INTERNATIONAL MYELOMA FOUNDATION

The International Myeloma Foundation presents

Teleconference Series:

Myeloma Update

POST ASCO/EHA/IMWG TELECONFERENCE

Thursday, June 27, 2019

4:00 pm Pacific / 5:00 pm Mountain
6:00 pm Central / 7:00 pm Eastern

Duration: 60 minutes (including Q & A)

Celgene

Takeda

myeloma.org

Dr. Brian GM Durie
Chairman of the Board
International Myeloma Foundation

Today's Featured Speaker

Brian GM Durie

Cedars-Sinai Medical Center

Dr. Durie is

- Chairman of the Board for the IMF
- Scientific Chair of the IMWG and Black Swan Research Initiative
- Co-Chair of the SWOG Myeloma Committee

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Recent Abstracts/Presentations/Publications

ASCO 2019

Abstracts: 5,600

Myeloma-related: 210

Oral presentations: 8

Plenary session presentation: 1

EHA 2019

Abstracts: 2,309

Myeloma-related: 199

Oral presentations: 13 (one presidential symp)

Posters: 182

… plus recent publications

Today's Topics

- Smoldering myeloma
- Frontline therapy
- Maintenance
- Relapse therapies
- New agents

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Smoldering Multiple Myeloma (SMM)

- **Risk classification**
  - What is High Risk Smoldering Multiple Myeloma? [HR SMM]

- **Treatment strategies**
  - Observation
  - Attempt to “prevent” progression to MM
  - Early treatment for myeloma to enhance long term outcomes

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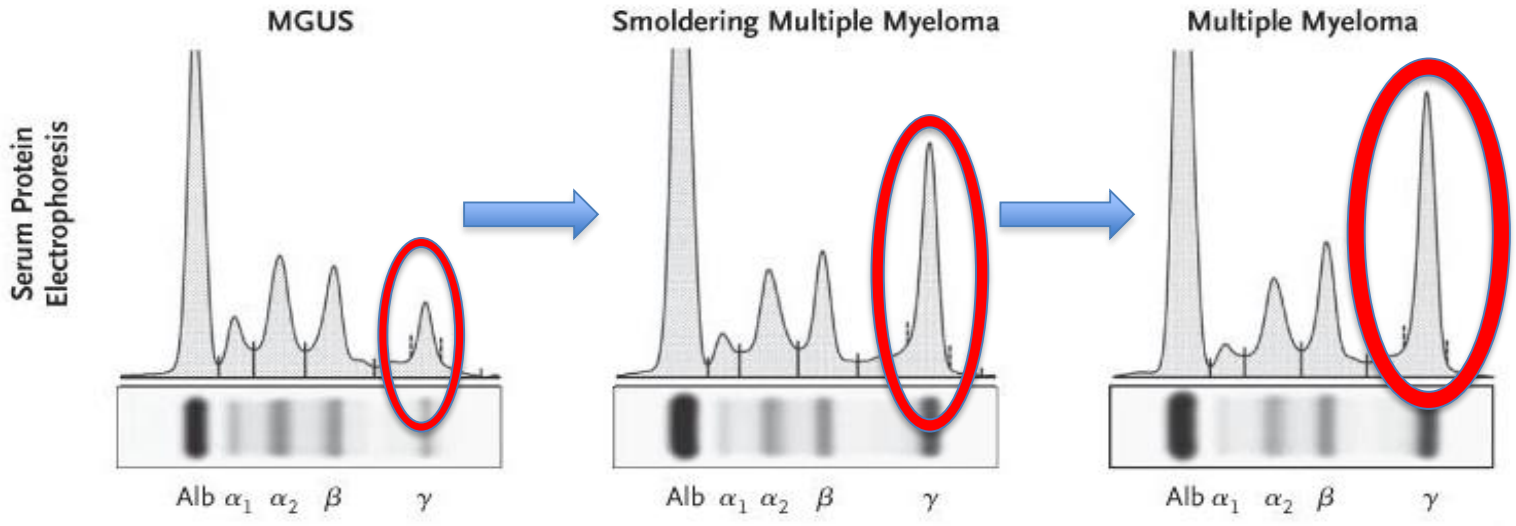
Smoldering Multiple Myeloma (SMM)



Increasing levels of monoclonal protein

Increasing marrow plasma cell percentage

Development of End Organ Damage

HR SMM

MDE

CRAB

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IMWG Project: New SMM Risk Score Tool*

2/20/20 Model

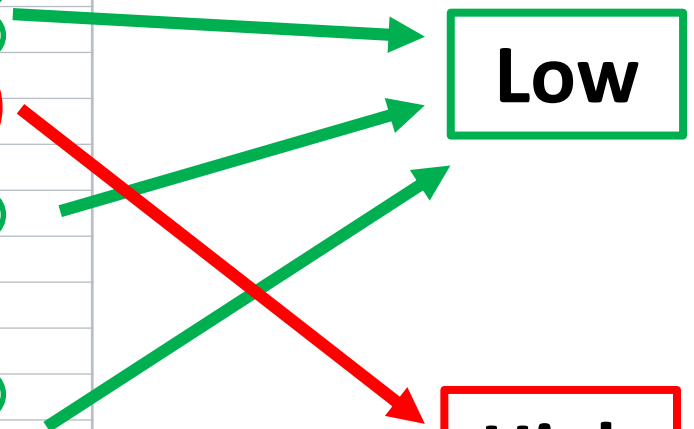
Risk Factor	Coefficient	Odds Ratio (95% CI)	P-value	Score
FLC Ratio				
0-10 (reference)	-	-	-	0
>10-25	0.69	1.99 (1.15, 3.45)	0.014	2
>25-40	0.96	2.61 (1.36, 4.99)	0.004	3
>40	1.56	4.73 (2.88, 7.77)	<0.0001	5
M protein (g/dL)				
0-1.5 (reference)	-	-	-	0
>1.5-3	0.95	2.59 (1.56, 4.31)	0.0002	3
>3	1.30	3.65 (2.02, 6.61)	<0.0001	4
BMPC%				
0-15 (reference)	-	-	-	0
>15-20	0.57	1.77 (1.03, 3.06)	0.04	2
>20-30	1.01	2.74 (1.6, 4.68)	0.0002	3
>30-40	1.57	4.82 (2.5, 9.28)	<0.0001	5
>40	2.00	7.42 (3.23, 17.02)	<0.0001	6
FiSH abnormality	0.83	2.28 (1.53, 3.42)	<0.0001	2

20

2

20

Risk Score



***689 of the original 2286 had complete data for all risk factors. Logistic regression analyses performed. Principal investigators: Mateos; Kumar; San Miguel; Durie. ASCO abstract #8000; also EHA abstract.**

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Key Factors for Progression at 2 years

MDE
(**M**yeloma **D**efining **E**vents)

- BMPC % = ≥ 60%
- FLC Ratio = ≥ 100
- MRI = ≥ 2 lesions

HR SMM

- BMPC % = 20 – < 60%
- FLC Ratio = 10 – < 100
- [MRI = 0 or 1]
- Serum spike = > 1.5
- FiSH abnormalities

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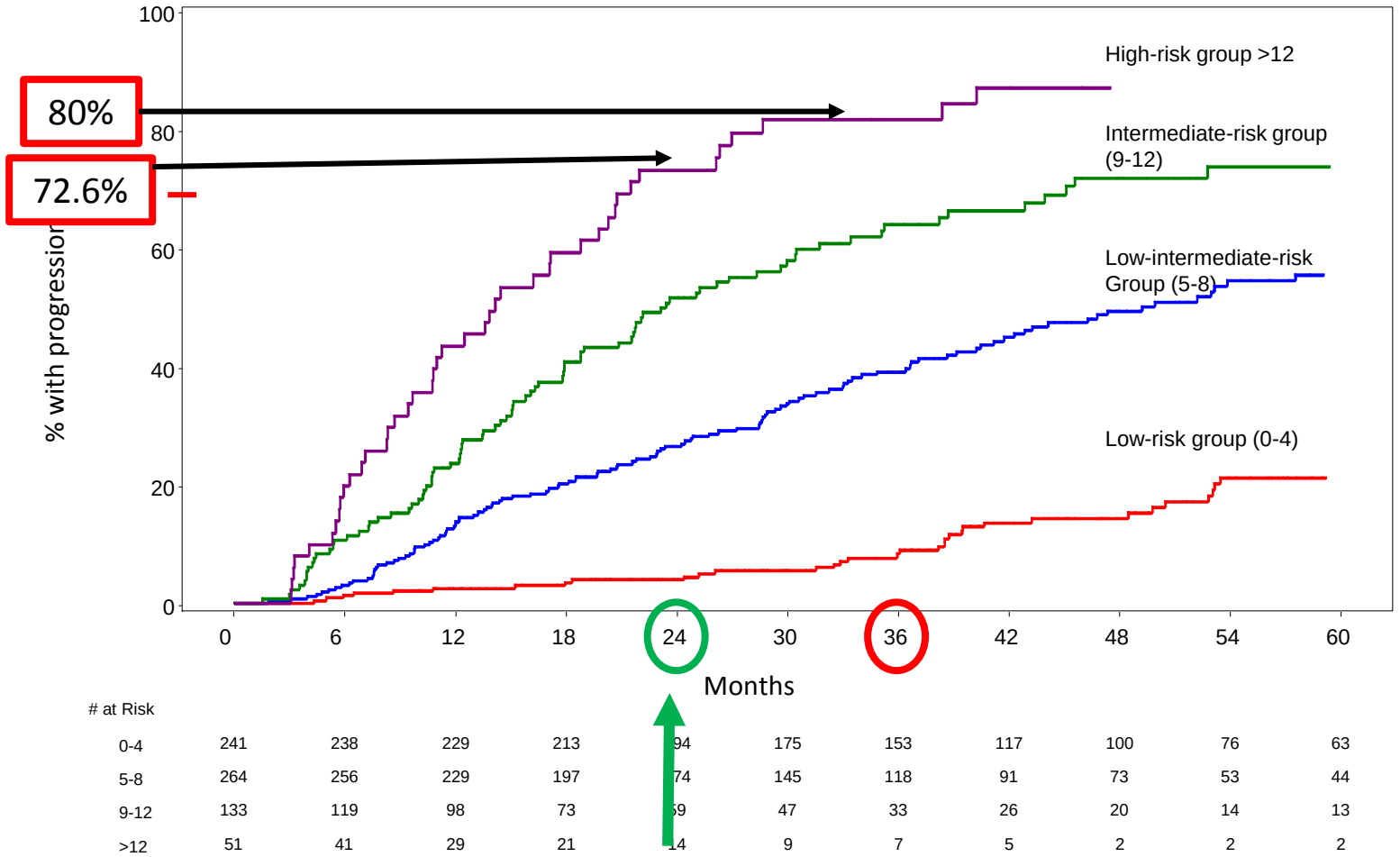
Risk of Progression at 2 years



Risk Stratification Groups	Hazard Ratio (95% CI) Versus Low-risk group (censored 2 year)
0-4	**Reference**
5-8	**7.56 (3.77 to 15.2)**
9-12	**17.3 (8.63 to 34.8)**
>12	**31.9 (15.4 to 66.3)**

