NYU Langone Health

Perlmutter Cancer Center

Multiple Myeloma Research Program

ASH 2022 UPDATE - MULTIPLE MYELOMA

FAITH DAVIES

Professor of Medicine, NYU Grossman School of Medicine.

DISCLOSURES

Advisory boards

- Amgen
- AbbVie
- BMS/Celgene
- GSK
- Janssen
- Meridian Therapeutics
- Oncopeptide
- Regeneron
- Sanofi
- Takeda

Off label drug use – bispecific antibodies and ADCs

Areas with new important data

- Data concerning population screening for plasma cell dyscrasia (iSTOP study)
- Treatment of high risk smoldering
- Upfront therapy – frail, high risk
- Maintenance
- Relapse therapy
- Disease monitoring (MRD analysis, mass spec)

- Single cell analysis of tumor and microenvironment

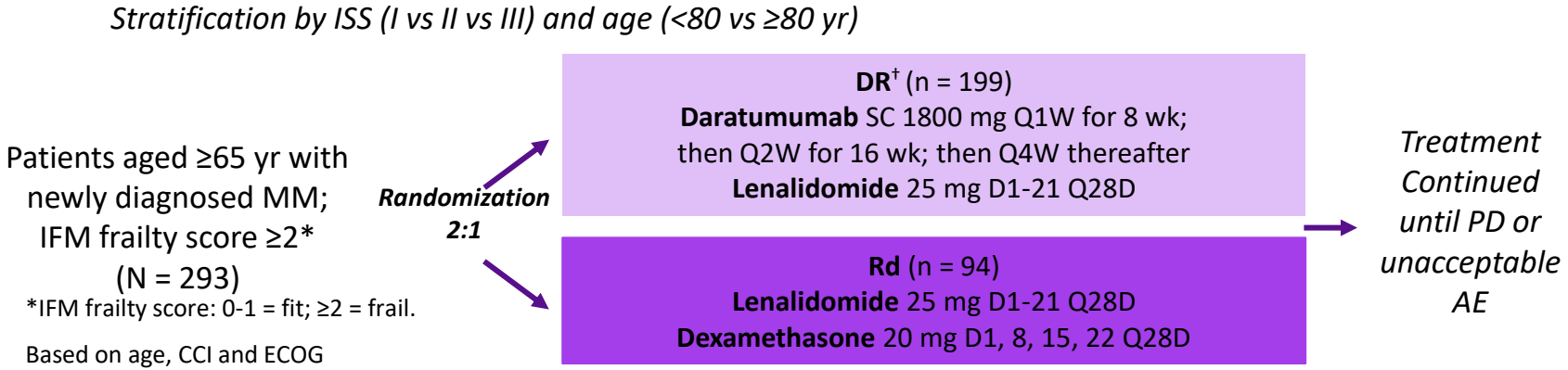
Newly diagnosed – Elderly frail patients

- Fitness and ability to tolerate MM treatment varies among older patients
  - Frailty is associated with increased risk of death, disease progression, higher rates of non-hematologic AEs, and treatment discontinuation in patients with MM
- DRd is a standard regimen for newly diagnosed transplant-ineligible patients with MM, but rates of pneumonia are higher with DRd vs Rd, particularly in frail patients
- IFM 2017-03 is a phase III trial evaluating whether a dexamethasone-sparing regimen of daratumumab + lenalidomide would be effective and limit toxicity in frail patients compared with lenalidomide + dexamethasone[5]
  - Current interim analysis at 12 months of therapy reported on response and safety[5]

Manier et al . ASH 2022. Abstr 569.

IFM 2017-03

- Randomized, open-label, multicenter phase III trial



†DR included low-dose dexamethasone 20 mg/wk during cycles 1,2, along with SC daratumumab dosing.

- Primary endpoint: PFS (not yet reported)
- Interim analysis at 12 mo of therapy: ORR, ≥ VGPR, MRD rate, grade ≥3 AEs

Manier et al . ASH 2022. Abstr 569.

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Baseline Characteristics

Characteristic	DR (n = 199)	Rd (n = 94)
Median age, yr (range)	81 (68-92)	81 (68-90)
Age category, n (%) ▪ 65 to <70 yr ▪ 70 to <75 yr ▪ 75 to <80 yr ▪ ≥80 yr	 2 (1) 30 (15) 49 (25) 118 (59)	 2 (2) 13 (14) 19 (20) 61 (65)
Female, n (%)	101 (51)	48 (51)
ECOG PS 0/1/2, %	10/46/44	10/50/40
Charlson ≤1, n (%)	113 (58)	57 (61)
IFM frailty score, n (%) ▪ ≤1 ▪ 2 ▪ 3 ▪ 4 ▪ 5	 0 57 (29) 81 (41) 44 (22) 17 (9)	 0 35 (37) 26 (28) 24 (26) 9 (10)

Characteristic	DR (n = 199)	Rd (n = 94)
ISS disease stage I/II/III, %	17/51/32	19/53/28
Measurable disease type, n (%) ▪ IgG ▪ IgA ▪ PBJ only ▪ SFLC only	 113 (57) 38 (19) 21 (11) 27 (14)	 49 (52) 20 (21) 10 (11) 15 (16)
Cytogenetics profile,* n (%) ▪ Standard risk ▪ High risk ▪ del17p ▪ t(4;14) ▪ t(14;16)	 148 (83) 31 (17) 16 (9) 9 (5) 6 (3)	 60 (78) 17 (22) 11 (14) 5 (6) 3 (3)
Creatinine clearance, n (%) ▪ <30 mL/min ▪ 30 to <60 mL/min ▪ ≥60 mL/min	 1 (1) 119 (60) 79 (40)	 3 (3) 50 (53) 41 (44)

Manier et al . ASH 2022. Abstr 569.

Response Rates

Response	DR (n = 199)	Rd (n = 94)	*P* Value
ORR, %	96	85	.001
▪ CR	17	10	
▪ VGPR	47	33	
▪ PR	32	42	
≥ VGPR	64	43	
MRD at 10^{-5} by NGS,* %	10	3	.012

- Similar improvement in rate of ≥ VGPR with DR across all subgroups analyzed, including IFM frailty score (*P* = .87) and cytogenetic risk (*P* = .29)
- Fewer discontinuations in DR arm vs Rd arm (32% vs 45%)

Manier et al . ASH 2022. Abstr 569.

*Patients with missing data were considered MRD positive.

Safety

Most Common Grade ≥3 AEs	DR (n = 199)	Rd (n = 94)	*P* Value
Any grade ≥3 AE, n (%)	164 (82)	64 (68)	.010
SAE, n (%)	109 (55)	59 (63)	.21
Grade ≥3 hematologic AEs, n (%)	109 (55)	24 (26)	<.0001
▪ Anemia	21 (11)	2 (2)	.010
▪ Neutropenia	91 (46)	17 (18)	<.0001
▪ Thrombocytopenia	18 (9)	3 (3)	.089
Grade ≥3 infection, n (%)	26 (13)	17 (18)	.29
▪ Non–COVID-19 infections	17 (9)	13 (14)	.21
▪ Pneumonia	5 (3)	7 (7)	.060
▪ COVID-19	9 (5)	4 (4)	1
Treatment discontinuation for AE, n (%)	27 (14)	15 (16)	.65

Manier et al . ASH 2022. Abstr 569.

Safety by IFM Frailty Score Subgroups

Most Common Grade ≥3 AEs	IFM Frailty Score 2 + 3 (n = 199)			IFM Frailty Score 4 + 5 (n = 94)		
	DR (n = 138)	Rd (n = 61)	*P* Value	DR (n = 61)	Rd (n = 33)	*P* Value
SAE, n (%)	74 (54)	35 (57)	.65	35 (57)	24 (73)	.18
Infection, n (%)	13 (9)	8 (13)	.46	13 (21)	9 (27)	.61
▪ Non–COVID-19 infections	10 (7)	6 (10)	.58	7 (11)	7 (21)	.23
▪ Pneumonia	2 (1)	3 (5)	.17	3 (5)	4 (12)	.24
▪ COVID-19	3 (2)	2 (3)	.64	6 (10)	2 (6)	.71

Manier et al . ASH 2022. Abstr 569.

Conclusions

- In phase III IFM 2017-03 trial assessing frail patients with newly diagnosed MM, DR was associated with higher response rates vs Rd
  - ORR: 96% with DR vs 85% with Rd
  - Higher MRD negativity rates (10% vs 3%, respectively) and rapid responses
- DR associated with favorable safety profile and no increased risk of infection or pneumonia compared to Rd
  - Treatment discontinuation rates were similar between arms
- Encouraging potential for dexamethasone-sparing strategy in frail patients, but longer follow-up is needed, with PFS

Manier et al . ASH 2022. Abstr 569.

64th ASH
Annual Meeting

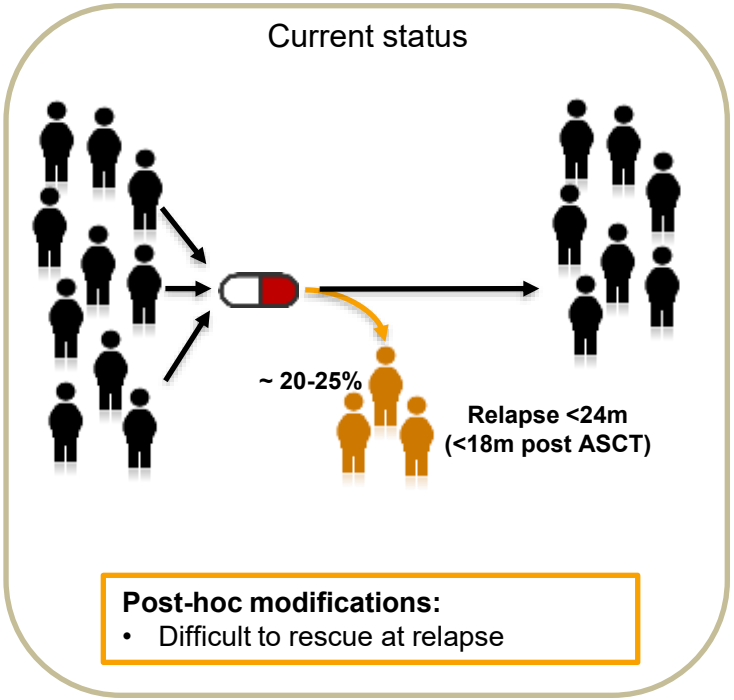
Extended intensified post-ASCT consolidation with Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (Dara-VRd) for Ultra-High Risk (UHiR) Newly Diagnosed Myeloma (NDMM) and Primary Plasma Cell Leukemia (pPCL): the UK OPTIMUM/MUKnine Trial.

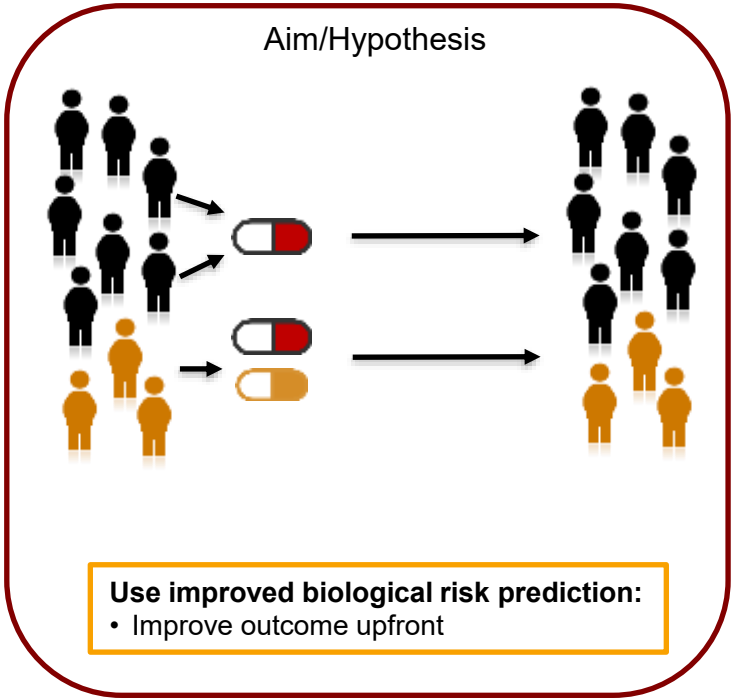
Martin Kaiser, Andrew Hall, Isabelle Smith, Ruth M De Tute, Sadie Roberts, Emma Ingleson, Kristian Bowles, Mamta Garg, Anand Lokare, Christina Messiou, Richard Houlston, Graham Jackson, Gordon Cook, Guy Pratt, Mark T Drayson, Roger G. Owen, Sarah R Brown, Matthew W Jenner

The Institute for Cancer Research, London, United Kingdom; Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom; HMDS Laboratory, St James' Institute of Oncology, Leeds, United Kingdom; Norfolk and Norwich University Hospitals NHS Trust, Norwich, United Kingdom; Haematology, Leicester Royal Infirmary/University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; Birmingham Heartlands Hospital, Birmingham, United Kingdom; Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom; Department of Haematology, University of Newcastle, Newcastle-upon-Tyne, United Kingdom; University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; University of Leeds, Leeds, United Kingdom; Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom; CTRU, University of Leeds, Leeds, United Kingdom; University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom

UK MYELOMA RESEARCH ALLIANCE

High-Risk MM - the unmet need



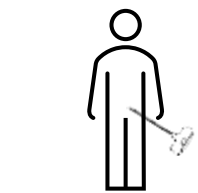


ASCT = autologous stem cell transplantation

Currently no uniform treatment standard

UK multi-centre phase 2 trial for UHiR MM and PCL - Screening protocol

39 NHS hospitals
Mostly community (DGH)
Sep 2017 – Jul 2019



Suspected or confirmed NDMM/PCL
Recruited to OPTIMUM Screening (n=472)

