Biology, indications and responses-CAR-T

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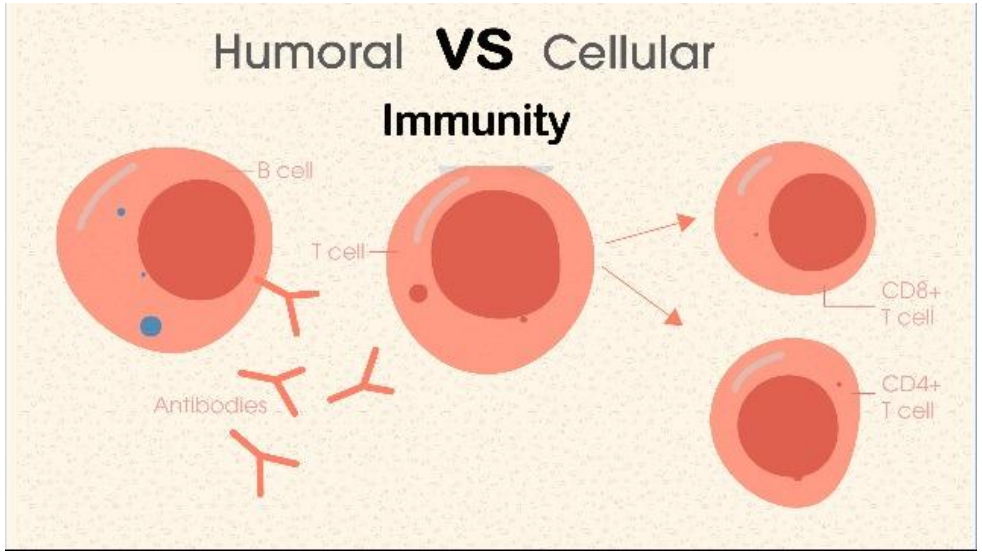
Rambam
13.11.2025

The biology behind the CAR

The specific immune response may be divided into two parts:

(1)the humoral response

(2)the cellular response



Both are mediated via lymphocytes!

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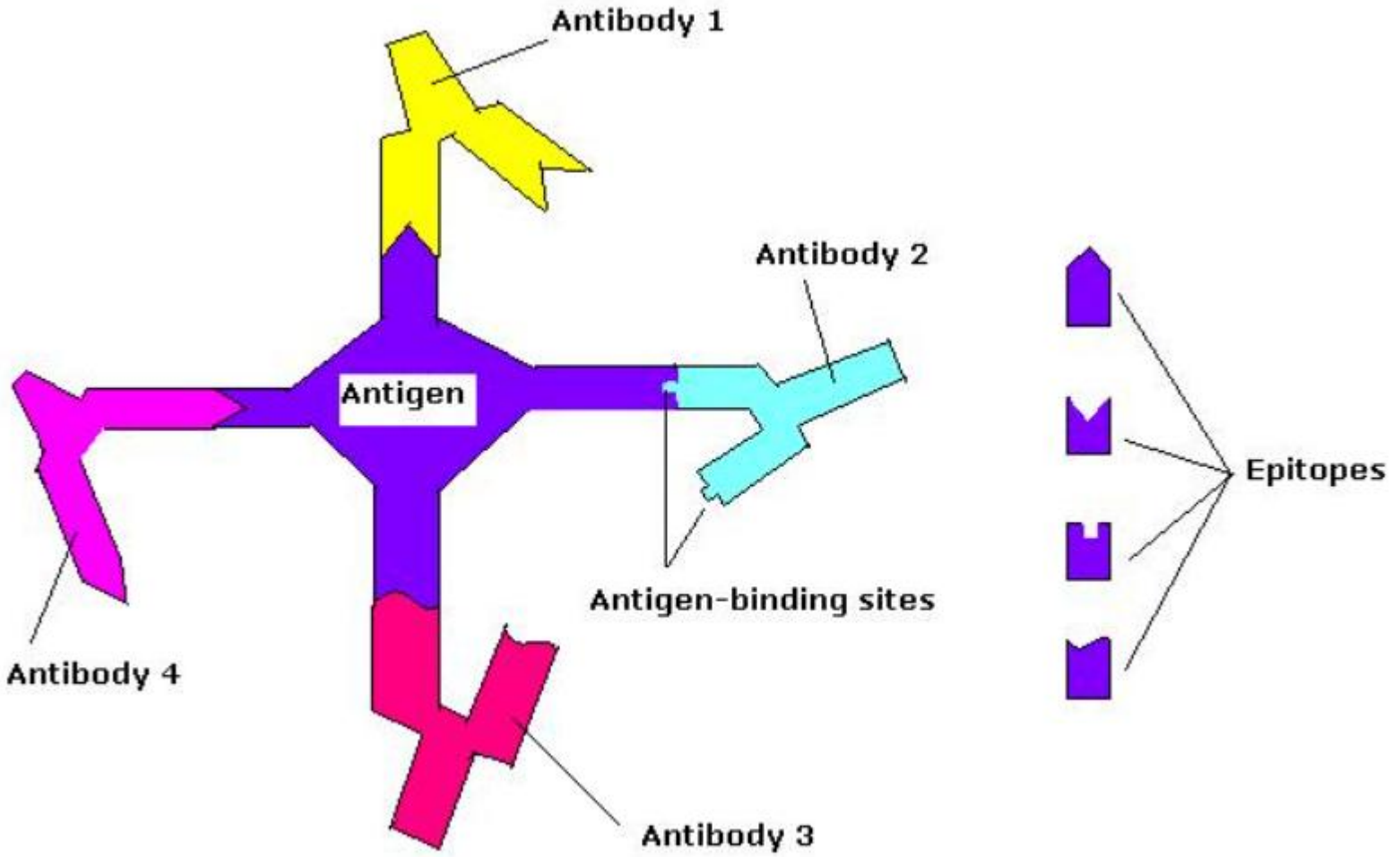
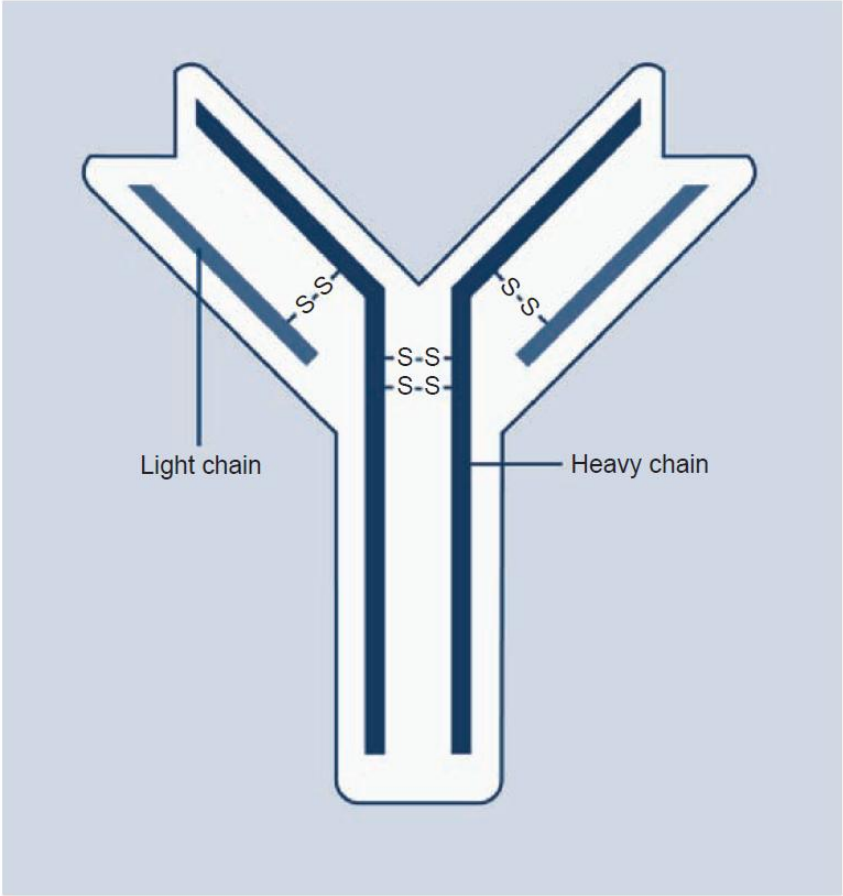


Antigen

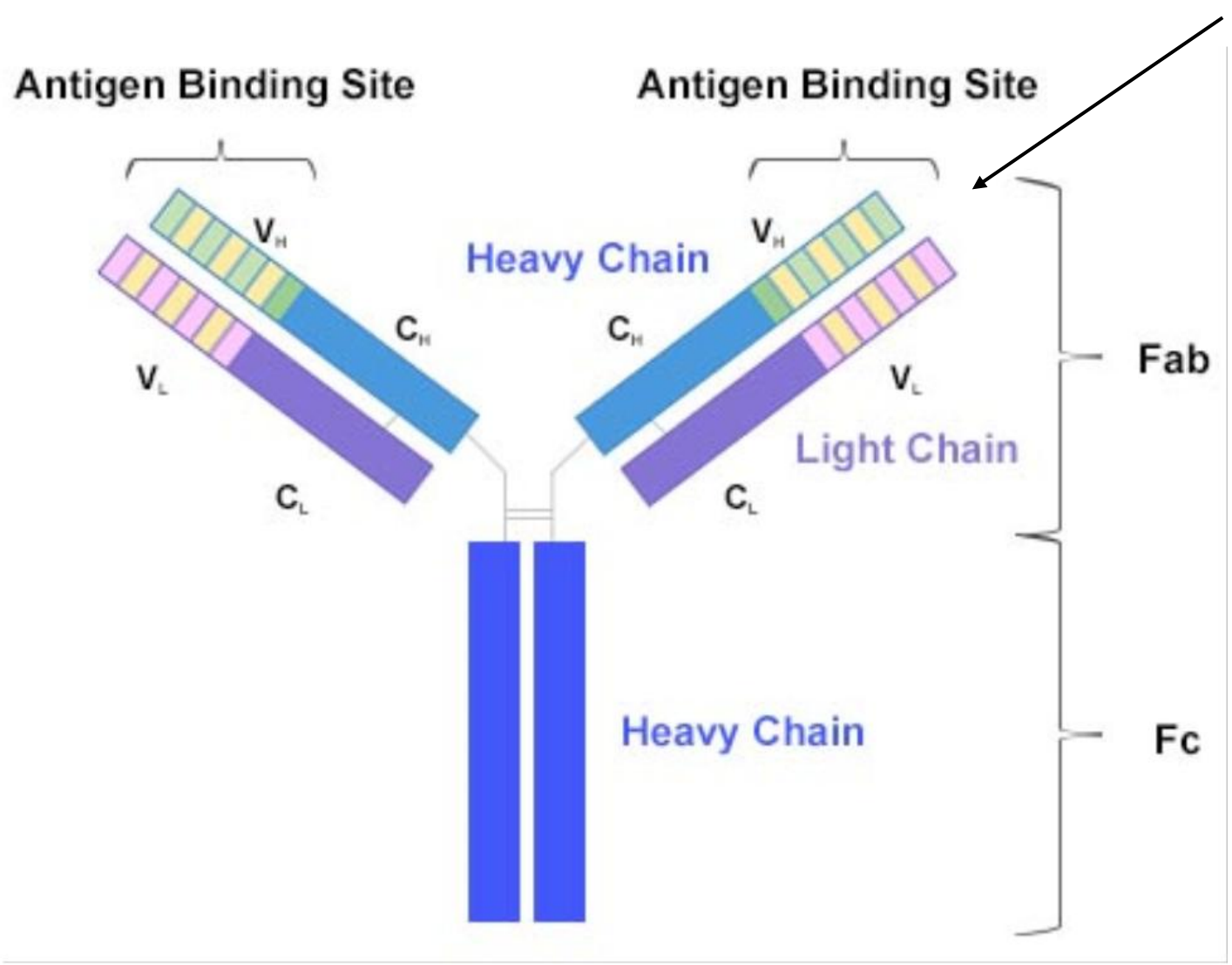
- Some low-molecular-weight molecules called *haptens* are unable to evoke an immune response but can react with existing antibodies.
- These molecules need to be coupled to a carrier molecule to be antigenic.
- Certain structures such as lipids and DNA are generally poor antigens.

Antibody

2 H chains- connected by disulfide bond between 2 cysteine residues
2 L chains



Antibody



Idiotype determinant

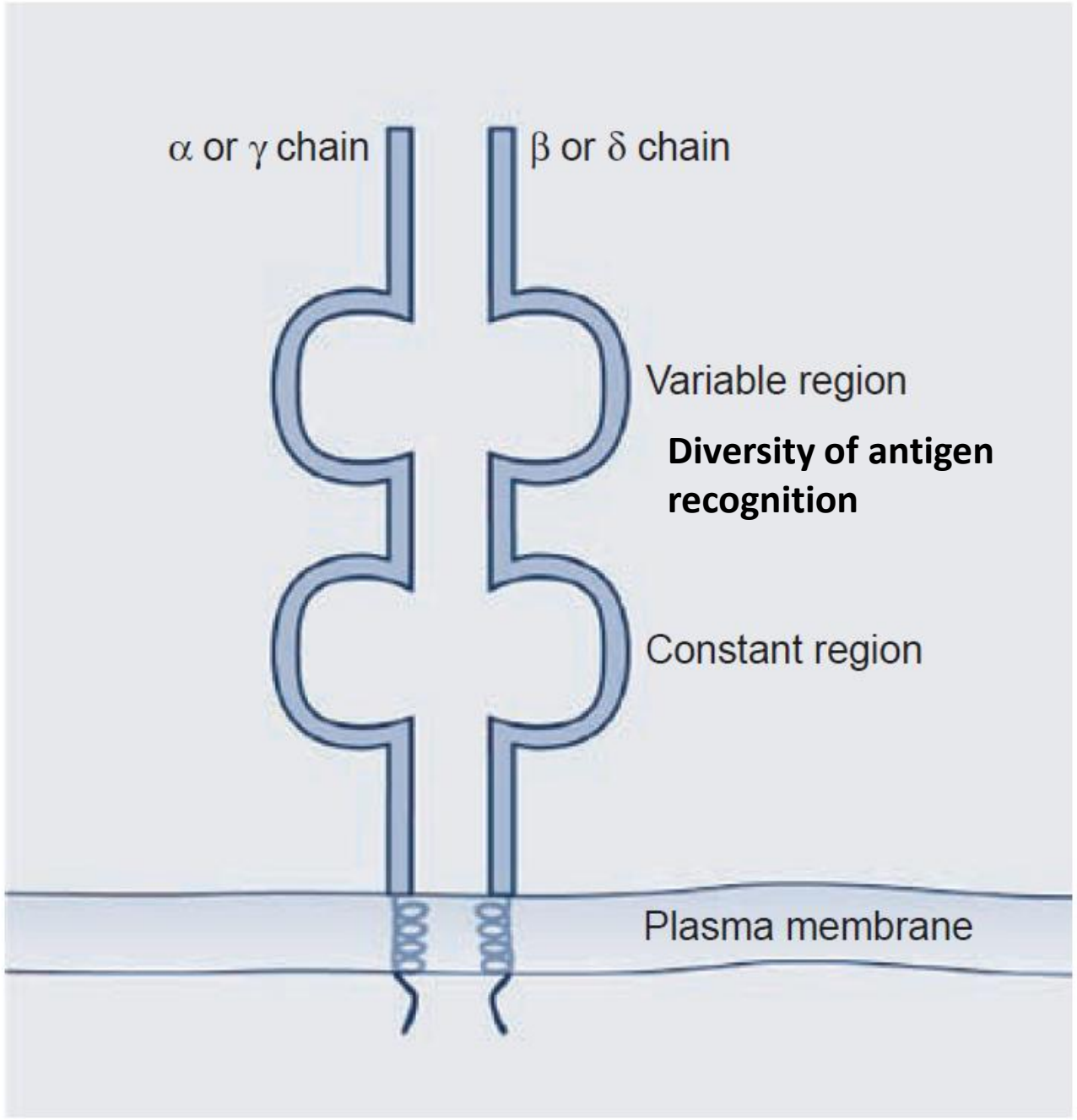
Variable region

Constant region

T cell

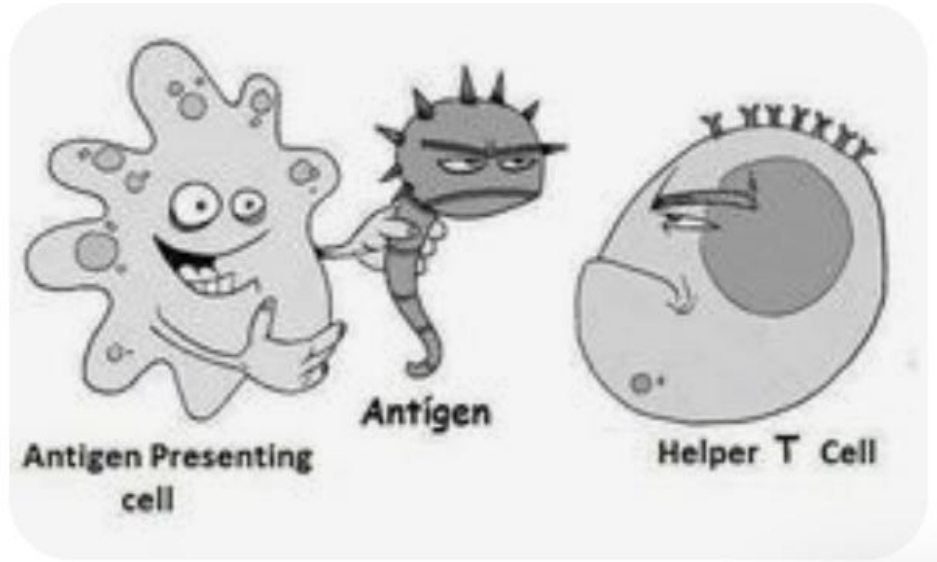
- Each T cell is also committed to a given antigen and recognizes it by TCRs.
- They may have TCR composed of gamma and delta chains or TCR composed of another heterodimer of alpha and beta chains.
- These TCR are associated with a group of transmembrance proteins on the CD3 molecule, which takes the antigen recognition signal inside the cell.

