

# Extra-medullary Disease Biology, prognosis, Treatment

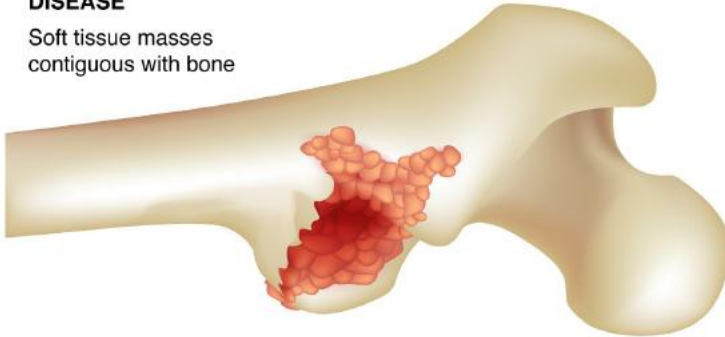
Prof Dr Meral Beksac  
İstinye University  
Ankara Liv Hospital



# Clinical features

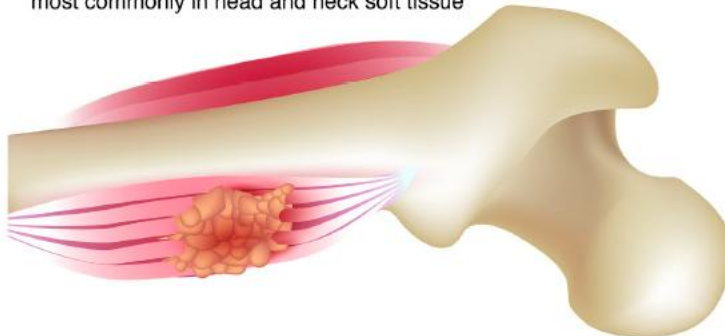
## PARAMEDULLARY DISEASE

Soft tissue masses contiguous with bone



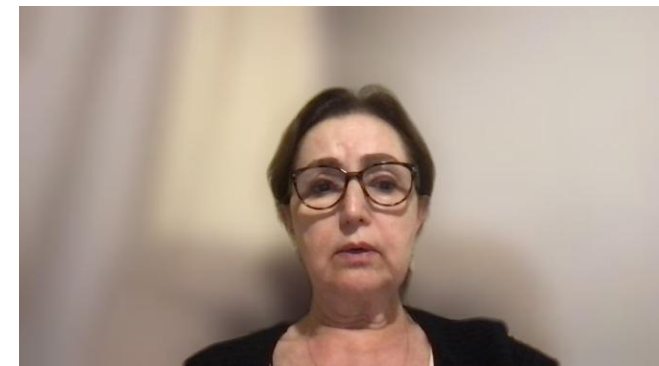
## SOFT TISSUE EMD

Soft tissue masses not contiguous with bone, most commonly in head and neck soft tissue



## ORGAN-ASSOCIATED EMD

Soft tissue plasmacytoma not contiguous with bone, most commonly in liver and pleural fluid



# outline

- Prognostic role
  - at diagnosis vs. relapse
  - preASCT vs. postASCT
  - Para-osseous vs. soft tissue EMD
- Approach to treatment
- Possibility of targeted therapy
- Response assessment

## incidence:

Table I. Plasmacytomas in multiple myeloma: incidence at diagnosis and at relapse.

	Paraskeletal (PS), %*	Extramedullary (EMD), %†
At diagnosis	7–34.4	1.75–4.5
At relapse‡	6–34.2	3.4–10

## Barcelona data:

At diagnosis: 1.9% EMD 17.6% PS

At relapse-1: 5.1% EMD 14.6% PS

Rosinol L Beksac M et al  
Blade J et al Blood Canc



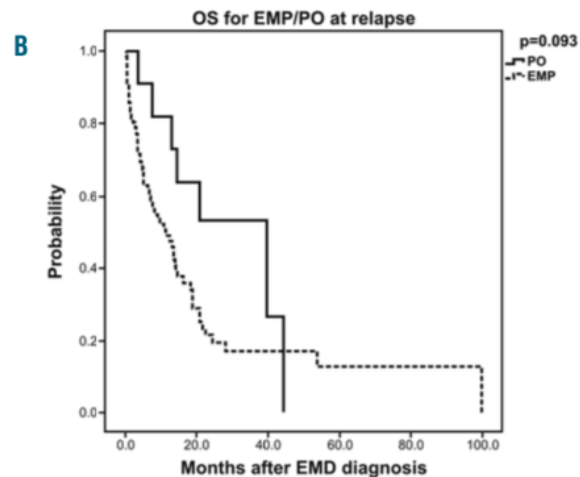
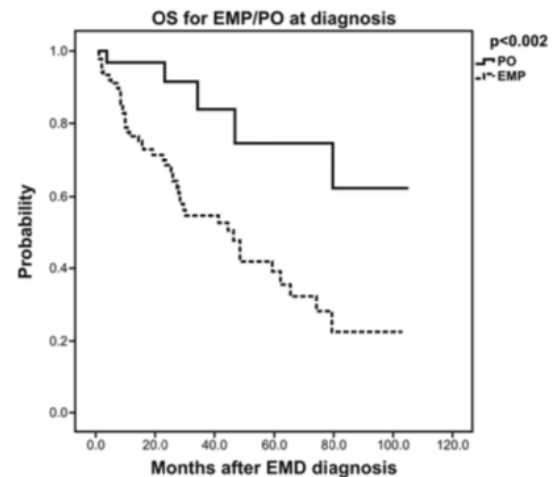
## Revised Table-2

### Beksac M et al Haematologica 2020 105(1):201-208

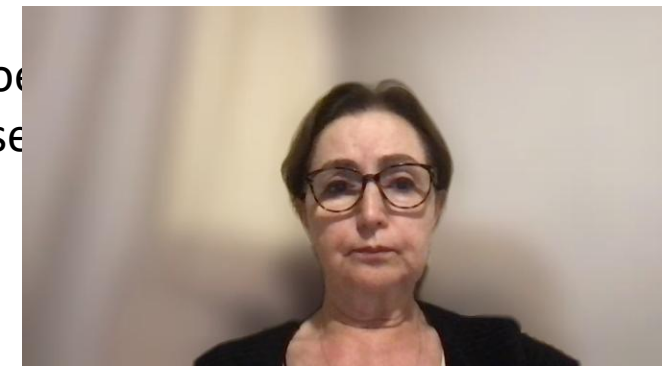
**Table 2.** Comparison of response, survival outcomes of extramedullary plasmacytomas (EMP) or paraosseous (PO) patients either at diagnosis or at relapse.

	CR (%)	PFS (mos)	OS (mos)
EMP			
diagnosis (n=92)	19.3	38.9 (95% CI: 23.6-54.2)	46.5 (95% CI: 25.5-67.5)
relapse (n=84)	9	13.6 (95% CI: 11.6-15.6)	11.4 (95% CI: 6.6-16.2)
PO			
diagnosis (n=38)	34.2	51.7 (95% CI: 13.5-89.9)	NR
relapse (n=12)	54.5	20.9 (95% CI: 10.3-31.5)	39.8 (95% CI: 12.7-66.9)

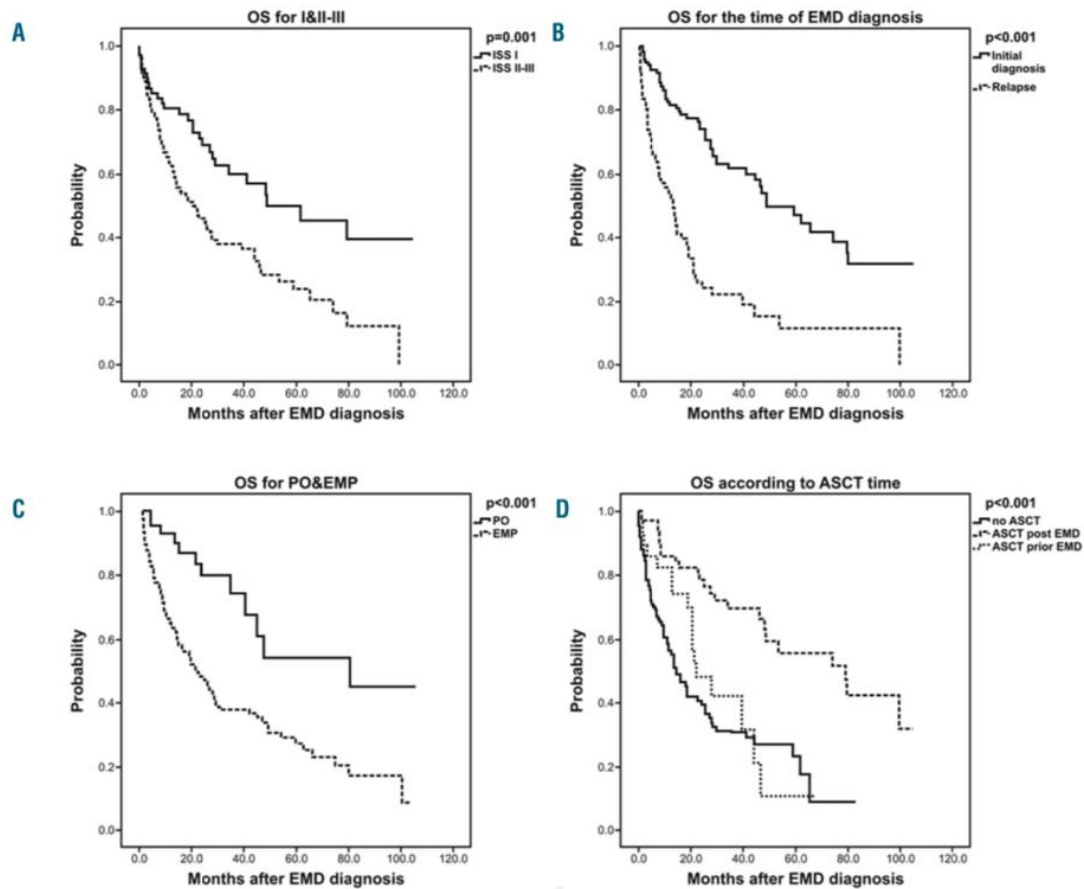
CR: complete response; PFS: progression-free survival; OS: overall survival.



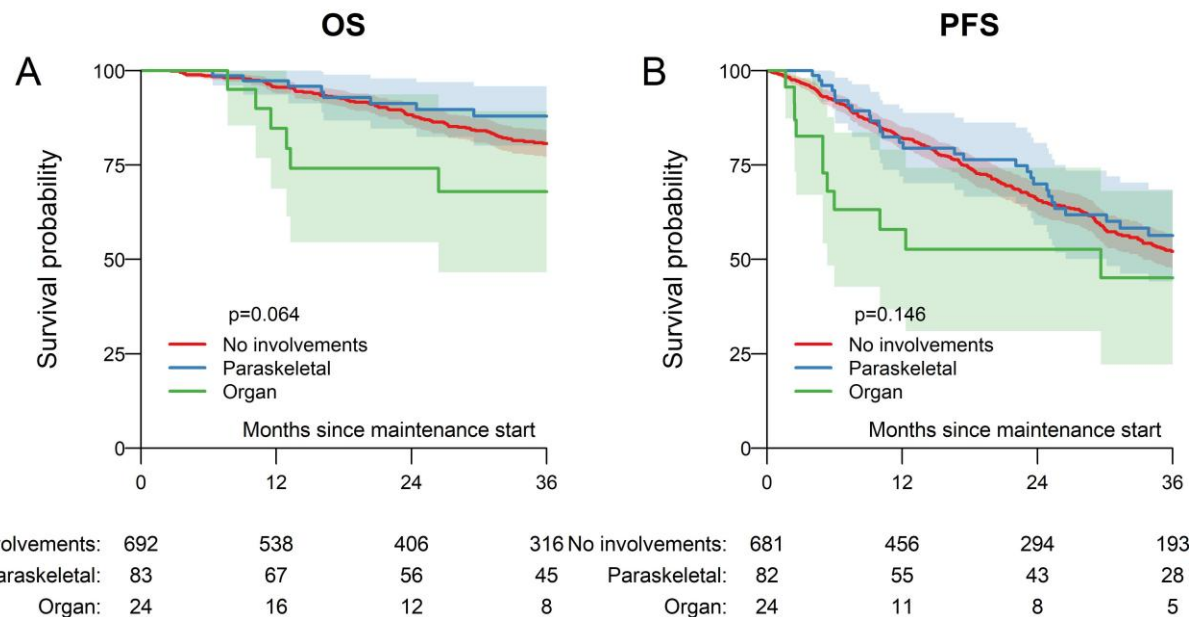
Paraosseous  
at relapse



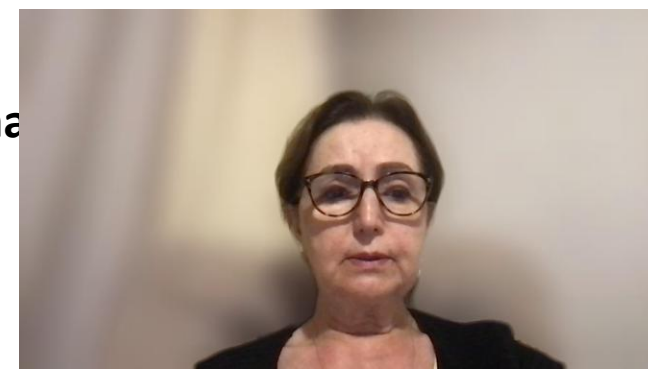




Beksac et al Haematologica 2020  
BMSG

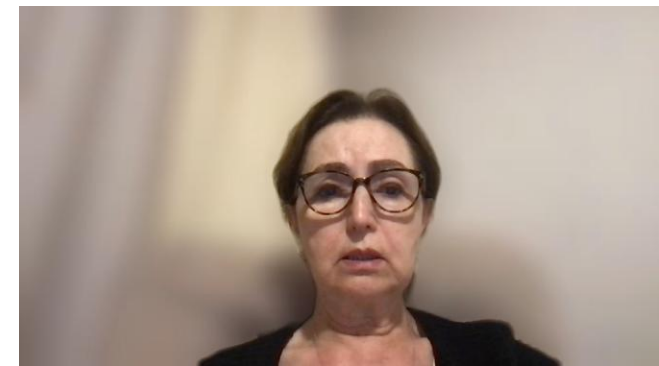


Gagelmann et al Eur J Haema  
BMT



### Retrospective data results

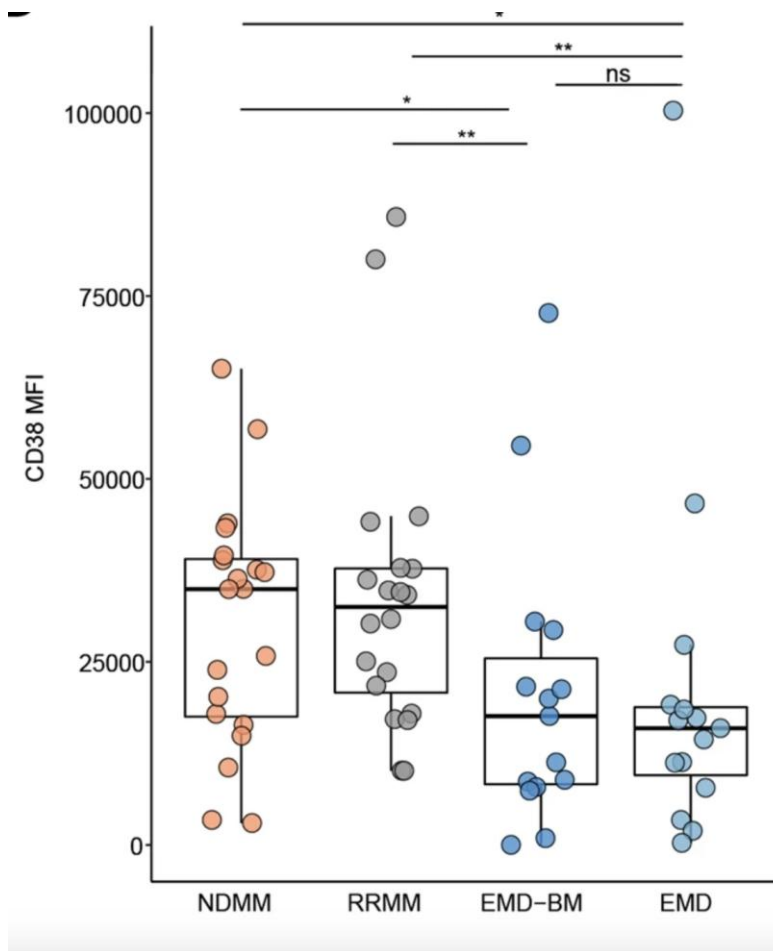
- Incidence and clinical success rate of EMD is increasing
- AHCT improves outcome
- Paraosseous plasmacytoma at diagnosis displays similar outcome to no-EMD but
- at relapse both paraosseous and soft tissue EMD are poor prognostic
- EMD prior to AHCT is of worse outcome compared to EMD presenting at post-AHCT
- Patients with EMD at diagnosis tend to relapse with EMD



