Pilot study: Carfilzomib, Lenalidomide, and Dexamethasone in High-Risk Smoldering Multiple Myeloma

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Disclosures

- **No disclosures**
- **Off-label use of carfilzomib**

Risk of Developing Multiple Myeloma Varies Greatly in SMM

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Mayo Clinic (n=273)

No. of risk factors	No. of patients, n (%)	Progression at 5 years
1	76 (28)	25%
2	115 (42)	51%
3	82 (30)	76%

Risk factors:

- **BMPCs >10%**
- **M-protein >3 g/dL**
- **FLC-ratio <0.125 or >8**

Dispenzieri et al. *Blood* 2008

PETHEMA Study Group (n=89)

No. of risk factors	No. of patients, n (%)	Progression at 5 years
0	28 (31)	4%
1	22 (25)	46%
2	39 (44)	72%

Risk factors:

- **≥95% abnormal plasma cells***
- **Immunoparesis**

*Incl decreased CD38 expression, expression of CD56, and absence of CD19 and/or CD45

Pérez-Persona et al. *Blood* 2007

Current IMWG Clinical Recommendations for SMM[1]

- **Repeat lab tests after 2-3 months. If stable, repeat every 4-6 months for a year, and if stable every 6-12 months**

- **Treatment not indicated unless part of a clinical trial. Consider clinical trials designed to delay and/or prevent MM**

- **In high-risk SMM, Rev/Dex has a 12% CR rate. Compared to observation, Rev/Dex has better PFS (HR=5.6) and OS (HR=3.5)[2]**

[1]Kyle et al. *Leukemia 2010;* [2]San-Miguel et al. *ASH 2012*

Study Design and Dosing

Study open for high-risk smoldering multiple myeloma pts ≥18 years old

8 cycles CRd Combination Therapy

Carfilzomib 20/36 mg/m^2,
day 1, 2, 8, 9, 15, 16

Lenalidomide 25 mg/day,
day 1-21

Dexamethasone 20/10 mg
day 1, 2, 8, 9, 15, 16, 22, 23

SD or better?

12 cycles Rev Extended Dosing

Lenalidomide 10 mg/day, day 1-21

- **Each cycle is 28 days**
- **Stem cell harvest after ≥4 cycles of CRd for patients <70-75 yrs**
- **C1D1/2 – Carfilzomib dose is 20 mg/m^2**
- **C1- 4 – Dex dose is 20 mg, C5- 8 – Dex dose is 10 mg**

Objectives of Study

Primary Objective

Response rate

Secondary Objectives

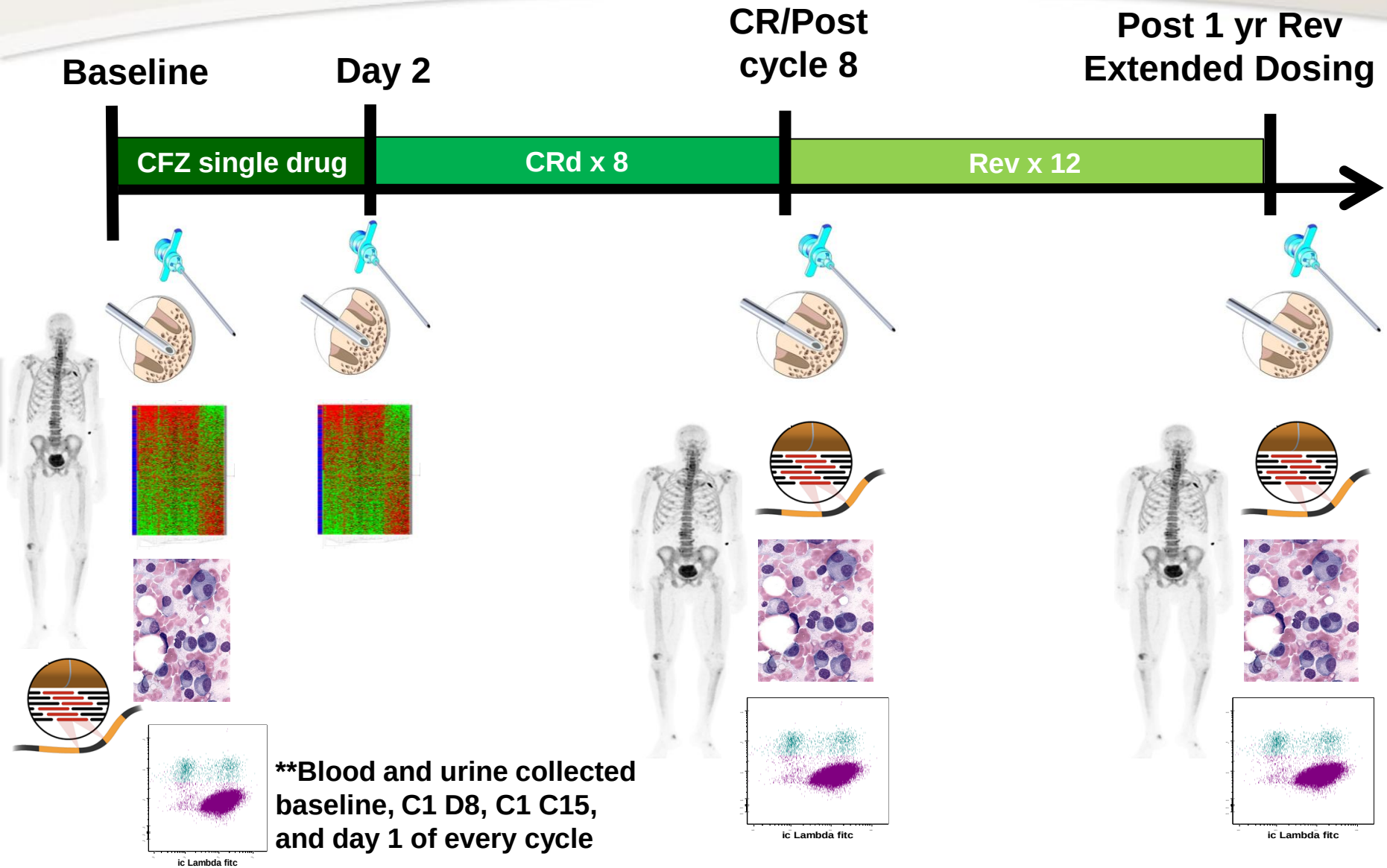
- **Correlatives: GEP, biomarkers, proteasomes, flow cytometry, PCR, FDG PET-CT**
- Clinical: DOR, PFS, OS, toxicity

Designed to enroll 12 evaluable patients

- Single arm, Phase II (pilot) study designed to evaluated efficacy of CRd in high-risk SMM patients

