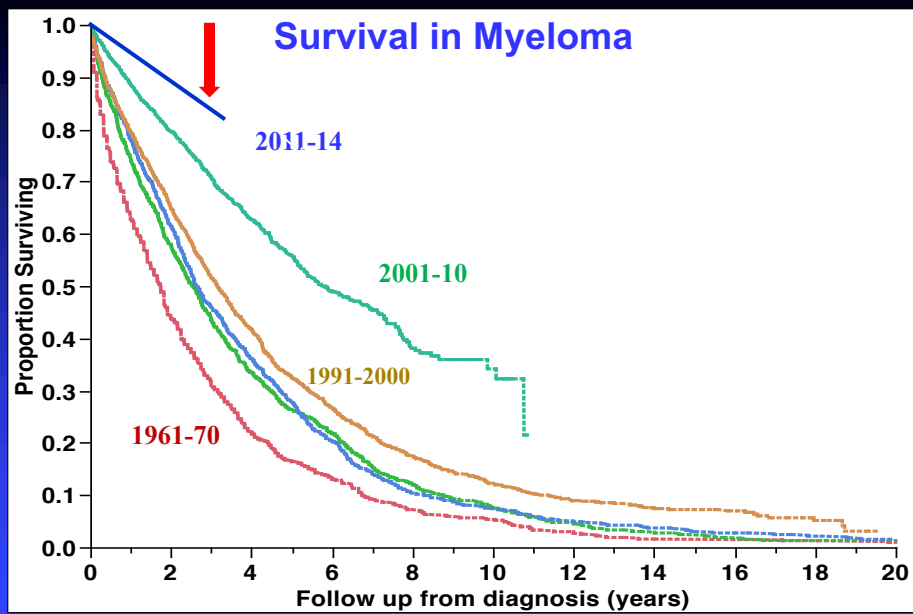


Myeloma

Closer to a Cure than Ever Before

Jeffrey Wolf, MD
Myeloma Program
University of California,
San Francisco



Kumar S. Blood 2008;111: 2516 – 2520; Kumar S. Leukemia (2014) 28, 1122–1128.

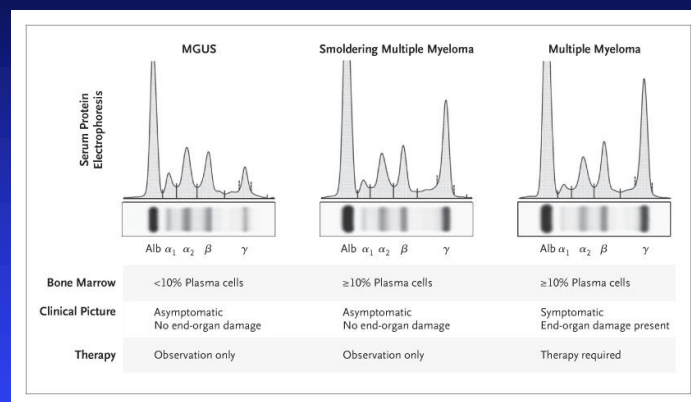
Changes in Diagnosis

Free Light Chain Ratio

Percentage Plasma Cells on Diagnostic Marrow

Use of Modern Imaging

Characteristics of Active Multiple Myeloma and Its Precursors



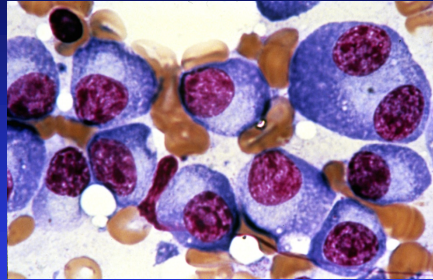
Kyle R et al. N Engl J Med 2007;356:2582-2590

Myeloma

■ MM is characterized by:

- Excessive numbers of abnormal plasma cells in the bone marrow
- ◆ Overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD) or free antibody light chains
- ◆ concomitant drop in other immunoglobulins
- ◆ **CRAB Criteria**

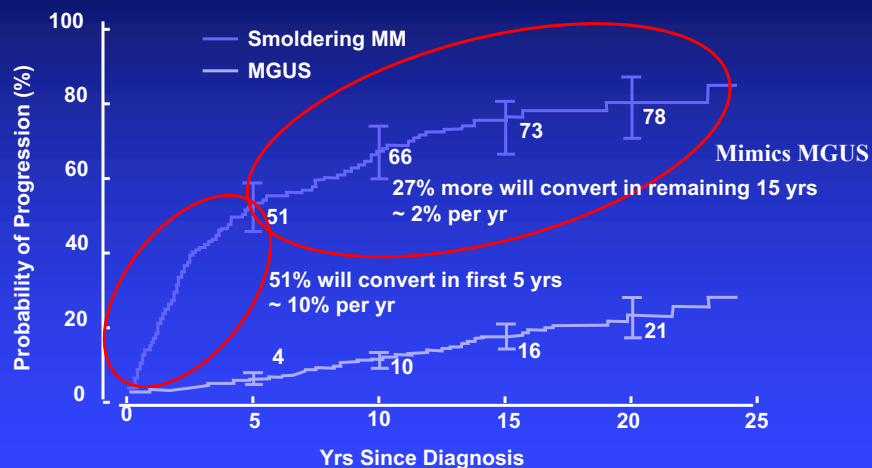
- ◆ **HyperCalcemia**
- ◆ **Renal**
- ◆ **Anemia**
- ◆ **Bone Lesions**



Reproduced with permission from the Multiple Myeloma Research Foundation Web site. Available at: http://www.multiplemyeloma.org/about_myeloma/index.html

Kufe. *Cancer Medicine*. 6th ed. 2003:2219.

