Best of ASH 2019

What Patients and Caregivers Need to Know

IMWG
INTERNATIONAL MYELOMA WORKING GROUP
A Research Division of International Myeloma Foundation

Brian G.M. Durie, MD

Thursday, January 9th, 2020

INTERNATIONAL MYELOMA FOUNDATION

IMF AT 30 YEARS

- 2020 is the 30 year anniversary

INTERNATIONAL MYELOMA FOUNDATION

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AMN ASIAN MYELOMA NETWORK
A Research Division of International Myeloma Foundation

NURSE LEADERSHIP BOARD
A Division of International Myeloma Foundation

GMAN GLOBAL MYELOMA ACTION NETWORK
A Division of International Myeloma Foundation

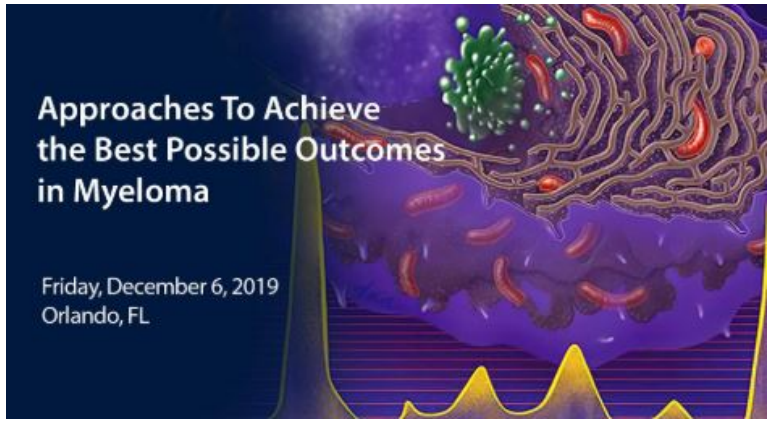
- This year will be pivotal for key projects for:
  - CURE

BLACK SWAN RESEARCH INITIATIVE
Signature Project of the International Myeloma Foundation

  - PREVENTION

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

IMF RESOURCES LINKED TO ASH 2019



- IMF at ASH 2019
- Dr. Durie's Blog
  - Takeaways from ASH 2019
  - ASH 2019 Update: Late-Breaking Abstracts
  - ASH Top 10 for 2019: Immune therapies again dominate news
- Satellite Symposium: Approaches to Achieve the Best Possible Outcomes in Myeloma
- Support Group Leaders at ASH: Tweets/Blogs
- ASH Doctor Interviews
- IMWG Conference Series

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KEY TAKEAWAYS FOR ASH 2019

- Smoldering myeloma
- Frontline therapy
- Potential precision medicine approaches
- CAR T therapy/Bispecific T Cell Engagers/MoAbs
- Novel agents/combinations

SMOLDERING MYELOMA

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

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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

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**

Black Swan Trials

TO CURE THE DISEASE:

- **KRD + ASCT + Consol + Maint (CESAR)**
- **KRD + Dara +/- ASCT..... (ASCENT)**
- **iSTOPMM protocols**

BLACK SWAN
RESEARCH INITIATIVE
Signature Project of the International Myeloma Foundation

ASH 2019: CESAR TRIAL RESULTS

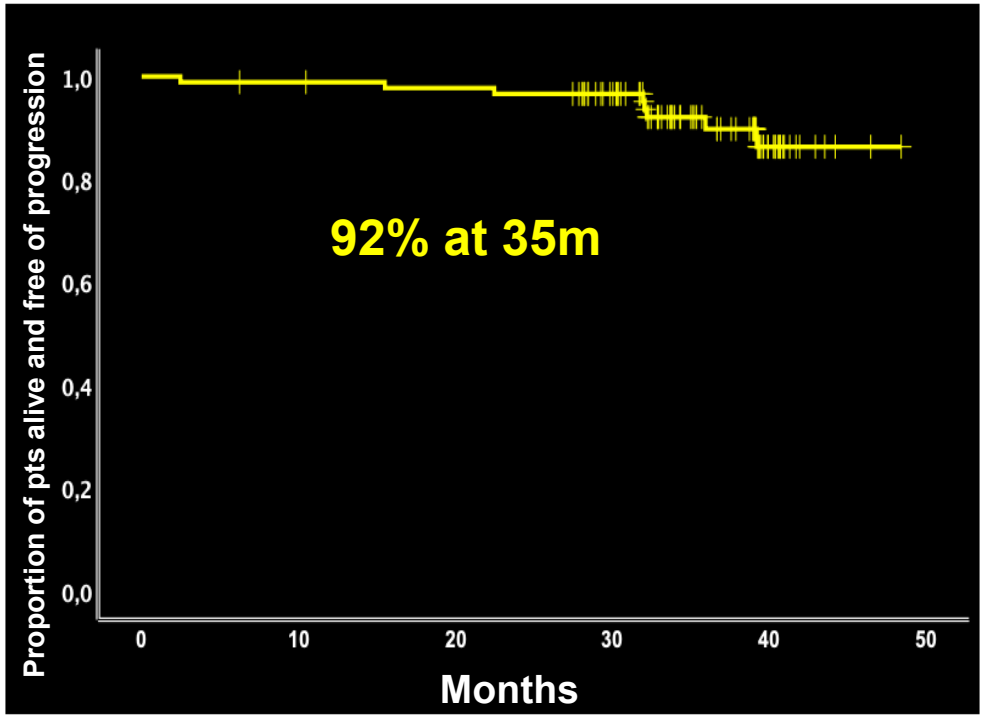
Improvement in the quality of response over the treatment

	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

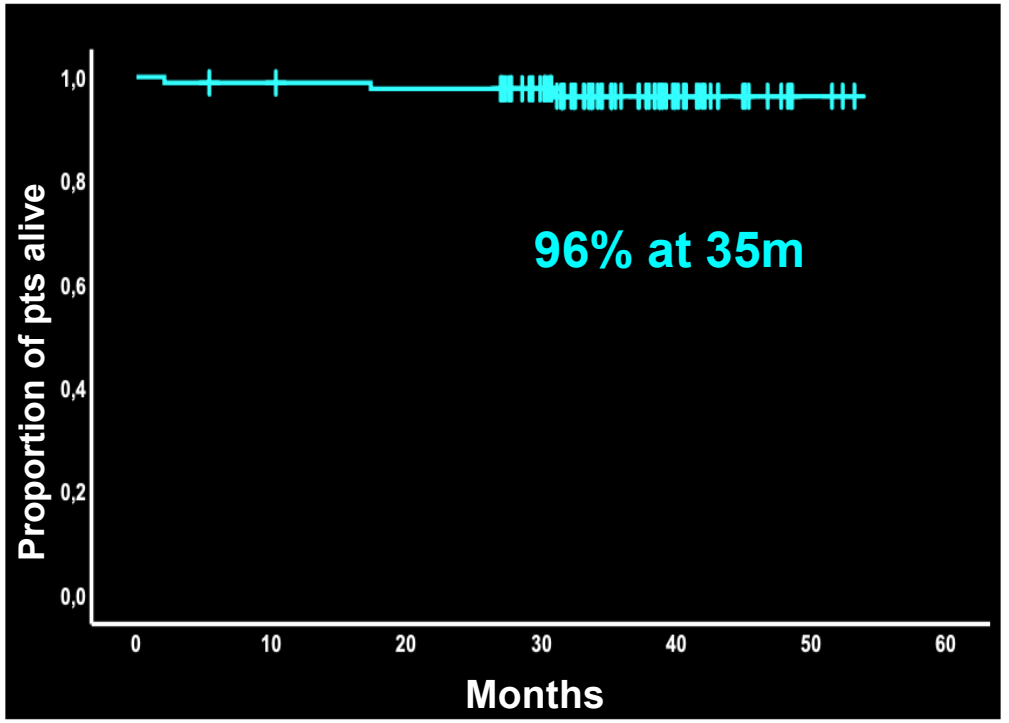
CESAR TRIAL: PFS AND OS RESULTS

PFS



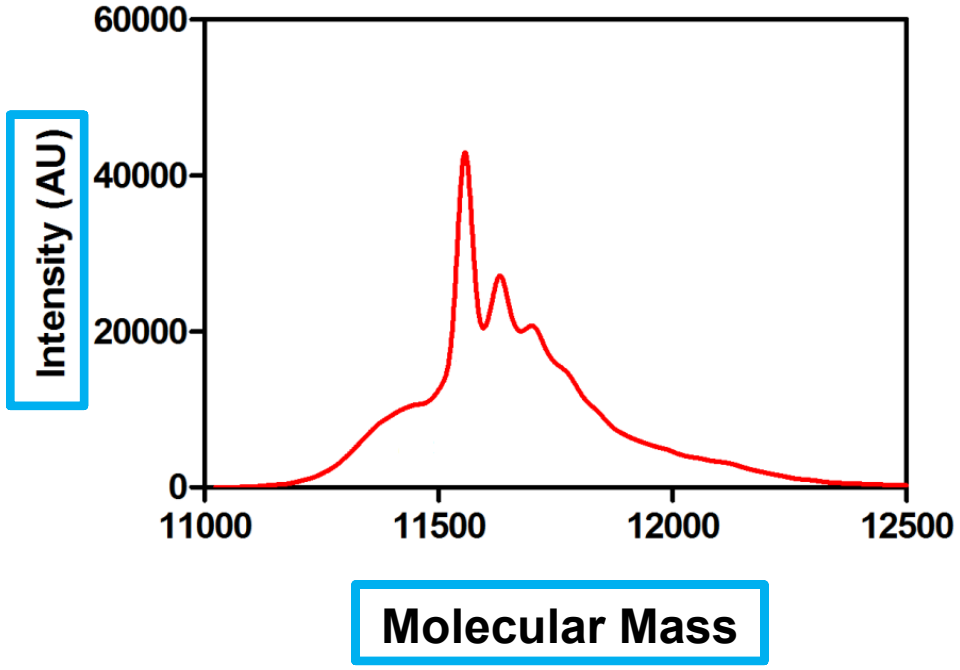
6 pts did progress and in 5 pts PD was biological and 4 pts were at ultra high risk

OS



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

ROLE OF QiP-MASS SPECTROMETRY FOR MONITORING

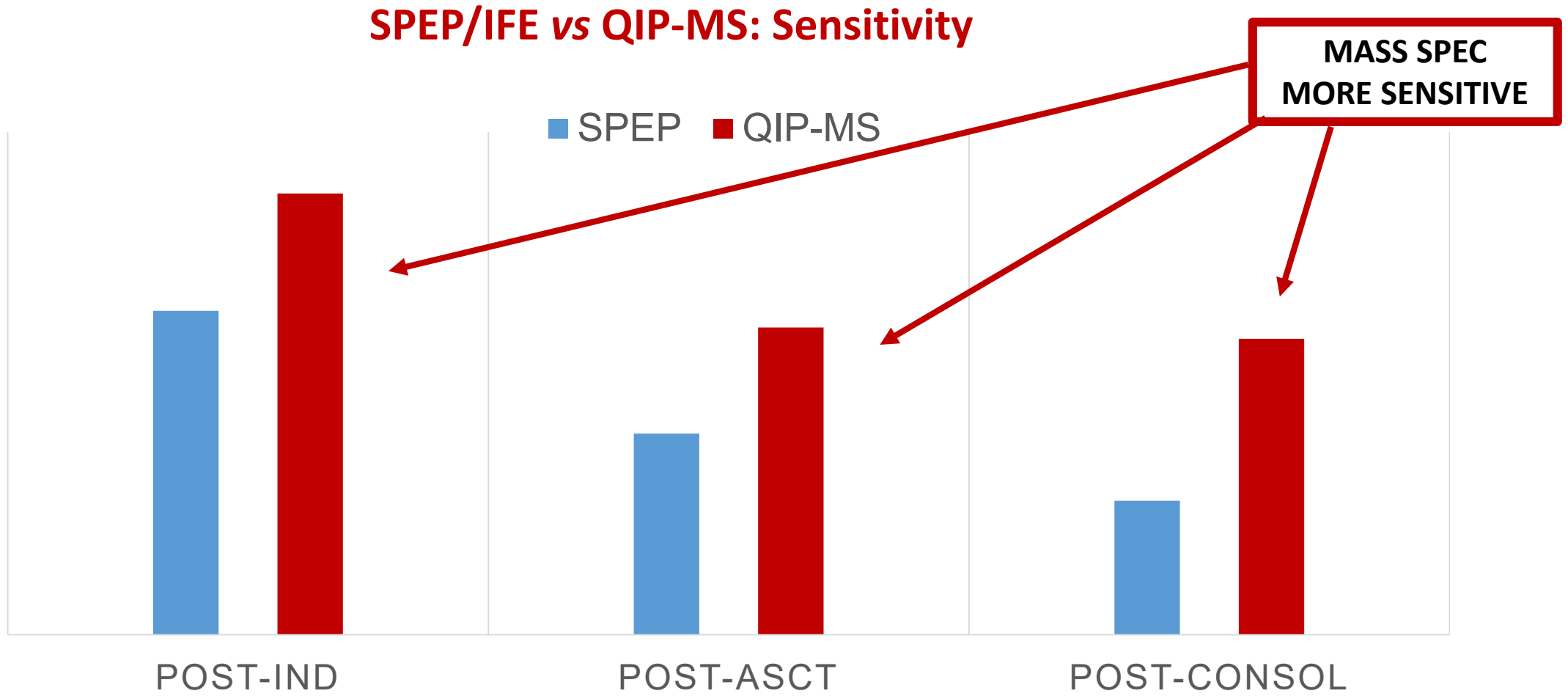


- **Molecular mass defines clonality**
- **Intensity indicates amount of monoclonal protein**

