# Management of Multiple Myeloma: Board Review

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# Disclosures

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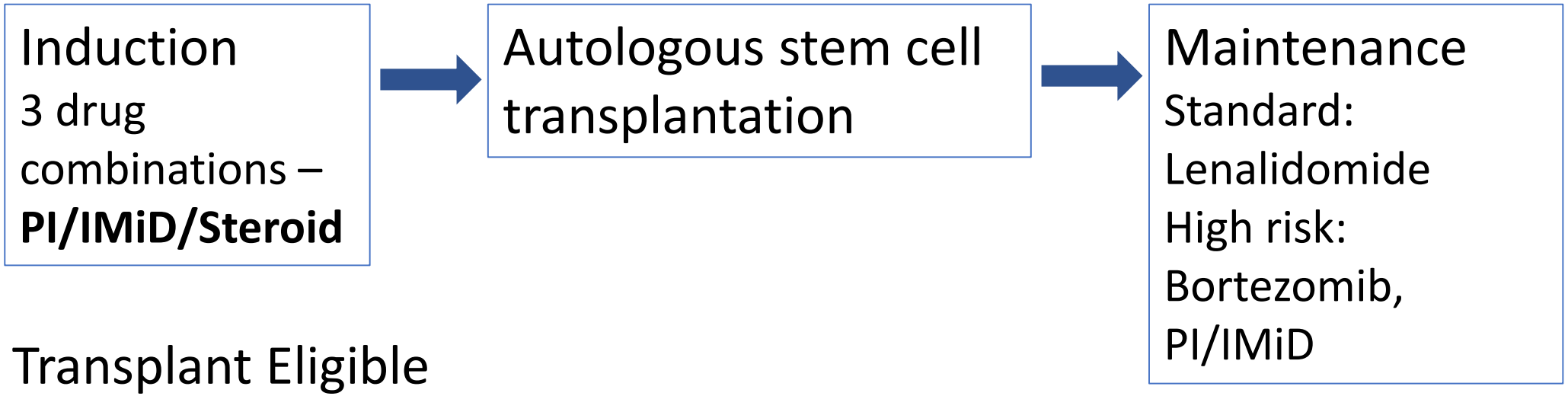
# Goals

- Review risk stratification for multiple myeloma
- Review treatment strategies for transplant eligible multiple myeloma
- Review treatment strategies for transplant-ineligible multiple myeloma
- Discuss treatment of relapsed/refractory multiple myeloma

# What is the current best practice for treatment?

Transplant Eligible




Not Transplant Eligible


Supportive Care

# Risk stratification in multiple myeloma

- Disease burden – beta 2 microglobulin, LDH
- Tumor-specific factors – circulating plasma cells (extreme example is plasma cell leukemia)
- Genetic factors - chromosomal abnormalities

# Revised-International Staging System for Myeloma

| ISS or R-ISS Stage | ISS Criteria | R-ISS Criteria |
|---|---|---|
| I | Serum beta-2 microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL | ISS Stage I AND standard risk CA by iFISH and normal LDH |
| II | Not ISS stage I or III | Not R-ISS stage I or III |
| III | Serum beta-2 microglobulin ≥ 5.5 mg/L | ISS Stage III AND either high-risk CA by iFISH or high LDH |

Palumbo et al, JCO 2015

# Incidence of chromosomal abnormalities in multiple myeloma

| Genomic aberration | Incidence, % (no. of patients analyzed for the aberration) |
|---|---|
| del(13) | 48 (936) |
| t(11;14)(q13;q32) | 21 (746) |
| t(4;14)(p16;q32) | 14 (716) |
| Hyperdiploidy | 39 (657) |
| MYC translocations | 13 (571) |
| del(17p) | 11 (532) |

Avet-Loiseau et al, Blood 2007

# What does “high-risk” myeloma mean?

- Outcomes for many patients with myeloma are improving
- However, a subset of patients (20-25%) with certain biologic, genetic, and excess disease burden have poorer outcomes, even with novel agents and new therapies
- New strategies to identify and offer more effective treatments for these patients are needed

# Current conception of high risk myeloma by the IWMG and others

- IMWG: Revised ISS definition of high-risk
  - ISS Stage III (Elevated Beta-2 Microglobulin (> 5.5 mg/L))
  - **AND**
    - 1. High risk Chromosomal abnormalities:
      - Deletion 17p
      - t(4;14), t(14;16)
  - **OR**
    - 2. Serum LDH > upper limit of normal
- Circulating tumor cells (plasma cells – extreme case is plasma cell leukemia)
- Gene expression profiling
- Complex karyotypes
- Other chromosomal changes: 1p deletion or 1q amplification on FISH; t(14;20) translocation on FISH
- Extramedullary disease
- Plasmablastic morphology

WJ Chang et al Leukemia 2014

# High Risk Chromosomal Changes

- IgH translocations – 40% of cases (chr 14)
  - t(4;14): 4p16 – *FGFR3* – deregulation of fibroblast growth factor
  - t(14;16): 16q23 – *MAF* – deregulation of *c-MAF* proto-oncogene
  - t(14;20): 20q11 – *MAFB* – deregulation of *MAFB* oncogene

- Del(17p) – *p53* – clonal immortalization, resistance to apoptosis

- 1q amplification – *CKS1B* – activation of cyclin dependent kinase → deregulation of cell cycle control

Sonneveld et al Blood 2016

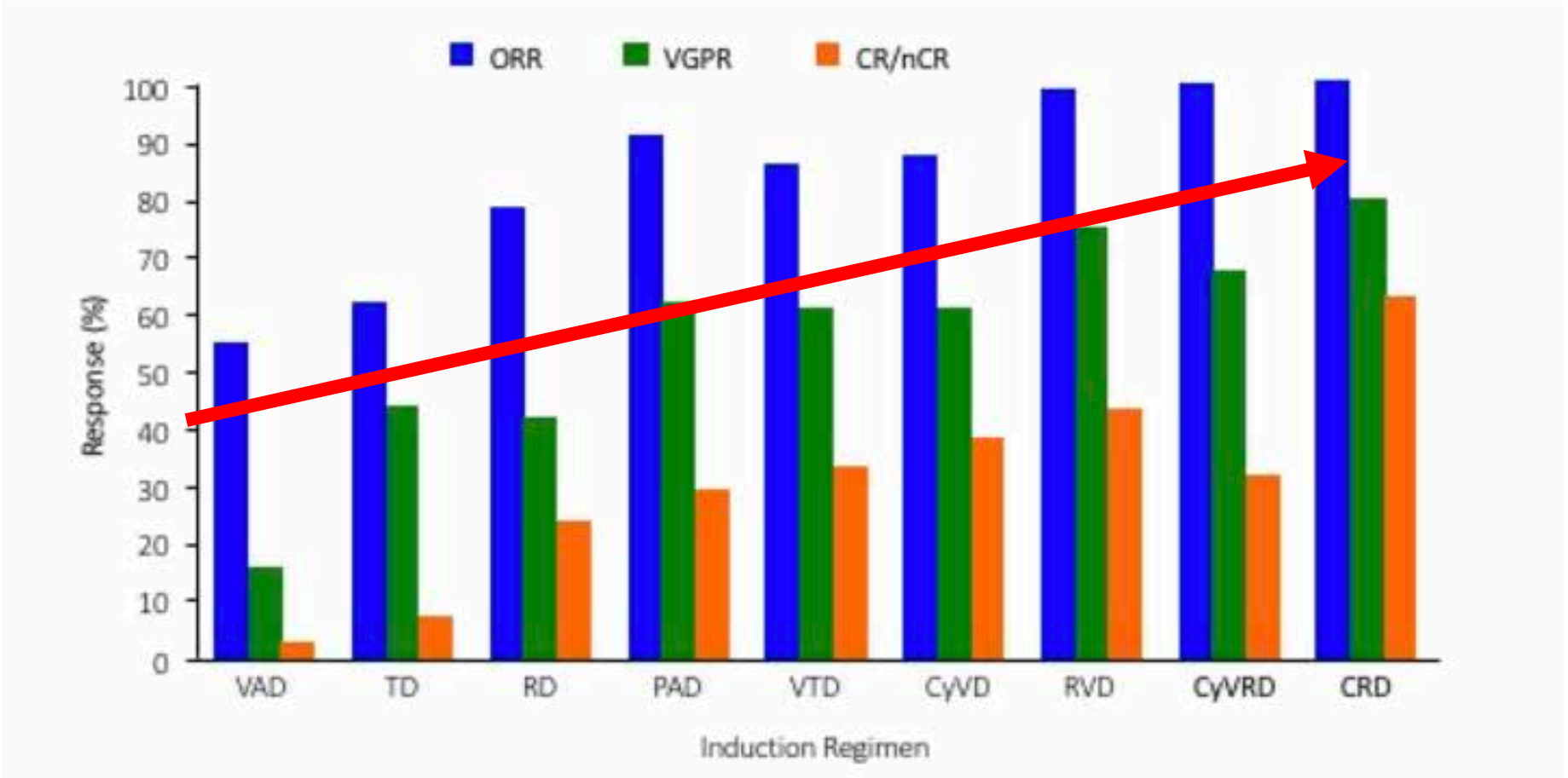
# What is the preferred upfront treatment approach?

- Induction with IMID/PI 3 drug combination, followed by autologous stem cell transplantation (Attal, NEJM 2017)
- On the horizon: 4 drug induction including a monoclonal antibody – CASSIOPEIA – Dara-VTD, and GRIFFIN - DaraRVD
- Maintenance therapy with IMID post transplant, for standard risk (McCarthy JCO 2017)
- Maintenance therapy with PI post transplant for high-risk cytogenetics (Del(17p) and t(4;14) (HOVON-65)
- Intravenous bisphosphonates (MRC IX trial)

# Multiple Myeloma Approved Drugs

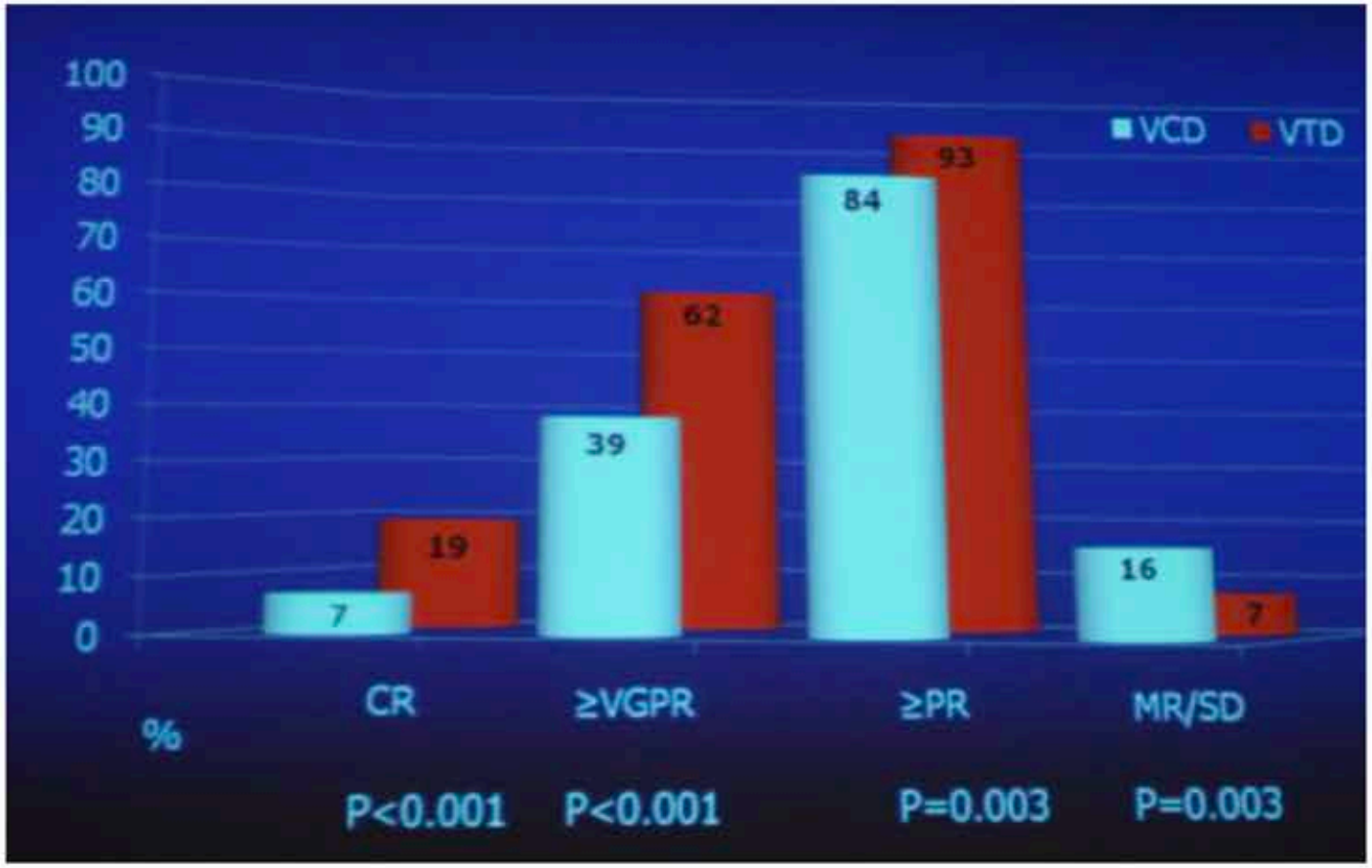
- Proteasome inhibitors
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- Immunomodulatory agents
  - Lenalidomide
  - Pomalidomide
  - Thalidomide
- Selective Inhibitors of Nuclear Export (SINE)
  - Selinexor
- Monoclonal antibodies
  - Daratumumab (CD38)
  - Isatuximab (CD38)
  - Elotuzumab (SLAMF7)
- Alkylating agents
  - Melphalan
  - Cyclophosphamide
  - Bendamustine
- HDAC Inhibitors
  - Panobinostat

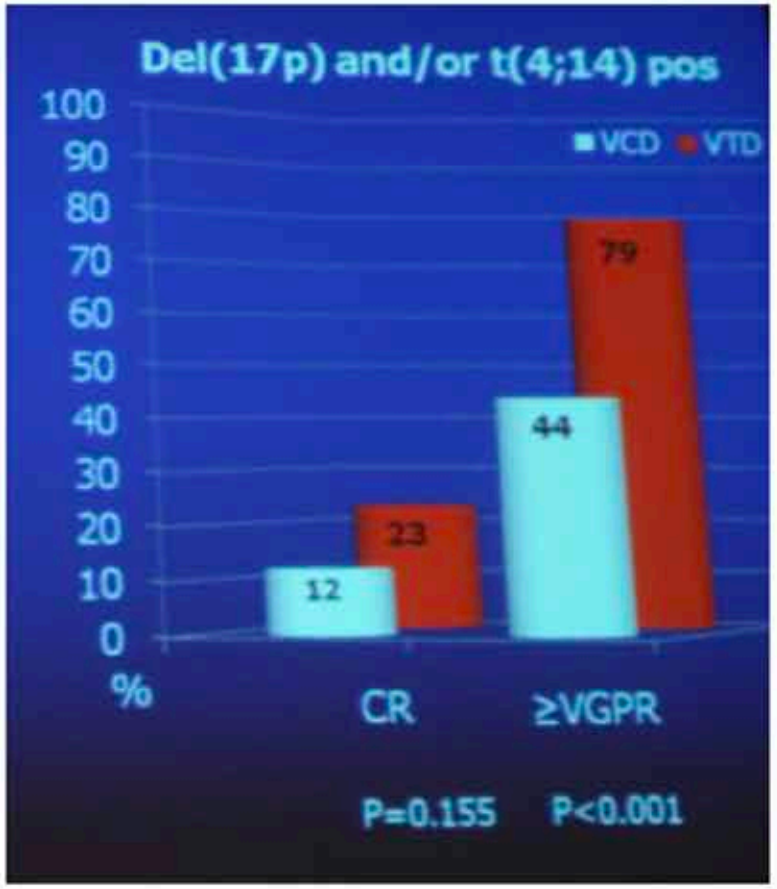
**The overall, more than VGPR and nCR/CR rates for a selection of phase 2 and phase 3 trials incorporating novel agents.**




A. Keith Stewart et al. Blood 2009;114:5436-5443;
Jakubowiak et al, Blood 2012

# Does it matter which 3 drugs are used?




Cavo M et al, ASH 2014

# IMID/PI Combination most effective

**Table 1.** Response to VTD and VCD induction therapy

| *All patients* | *VTD (n = 236)* | *VCD (n = 236)* | P |
|---|---|---|---|
| Complete response | 44 (19%; 14–24) | 13 (6%; 3–8) | < 0.001 |
| Very good partial response or better | 151 (64%; 58–70) | 87 (37%; 31–43) | < 0.001 |
| Partial response or better | 220 (93%; 90–96) | 192 (81%; 76–86) | < 0.001 |
| Stable disease | 16 (7%; 4–10) | 38 (16%; 11–21) | 0.001 |
| Progressive disease | 0 (0%) | 6 (3%; 1–5) | 0.015 |
| *Patients with ISS 2-3* | *VTD (n = 129)* | *VCD (n = 129)* | |
| Complete response | 26 (20%; 13–27) | 5 (4%; 1–7) | < 0.001 |
| Very good partial response or better | 86 (67%; 59–75) | 45 (35%; 27–43) | < 0.001 |
| *Patients with t(4;14) and/or del(17p)* | *VTD (n = 53)* | *VCD (n = 53)* | |
| Complete response | 12 (23%; 11–34) | 4 (8%; 0–15) | 0.030 |
| Very good partial response or better | 44 (83%; 73–93) | 25 (47%; 34–61) | < 0.001 |

Abbreviations: ISS, international staging system; VCD, bortezomib with cyclophosphamide plus dexamethasone; VTD, bortezomib with thalidomide plus dexamethasone. Data are number of patients (%; 95% CI). Comparisons were performed by $\chi^2$ test or Fisher's test, as appropriate.

