# IMWG Conference Series: ASH 2017

## Making Sense of Treatment

### Monday, December 11, 2017

### Atlanta, GA

# Tonight's Speakers

**Brian GM Durie**
**Cedars Sinai Medical Center**

**Joseph Mikhael**
**Mayo Clinic Scottsdale**

**Paul Richardson**
**Dana-Farber Cancer Institute**

# Tonight's Topics

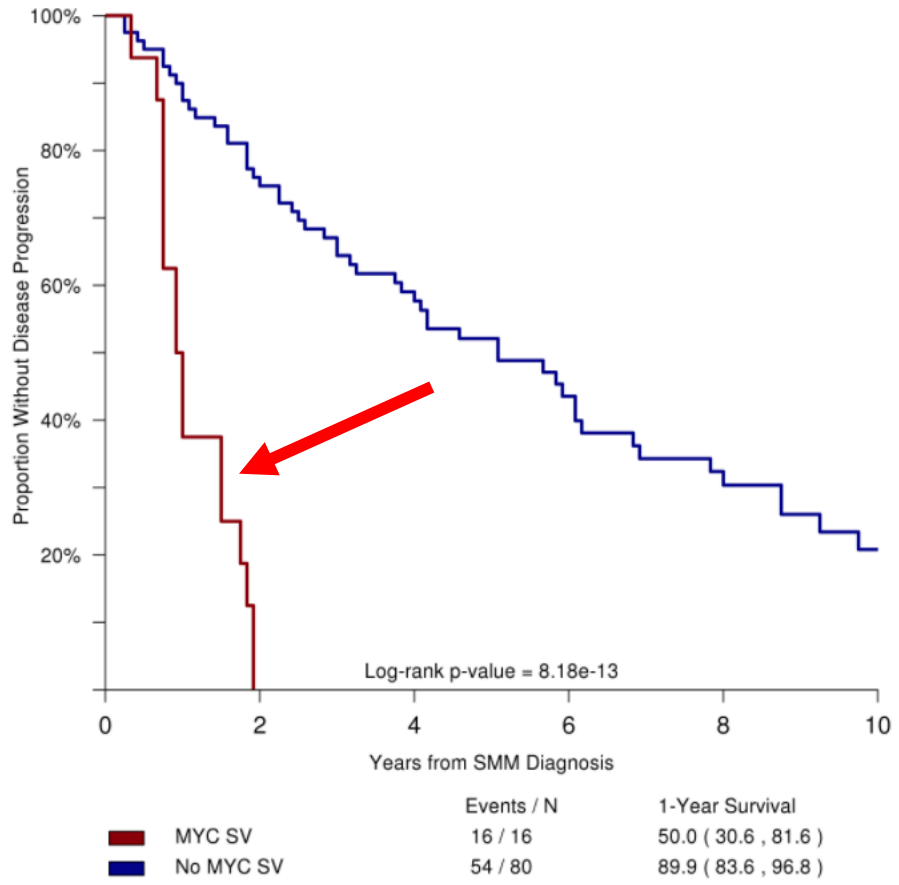
- Priorities for early disease
- Frontline options
- Role of ASCT
- Maintenance recommendations
- Early relapse management
- New therapies

# Priorities for Early Disease

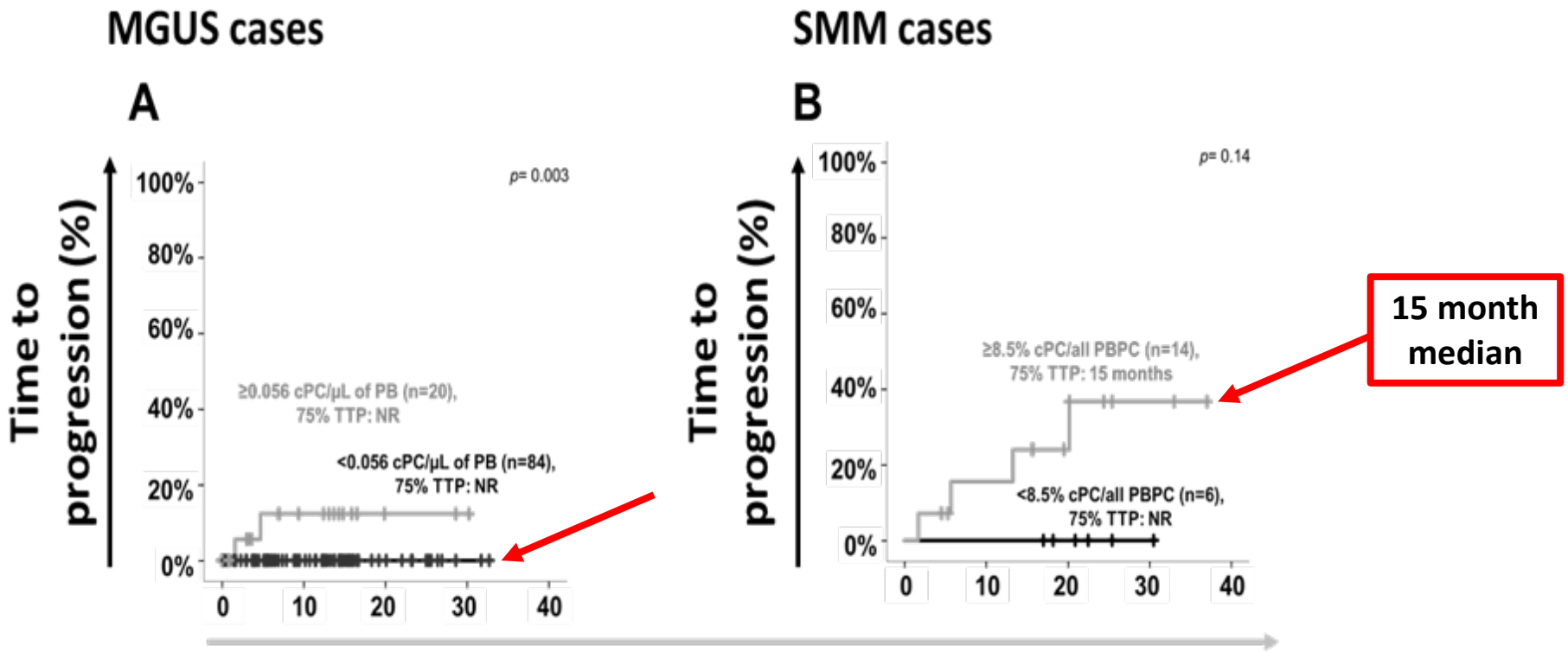
ASH 2017

# Abstract #393: MYC Translocations Identified By Sequencing Panel in Smoldering Multiple Myeloma Strongly Predict for Rapid Progression to MM

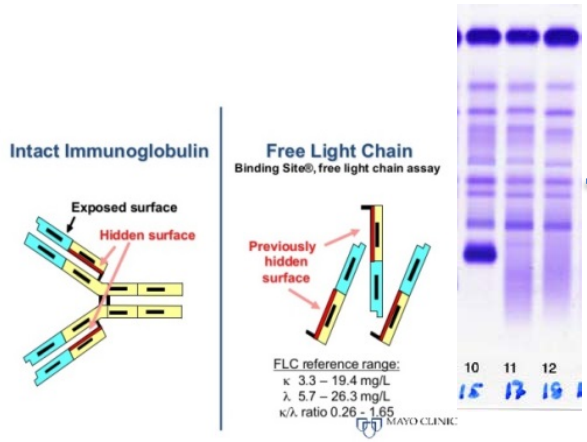
***Niamh Keane, MB, MRCP***[1,2*], *Caleb K Stein, MS*[3*], *Daniel Angelov, MSc, MB*[3*], *Shulan Tian*[4*], *David Viswanatha, MD*[5], *Shaji K. Kumar, MD*[5], *Angela Dispenzieri, MD*[5], *Veronica Gonzalez De La Calle, MD*[3*], *Kristine Misund, PhD*[3,6*], *Robert A Kyle, M.D*[5], *Michael E O'Dwyer, MD*[2], *Rafael Fonseca, MD*[3], *A. Keith Stewart, MBChB, MBA*[7], *Esteban Braggio, PhD*[8], *Yan Asmann, PhD*[4], *S. Vincent Rajkumar, MD*[5] *and P. Leif Bergsagel, MD*[8]



# Peripheral Blood Results with NGF in MGUS & SMM



# iStopMM: largest population-based study




All Icelanders > 40 years
N=148 000

4500-5000 with MGUS/SMM

Without MGUS/SMM

R

No further work-up
N=1500

IMWG Recommendations
N=1500

Intervention arm
N=1500

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

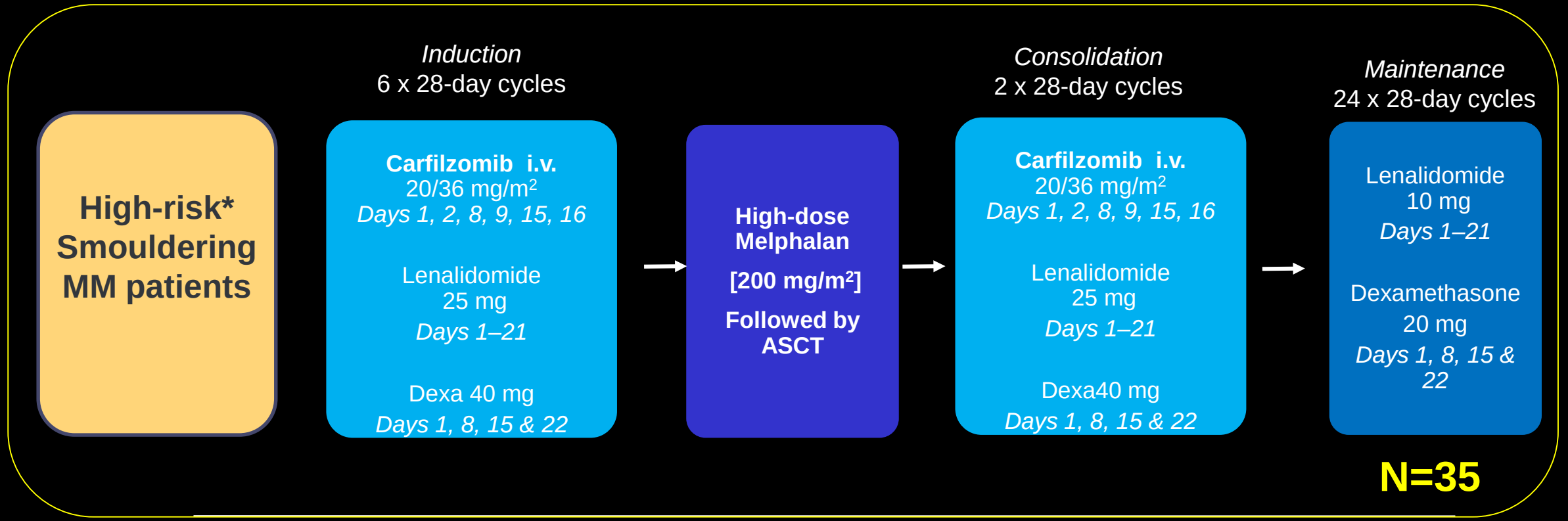
# Question

**What do you foresee will be the best way to diagnose early disease?**

# Management of High-Risk Smoldering Myeloma

# GEM-CESAR: Study Design

- Multicenter, open-label, randomized phase II trial




***High-risk was defined according to the Mayo and/or Spanish models***

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening and if bone disease was detected in the CT or PET-CT, patients were excluded