TCR



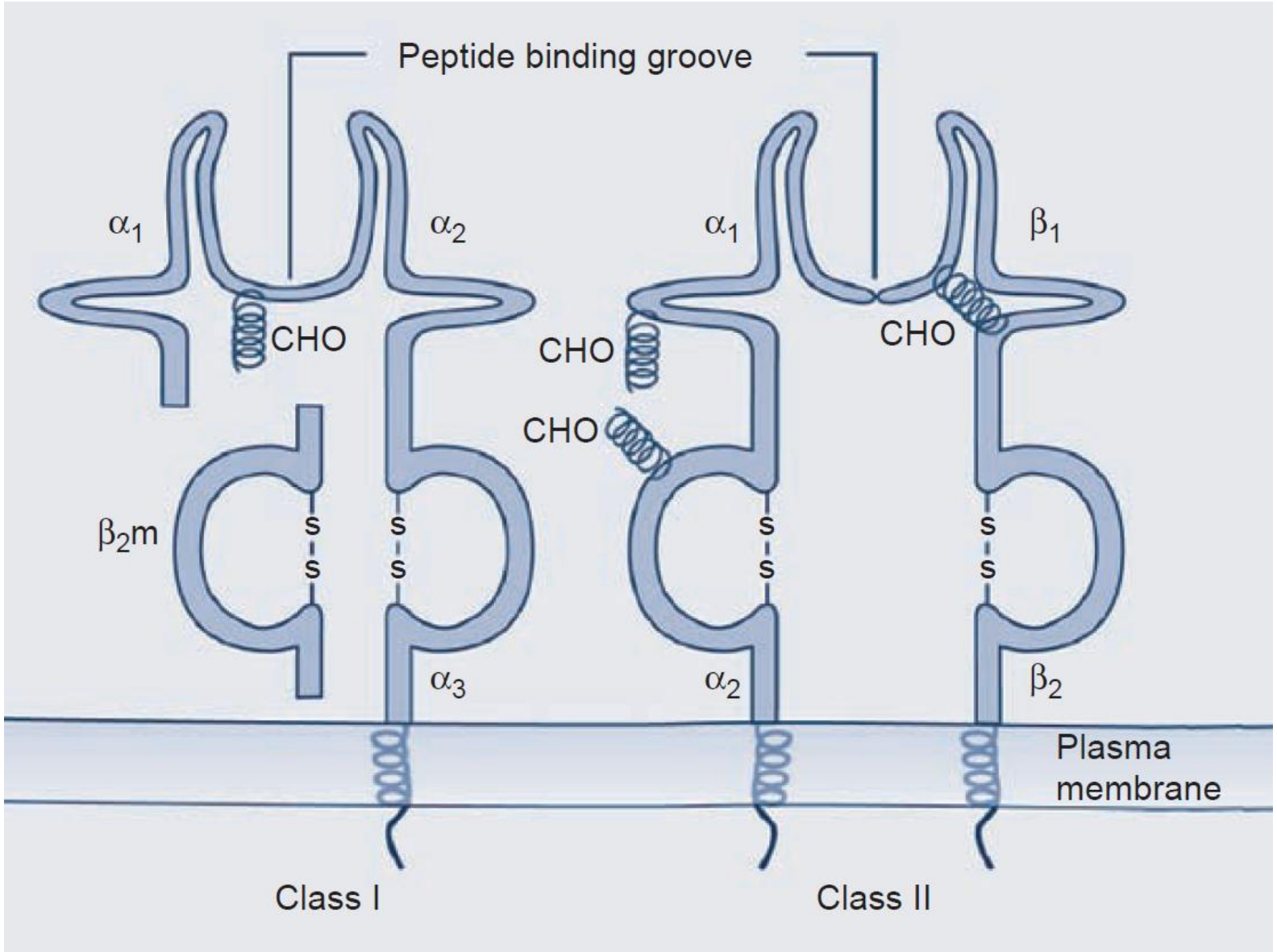
- Signal transduction via the CD3 complex is regulated by a series of kinases, which are associated with the tails of the CD3–TCR complex and regulate phosphorylation.

How do T cells recognize peptides?


Antigen Presenting cell
Antigen
Helper T Cell

MHC- major histocompatibility complex

- TCR complex recognize small peptides presented by MHC on T cells



MHC- major histocompatibility complex

- Human histocompatibility antigens are also known as human leucocyte antigens (HLA), a term that is synonymous with the MHC complex.
- These antigens are cell surface glycoproteins classified as type I or type II.
- They can produce genetic polymorphism with multiple alleles at each site, thus permitting a great deal of genetic variability between given individuals

MHC- major histocompatibility complex

- Helper T cells (CD4) recognize class II antigens while suppressor cytotoxic T cells (CD8) recognize class I antigens.

- Because of the rather low affinity of the reactions, recognition of processed antigen alone is not sufficient to activate T cells.

- Soluble interleukins are needed to complete the picture and are generated during the antigen
- processing.

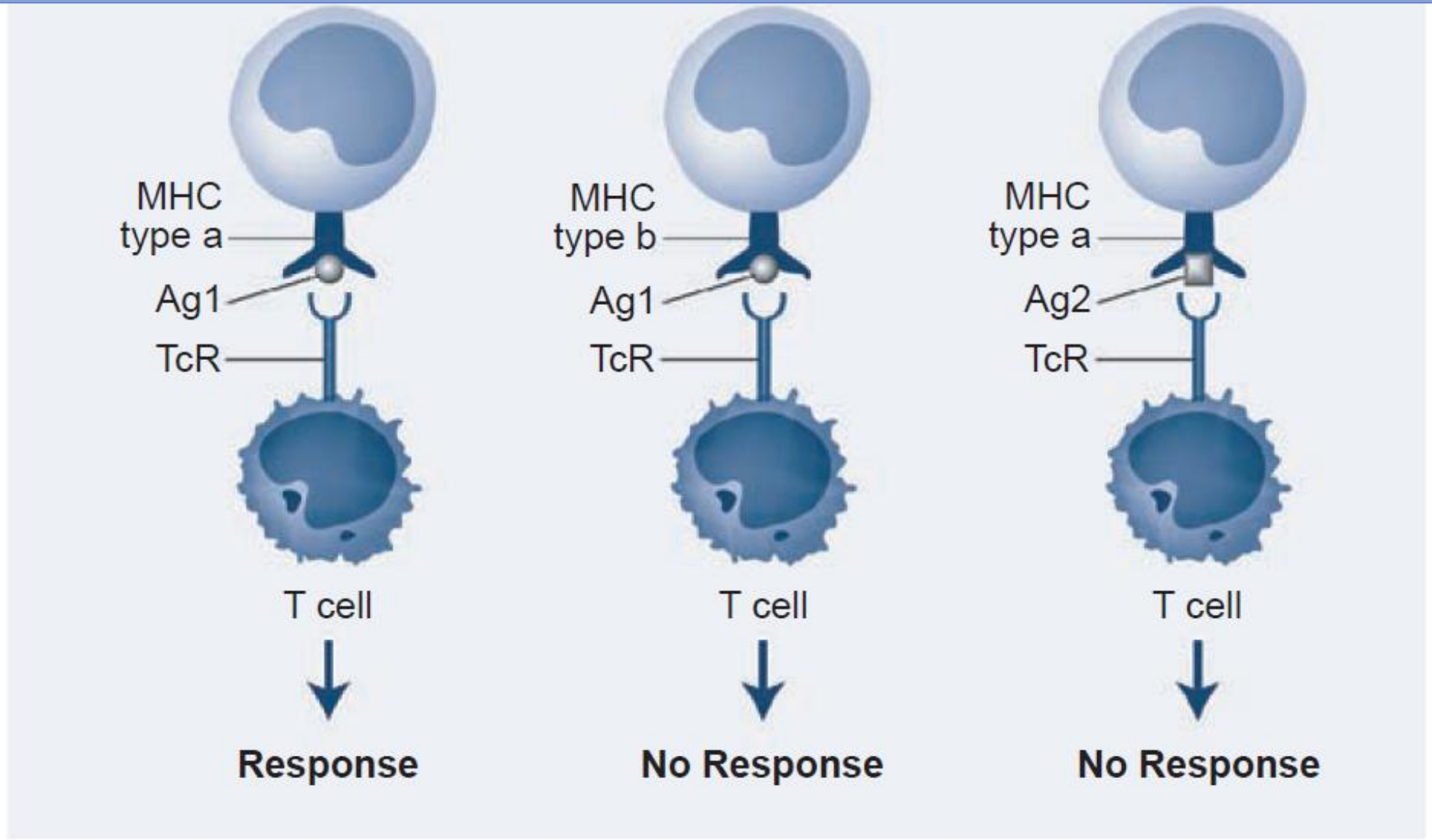
MHC- major histocompatibility complex

- Recognition of antigen by T cells is **MHC restricted.**
- Therefore, any given individual is only able to recognize antigen as part of a complex of antigenic peptide and self.

MHC- major histocompatibility complex

APC

T CELL



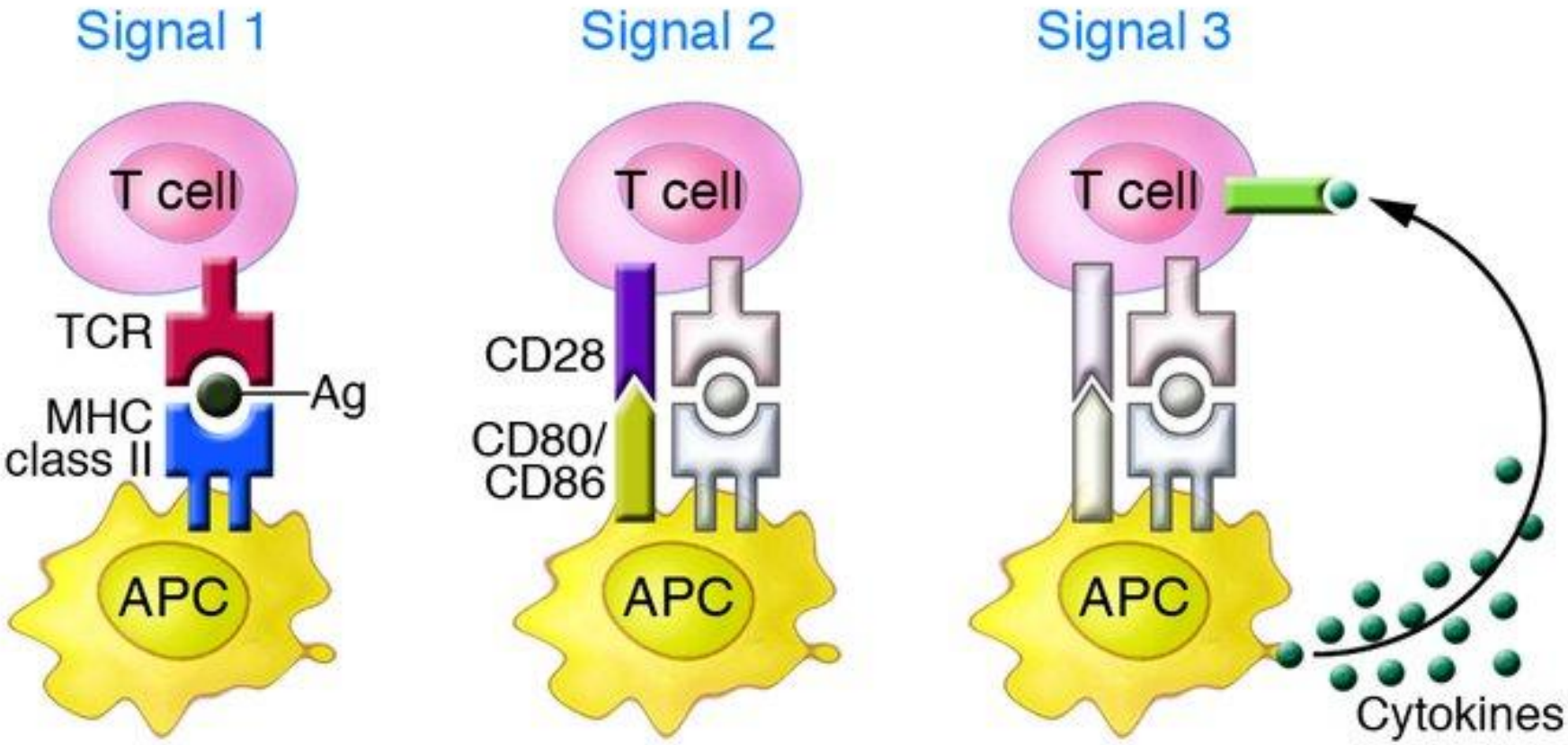
MHC- major histocompatibility complex

MHC class I	MHC class II
Comprised of an MHC-encoded a chain and a b2-microglobulin chain	Comprised of MHC-encoded a and b chains
Present on most cells	Present only on antigen-presenting cells
Bind endogenous antigens synthesized in a cell	Binds exogenous antigens
Present antigen to cytotoxic T cell lymphocytes	Present antigen to helper T cell lymphocytes
Bind CD8 adhesion molecules on cytotoxic T cells	Bind CD4 adhesion molecules on helper T cells
Presence of foreign or over-abundant antigens targets cell for destruction	Presence of foreign antigens induces antibody production, and attracts immune cells to area of infection

MONOCYTES. MACROPHAGES. B CELLS DENDRITIC

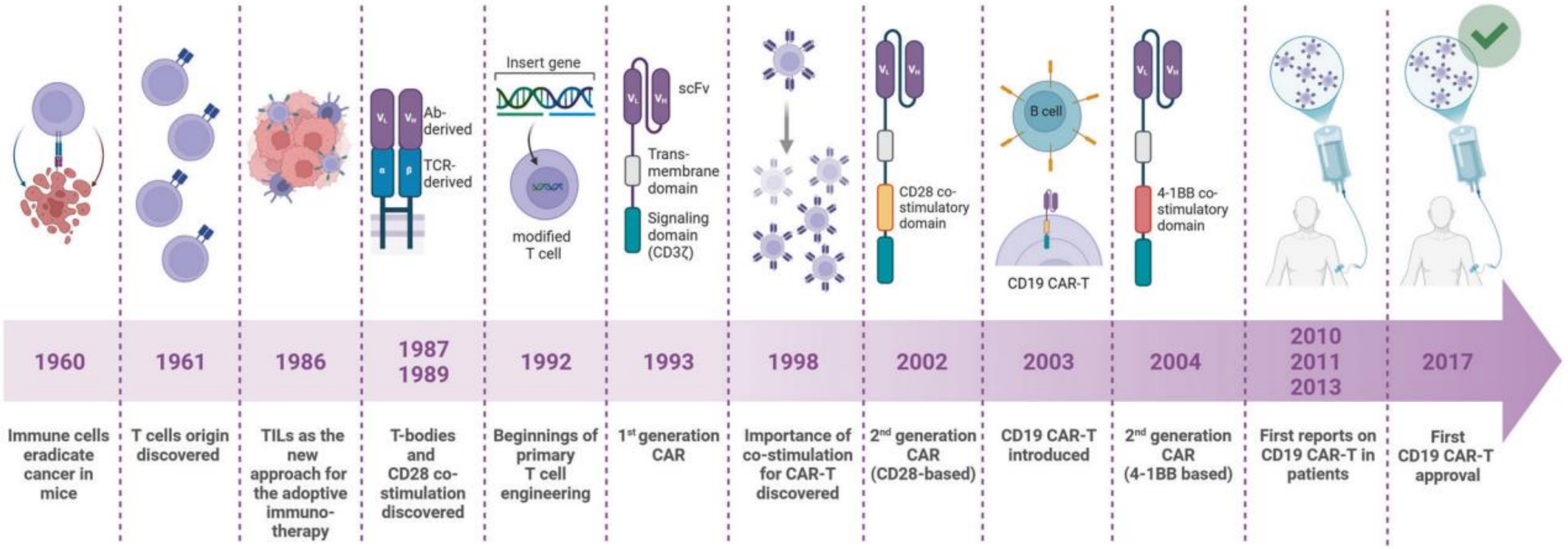
Is the binding enough for the T cell????

Figure 1: APC-derived cytokines and T cell polarization in autoimmune inflammation



