How will immunotherapy reshape the treatment of multiple myeloma?

March, Torino

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VUmc
Cancer Center Amsterdam

Disclosures

- Advisory boards for Janssen Pharmaceuticals, Amgen, Celgene, Bristol-Myers Squibb, Novartis, Roche, Takeda, GSK, Sanofi, Bayer and Servier
- Research funding from Janssen Pharmaceutical, Amgen, Celgene, Novartis, Cellectis, and Bristol-Myers Squibb

Myeloma therapy: what's available ?

IMiDs
-thalidomide
-lenalidomide
-pomalidomide

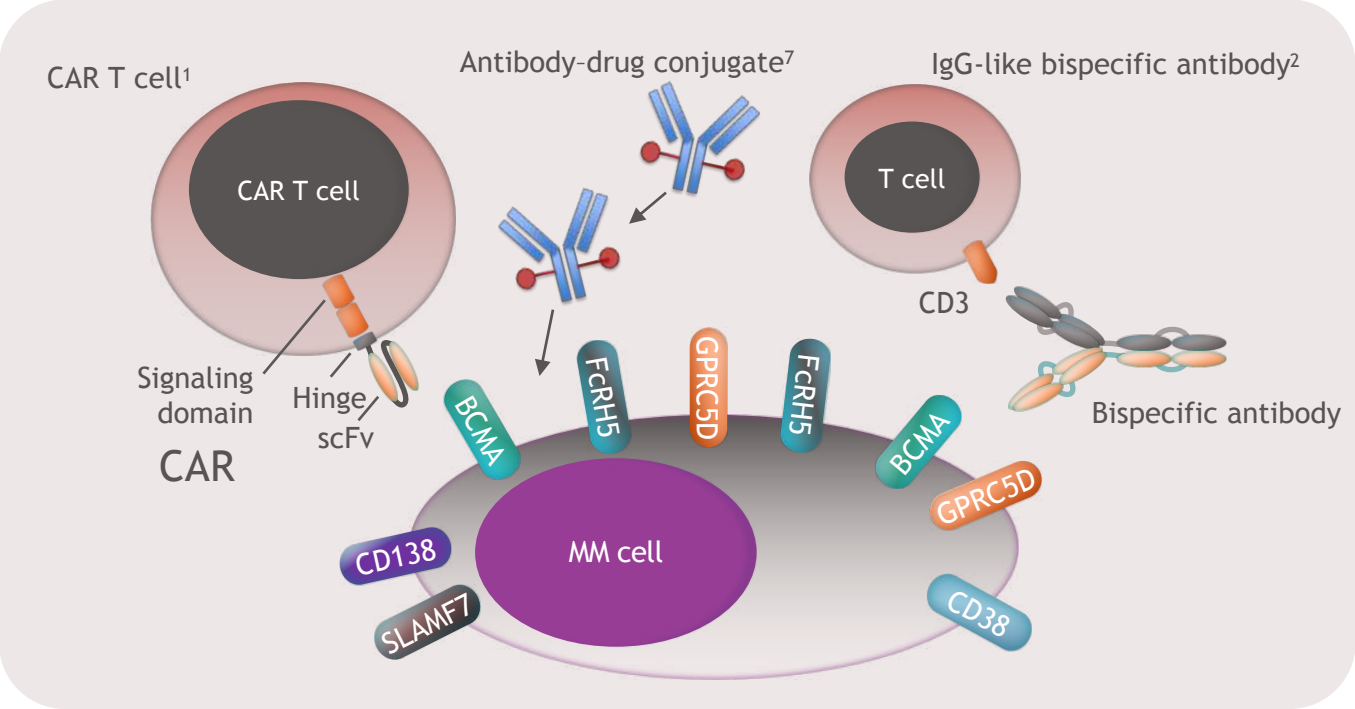
PIs
-ixa
-bort
-carfil

Steroids
-dexamethasone
-prednisone

Alkylators
-melphalan
-cyclophosphamide

CD38 mAbs
-daratumumab
-isatuximab

New-generation immunotherapies in MM (T-cell redirecting therapies: >60% response rates in heavily pretreated MM)



- **ADC:**
  Belantamab
  MEDI2228
- **Bispecifics:**
  AMG701
  Teclistamab, talquetamab
  Elranatamab
  REGN5458
  TNB-383B
  CC-93269
  Cevostamab
- **CAR T:**
  Ide-cel
  Cilta-cel
  p-BCMA-101
  CT053
  ALLO-715

BCMA:[3]
- Selectively overexpressed in plasma cells
- Promotes proliferation and survival of MM cells

GPRC5D:[4,5]
- Highly and selectively expressed in MM
- Distribution is similar to but independent of BCMA

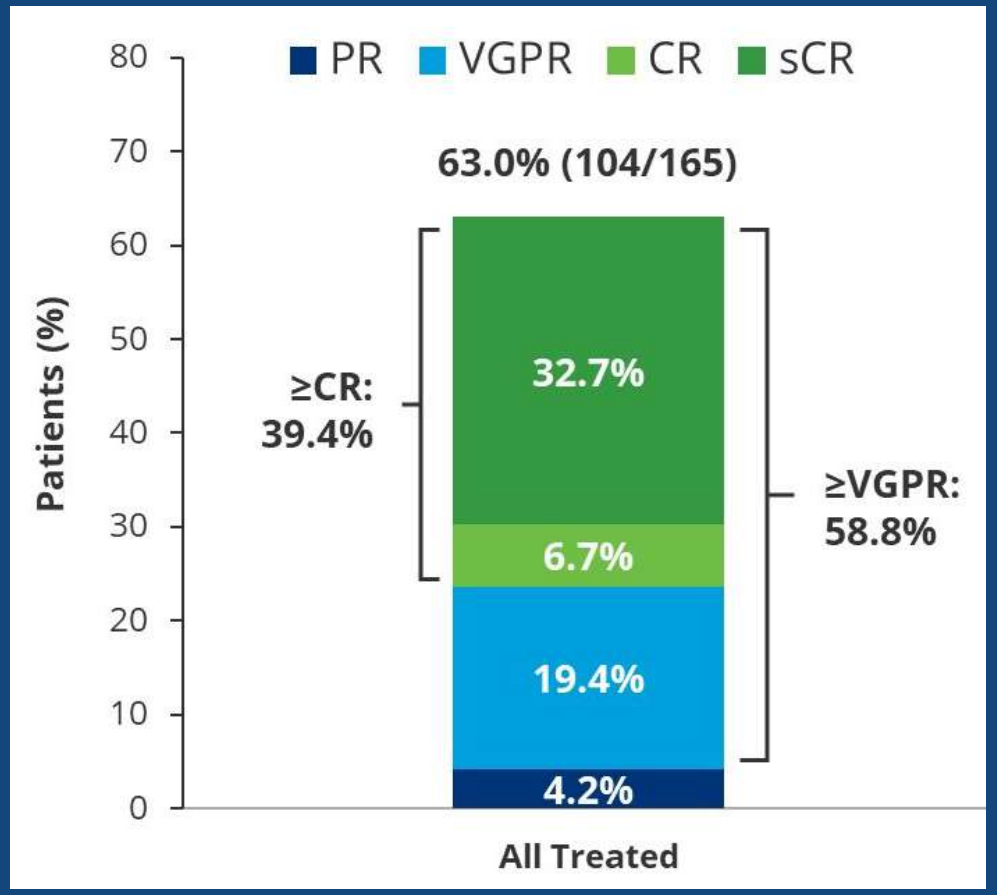
FCRH5:[6]
- High levels of expression on MM cells
- Normally expressed in plasma cells only

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; FcRH5, Fc receptor-like 5; GPRC5D, ide-cel, idecabtagene vicleucel; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; scFv, single chain variable fragment.

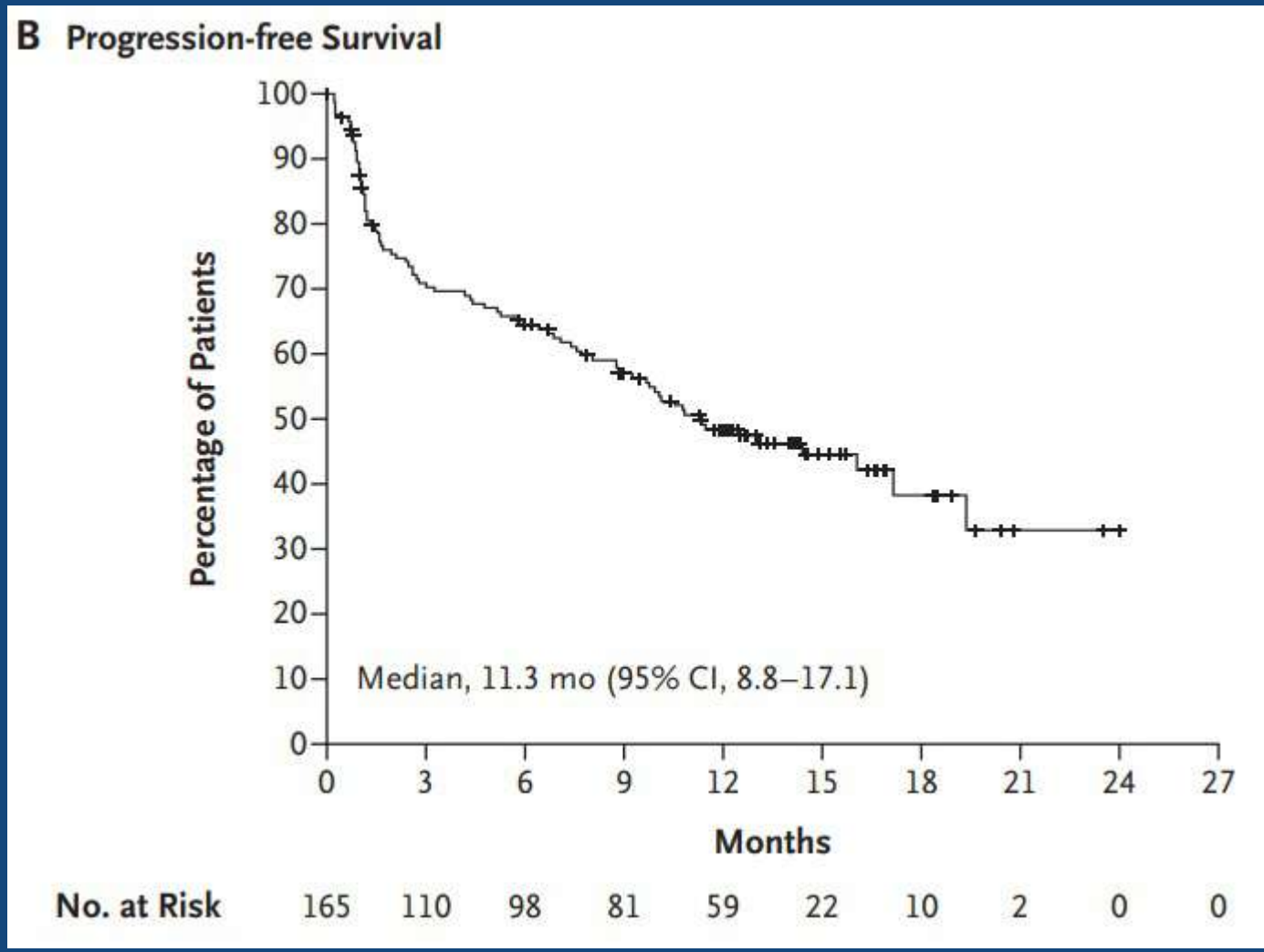
1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538-49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij et al. Blood Advances, 2020;5(8);2195-2215. 5. Smith EL, et al. Sci Transl Med. 2020;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-395. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155.

Images adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.

TECLISTAMAB (MajesTEC-1): EMA approved (24 august 2022); FDA approved



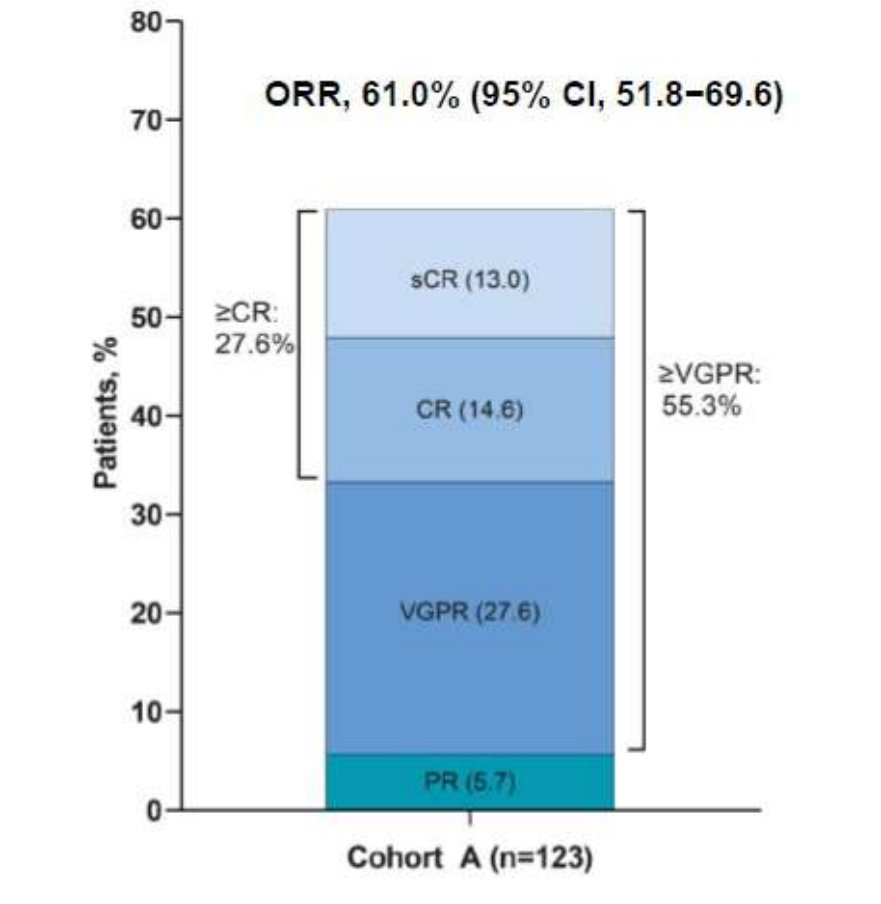
Median prior regimens: 5
Median follow-up: 14.1 months

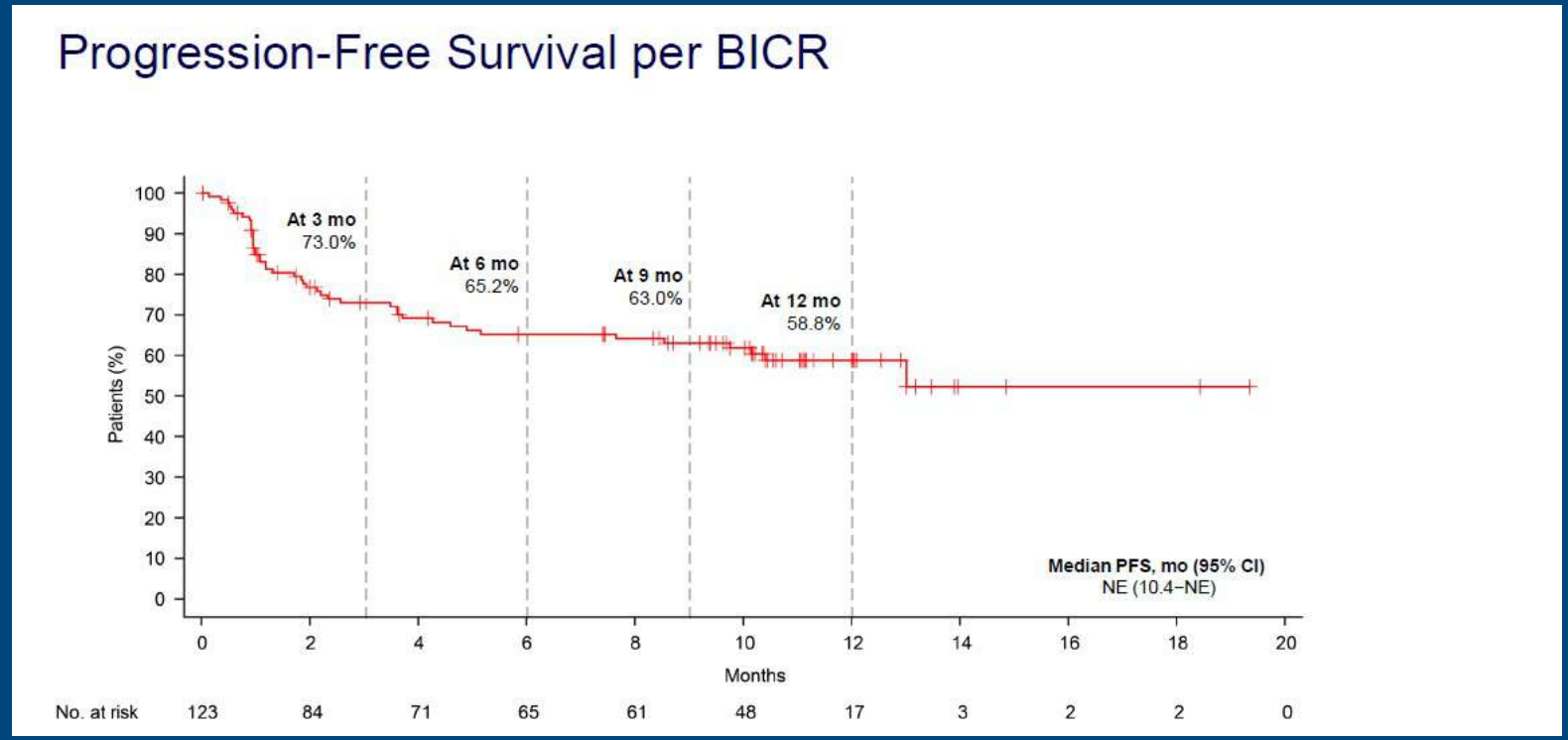


CR, complete response; PR, partial response; sCR, stringent CR; VGPR, very good PR

https://www.jnj.com/janssen-marks-first-approval-worldwide-for-tecvayli-teclistamab-with-ec-authorisation-of-first-in-class-bispecific-antibody-for-the-treatment-of-patients-with-multiple-myeloma (accessed October 2022)
Nooka A et al. ASCO 2022;abstract 8007 (oral presentation); Moreau P et al. N Eng J Med 2022;387(6):495-05.

