NCCN 11th Annual Congress:
Hematologic Malignancies™

# Patient Case Studies & Panel Discussion

**Panelists:** Carol Ann Huff, MD, *The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins*; Ola Landgren, MD, PhD, *Memorial Sloan Kettering Cancer Center*; George Somlo, MD, *City of Hope Comprehensive Cancer Center*

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# CASE 1

George Somlo, MD

*City of Hope Comprehensive Cancer Center*

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# Educational Objectives

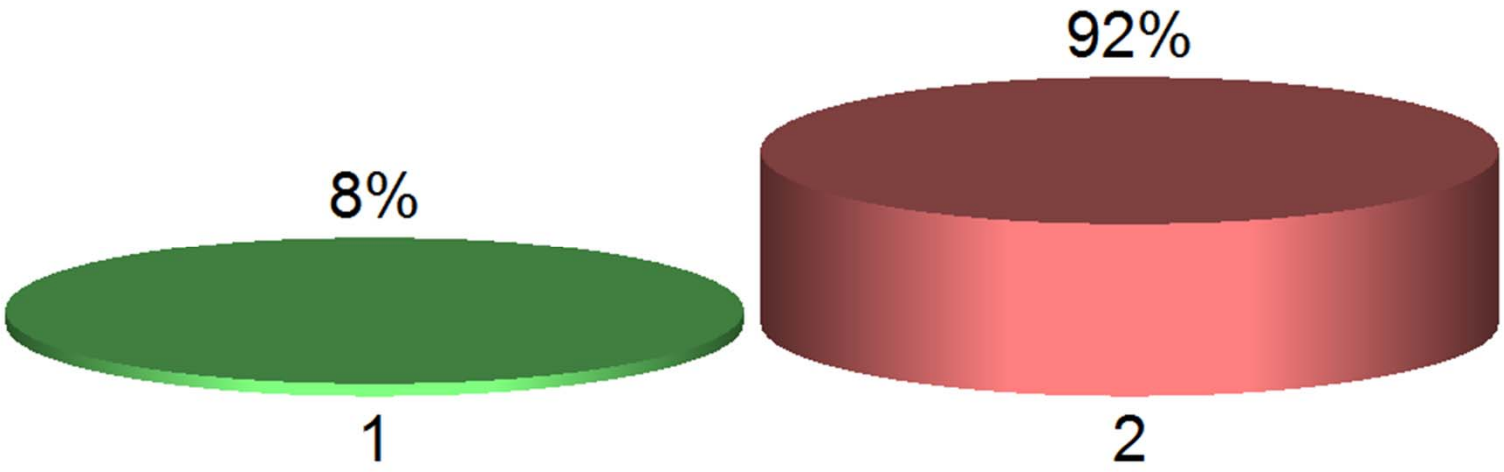
- Discuss considerations required for diagnosing different subtypes and managing MGUS
- Individualize strategies between observation vs. treatment based on assessing risk factors and monitoring for evolution into smoldering or active myeloma.

## Audience Polling Results

# True or False:

**MGUS will evolve into MM in every case.**

1. True
2. False

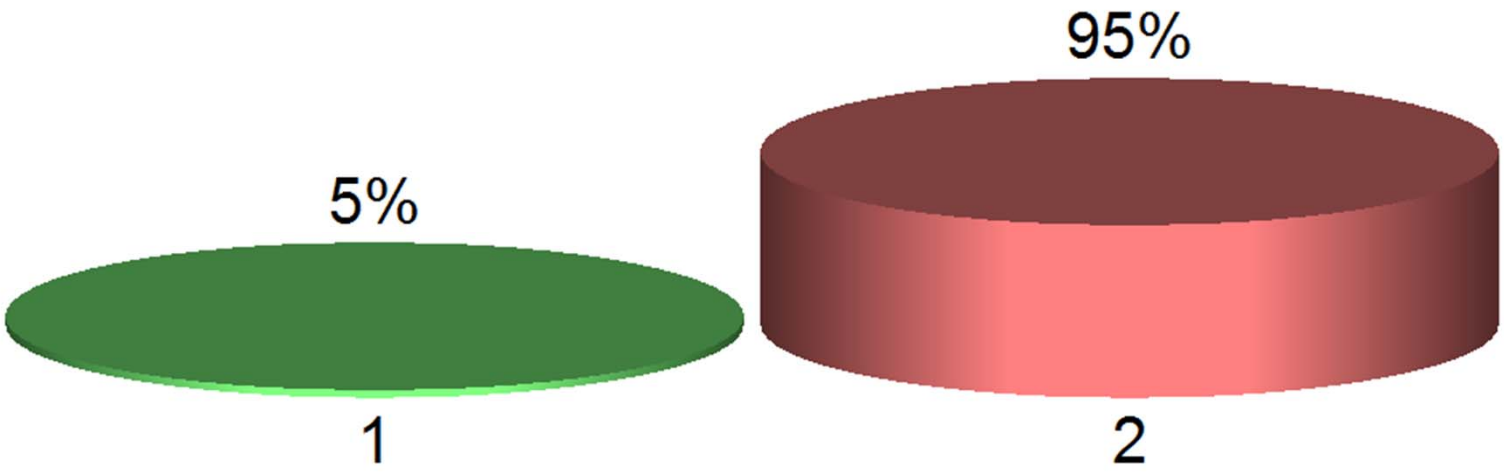


## Audience Polling Results

# True or False:

**There is never any chromosomal abnormality at the MGUS stage.**

1. True
2. False

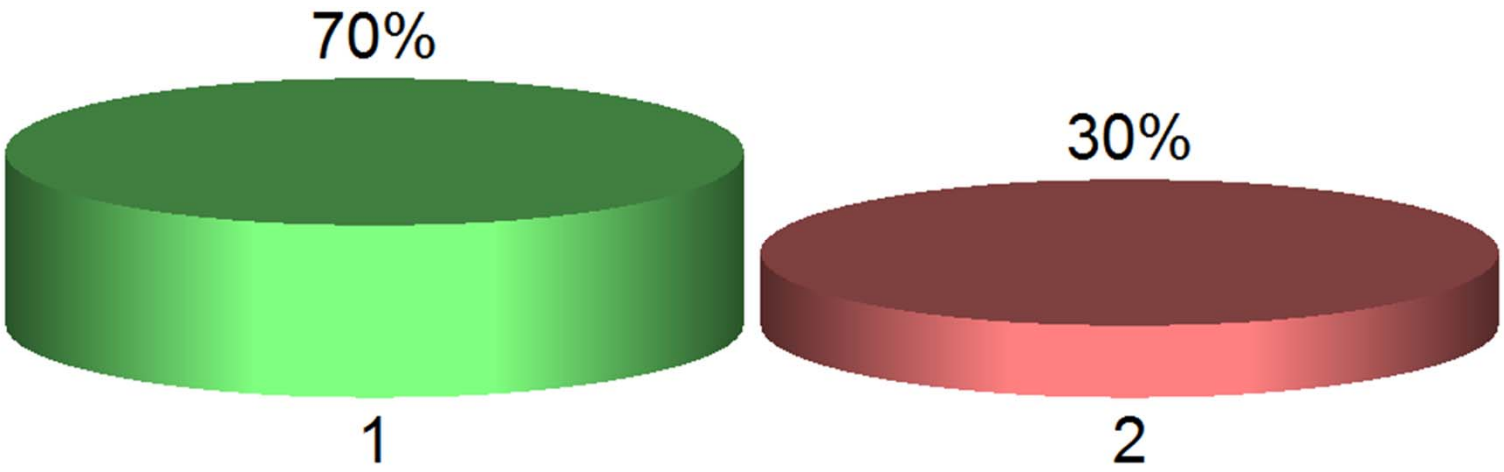


## Audience Polling Results

# True or False:

**Close monitoring of patients with MGUS may improve survival.**

1. True
2. False



# Case Study

- 65 y old male presents with sudden back pain after playing golf.  His last physical evaluation and MD visit occurred 5 years prior.
- His primary provider orders a series of diagnostic tests including a comprehensive chemistry panel, which are scheduled in 4 weeks.
- By the time the tests are done, the patient is completely asymptomatic, the chemistry panel reveals an elevated total protein but no other abnormalities; CBC, differential, platelets are normal; SPEP/IFE ordered reveal a monoclonal IgG kappa spike.

