HIGHLIGHTS OF MYELOMA ROUNDS

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TARGET AUDIENCE

This CE activity is intended for hematologists-oncologists, medical oncologists, nurse practitioners, nurses and pharmacists involved in the care of patients with myeloma.

EDUCATIONAL OBJECTIVES

After completing this CE activity, the participant should be better able to:

- Describe the latest developments in myeloma, including current and emerging treatments
- Engage patients and caregivers in discussions on clinical trials, newly approved therapies and emerging therapies for myeloma, including combination therapies, CAR T-cell therapy and bispecific antibodies
- Identify strategies for optimal patient care
- Apply evidence-based treatment strategies
- Access patient support resources

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SPEAKERS

Edward A. Stadtmauer, MD (Chair, Myeloma Rounds, Philadelphia)
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow, and Shaffer Families'
President's Distinguished Professor
University of Pennsylvania Abramson Cancer Center
Philadelphia, PA

Cindy Varga, MD (Chair, Myeloma Rounds, Winston-Salem)
Associate Professor
Atrium Health Levine Cancer Institute
Plasma Cell Dyscrasia Division
Department of Hematology and Oncology
Charlotte, NC

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3

Highlights of Myeloma Rounds

Updates in Clinical Research in 2023

Cindy Varga, MD
Associate Professor
Atrium Health Levine Cancer Institute
Plasma Cell Dyscrasia Division
Department of Hematology and Oncology
Charlotte, NC

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4

Iberdomide Maintenance after Autologous Stem Cell Transplantation in Newly Diagnosed MM: First Results of the Phase 2 EMN26 Study

Niels W.C.J. Van De Donk[1], Cyrille Touzeau[2], EvangelosTerpos[3], Aurore Perrot[4], Roberto Mina[5,6], Maaike de Ruijter[1], Elisabetta Antonioli[7], Eirini Katodritou[8],Norbert Pescosta[9], Paulus A.F. Geerts[10], Cécile Sonntag[11], Ruth Wester[12], Angelo Belotti[13], Silvia Mangiacavalli[14],Massimo Offidani[15], Mattia D'Agostino[5,6], Mark van Duin[12], Michele Cavo[16], Sara Aquino[17], Alessandra Lombardo[18], Mark-David Levin[19], Cyrille Hulin[20], Mario Boccadoro[21], Pieter Sonneveld[12] and Francesca Gay[5]

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5

INTRODUCTION

- Maintenance lenalidomide post ASCT is currently the standard of care
- About 25% of patients will discontinue Len maintenance due to poor tolerance or adverse events
- There is unmet need for improved maintenance drugs with better efficacy and tolerability
- Iberdomide is a novel oral cereblon E3 ligase modulator (CELMoD) with greater immunomodulatory effects than IMiDs

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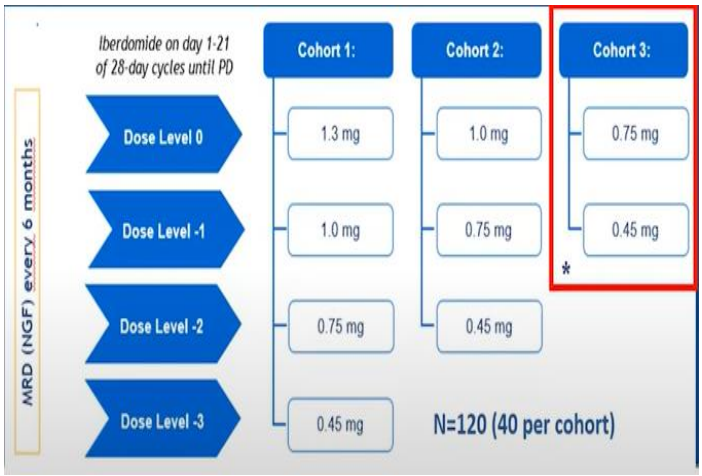
EMN26

- Eligibility criteria
  - IMid-PI induction
  - At least a PR after ASCT
- Primary endpoint:
  - Efficacy (response improvement within 6 mos)
- Secondary endpoints
  - MRD by NGF
  - Adverse events
  - PFS



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Treatment disposition and treatment exposure

Patient disposition (all cycles)	1.3 mg cohort (N = 40)	1.0 mg cohort (N = 40)	0.75 mg cohort (N = 40)
Follow-up, median (IQR), months	14.6 (11.6-19.6)	17.0 (13.1–20.7)	4.7 (3.3-6.3)
Ongoing, n (%)	30 (75)	34 (85)	37 (92)
Discontinued, n (%)	10 (25)	6 (15)	3 (8)
Death*	2 (5)	0	0
Adverse event	6 (15)	2 (5)	1 (3)
Progression of disease	2 (5)	4 (10)	2 (5)

Treatment exposure cycles 1-12	1.3 mg cohort (N = 40)	1.0 mg cohort (N = 40)	0.75 mg cohort (N = 40)
Treatment duration, median (IQR), weeks	49.9 (47.9-52.6)	49.4 (47.5-51.5)	24 (17.0-31.4)
Cycles received, median (IQR)	12 (12-12)	12 (12-12)	6 (5-7)
Dose reduction, n (%)	18 (45)	15 (38)	4 (10)
Discontinuation due to adverse event, n (%)	4 (10)	1 (3)	1 (3)
Relative dose intensity (%), median (IQR)	90 (80-96)	89 (75-79)	92 (85-97)

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EMN26: Hematologic safety profile: cycles 1-12

AE, n (%)	1.3 mg cohort (n-=40)		1.0 mg cohort (n=40)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Neutropenia	4 (10)	20 (50)	4 (10)	17 (42)
Febrile neutropenia	0	0	0	1 (2)
Thrombocytopenia	6 (15)	0	4 (10)	0
Anemia	2 (5)	0	6 (15)	0
Lymphopenia	3 (8)	1 (2)	2 (5)	1 (2)

- The most common hematologic AE was neutropenia
  - There was only 1 case of febrile neutropenia in the 1.0 mg iberdomide cohort

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EMN26: Non-hematologic safety profile: cycles 1-12

Most frequent (≥ 20% all grade) TEAEs and events of interest, n (%)

AE, n (%)	1.3 mg cohort (n-=40)		1.0 mg cohort (n=40)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Fatigue	7 (18)	6 (15)	7 (18)	4 (10)
Diarrhea	2 (5)	0	8 (20)	0
Constipation	2 (5)	0	2 (5)	0
Peripheral neuropathy	6 (15)	1 (3)	5 (13)	0
Hyper/hypothyroidism	4 (10)	0	9 (23)	0
Rash*	8 (20)	4 (10)	7 (18)	1 (3)
Venous thromboembolism	0	0	0	0
Infections	22 (55)	4 (10)	21 (52)	5 (13)
COVID-19	7 (18)	0	12 (30)	0
Pneumonia	3 (8)	2 (5)*	1 (3)	2 (5)**

*1 of 2 cases is PJP infection
** 1 of 2 cases is PJP infection

The majority of non-hematologic AEs were low grade

No second primary malignancies reported

Rash was transient and occurred mainly during first cycle

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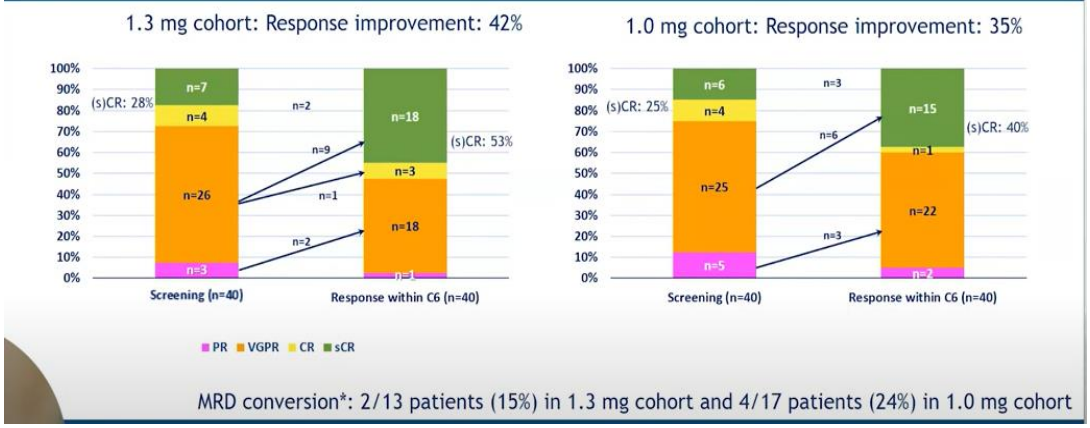
10

EMN26: Response improvement during first 6 cycles



MRD conversion*: 2/13 patients (15%) in 1.3 mg cohort and 4/17 patients (24%) in 1.0 mg cohort

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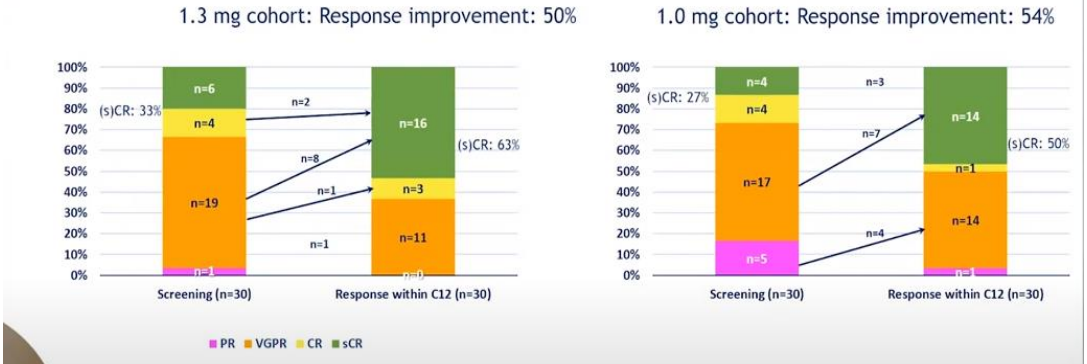
11

EMN26: Response improvement during first 12 cycles

→ responses improve over time



MRD conversion*: 7/12 patients (58%) in 1.3 mg cohort and 5/17 patients (29%) in 1.0 mg cohort

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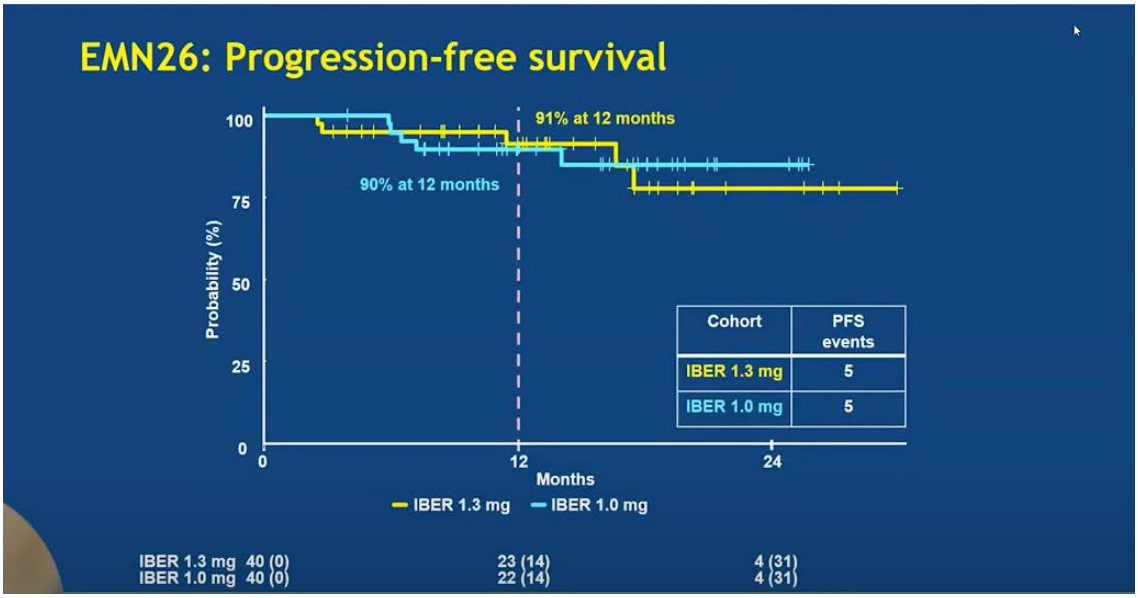
12



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13

CONCLUSIONS

- Iberdomide maintenance results in an improvement in response over time in patients who received IMiD/PI-based induction +/- antiCD38 and ASCT
  - Iberdomide demonstrate at least a 50% improvement of response at cycle 12
  - Len demonstrated 31% improvement of response at cycle 12 in the EMN02 trial
- Promising MRD conversion data with iberdomide post ASCT was observed
- Iberdomide showed manageable toxicity
- Excalibur trial
  - Ongoing phase III registrational trial of iberdomide vs. lenalidomide maintenance post transplant (NCT05827016)

