

***Multiple Myeloma: Induction,
Consolidation and Maintenance Therapy***

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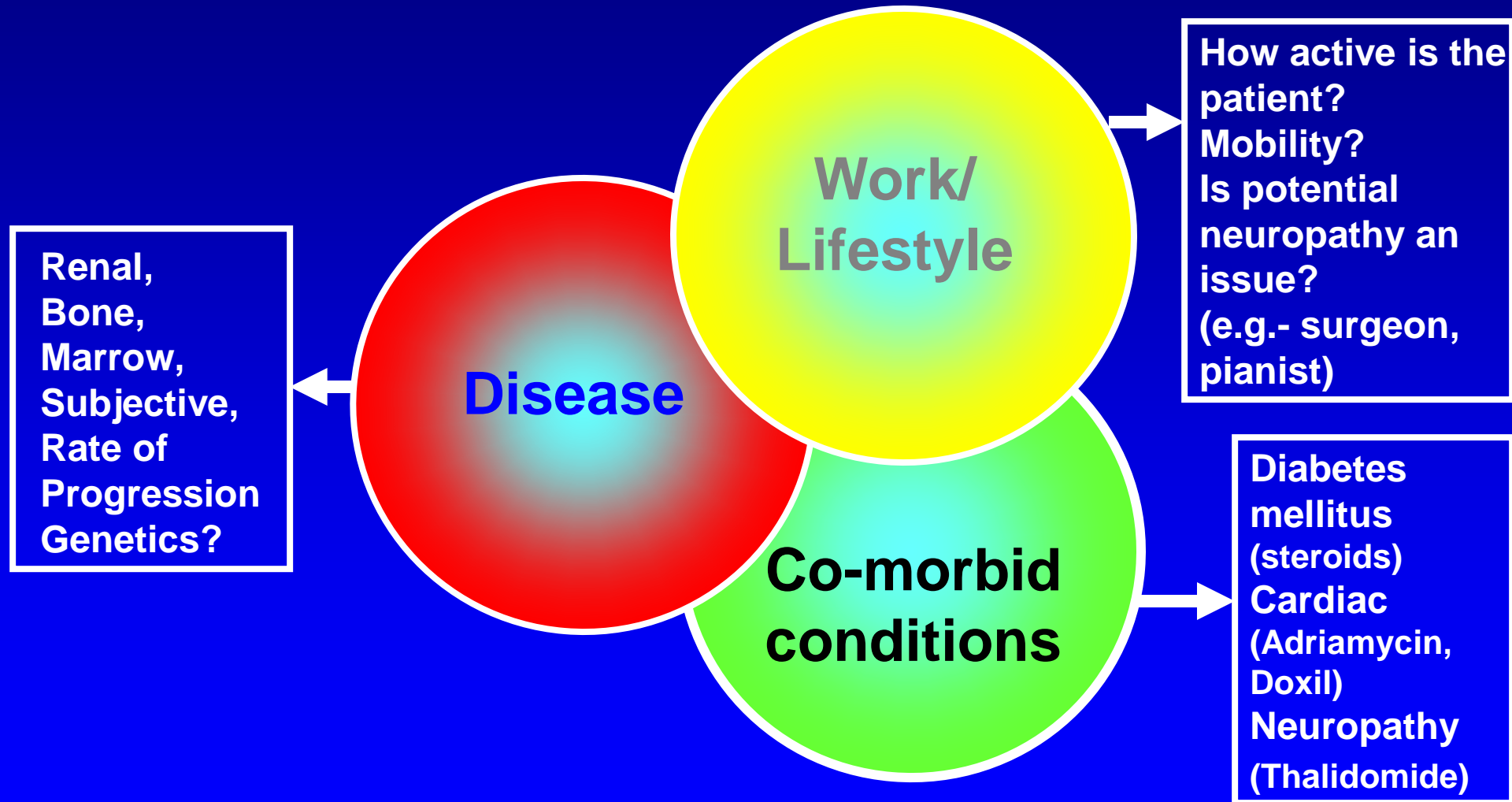
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Los Angeles, CA

Establish the Goals of Therapy for the Individual Myeloma Patient

- ▶ Patient wants the longest life (OVERALL SURVIVAL and not simply a delay in disease returning) possible w/ **therapy and a disease** that has the least impact on their life!
 - ▶ That does not necessarily mean they want the regimen w/ the highest % of CRs
 - Remember that CRs in myeloma are
 - ❖ based on paraprotein
 - ❖ **NOT** really molecular CRs even when MRD is negative
 - Very little difference in tumor burden between pts w/ stable disease and so-called CR

Individualize your choice for the myeloma patient based on:



Advances in Induction Therapy 2018

- ▶ **Triplets show superior outcome to doublets**
 - ▶ **R(Len)V(Bort)Dex vs RD SWOG study¹**
 - ▶ **Many different triplets w/ Dex**
 - ▶ **Proteasome inhibitor-based**
 - ▶ **Bortezomib w/ R, PLD, CY, or MEL**
 - ▶ **Carfilzomib w/ R, CY**
 - ▶ **Lenalidomide (R)-based- above**
- ▶ **Quadruplets show superior outcome to triplets- Daratumumab+VMP vs VMP study²**

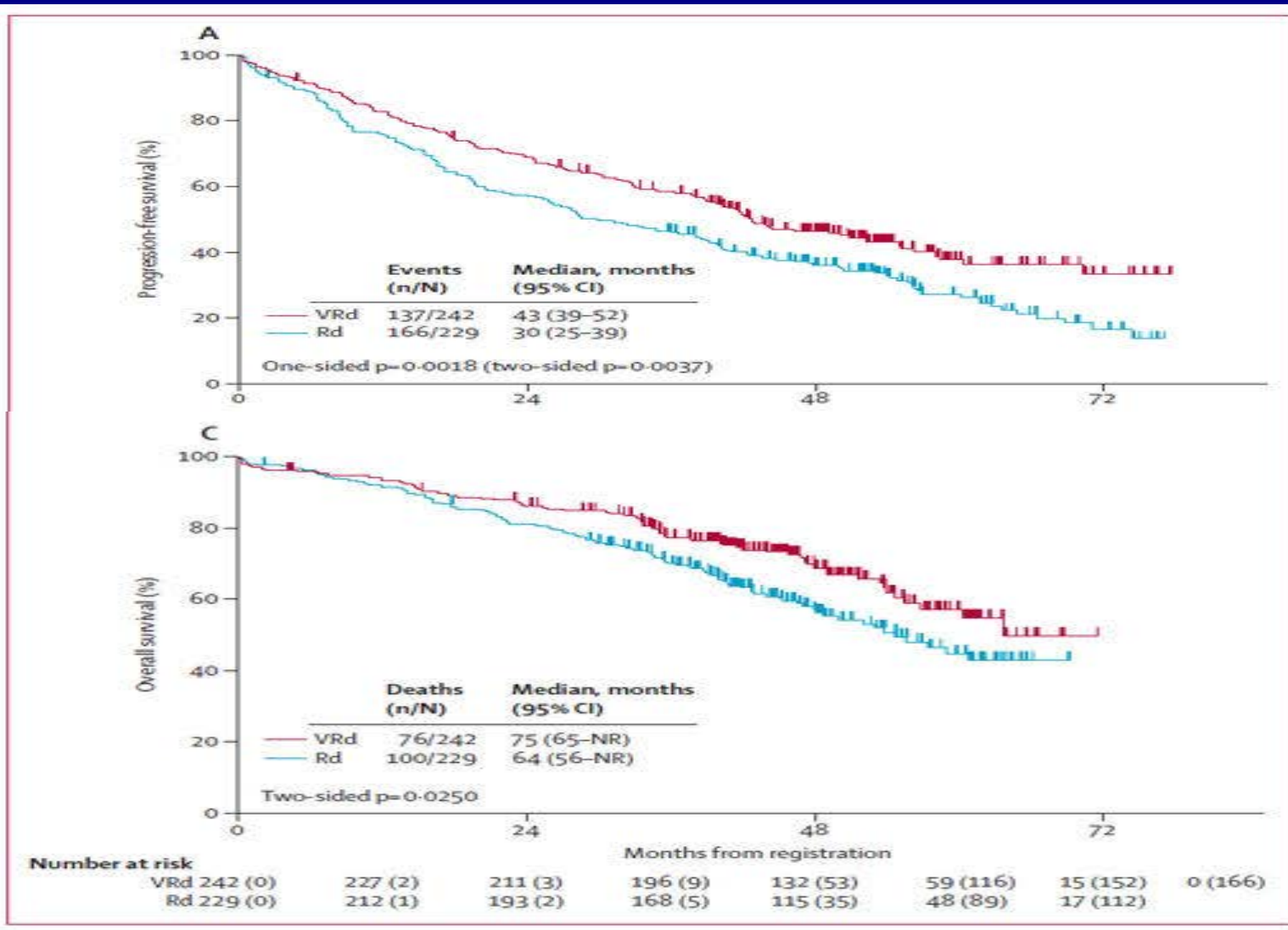
¹Durie et al. Lancet 2017; ²Mateos et al. N Engl J Med 2018