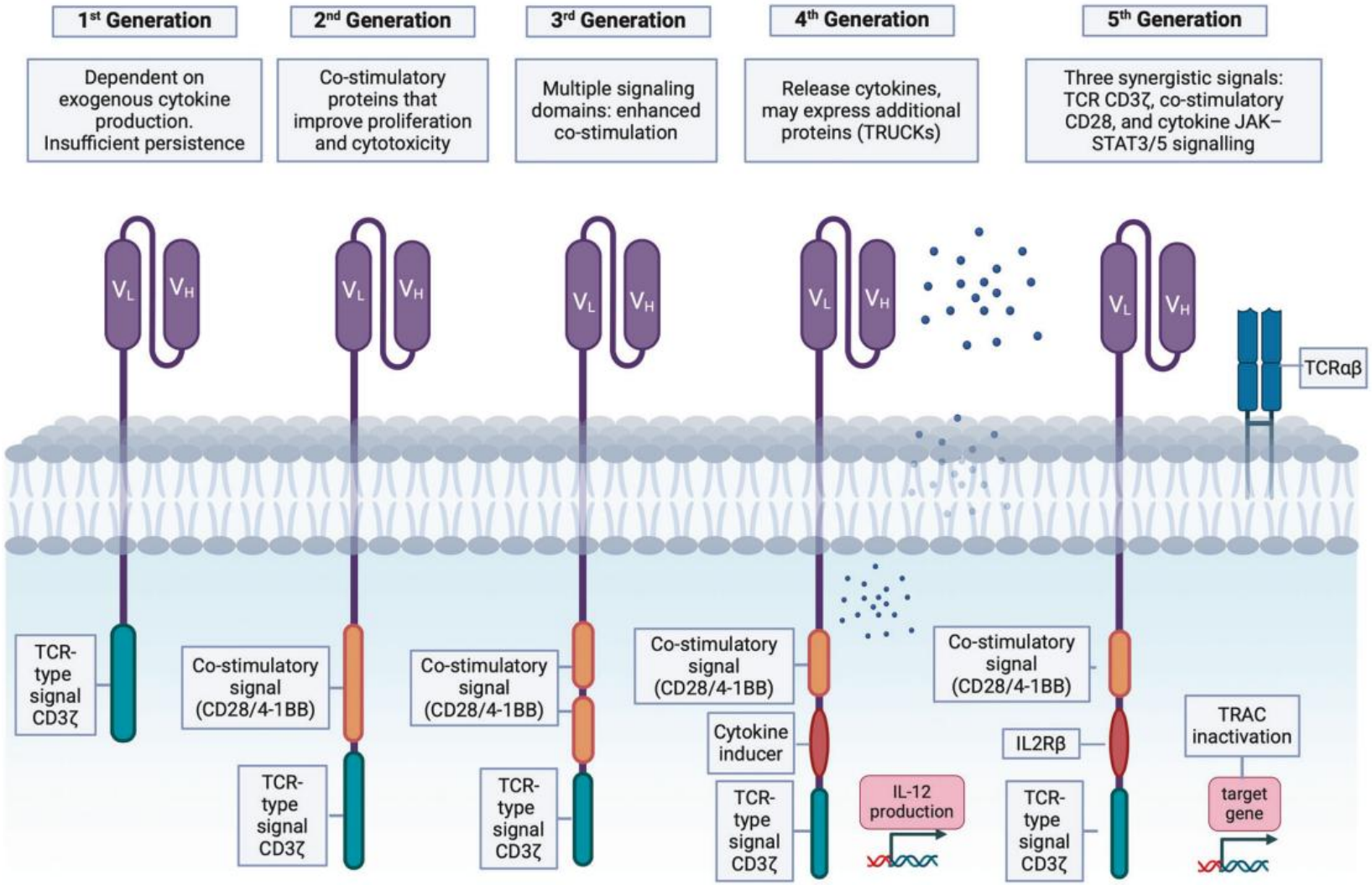
J Clin Invest DOI: 10.1172/JCI31720

From idea to practice



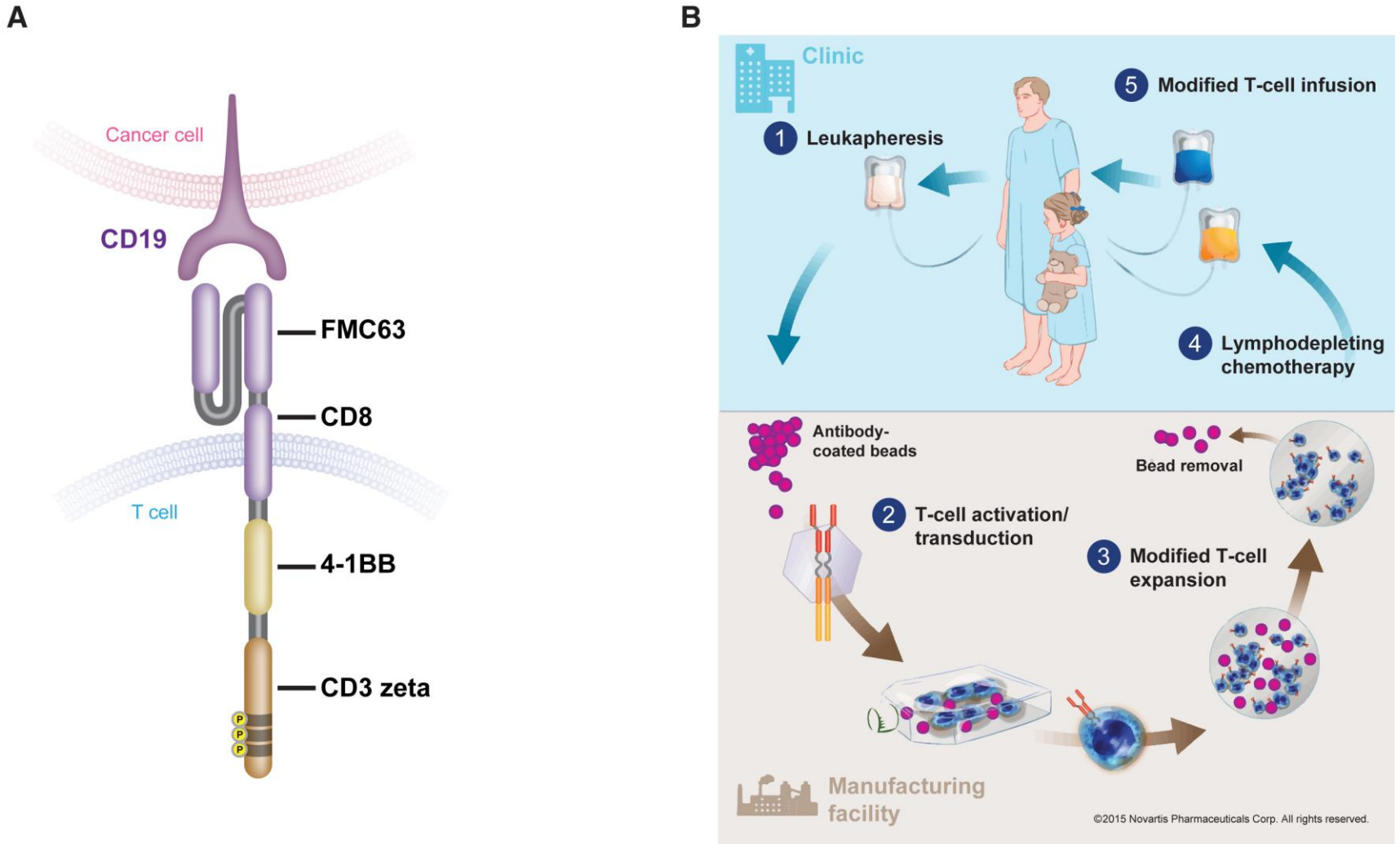
Zugasti et al. 2025

CAR options



Zugasti et al. 2025

From idea to practice



Molecular Therapy - Methods & Clinical Development 2020 16136-144DOI: (10.1016/j.omtm.2019.11.018)

Cross priming

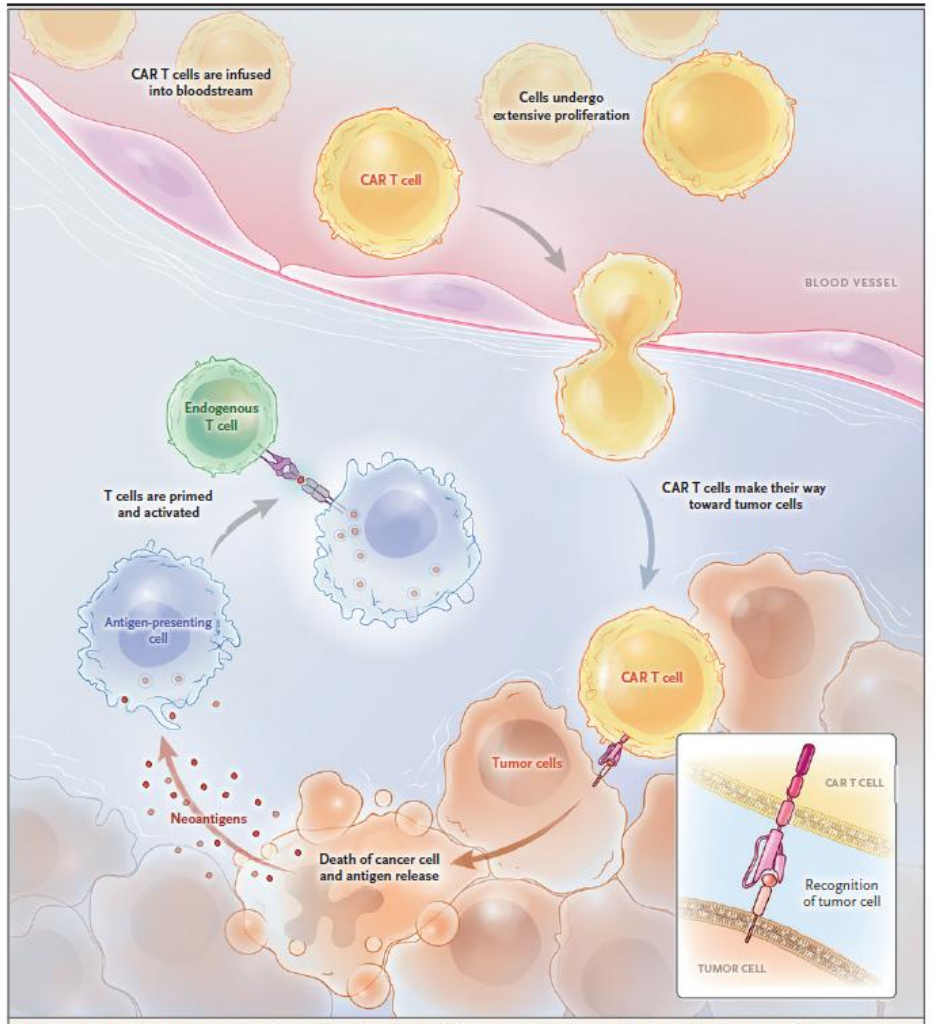


Figure 1. Chimeric Antigen Receptor (CAR) T Cells Engrafting, Trafficking to Tumor, and Proliferating Extensively after Infusion.
After infusion, CAR T cells leave the blood and travel to sites of tumor, where they identify and kill tumor cells. This can trigger extensive proliferation of CAR T cells and the release of tumor antigens, which activates the immune system to recruit non–CAR T cells, thus eliciting further antitumor responses in a process known as cross priming.

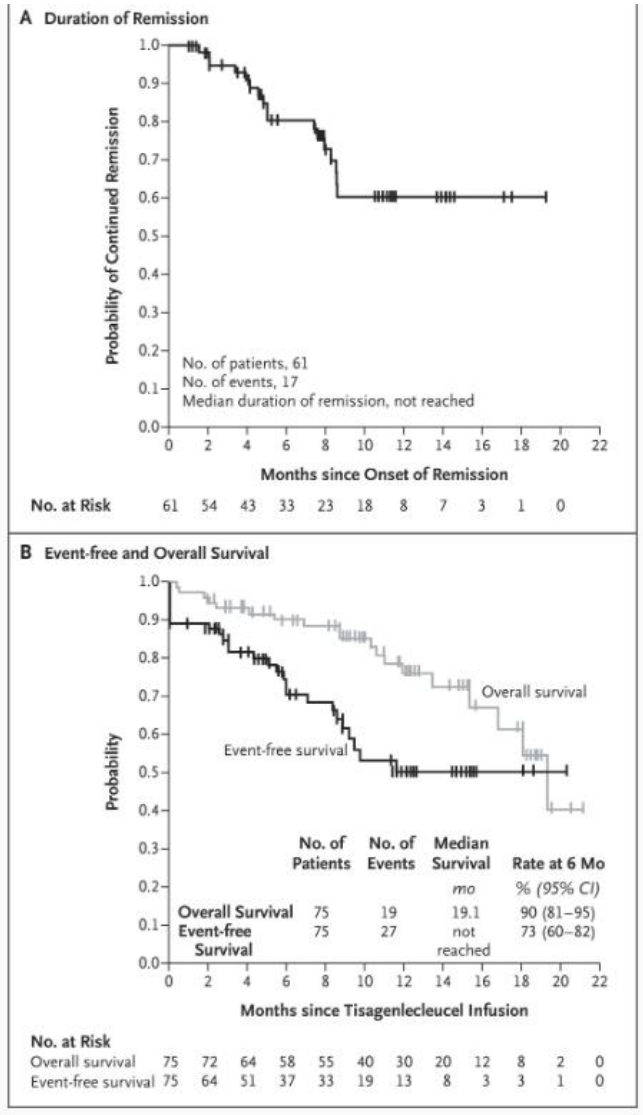
FDA/EMA approvals

Table 1 EMA-approved CAR T therapies for B cell malignancies and multiple myeloma (*as of September 2024*)

Product:	**Kymriah**	**Yescarta**	**Tecartus**	**Breyanzi**	**Abecma**	**Carvykti**
Active substance	Tisagenlecleucel	Axicabtagene-ciloleucel	Brexucabtagene autoleucel	Lisocabtagene maraleucel	Idecabtagene-vicleucel	Ciltacabtagenum autoleucelum
Manufacturer	Novartis	Kyte/Gilead	Kyte/Gilead	BMS	BMS	Janssen
Approval (EMA)	2018	2018	2020	2022	2021	2022
Target	CD19	CD19	CD19	CD19	BCMA	BCMA
Costimulatory signal	4–1BB	CD28	CD28	4–1BB	4–1BB	4–1BB
Indication	r/r B-ALL (age ≤25, 3rd line) r/r DLBC (3rd line) r/r FL (3rd line)	r/r DLBCL, HGBCL (2nd line[a]) PMBCL (3rd line) r/r FL (4th line)	r/r MCL (3rd line incl. BTK-inhibitor) r/r B-ALL (age ≥26, 3rd line)	r/r DLBCL, PMBCL, HGBCL (2nd line[a]) FL3B (2nd line[a])	r/r MM (3rd line[b])	r/r MM (2nd line[c])

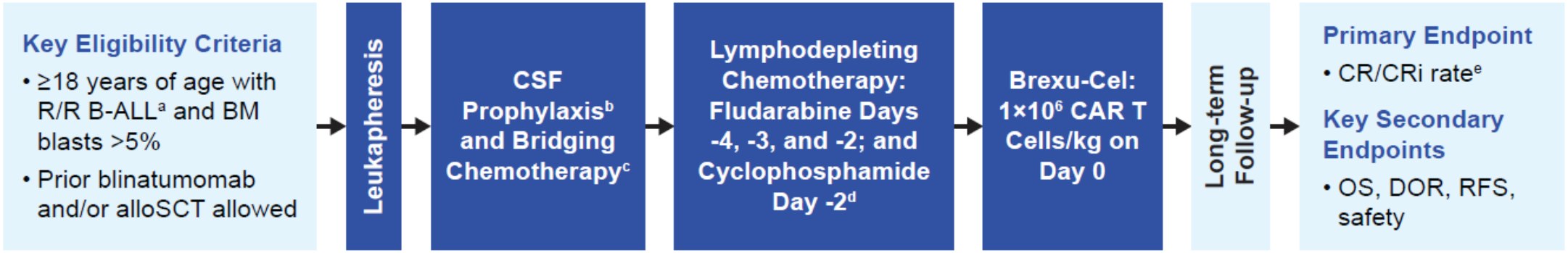
Breyanzi-CLL, Obe-cel-ALL

B-ALL-Eliana



Maude et al.2018. NEJM

B-ALL-Zuma 3



- ZUMA-3 is a multicenter, single-arm, Phase 1 and 2 study evaluating safety and efficacy of brexu-cel (NCT02614066); methods have been previously reported.
- Updated endpoints were assessed in pooled Phase 1 and 2 patients treated at the pivotal dose of brexu-cel (N=78), based on the EU approval

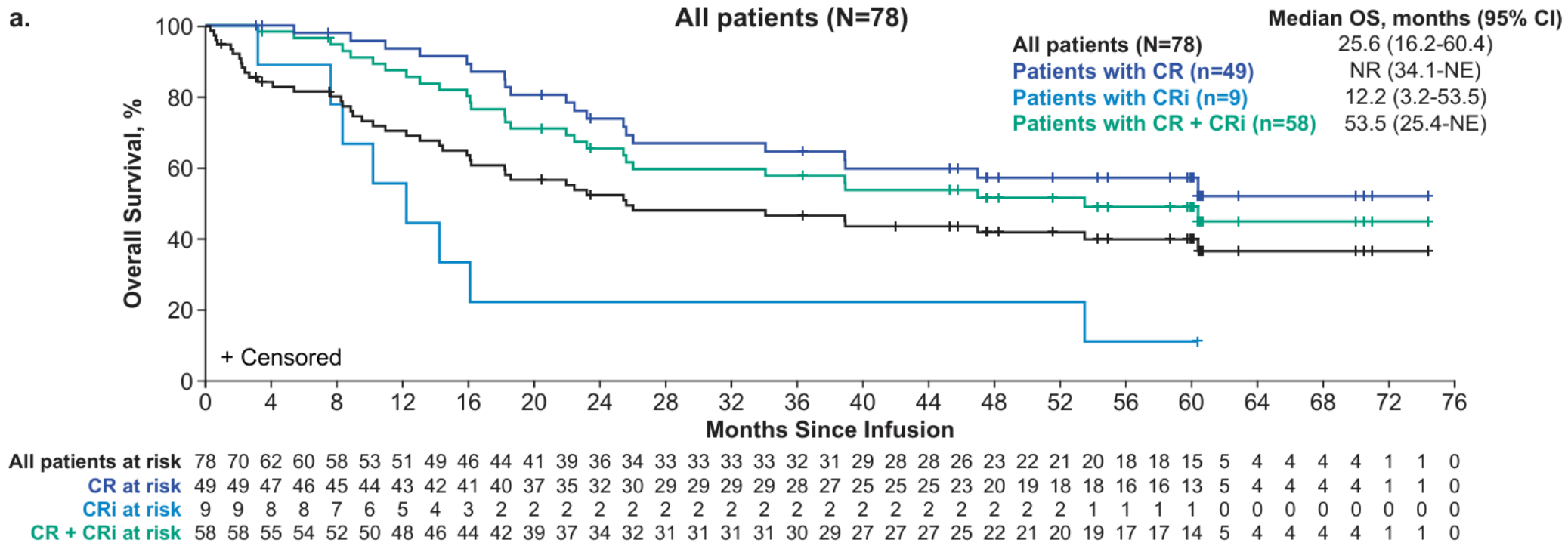
- Consolidative subsequent allogeneic stem cell transplantation (alloSCT) was allowed per physician's discretion

[a]R/R disease was defined as primary refractory, first relapse within 12 months, R/R after ≥2 prior lines of systemic therapy or relapsed after alloSCT. [b]All patients received CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines. [c]Bridging chemotherapy was recommended for all patients, particularly those with >25% marrow blasts or >1000 blasts/µL of peripheral blood at screening, per physician's discretion. [d]Fludarabine 25 mg/m^2 IV on Days -4, -3, -2 and cyclophosphamide 900 mg/m^2 IV on Day -2. [e]Disease assessment was performed per IRRC through the Month 24 visit or until disease progression. Disease assessment after the Month 24 visit for patients whose disease had not progressed was performed per standard of care via investigator assessment.

alloSCT: allogeneic stem cell transplantation; BM: bone marrow; brexu-cel: brexucabtagene autoleucel; CAR: chimeric antigen receptor; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; CSF: cerebrospinal fluid; DOR: duration of remission; EU: European Union; IV: intravenously; OS: overall survival; RFS: relapse-free survival; R/R B-ALL: relapsed or refractory B-cell acute lymphocytic leukemia.

3. Shah BD, *et al. Lancet* 2021; 398: 491–502.

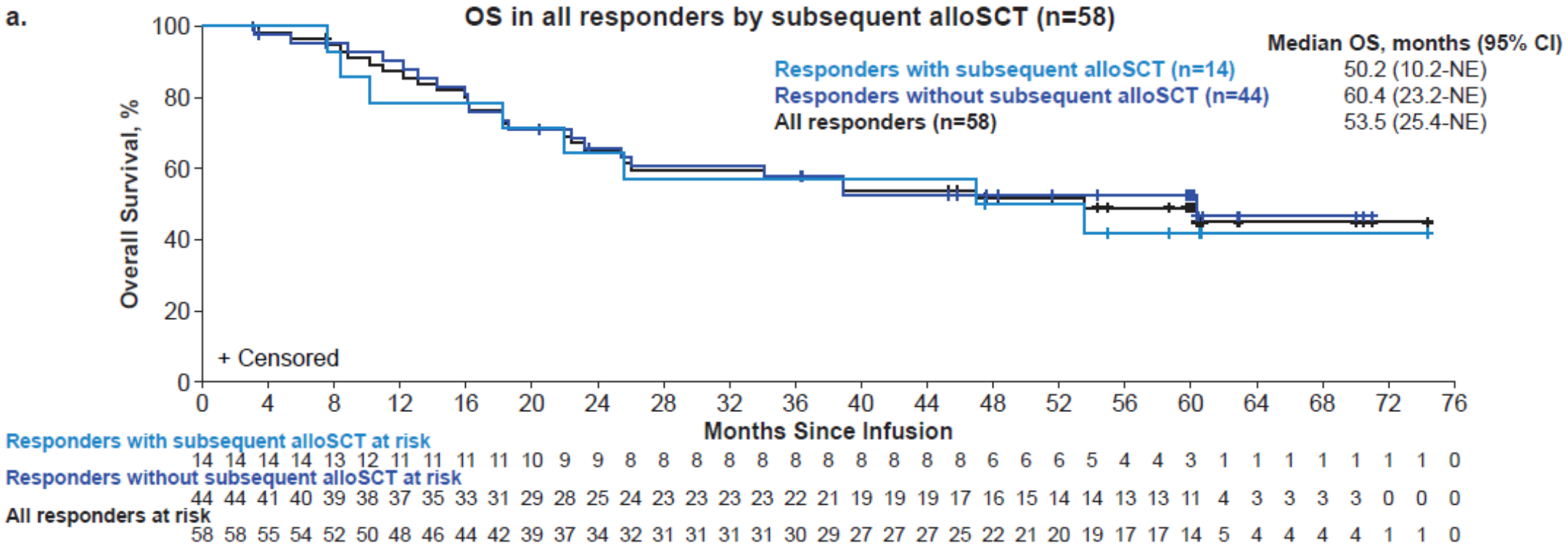
B-ALL-Zuma 3



- The median OS was 25.6 months (95% CI, 16.2–60.4) for Phase 1 and 2 treated patients (N=78), which was unchanged since the 4-year analysis, and the 5-year OS rate was 40% .
- Per investigator review, responders (CR/CRi; n=58) reached a median OS of 53.5 months (95% CI, 25.4–not estimable [NE]) and those with a CR (n=49) had not reached a median OS (95% CI, 34.1–NE)

Data cutoff date: July 23, 2024. Response status was assessed by investigator review.
CR: complete remission; CRi: complete remission with incomplete hematologic recovery; NE: not estimable; NR: not reached; OS: overall survival.
4. Oluwole OO, *et al. J Clin Oncol* 2024; 42(Suppl 16): 6531.