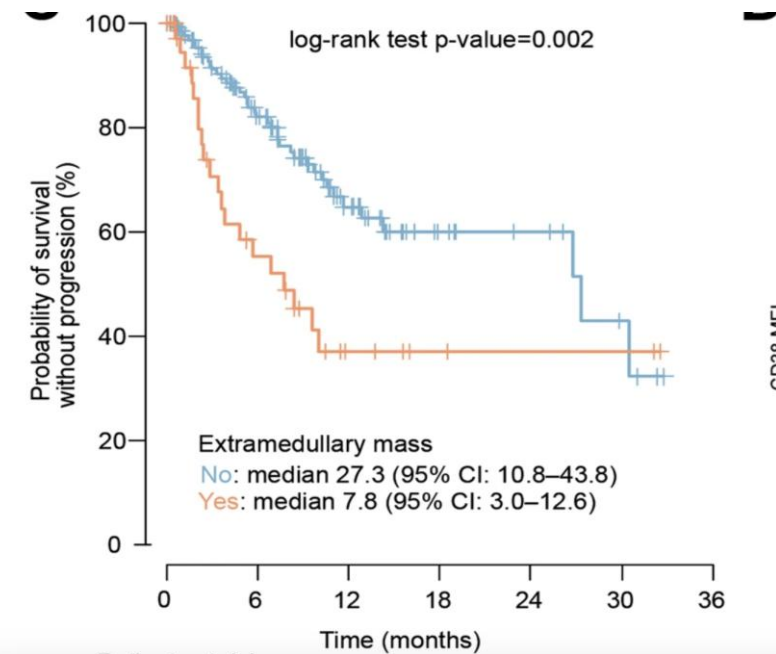
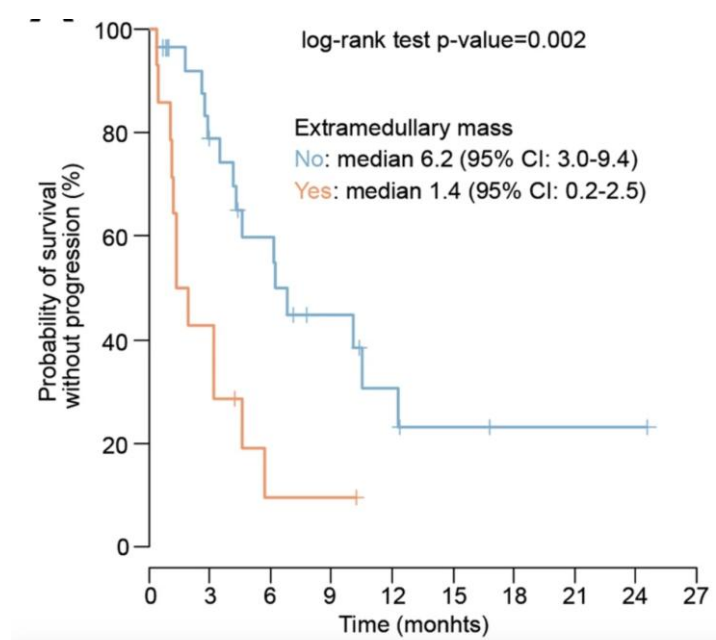
# Biology of EMD



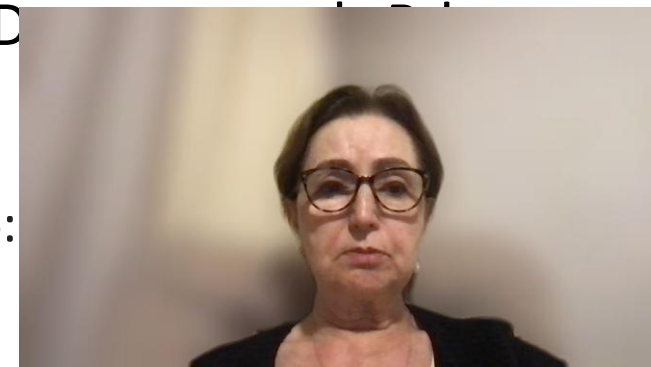
## CD38 expression



## RRMM: EMD effect



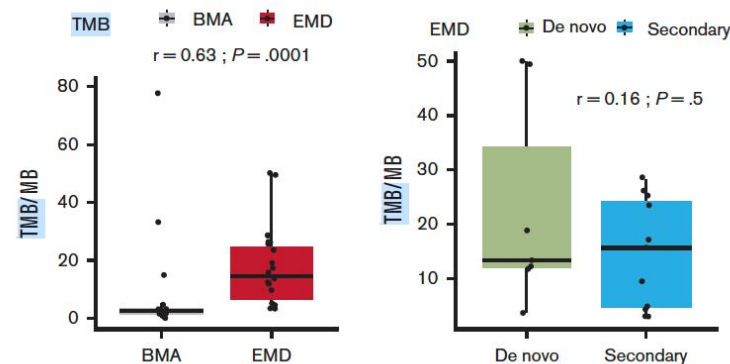
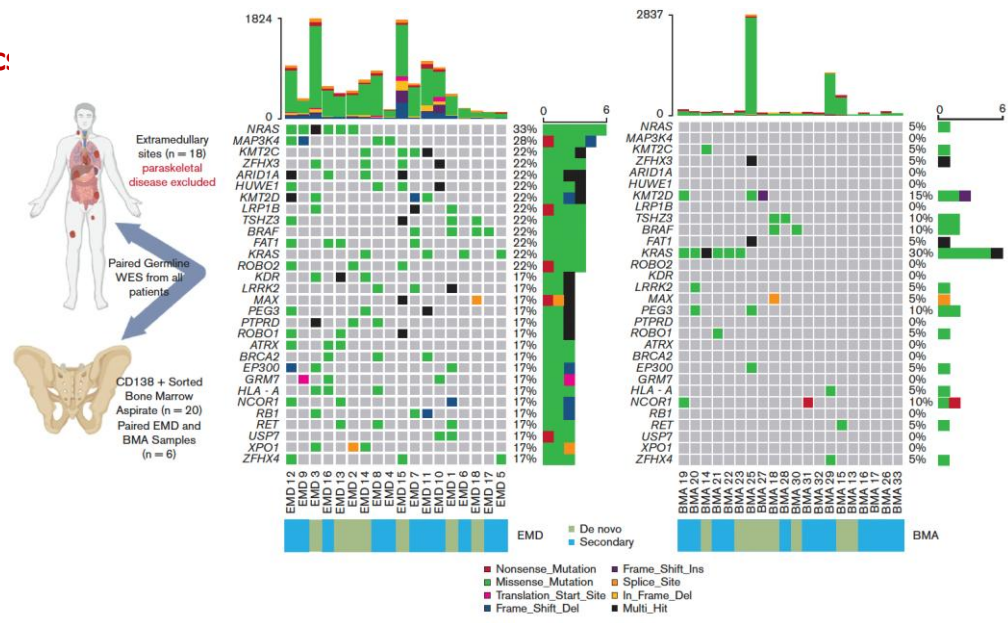
Jelinek et al Leukemia 2022;36:



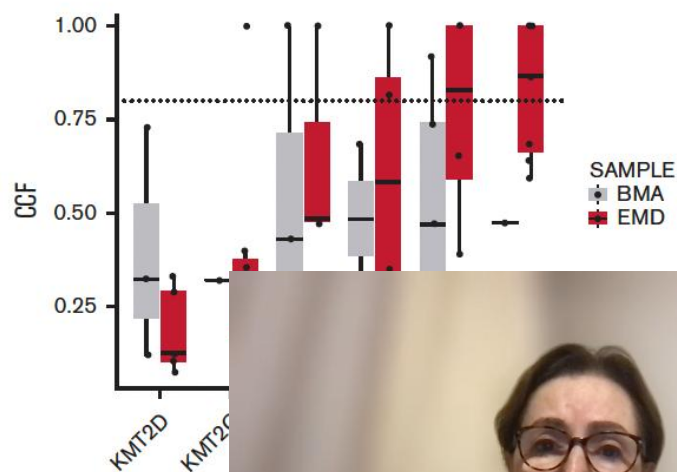


# Marrow is not equal to EMD

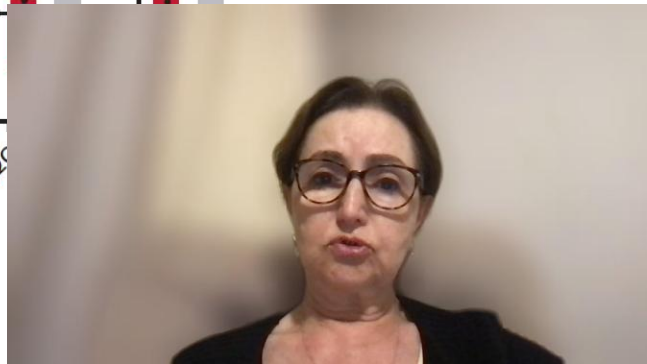
EMD: Genomic



Mutational burden is increased

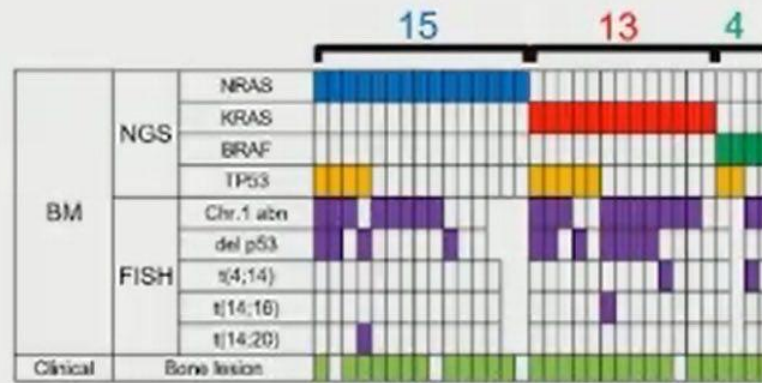


Zanwar et al Blood 2025;9(15):3979-87

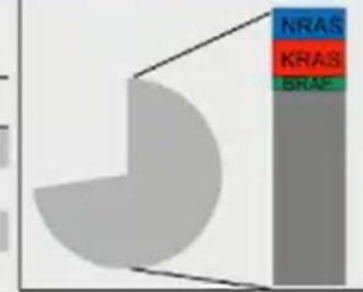


## Profile of 111 BM-NRAS/KRAS/BRAF patients

w/ EMD  
(32)

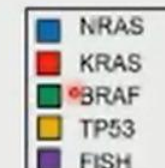
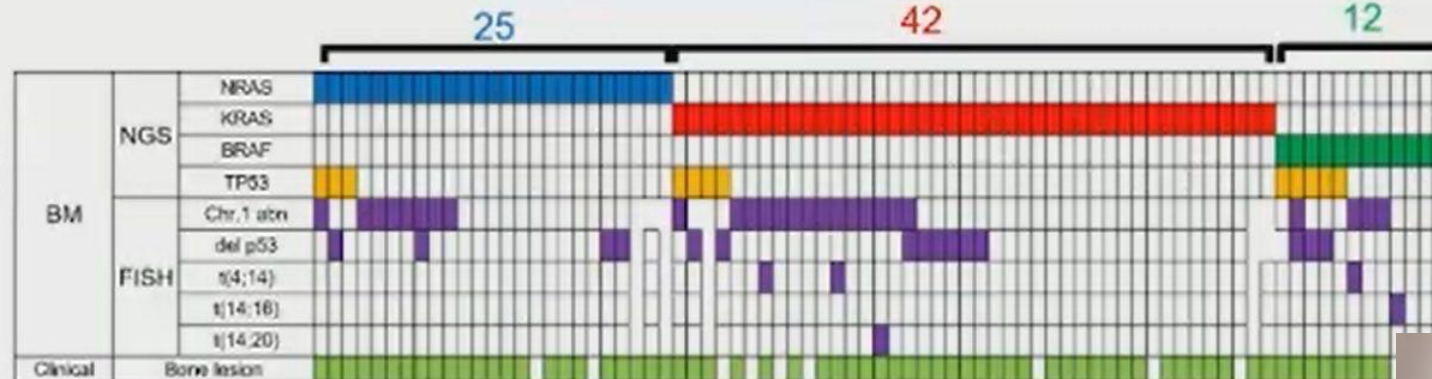


	w/ EMD	w/o EMD
TP53 mut	37.5%	15.2%
Chr.1 abn	63.0%	36.1%
Del p53	44.4%	20.1%
t(4;14)	10.7%	4.0%
t(14;16)	3.6%	1.3%
t(14;20)	3.6%	1.3%
Bone lesion	87.5%	84.8%



	NRAS (40)		KRAS (55)		BRAF (16)	
	w/ EMD	w/o EMD	w/ EMD	w/o EMD	w/ EMD	w/o EMD
Number	15	25	13	42	4	12
%	37.5	63.5	23.6	76.4	25.0	75.0

w/o EMD  
(79)



**EMD:** Chromosome 1q abnormalities(**63%**) and p53 Mutation(**37%**)or d  
**Non-EMD:** Chr 1q abn (**36%**) and p53 mutation (**15 %**) del p53(**20%**)

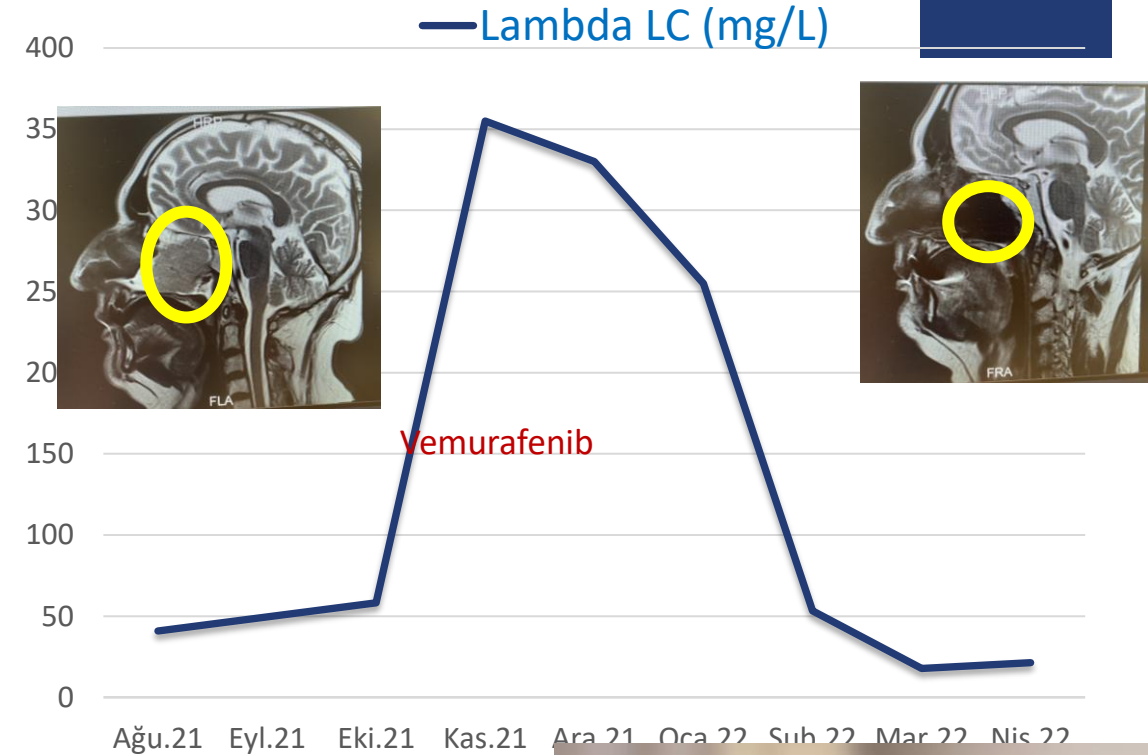
Nakamoto- Matsu





# 59 y male patient $\lambda$ light chain MM

- December 2009: pelvic plasmacytoma at Dx
- 1<sup>st</sup> line: 3xVAD, ASCT (2010), CR
- 2014: relapse with supraclavicular paraosseous plasmacytoma
- 2<sup>nd</sup> line: VCDx6, Bortezomib maintenance, sCR
- June 2016: relapse with thoracic paraosseous lesion
- 3<sup>rd</sup> line: Rdx15, CR
- January 2018: relapse with multiple EMPs
- 4<sup>th</sup> line: Pom-Vd x8, Pom-Dex x2, PR
- December 2018: involved FLC  $\uparrow$
- 5<sup>th</sup> line: Pom-Cy-Dex x5, CR
- June 2019: relapse with suprasternal paraosseous lesion
- 6<sup>th</sup> line: Pom-Vd x2, Pom-Dex x2, PR
- October 2019: bortezomib induced PNP and diarrhea
- November 2019: involved FLC  $\uparrow$  and suprasternal lesion size  $\uparrow$
- 7<sup>th</sup> line: Carf-Benda x1, Carf-Cy-Dex x4, PR
- March 2020: progress with new EMP, RT
- 8<sup>th</sup> line: Dara-Rd, Dara-VRd, VGPR
- December 2020: relapse with periorbital EMP, RT and Cyber knife
- 9<sup>th</sup> line: DCEP x2, Dexamethasone-BEAM, PR
- December 2021: progress with nasal EMP in the sphenoid sinus
- 10<sup>th</sup> line: Selinexor-Carf-Dex x1
- Nasal EMP NGS: BRAF mutation (+)
- 11<sup>th</sup> line: January 2022: Vemurafenib initiated VGPR
- Local recurrence August 2022: reoperated RT
- Pelvic new EMD 7 cm in diameter Dabrafenib initiated Response duration 10 months
- Eltranamab PR in EMD but no hematological response
- Modakafusp