# Case Study

- The hematology consultant performs a complete myeloma work-up including bone imaging, free light chain testing in urine and in blood, and a bone marrow biopsy.
- There are no skeletal lesions, the free light chain ratio is > 1.65, there is an M protein of 1.3 g/dL, and the marrow contains 8% clonal plasma cells, no sign of amyloidosis.  FISH : clonal t(4:14).

# Updated IMWG Criteria for Diagnosis of MGUS and Smoldering Myeloma

**MGUS**

Myeloma protein < 3 g/dL

Bone marrow clonal involvement < 10%

No myeloma defining events*

**Smoldering Myeloma**

M protein ≥ 3 g/dL

BM clonal involvement ≥ 10-60%

No myeloma defining events*

*__C__: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
__R__: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
__A__: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
__B__: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

# MGUS

- Incidence is 3-4% in the population over age 50
- Family Hx and AA race are associated with higher risk for MGUS
- Non-IgM subtype may evolve into smoldering or symptomatic MM
- IgM subtype: may evolve into Waldenström's Macroglobulinemia
- Light chain MGUS: may evolve into light chain MM

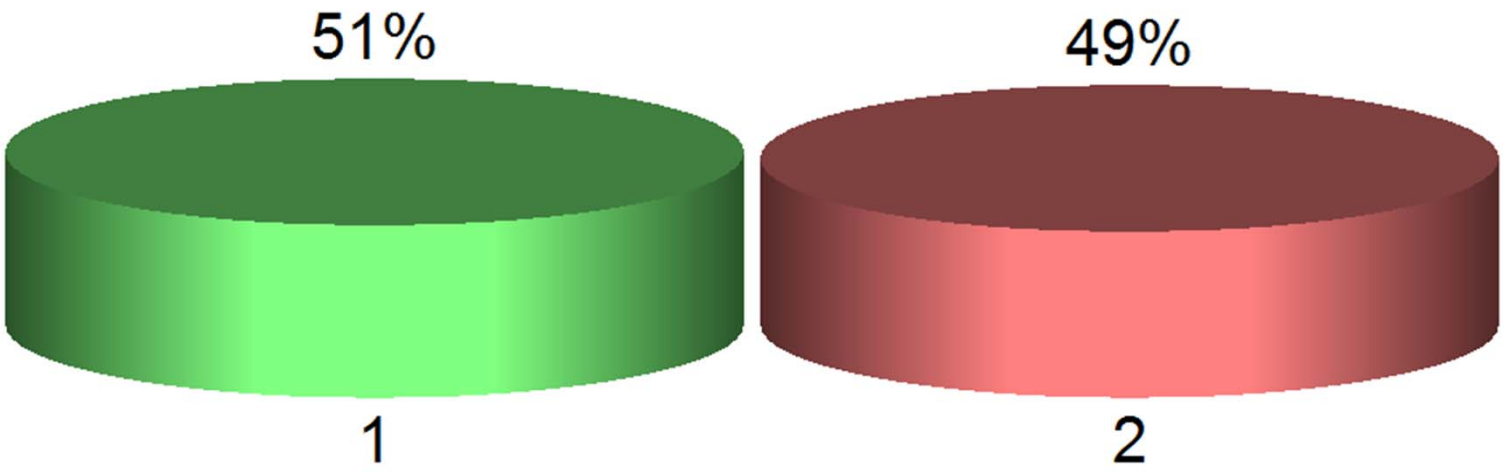
Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548. Manier et al. ASCO Educational Book 2016 e400-406.

## Audience Polling Results

# True or False:

**MGUS will evolve into MM at 1.5% per year regardless of the type and amount of M protein.**

1. True
2. False



# Risk Factors for MGUS Progression and Reason for Monitoring Patients with MGUS Carefully

| M protein < 1.5 g/dL, IgG subtype, normal free light chain ratio | Cumulative absolute risk of Progression at 20 years |
|---|---|
| ***Low Risk*** | 5 |
| IgG protein, < 1.5 g/dL, normal free light chain ratio | |
| ***Low Intermediate*** Risk: 1 risk factor | 21 |
| ***High Intermediate*** Risk: 2 risk factors | 37 |
| ***High Risk***: 3 risk factors | 65 |

Rajkumar et al, Blood.2005;106:812-817; Sigurdardottir EE et al. Jama Oncol 2015. 1:168-74

# Risk Factors for MGUS Progression

| Factor, % | 2-Yr Progression |
|---|---|
| High levels of circulating plasma cells | 80 |
| Bone marrow plasma cell proliferative rate | 80 |
| Transformation into smoldering multiple myeloma | 65 |
| Abnormal plasma cell phenotype ≥ 95% plus immunoparesis | 50 |
| t(4;14), 1q amp, del(17p) | 50 |
| Decreased clearance by ≥ 25% and rise in urinary monoclonal protein or serum free light-chain concentrations | NA |

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

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# NCCN Guidelines Version 1.2017
# Multiple Myeloma

## STAGING SYSTEMS FOR MULTIPLE MYELOMA[1]

| Stage | International Staging System (ISS) | Revised-ISS (R-ISS) |
|---|---|---|
| I | Serum beta-2 microglobulin <3.5 mg/L,<br>Serum albumin ≥3.5 g/dL | ISS stage I and standard-risk chromosomal abnormalities by iFISH[2]<br>and<br>Serum LDH ≤ the upper limit of normal |
| II | Not ISS stage I or III | Not R-ISS stage I or III |
| III | Serum beta-2 microglobulin ≥5.5 mg/L | ISS stage III and either high-risk chromosomal abnormalities by iFISH<br>or<br>Serum LDH > the upper limit of normal |

[1]Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: A report from International Myeloma Working Group. J Clin Oncol 2015;33:2863-2869.

MYEL-B

# Post-Discussion Answers

- **MGUS will evolve into MM in every case. FALSE**
- **MGUS will evolve into MM at 1.5% per year regardless of the type and amount of M protein. FALSE**
- **There is never any chromosomal abnormality at the MGUS stage. FALSE**
- **Close monitoring of patients with MGUS may improve survival. TRUE**

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# CASE 2

Carol Ann Huff, MD
*The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins*

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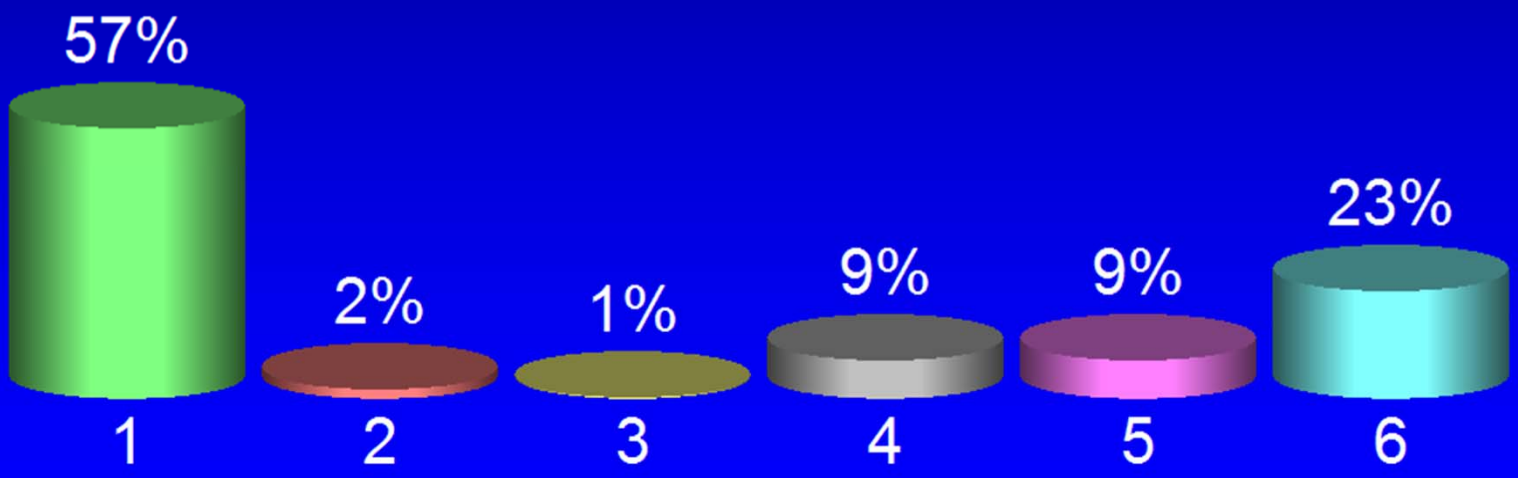
# Case Presentation

