Global Multiple Myeloma Academy

Global Multiple Myeloma Academy

Emerging and Practical Concepts in Multiple Myeloma

23–24 June 2022 – Latin America and Canada

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Global Multiple Myeloma Academy

Welcome and Meeting Overview

Rafael Fonseca, MD

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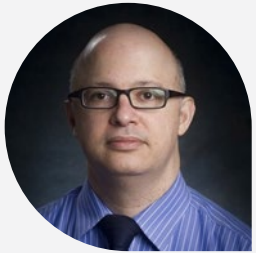
Faculty

Chair

Rafael Fonseca, MD
Mayo Clinic Cancer Center, USA

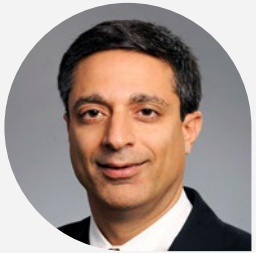
Keith Stewart, MBChB, MBA
Princess Margaret Cancer Centre, Canada

Vania Hungria, MD, PhD
São Germano Clinic, Brazil



Luciano Costa, MD, PhD
University of Alabama at Birmingham, USA

Eloisa Riva, MD
Hospital de Clínicas, Uruguay



Sagar Lonial, MD, FACP
Emory University, USA

Objectives of the Program

Share key data from recent conferences that could lead to improved treatment and management for patients with myeloma

Discuss early treatment strategies for smoldering myeloma and initial therapies for multiple myeloma

Provide insights into the evolving role of minimal residual disease (MRD) monitoring in the management of patients with multiple myeloma

Present the latest research on identifying multiple myeloma patients at high risk for early relapse, and management strategies for early relapse

Discuss the benefits and limitations of current options for treating patients with multiple myeloma refractory to multiple therapeutic modalities

Explore regional challenges in the treatment of multiple myeloma across Latin America

LATAM Agenda Day 1

Time UTC-3	Topic	Time	Speaker
15.30 – 15.40	**Welcome and Meeting Overview**	10 min	Rafael Fonseca, MD
15.40 – 16.00	**Diagnosis and Risk Stratification of Multiple Myeloma**	20 min	Vania Hungria, MD, PhD
16.00 – 16.25	**Smoldering Multiple Myeloma: Current and Future Developments**	25 min	Sagar Lonial, MD, FACP
16.25 – 16.50	**Newly Diagnosed Transplant-Eligible Multiple Myeloma: Frontline Therapy and the Role of Transplantation**	25 min	Luciano Costa, MD, PhD
16.50 – 17.10	**Debate** • Is myeloma curable or not?	20 min	Rafael Fonseca, MD (yes) vs Eloisa Riva, MD (no)
17.10 – 17.20	**Break**	10 min	
17.20 – 17.45	**Advances in Consolidation and Maintenance Therapy: Latest Updates and MRD-Guided Therapy**	25 min	Luciano Costa, MD, PhD
17.45 – 18.10	**Treatment Considerations for Newly Diagnosed Transplant-Ineligible Patients**	25 min	Keith Stewart, MBChB, MBA
18.10 – 18.35	**Interactive Discussion and Q&A** • Regional challenges of MM diagnosis and treatment • Questions from audience	25 min	All faculty discussion
18.35 – 18.55	**Debate** • Smoldering myeloma: To treat or not to treat?	20 min	Sagar Lonial, MD, FACP (yes) vs Keith Stewart, MBChB, MBA (no)
18.55 – 19.00	**Session Close** • ARS questions	5 min	Rafael Fonseca, MD

LATAM Agenda Day 2

Time UTC-3	Topic	Time	Speaker
15.30 – 15.40	**Session Open**	10 min	Rafael Fonseca, MD
15.40 – 16.00	**Defining and Understanding High-Risk Multiple Myeloma**	20 min	Eloisa Riva, MD
16.00 – 16.25	**Early Relapse of Multiple Myeloma: Current and Emerging Treatment Options**	25 min	Rafael Fonseca, MD
16.25 – 16.45	**Patient Case Discussion and Q&A: Relapsed/Refractory Multiple Myeloma** Case 1 from the region	20 min	Ana Luiza Silva, MD
16.45 – 16.55	**Break**	10 min	
16.55 – 17.20	**Management of Heavily Pretreated Multiple Myeloma**	25 min	Keith Stewart, MBChB, MBA
17.20 – 17.40	**Patient Case Discussion and Q&A: Relapsed/Refractory Multiple Myeloma** Case 2 from the region	20 min	Lucía Pérez Baliero, MD
17.40 – 18.30	**Beyond the Horizon: New and Future Multiple Myeloma Treatment Approaches** • Optimal use of treatment choices in relapsed/refractory MM – Bispecifics in MM – CAR Ts in MM	 25 min 25 min	 Vania Hungria, MD, PhD (bispecifics), Luciano Costa, MD, PhD (CAR T)
18.30 – 18.55	**Interactive Discussion and Q&A** • Treatment landscape evolution	25 min	All faculty discussion
18.55 – 19.00	**Session Close**	5 min	Rafael Fonseca, MD

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Introduction to the Audience Response System

Rafael Fonseca, MD

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Question 1

In what country do you currently practice?

a) Argentina
b) Brazil
c) Canada
d) Colombia
e) Cuba
f) Mexico
g) Peru
h) Uruguay
i) Venezuela
j) Other

Question 2

Which of the following is not part of the new criteria for treatment initiation in MM?

a) Plasma cells >60%
b) Deletion 17p
c) Two or more lesions on an MRI
d) Extreme abnormalities in the free light chains

Question 3

Which of the following is not true in the treatment of newly diagnosed MM?

a) Deep responses are associated with better outcomes
b) VGPR is an accepted benchmark as evidence of a good response
c) Clinical trials are considering risk stratification
d) Regimens that contain daratumumab have further increased response rates
e) Maintenance prolongs overall survival for MM patients

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Diagnosis and Risk Stratification of Multiple Myeloma

Vania Hungria, MD, PhD

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Diagnosis and Risk Stratification of Multiple Myeloma

Vania Tietsche de Moraes Hungria, MD, PhD

Associate Professor of Hematology at Santa Casa Medical School
Clinical Director at Clínica São Germano
São Paulo, Brazil

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Oncologia

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Disclosures

Honoraria: Amgen, BMS, Celgene, GSK, Janssen, Pfizer, Sanofi, Takeda

Diagnosis

Question for the Audience

Which biomarker below defines multiple myeloma?

a) Clonal bone marrow plasma cell percentage ≥30%
b) Clonal bone marrow plasma cell percentage ≥60%
c) >3 focal lesions on MRI studies
d) Involved:uninvolved serum free light chain ratio ≥*30*

Criteria for Diagnosis of Myeloma

	MGUS	SMM	Symptomatic MM
Monoclonal component	<3 g/dL serum	≥3 g/dL serum	Present
	AND	AND/OR	AND
BM PC	<10%	≥10%	≥10%
	AND	AND	AND
End-organ damage*	Absent	Absent	Present

Calcium
>0.25 mmol/L above upper limit of normal, or >2.75 mmol/L

Renal
Creatinine >173 mmol/L, 2 mg/dL

Anemia
Hemoglobin 2 g/dL below lower limit of normal, or <10 g/dL

Bone
Lytic lesions or osteoporosis with compression fractures

International Myeloma Working Group. *Br J Haematol*. 2003;121:749-757.

Panel: Revised International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma and Smoldering Multiple Myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any 1 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
    - Hypercalcemia: 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)
    - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
    - Bone lesions: 1 or more osteolytic lesions on skeletal radiography, **CT, or PET-CT‡**
  - ✓ **Any 1 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¶

**Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡PET-CT = ^{18}F-fluorodeoxyglucose PET with CT. If bone marrow has <10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.*

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

Panel: Revised International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma and Smoldering Multiple Myeloma

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    - Clonal bone marrow plasma cell percentage* ≥60%
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    - >1 focal lesions on MRI studies¶

→ **Subgroup of SMM patients who require treatment**

**Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡PET-CT = ^{18}F-fluorodeoxyglucose PET with CT. If bone marrow has <10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.*

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

Panel: Revised International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma and Smoldering Multiple Myeloma

Definition of smoldering multiple myeloma

Both criteria must be met

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells **10%–60%**
- Absence of myeloma defining events or amyloidosis

**Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡PET-CT = ^{18}F-fluorodeoxyglucose PET with CT. If bone marrow has <10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.*

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

Potential Future Biomarkers for Diagnosis of Multiple Myeloma

	2-year probability of progression
High levels of circulating plasma cells	80%
Abnormal plasma cell immunophenotype ≥95% plus immunoparesis	50%
Evolution of smoldering multiple myeloma*	65%
Cytogenetic subtypes: t(4;14), 1q amp, or del 17p	50%
High bone marrow plasma cell proliferative rate	80%
Unexplained decrease in creatinine clearance by ≥25% accompanied by a rise in urinary monoclonal protein or serum free light-chain concentrations	Not known

**Increase in serum monoclonal protein by ≥10% on each of 2successive evaluations within a 6-month period.*

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

Prognosis and Risk Stratification

Question for the Audience

The Revised International Staging System includes:

a) ISS
b) LDH
c) Cytogenetic abnormality
d) All of the above

Prognosis

Assessment of multiple factors

- Host characteristics: advanced age, frailty, performance status, comorbidities
- Tumor burden: staging
- Biology: plasma cell genetics
- Response to therapy

Tumor Burden

"International Staging System"

Stage ISS	Criteria	Median Survival (months)
I	Serum β_2-microglobulin <3.5 mg/L Serum albumin ≥3.5 mg/L	62
II	Not stage I or III	44
III	Serum β_2-microglobulin ≥5.5 mg/L	29

Greipp PR, et al. *J Clin Oncol*. 2005;23:3412-3420.

Biology

Cytogenetic Risk Classification

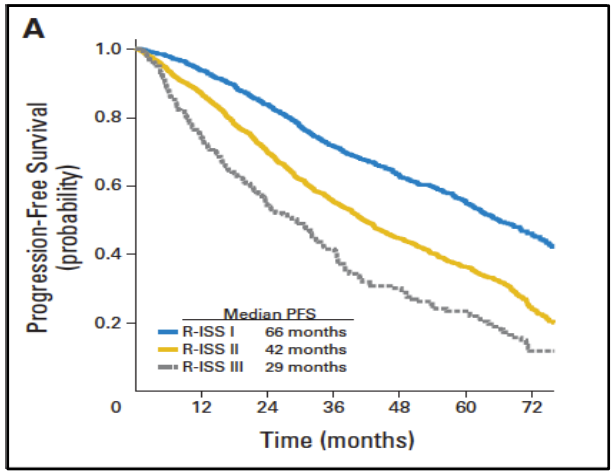
Cytogenetic abnormality	Genes affected	Percentage in MM	Prognosis
Trisomies	Odd-numbered chromosomes	40–50	Favorable
Monosomy 13	*RB1*	45–50	Intermediate
1q gain	*CKS1B* and others	35–40	Poor
1p del	*FAM46C*, *CDKN2C,* and *FAF1*	30	Poor
MYC 8q24	*MYC*	15–20	Poor
t(4;14)	*FGFR3* and *MMSET*	15	Poor/Intermediate
t(11;14)	*CCND1*	15	Favorable
17p del	*TP53*	10	Poor
t(6;14)	*CCND3*	5	Favorable
t(14;16)	*c-MAF*	5	Poor
t(14;20)	*MAFB*	1	Poor

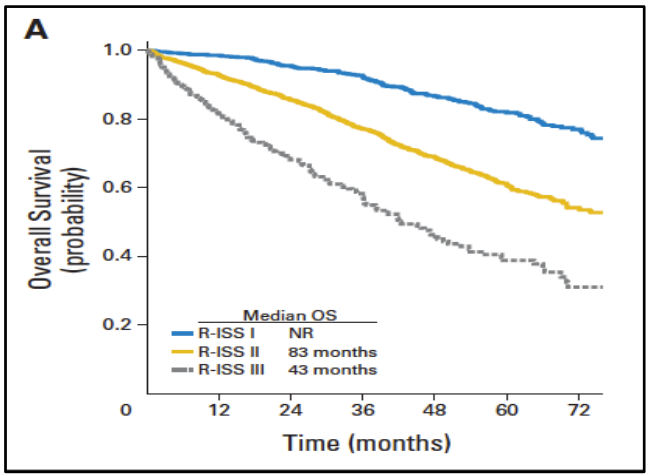
Munshi NC, et al. *Blood*. 2011;117:4696-4700.

Revised International Staging System (R-ISS)

R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

High-risk CA includes the presence of del(17p) and/or t(4;14) and/or t(14;16)





CA, cytogenetic abnormality; LDH, lactate dehydrogenase ; NR, not recorded; PFS, progression-free survival.

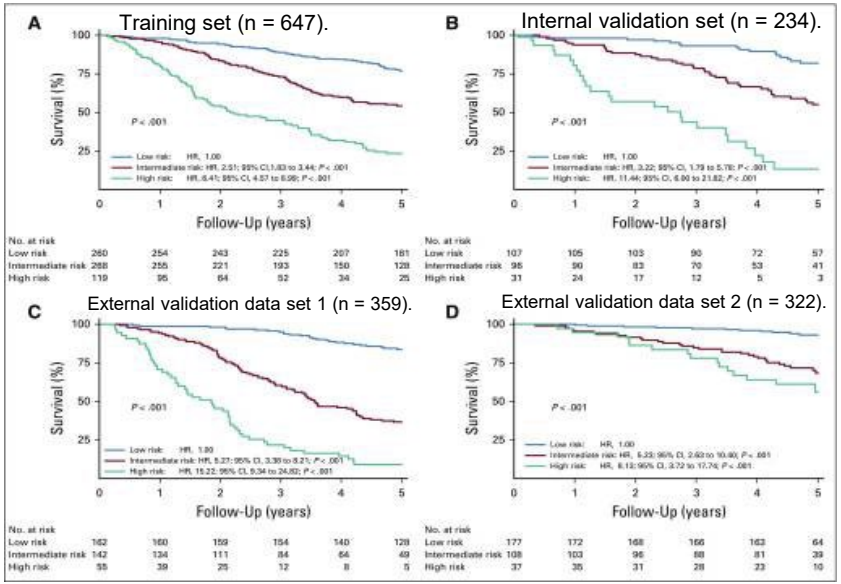
Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2869.

Development and Validation of a Cytogenetic Prognostic Index Predicting Survival in Multiple Myeloma

The prognostic impact of del(17p); t(4;14); del(1p32); 1q21 gain; and trisomies 3, 5, and 21 in a cohort of newly diagnosed patients with MM, from 4 randomized IFM clinical trials (n = 1,635).

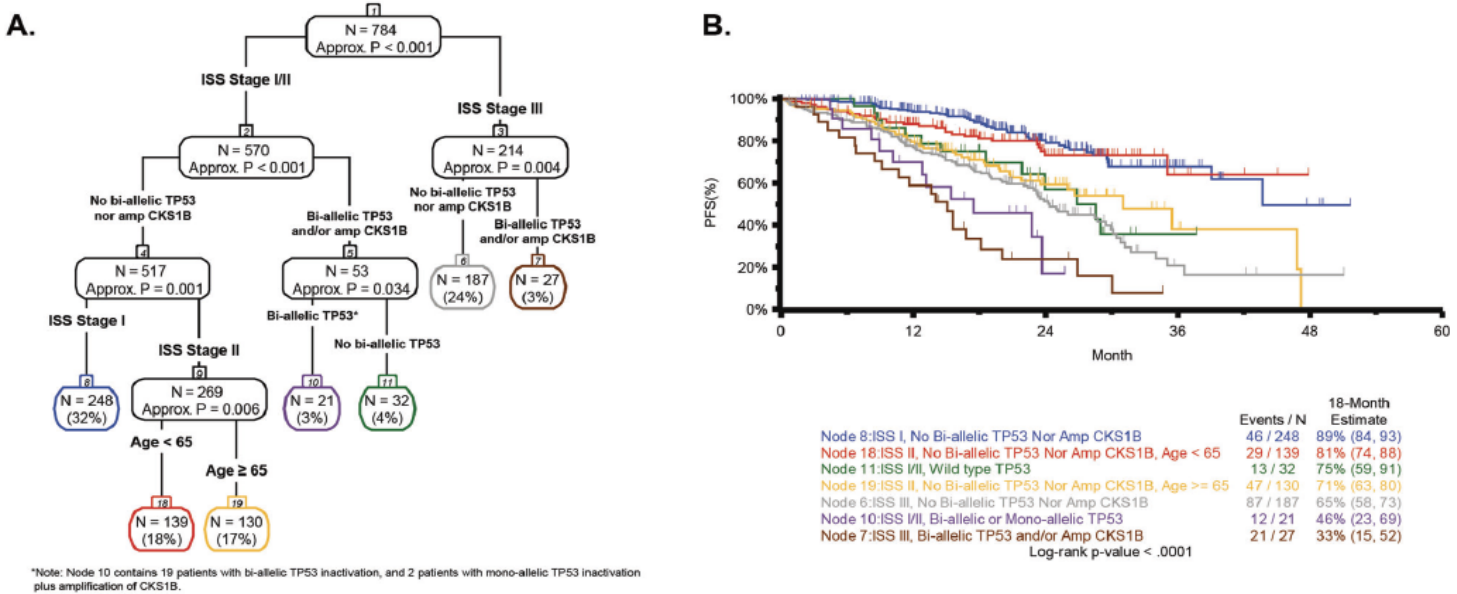
Trisomy 5	=	- 0.3
Trisomy 21	=	0.3
t(4;14)	=	0.4
1q gain	=	0,5
Del(1p32)	=	0.8
Del(17p)	=	1.2

Score ≤ 0 Good prognosis
Score >0 and ≤ 1 Intermediate prognosis
Score >1 Poor prognosis



Perrot A, et al. *J Clin Oncol.* 2019;37:1657-1665.

A High-Risk Double-Hit Group of NDMM Identified by Genomic Analysis



A high-risk subgroup was defined by recursive partitioning using either a) biallelic *TP53* inactivation or b) amplification (≥4 copies) of *CKS1B* (1q21) on the background of International Staging System III, composing 6.1% of the population (median PFS = 15.4 months; OS = 20.7 months)

PFS, progression-free survival; ISS, International Staging System; NDMM, newly diagnosed multiple myeloma; OS, overall survival.

Walker B, et al. *Leukemia*. 2019;33:159-170.

Mayo Clinic Risk Stratification for Multiple Myeloma: mSMART

- High Risk genetic Abnormalities [a,b]
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High Plasma Cell S-phase[c]
- GEP: High risk signature

- Double Hit Myeloma: Any 2 high risk genetic abnormalities
- Triple Hit Myeloma: 3 or more high risk genetic abnormalities

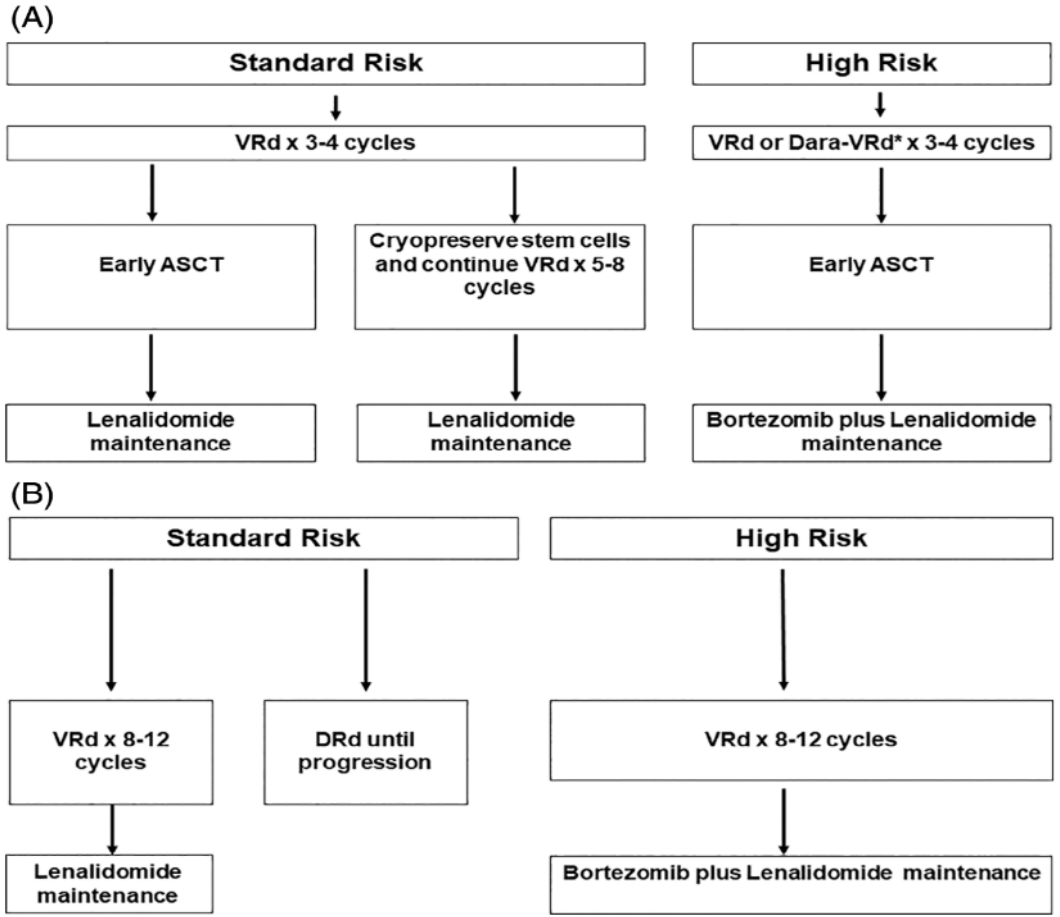
All others including:

- Trisomies
- t(11;14)[d]
- t(6;14)

[a] Trisomies may ameliorate
[b] By FISH or equivalent method
[c] Cut-offs vary
[d] t(11;14) may be associated with plasma cell leukemia

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. //last reviewed March 2022

Approach to the treatment of newly diagnosed multiple myeloma in transplant-eligible (A) and transplant-ineligible (B) patients



Dispenzieri A, et al. *Mayo Clin Proc*. 2007;82:323-341; Kumar SK, et al. *Mayo Clin Proc.* 2009 84:1095-1110; Mikhael JR, et al. *Mayo Clin Proc*. 2013;88:360-376.

Response to Therapy

MRD Is a Powerful Prognostic Factor

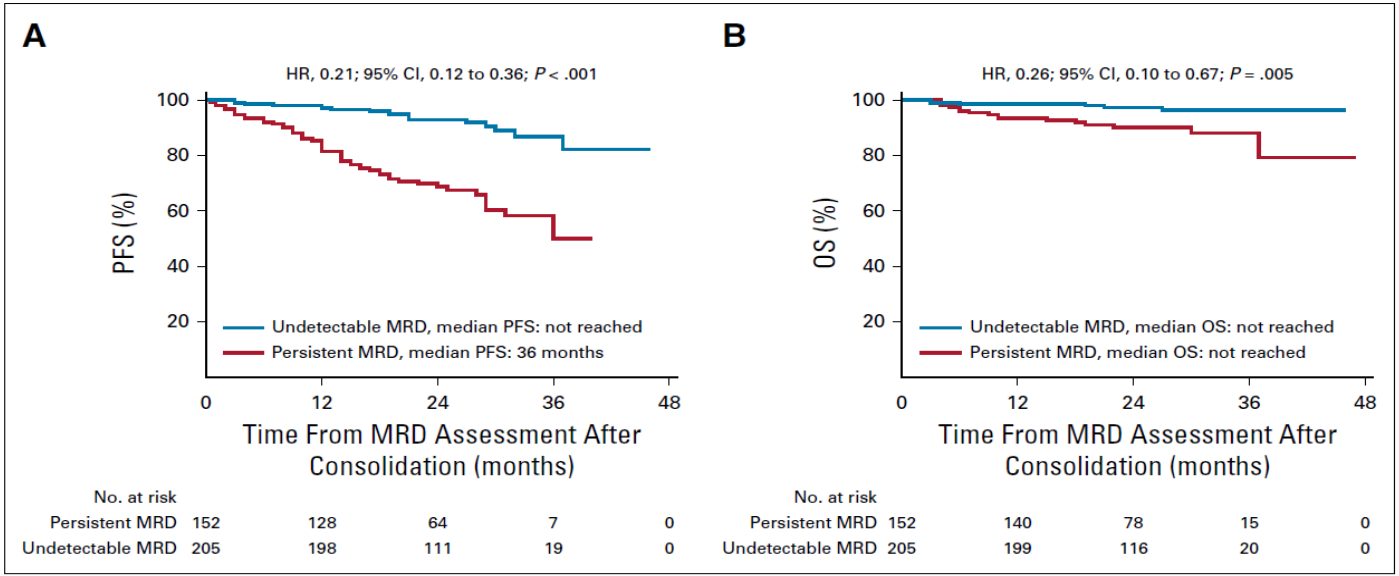


FIG 2. Survival according to undetectable *v* persistent measurable residual disease (MRD). The Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS) after MRD assessment after consolidation (n = 357). HR, hazard ratio.

Paiva B, et al. *J Clin Oncol*. 2020;38:784-792.

Conclusions

- ✓ Biomarkers and end-organ damage are important in making a distinction between MGUS, SMM, and multiple myeloma
- ✓ Imaging is very important for diagnostic assessment
- ✓ There is much progress in elucidating biomarkers that determine prognosis
- ✓ These advances will help to move toward precision medicine and individualized patient management

Thank you!
Gracias!
Obrigada!

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Discussion

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Smoldering Multiple Myeloma: Current and Future Developments

Sagar Lonial, MD, FACP

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

EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

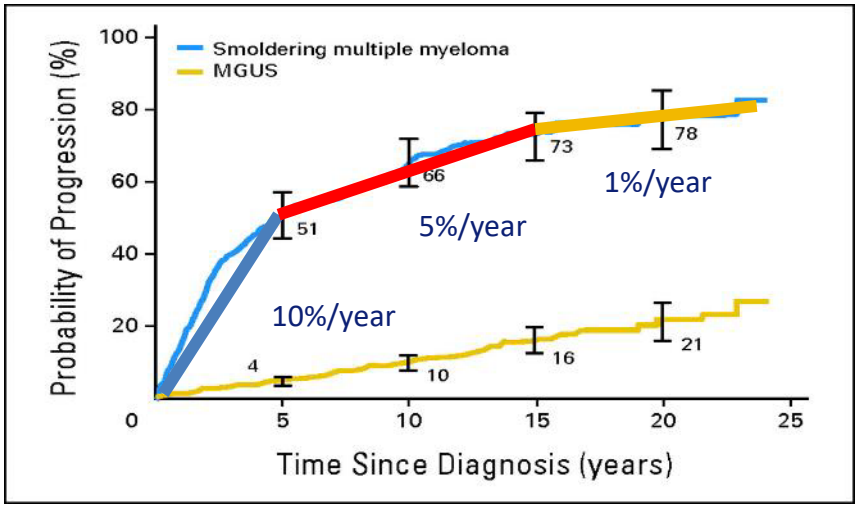
Considerations in SMM

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 for the Audience

Which of the following are NOT part of the Mayo 2018 20/2/20 criteria for risk stratification of SMM

a) >20% plasma cells in the marrow
b) M spike >2gm
c) High risk genetics or FISH
d) Free light chain ratio >20

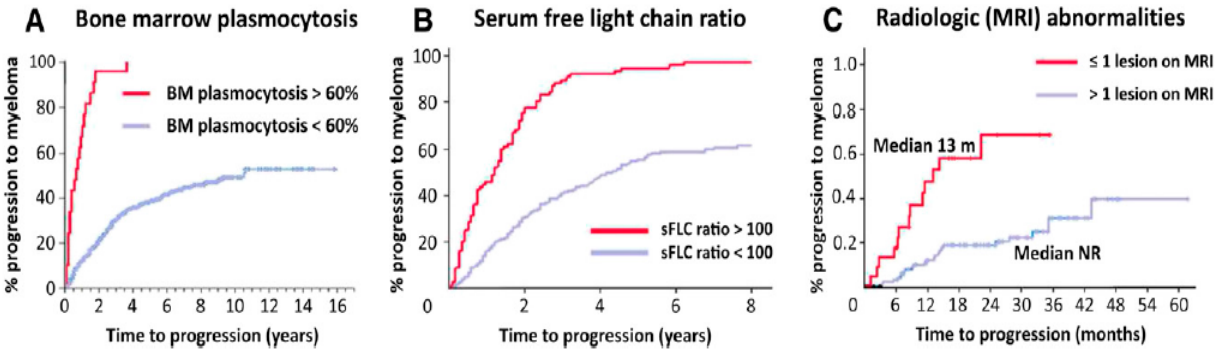


MGUS

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

SMM

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

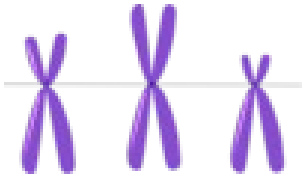


Myeloma-defining events

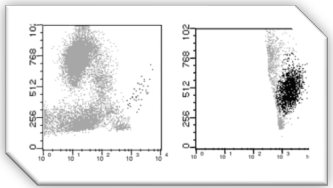
Bladé J, et al. *J Clin Oncol* 2010;28:690-697; Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

Risk Factors for Progression in SMM

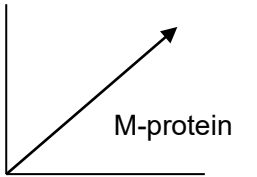
Tumor burden
BMPCs ≥10%
M-protein ≥3 g/L
FLC ratio <0.125 or >8
BJ proteinuria
PB CTC >5 × 10E6/l



PC characteristics
t(4;14)
del 17p
gain 1q
Hyperdiploidy
Genetics



Immunophenotypic characteristics:
≥95% aberrant PC
Immunoparesis

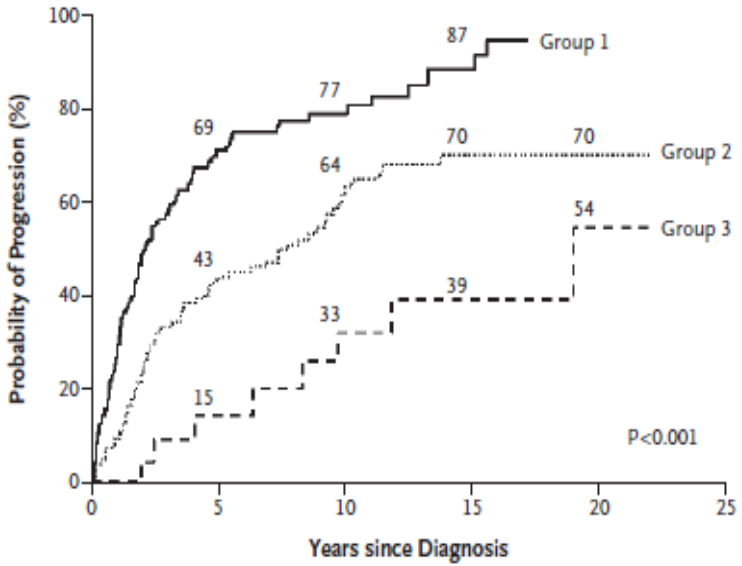


Tumor dynamics:
evolving M-protein

Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590; Kyle RA, et al. *Leukemia.* 2010;24:1121-1127; Gonzáles-Calle V, et al. *Leukemia.* 2016;30:2026-2031; Dispenzieri A, et al. *Blood.* 2008;111:785-789; Pérez-Persona E, et al. *Blood.* 2007;110:2586-2592.

Mayo Risk Model

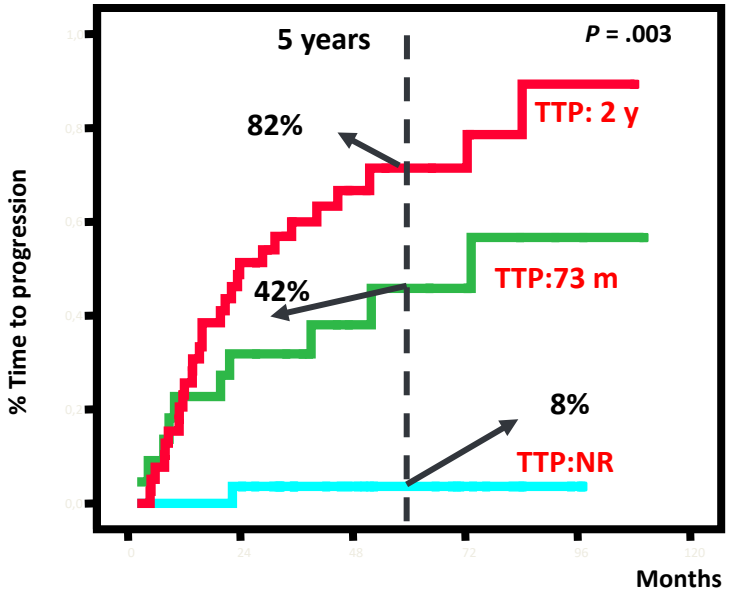
PCs BM infiltration and
Serum M-component level



Group 1: PCBM ≥10% + MC ≥3 g/dL
Group 2: PCBM ≥10% + MC <3 g/dL
Group 3: PCBM <10% + MC ≥3 g/dL

PETHEMA Risk Model

Aberrant PCs by immunophenotype plus immunoparesis



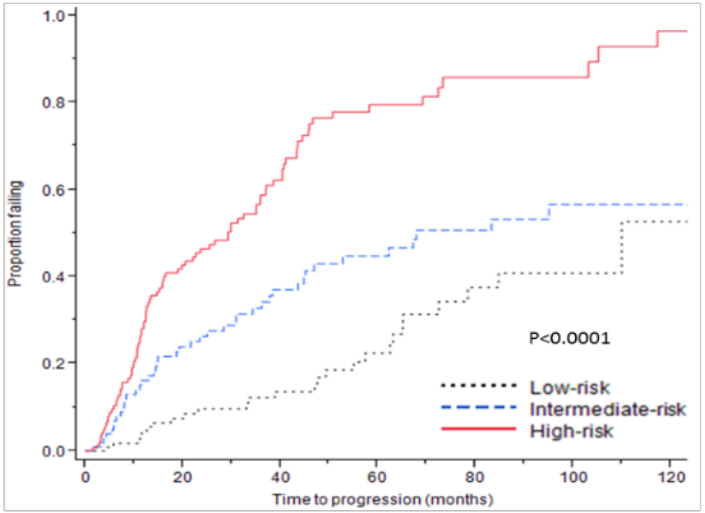
Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590.

Risk Scores

Risk score	factors	Low risk (Med TTP mo)	Intermediate (med TTP mo)	High (med TTP mo)
Pethema (1,2)	1) presence of an aberrant PC immunophenotype in >95% of clonal PCs and 2) immunoparesis (reduction in ≥1 uninvolved immunoglobulins by >25% compared to normal).	NR	73	24
MAYO (3,4)	(1) BMPCs ≥ 10%; (2) M-protein ≥30 g/L; and (3) FLC ratio <0.125 or >8	152	96	24
MAYO 20/2/20 (4)	BMPC ≥ 20% Mprot ≥ 20 g/l FLC ratio > 20	109.8	67.8	29.2
SWOG (5)	Serum M spike ≥30 g/L Involved FLC > 250 mg/L GEP risk score >-0.26	2 yrs PFS 3%	2 yrs PFS 29.1%	2 yrs PFS 70.6%
Deense risicoclass (7)	M-protein ≥30 g/L Immunoparesis	2 yrs PFS 5%	2 yrs PFS 21%	2 yrs PFS 50%
Barcelona Group (8)	Evolving Mproteine	13 months (71% at 36 months)		
Pennsylvania risk score (9)	BMPC% >40 sFLC ratio ≥18 Albumin ≤ 35 g/l	2 yrs PFS 16%	2 yrs PFS 44%	2 yrs PFS 81%

1. Pérez-Persona E, et al. *Blood.* 2007;110:2586-2592; 2. Pérez-Persona E, et al. *Br J Haematol.* 20010;148:110-114; 3. Kyle RA, et al. *N Engl J Med*. 2007;356:2582-2590; 4. Dispenzieri A, et al. *Blood.* 2008;111:785-789; 5. Lakshman A, et al. *Blood Cancer J*. 2018;8:59; 6. Dhodapkar MV, et al. *Blood*. 2014;123:78-85; 7. Sorrig R, et al. *Eur J Haematol.* 2016;97:303-309; 8. Fernandez de Larrea C, et al. *Leukemia.* 2008;22:1651-1657; 9. Waxman AJ, et al. *Leukemia*. 2015;29:751-753.

20-2-20 Risk Model



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)

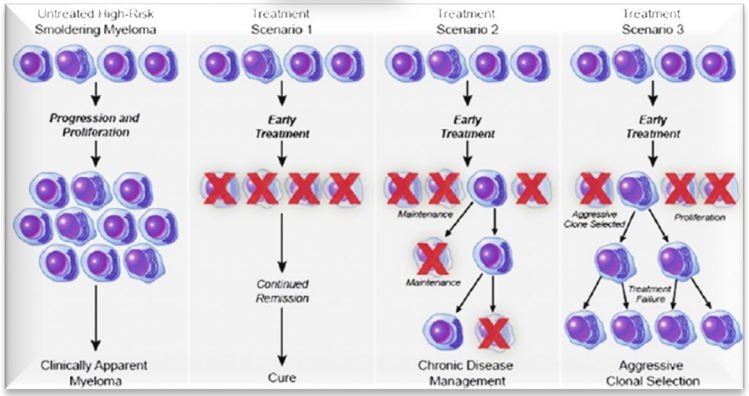
BMPC% bone marrow-plasma cell percentage, *CI* 95% confidence intervals, *FLCr* involved to uninvolved free light chain ratio, *OR* odds ratio

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

SMM: To Treat or Not?

- Delaying symptomatic progression
- Maintain/increase quality of life by treating early
- Possibility of cure?

