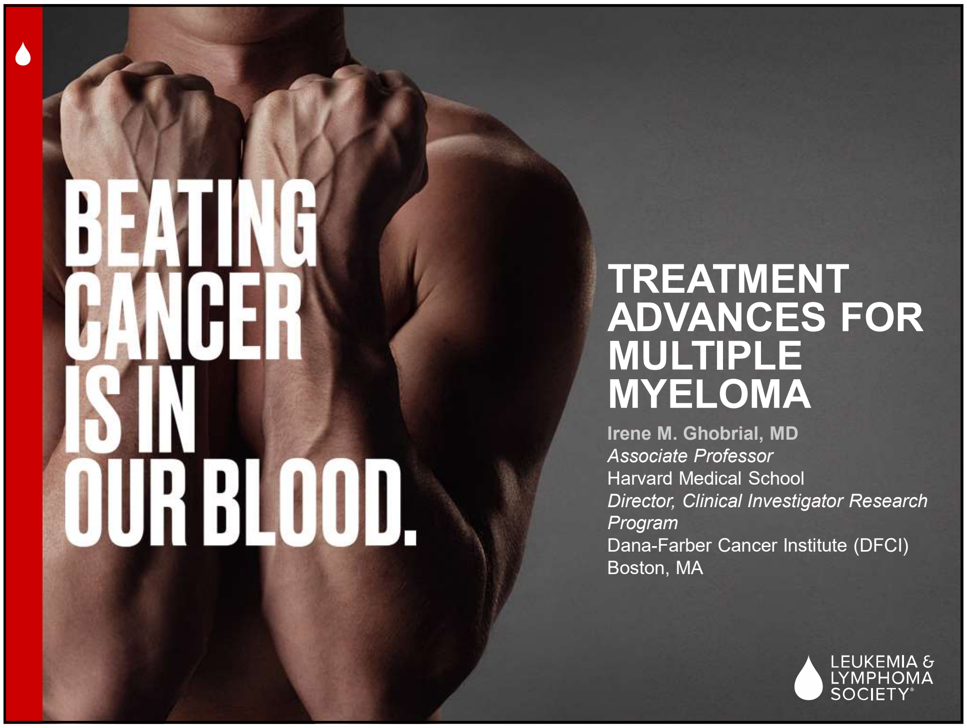

# TREATMENT ADVANCES FOR MULTIPLE MYELOMA

**Irene M. Ghobrial, MD**
*Associate Professor*
Harvard Medical School
*Director, Clinical Investigator Research Program*
Dana-Farber Cancer Institute (DFCI)
Boston, MA

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## DISCLOSURES

*Treatment Advances for Multiple Myeloma*

**Advisory boards for:**

**Celgene, Takeda, Sanofi, BMS, and Janssen**

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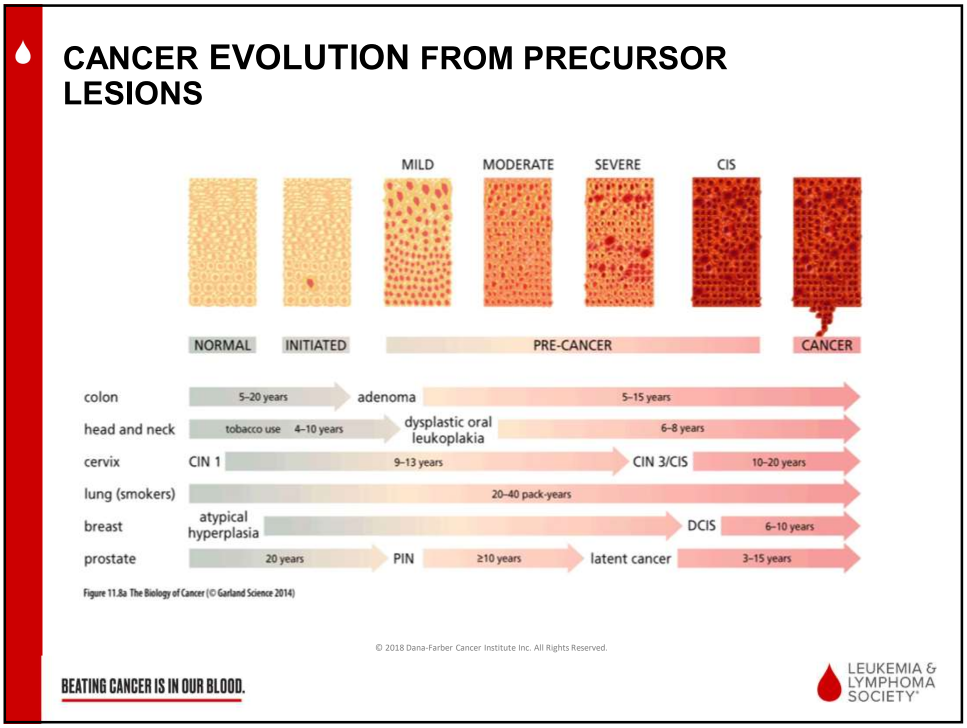
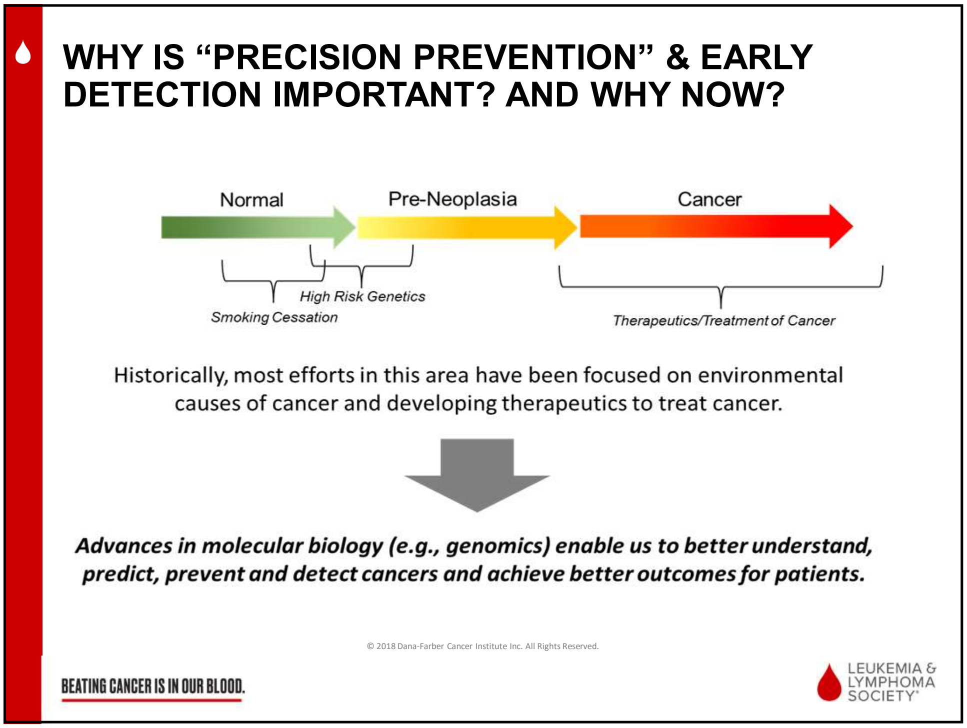


# CANCER EVOLUTION FROM PRECURSOR LESIONS

Figure 11.8a The Biology of Cancer (© Garland Science 2014)

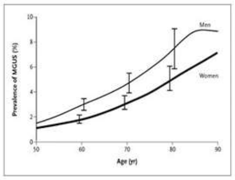


# WHY IS “PRECISION PREVENTION” & EARLY DETECTION IMPORTANT? AND WHY NOW?

Historically, most efforts in this area have been focused on environmental causes of cancer and developing therapeutics to treat cancer.

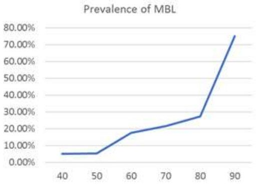
***Advances in molecular biology (e.g., genomics) enable us to better understand, predict, prevent and detect cancers and achieve better outcomes for patients.***

# COMPARISON OF COMMON AGING-ASSOCIATED CLONAL HEMATOLOGIC PRECURSOR STATES



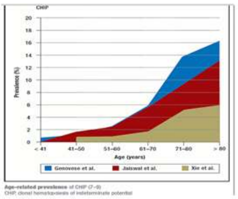
Incidence of monoclonal gammopathy of undetermined significance (MGUS)

Kyle R et al *NEJM* 2006



Incidence of monoclonal B cell lymphocytosis (MBL)

Nieto WG et al *Blood* 2009



Incidence of mutations in preleukemic driver genes… clonal hematopoiesis of indeterminate potential (CHIP)

Jaiswal et al, NEJM 2014

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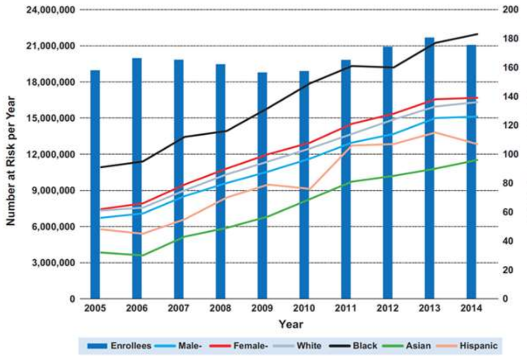
# MGUS IS A VERY COMMON CONDITION



- **3% of population at age 50**
- **Increases with age**

- **3 times more common in AA**
- **Younger age for AA**

- **3 times more in familial cases**

G. RS et al., *Leukemia*, 2016

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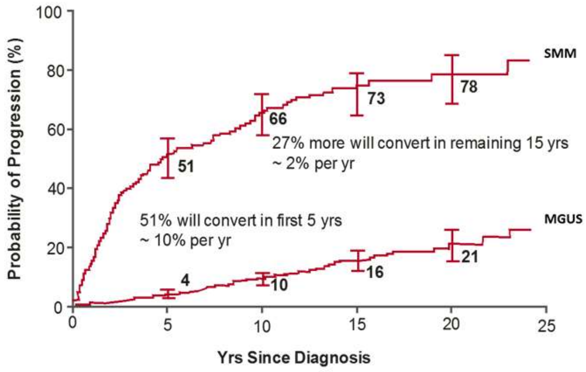
# PROGRESSION OF MGUS AND SMOLDERING MM

