

IMWG CONFERENCE SERIES 2019

THE BEST OF ASH



Brian G.M. Durie, MD

María V Mateos, MD

Joseph Mikhael, MD

Monday, December 9th, 2019

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Oncology



O N C O L O G Y



PHARMACEUTICAL COMPANIES OF *Johnson+Johnson*

TONIGHT'S SPEAKERS

Monday
DEC 9
2019

THE
IMWG CONFERENCE SERIES
"Making Sense of Treatment"

watch the **LIVESTREAM**: 5:30 PM PT/7:30 PM CT/8:30 PM ET
(replay will also be available)



Joseph Mikhael, MD

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



Brian G. M. Durie, MD

Brian GM Durie
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Maria V. Mateos, MD

**María-Victoria
Mateos**
University of Salamanca

IMWGconferenceseries.myeloma.org

TOPICS FOR DISCUSSION

- **Smoldering myeloma**
- **Frontline therapy**
- **Significance of FISH testing**
- **CAR T therapy/Bispecific T Cell Engagers/MoAb**
- **Novel agents/combinations**

SMOLDERING MYELOMA

- **What is HR-SMM?**
- **How should it be managed?**

IMWG Classification of HR SMM

Progression by Risk Group (n = 1151 pts)

2/20/20 Model

FLC Ratio **20**

Serum M Protein **2 g/dl**

Bone Marrow Plasma Cell % **20%**

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

Risk Score

Low Risk

High Risk

New SMM Risk Score Tool

Rationale for Early Intervention

➤ To treat the disease early: to achieve cure

- *Early detection and intervention is a pre-requisite for cure in most malignancies*
- *Why is the standard of care in MM **no treatment** until CRAB? Risk of harm: clonal selection, toxicities.*

Numerous clinical trials in SMM (~ 51 in clinicaltrials.gov)

TO DELAY THE DISEASE PROGRESSION:

- Len-Dex vs observation: +PFS & OS
- Len vs observation: +PFS
- Elo-Rd: *Positive results*
- Ixaz-Rd: *Positive results*
- Daratumumab: *Positive results*
- KRd: *Positive results (12 cases MRD- 92%)*
- Pembrolizumab; Nivolumab-Rd; Isatuximab

TO CURE THE DISEASE:

- KRD + ASCT + Consol + Maint (CESAR)
- KRD + Dara..... (ASCENT)

**781 Curative Strategy (GEM-CESAR) for High-Risk Smoldering Myeloma (SMM):
Carfilzomib, Lenalidomide and Dexamethasone (KRd) As Induction Followed By HDT-
ASCT, Consolidation with Krd and Maintenance with Rd**

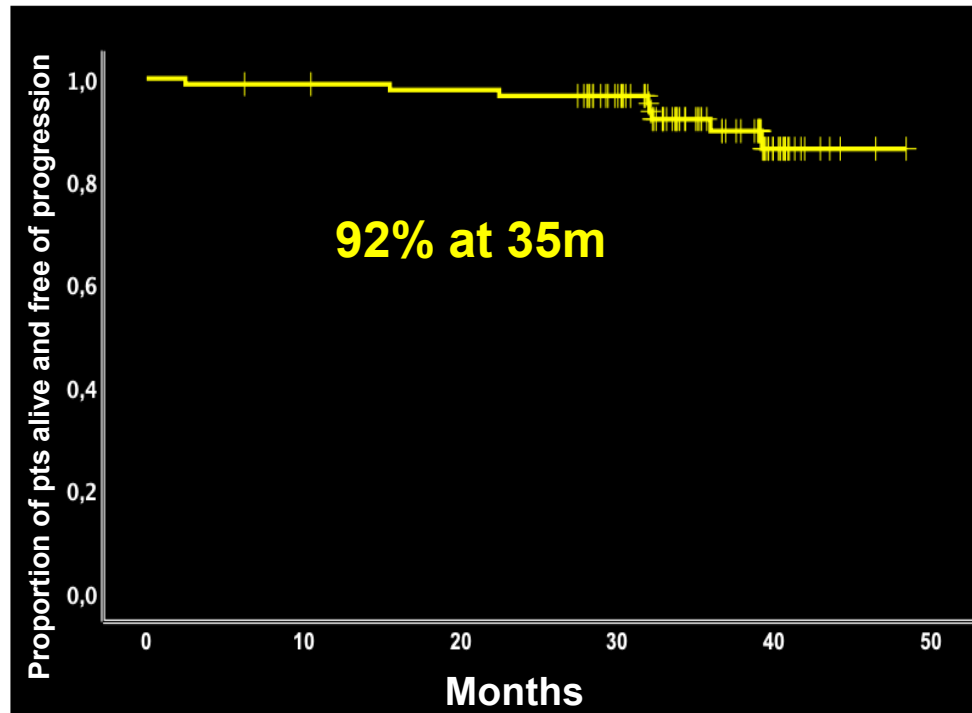
Improvement in the quality of response over the treatment

	Induction (KRdx6) N = 77	HDT/ASCT N = 77	Consolidation (KRdx2) N = 77	Maintenance (Rdx1y) N = 77
≥CR	43%	63%	75%	81%
VGPR	43%	24%	18%	13%
PR	13%	13%	7%	5%
PD				1%*
MRD-negative	33%	49%	62%	62%

* Progressive disease was biological at the end of maintenance and the MRD was positive

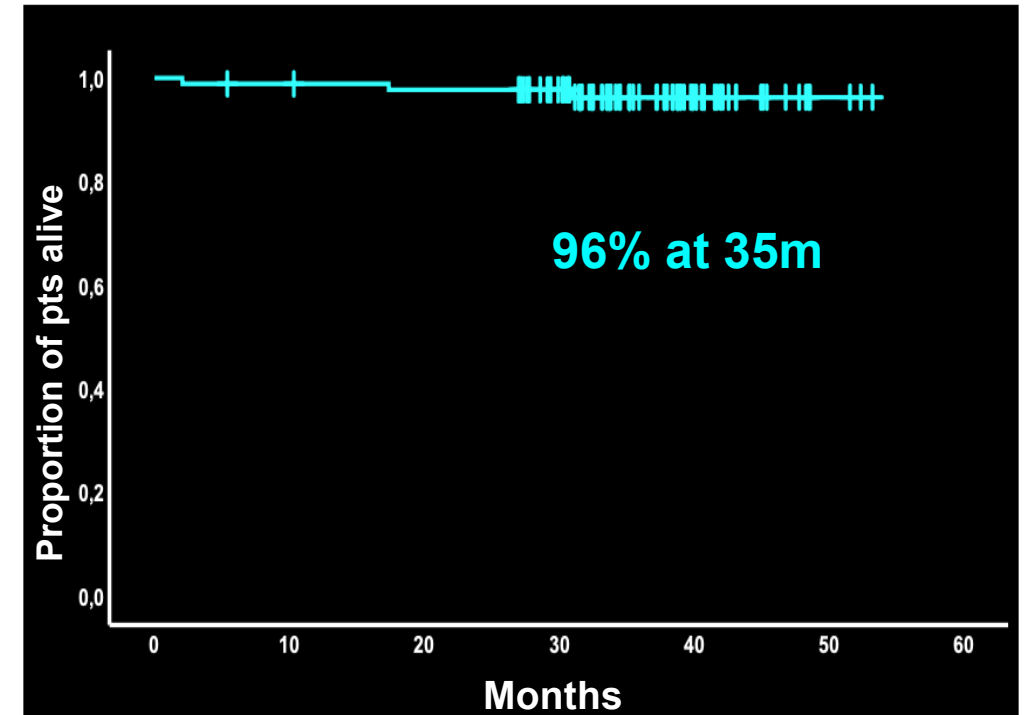
**781 Curative Strategy (GEM-CESAR) for High-Risk Smoldering Myeloma (SMM):
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ASCT, Consolidation with Krd and Maintenance with Rd**

PFS



6 pts did progress and in 5 pts PD was biological and 4 pts were at ultra high risk