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14

NON-INVASIVE MRD TESTING

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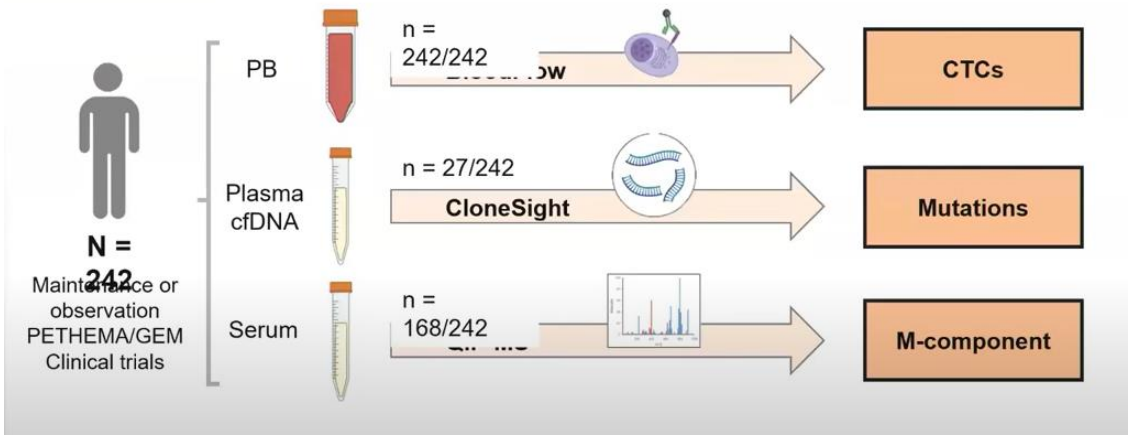
Investigate the complementarity and prognostic value of new multimodal minimally invasive MRD assessment in MM



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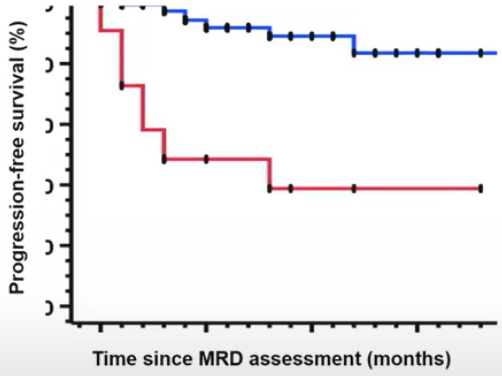
Gonzalez et al. ASH Annual Meeting 2023 Abstract #0339

16

Prognostic value of MRD assessment using BloodFlow

MRD+ associated with 12-fold increment in the risk of progression and/or death



MRD	No.	Median PFS	PFS @1y	Hazard ratio
Negative	220	NR	94%	11.7 (P < .001)
Positive	22	3 mo	46%	

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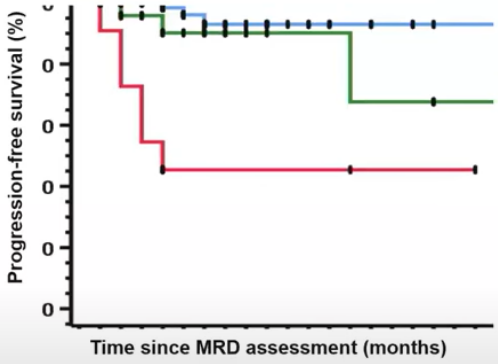
17

MRD assessment in PB using BloodFlow and in BM using NGF

Analysis restricted to 136 patients with paired samples



MRD PB / BM	No.	Median PFS	PFS @1y	Hazard ratio
- / -	99	NR	97%	-
- / + & +/-	26	NR	88%	3.4 (P = .14)
+ / +	11	3 mo	45%	19.7 (P < .001)

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18

BloodFlow and QIP-MS showed more balanced NPV and PPV

CloneSight showed the highest PPV but low NPV

BloodFlow	QIP-MS
78% NPV 96% PPV	82% NPV 70.5% PPV

Are these methods complementary for improved prediction of PFS?

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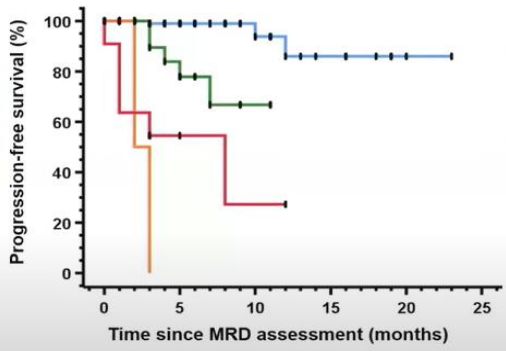
19

Complementarity between BloodFlow and QIP-MS

3/129 (2%) double negative MRD patients progressed thus far



MRD BF & QIP-MS	No.	Median PFS	PFS @1y	Hazard ratio
-/-	129	NR	98%	-
-/+	26	NR	80%	9.8 (P = .002)
+/-	2	2 mo	0%	97.7 (P < .001)
+/+	11	8 mo	46%	29.5 (P < .001)

Double-negative MRD detection in PB and serum using BloodFlow and QIP-MS achieved a **NPV of 84%** (ie, MRD negativity in BM using NGF)

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20

CONCLUSIONS

- BloodFlow and QIP-MS are empowered to detect MRD with high sensitivity in PB and serum
- The presence of CTCs was systematically associated with dismal PFS
- BloodFlow showed very high PPV and QIP-MS achieved the highest NPV
- The complementarity between these methods enabled the identification of multimodal MRD negative patients with very low risk of relapse
- This study paves the way towards minimally invasive MRD assessment in MM patients on maintenance or observation

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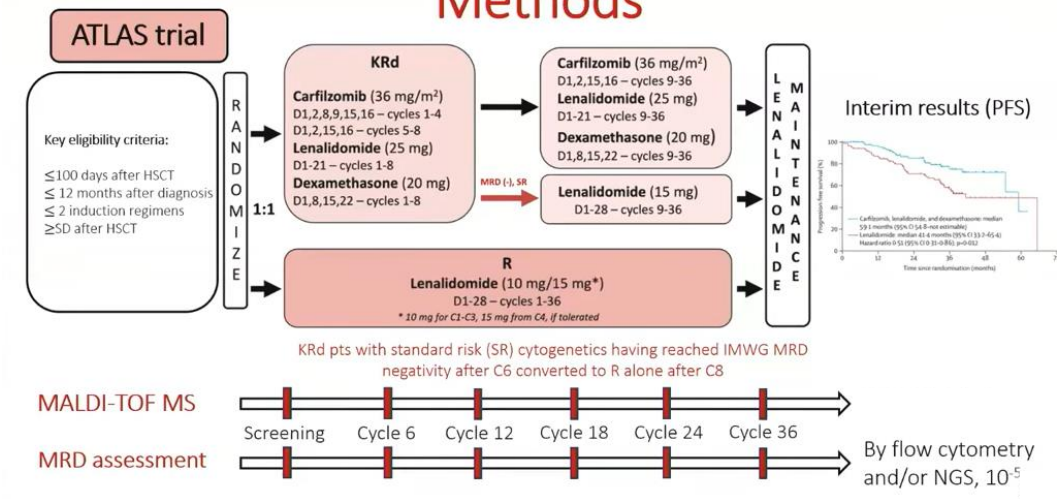
21

Methods



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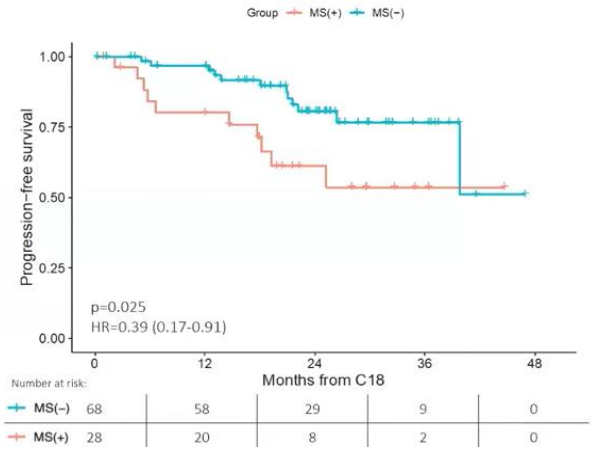
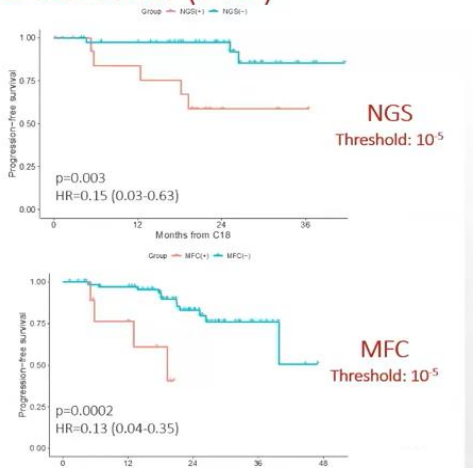
Kubicki et al. ASH Annual Meeting 2023 Abstract #0340

22

MS (-) status post cycle 18 was associated with superior progression-free survival (PFS)





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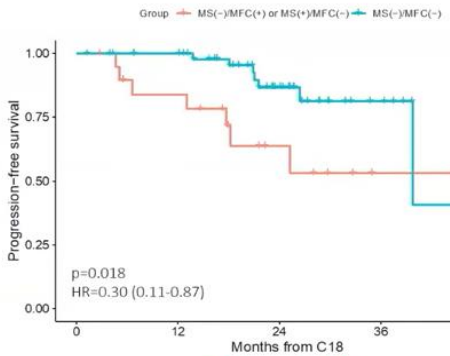
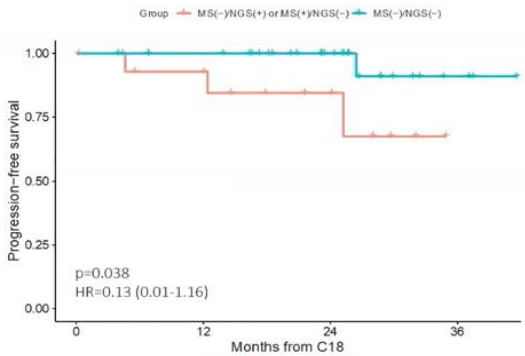
Kubicki et al. ASH Annual Meeting 2023 Abstract #0340

23

Double (MS and MRD) negativity is associated with favorable outcomes



MFC and MS



NGS and MS

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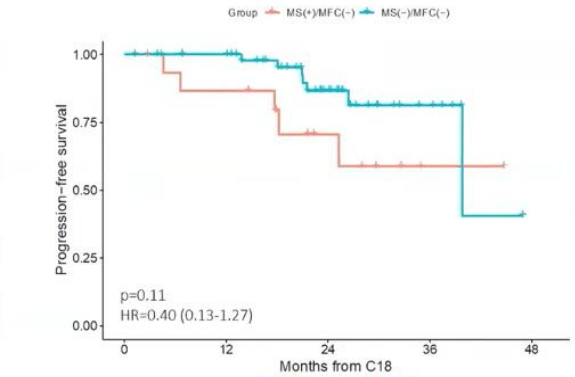
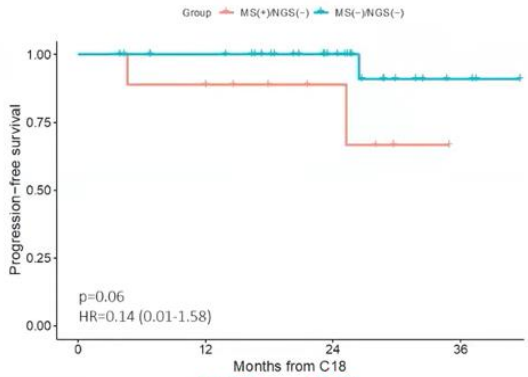
Kubicki et al. ASH Annual Meeting 2023 Abstract #0340

24

MS results may add prognostic value to MRD negative status



MFC and MS



NGS and MS

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25

CONCLUSIONS

- MS-based disease assessment in the post ASCT setting maybe feasible.
- Prognostic significance of MS negativity increase with time.
- MS is complementing BM-based MRD assessments.
- Further prospective studies are needed confirm these conclusions.

