Melissa Alsina, MD

Novel Approaches in the Management of Multiple Myeloma.

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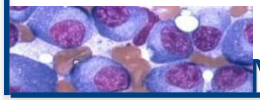
Novel Approaches in the Management of Multiple Myeloma

Melissa Alsina, MD
Moffitt Cancer Center Tampa. FL

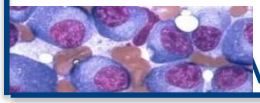


MMWG Moffitt Myeloma Working Group

MOFFITT CANCER CENTER

Relapsed/Refractory Myeloma: Choice Is Good!

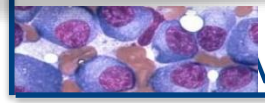
- Relapsed/refractory multiple myeloma is treatable
- Patients typically receive multiple lines of therapy
- Treatment may sometimes be continued for an extended period
- Six new drugs (Carfilzomib, Pomalimomide, Panobinostat, Daratumumab, Elotuzumab, Ixazomib) introduced in last 4 years
- With the introduction of each new drug, potential for additional combinations
- Many promising new drugs/new combinations in clinical development—always consider a clinical trial



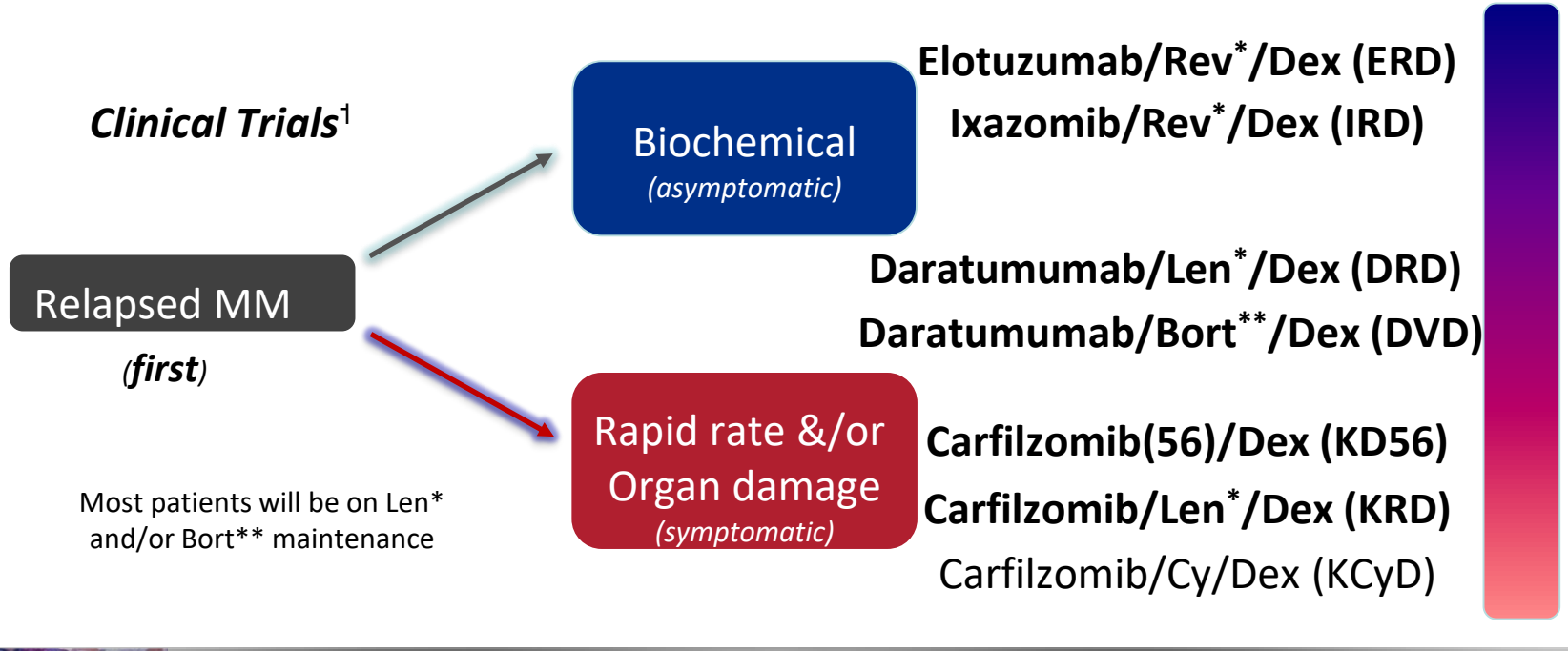
There is a growing number of improving therapies in Multiple Myeloma?

Steroids	Conventional Chemo	IMiDs	Proteasome Inhibitors	HDAC inhibitors	Monoclonal antibodies
Prednisone	Melphalan	Thalidomide	**Bortezomib**	**Panobinostat**	**Daratumumab (anti- CD38)**
Dexamethasone	**Cyclophosphamide**	**Lenalidomide**	**Carfilzomib, (ow-high dose)**	*Citarinostat (ACY 241)*	**Elotuzumab: (anti CS1/SLAMF7)**
	Doxil	**Pomalidomide**	**Ixazomib**		*Isatuximab (anti-CD38)*
	DCEP/D-PACE		*Oprozomib*		MOR202 (anti-CD38)
	BCNU		Marizomib NPI0052		
	Bendamustine				

Overcome resistance: *Nelfinavir, Clarithromycin,* ***Selinexor*** *(KPT330)*
Activation of Immunity: *Nivolumab (Anti-PDL1), Pembrolizumab (Anti-PD-1, but ?), Durvalumab (anti-PDL1)*
Cellular Immunotherpy: ***CART****, TCR, Marrow Infiltrating Lymphocytes (MILs)*
Targeting Molecular Subtypes: ***Venetoclax***
Antibody Drug Conjugates*:* ***GSK2857916***