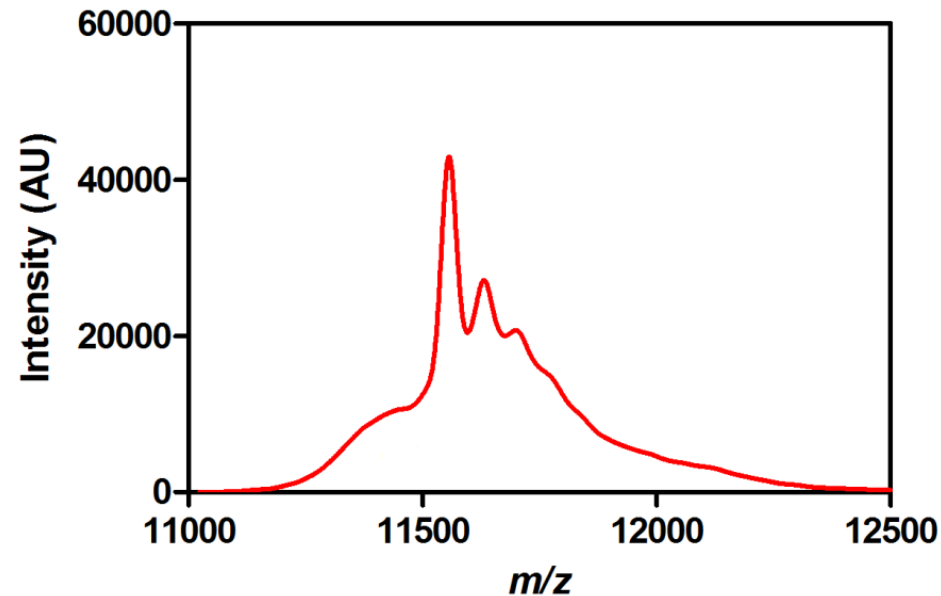
OS



3 pts died and in only one was treatment-related death

The Innovative Approach

Identify M-protein molecular mass with high precision and accuracy

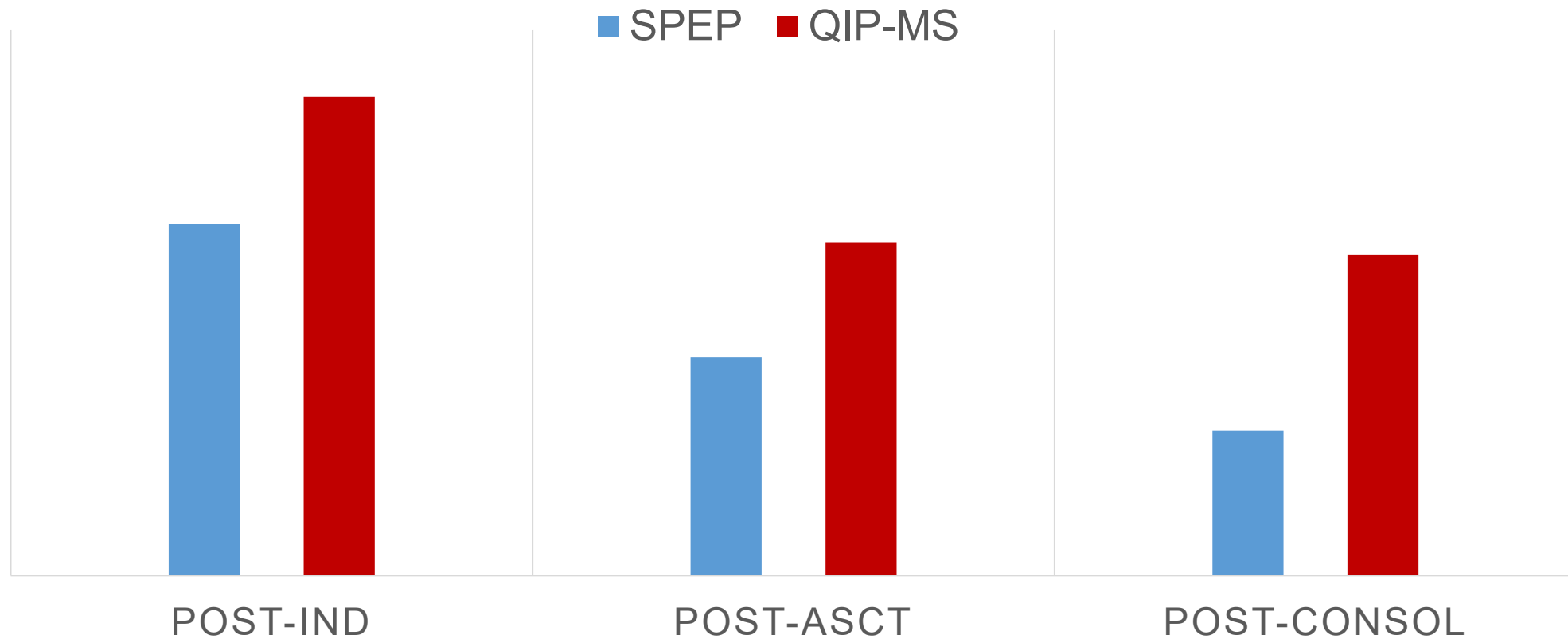


**Molecular mass defines
clonality / intensity
defines abundance**

The result is a highly sensitive and specific approach to monitor M-proteins

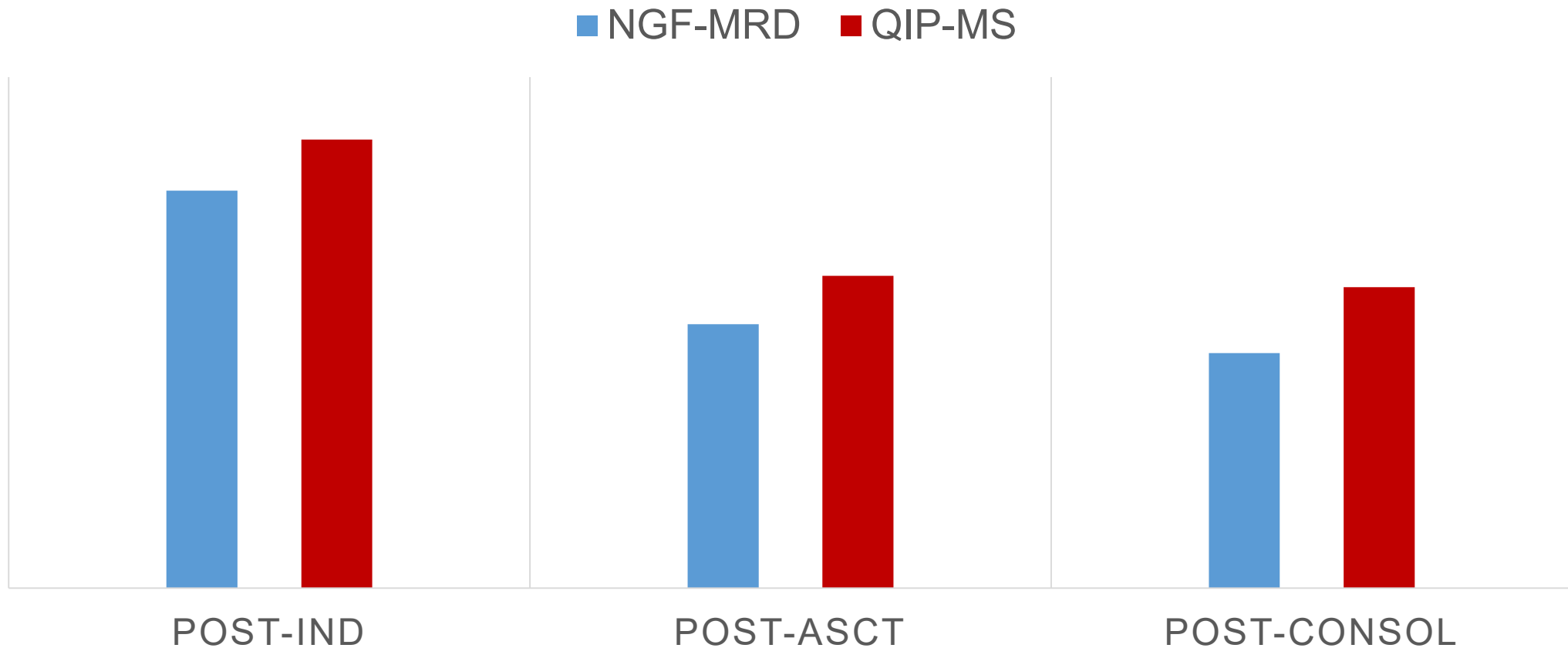
581 Qip-Mass Spectrometry in High Risk Smoldering Multiple Myeloma Patients Included in the GEM-CESAR Trial: Comparison with Conventional and Minimal Residual Disease IMWG Response Assessment

SPEP/IFE vs QIP-MS: Sensitivity



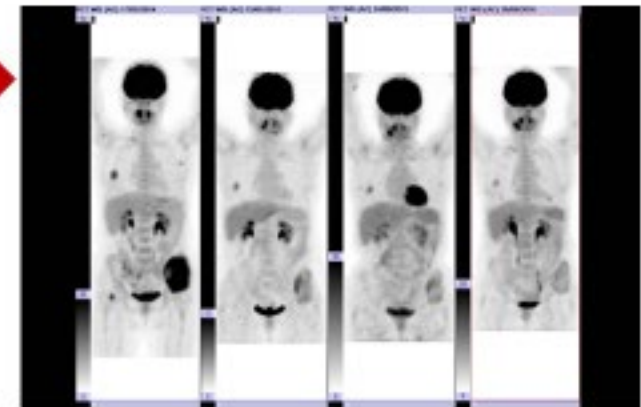
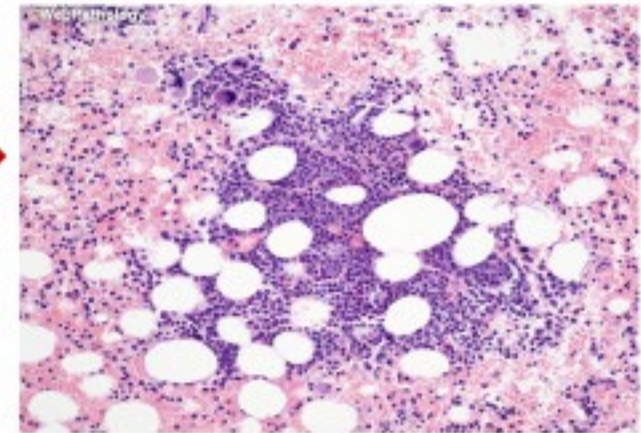
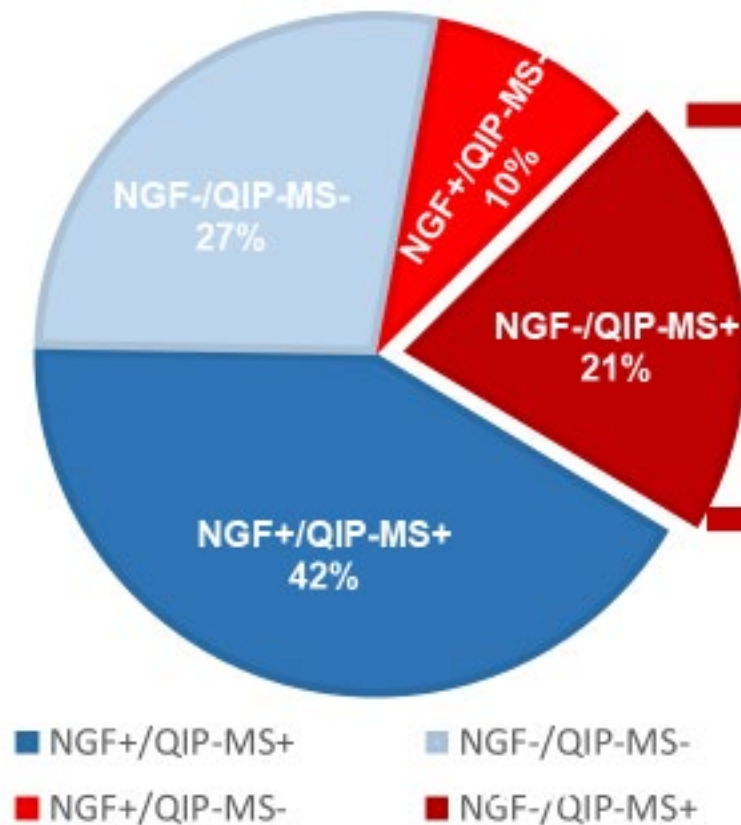
581 Qip-Mass Spectrometry in High Risk Smoldering Multiple Myeloma Patients Included in the GEM-CESAR Trial: Comparison with Conventional and Minimal Residual Disease IMWG Response Assessment

NGF-MRD vs QIP-MS: Sensitivity



581 Qip-Mass Spectrometry in High Risk Smoldering Multiple Myeloma Patients Included in the GEM-CESAR Trial: Comparison with Conventional and Minimal Residual Disease IMWG Response Assessment

NGF-MRD - vs QIP-MS+



SMOLDERING MYELOMA

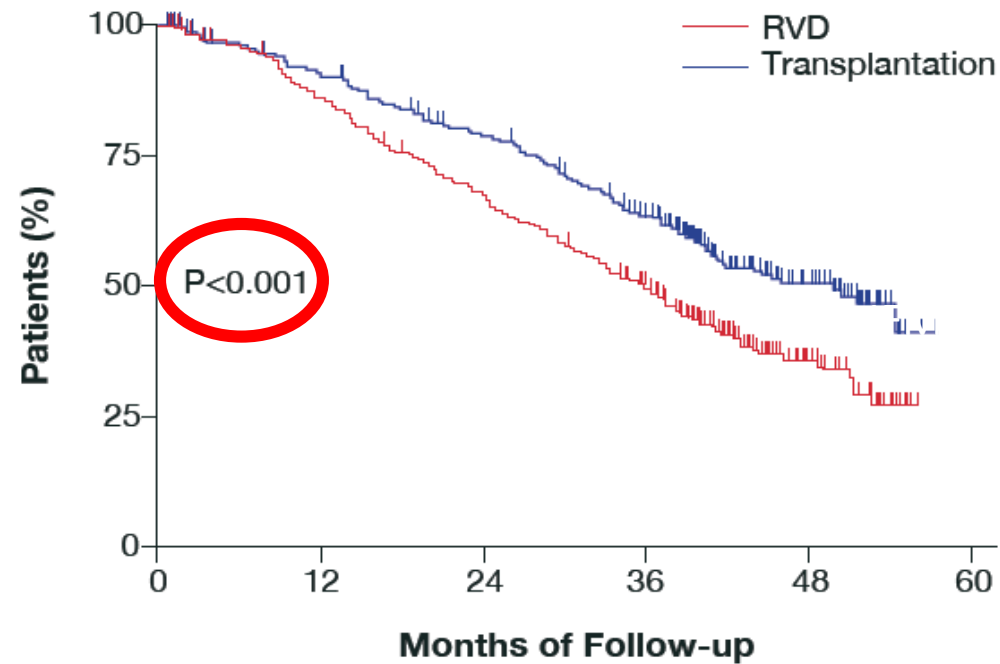
- **Are current HR SMM criteria good enough?**
- **Are we starting to CURE some patients?**
- **Is single-agent therapy appropriate?**
- **Will mass spectrometry help with monitoring?**

FRONTLINE THERAPY

- **What is best?**
- **Are dara + triplet regimens the way forward?**

VRd + ASCT: IFM 2009 STUDY

PFS

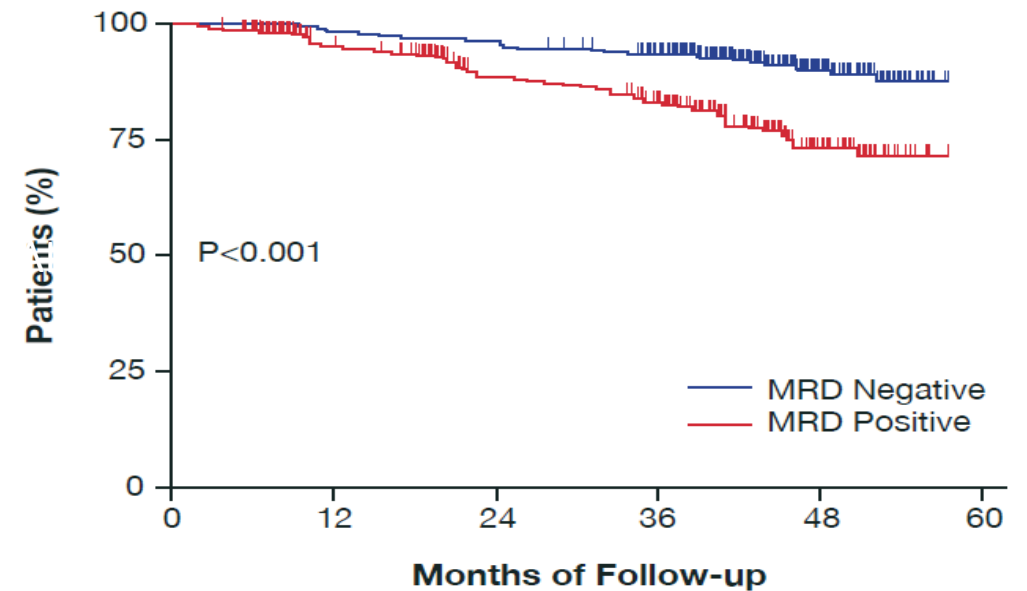


No. at Risk

RVD	350	294	228	157	32	0
Transplantation	350	308	264	196	50	0

OS

S1B



No. at Risk

MRD Negative	0	311	379	347	119	0
MRD Positive	700	358	259	227	65	0

VRD x 6, 458 Patients GEM2012 trial



blood[®]

Prepublished online September 4, 2019;
doi:10.1182/blood.2019000241

Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplantation in multiple myeloma

Laura Rosiñol, Albert Oriol, Rafael Rios, Anna Sureda, María-Jesús Blanchard, Miguel Teodoro Hernández, Rafael Martínez-Martínez, Jose M Moraleda, Isidro Jarque, Juan Bargay, Mercedes Gironella, Felipe de Arriba, Luis Palomera, Yolanda Gonzalez-Montes, Josep Martí, Isabel Krsnik, Jose M Arguiñano, Maria-Esther Gonzalez, Ana Pilar Gonzalez, Luis Felipe Casado, Lucia Lopez-Anglada, Bruno Paiva, Maria-Victoria Mateos, Jesus San Miguel, Juan-José Lahuerta and Joan Bladé