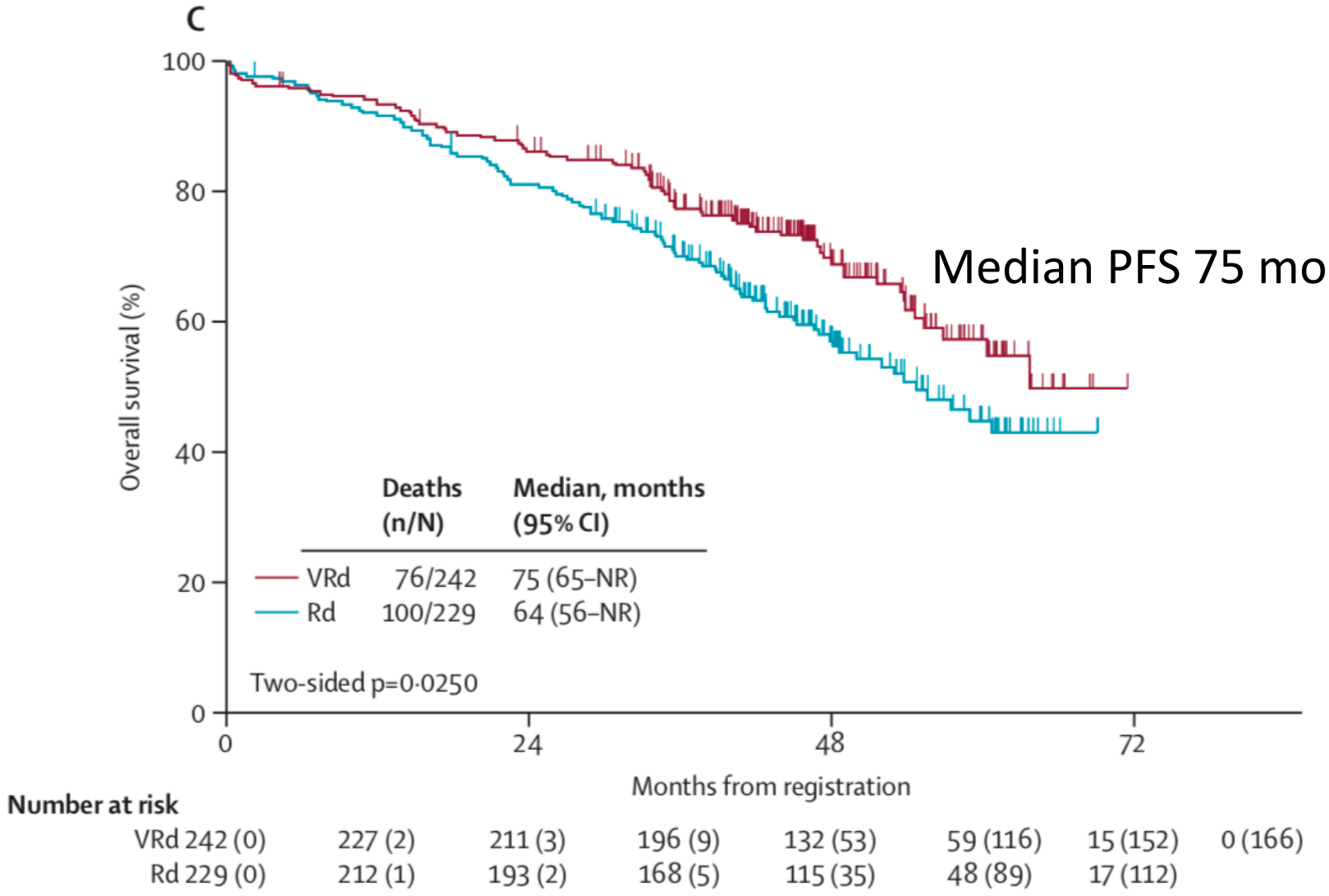
Cavo et al, Leukemia 2016

# Triple drug induction is superior to doublet

| | **Patients given bortezomib with lenalidomide and dexamethasone (VRd group; n=216)*** | **Patients given lenalidomide and dexamethasone (Rd group; n=214)*** |
|---|---|---|
| Confirmed response | 34 (15·7%) | 18 (8·4%) |
| Very good partial response | 60 (27·8%) | 50 (23·4%) |
| Partial response | 82 (38%) | 85 (39·7%) |
| Overall response rate (partial response or better) | **176 (81·5%)** | **153 (71·5%)** |
| Stable disease | 34 (15·7%) | 52 (24·3%) |
| Stable disease or better | 210 (97·2%) | 205 (95·8%) |
| Progressive disease or death | 6 (2·8%) | 9 (4·2%) |

Durie B et al Lancet 2017

# Superiority of RVD over Rd: SWOG S0777

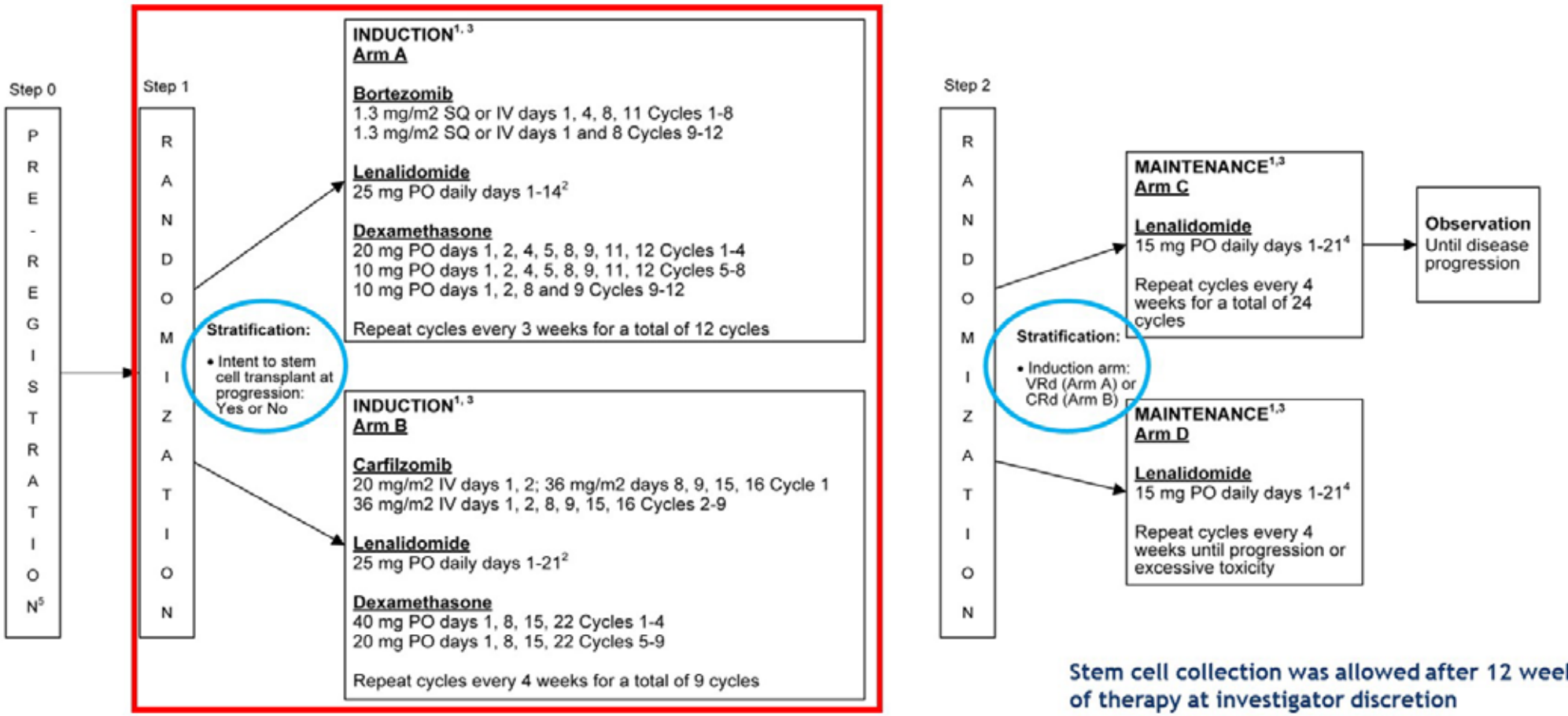



Median PFS 75 months

Durie B et al Lancet 2017

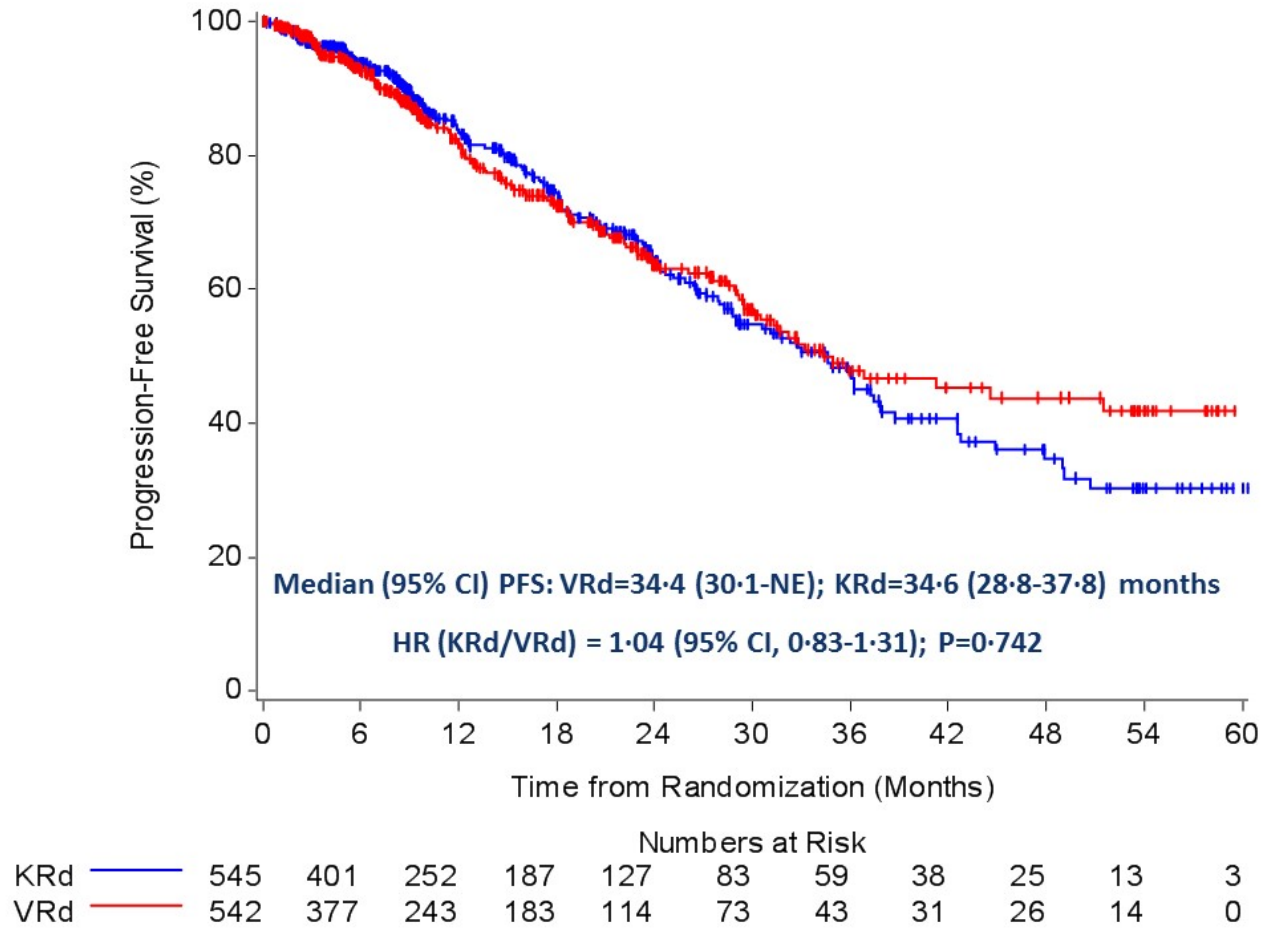
# ENDURANCE: RVd vs KRd, ASCO 2020

## Patient Randomization and Treatment Schedule




Stem cell collection was allowed after 12 weeks of therapy at investigator discretion

# Progression Free Survival from Induction Randomization




- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients >/= 70 years, median PFS(95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31·7 (28·5-44·6) and KRd = 32·8 (27·2-37·5) months

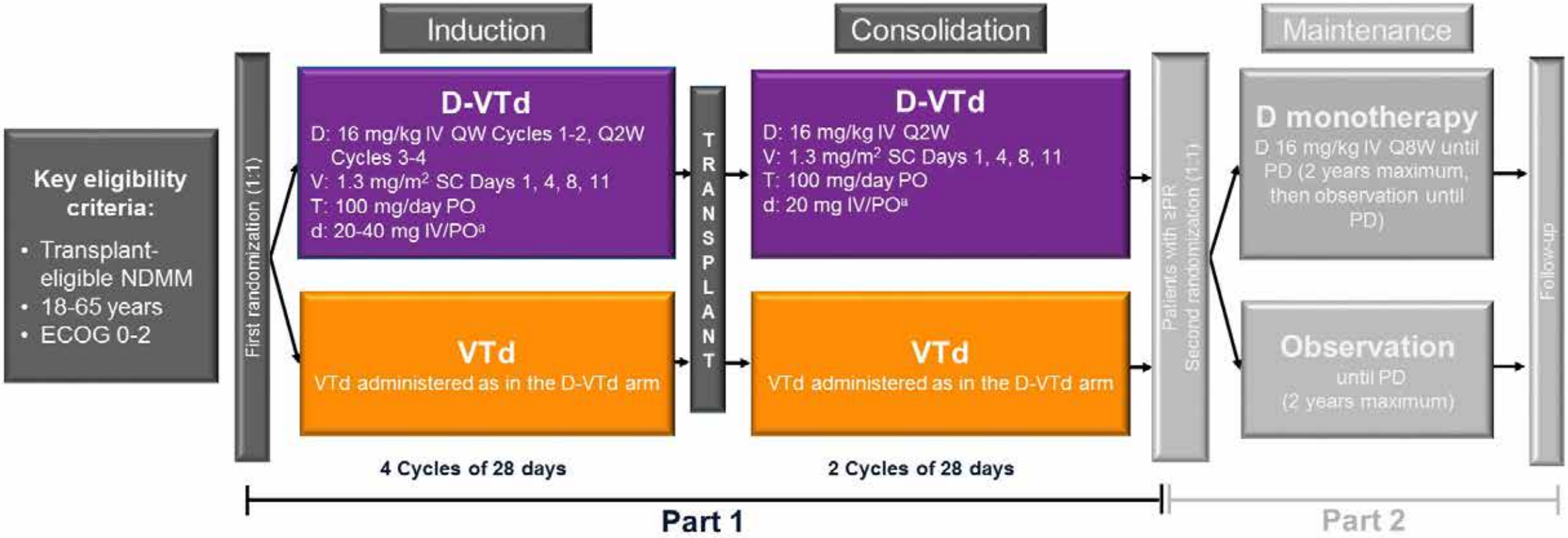
# 4 drug combinations

- RVd is the standard of care for newly diagnosed MM… but does adding a CD38 antibody improve outcomes?

- 2 key studies in transplant eligible MM:
  - CASSIOPEIA: Daratumumab + VTd vs VTd
  - GRIFFIN: Daratumumab + RVd vs RVd

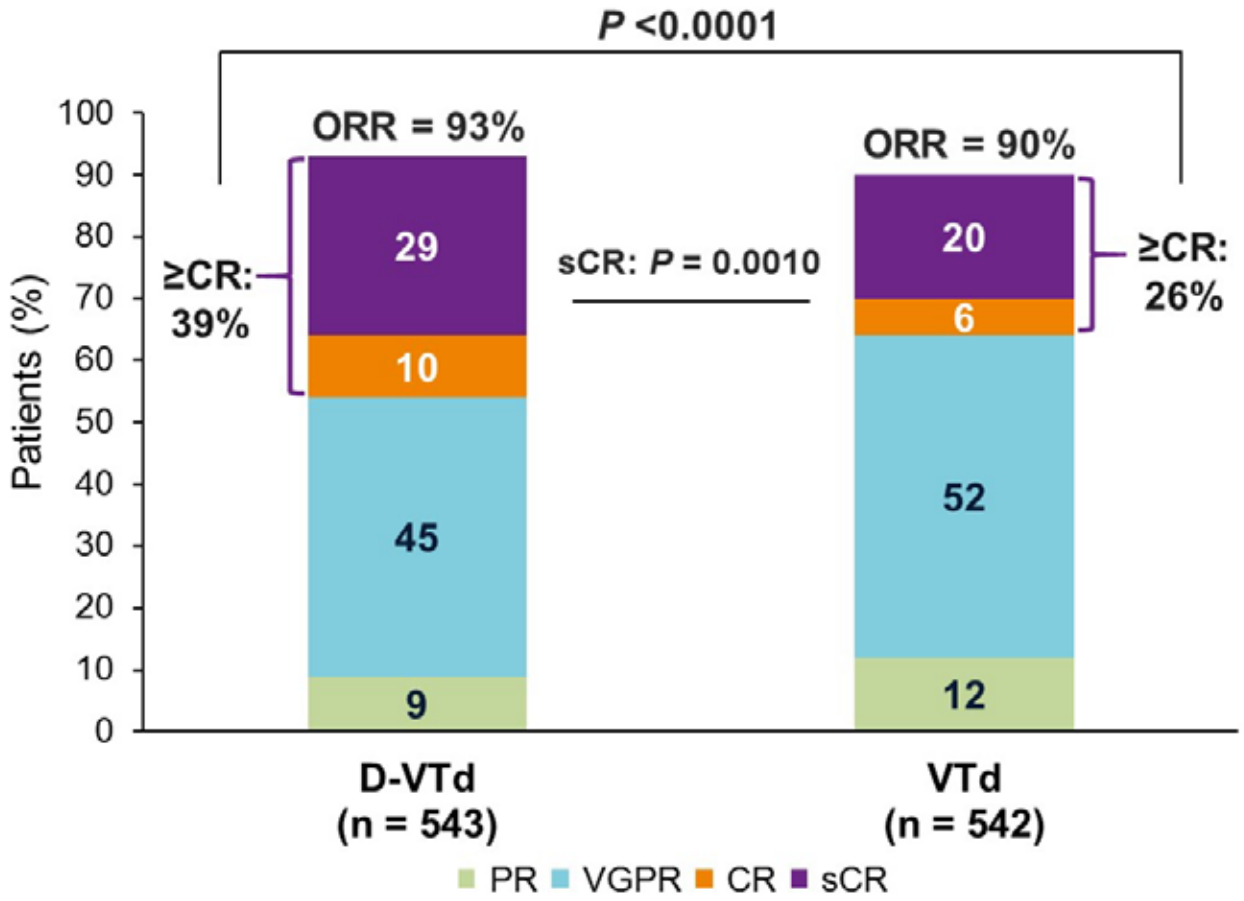
# CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017




D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease.
[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

# Efficacy: Post-consolidation Depth of Response




- Primary endpoint
  - Post-consolidation sCR
    - 29% D-VTd vs 20% VTd
    - Odds ratio, 1.60; 95% CI, 1.21-2.12; *P* = 0.0010

- sCR definition
  - All required:
    - SIFE negative
    - UIFE negative
    - <5% plasma cells in the BM
    - Four-color flow negativity
    - Normal FLC ratio
    - Disappearance of all plasmacytomas

**The addition of daratumumab to VTd improved depth of response**

ORR, overall response rate; VGPR, very good partial response; CI, confidence interval; SIFE, serum immunofixation; UIFE, urine immunofixation; BM, bone marrow; FLC, free light chain.