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

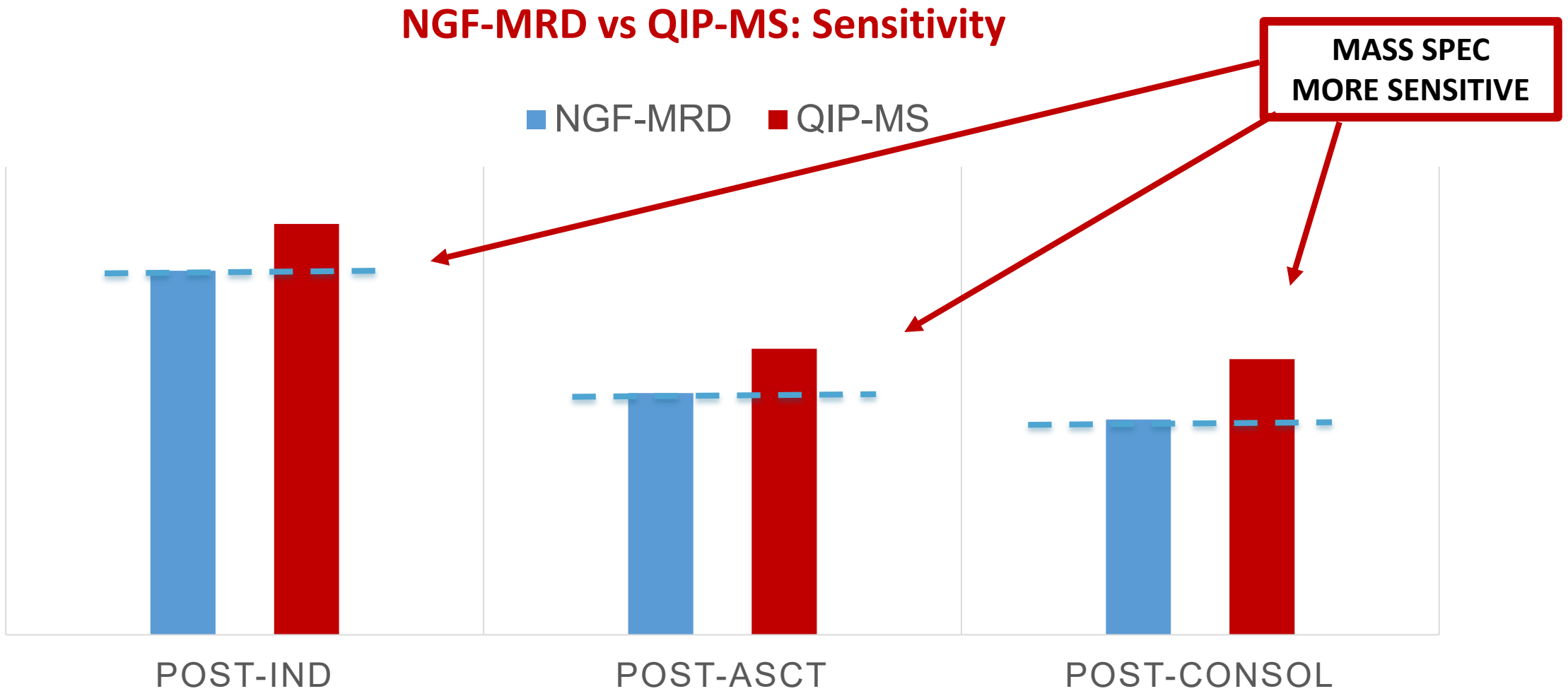
Noemi Puig, MD, PhD, et. al.

MONITORING IN THE CESAR TRIAL



Noemi Puig, MD, PhD, et. al.

COMPARISON OF QiP-MS AND NGF-MRD

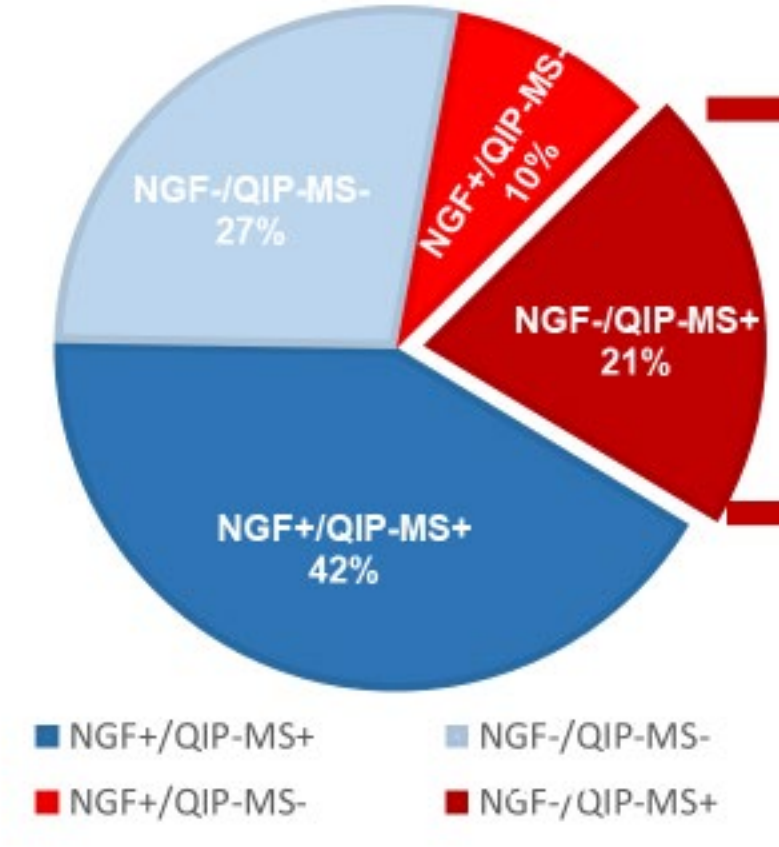


Only relapse was NGF -, but QiP-MS +

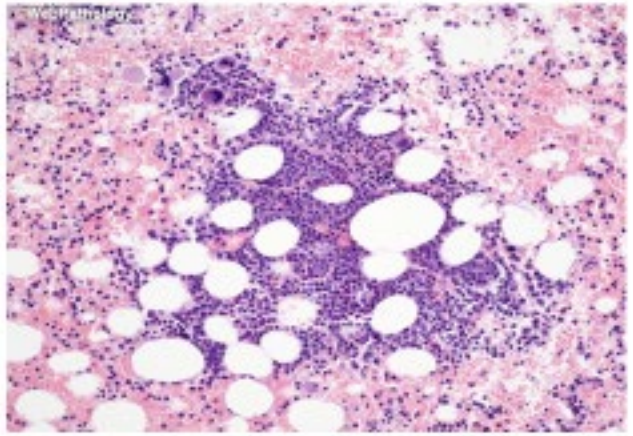
Noemi Puig, MD, PhD, et. al.

EXPLANATIONS FOR BONE MARROW MRD NEGATIVE BUT QiP-MS POSTIVE

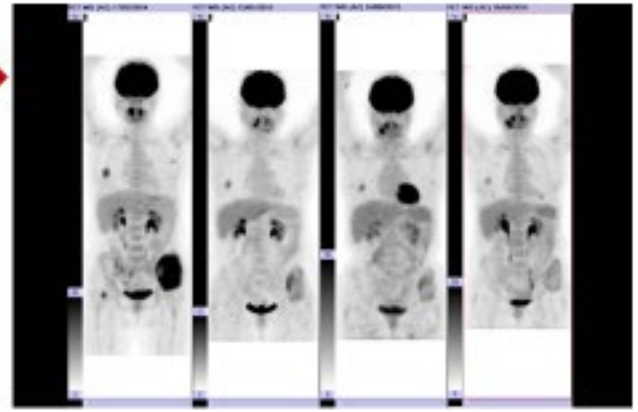
NGF-MRD - *vs* QIP-MS+



PATCHY DISEASE

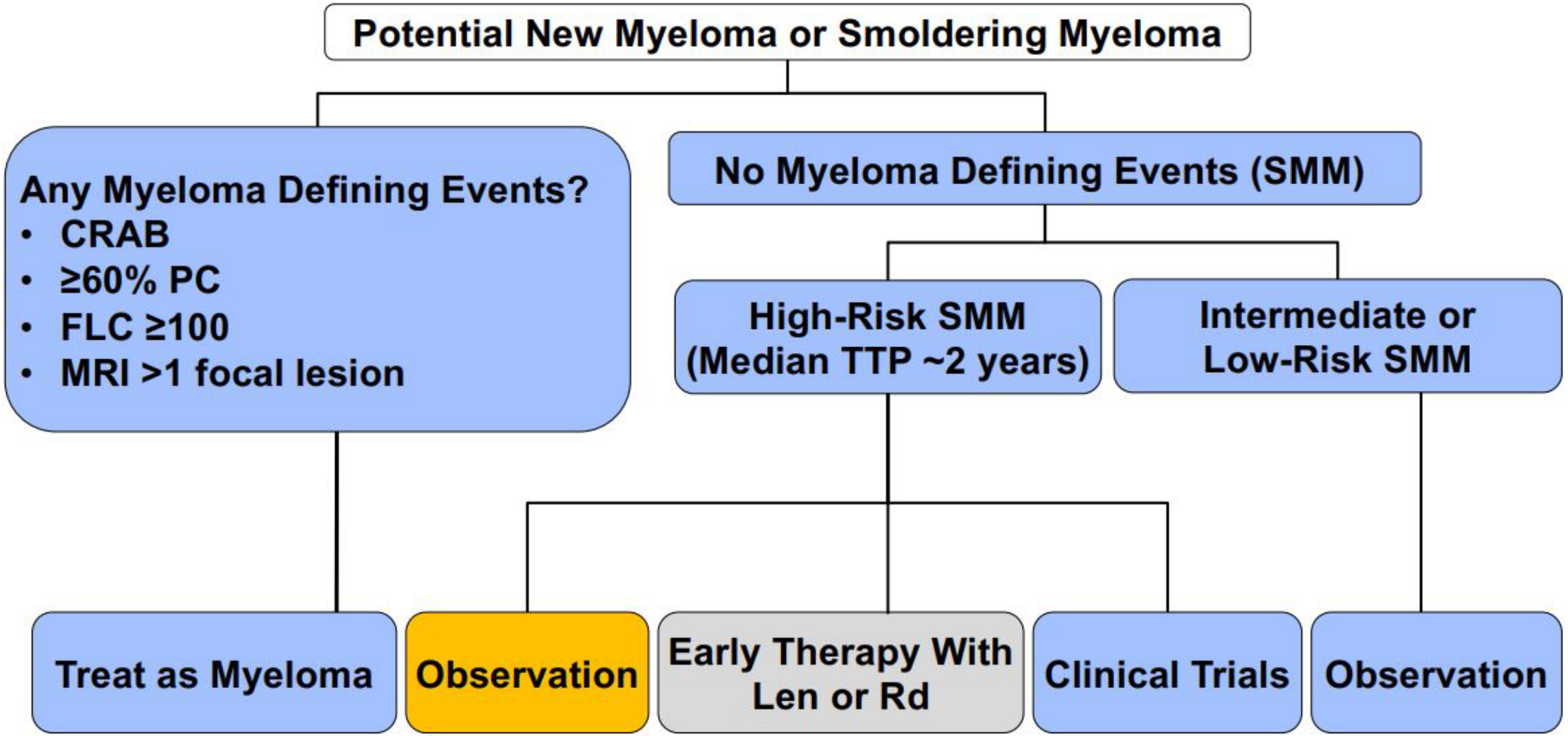


EXTRAMEDULLARY LESIONS



Noemi Puig, MD, PhD, et. al.

WHEN SHOULD TREATMENT BE STARTED



FRONTLINE THERAPY

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

***or isatuximab…**

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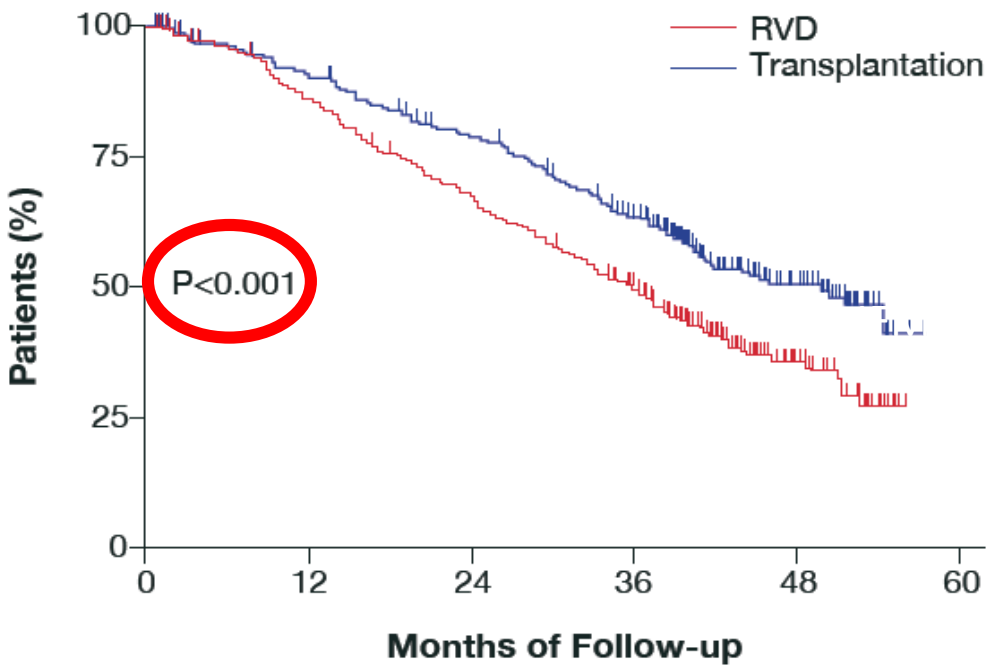
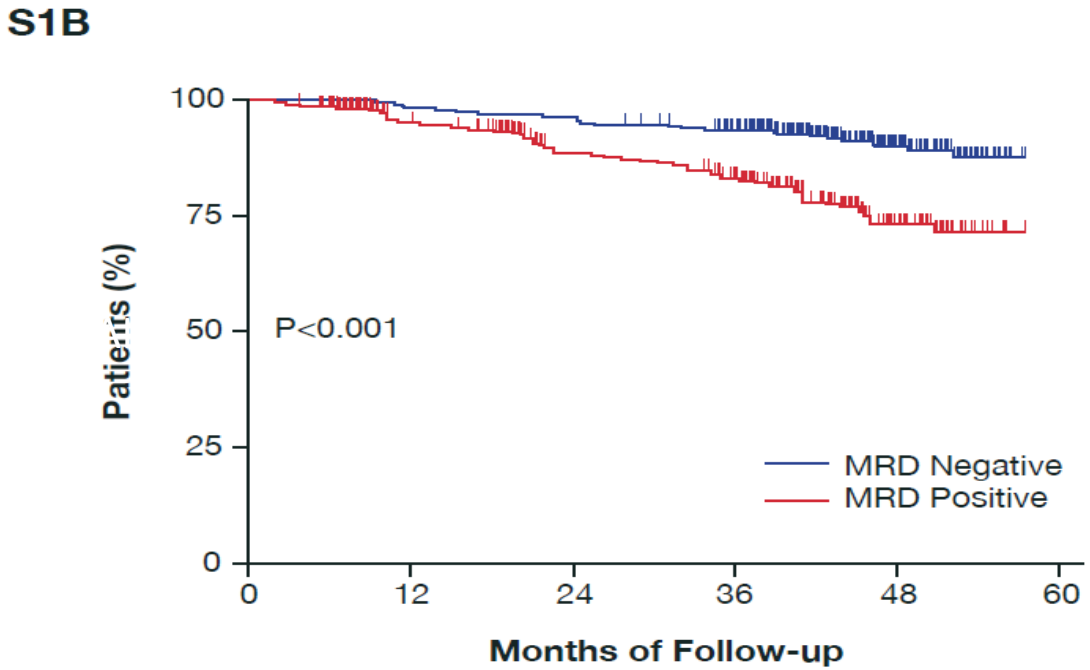
TRIPLE RESULTS: VRd + ASCT: IFM 2009 STUDY