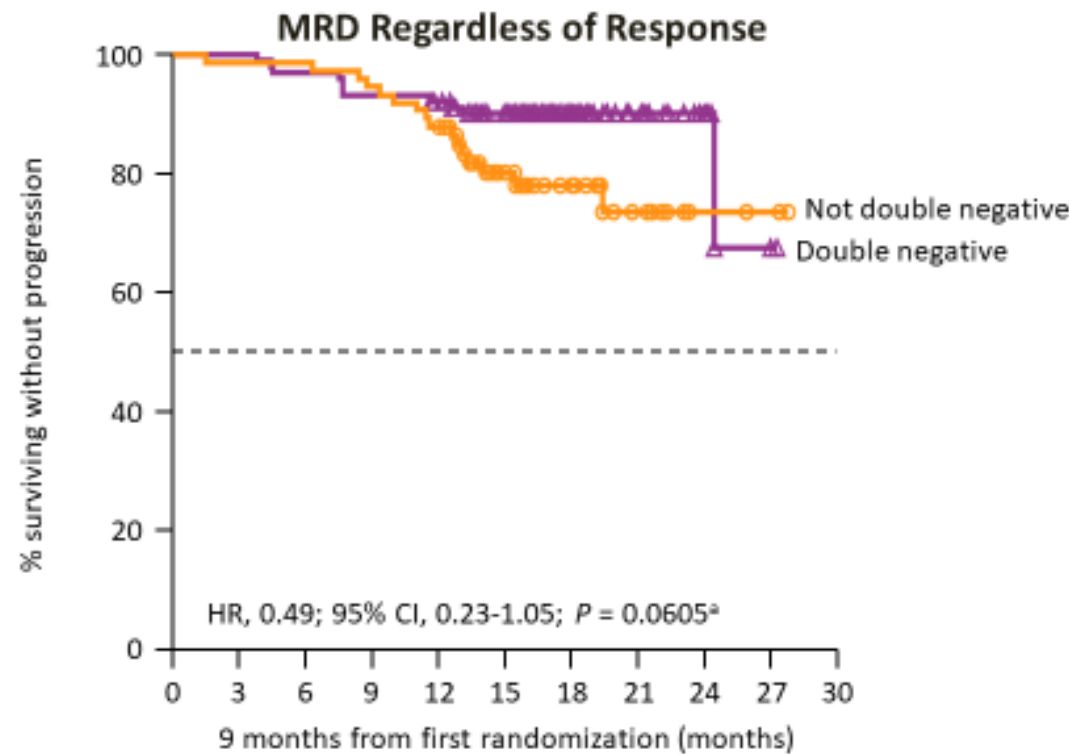
VELCADE

- **2x each week SQ for 2 weeks**
- **Q4 week cycles**

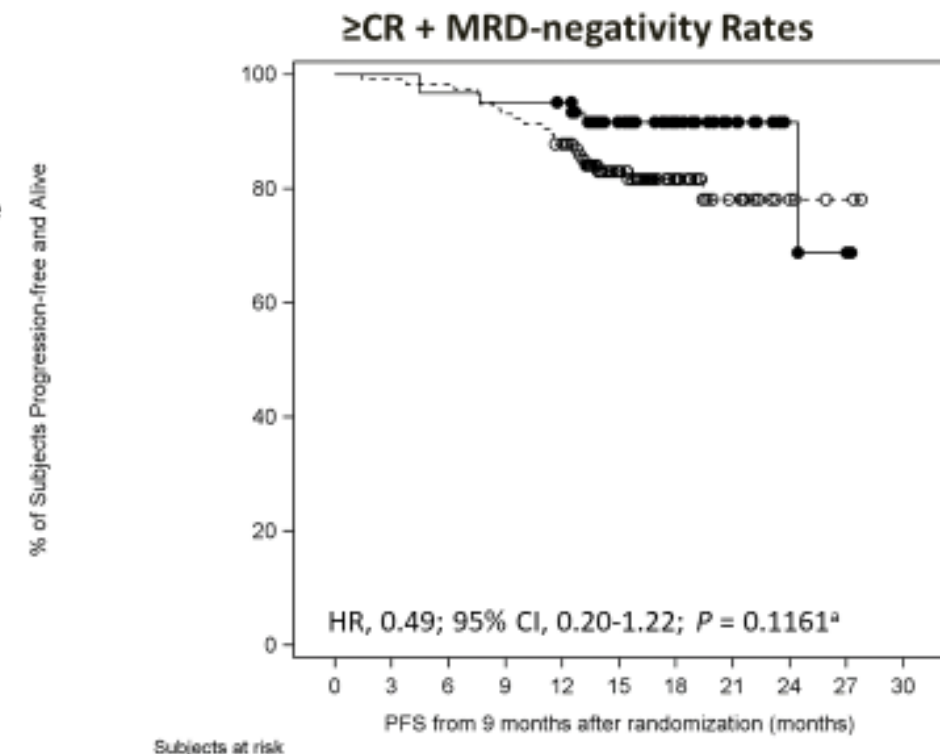
Dara VTd versus VTd (Cassiopeia)

PFS From First Randomization

Landmark Analysis for PFS by Double-negativity Rate for MRD (MFC; 10^{-5}) and PET/CT Post-consolidation



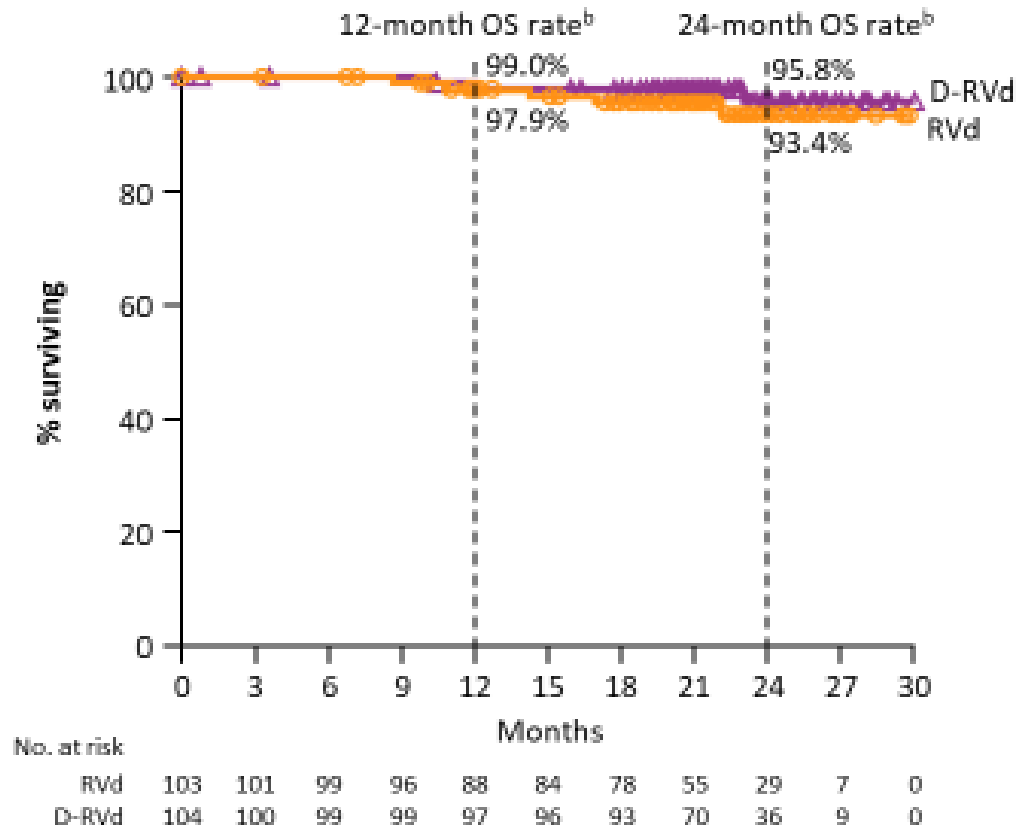
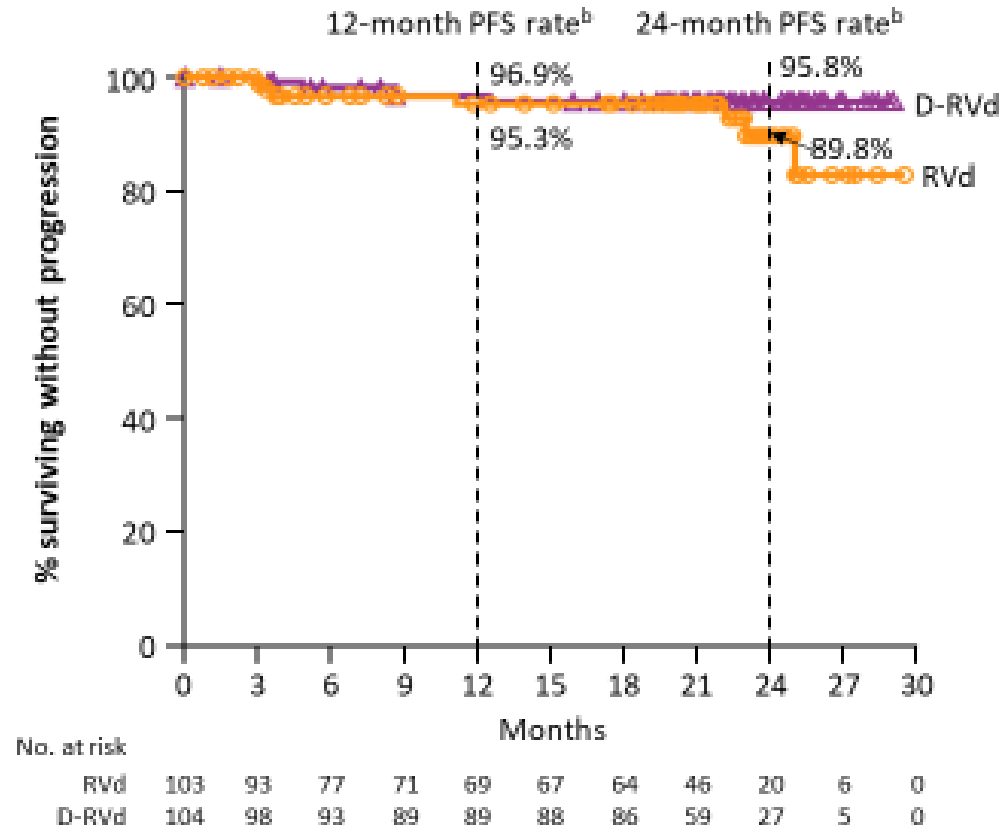
No. at risk	102	102	99	95	92	63	35	18	6	2	0
Double negative	74	73	73	70	65	41	25	12	3	2	0
Not double negative											



Subjects at risk	61	61	59	58	57	39	25	14	4	2	0
Double Negative and CR+	115	114	113	107	100	65	35	16	5	2	0
Not Double Negative or VGPR-											

691 Depth of Response to Daratumumab (DARA), Lenalidomide, Bortezomib, and Dexamethasone (RVd) Improves over Time in Patients (pts) with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Griffin Study Update

- Median follow-up = 22.1 months

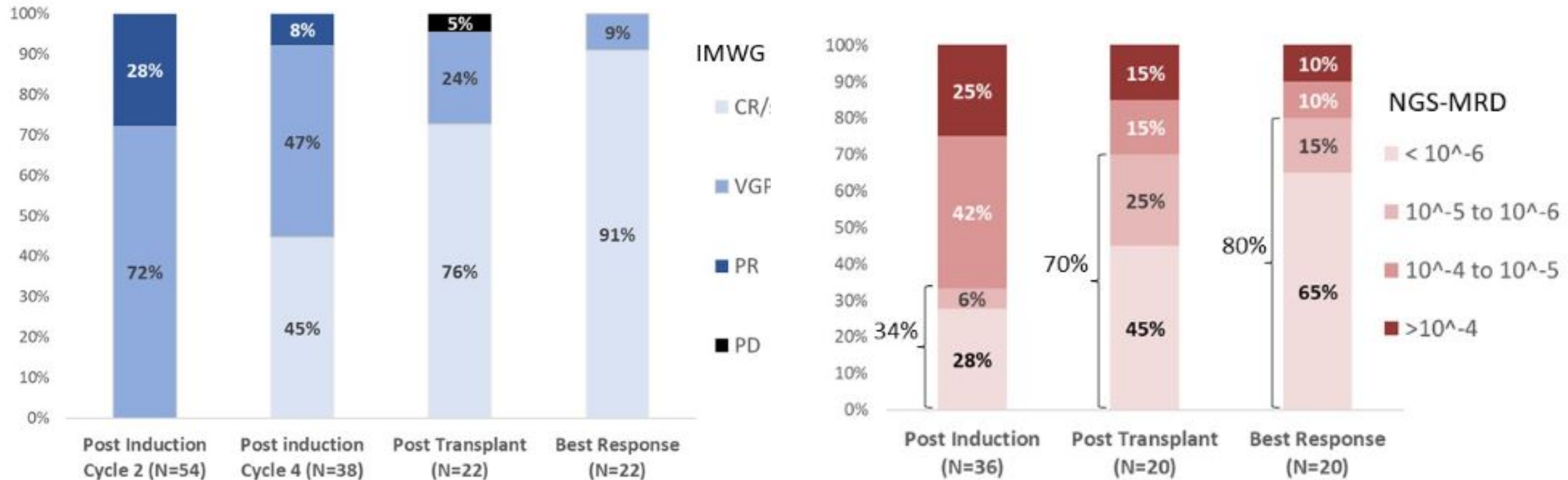


Median PFS and OS not reached for D-RVd and RVd

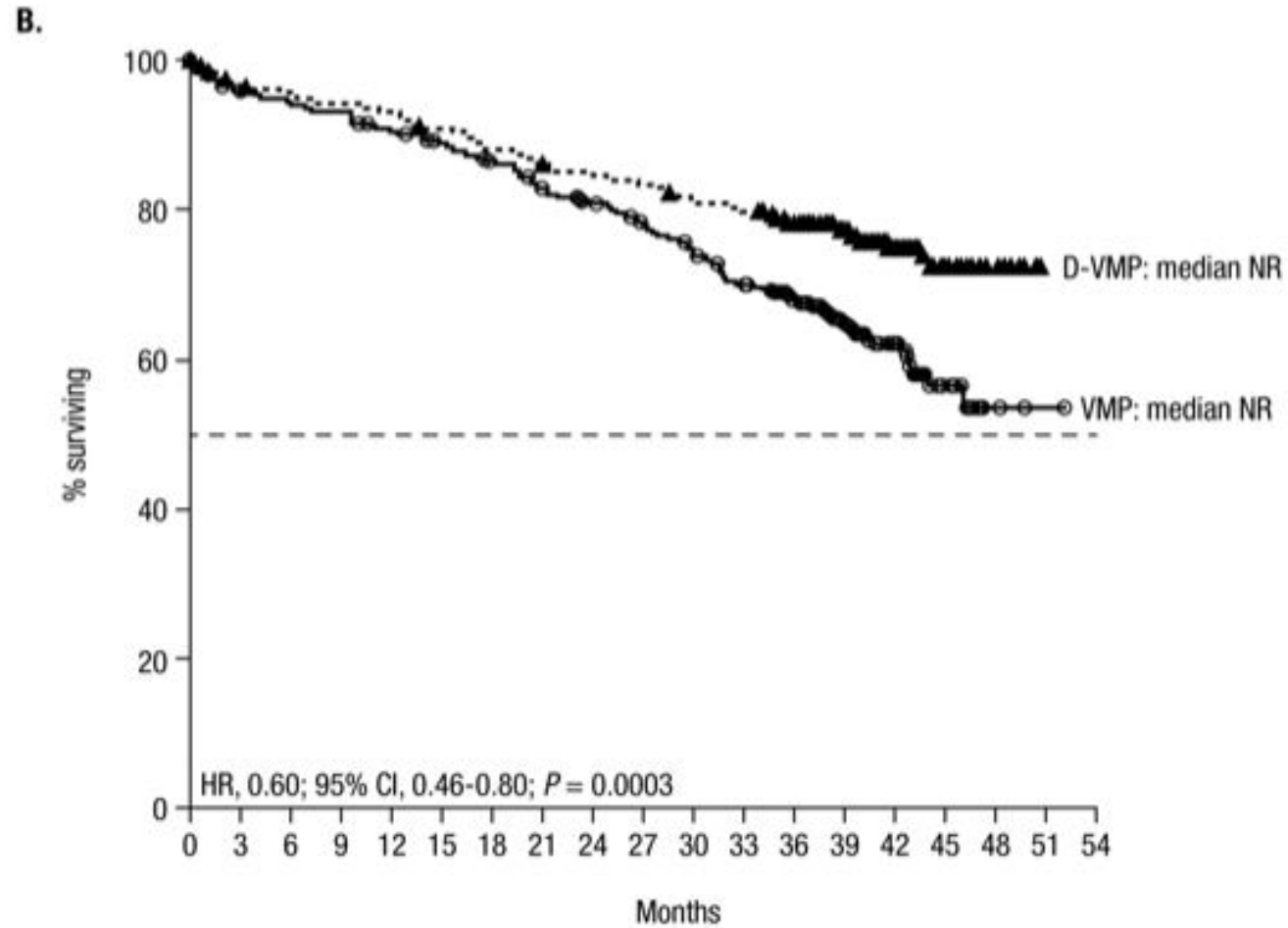
^aITT population. ^bKaplan-Meier estimate.

