APSHO Regional Lecture Series

Accredited Educational Activities for Advanced Practitioners in Oncology

Collaborative Practice in the Management of Patients With Cancer

Relapsed or Refractory Multiple Myeloma

Program Chair

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APSHO Regional Lecture Series

Disclosures

Faculty

Ms. Kurtin has served as consultant for Amgen, BMS, Celgene, Genentech, Incyte, Janssen, Novartis, Takeda, and Pharmacyclics.

Planning Committee

Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has nothing to disclose. Alana Brody, Terry Logan, Lynn Rubin, and Wendy Smith (MEI) have nothing to disclose. Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose. Claudine Kiffer and Annie Yueh (Harborside Press) have nothing to disclose.

Learning Objectives

- Describe the various mechanisms of action of agents used to treat multiple myeloma (MM)
- Apply the principles of risk-adapted treatment using case-based scenarios to illustrate the impact of patient attributes and disease-specific attributes in MM
- Manage toxicities associated with newer agents used to treat MM
- Apply the principles of adjunctive supportive care in the treatment of patients with MM

NON-TRANSPLANT ELIGIBLE AND RELAPSED OR REFRACTORY DISEASE

General Approach to Therapy in the Older Adult

Patient Characteristics	Approach to Treatment
Functionally independent without co-morbidities	Candidates for most forms of therapy with consideration of goals of treatment/expected outcomes.
Intermediate functional impairment unable to tolerate intensive life-prolonging curative therapy	Application of individualized pharmacological approach
Major functional impairments or complex co-morbidities	Palliative therapies with supportive care
Poor prognosis and limited functional status	Symptom management and supportive care

NCCN Senior Adult Oncology, 2016, v1; Kurtin, S. *J Adv Pract Oncol* 2010;1:19–29

Functional Status, Co-morbidities, Frailty, and Vulnerability

- **Functional Status: Measures by ECOG and KPS**
  - ADLs: ability to bathe, dress, toilet and maintain continence, transfer, and eat independently
  - IADLs: finances, shopping, housekeeping, transportation, and self-medication
- **Co-morbidities**
  - Cardiovascular, renal, hepatic, pulmonary, endocrine, rheumatologic disease and other cancers
  - Number, severity, controlled or uncontrolled
- **Frailty**
  - Weight loss, weakness, poor nutritional intake, cognitive impairment and poor endurance
  - Cardiovascular Health Study (n=5317): frailty associated with hospitalization, falls, declining ADLs including diminished mobility, and death (P<.001)
- **Vulnerability**
  - A complex of comorbidity (presence of chronic diseases or conditions), disability (physical or mental impairment), and frailty (fatigue, low activity) that could prevent adequate therapy.

Palumbo et al, *Blood* 2011; 118:4519-29; Kumar et al, *CA Cancer J Clin*. 2010. doi:10.3322/caac.20059; Balducci & Extermann, *Oncologist*. 2000;5:224–237

Suggested Dose Modifications for ≥ 1 Risk Factor: Age ≥ 75 yr, Presence of Comorbidities, Frailty or Disability

Drug	Initial/standard dose	Reduced dose	Further reduction if needed
Dexamethasone	40 mg/d 1,8,15,22 every 4 weeks	20 mg/d 1,8,15,22 every 4 weeks	10 mg/d 1,8,15,22 every 4 weeks
Melphalan	0.25 mg/kg or 9 mg/m^2 d 1–4 every 4–6 weeks	0.18 mg/kg or 7.5 mg/m2 d 1–4 every 4–6 weeks	0.13 mg/kg or 5 mg/m^2 d 1–4 every 4–6 weeks
Thalidomide	Thalidomide 100 mg/d	Thalidomide 50 mg/d	Thalidomide 50 mg qod
Lenalidomide (plus dexamethasone)	25 mg/d days 1–21 every 4 weeks	15 mg/d days 1–21 every 4 weeks	10 mg/d days 1–21 every 4 weeks
Bortezomib	1.3 mg/m^2 twice weekly days 1,4,8,11 every 3 weeks	1.3 mg/m^2 once weekly days 1,8,15,22 every 5 weeks	1.0 mg/m^2 once weekly days 1,8,15,22 every 5 weeks

Palumbo A, et al. (2013). *Blood Rev* 27(3):133-142.

