21-22 novembre 2025

PharmacON

Roma, Hilton Airport 2025

Come cambia la farmacia oncologica tra terapie avanzate, modelli gestionali e aspetti regolatori

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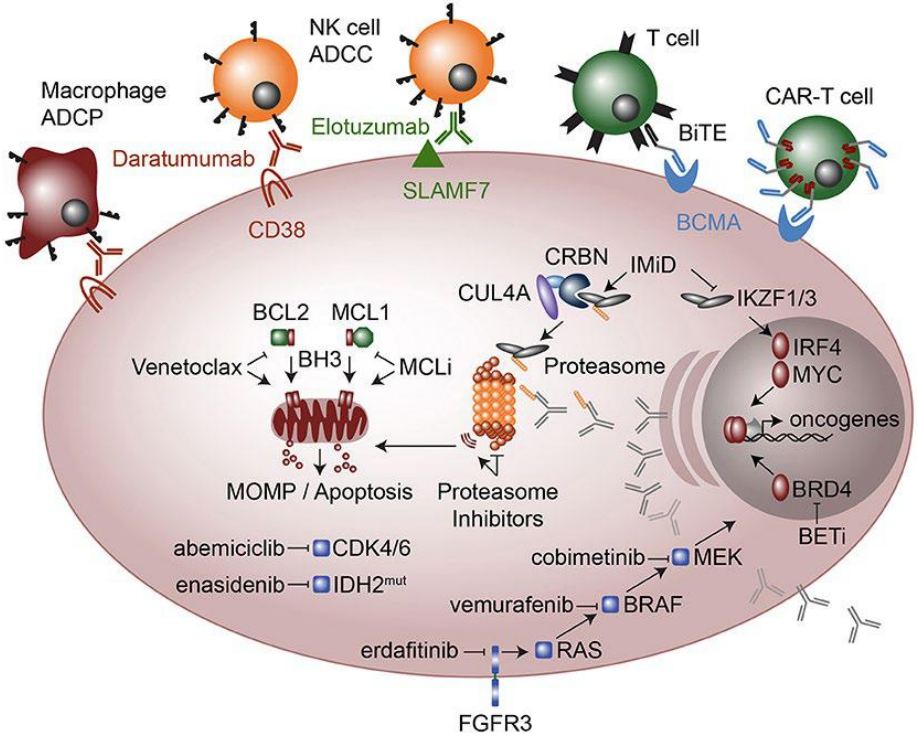
Nuove Frontiere Terapeutiche Nel Trattamento delle Patologie Ematologiche: Focus on Mieloma Multiplo

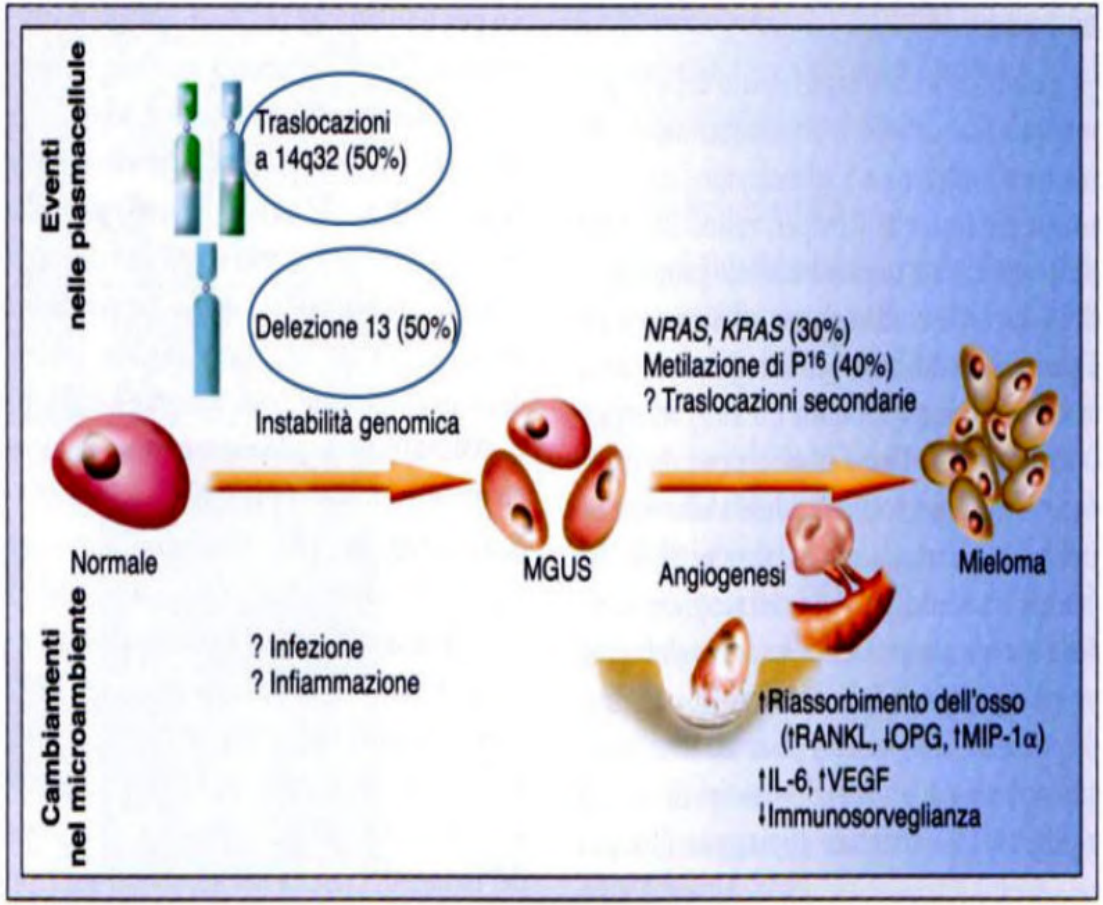


MIELOMA MULTIPLO

Il Mieloma Multiplo (MM)è una neoplasia delle plasmacellule che rappresenta
- 1%-1.8% di tutte le malattie neoplastiche e il 10-15% delle neoplasie ematologiche con una incidenza stimata in Europa di 4.5-6.0/100 000/anno.
- E' caratteristica dei soggetti anziani, con un' età mediana alla diagnosi di circa 70 anni, ~ 30% dei pazienti con più di 75 anni e <10% con età compresa fra 20 e 40 anni.
-Non si conoscono fattori di rischio certi associati alla sua insorgenza
- Il MM attivo o sintomatico è preceduto nella maggior parte dei casi da una fase di "gammopatia monoclonale di incerto significato" (MGUS) e da una fase di "mieloma multiplo indolente" o smouldering (SMM), entrambe fasi asintomatiche e pertanto spesso non clinicamente evidenziate.
- Nonostante l'incremento della sopravvivenza dei pazienti negli ultimi 20 anni, con una OS a 5 anni pari al 61.1%, solo il 10-15% raggiunge una sopravvivenza paragonabile a quella della popolazione generale.

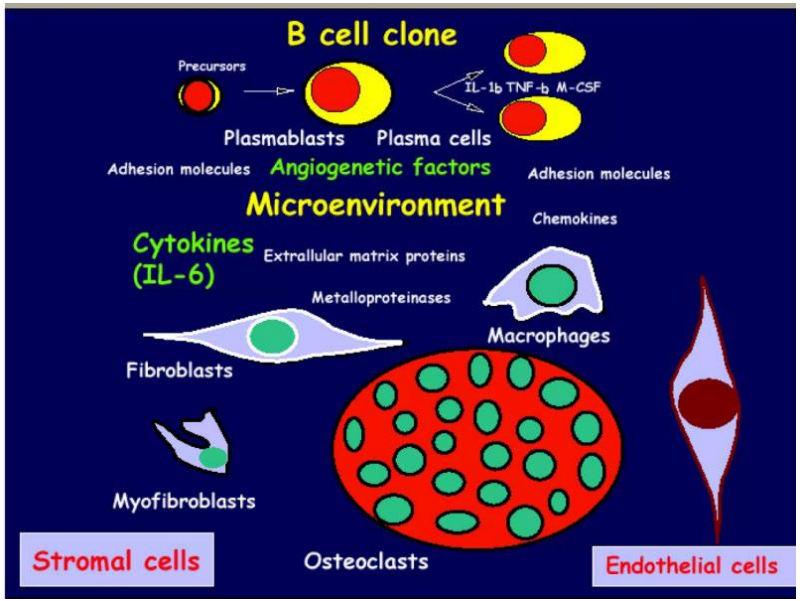
DISCRASIE PLASMACELLULARI

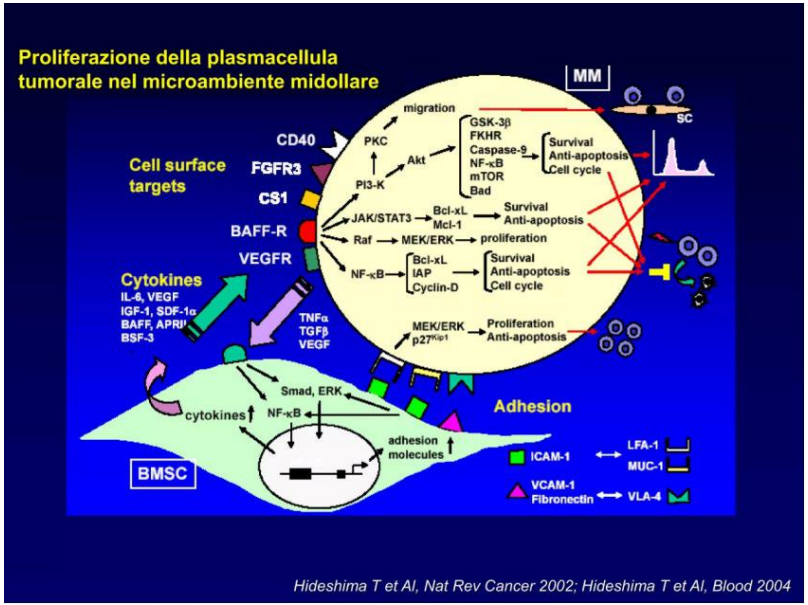
Diagnosi	Definizione
MGUS (non-IgM)	• Componente monoclonale (non IgM) < 3 g/dl • Plasmacellule midollari monoclonali < 10% • Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare
MGUS a catene leggere (light chain)	• Rapporto catene leggere libere sieriche alterato (<0.26 o >1.65) con incremento relativo nella catena kappa o lambda • Assenza di catena leggera presente all'immunofissazione • Proteinuria monoclonale < 500 mg/die • Plasmacellule midollari monoclonali < 10% • Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare
SMM plasmacellule monoclonali midollari	• Componente monoclonale IgG o IgA ≥ 3g/dl e proteinuria monoclonale ≥ 500 mg/die e/o 10-60% di • Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare
MM	• ≥10% di plasmacellule monoclonali midollari o biopsia diagnostica per plasmocitoma osseo o solitario e almeno 1 dei seguenti Myeloma Defining Events: – Ipercalcemia (calcio sierico >0.25 mmol/L/1 mg/dl rispetto al limite superiore o > 2.75 mmol/L/11 mg/dl) – Insufficienza renale: clearance della creatinina < 40 ml/min o creatinina sierica >177 µmol/l (>2 mg/dl) – Anemia: riduzione dei valori di Hb > 2 g/dl rispetto al limite inferiore normale o Hb < 10 g/dl – Lesioni ossee: 1 o più lesioni osteolitiche in radiografia convenzionale, tomografia computerizzata (TC) o tomografia ad emissione di positroni (PET)- TC – Plasmacellule monoclonali midollari ≥60% – Rapporto tra catene leggere libere sieriche (catena coinvolta / non coinvolta) > 100 – ≥1 lesione focale in RMN
Plasmocitoma solitario	• Plasmacellule monoclonali su lesione ossea solitaria o tessuto molle • Assenza di plasmacellule monoclonali su midollo emopoietico • Assenza di lesioni radiologiche (eccetto la lesione solitaria primitiva) • Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare
Plasmocitoma solitario con minima invasione midollare	• Plasmacellule monoclonali su lesione ossea solitaria o tessuto molle • Plasmacellule monoclonali midollari <10% • Assenza di lesioni radiologiche (eccetto la lesione solitaria primitiva) • Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare



Proliferazione delle cellule di mieloma e progressione della malattia

Proliferazione delle Plasmacellule nel Microambiente Midollare





Hideshima T et Al, Nat Rev Cancer 2002; Hideshima T et Al, Blood 2004

nature reviews clinical oncology

https://doi.o

Evidence-based guidelines

EHA–EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma

A list of authors and their affiliations appears at the end of the paper

MIELOMA MULTIPLO

Plasmacellule monoclonali midollare >10% o plasmocitoma extramidollare e almeno 1 dei seguenti segni/sintomi di malattia:

- Ipercalcemia (calcio sierico ≥ 11 mg/dl o >1 mg/dl rispetto al limite superiore).
- Insufficienza renale (clearance della creatinina < 40 ml/min o creatinina sierica ≥ 2mg/dl)
- Anemia (Hb > 2g/dl al limite inferiore di norma o Hb < 10 g/dl)
- Lesioni osteolitiche: 1 o più lesioni osteolitiche evidenziate mediante Rx, Tc o PET/TC
- Plasmacellule monoclonali ≥ 60%
- K/L libere sieriche >100
- ≥1 lesione focali evidenziata mediante RMN

Table: ISS Staging and Risk Stratification Systems in Multiple Myeloma[1]

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)	R2-ISS*
I	Serum beta-2 microglobulin (Sβ2M) <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH and Serum LDH ≤ the upper limit of normal	Low-risk: 0 points • Not ISS stage II or III • Serum LDH ≤ the upper limit of normal • del(17p), t(4;14), 1q+: Not detected
II	Not ISS stage I or III	Not R-ISS stage I or III	Low-intermediate risk: 0.5-1 points • ISS stage II or • Serum LDH > the upper limit of normal or • Del(17p) or t(4;14) or 1q+: Detected
III	Sβ2M ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by FISH or Serum LDH > the upper limit of normal	Intermediate-high risk: 1.5-2.5 points • Any combination of high-risk features which equals a score of 1.5-2.5
IV	—	—	High-risk: 3-5 points • Any combination of high-risk features which equals a score of 3-5

FISH = fluorescence in situ hybridization; LDH = lactate dehydrogenase.

*For R2-ISS: Risk factors are assigned a numeric value reflecting their influence on overall survival: ISS-III = 1.5 points, ISS-II = 1 point, del(17p) = 1 point, t(4;14) = 1 point, 1q+ = 0.5 points, and serum LDH > the upper limit of normal = 1 point.[1]

IMS/IMWG consensus on high risk myeloma definition

Del17p
in more than 20% of sorted plasma cells

TP53 mut
(no threshold VAF)

Biallelic Del(1p32)

2 among
- **t(4;14)** or **t(14;16)** or **t(14;20)**
- **Gain/amp 1q**
- **Monoallelic del(1p32)**

β2M ≥5.5mg/L
(if creat <1.2mg/dL)

Avet-Loiseau et al. J Clin Oncol, in print, 2025

Four NDMM risk groups (R2-ISS)

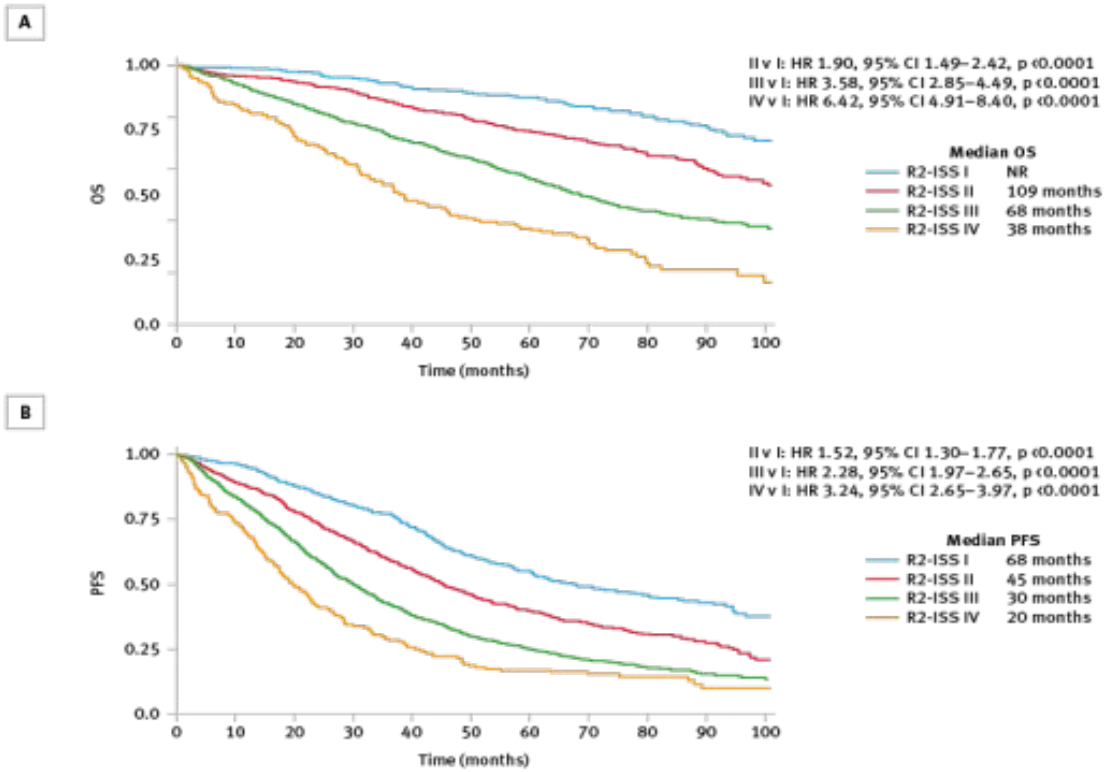
combining serum biomarkers and chromosomal abnormalities.

The risk groups had different OS and PFS respectively using standard-of-care (SOC) therapies

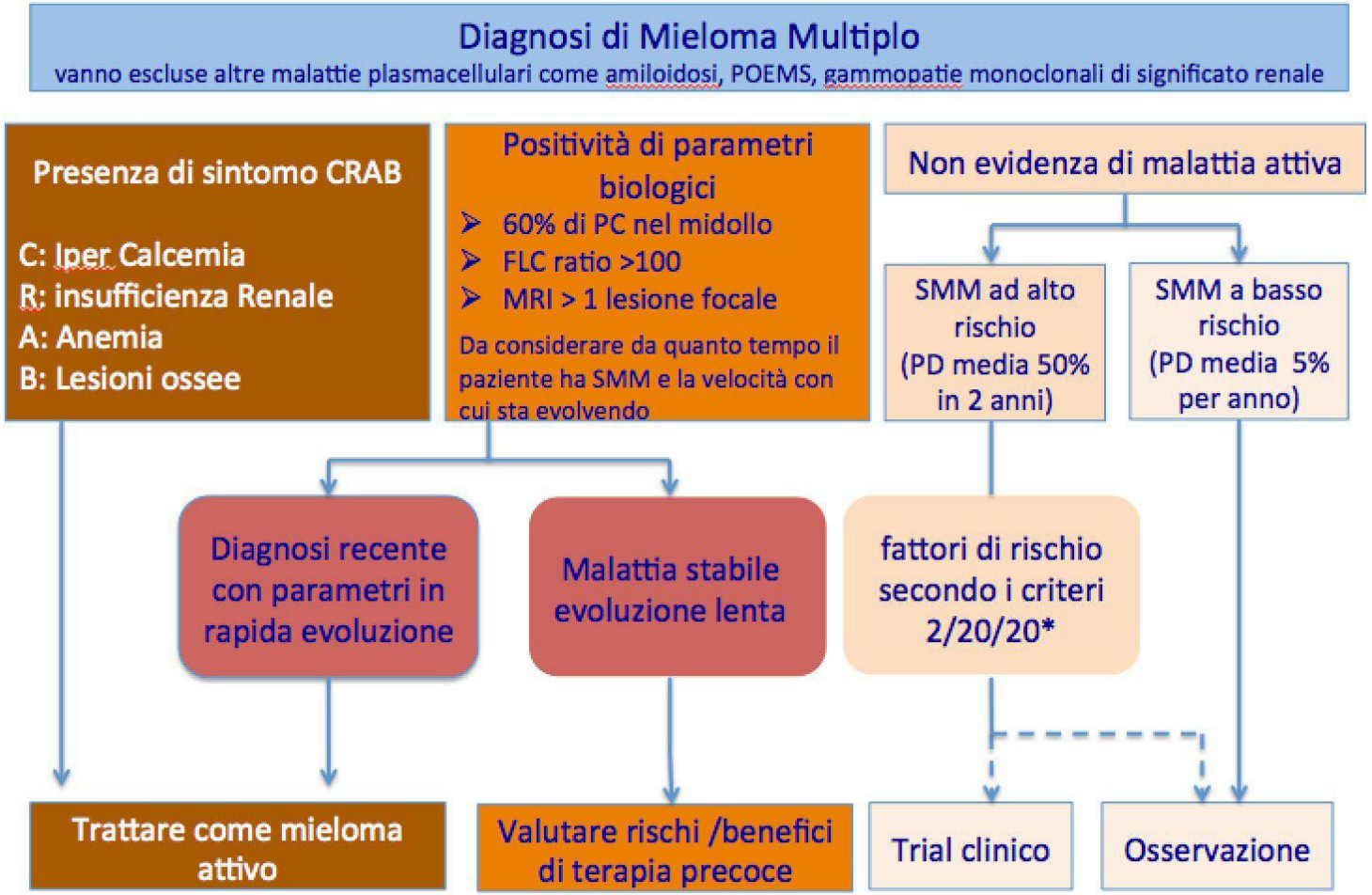
- **low (19.2% of patients)** median **OS not reached**, median **PFS 68 months**
- **low–intermediate (30.8% pts)** median **OS 109.2 monts,** median **PFS 45.5 months**
- **intermediate–high (41.2% pts)** median **OS 68.5 month,** median **PFS 30.2 months**
- **high (8.8% pts)** median **OS 37.9 months,** median **PFS 19.9 months**

- **Circulating plasma cells (CPCs), the evaluation of M protein using mass spectrom, and gene expression profiling are new criteria for evaluation of risk**

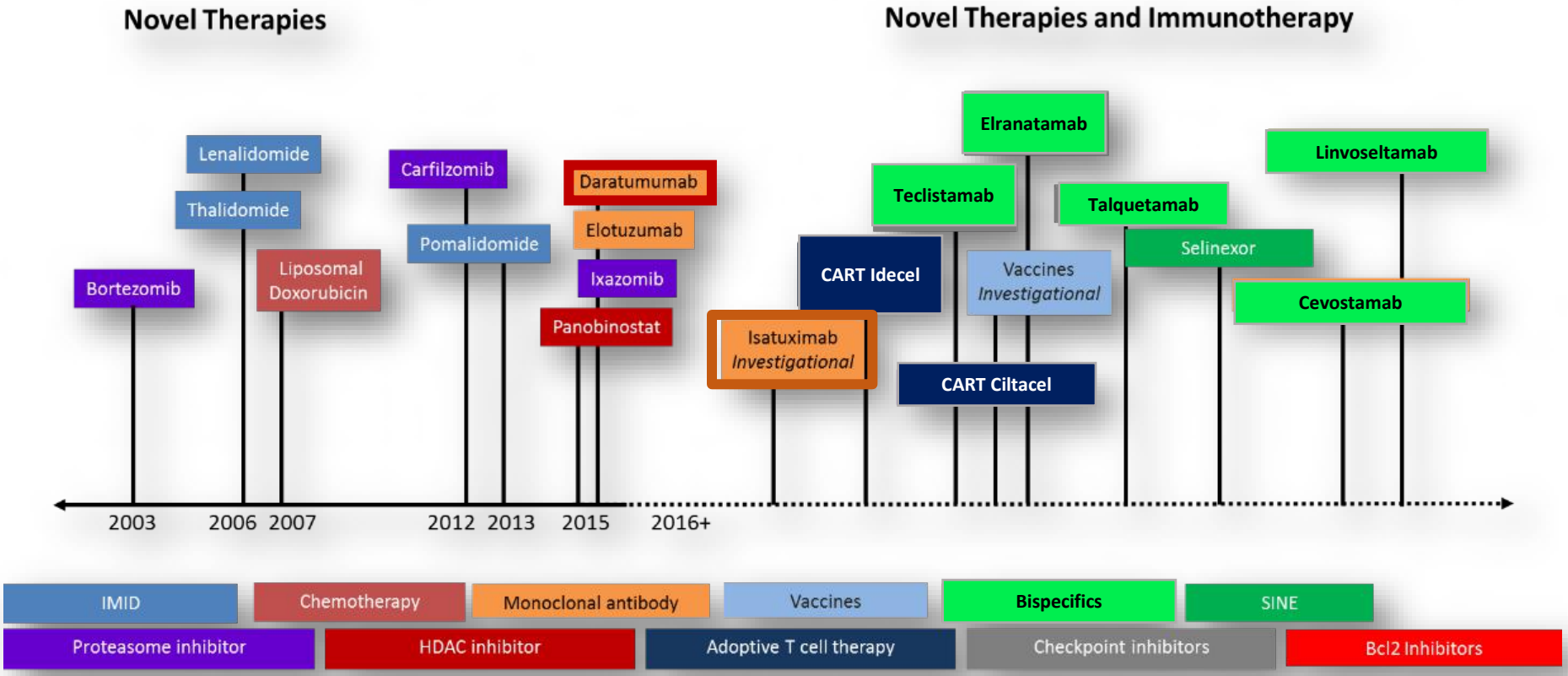
Figura 1. Endpoints nei pazienti del training set stratificati in base all'R2-ISS



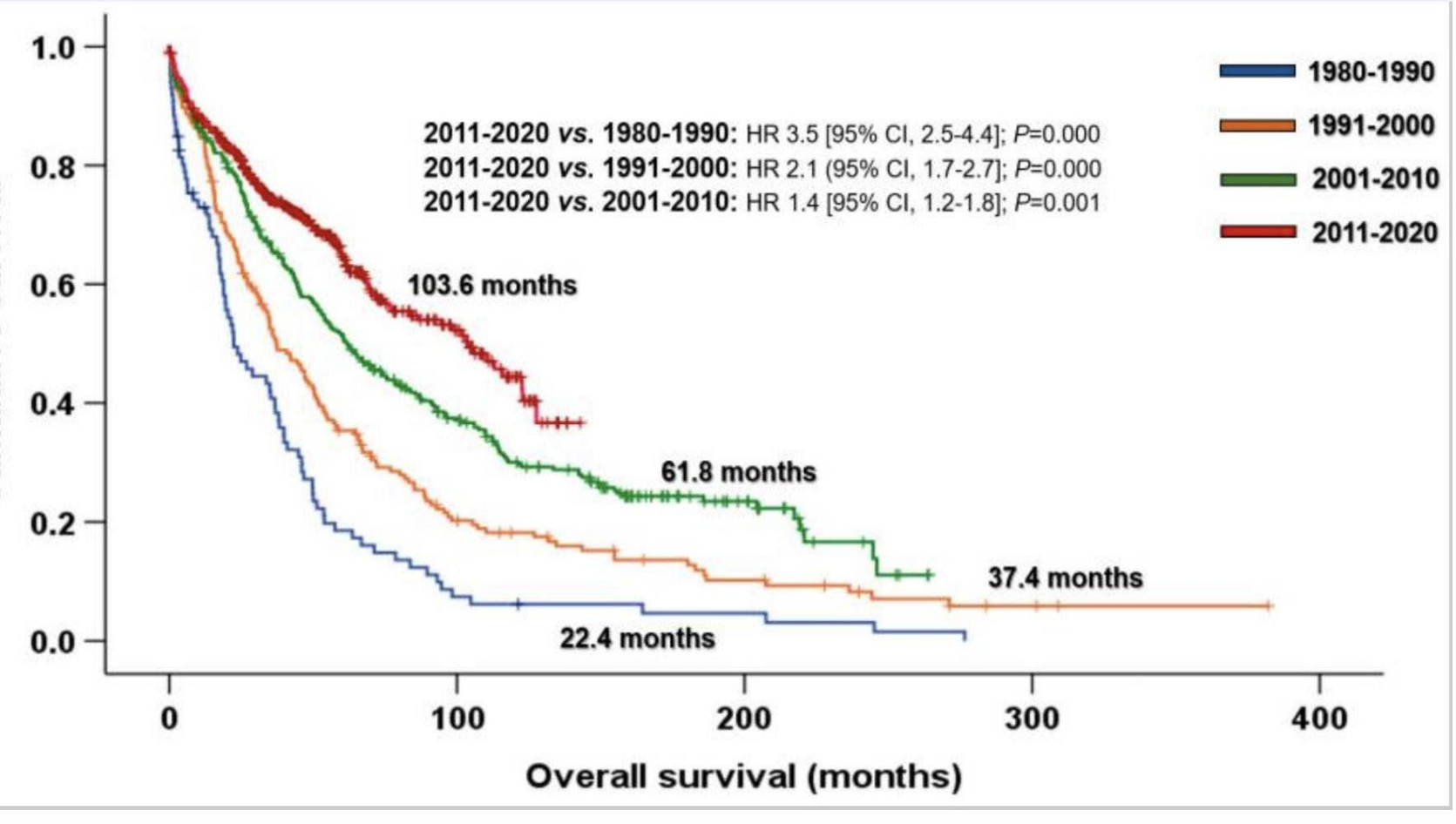
A. OS; B. PFS.
Mod. da D'Agostino M, et al. J Clin Oncol 2022; JCO2102614