- Targeting 5 or more patients with a VGPR provides strong evidence that the true probability of a VGPR is consistent with ≥50%

Approach to Correlatives



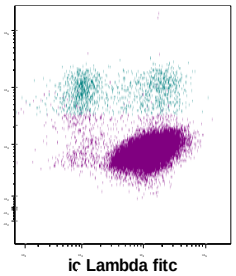
**Blood and urine collected baseline, C1 D8, C1 C15, and day 1 of every cycle

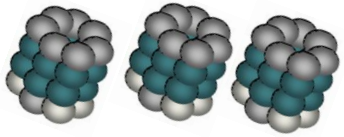
Bone Marrow Studies

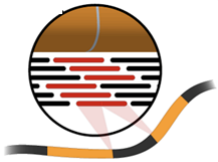
Bone marrow aspirate

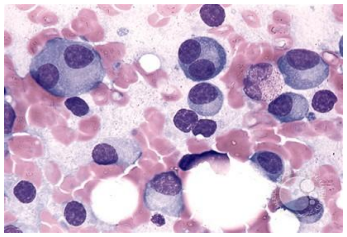
- CD138+
  - DNA/RNA profiling
  - Flow Cytometry
  - Proteasomes
  - PCR assays DNA/RNA
- CD138-
  - Micro-environment studies
- Supernatant
  - Biomarkers, e.g. miRNA

SIGNALGENETICS









Results: Patient Characteristics

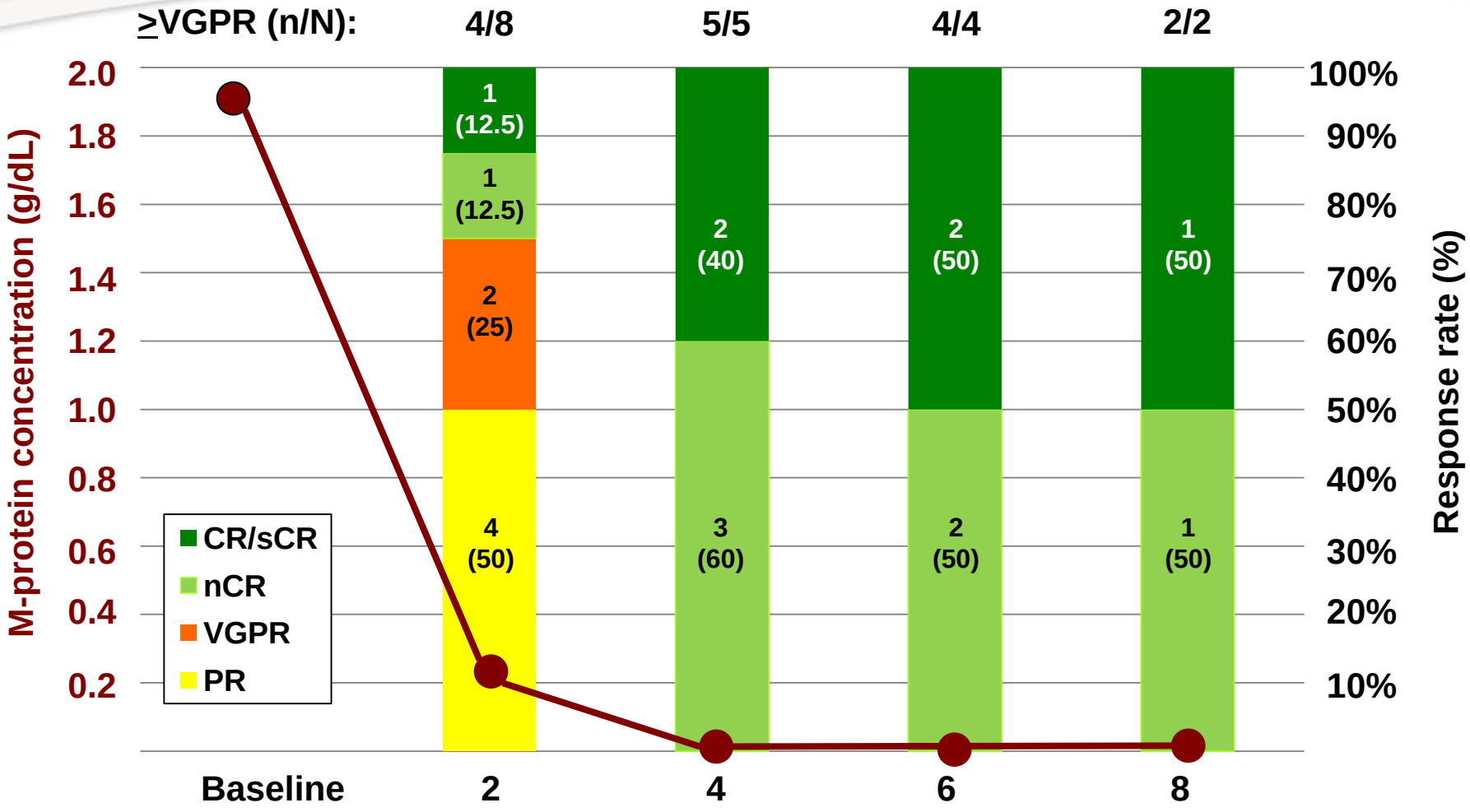
Variable	
Patients enrolled (Mar -13)	10
Patients completed two cycles (evaluable)	8
Median age, yrs (range)	55 (48-61)
Male sex, n (%)	3 (37.5)
Isotype, n (%) *IgG* *Kappa light-chain*	 7 (87.5) 1 (12.5)
Cytogenetics *n/N(%)** Normal	 8/8 (100)
FISH *n/N(%)*** -RB1 deletion (13q14) -7q31/7cen -IGH (14q32) -P53 (17p13.1)	 4/4 (100) 1/4 (25) 1/4 (25) 1/4 (25)
Median cycles of CRd-R received	5.5 cycles (2-9)
Patients completed 4 cycles of CRd	5

Cytogenetics not available for 1 patient ; **FISH not available for 4 patients

Response Rate (≥VGPR)

- **Primary Objective:**
  - In the first 8 patients, 7 have obtained a ≥VGPR

Response Rates and Mean M-protein Concentration (g/dL)