Case Study 2: 75-year-old Female

Initial Presentation to PCP: August 2011

- 75-year-old female
- Hypertension, A. fib
- Performance status 1
- Symptoms: fatigue, constipation, increased forgetfulness, back and leg pain
- x-ray revealed lytic lesions
- **Referred to heme/onc**

Case Study 2: 75-year-old Female

- Hg: 8.6 g/dL
- B2M: 4.13 mg/dL
- Albumin: 2.8 g/dL
- Calcium: 9.8 g/dL
- Cr: 1.4 mg/dL
- M-protein: 12 g/dL
- IgA: 3724 mg/dL
- Lambda FLC: 9.35 mg/L
- LDH: 340 (180=ULN)
- BMPC: 70%
- Cytogenetics: Normal Female 46xx[20]
- FISH: gain of 1q21 along with a t(11;14).

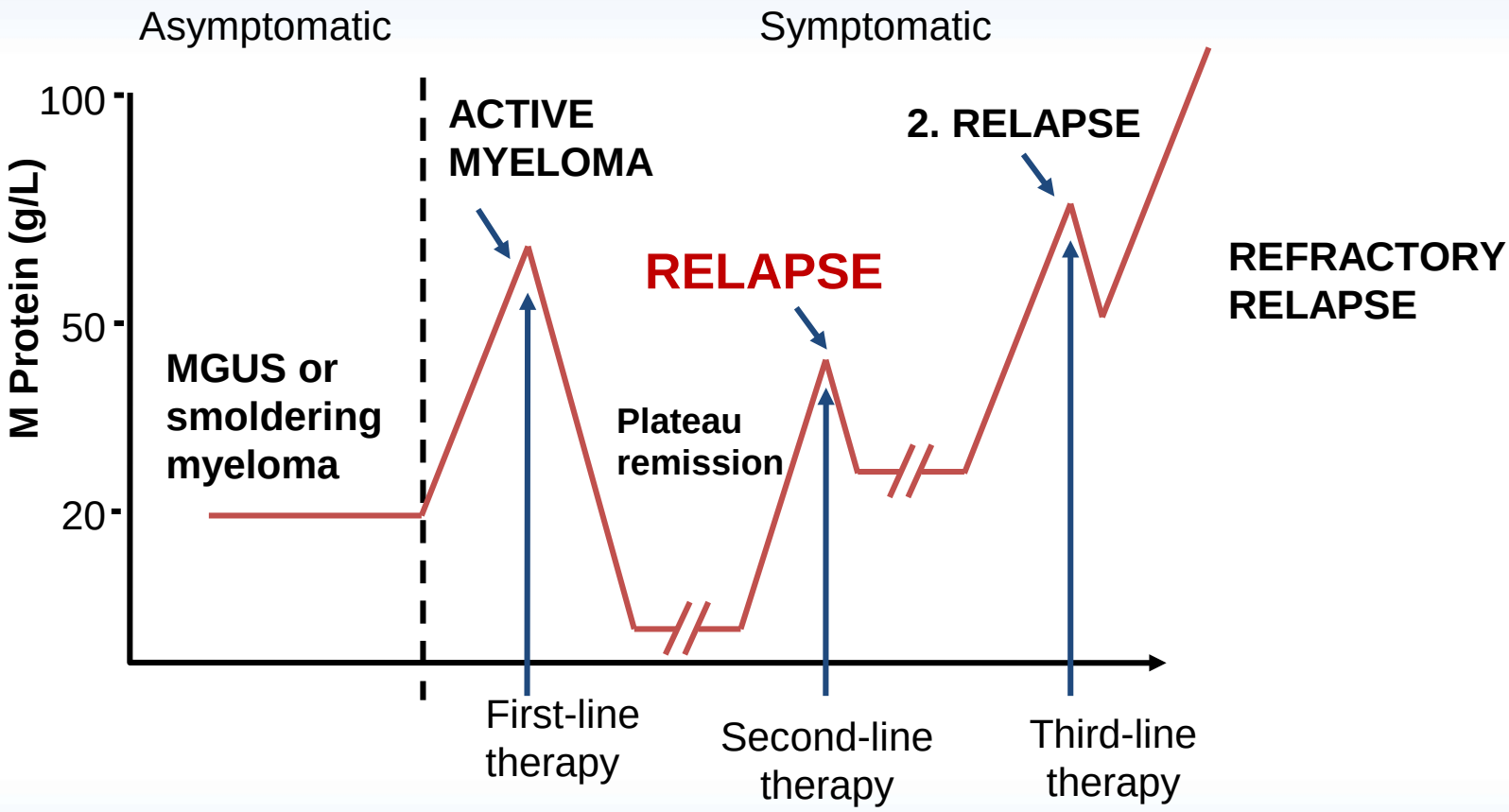
Diagnosis: IgA Lambda Myeloma, ISS Stage II