- A 72 year old male is referred by his primary care provider for evaluation of a monoclonal gammopathy. He is asymptomatic and his examination is normal.
- FHx: + Myeloma (Mother 90s)
- Labs:
  - WBC 6.34, Hb 11.9, Hct 36.9, plt 240K.
  - BUN 14, Cr 1.1, T Prot 6.1, Alb 4.1., Calcium 8.9
  - IgG 607, IgA 45, IgM 26.
  - SPEP (-). Serum IFE + lambda light chains
  - Kappa 8.4, Lambda 273, k/l ratio 0.03
  - 24 hr Urine – 130 mg protein – no M spike
  - Beta-2 microglobulin: 1.86
  - LDH: 140
  - UIFE: lambda light chains
  - Skeletal survey: no lytic lesions

## Audience Polling Results

**Q1: What, if any, additional testing would you like at this time?**

1. Bone Marrow Aspirate and Biopsy
2. PET CT scan
3. Whole body MRI
4. FISH studies
5. Nothing more
6. All of the above

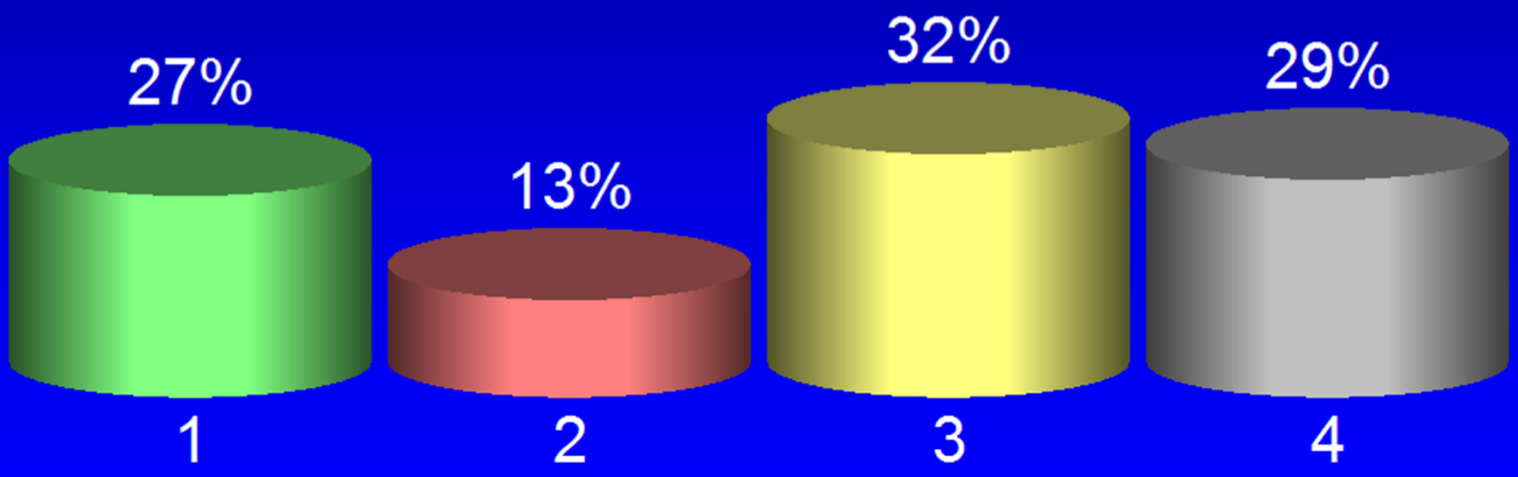


- A bone marrow aspiration and biopsy is done and shows:
  - 10% lambda-restricted plasma cells
  - A diagnosis of multiple myeloma is made.

## Audience Polling Results

**Q2. What will you do next?**

1. PET-CT scan
2. Whole body MRI
3. Watch and wait
4. Begin treatment



# Updated IMWG Criteria for Diagnosis of Multiple Myeloma

| MGUS | Smoldering | Multiple Myeloma |
|---|---|---|
| ▪ M protein < 3 g/dL<br>▪ Clonal plasma cells in BM < 10%<br>▪ No myeloma defining events | ▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)<br>▪ Clonal plasma cells in BM ≥ 10% to 60%<br>▪ No myeloma defining events | ▪ Underlying plasma cell proliferative disorder<br>▪ AND 1 or more myeloma defining events<br>▪ ≥ 1 CRAB* feature<br>▪ Clonal plasma cells in BM ≥ 60%<br>▪ Serum free light chain ratio ≥ 100<br>▪ > 1 MRI focal lesion |

*C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

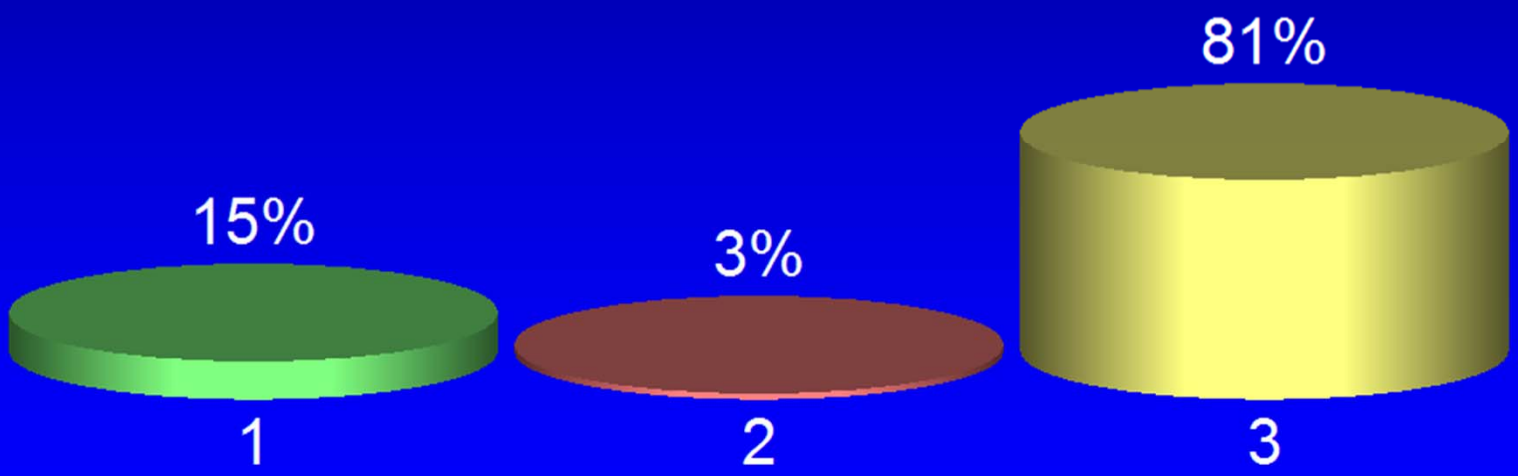
Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

- **PET-CT scan demonstrates no bone lesions and a diagnosis of smoldering myeloma is made.**

## Audience Polling Results

**Q3. On the basis of the available information, what would you do next?**

1. Begin systemic therapy
2. Repeat lab work in one year
3. Repeat lab work in three months



# Smoldering Myeloma: Risk Factors for Progression

**Mayo Clinic (N = 273)**

| Risk Factors, n | Patients, n (%) | Progression at 5 Yrs, % |
|---|---|---|
| 1 | 81 (28) | 25 |
| 2 | 114 (42) | 51 |
| 3 | 78 (30) | 76 |