# GEM-CESAR:
# Improvement of the quality of response over the treatment (n=35)

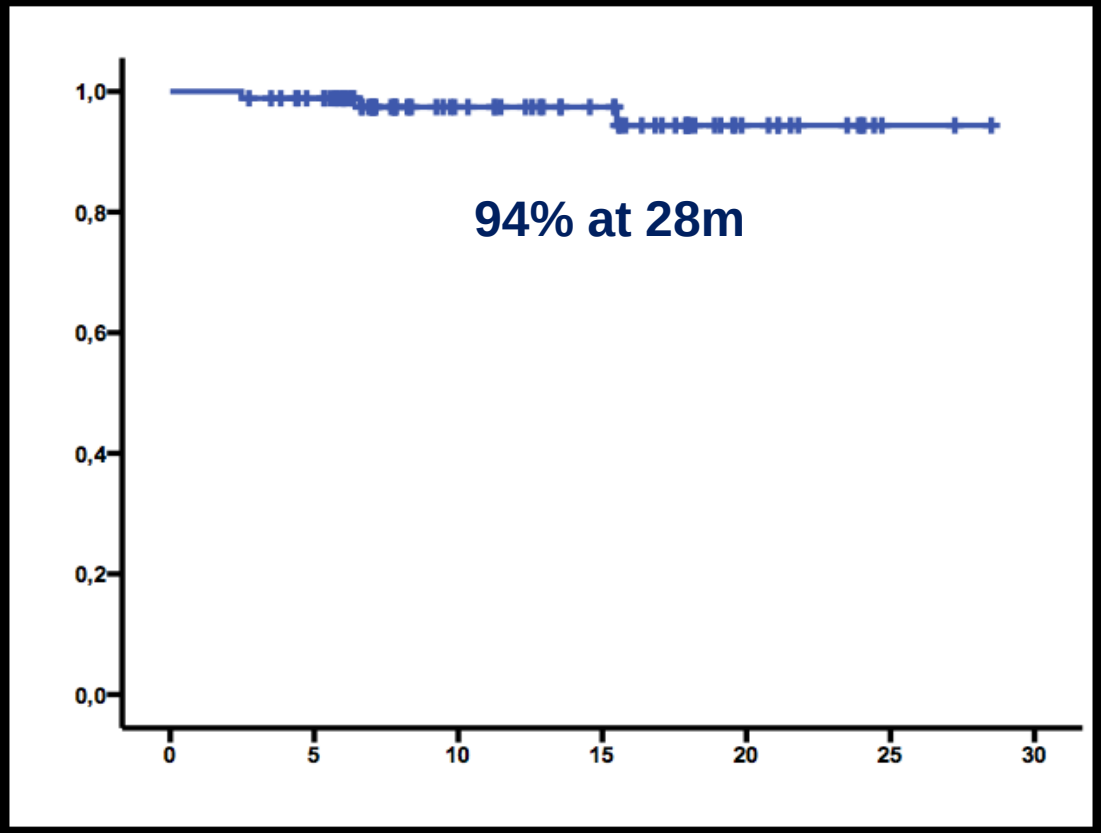
| | Induction (KRdx6) N = 35 | HDT/ASCT N = 35 | Consolidation (KRdx2) N = 35 |
|---|---|---|---|
| **≥CR** | **49%** | **62%** | **74%** |
| **VGPR** | 37% | 23% | 20% |
| **PR** | 14% | 14% | 6% |
| **MRD-negative** | **26%** | **47%** | **62%** |

# GEM-CESAR Outcomes

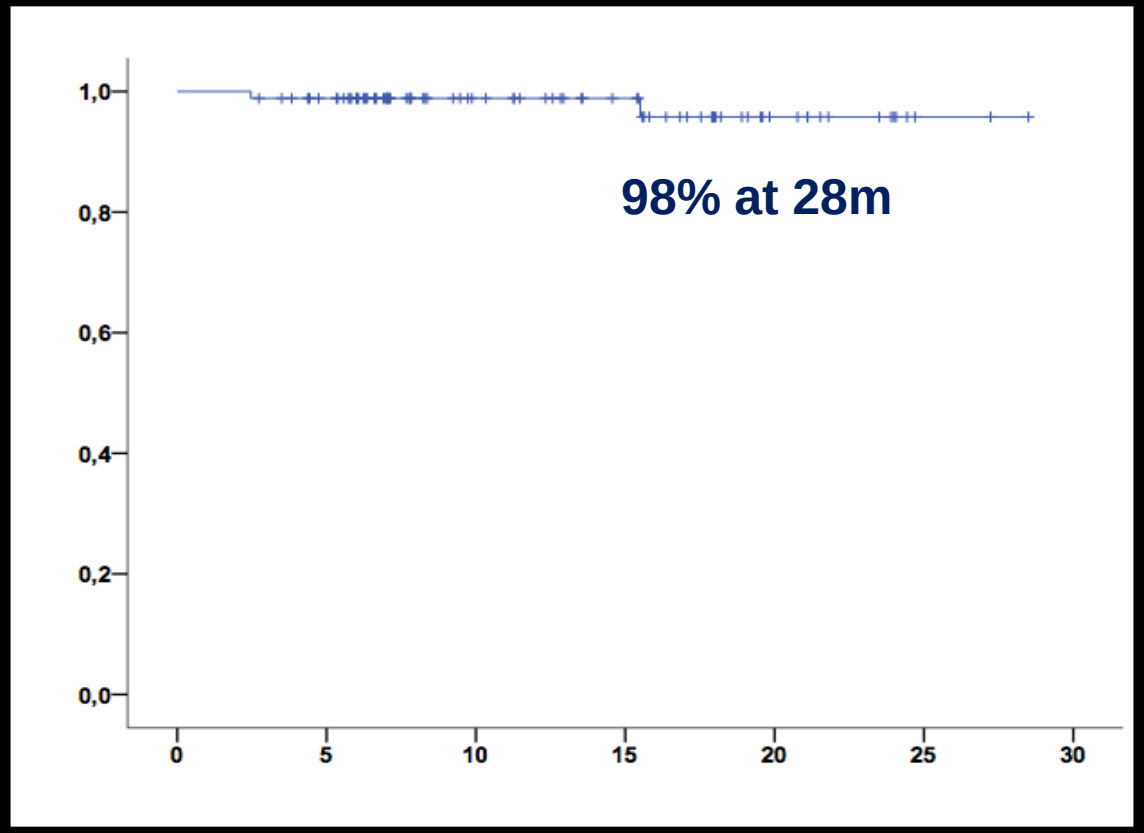
PFS

Median follow-up: 10 (1-28)

OS



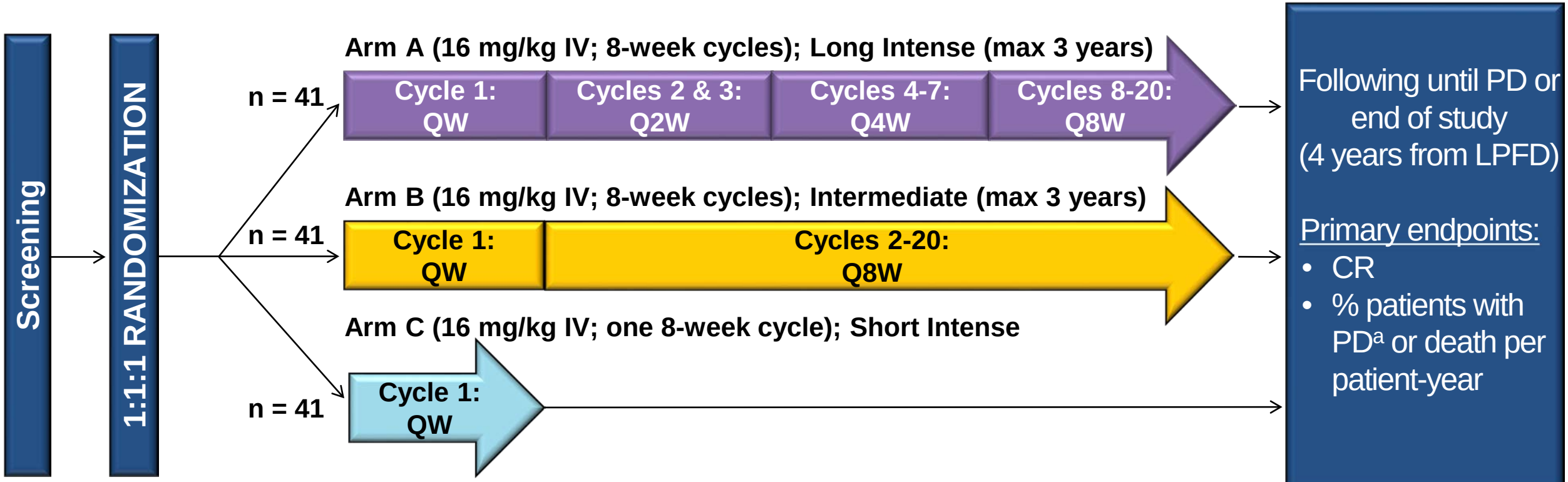

Two patients experienced relapse from CR before the end of induction and they proceeded to subsequent therapy




Two deaths: one patient who relapsed from CR and was refractory and died due to disease progression; other patient due to massive ischemic stroke during induction

# And the more gentle approach…

# Daratumumab Monotherapy in SMM




[a]As defined by 2014 IMWG criteria for SMM.

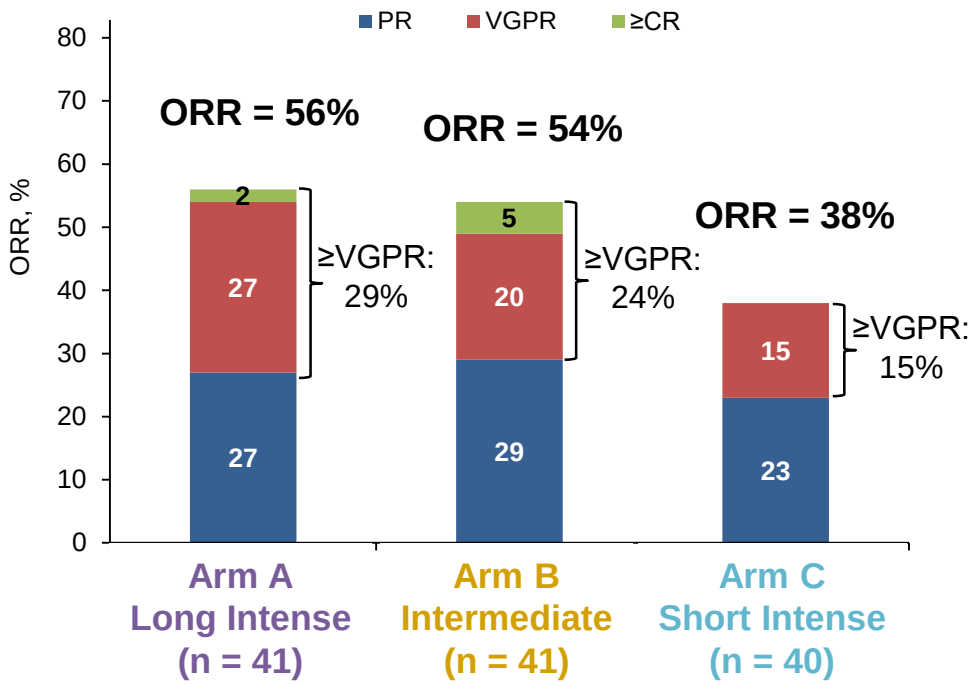


IV, intravenous; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; PD, progressive disease; LPFD, last patient, first dose; CR, complete response.