Response Rates

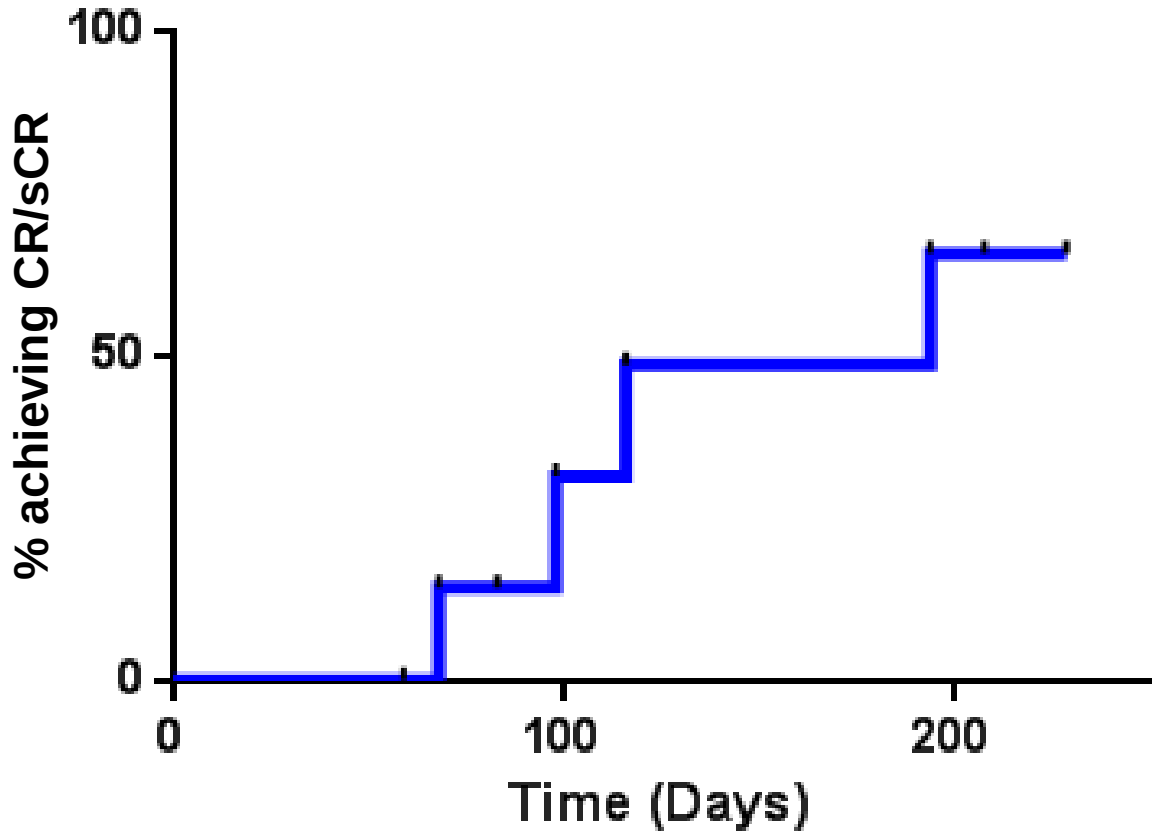
*Median 5.5 cycles of CRd-R

Response	2 cycles n/N(%)	4 cycles n/N(%)	*Best response n/N(%)
ORR (≥PR)	8/8(100)	5/5(100)	8/8(100)
≥VGPR	4/8(50)	0	7/8(87.5)
nCR/CR/sCR	2/8(25)	5/5(100)	6/8(75)
VGPR	2/8(25)	0	1/8(12.5)
PR	4/8(50)	0	1/8(12.5)
SD	0	0	0

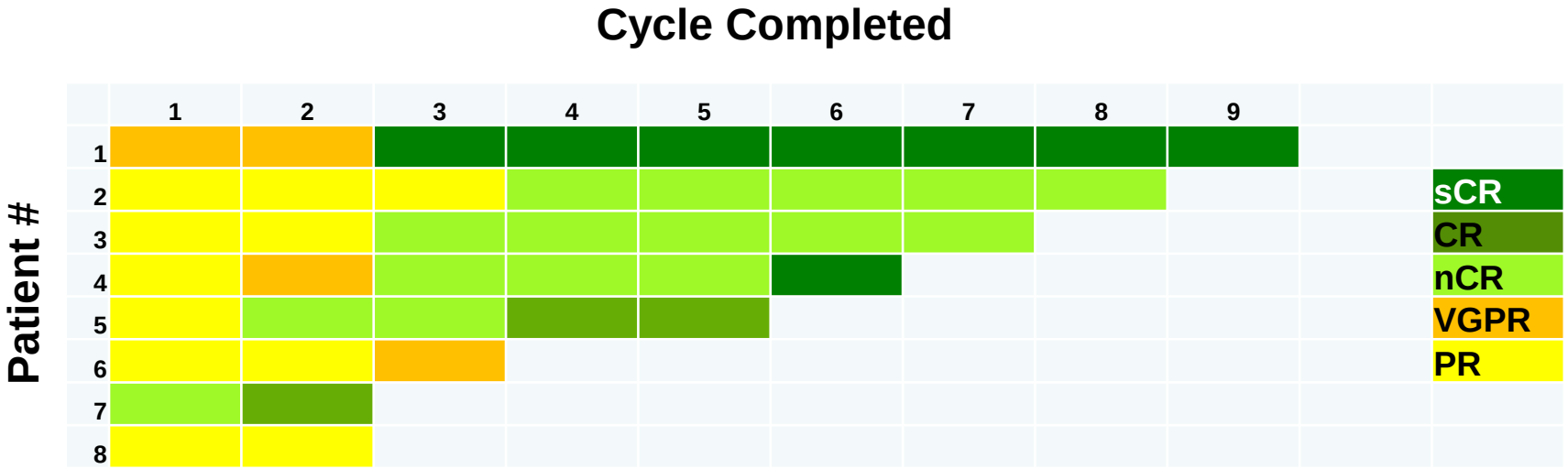
Based on small numbers, response rates are non-differential by FISH/cytogenetics

Time to CR/sCR

Among 4/8 patients reaching CR/sCR the median time was 107 days



Individual Response Rates



- 1 patient currently on rev extended dosing
- 1 patient (patient # 4) came off study after 6 combination cycles of CRd due to CHF and decrease in EF% – maintains sCR 3 months after stopping therapy