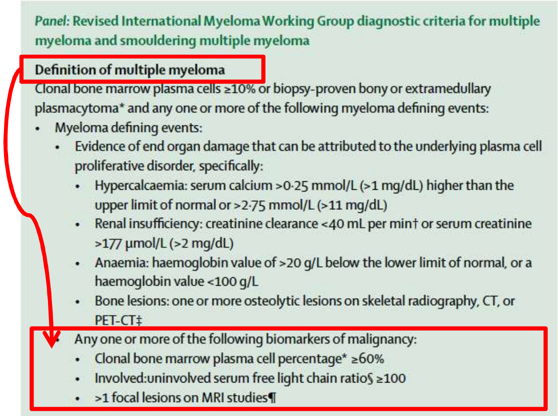


51% will convert in first 5 yrs
~ 10% per yr

27% more will convert in remaining 15 yrs
~ 2% per yr

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

# WHICH PATIENT POPULATION TO CONSIDER FOR SMM?



*Panel*: **Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma**

**Definition of multiple myeloma**

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

*Rajkumar et al. Lancet Oncology 2014; 15: e538-48*

# WHICH PATIENT POPULATION TO CONSIDER FOR HIGH-RISK SMM?

**Identification of high-risk SMM→ 50% of progression risk at 2 yrs**

- ***Mayo Clinic:*** ≥10% clonal plasma cell bone marrow infiltration, and ≥30g/L of serum M-protein, and serum-free light ratio >0.125 or <8
- ***Spanish:*** ≥95% of aberrrant plasma cells measured by flow plus >25% decrease in one or both uninvolved immunoglogulins
- ***Heidelberg:*** Tumor mass defined by Mayo risk model plus t(4;14)/del17p/gains of 1q/
- ***Japanese:*** Beta 2-microglobulin ≥ 2.5 mg/L plus M-protein increment rate > 1 mg/dL/day
- ***SWOG:*** serum M-protein ≥2 g/dL plus involved free light chain >25 and GEP >-0.26 (71% of risk progression at 2 yrs)
- ***PENN:*** ≥ 40% clonal PCBM infiltration plus sFLC ratio ≥ 50 plus Albumin □ 3.5 mg/dL (81% of risk at 2 yrs)
- ***Czech & Heidelberg:*** immunoparesis plus serum M-protein ≥ 2.3 g/dL plus involved/uninvolved sFLC > 30 **(81% of risk at 2 yrs)**
- ***Barcelona:*** evolving pattern plus serum M-protein ≥ 3 g/dL plus immunoparesis **(80% of risk at 2 yrs)**

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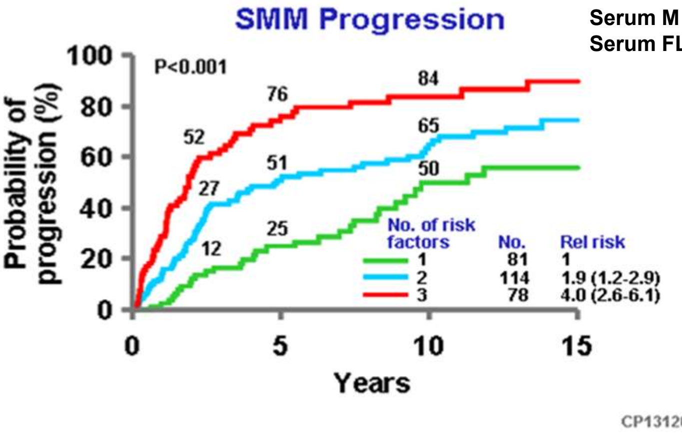
# MAYO CLINIC MODEL: SERUM IMMUNOGLOBULIN FREE-LIGHT CHAIN (FLC) RATIO (N:273)

**PCsBM Infiltration ≥ 10%**
**Serum M protein ≥ 3 g/dL**
**Serum FLC ratio <1/8 or >8**



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*Dispenzieri A. Blood 2008; 111:785-9*

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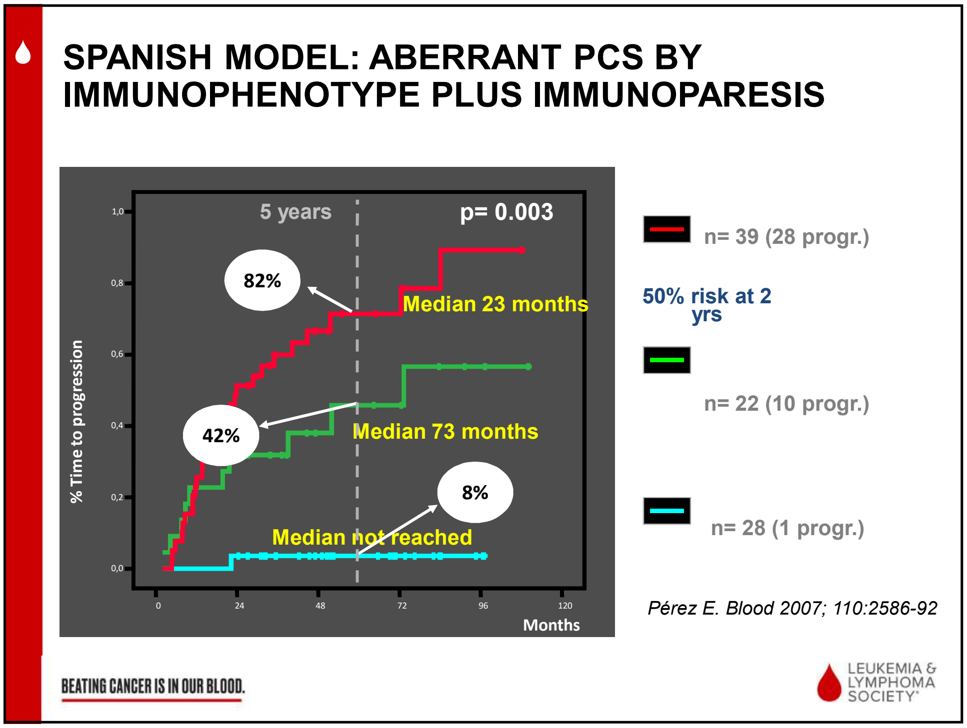

# SPANISH MODEL: ABERRANT PCS BY IMMUNOPHENOTYPE PLUS IMMUNOPARESIS

🟥 n= 39 (28 progr.)

50% risk at 2 yrs

🟩 n= 22 (10 progr.)

🟦 n= 28 (1 progr.)

*Pérez E. Blood 2007; 110:2586-92*

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# DEL(17P), T(4;14), AND +1Q21 PREDICT PROGRESSION FROM SMOLDERING TO SYMPTOMATIC MM (N=248)

**del(17p13), t(4;14), +1q21 showed significant impact on TTP**

| | TTP | P |
|---|---|---|
| All pts | 4.9 years | |
| +1q21 versus no gain of 1q21 | 3.7 years 5.3 years | 0.013 |
| del(17p13) versus no del(17p13) | 2.7 versus 4.9 years | 0.019 |
| t(4;14) versus no t(4;14) | 2.9 versus 5.2 years | 0.021 |
| HD versus NHD | 3.9 versus 5.7 years | 0.036 |

**Multivariate analysis: t(4;14), +1q21, HD, reduction of uninvolved immunoglobulins and risk score defined by Kyle et al. as independent factors for adverse outcome**

**Conclusion: specific chromosomal aberrations drive transition from asymptomatic to symptomatic disease**

*Neben et al. JCO 2013*

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# WHICH PATIENT POPULATION TO CONSIDER FOR HIGH-RISK SMM?

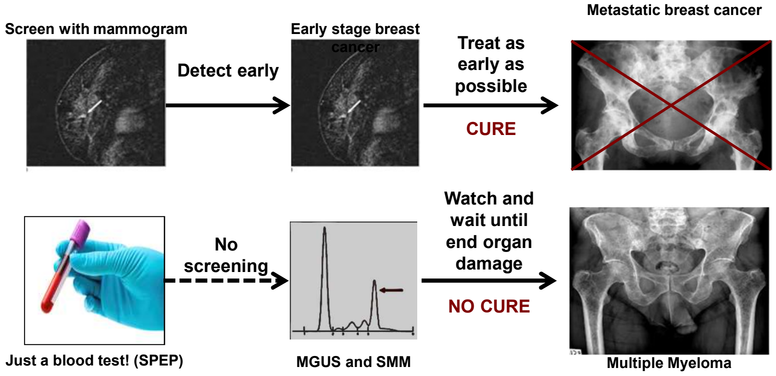
***Each model appears to identify patients at high risk, with some but not complete overlap***

**Bone marrow clonal plasma cells ≥10% and any one or more of the following:**

- Serum M protein ≥3.0gm/dL
- IgA SMM
- Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
- Serum involved/uninvolved free light chain ratio ≥8 (but less than 100)
- Progressive increase in M protein level (Evolving type of SMM)†
- Bone marrow clonal plasma cells 50-60%
- Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes
- t (4;14) or del 17p or 1q gain
- Increased circulating plasma cells
- MRI with diffuse abnormalities or 1 focal lesion (≥5mm)
- PET-CT with one focal lesion (≥5mm) with increased uptake without underlying osteolytic bone destruction
- Monoclonal light chain excretion of 500mg/24 hours or higher

