Extra-Medullary Myeloma

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Disclosures

- Consulting & advisory role: J&J Innovative Medicine, Sanofi, BMS, Takeda, Pfizer
- Speaker’s Bureau: GSK, Amgen
- Research Funding: J&J Innovative Medicine, Takeda

Case #1

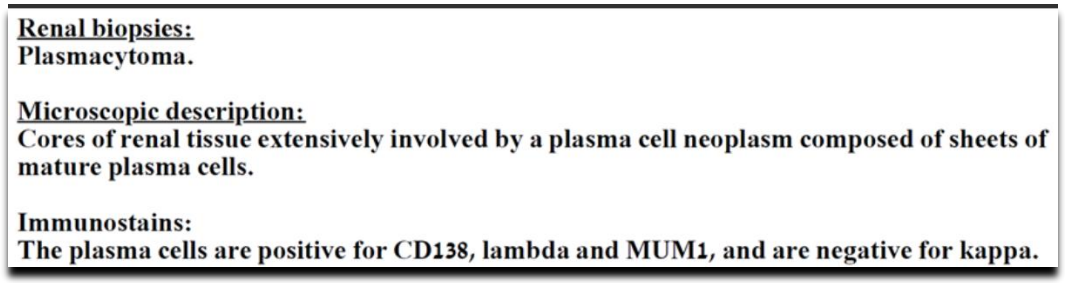
- 78 y.o. women, SMM diagnosed in 2006, active MM diagnosed 2016, with bone disease
- Disease course:

  Ln #1: VCD – ASCT – Len mtns → 03.20218 relapse with lytic and para-skeletal disease
  Ln #2: Dara – Pom dex → Pom monotherapy → 05.2019 oligosecretory PD

  Ln #3: Belantamab → 8/2019 discontinued d/t ocular toxicity

  Ln #4: Kd → 5.2024 relapse with EMD, kidney mass (Bx diagnosis)

M-protein 4 g/dL, Lambda LC 243 mg/L, Kappa 10 mg/L ratio 24



Renal biopsies:
Plasmacytoma.

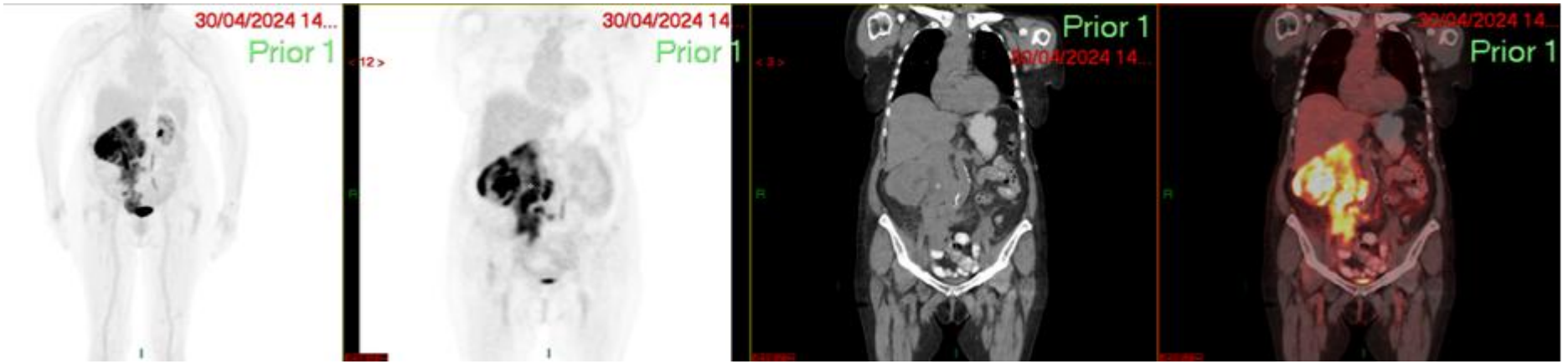
Microscopic description:
Cores of renal tissue extensively involved by a plasma cell neoplasm composed of sheets of mature plasma cells.

Immunostains:
The plasma cells are positive for CD138, lambda and MUM1, and are negative for kappa.

Bone marrow biopsy: 3% PCs clonal for Lambda
FISH with no aberrations

PETCT revealed extensive EMD involving the Rt Kidney, Rt ureter, uterus, bladder, and RT lymphadenopathy, Rt abdominal wall . Multiple lytic and sclerotic lesions in pelvis and spine, without FDG uptake

Case #1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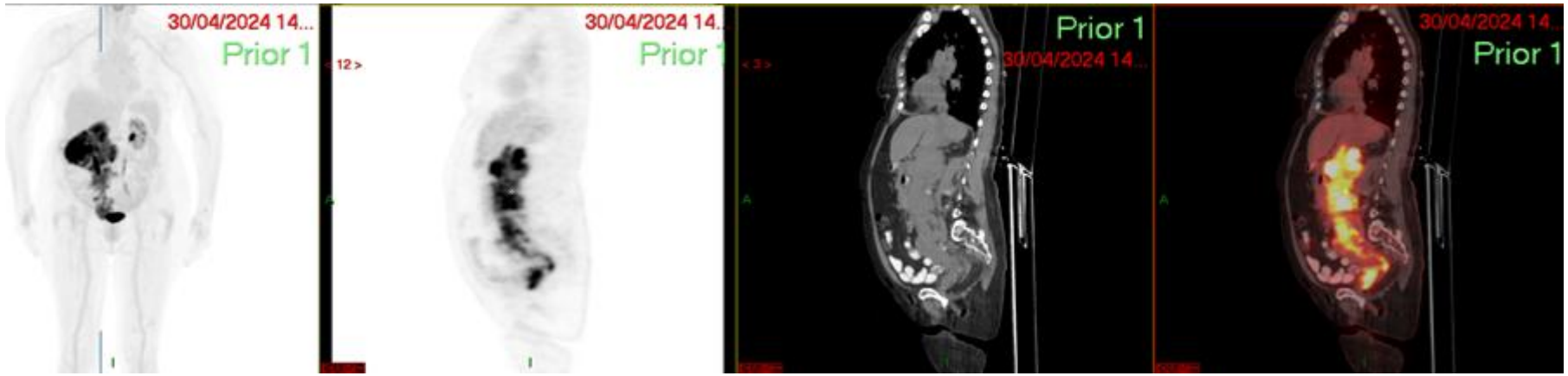
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Question #1

Patients is classified as….

1. Para-Skeletal
2. Extra-medullary myeloma (EMD)
3. Non-secretory myeloma
4. High risk Myeloma

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Myeloma Extra-Medullary Disease (EMD)

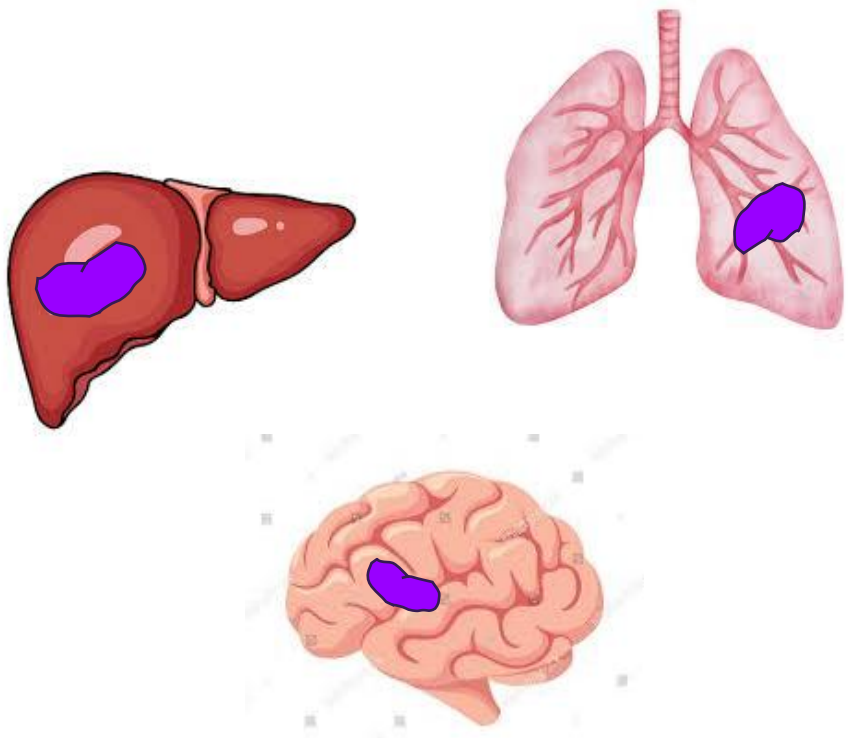
- A subset of Myeloma patients develop clonal plasma cell that escape and grow outside the bone marrow, termed **soft tissue plasmacytoma**
  - *True* Extramedullary plasmacytoma: non- bone adjacent, hematogenic spread → represent a different biological entity
  - Para-Medullary (=para-skeletal): bone adjacent, arising from adjacent bone marrow
  - Solitary plasmacytoma: with <10% plasma cells in the BM or without BM involvement
    → NOT considered EMD

- EMD is an aggressive form of MM:
  - Ability to thrive and grow independent of the bone marrow microenvironment
  - Linked to high-risk genetic features, increased proliferation, evasion of apoptosis
  - Resistance to therapies
  - Poor prognosis

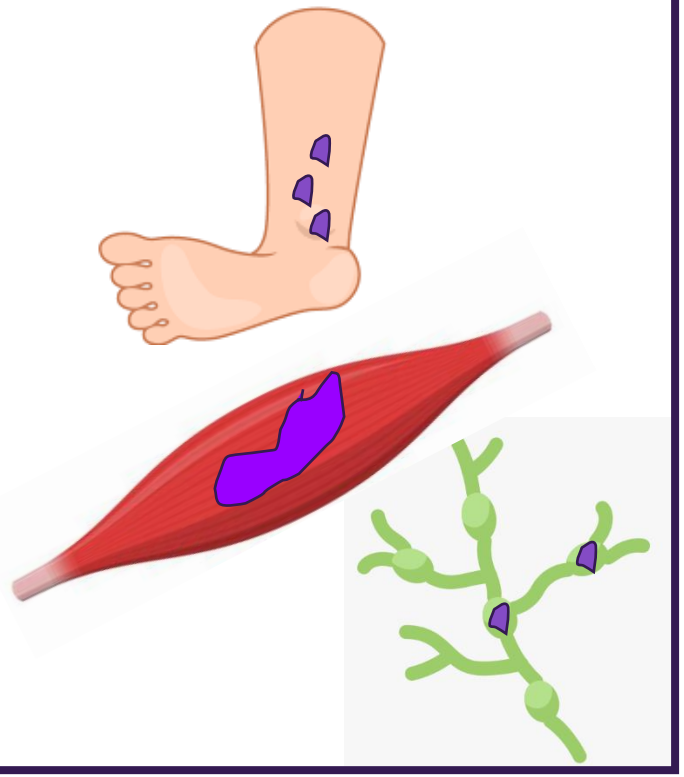
Soft Tissue Plasmacytoma

Extra-Medullary Disease (EMD)

Visceral



Skin & Soft Tissue



Para-Medullary = Para-Skeletal

Article https://doi.org/10.1038/s41591-023-02528-9

Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results

Alexander M. Lesokhin[1], Michael H. Tomasson[2], Bertrand Arnulf[3], Nizar J. Bahlis[4], H. Miles Prince[5], Ruben Niesvizky[6], Paula Rodríguez-Otero[7],

Table 1 | Baseline characteristics and prior treatment

Cytogenetic risk, *n* (%)	
Standard	83 (67.5)
High[b]	31 (25.2)
Missing	9 (7.3)
Extramedullary disease by BICR, *n* (%)[c]	39 (31.7)
Bone marrow plasma cells, *n* (%)	
<50%	89 (72.4)
≥50%	26 (21.1)

t(4;14), t(14;16) and del(17p) chromosomal abnormalities. [c]Extramedullary disease was defined as the presence of any plasmacytoma (extramedullary and/or paramedullary with a soft-tissue component). [d]Poor prognosis feature refers to at least one of the following: ECOG

Published online: 15 August 2023 Nature Medicine

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D.,

Table 1. Baseline Characteristics of the Patients Who Received Idecabtagene Vicleucel (Ide-cel).*

Characteristic		Ide-cel Target Dose of CAR+ T Cells		Total (N=128)
Extramedullary disease — no. (%)†	0	34 (49)	16 (30)	50 (39)
High tumor burden — no. (%)‡	3 (75)	34 (49)	28 (52)	65 (51)

Table 1. (Continued.)

