Best of ASH 2017

Brian GM Durie, MD

Thursday, January 11, 2018

International Myeloma Working Group
A RESEARCH DIVISION OF THE IMF

imf
International Myeloma Foundation

ASH Overview 2017

Total myeloma abstracts: 981

Important/Interesting:

oral ~40

posters ~60

} **100**

Which abstracts impact patient care for 2018?

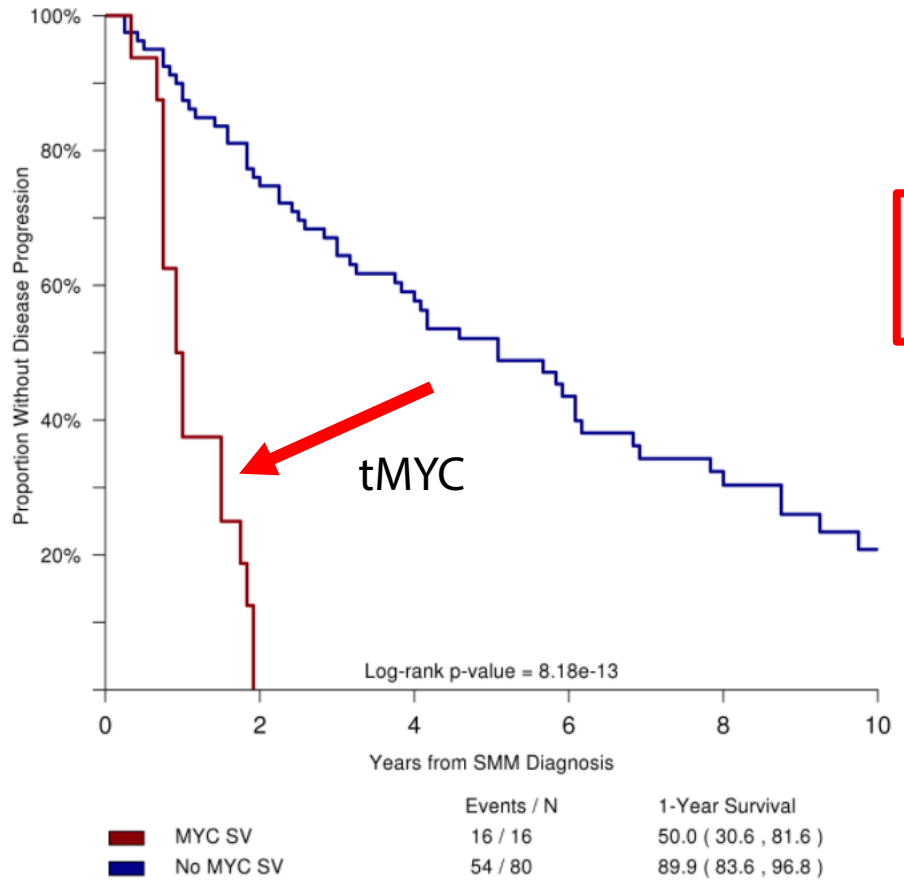
Main Topics for Discussion

- Early disease
- Treatment of SMM
- Frontline therapy
- Maintenance
- Relapse therapy
- New therapies

ASH 2017

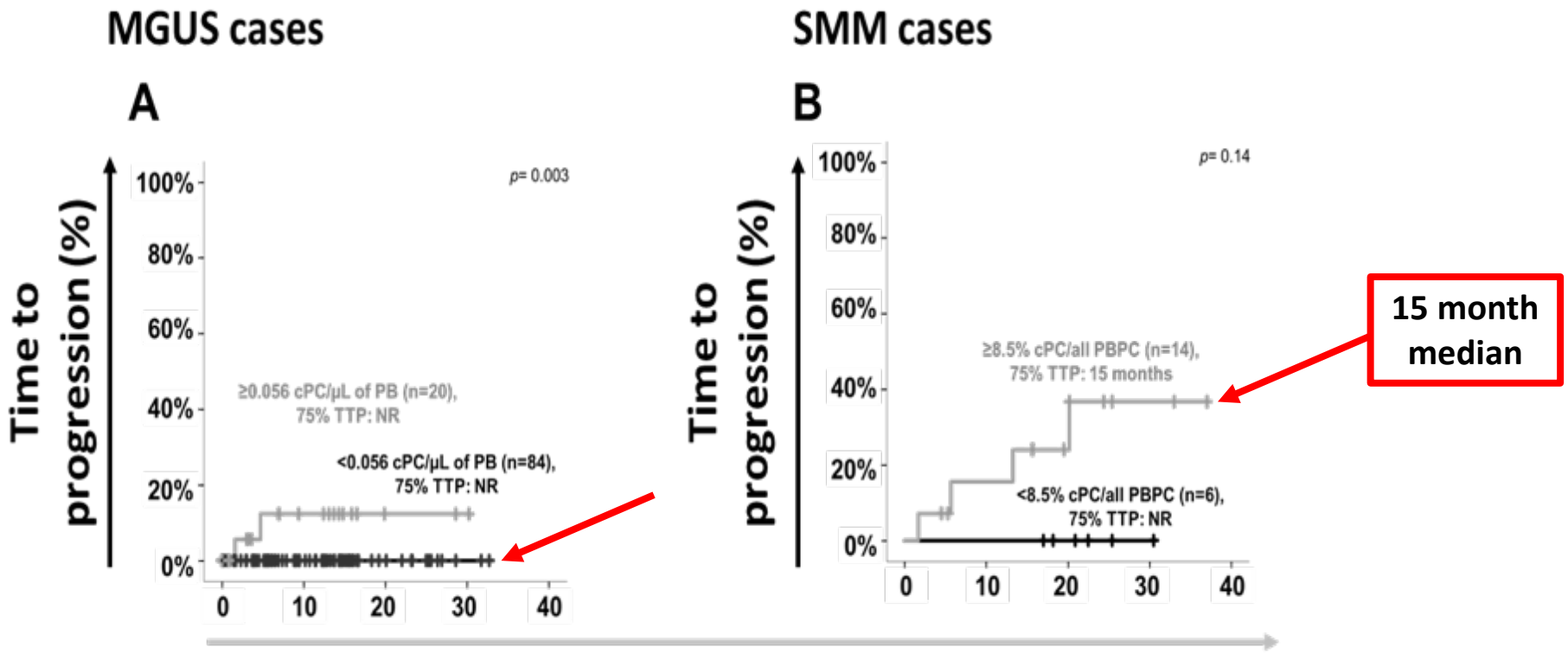
Abstract #393: Impact of MYC Translocations in Smoldering Myeloma

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]

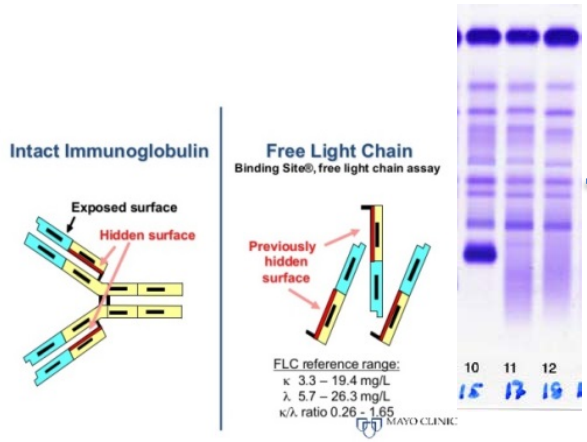


Rapid progression to myeloma

Impact of Plasma Cells in the Blood



iStopMM: largest population-based study of MGUS/SMM



All Icelanders > 40 years
N=148 000

4500-5000 with MGUS/SMM

Without MGUS/SMM

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

R

No further work-up
N=1500

IMWG Recommendations
N=1500

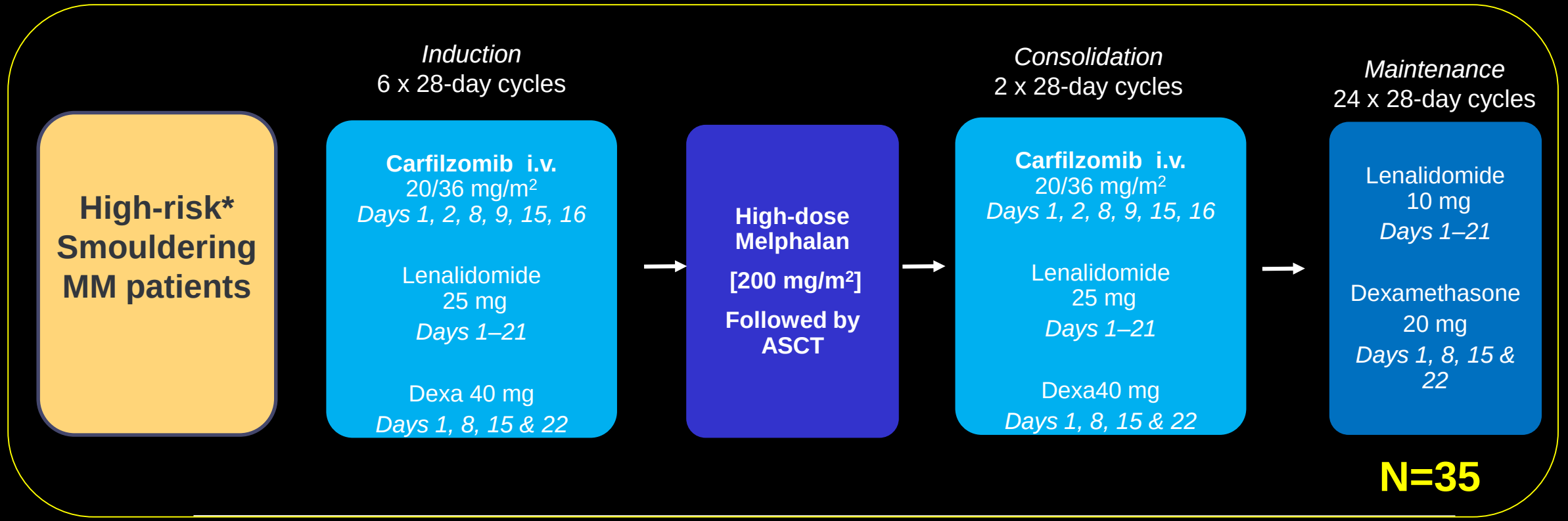
Intervention arm
N=1500

KRd for HRSMM

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)