Enrollment

Did not have a symptomatic Multiple Myeloma or PCL diagnosis (n=60)
- Asymptomatic Myeloma (n=22)
- MGUS (n=14)
- Other (n=16)
- No confirmed diagnosis (n=8)

Central sample

Multiple Myeloma or PCL diagnosis (n=412)

Genetic & GEP Risk screening

87% complete screening result

Risk screening result (n=412)
- **Ultra High risk (n=138)**
- Non-high risk (n=221)
- Partial result (n=24)
- Missing risk result (n=29)

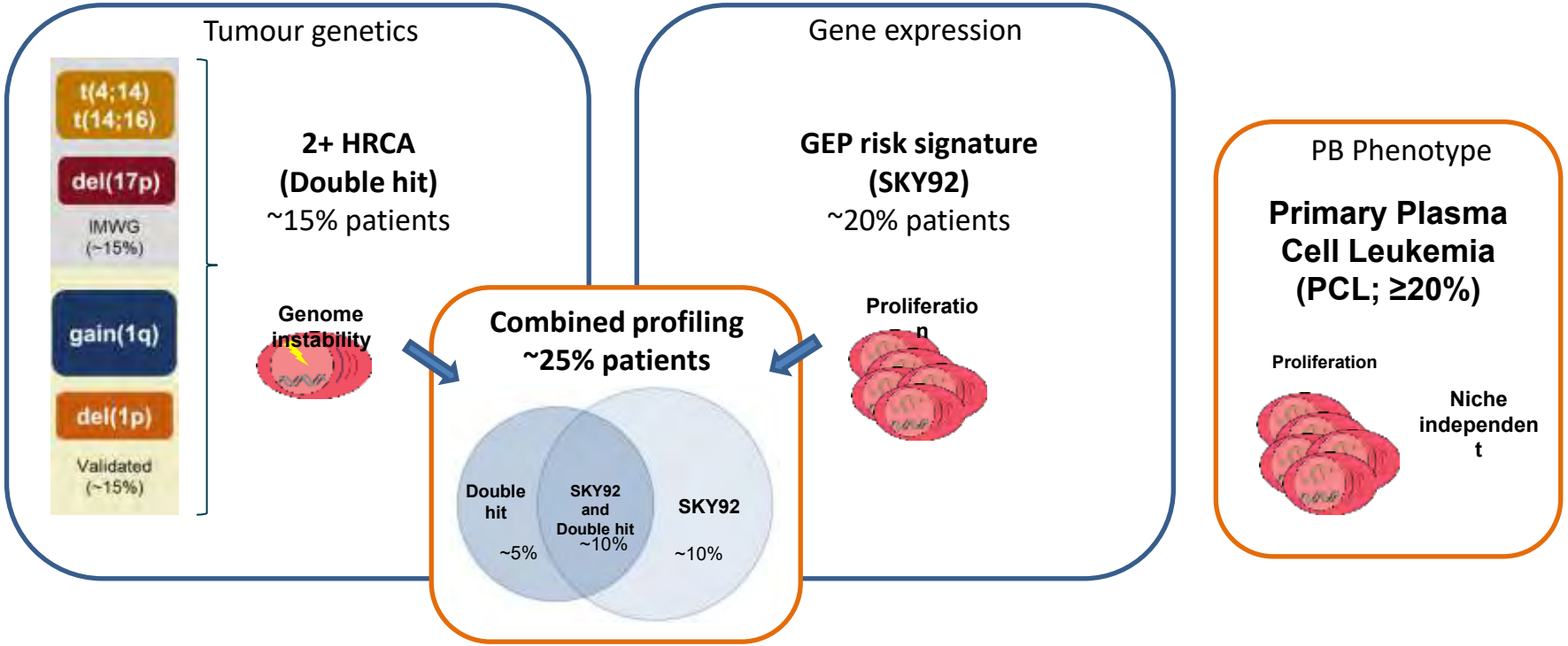
Recruitment 10 months ahead of projection

Remained in OPTIMUM Screening
(n=305; including 30 high risk patients)
- Standard of Care therapy – Data collection

Registered and eligible for OPTIMUM Treatment Trial (n=107)

Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

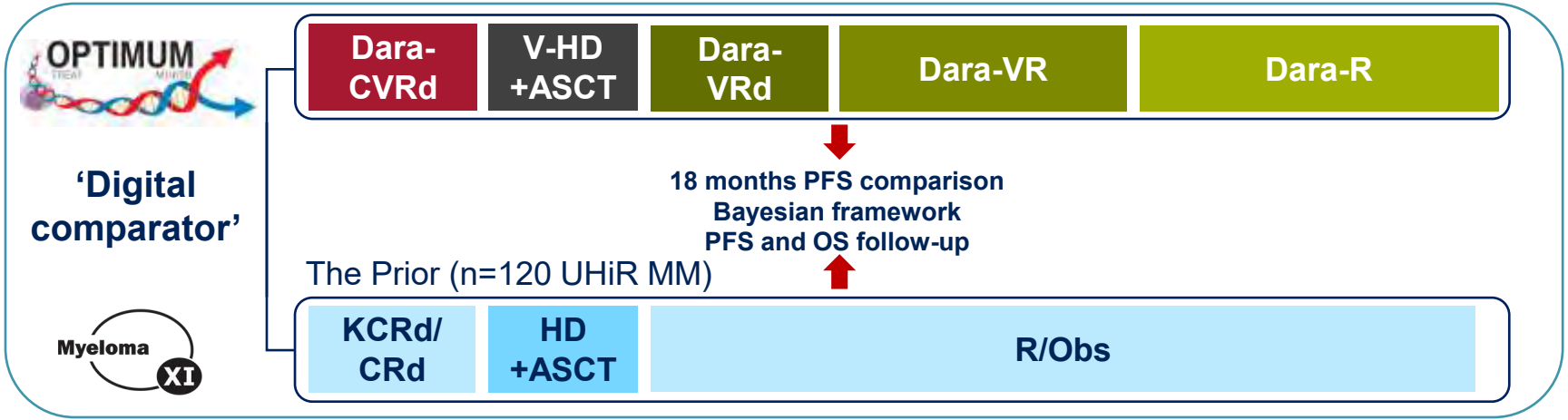
Trial screening for UHiR MM, inclusive for PCL



Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Shah V, et al., Leukemia 2018, Shah V, et al., Leukemia 2020, Gowda L, et al., *Bone Marrow Transplantation*, 54 (1089-1093), 2019

Clinical UHiR context – digital comparator trial



OPTIMUM design (appraisal framework for external comparator trials (Thorlund et al., 2020))**:**

- **Currently no treatment standard for UHiR group – UK standard at design: VTD, single ASCT, observation**
- **Mirrored molecular UHiR criteria** (Double hit and/or SKY92 risk signature)
- **Contemporaneous external dataset: most recent UK phase 3 Myeloma XI trial for NDMM**
  - KCRd (carfilzomib, cyclophosphamide, lenalidomide, dexamethasone) or CRd induction
    At time of design randomisation result not yet available
- **Recruitment in same healthcare system**
  - Same NHS hospitals/geography, virtually identical trial entry criteria

Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Brown S, et al., BMJ Open 2020
Jackson G., et al., PLOS Med 2021

Trial therapy

Bridging
Max
2 cycles

SOC (VTD CVD)

Induction
Max 6 cycles
(incl bridging)

Dara-CVRd

Daratumumab iv 16 mg/kg
Cycle 1&2: Days 1, 8, 15
Cycle 3+: Day 1
Cyclophosphamide po 500 mg
Days 1, 8
Bortezomib sc 1.3 mg/m^2
Days 1, 4, 8, 11*
Lenalidomide po 25 mg
Days 1-14
Dexamethasone po 40 mg†
Days 1, 4, 8, 11

21d cycles

Stem Cell Mobilisation

V-HD-MEL +ASCT

Melphalan iv 200 mg/m^2
Day -1
Autologous Stem Cell Translantation
Day 0

Bortezomib 1.3 mg/m^2
Days -1, +5, +14,*
Weekly after haematopoietic recovery

Consolidation 1
6 Cycles
Start 100-120d post ASCT

Dara-VRd

Daratumumab sc
1800 mg Day 1
Bortezomib sc 1.3 mg/m^2
Days 1, 8, 15, 22*
Lenalidomide po 25 mg
Days 1-21
Dexamethasone po 40 mg †
Day 1, 8, 15, 22

28d cycles

Consolidation 2
12 Cycles

Dara-VR

Daratumumab sc
1800 mg Day 1
Bortezomib sc 1.3 mg/m^2
Days 1, 8, 15*
Lenalidomide po 25 mg
Days 1-21

28d cycles

Maintenance
Until progression

Dara-R

Daratumumab sc
1800 mg Day 1
Lenalidomide po 25 mg
Days 1-21

28d cycles

*Permissive bortezomib dose reduction schedule
†20mg for elderly/frailer

MRD time points

Trial objectives

Evaluate efficacy of Dara-(C)VRd before and after ASCT in Ultra High-Risk MM and PCL

- Progression free survival at 18 months compared against The Prior
- **Progression free and overall survival end of Consolidation 2**
- MRD at key timepoints

- Determine safety and toxicity of Dara-CVRd induction and Dara-VRd consolidation

Brown S, et al., BMJ Open 2021

UHiR populations: OPTIMUM and Myeloma XI

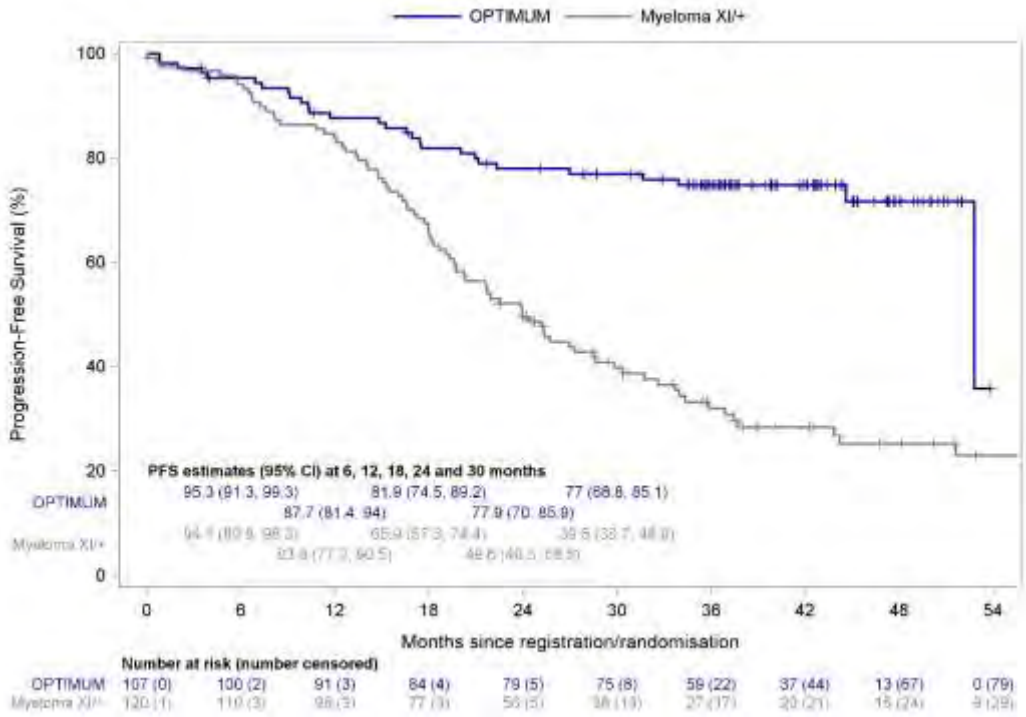
Patient Characteristics	OPTIMUM (n=107)	Myeloma XI (n=120)
Median age, yrs (range)	60 (35-78)	62 (33-69)
Male, n (%)	64 (60%)	69 (58%)
ISS Stage 1, n (%)	29 (27%)	23 (19%)
Stage 2, n (%)	43 (40%)	53 (44%)
Stage 3, n (%)	34 (32%)	38 (32%)
missing, n (%)	1 (1%)	6 (5%)
ECOG Performance Status		
0, n (%)	51 (48%)	47 (39%)
1, n (%)	42 (39%)	46 (38%)
≥2, n (%)	10 (9%)	22 (18%)
missing, n (%)	4 (4%)	5 (4%)
Molecular profiles		
Double hit genetics, n (%)	57 (53%)	55 (56%)*
SKY92 risk signature present, n (%)	82 (77%)	72 (72%)*
Both Double hit and SKY92, n (%)	33 (31%)	28 (29%)*