860 Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd) Induction, Autologous Transplantation and Post-Transplant, Response-Adapted, Measurable Residual Disease (MRD)-Based Dara-Krd Consolidation in Patients with Newly Diagnosed Multiple Myeloma (NDMM)

Luciano J. Costa, MD, PhD¹, Saurabh Chhabra, MD², Kelly N. Godby, MD^{3}, Eva Medvedova, MD^{4*}, Robert F. Cornell, MD, MS⁵, Aric C. Hall, MD^{6*}, Rebecca W. Silberman, MD⁴, Racquel Innis-Shelton, MD⁷, Binod Dhakal, MBBS⁸, Diego Deldiaquez, MD^{3*}, Pamela Hardwick, RN^{3*}, Yelak Biru^{9*}, James L. Omel, MD^{10*}, Parameswaran Hari, MD¹¹ and Natalie Scott Callander, MD¹²*



859 Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Overall Survival in Alcyone



No. at risk	356	331	325	322	312	302	292	278	269	257	242	226	198	132	73	27	3	1	0
VMP	356	331	325	322	312	302	292	278	269	257	242	226	198	132	73	27	3	1	0
D-VMP	350	330	327	322	318	309	301	292	288	283	275	270	248	171	97	40	12	0	0

FRONTLINE THERAPY

Will dara + triplet become the “standard of care”?

- **dara-VRd (Griffin)**
- **dara-KRd (for high risk)**
- **dara-VTd (if R not available)**
- **dara-VMP (for non-transplant)**
- **dara-IRd (for non-transplant)**

OR will we stick with?

- **dara Rd (MAIA)**
- **VRd (modified)**
- **Other triplets**

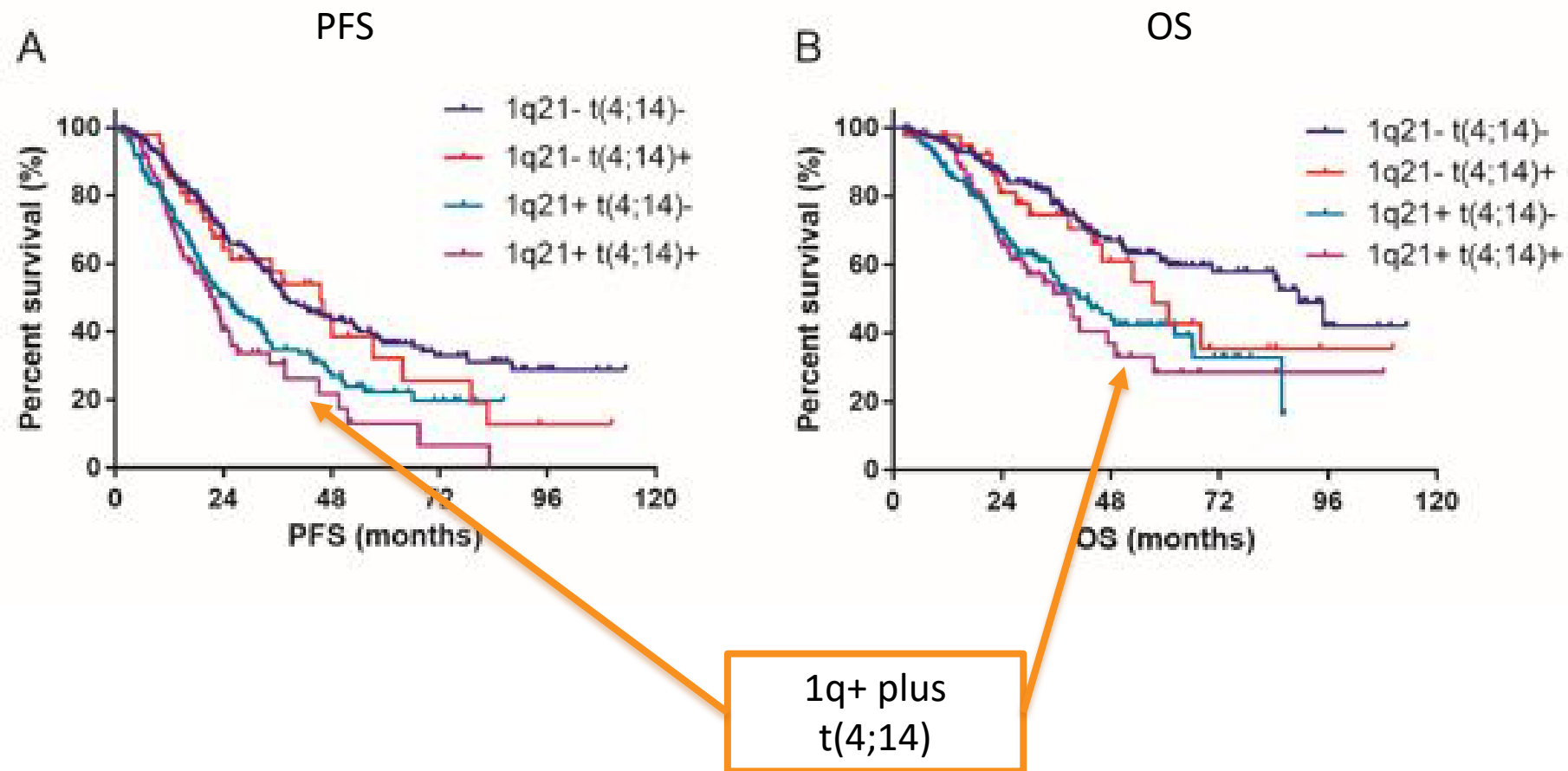
...and save quadruplets for later?

WHAT IS THE IMPACT OF FISH TESTING?

- **1q21 gain**
- **t(11;14)**

4343 1q21 Gain May Challenge the Role of t(4;14) As an Adverse Prognostic Marker of Multiple Myeloma

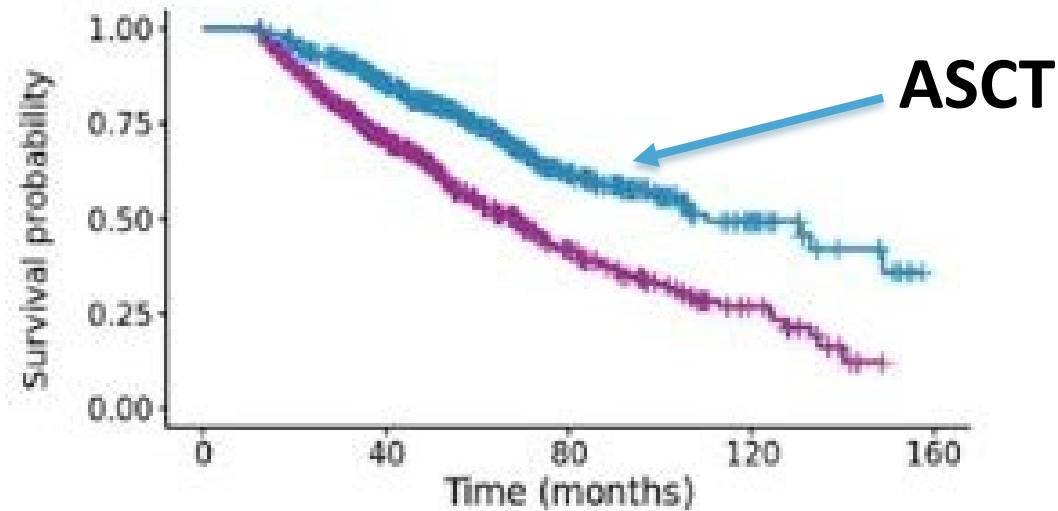
Chenxing Du^{1*}, An Gang, MD^{2*}, Yan Xu^{2*}, Xuehan Mao, MD^{2*}, Yuting Yan^{3*}, Jiahui Liu^{4*}, Huishou Fan^{4*}, Weiwei Sui^{2*}, Shuhui Deng, MD^{2*}, Li Zengjun^{2*}, Chengwen Li^{5*}, Shuhua Yi, MD^{2*}, Mu Hao^{6*}, Dehui Zou, MD^{2*}, Fenghuang Zhan, MD, PhD⁷, Yu-Tzu Tai, PhD⁸, Kenneth C. Anderson, MD⁹ and Lugui Qiu, MD, PhD¹



4580 Role of High-Dose Melphalan and Autologous Stem Cell Transplantation in Multiple Myeloma Patients Presenting with t(11;14)

Eduardo Sobejano, et. al.

Overall Survival



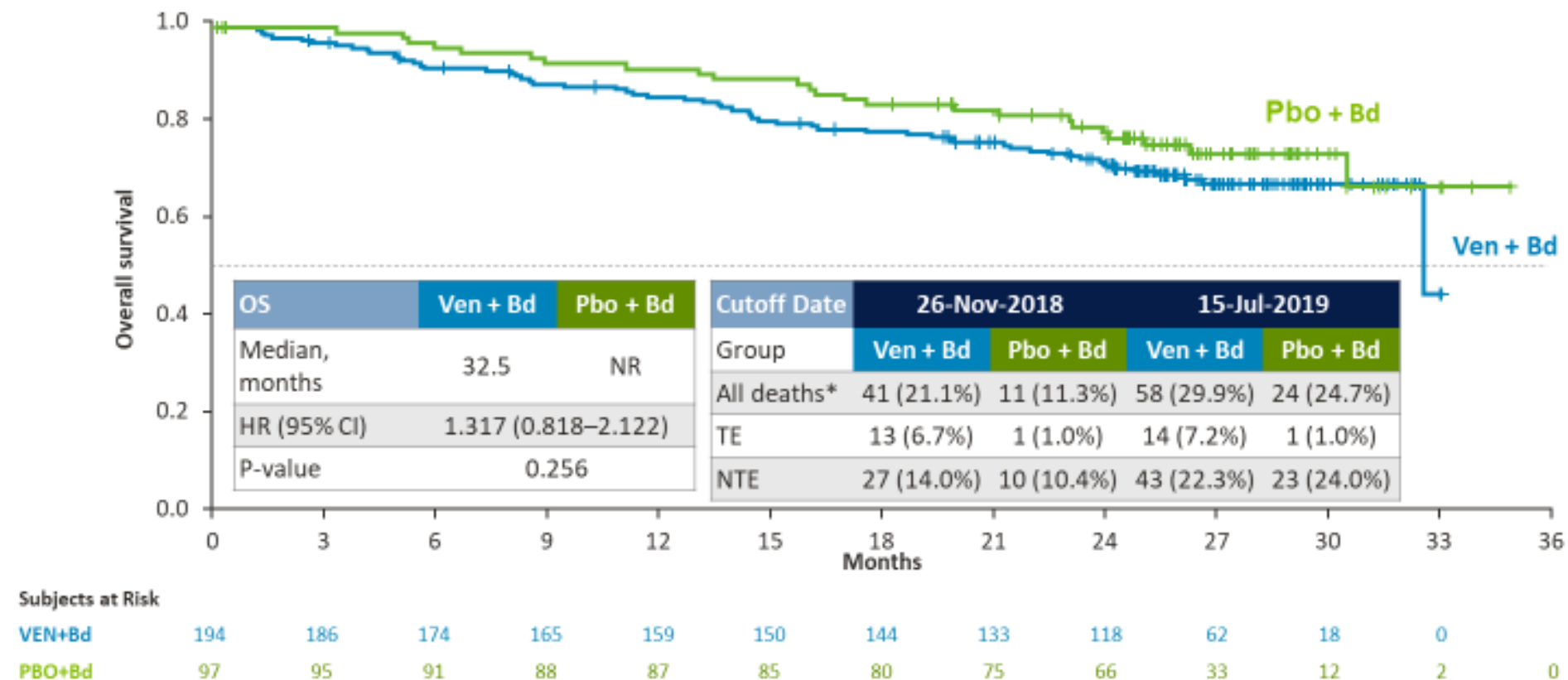
Number at risk

No stem cell	449	251	68	16	0
stem cell within 1 year	510	362	99	21	0

Figure 3: Survival of patients by stem cell transplant received within 12 months of the first line of therapy, from date of diagnosis

1888 Updated Analysis of Bellini, a Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

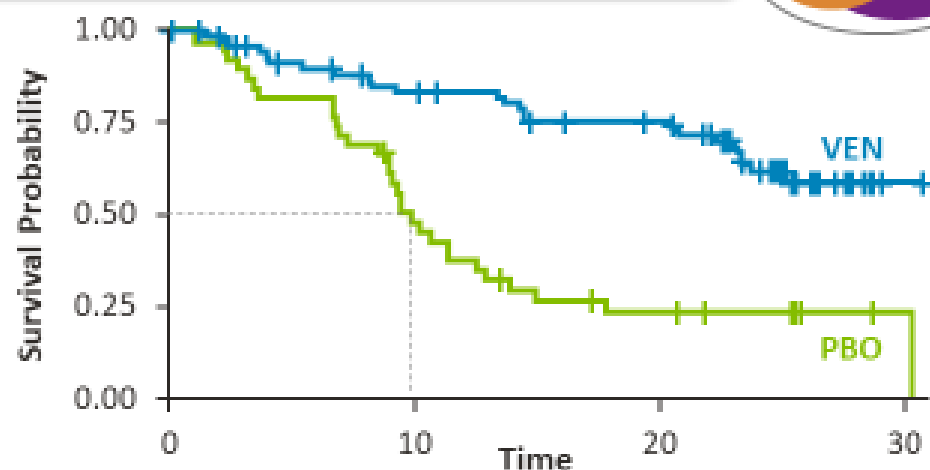
BELLINI – Overall Survival (ITT) (as of 15-July-2019)



Philippe Moreau, MD, et. al.