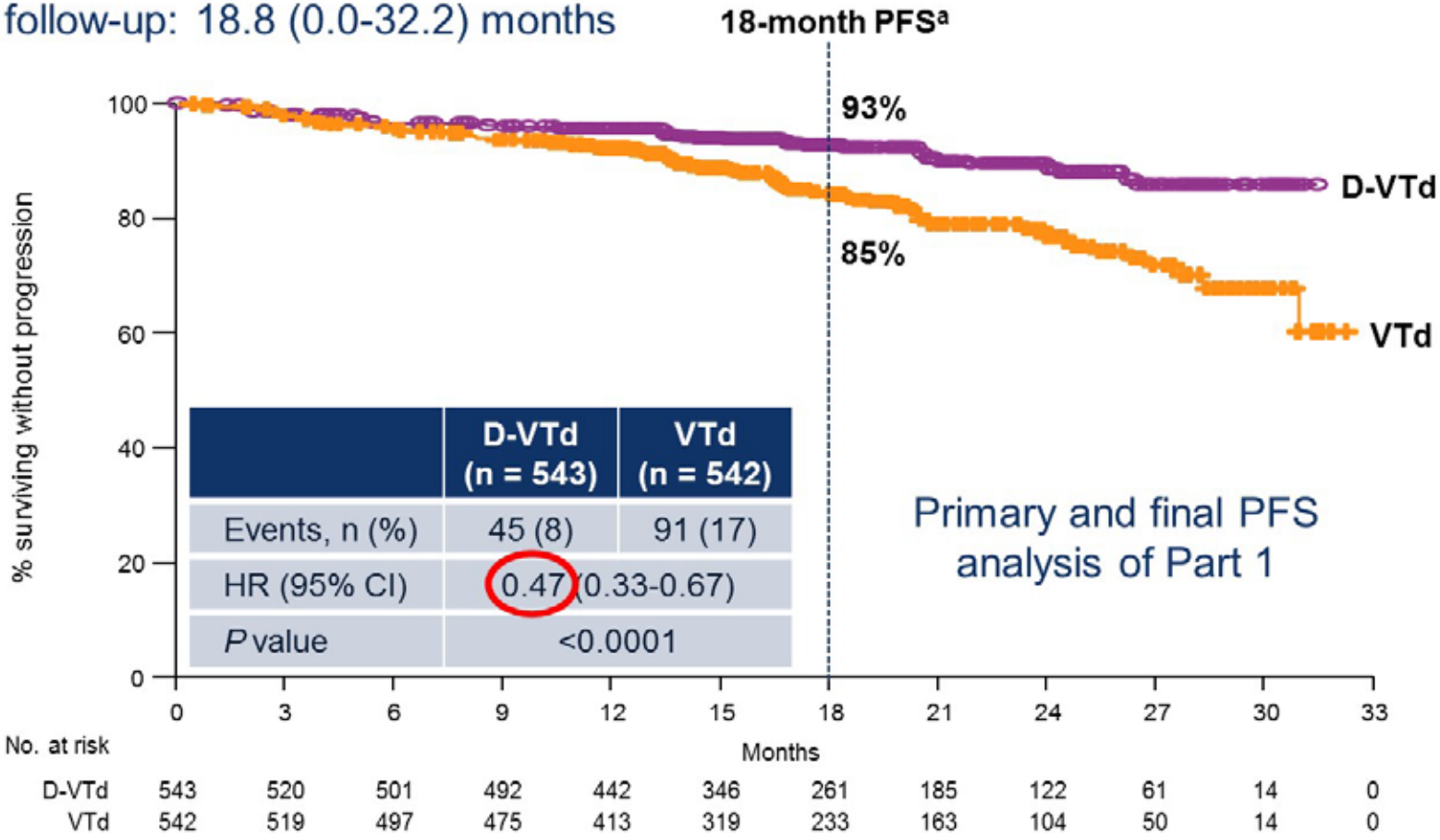




Presented By Philippe Moreau at 2019 ASCO Annual Meeting

# Efficacy: PFS From First Randomization

- Median (range) follow-up: 18.8 (0.0-32.2) months




| | D-VTd (n = 543) | VTd (n = 542) |
|---|---|---|
| Events, n (%) | 45 (8) | 91 (17) |
| HR (95% CI) | 0.47 (0.33-0.67) | |
| *P* value | <0.0001 | |

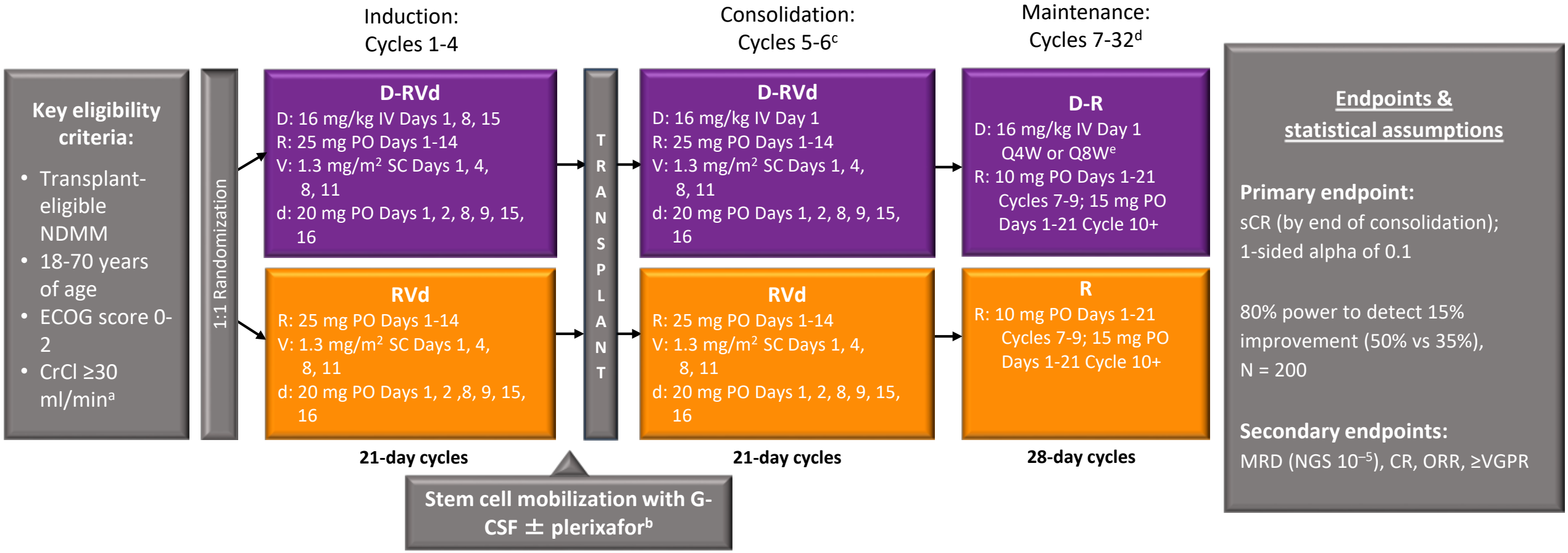
Primary and final PFS analysis of Part 1

**53% reduction in the risk of progression or death in the D-VTd arm**

HR, hazard ratio.
[a]Kaplan-Meier estimate.

# GRIFFIN (NCT02874742): Randomized Phase

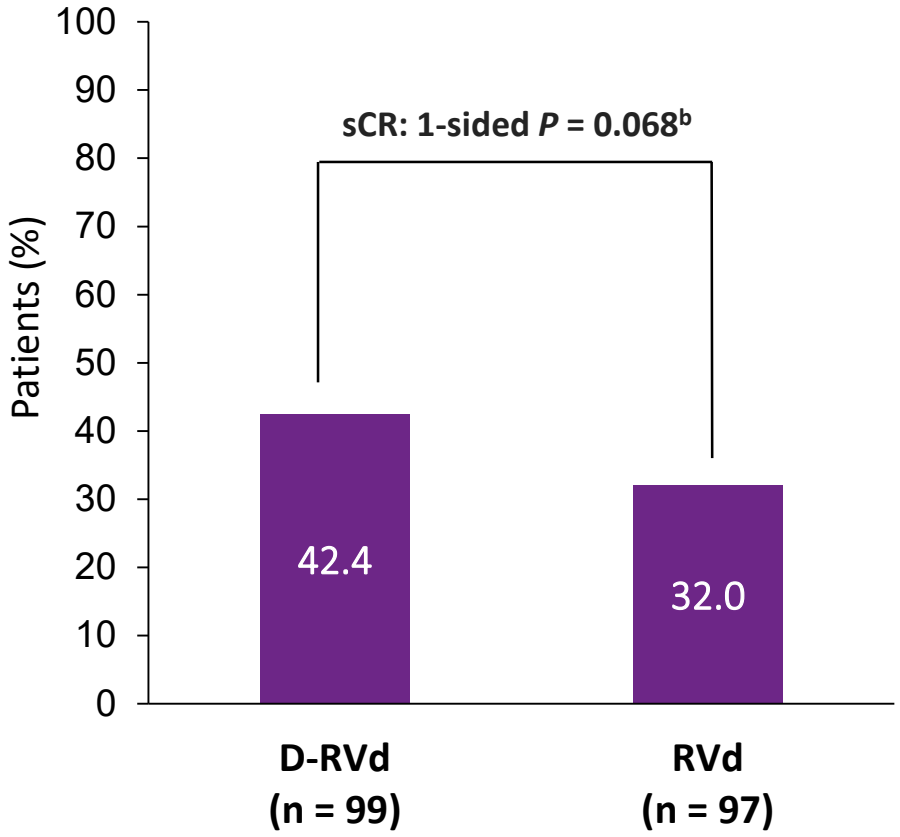
- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018



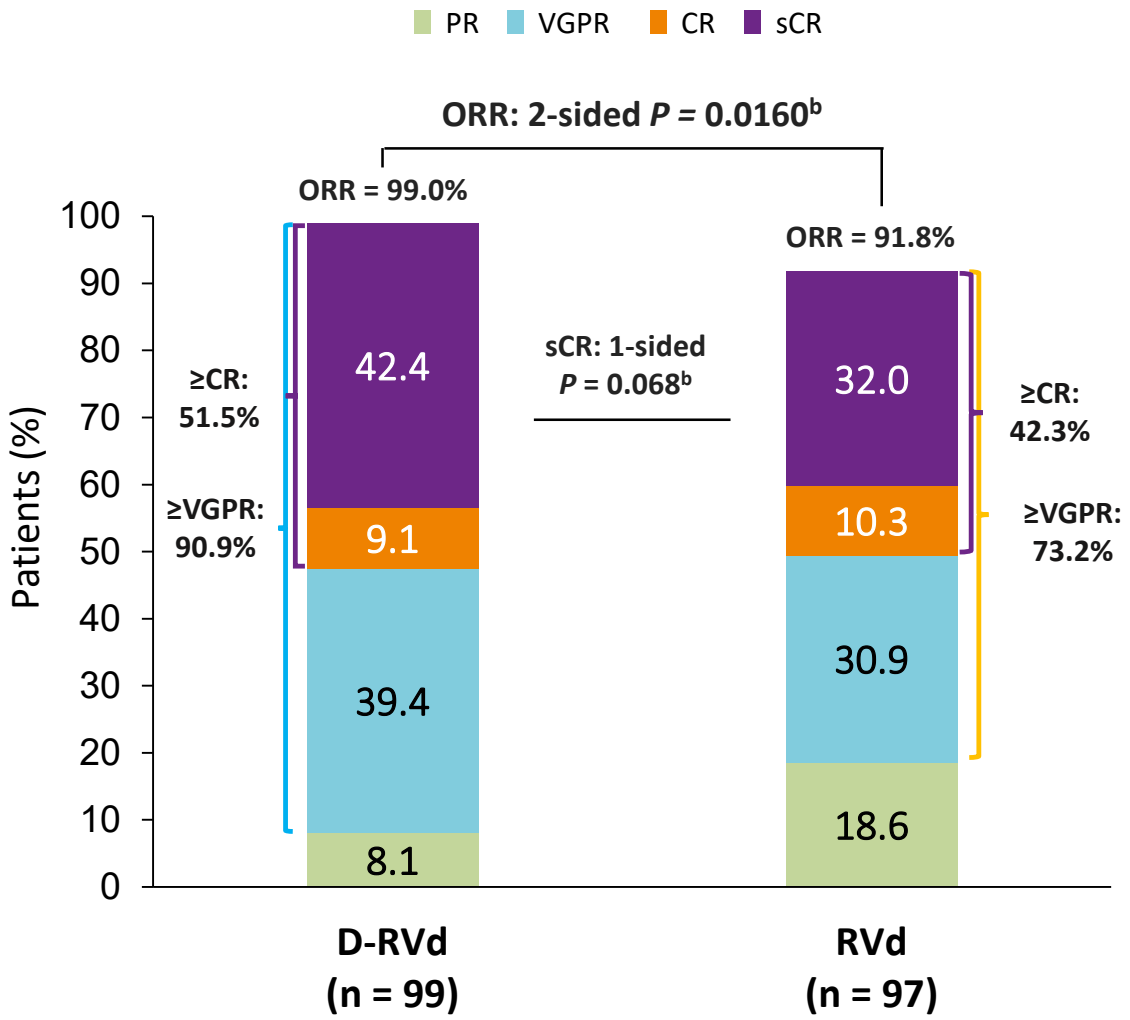

Voorhees P et al. ASH Annual Meeting, Orlando, 2019

# Primary Endpoint: sCR by the End of Consolidation[a]

- **Primary endpoint met at pre-set 1-sided alpha of 0.1**
  - sCR by end of consolidation
    - 42.4% D-RVd vs 32.0% RVd
    - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = 0.068[b]




Post-consolidation depth of response[a]




Voorhees P et al. ASH Annual Meeting, Orlando, 2019

# Treatment considerations for high-risk chromosomal abnormalities

- IFM 2005 01 – bortezomib showed better EFS and OS for patients with t(4;14)
- HOVON65/GMMG-HD4 – bortezomib based induction and maintenance showed improved outcomes for Del(17p)
- GIMEMA trial of VTD vs TD – in t(4;14) pts, OS was improved with VTD
- Conclusion: bortezomib *partly* overcomes the adverse effect of t(4;14) on PFS and SO, and del(17p) on PFS

Sonneveld et al, Blood 2016

# Summary

- Modern PI/IMID combinations can overcome high-risk changes and improve outcomes for standard risk patients
- 4 drug combinations including a CD38 antibody are likely the future of induction therapy
- Can consider alkylator/PI combo for acute renal insufficiency, change to IMID/PI after renal function improves
- Goal of induction: deep response!
  - Usually like to see at least PR, ideally VGPR or better before autologous transplant

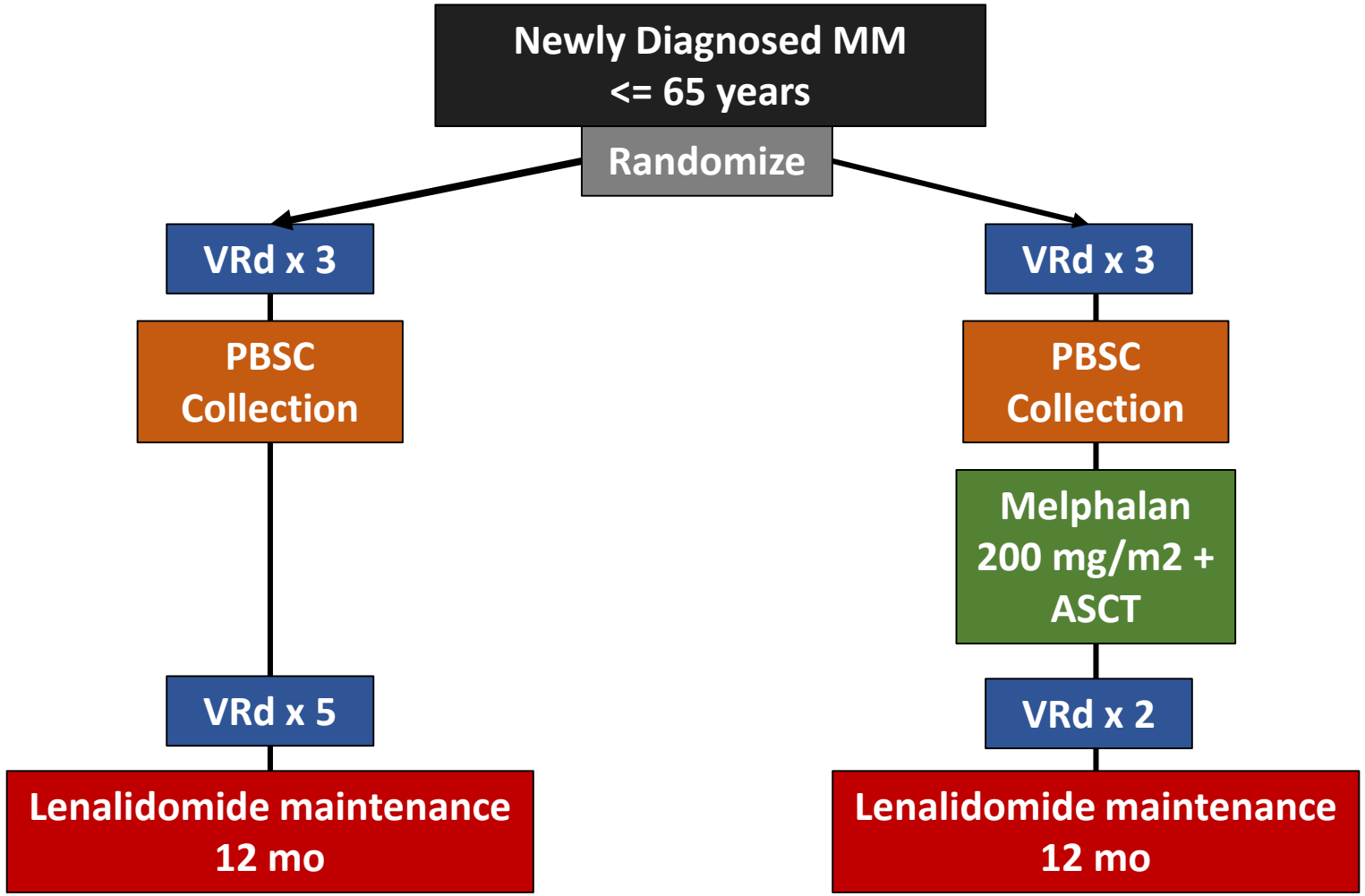
# Autologous stem cell transplantation for multiple myeloma