* in relation to 98 patients with complete GEP and genetic profiles

Comparable clinical & molecular characteristics

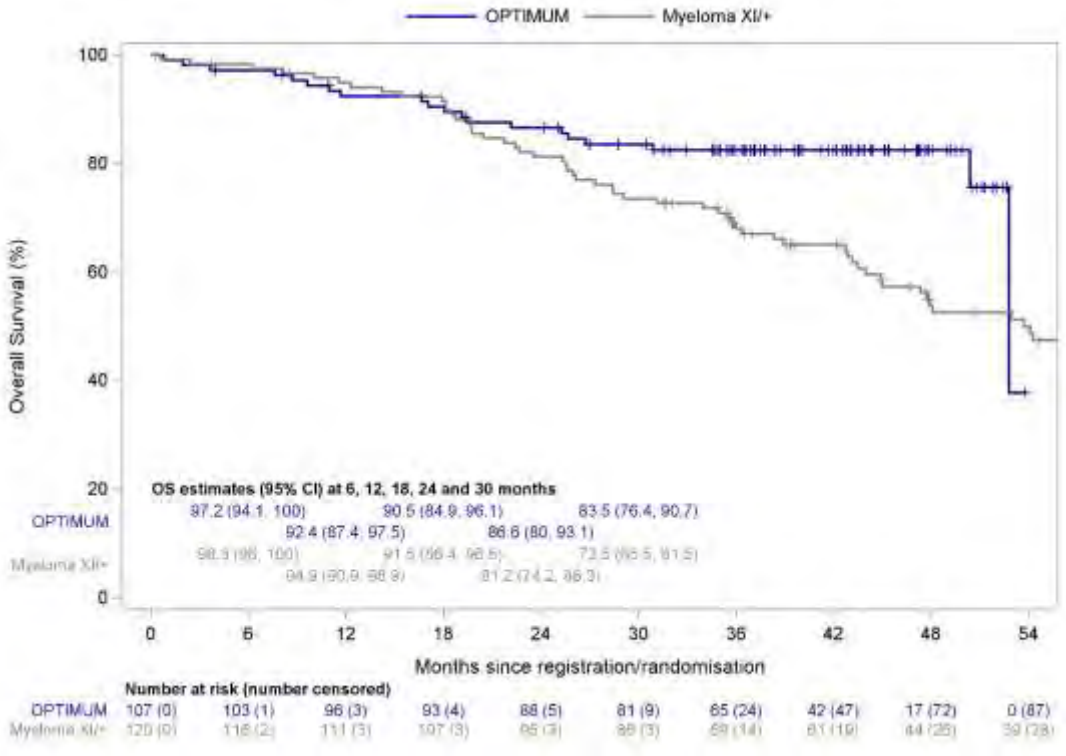
Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Extended Follow-up: End of Dara-VR Consolidation 2
OPTIMUM vs. Myeloma XI: PFS



Median follow-up
41.2 months

Extended Follow-up: End of Dara-VR Consolidation
OPTIMUM vs. Myeloma XI: OS



Median follow-up
41.2 months

Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Dose Reductions during Consolidation 2

n=80 patients, including earlier reductions

Trial protocol encouraged early reductions (grade 1 AR)

Modification of therapy	Daratumumab	Bortezomib	Lenalidomide
No modification	79 (98.8%)	48 (69.0%)	46 (57.5%)
Hematological toxicity	0 (0%)	11 (28.8%)	17 (21.3%)
Non-Hematological toxicity	0 (0%)	26 (32.5%)	20 (25.0%)
Other	1 (1.3%)	1 (1.3%)	3 (3.8%)

Summary

- Collaborative trial designed with patients to address unmet need within healthcare system requirements
- Extended intensified consolidation with Dara-VR(d) is an effective treatment option for UHiR MM and PCL patients
- Continued improvement of PFS for OPTIMUM vs. Myeloma XI UHiR patients
- Early positive OS signal for OPTIMUM vs Myeloma XI UHiR patients
- Ongoing intensive consolidation required individualised dose reductions, but was tolerable for most patients, with cytopenia and infection main AEs
- OPTIMUM design explicitly balanced intensity and toxicity vs. high unmet need
- Successful recruitment suggests high unmet need for better diagnostics and therapy
- Results support allocation of resources to unmet need in restricted healthcare systems

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

Charlotte Pawlyn[1,2], Tom Menzies[3], Faith Davies[4], Ruth de Tute[5], Rowena Henderson[3], Gordon Cook[3,6], Matthew Jenner[7], John Jones[8], Martin Kaiser[1,2], Mark Drayson[9], Roger Owen[8], David Cairns[3], Gareth Morgan[4], Graham Jackson[10]

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

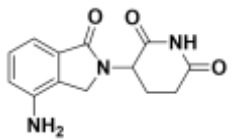
On behalf of the Myeloma XI Trial Management Group and NCRI Haem-Onc Clinical Studies Group

Lenalidomide maintenance after ASCT

Induction

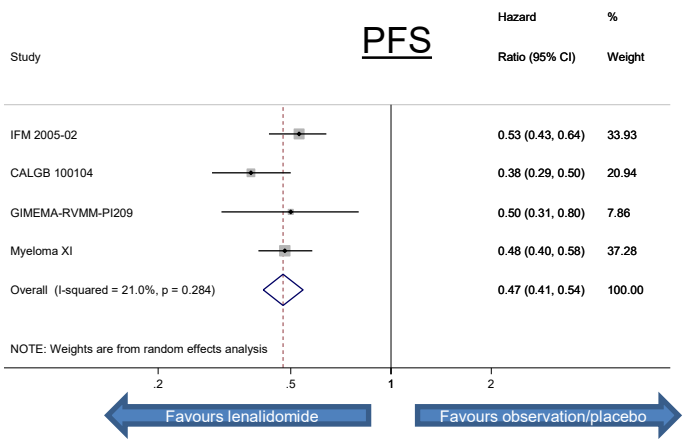
ASCT/consolidation

Maintenance

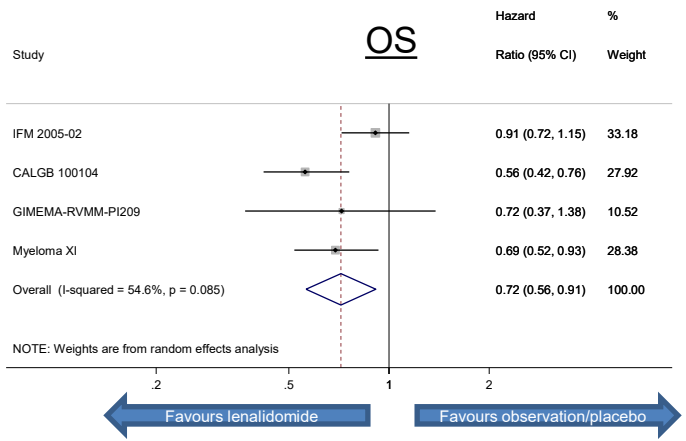


Lenalidomide

PFS

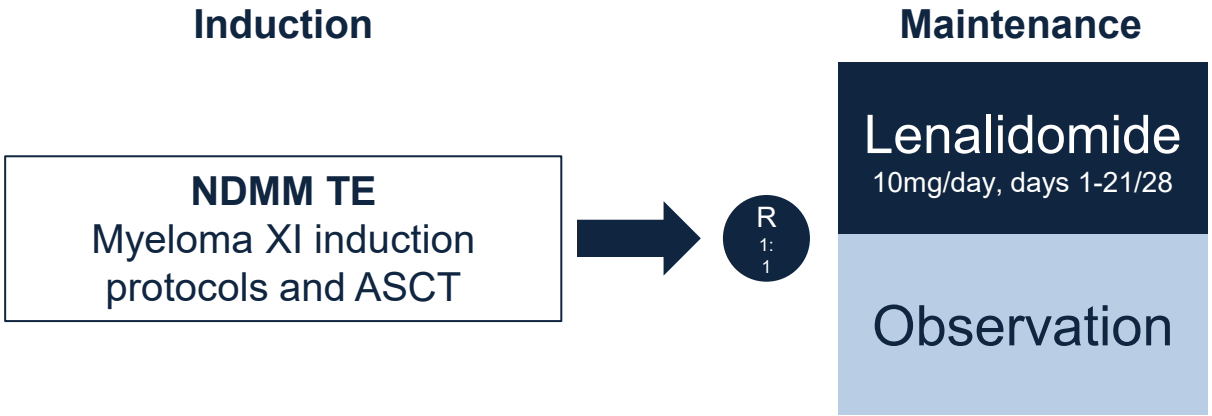


OS



Attal M, et al. N Engl J Med. 2012;366:1782-91, McCarthy PL, et al. N Engl J Med. 2012;366:1700-81, Palumbo A, et al. N Engl J Med. 2014;371:895-905, McCarthy PL et al., J Clin Oncol. 2017 Oct 10;35(29):3279-3289, Jackson GH, et al. Lancet Oncol 2019;20(1) 57-73

Myeloma XI



N=1248

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

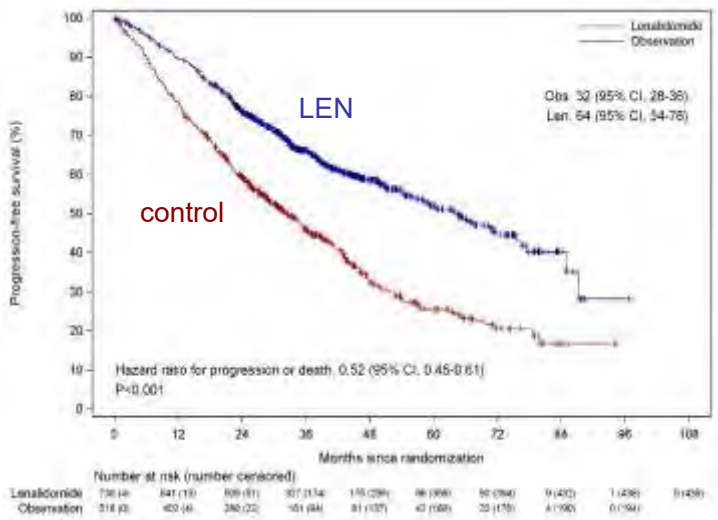
Exclusion criteria

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

Pawlyn et al ASH 2022, Abstract 570

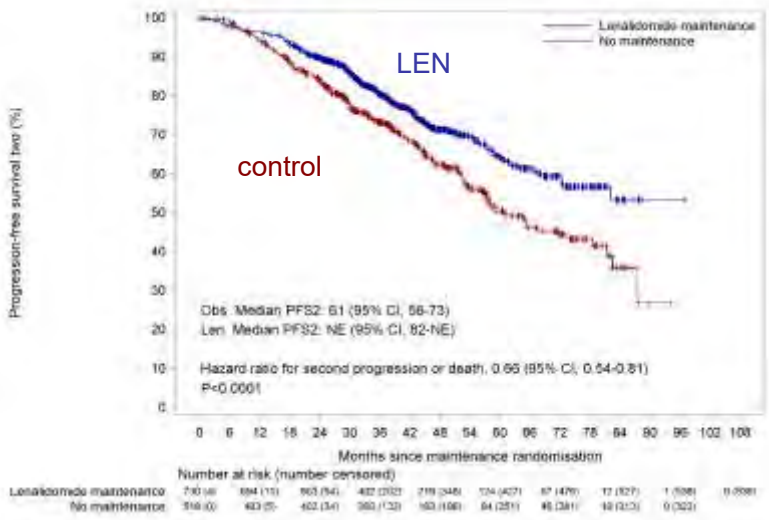
Outcomes from maintenance randomisation – overall population