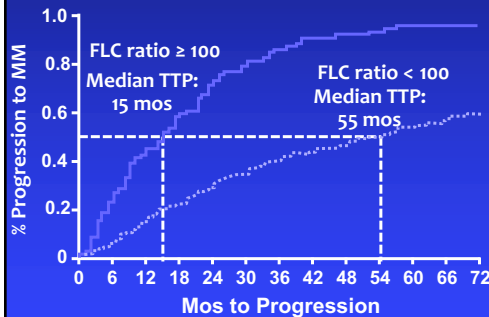
Smoldering Multiple Myeloma



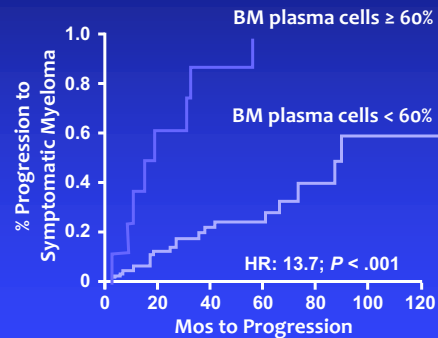
Kyle RA, et al. *N Engl J Med*. 2007;356:2582-2590. Greipp PR, et al. *J Clin Oncol*. 2005;23:3412-3420.

Biomarkers to Predict Risk of Progression

- FLC ratio ≥ 100 predicts risk ($P < .0001$)



- Clonal plasma cells in BM predicts risk ($P < .001$)



Larsen JT, et al. Leukemia. 2013;27:941-946. Kastritis E, et al. Leukemia. 2013;27:947-953.

Updated IMWG Criteria for Diagnosis of Multiple Myeloma

MGUS

- M protein < 3 g/dL
- Clonal plasma cells in BM $< 10\%$
- No myeloma defining events

Smoldering Myeloma

- M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
- Clonal plasma cells in BM $\geq 10\%$ to 60%
- No myeloma defining events

Multiple Myeloma

- Underlying plasma cell proliferative disorder
- AND 1 or more myeloma defining events
 - ≥ 1 CRAB* feature
 - Clonal plasma cells in BM $\geq 60\%$
 - Serum free light chain ratio ≥ 100
 - > 1 MRI focal lesion

*C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)

R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)

A: Anemia (Hb < 10 g/dL or 2 g/dL $<$ normal)

B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

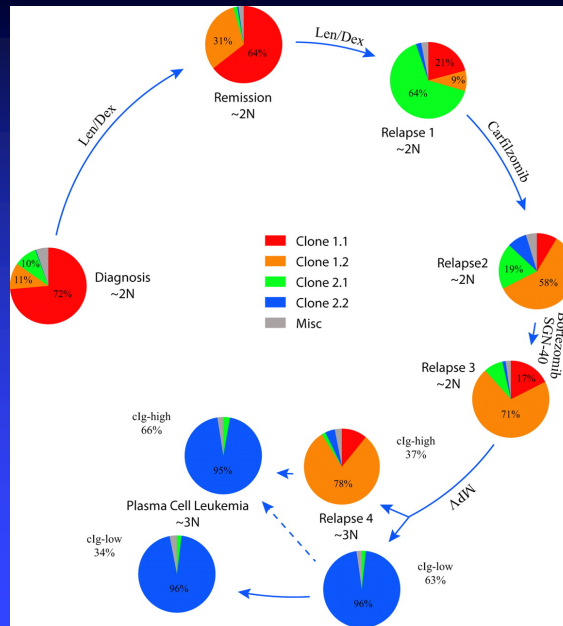
Why are we Failing to Achieve
Long Term Survival In 25% of
Patients?

Clonal Competition with
Alternating Dominance
in Multiple Myeloma

Clonal Competition with Alternating Dominance in Multiple Myeloma
Based on iFISH and Array Comparative Genomic Hybridization (aCGH) at 7 time points

Pt with t(4;14)

Keats, et.al.
Blood, 2012



New Staging

Revised International Staging System R-ISS

R-ISS

■ Stage I

- ◆ B2M < 3.5 mg/L
- ◆ Albumin $\geq$ 3.5 gm/dL

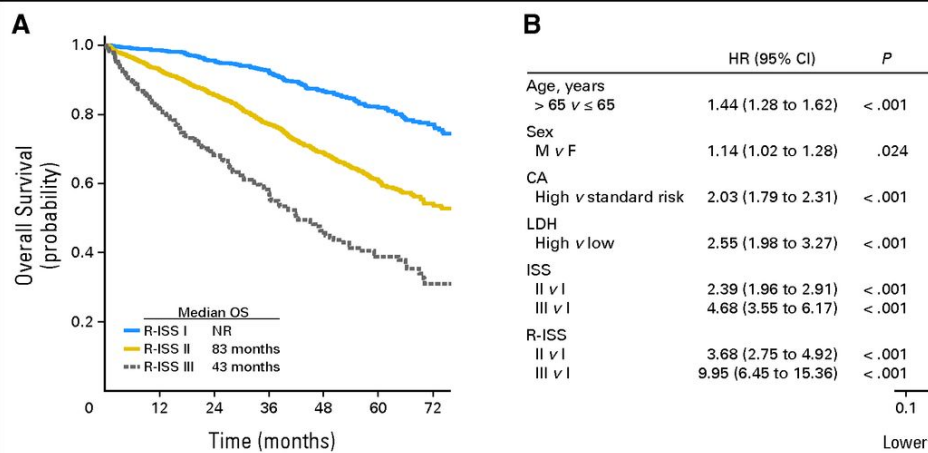
■ Stage II

- ◆ Not Stages I or II

■ Stage III

- ◆ B2M $\geq$ 5.5 mg/L
- ◆ LDH > ULN
- ◆ Abnormal iFISH (del (17p), t(4;14), t(14;16))

Revised ISS



(A) Overall survival (OS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm.