- Selection of resistant clone?
- Toxicity
- Cost of treatment
- Overtreatment



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

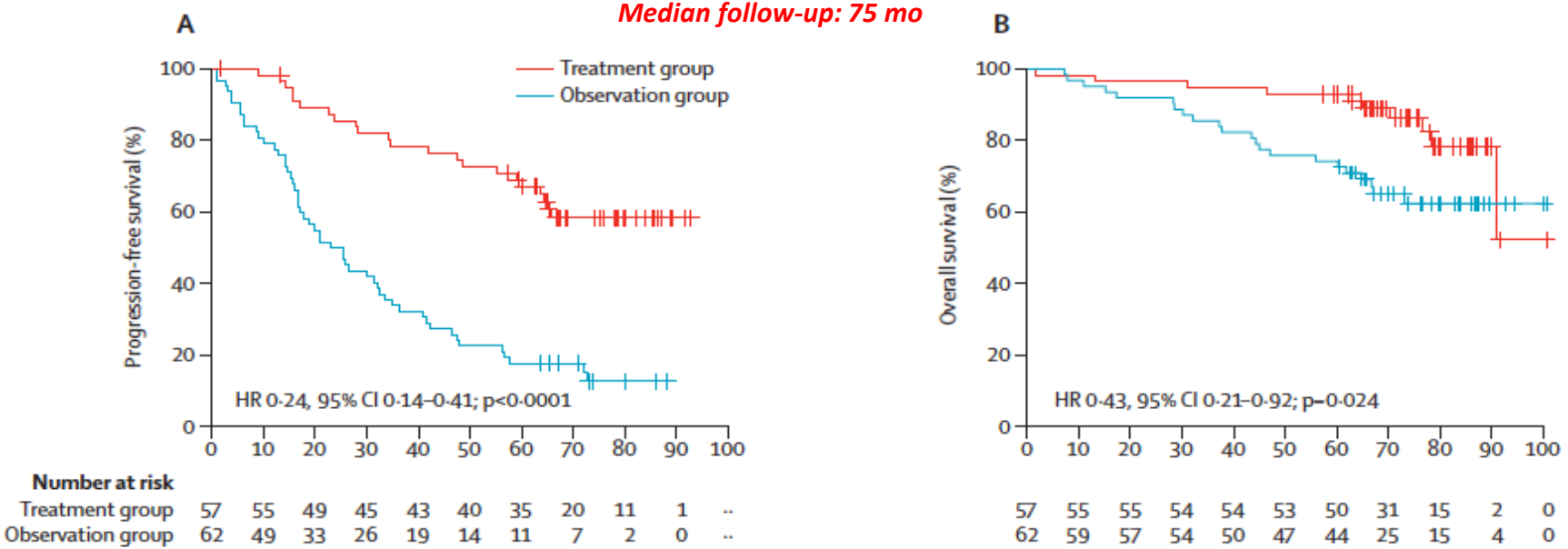
Pros
- High ORR
- Deep responses

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

Treatment Aimed at Delaying Progression

QuiRedex Phase III Trial: Len + Dex vs No Treatment in High-Risk SMM (n = 119)

Median follow-up: 75 mo

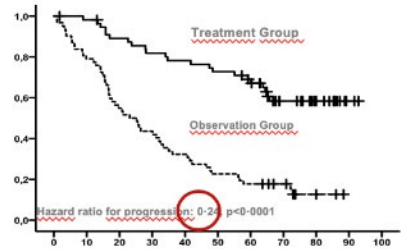


Early treatment with Rd significantly delayed the TTP to myeloma with a benefit in OS

Mateos MV, et al. *N Engl J Med*. 2013;369:438-447; Mateos MV, et al. *Lancet Oncol*. 2016;17:1127-1136.

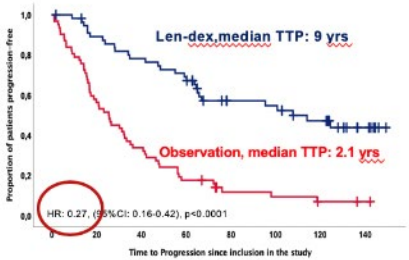
Update for Original SMM Trial From Spanish Group

Median f/u: 6.2 year



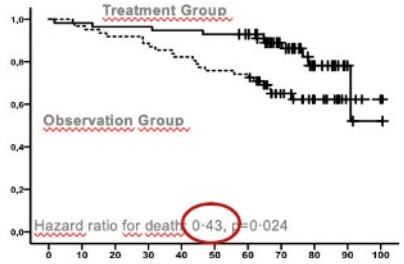
Mateos MV, et al. Lancet Oncology 2016

Median f/u: 10.8 years



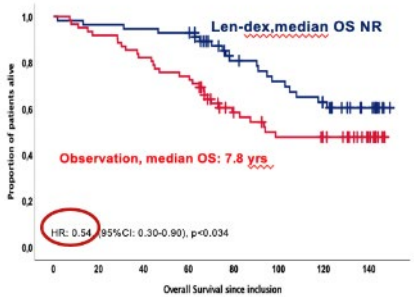
TTP

Median f/u: 6.2 year



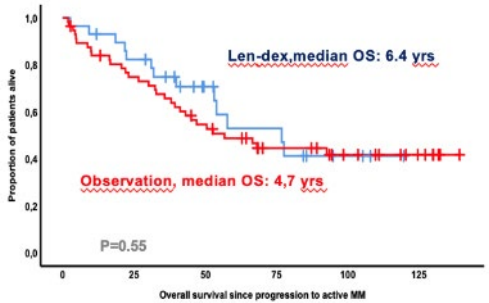
Mateos MV, et al. Lancet Oncology 2016

Median f/u: 10.8 years



OS

Median f/u: 10.8years



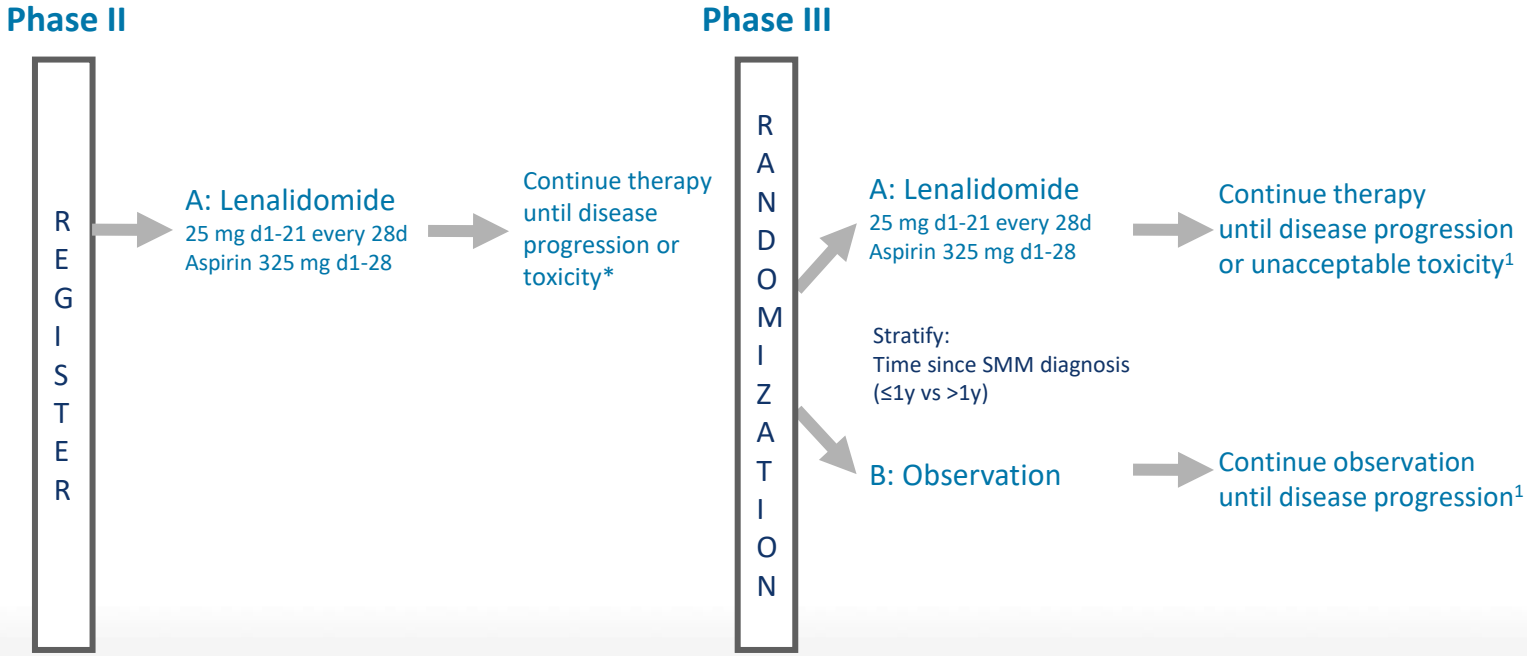
OS post-progression shows no induced resistance

Mateos MV, et al. EHA 2020. Abstract EP950.

Schema

E3A06: **Phase II/III Study**

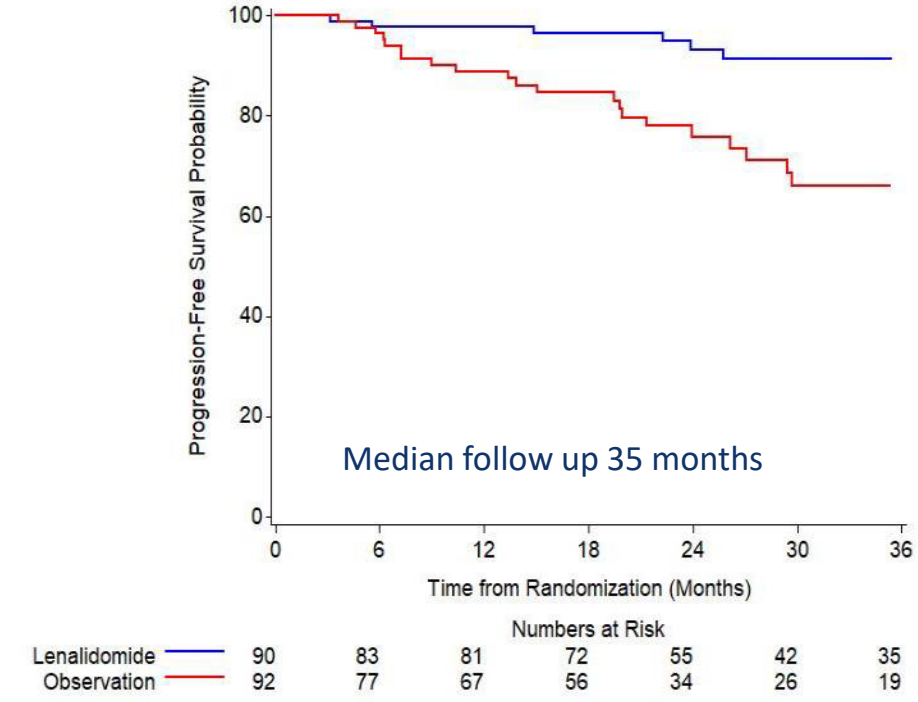
A: Lenalidomide vs B: Observation



*Mobilize stem cells following 4–6 cycles of therapy. While stem cell collection is strongly suggested, it is not required.

Lonial S, et al. *J Clin Oncol*. 2019;38:1126-1137.

Phase III PFS ITT*



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

One-sided stratified log-rank test *P* = .0005

Phase III 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 second 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.**

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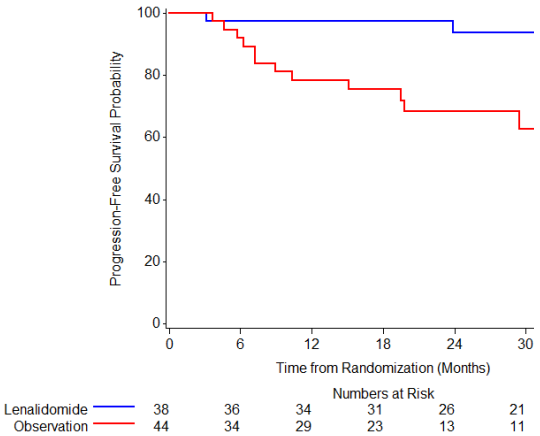
ECOG-ACRIN cancer research group

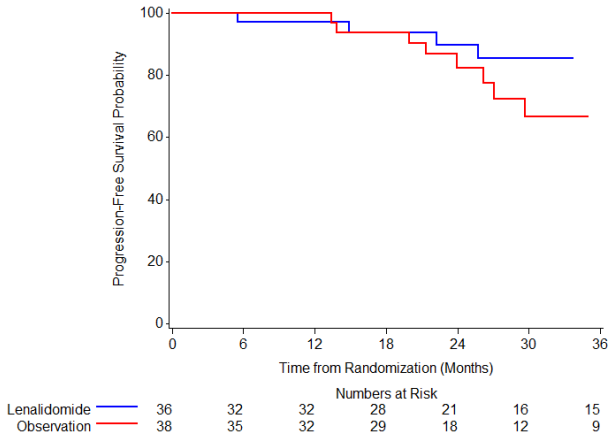
Reshaping the future of patient care

Lonial S, et al. *J Clin Oncol*. 2019;38:1126-1137.

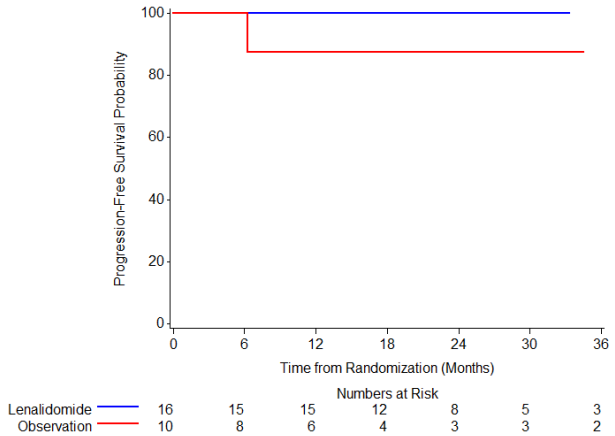
Phase III PFS by Mayo 2018 Risk Criteria



High Risk



Intermediate Risk



Low Risk

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Lonial S, et al. *J Clin Oncol*. 2019;38:1126-1137.

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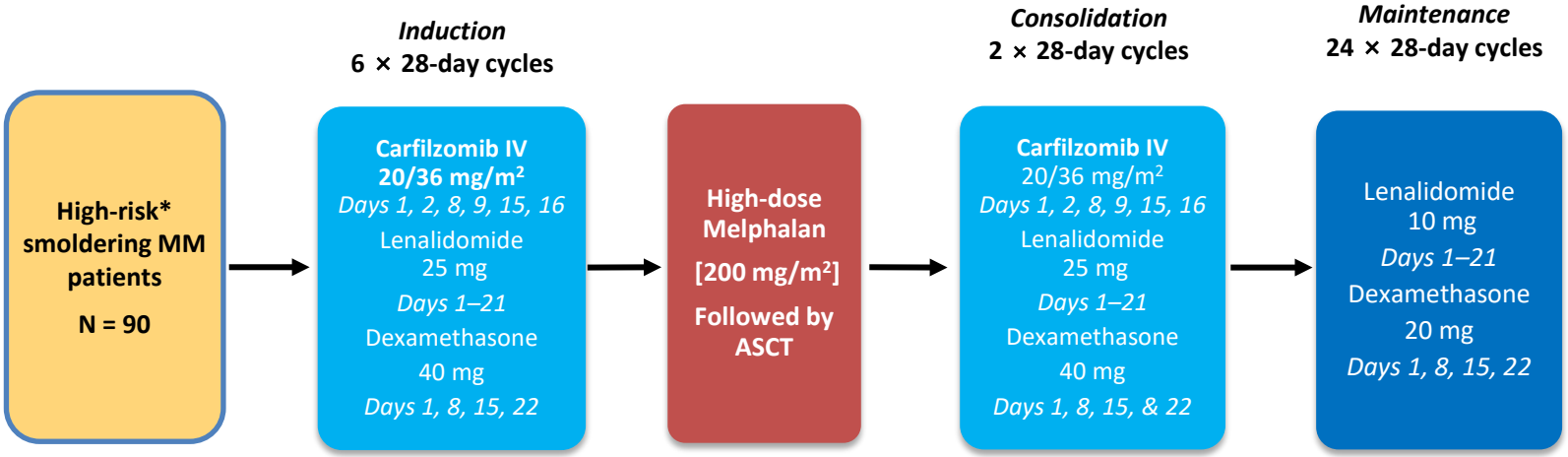
Treatment Aimed at Cure

GEM-CESAR Trial for High-Risk SMM

- Multicenter, open-label, phase II trial



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

- Patients with any 1 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

Courtesy of Prof M.V. Mateos.

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 negative	**27 (30%)**	**47 (56%)**	**51 (63%)**	**36 (67%)**	**15 (56%)**

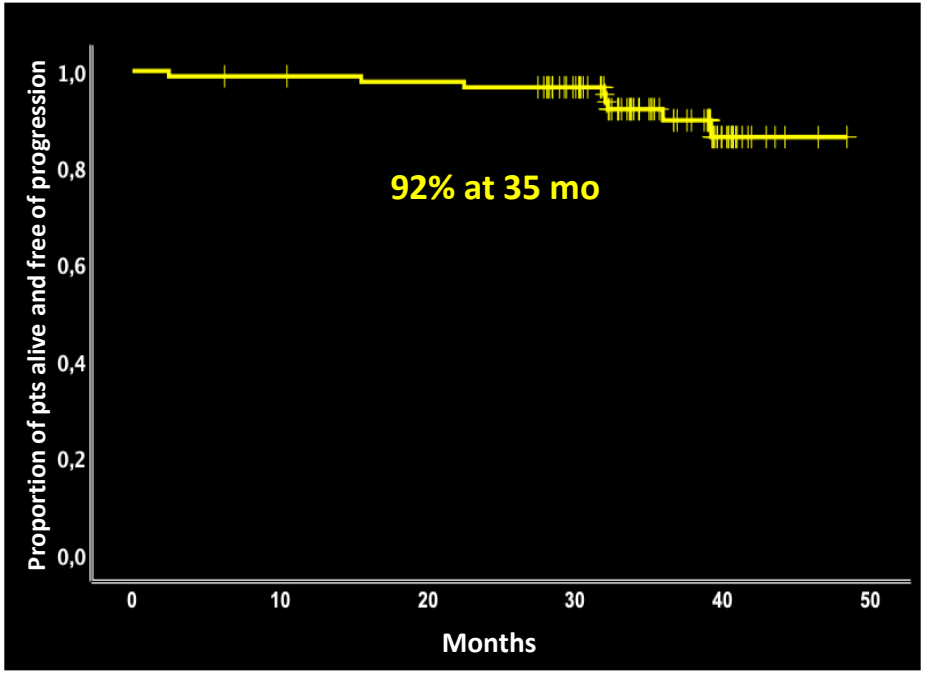
***Progressive disease was biologic in 1 patient and clinical in 1 patient.**

Courtesy of Prof M.V. Mateos.

GEM-CESAR – Outcomes

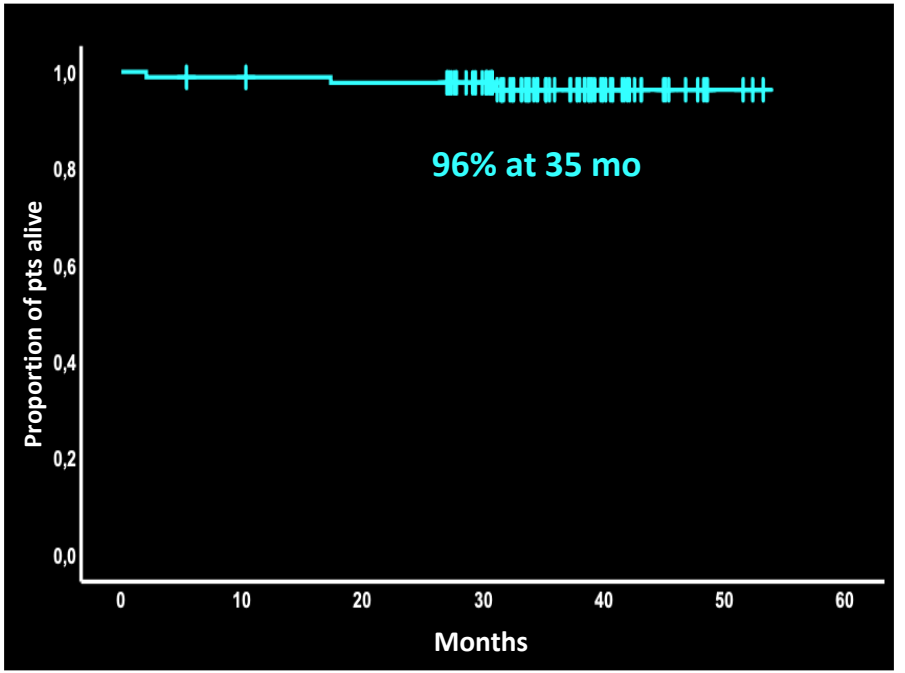
Median follow-up: 35,2 (5.4–53.2)

PFS



6 patients had disease progression, 5 patients' PD was biologic, and 4 patients were at ultra-high risk

OS



3 patients died; only 1 was a treatment-related death

Mateos MV, et al. ASH 2019. Abstract 781.

ASCENT: KRd-D

Primary endpoint: Rate of confirmed sCR

Secondary objectives: Safety, PFS, OS, MRD negativity

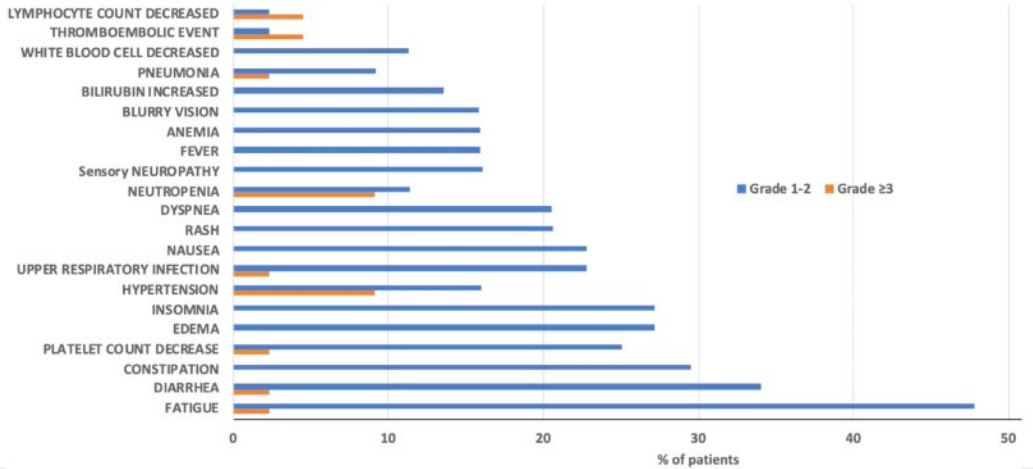
Study design

INDUCTION
(4-week cycles for 6 cycles)
- Carfilzomib (36 mg/m² twice weekly or 56mg/m² 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/m² twice weekly or 56mg/m² 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 wee
- Daratumumab (q 8 weeks)

Toxicity profile



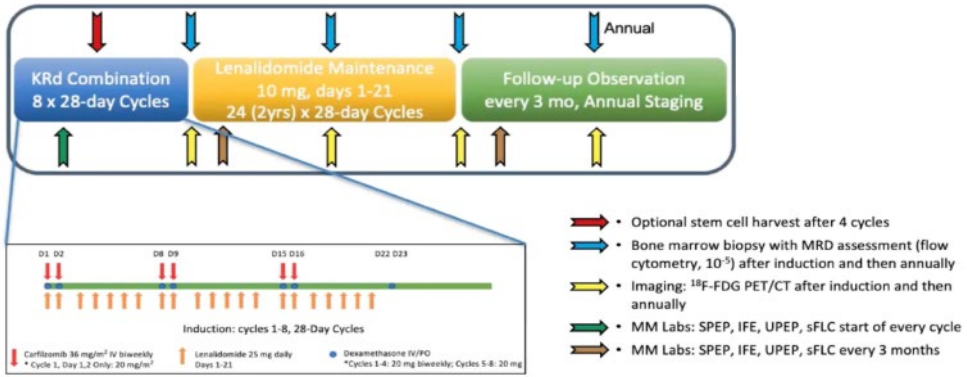
Results to date

- 54 patients accrued
- Median patient age = 63 years
- 6% have completed maintenance, 56% consolidation, 80% induction, and 17% in induction phase
- ≥1 patient needed a dose modification
- Grade ≥3 AE seen in 43% of patients

Quadruplet regimen KRd-D is well tolerated in high-risk SMM

AE, adverse event; CR, complete response; KRd-D, carfilzomib, lenalidomide, dexamethasone, daratumumab; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response.

Kumar SK, et al. ASH 2020: Abstract 2285.



- Primary objective: Determine MRD-negative CR rate
- Key secondary objectives: PFS (clinical and biochemical), ORR, DOR, duration of MRD negativity (MFC, sensitivity 10^{-5}), and safety

- Median patient age = 59 years
- 37% had disease with high-risk cytogenetic features

Benefit vs risk of KRd-R in SMM is favorable, but future trials needed to confirm results

Progression to symptomatic MM and survival

Progression-Free Survival N=54	Progression to MM (clinical PFS)	Biochemical Progression (biochemical PFS)	Overall Survival
Events, n	2	4	0
Median, months	Not Reached	Not Reached	Not Reached
8-year Milestone (95% CI)	91.0% (67.1–97.8%)	80.2% (54.1–92.4%)	100%

Sustained MRD negativity

MRD Negativity (flow 10^{-5})	N=50 (95% CI)
MRDneg CR Rate, n	35 (70.2%: 55.4–82.1%)
MRDneg CR Duration	
Median, months	66.8 mo (39.5–not estimable)
2-year Sustained	79.8% (57.7–91.2%)
5-year Sustained	53.2% (27.7–73.3%)
7-year Sustained	39.9% (17.1–62.0%)
MRDneg ≥VGPR Rate, n	38 (76.0%: 61.8–86.9%)
MRDneg ≥VGPR Duration	
Median, months	66.8 mo (39.5–not estimable)
2-year Sustained	77.5% (56.0–89.4%)
5-year Sustained	51.6% (27.0–71.6%)
7-year Sustained	39.9% (16.7–62.5%)

CR, complete response; DOR, duration od response; IFE, immunofixation electrophoresis; IV, intravenous; MM, multiple myeloma; KRd, carfilzomib, lenalidomide, dexamethasone; MFC, multiparameter flow cytometry; MRD, minimal residual disease; nCR, near complete response; ORR, overall response rate; PFS, progression-free survival; -R, lenalidomide maintenance sCR, stringent complete response; sFLC, serum free light chain; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; VGPR, very good partial response.

Kazandjian D, et al. ASH 2020. Abstract 548.

Randomized Trials Comparing 2 Treatment Options

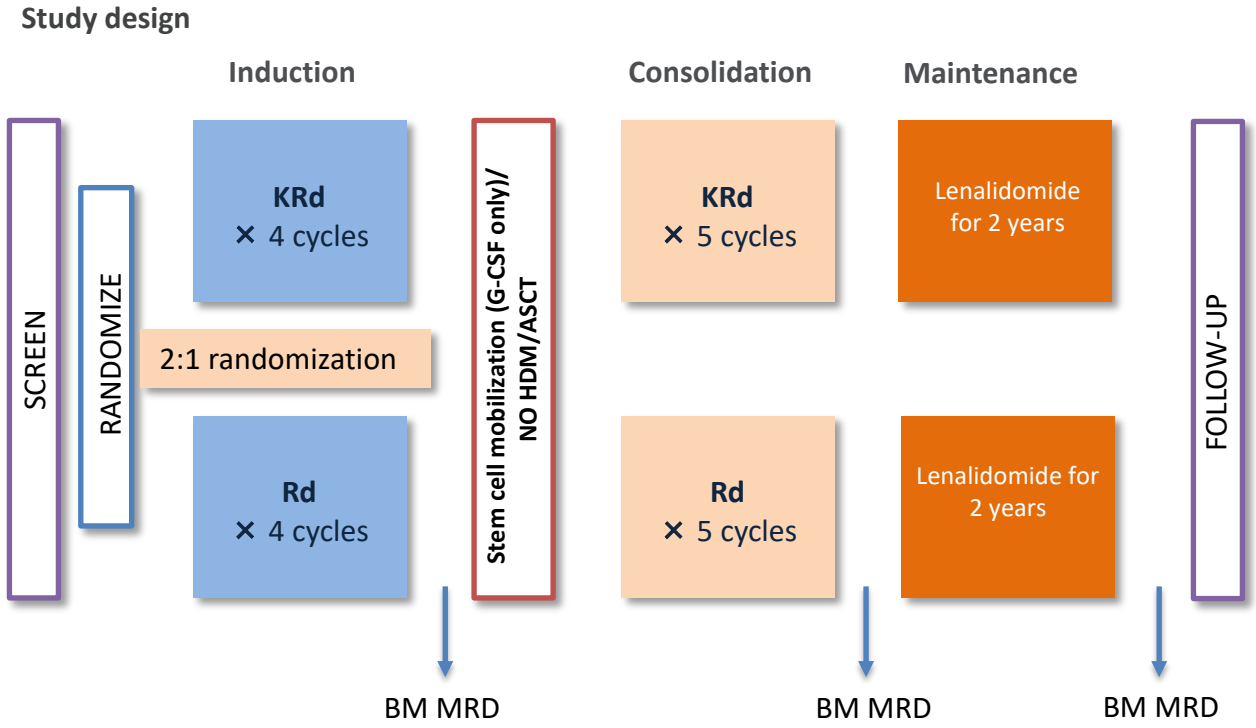
Randomized Phase II Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone vs Lenalidomide and Dexamethasone in High-Risk Smoldering Multiple Myeloma: HOVON147/EMN15

Carfilzomib <u>once weekly:</u>
56 mg/m^2 days 1, 8, 15
(first cycle day 1: 20 mg/m^2)

Primary endpoint: PFS
Secondary objectives: MRD negativity (NGF, NGS), ORR, Safety, PFS2, OS

N = 120
High-risk SMM based on Mayo or PETHEMA criteria

Participating centers/countries
- *Netherlands;* A. Broijl
- *USA;* N. Korde
- *Norway;* F. Schjesvold
- *Czech Republic;* R. Hajek
- *Italy;* M. Bocadoro



Lenalidomide as Backbone for the Treatment of Intermediate- to High-Risk SMM Patients

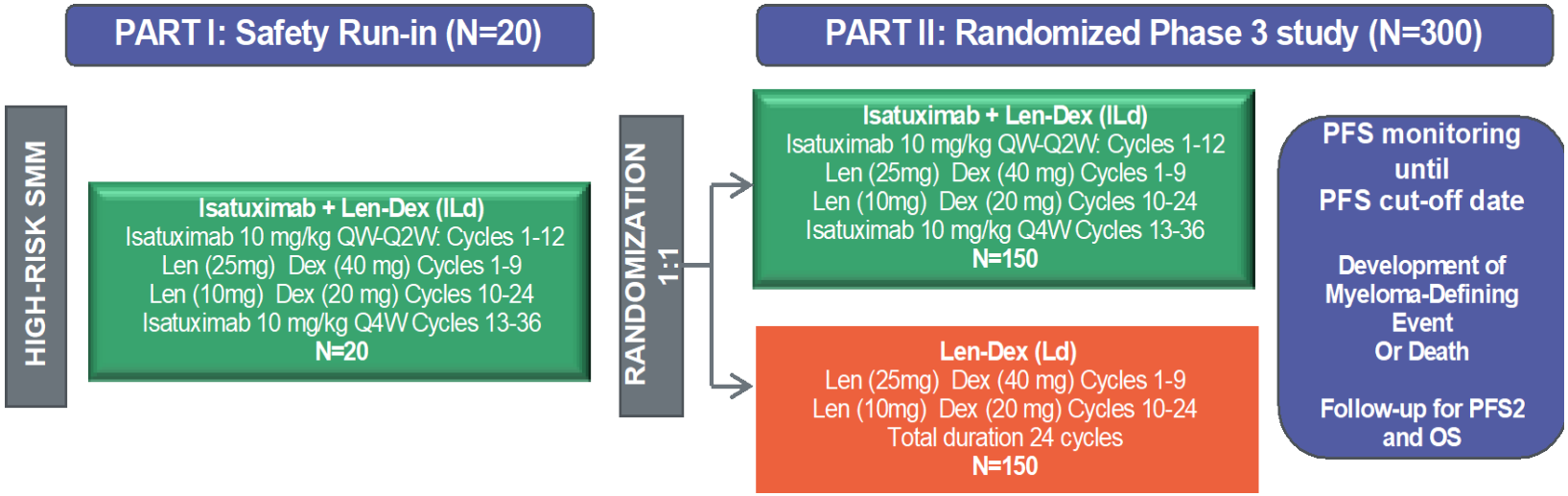
Elo-Rd/Ixa-Rd/KRd

	Phase	n	ORR/CR/MRD negative	PFS/OS
Elo-Rd	II	50	84%/6%/NE	100%/1 death
Ixa-Rd	II	26	89%/19%/12%	100%/-
KRd	II	12	100%/100%	-
Isatuximab monotherapy	II	24	63%/-/5% (CR pts)	At 14 mo: 90%
Dara monotherapy intense/interim/short	II	41/41/41	CR: 4.9%/9.8%/0%	At 24 mo: 90%/82%/75%

"Exciting results" even better than Rd alone but . . . these are not randomized trials.
We need to measure the efficacy of the combinations with more modern approaches beyond response rates and CR rates.

Ghobrial I, et al. ASH 2018. Abstract 154; Ghobrial I, et al. ASH 2018. Abstract 804; Landgren O, et al. *JAMA*. 2018.

Rd ± Isatuximab in HR-SMM Patients: Phase III ITHACA Study



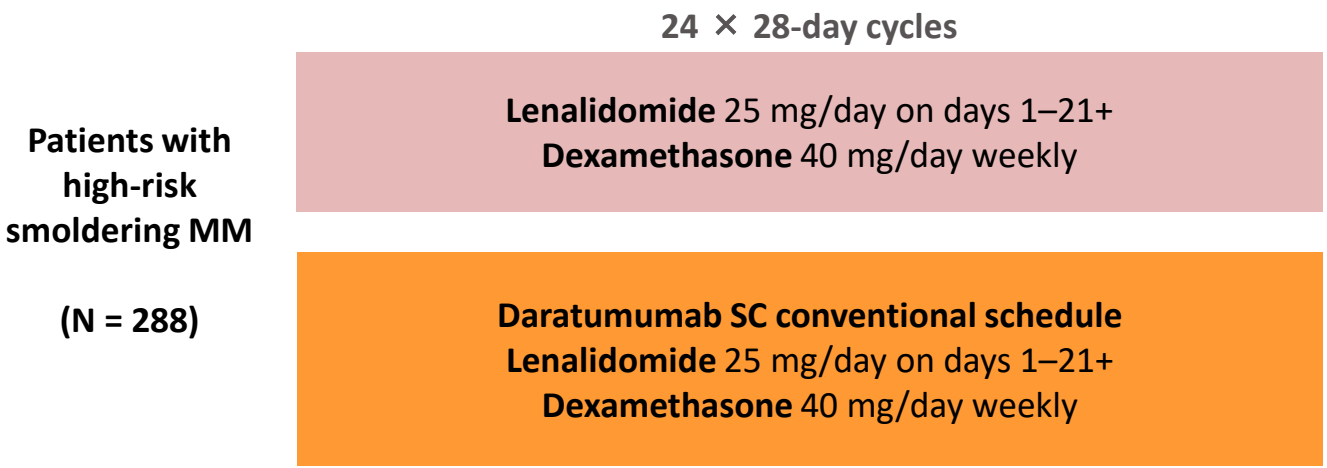
Stratification on

- **Age (≤65 vs >65)**
- **BMPC (<20% vs ≥20%)**
- **Serum involved/uninvolved FLC ratio (≤20 vs >20 but ≤100)**

Inclusion criteria

- **IMWG model 2/20/20**
- **Presence of ≥10% BMPC and at least 1 of the following: serum M-protein ≥3 g/dL, i/uFLC ratio ≥8, ≥95% of BMPCs phenotypically aberrant plus immunoparesis, evolving pattern**

Rd ± Daratumumab in HR-SMM Patients: Phase III Trial (ECOG)



Primary endpoints

- **Overall survival**
- **Functional Assessment of Cancer Therapy-General score**

Inclusion criteria

- **Presence of ≥10% and <60% BMPC and at least 1 of the following: serum M-protein ≥3g/dL, i/uFLC ratio ≥8, or high-risk CA**

Ongoing Clinical Trial

Clinical trial and design	Therapy	Comments and preliminary results
NCT01169337 (ECOG E3A06), randomized [54]	Lenalidomide vs observation	Last report at ASH 2013. Primary outcome data in 2026
NCT02279394, Phase 2 [56]	Elotuzumab + Rd	ORR: 84%. Clinical benefit: 100%
NCT01484275, randomized, double-blinded Phase 2 [51]	Siltuximab vs placebo	1-yr PFS: 84% vs 74%
NCT02316106, Centaurus trial, Phase 2; three different dose schedules [58]	Daratumumab iv	123 patients. 2-yr PFS 90% in 'long' arm
NCT03301220, Aquila trial, randomized*	Daratumumab sc for 3 yrs vs active monitoring phase	360 patients. No results yet. Estimated primary completion date: December 2021
NCT02916771, Phase 2 [59]	Ixazomib + Rd for 2 yrs (dexamethasone for only 9 months)	28 patients. ≥PR: 85.5%. Estimated primary completion date: April 2020
NCT02960555, Phase 2*	Isatuximab for 2.5 yrs	61 patients. Estimated primary completion date: February 2022
NCT03289299, ASCENT trial, Phase 2 [60]	KRd+daratumumab x 6 cycles (induction) KRd+daratumumab x 6 cycles (consolidation) Rd x 12 cycles (maintenance)	83 patients Estimated primary completion date: June 2022
NCT02415413, CESAR trial, Phase 2 [61]	KRd x 6 cycles (induction) ASCT + KRd x 2 cycles (consolidation) Rd x 24 cycles	90 patients. Estimated primary completion date: finished. ORR: 100%. ≥CR: 63% MRD-ve rate: 55%

Hernandez JA, et al. *Expert Rev Hematol*. 2019;12:345-354.