B-ALL-Zuma 3

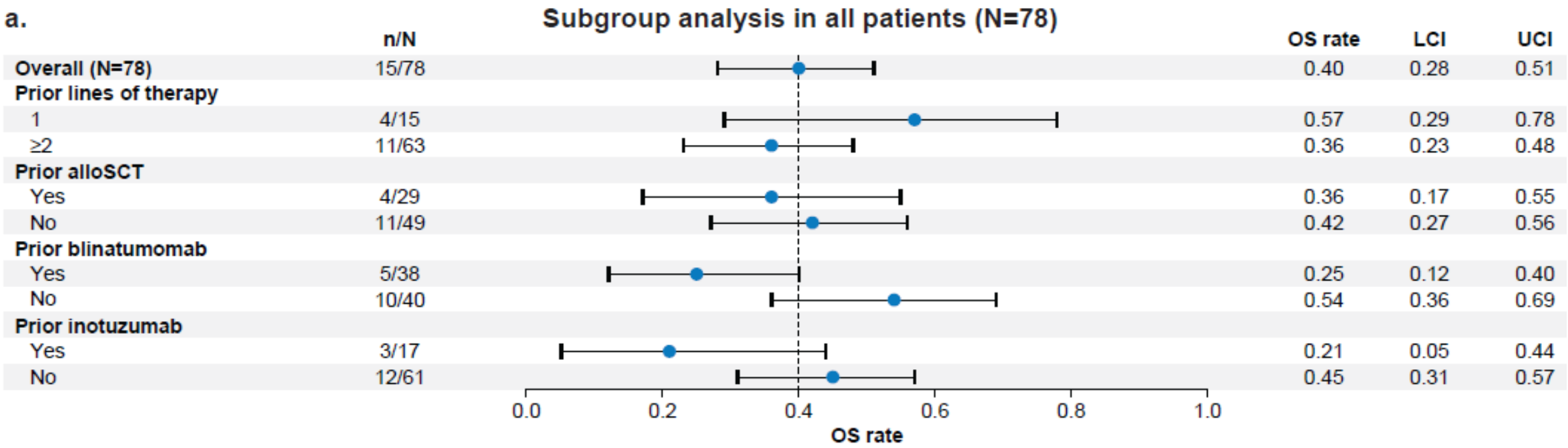


- Median OS was 50.2 months (95% CI, 10.2–NE) in all responders (per investigator review, n=58) who received subsequent alloSCT (n=14) and 60.4 months (95% CI, 23.2–NE) in responders who did not receive subsequent alloSCT (n=44; **Figure 4a**); the 5-year OS rates were 42% (95% CI, 16.4–65.4) and 52% (95% CI, 35.8–66.5), respectively

Data cutoff date: July 23, 2024. Response status was assessed by investigator review.
AlloSCT: allogeneic stem cell transplantation; NE: not estimable; OS: overall survival.

B-ALL-Zuma 3

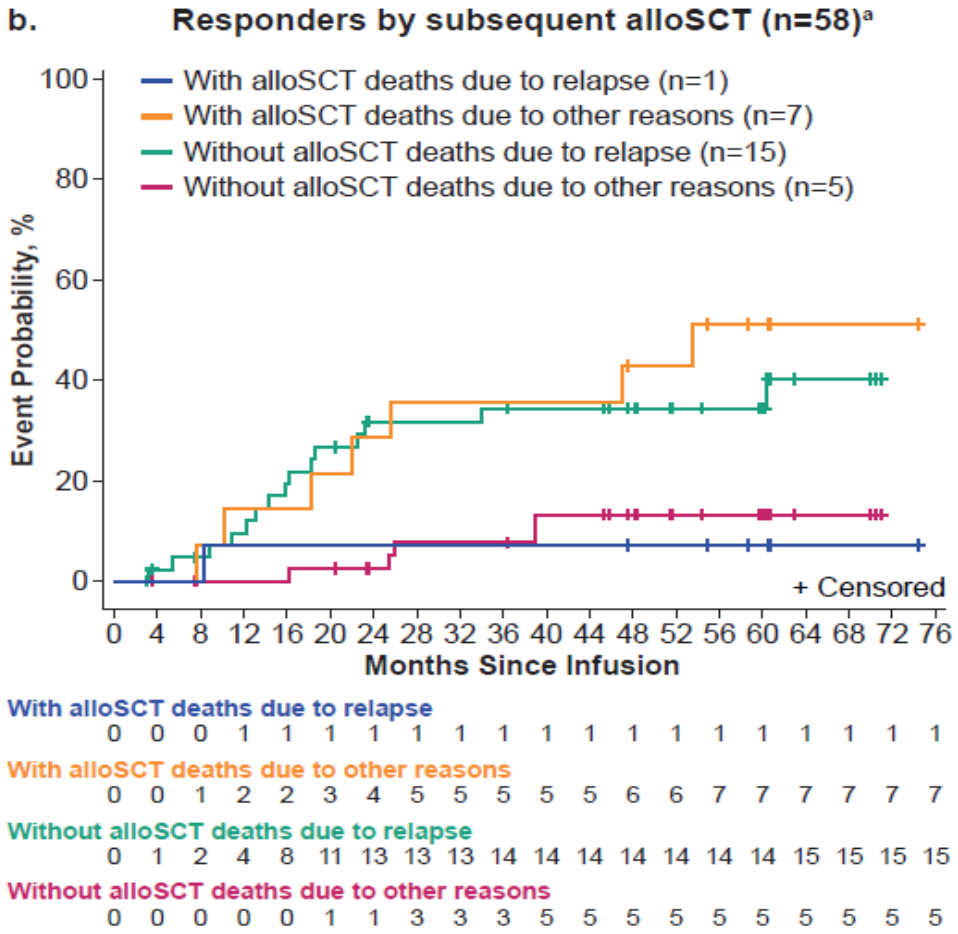
a.



- In the subgroup analysis of all treated patients, the 5-year OS rates were (**Figure 5a**):
  - 57% for patients with 1 prior therapy (n=15) and 36% for patients with ≥2 prior therapies (n=63)
  - 36% for patients with prior alloSCT (n=29) and 42% for patients without prior alloSCT (n=49)
  - 25% for patients with prior blinatumomab (n=38) and 54% for patients without (n=40) prior blinatumomab
  - 21% for patients with prior inotuzumab (n=17) and 45% for patients without prior inotuzumab (n=61)

Data cutoff date: July 23, 2024. The dotted vertical line represents the point estimate of overall population.
alloSCT: allogeneic stem cell transplantation; LCI: lower confidence interval; OS: overall survival; UCI: upper confidence interval.

B-ALL-Zuma 3



- Of the 14 responders who received subsequent alloSCT, 8 had died by OS data cutoff, 1 (7%) due to relapse and 7 (50%) due to non-relapse–related reasons (**Figure 6b**)
  - The estimated 60-month cumulative incidence of relapse-related mortality and non-relapse–related mortality in responders with subsequent alloSCT were 7% (0.4–28.6) and 51% (21.4–74.8), respectively
  - Whereas the estimated 60-month cumulative incidence of relapse-related mortality and non-relapse–related mortality in responders without subsequent alloSCT were 34% (20.2–49.1) and 13% (4.7–26.2), respectively
  - Since the 4-year analysis,1 new adverse event and death were reported, both in the same patient who had previously received post–brexu-cel alloSCT, cervical cancer and death due to pulmonary failure (both deemed unrelated to brexu-cel)
- No secondary T-cell malignancies were reported in ZUMA-3 at any time

[a]There was high censorship in patient subgroups due to high survival rate. Response status was assessed by investigator review.
alloSCT: allogeneic stem cell transplant; brexu-cel: brexucabtagene autoleucel; OS: overall survival.

B-ALL-Zuma 3

- Brexu-cel continued to demonstrate long-term benefits to patients, with **a 40% OS rate at 5 years**
  - Responders had the greatest benefit with a median OS of >5 years for patients with CR/CRi per investigator review (n=58), and not reached for those with CR (n=47)
- **Patients benefited from brexu-cel regardless of age, prior therapy, or subsequent alloSCT status**, though benefits were less apparent in patients *with prior blinatumomab or prior inotuzumab*
- Responders with subsequent alloSCT had numerically lower median OS and a numerically higher rate of non-relapse–related mortality than responders without subsequent alloSCT
- Small sample sizes and/or unbalanced patient characteristics limit interpretation of post hoc subgroup and subsequent alloSCT analyses
- The long-term safety was favorable, with no new safety signals observed
- **Further studies are needed to fully understand how prior therapies and subsequent alloSCT may impact long-term outcomes in patients with R/R B-ALL treated with brexu-cel**

alloSCT: allogeneic stem cell transplant; brexu-cel: brexucabtagene autoleucel; CAR: chimeric antigen receptor; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; OS: overall survival; R/R B-ALL: relapsed/refractory B-cell acute lymphocytic leukemia.

Oluwole *et al.* EHA 2025 (Abstract PF374; poster presentation)

Pivotal CAR-T trials in aggressive lymphoma

Agent Pivotal Trial	Axicabtagene ciloleucel ZUMA-1	Tisagenlecleucel JULIET	Lisocabtagene maraleucel TRANSCEND-NHL-001
Study overview	Phase 2, single-arm, open-label N=101	Phase 2, single-arm, open-label N=115	Phase 1, single-arm, open-label N=269
Disease	R/R DLBCL/PMBCL/TFL	R/R DLBCL/TFL	R/R DLBCL/HGBCL/DLBCL transformed from indolent lymphoma/PMBCL/FL3B
Line of therapy	Refractory to 1L therapy, or non-responder to 2L+ therapy, or failed ASCT ≤12 months Chemotherapy including anti-CD20 and anthracycline	After 2L+ therapy including rituximab and anthracycline Failed ASCT or ineligible for or not consenting to ASCT	After 2L+ therapy including chemoimmunotherapy with anti-CD20 and anthracycline Could have received ASCT
Prior allo-SCT allowed	No	No	Yes
ECOG PS	0/1	0/1	0/1/2
Bridging therapy allowed	No	Yes	Yes
Lymphodepleting chemotherapy	500 mg/m^2 cyclophosphamide IV and 30 mg/m^2 fludarabine IV × 3 days	250 mg/m^2 cyclophosphamide IV and 25 mg/m^2 fludarabine IV × 3 days or 90 mg/m^2 bendamustine IV × 2 days	300 mg/m^2 cyclophosphamide IV and 30 mg/m^2 fludarabine IV × 3 days

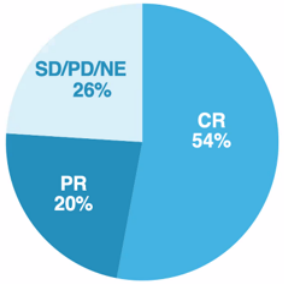
Neelapu et al, NEJM 2017
Locke et al, Lancet Oncology 2019
Schuster et al. NEJM 2019
Abramson et al, Lancet 2020

Response rate in aggressive lymphoma

ZUMA-1 – Response Rates

27.1 months' median follow-up

ORR: 74% (N=101)
CR: 54%

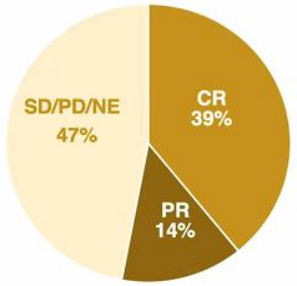


36% of patients had an ongoing response at 27.1 months' median follow-up[2]
Median time to response was 1 month (range 0.8–12.2)

JULIET – Response Rates

40.3 months' median follow-up

ORR: 53% (N=115)
CR: 39%

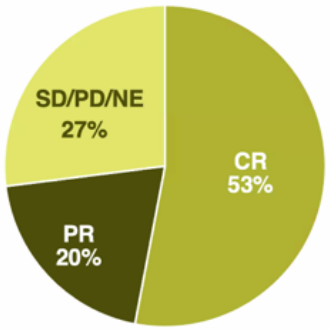


86% of patients who achieved CR at 6 months were estimated to maintain response at 36 months

Jaeger U, *et al.* ASH 2020.
Schuster SJ, *et al. N Engl J Med* 2019; 380:45–56.

TRANSCEND-NHL-001 – Response Rates

ORR: 73% (N=256)
CR: 53%



65% of patients who achieved CR were estimated to have duration of response at 1 year; median time to response was 1.0 month (range 0.7–8.9)

Roschewski et al, NEJM 2022

Abramson JS, *et al. Lancet* 2020; 396:839–852

Toxicities in aggressive lymphoma

Therapy	Trial	CRS Rate (Overall)	**CRS Rate (Grade ≥3)**	Median Time to CRS Onset	ICANS Rate (Overall)	**ICANS Rate (Grade ≥3)**	Median Time to ICANS Onset
Axi-cel	ZUMA-1	93%	**13%**	2 days (1-12)	64%	**28%**	5 days (1-17)
Tisa-cel	JULIET	58%	**22%**	3 days (within 9 days)	21%	**12%**	6 days(1-17)
Liso-cel	TRANSCEND	42%	**2%**	5 days (1-14)	30%	**10%**	9 days(1-66)

Pivotal second line

	Axicabtagene ciloleucel ZUMA-7[1,2] (N=359)	Lisocabtagene maraleucel TRANSFORM[3] (N=184)	Tisagenlecleucel BELINDA[4,5] (N=322)
Inclusion criteria	R/R <12 months after 1L (rituximab + anthracycline); ECOG PS 0, 1; "Candidate" to ASCT		
	Age ≥18 years	Age 18–75 years	Age ≥18 years
Primary endpoint	**EFS** (time from randomisation to progression, start of new therapy, death from any cause, or no PR/CR at Day 150)	**EFS** (time from randomisation to death, progression of disease, fail to achieve PR/CR by 9 weeks or start of new therapy)	**EFS** (time from randomisation to stable disease or progression at or after Week 12, or death)[a]
Stratification	Refractory vs. relapsed aaIPI	Refractory vs. relapsed aaIPI	Region (US vs. non-US) R/R <6 months vs. 6–12 months aaIPI
Bridging	Glucocorticoids	Chemo-Immunotherapy	Chemo-Immunothrapy
Conditioning	Fludarabine 30 mg/m^2 Cyclophosphamide 500 mg/m^2 × 3 days	Fludarabine 30 mg/m^2 Cyclophosphamide 300 mg/m^2 × 3 days	Fludarabine 25 mg/m^2 Cyclophosphamide 250 mg/m^2 × 3 days
Dosing	2 × 10^6 CAR T cells/kg	100 × 10^6 CAR T cells	0.6–6.0 × 10^8 CAR T+ viable T cells
Crossover	Not included	Yes	Yes

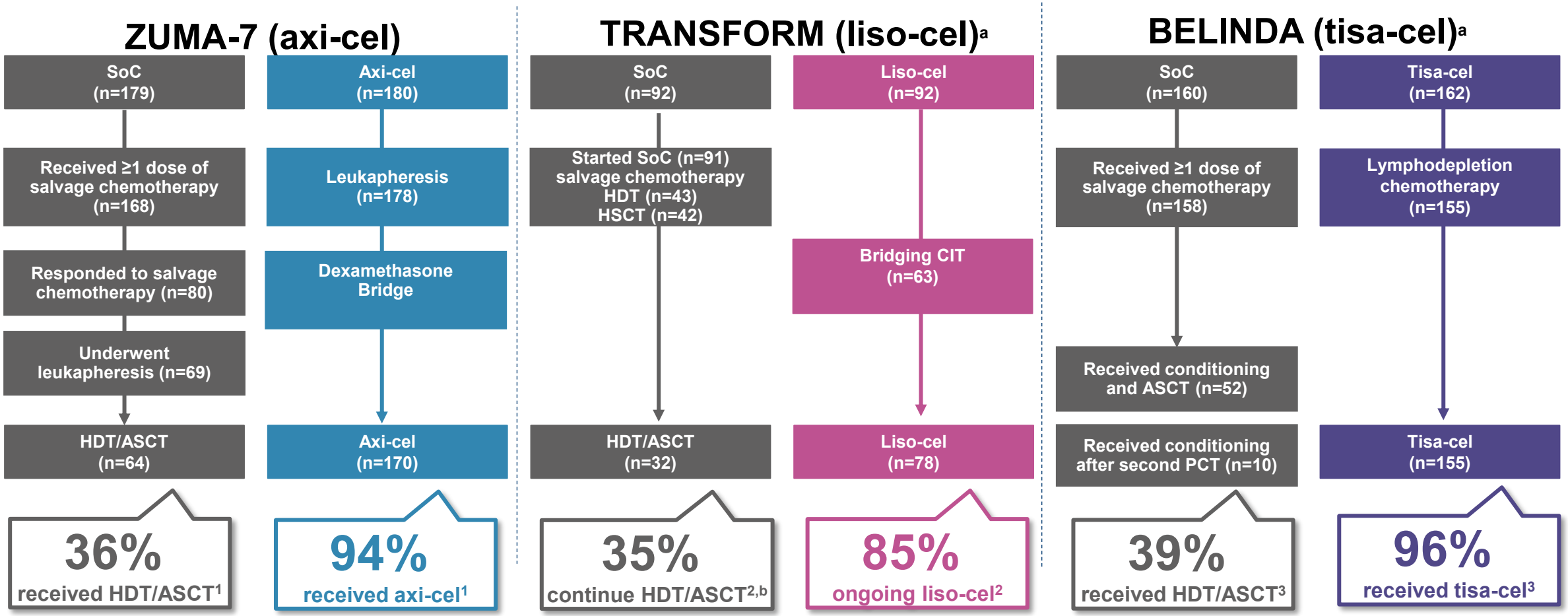
Cross-study comparisons cannot be made due to differences in study designs, endpoint definitions and patient populations

[a] Response assessment before Week 12 did not represent a failure in either group and was not considered for primary endpoint

1L: first line; aaIPI: age-adjusted International Prognostic Index; CIT: chemoimmunotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; EFS: event-free survival

1. Locke FL, *et al.* ASH 2021 (Abstract 2). 2. Locke FL, *et al. N Engl J Med* 2022; 386:640–654. 3. Kamdar M, *et al. Lancet* 2022; 399:2294–2308.
4. Bishop MR, *et al.* ASH 2021 (Abstract LBA6). 5. Bishop MR, *et al. N Engl J Med* 2022; 386: 629–639.

Pivotal second line



Reasons for patient discontinuations included: progressive disease, insufficient response, adverse events, death, protocol deviation and consent withdrawal

Conclusions cannot be drawn from cross-study comparisons due to differences in study design, patient population and length of follow-up.
These studies were not designed to assess the percentage of patients successfully receiving ASCT treatment

[a] All patients underwent leukapheresis before randomisation; [b] Patients continuing SoC after 6 months

Axi-cel: axicabtagene ciloleucel; HDT: high-dose chemotherapy; HSCT: high-dose chemotherapy and autologous stem cell transplant; liso-cel: lisocabtagene maraleucel; PCT: platinum-based immunochemotherapy; PD: progressive disease; SD: stable disease; tisa-cel: tisagenlecleucel

1. Locke FL, *et al. N Engl J Med* 2022; 386:640–654. 2. Kamdar M, *et al. Lancet* 2022; 399:2294–2308. 3. Bishop MR, *et al. N Engl J Med* 2022; 386:629–639.

