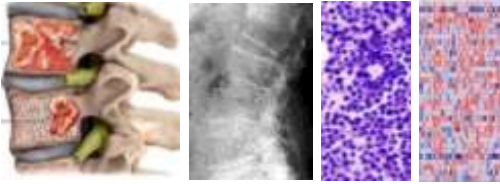


# Multiple myeloma: an overview and looking into the future



Advanced Oncology Education Series,  
Advancements in Cancer Clinical Trials Research:  
A snapshot from the NCI Center for Cancer Research

Ola Landgren, MD; Mary Ann Yancey, RN; Marcia Mulquin, RN  
[www.multiplemyeloma.cancer.gov](http://www.multiplemyeloma.cancer.gov)

---

---

---

---

---

---

---

---

## Outline

- Clinical presentation of multiple myeloma (symptoms, diagnosis, prognosis, basic therapeutic strategies, complications)
- Risk stratify myeloma precursor disease
- Future directions for multiple myeloma and its precursor disease (new therapeutic strategies, new types of drugs, role of early intervention)

---

---

---

---

---

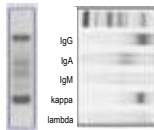
---

---

---

## Previously healthy 64-year-old man

- Presents with persistent pain in his lower back and fatigue
- CBC reveals a hemoglobin level of 9.6 g/dL
- A monoclonal (M) protein is detected on serum protein electrophoresis (IgG kappa)
- Radiologic skeletal bone survey shows lytic bone lesions of the vertebrae and the pelvis



---

---

---

---

---

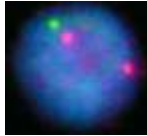
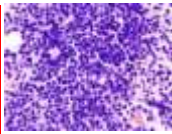
---

---

---

### Previously healthy 64-year-old man

- Multiple myeloma (MM) is confirmed by bone marrow aspiration showing infiltrate of plasma cells
- Serum calcium and creatinine levels are normal
- Albumin is 3.7 g/dL and beta2 microglobulin is 2.8 mg/L
- Fluorescence in situ hybridization (FISH) of bone marrow plasma cells shows deletion of chromosome 13



---

---

---

---

---

---

---

---

### Previously healthy 64-year-old man

- **Interpretation:**
  - Relatively young age
  - Absence of coexisting illnesses
- **A hematologist recommends:**
  - Induction therapy followed by...
  - High dose therapy with autologous hematopoietic stem cell transplantation (ASCT) as initial treatment

---

---

---

---

---

---

---

---

### Multiple myeloma in the U.S.

- 20,580 new cases (11,680 men; 8,980 women) and 10,580 deaths per year
- Average age at dx 65-70 yrs (<40 yrs; ~2%)
- The 2<sup>nd</sup> most common hematologic malignancy in whites; in Blacks it is #1

---

---

---

---

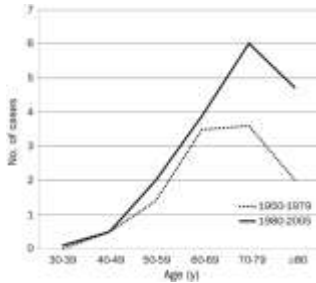
---

---

---

---

## Myeloma an increasing problem due to the aging population



- Many diagnosed at age 70-75 year
- Proportion of patients 80+ years **doubled** from 16% to 31%
- Therefore, median age increased from 70 to 74 years

Turesson et al, Mayo Clin Proc 2010

---

---

---

---

---

---

---

---

## Symptoms

---

---

---

---

---

---

---

---

## Common symptoms at multiple myeloma diagnosis

- Bone pain
- Fatigue
- Weight loss
- Parasthesias
  
- ~10% are asymptomatic/have only mild symptoms at dx

Kyle and Rajkumar, N Engl J Med 2004

---

---

---

---

---

---

---

---

## Clinical hallmarks of multiple myeloma

- **Hypercalcemia**
- **Renal failure**
- **Anemia**
- **Bone destructions (lytic lesions)**
- **Increased risk of infections**
- **Presence of *monoclonal protein***