* Percentages may not total 100 because of rounding. BCMA denotes B-cell maturation antigen, and HSCT hematopoietic stem-cell transplantation.

† Extramedullary disease was defined as paraskeletal soft-tissue masses, soft-tissue masses spreading outside the bone marrow, or both.

ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

Authors: Philippe Moreau, M.D., Alfred L. Garfall, M.D., Niels W.C.J. van de Donk, M.D., Ph.D., Hareth Nahi, M.D., Ph.D., Jesús F. San-Miguel, M.D., Ph.D., Albert Oriol, M.D., Ph.D., Ajay K. Nooka, M.D., +26, and Saad Z. Usmani, M.D. Author Info & Affiliations

Published June 5, 2022 | **N Engl J Med 2022;387:495-505** | **DOI: 10.1056/NEJMoa2203478** | **VOL. 387 NO. 6**

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Phase 1 (N=40)	Phase 2 (N=125)
Age		
Median time since diagnosis (range) — yr	5.6 (0.8–17.4)	6.2 (0.9–22.7)
≥1 Extramedullary plasmacytoma — no. (%)†	8 (20.0)	20 (16.0)
≥60% Plasma cells in bone marrow — no./total no. (%)	3/38 (7.9)	15/122 (12.3)

* Race was reported by the patients. Included in the category of "other" are 4 patients who did not report race, 2 who reported their race as other, and 1 who reported multiple races.
† Included in this category are patients with soft-tissue plasmacytomas that were not associated with bone.
‡ Scores on the Eastern Cooperative Oncology Group (ECOG) performance-status scale range from 0 to 5, with higher

EMD Epidemiology

Table 2. Incidence rates of EMD in studies of patients with MM.

Reference	No. of patients	Time period covered	Diagnostic approach	Incidence
Montefusco et al. [26]	2322	2010–2018 (across all studies)	Skeletal survey, MRI, or CT; and/or physical examination	NDMM: 0.5%
Gagelmann et al. [28]	3744	2005–2014	NR	NDMM: 3.7%
Deng et al. [18]	834	1993–2013	X-ray, US, CT, physical examination; histologically confirmed where possible	NDMM: 4.8% RRMM: 3.4%
Weinstock et al. [29]	663	2005–2011	Pathological or radiological evidence of EMD at any time following the initial diagnosis of MM	RRMM: 8.3%
Pour et al. [23]	226	2005–2008	US, CT, or MRI	RRMM: 14%
Rasche et al. [21]	357	2007–2010	Cytology, biopsy of clinical/radiological lesions	RRMM: 6.7%
Short et al. [30]	174	2007–2011	PET/CT, MRI	NDMM: 1.7% RRMM: 7.5%

CT computed tomography, *MRI* magnetic resonance imaging, *NR* not reported, *PET* positron emission tomography, *US* ultrasound.

- Systematic review of literature, 2010-2020, identified 29 records
- Assessment by visual inspection, palpation, CT, PETCT, MRI, detection is dependent on imaging modality
- Recent series estimated EMD prevalence of 0.5-5.2% in NDMM >20% and up to 30% in RRMM

Blade J et al. Blood Cancer Journal (2022) 12:45

Sites of EMD involvement

Balkan/Barcelona Series*

Anatomical locations of EMP	
Soft tissue (muscle/skin) n (%)	55 (24.3 %)
Lymph nodes, n (%)	23 (10.2 %)
Pleural, n (%)	27 (11.9 %)
Liver, n (%)	21 (9.3 %)
Central nervous system, n (%)	14 (6.2 %)
Abdominal, n (%)	9 (4.0 %)
Oropharynx, n (%)	8 (3.5 %)
Lung, n (%)	7 (3.1 %)
Testis, n (%)	4 (1.8 %)
Others, n (%)	4 (1.8 %)

Multinational series**

Involved sites	127	
Soft tissue/skin		37 (29.1%)
Pleura and lung		32 (25%)
Lymph nodes		22 (17.3%)
Liver		15 (11.8%)
CNS[b]		14 (11%)
Gastrointestinal		10 (7.9%)
Breast		10 (7.9%)
Pancreas		3 (2.4%)
Genitourinary organs		1 (0.8%)
Gums		1 (0.8%)
Spleen		1 (0.8%)

*Zanwar S et al. Am J Hematol. 2023;98:1540–1549

**Avivi I et al. Am J Hematol. 2019;94:1132–1140.

Risk factors for EMD

- Association of **high-risk cytogenetic features** including t(4;14), t(14;16), gain(1q21), and del(17p) with EMD has been reported, del(13q14) as risk factor for EMD at relapse
- Retrospective analysis of 234 2nd EMD patients (Czech registry) identified the following risk factors at time of diagnosis, to subsequently develop EMD:
  - younger age
  - high LDH levels
  - extensive osteolytic activity
  - immunoglobulin A or the non-secretory type of MM

Stork M et al. Br J Haematol 2022;196:954-962; Zanwar S et al. Am J Hematol. 2023;98:1540–1549

Pathogenesis of EMD

- Development of EMD occurs after MM cells lose anchorage and adhesion to the BM, allowing cells to migrate, proliferate, and survive outside the BM

- Although the mechanistic drivers of EMD remain incompletely understood, it is evident that EMD is complex and more heterogeneous than MM

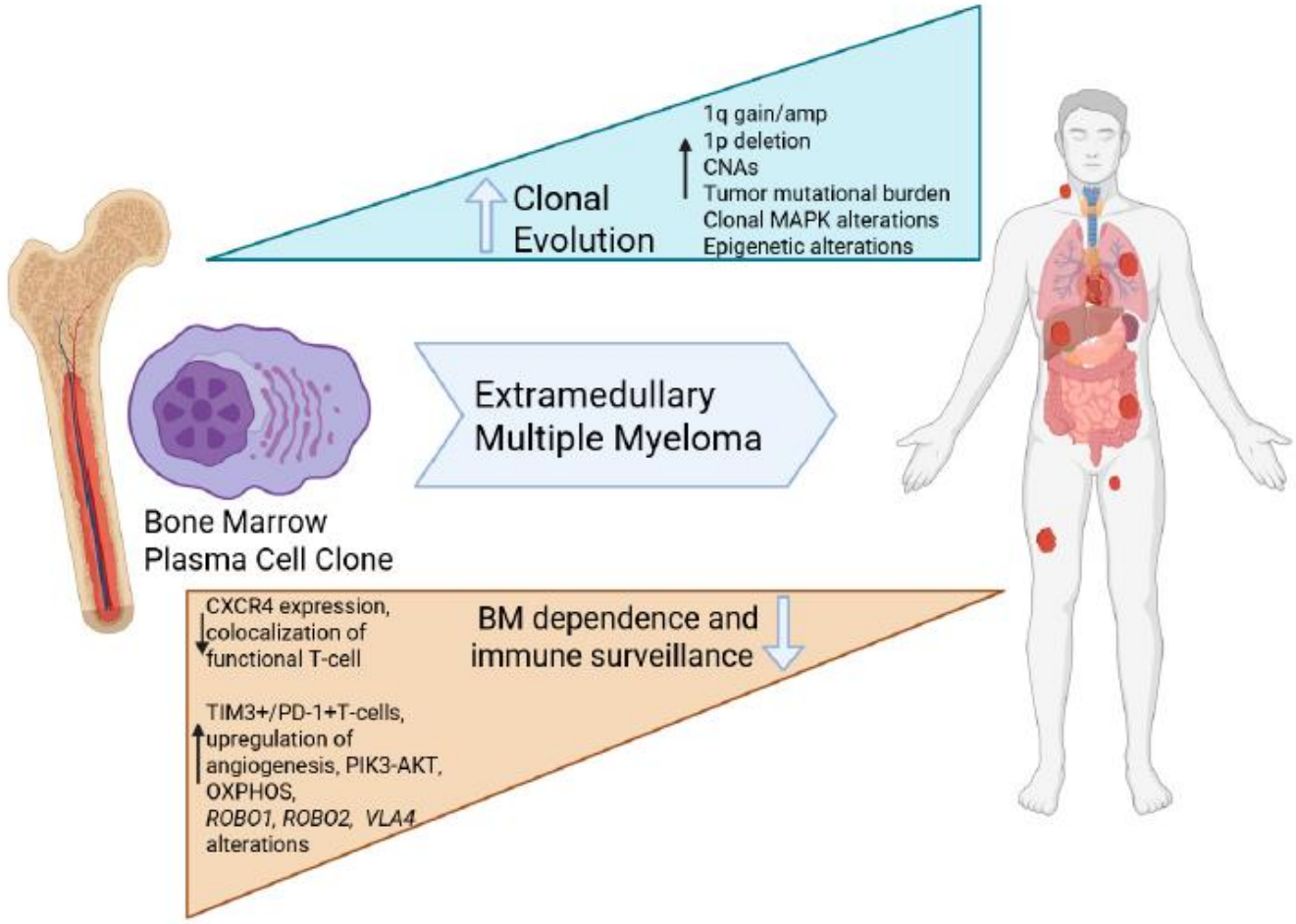
Ho M et al. Curr Oncol 2025;32; Jelinek T et al. Leukemia 2024;38:1323-1333

Molecular pathogenesis of EMD

- Extramedullary tumors are **enriched in MAPK alterations** that are frequently clonal, and a complex genomic profile with **higher mutational burden** and copy number abnormalities