PFS



No. at Risk						
RVD	350	294	228	157	32	0
Transplantation	350	308	264	196	50	0

OS



No. at Risk						
MRD Negative	0	311	379	347	119	0
MRD Positive	700	358	259	227	65	0

TRIPLET RESULTS: VRD x 6 for induction
458 Patients in 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

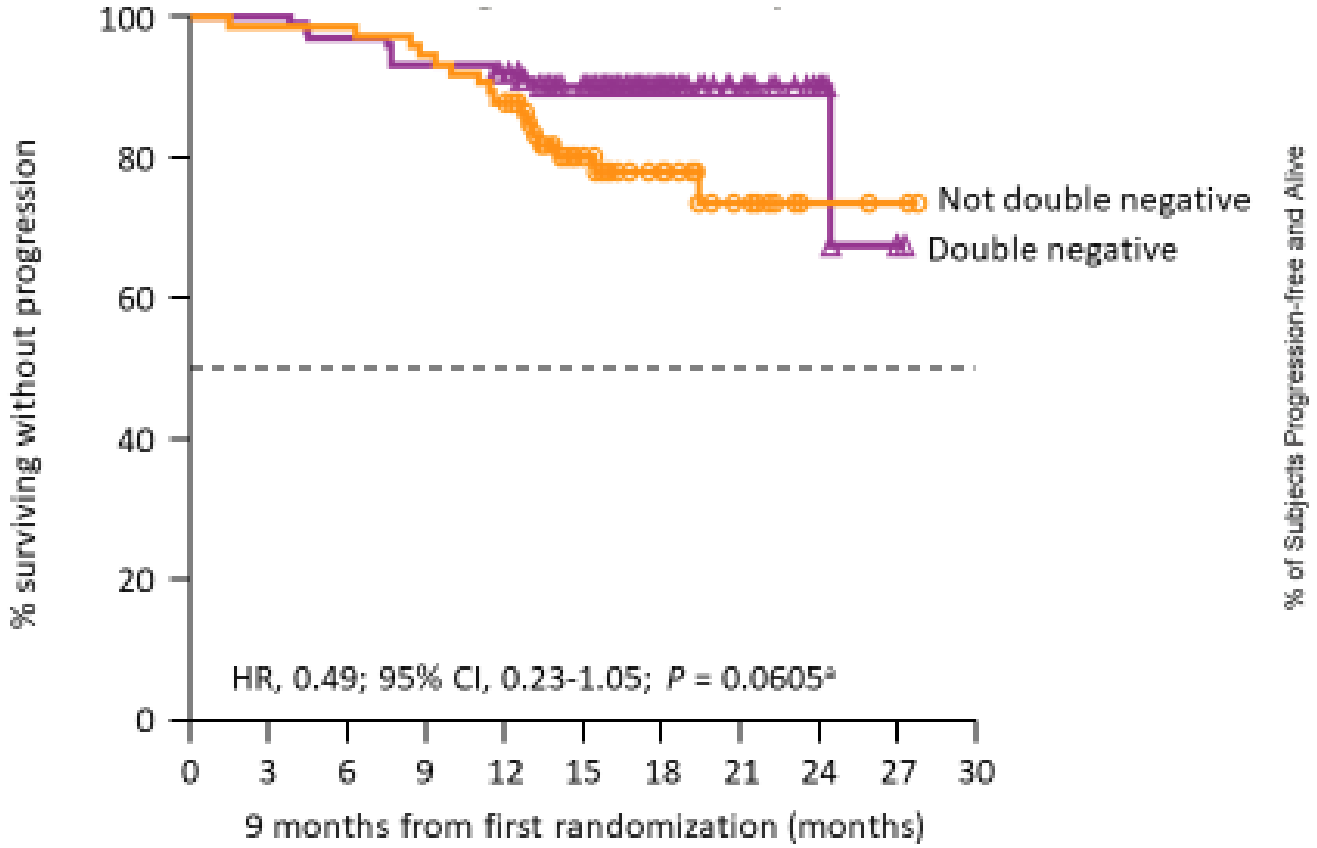
Laura Rosiñol, Albert Oriol, Rafael Rios, Anna Sureda, María-Jesús Blanchard, Miguel Teodoro Hernández, Rafael Martínez-Martínez, Jose M Moraleda, Isidro Jarque, Juan Bargay, Mercedes Gironella, Felipe de Arriba, Luis Palomera, Yolanda Gonzalez-Montes, Josep Marti, Isabel Krsnik, Jose M Arguiñano, Maria-Esther 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**

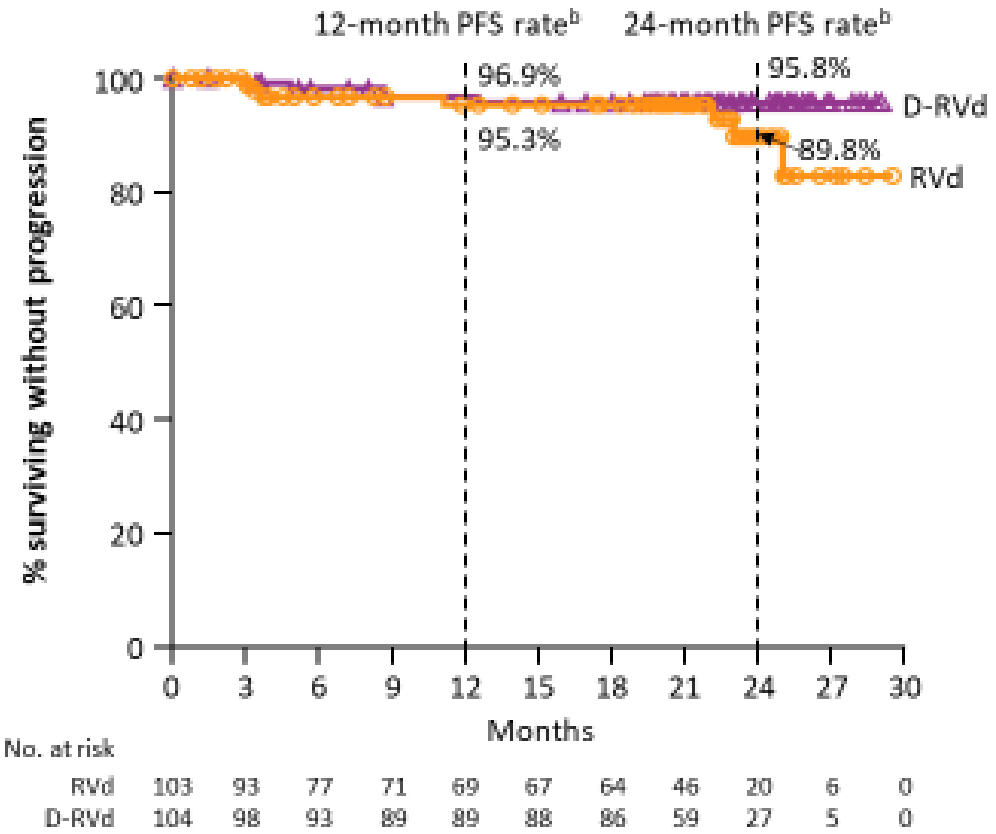
Dara plus VTd versus VTd (Cassiopeia)