Rajkumar et al, Blood 2015

# CAN EARLY SCREENING AND INTERVENTION PREVENT PROGRESSION IN MM?



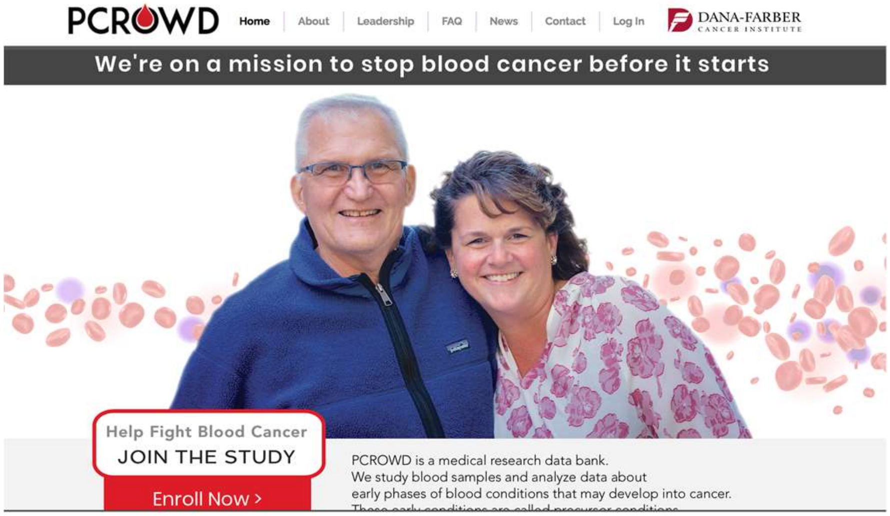
# NEW CPOP CLINIC (CENTER FOR PREVENTION OF PROGRESSION OF BLOOD CANCERS)

**Features**

**Aim and scope of clinic:** **To actively study patients** with precursor hematological malignancies and define mechanisms/therapies that prevent progression**, and to counsel patients** with incidentally discovered mutations**.**
**Goal:** have **DFCI be the center of excellence** for early precursor hematological conditions

CPOP
Center for Prevention of Progression of Blood Cancers

- **Multidisciplinary**
  - DFCI HM & BWH Hematology clinical staff, Medical Genetics, BWH Cardiology
- **Integration of research & clinical care**

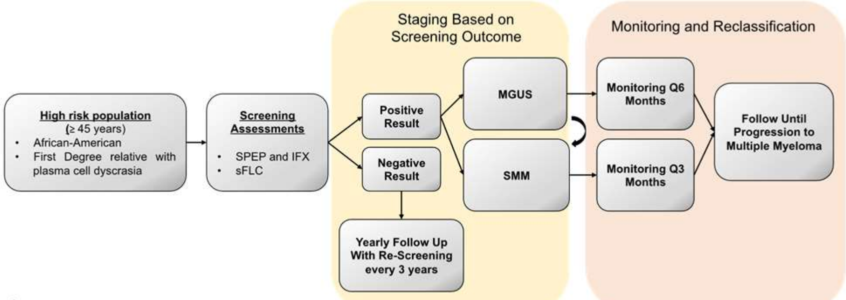


We're on a mission to stop blood cancer before it starts

PCROWD is a medical research data bank.
We study blood samples and analyze data about early phases of blood conditions that may develop into cancer.

pcrowd.dana-farber.org/

# (PREDICTING PROGRESSION OF DEVELOPING MYELOMA IN A HIGH-RISK SCREENED POPULATION, PROMISE)



**High risk population**
(≥ 45 years)
- African-American
- First Degree relative with plasma cell dyscrasia

**Screening Assessments**
- SPEP and IFX
- sFLC

Staging Based on Screening Outcome

**Positive Result**

**Negative Result**

**Yearly Follow Up With Re-Screening every 3 years**

**MGUS**

**SMM**

Monitoring and Reclassification

**Monitoring Q6 Months**

**Monitoring Q3 Months**

**Follow Until Progression to Multiple Myeloma**

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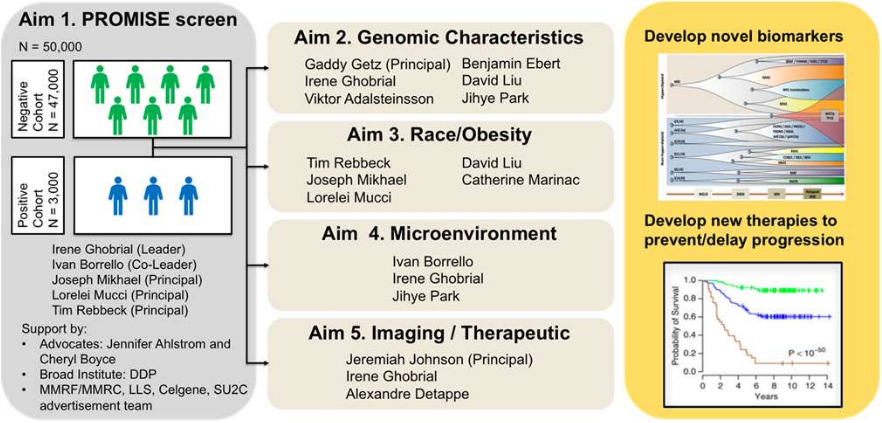
# PROJECT SUMMARY



## Aim 1. PROMISE screen

N = 50,000

Negative Cohort N = 47,000

Positive Cohort N = 3,000

Irene Ghobrial (Leader)
Ivan Borrello (Co-Leader)
Joseph Mikhael (Principal)
Lorelei Mucci (Principal)
Tim Rebbeck (Principal)

Support by:
- Advocates: Jennifer Ahlstrom and Cheryl Boyce
- Broad Institute: DDP
- MMRF/MMRC, LLS, Celgene, SU2C advertisement team

## Aim 2. Genomic Characteristics

Gaddy Getz (Principal)
Irene Ghobrial
Viktor Adalsteinsson
Benjamin Ebert
David Liu
Jihye Park

## Aim 3. Race/Obesity

Tim Rebbeck
Joseph Mikhael
Lorelei Mucci
David Liu
Catherine Marinac

## Aim 4. Microenvironment

Ivan Borrello
Irene Ghobrial
Jihye Park

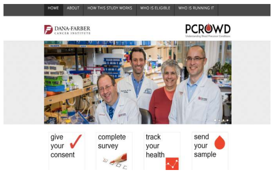
## Aim 5. Imaging / Therapeutic

Jeremiah Johnson (Principal)
Irene Ghobrial
Alexandre Detappe

**Develop novel biomarkers**

**Develop new therapies to prevent/delay progression**

# Collaboration and innovation



The PROMISE study

LEUKEMIA & LYMPHOMA SOCIETY®

MMRF MULTIPLE MYELOMA Research Foundation

Binding Site

Celgene Committed to improving the lives of patients worldwide®

STAND UP TO CANCER

magenta

BROAD INSTITUTE

MIT

JOHNS HOPKINS MEDICINE

MAYO CLINIC

HARVARD SCHOOL OF PUBLIC HEALTH

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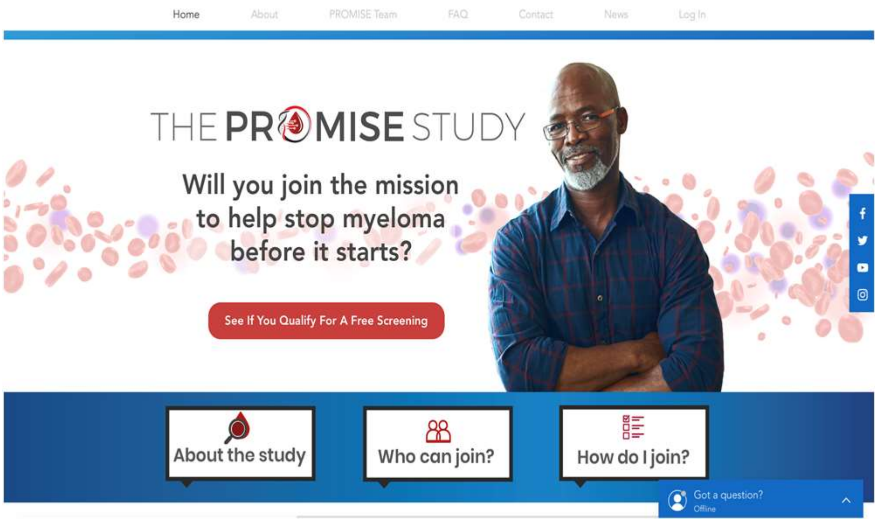

THE PROMISE STUDY

Will you join the mission to help stop myeloma before it starts?

https://www.enroll.promisestudy.org

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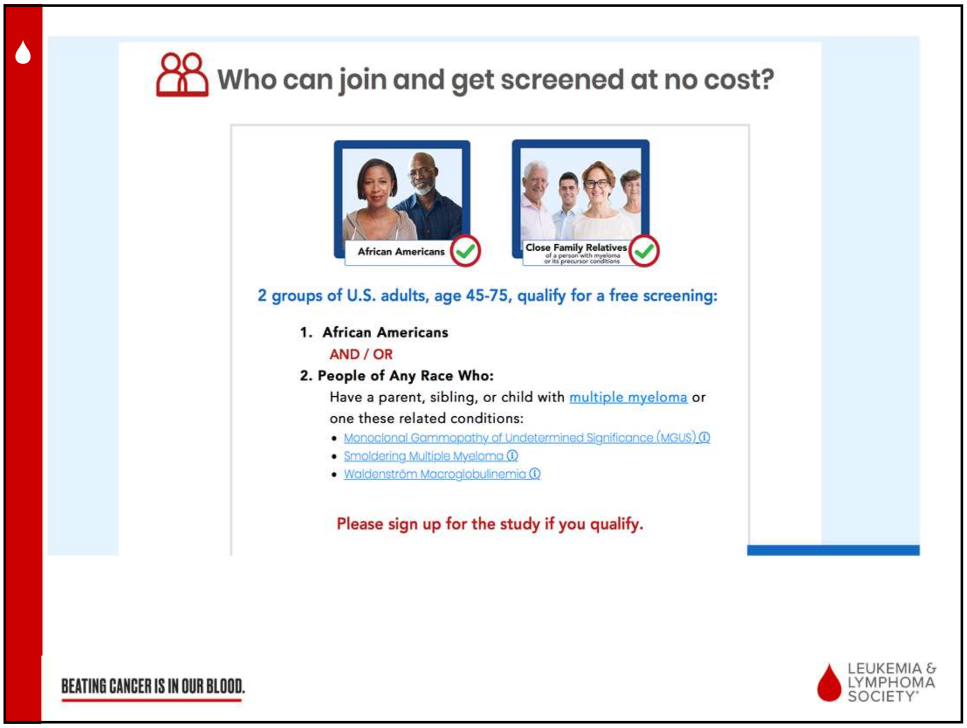

## Who can join and get screened at no cost?

2 groups of U.S. adults, age 45-75, qualify for a free screening:

1. **African Americans**

   AND / OR

2. **People of Any Race Who:**

   Have a parent, sibling, or child with multiple myeloma or one these related conditions:
   - Monoclonal Gammopathy of Undetermined Significance (MGUS) ⓘ
   - Smoldering Multiple Myeloma ⓘ
   - Waldenström Macroglobulinemia ⓘ

Please sign up for the study if you qualify.