Future Directions

- Both prevention and treatment approaches have value, but no head-to-head data
- Understand what really differentiates SMM that needs MM therapy from SMM that needs prevention
- Identify which patients at the MGUS stage could benefit from early intervention to reverse pathogenesis

Question for the Audience

Which of the following are NOT part of the Mayo 2018 20/2/20 criteria for risk stratification of SMM

a) >20% plasma cells in the marrow
b) M spike >2gm
c) High risk genetics or FISH
d) Free light chain ratio >20

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Patients and Families

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and the Clinical Research Team

IMS

Golfers Against Cancer
T.J. Martell Foundation

and many others who are part of the B-Cell Team

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

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Newly Diagnosed Transplant-Eligible Multiple Myeloma: Frontline Therapy and the Role of Transplantation

Luciano Costa, MD, PhD

APTITUDE HEALTH®

Newly Diagnosed Transplant-Eligible Multiple Myeloma

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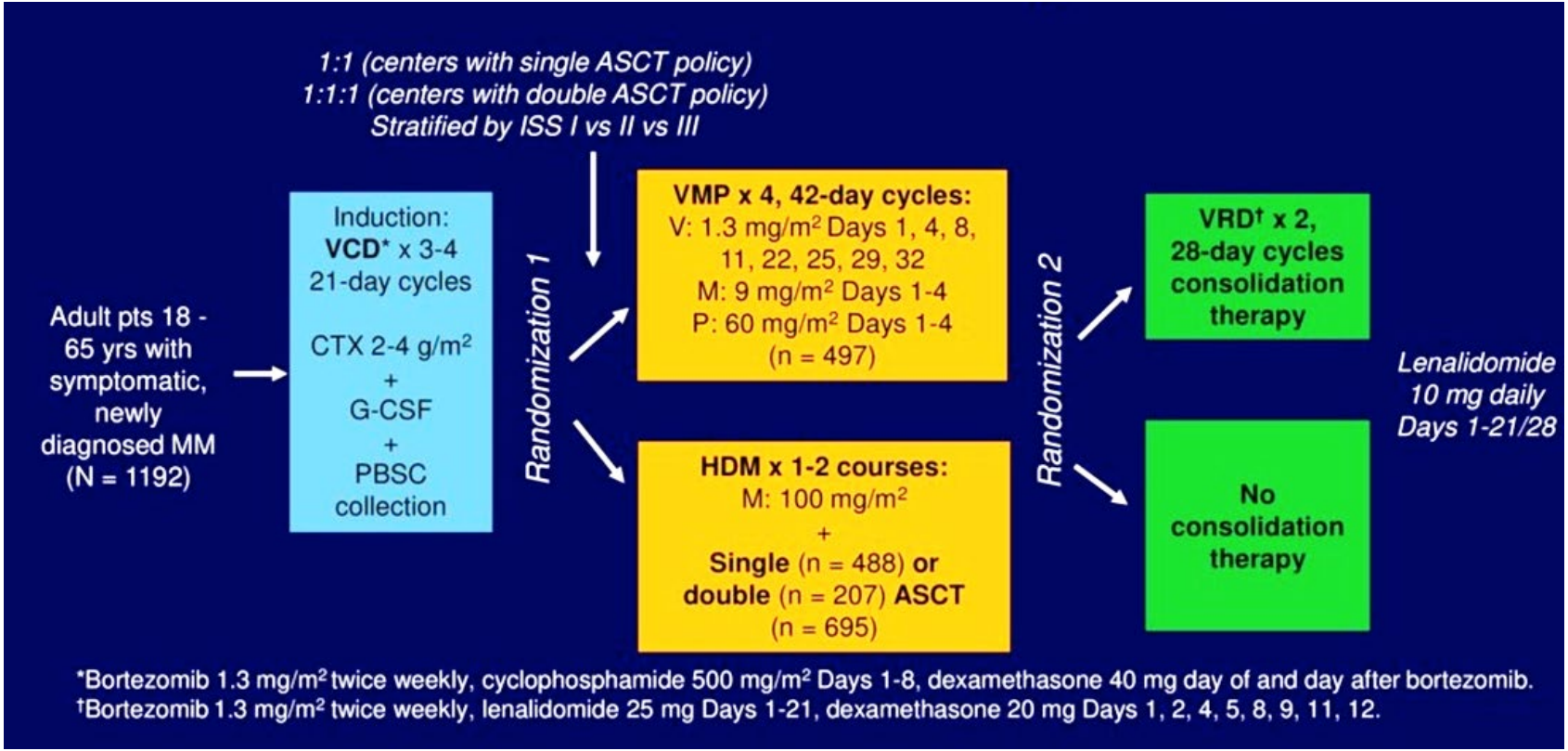
Question for the Audience

What statement best describe your approach to AHCT for Myeloma in 2022?

a) Appropriate for most patients younger than 75 as part of the upfront treatment
b) Appropriate for patients younger than 65 with high-risk disease as part of the upfront treatment
c) Best used as a salvage strategy for patients who develop disease progression
d) AHCT has no role in modern treatment of MM since same results can be obtained with therapies containing PI + IMiD

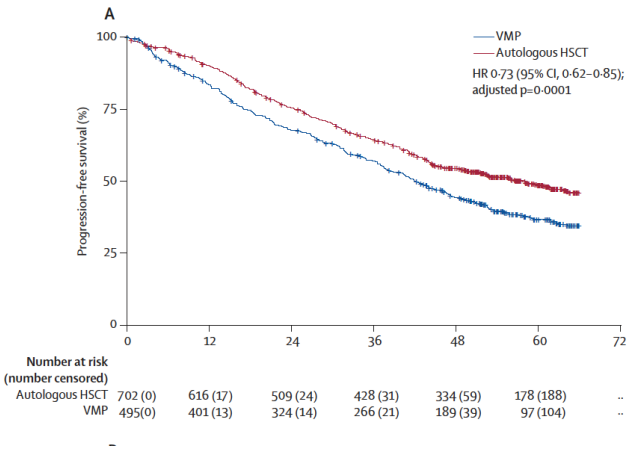
Transplant in the Era of Triplets

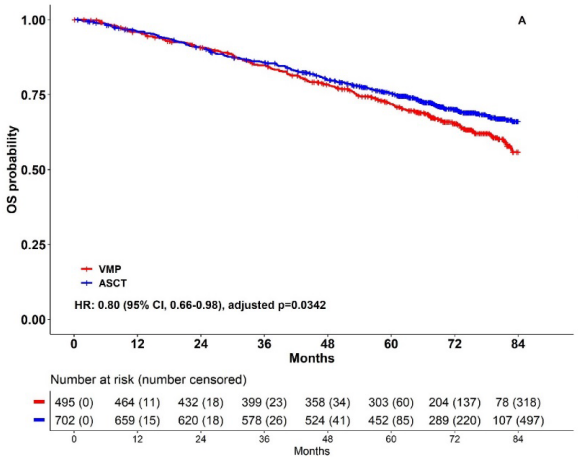
EMN02/HO95 Study Update

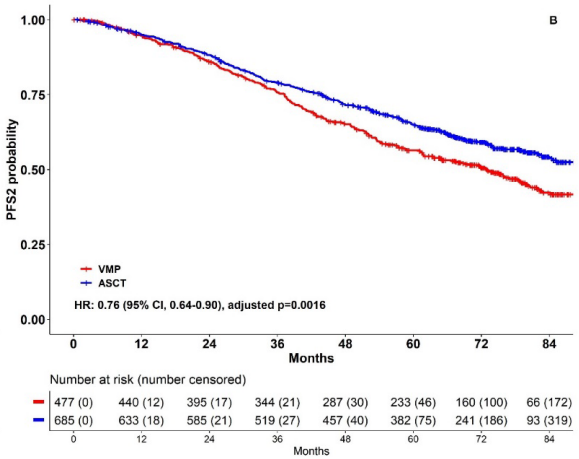


Cavo M, et al. *Lancet Haematol*. 2020;7:e456-e468.

Best Use of AHCT Is Upfront: EMN02/HO95 Study Update



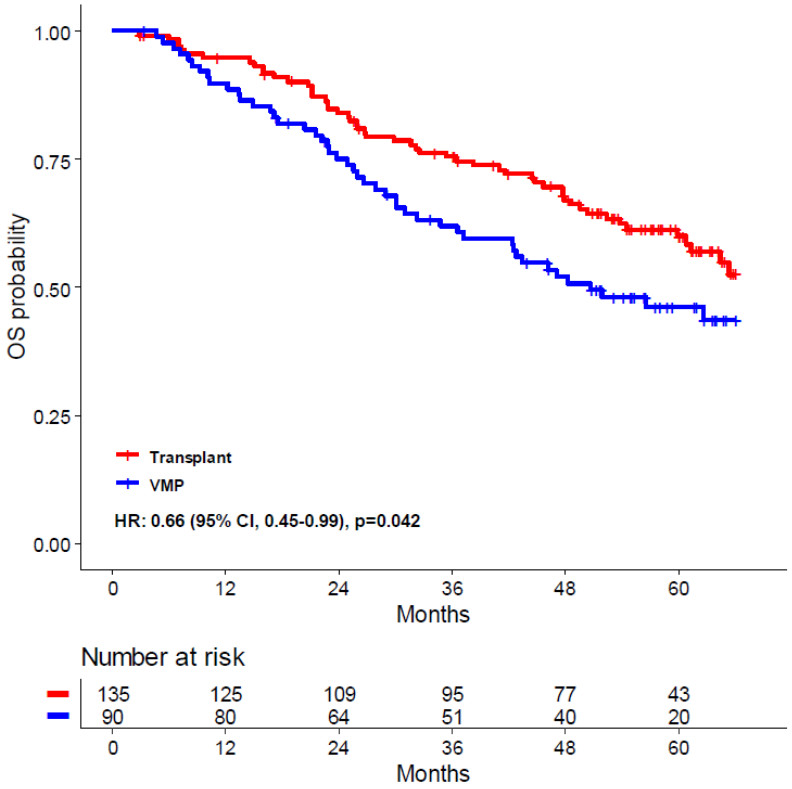


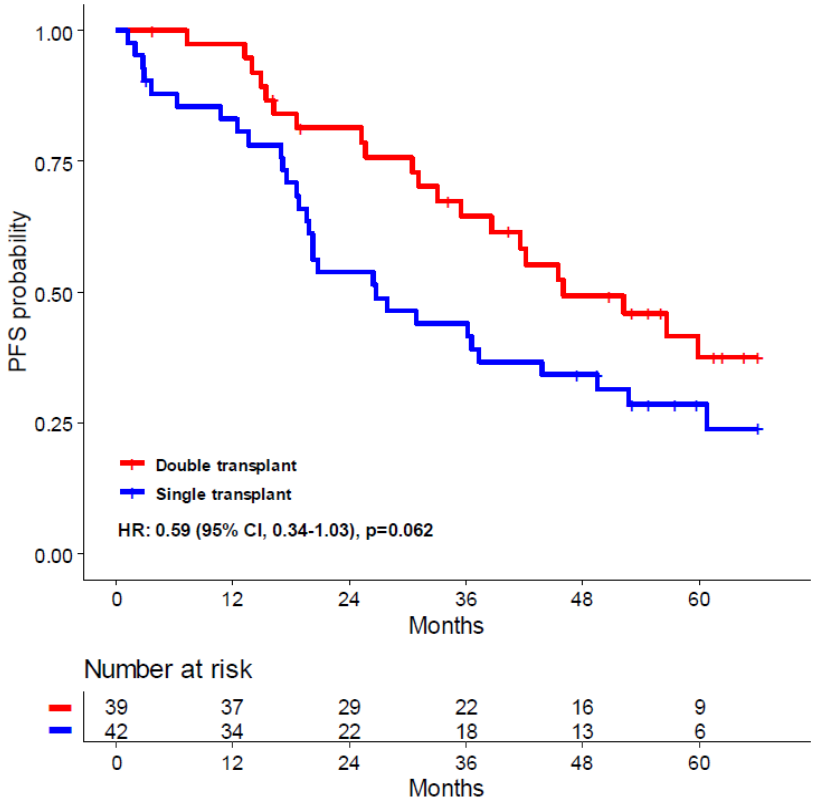


- Median FU of 75 months
- Better PFS, OS, and better PFS2 within early AHCT

Cavo M, et al. *Lancet Haematol*. 2020;7:e456-e468.

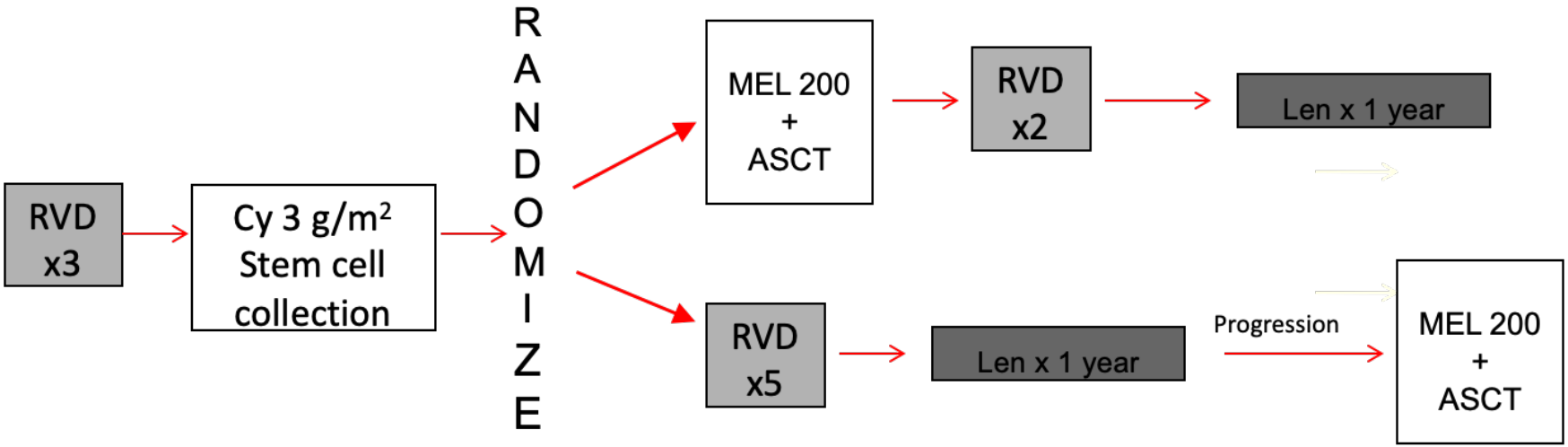
AHCT in Cytogenetic High-Risk MM: 1 Is Good, 2 May Be Better





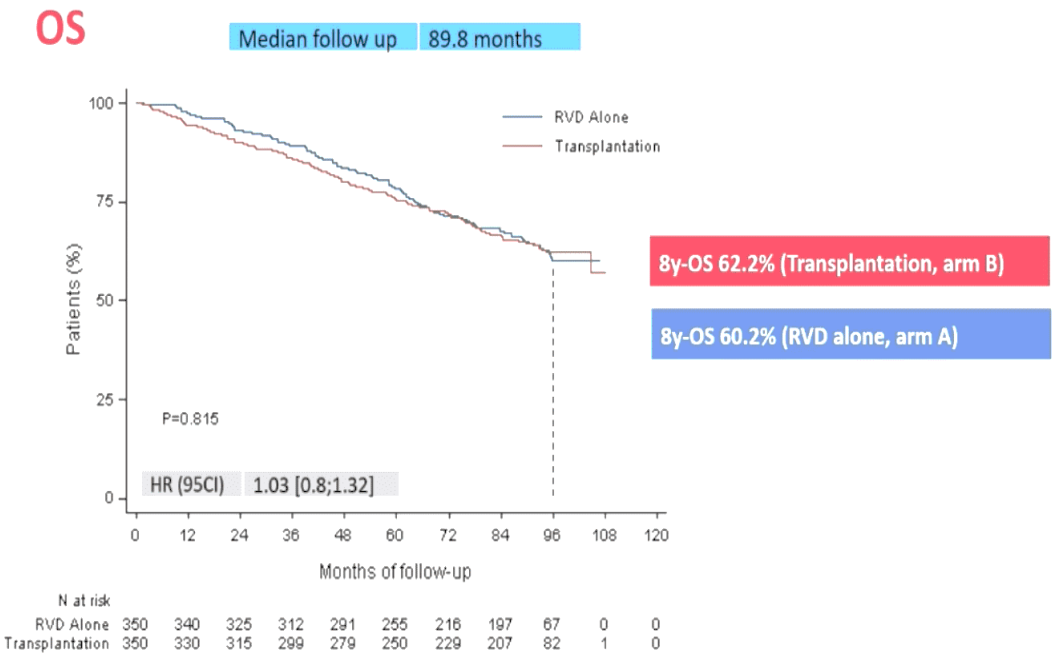
Cavo M, et al. *Lancet Haematol*. 2020;7:e456-e468.

IFM2009 Update



Perrot A, et al. ASH 2020. Abstract 143.

IFM2009 Update



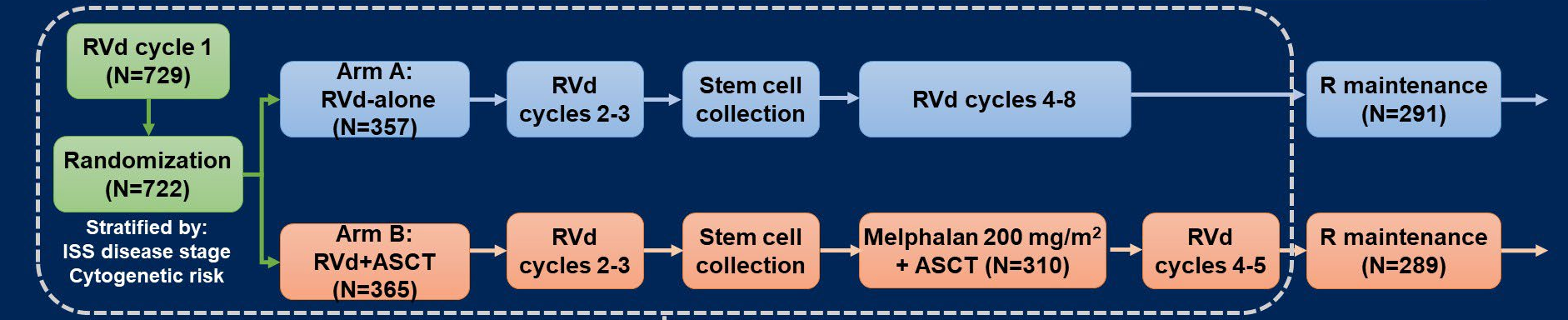
- Median FU of 93 months
- Better PFS in early AHCT (median 47.3 vs 35.0 mo)
- 77% of patients in the deferred AHCT arm have progressed

- 77% of patients who deferred and progressed received AHCT
- Similar PFS2
- Similar OS

Perrot A, et al. ASH 2020. Abstract 143.

DETERMINATION: study design and patient disposition

DETERMINATION: Delayed vs Early Transplant with Revlimid Maintenance and Antimyeloma Triple Therapy



Each RVd cycle (21 days):
R 25 mg/day PO, days 1-14
V 1.3 mg/m^2 IV/SC, days 1, 4, 8, 11
Dex 20/10 mg PO, days 1, 2, 4, 5, 8, 9, 11, 12

Induction ± ASCT + consolidation treatment duration = ~6 months

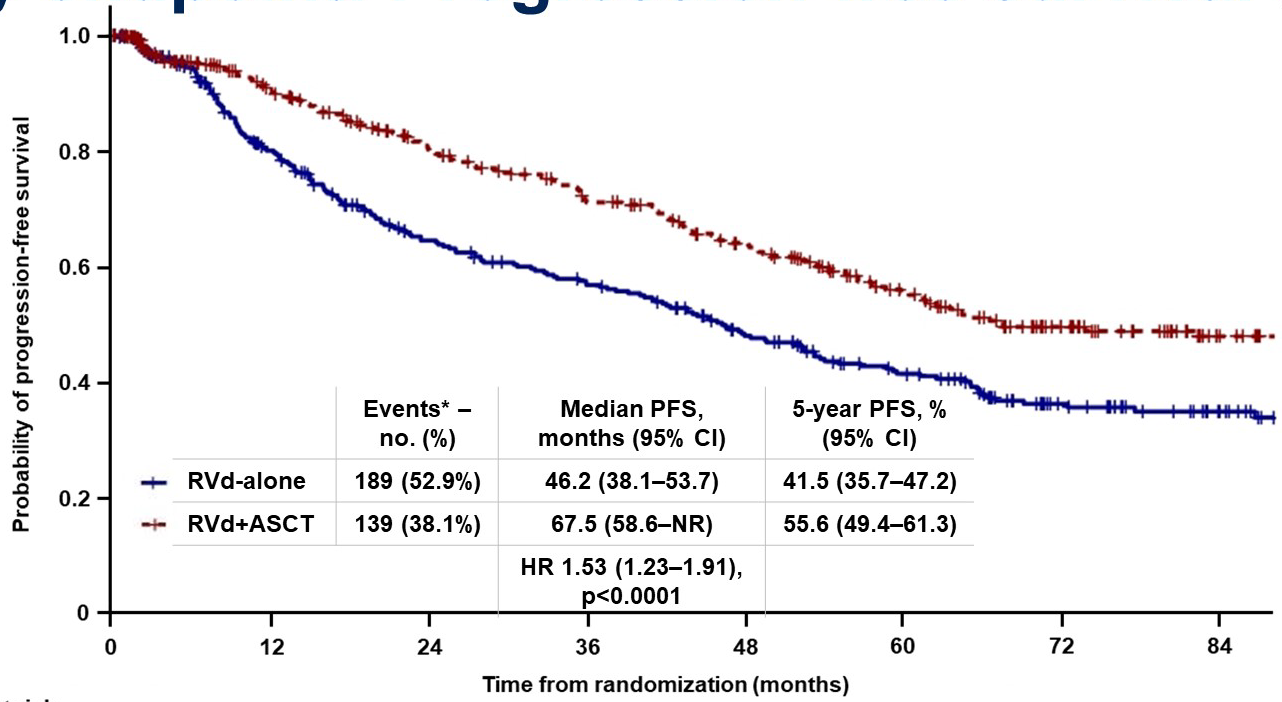
Lenalidomide maintenance
Months 1-3: 10 mg/day
Month 4 onwards: 15 mg/day

Primary endpoint: PFS

Secondary endpoints: response rates; DOR; TTP; OS; QoL; safety

d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

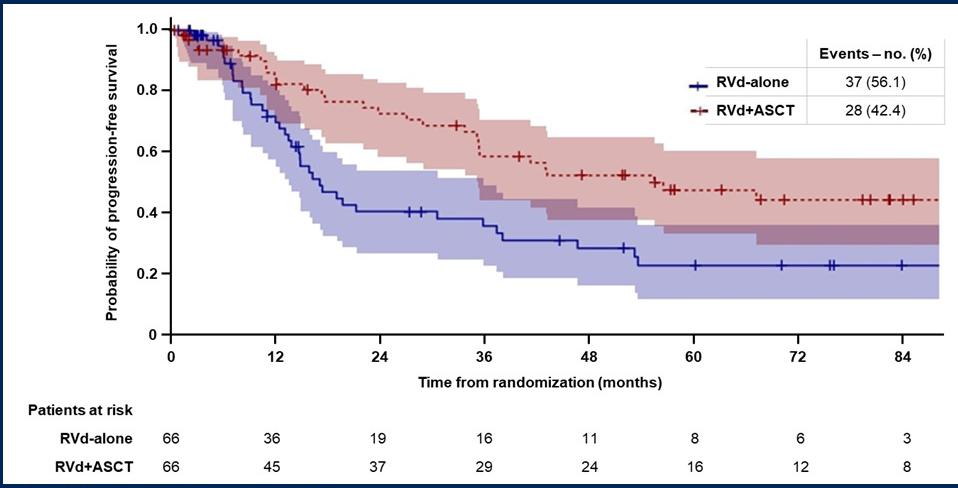
Primary endpoint: Progression-free survival (PFS)

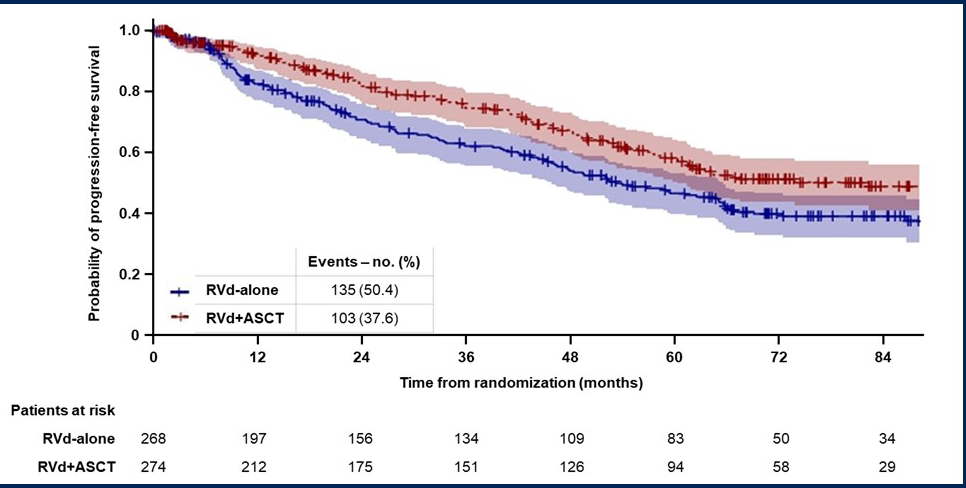


Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

CI, confidence interval; HR, hazard ratio; Data cutoff: 12/10/21. *PFS events: disease progression or death.

PFS by stratification factor – cytogenetic risk





Shaded areas indicate 95% CIs

Median PFS, months	RVd-alone	RVd+ASCT
High-risk	17.1	55.5
	HR 1.99 (95% CI 1.21–3.26)	

Median PFS, months	RVd-alone	RVd+ASCT
Standard-risk	53.2	82.3
	HR 1.38 (95% CI 1.07–1.79)	

Grade ≥3 treatment-related AEs (all treatment)

AE, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	78.2	94.2
Any hematologic	60.5	89.9
Any grade 5 (fatal) AE	0.3	1.6 *
Neutropenia	42.6	86.3
Thrombocytopenia	19.9	82.7
Leukopenia	19.6	39.7
Anemia	18.2	29.6
Lymphopenia	9.0	10.1
Febrile neutropenia	4.2	9.0
Diarrhea	3.9	4.9
Nausea	0.6	6.6
Mucositis oral	0	5.2
Fatigue	2.8	6.0
Fever	2.0	5.2
Pneumonia	5.0	9.0
Hypophosphatemia	9.5	8.2
Neuropathy	5.6	7.1

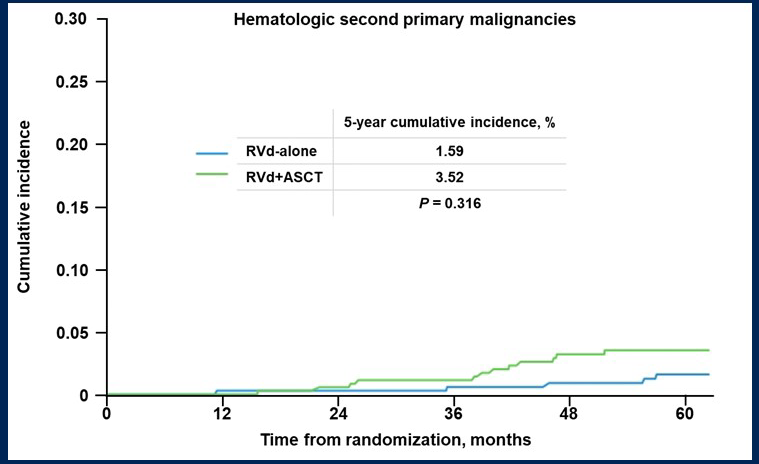
(S)AE, (serious) adverse event

- Rates of all grade ≥3 and of hematologic grade ≥3 treatment-related AEs during all treatment significantly higher with RVd + ASCT (both p<0.001)
  - Rates hematologic grade ≥3 treatment-related AEs during maintenance: 26.1% vs 41.9%
- Related SAEs:
  - Prior to maintenance: 40.3% vs 47.1%
  - During maintenance: 11.3% vs 16.6%

* Includes 1 death related to ASCT on Arm B identified after data cutoff; p=0.12

Second primary malignancies

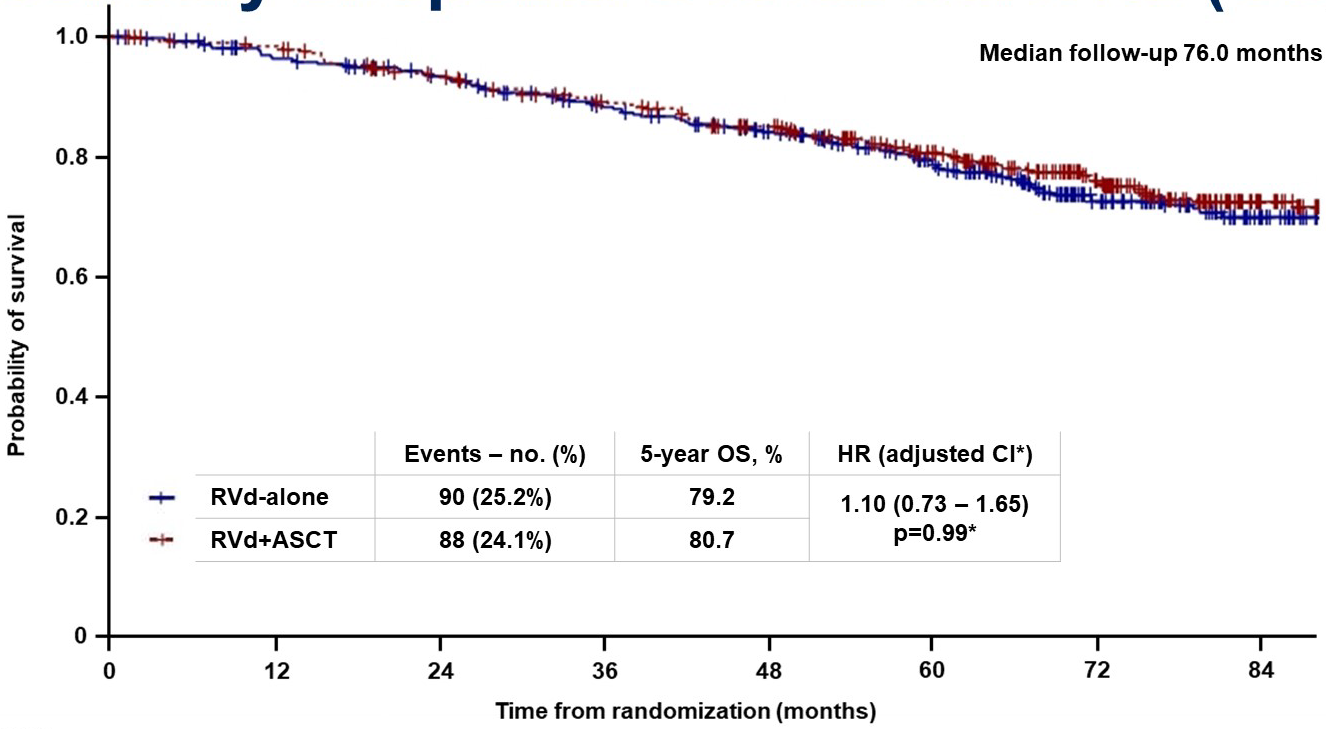
- 5-year cumulative incidence of SPMs (RVd-alone vs RVd+ASCT):
  - All : 9.7% vs 10.8%
  - Invasive: 4.9% vs 6.5%
  - Hematologic: 1.59% vs 3.52%



SPMs, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	10.4	10.7
Any invasive SPM	5.3	6.8
Any hematologic SPM	2.5	3.6
ALL, n	7	3
AML/MDS, n	0*	10*
CLL/CML, n	2	0
Any solid tumor SPM	3.4	3.3
Any non-invasive solid tumor SPM	0	0.5
Any non-melanoma skin cancer	5.9	4.1

* p=0.002

Key secondary endpoint: Overall survival (OS)



	Events – no. (%)	5-year OS, %	HR (adjusted CI*)
RVd-alone	90 (25.2%)	79.2	1.10 (0.73 – 1.65) p=0.99*
RVd+ASCT	88 (24.1%)	80.7	

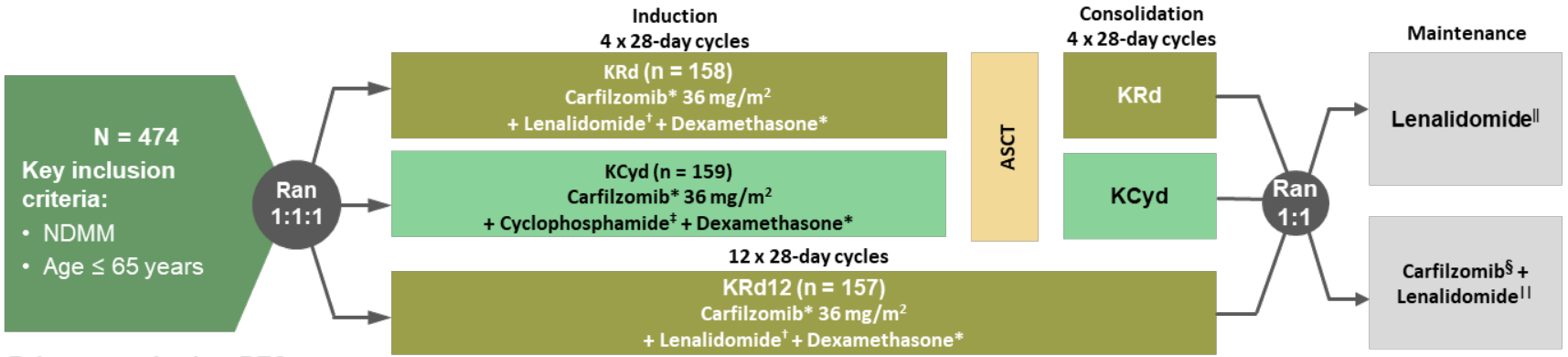
Patients at risk								
RVd-alone	357	332	313	285	258	214	143	88
RVd+ASCT	365	353	324	300	275	228	165	95

*CIs and p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes. Therefore, CIs use an α level of 0.05/7.

Data cutoff:12/10/21

FORTE Study Update

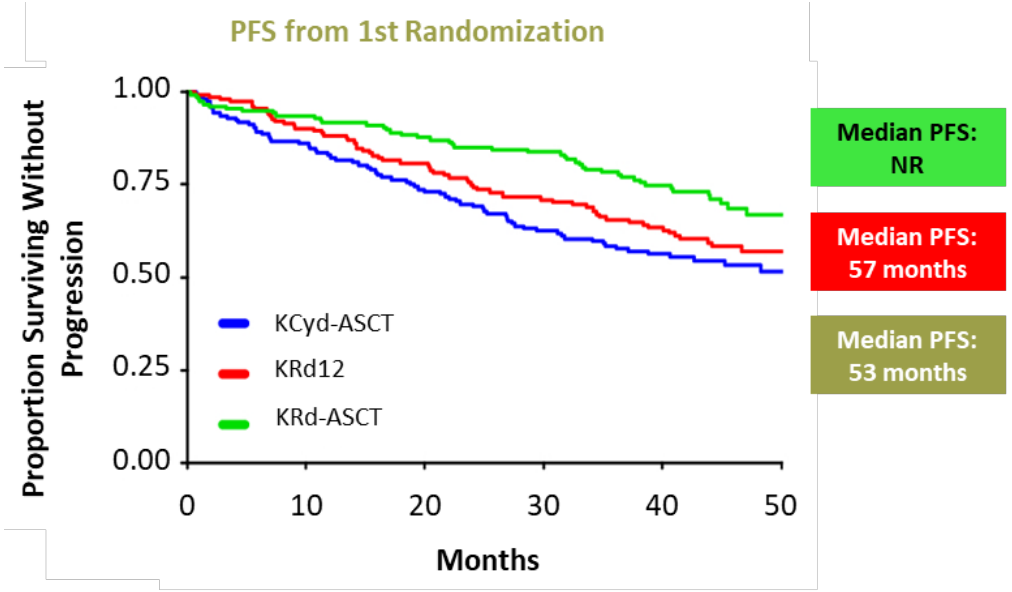
- The FORTE study previously demonstrated that KRd with or without ASCT led to deep responses and improved outcomes vs KCyd with ASCT in patients with NDMM
- This study evaluated PFS of 3 induction and 2 maintenance therapies in patients with NDMM
- The efficacy in different subgroups of patients and safety of the maintenance phase were also evaluated



Primary endpoint: PFS
Select Secondary endpoints: OS, safety

Gay F, et al. *Lancet Oncol*. 2021;22:1705-1720.

FORTE Study Update



	HR	*P*
KRd-ASCT vs KCyd-ASCT	0.53	<0.001
KRd-ASCT vs KRd12	0.64	0.023
KRd12 vs KCyd-ASCT	0.82	0.262

Treatment	3-year OS, %
KRd-ASCT	90
KRd12	90
KCyd-ASCT	83

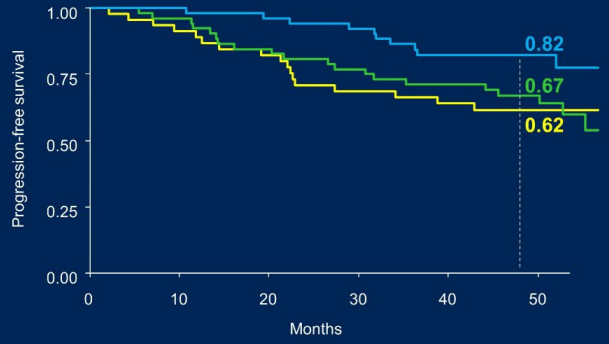
Gay F, et al. *Lancet Oncol*. 2021;22:1705-1720.