- Remains a cornerstone of management for eligible newly diagnosed patients – randomized trials show benefit for PFS
- Most recommend early or delayed transplant, rather than no transplant after induction therapy
- Very low treatment related mortality in modern era (1-2%)
- Acute regimen toxicities (mucositis, infections, diarrhea) are manageable

# Transplant eligible vs ineligible

- What factors are important?
- Age – not an absolute contraindication
- Comorbidities, general level of health (“eyeball test”)
- Patient preference

# IFM 2009: Study Design

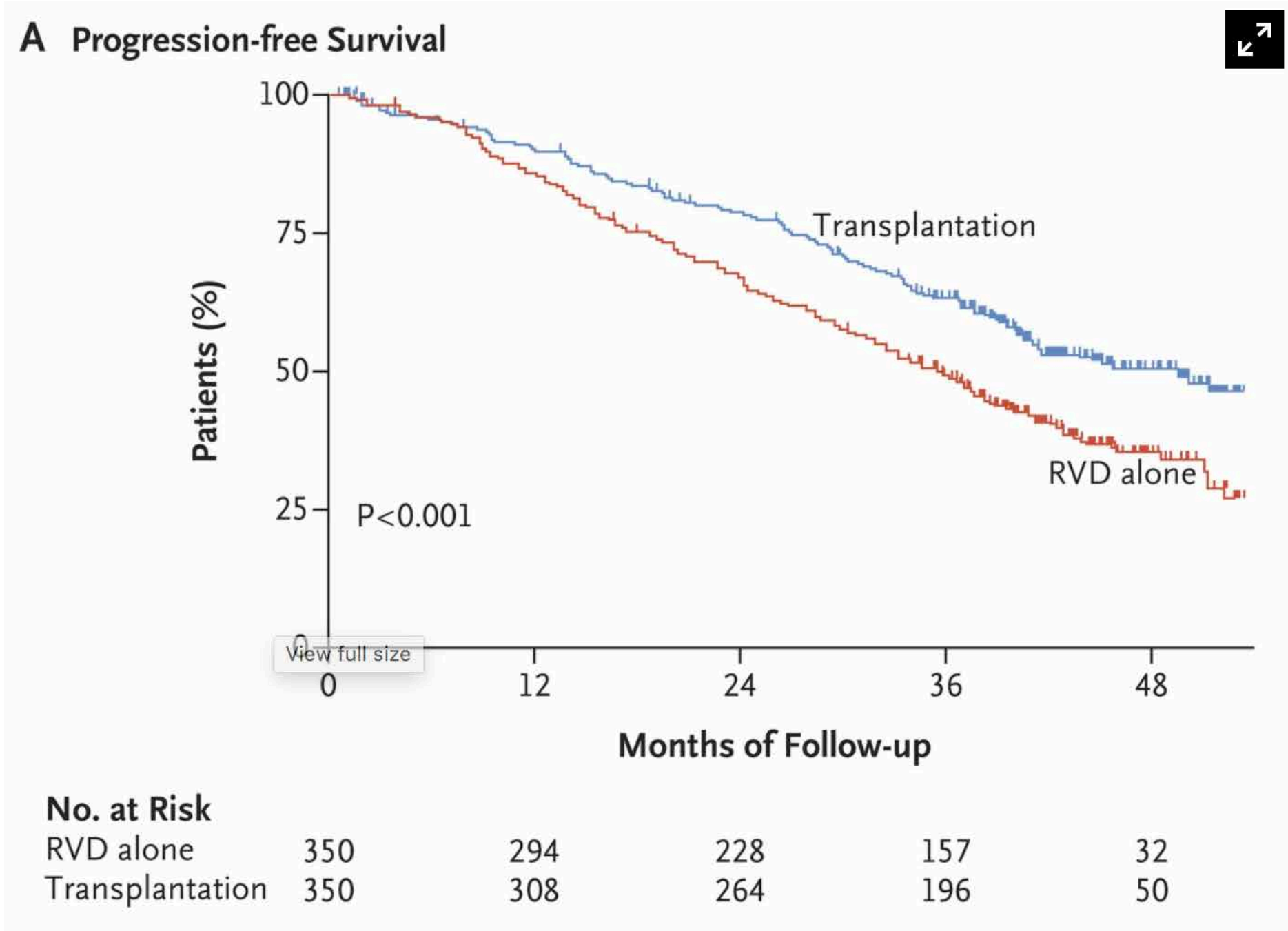



ASCT at relapse

Attal NEJM 2017

# IFM 2009 Results

- Median PFS significantly longer in the ASCT arm, 50 mos vs 36 months ($p<0.001$) – primary endpoint
- Benefit observed across all subgroups (high risk vs standard)
- Higher percentage of CR in the transplant arm
- No overall survival benefit observed


A Progression-free Survival
100
75
50
25
0
Patients (%)
Transplantation
RVD alone
P<0.001
View full size
0
12
24
36
48
Months of Follow-up
No. at Risk
RVD alone 350 294 228 157 32
Transplantation 350 308 264 196 50

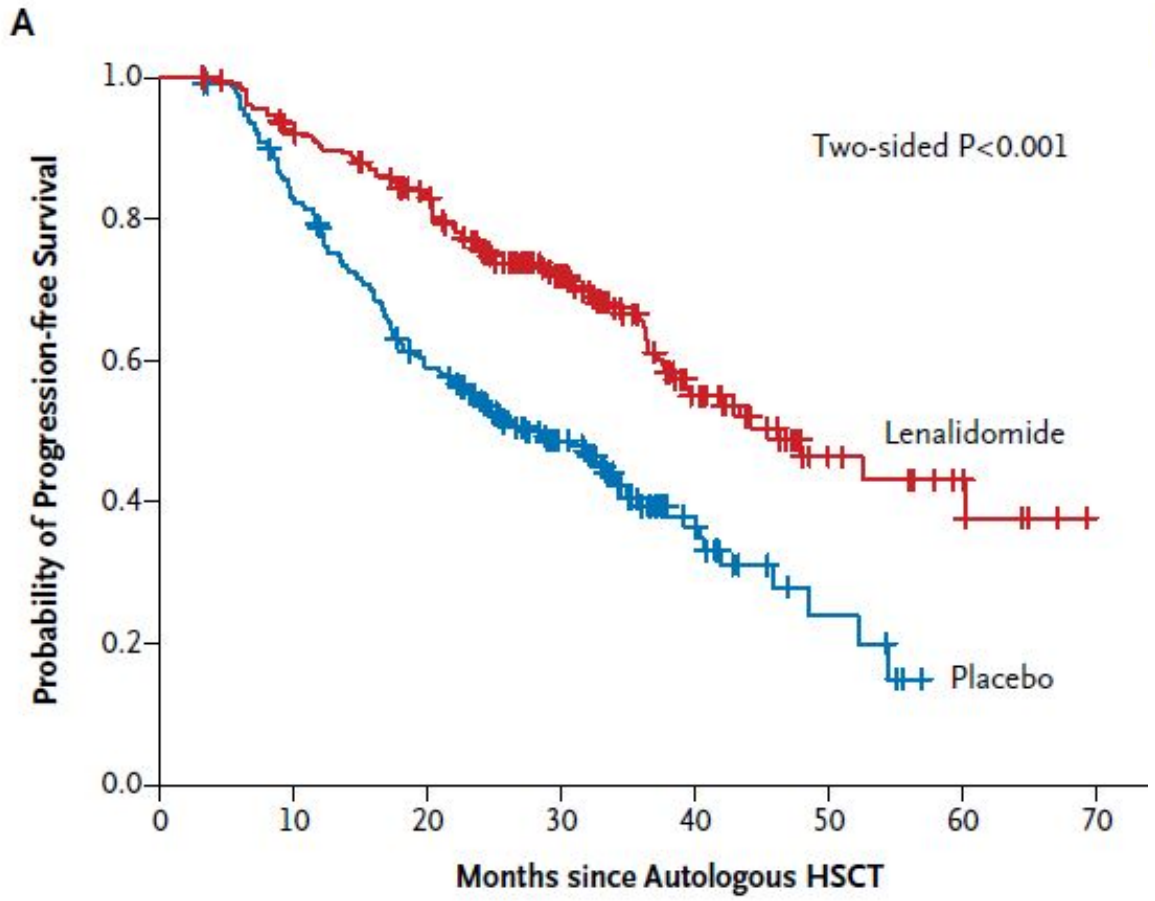
# Lenalidomide Maintenance Post ASCT Improves PFS

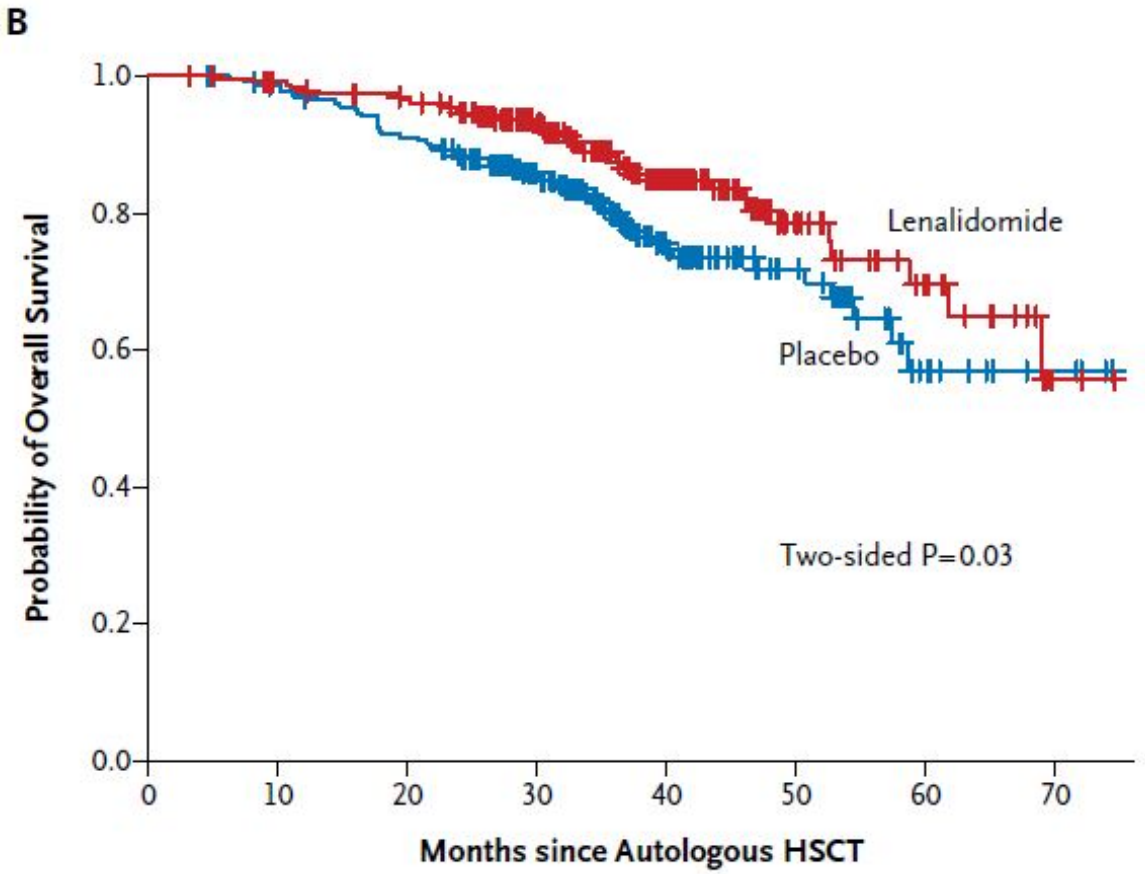
- Lenalidomide maintenance improves PFS post ASCT
  - Attal et al NEJM 2012:
    - 614 patients; Len maintenance 10 mg daily, increased to 15 mg if tolerated, vs Placebo
    - Primary end point: PFS
    - PFS 41 mos vs 23 mos, $p<0.001$.
  - Attal ASH 2013, update:
    - 5 year PFS: 42 vs 18 mo. No difference in 5 year OS!
  - Lenalidomide stopped at median of 2 years due to secondary primary malignancy (SPM) concern

# Lenalidomide Maintenance Post ASCT Improved PFS and OS in 1 study

- McCarthy et al, NEJM 2012
  - 460 patients, randomized to lenalidomide at starting dose of 10 mg, or placebo, post ASCT, daily, until progression
  - Median time to progression, 46 mo vs 27 mo ($p<0.001$)
  - 3 year OS rate 88% vs 80%

# Lenalidomide Maintenance Improves PFS and OS, McCarthy NEJM 2012



# Meta-Analysis of Lenalidomide Maintenance after ASCT

- McCarthy et al, JCO, July 2017
- Used documentation from 3 RCTS (CALGB 100104, GIMEMA , IFM 2005)
- 1208 patients in meta analysis
- Median OS:
  - Not reached for lenalidomide maintenance group
  - 86 months for the placebo/obs group
  - P = 0.001

# Summary – Lenalidomide Maintenance Post-ASCT

- Lenalidomide maintenance post ASCT improved PFS in several large studies
- Lenalidomide maintenance post-ASCT improved OS in one study (McCarthy et al)
- Meta analysis of 3 RCTs showed OS benefit with lenalidomide maintenance

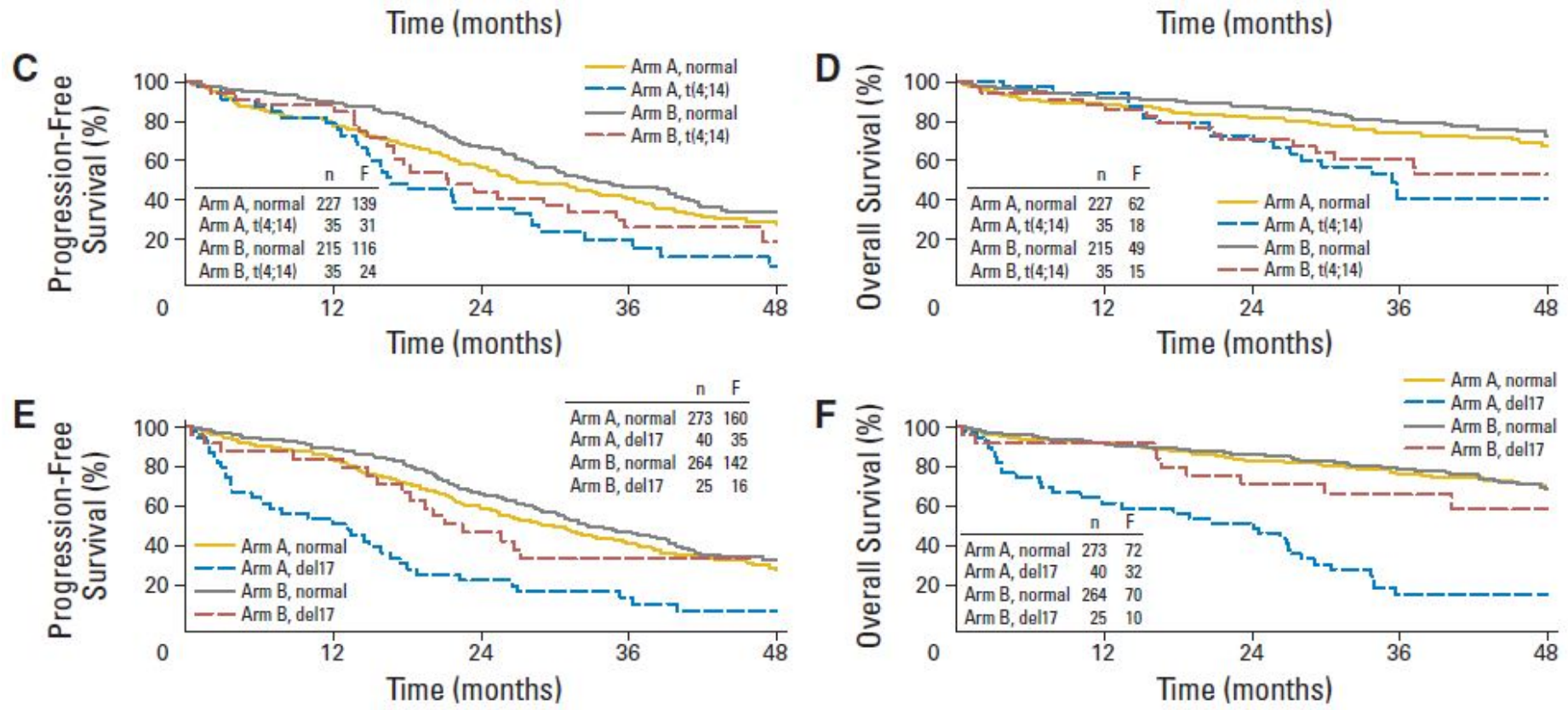
# Bortezomib Maintenance: HOVON-65/GMMG-HD4 Trial

- Study design:
  - Randomized study, PAD (bortezomib) vs VAD induction, followed by transplant, followed by maintenance with either
    - Thalidomide 50 mg daily x 2 years
    - Bortezomib 1.3 mg/m2 Q2week x 2 years
- CR rate superior:
  - After PAD induction, 15 vs 31%
  - After bortezomib maintenance, 34 vs 49%

Sonneveld et al JCO 2012

**t(4;14) - PFS**

**t(4;14) - OS**




**Del(17p)- PFS**

**Del(17p)- OS**

Sonneveld et al JCO 2012

# Bortezomib Maintenance Post ASCT Improves Outcome for Del(17p)

- Analysis of the HOVON-65 trial data
- Looked at the prognostic value of 12 chromosomal abnormalities
- Patients with t(4;14) receiving bortezomib based treatment had a prolonged median PFS (25.3 vs 21.7 mo), and improved 3 year OS rate (66 vs 44%)
- Patients with del(17p13) receiving bortezomib had a prolonged median PFS (26 vs 12 mos), improved 3 year OS (17 vs 69%)