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Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): A randomised, open-label, phase 3 trial



Advances in Induction Therapy 2018

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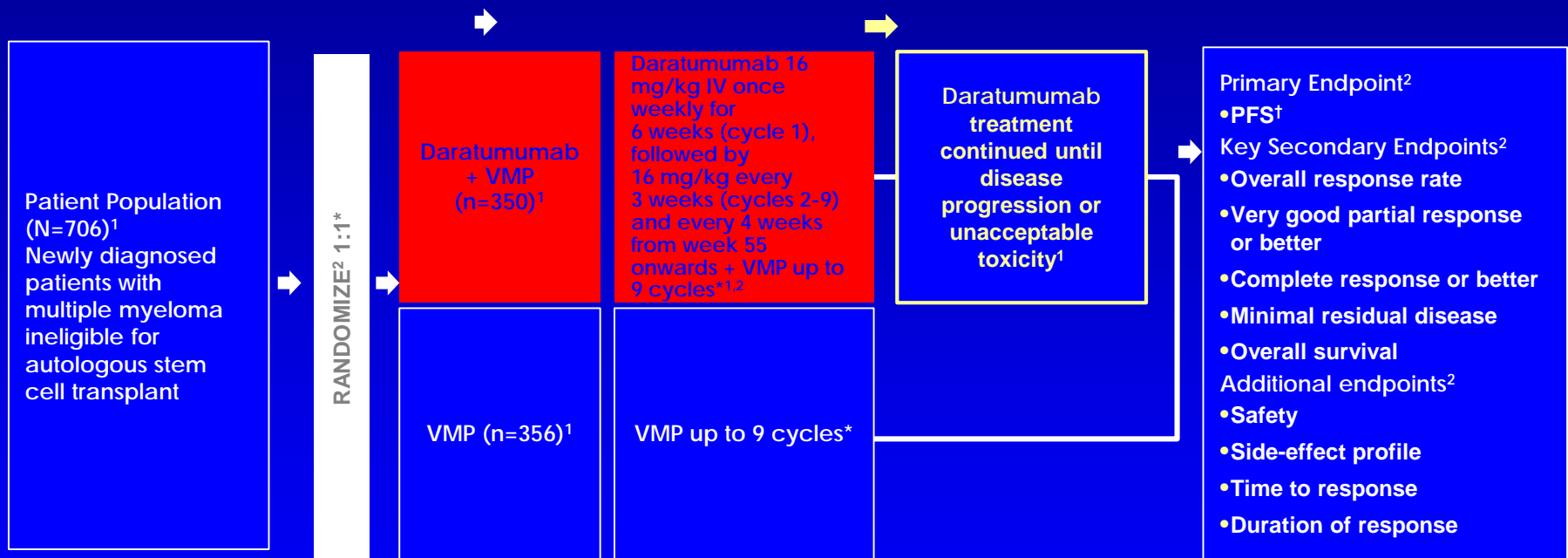
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ALCYONE: A Randomized, Open-Label, Active-Controlled, Multicenter, Phase 3 Trial of Daratumumab + VMP vs VMP



- Treatment with VMP has previously been established as an effective therapy for patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplant in several trials³⁻⁵

IV = intravenous; PFS = progression-free survival.

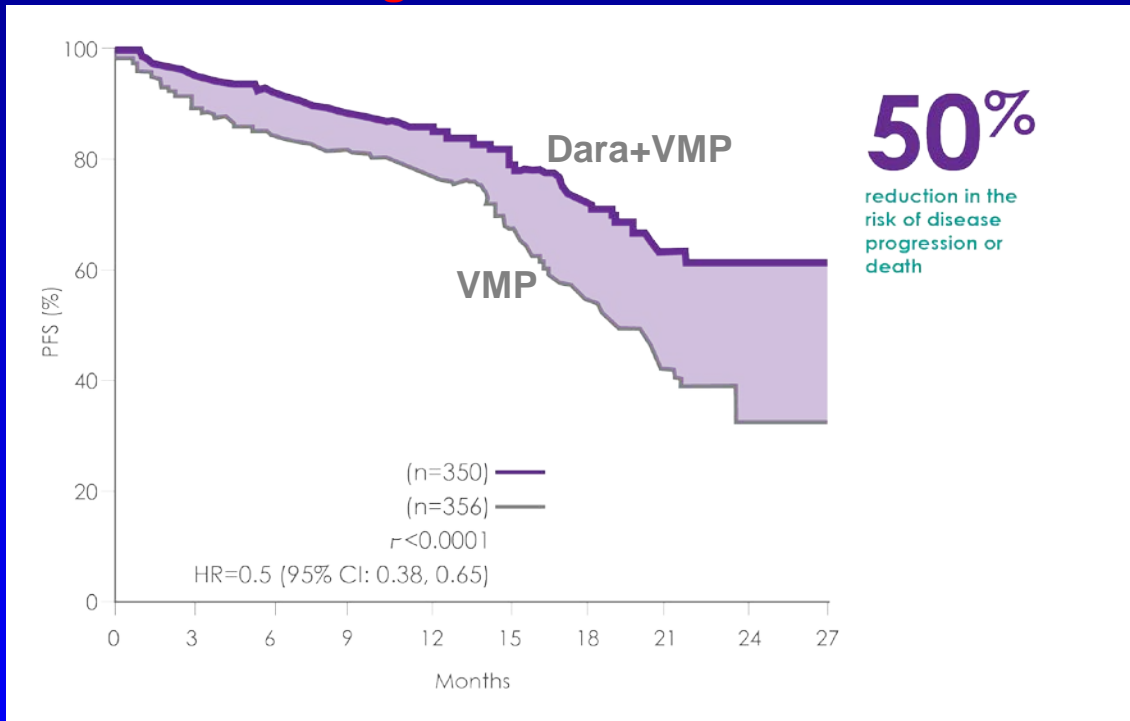
*Participants received bortezomib 1.3 mg/m² as subcutaneous injection, twice weekly at weeks 1, 2, 4, and 5 (cycle 1) followed by once weekly at weeks 1, 2, 4, and 5 (cycles 2 to 9); melphalan 9 mg/m²; and prednisone 60 mg/m² were orally administered on days 1 to 4 of the nine 6-week cycles (cycles 1-9). Per protocol, control arm discontinued VMP treatment after 9 cycles. Follow up for long-term survival is ongoing. [†]Efficacy was evaluated by PFS based on International Myeloma Working Group criteria.

1. Daratumumab [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 2. Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528. 3. Palumbo A, et al. *J Clin Oncol*. 2010;28(34):5101-5109.

4. San Miguel JF, et al. *N Engl J Med*. 2008;359(9):906-917. 5. Mateos MV, et al. *Lancet Oncol*. 2010;11(10):934-941.

Daratumumab + VMP Significantly Improved PFS vs VMP Alone*

Progression-Free Survival¹



- Median follow-up was 16.5 months²
- Median PFS had not yet been reached with Daratumumab + VMP vs 18.1 months with VMP alone¹

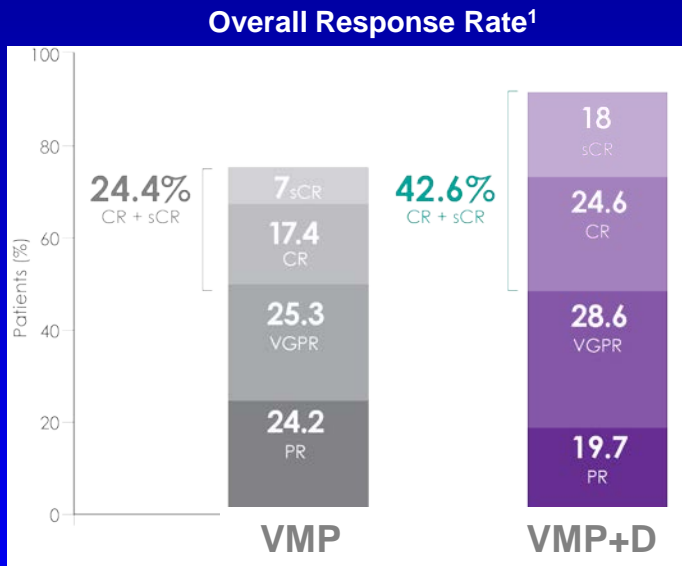
HR = hazard ratio

*Efficacy was evaluated by PFS based on International Myeloma Working Group criteria.

