Myeloma
Closer to a Cure than Ever Before

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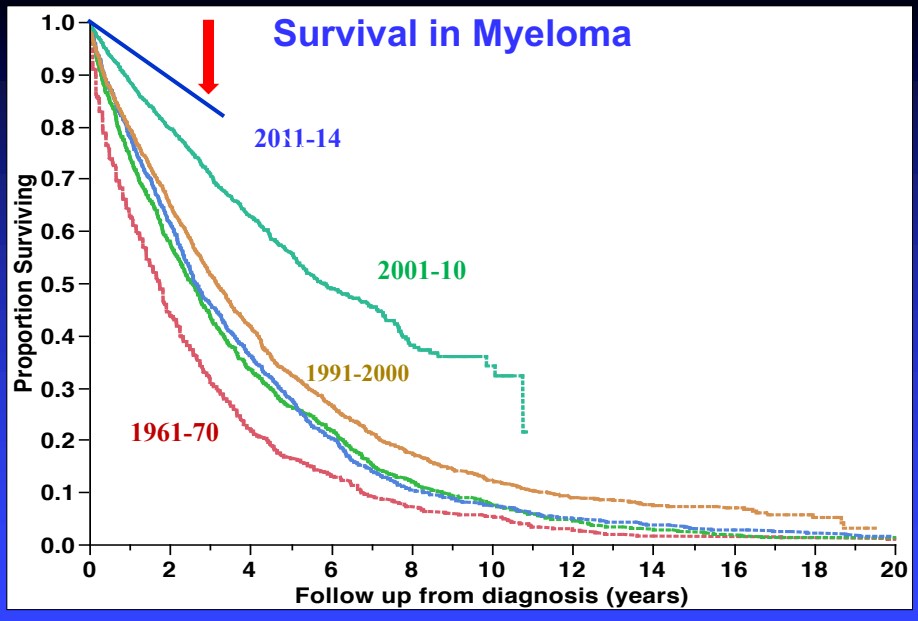


Kumar S. Blood 2008;111: 2516 – 2520; Kumar S. Leukemia (2014) 28, 1122–1128.

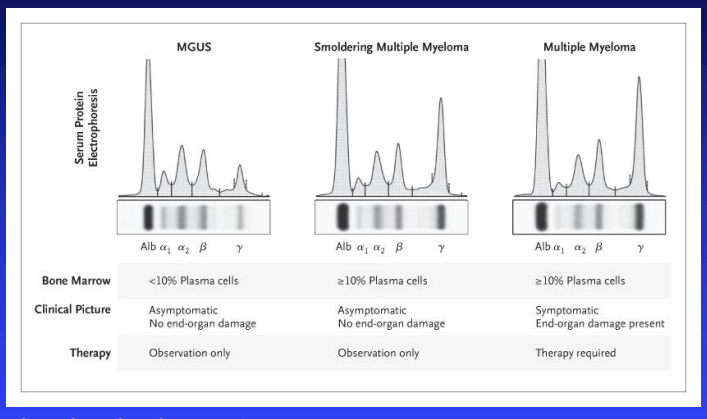
Changes in Diagnosis

Free Light Chain Ratio

Percentage Plasma Cells on Diagnostic Marrow

Use of Modern Imaging

Characteristics of Active Multiple Myeloma and Its Precursors



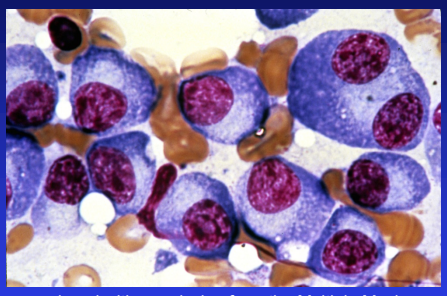
Bone Marrow	<10% Plasma cells	≥10% Plasma cells	≥10% Plasma cells
Clinical Picture	Asymptomatic No end-organ damage	Asymptomatic No end-organ damage	Symptomatic End-organ damage present
Therapy	Observation only	Observation only	Therapy required

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

The NEW ENGLAND JOURNAL of MEDICINE

Myeloma

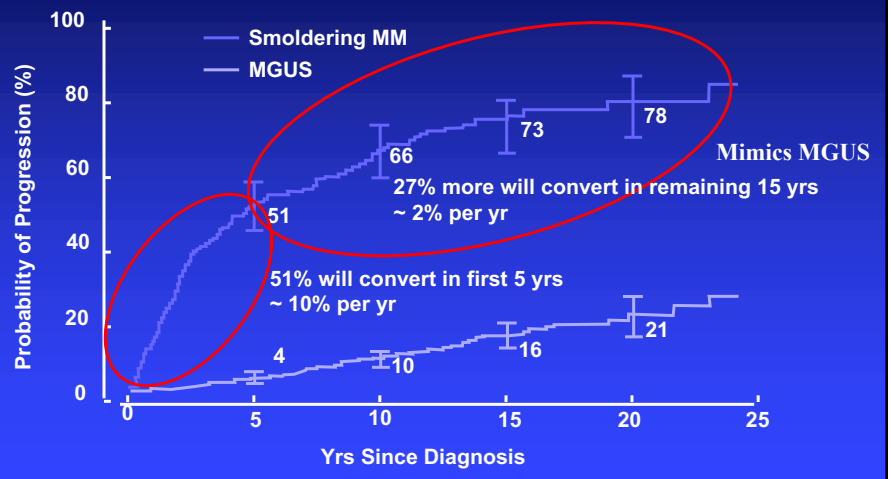
- MM is characterized by:
  - Excessive numbers of abnormal plasma cells in the bone marrow
  - Overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD) or free antibody light chains
  - concomitant drop in other immunoglobulins
  - **CRAB Criteria**
    - **HyperCalcemia**
    - **Renal**
    - **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.