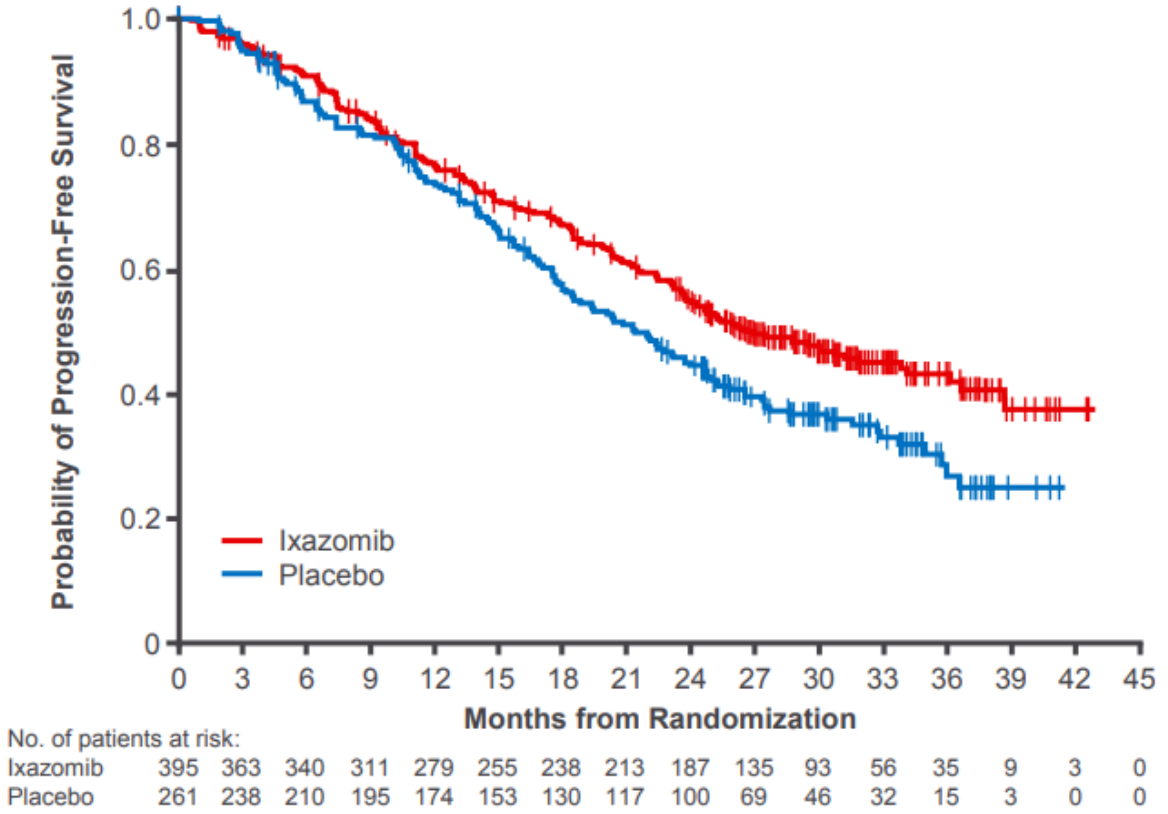
Neben et al. Blood 2012

# Summary – Bortezomib maintenance for high-risk myeloma

- Aggregate data from analysis of the HOVON-65/GMMG HD4 trial indicates a benefit for bortezomib maintenance post ASCT, given every 2 weeks for 2 years, particularly for those patients with the following chromosomal abnormalities:
  - **Del(17p)**
  - **t(4;14)**

# Ixazomib maintenance improves PFS post ASCT

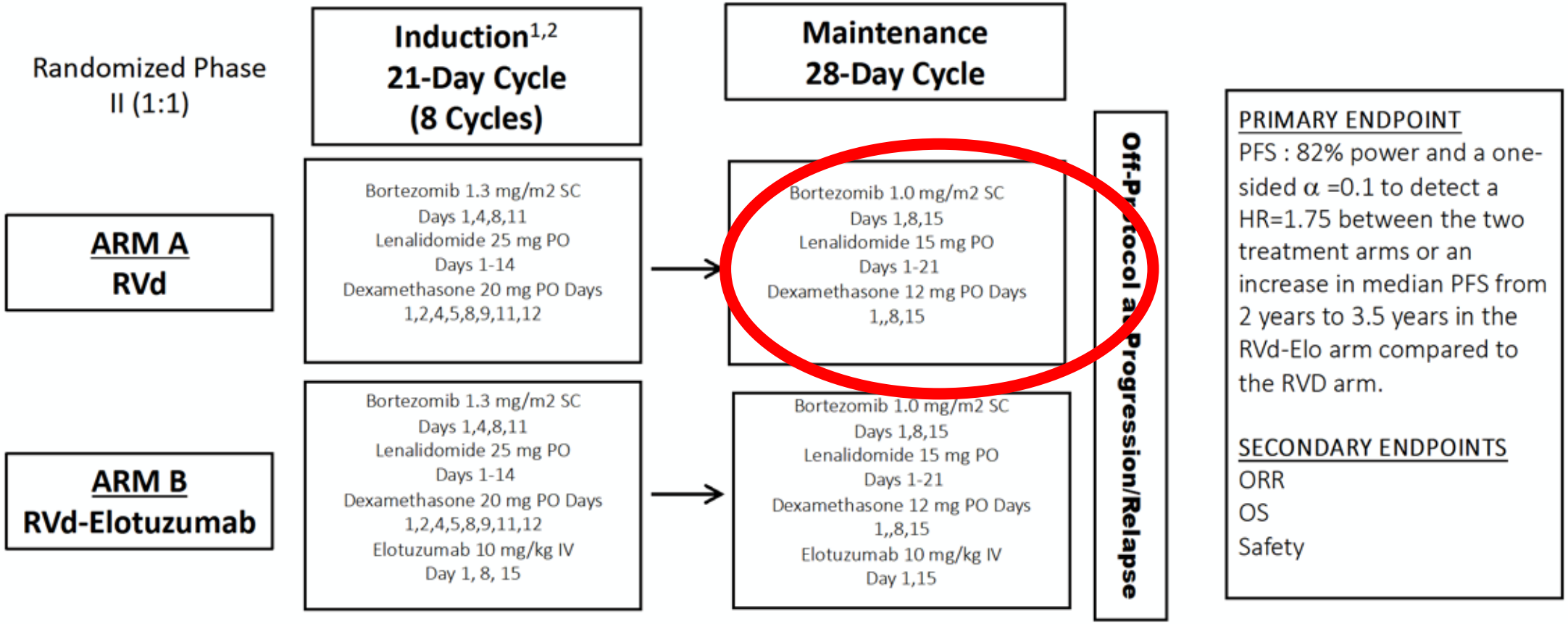
- 39% improvement in overall PFS from time of randomization for patients receiving ixazomib vs placebo maintenance:
  - HR: 0.72; 95% CI: 0.582-0.890
  - P=0.002
  - Median 26.5 months vs 21.3 months
- At a median follow-up of 31 months, median OS not reached in either treatment arm




Dimopoulos M et al, ASH Annual Conference 2018

# RVd Maintenance for high-risk MM

## SWOG 1211 Schema




1. ONE CYCLE OF PRIOR THERAPY ALLOWED PRIOR TO ENROLLMENT
2. STEM CELL COLLECTION ALLOWED AFTER CYCLE 2 ON PROTOCOL. ASCT ALLOWED OFF-PROTOCOL AT PROGRESSION/RELAPSE

SWOG CANCER RESEARCH NETWORK

Opened to all National Clinical Trials Network members

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Usmani S et al. EHA Annual Meeting 2020

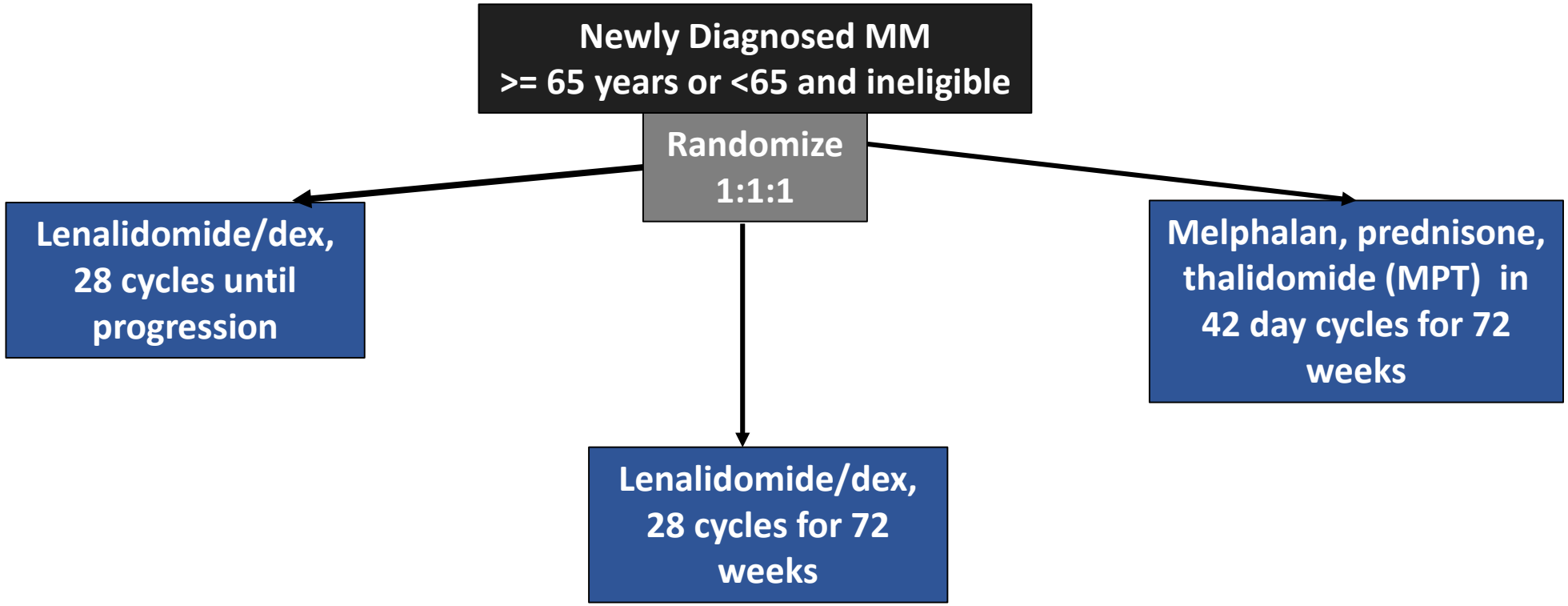
# Treatment of non-transplant eligible myeloma, newly diagnosed

- Consider triplet combination, or
  - IMID/PI Triplet combination – RVD lite
  - Daratumumab, lenalidomide, dexamethasone – MAIA trial

- Consider doublet for frail/elderly
  - Lenalidomide/low dose dexamethasone
  - Bortezomib/low dose dexamethasone

- Other options
  - Alkylator/PI combination (CyBorD)
  - Daratumumab+VMP (ALCYONE Trial, NEJM 2018) **

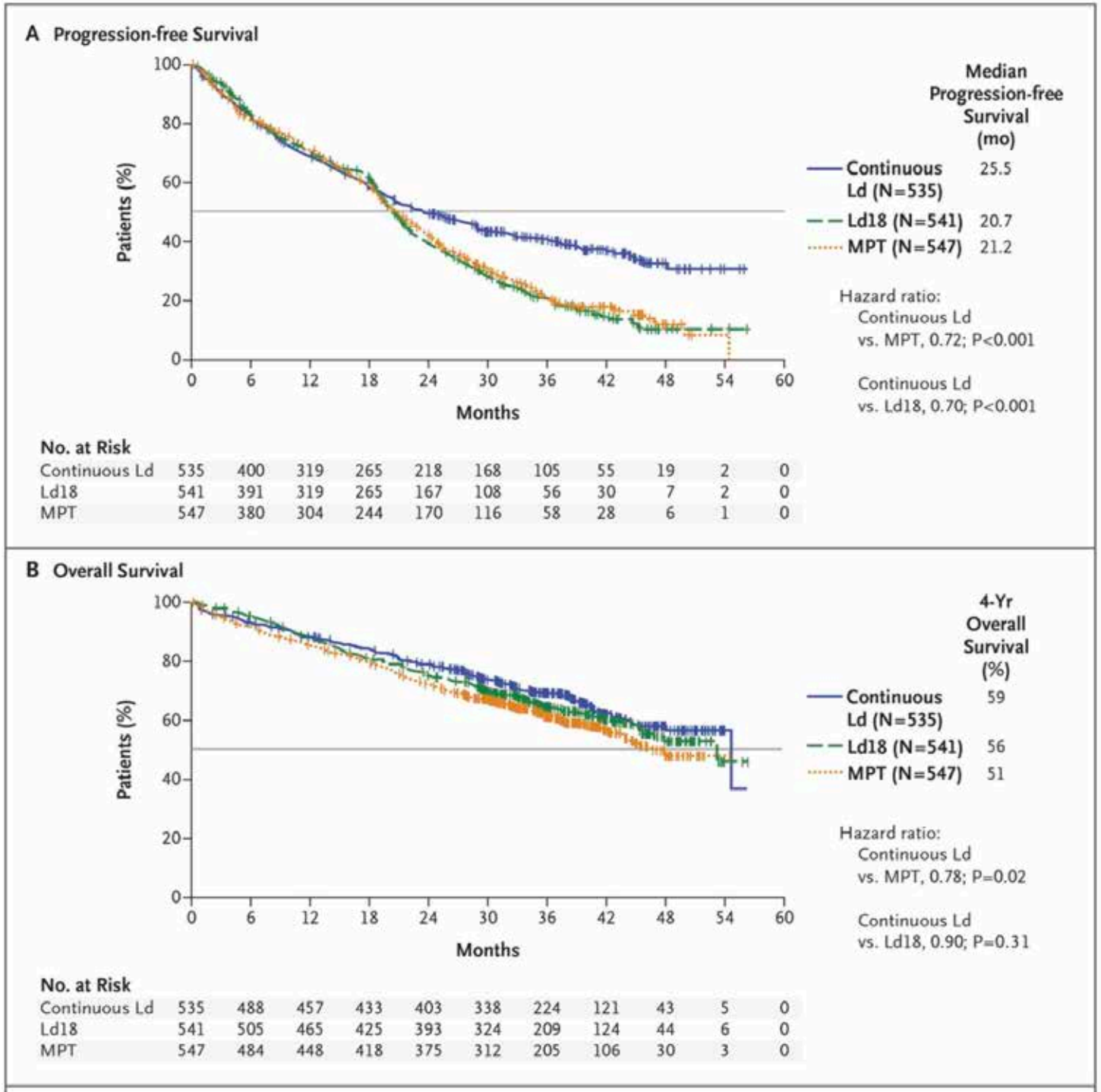
# FIRST Trial – Randomized study of Rd, MPT




Benboubker et al NEJM 2014

All patients received:

- Antithrombotic prophylaxis
  - Low dose aspirin, 70-100 mg/day
  - DVT/PET within 5 years: LMWH, Heparin, Warfarin




Benboubker et al NEJM 2014

**Table 2. Response Rates and Time to Response.**

| Variable | Continuous Lenalidomide–Dexamethasone (N=535) | Lenalidomide–Dexamethasone for 18 Cycles (N=541) | MPT (N=547) |
|---|---|---|---|
| Overall response — no. (%) | 402 (75)* | 397 (73)* | 341 (62) |
| Complete response | 81 (15) | 77 (14) | 51 (9) |
| Very good partial response | 152 (28) | 154 (28) | 103 (19) |
| Partial response | 169 (32) | 166 (31) | 187 (34) |
| Stable disease — no. (%) | 101 (19) | 111 (21) | 145 (27) |
| Progressive disease — no. (%) | 7 (1) | 12 (2) | 19 (3) |
| Response could not be evaluated — no. (%) | 25 (5) | 21 (4) | 42 (8) |
| Median time to response — mo† | 1.8‡ | 1.8‡ | 2.8 |

Benboubker et al NEJM 2014

# Modified RVD ("RVD-Lite") for elderly/frail

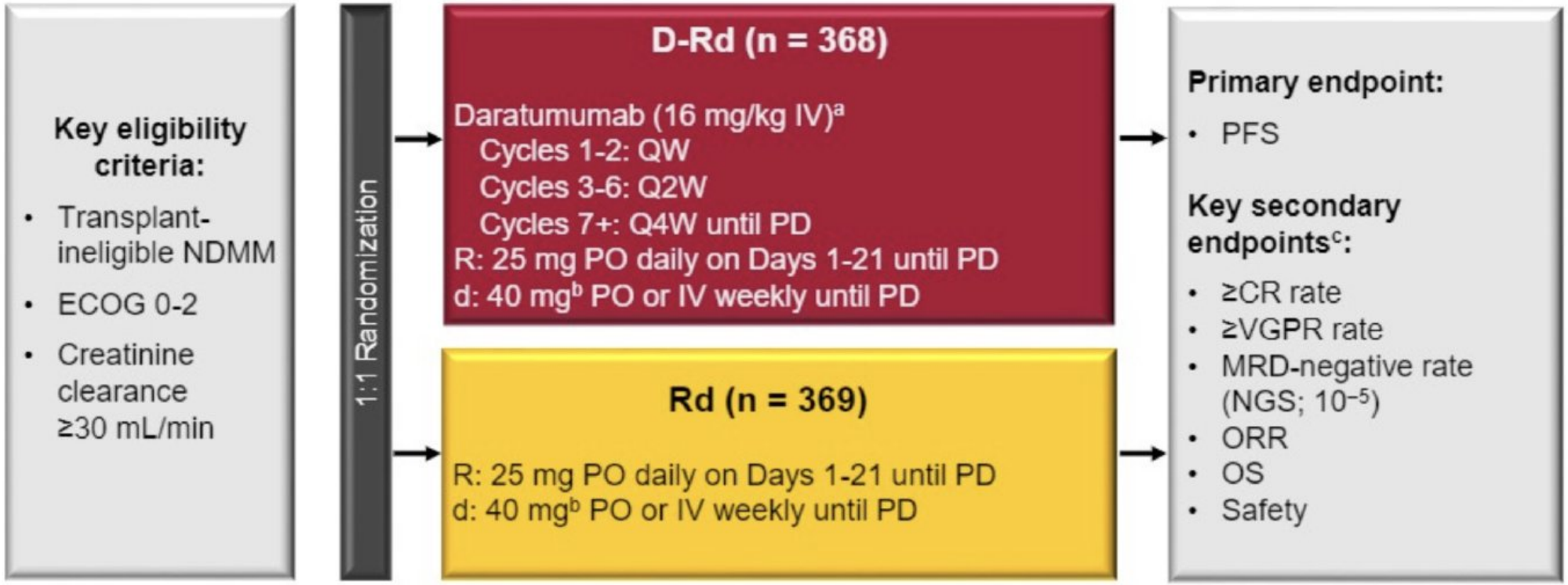
- Dosing
  - Lenalidomide 15 mg days 1-21 of a 35 day cycle
  - Bortezomib 1.3 mg/m2 weekly days 1, 8, 15, 22
  - Dexamethasone 20 mg twice weekly for pts ≤75 yrs and days 1, 8, 15, 22 for pts older than 75
- 53 patients treated
- Median age of patients: 72 years
- iORR - 90% (10 CR, 14 VGPR, 12 PR, 4 SD)
- Toxicities manageable:
  - Grade 3 or greater toxicities included hypophosphatemia in 15 (31%) and rash in 5 (10%) pts.
  - Fatigue most common, in 31/49 (63%) patients, mostly grade 1-2
  - Peripheral neuropathy of any grade was reported in 21/49 (43%) pts including grade 1 (11, 22%), 2 (9, 18%), and 3 (1, 2%).

