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Myeloma & Plasma Cell Dyscrasia

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Disclosures

In compliance with ACCME policy, ASH requires disclosures to the session audience:

Speaker

Anita D'Souza, MD

Disclosures

Research Funding: Abbvie; Caelum Bioscience; Janssen; Novartis; Prothena; Regeneron; Sanofi; Sorrento; Takeda; TeneoBio

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Membership on a Board or Advisory Committee: Bristol Myers Squibb; Janssen; Prothena

Discussion of off-label drug use: Not Applicable



Key Educational Objectives

By the end of this talk we will provide answers to these practical questions:

- When should we do **bone marrow biopsy** in **MGUS**?
- Is there a role for **dexamethasone-sparing induction** treatment in MM?
- Do we know the optimal **duration of lenalidomide maintenance** after ASCT?
- What are the **outcomes** of patients **progressing after BCMA CAR-T** cell therapies?
- What **future developments** do we anticipate in MM bispecific antibody therapies?



BONE MARROW BIOPSIES IN MGUS

When should we do **bone marrow biopsy** in **MGUS**?

Predicting the Need for Upfront Bone Marrow Sampling in Individuals with MGUS

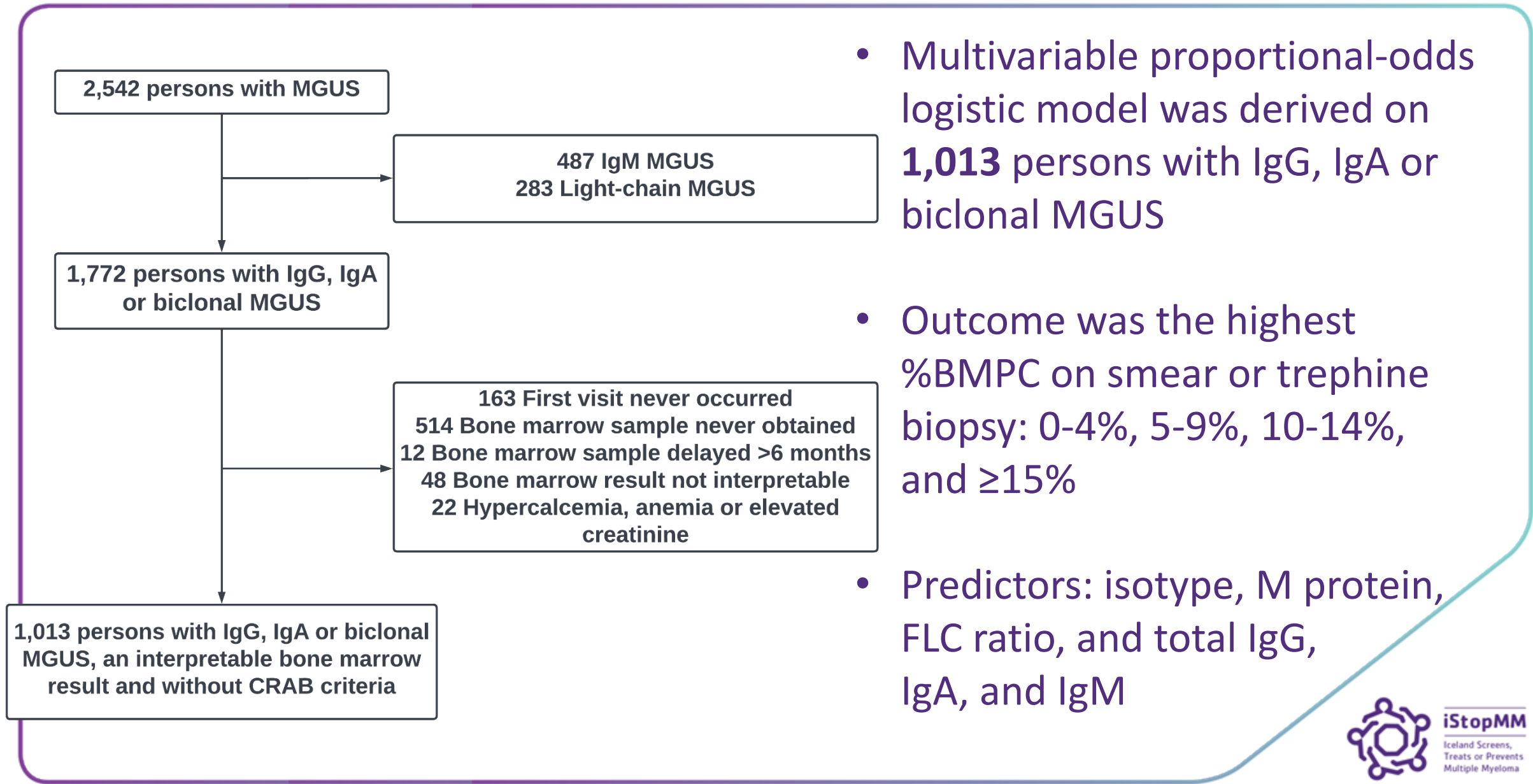
Derivation of a Multivariable Prediction Model Using the Prospective Population-Based iStopMM Cohort

Elias Eythorsson¹, Saemundur Rognvaldsson^{1,2}, Sigrun Thorsteinsdottir^{2,3}, Elin Ruth Reed², Guðrun Asta Sigurdardottir², Brynjar Vidarsson¹, Pall Torfi Onundarson^{1,2}, Bjarni A. Agnarsson^{1,2}, Margret Sigurdardottir¹, Isleifur Olafsson¹, Ingunn Thorsteinsdottir¹, Signy Vala Sveinsdottir¹, Fridbjorn Sigurdsson¹, Asdis Rosa Þordardottir², Runolfur Palsson^{1,2}, Olafur Skuli Indridason^{1,2}, Thorir Einarsson Long^{2,4}, Asbjorn Jonsson⁵, Gauti Kjartan Gislason², Andri Olafsson², Jon Sigurdsson², Hlif Steingrimsdottir¹, Malin Hultcrantz⁶, Brian G. M. Durie⁷, Stephen Harding⁸, Ola Landgren⁹, Thor Aspelund¹⁰, Thorvardur Jon Love², Sigurdur Yngvi Kristinsson^{1,2}

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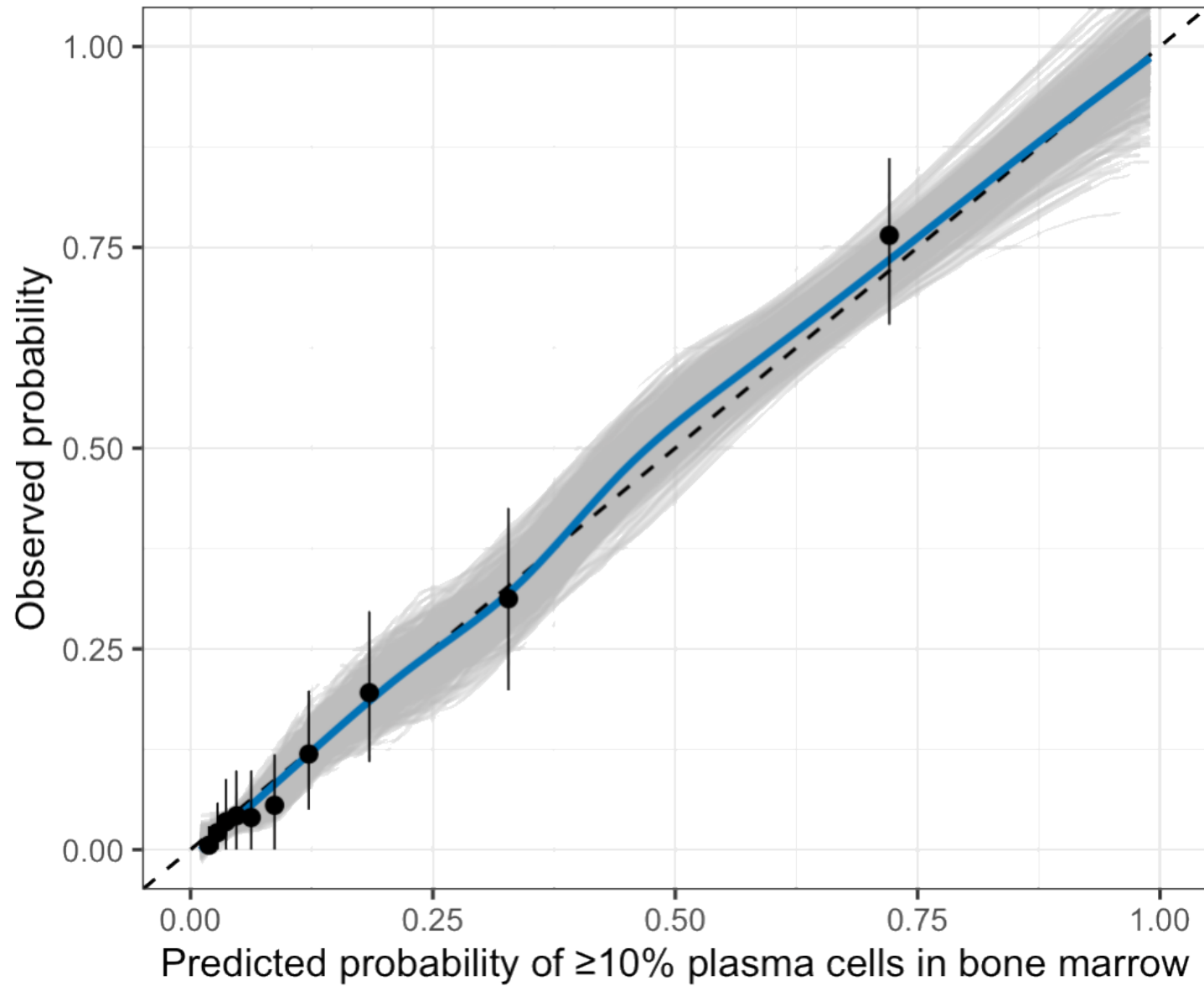
Email: elias.eythorsson@gmail.com, Twitter: @eliaseythorsson





