

HIGHLIGHTS IN EMATOLOGIA

TREVISO
7-8 NOVEMBRE 2025



Quali novità dell'algoritmo terapeutico in seconda linea?

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UOC Ematologia – Ospedale Ca' Foncello, Treviso

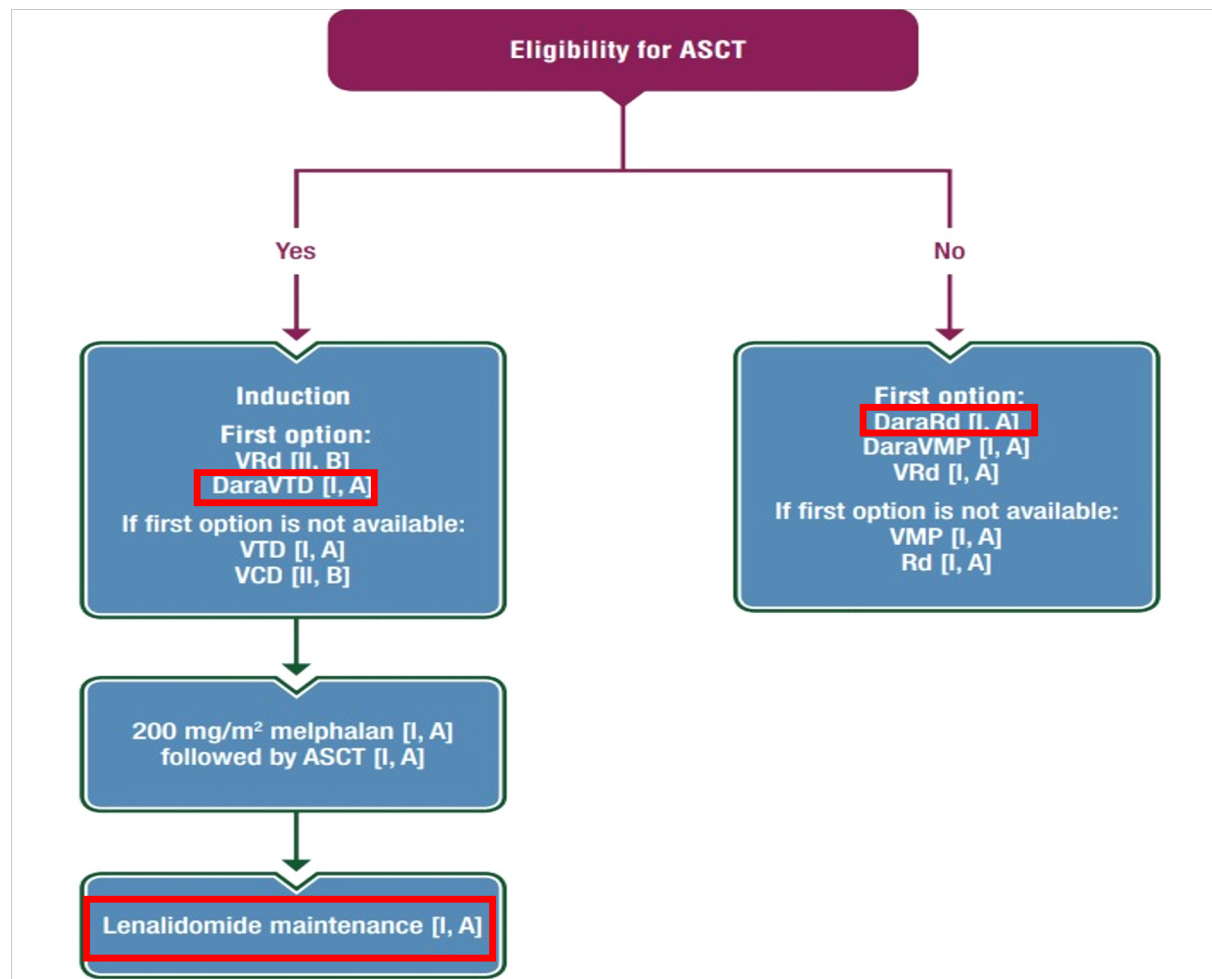


Disclosures of Anna Furlan

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen					x	x	x
Sanofi					x	x	
GSK					x	x	
Takeda					x	x	x
Bristol Myers Squibb					x		
Menarini						x	
Amgen						x	

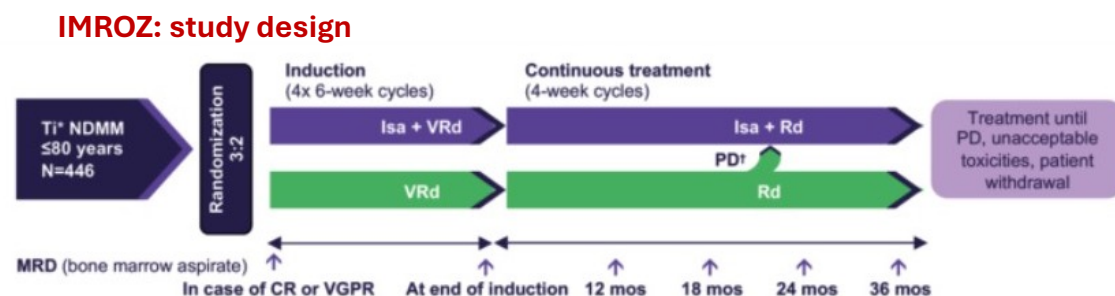
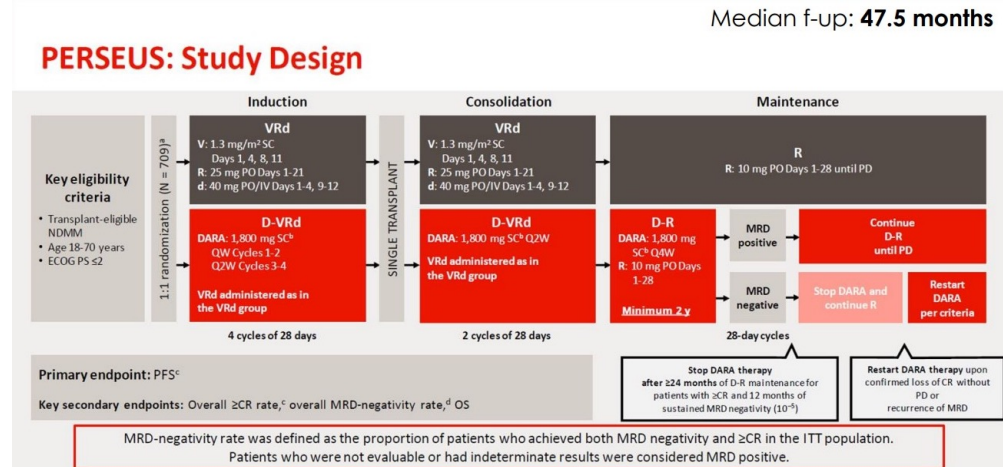
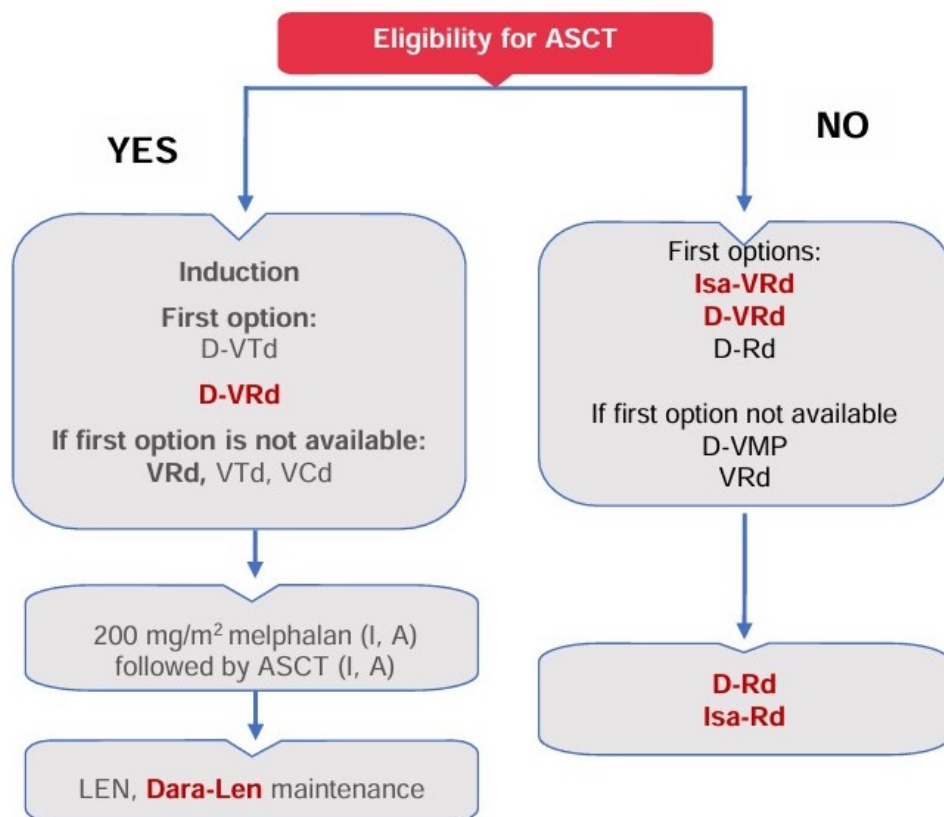
EHA-ESMO Clinical Practice Guidelines (2021)

La terapia di 1L. Lo stato attuale

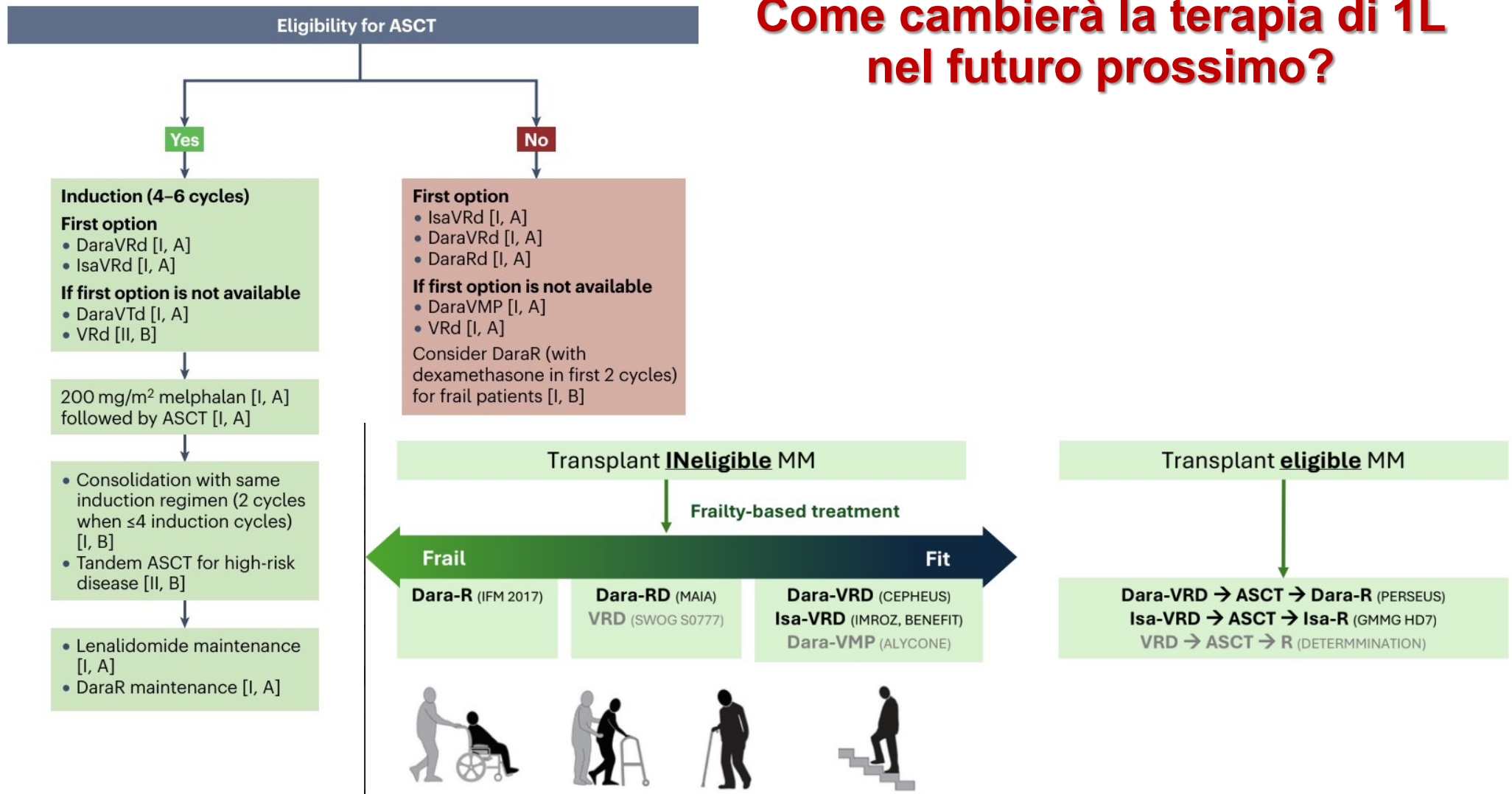


Dimopoulos MA et al, Ann Oncol 2021

Come cambierà la terapia di 1L nel futuro prossimo?

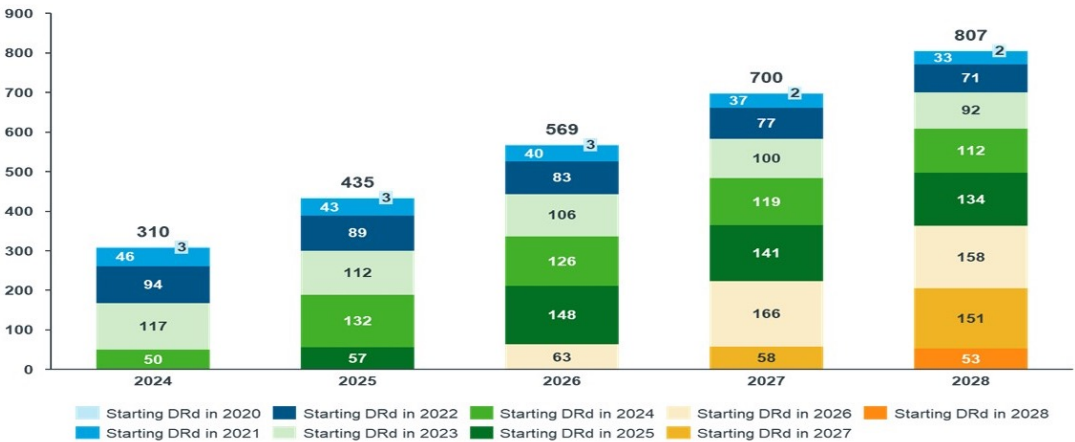


Come cambierà la terapia di 1L nel futuro prossimo?