Case Study 2: 75-year-old Female

- Initial treatment with VRd
  - Achieved a VGPR after 8 cycles of treatment
  - Patient relocated to live near children and decided to stop therapy after 8 cycles
- Concurrent supportive care
  - Pamidronate for 2 yr
  - DVT prophylaxis
  - Infection prophylaxis
- Re-established care with a local oncologist
- Off treatment for a total of 10 months
- Three incremental increases in IgA and lambda measures over a 5-month period
- IgA: 309 -> 427 -> 525 g/dL
- Lambda FLC: 1.86 -> 2.08 -> 4.63 mg/dL

RELAPSED AND RELAPSED REFRACTORY MM

Natural History of Multiple Myeloma



Adapted with permission from Durie B @ www.myeloma.org.

Monitoring for Response and Surveillance

Evaluation of treatment response until best response

- Heavy/light chain monthly with initiation of therapy, until best response
- CMPNL, CBC, diff, plts and other labs as indicated based on treatment plan and individual profile

Surveillance

- Myeloma panel every 3 months
- Skeletal survey yearly
- Other laboratory or diagnostic testing as indicated by individual disease and personal attributes

Kurtin et. al. (2016) *J Adv Pract Oncol*, 7(S1), S59-S70.

Monitoring for Response and Surveillance

Suspected relapse or progression

- Increase frequency of myeloma panel
- Repeat imaging as clinically indicated
- Repeat bone marrow biopsy to detect changes/clonal evolution with progression
- Continued monitoring for organ damage
- Evaluation of any residual adverse events
- Re-assess co-morbidities and fit vs. frail
- Infectious disease workup based on transplant history, infectious history, and treatment plan

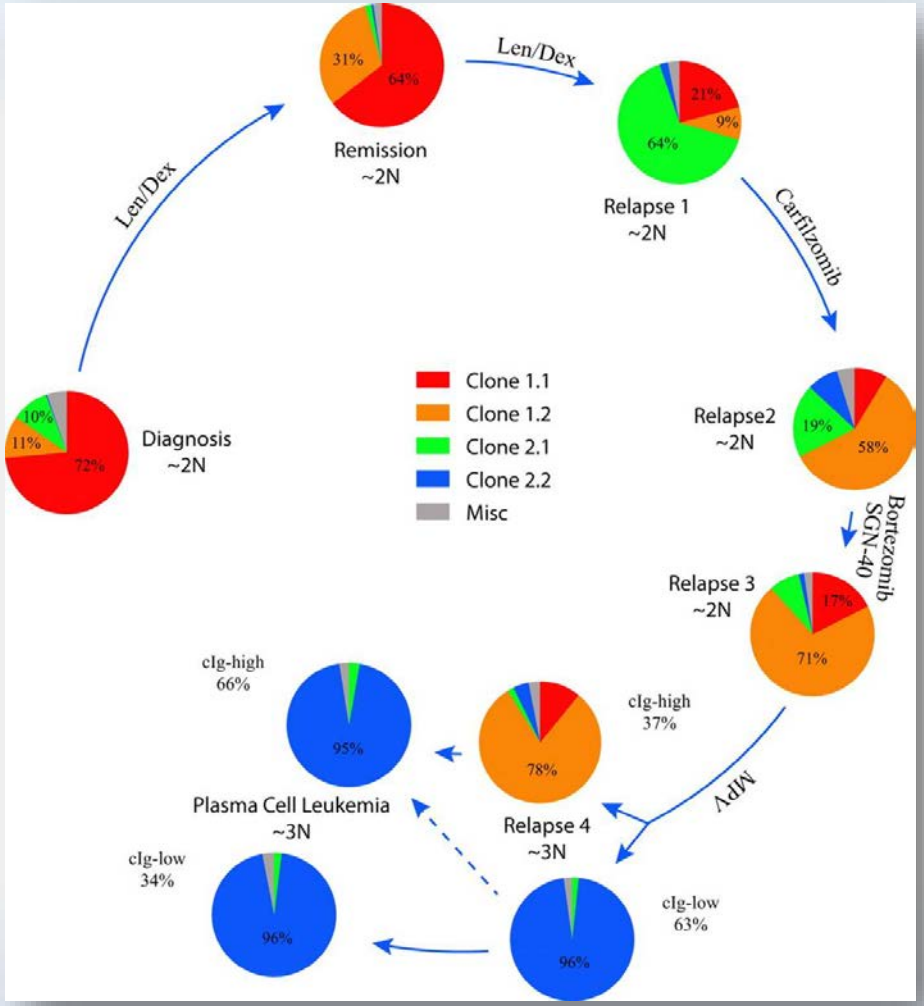
Kurtin et. al. (2016*) J Adv Pract Oncol*, 7(S1), S59-S70.