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26

Highlights of Myeloma Rounds

Initial Therapy of Multiple Myeloma

Edward A. Stadtmauer, MD
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow, and Shaffer Families'
President's Distinguished Professor
University of Pennsylvania Abramson Cancer Center
Philadelphia, PA

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CASE PRESENTATION

- 9/12/22: 35 yo AA woman with hx of pituitary adenoma and HTN presented to PCP with right shoulder pain. X-ray was unremarkable. Referred to Ortho.
- 11/28/22: Repeat x-ray showed large lytic lesion of right proximal humerus. MRI showed 7.5 x 4.6 x 4.7 cm lesion with complete replacement of acromion (Figure 1) and similar 4.3 x 2.4 x 4.8 cm mass replacing humeral head, both with extensive marrow replacement.
- 12/6/22: US-guided biopsy of right acromion mass shows sheets of small to intermediate sized atypical plasmacytoid cells that are CD38+, CD138+, CD117+ (subset) and CD79a+ (dim, small subset). Kappa and lambda ISH staining is weak. Ki-67 15%. Positive clonal IGH gene rearrangement.
- 12/7/22: CT CAP with large lucent lesion in T12 with possible inferior endplate fracture. Other small lucent lesions throughout skeleton.
- Hg 9.7, ca 12.7 alb 2.9, SPEP M-spike 3.9 g/dl IgG kappa, kappa 248.6, lambda 3,1, ratio 80.19, IgG 4221, B2M 4.91, LDH 247.
- 1/1-1/13/23: Admitted for intractable pain in right shoulder and lower back.
- 1/4/23: BM biopsy with hypercellular marrow (95%) and 80% involvement by kappa light chain-restricted plasma cells.

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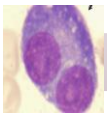
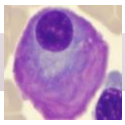
28

DISEASE TRAJECTORY



Stroma angiogenesis



and IL-6 dependent

Nonmalignant Accumulation

Malignant Transformation

Aggressive and Stromal Independent

- **Plasma Cell Leukemia**
- **Extramedullary Disease**

MGUS

- <10% bone marrow plasma cells
- <30 g/L M-protein
- No SLiM CRAB
- 1%/yr risk of progression to MM

Smoldering Myeloma

- 10-60% bone marrow plasma cells
- No SLiM CRAB
- ≥30 g/L M-protein (IgG or IgA) OR
- ≥500 mg/24 hr urinary protein
- No amyloidosis
- High-Risk 20, 20, 2
  - 20% PC
  - 20:1 ratio
  - 2 g/dl M-spike

Multiple Myeloma

- Clonal bone marrow ≥10% or bony/extramedullary plasmacytoma

AND

- Any ≥ 1 **SLiM CRAB feature (s)**:
  - **SLiM***
    - **S:** Clonal plasma cells in BM ≥60%
    - **Li:** Serum free light-chain ratio ≥100 mg/L
    - **M:** >1 MRI focal lesion ≥5 mm
  - **CRAB*** feature:
    - **C**: Calcium elevation (>11 mg/dL)
    - **R**: Renal insufficiency (Cr>2 mg/dL or CrCl<40 mL/min)
    - **A**: Anemia (Hgb<10 g/L)
    - **B**: Bone disease: (≥1 lytic lesion)

MGUS, monoclonal gammopathy of undetermined significance

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Rajkumar et al. *Lancet Oncol. 2014*;15(2):e538-e54.; Kuehl WM, et al. *Nat Rev Cancer*. 2002;2:175-187. Agarwal A, et al. *Clin Cancer Res*.2013;19:985-994. Durie BG, et al. *Hematol J*. 2003;4:379-398. Kurtin SE. *J Adv Pract Oncol*. 2010;1:19-29.

29

30

CYTOGENETIC CLASSIFICATION

STANDARD RISK

No abnormalities detected

OR

Abnormalities detected are not defined as high risk

HIGH RISK

Identified by FISH

- t(4;14)
- t(14;16)
- t(14;20)
- 17/(del 17p)
- gain(1q)[a]

Identified by karyotyping

- nonhyperdiploid karyotype
- del(13)

Genetic analysis

- Double hit (biallelic *TP53* inactivation or amplification of *CKS1B* [1q21])

Other disease characteristics

- Extramedullary disease
- Plasma cell leukemia

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Walker BA, Mavrommatis K, Wardell CP, et al. A high-risk, double-hit, group of newly diagnosed myeloma identified by genomic analysis. Leukemia. 2019;33(1):159-170).

30

NEW STAGING SYSTEM (R2-ISS)

- Addresses prognostic significance of +1q cytogenetic abnormality
- Contemporary cohorts (diagnosed 2005-2016)

1.

	B2M	Albumin
ISS stage 1	<3.5	≥3.5
ISS stage 2	All others	
ISS stage 3	>5.5	

2.

	Points
ISS stage 3	1.5
ISS stage 2	1
Del 17p	1
t(4:14)	1
Elevated LDH	1
Gain chr 1q	0.5

3.

Points	Stage	% pts	mPFS	mOS
0	1	19	68	NR
0.5-1	2	31	45	109
1.5-2.5	3	41	30	69
3-5	4	9	20	38

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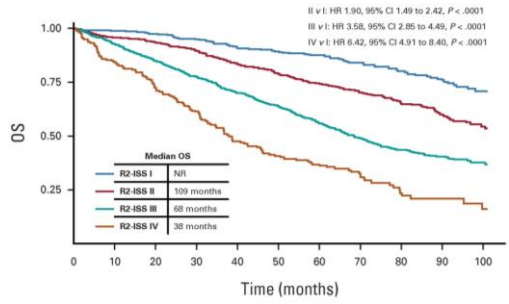
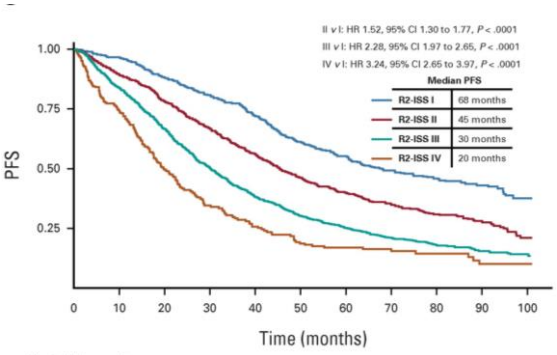
B2M, beta-2 macroglobulin; mOS, median overall survival; mPFS, median progression-free survival
D'Agostino M, et al., *J Clin Oncol,* 2022;40(29):3406-3418.

31





Stage	mPFS	mOS
1	68	NR
2	45	109
3	30	69
4	20	38

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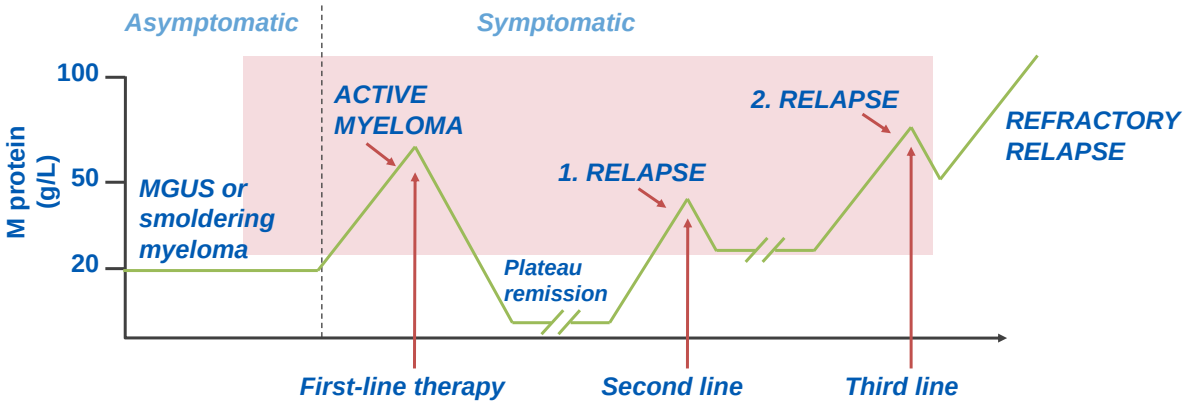
32

THE TRAJECTORY OF MYELOMA



Multiple myeloma is highly complex during progression and relapse due to genomic events and clonal evolution.

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Paul Richardson's ASH 2018 presentation.

33

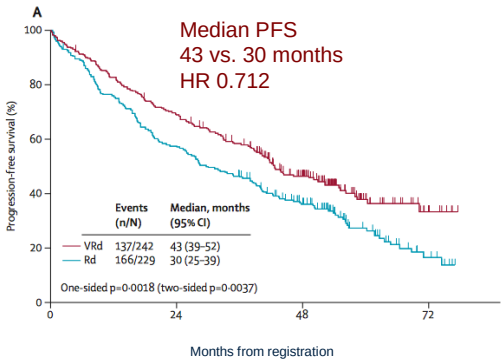
SWOG S0777

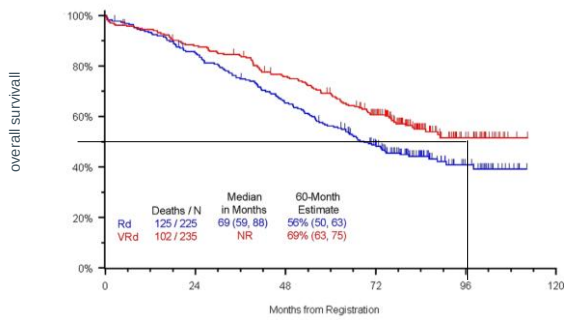
	RVd (8 x 21 days) (N=230)	Rd (6 x 28 days) (N=242)
Lenalidomide	25 mg days 1-14	25 mg days 1-21 of 28
Bortezomib	1.3 mg/m2 days 1, 4, 8, 11	
Dexamethasone	20 mg days 1, 2, 4, 5, 11, 12	20 mg days 1, 2, 4, 5, 11, 12

Collect Stem cells (optional)

Maintenance lenalidomide 25 mg days 1-21 of 28 + dex. 40 mg days 1, 8, 15

44% age >65; 69% intent to transplant; 33% ISS stage 3; CrCl ≥30 mL/min





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Durie et al., Lancet, 2016
Durie et al., Blood Cancer Journal (2020) 10(53)

34

S0777 TOLERABILITY IN OLDER PATIENTS; BORTEZOMIB SCHEDULE

- Once weekly bortezomib: Same OS/PFS, less peripheral neuropathy.
- Twice weekly bortezomib: Faster time to best response
- We often start with twice weekly dosing and switch to once weekly dosing after 1-2 cycles in patients with symptomatic complications.

Subgroup analysis of SWOG S0777 by age

Table 1. Age-stratified analyses of progression-free survival, overall survival, and safety in SWOG S0777.

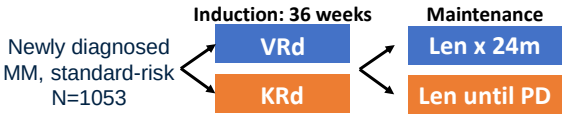
Outcome	Age <65 years (n=269)		Age ≥65 years (n=202)	
	VRd (n=149)	Rd (n=120)	VRd (n=93)	Rd (n=109)
Progression-free survival (PFS)				
• Median progression-free survival	55.4 months	36.6 months	33.1 months	25.8 months
• Hazard ratio (95% CI)	0.63 (0.46, 0.87)	Reference	0.83 (0.60, 1.16)	Reference
• Adjusted hazard ratio† (95% CI)	0.61 (0.45, 0.84)	Reference	0.90 (0.65, 1.26)	Reference
Overall survival (OS)				
• Median overall survival	Not reached	68.9 months	62.9 months	53.0 months
• Hazard ratio (95% CI)	0.61 (0.39, 0.97)	Reference	0.83 (0.55, 1.23)	Reference
• Adjusted hazard ratio† (95% CI)	0.62 (0.39, 0.99)	Reference	0.88 (0.59, 1.31)	Reference
Safety‡				
• Incidence of grade ≥3 treatment-emergent adverse events	87%	79%	93%	89%
• Incidence of treatment discontinuation due to toxicity	29%	18%	47%	26%

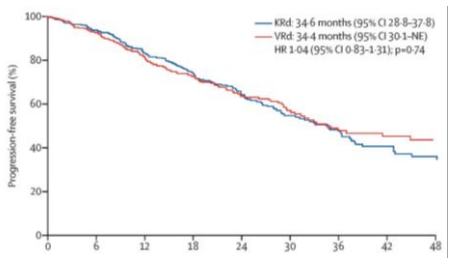
Abbreviations: VRd, bortezomib-lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; CI, confidence interval.
†Adjusted hazard ratio estimates reflect results from weighted Cox regression models where inverse-probability-of-treatment weighting (IPTW) was to balance the VRd and Rd trial arms on the following measured baseline characteristics within each age subgroup (≥65, <65 years): age, sex, International Staging System (ISS) stage, Eastern Cooperative Oncology Group (ECOG) performance status score, hemoglobin (<10 g/dL, >=10 g/dL), serum creatinine (<2 mg/dL, >= 2 mg/dL), cytogenetic risk by FISH test (high, intermediate, low, normal/missing/insufficient), and lactate dehydrogenase (<190 IU/L, >=190 IU/L). Absolute standardized differences for all covariates were <0.1 with IPTW.
‡ Eligible safety assessment population was n=467.