PATIENTS PROGRESSING TO 2L THERAPY AFTER RECEIVING DRd IN 1L BY YEAR AND COHORT
EPIDEMIOLOGICAL ESTIMATE IN ITALY BETWEEN 2024-2028

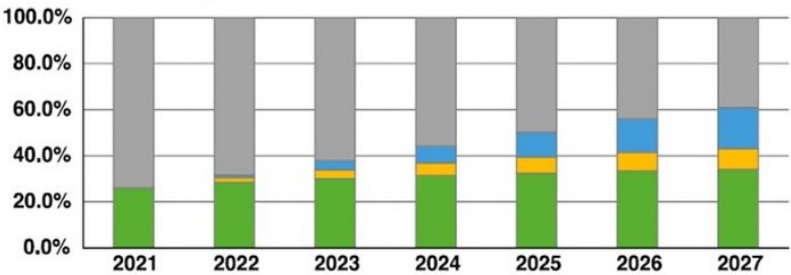
- Annual results show a **relevant increase of patients** treated with DRd in 1L progressing to the 2L over the forecast period, from **310 patients in 2024 to 807 in 2028**
- The **total number** of patients progressing to the 2L after 1L treatment with DRd is **~2,800** in the **period 2024-2028**



**Come cambieranno le
caratteristiche dei pazienti in
prima recidiva?**

Boccadoro M et al, SIE 2024

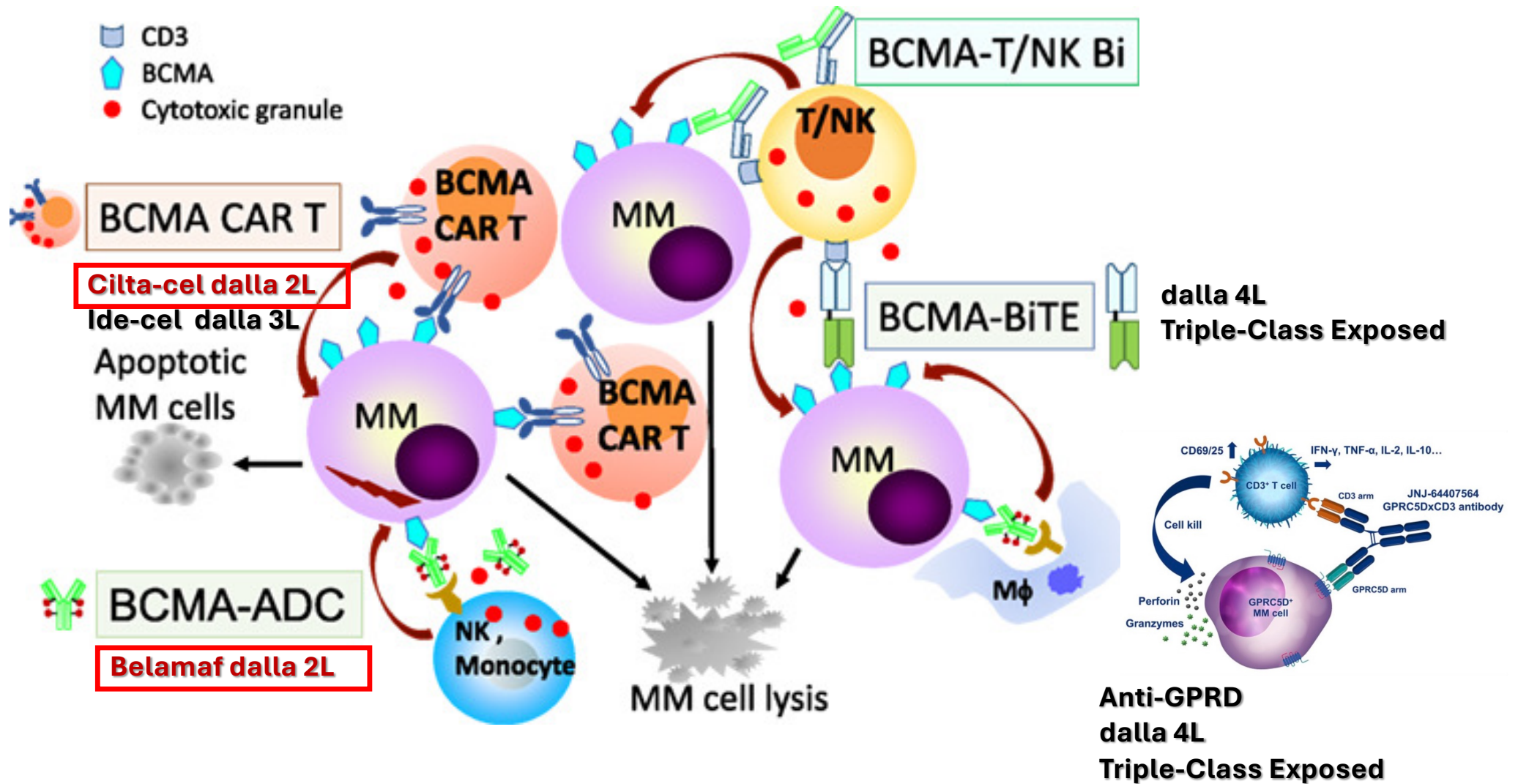
REFRACTORINESS TO LENALIDOMIDE AND ANTI-CD38 MOABS AFTER 1L TREATMENT
2 line therapy



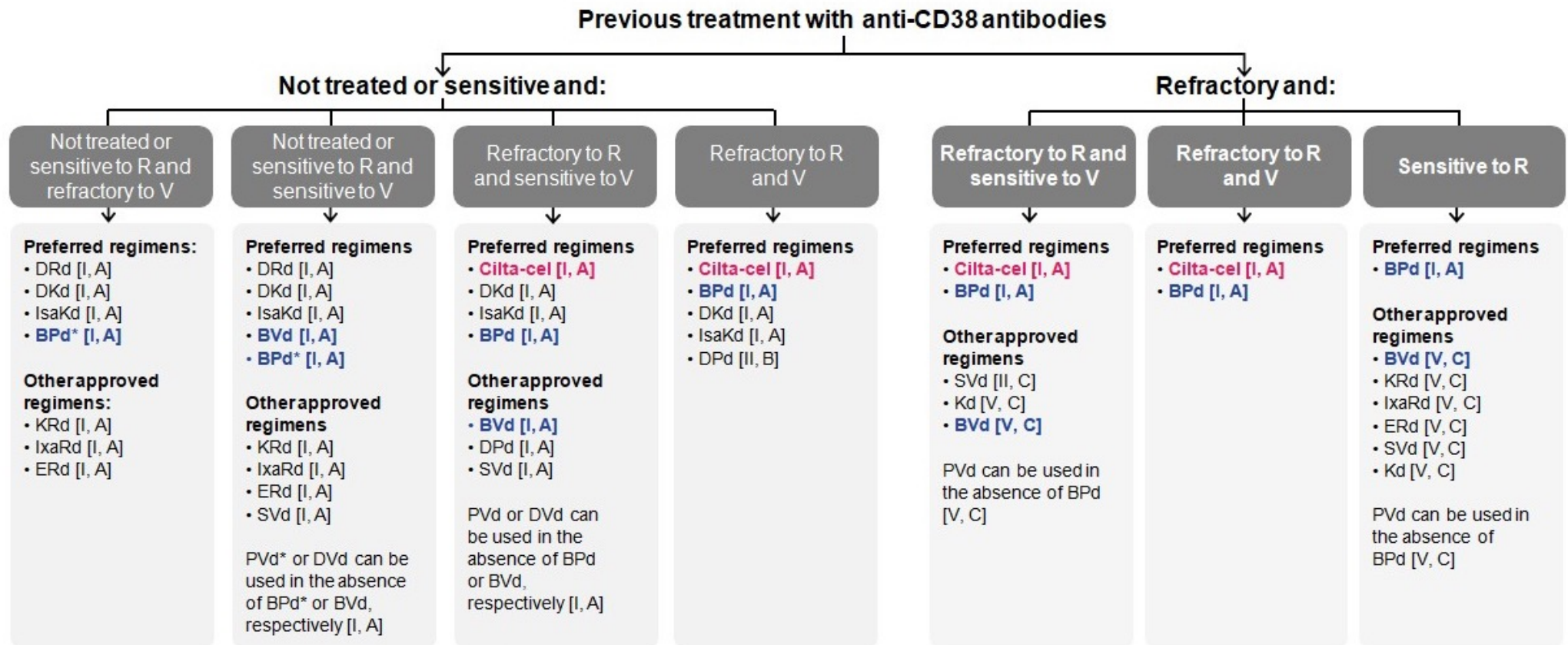
■ Not refractory neither to lenalidomide nor to anti-CD38 mAbs	74.0%	68.4%	62.3%	56.0%	49.8%	44.1%	39.2%
■ Refractory to both lenalidomide and anti-CD38 mAbs	0.0%	1.1%	3.8%	7.2%	10.8%	14.4%	17.8%
■ Refractory to anti-CD38 mAbs only	0.0%	1.9%	3.9%	5.5%	7.0%	8.3%	9.0%
■ Refractory to lenalidomide only	26.0%	28.6%	30.0%	31.4%	32.4%	33.3%	34.1%

Mina R et al, Clin Lymph Myel Leuk 2025

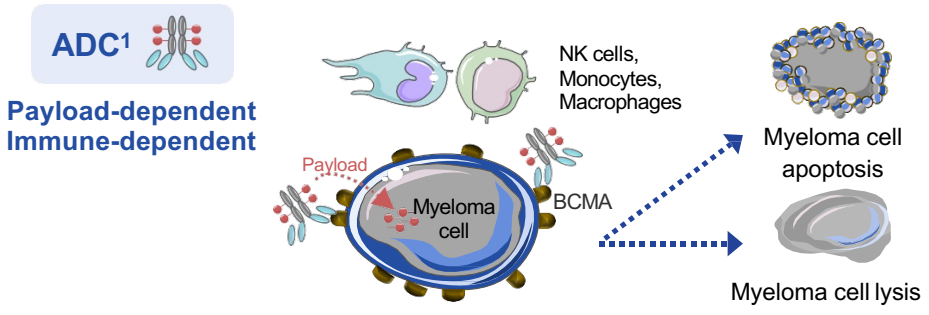
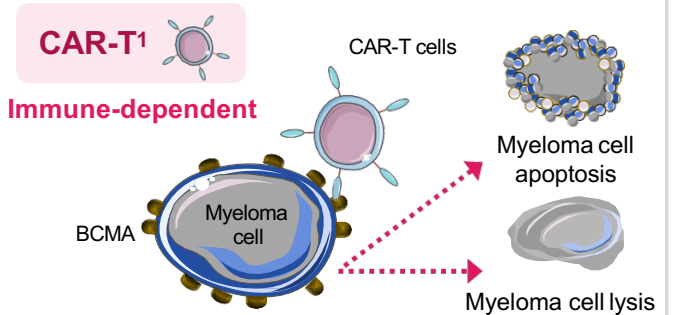
La rivoluzione dello scenario terapeutico nel RRMM



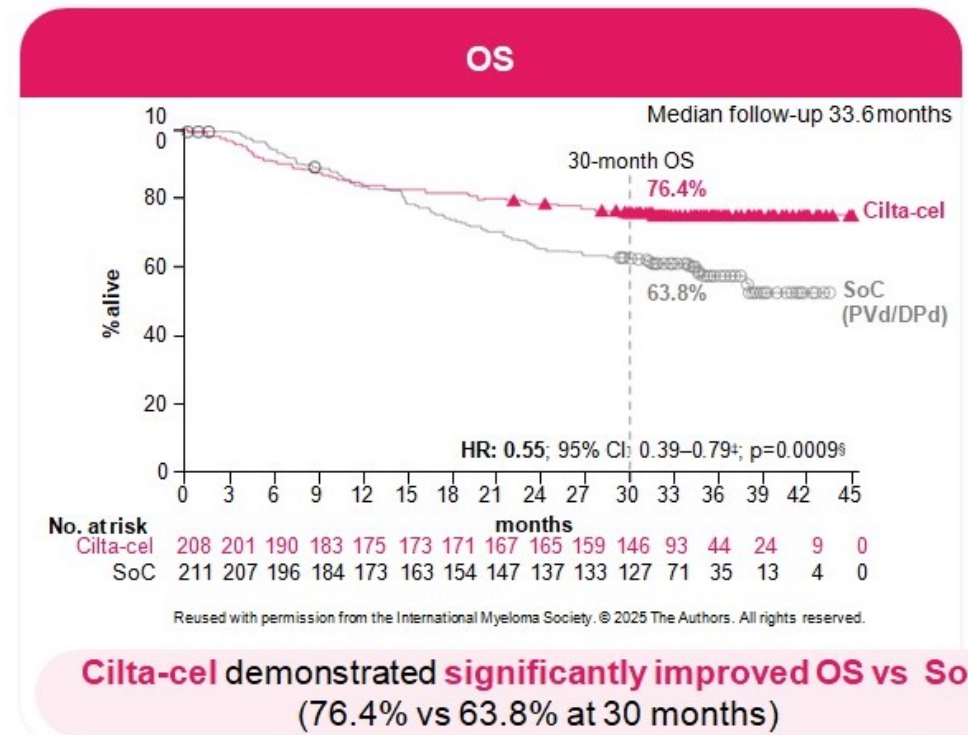
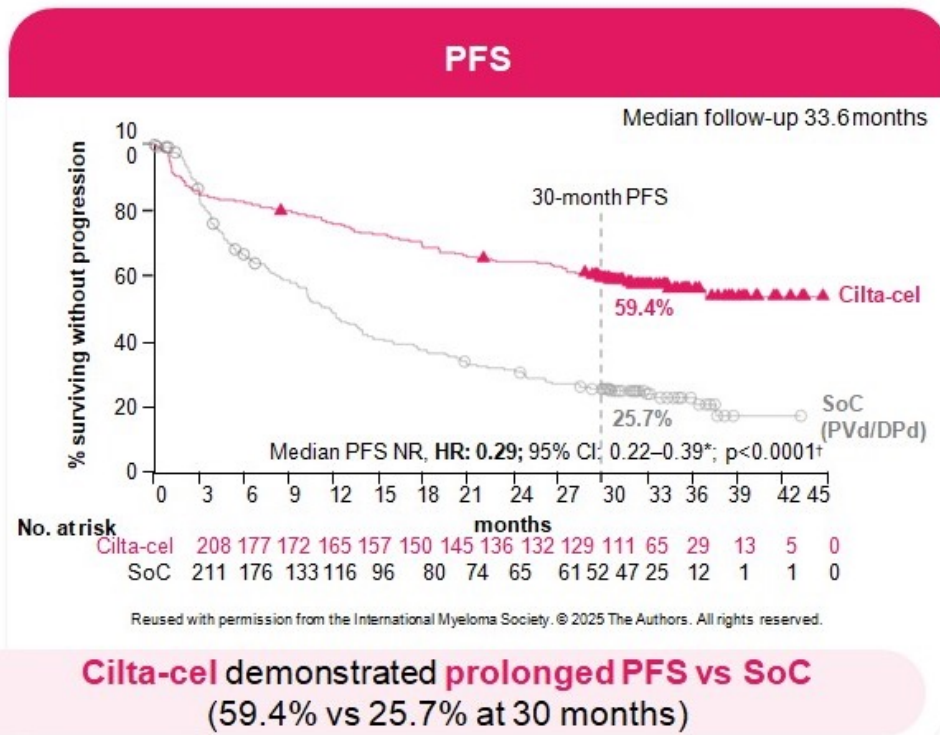
BCMA-TT in 2L: le linee guida EHA-EMN 2025



Trial di fase 3 sulle BCMA-TT in 2L

	Belantamab mafodotin		Cilta-cel
Mechanism of action	 ADC¹ Payload-dependent Immune-dependent NK cells, Monocytes, Macrophages Myeloma cell apoptosis Myeloma cell lysis		 CAR-T¹ Immune-dependent CAR-T cells Myeloma cell apoptosis Myeloma cell lysis
Pivotal trials	DREAMM-7 ²	DREAMM-8 ³	CARTITUDE-4 ⁴
Exploratory arm	BVd	BPd	Bridging therapy, Cilta-cel
Comparator arm	DVd	PVd	IC SoC (PVd or DPd)
Patient population	• ≥1 LoT • ECOG ≤2 • Exl: anti-CD38–refractory; previous anti-BCMA	• ≥1 LoT • Len-exposed • ECOG ≤1	• 1–3 LoT • Len-refractory, PI exposed (15% 3-class refractory) • ECOG ≤2
Primary endpoint	PFS		PFS

CARTITUDE-4: Cilta-cel vs SOC (PVd, DPd). PFS, OS



... Prima considerazione nel paziente in 2L, Len-ref: E' candidabile a CAR-T?

Nei pz eleggibili sia a CAR-T che a altre BCMA-TT, deve essere considerata prima la terapia con CAR-T



L'efficacia di CAR-T è massima in fase più precoce

La precedente esposizione ad altra BCMA-TT (BsAbs, ADC) potrebbe impattare negativamente sulla risposta a CAR-T

Fattori correlati al paziente:

E' eleggibile per fitness e comorbidità (riserva cardiopolmonare, midollare)?
Accessibilità/logistica/caregiver?