Toxicity

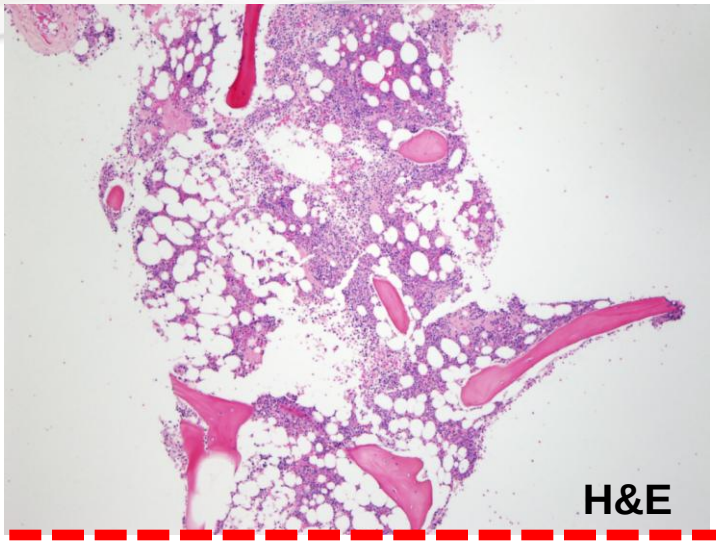
	Grade 3/4, n(%)
Nonhematologic	
LFT elevation	1 (12.5)
Fatigue	0
Rash/Pruritus	2 (25)
Dyspnea	0
Heart Failure	1 (12.5)
Constitutional (chills, fever, anorexia, hot flashes)	0
Mood alterations (anxiety, cognition, confusion, insomnia)	0
Electrolyte disturbances	0
Hematologic	
Lymphopenia	2 (25)
Anemia	1 (12.5)
Neutropenia	1 (12.5)
Thrombocytopenia	1 (12.5)

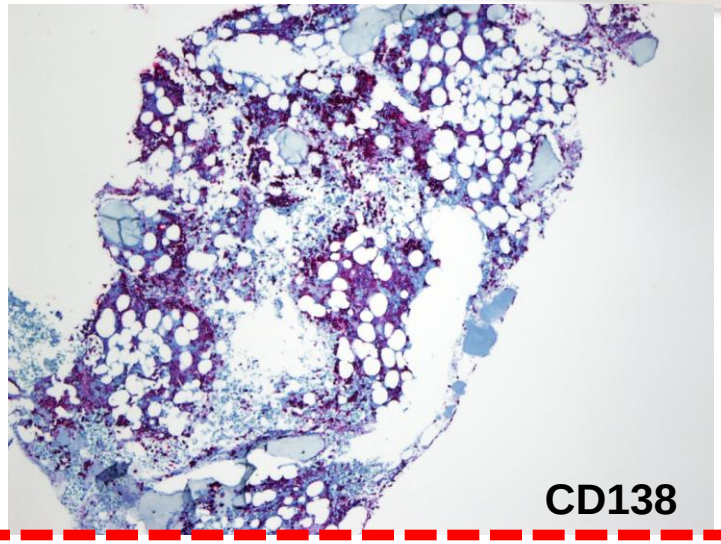
Dose Reductions on 2 patients (1 patient had two dose reductions): decreased Dex for mood alterations (n=1), decreased lenalidomide for rash (n=2)

Individual Patient Response

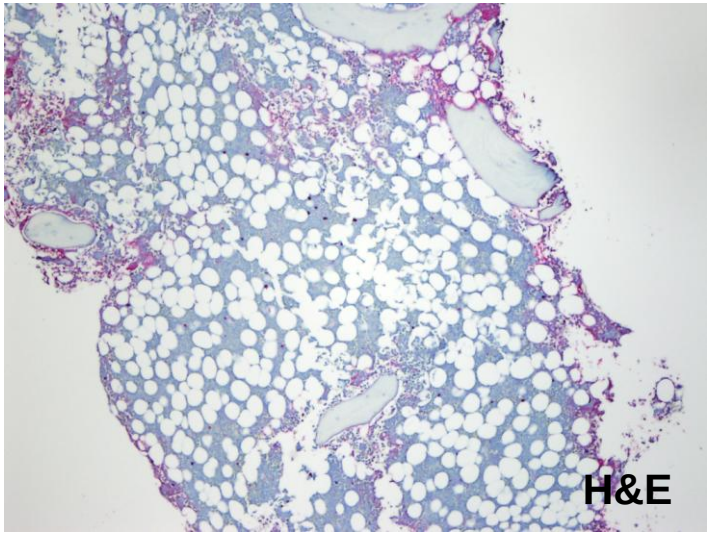
Histopathology

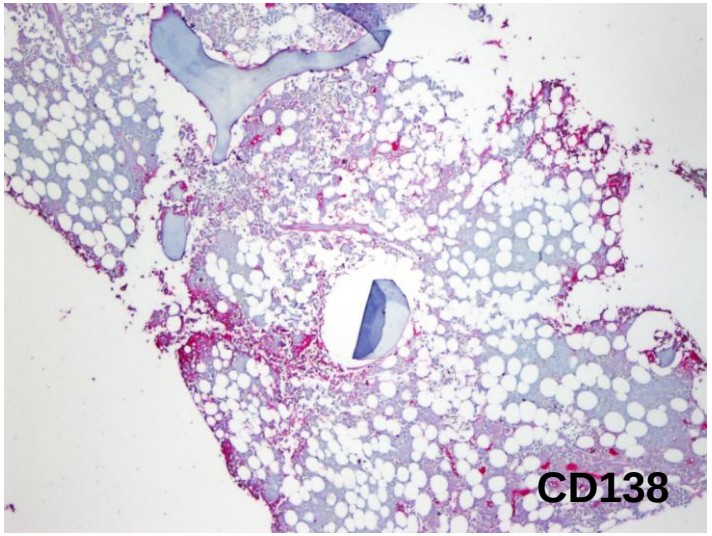
Baseline





Post CRd

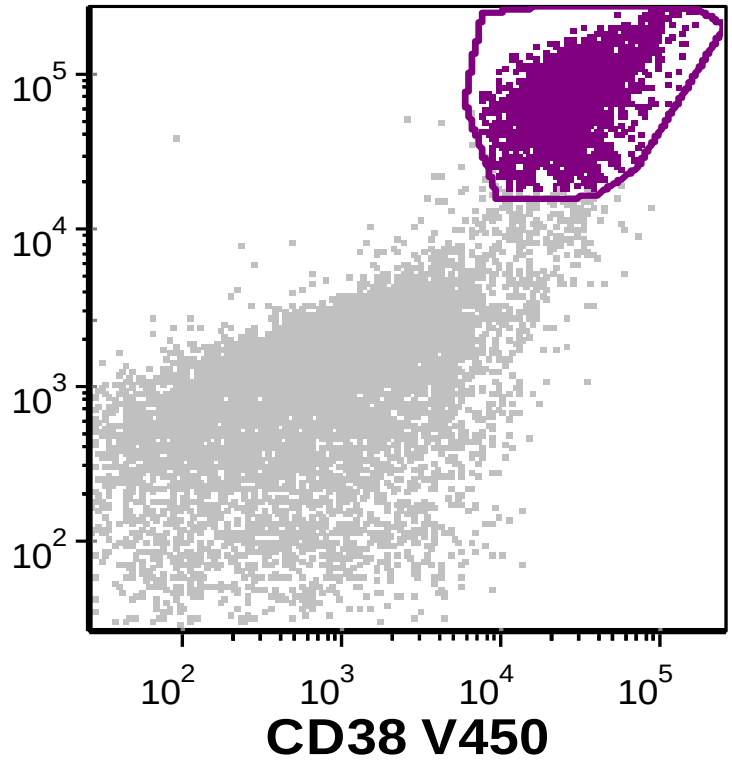




Provided by Irina Maric

Assessing MRD by Flow Cytometry

Gating strategy to analyze plasma cells (CD138+CD38+)