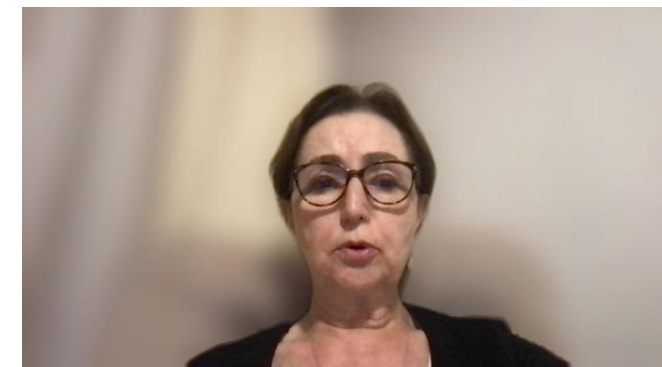
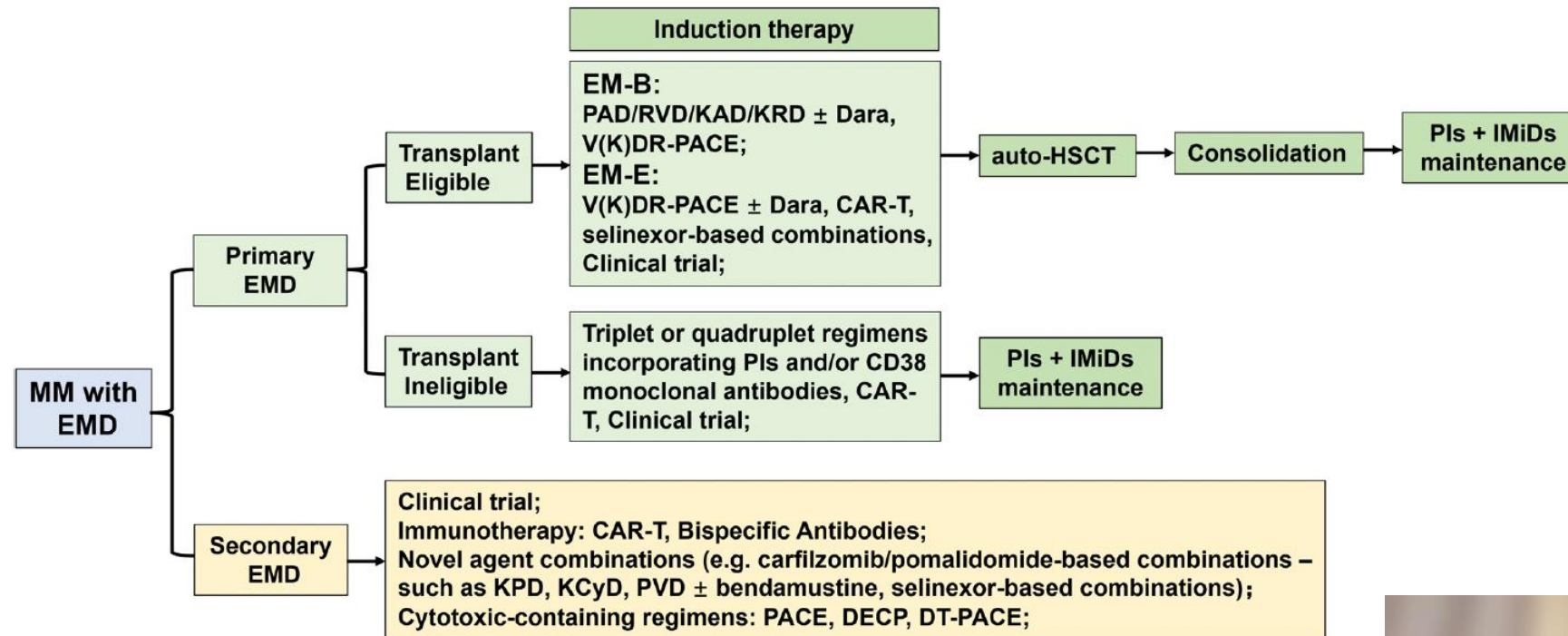
Seval GC, Beksac M et al. 19th IMS Annual Meeting



# How to treat EMD?









Contents lists available at ScienceDirect

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Research paper

## Evaluation of isatuximab in patients with soft-tissue plasmacytomas: An analysis from ICARIA-MM and IKEMA<sup>☆</sup>

Meral Beksac<sup>a, \*</sup>, Ivan Spicka<sup>b</sup>, Roman Hajek<sup>c</sup>, Sara Bringhen<sup>d</sup>, Tomas Jelínek<sup>e</sup>, Thomas Martin<sup>f</sup>, Gabor Mikala<sup>g</sup>, Philippe Moreau<sup>h</sup>, Argiris Symeonidis<sup>i</sup>, Andreea M. Rawlings<sup>j</sup>, Helgi van de Velde<sup>j</sup>, Paul G. Richardson<sup>k</sup>

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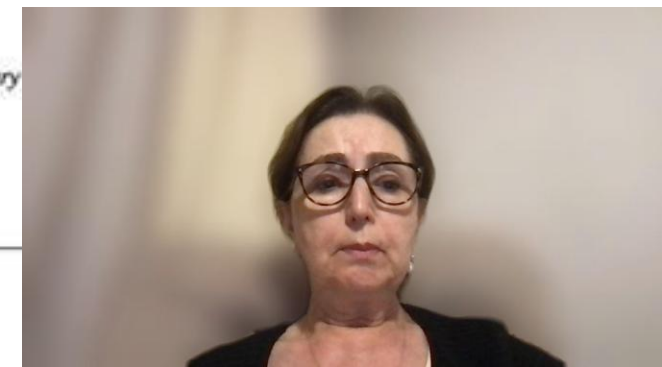
<sup>g</sup> National Institute for Hematology and Infectious Diseases, Department of Hematology and Stem Cell Transplantation, South Pest Central Hospital, Budapest, Hungary

<sup>h</sup> Hematology Department, Nantes University Hospital, Nantes, France

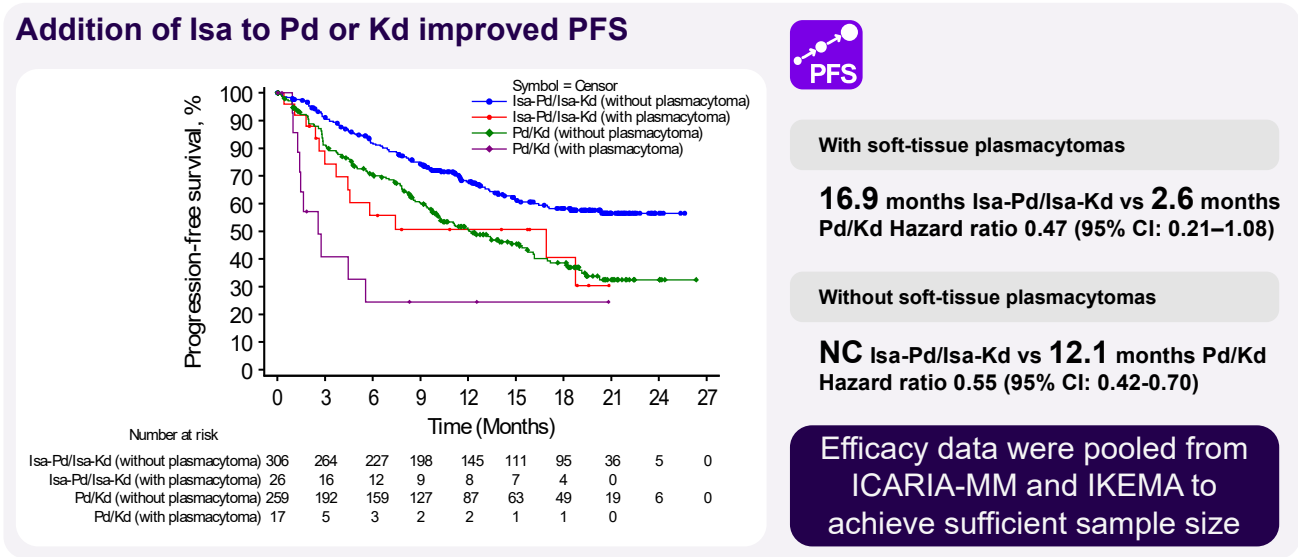
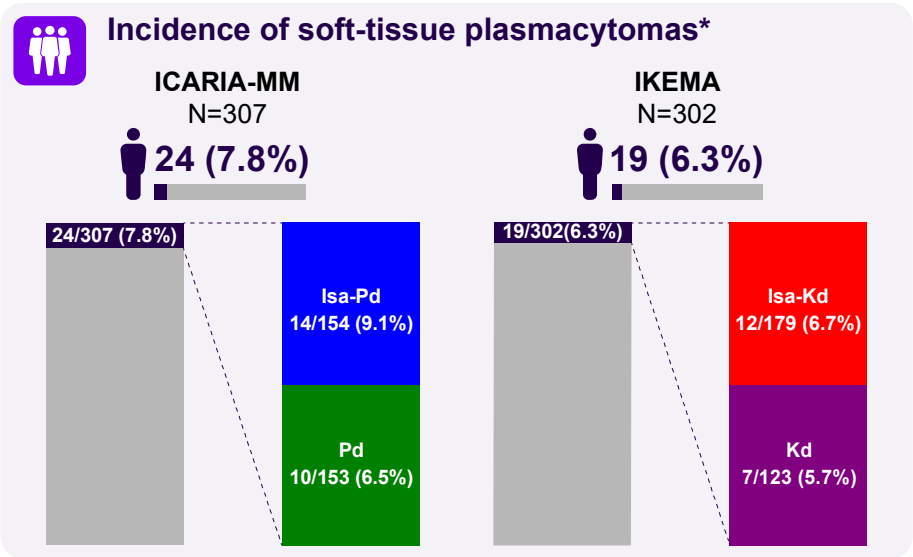
<sup>i</sup> Hematology Division, Department of Internal Medicine, University of Patras Medical School, Patras, Greece

<sup>j</sup> Sanofi, Cambridge, MA, USA

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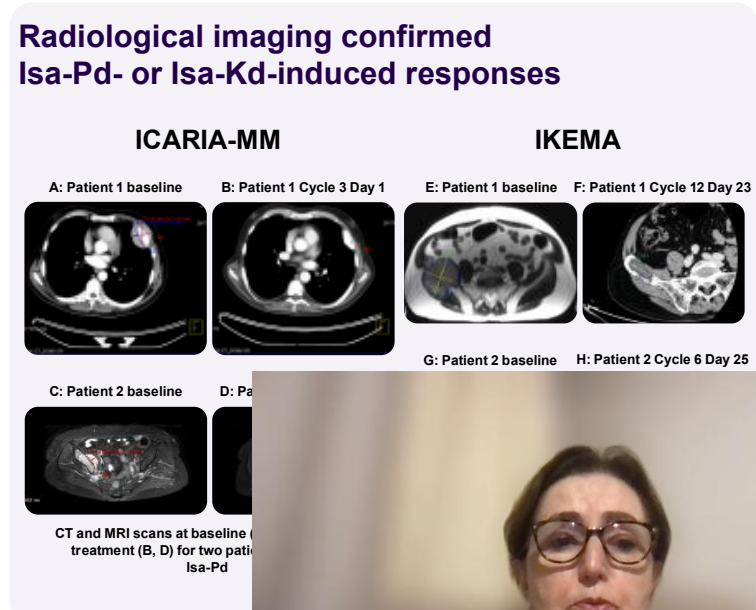
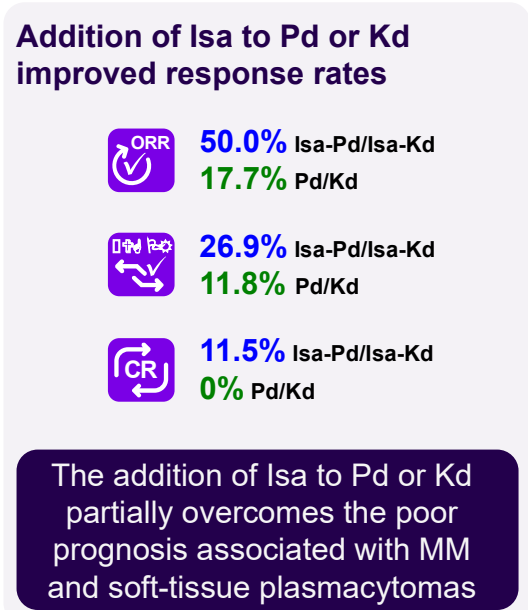
Evaluation of isatuximab in patients with soft-tissue plasmacytomas: Post hoc analysis from ICARIA-MM and IKEMA



**Safety**

	ICARIA-MM		IKEMA	
	Isa-Pd (n=14)	Pd (n=10)	Isa-Kd (n=12)	Kd (n=7)
Any TEAE	100.0	90.0	100.0	71.4
Grade 5 TEAE	85.7	70.0	100.0	57.1
Grade 5 TEAE	7.1	30.0	16.7	14.3
Serious TEAE	57.1	60.0	75.0	57.1
TEAE leading to definitive discontinuation	0	10.0	0	14.3
Duration of exposure in weeks, median (min–max)	36.9 (6–72)	8.4 (1–19)	41.9 (2–87)	29.9 (4–83)

The incidence of TEAEs should be interpreted in the context of the difference in treatment exposure between the treatment arms



\* As per Independent Response Committee  
CI, confidence interval, CR, complete response; CT, computerized tomography; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRI, magnetic resonance imaging; ORR, overall response rate; P, progression-free survival; TEAE, treatment-emergent adverse event; VGPR, very good partial response



RESEARCH

# Outcomes in patients with relapsed/refractory multiple myeloma with extramedullary disease: a meta-analysis

Peter M. Voorhees<sup>1</sup> · Shaji Kumar<sup>2</sup> · Saad Z. Usmani<sup>3</sup> · Jing Christine Ye<sup>4</sup> · Yael C. Cohen<sup>5,6</sup> · Emma Scott<sup>7</sup> · Robin L. Carson<sup>7</sup> · Christoph Heuck<sup>7</sup> · Ryan Gan<sup>8</sup> · Benjamin Ackerman<sup>8</sup> · Jenny Zhang<sup>7</sup> · Eleanor Caplan<sup>9</sup> · Trilok Parekh<sup>8</sup> · María-Victoria Mateos<sup>10</sup>

### Published studies

NCT number	Study name	Phase	Treatment arms
NCT02336815	STORM	2	Selinexor and dexamethasone
NCT02990338	ICARIA	3	Pomalidomide, dexamethasone, isatuximab (Isa-Pd) and pomalidomide, dexamethasone (Pd)
NCT03275285	IKEMA	3	Carfilzomib, dexamethasone, isatuximab (Isa-Kd) and carfilzomib, dexamethasone (Kd)