Elranatamab (MagnetisMM 3)





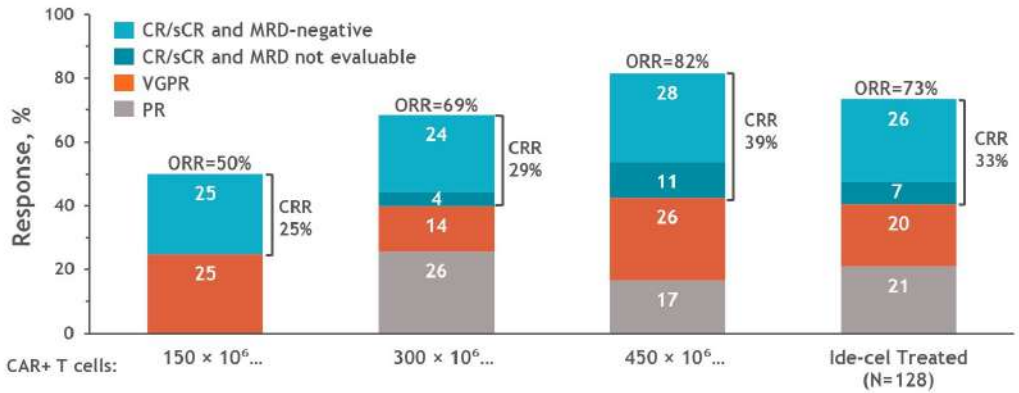
Median prior regimens: 5
Median follow-up: 10.4 months

BICR, blinded independent central review; CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Bahlis N et al. ASH 2022;abstract 159 (oral presentation)

Ide-cel (KarMMa): FDA/EMA approved

Best Overall Response

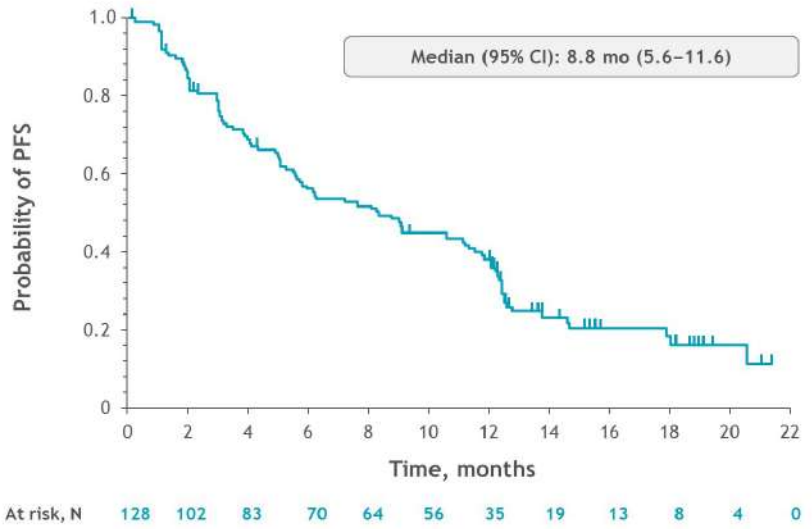


- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

Data cutoff: 14 Jan 2020. MRD-negative defined as <10⁻⁵ nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered. Values may not add up due to rounding. CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (sPR); PR, partial response; VGPR, very good PR. *P value at the primary data cutoff with same ORR and 95% CI.

5

Progression-Free Survival



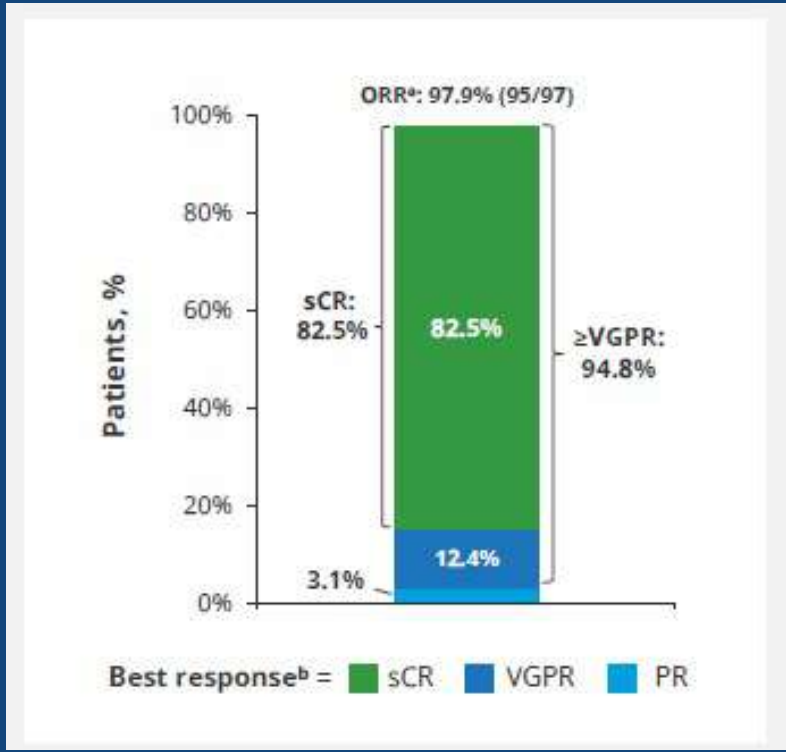
Data cutoff: 14 Jan 2020. PFS, progression-free survival.

11

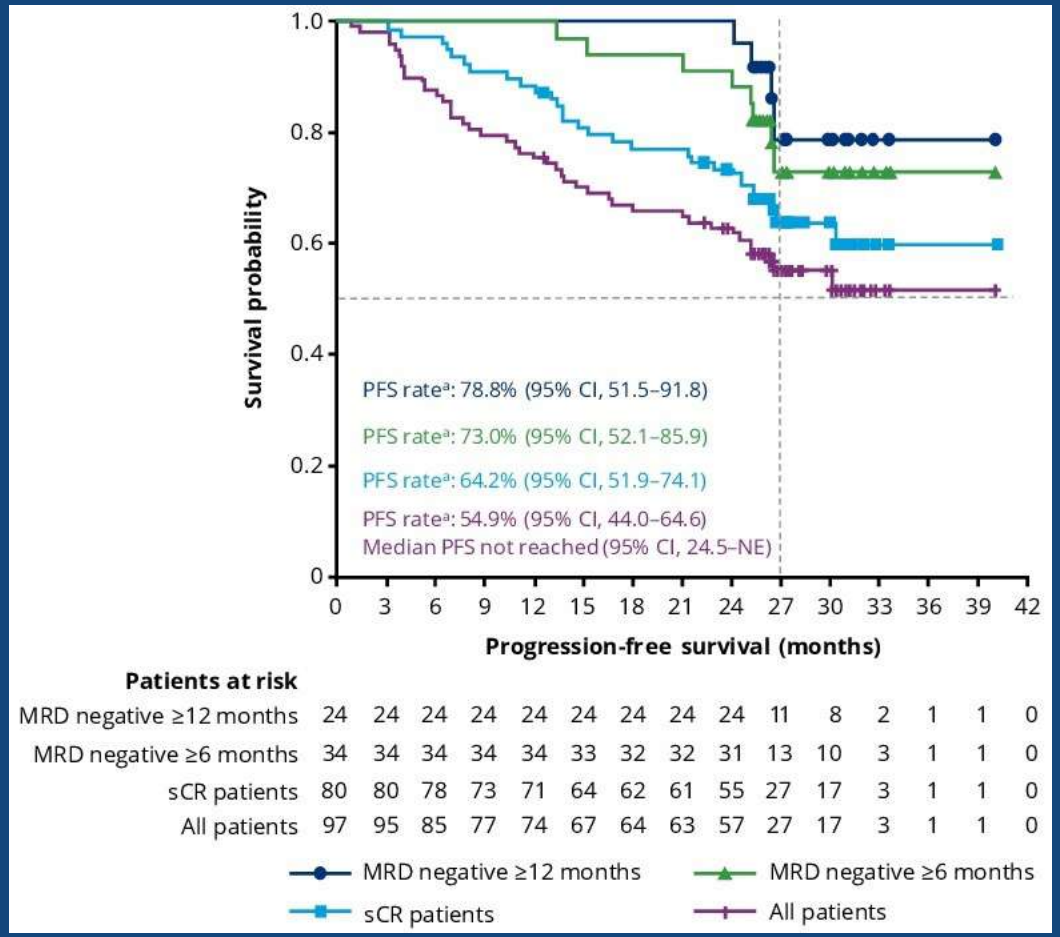
Median prior regimens: 6
Median follow-up: 13.3 months

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-idecabtagene-vicleucel-multiple-myeloma (Accessed Oct 2022); https://www.ema.europa.eu/en/medicines/human/EPAR/abecma (accessed Oct 2022); Munshi N et al N Eng J Med 2021; 384(8):705-716; Munshi ASCO 2020;abstract 8503 (oral presentation).

Cilta-cel (CARTITUDE-1): FDA/EMA approved



[a]ORR assessed by independent review committee.
[b]No patient had CR or stable disease



[a]27-month PFS rate.

Median prior regimens: 6
Median follow-up: 28 months

CR, complete response; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ciltacabtagene-autoleucel-relapsed-or-refractory-multiple-myeloma (accessed oct 2022);
https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti (accessed Oct 2022);
Usmani S et al. ASCO 2022;abstract 8028 (poster presentation).

Myeloma therapy: what's (soon…) available ?

IMiDs
-thalidomide
-lenalidomide
-pomalidomide

PIs
-ixa
-bort
-carfil

Steroids
-dexamethasone
-prednisone

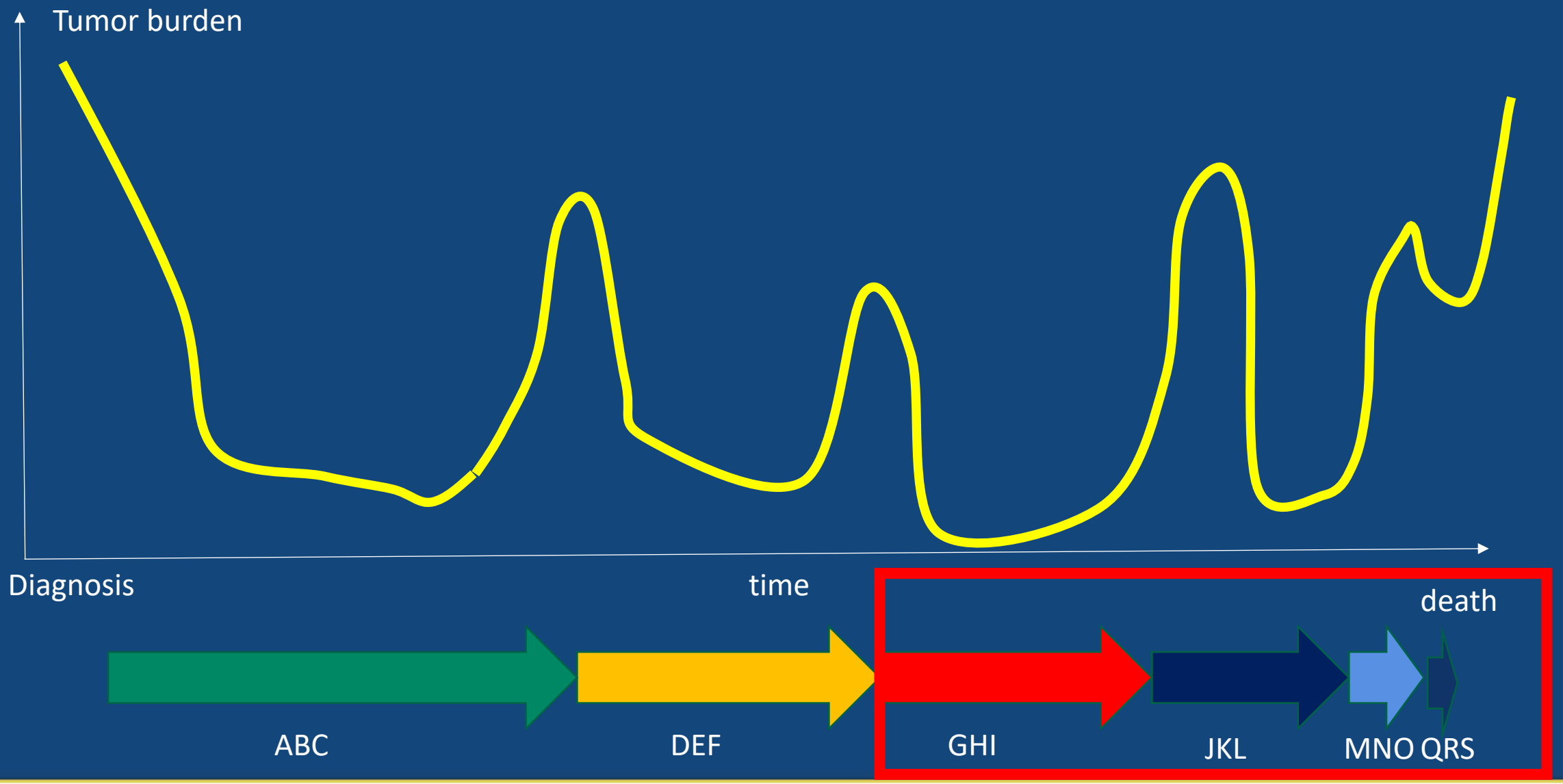
Alkylators
-melphalan
-cyclophosphamide

CD38 mAbs
-daratumumab
-isatuximab

TCE
-teclistamab
-elranatamab

CAR T
-ide-cel
-cilta-cel

How we currently treat MM



van de Donk N, personal opinion.

How can we improve survival of MM patients?

- 1. Earlier use of T-cell redirecting therapies
- 2. Combination strategies
- 3. Synergistic sequence of agents
- 4. Next generation of immunotherapies

1. Earlier use of best drugs

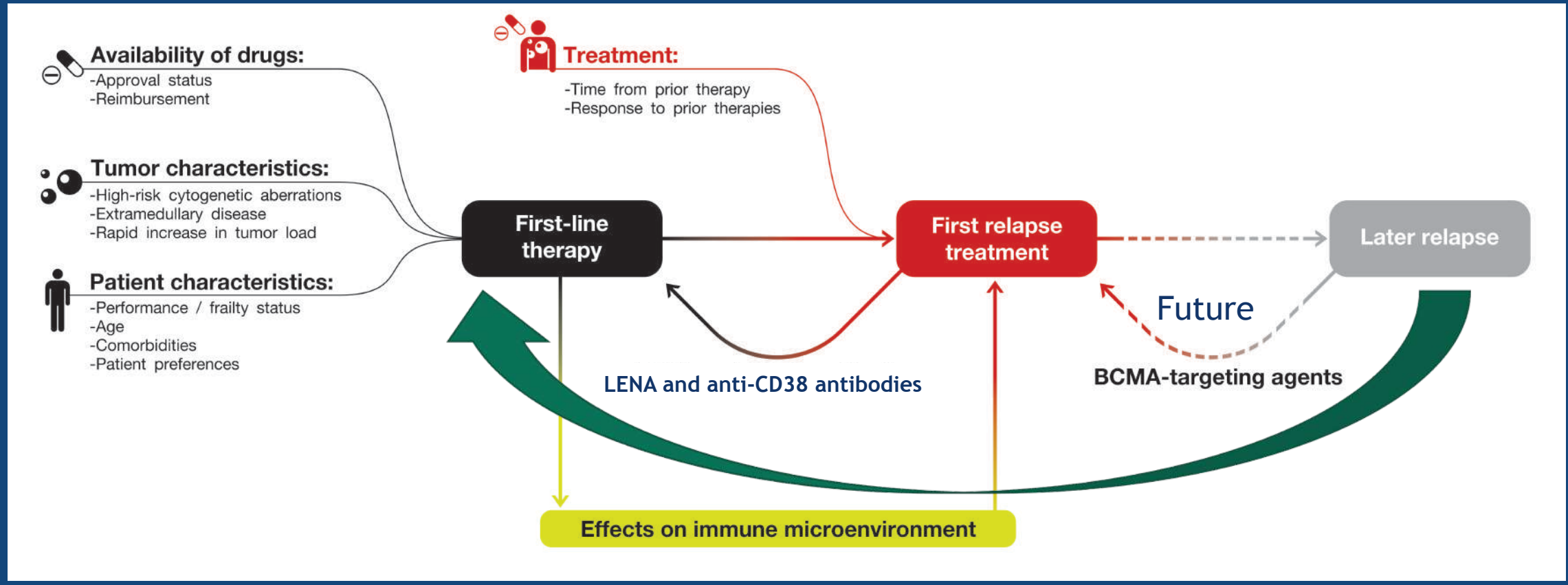
- Approval of T-cell redirecting therapies in advanced myeloma

Rationale of earlier use

- Use of best drugs early in treatment course
  - Only two thirds of patients receive more than 1 line of therapy (more common in elderly patients
  - Deepest remission → To preserve quality of life
    - (QoL diminishes with each progression because of cumulative burden of therapy and disease-related complications)
  - Superior T-cell fitness in earlier lines of therapy vs advanced disease

  - PROOF OF CONCEPTS → KARMMA-3 /CARTITUDE-4 / MAJESTEC-4 etc

Lenalidomide and CD38 antibodies increasingly used as part of first-line therapy



- Increasing fraction of patients will have lenalidomide-refractory disease and prior bortezomib exposure at the time of first progression
- Subset of these patients will also have daratumumab-refractory disease at the time of first progression

BCMA, B-cell maturation antigen

van de Donk N. Hematology Am Soc Hematol Educ Program 2020;(1):248-258.