Total Risk score	2 year progression n (%)
0-4	9 / 241 **(3.7%)**
5-8	67 / 264 **(25.4%)**
9-12	65 / 133 **(48.9%)**
>12	37 / 51 **(72.6%)**

For **LOW-RISK**: 96% prediction of non-progression at 2 years

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E3A06: RANDOMIZED PHASE III TRIAL OF LENALIDOMIDE VERSUS OBSERVATION ALONE IN PATIENTS WITH ASYMPTOMATIC HIGH-RISK SMOLDERING MULTIPLE MYELOMA

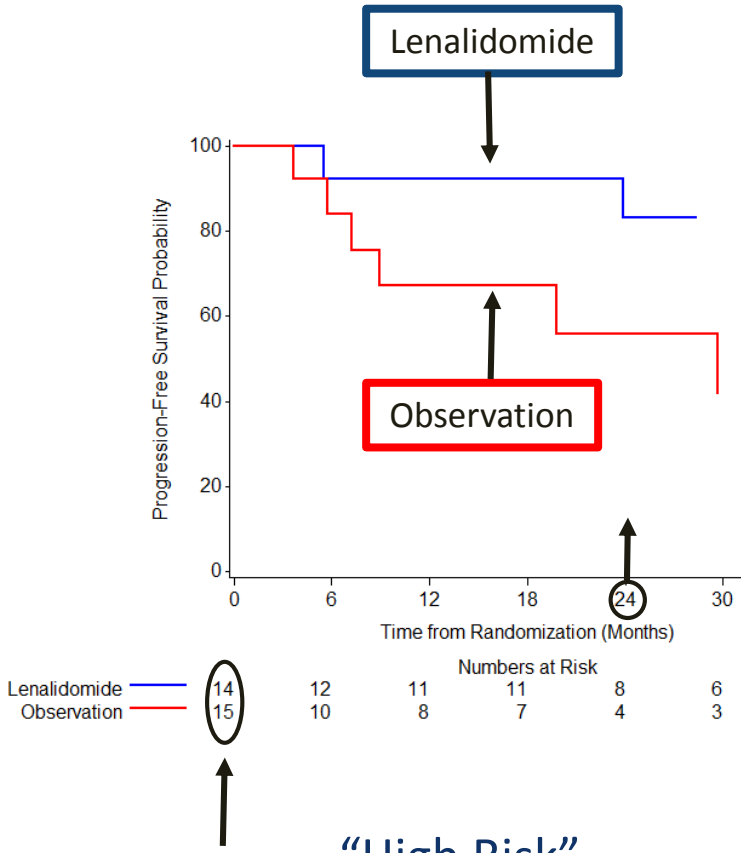
Sagar Lonial, M.D., Susanna Jacobus, M.Sc., Rafael Fonseca, M.D., Matthias Weiss, M.D., Shaji Kumar, M.D., Robert Z. Orlowski, M.D., Ph.D., Jonathan L. Kaufman, M.D., Abdulraheem M. Yacoub, M.D., Francis K. Buadi, M.D., Timothy O'Brien, M.D., Jeffrey V. Matous, M.D., Daniel M. Anderson, M.D., Robert V. Emmons, M.D., Anuj Mahindra, M.D., Lynne I. Wagner Ph.D., Madhav V. Dhodapkar, M.B.B.S., S. Vincent Rajkumar, M.D.

Acknowledgement: This study was coordinated by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under the following award numbers: CA180820, CA180794, CA180790, CA180853, CA180858, CA180864, CA189805, CA189863, CA189870, CA180888, CA180826, (IF QOL: CA189828) . The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, nor does mention of Co-authors, study sponsor, etc.

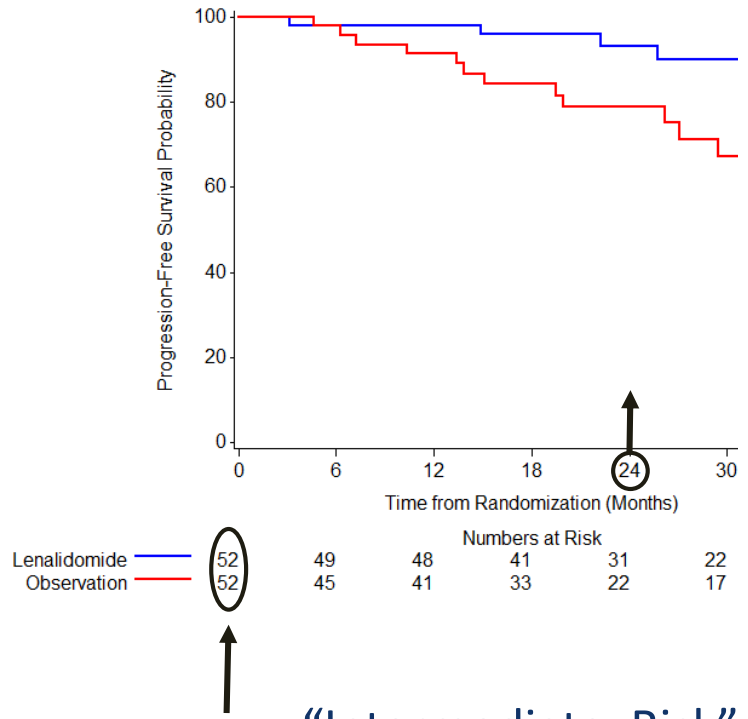
EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

ECOG-ACRIN cancer research group
Reshaping the future of patient care

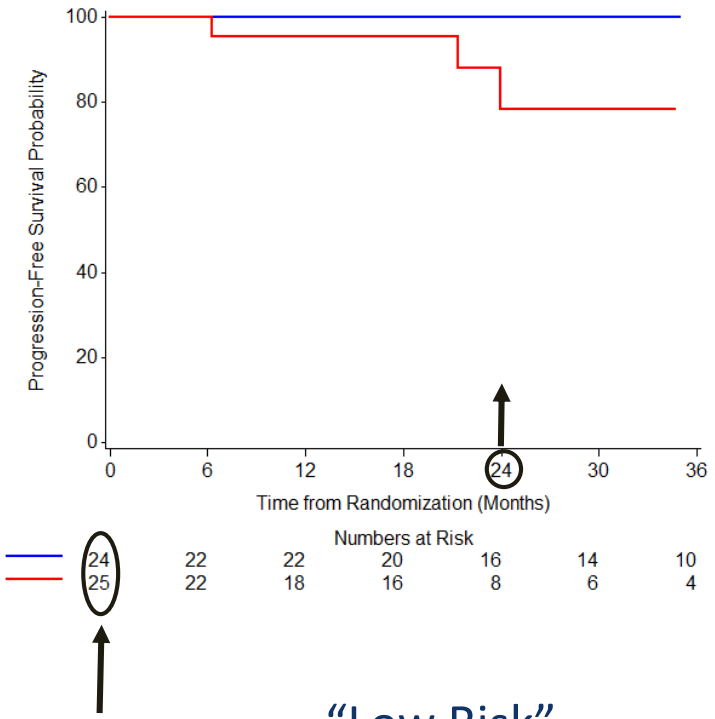
Phase III PFS by Mayo 2008 Risk Criteria



"High Risk"
29/182 (16%)



"Intermediate Risk"
104/182 (57%)

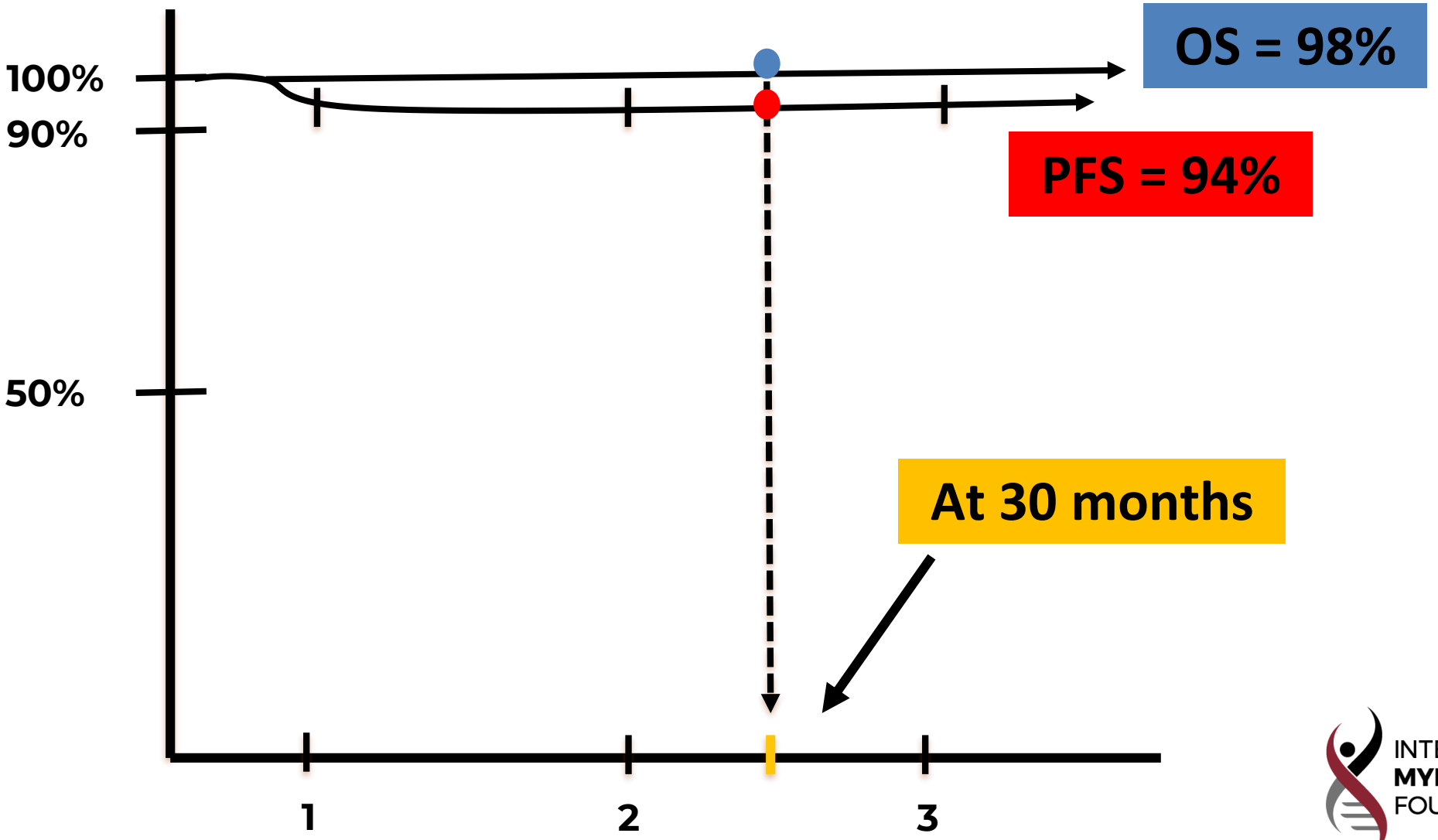


"Low Risk"
49/182 (27%)

Only 14 patients with HR SMM received lenalidomide.

