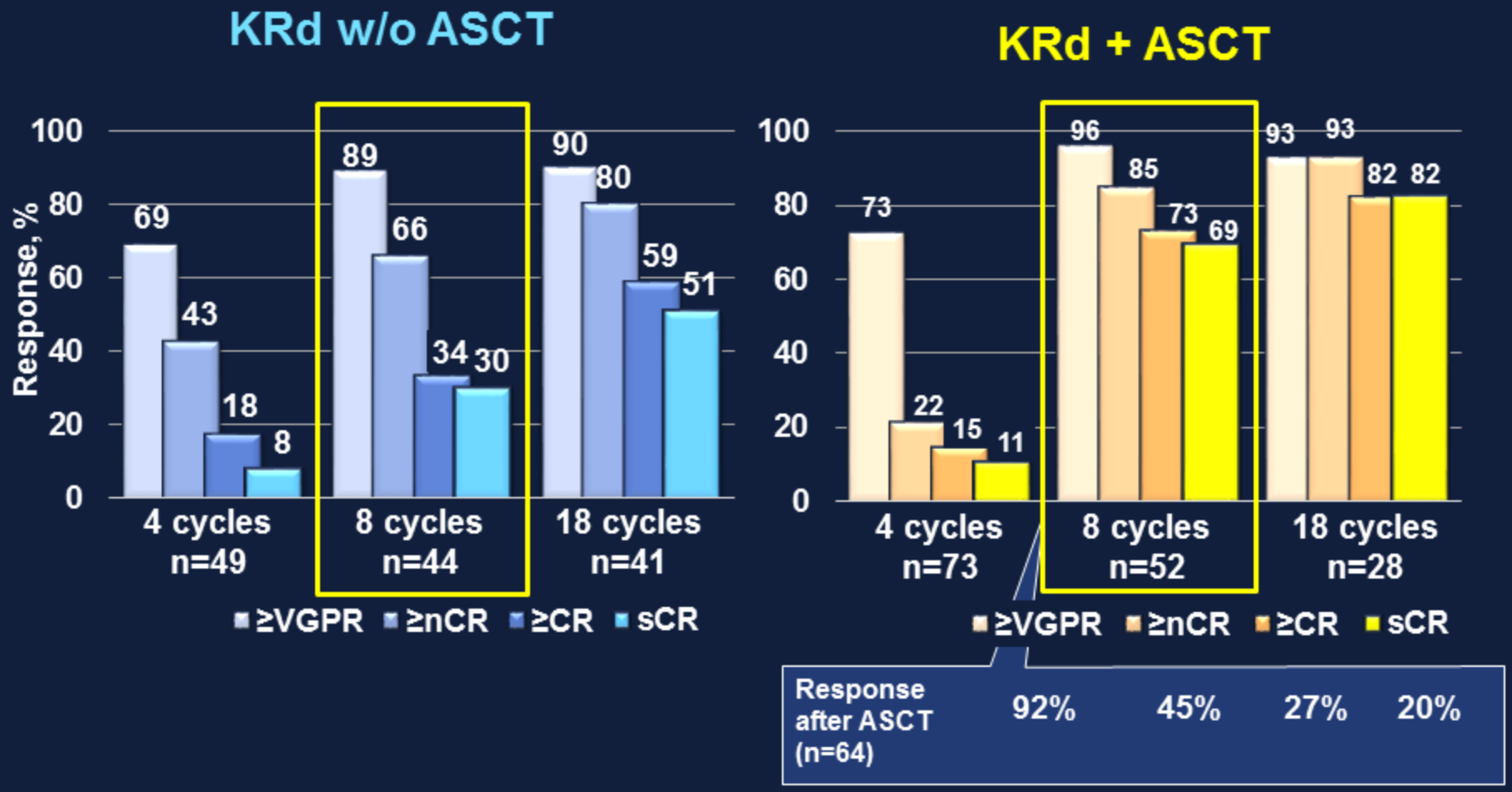

Mel200–ASCT, melphalan 200 mg/m2 followed by autologous stem cell transplantation; CC+R, conventional chemotherapy + lenalidomide; OS, overall survival.

