Multiple Myeloma: Induction, Consolidation and Maintenance Therapy

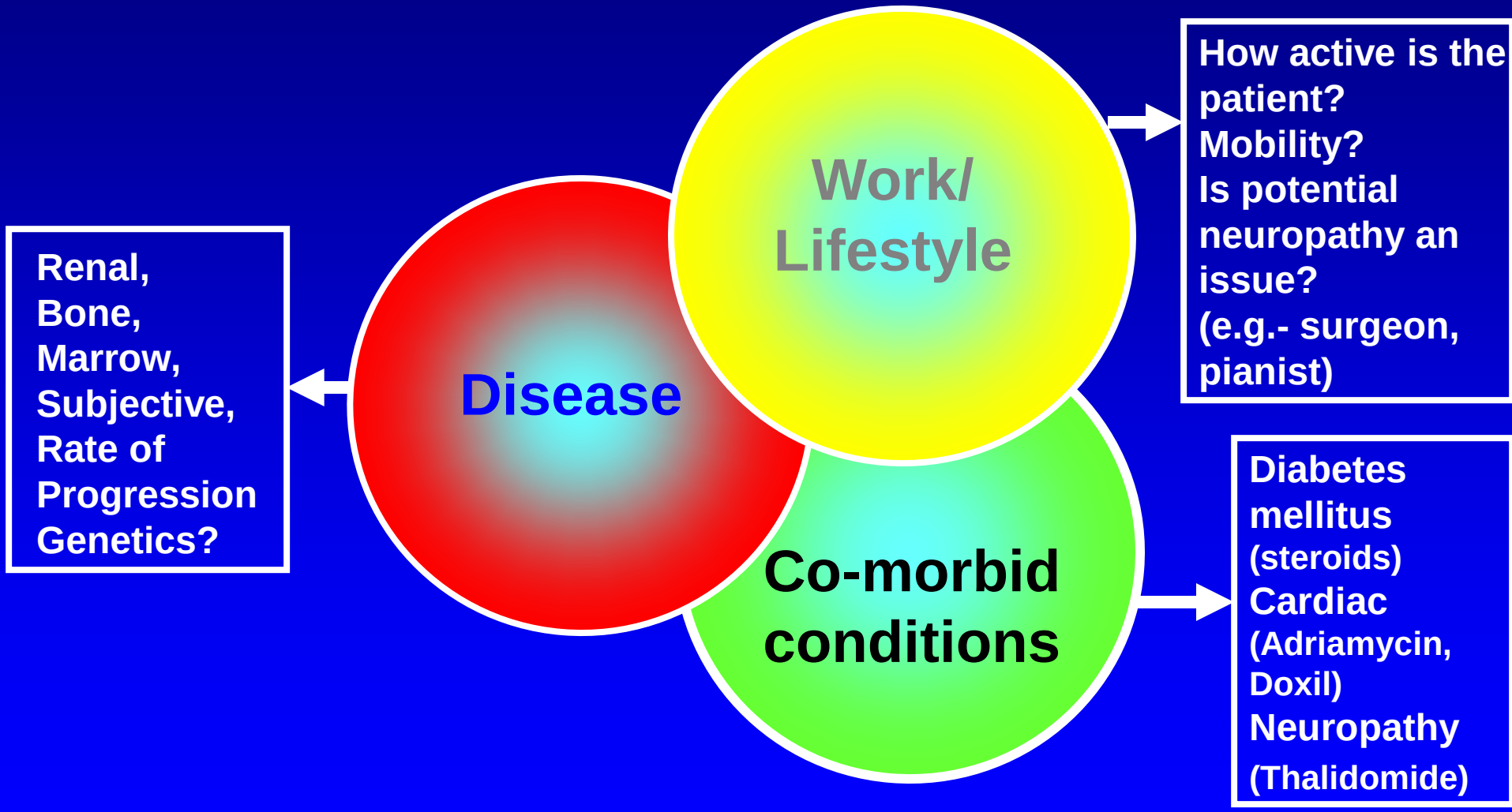
James R. Berenson, MD

Medical & Scientific Director
Institute for Myeloma & Bone Cancer Research
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 study[1]
  - 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 study[2]

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

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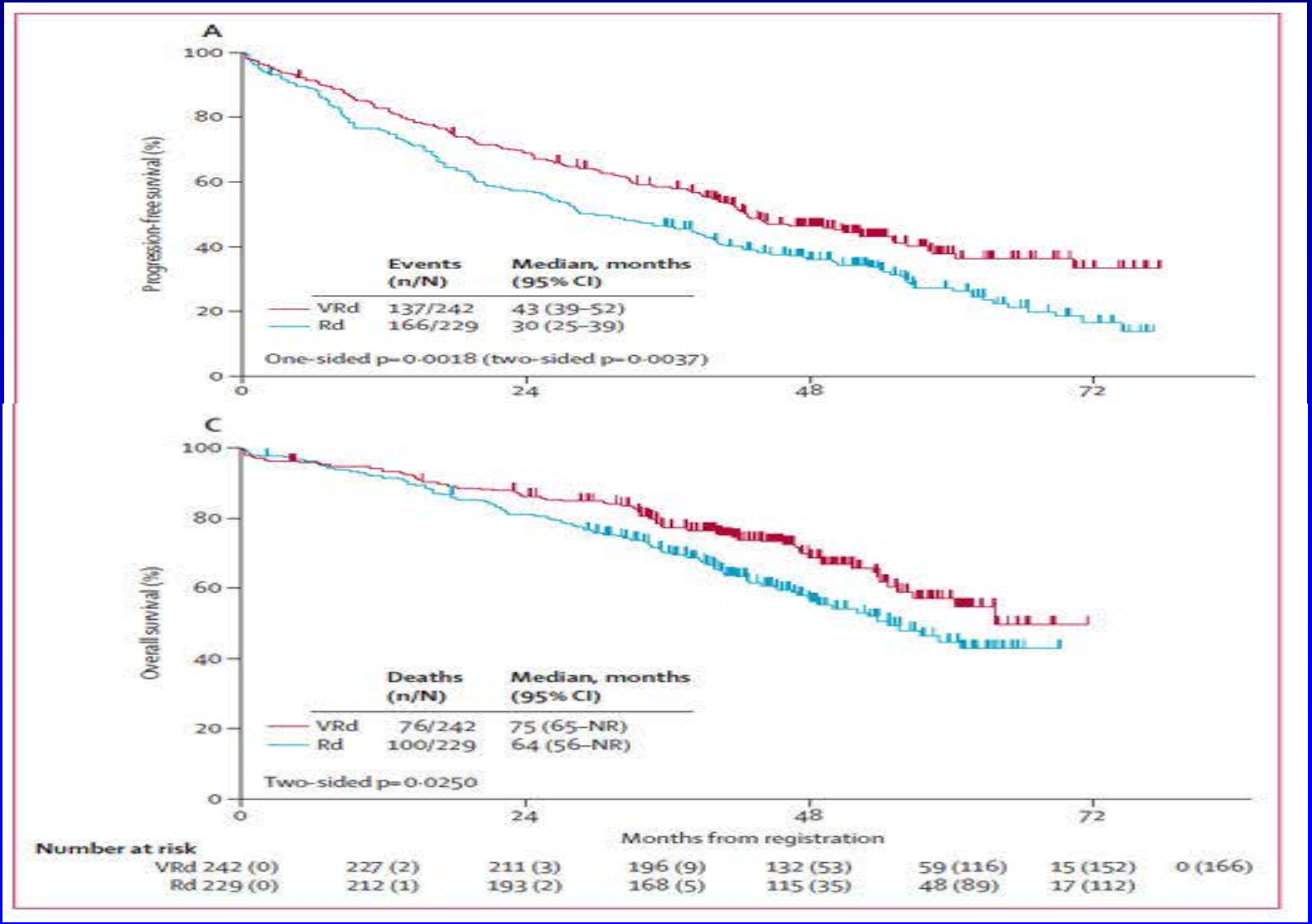
Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): A randomised, open-label, phase 3 trial