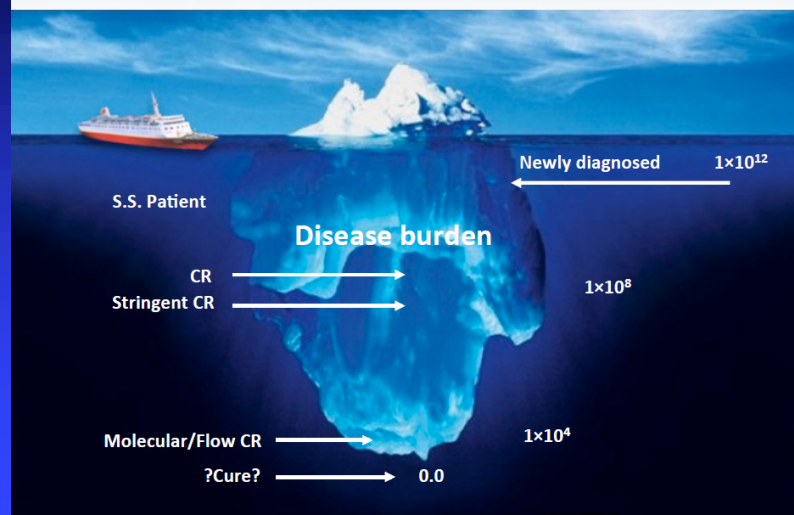
Antonio Palumbo et al. JCO, 2015

Evidence that Depth of Response Matters

CR and MRD

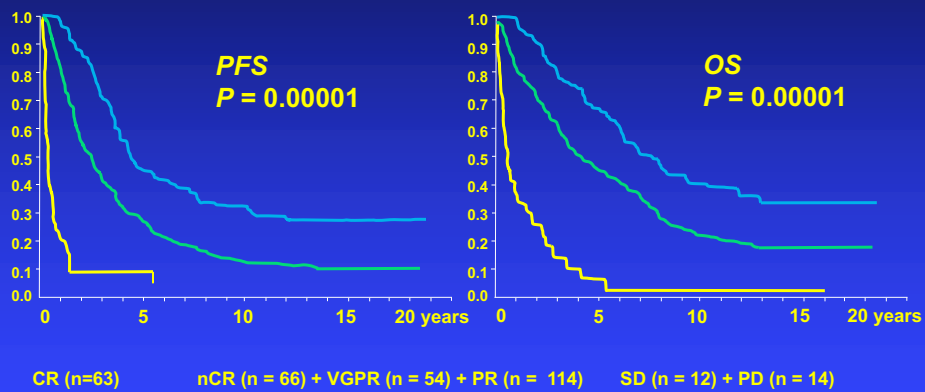
The Iceberg

Getting to Minimal Residual Disease (MRD)



CR vs nCR / VGPR / PR vs Less

Prognostic effect of CR patients vs those in nCR or VGPR or PR vs patients with SD or PD after HDT/ASCT



Martinez-Lopez J, et al. *Blood*. 2011;118:529-534.

Minimal Residual Disease (MRD)

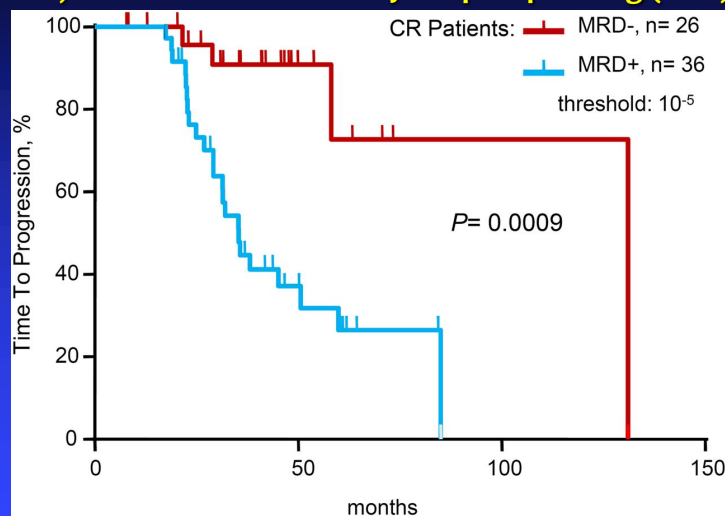
Standard Flow – 10^{-4}

EuroFlow (8 color) – 10^{-5}

Next Generation Sequencing – 10^{-6}

Spanish Retrospective Look at MRD and Survival

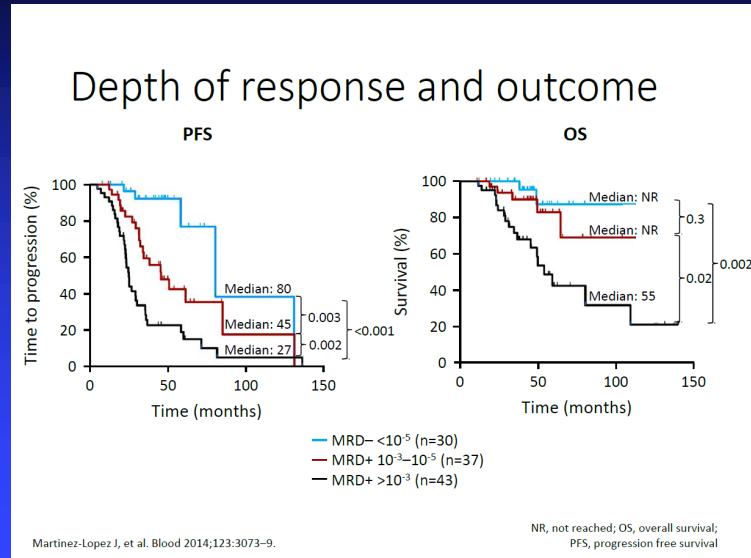
Time to progression for patients achieving conventional complete remission (CR), according to minimal residual disease (MRD) status as determined by deep sequencing (NGS).



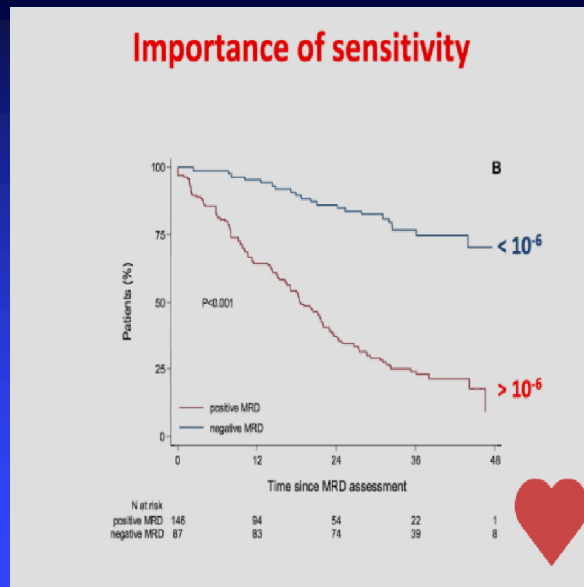
Martinez-Lopez J et al. Blood 2014;123:3073-3079