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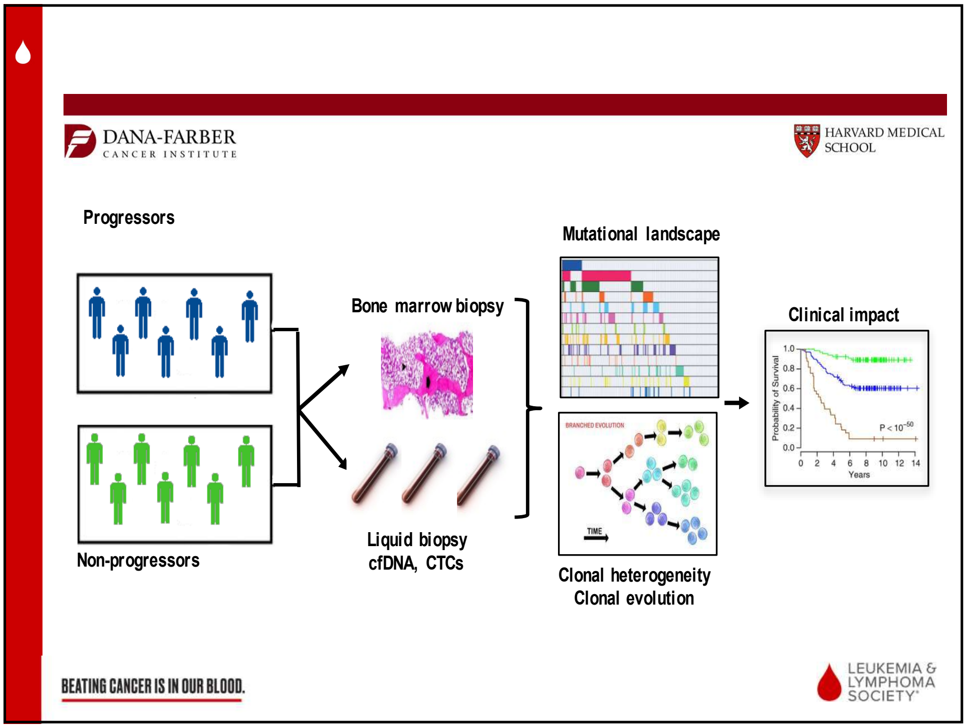

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Progressors

Non-progressors

Bone marrow biopsy

Liquid biopsy
cfDNA, CTCs

Mutational landscape

Clonal heterogeneity
Clonal evolution

Clinical impact

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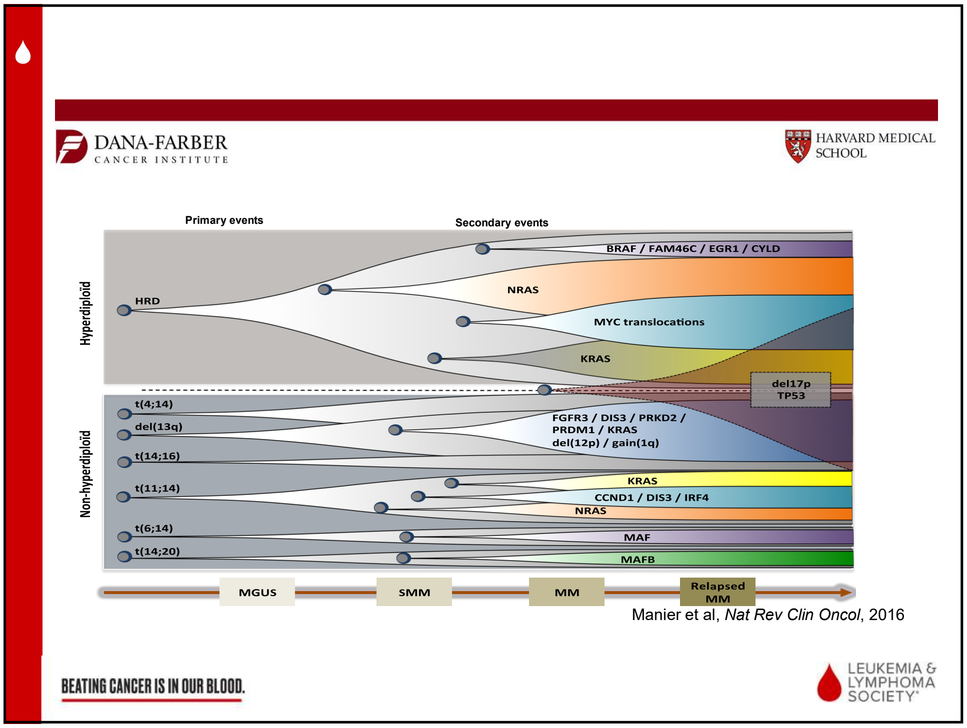
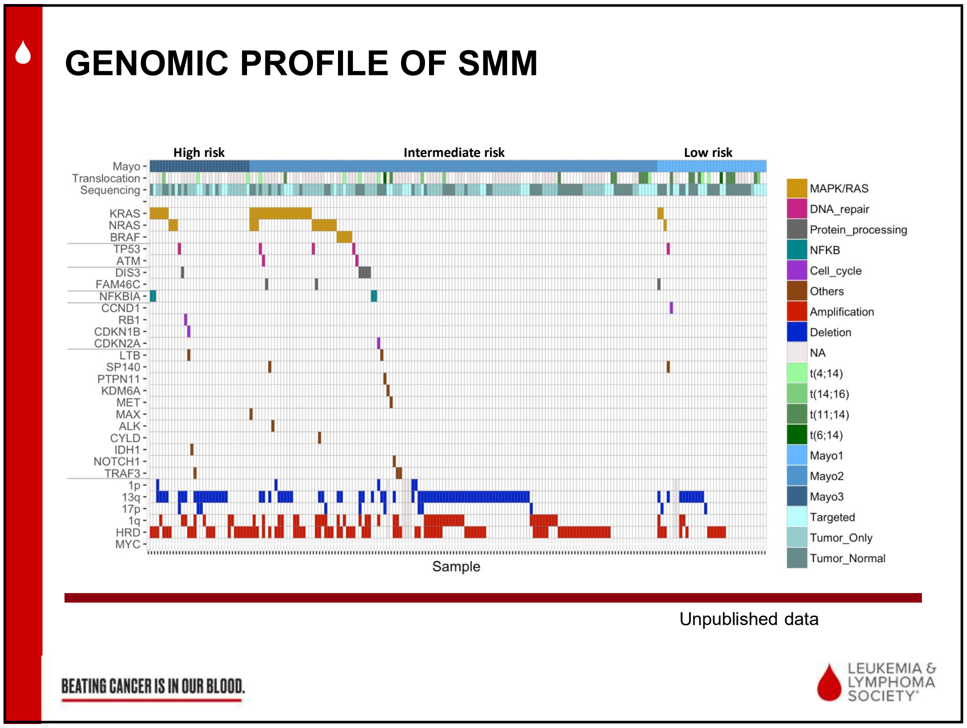
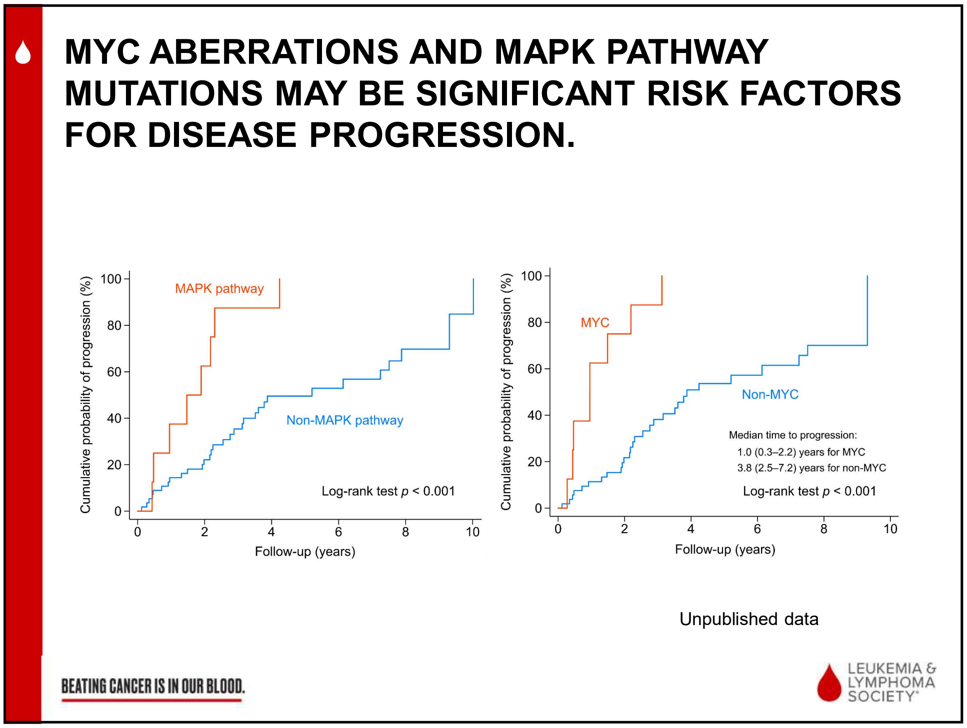