Durie et al. Lancet 2017

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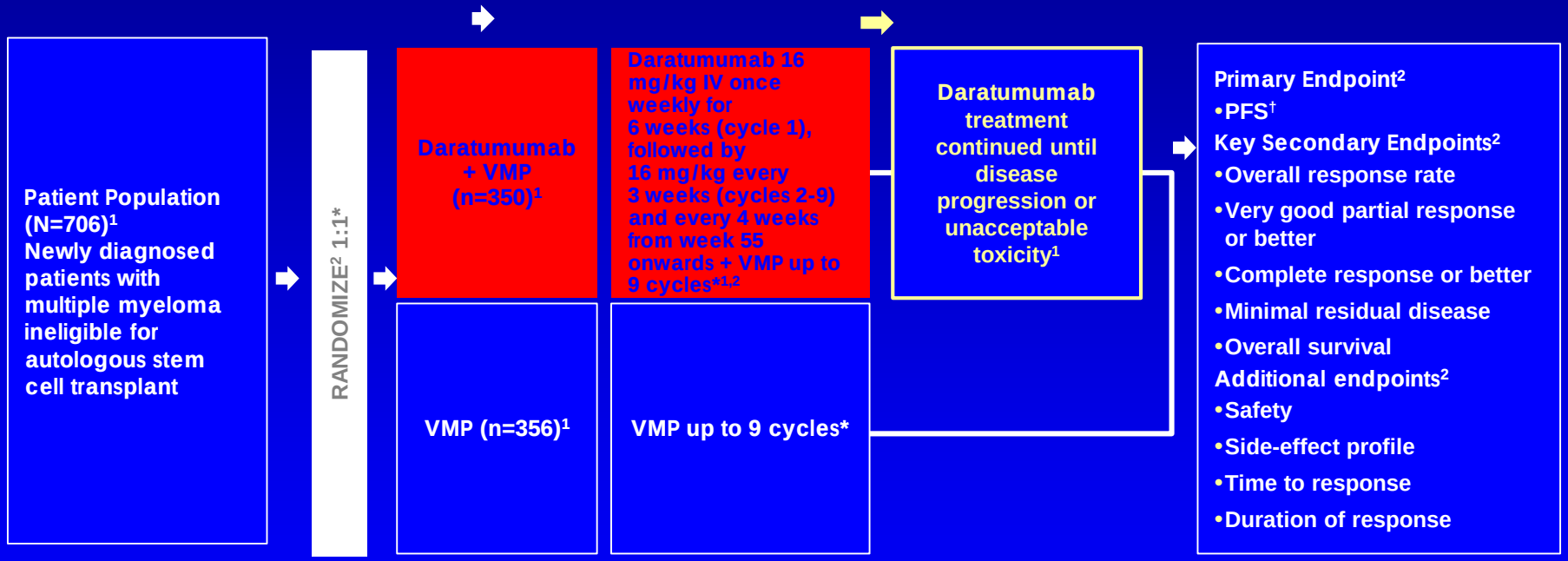
ALCYONE: A Randomized, Open-Label, Active-Controlled, Multicenter, Phase 3 Trial of Daratumumab + VMP vs VMP



- 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 trials[3-5]

IV = intravenous; PFS = progression-free survival.

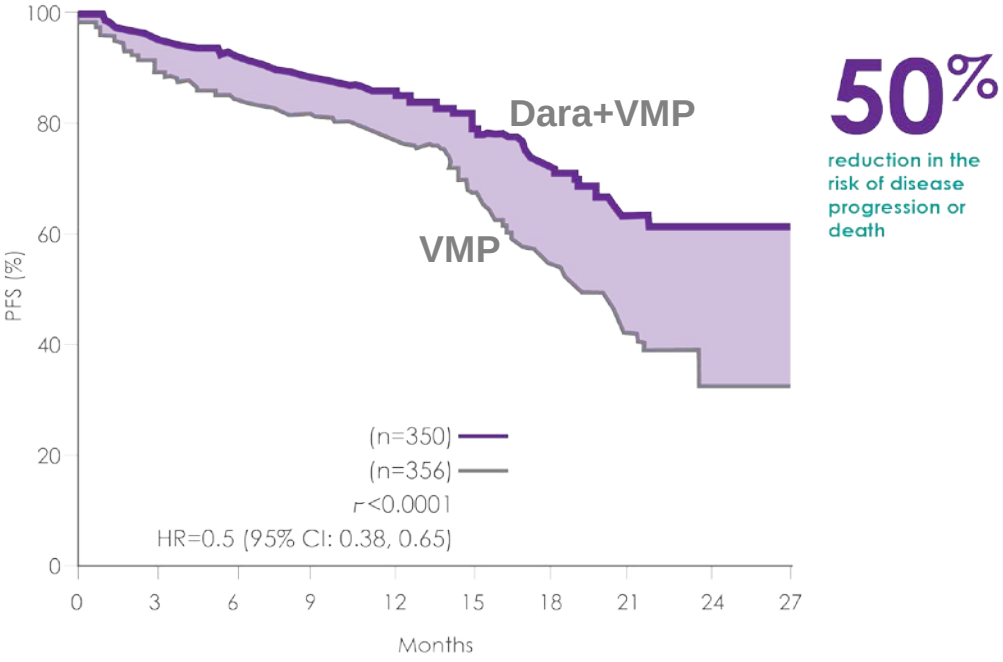
*Participants received bortezomib 1.3 mg/m^2 as subcutaneous injection, twice weekly at weeks 1, 2, 4, and 5 (cycle 1) followed by once weekly at weeks 1, 2, 4, and 5 (cycles 2 to 9); melphalan 9 mg/m^2; and prednisone 60 mg/m^2 were orally administered on days 1 to 4 of the nine 6-week cycles (cycles 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.

Mateos et al. N Engl J Med 2018

Daratumumab + VMP Significantly Improved PFS vs VMP Alone*

Progression-Free Survival[1]



- Median follow-up was 16.5 months[2]
- Median PFS had not yet been reached with Daratumumab + VMP vs 18.1 months with VMP alone[1]

HR = hazard ratio
*Efficacy was evaluated by PFS based on International Myeloma Working Group criteria.

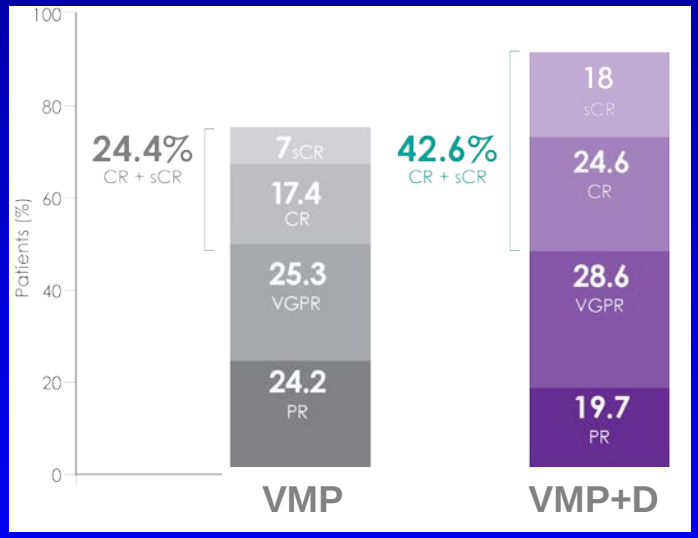
1. Daratumumab® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 2. Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528.