Diagnosi di Mieloma Multiplo
vanno escluse altre malattie plasmacellulari come amiloidosi, POEMS, gammopatie monoclonali di significato renale
Presenza di sintomo CRAB
C: Iper Calcemia
R: insufficienza Renale
A: Anemia
B: Lesioni ossee
Positività di parametri biologici
60% di PC nel midollo
FLC ratio >100
MRI > 1 lesione focale
Da considerare da quanto tempo il paziente ha SMM e la velocità con cui sta evolvendo
Non evidenza di malattia attiva
SMM ad alto rischio (PD media 50% in 2 anni)
SMM a basso rischio (PD media 5% per anno)
Diagnosi recente con parametri in rapida evoluzione
Malattia stabile evoluzione lenta
fattori di rischio secondo i criteri 2/20/20*
Trattare come mieloma attivo
Valutare rischi /benefici di terapia precoce
Trial clinico
Osservazione

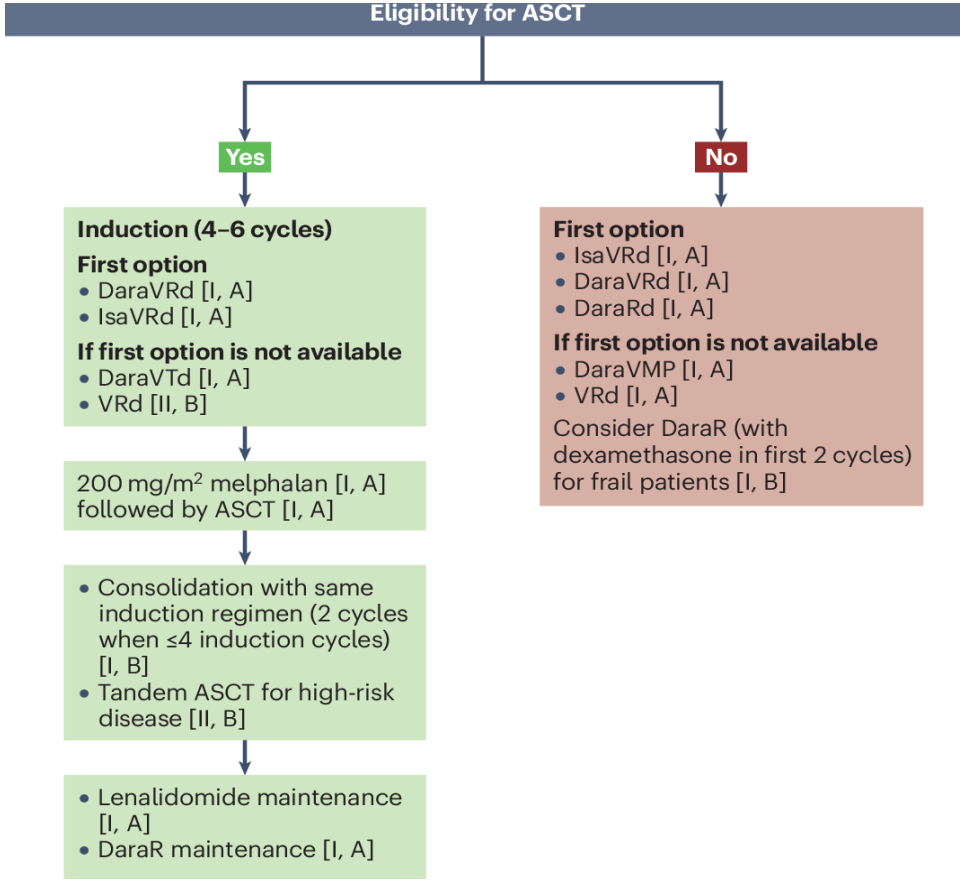
Myeloma Therapy Development



Overall survival by decades

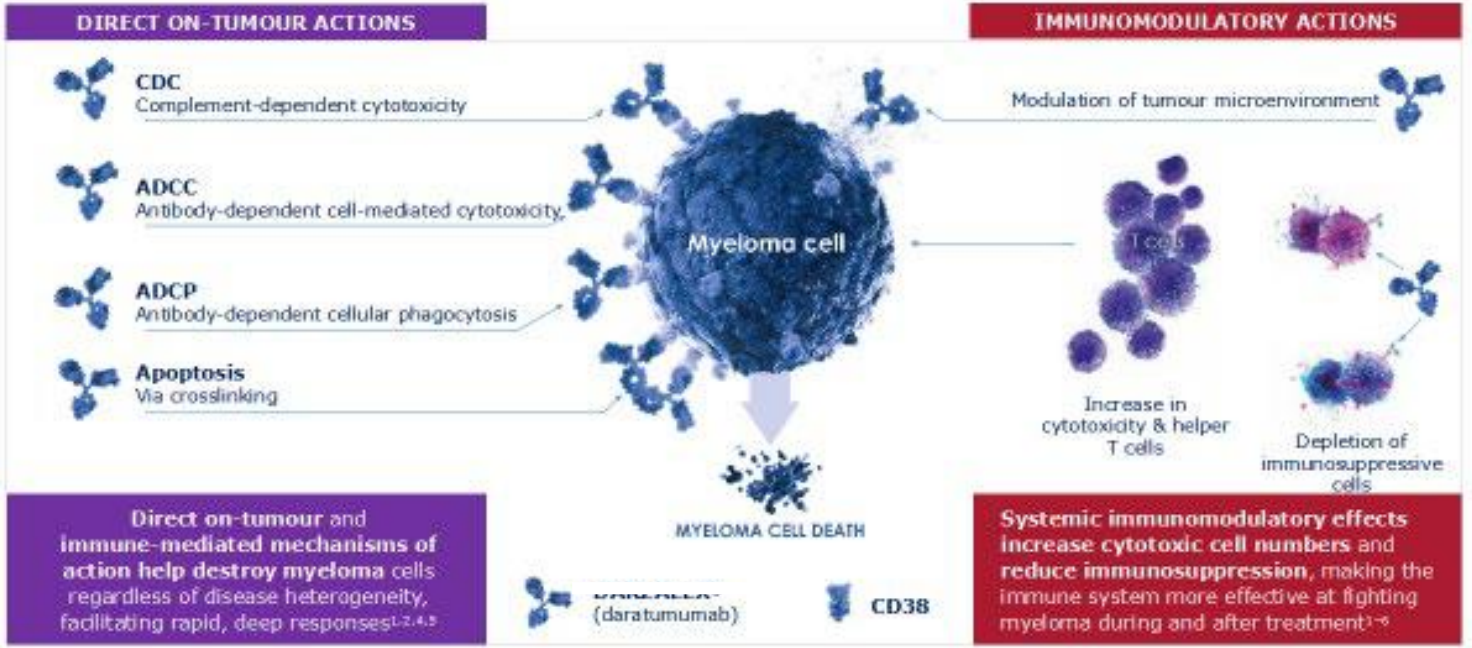


EHA-EMN 2025 Clinical Practice Guidelines Recommendations for MM front-line therapy.



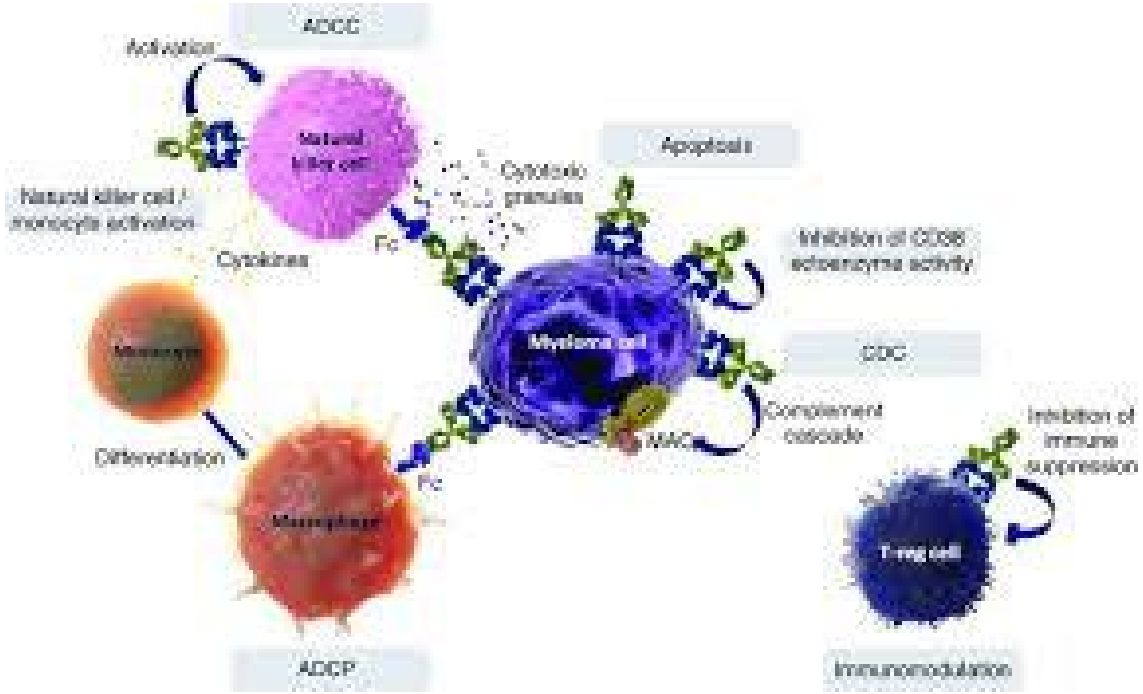
Daratumumab is a fully human MAb that targets CD38[1]

a cell surface antigen that is highly expressed on myeloma cells[2,3]

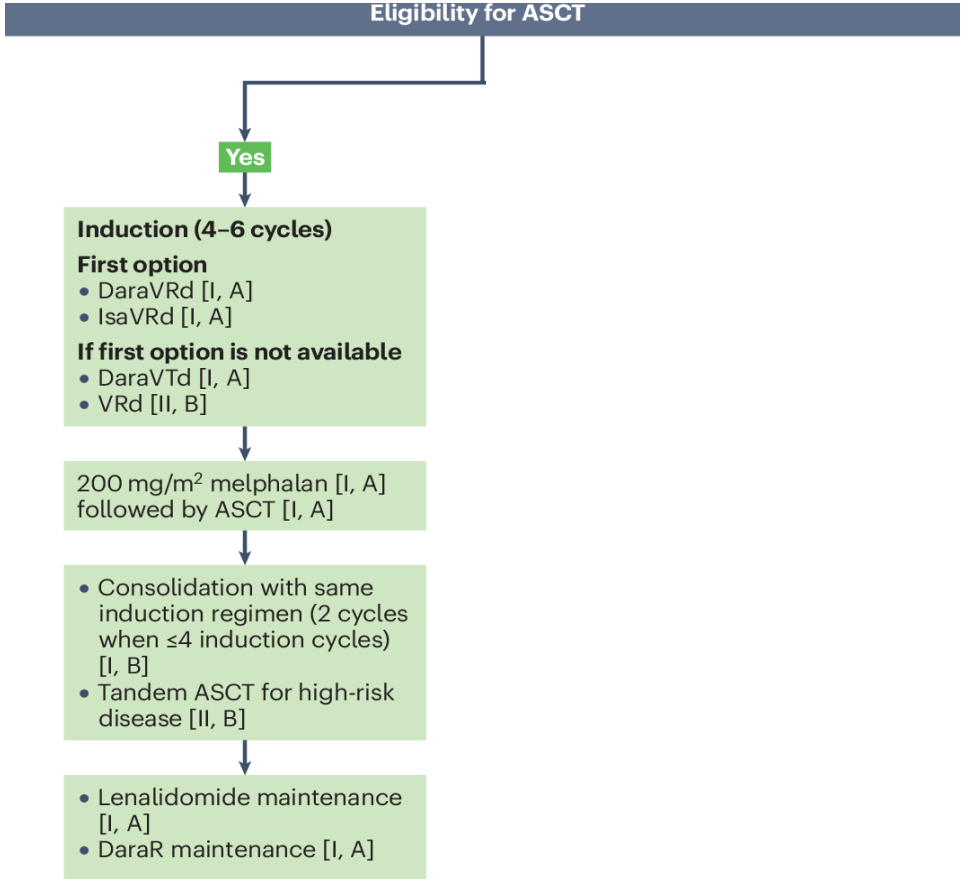


1. Draft D[illegible]) Summary of Product Characteristics. TBC. 2. Plesner T, Krejcik J. *Front Immunol*. 2018;9:1228. 3. Adams HC 3rd, *et al. Cytometry A*. 2019;95:279–289. 4. Dimopoulos MA, *et al*. Oral presentation at the 60th American Society of Hematology annual meeting. December 1–4, 2018; San Diego, CA; #3270. 5. McKeage K, Lyseng-Williamson KA. *Drugs Ther Perspect*. 2016;32:463–469. 6. Johnson SK, *et al. Blood*. 2018;132:4466.

Isatuxímab anticorpo monoclonale derivato da IgG1 che si lega a uno specifico epitopo extracellulare del recettore CD38.

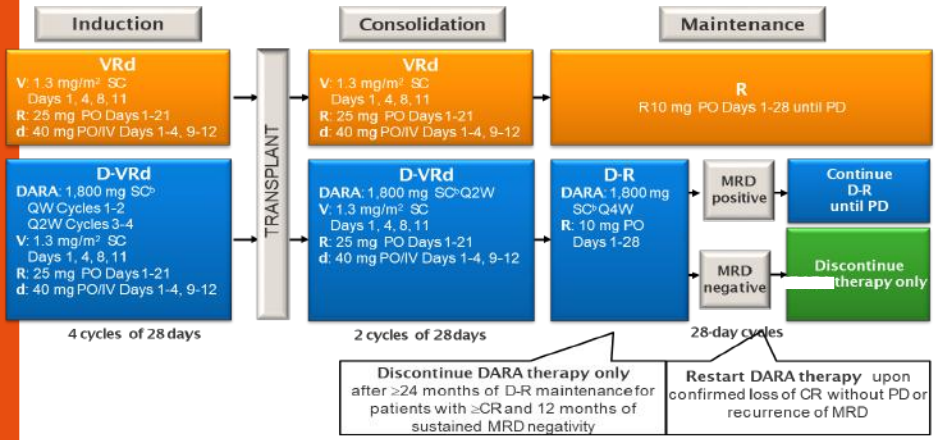


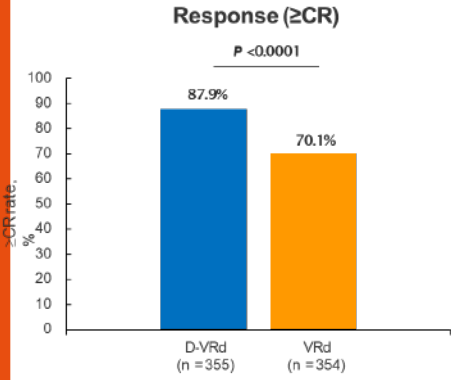
EHA-EMN 2025 Clinical Practice Guidelines Recommendations for MM front-line therapy.

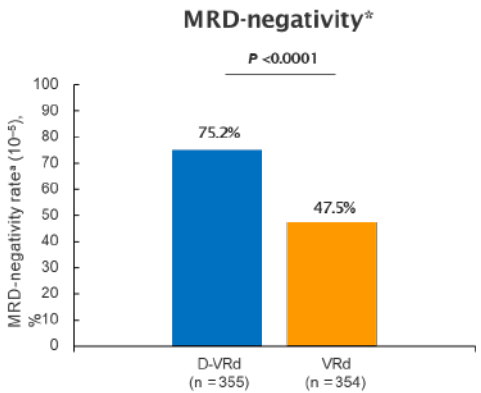


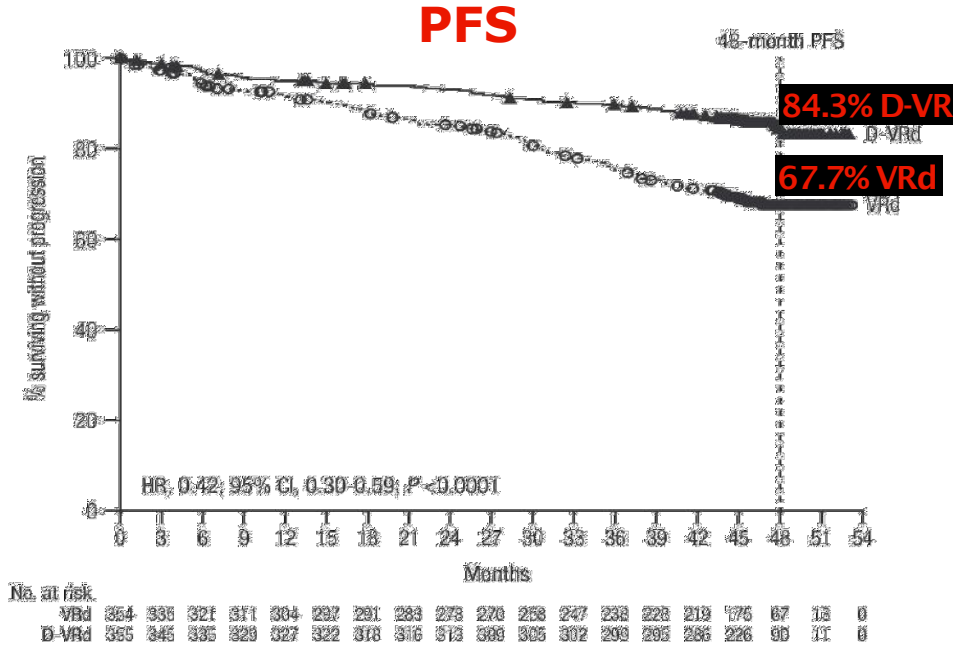
Perseus Trial: DARA +VRd Vs Vrd TE NDMM Sum Up

Median FUp 47,5 m









SAFETY

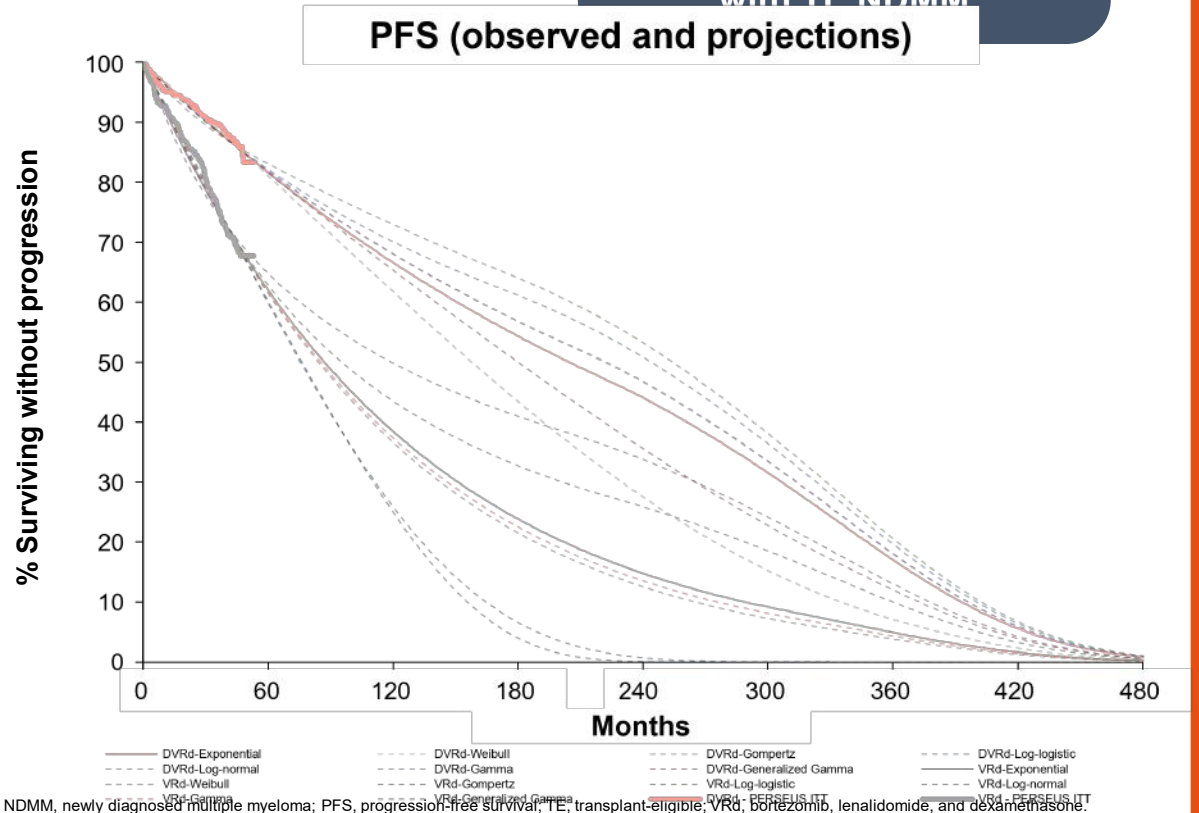
Neutropenia (62.1%/51.0%), thrombocytopenia (29.1%/17.3%), diarrhea (10.5%/7.8%), pneumonia (10.5%/6.1%), and febrile neutropenia (9.4%/10.1%)
Serious TEAEs leading to treatment discontinuation 8.8% D-VRd versus 21.3% VRd

PERSEUS: Estimated PFS Projections

TE NDMM

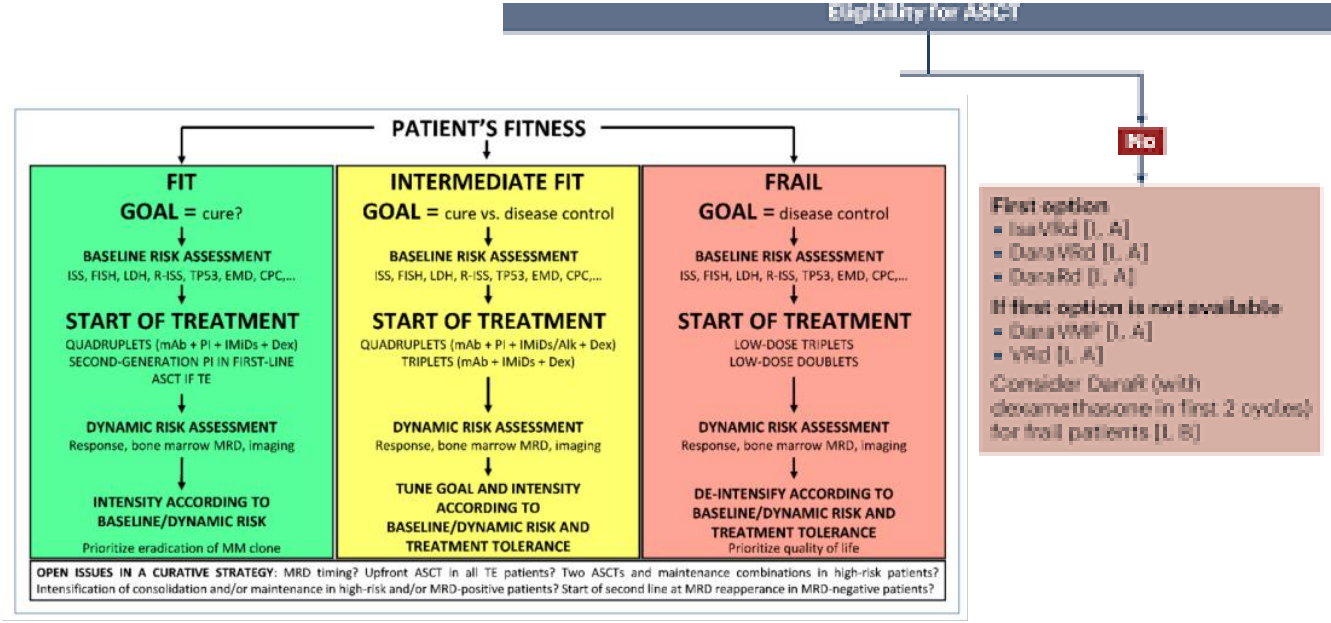
PFS projections were significantly longer with DVRd vs VRd across all 7 distributions in patients with TE NDMM

- **Median PFS not reached in the ITT population**
- **Estimated median PFS**
  - Range across **all** distributions:
    - **DVRd: 158–255 months**
    - VRd: 76–119 months
  - **Best-fit:**
    - **DVRd: 205 months**
    - VRd: 87 months



DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; TE, transplant-eligible; VRd, bortezomib, lenalidomide, and dexamethasone.

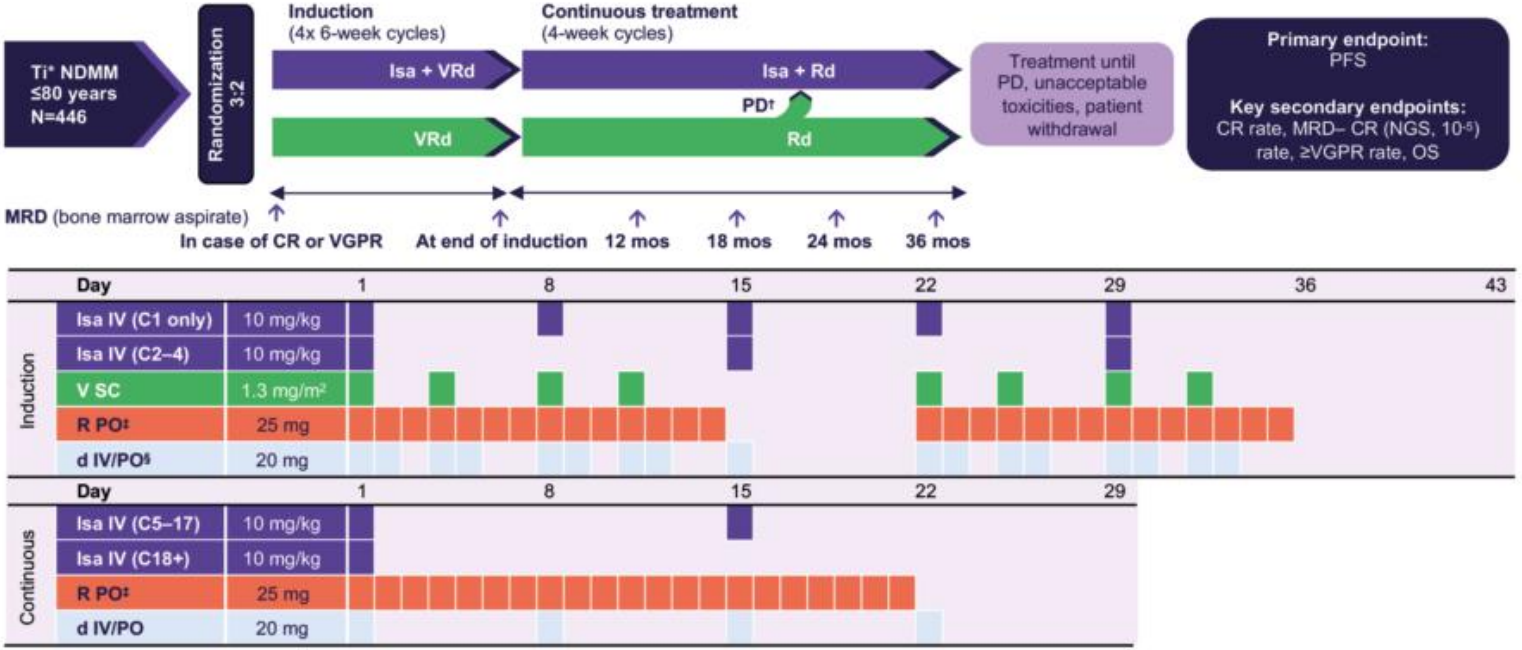
EHA-EMN 2025 Clinical Practice Guidelines Recommendations for MM front-line therapy.