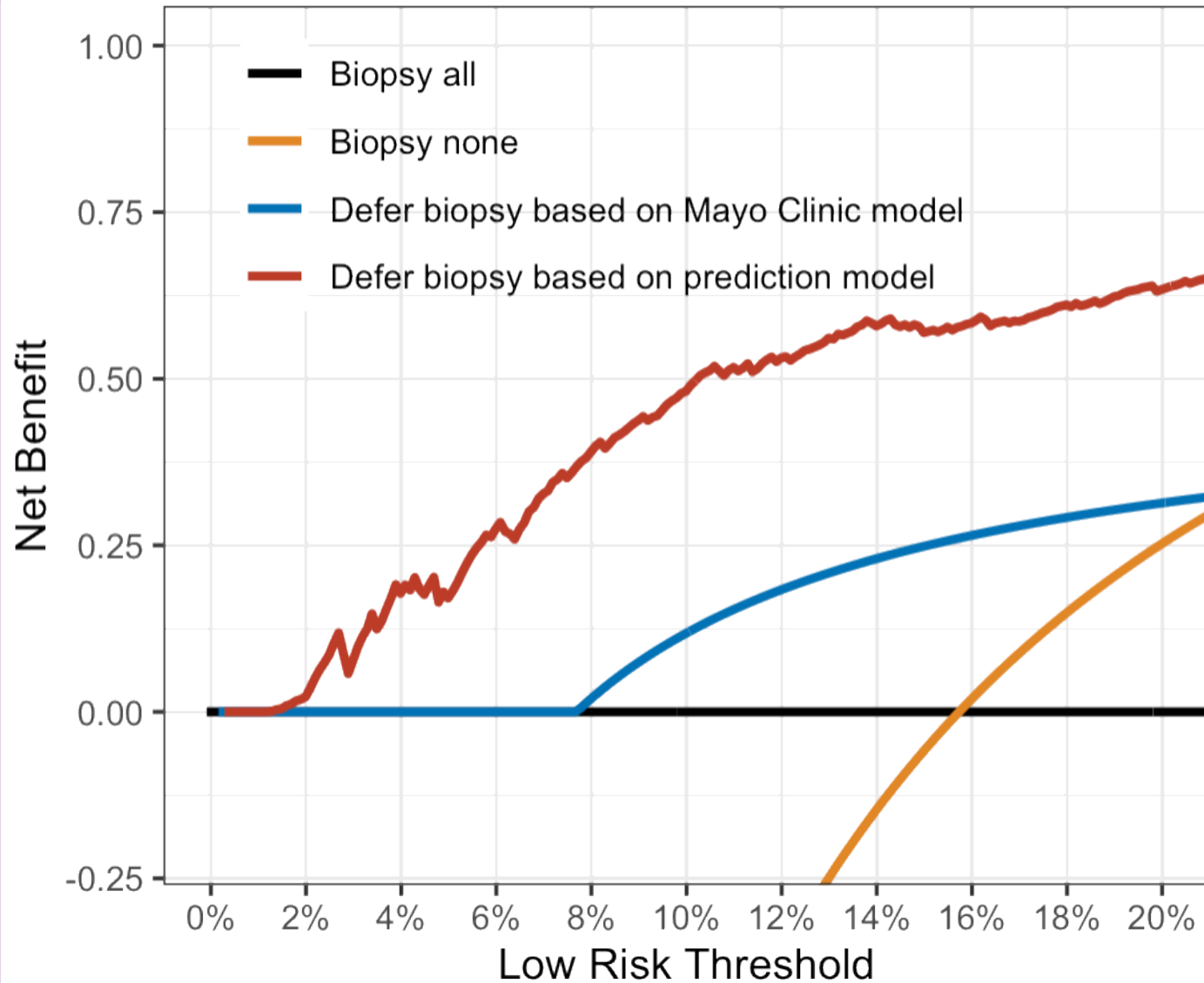
- Multivariable proportional-odds logistic model was derived on **1,013** persons with IgG, IgA or biconal MGUS
- Outcome was the highest %BMPC on smear or trephine biopsy: 0-4%, 5-9%, 10-14%, and $\geq 15\%$
- Predictors: isotype, M protein, FLC ratio, and total IgG, IgA, and IgM

Variable	Median [IQR] or <i>n</i> (%)
Age	68 [60-74]
Sex = Male	545 (53.8)
Isotype	
Biclonal	148 (14.6)
IgA	198 (19.5)
IgG	667 (65.8)
M protein (g/L)	2.59 [1.61 - 4.68]
FLC ratio	1.19 [0.85 - 1.79]
IgG (g/L)	10.29 [8.55 - 12.49]
IgA (g/L)	2.11 [1.31 - 3.14]
IgM (g/L)	0.72 [0.50 - 1.13]
Proportion of bone marrow plasma cells (BMPC)	
0-5%	438 (43)
6-10%	415 (41)
11-15%	92 (9.1)
>15%	68 (6.7)



<https://istopmm.com/riskmodel/>





- At a threshold of **5%** predicted risk, the negative predictive value was **97.3%** (95%CI 95.0-98.5) and BM sampling could be avoided in **366 (36.1%)** participants

DEXAMETHASONE-SPARING INDUCTION REGIMEN

Is there a role for **dexamethasone-sparing induction** treatment in MM?





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A Dexamethasone Sparing-Regimen with Daratumumab and Lenalidomide in Frail Patients with Newly-Diagnosed Multiple Myeloma: Efficacy and Safety Analysis of the Phase 3 IFM2017-03 Trial

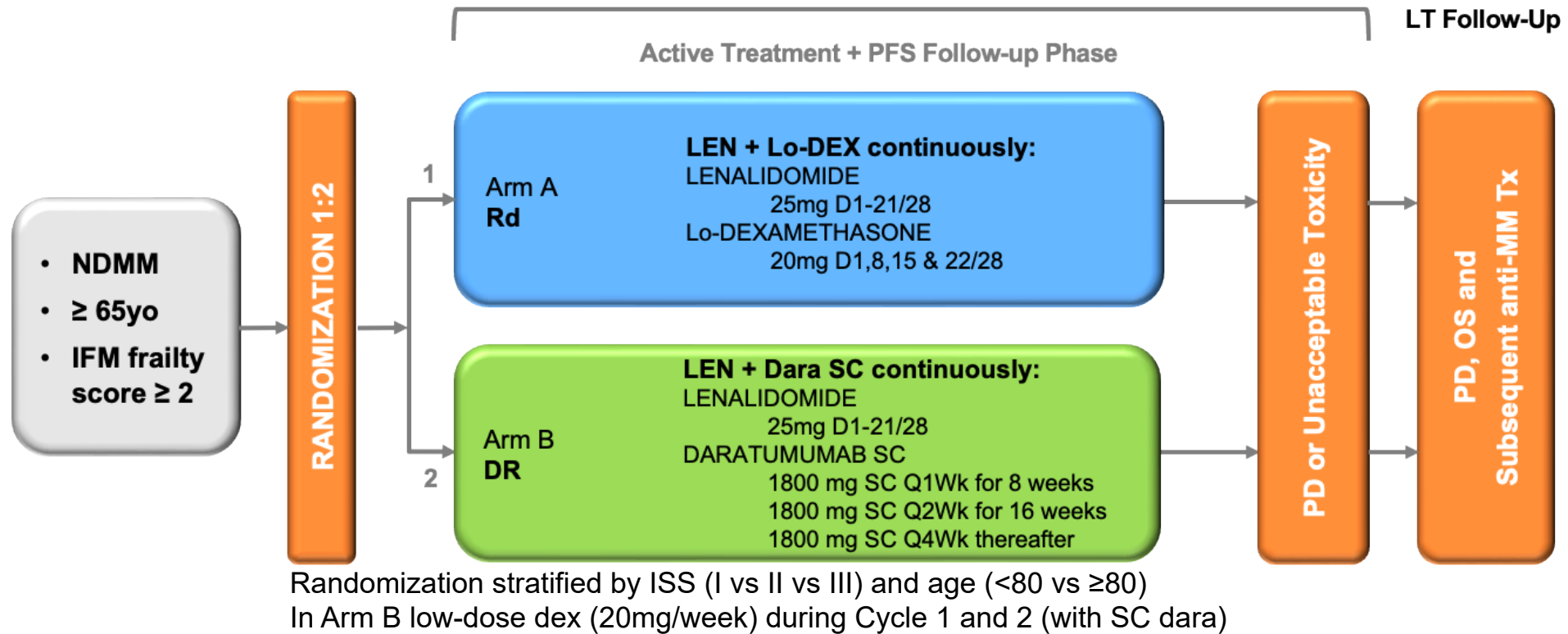
Manier, J. Corre, C. Hulin, K. Laribi, C. Araujo, G.M. Pica, C. Touzeau, P. Godmer, B. Slama, L. Karlin, F. Orsini Piocelle, M. Dib, M. Macro, L. Sanhes, A. Perrot, J.Y. Mary, J. Lambert, H. Avet-Loiseau, P. Moreau, X. Leleu, T. Facon



