EMORY WINSHIP CANCER INSTITUTE

A Cancer Center Designated by the National Cancer Institute

EMORY UNIVERSITY SCHOOL OF MEDICINE

# Early therapy for SMM?

Sagar Lonial, MD
Professor and Chair
Department of Hematology and Medical Oncology
Anne and Bernard Gray Professor in Cancer
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

# Question/Challange

- You are caring for a patient who has a 50% risk of developing cancer within 2-4 years
- You have a treatment that can reduce that risk by 90% and you take it for 2 years
- The treatment is oral and is generally well tolerated

- Would you offer this approach to your patient

# Points to Consider

- Genetically SMM looks identical to MM
  - The concept of ‘curative treatment’ earlier is interesting, but not currently supported by data
- What differentiates SMM from MM is immune control
  - Aggressive Tx that suppresses immunity may make things worse.
- We as a community have made the leap to say that prevention of organ damage is an important goal
  - Biomarker driven criteria for definition of MM

# Updated IMWG Criteria for Diagnosis of Multiple Myeloma

| MGUS | Smoldering Myeloma | 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% - 60%<br>• No myeloma defining events | • Underlying plasma cell proliferative disorder<br>**AND**<br>• 1 or more myeloma defining events including either:<br>✓≥ 1 **CRAB** feature(s)<br>**OR**<br>✓≥ 1 **Biomarker Driven** |

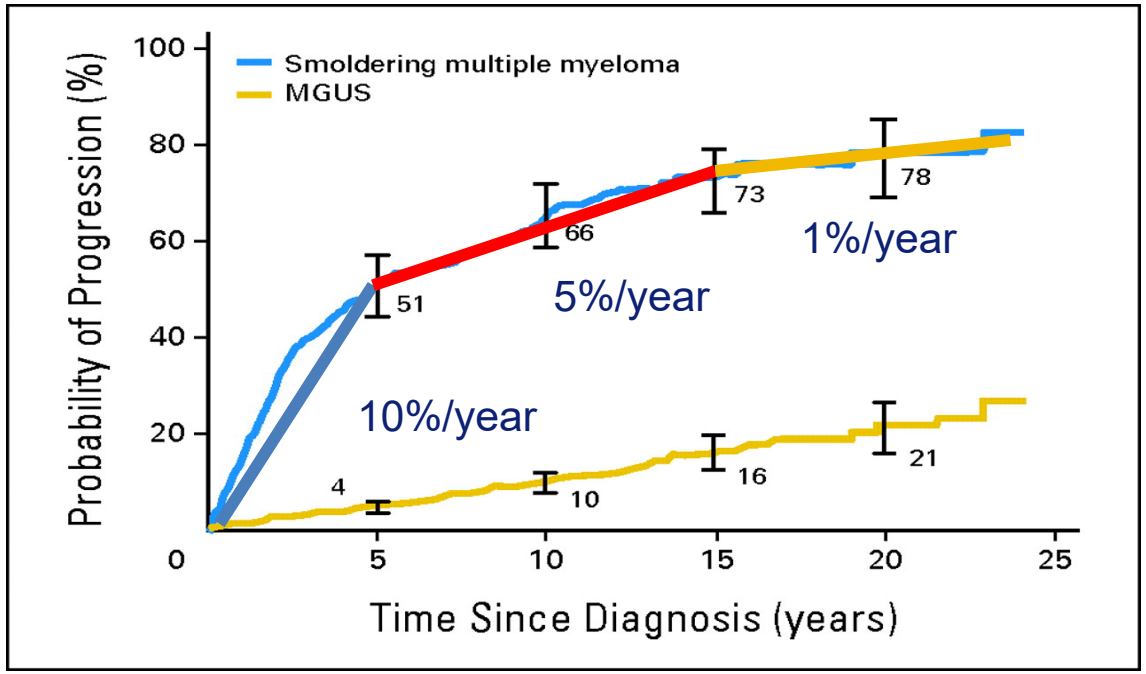
C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

Biomarker driven (1) Sixty-percent (≥60%) clonal PCs by BM; (2) serum free Light chain ratio involved:uninvolved ≥100; (3) >1 focal lesion detected by MRI



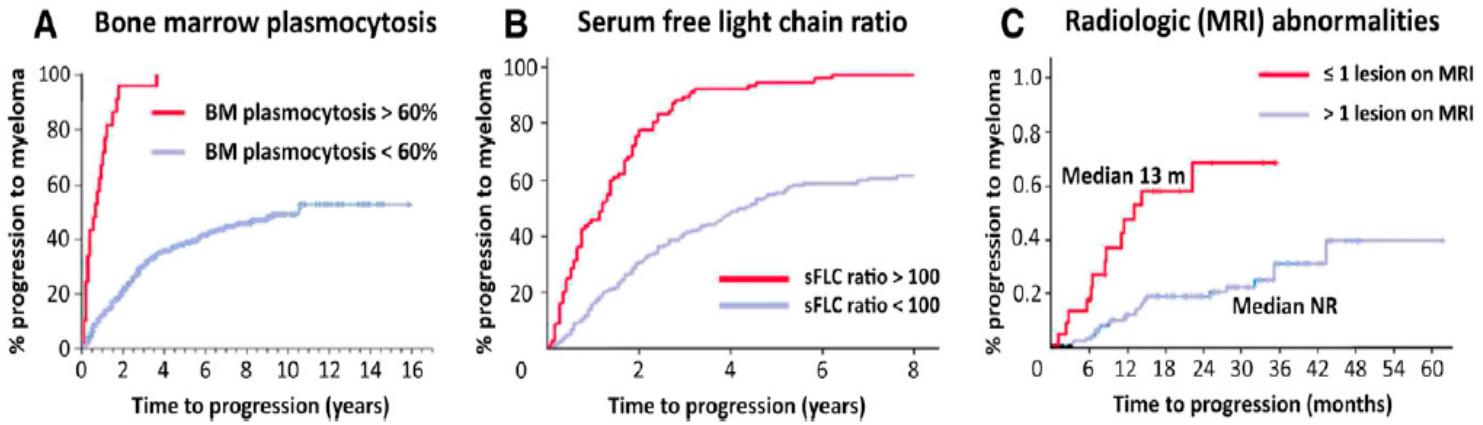
Rajkumar SV, et al. *Lancet Oncol*. 2014;15:e538-e548.