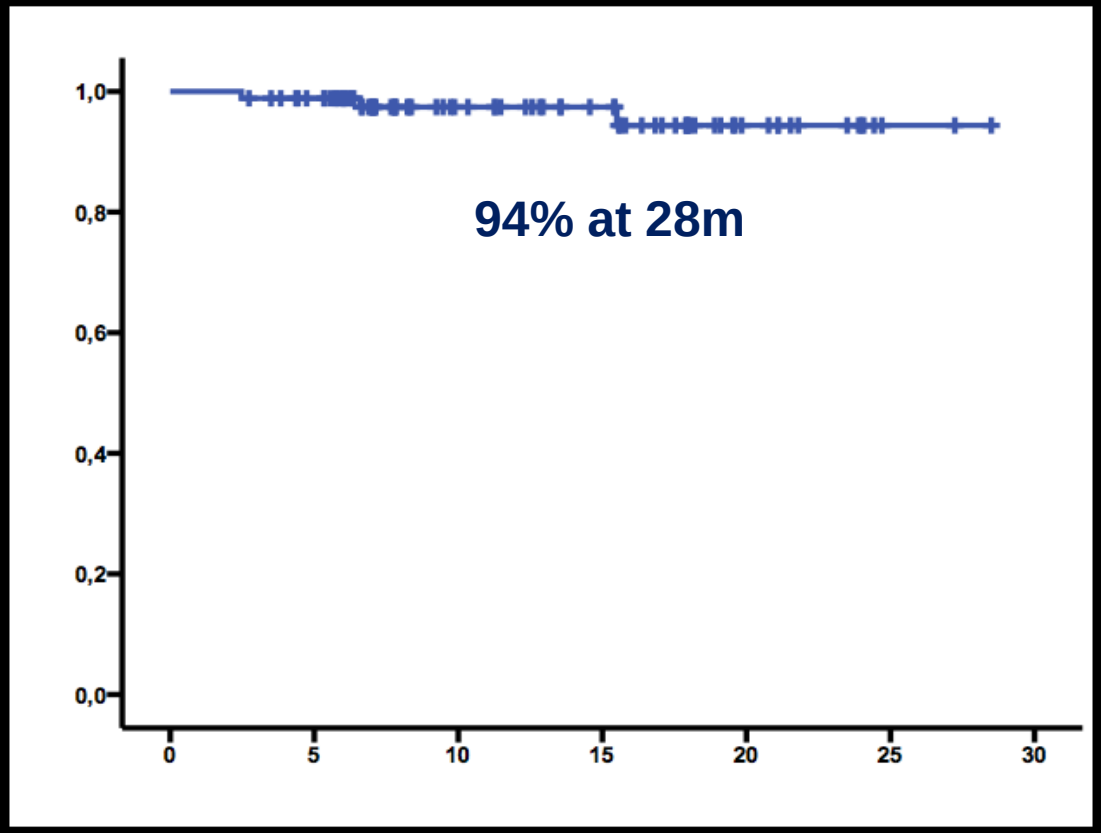
	Induction (KRdx6) N = 35	HDT/ASCT N = 35	Consolidation (KRdx2) N = 35
≥CR	**49%**	**62%**	**74%**
VGPR	37%	23%	20%
PR	14%	14%	6%
MRD-negative	**26%**	**47%**	**62%**

GEM-CESAR Outcomes

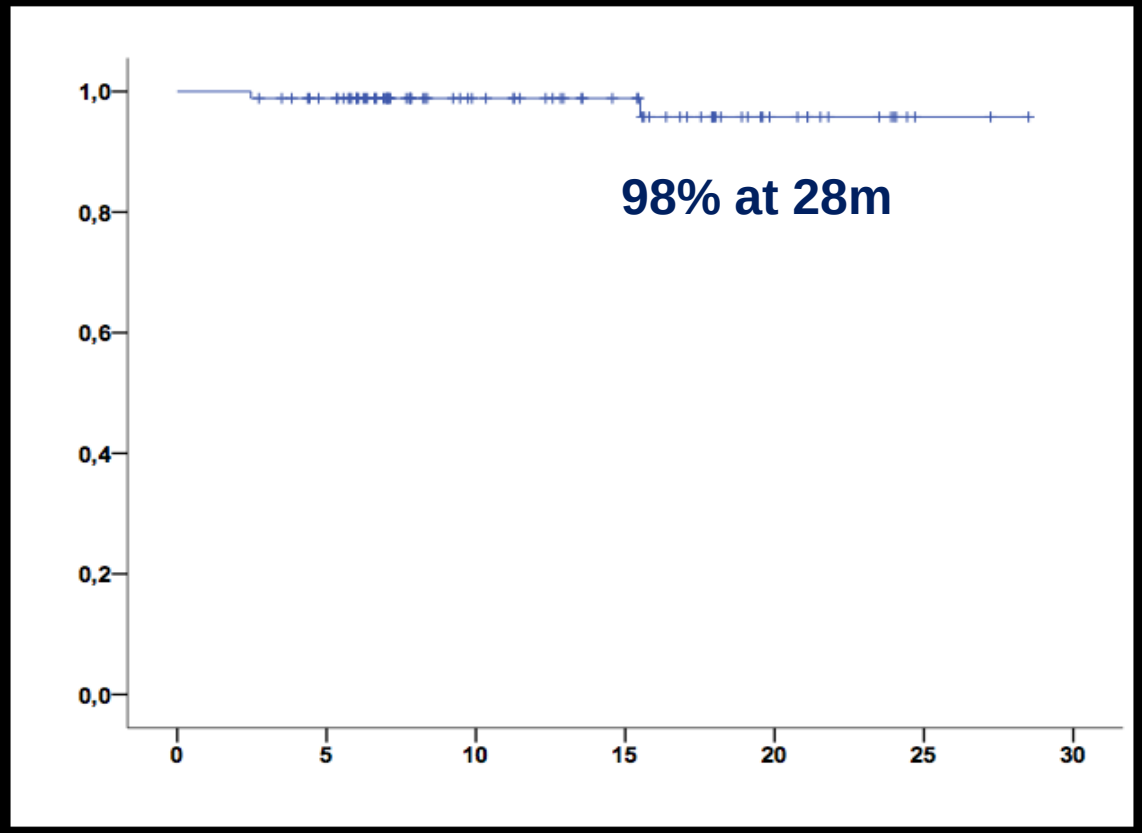
PFS

Median follow-up: 10 (1-28)

OS



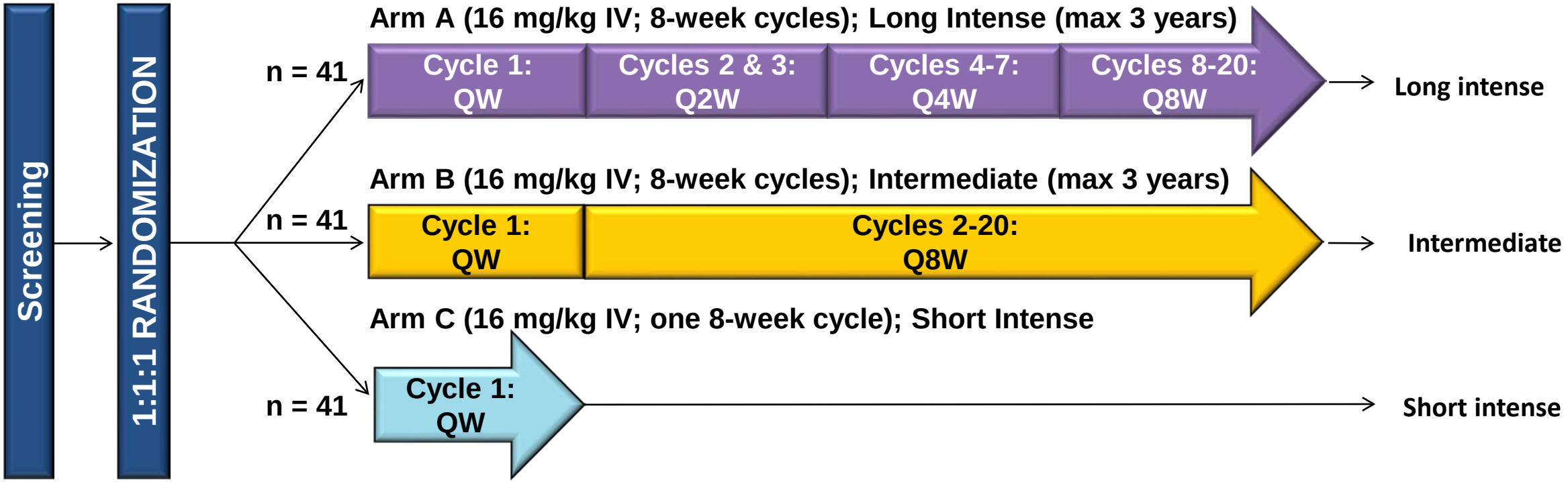
Two patients experienced relapse from CR before the end of induction and they proceeded to subsequent therapy



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…

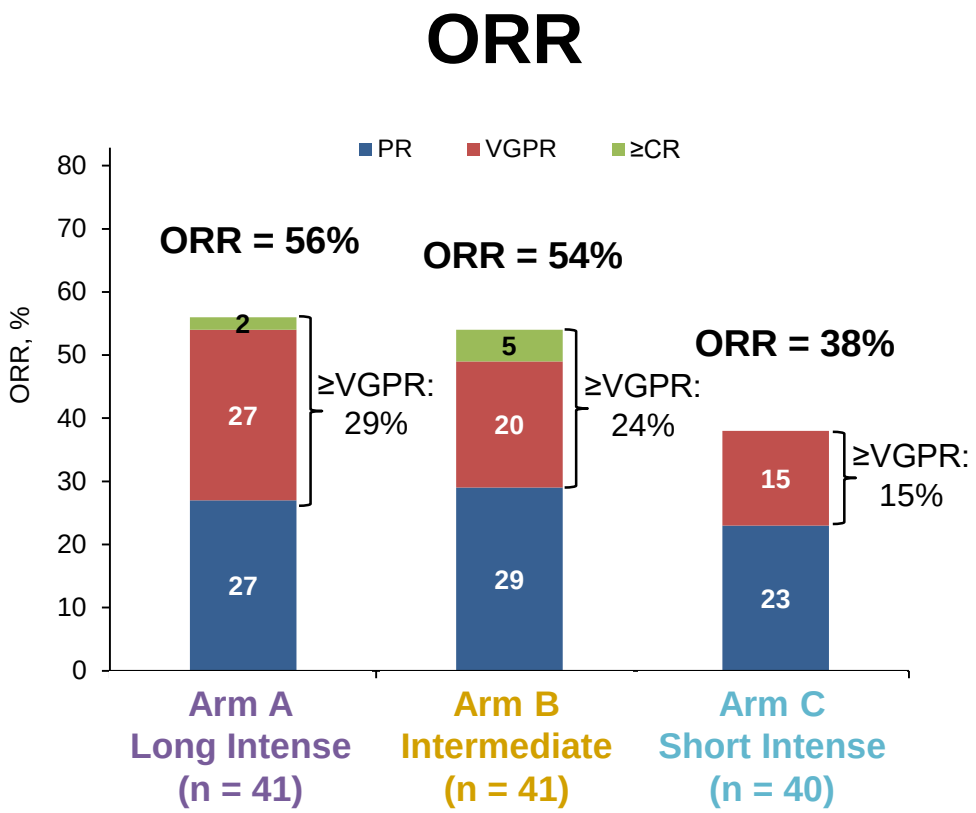
CENTAURUS Study Design: Daratumumab in SMM



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.