Case 1

- June 2019 Multiple myeloma with extensive bone disease and anemia
- Hyperdiploidy (standard-risk)
- R-ISS stage 2
- TREATMENT: VTD→ HDM+auto-SCT➔ complete response
- Feb 2020 start lenalidomide maintenance

Case 1

- June 2019 Multiple myeloma with extensive bone disease and anemia
- Hyperdiploidy (standard-risk)
- R-ISS stage 2
- TREATMENT: VTD→ HDM+auto-SCT (nov 2019)➔ VGPR (M-pro NTQ)
- Feb 2020 start lenalidomide maintenance
- May 2020 biochemical progression with rapid increase in M-protein

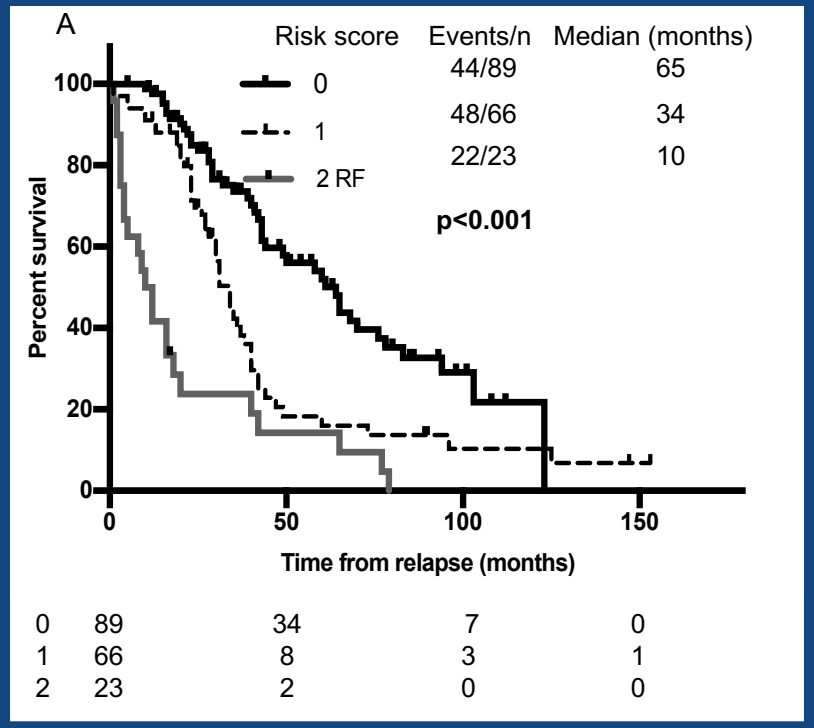
- **➔ Early relapse (6 months after HDM)**

What now !

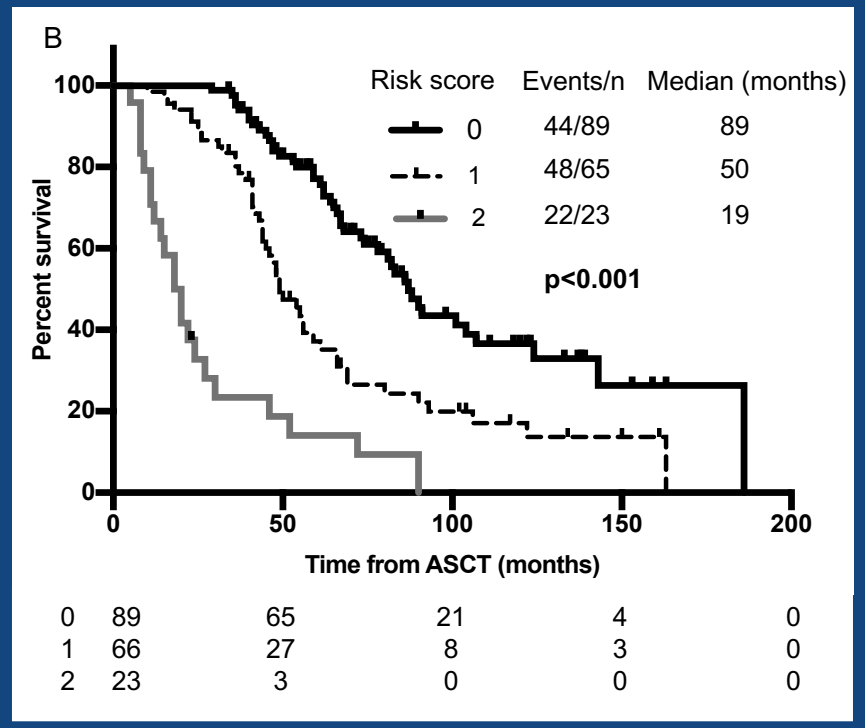
- Prognosis ?
- Treatment ?

A new prognostic model for patients relapsing from upfront ASCT : independent effect of PFS1 (UCLH data)

Post-relapse survival



OS



Risk score	Timing of relapse	ISS stage
0	>12 months	ISS 1
1	Either ≤12 months Or >12 months	ISS 1 ISS 2 or 3
2	≤12 months	ISS 2 or 3

- **Early relapse** (≤12m) was associated with shorter PRS (18 vs 49 months, p<0.001) and OS (27 vs 85 months

Chavda S et al. Br J Haematol 2019;185(2):350-353

ASCT, autologous stem cell transplant; ISS, International Staging System; OS, overall survival; PRS, post-relapse survival

What now? Prognosis

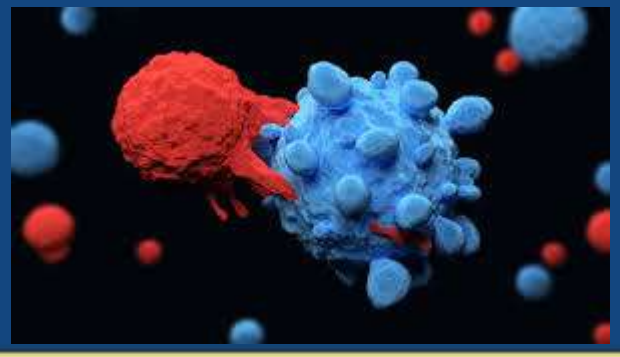
Study	Number of patients	Definition early relapse	% early relapse	Post-relapse survival (months)	OS from diagnosis (months)
UCL 2019[1]	269	<12 months after HDM	27%	18 vs 49	27 vs 85
DK 2018[2]	575	<12 months after HDM	17.9%	NA	26.1 vs 95.3
Ong 2016[3]	215	<12 months after HDM	18%	11 vs NA	16 vs 122
Mayo 2016[4]	561	<12 months after HDM	5.8%	NA	23.1 vs 122.2
Mayo 2008[5]	494	<12 months after HDM	24%	10.8 vs 41.8	20.1 vs 82.5
Jimenez-Zepeda[6]	184	<12 months after HDM	15%	NA	20 vs 93

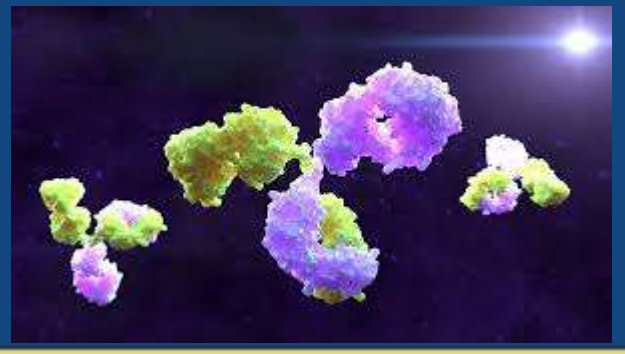
NA, not assessed

1. Chavda S et al. B J Haematol 2019;185(2):350-3; 2. Helm-Petersen S et al. Leukemia 2018;32(9):2054-7; 3. Ong SY et al. Bone Marrow Transplant 2016; 51(7):933-7; 4. Majithia N et al. Leukemia 2016;30(11):2208-13; 5. Kumar S et al. Bone Marrow Transplant 2008;42(6):413-20; 6. Jimenez-Zepeda VH et al. Bone Marrow Transplant 2015;50(2):204-8.

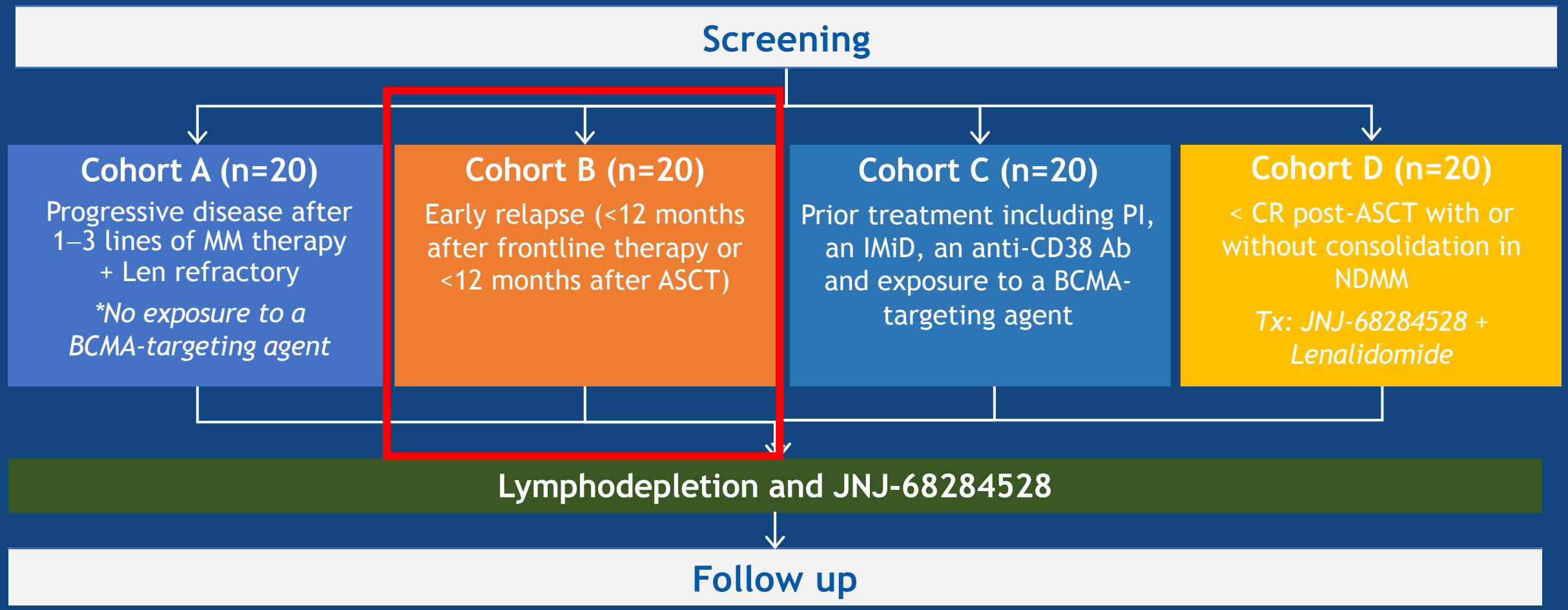
Early relapse represents an unmet medical need

- New treatment strategies needed !
- **Incorporation of new novel agents with novel mechanisms of action to** achieve MRD-negative disease
  - T-cell redirecting therapies promising
    - BCMA-targeting CAR T-cell therapy (ide-cel, JNJ-4528)
    - T-cell redirecting bispecific antibodies directed against BCMA or GPRC5D
- Strategies to **sustain MRD-negative** disease





CARTITUDE-2 study design



Clinicaltrials.gov identifier: NCT04133636

CASE 1

- Vd bridging
- Flu/cy conditioning
- 15 sept 2020 CAR T cell infusion
  - Grade 1 CRS
  - Infections (still receiving IVIG)

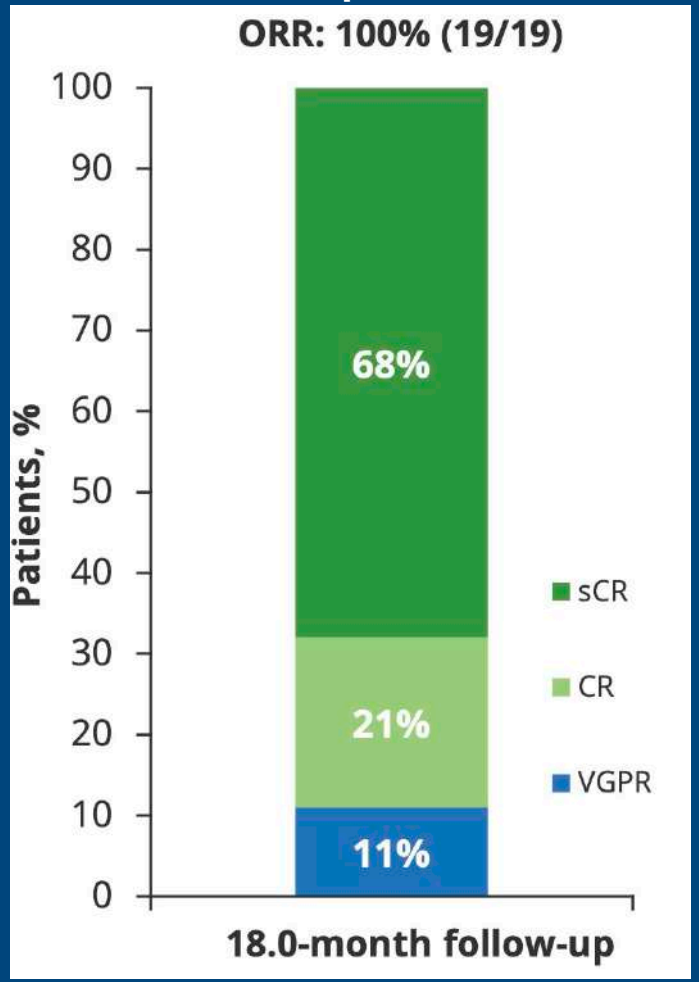
CASE 1

- Response: stringent Complete Remission which persists until now (2.5 years after CAR T-cell infusion
- 1 shot therapy vs continuous use of drugs and expected rapid development of multi-drug resistance (short remission durations)
- Good and preserved quality of life

CARTITUDE-2: Response and safety

Cohort B – relapse within 12 months after ASCT or start of therapy

Responses



AEs

AEs ≥20%, n (%)	N=19	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	18 (95)	17 (90)
Anemia	11 (58)	9 (47)
Thrombocytopenia	11 (58)	5 (26)
Lymphopenia	9 (47)	9 (47)
Leukopenia	6 (32)	6 (32)
CAR-T–related AEs		
CRS	16 (84)	1 (5)
Neurotoxicity	5 (26)	1 (5)
ICANS	1 (5)	0
Other	4 (21)	1 (5)
MNT/parkinsonism	1 (5)	1 (5)

- **Median follow-up**: 18 months
- **Median time to first response**: 0.95 months
- **Median duration of response**: not reached
- 18 month PFS rate: 83%
- 18 months OS rate: 83%
- 14/15 patients were evaluable and were MRD negative (10^{-5}, NGS)

- 3 deaths occurred due to PD
- 2/3 had MM with high-risk cytogenetic characteristics; none had EMD

ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; EMD, extramedullary disease; ICANS, immune effector cell-associated neurotoxicity syndrome; MNT, movement neurocognitive syndrome; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; PD, progressive disease; sCR, stringent complete response; VGPR, very good partial response

van de Donk N et al. ASH 2022;abstract 3354 (poster presentation)

2. Combination therapy

- T-cell redirecting therapies approved as monotherapies

- Combination therapy to prevent outgrowth of resistant clone

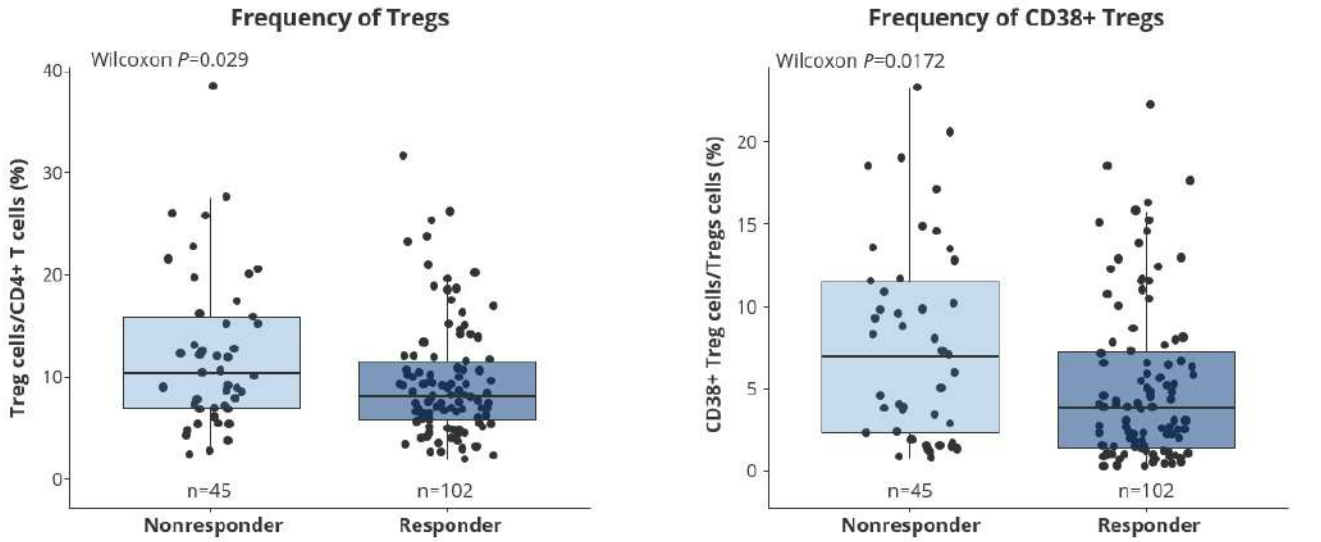
➔ agents with synergistic MoA (components target different biological mechanisms)

➔ agents with different mechanisms of resistance

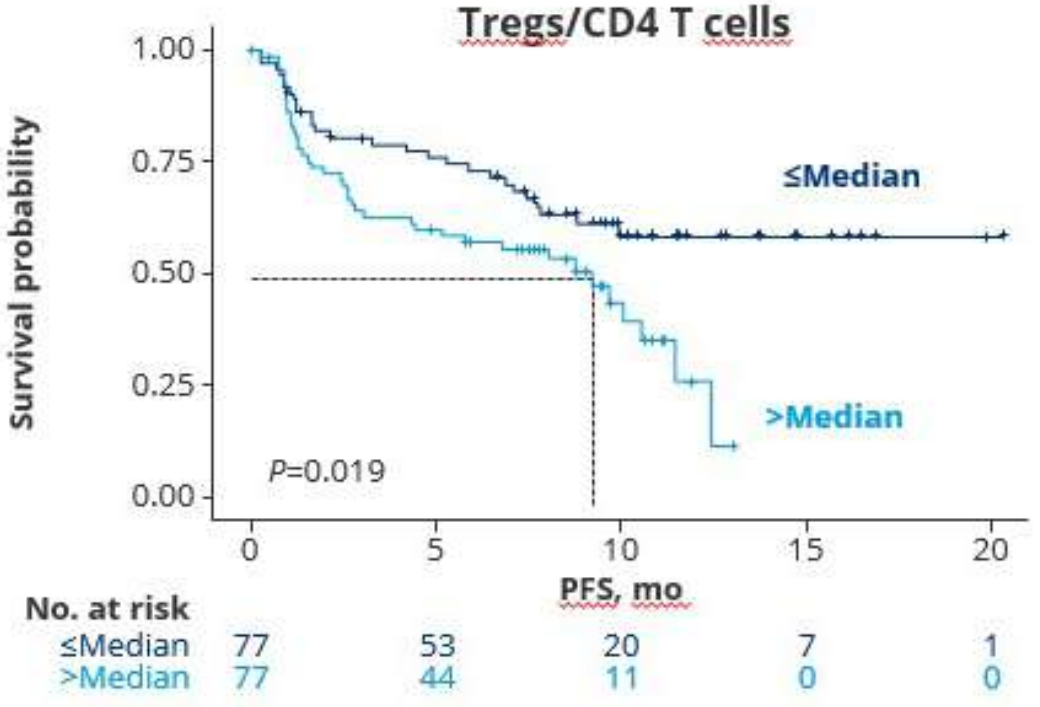
➔ agents with non-overlapping toxicity profiles