O'Donnell et al ASH 2015

# Dara-Rd vs Rd: MAIA Trial – Study Design

## MAIA Study Design

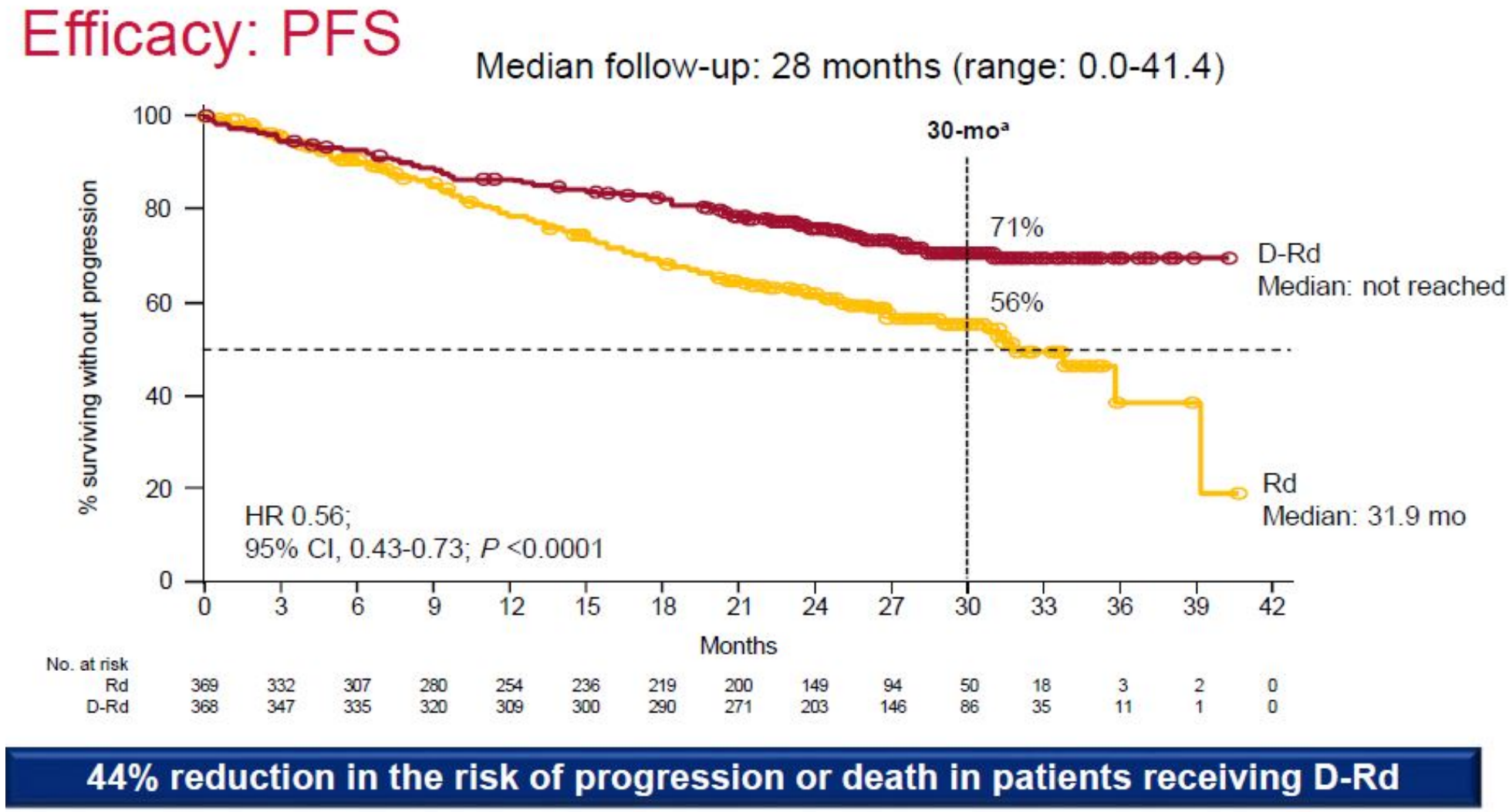
- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)




[a]On days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.
[b]For patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.
[c]Efficacy endpoints were sequentially tested in the order shown.

Facon T, Kumar SK, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Abstract #LBA-2. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.

# MAIA Trial: Dara-Rd vs Rd Upfront Treatment for ASCT-ineligible NDMM Patients




**44% reduction in the risk of progression or death in patients receiving D-Rd**

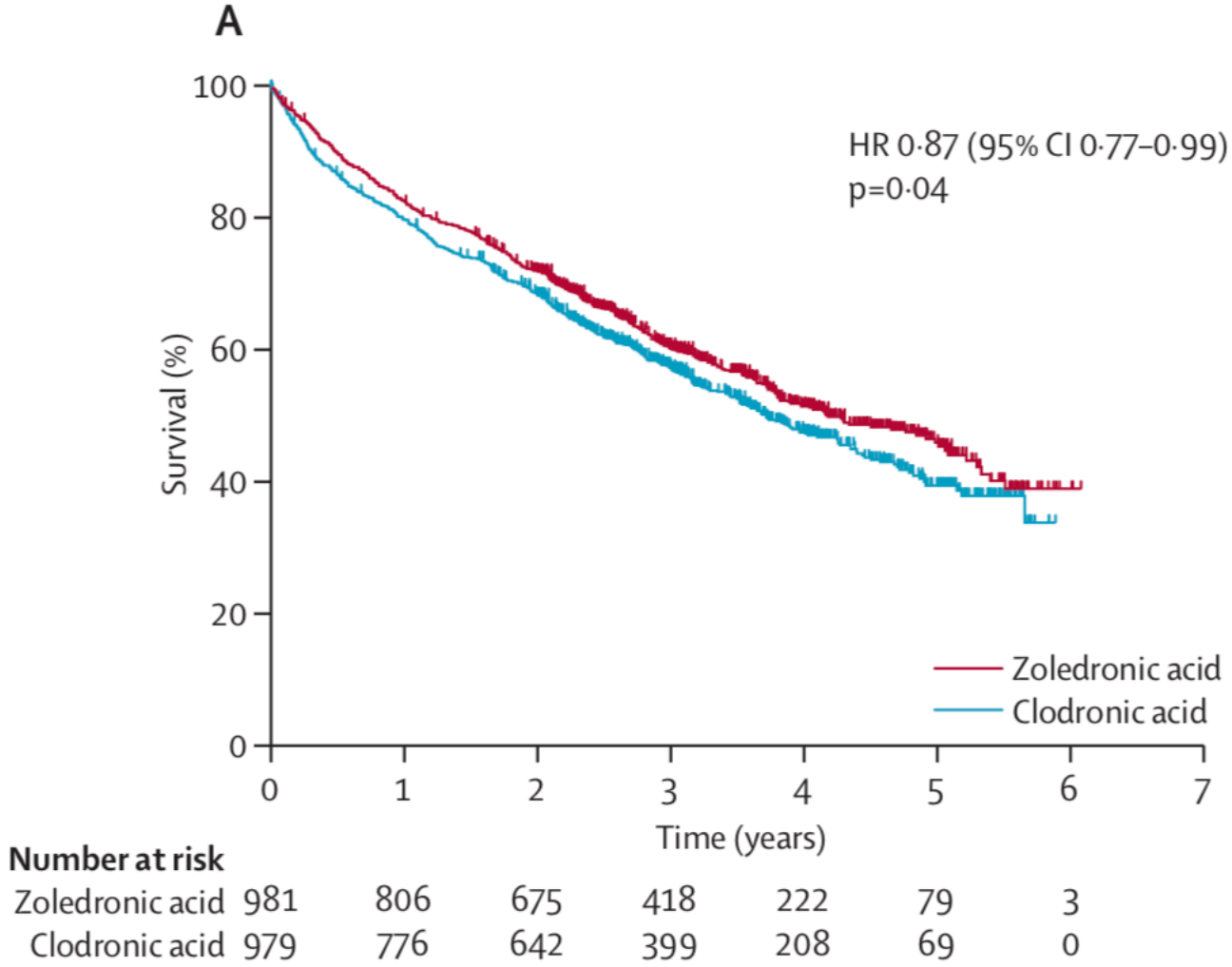
Facon T, Kumar SK, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Abstract #LBA-2. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.

# Myeloma therapy - dosing in frail patients

| Frontline treatment | Second-line treatment | Following lines of treatment |
|---|---|---|
| **Lenalidomide-steroid**<br>R*: 10-15 mg/d, d 1-21<br>d: 10 mg/d once weekly or<br>P: 25 mg/d every other d | **Bortezomib-steroid**<br>V: 1.3 mg/m$^2$ once weekly<br>d: 10 mg/d once weekly or<br>P: 25 mg/d every other d | **Melphalan-prednisone**<br>M: 2 mg every other d<br>P: 25 mg/d every other d |
| **Bortezomib-steroid**<br>V: 1.3 mg/m$^2$ once weekly<br>d: 10 mg/d once weekly or<br>P: 25 mg/d every other d | **Lenalidomide-steroid**<br>R*: 10-15 mg/d, d 1-21<br>d: 10 mg/d once weekly or<br>P: 25 mg/d every other d | **Cyclophosphamide-prednisone**<br>C: 50 mg every other d<br>P: 25 mg/d every other d |
| | Re-treatment | **Thalidomide-prednisone**<br>T: 50 mg every other d<br>P: 25 mg/d every other d |

# Bisphosphonates for bone health in multiple myeloma: MRC IX trial

- Randomized study comparing first-line treatment with zoledronic acid as compared with clodronate in newly diagnosed MM: MRC IX
- Only reported bisphosphonate to show survival benefit (5.5 mos)
- 3-4% risk of ONJ seen in this study



# Supportive care – hypercalcemia, HSV/VZV and VTE

- Hypercalcemia:
  - Hydration, bisphosphonates (Zoledronic acid), steroids, +/- calcitonin

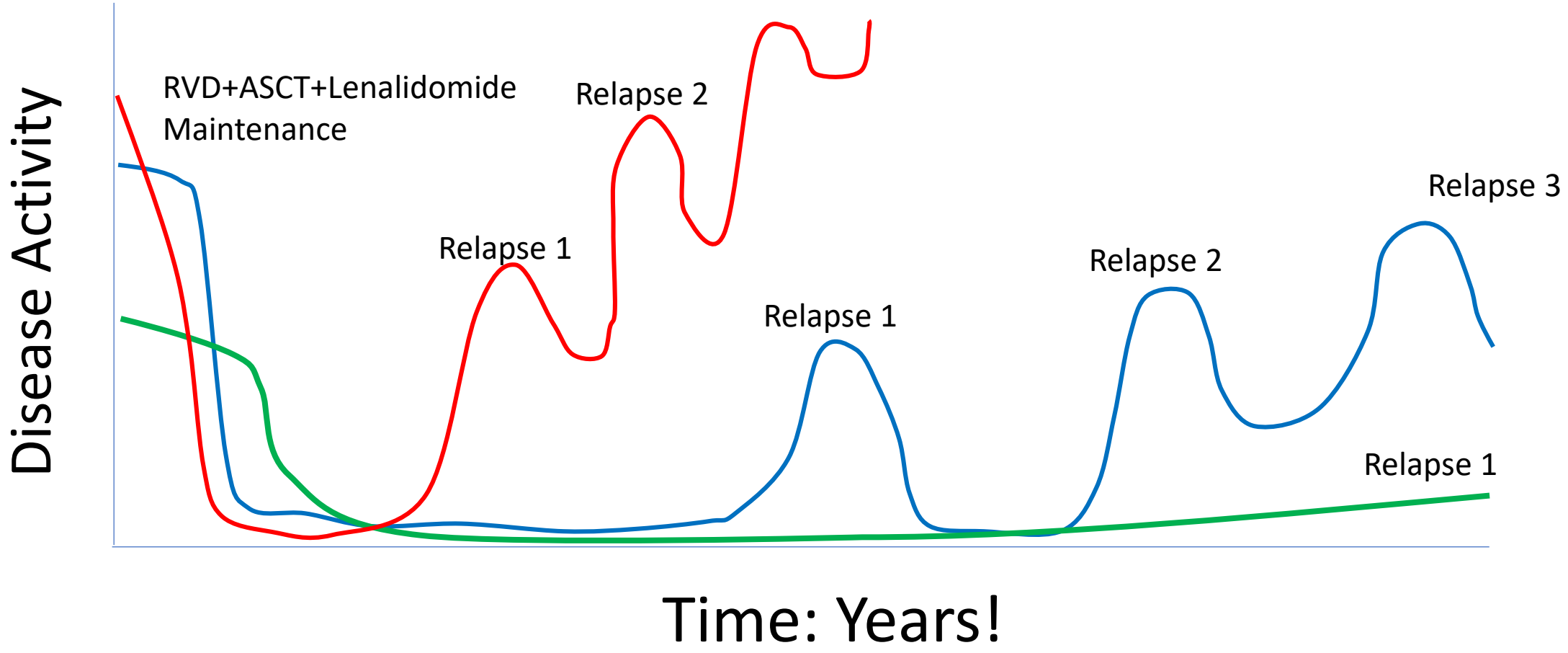
- Herpes zoster prophylaxis
  - Acyclovir or valacyclovir
  - For ALL patients receiving proteasome inhibitors or daratumumab

- VTE
  - Aspirin 81-325 mg PO daily for all patients receiving IMiDs
  - Therapeutic anticoagulation for patients at high risk for VTE

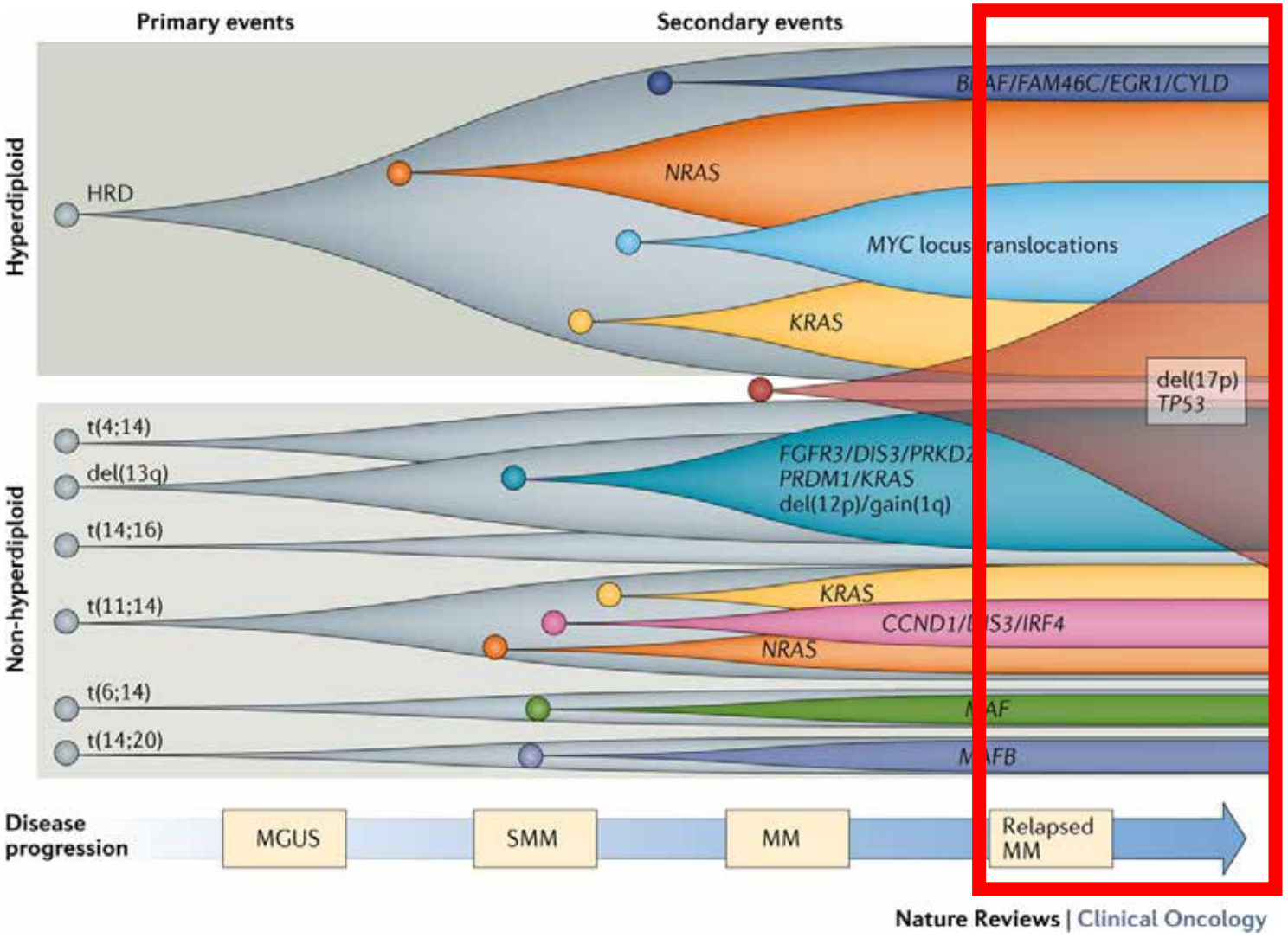
# Why does treating relapsed MM seem so challenging?


Dingli D et al, Mayo clin Proc 2017 Apr;92(4):578-598; R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

# Relapsed Multiple Myeloma is Not One Disease!



# Relapsed MM is a Biologically and Genetically Heterogeneous Disease




Manier, S. *et al.* (2016) Genomic complexity of multiple myeloma and its clinical implications
*Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2016.122

# Key Questions to Ask for R/R MM

- 1. Sensitivity to PI/IMID/CD38?
- 2. Toxicity from prior therapy, and baseline comorbidities?
- 3. Urgent need to treat / how aggressive?
- 4. Prior autologous stem cell transplant?

