Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA
HEMATOLOGÍA EN 48H
[LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]
X EDICIÓN

ACTUALÍZATE 48 HORAS

Pronóstico y tratamiento de pacientes con mieloma refractario

Enrique M. Ocio

Hospital Universitario Marqués de Valdecilla (IDIVAL)

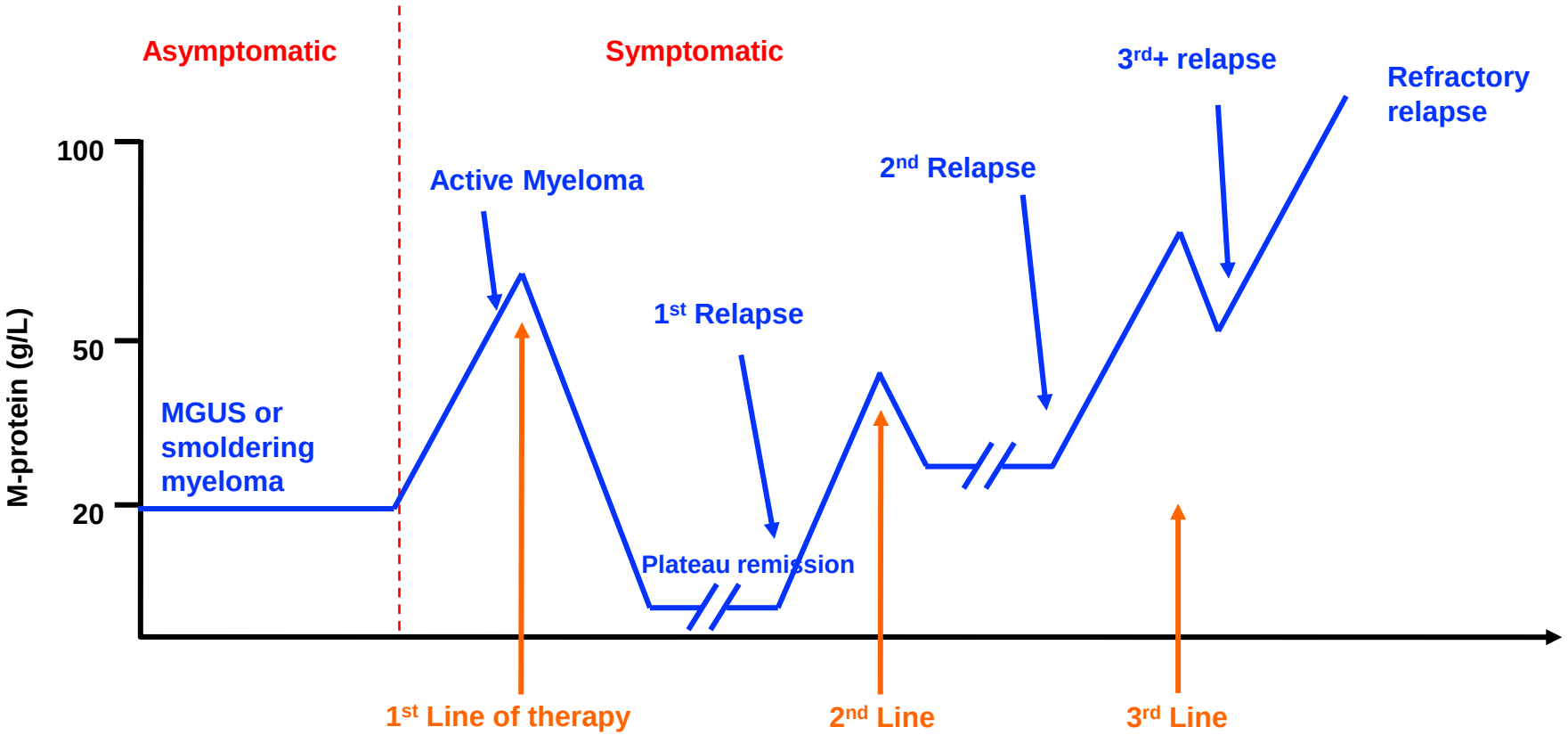
Universidad de Cantabria

Santander

Disclosures

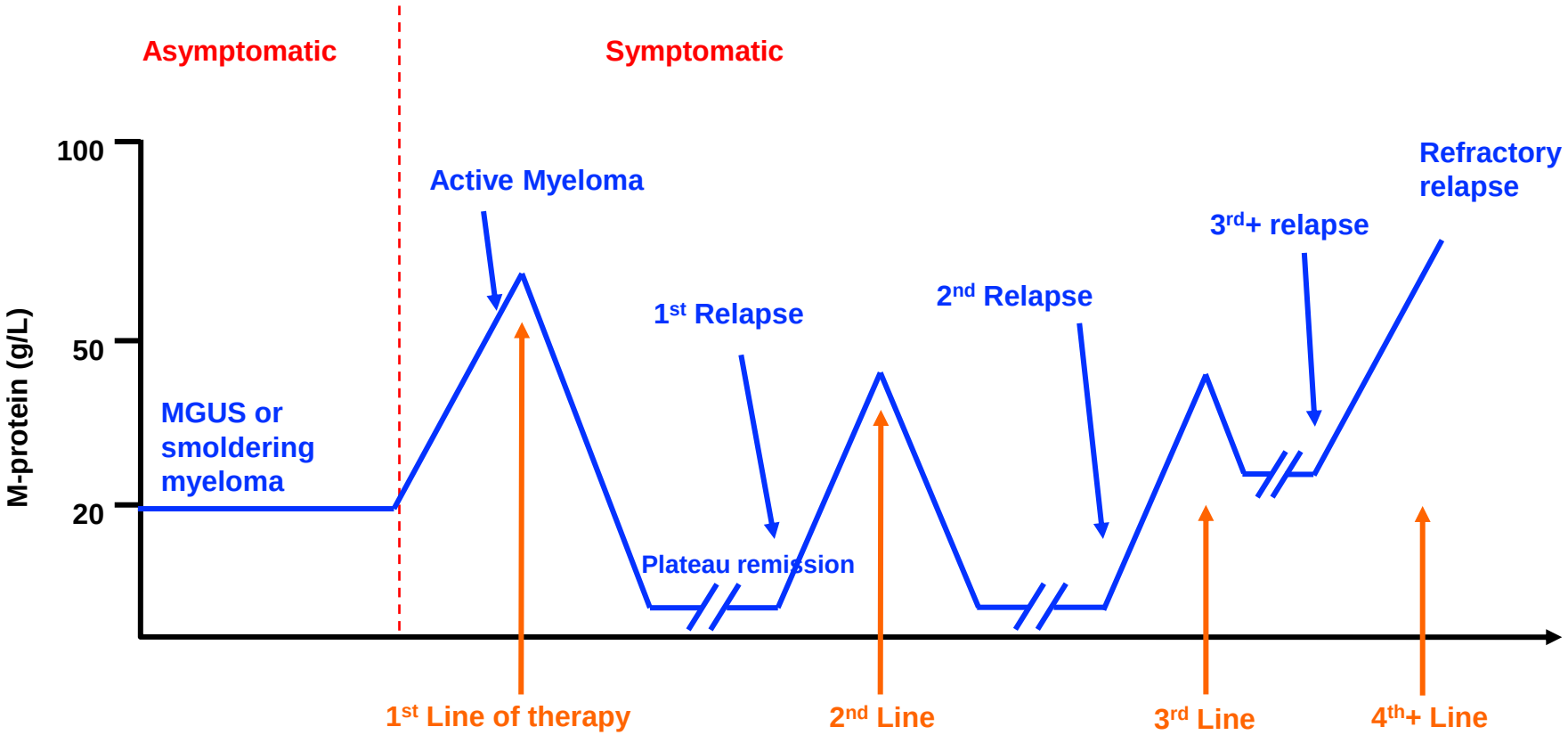
Honoraria / Consultancy	**Janssen; Sanofi; Pfizer; Abbvie; GSK; BMS; Regeneron; Oncopeptides; Menarini-Stemline; Astra-Zeneca; Takeda; Amgen**
Research Support	**GSK, Oncopeptides**
Support for formation	**Janssen; Sanofi; GSK; BMS; Lilly**

Natural History of MM patients



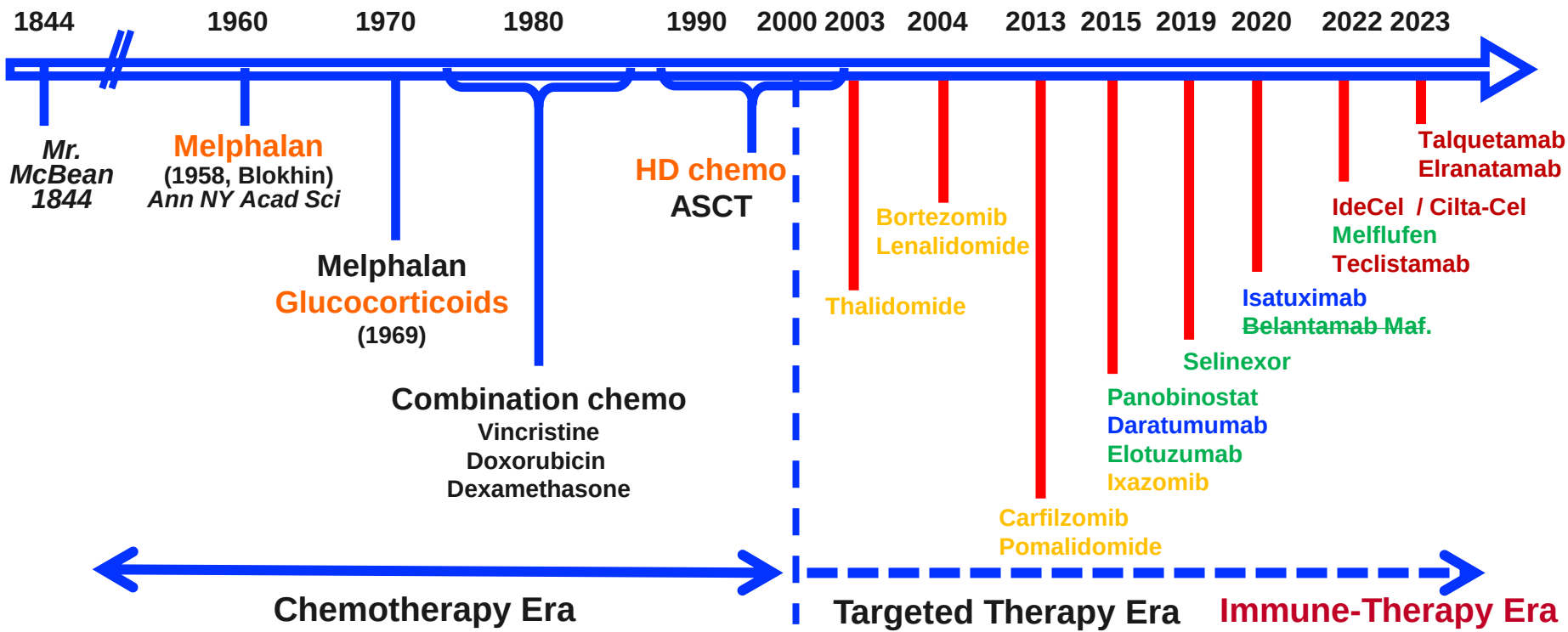
MGUS, monoclonal gammopathy of undetermined significance

Natural History of MM patients



MGUS, monoclonal gammopathy of undetermined significance

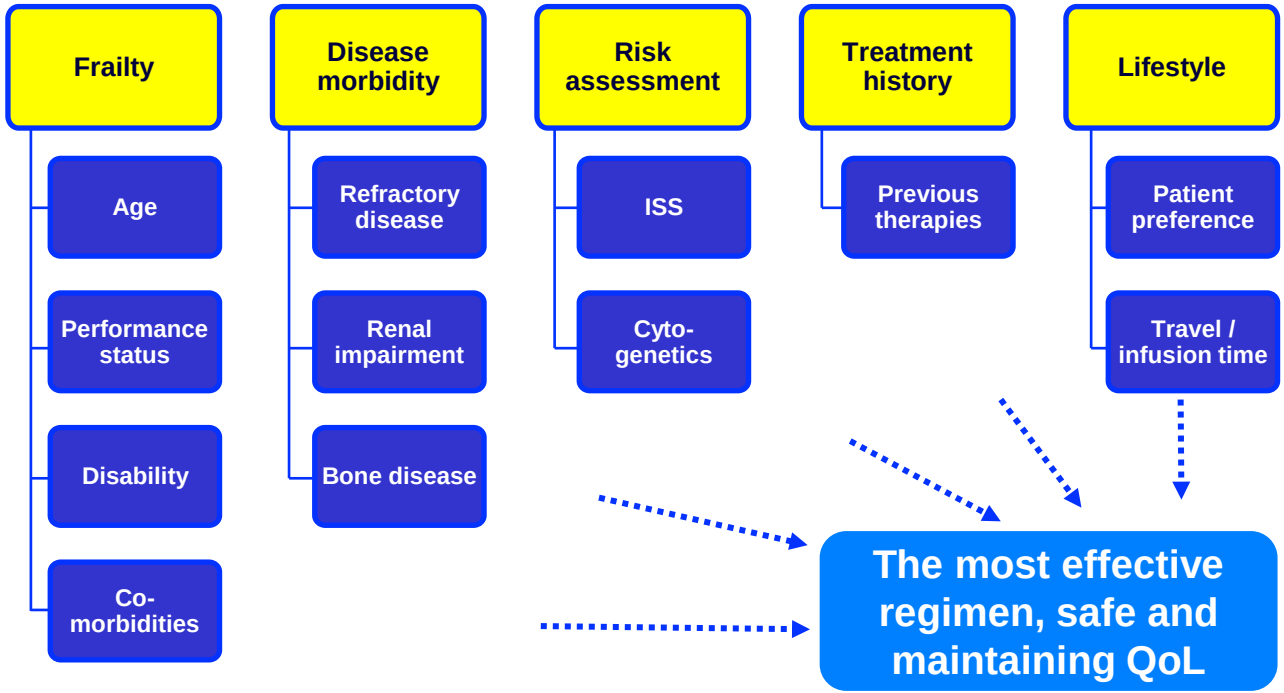
Treatment of MM



17 novel agents approved for MM in this century

Strategies at relapse: How to make the right choice?

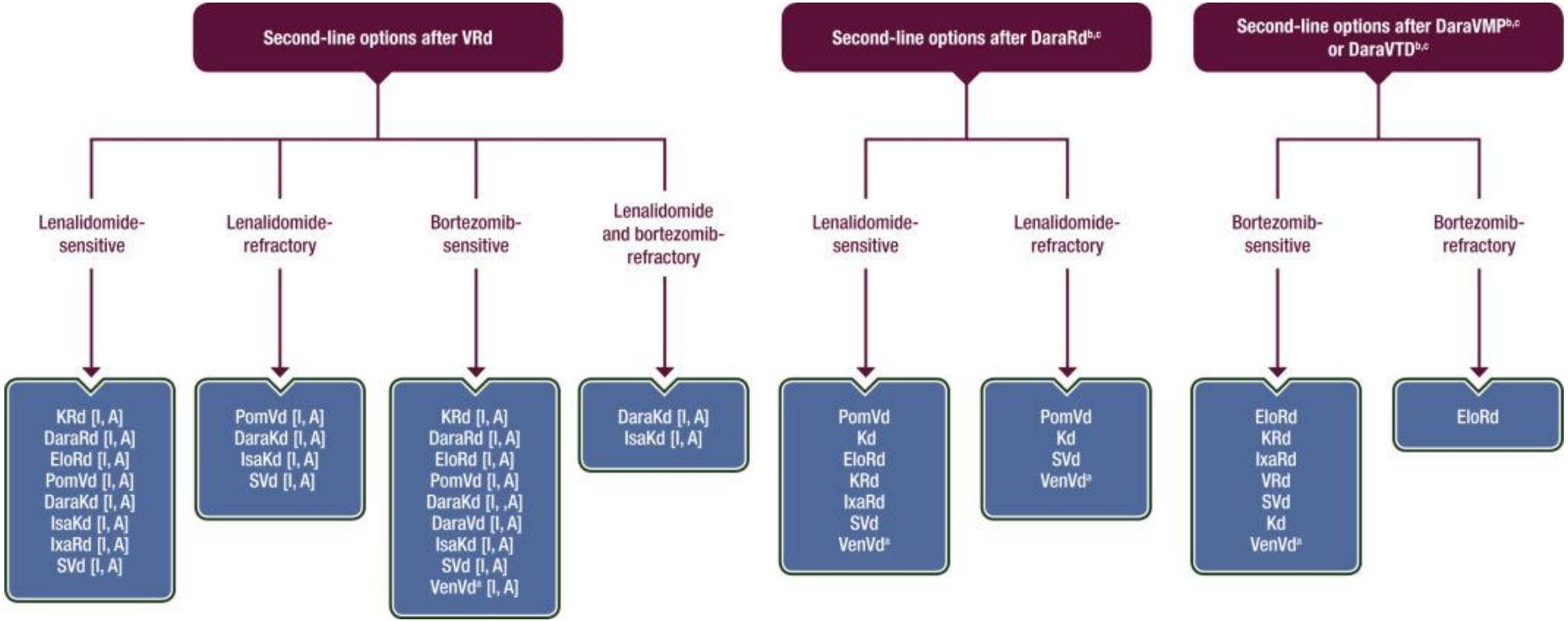
Disease and patient-based factors



•ISS, International Staging System.