Non-responders to teclistamab have an unfavorable immune profile

Baseline Frequency of Regulatory T Cells in Peripheral Blood



- Tregs, which are key regulators of immune response, are found at a higher frequency in patients not achieving a clinical response



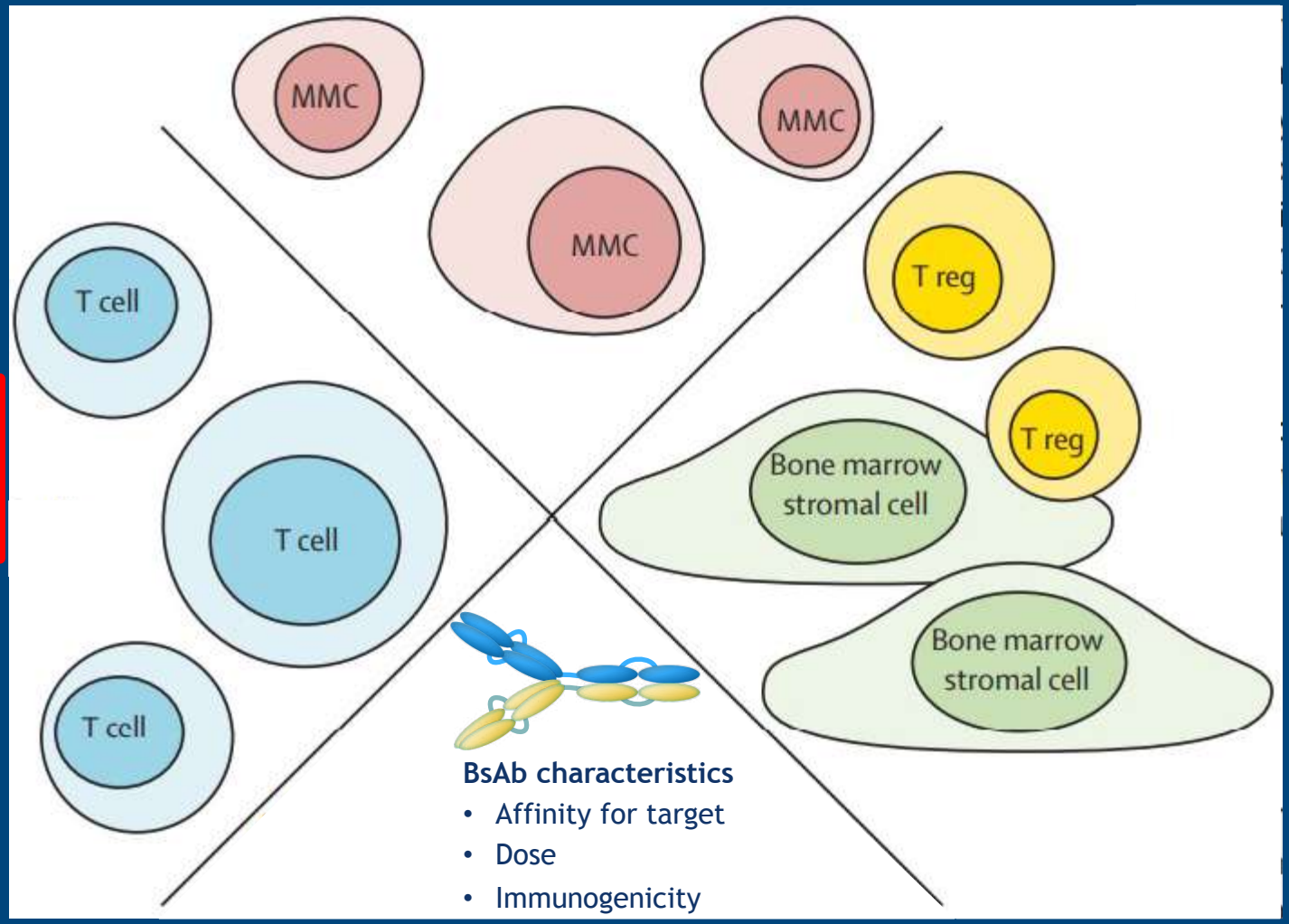
PFS, progression-free survival; Treg, regulatory T cell

Cortes-Selva D et al. ASH 2022;abstract 97 (oral presentation)

Mechanisms of resistance

Tumor-related features
- BCMA expression
- Antigen loss or diminished antigen expression
- Soluble BCMA
- Tumor load

- High-risk cytogenetic features
- Extramedullary disease
- Inhibitory receptors and ligands, which suppress T-cell function



T-cell characteristics
- T-cell frequency
- T-cell fitness

IMiD/CelMOD

BsAb characteristics
- Affinity for target
- Dose
- Immunogenicity

MM microenvironment-related factors
- BM stromal cells
- Immune suppressor cells

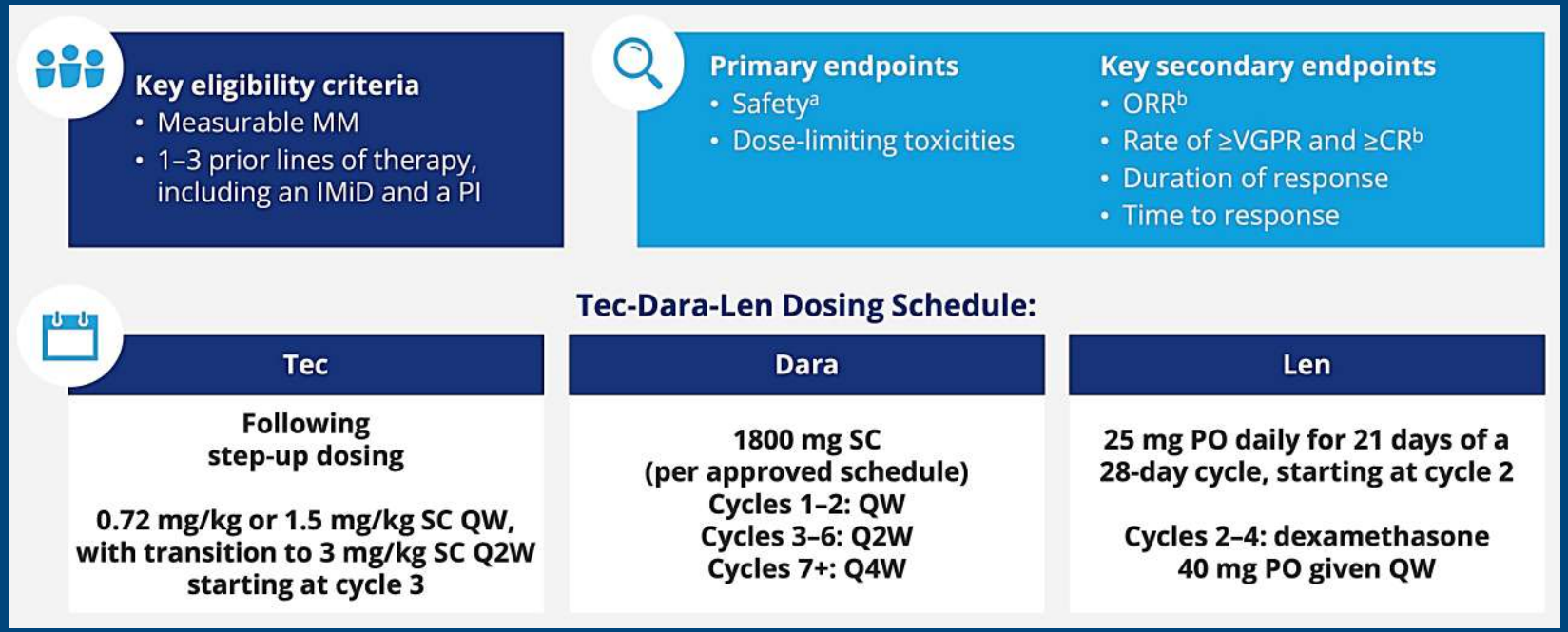
CD38 antibody: Elimination of Tregs

BCMA, B-cell maturation antigen; BM, bone marrow; BsAb, bispecific antibody; IMiD, immunomodulatory drug; MMC, multiple myeloma cell; Tregs, regulatory T-cells

Adapted from: van de Donk N et al. Blood Cancer Discov 2021;2:302–18

MajesTEC-2: Design and baseline characteristics

MajesTEC-2 design



Baseline characteristics

Characteristic	Dara 1800 mg SC Len 25 mg PO	
	Tec 0.72 mg/kg SC (n=13)	Tec 1.5 mg/kg SC (n=19)
Age (years), median (range)	65 (38-71)	60 (46-75)
High-risk cytogenetics, n (%) Includes ≥1 (t4;14), t(4;16), and del17p	3/12 (25.0)	7/15 (46.7)
Prior lines of therapy, median (range)	2 (1-3)	2 (1-3)
Refractory to anti-CD38 mAb, n (%)	3 (23.1)	3 (15.8)
Refractory to lenalidomide, n (%)	6 (46.2)	3 (15.8)

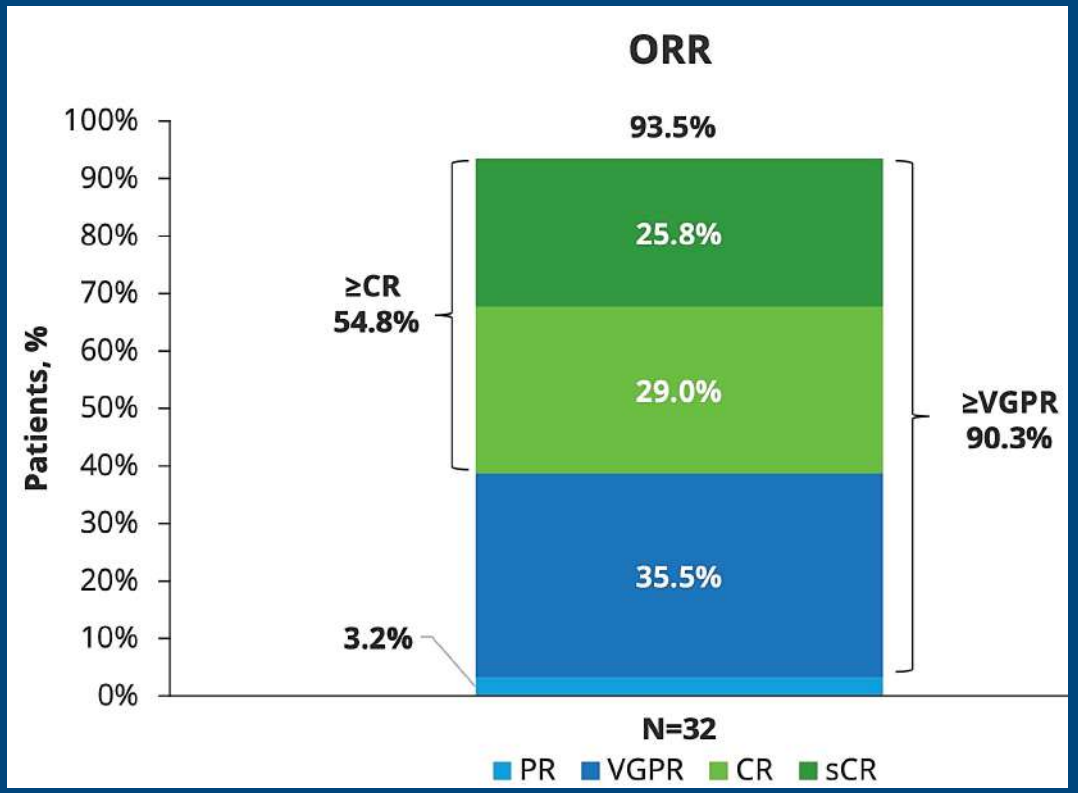
[a]AEs assessed per CTCAE v5.0, except for CRS and ICANS, which were graded per ASTCT guidelines.
[b]Assessed per IMWG 2016 criteria. ≥VGPR, very good partial response or better; ≥CR, CR or better;

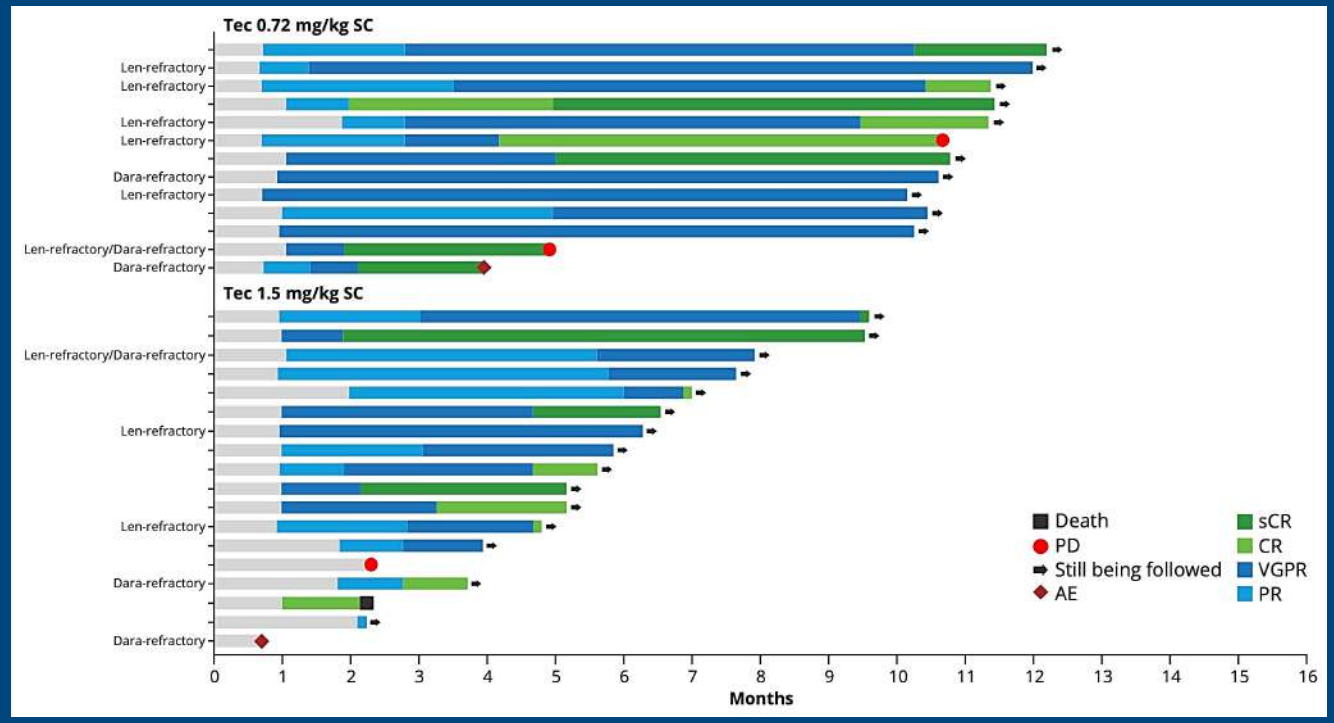
AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for AEs; ICANS, immune effector cell-associated neurotoxicity syndrome; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor; PO, by mouth; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; SC, subcutaneous; tec-dara-len, teclistamab, daratumumab, and lenalidomide

Searle E et al. ASH 2022;abstract 160 (oral presentation)

MajesTEC-2: Response to tec-dara-len

- **Median follow-up:** 8.4 months
- 25/31 (80.6%) remain progression free





Responses deepened over time, and mDOR has not been reached

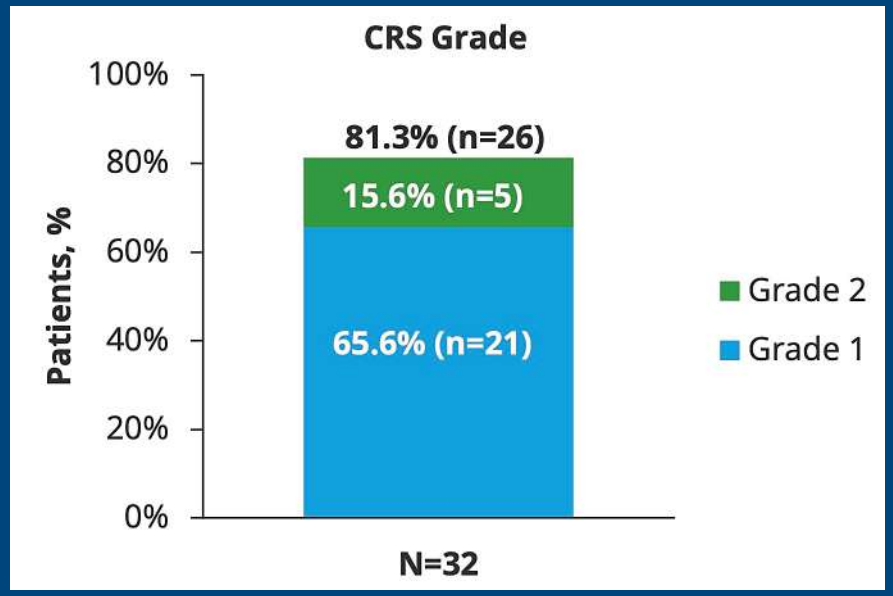
CR, complete response; mDOR, median duration of response; PD, progressive disease; PR, partial response; SC, subcutaneous; sCR, stringent complete response; tec-dara-len, teclistamab, daratumumab, lenalidomide; VGPR, very good partial response

Searle E et al. ASH 2022;abstract 160 (oral presentation)