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

# CENTAURUS: Efficacy

## ORR



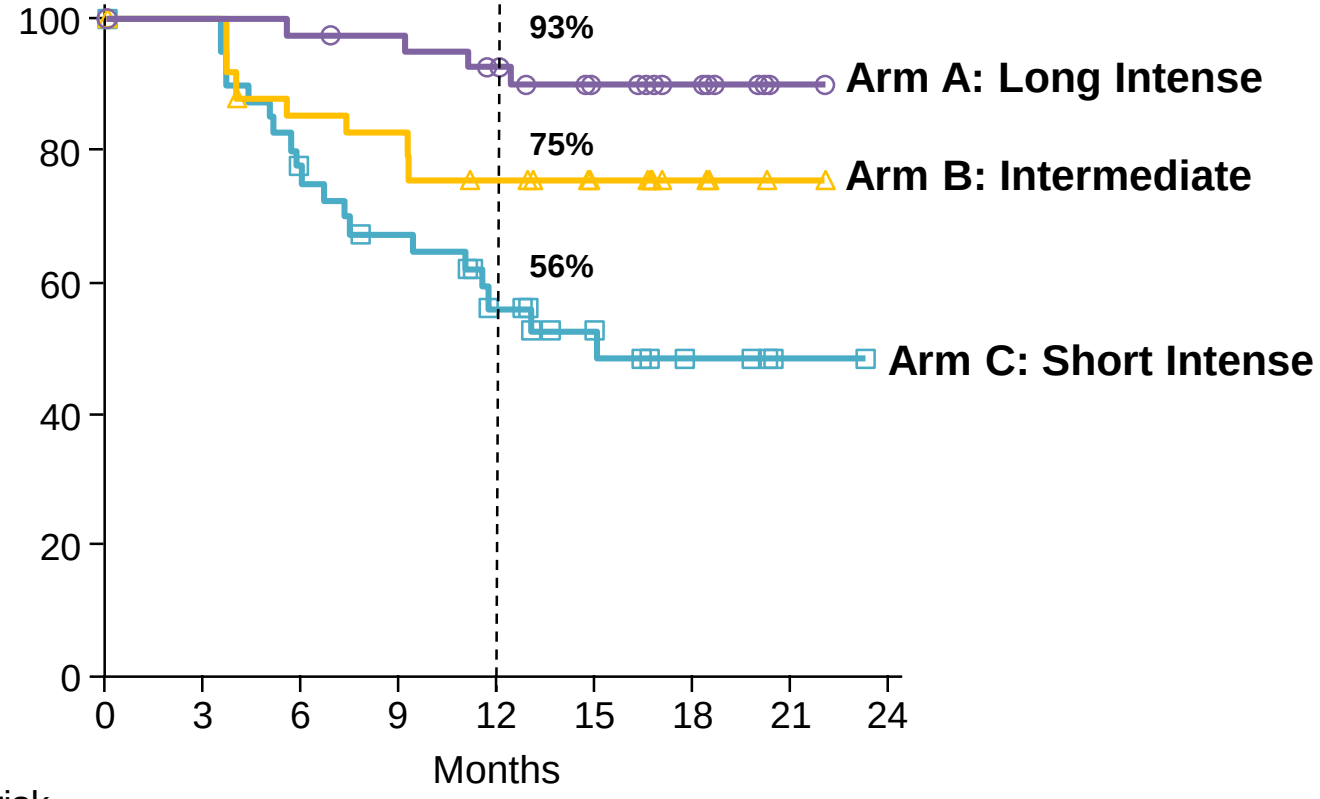

**Daratumumab single agent shows activity in SMM**

- Co-primary endpoint of median PFS ≥24 months was met
- Co-primary endpoint of CR (>15%) was not met



ORR, overall response rate; PR, partial response; VGPR, very good partial response; PFS, progression-free survival.

# CENTAURUS: PFS (Biochemical or Diagnostic)




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Long Intense | 41 | 41 | 40 | 39 | 36 | 21 | 12 | 1 | 0 |
| Intermediate | 41 | 41 | 34 | 33 | 28 | 16 | 7 | 1 | 0 |
| Short Intense | 41 | 40 | 30 | 25 | 18 | 13 | 5 | 1 | 0 |

**Extended daratumumab dosing prolongs biochemical/diagnostic PFS**

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

# Question

**There are these two approaches to early/smoldering disease:**

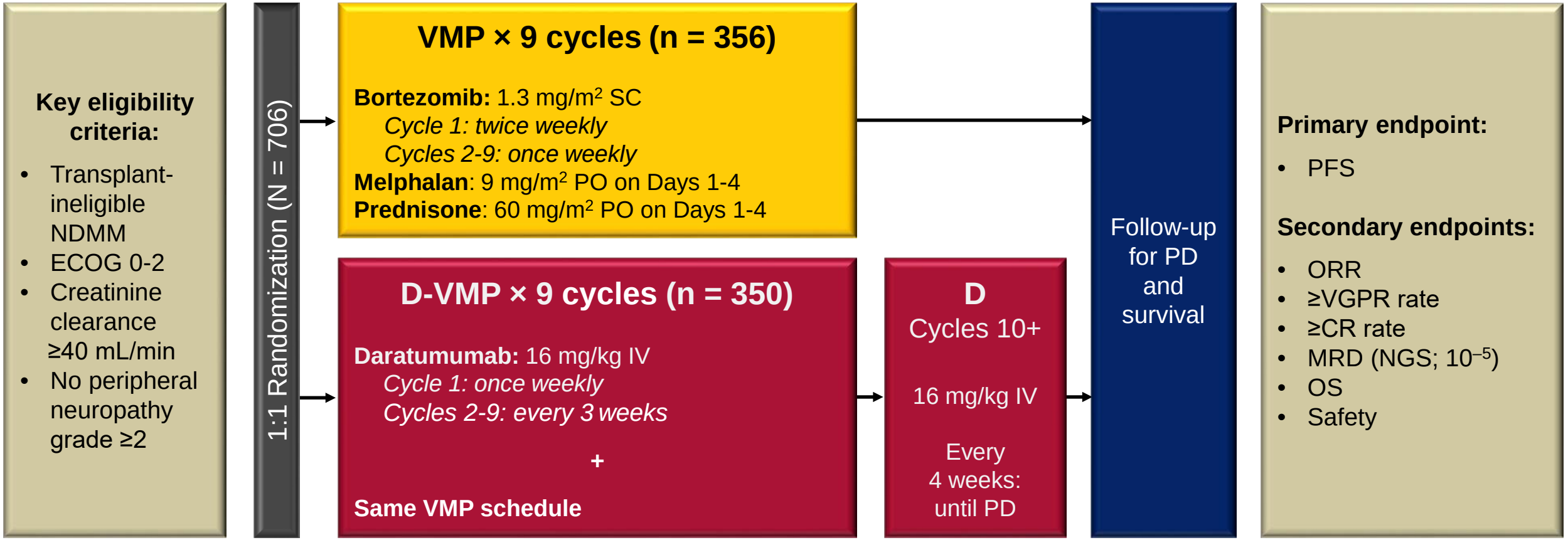
- **Attempted “Cure”**
- **Control**

**Which do you favor?**

# Frontline Options

# First in the non-transplant setting

# ALCYONE Study Design




**Stratification factors**

- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

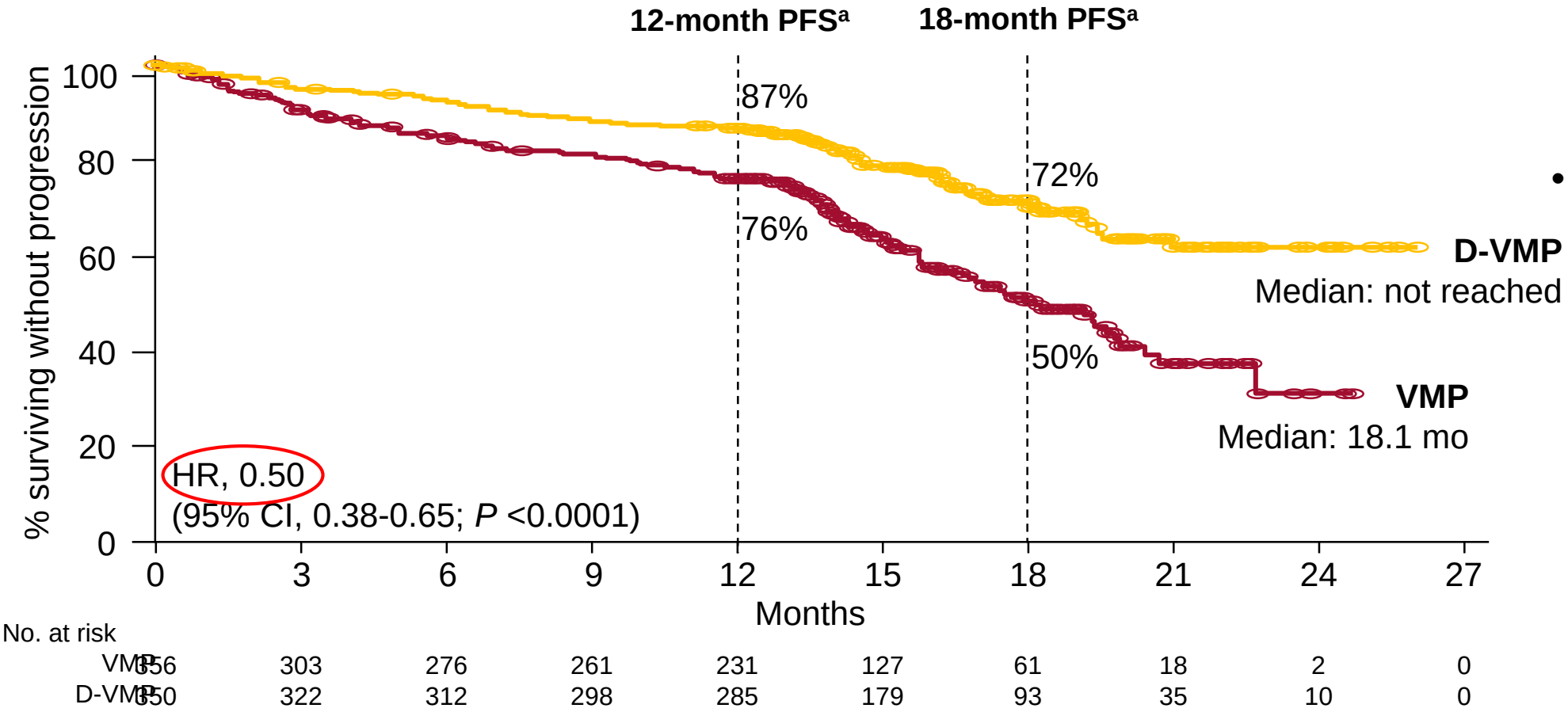
**Statistical analyses**

- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events



NDMM, newly diagnosed multiple myeloma; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; VMP, bortezomib/melphalan/prednisone; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; OS, overall survival.

# Efficacy: PFS



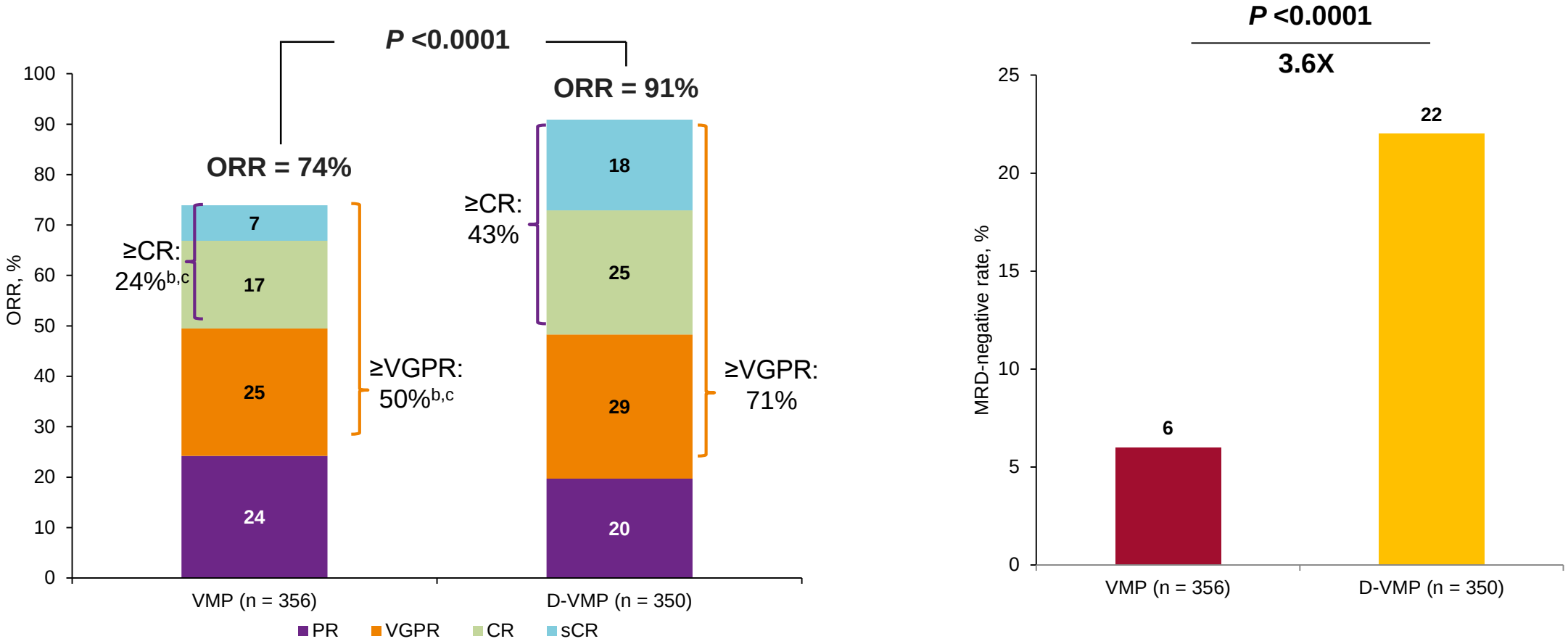

- **Median (range) follow-up: 16.5 (0.1-28.1) months**
- **Consistent PFS treatment benefit across subgroups**

**50% reduction in the risk of progression or death in patients receiving D-VMP**



PFS, progression-free survival; VMP, bortezomib/melphalan/prednisone; D, daratumumab; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

# Efficacy: ORR[a] and MRD (NGS; $10^{-5}$ Threshold)







**Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP**
**>3-fold higher MRD-negativity rate with D-VMP**



ORR, overall response rate; VMP, bortezomib/melphalan/prednisone; D, daratumumab; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response. MRD, minimal residual disease; NGS, next-generation sequencing using clonoSEQ version 2.0 (Adaptive) [a]Intent-to-treat population. [b]*P* value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test. [c]*P* <0.0001.