1. Daratumumab® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 2. Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528.

Significant Improvement in ORRs with Daratumumab + VMP

91% ORR with Daratumumab + VMP vs 74% ORR with VMP alone ($P < 0.0001$)¹



Speed of Response

- In the Daratumumab + VMP arm, the median time to response was 0.79 months (range: 0.4 to 15.5 months) vs 0.82 months (range: 0.7 to 12.6 months) in the VMP group¹

Depth of Response

- 42.6% of patients achieved CR or better with Daratumumab + VMP vs 24.4% with VMP alone¹

Duration of Response

- Median duration of response had not yet been reached with Daratumumab + VMP vs 21.3 months with VMP alone (range: 0.5+ to 23.7+), at a median follow-up of 16.5 months^{1,2}

CR = complete response; ORR = overall response rate; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.
1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 2. Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528.

ALCYONE Trial

- **Addition of daratumumab to VMP improves ORR, CR and most importantly PFS**
- **No additional safety issues were identified including cytopenias**
- **However, VMP is not a widely used upfront regimen in the United States**
 - **Whether a similar advantage of adding daratumumab to other triplets such as RVD is unknown**
 - **Whether this adds to ASCT is unknown**

Advances in Consolidation Therapy 2018

- ▶ **None really of significance**
- ▶ **However, let's consider autologous transplant as consolidation therapy and discuss its role in 2018**

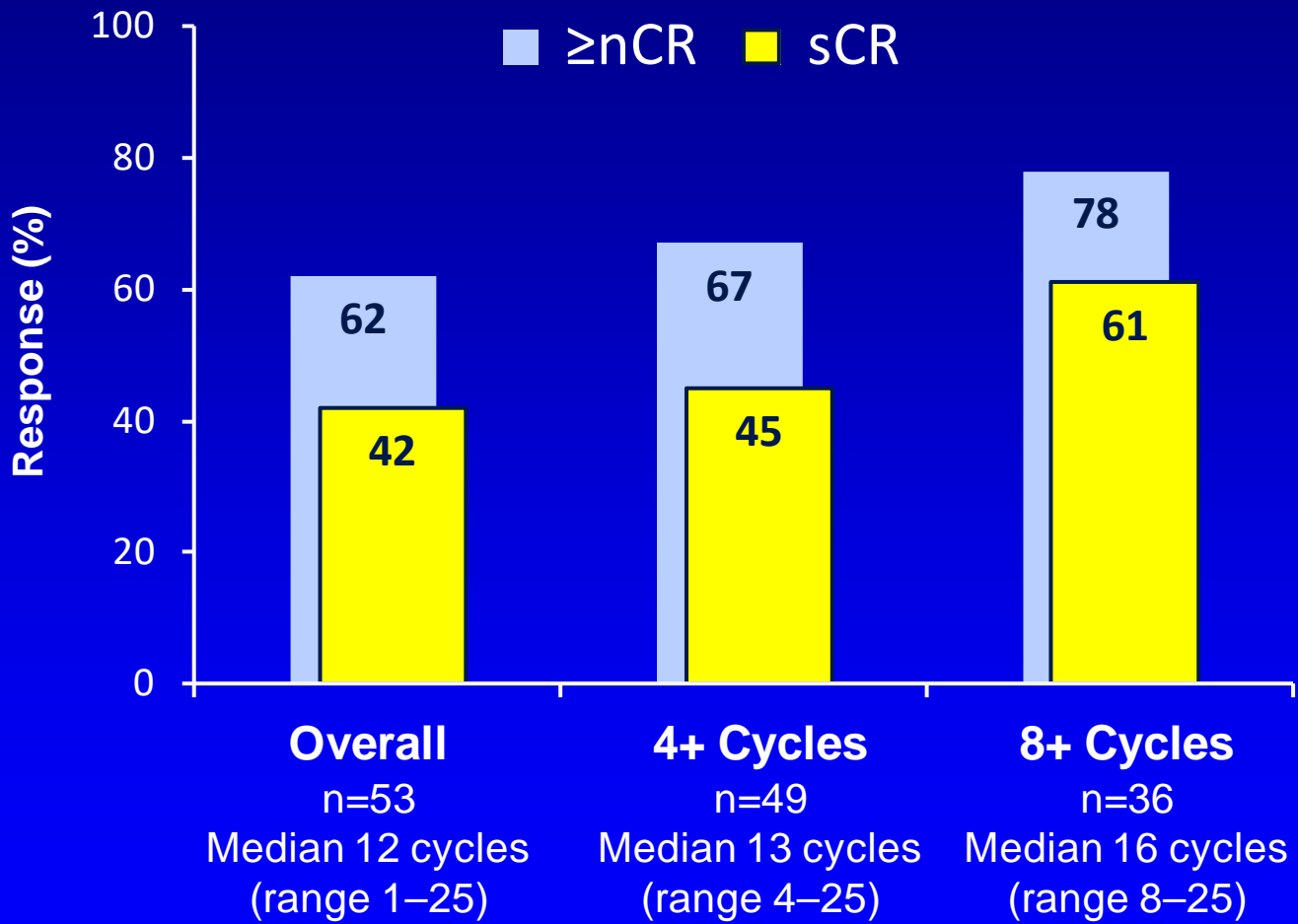
Arguments for Transplant in Myeloma

- ▶ **Highest CR rates**
 - **Higher CR associated w/**
 - ❖ **delay in time to progression (TTP)**
 - ❖ **prolonged progression free survival (PFS)**
- ▶ **Older randomized trials show PFS/TTP and in some cases an overall survival advantage**
- ▶ **No additional therapy required following the transplant**

Arguments for Transplant in Myeloma

- ▶ **Highest CR rates and**
 - **Higher CR are associated w/**
 - ❖ **delay in TTP**
 - ❖ **prolonged PFS**
- ▶ **Older randomized trials show PFS/TTP and in some cases an overall survival advantage**
- ▶ **No additional therapy required following the transplant**

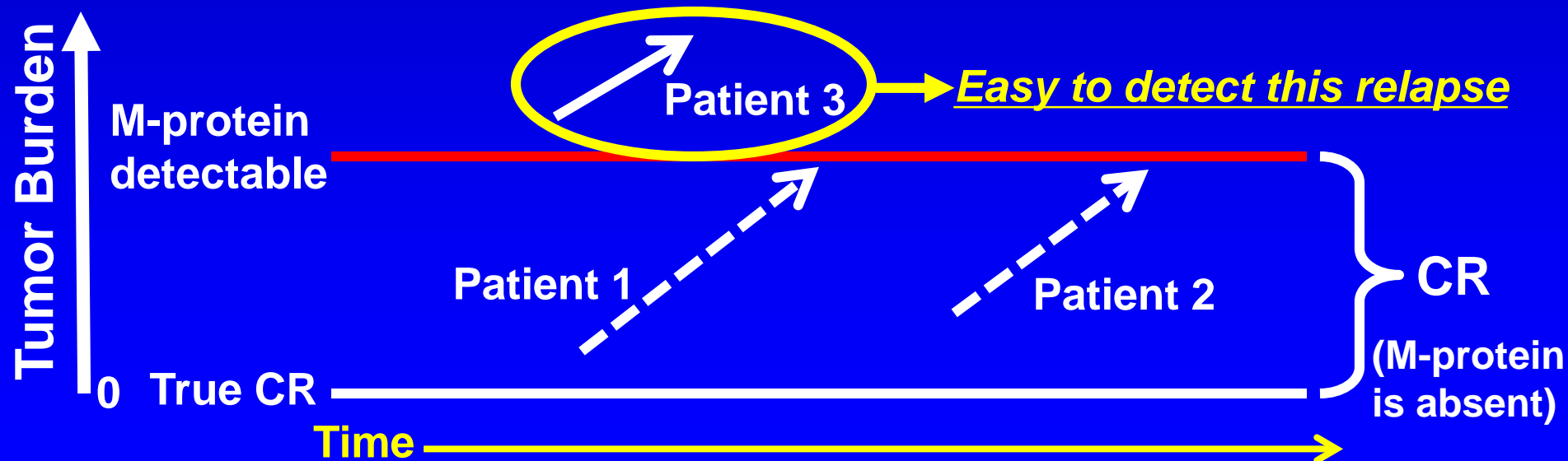
Now the Highest CR Rates are w/o HDT: Frontline Carfilzomib, Lenalidomide and Dexamethasone



Why does CR compared to < CR delay TTP/PFS w/o improvement in OS?