MajesTEC-2: Safety profile

Hematological AEs

AE (any Grade: ≥25% and/or Grade 3/4: ≥10%), n (%)	N=32	
	Any Grade	Grade 3/4
Neutropenia	27 (84.4)	25 (78.1)
Thrombocytopenia	8 (25.0)	5 (15.6)
Anemia	7 (21.9)	4 (12.5)
Febrile neutropenia	4 (12.5)	4 (12.5)
Lymphopenia	4 (12.5)	4 (12.5)



Non-hematological AEs

AE (any Grade: ≥25% and/or Grade 3/4: ≥10%), n (%)	N=32	
	Any Grade	Grade 3/4
CRS	26 (81.3)	0
Fatigue	15 (46.9)	2 (6.3)
Diarrhea	15 (46.9)	0
Cough	13 (40.6)	1 (3.1)
COVID-19	12 (37.5)	4 (12.5)
Insomnia	12 (37.5)	1 (3.1)
Hypophosphatemia	10 (31.3)	2 (6.3)
Pyrexia	10 (31.3)	1 (3.1)
Upper respiratory tract infection	10 (31.3)	0
Nausea	10 (31.3)	0
ALT increased	9 (28.1)	3 (9.4)
Pneumonia	8 (25.0)	5 (15.6)

- No ICANS reported
- Grade 3/4 events occurred in 29 (90.6%) patients
- Patients with ≥1 infection: any grade 29 (90.6%); grade 3/4 12 (37.5%)
- 2 fatal AEs (COVID-19 and multiorgan failure due to sepsis)
- CRS median onset and duration was 2 days and 97% (37/38) occurred during cycle 1

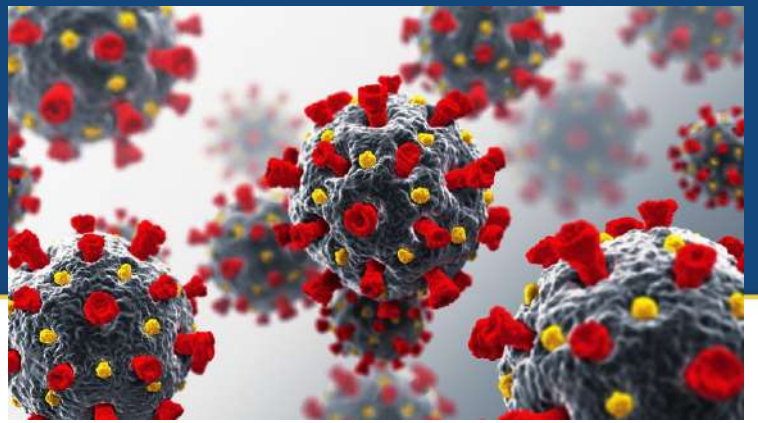
ALT, alanine transaminase; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

Impact on normal immune function : Infections

- BCMA BsAb: depletion of normal plasma cells + normal B-cells, and T-cell exhaustion
- DARA: depletion of normal plasma cells + NK cells
- IMiD/CELMoD: B-cell depletion

➔Infectious prophylaxis is crucial (my cocktail: cotrim/valacyclovir/IVIG)

➔Studies needed to investigate fixed duration treatment or maintenance to allow for immune reconstitution



Novel CELMoD agent: IBER *(preclinical data)*

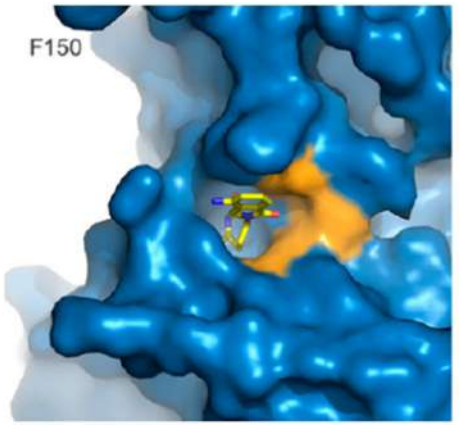
IBER has enhanced affinity for binding to CRBN

- Rapid protein degradation
- Increased depth of protein degradation
- At lower concentrations than needed with LEN or POM

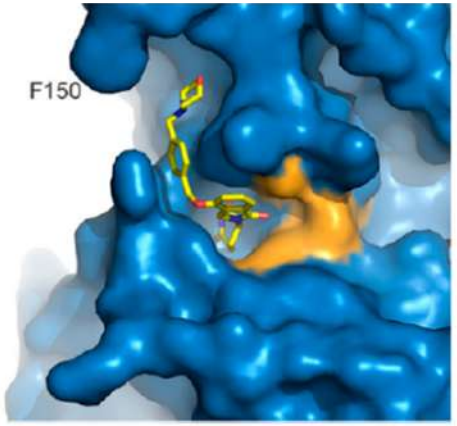
→ **Increased efficacy in preclinical studies**

Binding-surface interactions with CRBN

CRBN: LEN



CRBN: IBER



EC_{50}, nM^2	Ikaros	Aiolos
LEN	67	87
POM	24	22
IBER	1	0.5

In preclinical models, IBER is a novel CELMoD agent that:

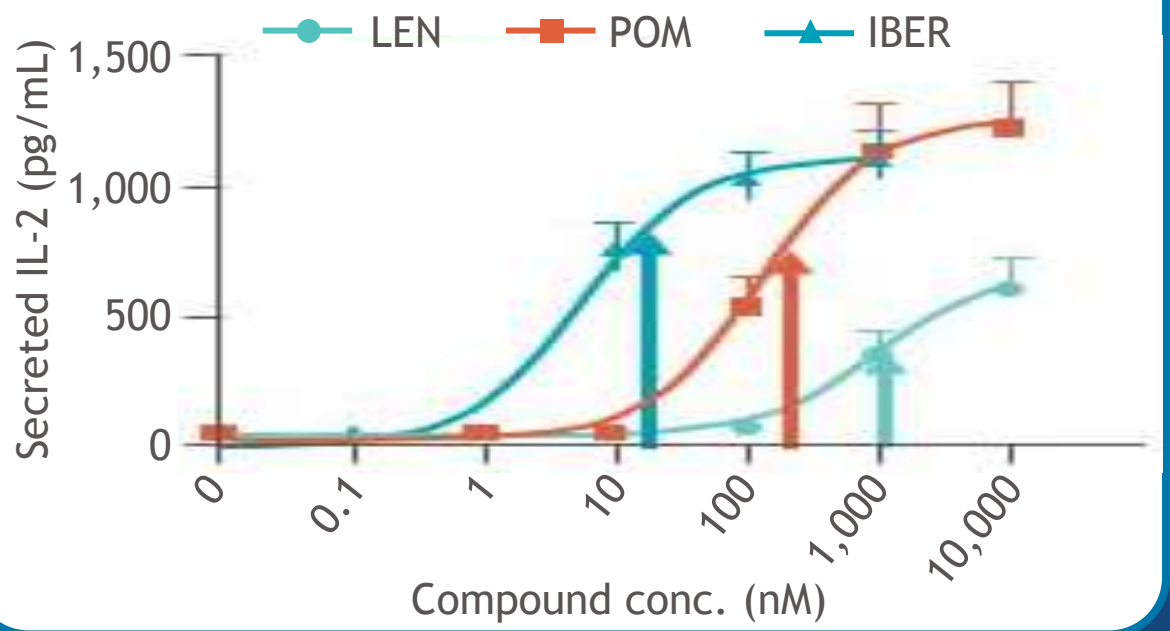
- Co-opts CRBN to enable enhanced degradation of target proteins; 20 times higher affinity than LEN or POM
- Is 20-fold more efficient than LEN or POM in degrading substrates

CRBN, cereblon; EC50, half-maximal effective concentration; len, lenalidomide; pom, pomalidomide

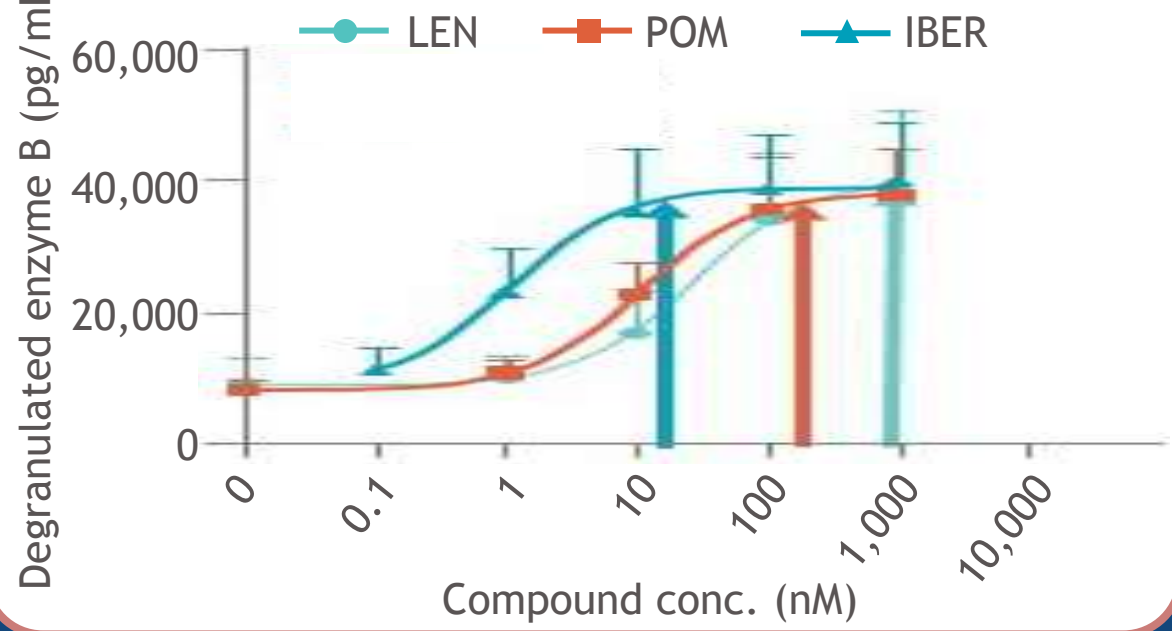
Hansen JD et al. J Med Chem. 2020;63:6648–76.
Matyskiela ME et al. J Med Chem. 2018;61:535–42.

IBER induces more potent immune stimulation than LEN/POM *(preclinical data)*

IL-2



Enzyme B



IBER induces cytokine secretion from PBMCs more potently than IMiD agents

Bort, bortezomib; Conc., concentration; IL-2, interleukin-2; len, lenalidomide; PBMC, peripheral blood mononuclear cell; pom, pomalidomide

Amatangelo M et al. ASH 2020;abstract 1359 (poster presentation).

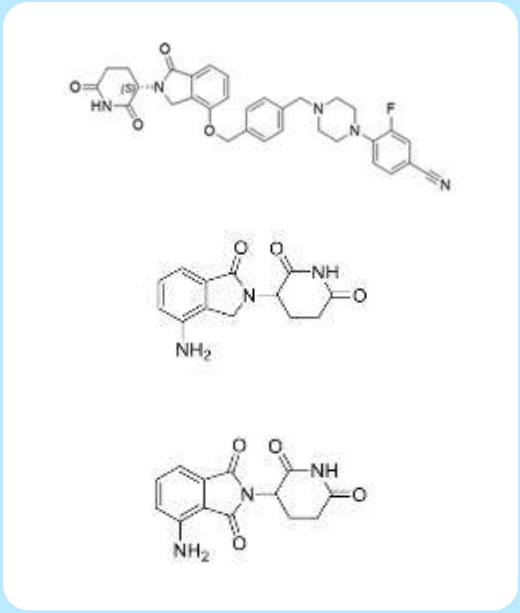
Novel CELMoD® agent: Mezigdomide (CC-92480) *(preclinical data)*

Mezigdomide (CC-92480) is a novel CELMoD® agent, with a distinct chemical structure from LEN and POM, higher affinity for CRBN, and more efficient substrate degradation

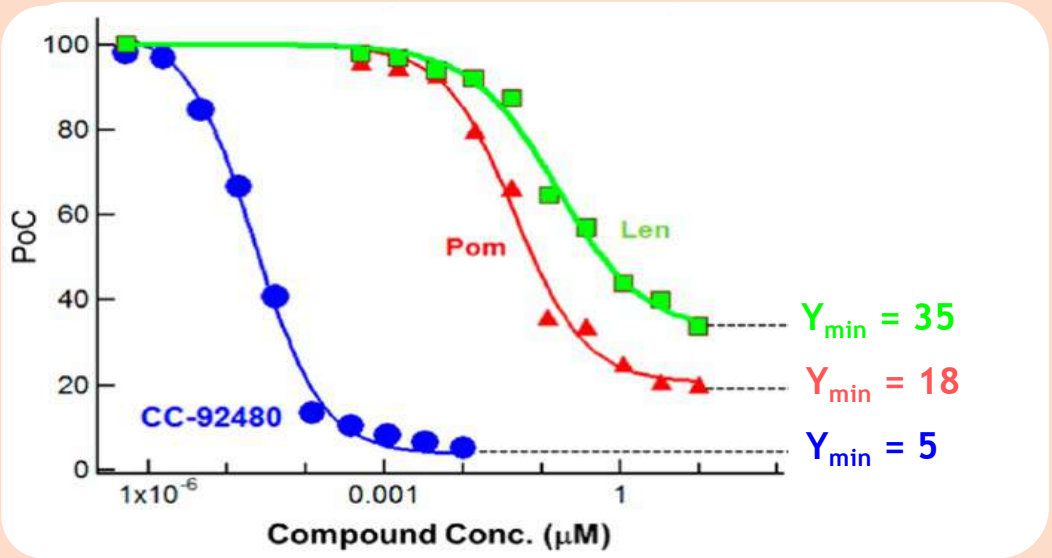
CC-92480

LEN

POM



Substrate (Aiolos) degradation efficiency



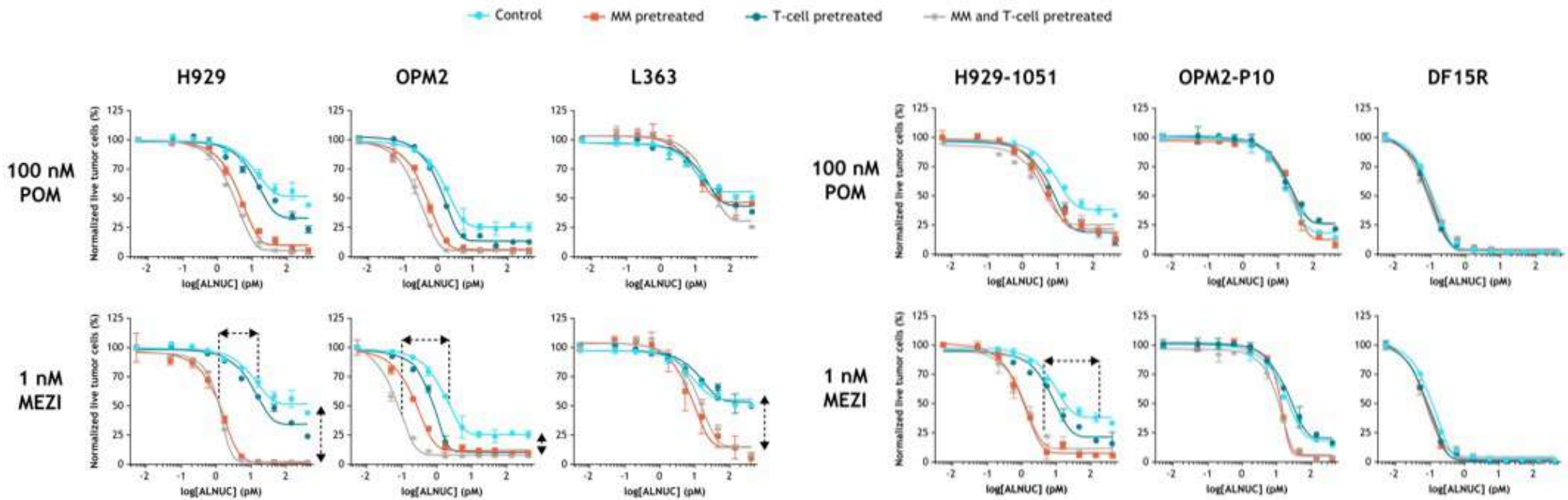
CC-92480 is an investigational product, currently not approved by any regulatory agency.

Y_{min} is the lowest point of the dose-response degradation curve and denotes the minimum percentage protein remaining

Hansen JD et al. J Med Chem. 2020;63:6648-76

Potential for synergy: CELMoD and T-cell redirecting therapies

Figure 3. Pretreatment of target MM cells with MEZI for 72 hours led to enhanced cytotoxic activity of ALNUC



Gaffney ASH 2022

3. Synergistic sequence of agents

- We are now using T-cell redirecting therapies in end-stage MM (prior line of therapy is highly heterogeneous)

- Can we improve?

  →A → B > B → A

  →Better understanding needed of best sequence of agents !