# The differences in outcomes vary by time




**MGUS**
- Serum M protein<30 g/L
- Urine M-protein < 500 mg/24h
- BMPC clone <10%
- Absence MDEs of amyloidose

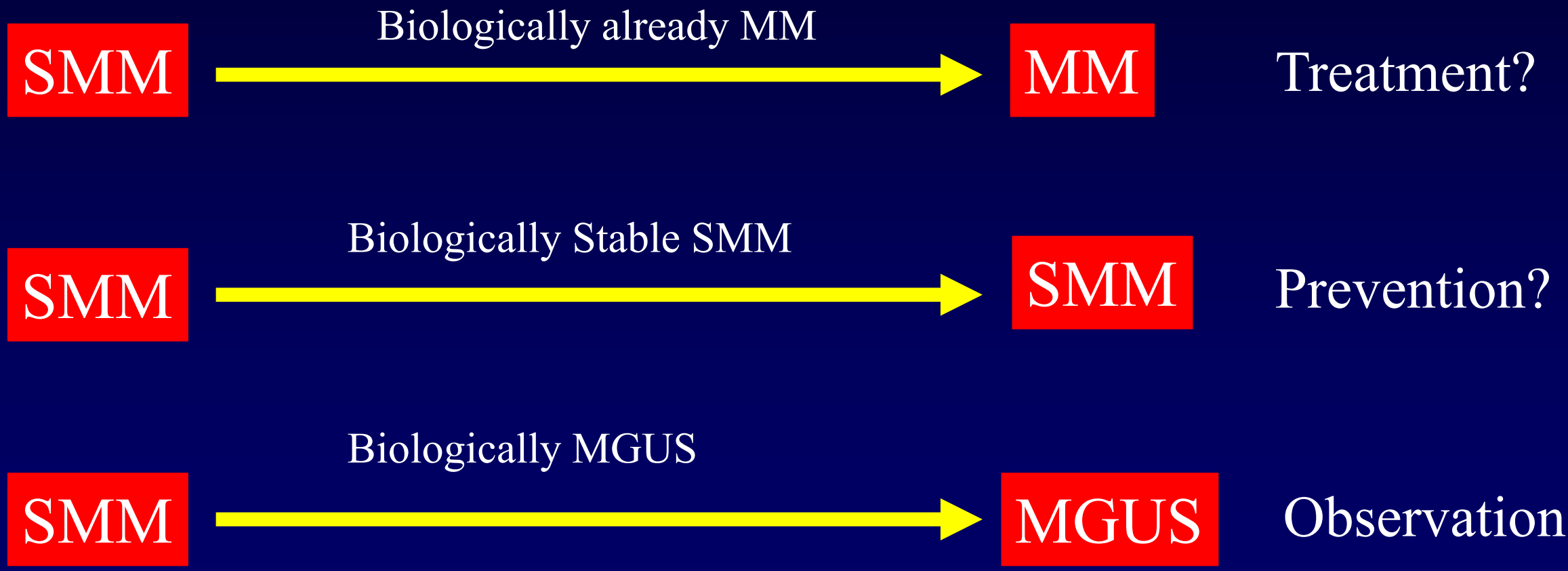
**SMM**
- Serum M protein ≥ 30 g/L and/or
- BMPC clone >10%, but <60% and/or
- Urine Mprot ≥ 500 mg/24h
- Absence MDEs or amyloidosis



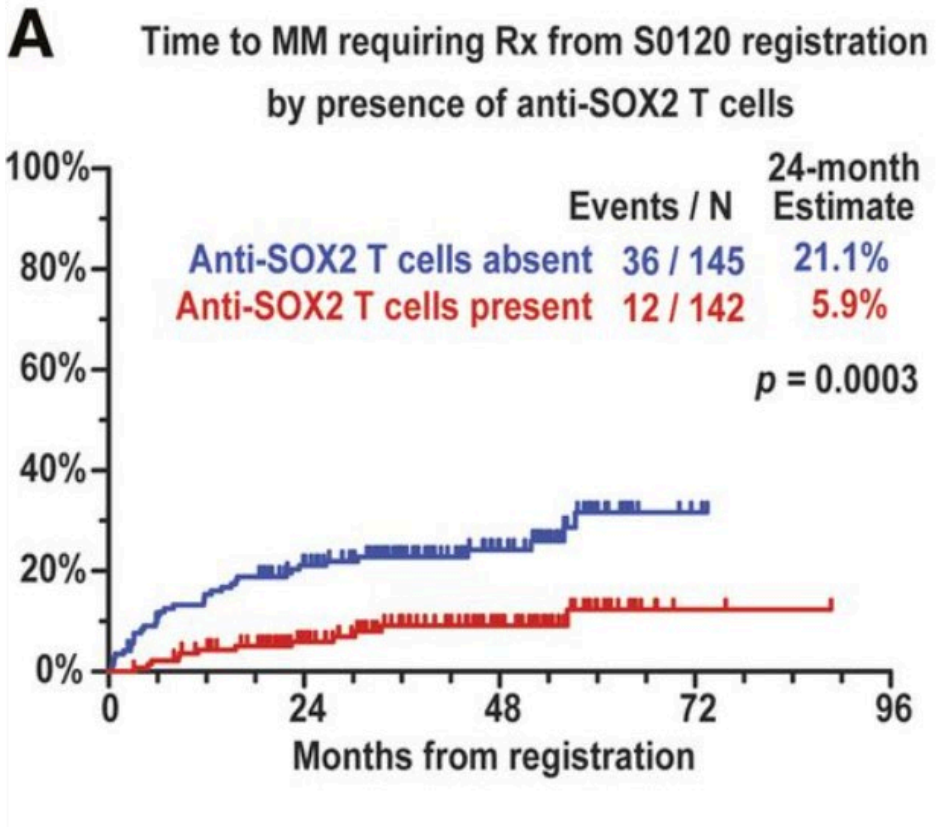

Myeloma defining events

*Bladé J et al. JCO 2010;28:690-697*
*Rajkumar, lancet oncol 2014*

# Types of SMM

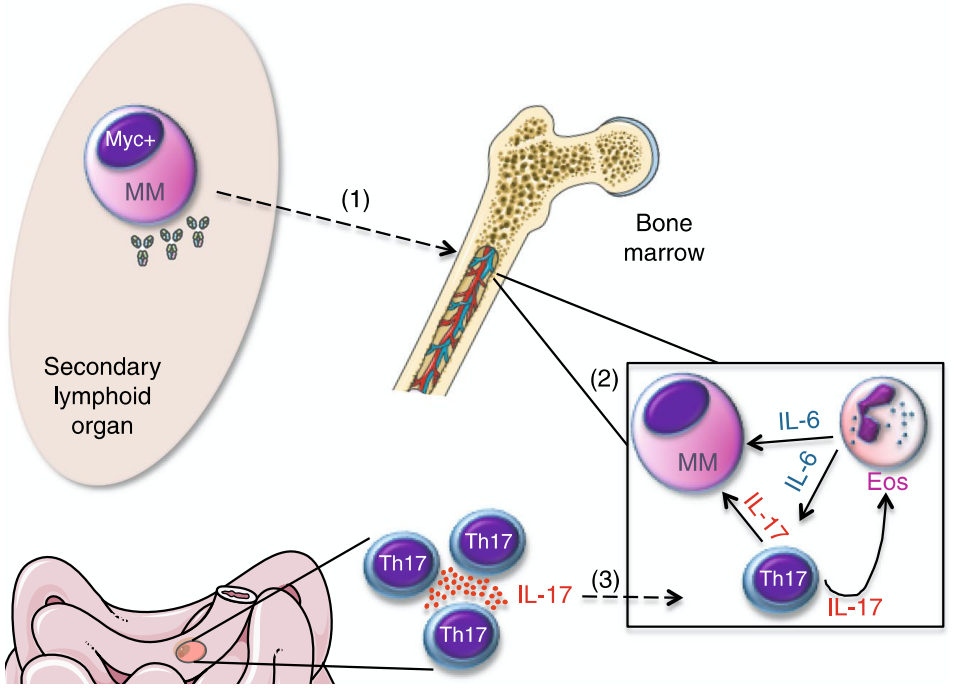

SMM
Biologically already MM
MM
Treatment?
SMM
Biologically Stable SMM
SMM
Prevention?
SMM
Biologically MGUS
MGUS
Observation