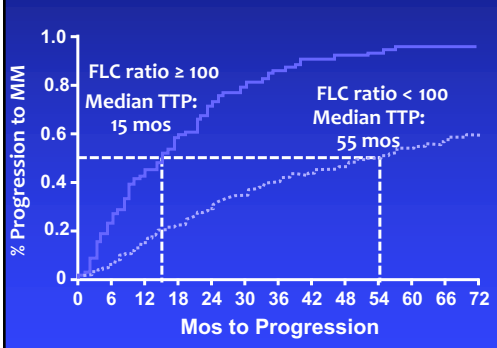
Smoldering Multiple Myeloma

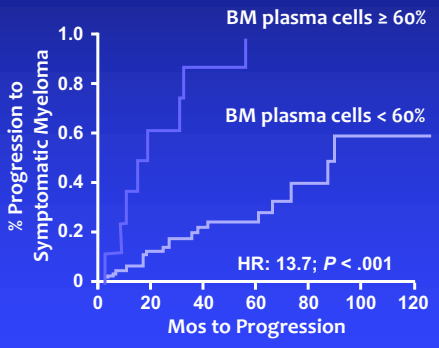


Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

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	Smoldering Myeloma	Multiple Myeloma
▪ M protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma defining events	▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma defining events	▪ Underlying plasma cell proliferative disorder ▪ AND 1 or more myeloma defining events ▪ ≥ 1 CRAB* feature ▪ Clonal plasma cells in BM ≥ 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)

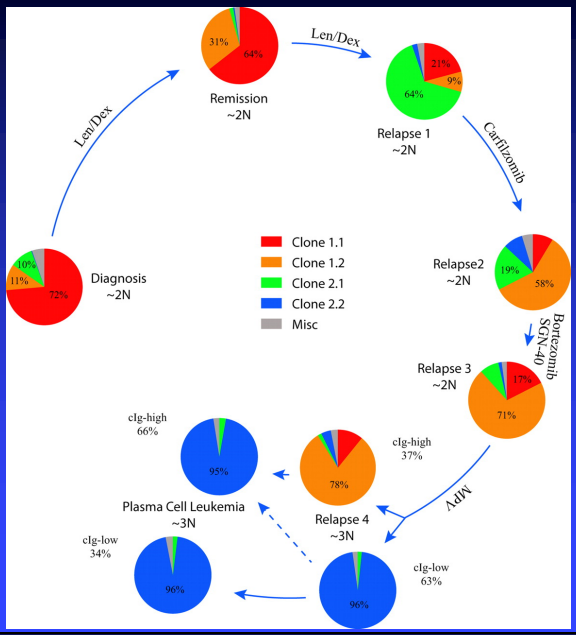
Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

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

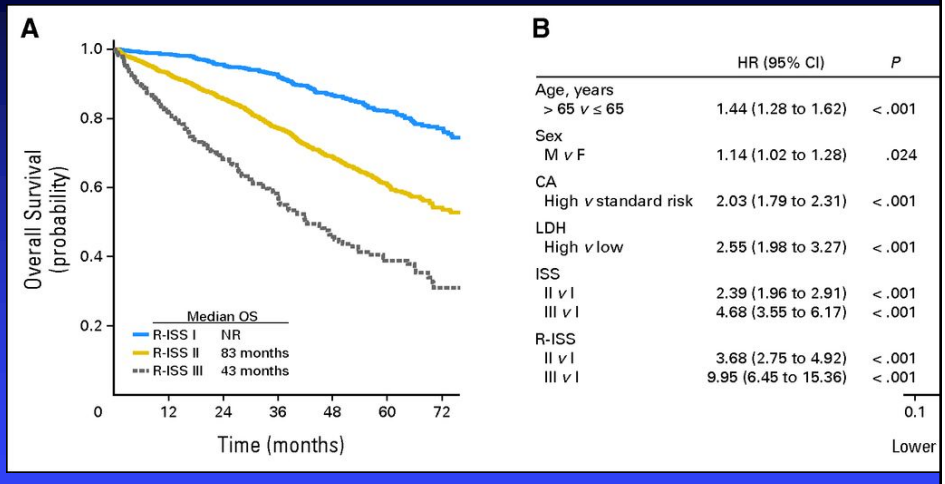
New Staging

Revised International Staging System
R-ISS

R-ISS

- Stage I
  - B2M < 3.5 mg/L
  - Albumin ≥ 3.5 gm/dL
- Stage II
  - Not Stages I or II
- Stage III
  - B2M ≥ 5.5 mg/L
  - LDH > ULN
  - Abnormal iFISH (del (17p), t(4;14), t(14;16))

Revised ISS



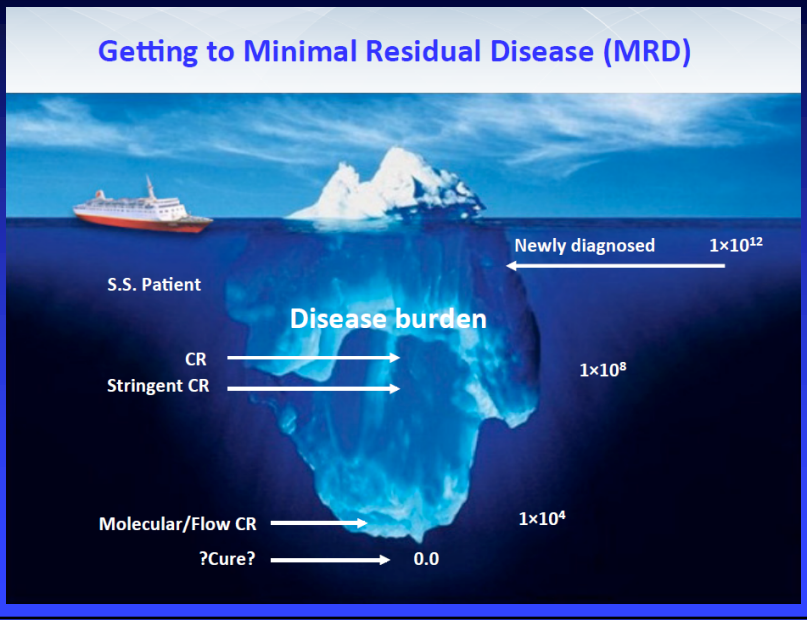
(A) Overall survival (OS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm.