- These are not true CRs
 - ❖ based on M-protein becoming undetectable
- PCR-based molecular and FC CRs are only as sensitive as the assay

Why do higher CR rates consistently delay TTP?



Arguments for Transplant in Myeloma

- ▶ **Highest CR rates and**
 - **Higher CR rates are associated w/**
 - ❖ **delay in TTP (cannot measure progression)**
 - ❖ **prolonged PFS (cannot measure progression)**
- ▶ **Older randomized trials show PFS/TTP and in some cases an overall survival advantage**
- ▶ **No additional therapy required following the transplant**

Transplants: Results from Randomized Trials and Meta-analyses

- No consistent advantage in overall survival (OS) from randomized Phase III trials **EVEN PRIOR** to the availability of new drugs (IMiDs, PIs)
 - Older French & MRC trials- Yes!
 - PETHEMA trial- No!
- Only PFS **BUT** no OS advantage in recent trials
 - Palumbo et al.- even w/ tandem transplants vs MP
 - IFM French trial- vs RVD
 - Meta-analyses show PFS **BUT** no OS advantage
- **Early vs Late (at time of progressive disease)**
 - No difference in overall survival from French and US Intergroup trials

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Maintenance Studies 1 (US) and 2 (EU) evaluated lenalidomide 10 mg daily until progression or unacceptable toxicity in >1000 patients post auto-HSCT^{1,2}

Trial Design

- Randomized, double-blind, placebo-controlled studies conducted in newly diagnosed patients post auto-HSCT following induction therapy

Select Inclusion Criteria

- Patients aged 18-70 years in Study 1; <65 years in Study 2 at the time of diagnosis
- In both studies, patients needed at least a stable disease response following hematologic recovery and CrCl ≥ 30 mL/min

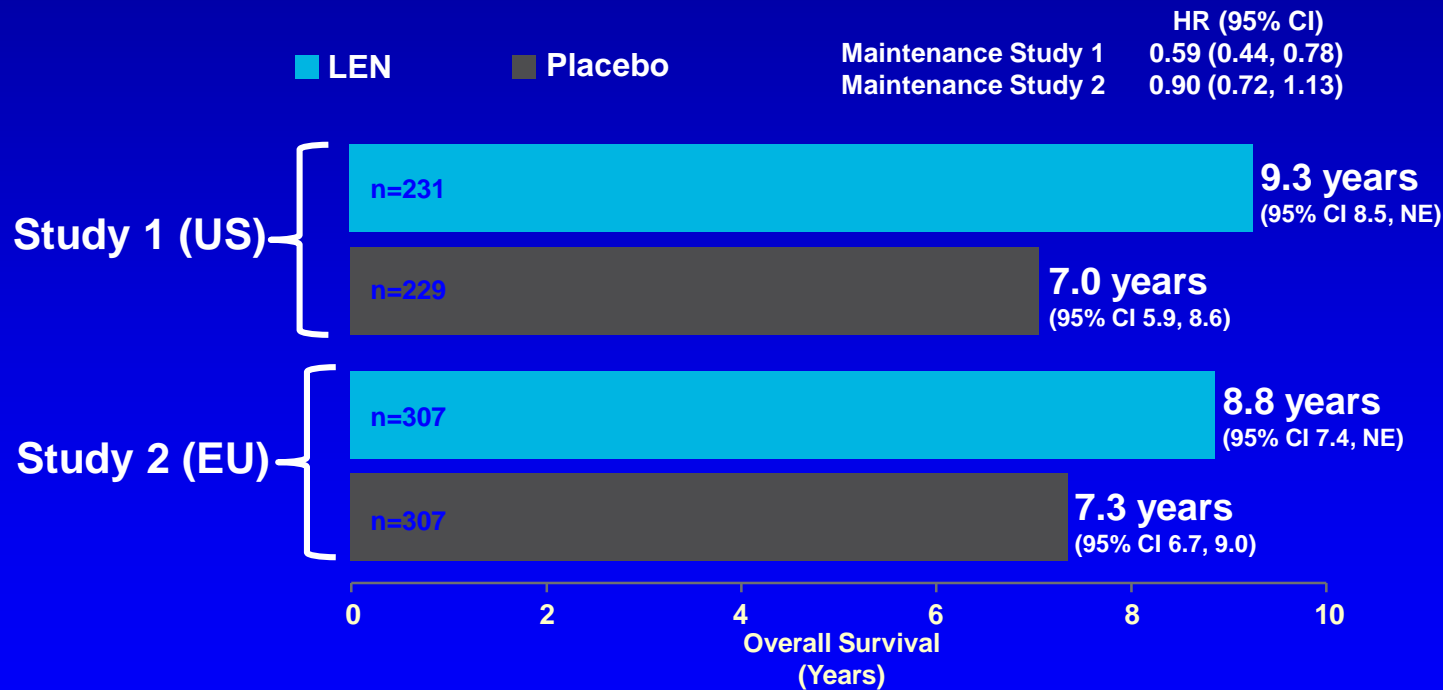
CrCl, creatinine clearance.

*PFS was defined from randomization to the date of progression or death, whichever occurred first.

References: 1. REVLIMID [package insert]. Summit, NJ: Celgene Corp; 2017. 2. Data on file. Celgene Corp; 2017.

Overall Survival Data for Lenalidomide (LEN) Maintenance Therapy From the Two Pivotal Post-Autotransplant Studies

Median Overall Survival for Maintenance Studies 1 and 2



Thus, maintenance LEN therapy is standard of care posttransplant

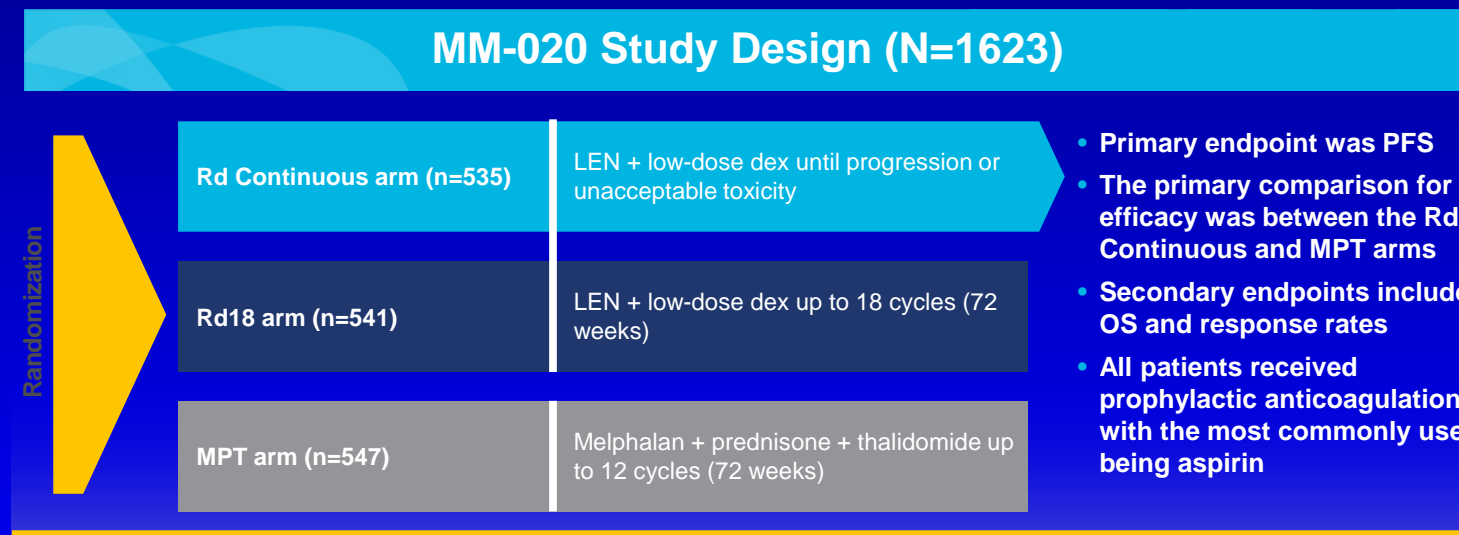
Transplants in 2017 for Myeloma

- ▶ **No overall survival (OS) advantage of early autotransplant from any recent randomized trials**
- ▶ **Highest CR rates are w/o transplant (i.e. CLD)**
- ▶ **All patients now receive posttransplant maintenance lenalidomide so there is no treatment-free interval**
- ▶ **Treatment options are rapidly increasing**
 - **Thus, compromising a patient's ability to receive these options because of toxicity from high dose therapy is important to consider**
 - **Also be careful interpreting results (especially OS) from trials where treatment options are limited**
- ▶ **As MM patients are living longer, optimizing QOL becomes of increasing importance**