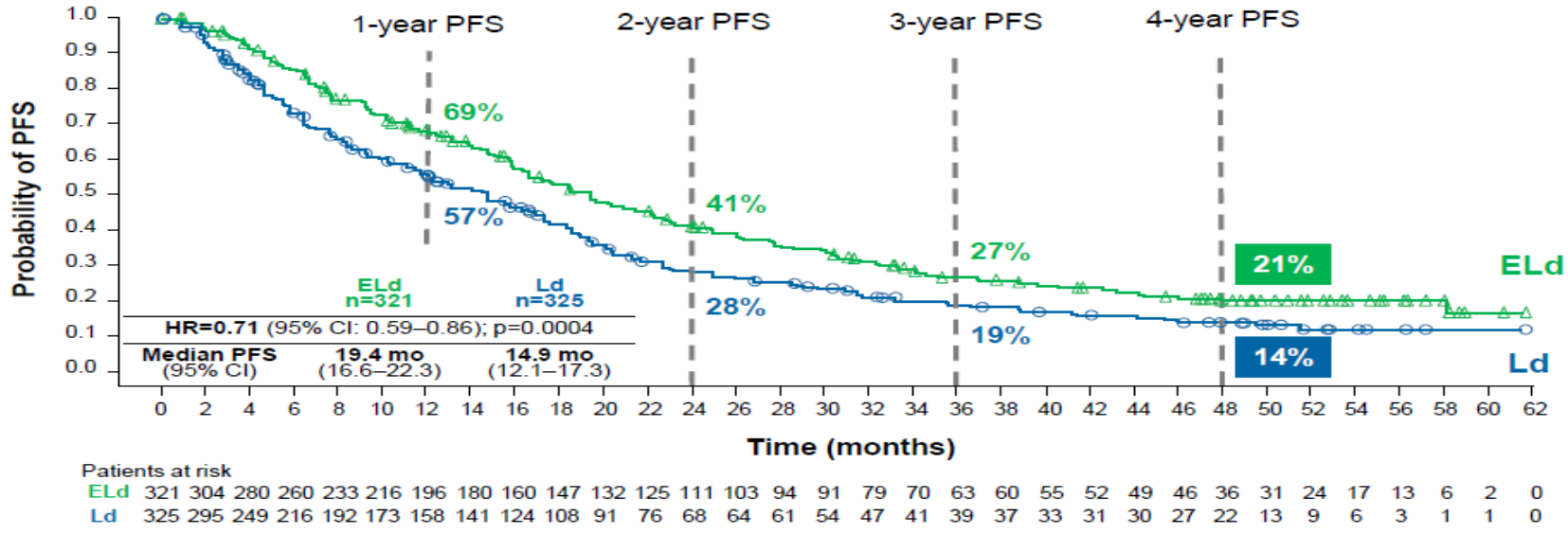


First Relapse Treatment Algorithm



Biochemical: Phase 3 ELOQUENT

Elotuzumab/Rev/Dex vs Rev/Dex in RRMM



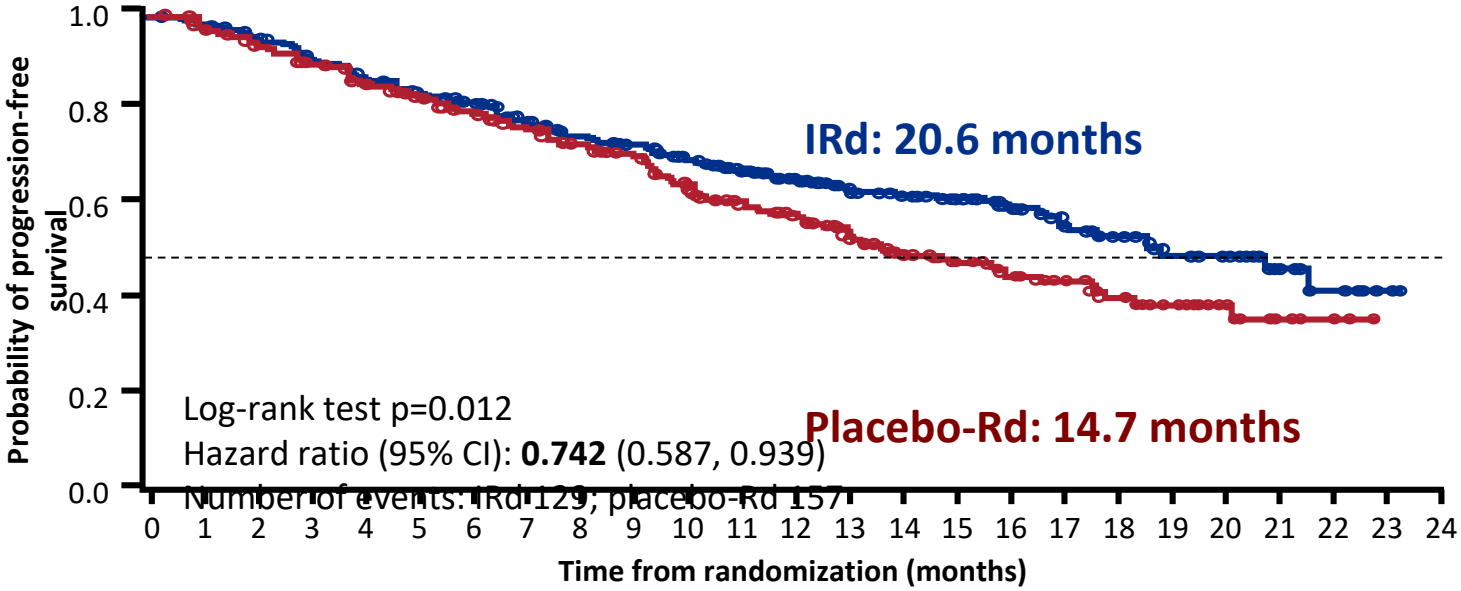
In addition: median OS at 4 year 50% vs 43%

Lonial, et al. *N Engl J Med*. 2015;373, 621–31

Dimopoulus et al EHA 2017

Biochemical: Tourmaline-MM1 Study

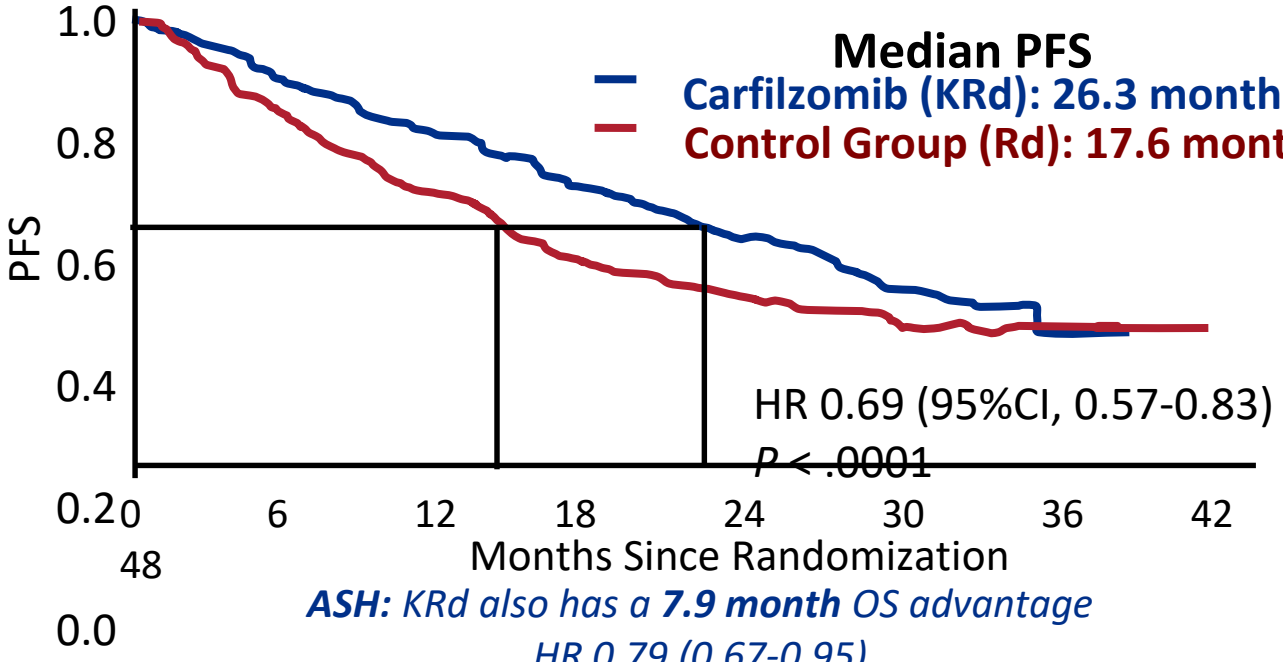
Ixazomib/Rd vs Rd



Moreau, et al. *Blood* 2015 126:727.