PFS



Hazard Ratio 0.52*

PFS2



Hazard Ratio 0.66*

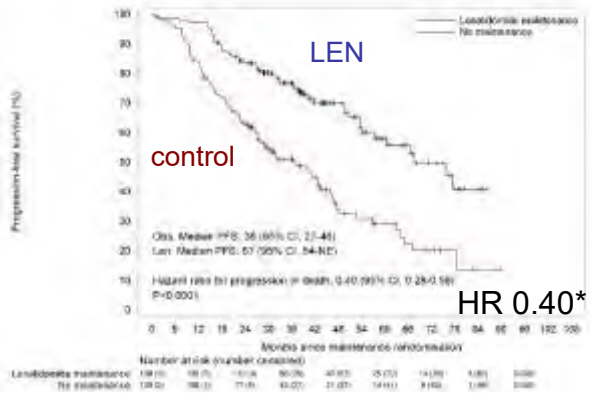
Pawlyn et al ASH 2022, Abstract 570

*p<0.05

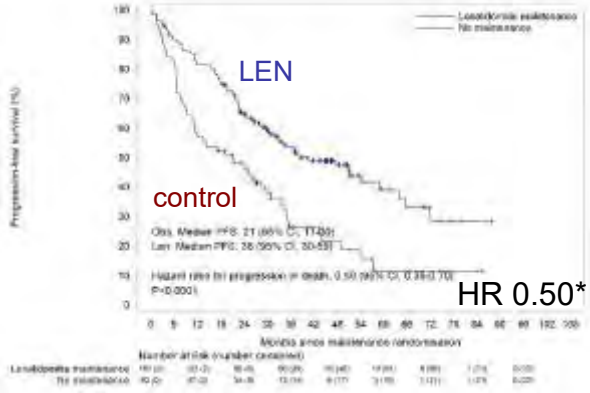
Outcomes from maintenance randomisation

Genetic risk status

S
R

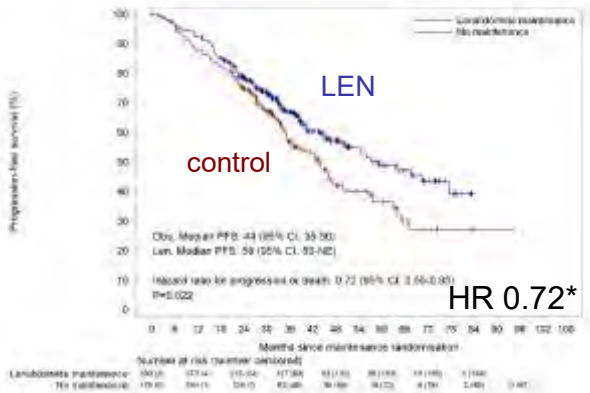


HR/UHR

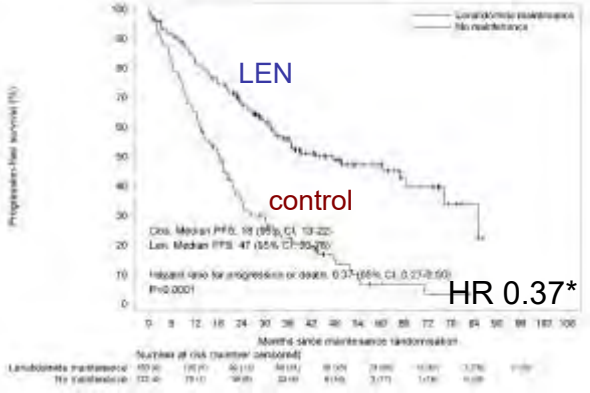


MRD status

MRD -ve



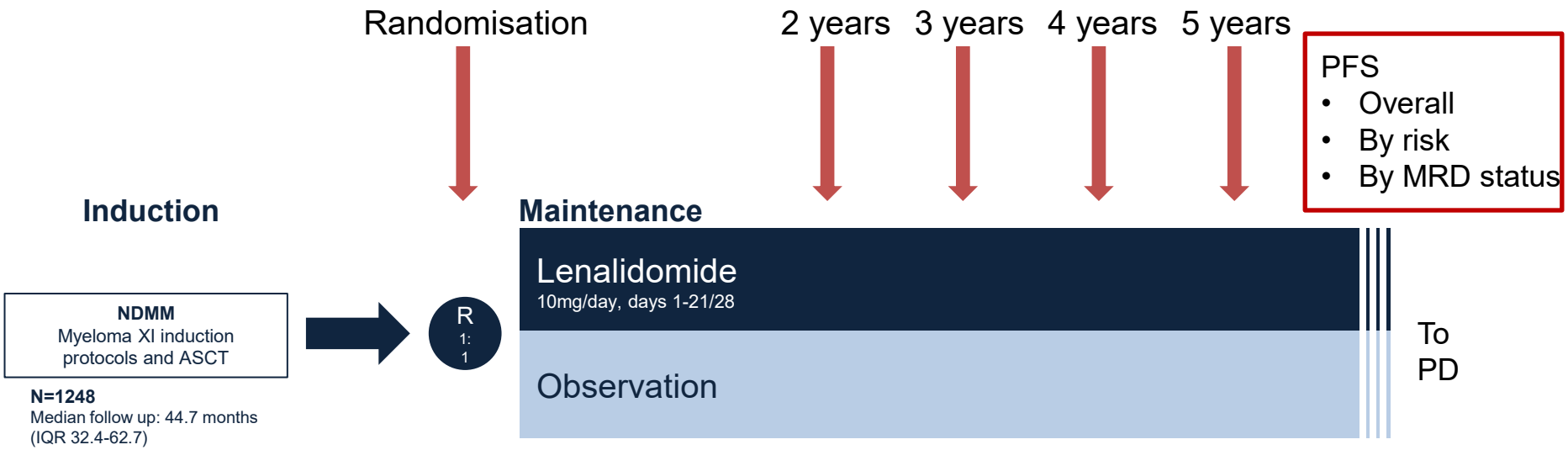
MRD +ve



*p<0.05

MRD status was assessed by flow cytometry (median sensitivity $4x10^5$)

Multiple landmark analyses

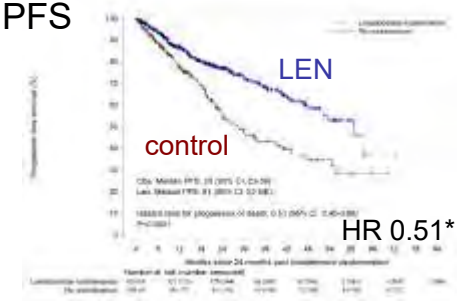
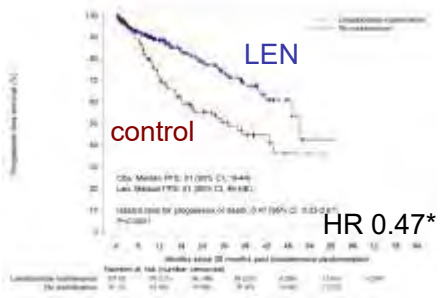
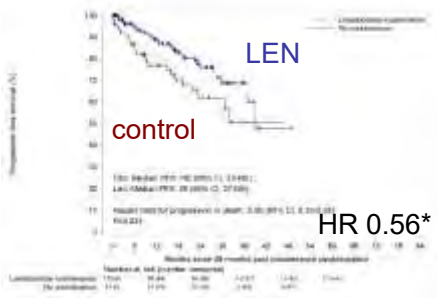
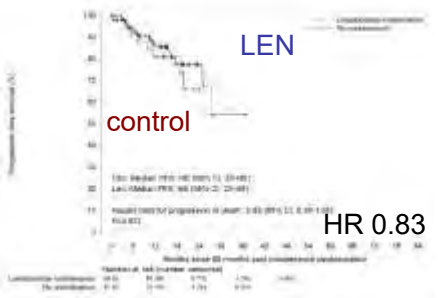
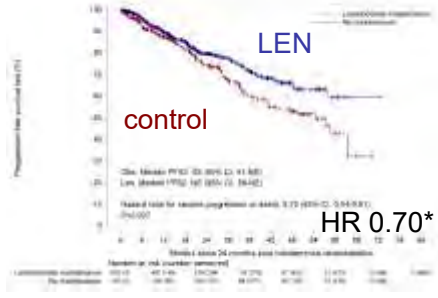
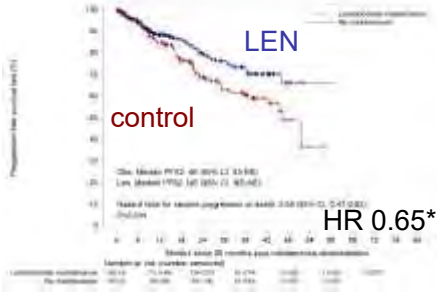
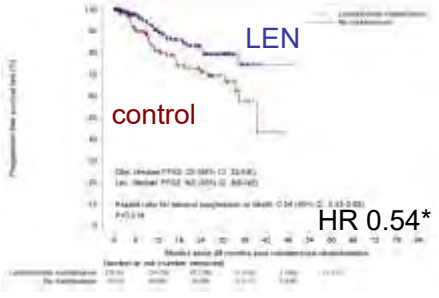
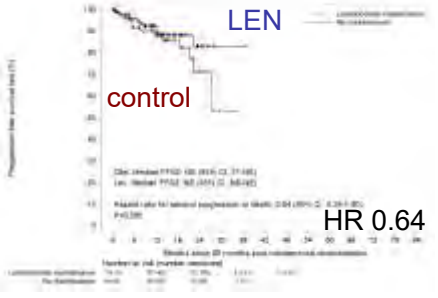


Median duration of lenalidomide therapy 28 cycles (range 1-96)

- Patients still on therapy 330/730 (45%)

Pawlyn et al ASH 2022, Abstract 570

Outcomes from multiple landmarks – overall population

	2 years	3 years	4 years	5 years
PFS				
PFS2				

*p<0.05

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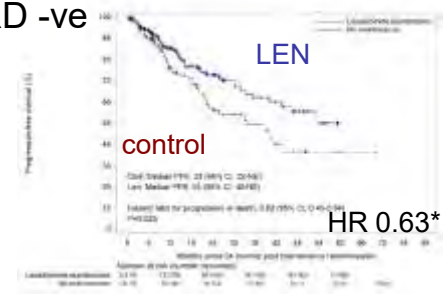
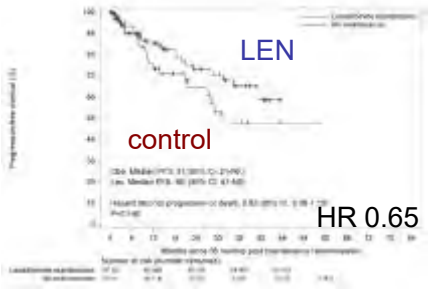
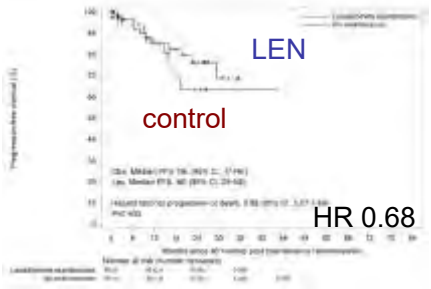
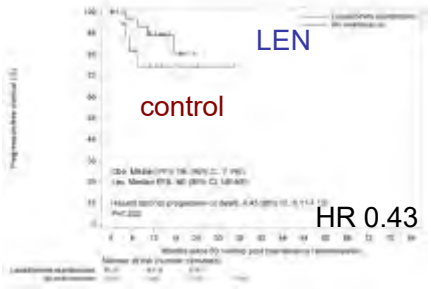
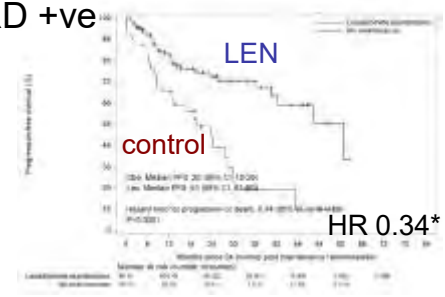
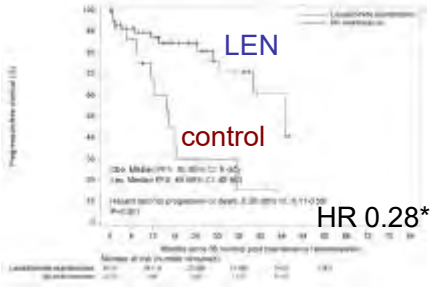
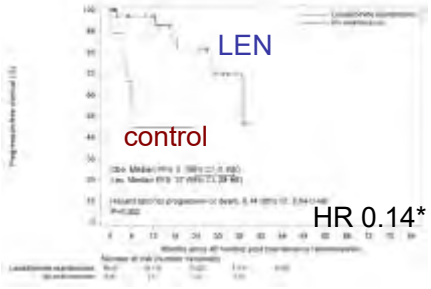
Outcomes from multiple landmarks – by MRD status

PFS

	2 years	3 years	4 years	5 years
MRD -ve				
MRD +ve				

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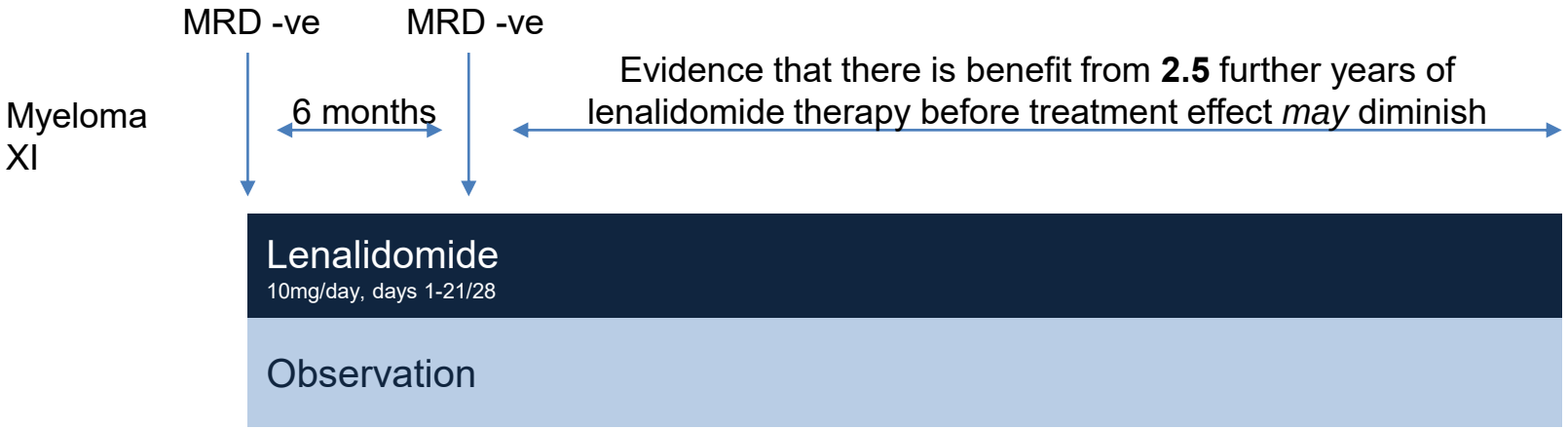
Can this help us personalise therapy?