Abstract 569



IFM 2017-03 – Study design



Primary endpoint: PFS

→ **Interim analysis endpoints:** 12-months-therapy data cut:

- Overall response rate,
- VGPR or better rate,
- MRD rate,
- Occurrence of grade 3 or more side effects

IFM 2017-03 – Patients characteristics

Characteristics	DR group (N=199)	Rd group (N=94)
Median age (range) - yr	81 (68-92)	81 (68-90)
Age category – no. (%)		
65 to < 70 yr	2 (1%)	2 (2%)
70 to < 75 yr	30 (15%)	13 (14%)
75 to < 80 yr	49 (25%)	19 (20%)
≥ 80 yr	118 (59%)	61 (65%)
Sex - no. (%)		
Female	101 (51%)	48 (51%)
Male	98 (49%)	46 (49%)
ECOG – no. (%)		
0	21 (10%)	9 (10%)
1	93 (46%)	47 (50%)
2	86 (44%)	38 (40%)
Charlson – no. (%)		
≤ 1	113 (58%)	57 (61%)
> 1	87 (42%)	37 (39%)
IFM frailty score – no. (%)		
≤ 1	0	0
2	57 (29%)	35 (37%)
3	81 (41%)	26 (28%)
4	44 (22%)	24 (26%)
5	17 (9%)	9 (10%)

Characteristics	DR group (N=199)	Rd group (N=94)
ISS disease stage – no. (%)		
I	33 (17%)	18 (19%)
II	102 (51%)	49 (53%)
III	64 (32%)	26 (28%)
NA	0	1
Type of measurable disease – no (%)		
IgG	113 (57%)	49 (52%)
IgA	38 (19%)	20 (21%)
PBJ only	21 (11%)	10 (11%)
SFLC only	27 (14%)	15 (16%)
Cytogenetics profile* – no (%)		
Standard risk	148 (83%)	60 (78%)
High risk	31 (17%)	17 (22%)
NA	20	17
del17p	16 (9%)	11 (14%)
t(4;14)	9 (5%)	5 (6%)
t(14;16)	6 (3%)	3 (3%)
Creatinine clearance – no. (%)		
< 30mL/min	1 (1%)	3 (3%)
30 to < 60mL/min	119 (60%)	50 (53%)
≥ 60 mL/min	79 (40%)	41 (44%)

* del17p, t(4;14), t(14;16)

IFM 2017-03 – Frailty scores

IMWG frailty score¹

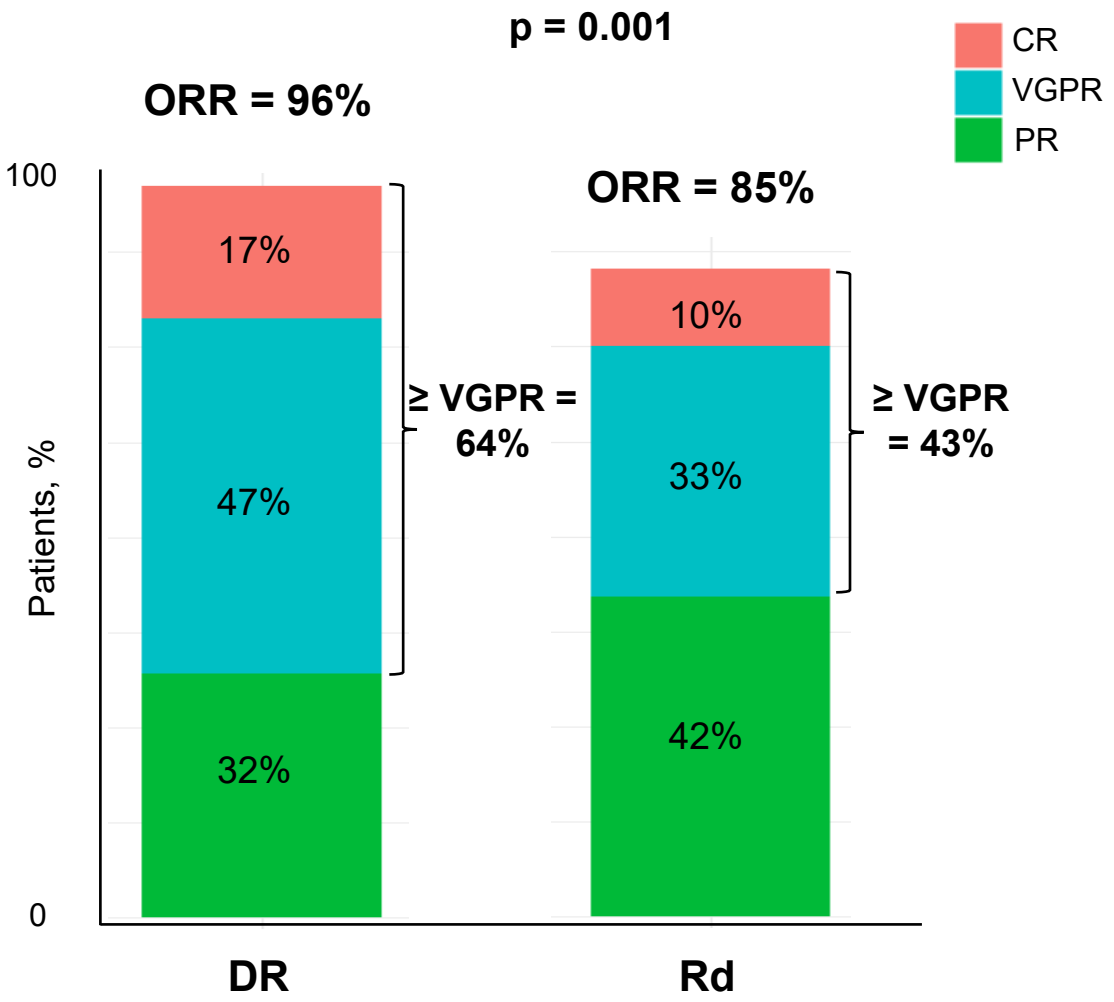
Score assessment		Score
Age (year)	≤75	0
	76-80	1
	>80	2
Activity of Daily Living	>4	0
	≥4	1
Instrumental Activity of Daily Living	>5	0
	≤5	1
Charlson Comorbidity Index	≤1	0
	≥2	1
Score assessment		Total score
Fit		0
Intermediate		1
Frail		≥2

Simplified IFM frailty score²

Score assessment		Score
Age (year)	≤75	0
	76-80	1
	>80	2
Charlson Comorbidity Index	≤1	0
	≥2	1
ECOG	0	0
	1	1
	≥2	2
Score assessment		Total score
Fit		0-1
Frail		≥2

¹Palumbo et al. *Blood* 2015, ²Facon et al. *Leukemia* 2020

IFM 2017-03 – Best response rate



Best overall response rate was significantly higher with DR

IFM 2017-03 – Most common grade ≥ 3 AEs

	DR group (n=199) Grade ≥ 3	Rd group (n=94) Grade ≥ 3	P value
All grade ≥ 3 AEs, % (n)	82% (164)	68% (64)	0.010
SAE, % (n)	55% (109)	63% (59)	0.21
Hematologic, % (n)	55% (109)	26% (24)	<0.0001
anemia	11% (21)	2% (2)	0.010
neutropenia	46% (91)	18% (17)	<0.0001
thrombocytopenia	9% (18)	3% (3)	0.089
Infection, % (n)	13% (26)	18% (17)	0.29
non-COVID infections	9% (17)	14% (13)	0.21
pneumonia	3% (5)	7% (7)	0.060
COVID	5% (9)	4% (4)	1