Antonio Palumbo et al. JCO, 2015

Evidence that Depth of Response Matters

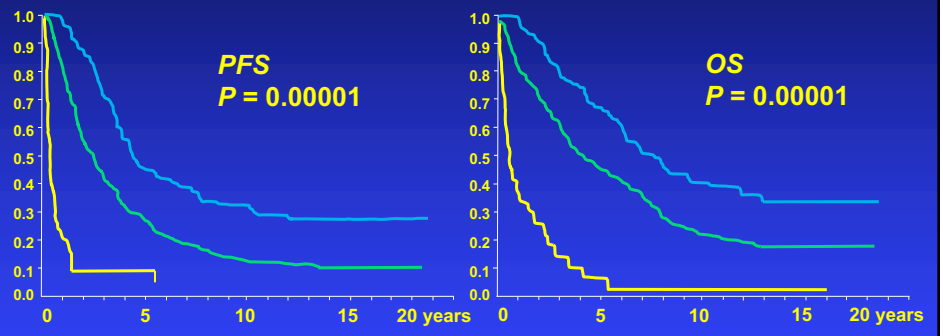
CR and MRD

The Iceberg



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



CR (n=63)

nCR (n = 66) + VGPR (n = 54) + PR (n = 114)

SD (n = 12) + PD (n = 14)

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

Minimal Residual Disease (MRD)

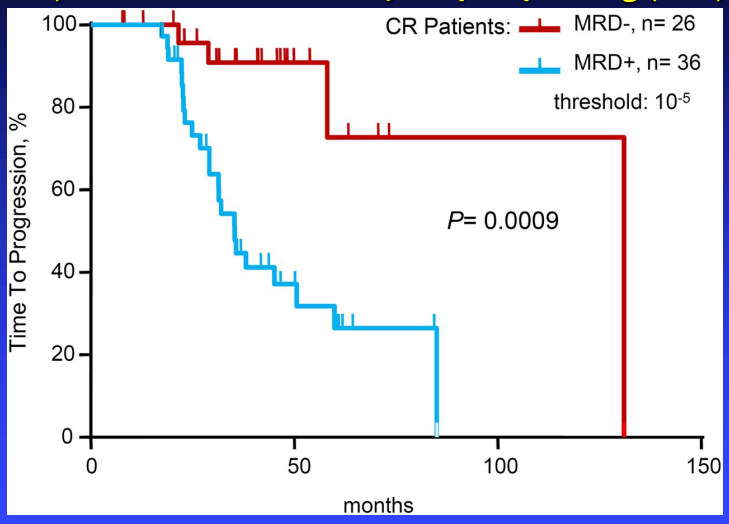
Standard Flow – 10^{-4}

EuroFlow (8 color) – 10^{-5}

Next Generation Sequencing – 10^{-6}

Spanish Retrospective Look at MRD and Survival

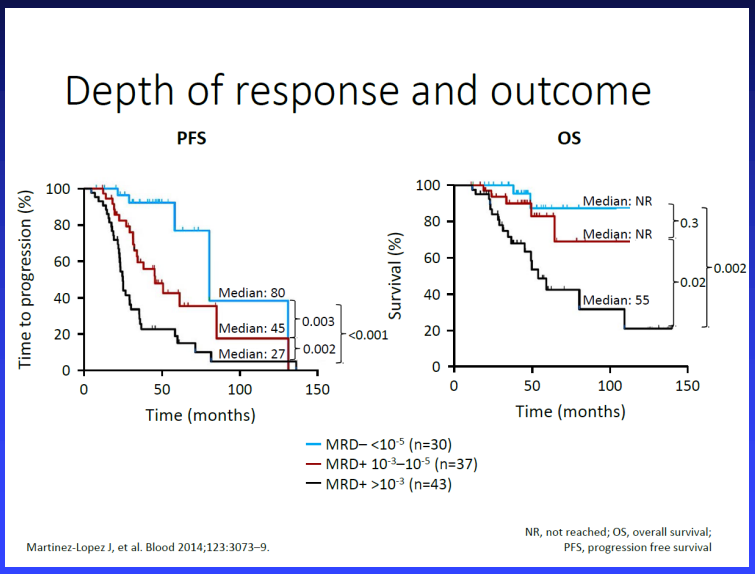
Time to progression for patients achieving conventional complete remission (CR), according to minimal residual disease (MRD) status as determined by deep sequencing (NGS).



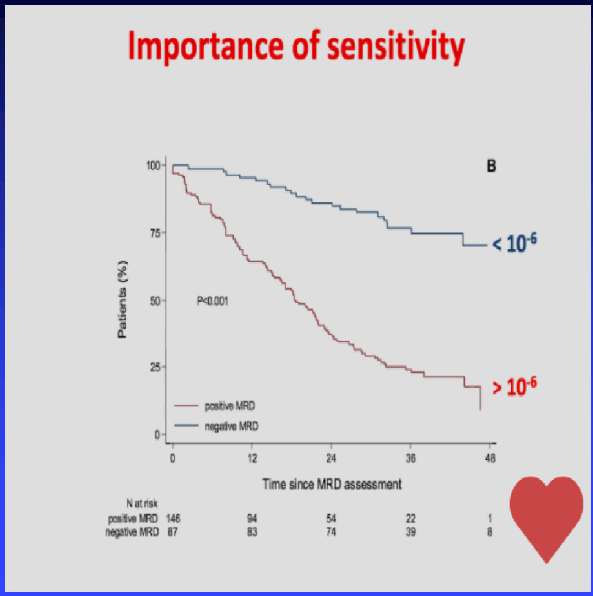
Martinez-Lopez J et al. Blood 2014;123:3073-3079