MM-020: A Phase 3 trial in MM that evaluated ≥ 1600 newly diagnosed MM patients^{1,2}

MM-020 was a randomized, multicenter, open-label, 3-arm study that evaluated lenalidomide (LEN) + dex (Rd) until progression in newly diagnosed patients who did not receive an auto-HSCT

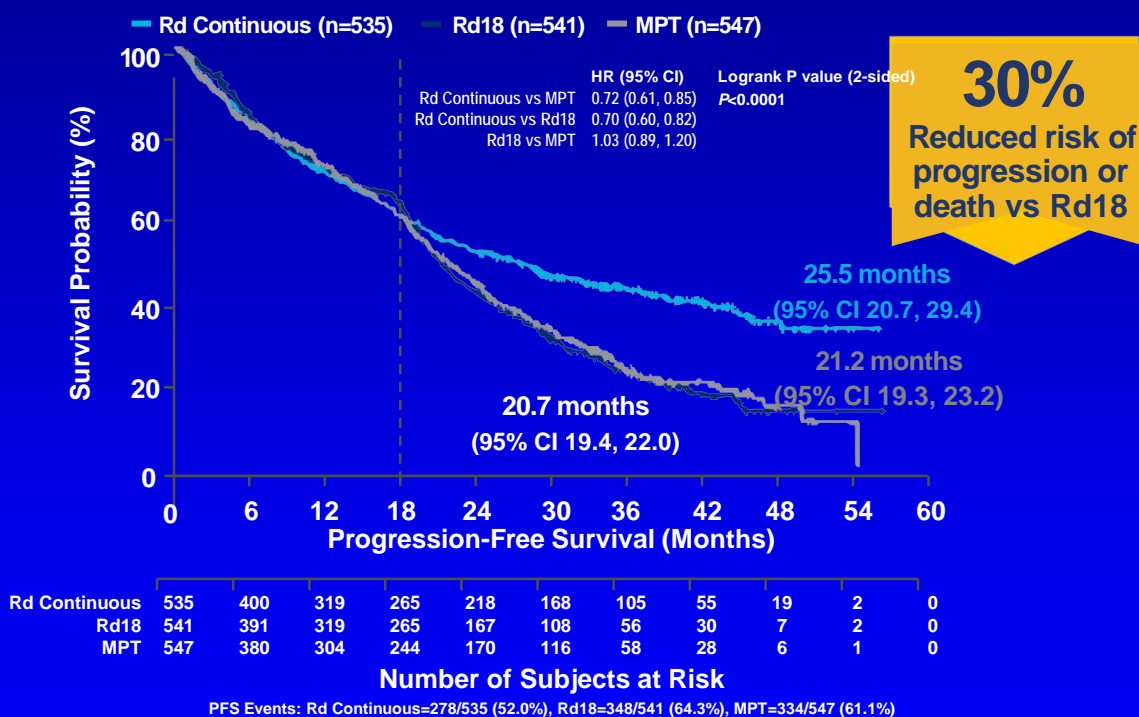
- Patients were ≥ 65 years OR < 65 years and refused or did not have access to an auto-HSCT



- The dose of LEN in the clinical trial was 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles with low-dose oral dex on Days 1, 8, 15, and 22 for 18 cycles
 - The dose for dex is 40 mg orally for patients ≤ 75 years or 20 mg orally for patients > 75 years
- In RD Continuous arm, LEN and dex were continued

Rd Continuous extended PFS vs Rd 18

Median PFS in MM-020



Rd Continuous also reduced the risk of progression or death by 28% compared with fixed-cycle MPT treatment

A Potential New Oral Proteasome Inhibitor Option for Maintenance Therapy for MM

Press Release from Takeda on 7-11-18

Phase 3 Trial of Ixazomib as Maintenance Therapy Met Primary Endpoint Demonstrating Statistically Significant Improvement in Progression-Free Survival in Patients with Multiple Myeloma Post-Transplant

TOURMALINE-MM3 is a randomized, placebo-controlled, double-blind Phase 3 study of 656 patients, designed to determine the effect of ixazomib maintenance therapy on progression-free survival (PFS), compared to placebo, in participants with multiple myeloma who have had a response (complete response [CR], very good partial response [VGPR], or partial response [PR]) to induction therapy followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT). The primary endpoint is progression-free survival (PFS). A key secondary endpoint includes overall survival (OS). For additional information:

<https://www.clinicaltrials.gov/ct2/show/NCT02181413>.

-Abstract to be Submitted for Presentation at the 2018 ASH Annual Meeting-

A Role for JAK inhibitors for MM Patients

Phase 1 Trial of Ruxolitinib (RUX), Lenalidomide and Methylprednisolone for Relapsed/Refractory Multiple Myeloma Patients

Background

- ❖ RUX is an oral, selective inhibitor of JAK1 and JAK2
- ❖ FDA-approved for the treatment of myelofibrosis and polycythemia vera
- ❖ Enhances the inhibition of growth of multiple myeloma (MM) by lenalidomide and dexamethasone² in
 - MM cell lines and primary MM cells
 - human MM xenografts in immunodeficient mice
 - ✓ LAG_K-1A (bortezomib/melphalan-sensitive)
 - ✓ LAG_K-2 (bortezomib/melphalan-resistant)

Study Design

Dose escalation/de-escalation schema

Dose Level	Ruxolitinib Days 1-28	Lenalidomide Days 1-21	Methylprednisolone Days 1-28
Dose Level -2	5 mg QD	2.5 mg QD	40 mg QOD
Dose Level -1	5 mg BID	2.5 mg QD	40 mg QOD
Dose Level 0	5 mg BID	5 mg QD	40 mg QOD
Dose Level 1	10 mg BID	5 mg QD	40 mg QOD
Dose Level 2	15 mg BID	5 mg QD	40 mg QOD
Dose Level 3	15 mg BID	10 mg QD	40 mg QOD

