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

James Berenson, Jennifer To, Carley Turner, Tanya M. Spektor, Benjamin Eades, Regina A. Swift, Gary Schwartz, Shahrooz Eshaghian, Laura Stampleman, Robert A. Moss, Stephen Lim, and Robert Vescio

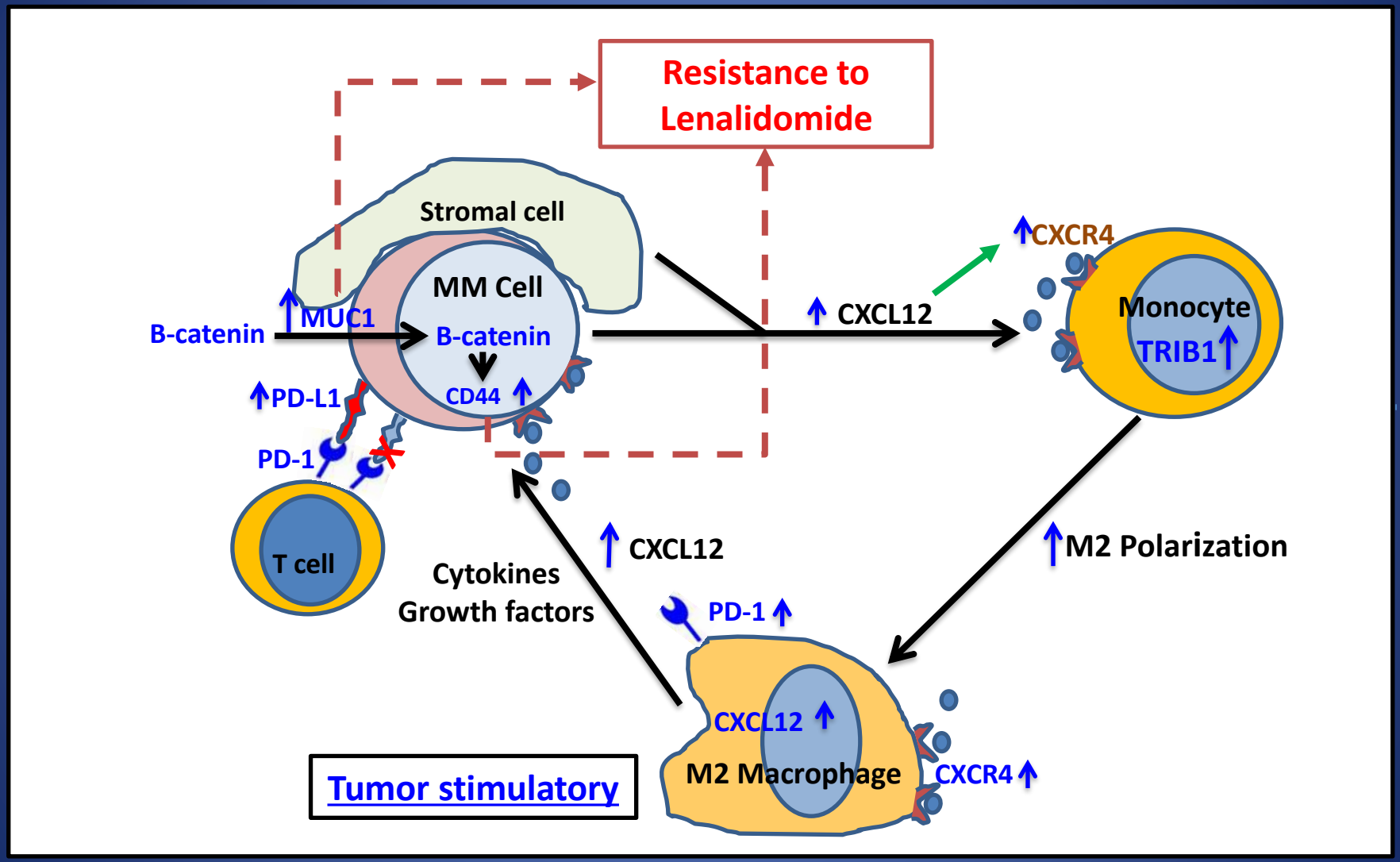
Oncotherapeutics, OncoTracker, and
Institute for Myeloma and Bone Cancer Research
West Hollywood, CA

Background: JAK Inhibitor Ruxolitinib in Myeloma

- Oral, selective inhibitor of JAK1 and JAK2
- FDA-approved for the treatment of myelofibrosis and polycythemia vera[1]
- Enhances the inhibition of growth of multiple myeloma (MM) by lenalidomide and dexamethasone[2] in:
  - MM cell lines U266 and RPMI8226
  - primary tumor cells derived from MM patients
  - human MM xenografts in immunodeficient mice
    - ✓ LAGκ-1A (bortezomib/melphalan-sensitive)
    - ✓ LAGκ-2 (bortezomib/melphalan-resistant)