Clegg A et al. *Lancet* 2013;381:752–762; Handforth C et al. *Ann Oncol* 2015;26:1091–1101; Chen X et al. *Clin Interv Aging* 2014;9:433–441; Palumbo A et al. *Blood* 2015;125:2068–2074; Jhaveri D et al. *Haematologica* 2016;101:1–881 (Abstract E1312); Sonneveld P et al. *Leukemia* 2013;27:1959–1969; Faiman BM et al. *Clin J Oncol Nurs* 2011;15:66–76; Miceli TS et al. *Clin J Oncol Nurs* 2011;15:9–23; Greipp PR et al. *J Clin Oncol* 2005;23:3412–3420; Binder M et al. *Haematologica* 2016;101:P665; Merz M et al. *Haematologica* 2016;101:P650; Chng WJ et al. *Leukemia* 2016;30:1071–1078; Chung TH et al. *PLoS One* 2013;20:e66361; Sonneveld P et al. *Leukemia* 2013;27:1959–1969; Sonneveld P et al. *Lancet Oncol* 2016;16:427; Williams LA et al. *J Clin Oncol* 2016;34:e18127; Ramasamy K et al. *Haematologica* 2017;102:E1457.

ESMO Guidelines



Dimopoulos et al. Ann Oncol. 2021

To Len or not to Len?

To Anti-CD38 or not to Anti-CD38?

Treatment Possibilities at relapse: 1st & 2nd situation

First Relapses

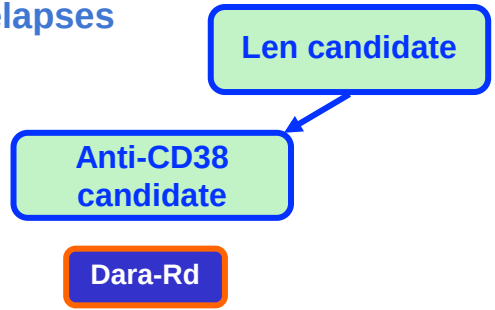
Treatment Possibilities at relapse: 1st & 2nd situation

First Relapses

D-VTd / D-VRd → ASCT → No maint. until PD

Treatment Possibilities at relapse: 1st & 2nd situation

First Relapses



D-VTd / D-VRd → ASCT → No maint. until PD

Treatment Possibilities at relapse: 1st & 2nd situation

First Relapses

Len candidate

Anti-CD38 candidate

Dara-Rd

D-VTd / D-VRd → ASCT → No maint. until PD

	DaraRd vs Rd[1,2] POLLUX
PFS (months)	44.5 vs 17.5 m
HR (95% CI)	0.44 (0.35–0.55)
ORR, %	93
≥ CR, %	57 (MRD 30%)
DOR, months	NE
OS HR (95% CI)	0.44 (0.35–0.55)

1. Dimopoulos M, NEJM 2016; 2. Bahlis NJ Leukemia 2020;
3. Stewart AK, NEJM 2015; 4. Siegel DS, JCO 2018;
5. Lonial S, NEJM 2015; 6. Dimopoulos MA, BJH 2017;
7. Moreau P, NEJM 2016.

Treatment Possibilities at relapse: 1st & 2nd situation

First Relapses

Len candidate

Anti-CD38 candidate

Dara-Rd

D-VTd / D-VRd → ASCT → No maint. until PD

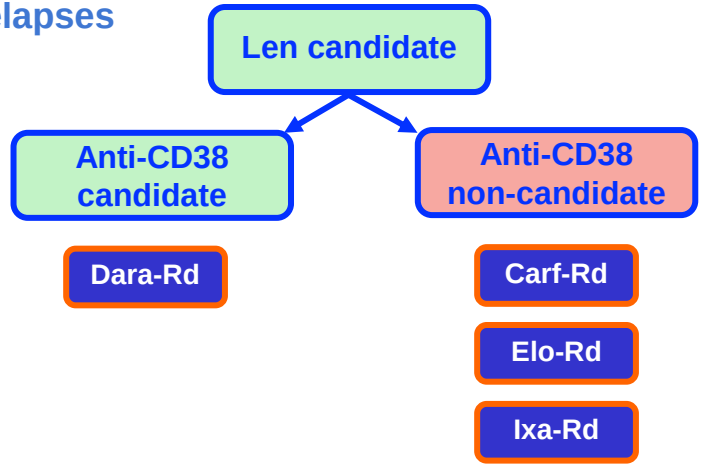
D-VMP + D

	DaraRd vs Rd[1,2] POLLUX
PFS (months)	44.5 vs 17.5 m
HR (95% CI)	0.44 (0.35–0.55)
ORR, %	93
≥ CR, %	57 (MRD 30%)
DOR, months	NE
OS HR (95% CI)	0.44 (0.35–0.55)

1. Dimopoulos M, NEJM 2016; 2. Bahlis NJ Leukemia 2020;
3. Stewart AK, NEJM 2015; 4. Siegel DS, JCO 2018;
5. Lonial S, NEJM 2015; 6. Dimopoulos MA, BJH 2017;
7. Moreau P, NEJM 2016.

Treatment Possibilities at relapse: 1st & 2nd situation

First Relapses



D-VTd / D-VRd → ASCT → No maint. until PD

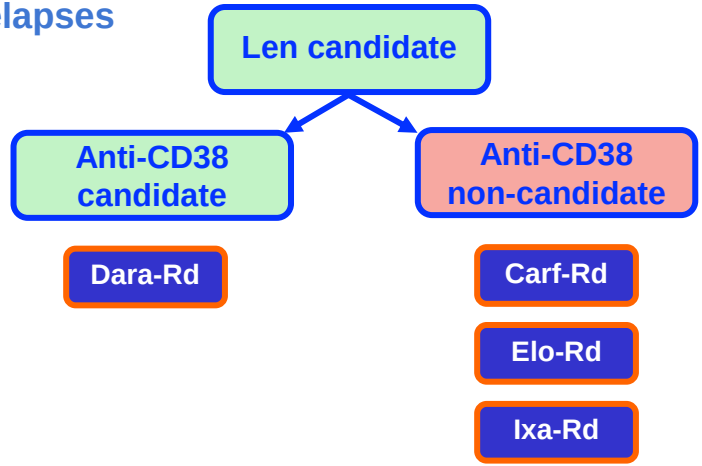
D-VMP + D

	DaraRd vs Rd[1,2] POLLUX
PFS (months)	44.5 vs 17.5 m
HR (95% CI)	0.44 (0.35–0.55)
ORR, %	93
≥ CR, %	57 (MRD 30%)
DOR, months	NE
OS HR (95% CI)	0.44 (0.35–0.55)

1. Dimopoulos M, NEJM 2016; 2. Bahlis NJ Leukemia 2020;
3. Stewart AK, NEJM 2015; 4. Siegel DS, JCO 2018;
5. Lonial S, NEJM 2015; 6. Dimopoulos MA, BJH 2017;
7. Moreau P, NEJM 2016.

Treatment Possibilities at relapse: 1st & 2nd situation

First Relapses



D-VTd / D-VRd → ASCT → No maint. until PD

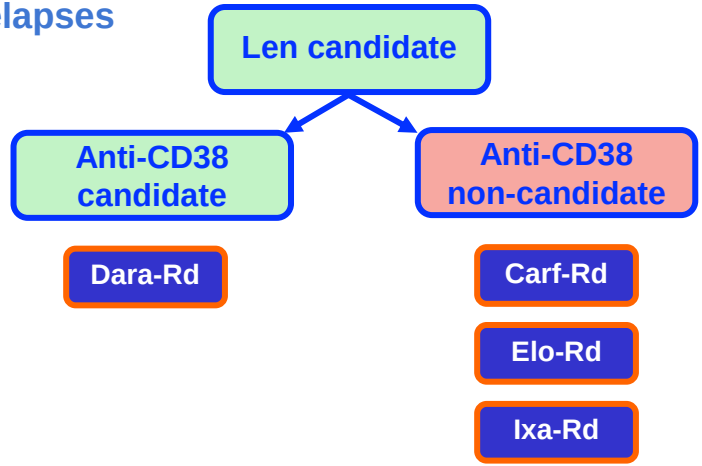
D-VMP + D

	DaraRd vs Rd[1,2] POLLUX
PFS (months)	44.5 vs 17.5 m
HR (95% CI)	0.44 (0.35–0.55)
ORR, %	93
≥ CR, %	57 (MRD 30%)
DOR, months	NE
OS HR (95% CI)	0.44 (0.35–0.55)

1. Dimopoulos M, NEJM 2016; 2. Bahlis NJ Leukemia 2020;
3. Stewart AK, NEJM 2015; 4. Siegel DS, JCO 2018;
5. Lonial S, NEJM 2015; 6. Dimopoulos MA, BJH 2017;
7. Moreau P, NEJM 2016.

Treatment Possibilities at relapse: 1st & 2nd situation

First Relapses



D-VTd / D-VRd → ASCT → No maint. until PD

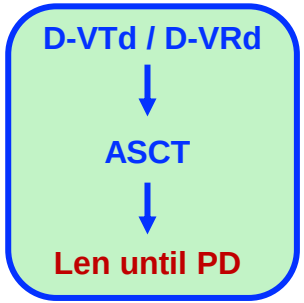
D-VMP + D

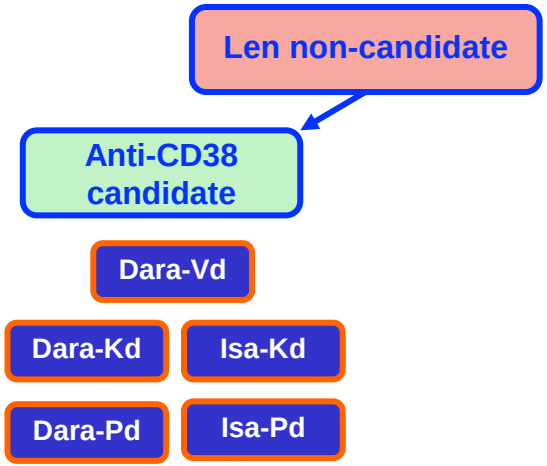
	DaraRd vs Rd[1,2] POLLUX	KRd vs Rd[3,4] ASPIRE	ERd vs Rd[5,6] ELOQUENT-2	IRd vs Rd[7] TOURMALINE-MM1
PFS (months)	44.5 vs 17.5 m	26.3 vs 17.6 m	19.4 vs 14.9 m	20.6 vs. 14.7 m
HR (95% CI)	0.44 (0.35–0.55)	0.67 (0.558–0.803)	0.71 (0.59–0.86)	0.74 (0.59–0.94)
ORR, %	93	87	79	78
≥ CR, %	57 (MRD 30%)	32	5	14
DOR, months	NE	28.6	21.2	20.5
OS HR (95% CI)	0.44 (0.35–0.55)	0.79 (0.63–0.99) 48 vs. 40 m	0.78 (0.63–0.96) 43.7 vs 39.6 m	NE

1. Dimopoulos M, NEJM 2016; 2. Bahlis NJ Leukemia 2020;
3. Stewart AK, NEJM 2015; 4. Siegel DS, JCO 2018;
5. Lonial S, NEJM 2015; 6. Dimopoulos MA, BJH 2017;
7. Moreau P, NEJM 2016.

Treatment Possibilities at relapse: 3rd situation

First Relapses





Efficacy	DaraVd vs Vd[1,2] CASTOR (n=499)	DaraKd vs Kd[3,4] CANDOR (n=466)	IsaKd vs Kd[5] IKEMA (n=302)	DaraPd vs Pd[6] APOLLO (n=304)	IsaPd vs Pd[7] ICARIA (n=304)
Prior lines	*2 (1-10)*	*2 (1-3)*	*2 (1-4)*	*2 (1-5)*	*3 (2-11)*
% Len Refr.	*Unk. (33% IMiDs)*	*32%*	*32%*	*79%*	*94%*
PFS (months)	16.7 vs 7.1 m	28.6 vs 15.2	NA vs 19.1	12.1 vs 7	11.5 vs 6.5
HR (95% CI)	0.31 (0.25 – 0.40)	0.59 (0.45–0.78)	0.53 (0.31–0.88)	0.63 (0.48-0.83)	0.59 (0.43-0.81)
ORR, %	92	84	87	69	60
≥ CR, %	*43 (MRD neg 20%)*	29	40 *(MRD neg 30%)*	27	5

1. Palumbo A, NEJM 2016; 2. Mateos MV, Clin Lymphoma M. Leuk. 2020;
3. Dimopoulos, Lancet 2020; 4. Usmani S, Lancet Oncol. 2022; 5. Moreau. Lancet 2021; 6. Dimopoulos M. Lancet Oncol. 2021; 7. Attal, Lancet 2019.

Treatment Possibilities at relapse: 4th situation

First Relapses

Len non-candidate

Anti-CD38 non-candidate

DRd

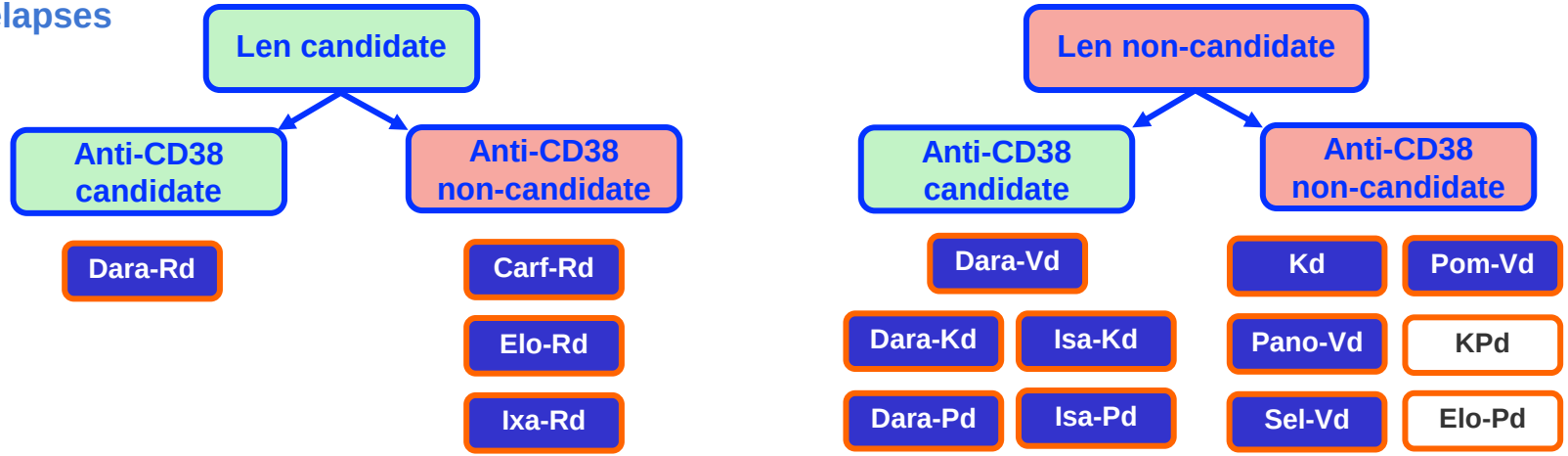
Kd	Pom-Vd
Pano-Vd	KPd
Sel-Vd	Elo-Pd

Efficacy	Kd vs Vd[1,2] ENDEAVOR (n=929)	PanoVd vs Vd[3-5] PANORAMA-1 (n=147)*	Sel-Vd vs Vd[6] BOSTON (n=402)	PVd vs Vd[7,8] OPTIMISMM (n=559)	EloPd vs Pd[9] ELOQUENT-3 (n=117)
Prior lines	*2 (1-3)*	*3 (2-3)*	*2 (1-3)*	*2 (1-3)*	*3 (2-8)*
% Len Refr.	*25%*	*50% prior Len*	*38% prior Len*	*71%*	*98%*
PFS (months)	**18.7 vs 9.4 m**	**12.5 vs 4.7 m**	**13.9 vs 9.5**	**11.2 vs 7.1 m**	**10.3 vs 4.7**
HR (95% CI)	**0.53 (0.44 – 0.63)**	**0.47 (0.31-0.72)**	**0.70 (0.53-0.93)**	**0.61 (0.49 – 0.77)**	**0.54 (0.34-0.86)**
ORR, %	**77**	**59**	**76**	**82**	**53**
≥ CR, %	**13**	**-**	**17**	**16**	**8**
OS HR (95% CI)	**0.79** (0.65–0.96) 47.6 vs. 40 m	** Approved population ≥2 prior regimens including BTZ & IMiD*			