Cook et al., Am J Hematol (epub ahead of print) doi: 10.1002/ajh.26074.
Durie et al., ASH 2022, abstract 4497

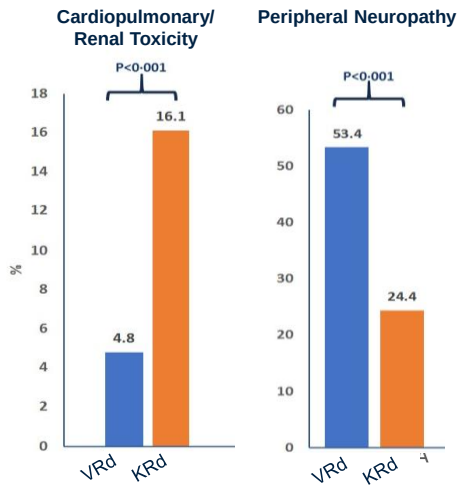
35

CARFILZOMIB IN FIRST-LINE THERAPY ENDURANCE (ECOG E1A11)





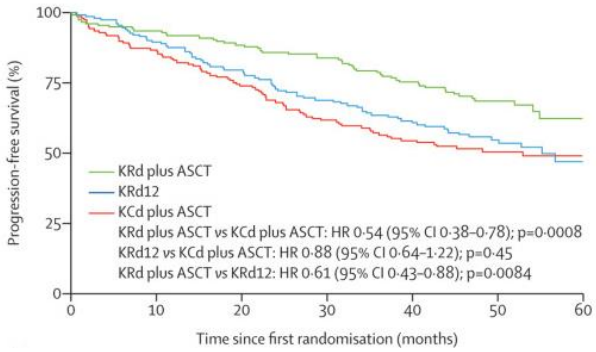
	Bortezomib, lenalidomide, and dexamethasone group (n=527)	Carfilzomib, lenalidomide, and dexamethasone group (n=526)	p value
Negative for minimal residual disease	38 (7%; 5–10)	54 (10%; 8–13)	0·079
Complete response or better	78 (15%; 12–18)	96 (18%; 15–22)	0·13
Very good partial response or better	341 (65%; 61–69)	388 (74%; 70–77)	0·0015
Partial response or better	444 (84%; 81–87)	456 (87%; 84–90)	0·26



Kumar et al., Lancet Oncology (2020) 21:1317
ASCO 2020 LBA3

36

HIGH-DOSE MELPHALAN + AUTO SCT CONSOLIDATION FORTE TRIAL



Significant PFS advantage with auto SCT even with intensive KRD induction.

Intensive induction/maintenance does not eliminate benefit of auto SCT

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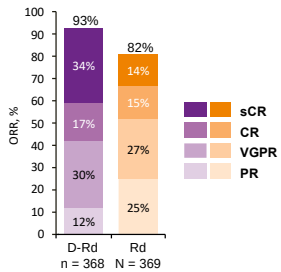
Gay et al., Lancet Oncology (2021) 22:1705

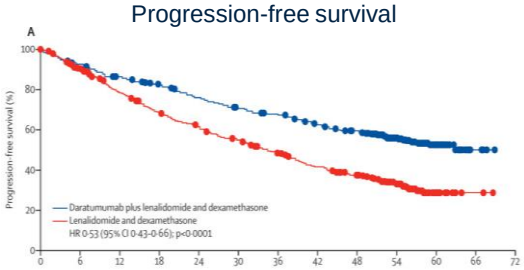
37

DARATUMUMAB IN NEWLY DIAGNOSED, TRANSPLANT-INELIGIBLE MM: MAIA

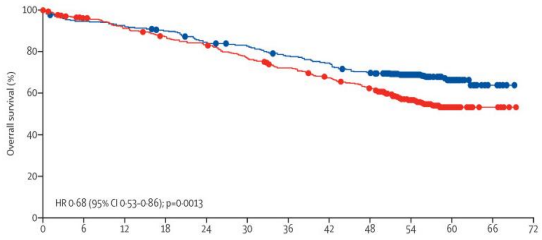
	Rd (N=365)	Dara-Rd (N=364)
Lenalidomide	25 mg d1-21 of 28	25 mg d1-21 of 28
Daratumumab		16 mg/kg qw → q2w → q4w
Dexamethasone	40 mg weekly	40 mg weekly



Progression-free survival



Overall survival



Among pts receiving subsequent therapy, 46% of control group received daratumumab at some point.

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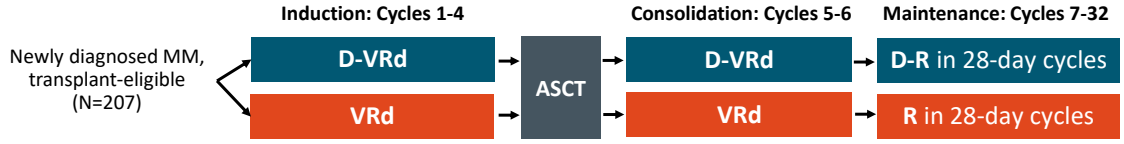
Facon et al., Lancet Oncology 2021 22(11):1582

38

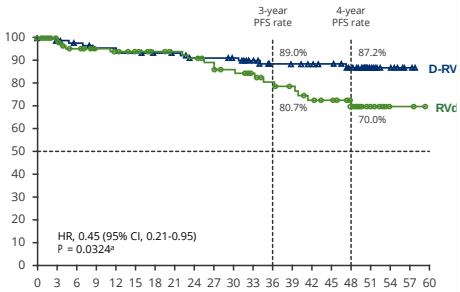
DARATUMUMAB + VRD
GRIFFIN STUDY

Primary endpoint: sCR by end of consolidation
Secondary endpoints: MRD, ORR, PFS, OS

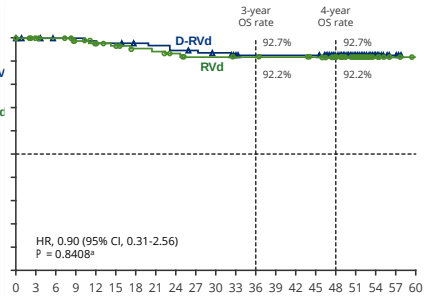


	D-VRd	VRd
ORR post ind.	98%	92%
sCR post cons.	42%	32%
sCR end of study (p=0.0005)	67%	48%

Progression-free Survival



Overall Survival



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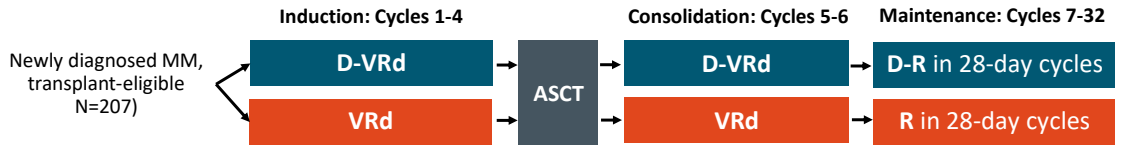
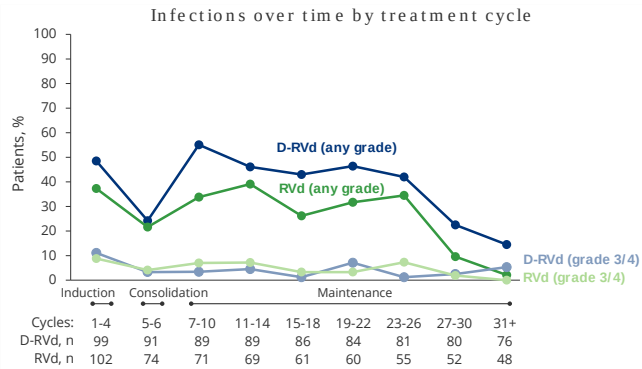
Sborov et al., IMS 2022

39

DARATUMUMAB + VRD
GRIFFIN STUDY

Primary endpoint: sCR by end of consolidation
Secondary endpoints: MRD, ORR, PFS, OS





More infections with D-RVd but no difference in high-grade infections

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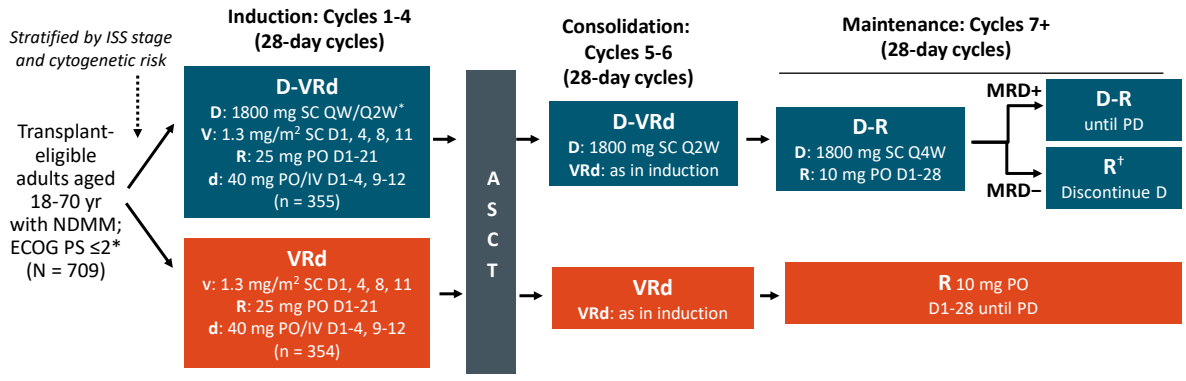
Sborov et al., IMS 2022

40

PERSEUS: Study VRd +/-Daratumumab, ASCT, R +/- D

- Multicenter, open-label, randomized phase III trial; current analysis median f/u: 47.5 mo



*QW during cycles 1-2, Q2W during cycles 3-4. †D discontinued after ≥24 mo in patients with ≥CR and 12 mo sustained MRD negativity; D restarted upon confirmed loss of CR without PD or MRD recurrence.

- **Primary endpoint:** PFS
- **Key secondary endpoints:** ≥CR rate, MRD negativity rate, OS

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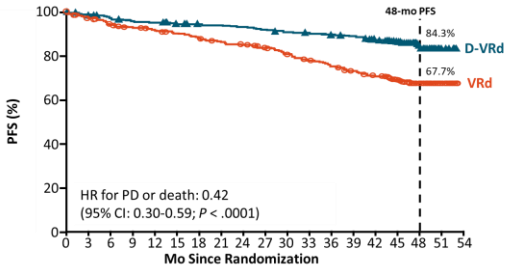
Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2023;[Epub].

41

PERSEUS: Study VRd +/-Daratumumab, ASCT, R +/- D



Efficacy Outcome	D-VRd (n = 355)	VRd (n = 354)	OR (95% CI)	*P* Value
≥CR, %	87.9	70.1	3.13 (2.11-4.65)	<.001
▪ sCR	69.3	44.6		
▪ CR	18.6	25.4		
MRD negativity, %				
▪ 10^{-5}	75.2	47.5	3.40 (2.47-4.69)	<.0001
▪ 10^{-6}	65.1	32.2	3.97 (2.90-5.43)	<.0001
Sustained MRD negativity (10^{-5}) ≥12 mo, %	64.8	29.7	4.42 (3.22-6.08)	<.0001

48-mo PFS rate: 84.3% vs 67.7% (HR: 0.42; P <.0001)

≥CR rate: 87.9% vs 70.1% (P <.001)
MRD negativity (10-5) rate: 75.2% vs 47.5% (P < .001)
64% on D-R maintenance for ≥ 2 yr stopped D after achieving sustained MRD negativity

Secondary malignancies occurred in 10.7% (37) of patients in the D-VRd arm and 7.2% (n = 25) in the VRd arm
Increased respiratory infections and pneumonias

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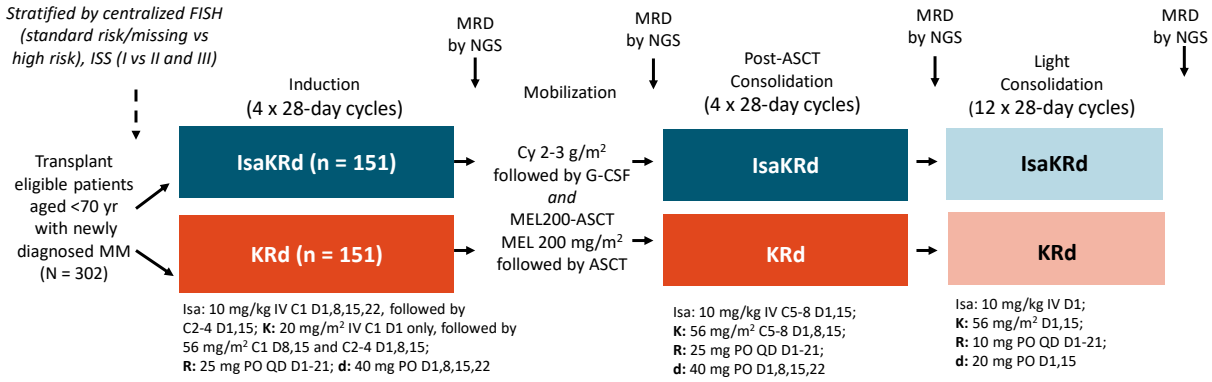
Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2023;[Epub].