# Immunity predicts time to progression




Dhodapkar et al, *Blood* 2015

# Myeloma progression can be driven by Th17 cells induced by specific gut microbiota




Calcinotto et al, Nat Comms 2018

# Approaches to Smoldering

Immunologic Therapy
Prevention Approach

Intensive therapy
Curative Intent

Len, Len/Dex, Dara

IRD, KRD, ERD

Cesar, Ascent

**Pros**
-Fewer side effects
-More likely to induce long term effects

**Cons**
-low ORR
-does not eliminate the clone

**Pros**
-High ORR
-Deep responses

**Cons**
-Toxicity similar to MM Tx
-May result in resistant clones

# Risk stratification in SMM: Too Many Choices…..

**Identification of features predicting 50% of progression risk in patients with Smoldering Myeloma**

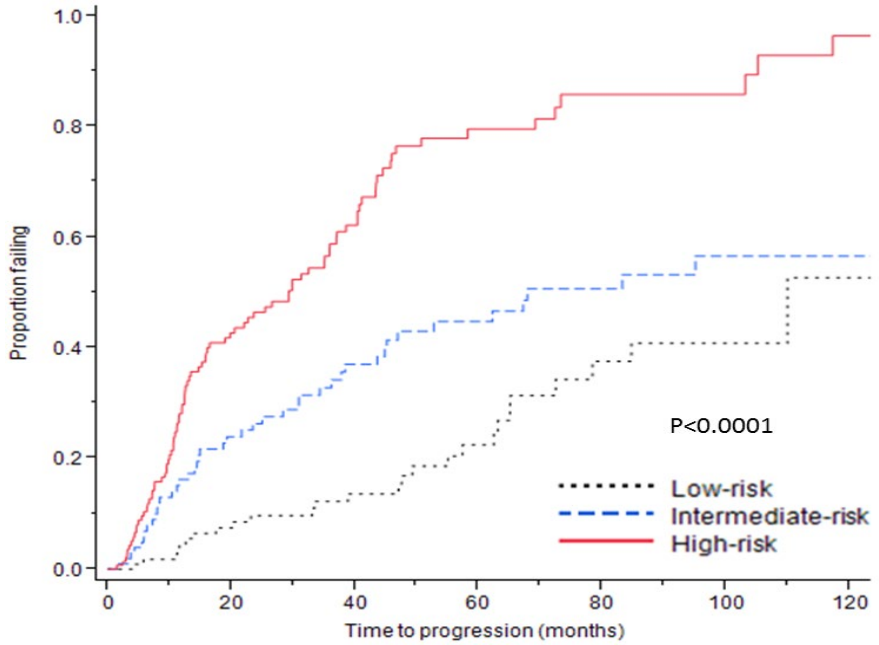
| |
|---|
| Serum M protein ≥30g/L |
| IgA SMM |
| Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes |
| Serum involved/uninvolved FLC ratio ≥8 (but <100) |
| Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period) |
| Clonal BMPCs 50%-60% |
| Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes |
| t(4;14) or del(17p) or 1q gain |
| Increased circulating PCs |
| MRI with diffuse abnormalities or 1 focal lesion |
| PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction |

- Ongoing trials, irrespective of the model systems used, have targeted a group of patients with a 50% risk of progression at 2 years (approx.) and have shown benefit

EMORY WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

Rajkumar SV, et al. *Blood.* 2015;125:3069-3075.

# Revised risk stratification (20/2/20)




**Factors**

- BMPC >20%
- M Spike >2g/dL
- FLC ratio >20

**Stratification**

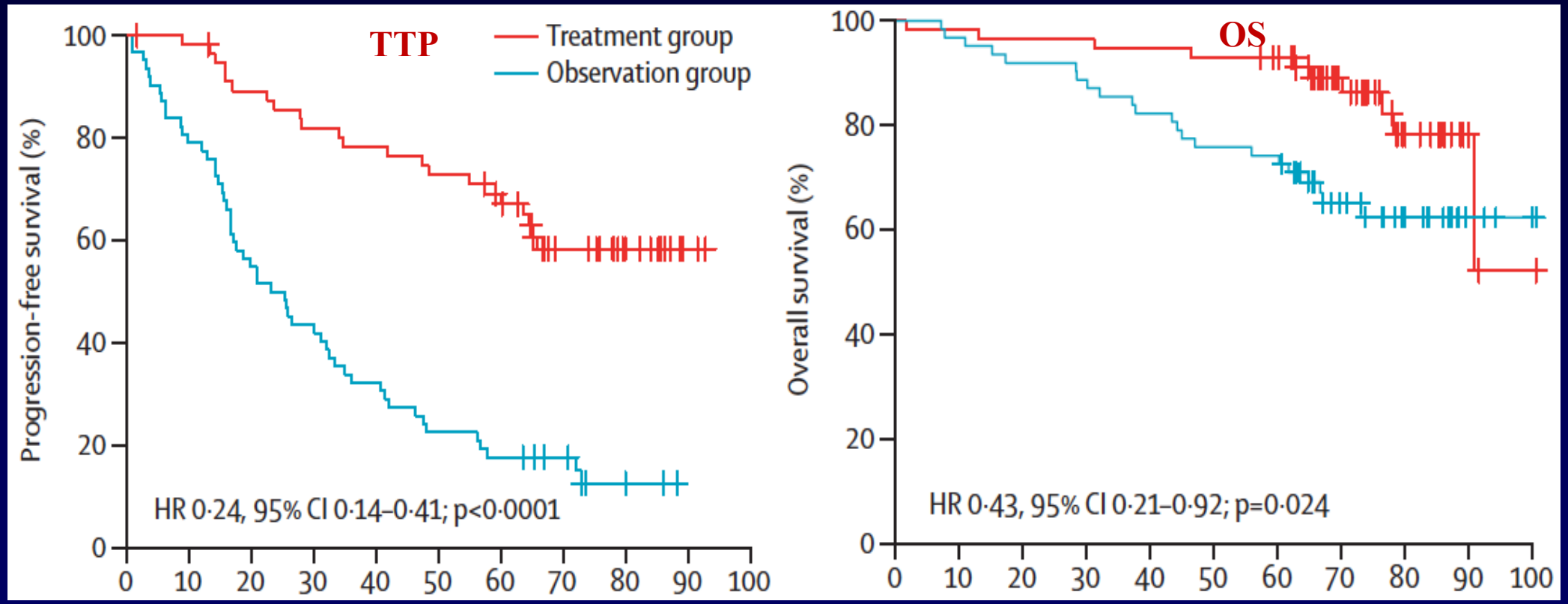
Low-risk: 0 Intermediate-risk: 1
high-risk: >=2

| Time from diagnosis (years) | Low risk ($n = 143$) | Intermediate risk ($n = 121$) | | High risk ($n = 153$) | |
|---|---|---|---|---|---|
| | Estimated rate of progression (%) | Rate of progression, % (CI) | OR for progression relative to low-risk group (CI) | Rate of progression, % (CI) | OR for progression relative to low-risk group (CI) |
| 2 | 9.7 (5.3–17.1) | 26.3 (18.4–36.2) | 2.71 (1.08–6.83) | 47.4 (38.6–56.4) | 4.89 (2.25–10.69) |
| 5 | 22.5 (14.2–33.6) | 46.7 (35.8–57.9) | 2.08 (1.07–4.08) | 81.5 (71.3–88.6) | 3.63 (2.12–6.22) |
| 10 | 52.7 (30.1–74.2) | 65.3 (45.5–80.9) | 1.24 (0.61–2.69) | 96.5 (80.9–99.4) | 1.83 (1.09–3.30) |

*BMPC%* bone marrow-plasma cell percentage, *CI* 95% confidence intervals, *FLCr* involved to uninvolved free light chain ratio, *OR* odds ratio

Lakshman A, et al. *Blood Cancer J*. 2018;8:59.

# First Demonstration of Benefit for Early Therapy

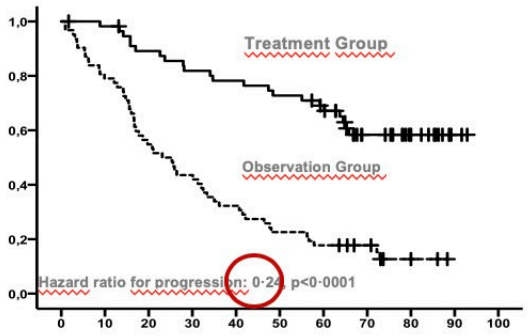



QuiRedex phase 3 trial: Rd vs observation in **high-risk** SMM

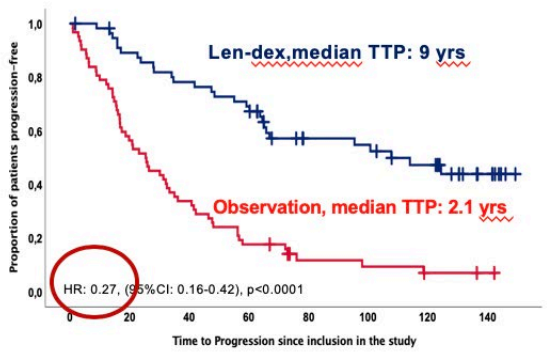
Mateos MV, et al, *N Engl J Med*, 2013;369:438-447.