[1]Rosenthal, A. & Mesa, R.A. (2014). Janus kinase inhibitors for the treatment of myeloproliferative neoplasms. *Expert Opin. Pharmacother.* **15**, 1265–76
[2]Chen, H., Sanchez, E., Li, M., et al. (2014). Anti-myeloma activity by the combination of the JAK2 inhibitor ruxolitinib with lenalidomide and corticosteroids. *Blood,* 124:2114

Rationale for JAK1/2 Inhibition in Combination with Lenalidomide for Treatment of MM



[2]Chen, H., Sanchez, E., Li, M., et al. (2014). Anti-myeloma activity by the combination of the JAK2 inhibitor ruxolitinib with lenalidomide and corticosteroids. *Blood,* 124:2114

[3]Chen, H., Sanchez, E., Li, M., et al. (2014). Increased M2 macrophages in multiple myeloma patients with progressive disease and down-regulated polarization with the JAK2 inhibitor ruxolitinib. *Blood.* 124:4106

[4]Satoh T, Kidoya H, Naito, H., et al. (2013). Critical role of Trib1 in differentiation of tissue-resident M2-like macrophages. *Nature.* 495:524-528

[5]Yin, L., Tagde, A., Gali, R., et al. (2017). Muc1-C is a target in lenalidomide resistant multiple myeloma. *BJH.* 178:914-926

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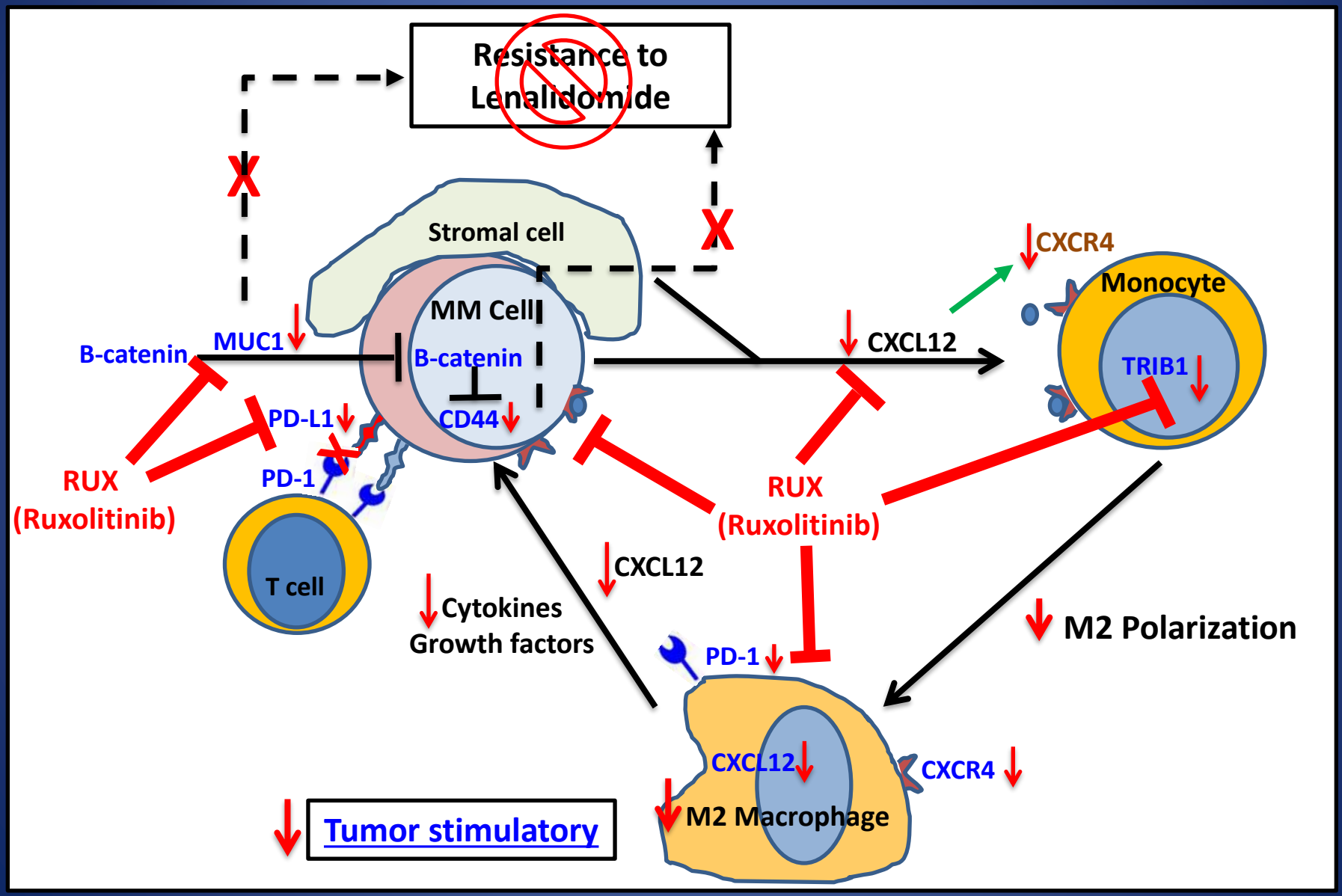