- **Analyze 3-4 x 10^6 bone marrow cells**
- **8-color flow panel***
  - CD38
  - CD138
  - CD19
  - CD20
  - CD56
  - CD45
  - CD27
  - CD28
- **MRD negative: <20 abnormal plasma cells detected**

***European Myeloma Network Gating Criteria**

MRD Status after CRd therapy

Flow cytometry of bone marrow aspirate

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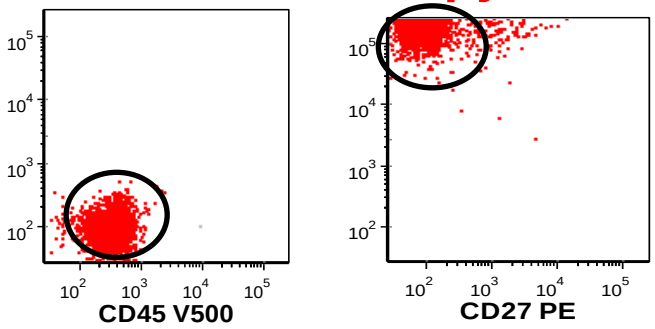
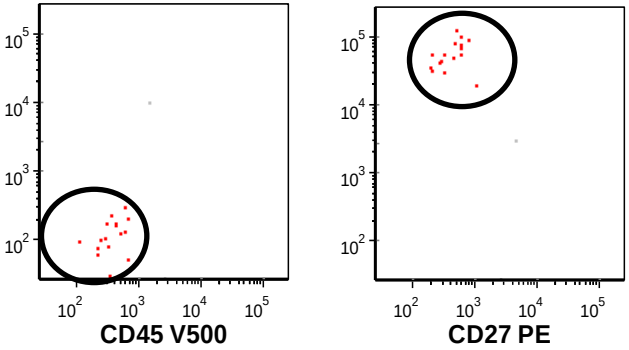
Abnormal PC's CD19-, CD45 -, CD56 +, CD 27-