Mateos et al. N Engl J Med 2018

Significant Improvement in ORRs with Daratumumab + VMP

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

Overall Response Rate[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 group[1]**

Depth of Response

- **42.6% of patients achieved CR or better with Daratumumab + VMP vs 24.4% with VMP alone[1]**

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.

Mateos et al. N Engl J Med 2018

ALCYONE Trial

- Addition of daratumumab to VMP improves ORR, CR and most importantly PFS
- No additional safety issues were identified including cyotpenias

- 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

Mateos et al. N Engl J Med 2018

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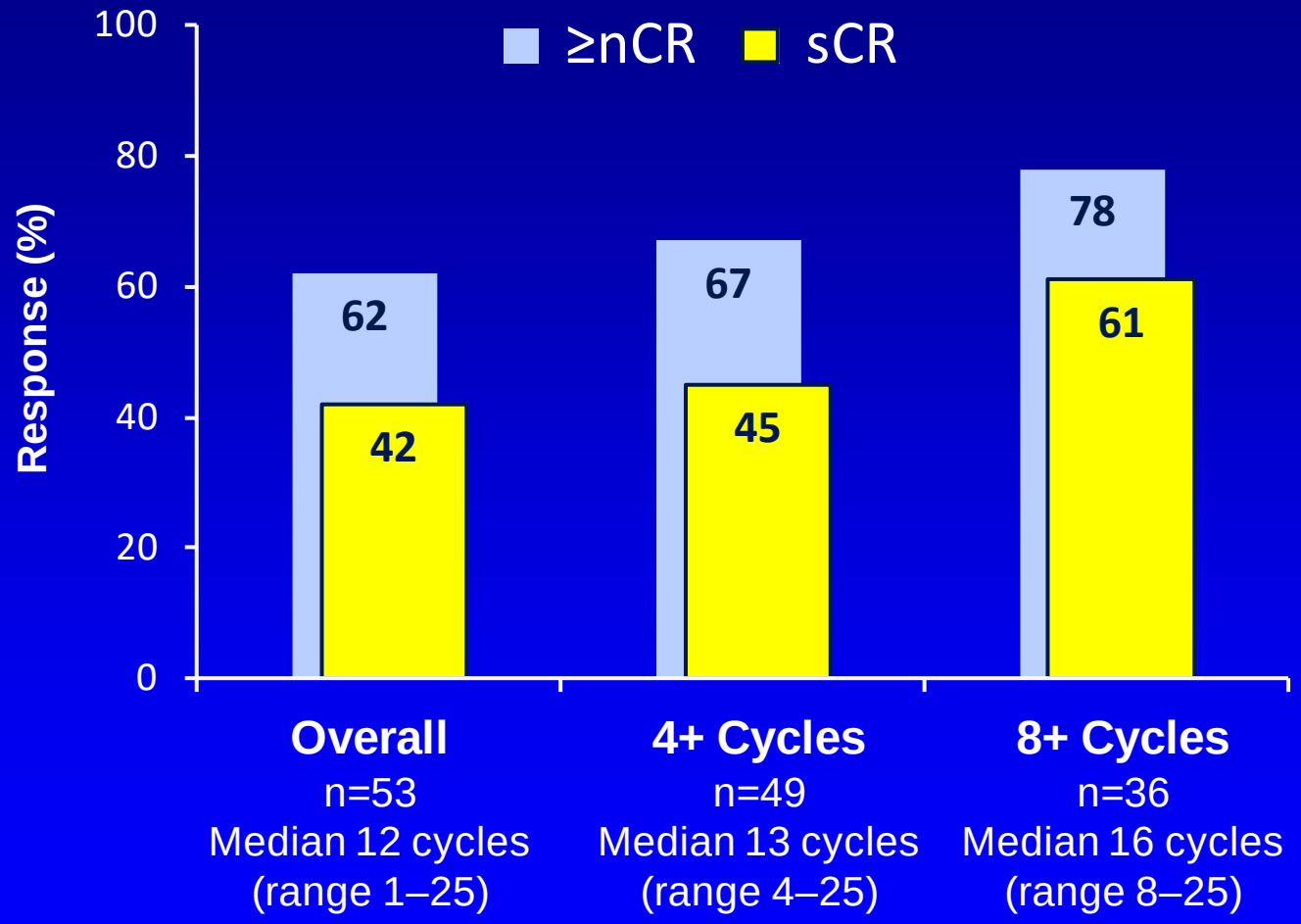
Now the Highest CR Rates are w/o HDT:
Frontline Carfilzomib, Lenalidomide and Dexamethasone

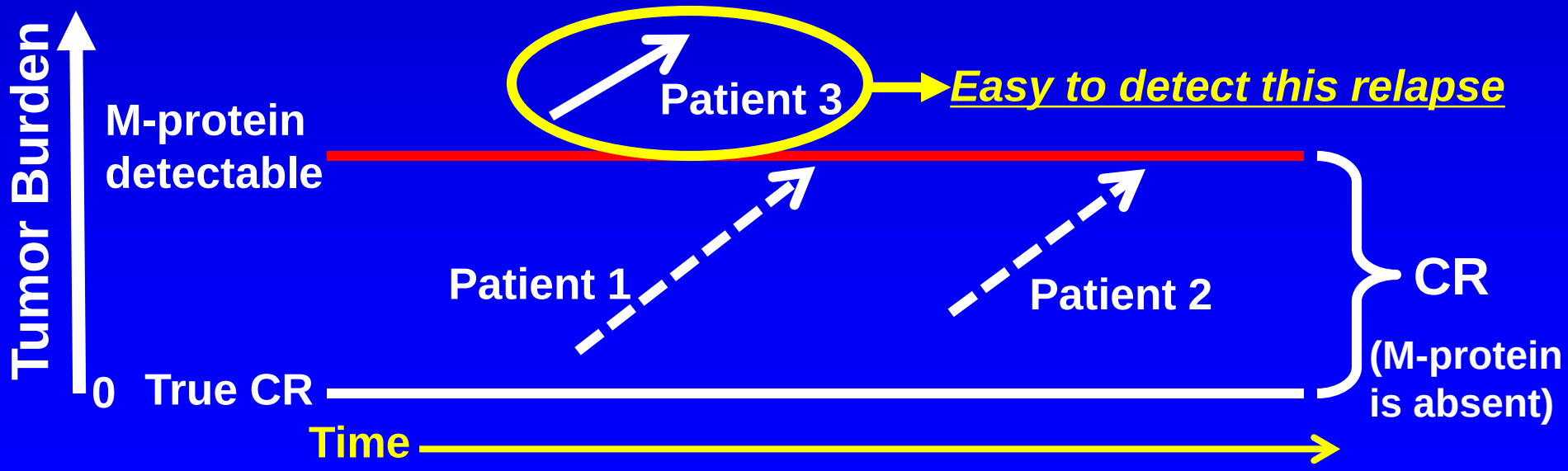


Jakubowiak AJ, et al. *ASCO 2012.*, Blood 2012; 120(9):1801-9

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

Attal et al. N Engl J Med 1996; Child et al. N Engl J Med 2003; Blade et al. Blood 2006; Fermand et al. 1998; Barlogie et al. J Clin Oncol 2006; Palumbo et al. N Engl J Med 2014; Attal et al. N Engl J Med 2017; Faussner et al. Anticancer Res 2012