Progression-free survival: Random 1

KRd_ASCT vs. KRd12 vs. KCd_ASCT

Median follow-up from Random 1: 51 months (IQR 46-55)

Standard risk (N=153)

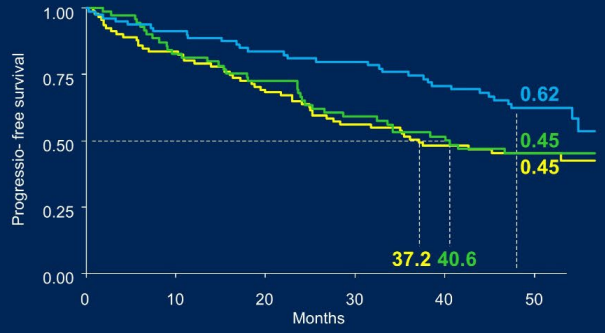


KRd_ASCT vs. KCd_ASCT: HR 0.44, p=0.04

KRd_ASCT vs. KRd12: HR 0.46, p=0.04

KRd12 vs. KCd_ASCT : HR 0.96, p=0.9

High risk (N=243)

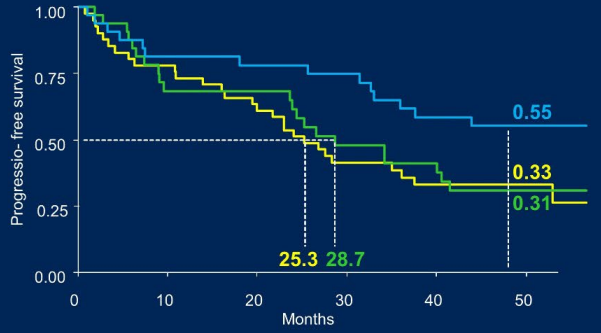


KRd_ASCT vs. KCd_ASCT: HR 0.57, p=0.01

KRd_ASCT vs. KRd12: HR 0.6, p=0.04

KRd12 vs. KCd_ASCT: HR 0.95, p=0.8

Double hit (N=105)



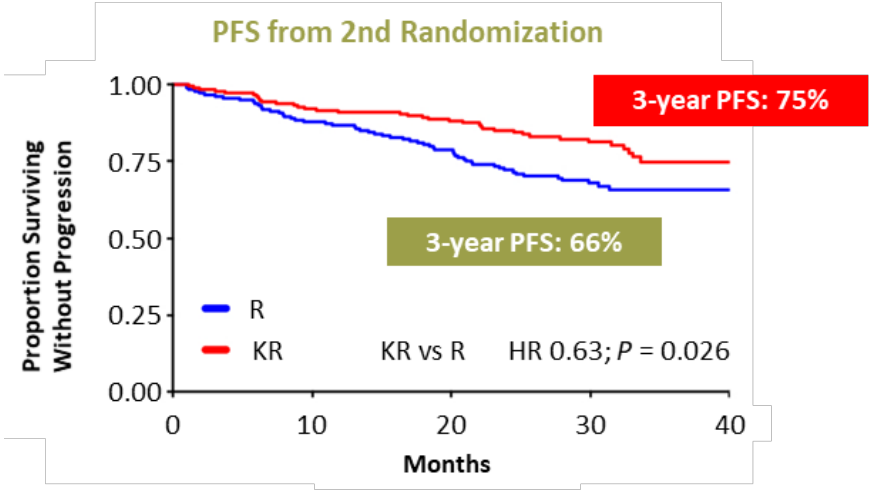
KRd_ASCT vs. KCd_ASCT: HR 0.49, p=0.03

KRd_ASCT vs. KRd12: HR 0.53, p=0.07

KRd12 vs. KCd_ASCT: HR 0.91, p=0.75

Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; HR, hazard ratio; CI, confidence interval; p, p-value; iQR, interquartile range.

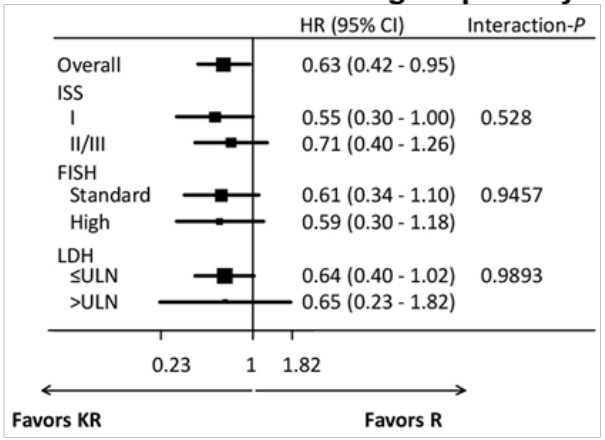
FORTE Study Update



Treatment	Patients MRD(+) That Turned MRD(–), %	*P*
R	32	0.04
KR	46	

Treatment	3-year OS, %
R	90
KR	90

PFS from R2: KR vs R Subgroup Analyses

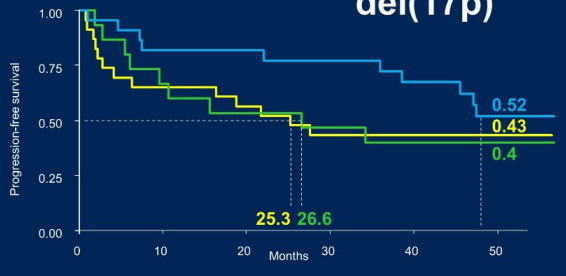


Gay F, et al. *Lancet Oncol*. 2021;22:1705-1720.

Progression-free survival: Random 1

KRd_ASCT vs. KRd12 vs. KCd_ASCT

del(17p)

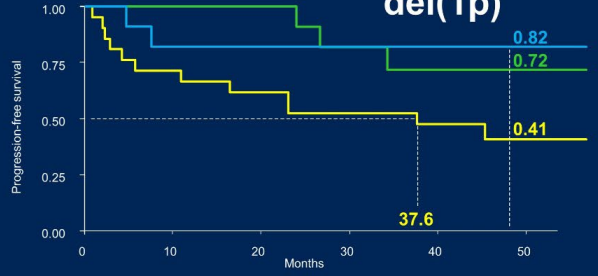


KRd_ASCT vs. KCd_ASCT: HR 0.57, p=0.185

KRd_ASCT vs. KRd12: HR 0.61, p=0.28

KRd12 vs. KCd_ASCT: HR 0.94, p=0.89

del(1p)

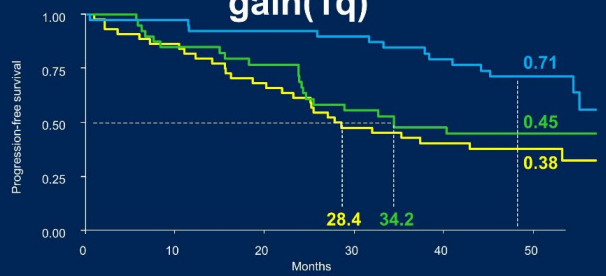


KRd_ASCT vs. KCd_ASCT: HR 0.24, p=0.06

KRd_ASCT vs. KRd12: HR 0.73, p=0.72

KRd12 vs. KCd_ASCT: HR 0.33, p=0.09

gain(1q)

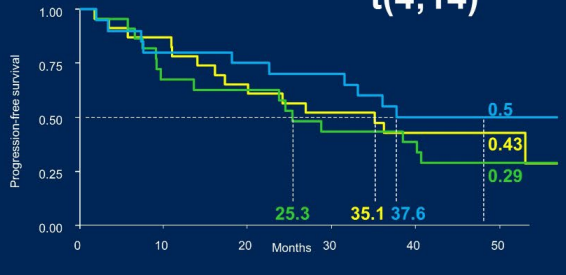


KRd_ASCT vs. KCd_ASCT: HR 0.35, p=0.001

KRd_ASCT vs. KRd12: HR 0.45, p=0.02

KRd12 vs. KCd_ASCT: HR 0.78, p=0.38

t(4;14)

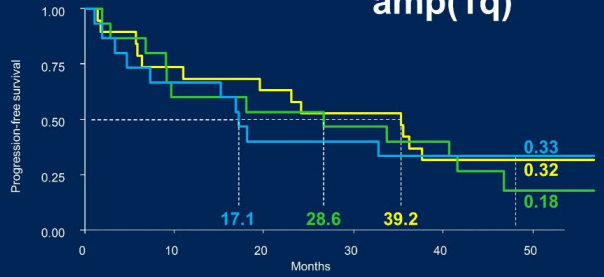


KRd_ASCT vs. KCd_ASCT: HR 0.73, p=0.44

KRd_ASCT vs. KRd12: HR 0.59, p=0.19

KRd12 vs. KCd_ASCT: HR 1.23, p=0.57

amp(1q)



KRd_ASCT vs. KCd_ASCT: HR 1.16, p=0.72

KRd_ASCT vs. KRd12: HR 0.87, p=0.73

KRd12 vs. KCd_ASCT: HR 1.34, p=0.46

KCd_ASCT

KRd_ASCT

KRd12

3-year PFS reported in the figure.

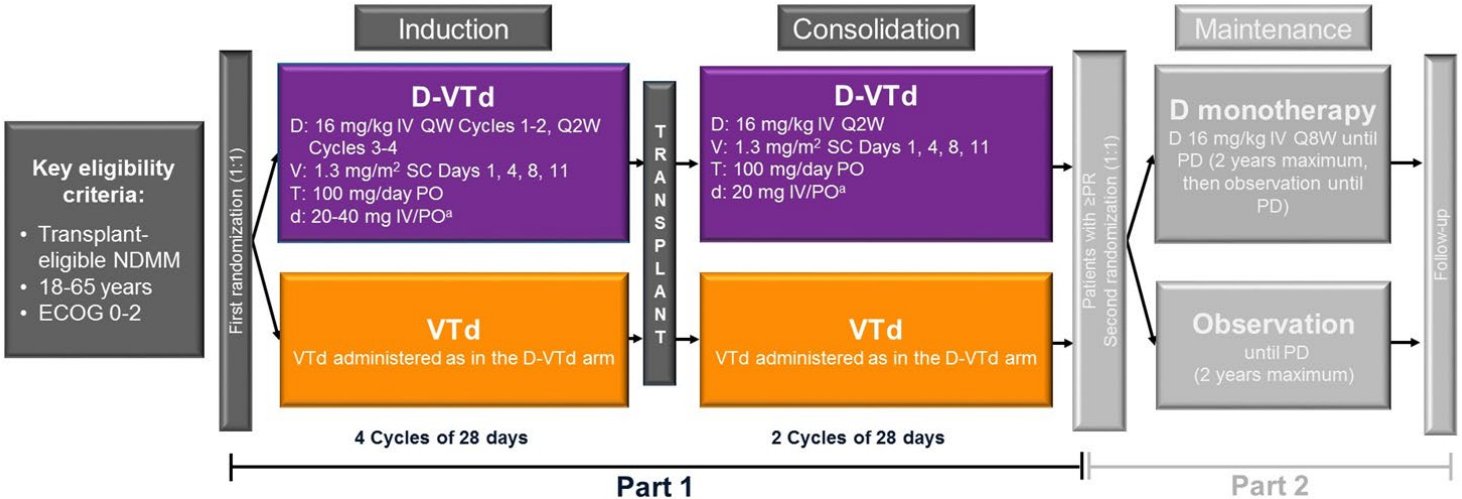
Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; PFS, progression-free survival; p, p-value; HR, hazard ratio.

Quadruplet Regimens

CD38 MoAb in Induction Prior to AHCT: CASSIOPEIA

CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017



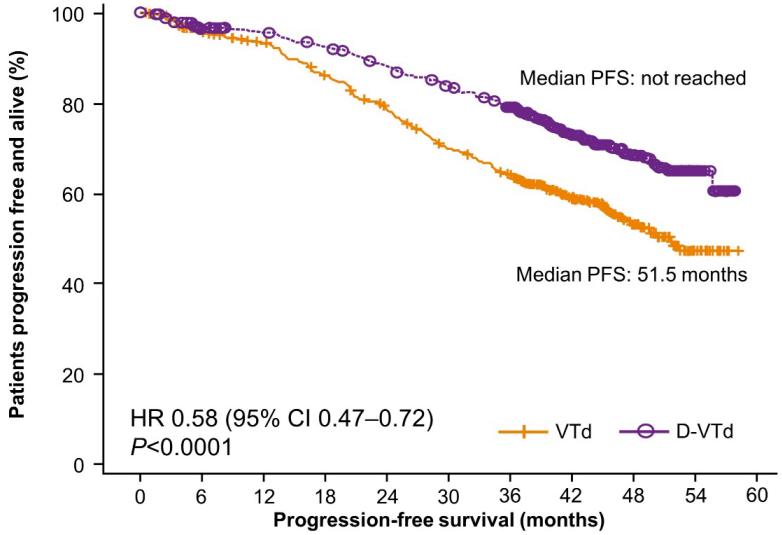
D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease.
[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

Moreau P, et al. *Lancet*. 2019;394:29-38.

Updated Analyses From First Randomization Confirm Benefits of D-VTd vs VTd Induction/Consolidation

Median follow-up: 44.5 months

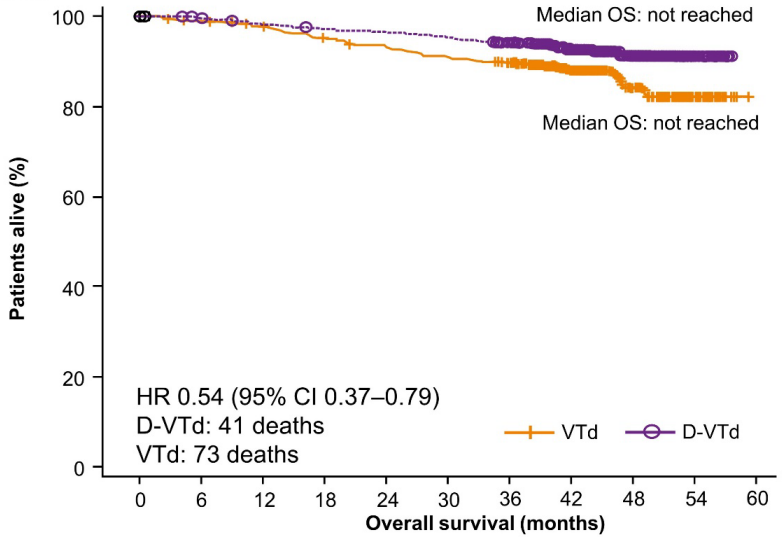
PFS



Patients at risk

VTd	542	499	472	434	391	345	312	191	90	26	0
D-VTd	543	507	495	478	452	426	395	237	119	29	0

OS



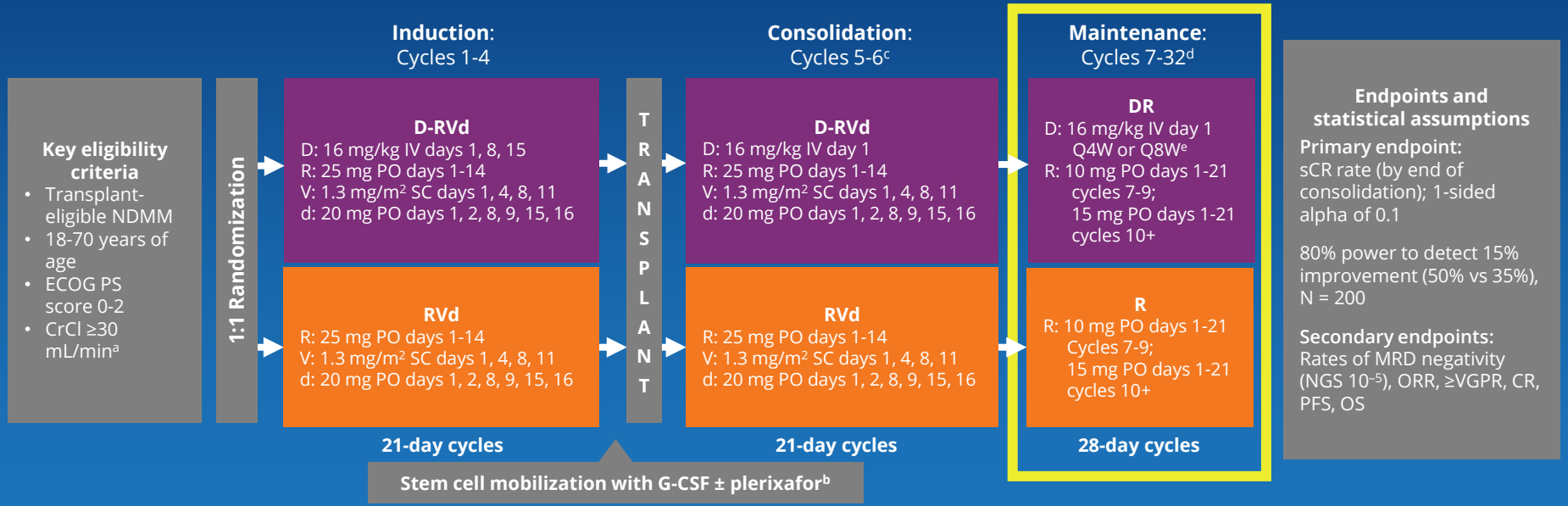
Patients at risk

VTd	542	531	521	505	494	481	468	305	151	42	0
D-VTd	543	536	526	520	517	510	498	327	162	37	0

CI, confidence interval; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; VTd, bortezomib, thalidomide, and dexamethasone.

GRIFFIN: Study Design of the Randomized Phase

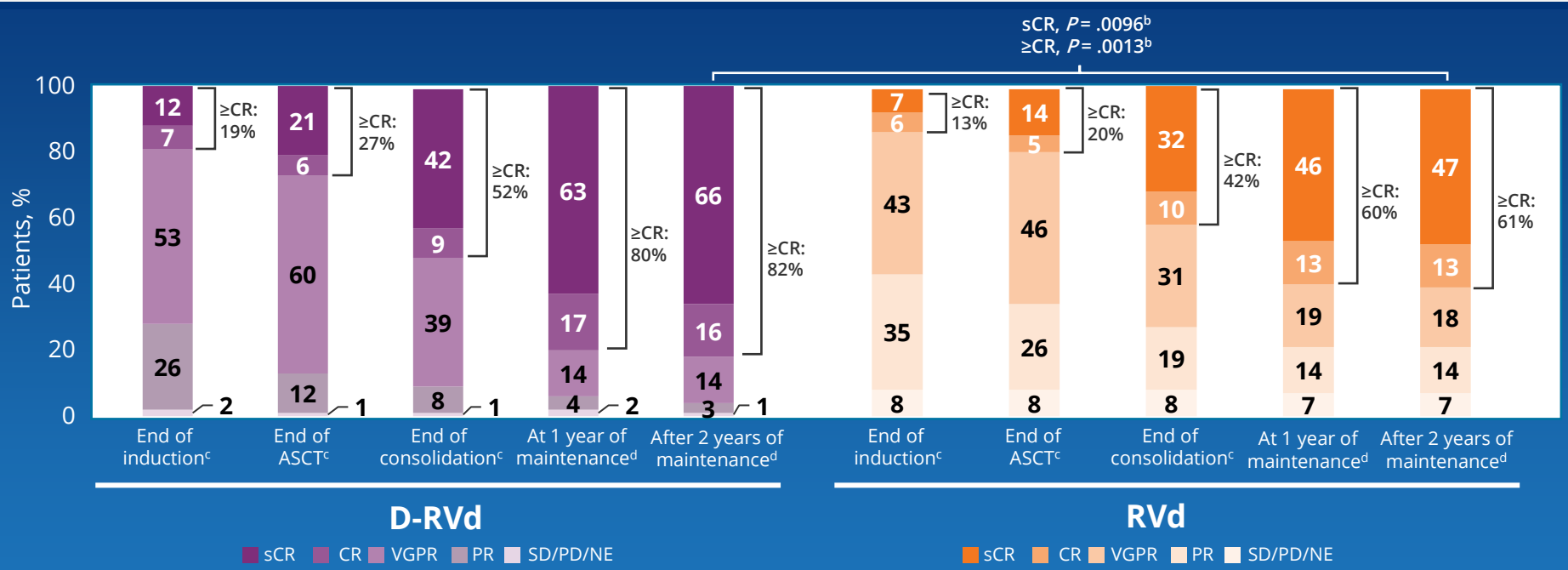
- Phase IIa study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in the United States with enrollment between December 2016 and April 2018



ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; PO, oral; SC, subcutaneous; G-CSF, granulocyte colony-stimulating factor; Q4W, every 4 weeks; Q8W, every 8 weeks; NGS, next-generation sequencing; ORR, overall response rate; VGPR, very good partial response; CR, complete response; PFS, progression-free survival; OS, overall survival. [a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60-100 days post-transplant. [d]Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W on the basis of pharmacokinetic results from study SMM2001 (ClinicalTrials.gov Identifier: NCT02316106). In GRIFFIN, among the D-RVd group who received DR maintenance, 9 patients received DARA Q8W dosing, 57 received DARA Q4W dosing, and 23 switched from DARA Q8W to Q4W dosing.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual

GRIFFIN: Responses Deepened Over Time[a]

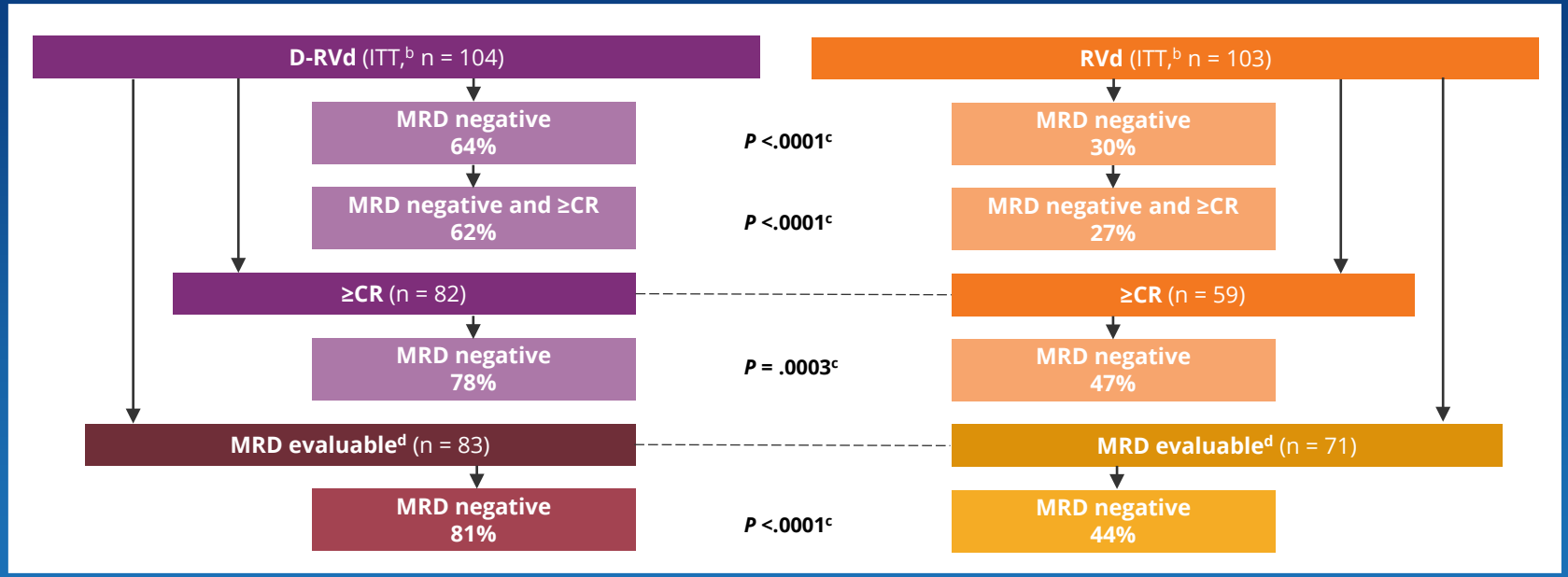


- Response rates for sCR and ≥CR were greater for D-RVd vs RVd at all time points, with the deepest responses occurring after 2 years of maintenance therapy

PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test. [c]Response rates are from the primary analysis cutoff (median follow-up: 13.5 mo), and the response-evaluable population included 196 patients (D-RVd, n = 99; RVd, n = 97). [d]Response rates for the maintenance phase have longer follow-up (median: 38.6 mo), and the response-evaluable population included 197 patients (D-RVd, n = 100; RVd, n = 97). Percentages may not add up due to rounding.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual

GRIFFIN: MRD Negativity[a] (10^{-5}) After 2 Years of Maintenance Therapy



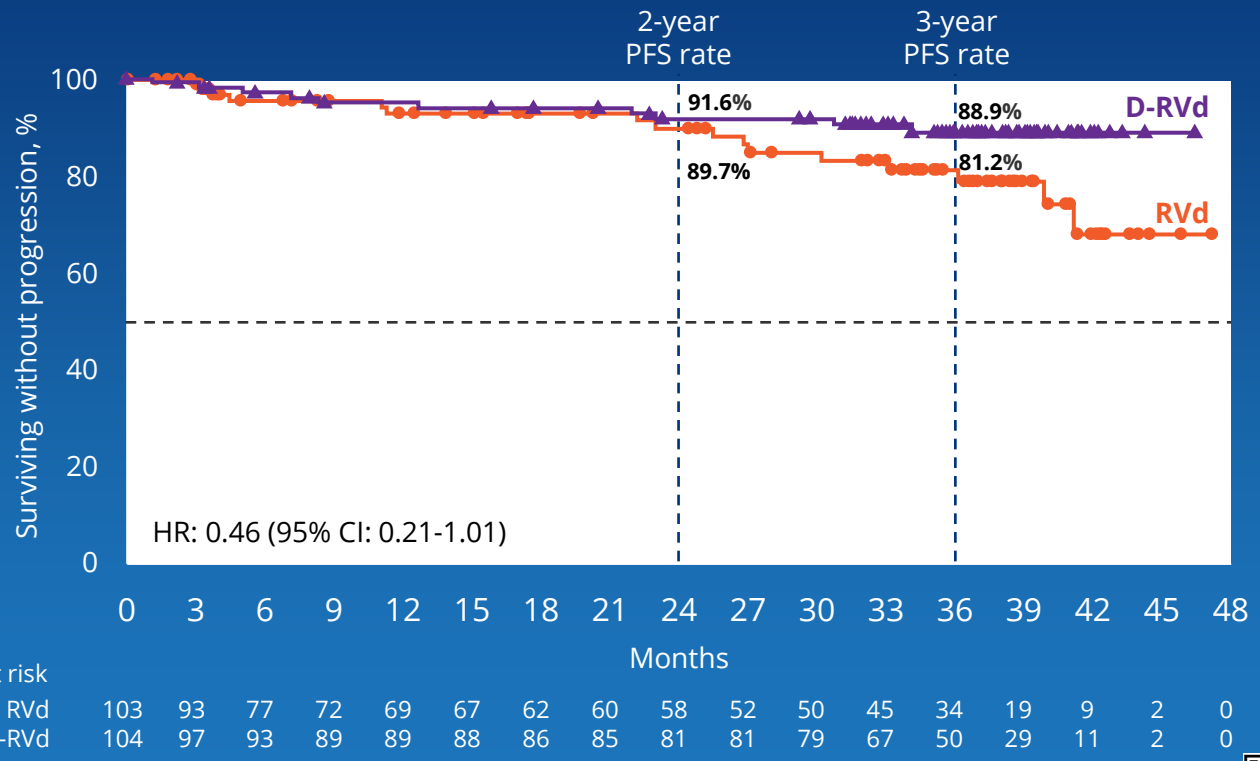
- Similarly, MRD-negativity (10^{-6}) rates favored D-RVd vs RVd in the ITT population (36% vs 15%, respectively; *P* = .0007), as well as among patients who achieved ≥CR (43% vs 22%; *P* = .0121)

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 38.6 months. [b]For the ITT population, patients with a missing or inconclusive assessment were considered MRD positive. [c]*P* values were calculated using the Fisher's exact test. [d]The MRD-evaluable population includes patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual

GRIFFIN: PFS in the ITT Population

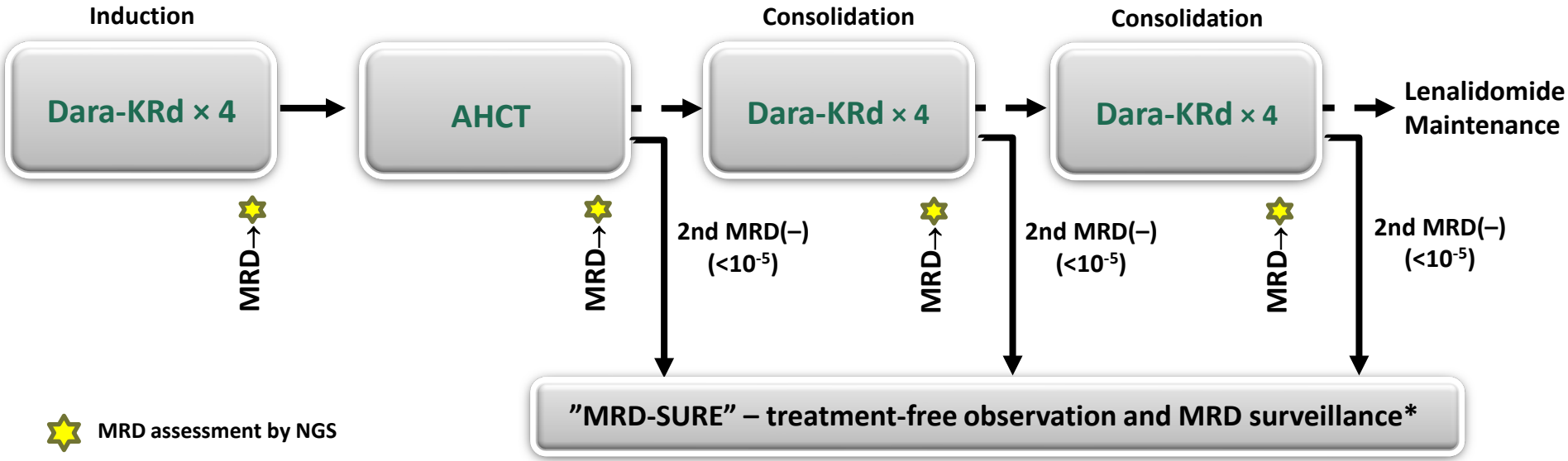
- Median follow-up: 38.6 months
- Median PFS was not reached in either group
- There is a positive trend toward improved PFS for D-RVd/DR vs RVd/R
- The separation of the PFS curves begins beyond 1 year of maintenance and suggests a benefit of prolonged DR therapy



HR, hazard ratio.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual

Treatment Augmentation and De-escalation: MASTER Trial

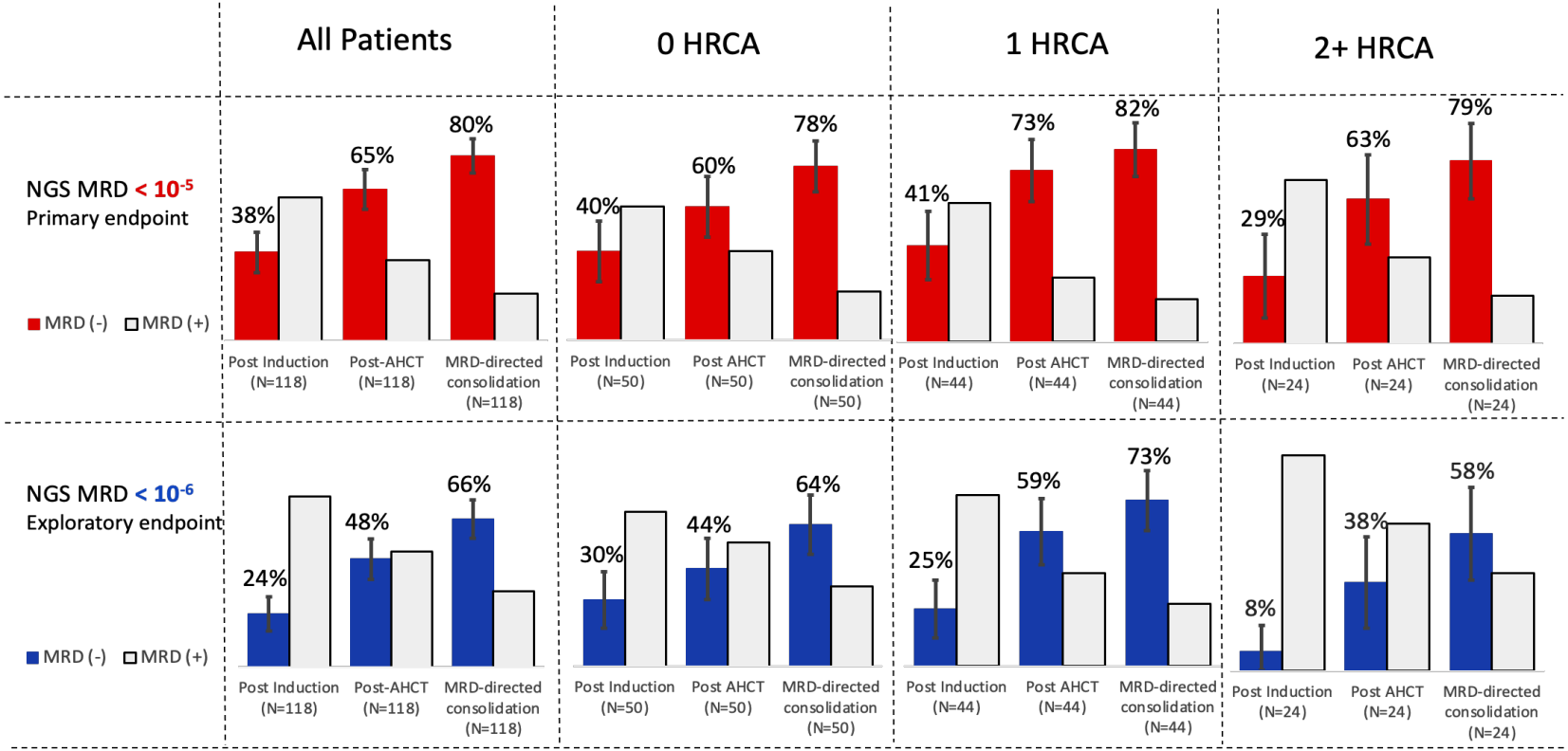


*Twenty-four and 72 weeks after completion of therapy.