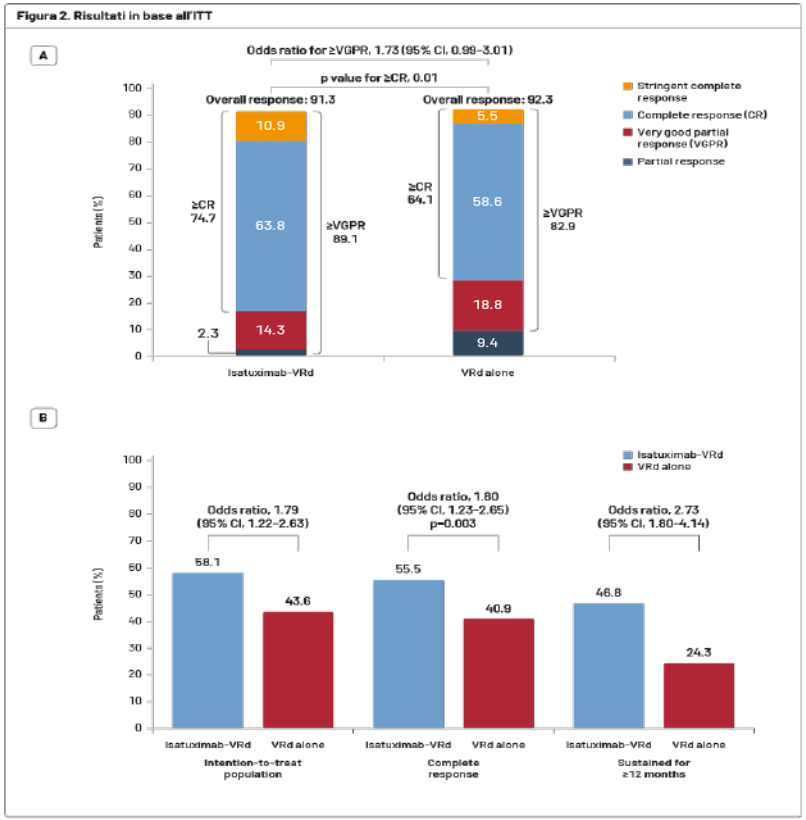
Patients who are not eligible for ASCT but have an IMWG FS of <2 and are <80 years old can receive two new SOC regimens: and DaraVRd [I, A], although at the time of writing, DaraVRd is pending approval by the EMA. is a valuable option in all transplant-ineligible patients, especially those with an IMWG FS of ≥1 [I, A]. A dexamethasone-sparing strategy (DaraR) should be considered in patients with an IMWG FS of ≥2 [I, B]. If none of the above-mentioned options is available, DaraVMP or VRd can be used [I, A].

M. A. Dimopoulos et al. - https://www.esmo.org/guidelines/haematological-malignancies/multiple-myeloma - Annals of Oncology 2021

Transplant NON eligible NDMM:
Anti-CD38 plus `/D ' induction and anti-CD38-R maintenance
IMROZ study

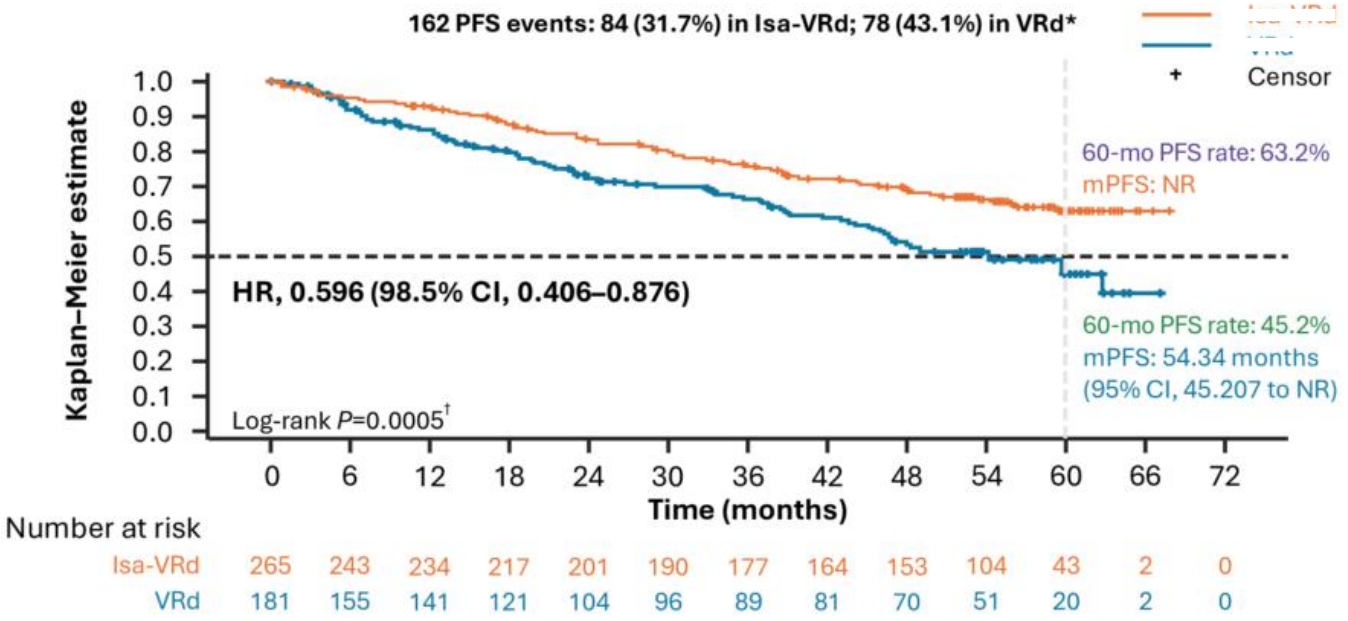


IMROZ



A. Tasso di risposta (criteri IMWG) B. MRD
Mod. da Facon T, et al. N Engl J Med 2024; doi: 10.1056/NEJMoa2400712

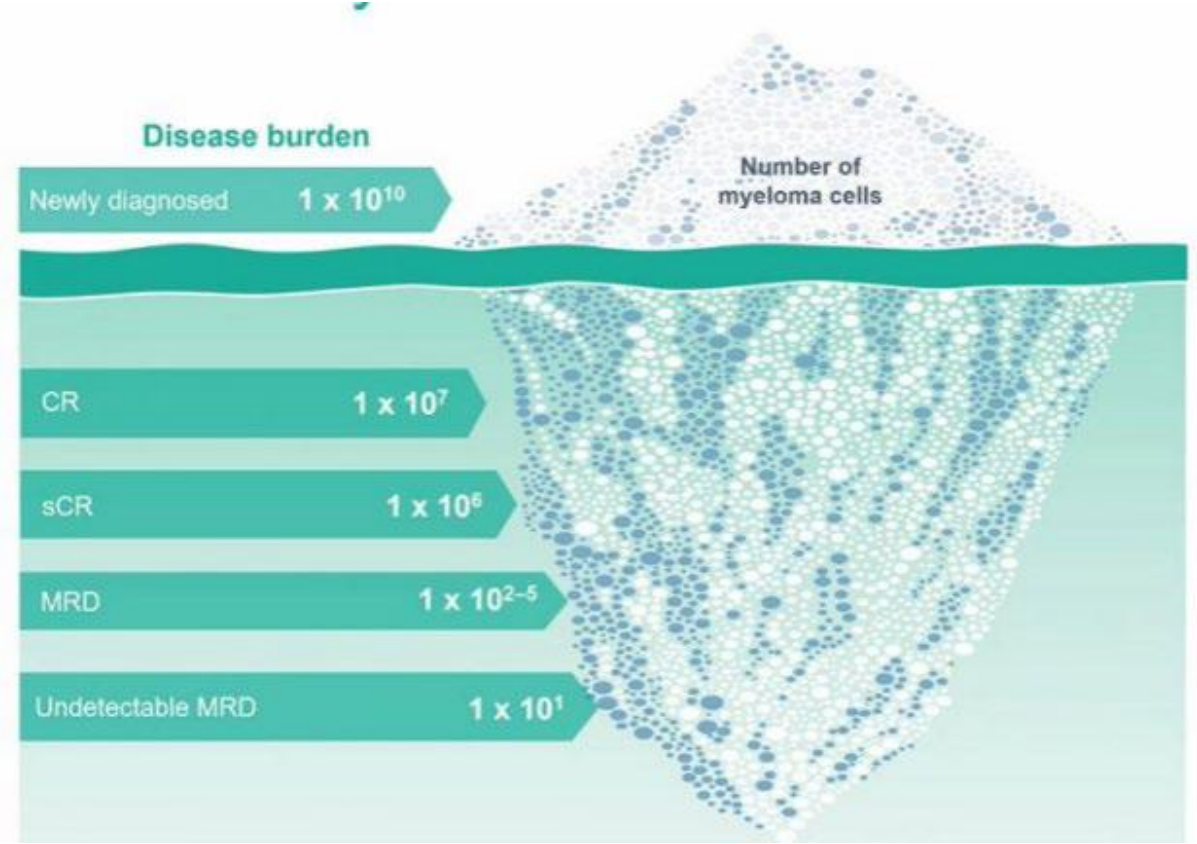
IMROZ efficacy



At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

Criteria of Response

MRD => the need to minimize the overall burden of the disease



International Myeloma Working Group (IMWG) MRD Criteria[1]

MRD negative: absence of aberrant clonal plasma in bone marrow aspirate, ruled out by an assay with minimum sensitivity of $1:10^5$ nucleated cells or higher (ie, 10^{-5} sensitivity)

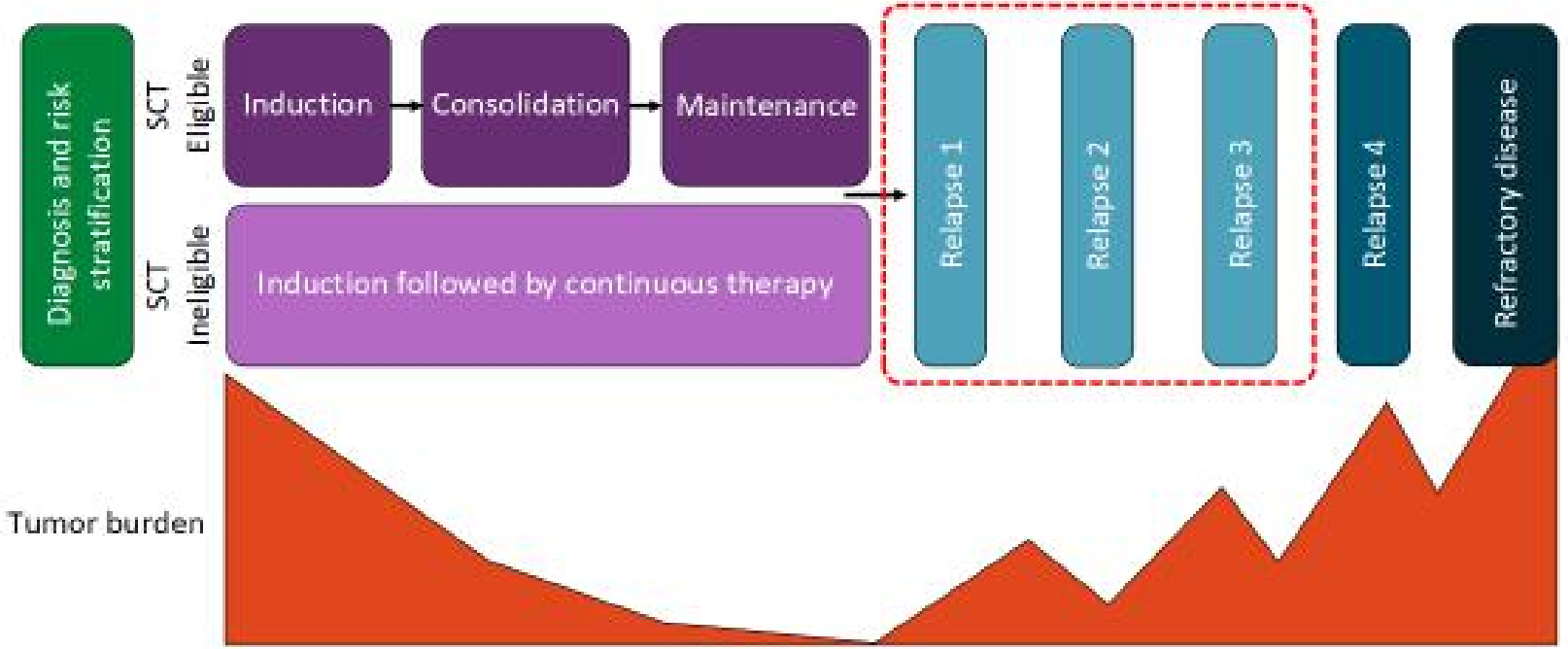
Sustained MRD negative: MRD negativity in the marrow (flow or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart; subsequent evaluations can be used to further specify the duration of negativity (eg, MRD negative at 5 years)

Imaging plus MRD negative: MRD negativity as defined by flow or NGS, plus disappearance of every area of increased tracer uptake found at baseline, a preceding PET/CT, decrease to less mediastinal blood pool SUV, or decrease to less than that of surrounding normal tissue

Based on flow cytometry or NGS (such as Euroflow standard operation procedure for MRD detection in MM, or other validated equivalent methods; LymphoSIGHT, or other validated equivalent method)

1. Kumar S et al. *Lancet Oncol.* 2016 ;17:e328-346.

Myeloma Treatment Paradigm



EHA-EMN 2025 Clinical Practice Guidelines Recommendations for MMRR II line therapy.

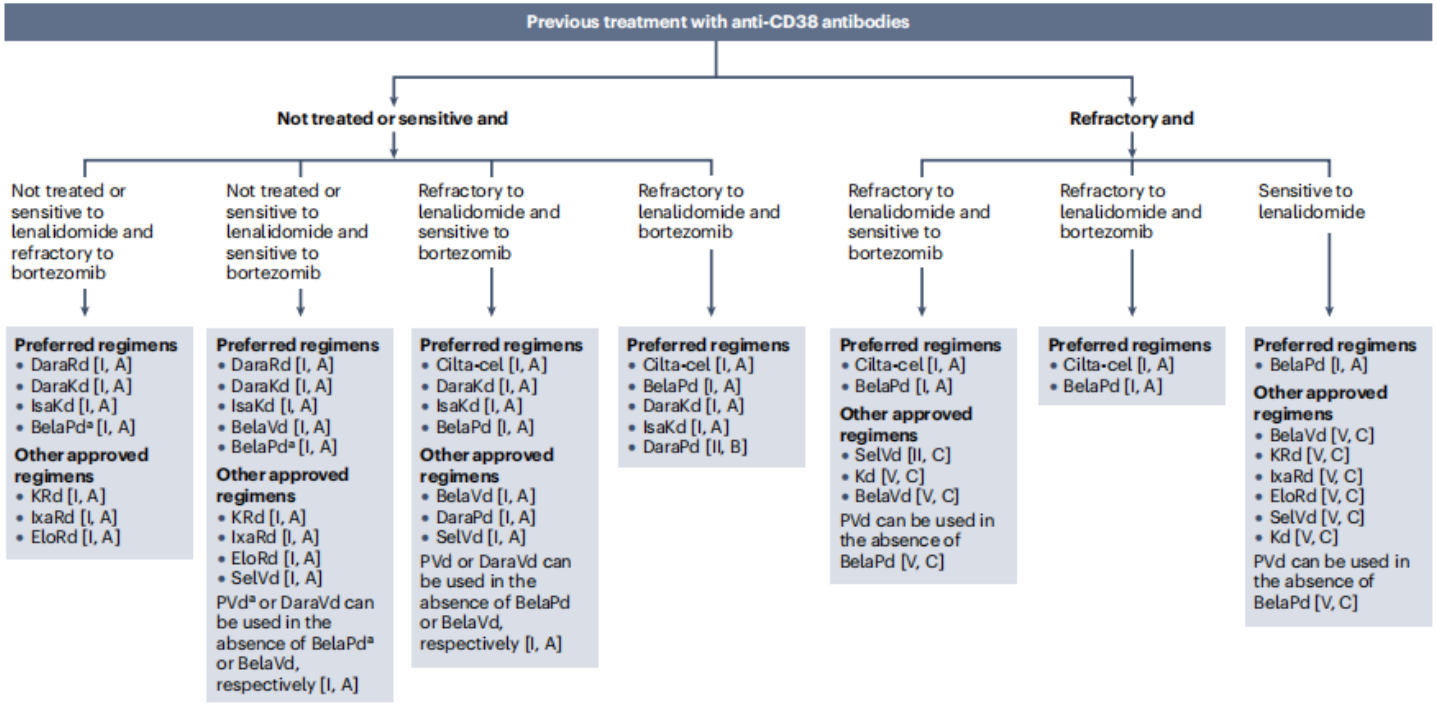
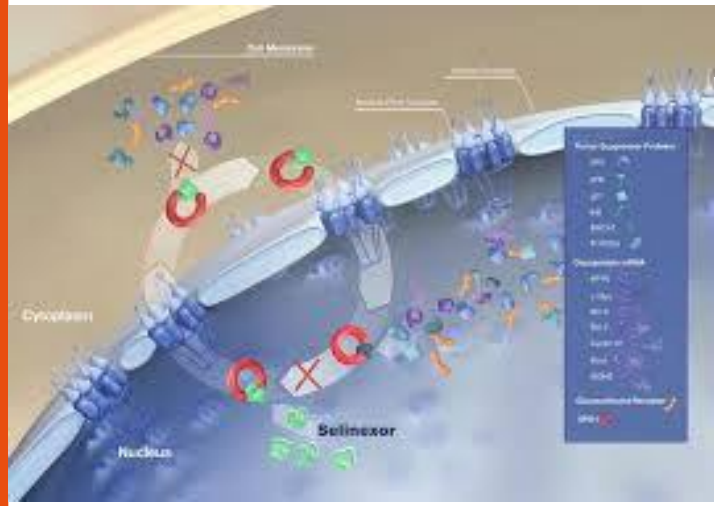


Fig. 2 | Recommendations for the treatment of patients with relapsed and/or refractory multiple myeloma at second line. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1). [a]Only in patients exposed to lenalidomide. Bela, belantamab mafodotin; cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; P, pomalidomide; R, lenalidomide; Sel, selinexor.

Selinexor: inibitore esportina1 XPO1 meccanismo d' azione



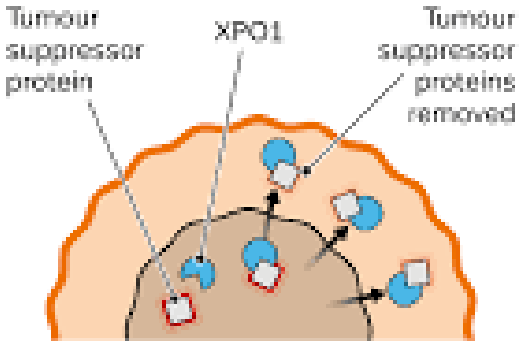


Figure 1. Myeloma cell uses XPO1 to move tumour suppressor proteins out of the nucleus, where they become inactive

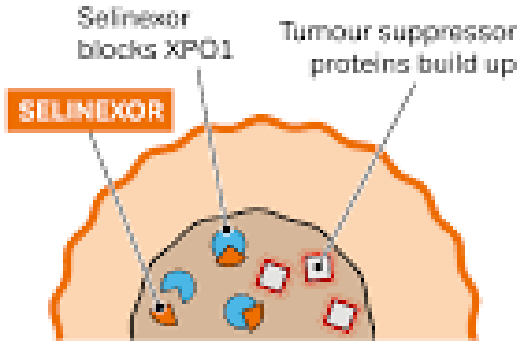
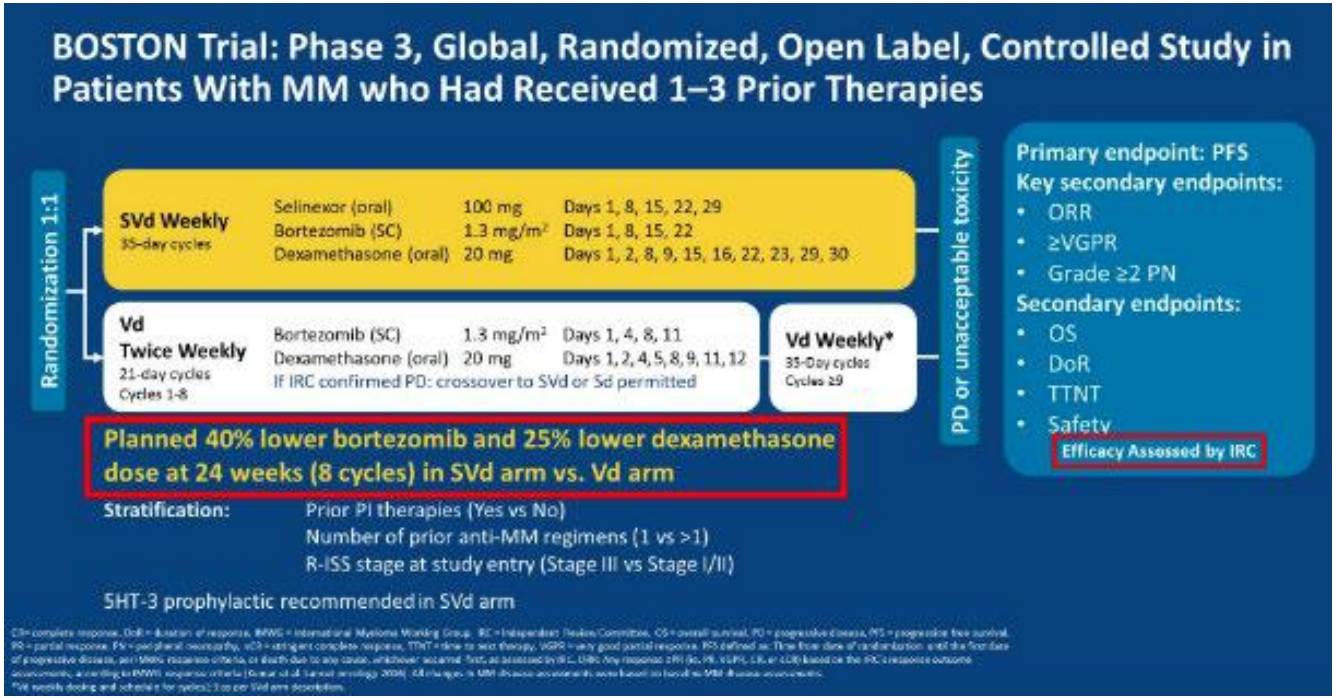


Figure 2. Selinexor attaches to XPO1, stopping it from working. This causes tumour suppressor proteins to build up in the myeloma cell, and the myeloma cell dies

Selinexor inibitore esportina1 XPO1



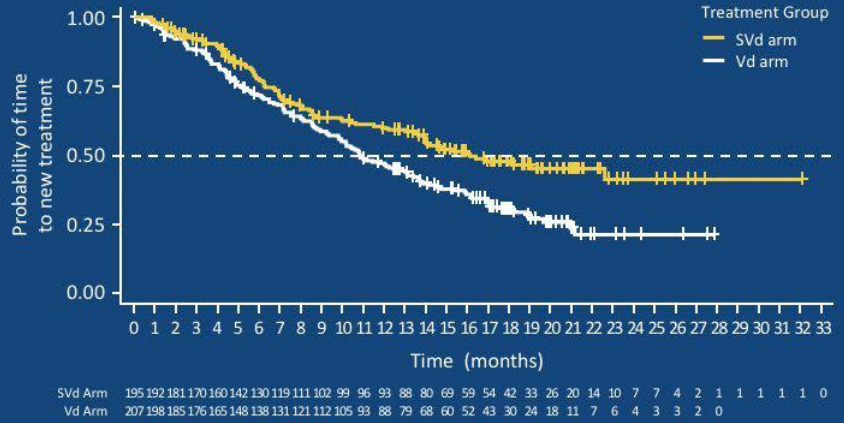
BOSTON Trial: Time to Next Therapy and Overall Survival Interim Analysis (109 Deaths [27%])

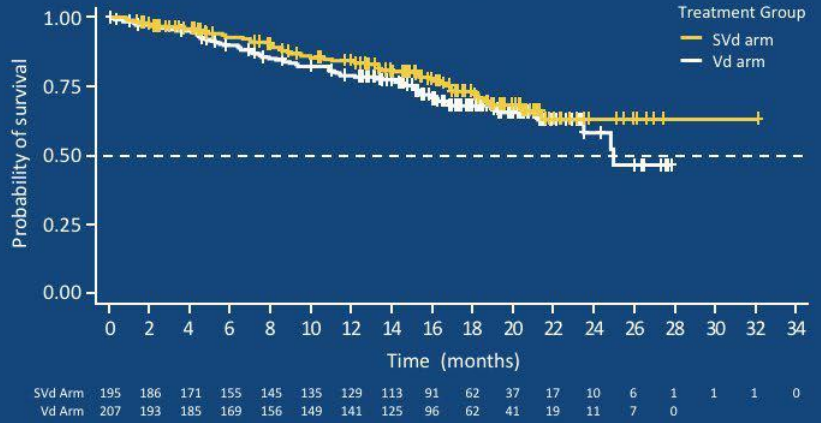
	SVd	Vd
Median TTNT (mos)	16.1	10.8

HR 0.66 (95% CI: 0.50, 0.86) *P=0.0012*

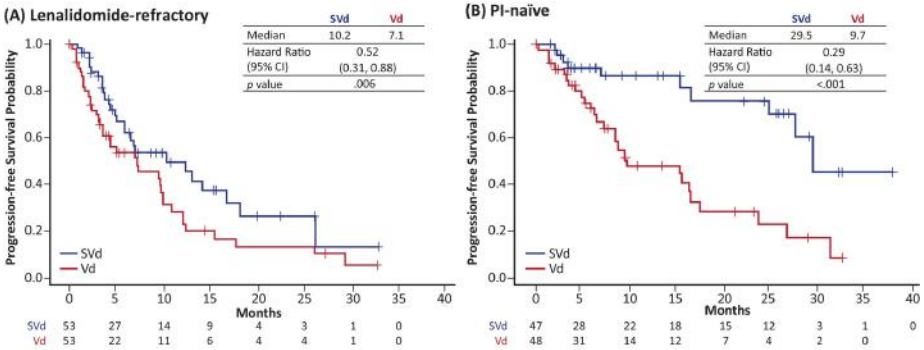
	SVd	Vd
# Death Events (n)	47	62
Median OS (mos)	Not Reached	25

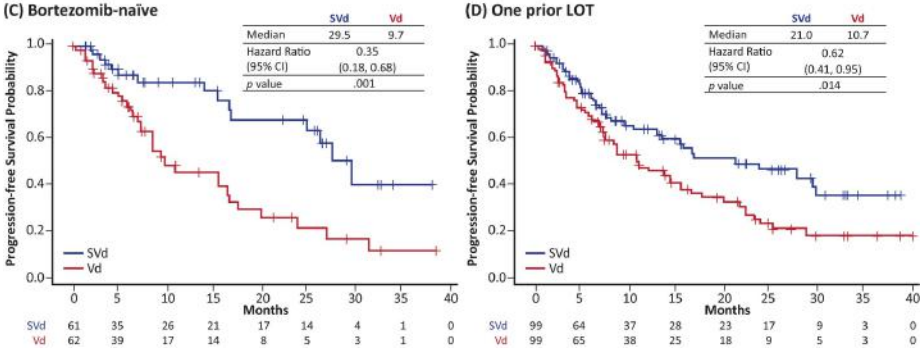
HR 0.84 (95% CI: 0.57, 1.23) *P=0.19*





Intention-to-treat (ITT) population N=402, Median Follow up 17.4 months. HR = Hazard Ratio, OS = Overall Survival, TTNT = Time to Next Therapy. Data cut-off February 18, 2020.