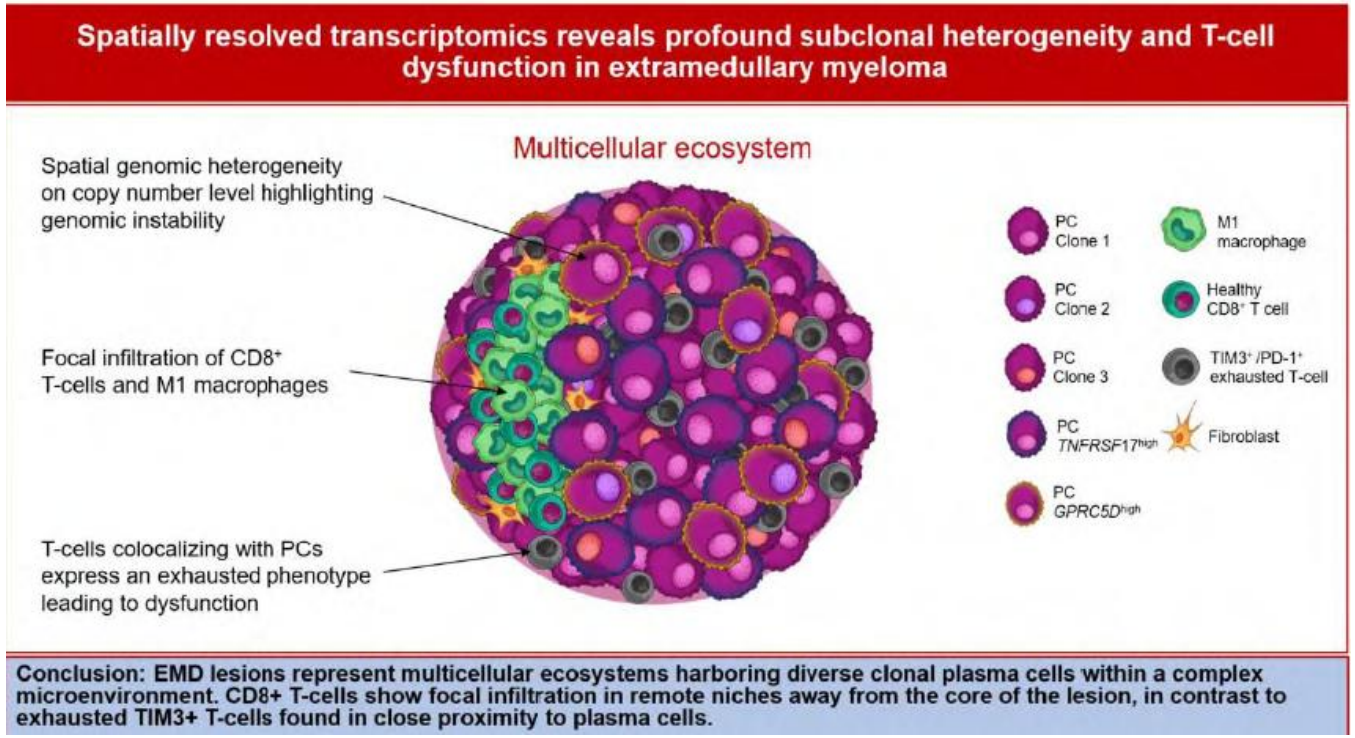
- The microenvironment is enriched in **exhausted T-cells**

- **Plasma cells demonstrated altered metabolic programming** and less dependence on BM, alterations in chemokine receptors and adhesion molecules, disruption of signaling regulating chemotaxis and adhesion to TME



Ho M et al. Curr Oncol 2025;32; Jelinek T et al. Leukemia 2024;38:1323-1333

EMD biology leading to aggressive course



- EMD mimics the architectural complexity of solid tumors marked by diverse Microenvironments & multiclonality
- EMD shows infiltration of active T-cells spatially confined to niches segregated from MM cells, potentially affecting therapeutic response

Mara J et al. Blood 2024.

Diagnostic Approach

- Diagnosis of EMD relies on sensitive and specific imaging modalities, alongside with standard Myeloma workup
  - ✓ PET-CT and whole-body MRI with diffusion-weighted imaging are the most effective modalities
  - ✓ Valuable also for monitoring response
- Directed biopsies may be needed when imaging or diagnosis is unclear
  - ✓ Distinct profiles in EMD: lack of CD38 expression, higher proliferative index, lower p27 expression, CCND-1 positivity, strong BCl-2 and Bcl-xl expression, CD56 downregulation, and CD44 up-regulation

✓ Experimental – mass spectrometry "liquid biopsy"

Vlachová M et al. Sci Rep 2024;14:18777; Rosinol L et al. Br J Haematol 2021;194:496-507.

Question #2

What is the reported OS for RRMM EMD prior to CART/BisAb

1. 2-4 months
2. 5-7 months
3. ~12 months
4. ~ 24 months

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Natural History & Response to Therapy

- Presence of EMD is a powerful negative prognostic factor in MM, with the relatively poor outcomes of such patients well described in multiple studies
- Survival is typically less than 2–3 years following the development of EMD during the disease course, and overall survival (OS) is consequently significantly shorter in patients with EMD compared to those without EMD
- Factors associated with inferior outcomes: secondary EMD, multiple organ involvement, CNS involvement, poor response to therapy, β_2-microglobulin >5mmol/L, and International Staging System (ISS) stage III disease

Outcomes by therapy

Reference Study type	Total number of patients/ number with EMD	Time period covered	Treatments	PFS	OS	Other
Novel agents (various) and/or SCT						
Avivi et al. [37] Retrospective	127 (all EMD)	2010–2018	First treatment included PIs (50%), IMiDs (39%), monoclonal antibodies (10%), and chemotherapy (53%)	–	–	57% ORR (≥ PR) across all treatments
Rasche et al. [21] Single-center registry	24 (all EMD)	2007–2010	Radiotherapy ($n = 16$) ASCT + intense dose chemotherapy ($n = 6$) Bortezomib ($n = 16$) Lenalidomide ($n = 12$) Pomalidomide (n	Median (95% CI): 2 months (0.08–3.92)	Median (95% CI): 7 months (3.56–10.43)	–
Beksac et al. [31, 38] Retrospective	96 EMD, $n = 84$	2010–2	Median number of treatment and [illegible]	Median (95% CI): 9.1 months (11.6–15.6)	Median (95% CI): 11.4 months (0.6–16.2)	Complete remission rate: 9% (vs 54.5% in patients with paraskeletal, $p < 0.001$)
IMiDs						
Short et al. [30] Phase 2 trial	16 (all EMD)	2007–20	Pomalidomide + low-dose dexamethasone	–	Median: 16 months	–
PIs						
Zhou et al. [39] Retrospective	45 EMD, $n = 25$		Bortezomib + dexamethasone-based	EMD significantly inferior PFS vs paraskeletal ($p = 0.004$)	EMD significantly inferior OS vs paraskeletal ($p = 0.04$)	–
Papanikolaou et al. [40] Retrospective	28 (all EMD)	1998–2011	At relapse:Bortezomib-containing regimens (32%) Platinum-containing (21%) Lenalidomide (21%) VAD (8%)	–	Median following relapse: 5 months Median from MM diagnosis: 38 months	–
Chemotherapy/radiotherapy						
Rasche et al. [41] Retrospective	11 (all EMD)	2007–2012	Dexa-BEAM (including dexamethasone, carmustine, cytarabine, etoposide, and melphalan)	Median: 4 months	–	Objective response (≥PR) achieved in 6/11 patients
Recently approved and investigational agents						
Richardson et al. [42] Phase 2	55 EMD, $n = 27$	Patients enrolled between Dec 2016 and Oct 2019	Melflufen + dexamethasone	–	–	ORR: Non-EMD, 32% Paraskeletal, 25% EMD, 22%
Wang et al. [43] Single-center	57 EMD, $n = 17$	2016–2018	LCAR-B38M	Median: 8.1 months (vs 25 months in non-EMD; $p < 0.001$)	Median: 13.9 months (vs NR in non-EMD; $p = 0.0019$)	82% ORR (≥ PR) vs 90% for non-EMD

ASCT autologous stem cell transplantation, *EMD* extramedullary disease, *MM* multiple myeloma, *NC* not calculable, *NR* not reached, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *VAD* vincristine/adriamycin/dexamethasone.

Small EMD Cohorts
Reports together para-skeletal/EMD
Non-recent years
Outcomes mostly poor <6mo OS
Pomalidomide 16mo OS
Melflufen (?)

Blade J et al. Blood Cancer Journal (2022) 12:45

EMD patients in LocoMMotion & MoMMent studies

- Non interventional , prospective real-world trials, triple class exposed MM patients
- Of 302 patients in the pooled analysis, 29 EMD patients were identified, 15 with true EMD
- Findings elucidated the poor outcomes with standard therapies in patients with heavily pretreated RRMM and EMD (compared to w/o EMD):

Heavily pretreated, triple-class exposed RRMM		
	With EMD	Without EMD
ORR, %	24.1	33.3
mPFS, months	2.7	5.1
mOS, months	7.2	15.5

Moreau P, et al. Clin Lymphoma Myeloma Leuk 2025

EMD outcomes from pooled clinical trials

- A meta-regression analysis of 9 clinical trials including daratumumab
- Among 158 EMD RRMM patients vs 2706 w/o EMD
- Patients with EMD had 87% worse chance of response (hazard ratio 0.13 [95% CI 0.09–0.20]) than those without

Voorhees P et al. EHA 2025

Therapeutic considerations – Considerations from expert panel (2021)

- NDMM:
  Treat as ultra-high risk; combine novel agents with chemotherapy (PACE); include auto-transplant, consider tandem
- RRMM:
  - Lymphoma-like regimen*: PACE / DT-PACE / DCEP / Dexa-BEAM / HDT/SCT
  - Novel agent combinations (e.g. carfilzomib-based combinations – such as KPD, KCyD, others - PVD, selinexor-based combinations, isatuximab-based combinations)
  - *Immunotherapy: CAR-T cell therapy, bi-specific antibodies (BisAbs)*

Rosinol L et al. British Journal of Haematology, 2021, 194, 496–507

Question #2

What is true regarding efficacy of CART and BiAb monotherapy for EMD

1. Response rates and DOR < non-EMD patients
2. ORR similar to non-EMD but DOR < non-EMD patients
3. Response rates and DOR similar to non-EMD patients
4. Data is still immature / insufficient to determine