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

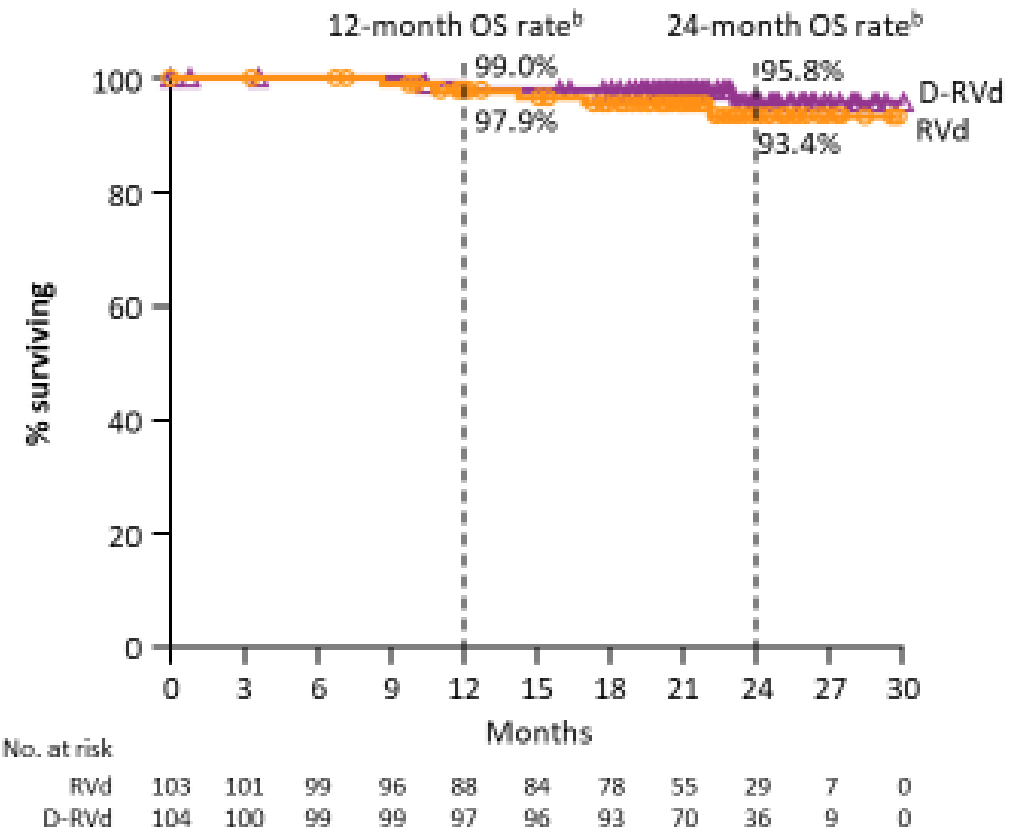


ASH Abstract #691: Dara plus VRd v VRd: Griffin Study Update

PFS



OS

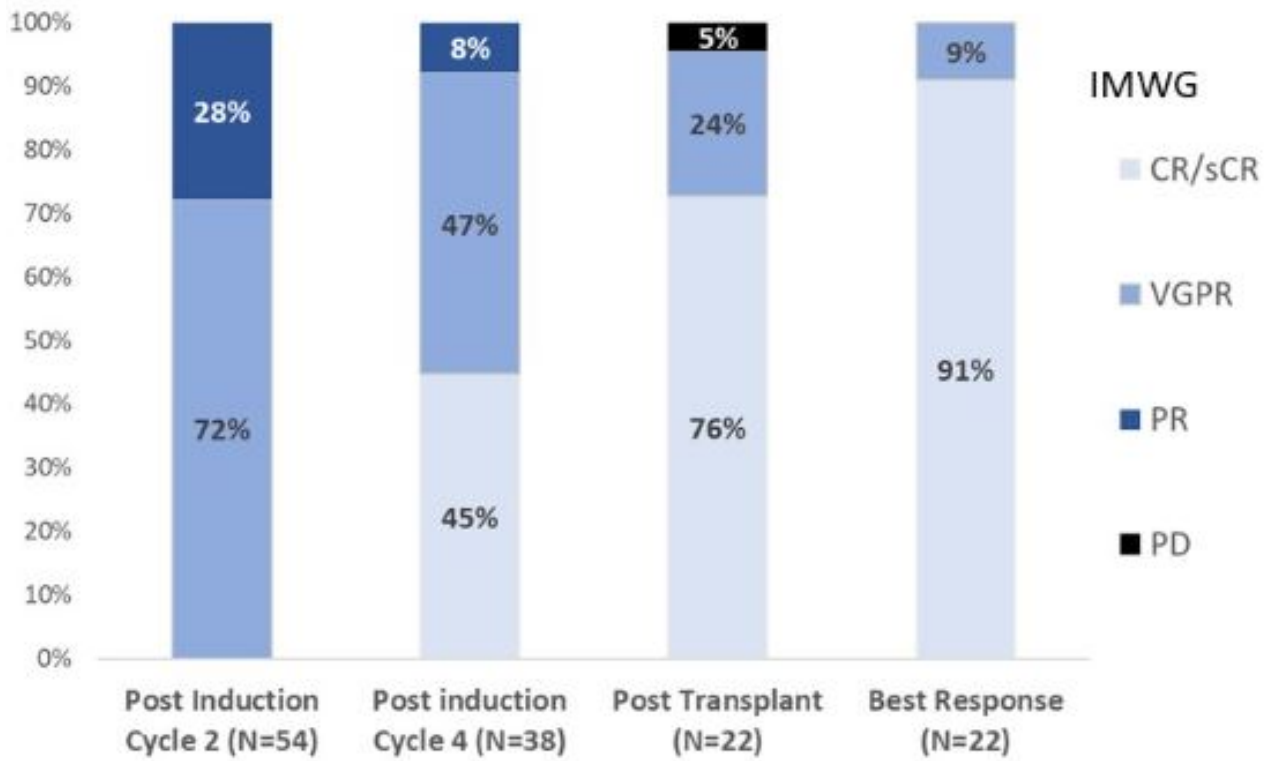


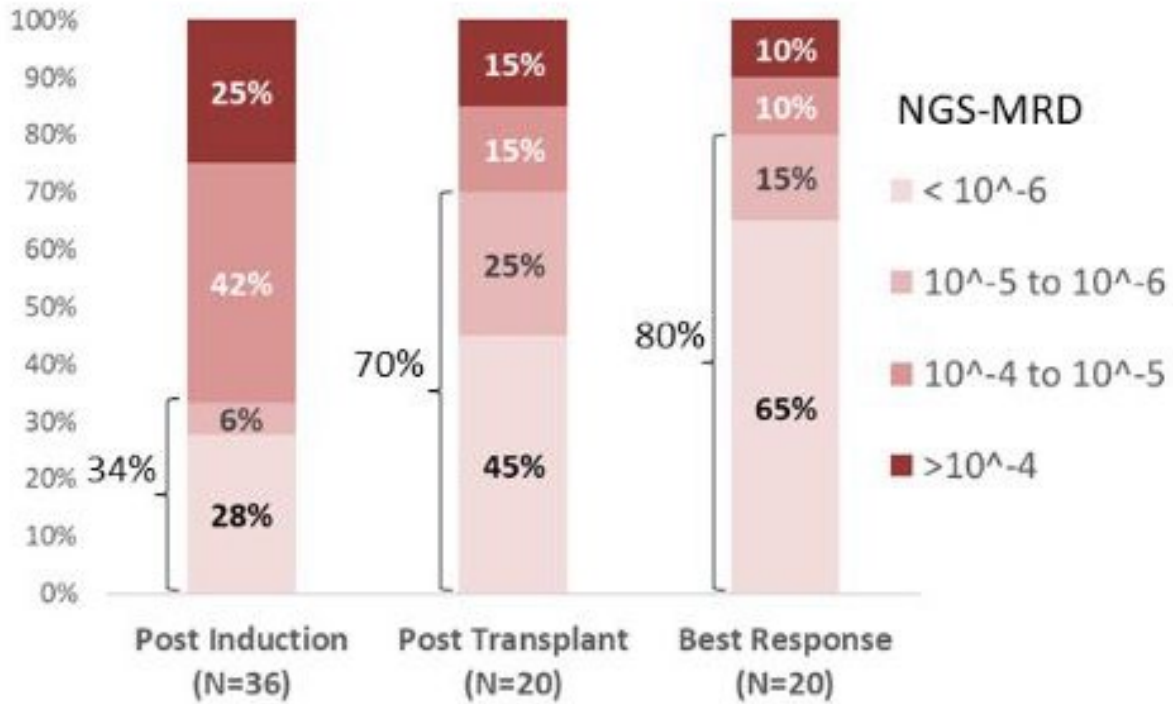
Median PFS and OS not reached for D-RVd and RVd

[a]ITT population. [b]Kaplan–Meier estimate.

Peter M. Voorhees, MD, et. al.

ASH Abstract #860: Dara KRd + ASCT





INCREASING

CR/sCR

INCREASING

MRD Neg @ ≥10^{-5} level

Maximum benefit = 65% @ ≥10^{-6} level

FRONTLINE THERAPY

Will dara* + triplet become the "standard of care"?

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

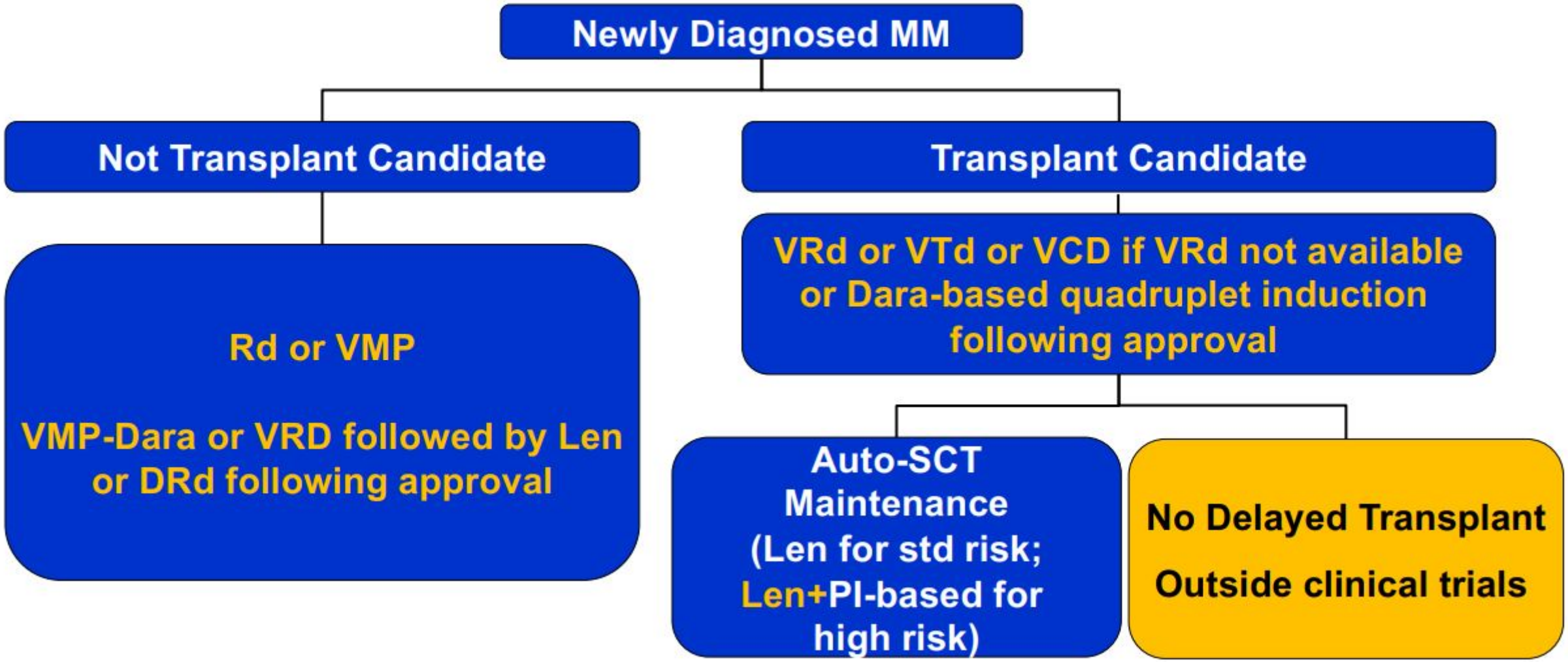
OR will we stick with?

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

…and save quadruplets for later?

***or isatuximab…**

MYELOMA: FRONTLINE TREATMENT



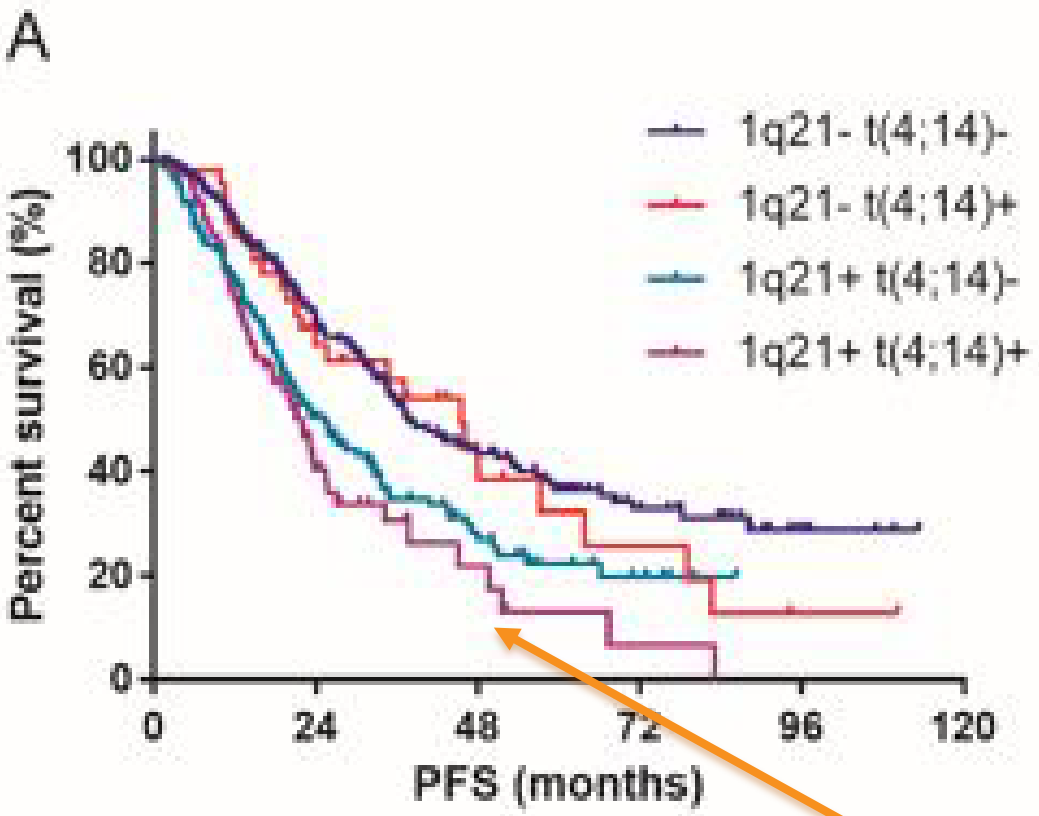
Potential Precision Medicine Approaches

New Data at ASH

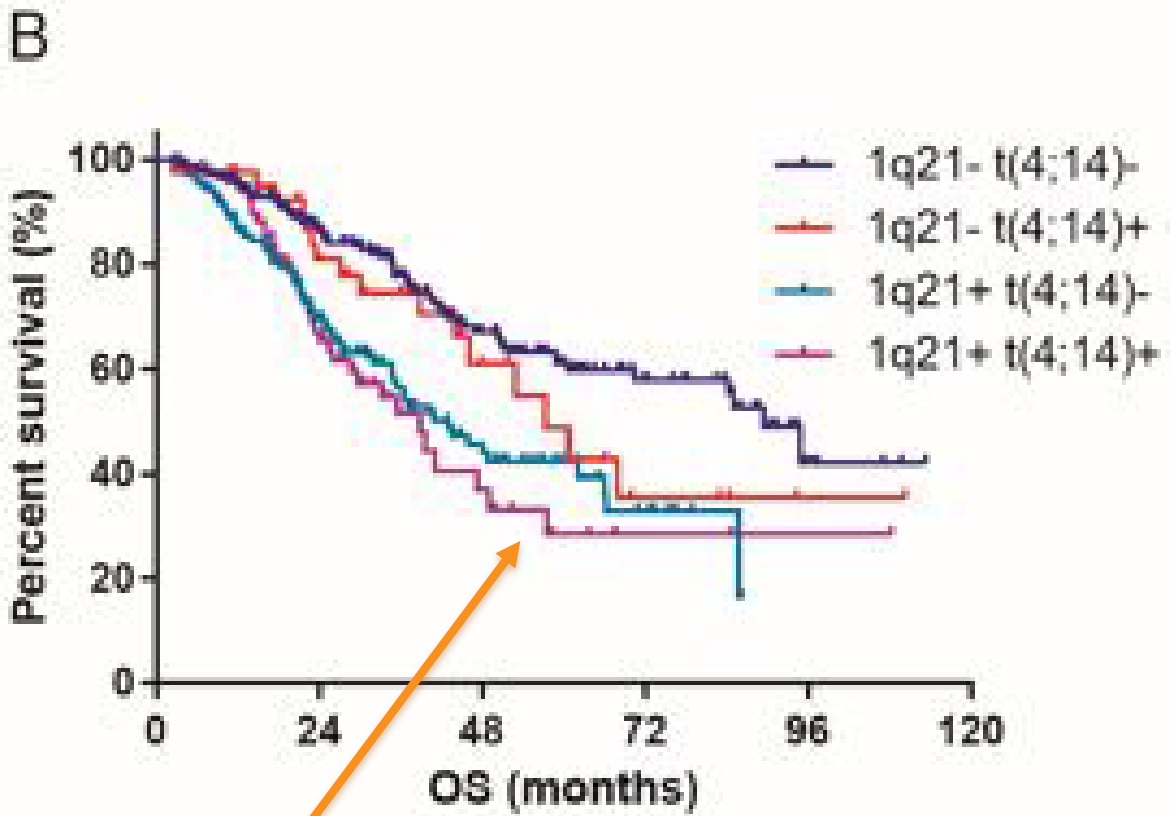
- 1q21 gain
- t(11;14)
- Role of ASCT and VENETOCLAX
- Therapy for primary systemic amyloidosis
- Unfit/frail patients with NDMM: HOVON 143 IXA/Dara/Dex

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

PFS



OS

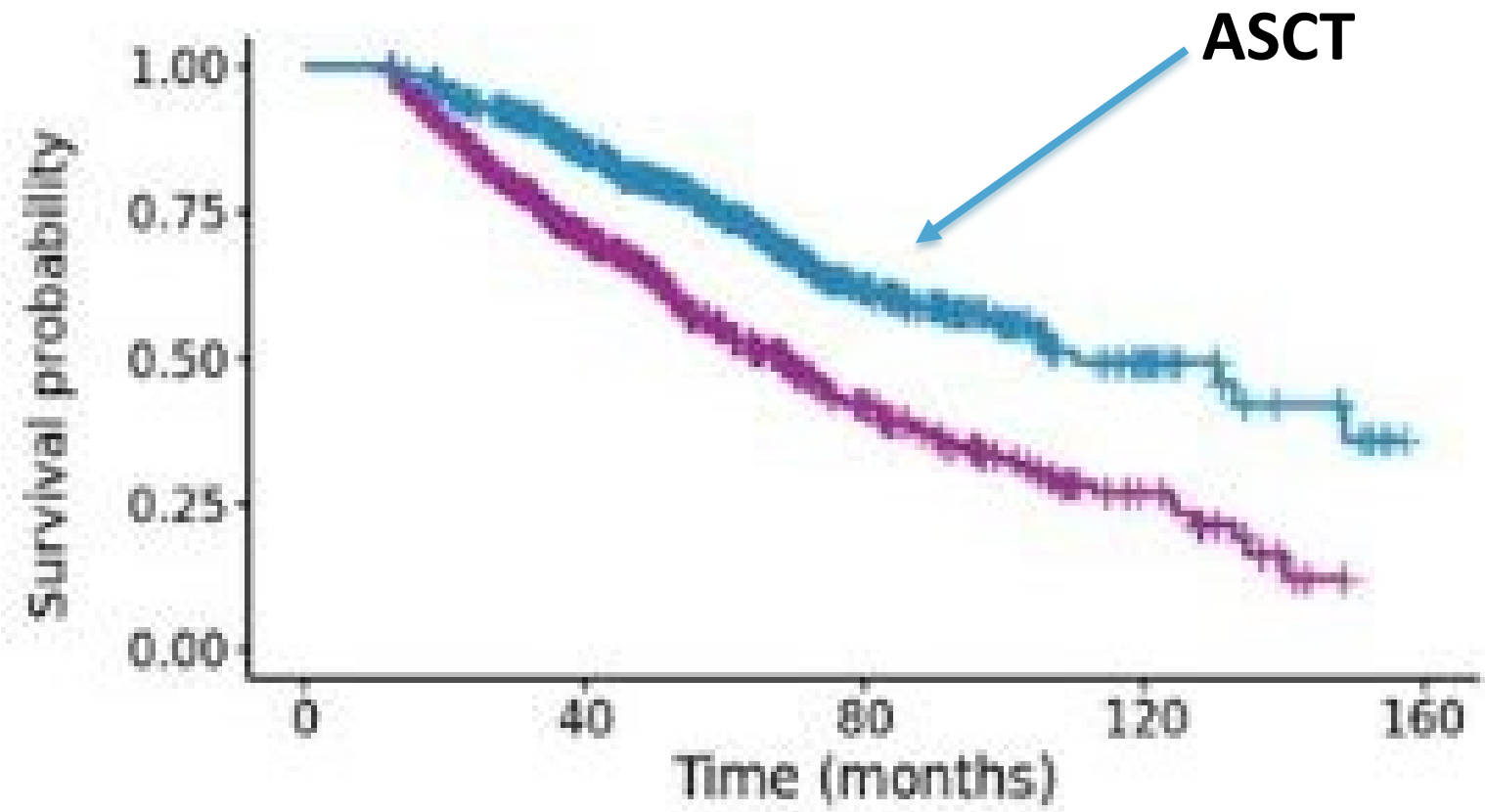


1q+ plus t(4;14)