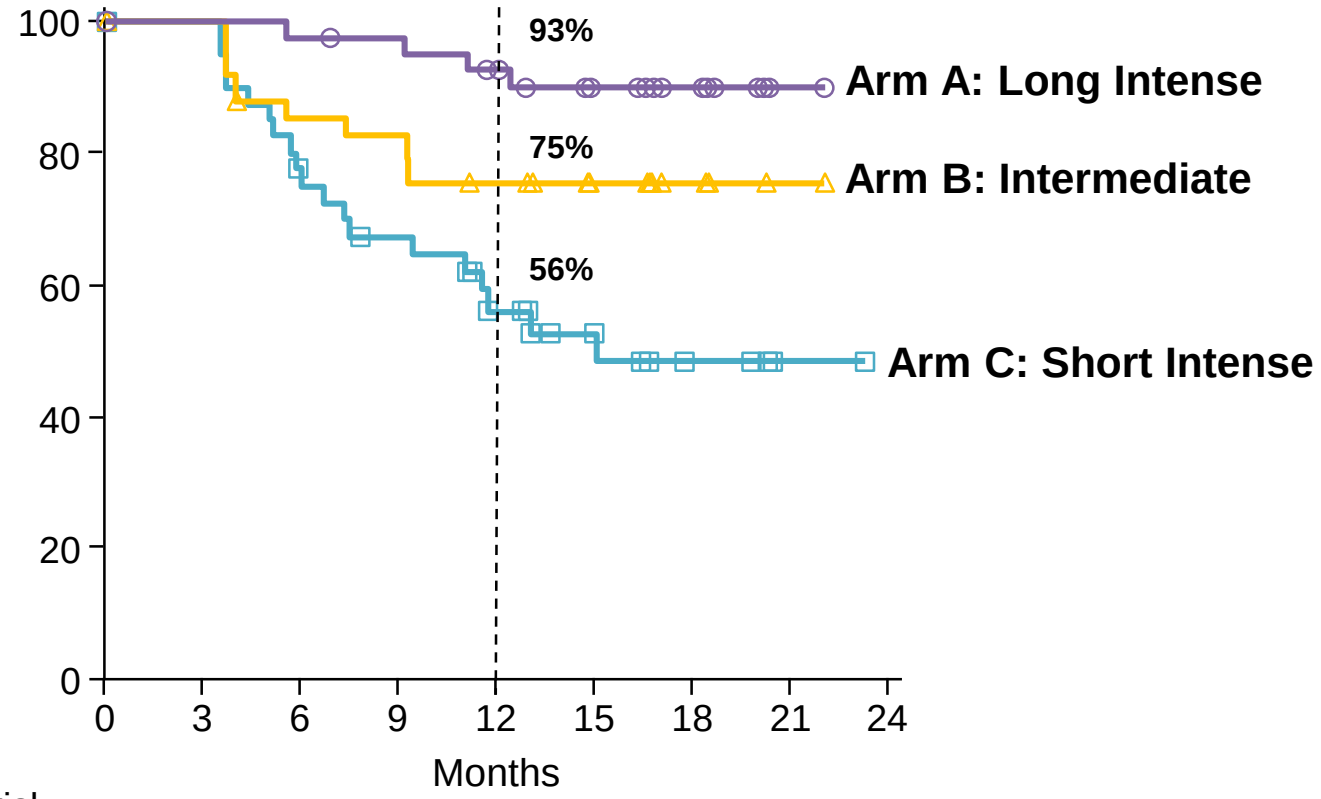
1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

CENTAURUS: Efficacy



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

CENTAURUS: PFS



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

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

Current Status

Two approaches to early/smoldering disease:

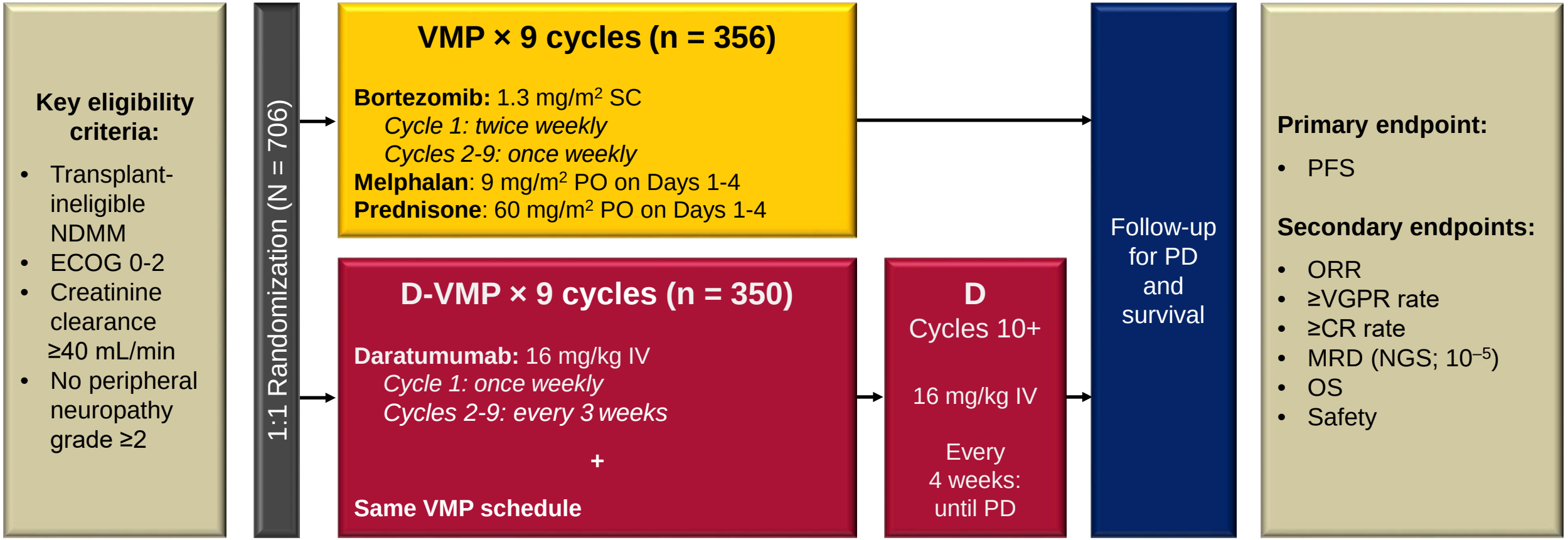
- **Attempted “Cure”**
- **Control**

Further studies and follow up required

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)

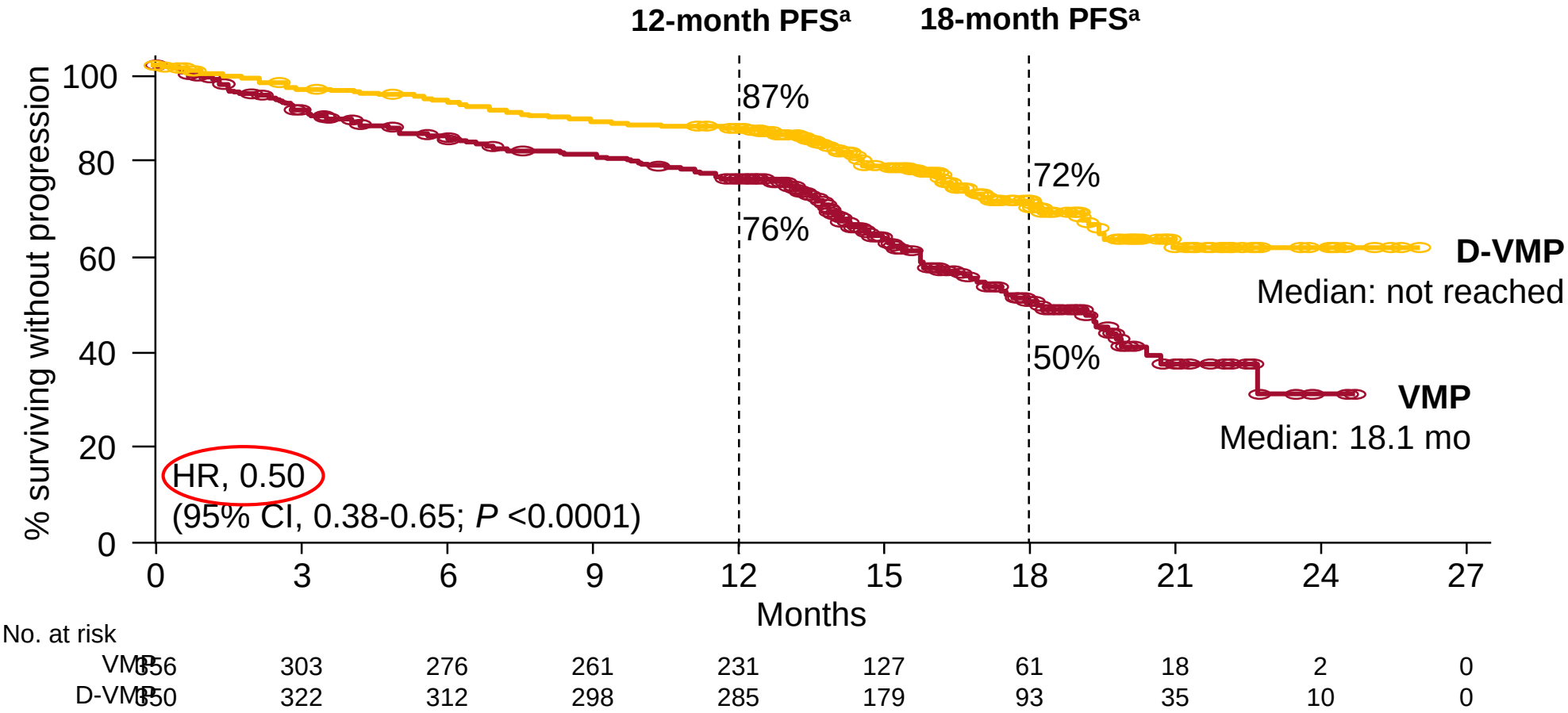
- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

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.

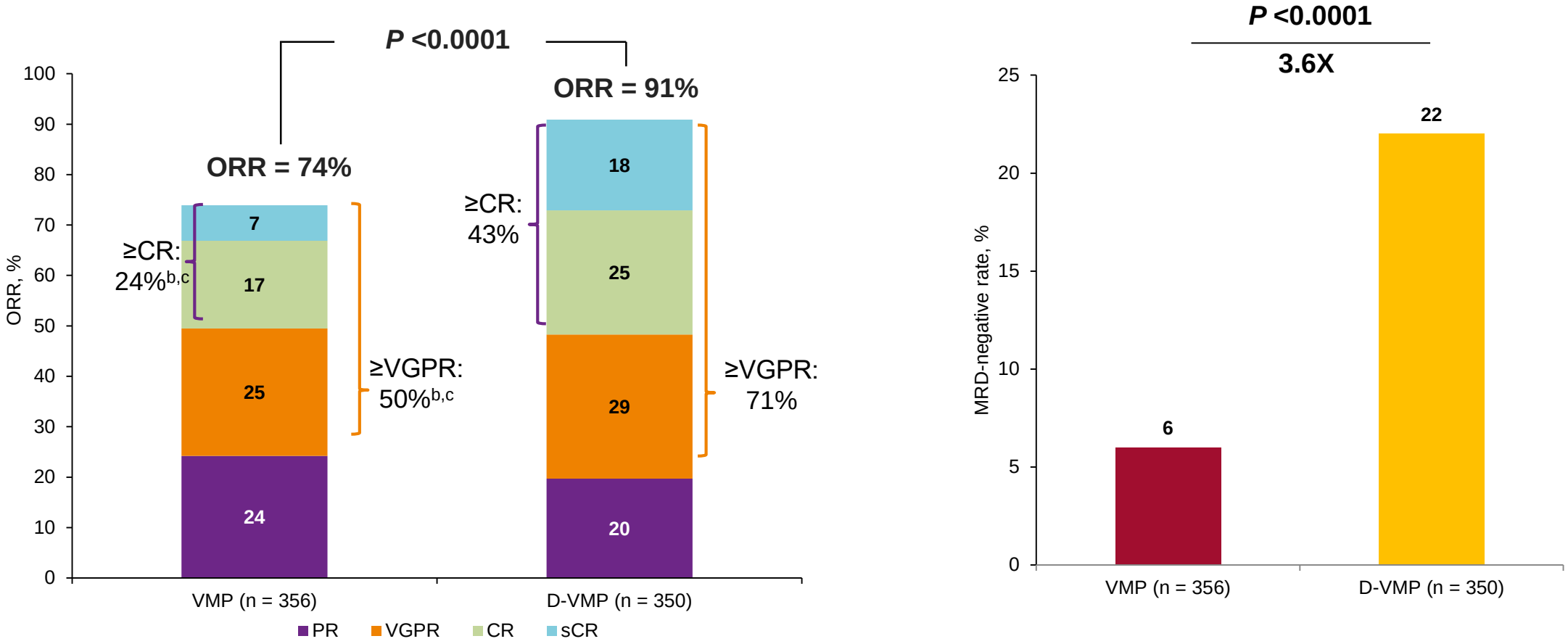
Efficacy: PFS



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 the new standard of care?