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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

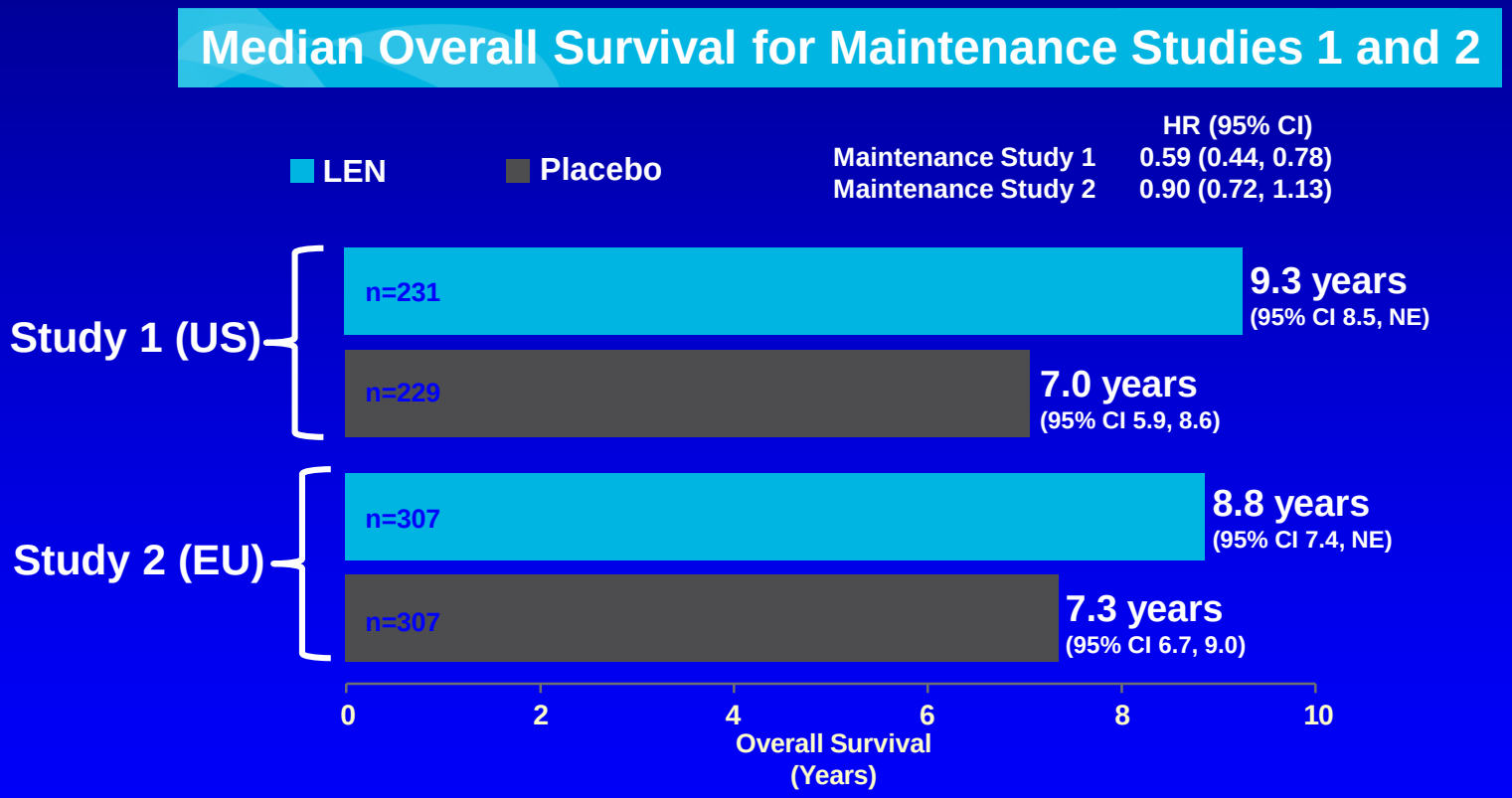
- Patients aged 18-70 years in Study 1; <65 years in Study 2 at the time of diagnosis
- In both studies, patients needed at least a stable disease response following hematologic recovery and CrCl ≥30 mL/min

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



Thus, maintenance LEN therapy is standard of care posttransplant

Transplants in 2017 for Myeloma

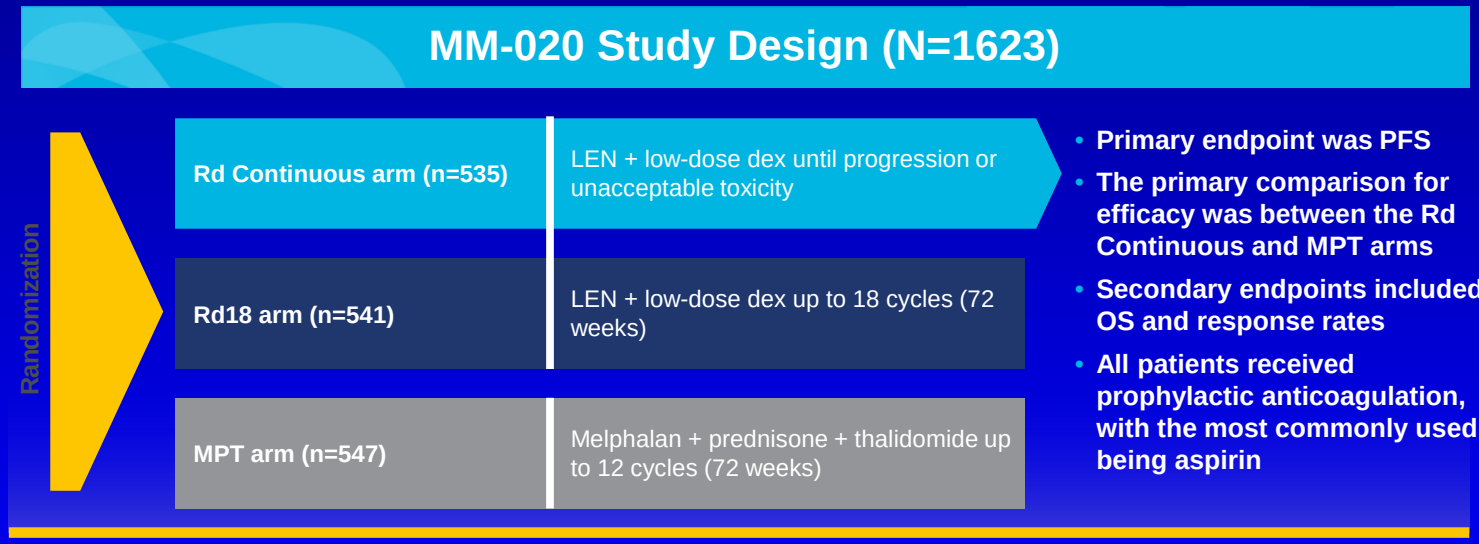
- No overall survival (OS) advantage of early autotransplant from any recent randomized trials
- Highest CR rates are w/o transplant (i.e. CLD)
- All patients now receive posttransplant maintenance lenalidomide so there is no treatment-free interval
- Treatment options are rapidly increasing
  - Thus, 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