# Update for Original SMM trial from Spanish Group

**Median f/u: 6.2 year**



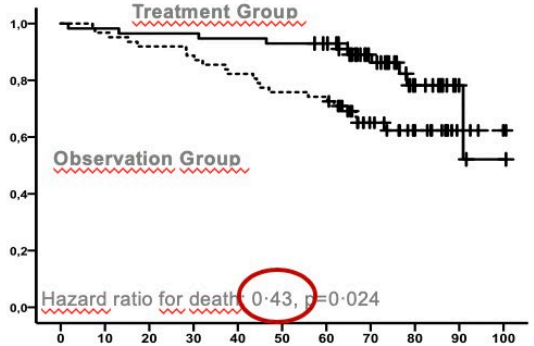

**Median f/u: 10.8 years**



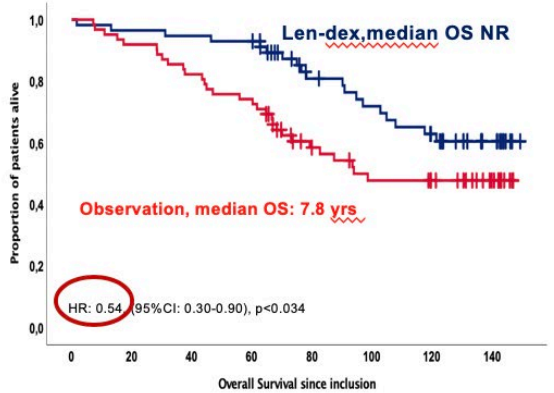

Mateos MV, et al. Lancet Oncology 2016

TTP

**Median f/u: 6.2 year**



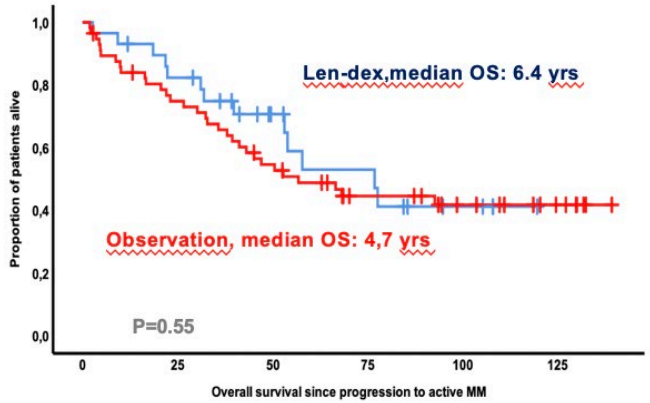

**Median f/u: 10.8 years**




Mateos MV, et al. Lancet Oncology 2016

OS

**Median f/u: 10.8years**

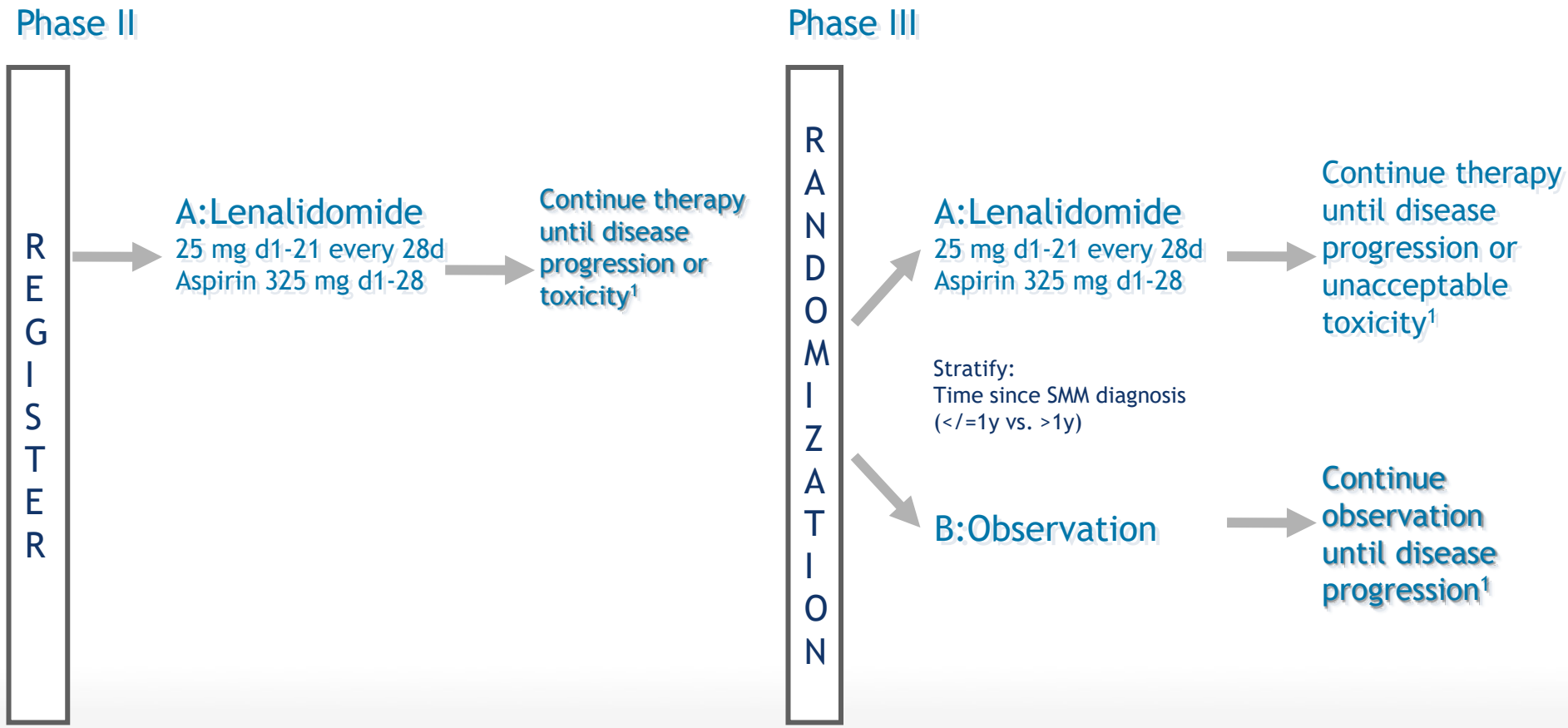



OS post progression shows no induced resistance

Mateos et al, EHA 2020

# Schema

## E3A06: Phase II/III Study
## A: Lenalidomide vs B: Observation



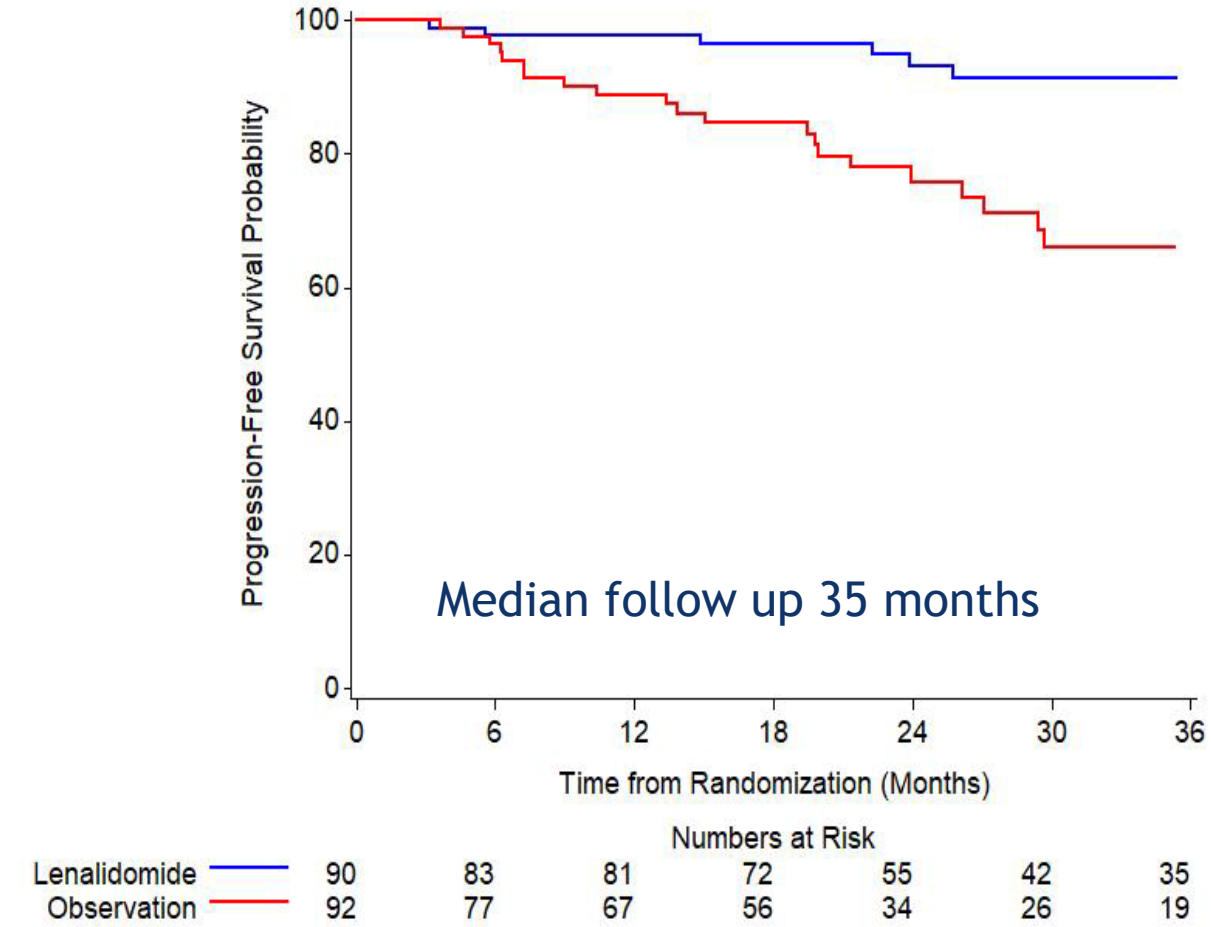

[1]Mobilize stem cells following 4-6 cycles of therapy. While stem cell collection is suggested strongly, it is not required

Lonial S, et al. ASCO 2019. Abstract 8001.

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

ECOG-ACRIN cancer research group
Reshaping the future of patient care

# Phase III PFS ITT^




**Treatment Hazard Ratio = 0.28 [95% CI: (0.12-0.63)]**

**one-sided stratified log-rank test p-value = 0.0005**

| Phase 3 PFS | Len | Obs |
|---|---|---|
| **1 yr** | 0.98 | 0.89 |
| **2 yr** | 0.93 | 0.76 |
| **3 yr** | 0.91 | 0.66 |