Further Evidence that MRD Matters



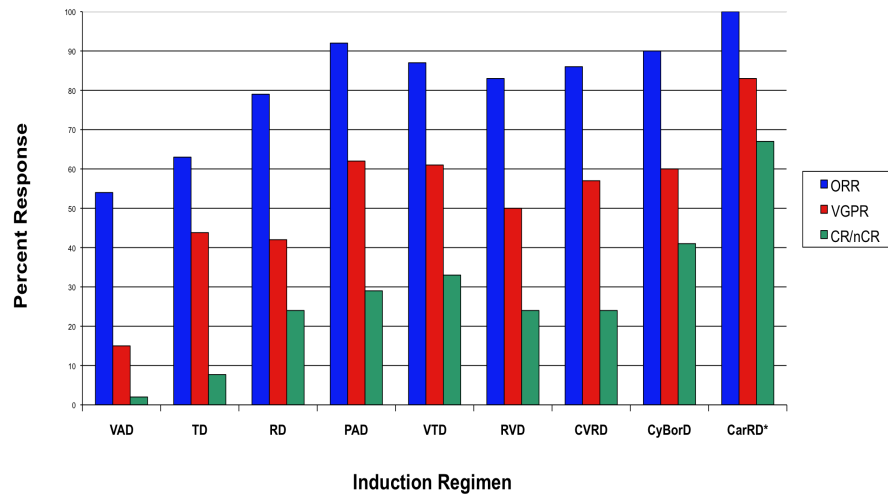
IFM/DFCI 2009



Frontline Therapy for Patients Eligible (or Ineligible) for Transplant

 MAYO CLINIC Discovery of Active Drugs in Multiple Myeloma			
Old Drugs (1960s)	Approved Drugs (2003-2007)	Recently Approved Drugs (2013-2015)	Future Drugs
▪ Melphalan ▪ Cytosan ▪ Prednisone ▪ Dexamethasone ▪ Doxorubicin	▪ Bortezomib ▪ Thalidomide ▪ Lenalidomide ▪ Liposomal doxorubicin	▪ Carfilzomib ▪ Pomalidomide ▪ Panobinostat ▪ Daratumumab ▪ Ixazomib ▪ Elotuzumab	▪ Oprozomib ▪ Marizomib ▪ Isatuximab ▪ Venetoclax ▪ Selinexor ▪ CAR-T ▪ BiTES ▪ ADCs

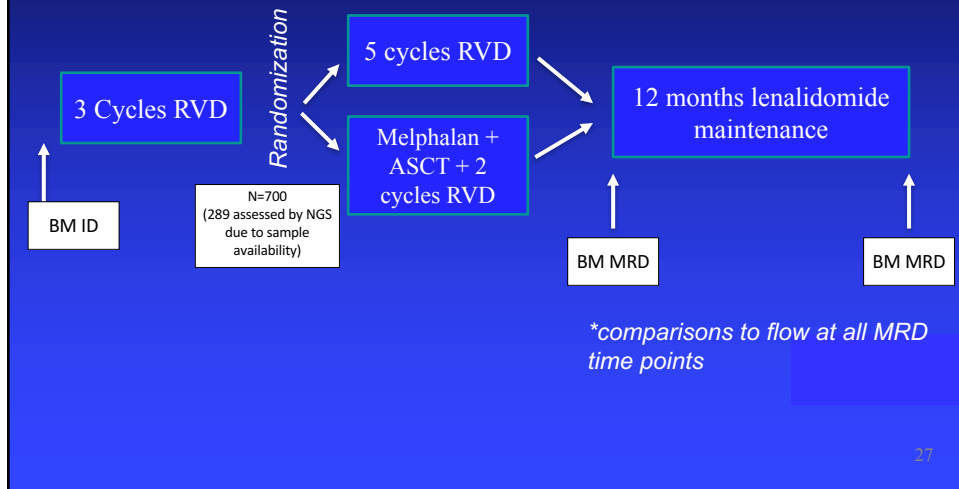
Improving Response Rates with Combination Therapies for Induction