# Treatment Schema



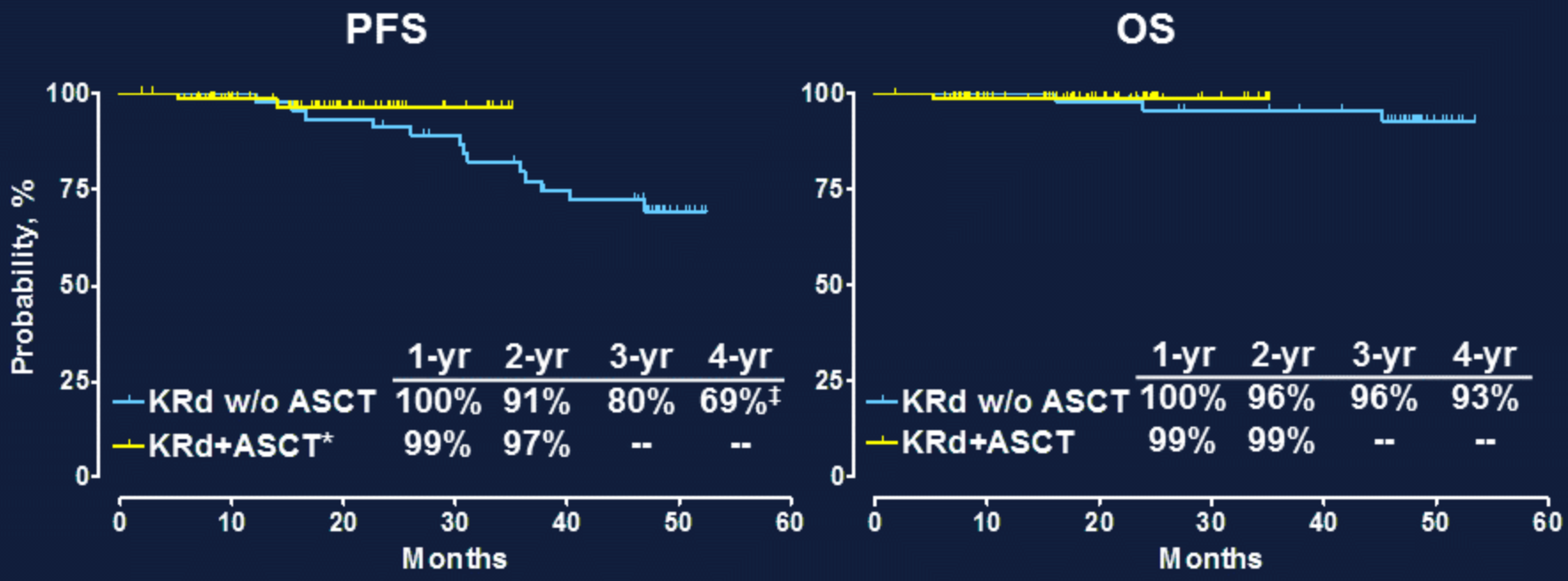

*CR or suspected ≥CR (exploratory)