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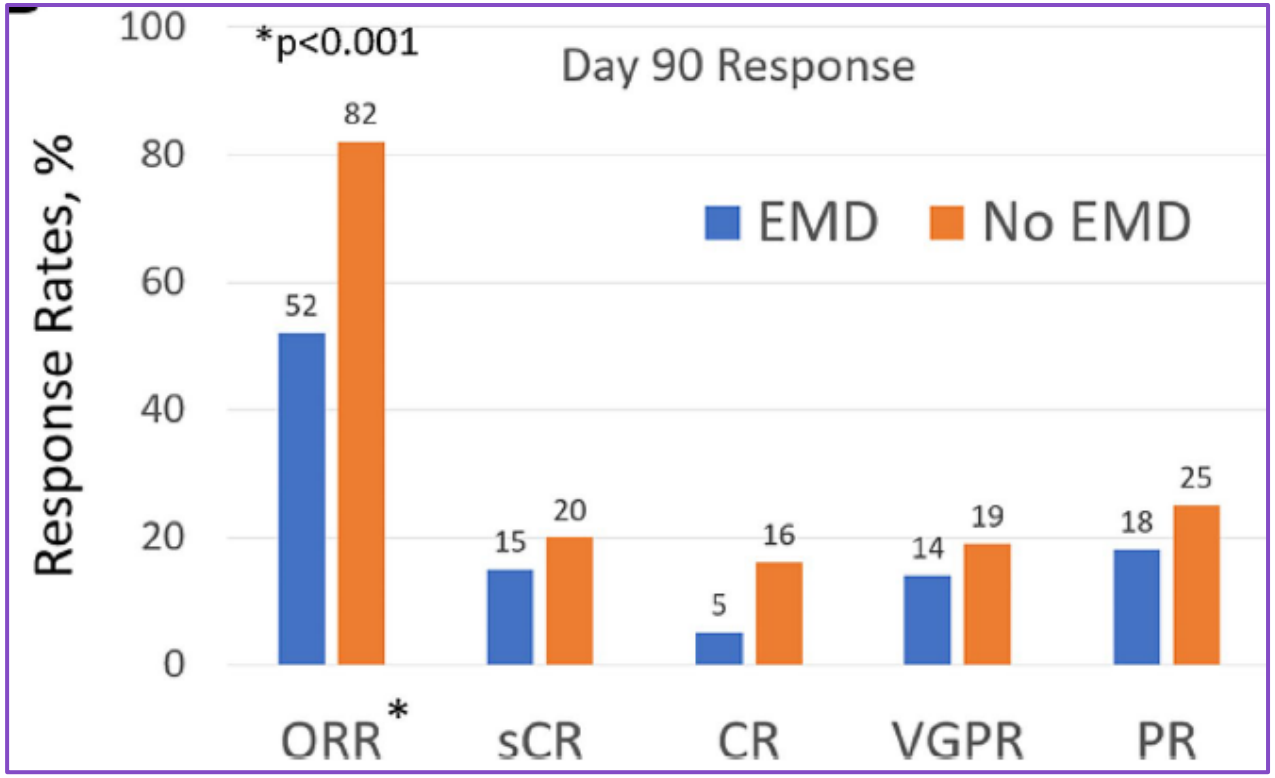
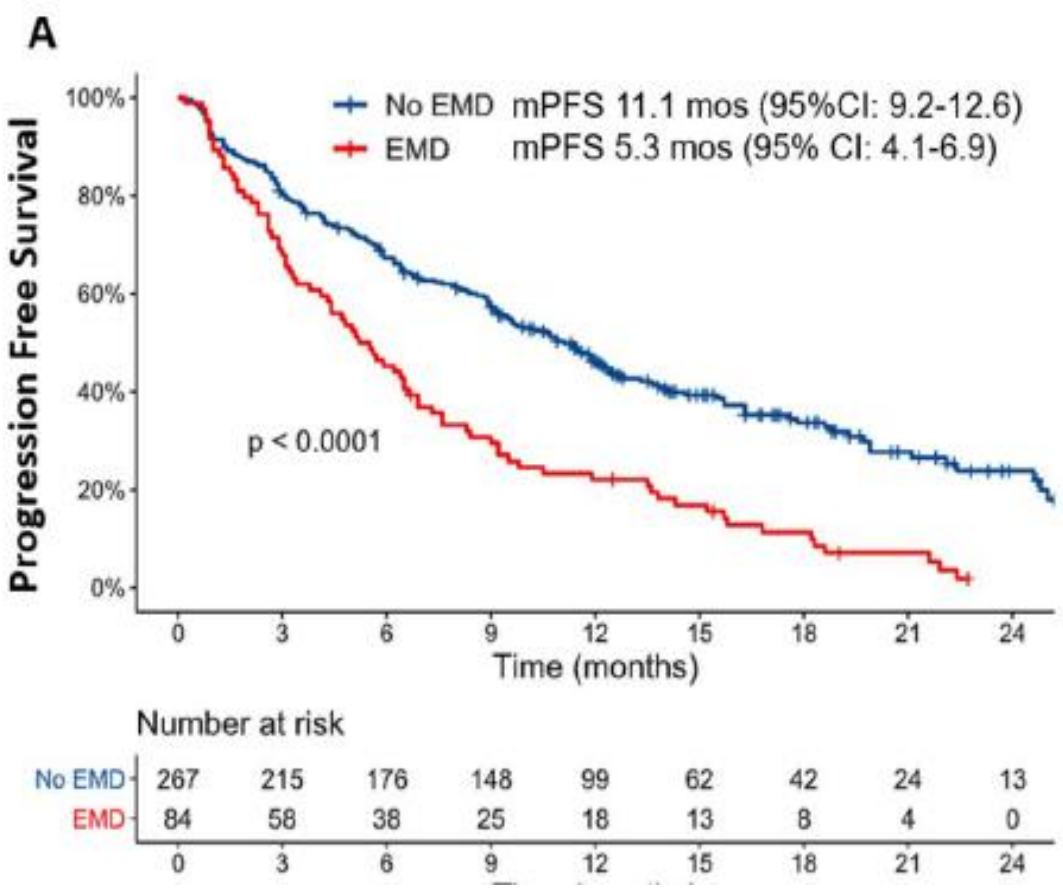
EMD response to CART

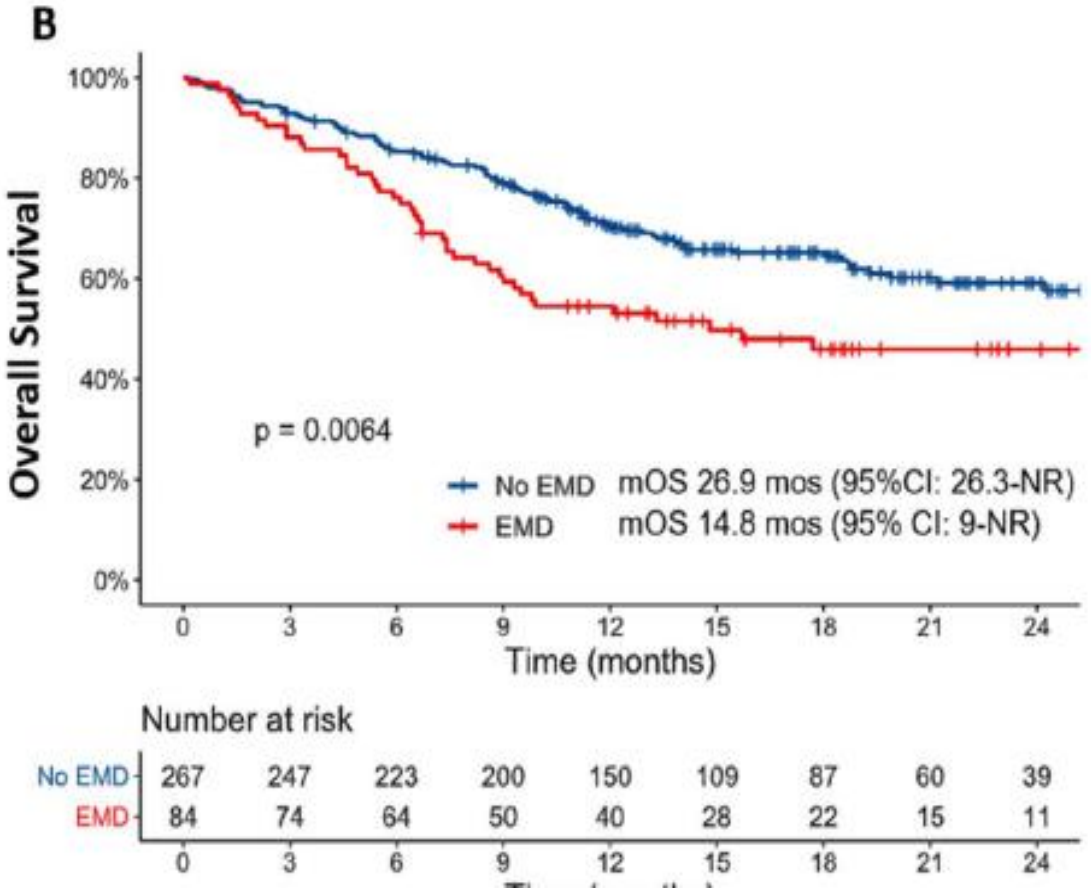
- Retrospective multi-site study, 11 US academic sites, May 2021- Apr 2023
- 84 / 351 patients (24%) infused with ide-cell had true EMD prior to infusion
- EMD patients were younger (med 62), had poorer performance status, worse drug resistance and higher inflammatory biomarkers compared to non-EMD