1888 Updated Analysis of Bellini, a Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

PFS per INV
t(11;14) or $BCL2^{high}$

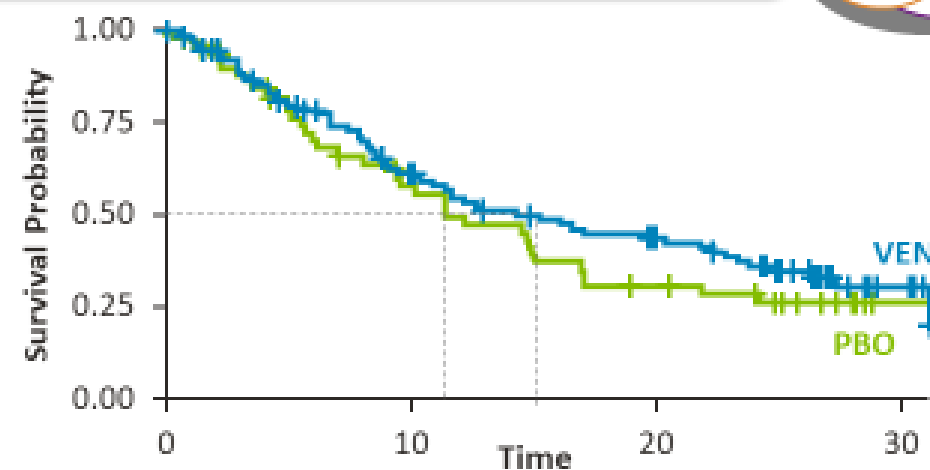


Number at risk

PBO+Bd	40	18	7	1
VEN+Bd	74	53	43	1

PFS	Ven+Bd	Pbo+Bd
Median, months	Not reached	9.89
HR (95% CI)	0.30 (0.17–0.53)	
P-value	<0.001	

PFS per INV
non-t(11;14) and $BCL2^{low}$



Number at risk

PBO+Bd	54	28	14	1
VEN+Bd	110	56	35	7

PFS	Ven+Bd	Pbo+Bd
Median, months	15.3	11.5
HR (95% CI)	0.85 (0.56–1.30)	
P-value	0.451	

DO YOU FORESEE “PRECISION MEDICINE” APPROACHES FOR t(11;14), 1q+ and OTHERS?

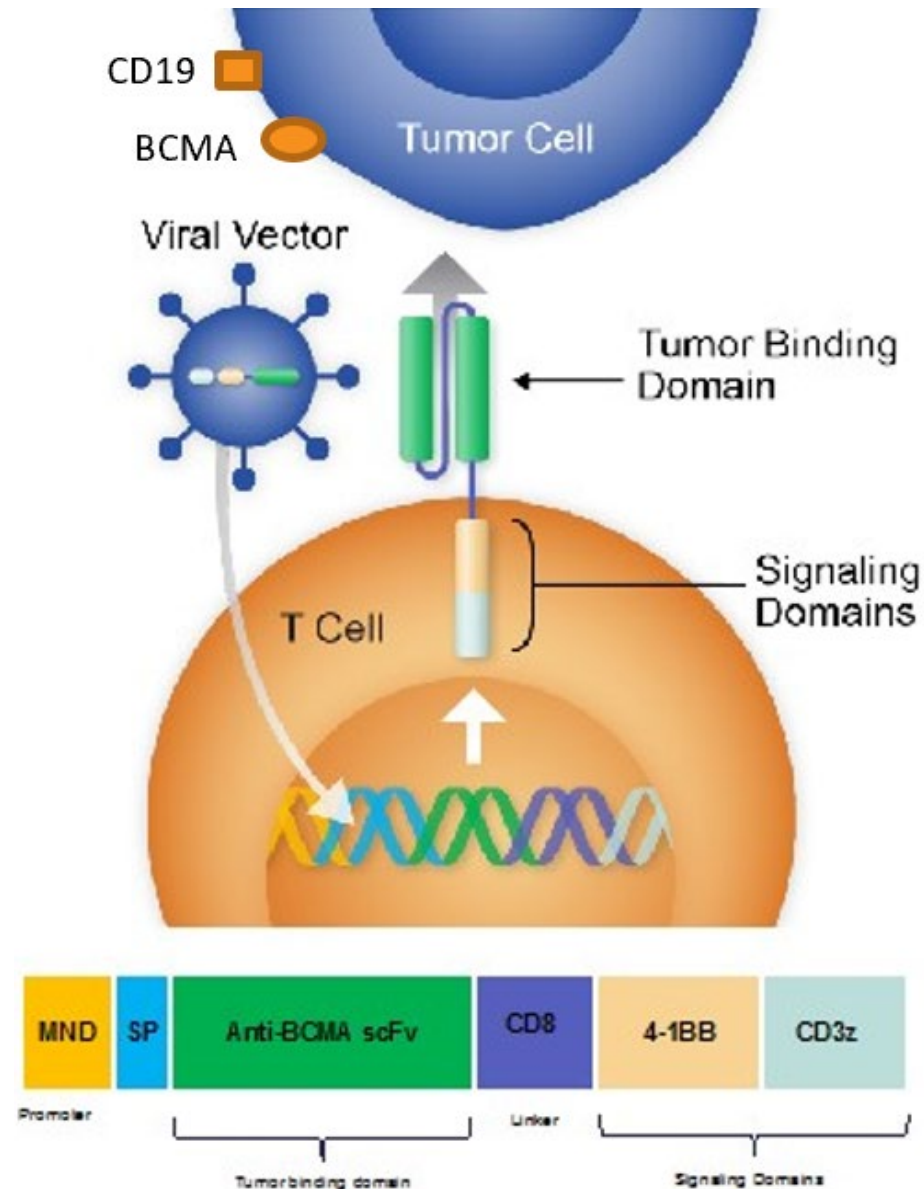
- **1q+ plus t(4;14): treat as high risk?**
- **t(11;14): treat incorporating:**
 - **venetoclax?**
 - **ASCT?**

IMMUNE THERAPY RESULTS DOMINATE ASH 2019

- **CAR T Therapy**
- **Bispecific T Cell Engagers**
- **GSK 2857916 (“belamaf”)**

Chimeric Antigen Receptor (CAR) Therapy for Multiple Myeloma

*Is CAR T
Therapy a
Game Changer
in MM?*



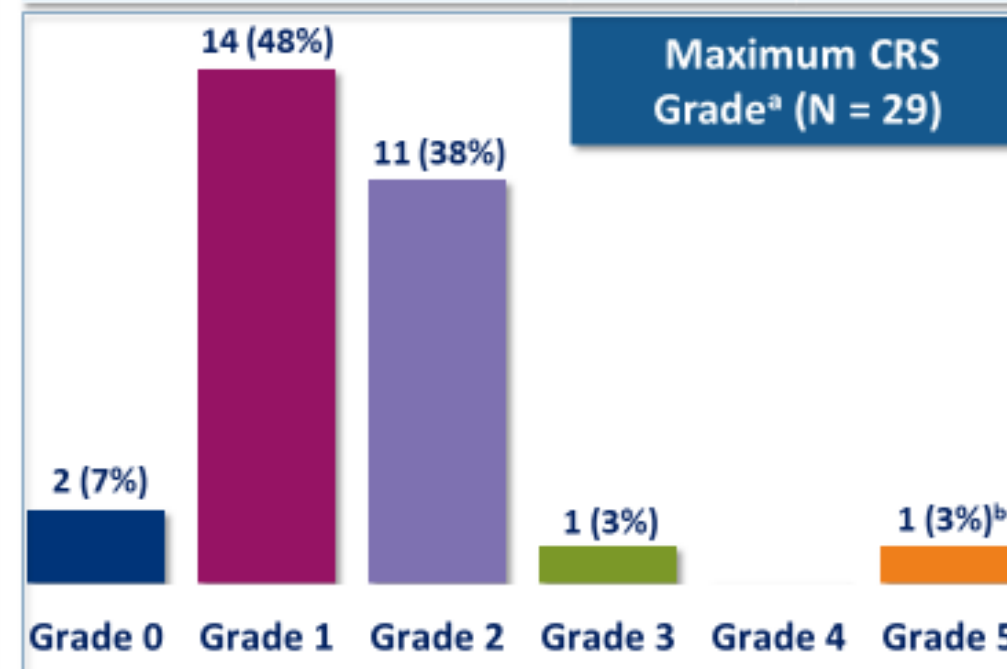
Kochenderfer, et al. 2016.
Ali. Blood. 2016;128:1688.

577 Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM)

CARTITUDE-1: Safety

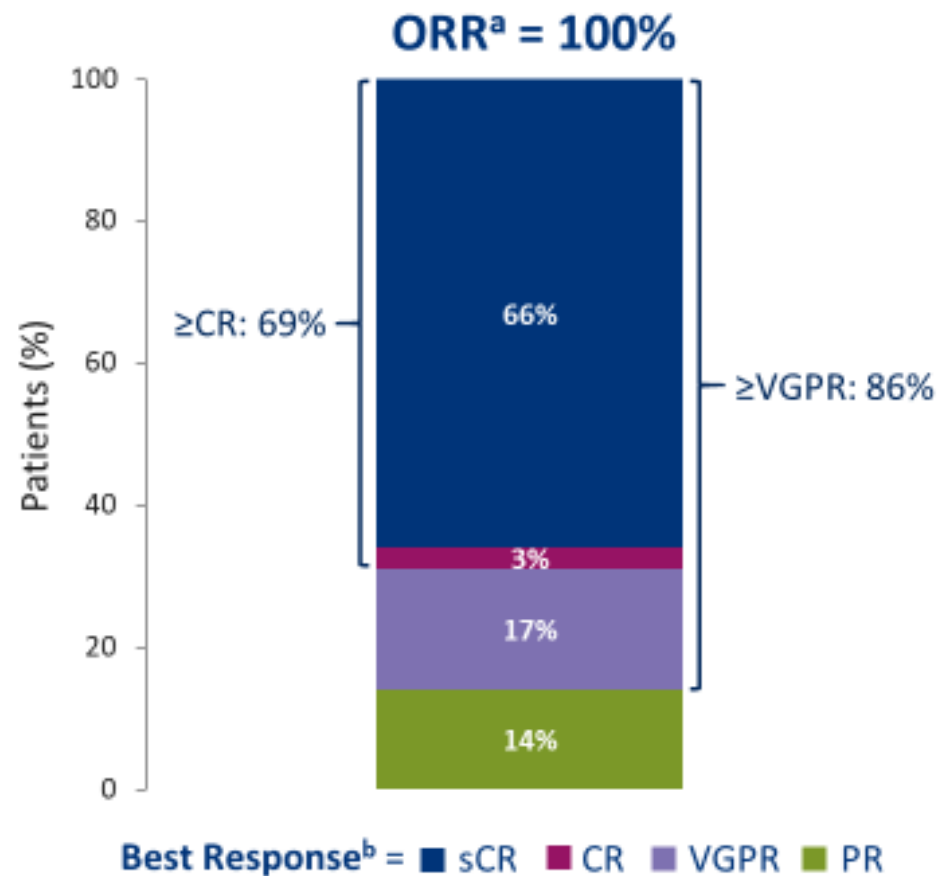
Hematologic AEs (≥25% All Grade)	N = 29	
	All Grade	Grade ≥3
Neutropenia	27 (93)	27 (93)
Anemia	25 (86)	16 (55)
Thrombocytopenia	25 (86)	20 (69)
Leukopenia	15 (52)	15 (52)
Lymphopenia	13 (45)	9 (31)
Non-Hematologic AEs (≥25% All Grade)		
Increased AST	9 (31)	2 (7)
Increased ALT	8 (28)	1 (3)
Diarrhea	8 (28)	1 (3)
Upper respiratory tract infection	8 (28)	0

CAR-T-associated AEs	N = 29	
	All Grade	Grade ≥3
Neurotoxicity consistent with ICANS ^b	3 (10)	1 (3)



577 Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM)

CARTITUDE-1: Early, Deep Responses and High Response Rate



- ORR and depth of response were independent of BCMA expression on MM cells at baseline
- Median time to first response = 1 mo (1 – 3)
- Median time to ≥CR = 1 mo (1 – 9)
- 100% patients evaluable for MRD were MRD negative
- 27 / 29 patients remain progression free at 6 months median follow-up