Manier et al, *Nat Rev Clin Oncol*, 2016



# GENOMIC PROFILE OF SMM

Unpublished data



# MYC ABERRATIONS AND MAPK PATHWAY MUTATIONS MAY BE SIGNIFICANT RISK FACTORS FOR DISEASE PROGRESSION.

Unpublished data

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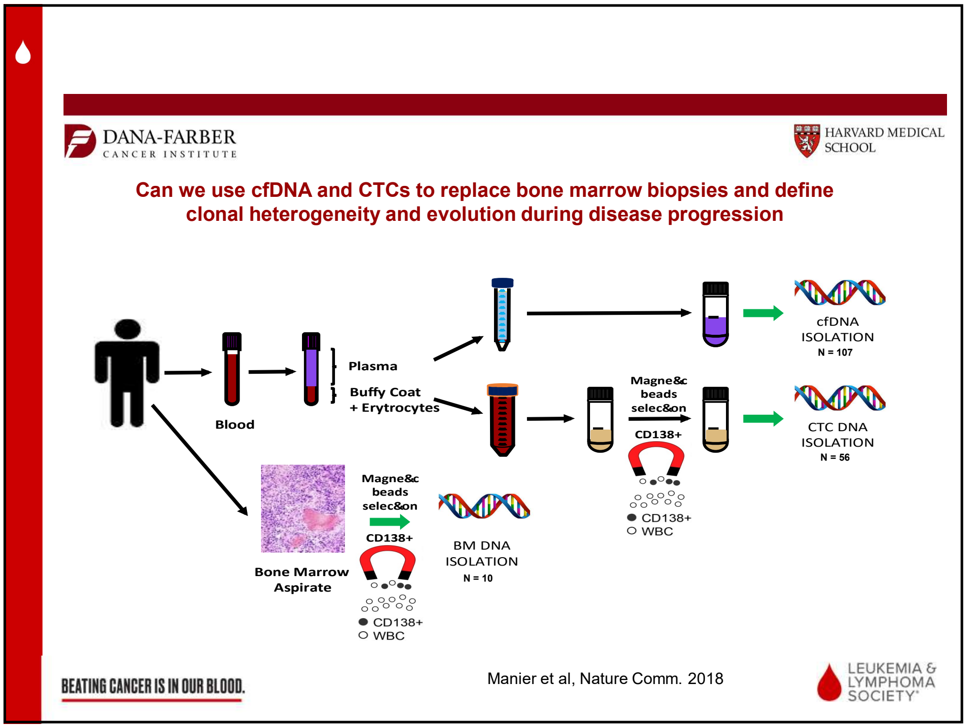

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**Can we use cfDNA and CTCs to replace bone marrow biopsies and define clonal heterogeneity and evolution during disease progression**

Manier et al, Nature Comm. 2018

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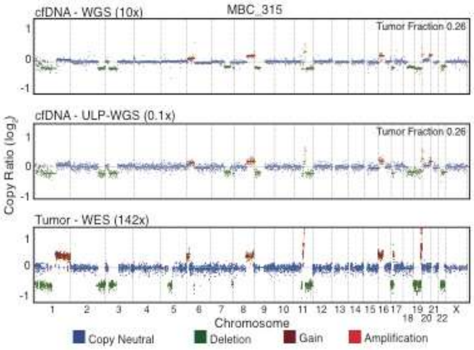
## Characterize somatic aberrations present in cfDNA and CTCs as biomarkers of progression

**To be clinically relevant, WES of cfDNA must be**

1. Cost-effective and accurate
2. Offer suitable proxy for conventional biopsy
3. Possible for most patients with metastatic cancer



Adalsteinsson, Ha, Freeman et al., Nature Comm 2017
Lohr, Aldalsteinsson, Cibulskis et al. *Nat Biotechnol*, 2014

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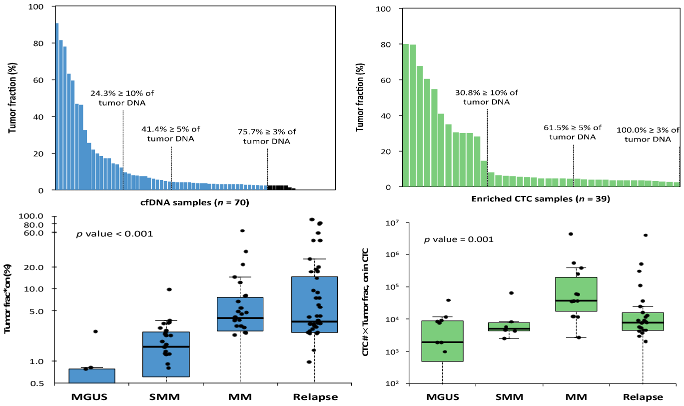
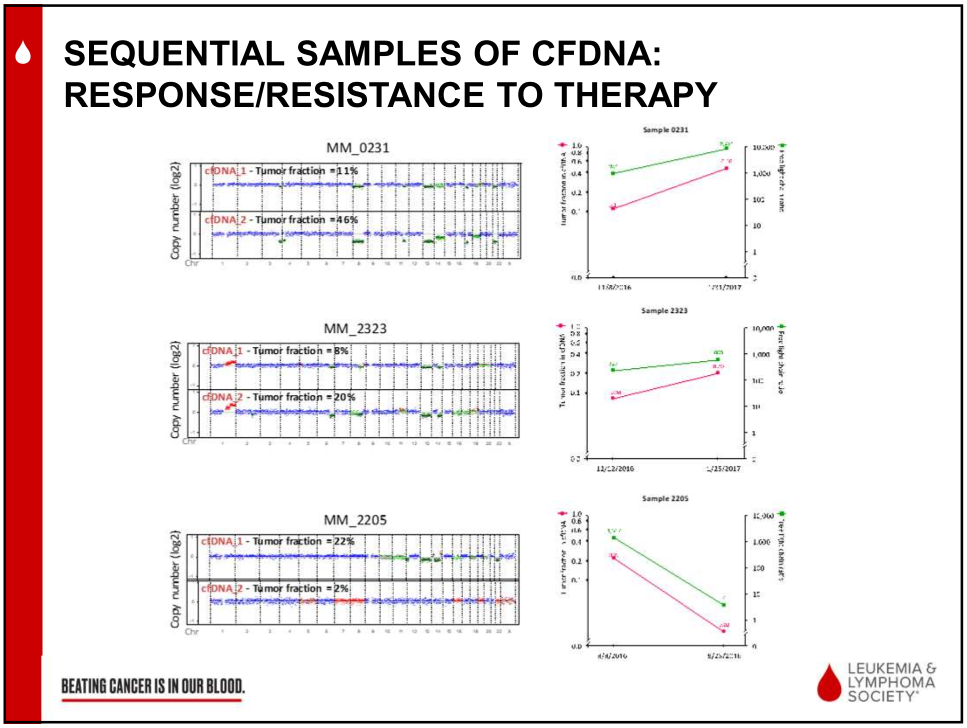
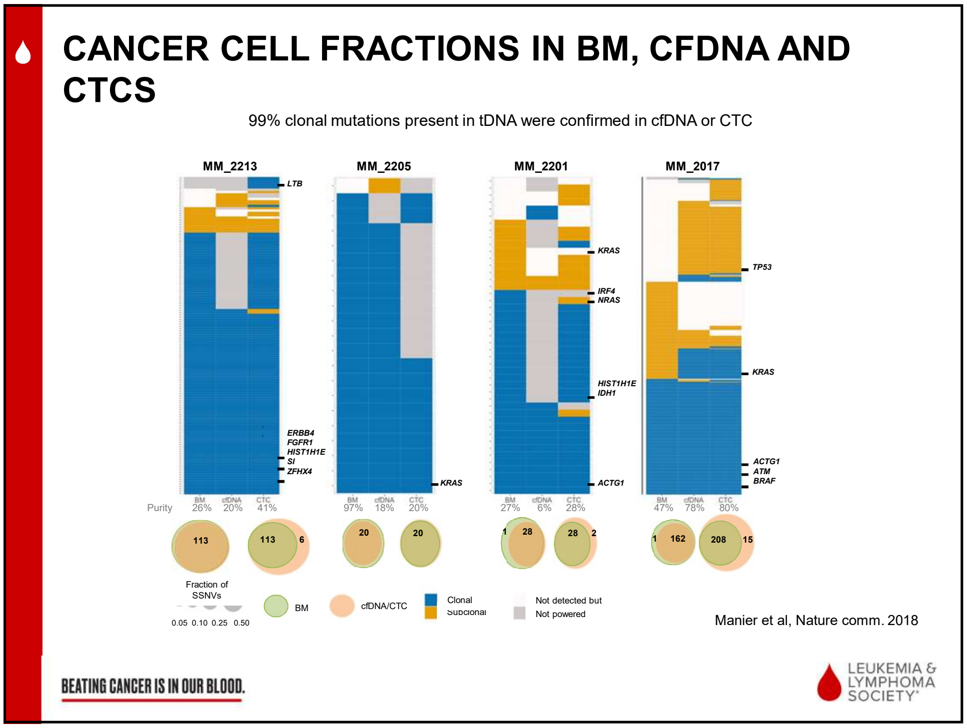
## CIRCULATING FREE DNA AND CTCS BY ULP-WGS IN MM



Manier et al, Nature Comm 2018



## SEQUENTIAL SAMPLES OF CFDNA: RESPONSE/RESISTANCE TO THERAPY



## CANCER CELL FRACTIONS IN BM, CFDNA AND CTCS

99% clonal mutations present in tDNA were confirmed in cfDNA or CTC

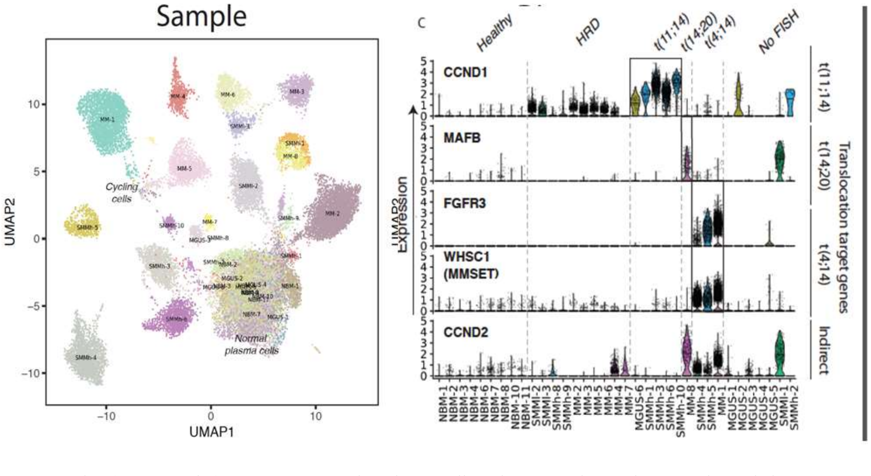
Manier et al, Nature comm. 2018

**Stephen Paget, 1855–1926.** Ha elaborato alla fine del XIX secolo la teoria detta "seed and soil" (seme e terreno) per spiegare il processo di metastatizzazione. Questa teoria è tutt'ora attuale.