NON-TRANSPLANT

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**

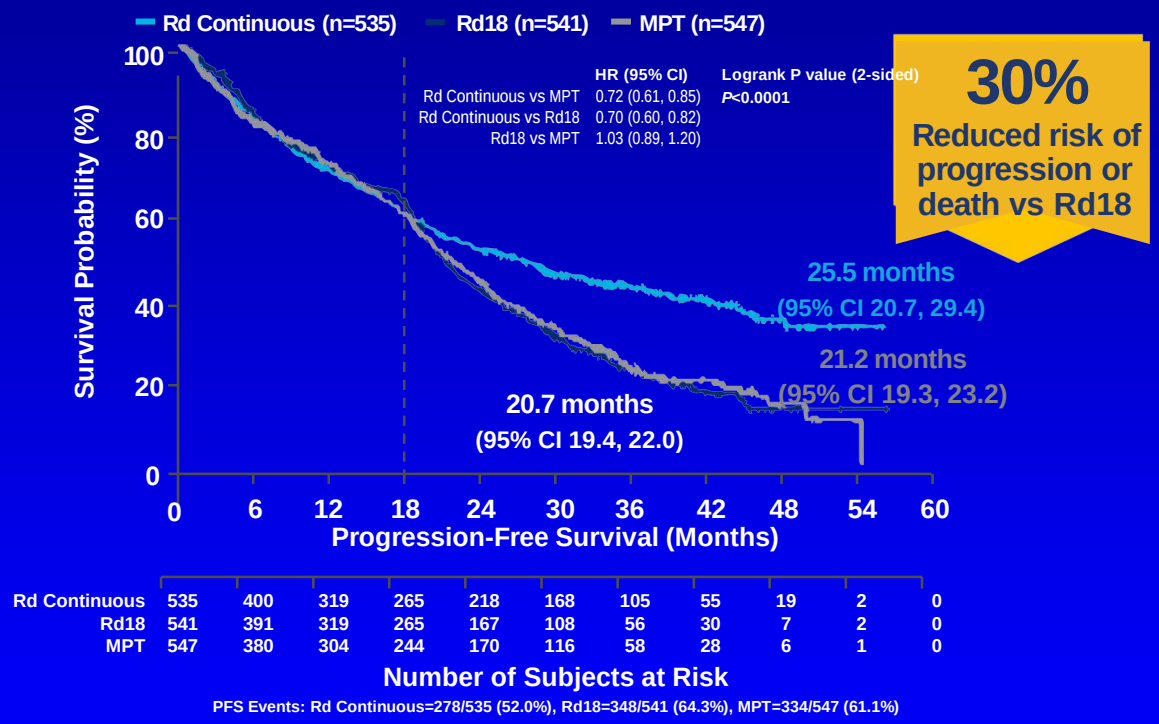


- **The dose of LEN in the clinical trial was 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles with low-dose oral dex on Days 1, 8, 15, and 22 for 18 cycles**
  - **The dose for dex is 40 mg orally for patients ≤75 years or 20 mg orally for patients >75 years**
- **In RD Continuous arm,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

References: 1. Lenalidomide [package insert]. Summit, NJ: Celgene Corp; 2017. 2. National Institutes of Health. Search Results: Multiple Myeloma Clinical Trial. Clinicaltrials.gov. Accessed December 6, 2016.

Rd Continuous extended PFS vs Rd 18

Median PFS in MM-020



PFS Events: Rd Continuous=278/535 (52.0%), Rd18=348/541 (64.3%), MPT=334/547 (61.1%)

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 dexamethasone[2] in
  - MM cell lines and primary MM cells
  - human MM xenografts in immunodeficient mice
    - ✓ LAGκ-1A (bortezomib/melphalan-sensitive)
    - ✓ LAGκ-2 (bortezomib/melphalan-resistant)

Berenson et al. ASCO 2018

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

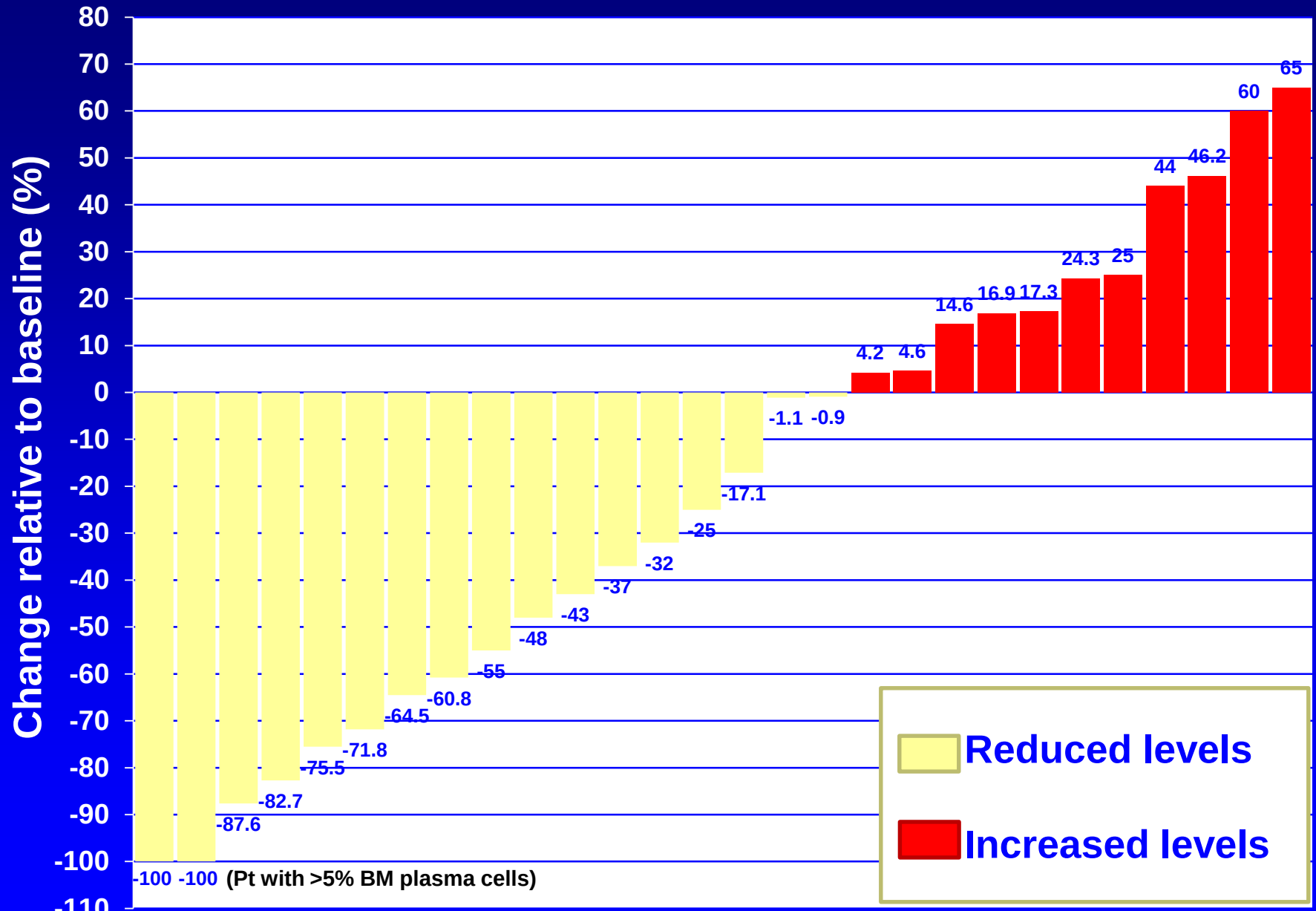
Response Summary/Efficacy Endpoints

❖ 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



26 pts (2pts were analyzed for response using both M-protein and 24h urine M-protein)