1. Dimopoulos MA. Lancet Oncol 2016 & Lancet Oncol 2017; 3. San Miguel, Lancet Oncol 2014; 4. Richardson, Blood 2016; 5. San Miguel JF, Lancet Hemat 2016; 6. Grosicki S. Lancet 2020; 7. Richardson, Lancet Oncol. 2019. 8. Dimopoulos, Leukemia 2020. 9. Dimopoulos, NEJM 2018

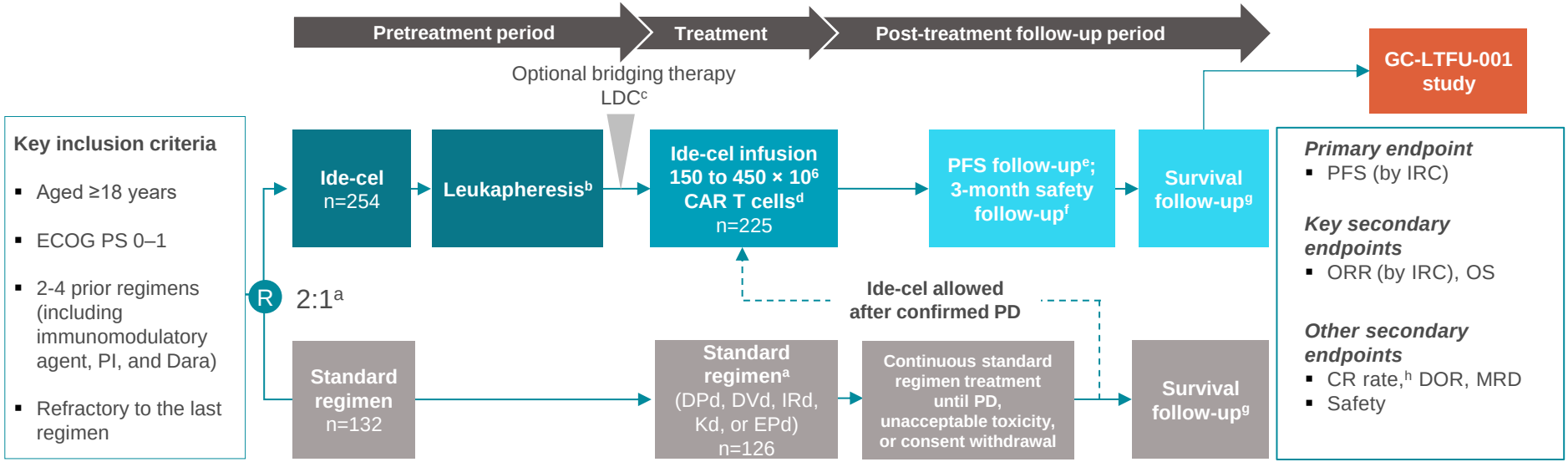
Treatment Possibilities at relapse

First Relapses



Are new agents coming for these 1st relapses?

KarMMa-3 Ide-Cel vs SOC in 2-4 prior lines of therapy



Stratification factors

- Age (<65 vs ≥65 years)
- Number of prior regimens (2 vs 3 or 4)
- High-risk cytogenetics (t[4;14], t[14;16], or del[17p]; yes vs absent/unknown)

Data cutoff: April 18, 2022

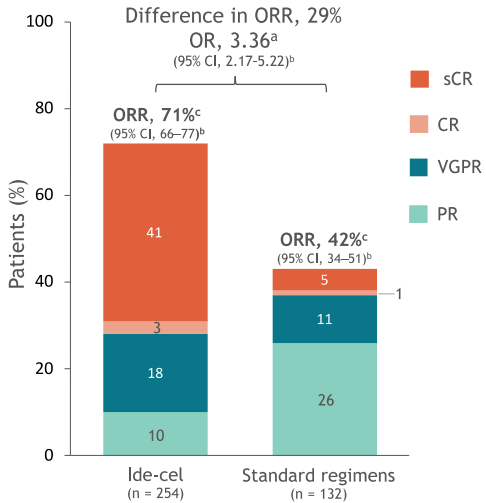
Median (range) duration of follow-up: 18.6 (0.4–35.4) months

In the ide-cel arm, the treated population of patients who underwent either leukapheresis, bridging therapy, LDC, or ide-cel treatment was used to assess AEs; the safety population of patients who received ide-cel was used to assess TRAEs, iiNT, and CRS. [a]Based on the patient's most recent treatment regimen and investigator's discretion. [b]Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd may be given as BT while ide-cel is being manufactured. [c]3 days fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2. [d]Doses ≤540 x 106 cells were permitted. [e]Monthly for patients randomised to ide-cel for 24-months, then every 3 months until PD. [f]Patients randomised to standard regimens and received subsequent ide-cel therapy. [g]Patients were followed up every 3 months after PD until end of trial; 5 years after last patient randomised. [h]By IRC. AE, adverse event; CR, complete response; Dara, daratumumab; DOR, duration of response; DPd, daratumumab/pomalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasonel; ECOG PS, Eastern Cooperative Oncology Group performance status; EPd, elotuzumab/pomalidomide/dexamethasone; IRC, Independent Response Committee; IRd, ixazomib/lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; LDC, lymphodepleting chemotherapy; MRD, minimal residual disease; PD, progressive disease; PI, proteasome inhibitor; R, randomisation; TRAE, treatment-related AE.

Rodriguez-Otero P, et al. N Engl J Med. 2023;388:1002–1014

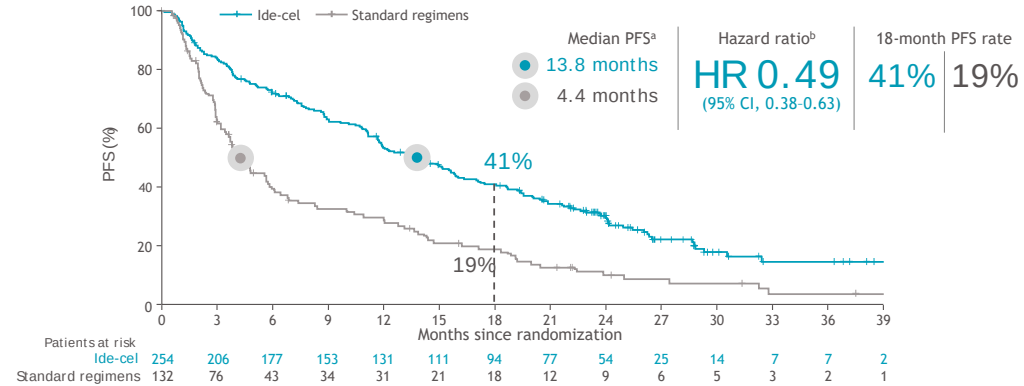
KarMMa-3 Ide-Cel vs SOC in 2-4 prior lines of therapy

n=386 (2:1 randomization) ***3 (2-4) prior lines; 65% TCR***

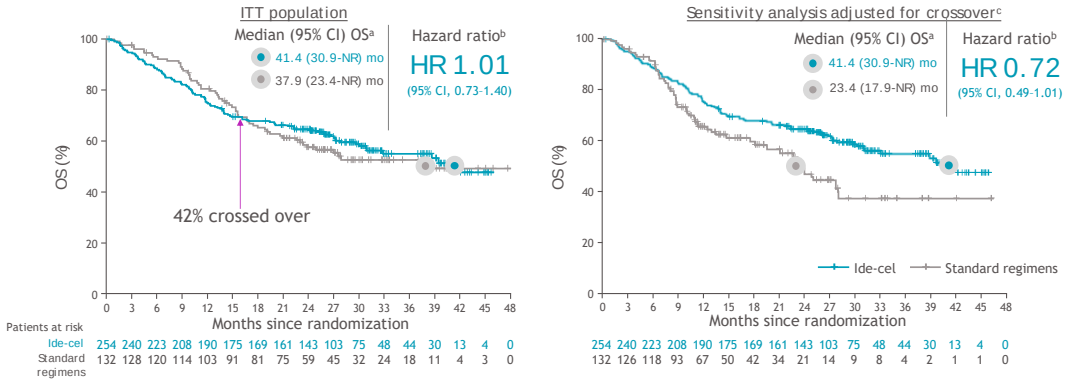


CR & MRD neg (10^{-5} by NGS)
35% vs 2%

PFS



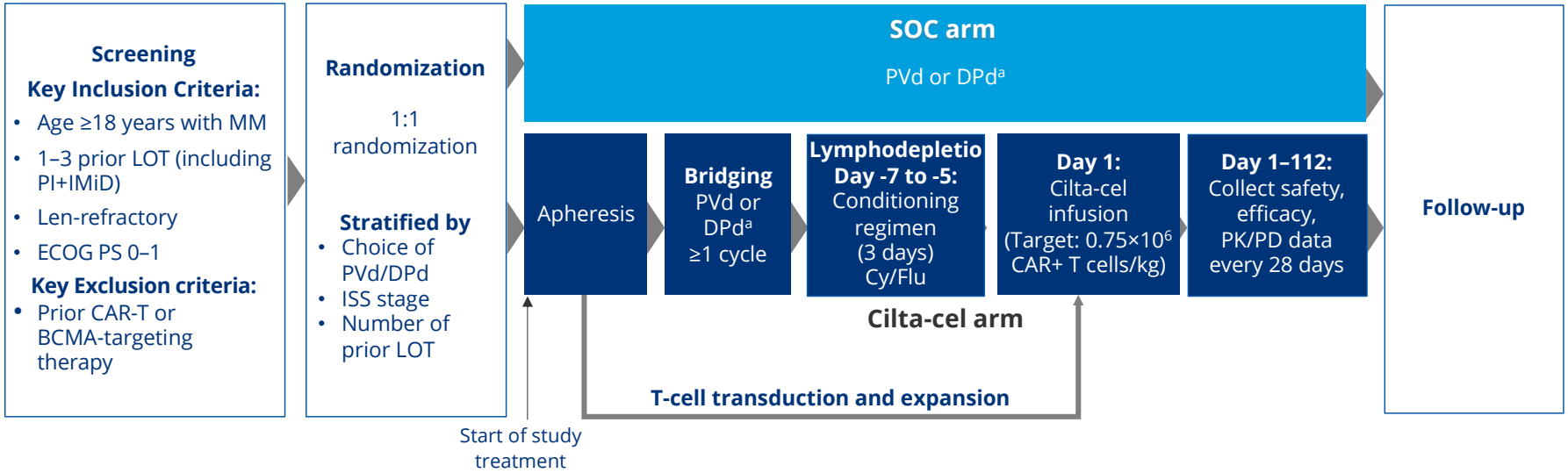
OS



56% pts in the SOC arm crossed over to receive ide-cel

Rodriguez-Otero P, et al. N Engl J Med. 2023;388:1002–1014 & ASH 2023. A1028

Cartitude-4: Cilta-Cel vs SOC in 1-3 prior lines of therapy

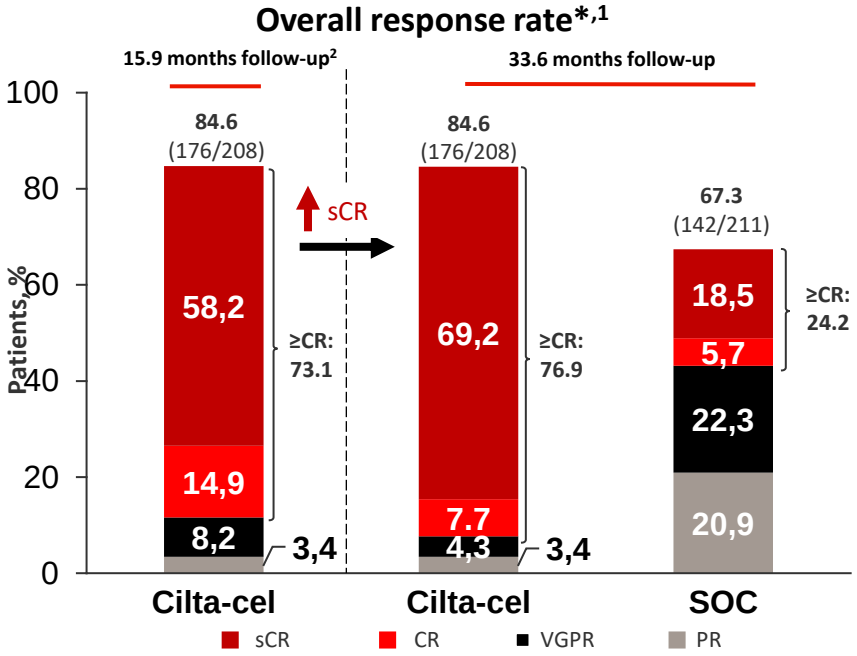


Primary endpoint
- **PFS[b]**

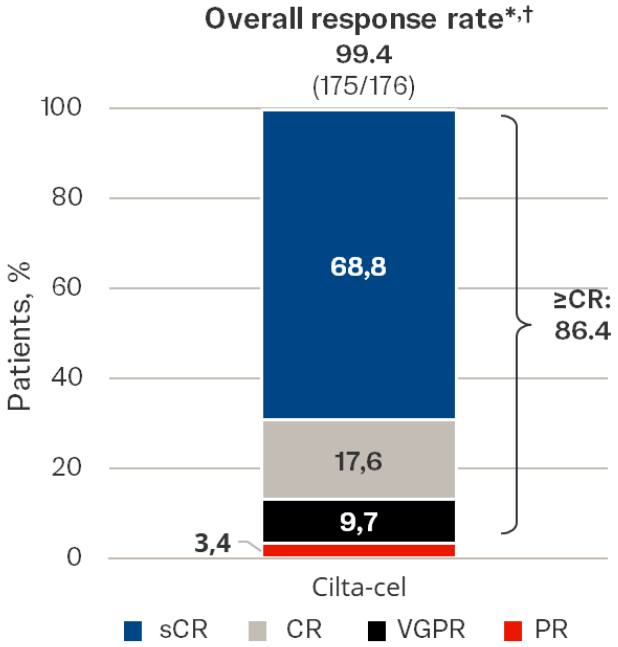
Secondary endpoints
- **Efficacy: ≥CR, ORR, MRD negativity, OS**
- **Safety**
- **PROs**

[a]Physicians' choice. [b]Time from randomization to disease progression/death.
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Score; IMiD, immunomodulatory drug; ISS, international staging system; Len, lenalidomidel; LOT, lines of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PI, proteasome inhibitor; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient reported outcomes. PVd, pomalidomide, bortezomib, and dexamethasone.