Zuma 7

Phase 3, randomised, open-label study of patients with R/R DLBCL treated with axi-cel vs. SoC (N=359)

Characteristic		Axi-cel (ITT; n=180)	SoC (ITT; n=179)	Overall (n=359)
Median age (range), years		58 (21–80)	60 (26–81)	59 (21–81)
≥65 years, n (%)		51 (28)	58 (32)	109 (30)
Disease stage III–IV, n (%)		139 (77)	146 (82)	285 (79)
sAAIPI of 2–3,[a] n (%)		82 (46)	79 (44)	161 (45)
Response to 1L therapy,[a] n (%)	Primary refractory	133 (74)	131 (73)	264 (74)
	Relapse ≤12 months of 1L therapy	47 (26)	48 (27)	95 (26)
Prognostic marker as per central laboratory, n (%)	HGBL (including double-/triple-hit)	31 (17)	25 (14)	56 (16)
	Double expressor lymphoma	57 (32)	62 (35)	119 (33)
	MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH level[b]		101 (56)	94 (53)	195 (54)

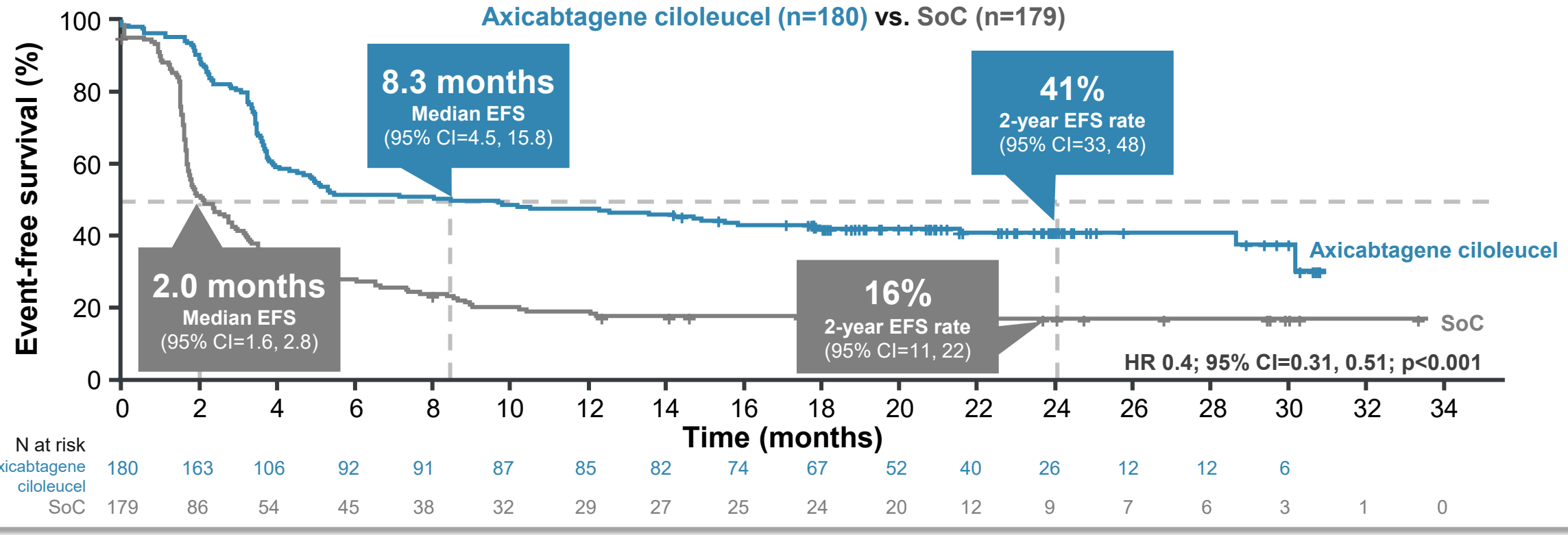
[a] As reported by investigator at the time of randomisation; [b] Lactate dehydrogenase level greater than upper limit of normal as per local laboratory reference range
HGBL: high-grade B-cell lymphoma; ITT: intention to treat; LDH: lactate dehydrogenase; sAAIPI: second-line age-adjusted International Prognostic Index score; SoC: standard of care
Locke FL, *et al. N Engl J Med* 2022; 386:640–654.

Zuma 7

mFU: 24.9 months

ZUMA-7: Phase 3, randomised, multicentre trial of axicabtagene ciloleucel vs. SoC as 2L treatment in patients with R/R LBCL (N=359)[1]

Primary endpoint: Event-free survival



[a] Salvage chemotherapy +/- HDT-ASCT
CI: confidence interval; EFS: event-free survival; HR: hazard ratio; mFU: median follow up
Locke FL, *et al. N Engl J Med* 2022; 386:640–654.

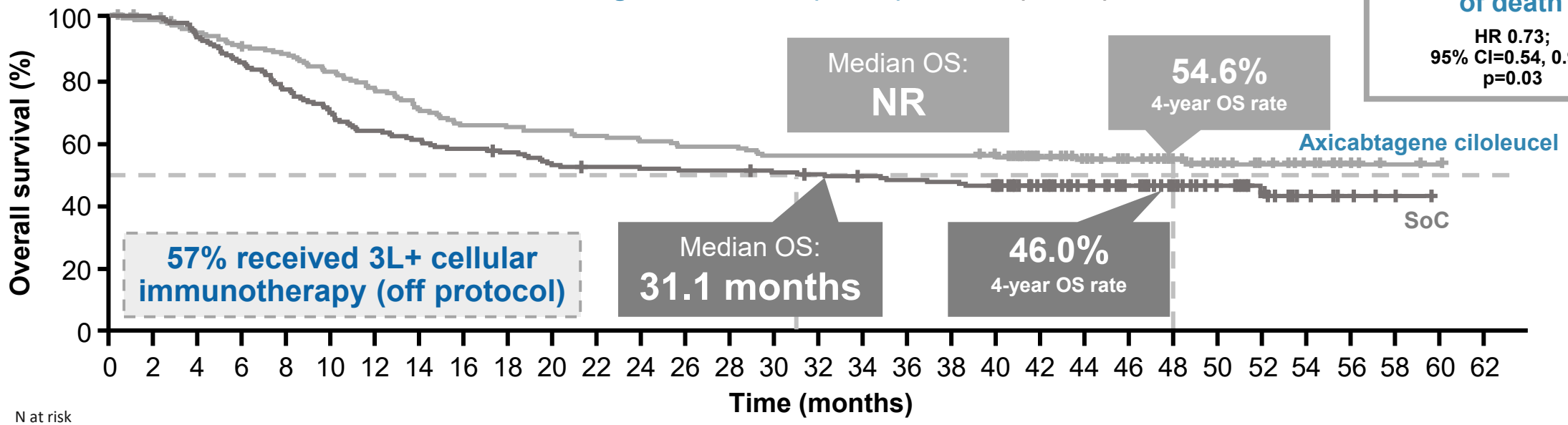
Zuma 7

mFU: 47.2 months[1]

ZUMA-7: Phase 3, randomised, multicentre trial of axicabtagene ciloleucel vs. SoC as 2L treatment in patients with R/R LBCL (N=359)[1]

Overall survival

Axicabtagene ciloleucel (n=180) vs. SoC (n=179)



N at risk

Axicabtagene ciloleucel	180	177	170	161	157	147	136	125	117	116	114	111	108	105	105	100	100	100	100	100	96	80	67	54	41	29	20	14	4	2	1	0
SoC	179	176	163	149	134	121	111	106	101	98	91	89	88	87	87	85	83	81	79	78	73	63	51	41	31	19	14	7	4	1	0	

27%
reduction in risk of death
HR 0.73; 95% CI=0.54, 0.98; p=0.03

Axicabtagene ciloleucel demonstrates superior overall survival in 2L DLBCL R/R ≤12 months vs. SoC[1–4,a]

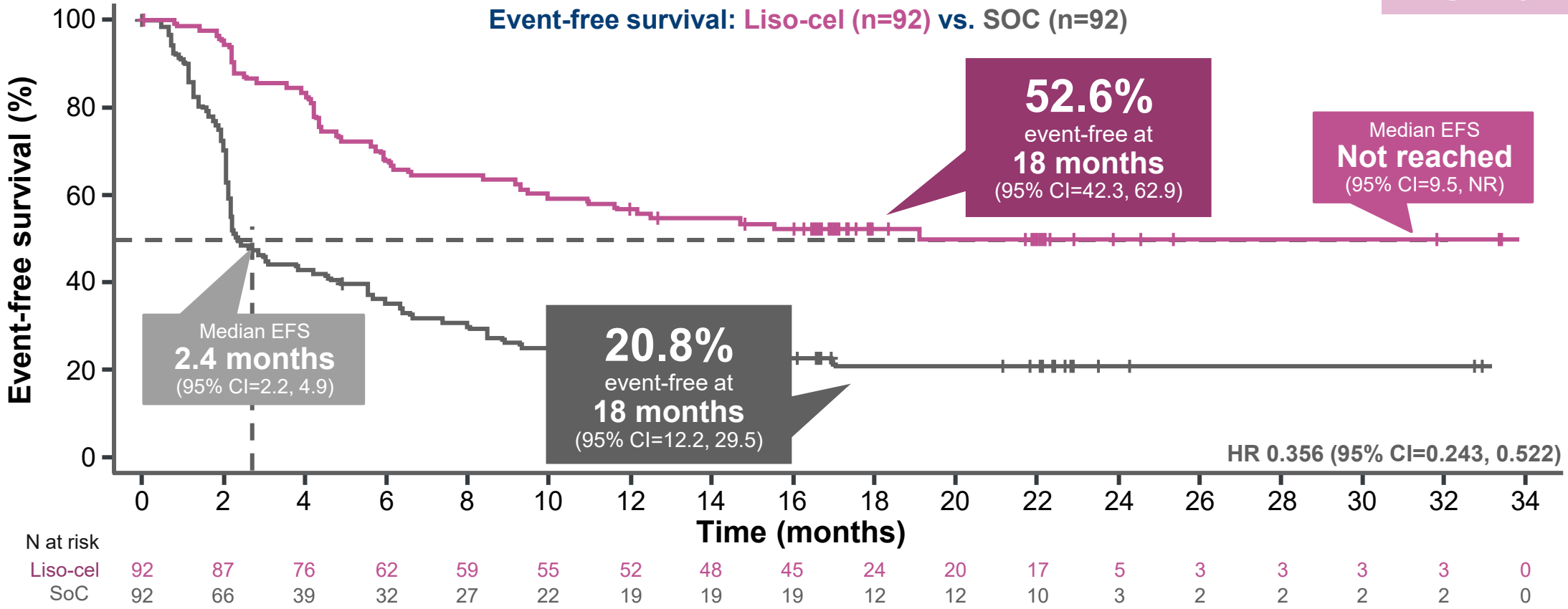
[a] Salvage chemotherapy +/- HDT + ASCT[1–4]

LBCL: large B-cell lymphoma; NR: not reached; OS: overall survival

1. Westin JR, *et al. N Engl J Med* 2023; 389:148–157. 2. Axicabtagene ciloleucel SmPC (Feb 2024; available at www.ema.europa.eu).
3. Bishop MR, *et al. N Engl J Med* 2022; 386:629–639. 4. Abramson JS, *et al. Blood* 2023; 141:1675–1684.

TRANSFORM

mFU 17.5 months

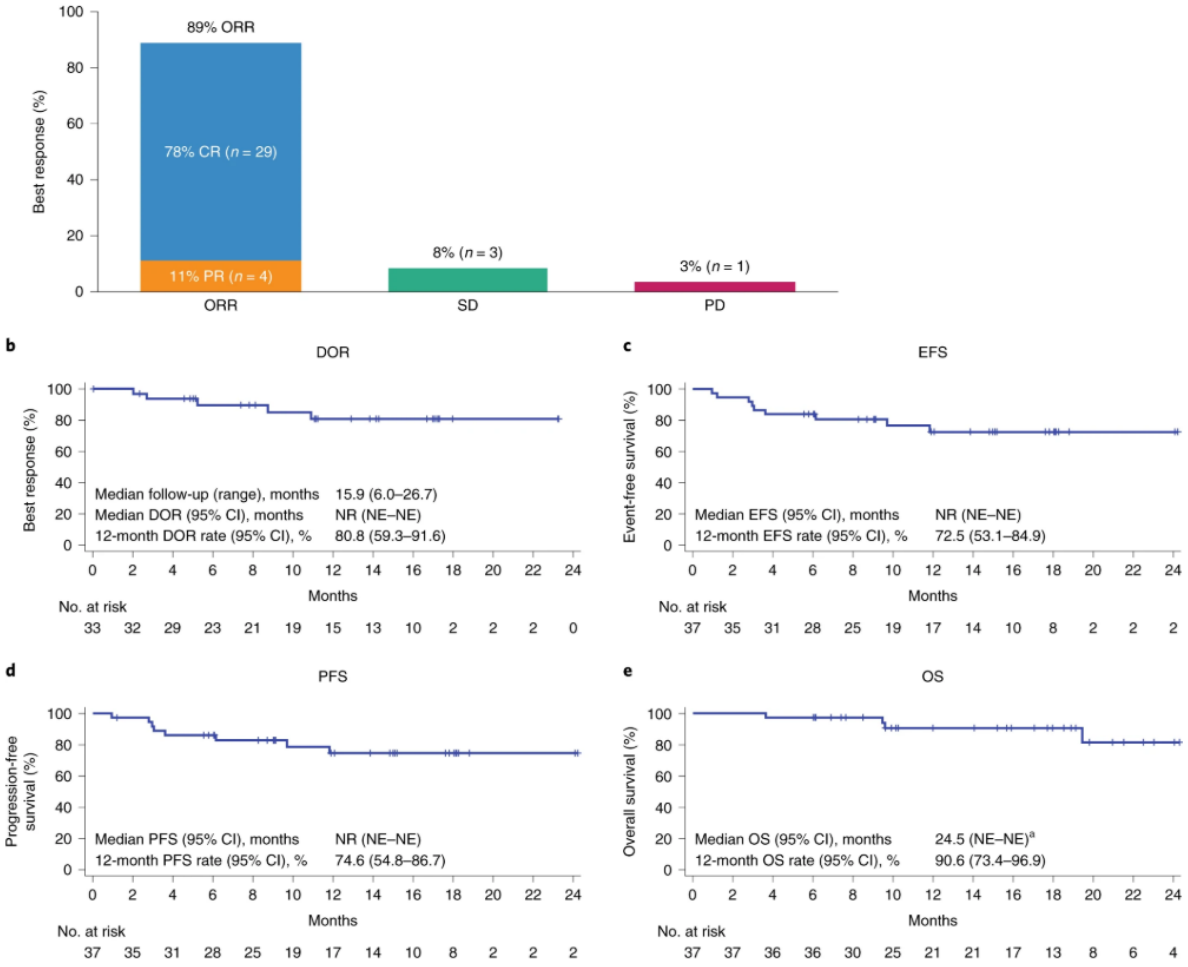


The primary endpoint was met showing an EFS HR of 0.36, representing a 64% reduction in risk of events vs. SoC

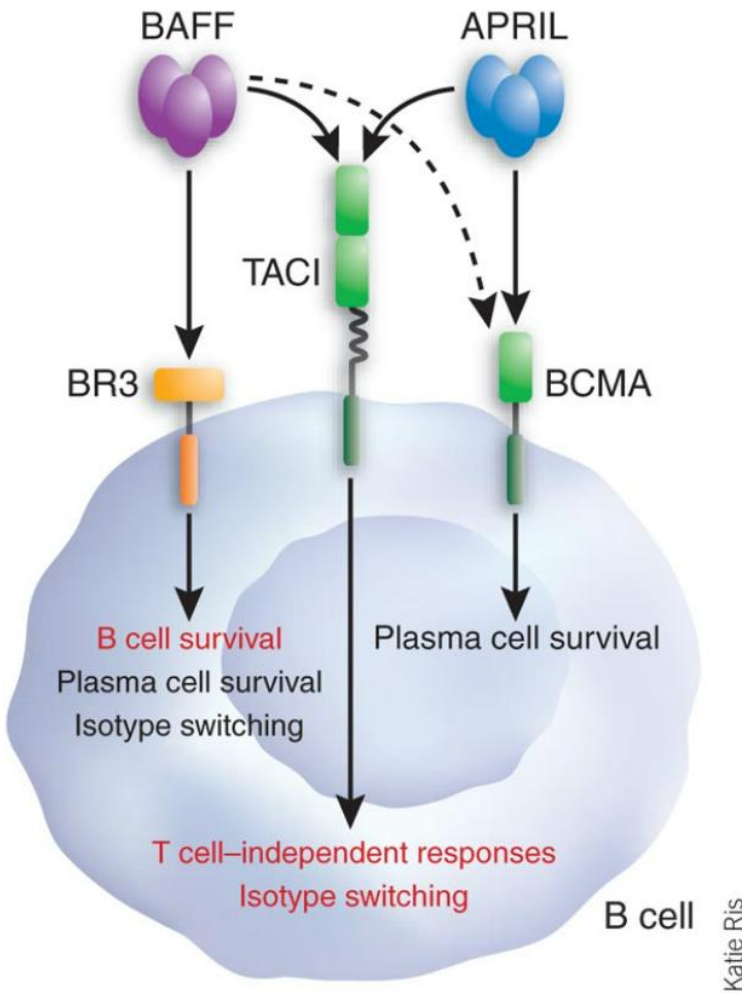
NR: not reached, SOC; Standard of Care

1. Abramson JS, *et al.* ASH 2022 (Abstract 655; oral).

Do we have evidence for CAR-T therapy being used as first-line treatment in lymphoma?



Multiple myeloma



KarMMa

BCMA CAR T Cell Therapy: KarMMa study: Idecabtagene vicleucel (ABECMA; ide-cel; bb2121) approved by FDA/EMA 2021

Uniklinikum Würzburg

- Open-label, single arm study: N=140
- ≥ 3 prior therapies (including an IMiD, a PI and an anti-CD38 antibody); median: 6 lines of prior therapy
- 94% of patients refractory to anti-CD38 antibody; 84% triple-refractory, EMD: 39%
- Median follow-up: 11.3 months

Efficacy

	Ide-cel Treated Population			
	150×10^6 CAR+ T cells (N=4)	300×10^6 CAR+ T cells (N=70)	450×10^6 CAR+ T cells (N=54)	$150–450 \times 10^6$ CAR+ T cells (N=128)
ORR, n (%)	2 (50.0)	48 (68.6)	44 (81.5)	94 (73.4)
CR/sCR, n (%)	1 (25.0)	20 (28.6)	19 (35.2)	40 (31.3)
Median DoR, months	---	9.9	11.3	10.6
Median PFS, months	---	5.8	11.3	8.6

Median DOR and median PFS are not reported for the 150×10^6 CAR+ T cells dose group due to the small number of evaluable patients

- Grade ≥ 3 CRS: 5.5%
- Grade ≥ 3 investigator identified neurotoxicity events: 3.1%

In the subgroup of pts. achieving a CR: DOR 21.9 mo.