**Table 1** Clinical studies included in analyses

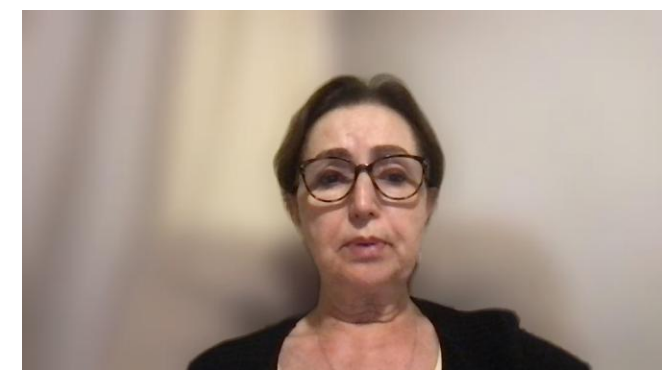
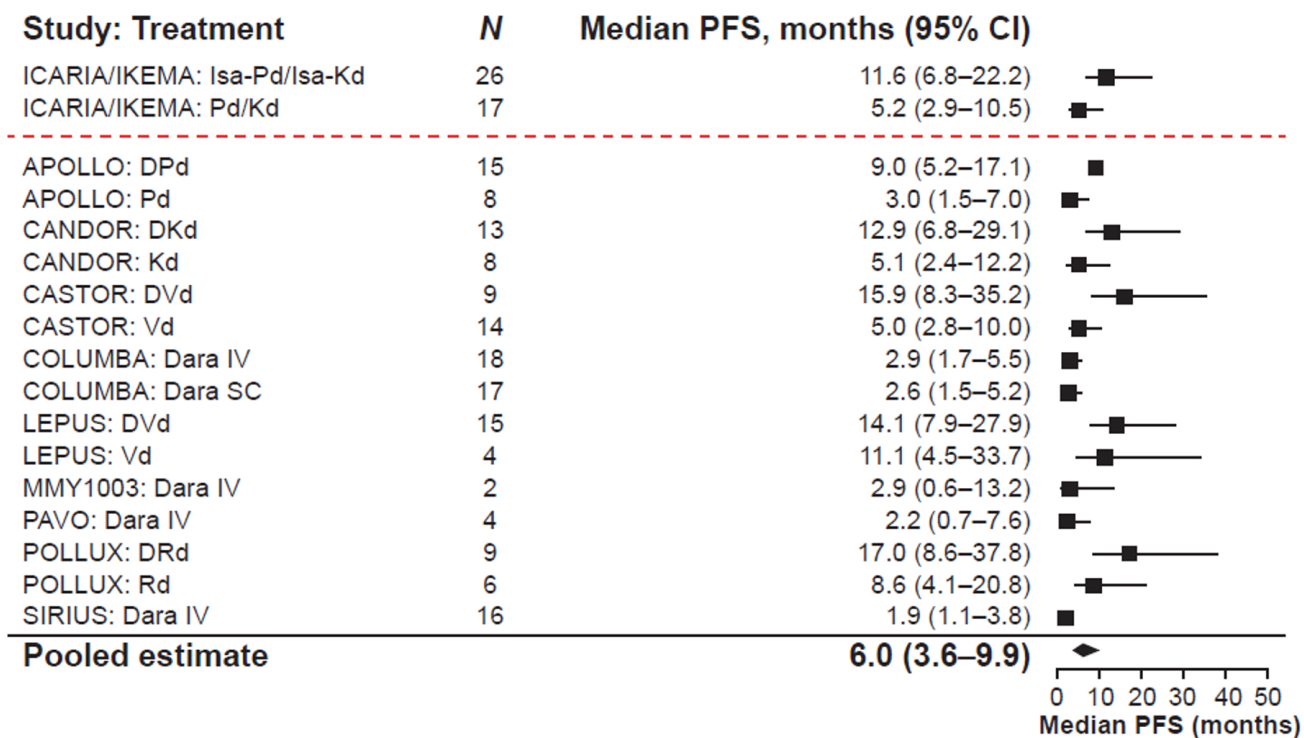
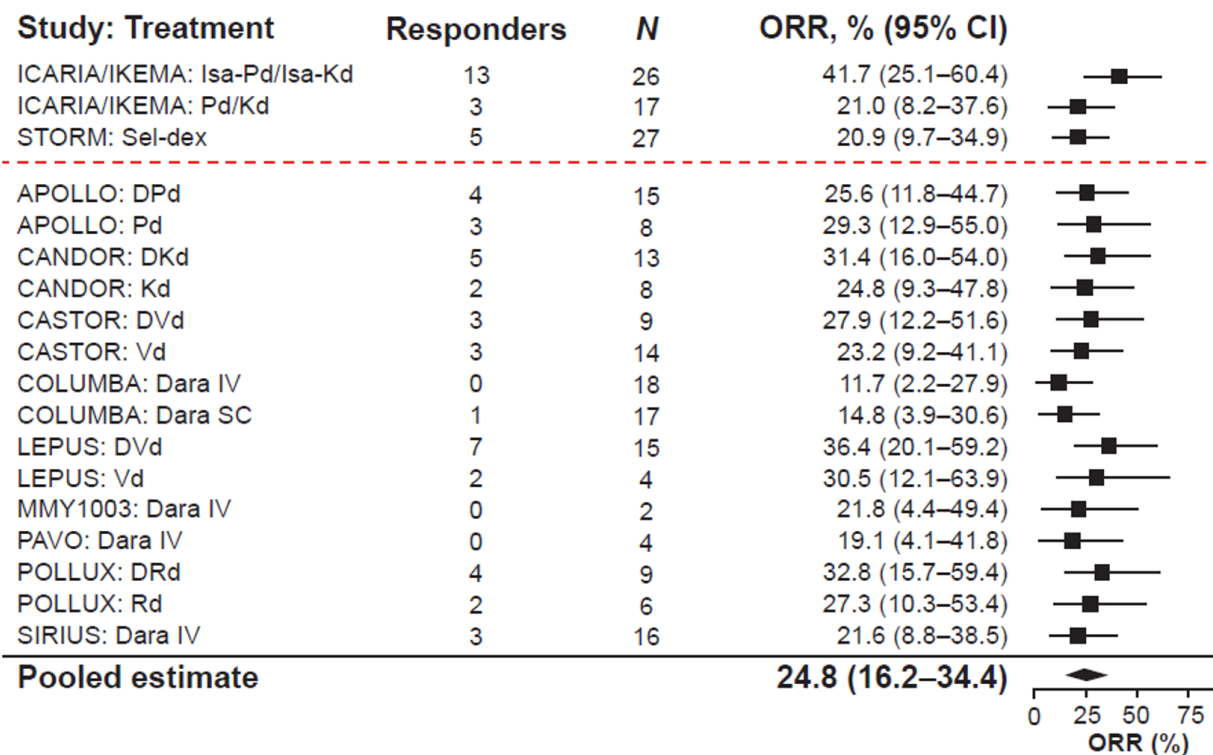
### Historical studies

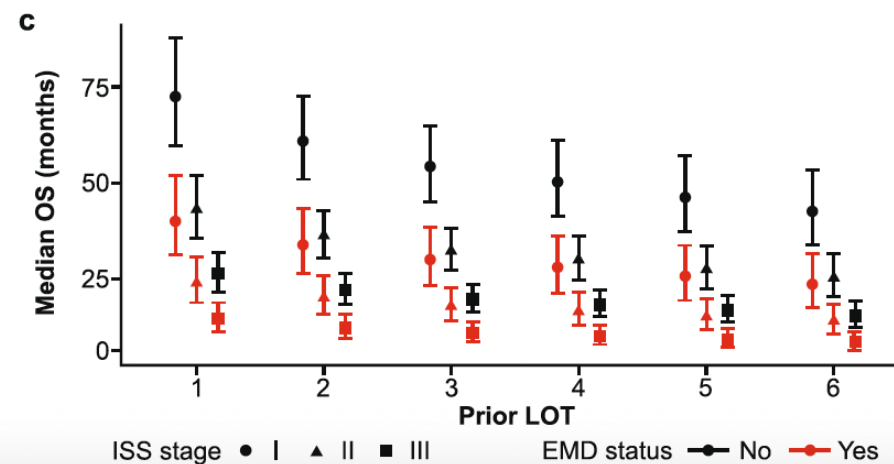
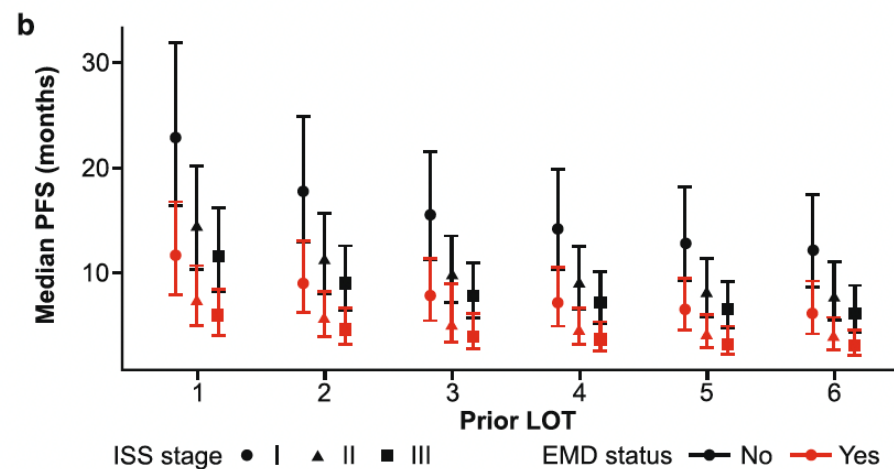
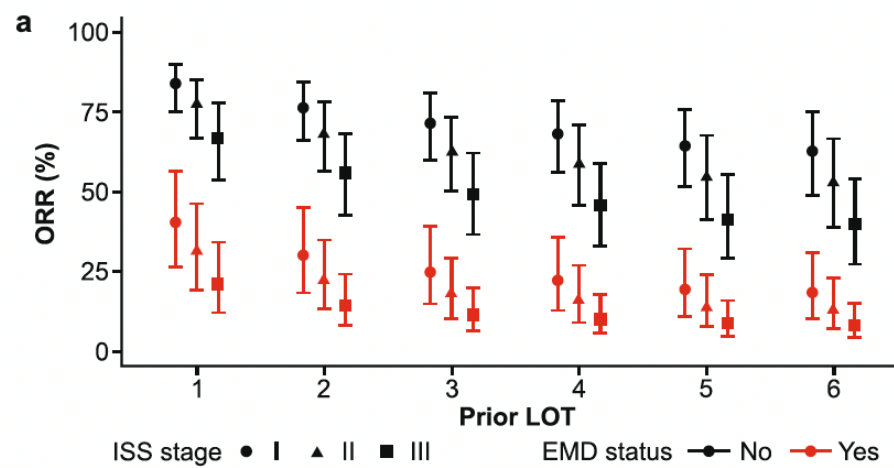
NCT number	Study name	Phase	Treatment arms
NCT02852837	Not available	1	Daratumumab IV
NCT02519452	PAVO	1b	Daratumumab SC with rHuPH20
NCT01985126	SIRIUS	2	Daratumumab IV
NCT03180736	APOLLO	3	Pomalidomide, dexamethasone, daratumumab (DpD) and pomalidomide, dexamethasone (Pd)
NCT03158688	CANDOR	3	Carfilzomib, dexamethasone, daratumumab (DKd) and carfilzomib, dexamethasone (Kd)
NCT02136134	CASTOR	3	Daratumumab, bortezomib, dexamethasone (DVd) and bortezomib, dexamethasone (Vd)
NCT03277105	COLUMBA	3	Daratumumab IV or SC
NCT03234972	LEPUS	3	Daratumumab, bortezomib, dexamethasone (DVd) and bortezomib,

NCT02076009 PO

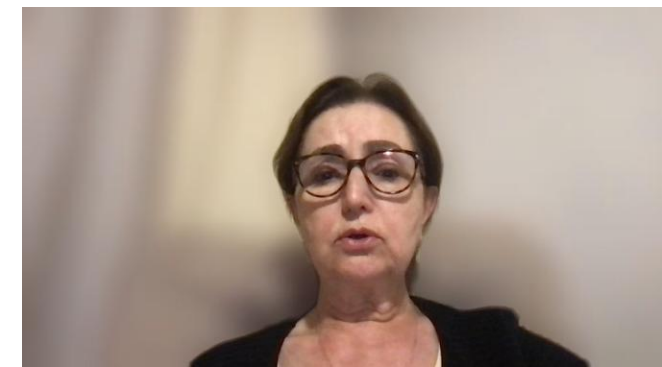










EMD (+) patients perform poorly  
With advance in each LOT and ISS



# Prospective EMD focused trial



Daratumumab-based quadruplet for patients with extramedullary multiple myeloma: Results from the Phase II prospective EMN19 study

Meral Beksac<sup>1,2</sup>  | Tulin Fıratlı Tuglular<sup>3</sup> | Francesca Gay<sup>4</sup> | Roberto Mina<sup>4</sup> | Eirini Katodritou<sup>5</sup>  | Ali Unal<sup>6</sup> | Michele Cavo<sup>7</sup> | Guner Hayri Ozsan<sup>8</sup> | Vincent H. J. van der Velden<sup>9</sup> | Berna H. Beverloo<sup>10</sup> | Michael Vermeulen<sup>11</sup> | Mark van Duin<sup>11</sup> | Guldane Cengiz Seval<sup>2</sup> | Omur Gokmen Sevindik<sup>12</sup> | Serena Merante<sup>13</sup> | Kyriaki Manousou<sup>14</sup> | Peter Sonneveld<sup>11</sup> | Elena Zamagni<sup>15</sup> | Evangelos Terpos<sup>16</sup>

EMN19

TABLE 1 Patient characteristics at baseline, overall, and by multiple myeloma stage. (continued on next page)

	All patients (N = 40)	Patients with NDMM (n = 29)	Patients with RMM (n = 11)
Age, years	58.0 (37.0–77.0)	58.0 (44.0–77.0)	58.0 (37.0–72.0)
Male	22 (55.0)	17 (58.6)	5 (45.5)
ECOG PS (at screening)			
0	26 (65.0)	21 (72.4)	5 (45.5)
1	12 (30.0)	7 (24.1)	5 (45.5)
2	2 (5.0)	1 (3.4)	1 (9.1)
Type of measurable disease <sup>a</sup>			
Serum FLC	31 (77.5)	22 (75.9)	9 (81.8)
Serum M-protein	24 (60.0)	20 (69.0)	4 (36.4)
Urine M-protein	14 (35.0)	11 (37.9)	3 (27.3)
Extramedullary plasmacytomas by type			
EMD plasmacytomas	22 (55.0)	17 (58.6)	5 (45.5)
PS plasmacytomas	14 (35.0)	11 (37.9)	3 (27.3)
EMD and PS plasmacytomas	4 (10.0)	1 (3.4)	3 (27.3)

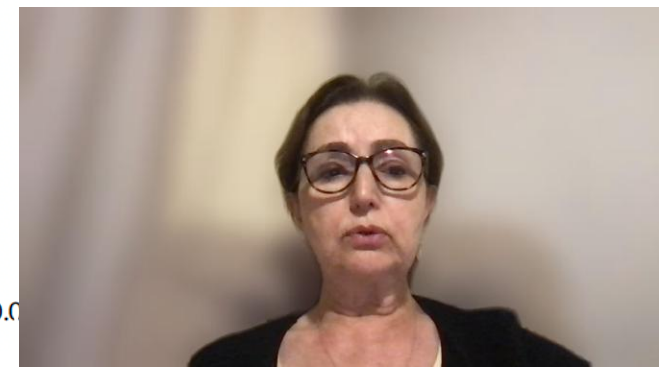




# NDMM vs. RRMM

## cytogenetic risk, ISS, marrow PC, CTC are comparable

	All patients (N = 40).	Patients with NDMM (n = 29).	Patients with RMM (n = 11)
High-risk cytogenetics			
Yes	6 (15.0)	4 (13.8)	2 (18.2)
No	19 (47.5)	14 (48.3)	5 (45.5)
Not reported	15 (37.5)	11 (37.9)	4 (36.4)
ISS stage			
I	19 (47.5)	16 (55.2)	3 (27.3)
II	14 (35.0)	8 (27.6)	6 (54.5)
III	7 (17.5)	5 (17.2)	2 (18.2)
Revised ISS stage			
I	8 (20.0)	6 (20.7)	2 (18.2)
II	15 (37.5)	11 (37.9)	4 (36.4)
III	3 (7.5)	1 (3.4)	2 (18.2)
Unknown	14 (35.0)	11 (37.9)	
Bone marrow plasma cell categories			
0.0%–10.0%	14 (35.0)	7 (24.1)	
>10.0% and <60.0%	17 (42.5)	14 (48.3)	
≥60.0%	9 (22.5)	8 (31.0)	
Circulating tumor cells	0.002 (0.000–0.353)	0.002 (0.000–0.353)	0.0



# Response rates are better among NDMM

All patients (N = 40).    Patients with NDMM (n = 29).    Patients with RMM (n = 11)

## Best hematological response without or before ASCT<sup>a,b</sup>

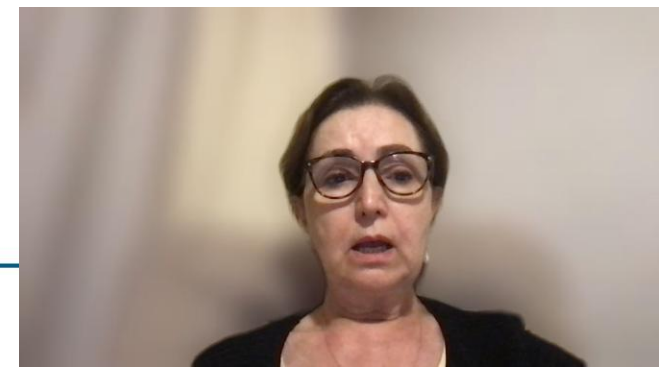
CR or better	15 (37.5)	13 (44.8)	2 (18.2)	0.158
VGPR or better	29 (72.5)	23 (79.3)	6 (54.5)	0.137

## Minimal residual disease status

Negative	15 (37.5)	13 (44.8)	2 (18.2)	0.158
Negative; among patients with $\geq$ CR (n = 14)	12 (30.0)	10 (34.5)	2 (18.2)	
Negative; among patients with $\geq$ VGPR (n = 16)	13 (32.5)	11 (37.9)	2 (18.2)	
Positive	4 (10.0)	3 (10.3)	1 (9.1)	
Not reported	21 (52.5)	13 (44.8)	8 (72.7)	