Study Design

- Phase 1, multicenter, open-label study evaluating the safety and efficacy of an all oral regimen of ruxolitinib, lenalidomide and methylprednisolone for relapsed/refractory (RR) MM patients

- A traditional 3+3 dose escalation

- Key inclusion criteria
  - ✓ currently show progressive disease
  - ✓ received ≥ 3 lines of prior anti-MM therapy
    - ➢ failed lenalidomide and a proteasome inhibitor
  - ✓ CrCl ≥ 60 mL/min
  - ✓ Absolute neutrophil count ≥ 1.5 x 10^9/L
  - ✓ Platelet count ≥ 75 x 10^9/L
  - ✓ Hemoglobin ≥ 8.0 g/dL

Study Objectives

- **Primary**
  - **Safety and tolerability**
  - **Efficacy: Rates of**
    - ✓ **Overall response (CR+VGPR+PR)**
    - ✓ **Clinical benefit (CR+VGPR+PR+MR)**
- **Secondary**
  - **Progression-free survival (PFS)**
  - **Duration of response (DOR)**
- **Exploratory**
  - **Evaluation of serum B-cell maturation antigen levels during study treatment**

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

28-days/cycle

Demographics

# of Pts Enrolled	28
# of Pts that Received Study Drug	28
# of Pts that Received Study Drug in Dose Level 3	19
# of Pts Evaluable for Efficacy*	26
# of Pts Evaluable for Safety	28
# of Screen Failures	3
Pt Demographics	
Median Age in Years (Range)	67 (49-81)
Sex: M, F	17, 11
Race: White, Hispanic/Latino, African American/Black	25, 1, 2
Ig Isotypes	
IgG lambda, IgG kappa	5, 9
IgA lambda, IgA kappa	3, 3
Free kappa, free lambda	5, 3
Other	
Median time since diagnosis when treatment started (months, range)	56 (7-132)

*2 pts came off the study prior to completion of Cycle 1 (on Day 2 and 7); and, therefore, were not evaluable for efficacy. Both pts withdrew consent from this clinical study by patient choice.

Patients with High Risk Cytogenetics

Cytogenetic Abnormality	# of Pts
del(17p)	5
del(17p) and t(14;16)	1
t(14;16)	1
t(4;14)	2
Total	9 (32%)

Prior Treatments

Prior Regimens	Median (Range)
# Prior Regimens	6 (3-10)
Lenalidomide-containing (# pts)	28
Pomalidomide-containing (# pts)	26
Bortezomib-containing (# pts)	24
Carfilzomib-containing (# pts)	16

Status of Patients*

Dose Levels	
# of Pts at Dose Level 0	3
# of Pts at Dose Level 1	3
# of Pts at Dose Level 2	3
# of Pts at Dose Level 3	19
# of DLTs (dose-limiting toxicities)	0
# of active patients	9
Pt 11	Cycle 10
Pt 13	Cycle 9
Pt 17	Cycle 7
Pt 22	Cycle 5
Pt 23	Cycle 5
Pt 28	Cycle 3
Pt 29	Cycle 3
Pt 30	Cycle 3
Pt 31	Cycle 2
Median follow up [months] (range)	2.6 (0.1-8.4)