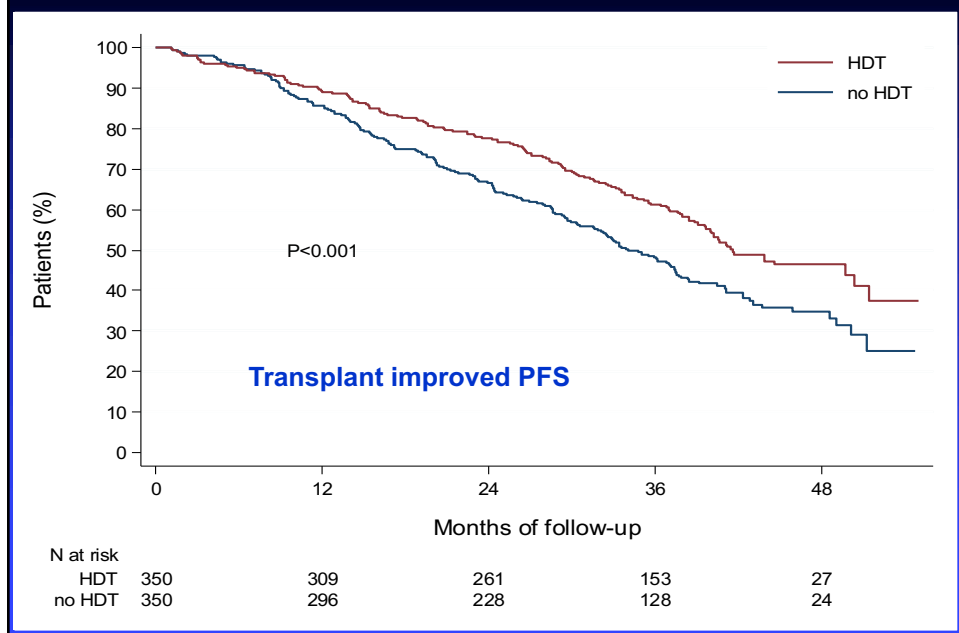
Role of Autologous Transplant

IFM/DFCI 2009

IFM/DFCI Study Schema

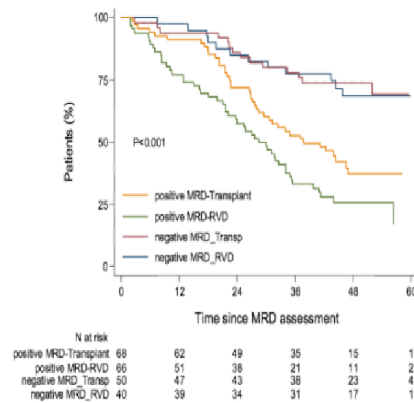


IFM/DFCI 2009



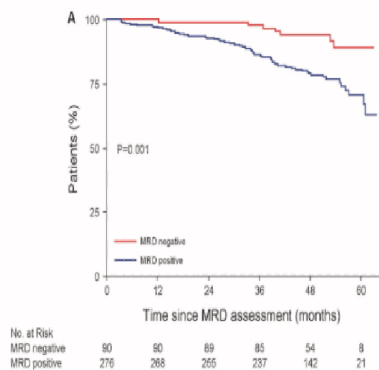
Impact of Treatment Arm on MRD and PFS

Impact of treatment arm?



IFM/DFCI 2009 MRD Impact on OS

Impact on OS

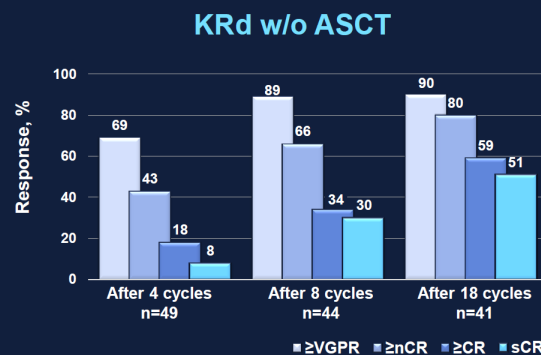


Further Evidence for Role of Auto ASCT

KRd (? Improvement over RVd?)