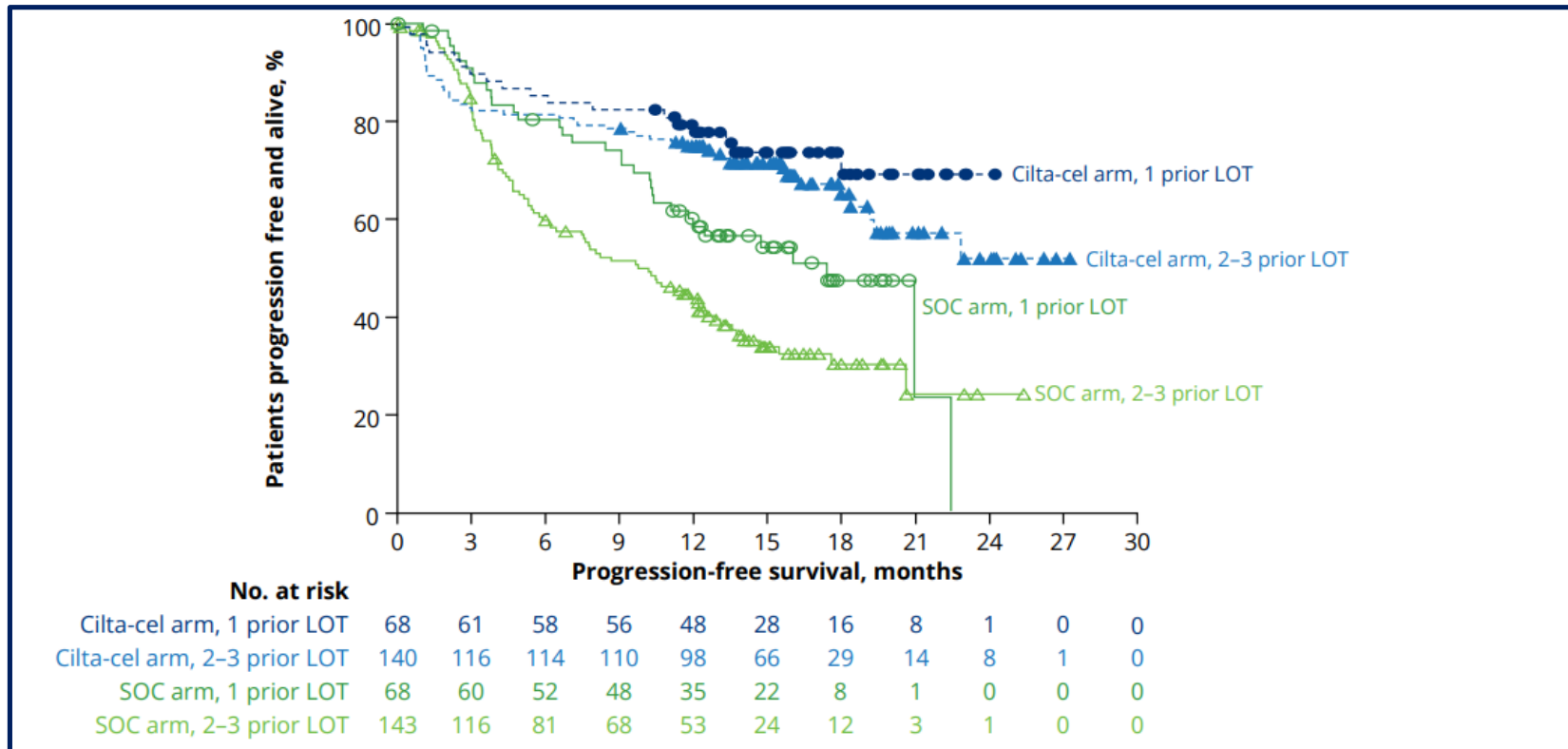
Fattori correlati alla malattia:

Può beneficiare di CAR-T? (rischio citogenetico, EMD, status di exp/ref)
La cinetica/burden/caratteristiche cliniche della malattia sono compatibili con i tempi di manufacturing/è disponibile Holding/Bridging therapy efficace?

Lin Y et al, Consensus guidelines and recommendations for the management and response assessment of chimeric antigen receptor T-cell therapy in clinical practice for relapsed and refractory multiple myeloma: a report from the International Myeloma Working Group Immunotherapy Committee. Lancet 2024

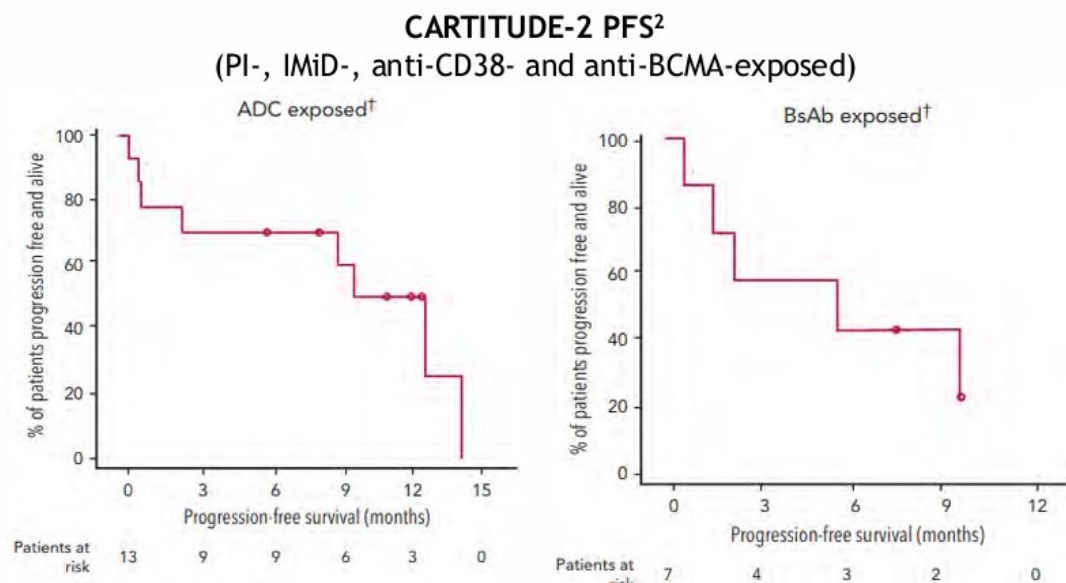
CARTITUDE-4: Cilta-cel vs SOC.

Impatto del numero di linee di terapia precedenti sull'outcome



Nei pz trattati con Cilta-cel, l'outcome (PFS) è migliore in quelli che avevano ricevuto 1 pLT vs 2-3 pLT

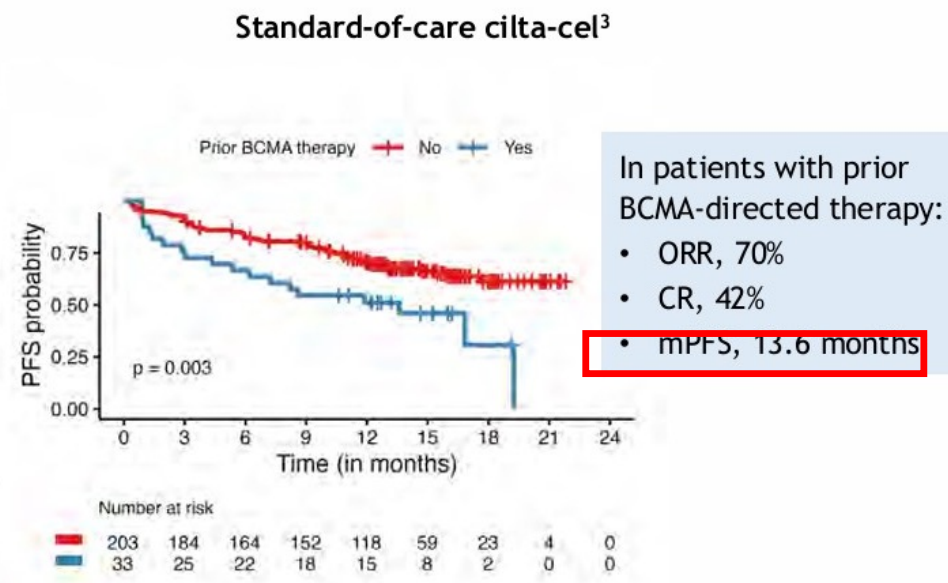
Cilta-cel: Impatto di precedente BCMA-TT sull'outcome



Cohort C (PI, IMiDs, aCD38, **BCMA-TT-exposed**)

mDOR 11.5 m

mPFS 9.1 m



Cohen AD, et al. Blood 2023

Sidana S, et al. Blood 2025

... Prima considerazione nel pz in 2L, Len-ref E' candidabile a CAR-T?

Nei pz eleggibili sia a CAR-T che a altre terapie BCMA-TT, deve essere considerata prima terapia con CAR-T



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Fattori correlati al paziente:

E' eleggibile per fitness e comorbidità (riserva cardiopolmonare, midollare)?

Accessibilità/logistica/caregiver?

Fattori correlati alla malattia:

Può beneficiare di CAR-T? (rischio citogenetico, EMD, status di exp/ref)

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... Prima considerazione nel pz in 2L, Len-ref: E' candidabile a CAR-T?



Nei pz eleggibili sia a CAR-T che a altre terapie aBCMA, deve essere considerata prima terapia con CAR-T

L'efficacia di CAR-T è massima in fase più precoce

La precedente esposizione ad altra terapia aBCMA (BsAbs, ADC) potrebbe impattare negativamente sulla risposta a CAR-T

Fattori correlati al paziente:

E' eleggibile per fitness e comorbidità (riserva cardiopolmonare, midollare)?
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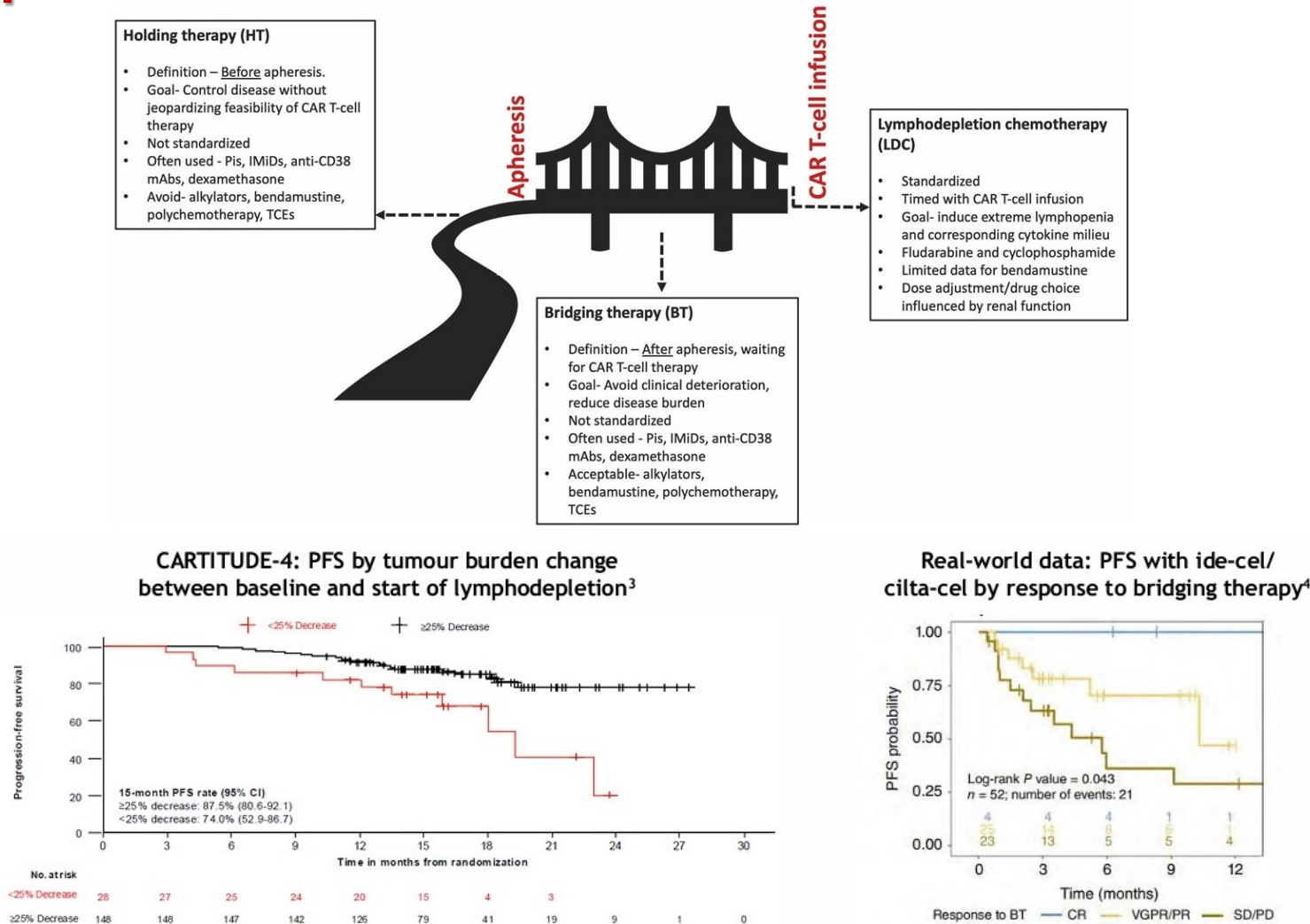
Fattori correlati alla malattia:

Può beneficiare di CAR-T? (rischio citogenetico, EMD, timing della recidiva)

La cinetica/burden/caratteristiche cliniche della malattia sono compatibili con i tempi di manufacturing
E' disponibile Holding/Bridging therapy efficace?

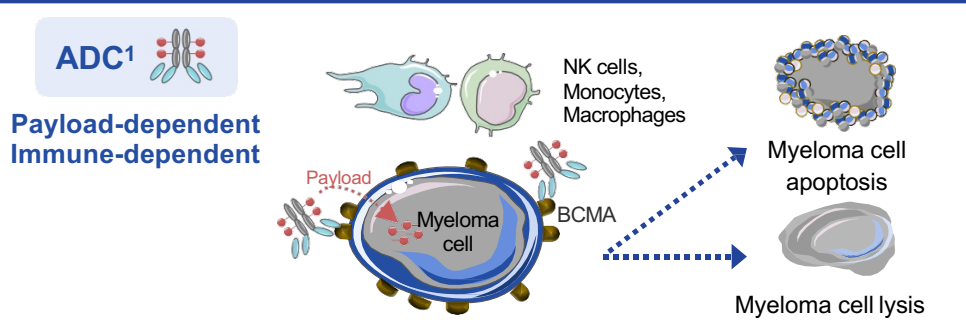
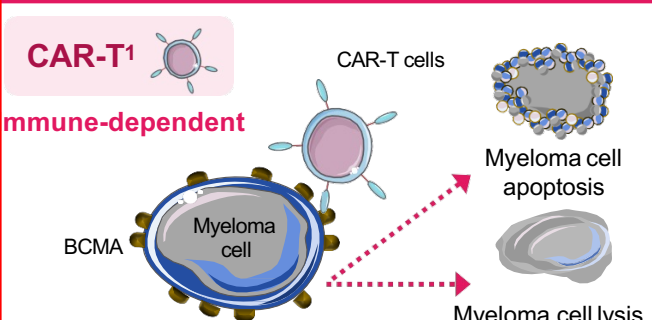
Lin Y et al, Consensus guidelines and recommendations for the management and response assessment of chimeric antigen receptor T-cell therapy in clinical practice for relapsed and refractory multiple myeloma: a report from the International Myeloma Working Group Immunotherapy Committee. Lancet 2024

CAR-T: Impatto della riduzione del burden di malattia sull'outcome



Anguille S et al, IMS 2024 (Abs P-005) Fandrei D et al, Blood Cancer Discov 2025

Trial di fase 3 sulle BCMA-TT in 2L

	Belantamab mafodotin		Cilta-cel
Mechanism of action	 ADC¹ Payload-dependent Immune-dependent Myeloma cell BCMA Myeloma cell apoptosis Myeloma cell lysis NK cells, Monocytes, Macrophages		 CAR-T¹ Immune-dependent Myeloma cell BCMA Myeloma cell apoptosis Myeloma cell lysis CAR-T cells
Pivotal trials	DREAMM-7 ²	DREAMM-8 ³	CARTITUDE-4 ⁴
Exploratory arm	BVd	BPd	Bridging therapy, Cilta-cel
Comparator arm	DVd	PVd	IC SoC (PVd or DPd)
Patient population	• ≥1 LoT • ECOG ≤2 • Exl: anti-CD38–refractory; previous anti-BCMA		• 1–3 LoT • Len-refractory, PI exposed (15% 3-class refractory) • ECOG ≤2
Primary endpoint	PFS		PFS

DREAMM-8: BelaPd vs PVd. PFS, OS

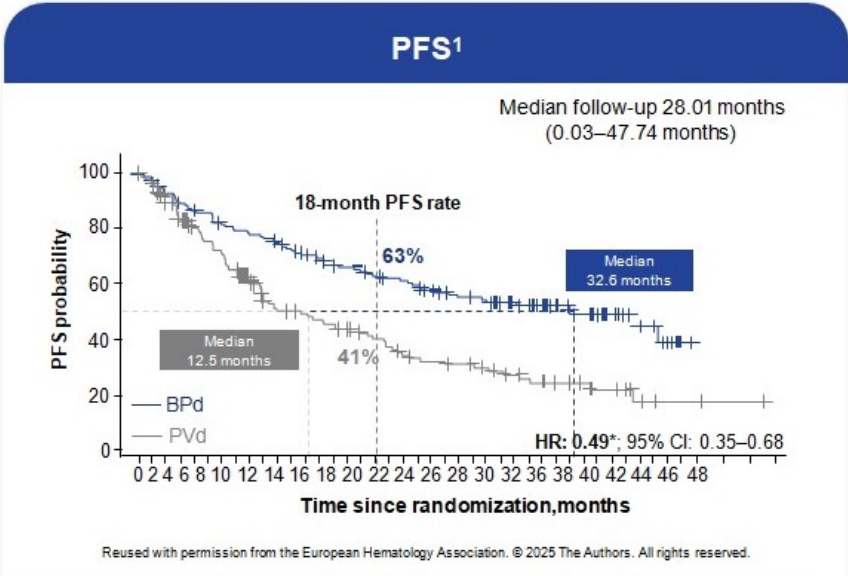
- Eligibility criteria
- Adults with MM
 - ≥1 prior line of MM therapy including LEN
 - Documented PD during or after their most recent therapy
 - No prior treatment with anti-BCMA or pomalidomide; not refractory/intolerant to bortezomib