# SEED AND SOIL:
# ADAPTATION TO THE BM NICHE

Hawaiian silversword developed differently in different environments

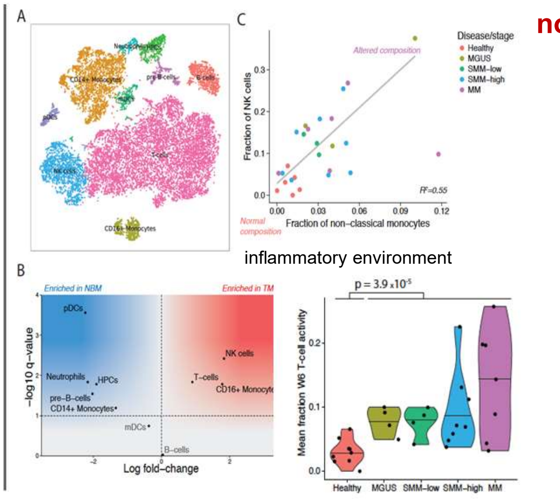
Princeton guide to Ecology



RNA sequencing (10x genomics) to CD138-expressing plasma cells and CD45+ microenvironmental populations. Analyzed 88.8K single cells from 67 samples representing a cohort of 27 patients and 9 healthy donors.

Unpublished data

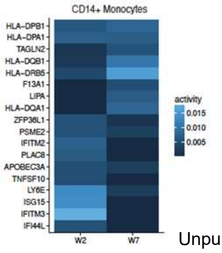
## Immune cell regulation in disease progression from normal, MGUS to overt MM



inflammatory environment

Interferon type-1 target genes

W2 activity (APOBEC3A upregulation)
W7 activity (antigen presentation).



Unpublished data

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## THE ROLE OF CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL (CHIP) IN MULTIPLE MYELOMA: IMMUNOMODULATOR MAINTENANCE POST AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) PREDICTS BETTER OUTCOME

Tarek H. Mouhieddine, Jihye Park, Robert Redd, Matthew Leventhal, Christopher J. Gibson, Salomon Manier, Amin Nassar, Kalvis Hornburg, Marzia Capelletti, Daisy Huynh, Mark W. Bustoros, Romanos Sklavenitits Pistofidis, Kalvis Hornburg, Henry Dumke, Muhieddine M Itani, Cody J Boehner, Chia-Jen Liu, Saud H. AlDubayan, Brendan Reardon, Eliezer M. Van Allen, Daniel Auclair, Robert L. Schlossman, Nikhil C. Munshi, Kenneth C. Anderson, David P. Steensma, Jacob P. Laubach, Paul G. Richardson, Jerome Ritz, Benjamin L. Ebert, Robert J. Soiffer, Chip Stewart, Gad Getz, Donna Neuberg, & Irene M. Ghobrial

2018 ASH Annual Meeting and Exposition
December 3rd, 2018

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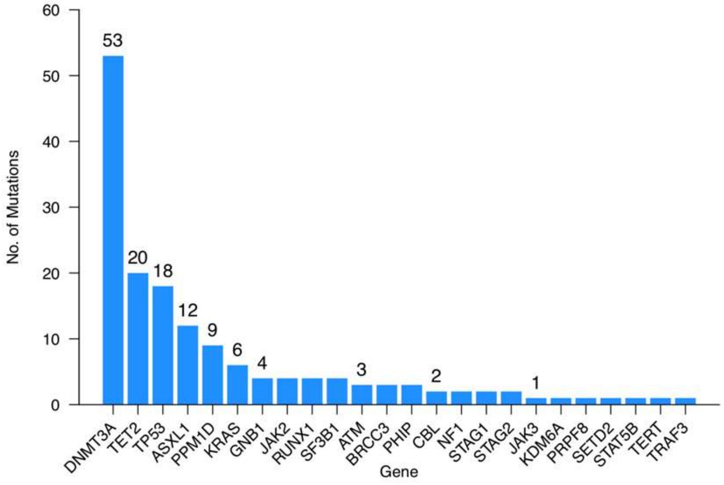
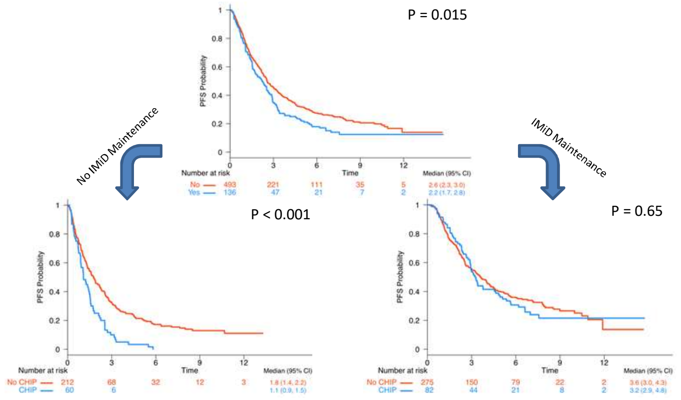
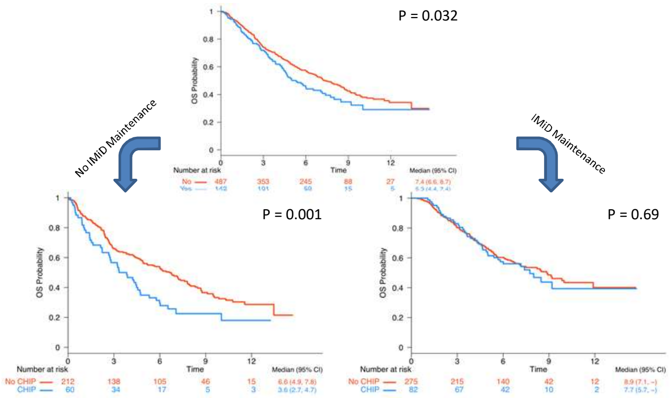
# MOST COMMON MUTATED GENES IN MM



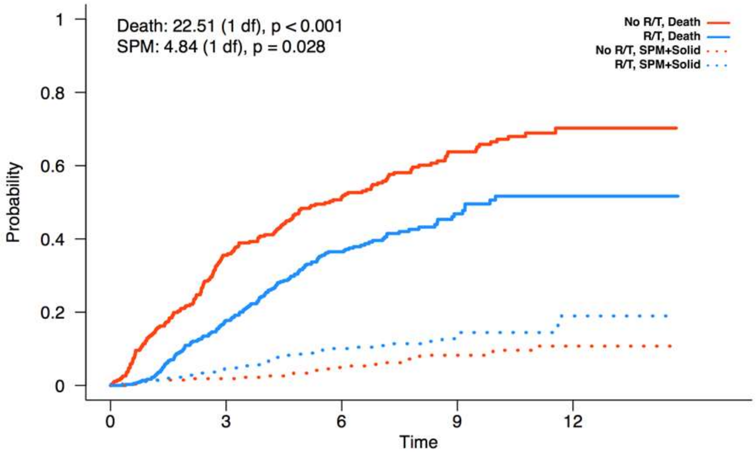
# CHIP DECREASES PFS WHICH IMPROVES WITH IMIDS



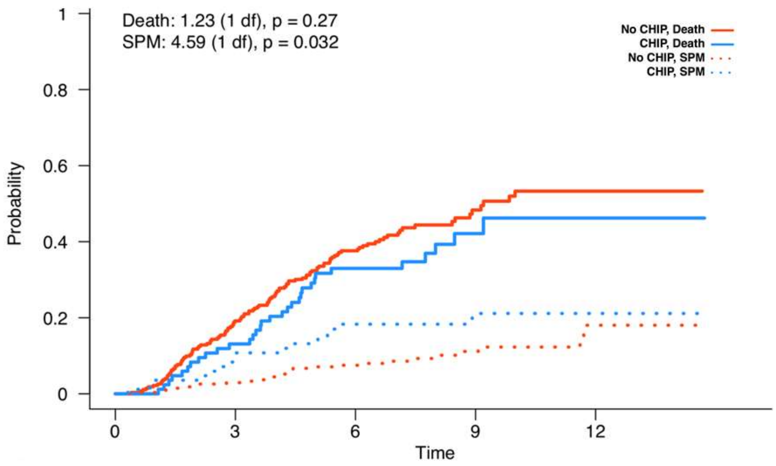
# CHIP DECREASES OS WHICH IMPROVES WITH IMIDS



# IMIDS DECREASE PROBABILITY OF DEATH BUT INCREASE SUSCEPTIBILITY TO 2$^{ND}$ SOLID AND HEMATOLOGIC MALIGNANCIES



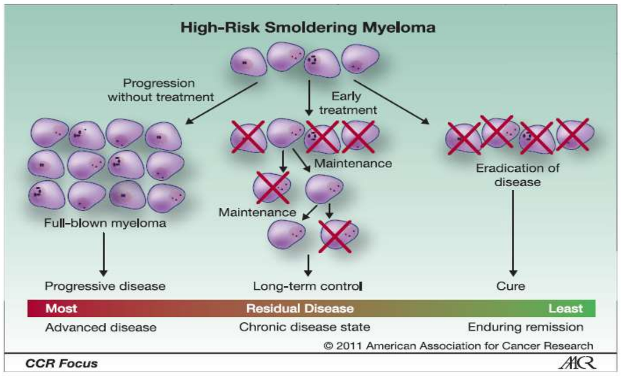
## WITH IMIDS, CHIP DOES NOT INCREASE PROBABILITY OF DEATH BUT INCREASES SUSCEPTIBILITY TO 2ND MALIGNANCIES