MRD +ve – continue maintenance to progression

MRD –ve:

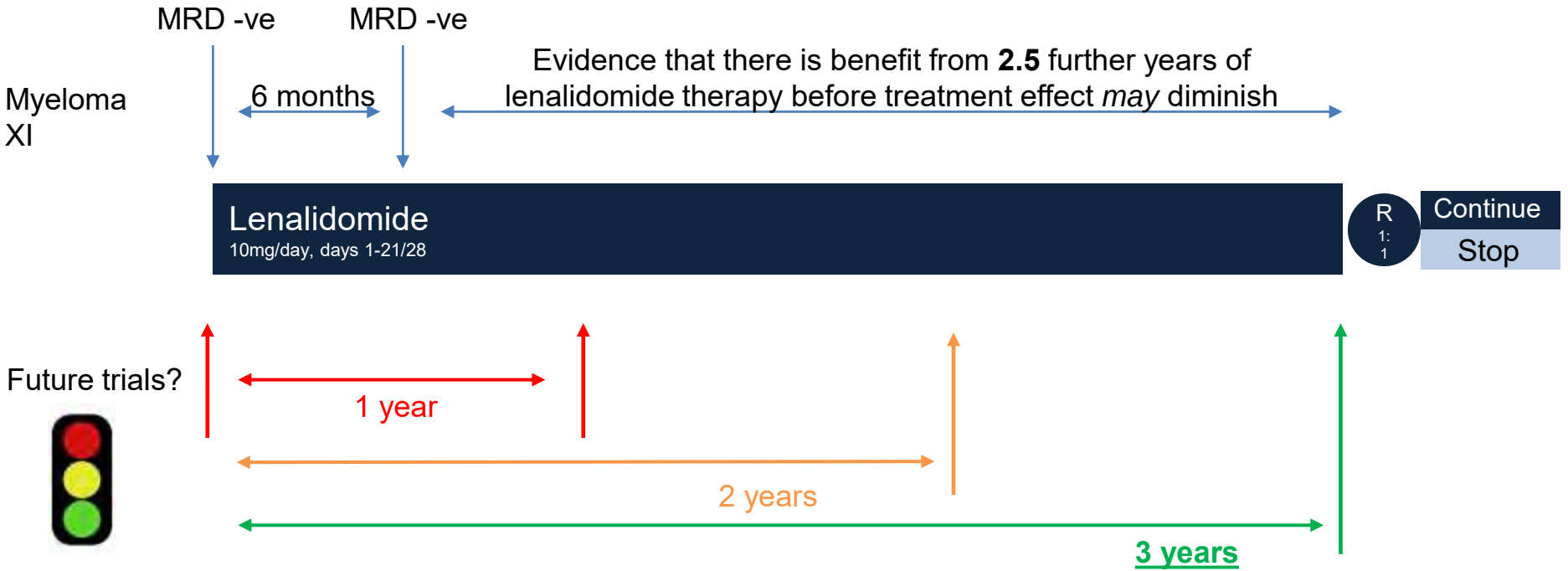


Pawlyn et al ASH 2022, Abstract 570

Can this help us personalise therapy?

MRD +ve – continue maintenance to progression

MRD –ve:



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Conclusions

- These data suggest an ongoing PFS benefit associated with continuing lenalidomide maintenance beyond **at least 4-5 years** in the overall patient population

- Even in patients with sustained MRD negativity, there is evidence of benefit from continuing lenalidomide maintenance for **at least 3 years** in total
  - Randomised trials to address the impact of stopping lenalidomide maintenance in patients with sustained MRD negativity could be considered, at no earlier than 3 years

- In patients who are MRD +ve these data support continuing lenalidomide until disease progression

- No evidence of cumulative haematological toxicity was identified

- These findings emphasise the need for long term follow up of maintenance studies to enable the exploration of such questions
  - There is a planned powered OS update of Myeloma XI in 2023

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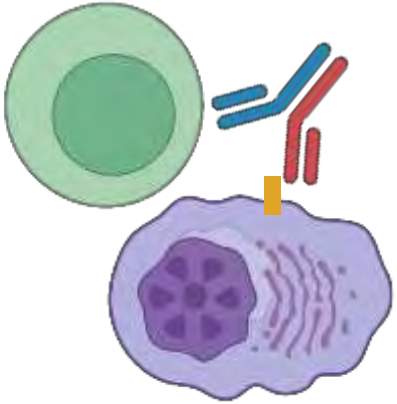
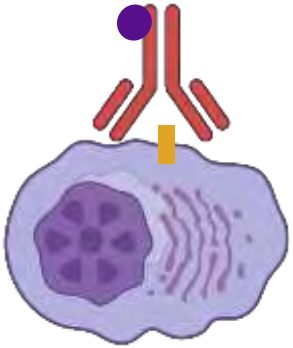
Relapsed disease



Bispecific antibodies

BCMA-CD3
Elranatamab

GPRC5D-CD3
Talquetamab



Antibody drug conjugates

CD38-attenuated IFNα
Modakafusp alfa

Elranatamab

FDA's Breakthrough Designation

MagnetisMM-3 Study

- MagnetisMM-3 is an open-label, multicenter, non-randomized, phase 2 study

Patients with RRMM

Key inclusion criteria:
- Refractory to ≥1 each of the following: proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody[a]
- ECOG performance status ≤2
- Creatinine clearance ≥30 mL/min
- Platelets ≥25 × 10^9/L
- ANC ≥1.0 × 10^9/L
- Hemoglobin ≥8 g/dL

Cohort A (n=123)
No prior BCMA-directed treatment

Cohort B (n=64)
Prior BCMA-directed ADC or CAR-T

- Patients will be followed for ~2 y from enrollment

Elranatamab 76 mg SC QW on a 28-d cycle

Primary endpoint
- ORR by BICR[b]

Secondary endpoints
- Duration of response[b,c]
- CR rate[b,c]
- ORR[c]
- ORR by baseline extramedullary disease status[b]
- Duration of CR[b,c]
- Time-to-response[b,c]
- PFS[b,c]
- MRD-negativity rate
- OS
- Safety
- Pharmacokinetics

[a] Refractory was defined as having disease progression while on therapy or within 60 d of last dose in any line, regardless of response
[b] By BICR assessment per IMWG response criteria (Kumar S, et al. Lancet Oncol 2016;17:e328-46)
[c] By investigator assessment per IMWG response criteria
ADC=antibody drug conjugate; ANC=absolute neutrophil count; BCMA=B-cell maturation antigen; BICR=blinded independent central review; CAR-T=chimeric antigen receptor T-cell; CR=complete response; ECOG=Eastern Cooperative Oncology Group; IMWG=International Myeloma Working Group; MRD=minimal residual disease; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QW=once weekly; SC=subcutaneous

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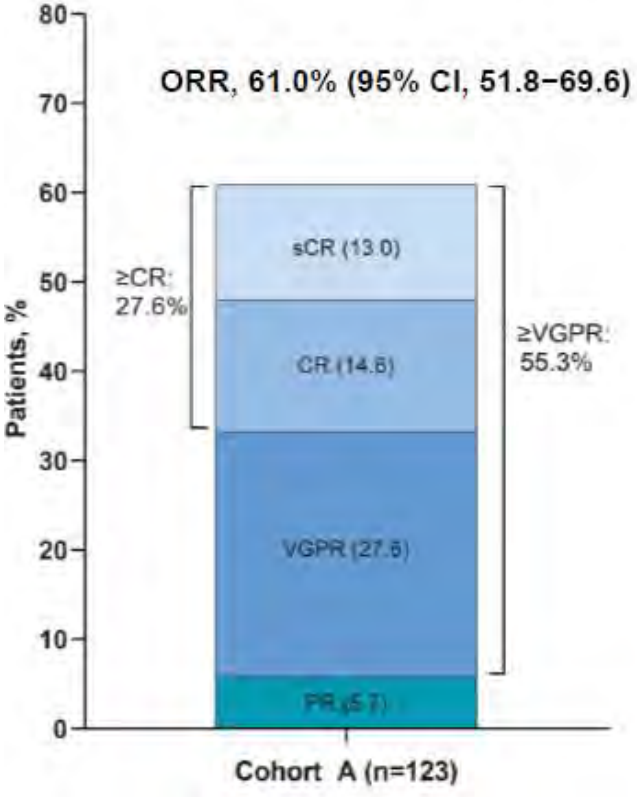
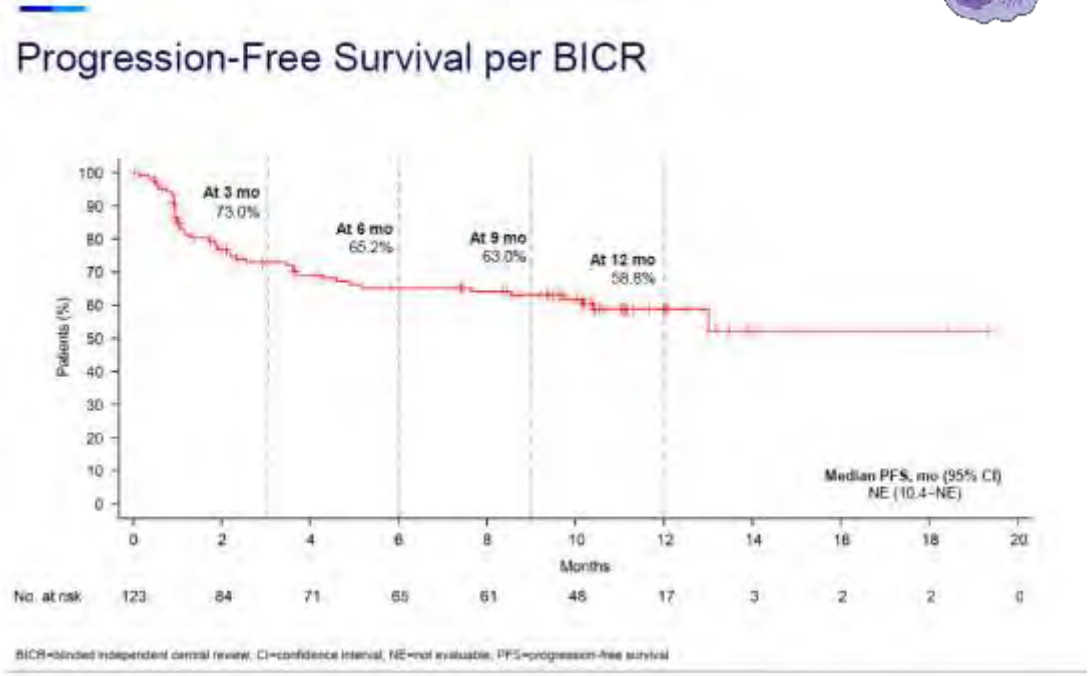
Elranatamab – MagnetisMM-3



Bahlis N et al ASH 2022, Abstract 159



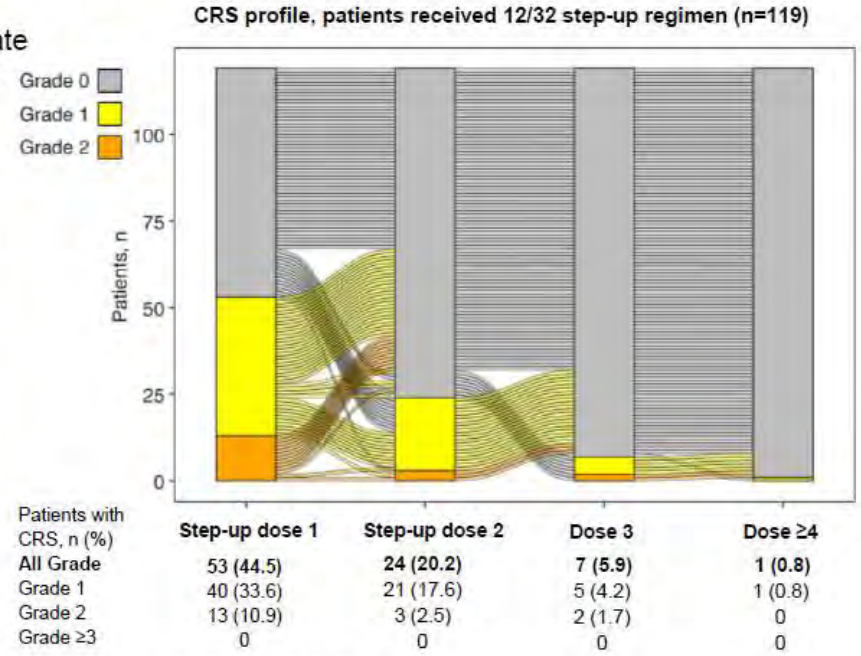
Median OS not yet reached

Elranatamab – MagnetisMM-3

AEs of Special Interest: CRS and ICANS

- The step-up priming regimen successfully mitigated the rate and severity of CRS, and the CRS profile was predictable

TEAE of special interest	12/32 mg step-up regimen (n=119)[a] CRS	ICANS
Patients with TEAE, n (%)	67 (56.3)	4 (3.4)
Maximum Grade 1	50 (42.0)	1 (0.8)
Maximum Grade 2	17 (14.3)	3 (2.5)
Maximum Grade ≥3	0	0
Patients with >1 TEAE, n (%)	18 (15.1)	1 (0.8)
Median time to onset of TEAE, d (range)	2.0 (1.0–9.0)	2.5 (1.0–4.0)
Median time to resolution of TEAE, d (range)	2.0 (1.0–19.0)	2.0 (1.0–6.0)
Patients who received tocilizumab[b] or steroids, n (%)		
Tocilizumab	27 (22.7)	2 (1.7)
Steroids	10 (8.4)	2 (1.7)
Permanent discontinuation due to AE, n (%)	0	0



[a] Patients who received 1 step-up priming dose of 44 mg in Wk 1 were excluded from this CRS and ICANS analysis (n=4); [b] Includes tocilizumab and siltuximab
CRS and ICANS which were graded by American Society for Transplant and Cellular Therapy criteria (Lee DW, et al. Biol Blood Marrow Trans 2019;25:62)
AE=adverse event; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; TEAE=treatment-emergent adverse event

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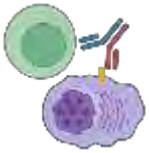
Elranatamab – MagnetisMM-3



AEs of Special Interest: Infections

- Infections were reported in 66.7% (Grade 3/4, 35.0%) of patients
  - Median time to first onset of infections was 47.5 (range, 1.0–295.0) days
- COVID-19 related TEAEs were reported in 31 (25.2%) patients
  - 2 (1.6%) patients died due to COVID-19 pneumonia, both considered unrelated to treatment by the investigator
- 8 (6.5%) patients had an infection that led to permanent discontinuation of elranatamab
  - Most common infection TEAEs leading to treatment discontinuation were septic shock (n=2) and sepsis (n=2)
- Among patients with quantitative IgG data (n=101), 76 (75.2%) patients had IgG level <400 mg/dL during the study
- Overall, 50 (40.7%) patients received IVIG during the study

n (%)	Cohort A (N=123)	
	Any grade	Grade 3/4
Infection TEAEs in ≥5% of patients		
COVID-19 related[a]	31 (25.2)	14 (11.4)
Upper respiratory tract infection	22 (17.9)	0
Pneumonia	15 (12.2)	7 (5.7)
Urinary tract infection	11 (8.9)	4 (3.3)
Sinusitis	11 (8.9)	2 (1.6)
TEAEs of interest		
Pneumocystis jirovecii pneumonia	6 (4.9)	5 (4.1)
CMV infection reactivation	6 (4.9)	2 (1.6)
CMV infection	4 (3.3)	0