# Key Phase 3 Trials for Relapsed MM

| Trial | Regimen and Comparator | Prior Therapies | N | Median PFS, Mo | Population |
|---|---|---|---|---|---|
| POLLUX[a] | DRd vs Rd | ≥1 | 569 | NR vs 18.4 | IMiD sensitive |
| ELOQUENT-2[b] | ERd vs Rd | 1 – 3 | 646 | 19.4 vs 14.9 | IMiD sensitive |
| ASPIRE[c] | KRd vs Rd | 1 – 3 | 792 | 26.3 vs 17.6 | PI/IMiD sensitive |
| CANDOR[d] | KDd vs Kd | 1 – 3 | 466 | NR vs 15.8 | PR to ≥ 1 prior line |
| CASTOR[e] | DVd vs Vd | ≥1 | 498 | NR vs 7.2 | PI sensitive |
| ENDEAVOR[f] | Kd vs Vd | 1 – 3 | 929 | 18.7 vs 9.4 | PI sensitive |
| PANORAMA[g] | PanoVd vs Vd | 1 – 3 | 768 | 12 vs 8.7 | PI sensitive |
| ARROW[h] | Kd weekly vs Kd twice wk | ≥2 | 478 | 11.2 vs 7.6 | Carfilzomib naive |

[a] Dimopoulos et al, NEJM 2016 Oct 6:275(14):1319-1331; [b] Lonial S et al, NEJM 2015 Aug 13;373(7):621-31; [c] Stewart AK et al, NEJM 2015 Jan 8;372(2):142-52; [d] Dimopoulos et al, Lancet 2020; [e] Palumbo et al, NEJM 2016 Aug 25;375(8):754-66; [f] Dimopoulos et al Lancet Oncol 2016 Jan;17(1):27-38 [g] San-Miguel JF et al, Lancet Haematol 2016 Nov;3(11):e506-e515; Moreau P et al, Lancet Oncol 2018 Jul;19(7):953-964

# In General, 3 Drugs >> 2 Drugs

- Many studies have shown that 3 drug treatment is superior to 2 drug therapy for relapsed multiple myeloma
- In general, 3 drug regimens should be the standard for treatment of relapsed MM
- However, cannot always use a one size fits all approach – personalization is key

# Toxicities from Prior Therapy & Other Comorbidities to Consider

- Bortezomib – peripheral neuropathy (with or without pain)
- COPD/Asthma – can use daratumumab, but cautiously
- Congestive heart failure – careful with carfilzomib
- General frailty – 2 drug vs 3 drug

# Carfilzomib for Relapsed Multiple Myeloma

- Options for use:
  - Carfilzomib + Dexathasone (ENDEAVOR)[a]
  - Carfilzomib + IMID (ASPIRE)[b]
  - Carfilzomib + Alkylator[c]
  - Carfilzomib + Monoclonal Antibody (MMY1001)[d]
- Is retreatment with bortezomib an option?
- Choice of PI should be driven by safety issues, patient preference (e.g., peripheral neuropathy history, or cardiac/renal issues)
- Consider for 'aggressive relapse' – proteasome inhibitors tend to work quickly

a. Dimopoulos et al Lancet Oncol 2016 Jan;17(1):27-38; b. Stewart AK et al, NEJM 2015 Jan 8;372(2):142-52 c. Bringhen et al, Blood 2014 Jul 3;124(1):63-9; d. Chari A et al, ASCO Annual Conference 2018

# Weekly Carfilzomib – ARROW Trial

**Arm A: Once-weekly carfilzomib + dex**

*(30 min infusion of K)*

Carfilzomib 20 mg/m$^2$ IV D1 (Cycle 1)
Carfilzomib 70 mg/m$^2$ IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

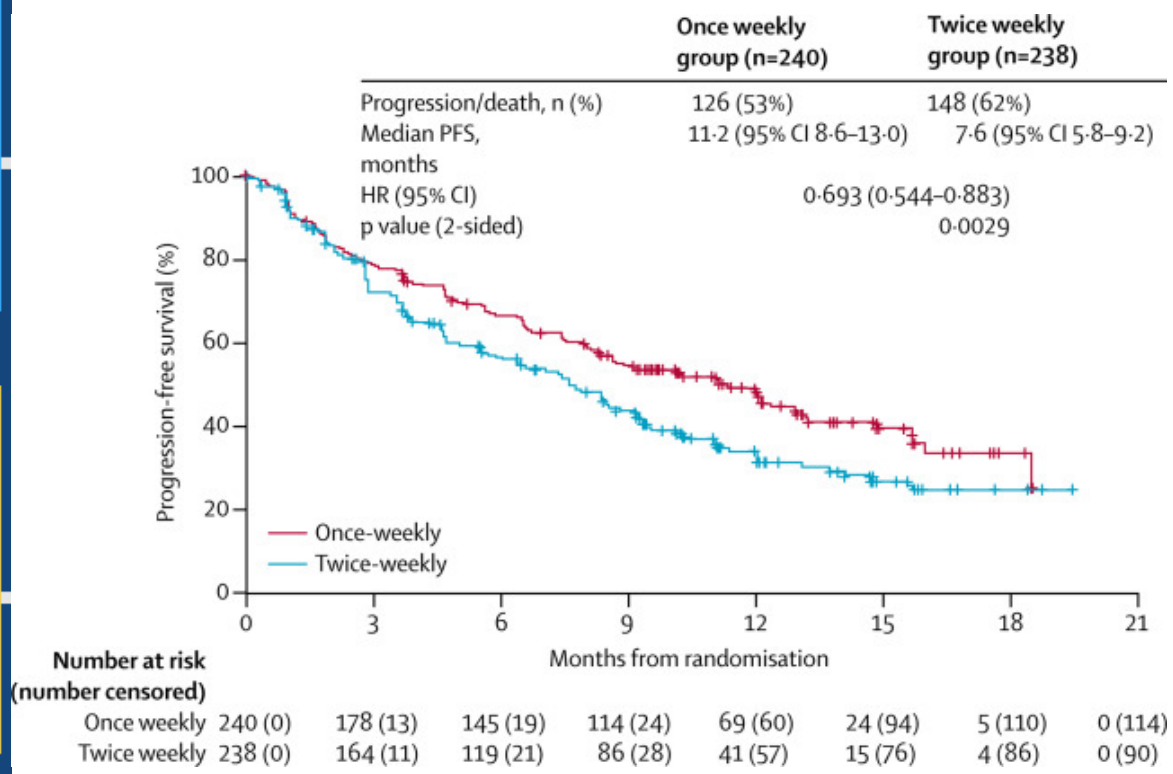
*28-day cycles*

**Arm B: Twice-weekly carfilzomib + dex**

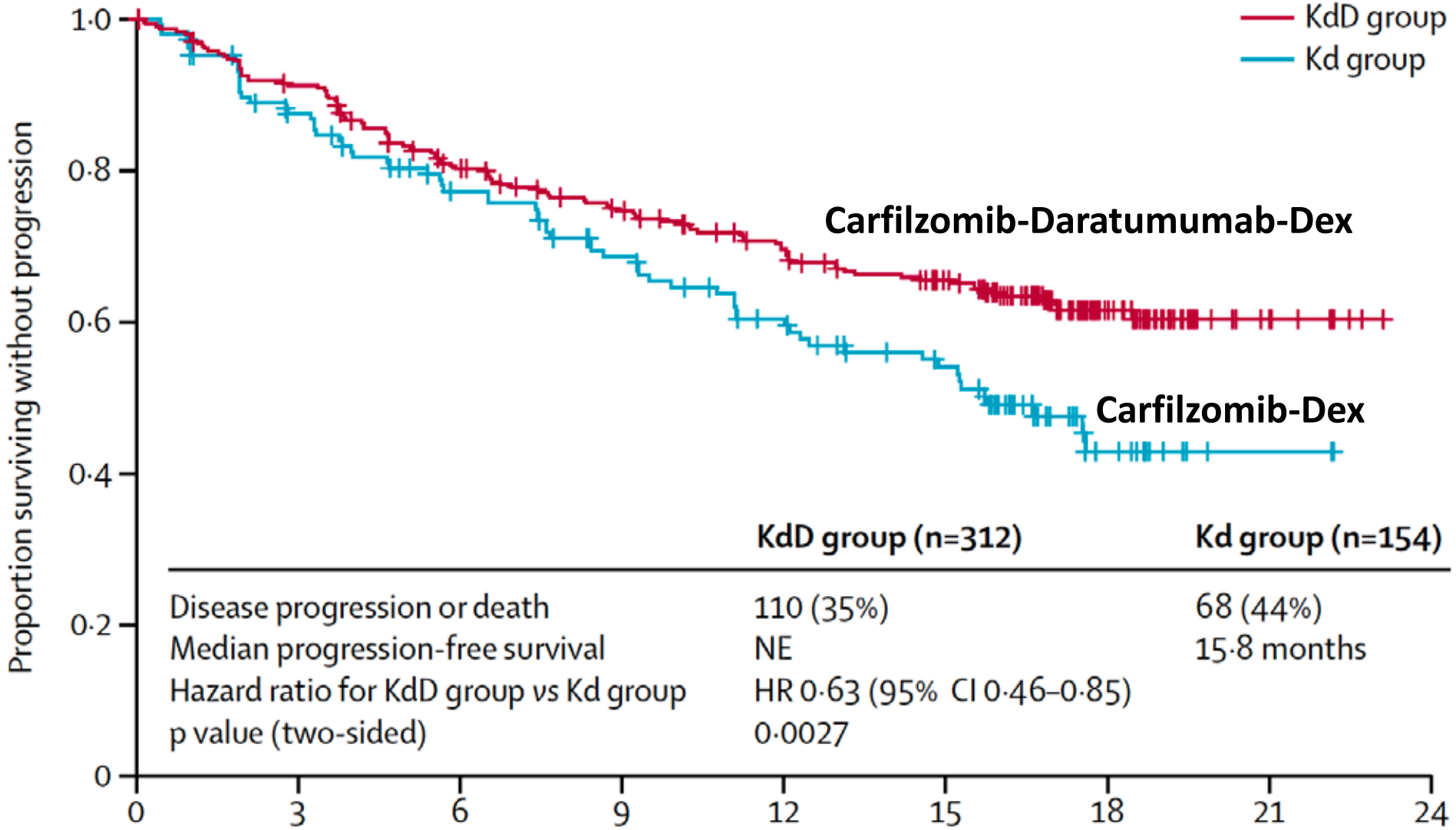
*(10 min infusion of K)*

Carfilzomib 20 mg/m$^2$ IV D1, 2 (Cycle 1)
Carfilzomib 27 mg/m$^2$ IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

**Primary end point: PFS**




Moreau P et al, Lancet Oncology 2018 Jul;19(7):953-964




| | KdD group (n=312) | Kd group (n=154) |
|---|---|---|
| Disease progression or death | 110 (35%) | 68 (44%) |
| Median progression-free survival | NE | 15·8 months |
| Hazard ratio for KdD group *vs* Kd group | HR 0·63 (95% CI 0·46–0·85) | |
| p value (two-sided) | 0·0027 | |

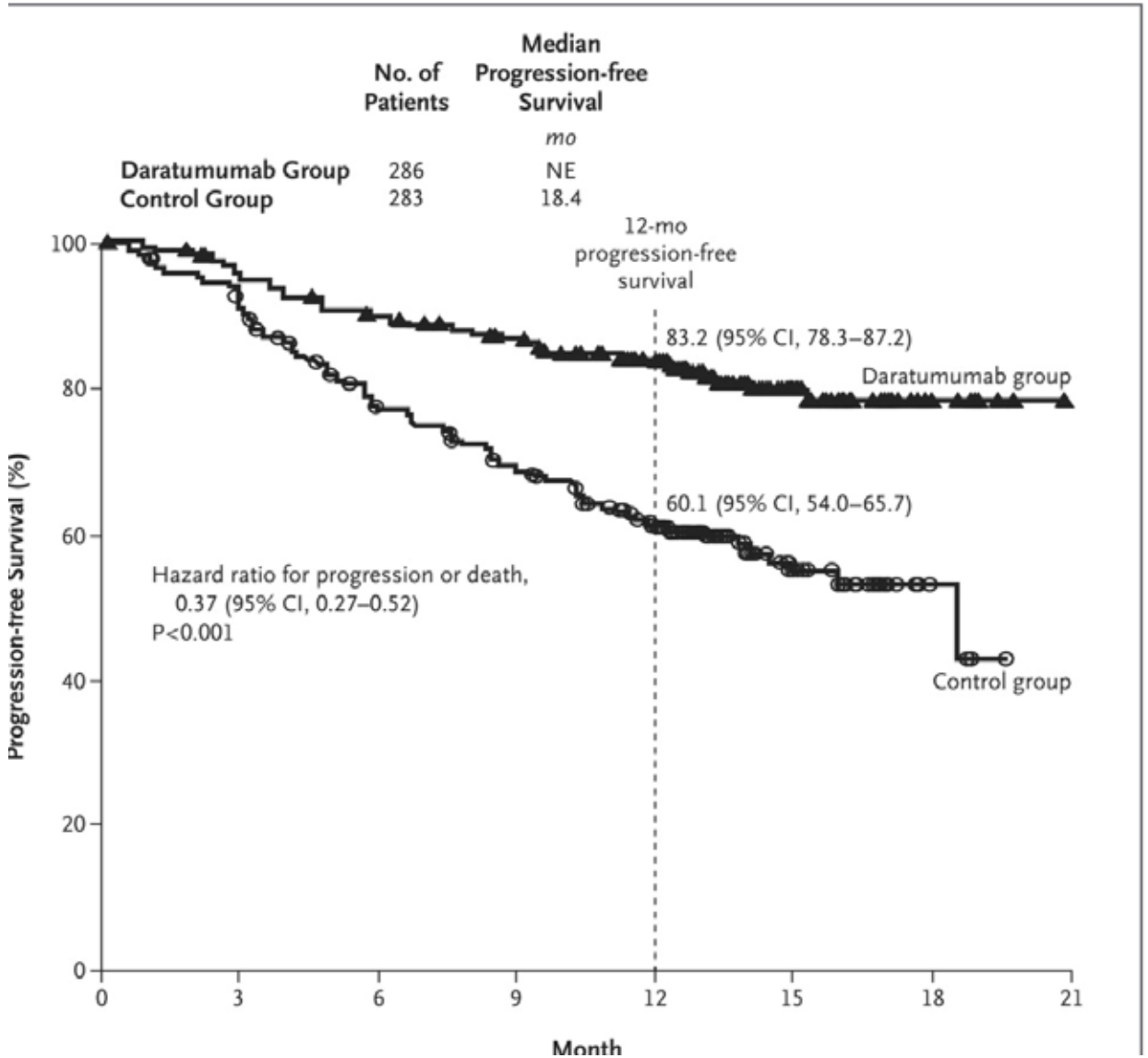
**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| KdD group | 312 | 279 | 236 | 211 | 189 | 165 | 57 | 14 | 0 |
| Kd group | 154 | 122 | 100 | 85 | 70 | 55 | 13 | 2 | 0 |

Dimopoulos et al. Lancet 2020

# Daratumumab for Relapsed MM

- Daratumumab, lenalidomide, and dexamethasone
  - POLLUX Trial, NEJM 2016[a]
- Daratumumab, bortezomib, dexamethasone
  - CASTOR Trial, NEJM 2016[b]
- Daratumumab, pomalidomide, dexamethasone
  - EQUULEUS, Blood 2017[c]
- Daratumumab and dexamethasone
  - SIRIUS Trial, Blood 2016[d]

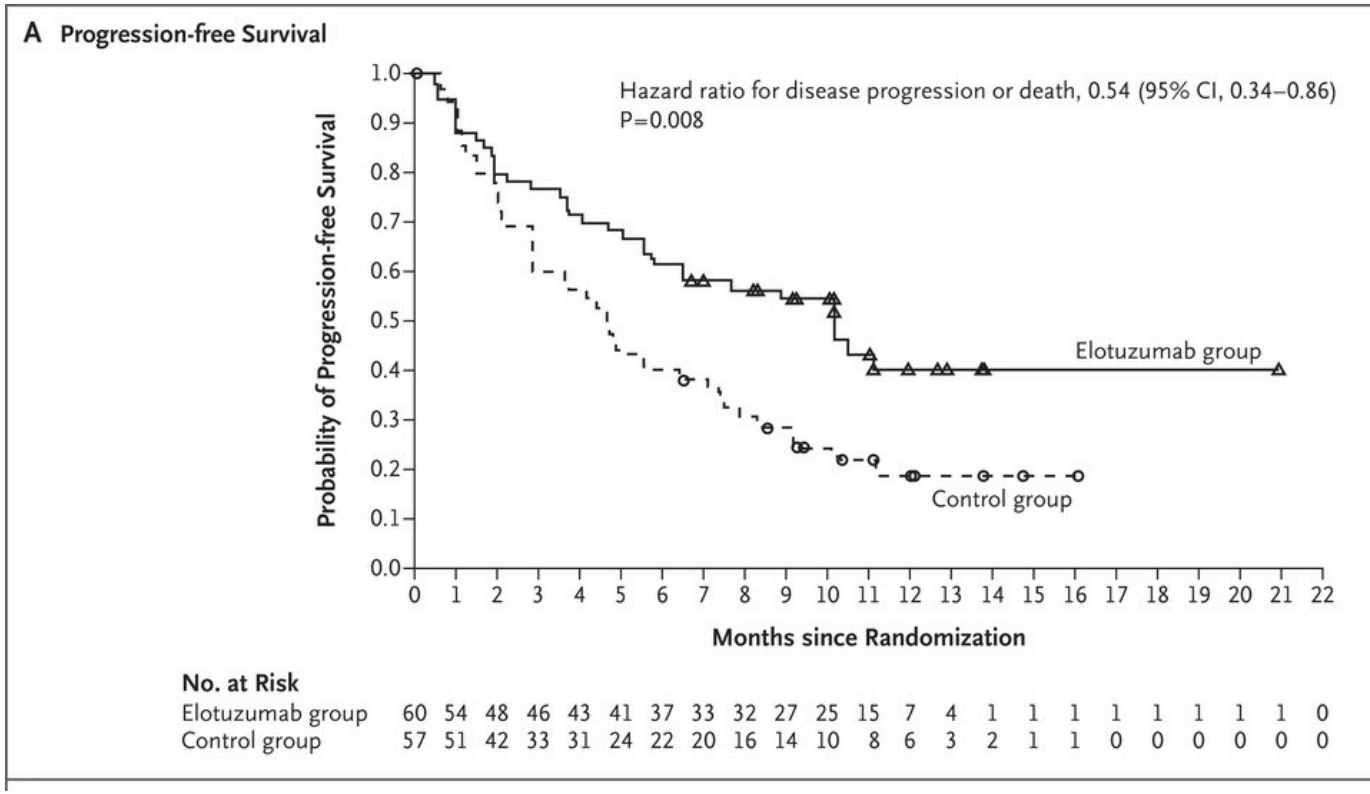




a.Dimopoulos et al, NEJM 2016 Oct 6:275(14):1319-1331
b. Palumbo et al, NEJM 2016 Aug 25;375(8):754-66
c. Chari A et al, Blood 2017 Aug 24;130(8):974-981
d. Lonial S et al, Lancet 2016 Apr 9;387(10027):1551-60

# Elotozumab / IMiD for Relapsed MM

- Important – Elotuzumab has no single agent activity
- SLAMF7 Monoclonal Antibody
- ELOQUENT-2 Trial: Elotuzumab, lenalidomide, dexamethasone[a]
- ELOQUENT-3 Trial: Elotuzumab, pomalidomide, dexamethasone[b]