Prior treatments, n (%)	ITT population			
	BPd (N=155)		PVd (N=147)	
Prior LOT				
1	82 (53)		77 (52)	
2 or 3	54 (35)		48 (33)	
≥4	19 (12)		22 (15)	
Prior ASCT	99 (64)		82 (56)	
Prior treatment	Exposed	Refractory	Exposed	Refractory
Prior proteasome inhibitor				
Bortezomib	140 (90)	40 (26)	136 (93)	35 (24)
Carfilzomib	134 (86)	16 (10)	130 (88)	8 (5)
Ixazomib	34 (22)	18 (12)	37 (25)	23 (16)
	11 (7)	8 (5)	15 (10)	11 (7)
Prior immunomodulatory drug ^a	155 (100)	127 (82)	147 (100)	111 (76)
Lenalidomide	155 (100)	125 (81)	147 (100)	111 (76)
Thalidomide	49 (32)	9 (6)	48 (33)	6 (4)
Prior anti-CD38 monoclonal antibody ^b	38 (25)	35 (23)	42 (29)	36 (24)
Daratumumab	36 (23)	33 (21)	39 (27)	34 (23)
Isatuximab	2 (1)	2 (1)	3 (2)	2 (1)

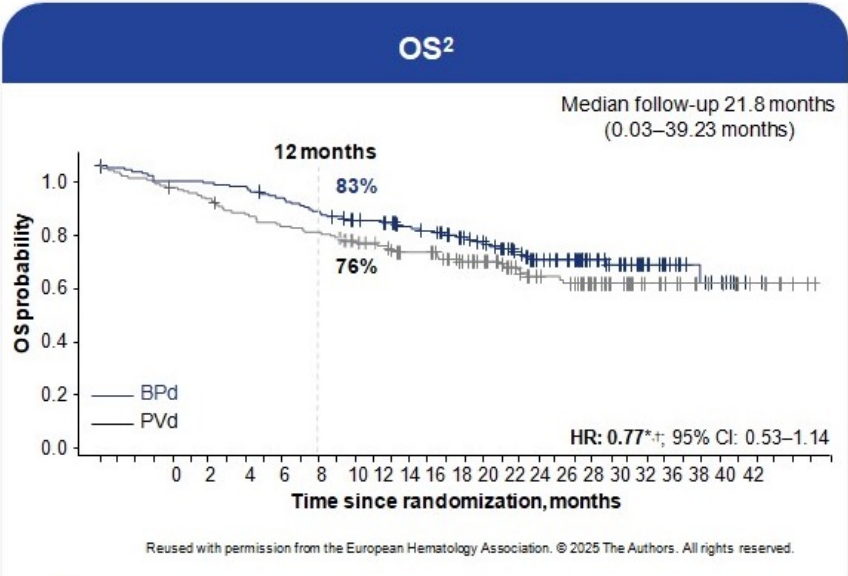
Reprinted from Dimopoulos MA, et al. N Engl J Med. 2024;391(5):408-421. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

In the BPd group:

- 90% received prior PI
- 81% were lenalidomide refractory



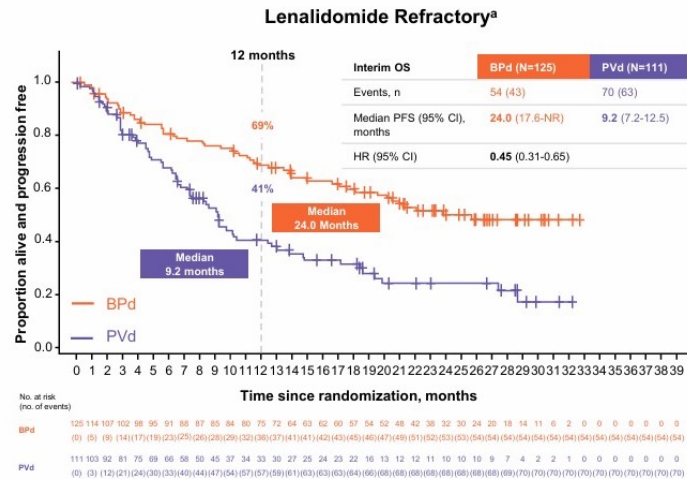
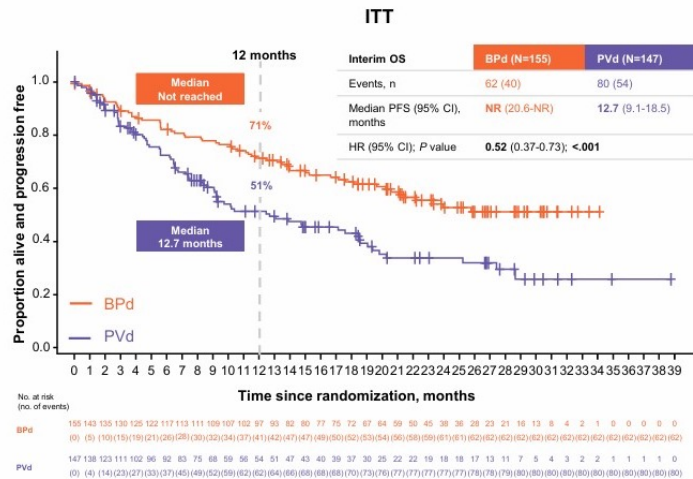
BPd demonstrated prolonged median PFS vs PVd (32.6 months vs 12.5 months)



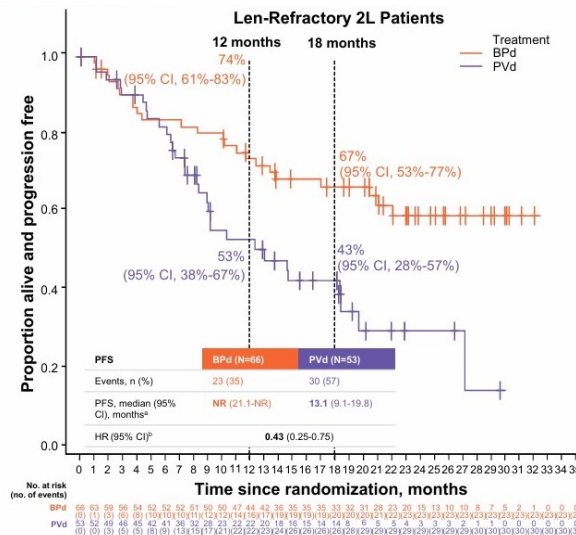
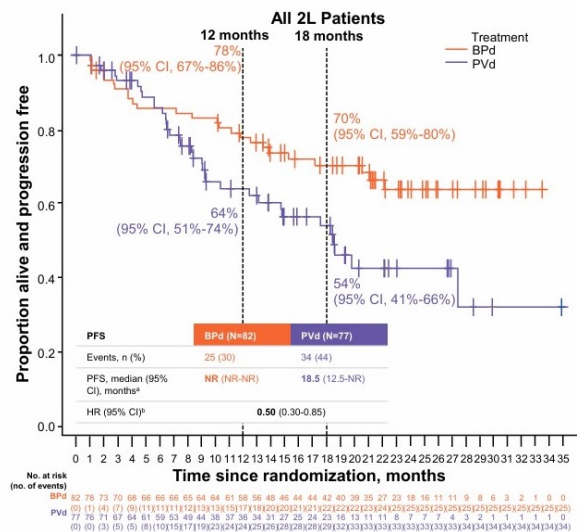
BPd demonstrated an early trend for OS benefit vs PVd

Dimopoulos MA, et al. EHA 2025. Poster PF728. Trudel S, et al. EHA 2024. Oral LB3440.

DREAMM-8: BelaPd vs PVd in pazienti Len-ref/Len-ref in 2L



Len-ref
BelaPd vs PVd
mPFS 24.0 vs 9.2 m
HR 0.45



Len-ref 2L
BelaPd vs PVd
mPFS NR vs 13.1 m
HR 0.43

Trudel S, et al. IMS 2024. Oral presentation OA-62.

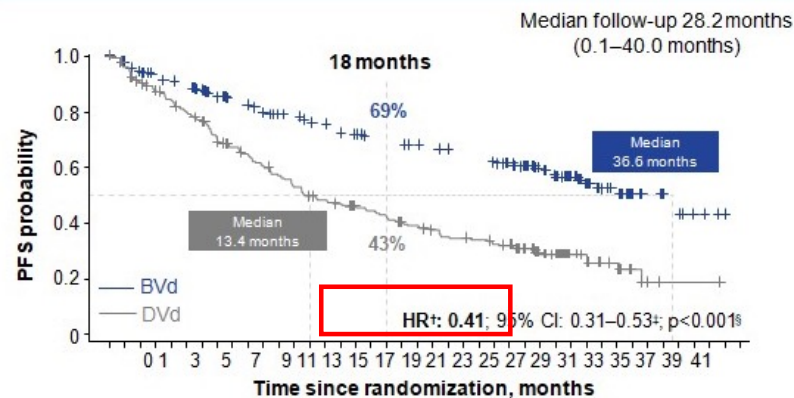
DREAMM-7: BelaVd vs DVd. PFS e OS

Eligibility criteria

- Patients aged ≥ 18 years with MM
- ≥ 1 prior line of MM therapy and documented PD during or after the most recent therapy
- No prior treatment with anti-BCMA
- Not refractory or intolerant to daratumumab or bortezomib

Prior treatments, n (%)	ITT population	
	BVd (N=243)	DVd (N=251)
Prior LOTS		
1	125 (51)	125 (50)
2 or 3	88 (36)	99 (39)
4+	30 (12)	27 (11)
Prior PI		
Prior bortezomib	210 (86)	211 (84)
Prior immunomodulatory drug		
Prior thalidomide	121 (50)	144 (57)
Prior lenalidomide	127 (52)	130 (52)
Refractory to lenalidomide	79 (33)	87 (35)
Prior daratumumab		
Prior ASCT	164 (67)	173 (69)

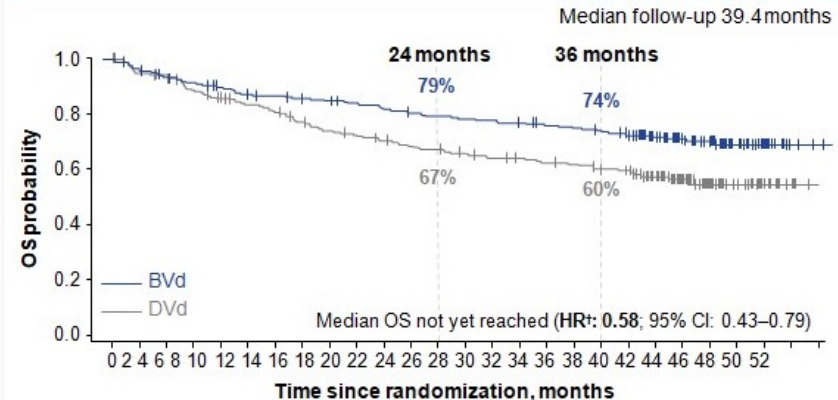
PFS*1



From Hungria V, et al. *N Engl J Med*. 2024;391(5):393–407. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

BVd demonstrated significantly prolonged mPFS vs DVd (36.6 vs 13.4 months)

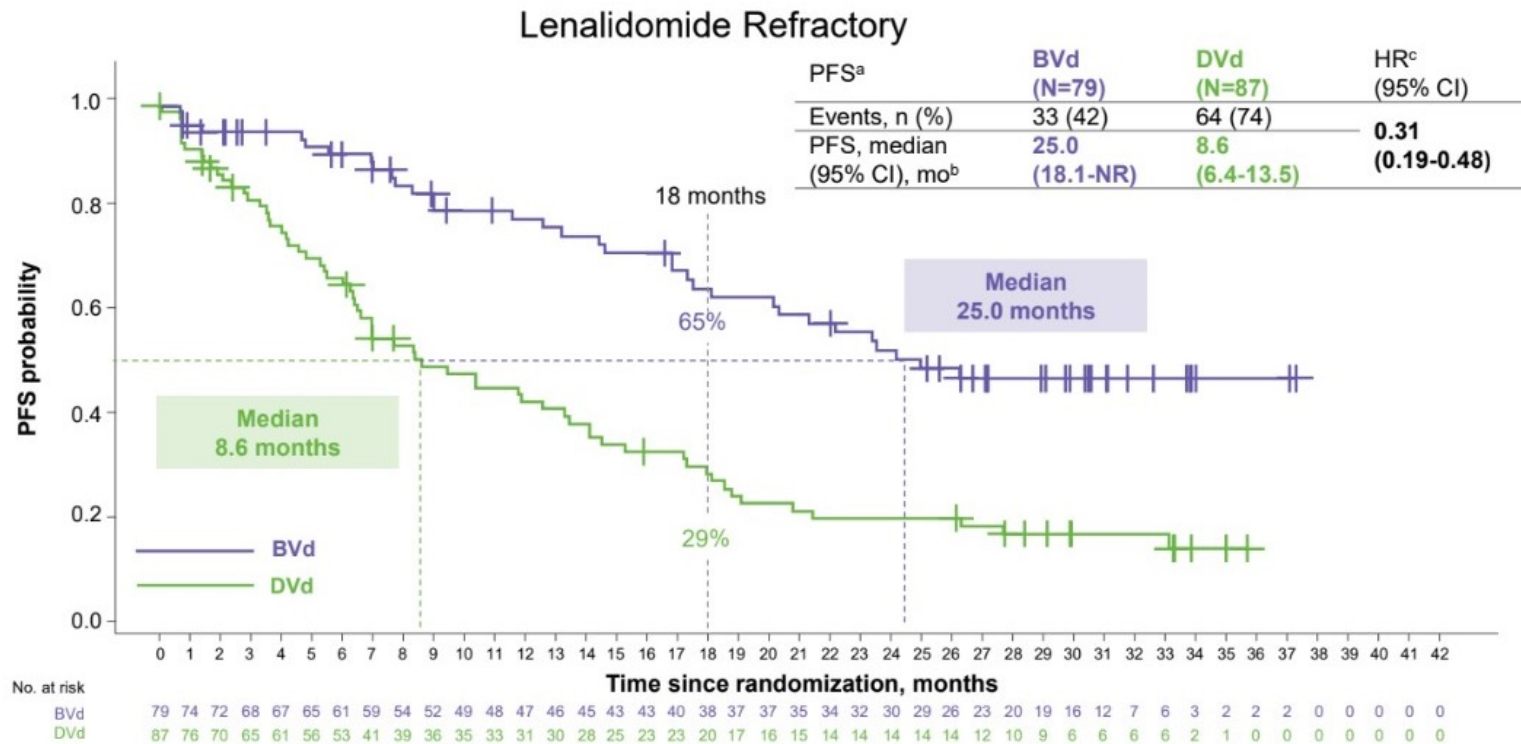
OS*2



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Predicted median OS is 33 months longer with BVd vs DVd (84 months vs 51 months)[¶]

DREAMM-7: BelaVd vs DVd in pazienti Len-ref



Len-ref

BelaVd vs DVd
mPFS 24.0 vs 8.6 m
HR 0.31

Trudel S, et al. IMS 2024. Oral presentation OA-62.