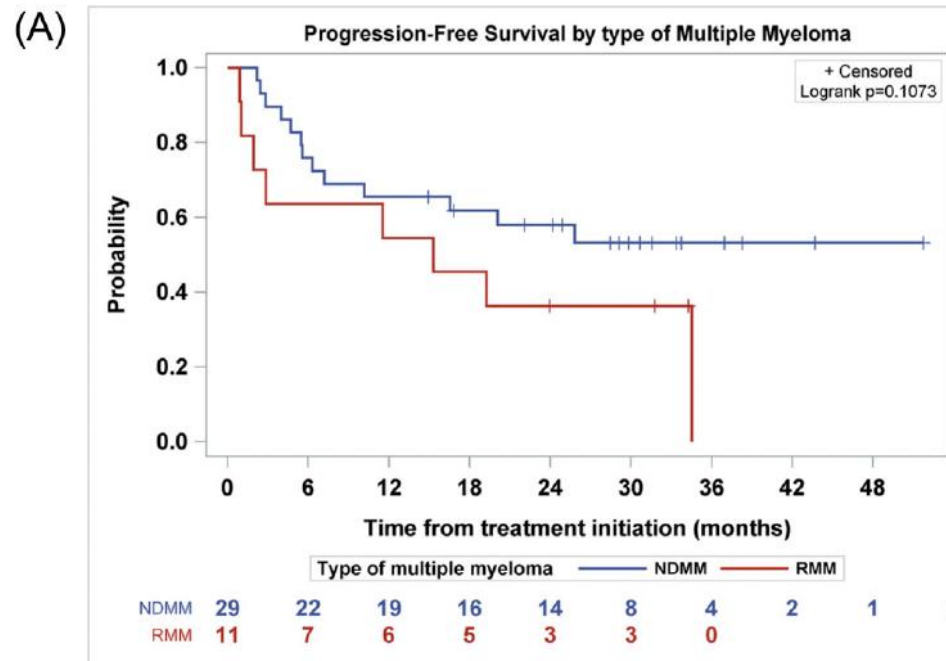
## Best metabolic response<sup>c</sup>

Complete metabolic response	20 (50.0)	16 (55.2)	4 (36.4)	0.480
Complete metabolic response and no plasmacytomas	8 (20.0)	7 (24.1)	1 (9.1)	
Complete metabolic response irrespective of a persistent mass on PET/CT	12 (30.0)	9 (31.0)	3 (27.3)	
Partial metabolic response	9 (22.5)	8 (27.6)	1 (9.1)	
Stable metabolic disease	2 (5.0)	2 (6.9)	-	
Progressive metabolic disease	7 (17.5)	2 (6.9)	5 (45.5)	
No response	2 (5.0)	1 (3.4)	1 (9.1)	
Time to best metabolic response, months <sup>b</sup>	3.5 (1.2–36.4)	3.6 (1.2–36.4)	2.7 (2.3–5.9)	
Time to first metabolic response, months <sup>c</sup>	3.5 (1.2–36.4)	3.5 (1.2–36.4)	2.7 (2.3–5.9)	



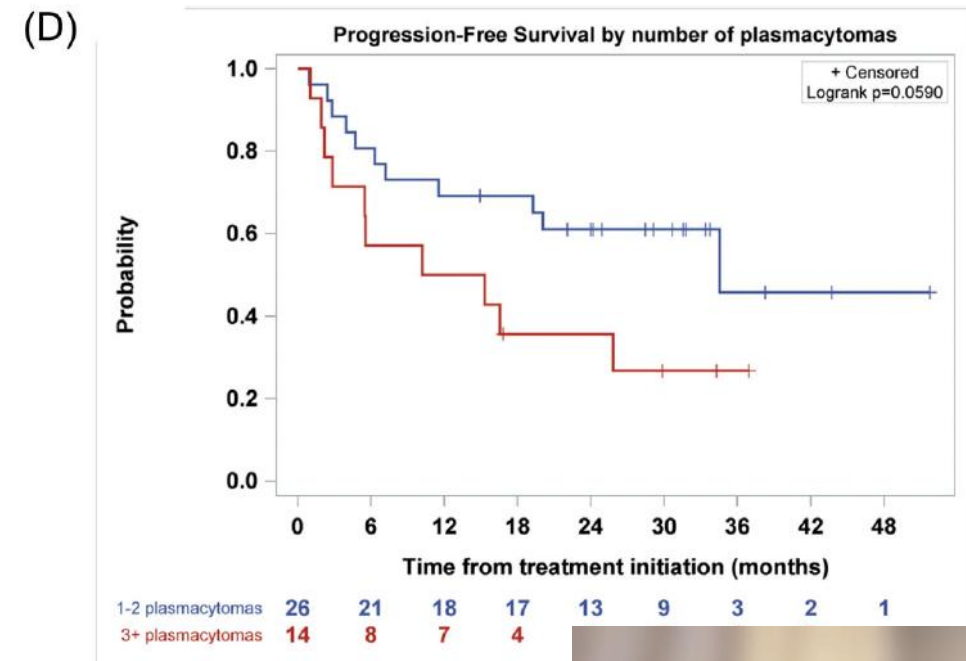
# EMN19

## PFS is better for NDMM and with less number of plasmacytomas



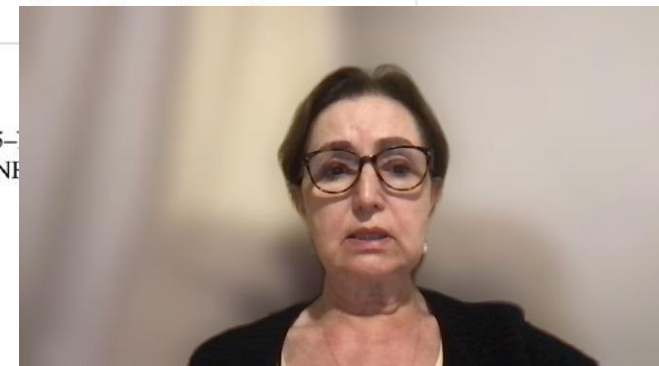
Median (95% CI) PFS in months

- Patients with NDMM: NR (7.2–NR)
- Patients with RMM: 15.3 (1.0–NR)



Median (95% CI) PFS in months

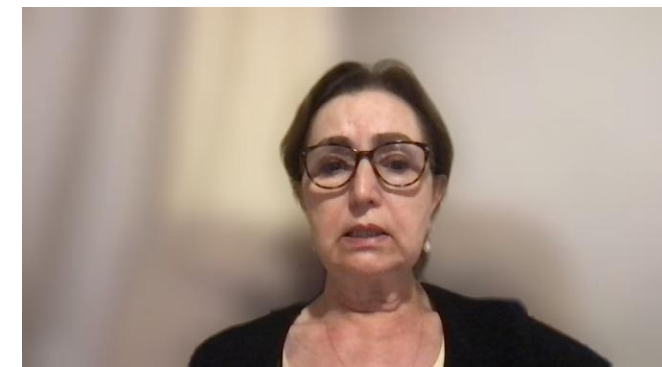
- Patients with 1–2 plasmacytomas: 34.5 (11.5–NR)
- Patients with ≥3 plasmacytomas: 12.8 (2.2–NR)



**TABLE 7.** Proposed Refinement of PET Response Criteria After Therapy

PET Response After Therapy	Response Criteria
Complete metabolic response	Uptake $\leq$ liver activity in BM sites and FLs previously involved (including extramedullary and paramedullary disease [DS score 1-3])
Partial metabolic response	Decrease in number and/or activity of BM/FLs present at baseline, but persistence of lesion(s) with uptake $>$ liver activity (DS score 4 or 5)
Stable metabolic disease	No significant change in BM/FLs compared with baseline
Progressive metabolic disease	New FLs compared with baseline consistent with myeloma

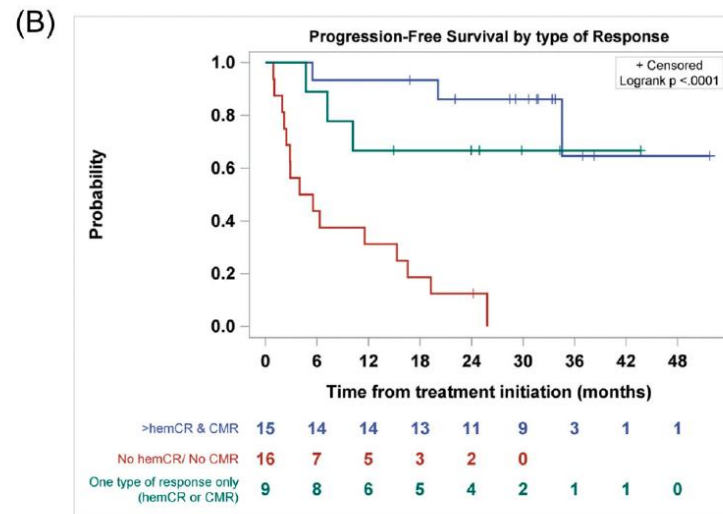
Zamagni et al J Clin Oncol (2021) 39(2):116–25





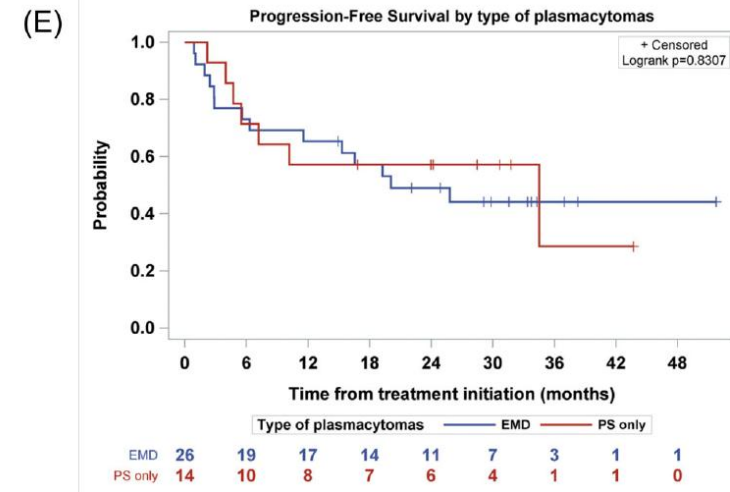
# EMN19

Deep and durable  
within & outside of marrow responses are possible  
Paraosseous = EMD



Median (95% CI) PFS in months

- Patients with hematologic  $\geq$ CR and CMR: NR (34.5–NR);
- Patients with hematologic  $\geq$ CR or CMR: NR (4.7–NR);
- Patients with no hematologic  $\geq$ CR and no CMR: 4.8 (2.2–15.3)



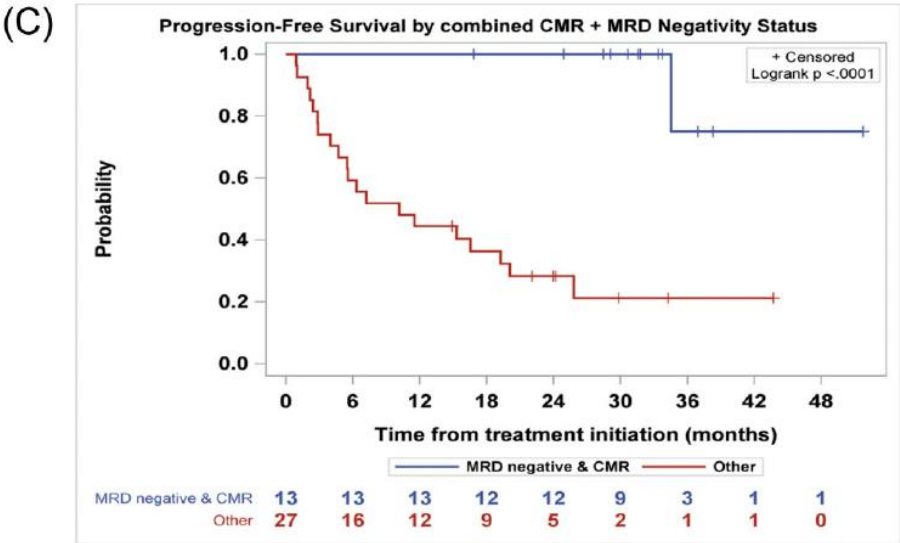
Median (95% CI) PFS in months

- Patients with EMD: 20.1 (6.3–NR);
- Patients with PS only: 34.5 (4.7–NR)

(F)



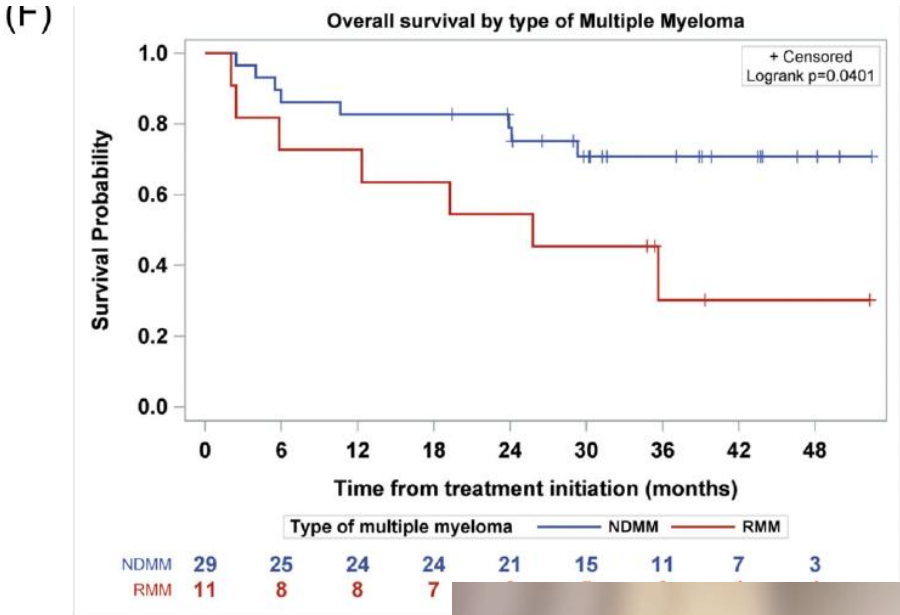
MRD(-) & complete metabolic responses are the most durable



Median (95% CI) PFS in months

- Patients with MRD negative and CMR: NR (34.5–NR);
- Patients without MRD negative and CMR: 10.2 (4.0–20.1)

NDMM perform better than first relapse MM



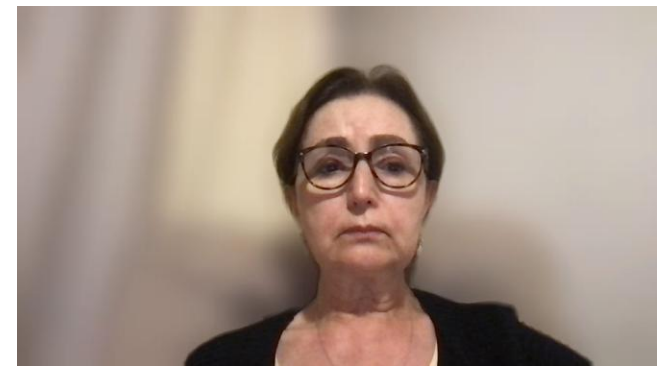
Median (95% CI) OS in months

- Patients with NDMM: NR (29.3–NR);
- Patients with RMM: 25.8 (2.4–NR)



# Take aways from EMN19

- ❖ Among NDMM DaraVCD three years of treatment is tolerable and effective attaining durable CMR & MRD(-)
- ❖ Tumour volume and number of EMD are prognostic
- ❖ Outcome of both para-osseous and EMD are less than non-EMD
- ❖ Circulating clonal plasma cells are associated with ISS but not EMD



# Role of new immunotherapeutics





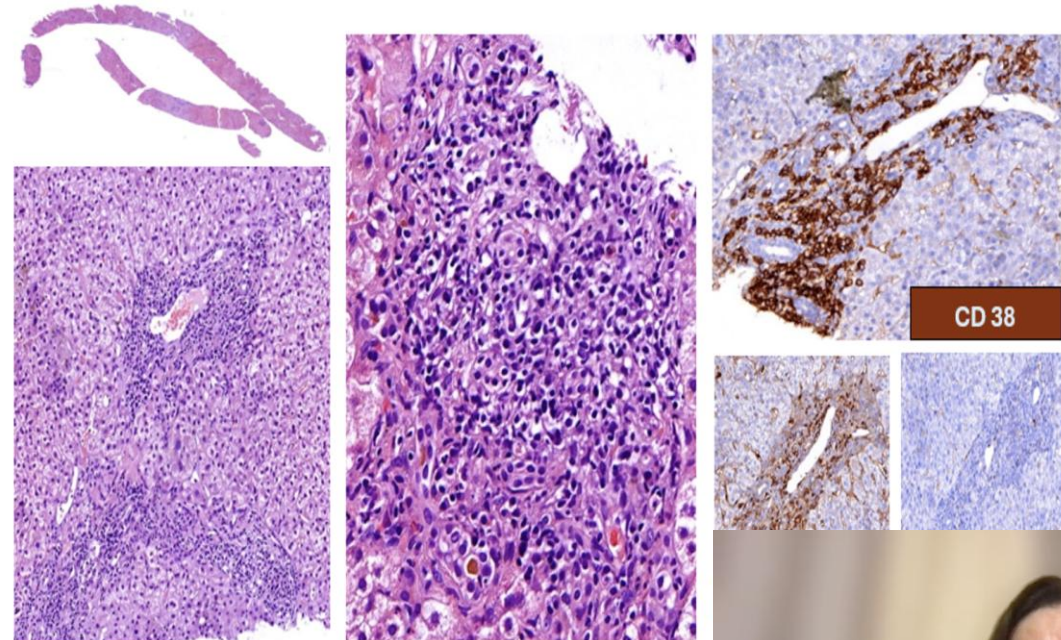
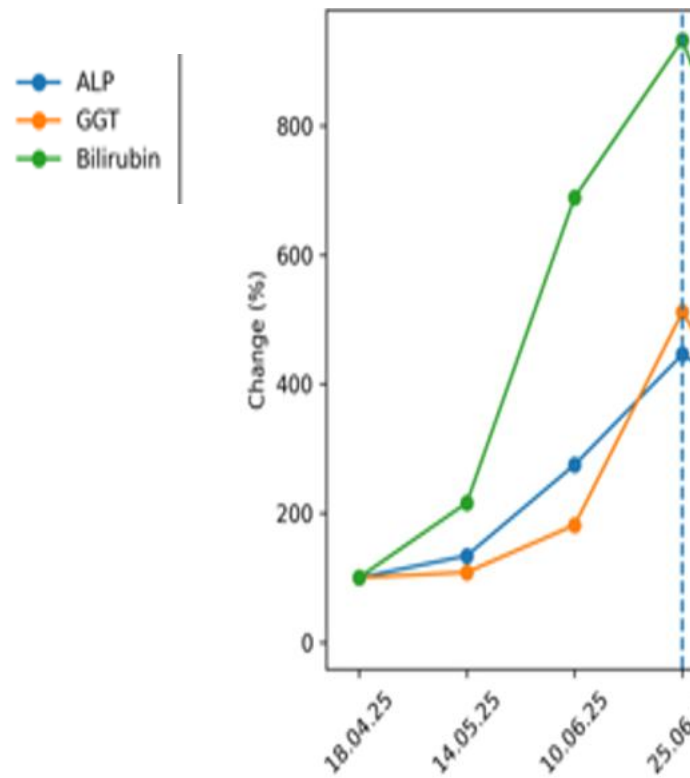
# 51-year-old male