# Frontline: Non-ASCT

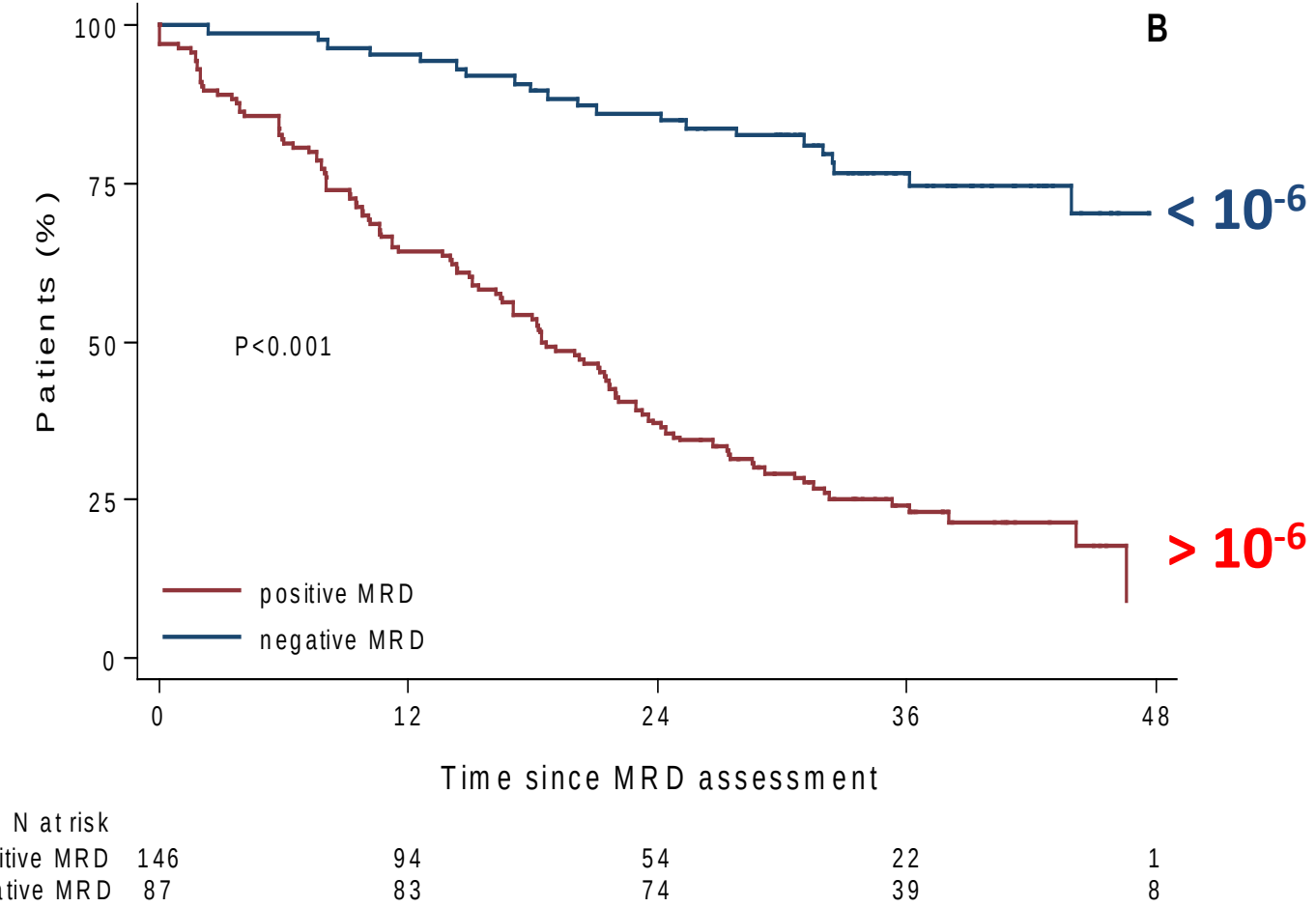
**Will Dara VMP be new standard of care?**

**OR**

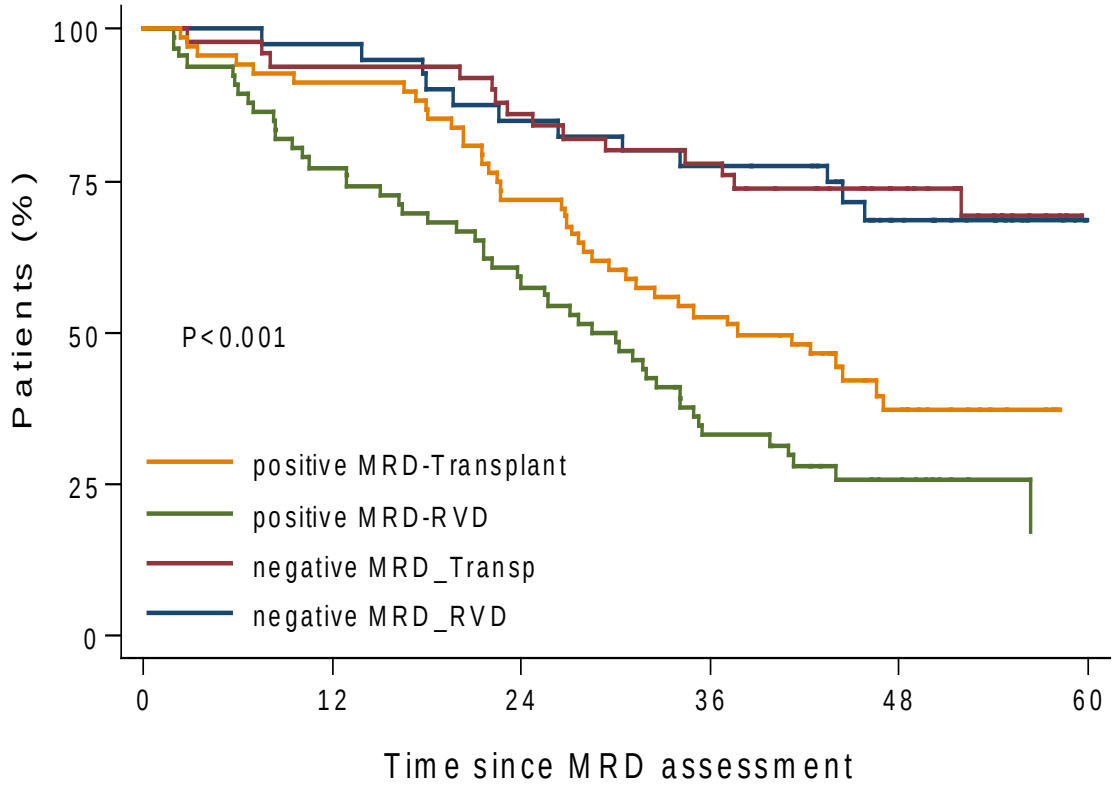
- **Dara Rd**
- **Dara Vd**
- **Dara VRd (lite)**
- **Dara KRd**
- **Other**