Zanwar *et al. Journal of Hematology & Oncology* (2024) 17:42

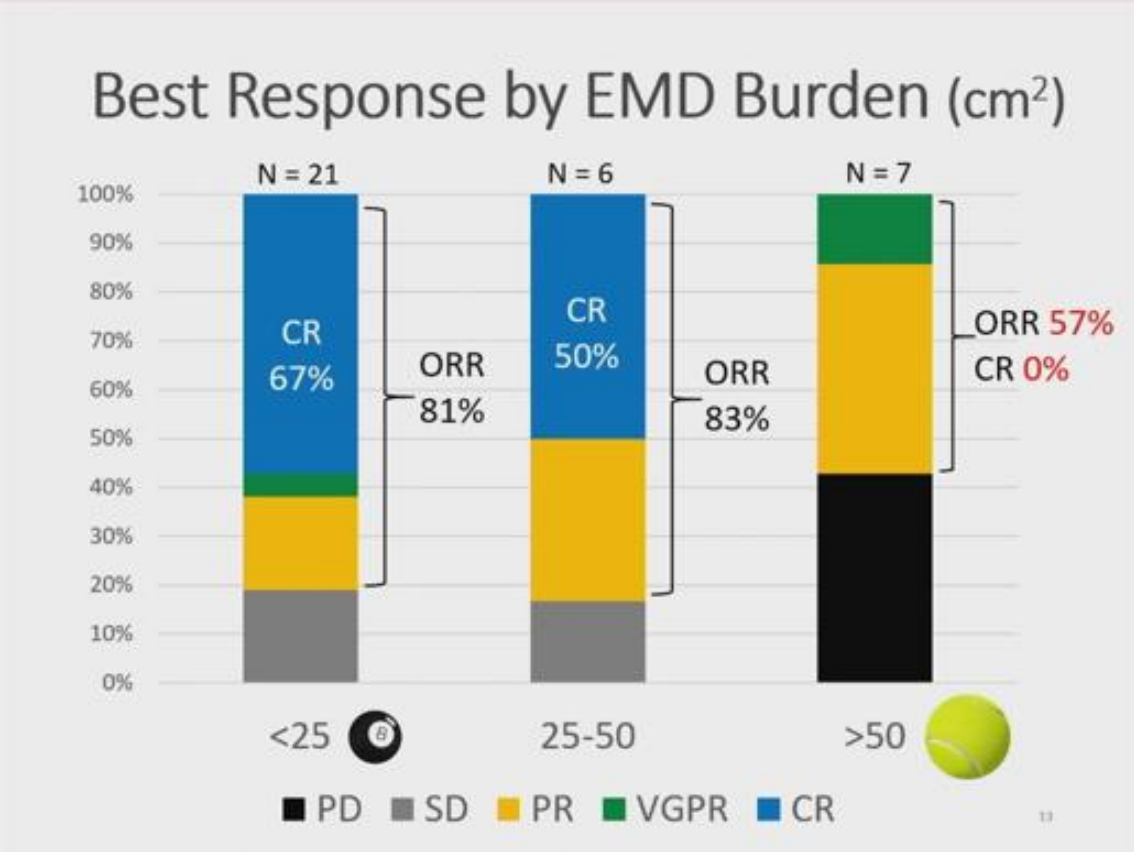
EMD response to CART

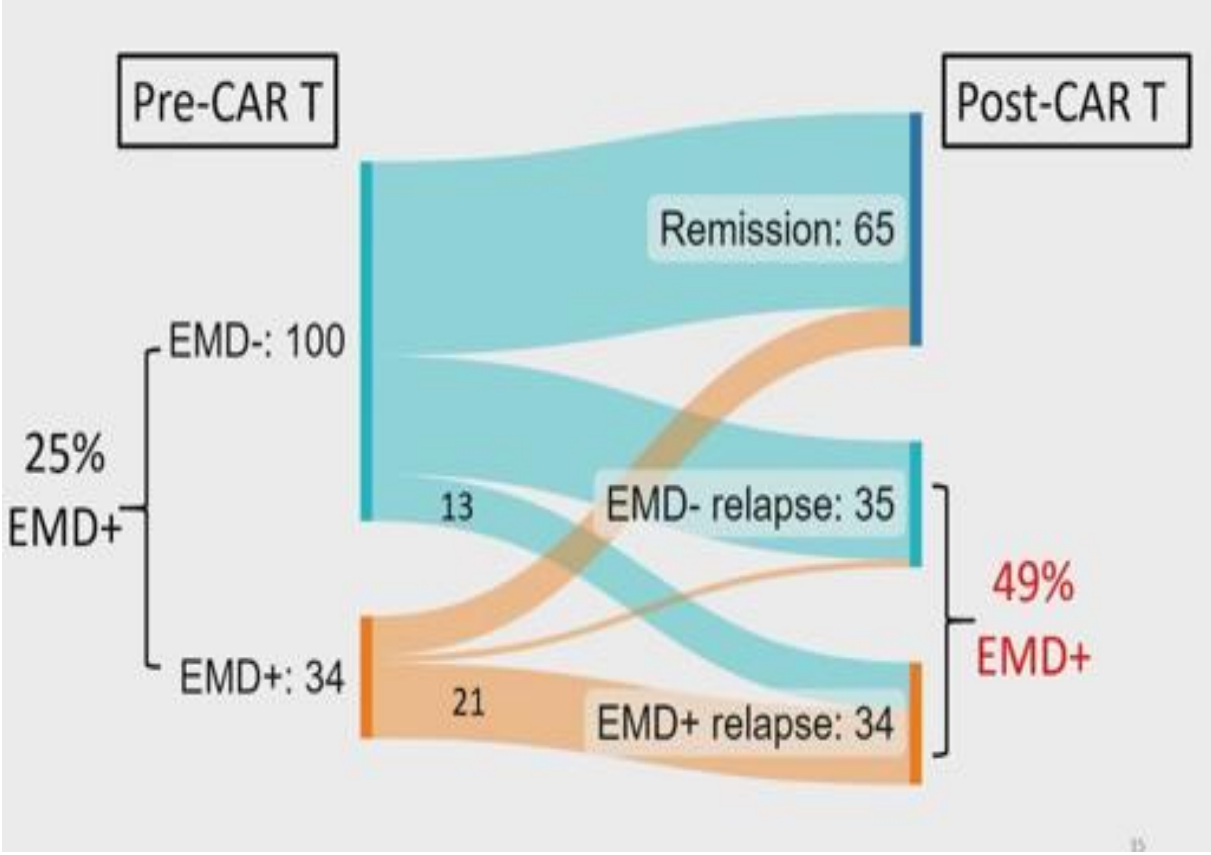




Zanwar *et al. Journal of Hematology & Oncology* (2024) 17:42

134 pts MM treated with CART at Mt Sinai, 2017-2023, 34 with true EMD prior to CART Tx





Inferior responses with larger EMD masses

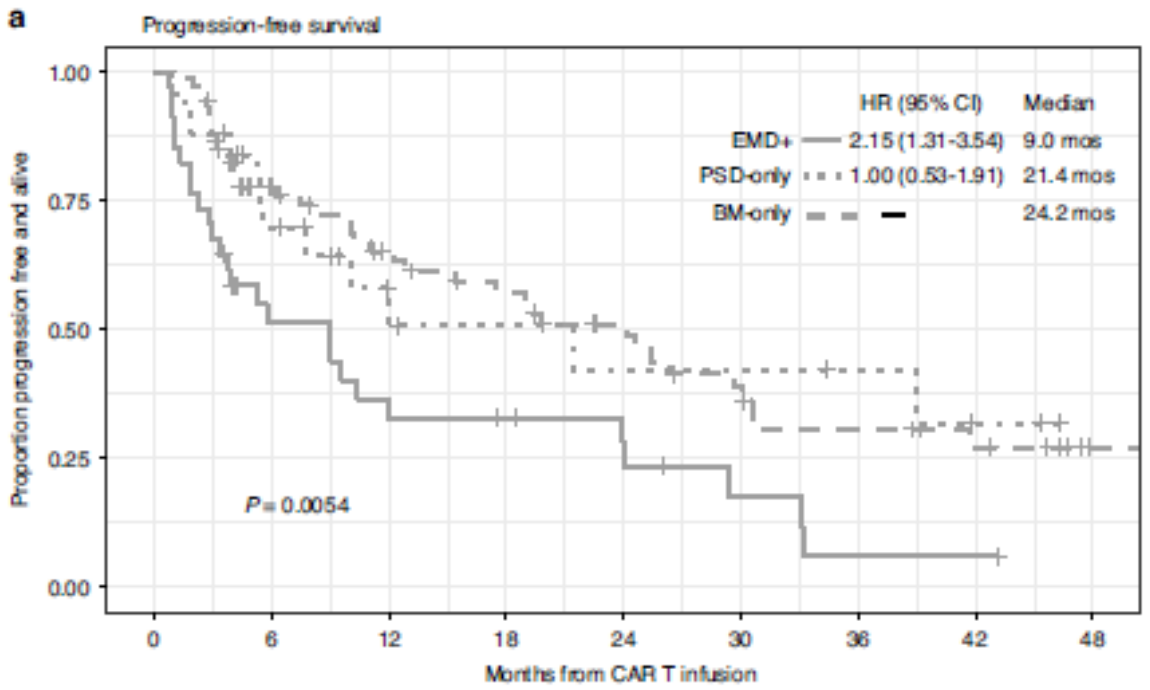
(sum of product or largest perpendicular diameter CM²)

Increased EMD prevalence in post-CART relapse

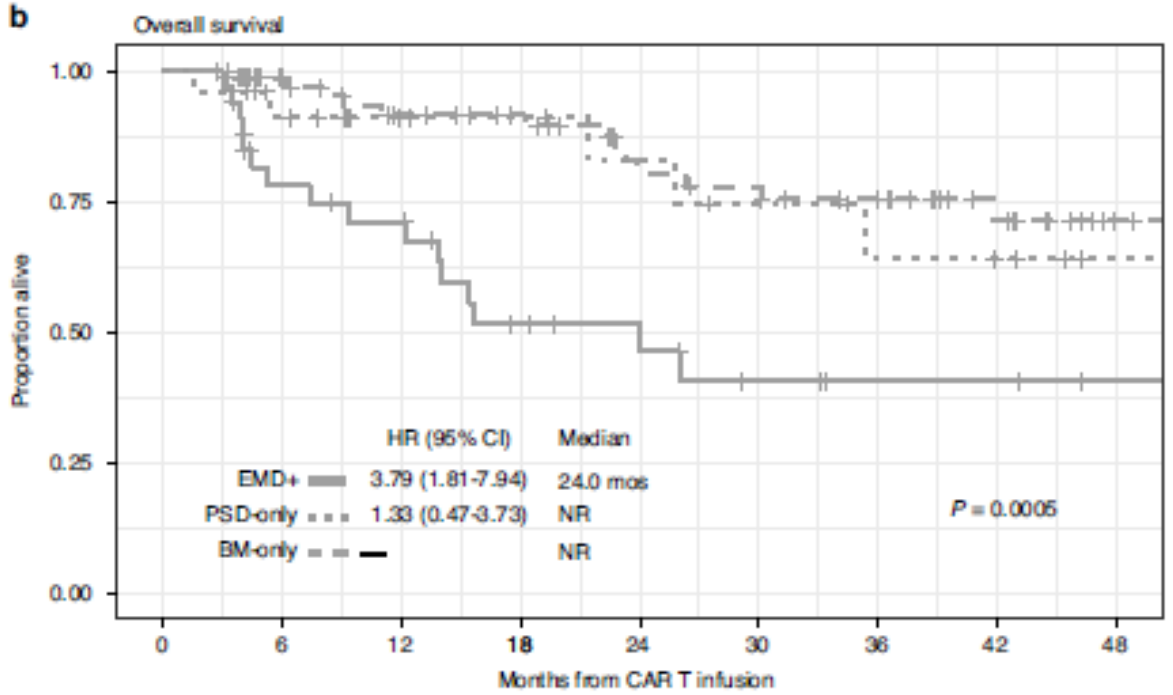
Dima D et al. Blood Cancer J 2024;14:90.

Inferior PFS & OS for MM patients with true EMD treated with CART, compared to para-skeletal / BM only

PFS

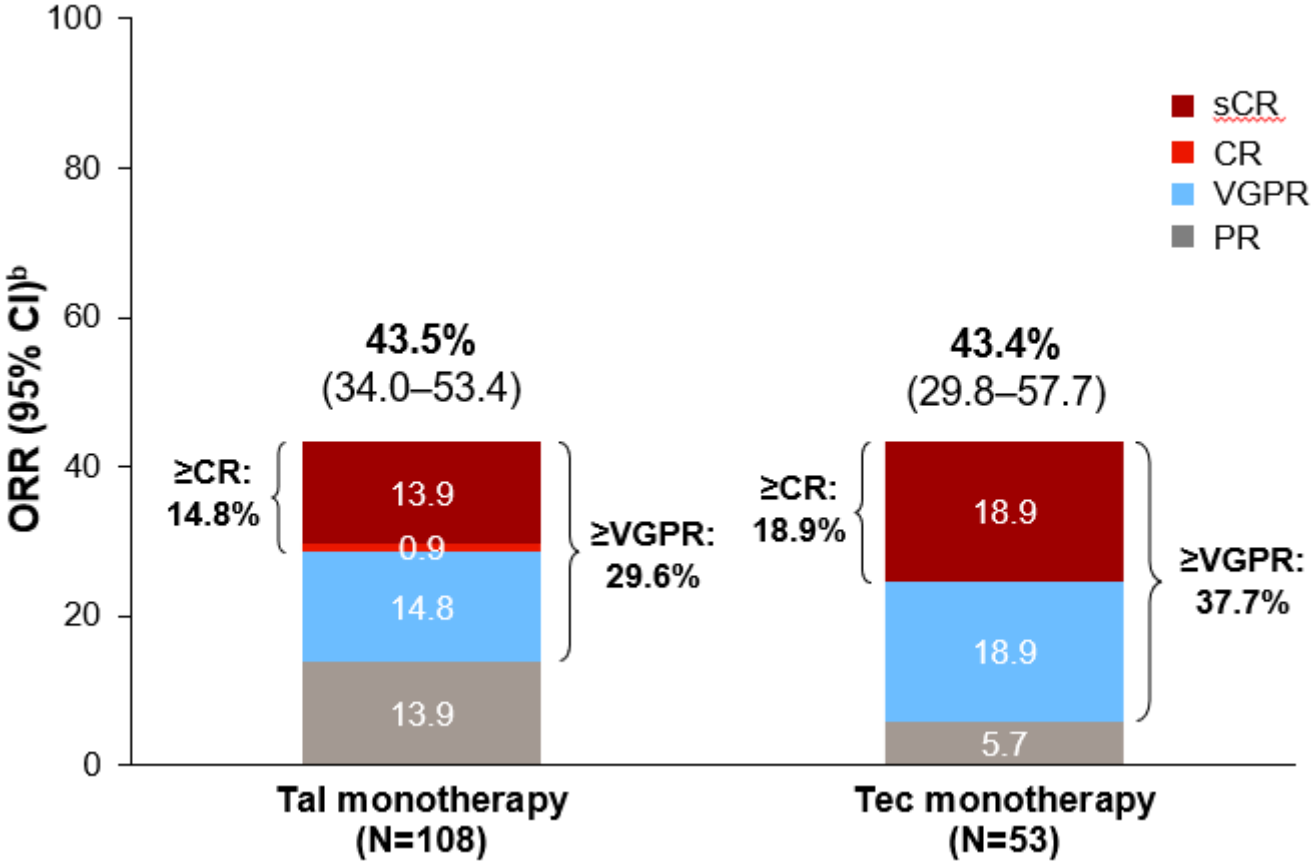


OS



Dima D et al. Blood Cancer J 2024;14:90.

EMD response to BisAb monotherapy: Teclistamab or Talquetamab



Data on file, JnJ.