CURATIVE STRATEGY (GEM-CESAR) FOR HIGH-RISK SMOLDERING MYELOMA

CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (KRD) AS INDUCTION FOLLOWED BY HDT-ASCT, CONSOLIDATION WITH KRD AND MAINTENANCE WITH RD*



*EHA abstract

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Smoldering Multiple Myeloma (SMM)

- **Treatment strategies**
  - Review carefully
  - Be aware of concerns about using Revlimid as a single agent early (as a “preventative”)
    - Emergence of IMiD resistance
    - Need for ongoing therapy
    - Side effects [51% discontinued therapy]/ costs (??? reimbursement for non-FDA approved indication)
    - Second malignancies increased

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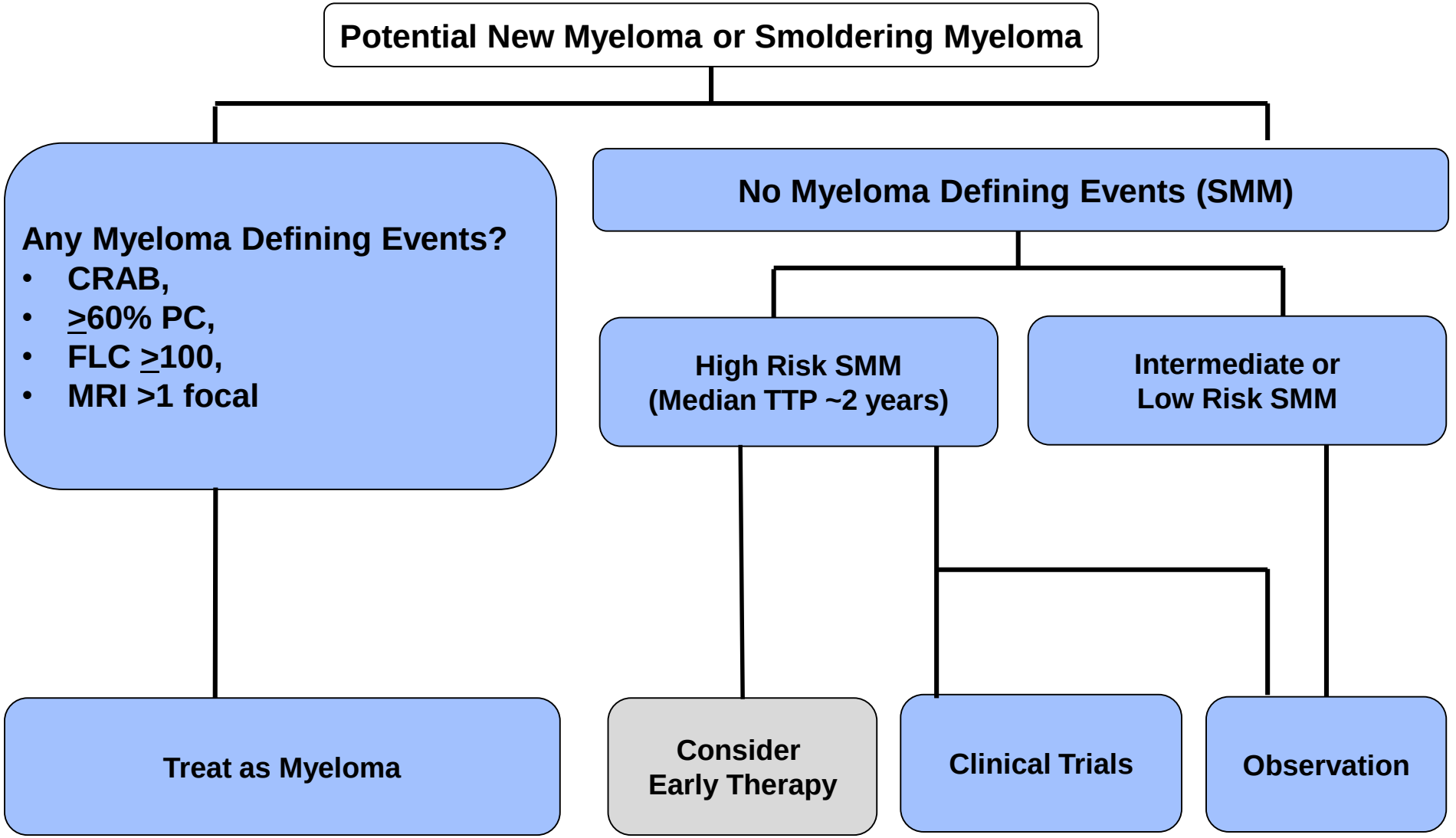
When Should Treatment Be Initiated?



Adopted 2019

Frontline: Key Question

Can we improve on VRd triplet?

- VRd [VTd]

→

- KRd FORTE Trial
- DRd MAIA Trial
- KCd

TRIPLET

→

- Dara VRd
- Dara VTd
- Dara KRd

QUADRUPLET

CASSIOPEIA Trial

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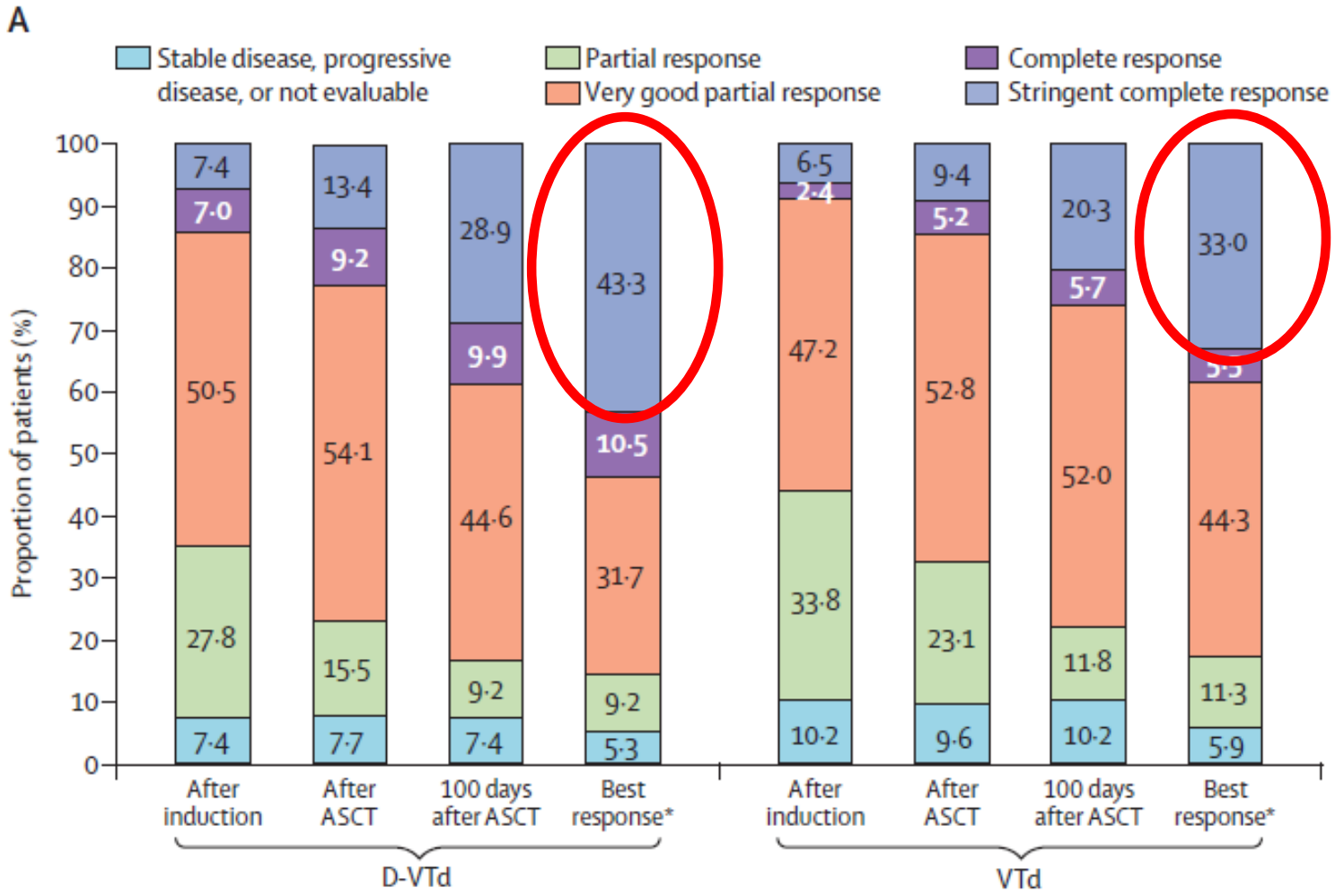
PHASE 3 RANDOMIZED STUDY OF Dara VTd VERSUS VTd

TRANSPLANT ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA: PART 1 CASSIOPEIA RESULTS*