Kyle and Rajkumar, *N Engl J Med* 2004

---

---

---

---

---

---

---

---

## Clinical work-up and diagnostic criteria

---

---

---

---

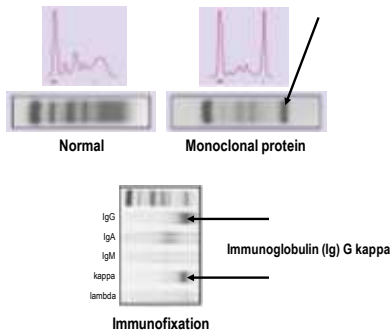
---

---

---

---

## Serum protein electrophoresis



Katzmann et al, *Electrophoresis* 1997

---

---

---

---

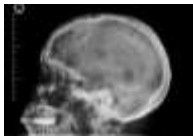
---

---

---

---

Skeletal X-ray shows punched-out lytic lesions, diffuse osteoporosis, and fractures



For MM work-up, bones should be evaluated with a complete "skeletal survey", including:

- Skull
- Spine
- Pelvis
- Extremities (including forearms and legs)



---

---

---

---

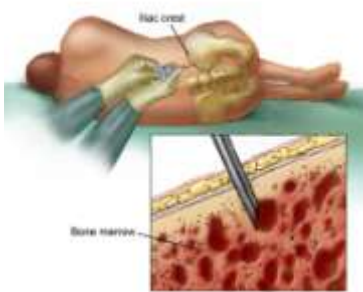
---

---

---

---

Bone marrow biopsy



---

---

---

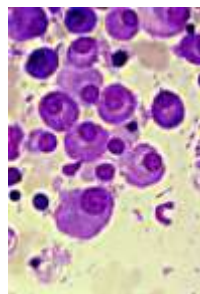
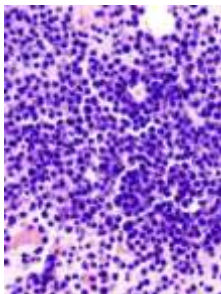
---

---

---

---

---



---

---

---

---

---

---

---

---

## Diagnostic criteria

	Monoclonal gammopathy of undetermined significance (MGUS)	Smoldering myeloma (SMM)	Multiple myeloma (MM)
Monoclonal (M)-protein in serum	<3 g/dL	>3 g/dL	Any
Monoclonal plasma cells in bone marrow	AND <10%	OR >10%	Any
End-organ damage	No	No	Yes
Comment	Requires exclusion of all other B-cell lymphoproliferative disorders	Requires exclusion of all other B-cell lymphoproliferative disorders	End-organ damage: • Hypercalcemia • Renal failure • Anemia • Lytic bone lesions

Kyle et al, Leukemia 2010

---

---

---

---

---

---

---

---

---

---

## Differential diagnosis

- MGUS
- SMM
- Solitary plasmacytoma
- Amyloidosis
- Light chain deposition disease
- Waldenström's macroglobulinemia
- Lymphoproliferative disorders
- Infections (e.g. CMV)
- Rheumatologic autoimmune disorders
- Certain skin or neurologic disorders

---

---

---

---

---

---

---

---

---

---

## Prognosis

---

---

---

---

---

---

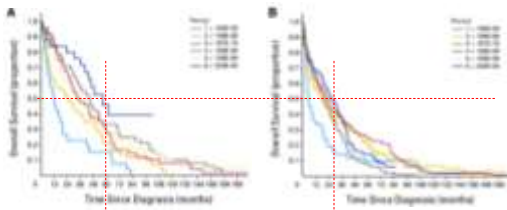
---

---

---

---

## Overall survival according to age and date of diagnosis



(A)  $\leq 65$  years old ( $n = 242$ ) and (B)  $> 65$  years old ( $n = 431$ ). Periods of diagnosis were as follows: 1 = 1950 to 1959; 2 = 1960 to 1969; 3 = 1970 to 1979; 4 = 1980 to 1989; 5 = 1990 to 1999; and 6 = 2000 to 2005.