Symptomatic: Phase 3 ASPIRE

KRd vs Rd in RRMM



ASH: *KRd also has a* ***7.9 month*** *OS advantage*

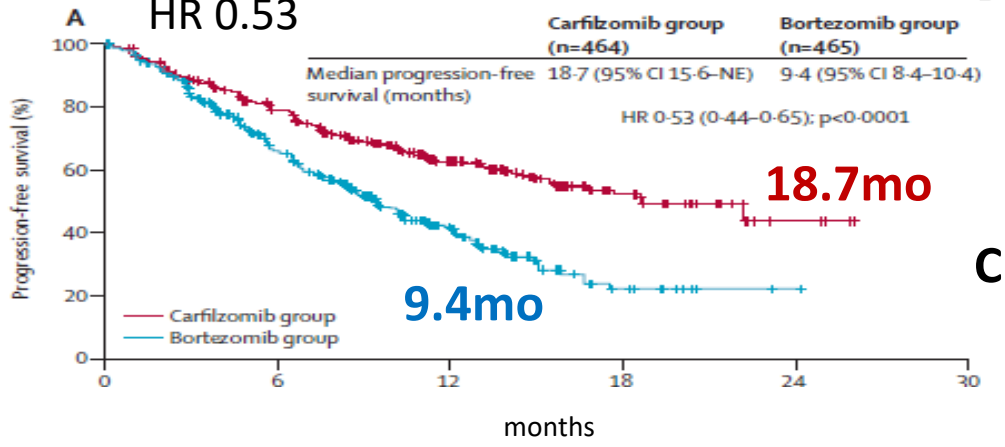
HR 0.79 (0.67-0.95)

Stewart et al ASH 2017; 130:743
Stewart , et al. *N Engl J Med*. 2015;372:142-152.

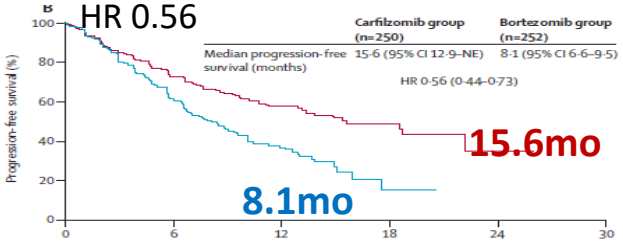
Symptomatic: ENDEAVOR Study

Carfilzomib & Dex (Kd56) vs Bortezomib & Dex (Vd)

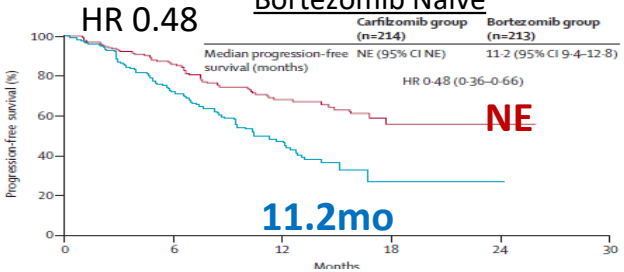
A. Total Population



B. Prior Bortezomib



C. Bortezomib Naive



***ASH:** KD56 has a **7.6 month** OS advantage*

Dimopoulos, et al *Lancet Oncol*. 2016;17(1):27-38.