CR + MRD negative: 33.7% versus 19.9%

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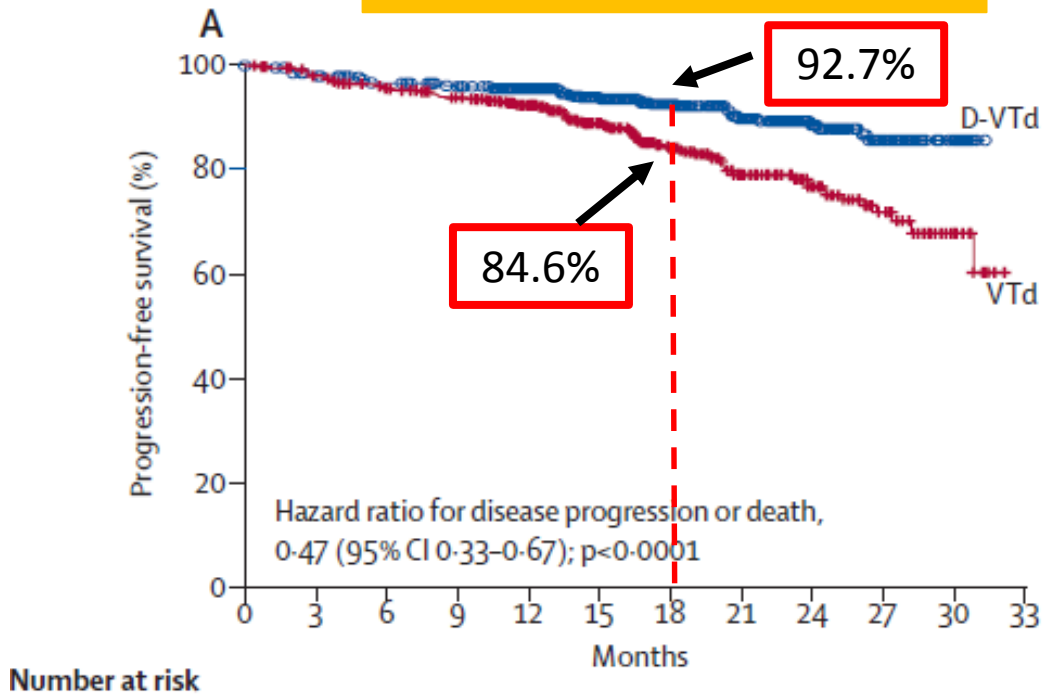
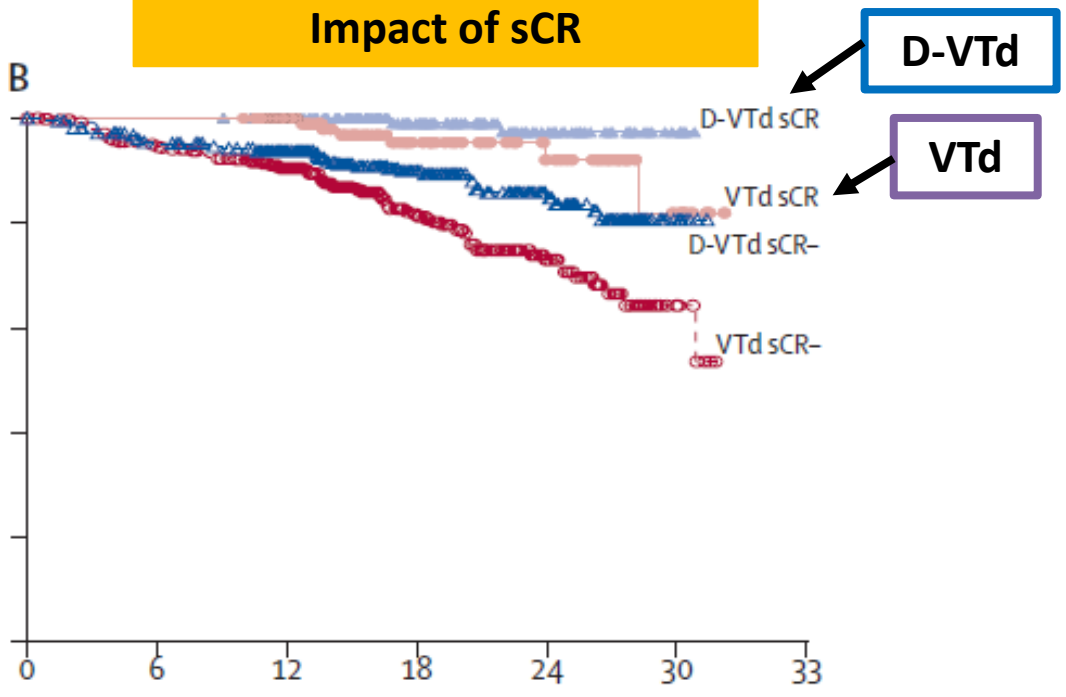
PHASE 3 RANDOMIZED STUDY OF Dara VTd VERSUS VTd

Progression Free Survival



Number at risk												
D-VTd	543	520	501	492	442	346	261	185	122	61	14	0
VTd	542	519	497	475	413	319	233	163	104	50	14	0

Impact of sCR



Number at risk							
D-VTd sCR	157	157	148	89	37	5	0
VTd sCR	110	110	100	57	27	6	0
D-VTd sCR–	386	344	294	172	85	9	0
VTd sCR–	432	387	313	176	77	8	0

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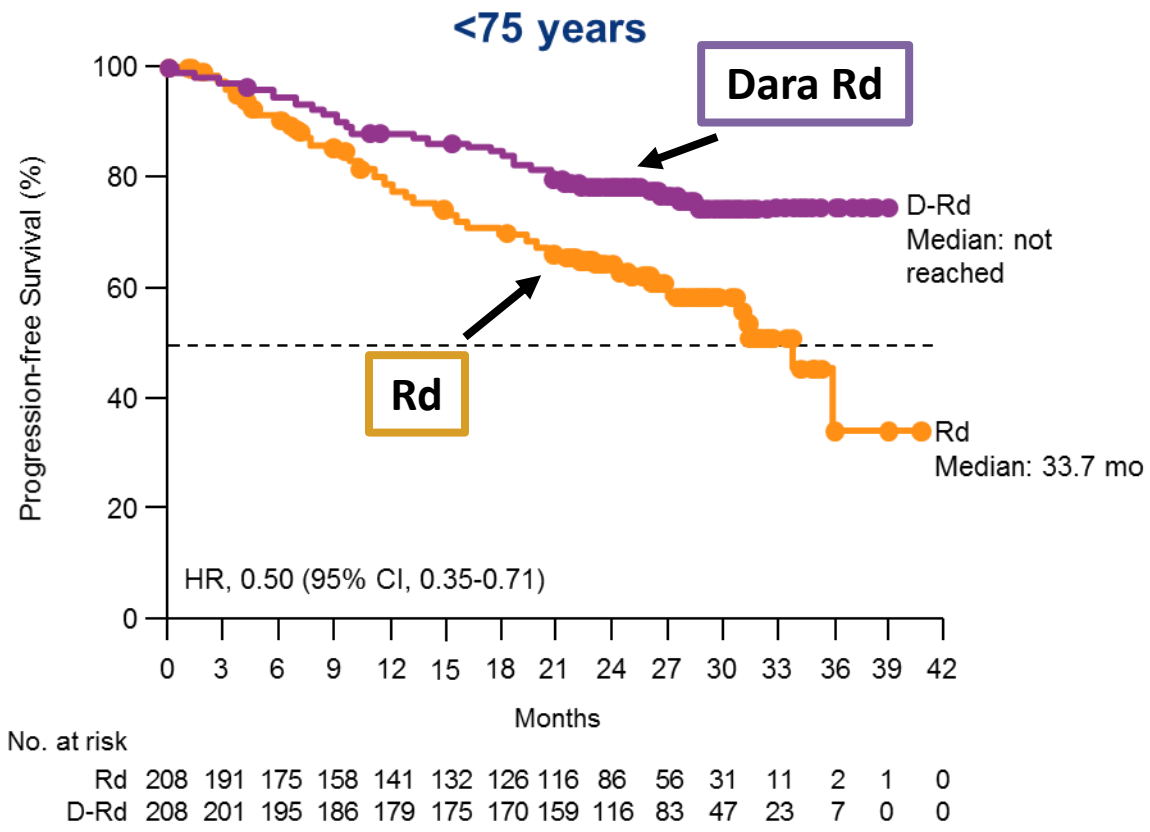
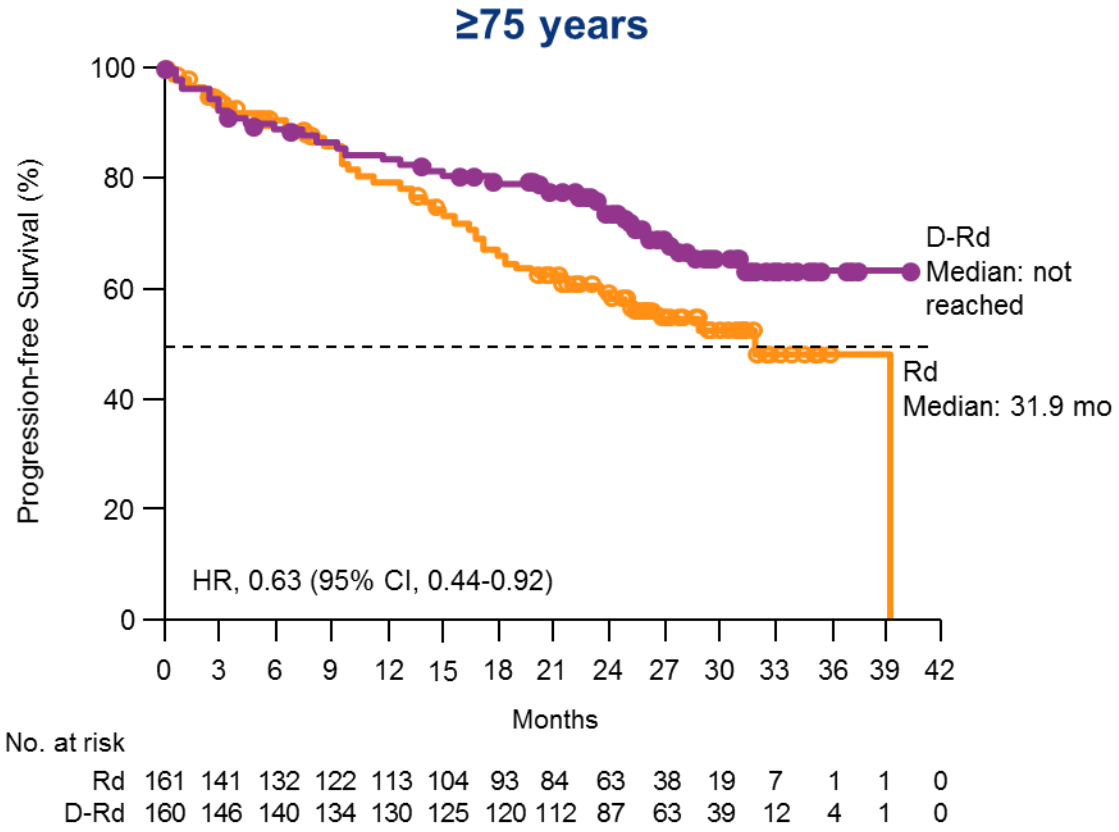
MAIA: PFS by Age Group

- Median follow-up: 28 months (range: 0.0-41.4)