✓ <b>Presentation</b>	Progressive back pain
✓ <b>Performance status</b>	ECOG PS 2
✓ <b>Radiographic findings</b>	PET scan showed multiple scattered osseous lesions suspicious for myeloma; with cortical disruption and prominent extraosseous component in the costa, thoracal and lumbar vertebrae
✓ <b>Laboratory values</b>	Mprotein: 4.3 g/dL; FLC: 3450/7.5 mg/L; anemia (Hb: 7.3 g/dL); renal impairment (CrCl: 55 mL/min) and proteinuria: 3.8 gr/day ; beta2mg: 18.8 mg/dL
✓ <b>Bone marrow biopsy findings</b>	90% monoclonal plasma cells
✓ <b>Cytogenetic findings</b>	FISH results showed high-risk cytogenetics: 1q gain
✓ <b>Staging</b>	ISS-III , R-ISS: II but R2-ISS high
✓ <b>Transplant eligibility</b>	Transplant eligible due to age and fitness

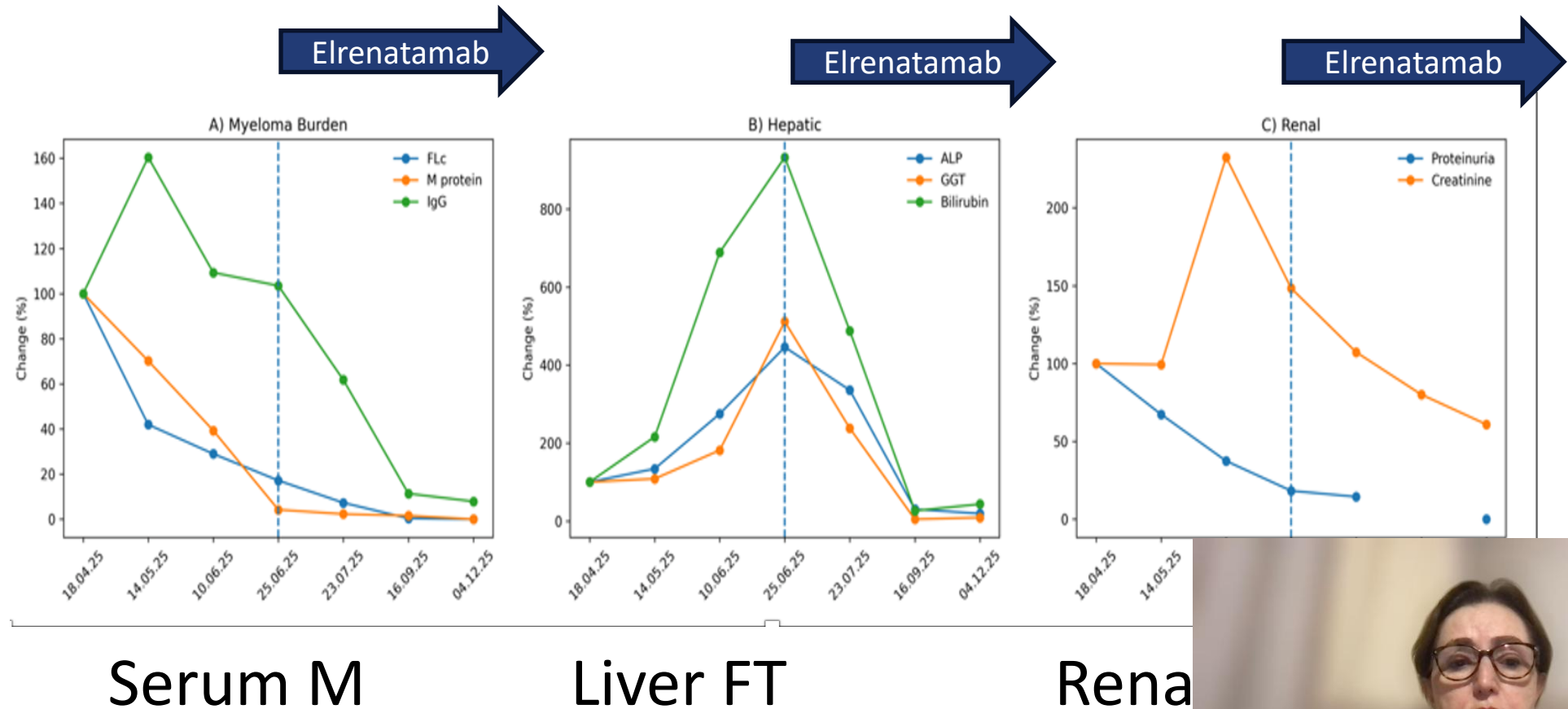


# CHOLESTASIS:

Bilirubin: 15.8 mg/dl, Alkaline Phosphatase: 1360 U/L, GGT: 1169 U/L

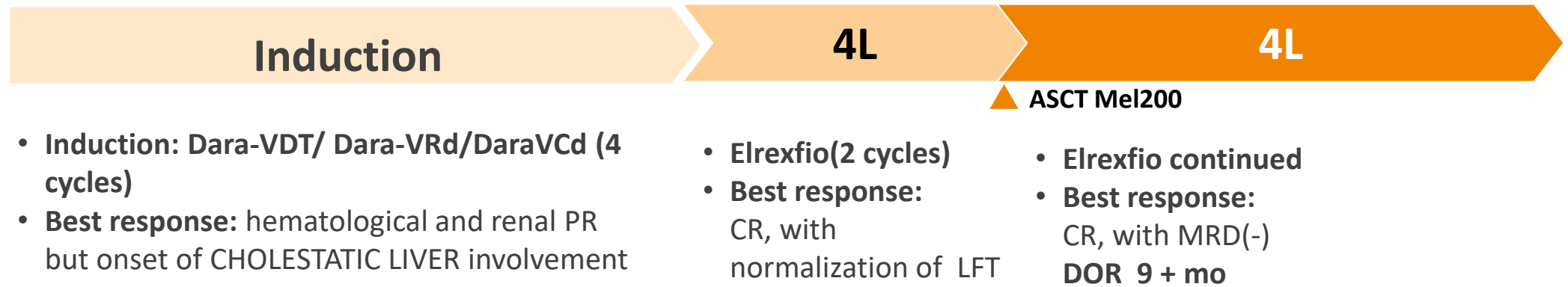


# TCR EMD not eligible for chemo or ASCT



# Treatment history

## SUMMARY



### Approach to Bone disease

Operated

Zoledronate and Vitamin D3

### Key AEs/toxicities

Myelosuppression (prolonged cyto antiBCMA initially Elthrombopag r

Frequent CMV reactivation , Valga





# Role of CART/Bispecifics



ARTICLE OPEN

The impact of extramedullary and paraskelatal plasmacytomas on treatment outcomes in multiple myeloma treated with teclistamab: U.S. Myeloma Immunotherapy Consortium real-world experience

Aimaz Afrough<sup>1,17</sup>, Danai Dima<sup>2,17</sup>, Beatrice Razzo<sup>3,4,17</sup>, Utkarsh Goel<sup>5</sup>, Aishwarya Sannareddy<sup>1</sup>, Oren Pasvolsky<sup>6</sup>, Mariola A. Vazquez-Martinez<sup>7</sup>, Christopher J. Ferreri<sup>8</sup>, Rahul Banerjee<sup>9</sup>, Jack Khouri<sup>5</sup>, James A. Davis<sup>10</sup>, Mahmoud R. Gaballa<sup>6</sup>, Alex Lieberman-Cribbin<sup>10</sup>, Masooma S. Rana<sup>11</sup>, Kelley Julian<sup>12</sup>, Faiz Anwer<sup>5</sup>, Leyla Shune<sup>13</sup>, Shaun DeJarnette<sup>13</sup>, Ariel F. Grajales-Cruz<sup>7</sup>, Evguenia Ouchveridze<sup>13</sup>, Gabriel De Avila<sup>7</sup>, Sandra P. Susanibar-Adaniya<sup>14</sup>, Andrew J. Portuguese<sup>15</sup>, Daniel Schrum<sup>16</sup>, Erin Eberwein<sup>14</sup>, Hitomi Hosoya<sup>11</sup>, Lekha Mikkilineni<sup>11</sup>, Gurbakhsh Kaur<sup>1</sup>, Joseph P. McGuirk<sup>13</sup>, Adriana Rossi<sup>10</sup>, Megan M. Herr<sup>15</sup>, Omar Castaneda<sup>7</sup>, Frederick L. Locke<sup>7</sup>, Shahzad Raza<sup>15</sup>, Yi Lin<sup>16</sup>, Shebli Atrash<sup>8</sup>, Douglas W. Sborov<sup>12</sup>, Peter M. Voorhees<sup>8</sup>, Shambavi Richard<sup>10</sup>, Alfred L. Garfall<sup>3</sup>, Surbhi Sidana<sup>11</sup>, Krina K. Patel<sup>6</sup>, Doris K. Hansen<sup>7</sup>, Andrew J. Cowan<sup>2,18</sup>, Larry D. Anderson Jr.<sup>1,18</sup> and Hans C. Lee<sup>6,18</sup>

Blood Cancer Journal (2026) 16:12

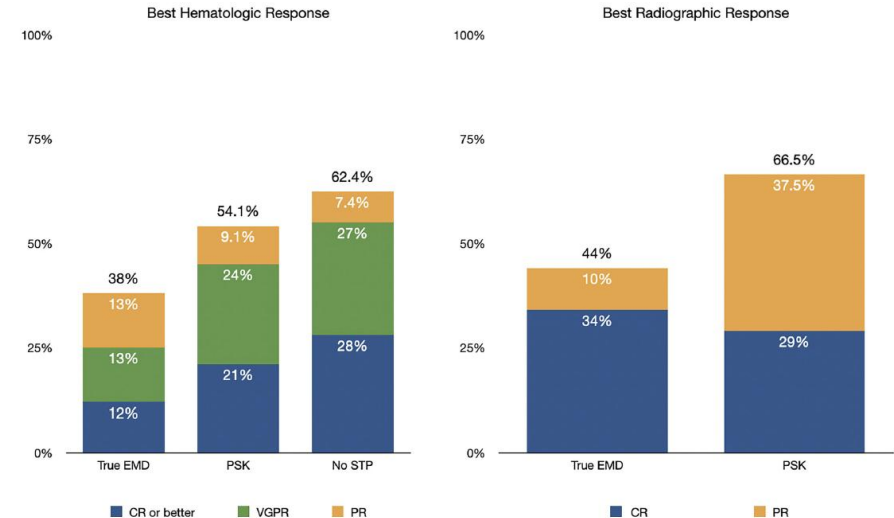


Fig. 1 Response with teclistamab according to STP type. STP soft tissue plasmacytoma, CR complete response, VGPR very good partial response, PR partial response.

A. Afrough et al.

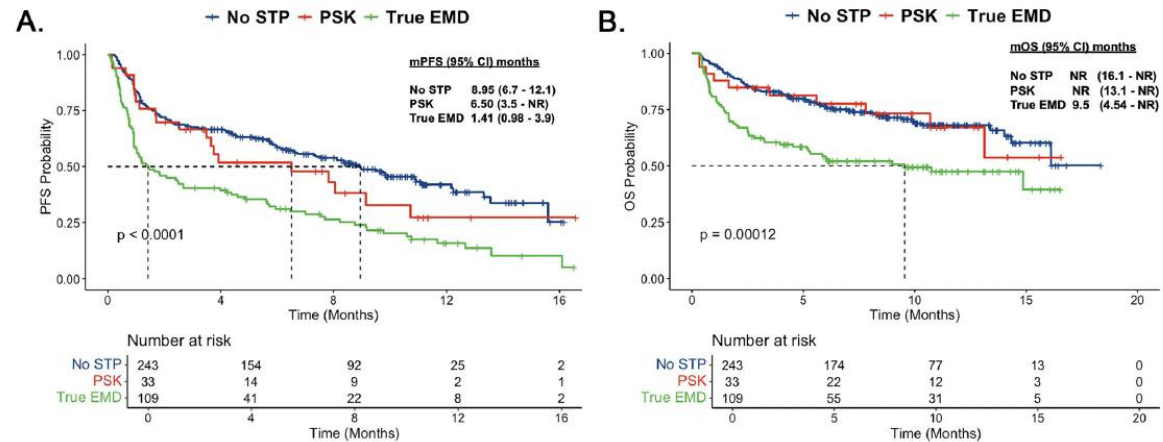


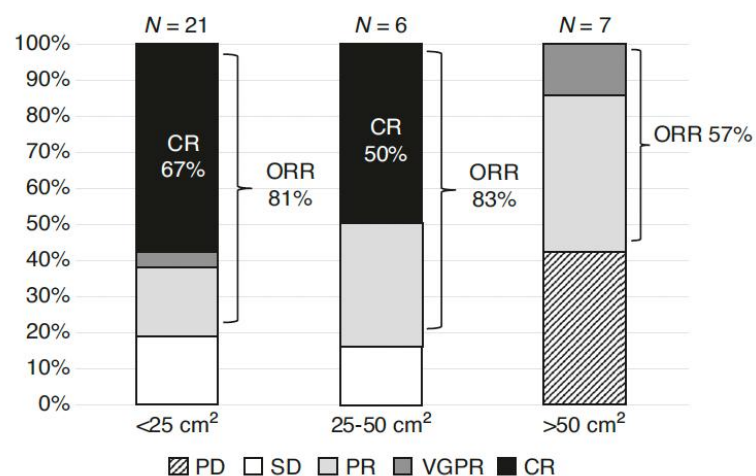
Fig. 2 Survival outcomes according to STP. Kaplan-Meier estimates of PFS (A) and OS (B) in patients with RRMM who received teclistamab. Total of 137 events (progressions  $n = 101$ ; deaths from any other causes  $n = 36$ ); The median PFS was 1.4 months (95% CI: 0.98–3.98) for the true-EMD, 6.51 months (95% CI: 3.48–NR) for the PSK, and 8.95 months (95% CI: 6.7–12.1) for the No-STP group ( $p < 0.0001$ ). The median OS was 9.54 months (95% CI: 4.54–NR) for the true-EMD, NR (95% CI: 13.12–NR) for the PSK, and NR for the No-STP group (95% CI: 16.1–NR) ( $p = 0.00012$ ).



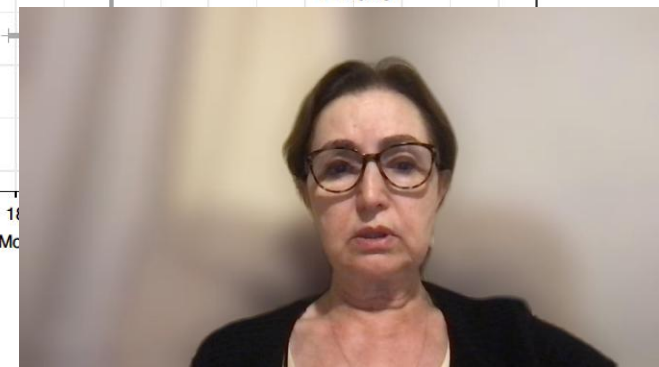
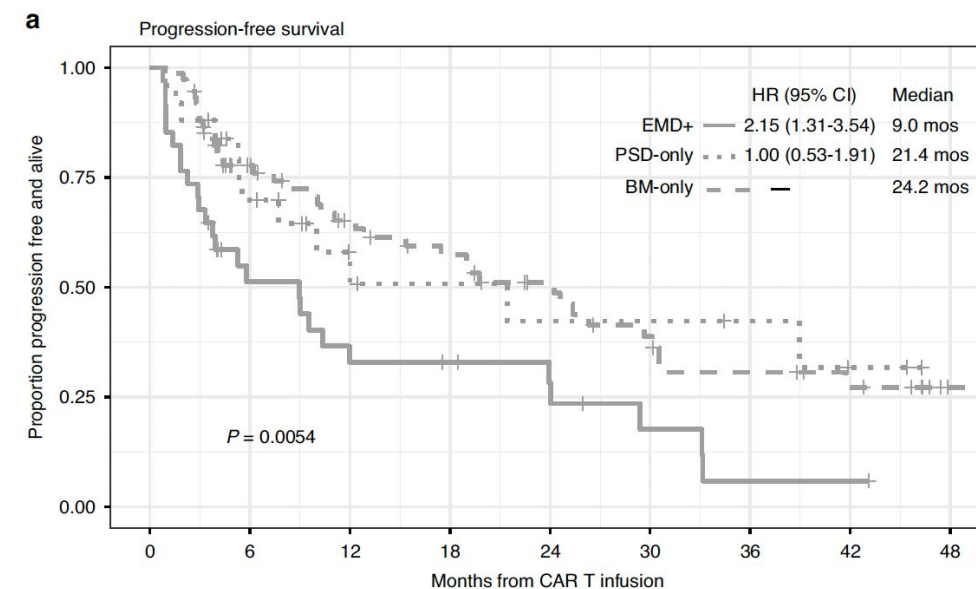
## ARTICLE

## Extramedullary disease but not paraskelatal disease portends inferior outcomes after CAR T cell therapy in multiple myeloma

Darren Pan<sup>1,2</sup>, Tarek H. Mouhieddine<sup>1</sup>, Tianxiang Sheng<sup>3</sup>, Weijia Fu<sup>3</sup>, Erin Moshier<sup>3</sup>, Joshua Richter<sup>1</sup>, Samir Parekh<sup>1</sup>, Sundar Jagannath<sup>1</sup>, Adriana C. Rossi<sup>1</sup>, Larysa J. Sanchez<sup>1</sup>, Santiago Thibaud<sup>1</sup>, Cesar Rodriguez<sup>1</sup>, Hearn J. Cho<sup>1</sup> and Shambavi Richard<sup>1</sup>



**Fig. 2 Best response by extramedullary disease burden.** Shown are the best responses to CAR T cell therapy among patients with EMD. Patients are separated into 3 groups by EMD burden: >25 cm<sup>2</sup>, 25–50 cm<sup>2</sup>, and >50 cm<sup>2</sup>.