IND Approvals for BCMA-CAR T Therapy in China

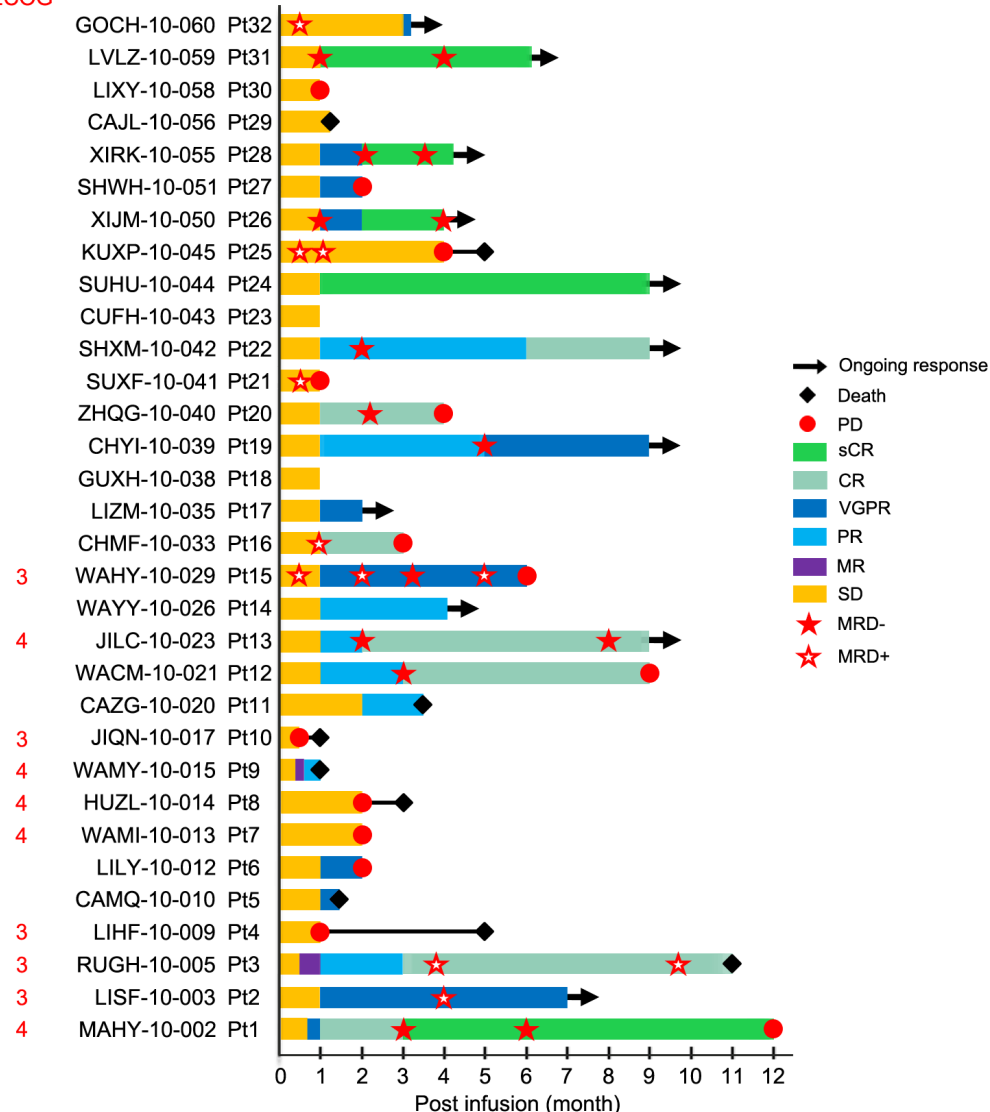
No.	Company	Product	Indication	Approved time
1	Nanjing Legend Biotech Co.,Ltd.	LCAR-B38M Chimeric Antigen Receptor T Cell (LCAR-B38M CAR-T)	R/R MM	2018.03
2	Shanghai HRAIN Biotechnology Co.,Ltd.	Human BCMA Targeted T Cells Injection (BCMA-CART)	R/R MM (BCMA+)	2018.12
3	Shanghai CARsgen therapeutics Co.,Ltd.	CT053(Human anti-BCMA CAR-T) Cell Infusion	R/R MM	2019.03
4	Nanjing IASO Biotherapeutics Co.,Ltd.	Fully human BCMA CAR T-cell Injection (humanized BCMA-CART)	R/R MM	2019.09

3154 Efficacy and Safety of CAR-T Therapy with Safety Switch Targeting Bcma for Patients with Relapsed/Refractory Multiple Myeloma in a Phase I Clinical Study

Hospital 1

HRAIN Product with Safety Switch

ECOG

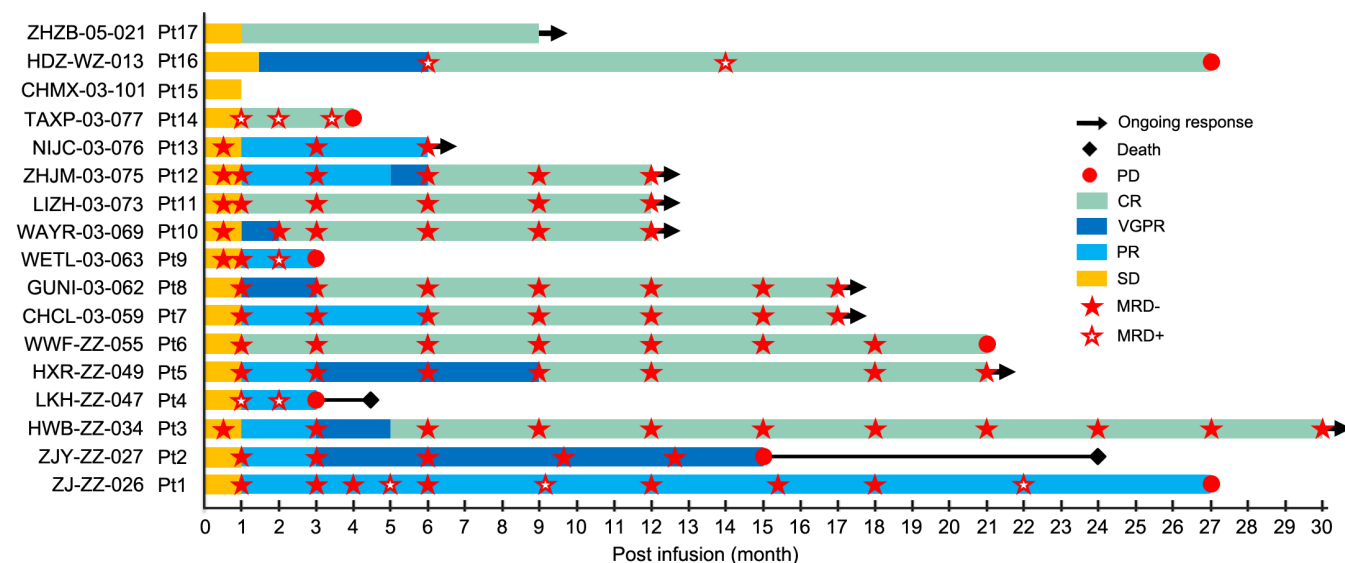


ORR: 38/49 (77.55%), ≥CR 43%

ECOG ≥3 ORR: 15/20 (75.00%)

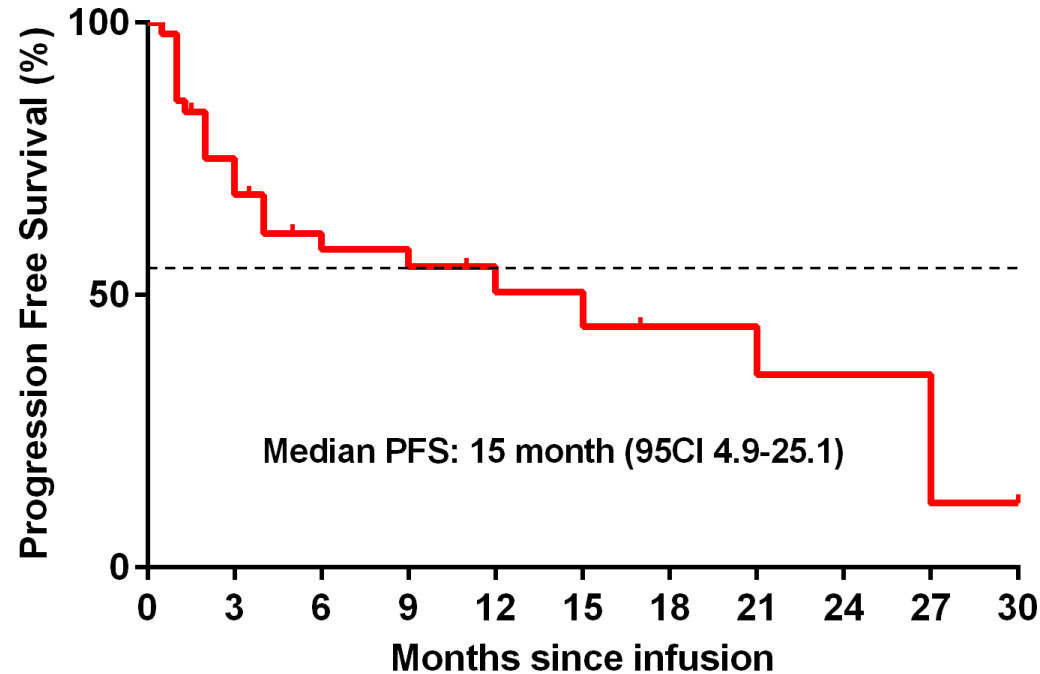
ECOG 0~2 ORR: 23/29 (79.31%)

Hospital 2 & 3



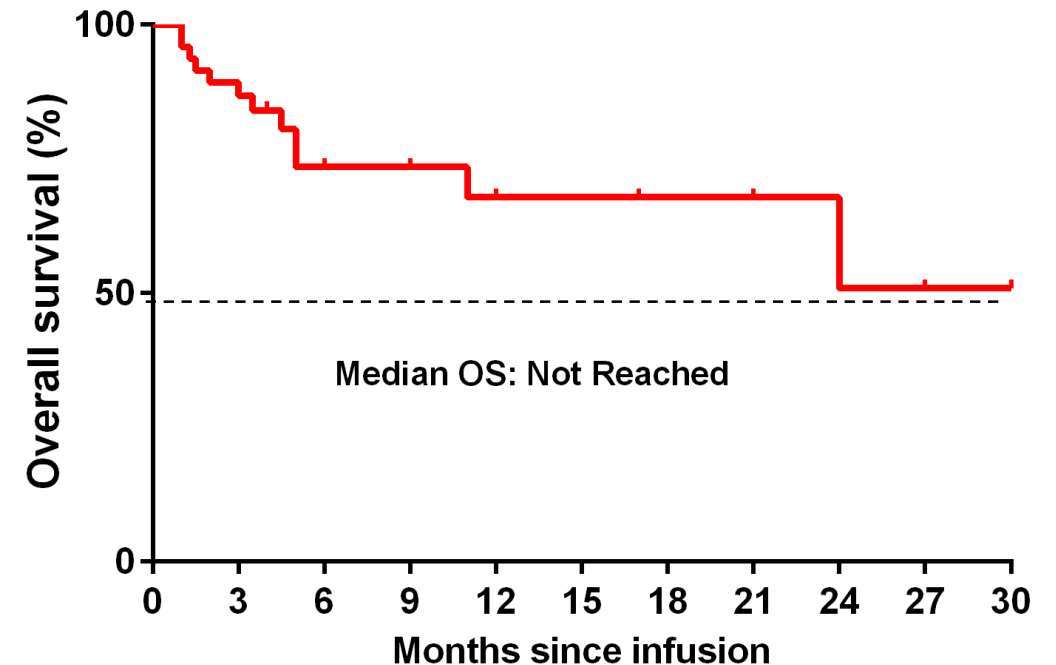
HRAIN product with safety switch: PFS and OS (n=49)

PFS



No. at Risk 49 34 21 18 12 8 7 5 5 3 1

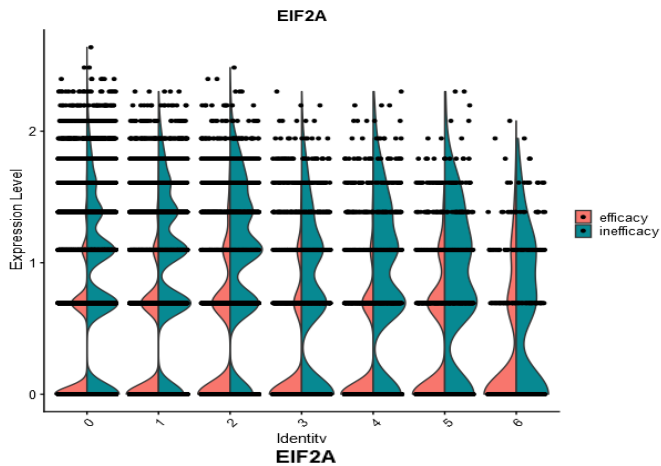
OS



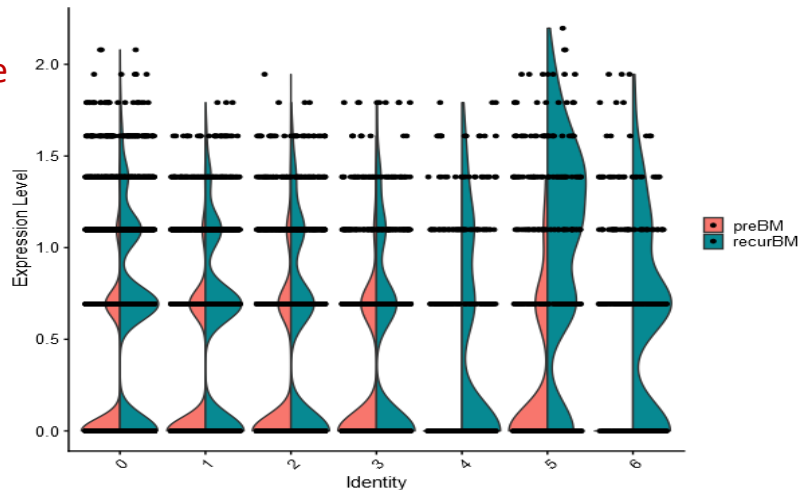
No. at Risk 49 36 20 17 12 12 8 6 4 3 1

Non-response and relapsed patients after BCMA-CAR T therapy: Upregulated mTOR pathway in BMPC

Single cell sequencing

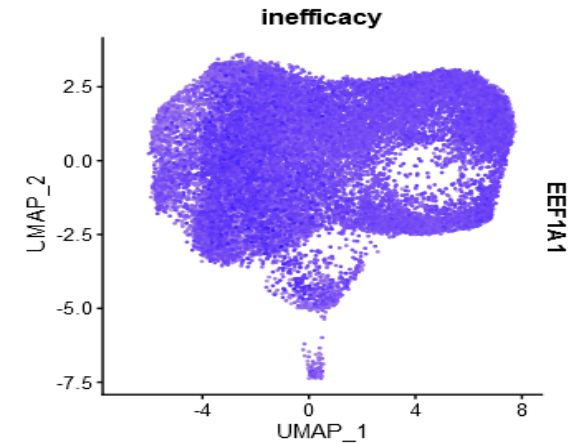
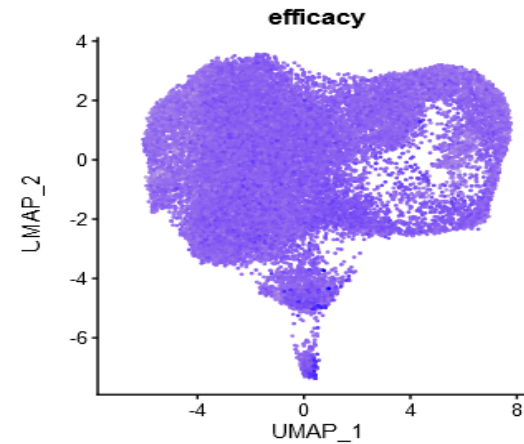