blood

Further Evidence that MRD Matters



IFM/DFCI 2009



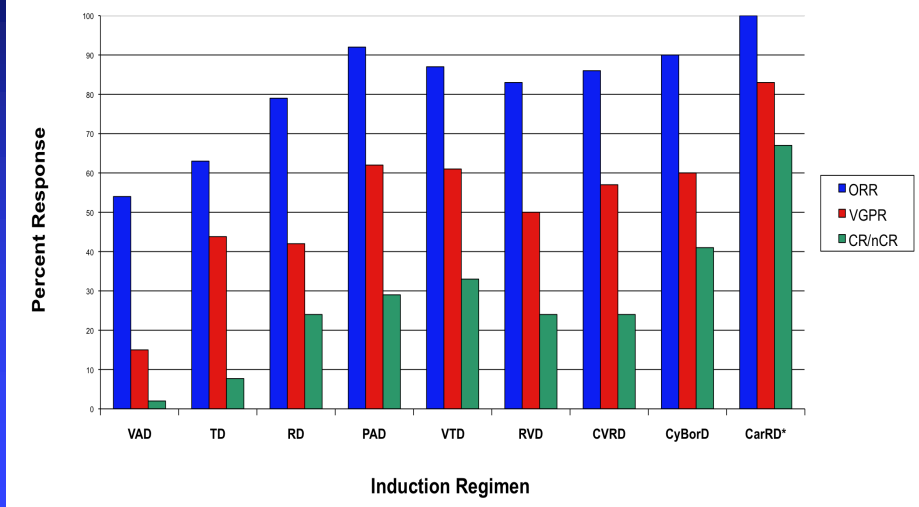
Frontline Therapy for Patients Eligible (or Ineligible) for Transplant

MAYO CLINIC

Discovery of Active Drugs in Multiple Myeloma

Old Drugs (1960s)	Approved Drugs (2003-2007)	Recently Approved Drugs (2013-2015)	Future Drugs
▪ Melphalan ▪ Cytoxan ▪ Prednisone ▪ Dexamethasone ▪ Doxorubicin	▪ Bortezomib ▪ Thalidomide ▪ Lenalidomide ▪ Liposomal doxorubicin	▪ Carfilzomib ▪ Pomalidomide ▪ Panobinostat ▪ Daratumumab ▪ Ixazomib ▪ Elotuzumab	▪ Oprozomib ▪ Marizomib ▪ Isatuximab ▪ Venetoclax ▪ Selinexor ▪ CAR-T ▪ BiTES ▪ ADCs

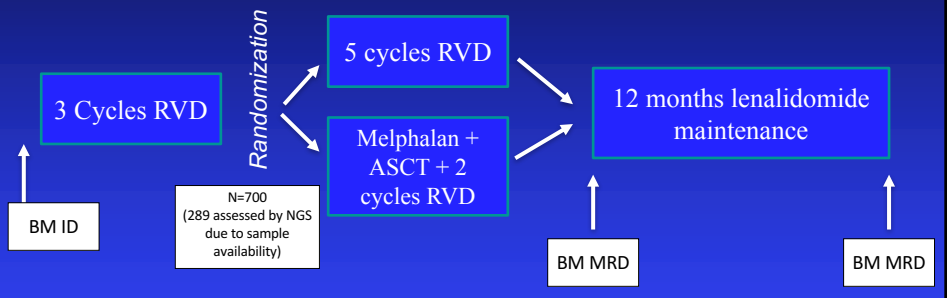
Improving Response Rates with Combination Therapies for Induction



Role of Autologous Transplant

IFM/DFCI 2009

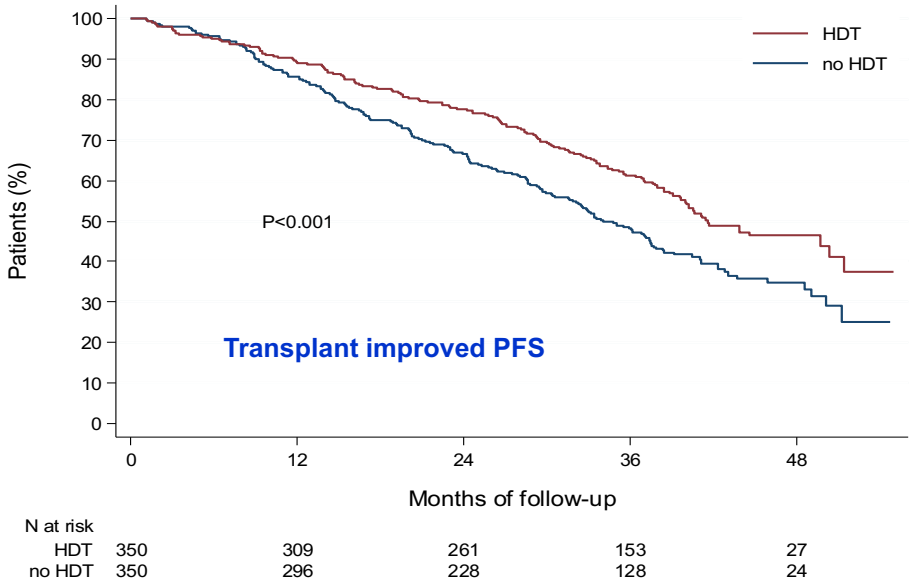
IFM/DFCI Study Schema



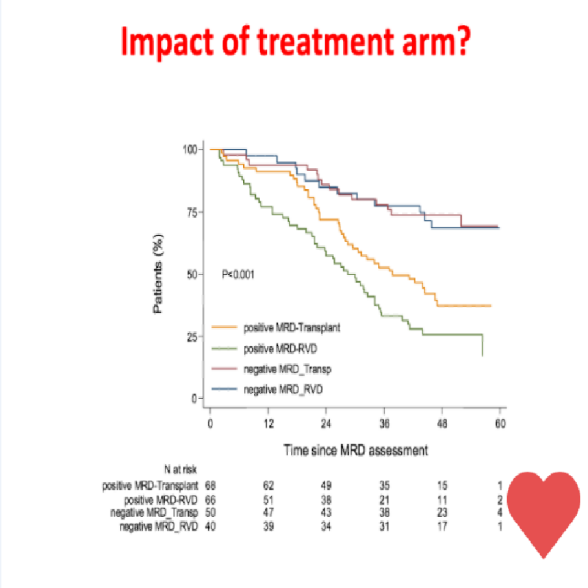
*comparisons to flow at all MRD time points