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

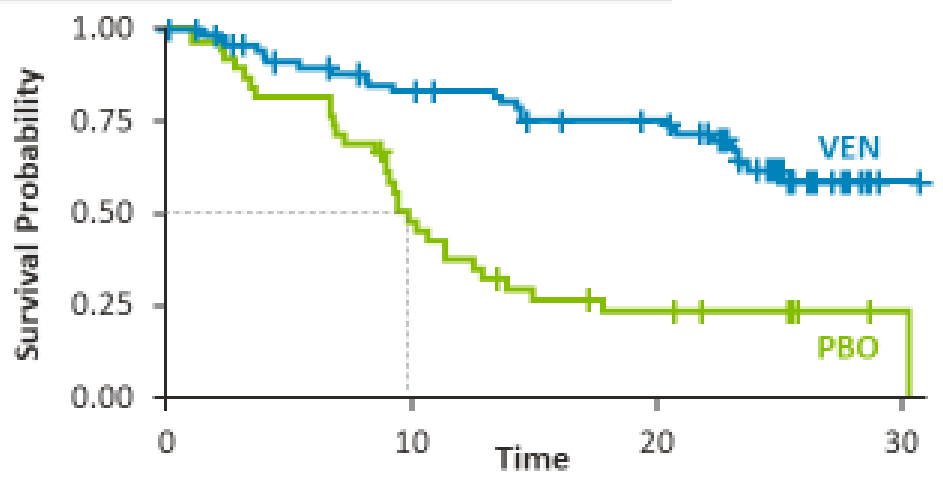
Eduardo Sobejano, et. al.

Overall Survival



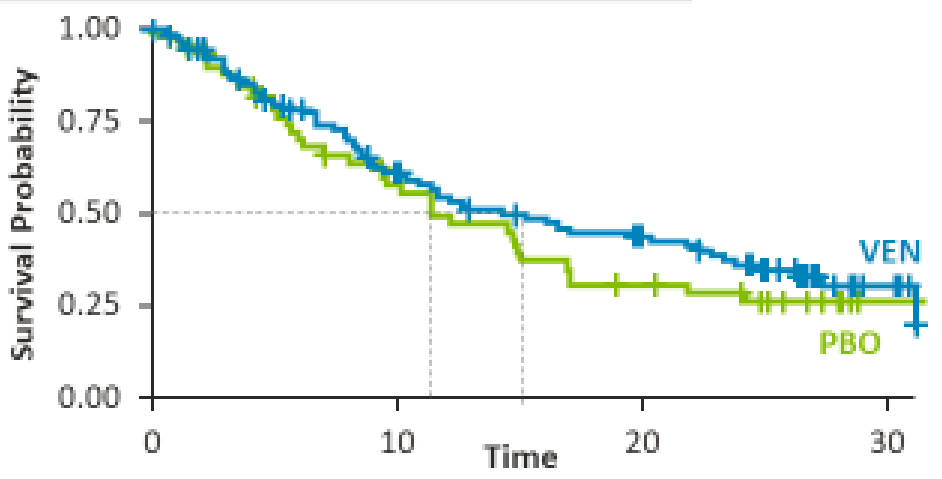
ASH Abstract #1888: Bortezomib and dexamethasone +/- VENETOCLAX: Update of BELLINI Phase 3 Trial

PFS



t(11;14) or BCL2^{HIGH}

PFS

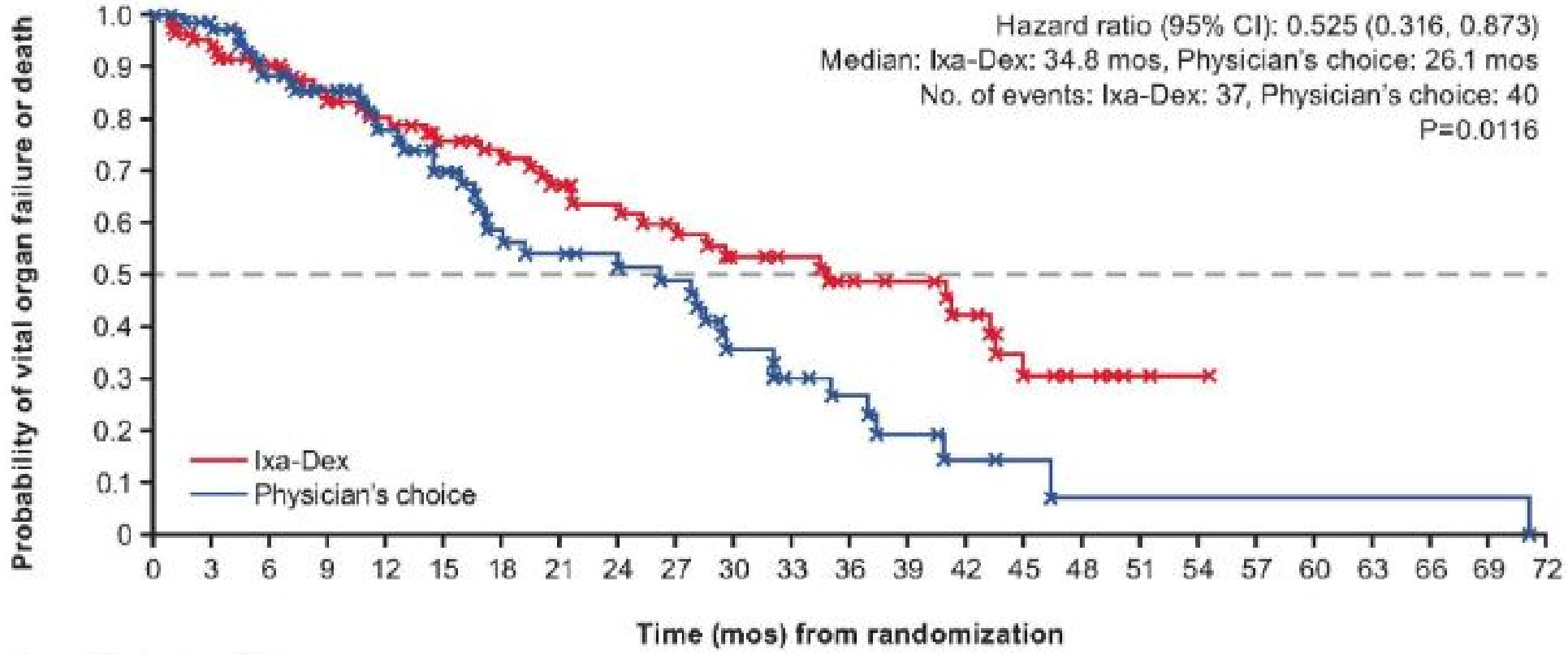


NON t(11;14) or BCL2^{LOW}

Philippe Moreau, MD, et. al.

ASH Abstract #139: Primary Results from the Phase 3 Tourmaline-AL1 Trial of Ixazomib-Dexamethasone Versus Physician's Choice of Therapy in Patients (Pts) with Relapsed/Refractory Primary Systemic AL Amyloidosis (RRAL)

Figure. Time to vital organ deterioration/death and efficacy outcomes (PA)



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WILL THERE BE "PRECISION MEDICINE" APPROACHES FOR t(11;14), 1q+ AND OTHERS?

- 1q+ plus t(4;14): clear high risk group!
- t(11;14): treat incorporating:
  - ASCT
  - Venetoclax
- IXA oral combinations for amyloid and unfit/frail

IMMUNE THERAPY RESULTS DOMINATE ASH 2019

- **CAR T Therapy**
- **Bispecific T Cell Engagers (BiTEs [Amgen]; BEATs; TCEs [BMS])**
- **GSK 2857916 (“belamaf”: MoAb/drug conjugate)**

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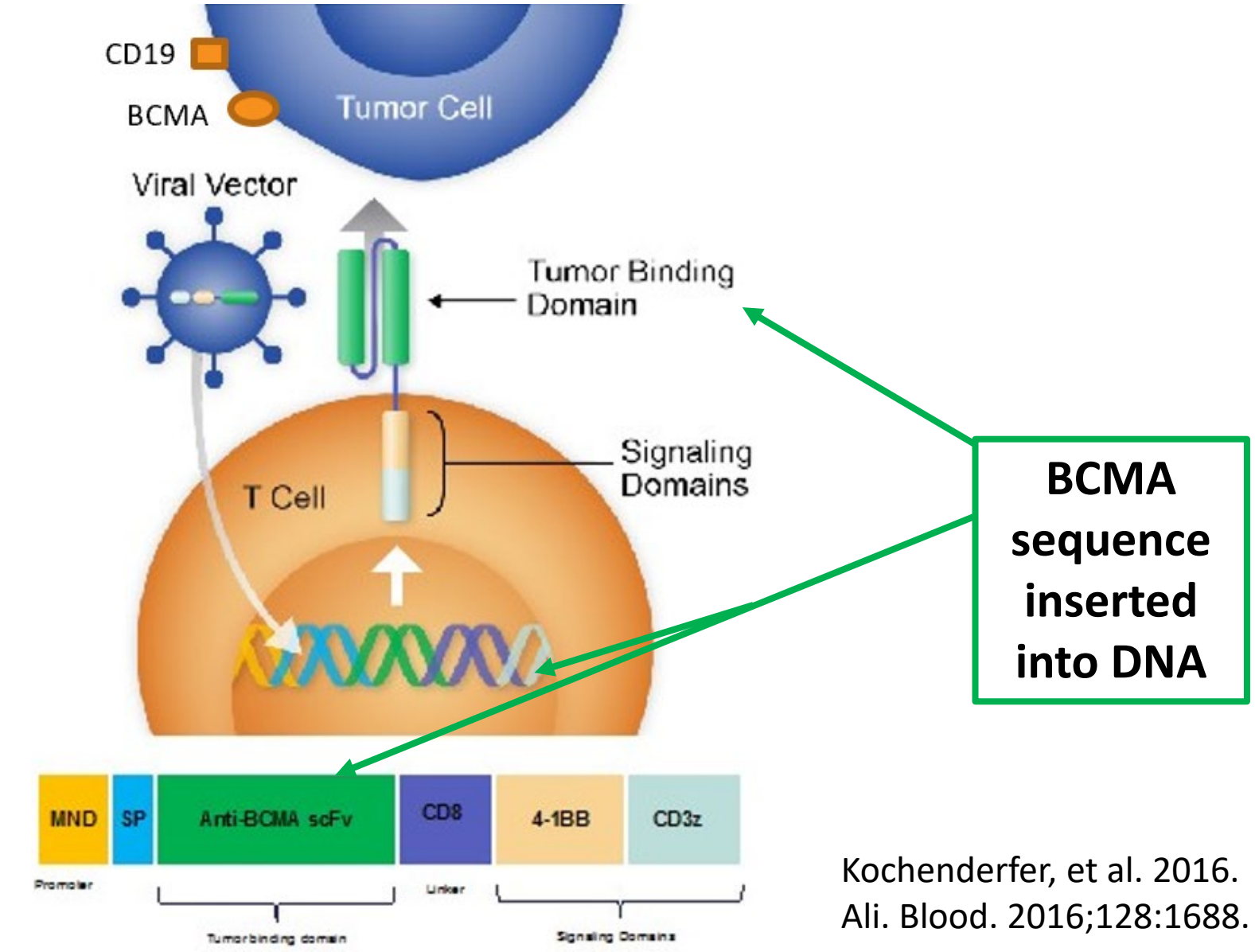
Chimeric Antigen Receptor (CAR) Therapy for Multiple Myeloma

Is CAR T Therapy a Game Changer in MM?



BCMA sequence inserted into DNA

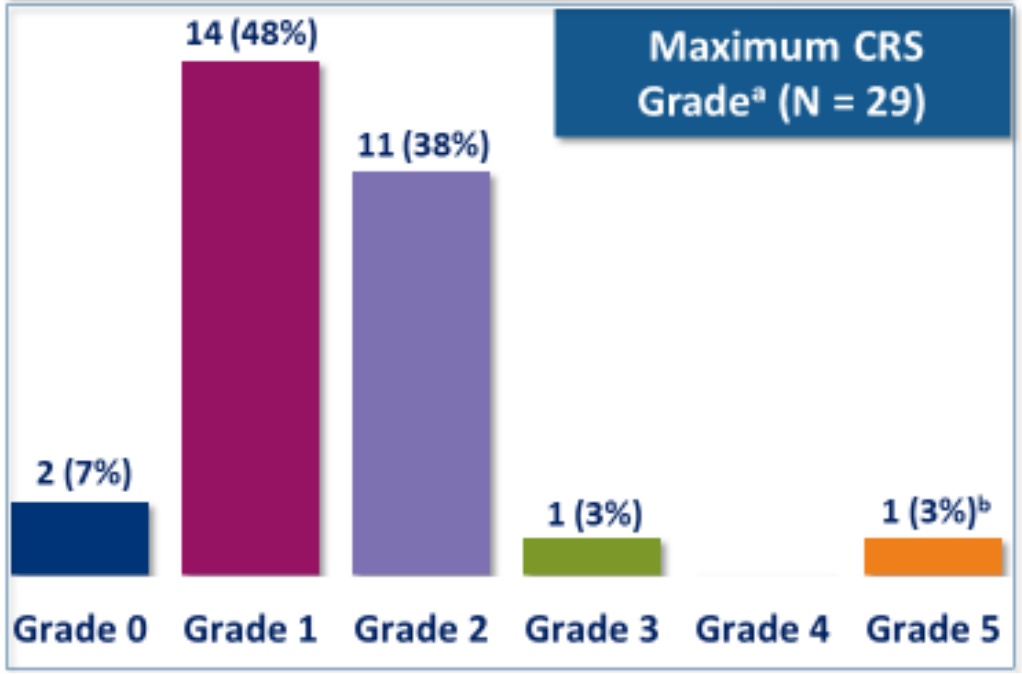
Kochenderfer, et al. 2016.
Ali. Blood. 2016;128:1688.