Relapsed and Relapsed Refractory MM

- ***Primary refractory***: failure to achieve any response to specific MM treatments, often 2 or 3 novel agent combination regimens
- ***Relapse***: development of clinically measurable disease or secondary organ effects after achieving a CR
- ***Progression***: development of clinically measurable signs of increase disease activity after achieving PR or disease plateau
  - Progression of disease is implied in the term “relapsed”
- ***Relapsed and refractory***: defined as a lack of response or disease progression on or within 60 days of the last therapy
  - The therapy in use at the time of progression is what the patient is refractory to

Kurtin, S. *J Adv Pract Oncol* 2013;4(suppl 1):5-14

Clonal Evolution in MM



MM clones detected by FISH and cytogenetics can evolve

At each relapse there is a change in the dominant clone

It is critical to re-evaluate the patient at each point of relapse to characterize the disease and select the best treatment

FISH = fluorescence in situ hybridization

Keats JJ, Chesi M, Egan JB, et al. *Blood*. 2012;120:1067-1076.

Considerations in Selecting Salvage Therapy

Time from previous therapy to relapse or progression	▪ > 6 mo may use similar agents ▪ Agents based on: – Time from previous therapy to relapse/progression – Any residual clinical conditions (neuropathy, renal function, etc.) – Newly FDA-approved agents for second line: carfilzomib, pomalidomide, ixazomib, panobinostat, elotuzumab ▪ < 6 mo consider alternative agents in combination
Refractory disease	▪ Clinical trial enrollment ▪ Newly FDA-approved agents
Reassess transplant options including allogeneic stem cell transplant on a clinical trial	▪ Previous ASCT: second ASCT if time to progression (TTP) > 2 yr ▪ Allogeneic SCT: clinical trial enrollment is recommended
Previous thalidomide	▪ Bortezomib or bortezomib/pegylated liposomal doxorubicin ▪ Lenalidomide/dexamethasone ▪ High-dose dexamethasone/carfilzomib/pomalidomide
Previous bortezomib	▪ Lenalidomide ▪ Bortezomib ▪ Carfilzomib/pomalidomide
Previous lenalidomide	▪ Bortezomib ▪ Ixazomib ▪ Carfilzomib/pomalidomide

Richardson PG, et al. *Oncology.* 2010;24(3 suppl):22-29.
NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.3.2016.

Retreatment With Bortezomib: RETRIEVE Trial

Clinical Trial Design

- Single arm, open-label phase II
- Patients who achieved ≥ PR on btz regimen and who relapsed >/= 6 months after prior bortezomib treatment
- n = 130