# Response Rates Over the Course Treatment




nCR, near complete response; VGPR, very good partial response

# Treatment Outcomes



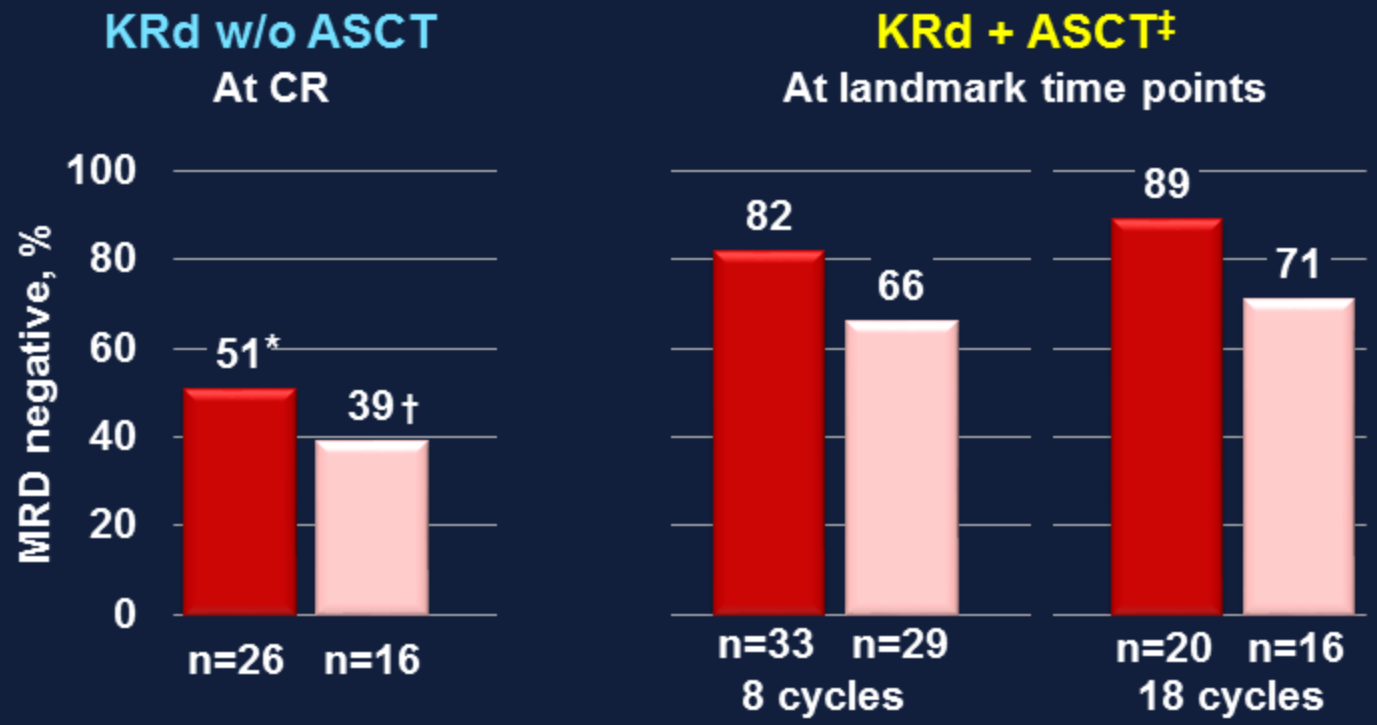

| | | Median f/u, mo |
|---|---|---|
| KRd w/o ASCT | n=46† | 47.6 |
| KRd+ASCT | N=76 | 17.5 |

*2 patients progressed (1 during pre-ASCT period; 1 after discontinued from the study after ASCT)
† Excludes 7 pts who discontinued to pursue ASCT
‡ Intent-to-treat (N=53), 4-year PFS 64%

At cut-off date 1/1/16

# MRD Evaluation

- Multiparameter Flow Cytometry (MFC)
  10 color
  Sensitivity: $10^{-4}$ – $10^{-5}$
- Next generation sequencing (NGS)
  Adaptive Biotechnologies
  Sensitivity: $10^{-6}$

