

IMWG Conference Series: Amsterdam 2019

Making Sense of Treatment



Wednesday, June 12, 2019

Today's Speakers



Brian GM Durie
Cedars Sinai Medical Center



Joseph Mikhael
Translational Genomics Research Institute (TGen)
City of Hope Cancer Center



Philippe Moreau
University of Nantes

Recent Abstracts/Presentations/Publications



ASCO 2019

Abstracts: 5600

Myeloma-related: 210

Oral presentations: 8*

Plenary session
presentation: 1



EUROPEAN
HEMATOLOGY
ASSOCIATION

EHA 2019

Abstracts: 2309

Myeloma-related: 199

Oral presentations: 13*
(one presidential symp)

Posters: 182*

*With one exception: all represented at EHA



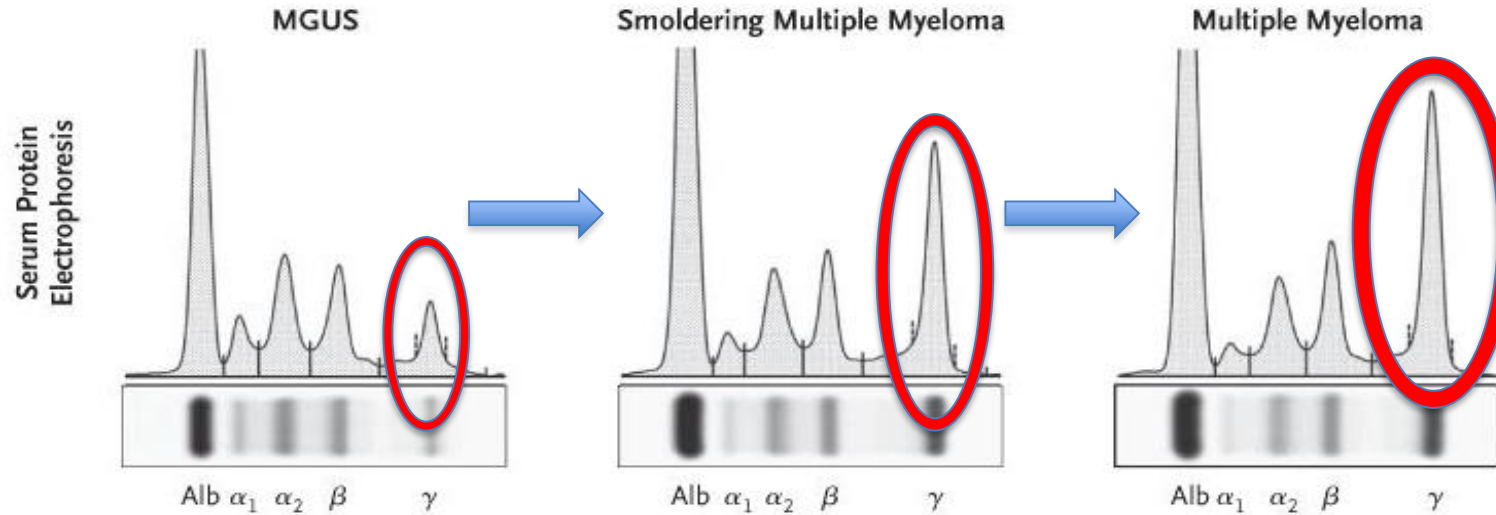
Today's Topics

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

Smoldering Myeloma (SMM)

- **Risk classification**
- **Treatment strategies**

Smoldering multiple myeloma



Increasing levels of monoclonal protein



Increasing marrow plasma cell percentage



Development of End Organ Damage



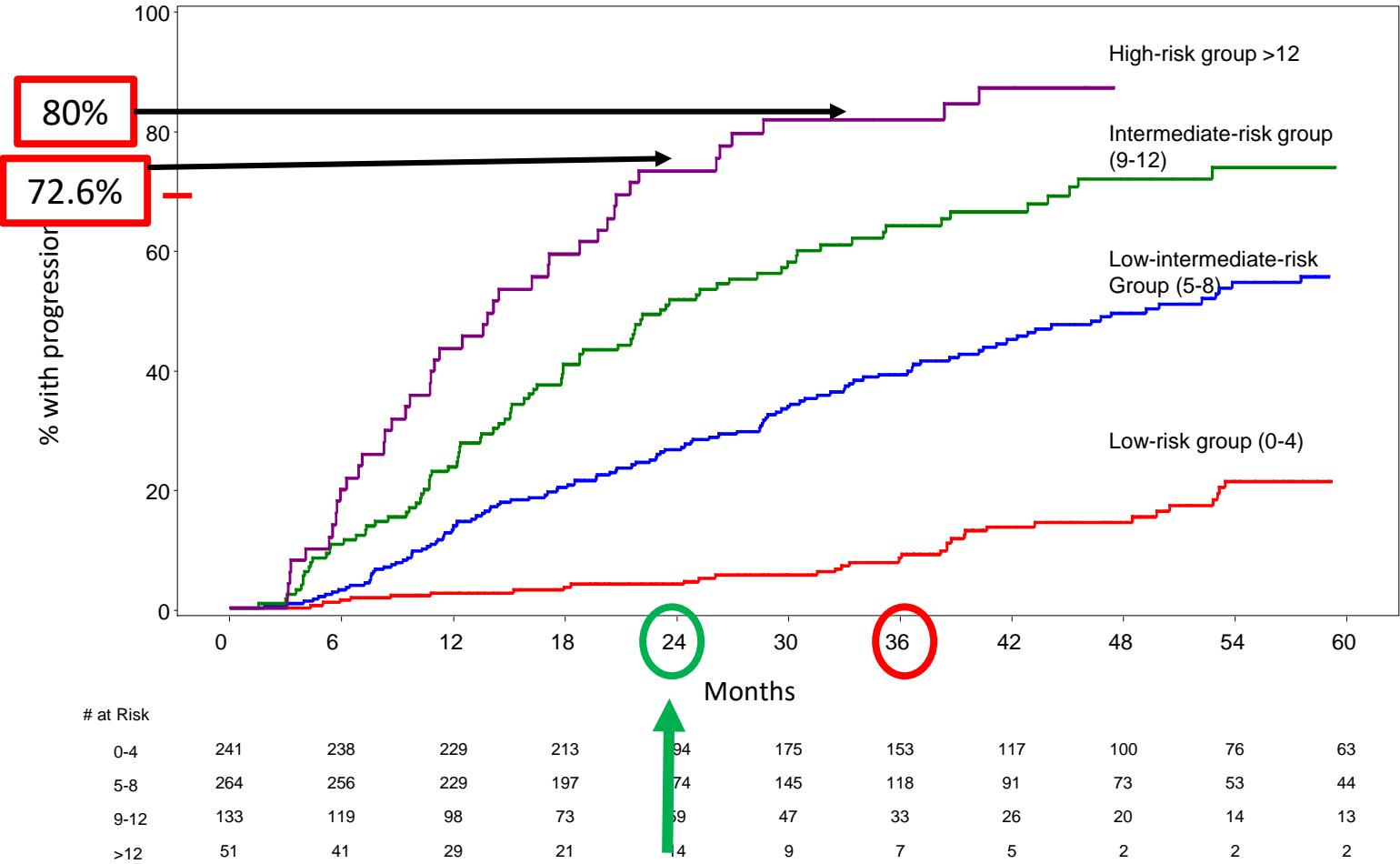
IMWG Project: New SMM Risk Score Tool*

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

Total Risk score	Predicted risk at 2-years	% of sample	
0	3.2	11.6	Low
2	6.2	8.1	34.9%
3	8.5	11.0	
4	11.6	4.2	
5	15.7	14.4	
6	20.8	6.8	
7	27	8.4	
8	34.3	8.7	
9	42.5	5.1	High
10	51	6.2	26.6%
11	59.5	4.9	
12	67.5	3.1	
13	74.6	2.3	
14	80.5	2.0	
15	85.4	1.7	
16+	89.2	1.3	

*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.