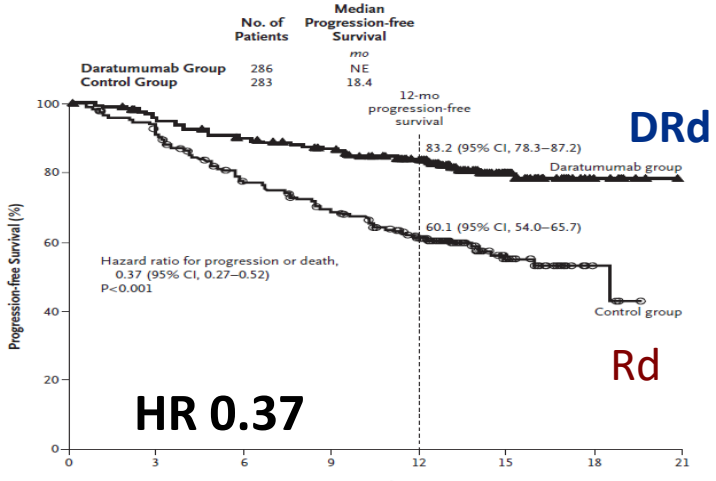
POLLUX and CASTOR

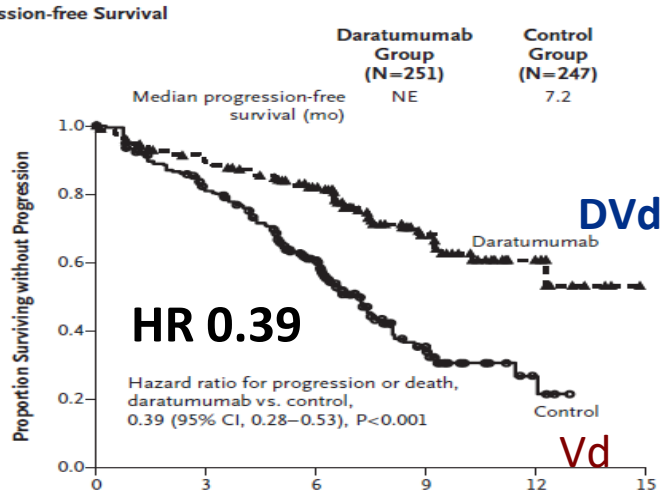
Daratumumab Combinations in RRMM

POLLUX: **DRd** vs Rd

CASTOR: **DVd** vs Vd

12 month PFS





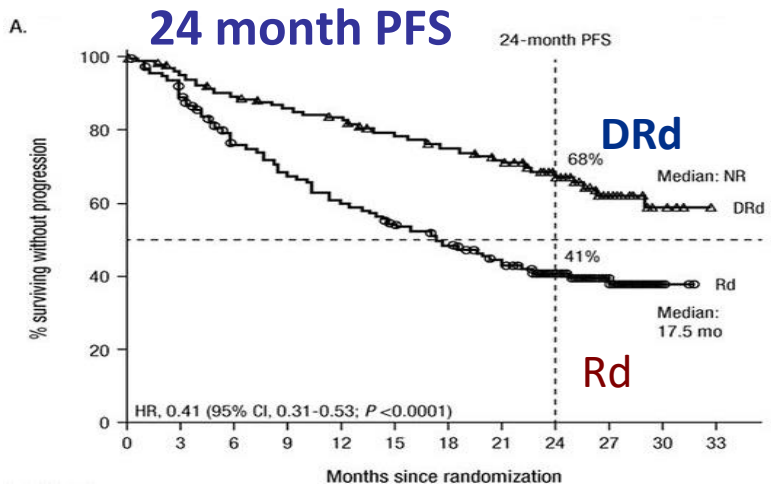
ORR: **92.9** vs 76.4

ORR: **82.9** vs 63.2

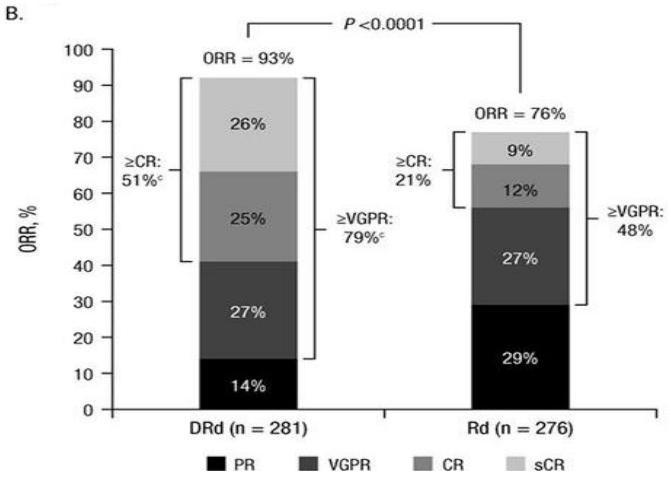
Dimopoulos et al NEJM 2016

Palumbo et al NEJM 2016

POLLUX Updates at ASH 2017

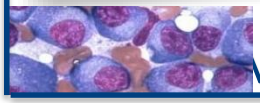


-median, NR vs 17.5 mo;
HR, 0.41 (95% CI, 0.31-053)



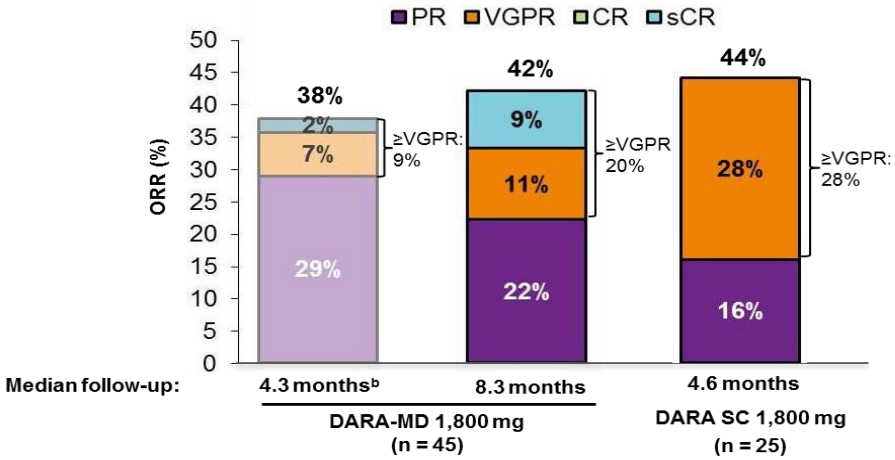
-At a sensitivity threshold of 10^{-5}, MRD-negative rates were 26% with DRd vs 6% for Rd (*P* <0.0001)

Dimopoulos et al ASH 2017; 130:739



A better way to deliver Daratumumab?

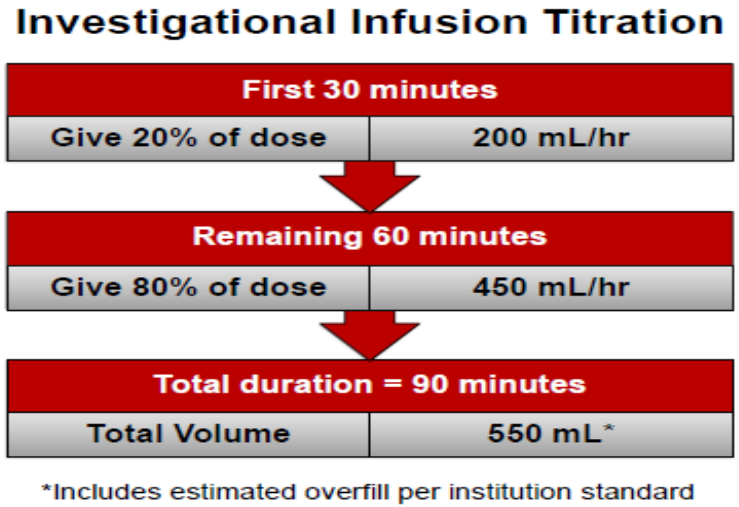
<u>Subcutaneous</u> Delivery of Daratumumab in Patients (pts) with Relapsed or Refractory Multiple Myeloma (RRMM): Pavo, an Open-Label, Multicenter, Dose Escalation Phase 1b Study. A. Chari et al ASH 2017



- DARA co-formulated with rhu hyaluronidase (DARA SC) enables dosing <u>in 3 to 5 minutes</u>
- DARA SC 1,800 mg achieves <u>greater maximum C_{trough}</u> compared with standard IV dose at C3D1
- Rate of IRRs with DARA <u>SC was 12%</u>; IRRs for DARA IV range between 45%-56% in RRMM[1-6]
- Clinical responses with DARA SC were observed with rates similar to DARA-IV

A better way to deliver Dara?

Ninety-Minute Daratumumab Infusion Is Safe in Multiple Myeloma. H. Barr et al ASH 2017



Summary:

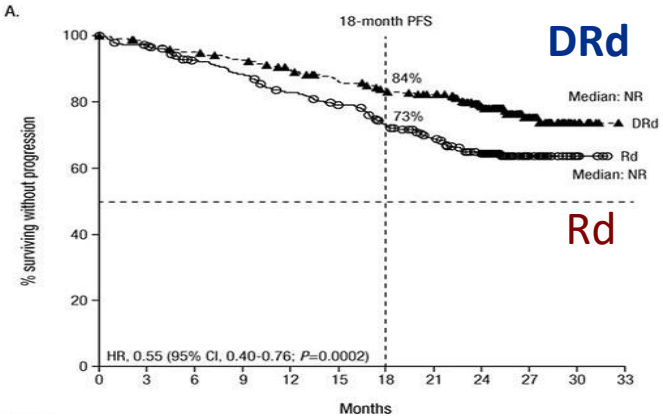
-28 patient were treated

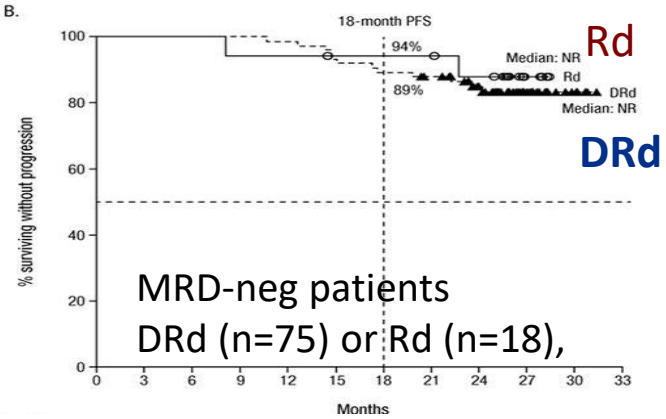
-<u>starting with the 3rd dose</u> Dara was given: 20% given over 30 min and 80% of 60 minutes.

-No grade 3 or above infusion reactions were observed.