Turesson et al., J Clin Oncol 2010

---

---

---

---

---

---

---

---

---

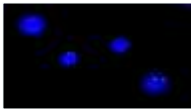
---

## Current clinical tools

- International Staging System (ISS)

Stage	Criteria	Median
I	Serum $\beta_2$ -microglobulin $< 3.5$ mg/L Serum albumin $\geq 3.5$ g/dL	62 mo.
II	Not stage I or III	44 mo.
III	Serum $\beta_2$ -microglobulin $\geq 5.5$ mg/L	29 mo.

- Adverse cytogenetic abnormalities (by FISH)



t(4;14)=15% of MM  
(dysregulation of FGFR3 and MMSET)



p53 deletion=10% of MM  
(loss of tumor suppressor gene)

---

---

---

---

---

---

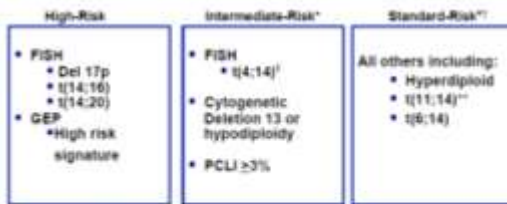
---

---

---

---

## Mayo Clinic “mSMART 2.0 classification” of active MM



\*\* Note that a subset of patients with these factors will be classified as high-risk by ISS.  
<sup>†</sup>IGH, MYC, and beta-2-MI + 3,6 may indicate worse prognosis.  
<sup>††</sup> Progression is worse when associated with high beta-2-MI and anemia.  
<sup>‡</sup>t(11;14) may be associated with plasmacytoid morphology.  
 Department of M. Mayo Clin Proc 2017;92:223-241. Advance et al Mayo Clin Proc 2018;93:1005-1019  
 4/2 Reviewed and updated: Jan 2019

---

---

---

---

---

---

---

---

---

---

## Gene expression reveals 7 molecular MM subtypes

### Associated with genetic lesions

- MF (MAF translocation)
- MS (MMSET/FGFR3 translocation)
- CD1 (Cyclin D1 or D3 translocation)
- CD2 (Cyclin D1 or D3 translocation)
- Hyperdiploid

### Associated with phenotype

- PR (proliferative)
- LB (low incidence of bone disease)