Paziente in prima recidiva (2L)

Len-ref

aCD38-sens

Bor-sens

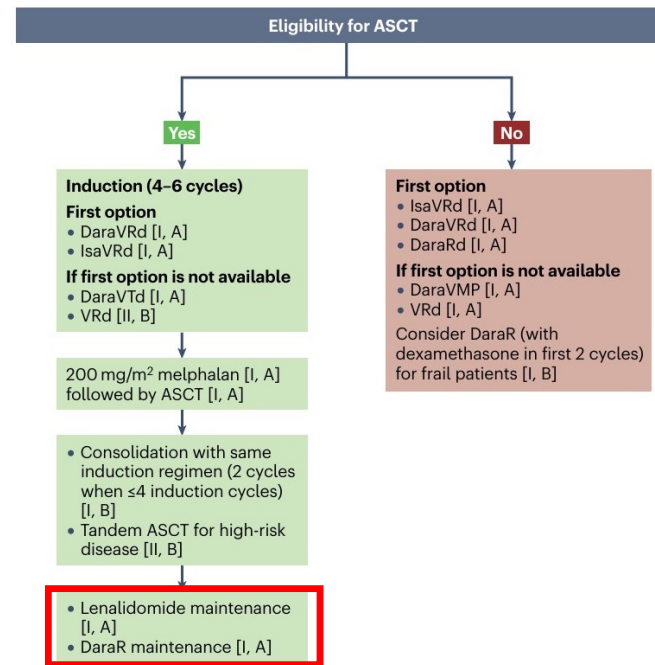
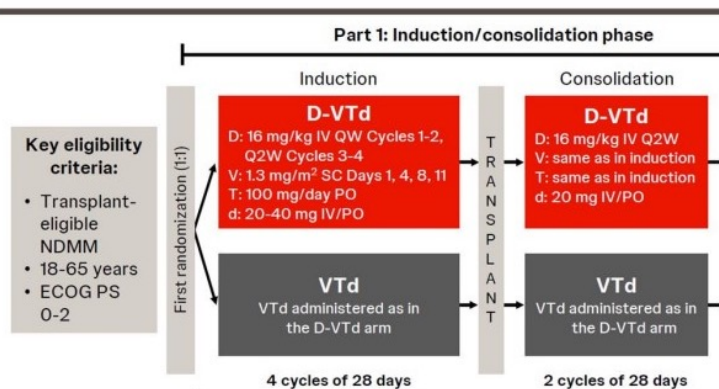
Progressione in corso di Len di mantenimento

- dopo DaraVTd
- dopo DaraVRd (sospensione di Dara di mantenimento per MRD-neg sostenuta)



CASSIOPEIA: Study Design

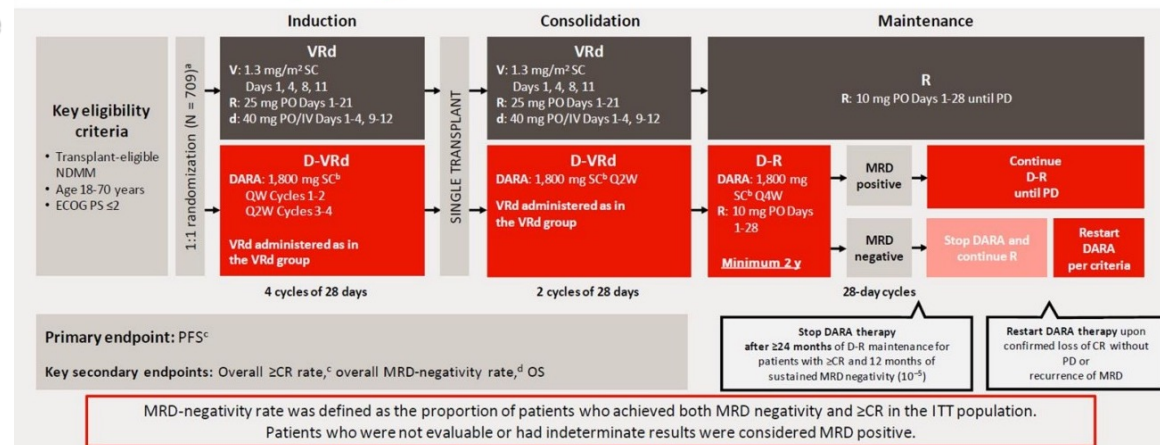
Len-maintenance



Len-maintenance

STOP Dara after sustained MRD-neg

PERSEUS: Study Design



Paziente in prima recidiva (2L)

Len-ref

aCD38-sens

Bor-sens

Progressione in corso di Len di mantenimento

- dopo DaraVTd

- dopo DaraVRd (sospensione di Dara di mantenimento per MRD neg sostenuta)

Cilta-cel

IsaKd

BelaPd*

Opzioni preferibili

BelaVd*

SelVd

DaraPd

Altre opzioni (seconda scelta)

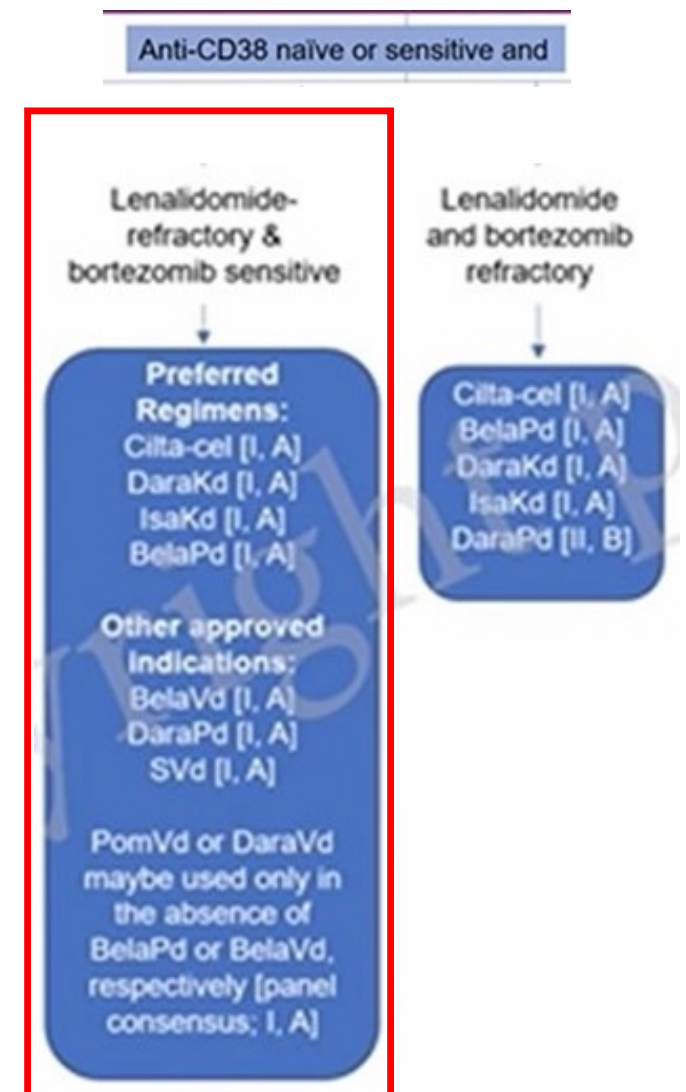
PVd

DaraVd

In mancanza di BelaPd e
BelaVd (outcome inferiori in
DREAMM-8 e DREAMM 7)

*Nella prospettiva di futura terapia con CAR-T sono preferibili regimi alternativi a Bela

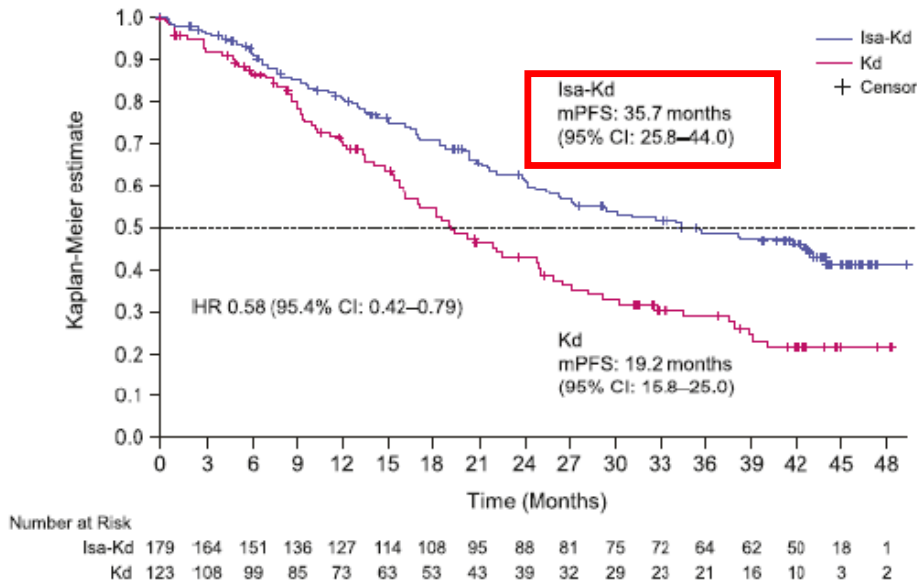
Bela preclude il successivo utilizzo di aBCMA CAR-T e del BsAbs aBCMA Elranatamab, NON di Teclistamab



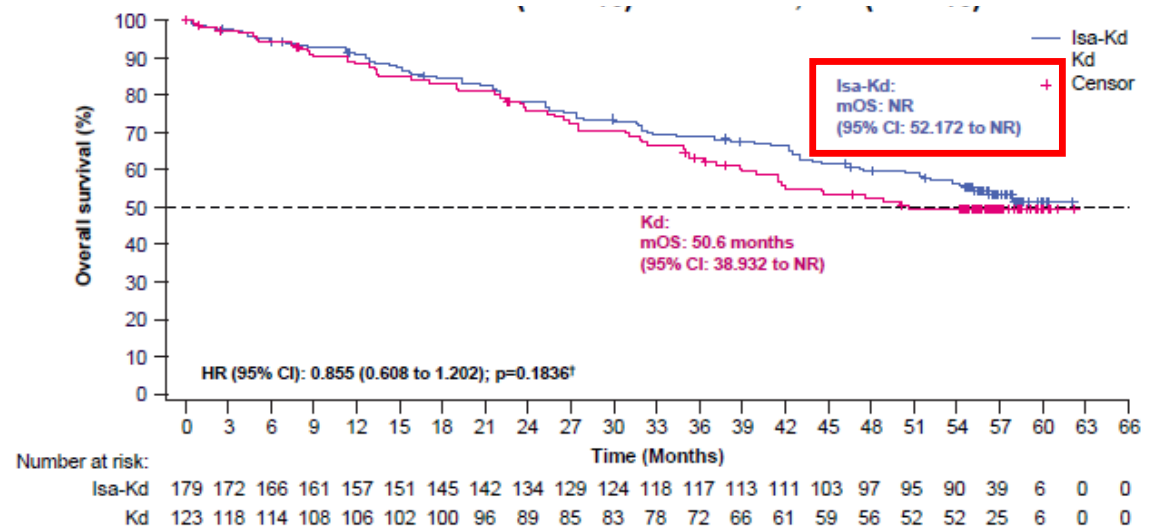
Dimopoulos MA et al, Nat Rev Clin Oncol 2025

IKEMA: IsaKd vs Kd. PFS e di OS

PFS (follow-up mediano 44 m)



OS (follow-up mediano 56.6 m)



Analisi finale di PFS (m follow-up 44 m): IsaKd vs Kd riduce il rischio di progressione e morte del 42% (HR 0.58)

Analisi finale di OS (m follow-up 56.6 m): IsaKd vs Kd riduce il rischio di morte del 14% (HR 0.86)

mOS NR (IsaKd) vs 50.6 m (Kd)

mOS stimato per IsaKd: **63 m** (95% CI: 59.69), corrisp a una differenza stimata in OS di 1 anno vs Kd

mPFS dopo 1 pLT: 38.2 (IsaKd) vs 28.2 m (Kd)

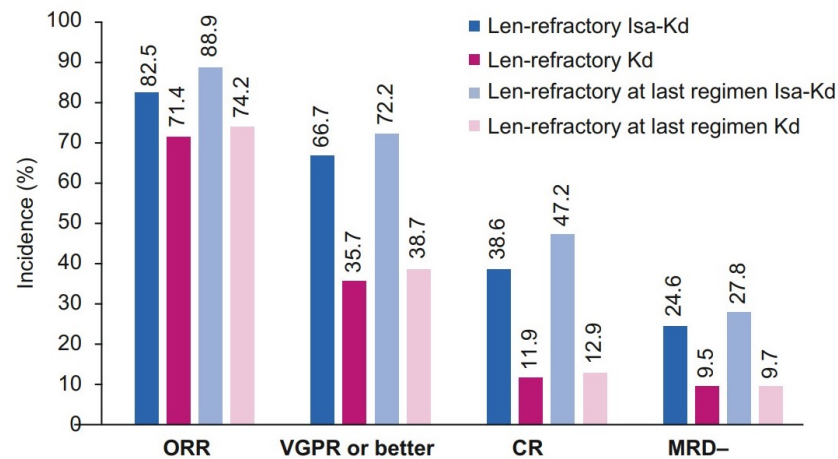
mPFS in late relapse: 42.7 (IsaKd) vs 21.9 (Kd)

Martin T et al, Blood Cancer 2023, Yong K et al, IMS 2023

IKEMA: IsaKd vs Kd nei pazienti Len-ref

(A)

Subgroup		Isa-Kd		Kd		Hazard ratio (95% CI)	P value for interaction
		No. of events/ total no.	mPFS, months (95% CI)	No. of events/ total no.	mPFS, months (95% CI)		
All patients		48/179	NC (NC-NC)	55/123	19.154 (15.770-NC)	0.531 (0.359-0.786)	
Number of prior lines of therapy	1	18/80	NC (NC-NC)	19/55	NC (15.376-NC)	0.589 (0.309-1.123)	0.6841
	>1	30/99	NC (NC-NC)	36/68	16.164 (13.437-19.450)	0.479 (0.294-0.778)	
Refractory to IMiD agent	Yes	28/78	NC (16.986-NC)	30/58	16.099 (13.437-NC)	0.629 (0.375-1.053)	0.3315
	No	20/101	NC (NC-NC)	25/65	NC (18.234-NC)	0.435 (0.241-0.784)	
Refractory to PI	Yes	19/56	NC (14.916-NC)	23/44	16.099 (9.922-NC)	0.616 (0.336-1.132)	0.6004
	No	29/123	NC (NC-NC)	32/79	NC (16.164-NC)	0.491 (0.297-0.813)	
Refractory to lenalidomide	Yes	23/57	NC (12.879-NC)	25/42	15.704 (9.922-17.183)	0.598 (0.339-1.055)	0.5568
	No	25/122	NC (NC-NC)	30/81	NC (18.234-NC)	0.479 (0.281-0.815)	
Refractory to bortezomib	Yes	18/52	NC (11.893-NC)	22/39	15.770 (9.922-NC)	0.620 (0.332-1.156)	0.6009
	No	30/127	NC (NC-NC)	33/84	NC (16.164-NC)	0.495 (0.302-0.813)	
Refractory to lenalidomide at last regimen	Yes	15/36	NC (11.433-NC)	17/31	16.164 (14.752-19.450)	0.692 (0.345-1.388)	0.3383
	No	33/143	NC (NC-NC)	38/92	NC (15.770-NC)	0.482 (0.302-0.769)	
Refractory to bortezomib at last regimen	Yes	8/32	NC (13.076-NC)	13/23	15.770 (4.830-NC)	0.383 (0.158-0.924)	0.3590
	No	40/147	NC (NC-NC)	42/100	20.271 (16.164-NC)	0.564 (0.365-0.870)	



La quota di pz Len-ref in IKEMA è limitata (32% rispettivamente)
La quota di pz Len-ref frontline è estremamente limitata (outcome NV)

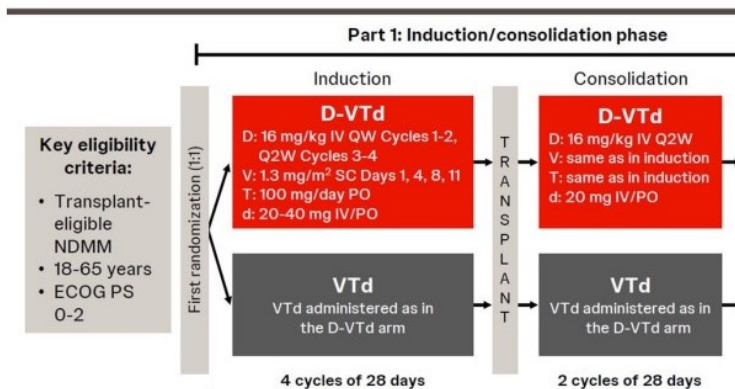
Sensibilità a anti-CD38 dopo esposizione: un problema aperto

- I pz esposti/refrattari a aCD38 sono stati esclusi dagli studi registrativi sui regimi RRMM aCD38-based (IsaKd, DPd)