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)

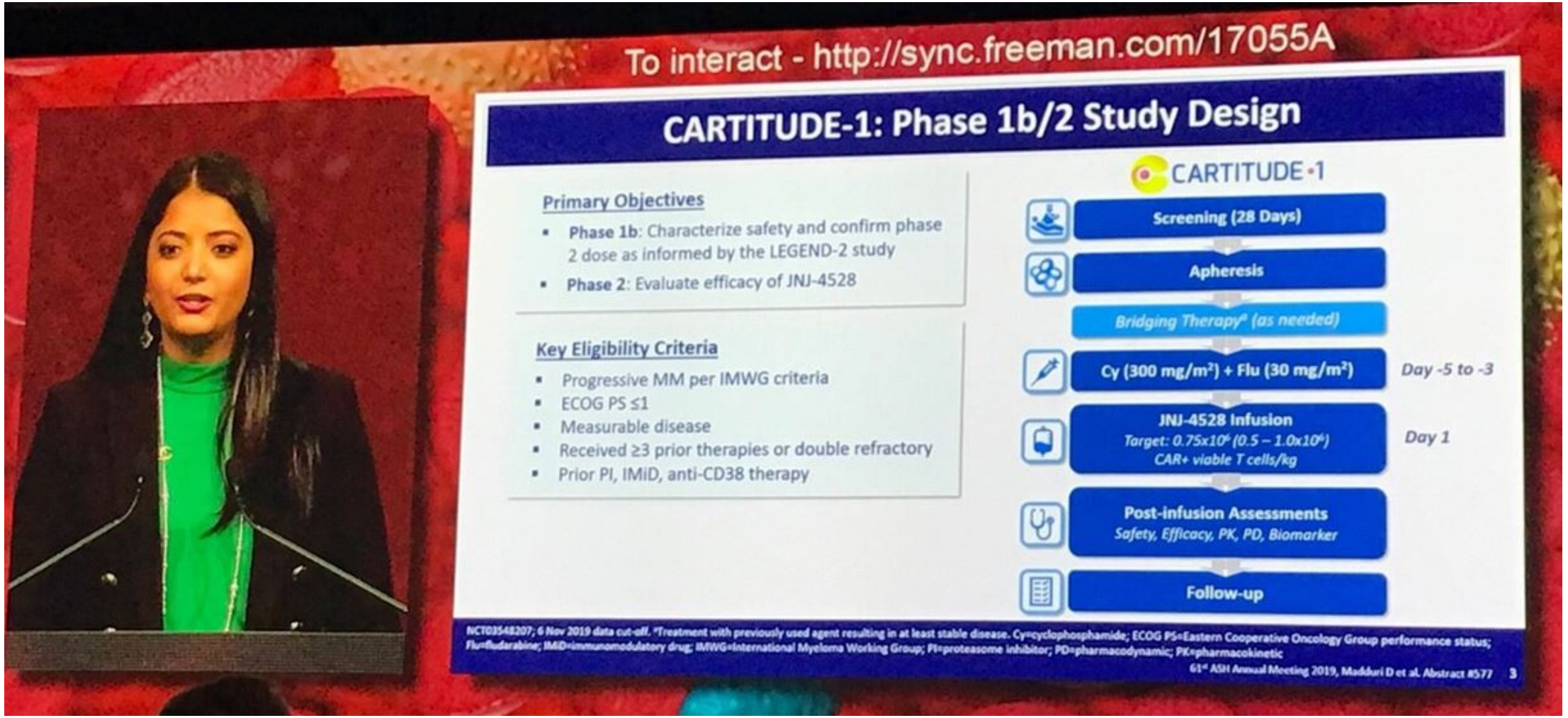
CARTITUDE-1: Safety

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)

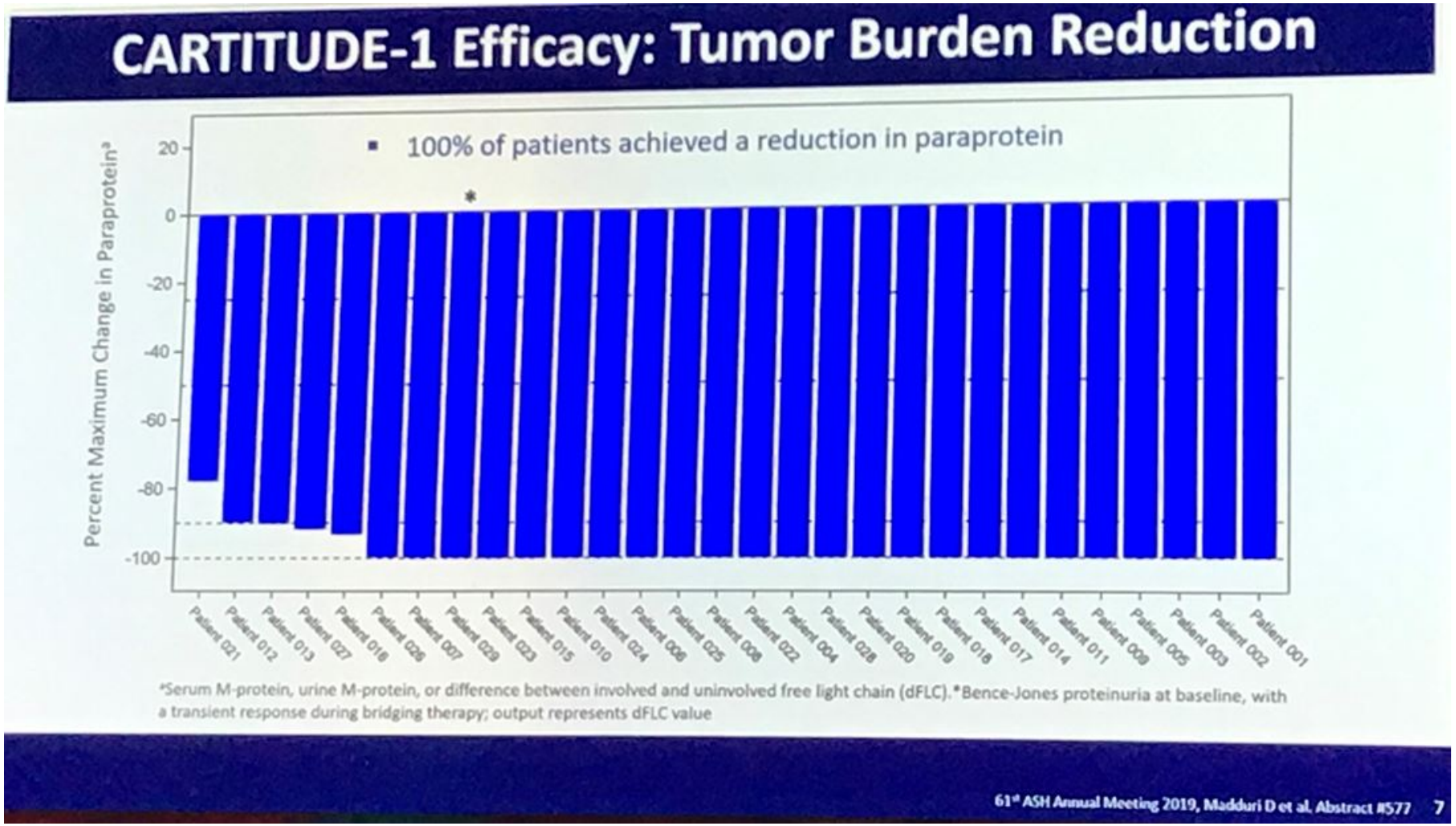


577 Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM)



Deepu Madduri, MD, et. al.

TIME FOR A PAUSE TO CONSIDER 100% RESPONSES!



Deepu Madduri, MD, et. al.

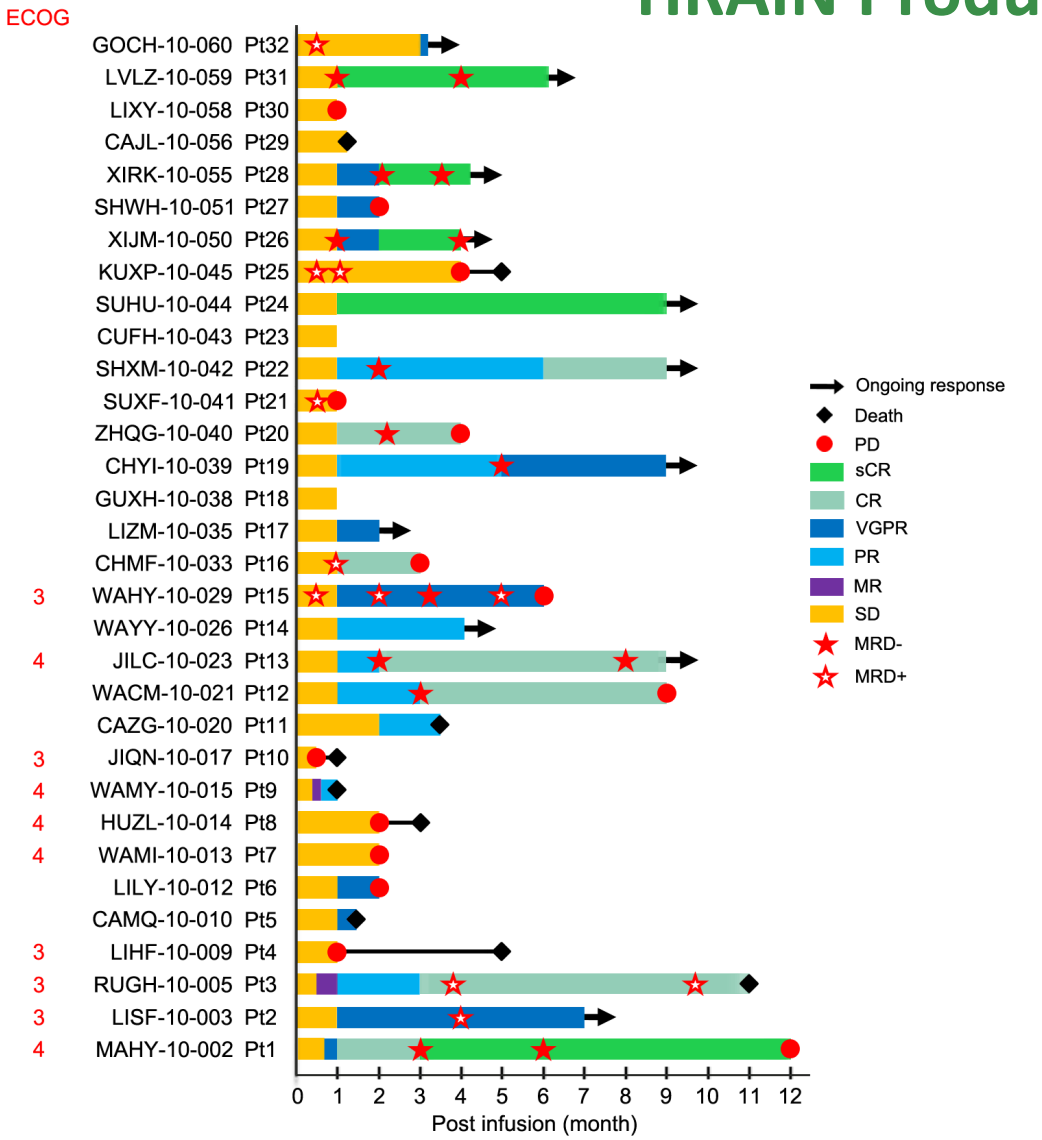
IND Approvals for BCMA-CAR T Therapy in China