27

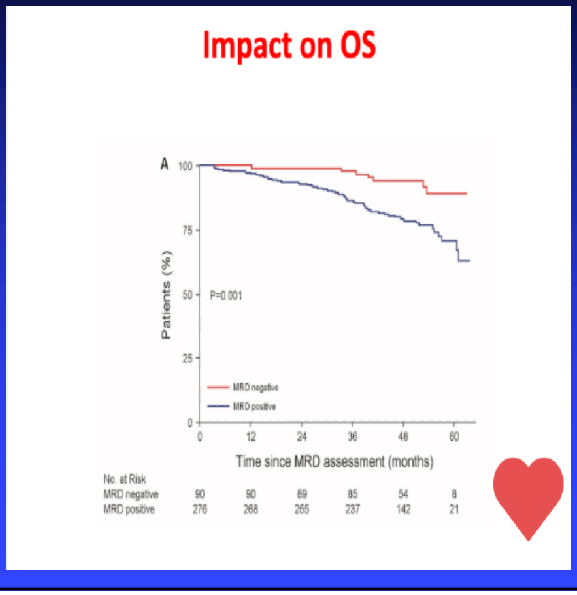
IFM/DFCI 2009



Impact of Treatment Arm on MRD and PFS



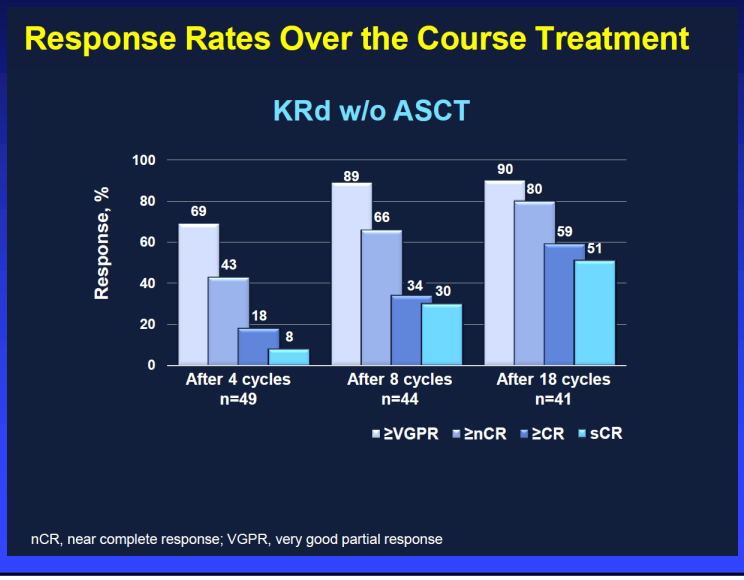
IFM/DFCI 2009
MRD Impact on OS



Further Evidence for Role of Auto ASCT

KRd (? Improvement over RVd?)