Jakubowiak, 2015

Response Rates Over the Course Treatment

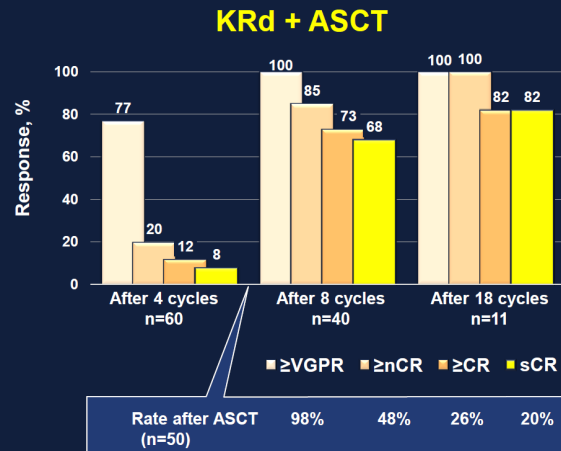


nCR, near complete response; VGPR, very good partial response

KRd + ASCT

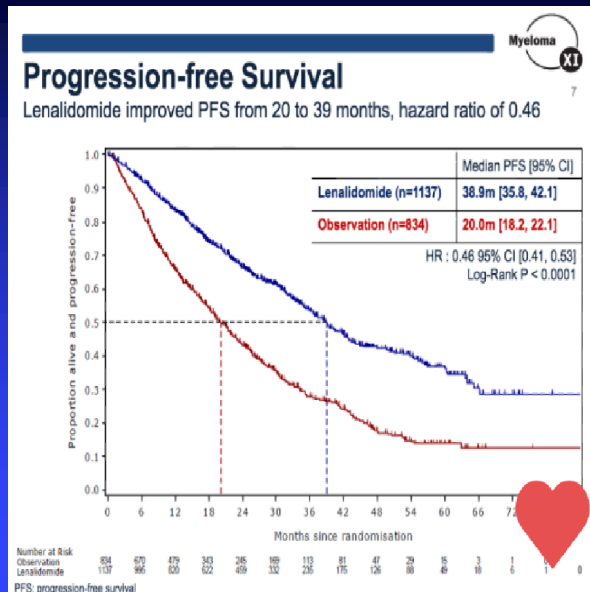
Zimmerman, 2016

Response Rates Over the Course Treatment

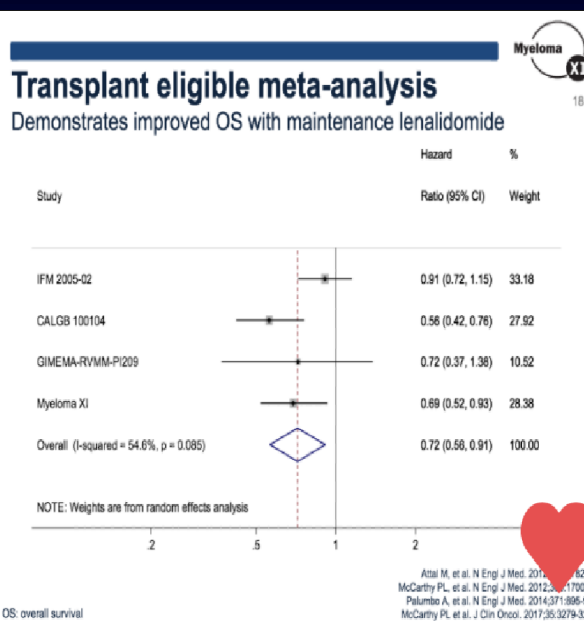


Role of Maintenance (Continuation) Therapy

Myeloma XI – Role of Lenalidomide Maintenance

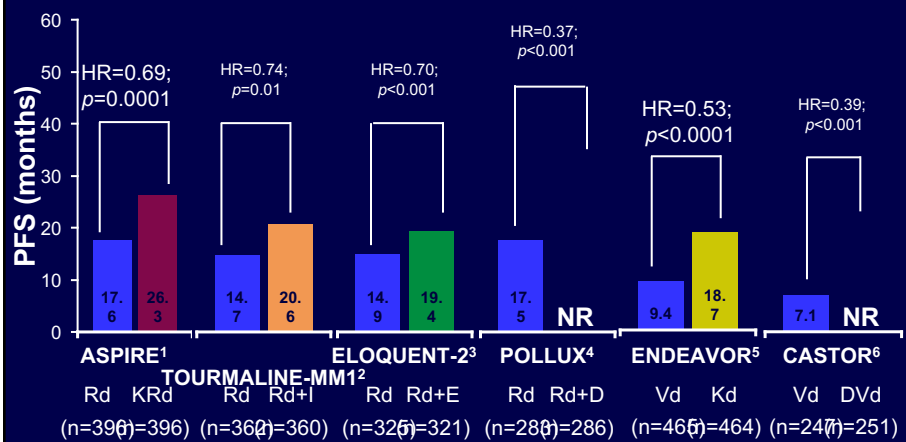


Maintenance Meta-Analysis



Treatment of Relapse

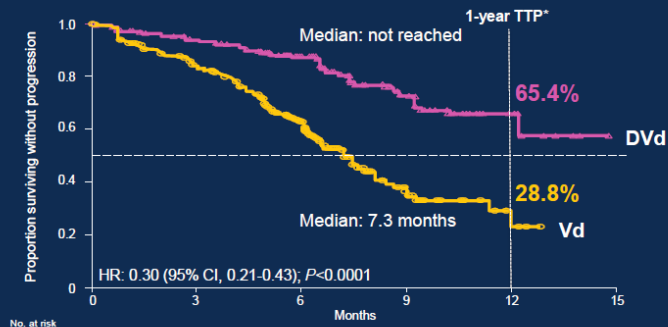
PFS in Recent Relapsed Phase 3 trials



HR, hazard ratio; NR, not reached; PFS, progression-free survival.
 1. Stewart AK, et al. *N Engl J Med* 2015;372:142-52; 2. Moreau P, et al. *N Engl J Med* 2016;374:1621-34; 3. Lonial S, et al. *N Engl J Med* 2015;373:621-31; 4. Bahlis NJ, et al. *ASCO* 2017, abstract #8025; 5. Dimopoulos ME, et al. *Lancet Oncol* 2016;17:27-38; 6. Lentzsch S, et al. *J Clin Oncol* 2017;35:Suppl (abstr 8036).

Castor: Vd vs Dara Vd

Time to Progression



70% reduction in the risk of disease progression for DVd vs Vd

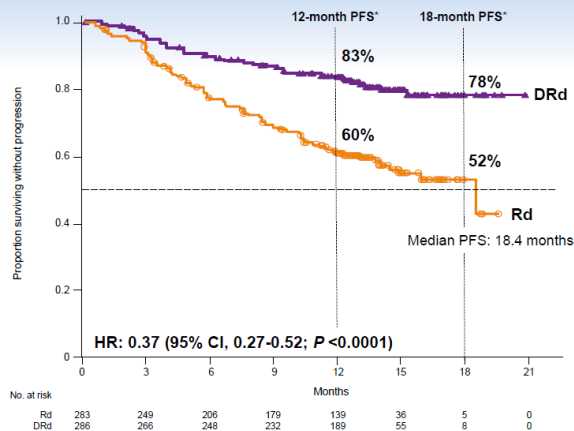
*KM estimate

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Pollux: Rd vs Dara Rd

Progression-free Survival



63% reduction in the risk of disease progression or death for DRd vs Rd

*KM estimate; HR, hazard ratio.

10

New and Variations on Old Therapies

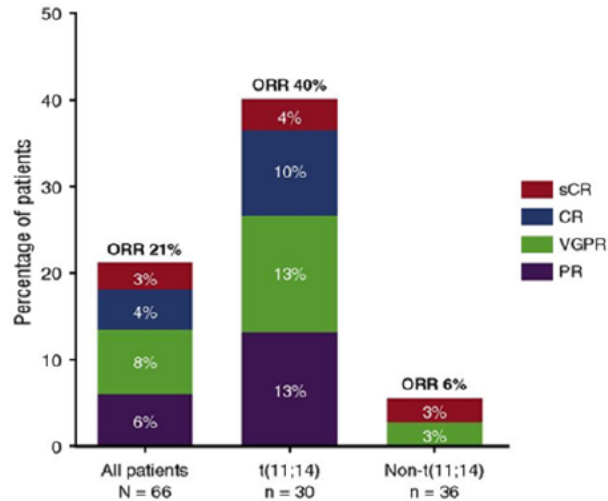
Venetoclax
90 Minute Daratumumab (Sub Q Coming)
Once Weekly Carfilzomib

Efficacy of Venetoclax as Targeted Therapy for Relapsed/Refractory t(11;14) Multiple Myeloma

Shaji Kumar, Jonathan L. Kaufman, Cristina Gasparetto, Joseph Mikhael, Ravi Vij, Brigitte Pegourie, Lofli Benboubker, Thierry Facon, Martine Amiot, Philippe Moreau, Elizabeth A. Punnoose, Stefanie Alzate, Martin Dunbar, Tu Xu, Suresh K. Agarwal, Sari Heitner Enschede, Joel D. Leverson, Jeremy A. Ross, Paulo C. Maciag, Maria Verdugo and Cyrille Touzeau

Blood 2017 :blood-2017-06-788786; doi: <https://doi.org/10.1182/blood-2017-06-788786>

Venetoclax in t(11;14) Mutated iFISH



Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab Induces Deep Responses in Relapsed / Refractory CLL

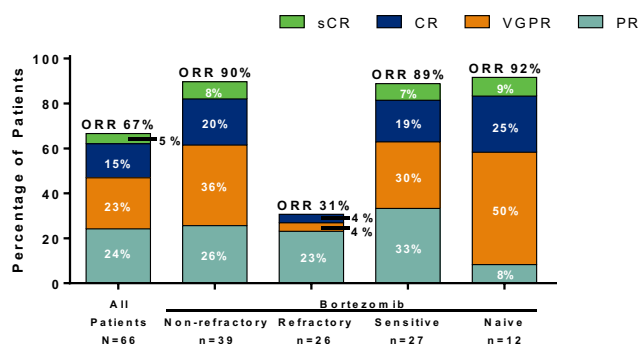
43

Venetoclax Combined With Bortezomib and Dexamethasone for Patients With Relapsed/Refractory Multiple Myeloma

Philippe Moreau,¹ Asher Chanan-Khan,² Andrew W. Roberts,³ Amit B. Agarwal,⁴ Thierry Facon,⁵ Shaji Kumar,⁶ Cyrille Touzeau,¹ Jaclyn Cordero,⁷ Jeremy Ross,⁷ Wijith Munasinghe,⁷ Jia Jia,⁷ Ahmed H. Salem,⁷ Joel Leverson,⁷ Paulo Maciag,⁷ Maria Verdugo,⁷ Simon J. Harrison⁸

American Society of Hematology – 58th Annual Meeting
 • San Diego, California, USA • December 4, 2016

Objective Responses



ORR=PR or better; numbers are based on evaluable patients per subgroups.