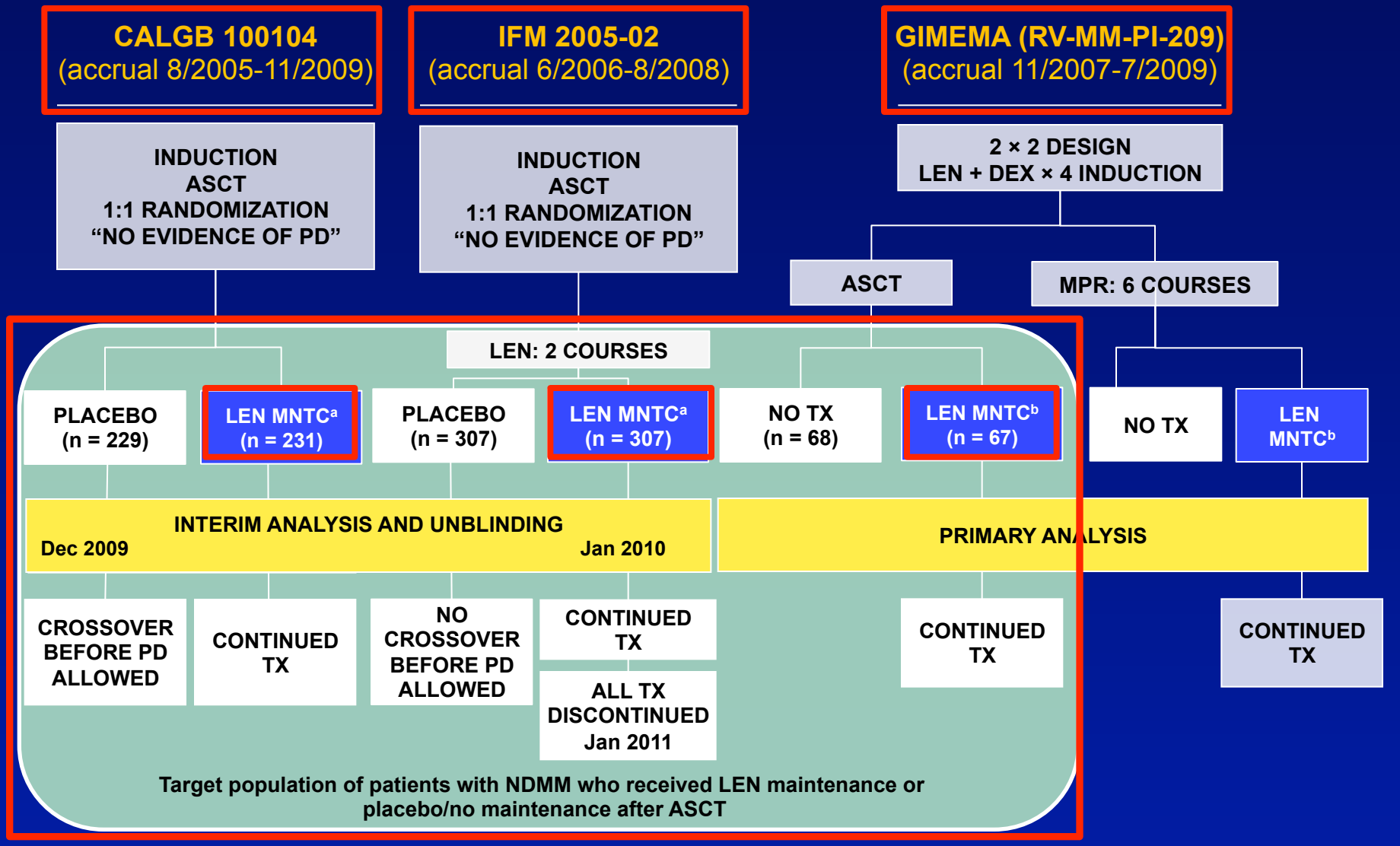



*Estimated rate based on 23 of 26 evaluated pts assessed for MRD by flow cytometry at CR/ suspected CR

†Estimated rate based on percentage of 13 pts in CR/sCR negative by NGS

‡Actual MRD rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles as per new IMWG MRD criteria (pts were considered MRD – negative only if in CR/sCR)