42

ISKIA EMN24: STUDY DESIGN

Primary endpoint: MRD negativity by NGS after post-ASCT consolidation
Secondary endpoints: MRD negativity after induction, PFS, sustained MRD negativity



- Compared with KRd, IsaKRd resulted in significantly higher postconsolidation 10-5 and 10-6 MRD negativity rates
- Higher rates of 10-5 and 10-6 MRD negativity observed after each treatment phase (induction, transplantation, consolidation)
- 10-5 and 10-6 MRD negativity increases observed in all subgroups, including high-risk and very high–risk disease
- No new safety issues identified with IsaKRd

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43

INITIAL THERAPY CONCLUSIONS

- Dara-VRD, VRd and dara-Rd are excellent options for first-line therapy supported by large, phase 3, RCTs
  - VRd → inadequate response → add daratumumab
  - Dara-Rd → inadequate response → add bortezomib
- Dara-Rd is preferred for older, transplant-ineligible population
- Emerging data for Dara-VRd for all patients especially with high-risk disease or aggressive initial presentation.
- Carfilzomib has limited role in first-line therapy [ECOG E1A11]
  - KRd has comparable PFS to VRd
  - Less peripheral neuropathy but higher cardiac and renal toxicity
  - CD38-KRD deeper response than KRD

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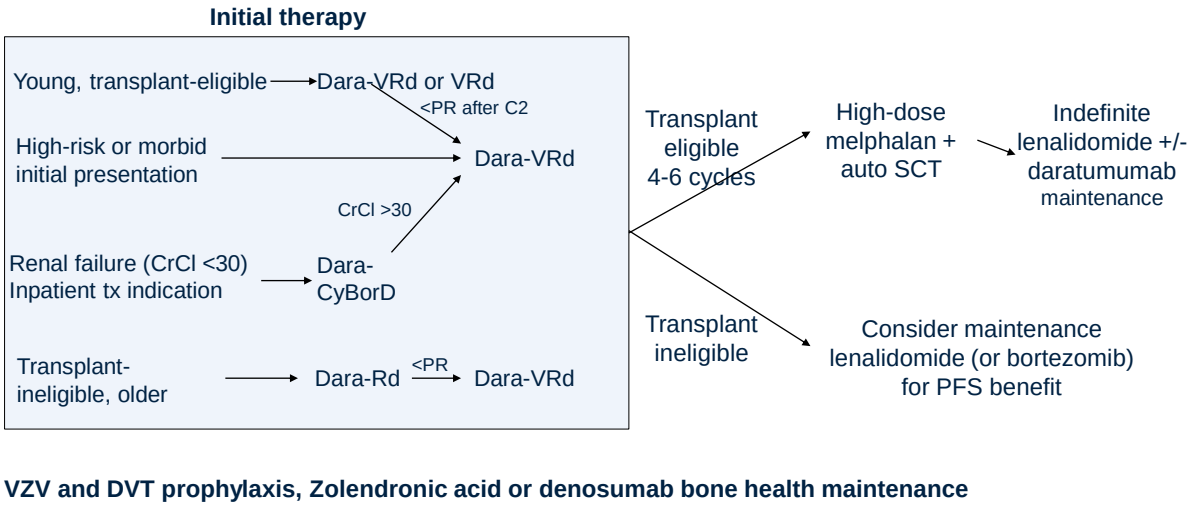
SUMMARY OF OUR APPROACH TO FIRST-LINE THERAPY



VZV and DVT prophylaxis, Zolendronic acid or denosumab bone health maintenance

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CASE

- 1/4/23: Bortezomib 1.3 mg/m2 (days 1, 4, and 8) and dexamethasone 40 mg daily x 4 days w/ acyclovir prophylaxis. Leuprolide for oncofertility (no time for egg preservation).
- 1/6/23: Palliative RT to right shoulder and left humerus for pain control.
- 1/10/23: IR-guided T12 percutaneous vertebroplasty.
- Discharged with pain regimen and plan for D-VRd as outpatient as per GRIFFIN trial.
- Lenalidomide to start post-IUD placement.
- Abnormal with gains of chromosomes or segments 1q (3 copies), 9, 17p and 19 and losses of 8p, 16p and 17p in mixed states representing clonal diversity.
- NGS: APC (7.0%), BRCA2 (51.3%; VUS), CARD11 (4.6%), CUX1 (9.3%), DOT1L (13.2%), two ERBB2 variants (5.0% and 5.6%), ETV6 (49.7%), two GEN1 variants (49.7% and 51.7%), KMT2C (49.2%), MYCL (4.8%), NTRK3 (46.5%), PBRM1 (47.2%), PIK3R2 (8.2%), TET2 (6.6%), WHSC1 (5.9%).
- FISH: Positive for t(14;16) in 57 of 100 cells, 17p/TP53 deletion in 23 of 100 cells, IGH rearrangement in 59 cells of 100 cells.
- R-ISS Stage II (42 months median progression-free survival) with triple hit myeloma.

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46

CASE

- 1/16/23: C2 D-Vd
- 1/24/23: Started lenalidomide with aspirin prophylaxis; held on 1/31/23 for orthopedic surgery on 2/8/23.
- 2/8/23: Underwent right humeral cooled radiofrequency ablation, ORIF surgery, cementoplasty, and proximal humeral resection with improvement in pain.
- 2/15-2/28/23: Admitted for hypercalcemia and acute kidney injury, Zolendronate and IVF.
- Pulse dexamethasone 40 mg x 4 days.
- Worse low back pain worse → MRI with new lesions in T7, T8, T10, T11, L1 and sacrum. New T8 pathologic compression fracture with partial retropulsion at T8 and T12 causing mild to moderate canal stenosis. M-spike 3.2
- Initiated KD-PACE based on ultra high-risk cytogenetic profile (C1 completed 3/30/23).
- 4/6/23: Repeat BM biopsy with hypercellular marrow (85%) with trilineage hematopoiesis due to growth factor support without evidence of plasma cell neoplasm. CMA without high-risk cytogenetics.
- 4/18/23: Stem cell collection (target 8 million CD34 cells/kg; collected 15.61 million CD34 cells/kg).
- 4/24/23: Melphalan-conditioned autoHSCT (possible tandem autoHSCT pending MRD status), followed by KR maintenance until progression.

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47

Highlights of Myeloma Rounds

Sequencing of Bispecifics and CARTS

Cindy Varga, MD
Associate Professor
Atrium Health Levine Cancer Institute
Plasma Cell Dyscrasia Division
Department of Hematology and Oncology
Charlotte, NC

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48

CASE

- 67F with IgG kappa MM, R-ISS III, diagnosed in 2019
  - Normal FISH
  - Extensive plasmacytomas of the bone and spine
- s/p ***XRT*** at multiple sites
- s/p multiple lines of therapy:
  - 6/2019 -1/2020: ***RVD***
  - 3/4/2020: ***MEL200/SCT - Len***
  - 1/2021-12/2021: ***Dara-Kd***
  - 2/2022-10/2022: ***Cy-Pom-Dex***

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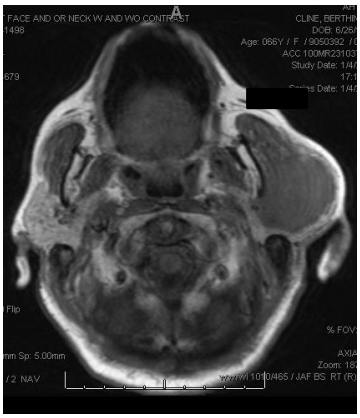
WHAT SHOULD NEXT THERAPY BE?

- 12/22/22: TNB383 on clinical trial
- 01/04/23: Rapidly enlarging paramedullary lesions
  - L jaw mass, cranial nerve 7 palsy, sacral mass and large sternal mass



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MECHANISMS OF RESISTANCE

- Decreased antigen expression
- T Cell exhaustion, possibly exacerbated by previous lines of therapy
- Tumor microenvironment

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51

RECENT FDA APPROVALS

Drug	Class	Target	Date	Indication
Ide-cel	CART	BCMA	March 26, 2021	Following 4 or more lines
Cilta-cel	CART	BCMA	February 28, 2002	Following 4 or more lines
Teclistamab	BiAb	BCMA	October 25, 2002	Following 4 or more lines
Talquetamab	BiAb	GPRC5D	August 9, 2023	Following 4 or more lines
Erlantamab	BiAb	BCMA	August 14, 2023	Following 4 or more lines

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BISPECIFIC AB V. CAR T

	Pros	Cons	Notes
Bispecific Abs	Off the shelf Lower rates of ICANS/CRS	Continuous dosing Lower ORR Infections	Multiple Targets
CART	One time dose Higher ORR	Higher CRS/ICANS Manufacturing/Availability Issues Infections Use of lymphodepleting chemo	

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53

CLINICAL TRIALS AND OBSERVATIONS

Efficacy and safety of cilta-cel in patients with progressive multiple myeloma after exposure to other BCMA-targeting agents

Adam D. Cohen,[1] María-Victoria Mateos,[2] Yael C. Cohen,[3] Paula Rodriguez-Otero,[4] Bruno Paiva,[4] Niels W. C. J. van de Donk,[5] Thomas Martin,[6] Attaya Suvannasankha,[7] Kevin C. De Braganca,[8] Christina Corsale,[8] Jordan M. Schecter,[8] Helen Varsos,[8] William Deraedt,[9] Liwei Wang,[8] Martin Vogel,[10] Tito Roccia,[10] Xiaoying Xu,[8] Pankaj Mistry,[11] Enrique Zudaire,[12] Muhammad Akram,[13] Tonia Nesheiwat,[13] Lida Pacaud,[13] Irit Avivi,[3] and Jesus San-Miguel[4]

Table 3. Response to cilta-cel

	Full cohort N = 20	ADC exposed* N = 13	Bispecific exposed* N = 7
Overall response rate,† % (95% CI)	60.0 (36.1-80.9)	61.5 (31.6-86.1)	57.1 (18.4-90.1)
Best response, rate, n (%)			
Stringent complete response	1 (5.0)	1 (7.7)	0
Complete response	5 (25.0)	4 (30.8)	1 (14.3)
Very good partial response	5 (25.0)	3 (23.1)	2 (28.6)
Partial response	1 (5.0)	0	1 (14.3)
Minimal response‡	1 (5.0)	0	1 (14.3)
Stable disease	3 (15.0)	2 (15.4)	1 (14.3)
Progressive disease	3 (15.0)	3 (23.1)	0
Not evaluable‡,§	1 (5.0)	0	1 (14.3)
≥VGPR	11 (55.0)	8 (61.5)	3 (42.9)
Median duration of response (95% CI), mo	11.5 (7.9-NE)	11.5 (7.9-NE)	8.2 (4.4-NE)
Median time to first response (range), mo	0.95 (0.9-6.0)	0.97 (0.9-5.1)	0.92 (0.9-6.0)
Median time to best response (range), mo	2.22 (0.9-9.9)	2.58 (0.9-9.9)	1.41 (0.9-7.0)
MRD negativity, n (%)			
No. of patients evaluable at 10^{-5}	10	7	3
Rate, n (%)	7 (70.0)	5 (71.4)	2 (66.7)

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TIMING OF B-CELL MUTATION ANTIGEN (BCMA)-TARGETING TREATMENT

Treatments	Total cilta-cel N=18*	
	Responders N = 12	Non-responders N = 6
Duration of last anti-BCMA treatment, days Median Range	 29.5 1-277	 63.5 22-527
Time from last anti-BCMA treatment to apheresis, days Median Range	 161.0 26-695	 56.5 40-895
Time from last anti-BCMA treatment and cilta-cel infusion, days Median Range	 235.0 62-749	 117.5 95-944

* Two patients died before confirmed disease evaluations and were excluded from the analysis.

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Cohen, A et al Blood 2023

55

IMMUNOBIOLOGY AND IMMUNOTHERAPY | MARCH 21, 2023

Sequencing T-cell redirection therapies leads to deep and durable responses in patients with relapsed/refractory myeloma

Tarek H. Mouhieddine, Oliver Van Oekelen, David T. Melnekoff, Jeanne Li, Yogita Ghodke-Puranik, Guido Lancman, Santiago Thibaud, Darren Pan, Sridevi Rajeeve, Sarita Agte, Adolfo Aleman, Larysa Sanchez, Shambavi Richard, Adriana Rossi, Joshua Richter, Hearn Jay Cho, Cesar Rodriguez, Alessandro Lagana, Erin Moshier, Ajai Chari, Sundar Jagannath, Samir Parekh

- 58 Patients progressing after **Bispecific Ab** therapy.
  - Median of 6 prior therapy lines
  - 89% were triple-class refractory
  - 44% were penta-drug refractory
- Patients were followed for a median of 30.5 months and received a median of 2 additional salvage therapies (range, 1-9).