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 ≥ Grade 3 AEs, including cytopenias**

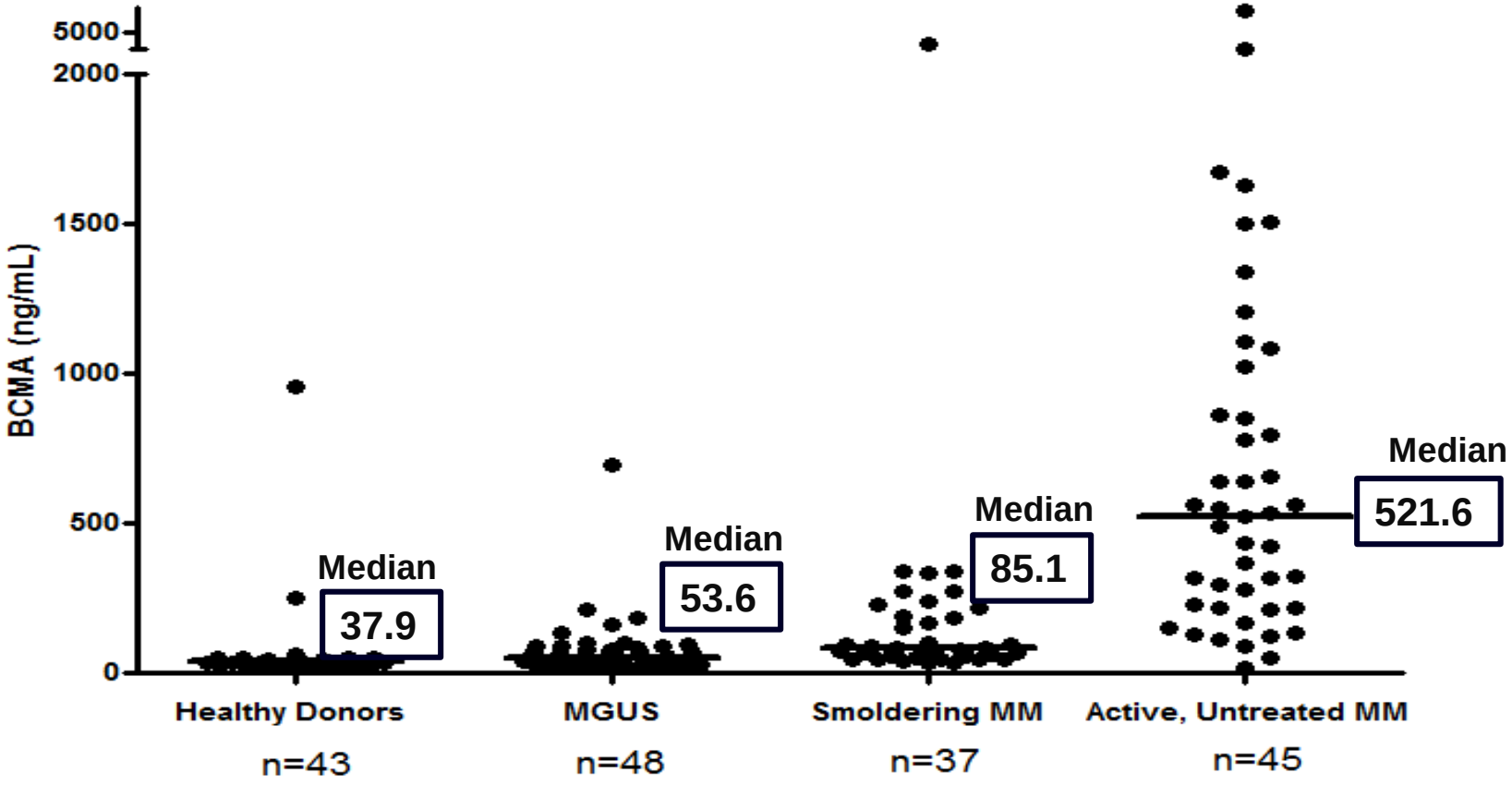
- ***These promising results have led to expansion of the current trial, and provide the basis for exploration of this and other JAK inhibitor-containing combinations for treating patients with MM and other malignant diseases***

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

Ghermezi et al. Haematologica 2017; Udd et al. IMW 2017

sBCMA Levels* Are Increased in Patients w/ Monoclonal Gammopathies



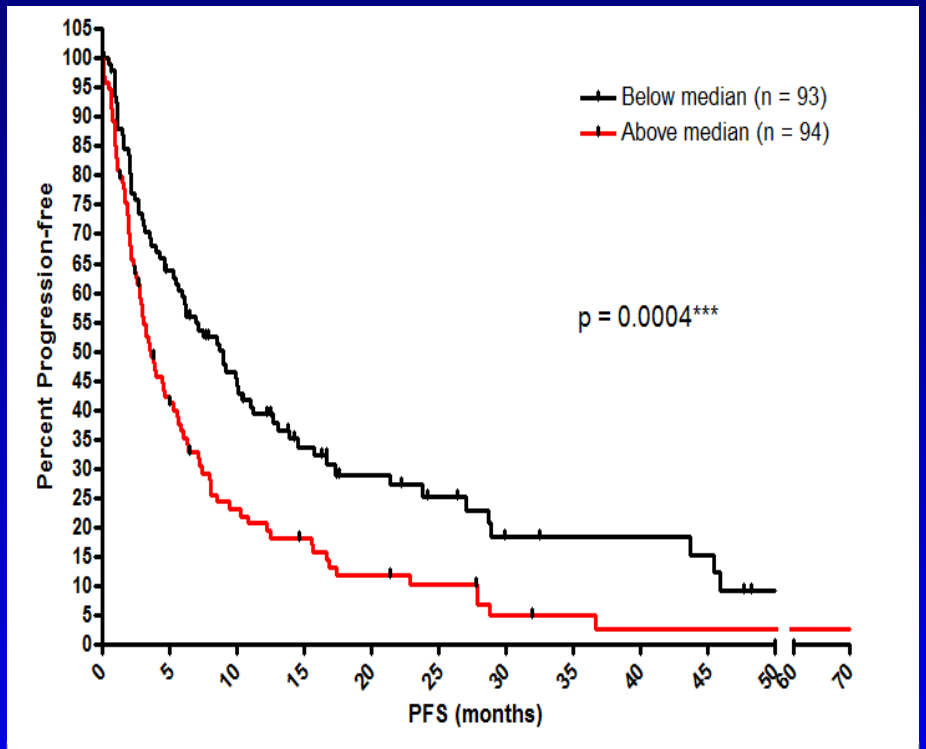
Median Serum BCMA Levels (ng/mL):
Healthy Donors: 37.9 (range, 14.1-958.1)
MGUS: 53.6 (range, 11.7-693.3)
Smoldering MM: 85.1 (range, 31.6-2956.0)
Active, Untreated MM: 521.6 (range, 17.8-9027.0)