*Data cut off as of May 1, 2018

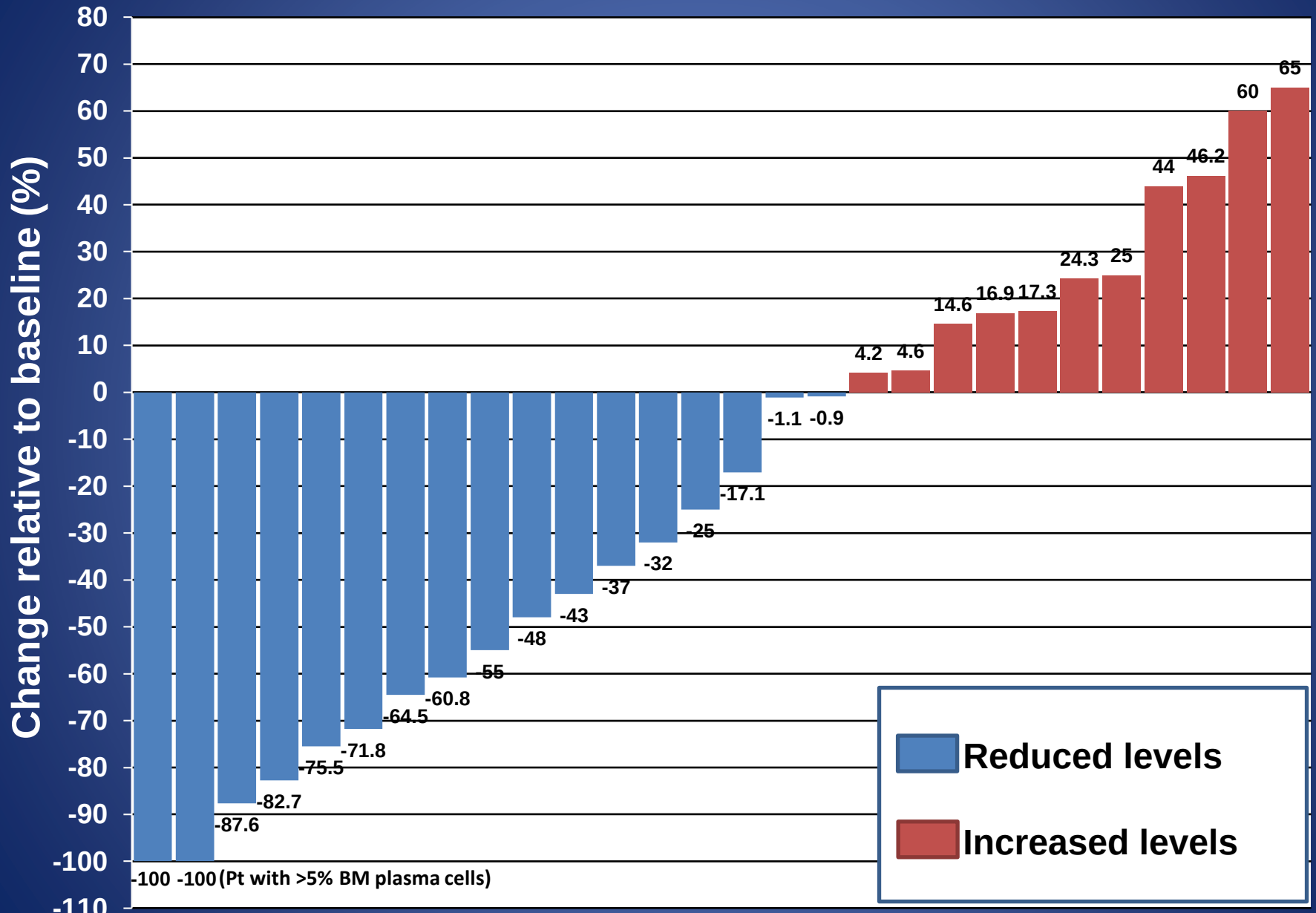
Response Summary/Efficacy Endpoints

❖ 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)