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 1 Clinical Study

HRAIN Product with Safety Switch

Hospital 1

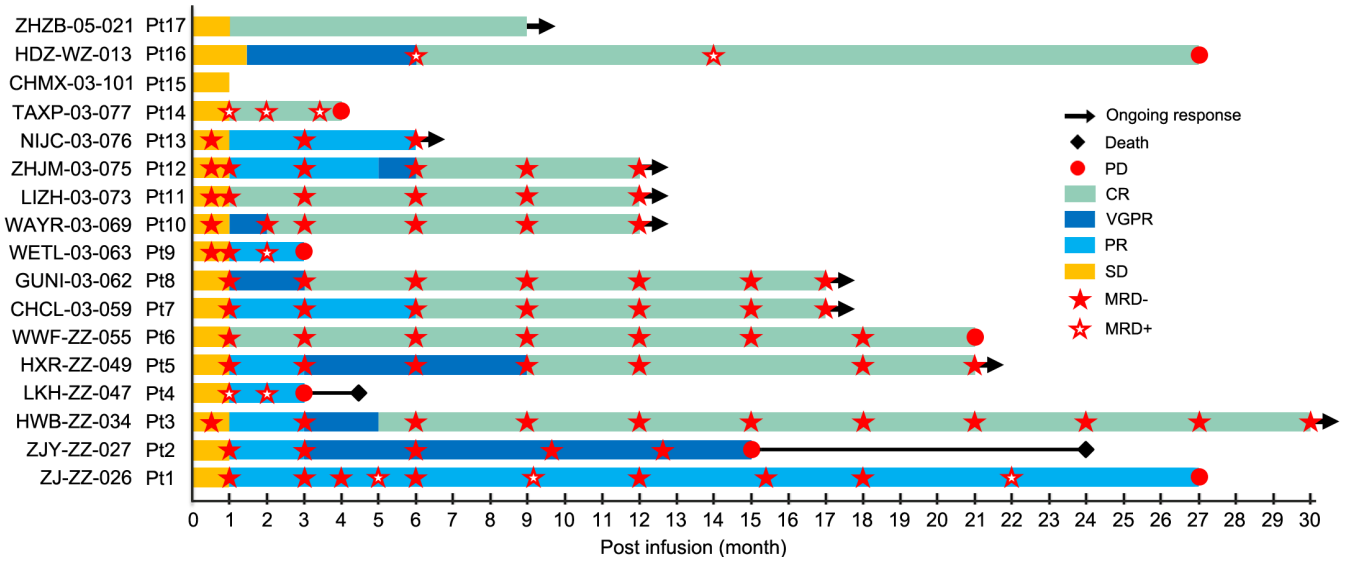


ORR: 38/49 (77.55%), ≥CR 43%

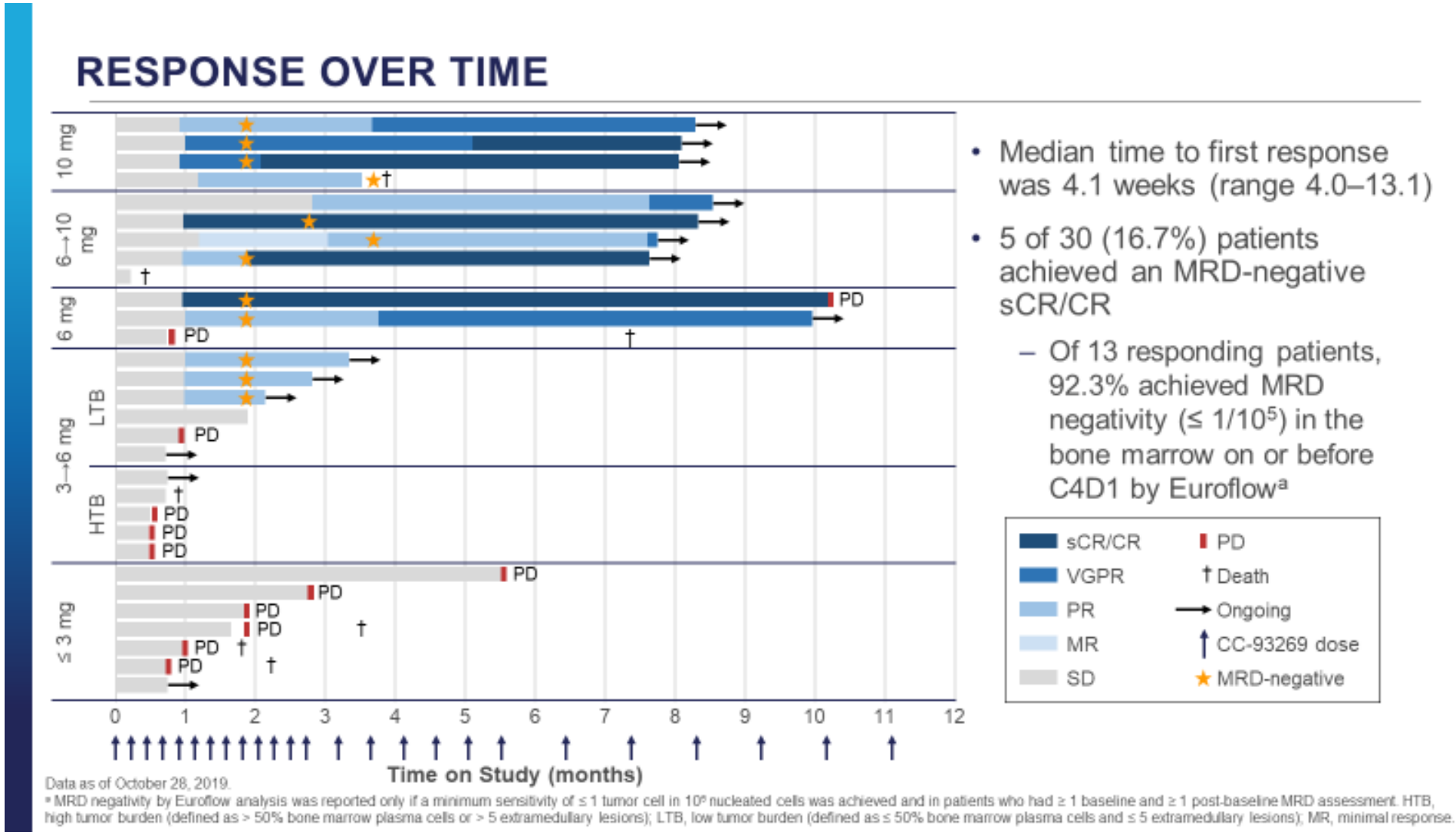
ECOG ≥3 ORR: 15/20 (75.00%)

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

Hospital 2 & 3

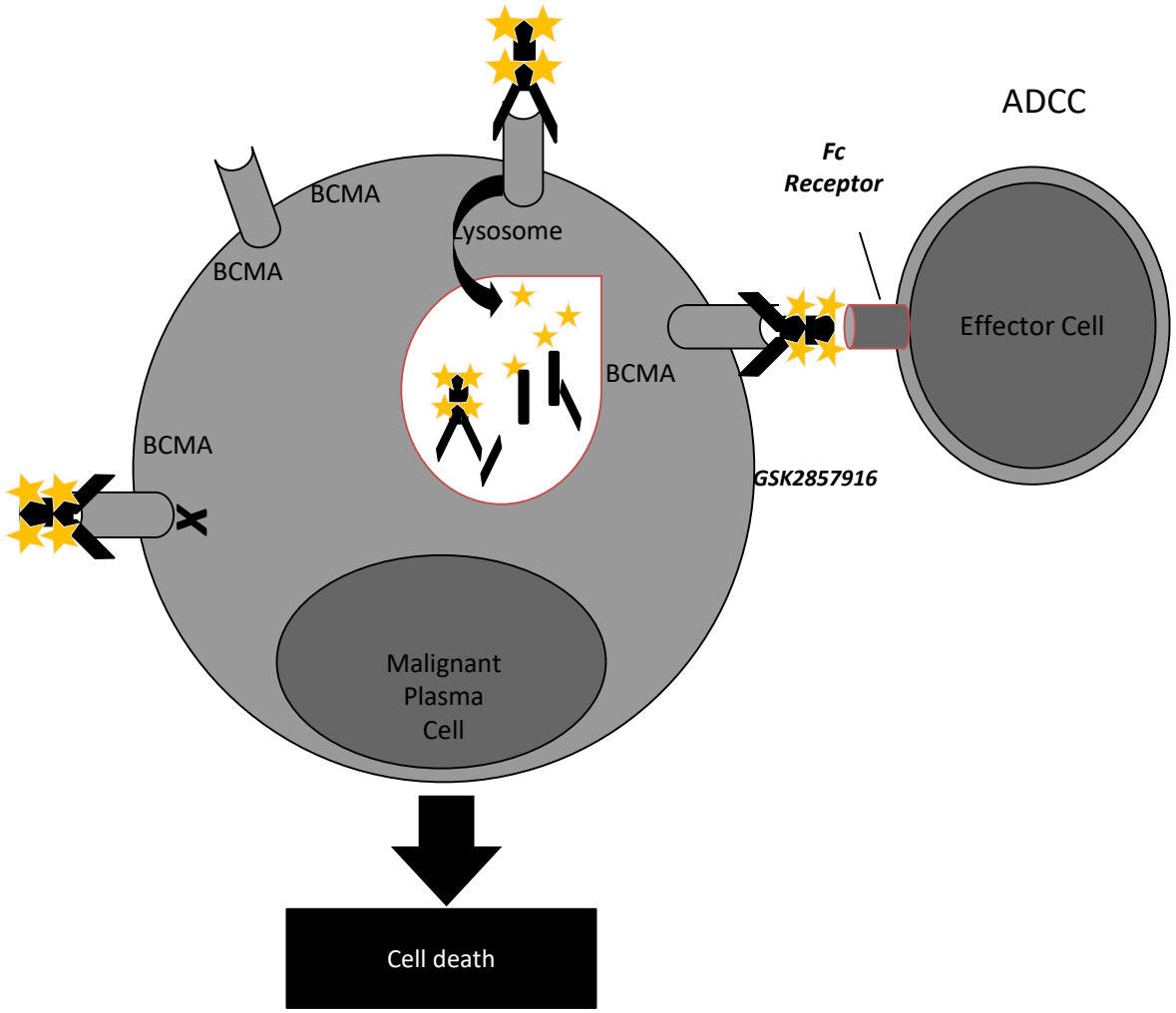


ASH Abstract #143: Anti-BCMA [2] T Cell Engager (TCE): Phase 1 Trial of CC 93249



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**

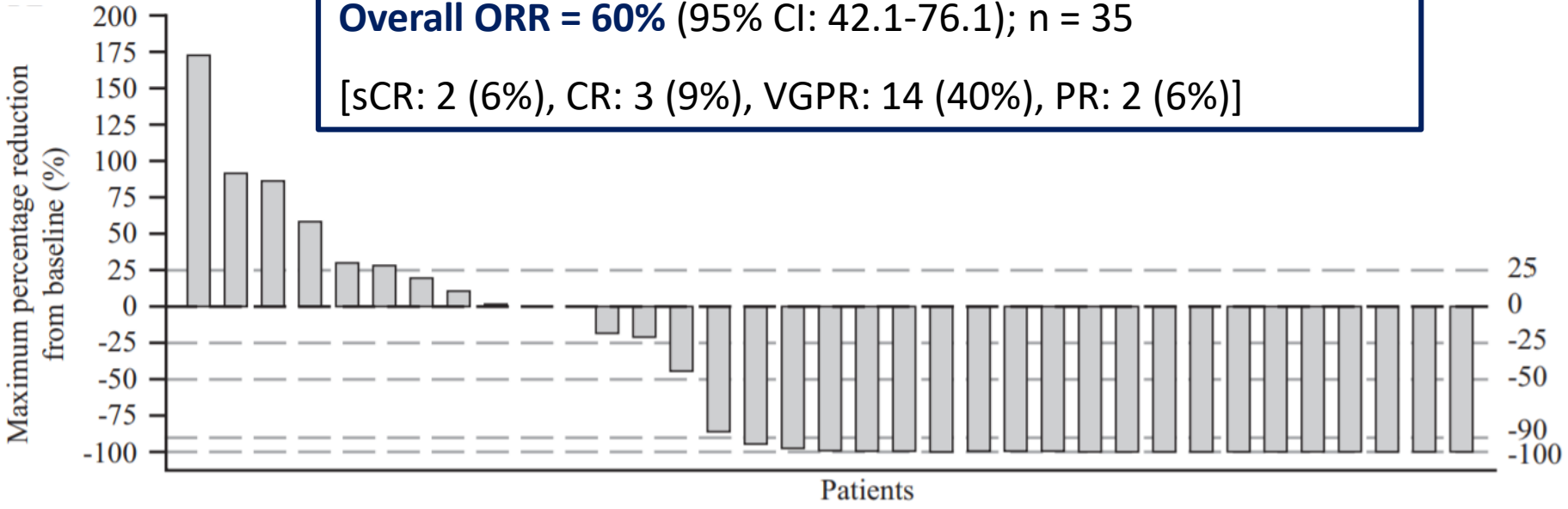
Tai. Blood. 2014;123:3128.

Belantamab Mafodotin: Efficacy in Multiple Myeloma

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

Overall ORR = 60% (95% CI: 42.1-76.1); n = 35

[sCR: 2 (6%), CR: 3 (9%), VGPR: 14 (40%), PR: 2 (6%)]



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)

Trudel. Blood Cancer J. 2019;9:37.

ROLE OF IMMUNE THERAPIES

Clearly active in relapsed patient population

How should BCMA targeted therapy be used and sequenced?

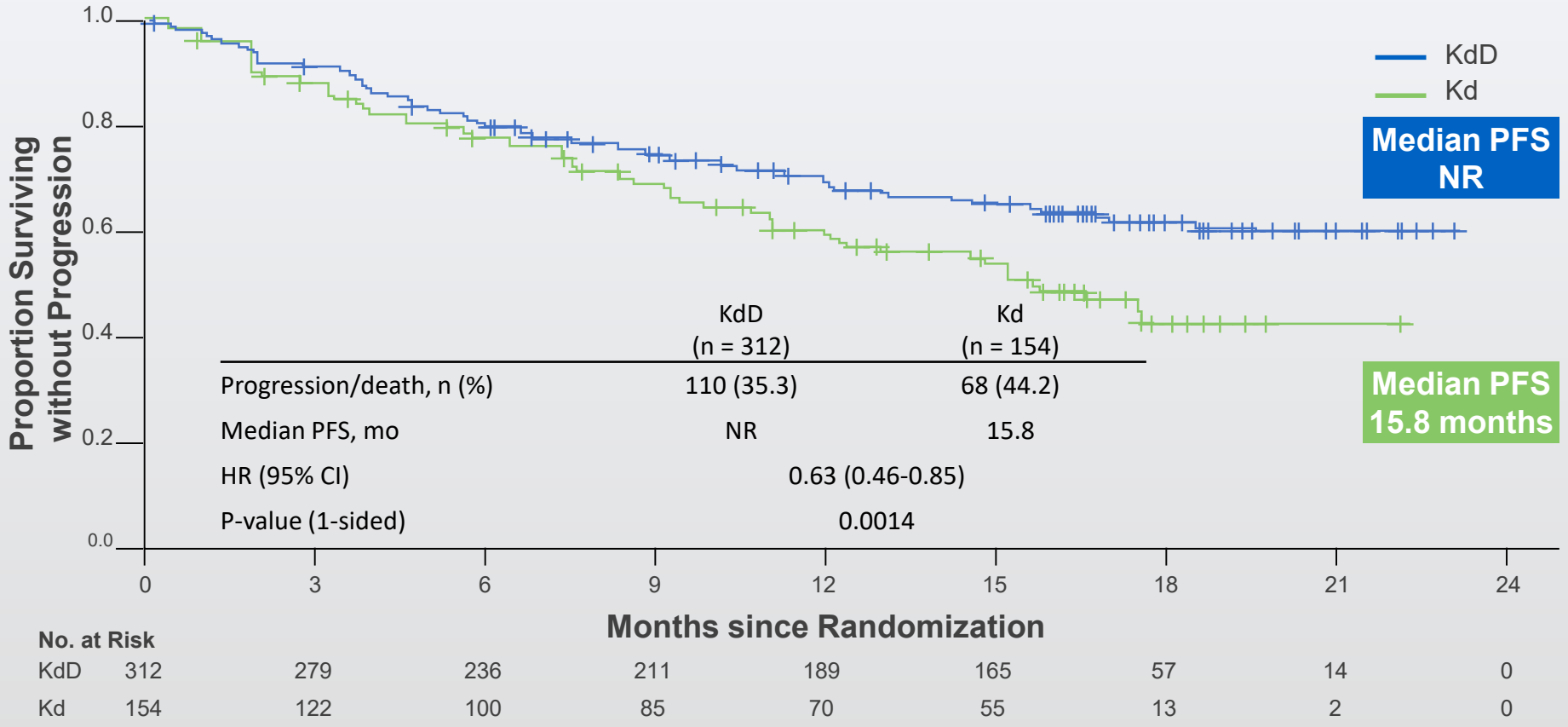
Is earlier use the best approach?