**PETHEMA Study Group (N = 89)**

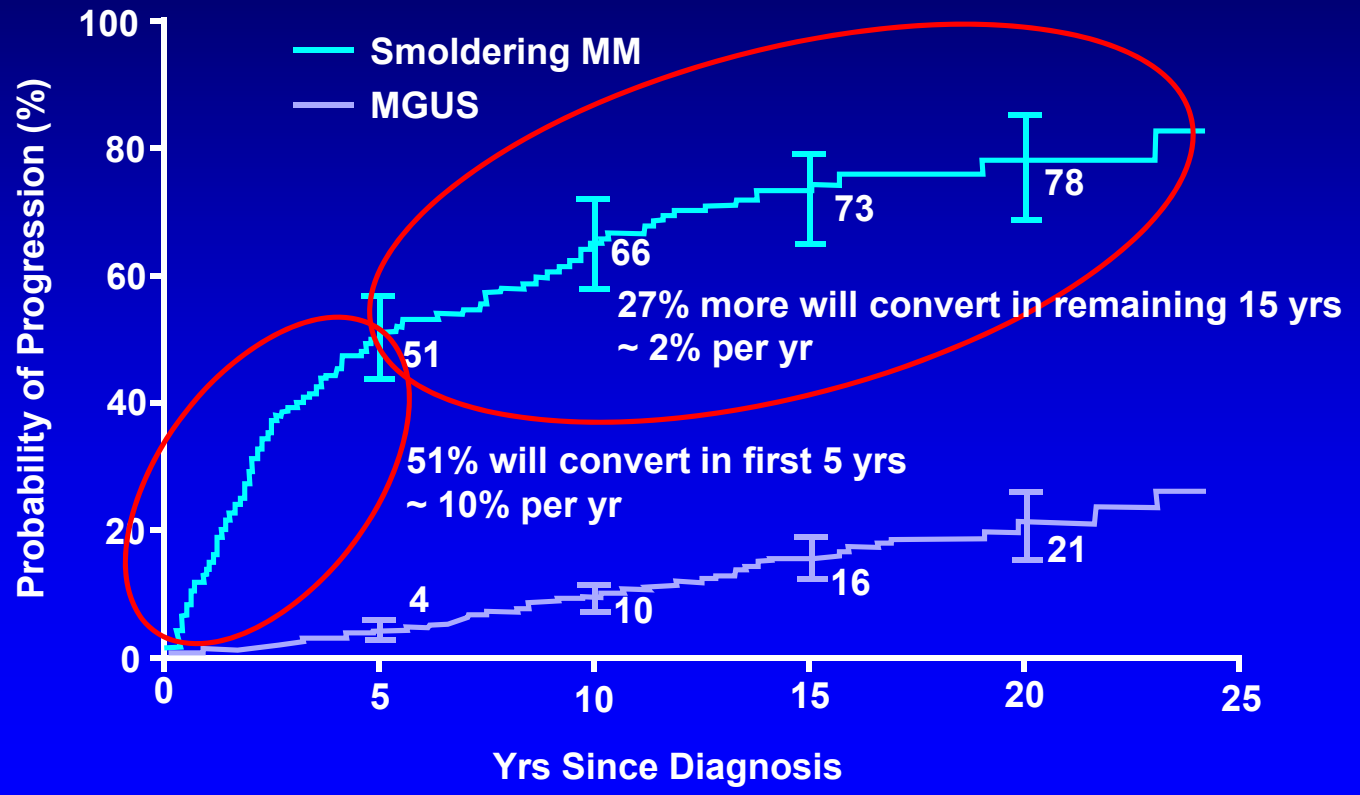
| Risk Factors, n | Patients, n (%) | Progression at 5 Yrs, % |
|---|---|---|
| 0 | 28 (31) | 4 |
| 1 | 22 (25) | 46 |
| 2 | 39 (44) | 72 |

## Risk factors

- Mayo Clinic[1]
  - BMPCs ≥ 10%
  - M-protein ≥ 3 g/dL
  - FLC ratio < 0.125 or > 8
- **PETHEMA[2]**
  - **≥ 95% abnormal plasma cells**
  - **Immunoparesis**
- **University of Salamanca[3]**
  - **BMPCs ≥ 10%**
  - **High M-protein: IgG ≥ 3 g/dL, IgA ≥ 2 g/dL, or Bence-Jones > 1 g/24 hrs**

Dispenzieri A, et al. Blood. 2008;111:785-789. 2. Pérez-Persona E, et al. Blood. 2007;110:2586-2592. Mateos MV, et al. N Engl J Med. 2013;369:438-437.

# Smoldering Multiple Myeloma



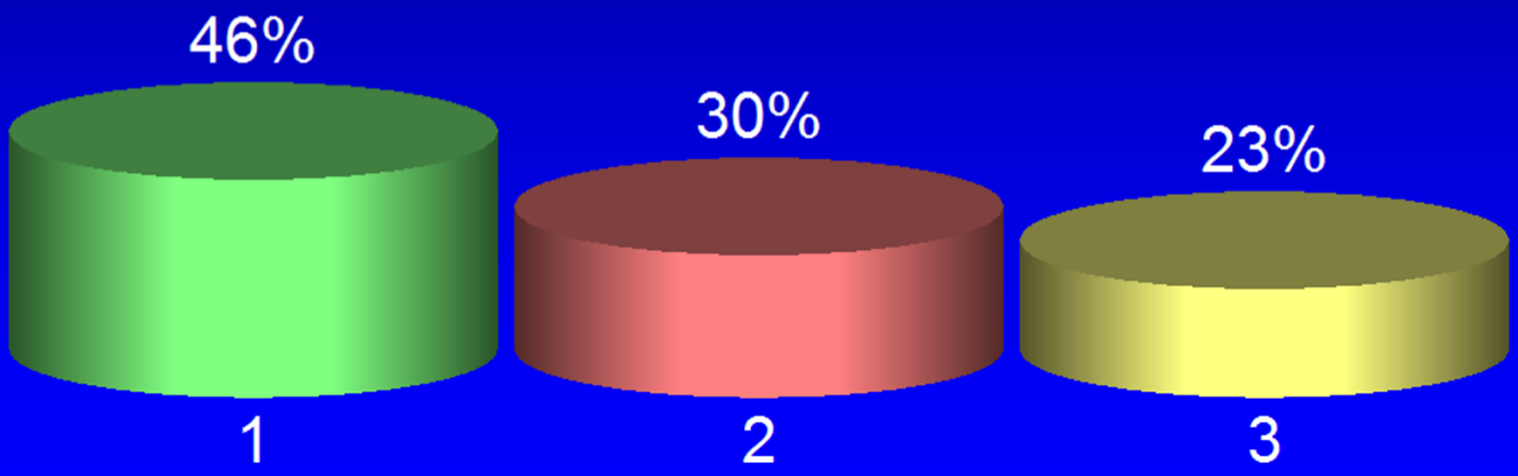

Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

- He is followed every three months with CBC, chemistry, serum light chains and 24 hour UPEP.
- Four years later,
  - WBC 5.78, Hb 11.2, Hct 35.2, plt 200K
  - BUN 17, Cr 1.0, Ca 9.3, T Prot 6.3, Alb 4.4
  - 24 hr Urine protein 450 mg (M spike 268 mg)
  - Kappa 1.9, lambda 444 and kappa/lamda ratio= 0.004
  - PET-CT – no bone lesions