	DR group (n=199)	Rd group (n=94)	P value
Treatment discontinuation for AE, % (n)	14% (27)	16% (15)	0.65

IFM 2017-03 – Most common grade ≥ 3 AEs, by IFM frailty score subgroups

	IFM frailty score 2 & 3 (n=199)			IFM frailty score 4 & 5 (n=94)		
	DR group (n=138) Grade ≥ 3	Rd group (n=61) Grade ≥ 3	P value	DR group (n=61) Grade ≥ 3	Rd group (n=33) Grade ≥ 3	P value
SAE, % (n)	54% (74)	57% (35)	0.65	57% (35)	73% (24)	0.18
Infection, % (n)	9% (13)	13% (8)	0.46	21% (13)	27% (9)	0.61
non-COVID infections	7% (10)	10% (6)	0.58	11% (7)	21% (7)	0.23
pneumonia	1% (2)	5% (3)	0.17	5% (3)	12% (4)	0.24
COVID	2% (3)	3% (2)	0.64	10% (6)	6% (2)	0.71

MAINTENANCE

Do we know the optimal **duration of lenalidomide maintenance** after ASCT?



Defining the optimum duration of lenalidomide maintenance after autologous stem cell transplant – data from the Myeloma XI trial.

Charlotte Pawlyn^{1,2}, Tom Menzies³, Faith Davies⁴, Ruth de Tute⁵, Rowena Henderson³, Gordon Cook^{3,6}, Matthew Jenner⁷, John Jones⁸, Martin Kaiser^{1,2}, Mark Drayson⁹, Roger Owen⁸, David Cairns³, Gareth Morgan⁴, Graham Jackson¹⁰

1) The Institute of Cancer Research, London, UK; 2) The Royal Marsden Hospital, London, UK; 3) Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK; 4) Perlmutter Cancer Center, NYU Langone Health, New York, US; 5) HMDS, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; 6) Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK; 7) University Hospital Southampton NHS Foundation Trust, Southampton, UK; 8) Kings College Hospital NHS Foundation Trust, London, UK; 9) Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK; 10) Department of Haematology, University of Newcastle, Newcastle-upon-Tyne, UK

On behalf of the Myeloma XI Trial Management Group and NCRI Haem-Onc Clinical Studies Group

Myeloma XI

Induction

NDMM TE
Myeloma XI induction protocols and ASCT



R
1:1

Maintenance

Lenalidomide
10mg/day, days 1-21/28

Observation

Planned to continue till disease progression

N=1,248

Median follow up: 44.7 months (IQR 32.4-62.7)

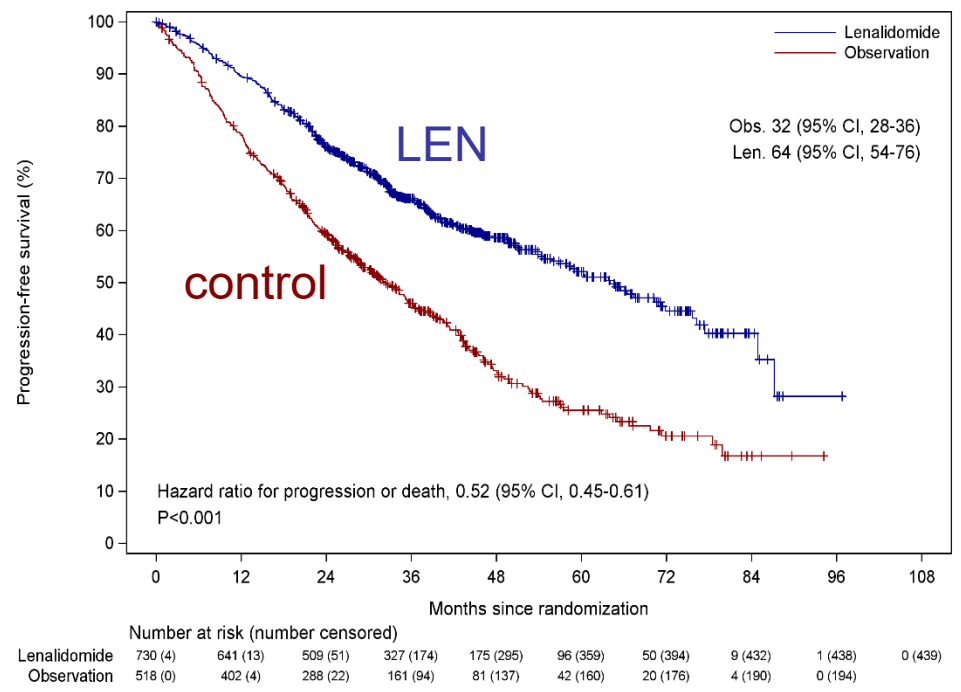
Exclusion criteria

- Failure to respond to lenalidomide as induction IMiD or progressive disease
- Previous or concurrent active malignancies
- Dialysis dependent renal failure

		Observation (n=518)	Lenalidomide (n=730)
Risk category	SR	122 (60.7%)	131 (48.3%)
	HiR	56 (27.9%)	102 (37.6%)
n (% of available data)	UHiR	23 (11.4%)	38 (14.0%)

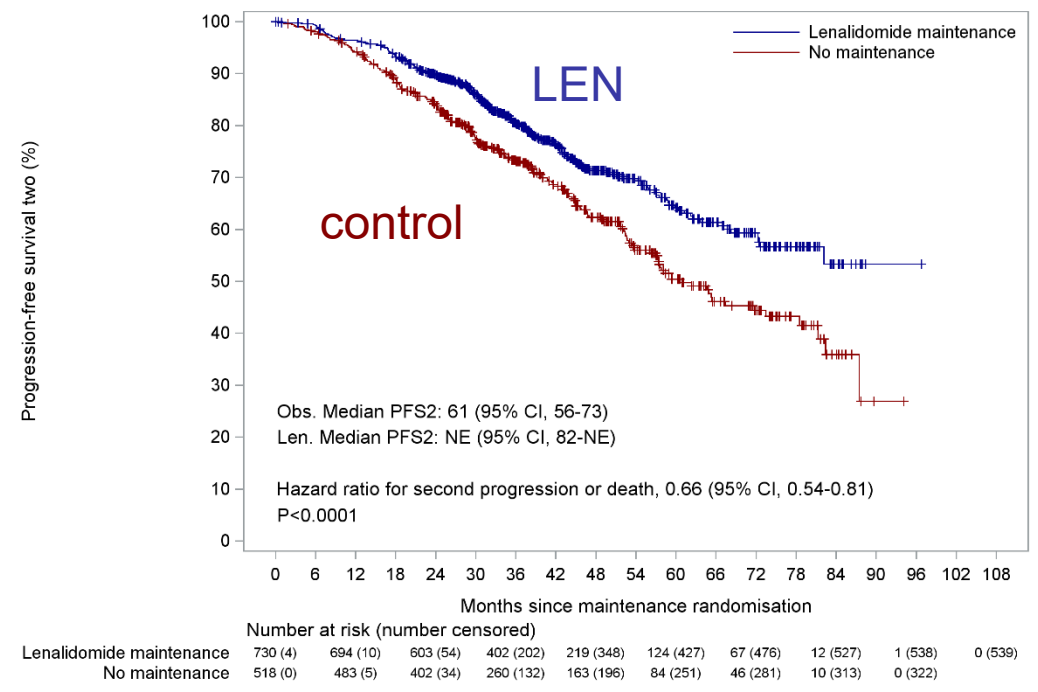
Outcomes from maintenance randomisation – overall population