Zhan et al, *Blood* 2006

---

---

---

---

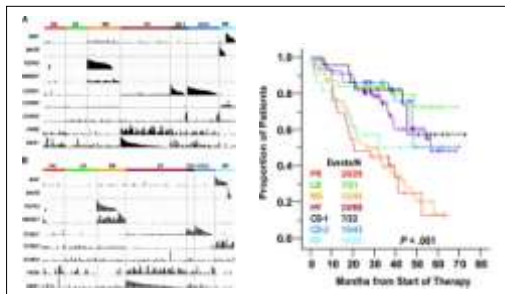
---

---

---

---

## Gene expression MM subtypes have different outcomes



Zhan et al, *Blood* 2006

---

---

---

---

---

---

---

---

## Current treatment principles

---

---

---

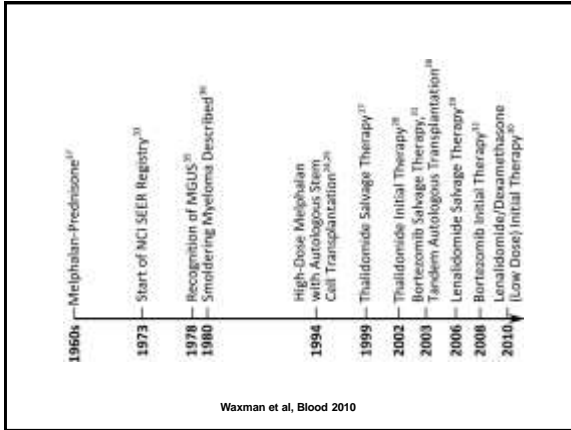
---

---

---

---

---




---

---

---

---

---

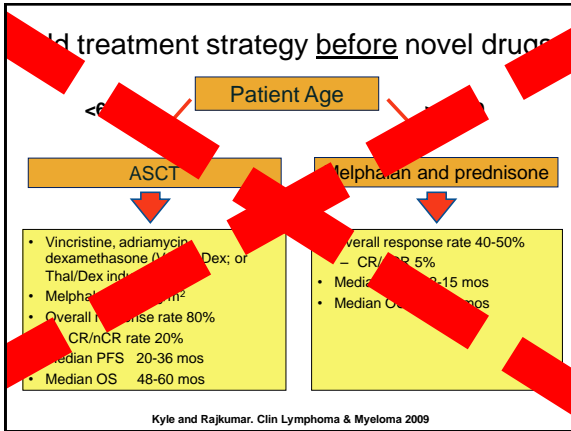
---

---

---

---

---




---

---

---

---

---

---

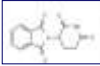
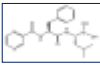
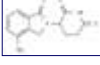
---

---

---

---

### Three of our novel myeloma drugs

Agent	Main Toxicities
<ul style="list-style-type: none"> <li>Thalidomide </li> </ul>	<ul style="list-style-type: none"> <li>Teratogenicity, peripheral neuropathy, constipation, sedation, rash, venous thromboembolism</li> </ul>
<ul style="list-style-type: none"> <li>Bortezomib </li> </ul>	<ul style="list-style-type: none"> <li>Fatigue, GI toxicity, peripheral neuropathy, decrease in platelets and neutrophils</li> </ul>
<ul style="list-style-type: none"> <li>Lenalidomide </li> </ul>	<ul style="list-style-type: none"> <li>Myelosuppression, venous thromboembolism</li> </ul>

---

---

---

---

---

---

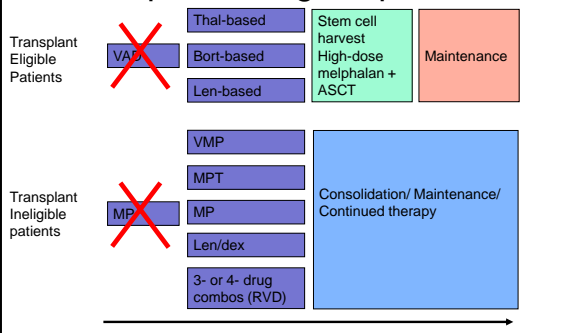
---

---

---

---

## Transplant eligible and transplant ineligible patients




---

---

---

---

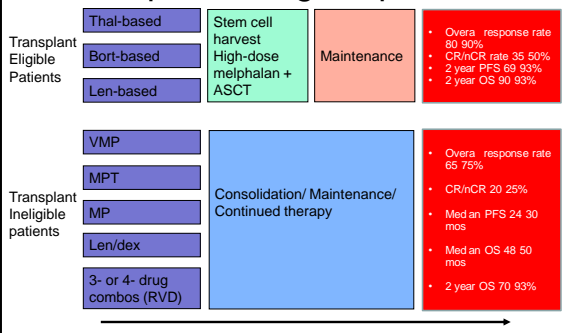
---

---

---

---

## Transplant eligible and transplant ineligible patients




---

---

---

---

---

---

---

---

## Treatment strategies for relapsed/refractory patients

- **Initial treatment can be repeated in selected patients**
  - Commonly used with alkylating agents (cyclophosphamide + prednisone is alternative to repeated MP)
  - Also high-dose melphalan + ASCT
  - Data emerging that novel agents can be used again
- **Novel agents can be introduced**
  - As single agents
  - With steroids
  - In 3-4 drug regimens with conventional chemotherapy and/or other novel agents

---

---

---

---

---

---

---

---

What is our current focus?