Costa LJ, et al. *J Clin Oncol*. 2021. Online ahead of print. doi: 10.1200/JCO.21.01935

MASTER trial

Best MRD Response by Phase of Therapy

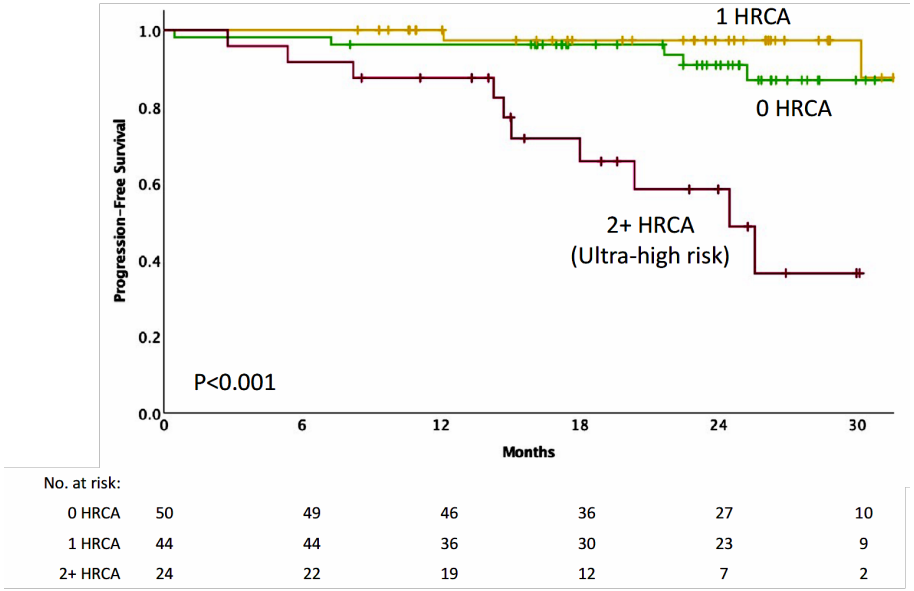


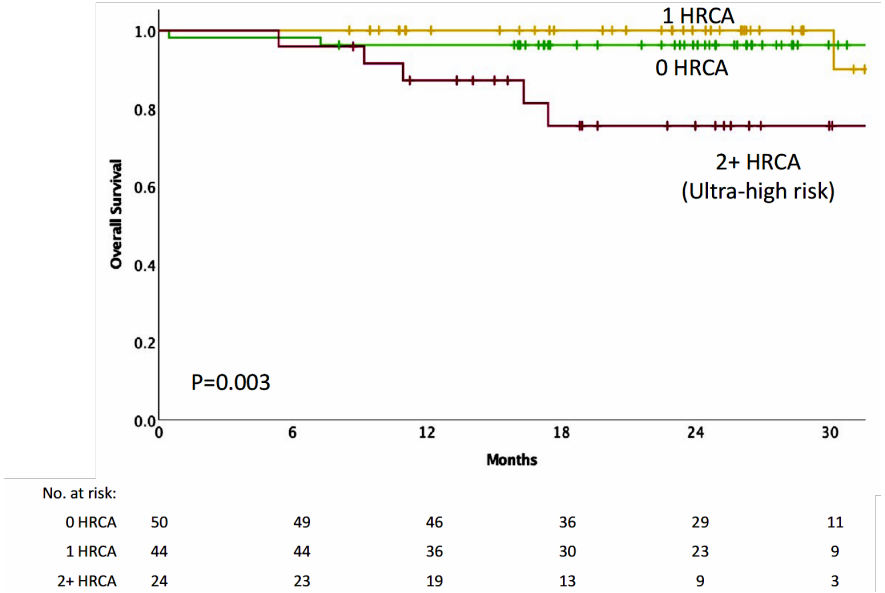
HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20), or del(17p)

Costa LJ, et al. *J Clin Oncol*. 2021. Online ahead of print. doi: 10.1200/JCO.21.01935

MASTER trial

Progression-Free and Overall Survival: MASTER Trial





2-year PFS	0 HRCA	91%
	1 HRCA	97%
	2+ HRCA	58%

2-year OS	0 HRCA	96%
	1 HRCA	100%
	2+ HRCA	76%

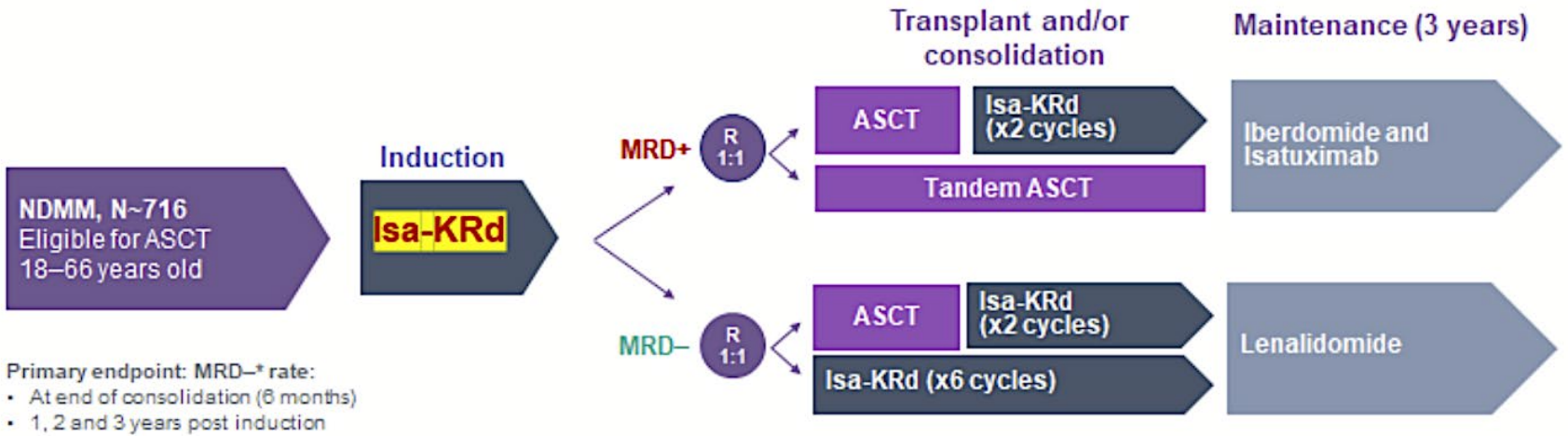
HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20), or del(17p)

Costa LJ, et al. *J Clin Oncol*. 2021. Online ahead of print. doi: 10.1200/JCO.21.01935

MASTER trial

Treatment Augmentation and De-escalation: MIDAS Trial

Sponsor: Intergroupe Francophone du Myelome (IFM)
Estimated primary completion: September 2024



*Primary analysis will evaluate MRD (NGS, 10^{-6} threshold)

Isa-KRd is an investigational combination that has not been approved by any regulatory authority. Sanofi does not recommend the use of their products outside the approved indication. Please consult your local label before prescribing

Courtesy of Prof Mohty.

Question for the Audience

What statement best describe your approach to AHCT for Myeloma in 2022?

a) Appropriate for most patients younger than 75 as part of the upfront treatment
b) Appropriate for patients younger than 65 with high-risk disease as part of the upfront treatment
c) Best used as a salvage strategy for patients who develop disease progression
d) AHCT has no role in modern treatment of MM since same results can be obtained with therapies containing PI + IMiD

Take-Home Message

- AHCT prolongs PFS in the setting of modern triplet therapy
- Combinations containing PI + IMiD are the backbone of induction therapy in TE-NDMM
- The addition of anti-CD38 MoAb to induction/consolidation prolongs PFS in TE-NDMM
- The role of AHCT in the setting of quadruplet induction, particularly among patients with early deep response, is being evaluated

Costa LJ, et al. *J Clin Oncol*. 2021. Online ahead of print. doi: 10.1200/JCO.21.01935

Thank you!

Global Multiple Myeloma Academy

Discussion

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Global Multiple Myeloma Academy

Debate:
Is Myeloma Curable or Not?

Rafael Fonseca (yes) vs Eloisa Riva (no)

APTITUDE HEALTH®

Pre-debate Question for the Audience

In your opinion, is multiple myeloma curable?

a) Yes

b) No

Global Multiple Myeloma Academy

Debate:
Is Myeloma Curable or Not?

Yes – Rafael Fonseca, MD

APTITUDE HEALTH®

MAYO CLINIC

Rafael Fonseca, MD
Chief Innovation Officer

Mayo Clinic in Arizona
Is Myeloma Curable? YES!

Phoenix, Arizona

Rochester, Minnesota

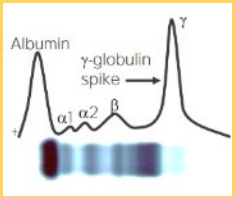
Jacksonville, Florida

MAYO CLINIC

Definition

- “Curable”
  - Simple and short treatment that results in disease eradication?

- Total eradication of the disease with normal life expectancy?
  - Can be
- Control of the disease with normal life expectancy?
  - Yes



@rfonsi1, fonseca.rafael@mayo.edu

MAYO CLINIC

Sustained CR: Cures?

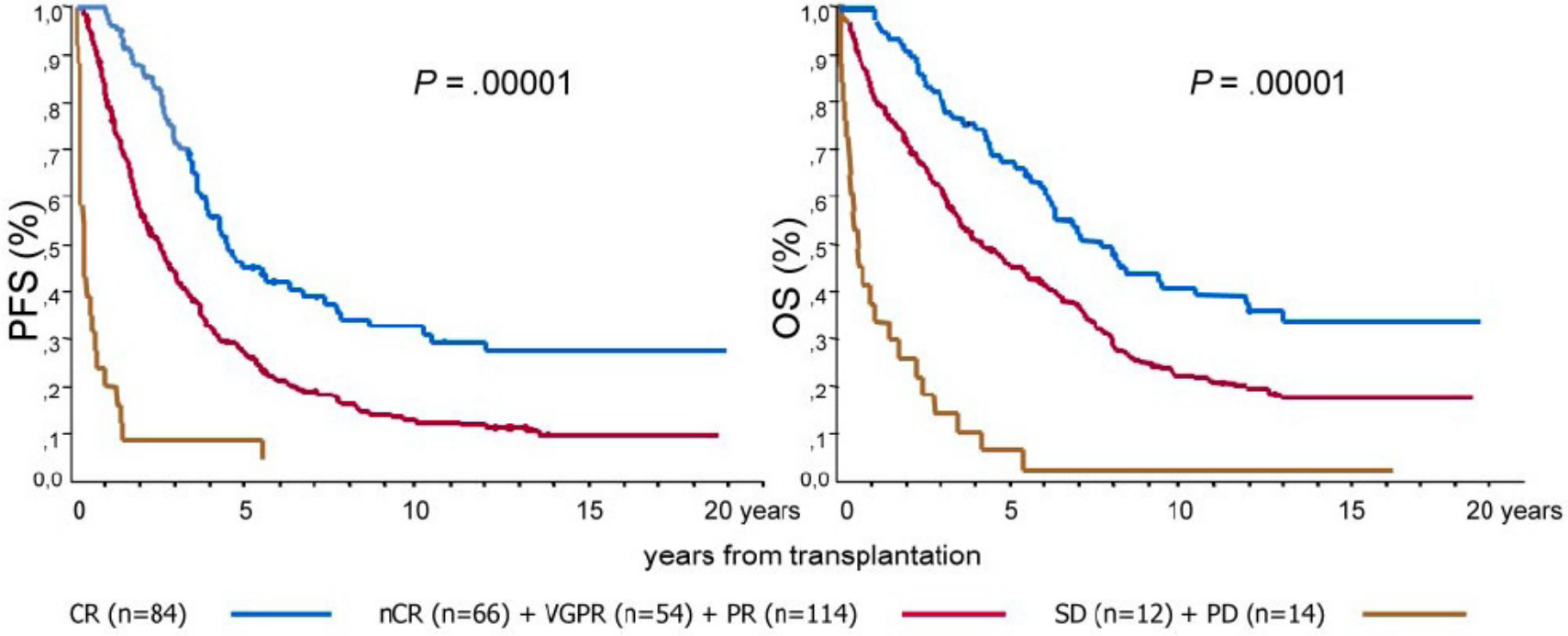


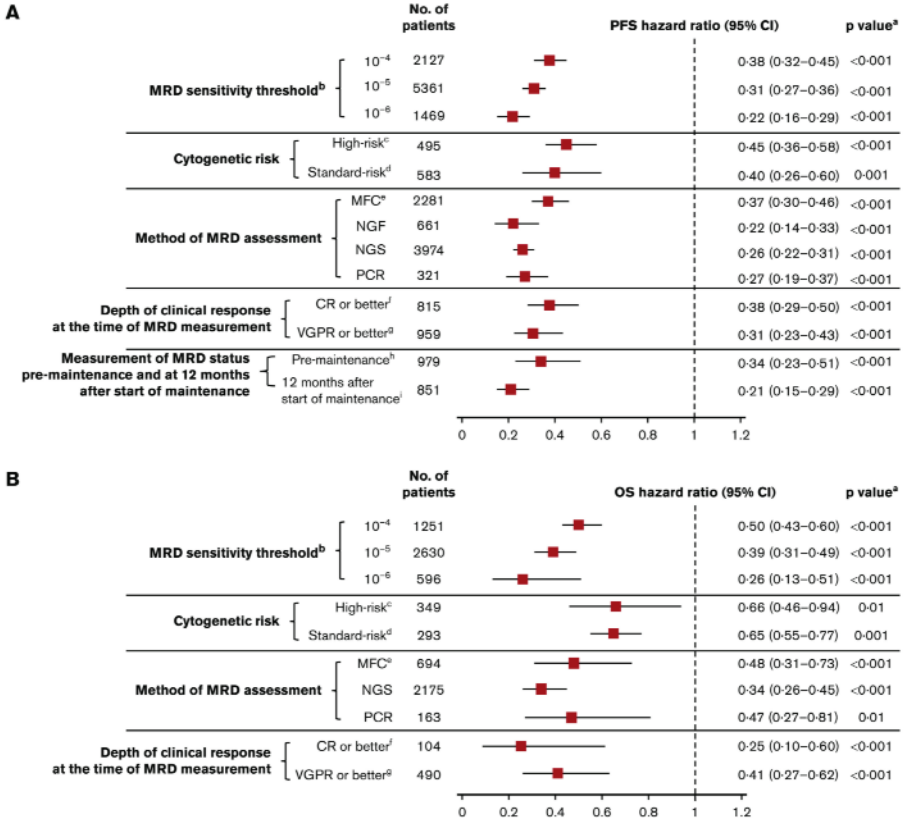
Figure 2. Prognostic effect of CR patients versus those in nCR or VGPR or PR versus patients with SD or PD after HDT/ASCT.

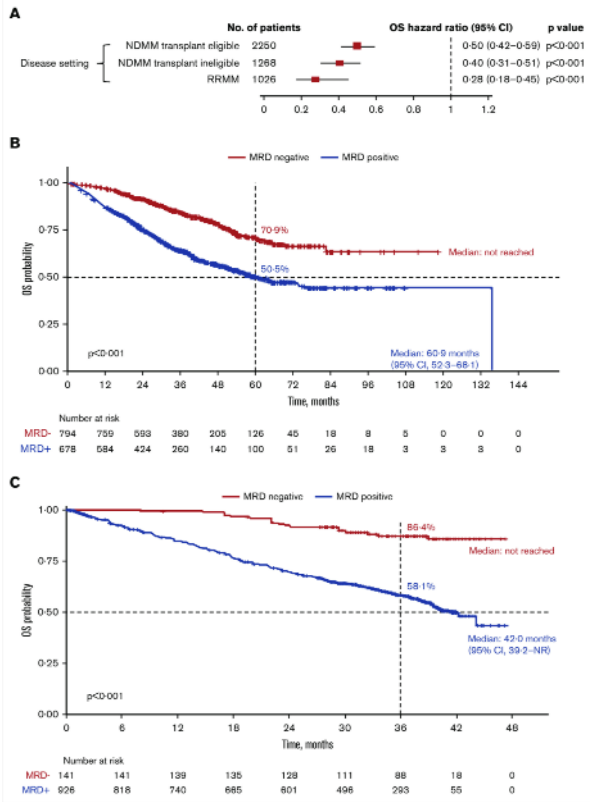
@rfonsi1, fonseca.rafael@mayo.edu

Martinez-Lopez J, et al. *Blood*. 2011;118:529-534.

MAYO CLINIC

Three Meta-analyses Validate MRD for Prognosis





@rfonsi1, fonseca.rafael@mayo.edu

Munshi NC, et al. *Blood Adv*. 2020;4:5988-5999; Landgren O, et al. *Bone Marrow Transplantation.* 2016;51:1568; Munshi NC, et al. *JAMA Oncol*. 2017;3:28-35.

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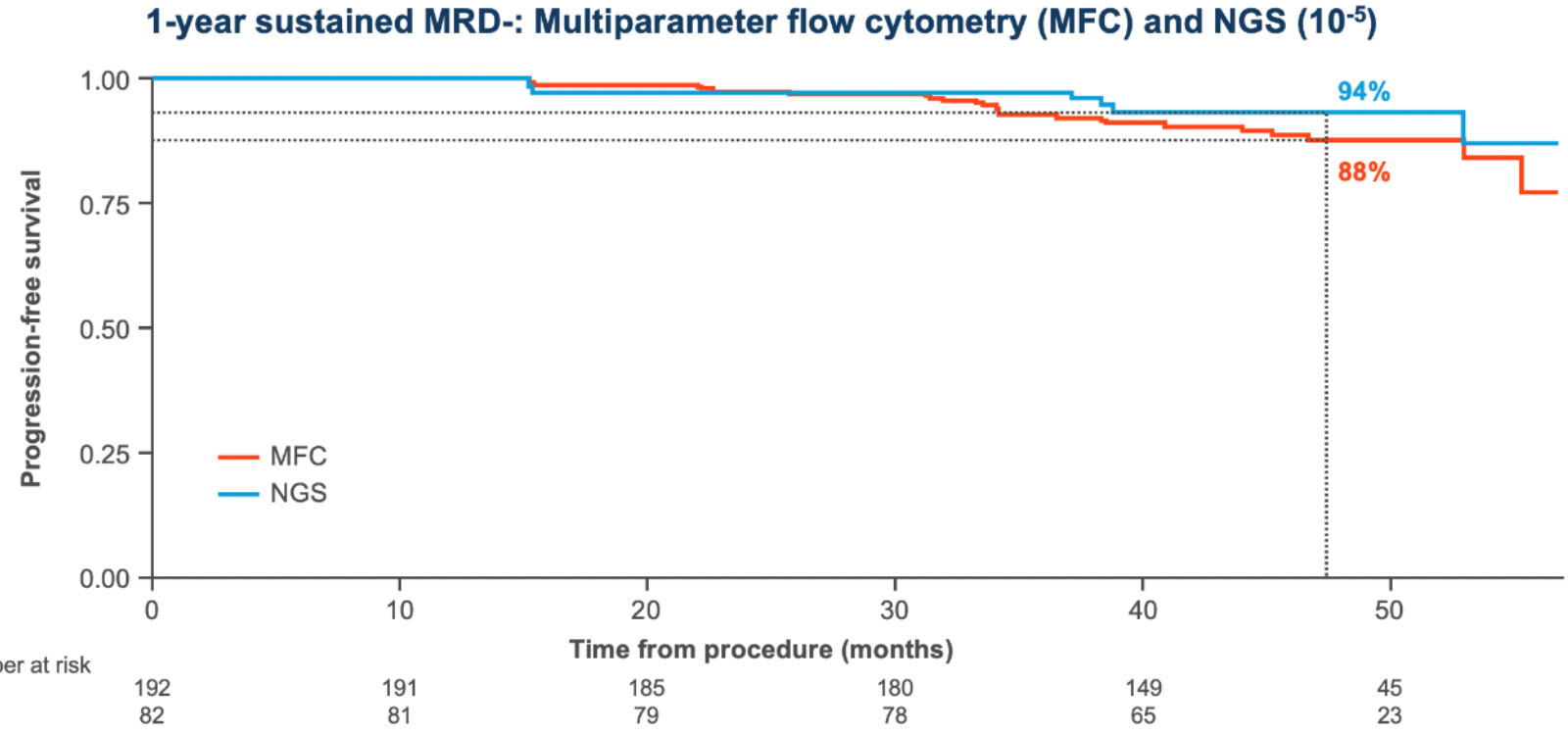
FORTE Sustained MRD Negativity



@rfonsi1, fonseca.rafael@mayo.edu

Gay F, et al. ASH 2020. Abstract 141.

MAYO CLINIC

Drive to MRD Negative

- 58 yr
- New diagnosis MM
- Induction with KRD
- Completed SCT
- 11/2018 MRD+
  - Dara-Rd
- Aug 2019 MRD+
  - More Dara-Rd
- Feb 2020 MRD–
  - R maintenance

SAMPLE-LEVEL MRD RESULT

No Residual Sequences Detected

ESTIMATED MRD VALUE:

0 residual clonal cells (Range: 0 - 2) **

Total nucleated cells evaluated from this sample: 1,299,985

The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

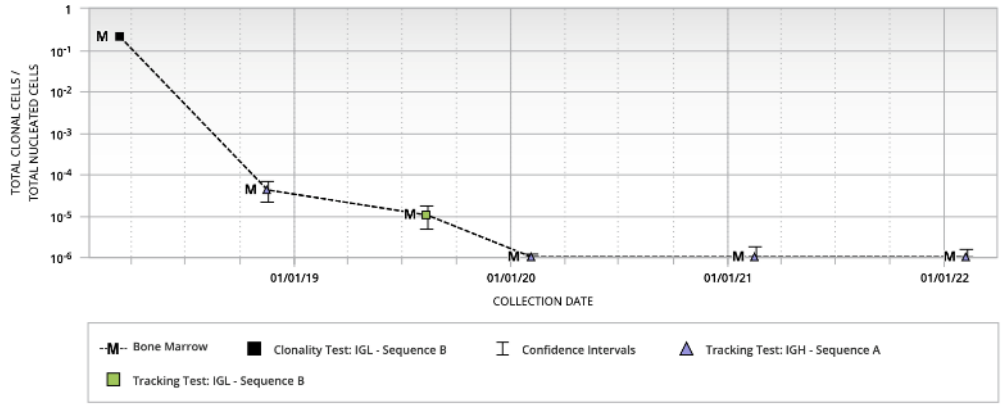
RESULTS SUMMARY

- Genomic DNA was extracted from a fresh bone marrow sample.
- The 2 dominant sequences identified in a diagnostic sample from this patient were not detected in this current sample.

** The sensitivity of this assay is directly related to the total number of cells (or cellular equivalents of genomic DNA) analyzed. There were 1,299,985 total nucleated cells evaluated from this sample.

▶ **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD result for each time point)*

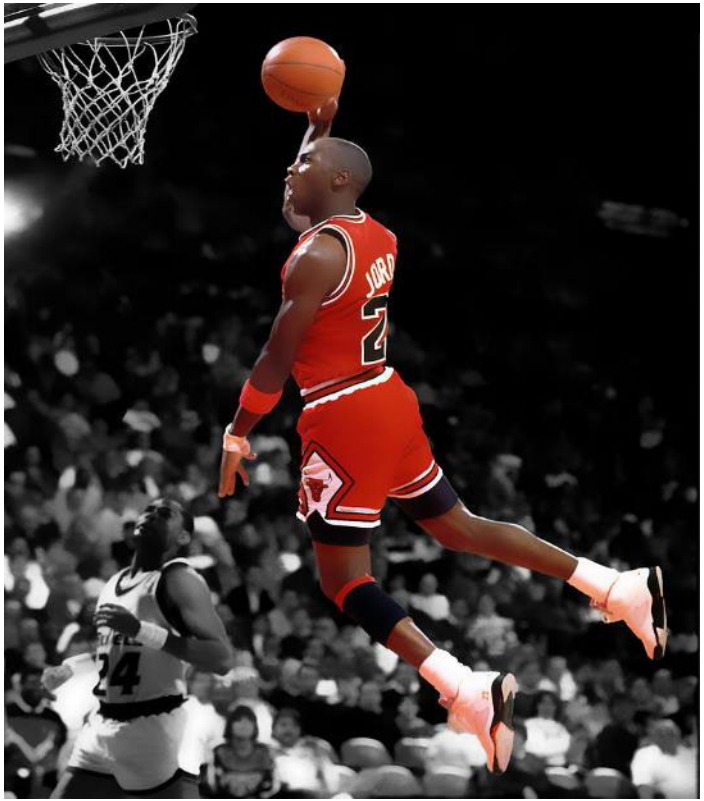


@rfonsi1, fonseca.rafael@mayo.edu

Fonseca, Personal.

MAYO CLINIC

Thank you!



@rfonsi1, fonseca.rafael@mayo.edu

Global Multiple Myeloma Academy

Debate:
Is Myeloma Curable or Not?

No – Eloisa Riva, MD

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What Do We Mean by “CURE”?

1963: “In time, probably a decade or 2 after treatment—there remains a group of disease-free survivors whose annual death rate from all causes is similar to that of a normal population group of the same sex and age distribution”[1]

1971: “ . . . cure should be unassociated with continuing morbidity from the disease or its treatment”[2]

1986: “Cure is growing old and dying from something else”[3]

2015: “The use of the word ‘cure’ in oncology is heterogeneous: 2/3 of published manuscripts containing that word in 2012 are not meeting the standard definitions”[4]

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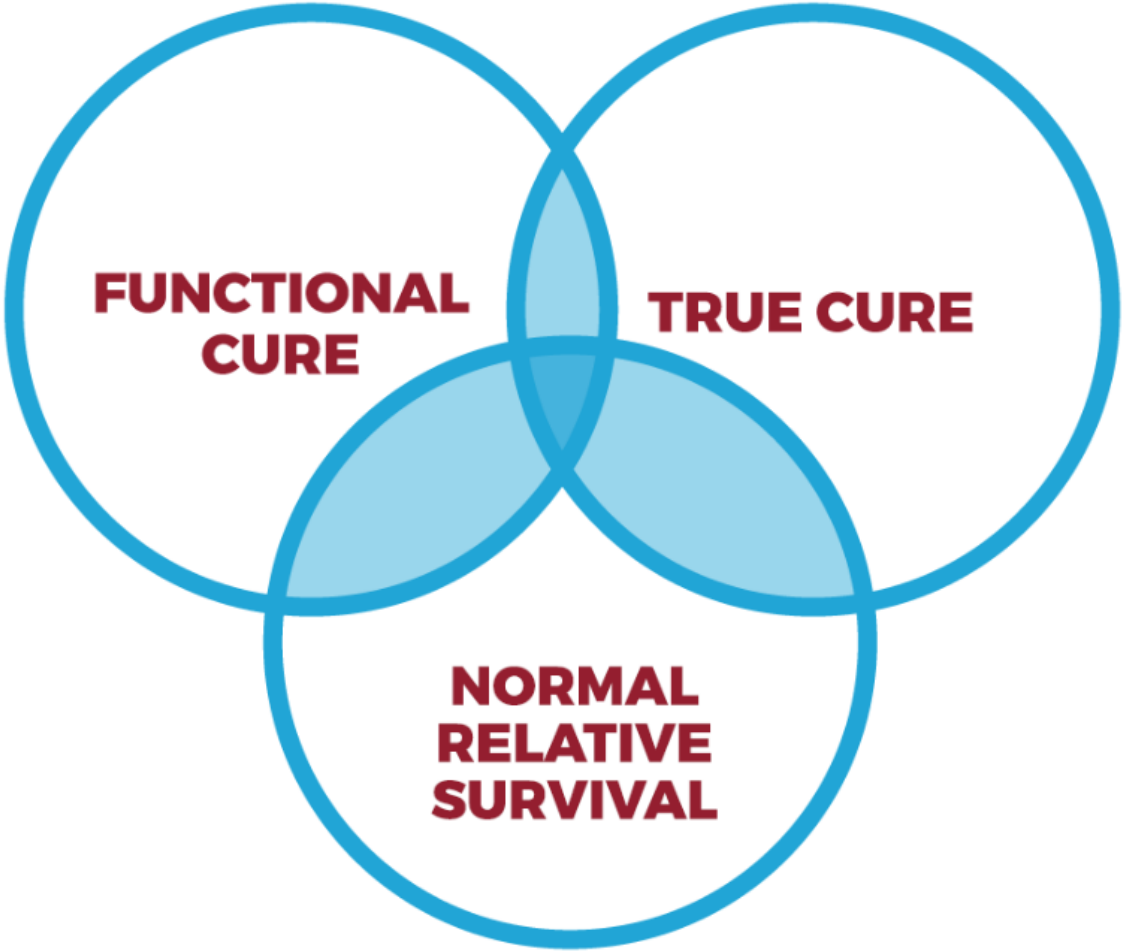
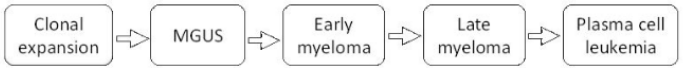
1. Easson EC, Russell MH. Cure of Hodgkin’s Disease. *Br Med J*. 1963;1:1704-1707; 2. Frei E 3rd, Gehan EA. Definition of Cure for Hodgkin’s Disease. *Cancer Res*. 1971;31:1828-1833; 3. Thompson F. Going for the Cure. 1989; 4. Prasad V. Use of the word “Cure” in the oncology literature. *Am J Hosp Palliat Care*. 2015;32:477-483.

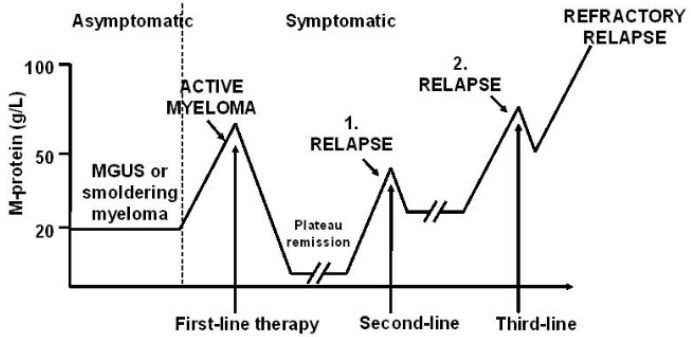
HOW DO MULTIPLE MYELOMA EXPERTS DEFINE CURE?



Natural History of MM

- Multiple myeloma (MM) is a heterogeneous disease with survival ranging from months to decades
- MM is still an incurable disease
- Drug resistance and disease refractoriness are the common terminal pathways leading to death





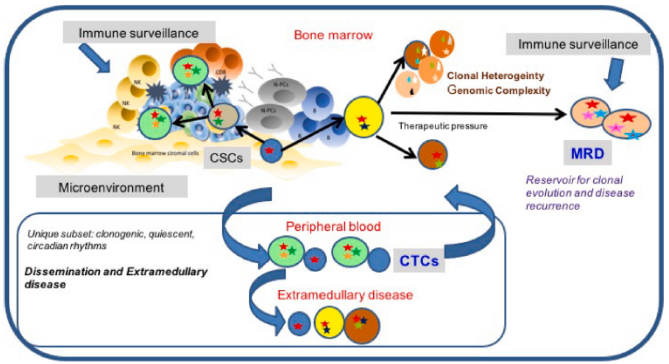


Fig. 1. Pathogenies of Multiple Myeloma: Circulating tumor cells (CTC) and minimal residual disease (MRD) clones represent aggressive clones driving disease dissemination and resistance. *(CTCs: circulating tumor cells, N-PC: normal plasma cells, NK: NK- cells, B: B-lymphocytes, CD8: CD8 + T-cells, MRD: minimal residual disease, CSCs: cancer stem cells).*

Palumbo A, et al. *Blood*. 2011;118:4519-4529.

Issue #1

- Median age at diagnosis is 69 years
- 35%–40% of patients are older than 75 years
  - Competing risks for dying from other diseases with controlled disease
- Observed vs expected survival in young patients with hematologic malignancies
  - “MM patients have 20-fold excess mortality risk compared to the background population at diagnosis and at 3 years after diagnosis”
  - Significant excess mortality risk compared with the matched background population in MM patients surviving 36 mo after diagnosis (SMR-36: 20.7 [14.7–28.3)

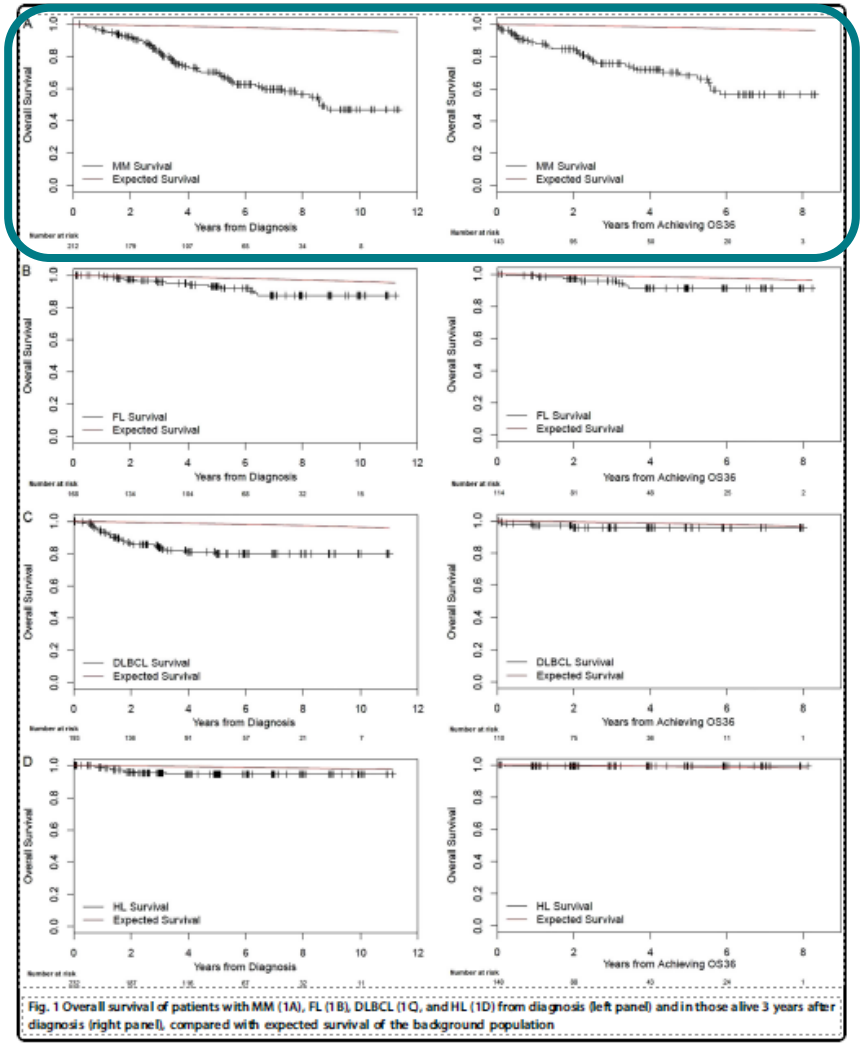
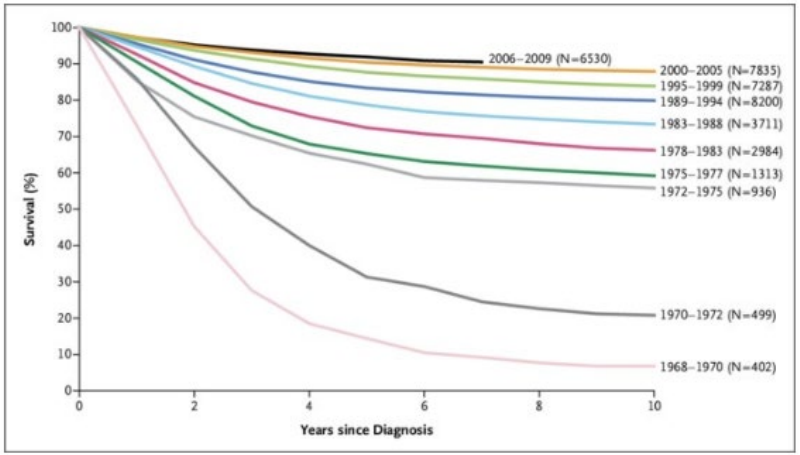


Fig. 1 Overall survival of patients with MM (1A), FL (1B), DLBCL (1C), and HL (1D) from diagnosis (left panel) and in those alive 3 years after diagnosis (right panel), compared with expected survival of the background population

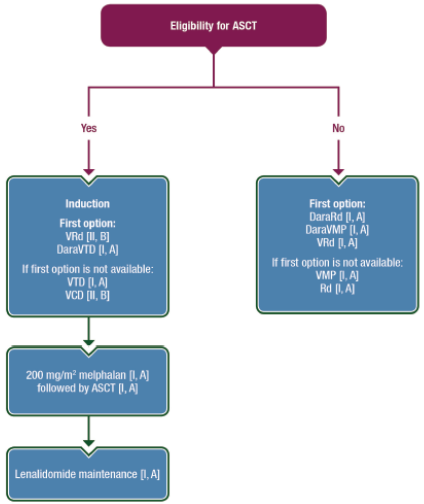
Ravi P, et al. *Blood Cancer J.* 2018;8:26.

Issue #2

> Cure requires that therapy is given for a **finite** period of time, and demonstration that a proportion of patients remain free of relapse for a prolonged period of time



If indefinite therapy is needed, we are "controlling" the disease



5.4.1 | Recommendations

- I recommend lenalidomide maintenance for standard-risk patients following ASCT. I also recommend lenalidomide maintenance following 8-12 cycles of VRd among patients who did not receive ASCT as part of initial therapy.
- I recommend maintenance with bortezomib alone or low intensity VRd for patients with high-risk multiple myeloma.

Hunger S, et al. *N Engl J Med.* 2015;373:1541-1552.

Issue #3

> Multiple layers of heterogeneity exist in MM

> Overcoming heterogeneity is a prerequisite for a true cure

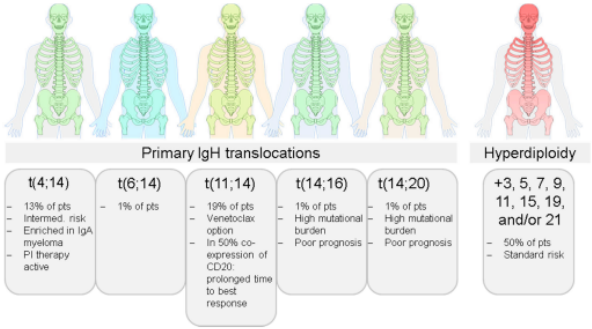


Figure 1. Inter-patient heterogeneity in Multiple Myeloma. The two main pathogenetic groups hyperdiploid and non-hyperdiploid can be distinguished in myeloma. However, there are multiple different initiating events at the chromosomal level, resulting in a high level of inter-patient heterogeneity in this disease, which is also reflected in heterogeneous treatment responses and outcomes.

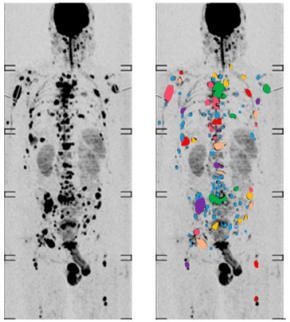


Figure 2. Intra-tumor heterogeneity in Multiple Myeloma. According to recent multi-region sequencing studies spatial genomic heterogeneity is a common phenomenon in myeloma. Tumor driver mutations and high-risk genomic aberrations can be restricted to one focal lesion and absent at other FLs or the iliac crest. Thus, an imaging finding with multiple FLs strongly suggests extensive intra-tumor heterogeneity.

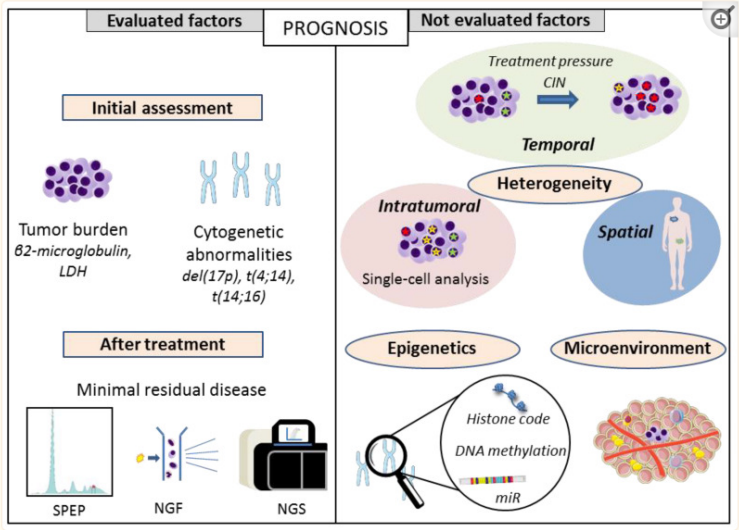


Figure 1

Prognostic factors: routinely evaluated versus not evaluated factors. SPEP: serum protein electrophoresis, NGF: next-generation flow, NGS: next-generation sequencing.