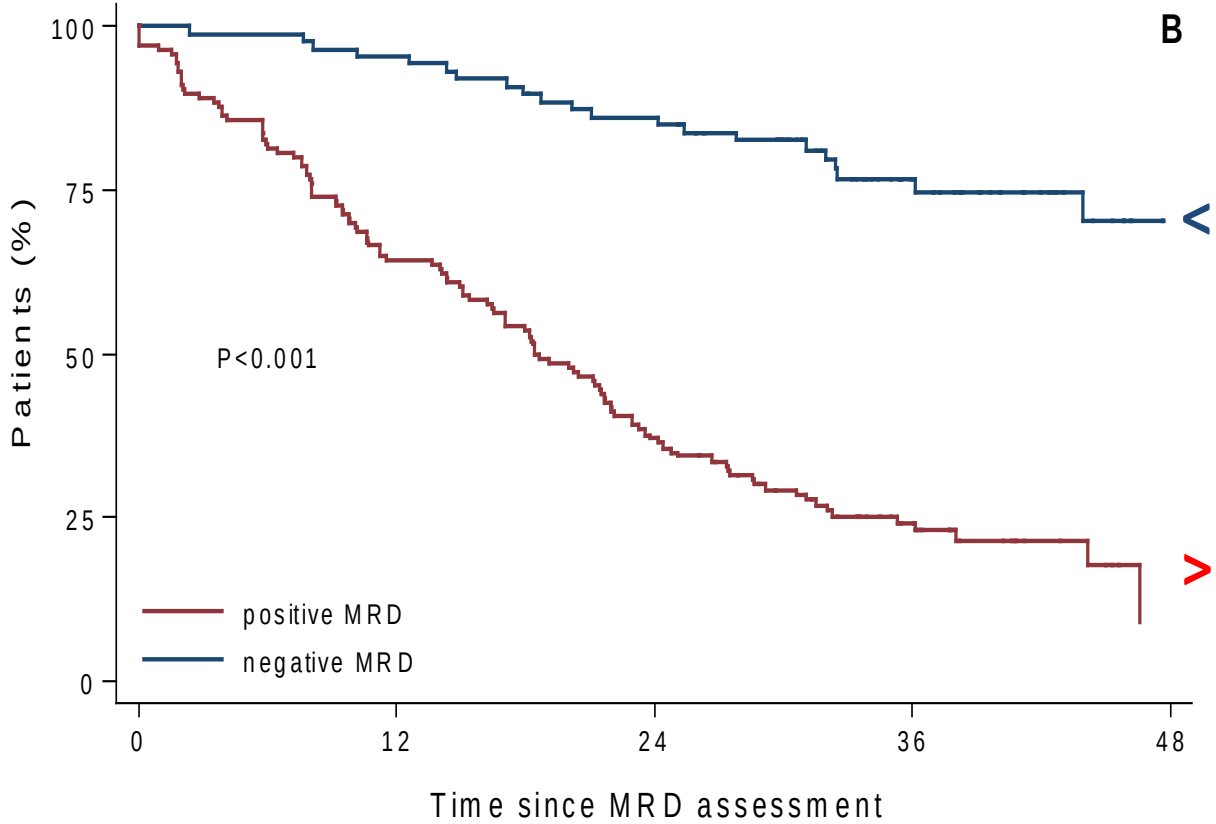
OR

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

[doublets for elderly/frail]

What about frontline in the transplant setting?

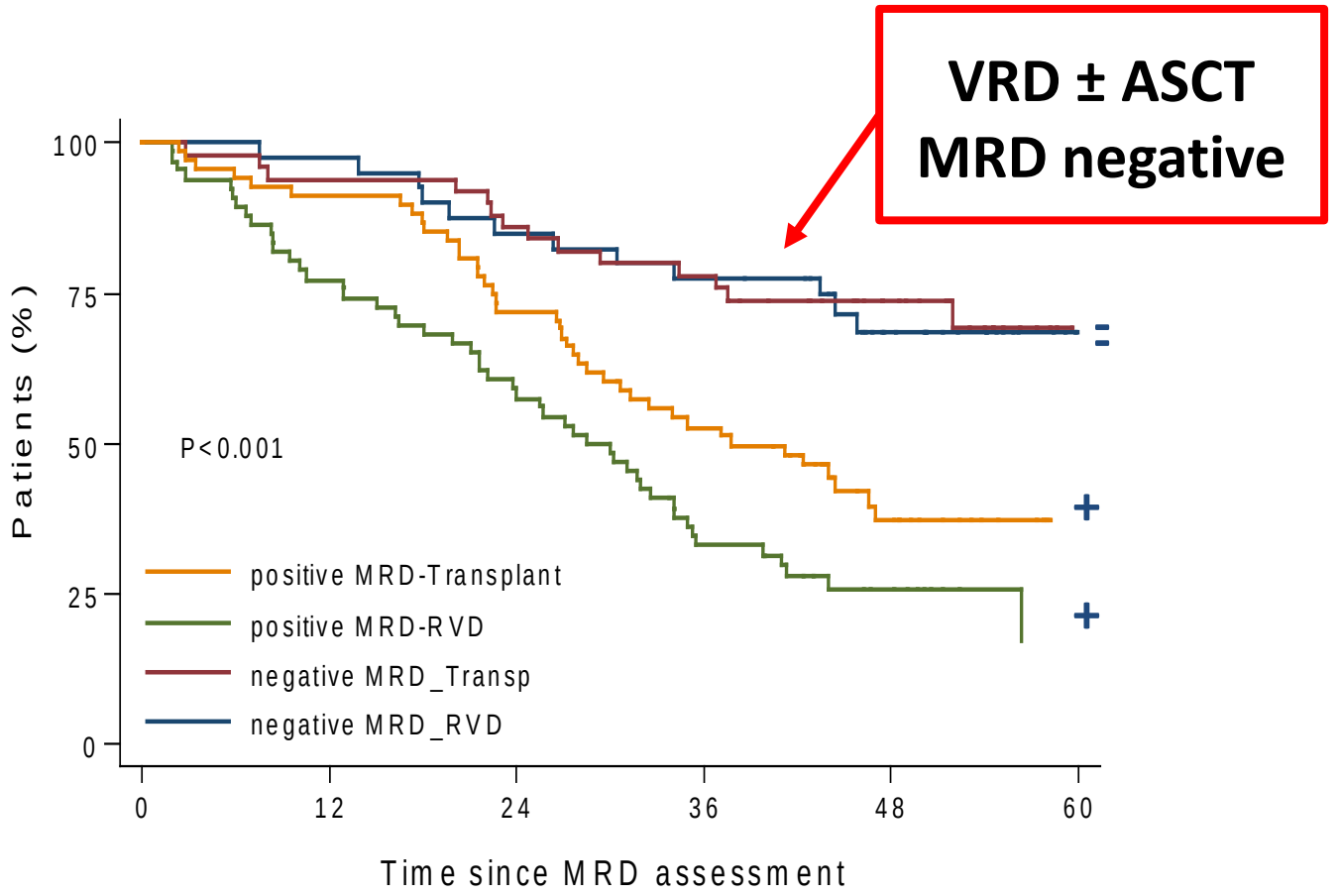
IFM 2009 Trial: VRd ± ASCT



< 10^{-6} MRD negative

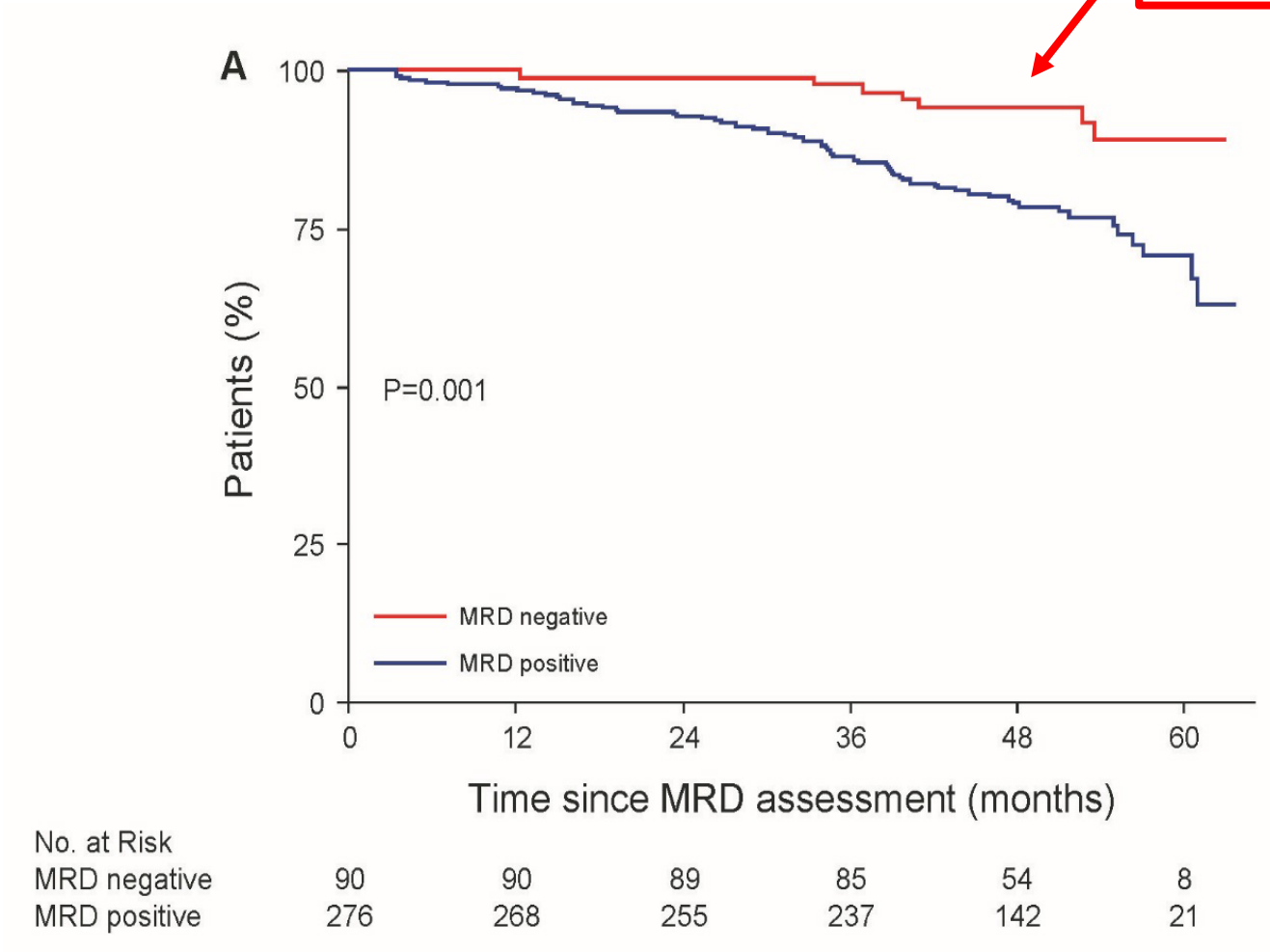
> 10^{-6} MRD positive

Impact of treatment arm?