---

---

---

---

---

---

---

---

Upfront therapy  
for multiple myeloma

---

---

---

---

---

---

---

---

### High response rates prior high-dose melphalan/ASCT

Pre-ASCT responses

Response (%)	CRD <sup>1</sup>			RVD <sup>2,3</sup>		
	2 cycles (n=25)	4 cycles (n=22)	8 cycles (n=12)	4 cycles (n=31) <sup>2</sup>	8 cycles (n=24) <sup>2</sup>	8 cycles (n=35) <sup>3</sup>
sCR/ CR/ nCR	24	36	67	12	33	57
≥VGPR	40	59	83	12	67	74
≥PR	96	100	100	78	100	100

CRD= carfilzomib + lenalidomide + dexamethasone  
RVD= lenalidomide + bortezomib + dexamethasone

<sup>1</sup>Jakubowiak et al. ASH 2010 (abstract 862); <sup>2</sup>Richardson et al. ASH 2009 (abstract 1218);  
<sup>3</sup>Richardson et al. Blood 2010

---

---

---

---

---

---

---

---

## Upfront versus delayed high-dose melphalan therapy/ASCT

NDMM patients  $\geq 18$  years with KPS  $\geq 60\%$

Induction:  
up to 8 3-week cycles

Len: 15 25 mg days 1 14  
Bz: 1.0/1.3 mg/m<sup>2</sup> days 1, 4, 8, 11  
Dex: 40/20 mg days 1 2 4 5 8 9 11 12

Responding patients ( $>PR$ )  
could choose to proceed to:

Proceed to ASCT after  
 $\geq 4$  cycles

Len: days 1 14 at MTD  
Bz: days 1 and 8 at MTD  
Dex: 10 mg days 1, 2, 8, 9

Maintenance:  
3-week cycles

- Primary objectives: determine the MTD and response rate of RVD at MTD
- Secondary objectives: response rates, DOR, PFS (with/without ASCT), OS, toxicity, stem cell collection/engraftment

Richardson PG, et al. *Blood*. 2009;114(22):501-502 (abstract 1218); updated ASH 2010

---

---

---

---

---

---

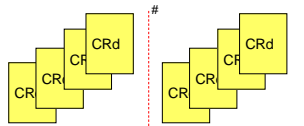
---

---

---

---

## Carfilzomib-based study for newly diagnosed multiple myeloma



C=36 mg/m<sup>2</sup>, d 1, 4, 8, 11, 15, 18  
R=25 mg, d 1-21/28  
d=40 mg/week

#=Harvest of stem cells (for eligible patients)

- PET/CT
- Molecular characterization
- Correlative science
- PET/CT
- MRD (if CR)
- Correlative science
- Outcome




---

---

---

---

---

---

---

---

---

---

Maintenance therapy  
(extended dosing) for multiple myeloma

---

---

---

---

---

---

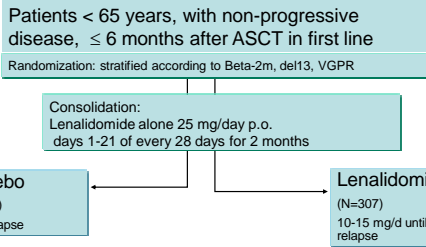
---

---

---

---

## IFM 2005-02: study design



Attal et al; ASH 2010 (abstract 310)