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

Ghermezi et al. Haematologica 2017

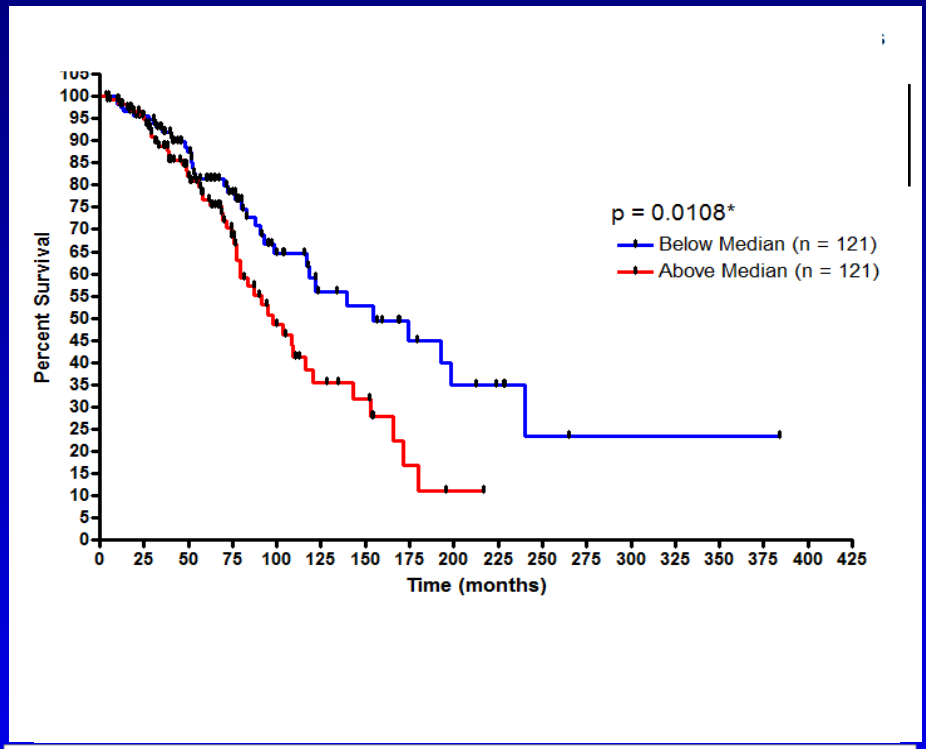
sBCMA Levels Above Median Predict Shorter Progression-free[1] And Overall Survival[2] of MM Patients



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

[1]obtained at start of new treatment



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

[2]from first sample

Ghermezi et al. Haematologica 2017

Compare Changes in sBCMA to Both Serum M-Protein and SFLC among MM Patients Receiving New Therapy[3]

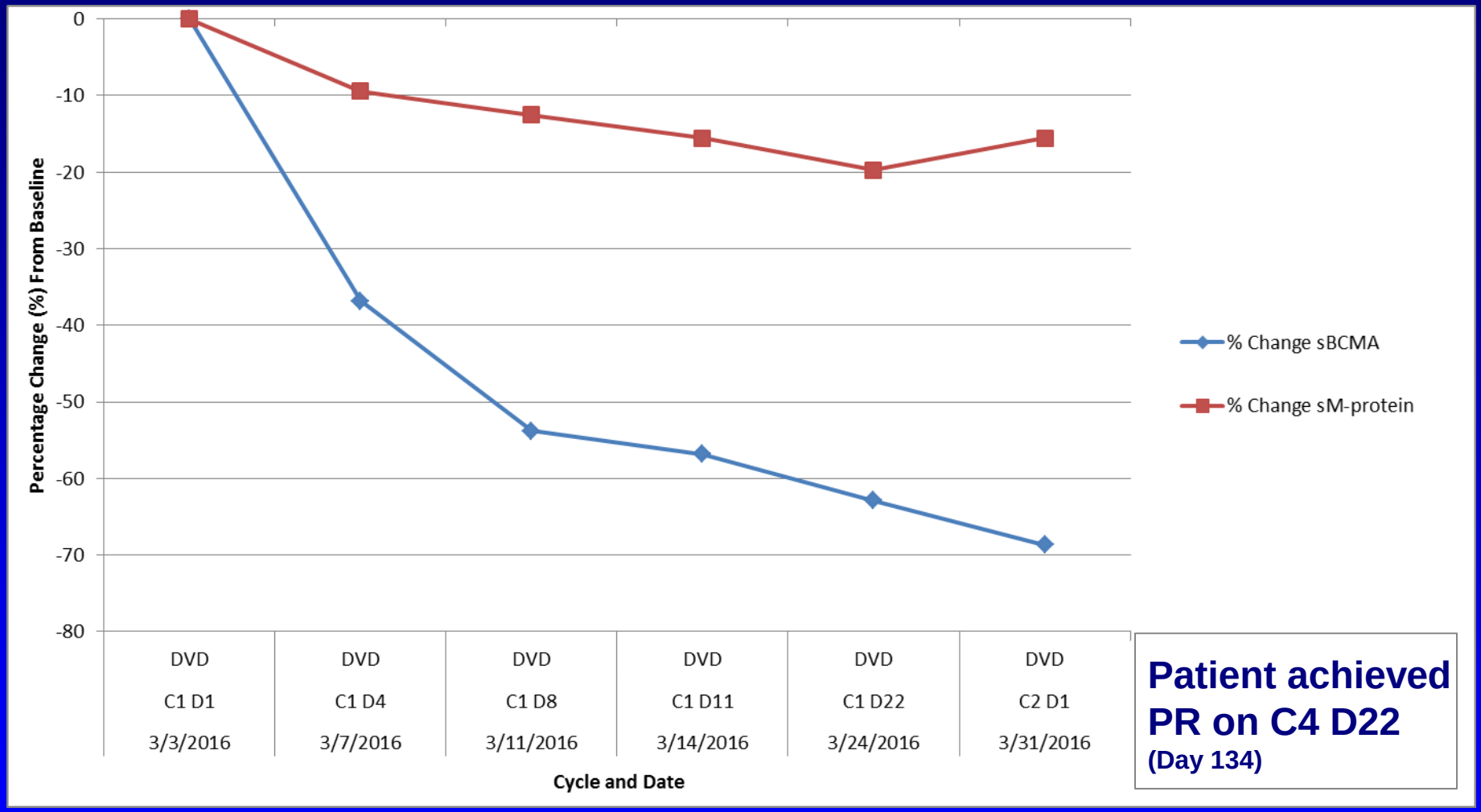
Rationale

- sBCMA has a much more rapid turnover in blood (half-life in blood is 24-36 hours[1]) than M-protein
- sBCMA levels are independent of renal function unlike SFLC[2]

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

[1]Sanchez et al. Clin Cancer Res 2016; [2]Ghermezi et al. Haematologica 2017; [3]Udd et al. IMW 2017