# Studies Included in Meta-Analysis (none initially powered for OS)

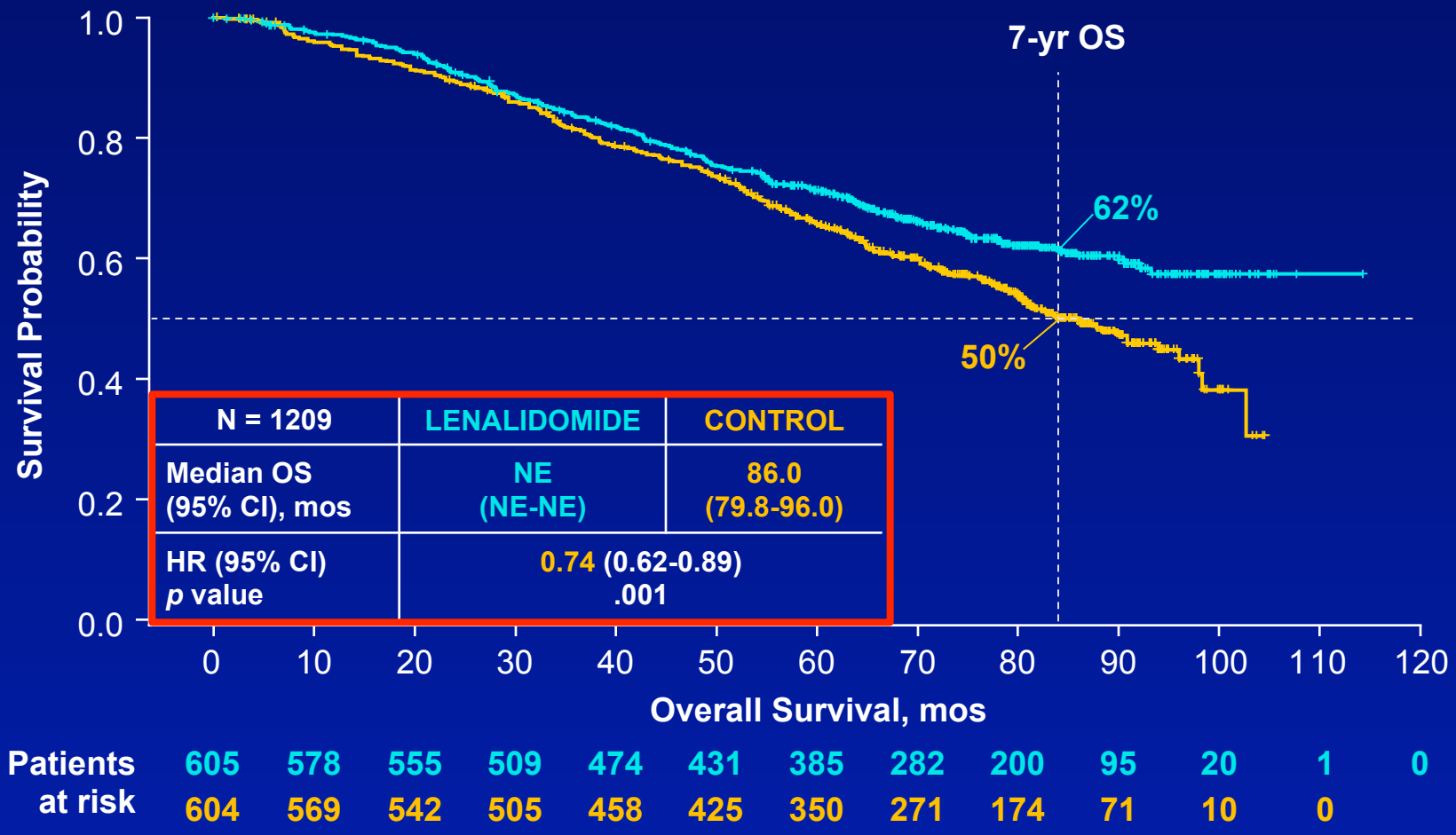



[a] Starting dose of 10 mg/day on days 1-28/28 was increased to 15 mg/day if tolerated and continued until PD. [b] Patients received 10 mg/day on days 1-21/28 until PD.
ASCT, autologous stem cell transplant; DEX, dexamethasone; LEN, lenalidomide; MNTC, maintenance; MPR, melphalan, prednisone, and lenalidomide; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; Tx, treatment.