Munshi N et al. NEJM 2021

KarMMa

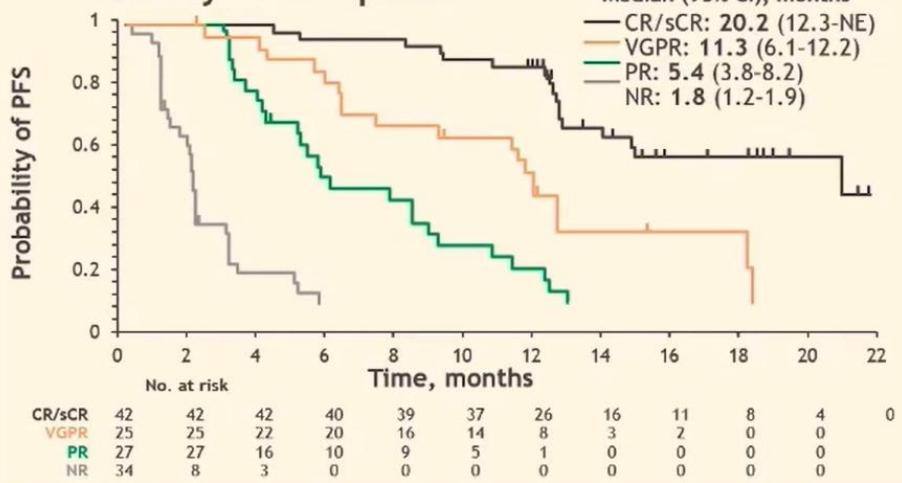
KarMMa Phase 2 study of ide-cel in RRMM

The KarMMa study evaluated the efficacy and safety of ide-cel at doses of **150-450 x 10^6 CAR+ T cells** in 128 patients with RRMM after a median of **six prior lines of therapy (84% triple refractory)**

All treated patients (N = 128) **ORR:** **73%** (CR/sCR: 33%)

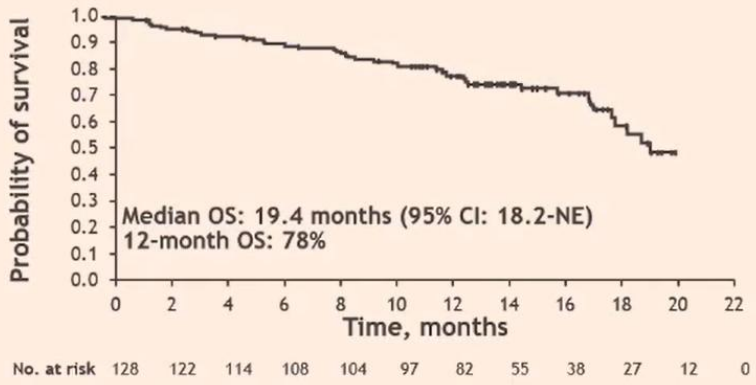
450 x 10^6 dose (n = 54) **ORR: 81%** (CR/sCR: 39%)

PFS by best response



Median PFS was 8.8 months in all patients and 20.2 months in those with CR/sCR

OS



Summary of safety

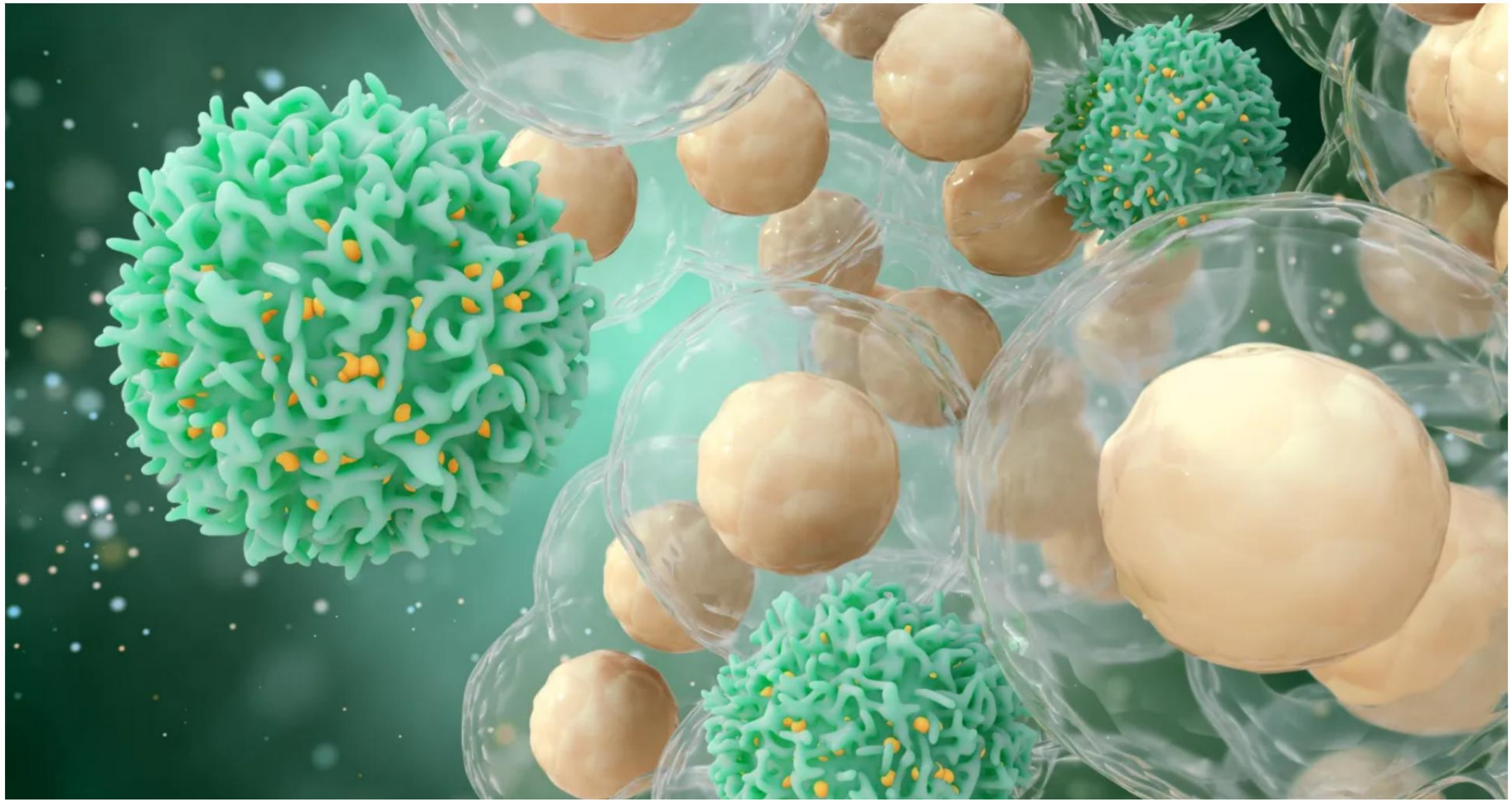
Key AEs of interest, n (%)	Any grade	Grade 3/4
Infections	88 (69)	28 (22)
CRS	107 (84)	7 (5)
Neurotoxic effect	23 (18)	4 (3)

No new safety signals reported

AE, adverse event; CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; ide-cel, idecabtagene vicleucel; NE, not estimable; NR, non-responder; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

Munshi NC, et al. N Engl J Med. 2021;384:705-716.

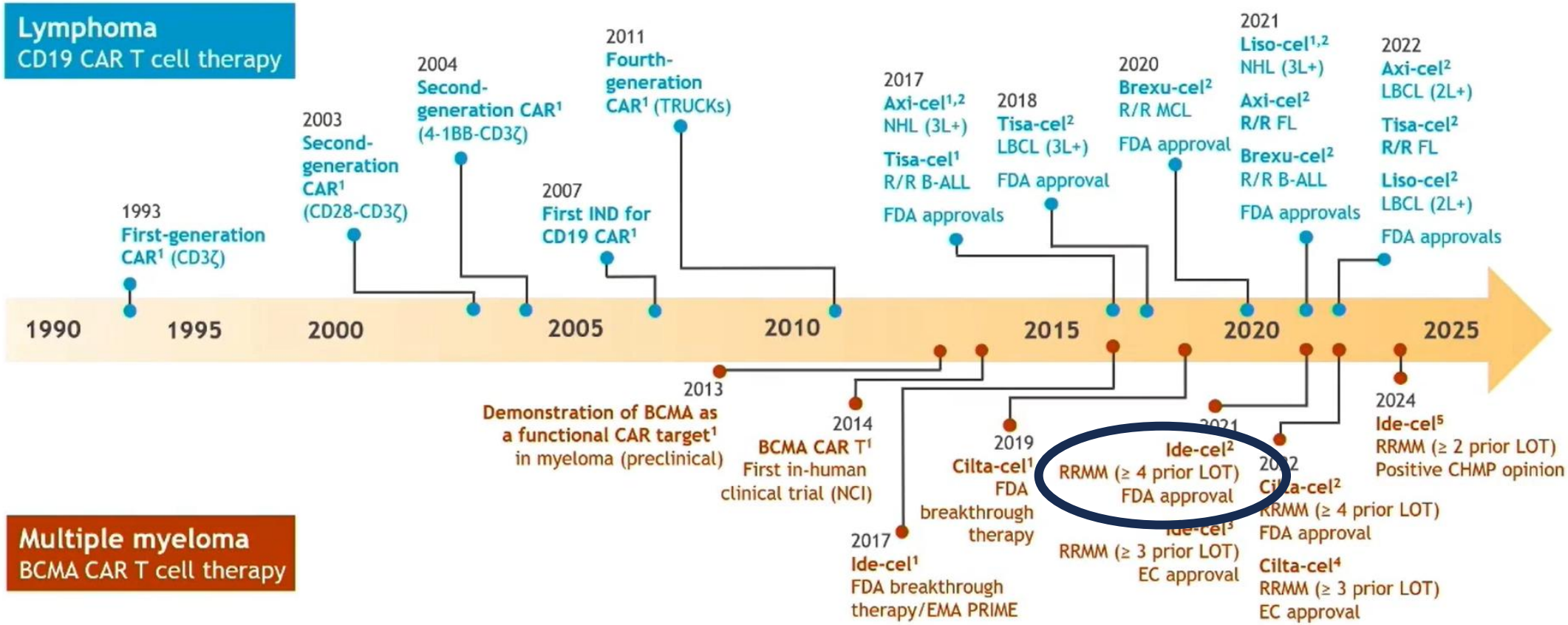
First FDA Approval of CAR T-Cell Therapy for Multiple Myeloma Marks Milestone for Patients



March 27, 2021

ABECMA

CAR T cell therapy developments in hematologic malignancies



2L, second line; 3L, third line; axi-cel, axicabtagene ciloleucel; B-ALL, B-cell acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; brexu-cel, brexucabtagene autoleucel; CAR, chimeric antigen receptor; CD, cluster of differentiation; CHMP, Committee for Medicinal Products for Human Use; cilta-cel, ciltacabtagene autoleucel; EC, European commission; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FL, follicular lymphoma; ide-cel, idecabtagene vicleucel; IND, Investigational New Drug; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; LOT, lines of therapy; MCL, mantle cell lymphoma; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; R/R, relapsed and/or refractory; RRMM, relapsed/refractory multiple myeloma; tisa-cel, tisagenlecleucel; TRUCK, T-cell redirected for universal cytokine-mediated killing.

1. Teoh PJ & Chng WG. Blood Cancer J. 2021;11:84; 2. Labanieh L & Mackall CL. Nature. 2023;614:635-648; 3. EMA Press Release. 2021. Available at: https://www.ema.europa.eu/en/news/first-cell-based-gene-therapy-treat-adult-patients-multiple-myeloma (accessed February 2024); 4. Johnson & Johnson Press Release. 2022. https://www.jnj.com/media-center/press-releases/european-commission-grants-conditional-approval-of-carvykti-ciltacabtagene-autoleucel-janssens-first-cell-therapy-for-the-treatment-of-patients-with-relapsed-and-refractory-multiple-myeloma (accessed February 2024); 5. BMS News. 2024. Available at: https://news.bms.com/news/corporate-financial/2024/Bristol-Myers-Squibb-Receives-Positive-CHMP-Opinion-for-CAR-T-Cell-Therapy-Abecma-idecabtagene-vicleucelin-Earlier-Lines-of-Therapy-for-Triple-Class-Exposed-Relapsed-and-Refractory-Multiple-Myeloma/default.aspx (accessed February 2024).

CARTITUDE- 1

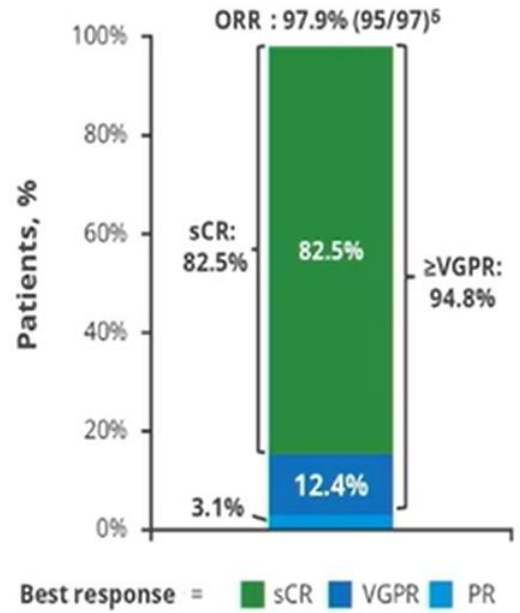
Cilta-cel: the CARTITUDE-1 trial (CARVYKTI)

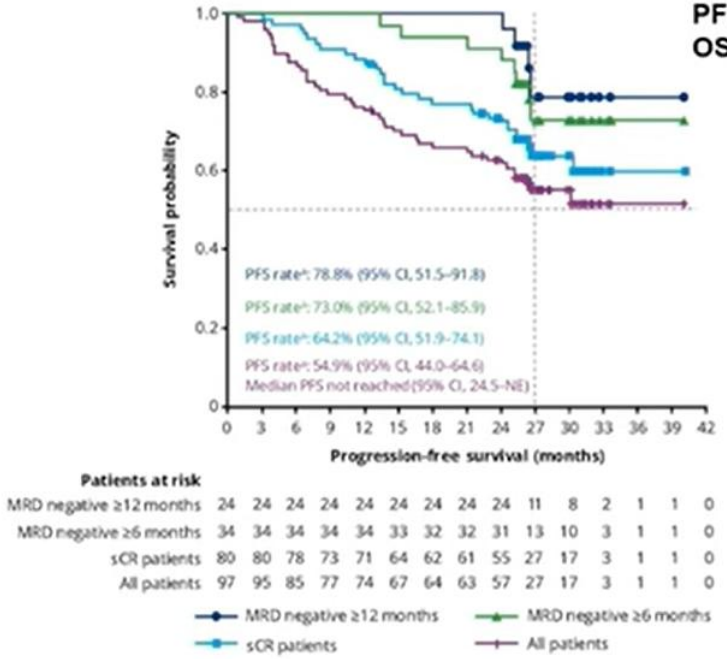
FDA approved in 2022
EMA approved in 2022

Uniklinikum Würzburg

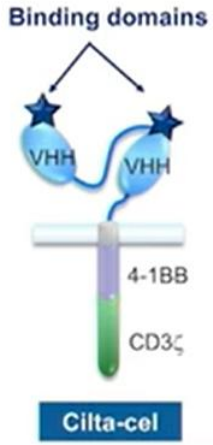
- **Second generation CAR-T cell, 2 anti-BCMA camelid VHH single domains, 4-1BB costimulatory domain[1]**

CARTITUDE-1, phase 2 study (N=97)[2]		
Median prior lines: 6 (3–18)	88% of patients were triple-class refractory	Bridging possible Flu-Cy lymphodepletion





PFS 34.9 mo
OS rate = 70.4%[5]



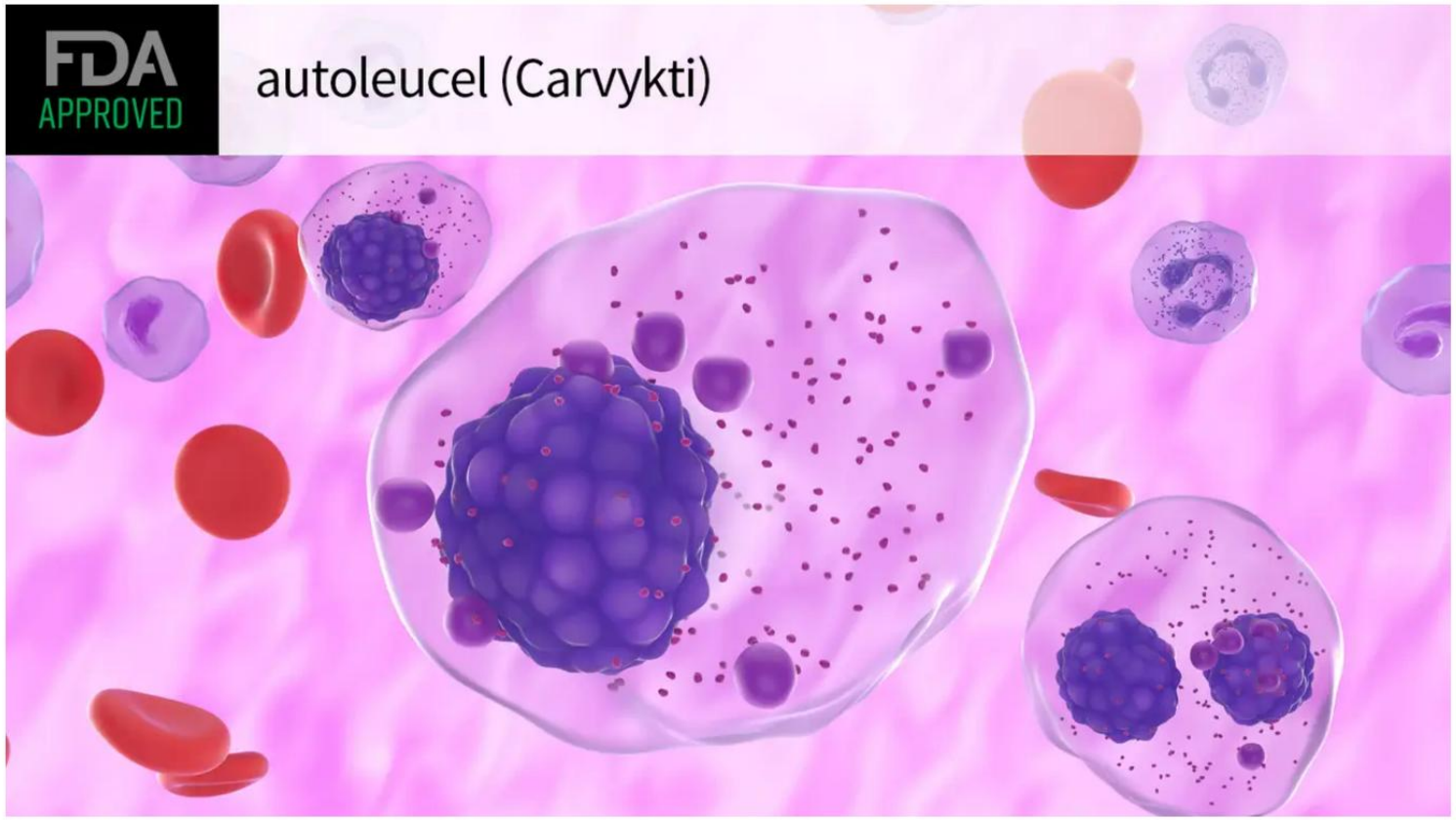
AE, n (%)	(N=97)[3] Any Grade	Grade ≥3
Hematologic		
Neutropenia	93 (96)	92 (95)
Anemia	79 (81)	66 (68)
Thrombocytopenia	77 (79)	58 (60)
CRS	92 (95)	5 (5)
Neurotoxicity	21 (22)	12 (12)
Other CAR T cell Neurotoxicity	12.46%	8.2%

1. Berdeja J et al. Lancet 2021;398(10297):314–24;
2. Martin T et al. J Clin Oncol 2022;doi: 10.1200/JCO.22.00842;
3. Usmani S et al. ASCO 2022;abstract 8028 (poster presentation)