---

---

---

---

---

---

---

---

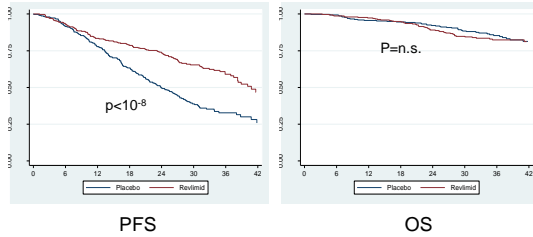
---

---

## IFM-2005-02: survival outcomes

Improvement in progression-free survival (placebo arm 24 months vs. lenalidomide arm 42 months)

No overall survival improvement



Attal et al; ASH 2010 (abstract 310)

---

---

---

---

---

---

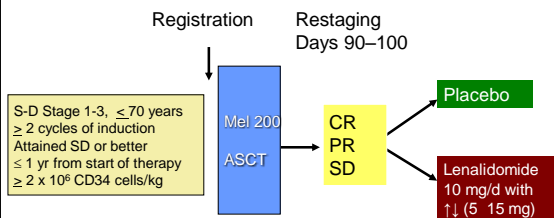
---

---

---

---

## CALGB 100104: study design



Patient stratification based on diagnostic  $\beta$ -2M and thalidomide and lenalidomide therapy during induction

McCarthy et al; ASH 2010 (abstract 37)

---

---

---

---

---

---

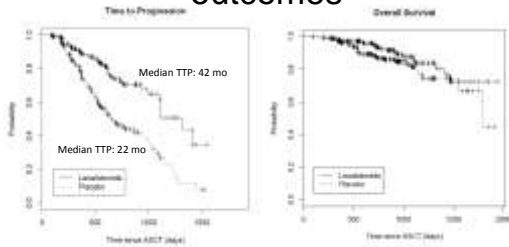
---

---

---

---

## CALGB 100104: survival outcomes



At median follow-up 28 months; better overall survival (lenalidomide 90% vs. placebo 83%;  $p=0.018$ )

McCarthy et al; ASH 2010 (abstract 37); Int'l Myeloma Workshop 2011 (abstract)

---

---

---

---

---

---

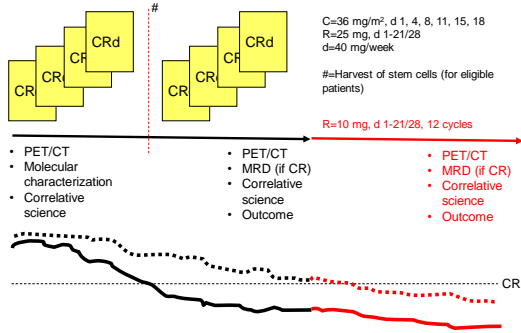
---

---

---

---

## Maintenance (extended dosing)




---

---

---

---

---

---

---

---

---

---

Management of smoldering multiple myeloma

---

---

---

---

---

---

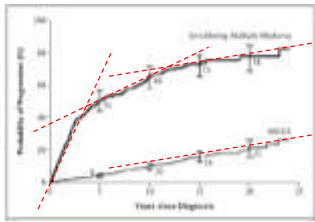
---

---

---

---

## Smoldering myeloma (SMM): the Mayo Clinic experience



- 276 SMM patients diagnosed 1970-1995
- 163 (59%) progressed
  - 158 multiple myeloma
  - 5 amyloidosis
- Overall risk of progression (per year):
  - 10% the first 5 years
  - 3% the next 5 years
  - 1% the last 10 years

Kyle et al. NEJM 2007

---

---

---

---

---

---

---

---

---

---

## Risk Stratification for Smoldering Myeloma (SMM)

Mayo Clinic (n=273)

PETHEMA Study Group (n=89)