## Audience Polling Results

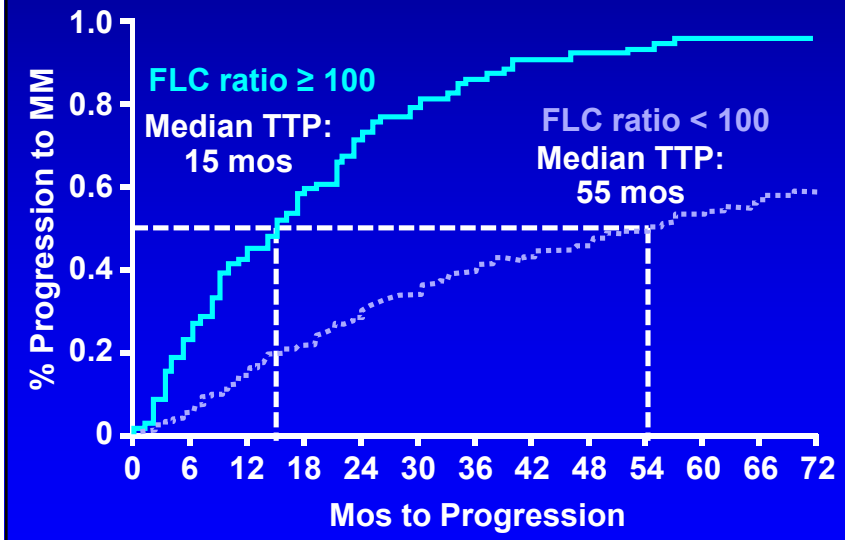
**Q4. What would you do next?**

1. Begin systemic therapy for active myeloma
2. Continue to watch and wait
3. Additional testing

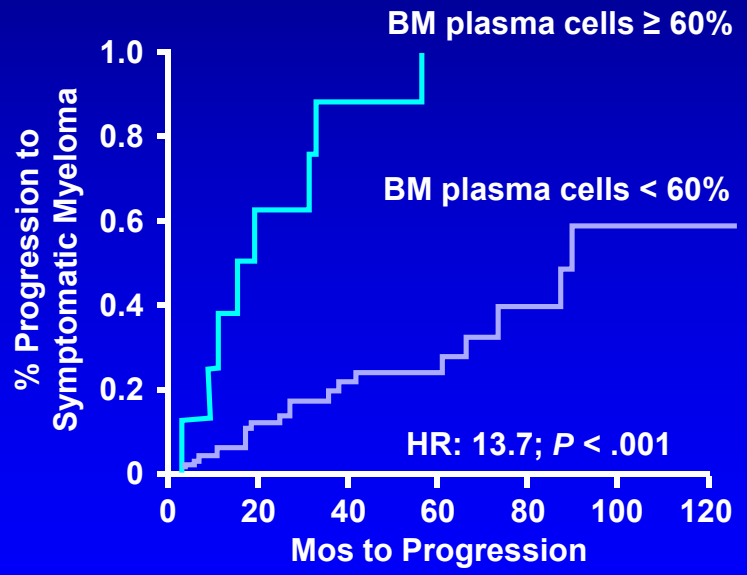


# Biomarkers to Predict Risk of Progression

**FLC ratio ≥ 100 predicts risk (*P* < .0001)**




**Clonal plasma cells in BM predicts risk (*P* < .001)**




Larsen JT, et al. Leukemia. 2013;27:941-946. Kastritis E, et al. Leukemia. 2013;27:947-953.

- Based on the serum light chain ratio, he now has active myeloma.
- Repeat BM biopsy showed t(11;14) which was unchanged from initial BM.
- The decision was made to initiate systemic therapy.

# Take Home Points

- The diagnostic criteria for smoldering myeloma (SMM) has been recently refined
- Like MGUS, smoldering myeloma can be further stratified (low, intermediate, high)
- SMM's highest risk of progression is in the first 5 years
- Currently, treatment of SMM should be limited to high risk disease or ideally on a clinical trial

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# CASE 3

Ola Landgren, MD, PhD
*Memorial Sloan Kettering Cancer Center*

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# Multiple myeloma with kidney failure 10 years ago…

- Chance of renal recovery ~20%
- One year survival <50%
- “Palliative” disease state

# Multiple myeloma with kidney failure in 2016

- Chance of renal recovery ~70%
- Two year survival ~70%
- A “medical emergency”

# 76-year-old female with relapsed light-chain myeloma

## 76-year-old female

- Diagnosed 2 yrs ago with light-chain (lambda) myeloma. Treated with lenalidomide/dexamethasone and obtained VGPR

- Presents with sFLC lambda 120 mg/dL and serum creatinine 6 mg/dL (566 µmol/L)
  - CrCl 9.7 mL/min
  - 4 g of urinary protein (3.4 g is lambda FLC)
  - Ca 10.4 mg/dL (2.6 mmol/L)
  - NSAID use

# 76-year-old female: baseline kidney status

- Two years ago – at myeloma diagnosis – creatinine was 1.0 mg/dL

- How severe is the acute kidney injury (AKI) *versus* chronic kidney injury (CKD)?

# Definitions of acute kidney injury (AKI)

| Urine output | KDIGO stage (kidney disease: improving global outcomes) | Serum creatinine | AKIN stage (acute kidney injury network) | Serum creatinine | RIFLE class (risk, injury, failure, loss, end-stage renal disease) | Serum creatinine or GFR |
|---|---|---|---|---|---|---|
| <0.5 mL/kg/h for 6 hours | Stage 1 | Increase of 1.5–1.9 times baseline or ≥27 µmol/L (≥0.3 mg/dL) increase | Stage 1 | Increase to >150–200% (1.5–2-fold) from baseline or ≥27 µmol/L (≥0.3 mg/dL) increase | Risk | Increase in serum creatinine x 2 or GFR decreased >25% |
| <0.5mL/kg/h for 12 hours | Stage 2 | Increase of 2–2.9 times baseline | Stage 2 | Increase to >200–300% (>2–3-fold) from baseline | Injury | Increase in serum creatinine x 2 or GFR decreased >50% |
| <0.3 mL/kg/h for 24 hours or anuria for 12 hours | Stage 3 | Increase of >3 times baseline or increase in serum creatinine to ≥354 µmol/L (≥4 mg/dL) or initiation of renal replacement therapy | Stage 3 | Increase to >300% (>3-fold) from baseline or ≥354 µmol/L (≥4 mg/dL) with an acute increase of >44µmol/L (>0.5 mg/dL) or initiation of renal replacement therapy | Failure | Increase in serum creatinine x 3 or serum creatinine ≥354 µmol/L (>4 mg/dL) with an acute rise ≥44 µmol/L (>0.5 mg/dL) or GFR decreased >75% |
| | | | | | ESRD | ESRD >3 months |

**Kristensen SD, et al. Eur Heart J 2014;35:2383–431**

# Chronic kidney disease (CKD) definitions, by GFR and albuminuria

| Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009) | | | | Albuminuria stages, description and range (mg/g) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | A1 | | A2 | A3 | |
| | | | | Optimal and high-normal | | High | Very high and nephrotic | |
| | | | | <10 | 10–29 | 30–299 | 300–1999 | ≥2000 |
| GFR stages, description and range (mL/min/1.73 m$^2$) | G1 | High and optimal | >105 | | | | | |
| | | | 90–104 | | | | | |
| | G2 | Mild | 75–89 | | | | | |
| | | | 60–74 | | | | | |
| | G3a | Mild–moderate | 45–59 | | | | | |
| | G3b | Moderate–severe | 30–44 | | | | | |
| | G4 | Severe | 15–29 | | | | | |
| | G5 | Kidney failure | <15 | | | | | |

***Colors reflect the ranking of adjusted relative risk***

**Levey AS, et al. Kidney Int 2011;80:17–28**

# 76-year-old female: relapsed myeloma with renal failure

- What has caused her AKI?
- How are we going to make the diagnosis?
- What are we going to do about it?

# Differential diagnosis of acute kidney injury in multiple myeloma

# Pathological classification of monoclonal Ig's in the kidney

Organized deposits or inclusions

Non-organized deposits or inclusions

Table 1. Pathologic classification of diseases with tissue deposition or precipitation of monoclonal Ig

| Organized | | | Nonorganized (granular) | |
|---|---|---|---|---|
| **Crystals** | **Fibrillar** | **Microtubular** | **MIDD (Randall type)** | **Other** |
| Myeloma cast nephropathy | Light chain amyloidosis | Type I and type II cryoglobulinemic glomerulonephritis | LCDD | Proliferative GN with monoclonal Ig deposits |
| Light chain proximal tubulopathy (with or without Fanconi syndrome) | Nonamyloid | Immunotactoid GN | LHCDD | Waldenström |
| Crystal-storing histocytosis | Fibrillary GN* | GOMMID | HCDD | Macroglobulinemia |

GN indicates glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; and HCDD, heavy-chain deposition disease.

*Mostly associated with polyclonal IgG deposits.