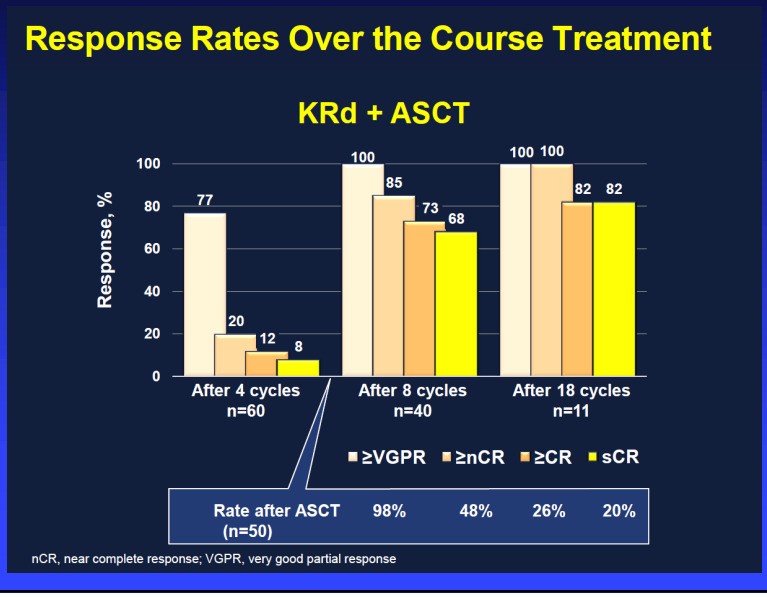
Jakubowiak, 2015



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

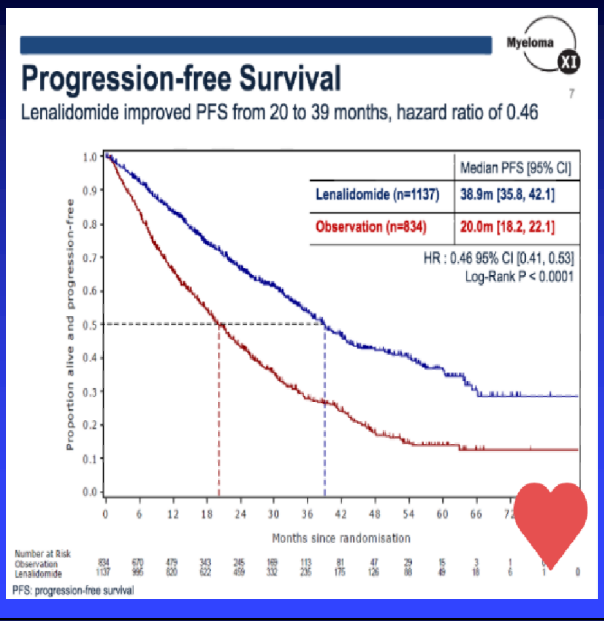
KRd + ASCT

Zimmerman, 2016

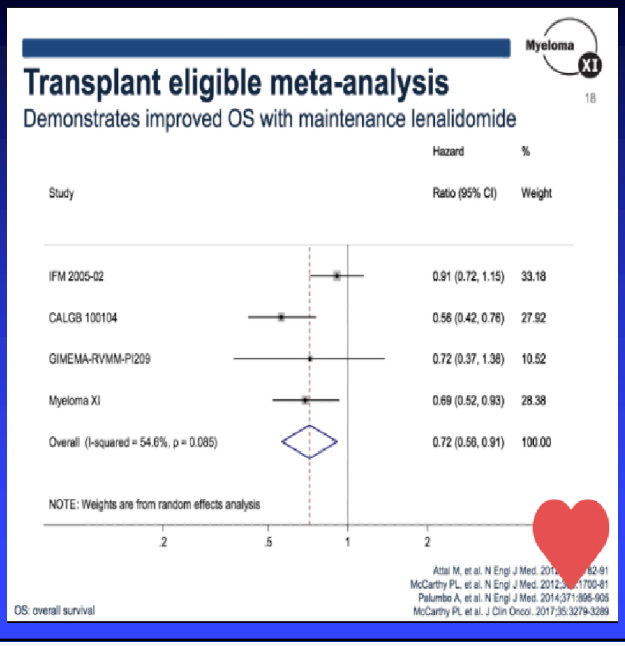


Role of Maintenance (Continuation) Therapy

Myeloma XI – Role of Lenalidomide Maintenance

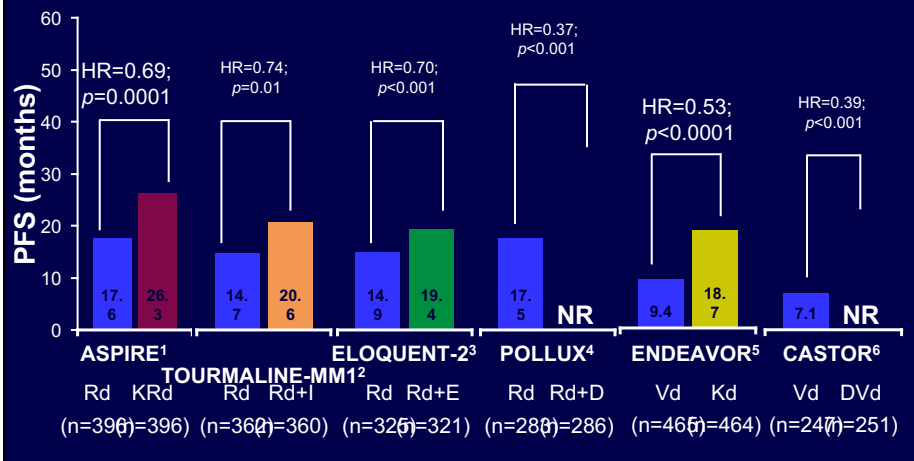


Maintenance Meta-Analysis



Treatment of Relapse

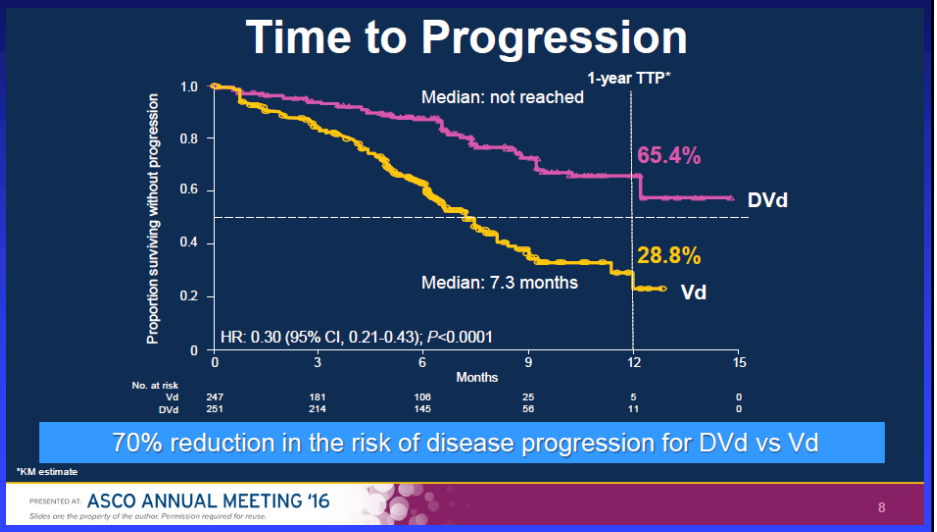
PFS in Recent Relapsed Phase 3 trials



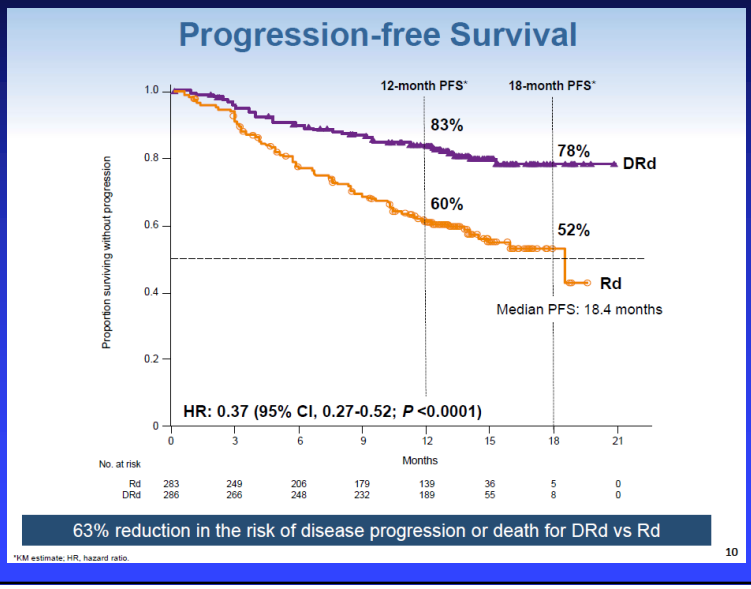
HR, hazard ratio; NR, not reached; PFS, progression-free survival.