Results

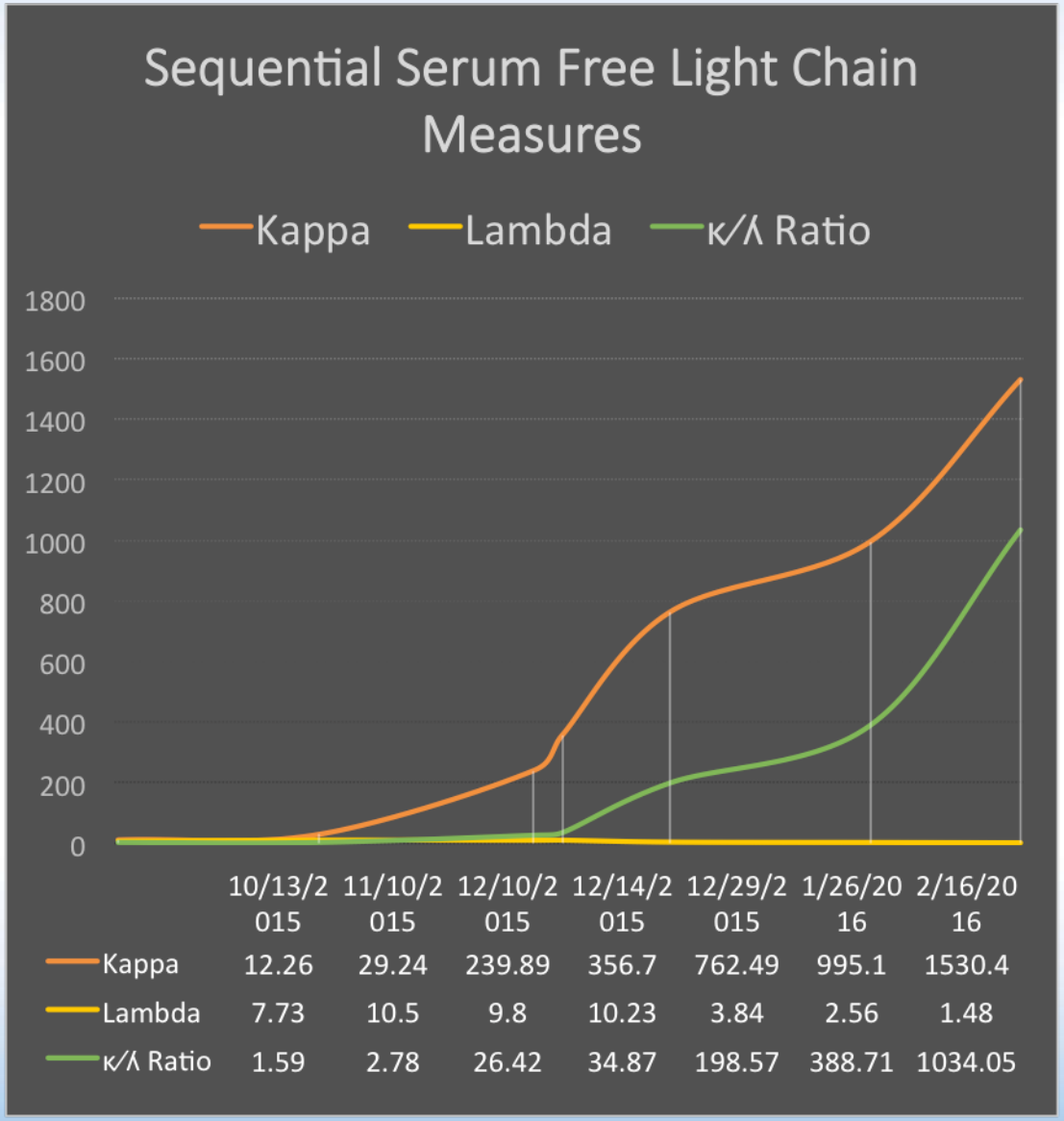
- Patients treated with bortezomib + dex
- 40% overall response rate (PR or better)
- Duration of response 6.5 months
- Safety profile consistent with bortezomib

FDA approved bortezomib retreatment August 2014

Type of previous non-bortezomib therapy	Patients receiving this therapy, N
Steroids	115
Alkylating agents	100
Anthracyclines	75
Thalidomide	40
Other	
Previous high-dose therapy/stem-cell transplant	39
Previous bortezomib treatment	
Bortezomib single agent	48
Bortezomib plus other agents	82

Petrucci MT, et al. *Br J Haematol*. 2013;160:649-659.

Case Study 1: Active Surveillance



	10/13/2015	11/10/2015	12/10/2015	12/14/2015	12/29/2015	1/26/2016	2/16/2016
Kappa	12.26	29.24	239.89	356.7	762.49	995.1	1530.4
Lambda	7.73	10.5	9.8	10.23	3.84	2.56	1.48
κ/λ Ratio	1.59	2.78	26.42	34.87	198.57	388.71	1034.05

Clinical Decision Making

What additional testing or investigations would you consider at this point and why?

Clinical Decision Making: What Additional Testing Would You Consider at This Point and Why?

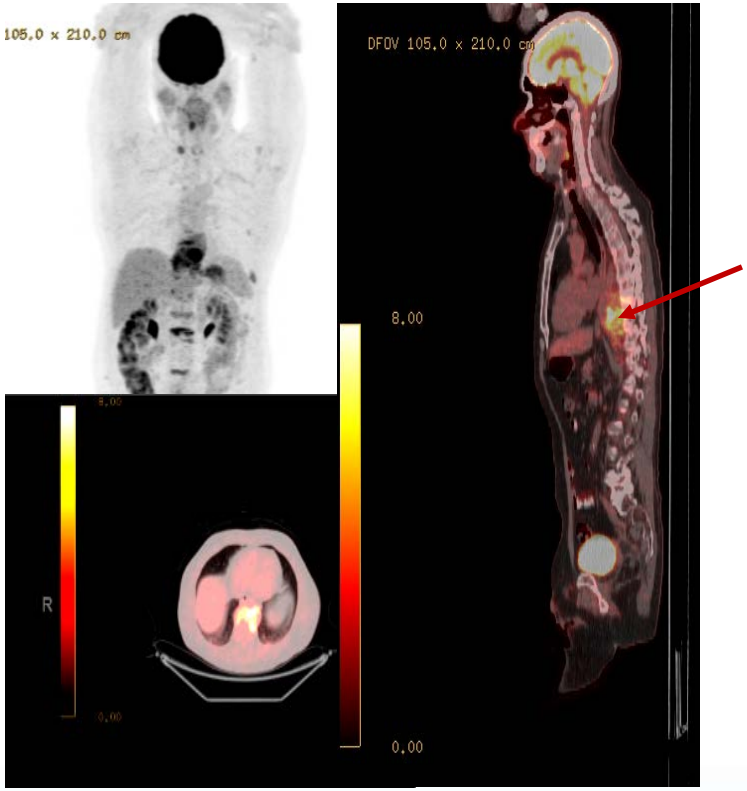
The kappa light chains and the kappa/lambda ratio have increased on three consecutive visits