Cartitude-4: Responses

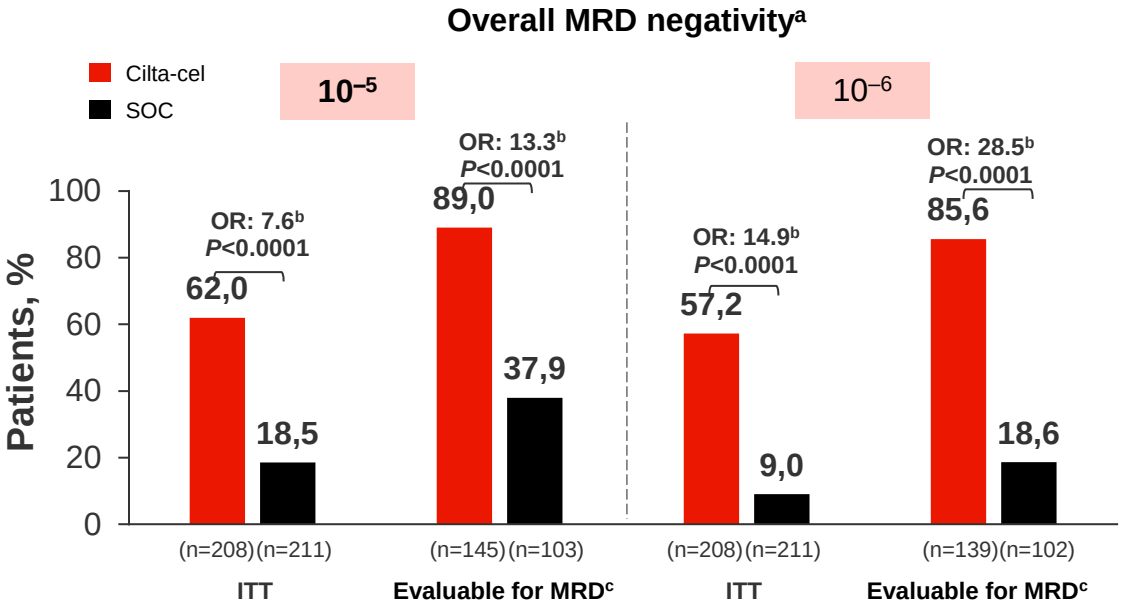


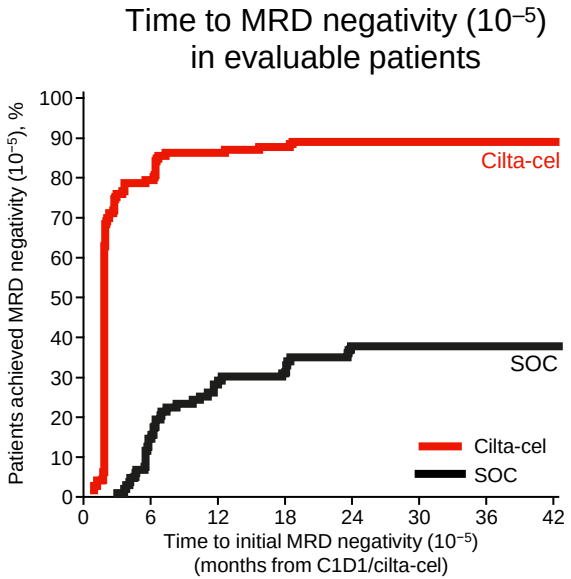
(As-treated population; 15.9-month follow-up)



1. Mateos M-V, et al. IMS; September 25–28, 2024; Rio de Janeiro, Brazil.
2. San-Miguel J, et al. N Engl J Med. 2023;389:335-47

Cartitude-4: Cilta-Cel in 1st relapses. MRD negativity





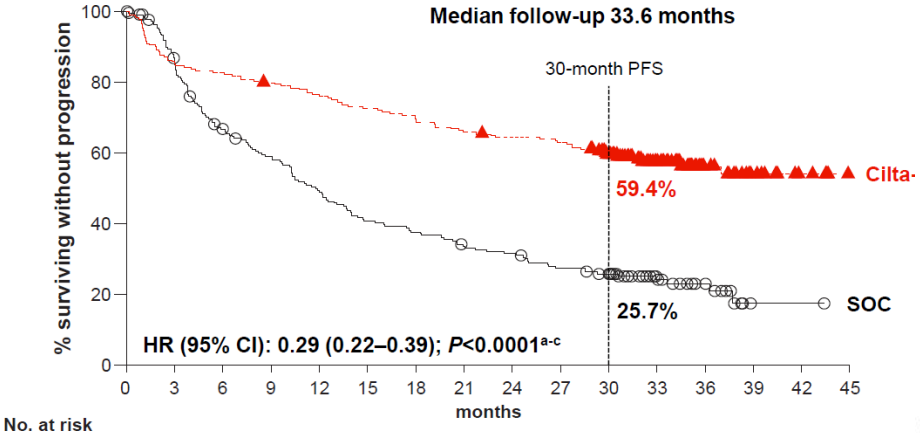
- 69% of evaluable patients achieved MRD negativity (10^{-5}) by day 56 (ITT, 48%), rising to 86% (ITT, 60%) by 6 months post cilta-cel infusion

High rates of overall MRD negativity are rapidly achieved with cilta-cel, and almost all cilta-cel patients negative at 10^{-5} were also negative at 10^{-6}

[a]Achievement of MRD negativity at any time after randomization and before next therapy. [b]Stratified Cochran-Mantel-Haenszel test. [c]Evaluable samples were those that passed calibration and QC and included sufficient cells for evaluation at the respective testing threshold.
cilta-cel, ciltacabtagene autoleucel; C1D1, cycle 1 day 1; ITT, intent-to-treat; MRD, minimal residual disease; OR, odds ratio; QC, quality control; SOC, standard of care.

Cartitude-4: Cilta-Cel in 1st relapses. Long term follow up

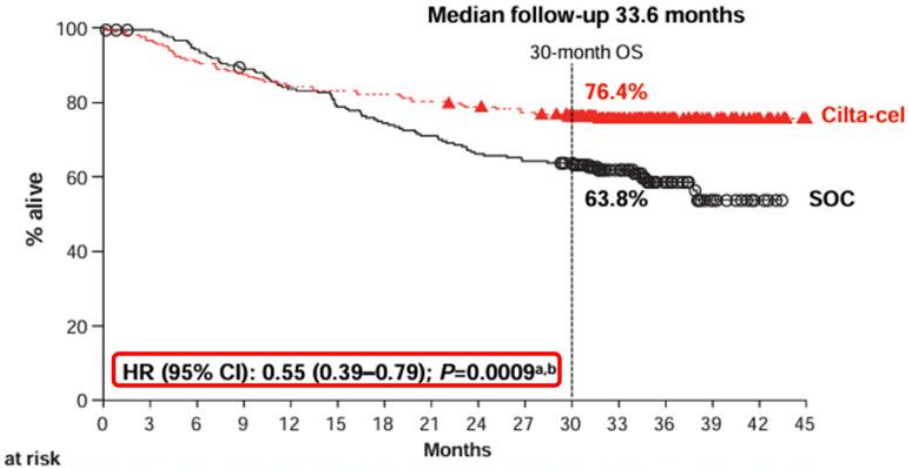
PFS (Primary endpoint)



No. at risk

Cilta-cel	208	177	172	165	157	150	145	136	132	129	111	65	29	13	5	0
SOC	211	176	133	116	96	80	74	65	61	52	47	25	12	1	1	0

OS



No. at risk

Cilta-cel	208	201	190	183	175	173	171	167	163	159	146	93	44	24	9	0
SOC	211	207	196	184	173	163	154	147	137	133	127	71	35	13	4	0

[a]Constant piecewise weighted log-rank test. [b]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks post randomization. [c]Nominal *P*-value.

[a]Log-rank test. *P*-value, 0.0009, crossed the prespecified boundary of 0.0108 as implemented by the Kim-DeMets spending function with parameter=2. [b]Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

And any data on Belantamab?

DREAMM-7: BelaVd vs DVd in RRMM

N= 494 RRMM pts after a median of 1PL.

52% of pts exposed to len and 35% Refr to len

Eligibility criteria

- Adults with MM
- ≥1 prior line of MM therapy, and documented PD during or after their most recent therapy
- No prior treatment with anti-BCMA
- Not refractory to or intolerant of daratumumab or bortezomib

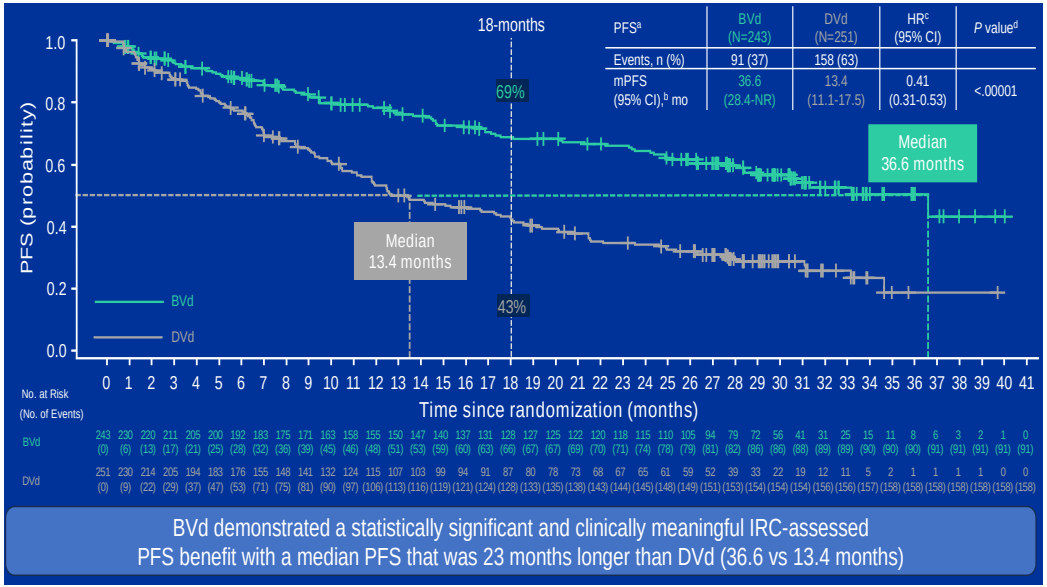
1:1 Randomization

Arm A (BVd)
- Belamaf IV 2.5 mg/kg q3w +
- Bortezomib 1.3 mg/m² SC on days 1,4,8, and 11 of cycles 1-8 (21-day cycles) + Dexamethasone 20 mg on the day of, and day after bortezomib[a] in cycles 1-8

Arm B (DVd)
- Daratumumab IV 16 mg/kg cycles 1-3; qw and cycles 4-8; q3w +
- Bortezomib 1.3 mg/m² SC on days 1,4,8, and 11 of cycles 1-8 (21-day cycles) + Dexamethasone 20 mg on the day of, and day after bortezomib[a] in cycles 1-8

Belamaf monotherapy IV 2.5 mg/kg q3w

Daratumumab monotherapy IV 16 mg/kg cycle 9+ q4w



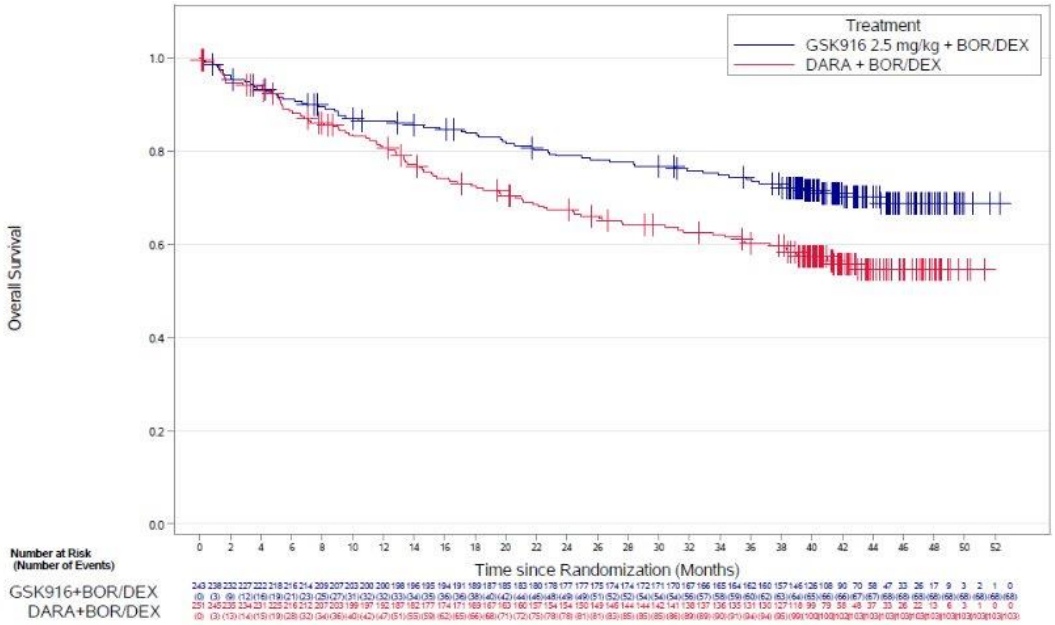
BVd demonstrated a statistically significant and clinically meaningful IRC-assessed PFS benefit with a median PFS that was 23 months longer than DVd (36.6 vs 13.4 months)

The study met all secondary end-points: ORR and CR rate (34% vs 17%) and MRD-ve rate (39% vs 17%), early benefit in OS as well as DoR

Safety profile is manageable. Ocular toxicity is present in 80% and 30% G3-4 according to CTCAE being blurred vision the most frequent. Dose reductions and interruptions allowed to keep patients on study and only 9% of patients required to discontinue belamaf

Mateos MV et al. ASCO plenary series 2024

DREAMM-7: BelaVd vs DVd in RRMM. OS



OS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	68 (28)	103 (41)
OS, median (95% CI), months[b]	**NR (NR-NR)**	**NR (41.0-NR)**
HR (95% CI)[c]	**0.58 (0.43-0.79)**	
P value[d]	**.00023**	
24-Month survival (95% CI), %	79 (73-84)	67 (61-73)
36-Month survival (95% CI), %	74 (68-79)	60 (54-66)

OS data have reached 34.6% maturity.

Median OS was not reached. Predicted median OS with BVd is 84.1 months and 51.0 months with DVd.[e]
DVd in the CASTOR study resulted in a median OS of 49.6 months.[1]

[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer-Crowley method. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib (no vs yes), and R-ISS stage at screening (I vs II or III), with a covariate of treatment. [d] *P* value is from a 1-sided stratified log-rank test. At 171 actual events (48.2% OS information fraction), OS was declared significant if the *P* value was <.00112. [e] Post hoc analysis was performed with simulation to predict median OS values in each arm using the observed data at the interim analysis, with a 39.4-month median follow-up to extrapolate time to death in ongoing censored patients. Predicted median OS values are subject to change as data mature.

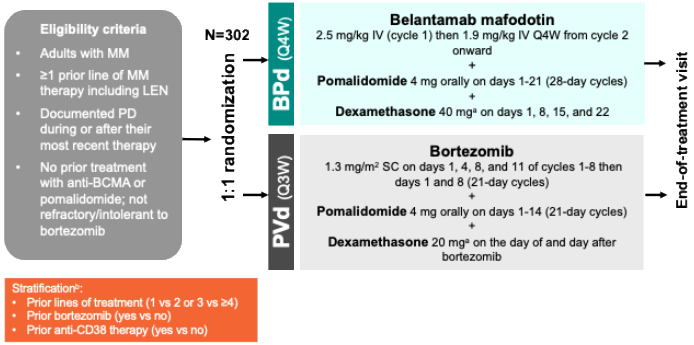
1. Sonneveld P, et al. *J Clin Oncol.* 2022;41(8):1600-1609.

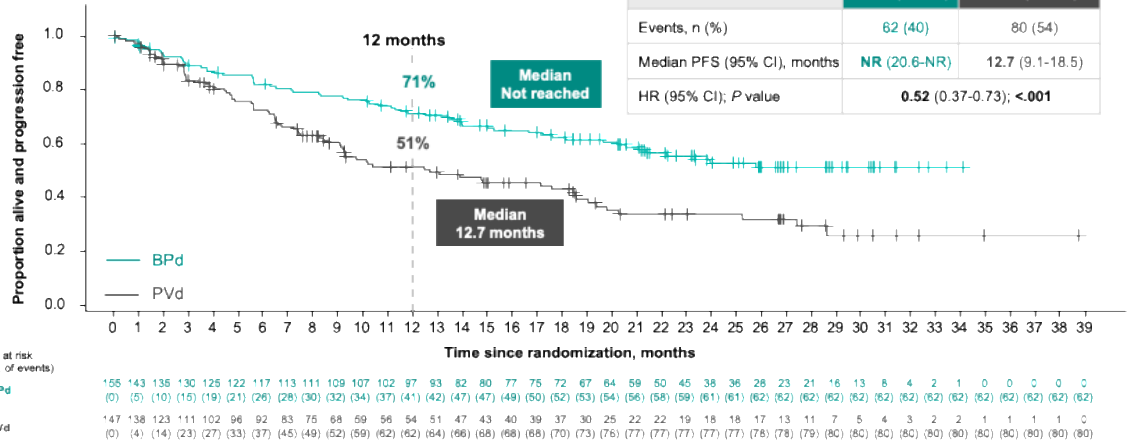
DREAMM-8: BelaPd vs PVd in RRMM

N= 302 RRMM pts after a median of 1PL.

100% of pts exposed to len and >75% Refr to len

25% prior anti-CD38





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	

ORR (77% vs 72%) and CR rate (40% vs 16%) and MRD-ve rate (32% vs 5%). Better PFS2 & DOR and positive OS trend for OS

Safety profile is manageable. Ocular toxicity is present in 89% and 43% G3-4 according to CTCAE being blurred vision in 79% & G3/4 17%.

Dose reductions and interruptions allowed to keep patients on study and only 9% of patients required to discontinue treatment

Median Follow-up: 21.8 months

Richardson PG et al. EHA 2024

Can we use Bispecifics earlier in the course of the disease?