ARTICLE OPEN

Activity of CAR-T cells and bispecific antibodies in multiple myeloma with extramedullary involvement

Maximilian J. Steinhardt<sup>1,7</sup>, Christoph Schaefer<sup>2,7</sup>, Lisa B. Leypoldt<sup>2,3</sup>, Igor-Wolfgang Blau<sup>4</sup>, Marie Harzer<sup>2</sup>, Xiang Zhou<sup>1</sup>, Christine Riedhammer<sup>1</sup>, Abdulaziz Kamili<sup>2</sup>, Ricardo Kosch<sup>2</sup>, Laura S. Topp<sup>1</sup>, Isabel Molwitz<sup>5</sup>, Nils-Ole Gross-Fengels<sup>5</sup>, Yasmin Fede Melzer<sup>1,5</sup>, Jule Artzenroth<sup>2</sup>, Maximilian Al-Bazaz<sup>2</sup>, Winfried Alsdorf<sup>2</sup>, Max S. Topp<sup>1</sup>, Johannes Duell<sup>1</sup>, Julia Mersi<sup>1</sup>, Johannes Waldschmidt<sup>1</sup>, Carsten Bokemeyer<sup>2</sup>, Hermann Einsele<sup>1</sup>, K. Martin Kortüm<sup>1</sup>, Katja Weisel<sup>2</sup> and Leo Rasche<sup>1,6</sup>

Blood Cancer Journal (2025) 15:126

M.J. Steinhardt et al.

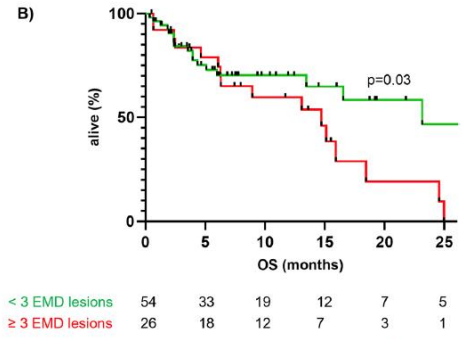
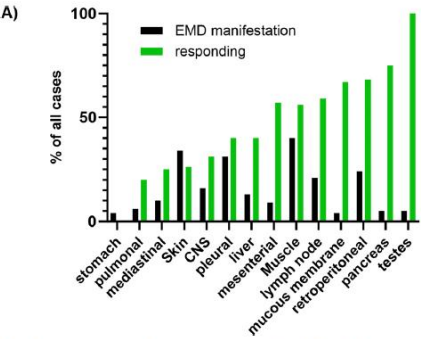


Fig. 3 EMD response by localization, and number of EMD lesions. A Analysis of EMD response by localization. B Analysis of EMD response by number of lesions.

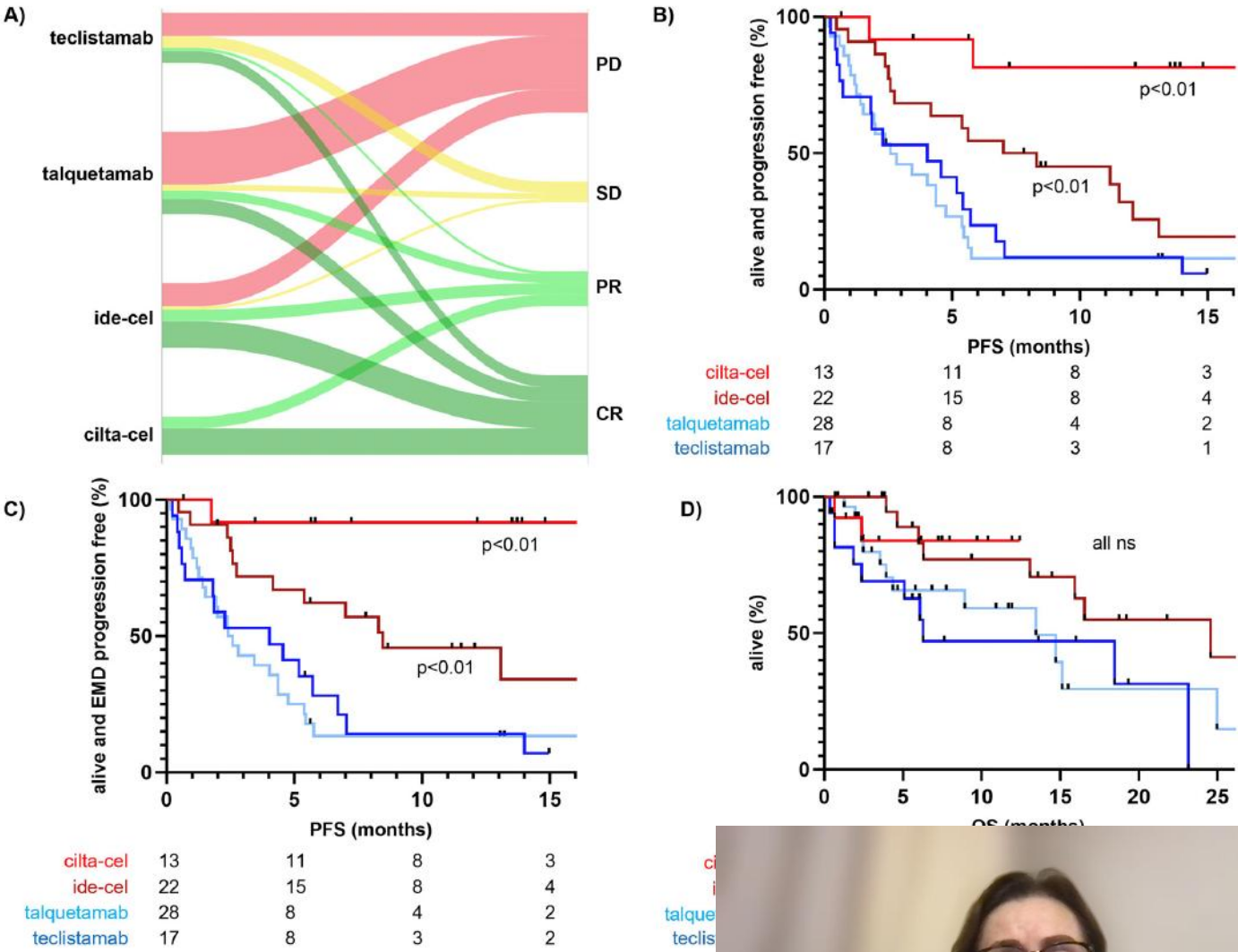


Fig. 1 Response, progression-free, and overall survival of EMD patients treated with different therapies. A Visual representation of response patterns in regard to therapy. B PFS (serology). C PFS (EMD). D OS.



*The* NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Talquetamab plus Teclistamab in Relapsed or Refractory Multiple Myeloma

Y.C. Cohen, H. Magen, M. Gatt, M. Sebag, K. Kim, C.-K. Min, E.M. Ocio,  
S.-S. Yoon, M.P. Chu, P. Rodríguez-Otero, I. Avivi, N.A. Quijano Cardé, A. Kumar,  
M. Krevvata, M.R. Peterson, L. Di Scala, E. Scott, B. Hilder, J. Vanak, A. Banerjee,  
A. Oriol, D. Morillo, and M.-V. Mateos, for the RedirecTT-1 Investigators  
and Study Group\*

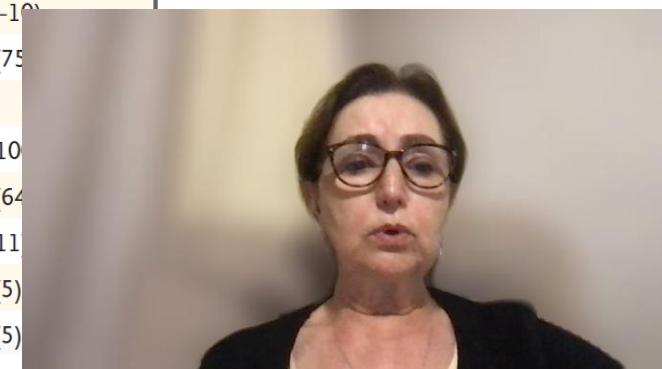




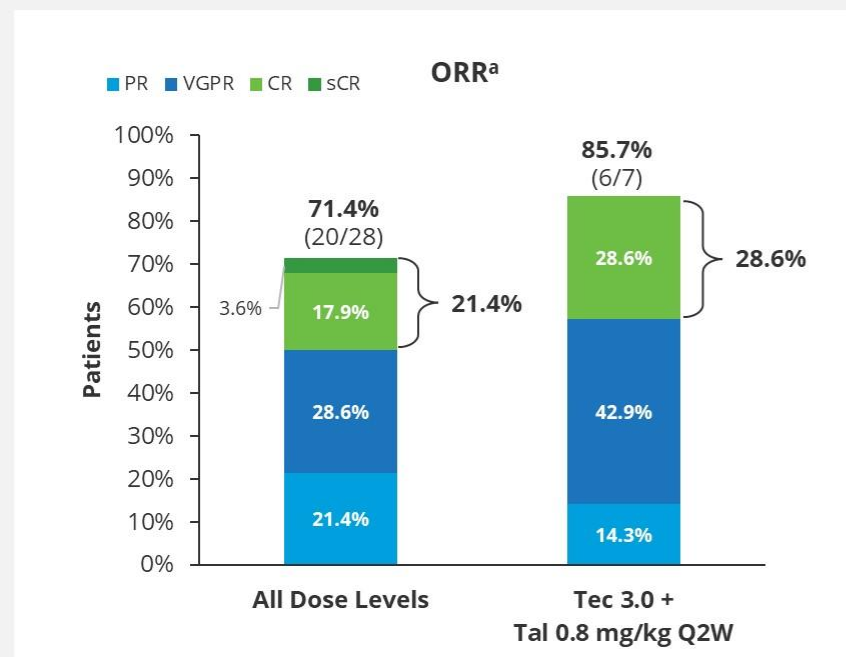
EMD

**Table 1. Baseline Characteristics of Patients Who Received Talquetamab plus Teclistamab.\***

Characteristic	All Dose Levels (N = 94)	Recommended Phase 2 Regimen (N = 44)
Median age (range) — yr	64.5 (39–81)	63 (41–80)
Male sex — no. (%)	49 (52)	23 (52)
Race — no. (%)†		
White	75 (80)	32 (73)
Asian	17 (18)	12 (27)
Black	1 (1)	0
Unknown	1 (1)	0
Bone marrow plasma cells ≥60% — no./total no. (%)‡	19/89 (21)	9/40 (22)
≥1 Extramedullary plasmacytoma — no. (%)§	34 (36)	18 (41)
High-risk cytogenetic profile — no./total no. (%)¶	21/51 (41)	8/19 (42)
International Staging System class — no./total no. (%)		
I	38/85 (45)	19/41 (46)
II	26/85 (31)	14/41 (34)
III	21/85 (25)	8/41 (20)
ECOG performance-status score — no. (%)**		
0	34 (36)	15 (34)
1	60 (64)	29 (66)
Median time since diagnosis (range) — yr	6.1 (0.3–14.6)	5.5 (0.3–12.9)
Median no. of previous lines of therapy (range)	4 (1–11)	4 (2–10)
Stem-cell transplantation — no. (%)	74 (79)	33 (75)
Exposure status — no. (%)		
Triple-class exposure	94 (100)	44 (100)
Penta-drug exposure	61 (65)	28 (64)
Belantamab mafodotin	18 (19)	5 (11)
Bispecific antibody††	7 (7)	2 (5)
CAR T-cell therapy	4 (4)	2 (5)



# RedirectTT-1: High ORR in Extramedullary Disease Subgroup

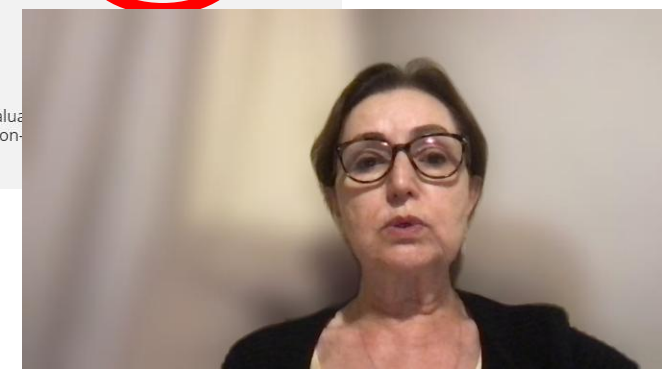


- All were soft tissue plasmacytomas
- At the RP2R (n=11):
  - Median follow-up 7.2 mo (range 0.7–14.2)
  - 85.7% (6/7) ORR
  - 28.6% (2/7) ≥CR

	All Dose Levels N=35	Tec 3.0 mg/kg + Tal 0.8 mg/kg Q2W N=11
Median DOR <sup>b</sup> , months (95% CI)	12.9 (4.17–NE)	NE (4.17–NE)
Median PFS, months (95% CI)	6.1 (2.5–9.9)	9.9 (2.4–NE)

Data cutoff date: Mar 16, 2023

<sup>a</sup>Response was assessed by investigators, based on International Myeloma Working Group criteria; response-evaluable patients have received ≥1 study treatment and have ≥1 post-baseline response evaluation by investigator. <sup>b</sup>Includes patients with confirmed responses. CR, complete response; DOR, duration of response; EMD, extramedullary disease; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; RP2R, recommended phase 2 regimen



ORIGINAL ARTICLE

# Talquetamab plus T in Relapsed or Refractory Multiple Myeloma

Y.C. Cohen, H. Magen, M. Gatt, M. Sebag, K. S.-S. Yoon, M.P. Chu, P. Rodríguez-Otero, I. Avivi, M. Krevvata, M.R. Peterson, L. Di Scala, E. Scott, A. Oriol, D. Morillo, and M.-V. Mateos, for the RedirecTT-1 Investigators