# What about frontline in the transplant setting?

# Importance of MRD sensitivity in IFM 2009 Trial
## VRd ± ASCT

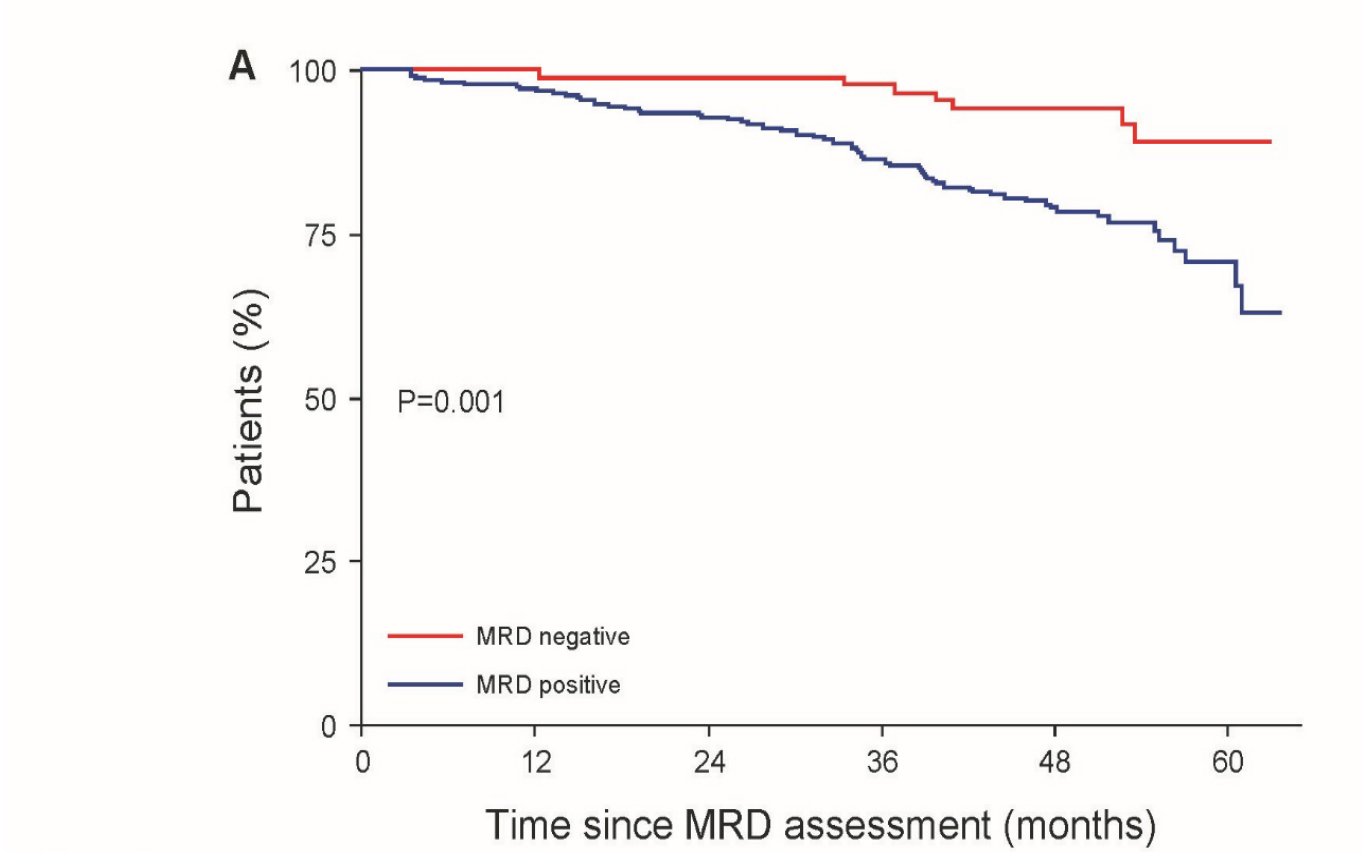


# Impact of treatment arm?



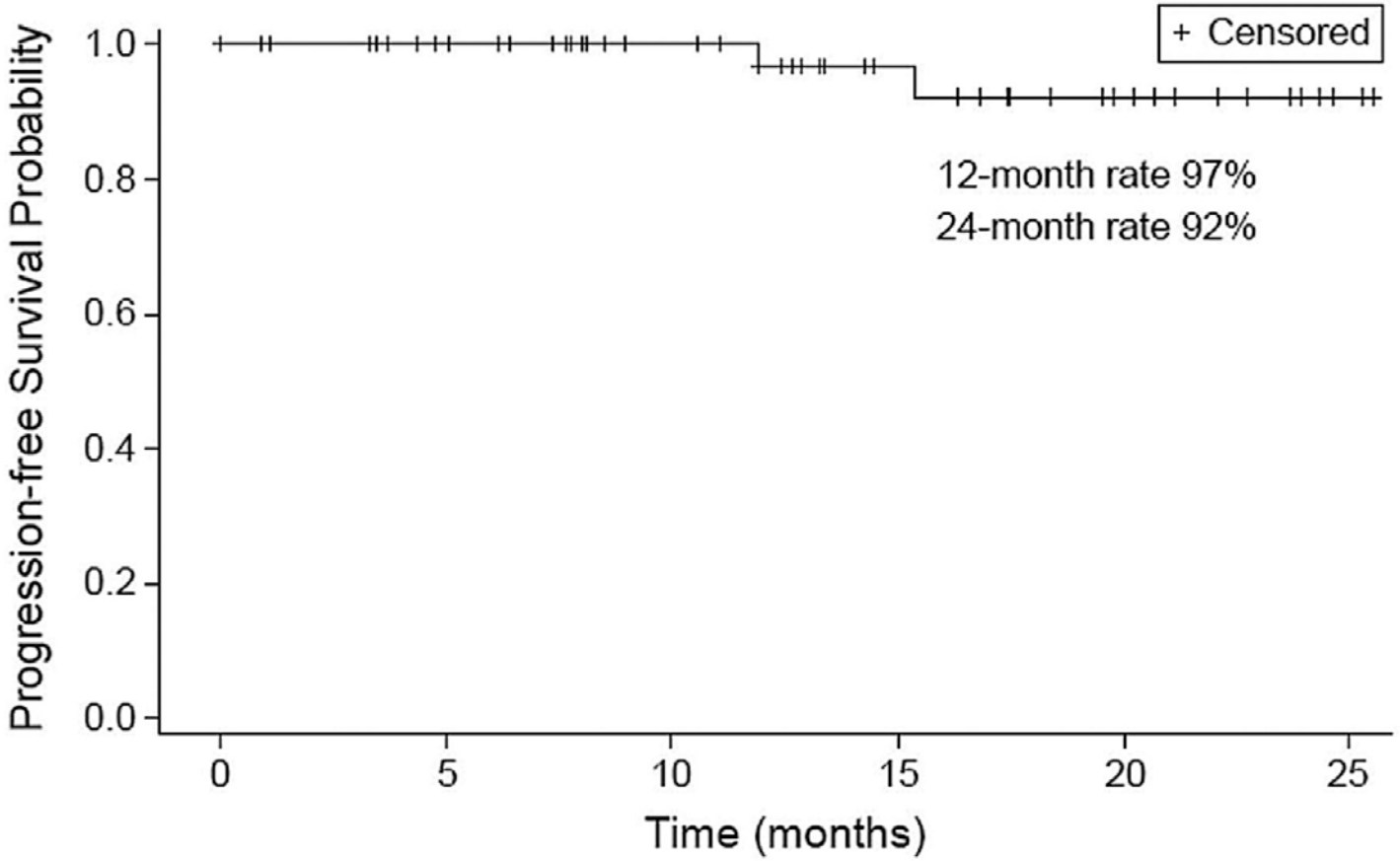

| N at risk | | | | | | |
|---|---|---|---|---|---|---|
| positive MRD-Transplant | 68 | 62 | 49 | 35 | 15 | 1 |
| positive MRD-RVD | 66 | 51 | 38 | 21 | 11 | 2 |
| negative MRD_Transp | 50 | 47 | 43 | 38 | 23 | 4 |
| negative MRD_RVD | 40 | 39 | 34 | 31 | 17 | 1 |

# Impact on OS




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| MRD negative | 90 | 90 | 89 | 85 | 54 | 8 |
| MRD positive | 276 | 268 | 255 | 237 | 142 | 21 |

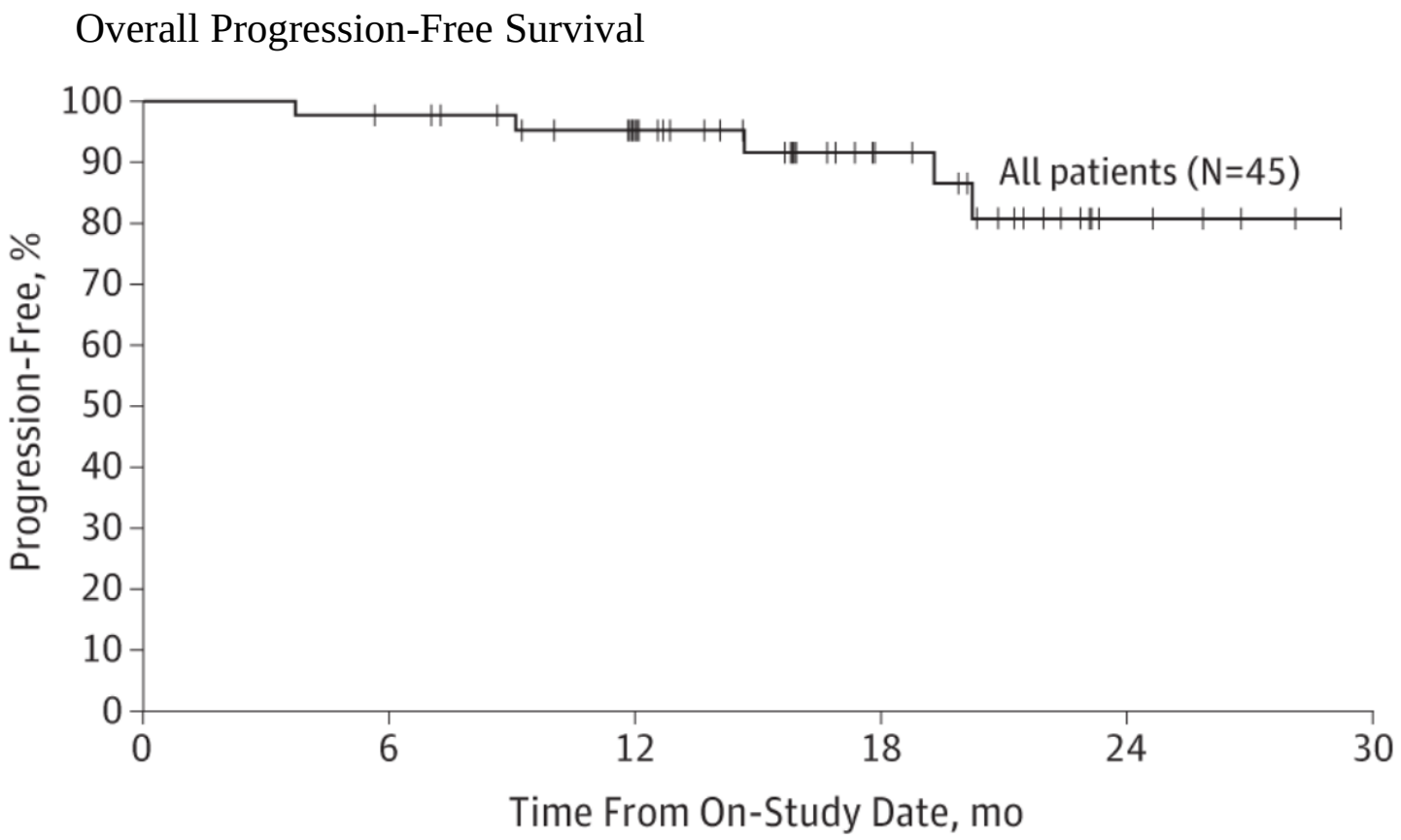
# A Phase I/II Trial of Carfilzomib/Lenalidomide/Dexamethasone With Lenalidomide Extension in Patients With Newly Diagnosed Multiple Myeloma (n=53)




Overall CR rate (n=53) = 42% (sCR)
MRD by Flow: Most negative

Jakubowiak AJ, et al. Blood 2012;120:1801-1809.

# Phase II trial of Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Newly Diagnosed Multiple Myeloma (n=45)




Overall CR rate 56%*
MRD by NGS negative in ~2/3 of CR

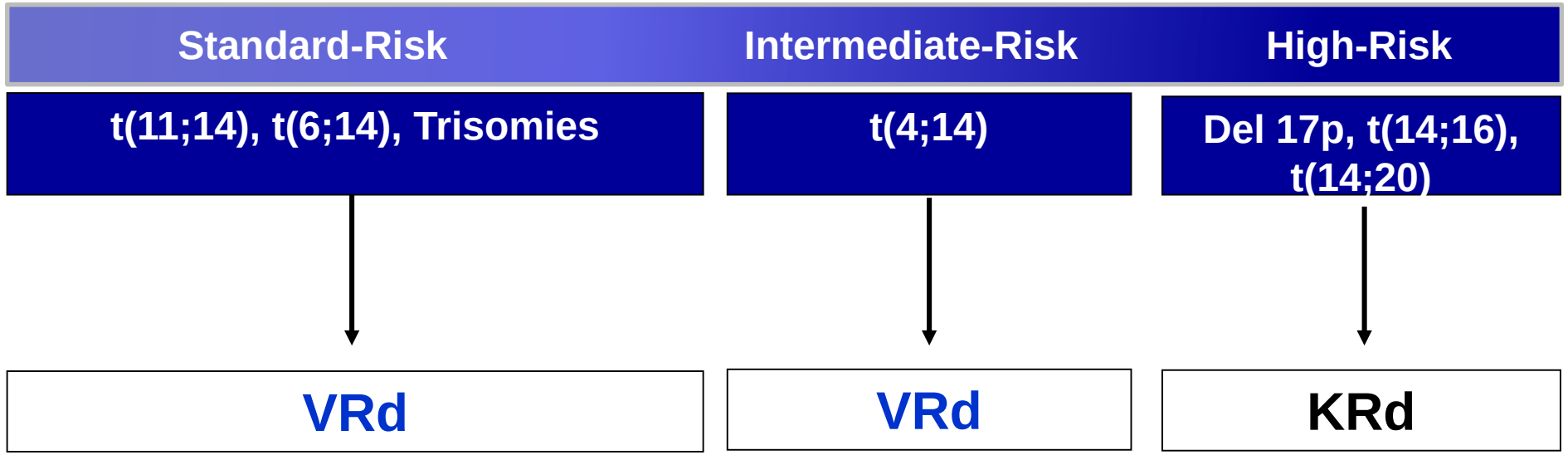
* VRd in IFM 2009: 48%

Korde N. et al. JAMA Oncol. 2015;1(6):746-754.
Attal M, et al. N Engl J Med. 2017;376:1311-1320.

MAYO CLINIC

msmart.org

# mSMART – Off-Study Transplant Eligible




Dispenzieri A, et al. Mayo Clin Proc 2007;82:323-341.
Kumar S, et al. Mayo Clin Proc 2009;84:1095-1110.
Mikhael J, et al. Mayo Clin Proc 2013;14:88:360-376.

# ASH 2017

## Abstract #3110: Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients with Newly Diagnosed Multiple Myeloma (MMY1001): Updated Results from an Open-Label, Phase 1b Study

*Ajai Chari[1*], Saad Z Usmani, MD[2], Amrita Krishnan, MD[3], Sagar Lonial, MD[4], Raymond Comenzo[5*], Kaida Wu[6], Jianping Wang[7*], Parul Doshi[6*], Brendan M Weiss, MD[8], Jordan Schecter[7*] and Andrzej J. Jakubowiak, MD[9]*