**^The DSMC advised release of data in fall 2018 when at the 2nd planned interim analysis (39% full information), the observed p-value from the one-sided stratified log-rank test crossed the related boundary of nominal significance**

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Lonial S, et al. JCO 2019.

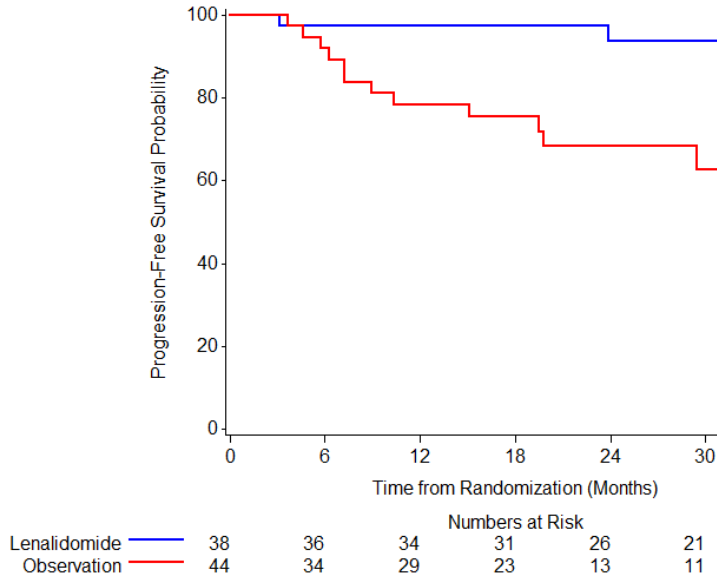
# Adverse Events

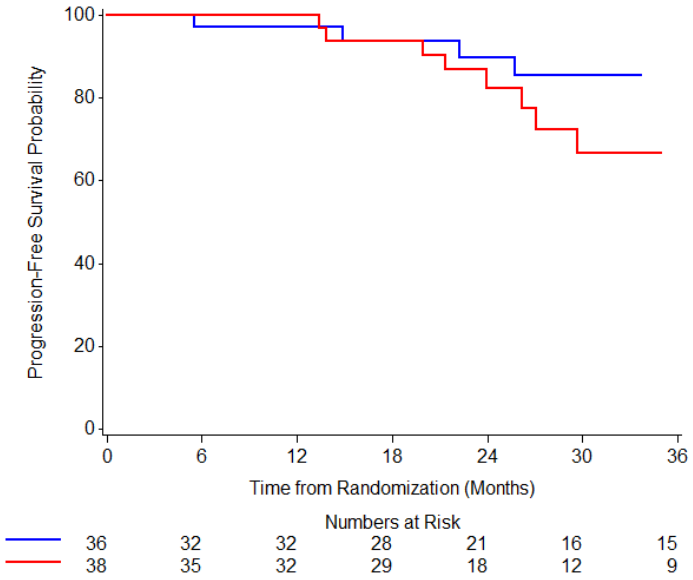
| Adverse Event | Lenalidomide Phase II [n=44] | | | Lenalidomide Phase III [n=88] | | |
|---|---|---|---|---|---|---|
| | Grade | | | Grade | | |
| | 3 | 4 | 5 | 3 | 4 | 5 |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| Hematologic | | | | | | |
| Neutrophil count decreased | 5 (11.4) | 2 (4.5) | - | 8 (9.1) | 4 (4.5) | - |
| Non-Hematologic | | | | | | |
| Alanine aminotransferase increased | 4 (9.1) | - | - | - | - | - |
| Infections | 4 (9.1) | 2 (4.5) | - | 9 (20.5) | - | - |
| Dehydration | 3 (6.8) | - | - | - | - | - |
| Dermatology/Skin | 2 (4.5) | - | - | 5 (5.7) | - | - |
| Dyspnea | - | - | - | 5 (5.7) | - | - |
| Fatigue | 5 (11.4) | - | - | 6 (6.8) | - | - |
| Hypertension | 3 (6.8) | - | - | 8 (9.1) | - | - |
| Hypokalemia | 4 (9.1) | - | - | 3 (3.4) | - | - |
| Surgical and Medical | 3 (6.8) | - | - | - | - | - |
| Overall Treatment-Related Toxicity | | | | | | |
| Non-Hematologic | 12 (27.3) | 3 (6.8) | 2 (4.5) | 25 (28.4) | - | - |
| Hematologic and Non-Hematologic* | 15 (34.1) | 5 (11.4) | 2 (4.5) | 31 (35.2) | 5 (5.7) | - |