Data cutoff of 19Aug2016 45

Dara Carfilzomib
Dexamethasone

D-Kd

Study Design: D-Kd Arm of MMY1001

- Open-label, non-randomized, multicenter, phase 1b study in RRMM patients
- Per protocol, DARA was administered as a **single first dose (n = 10)** or as a **split first dose (n = 75)**

Eligibility/treatment

- Relapsed MM
 - 1-3 prior lines of therapy, including bortezomib and an IMiD
 - Len-refractory patients allowed
- Carfilzomib-naïve
- ECOG status ≤2
- LVEF ≥40%
- ANC ≥1 × 10⁹/L
- Platelet count ≥75 × 10⁹/L

Dosing schedule (28-day cycles)

DARA:

- Split first dose^a: 8 mg/kg Days 1-2 of Cycle 1**
- Single first dose: 16 mg/kg on C1D1
- 16 mg/kg IV QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter until PD

Carfilzomib^b:

- 20 mg/m² IV Cycle 1 Day 1
- Escalated to 70 mg/m² Cycle 1 Day 8+; **weekly (Days 1, 8, 15)** until PD

Dexamethasone:

- 40 mg/week (Days 1, 8, 15, 22) IV or PO until PD

Endpoints

Primary

- Safety, tolerability

Secondary

- ORR
- OS

Exploratory

- PFS
- MRD (NGS)^c
- PK

^aIn 500-mL dilution volume.

^bBoth 20 mg/m² and 70 mg/m² were administered as 30-minute IV infusions.

^cAmong patients evaluated for MRD, MRD was assessed using NGS at time of suspected CR and at 12 and 18 months after initial dose. In cases where DARA is suspected of interfering with IFE and preventing clinical CR response calls, subjects with VGPR may also be evaluated for MRD.

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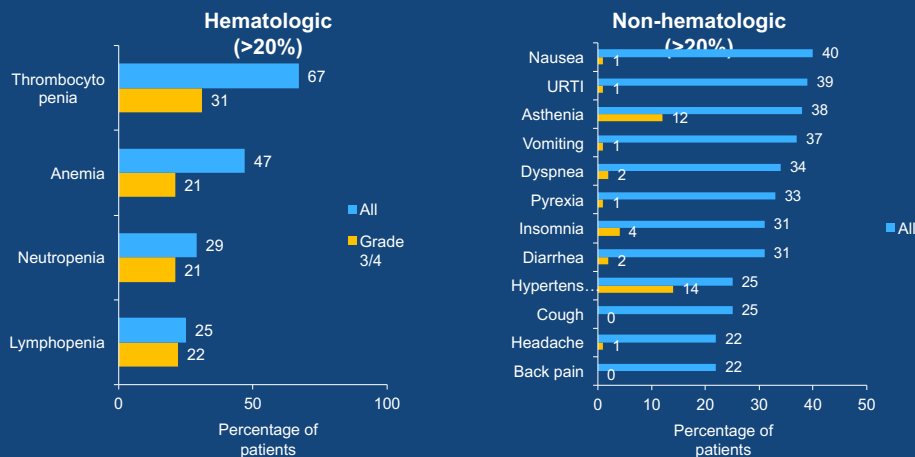
#ASCO18
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PRESENTED BY: Ajai Chari, MD

D-Kd: dexamethasone/carfilzomib/dexamethasone; IMiD, immunomodulatory drug; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; IV, intravenous; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, oral; OS, overall survival; NGS, next-generation sequencing; IFE, intact immunofluorescence.

4
7

Most Common TEAEs (All Treated)



- Low neutropenia rates with D-Kd in RRMM
- Similar safety profile observed for len-refractory patients

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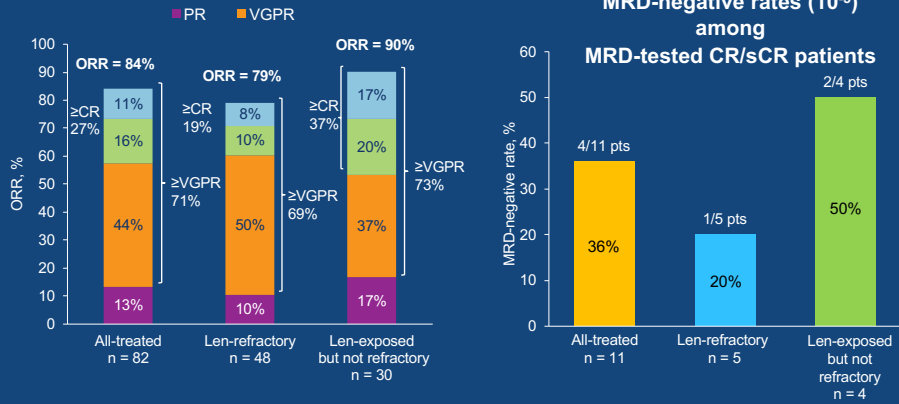
PRESENTED BY: Ajai Chari, MD

TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

4
8

Overall Response^a and Confirmed MRD-negative Rates

- Median follow-up: 12.0 months
- Optional MRD testing in 11 patients with CR/sCR; 4 were MRD negative at 10⁻⁵