Understanding starting material and pre-infusion patient characteristics associated with clinical outcomes

Least favorable | Most favorable

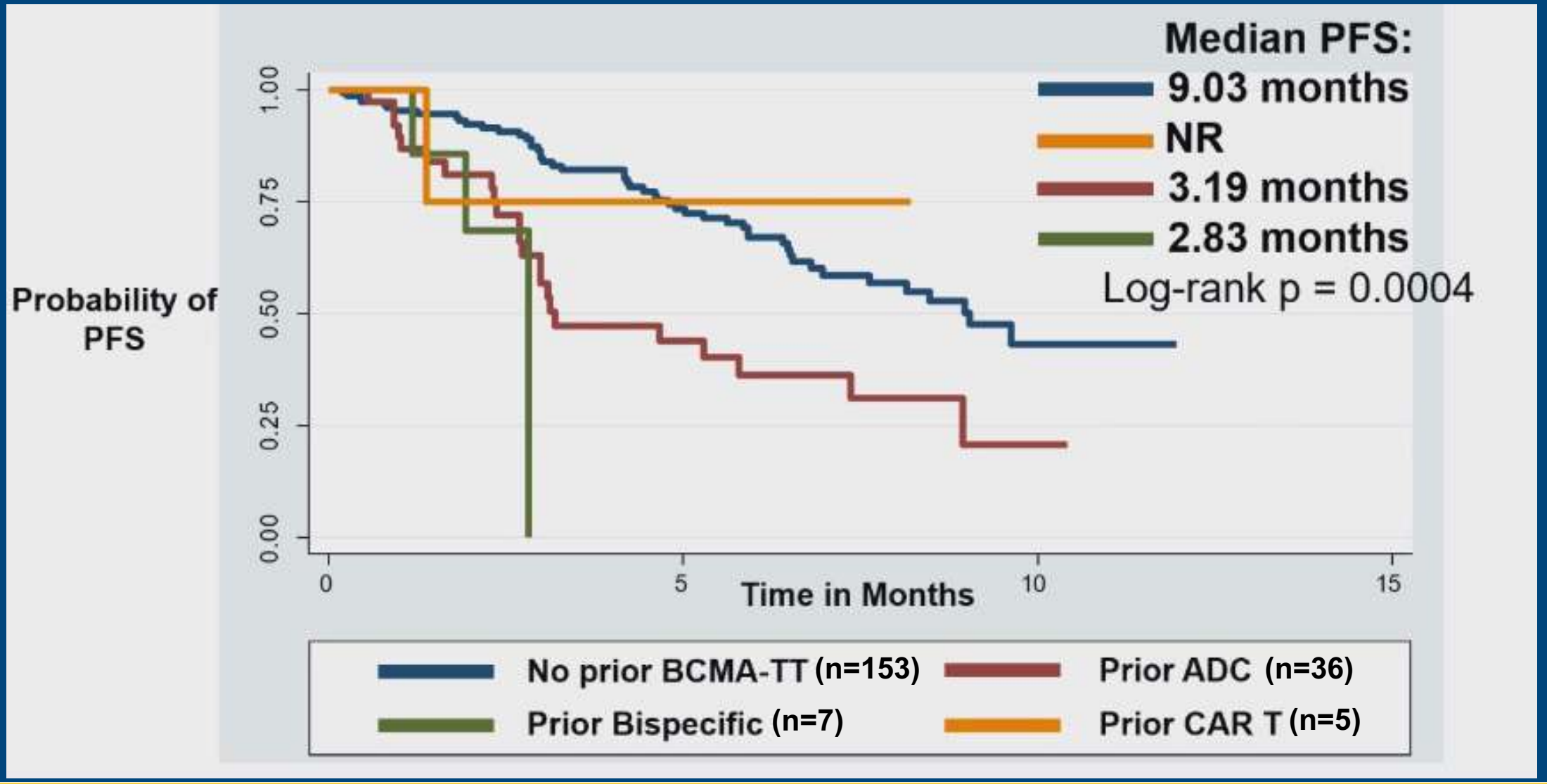
Feature	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Prior therapies	Recent alkylator, PI, TI ↑ Prior regimens	Recent alkylator, PI, TI	Recent alkylator, PI ↓ Prior regimens	Distant alkylator, PI, TI
Tumor burden	↑ sBCMA/M-protein	↑ sBCMA/M-protein ↑ LDH	↓ sBCMA/M-protein	↓ sBCMA/M-protein
Immune profile	↓ ALC ↑ Mono:Leuk	↑ ALC ↑ Mono:Leuk	↓ ALC ↓ Mono:Leuk	↑ ALC ↓ Mono:Leuk
Patient fitness	↓ Albumin ↓ Creatinine clearance	↓ Creatinine clearance	↑ Creatinine clearance	↑ Albumin ↓ Creatinine clearance
PBMC material	↓ CD3%	↓ CD4:CD8	↑ CD4:CD8 High quality phenotype	↑ CD3%
In-process	↓ Yield ↓ Early cell size	↓ Yield	↑ Yield ↑ Early cell size	↑ Yield
Drug product	↓ CD3/CAR% ↓ VCN	↓ CD3/CAR%	↑ CD3/CAR%	↑ CD3/CAR% ↑ VCN
Efficacy	mPFS: 3 mo CRR: 18%	mPFS: 7.9 mo CRR: 32%	mPFS: 11.7 mo CRR: 50%	mPFS: 14.5 mo CRR: 61%

Summary of patient and manufacturing features in each cluster colorized by their modeled effect on manufacturing and clinical outcomes.
ALC, absolute lymphocyte count; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; LDH, lactose dehydrogenase; leuk, leukocyte; mo, months; mono, monocytes; mPFS, median progression-free survival; M-protein, monoclonal protein; PBMC, peripheral blood mononuclear cells; PI, proteosome inhibitor; TI, topoisomerase inhibitor; VCN, vector copy number.

Low tumor burden, high ALC count, high cell yield, high CD3 count in the cell product, high % of CAR and distant alkylator therapy (ideally > 9 months) were associated with better outcomes after ide-cel

Rytlewski J et al. EHA 2022. Abstract#8021

PFS outcomes by type of prior BCMA-TT



ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; PFS, progression-free survival

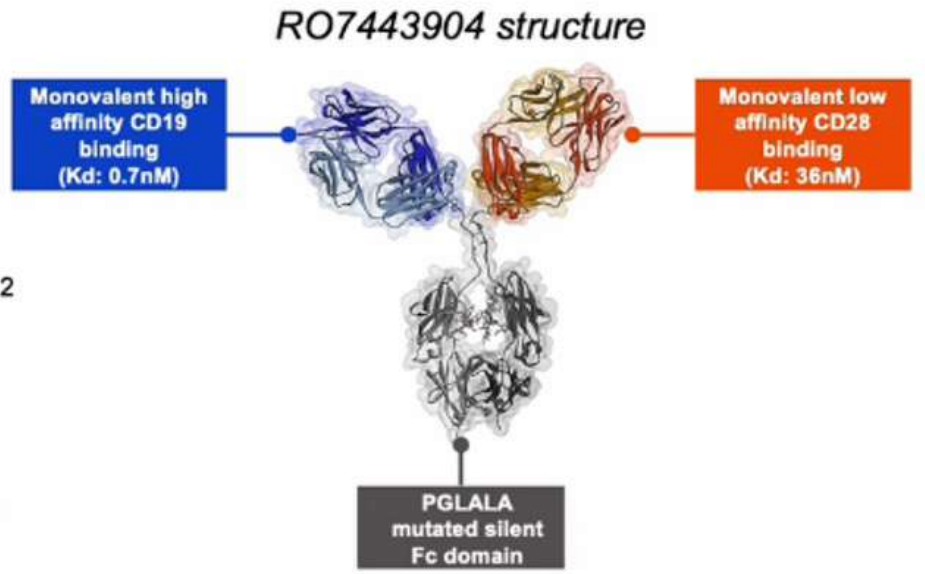
Ferreri C et al. ASH 2022;abstract 766 (oral presentation)

4. Next generation immunotherapies

Novel BsAb formats to improve response

- Include co-stimulation

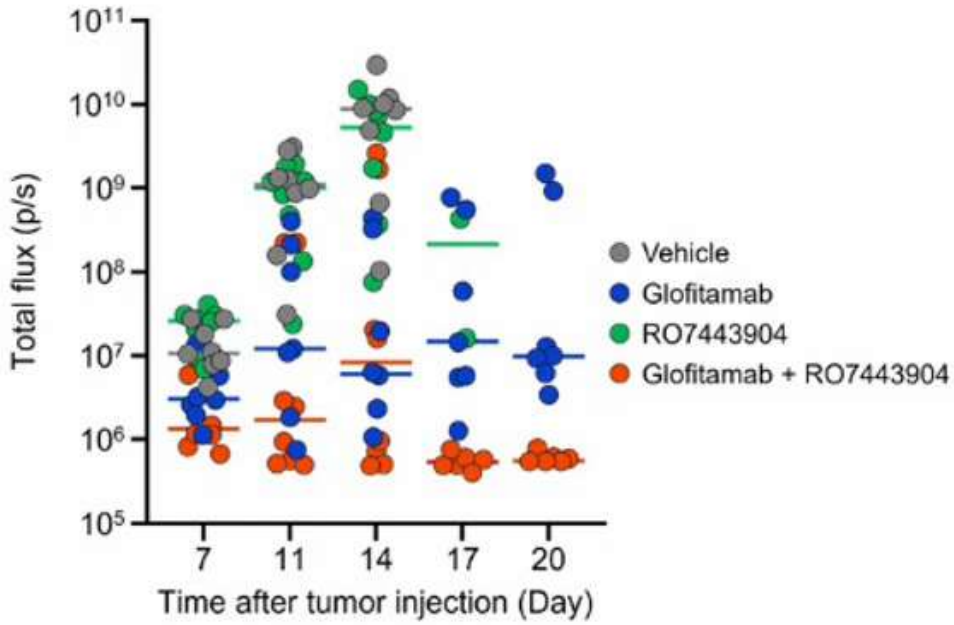
- RO7443904
  - CD19xCD28 costimulatory bispecific antibody-like fusion protein
  - designed to deliver a safe CD28 agonist signal[1]
  - activity strictly dependent on CD19 cross-linking
  - potential to augment activity of glofitamab in NHL[1,2]
- Glofitamab
  - CD20xCD3 T-cell engaging bispecific antibody[3]
  - significant single-agent activity in R/R indolent and aggressive NHL[4–6]



Costimulation improves antitumor activity

- Anti-tumor activity evaluated in mouse model of DLBCL
- RO7443904 + glofitamab > glofitamab alone
- No RO7443904 single-agent activity

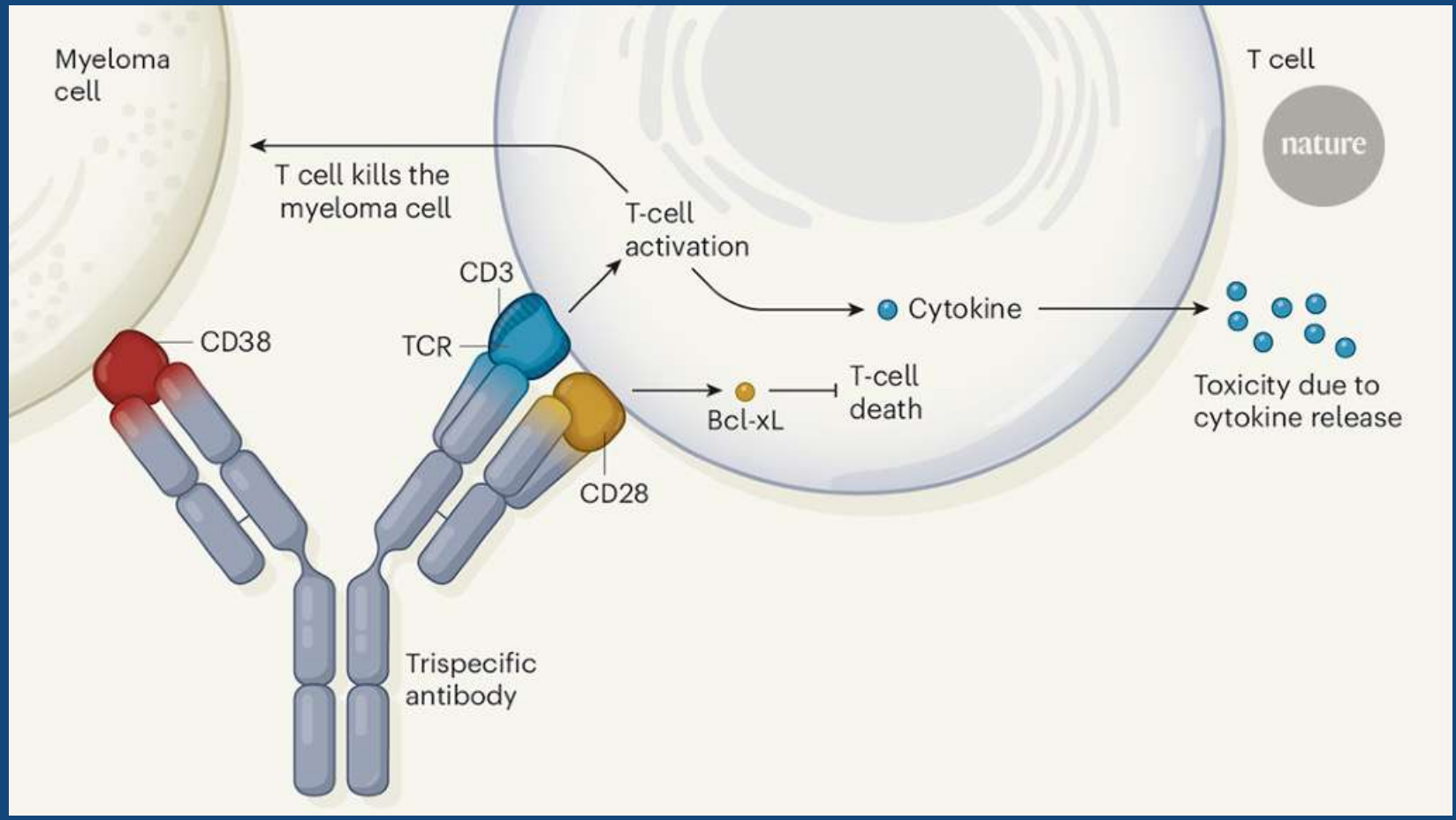
*Tumor growth inhibition in a mouse model of DLBCL**



*humanized NSG mice (7–8 mice/group) were implanted with WSU-DLCL2-Fluc lymphoma cells and treated once-weekly with glofitamab (0.15mg/kg IV) or RO7443904 (1mg/kg IV) alone or in combination starting at Day 3. Tumor growth was recorded with BLI measurement.
BLI, bioluminescence imaging; DLBCL, diffuse large B-cell lymphoma; IV, intravenous

Sam et al. ASH 2022. Poster 1360.