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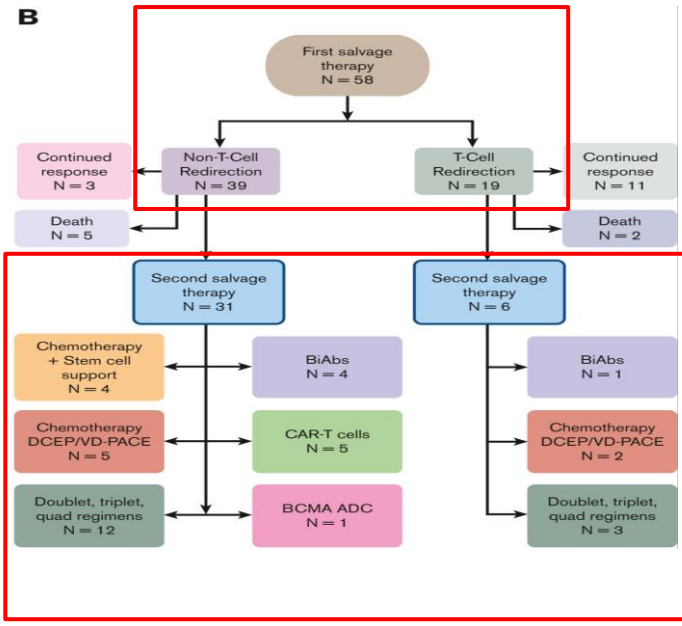
56



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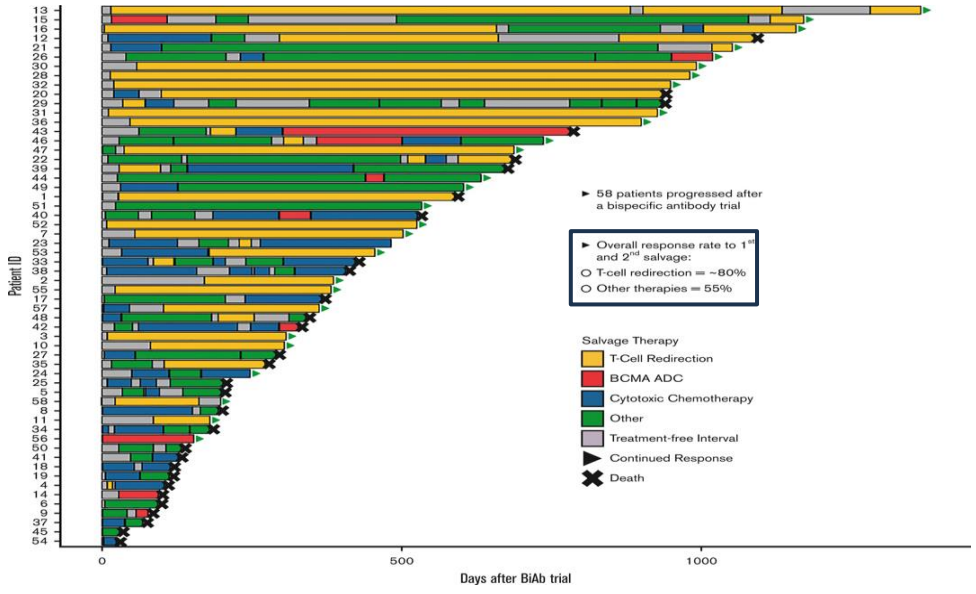
Mouhieddine et al. Blood Advances, 2023

57



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Mouhieddine et al. Blood Advances, 2023

58

Table 2.

Patient responses to FST

	Overall, N = 58	FST		*P* value
		T-cell redirection, N = 19	Other, N = 39	
Response to FST, n (%)				
Stringent complete response	4 (7)	4 (21)	0 (0)	<.0001*
Complete response	9 (15.5)	8 (42)	1 (3)	
VGPR	4 (7)	0 (0)	4 (10)	
Partial response	18 (31)	4 (21)	14 (36)	
Minimal response	2 (3)	0 (0)	2 (5)	
Stable disease	9 (15.5)	1 (5)	8 (20)	
Progressive disease	12 (21)	2 (11)	10 (26)	
ORR on FST, n (%)	35 (60)	16 (84)	19 (49)	.0095*
ORR on FST, 95% CI	47-73	60-97	32-65	
Clinical benefit rate on FST, n (%)	37 (64)	16 (84)	21 (54)	.0239*
Clinical benefit rate on FST, 95% CI	50-76	60-97	37-70	

* *P* value < .05.

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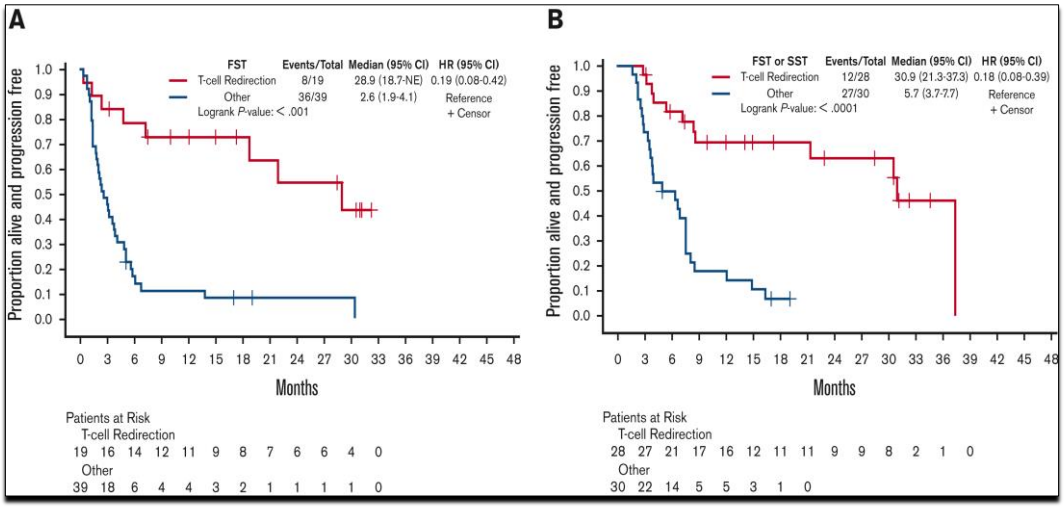
59



T-cell redirection therapy as first or second salvage was feasible and associated with a median PFS1 of 28.9 months, PFS2 of 30.9 months, and an OS of 62% at 2 years.

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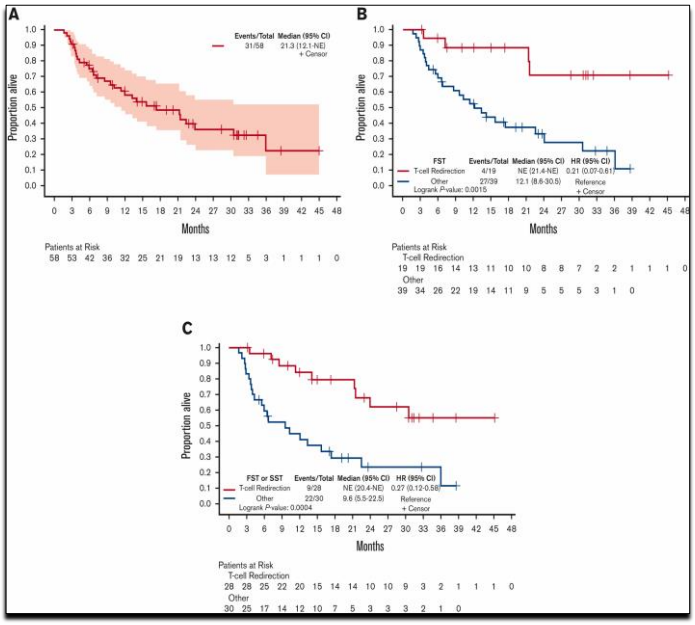
60



Salvage therapy with T-cell redirection enhances OS

(A) OS of the full cohort of 58 patients (mOS 21.3 mos)

(B) OS of 19 patients receiving T-cell redirection as the FST (mOS NR)

(C) OS of 28 patients receiving T-cell redirection as FST or SST (mOS NR) vs all others (mOS 9.6 mos)

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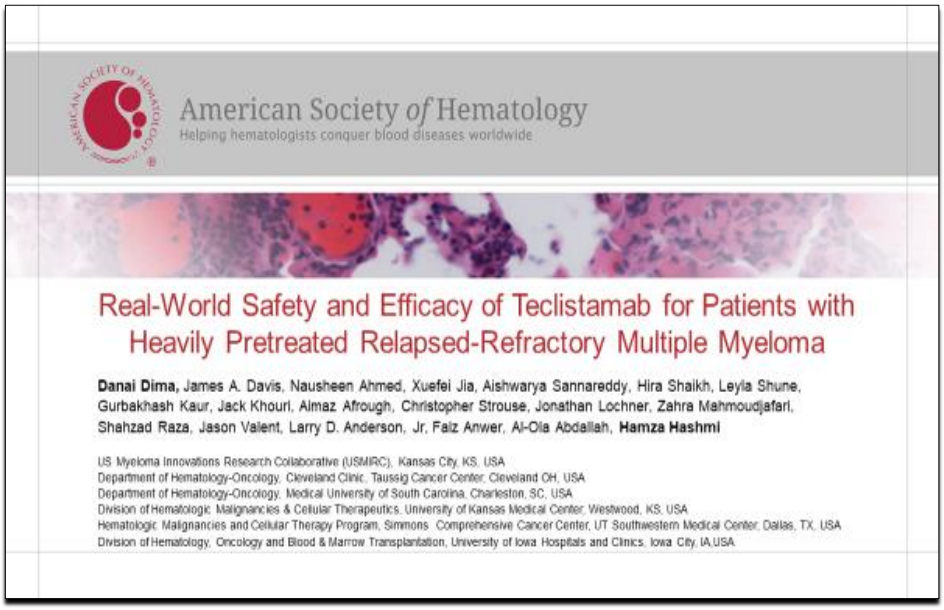
61



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Dima et al. ASH Annual Meeting 2023, Abstract #91

62

RESULTS: PATIENT CHARACTERISTICS

Patients Characteristics	N = 106	MTec-1 (N=165)
Age, years, median (range)	66.5 (35–87)	64 (33-84)
Age >70 years, n (%)	34 (32)	
Median time since diagnosis, years (range)	5.5 (0.5-20)	6.0 (0.8-22.7)
Number of prior lines of therapy (median, range)	6 (4–17)	5 (2-14)
>4 prior LOT, n (%)	80 (75)	
Non-Hispanic White, n (%) Non-Hispanic Black, n (%)	72 (68) 28 (26)	134 (81) 21 (13)
R-ISS stage III, n (%)	25/80 (31)	20/162 (12)
ECOG Performance Status ≥2, n (%)	35 (33)	–
High-risk cytogenetics, n (%)	56/95 (59)	38/148 (26)
Extramedullary disease (EMD), n (%)	45 (42)	28 (17)
Refractory status: **• Triple Refractory, n (%)** **• Penta refractory, n (%)**	97 (92) 68 (64)	128 (78) 50 (30)
Prior BCMA-directed Therapy	56 (53)	–
Prior autologous stem cell transplant, n (%)	61 (58)	135 (82)
Prior allogeneic stem cell transplant, n (%)	3 (3)	

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Dima et al. ASH Annual Meeting 2023, Abstract #91

63

RESULTS: RESPONSE TO TECLISTAMAB

Response (Full Cohort) N (%)	RWE cohort N=104	MajesTec-1 N=165
Overall response rate	**70 (66)**	**104 (63)**
Complete response or better	**31 (29)**	**65 (39.4)**
Very good partial response	18 (17)	32 (19.4)
Partial response	21 (20)	7 (4.2)
Minimal response	0	2 (1.2)
Stable disease	10 (9.5)	27 (16.4)
Progressive disease	**26 (24.5)**	**24 (14.5)**
Not evaluable	0	8 (4.8)

Subgroups of Interest	ORR, N (%)
Age>70 (n=34)	24 (71)
Non-Hispanic Black (n=28)	20 (71)
Pts ineligible for MajestEC-1 trial (n=88)	53 (60)
High-risk cytogenetics (n=56)	35 (63)
Triple Refractory (n=97)	62 (64)
Penta refractory (n=68)	46 (68)
Prior BCMA therapy	33 (59)
R-ISS III (n=25)	13 (52)
EMD (n=45)	21 (47)
Four or less prior LOT (n=26)	21 (81)
>4 lines of prior therapy (n=80)	49 (61)