MajesTec-3
1-3 PL. Len & PI
n=560

Teclistamab + Dara
vs
DPd / DVd

MagnetisMM-5
≥1 PL. Len & PI
n=580

Elranatamab
vs
DPd

Linker MM-3
2-4 PL. Len, PI & anti-CD38
N=380

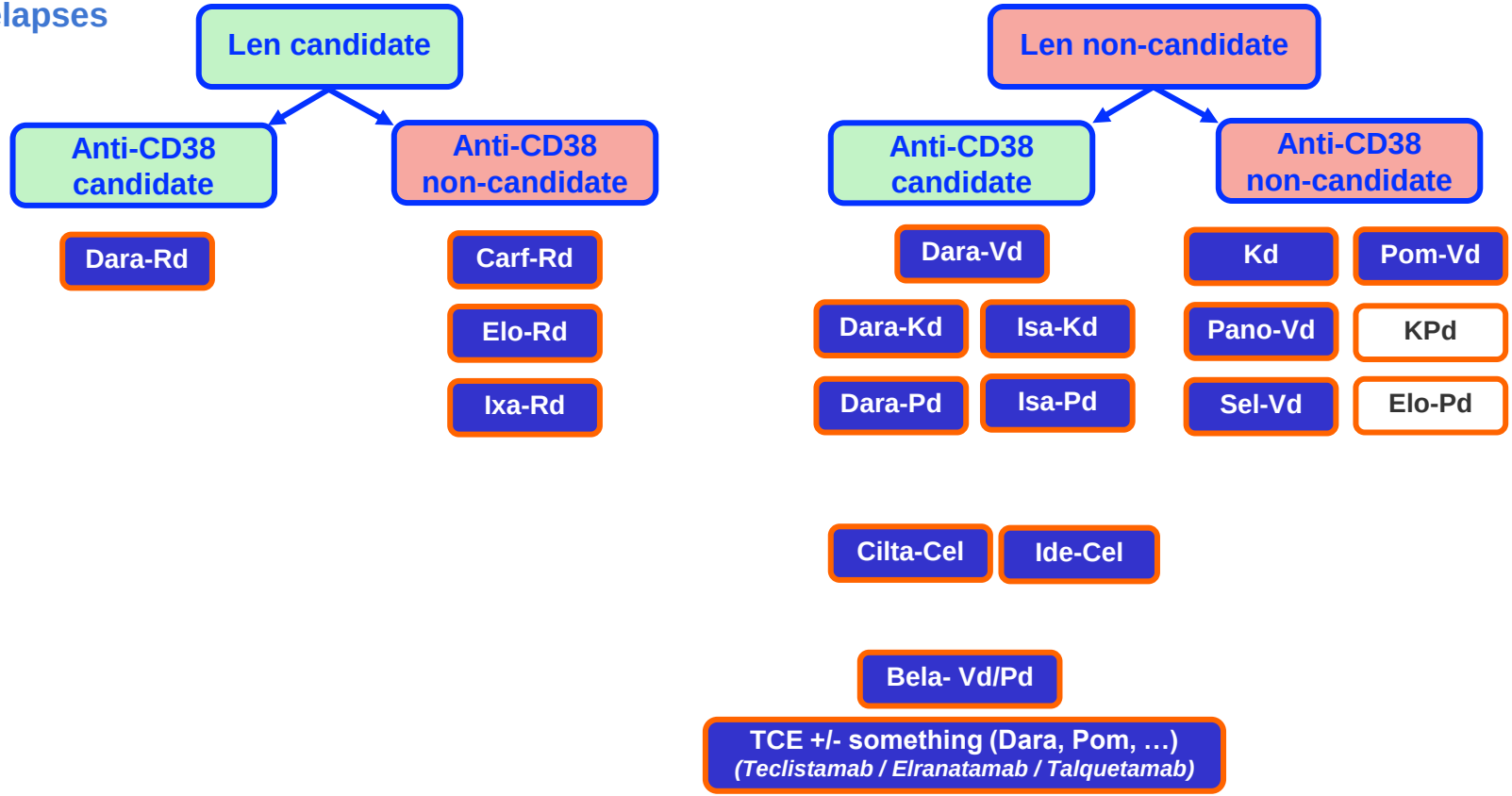
Linvoseltamab
vs
EloPd

Monumental-6
1-4 PL. Len & anti-CD38
N=795

Talque + Tecli
vs
Talquetamab + Pom
vs
EloPd / PVd

Treatment Possibilities at relapse

First Relapses



After 1 or 2 lines of therapy most patients have been exposed (or are refractory) to PI, IMiDs, Anti-CD38 MoAb: TCE or TCR

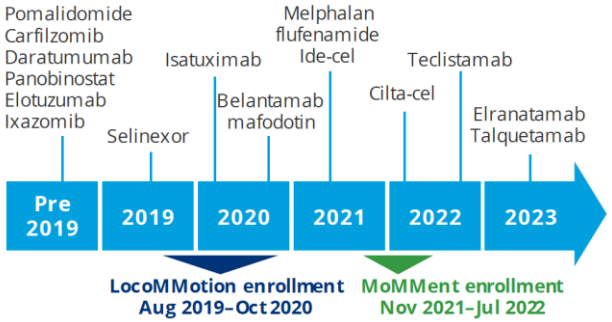
What is their outcome?

What can we offer them?

TCE pts: LocoMMotion & MoMMent

n=302 pts conducted in sites from Europe & US.

Received prior treatment with a PI, IMiD, and anti-CD38 mAb



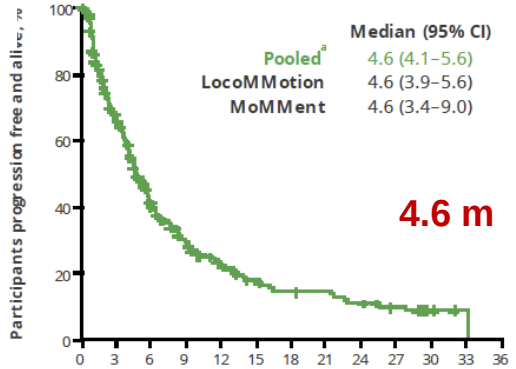
[a]Representative of initial regulatory approval across the US and EU.
cilta-cel, ciltacabtagene autoleucel; ide-cel, idecabtagene vicleucel.

ORR: 31.8%

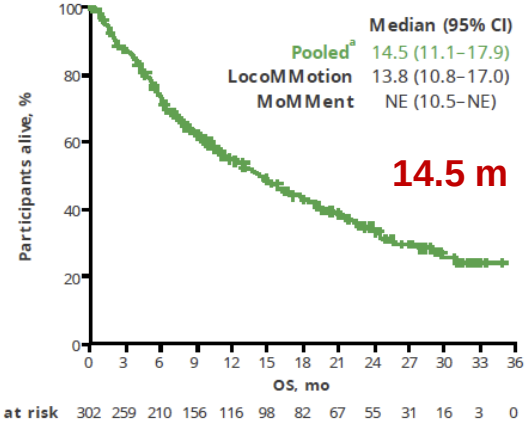
SOC treatment, n (%)	MoMMent (N=54)	LocoMMotion (N=248)	Pooled (N=302)
Pomalidomide-cyclophosphamide-dexamethasone	9 (16.7)	35 (14.1)	44 (14.6)
Carfilzomib-dexamethasone	5 (9.3)	35 (14.1)	40 (13.2)
Pomalidomide-dexamethasone	5 (9.3)	29 (11.7)	34 (11.3)
Belantamab mafodotin	11 (20.4)	4 (1.6)	15 (5.0)
Ixazomib-lenalidomide-dexamethasone	0	14 (5.6)	14 (4.6)
Elotuzumab-pomalidomide-dexamethasone	3 (5.6)	6 (2.4)	9 (3.0)
Ide-cel	4 (7.4)	0	4 (1.3)

*≥5% of patients in any dataset.

PFS



OS



Weisel K, et al. IMS 2023

EMA Approvals for TCE patients

- **Teclistamab, Elranatamab, Talquetamab** **Ide-Cel & Cilta-Cel**
  - **≥ 3 prior therapies** including 1 PI, 1 IMiD & 1 anti-CD38 MoAb **(triple-exposed),** and who have demonstrated disease progression on the last therapy.

- **Melflufen + Dex**
  - **≥ 3 prior lines of therapies** & refractory to at least 1 PI, 1 IMiD & 1 anti-CD38 MoAb **(triple-refractory)**, and who have demonstrated disease progression on or after the last therapy.
  - For patients with a prior ASCT, the time to progression should be at least **3 years from transplantation.**

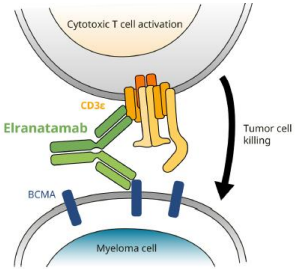
- **Selinexor + Dex**
  - **≥ 4 prior therapies** & refractory to at least 2 PIs, 2 IMiDs & 1 anti-CD38 MoAb **(penta-refractory)**, and who have demonstrated disease progression on the last therapy.

** Also Sel-Vd in ≥ 1 prior line of therapy*

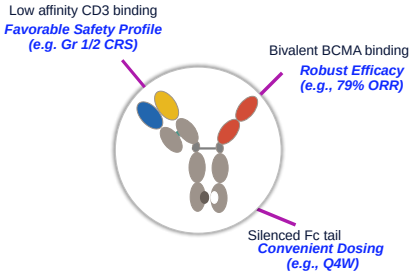
Bispecific antibodies or TCE (T cell engagers)

Anti-BCMA
Anti-GPRC5d
Anti-FcRH-5

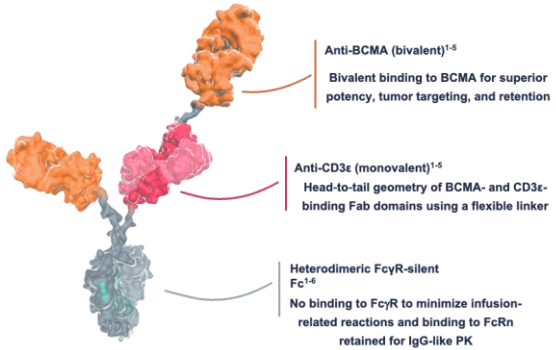
Elranatamab



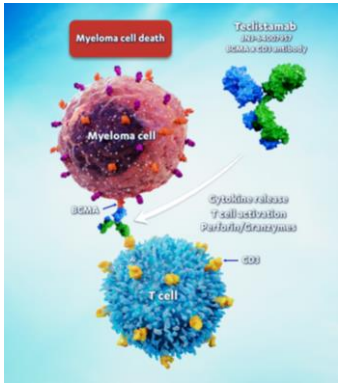
ABBV-383



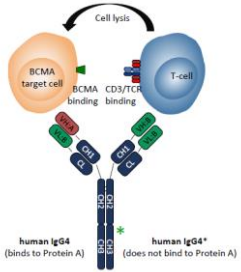
Alnuctamab



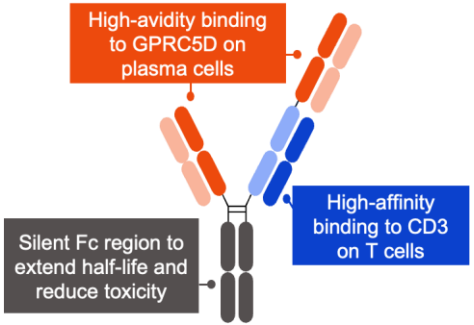
Teclistamab
Talquetamab



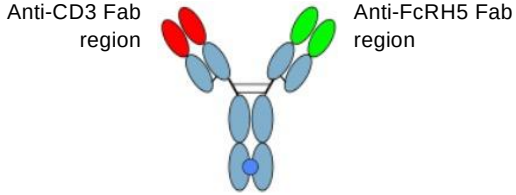
Linvoseltamab
REGN5458



Forimtamig
RG6234
RO7425781

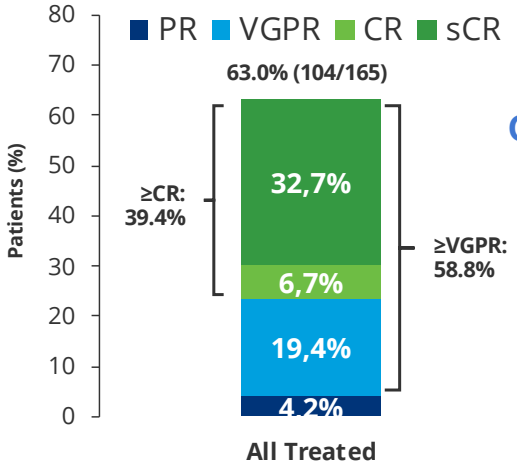


Cevostamab

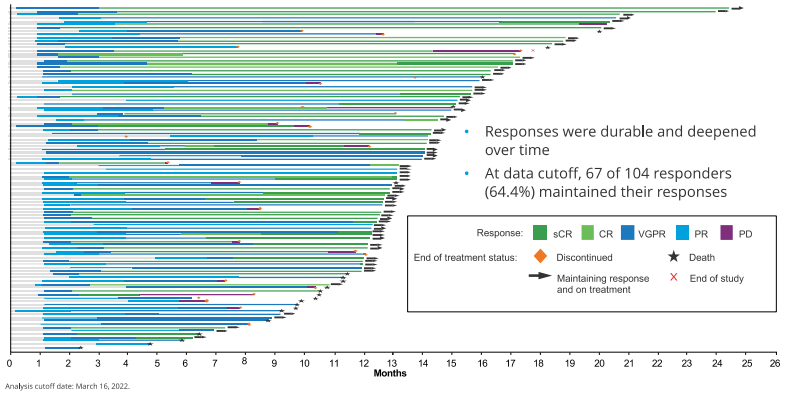


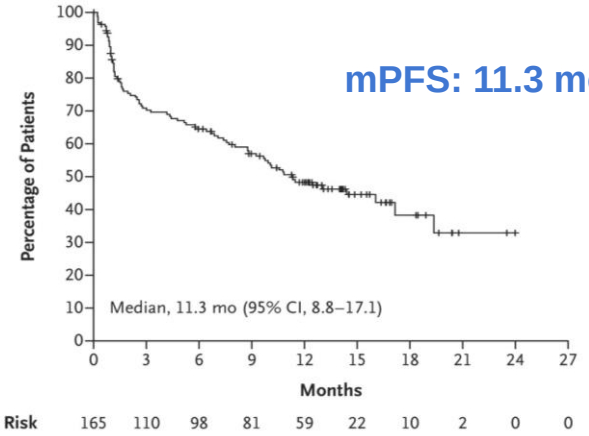
Teclistamab: MajesTEC-1

N=165 RRMM **5 (2-14) prior lines** **78% TCR**



ORR: 63%





mPFS: 11.3 months

CRS: 72% (<1% G3); Infections: 76% (45% G3/4)

Moreau et al. N Engl J Med 2022;387:495-505.