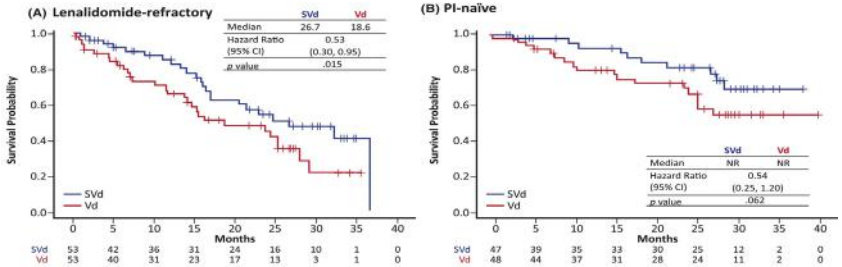
Progression-free survival PFS

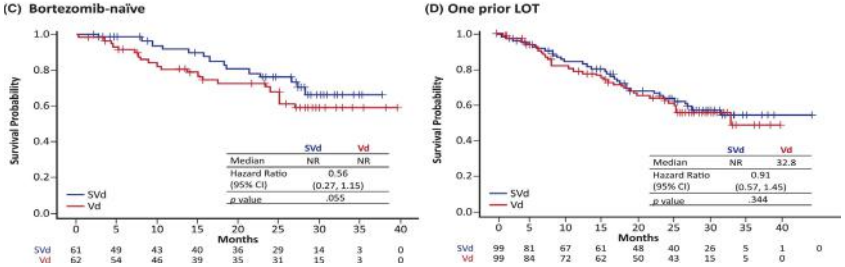
Impact of prior treatment on selinexor, bortezomib, dexamethasone outcomes in patients with relapsed/refractory multiple myeloma: Extended follow-up subgroup analysis of the BOSTON trial

Maria-Victoria Mateos, Monika Engelhardt, Xavier Leleu, Mercedes Gironella Mesa, Michele Cavo, Meletios Dimopoulos, Martina Bianco, Giovanni Marino Merlo, Charles la Porte … See all authors

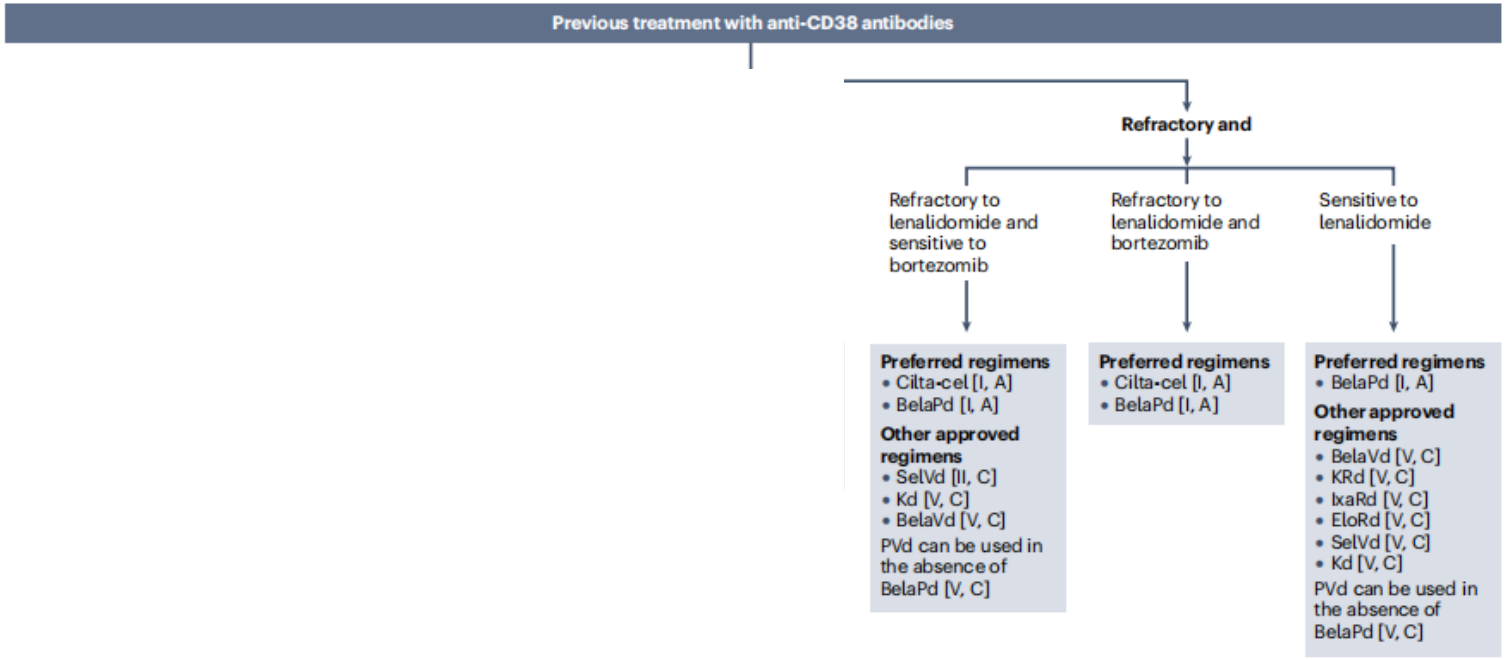
First published: 01 May 2024

Overall survival OS

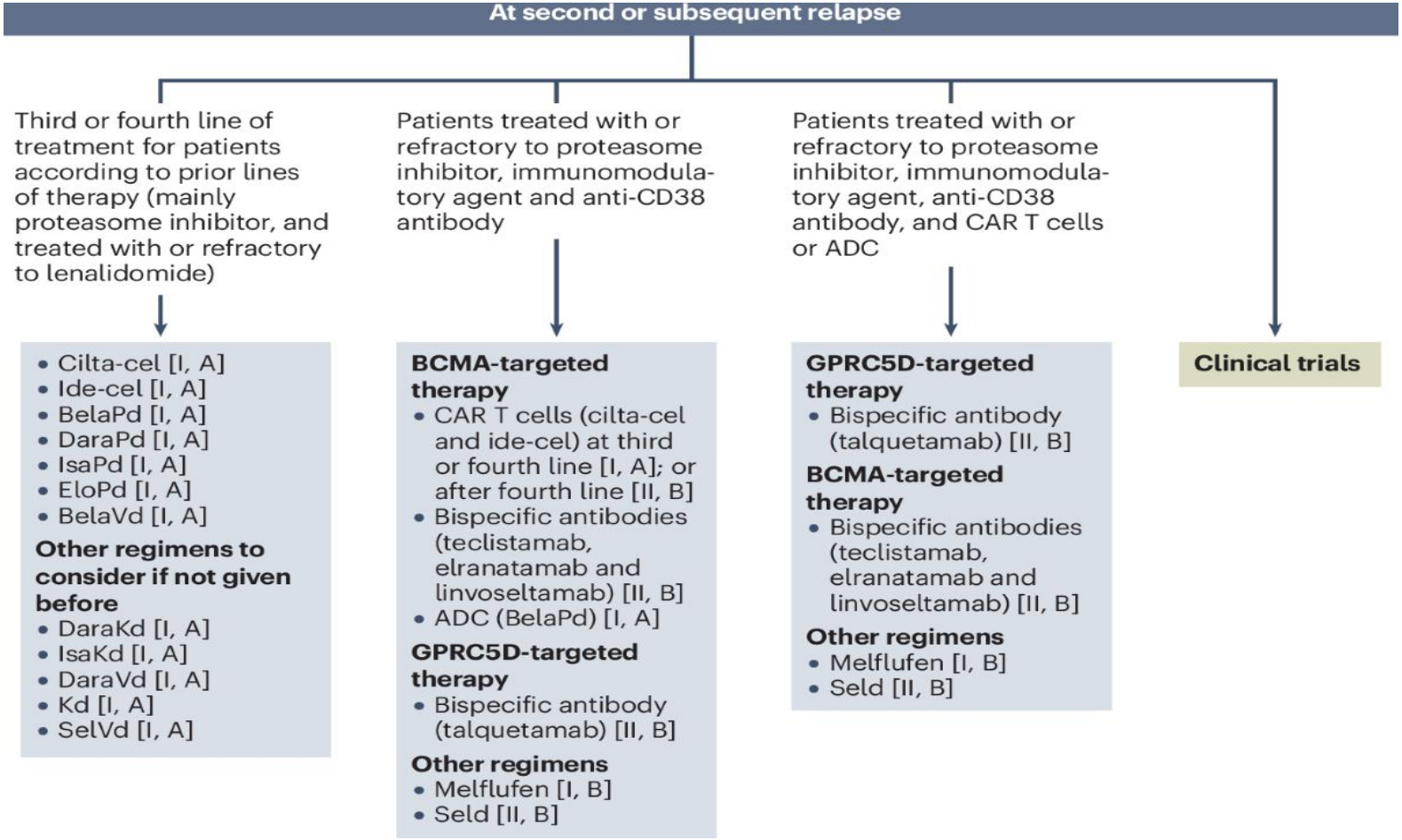




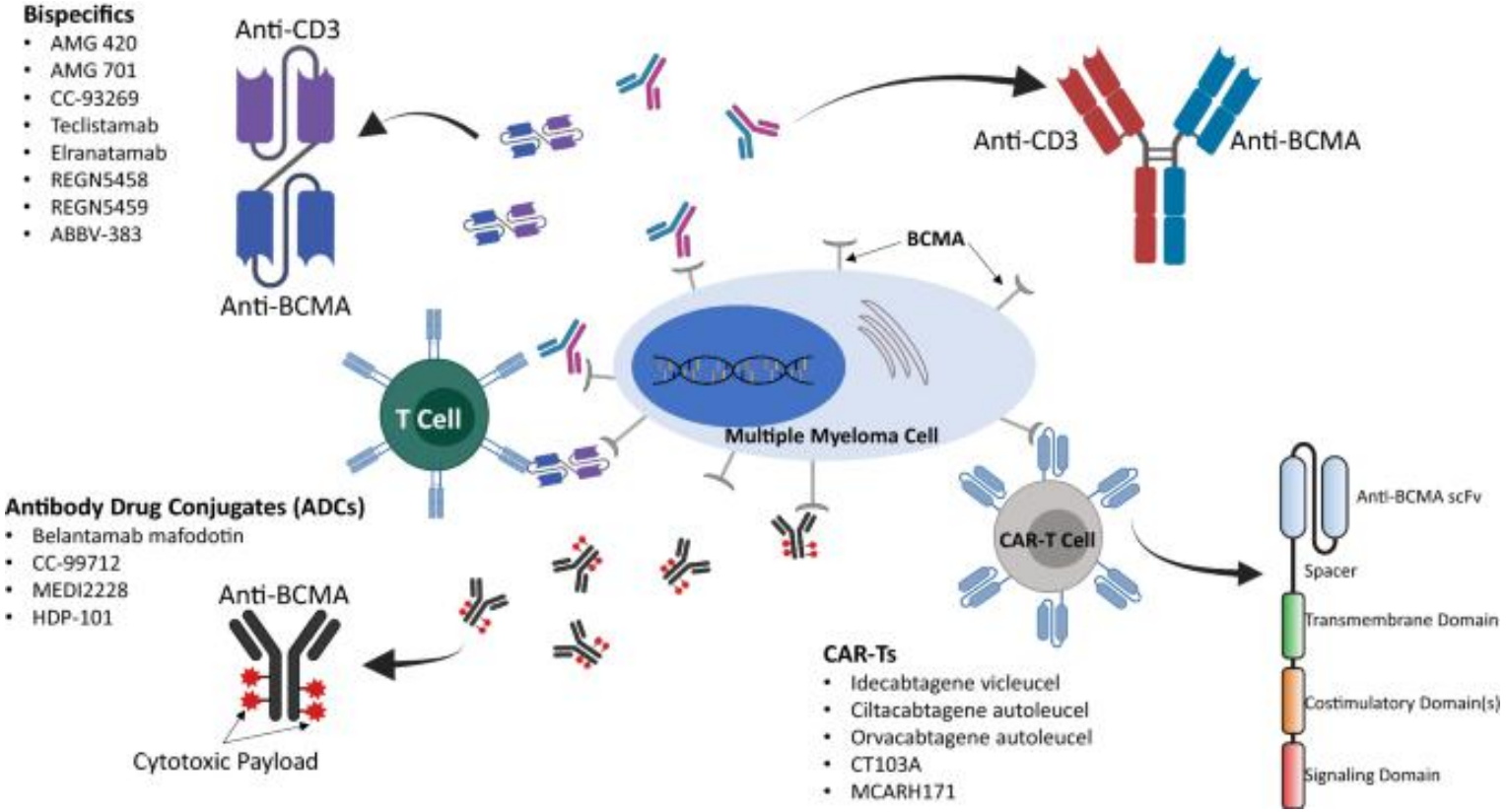
EHA-EMN 2025 Clinical Practice Guidelines Recommendations for MMRR II line therapy.



, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab;
uzumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; P, pomalidomide;
include supporting levels of evidence and have been graded (Supplementary K, lenalidomide; Sel, selinexor.
Table1). [a]Only in patients exposed to lenalidomide. Bela, belantamab mafodotin;

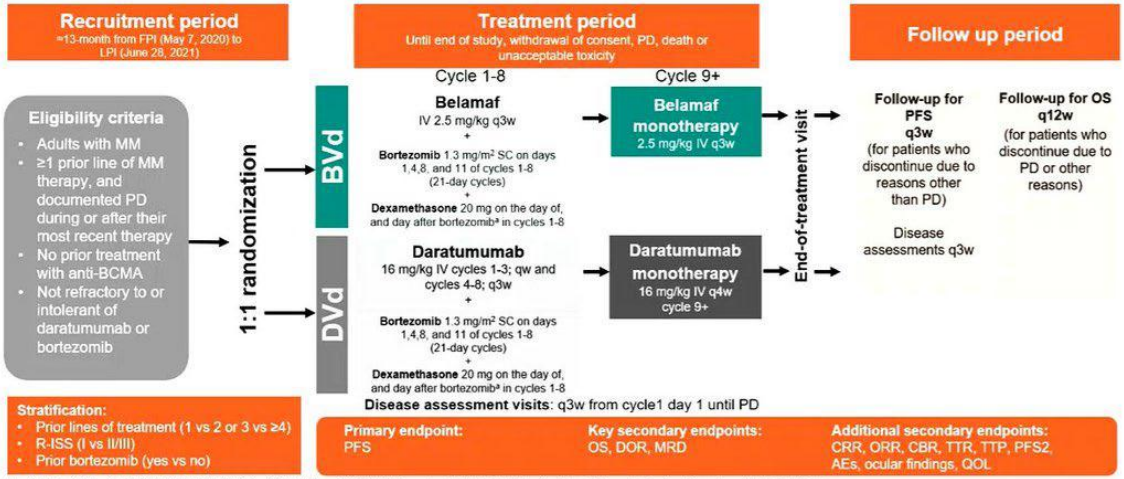

At second or subsequent relapse
Third or fourth line of treatment for patients according to prior lines of therapy (mainly proteasome inhibitor, and treated with or refractory to lenalidomide)
Patients treated with or refractory to proteasome inhibitor, immunomodulatory agent and anti-CD38 antibody
Patients treated with or refractory to proteasome inhibitor, immunomodulatory agent, anti-CD38 antibody, and CAR T cells or ADC
Clinical trials
• Cilta-cel [I, A]
• Ide-cel [I, A]
• BelaPd [I, A]
• DaraPd [I, A]
• IsaPd [I, A]
• EloPd [I, A]
• BelaVd [I, A]
Other regimens to consider if not given before
• DaraKd [I, A]
• IsaKd [I, A]
• DaraVd [I, A]
• Kd [I, A]
• SelVd [I, A]
BCMA-targeted therapy
• CAR T cells (cilta-cel and ide-cel) at third or fourth line [I, A]; or after fourth line [II, B]
• Bispecific antibodies (teclistamab, elranatamab and linvoseltamab) [II, B]
• ADC (BelaPd) [I, A]
GPRC5D-targeted therapy
• Bispecific antibody (talquetamab) [II, B]
Other regimens
• Melflufen [I, B]
• Seld [II, B]
GPRC5D-targeted therapy
• Bispecific antibody (talquetamab) [II, B]
BCMA-targeted therapy
• Bispecific antibodies (teclistamab, elranatamab and linvoseltamab) [II, B]
Other regimens
• Melflufen [I, B]
• Seld [II, B]

Antigene di maturazione delle cellule B: BCMA- target



Belantamab Mafodotin

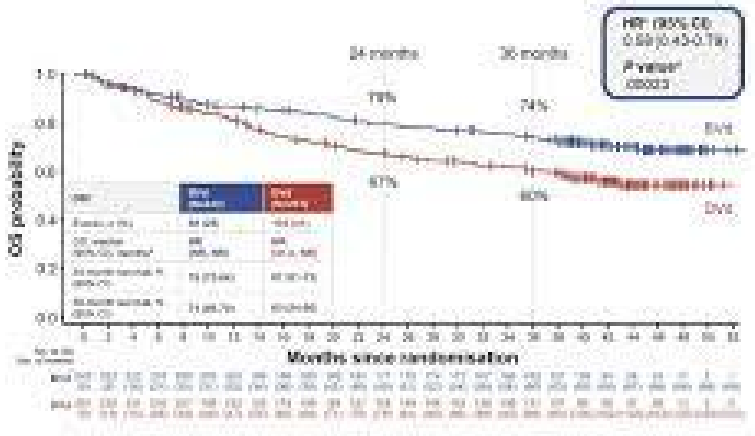
DREAMM-7: study design

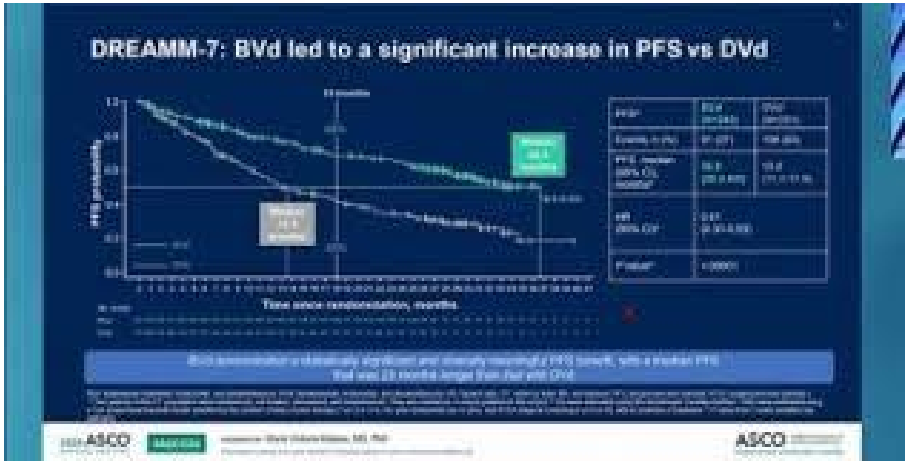


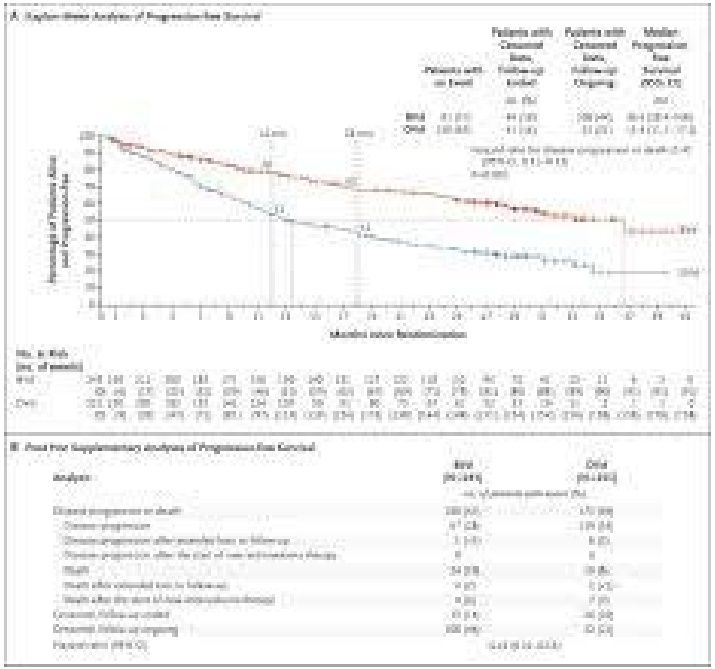
AE, adverse event; BVd, belantamab mafodotin, bortezomib, and dexamethasone; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; DVd, daratumumab, bortezomib, and dexamethasone; FPI, first-patient-in; IV, intravenous; LPI, last-patient-in; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks, q4w, every 4 weeks, q12w, every 12 weeks, qw, every week; QOL, quality of life; R-ISS, Revised International Staging System; SC, subcutaneous; TTP, time to progression; TTR, time to response.

[a]Reduce starting dose of dexamethasone to 10 mg for patients >75 years of age, who have a body mass index <18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting.

DREAMM-7 Overall Survival







EHA 2025

DREAMM-8: belantamab mafodotin + pomalidomida y dexametasona

DISEÑO

- Fase 3
- Etiqueta abierta
- Aleatorizado
- Multicéntrico

TRATAMIENTO

Pacientes asignados 1:1 a:

Brazo 1 (BPd) (155 pacientes):

ciclos de 28 días

ciclo 1: ***Belantamab mafodotin*** 2,5 mg/kg
ciclos 2+: ***Belantamab mafodotin*** 1,9 mg/kg cada 4 semanas
+
pomalidomida 4 mg días 1-21
+
dexametasona 40 mg días 1, 8, 15 y 22

Brazo 2 (PVd) (147 pacientes):

ciclos de 21 días

ciclos 1-8: ***bortezomib*** 1,3 mg/m2 días 1, 4, 8 y 11
ciclos 9+: ***bortezomib*** 1,3 mg/m2 días 1 y 8
+
pomalidomida 4 mg días 1-14
+
dexametasona 20 mg el día antes y después de bortezomib

PACIENTES

Criterios de inclusión ✅

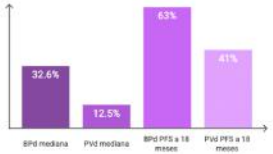
- ***Estado de bortezomib*** Sin enfermedad refractaria ni intolerancia a bortezomib
- ***Mieloma múltiple***
- ***Tratamiento previo*** Sin tratamiento previo anti-BCMA o pomalidomida
- ***Terapia previa*** ≥ 1 terapia previa, incluso lenalidomida
- ***Progresión de la enfermedad*** PD durante o después de la terapia reciente
- ***Puntuación ECOG*** ECOG 0-2

Criterios de exclusión ❌

- ***Terapia*** Terapia sistémica anti-MM o mAb <30 previa primera dosis
- ***Leucemia***
- ***Lesión previa*** de médula espinal alogénica
- ***Enfermedad renal*** activa
- ***Enfermedad corneal actual***
- ***Neuropatía periférica*** de grado ≥2 en curso
- ***Antecedentes de cáncer***

DESENLACES

- 35% BPd y 14% PVd continuaron el tratamiento.
- Se observó PFS en un 44% de BPd y en un 61% de PVd.



- El beneficio de PFS se mantuvo entre los subgrupos de estratificación y el brazo BPd se vio favorecido.

- La tripleta disminuye el riesgo de progresión o muerte en 51% (HR:0,49)

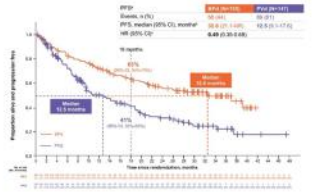


Imagen tomada de la presentación original con fines informativos. PFS.

DATOS CLAVE

302 Pacientes

- Citogenética de alto riesgo
- Enfermedad refractaria a lenalidomida
- Enfermedad refractaria a anti-CD38

Mediana de seguimiento
28,01 meses

SEGURIDAD

Los eventos de grado ≥3 fueron del 91% en el grupo BPd y del 74% en el grupo PVd. Los más frecuentes fueron:

de cualquier grado	BPd	PVd
Trombocitopenia	54%	41%
Neutropenia	65%	48%
Infecciones	83%	70%

Más del 30% de pacientes en cada grupo experimentó eventos oculares:

de cualquier grado	BPd	PVd
Visión borrosa	80%	18%
Sequedad	61%	10%
Sensación de algo dentro del ojo	61%	8%
Irritación	61%	10%
Fotofobia	48%	4%
Dolor ocular	30%	8%

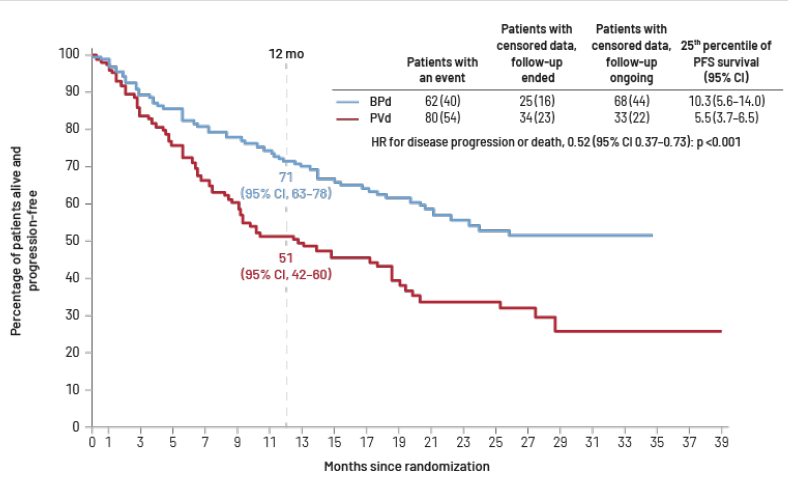
CONCLUSIÓN

BPd continuó demostrando un beneficio clínicamente significativo en la PFS frente a la PVd en pacientes con MMRR con ≥1 tratamiento previo.
Este beneficio se mantuvo en subgrupos clave, incluyendo pacientes con enfermedad refractaria a anti-CD38 y lenalidomida. Los datos respaldan la BPd como posible opción de tratamiento estándar en pacientes con MMRR.

Referencia: Meletios A. Dimopoulos*1, 2, Meral Beksac3, Ludek Pour4, Sosana Delimpasi5, Vladimir Vorobyev6, Hang Quach7, Ivan Špička8, Jakub Radocha9, Paweł Robak10, Kihyun Kim11, Michele Cavo12, Kazuhito Suzuki13, Kristin Morris14, Amy Phillips-Jones15, Ianire Garrobo Calleja16, Giulia Fulci17, Elisabet Manasanch18, Brandon E. Kremer18, Joanna Opalinska18, Maria-Victoria Mateos19, Suzanne Trudel20. UPDATED RESULTS FROM PHASE 3 DREAMM-8 STUDY OF BELANTAMAB MAFODOTIN PLUS POMALIDOMIDE AND DEXAMETHASONE VS POMALIDOMIDE PLUS BORTEZOMIB AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA, HemaSphere, 2025;9:(S1).

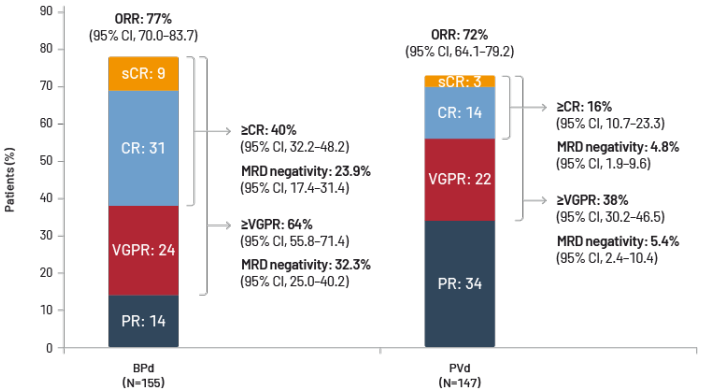
DREAMM 8 Belantamab Pomalidomide Desametasone

Figura 1. Risultati di PFS



Con BPd PFS mediana non raggiunta, con PVd PFS mediana 12,2 mesi
HR: hazard ratio
Mod. da Dimopoulos MA, et al. N Engl J Med 2024; 391: 408–421

Figura 2. Risposte in base all'ITT



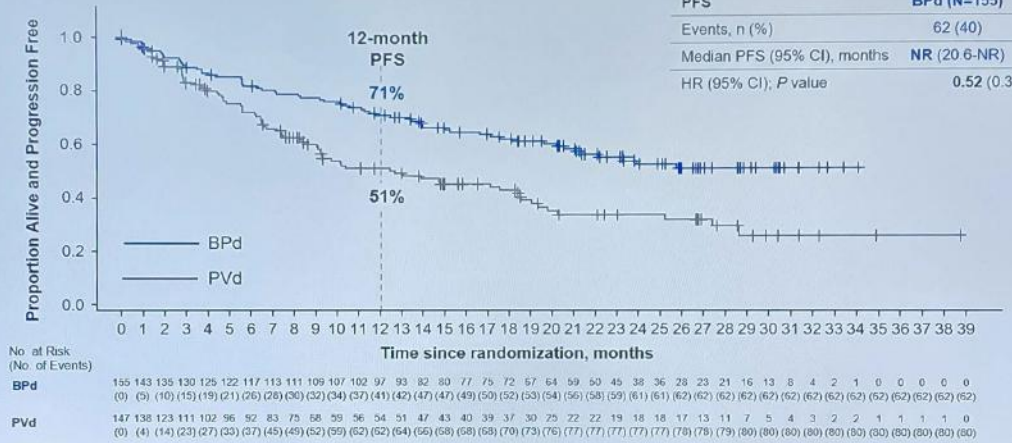
ITT: intention-to-treat; ORR: tasso di risposta globale; CR: risposta completa; PR: risposta parziale; VGPR: risposta parziale molto buona; sCR: risposta completa stringente; MRD: malattia residua misurabile
Mod. da Dimopoulos MA, et al. N Engl J Med 2024; 391: 408–421

DREAMM-8

Belantamab Mafodotin + Pd

Progression-Free Survival

BPd led to a statistically significant and clinically meaningful reduction in the risk of a PFS event



PFS	BPd (N=155)	PVd (N=147)
Events, n (%)	62 (40)	80 (54)
Median PFS (95% CI), months	**NR** (20.6-NR)	**12.7** (9.1-18.5)
HR (95% CI); *P* value	**0.52** (0.37-0.73); **<.001**	

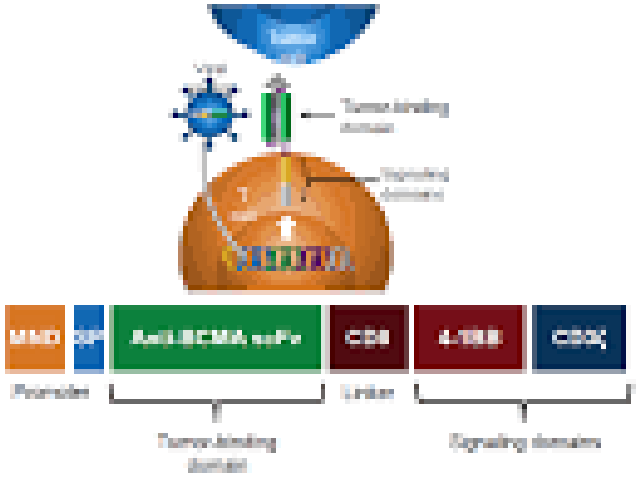
PFS HR<1 was also observed in difficult-to-treat subgroups including those with cytogenic or functional high-risk status, refractoriness to lenalidomide, or prior exposure to anti-CD38

The treatment effect (HR and corresponding 95% CIs) was estimated using the stratified Cox proportional hazards model, and the P value was produced based on the one-sided stratified log-rank test. Stratified analyses were adjusted for number of prior lines of therapy and prior bortezomib use.