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

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:**

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

Dispenzieri et al. *Blood* 2008

**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

High Risk SMM median TTP is <2 years

---

---

---

---

---

---

---

---

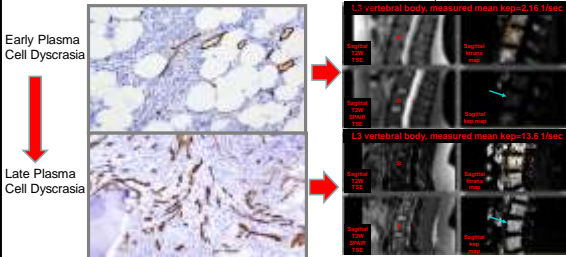
---

---

## Characterizing Natural Hx of MGUS and SMM Vasculature: IHC and DCE-MRI

CD 34 Stains to Assess Microvessel Density

DCE MRI measuring *Ke<sub>p</sub>*  
\* *Ke<sub>p</sub>* is the rate of contrast agent moving from extravascular space to intravascular



Analysis in our group shows no statistical difference in vascularity (MVD and DCE MRI) when comparing SMM cohort to MM cohort.

Berg, A. et al. (unpublished data)

---

---

---

---

---

---

---

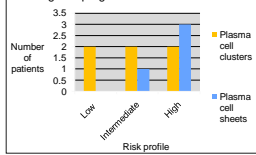
---

---

---

## High Risk SMM with Aggressive Features

Figure 4. Plasma cell sheeting is predictive of malignant progression in SMM



Plasma Cell Clustering



Plasma Cell Sheeting



Risk stratification based on PETHEMA model IHC staining CD 138 positive plasma cells

Berg, A. et al. (unpublished data)

---

---

---

---

---

---

---

---

---

---

## Current (IMWG 2010) clinical recommendations for SMM

- Baseline bone marrow biopsy and skeletal survey
- Repeat pertinent lab tests 2-3 months after initial recognition. If stable, repeat every 4-6 months for a year, and if stable every 6-12 months
- Treatment is not indicated unless it is part of a clinical trial. Consider clinical trials for selected patients; with the aim to delay and/or prevent progression to symptomatic myeloma

Kyle et al. Int'l Myeloma Working Group. Leukemia 2010

---

---

---

---

---

---

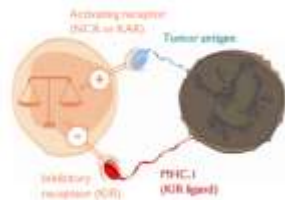
---

---

---

---

## Regulation of NK cell activity



Equilibrium between "activating" and "inhibiting" signals received from the target cell through *activatory* receptors and *inhibitory* receptors (**K**iller-cell **I**mmunoglobulin-like **R**eceptors; **KIR**)

---

---

---

---

---

---

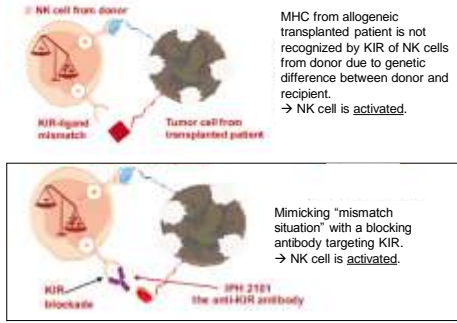
---

---

---

---

## MHC from transplanted patient not recognized by donor NK cells




---

---

---

---

---

---

---

---

## Imaging in multiple myeloma and its precursors

---

---

---

---

---

---

---

---

## Skeletal bone survey – still the gold standard...

For "myeloma work-up", bones are evaluated with a complete skeletal survey, including:

- Skull
- Spine
- Pelvis
- Extremities (including forearms and legs)

---

---

---

---

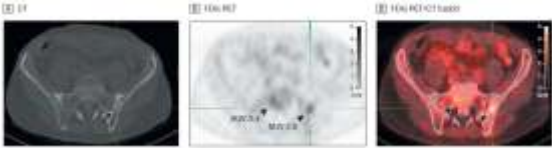
---

---

---

---

# SMM patient with back pain; skeletal survey was negative



**<sup>18</sup>F-FDG PET/CT showed metabolically active and anatomically visible lesions (arrowheads) in the sacrum (SUV 3.4) and the iliac bone (SUV 2.8)**