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



Pollux: Rd vs Dara Rd



New and Variations on Old Therapies

Venetoclax

90 Minute Daratumumab (Sub Q Coming)

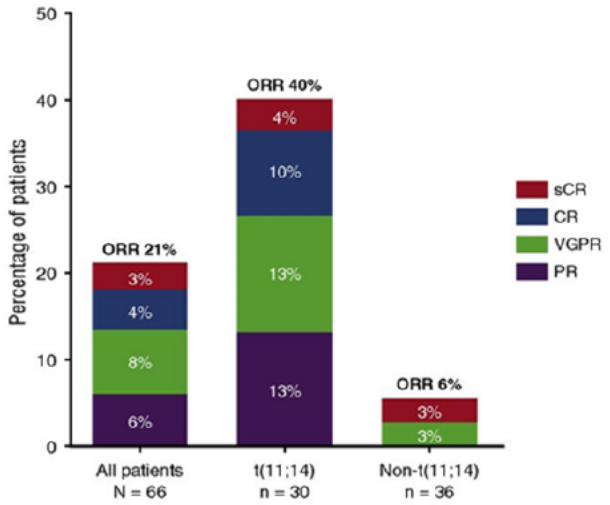
Once Weekly Carfilzomib

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, Lofti 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-1999 / GDC-0199) Combined with Rituximab Induces Deep Responses in Relapsed / Refractory CLL

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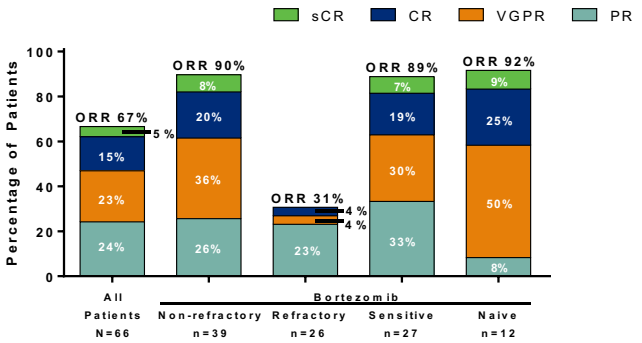
Venetoclax Combined With Bortezomib and Dexamethasone for Patients With Relapsed/Refractory Multiple Myeloma

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. Harrison[8]

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 × 10^9/L
- Platelet count ≥75 × 10^9/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/m^2 IV Cycle 1 Day 1
- Escalated to 70 mg/m^2 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

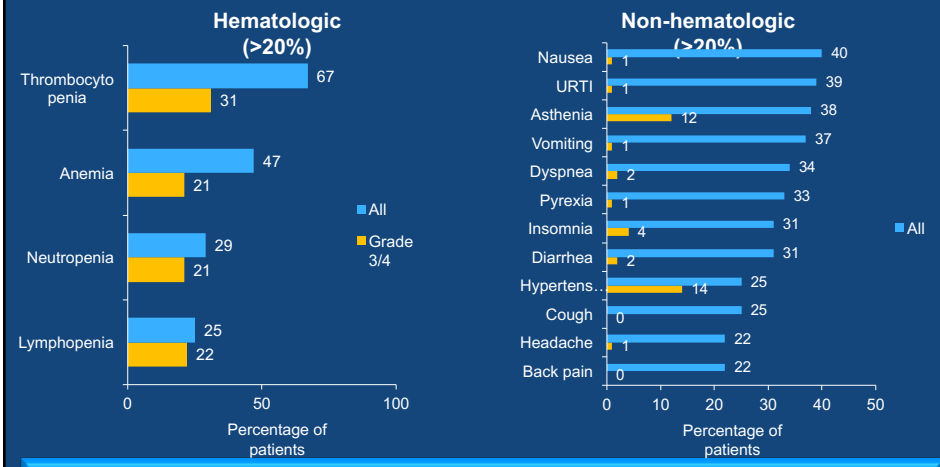
Exploratory

- PFS
- MRD (NGS)[c]
- PK

[a]In 500-mL dilution volume.
[b]Both 20 mg/m^2 and 70 mg/m^2 were administered as 30-minute IV infusions.
[c]Among 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.

D-Kd, daratumumab/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,

Most Common TEAEs (All Treated)

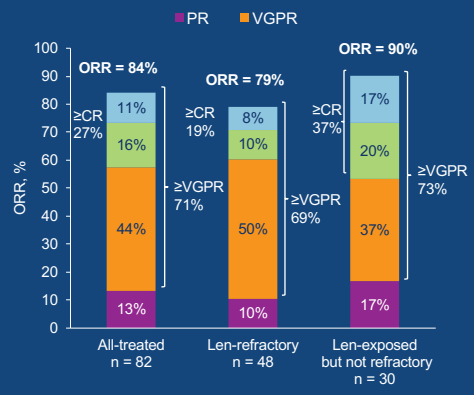


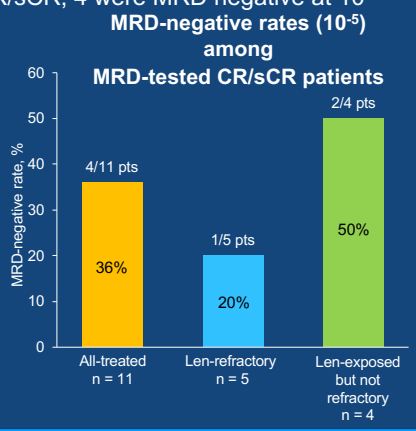
- **Low neutropenia rates with D-Kd in RRMM**
- **Similar safety profile observed for len-refractory patients**