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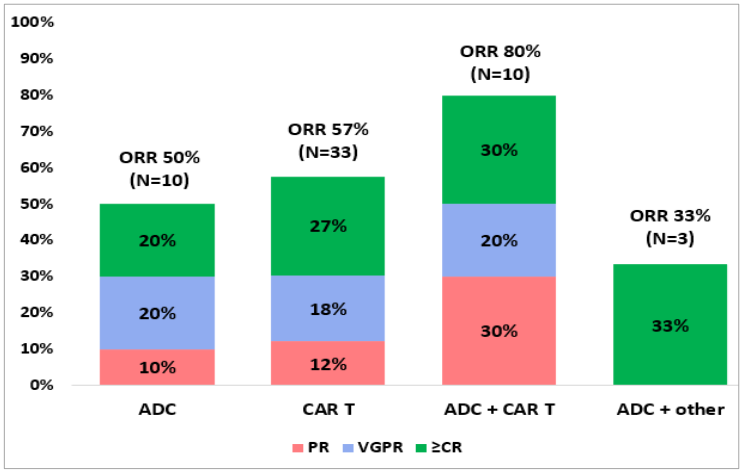
64

RESULTS: RESPONSE RATES TO TECLISTAMAB BY SPECIFIC TYPE OF PRIOR BCMA-DIRECTED THERAPY



Responders had a longer time since their last BCMA-DT (339 vs 205 days; p=0.072), c/t **non-responders**

Pts who started TEC within 3 mo from their last BCMA-DT had a lower ORR (42.9% vs 64.3%; p=0.27)

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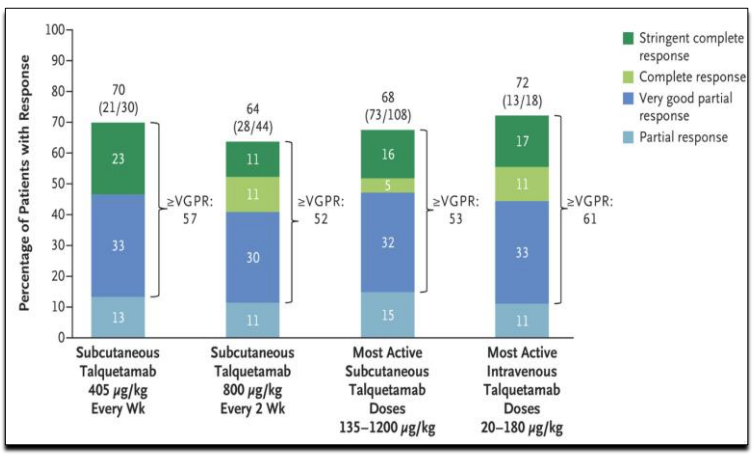
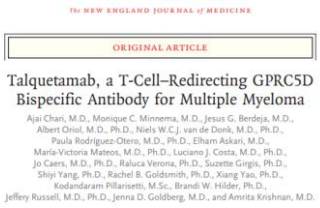
65

TALQUETAMAB




The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma

Ajai Chari, M.D., Monique C. Minnema, M.D., Jesus G. Berdeja, M.D., Albert Oriol, M.D., Ph.D., Niels W.C.J. van de Donk, M.D., Ph.D., Paula Rodríguez-Otero, M.D., Ph.D., Elham Askari, M.D., María-Victoria Mateos, M.D., Ph.D., Luciano J. Costa, M.D., Ph.D., Jo Caers, M.D., Ph.D., Raluca Verona, Ph.D., Suzette Girgis, Ph.D., Shiyi Yang, Ph.D., Rachel B. Goldsmith, Ph.D., Xiang Yao, Ph.D., Kodandaram Pillarisetti, M.Sc., Brandi W. Hilder, Ph.D., Jeffery Russell, M.D., Ph.D., Jenna D. Goldberg, M.D., and Amrita Krishnan, M.D.

"Among the 16 patients who received the doses recommended for a phase 2 study and who had had previous exposure to T-cell–redirecting B-cell maturation antigen (BCMA)–directed bispecific antibodies or chimeric antigen receptor (CAR) T-cell therapies, 8 (50%) had a response."

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Chari, A et al NEJM 2022

66

SUMMARY IN BCMA EXPOSED

Product	ORR in general population	Cohort size with Previous BCMA targeted therapy	ORR with previous BCMA exposure	Difference in ORR	NCT #
Teclistamab	63%	25	40%	23%	NCT04557098
Elranatamab	61%	13	54%	7%	NCT04649359
Talquetamab	70%	16	50%	20%	NCT03399799
Talquetamab + Daratumumab	78%	25	72%	6%	NCT04108195
Cevostamab	58%	43	56%	2%	NCT03275103
Cilta-cel	95%	20	60%	35%	NCT04133636
Ide-cel	88%	50	74%	14%	*real world comparison

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Ferrari et al Bood 2023
Patel et al ASCO 2023 Abstract 20049

67

CONCLUSIONS

- After treatment with a BiAb or CAR T, one can still exhibit favorable outcomes with T-cell redirection tx.
- Conventional salvage therapy demonstrated significantly lower PFS and OS rates.
- There was no statistically significant difference in PFS1 and OS between patients receiving a BiAb or CAR T-cell therapy as FST, indicating that both CAR T cells and BiAbs can have excellent outcomes.

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WHEN CHOOSING…

- Duration of therapy
- Dose (ie. phase 1 clinical trial?)
- Treatment-free interval
- Protein and genomic loss of target at the time of progression
  - Bispecifics are repeatedly targeting the same antigen, as opposed to the more one-and-done CAR Ts

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CASE CONTINUED…

- Pt was bridged to CAR T therapy with KD PACE therapy with good response in her plasmacytomas
- 4/26/23: Infusion of ciltacabtagene autoleucel therapy and attained an MRD neg sCR at 10-5 and 10-6
- 11/6/23: Relapsed with spinal cord compression s/p surgical decompression and XRT
- 12/2023: Started on talquetamab

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FUTURE DIRECTIONS

- Increasing antigen expression (gamma secretase inhibitor)
- Combine with other therapies (SOC, PD1, etc)
- Improving CART manufacturing, expansion, longevity
- Multiple antigen targeting
- Optimizing place in therapy

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Highlights of Myeloma Rounds

Smoldering Myeloma

Edward A. Stadtmauer, MD
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow, and Shaffer Families'
President's Distinguished Professor
University of Pennsylvania Abramson Cancer Center
Philadelphia, PA

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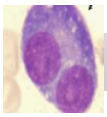
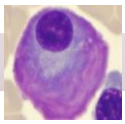
DISEASE TRAJECTORY

Nonmalignant Accumulation → *Stroma angiogenesis* → ***Malignant Transformation*** → *and IL-6 dependent* → ***Aggressive and Stromal Independent***


- **Plasma Cell Leukemia**
- **Extramedullary Disease**

MGUS

- <10% bone marrow plasma cells
- <30 g/L M-protein
- No SLiM CRAB
- 1%/yr risk of progression to MM

Smoldering Myeloma

- 10-60% bone marrow plasma cells
- No SLiM CRAB
- ≥30 g/L M-protein (IgG or IgA)
  OR
- ≥500 mg/24 hr urinary protein
- No amyloidosis
- High-Risk 20, 20, 2
  - 20% PC
  - 20:1 ratio
  - 2 g/dl M-spike

Multiple Myeloma

- Clonal bone marrow ≥10% or bony/extramedullary plasmacytoma

AND

- Any ≥ 1 **SLiM CRAB feature (s)**:
  - **SLiM***
    - **S:** Clonal plasma cells in BM ≥60%
    - **Li:** Serum free light-chain ratio ≥100 mg/L
    - **M:** >1 MRI focal lesion ≥5 mm
  - **CRAB*** feature:
    - **C**: Calcium elevation (>11 mg/dL)
    - **R**: Renal insufficiency (Cr>2 mg/dL or CrCl<40 mL/min)
    - **A**: Anemia (Hgb<10 g/L)
    - **B**: Bone disease: (≥1 lytic lesion)

MGUS, monoclonal gammopathy of undetermined significance

Rajkumar et al. *Lancet Oncol. 2014*;15(2):e538-e54.; Kuehl WM, et al. *Nat Rev Cancer*. 2002;2:175-187. Agarwal A, et al. *Clin Cancer Res*.2013;19:985-994. Durie BG, et al. *Hematol J*. 2003;4:379-398. Kurtin SE. *J Adv Pract Oncol*. 2010;1:19-29.

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SMOLDERING MYELOMA CLINICAL CASE

- 67-year-old male with history of synchronous NSCLC, CKD, HTN, T2DM
- Followed with local oncologist for NSCLC – was treated with RUL and RML lobectomies, followed by 4 cycles of adjuvant chemotherapy (cisplatin/pemetrexed), completed in 2020.
- Followed by nephrologist for CKD
- 2021 – UPEP shows monoclonal protein (118.88 mg/dL), SPEP negative
- 2022 – kidney function stable, full plasma cell dyscrasia workup is performed
- Initial Lab Evaluation
  - WBC: 12.1; Hgb: 16; Plt: 270, Creatinine: 1.76 mg/dL, Calcium: 10.5 mg/dL, SPEP: 0.1 g/dL monoclonal free lambda. UPEP (24 hr): 146.45 mg/dL monoclonal free lambda. Serum free lambda: 1911; serum free kappa: 35.5; ratio: 0.02, IgM: 35; IgA: 142; IgG: 1028, LDH: 180 units/L, Albumin: 4.8 g/dL, Beta 2 microglobulin: 3.30 mcg/mL
  - CT chest/abdomen/pelvis (performed for lung cancer surveillance): No osseous abnormalities. Complete skeletal survey: No lytic or blastic lesions
  - Bone Marrow Biopsy and FISH: Plasma cell disorder – monoclonal lambda plasma cells comprising 15% of marrow, Congo red negative, FISH – negative for multiple myeloma panel

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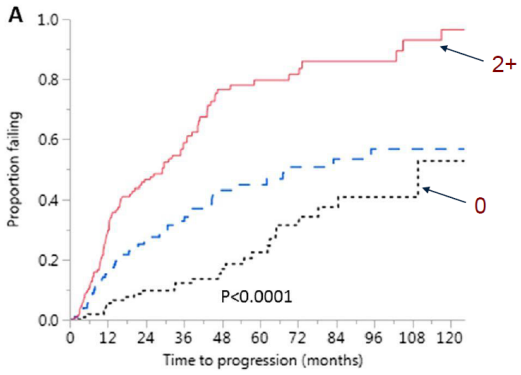
Revised risk criteria: "2/20/20"



Three-factor model:

Serum M-spike **>2** g/dL
BM **>20%** plasma cells
Light chain ratio **>20**

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)

Lakshman A et al. *Blood Cancer J*. 2018;8(6):59.

Penn Medicine Abramson Cancer Center 4

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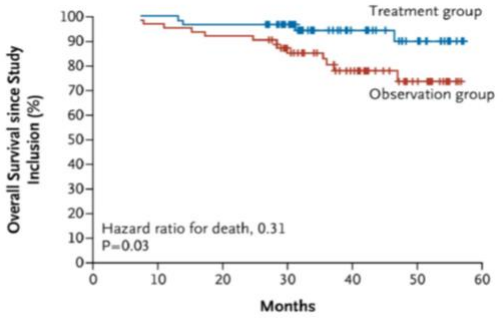
SHOULD WE TREAT HIGH-RISK SMOLDERING MYELOMA?

- Len-dex vs observation in high-risk SMM.
- Overall survival benefit to early treatment, but…
  - Control arm did not receive lenalidomide-based therapy at progression.
  - Treatment was withheld from control arm until CRAB features developed.
  - Advanced imaging was not used to assess for lytic bone lesions



Mateos MV, N Engl J Med 2013; 369:438-447

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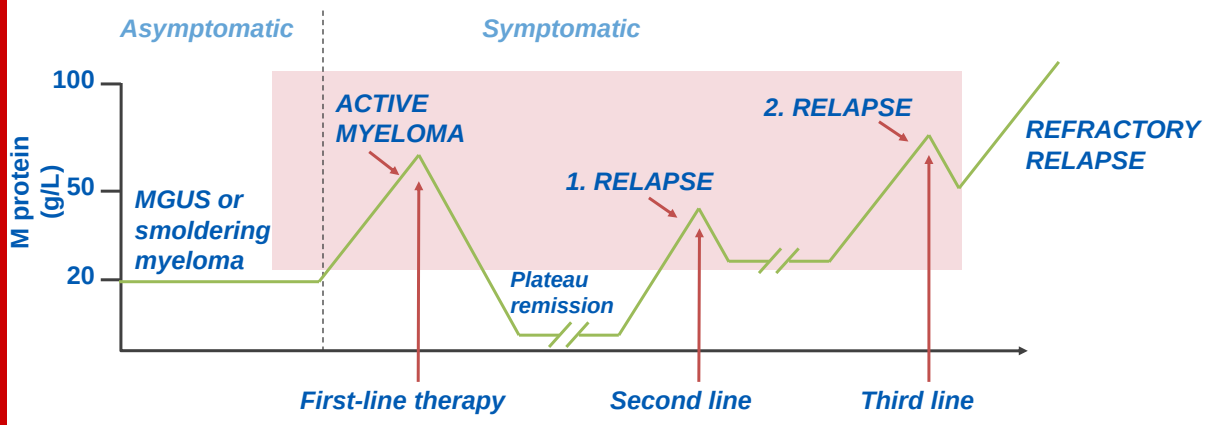
THE TRAJECTORY OF MYELOMA



Multiple myeloma is highly complex during progression and relapse due to genomic events and clonal evolution.