BPd, belamaf, pomalidomide, and dexamethasone; HR, hazard ratio; NR, not reported; PD, progressive disease; PFS, progression-free survival; PVd, pomalidomide, bortezomib, and dexamethasone.

Structure of BCMA CAR-T Constructs Approved in RRMM

Ide-cel structure:
Anti-BCMA single-chain variable fragment (scFv) fused to CD8 linker region and the CD137 (4-1BB) costimulatory; CD3ζ signaling domains[1]



Cilta-cel structure:
Two BCMA-targeting domains designed to confer avidity plus a 4-1BB costimulatory domain[2]

1. Rao NB et al. ASCO 2021. Abstract 8007. 2. Madduri D et al. ASH 2020. Abstract 177.

Chimeric antigen receptor (CAR) T cells are genetically engineered living drugs

Chimeric antigen receptor T cells (CAR-T) are genetically modified cells equipped with a new receptor to specifically recognize and destroy antigen-positive target cells. This receptor is an artificial fusion protein that comprises an extracellular antigen-binding domain, followed by a hinge region, a transmembrane domain, a costimulatory domain, and an intracellular signaling domain (Figure 1) [Citation1]. A major advantage of CAR-T is the major histocompatibility complex (MHC)—independent target antigen recognition [Citation2,Citation3] since MHC-associated antigen presentation is decreased in malignant cells as part of the tumors immune evasion. Moreover, other than antibody-based targeted immunotherapies, CAR-T are a living drug, which proliferates and persists within the patient providing long-term tumor surveillance.

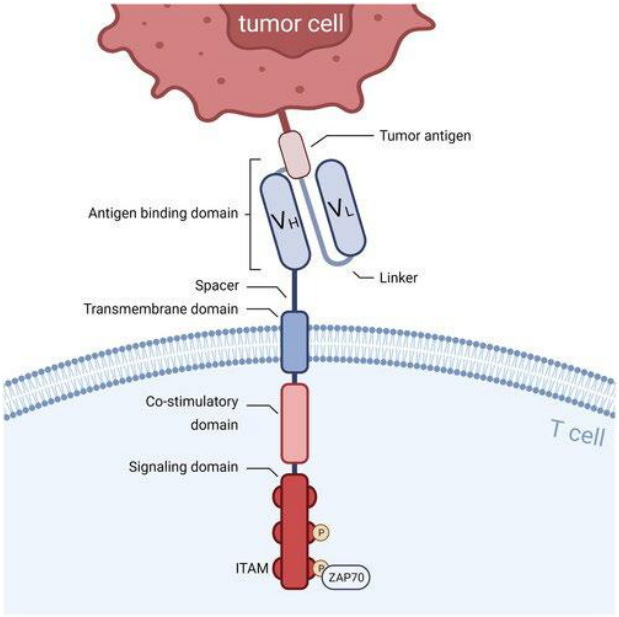
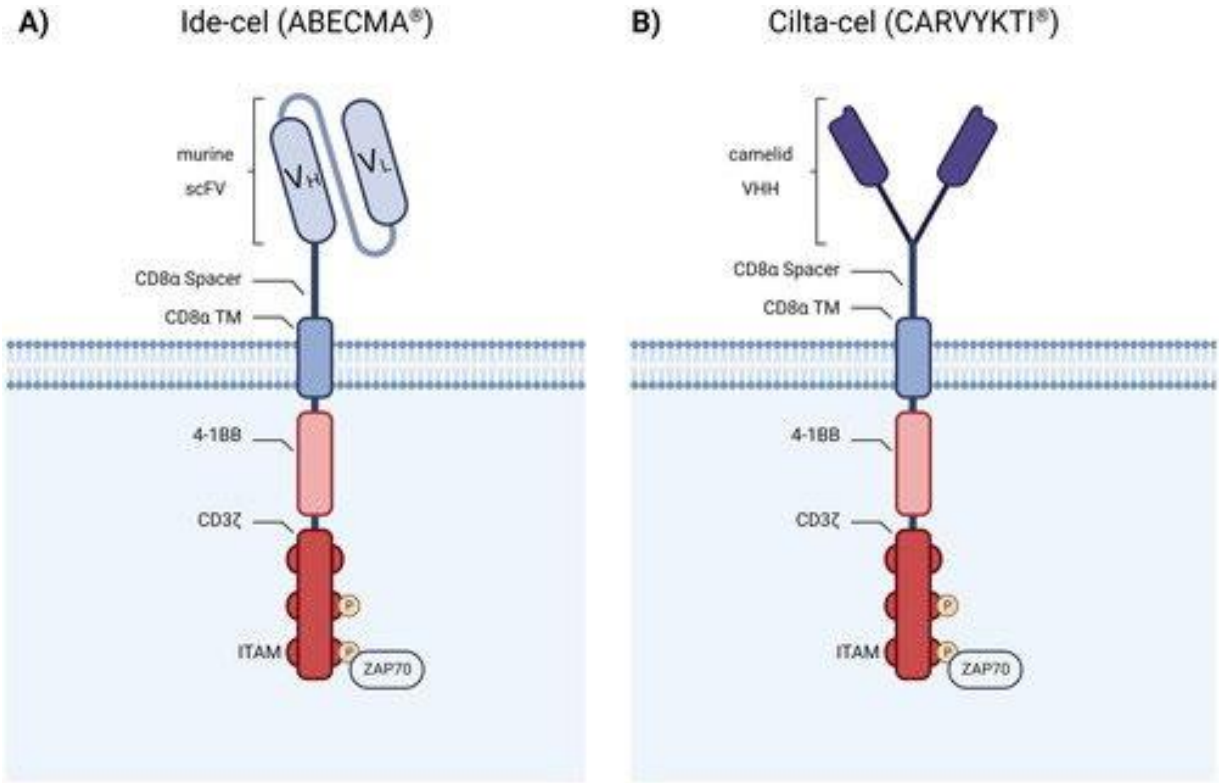


Figure 1. **General concept and structure of a chimeric antigen receptor T cell (CAR-T)**. CARs are artificial fusion proteins consisting of an antigen-binding domain, followed by a hinge region, a transmembrane domain, a costimulatory domain and an intracellular signaling domain. After recognition of its specific antigen on the surface of tumor cells, CARs initiate a cascade of cytotoxic signaling, leading to tumor lysis.


A)
Ide-cel (ABECMA®)
murine
scFV
VH
VL
CD8α Spacer
CD8α TM
4-1BB
CD3ζ
ITAM
ZAP70
B)
Cilta-cel (CARVYKTI®)
camelid
VHH
CD8α Spacer
CD8α TM
4-1BB
CD3ζ
ITAM
ZAP70

Cilta-cel is recommended as an effective treatment option for patients with MM in the second line and beyond[1]

Structure of cilta-cel[2–4]

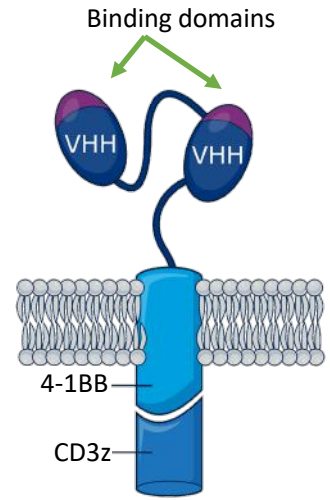


Image created by J&J.

Cilta-cel is an autologous CAR-T therapy with two BCMA-targeting, single-domain antibodies designed to confer avidity[3–5]

Cilta-cel is indicated for the treatment of adult patients with RRMM who have received at least one previous therapy (including an IMiD and a PI), have demonstrated disease progression on the prior therapy and are refractory to lenalidomide[3]

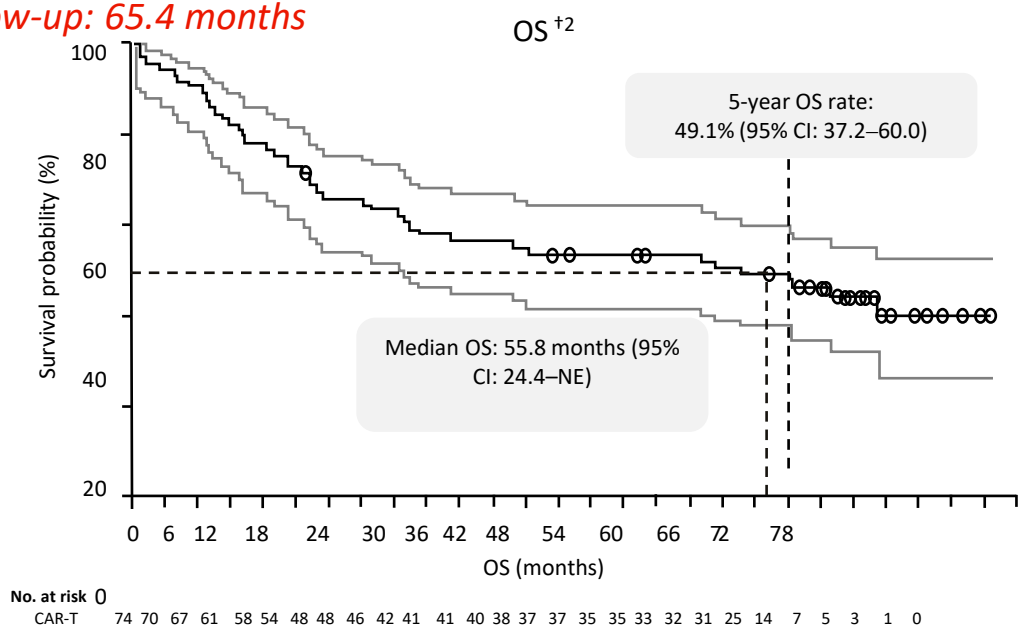
As of 2025, new EHA-EMN guidelines recommend cilta-cel as a valuable later-line treatment option for patients with RRMM who have not already received cilta-cel as an early-line therapy. This inclusion in the EHA-EMN guidelines helps fill an unmet medical need in this difficult-to-treat population[1]

LEGEND-2 supported the use of cilta-cel as a treatment for patients with RRMM

Data cut-off: 30 November 2022; median follow-up: 65.4 months

LEGEND-2, the first-in-human, Phase 1 study of LCAR-B38M,* showed **deep and durable responses** in patients with RRMM[1,2]

- Median OS was 55.8 months (95% CI: 24.4–NE)[2]
- Median DOR was 23.3 months (95% CI: 13.0–36.5)[2]
- Median PFS was 18.0 months (95% CI: 10.6–26.6)[2]
  - In total, 16% of patients were alive and disease-free ≥5 years after treatment
  - At the data cut-off, 44.6% of patients were alive



Results from LEGEND-2 informed the design of the Phase 1b/2 CARTITUDE-1 study[2]

CARTITUDE-1: A Phase 1b/2 study of cilta-cel to treat RRMM[1]

Primary objectives

- Phase 1b: Characterise the safety of cilta-cel and establish the recommended Phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel (ORR)

Secondary objectives

- Characterise the safety, PK/PD and immunogenicity of cilta-cel
- Further characterise the efficacy of cilta-cel

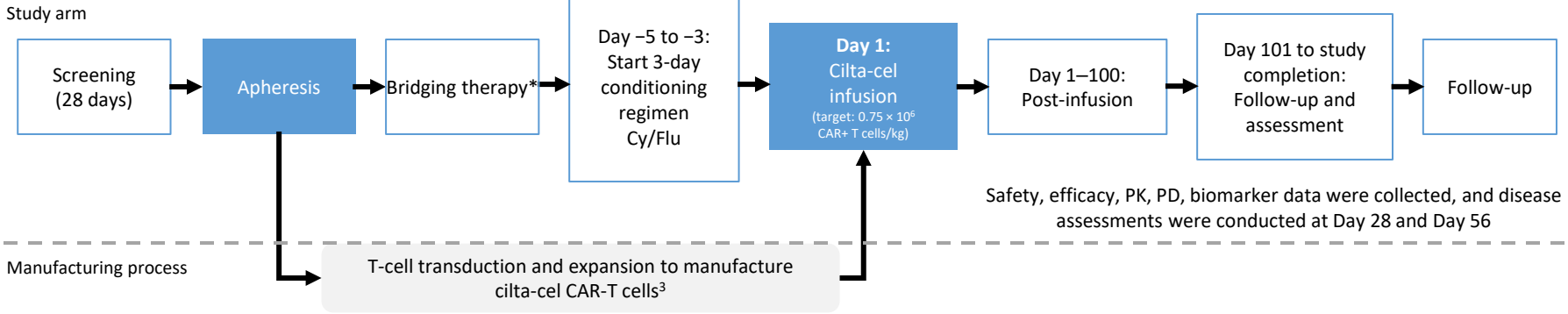
Key inclusion criteria

- Aged ≥18 years
- MM with measurable disease and ≥3 prior treatment regimens (or double refractory to IMiD and PI)
- Prior PI, IMiD and anti-CD38 antibody
- Disease progression within 12 months of the last treatment initiation
- ECOG performance status ≤1

Key exclusion criteria

- Prior CAR-T therapy or BCMA-targeted treatment; other malignancy
- Unresolved toxicity from prior treatment
- Prior allogeneic SCT ≤6 months before apheresis
- Prior ASCT ≤12 weeks before apheresis
- Known active CNS involvement or certain pathologies

Study design[1,2]

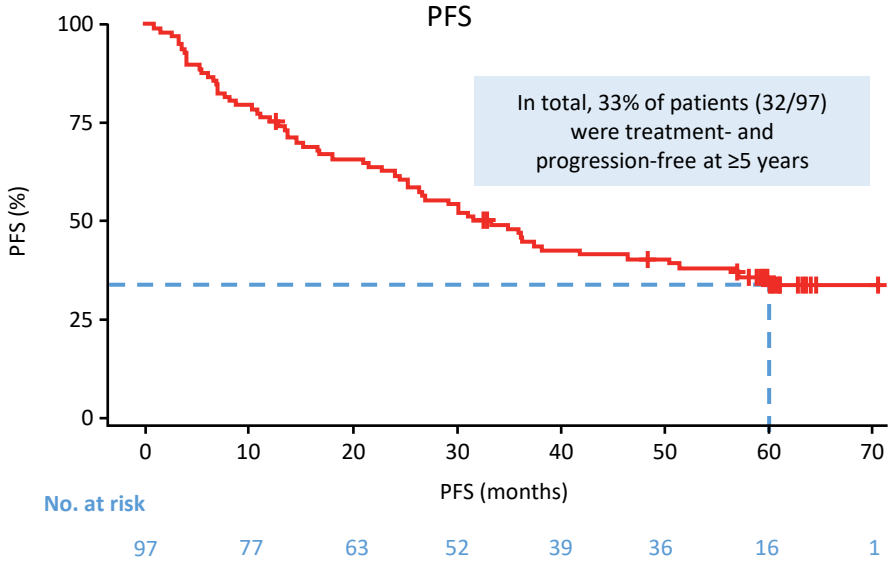


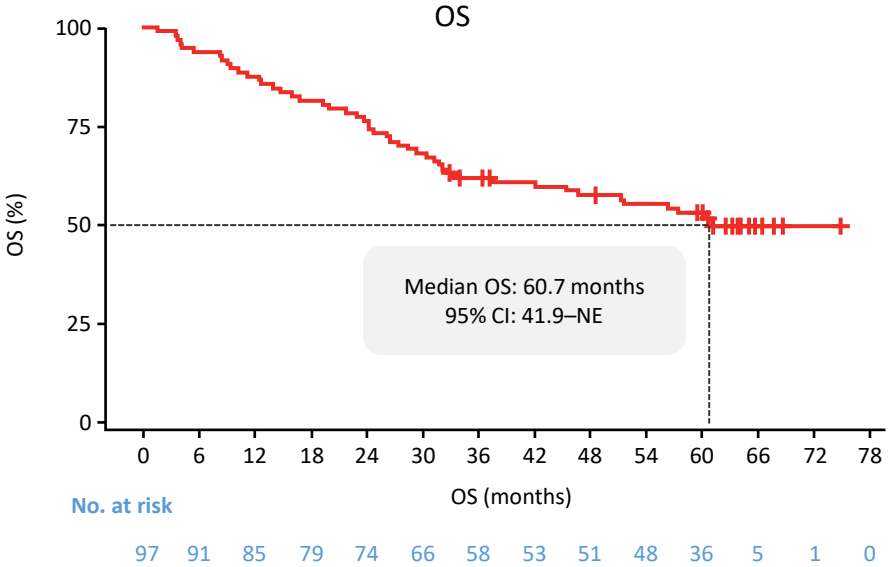
*Treatment with previously used agent resulting in at least stable disease.[1,2]

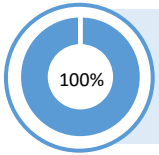
ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel;

After a single infusion of cilta-cel, one-third of patients with triple-class exposed RRMM were progression-free for ≥5 years

Data cut-off: February 2025; median follow-up: 61.3 months

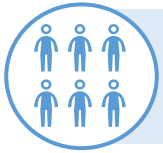






Deep and durable MRD-negativity was observed

- *Among 12 patients who achieved sCR at a single centre, 100% were MRD-negative serially and at ≥5 years*



Baseline characteristics were generally comparable between patients with/without PD within 5 years

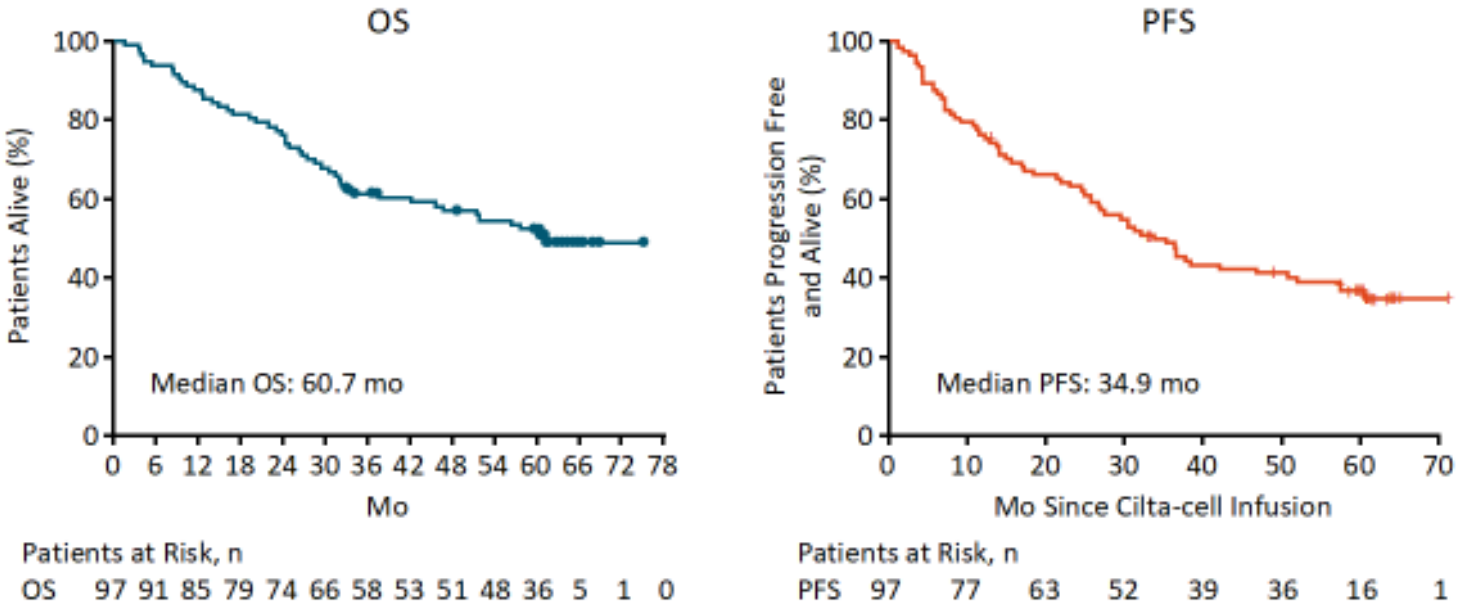
- *Including those with high-risk cytogenetics or extramedullary plasmacytomas at baseline*

CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response.

CP-544527

Jagannath S et al. *J Clin Oncol* 2025; doi: 10.1200/JCO-25-00760 [Epub ahead of print].

CARTITUDE-1 Phase Ib/II Trial of Cilta-cel in R/R MM: Long-term Survival Outcomes (≥5 Yr)

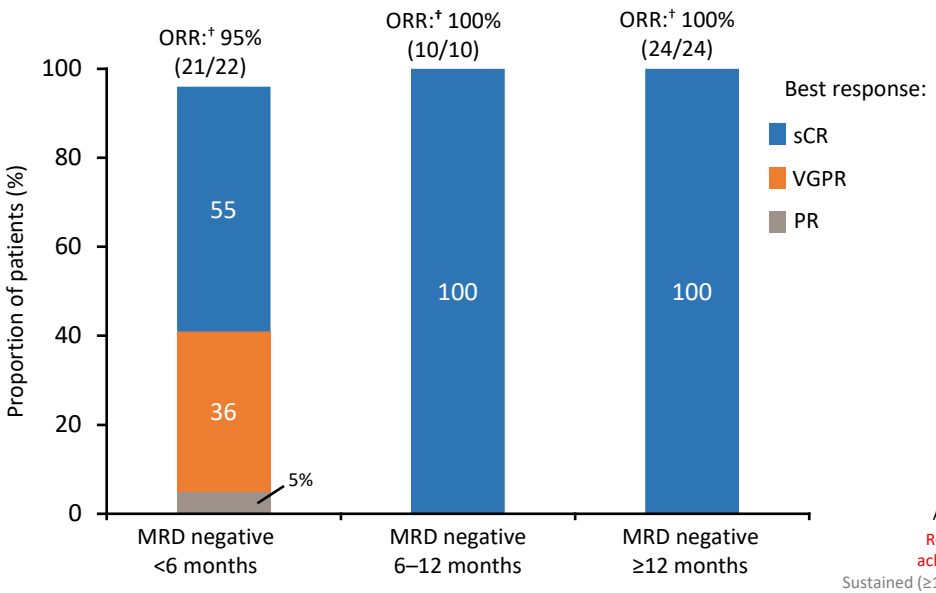


Median follow-up: 61.3 mo

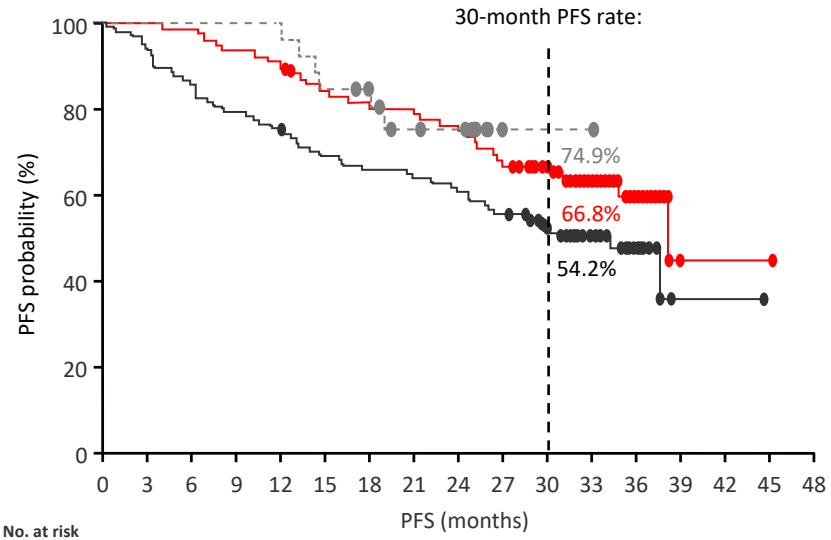
Jagannath. JCO. 2025;[Epub]

Outcomes were improved in patients reaching CR or sustained MRD negativity versus other patients

Response to cilta-cel in MRD subgroups
(Median follow-up: 27.7 months)*[1,2]



PFS by depth of response
(Median follow-up: 33.4 months)‡[3]



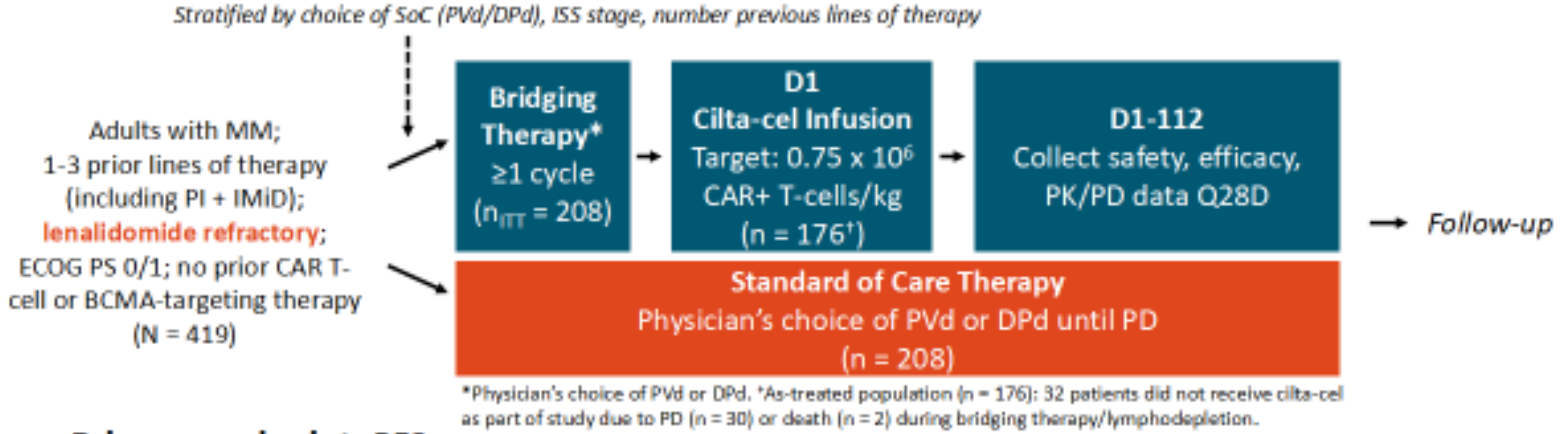
No. at risk																
All patients	97	94	85	77	74	67	64	63	60	54	44	25	13	2	1	1	0
Responders achieving CR§	76	76	75	71	69	63	61	60	57	51	42	25	13	2	1	1	0
Sustained (≥12 months) MRD negativity¶	26	26	26	26	26	22	18	11	9	2	1	1	0	0	0	0	0

*Data cut-off: 11 January 2022, median follow-up: 27.7 months;[1,2] †ORR may not sum appropriately as shown due to rounding;[1] ‡Data cut-off: 14 October 2022, median follow-up: 33.4 months;[3] §Patients had ≥CR at any time during the study, assessed by a computerised algorithm;[3] ¶Patients with sustained MRD negativity had ≥2 assessments 12 months apart with no MRD-positive samples in that interval.[3]

CP-544527

CARTITUDE-4: Cilta-cel vs SoC in Lenalidomide-Refractory MM

- Randomized, open-label phase III trial

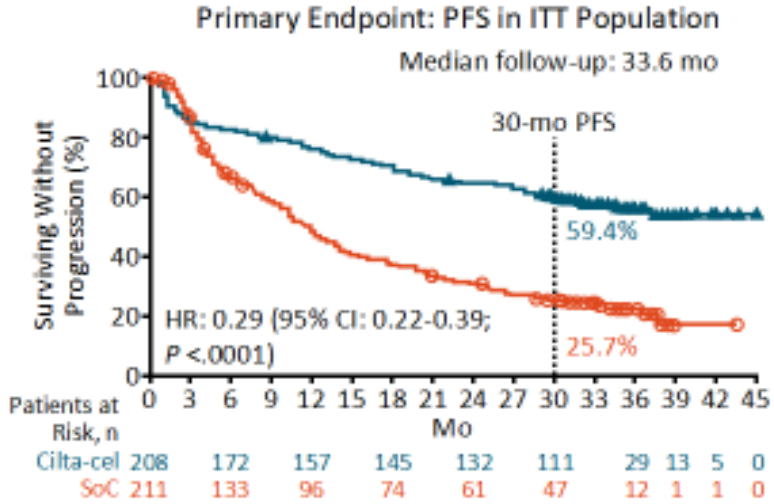


*Physician's choice of PVd or DPd. †As-treated population (n = 176): 32 patients did not receive cilta-cel as part of study due to PD (n = 30) or death (n = 2) during bridging therapy/lymphodepletion.