Patient 2832
Comparison of sBCMA to M-Protein During First Cycle of DVD*



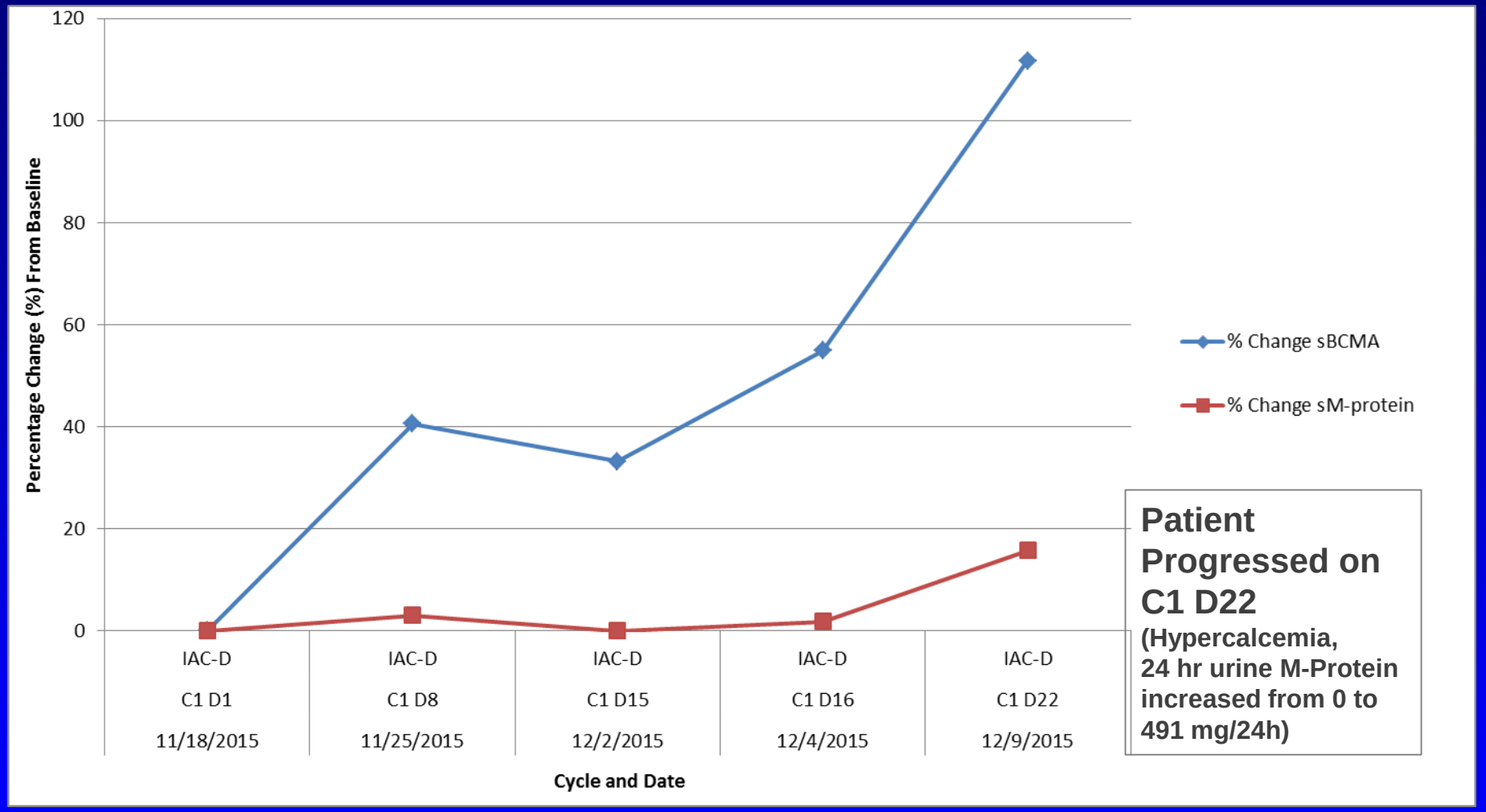
Patient achieved PR on C4 D22
(Day 134)

*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*

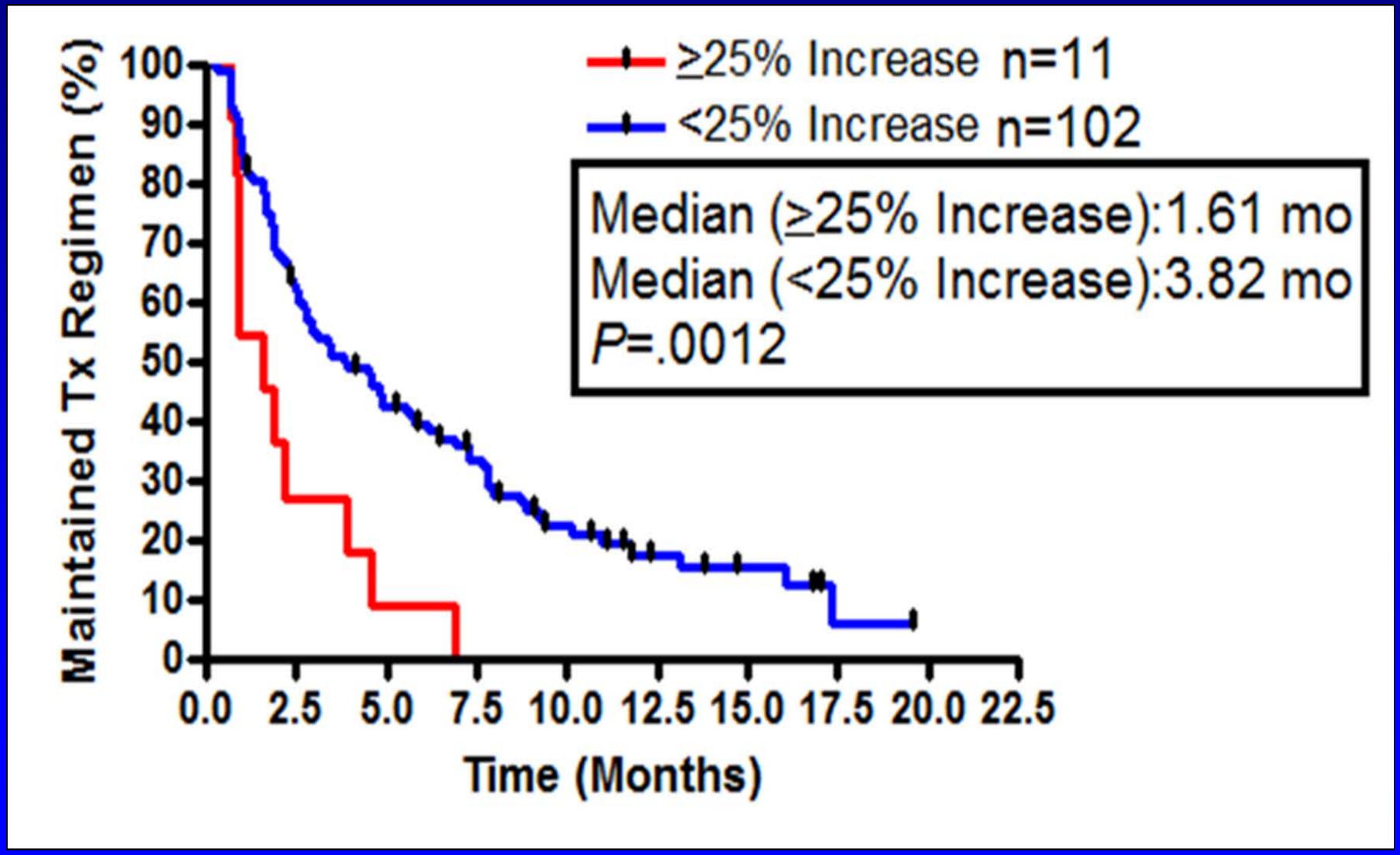


*IAC-D = ixazomib, vitamin C, cyclophosphamide, dexamethasone

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 (≥25% or < 25%) in sBCMA levels on C1D8



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- 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

Ghermezi et al. Haematologica 2017; Udd et al. IMW 2017