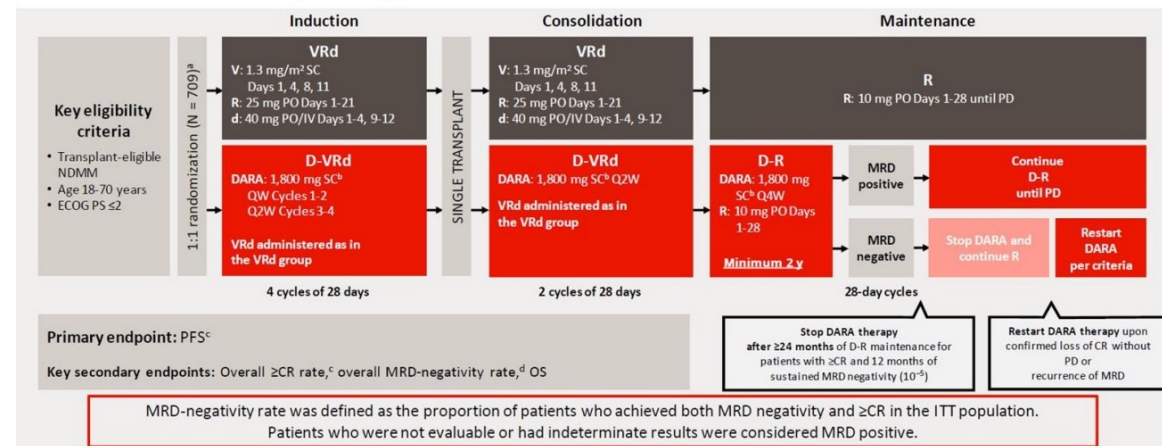
- L'impatto della precedente esposizione/refrattarietà e dell'intervallo aCD38-free dalla esposizione al ritrattamento non è noto

Dati limitati di Real World

CASSIOPEIA: Study Design **Len-maintenance**

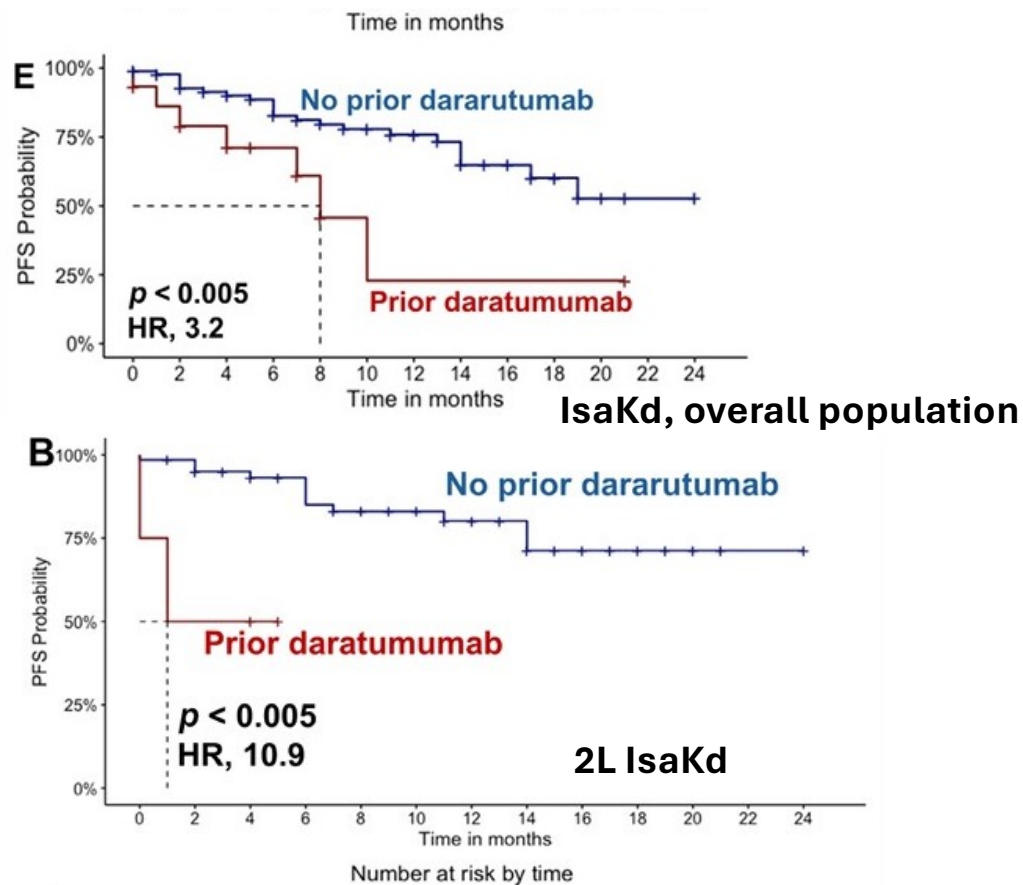


PERSEUS: Study Design



Len+Dara-maintenance
STOP Dara after sustained MRD neg

IsaKd dopo esposizione a Daratumumab. Dati di Real World



La precedente esposizione a Dara (15%, dei pz) impatta negativamente sulla PFS nei pz trattati con IsaKd, nella popolazione complessiva e in 2L¹

NB: non definita la percentuale di pz refrattari su quelli esposti;
non definito l'intervallo di tempo mediano dalla precedente esposizione;
limitato numero di pz esposti a Dara trattati con IsaKd in 2L

La refrattarietà a Dara impatta negativamente su ORR nei pz trattati con IsaKd; 41.7% vs 82.2% (studio IONA-MM)²

Paziente in prima recidiva (2L)

Len-ref

aCD38-sens

Bor-sens

Cilta-cel
IsaKd
BelaPd*

Opzioni preferibili

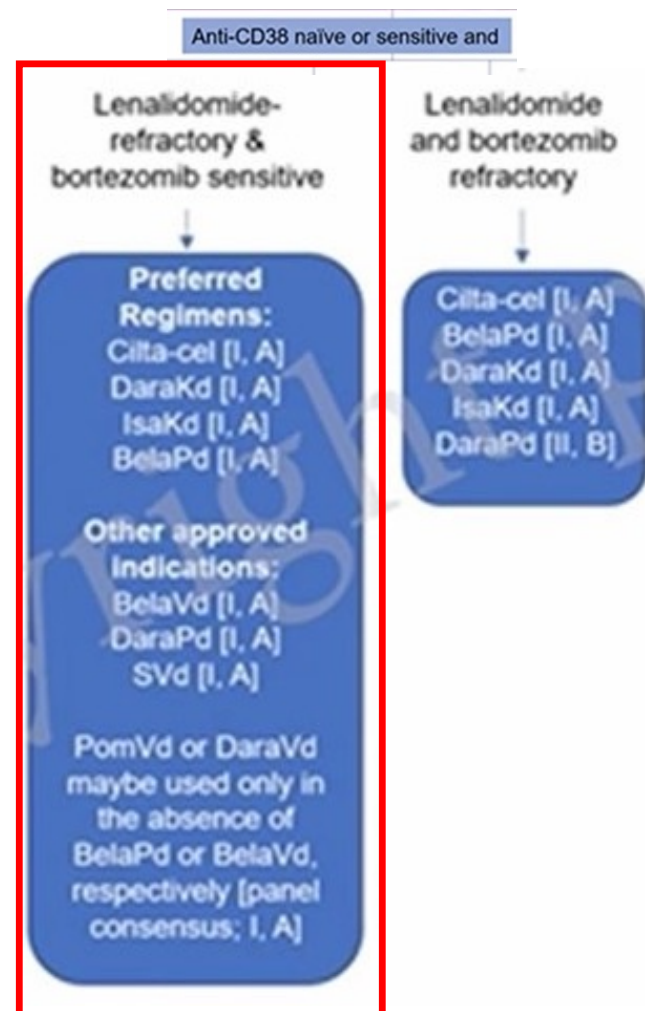
BelaVd*
SeIVd
DaraPd

Altre opzioni (seconda scelta)

PVd
DaraVd

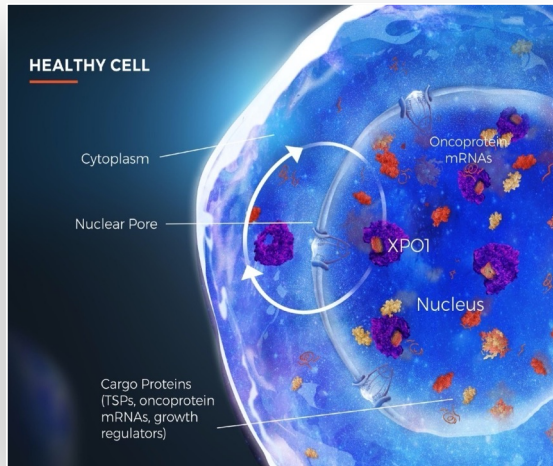
In mancanza di BelaPd e
BelaVd (outcome inferiori in
DREAMM-8 e DREAMM 7)

*Nella prospettiva di futura terapia con CAR-T sono preferibili regimi alternativi a Bela
Bela preclude il successivo utilizzo di aBCMA CAR-T e del BsAbs aBCMA Elranatamab, NON di Teclistamab



Nature Review Clinical Oncology, submitted 2025

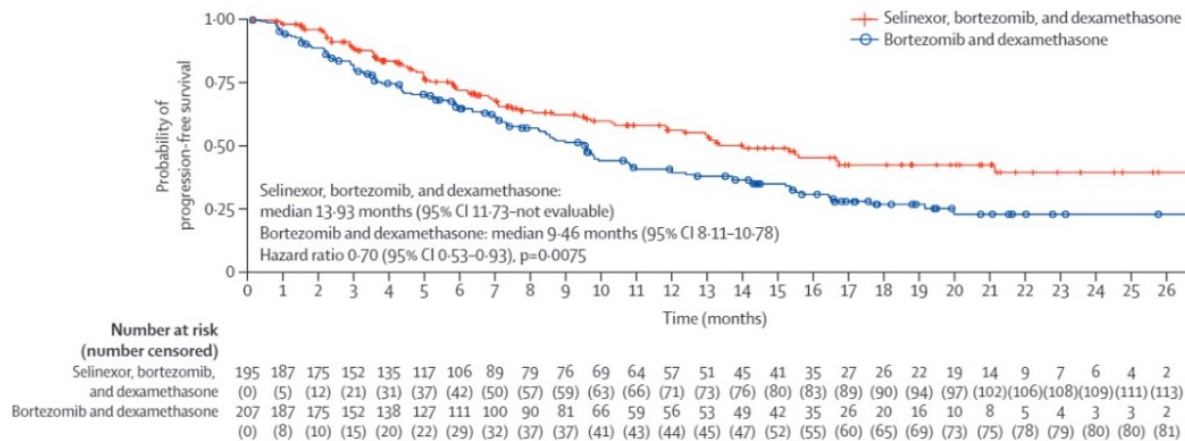
BOSTON: Selinexor-Vd vs Vd. ORR, PFS



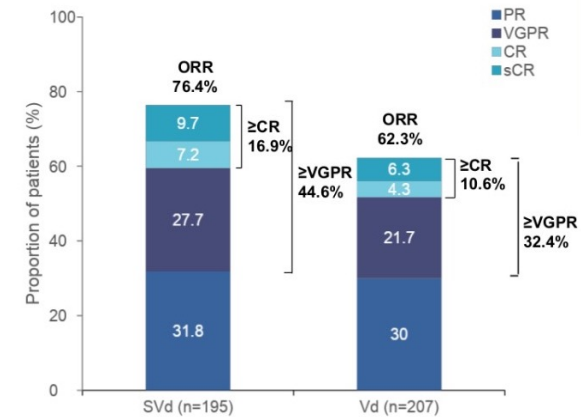
	SVd arm (n = 195)	Vd arm (n = 207)
Median PFS, months (95% CI)*	13.93 (11.73, NE)	9.46 (8.11, 10.78)
HR=0.70 (95% CI: 0.53, 0.93); one-sided <i>P</i> = .0075		

SVd vs Vd
vantaggio di
ORR e ≥VGPR
mPFS (HR 0.70, mPFS 13.9) vs

Kaplan-Meier estimates of progression-free survival among patients in the ITT population



Overall Response Rate



Grosicki S et al, Lancet 2020

BOSTON: SelVd vs Vd. Analisi di sottogruppo secondo precedenti LT

EFFICACY in 1 Prior LOT Patients

Table 4. Outcomes in 1 Prior LOT Patients

	SVd (n=99)	Vd (n=99)
Median PFS, months (95% CI)	21.0 (13.2, NR)	10.7 (7.3, 16.4)
PFS HR (95% CI)	0.62 (0.41, 0.95)	0.026
Median TTT, months (95% CI)	19.0 (15.3, 27.4)	12.9 (9.8, 16.2)
TTT HR (95% CI)	0.70 (0.49, 1.01)	0.056
p-value		
Overall response rate, %	80.8	66.7
OR (95% CI)	2.40 (1.22, 4.70)	0.010
p-value		
VGPR or better, %	52.5	29.3
OR (95% CI)	2.65 (1.46, 4.78)	0.001
p-value		

All p-values two sided

Figure 2. PFS in 1 Prior LOT Patients

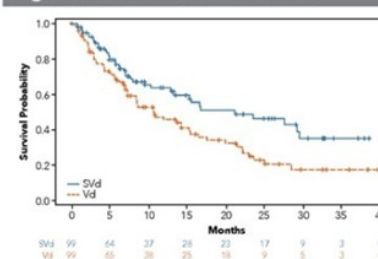
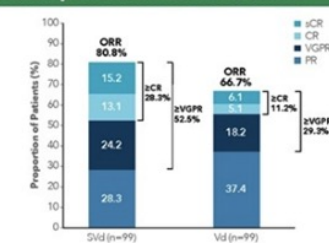


Figure 3. Response in 1 Prior LOT Patients



SVd vs Vs si associa a vantaggio di PFS, ORR e ≥VGPR in tutti i sottogruppi

EFFICACY in PI-Naïve Patients

Table 5. Outcomes in PI-Naïve Patients

	SVd (n=47)	Vd (n=48)
Median PFS, months (95% CI)	29.5 (27.5, NR)	9.7 (8.4, 23.7)
PFS HR (95% CI)	0.29 (0.14, 0.63)	<0.001
Median TTT, months (95% CI)	30.2 (26.7, NR)	10.8 (10.1, 21.2)
TTT HR (95% CI)	0.42 (0.23, 0.78)	0.004
p-value		
Overall response rate, %	76.6	70.8
OR (95% CI)	1.30 (0.51, 3.33)	0.581
p-value		
VGPR or better, %	53.2	41.7
OR (95% CI)	1.54 (0.68, 3.48)	0.308
p-value		

All p-values two sided

Figure 4. PFS in PI-Naïve Patients

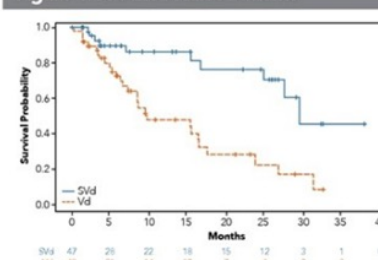
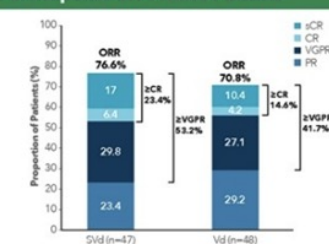


Figure 5. Response in PI-Naïve Patients



EFFICACY in Bortezomib-Naïve Patients

Table 6. Outcomes in Bortezomib-Naïve Patients

	SVd (n=61)	Vd (n=62)
Median PFS, months (95% CI)	29.5 (24.8, NR)	9.7 (8.4, 17.5)
PFS HR (95% CI)	0.35 (0.18, 0.68)	0.002
Median TTT, months (95% CI)	29.8 (22.7, NR)	12.9 (10.4, 21.2)
TTT HR (95% CI)	0.47 (0.28, 0.81)	0.006
p-value		
Overall response rate, %	75.4	69.4
OR (95% CI)	1.57 (0.68, 3.64)	0.295
p-value		
VGPR or better, %	49.2	41.9
OR (95% CI)	1.51 (0.73, 3.14)	0.275
p-value		

All p-values two sided

Figure 6. PFS in Bortezomib-Naïve Patients

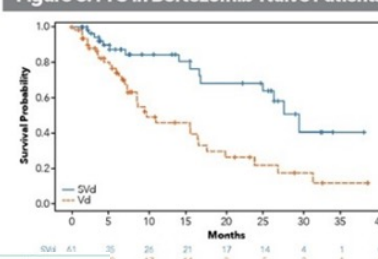
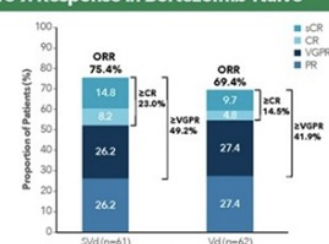


Figure 7. Response in Bortezomib-Naïve



CR, complete response; ORR, overall response rate; PR, partial response; iCR, stringent complete response; SVd, selinexor + bortezomib + doxorubicin; Vd, bortezomib + selinexor; VGPR, very good partial response.