PFS



Hazard Ratio 0.52*

PFS2



Hazard Ratio 0.66*

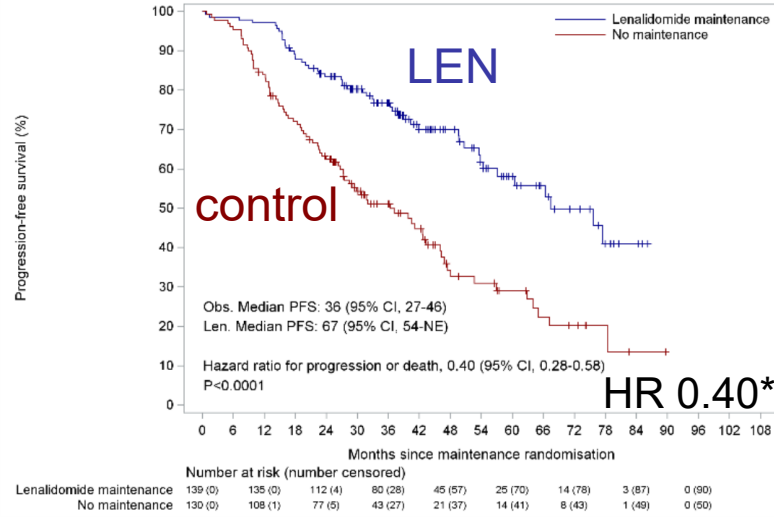
*p<0.05

Outcomes from maintenance randomisation

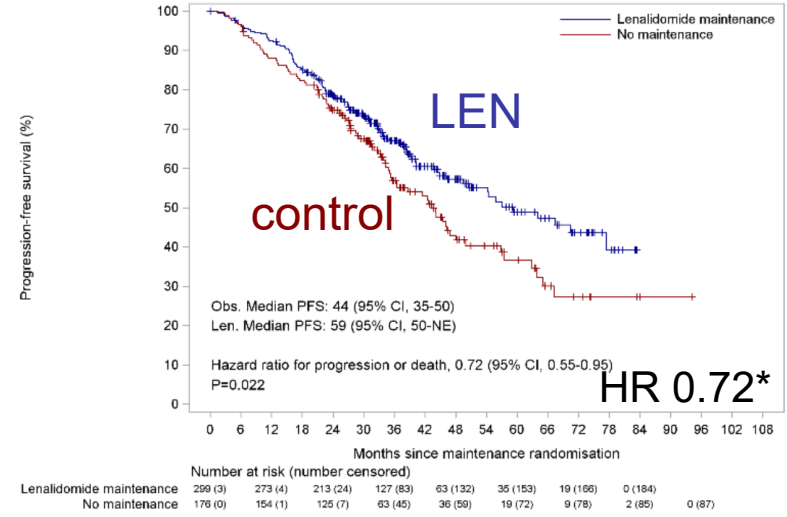
Genetic risk status

MRD status

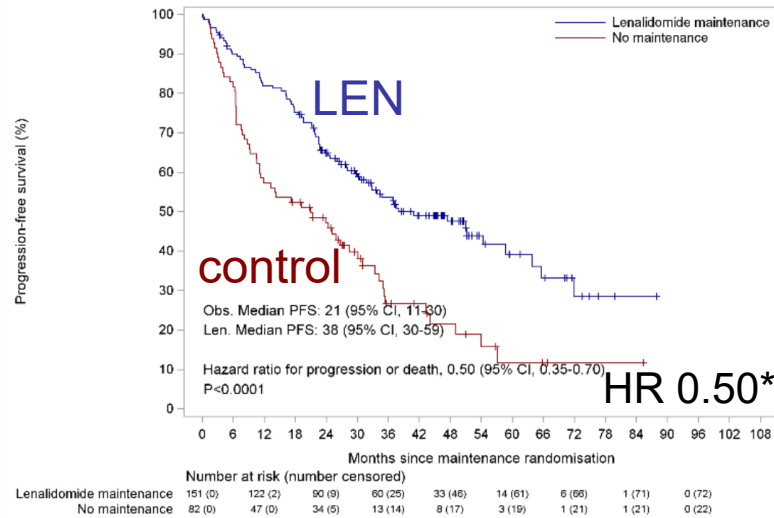
SR



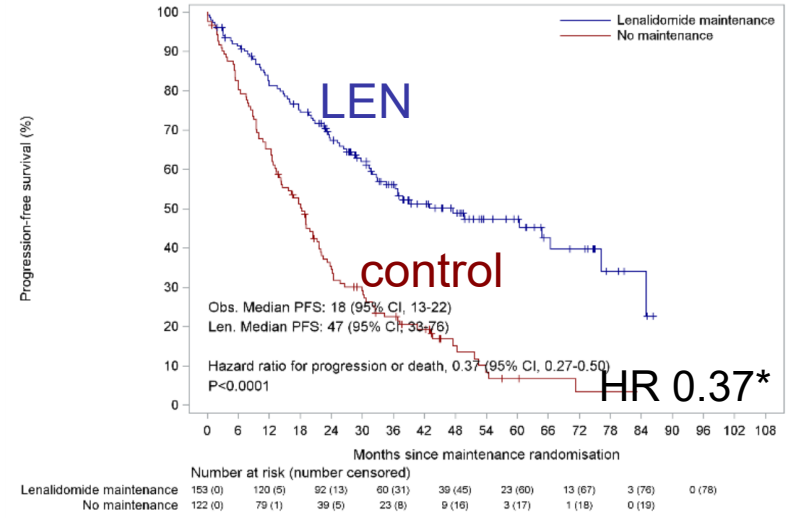
MRD -ve



HR/UHR



MRD +ve



*p<0.05

MRD status was assessed by flow cytometry (median sensitivity 4x10⁵)

Outcomes from multiple landmarks

– overall population

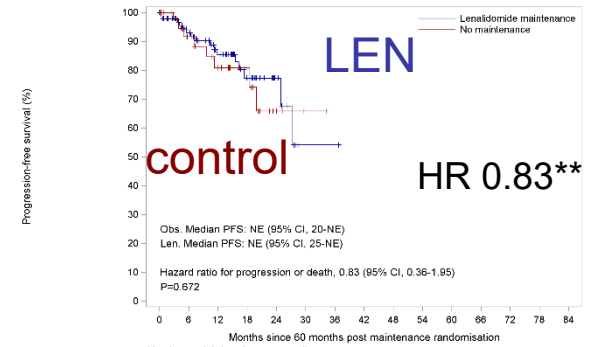
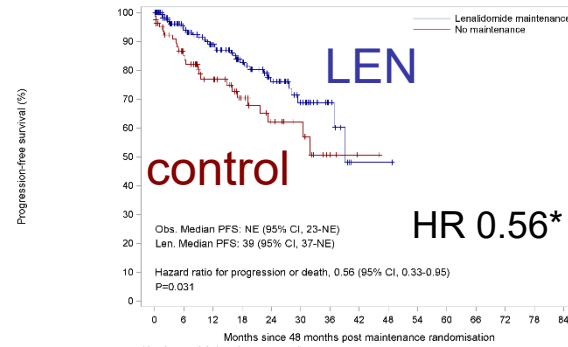
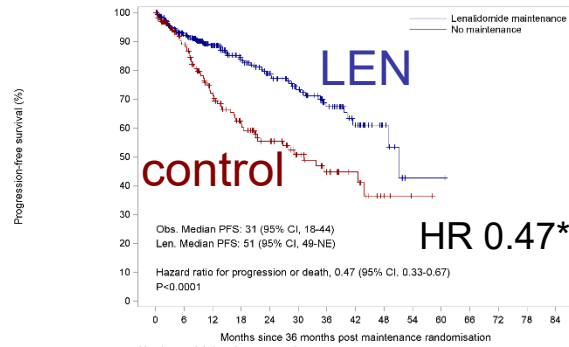
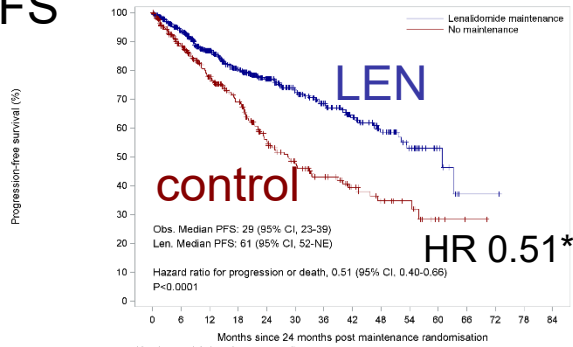
2 years

3 years

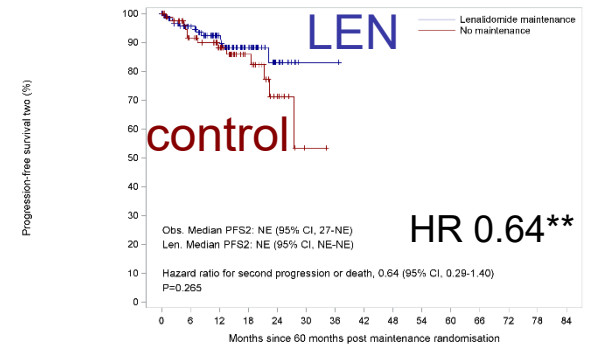
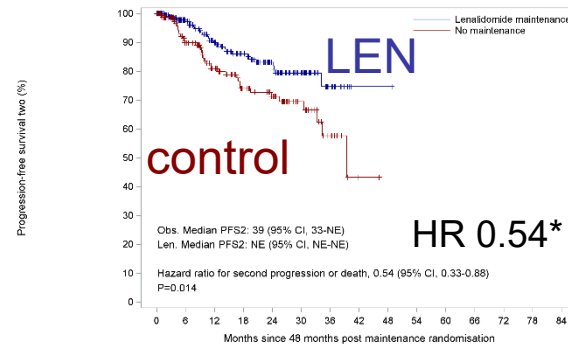
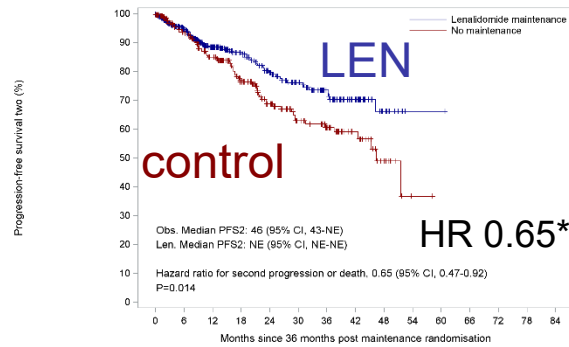
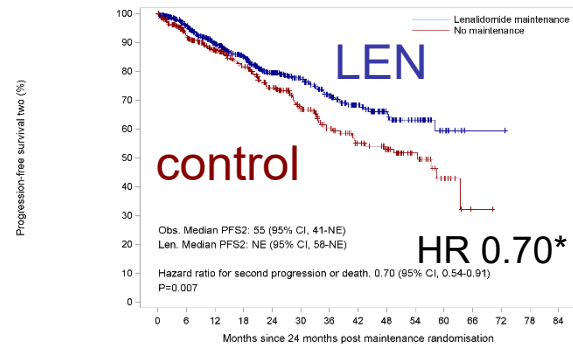
4 years