## SUMMARY

- CHIP has a 22% frequency in multiple myeloma
- CHIP, particularly the TET2 mutation, is associated with worse outcome in MM patients who underwent ASCT
- IMiD maintenance improves OS and PFS in patients harboring CHIP mutations
- Benefits of survival vs. risk of developing a SPM with IMiD maintenance
- Indications for CHIP screening in MM
- Future studies are warranted to understand the effect and mechanism of IMiDs on CHIP clones

# TREATMENT GOALS FOR HIGH-RISK SMOLDERING MYELOMA



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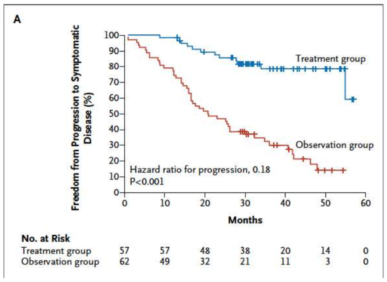
# Early Therapeutic Intervention

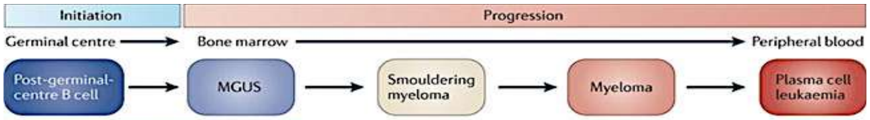
## Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D.,
Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D.,
Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D.,
Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D.,
Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D.,
Eduardo Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D.,
Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D.,
and Jesús-F. San Miguel, M.D., Ph.D.



Mateos MV, et al. NEJM 2013

## ONGOING CLINICAL TRIALS AT DFCI TO PREVENT PROGRESSION



MULTIPLE MYELOMA Research Foundation

BCRP BLOOD CANCER RESEARCH PARTNERSHIP

Completed accrual:
- Vaccine PVX-410
- Elotuzumab/Len/Dex for high risk SMM
- Daratumumab for intermediate/High risk SMM

Enrolling:
- Ixazomib/rev/dex for high risk SMM
- Dara for high-risk MGUS

Registration study: Daratumumab phase III

Neoantigen vaccine (Neon)

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# PHASE II TRIAL OF COMBINATION OF ELOTUZUMAB, LENALIDOMIDE, AND DEXAMETHASONE FOR HIGH-RISK SMOLDERING MULTIPLE MYELOMA

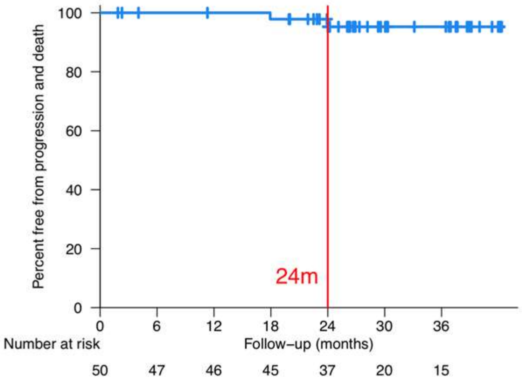
Chia-Jen Liu, **Irene M. Ghobrial**, Mark Bustoros, Kaitlen Reyes, Ashraf Badros, James Vredenburgh, Adam Boruchov, Jeffrey Matous, Aaron M. Caola, Bradley Rivotto, Alexandra Savell, Patrick Henrick, Kalvis Hornburg, Claudia Paba-Prada, Robert L. Schlossman, Jacob Laubach, Jacalyn Rosenblatt, Andrew J. Yee, Omar Nadeem, Rodrigo Maegawa, Divaya Bhutani, Andrzej Jakubowiak, Saad Z. Usmani, Manisha Bhutani, Joseph Cappuccio, Brianna Berrios, Kimberly Noonan, Tarek H. Mouhieddine, Karma Salem, Jihye Park, Oksana Zavidij, Salomon Manier, Nikhil Munshi, Kenneth Anderson, and Paul G. Richardson.

MMRC

**On behalf of MMRC and BCRP investigators**

BCRP BLOOD CANCER RESEARCH PARTNERSHIP

# PROGRESSION FREE SURVIVAL



- **Median follow up: 29 months (90% CI 27 - 30 months)**
- **Median PFS has not been reached**
- **36 months PFS is 95% (90% CI: 90-100%)**
- **EFS is 100% at 36 months (no progression to Myeloma SLIM-CRAB criteria)**

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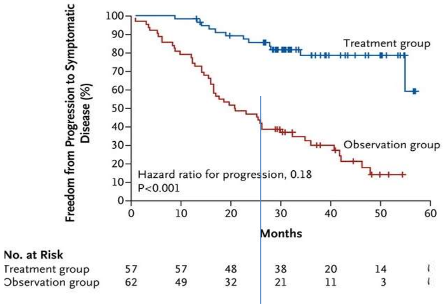


Lenalidomide and Dex trial phase III trial

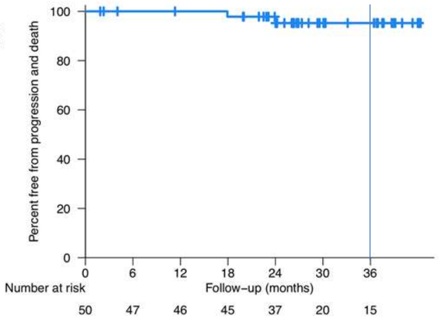
Mateos M et al. N Engl J Med 2013;369:438-447.

At 36 months, 77% of the patients in the treatment group vs. 30% of those in the observation group had progression-free survival

## PFS in relation to Rev-dex alone

**36 months PFS is 95% (90% CI: 90-100%)**

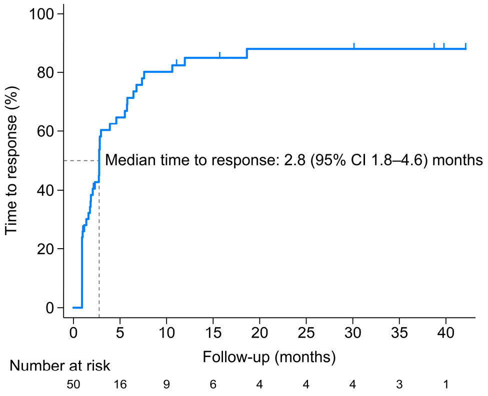
Elotuzumab-lenalidomide and



# RESPONSE RATE AND TIME TO RESPONSE

| Best response | *n* | % |
|---|---|---|
| CR | 3 | 6 |
| VGPR | 18 | 37 |
| PR | 20 | 41 |
| MR | 5 | 10 |
| SD | 3 | 6 |
| Response rate (≥ PR) | 41 | 84 |

*Evaluable patients, *n* = 49; one patient did not complete one cycle of therapy



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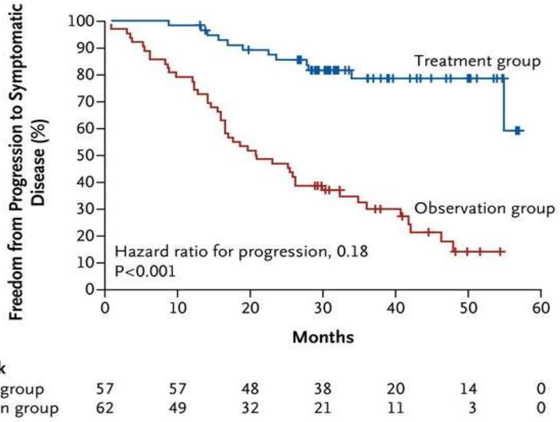
# LENALIDOMIDE AND DEX IN HIGH-RISK SMM

| Best Response | Induction Phase (%) |
|---|---|
| CR or PR | 45 (79) |
| sCR | 4 (7%) |
| CR | 8 (14) |
| VGPR | 6 (11) |
| PR | 37 (65) |
| SD | 12 (21) |



Mateos M et al. N Engl J Med 2013;369:438-447.

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# PHASE II TRIAL OF THE COMBINATION OF IXAZOMIB, LENALIDOMIDE, AND DEXAMETHASONE IN HIGH-RISK SMOLDERING MULTIPLE MYELOMA.

**Mark Bustoros**, Chia-Jen Liu, Kaitlen Reyes, Kathleen Guimond, Kalvis Hornburg, Rachel Styles, Alexandra Savell, Brianna Berrios, Diane Warren, Henry Dumke, Bradley Rivotto, Patrick Henrick, Emily Scranton, Houry Leblebjian, Robert Schlossman, Nikhil Munshi, Jacob Laubach, Kenneth C Anderson, Paul Richardson, and **Irene M. Ghobrial.**

*The Center for Prevention of Progression of Blood Cancers, Dana-Farber Cancer Institute, Harvard Medical School.

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# EXCLUSION CRITERIA

**- Evidence of CRAB criteria which include the following:**

- Increased calcium levels (corrected serum calcium >0.25 mmol/dL above the upper limit of normal or >.275 mmol/dL)
- Renal insufficiency (attributable to MM)
- Anemia (Hb 2g/dL below the lower limit of normal or <10g/dL) related to MM
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)

**- Evidence of any of the following updated criteria :**

- Bone marrow plasma cells >60%
- Serum involved/uninvolved FLC ratio ≥100 (light chain smoldering MM is allowed)
- MRI with more than one focal lesion.