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%)

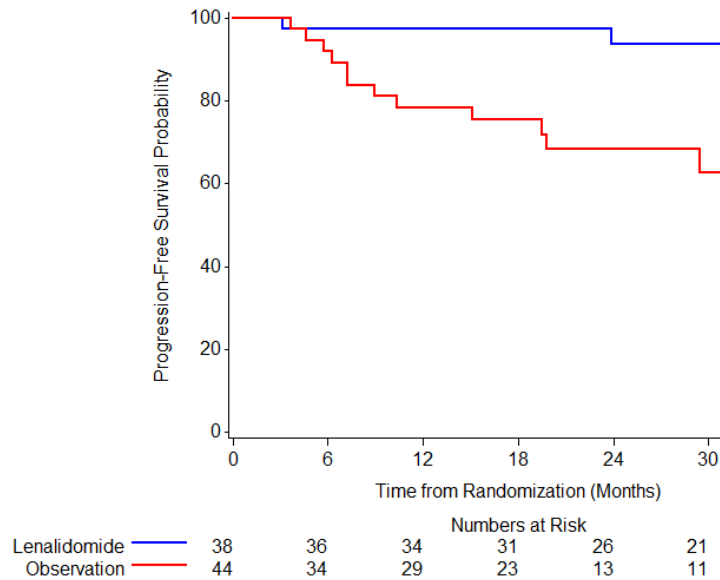
For **LOW-RISK**: 96% prediction of non-progression at 2 years

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

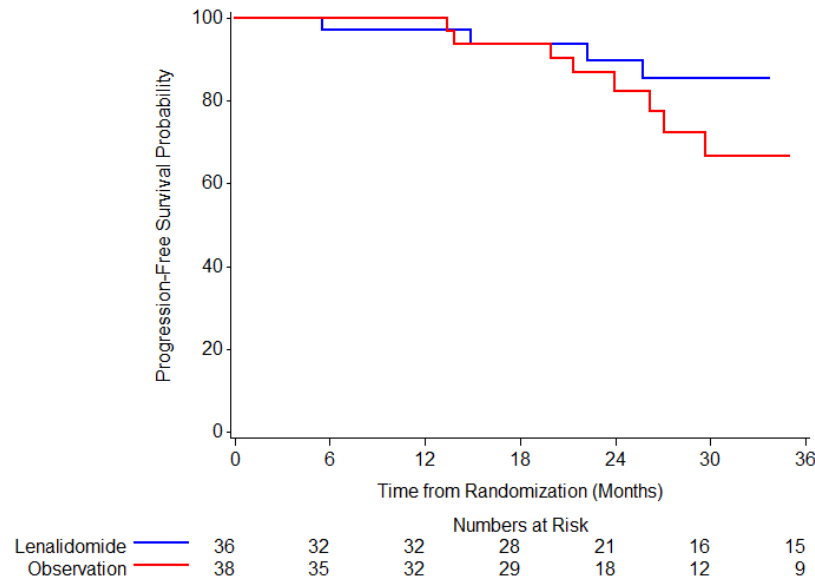
Sagar Lonial, M.D., Susanna Jacobus, M.Sc., Rafael Fonseca, M.D., Matthias Weiss, M.D., Shaji Kumar, M.D., Robert Z. Orlowski, M.D., Ph.D., Jonathan L. Kaufman, M.D., Abdulraheem M. Yacoub, M.D., Francis K. Buadi, M.D., Timothy O'Brien, M.D., Jeffrey V. Matous, M.D., Daniel M. Anderson, M.D., Robert 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.

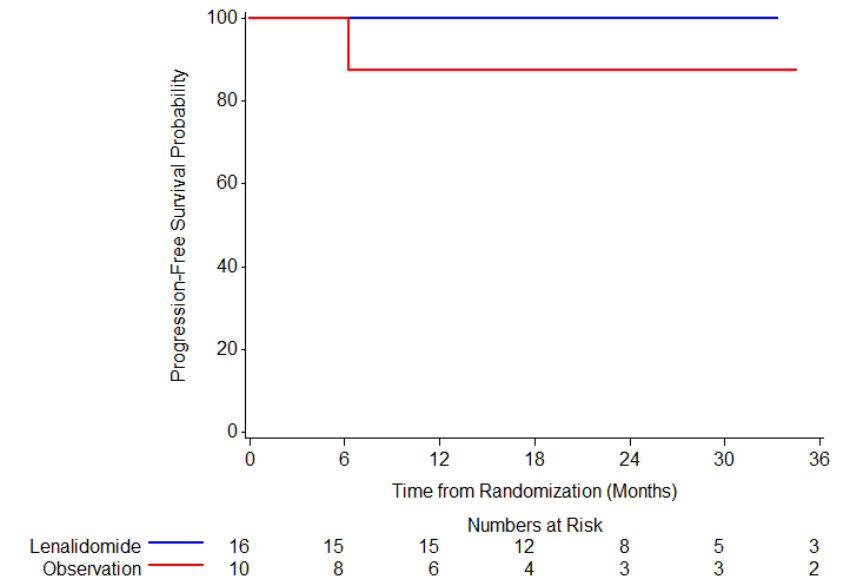
Phase III PFS by Mayo 2018 Risk Criteria



High Risk



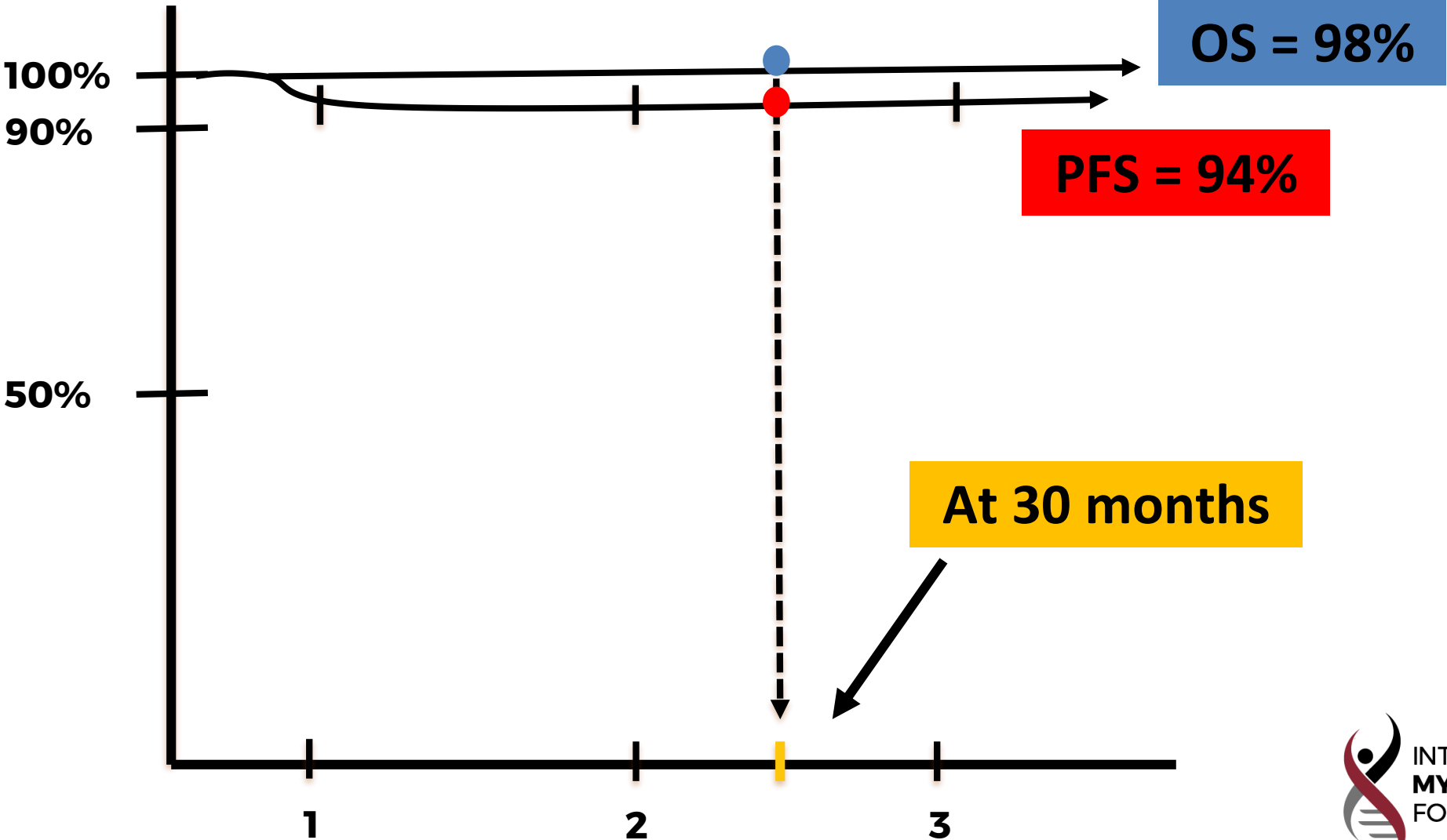
Intermediate Risk



Low Risk

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

Smoldering Myeloma (SMM)