- **For consolidation?**
- **At first relapse?**

NOVEL AGENTS OR COMBINATION AT RELAPSE

- dara/Kyprolis/dex (CANDOR): LBA-6 (ASH 2019)
- dara/Pom/dex
- Kyprolis/Pom/dex
- iberdomide (CC-220)
- melflufen
- I^{131} CLR 1404 (lipid rafts target)

Dara Kd Demonstrated Significantly Longer Progression-Free Survival Versus Kd: CANDOR Study



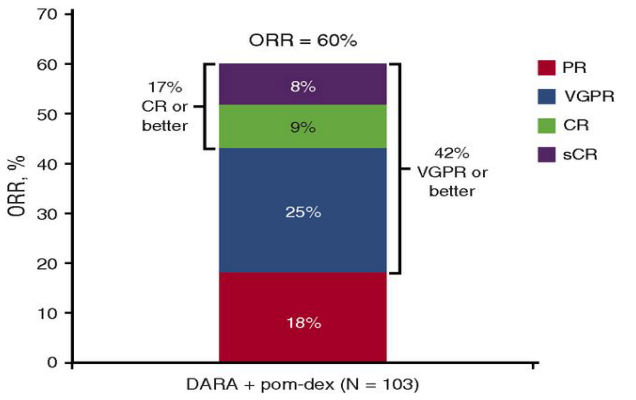
Median OS was not reached in either arm at a median follow-up of 17 months (HR, 0.75; 95% CI, 0.49–1.13; P=0.08)

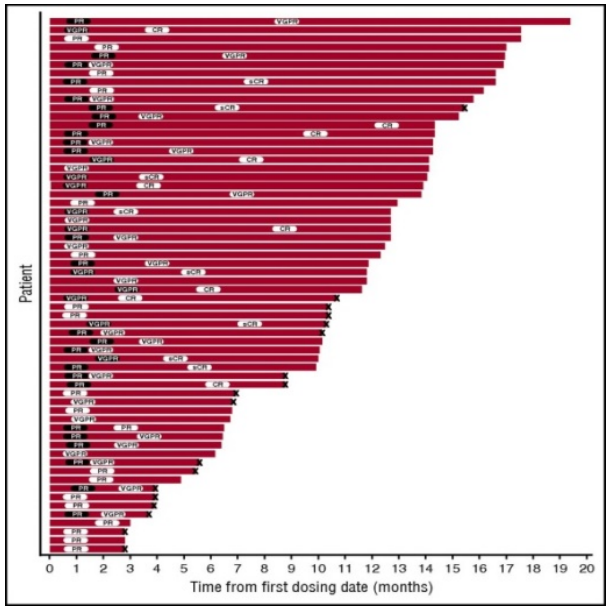
Treatment with KdD resulted in a 37% reduction in the risk of progression or death vs Kd in patients with RRMM

CI, confidence interval; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; NE, not estimable; NR, not reached; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed and/or refractory multiple myeloma.

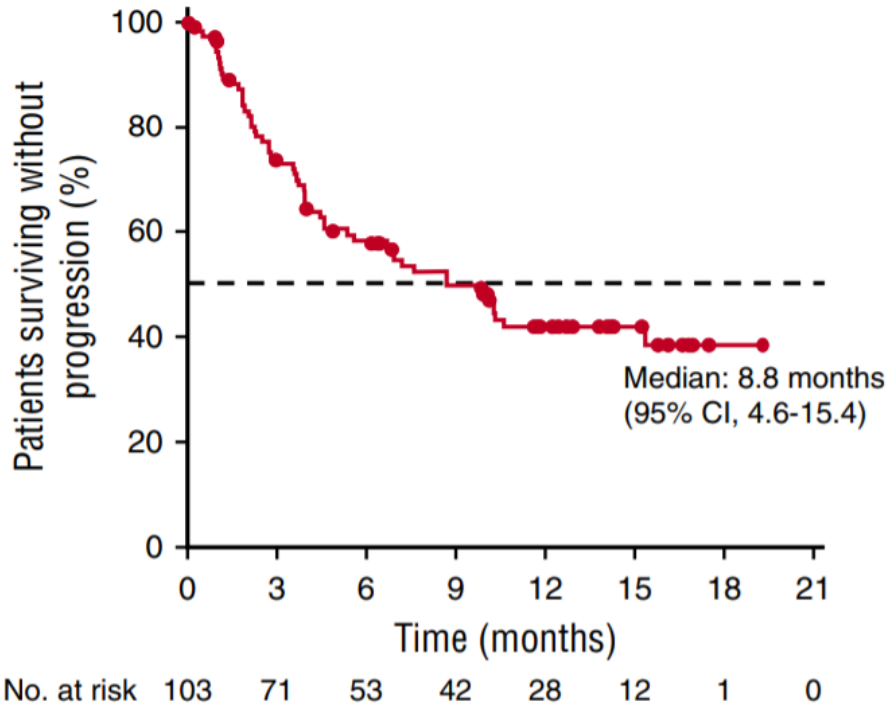
Usmani et al. Presented at: 61st American Society of Hematology Meeting and Exposition; December 7-10, 2019; Orlando, FL. Abstract LBA-6.

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

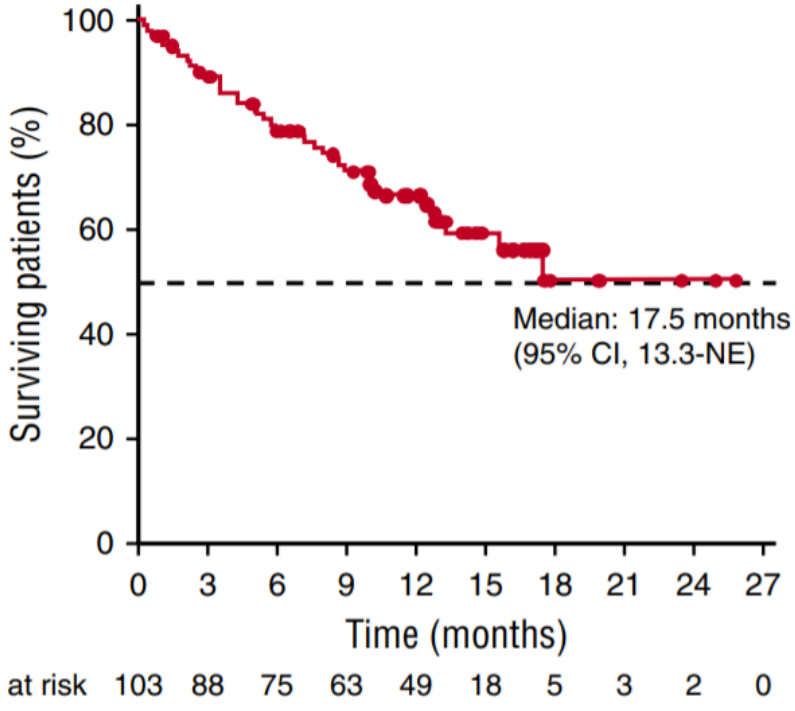




PFS

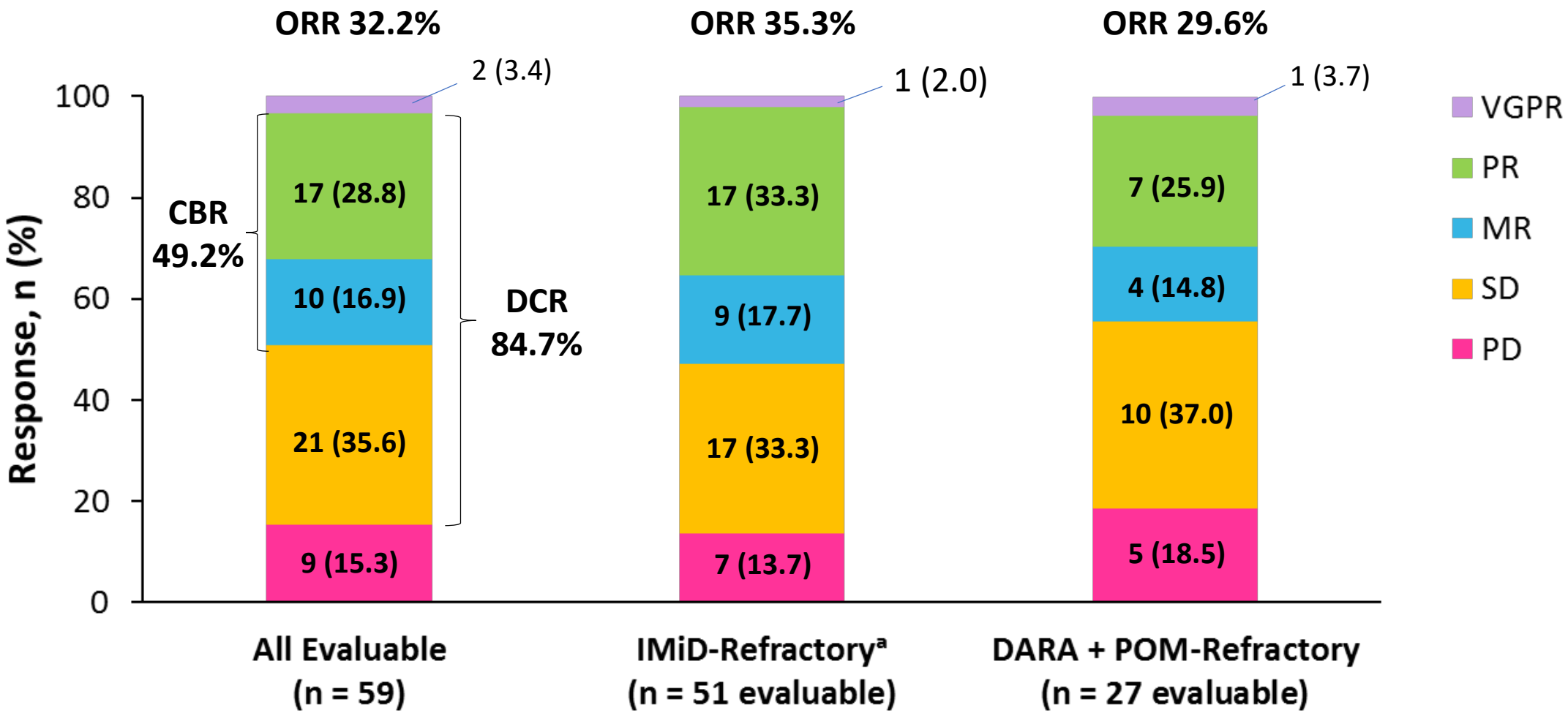


OS



Chari. Blood. 2017;130:974.

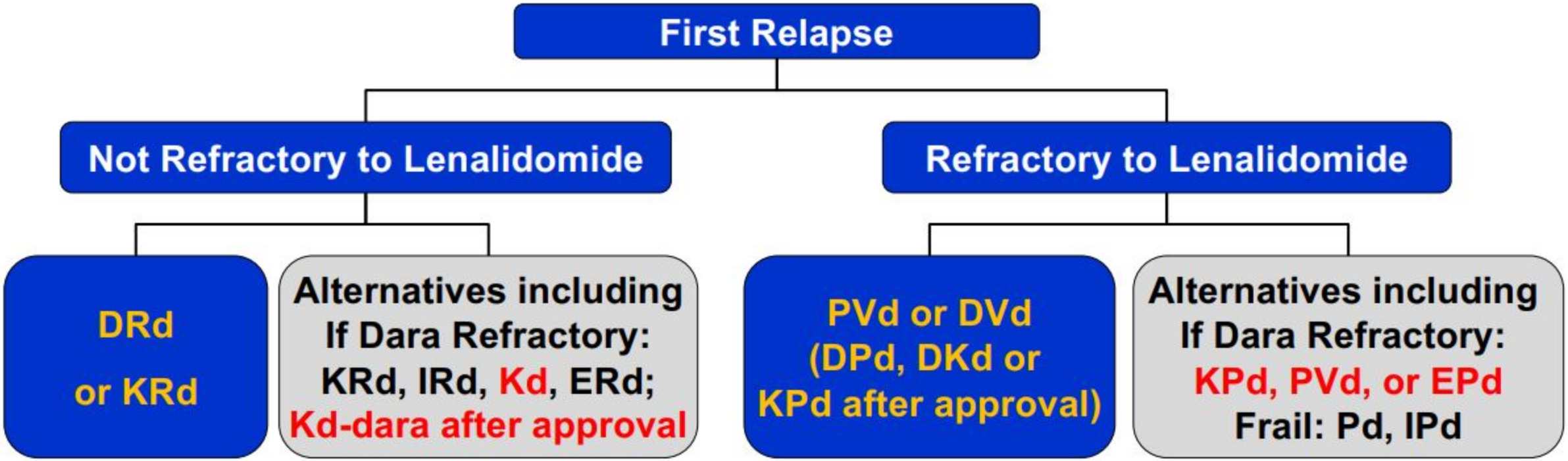
IBERDOMIDE (CC-220): Cohort B Response Results



[a]Includes Len or Pom

Lonial. ASCO 2019. Abstract 8006.

MYELOMA: FIRST RELAPSE



MYELOMA: SECOND OR HIGHER RELAPSE

First Relapse Options	Additional Options
• Any first relapse options that have not been tried (2 new drugs; triplet preferred) Isa-Pd, or DPd, or DKd, or KPd after approval	• VDT-PACE like anthracycline containing regimens • Melphalan/melflufen • Adding Panobinostat • Quadruplet regimens • CART • Bispecific • Conjugated BCMA • Selinexor • Referral for clinical trials always if available

Thank you for watching!

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