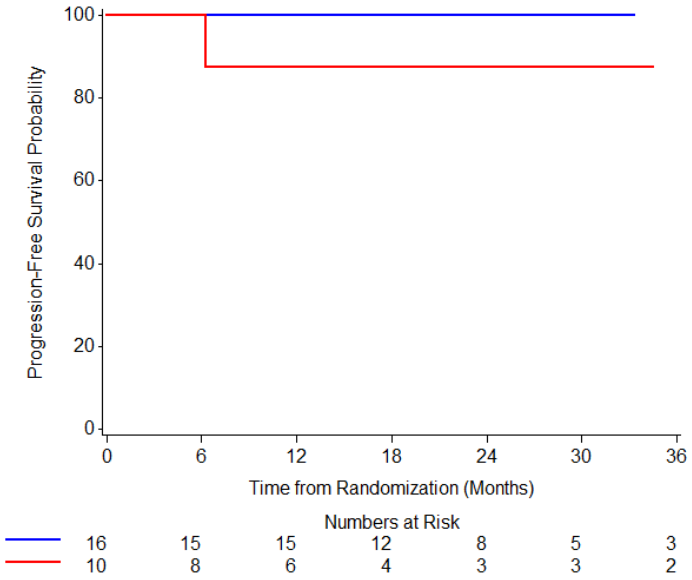
*Grade 3 Hematologic AEs not required reporting

Lonial S, et al. JCO 2019.

# Phase III PFS by Mayo 2018 Risk Criteria




High Risk

Intermediate Risk

Low Risk

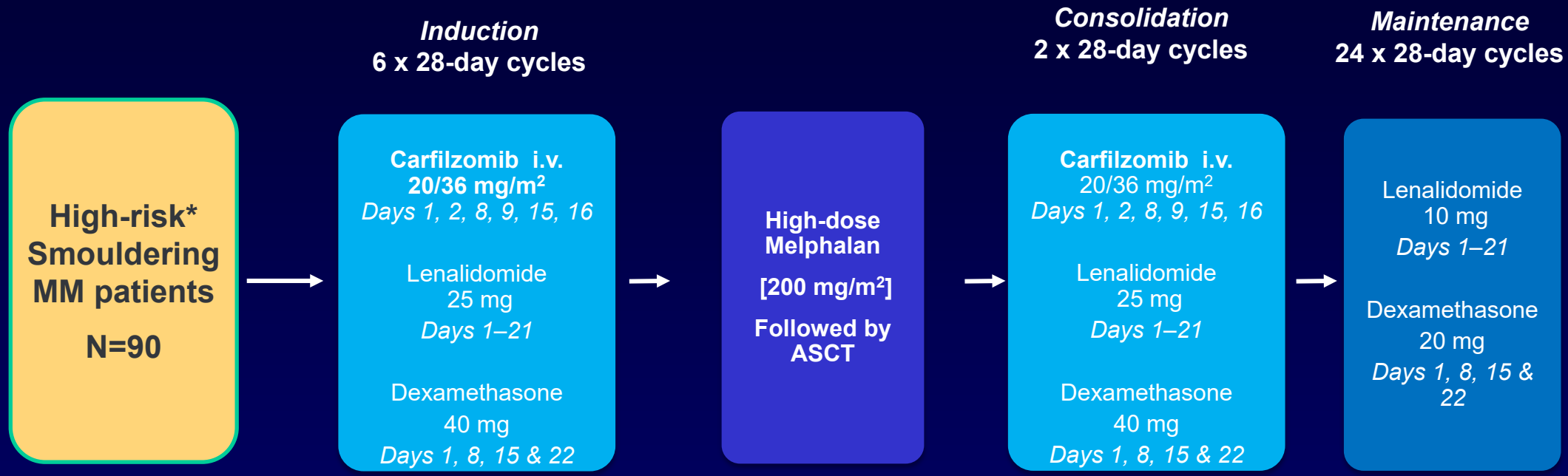
EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Lonial S, et al. JCO 2019.

ECOG-ACRIN cancer research group
Reshaping the future of patient care

# GEM-CESAR: Study Design

- Multicenter, open-label, phase II trial




***High-risk was defined according to the Mayo and/or Spanish models***

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening and if bone disease was detected by CT or PET-CT, patients were excluded

Mateos et al, ASH 2019

# GEM-CESAR
# Consolidation: Efficacy (n=81)

| Response category | Induction (n=90) | HDT-ASCT (n=83) | Consolidation (n=81) | High-risk (n=54) | Ultra high-risk (n=27) |
|---|---|---|---|---|---|
| **ORR, n(%)** | **85 (94%)** | **82 (99%)** | **81 (100%)** | **54 (100%)** | **27 (100%)** |
| **≥CR** | **37 (41%)** | **53 (64%)** | **61 (76%)** | **41 (76%)** | **20 (74%)** |
| VGPR | 35 (39%) | 18 (22%) | 15 (19%) | 10 (19%) | 5 (19%) |
| PR | 13 (14%) | 11 (13%) | 5 (6%) | 2 (4%) | 2 (7%) |
| SD | 1 (1) | 1 (1) | - | - | - |
| Progressive disease | 2 (3%) | - | - | - | - |
| MRD –ve, | 27 (30%) | 47 (56%) | 51 (63%) | 36 (67%) | 15 (56%) |

Mateos et al, ASH 2019

# GEM-CESAR
# Induction: Safety profile (n=90)

| Adverse Events | Induction (n=90) | |
|---|---|---|
| **Hematological toxicity, n(%)** | Grade 1-2 | Grade 3-4 |
| - **Anemia** | 7 (7%) | - |
| **- Neutropenia** | 6 (7%) | **3 (3%)** |
| **- Thrombocytopenia** | 9 (10%) | **5 (5%)** |
| **Non- Hematological toxicity, n(%)** | | |
| - Astenia | 10 (11%) | 1 (1%) |
| - Diarrea/Constipation | 6 (7%)/5 (5%) | 1 (1%)/- |
| **- Infections** | 17 (19%) | **9 (10%)*** |
| **- Skin rash** | 14 (15) | **8 (9%)** |
| **- Cardiologic events** | 1 (1%) | **1 (1%)** |
| - Deep venous thrombosis | 2 (2%) | 1 (1%) |
| **- Hypertension** | 3 (3%) | - |

**Pneumoniae G1-2 (2 pts) and G3-4 (2 pts); Atrial fibrillation G1 (1pt); Cardiac failure G3 (1pt); Hypertension G2 (3 pts)**