Response rates with novel immunotherapies and ADCs in patients with RRMM

	EMD in real-world studies of CAR-T				EMD in clinical trials of bispecific antibodies and ADCs							
Therapy	**Ide-cel**		**BCMA CAR-T**		**Teclistamab**		**Elranatamab**		**Talquetamab[a]**		**Belantamab mafodotin**	
EMD Type and Comparator	True EMD[b] (n=84)	Non-EMD (n=267)	True EMD[c] (n=47)	Non-EMD (n=105)	True EMD[d] (n=28)	Non-EMD (n=165)	True and paramedullary EMD[e] (n=39)	Non-EMD (n=84)	True EMD[d] (n=154)	Non-EMD (n=41)	EMD undefined (n=22)	Total population (n=97)
ORR	52%	82%	58%	96%	35.7%	68.6%	38.5%	71.4%	41.4	69%	5%	32%

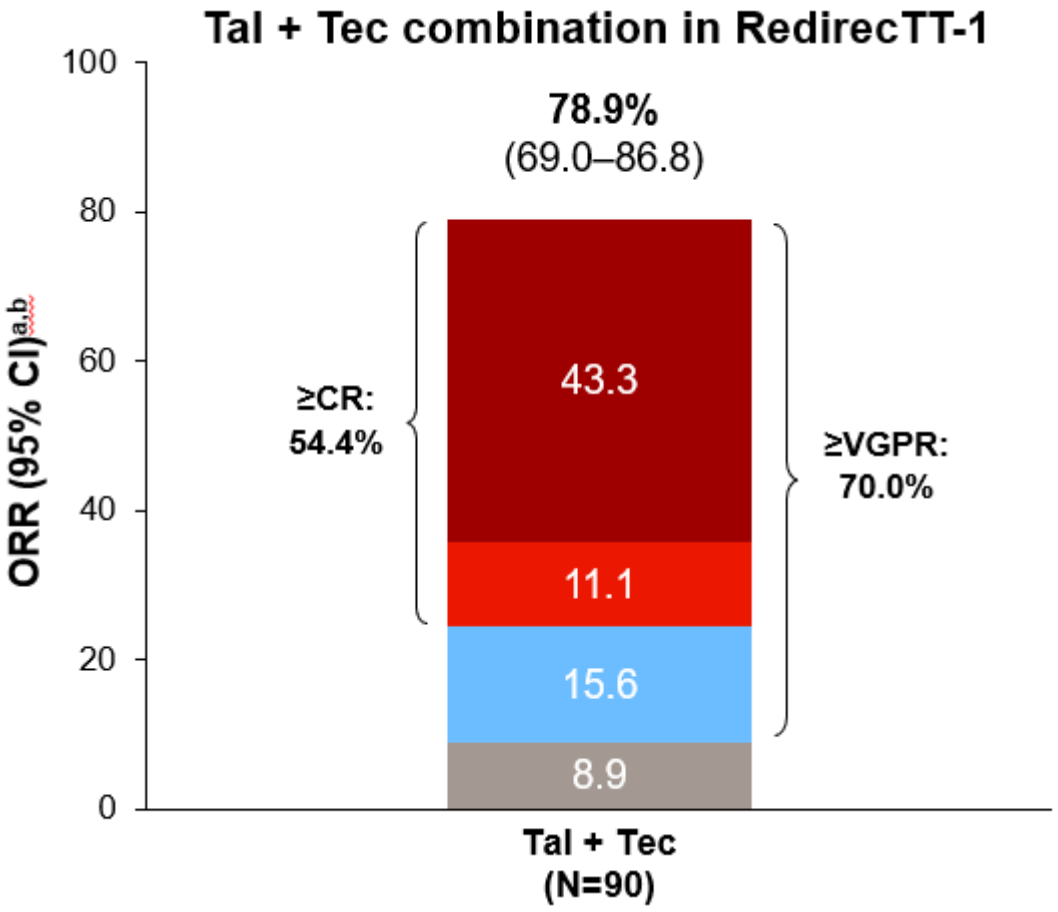
[a]0.8 mg/kg biweekly dose; [b]Patients with both true EMD and paramedullary EMD were classified as true EMD, and patients with paramedullary EMD were classified as non-EMD; [c]defined as bone-independent (only) tumors of plasma cells growing at anatomical sites outside of the bone marrow detected within 30 days of CAR T-cell infusion; [d]defined as soft-tissue plasmacytomas that were not associated with bone; [e]defined as the presence of any plasmacytoma (extramedullary and/or paramedullary with a soft-tissue component)

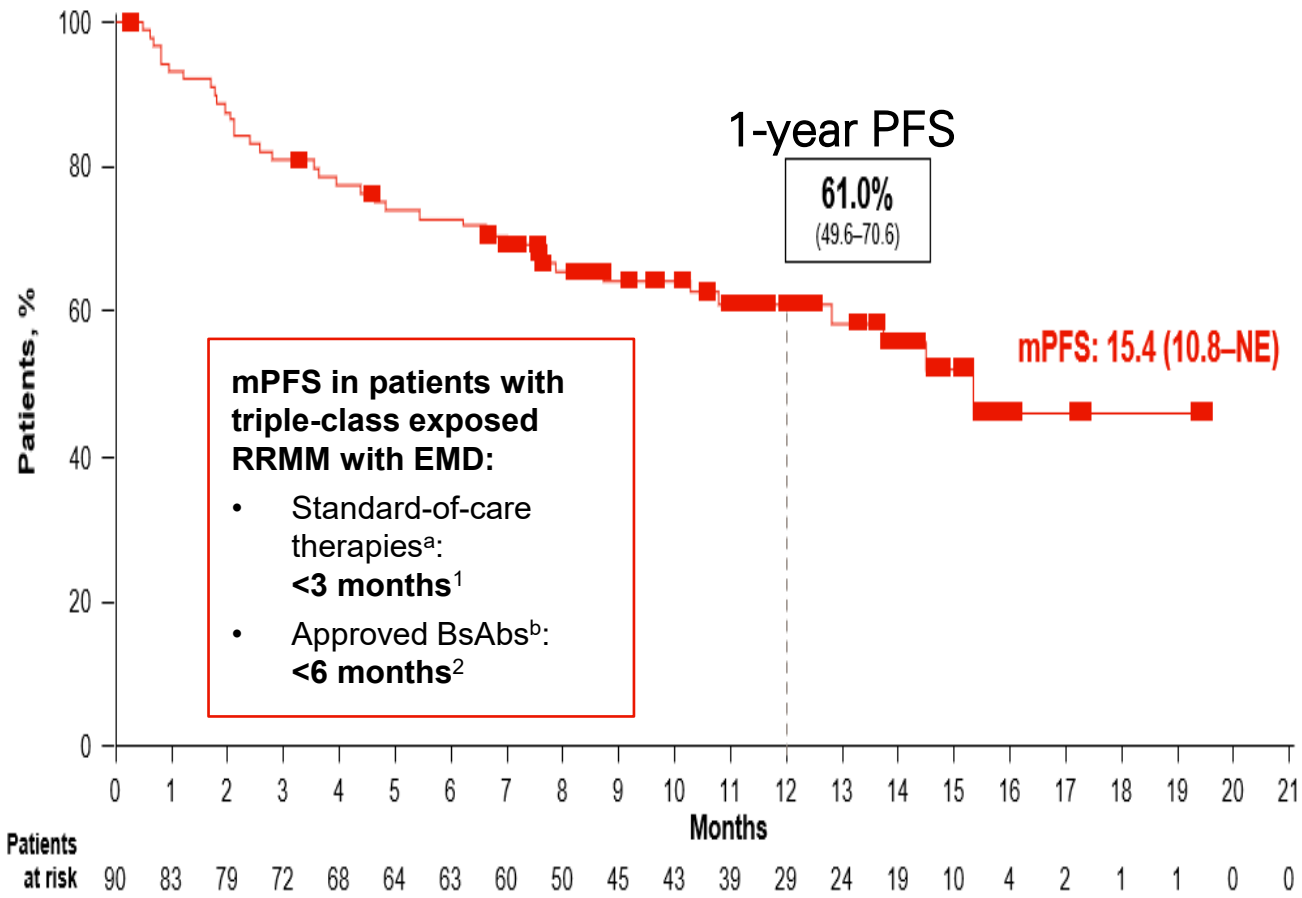
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; EMD, extramedullary disease; ide-cel, idecabtagene vicleucel; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma.

Dima D, et al. Blood Cancer J 2024;14:90. Zanwar S, et al. J Hematol Oncol 2024;17:42. Moreau P et al. N Engl J Med 2022;387:495-505. Lesokhin AM et al. Nat Med 2023;29:2259-2267

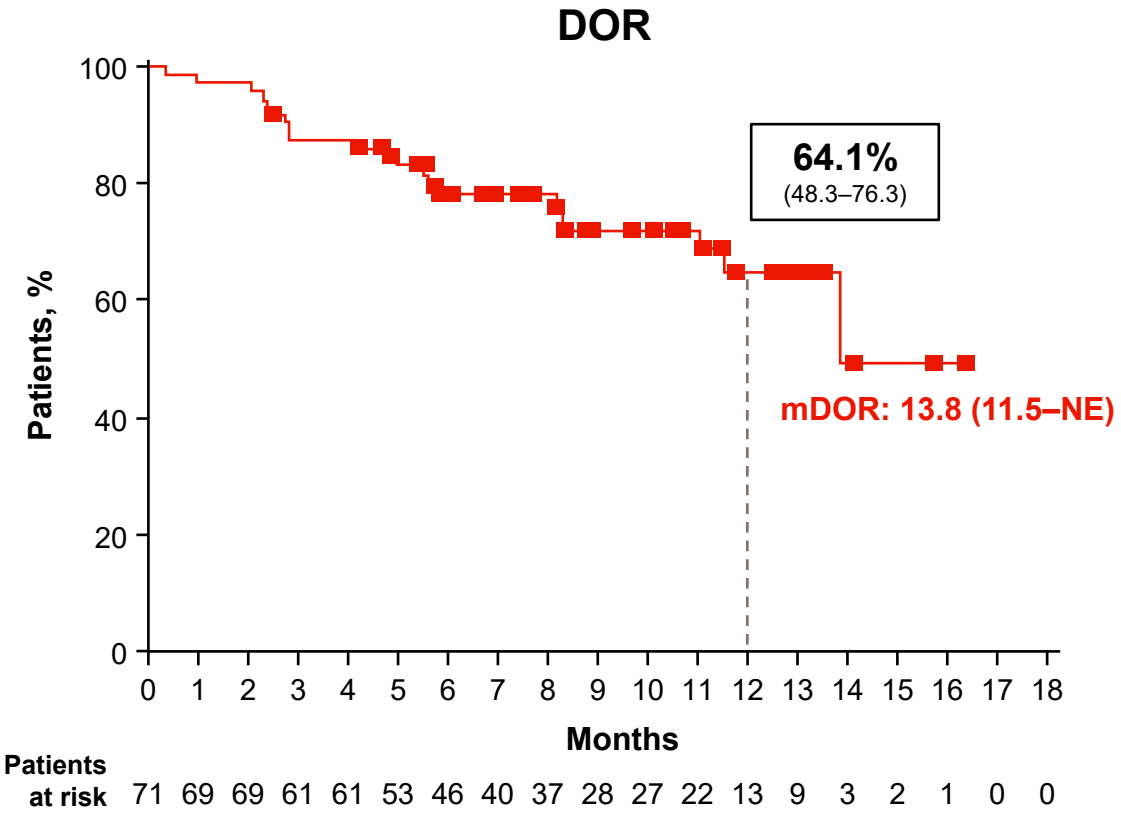
Chari A, et al . Lancet Haematol 2025;12:e269-e281. Lonial S, et al. Cancer 2021;127:4198-4212.