RWE Teclistamab in USA

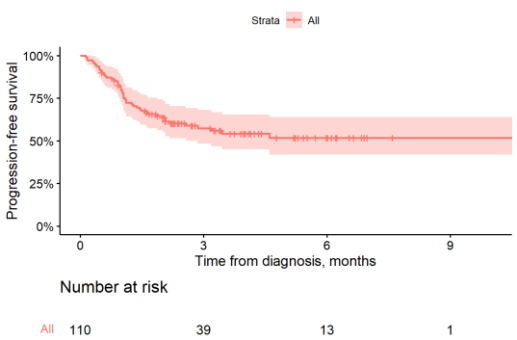
110 pts 76% penta-class refractory (vs 30% in MajesTEC-1); 35% prior BCMA

ORR = 62% …. ≥ *VGPR: 51%, CR: 20%*

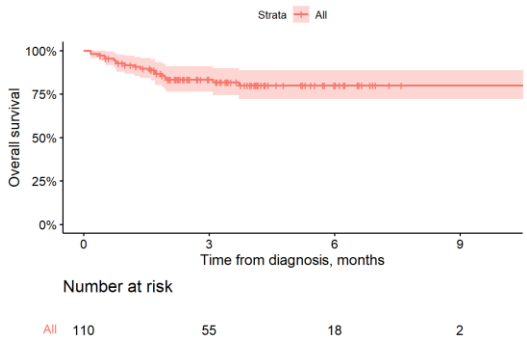
Median time to best response 1.67 (0.19-5.91) months

- **CRS:** 56%; G3/4 in 5%
- **ICANS:** 11%; G3/4 5% (1 death)
- **Infections: 78 in 44 pts**
  Bacterial (48%), viral (45%) and fungal (6.7%)

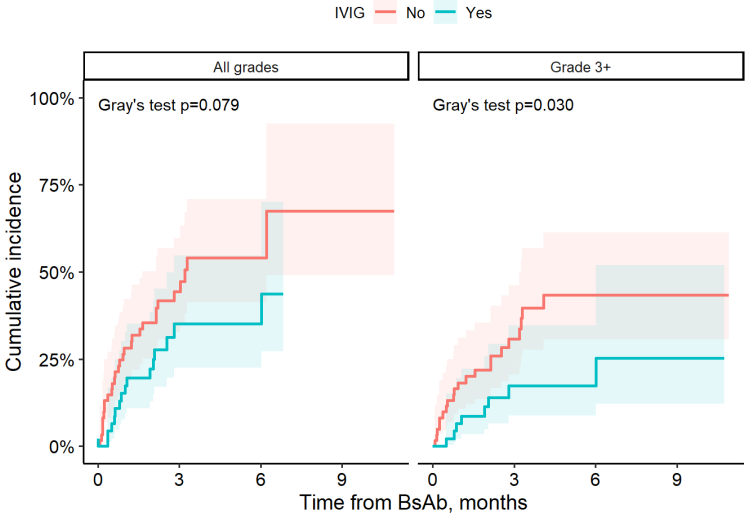
6-month PFS 52%
(95% CI:42-64%)



6-month OS 80%
(95% CI: 72-89%)



Impact of Primary IVIG prophylaxis



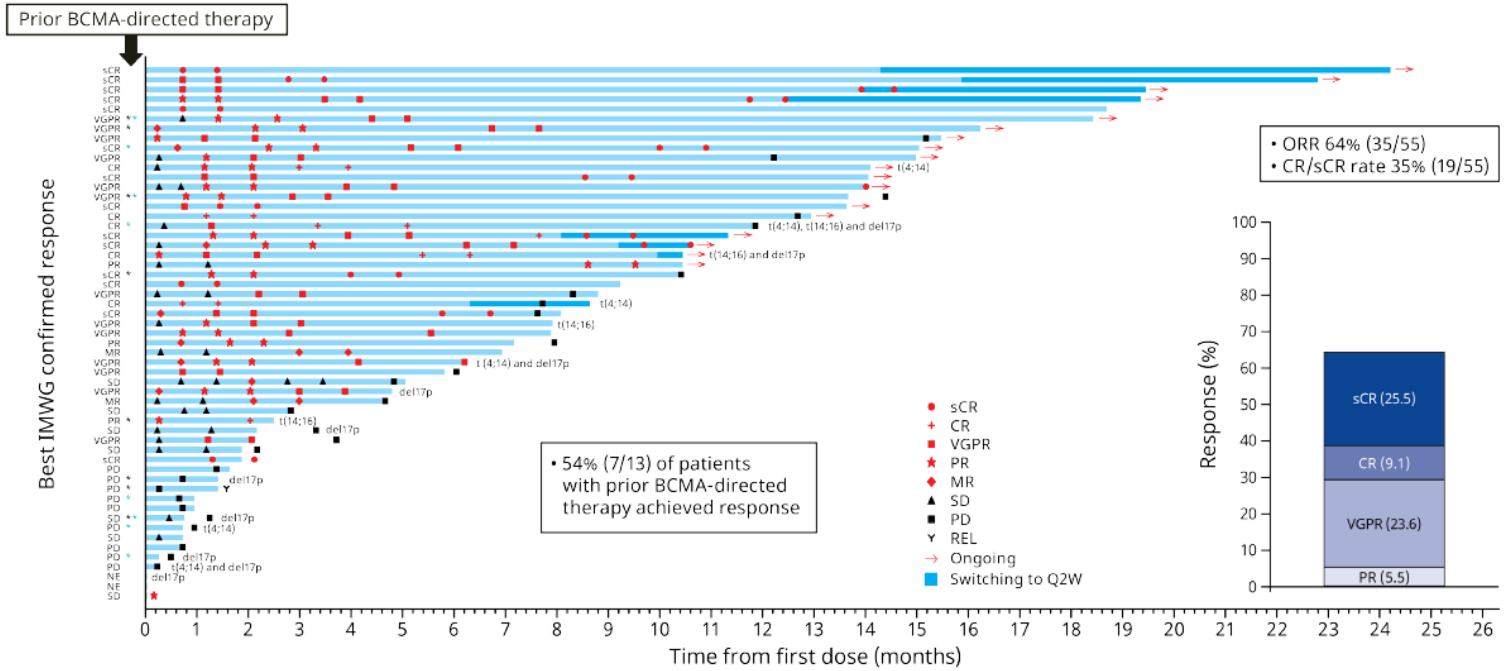
Outpatient step-up doses in 9 (9%) pts
For inpatients, the median duration of stay was 9 days

Median follow up: 3.5 months

Mohan. ASH 2023. A545

MagnetisMM-1: Phase I Elranatamab in RRMM

Duration of Treatment and Best Overall Response for All Patients



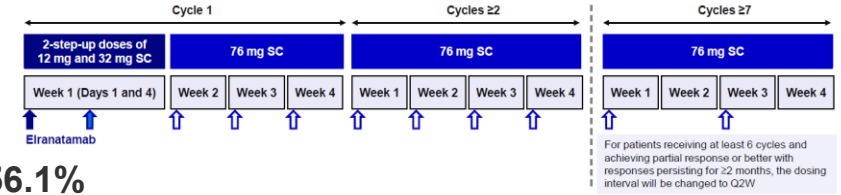
Data cut-off was February 8, 2022.

* Prior anti-BCMA ADC. * Prior BCMA-targeted CAR-T. Swimmer plot depicts disease assessments relevant to first response, confirmation of response, deepening of response, and best response.

ADC=antibody drug conjugate; BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor T-cell therapy; CR=complete response; IMWG=International Myeloma Working Group; MR=minimal response; NE=not evaluable; ORR=objective response rate; PD=progressive disease; PR=partial response; Q2W=twice weekly; REL=relapse; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response

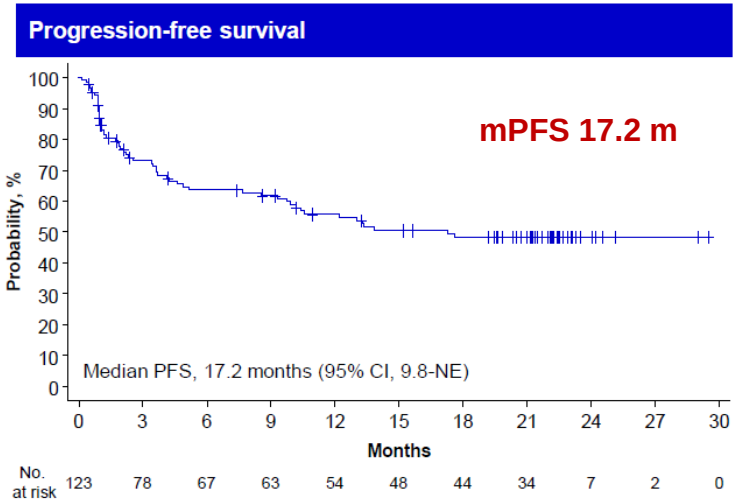
Elranatamab in RRMM. Phase I MagnetisMM-1

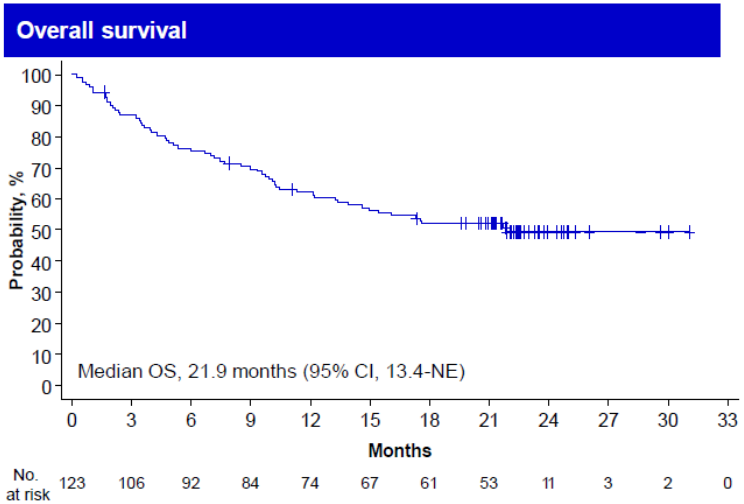
5 (2-22) Prior Lines **97% triple-class Ref. Penta-ref: 42%**



ORR 61% (95% CI: 51.8-69.6%) **≥ CR 35.0%; ≥VGPR 56.1%**

MRD-negativity at the threshold of 10−5 was achieved by 89.7% of those patients in CR/sCR (n=29)





Median Follow up 17.6 months

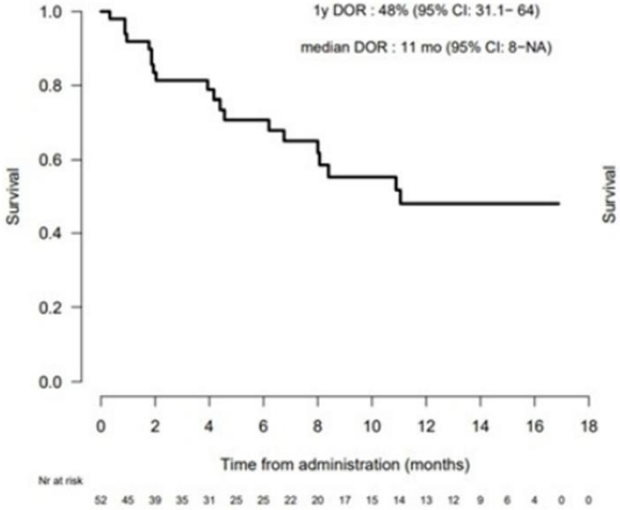
Mohty M et al. ASCO2023 & EHA23; Lesokhin A et al. Nat Med. 2023; Tomasson et al. ASH 2023 3385

RWE Elranatamab (BCMA-CD3 TCE). French compassionate use program

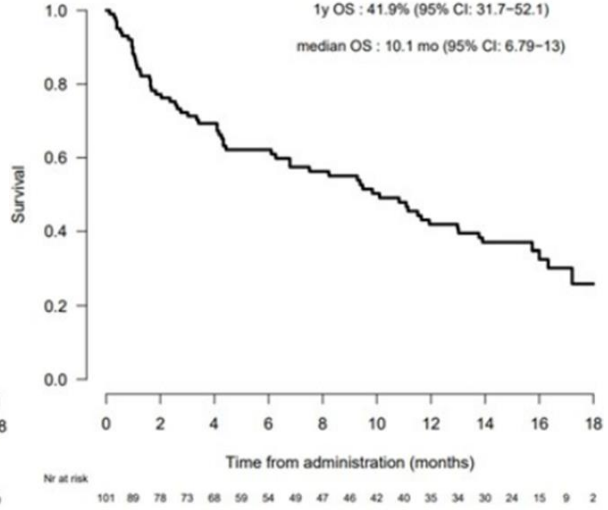
n=101 RRMM pts. Median age: 68 (62-75y). Median nº PL: 5 (1-7) TCR: 52.5%

ORR 51.5%; ≥VGPR 42%

Duration of Response (DoR)



Overall survival



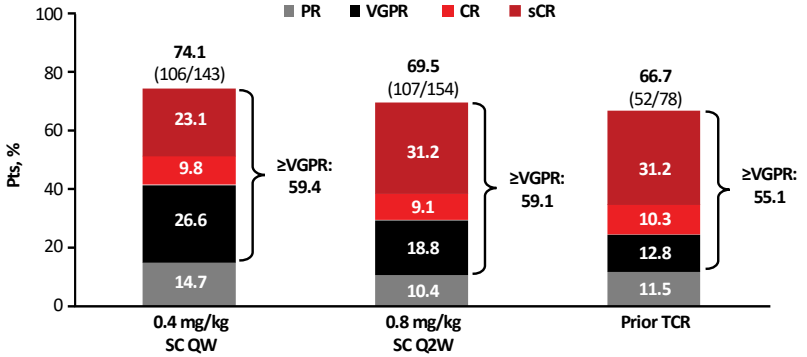
Safety profile

Toxicities (%)	Study Population (N=101)
Cytokine release syndrome	
Grade 1	35 (35%)
Grade 2	10 (10%)
Grade3	0
Grade 4	0
Grade 5	
Immune effector cell-associated neurotoxicity syndrome	1 (1%)
Grade 1	1 (1%)
Grade 2	0
Grade3	0
Grade 4	1 (1%)
Grade 5	
Infections	50 (49%)
Severe infection (grade ≥ 3)	24 (24%)
Intravenous immunoglobulin supplementation	51 (50%)

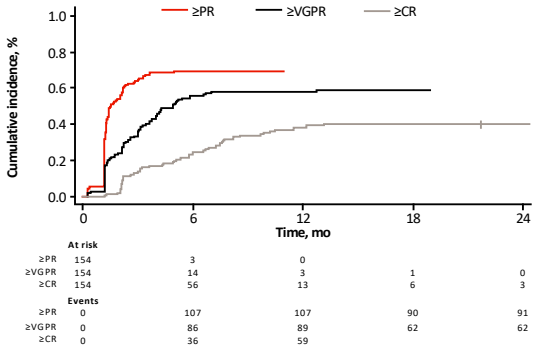
Mohty M et al. Poster presentation, EHA 2024. Poster 906

Monumental-1: Talquetamab (anti-GPRC5D). Long term results

0.4 mg/kg SC QW	(Ph1 n=21; Ph2 n=122).	EMD 23%,	HR-CA 31%,	TCE 100%, TCR 74.1%
0.8 mg/kg SC Q2W	(Ph1 n=36; Ph2 n=109).	EMD 25.5%,	HR-CA 28.9%,	TCE 100%, TCR 69%
Prior TCR	(Ph1 n=17; Ph2 n=34).	EMD 31.4%,	HR-CA 40.9%,	TCE 100%, TCR 84.3%. Prior CAR n=36 Prior BsAb n=18 (3 patients received both)

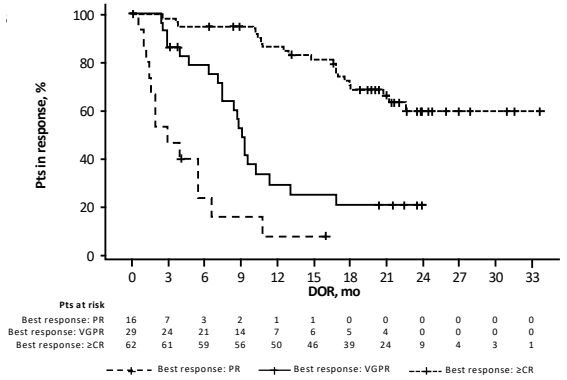


DOR by depth of response



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)