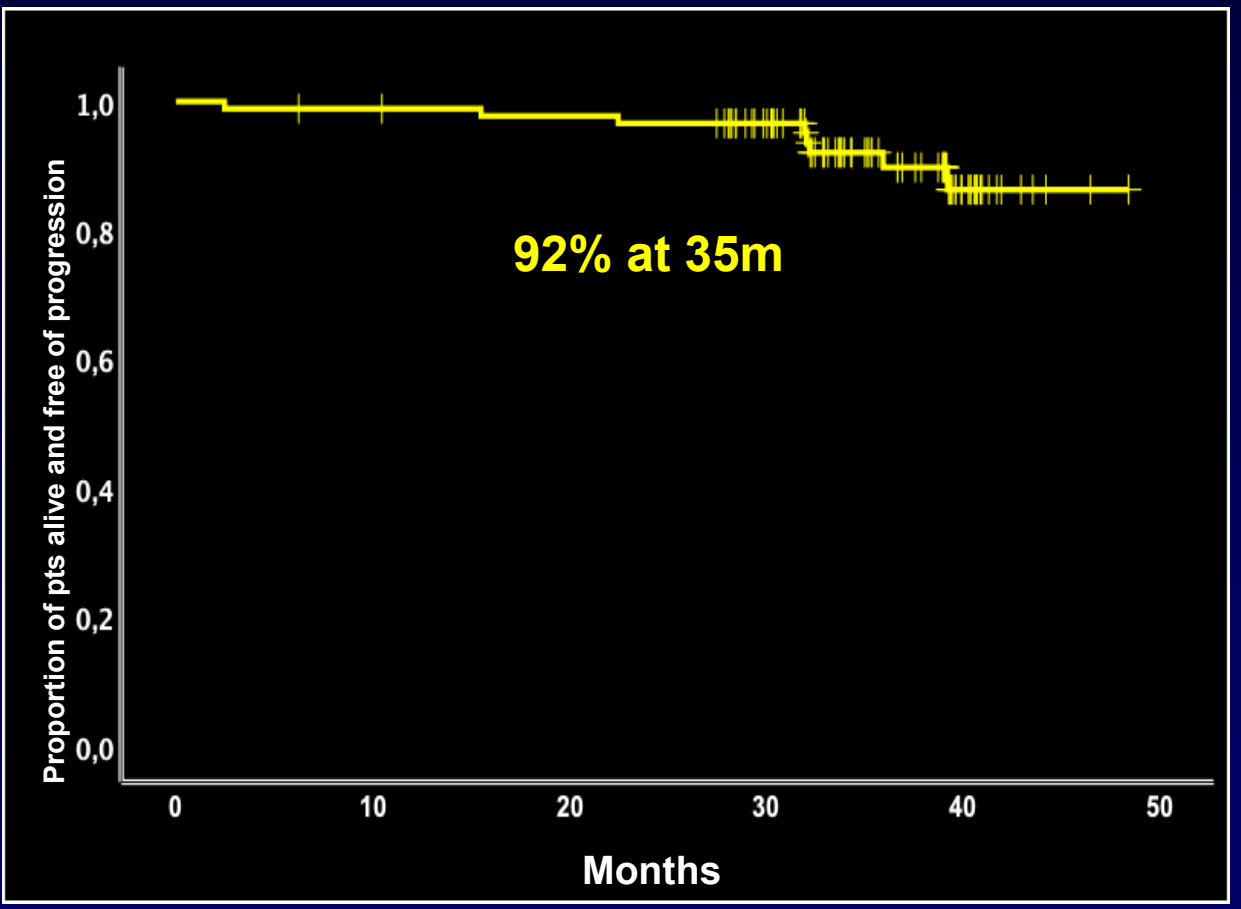
*** 1 pt developped G5 AEs consisting on massive ischemic stroke after respiratory infection**

Mateos et al, ASH 2019

# GEM-CESAR Outcomes

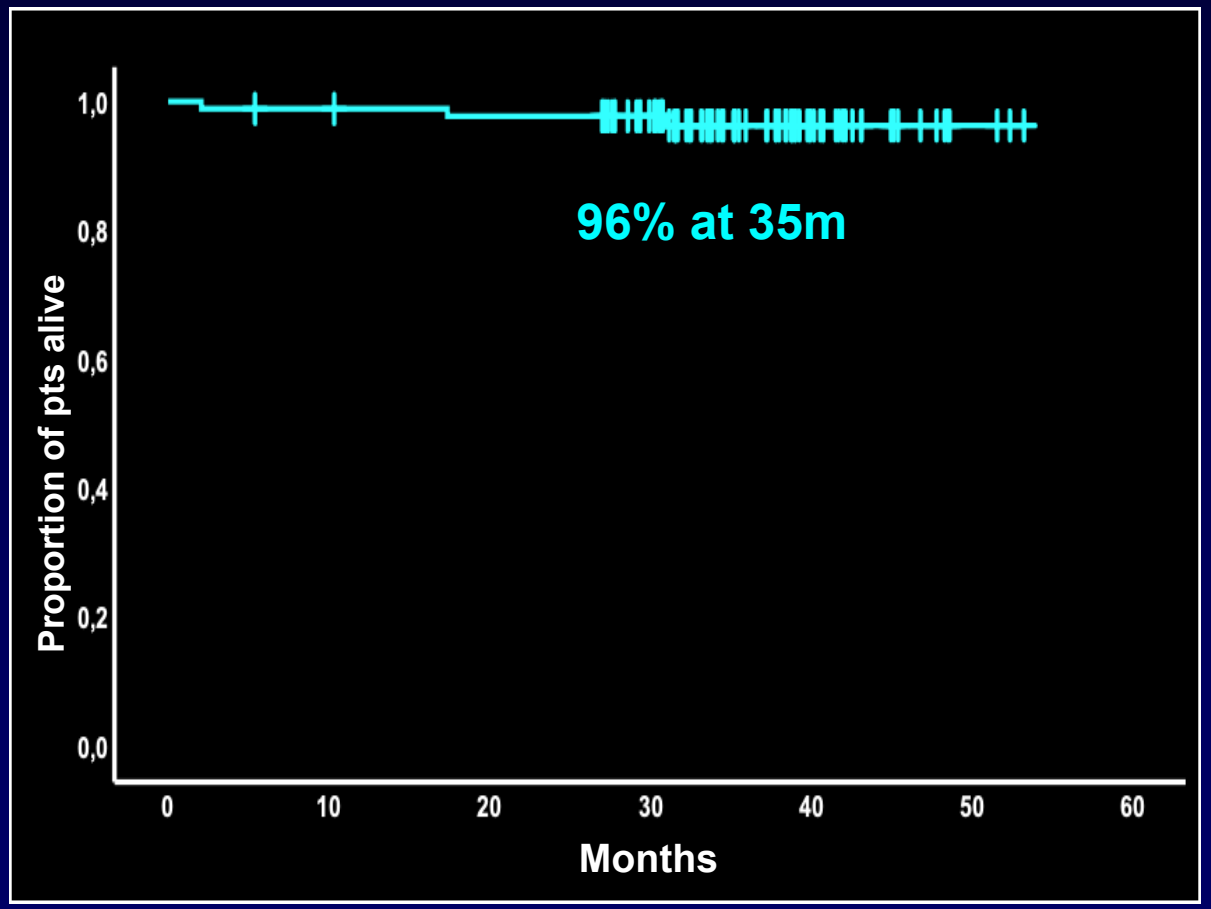
Median follow-up: 35,2 (5.4-53.2)

## PFS




6 pts did progress and in 5 pts PD was biological and 4 pts were at ultra high risk