NO DLTs OBSERVED

28-days/cycle

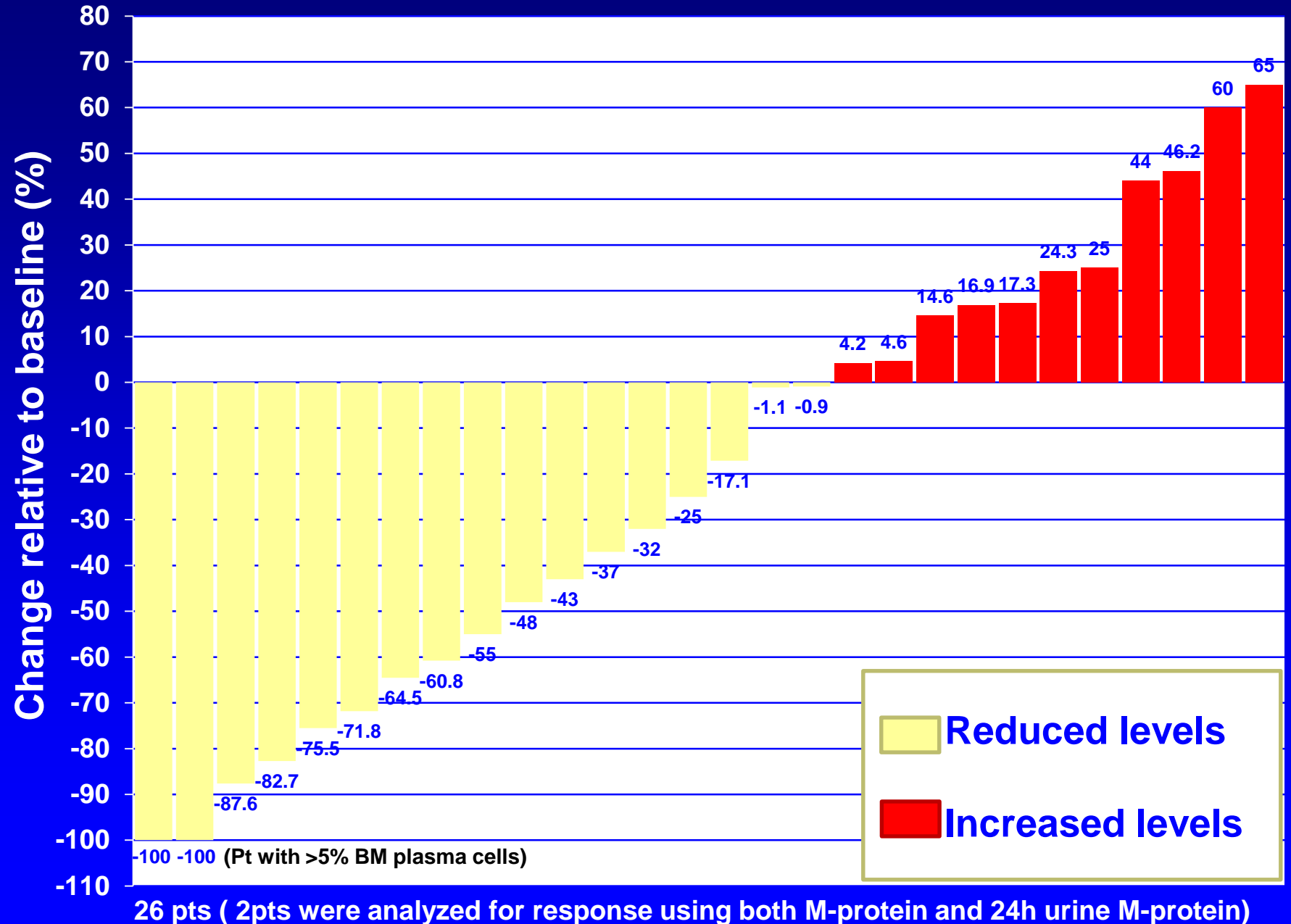
Response Summary/Efficacy Endpoints

❖ Response rates for all 26 evaluable patients

Response Status	# of Pts (%)
Complete Response (CR)	1 (4)
Very Good Partial Response (VGPR)	1 (4)
Partial Response (PR)	8 (31)
Minimal Response (MR)	3 (11)
Stable Disease (SD)	10 (39)
Progressive Disease (PD)	3 (11)
ORR (CR+VGPR+PR)	10 (39)
CBR (CR+VGPR+PR+MR)	13* (50)

***All 13 responding pts were refractory to lenalidomide (progressed while on or w/i 8 wks of last dose)**

Best Response: Waterfall Plot of % Change in Myeloma Markers



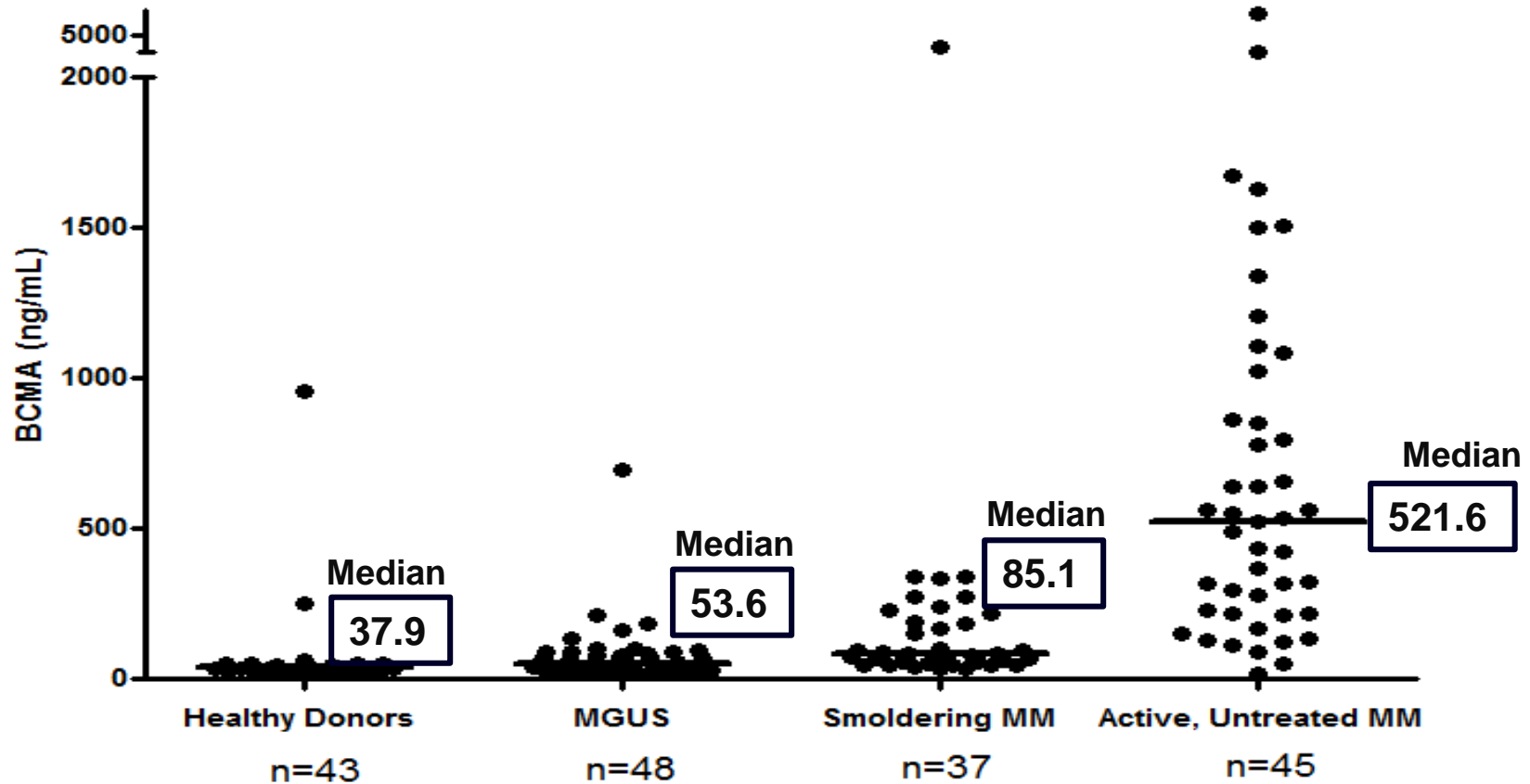
Conclusions

- ❖ This is the first clinical trial demonstrating activity of JAK inhibitors for treating MM patients
- ❖ The combination of the JAK1/2 inhibitor ruxolitinib, lenalidomide and methylprednisolone overcomes resistance to lenalidomide for half of heavily pre-treated RRMM patients
 - ✓ All responding patients were lenalidomide refractory
- ❖ This all oral combination was well tolerated with few \geq Grade 3 AEs, including cytopenias
- ❖ *These promising results have led to expansion of the current trial, and provide the basis for exploration of this and other JAK inhibitor-containing combinations for treating patients with MM and other malignant diseases*

Serum B-cell Maturation Antigen (sBCMA) Levels in MM Patients

- **Are elevated**
- **Correlate with clinical status (response vs progressive disease)**
- **Can be used to track response to treatment**
- **Predicts PFS and OS**

sBCMA Levels* Are Increased in Patients w/ Monoclonal Gammopathies

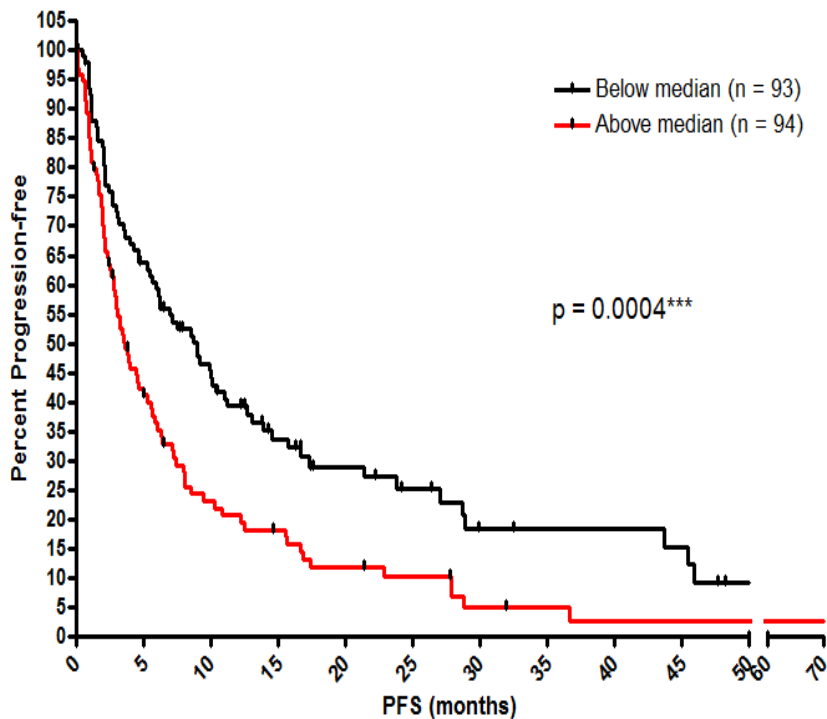


Median Serum BCMA Levels (ng/mL):
Healthy Donors: 37.9 (range, 14.1-958.1)
MGUS: 53.6 (range, 11.7-693.3)
Smoldering MM: 85.1 (range, 31.6-2956.0)
Active, Untreated MM: 521.6 (range, 17.8-9027.0)