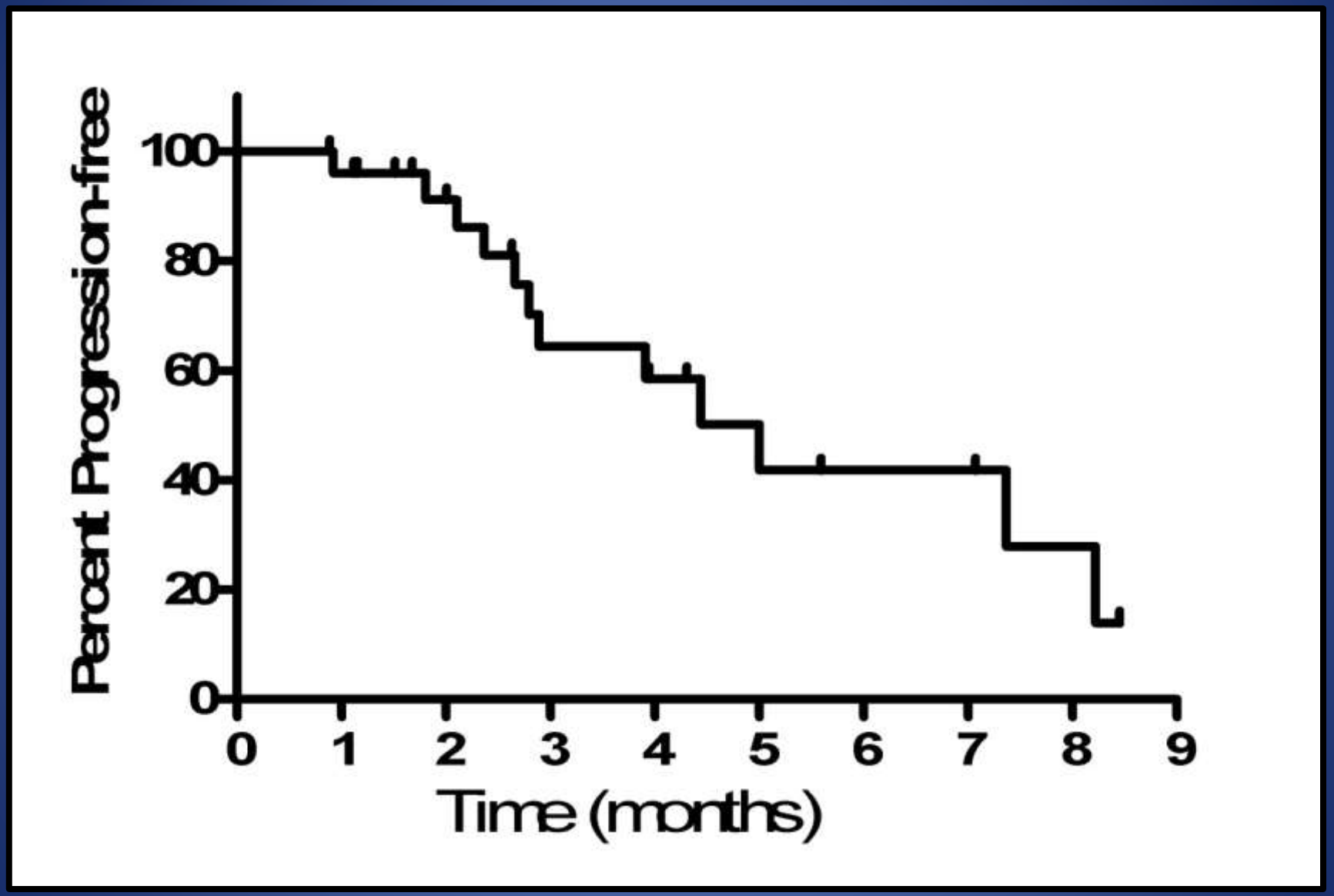
*All 13 responding pts were refractory to lenalidomide (progressed while on or w/i 8 wks of last dose)

Best Response: Waterfall Plot



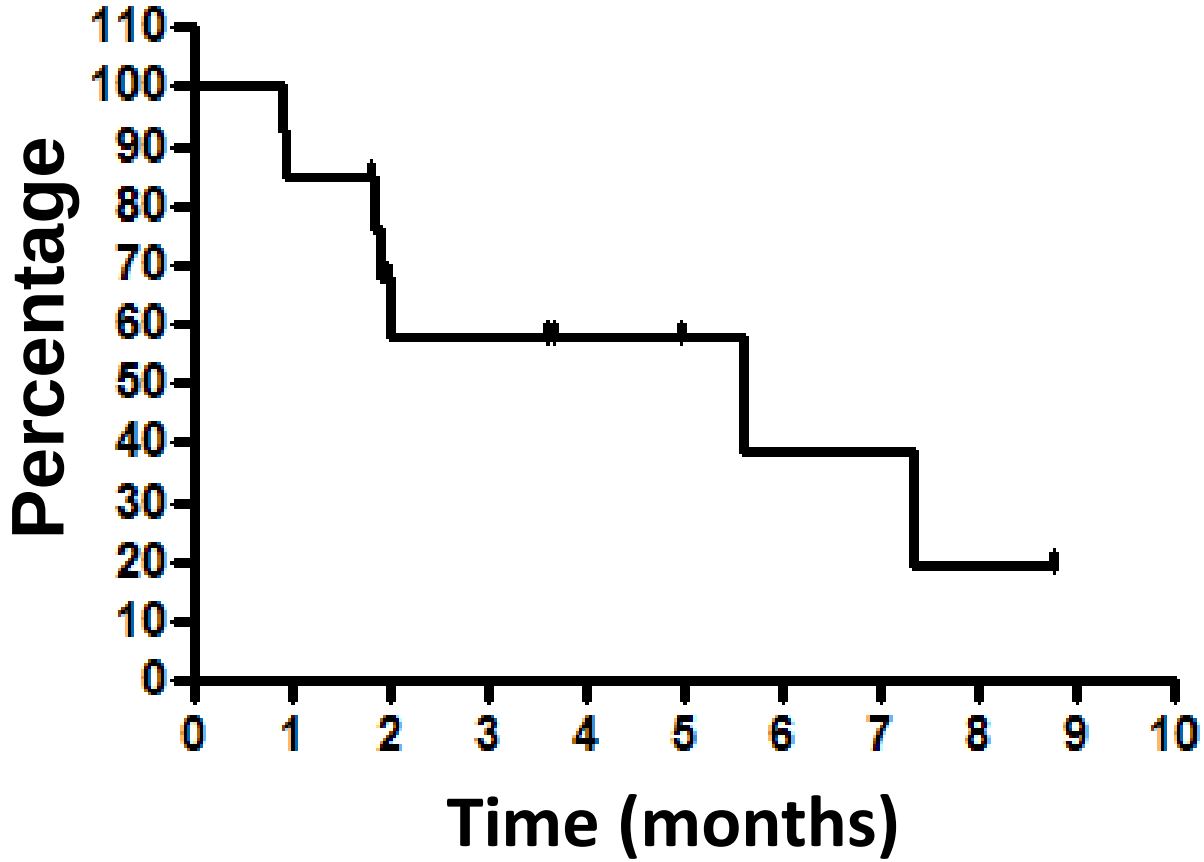
26 pts (2pts were analyzed for response using both M-protein and 24h urine M-protein)