**Leung N, et al. Blood 2012;120:4292–5**

# Light chain deposition disease

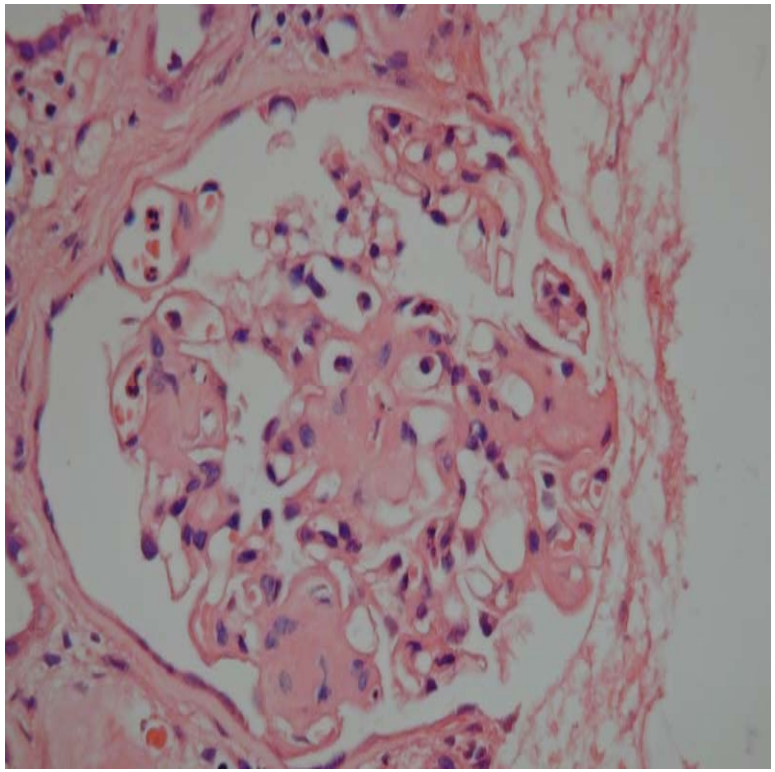


**Image courtesy of C. Hutchison**

# Renal amyloidosis

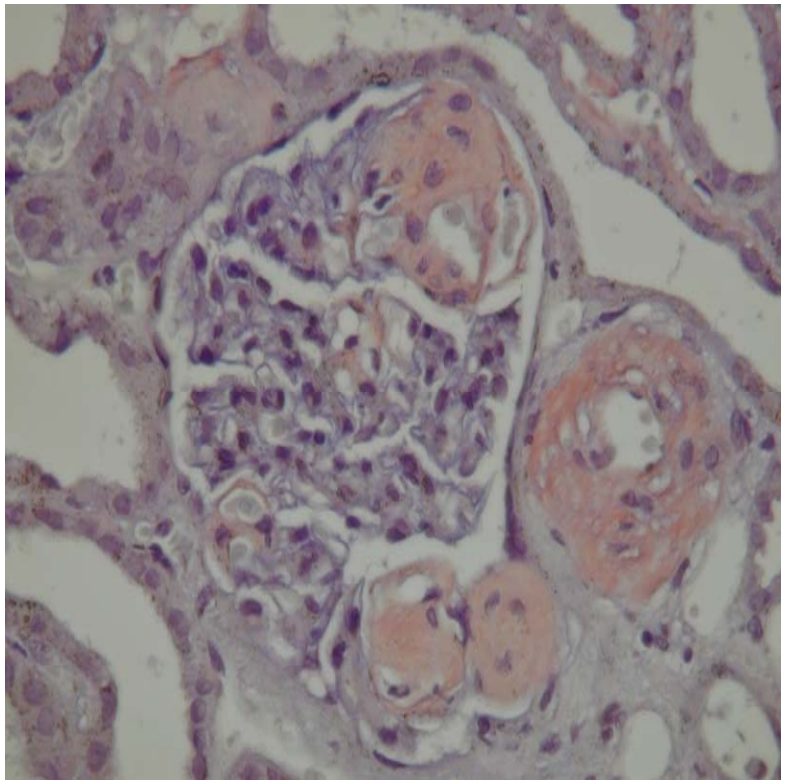
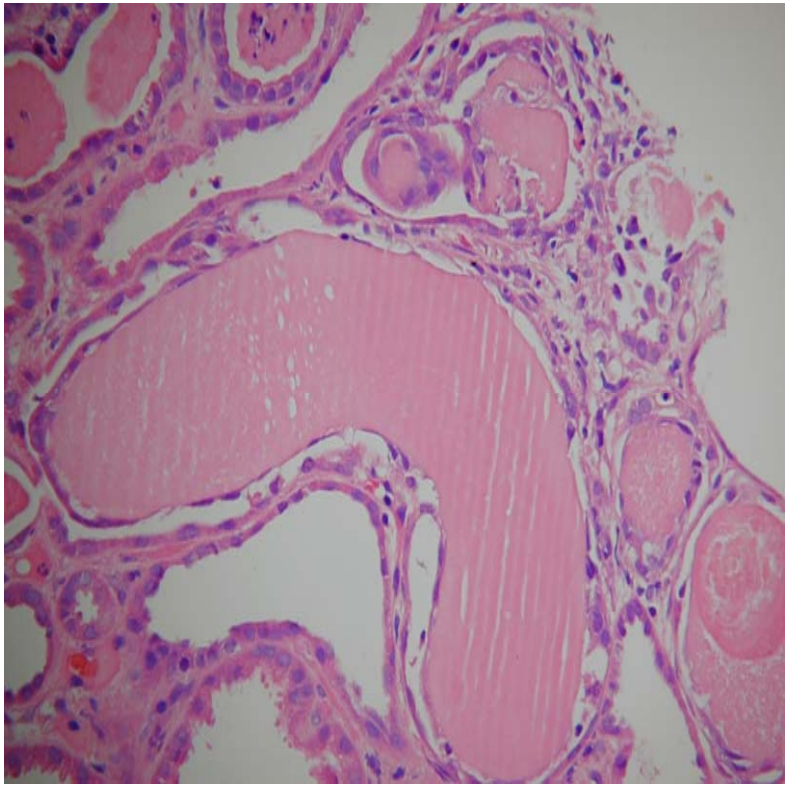


**Image courtesy of C. Hutchison**

# Cast nephropathy/myeloma kidney



**Accounts for 80-90% of severe renal failures in multiple myeloma**

**Image courtesy of C. Hutchison**

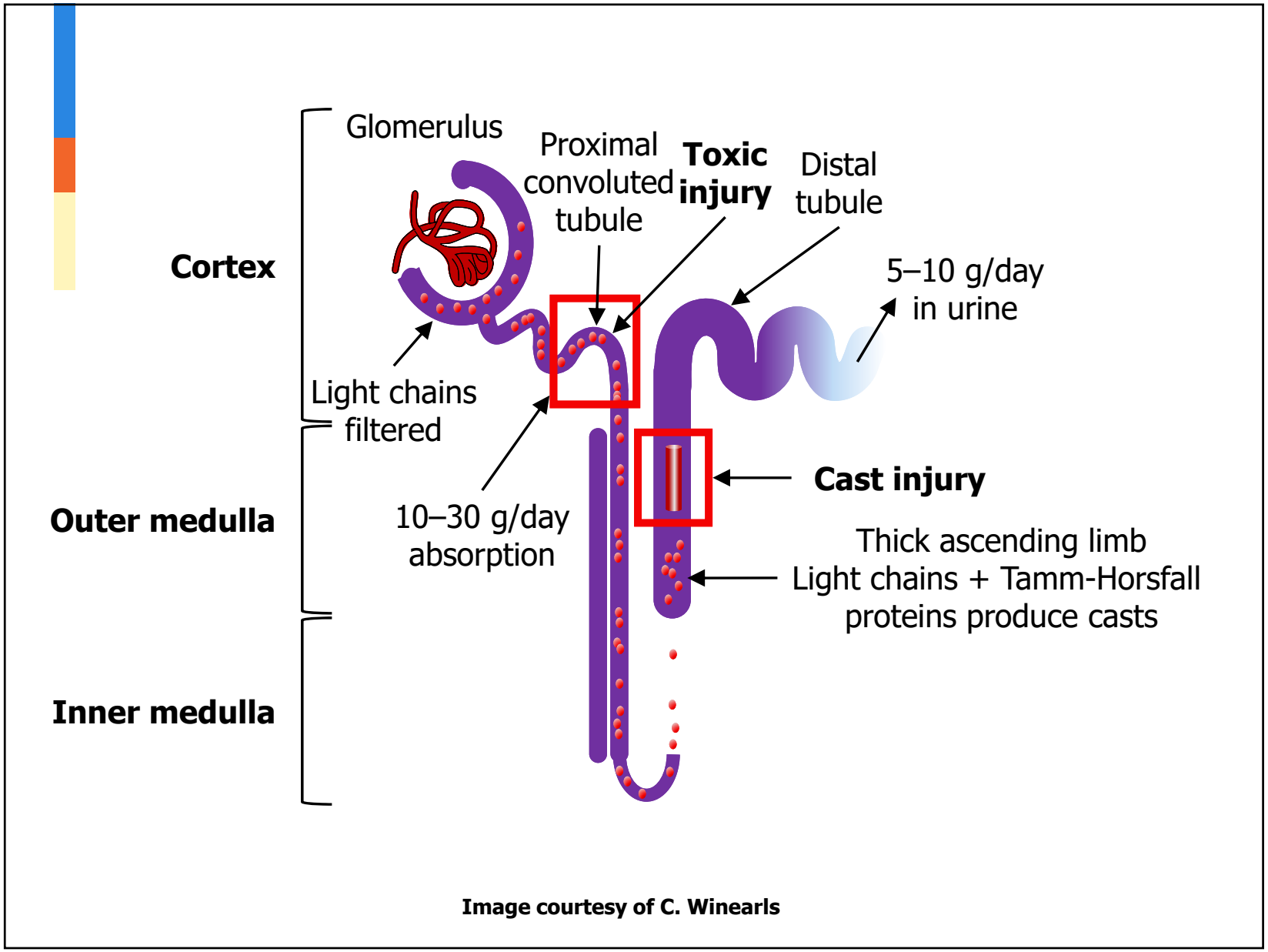
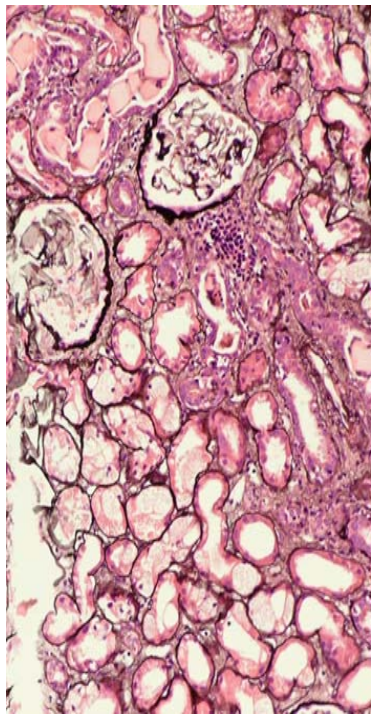