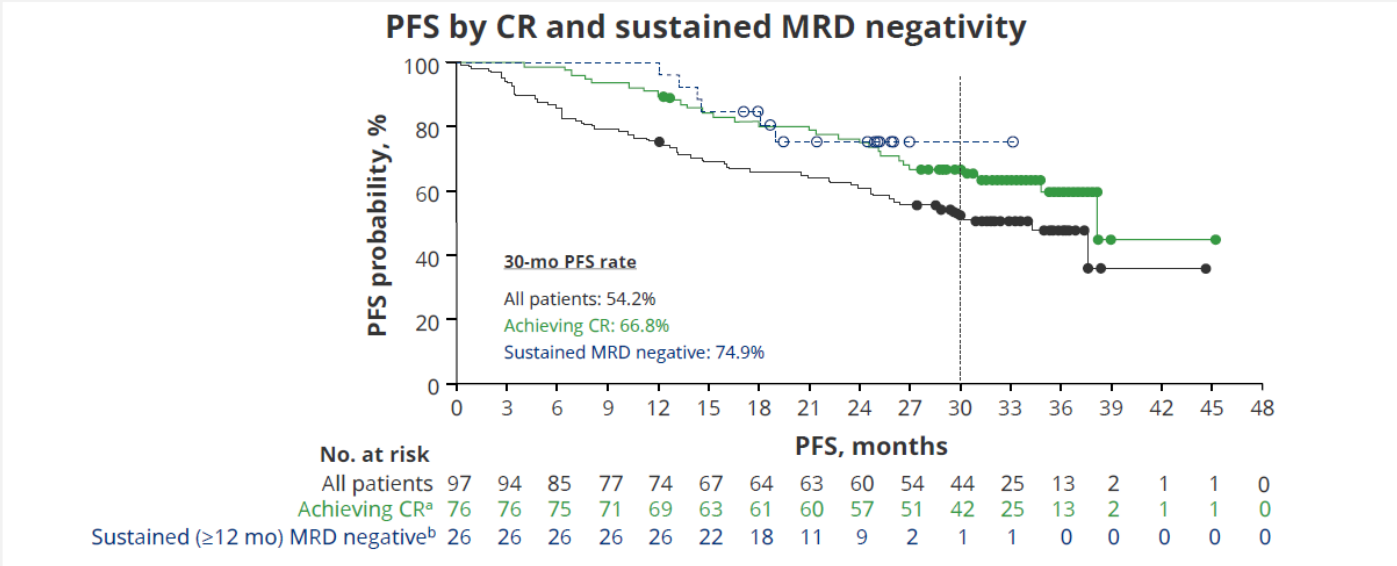
DOR in the Q2W cohort



Rasche L et al, poster presentation EHA 2024; #P915

Cilta-Cel in Multiple Myeloma: Cartitude-1

- Achieving CR or sustained MRD negativity was associated with prolonged PFS

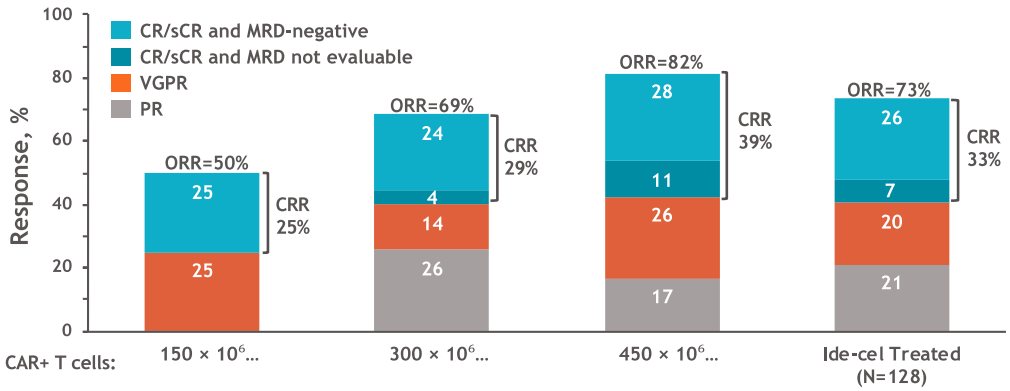


[a]Patients had ≥CR at any time during the study, assessed by computerized algorithm. [b]Patients that were MRD evaluable had a baseline clone identified, sufficient follow-up for assessment, and ≥2 MRD-negative assessments 12 months apart, with no MRD-positive samples in that interval.
cilta-cel, ciltacabtagene autoleucel; CR, complete response; MRD, minimal residual disease; mPFS, median progression-free survival; NE, not estimable, NR, not reached; PFS, progression-free survival sCR, stringent complete response.

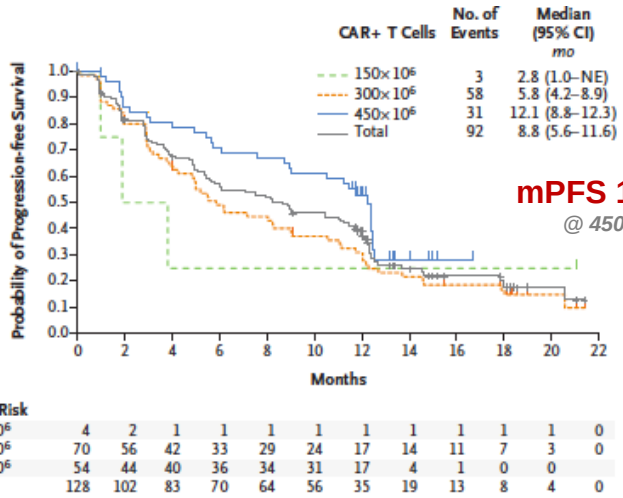
Berdeja J. Lancet 2021 Jul 24;398(10297):314-324; Usmani ASCO22 P8028 & Lin EHA22 P961
Lin. ASCO23 PD8009; Munshi. EHA23. S202

Ide-Cel in Multiple Myeloma: KarMMa-2

n=128. 6 (3 - 16) prior lines 84% triple-class refractory



mPFS by dose



mPFS 12.1 m
@ 450x10⁶

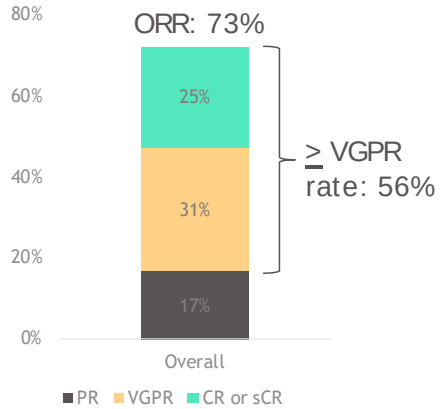
Main AEs

Key AEs of interest, n (%)	Any grade	Grade 3/4
Infections	88 (69)	28 (22)
CRS	107 (84)	7 (5)
Neurotoxic effect	23 (18)	4 (3)

Munshi N Engl J Med. 2021 Feb 25;384(8):705-716

RWE Ide-Cel in Multiple Myeloma

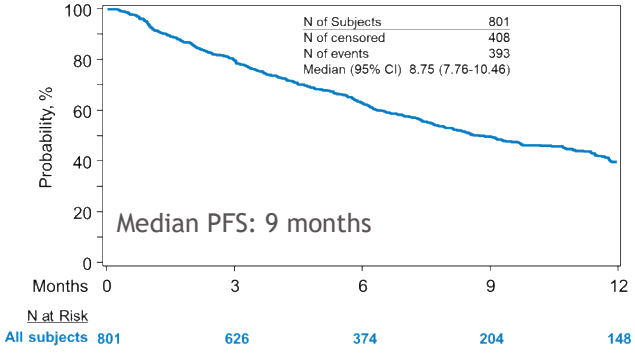
n=821 pts. 66 years (29-90) **7 (4-21) prior lines** **97% TCE & 60% PCE**



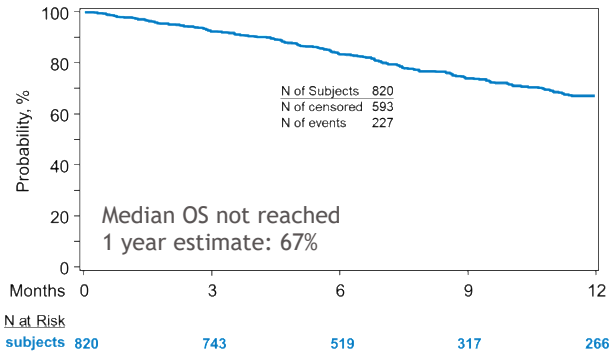
Response data available in 810 patients.

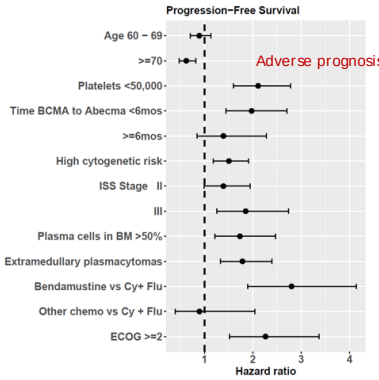
	ORR	CR rate
Lymphodepletion Therapy		
Flu/Cy	74%	26%
Bendamustine	43%	10%
Others	72%	25%
Prior BCMA therapy		
No Prior BCMA therapy	74%	26%
Prior BCMA therapy	58%	16%

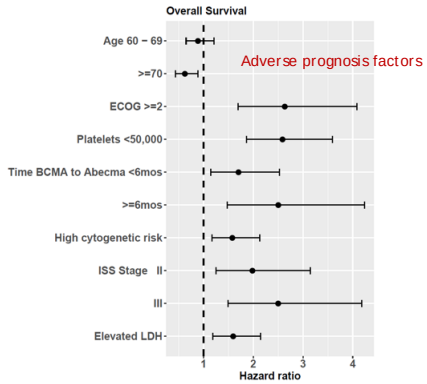
Progression-free Survival



Overall Survival







CRS: *80%; G≥3 3%*

4 (0.5%) G5

ICANS: *28%; G≥3 5%*

1 (0.1%) G5

Clin. Sign. Infect.: *45%*

Prolonged cytopenias

11% Neutropenia

24% Thrombocytop.

Sidana. ASH 23. A1027

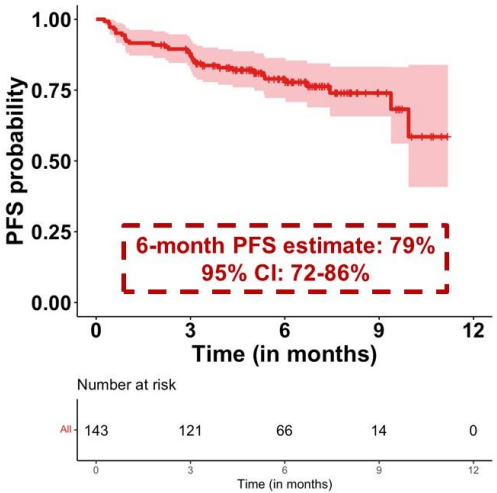
RWE Cilta-Cel in Multiple Myeloma

n=143 64 years (30-79); EMD, 31%; PCL, 7% 6 (3–18) PL; prior BCMA, 12%; triple-refractory, 71%; penta-refractory, 34%

80% received bridging therapy ≥PR after bridging; 30%
16% received lymphodepletion chemotherapy other than fludarabine + cyclophosphamide
57% of the patients did not meet CARTITUDE-1 trial eligibility due to comorbidities or prior BCMA therapy

ORR: 84% **≥CR: 53%**

PFS



RW safety of cilta-cel

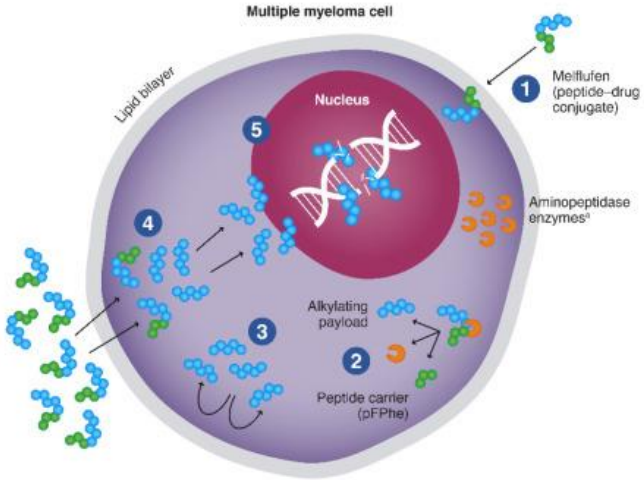
Characteristic	Cilta-cel (N=143)	CARTITUDE-1 [2,3] (N=97)
Any CRS*, n (%)	114 (80)	92 (95)
Grade ≥ 3	7 (5)	4 (4)
Any ICANS*, n (%)	24 (18)	16 (17)
Grade ≥ 3	8 (6)	2 (2)
Any delayed NT, n (%)	17 (12)	12 (12)
Parkinsonism	2 (1)	4 (4)
Bell's/CN Palsy	9 (6)	2 (2)
Other	6 (4)	6 (6)
Day of onset, median [IQR]	25 [21-32]	27 [16-73]
Delayed NT Resolution	6 (35)	6 (50)
Time to resolution (days), median [IQR]	58 [33-94]	75 [28-159]

Total of 22 deaths (15%) in SOC population:
- N=8 due to myeloma progression
- N=14 (10%) due to NRM
  - Gr5 CRS (N=3), concomitant CRS/infection (N=1), Gr5 ICANS (N=1), delayed NT (N=2), IEC-associated HLH-like syndrome (N=1), and infections (N=6)

Median follow-up 5.8 months

1. Hansen DK, et al. ASCO 2023 (Abstract no. 8012 – presentation);
2. Berdeja JG et al. Lancet 2021;398:1216; 3. Martin T, et al J Clin Oncol 2023;41:1265–1274.

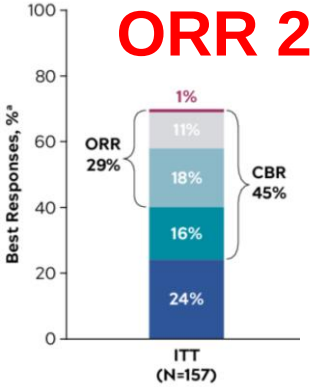
Melflufen: PDC (Peptide-Drug Conjugate)

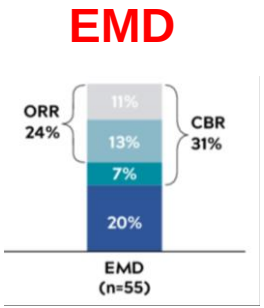


1. Melflufen (melphalan flufenamide) is highly lipophilic and readily diffuses through the cell membrane
2. Once inside the myeloma cell, melflufen is cleaved by aminopeptidases to release the alkylating payload
3. The hydrophilic alkylating payload remains entrapped within the cell
4. Increased diffusion of melflufen into the cell is driven by a high concentration gradient between the outside environment and the inside of the cell
5. Within the nucleus, the alkylating payload induces DNA damage resulting in cell death

HORIZON trial

n= 154 ***5 (2-12) prior lines***





mPFS: 4.2 m

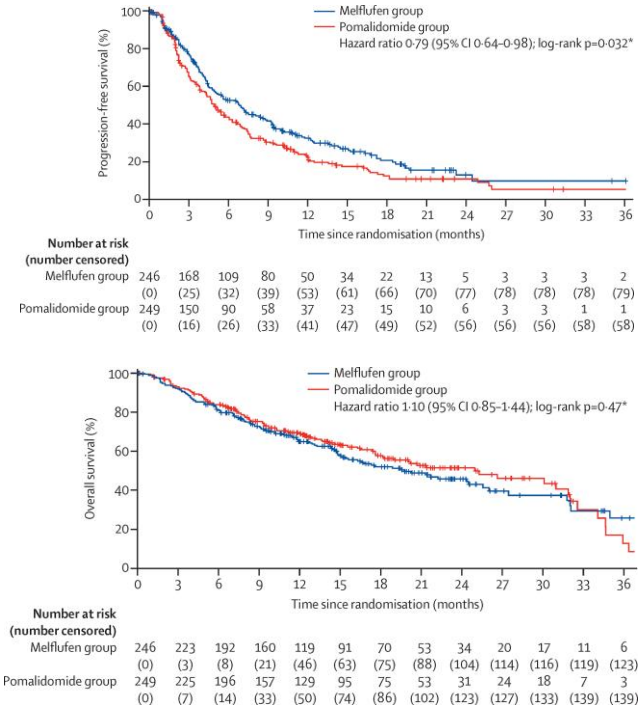
Hem. toxicity ***(thrombocytopenia)***

1. Chauhan et al. (2013) Clin Cancer Res 19(11): 3019-303.
2. Mateos MV. J Clin Med. 2020 Sep 27;9(10):3120
3. Ocio EM. Expert Rev Clin Pharmacol. 2022 Apr;15(4):371-382

Richardson PG. JCO 2020

Phase III Ocean Study: Melflufen + Dex vs Pom-Dex

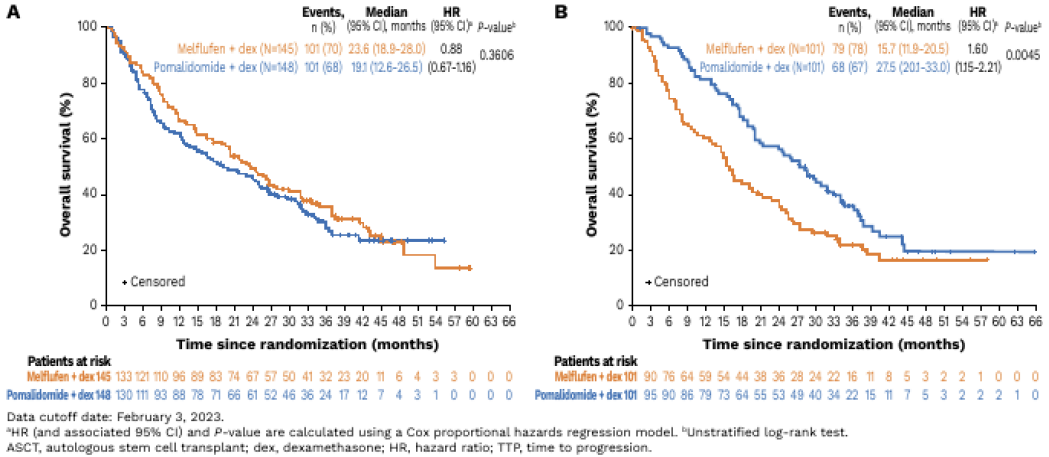
N=495 pts with RRMM. 3 (2-3) prior lines of therapy



Schjesvold et al. Lancet Haematol. 2022 Feb;9(2):e98-e110

Post-hoc Analysis. OS by prior treatment group

Figure 3. Overall Survival in (A) Patients Without ASCT or TTP >36 Months After ASCT and (B) Patients With TTP <36 Months After ASCT



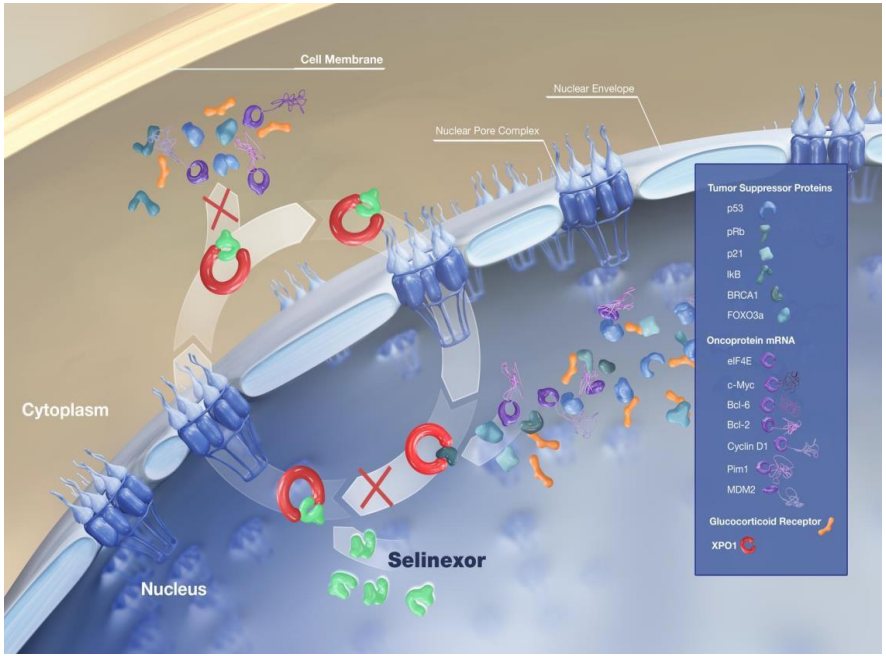
Data cutoff date: February 3, 2023.
[a]HR (and associated 95% CI) and *P*-value are calculated using a Cox proportional hazards regression model. [b]Unstratified log-rank test.
ASCT, autologous stem cell transplant; dex, dexamethasone; HR, hazard ratio; TTP, time to progression.