Responses are anticipated to deepen over longer follow-up

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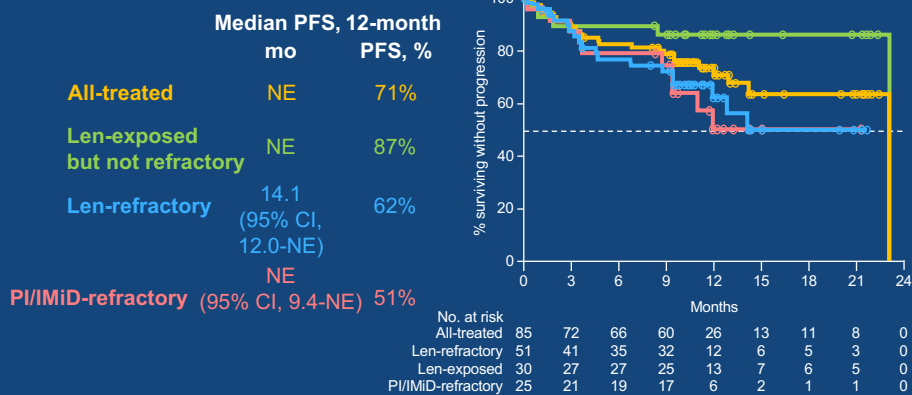
PRESENTED BY: Ajai Chari, MD

PR, partial response; sCR, stringent complete response.
*In response-evaluable patients (received at least 1 administration of any component of study treatment and have at least 1 post baseline disease assessment) who were treated more than 2 cycles or discontinued study treatment.

4
9

Progression-free Survival Across Subgroups

- Median follow-up: 12.0 months



Encouraging PFS observed in lenalidomide- and PI/IMiD-refractory patients

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PRESENTED BY: Ajai Chari, MD, not estimable.

5
0

■ Ninety-Minute Daratumumab Infusion Is Safe in Multiple Myeloma

■ Hallie Barr, et. al.

■ Blood 2017 130:1889;

Table 1

Daratumumab Infusion Rates					
Dose	Total Volume ¹	Initial Rate	Rate Increment	Max Rate	Time ²
Standard of care first dose	1050 mL	50 mL/hr	50 mL/hr every 1 hr	200 mL/hr	6.5 hrs
Standard of care second dose	550 mL	50 mL/hr	50 mL/hr every 1 hr	200 mL/hr	4.5 hrs
Standard of care dose 2-3	550 mL	100 mL/hr	50 mL/hr every 1 hr	200 mL/hr	3.5 hrs
Investigational dose 2-3	550 mL	200 mL/hr	30 minutes	450 mL/hr	1.5 hrs

¹Includes estimated overfill per institution standard; ²Estimated

Table 2

Baseline Characteristics	
Age, years	
Median (range)	67 (44-90)
Gender, n (%)	
Male	19 (67.9)
Female	9 (32.1)
Race, n (%)	
Caucasian	24 (85.7)
African American	3 (10.7)
Other	1 (3.6)
Number of prior daratumumab doses	
Median (range)	5 (2-26)
Pre-medication Use	
Dexamethasone, n (%)	23 (82.1)
Acetaminophen, n (%)	27 (96.4)
Diphenhydramine, n (%)	27 (96.4)
Famotidine, n (%)	28 (100)
Montelukast, n (%)	8 (28.6)
Hydroxyzine, n (%)	1 (3.6)
Delayed Dexamethasone Use	
Yes, n (%)	10 (35.7)

BCMA CAR-T Cell Therapy

Summary of Ongoing BCMA CAR-T Trials for MM

Name	Anti-BCMA CAR	Bb2121	LCAR-B38M	CART-BCMA
Group	NCI	Bluebird/ Celgene	Nanjng/Legend Biotech	Novartis/Penn
Binder/co-stimulatory signal	Murine/CD3 ζ , CD28	Murine/CD3 ζ , 4-1BB	Murine/CD3 ζ , 4-1BB	Fully human/CD3 ζ , 4-1BB
Transfection	γ -retroviral	Lentiviral	Lentiviral	Lentiviral
BCMA expression required?	Yes	Yes	Yes	No

BB 2121 PHASE I: TUMOR RESPONSE BY MRD

Response	50 × 10 ⁶	150 × 10 ⁶	450 × 10 ⁶	800 × 10 ⁶	Total
MRD-evaluable responders	0	4	11	1	16
MRD-neg ^a	0	4 (100)	11 (100)	1 (100)	16 (100)

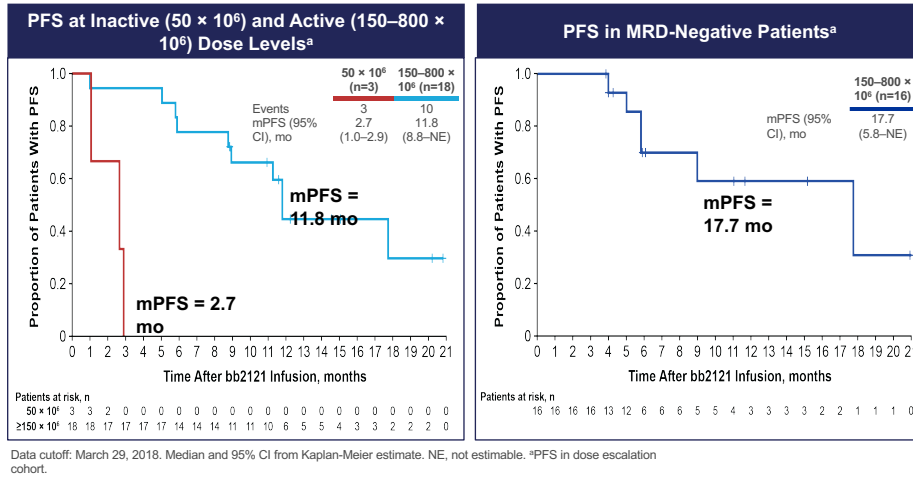
Data cutoff: March 29, 2018. ^a

Of 16 MRD-negative responses: 4 at 10⁻⁶, 11 at 10⁻⁵, 1 at 10⁻⁴ sensitivity
by Adaptive next-generation sequencing assay.

- All responding patients evaluated for MRD were MRD negative at 1 or more time points
- 2 nonresponders evaluated for MRD were MRD positive at month 1

BB 2121 PHASE I: PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses ($\geq 150 \times 10^6$ CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative



BB 2121 Phase I

Figure 4. Duration of Partial Response or Better in MRD-Negative Patients