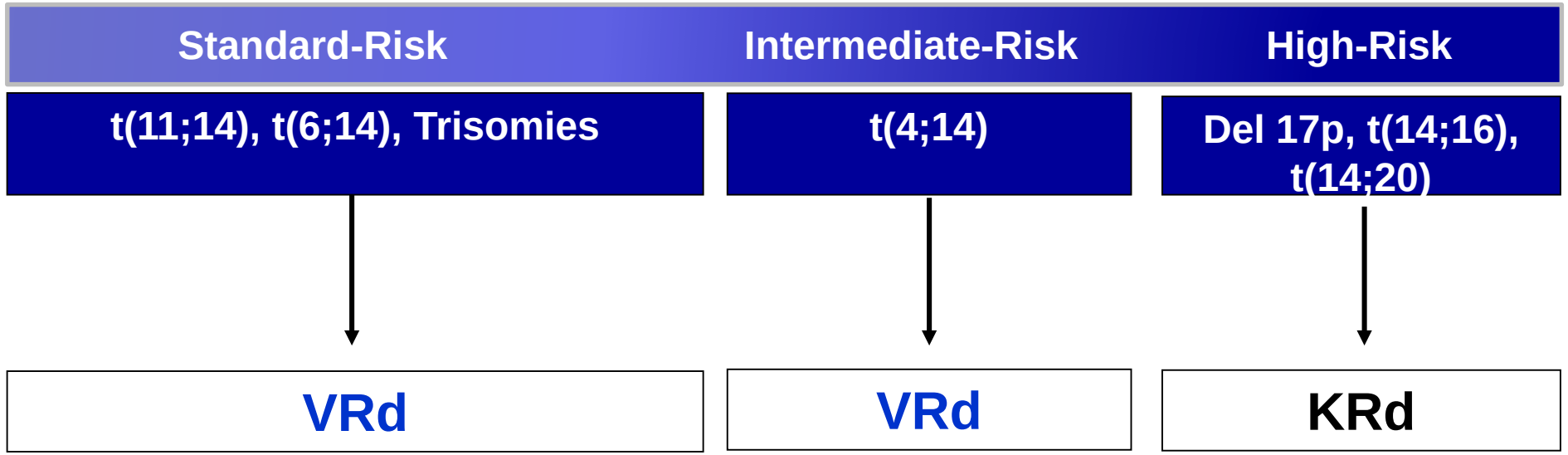


N at risk						
positive MRD-Transplant	68	62	49	35	15	1
positive MRD-RVD	66	51	38	21	11	2
negative MRD_Transp	50	47	43	38	23	4
negative MRD_RVD	40	39	34	31	17	1

Overall Survival



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.

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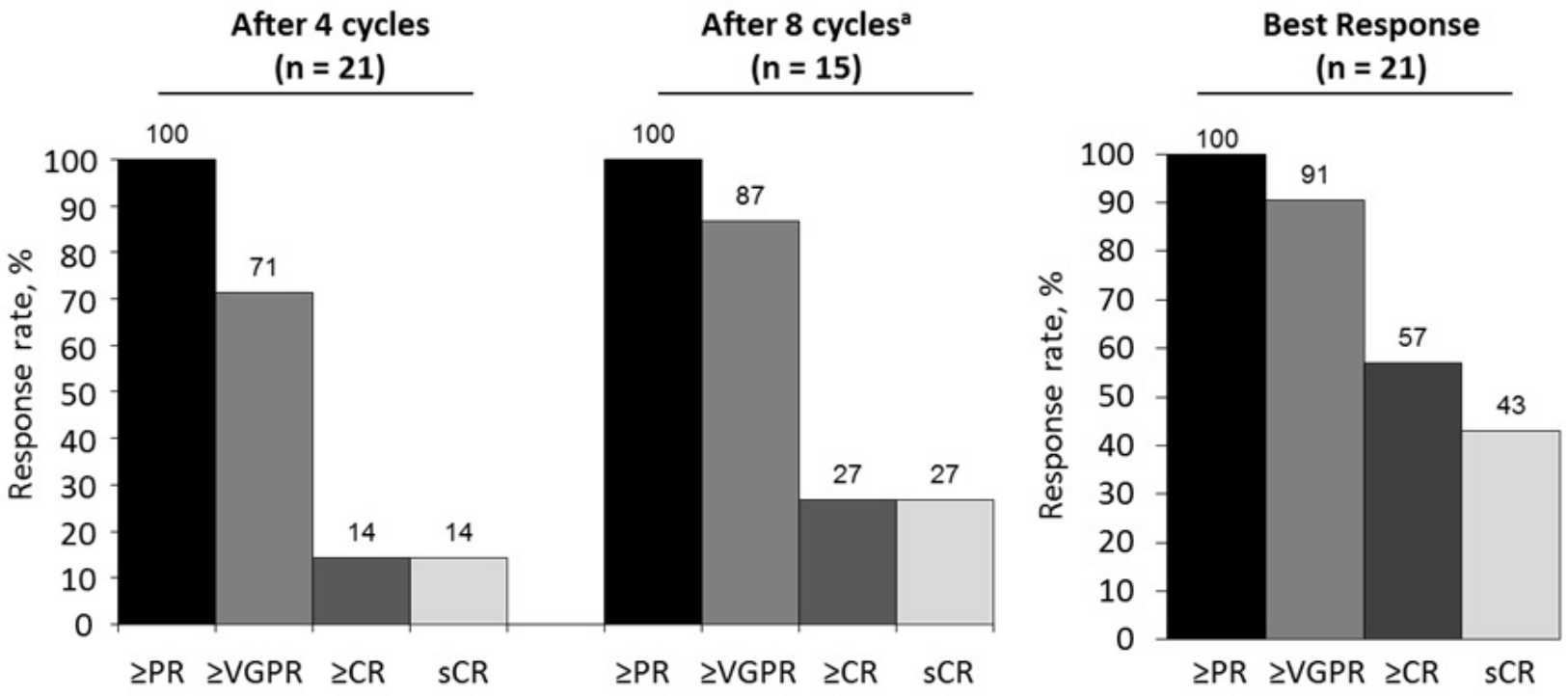
Abstract #3110: Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Newly Diagnosed Myeloma