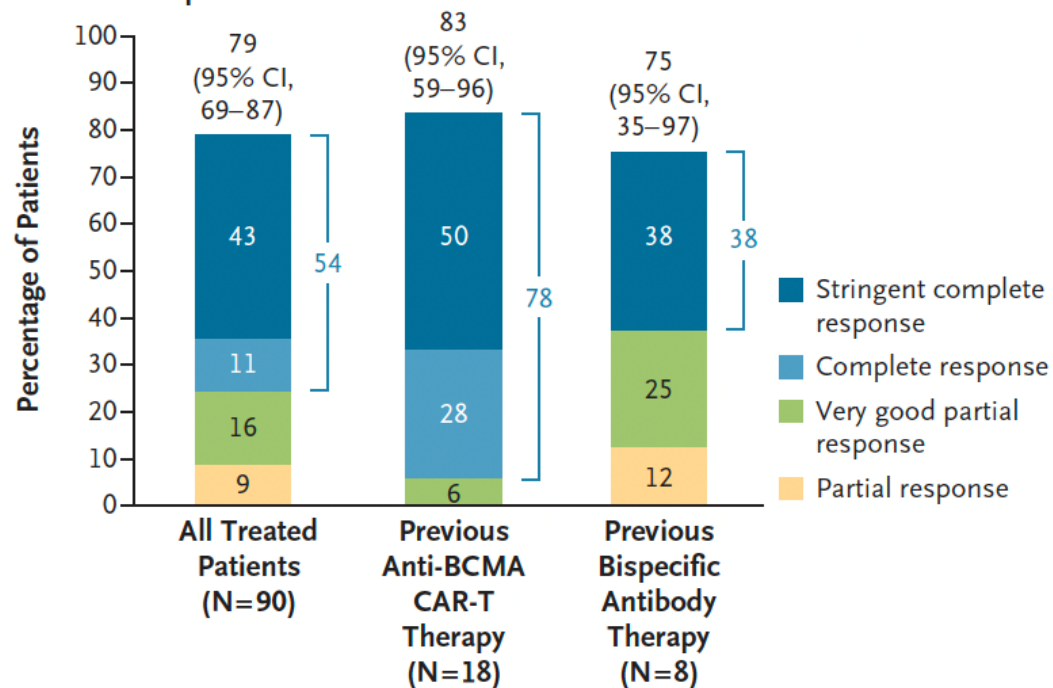
ORIGINAL ARTICLE

# Dual Targeting of Extramedullary Myeloma with Talquetamab and Teclistamab

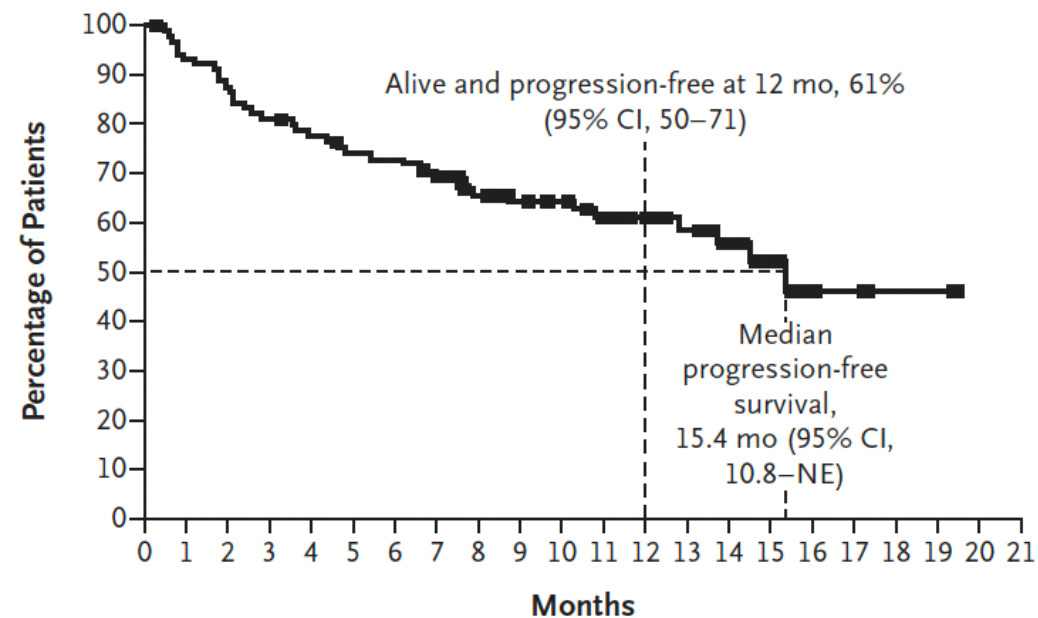
S. Kumar,<sup>1</sup> M.-V. Mateos,<sup>2,5</sup> J.C. Ye,<sup>6</sup> S. Atrash,<sup>7</sup> H. Magen,<sup>8</sup> H. Quach,<sup>9</sup> M.P. Chu,<sup>10</sup> S. Trudel,<sup>11</sup> J. Richter,<sup>12</sup> P. Rodríguez-Otero,<sup>13</sup> H. Chuah,<sup>14</sup> M. Gatt,<sup>15</sup> E. Medvedova,<sup>16</sup> S. Raza,<sup>17</sup> D.H. Yoon,<sup>18</sup> L. Rosiñol,<sup>21</sup> K. Onodera,<sup>22</sup> E. Scott,<sup>23</sup> C. Heuck,<sup>23</sup> J. L. O'Rourke,<sup>23</sup> P. Thakkar,<sup>24</sup> M. Festa,<sup>25</sup> L. Huang,<sup>23</sup> L. Pei,<sup>24</sup> J. Lu,<sup>27</sup> N. Au,<sup>23</sup> M. Krevvata,<sup>23</sup> S.Z. Usmani, for the RedirecTT-1 Investigators



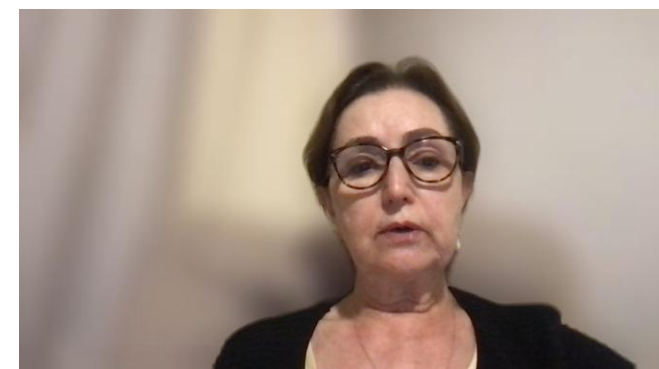
### A Overall Response



### C Progression-free Survival



No. at Risk 90 83 79 72 68 64 63 60 50 45 43 39 29 24 19 10 4 2 1 1 0 0







CRITICAL REVIEW OPEN ACCESS

# Extramedullary Disease—Achilles Heel in Myeloma?

Shaji Kumar<sup>1</sup> | Joshua Richter<sup>2</sup> | Saad Z. Usmani<sup>3</sup> | Yael C. Cohen<sup>4,5</sup> | Jing Christine Ye<sup>6</sup> | Maria-Victoria Mateos<sup>7</sup> | Vania Hungria<sup>8</sup> | Elena Zamagni<sup>9</sup>

American Journal of Hematology, 2026; 101:521–536

TABLE 2 | Response rates with novel immunotherapies in patients with RRMM [107, 118–123].

EMD in real-world studies of CAR-T							EMD in clinical trials of ADCs and bispecific antibodies						
Therapy	Ide-cel [118]		BCMA CAR-T [107]		Belantamab mafodotin [123]		Teclistamab [119]		Elranatamab [120]		Talquetamab [122] <sup>a</sup>		Teclistamab + Talquetamab [121]
	True EMD <sup>b</sup> (n = 84)	Non-EMD (n = 267)	True EMD <sup>c</sup> (n = 47)	Non-EMD (n = 105)	EMD undefined (n = 22)	Total population (n = 97)	True EMD <sup>d</sup> (n = 28)	Non-EMD (n = 165)	True and paramedullary EMD <sup>e</sup> (n = 39)	Non-EMD (n = 84)	True EMD <sup>d</sup> (n = 154)	Non-EMD (n = 41)	True EMD <sup>f</sup> (N = 90)
ORR	52%	82%	58%	96%	5%	32%	35.7%	68.6%	38.5%	71.4%	41.4	69%	79%

Abbreviations: ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMD, extramedullary disease; ide-cel, idecabtagene vicleucel; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma. Shaded columns report data from patients with true EMD.

<sup>a</sup>0.8 mg/kg biweekly dose.

<sup>b</sup>Patients with both true EMD and paramedullary EMD were classified as true EMD, and patients with paramedullary EMD only were classified as non-EMD.

<sup>c</sup>Defined as bone-independent (only) tumors of plasma cells growing at anatomical sites outside of the bone marrow detected within 30 days of CAR T-cell infusion.

<sup>d</sup>Defined as soft tissue plasmacytomas that were not associated with bone.

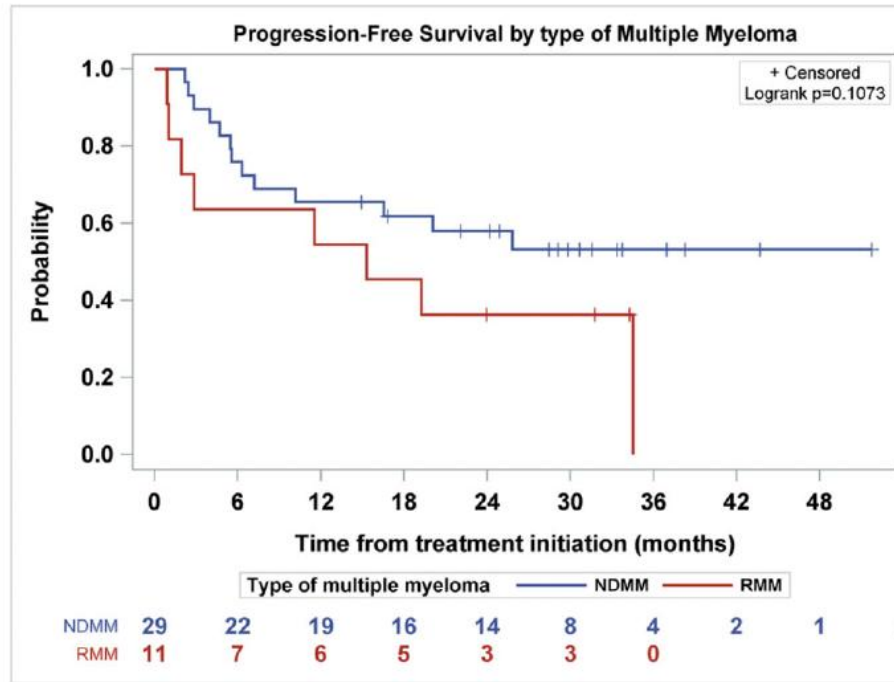
<sup>e</sup>Defined as the presence of any plasmacytoma (extramedullary and/or paramedullary with a soft tissue component).

<sup>f</sup>≥ 1 nonradiated bone-independent soft tissue plasmacytoma ≥ 2 cm in greatest dimension confirmed by central review of PET-CT scans or whole-body MRI (with sponsor approval).





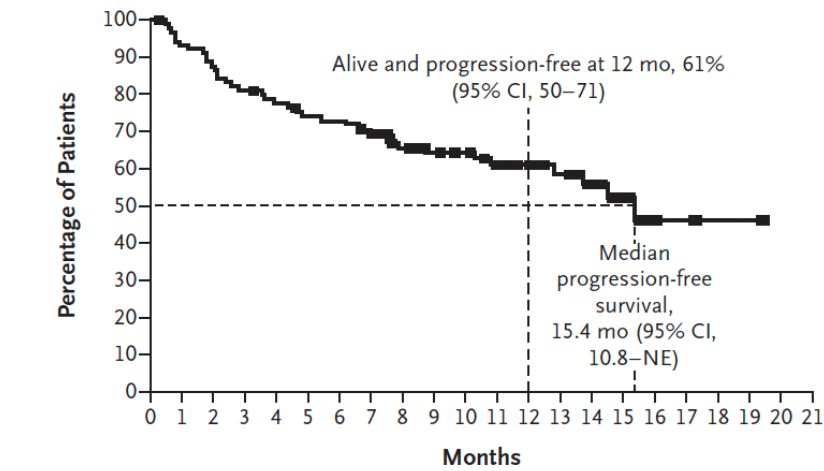
(A)



Median (95% CI) PFS in months

- Patients with NDMM: NR (7.2–NR)
- Patients with RMM: 15.3 (1.0–NR)

**Progression-free Survival**



No. at Risk 90 83 79 72 68 64 63 60 50 45 43 39 29 24 19 10 4 2 1 1 0 0

Beksac et al Hemasphere 2026

Kumar et al N Engl J Med 202



# Role of novel drugs: Selinexor, Melflufen, Mezigdomide





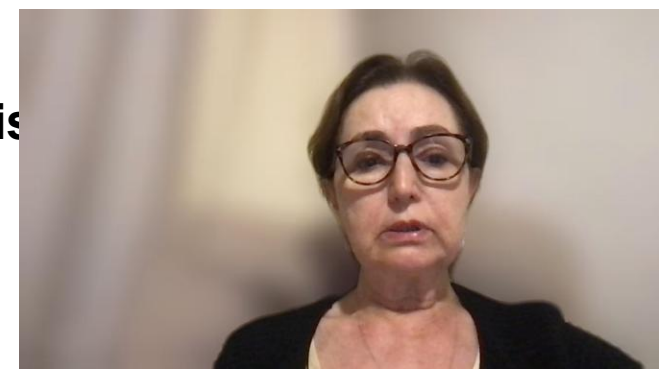
American Society of Hematology  
2021 L Street NW, Suite 900,  
Washington, DC 20036  
Phone: 202-776-0544 | Fax 202-776-0545  
bloodadvances@hematology.org

## **Efficacy and Safety of Selinexor Combined with VRD in Newly Diagnosed Multiple Myeloma with EMD: A Phase 2 Trial**

Tracking no: ADV-2025-018945R1

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**October 17, 2022 and November 27, 2025, 30 patients were enrolled**  
**A multicentric study from China**  
**High-risk cytogenetics were present in 31.0%, and 27.6% met ultra-high-risk**



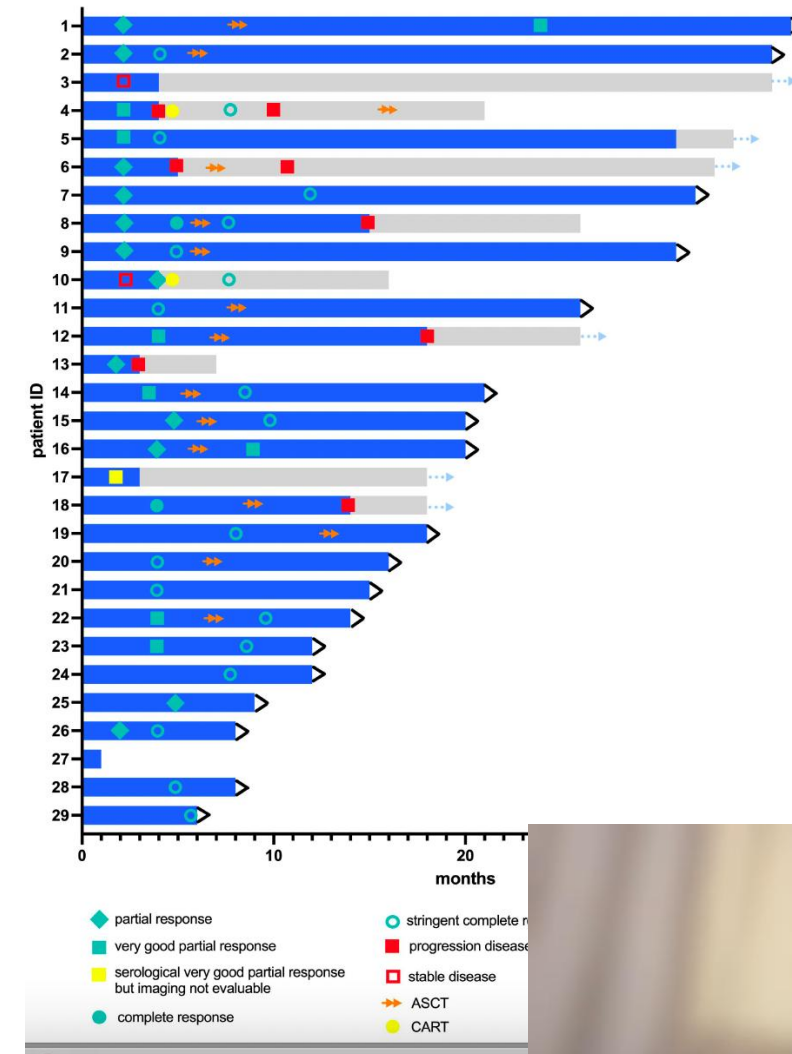
**ORR was 89.7% (sCR 58.6%, CR 3.4%, VGPR 10.3%, PR 17.2%).**

**Imaging documented EMD regression in 89.7%  
(complete resolution 79.3%, partial 10.3%);**

**12-month PFS and OS rates were 87.9% and 96.3%,**

**EMN19 response rates:  
44.8% CR and >VGPR 79.3 %  
37.9% MRD(-) and 55.2 % CMR**

Figure 1 Time from first dose(months)



# CONCLUSION

**PET-CT:** a crucial diagnostic and response assessment tool to measure metabolic tumour volume(MTV) **spatial heterogeneity & genomic complexity**

**Incidence:** <10%(NDMM) >30% (RMM)  
soft tissue > paraosseous EMD are poor **prognostic**

## Treatment:

### **Frontline therapy :**

Chemo-radiotherapy + ASCT

Quadruplet in NDMM Transplant Ineligible+ 2 drug maintenance

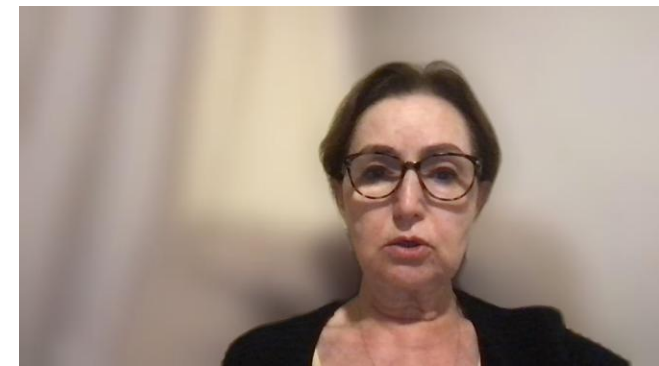
Quadruplet + ASCT + 2-drug maintenance

### **Relapse :**

Cilta-cel or dual bispecific antibodies or trispecific

Targeting BRAF, Selinexor

**Clinical trials are needed**





**MmGTr**  
MYELOMA GROUP TÜRKİYE

Teşekkürler  
Thank you  
Danke schön  
Grazia  
Merci beaucoup

**liv**  
HOSPITAL

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