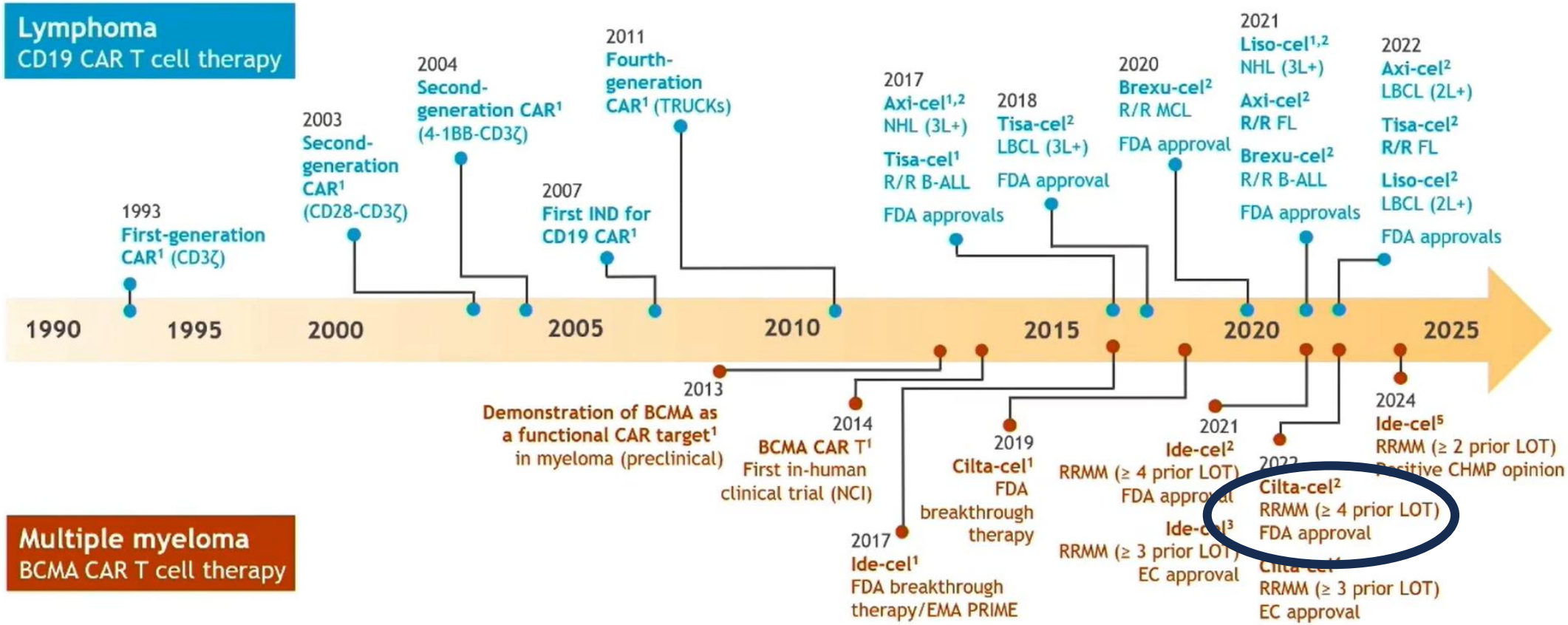
Second CAR T-Cell Therapy Approved for Myeloma

— BCMA-directed ciltacabtagene autoleucel led to responses in 98%

by Mike Bassett, Staff Writer, MedPage Today March 1, 2022



CAR T cell therapy developments in hematologic malignancies



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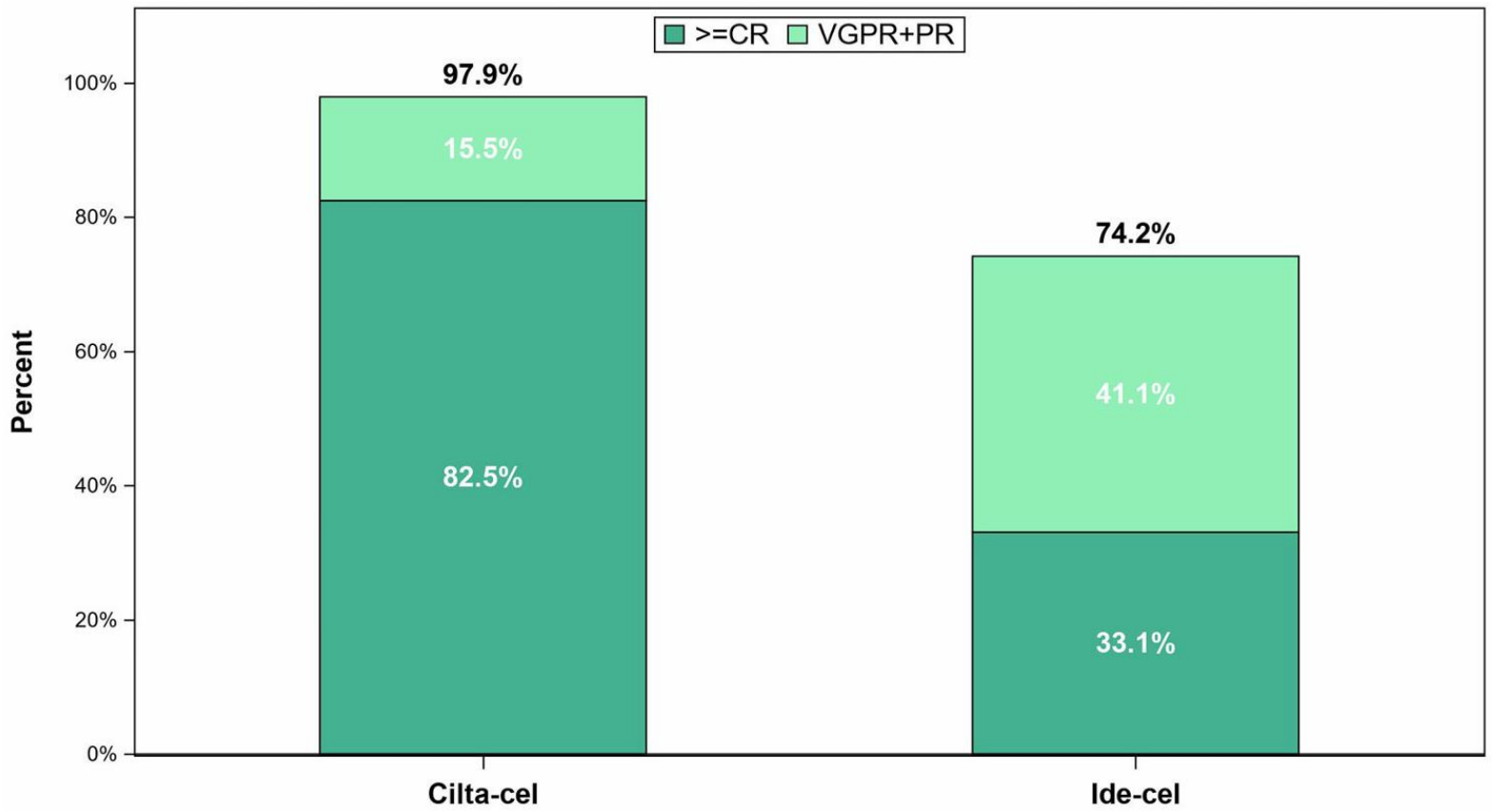
1. Teoh PJ & Chng WG. Blood Cancer J. 2021;11:84; 2. Labanieh L & Mackall CL. Nature. 2023;614:635-648; 3. EMA Press Release. 2021. Available at: https://www.ema.europa.eu/en/news/first-cell-based-gene-therapy-treat-adult-patients-multiple-myeloma (accessed February 2024); 4. Johnson & Johnson Press Release. 2022. https://www.jnj.com/media-center/press-releases/european-commission-grants-conditional-approval-of-carvykti-ciltacabtagene-autoleucel-janssens-first-cell-therapy-for-the-treatment-of-patients-with-relapsed-and-refractory-multiple-myeloma (accessed February 2024); 5. BMS News. 2024. Available at: https://news.bms.com/news/corporate-financial/2024/Bristol-Myers-Squibb-Receives-Positive-CHMP-Opinion-for-CAR-T-Cell-Therapy-Abecma-idecabtagene-vicleucelin-Earlier-Lines-of-Therapy-for-Triple-Class-Exposed-Relapsed-and-Refractory-Multiple-Myeloma/default.aspx (accessed February 2024).

Ide-cel vs Cilta-cel

	Ide-cel (KarMMa-1)	Cilta-cel (CARTITUDE-1)
Trial phase	2	1b/2
No. of patients infused (enrolled)	128 (140)	97 (113)
Median age (range),† y	61 (33–78)	Not reported
Median time since diagnosis (range),† y	6 (1–18)	5.9 (4.4–8.4)
Median No. of prior lines (range)†	6 (3–16)	6 (4–8)
EMD,† No. (%)	50 (39)	13 (13)
ECOG,† No. (%)		
0	57 (45)	39 (40)
1	68 (53)	54 (56)
≥2	3 (2)	4 (4)
R-ISS†		
I	14 (11)	61 (63)
II	90 (70)	22 (23)
III	21 (16)	14 (14)
Unknown	3 (2)	0
Cytogenetic abnormalities†		
High risk	45 (35)	23 (24)
del(17p)	23 (18)	19 (20)
t(4;14)	23 (18)	2 (2)
t(14;16)	6 (5)	3 (3)
Prior ASCT†	120 (94)	87 (90)
Prior treatment refractory status†		
IMiD	126 (98)	Not grouped (highest is Len with 96, 99%)
PI	116 (91)	Not grouped (highest is V with 92, 95%)
Anti-CD38	120 (94)	94 (97)
Triple-class refractory	108 (84)	85 (88)
Penta drug refractory	33 (26)	41 (42)
No. (%) requiring bridging therapy†	112 (88)	Not reported

Ide-cel vs Cilta-cel




Current Medical Research and Opinion

Updated results from a matching-adjusted indirect comparison of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma

Tom Martin, Saad Z. Usmani, Jordan M. Schecter, Tito Roccia, Carolyn C. Jackson, William Deraedt, Tzu-min Yeh, Arnob Banerjee, Lida Pacaud, Ashraf Garrett, Meaghan Bartlett, Anja Haltner, Suzy Van Sanden, Joris Diels, Satish Valluri & Imtiaz A. Samjoo

To cite this article: Tom Martin, Saad Z. Usmani, Jordan M. Schecter, Tito Roccia, Carolyn C. Jackson, William Deraedt, Tzu-min Yeh, Arnob Banerjee, Lida Pacaud, Ashraf Garrett, Meaghan Bartlett, Anja Haltner, Suzy Van Sanden, Joris Diels, Satish Valluri & Imtiaz A. Samjoo (2023) Updated results from a matching-adjusted indirect comparison of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma, Current Medical Research and Opinion, 39:1, 81-89, DOI: 10.1080/03007995.2022.2139052

To link to this article: https://doi.org/10.1080/03007995.2022.2139052

Figure 1. Overall response rates prior to adjustment for cilta-cel and ide-cel. Abbreviations. CR, complete response; PR, partial response; VGPR, very good partial response.

Ide-cel vs Cilta-cel

Table 2. Response rates and comparative efficacy for cilta-cel versus ide-cel.

	Unadjusted comparison			Base case adjusted[a] comparison using FDA-approved doses cohort			All variables adjusted[b] comparison using FDA-approved doses cohort (sensitivity)		
	Observed response rate		OR[c] (95% CI), *p* value	Adjusted response rate	OR[c] (95% CI), *p* value	Relative risk[d]	Adjusted response rate	OR[c] (95% CI), *p* value	Relative risk[d]
	Ide-cel	Cilta-cel	Cilta-cel vs ide-cel	Cilta-cel	Cilta-cel vs ide-cel	Cilta-cel vs ide-cel	Cilta-cel	Cilta-cel vs ide-cel	Cilta-cel vs ide-cel
Overall response rate	74.2%	97.9%	16.52 (3.85, 70.93), $p = .0002$	99.6%	94.93 (21.86, 412.25), $p < .0001$	1.34	99.5%	70.53 (12.23, 406.82), $p < .0001$	1.34
Complete response or better rate	33.1%	82.5%	9.53 (5.01, 18.13), $p < .0001$	73.6%	5.65 (2.51, 12.69), $p < .0001$	2.23	68.8%	4.47 (1.95, 10.26), $p = .0004$	2.08

Abbreviations. CI, confidence interval; ESS, effective sample size; FDA, Food and Drug Administration; OR, odds ratio.

[a]Patients from CARTITUDE-1 who satisfied KarMMa's eligibility criteria were adjusted for refractory status, cytogenetic profile, revised International Staging System stage, and all plasmacytomas in the base case analysis.

[b]Patients from CARTITUDE-1 who satisfied KarMMa's eligibility criteria were adjusted for refractory status, cytogenetic profile, revised International Staging System stage, all plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, age, prior stem cell transplant, Eastern Cooperative Oncology Group status, and sex in the sensitivity analysis.

[c]Odds ratios (ORs) >1 are in favor of cilta-cel versus ide-cel.

[d]Relative risks are equal to the ratio of the adjusted response rates for cilta-cel versus the observed response rates for ide-cel.

Bridging and manufacturing time

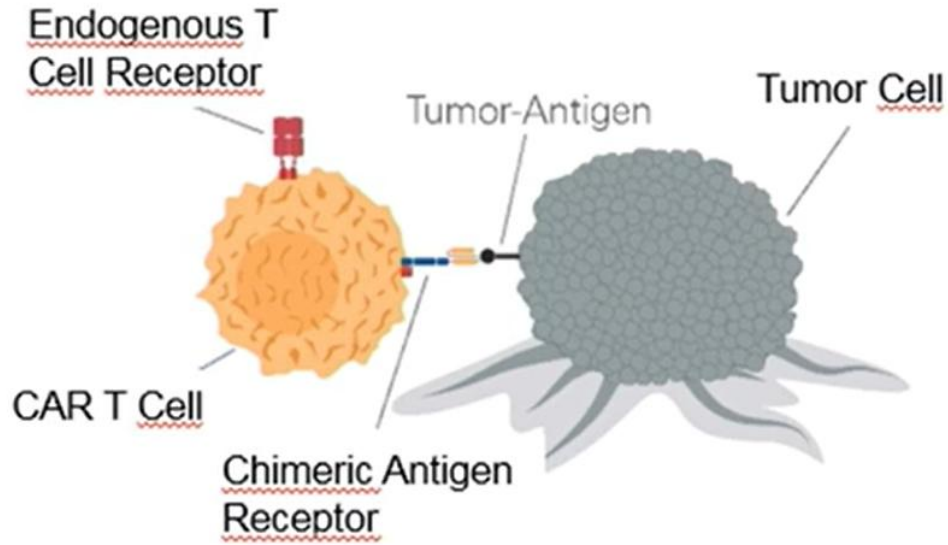
- Current manufacturing time for these products-28 days
- Over 80% required bridging-Very important in reducing toxicity!!
- 8-14% dropped out prior to infusion- mostly due to **disease progression, adverse events or cell manufacturing failure**

- How to overcome? Allogeneic CAR-T cells/ T-charge (in-vivo expansion)

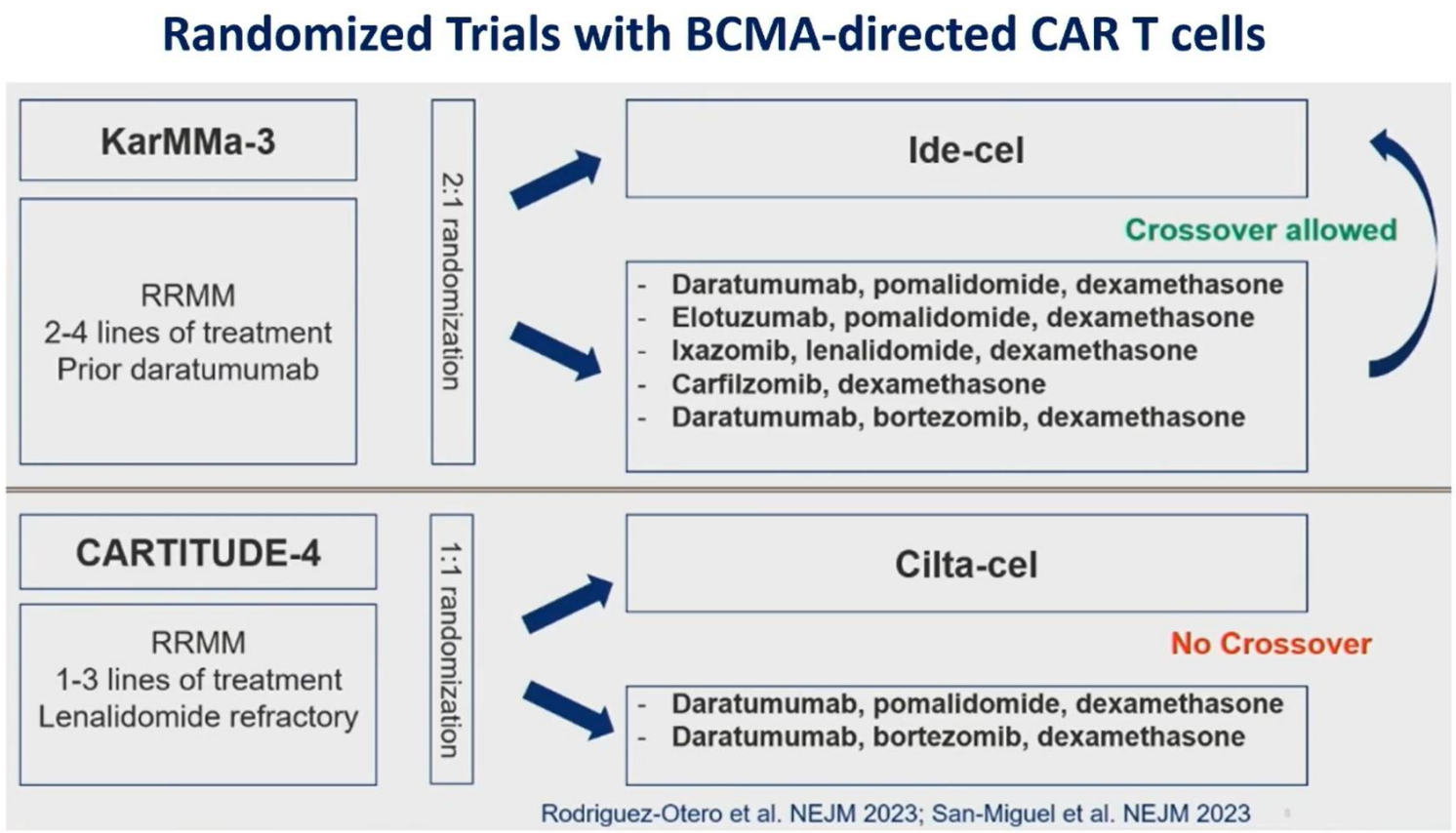
Why earlier application of CAR T cell therapy?