One case

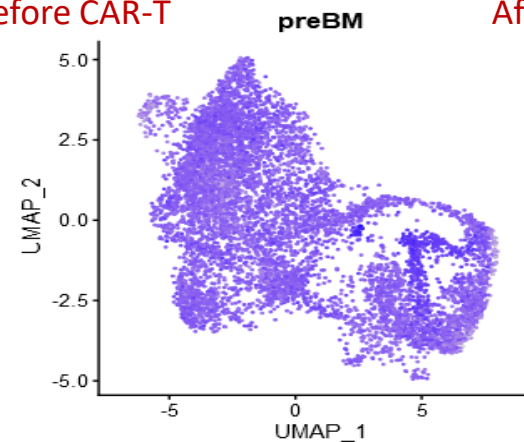


Response—preBM:
#1-7854 cells
#2-9144 cells
#3-8733 cells

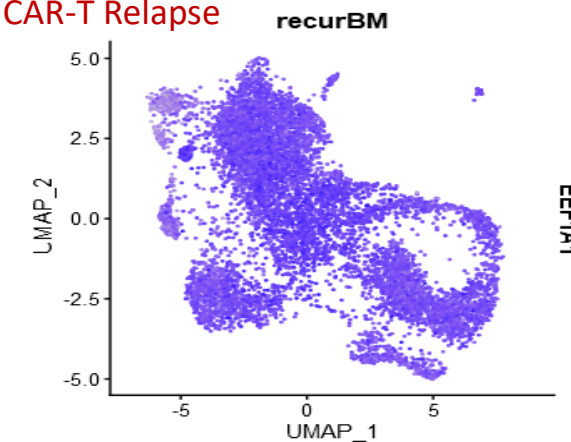
Non-response—preBM:
#4-5660 cells
#5-6485 cells
#6-10367 cells



Before CAR-T

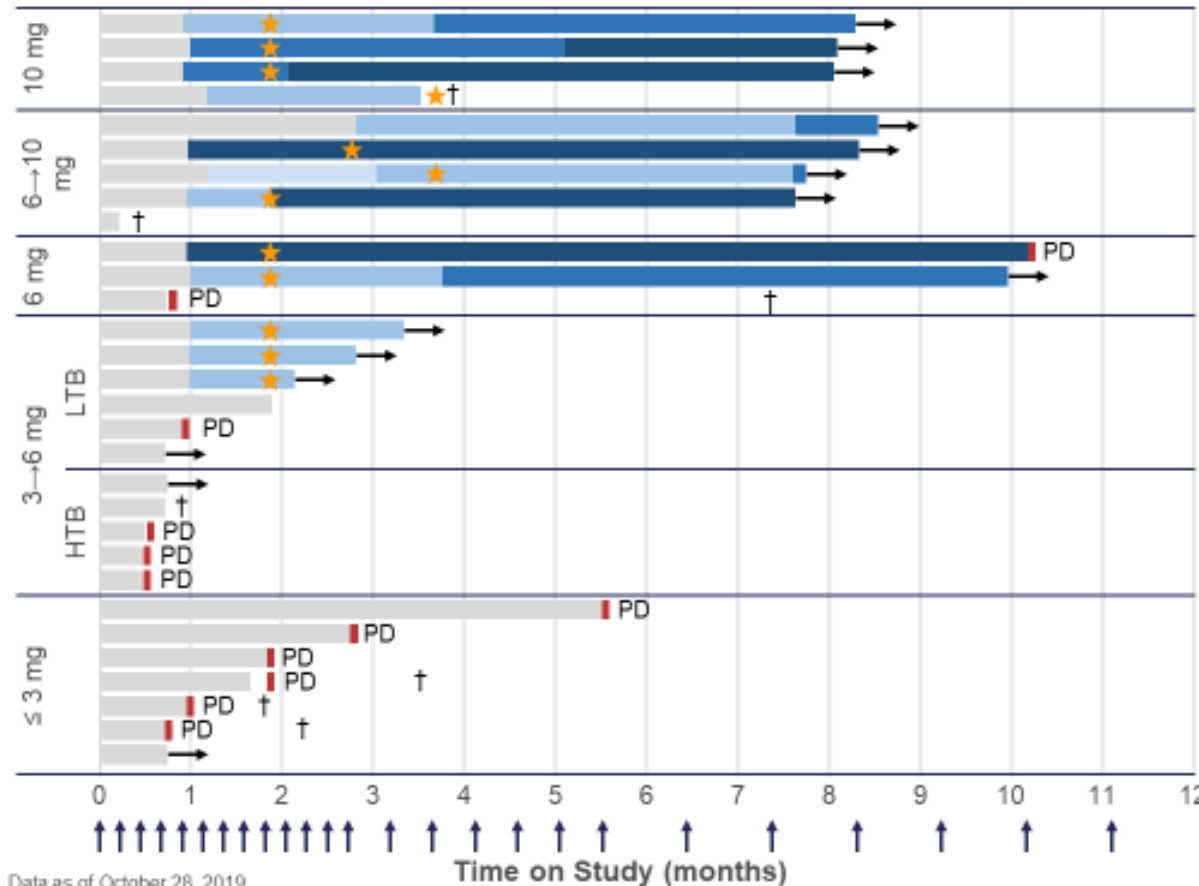


After CAR-T Relapse



143 First Clinical Study of the B-Cell Maturation Antigen (BCMA) 2+1 T Cell Engager (TCE) CC-93269 in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Interim Results of a Phase 1 Multicenter Trial

RESPONSE OVER TIME



- Median time to first response was 4.1 weeks (range 4.0–13.1)
- 5 of 30 (16.7%) patients achieved an MRD-negative sCR/CR
 - Of 13 responding patients, 92.3% achieved MRD negativity ($\leq 1/10^5$) in the bone marrow on or before C4D1 by Euroflow^a

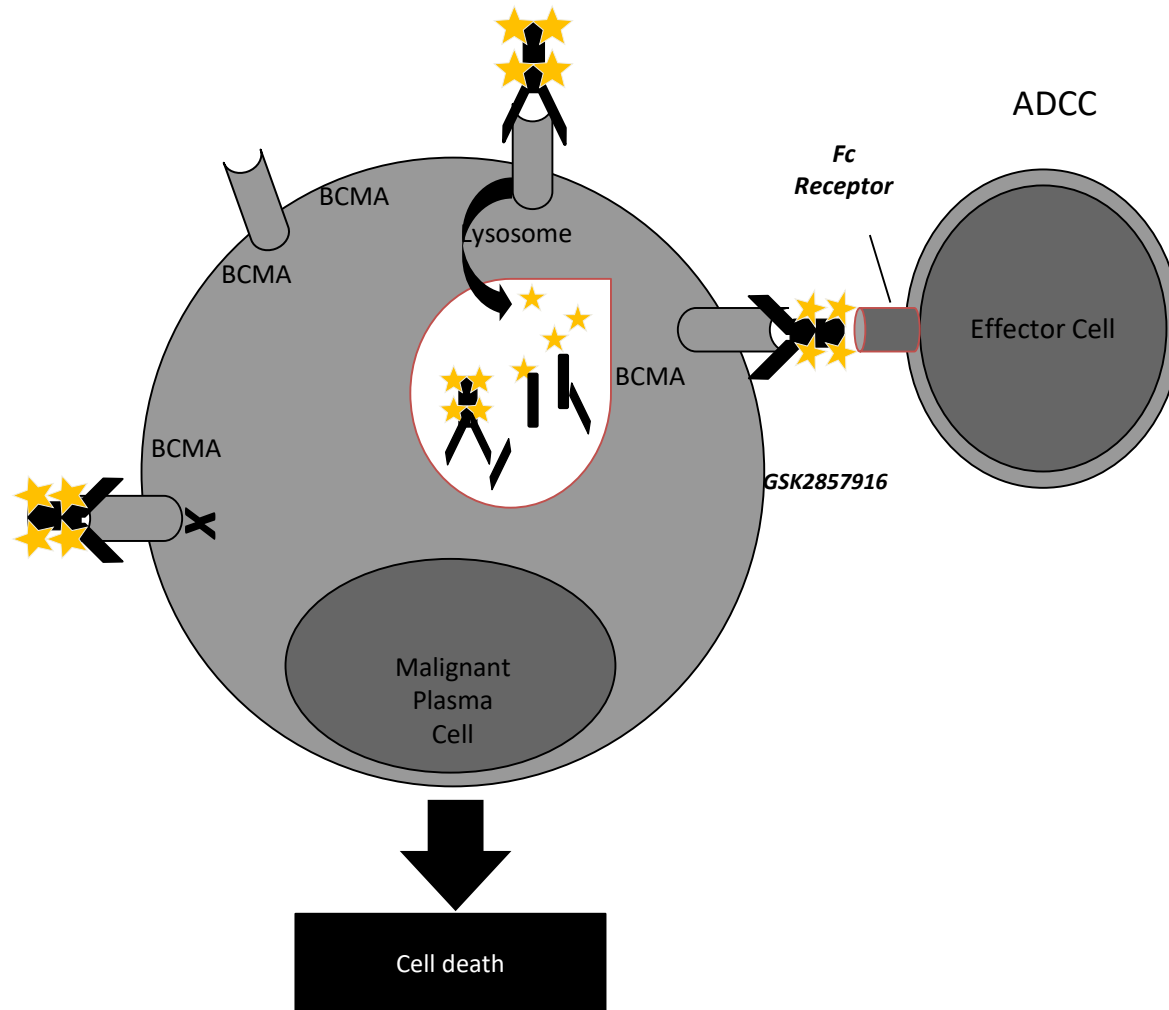


Data as of October 28, 2019.

^aMRD negativity by Euroflow analysis was reported only if a minimum sensitivity of ≤ 1 tumor cell in 10^6 nucleated cells was achieved and in patients who had ≥ 1 baseline and ≥ 1 post-baseline MRD assessment. HTB, high tumor burden (defined as $> 50\%$ bone marrow plasma cells or > 5 extramedullary lesions); LTB, low tumor burden (defined as $\leq 50\%$ bone marrow plasma cells and ≤ 5 extramedullary lesions); MR, minimal response.

Luciano J. Costa, MD, PhD, et. al.

Belatamab Mafodotin (GSK2857916): a BCMA-Targeted Antibody Drug Conjugate



Fc region of the Antibody

—Target specific
—Enhanced ADCC

Linker

—Stable in circulation

Drug

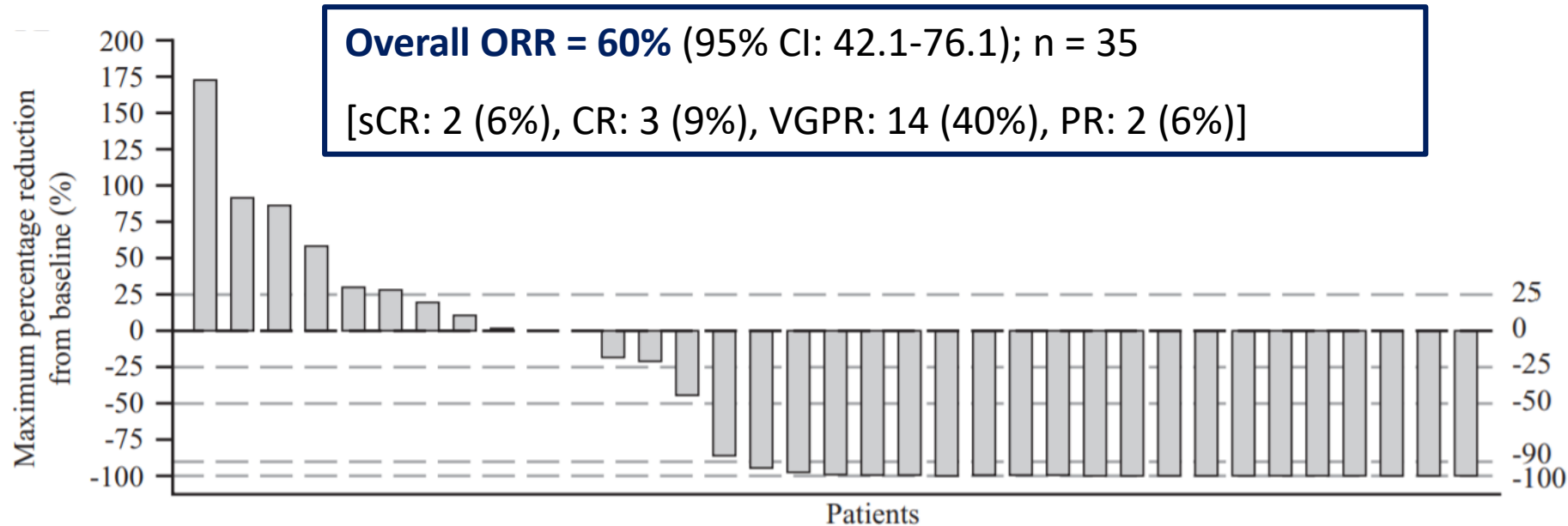
—MMAF (non cell permeable, highly potent auristatin)

Mechanisms of Action:

1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death

Belantamab Mafodotin: Efficacy in Multiple Myeloma

DREAMM – 1: single agent dose expansion results
Dose 3.4 mg/kg every 3 weeks, 1hr infusion



Heavily pretreated - 89% double refractory;
- 34% double + dara refractory
29% with high-risk cytogenetics

Efficacy in refractory populations

Patients refractory to IMiD and PI (n = 32)

ORR: 56.3%
(95% CI: 37.7-73.6)

Patients previously treated with dara AND refractory to IMiD and PI (n = 13)

ORR: 38.5%
(95% CI: 13.9-68.4)