- Dara-KRd: safe and effective

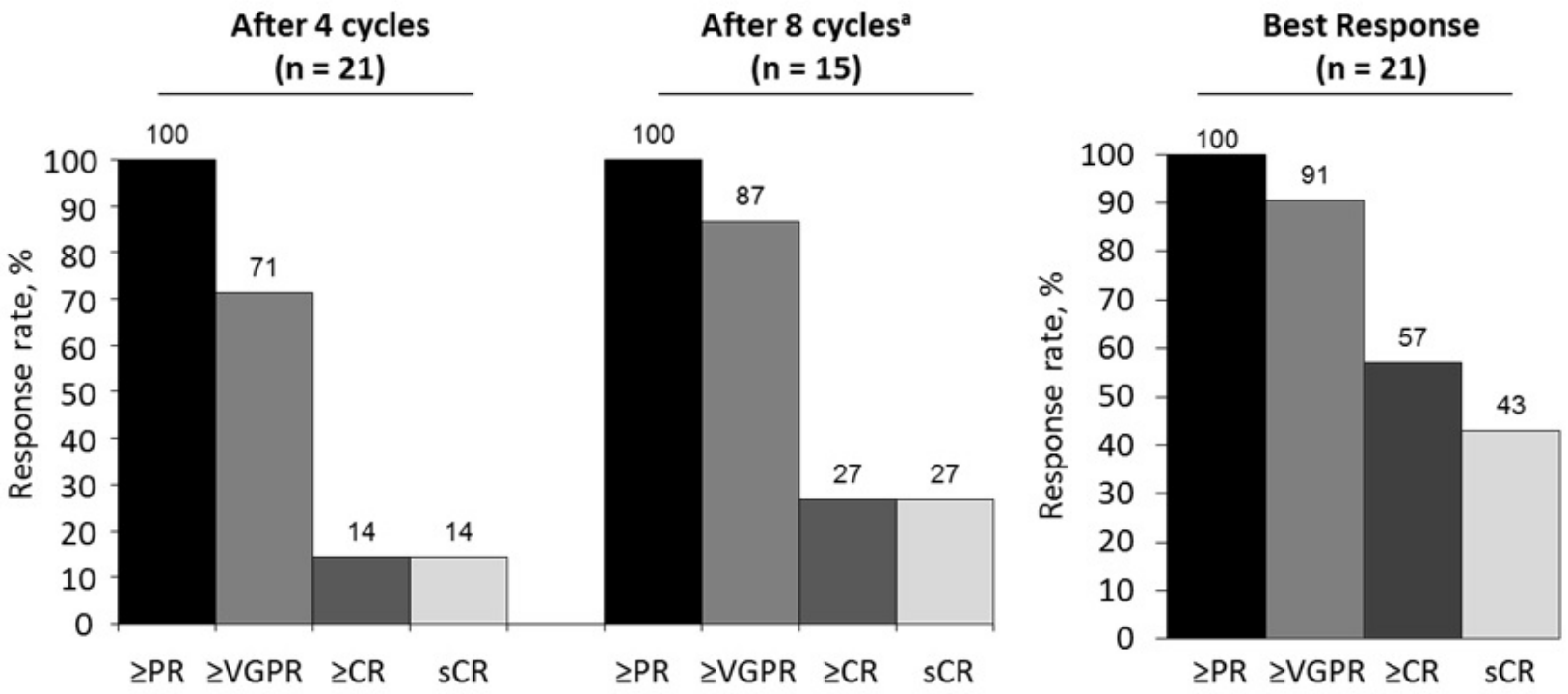
**Table. Echocardiogram Assessment**

| Time Point | Left Ventricular Ejection Fraction Median (range) |
|---|---|
| Baseline (n = 22) | 60 (55-77) |
| Cycle 3 (n = 20) | 60 (55-78) |
| Cycle 6 (n = 16) | 59 (50-70) |
| Cycle 9 (n = 15) | 60 (50-69) |
| Cycle 12 (n = 12) | 61 (56-75) |

# ASH 2017

## Abstract #3110: Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients with Newly Diagnosed Multiple Myeloma (MMY1001): Updated Results from an Open-Label, Phase 1b Study

**Figure. Best confirmed response rates with DARA+KRd**




[a]5 patients who proceeded to ASCT before Cycle 8 and 1 patient who discontinued due to progressive disease at Cycle 7 were excluded.

# Question

**How do you select frontline therapy in the ASCT setting?**

# Maintenance Recommendations

ASH 2017

# Abstract #904: Minimal Residual Disease in the Maintenance Setting in Myeloma: Prognostic Significance and Impact of Lenalidomide

***Ruth M De Tute, BSc, MSc***[1*], *David Cairns, BSc, MSc, PhD*[2*], *Andy Rawstron, PhD*[3*], *Charlotte Pawlyn, BA, PhD, MBBChir, MRCP, FRCPath*[4], *Faith E. Davies, MD*[5,6], *John R Jones, MD*[6*], *Martin F Kaiser, MD*[6], *Anna Hockaday*[2*], *Alina Striha, MSc*[2*], *Rowena Henderson, PhD*[2*], *Gordon Cook, PhD*[7*], *Nigel H. Russell*[8], *Mark T Drayson, MD, PhD*[9*], *Matthew W Jenner*[10*], *Walter M Gregory, PhD*[2*], *Graham Jackson, MD, PhD*[11], *Gareth J. Morgan, MD, PhD*[5] *and Roger G. Owen, MD*[3*]

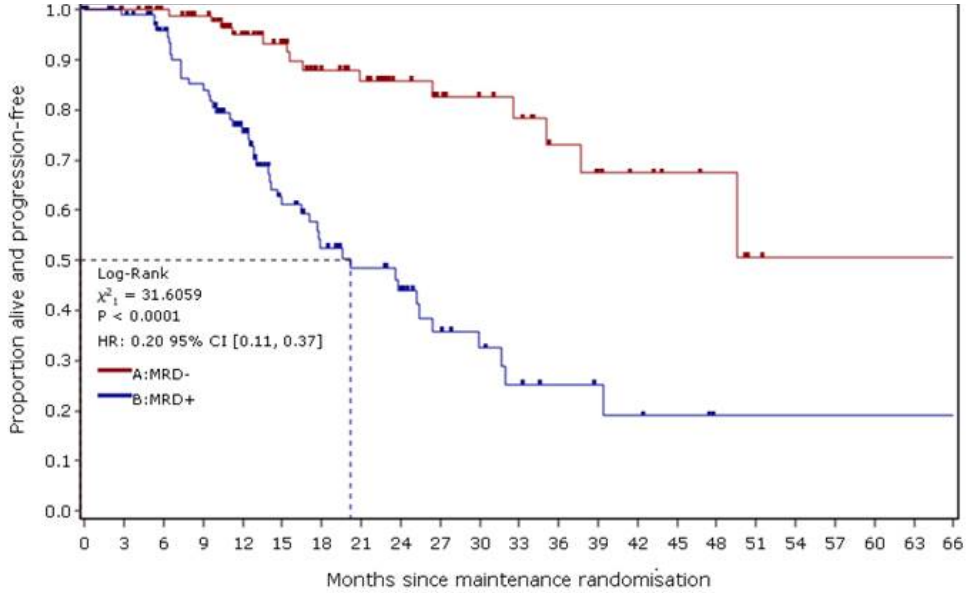
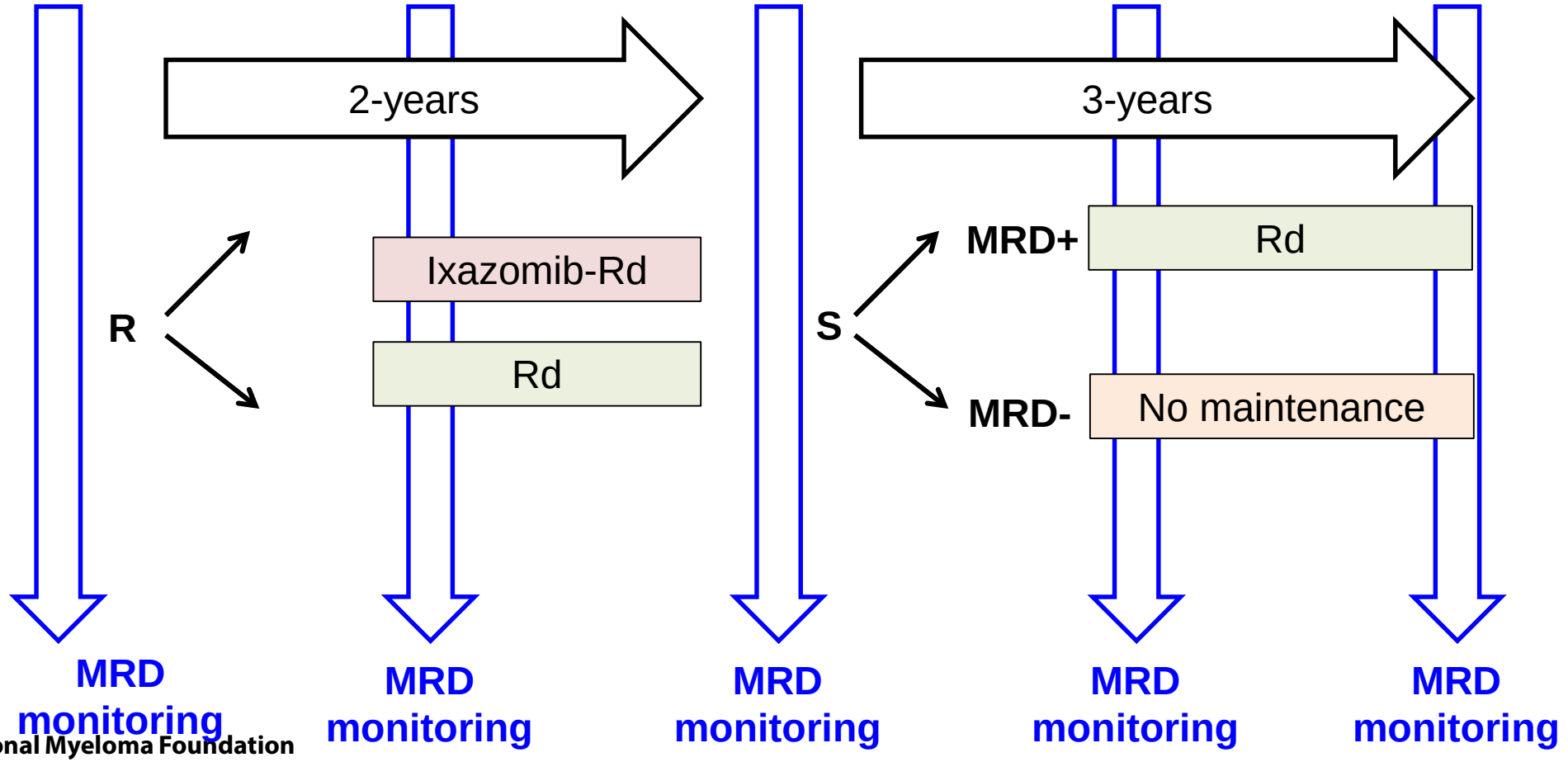



Figure 1 (a). Impact of MRD result for patients with an informative sample at six months post maintenance randomisation. Progression-free survival is greatly superior in the MRD-negative patients (>50 months vs 20 months, p<0.0001, HR 0.2, 95% CI 0.11-0.37).

# Protocol Example

## GEM2014MAIN: role of MRD in optimizing duration of maintenance



# Question

**Is maintenance “standard of care” now?**

**If so: with what?**

# Early Relapse Management

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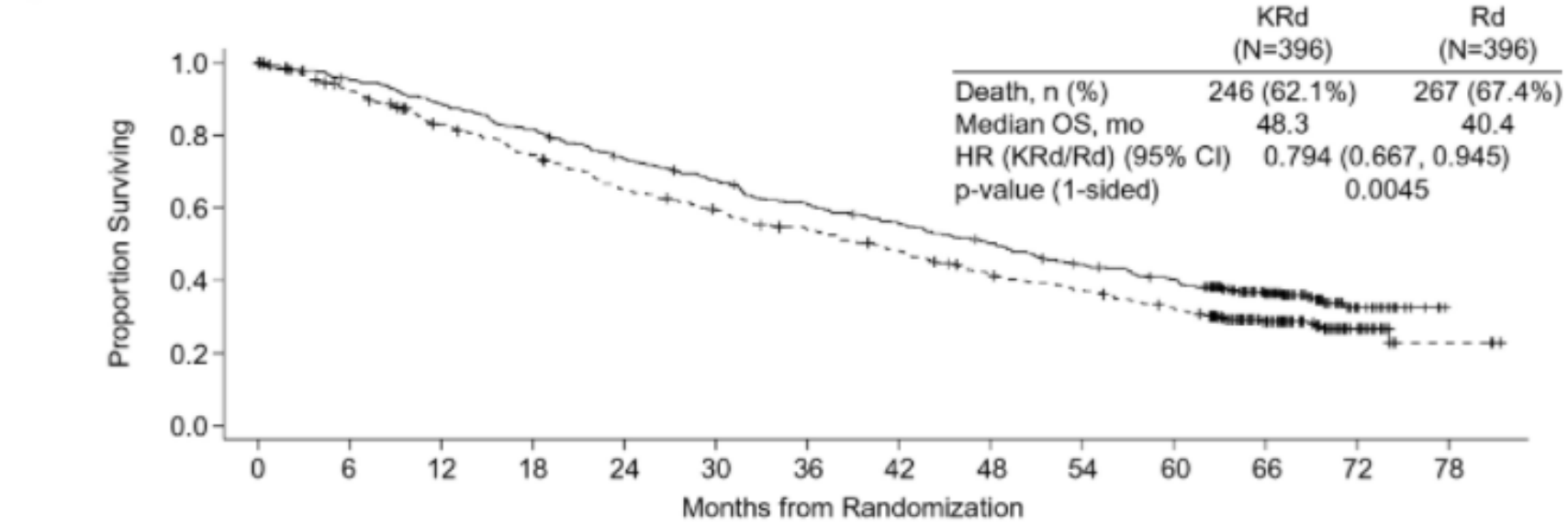
# Abstract #743: Final Analysis from the Randomized Phase 3 Aspire Trial