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

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}





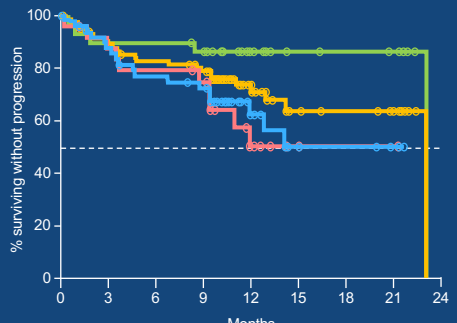
Responses are anticipated to deepen over longer follow-up

PR, partial response; sCR, stringent complete response.
[a]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.

Progression-free Survival Across Subgroups

- Median follow-up: 12.0 months

	Median PFS, mo	12-month PFS, %
All-treated	NE	71%
Len-exposed but not refractory	NE	87%
Len-refractory	14.1 (95% CI, 12.0-NE)	62%
PI/IMiD-refractory	NE (95% CI, 9.4-NE)	51%



No. at risk									
All-treated	85	72	66	60	26	13	11	8	0
Len-refractory	51	41	35	32	12	6	5	3	0
Len-exposed	30	27	27	25	13	7	6	5	0
PI/IMiD-refractory	25	21	19	17	6	2	1	1	0

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

NE, not estimable.

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 ≥ 3	550 mL	100 mL/hr	50 mL/hr every 1 hr	200 mL/hr	3.5 hrs
Investigational dose ≥ 3	550 mL	200 mL/hr	30 minutes	450 mL/hr	1.5 hrs

[1]Includes estimated overfill per institution standard; [2]Estimated

Table 2

Baseline Characteristics	
Age, years Median (range)	 67 (44-90)
Gender, n (%) Male Female	 19 (67.9) 9 (32.1)
Race, n (%) Caucasian African American Other	 24 (85.7) 3 (10.7) 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/CD3ζ, CD28	Murine/CD3ζ, 4-1BB	Murine/CD3ζ, 4-1BB	Fully human/CD3ζ, 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]

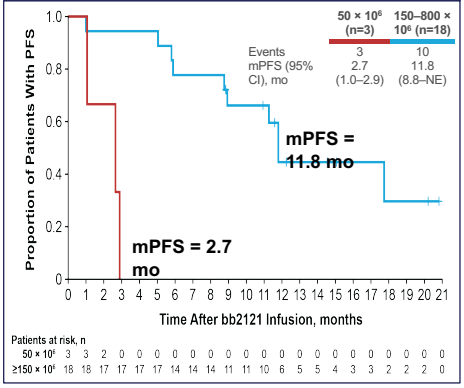
Of 16 MRD-negative responses: 4 at 10^{-6}, 11 at 10^{-5}, 1 at 10^{-4} sensitivity by Adaptive next-generation sequencing assay.

- 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

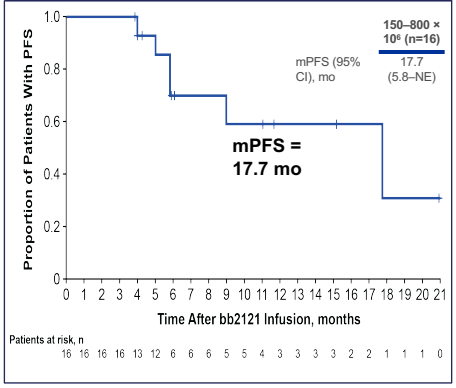
BB 2121 PHASE I: PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 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

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]

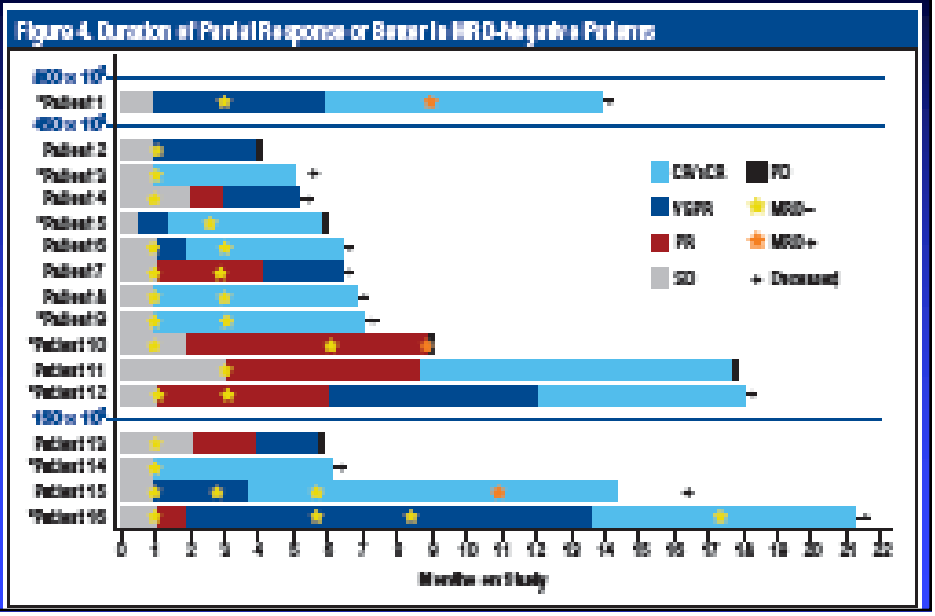


PFS in MRD-Negative Patients[a]



Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [a]PFS in dose escalation cohort.

BB 2121 Phase I




Cancer


Thank You