[a] Includes preferred terms in COVID-19 (narrow) standardized MedDRA queries

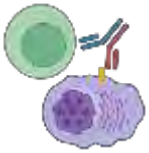
Administration of antibacterial and/or antiviral agents for infection prophylaxis was permitted for patients at increased risk of infection in accordance with local standard of care practice and/or institutional guidelines

AE=adverse event; CMV=cytomegalovirus; IgG=immunoglobin G; IVIG=intravenous immunoglobin; MedDRA=*Medical Dictionary for Regulatory Activities* Terminology; TEAE=treatment-emergent adverse event

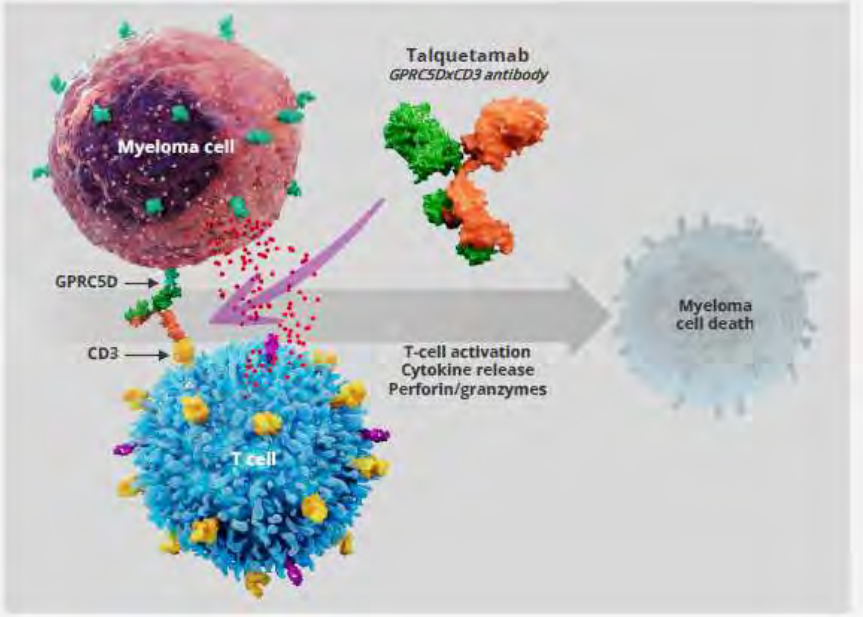
Bahlis N et al ASH 2022, Abstract 159

Talquetamab – MonumenTAL-1

FDA's Breakthrough Designation



- **Talquetamab is a novel first-in-class, off-the-shelf, T-cell redirecting bispecific antibody** directed against a new antigen target called GPRC5D[1,2]
- **GPRC5D is a novel antigen target in myeloma** that is highly expressed on malignant plasma cells with limited expression in normal human tissues,[3-6] including hematopoietic stem cells[7]
- **Talquetamab has shown an ORR of 64–70%** with QW and Q2W dosing in the MonumenTAL-1 study (NCT03399799/NCT04634552)[8]
- **Updated results** from the **MonumenTAL-1 study** are presented, including all patients treated at each RP2D for the first time, as well as a cohort of patients with prior CAR-T cell or bispecific antibody treatment



Chari AJ et al ASH 2022, Abstract 157

Phase 1 experience – 232 pt, 70% ORR and 10.2m median PFS
Chari et al N Engl J Med. 2022 Dec 15;387(24):2232-2244

Talquetamab – MonumenTAL-1

RP2D 0.4 mg/kg QW SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

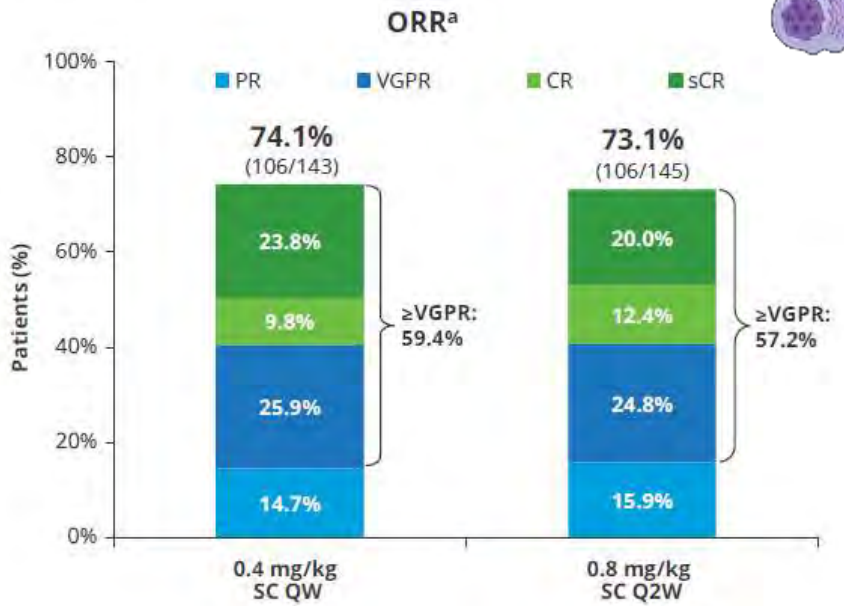
(Phase 1 [n=21] + Phase 2 [n=122]: N=143)

RP2D 0.8 mg/kg Q2W SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

(Phase 1 [n=36] + Phase 2 [n=109]: N=145)

Prior T-cell redirection (QW and Q2W)
Previously exposed to T-cell redirection therapies
Dosed with either 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC

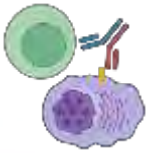
(Phase 1 [n=17] + Phase 2 [n=34]: N=51)



ORR 63%
72% prior CART
44% prior bispecific

Chari AJ et al ASH 2022, Abstract 157

Talquetamab – MonumenTAL-1



Hematologic adverse events

AEs (≥20% of any RP2D cohort), n (%)	0.4 mg/kg SC QW[a] (n=143) mFU, 11.0 months[b]		0.8 mg/kg SC Q2W[a] (n=145) mFU, 5.1 months[c]	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Anemia	64 (44.8)	45 (31.5)	57 (39.3)	36 (24.8)
Neutropenia	49 (34.3)	44 (30.8)	41 (28.3)	32 (22.1)
Lymphopenia	40 (28.0)	37 (25.9)	38 (26.2)	37 (25.5)
Thrombocytopenia	39 (27.3)	29 (20.3)	39 (26.9)	24 (16.6)

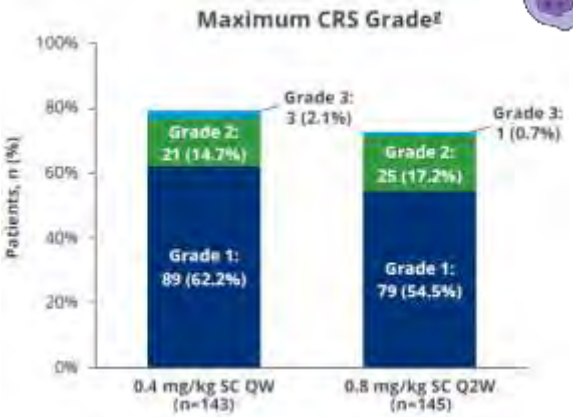
- Most high-grade AEs were cytopenias
- Cytopenias were generally limited to the first few cycles

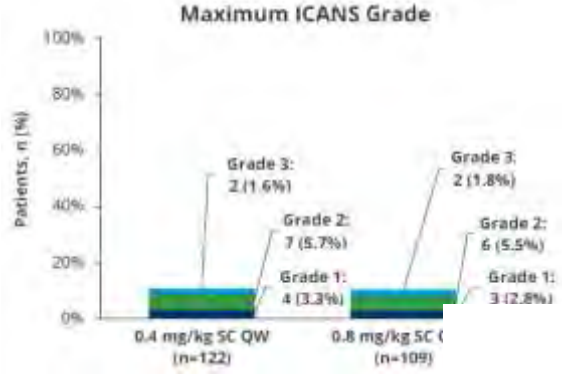
Infections

- At 0.4 mg/kg QW and 0.8 mg/kg Q2W:
  - Infections occurred in 57.3% and 50.3%
    - Grade 3/4 in 16.8% and 11.7%
  - 5 (3.5%)[d] and 4 (2.8%)[e] patients had opportunistic infections
  - 13 (9.1%) and 16 (11.0%) patients had COVID-19
    - Grade 3/4 in 0.7% and 2.1%
    - 2 patients died from COVID-19
- 13.3% and 9.7% of patients received IVIg, respectively

AEs (≥20% of any RP2D cohort), n (%)	0.4 mg/kg SC QW[a] (n=143) mFU, 11.0 months[b]		0.8 mg/kg SC Q2W[a] (n=145) mFU, 5.1 months[c]	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
CRS	113 (79.0)	3 (2.1)	105 (72.4)	1 (0.7)
Skin-related AEs[d]	80 (55.9)	0	98 (67.6)	1 (0.7)
Nail-related AEs[e]	74 (51.7)	0	63 (43.4)	0
Dysgeusia[f]	69 (48.3)	NA	67 (46.2)	NA
Rash-related AEs[g]	56 (39.2)	2 (1.4)	39 (26.9)	8 (5.5)
Weight decreased	57 (39.9)	3 (2.1)	47 (32.4)	2 (1.4)
Pyrexia	53 (37.1)	4 (2.8)	35 (24.1)	1 (0.7)
Asthenia	37 (25.9)	3 (2.1)	13 (9.0)	2 (1.4)
Dry mouth	36 (25.2)	0	53 (36.6)	0
Diarrhea	34 (23.8)	3 (2.1)	32 (22.1)	0
Dysphagia	34 (23.8)	0	33 (22.8)	3 (2.1)
Fatigue	32 (22.4)	5 (3.5)	29 (20.0)	1 (0.7)
Decreased appetite	25 (17.5)	2 (1.4)	29 (20.0)	2 (1.4)

- **Low rates of grade 3/4 nonhematologic AEs** were observed
- **Low rates of discontinuation due to AEs** were observed with QW (4.9%) and Q2W (6.2%) schedules
- **Most common AEs were CRS, skin-related events, nail-related events, and dysgeusia**
  - Rates of high-grade skin, nail, and rash-related events were low
  - Dysgeusia was managed with supportive care, and at times with dose reduction
- At 0.4 mg/kg QW and at 0.8 mg/kg Q2W,
  - 8.4% and 13.8% had dose delays due to AEs
  - 14.7% and 6.2% had dose reductions due to AEs
- At time of data cut-off, no patients in these cohorts died due to drug-related AEs

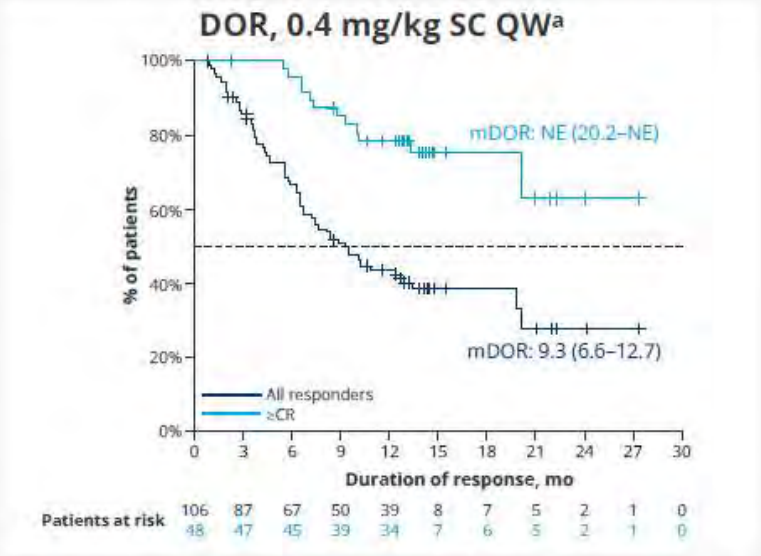


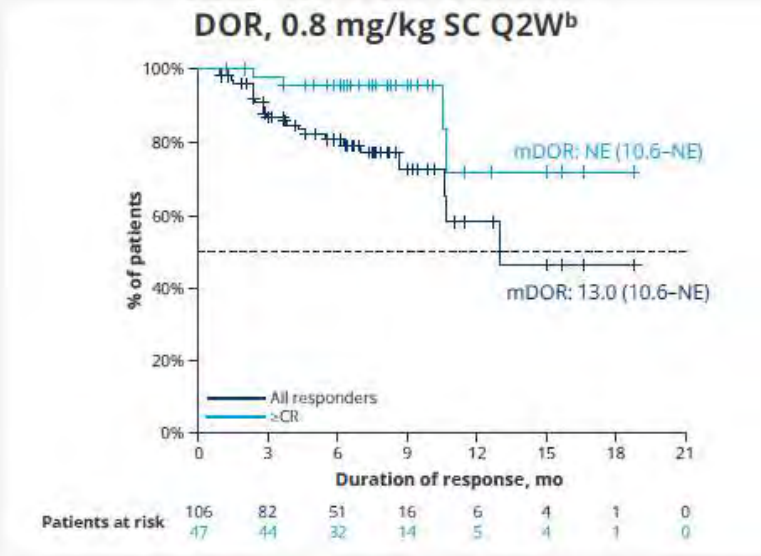


Chari AJ et al ASH 2022, Abstract 157

Talquetamab – MonumenTAL-1

- Treatment at both doses led to durable responses
  - Median DOR not reached for those patients who achieved ≥CR





mPFS: 7.5 months (95% CI: 5.7–9.4; 33% censored)