- Bone marrow biopsy: no evidence of disease, normal cytogenetics and normal FISH results
- PET/CT

The patient describes a sense of pressure radiating from the sub-sternal region to the back, most notable when flat in bed

- Echocardiogram: EF 64%, no pericardial effusion, normal wall motion
- EKG unremarkable

Case Study Continued…



2-16-2016

PET/CT: 2/16/16 compared to baseline scan on 1/19/15

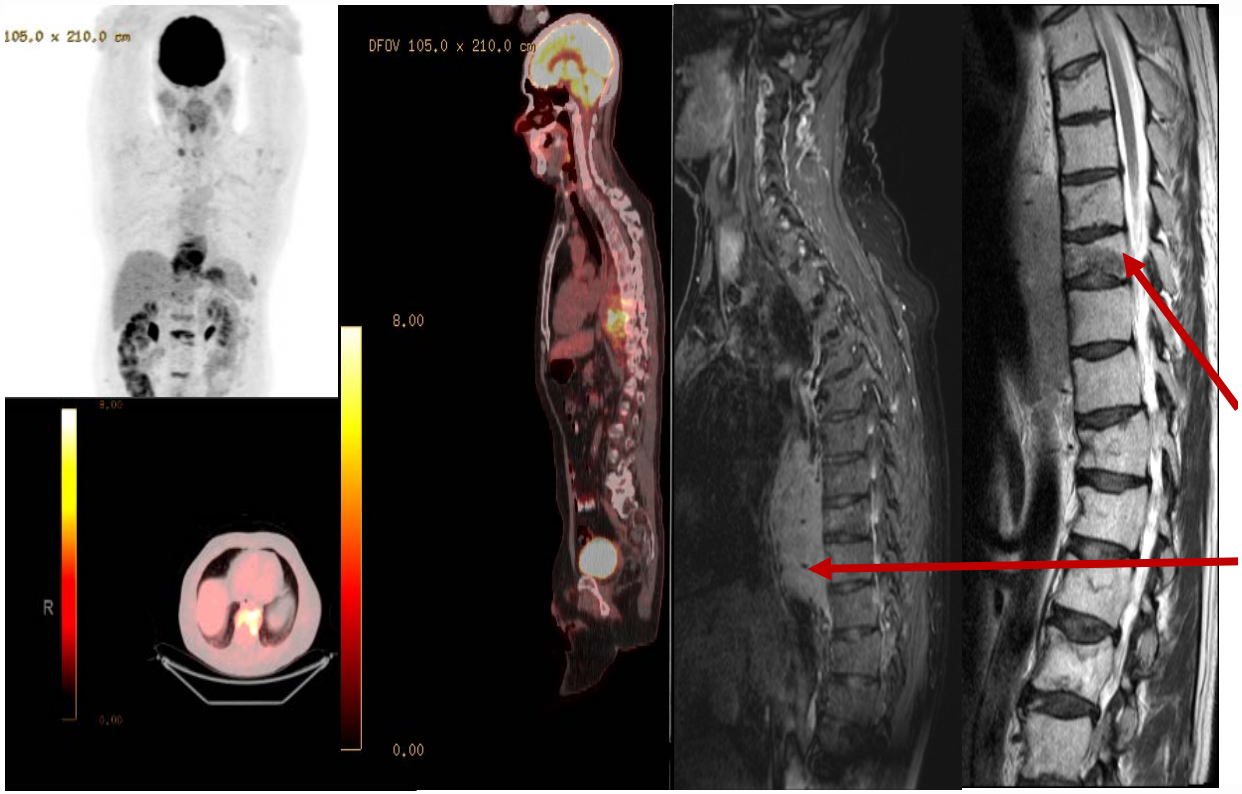
1. Interval progression of disease in the form of an enlarging, increasingly FDG avid (SUV 29.5) para-aortic mass ***consistent with known multiple myeloma***

2. Previously identified FDG avid mixed lytic/sclerotic osseous lesions involving the axial skeleton demonstrate no significant interval change

Clinical Decision Making/Discussion

What additional testing or investigations would you consider at this point and why?