# Overall Survival: Median Follow-Up of 80 Months

**26% reduction in risk of death**

**2.5-year increase in median overall survival[a]**



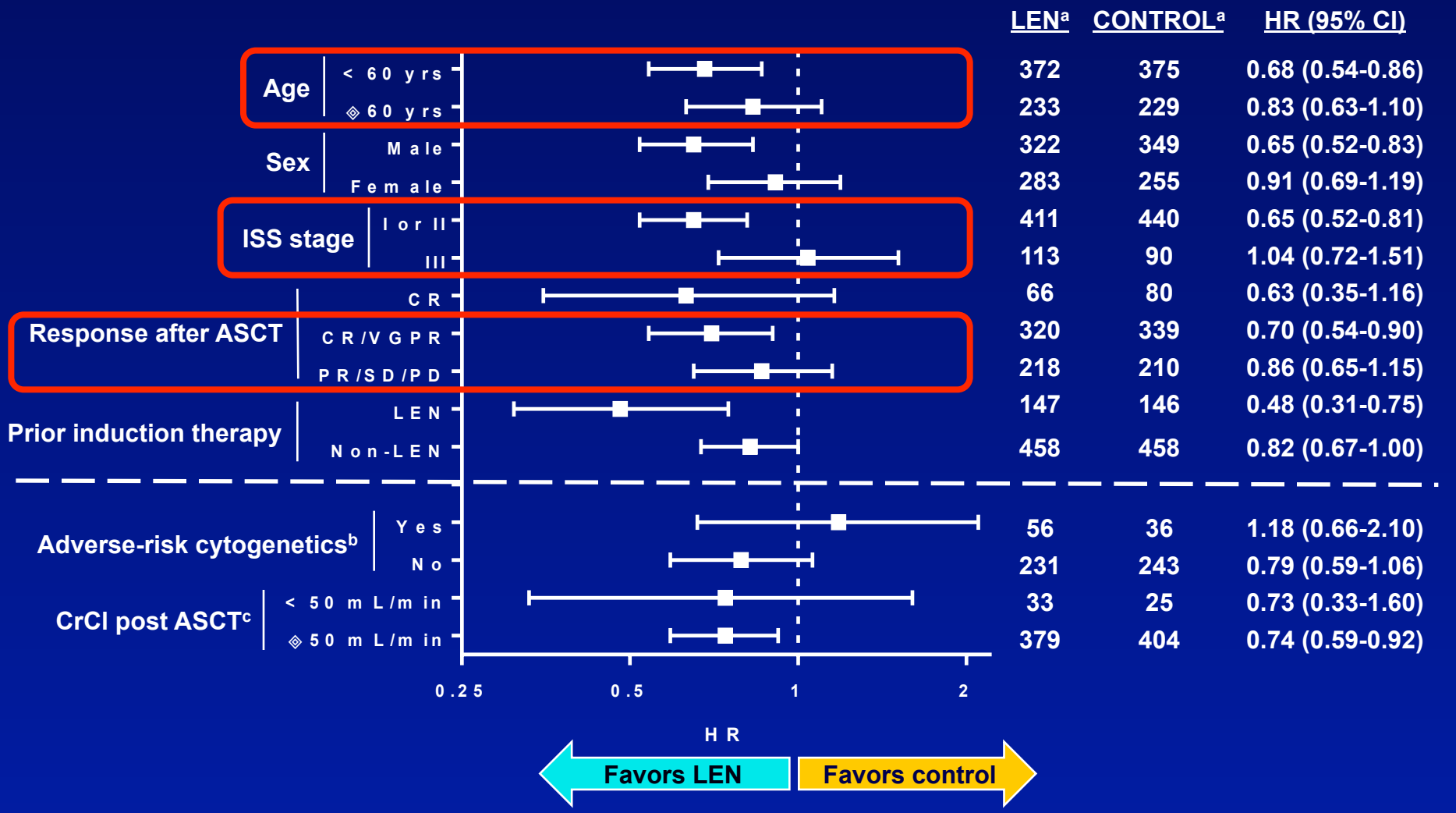

| N = 1209 | LENALIDOMIDE | CONTROL |
|---|---|---|
| Median OS (95% CI), mos | NE (NE-NE) | 86.0 (79.8-96.0) |
| HR (95% CI) *p* value | 0.74 (0.62-0.89) .001 | |

| Patients at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 605 | 578 | 555 | 509 | 474 | 431 | 385 | 282 | 200 | 95 | 20 | 1 | 0 |
| | 604 | 569 | 542 | 505 | 458 | 425 | 350 | 271 | 174 | 71 | 10 | 0 | |

[a] Median for lenalidomide treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median, 86 months; HR = 0.74).

HR, hazard ratio; NE, not estimable; OS, overall survival.

# Overall Survival: Subgroup Analysis




[a] Number of patients. [b] Cytogenetic data were available only for the IFM and GIMEMA studies. [c] CrCl post-ASCT data were available only for the CALGB and IFM studies.
ASCT, autologous stem cell transplant; CR, complete response; CrCl, creatinine clearance; HR, hazard ratio; ISS, International Staging System; LEN, lenalidomide; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.