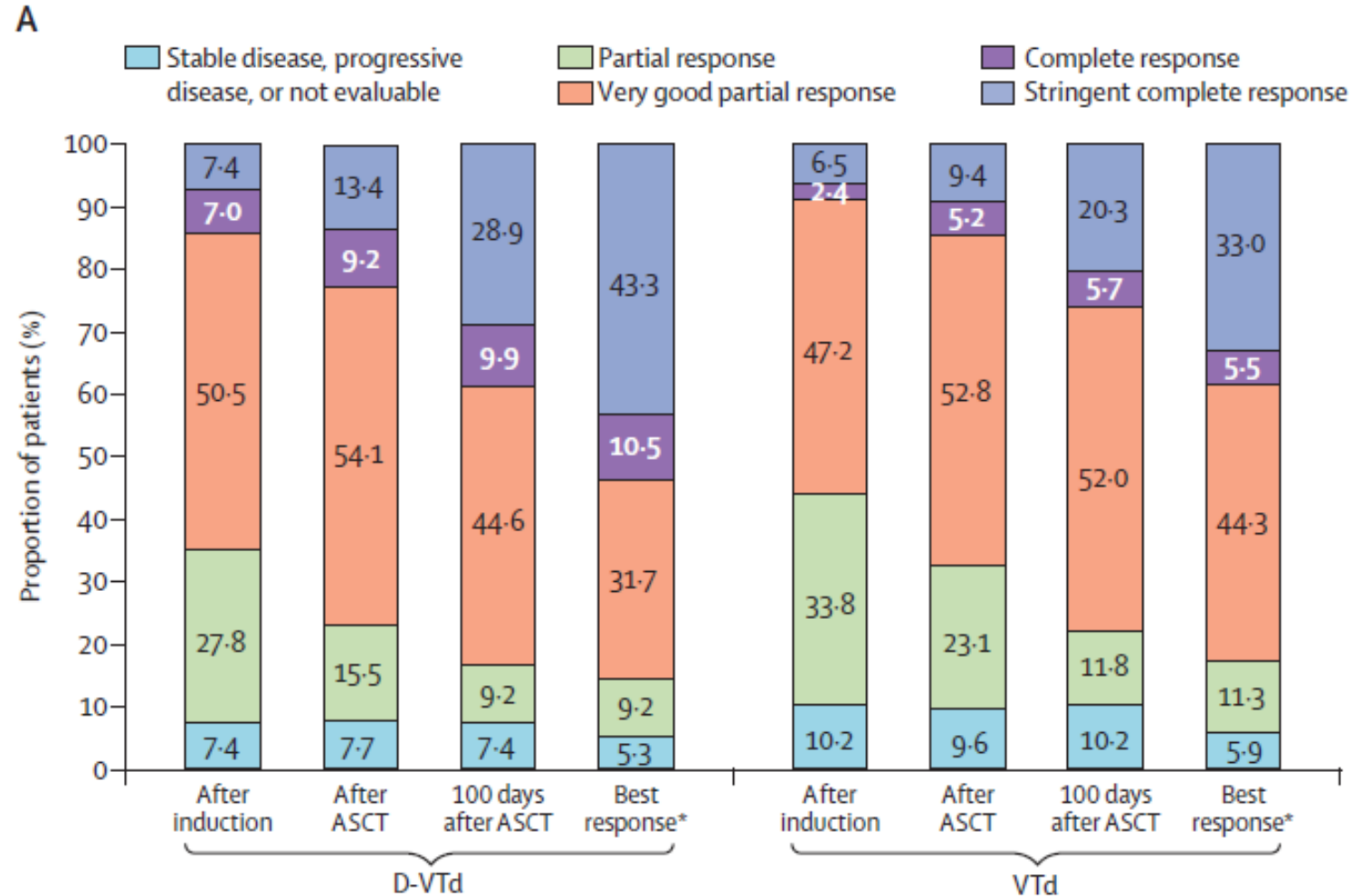
- **Risk classification**
- **Treatment strategies**

Frontline Therapy

- **CASSIOPEIA: Dara VTd versus VTd**
- **MAIA: Dara len/dex versus len/dex**
- **SQ Dara**
- **Forte: KRd ± ASCT**
- **t(11;14) impact**

PHASE 3 RANDOMIZED STUDY OF Dara VTd VERSUS VTd

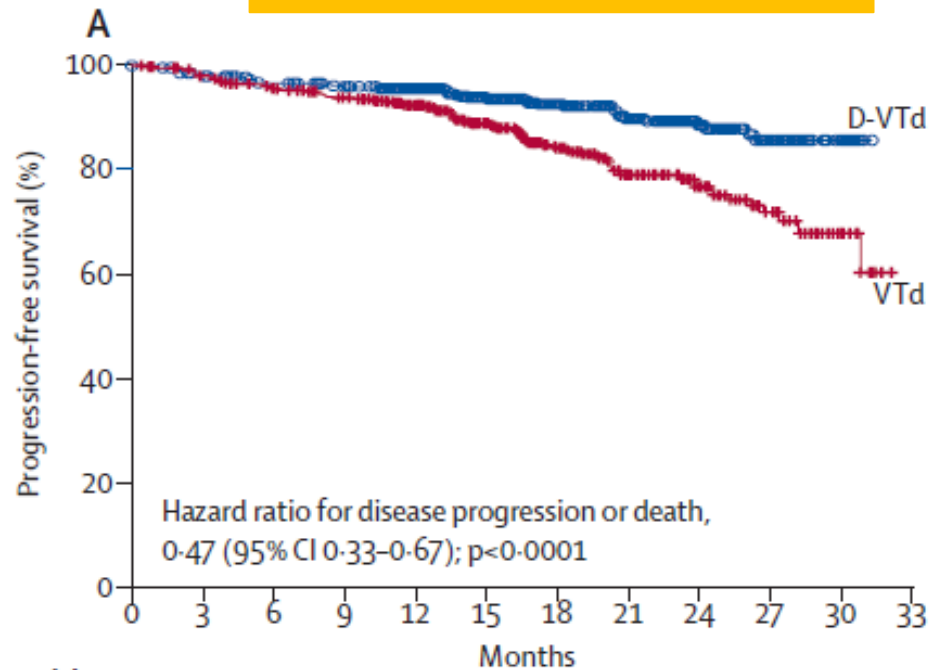
TRANSPLANT ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA: PART 1 CASSIOPEIA RESULTS*