POLLUX Updates at ASH 2017

PFS2 (at 18months)



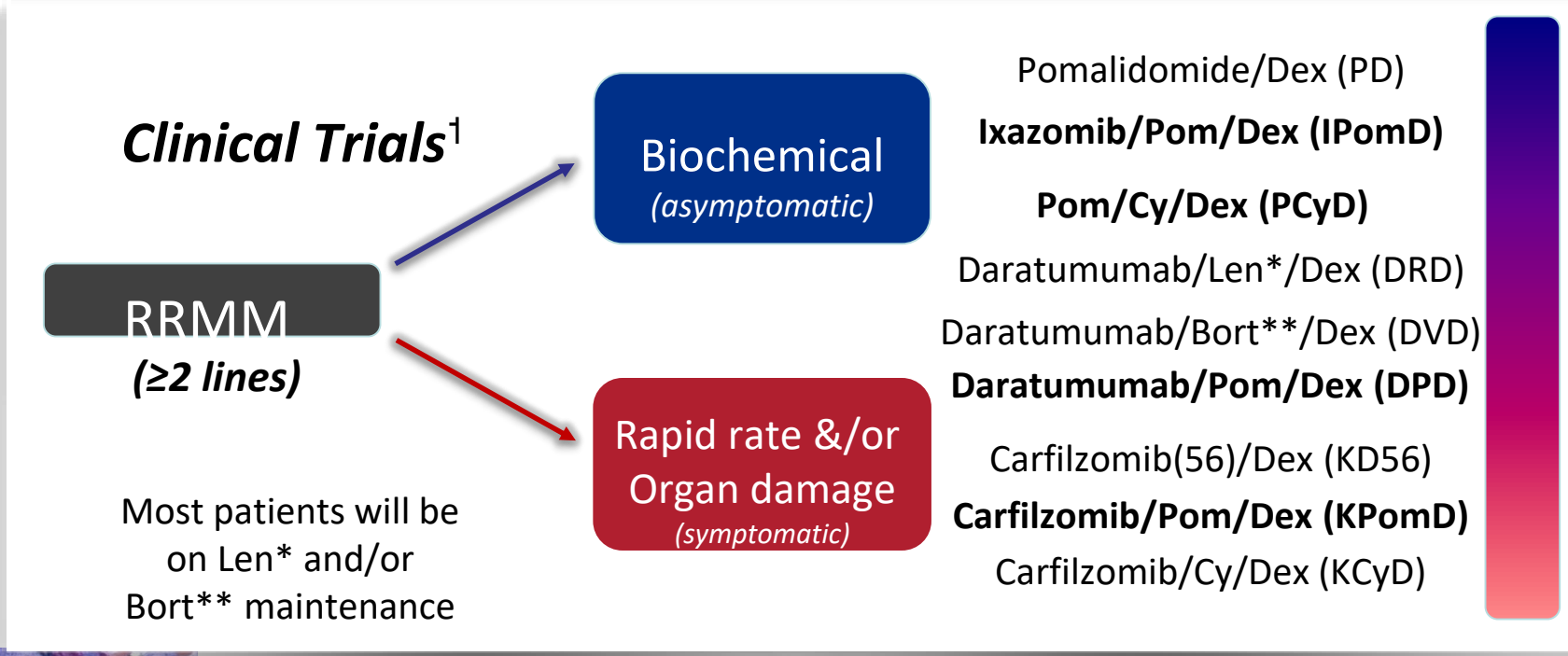


-PFS2 was significantly improved in ITT (HR, 0.55; 95% CI, 0.40-0.76; *P*=0.0002)