Progression Free Survival (PFS)



- Median PFS for all 26 pts is 5.0 months

Duration of Response (DOR)



❖ Median DOR for 13 responding pts is 5.6 months

Safety

- No DLTs
- The three most common Grade ≥ 3 adverse events (AEs)

AE	Grade	Patient N (%)
Thrombocytopenia	3	3 (11)
Gastrointestinal bleeding	3	3 (11)
Anemia	3	2 (7)

- Serious adverse events (SAEs)

Pt ID	SAE Description	Relationship to Ruxolitinib
1	Gastrointestinal bleeding	No
6	Gastrointestinal bleeding	No
11	Cerebral vascular accident*	No
11	Non-purulent cellulitis	No
12	Humeral fracture	No
16	Enterocolitis	No
16	Nausea, vomiting and diarrhea	No
17	Cellulitis	No
17	Acute inferior wall myocardial infarction§	No
19	Fever, confusion	Yes
23	Pneumonia	Yes
25	Atrial fibrillation, sepsis	Yes
26	Hypoxia, anemia, neutropenic sepsis	Yes
26	Renal insufficiency	No
26	Disease progression with death as outcome†	No

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

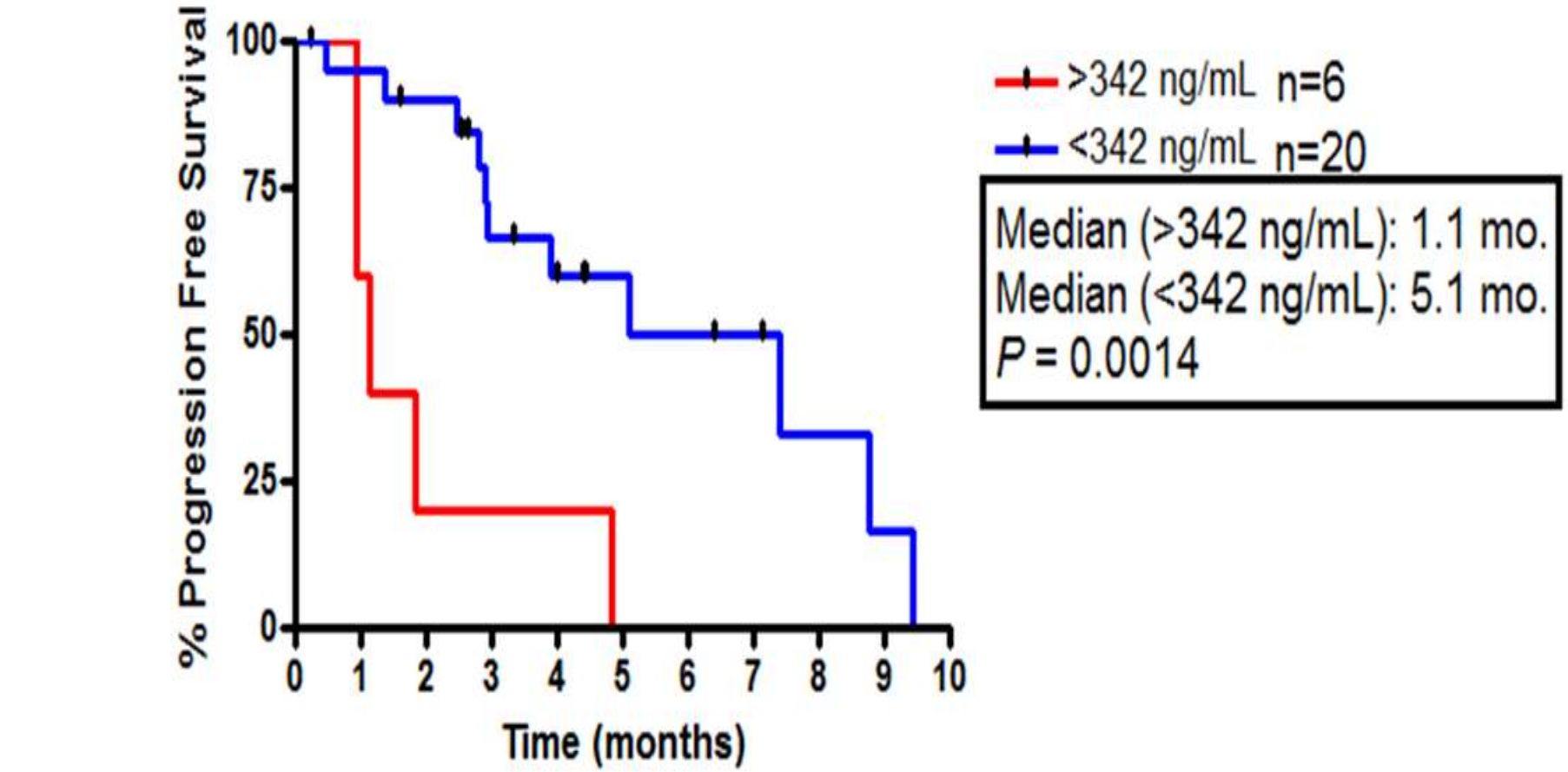
- Are elevated
- Correlate with clinical status (response vs progressive disease)
- Can be used to track response to treatment
  - rapid turnover allows quicker assessment of response
  - independent of renal function
  - more reliable than SFLC
- Predicts PFS and OS