TsAbs: dual targeting

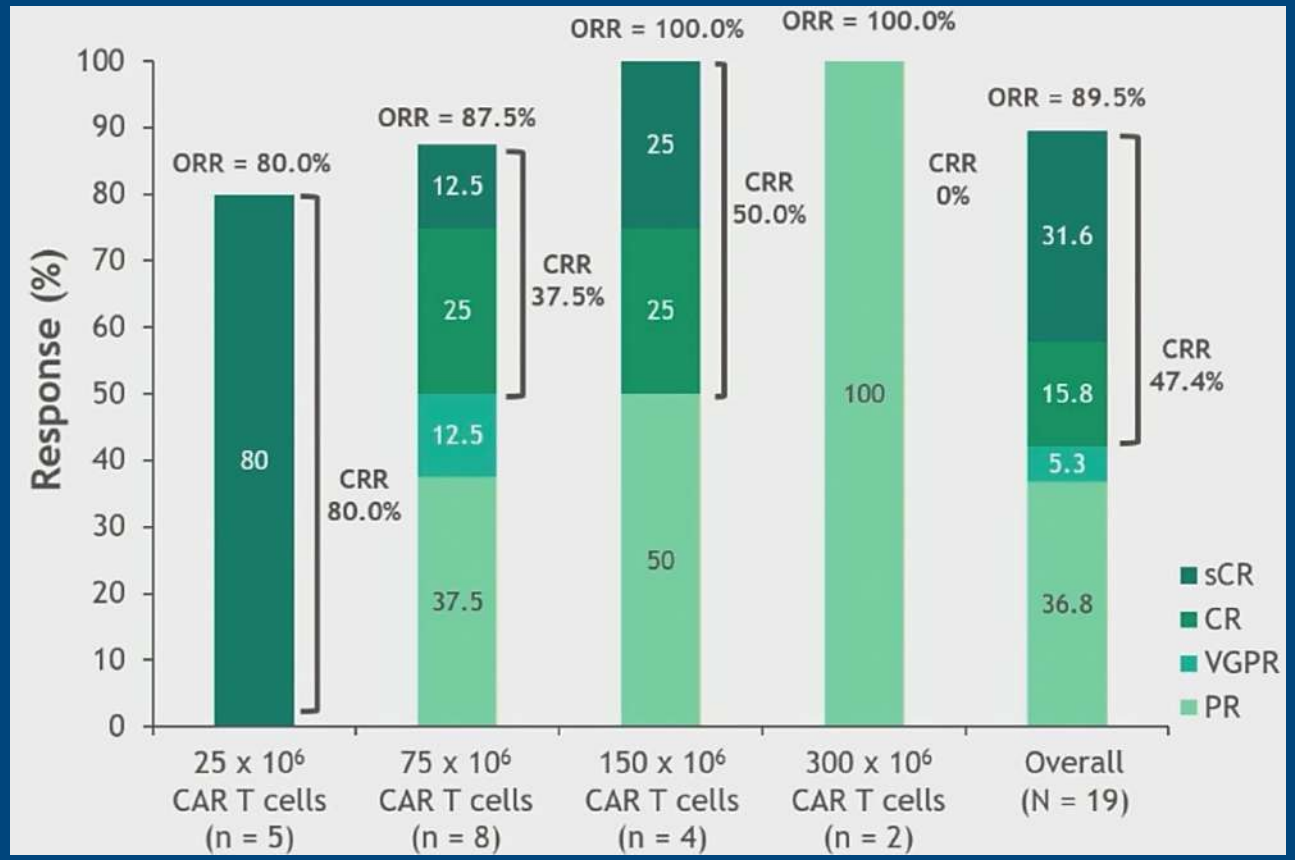


Wu Nature Cancer 2019

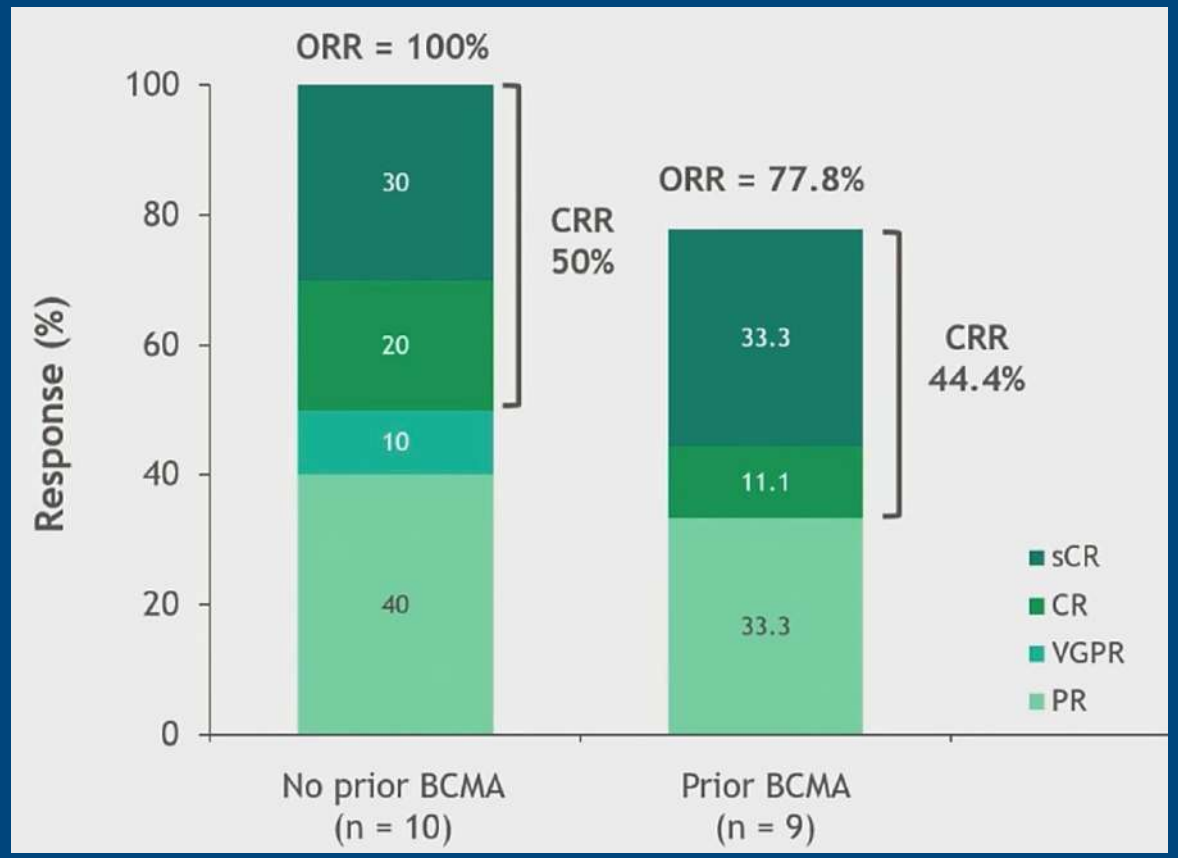
Novel CAR T formats to improve response

GPRC5D-targeting CAR-T cell therapy: Response

ORR



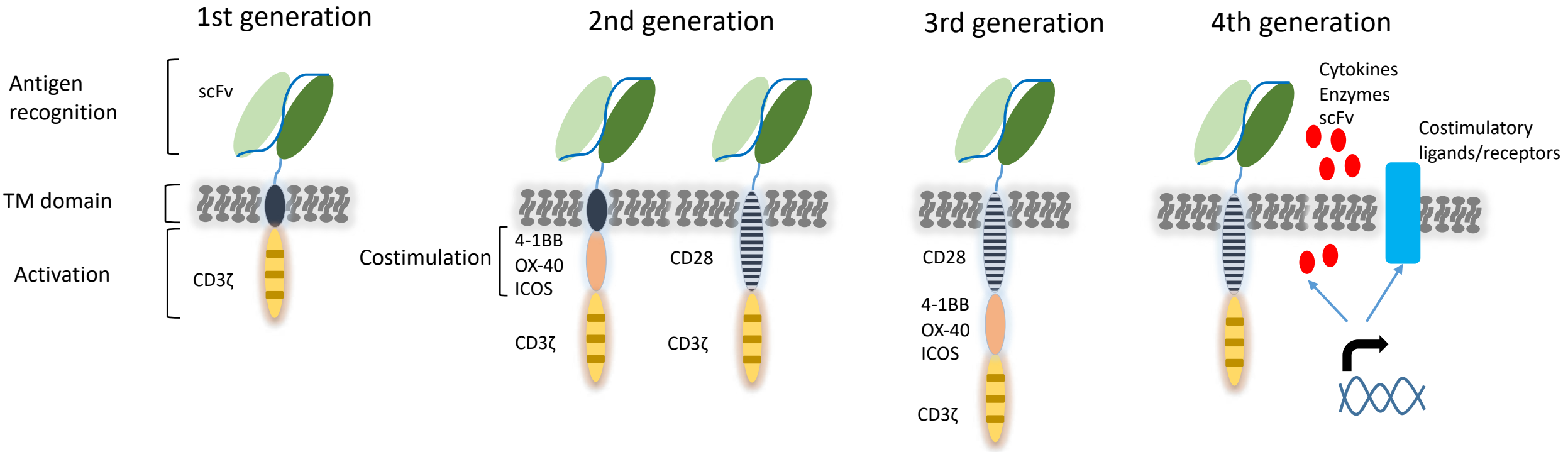
ORR in patients with and without experience of BCMA-targeting therapy



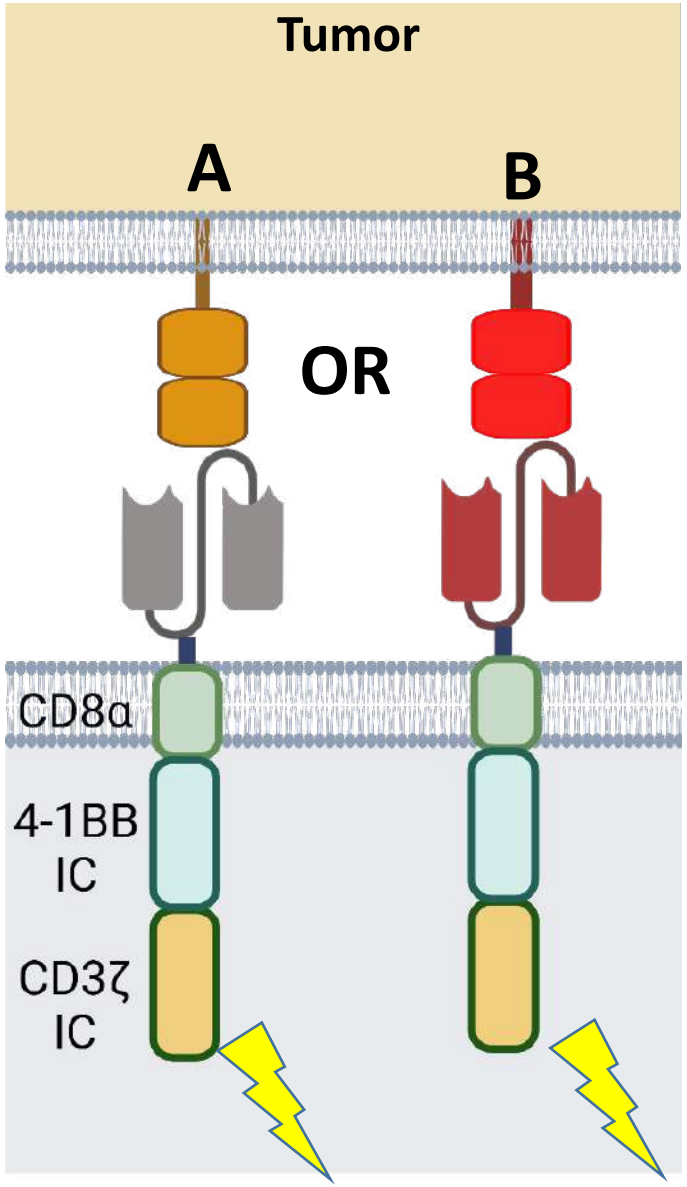
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRR, clinical response rate; ORR, overall response rate; PR, partial response; sCR, stringent response rate; VGPR, very good response rate

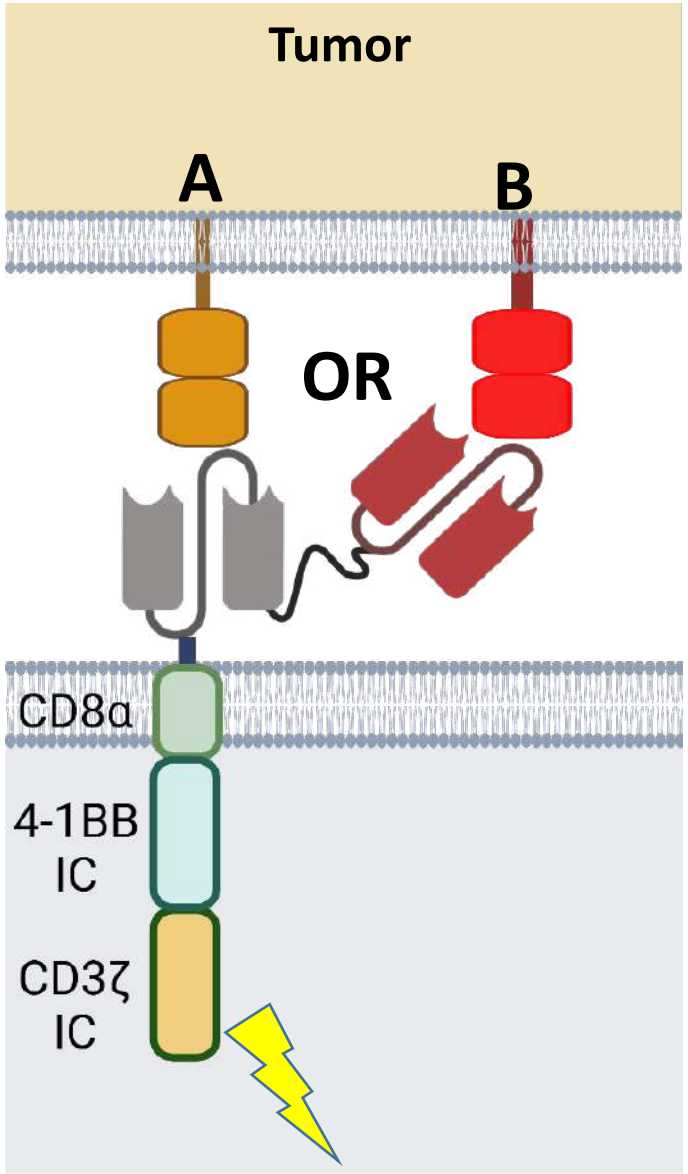
Berdeja J et al. ASH 2022;abstract 364 (oral presentation)

Chimeric antigen receptors



Multi-targeting with CARs: OR Gates



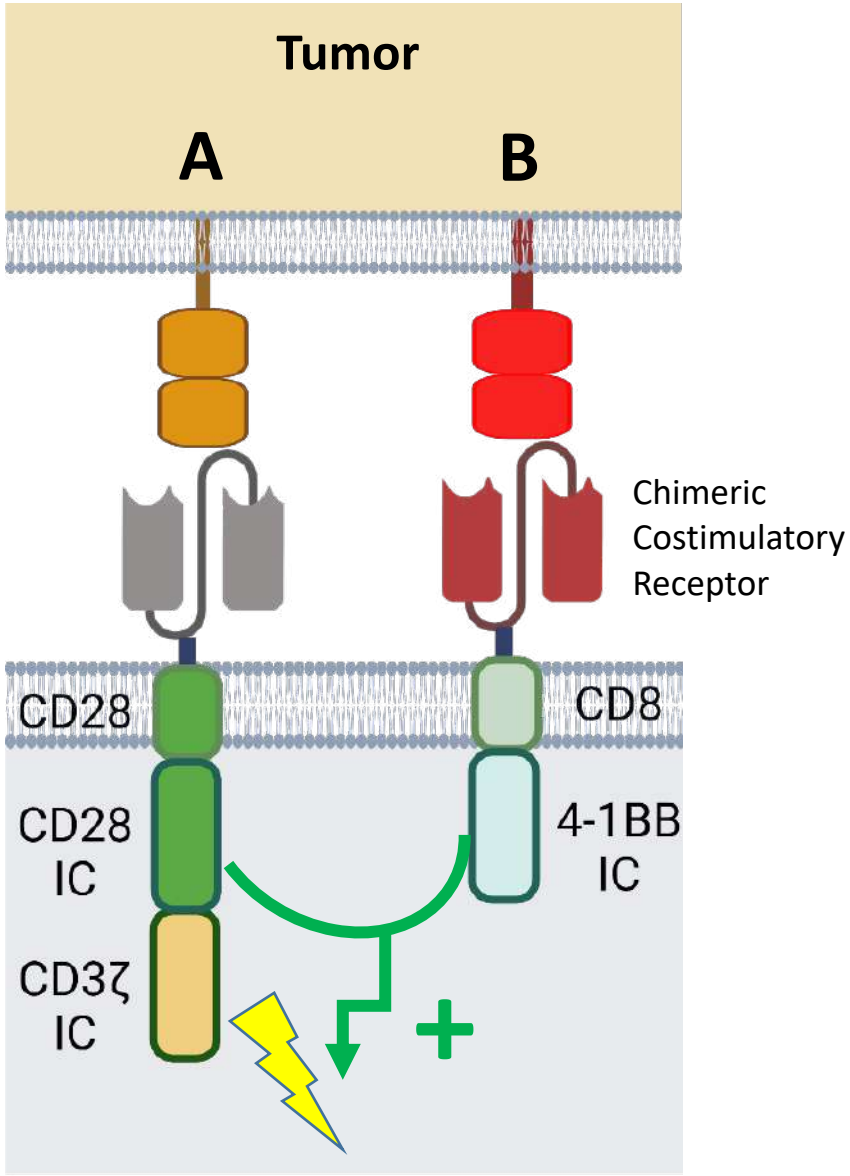


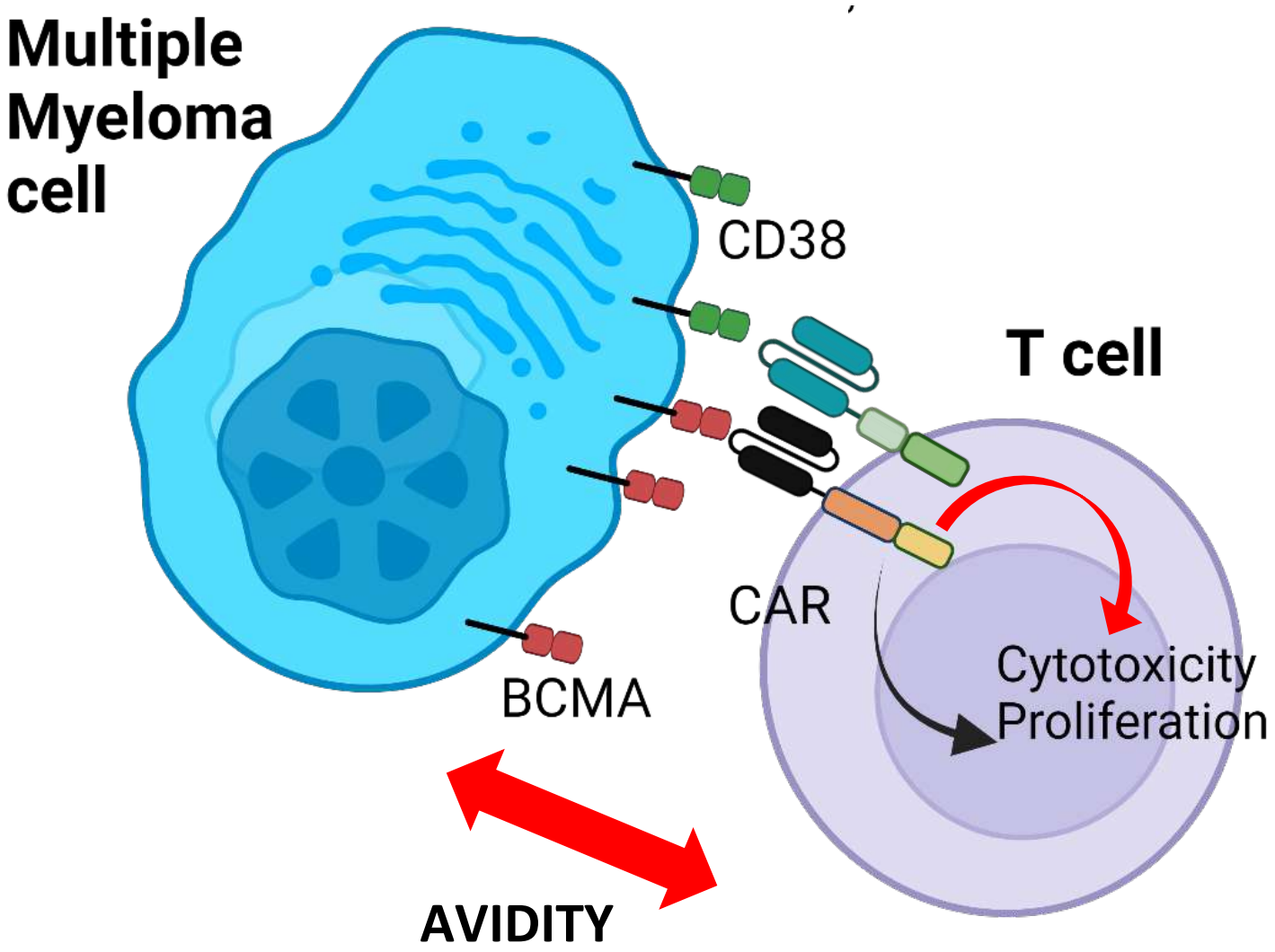
- Restricted to tumor-specific antigens
- No clinical proof of overcoming antigen low relapses
- Multivalent binding leads to better anti-tumor effect
  - Mechanism?
  - Binding requirements?
  - Receptor design requirements?