-MRD-negative (10^{-5}) no significant differences in PFS2 were observed

Dimopoulos et al ASH 2017; 130:739

Relapse and/or Refractory (RRMM) Treatment Algorithm

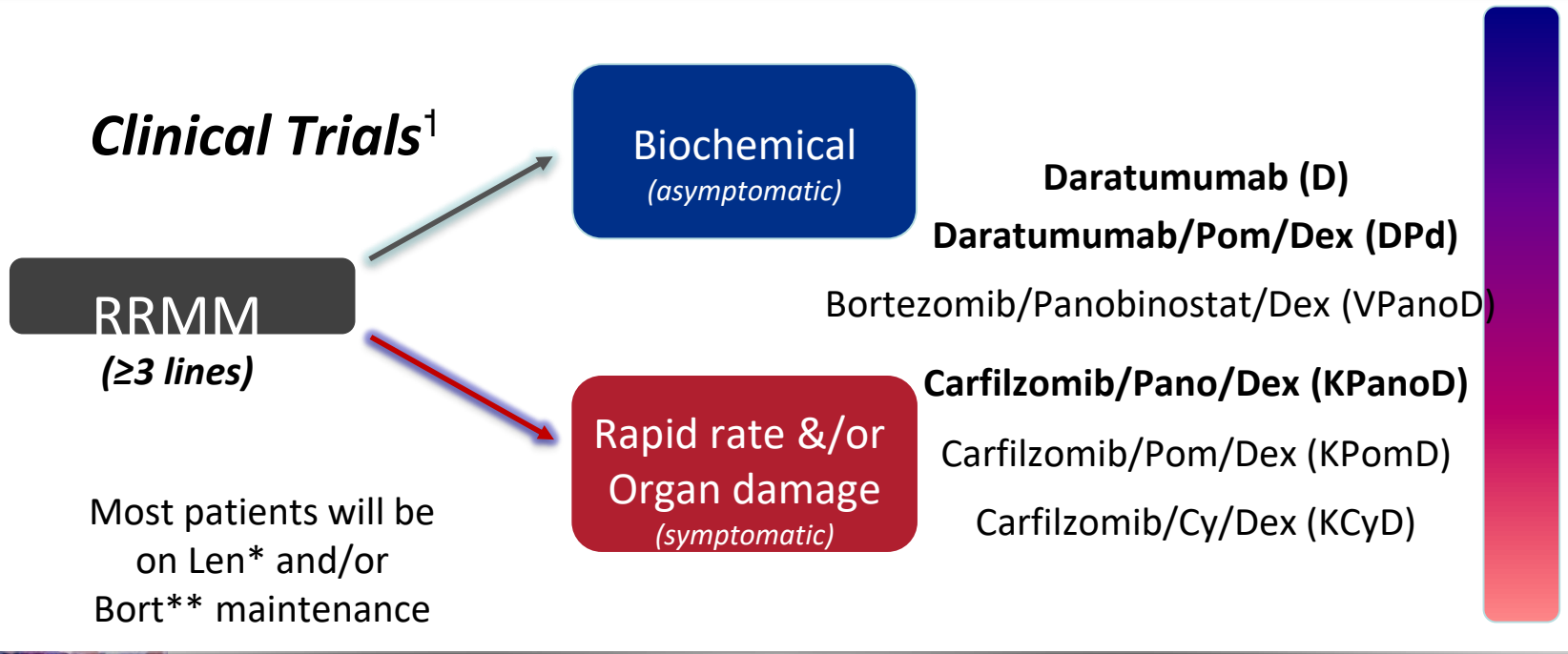


Pomalidomide-Based Studies

	N	Dose / Schedule	ORR	PFS
Pomalidomide Dex[1]	113	Pom 4 mg D1-21 Dex 40 mg weekly	33%	4.2
+ Clarithromycin[2]	114	Pom 4 mg D1-21 Dex 40 mg weekly Clarithromycin 500 mg BID	61.4%	8.1
+ Bortezomib [3]	20	Bort: 1.3 mg/m2 D1,4,8,11 Pom: 4 mg D1-14 Dex: 20mg D1,2,4,5,8,9,11,12	75%	N/A
+ Bortezomib (1-4 prior lines but Len refractory)[4]	50	Pom: 4mg PO D1-21 Bort: 1-1.3 mg/m2 IV/SC D1,8,15,22 Dex: 40 mg weekly	81%	17
+ Carfilzomib[5]	67	Carfil: 20/27 mg/m2 D1,2,8,9,15,16 Pom: 4 mg D1-21 Dex: 40 mg weekly	70%	9.7
+ Carfizlomib[6]	32	Carfil: 20/27 mg/m2 D1,2,8,9,15,16 Pom: 4 mg D1-21 Dex: 40 mg weekly	50%	7.2
+ Liposomal Doxorubicin[7]	29	PLD: 5 mg/m2 IVD1,4,8,11 Pom: 4 mg D1-21 Dex: 40 mg weekly	34.5%	N/A
+ Cyclophosphamide[8]	55	Cy: 50 mg PO QOD Pom 2.5 mg 28/28 Pred 50 mg QOD	51%	10.4
+/- Cyclophosphamide[9]	70	Pom 4 mg D1-21 Dex 40 mg weekly +/- Cy 400 mg PO D1,8,15	39% 65%	4.4 9.5
+ Daratumumab[10]	**103**	**Pom 4mg D1-21 Dex 40 mg weekly Daratumumab**	**60%**	**8.8**
+ Ixazomib	**31**	**Ixazomib 4mg ays 1,8 and 15 Pom 4mg days 1-21 Dex 40mg/20mg weekly**	**48%**	**8.6**

[1]-Richardson et al. *Blood* 2014;123:1826-32.
[2]-Mark et al. *Blood.* 2013; 122:1955.
[3]- Richardson et al. *Blood.*2013;122.
[4]- Lacy et al. *Blood.* 2014;120:304.
[5]-Shah et al. *Blood.* 2013;122:690.
[6]-Shah et al. *Blood.* 2015;126:2284-90
[7]-Berenson et al. *Blood.* 2013;122:3218.
[8]-Larocca et al. *Blood* 2013;122:2799-806
[9]-Baz, et *al. Blood. 2016*;127:2561-8.
[10]-Chari, et. *Blood*. 2017;130:974-981.
[11]- Krishnan et al. Leuk 2017;

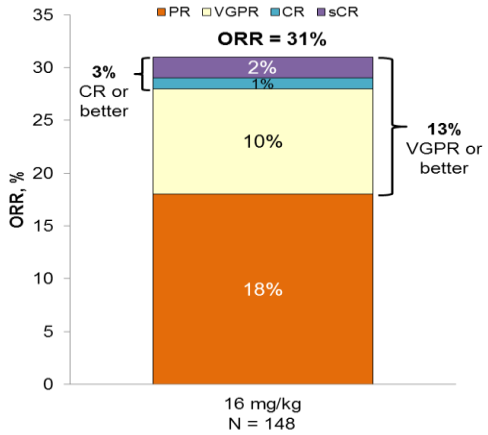
Relapse and/or Refractory (RRMM) Treatment Algorithm



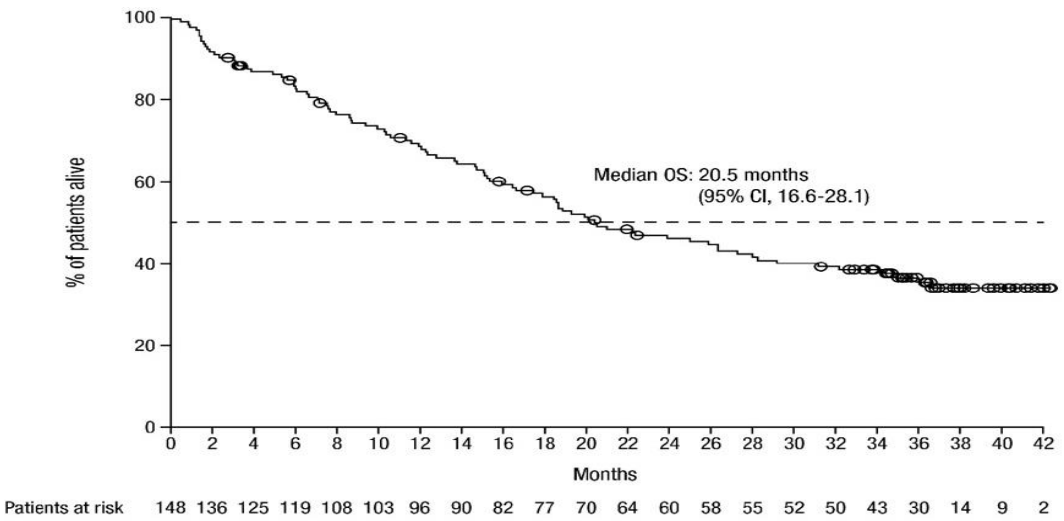
SIRIUS & GEN501

Overall response rates & updated Overall survival

A.



B. Overall survival



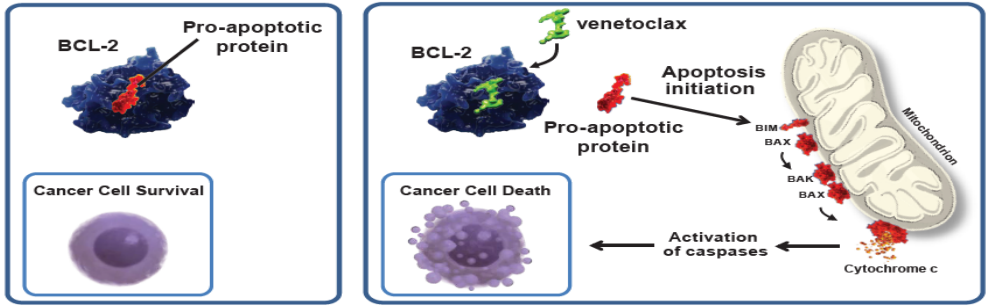
Usmani et al ASH 2017; Usmani, et al. *Blood.* 2015;126:4498.

The Future of MM Therapy?

Venetoclax

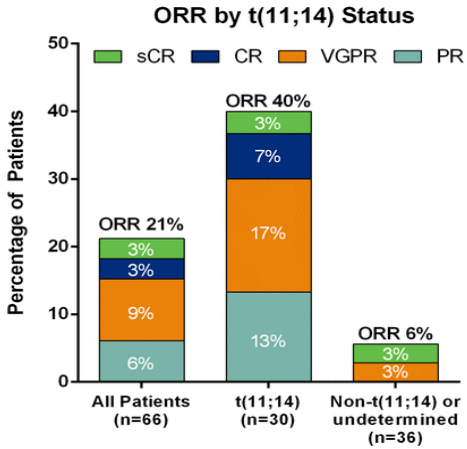
Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results from a Phase I Study

Shaji Kumar et al ASH 2016



BCL-2 overexpression allows cancer cells to evade apoptosis.

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins.