RedirecTT-1 Phase 2 Tal + Tec: Dual-Antigen Targeting in Patients With True EMD Led to Higher ORR and ≥CR Rate

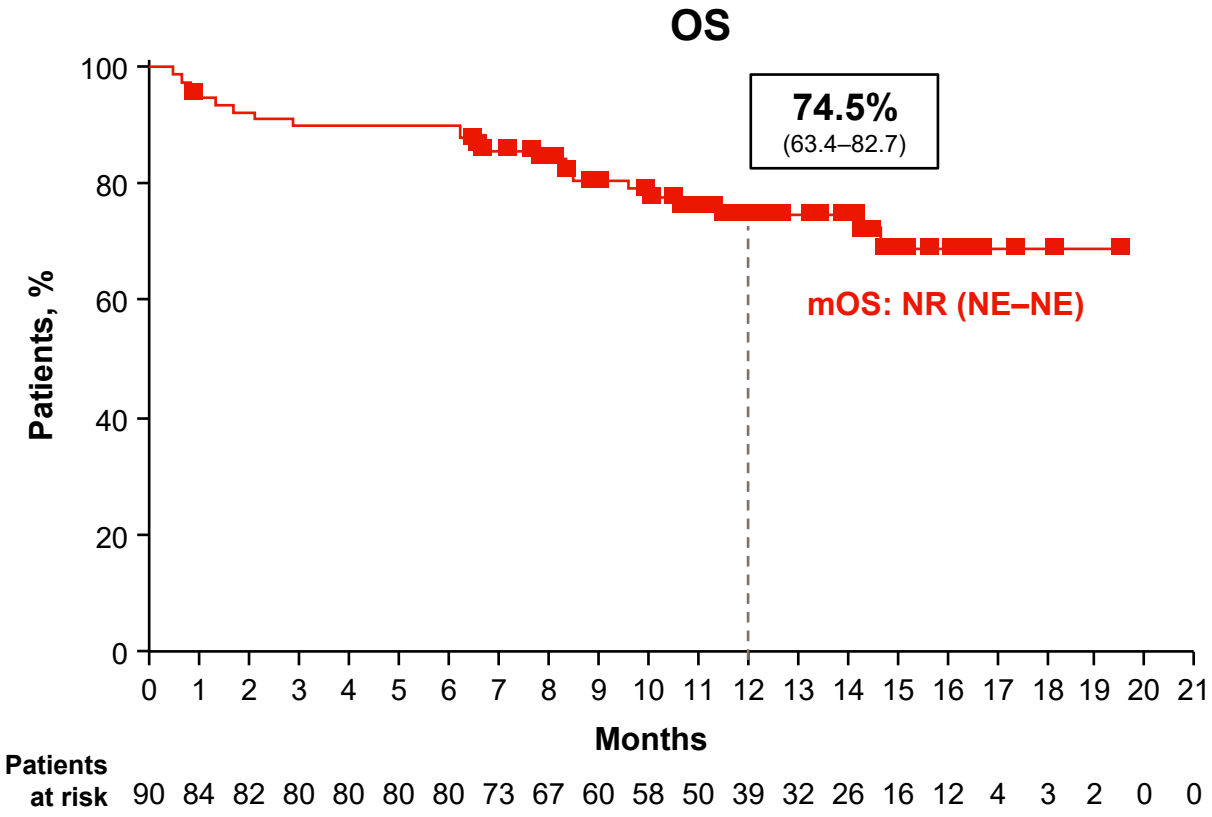




RedirecTT-1 Phase 2 Tal + Tec: Durable Responses and Prolonged Survival in Patients With True EMD



Estimated 12-month freedom from progression rate was 64%



Estimated 12-month OS rate was 75%

Data cut-off date: March 18, 2025. Median follow-up: 12.6 months.
Medians and rates shown with 95% CIs. NR, not reported.

Presented by S Kumar at the European Hematology Association (EHA) 2025 Hybrid Congress; June 12–15, 2025; Milan, Italy

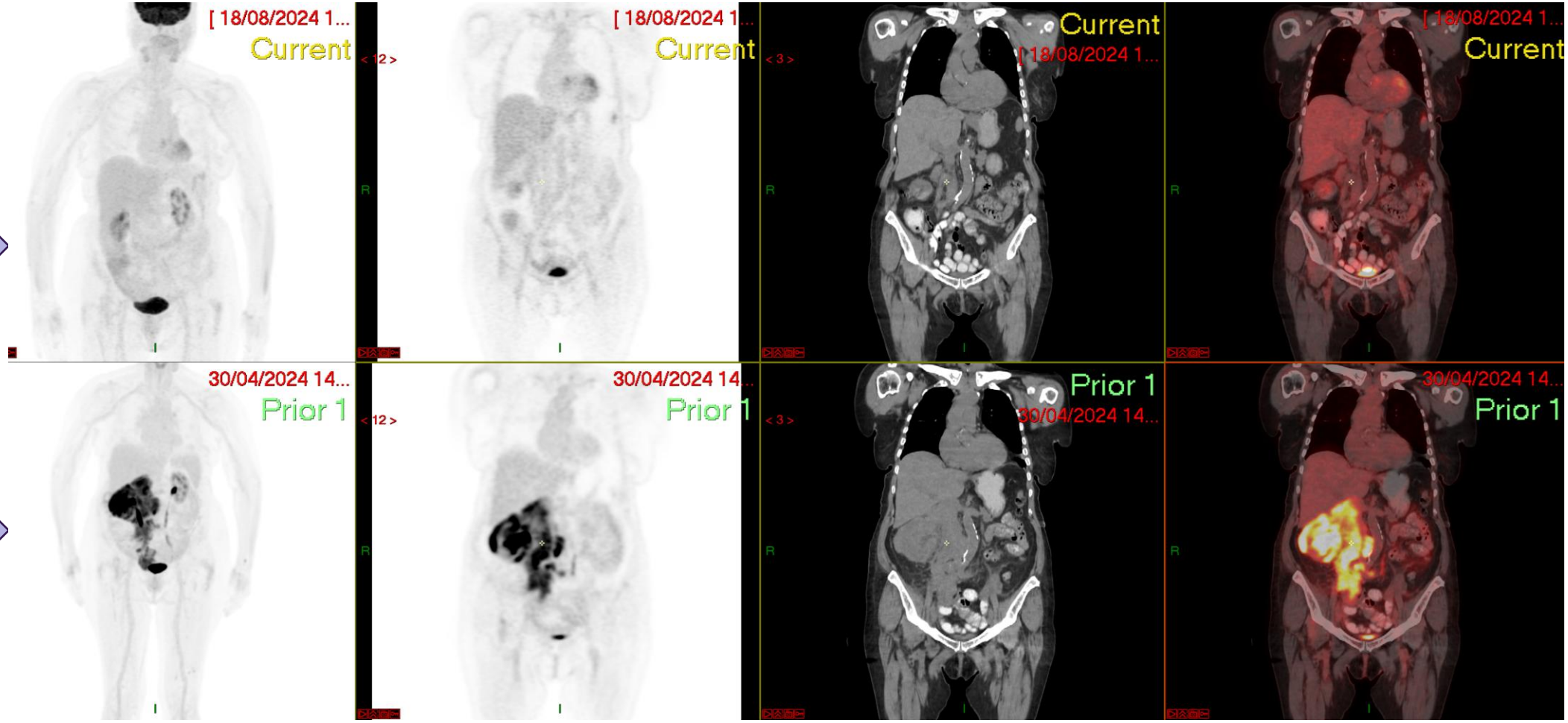
Case follow-up

→ Penta refractory patient + BCMA-ADC refractory, extensive EMD

➢ Patient enrolled into RedirecTT-1 study
achieved CR / MRD negativity, maintained until now (>1 years)

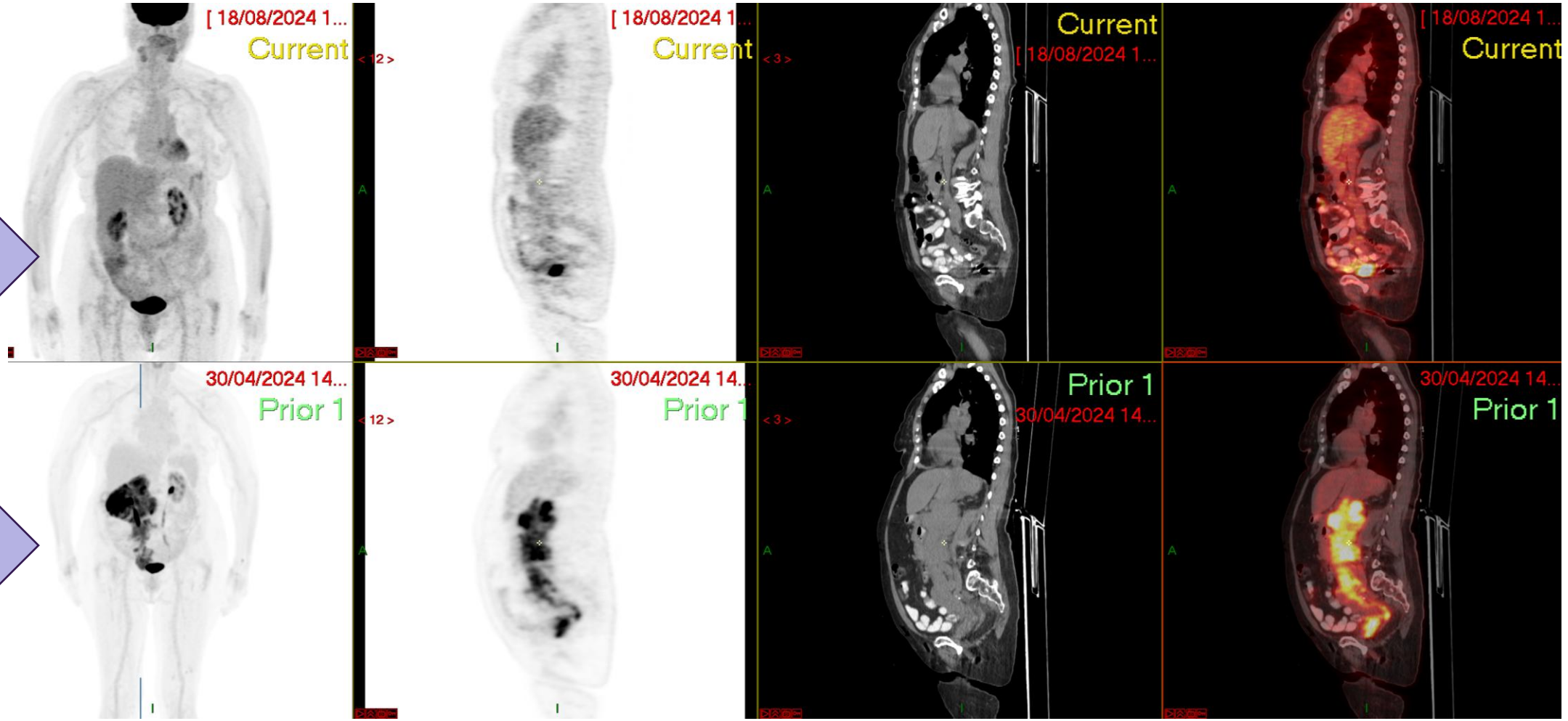
After 4 months of Tal+Tec

At study enrollment 30-APR-2024



After 4 months of Tal+Tec

At study enrollment 30-APR-2024



Case #2

- A 68 YO man, diagnosed with myeloma in 2022, high risk – del17p & t(11:14).
- After 7 LOT, including bortezomib, lenalidomide, ASCT, carfilzomib, pomalidomide, venetoclax, Talquetamab, Teclistamab
- Now with aggressive relapse including extensive bone, paraskeletal and EMD, cord compression at L3
- Patient is bed-ridden, hospice care
- Biopsy from sternal mass reveals a BRAF-V600E mutation with a high allele frequency, mutation associated with MAPK alterations
- Patient was initiated BRAF inhibitor + MEK inhibitor (Vemurafenib + Trametinib)