ROLE OF IMMUNE THERAPIES

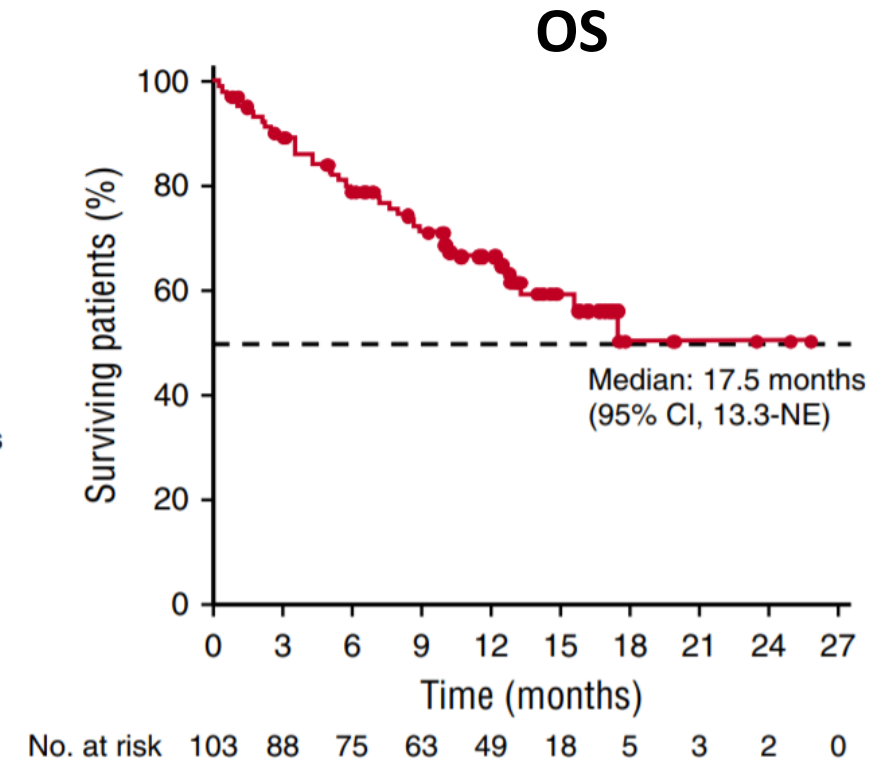
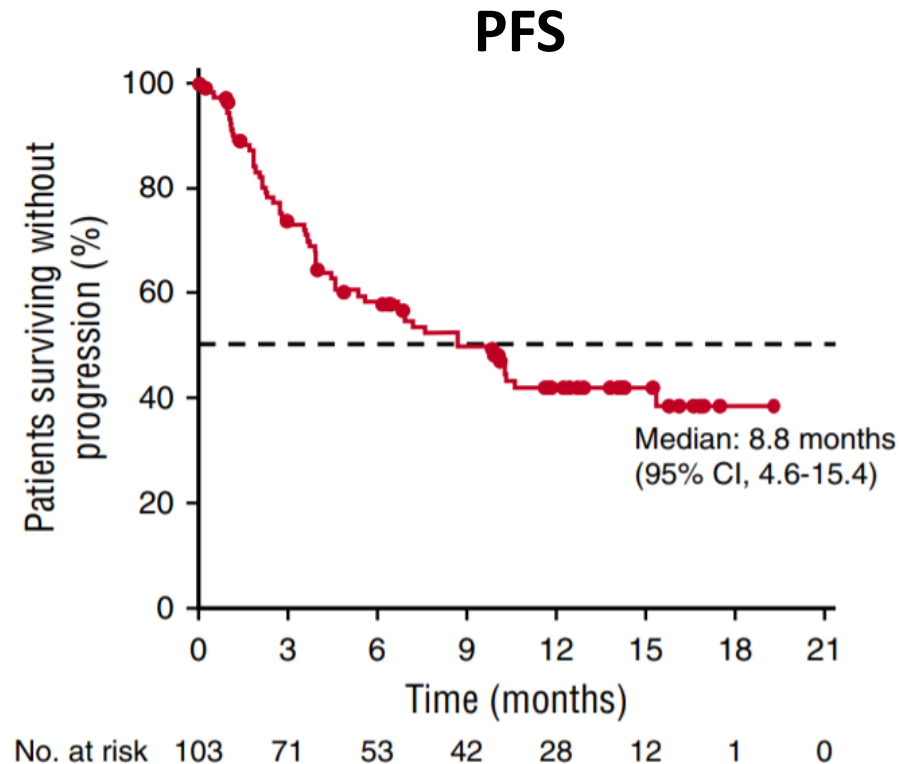
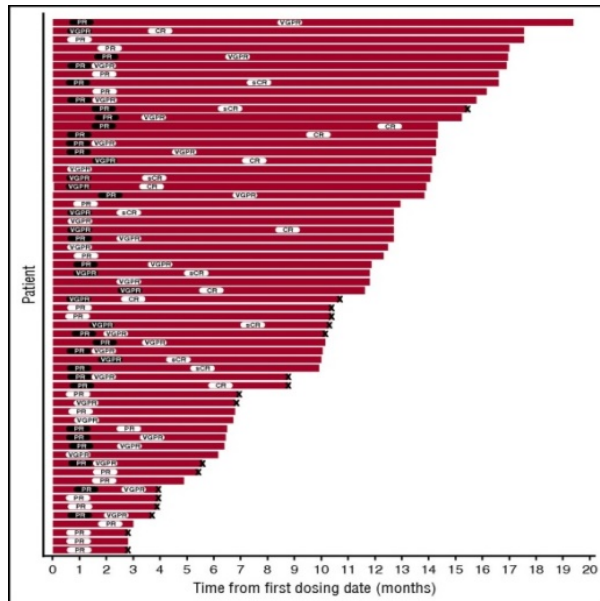
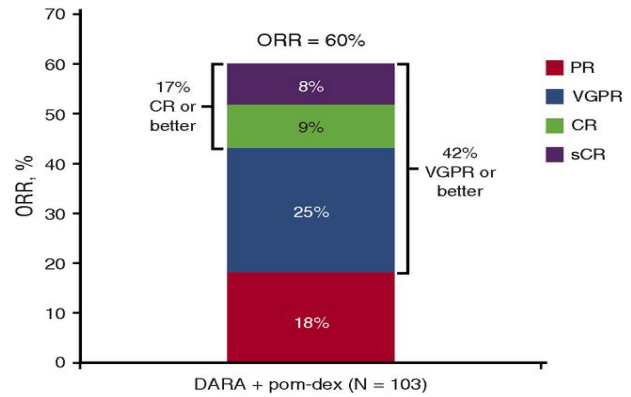
Clearly active in relapsed patient population

- **How will BCMA targeted therapy be used and sequenced?**
- **Is earlier use the best approach?**
 - **For consolidation?**
 - **At first relapse?**

NOVEL AGENTS OR COMBINATION AT RELAPSE

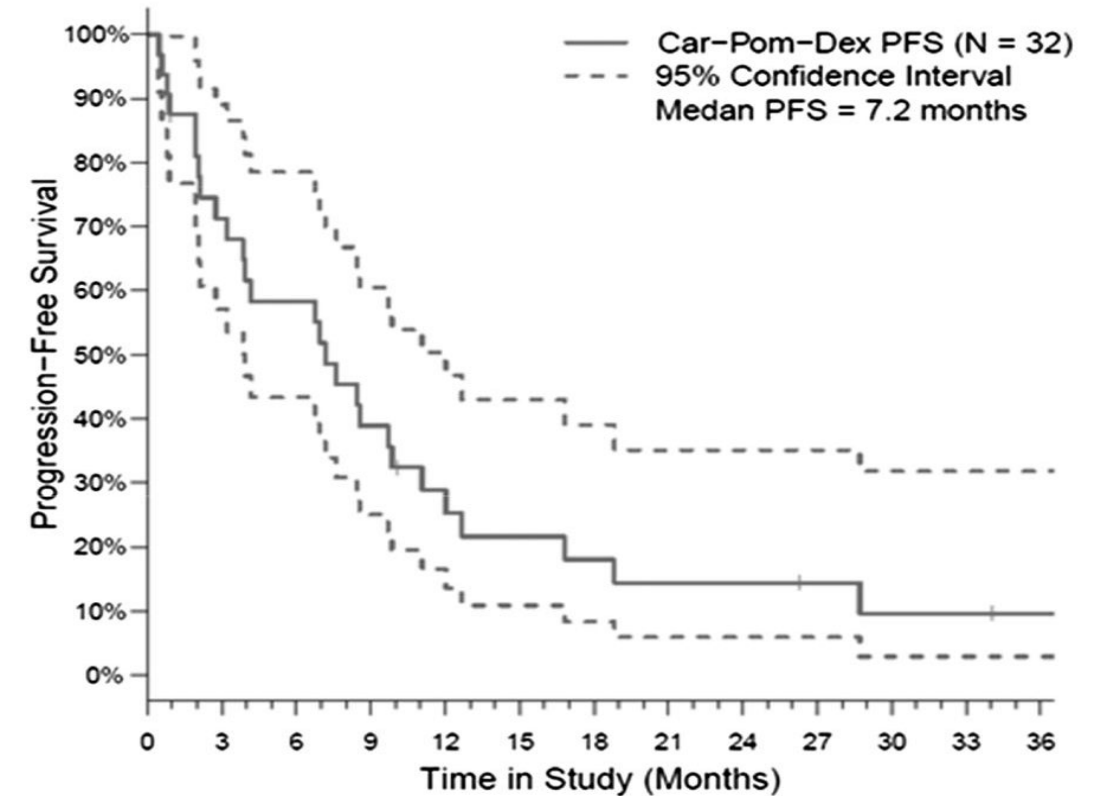
- **dara/Kyprolis/dex (CANDOR): LBA-6**
- **dara/Pom/dex**
- **Kyprolis/Pom/dex**
- **iberdomide (CC-220)**
- **melflufen**
- **I ¹³¹ CLR 1404 (lipid rafts target)**

Daratumumab-Pom-Dex: Phase II Trial (n = 103)

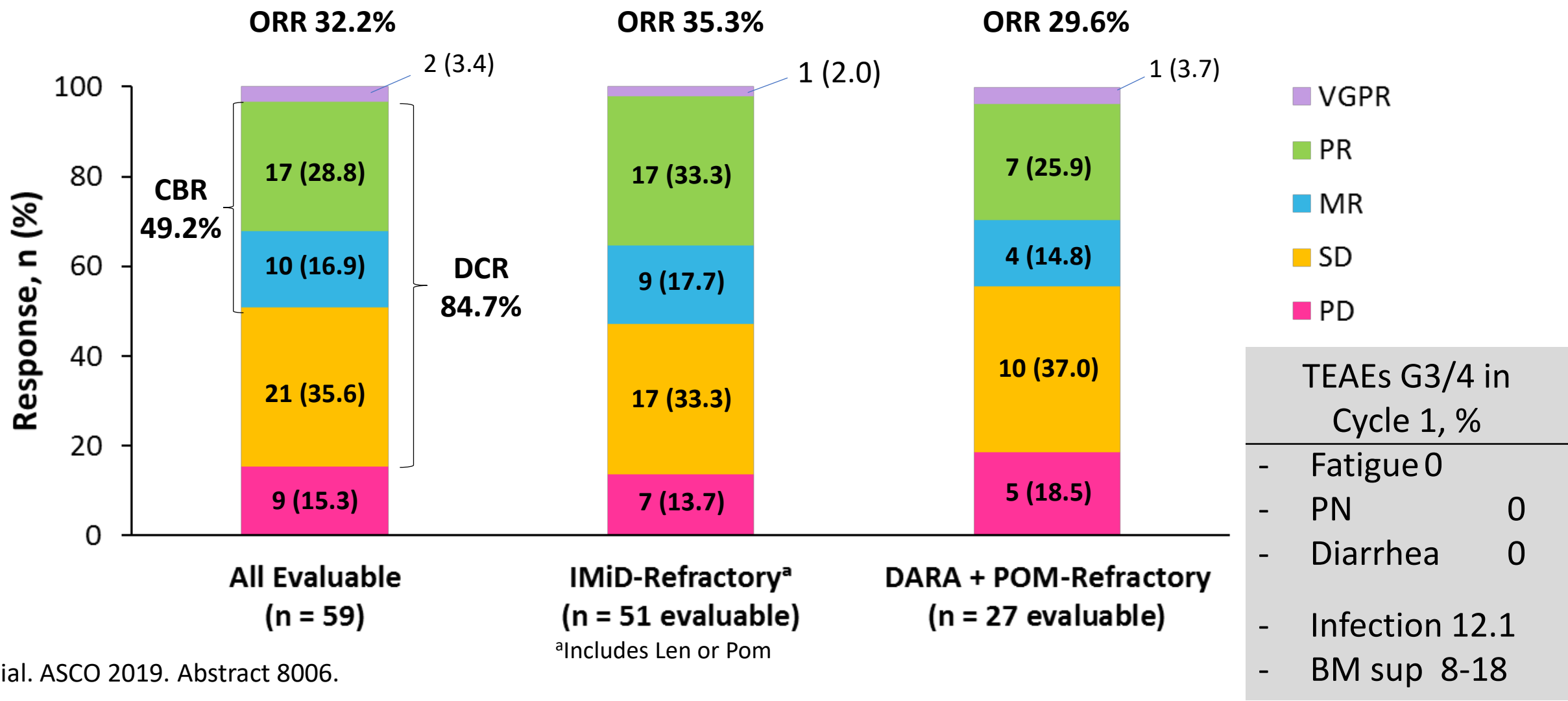


Carfilzomib-Pom-Dex: Phase I Trial (N = 32)

Response category, n (%)	All evaluable patients (N = 32)
ORR	16 (50)
VGPR	5 (16)
PR	11 (34)
MR	5 (16)
SD	8 (25)
PD	3 (9)



IBERDOMIDE (CC-220): Cohort B Response Results



Lonial. ASCO 2019. Abstract 8006.

Triple Class Refractory: When All Else Fails

Chemotherapy	HDAC Inhibitors/ XPO inhibitors	Monoclonal Antibodies	IMiDs / CelMODs/ Novel Drugs	BCMA Abs	Cellular therapies
Doxorubicin, Liposomal doxorubicin	Panobinostat	Isatuximab, SAR442085	CC-220 (Iberdomide), CC-94480	AMG-420, AMG-701, CC-93269	Idecabtagene vicleucel (bb2121), bb21217, JCRH125
Cyclophosphamide, Bendamustine, Melphalan	Vorinostat	TAK-079, TAK-573, TAK-169	Venetoclax	TNB-3838, PF-06863135, REGN5458,	LCAR38, P-BCMA
PACE, HyperCAD	Selinexor	MOR202, Others	Melflufen	Belantamab Mafodotin, MEDI2228, CC-99712	Many others Penn/NIH/Seattle

*Blue = available

*Purple = being tested in clinical trials

NEW THERAPY OPTIONS IN THE RELAPSE SETTING

How do you prioritize for:

- **Early Relapse (1-3 prior regimens)?**
- **Later Relapse?**

Thank you for watching!

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