Kumar S, et al. *Blood.* 2017

Kumar S, et al. *Blood.* 2017; 130: 2401

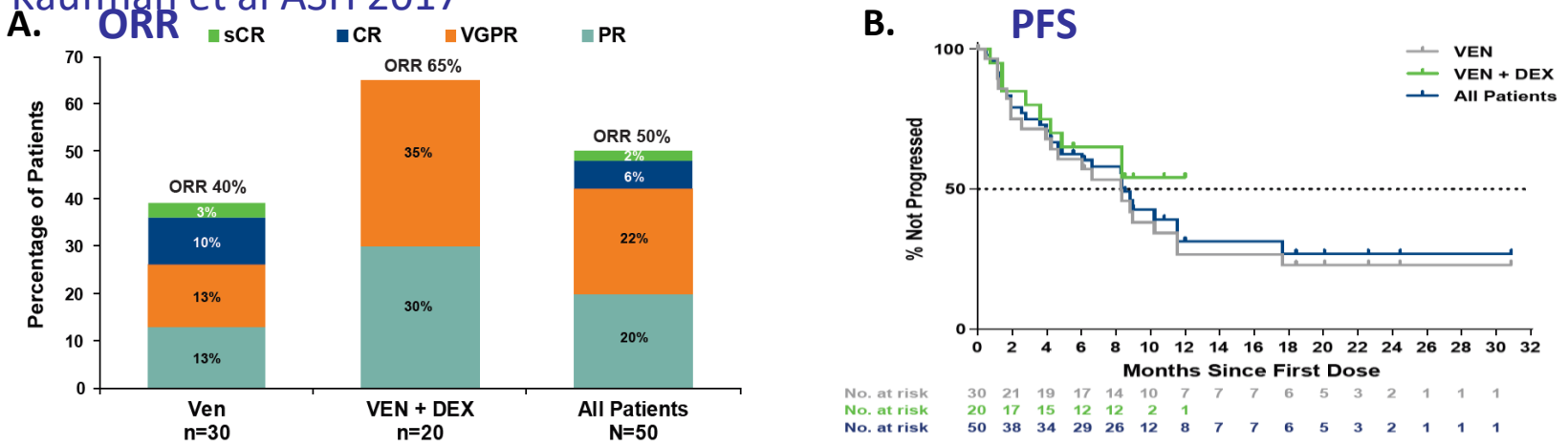
Moreau et al Blood 2017

The Future of MM Therapy?

Venetoclax

Phase 1 Study of Venetoclax in Combination with Dexamethasone As Targeted Therapy for t(11;14) Relapsed/Refractory Multiple Myeloma

J. Kaufman et al ASH 2017



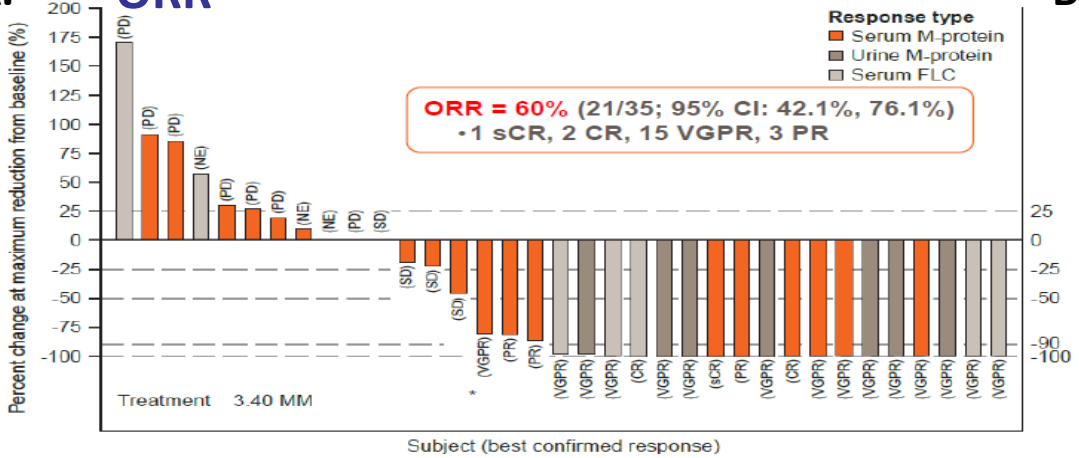
Kaufmam et al. *ASH.* 2017.

The Future of MM Therapy?

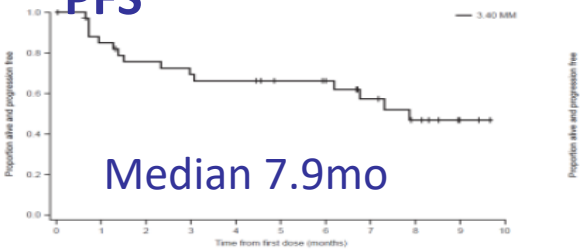
GSK2857916- mAb BCMA- drug conjugate

Deep and Durable Responses in Patients with RRMM treated with GSK2857916, an Antibody Drug Conjugate against BCMA: Preliminary Results from Part 2 of Study BMA117159. Suzanne Trudel et al ASH 2017

A. ORR



B. PFS

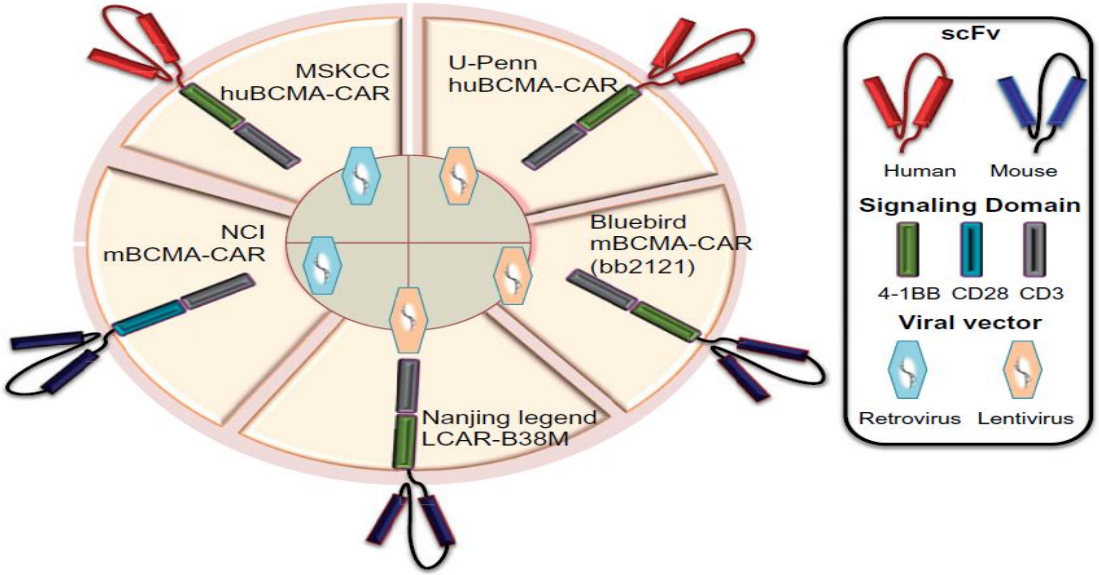


Number of subjects	**35**
Progressed or died	15 (43%)
Censored, f/u ended	3 (9%)
Censored, f/u ongoing	17 (49%)

Progression-free survival (months)	
Q1 (95% CI)	2.3 (0.7, 6.8)
Median (95% CI)	**7.9 (3.1, -)**
Q3 (95% CI)	N/A