Before therapy



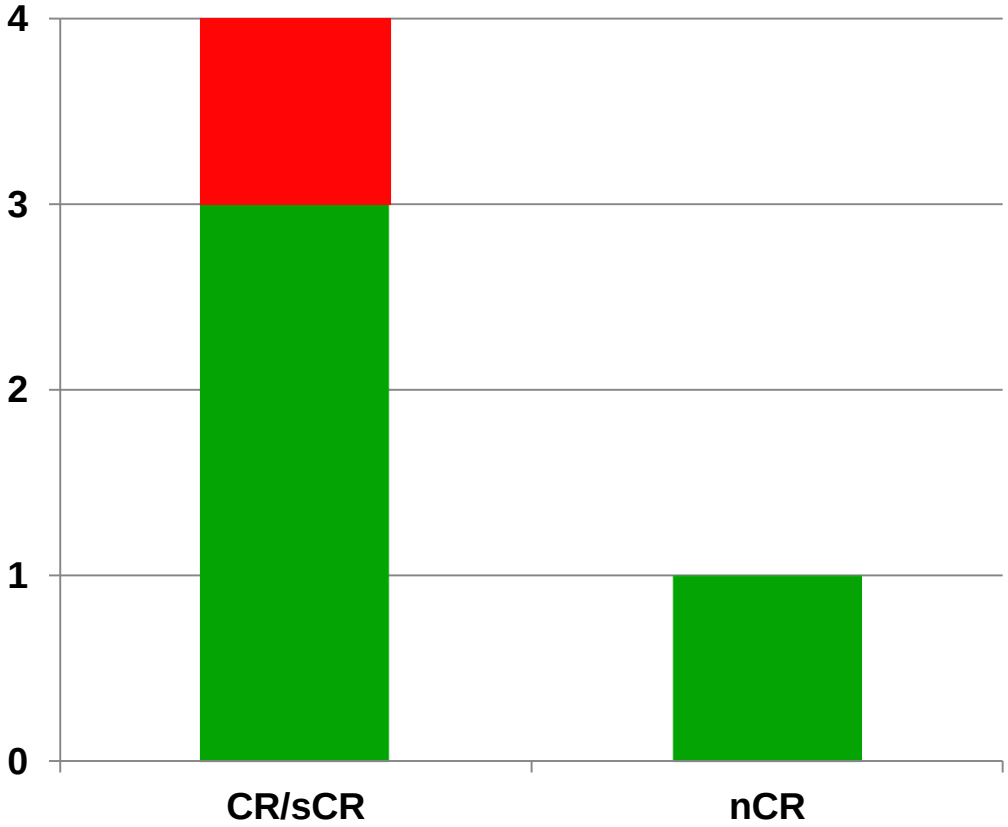
Post therapy



Among patients achieving sCR/CR/nCR, 4/5 (80%) are MRD negative

MRD NEGATIVE

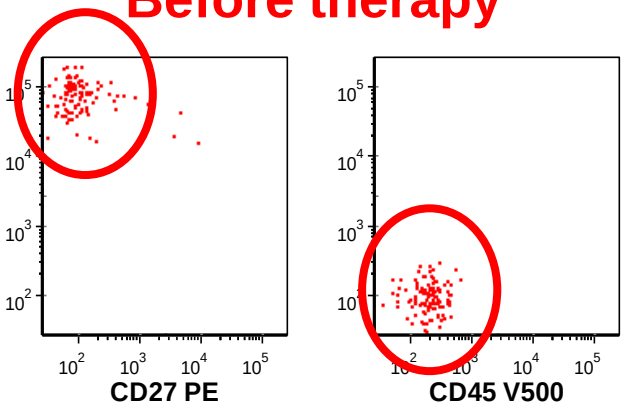
MRD POSITIVE

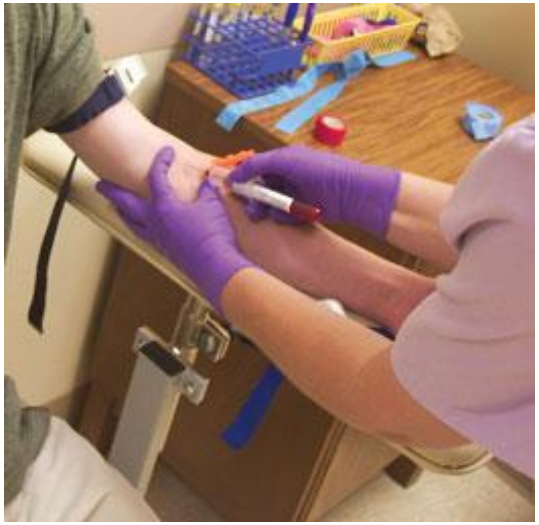


MRD Status after CRd therapy

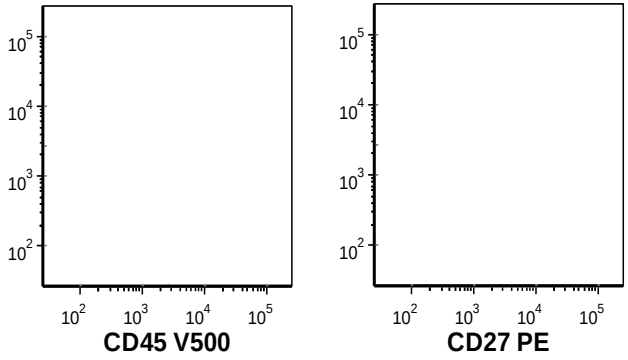
Flow cytometry of peripheral blood

Before therapy





Post therapy



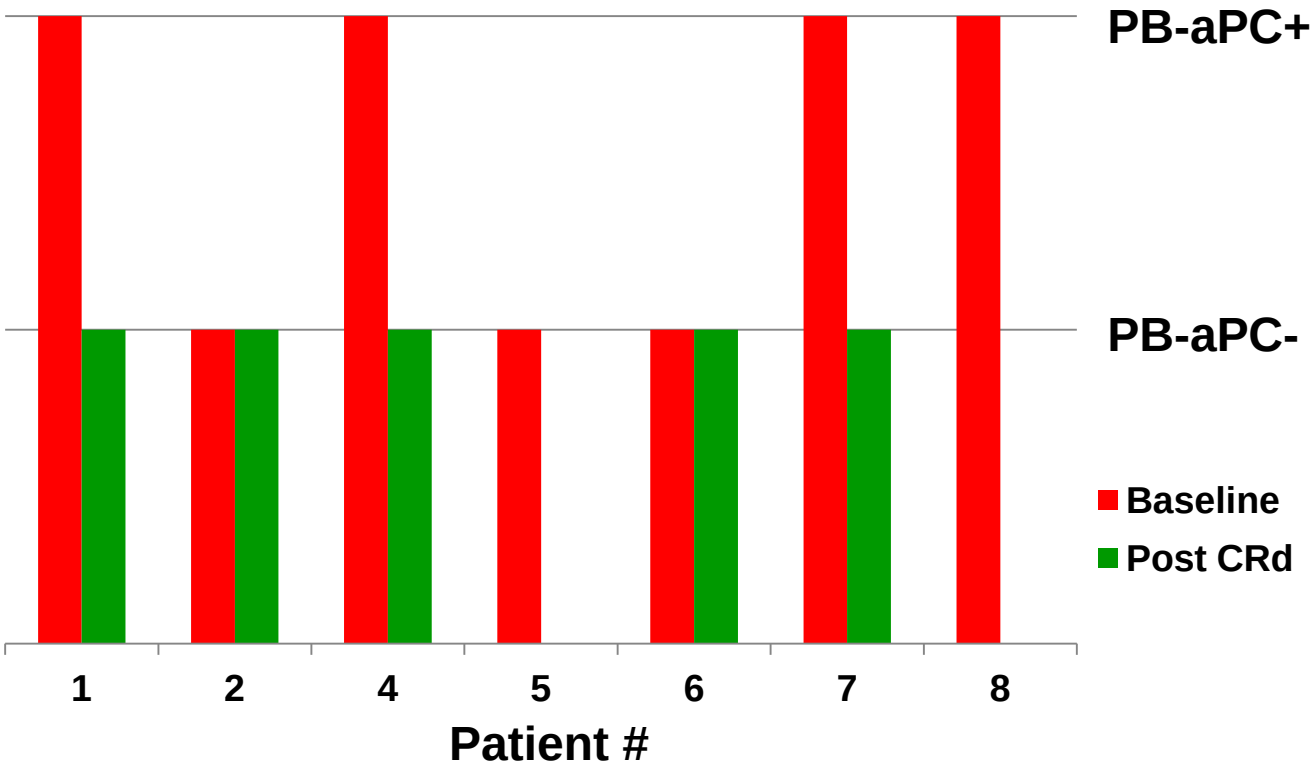
- Analyze 3-4 x 10^6 peripheral blood cells
- 8-color flow panel
- Circulating abnormal peripheral plasma cells (PB-aPC +) positive:

  <20 abnormal cells = MRD neg

Circulating Plasma Cells

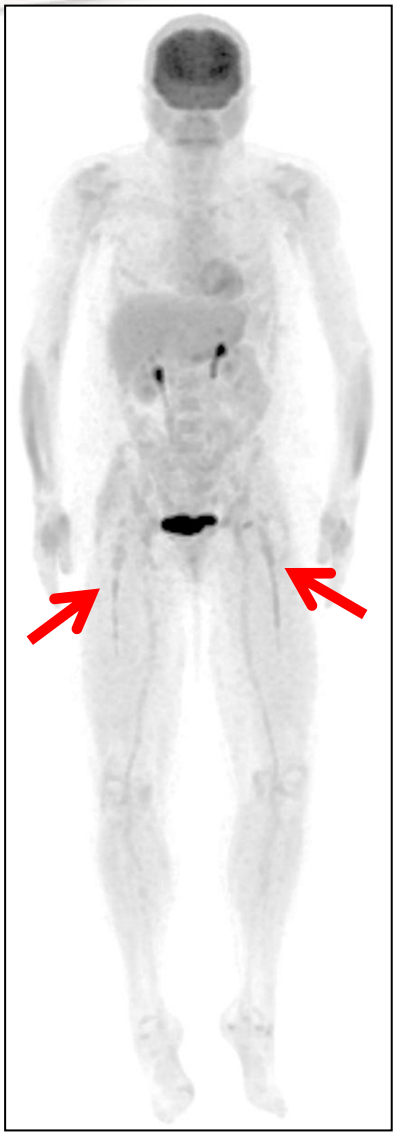
PB-aPC +

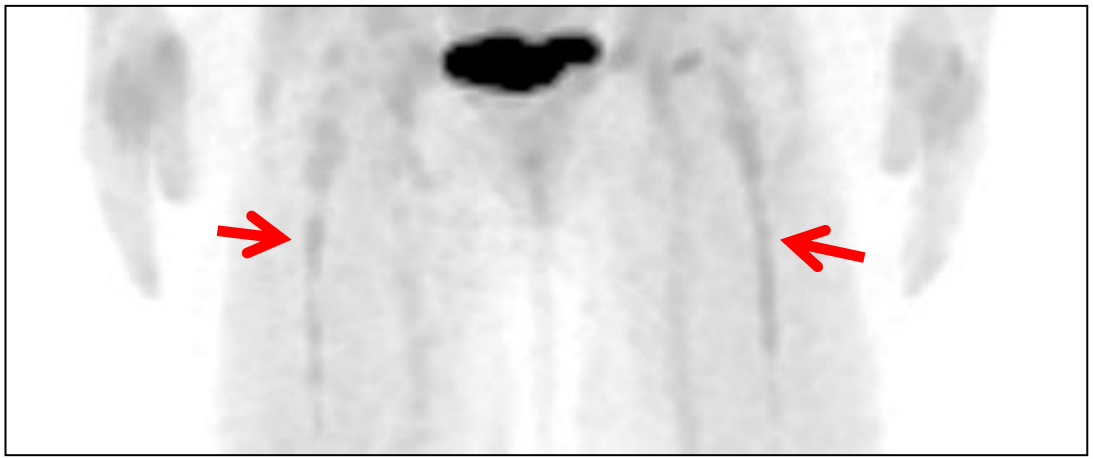
- 4/7 patients demonstrate circulating PB-aPC+ at baseline
- Among the 5 patients assessed after CRd therapy thus far, 3 became PB-aPC- after CRd and 2 remain PB-aPC –



Patient #3 baseline sample not performed

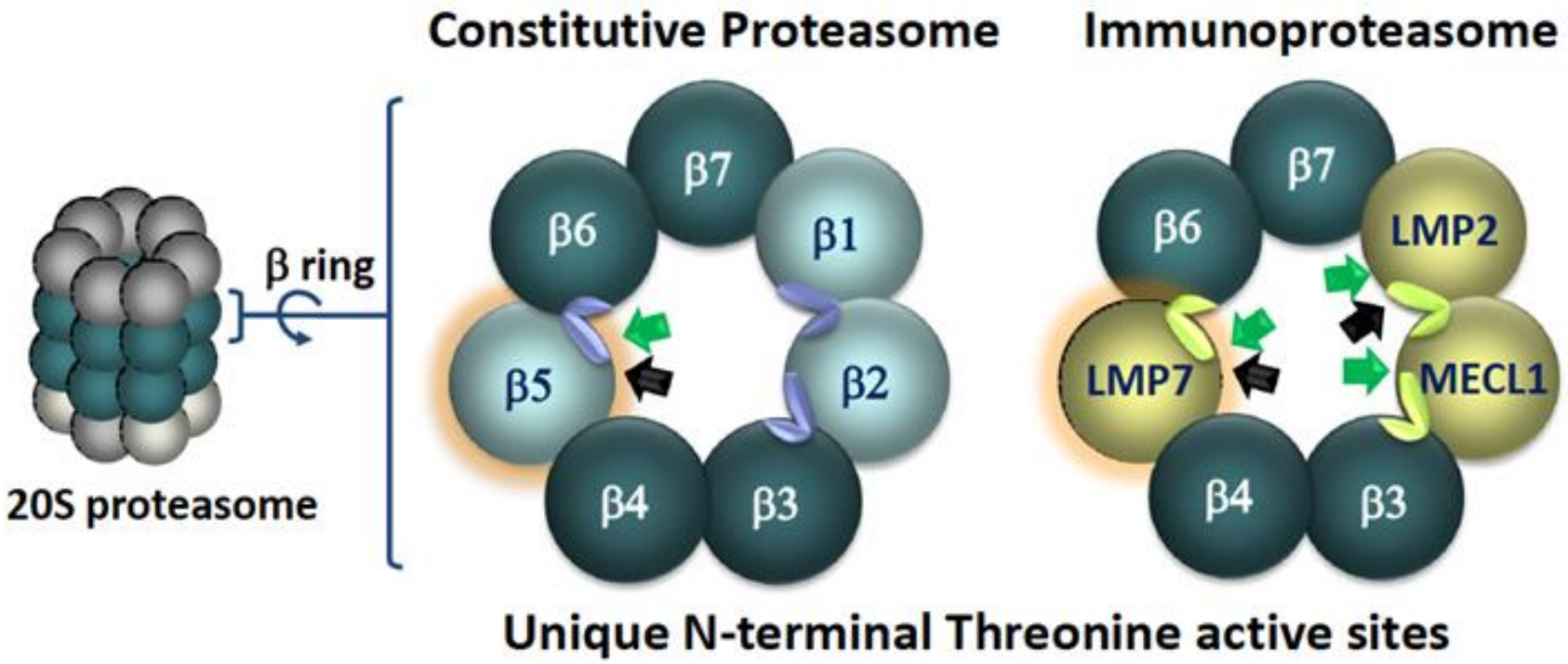
Increased FDG PET-CT bone marrow uptake prior therapy





- During screening for the trial, many SMM patients had bone lesions detectable by CT or PET-CT; these patients were ineligible for the trial (due to multiple myeloma)
- Among SMM without bone lesions, ~30% had increased PET uptake in the bone marrow

Proteasome subunits

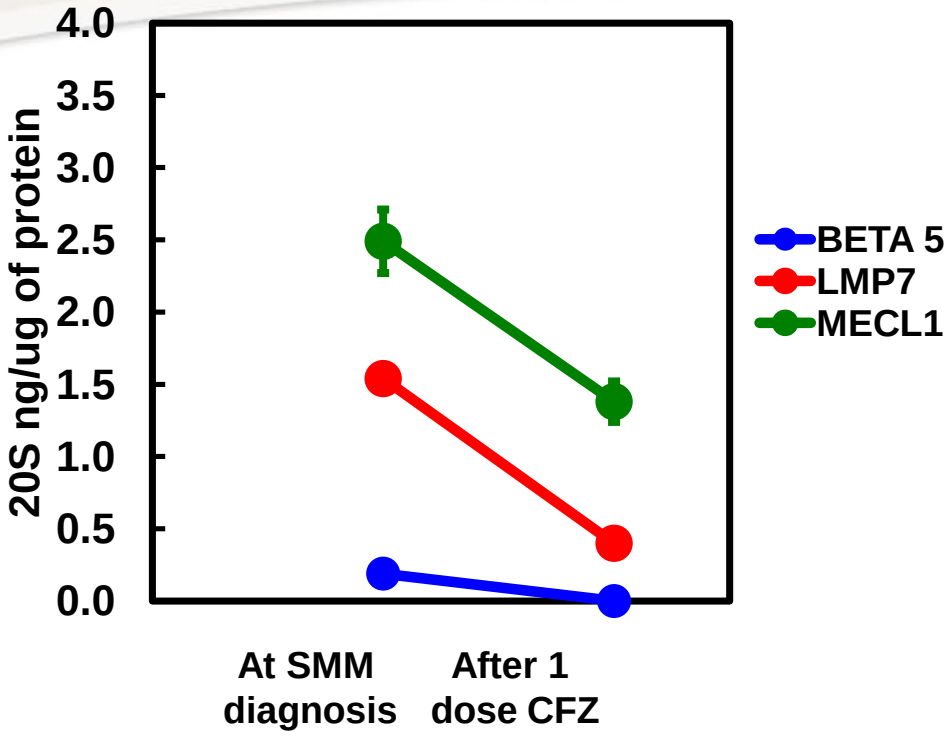


- **Carfilzomib**
  - **1º targets *β*5 and LMP7**
  - **2º targets LMP2 and MECL1**