✓ ***Thus, we assessed sBCMA using an ELISA at baseline and weekly through cycle 2 day 1 (C2D1), and then subsequently once per cycle***

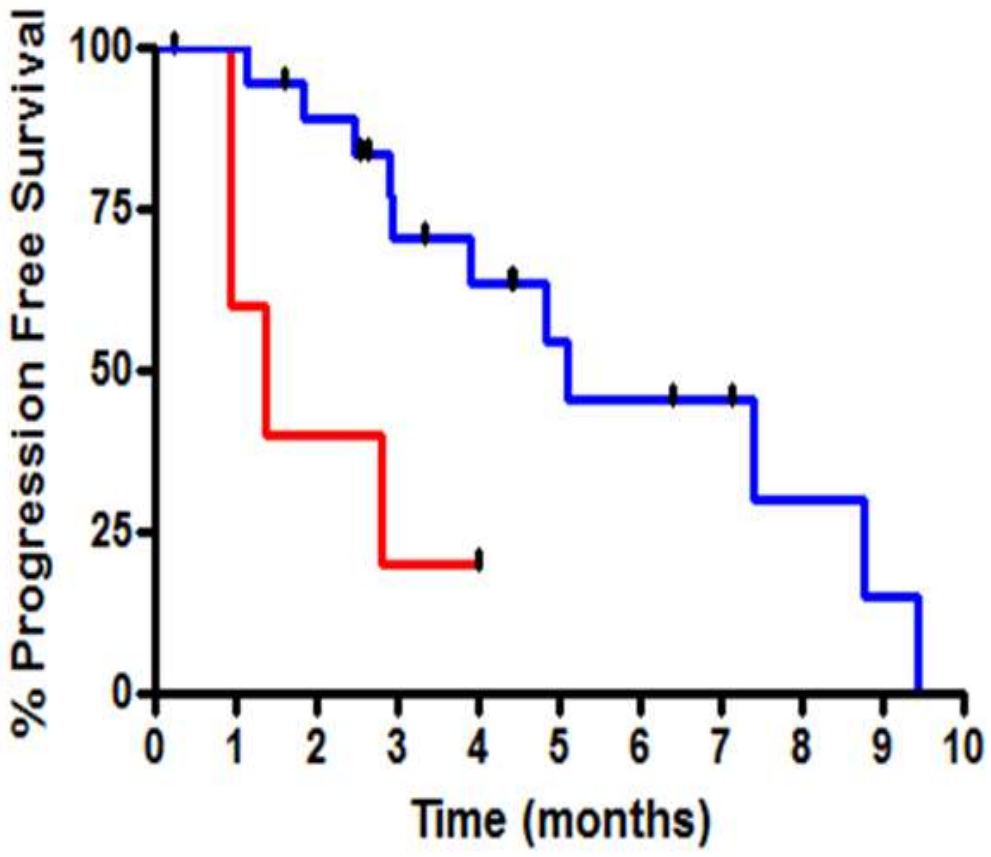
✓ ***This is the first clinical trial to assess sBCMA levels prospectively***