Schjesvold et al. ASH 2023 P2018

EMA approved for MM pts who have received at least 3 prior lines of therapy, refractory to PI, IMiDs, & anti-CD38 and >3 years after ASCT.

XPO1 inhibitor: Selinexor

First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-4]



- **Exportin 1 (XPO1) is the major nuclear export protein for**
  - **Tumor suppressor proteins (TSPs, e.g., p53, IkB and FOXO)**
  - **eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)**
  - **Glucocorticoid receptor (GR)**
- **XPO1 is overexpressed in MM**
  - **High XPO1 levels enable cancer cells to escape TSP-mediated cell cycle arrest and apoptosis**
  - **XPO1 levels correlate with poor prognosis and drug resistance**
- **Selinexor is an oral selective XPO1 inhibitor that:**
  - **Reactivates multiple TSPs by preventing nuclear export**
  - **Inhibits oncoprotein translation**
  - **Reactivates GR signaling in presence of dexamethasone**

1. Gupta A, et al. Therapeutic targeting of nuclear export inhibition in lung cancer. J Thorac Oncol. 2017;12(9):1446-1450.
2. Sun Q, et al. Inhibiting cancer cell hallmark features through nuclear export inhibition. Signal Transduct Target Ther. 2016;1:16010.
3. Gandhi UH, et al. Clinical implications of targeting XPO1-mediated nuclear export in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2018;18(5):335-345.
4. Gravina GL, et al. Nucleo-cytoplasmic transport as a therapeutic target of cancer. J Hematol Oncol. 2014;7:85.

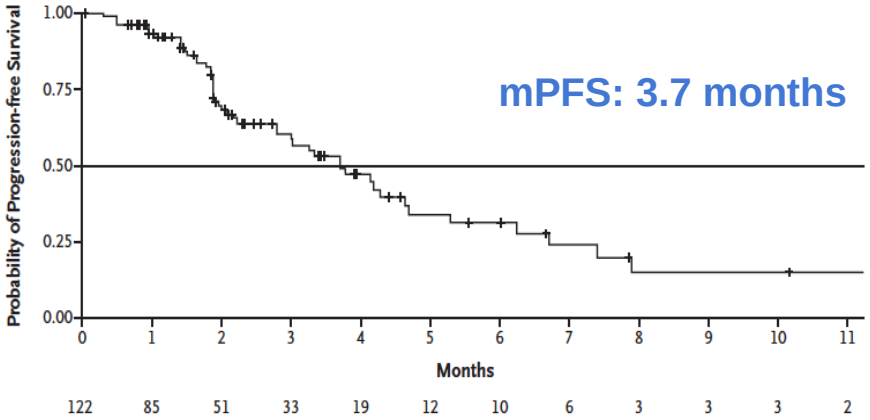
Selinexor plus dex (STORM study) in Penta-refractory MM

n=122 pts **7 (3-18) prior lines** **Penta refractory (bor, carf, len, pom & CD38 mAbs)**

ORR: 26% ***(6.5% VGPR (2 sCR))***

Median DOR: 4.4 months

Median OS: 8.6 months



mPFS: 3.7 months

Main AEs: Thromboc. (67%, 53% G3-4), anemia (46%, 28% G3-4), fatigue (68%; 21% G3-4)

GI: nausea (67% 10% G3/4), anorexia 50%; 2% G3/4), weight loss (46%; 0% G3/4)

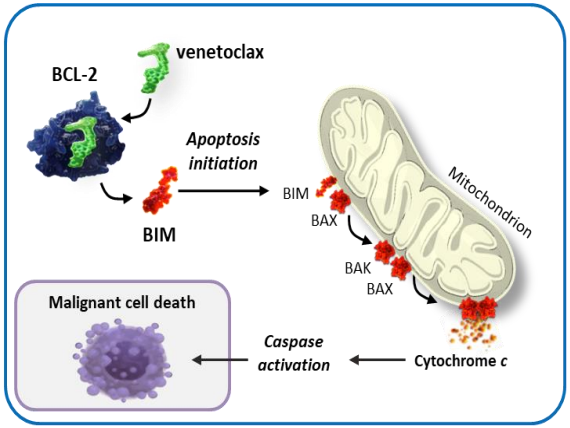
Chari, et al. NEJM 2019;381:727-38

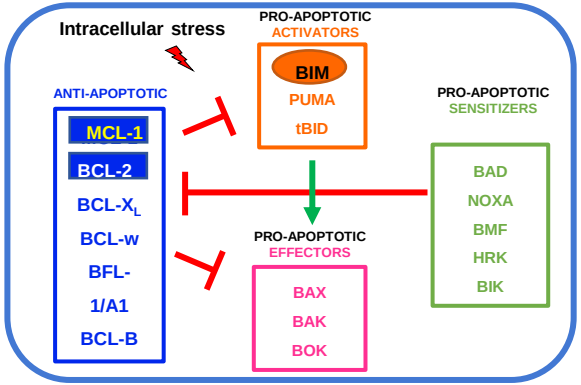
BOSTON: Selinexor-Vd *Dimopoulos. ASCO 2020* **+Kd** *Jakubowiak. BJH 2019 & Schiller. ASH 2022. P4516*

+Ld *White. ASH 2020* **+Pd** *White. ASH 2021* **+Dara-d** *Gasparetto. ASCO 2020* **+DaraVd** *Rodríguez-Otero. ASH 2021*

HR Cytogenetics *Nooka, et al. ASH 2019* **EMD** *Yee, et al. ASH 2019* **prior Dara** *Lentz. ASH 2021* **prior BCMA** *Beljevic. ASH 2021*

Venetoclax (Bcl-2 inhibitor)

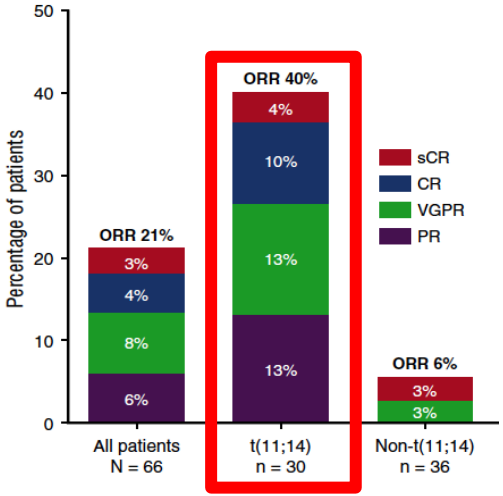




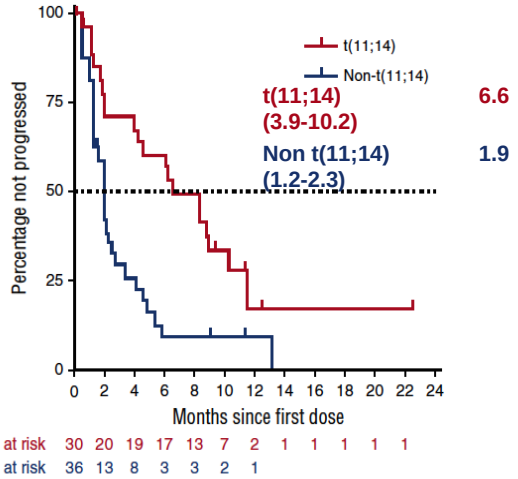
n=66 RRMM pts with 5 prior lines

Best Response

40% *vs* 6%



Time to Progression

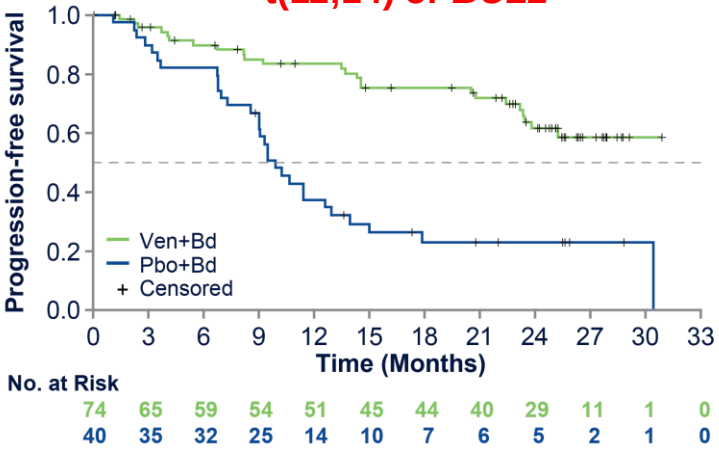


Main toxicities are mild GI symptoms and Hem

Kumar, et al. Blood 2017

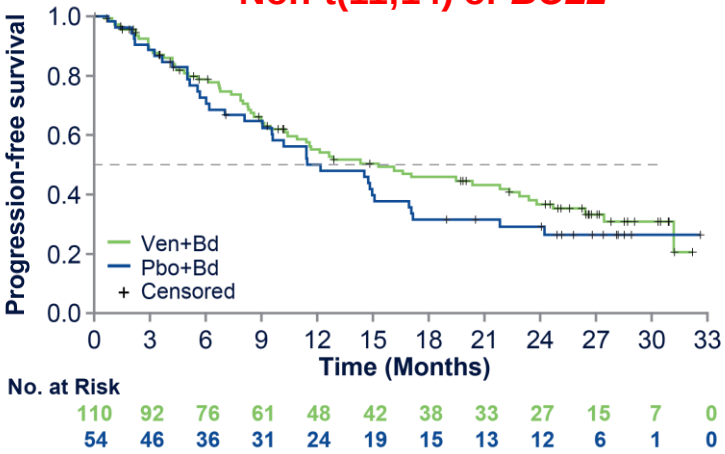
Phase III Bellini: Venetoclax-Bd vs Bd

t(11;14) or *BCL2*^{high}



PFS	Ven+Bd	Pbo+Bd
Median, months	Not reached	9.9
HR (95% CI)	0.30 (0.17, 0.53)	
P-value	<0.001	

Non-t(11;14) or *BCL2*^{low}



PFS	Ven+Bd	Pbo+Bd
Median, months	15.3	11.5
HR (95% CI)	0.85 (0.56, 1.30)	
P-value	0.451	

PFS for t(11;14): 36.8 vs 9.3 (HR, 0.12 [95% CI, 0.03–0.44])

Kumar, et al. Lancet Oncol 2020 & ASH 2021

High BCL2 gene expression was determined by qPCR

Phase III Canova: Venetoclax-d vs Pd in t(11;14) pts

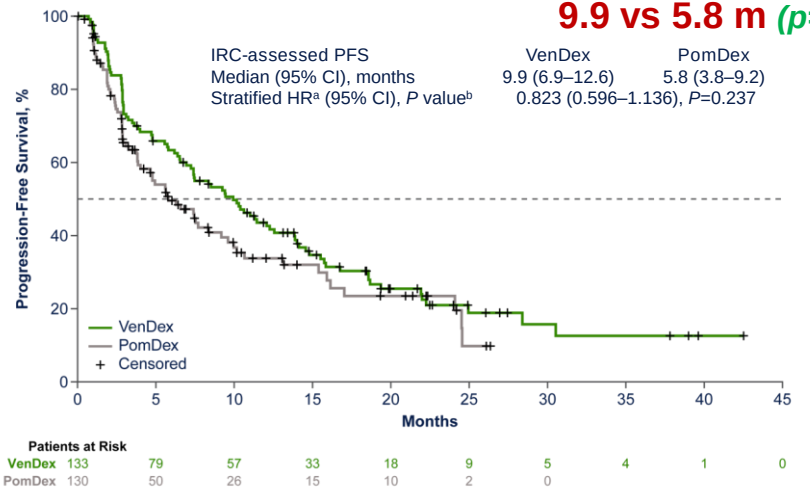
N=263 t(11;14) RRMM pts **2.5 (2-8) prior lines of therapy.** **96% Len Refr 37% Anti-CD38 Refr.**

ORR: 62% vs 35%

PFS

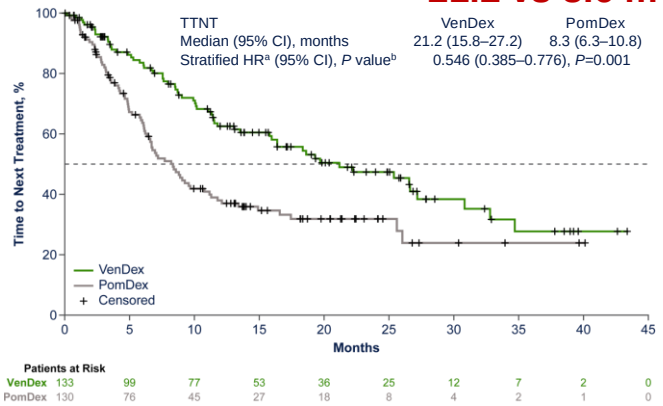
(Primary endpoint)

9.9 vs 5.8 m ***(p=0.237)***



TTNT

21.2 vs 8.6 m ***(p=0.001)***



Safety profile of VenDex was consistent with the known safety profile of venetoclax, with no new safety signals observed

mOS: 32.4 vs 24.5 m ***(HR 0.697 (0.472–1.029), P=0.067***

Mateos MV, et al. IMS 2023. OA 52

Current questions

- **1st relapse is well covered.** Concern for post-DRd.
  - Now Cilta-Cel available. Future: Bela comb. & TCE
- **At subsequent relapses most patients are TCE or TCR**
  - Several options approved
    - Cilta-Cel & Ide-Cel
    - Teclistamab, Elranatamab & Talquetamab
    - Selinexor, Melflufen, Venetoclax
- Questions:
  - Availability/Reimbursement?
  - Car-T vs TCE? ……. Sequencing?
  - **Adapt treatment** based on risk, response, safety & tolerability

Acknowledgments

University of Cantabria

Hematología Valdecilla

University Hospital "Marqués de Valdecilla"
&
Valdecilla Biomedical Research Institute

Cancer Research Center & University Hospital

Salamanca, Spain

Jesús F. San Miguel

Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA
HEMATOLOGÍA EN 48H
[LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]
X EDICIÓN

ACTUALÍZATE 48 HORAS

Pronóstico y tratamiento de pacientes con mieloma refractario

Enrique M. Ocio

Hospital Universitario Marqués de Valdecilla (IDIVAL)

Universidad de Cantabria

Santander