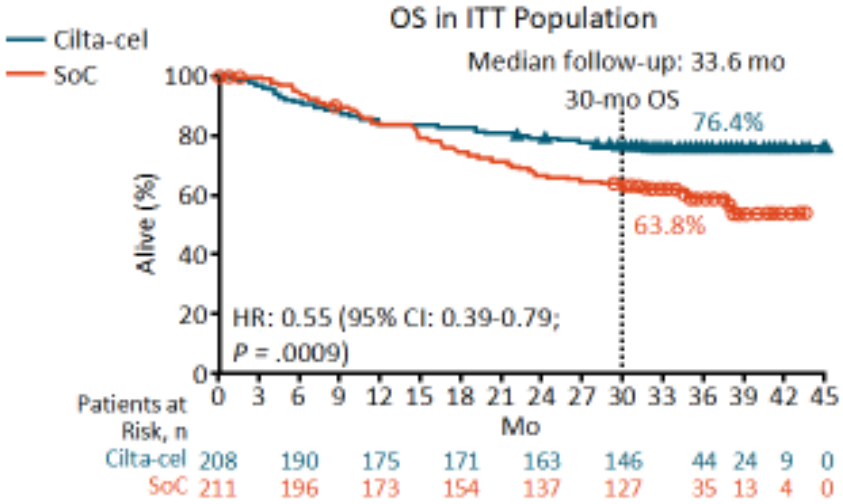
- **Primary endpoint:** PFS
- **Secondary endpoints:** ≥ CR, ORR, MRD negativity, OS, safety, PROs
- Current analysis after 15.9 mo median follow-up (range: 0.1-27 mo)

San-Miguel. NEJM. 2023;389:335. NCT04181827.

CARTITUDE-4 (Update): PFS and OS After 34 Mo of Follow-up



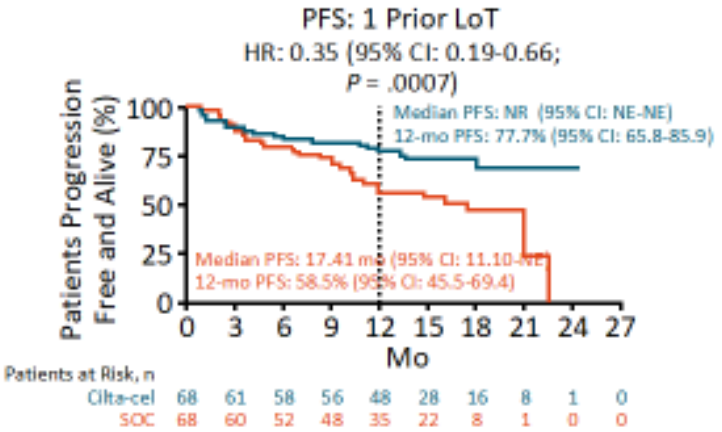
- There was a consistent reduction in the risk of progression or death with cilta-cel across all prespecified subgroups regardless of prior lines of tx, ISS staging, presence/absence of soft tissue plasmacytomas, tumor burden status, cytogenetic risk at baseline, tx refractory status, or prior exposure to daratumumab ± bortezomib

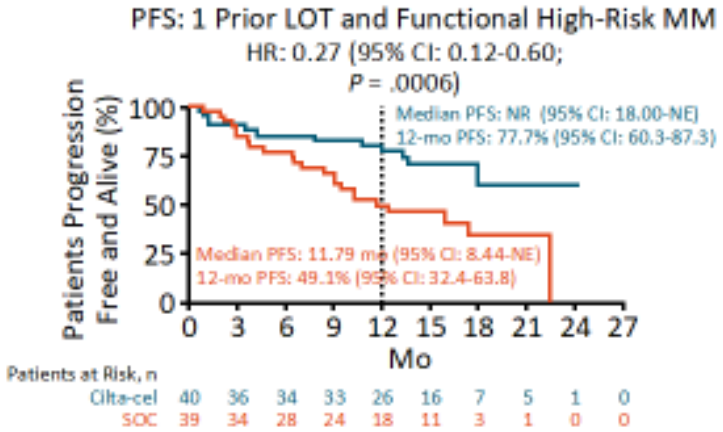


- There was a consistent reduction in risk of death with cilta-cel across most prespecified subgroups except ISS stage III, which had 12 patients in the cilta-cel arm and 14 patients in the SoC arm

Mateos. IMS 2024. Abstr OA-65.

CARTITUDE-4 (Patients With Functional High-Risk MM): PFS, Response, and MRD Negativity



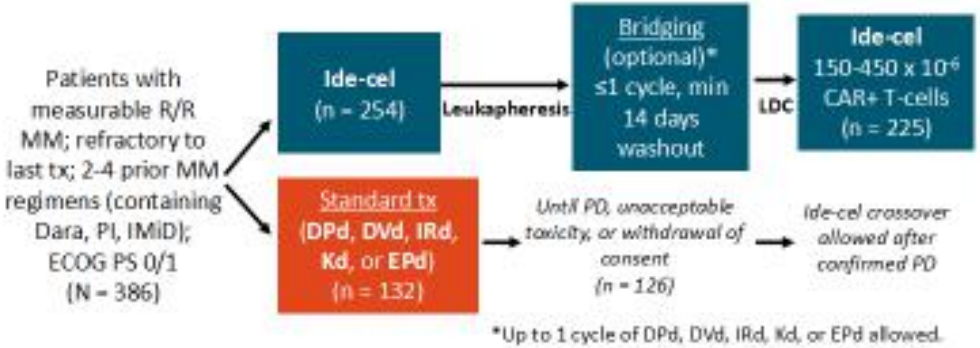


Response, %	Received Cilta-cel After 1 Prior LoT (n = 61)	Received Cilta-cel After 1 Prior LoT and Have Functional High-Risk MM (n = 35)
ORR	90	88
≥CR	71	68
MRD negativity (10^{-5})	63	65

Weisel. EHA 2024. Abstr P959.

KarMMa-3: Trial Design and Baseline Characteristics

- International, open-label, randomized phase III trial



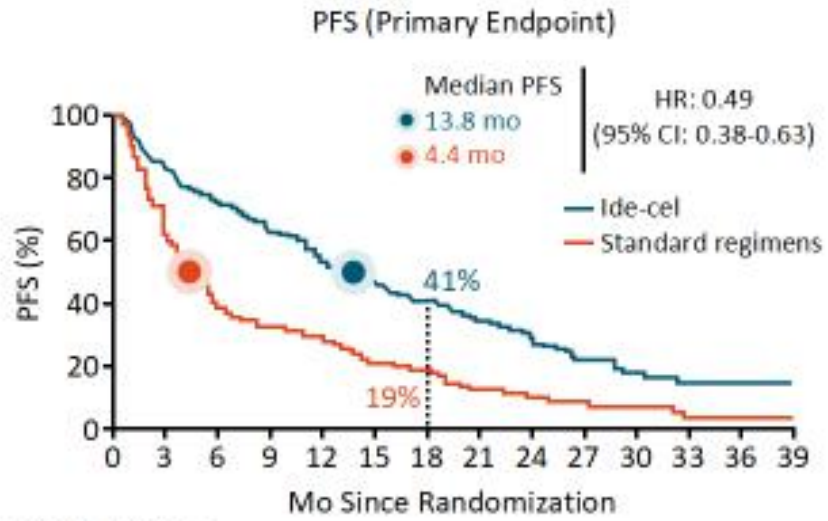
- **Primary endpoint:** PFS (IRC)
- **Key secondary endpoints:** ORR (IRC), OS
- **Exploratory endpoints:** CR rate (IRC), DoR, MRD-negative CR, PFS2, safety

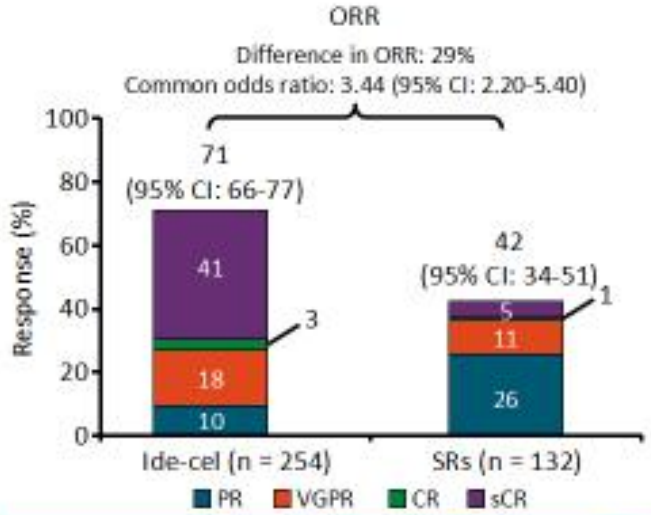
Characteristic		Ide-cel (n = 254)	SoC (n = 132)
Median age, yr (range)		63 (30-81)	63 (42-83)
R-ISS stage, n (%)	• I	50 (20)	26 (20)
	• II	150 (59)	82 (62)
	• III	31 (12)	14 (11)
EMP, n (%)		61 (24)	32 (24)
High tumor burden*, n (%)		71 (28)	34 (26)
High-risk cytogenetics, n (%)	• Any	166 (65)	82 (62)
	• del(17p)	66 (26)	42 (32
	• t(4;14)	43 (17)	18 (14)
	• t(14;16)	8 (3)	4 (3)
	• 1q gain/amp	124 (49)	51 (39)
Ultra–high-risk cytogenetics, n (%)		67 (26)	29 (22)
Median no. of prior regimens (range)		3 (2-4)	3 (2-4)
Dara refractory, n (%)		242 (95)	123 (93)
Triple-class refractory, n (%)		164 (65)	89 (67)

*≥50% CD138+ plasma cells in BM.

Allawadhi. Blood. 2024;144:2389. NCT03651128.

KarMMa-3: PFS and Response



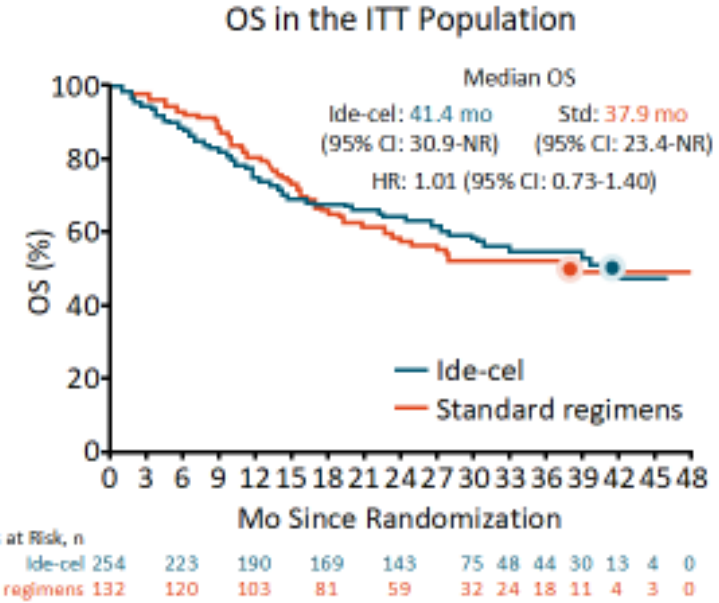


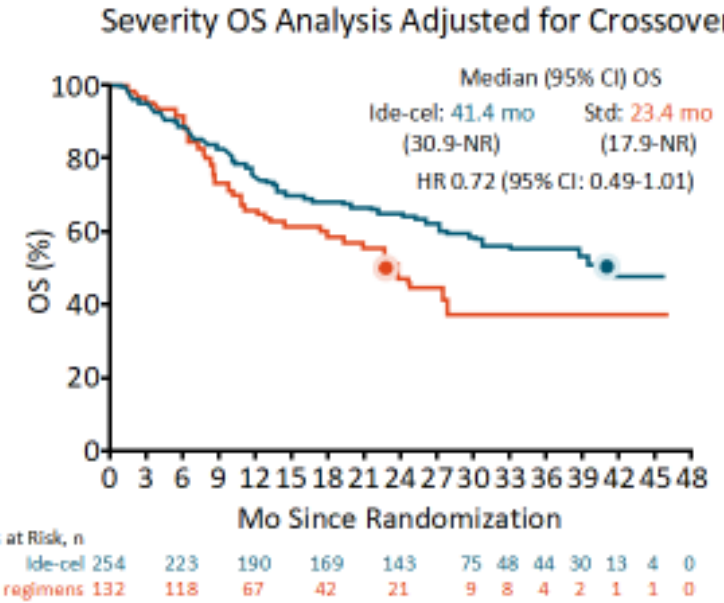
DoR	Ide-cel (n = 254)	SoC (n = 132)
Median DoR, mo (95% CI)	16.6 (12.1-19.6)	9.7 (5.5-16.1)

Median follow-up: 30.9 mo

Allawadhi. Blood. 2024;144:2389.

KarMMa-3: OS



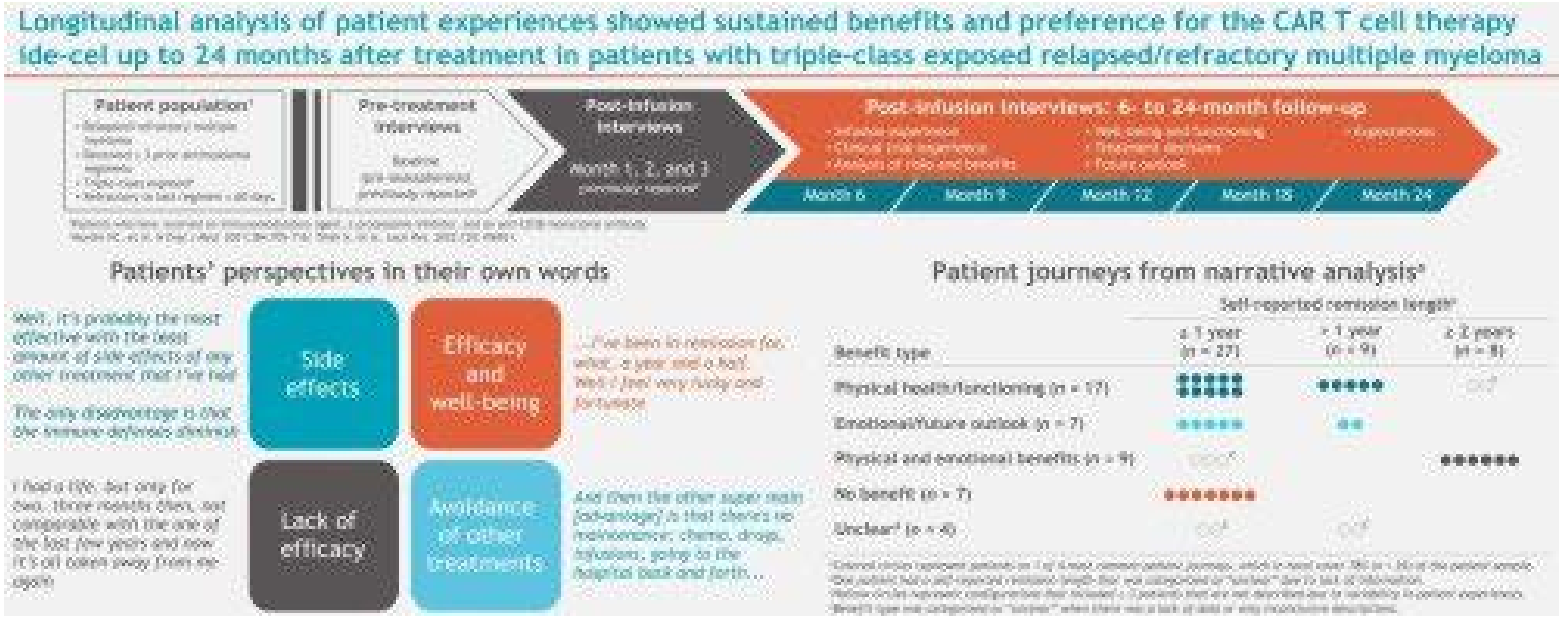


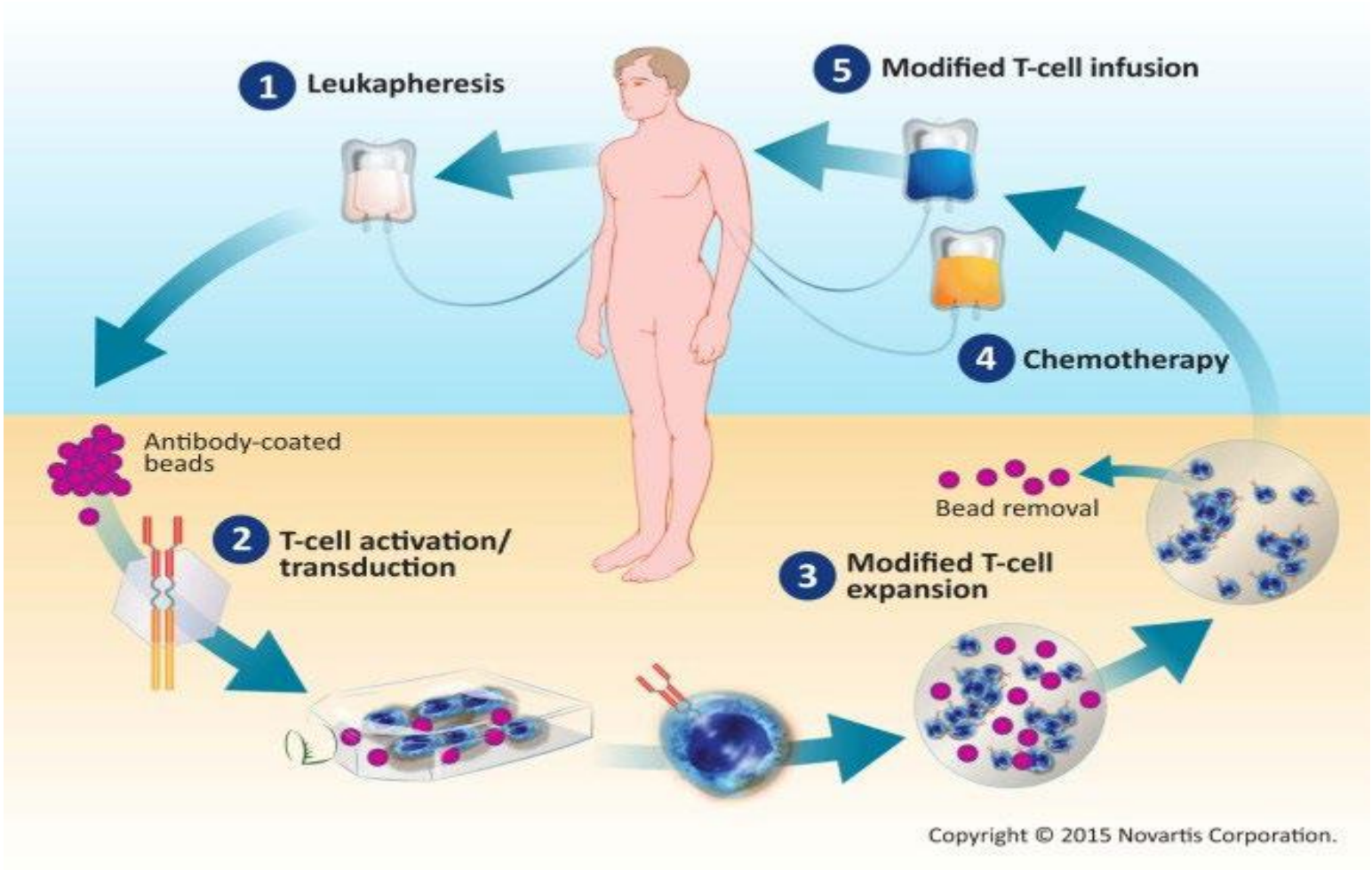
- 56% of patients in the SoC arm crossed over to receive ide-cel

Median follow-up: 30.9 mo

Allawadhi. Blood. 2024;144:2389.

Idecel


Longitudinal analysis of patient experiences showed sustained benefits and preference for the CAR T cell therapy ide-cel up to 24 months after treatment in patients with triple-class exposed relapsed/refractory multiple myeloma
Patient population
Pre-treatment interviews
Post-infusion interviews
Month 1, 2, and 3
Post-infusion interviews: 6- to 24-month follow-up
Month 6
Month 9
Month 12
Month 18
Month 24
Patients' perspectives in their own words
Well, it's probably the most effective with the least amount of side effects of any other treatment that I've had
The only disadvantage is that the immune deficiency obviously
I had a life, but only for two, three months then, not comparable with the one of the last few years and now it's all taken away from me again
Side effects
Efficacy and well-being
Lack of efficacy
Avoidance of other treatments
...I've been in remission for, what, a year and a half. Well I feel very lucky and fortunate
And then the other super main [advantage] is that there's no maintenance: chemo, drugs, infusions, going to the hospital back and forth...
Patient journeys from narrative analysis
Self-reported remission length
Benefit type
≤ 1 year (n = 27)
> 1 year (n = 9)
≥ 2 years (n = 8)
Physical health/functioning (n = 17)
Emotional/future outlook (n = 7)
Physical and emotional benefits (n = 9)
No benefit (n = 7)
Unclear (n = 4)


1 Leukapheresis
5 Modified T-cell infusion
4 Chemotherapy
Antibody-coated beads
2 T-cell activation/ transduction
Bead removal
3 Modified T-cell expansion
Copyright © 2015 Novartis Corporation.

Bispecific Therapy Options for Multiple Myeloma

- "Off-the-shelf" immunotherapy with multiple binding domains
  - Target different tumor antigens like BCMA, GPRC5D, FcRH5
  - Also binds to immune cell targets, including CD3 (T-cell)
    - Teclistamab*: CD3 x BCMA
    - Elranatamab*: CD3 x BCMA
    - Talquetamab*: CD3 x GPRC5D
    - Cevostamab: CD3 x FcRH5
    - Linvoseltamab*: CD3 x BCMA
    - Etentamig: CD3 x BCMA

*FDA approved for treating adults with R/R MM after ≥4 prior lines of therapy, including a PI, IMiD, and anti-CD38 mAb.

- Variable administration: SC or IV options with required step-up dosing

Elranatamab-bcmm PI. Teclistamab-cqyv PI. Talquetamab-tgvs PI. van de Donk. Lancet. 2023;402:142.

Teclistamab è il primo anticorpo monoclonale bispecifico BCMA x CD3 off-the-shelf

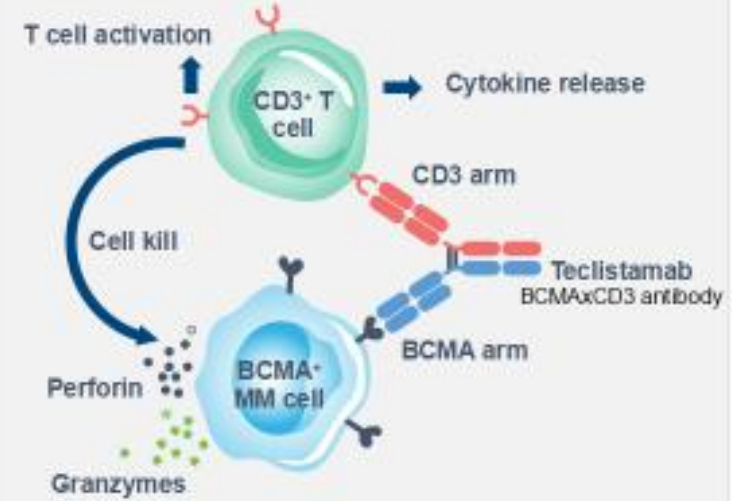
in monoterapia è indicato per il trattamento di pazienti adulti affetti da mieloma multiplo recidivato e refrattario che abbiano ricevuto almeno tre precedenti terapie, compresi un agente immunomodulatore, un inibitore del proteasoma e un anticorpo anti-CD38, e che abbiano evidenziato progressione della malattia durante l'ultima terapia

Teclistamab è un mAb bispecifico che ha come bersaglio due diversi antigeni (BCMA e CD3) per aiutare il sistema immunitario a combattere il cancro

Teclistamab è stato rimborsato con Registro di monitoraggio che prevede la prescrivibilità dopo 3 linee precedenti di terapia

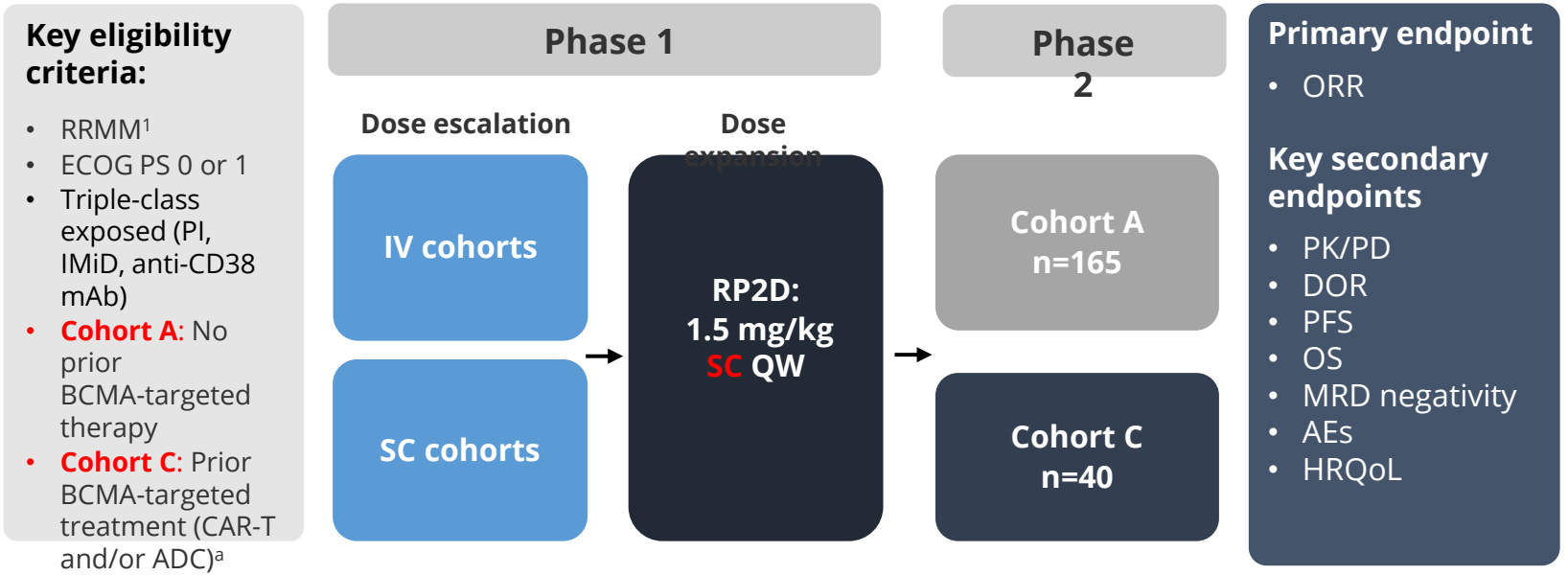
I pazienti riceveranno teclistamab sotto forma di iniezione sottocutanea (SC)

Meccanismo d'azione



Teclistamab: Phase 2 Study Design

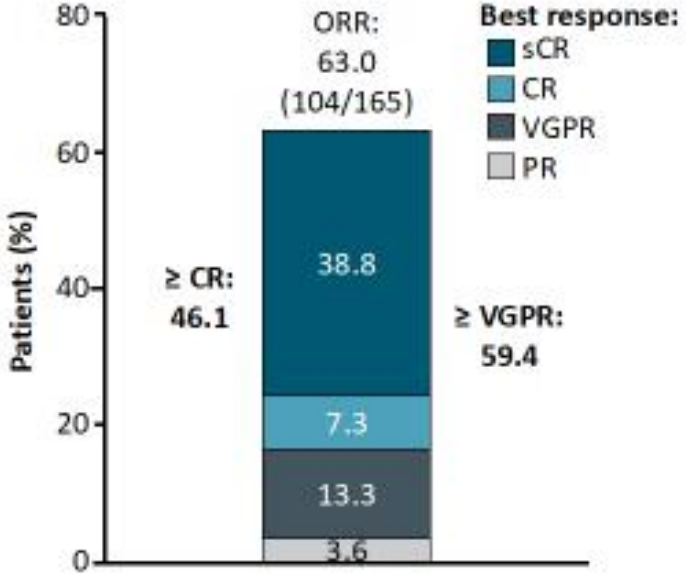
Initial Phase I investigations identified the recommended Phase II dose (RP2D) of teclistamab as a QW SC injection of 1.5 mg/kg, as opposed to IV

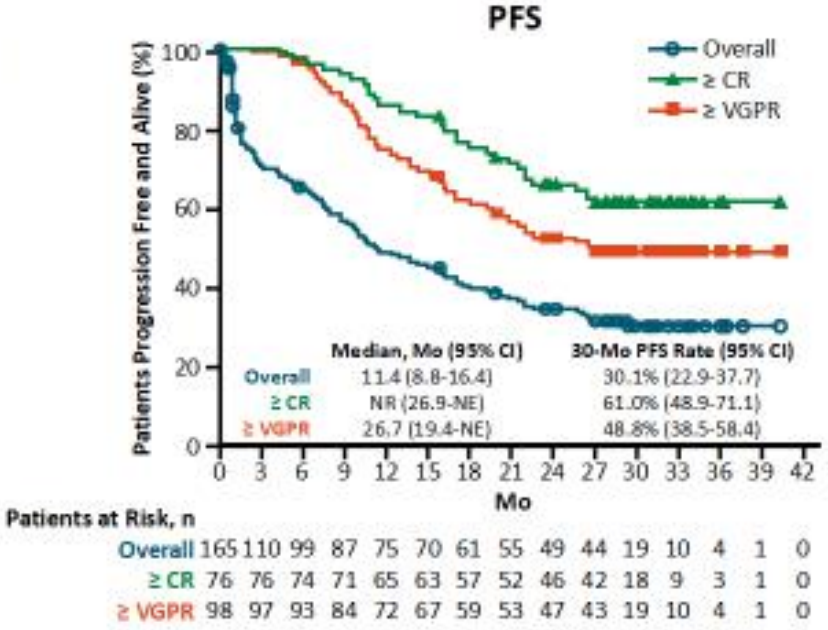


NOTE: RP2D was 1.5 mg/kg SC with 0.06 and 0.3 mg/kg step-up doses. [a]Cohort B is not planned for enrollment.[4] [b]Schedule change to biweekly (every other week) dosing was permitted based on response.[2] [c]In cohort C, a Simon's 2-stage design was used to test the null hypothesis that the ORR was ≤15% vs ≥35%.[3] [d]Baseline clones were obtained for all patients. All MRD assessments were done by NGS.[3]

BCMA, B-cell maturation antigen; CR, complete response; DOR, duration of response; LPI, last patient in; mAb, monoclonal antibody; MM, multiple myeloma; MRD, minimal residual disease; NGS, next generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PROs, patient reported outcomes; RP2D, recommended phase 2 dose; RR, relapsed/refractory; SC, subcutaneous; sCR, stringent complete response; TTR, time to response; VGPR, very good partial response.