Best confirmed response rates with DARA+KRd



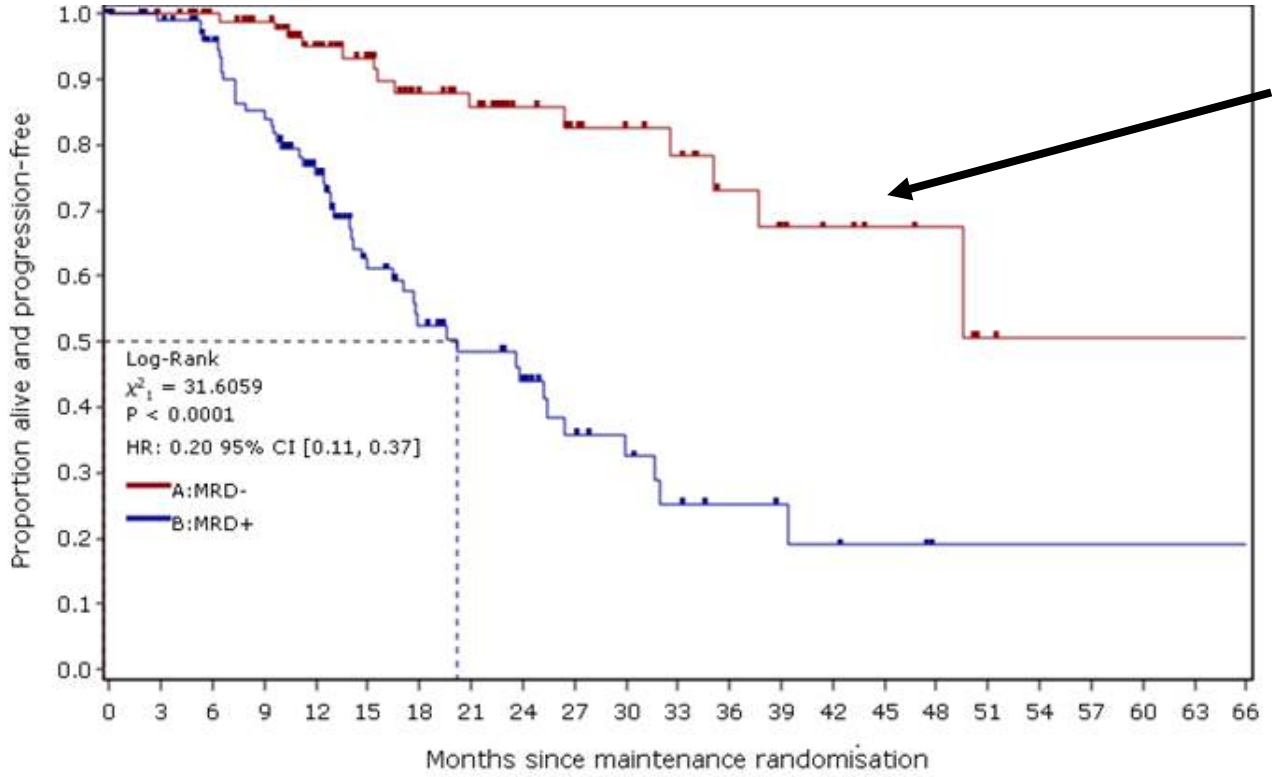
KRd + Dara is effective and safe

Maintenance Recommendations

ASH 2017

Abstract #904: Minimal Residual Disease in the Maintenance Setting

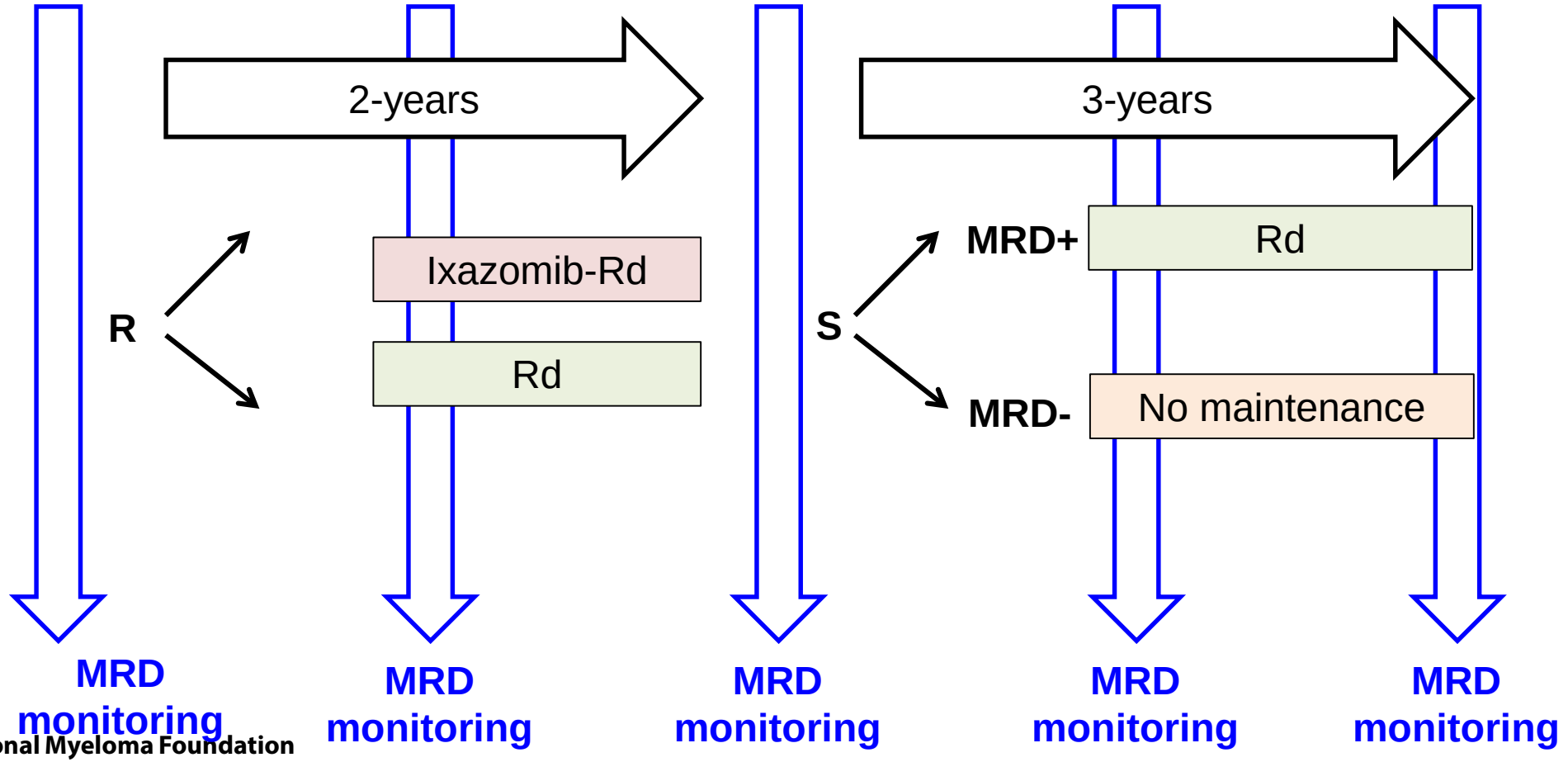
Ruth M De Tute, BSc, MSc[1*], *David Cairns, BSc, MSc, PhD*[2*], *Andy Rawstron, PhD*[3*], *Charlotte Pawlyn, BA, PhD, MBBChir, MRCP, FRCPath*[4], *Faith E. Davies, MD*[5,6], *John R Jones, MD*[6*], *Martin F Kaiser, MD*[6], *Anna Hockaday*[2*], *Alina Striha, MSc*[2*], *Rowena Henderson, PhD*[2*], *Gordon 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*]



Achievement of MRD negative on LEN maintenance

Protocol Example

GEM2014MAIN: role of MRD in optimizing duration of maintenance



Early Relapse Management

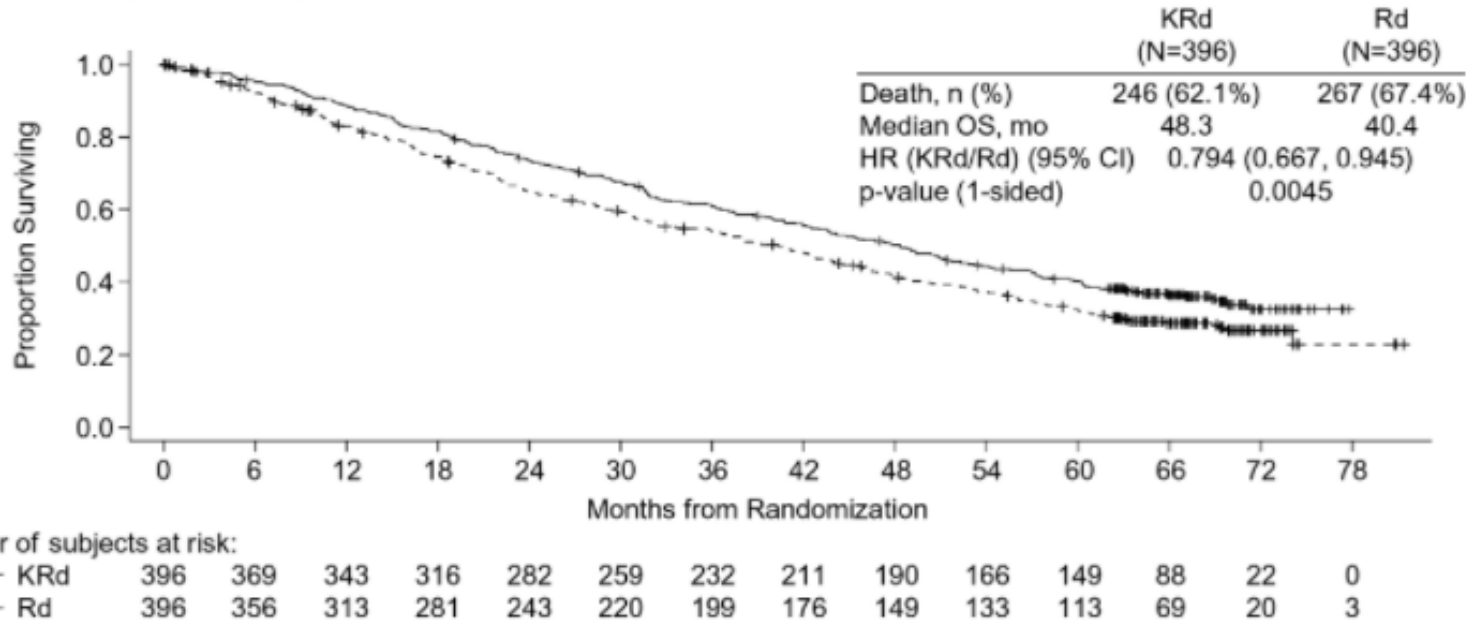
ASH 2017

Abstract #743: Relapsed/Refractory Multiple Myeloma (RRMM) Treated with Carfilzomib, Lenalidomide and Dexamethasone (KRd) Versus Lenalidomide and Dexamethasone (Rd)

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



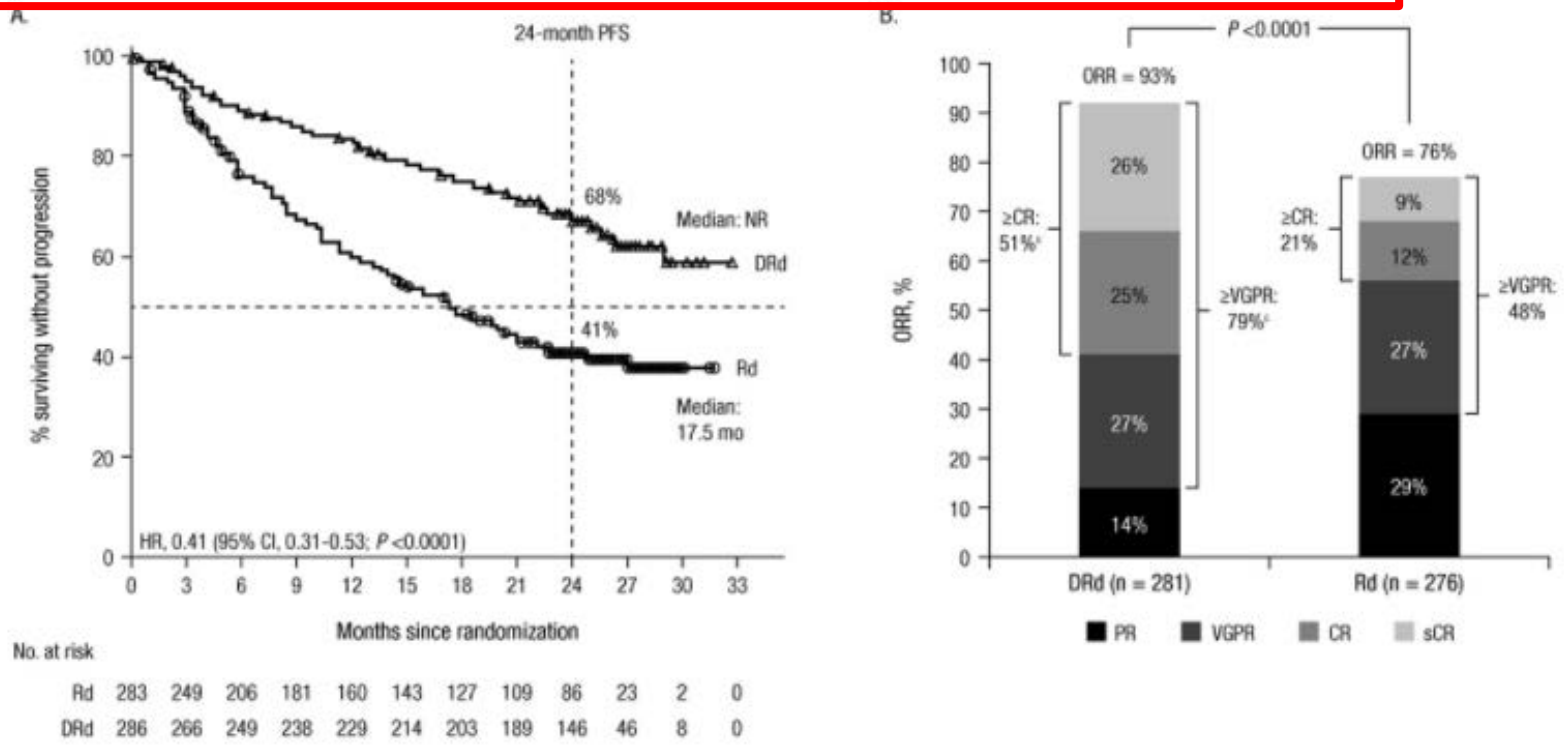
8 month survival benefit with KRd versus Rd