**Image courtesy of C. Winearls**

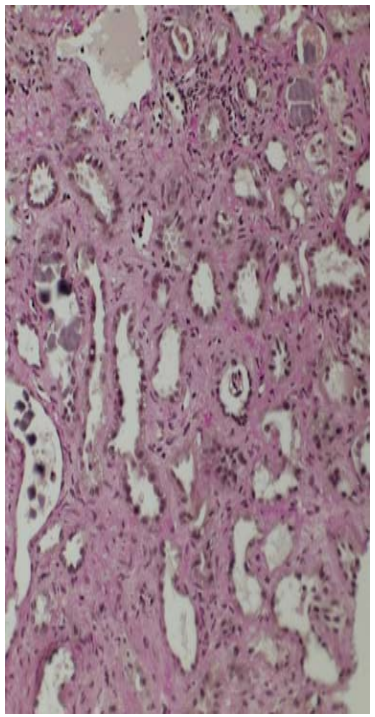
# Rapid renal scarring in myeloma kidney

**Presentation biopsy**



6 weeks

**Repeat biopsy**



**Basnayake K, et al. J Clin Pathol 2010;63:884–7**

# Risk of a kidney biopsy in this setting

**Four UK hospitals:**

- 1993 kidney biopsies
- 148 from M-protein pts

**Major bleed:**

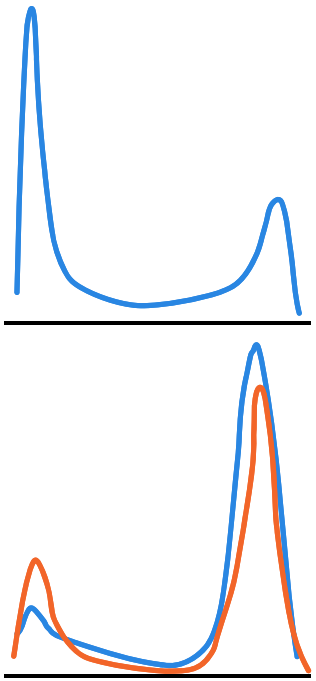
- 3.9% in general population
- 4.1% in the M-protein group

P=0.88

| Renal findings in patients with monoclonal gammopathies and associated haemorrhagic complications | | |
|---|---|---|
| Finding | Percentage (n) | Bleeding complications (n) |
| Amyloid | 23.7 (35) | 0 |
| Cast nephropathy | 62.2 (92) | 6 |
| Mixed amyloid and cast | 3.4 (5) | 0 |
| LCDD | 0.7 (1) | 0 |
| Intraglomerular crystal deposition | 0.7 (1) | 0 |
| Acute tubular necrosis (ATN) | 2.7 (4) | 0 |
| Other renal findings | 6.8 (10) | 0 |

Fish R, et al. Clin J Am Soc Nephrol 2010;5:1977–80

# What is in the urine?




Selective proteinuria –
Light chains predominate
**Myeloma cast nephropathy**

Non-selective proteinuria –
Or albumin predominance
Glomerular or tubular pathology
**AL amyloidosis**
**Monoclonal Ig deposition disease (MIDD)**
**Other monoclonal immunoglobulin-related or -unrelated condition**

**Dimopoulos MA, et al. J Clin Oncol 2016**

## 76-year-old female

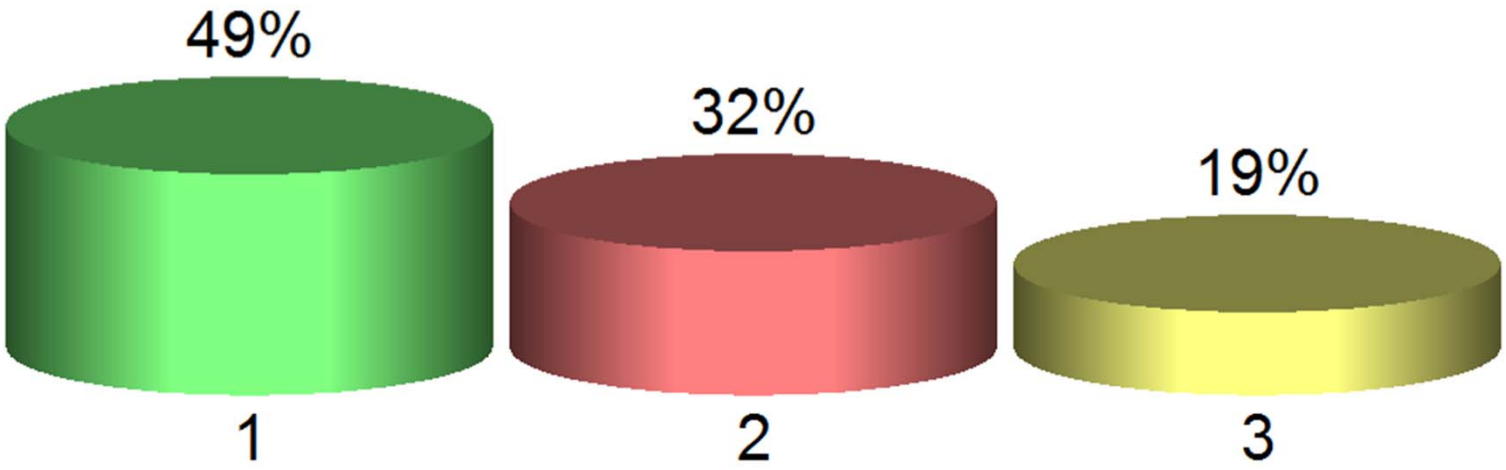
- Diagnosed 2 yrs ago with light-chain (lambda) myeloma. Treated with lenalidomide/dexamethasone and obtained VGPR

- Presents with sFLC lambda 120 mg/dL and serum creatinine 6 mg/dL (566 µmol/L)
  - CrCl 9.7 mL/min
  - 4 g of urinary protein (3.4 g is lambda FLC)
  - Ca 10.4 mg/dL (2.6 mmol/L)
  - NSAID use