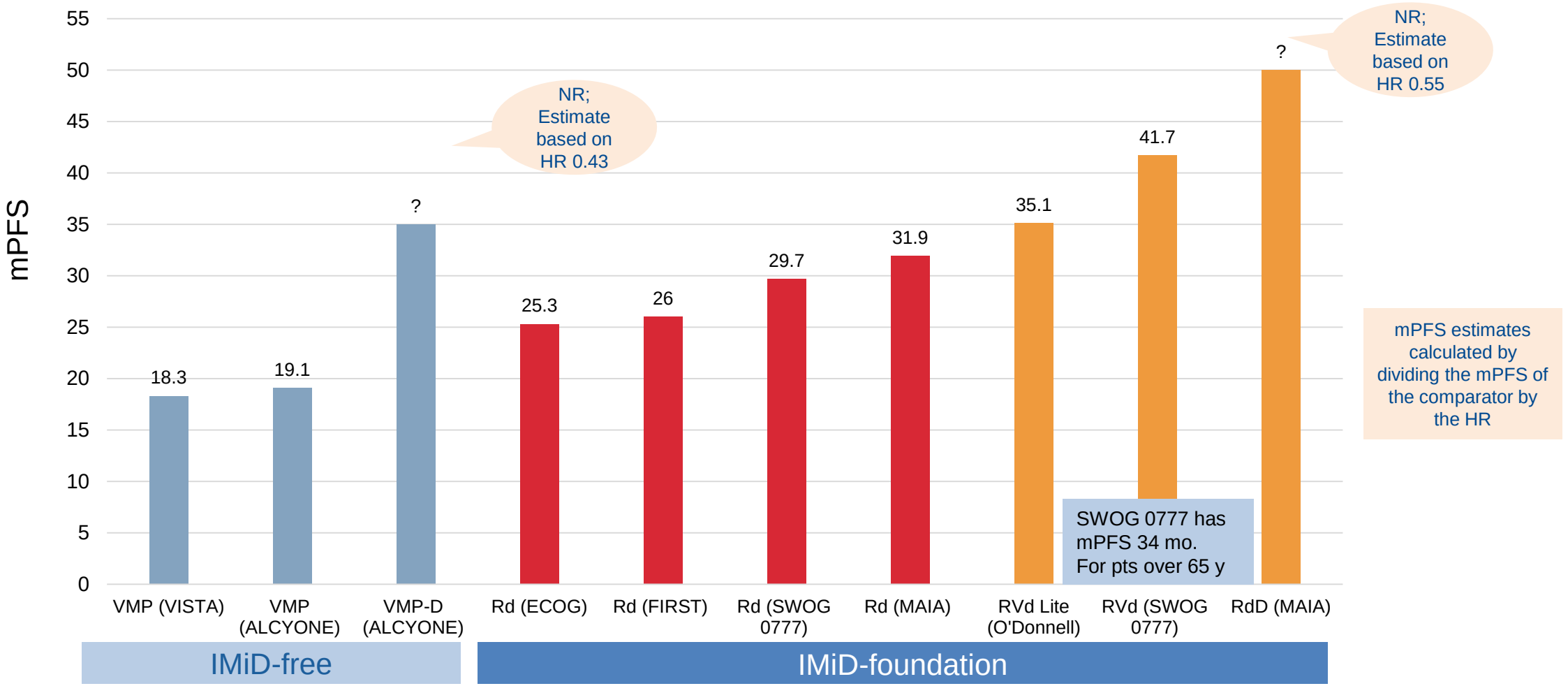




Median PFS was significantly prolonged for D-Rd versus Rd in both age groups

Usmani SZ, et al., ASCO 2019; abstract 8035, oral presentation

Overview of mPFS in recent phase 3 trials in NSCT NDMM



Direct comparison between trials is not intended and should not be inferred. HR, hazard ratio; NR, not reached; NSCT, non-stem cell transplant; PFS, progression-free survival; Rd, lenalidomide, low-dose dexamethasone; RdD, daratumumab, lenalidomide, dexamethasone; RVd, lenalidomide, bortezomib and dexamethasone; VMP; bortezomib, melphalan, prednisone.

1. Velcade [SmPC]. Beerse, Belgium: Janssen-Cilag International. 2014. 2. Dimopoulos M, et al. Blood. 2018;132:156. Presented at ASH 2018. 3. Rajkumar SV, et al. Lancet Oncol. 2010;11:29–37.
4. Facon T, et al.Blood.2018;131:301–310. 5. Revlimid. [SmPC]. Europe. 2019. 6. Facon T, et al. Blood. 2018;132:LBA-2. Presented at ASH 2018. 7. O'Donnell EK, et al. Br J Haematol. 2018;182:222–230

CARFILZOMIB LENALIDOMIDE DEXAMETHASONE (KRD) WITH OR WITHOUT TRANSPLANTATION

NEWLY DIAGNOSED MYELOMA (FORTE TRIAL): EFFICACY ACCORDING TO RISK STATUS

	Table 1A: Overall population		Table 1B: Subgroup analysis			
			R-ISS 1		R-ISS 2/3	
	KRd_ASCT_KRd N=158	KRd12 N=157	KRd_ASCT_KRd N=48	KRd12 N=39	KRd_ASCT_KRd N=92	KRd12 N=94
sCR	44%	43%	46%	49%	39%	38%
≥CR	60%	61%	60%	64%	56%	57%
≥VGPR	89%	87%	92%	79%	86%	86%
MRD negative	58%	54%	69%	62%	51%	47%

KRd + ASCT and KRd 12 cycles are equivalent!

*ASCO abstract #8002;
EHA abstract also

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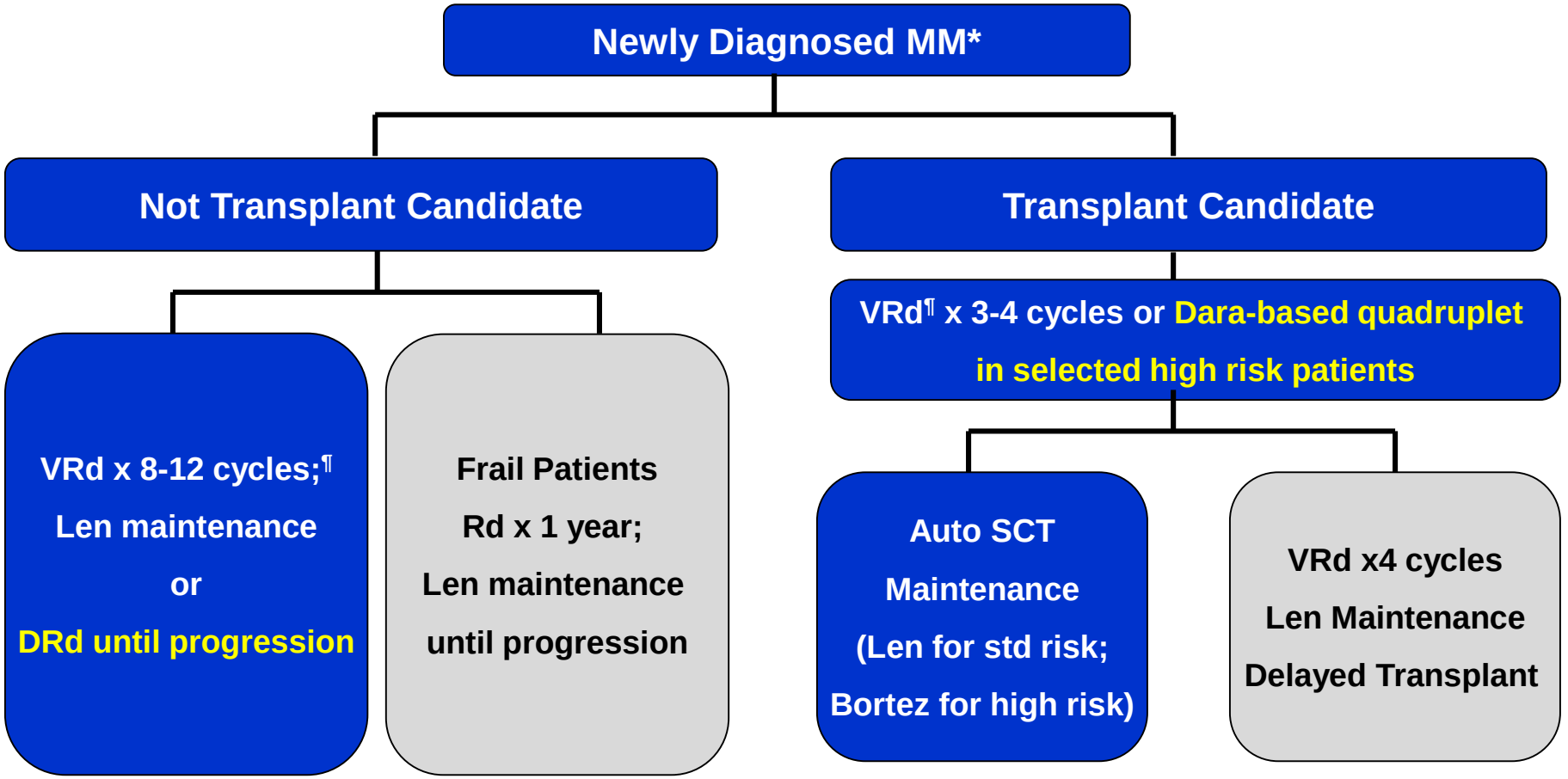
Myeloma: Frontline Treatment



*Based on CALGB 100104, S0777, IFM-2009, CTN 0702, HOVON, MAIA, CASSIOPEIA

¶ VTd/VCd if VRd not available

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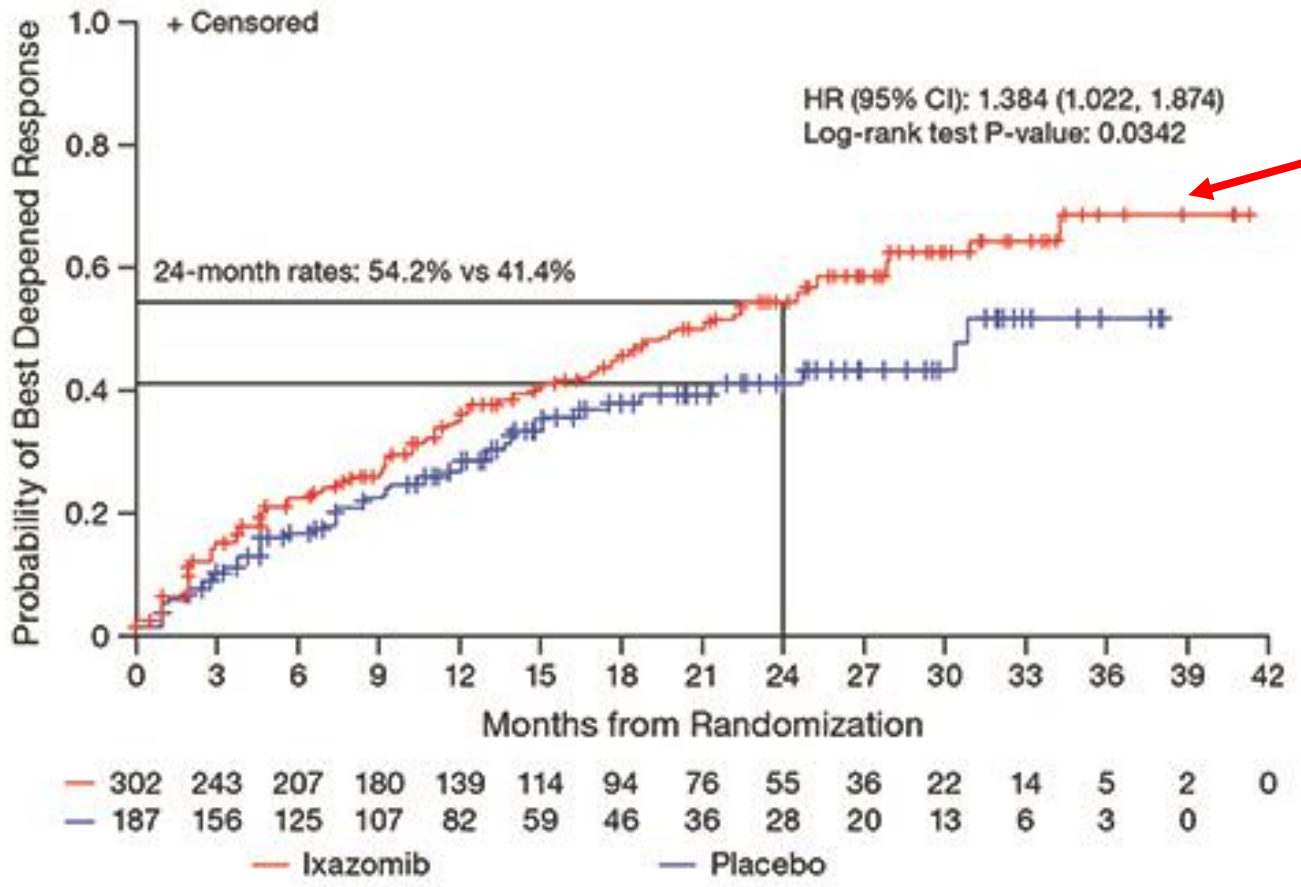
Maintenance