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

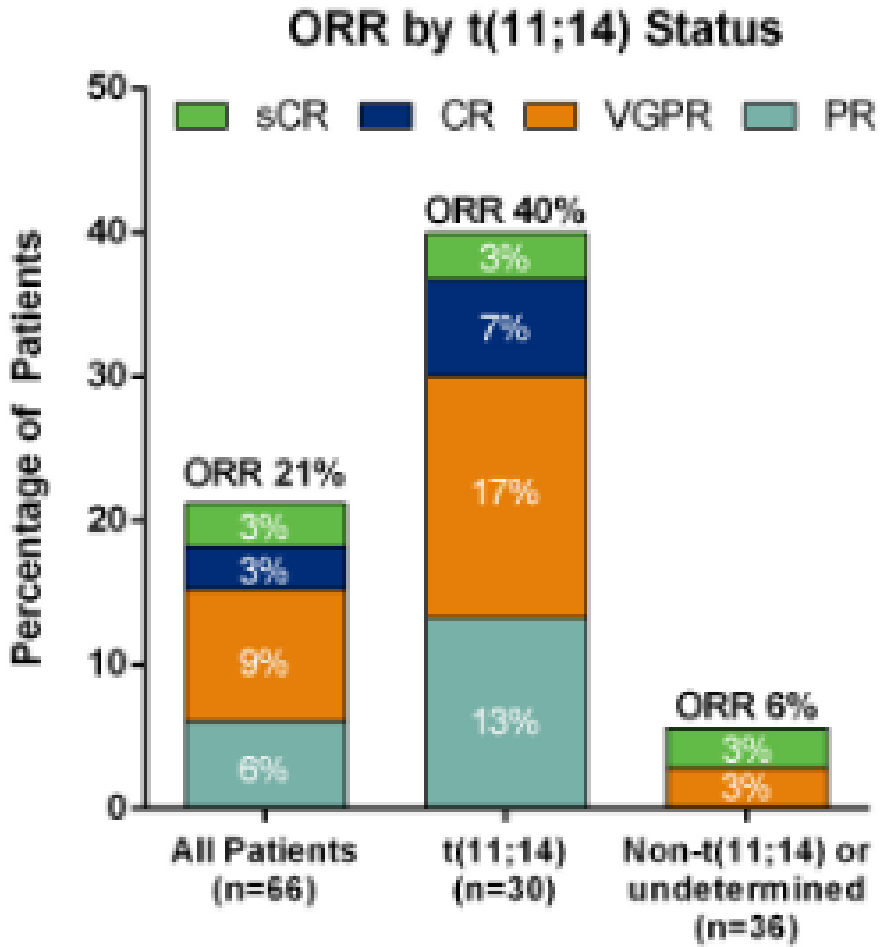


Abstract #838: subcutaneous Darzalex over 3-5 minutes

Abstract #507 & 508: Darzalex effective in amyloidosis

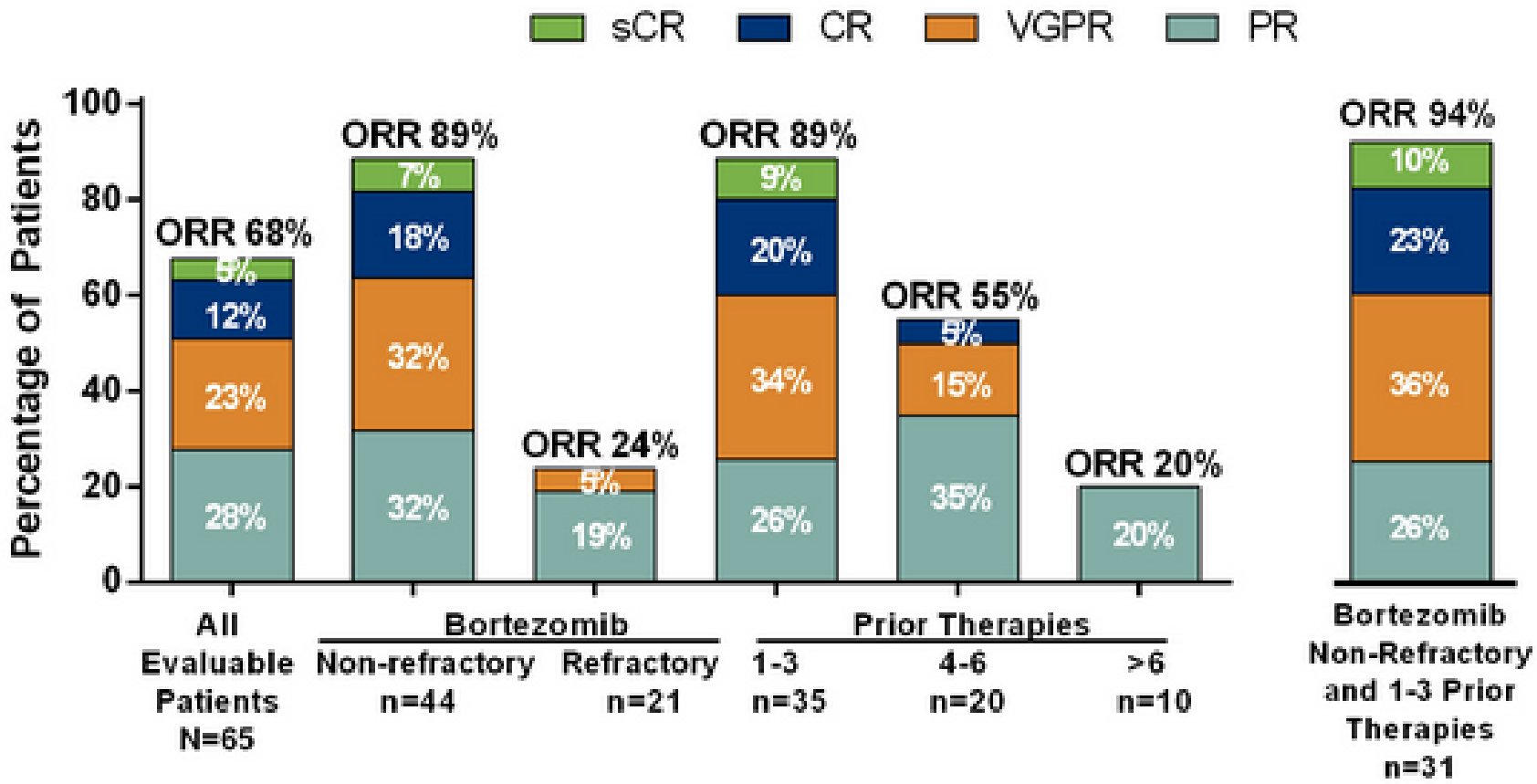
New Therapies

Venetoclax Monotherapy (N=66)



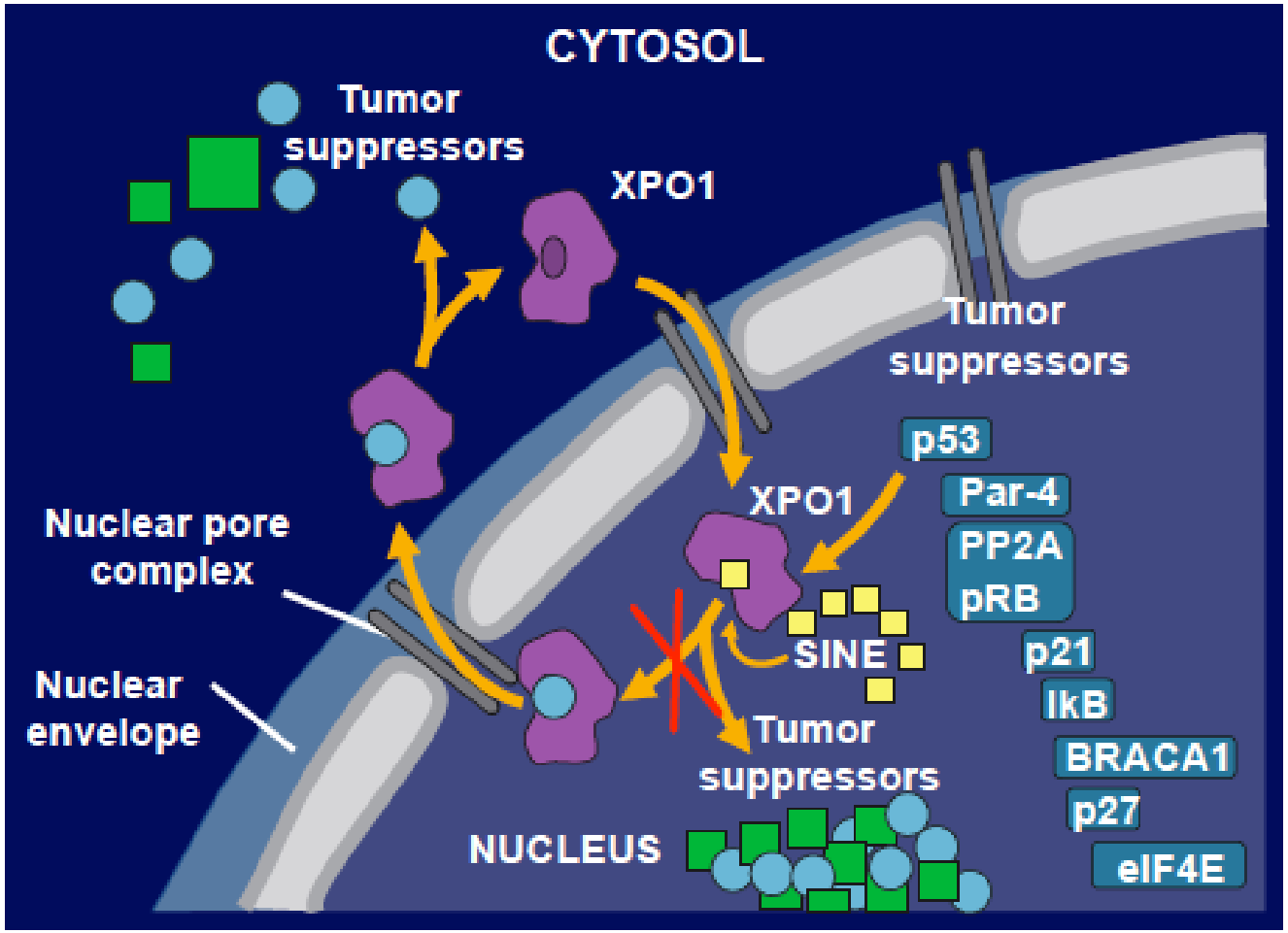
Kumar S, et al. ASH 2016. Abstract 488.
Published Blood: 30: 2401-2409, November 30, 2017