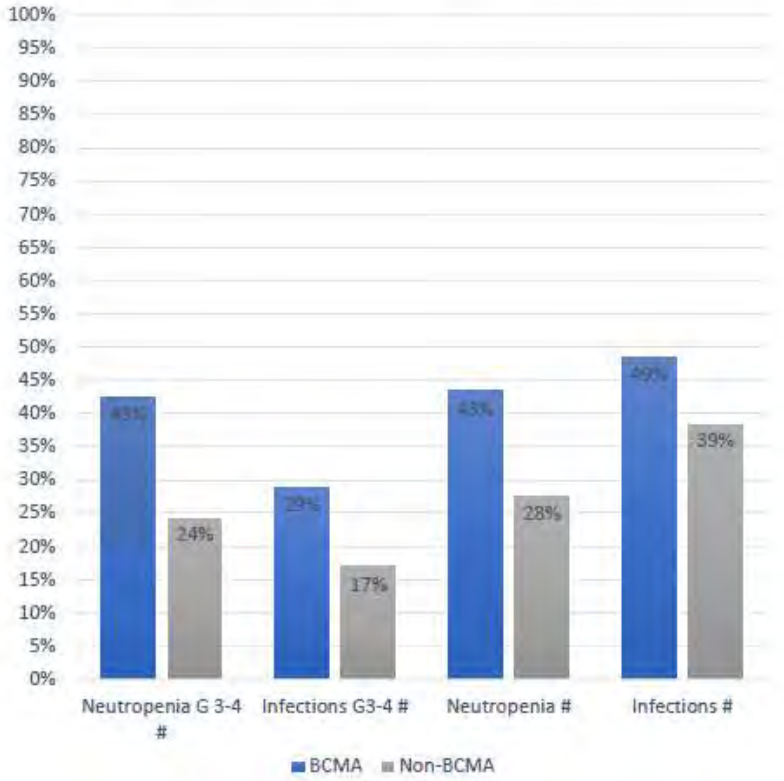
11.9 months (95% CI: 8.4–NE; 61% censored)

Chari AJ et al ASH 2022, Abstract 157

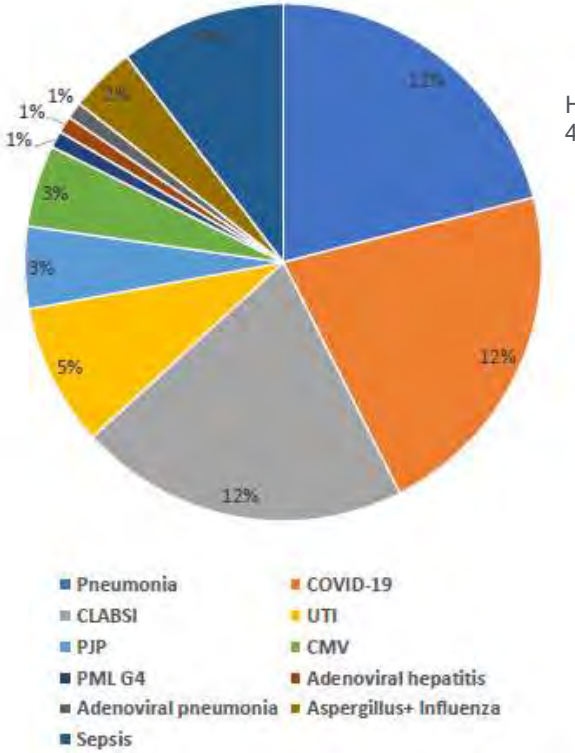
Infections with bispecific antibodies

10 trials
790 patients

BCMA vs Non-BCMA incidence of all grades and G3/4 infections and neutropenia.



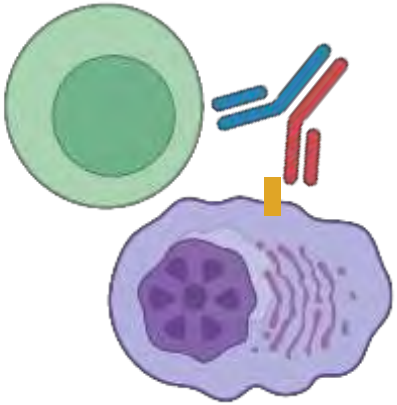
The incidence of specific infections related to BsAbs therapy.



Hypogamaglobulinemia
48.5%

Mazahreh F et al ASH 2022, Abstract 1909

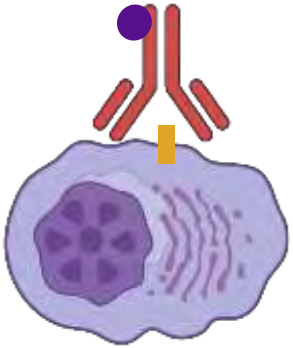
Outline



Bispecific antibodies

BCMA-CD3
Teclistamab
Elranatamab

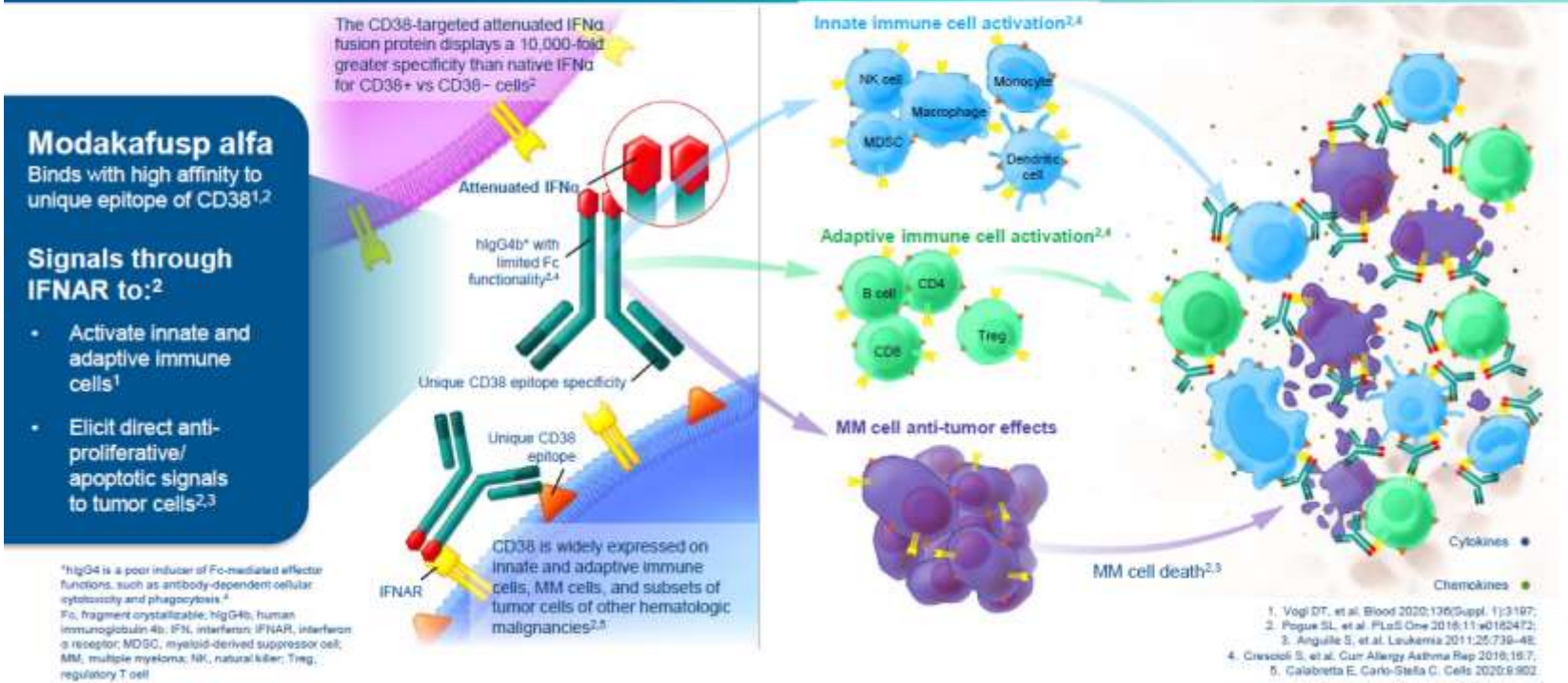
GPRC5D-CD3
Talquetamab



Antibody drug conjugates

CD38-attenuated IFNα
Modakafusp alfa

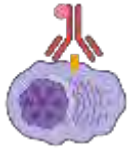
Modakafusp alfa is a first-in-class, innate immunity enhancer that functions through targeted next-generation IFN signaling

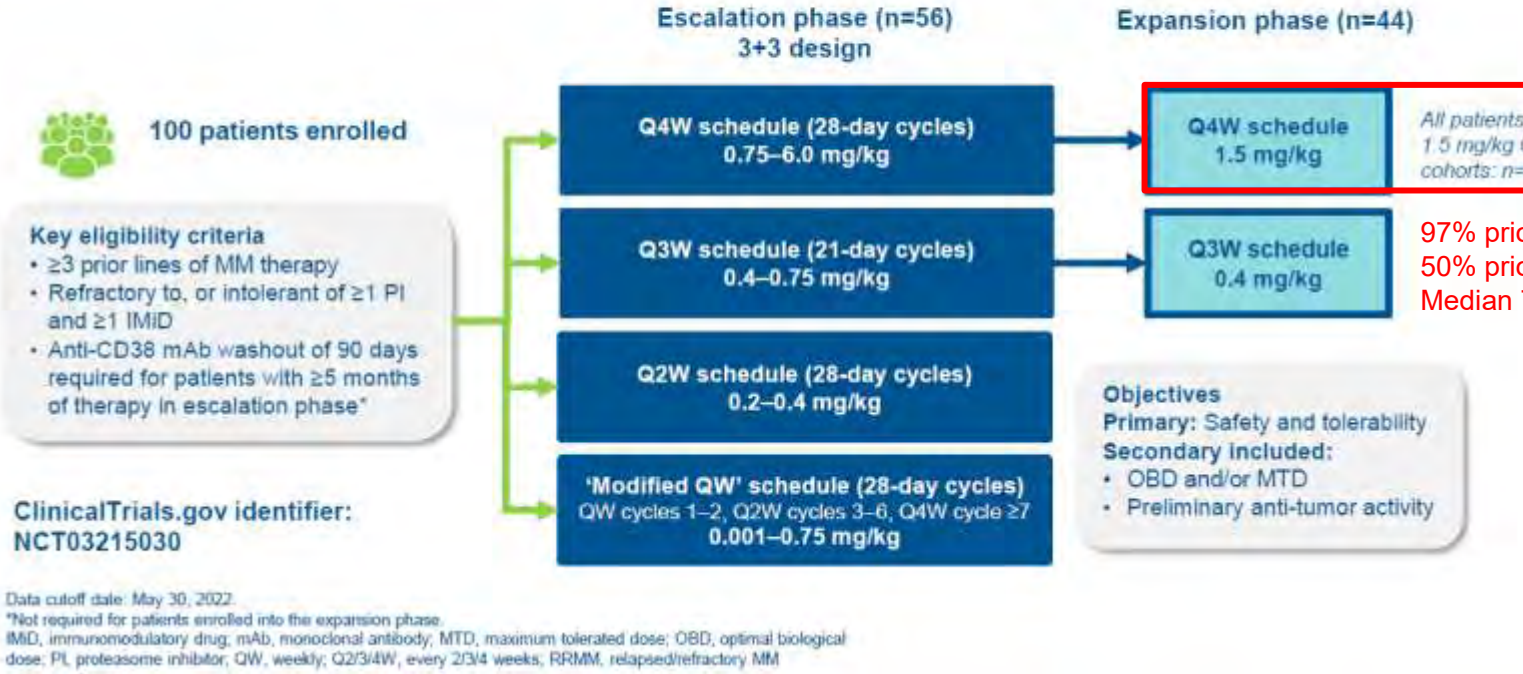


Modakafusp alfa is a first-in-class, immune-targeting, attenuated cytokine. It consists of 2 attenuated interferon (IFN)α2b molecules genetically fused to the Fc portion of an anti-CD38 IgG4 monoclonal antibody (mAb), allowing targeted delivery of IFNα to innate and adaptive immune cells, as well as myeloma cells.