**- Other exclusion criteria:**

- Other concurrent chemotherapy or immunotherapy for MM (Prior therapy with bisphosphonate or radiation therapy to a solitary plasmacytoma is allowed).
- Diagnosed or treated for another malignancy within 2 years of enrollment (Except BCC and SCC complete resection)
- Pregnant or nursing women

Rajkumar SV et al. *Lancet Oncology 2014*

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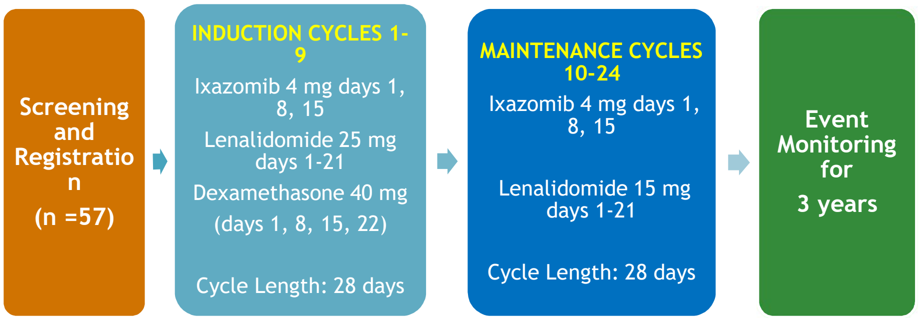
## INCLUSION CRITERIA

| - Age ≥ 18 years<br>- Bone marrow clonal plasma cells ≥10% and any one or more of the following: |
|---|
| - Serum M protein ≥3.0g/dL |
| - IgA SMM |
| - Immunoparesis with reduction of two uninvolved immunoglobulin isotypes |
| - Serum involved/uninvolved free light chain ratio ≥8 (but less than 100) |
| - Progressive increase in M protein level (Evolving type of SMM)† |
| - Bone marrow clonal plasma cells 50-60% |
| - Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes |
| - t (4;14) or del 17p or 1q gain |
| - MRI with diffuse abnormalities or 1 focal lesion |
| - PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction |
| - Monoclonal light chain excretion of 500mg/24 hours or higher* |

† Increase in serum monoclonal protein by ≥10% on two successive evaluations within a 6 month period.
* Monoclonal Light Chain Smoldering

Rajkumar SV, Mateos MV, Landgren O. *Blood 2014*

## STUDY DESIGN



**Screening and Registration**
**(n =57)**

**INDUCTION CYCLES 1-9**
Ixazomib 4 mg days 1, 8, 15
Lenalidomide 25 mg days 1-21
Dexamethasone 40 mg
(days 1, 8, 15, 22)
Cycle Length: 28 days

**MAINTENANCE CYCLES 10-24**
Ixazomib 4 mg days 1, 8, 15
Lenalidomide 15 mg days 1-21
Cycle Length: 28 days

**Event Monitoring for**
**3 years**

# BASELINE PATIENT CHARACTERISTICS

| Characteristics | Total (n = 29)<br>n | %|
|---|---|---|
| Median age, years (range) | 61 (41–73) | |
| Male sex | 15 | 51.7 |
| Heavy-chain type | | |
| IgG | 19 | 65.5 |
| IgA | 9 | 31.0 |
| No heavy chain | 1 | 3.5 |
| Light chain type | | |
| Kappa | 20 | 69.0 |
| Lambda | 9 | 31.0 |
| Median (range) | | |
| Plasma cell percentage | 20 (10–55) | |
| M-protein | 1.7 (0.4–4.1) | |
| Absolute FLC ratio | 11.6 (1.2–153.5) | |
| Calcium | 9.6 (8.7–10.4) | |
| Creatinine | 0.9 (0.6–1.3) | |
| Hemoglobin, g/dL | 13.0 (10.5–15.6) | |
| **Median treatment cycles** | 14 (3–22) | |
| **Median follow up time** | 15 months (4.2-22) | |

| High-risk criteria | Total (n = 29)<br>n | % |
|---|---|---|
| Bone marrow infiltration > 50% | 8 | 27.5 |
| M-protein ≥ 3.0 g/dL | 8 | 27.5 |
| FLC ratio > 8 | 19 | 65.5 |
| Immunoparesis | 22 | 75.8 |
| IgA isotype SMM | 9 | 31.0 |
| Evolving M-protein | 16 | 55.1 |
| High-risk cytogenetics* | 13 | 54.2 |

*High-risk cytogenetics are defined by the presence of t(4;14), t(14;16), 17p deletion, and 1q gain.

---

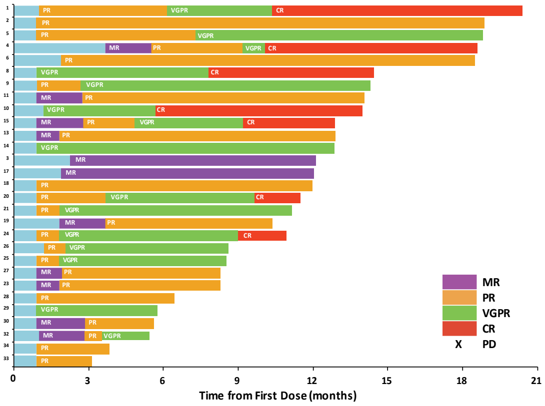
# RESPONSE TO THERAPY

| Best response | n | % |
|---|---|---|
| CR | 8 | 27.6 |
| VGPR | 7 | 24.1 |
| PR | 12 | 41.3 |
| MR | 2 | 6.9 |
| SD | 0 | 0.0 |
| **Progression*** | 0 | 0.0 |
| **Overall response rate*** | 27 | 93.1 |
| **Clinical response rate†** | 29 | 100.0 |

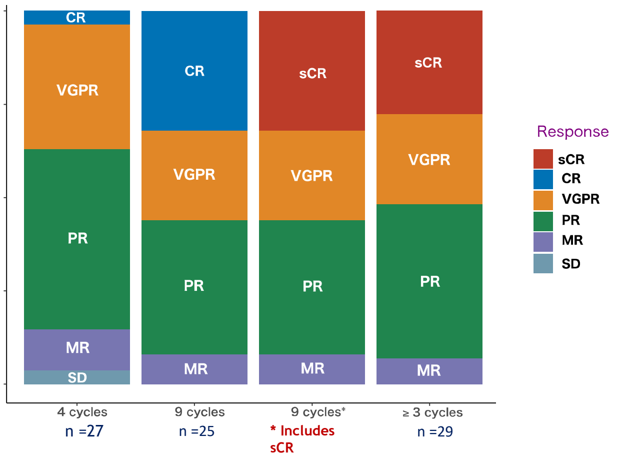
- Evaluable patients, *n* = 29.
- Includes progression to symptomatic myeloma or biological progression.

* Overall response rate includes CR, VGPR, and PR.

† Clinical response rate includes CR, VGPR, PR, and MR.



# RESPONSE TO THERAPY



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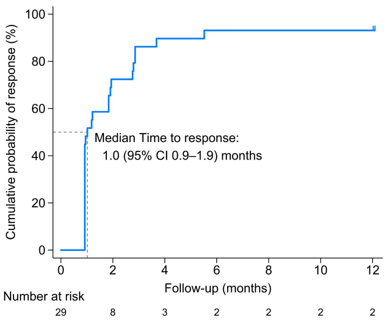
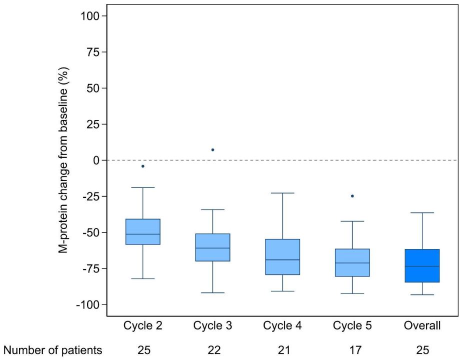
# RESPONSE TO THERAPY

Time to Response



M-protein Change from Baseline



## CONCLUSION

The combination of Ixazomib, lenalidomide, and dexamethasone is an effective and well-tolerated intervention in high-risk smoldering myeloma with ORR of 93.1% and 56% of patients achieving CR or VGPR to date.

The high response rate, convenient schedule with minimal toxicity observed to date are promising in this patient population at high risk of progression to symptomatic disease.

Further studies and longer follow up for disease progression are warranted.

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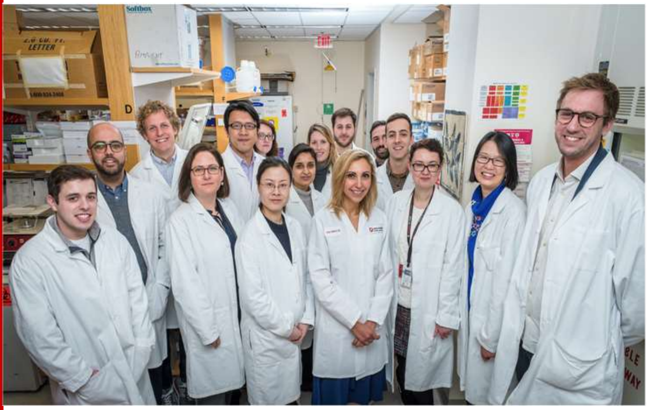

National Institutes of Health
Turning Discovery Into Health

SU2C STAND UP TO CANCER

MMRF MULTIPLE MYELOMA Research Foundation

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

http://ghobriallab.danafarberdev.org/

**Gad Getz, Viktor Adelsteinsson, Ken Anderson, Rob Soiffer, Nikhil Munshi, Paul Richardson, Ben Ebert.**
**Other collaborators:** David Scadden, Shaji Kumar, Ola Landgren, Antonio Palumbo, Herve Ave L'oiseau, Xavier Leleu,, Leif Bergsagel, Marta Chesi, Bruno Paiva, Jesus San Miguel, Richard Hynes, George Daley, Jon Licht, Gad Getz, David Root. Viktor Adalsteinsson

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## Q&A SESSION

*Treatment Advances for Multiple Myeloma*

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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## LLS EDUCATION & SUPPORT RESOURCES

- **Information Specialists**

  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - **EMAIL:** infocenter@LLS.org
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Caregiver Support:** www.LLS.org/caregiver
- **Free Education Booklets:** www.LLS.org/booklets
- **Free Telephone/Web Programs:** www.LLS.org/programs
- **Live, weekly Online Chats:** www.LLS.org/chat
- **LLS Community:** www.LLS.org/community

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## LLS EDUCATION & SUPPORT RESOURCES

- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: **www.thebloodline.org**

- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: **www.LLS.org/educationvideos**

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: **www.LLS.org/firstconnection**

- **Free Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: **www.LLS.org/nutrition**

- **What to Ask**

  Questions to ask the treatment team: **www.LLS.org/whattoask**

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: **www.LLS.org/support**

# THANK YOU

We have one goal: A world without blood cancers

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