Venetoclax + Bortezomib/Dex

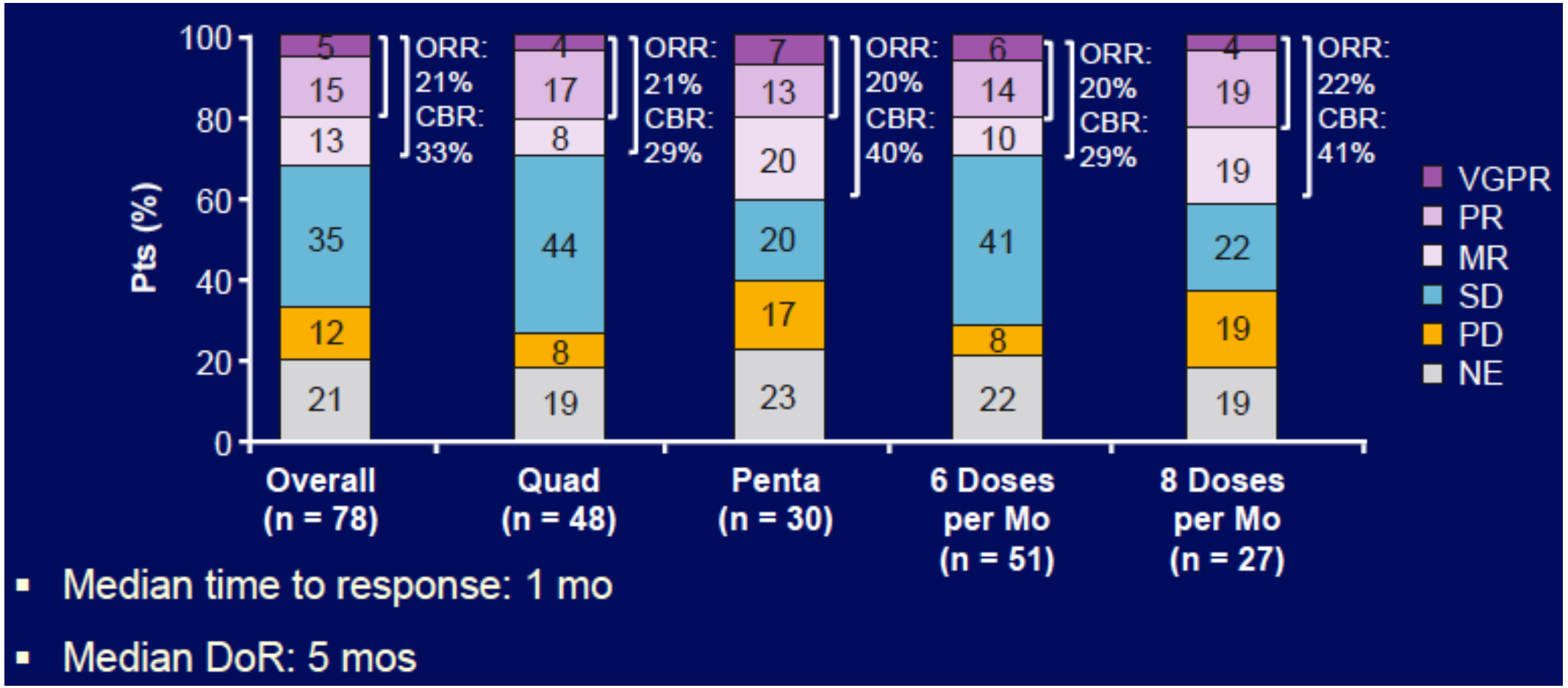


Moreau, P et al. ASH Abstract # 975, 2016.
Published Blood: 30: 2392-2400, November 30, 2017

Selective Inhibitor of Nuclear Export®



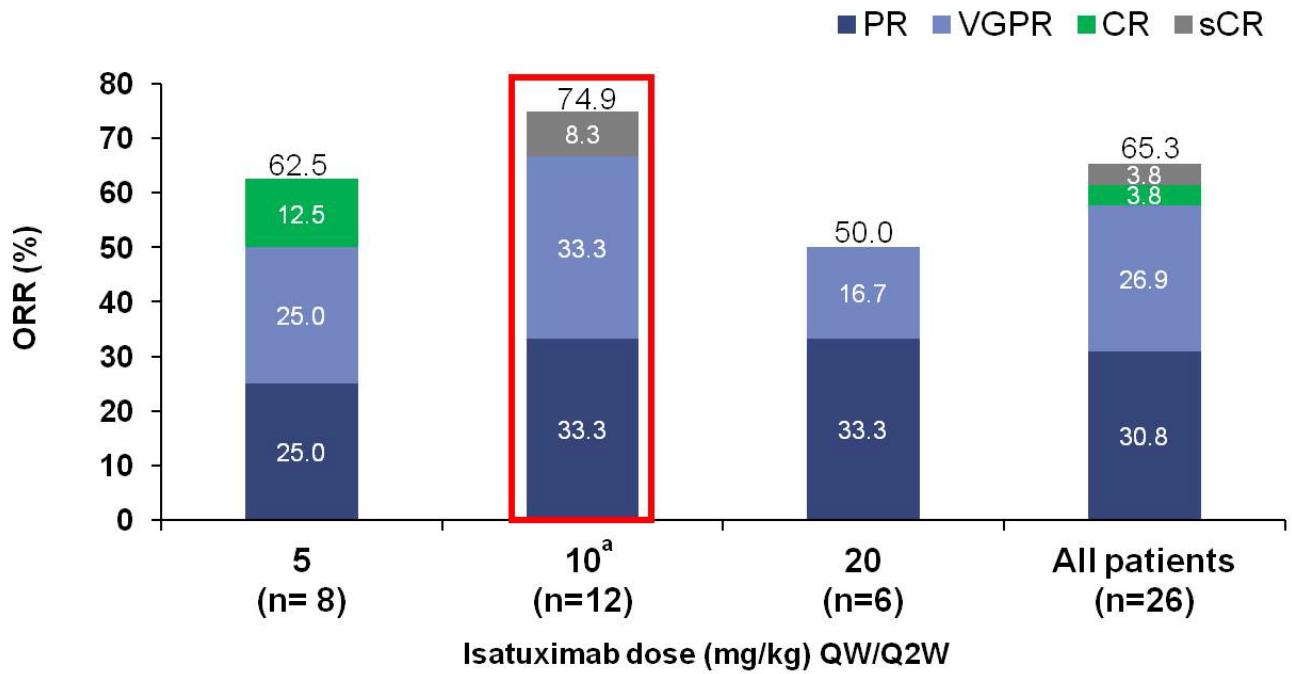
Phase II STORM Trial: Selinexor + Dex in R/R MM



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

Isatuximab (SAR650984): Anti-CD38 MoAb

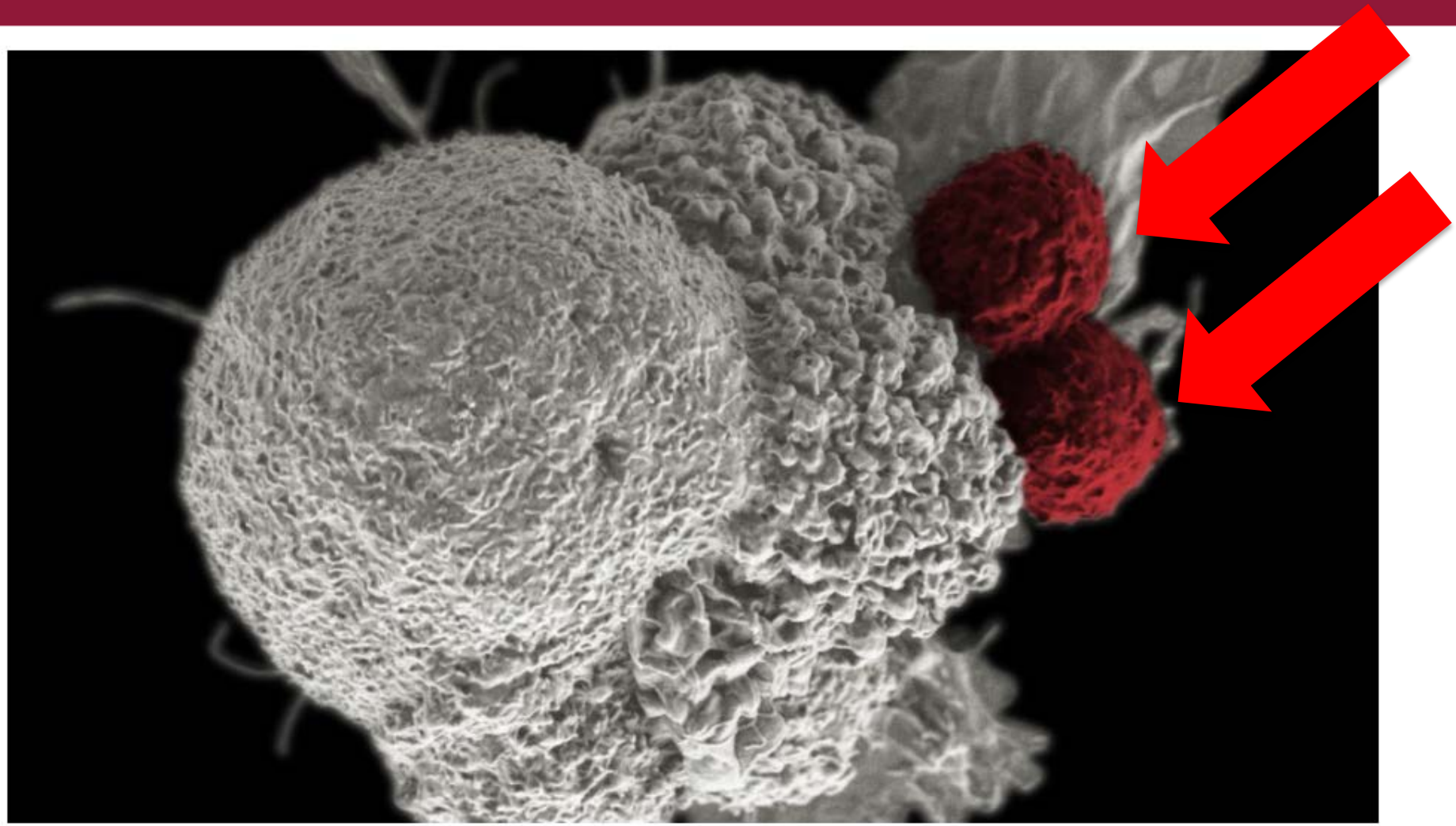
Response Summary (IMWG Criteria): Evaluable Patients



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

Two CAR T Cells Attacking Cancer Cell



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)

New Development Post-ASH

December 21, 2017

- Janssen Biotech, Inc. announced a worldwide collaboration and license agreement with Legend Biotech (a Nanjing, China-based entity*)
- The deal is to develop, manufacture and commercialize anti-BCMA CAR T-cell therapy
- The LCAR-B38M product is currently accepted for review by the Chinese FDA (CFDA)

*ASH abstract #3115: brief update– pictures of disappearing lesions, one MRD negative and one VGPR noted: no dose limiting toxicities

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%)**
- **6 sCR; 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			

“Clinical Pearls”

Abstract #	
#903 (UK trial)	Levofloxacin (Levaquin®) antibiotic can reduce infections in first 12 weeks
#1855 (US sites)	There are more cardiovascular events (including hypertension) with carfilzomib (Kyprolis®) versus bortezomib (Velcade®)
#3092 (Heidelberg)	If whole-body imaging otherwise negative, local therapy (surgery/radiation) is excellent choice
#3126 (Dana-Farber)	“RVd lite” (reduced dose Revlimid/Velcade/dex) is safe and effective in transplant-ineligible patients

ASH 2017 Wrap Up

- **Focus on early diagnosis and impact of early intervention**

- **Big discussions about CAR T cells**
  - **Benefit → ? Sustained MRD negative**
  - **Toxicity → ? Safe enough for broad use**
  - **Cost → ?? Realistic**

- **For further information, contact your personal healthcare team or the IMF InfoLine at 800-452 CURE (2873)**

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