*A. Keith Stewart, MBChB, MBA*[1], *David Siegel, MD, PhD*[2], *Heinz Ludwig, MD*[3], *Thierry Facon, MD*[4*], *Hartmut Goldschmidt, MD*[5], *Andrzej J. Jakubowiak, MD*[6], *Jesus F. San Miguel, MD*[7], *Mihaela Obreja*[8*], *Julie Blaedel*[8*] *and Meletios A. Dimopoulos*[9]

**Figure. OS KM Curve From the ITT**




Number of subjects at risk:

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| —— KRd | 396 | 369 | 343 | 316 | 282 | 259 | 232 | 211 | 190 | 166 | 149 | 88 | 22 | 0 |
| - - - - Rd | 396 | 356 | 313 | 281 | 243 | 220 | 199 | 176 | 149 | 133 | 113 | 69 | 20 | 3 |

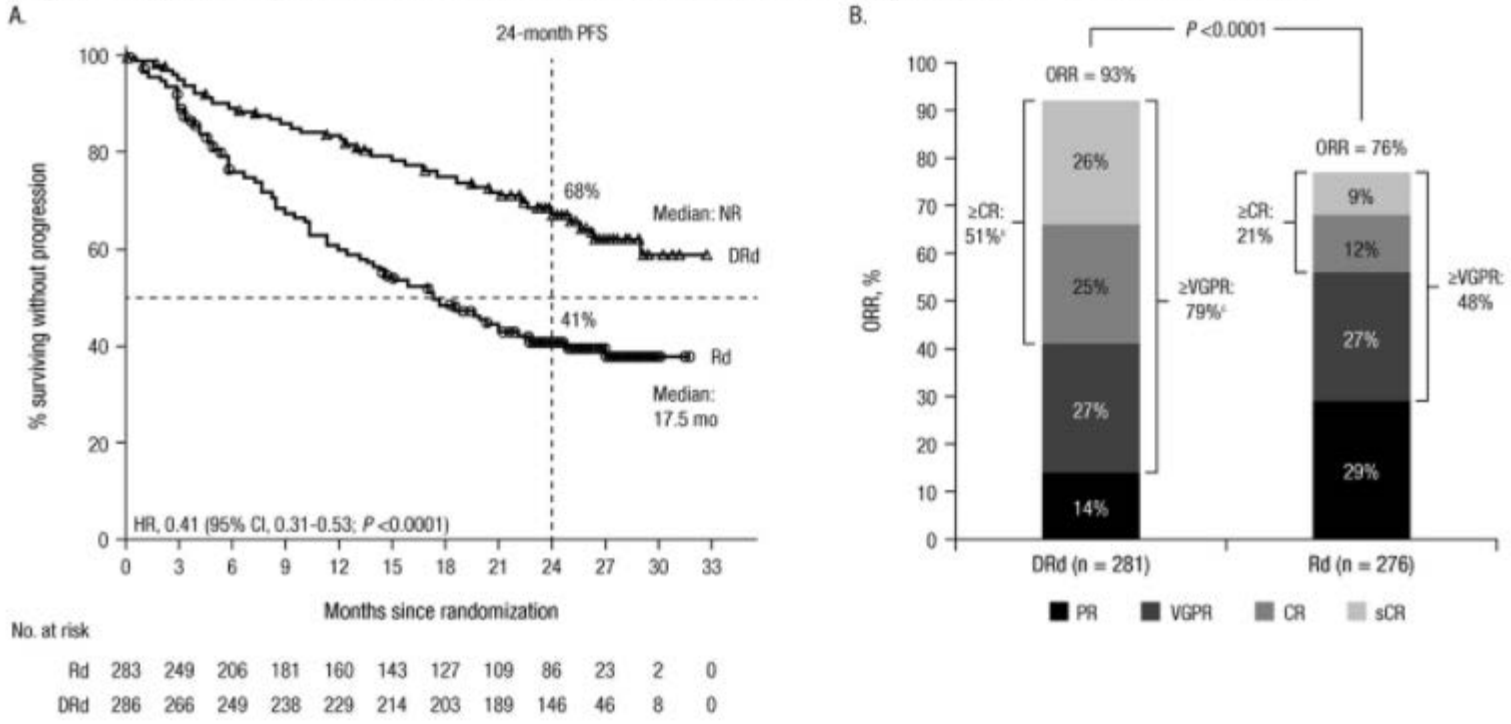
Medians were estimated using the Kaplan-Meier method. Hazard ratio and p-value were obtained from the stratified Cox regression and the stratified log-rank test, respectively.

ASH 2017

# Abstract #739: Updated Efficacy and Safety Analysis of Pollux

**Meletios A. Dimopoulos**[1], Darrell J. White, MD[2], Lofti Benboubker, MD[3*], Gordon Cook, MD, PhD[4*], Merav Leiba[5*], James Morton[6*], P. Joy Ho, MBBS, DPhil, FRACP, FRCPA, FFSc(RCPA)[7*], Kihyun Kim[8*], Naoki Takezako, MD, PhD[9], Sonali Trivedi[10*], Kaida Wu[10], Tineke Casneuf[11*], Christopher Chiu[10], Jordan Schecter[12*] and Philippe Moreau[13*]

**Figure 1: (A) Progression-free survival[a] and (B) overall response rate[b] with DRd vs Rd**




PFS, progression-free survival; ITT, intent-to-treat; ORR, overall response rate; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response.

[a]ITT population.

[b]Response evaluable population.

[c]$P$ <0.0001 for DRd versus Rd.

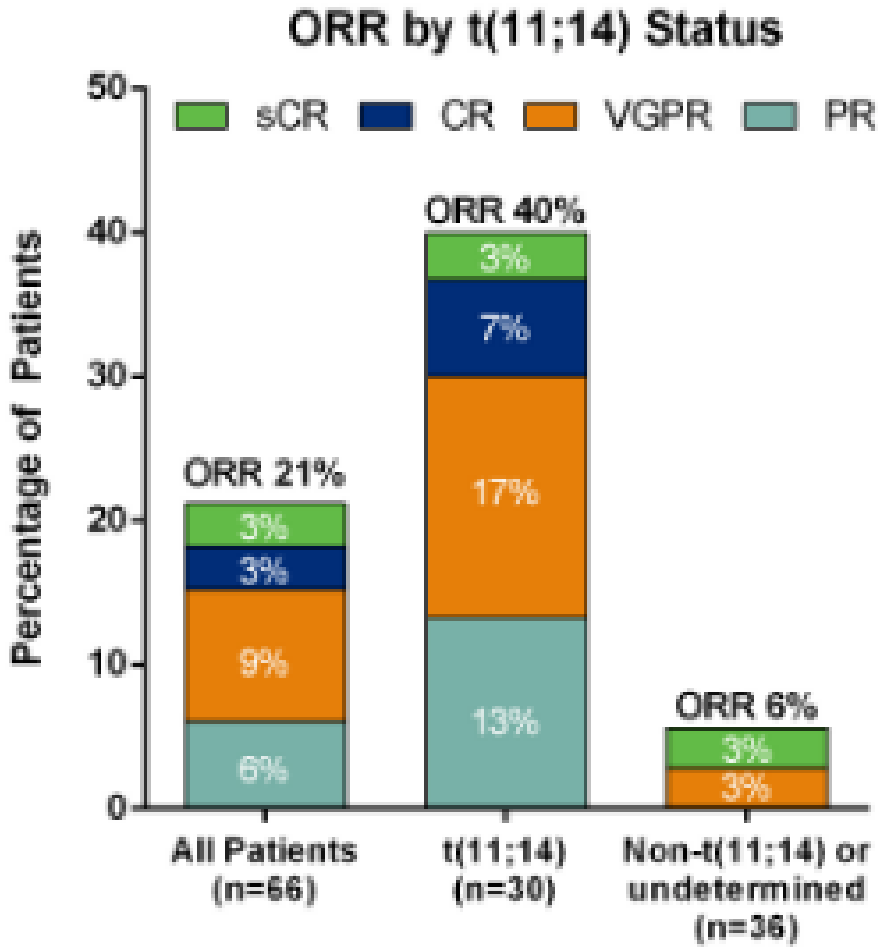
# Question

**How do you select therapy for early relapse (1-3 prior regimens)?**

**What are your “go to” options?**

# New Therapies

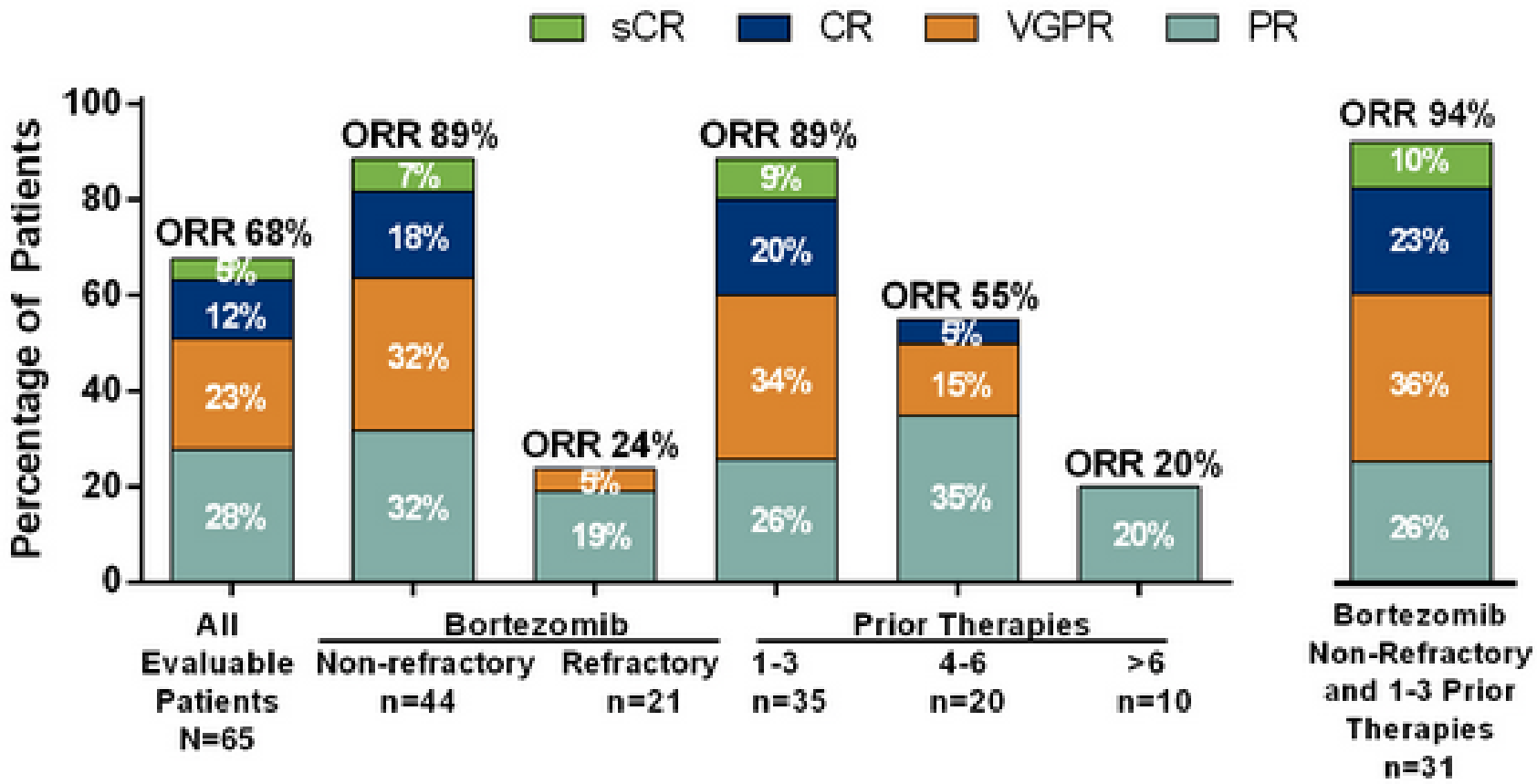
# Venetoclax Monotherapy (N=66)