## Audience Polling Results

**Would you biopsy?**

1. Yes
2. No
3. Seek a specialist opinion (ask a friend)



## Would you biopsy?

1. Yes
2. No
3. Seek a specialist opinion (ask a friend)

No biopsy

Myeloma kidney or acute tubular necrosis

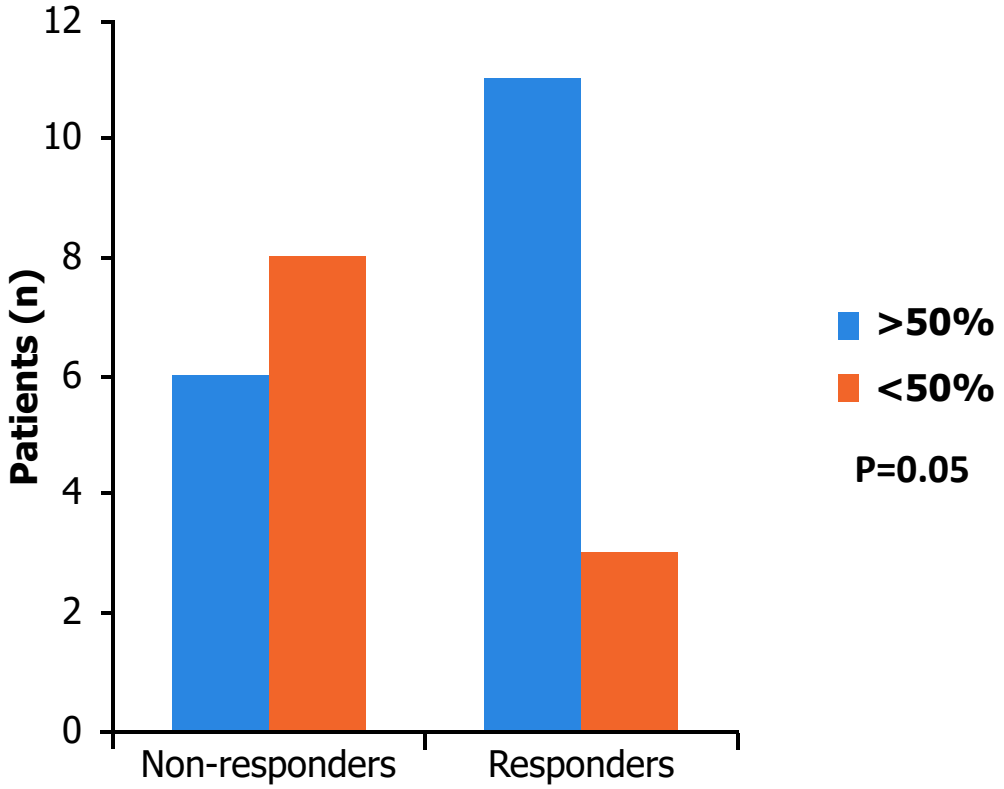
# Clinical management of renal insufficiency in myeloma

- Things to do:
  - Treat hypercalcemia (bisphosphonate, high-dose steroids and calcitonin)
  - Stop nephrotoxins
  - Fluid balance (>3 L day)

- Unsupported:
  - Alkalisation of urine

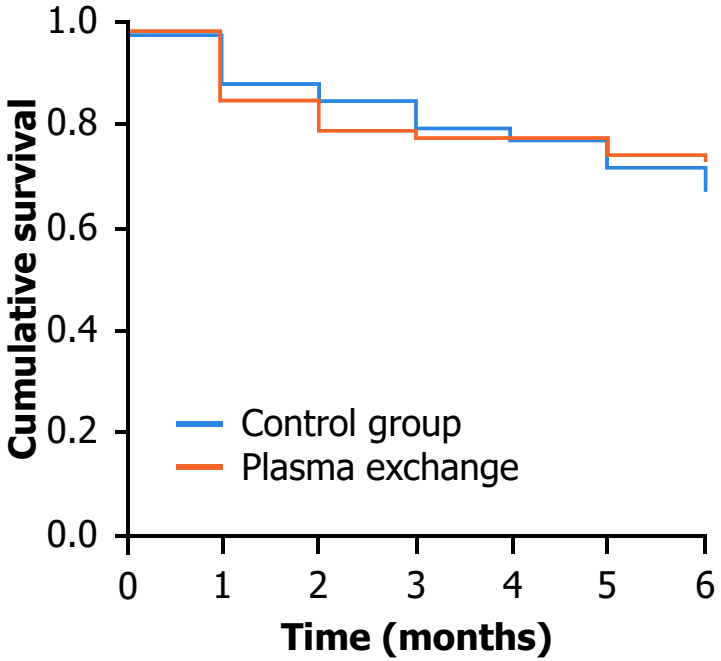
RI, renal impairment

# Reductions in serum FLCs improve renal outcomes in myeloma kidney




**Leung N, et al. Kidney Int 2008;73:1282–8**

# Randomized study of plasma exchange: no renal benefit, no survival benefit




| Patients at risk, n: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control group | 39 | 37 | 34 | 33 | 31 | 30 | 28 |
| Plasma exchange | 58 | 56 | 49 | 46 | 45 | 44 | 42 |

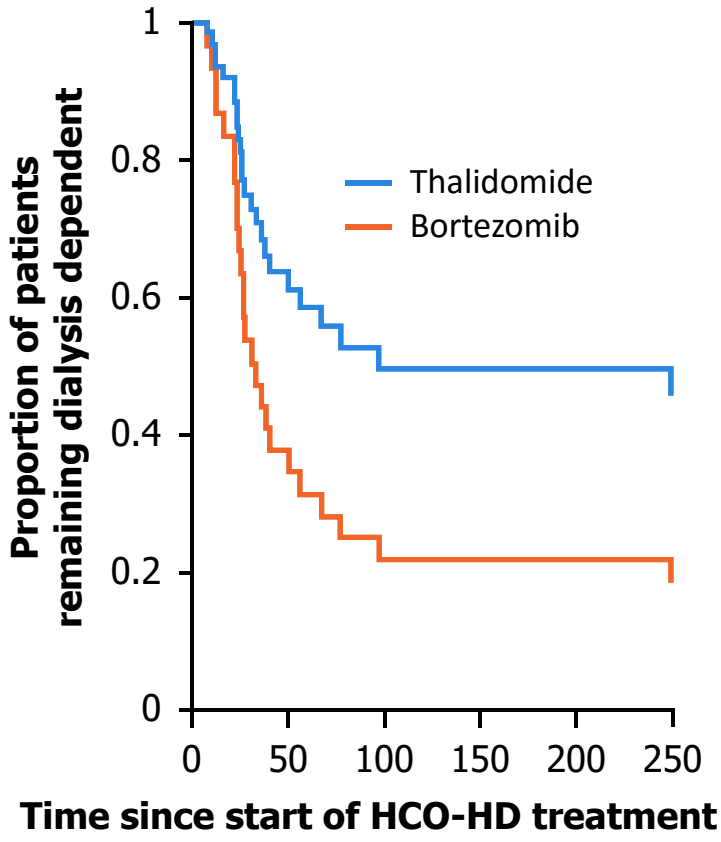
**Clark WF, et al. Ann Intern Med 2005;143:777–84**

# International myeloma working group (IMWG) guideline 2016

- Recommend proteasome inhibitor for treatment of myeloma-related renal impairment; given with dexamethasone
- Consider adding 3rd drug

**Dimopoulos MA, et al. J Clin Oncol 2016**

# Renal recovery is greater with proteasome inhibitor than IMiD

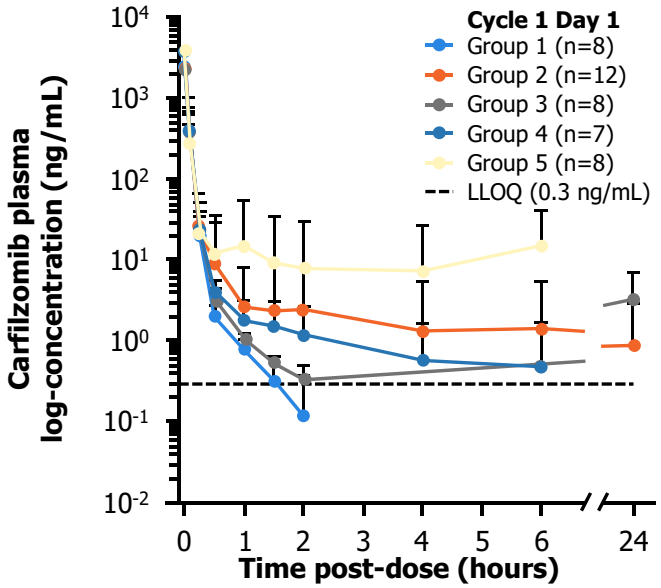



HCO-HD, high cut-off hemodialysis

Image courtesy of C. Hutchison

# Carfilzomib in myeloma patients with renal impairment

Pharmacokinetics and safety




- **No differences in carfilzomib clearance or exposure among patients with normal renal function and any group with renal impairment**
- **No difference in adverse events between renal groups**

**Badros AZ, et al. Leukemia 2013;27:1707–14**

# Clinical message to treating physician

- Myeloma and acute kidney injury (AKI) is a time critical emergency
- Get a diagnosis, start chemotherapy!
- Don't do a kidney biopsy in routine care. The bone marrow defines the treatment

# NCCN Member Institutions