5 years

PFS



PFS2



*p<0.05

**p=NS

Outcomes from multiple landmarks

– by MRD status

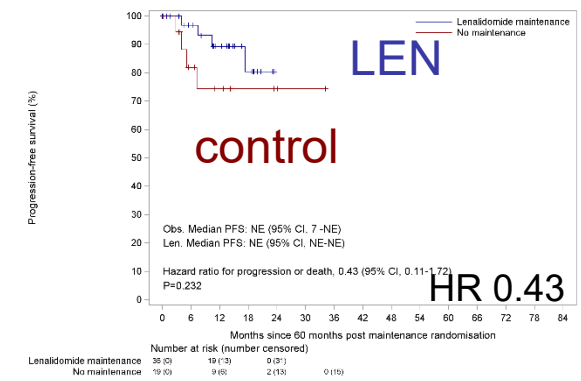
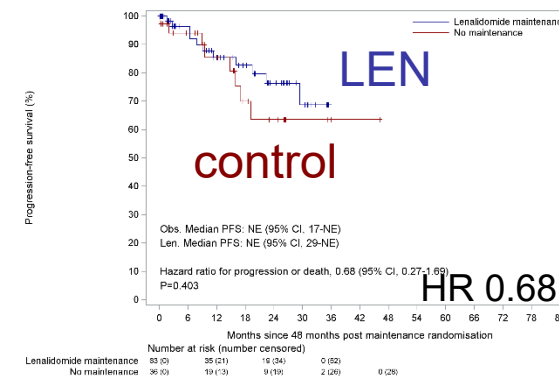
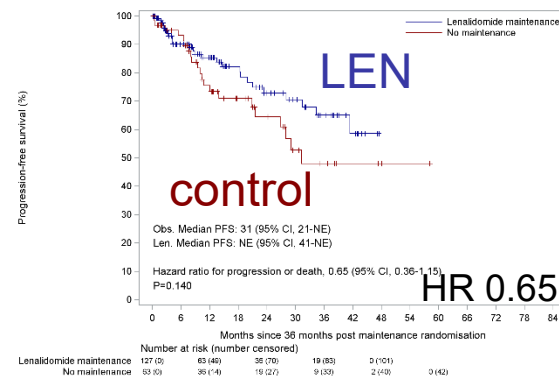
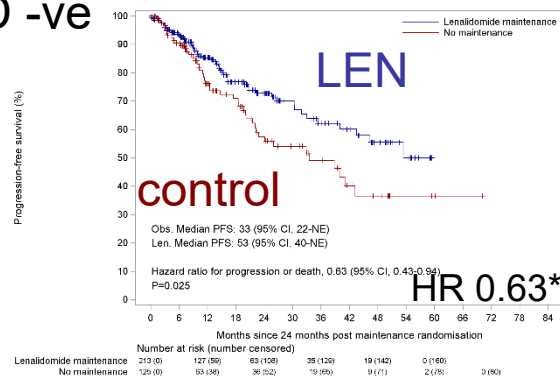
2 years

3 years

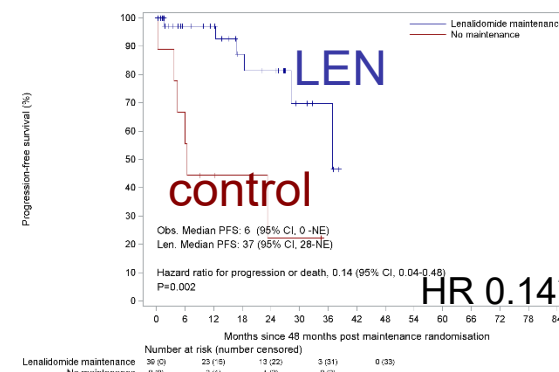
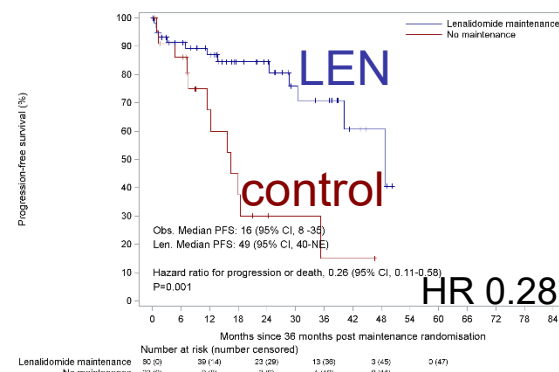
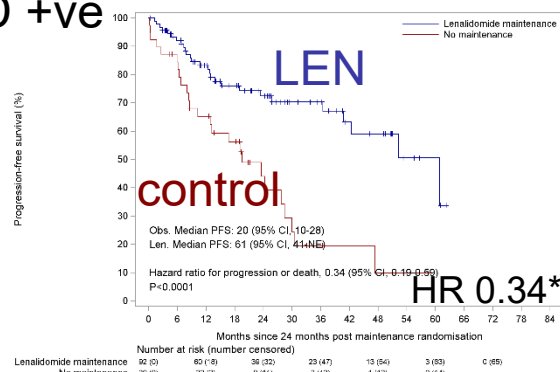
4 years

5 years

MRD -ve



MRD +ve



*p<0.05

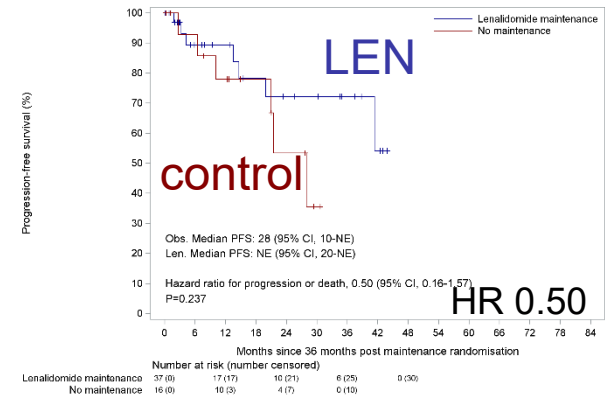
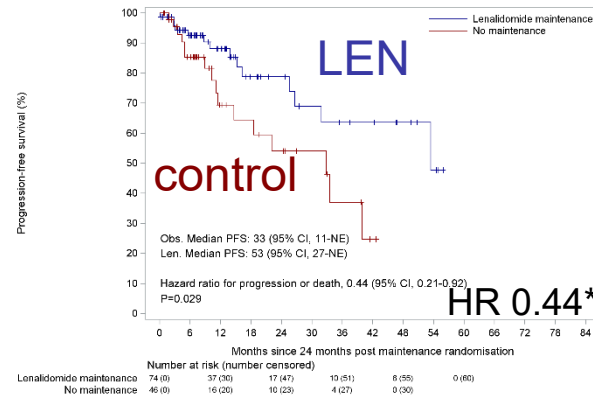
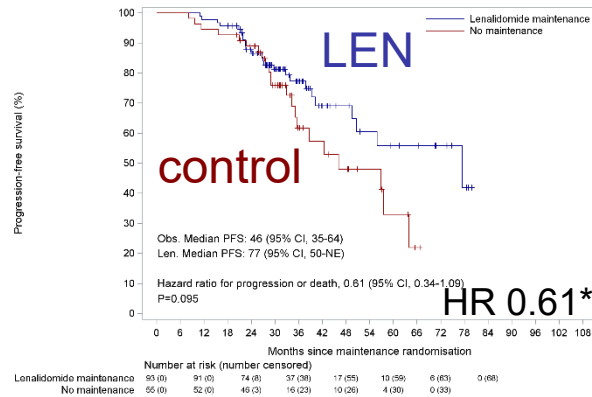
Outcomes from multiple landmarks – by sustained MRD