- **Ixazomib:** new data at EHA

DEEPENING RESPONSES SEEN WITH IXAZOMIB MAINTENANCE POST-AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT)

PROLONGED PROGRESSION-FREE SURVIVAL - ANALYSIS FROM THE TOURMALINE-MM3 STUDY*



Deepening best response PR/VGPR at entry

*EHA abstract: PS1382

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Relapse Therapies: New Data

- Elotuzumab Pd
- Isatuximab Pd versus Pd
- Dara Kd
- K in frail patients
- Selinexor/dara
- Venetoclax update [EHA: LBA]

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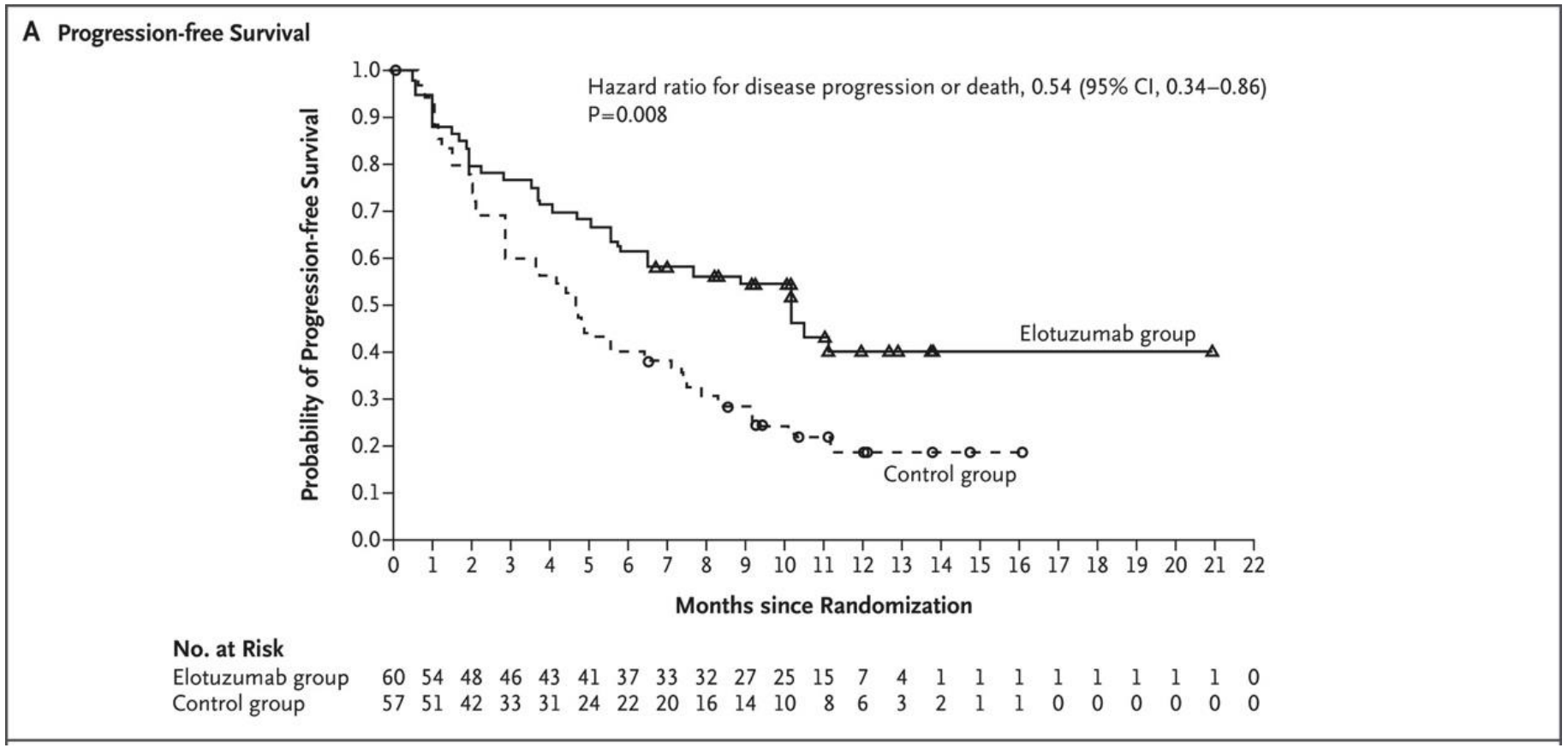
Elotuzumab-Pd vs Pd (PFS)



Dimopoulos MA, et al. N Engl J Med 2018;379:1811-1822.

The NEW ENGLAND JOURNAL of MEDICINE

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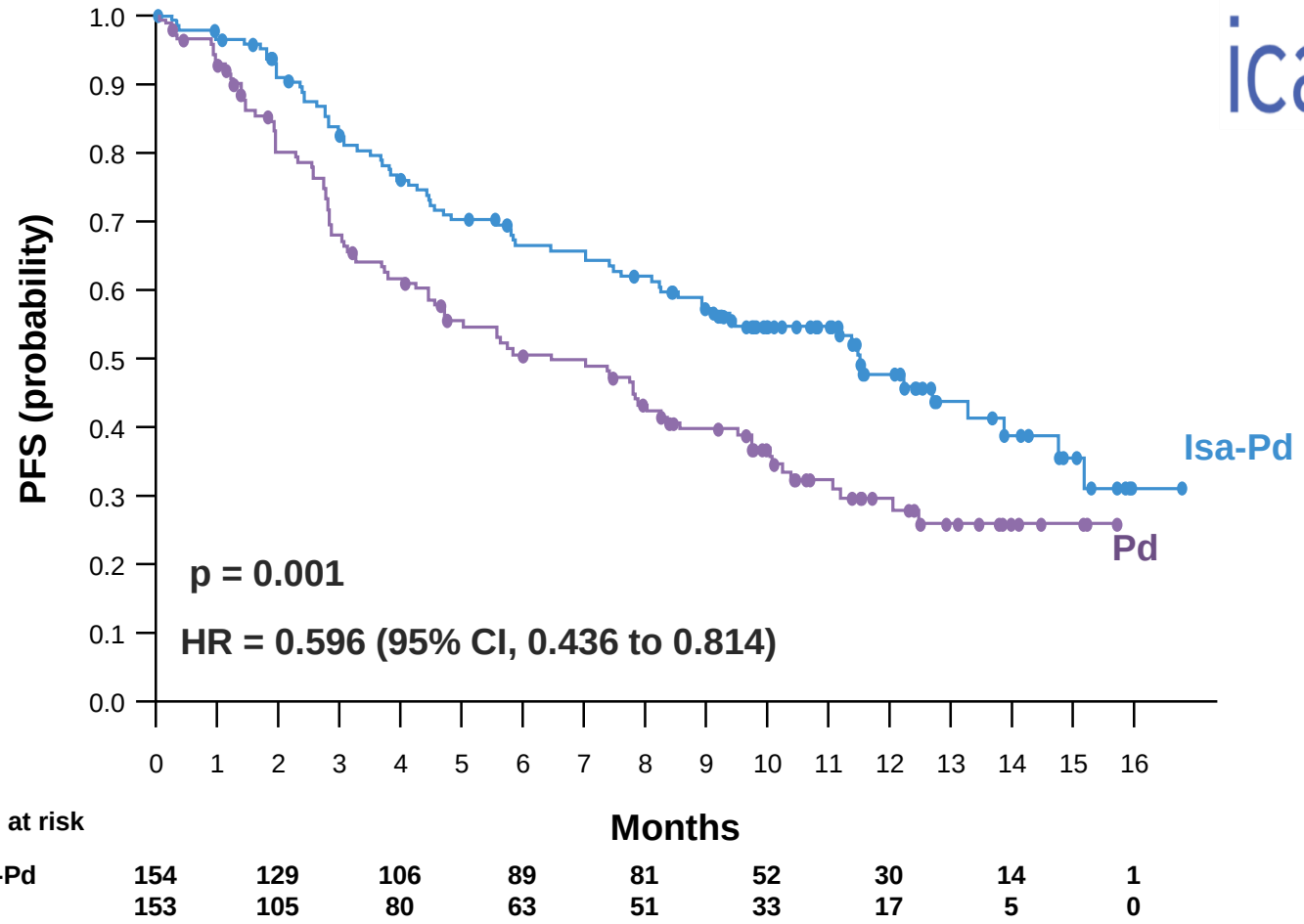
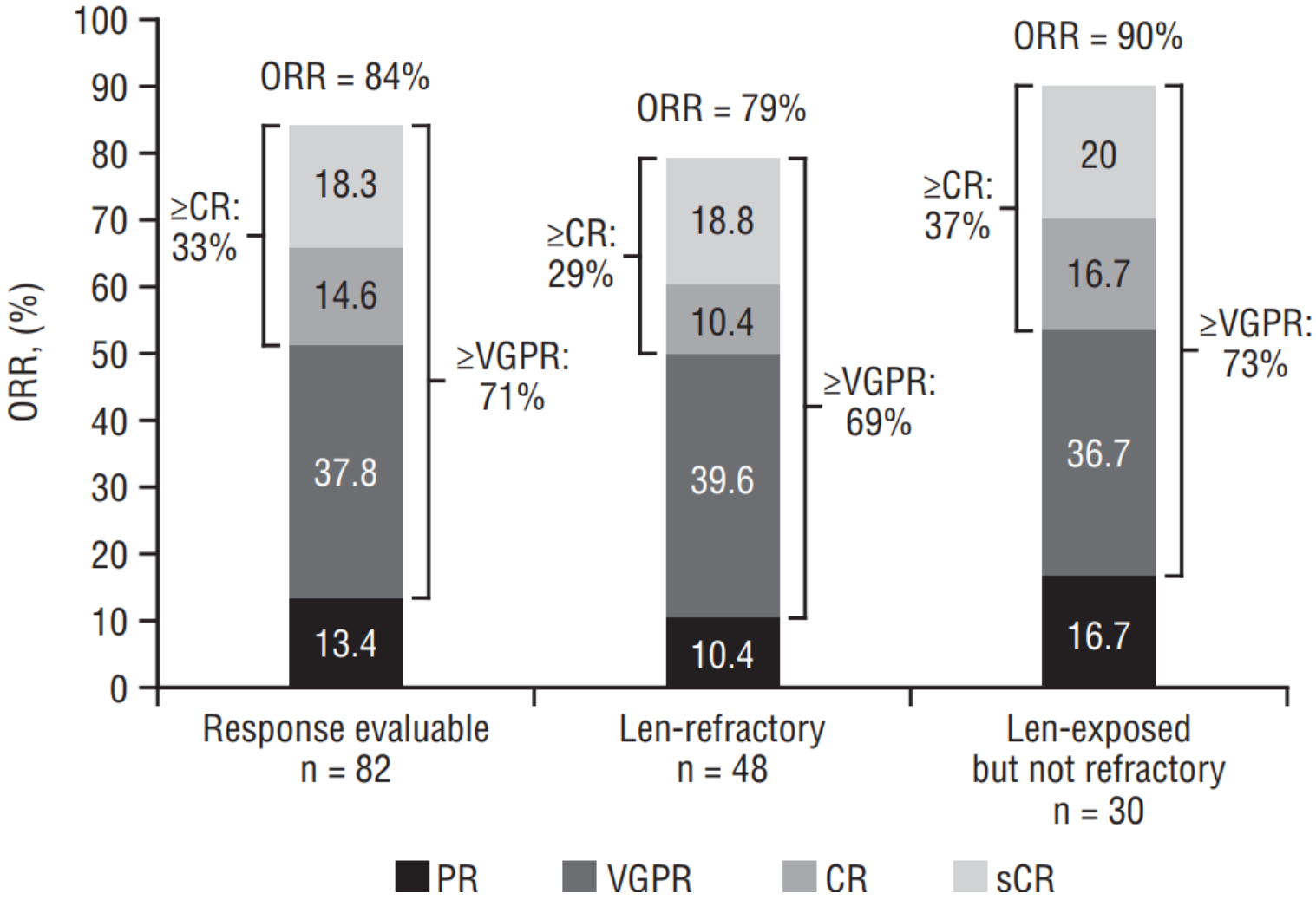
Isatuximab-Pd versus Pd