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

Higher sBCMA at Baseline Predicts Shorter PFS



Increase in sBCMA on C1D8 Predicts Shorter PFS



Increase n=6

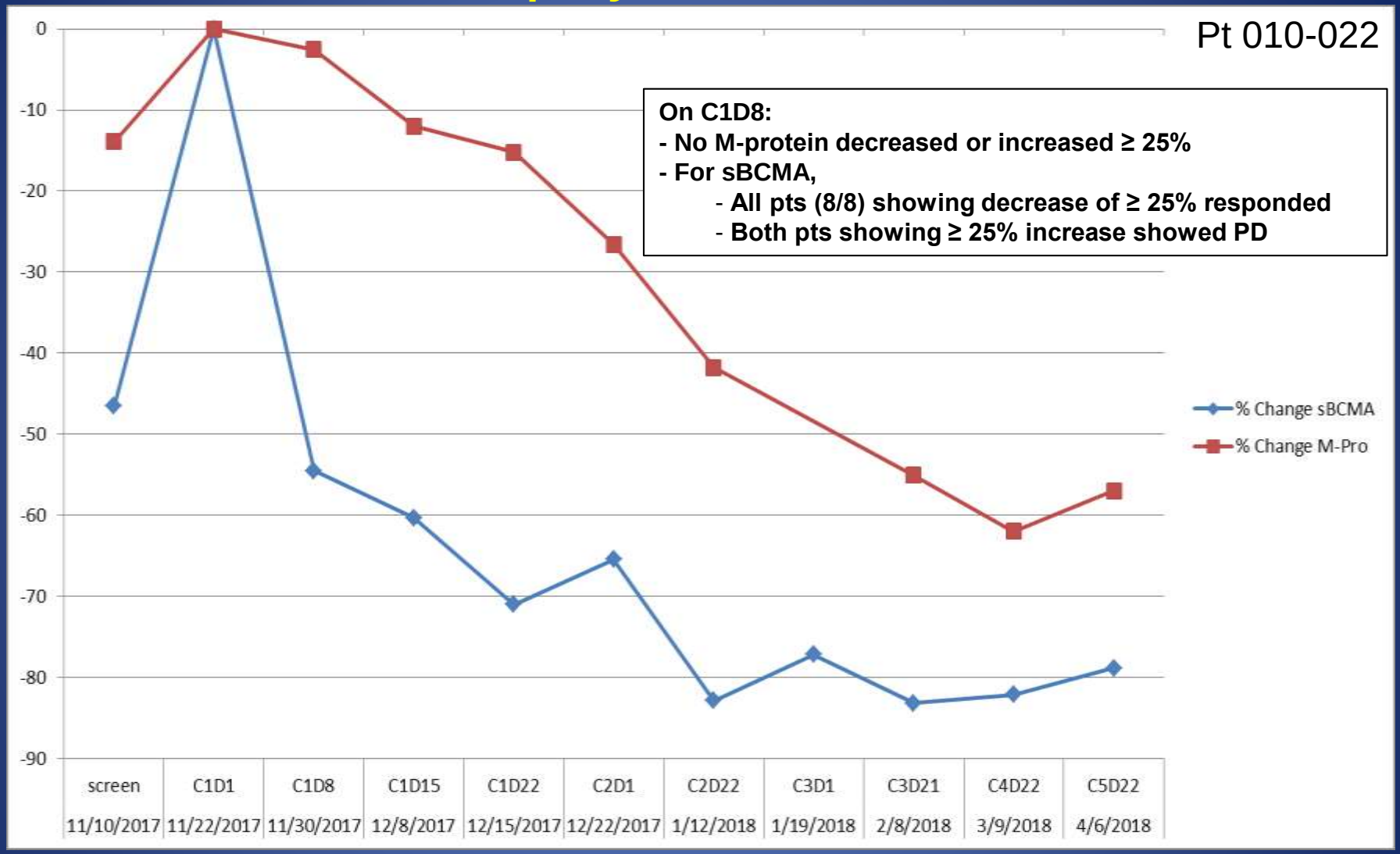
Decrease n=19

Median (Increase): 1.4 mo.

Median (Decrease): 5.1 mo.

P = 0.0091

sBCMA Shows Faster Reduction and Predicts Response Status More Rapidly than M-Protein



IgG Kappa
Best Response: PR
Ongoing (TOT = 135 days)

Baseline sBCMA: 85.33 ng/dL
Baseline M-Protein: 1.58 g/dL
Baseline sFLC: Kappa: 188.3 mg/L; Lambda: 5.5 mg/L
Baseline Creatinine: 0.9 mg/dL
Baseline QIGs: IgG: 1480 mg/dL; IgA: 9 mg/dL; IgM: 19 mg/dL

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**
- **We have also shown that baseline and monitoring serum BCMA can rapidly predict PFS and response status for MM patients**
- ***These promising results have led to expansion of the current clinical trial, and provide the basis for exploration of this and other JAK inhibitor-containing combinations for treating patients with MM and other malignant diseases***