Phase I/II MajesTEC-1: Teclistamab in R/R MM

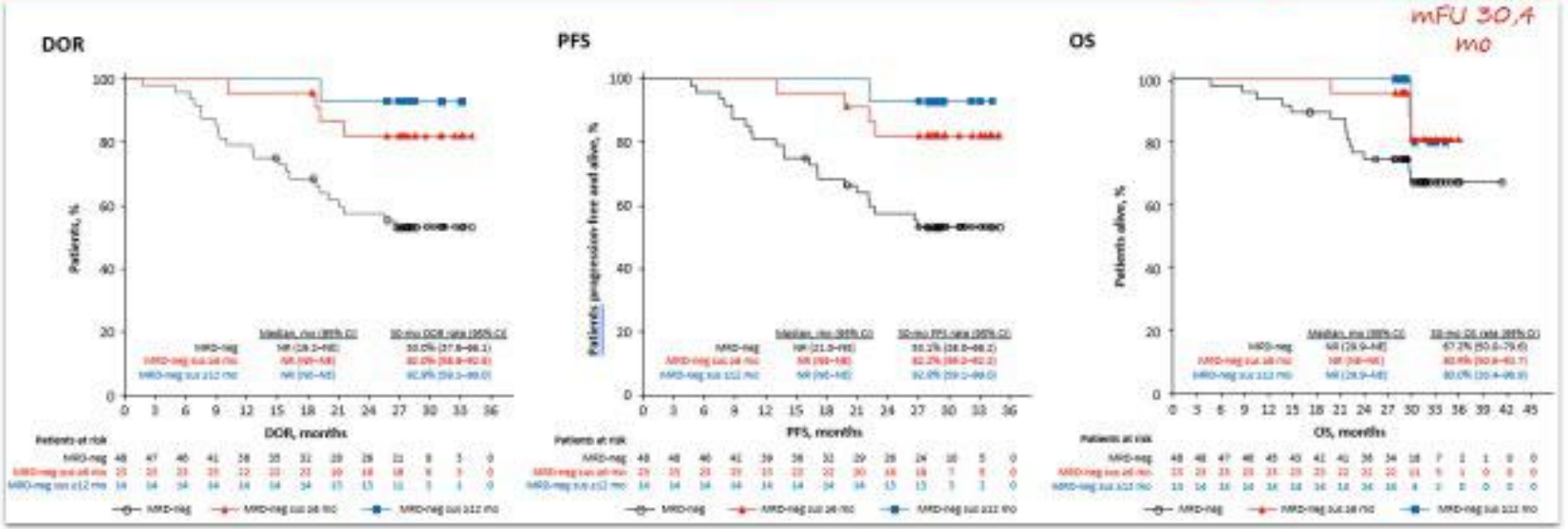




Moreau. NEJM. 2022;387:495. van de Donk. ASCO 2023. Abstr 8011. Garfall. ASCO 2024. Abstr 7540.

MajesTEC-1: DOR, PFS, and OS in MRD-neg patients

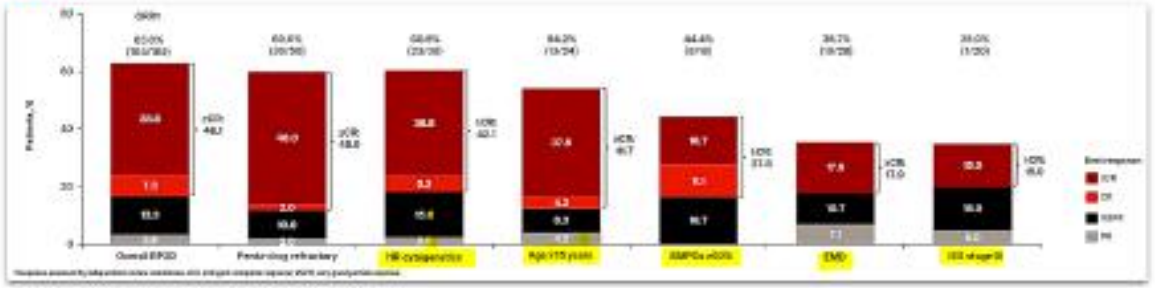
30-month DOR, PFS and OS rates were ≥80% for patients with sustained MRD negativity for ≥6 months



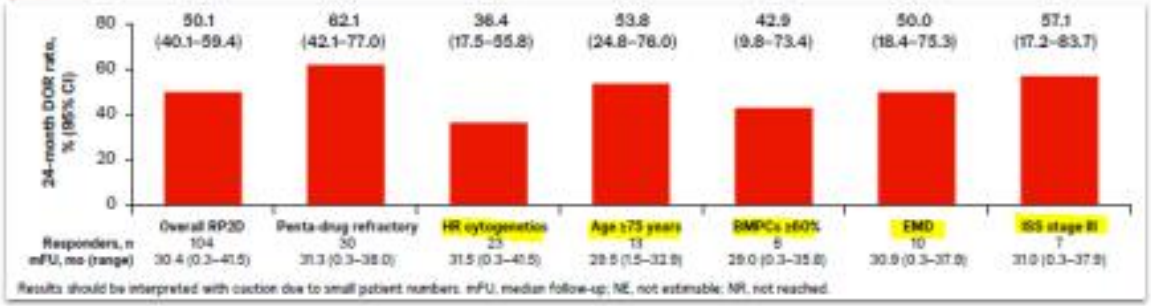
Garfall A L et al. ASCO 2024. P7540

Efficacy in patients with HR features

ORR



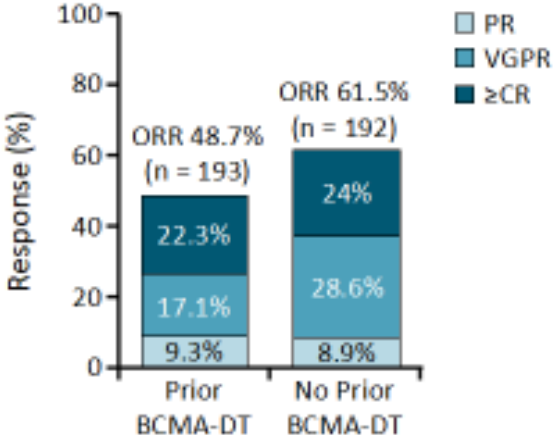
DOR



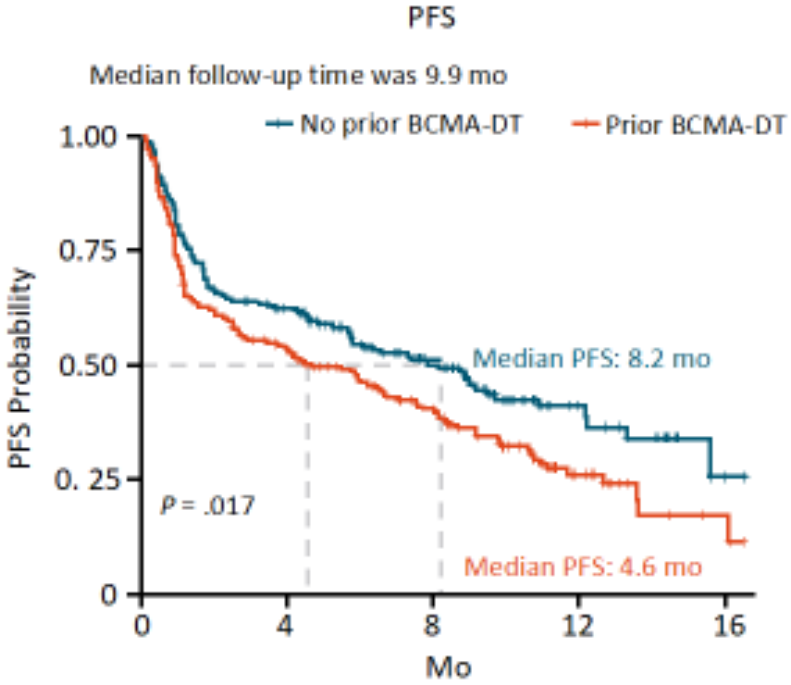
- Patients who are penta-drug refractory, have HR cytogenetics, or are age ≥75 years had ORR and ≥CR rates comparable with the overall population;
- patients with BMPCs ≥60%, EMD, or ISS stage III disease also derived benefit but remain difficult to treat

Costa et al, P923, EHA 2024

Real-World Evidence With Teclistamab in R/R MM: Response and PFS

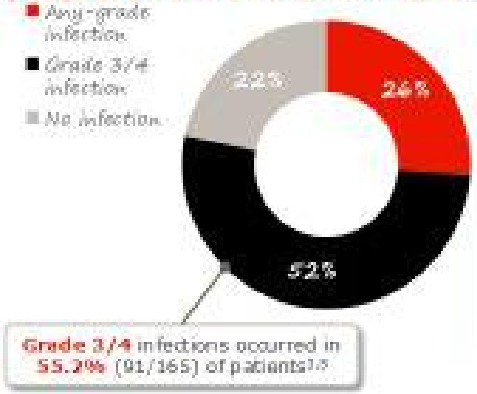


Prior BCMA-DT (Yes vs No)	*P*
ORR	.012
≥CR	.78
≥VGPR	.009



Dima. Blood Cancer J. 2025;15:111. Dima. ASH 2024. Abstr 897.

TECLISTAMAB THERAPY OFFERS A PREDICTABLE AND MANAGEABLE SAFETY PROFILE WITH LOW RATES OF DISCONTINUATIONS (<5%)1–3

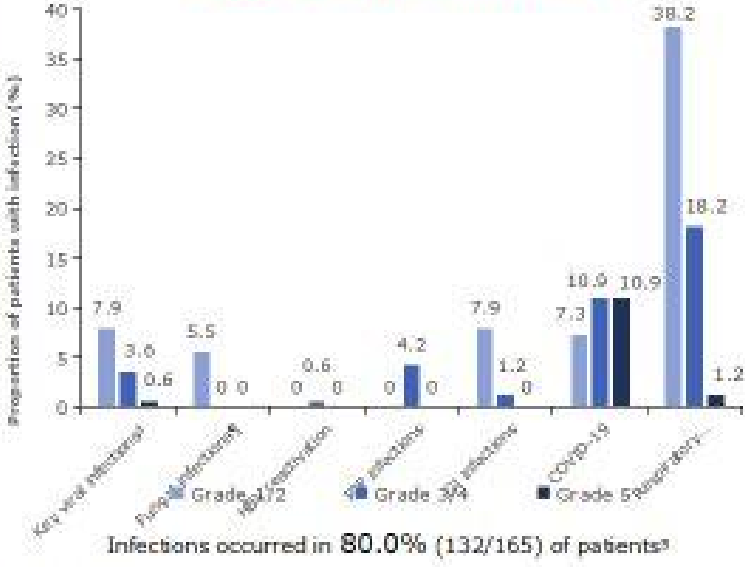


Grade 3/4 infections occurred in **55.2%** (91/165) of patients[2,3]

Incidence of discontinuation and death due to infection[2]	MajesTEC-1 population (N=165)
Discontinuation due to infection, n (%)*	5 (3.0)
Death due to infection, n (%)*	21 (12.7)
Median time to first onset of infection, months (range)	
Any-grade infection	1.7 (0.0–24.7)
Grade ≥3 infection	4.2 (0.0–34.6)

Prophylactic IVIG supplementation (aiming at keeping IgG >400 mg/dl) **significantly reduced the risk of developing serious (Grade ≥3) infections**[2]

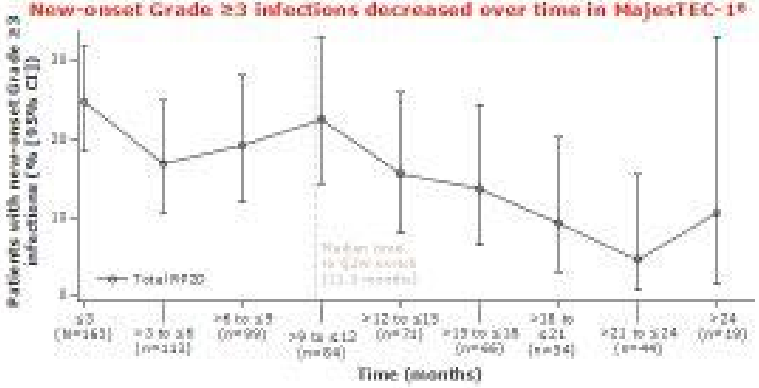
Incidence of infections in patients receiving teclistamab treatment in the MajesTEC-1 study[2]



Infections occurred in **80.0%** (132/165) of patients[2]

Fewer Grade ≥3 infections occurred between 1 year and 1.5 years of teclistamab treatment in patients who had **switched to Q2W dosing** by 1 year (**15.6%**) vs. those who remained on QW dosing at 1 year (**33.3%**)[2,3]

New-onset Grade ≥3 infections decreased over time in MajesTEC-1[3]



Footnotes are provided in the slide notes.

1. Moreau P, et al. N Engl J Med 2022;387:495–505; 2. Nooka A, et al. ASCO 2022. Oral Presentation 8007; 3. Van de Donk NWCJ, et al. ASCO 2023. Poster 8011; 4. TECVAYLI® (teclistamab) SmPC (EU) December 2022; 5. Nooka AK, et al. Cancer 2023; doi: 10.1002/cncr.35187; 6. Usmani SZ, et al. ASCO 2023. Poster 8024; 7. Frerichs K, et al. EHA 2022. Poster P1506.

Phase II MagnetisMM-3: Elranatamab for BCMA-Directed Therapy-Naive R/R MM (Cohort A)

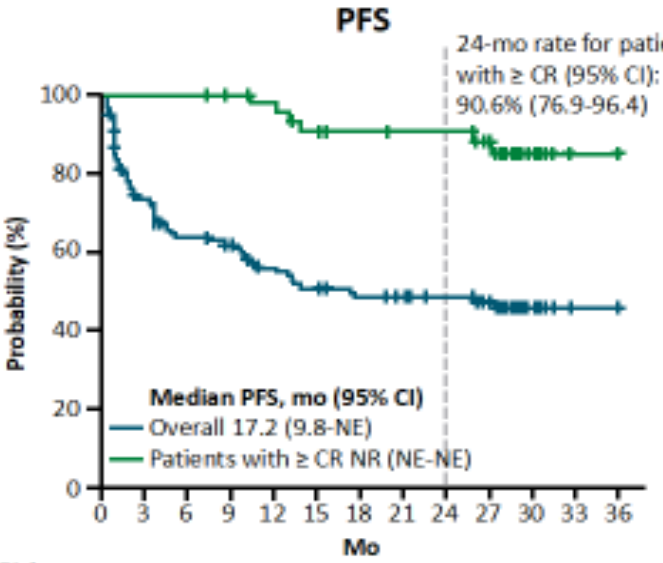
- Patients with MM refractory to ≥1 lines of therapy, including an IMiD, PI, and anti-CD38 mAb, and refractory to last line of therapy
  - 97% triple-class refractory
  - Median 5 prior lines of therapy (range: 2-22)
  - 25% with high-risk cytogenetics
  - 32% with extramedullary disease
- **Elranatamab:** 76 mg SC weekly with priming and/or premedication to reduce CRS
  - If weekly dosing given for ≥6 cycles with achievement of ≥ PR for ≥2 mo, then dosing interval changed to every 2 wk
- **Primary endpoint:** ORR
- **Secondary endpoint:** DoR, OS, PFS, safety

Response	N = 125
ORR, n (%)	**75 (61.0)**
▪ ≥ CR	46 (37.4)
▪ VGPR	23 (18.7)
▪ PR	6 (4.9)
Median DoR, mo	NE
▪ 2-yr DoR, % (95% CI)	66.9 (54.4-76.7)
Median DoR if:	
▪ ≥ VGPR	NE
▪ ≥ CR	NE

Median follow-up: 28.4 mo

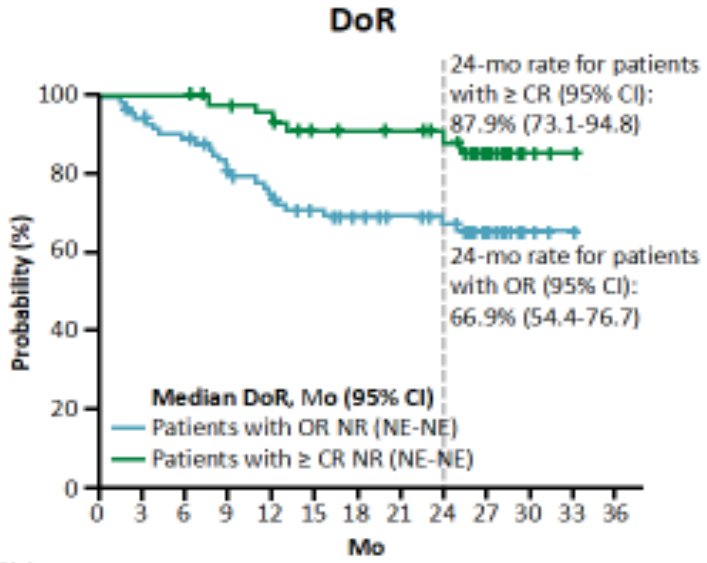
Lesokhin. Nat Med. 2023;29:2259. Mohty. EHA 2024. P932. Prince. ASH 2024. Abstr 4738. NCT04649359.

MagnetisMM-3: PFS and DoR



Patients at Risk, n

Overall	123	78	67	63	54	48	44	42	39	32	7	1	0
Patients with ≥ CR	46	46	46	44	42	38	36	35	35	28	7	1	0

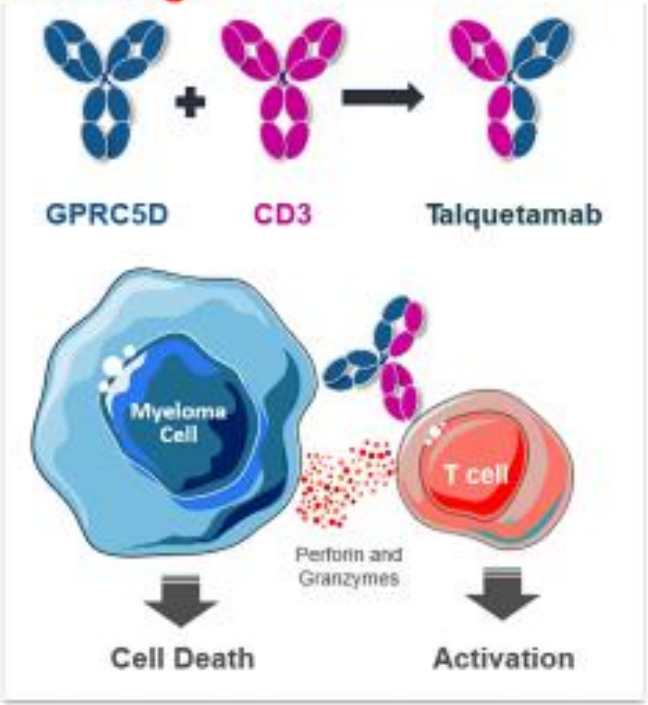


Patients at Risk, n

Patients with OR	75	70	65	57	50	45	41	38	35	18	3	1	0
Patients with ≥ CR	46	46	46	43	40	36	35	34	31	18	3	1	0

Mohty. EHA 2024. P932. Prince. ASH 2024. Abstr 4738.

Talquetamab: GPRC5D x CD3 Bispecific Antibody

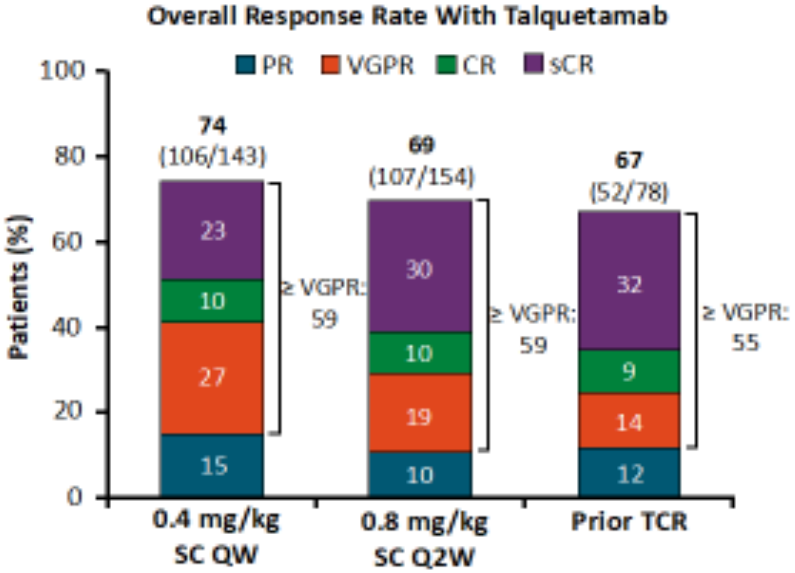


- Talquetamab is a first-in-class DuoBody® IgG4 PAA antibody that binds to both GPRC5D and CD3
- Talquetamab redirects T cells to GPRC5D-expressing myeloma cells to mediate cell killing
- Antitumor activity was demonstrated in primary myeloma cells and xenograft models of MM
- Talquetamab's pharmacokinetic profile presents an opportunity for less frequent SC dosing
- First-in-human phase 1 study is ongoing to evaluate talquetamab in patients with RRMM (NCT03399799)

Chari et al. 62nd ASH Meeting 2020. Abstract #290

Phase II MonumenTAL-1: Talquetamab in R/R MM

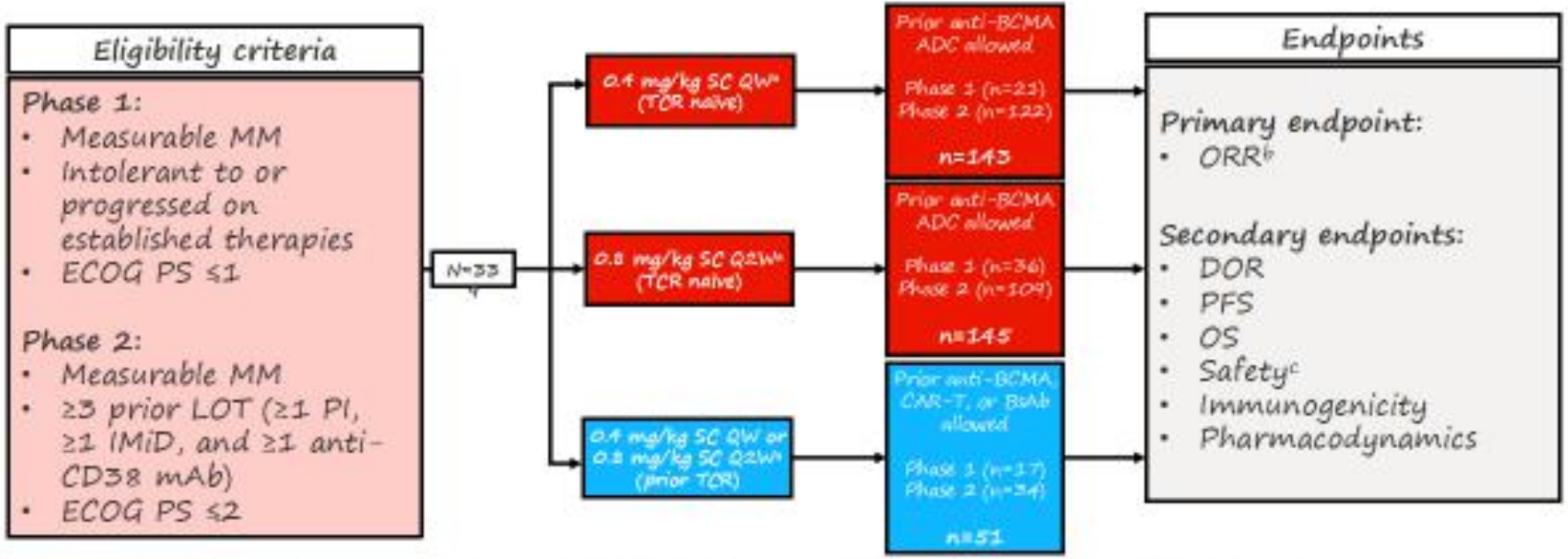
- Patients with R/R MM after ≥3 lines of therapy, including an IMiD, PI, anti-CD38 mAb
  - 71%-85% triple-class refractory
  - Median 5-6 prior lines of therapy across all cohorts
  - ~30% with high-risk cytogenetics; 23% to 32% with EMD
- **Talquetamab**: 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W with 2-3 step-up doses and/or premedication to reduce CRS
- **Primary endpoint:** DLTs
- **Key secondary endpoint:** ORR



In post hoc analyses, ORR was 72% in patients receiving previous CAR-T therapy and 58 in patients receiving previous bispecific antibody therapy

Chari. NEJM. 2022;387:2232. Schinke. ASCO 2023. Abstr 8036. Rasche. EHA 2024. Abstr P915. Chari. Lancet Haematol. 2025;12:e269.

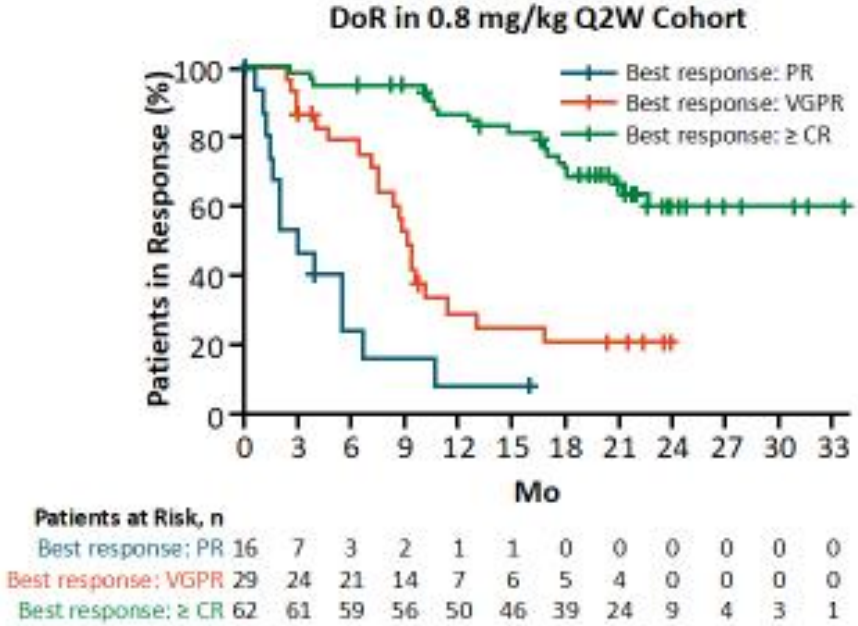
MonumenTAL-1: Phase 1/2 Study Design



[a]With 2–3 step-up doses. [b]Assessed by independent review committee using International Myeloma Working Group criteria. [c]Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome were graded by American Society for Transplantation and Cellular Therapy criteria; all other adverse events were graded by Common Terminology Criteria for Adverse Events v4.03.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CD38, cluster of differentiation 38; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; LOT, lines of therapy; mAb, monoclonal antibody; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; Q2W, every other week; QW, weekly; SC, subcutaneous; TCR, T-cell redirection therapy.