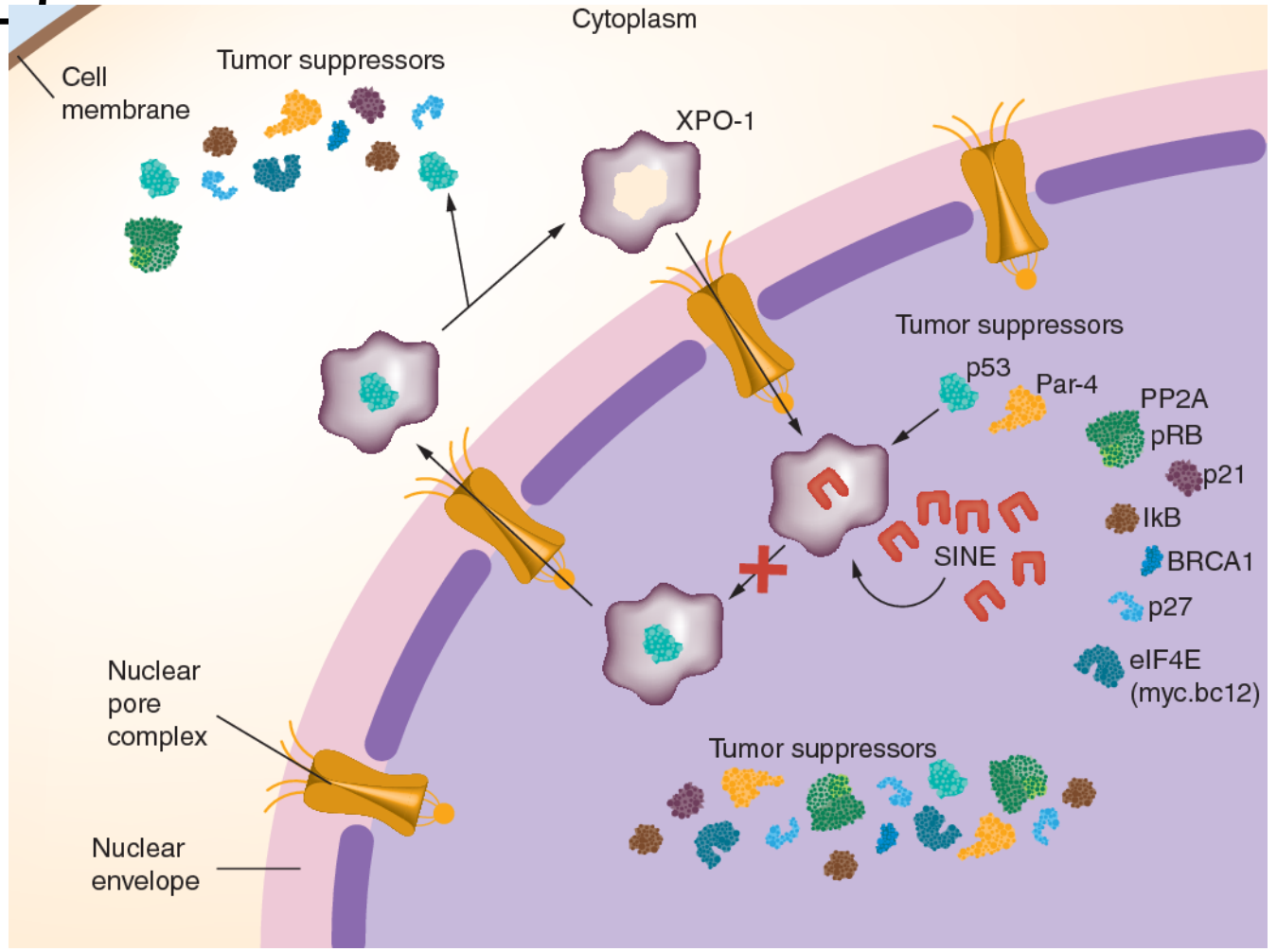




a. Lonial S et al, NEJM 2015 Aug 13;373(7):621-31
b. Dimopoulos et al NEJM 2018 Nov 8;379(19):1811-1822

# Selinexor: First in class, oral Selective Inhibitor of Nuclear Export (SINE)[1-3]

- Exportin 1 (XPO1): major nuclear export protein for:
  - Tumor suppressor proteins, Glucocorticoid receptor, oncoprotein mRNAs
- XPO1 – highly overexpressed in MM; correlate with poor prognosis, drug resistance

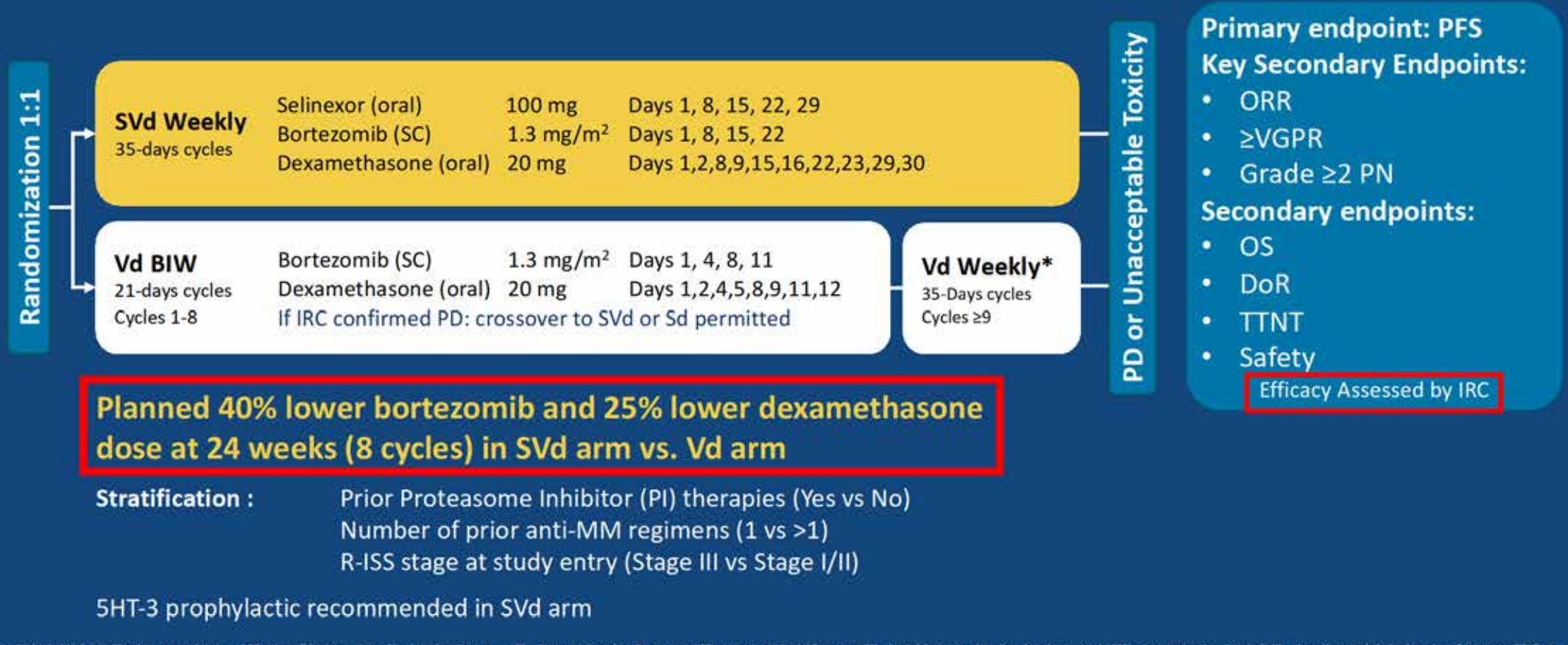



1. Schmidt et al, Leukemia, 2013; 2. Tai et al, Leukemia 2013; 3. Argueta et al, Oncotarget 2018, 4. Talati et al, Int J Hematologic Onc 2018

# Selinexor: Phase 2B STORM Trial

- STORM Trial: Selinexor 80 mg and Dexamethasone 20 mg twice weekly
- Population: PI/IMiD, Daratumumab resistant
- Overall response rate: 26.2%
  - sCR (2), VGPR (6), PR (24)
- Median PFS 3.7 mos (5.3 mos if ≥ PR), median OS of 8.6 months
- FDA Approval 7/2019 for relapsed multiple myeloma

# BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with Multiple Myeloma who Had Received 1-3 Prior Therapies




**Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in SVd arm vs. Vd arm**

**Stratification :** Prior Proteasome Inhibitor (PI) therapies (Yes vs No)
Number of prior anti-MM regimens (1 vs >1)
R-ISS stage at study entry (Stage III vs Stage I/II)

5HT-3 prophylactic recommended in SVd arm

MM = Multiple Myeloma, PD = Progressive Disease, ORR = Overall Response Rate, CR= Complete Response, sCR = Stringent Complete Response, VGPR = Very Good Partial Response, PR = Partial Response, PN = Peripheral Neuropathy PFS = Progression Free Survival, OS = Overall survival, DoR = Duration of Response, TTNT: time to Next Therapy, IRC = Independent Review Committee, IMWG = International Myeloma Working Group. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments. * Vd weekly dosing and schedule for cycles≥ 9 as per SVd arm description

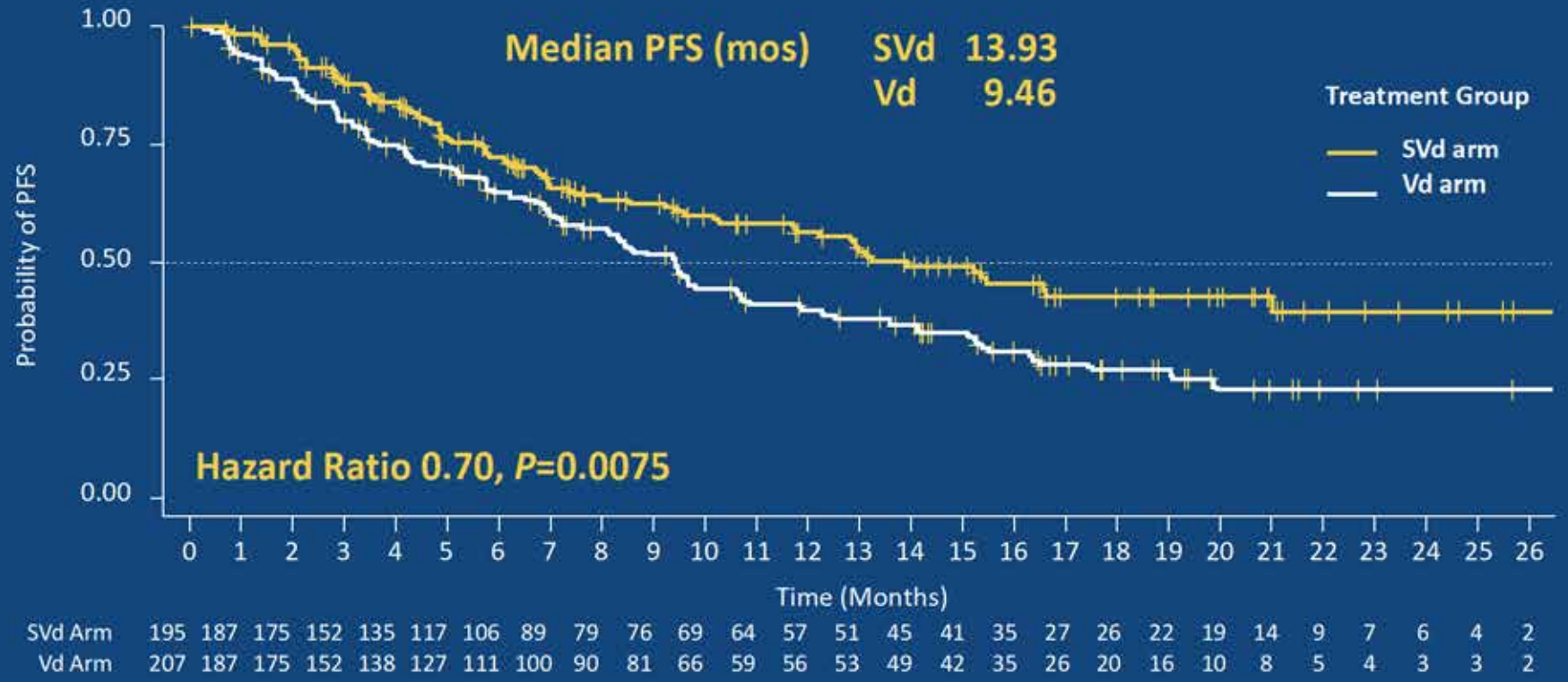




Dimopoulos MA et al, ASCO Annual Meeting 2020

# BOSTON Trial: PFS significantly longer with SVd compared to Vd

## Early and Sustained PFS benefit (assessed by IRC)




Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
*HR=Hazard Ratio 95% CI=0.53–0.93 one-sided *P* value

Median follow-up 13.2 and 16.5 months in SVd and Vd arms respectively





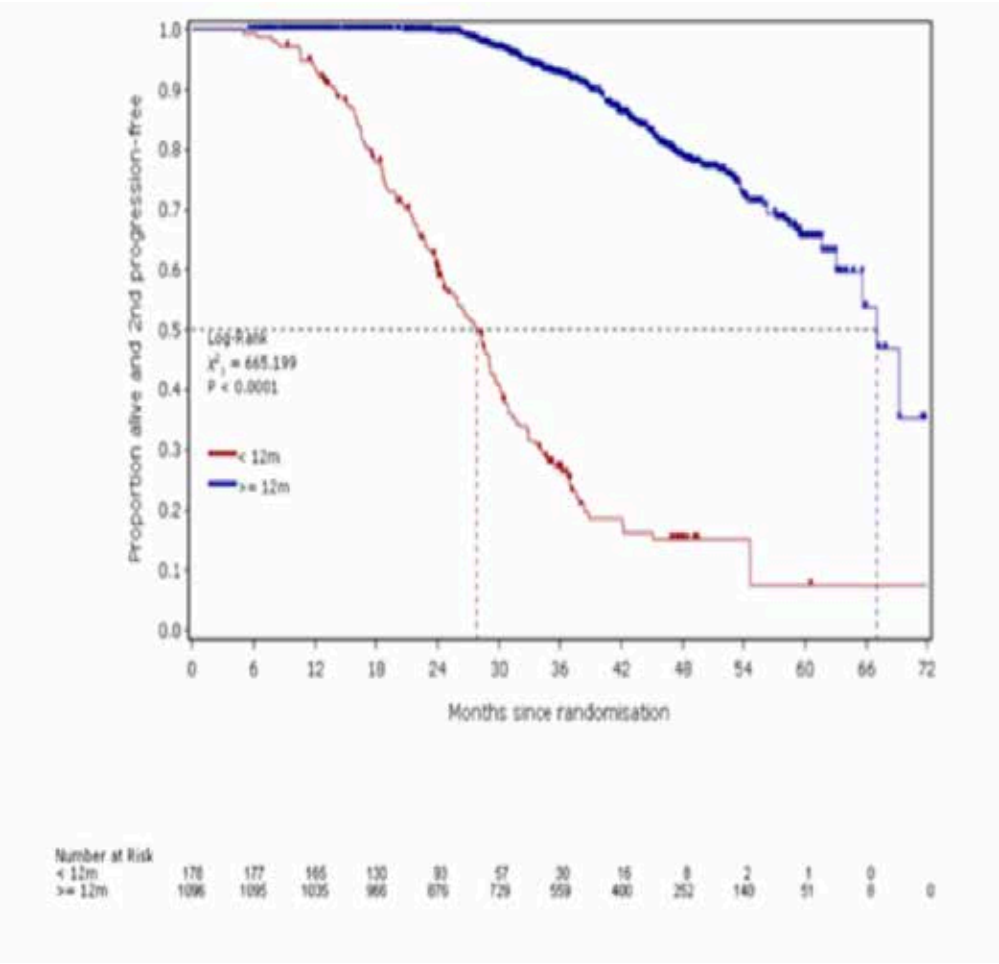
Dimopoulos MA et al, ASCO Annual Meeting 2020

# The Type, Timing of MM Relapse is Important

- Biochemical (i.e., rise in M protein or serum free light chains), vs clinical (i.e., new onset **CRAB** symptoms or extramedullary disease)

- Timing of relapse - example: relapse post autologous

  - In MRC IX Trial: Relapse at < 12 months post autologous stem cell transplant associated with worse PFS[a]




Bygrave CA et al, ASH Annual Conference 2018, San Diego

# Using Genetic Changes to Guide Treatment Choice

- High risk Myeloma: e.g., Del(17p), t(4;14), t(14;16), t(14;20), 1q+/1p-, continuous therapy, 3 drug regimens.

- t(11;14) – sensitivity to venetoclax, a BCL2 inhibitor – investigational at this time, not FDA approved

- Plasma cell leukemia – unique disease biology. Anthracycline based regimens (e.g., VTD PACE, Hyper CVAD)

# What About Late Relapse after Transplant?

- Current state of underlying organ function / frailty index?
- Stem cells still stored? (viability has been good at our center up to 10 years and beyond)
- Relapse on maintenance or not on maintenance?
- Age, willingness to undergo second transplant?

# When to consider 2nd transplant as a treatment for relapsed multiple myeloma

- A patient who previously underwent autologous transplantation may be eligible for a second transplant if the duration of remission from the first transplant was > 18-24 months (probably 3-4 years if on maintenance therapy).
- If no maintenance was received post transplant #1, then it should be considered strongly after transplant #2
- If initial therapy only included RVD and maintenance (no transplant), then autologous transplant should be STRONGLY considered as the next best therapy once in remission

Laubach et al, Leukemia 2016 May;30(5):1005-17; Attal et al, Blood 2017 Apr 6;376(14):1311-1320

# Outcomes for Salvage Transplant in Relapsed MM

| | Months from auto-SCT2, median (range) | |
|---|---|---|
| Time to progression after auto-SCT1 (N) | PFS | OS |
| <12 months (9) | 5.6 (3–8) | 12.6 (4–23) |
| <18 months (25) | 7.1 (6–8) | 19.4 (10–42) |
| <24 months (47) | 7.3 (6–10) | 22.7 (13–62) |
| <36 months (68) | 7.6 (7–12) | 30.5 (19–62) |

Gonsalves WI et al BMT 2013 Apr;48(4):568-73

# Summary

- Upfront myeloma treatment: transplant ineligible vs eligible; 3 drugs are superior (and 4, coming soon)!
- There are many options for treating relapsed multiple myeloma, and…

  Personalization is key!
- Choose therapies based on prior sensitivity, disease status, toxicities, and general state of the patient (frail vs robust)
- Autologous transplantation should be considered in appropriate patients

# Thank you – PATIENTS AND FAMILIES

- UW/FHCRC/SCCA Heme Malig/MM
  - Damian Green
  - Edward Libby
  - Pamela Becker
  - David Coffey
  - Leona Holmberg
  - Sherilyn Tuazon
  - Teresa Hyun
  - Ajay Gopal

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