Myeloma EMD - Take home messages

- EMD an aggressive form of myeloma, with poor prognosis
- EMD should be distinguished from para-skeletal disease
- May occur at myeloma presentation, more frequently at relapse, frequency is increasing
- Detection may be affected by imaging modality employed
- Complex biology, contributing to loss of anchoring to BM and independence from BM
- Patients tend to have high risk cytogenetics, and inherent drug resistance
- Until recently, PFS was <6 mo and OS <1yr for EMD at relapse
- Outcomes remain compromised with CART & BisAb monotherapies compared to non-EMD
- Dual targeting with Tal+ Tec in phase 2 RedirecTT-1 trial yielded deep and durable responses

Plasma Cell Leukemia (PCL)

- **Primary PCL** is the most aggressive disorder among plasma cell malignancies, being characterized by intrinsic genomic instability, high proliferative activity, frequent extramedullary plasmacytomas, and poor prognosis
- Revised doagnostic criteria (IMWG) - ≥ 5% circulating plasma cells (by morphology)

	Criteria	Incidence of PCL
Kyle et al.1974	Circulating plasma cells ≥ 20% ǂ AND Absolute count plasma cell count ≥ 2×10^9/L*	1-2%
IMWG 2013	Circulating plasma cells ≥ 20% ǂ OR Absolute count plasma cell count ≥ 2×10^9/L*	2%
IMWG 2021	Circulating plasma cells of ≥5%ǂ	3-4%

- Secondary PCL is leukemic evolution of pre-existing Myeloma, occurs in ~1% of RRMM, very short OS (1-2mo), more similar to HR RRMM

Carlos Fernández de Larrea et al Blood Cancer Journal 2021; Gong et al Current Oncology Reports 2024

Table 1. Comparison of some clinical and laboratory characteristics in patients with newly diagnosed multiple myeloma, primary plasma cell leukemia, and secondary plasma cell leukemia

	NDMM	PPCL	SPCL
Younger patients	+/−	++	+
Anemia	+	++	++
Thrombocytopenia	+/−	++	++
Hypercalcemia	+	++	++
Renal impairment	+	++	++
High LDH	+	+++	++
ß2-Microglobulin	+	+++	+
Lytic lesions	+++	++	+++
Bone marrow infiltration	++	+++	+++
Extramedullary involvement	+/−	++	+++
Phenotype CD20+	+/−	++	+/−
Phenotype CD56+	++	+/−	++
Light chains, non-secretory	+	++	++
t(11;14)	+	++	+/−
−17/del(17p13)	+	++	+++
del(1p32)/+1q21	++	++	+++
Hyperdiploidy	++	+/−	+

del, deletion; LDH, lactate dehydrogenase; NDMM, newly diagnosed multiple myeloma; PPCL, primary plasma cell leukemia; SPCL, secondary plasma cell leukemia; t, translocation.

PPCL:

Clinical Presentation:

- Younger
- High LDH and b2M
- Frequent (50%) Light chain or non-secretory disease
- Higher tumor burden with higher incidence of anemia, thrombocytopenia, hypercalcemia, renal failure
- Higher incidence of EMD, CNS

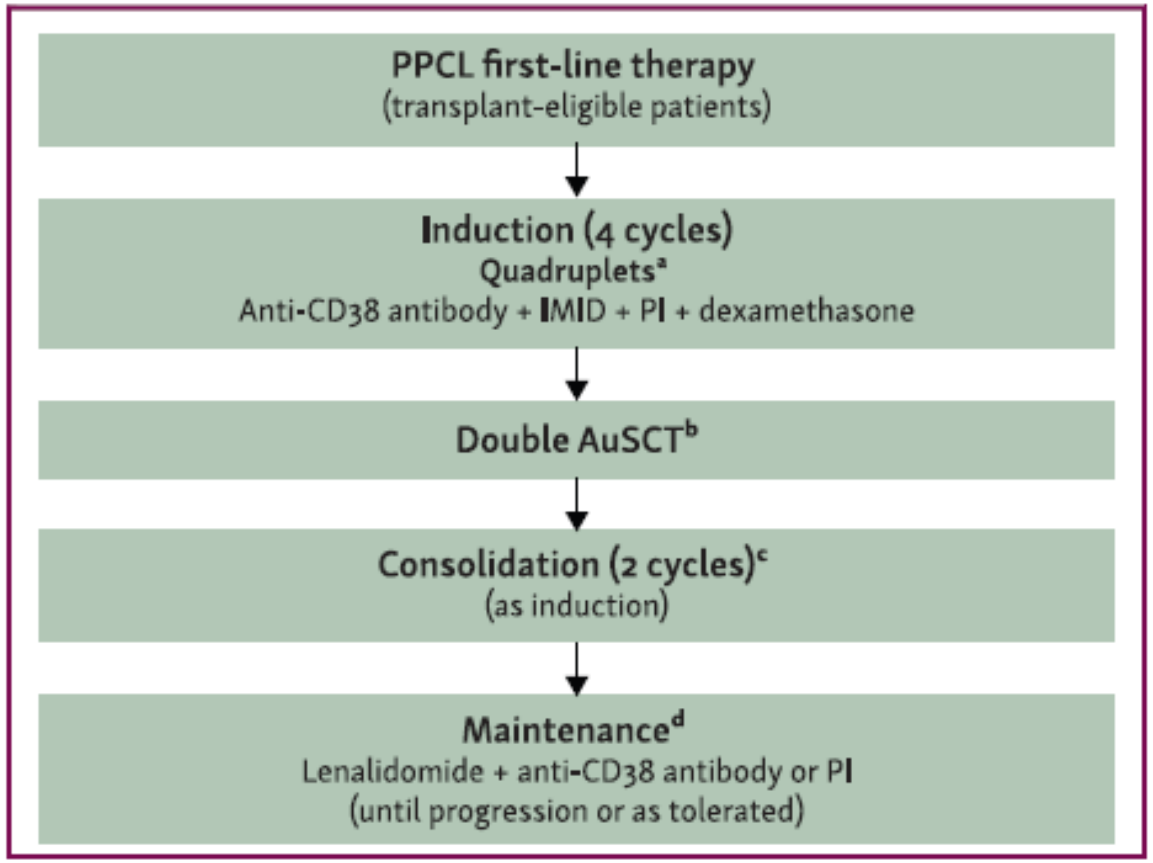
Biological characteristics

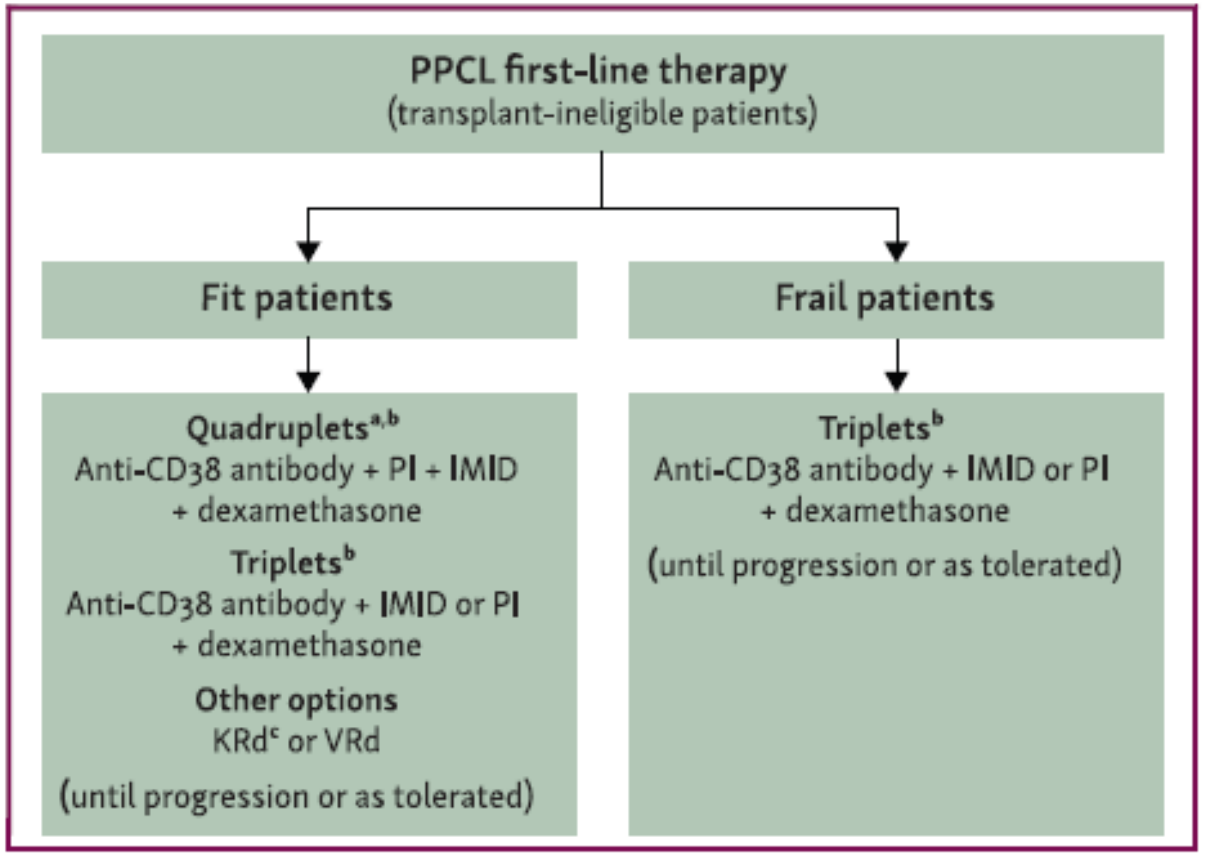
- Del17p, complex karyotype, hypodiploidy, chromosome 1 involvement
- IgH translocations (~87%)

  t(11,14) ~50% / t(14,16) ~ 16-47% / t(4,14) ~ 6-25%
- TP53 mutations or bi-allelic inactivation
- Double hit profile

https://doi.org/10.1016/j.annonc.2025.01.022

EMN recommendations for first-line therapy





https://doi.org/10.1016/j.annonc.2025.01.022

EMN recommendations for RR PPCL

Relapsed/Refractory PPCL

↓

- Use combinations with drugs not employed at diagnosis; i.e., new generation IMID and PI + dexamethasone + monoclonal antibodies or 'lymphoma-like' chemotherapy[a]
- CAR T or bispecific antibodies, if available
- Consider AlloSCT after complete remission following second-line therapy, for eligible patients if a donor is available
- Venetoclax ± other drugs, in patients with t(11;14)

Future directions?

- PPCL is a separate biological entity, yet, what is the overlap with ultra high risk MM
- Novel approaches:
  - Selinexor, venetoclax
  - CART, bispecifics (Tal+Tec???)

…. Data is limited, retrospective studies, low numbers of patients

Myeloma with CNS disease

- Multiple myeloma with CNS involvement is a rare form of EMD characterized by plasma cell infiltration of the CNS, meninges or cerebrospinal fluid (CSF)
- Very rare at diagnosis and around a fifth of extramedullary relapses, typically two or three years after the initial MM diagnosis .
- Diagnosis is based on imaging (mostly MRI), CSF analysis, or brain biopsy; clinical suspicion may be challenging in some cases
- CNS-MM has a particularly aggressive course, with very short PFS and survival < 1 year in most series
- Most data are retrospective series
- IMiD-based systemic therapy, intrathecal and radiation therapy appears to provide the best treatment outcome

Egan PA et al. Haematologica. 2020 Jul;105(7):1780-1790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