MonumenTAL-1: DoR and PFS Outcomes

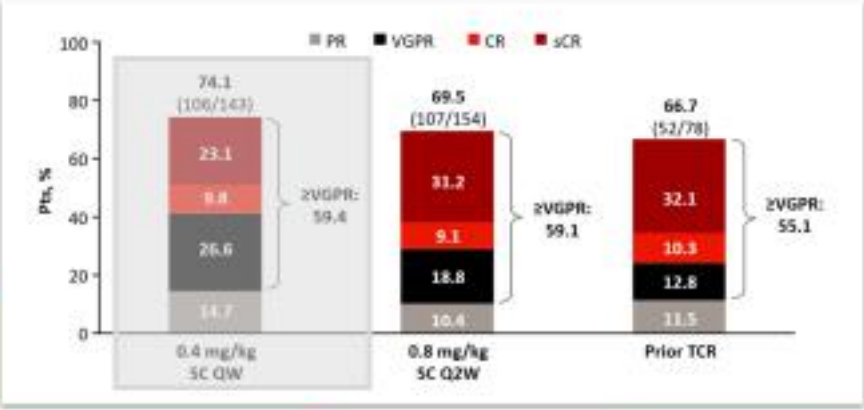


Outcome	0.4 mg/kg QW (n = 143)	0.8 mg/kg Q2W (n = 154)	Prior T-Cell Redirection Tx (n = 78)
Median f/u, mo	29.8	23.4	20.5
Median DoR, mo (95% CI)	9.5 (6.7-13.4)	17.5 (12.5-NE)	N/A
Median PFS, mo (95% CI)	7.5 (5.7-9.4)	11.2 (8.4-14.6)	7.7 (4.1-14.5)
24-mo OS, %	60.6	67.1	57.3

Rasche. EHA 2024. Abstr P915. Chari. Lancet Haematol. 2025;12:e269.

MonumenTAL-1: Efficacy outcomes

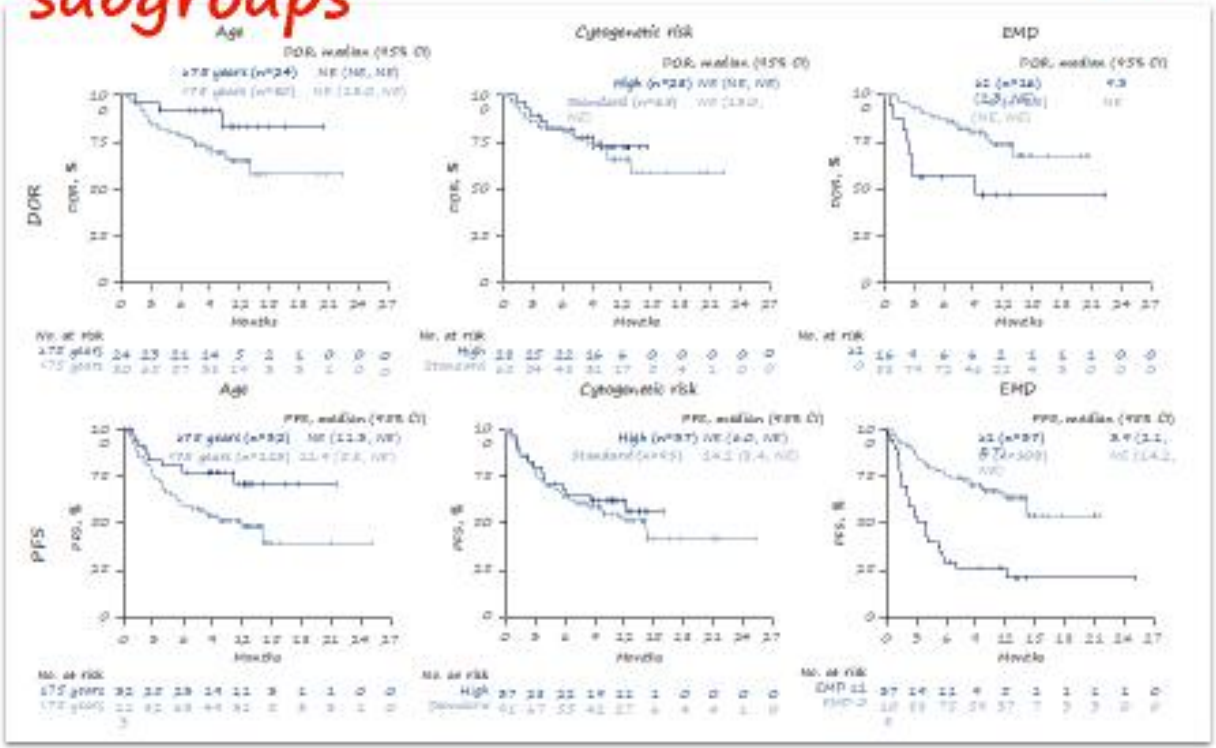
- mLoT 5
- Triple ref 75%
- Penta ref 20%
- Ref last line 89%



Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
mFU, mo	29.8	23.4	20.5
mDOR (95% CI),[a] mo	9.5 (6.7–13.4)	17.5 (12.5–NE)	N/A[b]
mDOR in pts with ≥CR (95% CI), mo	28.6 (19.4–NE)	NR (21.2–NE)	N/A[b]
mPFS (95% CI), mo	7.5 (5.7–9.4)	11.2 (8.4–14.6)	7.7 (4.1–14.5)
24-mo OS rate (95% CI), %	60.6 (51.7–68.4)	67.1 (58.3–74.4)	57.3 (43.5–68.9)

Rasche L et al. EHA 2024 P915

Monumental-1: Outcomes among select HR subgroups



- In high-risk vs standard-risk patients, DOR and PFS outcomes were similar for cytogenetic risk and showed differences for age and EMD subgroups in the Q2W cohort
- Similar data were observed in the QW cohort, except age, in which analyses were not performed

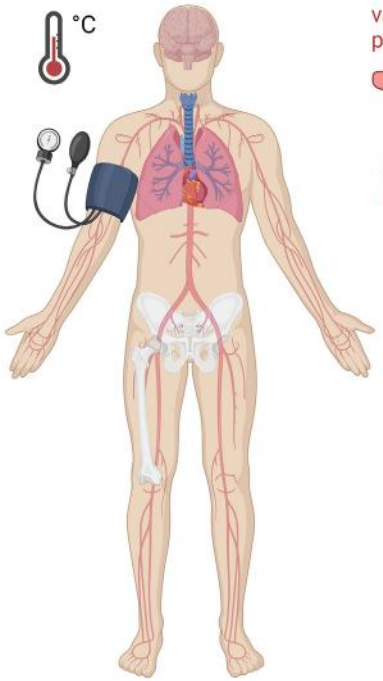
Krishnan A, et al. IMS 2023. Poster P-023

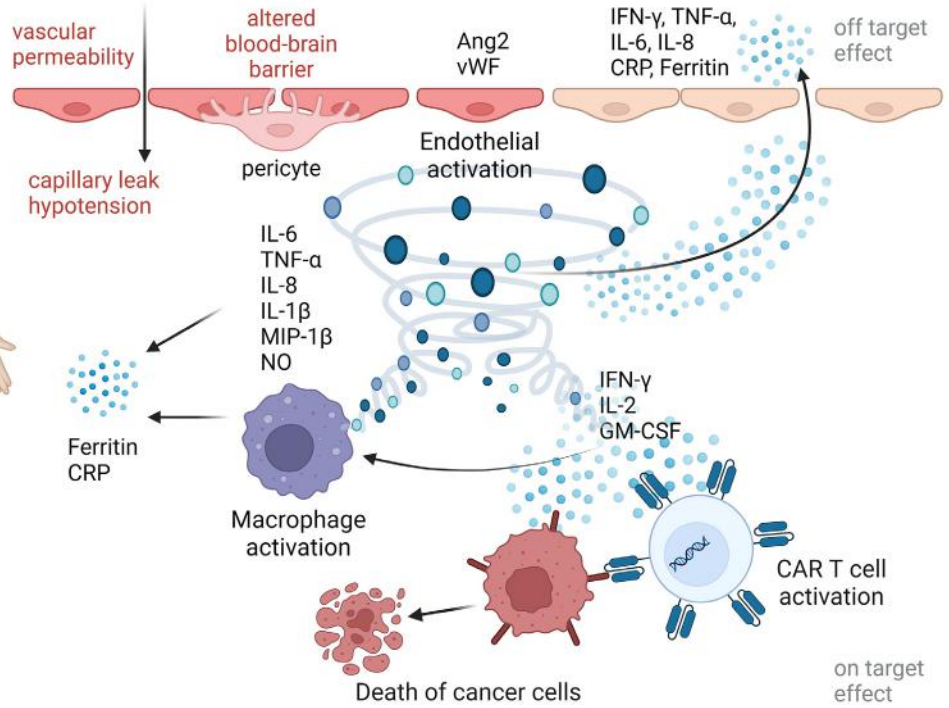
CRS and ICANS

Neurotoxicity/ICANS
Confusion
Tremor
Aphasia
Seizure
Cerebral edema
movement and
neurocognitive treatment-
emergent adverse events

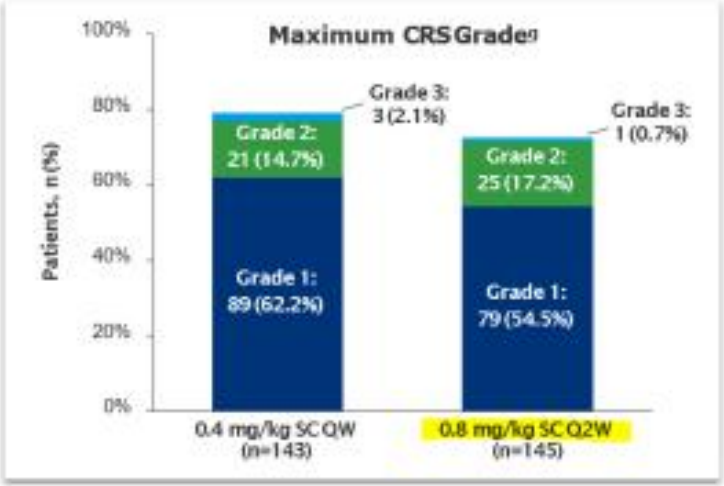
Cytokine release syndrome
Fever
Hypotension/Tachycardia
Hemodynamic instability
Capillary leak
Hypoxia/Respiratory failure
Organ dysfunction

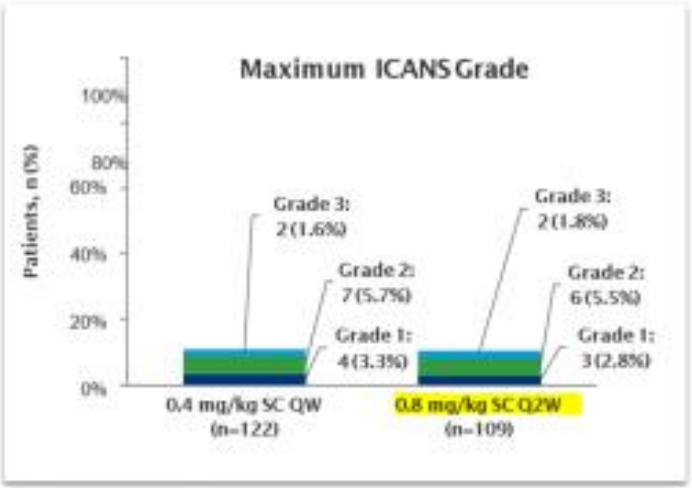
Hematotoxicity
Prolonged cytopenias
Infectious complications





MONUMENTAL-1: ICANS and CRS





Most CRS events were grade 1/2 and largely confined to the step-up doses and first full dose

- ICANS occurred in 10–11% of patients across RP2D groups
- Most ICANS events were grade 1 or 2
- 7–8% of patients received supportive measures for ICANS across RP2D groups, including tocilizumab and corticosteroids

Ajai Chari et al. - Oral Presentation #157 - ASH 2022

Box 2 | Summary of recommendations for the management of common complications in patients with multiple myeloma

Bone disease

- Antiresorptive agents should be given in addition to myeloma-directed therapy in all patients with MM and osteolytic disease at diagnosis [I, A].
- Denosumab is a reasonable option in patients with severe renal impairment, in whom aminobisphosphonates are not recommended; caution is needed owing to a high risk of hypocalcaemia [III, C].
- Zoledronic acid should be given monthly in patients with suboptimal response (PR or less) and at least for 4 years [I, A].
- In patients who have a CR or vgPR, 12–48 months of therapy with zoledronic acid seems adequate. At relapse, zoledronic acid should be reinitiated [III, B].
- Denosumab should be given every 4 weeks continuously. Discontinuation of denosumab is challenging owing to the lack of data on how to stop denosumab in patients with MM; until these data are available, discontinuation of denosumab must be followed by a dose of zoledronic acid (6–9 months after the last dose of denosumab) to prevent any 'rebound' phenomenon [III, B].
- Vitamin D and calcium supplementation is mandatory when administering either bisphosphonates or denosumab [I, A].
- Low-dose radiation therapy (up to 30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathological fracture, or for impending spinal cord compression [II, A].
- Balloon kyphoplasty should be considered for symptomatic vertebral compression fractures with refractory pain [II, B].
- Surgery is recommended for long-bone fractures, bony compression of the spinal cord, or vertebral column instability [II, A].

Anaemia

- Recombinant human erythropoietin and darbepoetin alfa for the treatment of myeloma-associated anaemia if other causes of anaemia have been excluded [II, B].
- G-CSF might be required to treat chemotherapy-induced severe neutropenia [II, B].

Infections

- Immediate therapy with broad-spectrum antibiotics [I, A].
- Prophylactic antibiotics (such as levofloxacin) for the first 3 months of initiation of therapy, especially in patients receiving lenalidomide or pomalidomide, or in those at high risk of infections [I, A].
- Sulfamethoxazole and trimethoprim are recommended for the prevention of *Pneumocystis jirovecii* infection [I, A].
- Acyclovir or valacyclovir for herpes zoster prophylaxis is recommended in patients receiving proteasome inhibitors, anti-CD38 antibodies and BCMA-targeted therapies [II, A].
- Vaccination for influenza, varicella zoster (inactivated vaccine), SARS-CoV-2 and pneumococcal infections [II, A] as well as for respiratory syncytial virus [III, C].
- Intravenous IgG prophylaxis is not routinely recommended although it is highly recommended in patients receiving either bispecific T cell engagers or CAR T cells [III, C]; it should be used in patients with low IgG levels (<400–500 mg) and in those with at least two severe infections requiring hospitalization during the previous year [II, B].

Impaired renal function

- Bortezomib-based regimens remain the cornerstone of the management of MM-related renal impairment [I, A].
- High-dose dexamethasone at least for the first month of therapy [II, B].
- Patients eligible for ASCT can receive DaraVTd or DaraVCd [II, B]. If reversal of renal impairment is observed, thalidomide or cyclophosphamide might be substituted by lenalidomide [panel consensus; V, B]. In patients who are ineligible for ASCT, DaraVCd or VMP can also be administered [II, B] but no data on this regimen in patients undergoing dialysis are available.
- Pomalidomide, carfilzomib, ixazomib, daratumumab and isatuximab need no dose modifications in patients with renal impairment [II, B].
- CAR T cells can be given in patients with mild to moderate renal impairment [II, B].
- Teclistamab can be given to patients with MM-related renal impairment, even including those undergoing dialysis [III, C].

ASCT, autologous stem cell transplantation; C, cyclophosphamide; CAR, chimeric antigen receptor; CR, complete response; d, dexamethasone; Dara, daratumumab; G-CSF, granulocyte colony-stimulating factor; M, melphalan; P, pomalidomide; PR, partial response; T, thalidomide; vgPR, very good partial response. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1).

Box 3 | Summary of recommendations for the management of toxicities derived from novel therapies in patients with multiple myeloma

Ocular toxicities

- Ophthalmology evaluation is recommended before each belantamab mafodotin infusion for the first four cycles [I, A].
- The treating physician can decide for the next dose administration or delay based on the vision-related anamnestic tool [II, B].
- Dose delays, dose reductions and prolonged intervals (every 8 to 12 weeks) between belantamab mafodotin administration lead to the recovery of ocular AEs without affecting the efficacy of the drug [I, A].

CRS

Grade 1

- Supportive care including analgesics and antipyretics [I, A].
- If fever persists, check for infections [I, A].
- Consider tocilizumab for persistent (>3 days) and refractory fever [I, A].

Grade 2

- Intravenous fluid bolus [I, A].
- Tocilizumab early if fever of ≥39°C persists, if hypotension persists despite the use of initial fluid bolus or after initiation of oxygen supplementation [II, B].
- If hypotension persists after a second fluid bolus and tocilizumab, transfer to the intensive care unit [I, A].
- Add dexamethasone if hypotension persists after anti-IL-6 antibodies, high risk of severe CRS, worsening hypoxia or clinical concern [panel consensus, IV, C].

Grade 3

- Consider intensive care [I, A].
- Administer tocilizumab [II, B].
- Add dexamethasone if no response within 24 h, increasing dose if refractory [II, B].
- Add anakinra if CRS unresponsive [panel consensus; III, C].
- Consider etanercept as clinically appropriate [panel consensus; III, C].

Grade 4

- Consider intensive care [I, A].
- Administer tocilizumab [II, B].
- Administer high-dose methylprednisolone [II, B].
- Add anakinra if CRS unresponsive [panel consensus; III, C].
- If CRS remains unresponsive consider alternative agents such as etanercept [panel consensus; III, C].

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Grade 1

- Observation.
- Withhold oral food, medicine and fluid intake and switch to intravenous intake.
- Haloperidol or lorazepam if patient is agitated [II, B].
- Consider early dexamethasone in high-risk patients [II, B].
- Start non-sedating AEDs if not already being administered [panel consensus; III, C].
- MRI of brain, lumbar puncture, funduscopic examination and/or EEG [I, A].

Grade 2

- Dexamethasone [II, B].
- If no improvement after 48 h, increase dexamethasone dose or administer alternative agents such as anakinra or tocilizumab in the concomitant presence of CRS [II, B].
- Start non-sedating AEDs if not already being administered [II, B].
- Consider EEG and CT or MRI [II, B].

Grade 3

- Dexamethasone [II, B].
- If no improvement after 24 h, increase dexamethasone dose [II, B], or administer high-dose methylprednisolone and/or alternative agents such as anakinra [panel consensus; IV, C].
- Start non-sedating AEDs if not already being administered [II, B].
- Consider EEG and CT or MRI [II, B].
- Acetazolamide if increased CSF pressure [panel consensus; IV, C].

Grade 4

- Dexamethasone [II, B].
- If refractory, administer high-dose methylprednisolone [panel consensus; IV, C].
- If ICANs remains refractory, consider alternative therapies including lymphodepletion with cyclophosphamide or other drugs [panel consensus; IV, C].
- Consider mechanical ventilation, EEG and CT or MRI [II, B].
- Drain CSF if increased CSF pressure [panel consensus; V, C].

AE, adverse event; AED, anti-epileptic drug; CRS, cytokine-release syndrome; CSF, cerebrospinal fluid; EEG, electroencephalography; ICANS, immune effector cell-associated neurotoxicity syndrome. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1). See ref. 161.

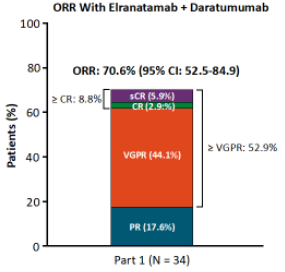
Bispecific Antibody-Based Combination Regimens in MM

Phase III MagnetisMM-5: Trial of Elranatamab + Daratumumab in R/R Multiple Myeloma

- Part 1 enrolled 34 adults with R/R MM with ≥3 lines of therapy, including lenalidomide and a PI and no history of treatment with a BCMA-targeting agent, and no anti-CD38 mAb within 6 mo of first dose
  - After step-up dosing, patients received 44 mg or 76 mg SC elranatamab + 1800 mg SC daratumumab
- **Primary endpoint:** DLT
- **Secondary endpoints:** ORR, CR, DoR, PFS, OS, MRD negativity, safety, and PK

Safety Summary:

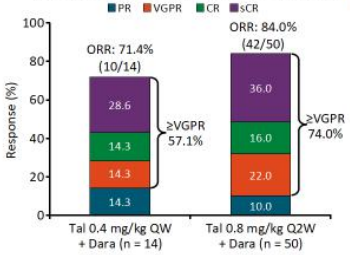
- No DLTs were observed, and safety profile was tolerable
- CRS: 47%, with no grade ≥3 CRS events
  - There were no treatment discontinuations due to CRS
- No patients experienced ICANS



NCT05020236. Grosicki. ASH 2023. Abstr 1921.

TRIMM-2 (Talquetamab + Daratumumab Cohort): Responses

Eligibility: Patients with MM after ≥3 LoTs or double refractory to a PI and IMiD; prior anti-CD38 mAb (>90 days and IMiD >7 days prior); refractory to anti-CD38 mAb and prior BsAb or CAR T allowed.

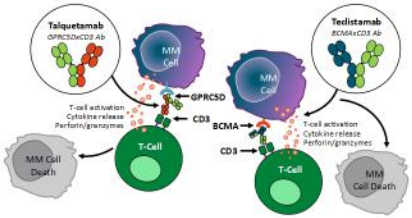


Outcome	Tal 0.4 mg/kg QW + Dara (n = 14)	Tal 0.8 mg/kg Q2W + Dara (n = 51)
Median f/u, mo (range)	16.8 (1.9-31.0)	15.0 (1.0-23.3)
Median time to first response, mo (range)	1.0 (0.9-2.4)	1.0 (0.9-8.3)
ORR, n (%)	3/3 (100)	5/5 (100)
▪ Anti-CD38 mAb naive	7/11 (63.6)	37/45 (82.2)
▪ Anti-CD38 mAb exposed	7/11 (63.6)	32/40 (80.0)
Anti-CD38 mAb refractory		
ORR in T-cell redirection therapy exposed, n (%)	4/6 (66.7)	15/19 (78.9)
▪ CAR T	1/2 (50.0)	8/9 (88.9)
▪ Bispecific Ab	4/5 (80.0)	7/10 (70.0)
Median time to first response, mo (range)	1.0 (0.9-2.4)	1.0 (0.9-8.3)

Dholaria. JCO. 2023;41. Abstr 8003.

Phase Ib/II RedirectTT-1: Teclistamab + Talquetamab in R/R Multiple Myeloma

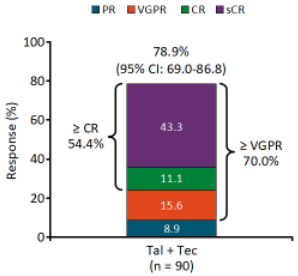
- Open-label, dose-escalation and expansion trial of teclistamab plus talquetamab in patients with R/R MM with previous exposure to a PI, IMiD, and anti-CD38 mAb and refractory to last line of therapy
  - Median prior LoT: 4 (1-11); extramedullary plasmacytomas: 36%; high-risk cytogenetics in 41%
- **Primary endpoints:** safety, RP2R; secondary endpoints: ORR, PK, immunogenicity

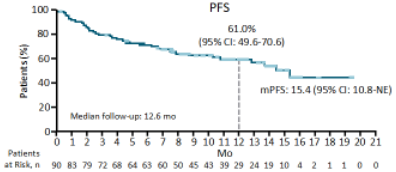


Mateos. EHA 2023. Abstr S190. NCT04586426. Cohen. NEJM. 2025;392:138.

RedirectTT-1: Patients With True EMD Response and PFS

Teclistamab + Talquetamab in R/R MM





Median PFS among patients with triple-class exposed R/R MM with EMD:

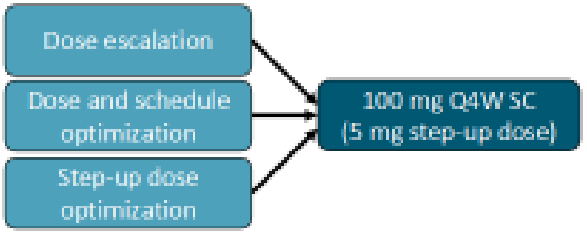
- SoC including Bab anti-CD38–based doublets and triplet regimens: <3 mo
- Approved bispecific antibodies including talquetamab and teclistamab: <6 mo

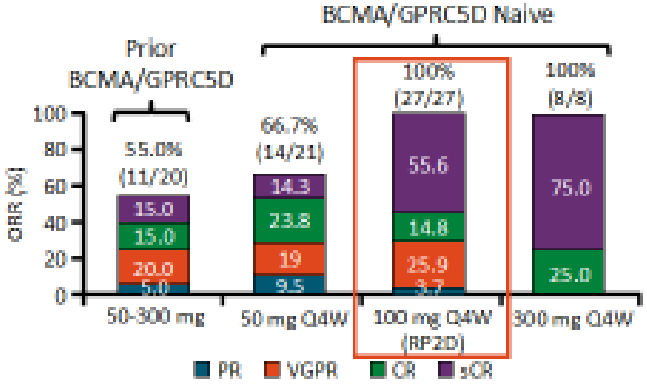
Kumar. EHA 2025. Abstr LB4001. Moreau. Clin Lymphoma Myeloma Leuk. 2025;25:646. Ho. Curr Oncol. 2025;32:182.

Next Generation of Targeted Immunotherapies: BCMA x GPRC5D x CD3 Trispecific Antibody

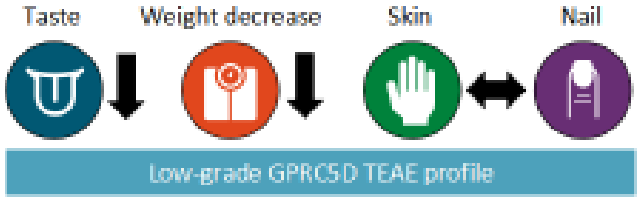
JNJ-5322 is a trispecific antibody targeting BCMA x GPRC5D x CD3 in MM cells

100 mg Q4W SC with 1 step-up dose selected as RP2D



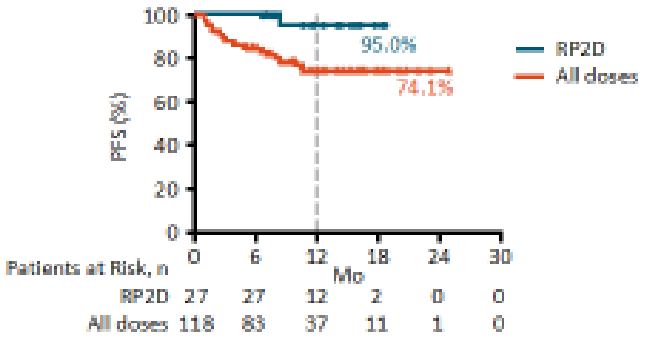


Improved or similar GPRC5D TEAEs



CRS with prophylactic tocilizumab: 20%, all grade 1

PFS Patients Naive to BCMA/GPRC5D



van de Donk. ASCO 2025. Abstr7505.

CONCLUSIONI

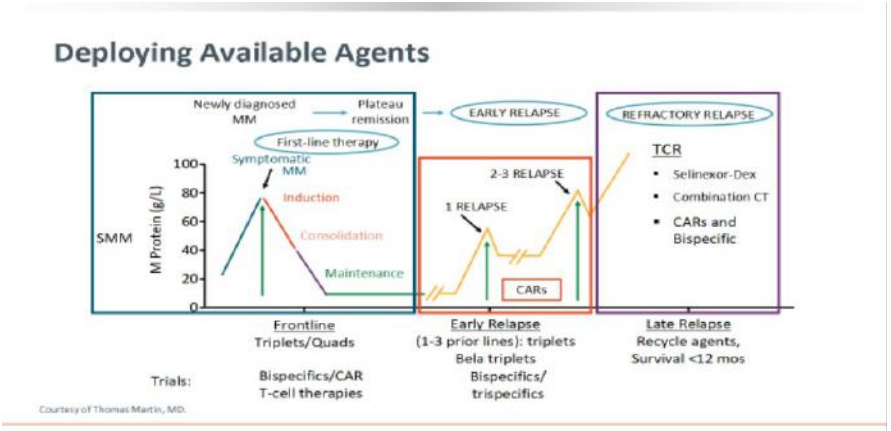
Dal gennaio 2021 al maggio 2025 sono stati approvati 14 nuovi farmaci o nuove combinazioni di farmaci da EMA e/o FDA.

LE nuove linee guida EHA EMN 2025 indicano le raccomandazioni per la diagnosi, follow-up e terapia del MM in differenti scenari clinici come disease refractory a Ab monoclonali anti-CD38 e lenalidomide, o four-class refractorines

C’è consenso sulla elevata efficacia dimostrata dai nuovi agenti terapeutici con necessità di formulare nuovi criteri di risposta che guidino le decisioni terapeutiche come interrompere la terapia di mantenimento o cambiare schema terapeutico per ottenere risposte pià pr0fonde e prolungate

Conclusions

- **Nuovi farmaci con differenti targets hanno mostrato dati promettenti nei paz con R/R MM**
- **La terapia con CAR T-cell dimostra elevata efficacia con risposte duraure e profonde nel MM**
- **L'uso in linee di terapia più precoci è ancora più efficace**
- **AbBispecifici sono attualmente approvati per la IV linea ma sono in corso studi in linee più precoci**
- **Il Sequencing ottimale per le terapie T-cell redirecting deve essere il goal**



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