Groettrup M. et al., Nat Rev Immunol. 2010; 10 (1): 73-78. Provided by Onyx

Proteasome activity

Pre and post carfilzomib exposure



- Proteasome activity assay (*Pro-CISE)*
- 20S CT-L Proteasome activity decreases by 80% 24 hrs after carfilzomib exposure
- Patient obtained PR after 1 cycle

Proteasome Level	β5 (ng/ug of protein) (% total 20S)	LMP7 (ng/ug of protein) (% total 20S)	Total 20S CT-L (ng/ug of protein)
At SMM diagnosis	0.19 ± 0.01 (11%)	1.54 ± 0.08 (89%)	1.73± 0.09
After 1 dose CFZ	0.00	0.40 ± 0.01	0.40 ± 0.15

Provided by Adriana Zingone

Summary and Conclusions

- **Among first 8 patients, 7 obtained ≥ VGPR; limited severe toxicities**
- **Rapid and deep responses; median time to CR/sCR (4 pts) was 107 days**
- **Best response rate (median 5.5 cycles)**
  - **nCR/sCR = 75% (6/8)**
  - **ORR (PR or better) = 100% (8/8)**

Summary and Conclusions

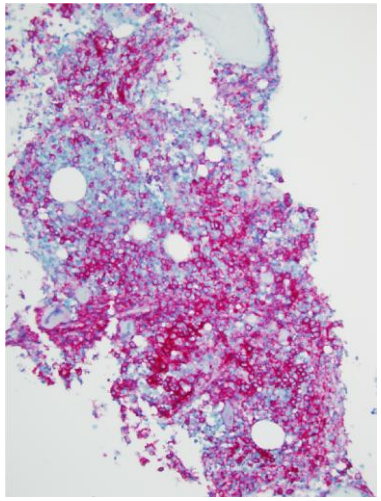
- Among 5 patients in nCR/sCR, 4 were MRD negative by flow cytometry
- Abnormal PET/CT uptake in the bone marrow in 1/3 of SMM pts prior therapy
- Pre/post (24 hours) exposure to carfilzomib shows 80% inhibition of proteasome (20s CT-L) activity in MM cells

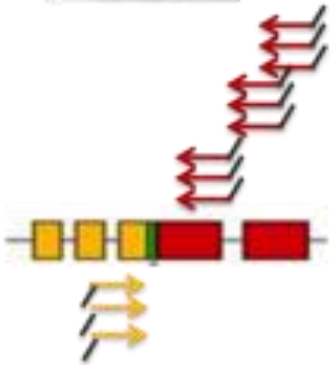
Future Directions

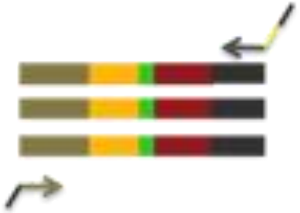
- With more effective therapies used in “early myeloma” (high-risk SMM), we need better markers to assess residual tumor burden beyond “traditional” CR rates

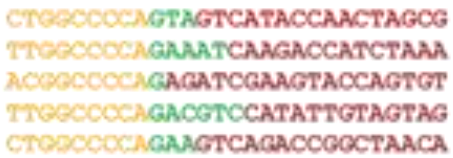
Detection of minimal residual disease (MRD) using VDJ sequencing

Tumor cells | **Extract DNA** | **Multiplex PCR to amplify VDJ** | **Common PCR to prepare for sequencing** | **Sequence ~1M 100bp reads**

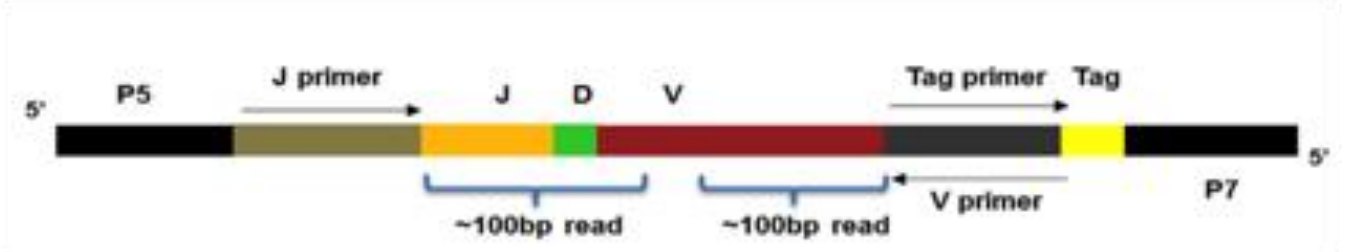








gDNA | PCR amplicons | Sequencing library | Sequence data



Sensitivity limited by total assessed cell number (>10^{-6})

Landgren, Willis et al, *unpublished data*

Labs and collaborators

NCI/NIH
Multiple myeloma Section
Metabolism Branch

- **Dr. Korde**
- Dr. Roschewski
- Dr. Manasanch
- Dr. Tageja
- Dr. Bhutani
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- Dr. Kwok
- Dr. Kanzandjan
- Dr. Flanders
- Dr. Zingone
- Mr. Costello
- RN Mulquin
- RN Zuchlinski
- Peter Wu

NIH Labs

- Dr. Staudt - Molecular pathogenesis and targeted therapy
- Dr. Choyke, Kurdziel - Molecular Imaging program
- Seth Steinberg - Statistics
- Drs. Maric, Calvo, Braylan – Hematopathology
- Dr. Arthur – Cytogenetics and FISH
- Drs. Stetler-Stevenson, Yuan - Flow cytometry
- Dr. Raffeld – Molecular pathology
- Dr. Trepel - Pharmacodynamic assay development
- Dr. Mock - Molecular therapy
- Dr. Robey - Bone marrow microenvironment
- Dr. Kuehl - Molecular pathogenesis

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Karolinska Institute
Signal Genetics

Thank you to our patients!

www.multiplemyeloma.cancer.gov

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