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Paul Richardson's ASH 2018 presentation

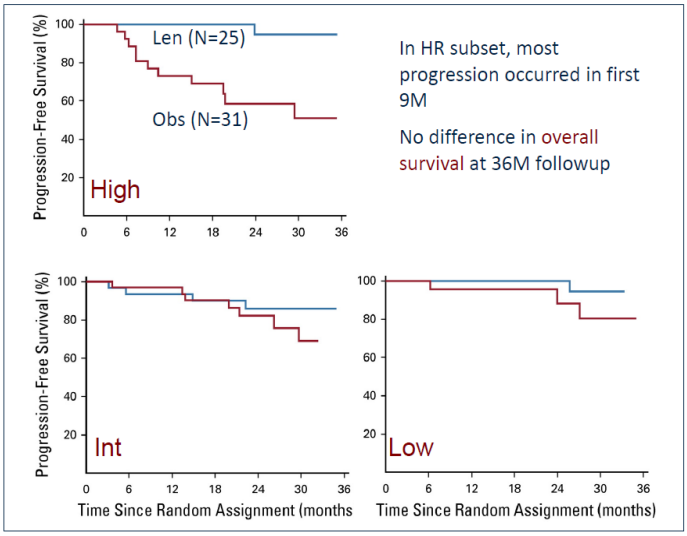
77

SHOULD WE TREAT HIGH-RISK SMOLDERING MYELOMA?

ECOG E3A06: Int-high risk SMM* → Randomize lenalidomide vs observation

*BMPC >10% + abnormal SFLC ratio

PFS by Mayo risk subgroups (2/20/20)



In HR subset, most progression occurred in first 9M

No difference in overall survival at 36M followup

	Len (n=90)	Obs (n=92)
Time since SMM dx (med)	2.6 mos.	3.4 mos.
Time since SMM dx (med) High-risk subset	1.3 mos.	0.9 mos.
Progression events		
Hypercalcemia	0	1
Anemia	4	8
Renal failure	0	3
Bone lesions or plasmacytoma	3	11

1 fatal PE in lenalidomide arm

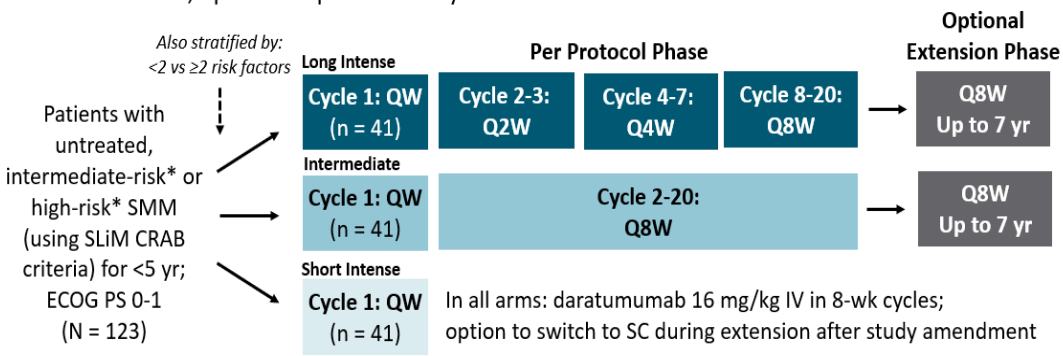
Lonial et al JCO 2019

Penn Medicine Abramson Cancer Center

78

FINAL ANALYSIS OF CENTAURUS: STUDY DESIGN

- Randomized, open-label phase II study



- **Primary endpoint:** ≥ CR, PD, or death per PY
- **Secondary endpoints:** ORR, PFS, OS

*Risk criteria: BM plasma cells ≥10% AND ≥1 of: serum M-protein ≥3 g/dL (IgA ≥2 g/dL), urine M-protein >500 mg/24 hr, abnormal FLC ratio (<0.126 or >8) with serum M-protein >1 to <3 g/dL, absolute involved sFLC ≥100 mg/L with abnormal FLC ratio (<0.126 or >8)

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Hofmeister. ASH 2017. Abstr 510. Landgren. ASH 2023. Abstr 210.

79

FINAL ANALYSIS OF CENTAURUS

Investigator-Assessed Response	Long (n = 41)	Intermediate (n = 41)	Short (n = 41)
ORR, %	58.5	53.7	37.5
▪ sCR	4.9	7.3	0
▪ CR	0	2.4	0
▪ VGPR	24.4	14.6	20.0
▪ PR	29.3	29.3	17.5
Median duration of response, mo	NR*	83.4*	72.7*

Outcome	Long (n = 41)	Intermediate (n = 41)	Short (n = 41)
PFS, mo			
▪ Median PFS (per protocol)	NR	NR	NR
▪ Including extension phase	NR	84.4	74.1
OS			
▪ Median, mo	NR	NR	NR
▪ 84-mo, %	81.3	89.5	88.1
▪ Events, n (%)	7 (17.1)	5 (12.2)	4 (9.8)
Median time to next treatment, mo	NR	NR	76.3

- At median follow-up of ~7 yr, daratumumab monotherapy continued to show clinical activity in patients with intermediate- or high-risk SMM[1]
  - Trend toward longer PFS and time to next treatment with long-intense dosing schedule
- No new safety concerns observed with extended daratumumab exposure

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SHOULD WE TREAT HIGH-RISK SMOLDERING MYELOMA?

- Many trials are investigating early treatment strategies
- In our opinion, current evidence does not favor early treatment
  - PFS as reported is not a clinically relevant endpoint
  - PFS benefit in E3A06 may be driven by SMM patients actively evolving to
  - OS benefit in QuiReDex may be due to absence of lenalidomide in observation arm at progression
- FDA has not approved any therapy for treatment of smoldering multiple myeloma
- Excellent discussion of these data: Raje and Yee, JCO 38:11 (2020) 119-1125.

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PATIENT SUMMARY

- 10% BMPC
- M-spike: <3 g/dL
- SFLCR: 0.02
- Mild hypercalcemia
- CKD of unclear etiology
- No anemia
- No bone lesions
- Kidney Biopsy: Global glomerulosclerosis, moderate, with glomerulopathy, Tubular atrophy and interstitial fibrosis, moderate, Arterio- and arteriolo-sclerosis and hyalinosis, moderate, Immunofluorescence microscopy is negative for paraprotein or significant immune complex deposition
- **Management**
  - Deferred initiation of treatment. Risk stratification: intermediate risk based on SFLCR (1 of 3 of the 20-2-20 criteria). No indication for smoldering myeloma treatment given not high-risk disease, Clinical evaluation and lab monitoring every 3 months

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Thank You!

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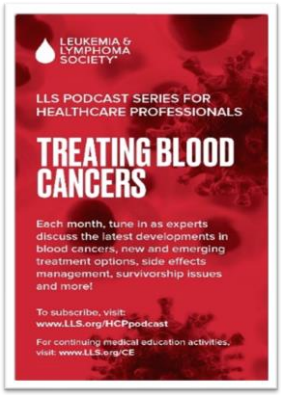
FREE LLS RESOURCES FOR HEALTHCARE PROVIDERS

- CME & CE courses: www.LLS.org/CE
- Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- Videos for HCPs: www.LLS.org/HCPvideos
- Podcast series for HCPs: www.LLS.org/HCPpodcast



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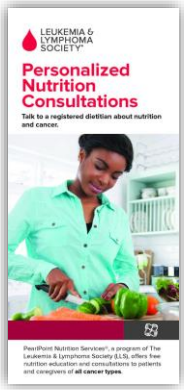
84

FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
  - www.LLS.org/IRC
- **Clinical Trial Nurse Navigators** – RNs and NPs provide a personalized service for patients seeking treatment in a clinical trial, sift through the information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC
- **Nutrition Education Services Center** – one-on-one consultation with a registered dietician for patients/caregivers of all cancer types (NESC).
  - www.LLS.org/Nutrition
- **Reach out Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: www.LLS.org/ContactUs
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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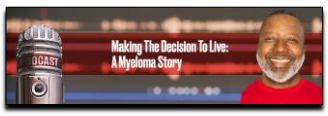
85

FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Webcasts, Videos, Podcasts, booklets**:
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast
  - www.LLS.org/Booklets
  - www.LLS.org/Myeloma



- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
    - Urgent Need
    - Patient Aid
    - Travel Assistance
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program

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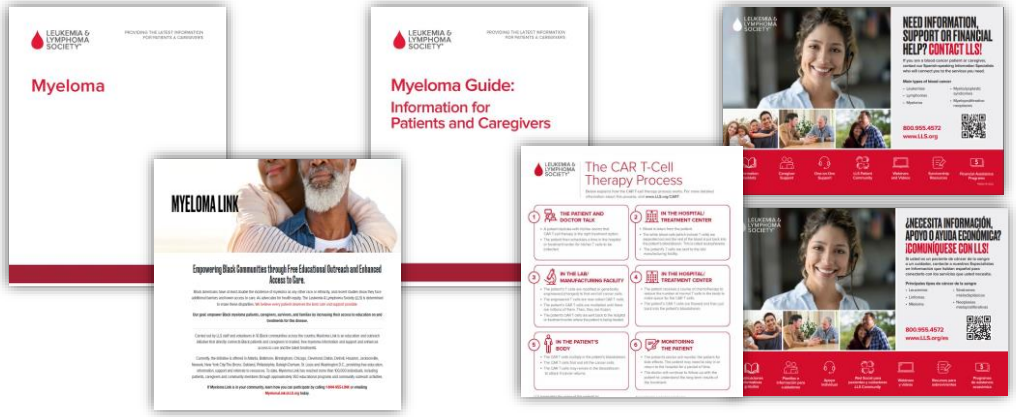
86

FREE LLS RESOURCES FOR YOUR PATIENTS



- www.LLS.org/Myelomalink

BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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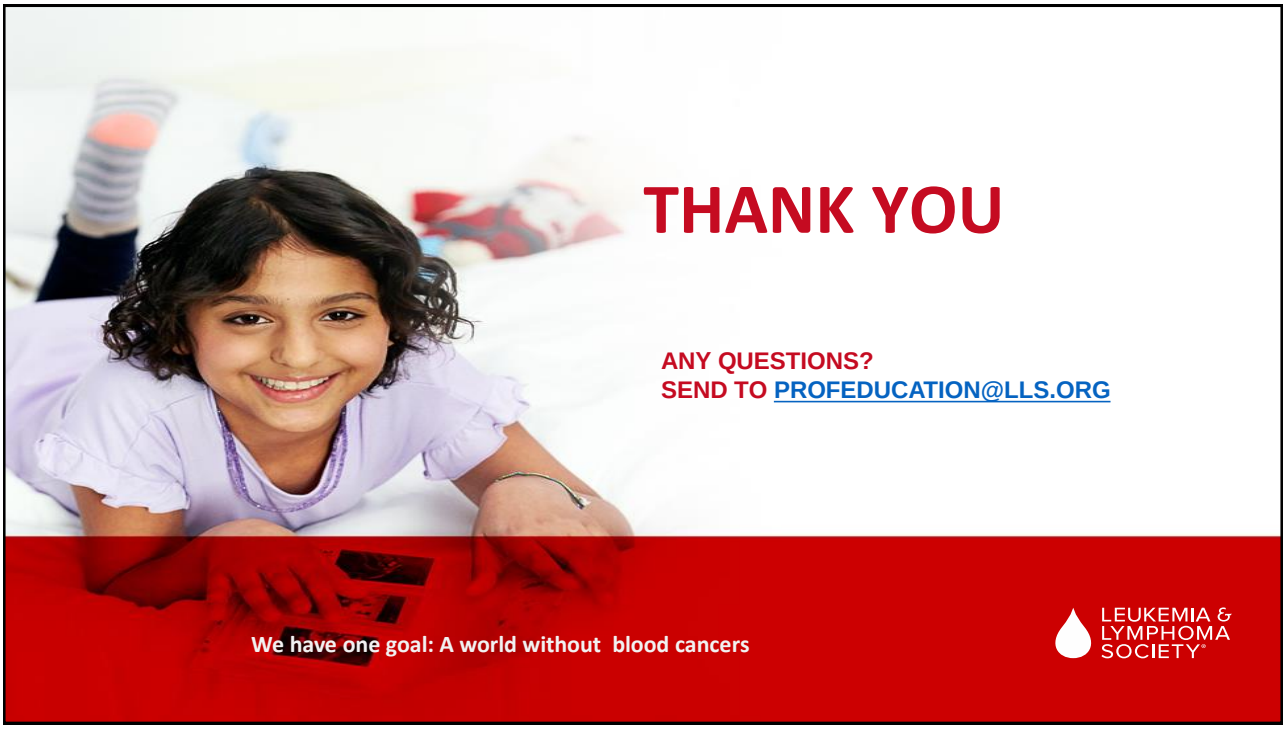
87



88