Vogl D et al ASH 2022, Abstract 565

First-in-human, phase 1/2 study of modakafusp alfa in heavily pre-treated patients with RRMM





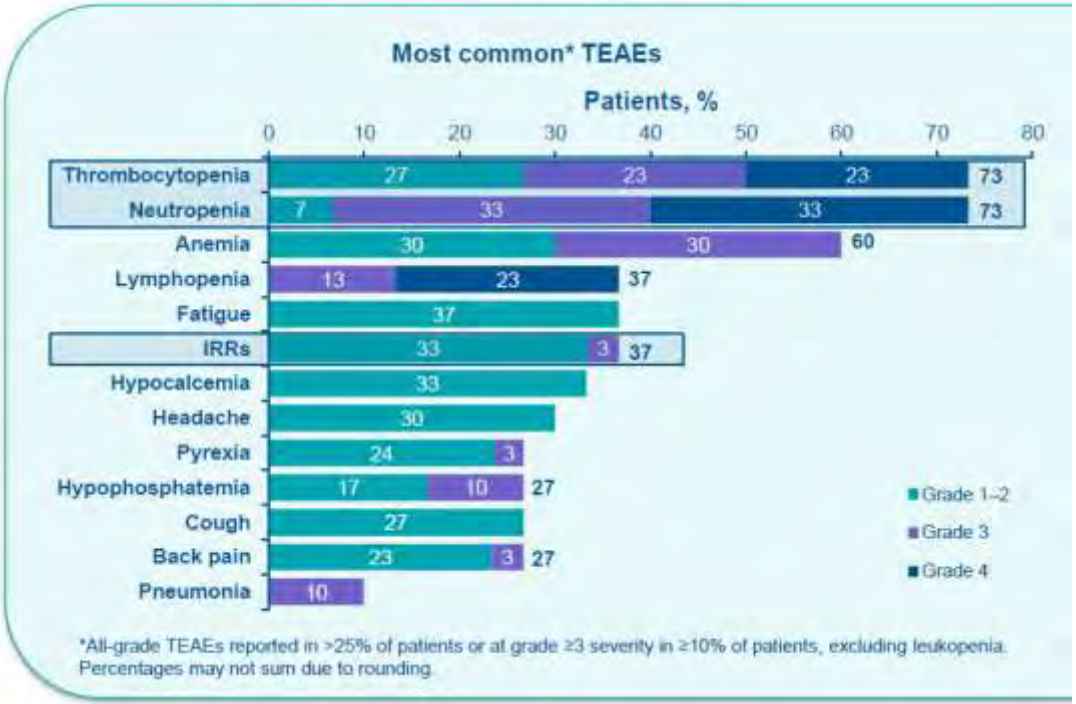
97% prior anti-CD38, 93% refractory
50% prior anti-BCMA
Median 7 prior lines

Vogl D et al ASH 2022, Abstract 565

Modakafusp alfa 1.5 mg/kg Q4W (n=30) adverse events were primarily hematologic

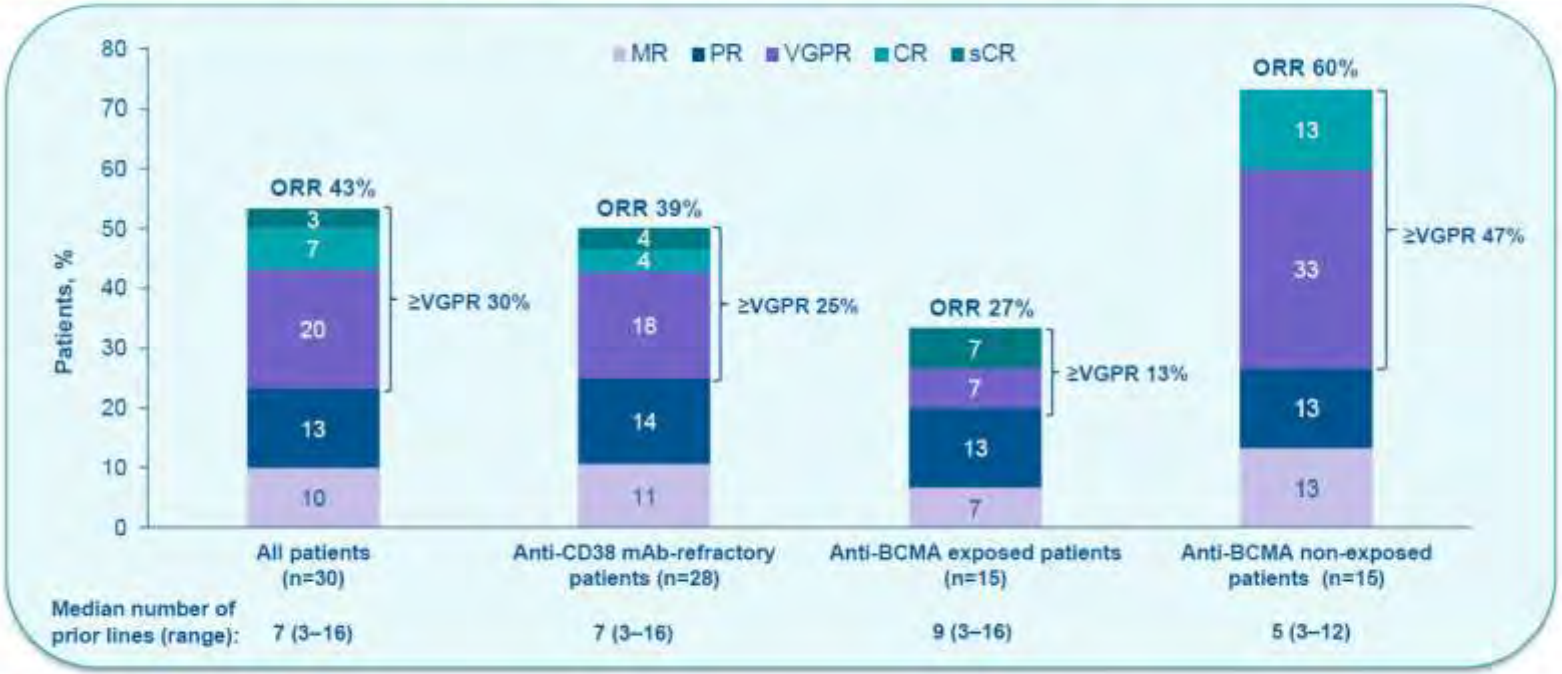
- 26 (87%) patients have discontinued treatment; 19 (73%) due to PD and 4 (15%) due to TEAEs
- Median duration of exposure: 4 cycles (range: 1–24)
- Thrombocytopenia and neutropenia mainly occurred in cycles 1–2, with counts usually recovering over time
- One patient had a grade 3 bleeding event and remained on study for 6 cycles until progressing
- Four patients had grade 3 infections (pneumonia, n=4; sinusitis, n=1)
- Aside from IRRs, there were no constitutional or neuropsychiatric effects typical of IFNα therapy

PD, progressive disease; TEAE, treatment-emergent adverse event



Vogl D et al ASH 2022, Abstract 565

Responses were observed with modakafusp alfa 1.5 mg/kg Q4W regardless of prior therapies or refractory status



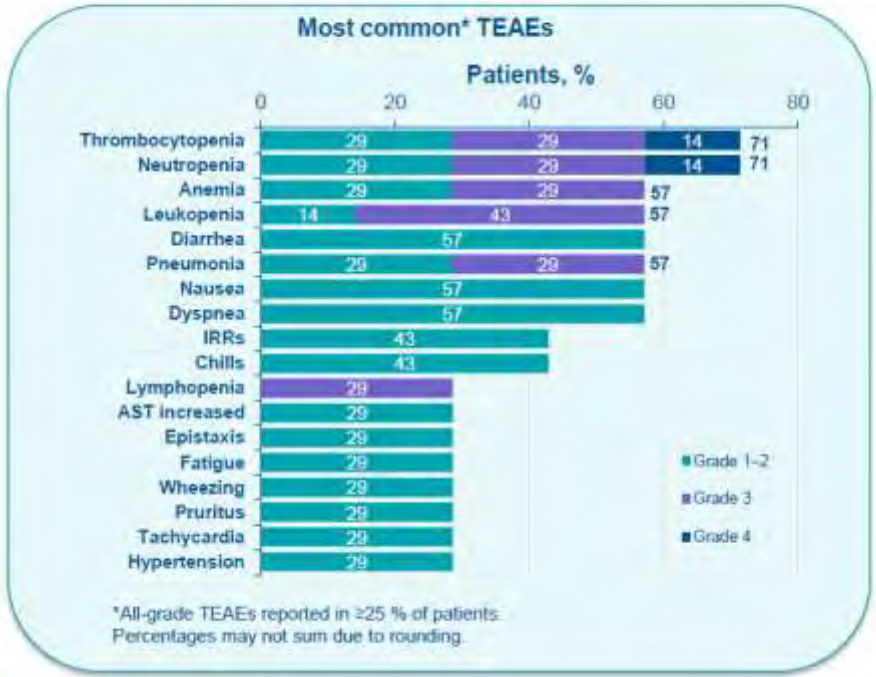
Percentages may not sum due to rounding.
CR, complete response; MR, minimal response; ORR, overall response rate of ≥PR; PR, partial response; sCR, stringent CR; VGPR, very good partial response

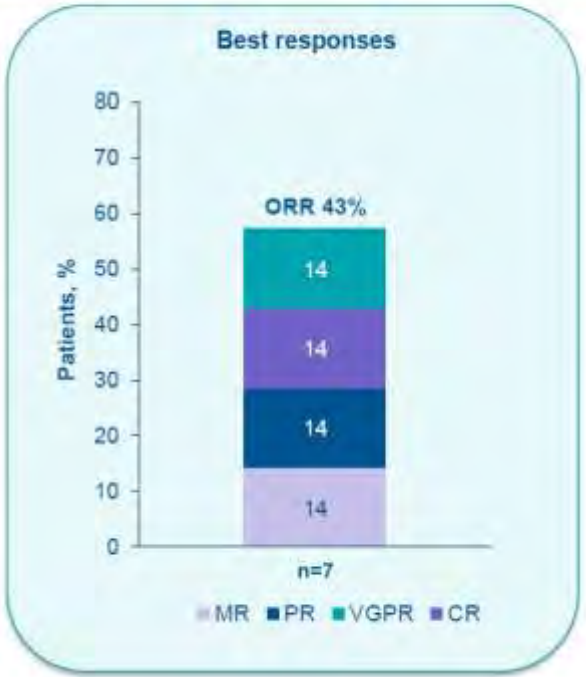
Median PFS 5.7m

Median duration of response 12.5m

Vogl D et al ASH 2022, Abstract 565

Safety and efficacy in the MTD cohort 3.0 mg/kg Q4W (n=7)



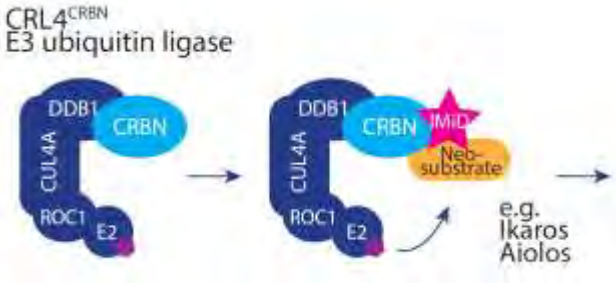


AST, aspartate aminotransferase

Study - 1.5 vs 3mg/kg ongoing

Vogl D et al ASH 2022, Abstract 565

CELMoDs



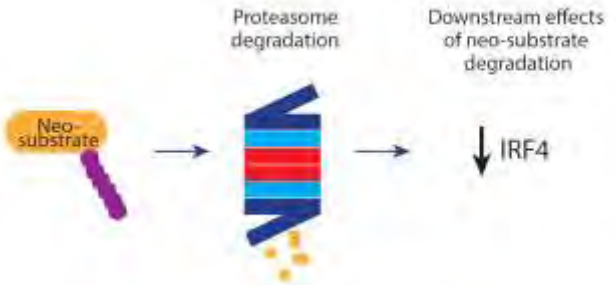


Table 1. Prior therapies

	All patients (N = 101)
No. of prior therapies, median (range)	6 (3–15)
Stem cell transplantation, n (%)	78 (77.2)
PI, n (%)	101 (100)
IMiD agent,[a] n (%)	101 (100)
POM as last prior regimen, n (%)	37 (36.6)
Anti-CD38 mAb, n (%)	101 (100)
Anti-BCMA therapy, n (%)	30 (29.7)
Antibody-drug conjugate, n (%)	22 (21.8)
CAR T cell therapy, n (%)	3 (3.0)
T-cell engager, n (%)	8 (7.9)

[a]LEN and POM.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; IMiD, immunomodulatory drug; LEN, lenalidomide; mAb, monoclonal antibody; PI, proteasome inhibitor; POM, pomalidomide.

Table 2. Summary of responses to MEZI + DEX

	All patients (N = 101)	Patients with plasmacytomas (n = 39)	Patients with prior anti-BCMA therapy (n = 30)
Response, n (%)			
ORR[a]	40 (39.6)	12 (30.8)	15 (50.0)
sCR	2 (2.0)	0	0
CR	3 (3.0)	2 (5.1)	1 (3.3)
VGPR	18 (17.8)	6 (15.4)	7 (23.3)
PR	17 (16.8)	4 (10.3)	7 (23.3)
MR	8 (7.9)	0	1 (3.3)
SD	38 (37.6)	21 (53.8)	11 (36.7)
PD	10 (9.9)	4 (10.3)	3 (10.0)
NE/Missing	5 (5.0)	2 (5.1)	0
DOR, median (95% CI), months	8.3 (5.4–NR)	NR	6.9 (4.0–NR)
PFS, median (95% CI), months	4.6 (3.2–6.3)	3.7 (2.3–4.9)	5.4 (2.1–9.4)

[a]Defined as PR or better.
BCMA, B-cell maturation antigen; CI, confidence interval; CR, complete response; DEX, dexamethasone; DOR, duration of response; MEZI, mezigdomide; MR, minimal response; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Richardson P et al ASH 2022, Abstract 568

Conclusions

- Personalizing therapy remains important
  - High-risk, frail etc
- Therapies with new modes of actions show impressive response rates in RRMM
  - Balance efficacy and toxicity
    - CRS, infections etc
- Determine the most appropriate place in disease to use
- Determine the day to day practicalities of how to introduce therapies into clinical practice

Acknowledgements

- My colleagues who kindly shared their slides

THANK YOU

NYU Langone Health