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Schavgoulidze A, et al. *Cancers.* 2021;13:1285.

Current Facts

- MM is not a single entity
- Long-term survival is achievable
- Current guidelines rely on indefinite treatment to CONTROL the disease
- Perhaps the cure is not far, but we are unable yet to cure MM
- Treating early-stage disease may prevent MM from developing

THANK YOU!!!

Post-debate Question for the Audience

In your opinion, is multiple myeloma curable?

a) Yes

b) No

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Break

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Advances in Consolidation and Maintenance Therapy: Latest Updates and MRD-Guided Therapy

Luciano Costa, MD, PhD

APTITUDE HEALTH®

Consolidation, Maintenance, and MRD-Adapted Therapy

Luciano J. Costa, MD, PhD
Mary and Bill Battle Professor of Multiple Myeloma
University of Alabama at Birmingham

ljcosta@uabmc.edu
@End_myeloma

Question for the Audience

What statement best describe the evidence for maintenance therapy in MM?

a) Lenalidomide, when applied post AHCT, prolongs PFS but not OS vs observation/placebo

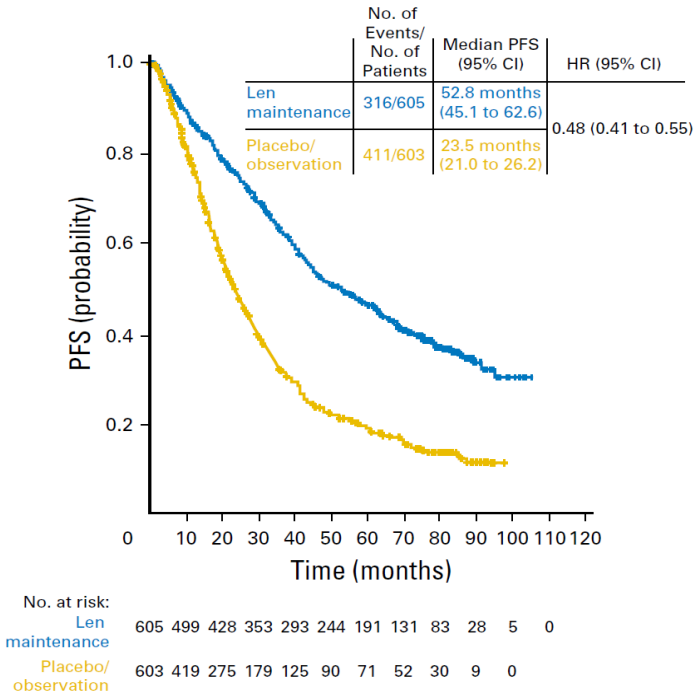
b) Ixazomib + lenalidomide, when applied post AHCT, prolongs PFS vs lenalidomide

c) Carfilzomib + lenalidomide maintenance yield better PFS than lenalidomide alone

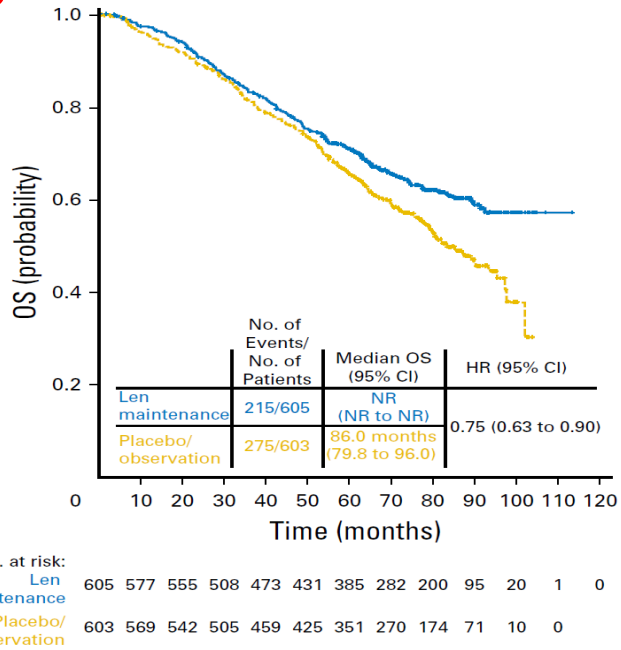
d) Daratumumab has an established role as maintenance therapy in patients treated with quadruplet induction regimens

Current Paradigm = Continuous Therapy

PFS



OS



McCarthy PL, et al. *J Clin Oncol*. 2017;35:3279-3289.

Caveats of Continuous Therapy

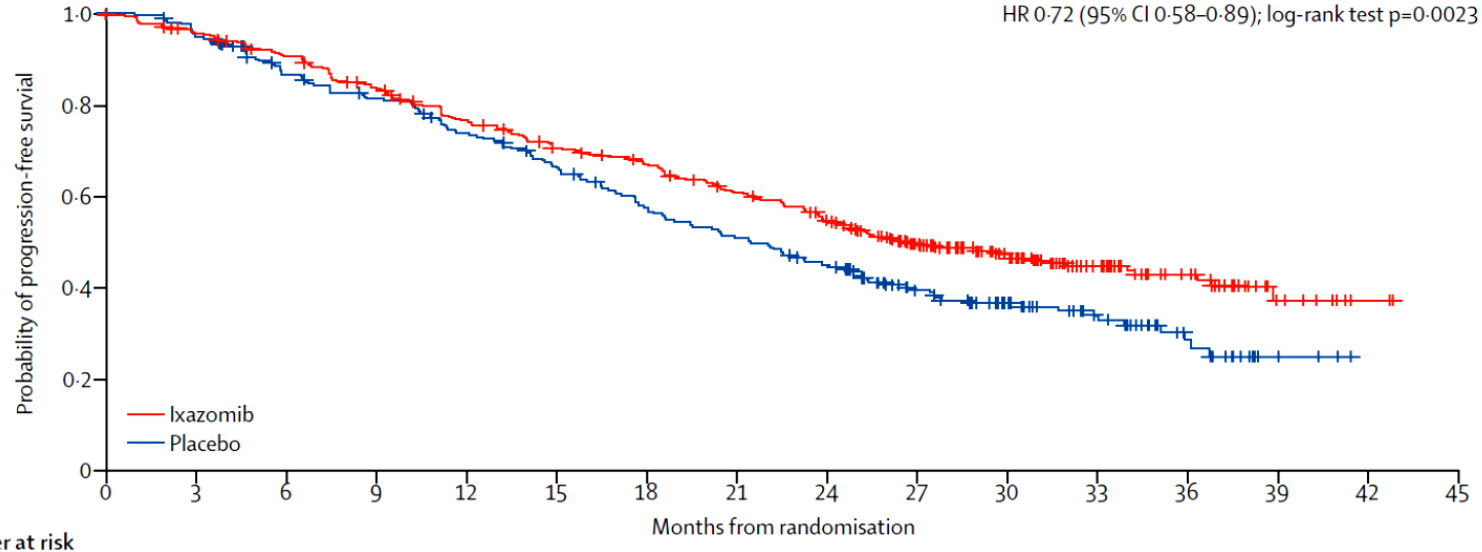
- Evidence for continuous therapy defined in setting of less-active therapy

USA CALGB Study

Induction regimen — no.			
Any use of bortezomib	98	91	189 (41)
Any use of lenalidomide	79	81	160 (35)
Any use of thalidomide	102	103	205 (45)
Bortezomib–lenalidomide‡	20	21	41 (9)
Bortezomib–thalidomide‡	33	27	60 (13)
Bortezomib without lenalidomide or thalidomide	43	40	83 (18)
Bortezomib with glucocorticoids, without lenalidomide or thalidomide	40	32	72 (16)
Bortezomib with lenalidomide and thalidomide	2	3	5 (1)
Lenalidomide without bortezomib	57	57	114 (25)
Thalidomide without bortezomib	67	72	139 (30)
Lenalidomide–glucocorticoids without bortezomib	56	56	112 (24)
Thalidomide–glucocorticoids without bortezomib	65	72	137 (30)
Other induction regimen without bortezomib, lenalidomide, or thalidomide	15	13	28 (6)
Other induction regimen not determined	0	1	1 (<1)

McCarthy PL, et al. *N Engl J Med*. 2012;366:1770-1781.

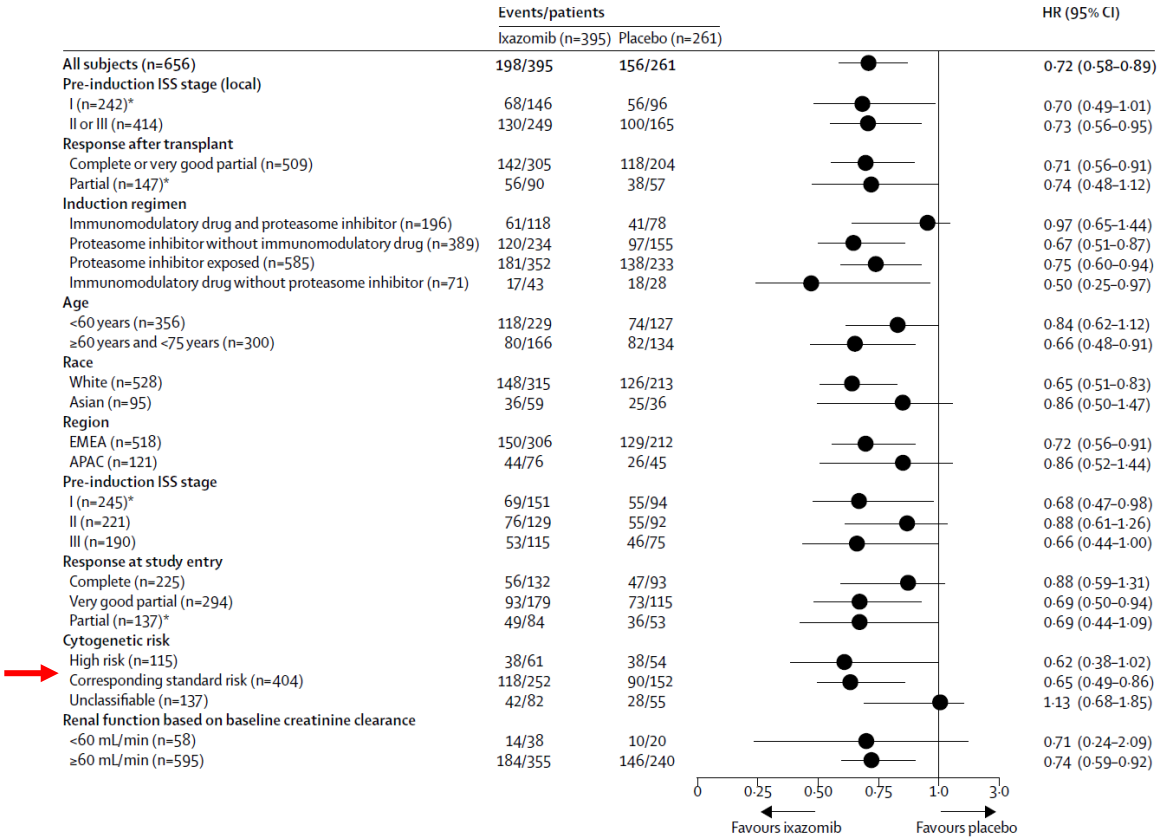
Ixazomib Maintenance



Number at risk (number censored)																
Ixazomib	395	363	340	311	279	255	238	213	187	135	93	56	35	9	3	0
	(0)	(15)	(19)	(22)	(26)	(30)	(33)	(37)	(41)	(76)	(112)	(146)	(165)	(188)	(194)	(197)
Placebo	261	238	210	195	174	153	130	117	100	69	46	32	15	3	0	0
	(0)	(10)	(18)	(20)	(22)	(25)	(27)	(27)	(29)	(50)	(68)	(78)	(91)	(102)	(105)	(105)

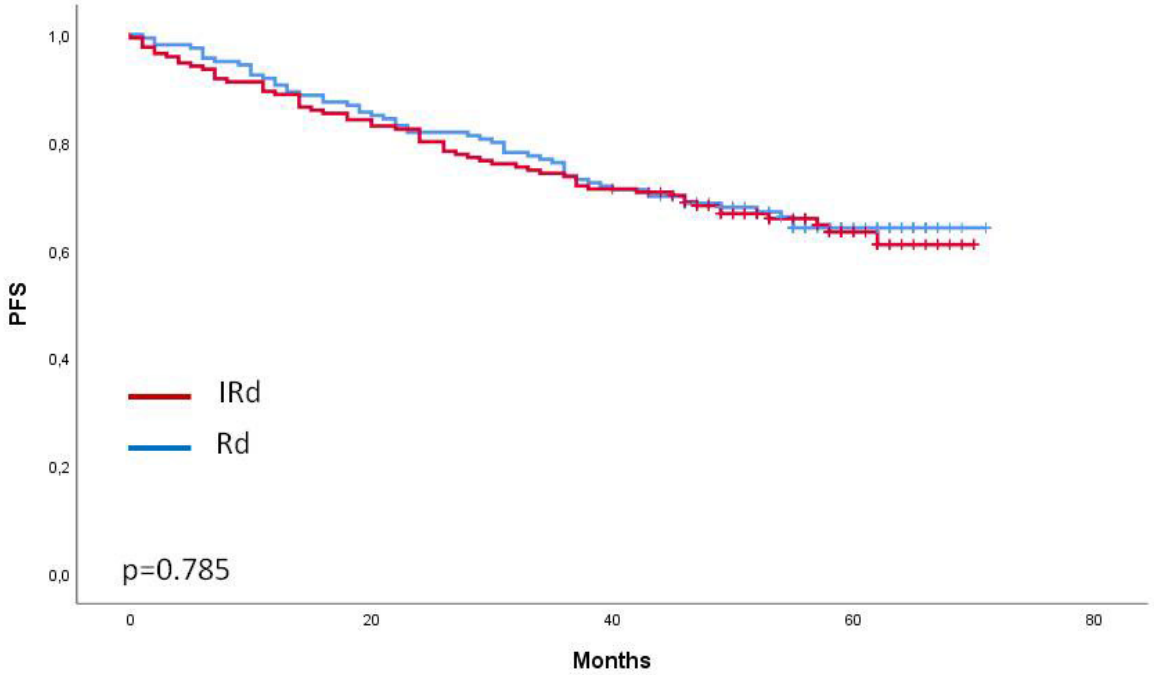
Dimopoulos MA, et al. *Lancet*. 2019;393:253-264.

Ixazomib Maintenance



Dimopoulos MA, et al. *Lancet*. 2019;393:253-264.

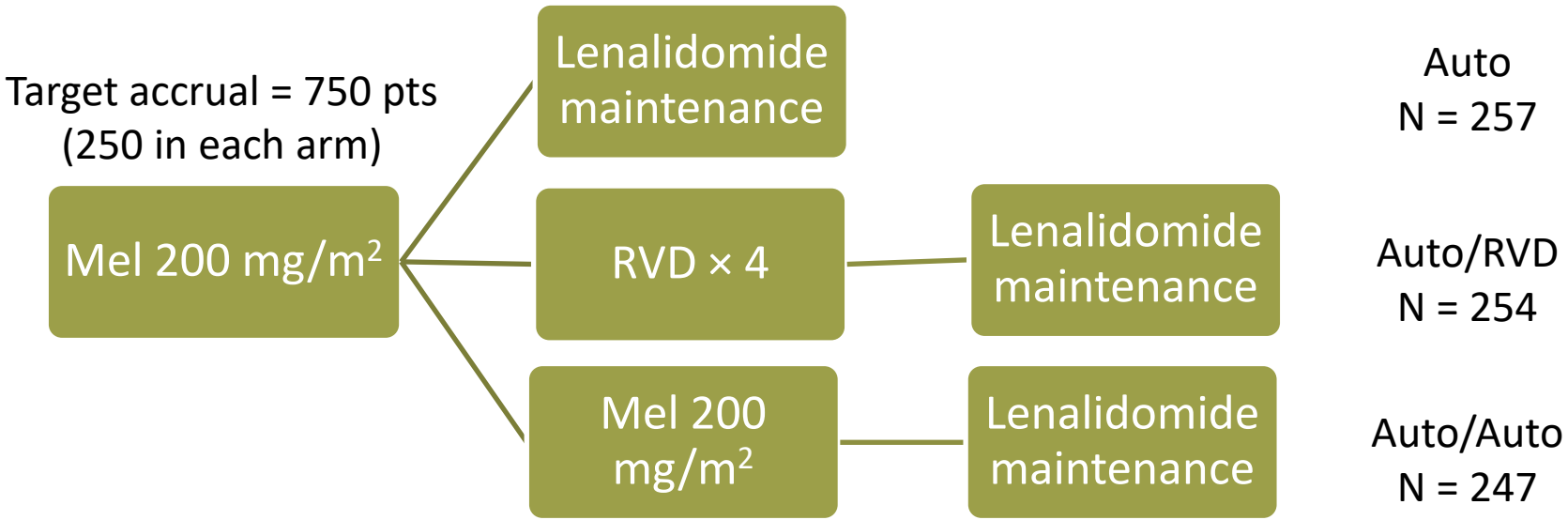
Ixazomib + Lenalidomide vs Lenalidomide as Maintenance Therapy: GEM2014MAIN Trial



Rosinol L, et al. ASH 2021. Abstract 466.

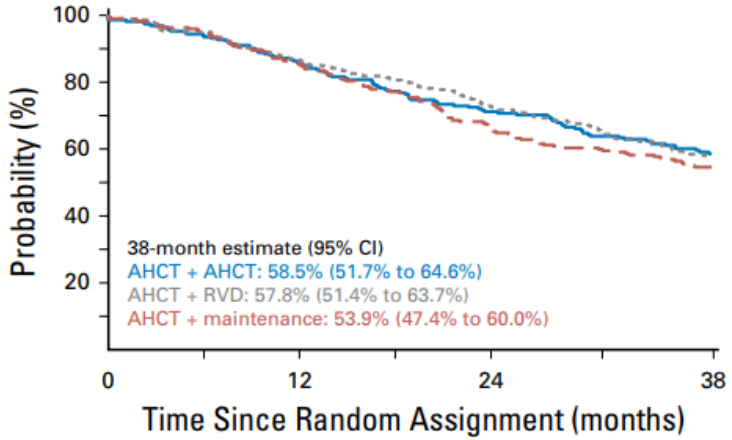
Any Role for Consolidation in the Setting of Optimal Maintenance?

STaMINA Trial – BMT CTN 0702

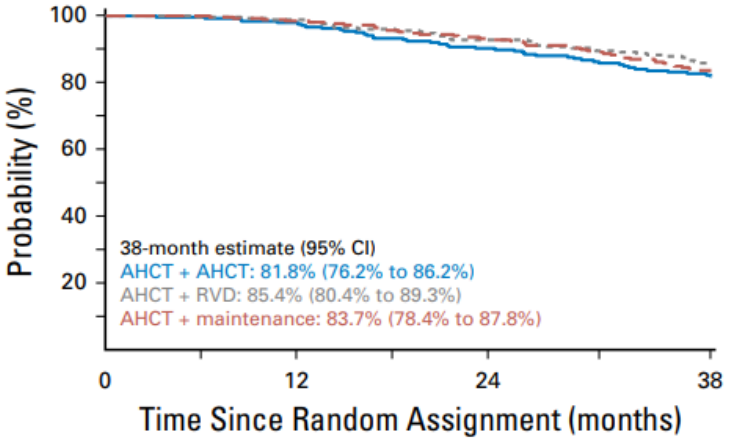


Courtesy of Prof Marcelo Pasquini.

Any Role for Consolidation in the Setting of Optimal Maintenance?



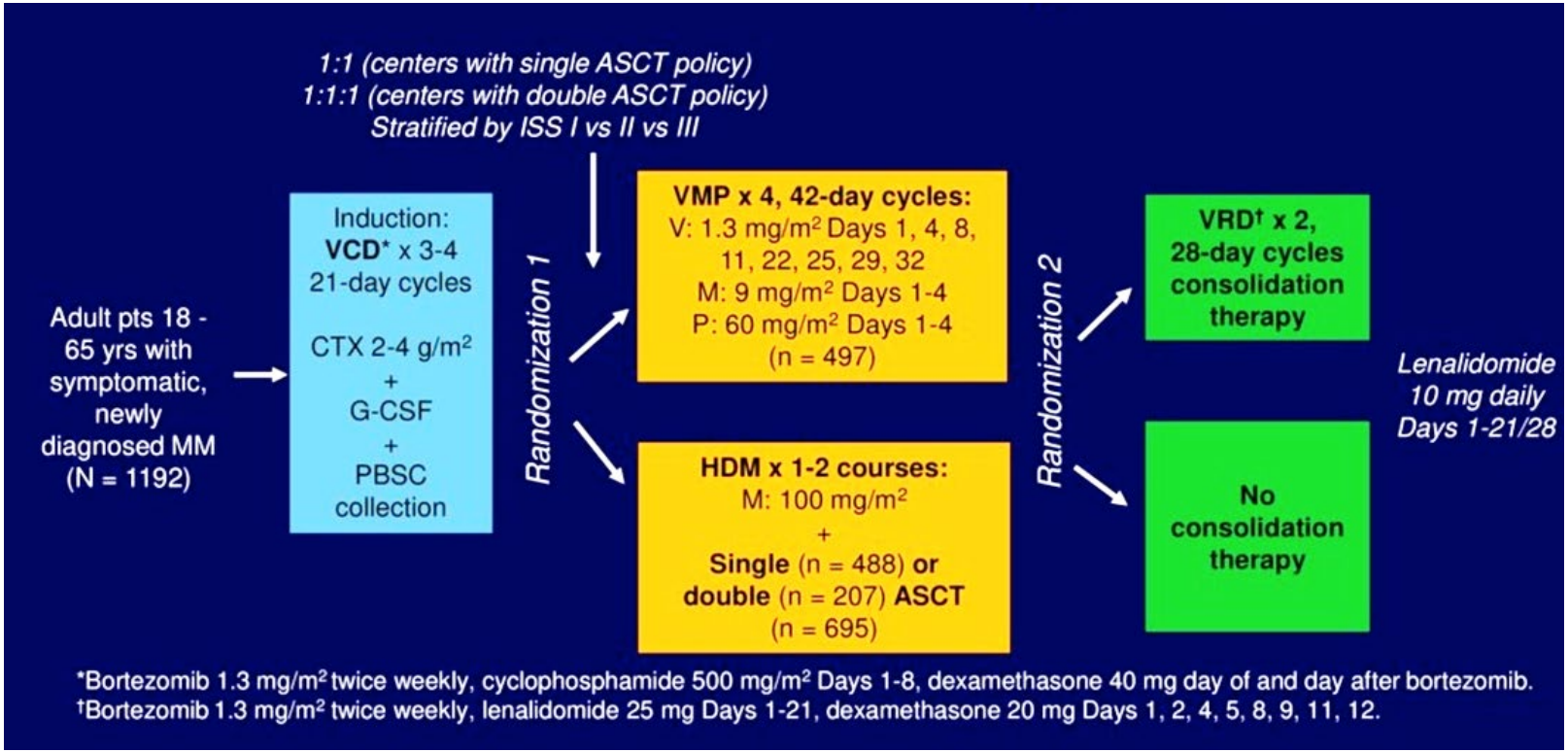
No. at risk:				
AHCT + AHCT	247	200	158	117
AHCT + RVD	254	216	179	130
AHCT + maintenance	257	214	164	111



No. at risk:				
AHCT + AHCT	247	232	208	182
AHCT + RVD	254	246	230	206
AHCT + maintenance	257	247	229	196

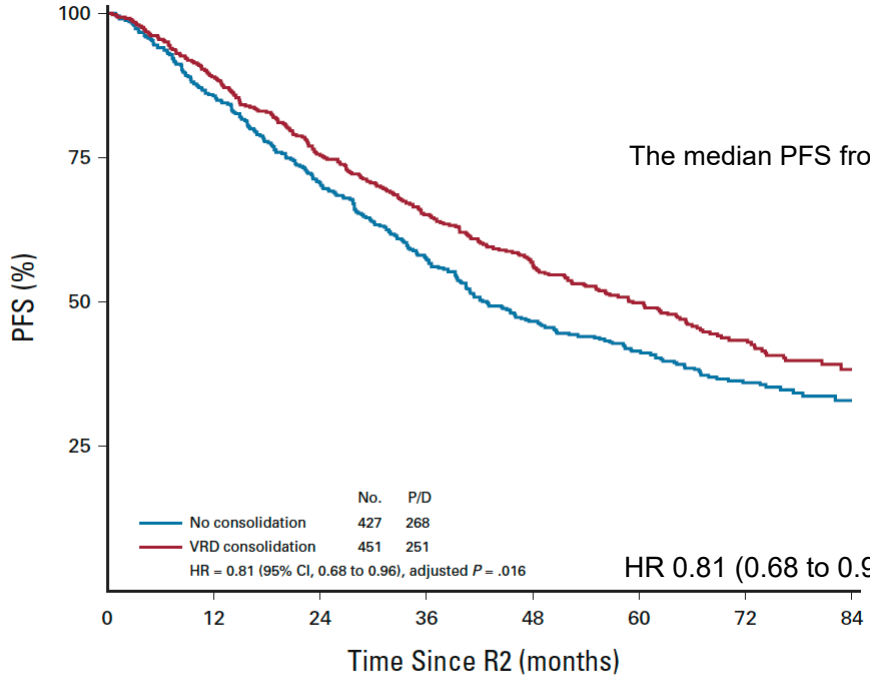
Courtesy of Prof Marcelo Pasquini.

Any Role for Consolidation in the Setting of Optimal Maintenance?



Sonneveld P, et al. *J Clin Oncol.* 2021;32:3613-3622.

Any Role for Consolidation in the Setting of Optimal Maintenance?



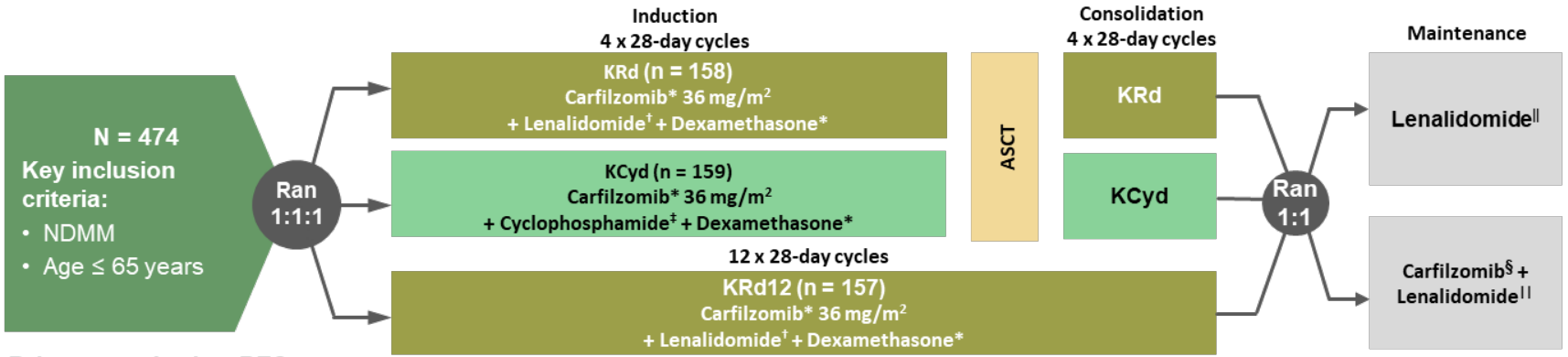
The median PFS from R2: 59.3 vs 42.9 months

HR 0.81 (0.68 to 0.96; *P* = .016)

Sonneveld P, et al. *J Clin Oncol.* 2021;32:3613-3622.

FORTE Study Update

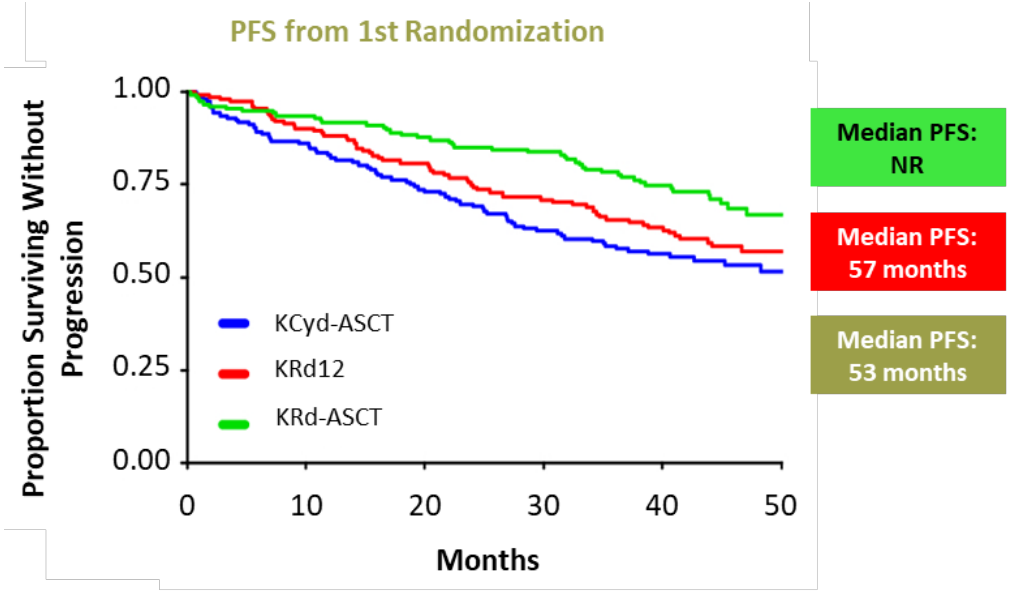
- The FORTE study previously demonstrated that KRd with or without ASCT led to deep responses and improved outcomes vs KCyd with ASCT in patients with NDMM
- This study evaluated PFS of 3 induction and 2 maintenance therapies in patients with NDMM
- The efficacy in different subgroups of patients and safety of the maintenance phase were also evaluated



Primary endpoint: PFS
Select Secondary endpoints: OS, safety

Gay F, et al. *Lancet Oncol*. 2021;22:1705-1720.

FORTE Study Update

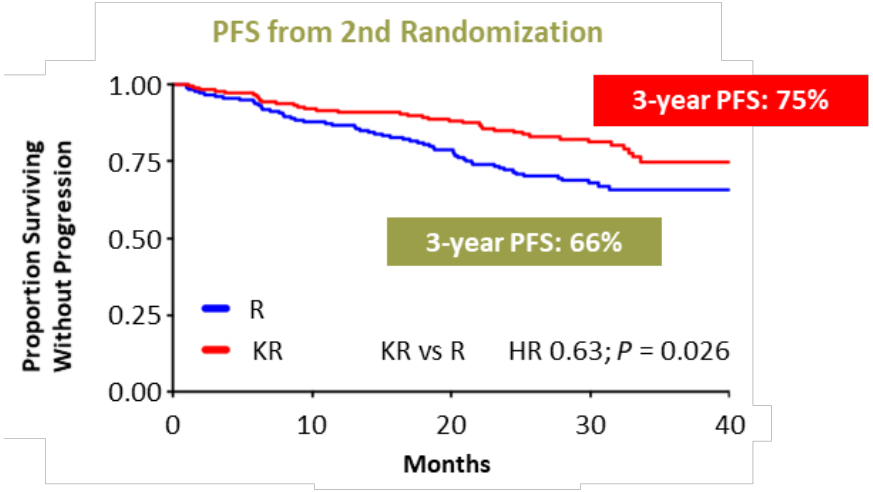


	HR	*P*
KRd-ASCT vs KCyd-ASCT	0.53	<0.001
KRd-ASCT vs KRd12	0.64	0.023
KRd12 vs KCyd-ASCT	0.82	0.262

Treatment	3-year OS, %
KRd-ASCT	90
KRd12	90
KCyd-ASCT	83

Gay F, et al. *Lancet Oncol*. 2021;22:1705-1720.

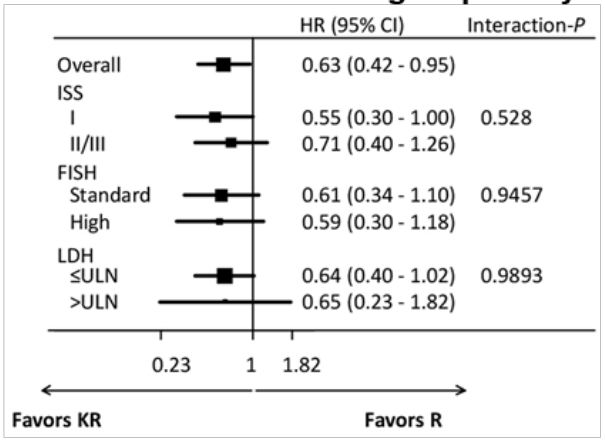
FORTE Study Update



Treatment	Patients MRD(+) That Turned MRD(–), %	*P*
R	32	0.04
KR	46	

Treatment	3-year OS, %
R	90
KR	90

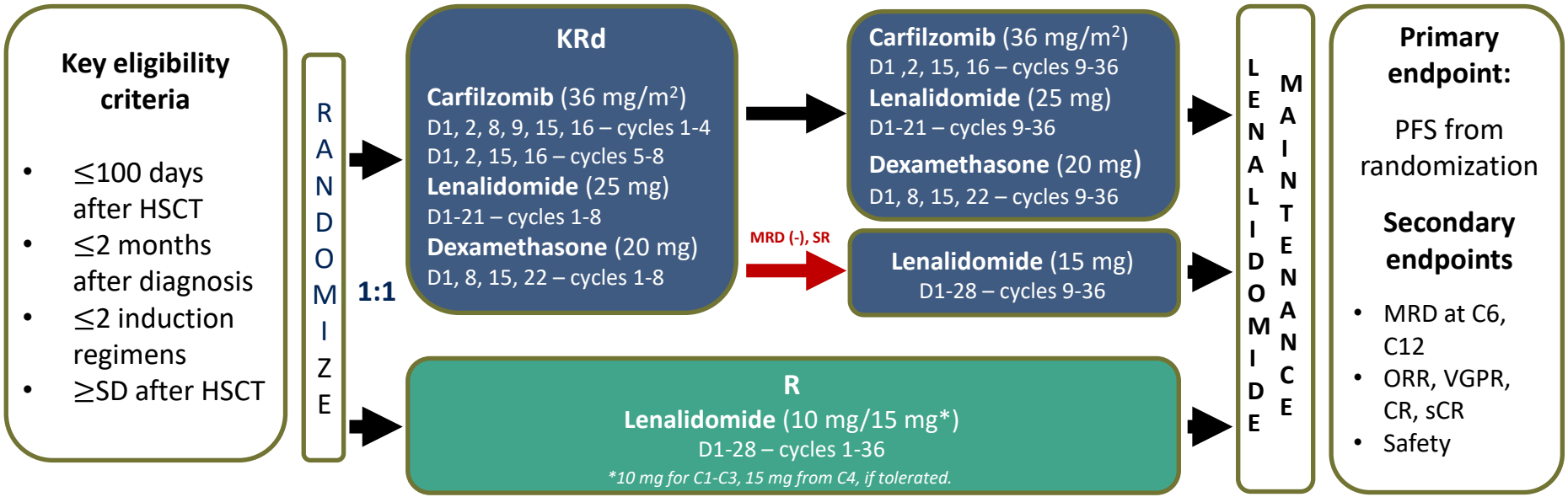
PFS from R2: KR vs R Subgroup Analyses



Gay F, et al. *Lancet Oncol*. 2021;22:1705-1720.

ATLAS: Study Design

Multicenter, randomized, open-label, phase III study



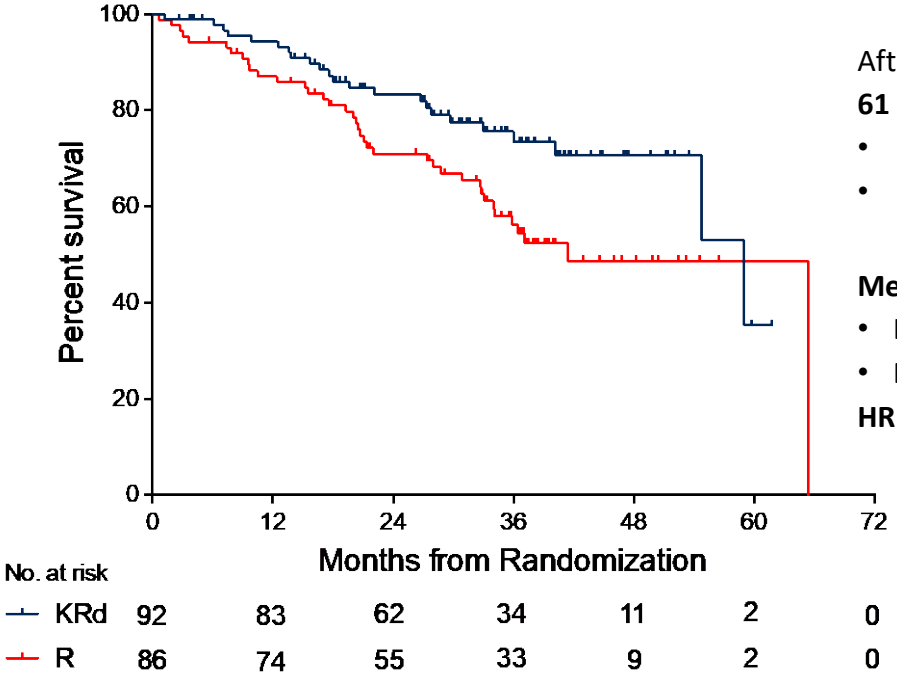
Stratification factors

- Post-transplant response (≥VGPR vs <VGPR)
- Standard (SR) vs high risk (HR) cytogenetics

KRd pts with SR cytogenetics having reached IMWG MRD negativity[1] after C6 converted to R alone after C8

Key eligibility criteria: 1. Kumar S, et al. *Lancet Oncol*. 2016;17:e328-e346.
Dytfeld D, et al. ASCO 2022. Abstract 8001.