---

---

---

---

---

---

---

---

# Molecular imaging from MGUS to MM

<sup>18</sup>F-NaF PET/CT  
to detect early  
bone lesions

*Exchange of hydroxyl ions  
in the hydroxy-apatite  
crystal: an indicator of  
bone mineralization*



Dynamic contrast-enhanced-MRI to  
visualize microcirculation patterns  
from MGUS to MM

<sup>18</sup>F-FDG PET/CT

---

---

---

---

---

---

---

---

Molecularly targeted therapies

---

---

---

---

---

---

---

---



## Upregulation of osteoclast activity and osteolytic lesions in MM

MEK inhibitors...

- Block osteoclast differentiation and formation
- Inhibit MM growth and survival factors produced by osteoclasts



Balakumaran et al. and Landgren, *Expert Rev Mol Diagn* 2010

---

---

---

---

---

---

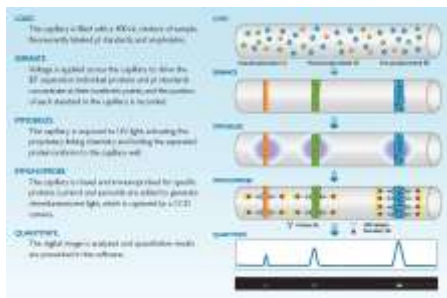
---

---

---

---

## NanoPro capillary isoelectric immunoassay to quantify pErk




---

---

---

---

---

---

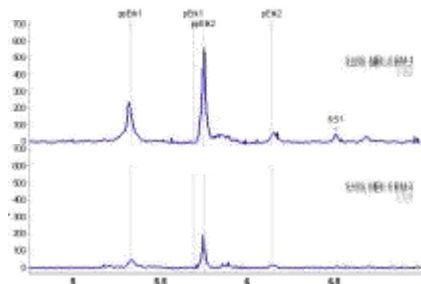
---

---

---

---

## Erk profile of *responding* patient treated with MEK inhibitor



Zingone et al. *unpublished data*

---

---

---

---

---

---

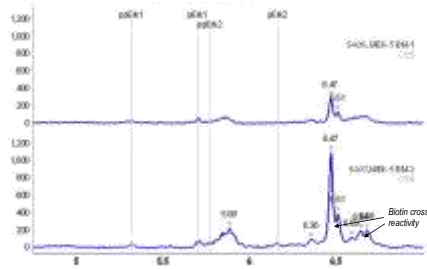
---

---

---

---

## Erk profile of *non-responding* patient treated with MEK inhibitor



Zingone et al, unpublished data

---

---

---

---

---

---

---

---

## Clinical myeloma studies at NCI in 2011-



- **Precursor disease (MGUS and smoldering myeloma)**
  - Natural history study (individualized profiling)
- **Smoldering myeloma treatment**
  - Anti-KIR
  - Carfilzomib (*coming soon*)
  - Oral proteasome inhibitor (*coming soon*)
- **Newly diagnosed multiple myeloma treatment**
  - Carfilzomib/revlimid/dex
- **Relapsed multiple myeloma treatment**
  - HDAC/mTOR inhibitors
  - Carfilzomib (*coming soon*)
  - MEK inhibitor
- **From precursor to multiple myeloma**
  - Molecular imaging study

---

---

---

---

---

---

---

---

***- Thank you very much  
for your attention!***

Mary Ann Yancey, RN ([yanceym@mail.nih.gov](mailto:yanceym@mail.nih.gov)); 301-435-9227  
 Marcia Mulquin, RN ([mmulquin@mail.nih.gov](mailto:mmulquin@mail.nih.gov)); 301-435-5613

[www.multiplemyeloma.cancer.gov](http://www.multiplemyeloma.cancer.gov)

---

---

---

---

---

---

---

---