## OS




3 pts died and in only one was treatment-related death

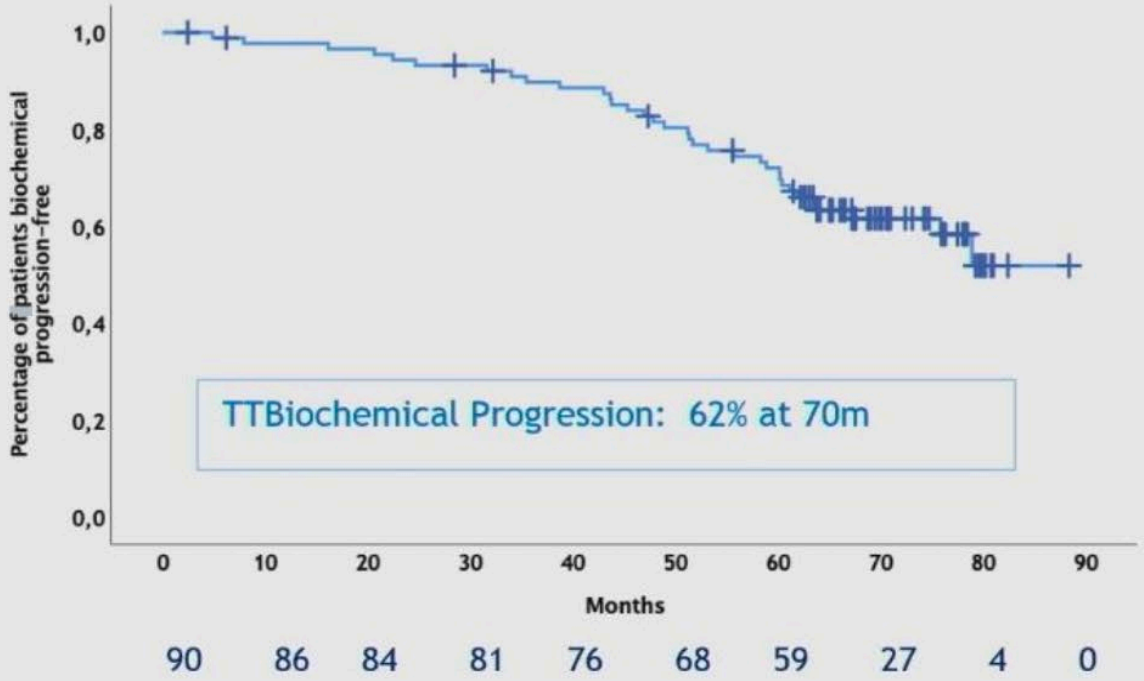
Mateos et al, ASH 2019

# GEM-CESAR :Outcomes: Time to Biochemical Progression to MM

Median follow-up: 70.1 (6.2-88.8) months

| Type of biochemical progression | n (%) |
|---|---|
| - Progressive disease | 8 (24%) |
| - Relapse from CR | 19 (56%) |
| - Ultrasensitive MRD relapse: Conversion from MRD-ve to +ve confirmed twice with sensitivity $\geq 10^{-5}$ or increase in >1log between 1st and 2nd determination (if sensitivity $10^{-6}$) | 7 (21%) |

TTP to biochemical progression




**34 pts progressed biochemically:** 9 pts during treatment phase and 8 during the first 4 years after trx and 17 (50%) between the 4th and 5th year post trasplant

# Ascent Trial

## Treatment

**INDUCTION**

(***4-week cycles for 6 cycles***)

- Carfilzomib (36 mg/m$^2$ twice weekly or 56mg/m$^2$ weekly)
- Lenalidomide (25 mg daily for three weeks)
- Daratumumab (weekly for 8, every other week for 16 weeks)
- Dexamethasone 40 mg weekly

**CONSOLIDATION**

(***4-week cycles for 6 cycles***)

- Carfilzomib (36 mg/m$^2$ twice weekly or 56mg/m$^2$ weekly)
- Lenalidomide (25 mg daily for three weeks)
- Daratumumab (every 4 weeks)
- Dexamethasone 20 mg weekly

**MAINTENANCE**

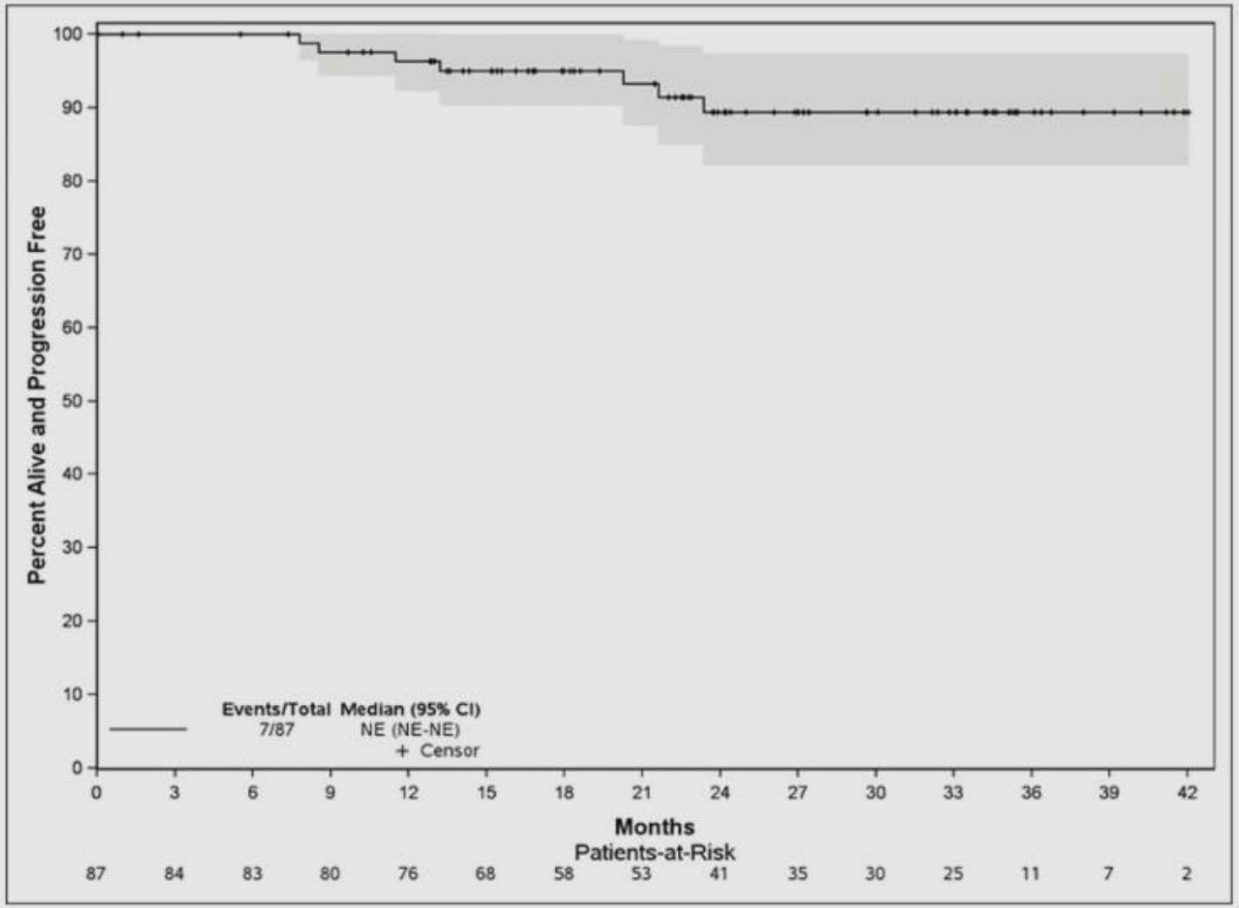
(***4-week cycles for 12 cycles***)

- Lenalidomide (10 mg daily for 3 weeks)
- Daratumumab (q 8 weeks)

# Ascent Trial

## Survival

- **4** patients have progressed, median PFS for the cohort has not been reached; PFS rate (95%CI) at 3 years was 89.9% (82.3-98.3%)
- **3** progressions were biochemical, **1** patient developed PCL 6 months after completing therapy



# Conclusions

- New definition for high risk SMM should be used across all studies
- For patients meeting the 20/2/20 high risk criteria, early therapy with len or len/dex should be considered **IF** a trial is not an option
- The question of prevention vs cure should be addressed in clinical trials, but absent an answer to that question, we should not continue to just *'Wait for more data'*
- **It is time to move towards early intervention for some patients**

# Patients and Families


**Thanks to:**

Jonathan Kaufman
Ajay Nooka
Craig Hofmeister
Madhav Dhodapkar
L.T. Heffner
Vikas Gupta
Nisha Joseph
Leon Bernal
Charise Gleason
Donald Harvey
Colleen Lewis
Amelia Langston
Y. Gu
S-Y Sun
Jing Chen
Mala Shanmugan
Larry Boise
Cathy Sharp
Jennifer Shipp

And the Clinical Research Team

IMS

Golfers Against Cancer
T.J. Martell Foundation

**And Many Others who are part of the B-cell Team**



sloni01@emory.edu