Progression-Free Survival



After median follow-up of 33.8 months there were

61 PFS events

- **23 in the KRd arm**
- **38 in the R arm**

Median PFS

- **KRd 59.0 months** (95% CI 52.5-NR)
- **R 41.1 months** (95% CI 33.4-65.4)

HR 0.56 (95% CI 0.34-0.93); ***P* = .026**

This early analysis was at 60% of expected 105 events for primary analysis, for which the *P* value criterion for significance (*P* = .05) was not adjusted for the interim nature of the comparison. Patients will be followed until the primary analysis, which will be adjusted accordingly.

HR, hazard ratio (log rank).

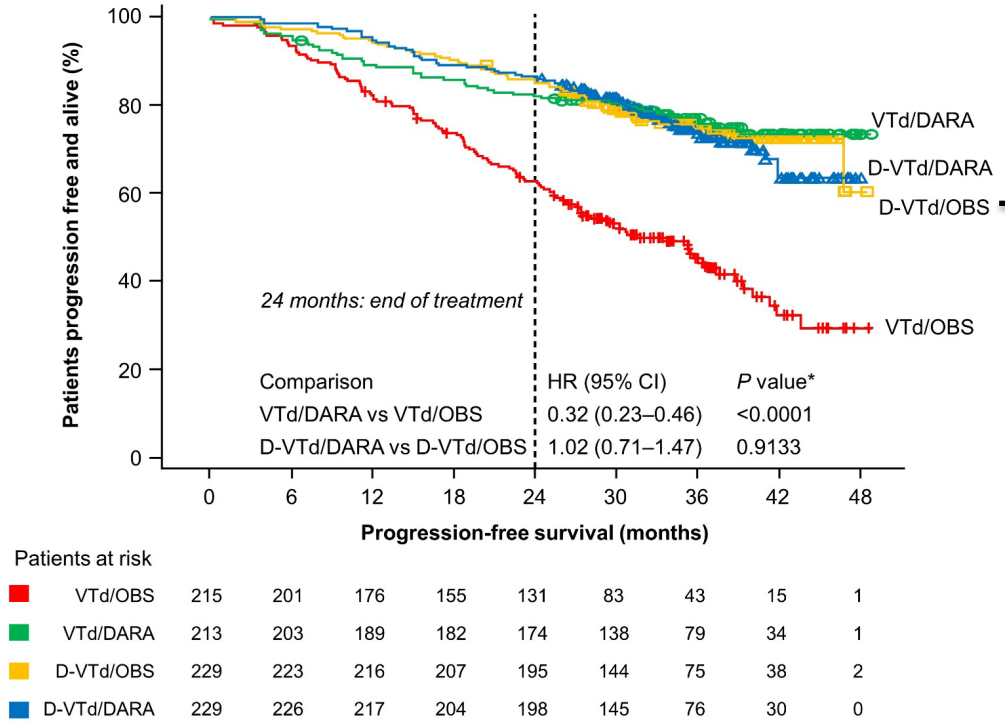
Dytfeld D, et al. ASCO 2022. Abstract 8001.

Toxicities

Adverse Events [grade 3+], n (%)	KRd n = 92	R n = 86
Hematologic Toxicities		
Neutropenia	44 (48)	51 (59)
Febrile neutropenia	4 (4)	5 (6)
Thrombocytopenia	12 (13)	6 (7)
Lymphopenia	7 (8)	2 (2)
Anemia	4 (4)	0 (0)
Toxicities of Particular Interest		
Cardiovascular	4 (4)	5 (6)
Infection	14 (15)	5 (6)
Secondary malignancy	2 (2)	2 (2)
Treatment-related death	1 (1)	0 (0)
Other Toxicities (>1% of pts)		
Elevated liver enzymes	5 (5)	0 (0)
Diarrhea	1 (1)	2 (2)
Neurologic	1 (1)	2 (2)
Rash	1 (1)	2 (2)
Dental	1 (1)	1 (1)
Flu-like symptoms	1 (1)	1 (1)
Hyperglycemia	2 (2)	0 (0)
Hypokalemia	1 (1)	1 (1)
Cataract	1 (1)	1 (1)

Dytfeld D, et al. ASCO 2022. Abstract 8001.

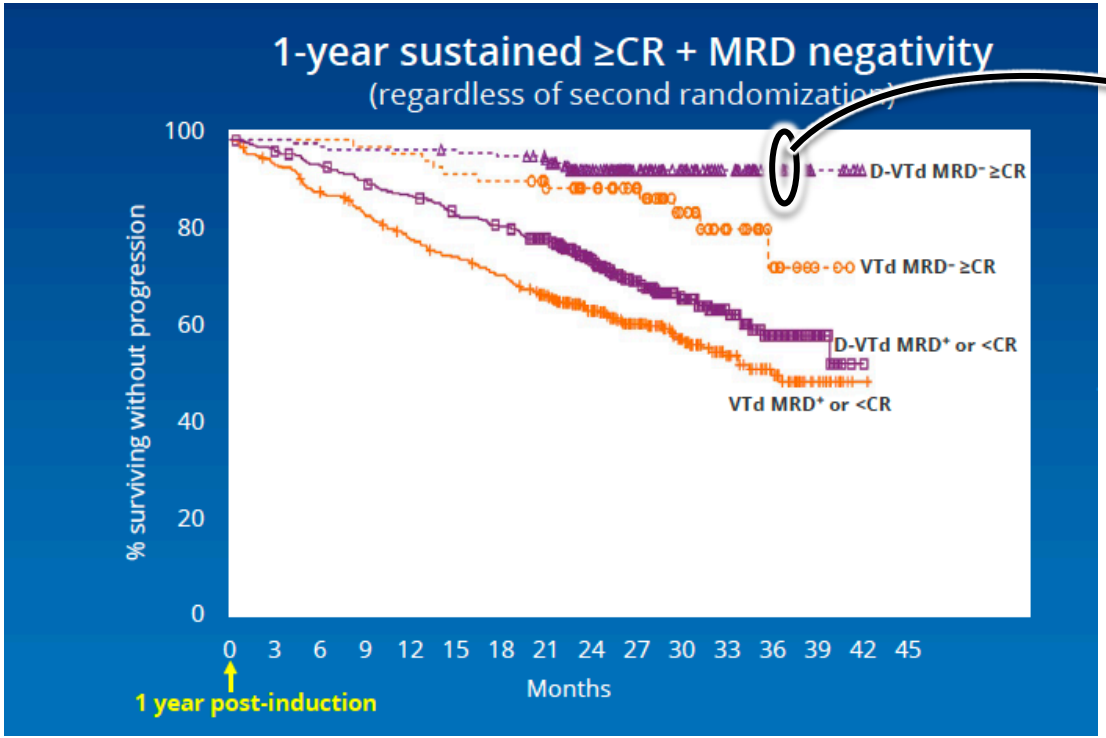
A Lesson From CASSIOPEIA Part 2: Context Matters!



Use of daratumumab in induction/consolidation appears to negate impact of daratumumab in maintenance

Moreau P, et al. ASCO 2021. Abstract 8004.

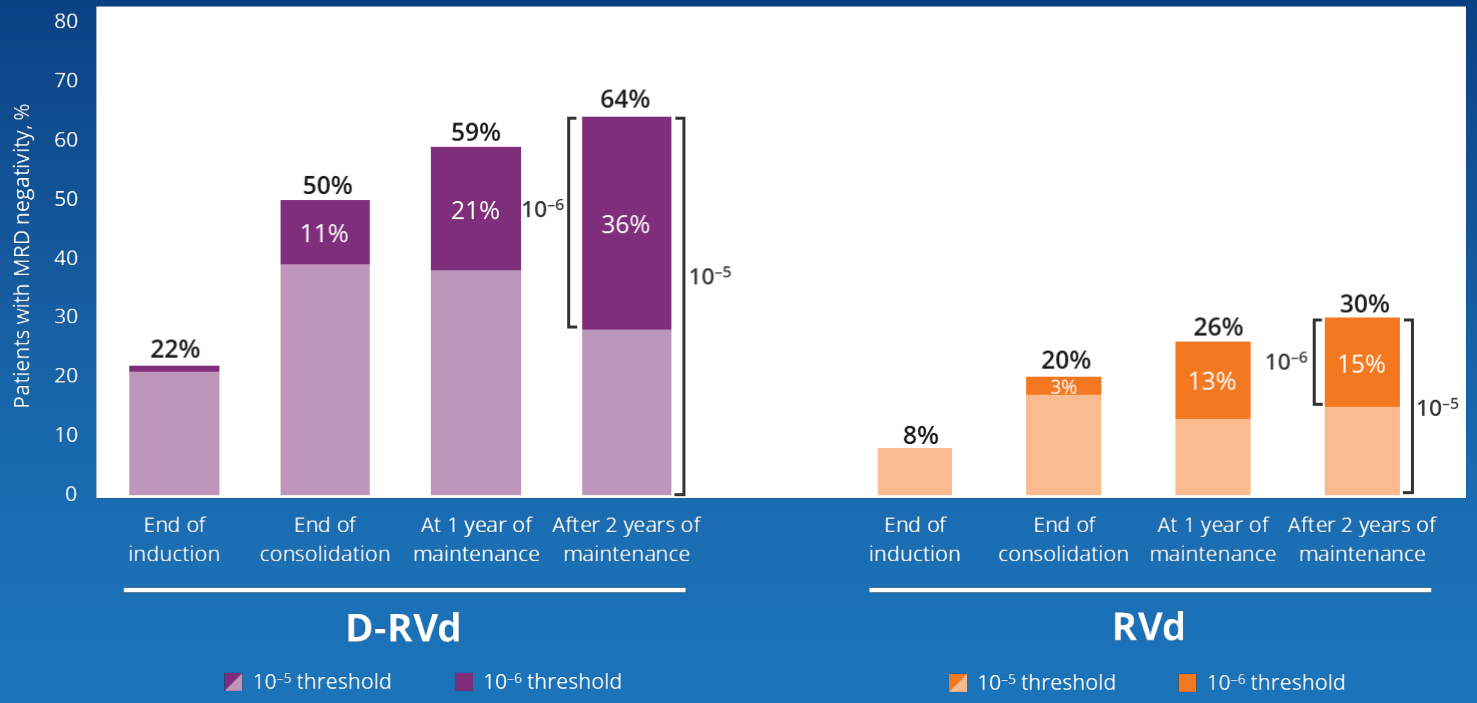
A Lesson From CASSIOPEIA Part 2: Context Matters!



- No maintenance therapy (or maintenance that did not have effect)
- Would lenalidomide (or anything) improve those results?

Avet-Loiseau H, et al. ASH 2021. Abstract 82.

GRIFFIN: MRD-Negativity[a] Rates Improved Throughout the DR Maintenance Period



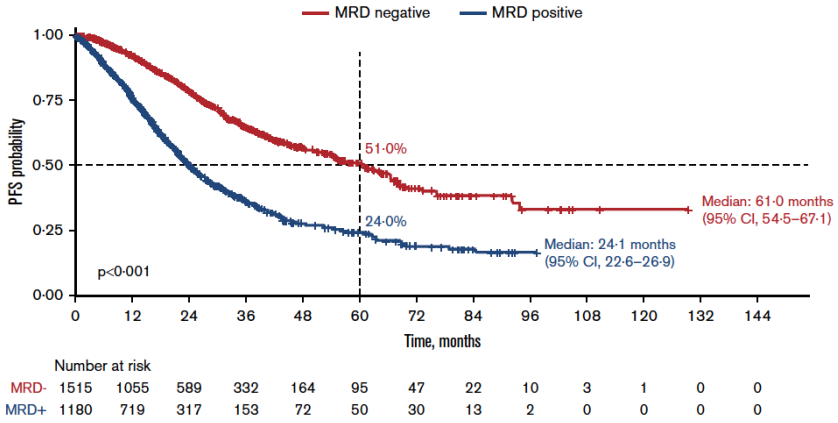
MRD-negative (10^{-5}) conversion rate

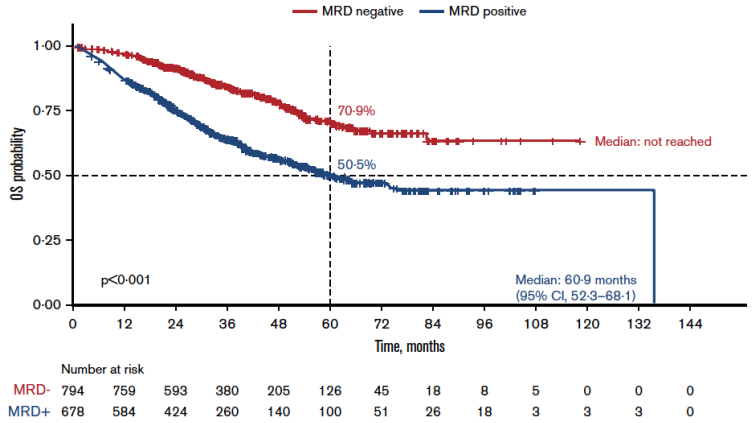
- 29% (15/52) of D-RVd patients and 12% (10/82) of RVd patients who were MRD positive at the end of consolidation became MRD negative after 2 years of DR or R maintenance

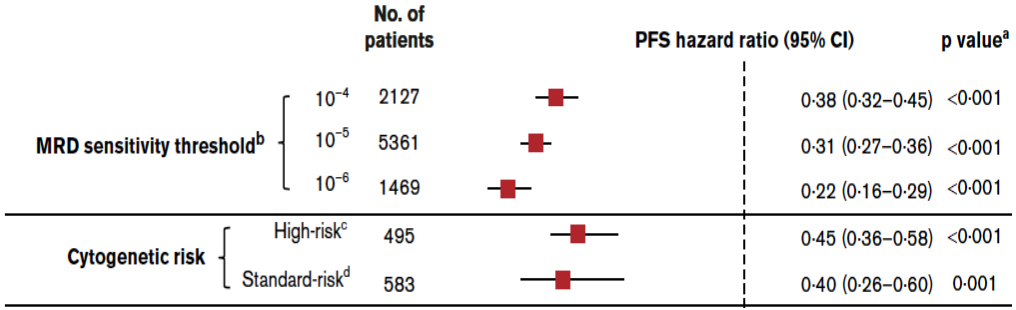
[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Bone marrow aspirates were assessed at baseline, at first evidence of suspected CR or sCR (including patients with VGPR or better and suspected DARA interference), at the end of induction and consolidation, and after 1 and 2 years of maintenance, regardless of response. Median follow-up was 38.6 months, and MRD-negativity rates are among the ITT population (D-RVd, n = 104; RVd, n = 103).

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual

MRD Strongly Predicts Outcomes



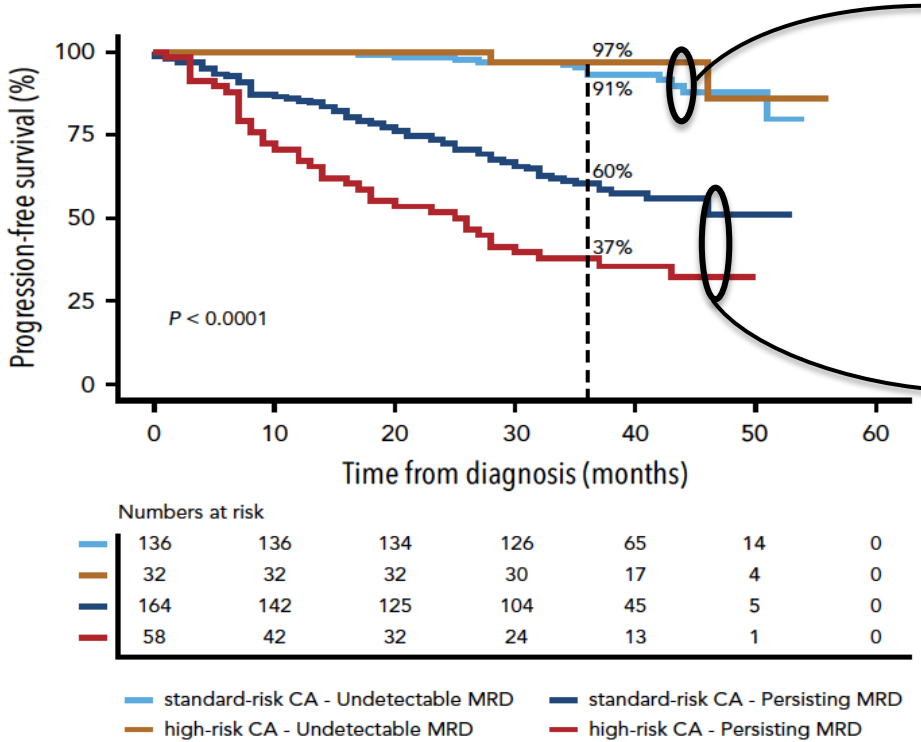




Munshi NC, et al. *Blood Adv*. 2020;4:5988-5999.

MRD May Abrogate Other Risk Factors = Optimal Dynamic Risk Assessment Tool

PETHEMA/GEM2012
(MRD <2 × 10^{-6})



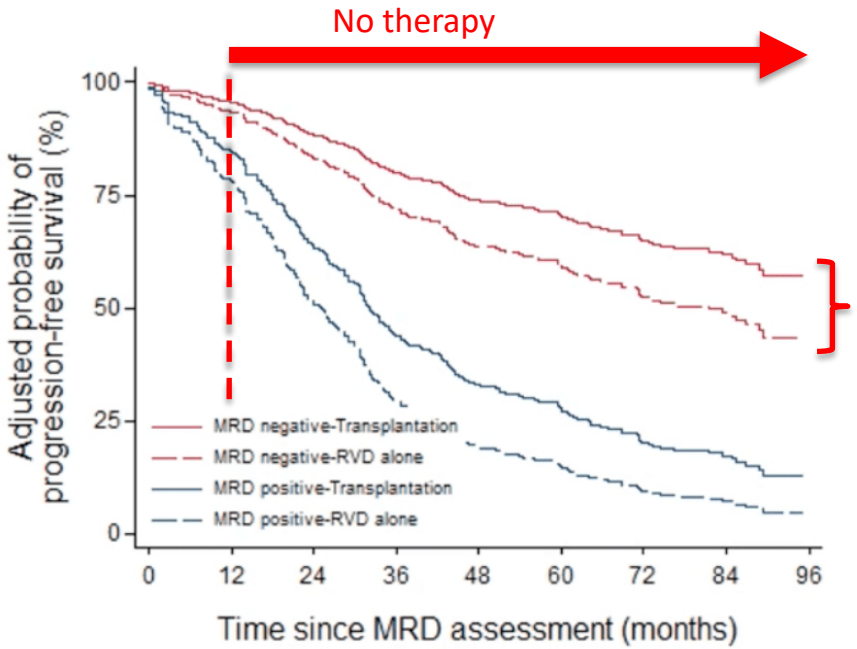
Opportunity for de-escalation

Need to employ new approaches

Goicoechea I, et al. *Blood*. 2021;137:49-60.

Patients Reaching MRD Negativity Have Excellent Prognosis Even Without Further Therapy

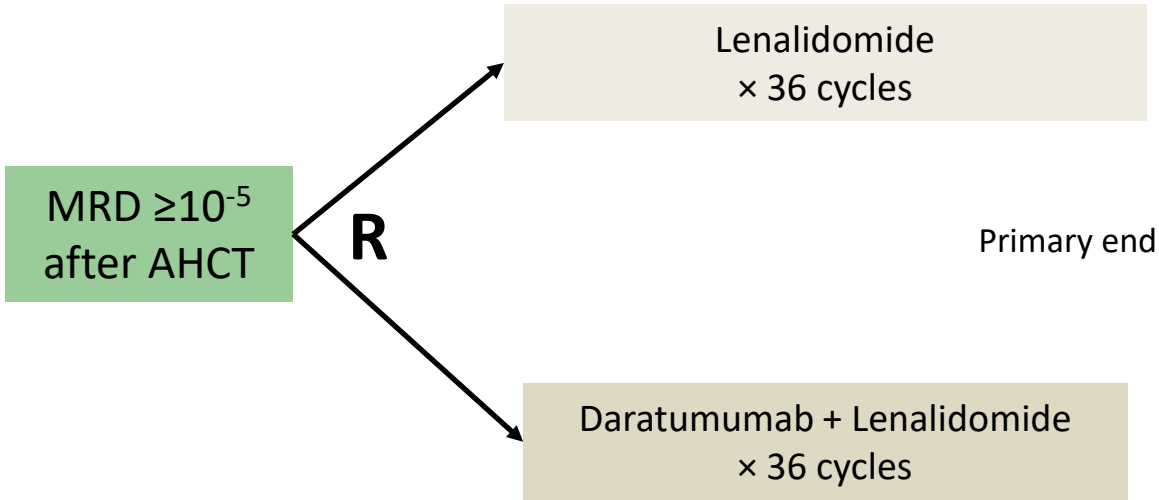
IFM 2009



Most patients have not progressed in 7 years despite no therapy

Perrot A, et al. ASH 2020. Abstract 143.

Treatment Augmentation: AURIGA Study



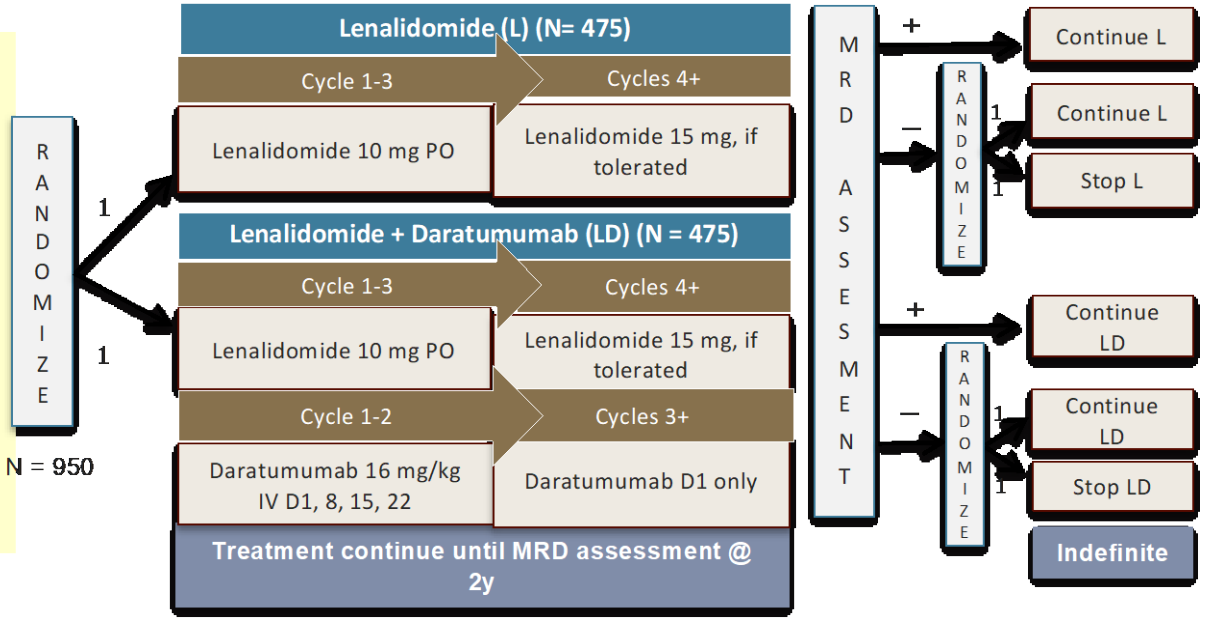
Primary endpoint: MRD conversion at 12 months

Shah N, et al. ASCO 2021. Abstract TPS8054.

Treatment Augmentation and De-escalation: DRAMMATIC Study (S1803)

Key eligibility

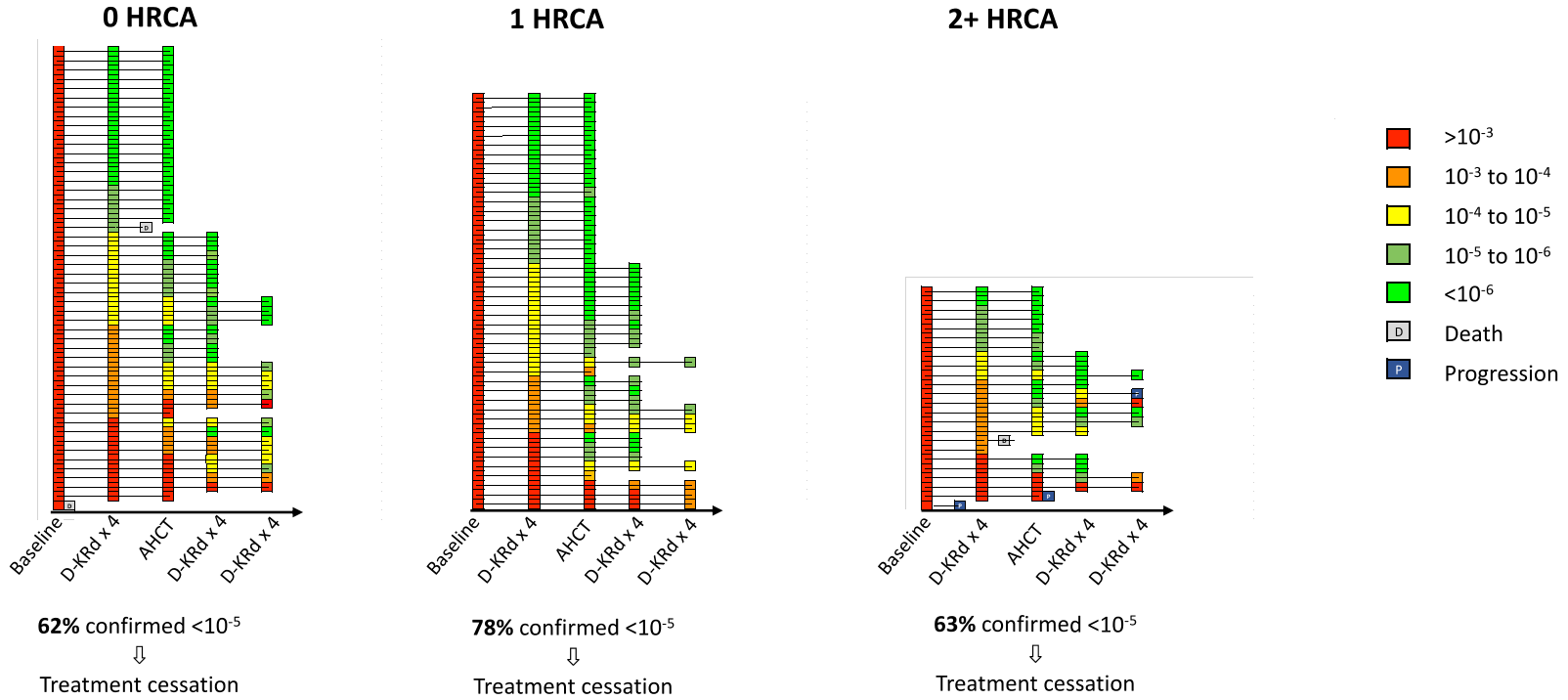
- First Registration: Study-Entry
  - Symptomatic multiple myeloma requiring systemic therapy prior to induction therapy and ASCT
  - Age 18-75
  - Zubrod Performance Status 0-2
- Second Registration: Eligibility
  - Lenalidomide REMS requirements
  - Lab normalization
  - ASCT related toxicity grade ≤ 1
- Third Registration: Second Randomization
  - Received 2 yr maintenance
  - MRD results



Krishnan A, et al. *Blood*. 2020;136(suppl 1):21-22.

Courtesy of Prof Chhabra.

Confirmed MRD Negativity Is Achievable in 71% With Response-Adapted Therapy



HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

Costa LJ, et al. *J Clin Oncol*. 2021. Online ahead of print. doi: 10.1200/JCO.21.01935

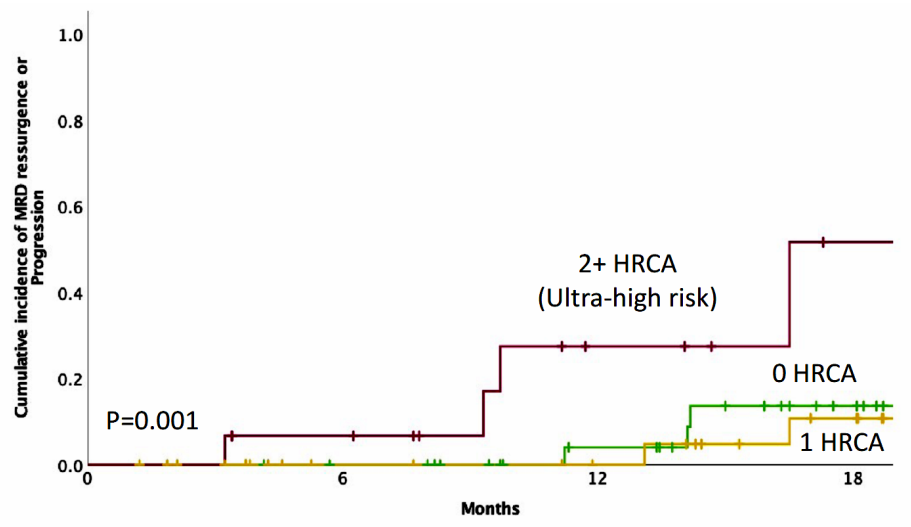
MASTER trial

MRD Surveillance as Alternative for Patients Reaching Confirmed MRD Negativity

- Risk of MRD resurgence or progression 12 months after treatment cessation
  - 0 HRCA: 4%
  - 1 HRCA: 0%
  - 2+ HRCA: 27%

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

Cumulative incidence of MRD resurgence or progression



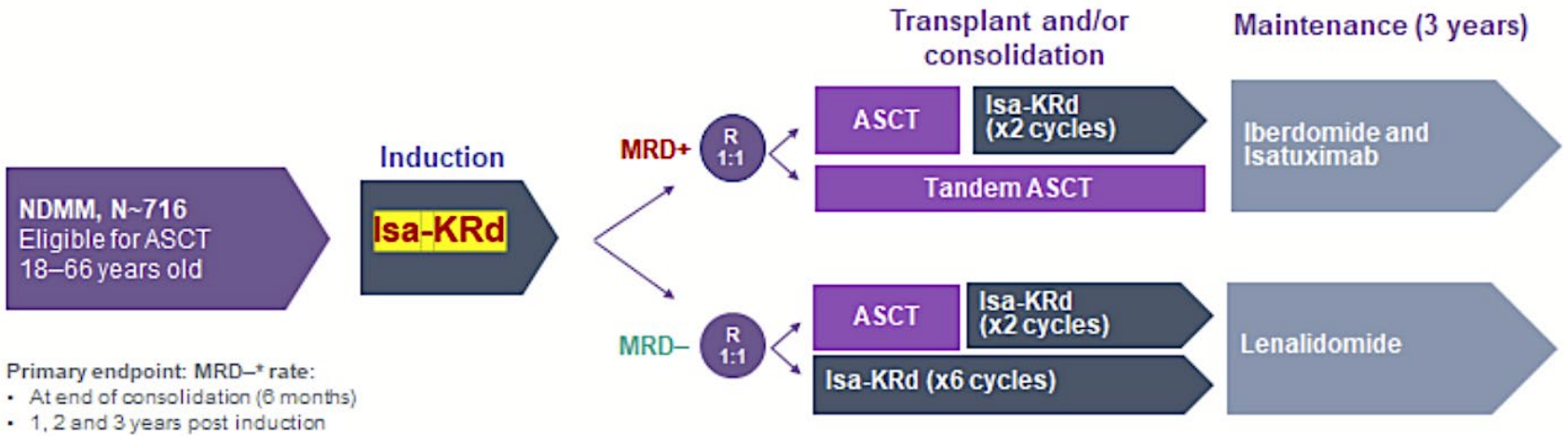
No. at risk:				
0 HRCA	33	31	23	12
1 HRCA	36	24	21	14
2+ HRCA	15	23	5	0

Costa LJ, et al. *J Clin Oncol*. 2021. Online ahead of print. doi: 10.1200/JCO.21.01935

MASTER trial

Treatment Augmentation and De-escalation: MIDAS Trial

Sponsor: Intergroupe Francophone du Myelome (IFM)
Estimated primary completion: September 2024

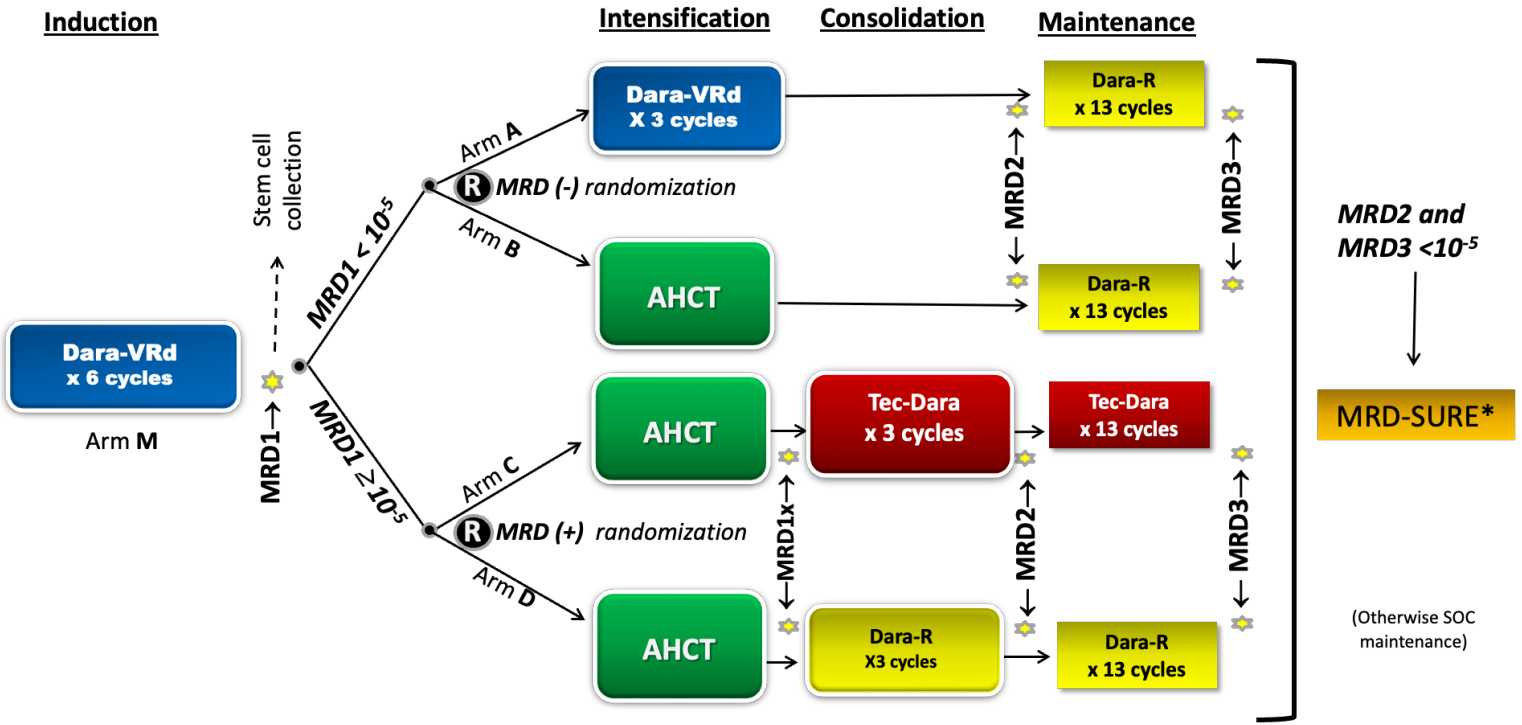


*Primary analysis will evaluate MRD (NGS, 10^{-6} threshold)

Isa-KRd is an investigational combination that has not been approved by any regulatory authority. Sanofi does not recommend the use of their products outside the approved indication. Please consult your local label before prescribing

Courtesy of Prof Mohty.

MASTER-2: Design



MRD assessment by ClonoSEQ®

*MRD-SURE – Treatment-free observation and MRD surveillance

https://clinicaltrials.gov/ct2/show/NCT05231629

Conclusions

- Lenalidomide is the legacy maintenance therapy post-AHCT therapy
- Impact of post-AHCT therapy is context-specific
- Role of PI in consolidation/maintenance to improve upon lenalidomide is controversial
  - Ixazomib: No
  - Bortezomib: Maybe
  - Carfilzomib: Yes
- Anti-CD38 MoAb
  - Highly impactful in anti-CD38–naive disease
  - Not compared with lenalidomide
  - Unclear role in addition to lenalidomide and in patients with prior anti-CD38 exposure
- Achievement of MRD negativity modulates risk of progression/death, informs risk/benefit considerations
- Prospective validation of MRD response-adapted strategies is underway

Question for the Audience

What statement best describe the evidence for maintenance therapy in MM?

a) Lenalidomide, when applied post AHCT, prolongs PFS but not OS vs observation/placebo

b) Ixazomib + lenalidomide, when applied post AHCT, prolongs PFS vs lenalidomide

c) Carfilzomib + lenalidomide maintenance yield better PFS than lenalidomide alone

d) Daratumumab has an established role as maintenance therapy in patients treated with quadruplet induction regimens

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Treatment Considerations for Newly Diagnosed Transplant-Ineligible Patients

Keith Stewart, MBChB, MBA

APTITUDE HEALTH®

Which of the following has not shown significant improvement in PFS?

A. VRd vs Rd

B. IRd vs Rd

C. Dara-Rd vs Rd

D. VMP-Dara vs VMP

E. Rd vs MPR

When using Rd as induction in an elderly patient, which of the following statements is true?