MRD negative: 33.7% versus 19.9%

PHASE 3 RANDOMIZED STUDY OF Dara VTd VERSUS VTd

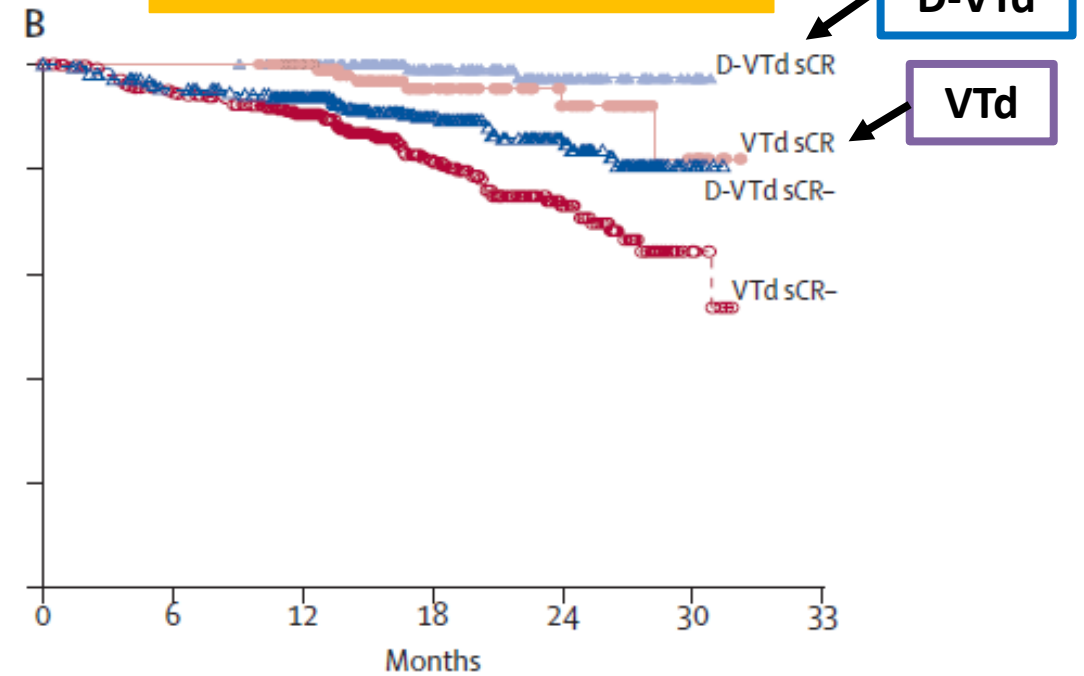
Progression Free Survival



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

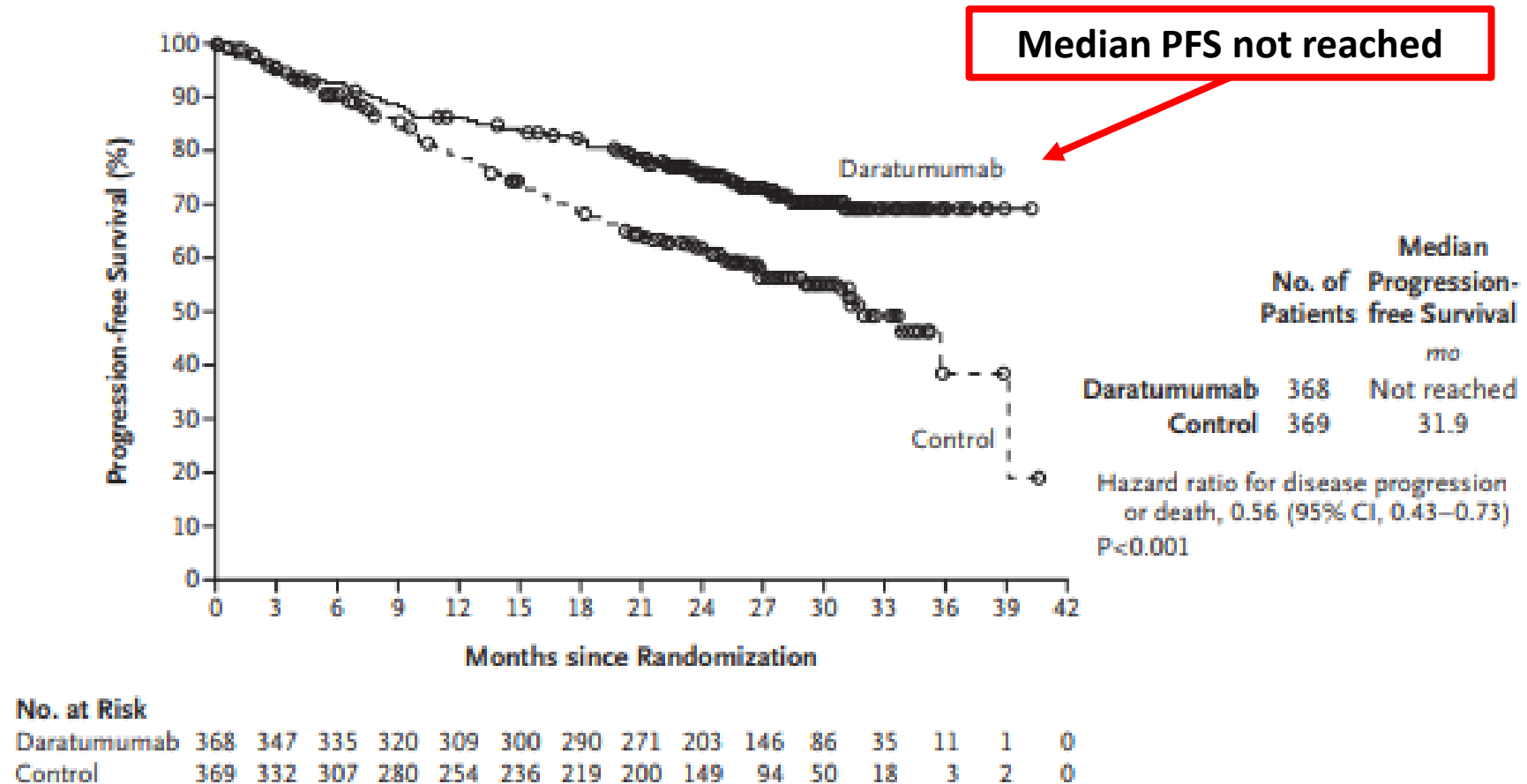
Impact of sCR



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

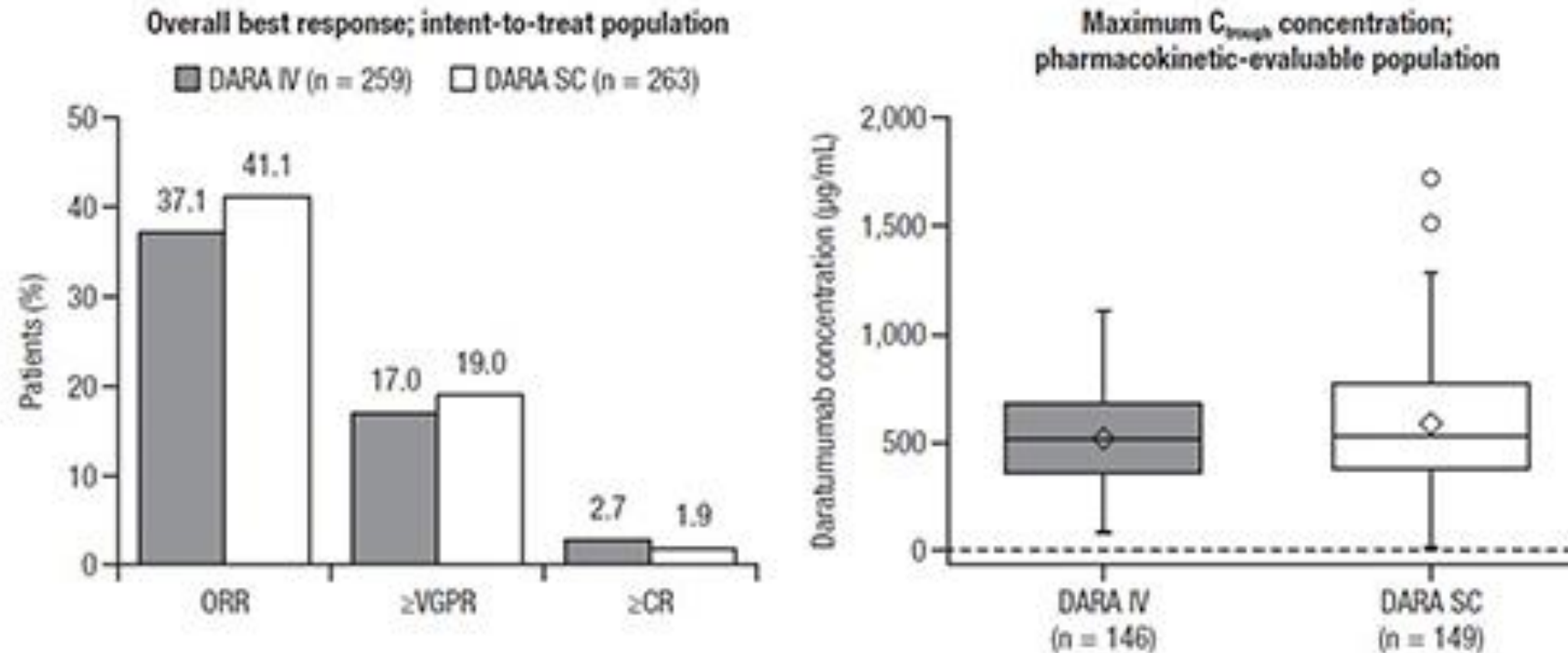
Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma* (MAIA)