HR 0.62
mPFS
improvement:
10 m

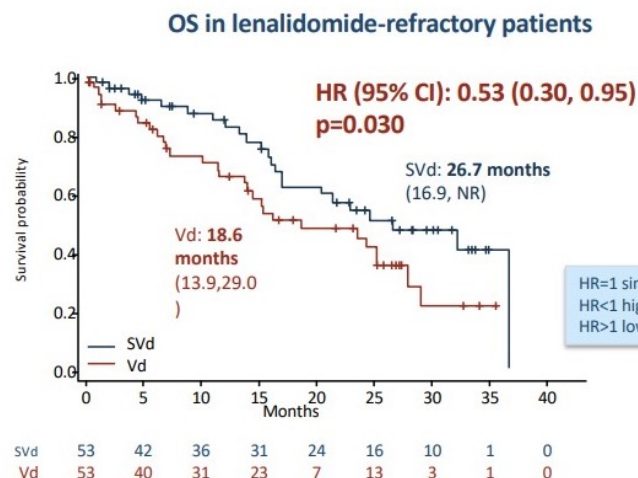
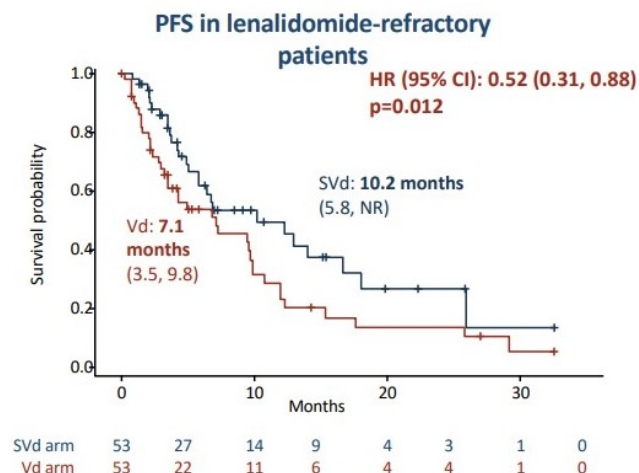
HR 0.29
mPFS
improvement:
20 m

HR 0.35
mPFS
improvement:
20 m

Prior Therapies, n (%)		
Bortezomib	134 (69)	145 (70)
Carfilzomib	20 (10)	21 (10)
Daratumumab	11 (6)	6 (3)
Lenalidomide	77 (39)	77 (37)
Pomalidomide	11 (6)	7 (3)
Ixazomib	6 (3)	3 (1)
Stem cell transplant [†]	76 (39)	63 (30)

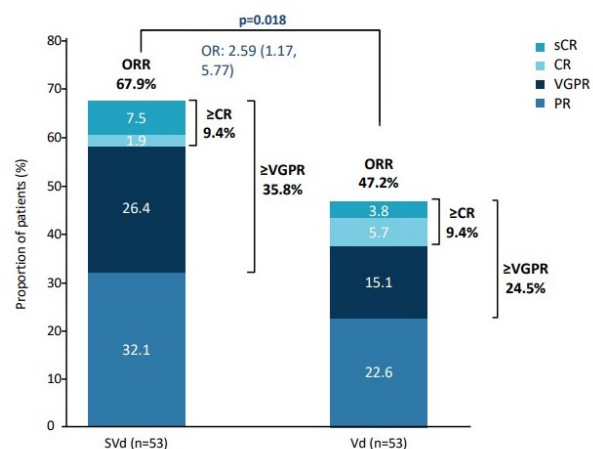
Mateos M-V et al. EHA 2023. Poster #917

BOSTON: SelVd vs Vd nei pazienti Len-refractory



Follow-up mediano
SVd 28.7 m
Vd 28.6 m

HR=1 similar efficacy observed in SVd vs Vd
HR<1 higher efficacy observed in SVd vs Vd
HR>1 lower efficacy observed in SVd vs Vd



Len-exposed: 39% e il 37% dei pz nei gruppi SVd e Vd, rispettivamente
Len-refractory: 27% e il 26% dei pz nei gruppi SVd e Vd, rispettivamente

Nei pz Len-ref SVd vs Vd si associa a un vantaggio statisticamente significativo di **PFS** (10.2 vs 7.1 mesi, HR 0.52)

Nei pz Len-ref trattati con SVd, la mPFS è inferiore (10.2 mesi) rispetto alla popolazione complessiva (13.9 mesi)

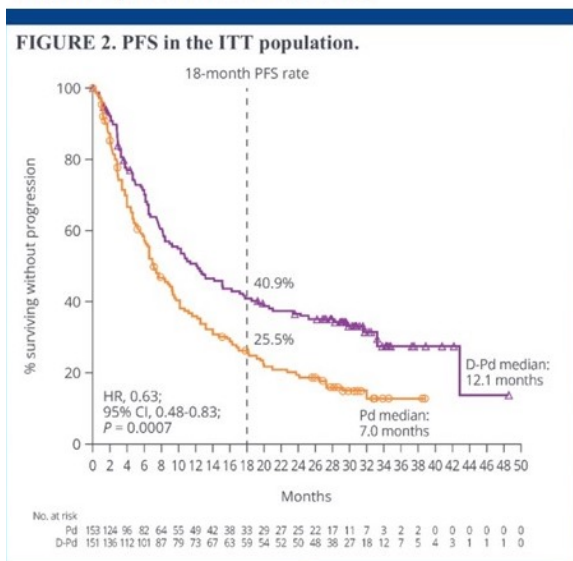
Nei pz Len-ref SVd vs Vd si associa a un vantaggio statisticamente significativo di **OS** (26.7 mesi vs 18.6 mesi, HR 0.53)

TTNT (13.0 mesi vs 7.6 mesi)

ORR (67.9% vs 47.2%, OR 2.59) e di ≥VGPR (35.8% vs 24.5%, OR 1.74)

APOLLO e MM-014: DaraPd nei pazienti Len-refractory

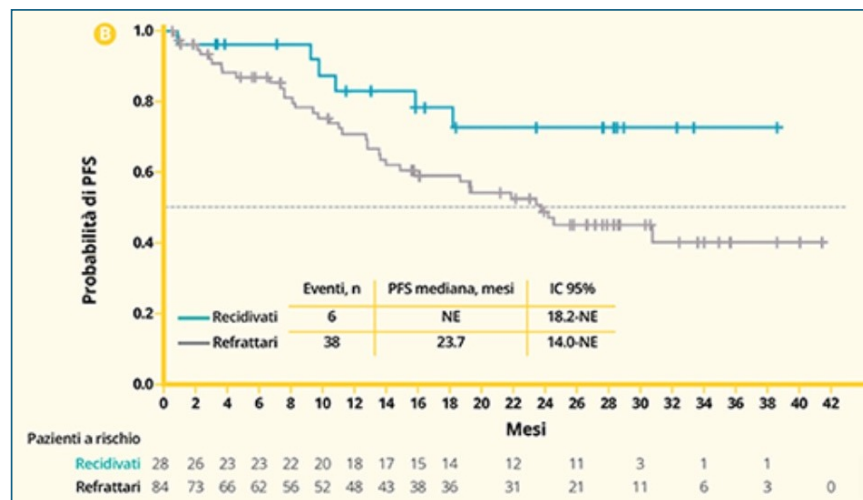
Follow up mediano: 30.7 mesi



Studio APOLLO (fase 3):

- DPd vs Pd: vantaggio di PFS, anche nei pz Len-ref
- **mPFS** nei pz Len-ref trattati con DPd (**9.8 m**) è inferiore vs Len-sens (31.6 m) e ITT (12.1 m)
- DPd vs Pd: vantaggio di OS (m follow-up 39.6 m, mOS 34.4 m vs 23.7 m, HR 0.82)

Len-ref 79%, Len-ref alla precedente LT 62%
di cui solo 11% con 1 precedente LT (Len-ref frontline)



Lo studio MM-014 (fase 2) ha valutato DPd :

- dopo 1 o 2 precedenti LT
- Len in linea immediatamente precedente (100% Len-exp, 75% Len-ref)

Nei pz **Len-ref** dopo 1-2 pLT

mPFS 23.7 m

PFS a 1 anno 70.9%

Bahlis NJ et al, Leuk Lymph 2022

Paziente in prima recidiva (2L)

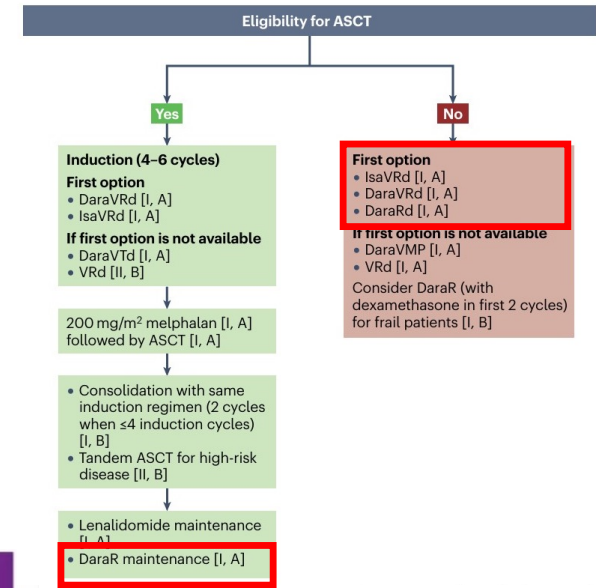
Len-ref aCD38-ref Bor-sens

Progressione in corso di mantenimento/t. continua con aCD38+Len

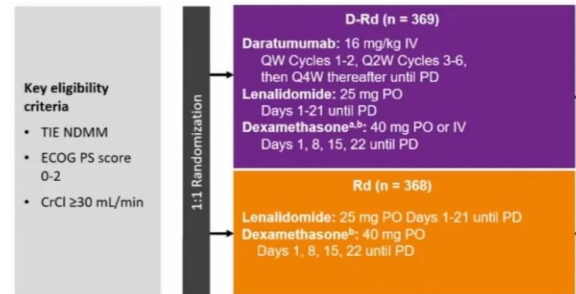
- In corso di DaraRd (NTE)

- In corso di IsaRd dopo IsaVRd o di DaraRd dopo DaraVRd (NTE)

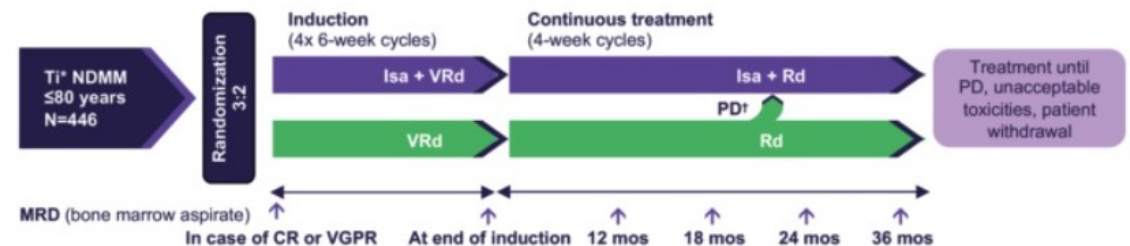
- In corso di DaraR dopo DaraVRd, nei pz che non hanno conseguito MRD neg sostenuta (TE)



Dara+Len continuous treatment



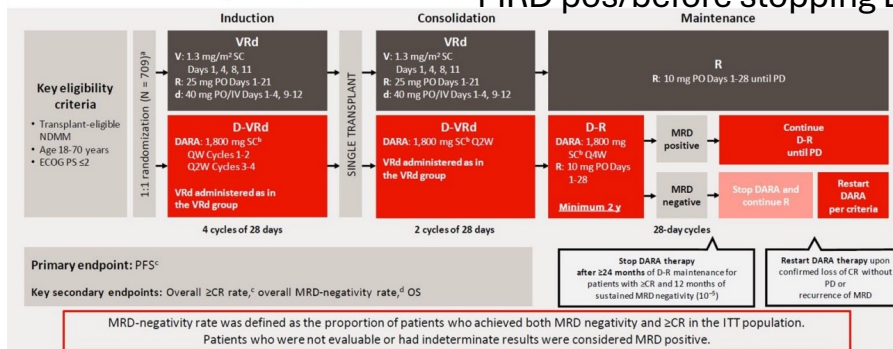
Isa+Len continuous treatment



Dara+Len maintenance

MRD pos/before stopping Dara

PERSEUS: Study Design



Paziente in prima recidiva (2L)

Len-ref
aCD38-ref
Bor-sens

Progressione in corso di mantenimento/terapia continua con aCD38+Len

- In corso di DaraRd (NTE)
- In corso di IsaR dopo IsaVRd o di DaraR dopo DaraVRd (NTE)
- In corso di DaraR dopo DaraVRd, nei pz che non hanno conseguito MRD neg sostenuta (TE)

Cilta-cel
BelaPd*

Opzioni preferibili

SelVd
Kd
(BelaVd)

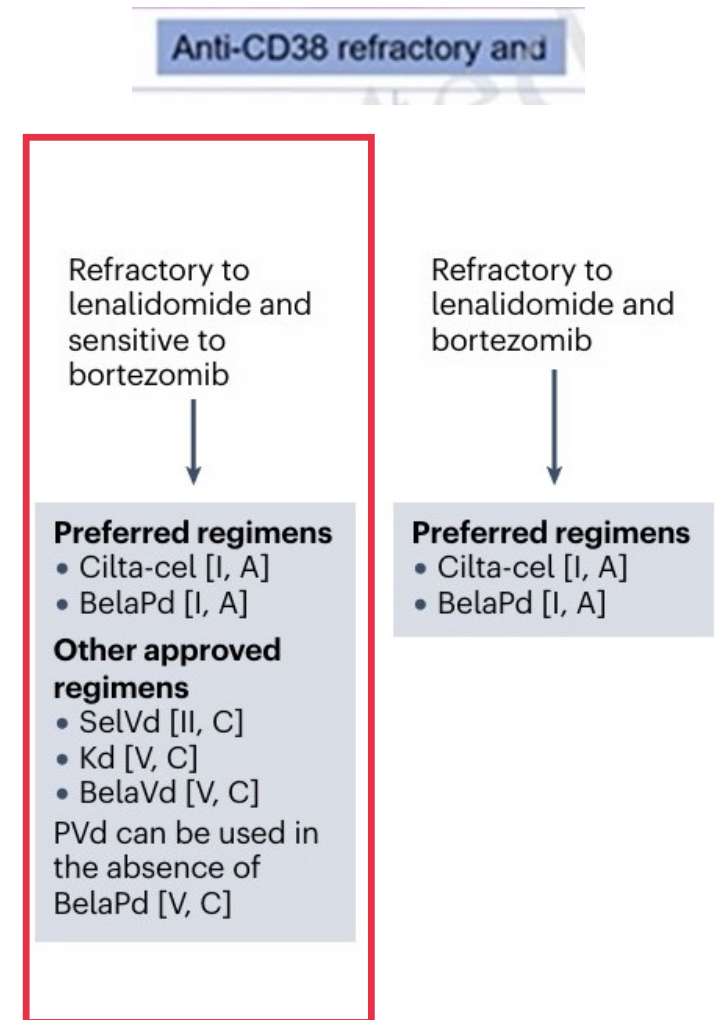
Altre opzioni (seconda scelta)

PVd

In mancanza di BelaPd (outcome inferiori in DREAMM-8)

*Nella prospettiva di futura terapia con CAR-T sono preferibili regimi alternativi a Bela.