A. Full-dose lenalidomide 25 mg continuous provides the best outcomes

B. Dexamethasone 20 mg weekly until progression provides optimal results

C. Fixed-duration therapy is recommended to avoid second primary malignancies

D. Lenalidomide 10 mg is recommended after fixed-duration lenalidomide and dexamethasone

E. Lenalidomide should not be used if creatinine clearance is <45

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Interactive Discussion and Q&A: Regional Challenges of Multiple Myeloma Diagnosis and Treatment

APTITUDE HEALTH®

Interactive Discussion

- Do you assess MRD for some of your patients?
- How long do you give maintenance?
- What are your solutions to overcome drug access limitations?
- What developments would you like to see in Latin America for MM patients?

Global Multiple Myeloma Academy

Debate:
Smoldering Myeloma – To Treat or Not to Treat?

Sagar Lonial (yes) vs Keith Stewart (no)

APTITUDE HEALTH®

Pre-debate Question for the Audience

In your opinion, is smoldering myeloma treatable?

a) Yes

b) No

Global Multiple Myeloma Academy

Debate:
Is Smoldering Myeloma Treatable or Not?

Yes – Sagar Lonial, MD, FACP

APTITUDE HEALTH®

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

EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Early Therapy for SMM: YES

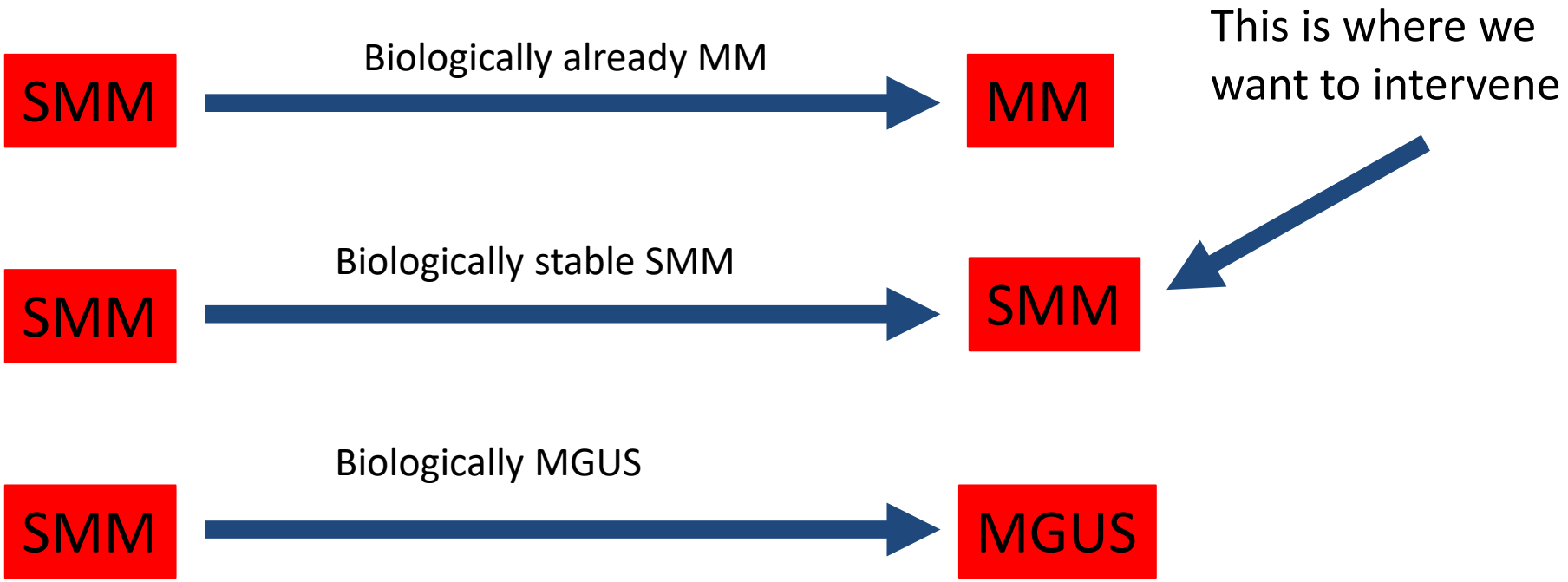
Sagar Lonial, MD
Professor and Chair
Department of Hematology and Medical Oncology
Anne and Bernard Gray Professor in Cancer
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

Question/Challenge

- 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 it is given for 2 years
- The treatment is oral and is generally well tolerated

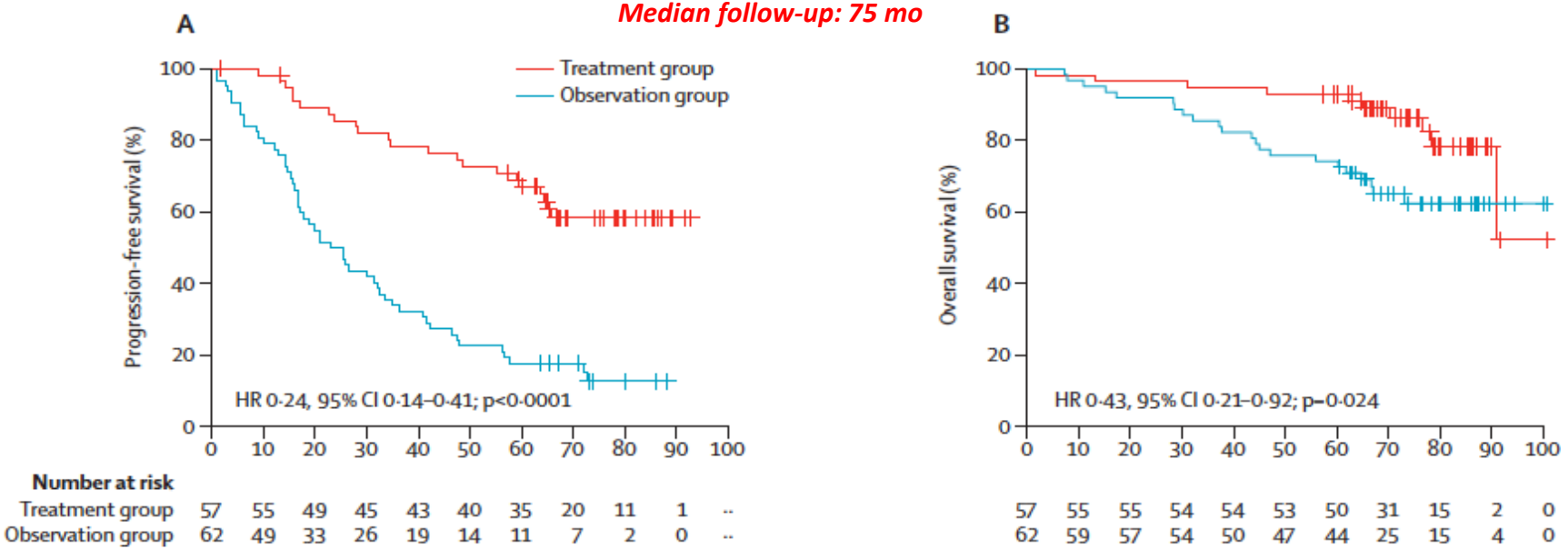
- Would you offer this approach to your patient?

Types of SMM


SMM
Biologically already MM
MM
This is where we want to intervene
SMM
Biologically stable SMM
SMM
SMM
Biologically MGUS
MGUS

QuiRedex Phase III Trial: Len + Dex vs No Treatment in High-Risk SMM (n = 119)

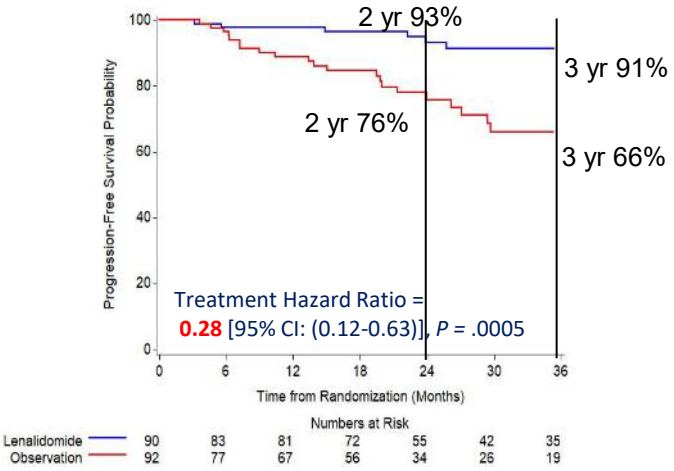
Median follow-up: 75 mo



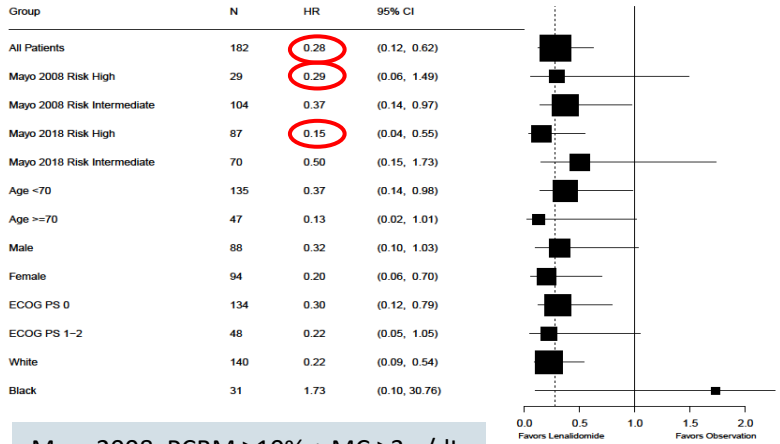
Early treatment with Rd significantly delayed the TTP to myeloma with a benefit in OS

Mateos MV, et al. *N Engl J Med*. 2013;369:438-447; Mateos MV, et al. *Lancet Oncol*. 2016;17:1127-1136.

E3A06: Len vs Observation in Patients With Asymptomatic High-Risk Smoldering Multiple Myeloma (N = 182)



Criteria: PCBM ≥10% and sFLC ratio >8 or <0.125



Group	N	HR	95% CI
All Patients	182	0.28	(0.12, 0.62)
Mayo 2008 Risk High	29	0.29	(0.06, 1.49)
Mayo 2008 Risk Intermediate	104	0.37	(0.14, 0.97)
Mayo 2018 Risk High	87	0.15	(0.04, 0.55)
Mayo 2018 Risk Intermediate	70	0.50	(0.15, 1.73)
Age <70	135	0.37	(0.14, 0.98)
Age >=70	47	0.13	(0.02, 1.01)
Male	88	0.32	(0.10, 1.03)
Female	94	0.20	(0.06, 0.70)
ECOG PS 0	134	0.30	(0.12, 0.79)
ECOG PS 1–2	48	0.22	(0.05, 1.05)
White	140	0.22	(0.09, 0.54)
Black	31	1.73	(0.10, 30.76)

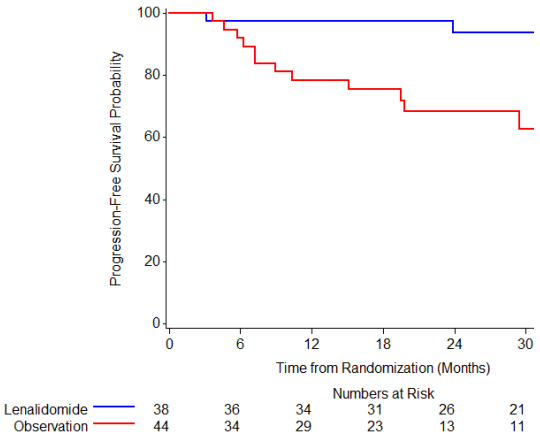
Mayo2008: PCBM ≥10% + MC ≥3 g/dL
Mayo2018: 2/20/20

- **N = 182, intermediate/high-risk SMM (BMPC ≥10% in aberrant [FLC] ratio [<0.26 or >1.65])**
- **1:1 randomization lenalidomide 25 mg day 1 to 21 in 28-day cycle vs observation**
- **Median FU 35 months, median time on Len 23 cycles, Len discontinued in 51% pt**

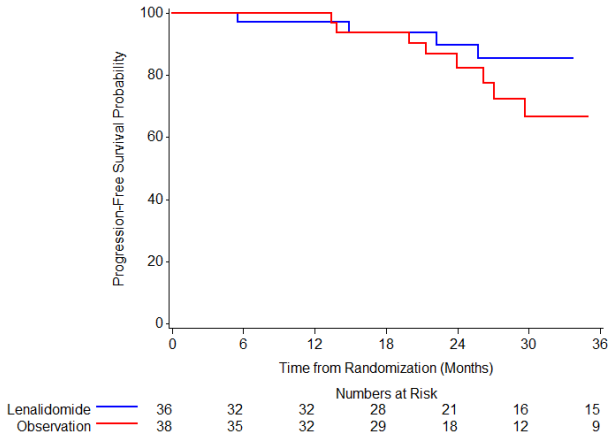
Early treatment with Len significantly prevented progression to MM, especially in the high-risk subgroup

Lonial S, et al. ASCO 2019. Oral presentation; Lonial S, et al. ASCP 2019. Abstract E3A06.

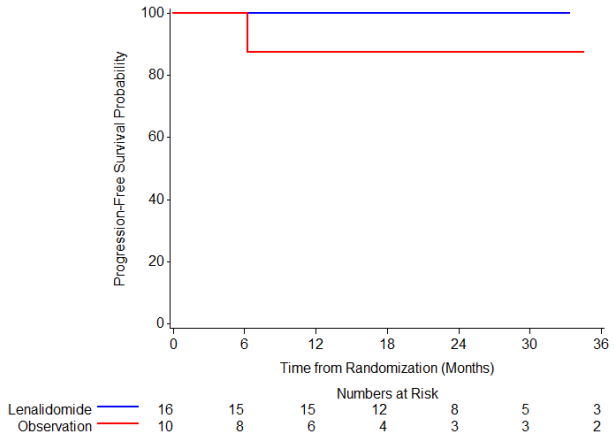
Phase III PFS by Mayo 2018 Risk Criteria



High Risk



Intermediate Risk



Low Risk

EMORY WINSHIP CANCER INSTITUTE

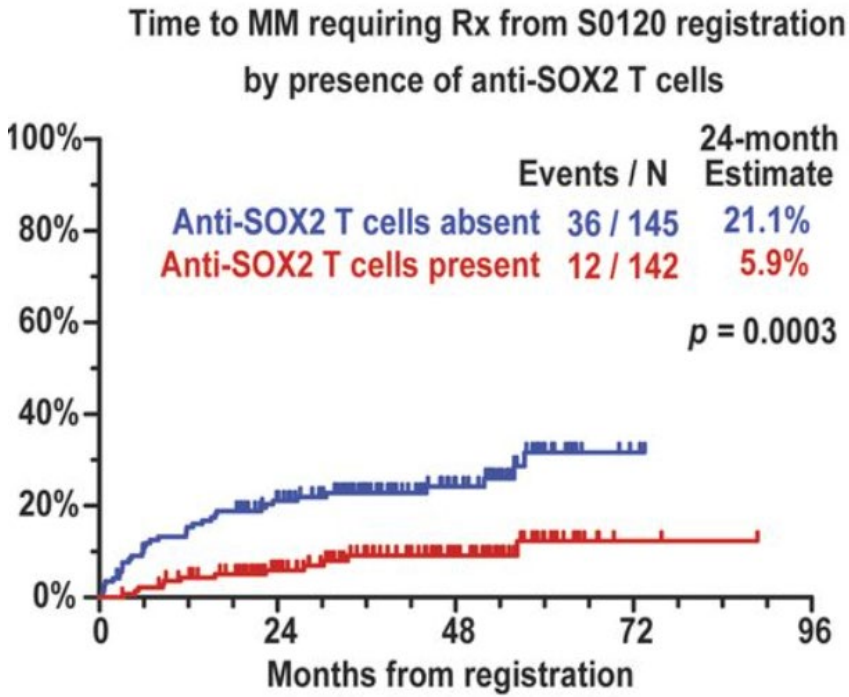
Lonial S, et al. *J Clin Oncol*. 2019;38:1126-1137.

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

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

Myeloma Is Not All About Genetics; Immune Regulation Is Also Key to Control



Dhodapkar MV, et al. *Blood.* 2015;126:2475-2478.

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

- **It is time to move toward early intervention for some patients**

Thanks to:

Jonathan Kaufman
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Mala Shanmugam
Larry Boise
Cathy Sharp

Patients and Families

sloni01@emory.edu

and the Clinical Research Team

IMS

Golfers Against Cancer
T.J. Martell Foundation

and many others who are part of the B-Cell Team

Global Multiple Myeloma Academy

Debate:
Is Smoldering Myeloma Treatable or Not?

No – Keith Stewart, MBChB, MBA

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SMOLDERING MM

Early therapies in SMM

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., Alt ol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., Edua varría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., an Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

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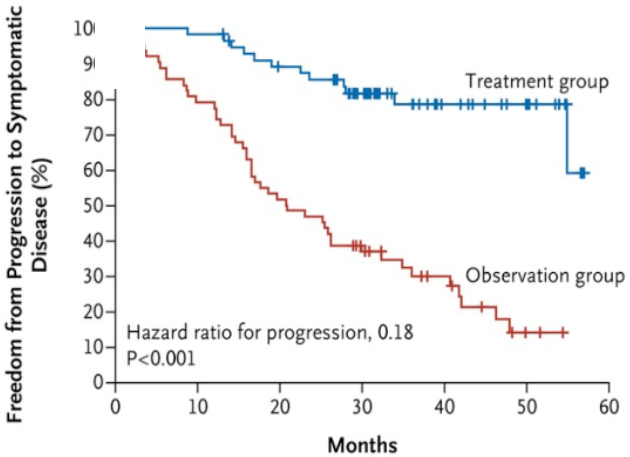
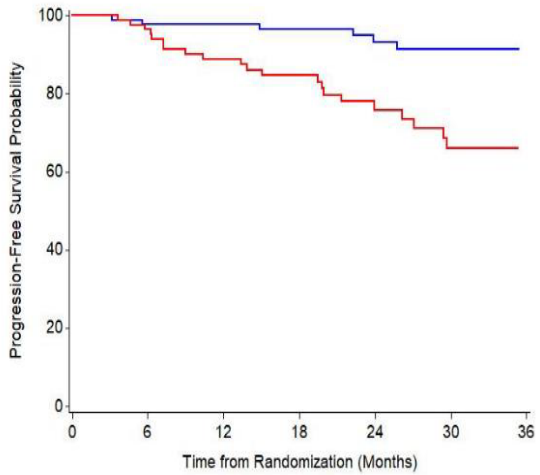


No. at Risk							
Treatment group	57	57	48	38	20	14	0
Observation group	62	49	32	21	11	3	0

rapid communication

Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

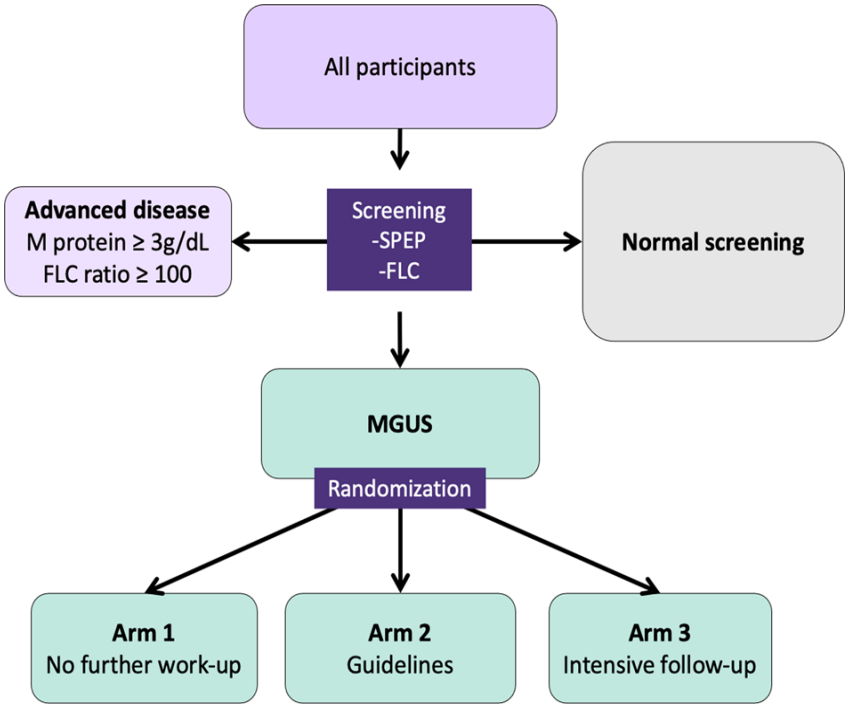
Sagar Lonial, MD[1]; Susanna Jacobus, MSc[2]; Rafael Fonseca, MD[3]; Matthias Weiss, MD[4]; Shaji Kumar, MD[5]; Robert Z. Orlowski, MD, PhD[6]; Jonathan L. Kaufman, MD[1]; Abdulraheem M. Yacoub, MD[7]; Francis K. Buadi, MD[5]; Timothy O'Brien, MD[8]; Jeffrey V. Matous, MD[9]; Daniel M. Anderson, MD[10]; Robert V. Emmons, MD[11]; Anuj Mahindra, MD[12]; Lynne I. Wagner, PhD[13]; Madhav V. Dhodapkar, MBBS[1]; and S. Vincent Rajkumar, MD[5]



Numbers at Risk							
Lenalidomide	90	83	81	72	55	42	35
Observation	92	77	67	56	34	26	19

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

The iStopMM study: >75,000 Icelanders



Medical history and clinical examination.
Blood work-up in all individuals.

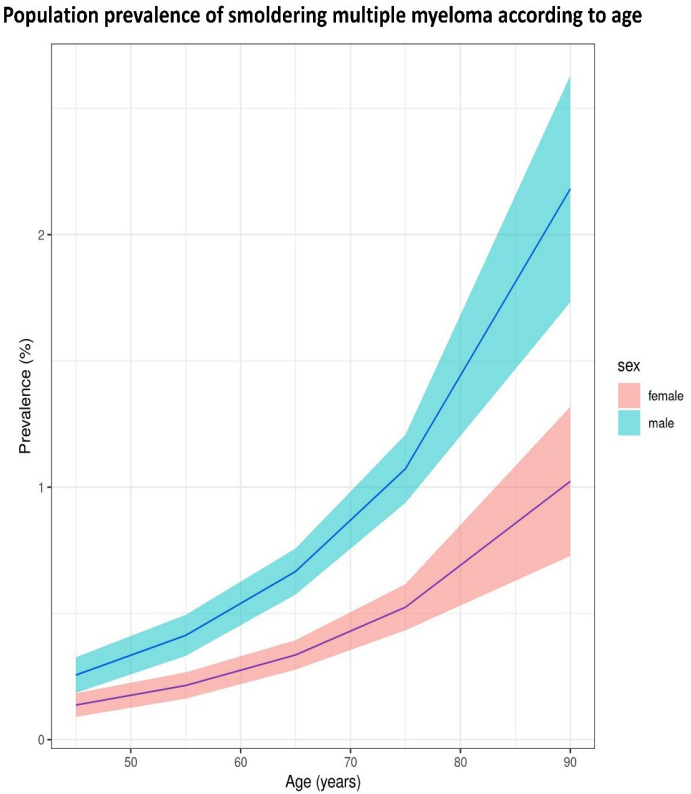
Ýr Sigurbergsdóttir A, et al. ASH 2021. Abstract 1618.

Prevalence of SMM

- 1,279 individuals were randomized to arm 3
- Bone marrow sampling performed in 970
- Of those, 105 (10.8%) were diagnosed with SMM

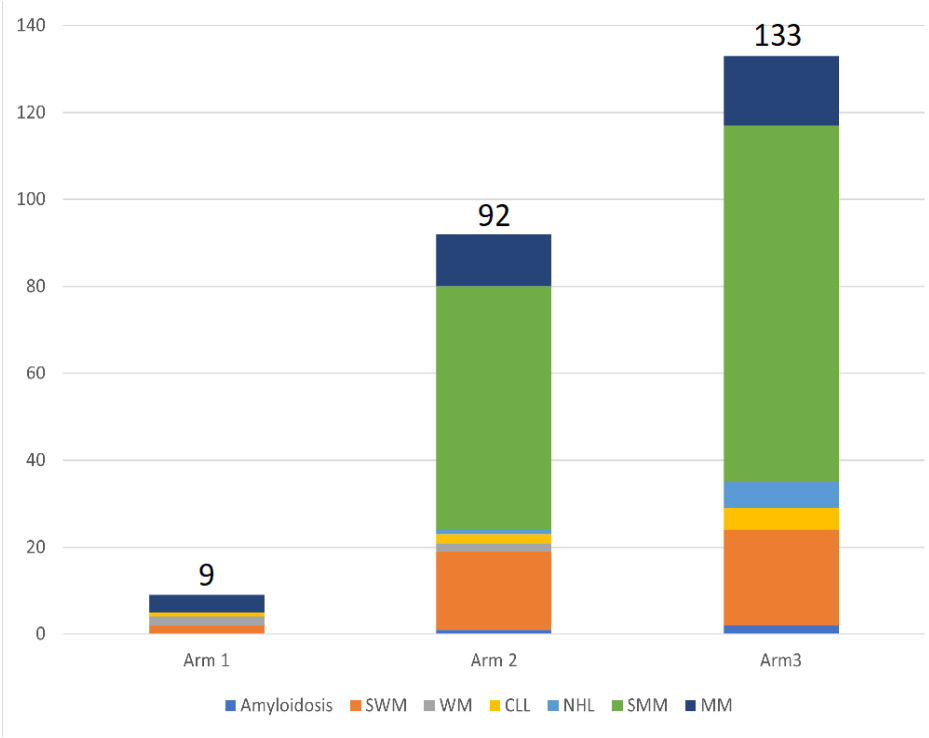
- The **prevalence of SMM** in the total population was estimated to be **0.53% (95% CI: 0.49-0.57%)** in individuals 40 years of age or older

- Prevalence in men 0.70% (95% CI: 0.64-0.75%)
- Prevalence in women 0.37% (95% CI: 0.32-0.41%)



Thorsteinsdottir S, et al. ASH 2021. Abstract 151.

Impact of screening, work-up, follow-up



Outcome	Arm 1	Arm 2	Arm 3	p-value
Any LP disorder	9	92	133	p<0.001
Amyloidosis	0	1	2	NS
SWM	2	18	22	p<0.001
WM	2	2	0	p=0.48
CLL	1	2	5	p=0.21
NHL	0	1	6	p=0.06
SMM	0	56	82	p<0.001
MM	4	12	16	p<0.001

Based on this

- 0.5% of people over age 40 have SMM (1 in 200)
- One-third have intermediate- to high-risk SMM (1 in 600)
- 0.17% of the population >40 would need treatment
- ~145 million people in USA are over age 40
- ~ 246,000 people have SMM
- If only high-risk treated = 0.17% or ~108,750 people

ARTICLE Open Access

Detection and prevalence of monoclonal gammopathy of undetermined significance: a study utilizing mass spectrometry-based monoclonal immunoglobulin rapid accurate mass measurement

David Murray[1], Shaji K. Kumar[2], Robert A. Kyle[2], Angela Dispenzieri[2], Surendra Dasari[3], Dirk R. Larson[4], Celine Vachon[3], James R. Cerhan[3] and S. Vincent Rajkumar[2]

Table 2 Estimated prevalence of monoclonal gammopathy of undetermined significance (MGUS).

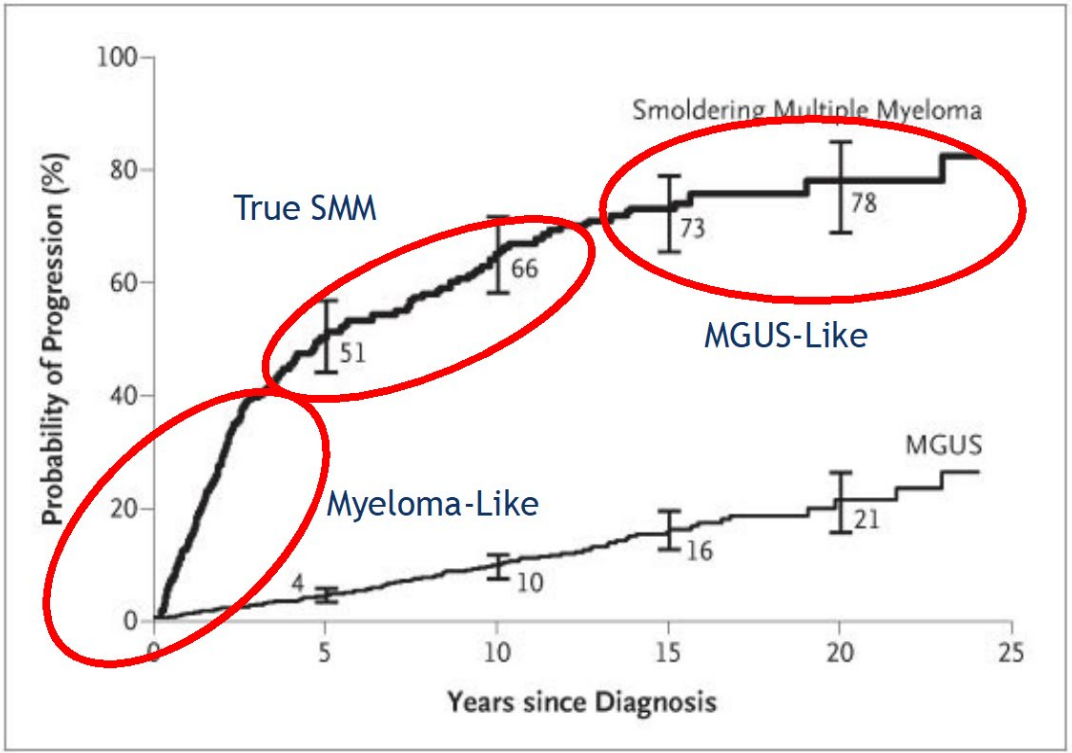
Method	Estimated prevalence
Serum protein electrophoresis, and confirmation by immunofixation if any abnormality detected	3.5%
Serum protein electrophoresis plus serum-free light-chain assay	4.2%
Serum immunofixation plus serum-free light-chain assay	4.4%
miRAMM plus serum-free light-chain assay	5.1%[a]

miRAMM monoclonal immunoglobulin rapid accurate mass measurement
[a]This estimate represents the lower limit of the estimated prevalence of MGUS

Murray et al. *Blood Cancer Journal* (2019)9:102
https://doi.org/10.1038/s41408-019-0263-z

Murray D, et al. *Blood Cancer J*. 2019;9:102.

Smoldering MM is a heterogeneous disease



So . . .

25% no myeloma for 20 years

50% no treatment for 5 years

High risk 50% no treatment for 2 years

Murray D, et al. *Blood Cancer J*. 2019;9:102.

Second primary malignancies

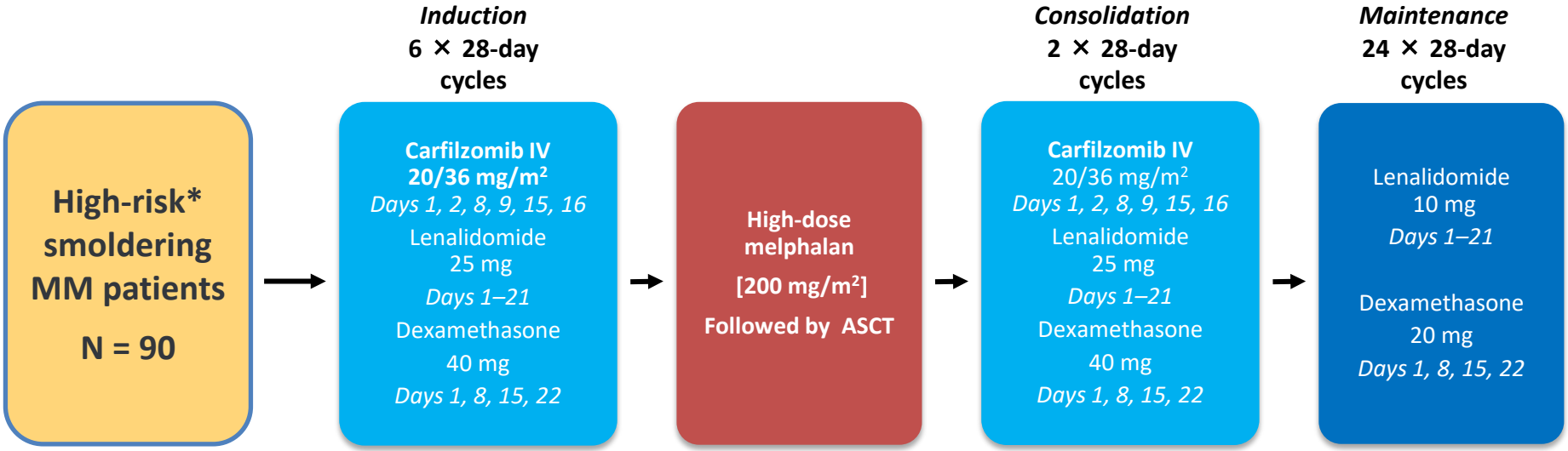
	Lenalidomide [n=44]	Lenalidomide [n=88]	Observation [n=92]
	Phase II	Phase III	
Category	N (%)	N (%)	N (%)
Hematologic Malignancies			
MDS	1 (2.3)	0 (0.0)	0 (0.0)
ALL	1 (2.3)	0 (0.0)	0 (0.0)
Hodgkin's disease	0 (0.0)	1 (1.1)	0 (0.0)
AML	0 (0.0)	0 (0.0)	0 (0.0)
NHL	0 (0.0)	0 (0.0)	0 (0.0)
Subtotal Heme	2 (4.5)	1 (1.1)	0 (0.0)
Solid Tumors	1 (2.3)	3 (3.4)	2 (2.2)
Total Invasive SPMs	**3 (6.8)**	**4 (4.5)**	**2 (2.2)**
Cumulative Incidence^	**4.9% (4y)**	**5.2% (3y)**	**3.5% (3y)**
Non-Melanoma Skin*	3 (6.8)	6 (6.8)	1 (1.1)
Total SPMs	**6 (13.6)**	**10 (11.4)**	**3 (3.4)**
Cumulative Incidence	**9.7% (4y)**	**11.0% (3y)**	**4.8% (3y)**

^Cumulative incidence estimates accounting for death as a competing risk
*Only first instance of non-melanoma skin was counted

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

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 1 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

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 negative	27 (30%)	47 (56%)	51 (63%)	36 (67%)	15 (56%)

GEM-CESAR: Induction – safety profile (n = 90)

Adverse events	Induction (n = 90)	
Hematologic toxicity, n (%)	Grade 1-2	Grade 3-4
• **Anemia**	7 (7%)	-
• **Neutropenia**	6 (7%)	**3 (3%)**
• **Thrombocytopenia**	9 (10%)	**5 (5%)**
Non-hematologic toxicity, n (%)		
• Asthenia	10 (11%)	1 (1%)
• Diarrhea/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%)	-

Pneumonia G1-2 (2 pts) and G3-4 (2 pts); atrial fibrillation G1 (1 pt); cardiac failure G3 (1 pt); hypertension G2 (3 pts)

***One patient developed G5 AEs consisting of massive ischemic stroke after respiratory infection.**

In summary

- Only high-risk should ever be considered for therapy
- Single-agent therapy is biologically illogical with emergent drug resistance inevitable
- Side effects are real even if for a minority
- Progress for “real” treatment is fast – what’s the rush unless curable?
- Even with highly aggressive therapy, not curable for many, especially high genetic risk
- So, trials only, randomized, and with long-term follow-up

Post-debate Question for the Audience

In your opinion, is smoldering myeloma treatable?

a) Yes

b) No

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Session Close – Audience Response Questions

Rafael Fonseca, MD

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Question 1

Which of the following is not part of the new criteria for treatment initiation in MM?

a) Plasma cells >60%
b) Deletion 17p
c) Two or more lesions on an MRI
d) Extreme abnormalities in the free light chains

Question 2

Which of the following is not true in the treatment of newly diagnosed MM?

a) Deep responses are associated with better outcomes
b) VGPR is an accepted benchmark as evidence of a good response
c) Clinical trials are considering risk stratification
d) Regimens that contain daratumumab have further increased response rates
e) Maintenance prolongs overall survival for MM patients

Thank You!

- Please complete the **evaluation survey** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the www.globalmmacademy.com website

THANK YOU!

LATAM Agenda Day 2

Time UTC-3	Topic	Time	Speaker
15.30 – 15.40	**Session Open**	10 min	Rafael Fonseca, MD
15.40 – 16.00	**Defining and Understanding High-Risk Multiple Myeloma**	20 min	Eloisa Riva, MD
16.00 – 16.25	**Early Relapse of Multiple Myeloma: Current and Emerging Treatment Options**	25 min	Rafael Fonseca, MD
16.25 – 16.45	**Patient Case Discussion and Q&A: Relapsed/Refractory Multiple Myeloma** Case 1 from the region	20 min	Ana Luiza Silva, MD
16.45 – 16.55	**Break**	10 min	
16.55 – 17.20	**Management of Heavily Pretreated Multiple Myeloma**	25 min	Keith Stewart, MBChB, MBA
17.20 – 17.40	**Patient Case Discussion and Q&A: Relapsed/Refractory Multiple Myeloma** Case 2 from the region	20 min	Lucía Pérez Baliero, MD
17.40 – 18.30	**Beyond the Horizon: New and Future Multiple Myeloma Treatment Approaches** • Optimal use of treatment choices in relapsed/refractory MM – Bispecifics in MM – CAR Ts in MM	 25 min 25 min	 Vania Hungria, MD, PhD (bispecifics), Luciano Costa, MD, PhD (CAR T)
18.30 – 18.55	**Interactive Discussion and Q&A** • Treatment landscape evolution	25 min	All faculty discussion
18.55 – 19.00	**Session Close**	5 min	Rafael Fonseca, MD

Global Multiple Myeloma Academy

Global Multiple Myeloma Academy Emerging and Practical Concepts in Multiple Myeloma

SEE YOU TOMORROW!

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