Relapsed MM



MRI: 2/18/16

Multiple levels of involvement of the thoracic spine with myeloma,
most significantly at T8 where there is a pathologic fracture

Large *pre*vertebral mass extends from T6 to T10

2-16-2016

2-18-2016

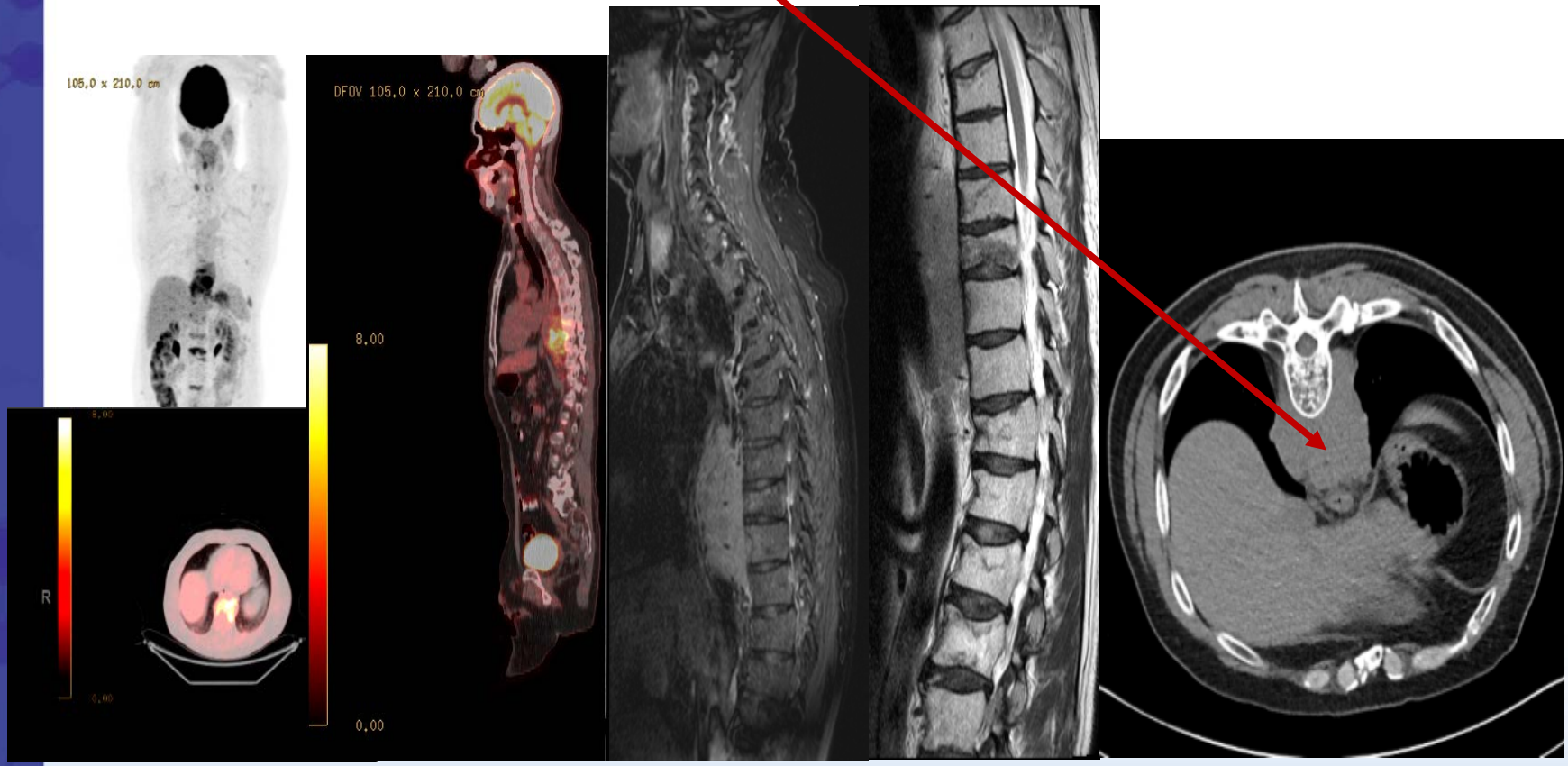
Clinical Decision Making: What Additional Testing Would You Consider at This Point and Why?