Kumar S, et al. ASH 2016. Abstract 488.
Published Blood: 30: 2401-2409, November 30, 2017

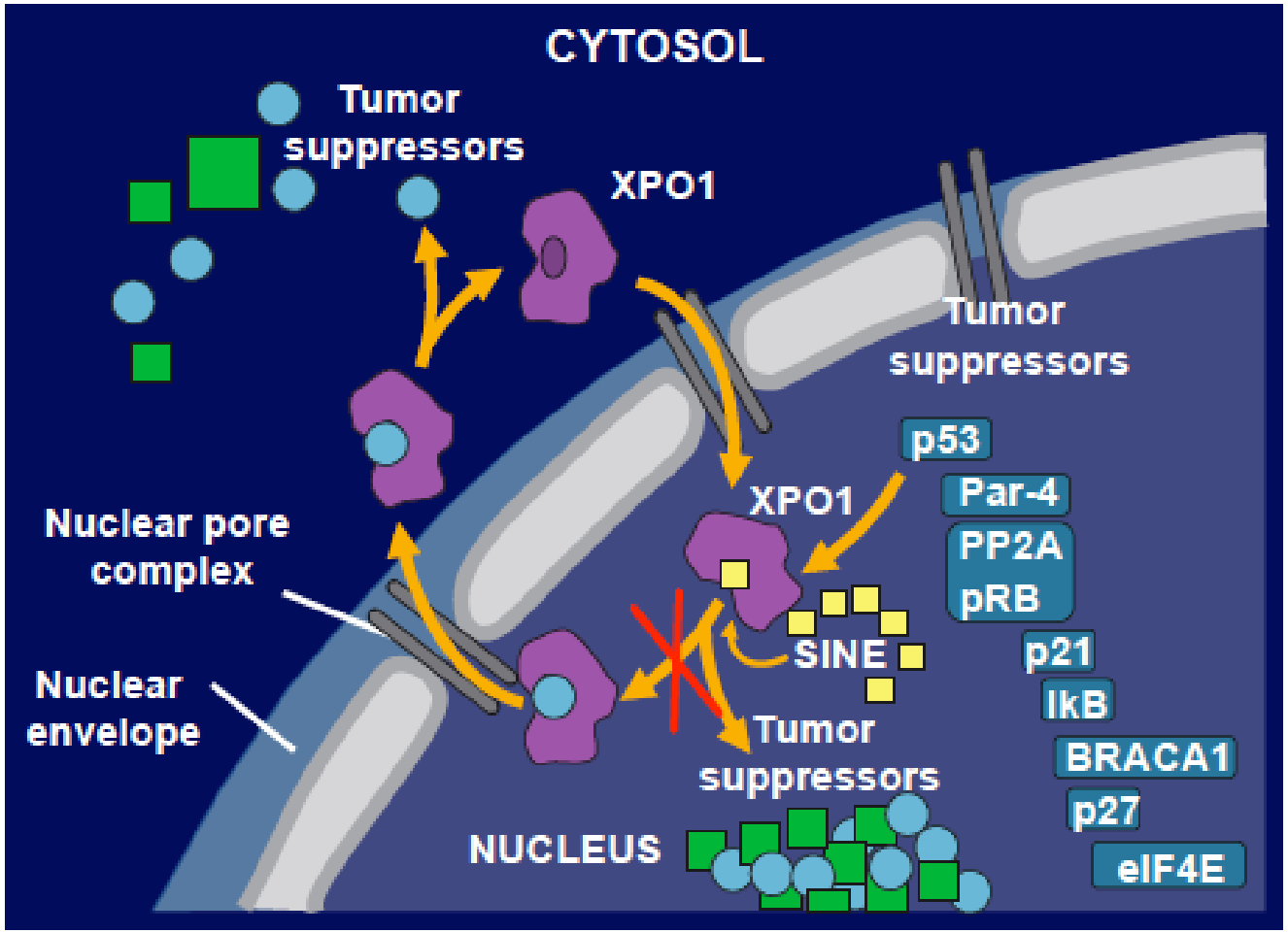
# Venetoclax + Bortezomib/Dex



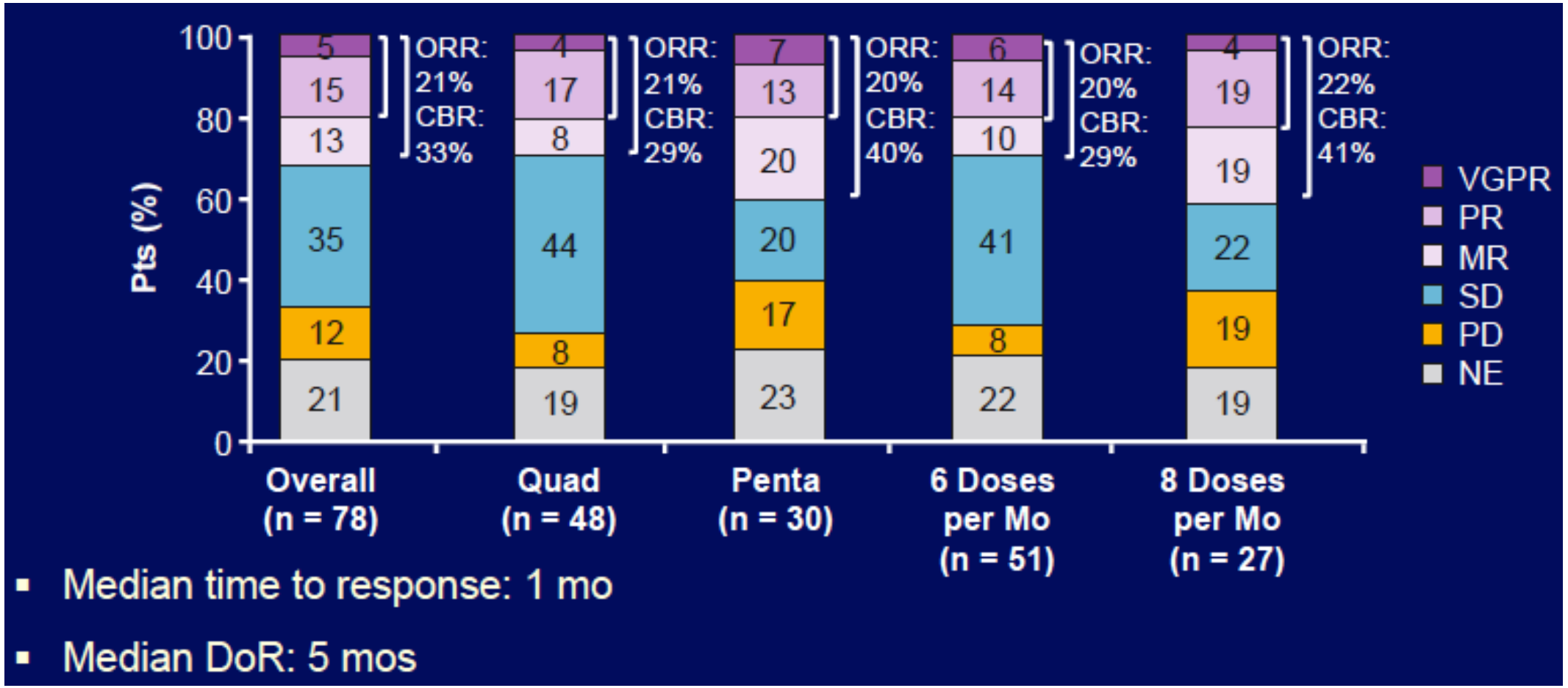



Moreau, P et al. ASH Abstract # 975, 2016.
Published Blood: 30: 2392-2400, November 30, 2017

# Selective Inhibitor of Nuclear Export®



# Phase II STORM Trial: Selinexor + Dex in R/R MM

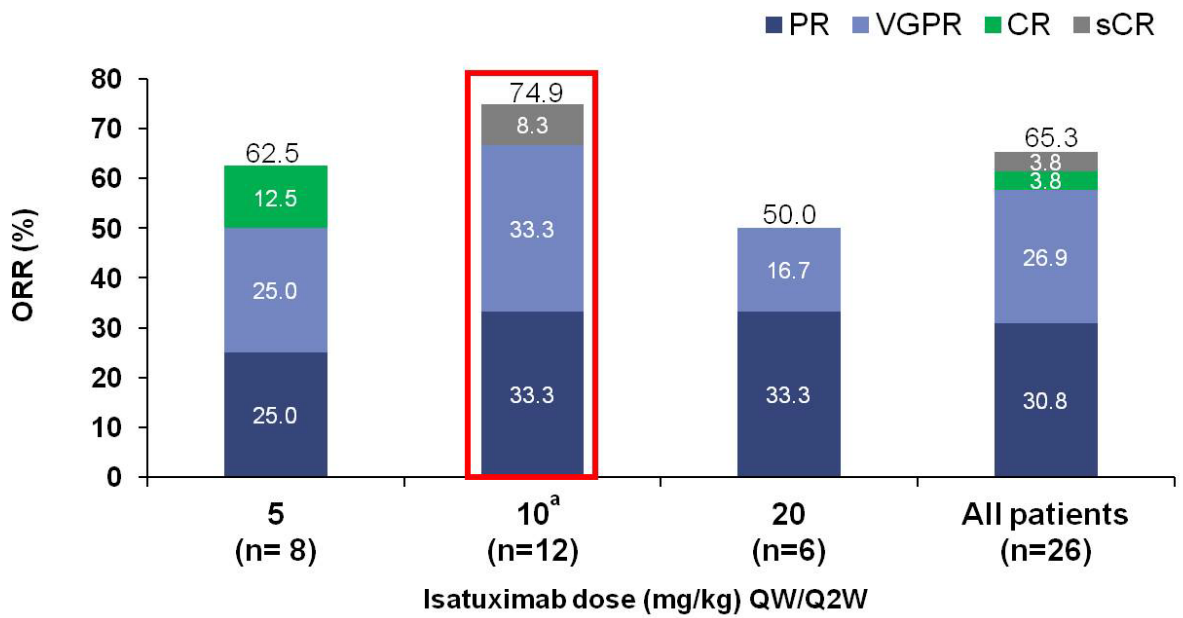





Vogl, DT et al. ASH Abstract # 491, 2016.

# Isatuximab (TCD14079): Anti-CD38 MoAb

## Response Summary (IMWG Criteria): Evaluable Patients




Five patients with high-risk cytogenetics (del17p or t[4:14]): 1 attained VGPR, 1 PR, and 1 minimal response

Patients who were Len, PI, or IMiD and PI refractory had an ORR of 60%, 50%, and 47%, respectively

**Data cut-off March 01, 2017.** [a]Data represent dose escalation cohort (n=9) and expansion cohort (n=3) combined. CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

# Anti-BCMA CAR T cell therapy: abstract #740*

- Dose escalation; phase 1
- Refractory disease ≥ 3 prior therapies (3-14)
- Fludara/Cyclo “prep”
- 21 evaluable patients
- At > 50 x $10^6$ bb2121 CAR T cells
  - ≥ CR = 56%
  - ≥ VGPR = 89%
- PFS: 71% at 9 months
- Cytokine release syndrome (CRS): 71%: 2 Gd3



*Berdeja: ASH 2017 et al (Bluebird/Celgene/NCI)

# GSK 2857916: Anti-BCMA Mab/drug conjugate: abstract #741

- Humanized IgGI anti-BCMA MoAb + auristatin-F
- Phase 1 study, Part 2 (expansion phase)
- 35 patients: ORR = 21/35 (60%)
- 6s CRs; 2 CR and 15 VGPR

# Classes of Drugs With Anti-MM Activity

| MAbs | Immuno-modulatory Agents | Proteasome Inhibitors | Cytotoxic CT | HDAC inhibitors | BCL2 inhibitor | Other |
|---|---|---|---|---|---|---|
| Daratumumab | Thalidomide | Bortezomib | Melphalan | Vorinostat | Venetoclax | Selinexor |
| Elotuzumab | Lenalidomide | Carfilzomib | Cyclophos-phamide | Panobinostat | | |
| Isatuximab | Pomalidomide | Ixazomib | PLD | ACY1215 | | CB-5093 |
| Pembrolizumab | | ONX 0912 | DCEP | | | GSK 2857916 |
| Atezolizumab | | Marizomib | BCNU | | | CAR-T cell |
| | | | Benda-mustine | | | |

# Question

**What do you feel are the most promising new therapies?**

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