Maintenance randomisation

2 years

3 years

Sustained MRD -ve



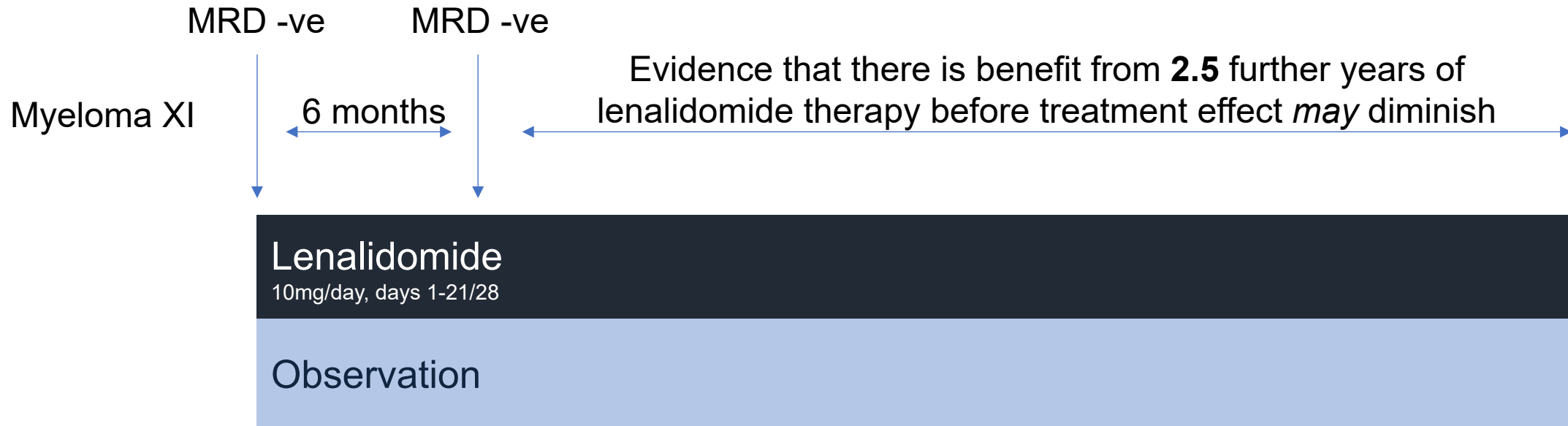
Patients with sustained MRD -ve for 6 months from start of therapy

*p<0.05

Can this help us personalise therapy?

MRD +ve – continue maintenance to progression

MRD -ve:



POST-CAR-T TREATMENT

What are the **outcomes** of patients **progressing after BCMA CAR-T** cell therapies?



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University of California
San Francisco

Clinical Outcomes and Salvage Therapies In Patients with Relapsed/Refractory Multiple Myeloma Following Progression on BCMA-Targeted CAR-T Therapy

Kevin Reyes¹, Yen-Chun Liu², Chiung-Yu Huang³, Rahul Banerjee^{4,5}, Thomas Martin⁴, Nina Shah⁴, Sandy Wong⁴, Jeffrey Wolf⁴, Shagun Arora⁴, Alfred Chung⁴

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2. Department of Statistical Science, Duke University, Durham, NC

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4. Division of Hematology and Oncology, Department of Medicine, University of California San Francisco, San Francisco, CA.

5. Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, WA.

Patient Characteristics

Characteristic	Patient Cohort (n = 81)
Age: Median (Range)	64 years (33-77)
Sex	Male = 60% (n=49) Female = 40% (n=32)
Type of MM	IgA = 20% (n=16) IgG = 64% (n=52) IgD = 1% (n=1) Light Chain only = 14% (n=11)
Extramedullary Disease Present	25% (n=20)
High Risk FISH	59% (n=40)
Baseline Plasma Cell Burden Prior to CAR-T Infusion: Median (Range)	35% (0%-100%)

Median Lines of Therapy: 7

Triple-Refractory*: 62% (n=50)

Penta-Refractory: 27% (n=22)

Clinical Trial CAR-T	Standard of Care CAR-T
n = 57	n = 24

Post-CAR-T Relapse Survival

Median Overall Survival

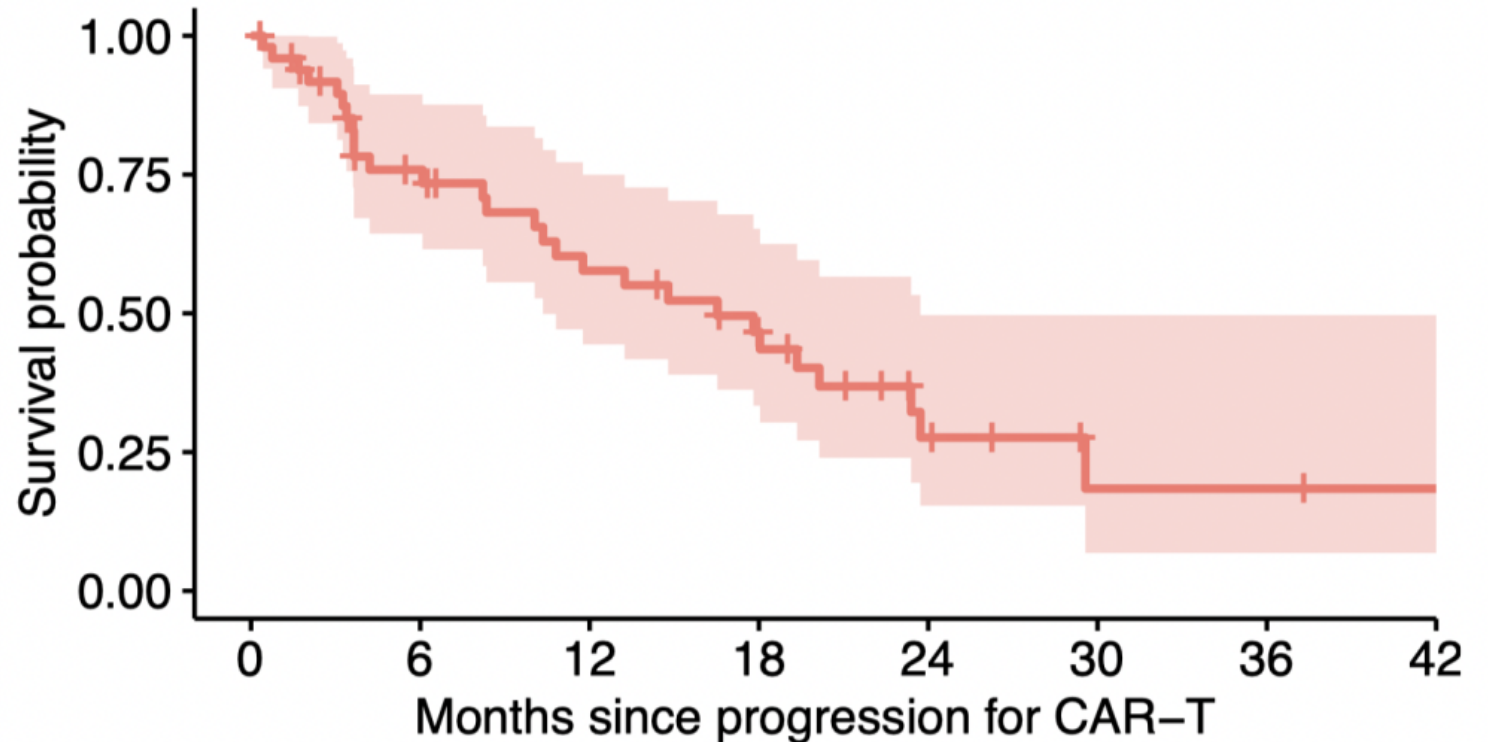
16.5 months (95% CI: 10.3 – 23.7 months)

1-Year Overall Survival

57% (95% CI: 44.4% – 75%)

2-Year Overall Survival

28% (95% CI: 15.4% – 50%)