*NEJM May 2019: 380; 22 pp 2104-2115

PHASE 3 STUDY OF SUBCUTANEOUS (SC) VERSUS INTRAVENOUS (IV) DARATUMUMAB ADMINISTRATION

PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA: COLUMBA



Dara SQ equivalent and SAFE

*ASCO abstract #8005; EHA abstract also

CARFILZOMIB LENALIDOMIDE DEXAMETHASONE (KRd) WITH OR WITHOUT TRANSPLANTATION

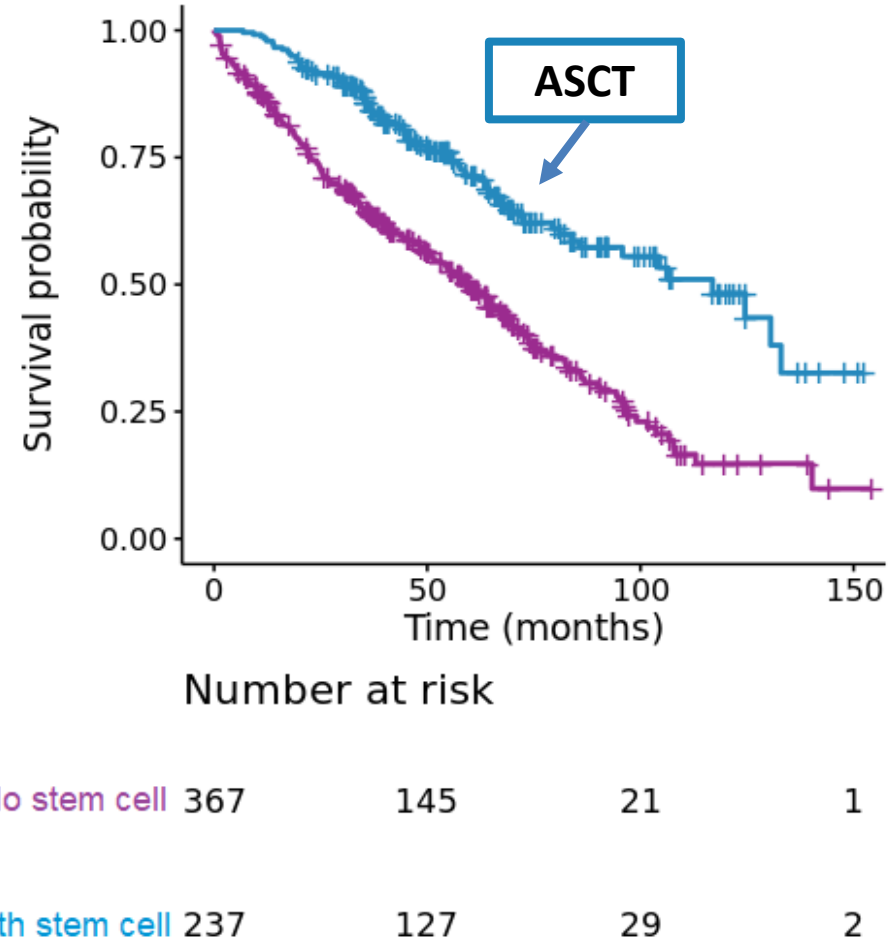
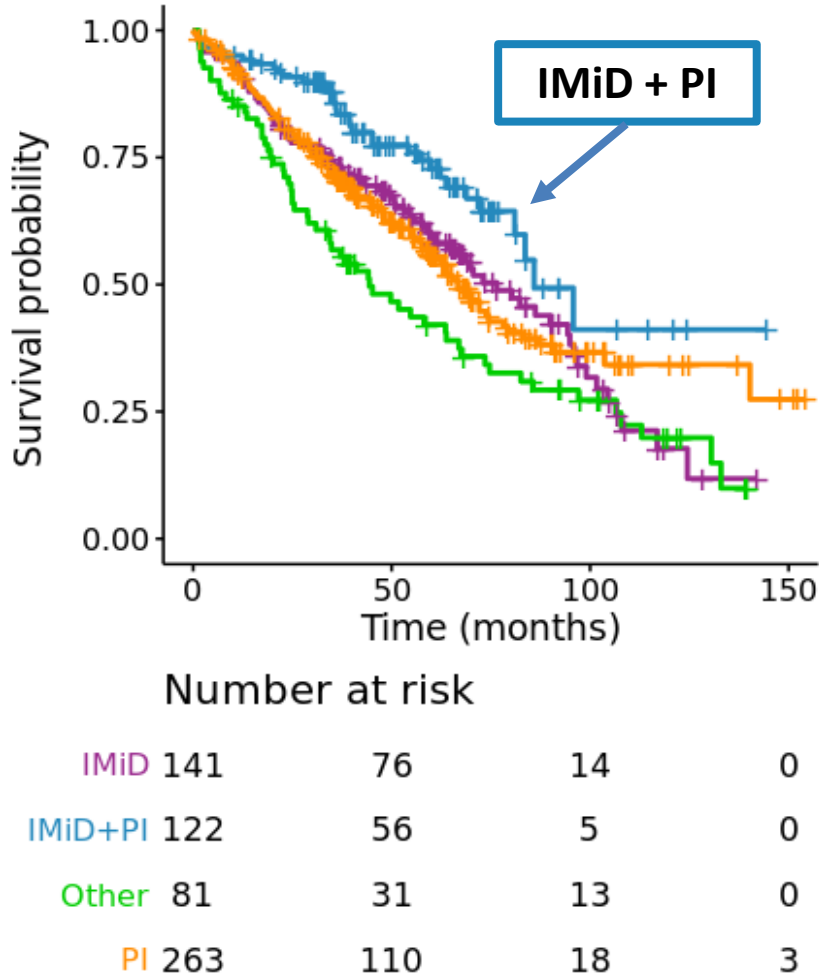
NEWLY DIAGNOSED MYELOMA (FORTE TRIAL): EFFICACY ACCORDING TO RISK STATUS

Table 1A: Overall population			Table 1B: Subgroup analysis			
	KRd_ASCT_KRd	KRd12	R-ISS 1		R-ISS 2/3	
	N=158	N=157	KRd_ASCT_KRd	KRd12	KRd_ASCT_KRd	KRd12
			N=48	N=39	N=92	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

Outcomes of patients with t(11;14) multiple myeloma: An International Myeloma Working Group*