p-values:
Healthy Donors vs MGUS: p=0.0109
Healthy Donors vs Smoldering MM: p<0.0001
Healthy Donors vs Active, Untreated MM: p<0.0001
MGUS vs Smoldering MM: p=0.0006
MGUS vs Active, Untreated MM: p<0.0001
Smoldering MM vs Active, Untreated MM: p<0.0001

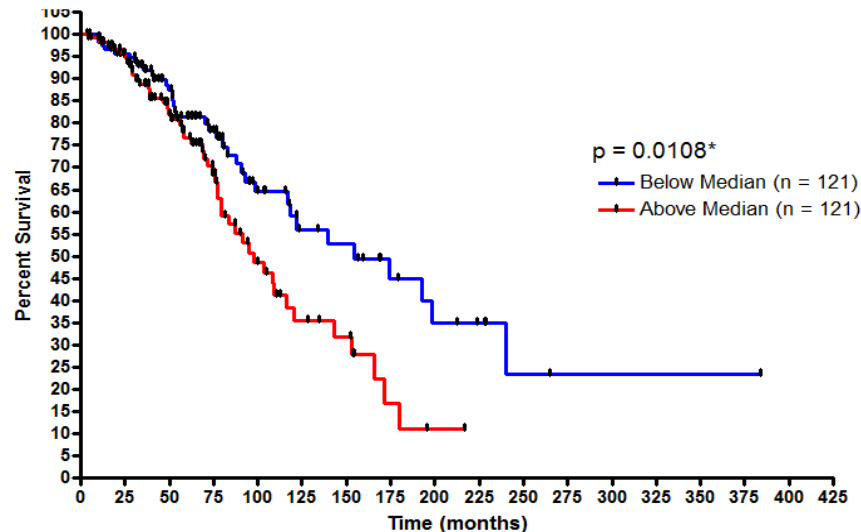
*serum diluted 1:500

sBCMA Levels Above Median Predict Shorter Progression-free¹ And Overall Survival² of MM Patients



Range (ng/mL): Below median: 14.39 – 320.31
Above median: 332.56 – 23051.74

Median PFS:
Below median: 9.0 months
Above median: 3.6 months



Range (ng/mL): Below median: 14.39 – 136.21
Above median: 136.21 – 23051.74

Median OS:
Below median: 155 Months
Above median: 98 months

¹obtained at start of new treatment

²from first sample

Compare Changes in sBCMA to Both Serum M-Protein and SFLC among MM Patients Receiving New Therapy³

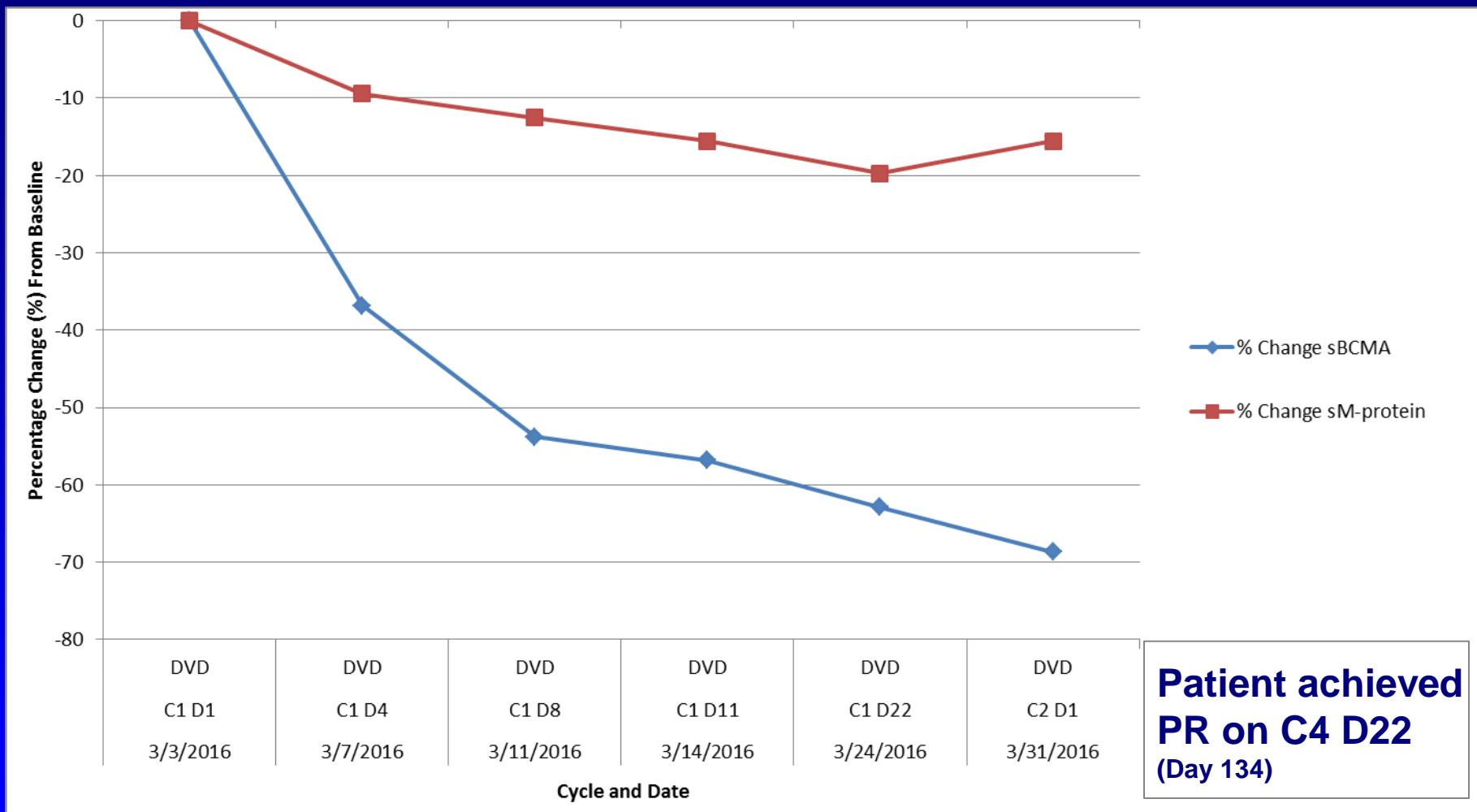
Rationale

- sBCMA has a much more rapid turnover in blood (half-life in blood is 24-36 hours¹) than M-protein
- sBCMA levels are independent of renal function unlike SFLC²

Thus, sBCMA may provide a more rapid and accurate assessment of response status for MM patients