Data cut-off 11 Oct, 2018
CI, confidence interval; d, dexamethasone; HR, Hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; mos, months; PFS, progression-free survival; P, pomalidomide

Richardson PG et al. ASCO 2019

Daratumumab Plus Carfilzomib and Dexamethasone



≥ VGPR ~70%

*Blood May 21, 2019: online

Once-Weekly Carfilzomib in Frail Patients

SUBGROUP ANALYSIS FROM THE PHASE 3 A.R.R.O.W. STUDY

Table: Rates of Selected Treatment-emergent Adverse Events (TEAEs) of Grade 3 and Above across Frailty Subgroups in Carfilzomib Arms of the A.R.R.O.W. Study

	Fit		Intermediate		Frail	
Grade ≥3 TEAEs of interest,[a] n (%)	Once-weekly Kd70, n=60	Twice-weekly Kd27, n=66	Once-weekly Kd70, n=88	Twice-weekly Kd27, n=101	Once-weekly Kd70, n=79	Twice-weekly Kd27, n=60
Peripheral neuropathy	0	1 (2)	0	0	0	0
Acute renal failure	0	3 (5)	6 (7)	6 (6)	3 (4)	4 (7)
Cardiac failure	1 (2)	1 (2)	3 (3)	3 (3)	3 (4)	5 (8)
Ischemic heart disease	1 (2)	0	0	1 (1)	0	1 (2)
Pulmonary hypertension	0	0	0	0	0	1 (2)

[a]Standardized MedDRA Queries – Narrow

- Once weekly tolerated in frail patients
- Also true in Endeavor and Aspire subgroup analysis (IFM)

*ASCO: abstract #8027; also EHA abstract

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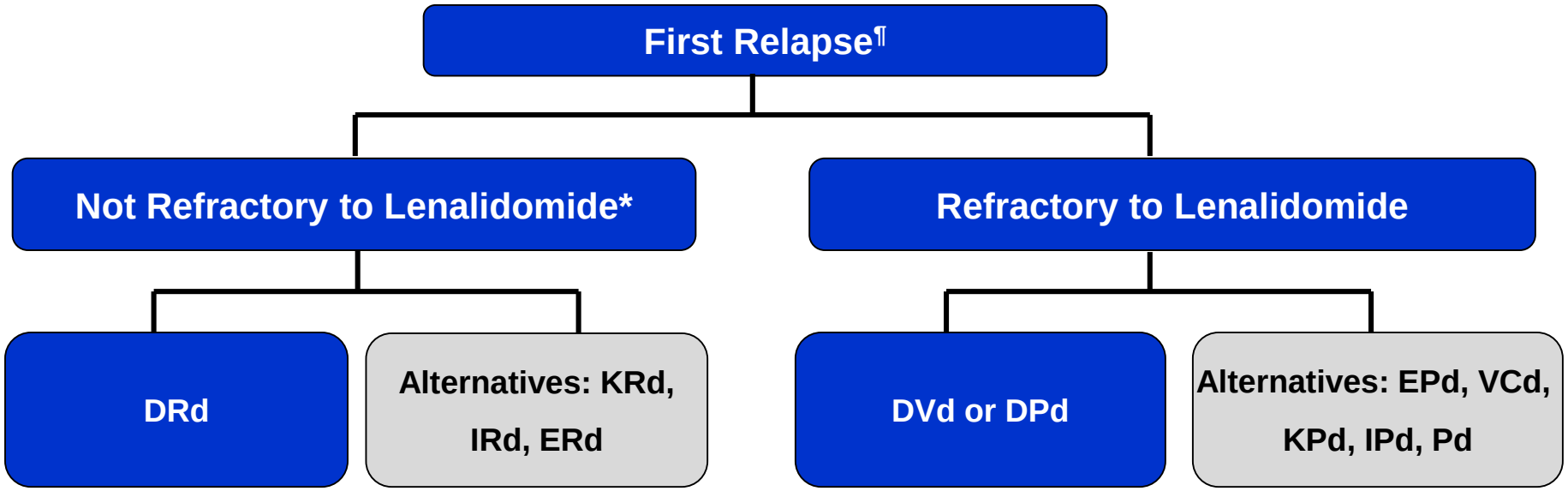
Myeloma: First Relapse



*Relapse occurring while off all therapy, or while on small doses of single-agent lenalidomide, or on bortezomib maintenance

¶ Consider salvage auto transplant in eligible patients

Rajkumar SV © 2019

Rajkumar SV, Kyle RA. Progress in Myeloma: A Monoclonal Breakthrough. N Engl J Med 2016;375:1390-1392

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Relapse Therapies

How do you select and sequence?

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Active Drugs in Multiple Myeloma

Old Drugs	Older Drugs (2003-2007)	Recently Approved Drugs (2013-2015)	Future Drugs
▪ Alkylators ▪ Steroids ▪ Interferon ▪ Anthracyclines	▪ Bortezomib ▪ Thalidomide ▪ Lenalidomide ▪ Liposomal doxorubicin	▪ Carfilzomib ▪ Pomalidomide ▪ Panobinostat ▪ Ixazomib ▪ Daratumumab ▪ Elotuzumab	▪ GSK 2857916 ▪ AMG 420 ▪ CAR-Ts ▪ Isatuximab ▪ Selinexor ▪ Venetoclax ▪ BiTEs [AMG 701 / EM 801 / JNJ 64007957] ▪ Anti CD 46 and 74 ▪ CelMODs [220/ 9284] ▪ DTP 3 ▪ BION 1301 ▪ JNJ 42756493

Rajkumar SV. 2019

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New Agent: Updates

- GSK 2857916
- AMG 420 BiTE
- CAR T
- CELMOD (CC220)
- Selinexor
- Venetoclax

Major target BCMA

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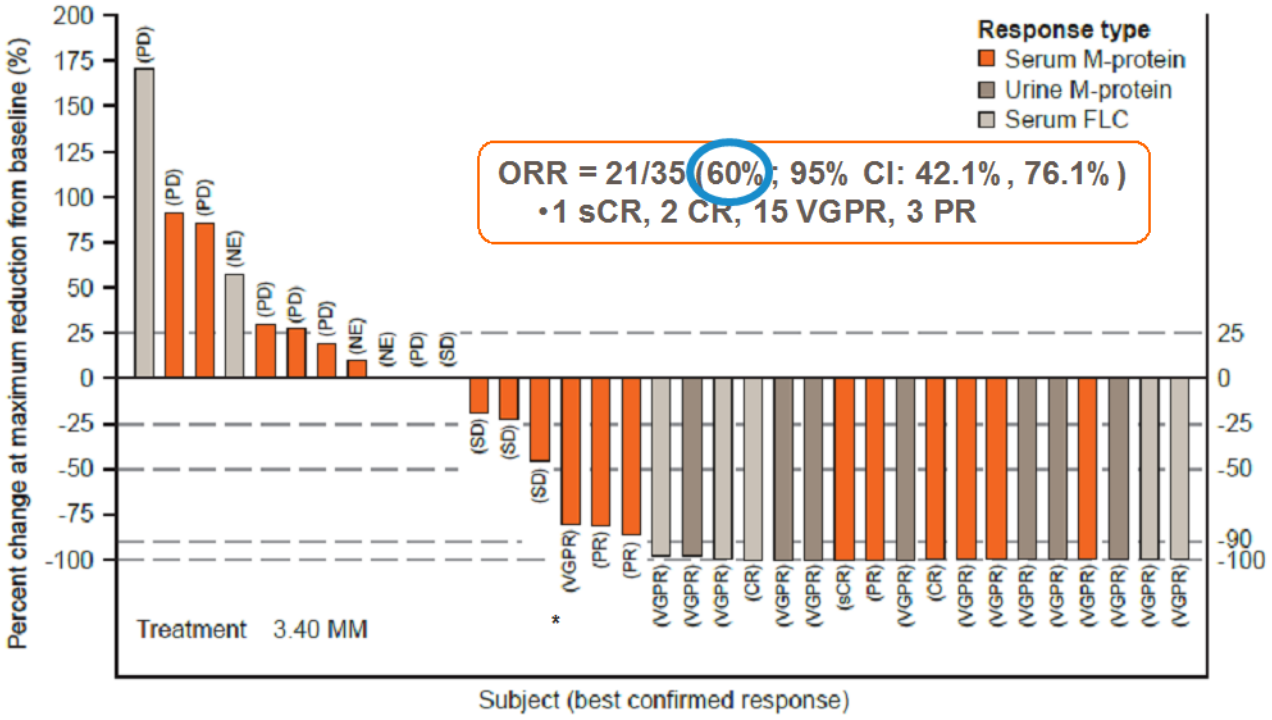
GSK-ADC: DREAMM1 Phase 2 Part 2