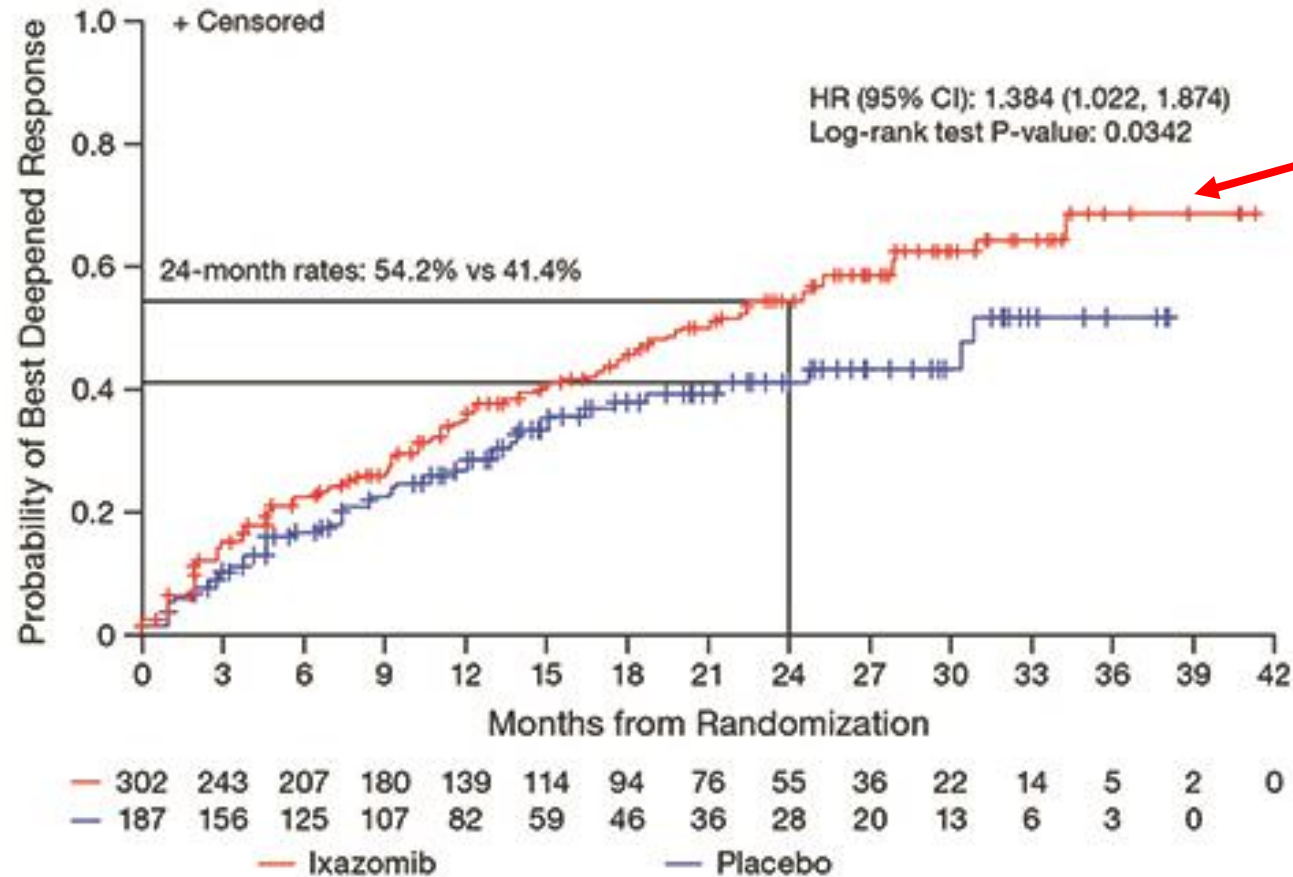
*ASCO: abstract #8015; also EHA abstract

Frontline Therapy

- **CASSIOPEIA: dara VTd versus VTd**
- **MAIA: dara len/dex versus len/dex**
- **SQ dara**
- **Forte: KRd \pm ASCT**
- **t(11;14) impact**

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

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



*EHA abstract: PS1382

Maintenance

- **Ixazomib**

Relapse Therapies

- **Isatuximab Pd versus Pd**
- **Dara Kd**
- **K in frail patients**
- **Elo Pd**
- **Selinexor/dara**

A phase III randomized, open label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone

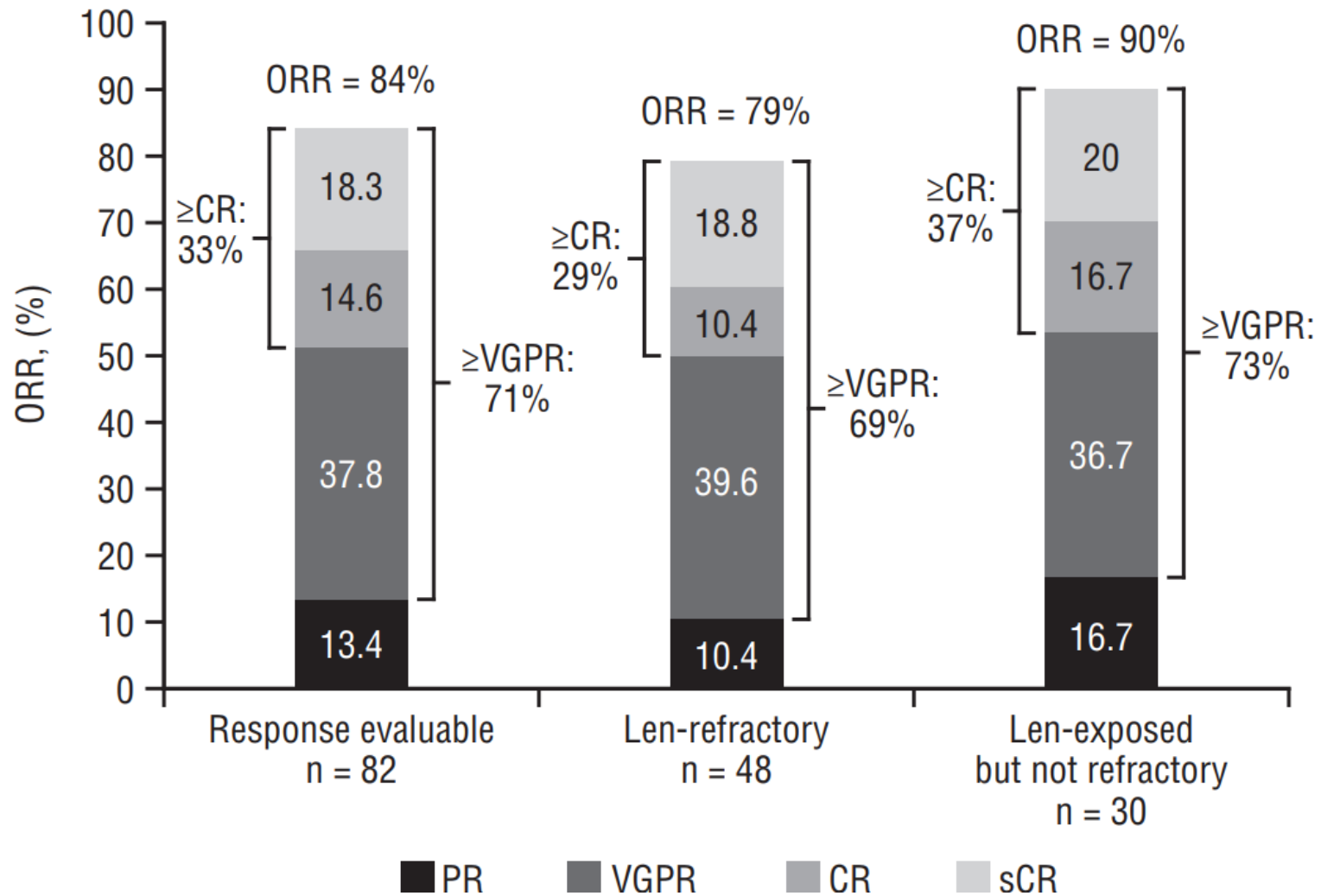
Patients with relapsed/refractory multiple myeloma (RRMM)

	Isa Pd	Pd alone
PFS	11.5 months	6.5 months
ORR	60.4%	35.3%
VGPR	31.8%	8.5%
MRD negative (10^{-5})	5.2%	0%



*ASCO: abstract #8004; also EHA abstract

Daratumumab Plus Carfilzomib and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma*



**≥ VGPR
~70%**

*Blood May 21, 2019: online

SAFETY AND EFFICACY OF ONCE-WEEKLY CARFILZOMIB DOSING 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)