A and B Tumor specific

Themeli Sci Trans Med 2021

The CAR+CCR strategy: the BETTER gate





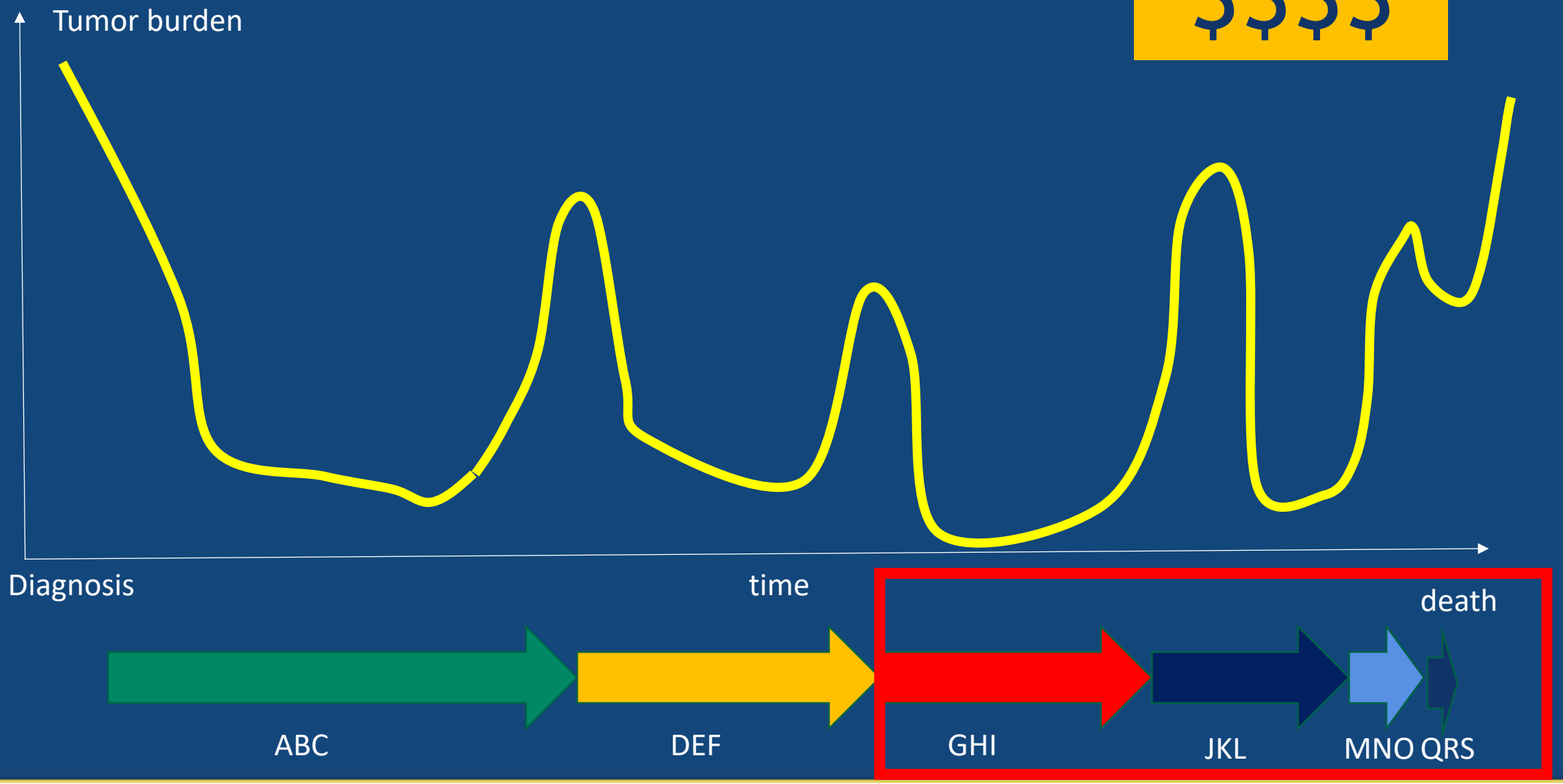
Themeli Sci Trans Med 2021

- 1. Earlier use of T-cell redirecting therapies
- 2. Combination strategies
- 3. Synergistic sequence of agents
- 4. Next generation of immunotherapies

Future….

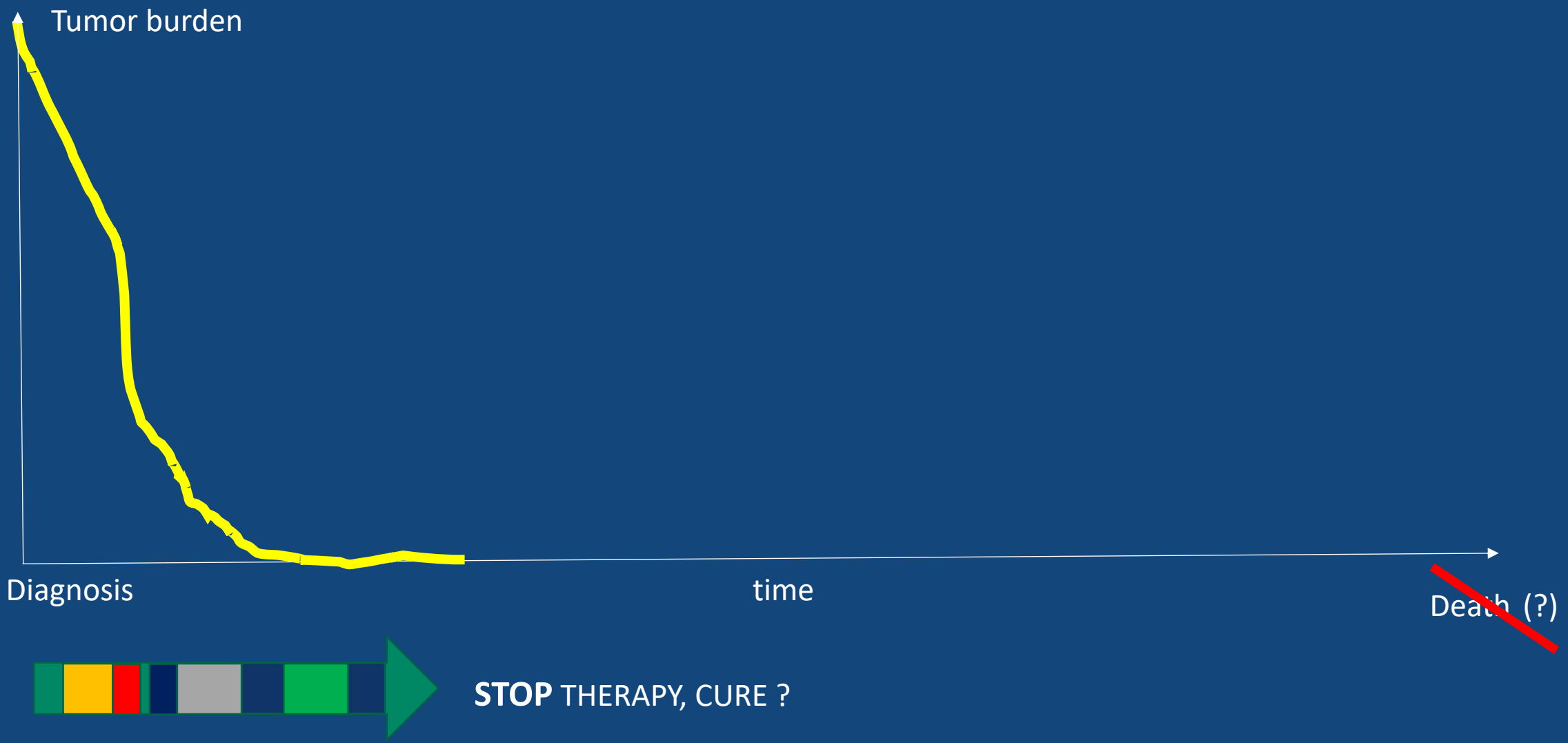
How we currently treat MM

$$$$



van de Donk N, personal opinion.

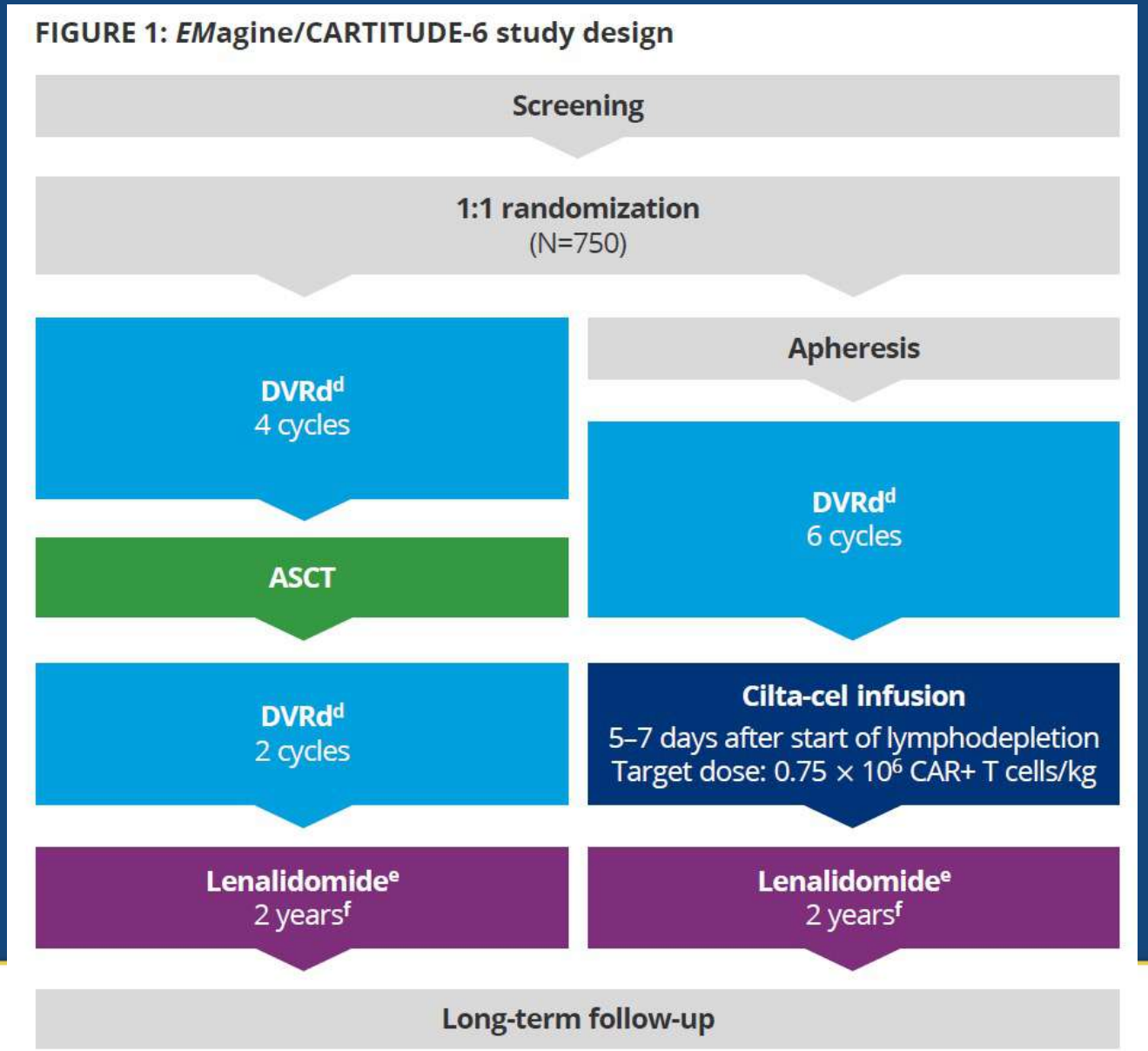
How we may treat MM in the future…..



STOP THERAPY, CURE ?

van de Donk N, personal opinion.

EMN28 (EMAGINE; CARTITUDE-6)



Boccadoro ASH 2022

Study Design

MajesTEC-4
EMN30/64007957MMY3003

Key eligibility criteria

- Newly Diagnosed MM
- Received 4-6 cycles of 3 or 4 drug-induction therapy that includes a PI and/or an IMiD with or without anti-CD38 antibody and a single or tandem ASCT

N=1500
1:1:1 randomization

Arm A: Tec-Len
(n=500)
Tec: C1-26 (C13-26 only participants who have not achieved CR or better)
Len: C2-26 (option to continue until PD per investigator's discretion)

Arm B: Len
(n=500)
Len: C1-26 (option to continue until PD per investigator's discretion)

Arm B: Teclistamab
(n=500)
Tec: C1-26

Primary endpoint:

- PFS

Secondary endpoints:

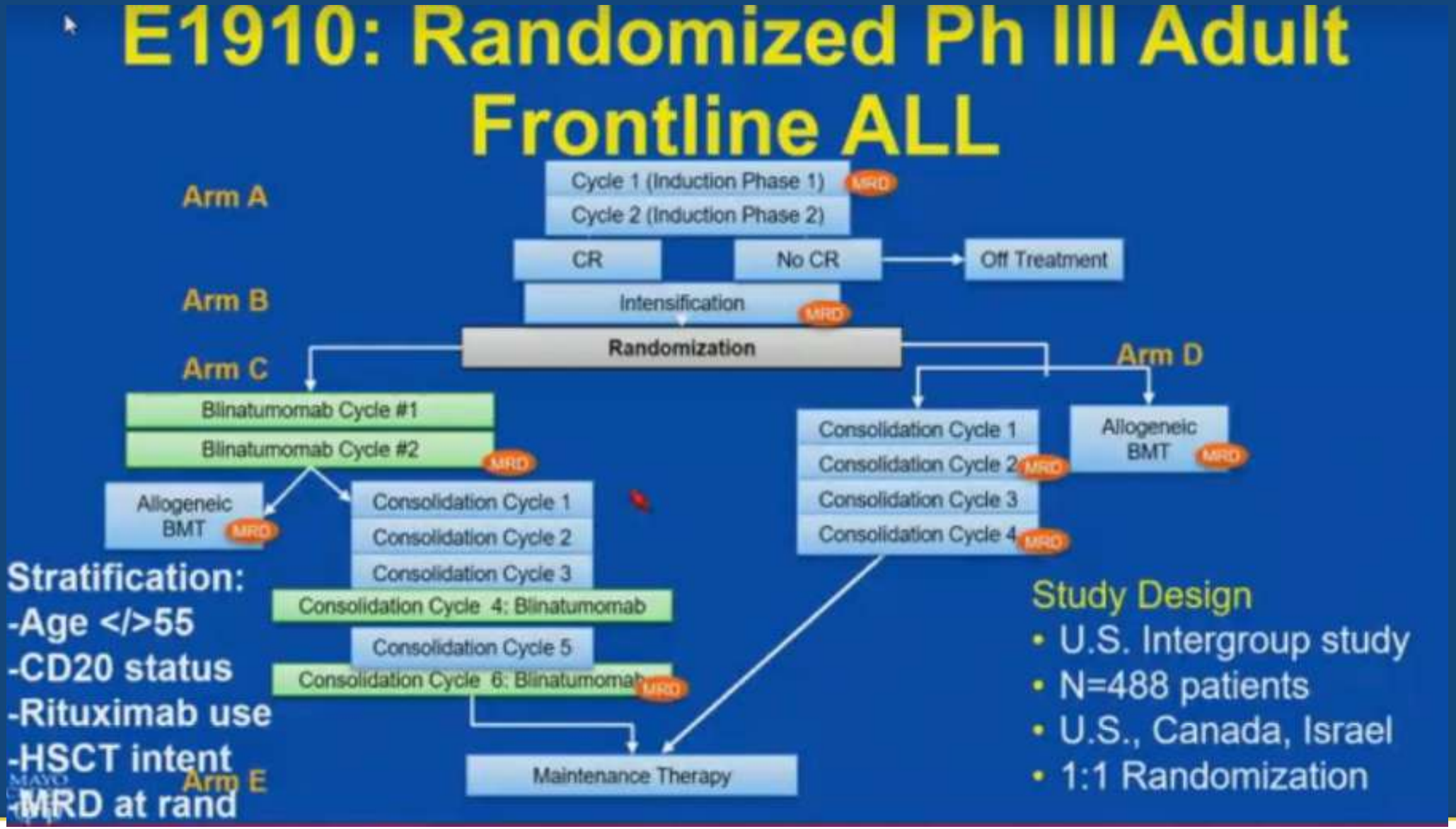
- CR+ rate
- MRD negativity rate
- Sustained MRD negativity
- CR conversion
- MRD conversion
- OS
- PFS2

heads

EMN
EUROPEAN MYELOMA NETWORK

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

ALL

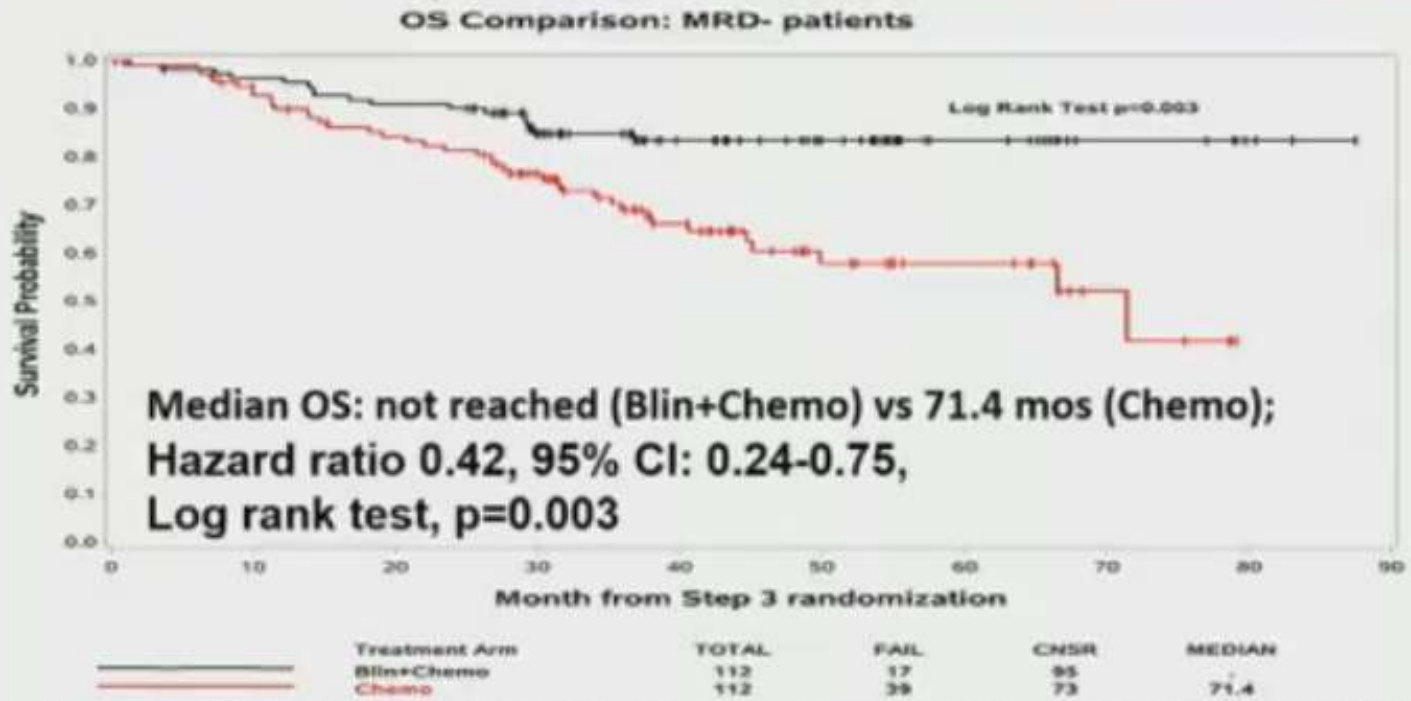


Litzow ASH 2022

ALL

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Overall Survival Comparison: MRD negative patients



Deaths on Blin+Chemo Arm=17 (2° to ALL=8, NRM=9), Chemo Arm=39 (2° to ALL=20, NRM=17, Unknown=2)

Litzow ASH 2022

Conclusions

- T-cell redirecting immunotherpies are improving survival of MM patients
  - EARLIER USE
  - COMBINATIONS
  - SEQUENCE OPTIMALIZATION
  - NEXT GEN

van de Donk N, personal opinion.