Post CAR-T Relapse Analysis

- Patients Who Relapsed from CAR-T & Received Subsequent Salvage Therapy: 45

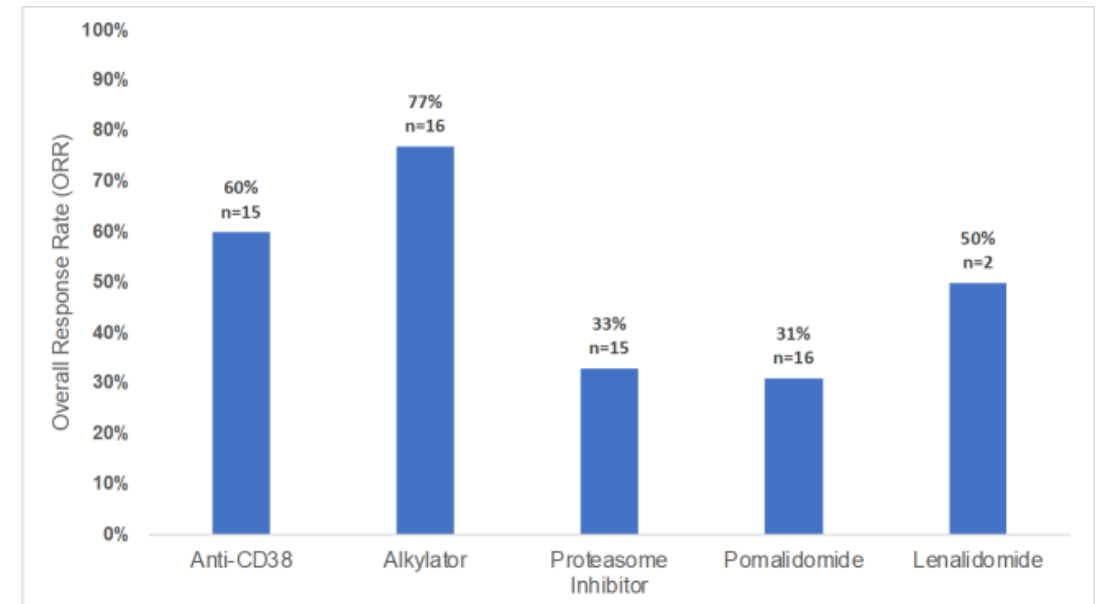
- Salvage Therapies Received Post-CART:

Median: 2 | Range: 1-8

- Median Follow up Time From Time of Initial BCMA CAR-T Progression: 10.3 mos

Next MM Therapy (n)	ORR	Median Duration on Therapy
BCMA CAR-T (7)	86%	8.3 months
BCMA BsAb (6)	50%	4.2 months
Belantamab (7)	29%	1.0 months
Anti-CD38 (22)	55%	2.9 months
Alkylator (47)	49%	1.3 months
Proteasome inhibitors (35)	40%	1.6 months
IMiDs (21)	38%	2.4 months
Selinexor (10)	40%	1.4 months
Venetoclax (7)	29%	1.3 months
Elotuzumab (4)	25%	2.5 months

Overall Response Rates with Retreatment using Previously Refractory Therapy



Subgroup Analysis: Patients treated with BCMA targeted therapies after BCMA CAR-T relapse

Best response to initial CAR-T therapy	Subsequent BCMA CAR-T	Subsequent BCMA BsAb	Subsequent Belantamab Mafodotin	Treatment Response:
sCR			PD	
sCR	VGPR			sCR
sCR	VGPR			CR
sCR		sCR		VGPR
VGPR		PD	PD	SD
VGPR	SD			PD
VGPR			PD	
VGPR			PD	
VGPR	VGPR			
VGPR			VGPR	
VGPR		SD		
VGPR			VGPR	
VGPR	VGPR			
PR	VGPR			
SD	VGPR	CR		
SD		CR		
PD		PD	PD	

NOVEL THERAPIES

What **future developments** do we anticipate in MM bispecific antibody therapies?



BCMA X CD3 BISPECIFIC ANTIBODIES

Drug	Median prior lines, n	ORR, %	CRS, %	ICANS, %	Infection%	Step-up/Dose
ABBV-383 (N=64) ¹	4 (3-12)	60% @ 60 mg (n=58) 83% @ 40 mg (n=6)	72-83% Gr 3; 0-2%	5%	43-50%	No, IV Q3W
Alnuctamab (N=47) ²	4	51%	53%	2%	NR	Yes, SC QW
Elranatamab (N=55) ³ (N=123) ⁴	5 (2-14) 5 (2-22)	64% 61%	67% 56%	3.8% 3.4%	NR	SC QW
RGN5458 (N=167) ⁵	6	75% @ ≥200 (n=24) 41% @ <200 (n=49)	48% Gr 3 0.3%	4%	52; 22%	Yes, IV QW -> Q2W
Teclistamab + Dara + Len (N= 32) ⁶	2 (1-3); 31% anti-CD38 exposed	94%	81% Gr ≥3 0	0	91% (38% Gr 3/4)	Yes, SC QW-> Q2W

1 Voorhees, P, et al. ASH 2022 Abstr 1919; 2 Wong, S et al. ASH 2022 Abstr 162; 3 Raje, N et al. ASH 2022 Abstr 157; 4 Bahlis, N et al. ASH 2022 Abstr 158; 5 Bumma, N et al. ASH 2022 Abstr 4555; 6 Searle E, et al. ASH 2022 Abstr 160

OTHER TARGETS

Drug	Target	Median prior lines, n	ORR, %	CRS, %	ICANS, %	Infection %	Step-up/Dose
Talquetamab ¹ (N=141 QW, 143 Q2W SC)	GPRC5D	5 (2-13) 5(2-17)	73-74% @RP2D	79% 3% Gr 3	7% @RP2D	57.3% and 50.3% (gr ¾ 16.8 and 11.7%)	3 step-up, SC dosing, skin/nail/oral toxicity
Forimtamig ² (N=51 IV, 57 SC)	GPRC5D	5 (2-15) 4 (2-14)	71% and 64%	82-79% ~2% Gr 3/4	9.8-12.3% Gr ≥3 3%	61% and 46% (Gr 3/4 22% and 26%)	Weekly step-up x 3 doses in C1, IV and SC, Q 2W
Cevostamab ³ (N=28)	FcRH5	4 (2-7)	50%	36% (2 Gr 3)	28%		Pretreatment with tocilizumab

1 Chari, A, et al. ASH 2022 Abstr 157; 2 Carlo-Stella, C et al. ASH 2022 Abstr 161; 3 Trudel, S et al. ASH 2022 Abstr 567

Clinical Question

A 58-year-old male is referred to you for generalized fatigue after developing a respiratory viral illness. His primary care physician performed a work-up which revealed an IgA lambda monoclonal gammopathy. His M-spike is 1.4 g/L with a FLC ratio of 0.9 (n 0.26-1.65). Total IgG level is 7 g/L (n 6-16 g/L), IgA level is 1.6 g/L (n 0.8-3 g/L), and IgM level is 0.4 g/L (n 0.4-2.5 g/L). His hemoglobin and creatinine are normal. When you see him, his fatigue has resolved, review of systems is negative, and physical examination is unremarkable. Your next steps include:

<https://istopmm.com/riskmodel/>

- A. No further work-up, annual follow up
- B. Bone marrow biopsy
- C. Get a PET/CT scan
- D. Start treatment with lenalidomide



Predicting the need for bone marrow sampling in MGUS

Choose units, defaults to the European convention (g/L)

- European convention (both M protein & immunoglobulins measured in g/L)
- USA convention (M protein measured in g/dL & immunoglobulins measured in mg/dL)

MGUS Isotype

- IgG
- IgA
- Biclonal

M protein concentration g/L

1.4

Free Light Chain (FLC) ratio

0.9

Total IgG g/L

7

Total IgA g/L

1.6

Total IgM g/L

0.4

*The predicted risk of having $\geq 10\%$ bone marrow plasma cells is **4%***

In a group of 100 such individuals, **4** will have $\geq 10\%$ bone marrow plasma cells on bone marrow sampling and **96** will not

Clinical Question

An 86-year-old female is referred to you for new onset low back pain. She notes severe fatigue in the last 3 months. Review of systems is positive for long-standing type 2 diabetes mellitus, and she has tingling and numbness in her lower extremities. On examination, her ECOG PS is 3. Rest of the examination is within normal limits. Laboratory examination shows a hemoglobin of 8.4 g/dl, total protein level is 9.1 g/dl, albumin 3.6 g/dl, beta2 microglobulin 4.6 mg/L, with normal renal function and calcium levels. Monoclonal protein studies show an IgG kappa M-spike of 4.7 and a free light chain ratio of 15.6. Bone marrow reveals 40% kappa-restricted plasma cells, normal karyotype, and a plasma cell-directed FISH shows no abnormalities. PET/CT scan shows multiple focal lytic lesions with FDG-avidity. Your next steps include:

- A. Watch and wait
- B. Bortezomib, lenalidomide, dexamethasone
- C. Daratumumab + lenalidomide
- D. Carfilzomib, lenalidomide, dexamethasone followed by autologous stem cell transplantation



Key Educational Objectives

- When should we do **bone marrow biopsy** in **MGUS**?
- Is there a role for **dexamethasone-sparing induction** treatment in MM?
- Do we know the optimal **duration of lenalidomide maintenance** after ASCT?
- What are the **outcomes** of patients **progressing after BCMA CAR-T** cell therapies?
- What **future developments** do we anticipate in MM bispecific antibody therapies?

Thank you!