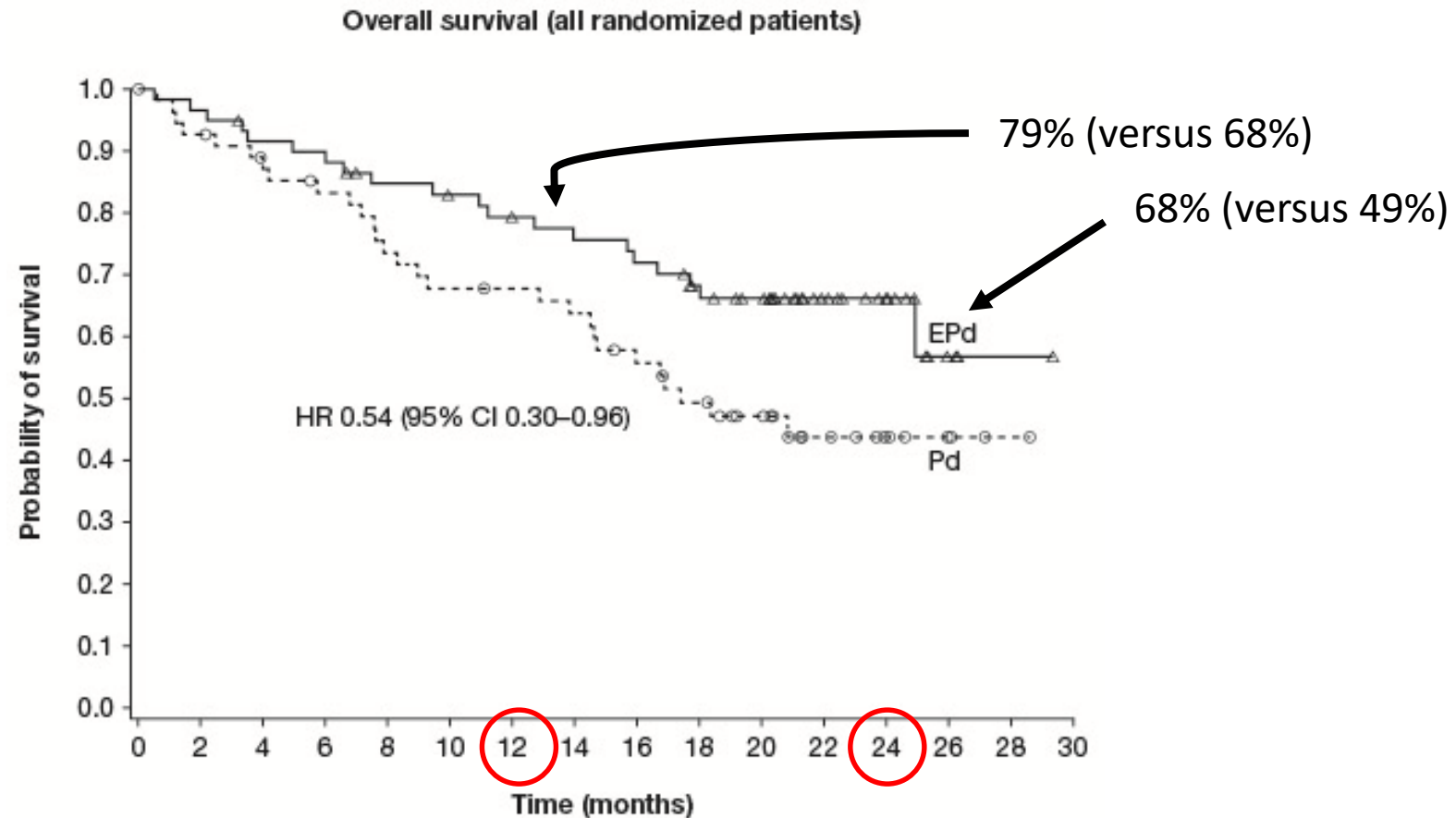
^aStandardized MedDRA Queries – Narrow

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

*ASCO: abstract #8027; also EHA abstract

ELOTUZUMAB PLUS POMALIDOMIDE AND DEXAMETHASONE FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA

EFFICACY RESULTS AFTER ADDITIONAL FOLLOW-UP OF THE PHASE 2, RANDOMIZED ELOQUENT-3 STUDY



Patients at risk

EPd	60	58	54	53	48	46	43	41	39	34	30	17	11	3	1	0
Pd	57	51	47	43	38	35	34	32	27	23	18	10	6	3	1	0

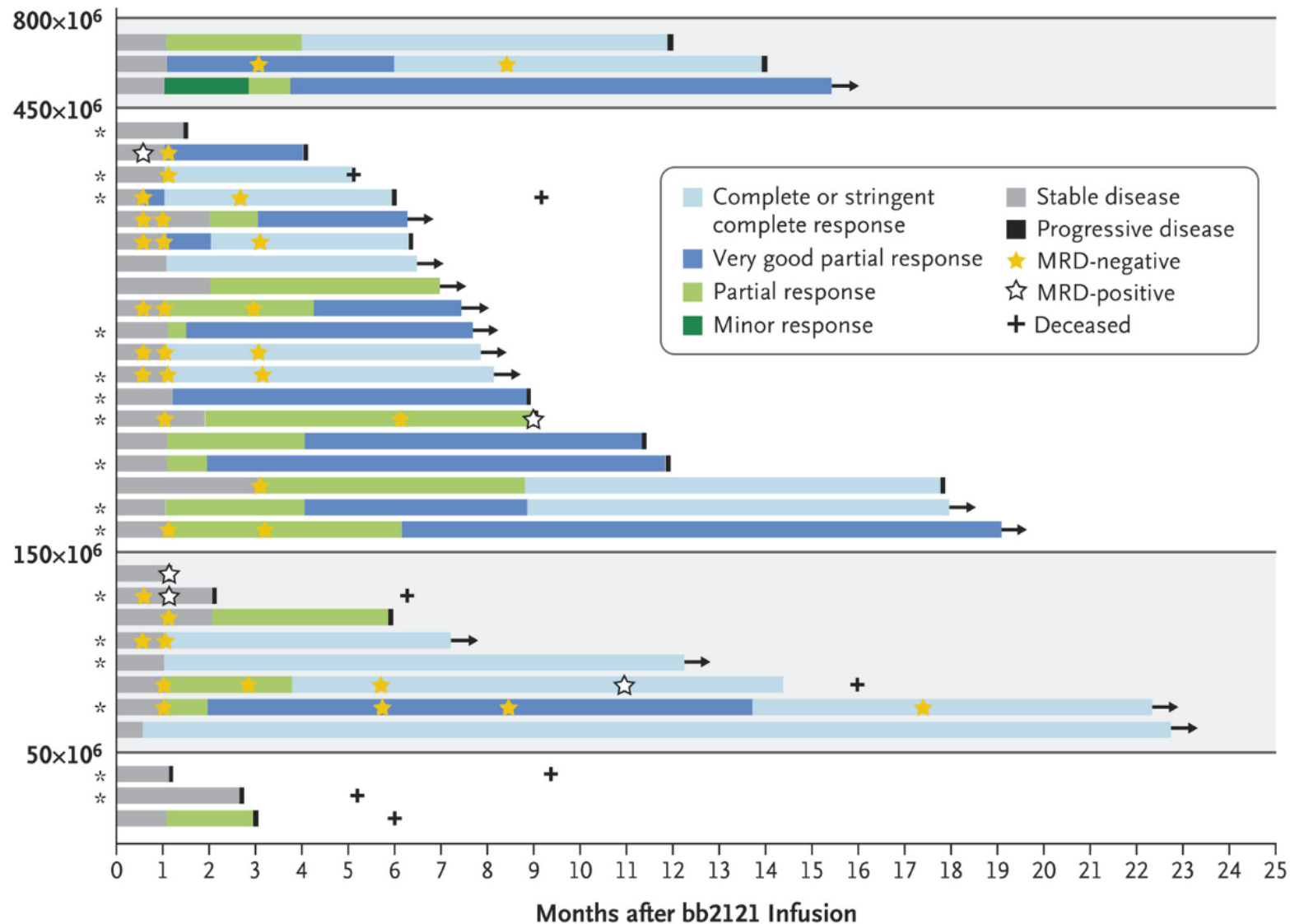
Relapse Therapies

How do you select and sequence?