The Future of MM Therapy?
CAR-T Therapy

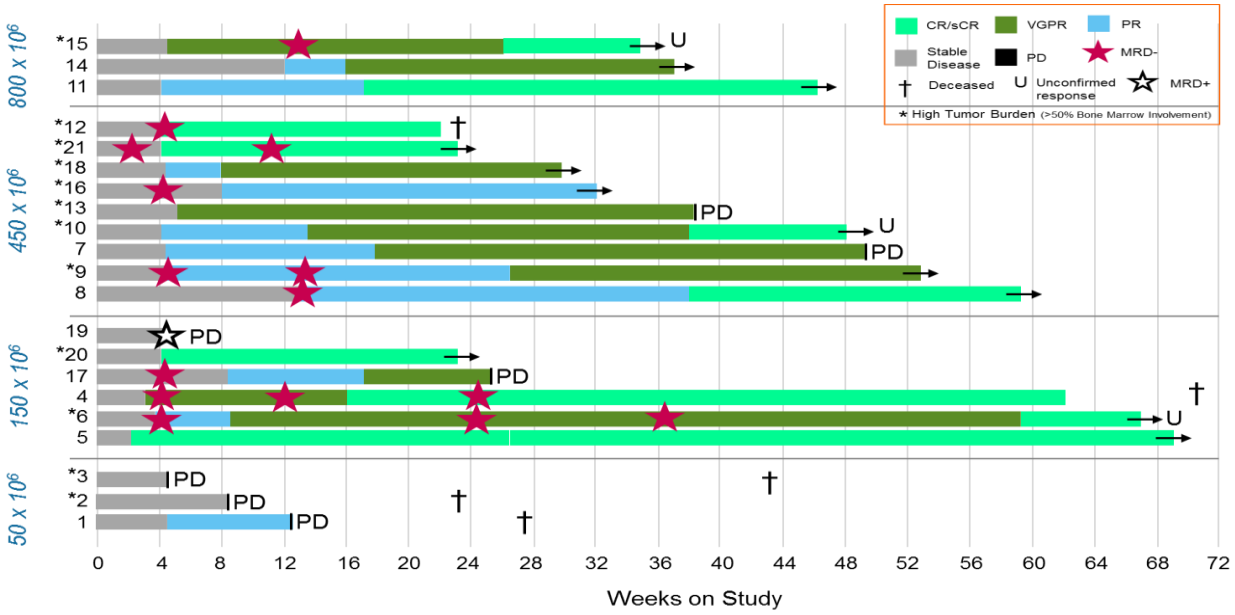
Updates in CART Therapy from ASH 2017



Ghosh et al L&L 2017

The Future of MM Therapy?
CAR-T Therapy

Updates in CART Therapy from ASH 2017



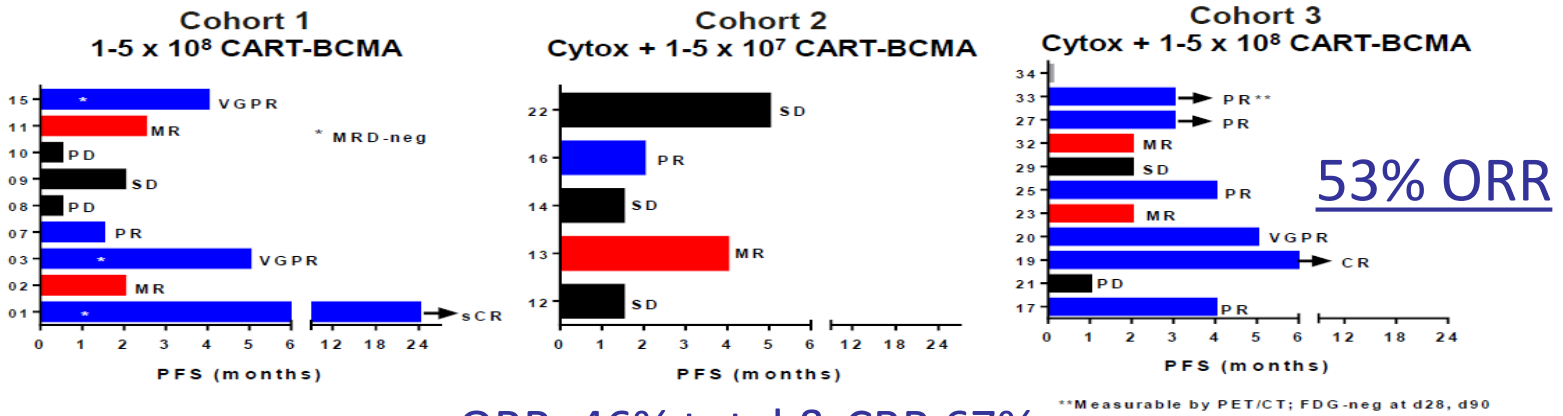
- 17/18 (**94%**) ORR, 10/18 (**56%**) CR at active doses
- 9/10 evaluable patients MRD negative
- Durable ongoing responses over 1 year
- Responses continue to improve as late as month 15 (VGPR to CR)
- Median PFS not reached in active dose cohorts
  - 4 patients progressed
  - Median follow up 40 weeks

bb2121: Berdeja J, et al. ASCO 2017; Berdeja et al. ASH 2017

The Future of MM Therapy?
CAR-T Therapy

Safety and Efficacy of B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) with Cyclophosphamide Conditioning for Refractory Multiple Myeloma (MM). UPenn huBCMA-CAR T cells

Adam D. Cohen et al ASH 2017,



ORR: 46% total & CBR 67%

The Future of MM Therapy?
CAR-T Therapy

Development and Evaluation of a Human Single Chain Variable Fragment (scFv) Derived BCMA Targeted CAR T Cell Vector Leads to a High Objective Response Rate in Patients with Advanced MM. MSKCC huBMCA CAR T cells

Eric L Smith et al ASH 2017

-~75% of patients (who could be evaluated for response) responded to this new CAR-T cell construct

T Cells Genetically Modified to Express an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor with a CD28 Costimulatory Moiety Cause Remissions of Poor-Prognosis Relapsed Multiple Myeloma. NCI mBCMA CAR T Cells

Jennifer Brudno et al ASH 2017

-Nine of 11 evaluable patients obtained objective anti-myeloma responses with 2 stringent complete responses, 5 very good partial responses, and 2 partial responses

Combined Infusion of CD19 and BCMA-Specific Chimeric Antigen Receptor T Cells for RRMM: Initial Saf`ety and Efficacy Report from a Clinical Pilot Study

Lingzhi Yan et al ASH 2017

-Combined administration of autologous/allogeneic CART-19 and CART-BCMA cells demonstrate promising in vivo expansion and clinical activity (9/10 ≥PR). All 10 developed CRS.

Conclusion

- ***There is no easy algorithm for managing relapsed/refractory myeloma, especially once facing IMID and PI refractory disease***
- Patient-specific issues and prior therapy should be used to determine choice of agents
- In the right patient population(s) effective new targeted agents will improve patient outcomes
- Novel mechanisms of drug delivery are being explored in clinical trials that will continue to change the landscape of MM
- New exciting targets and agents are being explored in numerous phase 1, 2, and 3 *clinical trials* that will continue to change the landscape of MM