The patient has a history of malignant melanoma on the right shoulder. Sentinel nodes were negative and margins were clear on wide excision.

What would you recommend at this point?

Relapsed MM

CT-guided biopsy ordered – confirmed MM
Referred to Radiation Oncology



2-16-2015

2-18-2015

2-22-2016

Pomalidomide

FDA approval: February 8, 2013
Class: IMiD
Administration: oral

- REMS program
  - Discuss administration with patient: 4 mg once daily on days 1-21 of 28-day cycle
  - Take without food
    - At least 2 hr before/after meals
    - Do not break, chew, or open the capsules
  - Adherence: consistent schedule (AM or PM)

Pomalidomide Common AEs (in > 30%)	
AE, all grades	**%**
Fatigue and asthenia	55
Neutropenia	52
Constipation	38
Nausea	36
Diarrhea	34
Dyspnea	34
Upper resp. tract infection	32
Back pain	32
Pyrexia (pom + dex)	30

Educate patients on

- DVT prophylaxis
- Infection risk/blood counts
- Fatigue
- Should not cause peripheral neuropathy

Pomalidomide [package insert].

Carfilzomib

FDA approval: July 20, 2012
Class: proteasome inhibitor
Administration:

- Premedicate: 4 mg dexamethasone before carfilzomib
  - All doses cycle 1; 1st dose cycle 2
  - Additional doses/cycles if infusion reactions
- Hydrate: 250 to 500 mL IV saline
  - Before carfilzomib; after (optional)
  - Monitor for overhydration
- Administer carfilzomib IV
  - Over ~ 10 min (longer if needed)
  - Rinse IV with saline before and after

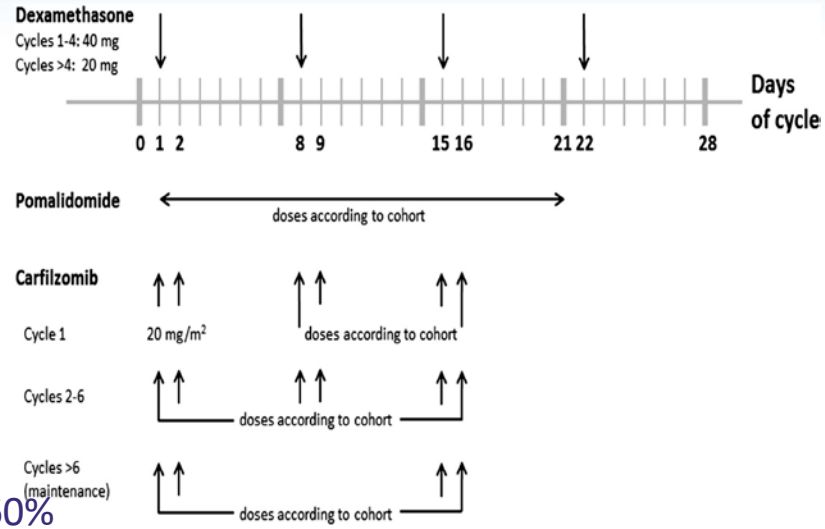
Carfilzomib AEs (All Grades) >30%	
AE	**%**
Fatigue	56
Anemia	47
Nausea	45
Thrombocytopenia	36
Dyspnea	35
Diarrhea	33
Pyrexia	30

- Monitor AEs, which may include cardiopulmonary
- The drug may require dose adjustment for toxicities; diuretics, inhalers; minimal peripheral neuropathy

Carfilzomib [package insert].

Carfilzomib/Pomalidomide/Dexamethasone (CPD; Car/Pom/Dex)

- Open-label, multicenter, phase 1, dose-escalation study
- Patients with RRMM, including lenalidomide (n=32)
  - Heavily pretreated patient population (median of 6 lines of prior therapy)
- Primary objective: Evaluate safety, determine MTD



Safety

- Hematologic adverse events (AEs) occurred in ≥ 60% of all patients, including 11 patients with grade ≥ 3 anemia
- Dyspnea was limited to grade 1/2 in 10 patients
- Peripheral neuropathy was uncommon and limited to grade 1/2
- Eight patients had dose reductions during therapy, and 7 patients discontinued treatment due to AEs
- Two deaths were noted on study due to pneumonia and pulmonary embolism (n = 1 each)

MTD of CPD (28-day cycle)

Carfilzomib 20/27 mg/m^2

Pomalidomide 4 mg

Dexamethasone 40 mg

www.clinicaltrials.gov as #NCT01464034

RRMM=relapsed/refractory multiple myeloma