New Agents

- **CAR T**
- **AMG 420 BiTE**
- **CELMOD (CC220)**

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

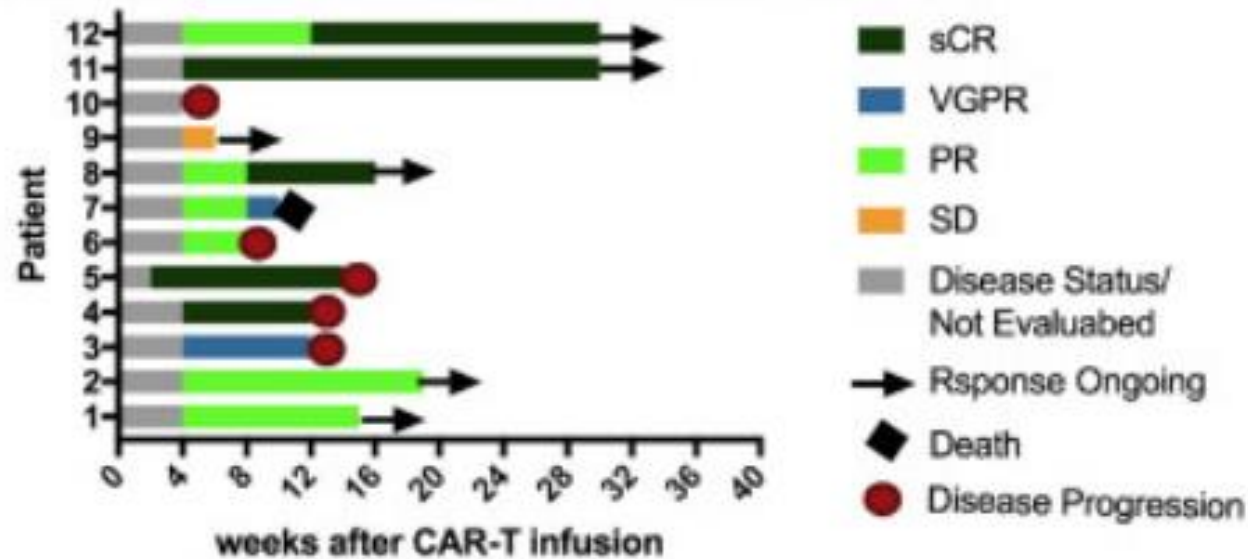


*NEJM May 2, 2019: pp 1726-1737

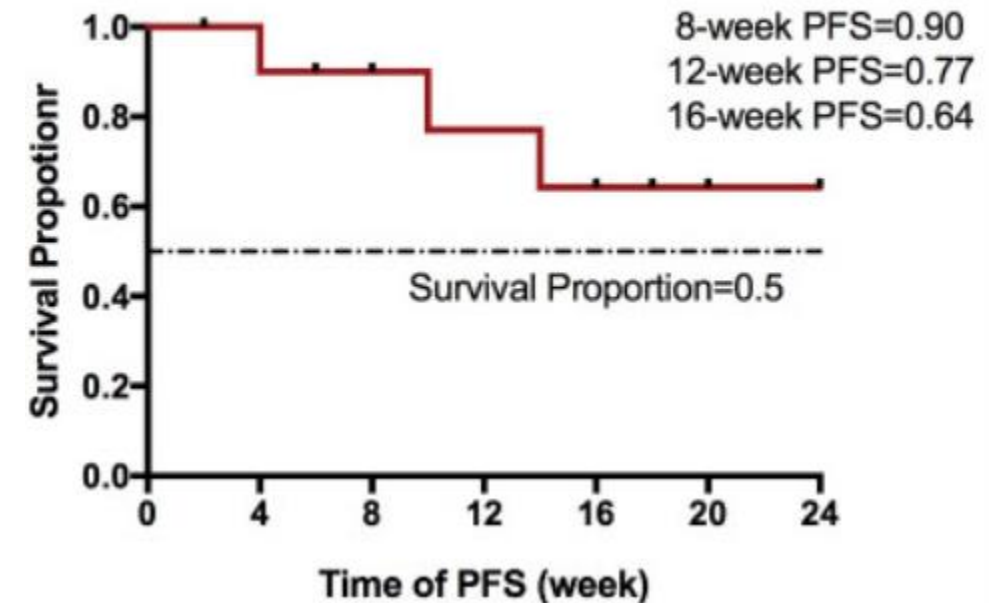
IMPROVED EFFICACY AND SAFETY OF A DUAL-TARGET CAR-T CELL THERAPY

TARGETING BCMA AND CD38 FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA FROM A PHASE I STUDY

Clinical Efficacy after anti-BCMA&CD38 CAR-T Infusion

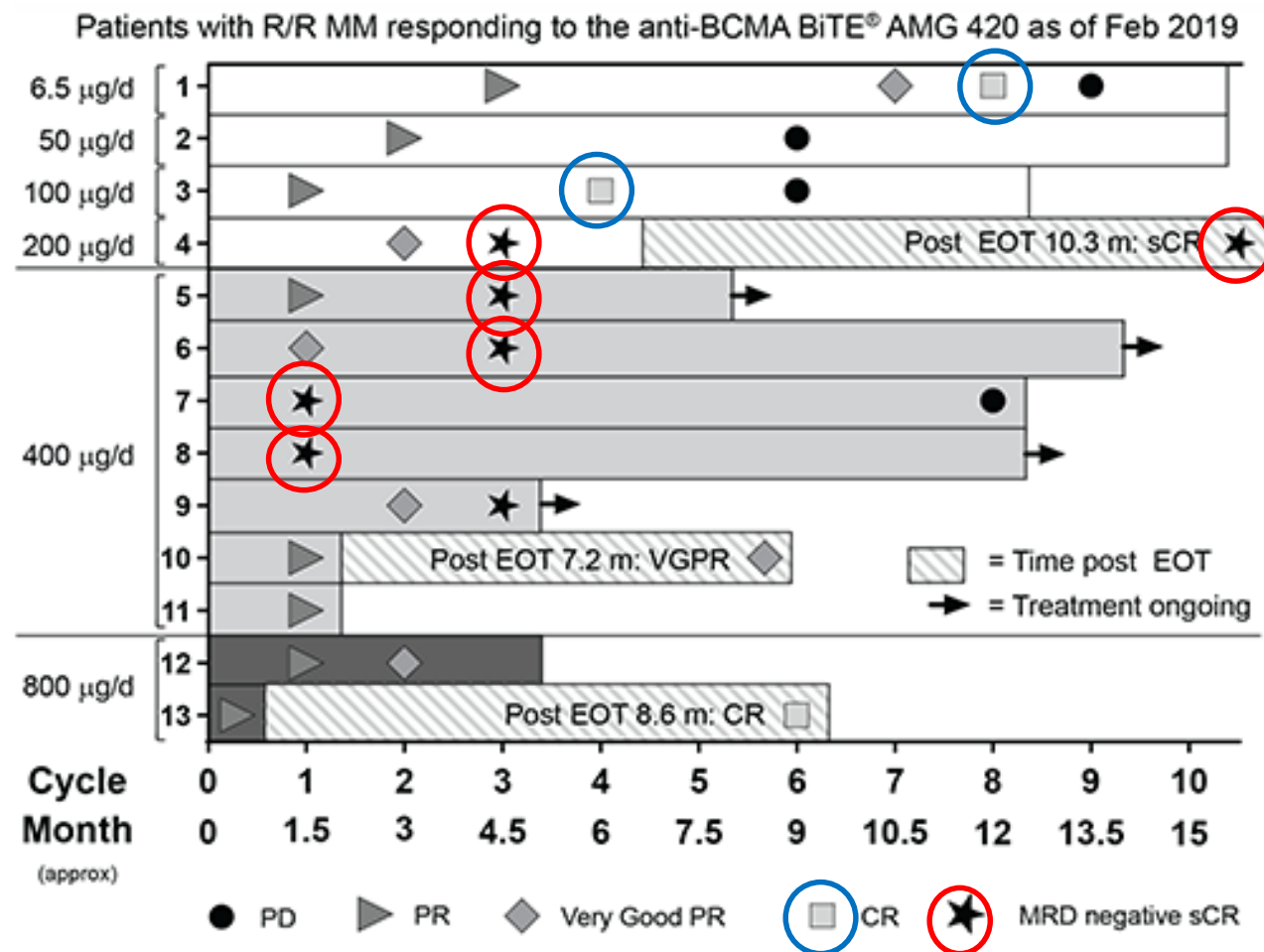


Progression-Free Survival of Patients with CAR-T Cell Therapy



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



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

Also: ASCO #2014 STORM trial update

New Therapies

- **What is your perspective on new therapies?**
 - **Which are top priority?**
 - **Which are promising?**
 - **Can any be offered in frontline or early disease?**

Other Interesting Abstracts

Examples

- ASCO #8020: BCMA as a biomarker
- ASCO #8023: Prognosis of 1q+ patients
- ASCO #8031: Importance of circulating plasma cells
- ASCO #8036: DNA mutations in blood
- ASCO #8053: Update on GSK 2857916

Final Thoughts

**What are key next trials
or studies?**

THANK YOU!

- **Experts**
- **Audience**
- **Sponsors**
- **Until next time!**



Thank you to our sponsors!