Bela preclude il successivo utilizzo di aBCMA CAR-T e del BsAbs aBCMA Elranatamab, NON di Teclistamab



Paziente in prima recidiva (2L)

Len-ref

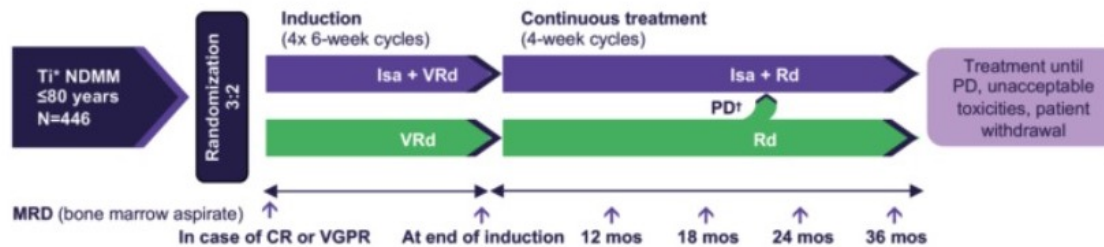
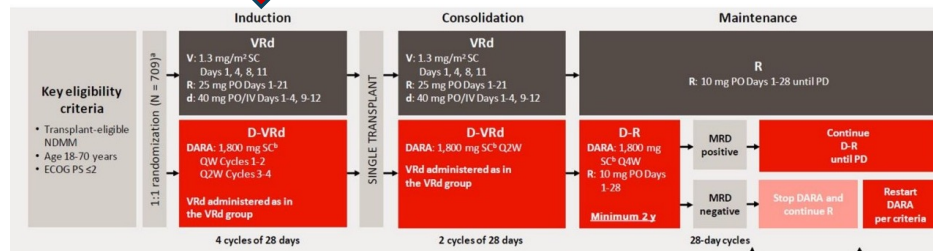
aCD38-ref

Bor-ref

Progressione in corso di

- DaraVRd

- IsaVRd

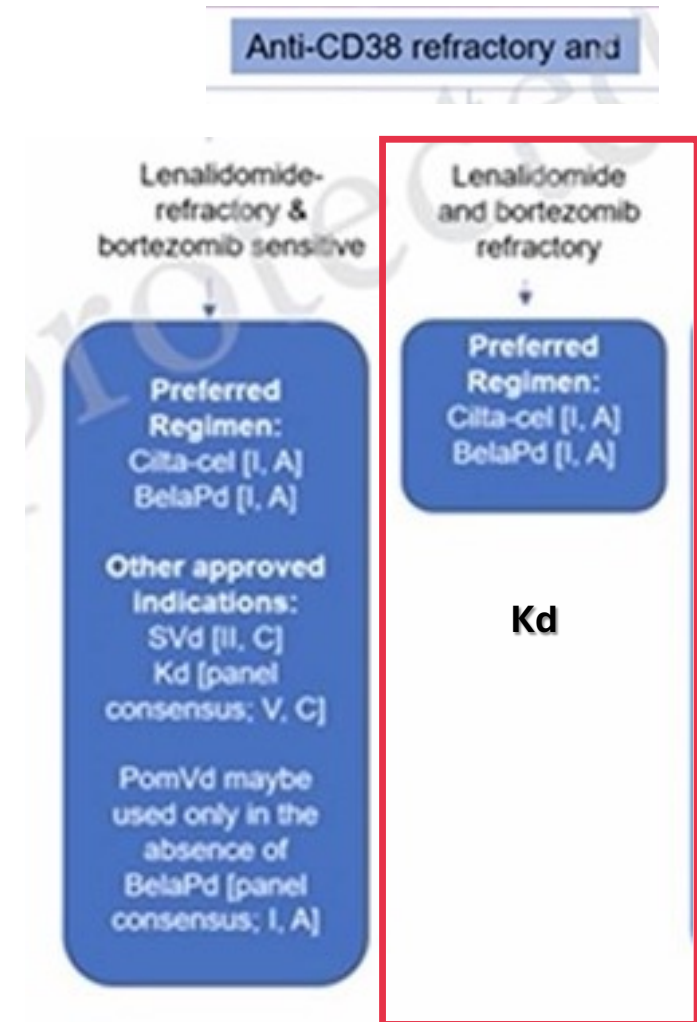


Cilta-cel
BelaPd

Opzioni preferibili

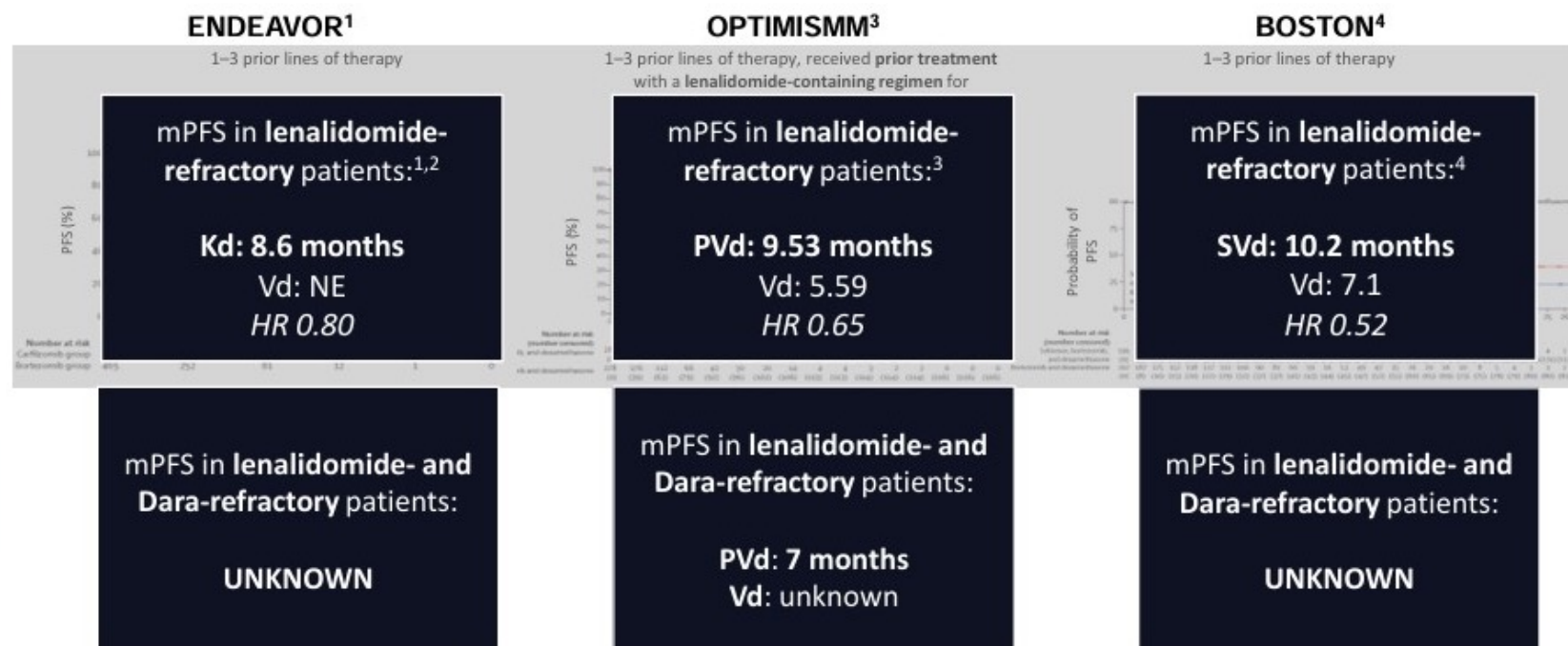
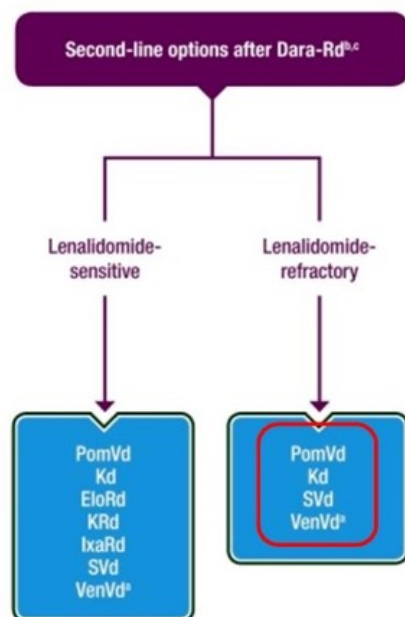
Kd

Altre opzioni (seconda scelta)



Kd

Doppia refrattarietà a Len e Dara in prima recidiva. Di quali dati disponiamo?



Nuove opzioni in 2L:

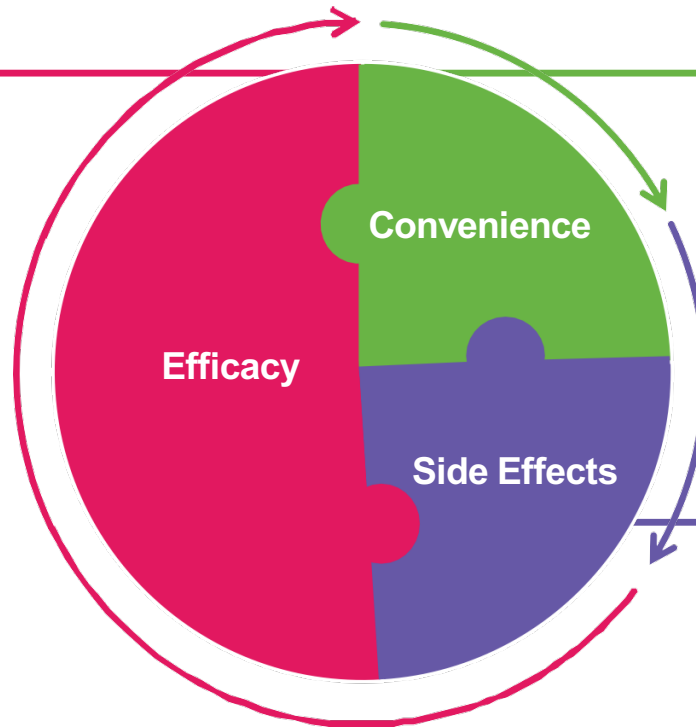
Ciltacel (CARTITUDE-4): 100% Len-ref
22% Dara-ref
mPFS in DR-ref: **UNKNOWN**

BelaPd (DREAMM-8): 80% Len-ref
25% Dara-ref
mPFS in DR-ref: **UNKNOWN**

Selezione del trattamento in prima recidiva (oltre le linee guida...)

Efficacy

- Will this treatment extend my life?
- Will my symptoms be reduced?



Ease/burden of administration

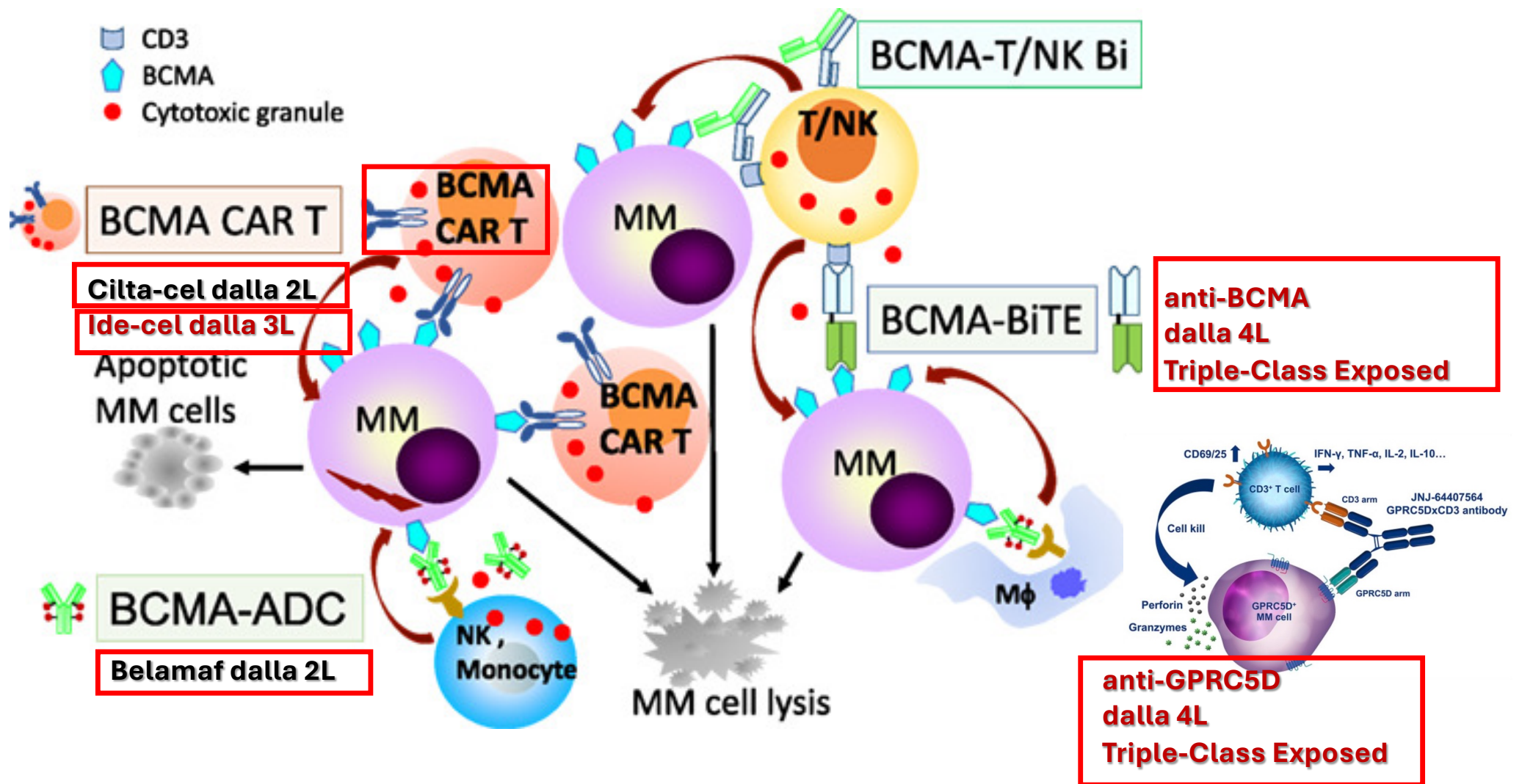
- Do I have to go to an academic center? Or my local doctor?
- How far away is the place I go to get treatment?
- How often do I have to get treatment?
- How much time does getting treatment take up?
- What actual and “hidden” costs will there be?

Side effects

- Are the side effects permanent? Or will they resolve?
- How could the drugs I am on impact my QoL?
- Is the trade-off “worth it”?

Selezione del trattamento in prima recidiva: BCMA-TT approvate

	Belantamab mafadotin	Cilta-cel
 Efficacy	Significant PFS and OS[†] benefit vs SoC	
 Safety/ tolerability	AEs experienced by almost all patients Ocular events can be managed and reversed with appropriate dose modifications and follow-up	AEs experienced by almost all patients Black box warning for risk of ICANS or CRS that require supportive care and can be permanent and/or fatal
 Treatment availability	Little to no wait time is required prior to administration	Cell manufacturing takes ~4 weeks
 Administration setting	Outpatient (no hospitalization required)	Specialized medical center and/or hospitals Inpatient monitoring for 10 days post-infusion
	30-min infusion	Lymphapheresis, bridging therapy, lymphodepletion
 Monitoring	Eye exam required before first 4 doses and as clinically indicated thereafter	Post-treatment monitoring for CRS/neurotoxicity requires patients to remain within proximity to an administration center for ≥4 weeks following administration
Duration	Continuous treatment until progression	“One shot” treatment (treatment-free interval)



CAR-T aBCMA, ADC aBCMA, BsAbs (aBCMA, non aBCMA). Quale sequencing?



International myeloma working group immunotherapy
committee recommendation on sequencing immunotherapy
for treatment of multiple myeloma

In un paziente potenzialmente candidabile sia a CAR-T, che ADC (Belamaf) che BsAbs-aBCMA, si raccomanda l'utilizzo prima di CAR-T aBCMA

- Efficacia superiore di CAR-T, tanto maggiore quanto più precoce l'utilizzo
- Efficacia di CAR-T inferiore dopo precedente aBCMA (ADC, BsAbs)
- Efficacia dei BsAbs (aBCMA, non-aBCMA) mantenuta dopo precedente CAR-T aBCMA, superiore per Talquetamab (da solo o in associazione)
- CAR-T è terapia “one shot”, che implica intervallo libero da trattamento con più opzioni di salvataggio alla progressione

Nei pz con malattia rapidamente progressiva con elevata probabilità di complicanze e deterioramento clinico (correlato alla malattia e/o alla terapia) nella fase di aferesi e di successiva Bridging therapy, **ADC/BsAbs (terapia off the shelf)** rappresentano una opzione preferibile vs CAR-T

La scelta della terapia di 2L nell'attuale panorama terapeutico

Conclusioni



La scelta della terapia di 2L oggi deve considerare:

- Dati di efficacia
- Aspetti logistici
- Tossicità/impatto sulla qualità di vita
- Caratteristiche del paziente (fitness, comorbidità – riserva cardiopolmonare e midollare)
- Caratteristiche della recidiva (timing, cinetica/burden, EMD, clinica, caratteristiche di aggressività biologica, citogenetica) che condizionano:
 - Probabilità di risposta alle terapia
 - Scelta di CAR-T (tempo di manufacturing) vs terapia con ADC, (BsAbs), altre opzioni (off the shelf)
- Potenziale impatto sulle successive linee terapeutiche, in particolare nella prospettiva di utilizzo di immunoterapie T-cell redirecting che sfruttano lo stesso target (BCMA) (induzione di down-regolazione/mutazioni dell'Ag; induzione di T-cell exhaustion)