Patient 2832

Comparison of sBCMA to M-Protein During First Cycle of DVD*



*DVD = dexamethasone, bortezomib and pegylated liposomal doxorubicin

IgG kappa MM

Response (by IMWG) as of C1 D22: SD

Baseline sBCMA: 684.9 ng/mL

Baseline serum M-Protein: 3.6 g/dL

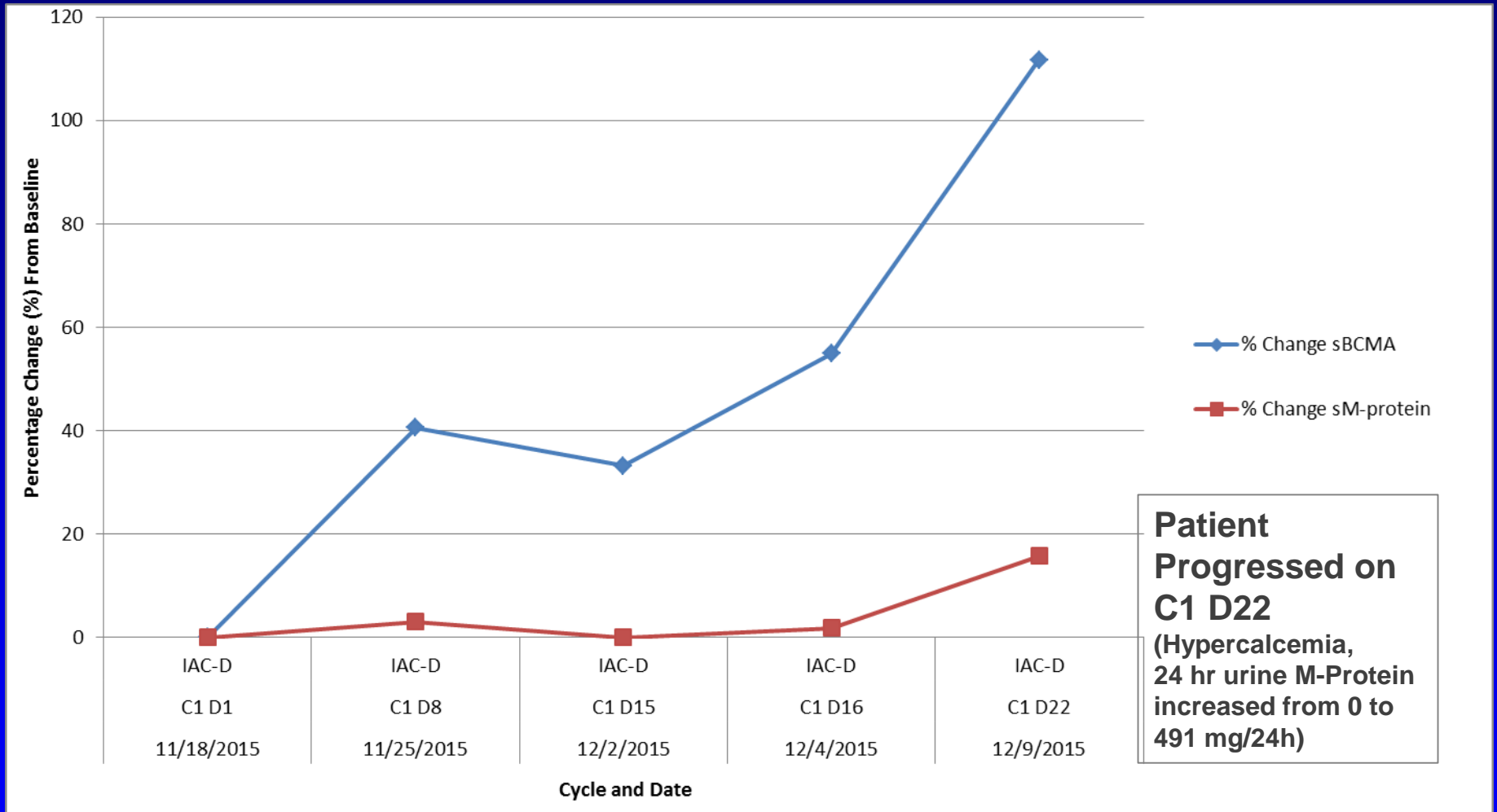
Baseline SFLC: 270.9 mg/L kappa; 6.4 mg/L lambda

Baseline serum creatinine: 0.7 mg/dL

Baseline QIGS: IgG: 4200 mg/dL; IgA: 15 mg/dL; IgM: 16 mg/dL

Patient 2763

Comparison of sBCMA to M-Protein During First Cycle of IAC-D*



*IAC-D = ixazomib, vitamin C, cyclophosphamide, dexamethasone

IgG kappa MM

Response (by IMWG) as of C1 D22: PD

Baseline sBCMA: 444.3 ng/mL

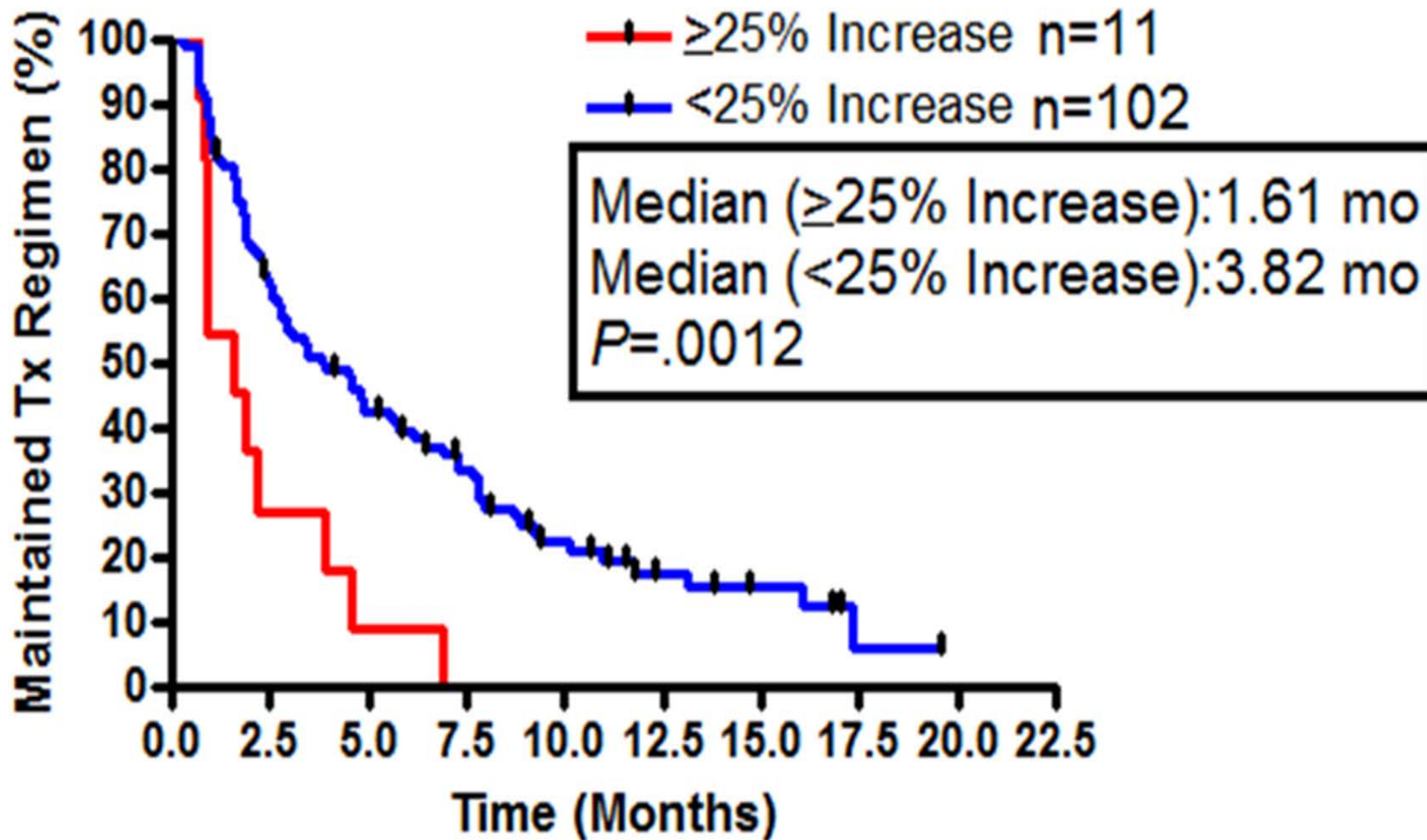
Baseline serum M-Protein: 3.3 g/dL

Baseline SFLC: 49.6 mg/L kappa; 1.6 mg/L lambda

Baseline serum creatinine: 1.7 mg/dL

Baseline QIGS: IgG: 2620 mg/dL; IgA: 15 mg/dL; IgM: 15 mg/dL

Time on treatment based on percentage change ($\geq 25\%$ or $< 25\%$) in sBCMA levels on C1D8



Serum B-cell Maturation Antigen (sBCMA) Levels in MM Patients

- **Are elevated**
- **Correlate with clinical status (response vs progressive disease)**
- **Can be used to track response to treatment**
 - **rapid turnover allows quicker assessment of response**
 - **independent of renal function**
 - **more reliable than SFLC**
 - **those with nonsecretory disease**
- **Predicts PFS and OS**