- Results at 3.4 mg/kg IV Q3 Wk



Updated Results

- ORR 60%
- 2 sCR
- 3 CR
- 14 VGPR
- 2 PR

- PFS: 12 months
- DOR: 14.3 months

- D/PI/IMiD refractory
  - PFS 6.2 m

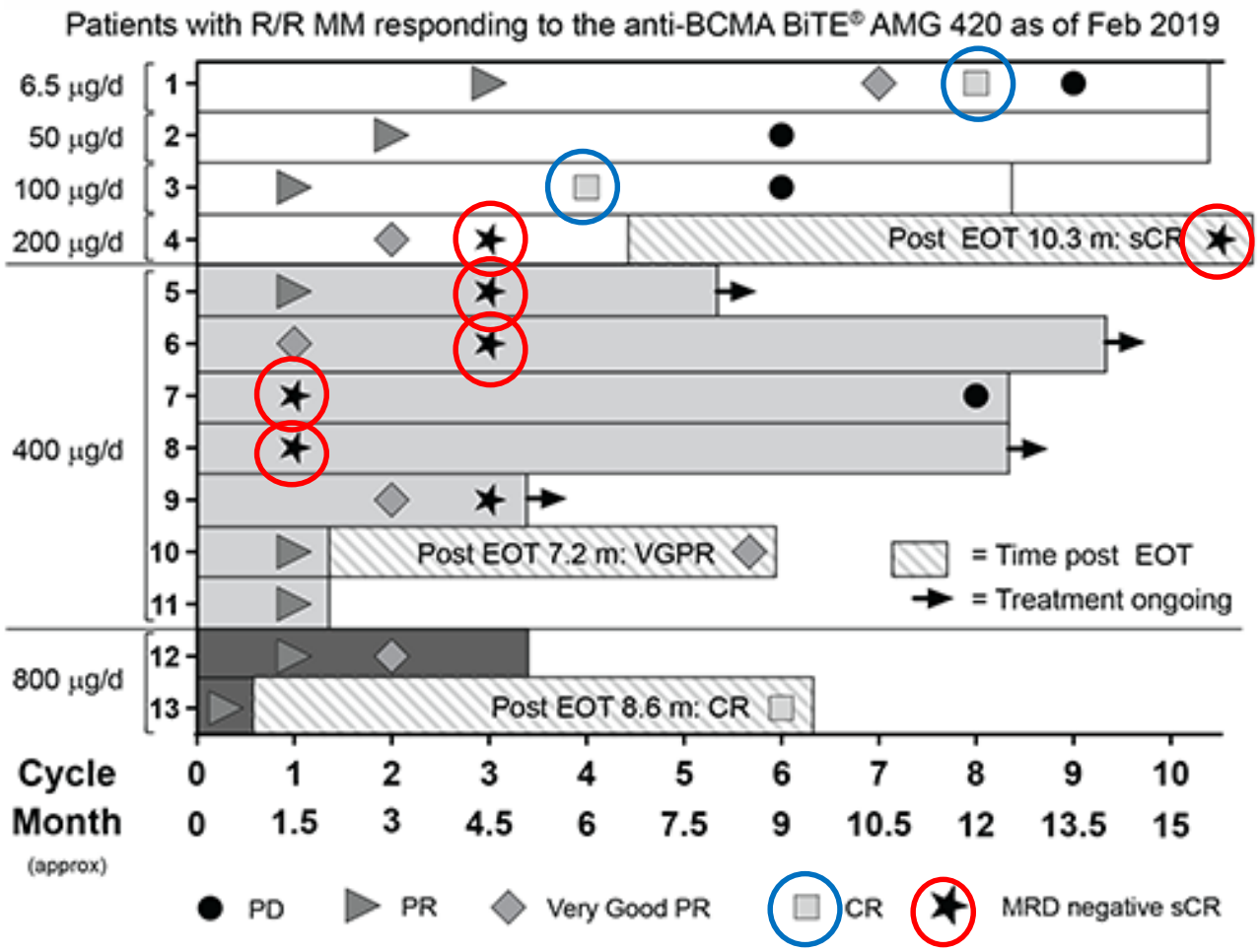
89% Double refractory;
34% double + Dara refractory
29% Cyto High-risk

Trudel et al. Ash 2017

Blood Cancer J 2019 Mar 20;9(4):37

EVALUATION OF AMG 420, AN ANTI-BCMA BISPECIFIC T-CELL ENGAGER (BITE®) IMMUNOTHERAPY

R/R MULTIPLE MYELOMA (MM) PATIENTS: UPDATED RESULTS OF A FIRST-IN-HUMAN (FIH) PHASE 1 DOSE ESCALATION STUDY



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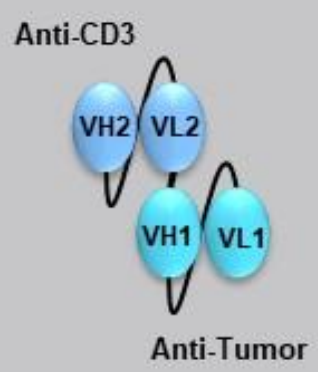
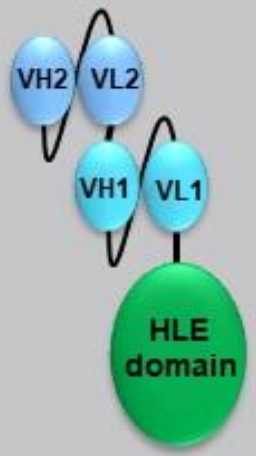
BiTE® FORMATS IN DEVELOPMENT

First-Generation	Half-Life Extended
 Molecule incorporates CD3 and Target Antigen Binding Regions Actual or Modeled *in vivo* Half-Life: 1–4 hours	 Molecule incorporates CD3 and Target Antigen Binding Regions; addition of HLE domain prolongs *in vivo* half-life Modeled *in vivo* Half-Life: Approximately 7 days
Dosing: Continuous infusion	Dosing: Weekly infusion

CD = cluster of differentiation; VH = variable domain, heavy chain; VL = variable domain, light chain

AMGEN

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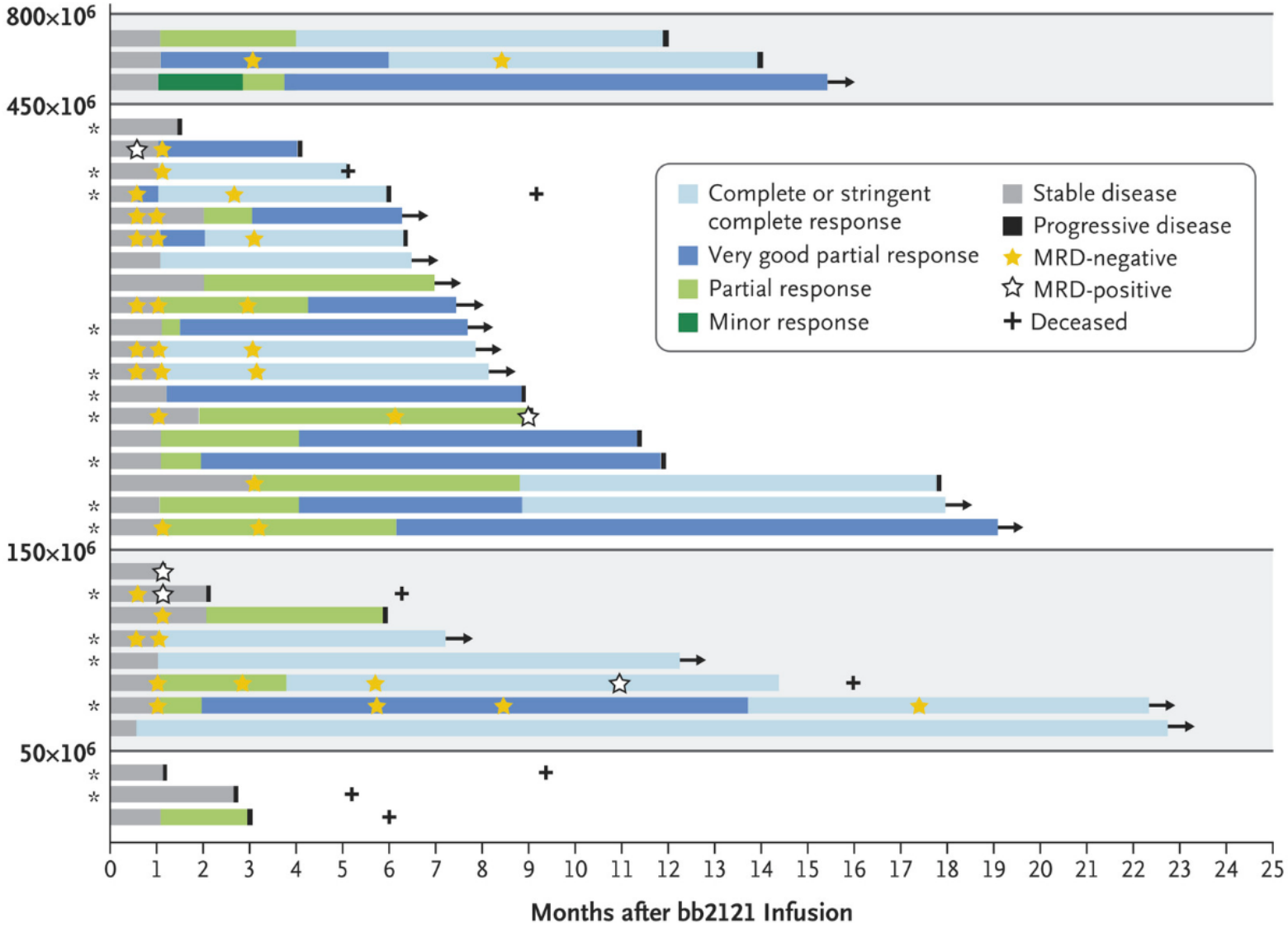
Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma*



*NEJM May 2, 2019: pp 1726-1737

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How Does BCMA Therapy Measure Up?

- In what order should we give these therapies?
- What line of therapy should we target?
- Will sequential BCMA therapies be possible
- Will CAR T cell therapy replace autoSCTx?

	GSK2857916	bb2121 (≥150 x 10^6 CAR T cells)	AMG-420
N	35	Escalation Group: 21	N = 42
Median Prior Lines of Therapy	57% ≥5 prior lines	7 regimens (3 – 14)	PLT. 4 (2-13)
Progression-free survival	12 months	11.8 months (17.7 months for MRD- pts)	PFS – NR
ORR CR/sCR VGPR PR	60% 9% 43% 9%	95.5% 50.0% 36.4% 9.1%	ORR 70% - 5 CR - 1 VGPR - 1 PR

GSK2857916: BCMA mAb Drug Conjugate
Vs
bb2121: BCMA CAR T Cell Therapy
Vs.
Bispecific – AMG-420

Trudel S et al. ASH 2017.
Raje N et al. ASCO 2018.
Olin RL et al. Bone Marrow Transplant 2009;43:417-22.
Cook G et al. Lancet Oncol 2014;15:874-85.

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FIRST CLINICAL (PHASE 1B/2A) STUDY OF IBERDOMIDE (CC-220; IBER)

A CELMOD, IN COMBINATION WITH DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Table 1. Responses in evaluable patients

Efficacy	IBER dose 0.3–1.2 mg + DEX (N=51)
Very good partial response	1
Partial response (PR)	15
Minimal response (MR)	10
Stable disease (SD)	19
Progressive disease	6
Overall response (≥PR, %)	16 (31)
Clinical benefit (≥MR, %)	26 (51)
Disease control (≥SD, %)	45 (88)

DEX, dexamethasone; IBER, iberdomide

Selinexor/ Dara

SAFETY AND EFFICACY OF COMBINATION OF SELINEXOR, DARATUMUMAB, AND DEXAMETHASONE (SDD) IN PATIENTS WITH MULTIPLE MYELOMA (MM) PREVIOUSLY EXPOSED TO PROTEASOME INHIBITORS AND IMMUNOMODULATORY DRUGS

- Selinexor 100 mg weekly combined with standard dara well-tolerated
- ORR = 77% without prior Selinexor or dara

Also: ASCO #2014 STORM trial update

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Venetoclax Update

- Anti-BCl-2 therapy
- **BELLINI Trial:** 41/194 patients in Venetoclax Vd died: 13 linked to therapy plus infection and progression
- Both PFS and OS benefit in patients with t(11;14): EHA 2019

CANOVA Trial for t(11;14) patients
Re-opened: Venetoclax/dex vs Pom/dex

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New Therapies

- **What is the current perspective?**
  - **Which are top priority?**
  - **Which are promising?**
  - **Can any be offered in frontline or early disease?**

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