Uniklinikum Würzburg

- Fitter T cells
  - Improved persistence of CAR T cells
  - Improved Myeloma Cell Killing
- Increased Immunogenicity of Tumor cells
  - No selection of resistent clones
  - Lower tumor burden
  - Lower proliferative potential of tumor cells
- Better Tolerability
  - High Attrition Rate with each treatment line
  - Lower hematotoxicity
  - Lower risk of secondary malignancies



Earlier lines



Mailankody, S., presented at ASH 2023

ORIGINAL ARTICLE

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

P. Rodriguez-Otero, S. Ailawadhi, B. Arnulf, K. Patel, M. Cavo, A.K. Nooka, S. Manier, N. Callander, L.J. Costa, R. Vij, N.J. Bahlis, P. Moreau, S.R. Solomon, M. Delforge, J. Berdeja, A. Truppel-Hartmann, Z. Yang, L. Favre-Kontula, F. Wu, J. Piasecki, M. Cook, and S. Giralt

- ide-cel (dose range, 150×106 to 450×106 CAR-positive T cells)
- A total of 386 patients underwent randomization: **254 to ide-cel** and **132 to a standard regimen.**
- At a median follow-up of **18.6 months**, the median progression-free survival was **13.3 months** in the ide-cel group, as compared with **4.4 months** in the standard-regimen group (hazard ratio for disease progression or death, 0.49; 95% confidence interval, 0.38 to 0.65; P<0.001).
- A response occurred in **71%** of the patients in the ide-cel group and in **42%** of those in the standard-regimen group.

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

P. Rodriguez-Otero, S. Ailawadhi, B. Arnulf, K. Patel, M. Cavo, A.K. Nooka, S. Manier, N. Callander, L.J. Costa, R. Vij, N.J. Bahlis, P. Moreau, S.R. Solomon, M. Delforge, J. Berdeja, A. Truppel-Hartmann, Z. Yang, L. Favre-Kontula, F. Wu, J. Piasecki, M. Cook, and S. Giralt

Table 1. (Continued.)

Characteristic	Ide-cel (N=254)	Standard Regimen (N=132)
Previous radiation therapy — no. (%)	90 (35)	46 (35)
Refractory status — no. (%)		
Immunomodulatory agent	224 (88)	124 (94)
Lenalidomide	186 (73)	104 (79)
Pomalidomide	127 (50)	70 (53)
Thalidomide	10 (4)	2 (2)
Proteasome inhibitor	189 (74)	95 (72)
Bortezomib	112 (44)	60 (45)
Carfilzomib	104 (41)	43 (33)
Ixazomib or ixazomib citrate	35 (14)	23 (17)
Anti-CD38 monoclonal antibody	242 (95)	124 (94)
Daratumumab	242 (95)	123 (93)
Isatuximab	1 (<1)	1 (1)
Double-class–refractory disease‡‡	169 (67)	91 (69)
Triple-class–refractory disease§§	164 (65)	89 (67)
Penta-refractory disease¶¶	15 (6)	5 (4)

ORIGINAL ARTICLE

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

P. Rodriguez-Otero, S. Ailawadhi, B. Arnulf, K. Patel, M. Cavo, A.K. Nooka, S. Manier, N. Callander, L.J. Costa, R. Vij, N.J. Bahlis, P. Moreau, S.R. Solomon, M. Delforge, J. Berdeja, A. Truppel-Hartmann, Z. Yang, L. Favre-Kontula, F. Wu,

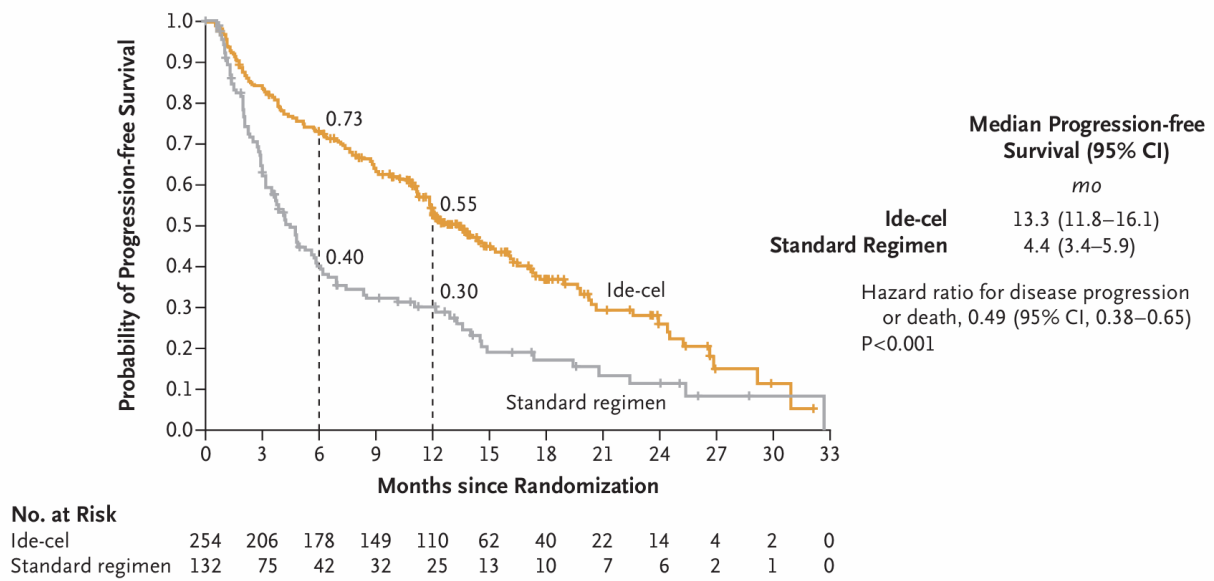
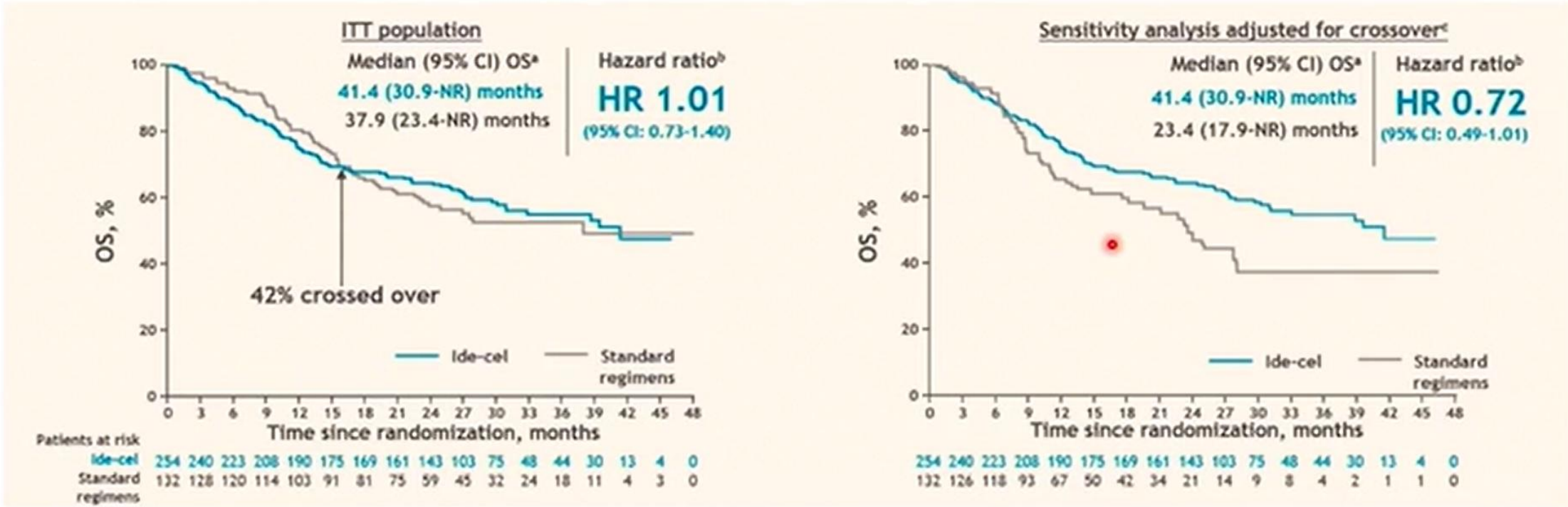


Figure 2. Progression-free Survival (Intention-to-Treat Population).

Progression-free survival was assessed by the independent response committee on the basis of International Myeloma Working Group criteria.[23] The P value was based on a stratified two-sided log-rank test. Data at the dashed lines show the probability of progression-free survival at 6 months and 12 months. Tick marks indicate censored data.

KarMMa-3 study: OS analysis confounded by substantial crossover



More than 50% of patients in the standard regimen arm received ide-cel as subsequent therapy upon confirmed PD, and the majority received ide-cel within 3-16 months of randomization

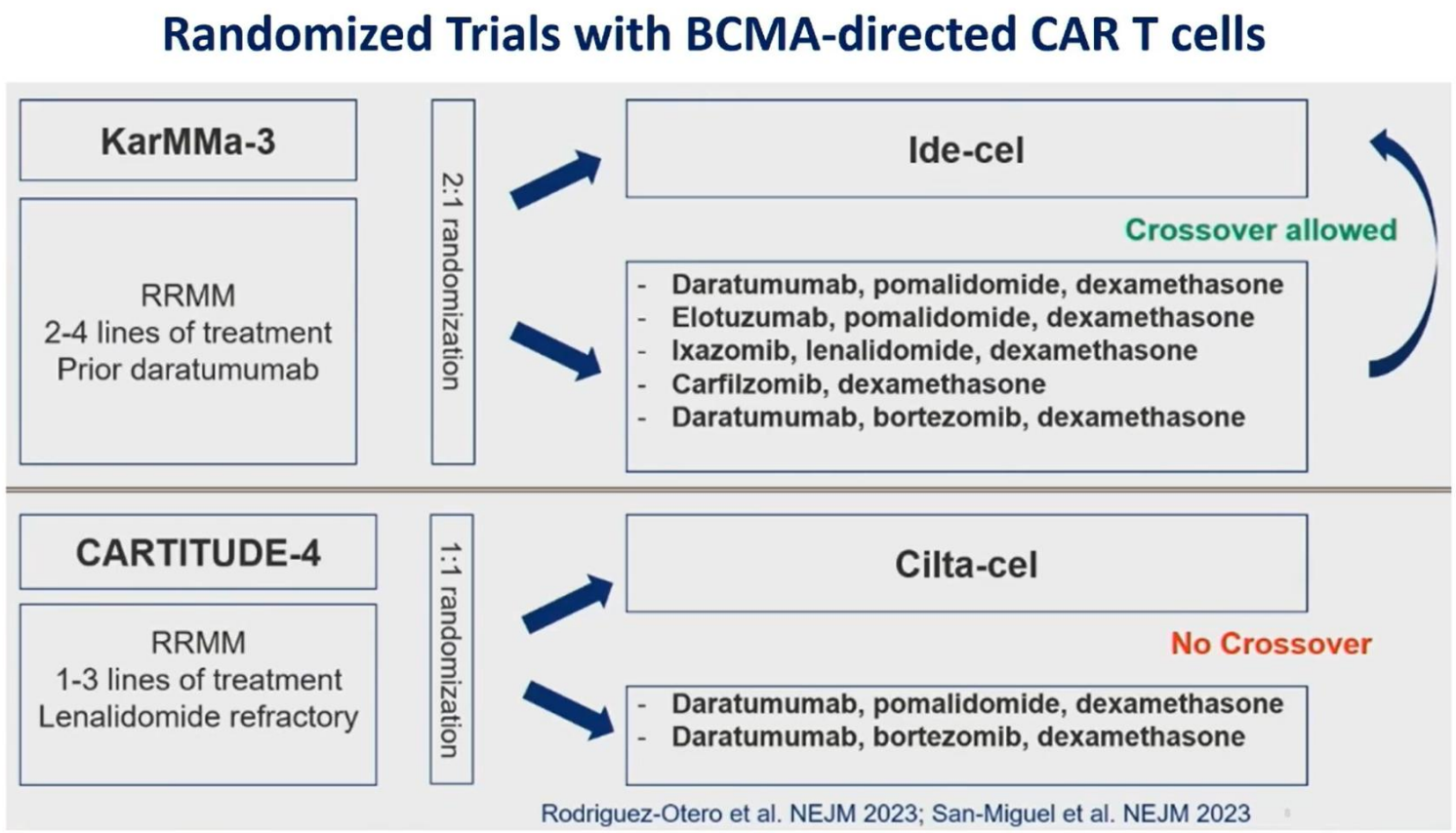
Prespecified crossover-adjusted analysis shows OS benefit of ide-cel

Information fraction for OS was 74% (n = 164/222 required events).
[a]Based on Kaplan-Meier approach; [b]Stratified HR is based on a univariate Cox proportional hazards model. CI is two-sided and calculated by bootstrap method; [c]Two-stage Weibull model without re-censoring (prespecified analysis).
CI, confidence interval; HR, hazard ratio; ide-cel, idecabtagene vicleucel; ITT, intent-to-treat; NR, not reached; OS, overall survival; PD, progressive disease.
Rodriguez Otero P, et al. ASH 2023. Abstract 1028.

Table 3. Adverse Events in the Treated Population and Cytokine Release Syndrome and Neurotoxic Events in the Safety Population.

Event	Ide-cel (N=250)			Standard Regimen (N=126)		
	Any Grade	Grade 3 or 4	Grade 5	Any Grade	Grade 3 or 4	Grade 5
Any adverse event — no. (%)*	248 (99)	233 (93)	36 (14)†	123 (98)	94 (75)	8 (6)†
Hematologic event	224 (90)	218 (87)	0	90 (71)	75 (60)	0
Neutropenia	195 (78)	189 (76)	0	55 (44)	50 (40)	0
Anemia	165 (66)	127 (51)	0	45 (36)	23 (18)	0
Thrombocytopenia	136 (54)	106 (42)	0	36 (29)	22 (17)	0
Lymphopenia	73 (29)	70 (28)	0	25 (20)	23 (18)	0
Leukopenia	72 (29)	71 (28)	0	15 (12)	11 (9)	0
Gastrointestinal event	182 (73)	13 (5)	0	65 (52)	5 (4)	0
Nausea	112 (45)	4 (2)	0	34 (27)	0	0
Diarrhea	85 (34)	4 (2)	0	30 (24)	4 (3)	0
Constipation	67 (27)	0	0	9 (7)	0	0
Vomiting	51 (20)	0	0	11 (9)	0	0
Other adverse event						
Infection	146 (58)	61 (24)	11 (4)	68 (54)	23 (18)	3 (2)
Hypophosphatemia	78 (31)	50 (20)	0	10 (8)	3 (2)	0
Hypokalemia	78 (31)	12 (5)	0	14 (11)	1 (1)	0
Fatigue	69 (28)	4 (2)	0	44 (35)	3 (2)	0
Pyrexia	69 (28)	2 (1)	0	22 (17)	1 (1)	0
Headache	59 (24)	0	0	24 (19)	1 (1)	0
Hypomagnesemia	52 (21)	2 (1)	0	6 (5)	1 (1)	0
Dyspnea	44 (18)	4 (2)	0	27 (21)	2 (2)	0
Cytokine release syndrome — no./total no. (%)‡	197/225 (88)	9/225 (4)	2/225 (1)§	0/126	0/126	0/126
Neurotoxic event — no./total no. (%)¶	34/225 (15)	7/225 (3)	0/225	0/126	0/126	0/126

Earlier lines



Mailankody, S., presented at ASH 2023

July, 2023

ORIGINAL ARTICLE

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

J. San-Miguel, B. Dhakal, K. Yong, A. Spencer, S. Anguille, M.-V. Mateos, C. Fernández de Larrea, J. Martínez-López, P. Moreau, C. Touzeau, X. Leleu, I. Avivi, M. Cavo, T. Ishida, S.J. Kim, W. Roeloffzen, N.W.C.J. van de Donk, D. Dytfeld, S. Sidana, L.J. Costa, A. Oriol, R. Popat, A.M. Khan, Y.C. Cohen, P.J. Ho, J. Griffin, N. Lendvai, C. Lonardi, A. Slaughter, J.M. Schecter, C.C. Jackson, K. Connors, K. Li, E. Zudaire, D. Chen, J. Gilbert, T. Yeh, S. Nagle, E. Florendo, L. Pacaud, N. Patel, S.J. Harrison, and H. Einsele

- A total of **419 patients** underwent randomization (**208** to receive **cilta-cel** and **211** to receive **standard care**).
- At a median follow-up of **15.9 months** (range, 0.1 to 27.3), the **median progression-free survival was not reached** in the **cilta-cel** group and was **11.8 months** in the **standard-care group** (hazard ratio, 0.26).
- Progression-free survival at 12 months was **75.9%** (95% CI, 69.4 to 81.1) in the cilta-cel group and **48.6%** (95% CI, 41.5 to 55.3) in the standard-care group.

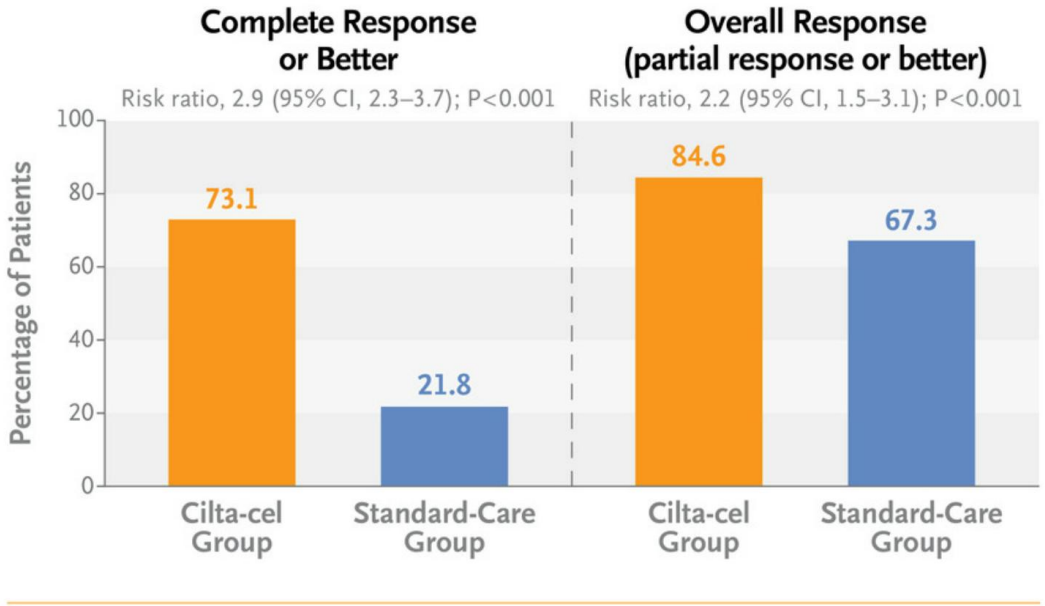
Table 1. (Continued.)

Characteristic	Cilta-cel (N=208)	Standard Care (N=211)
Previous lines of therapy — no. (%)		
1	68 (32.7)	68 (32.2)
2	83 (39.9)	87 (41.2)
3	57 (27.4)	56 (26.5)
Previous immunomodulatory drug — no. (%)	208 (100.0)	211 (100.0)
Lenalidomide	208 (100.0)	211 (100.0)
Pomalidomide	8 (3.8)	10 (4.7)
Previous anti-CD38 antibody	53 (25.5)	55 (26.1)
Daratumumab	51 (24.5)	54 (25.6)
Isatuximab	2 (1.0)	2 (0.9)
Previous proteasome inhibitor — no. (%)	208 (100.0)	211 (100.0)
Bortezomib	203 (97.6)	205 (97.2)
Carfilzomib	77 (37.0)	66 (31.3)
Ixazomib	21 (10.1)	21 (10.0)
Triple-class exposure — no. (%)‖	53 (25.5)	55 (26.1)
Penta-drug exposure — no. (%)**	14 (6.7)	10 (4.7)
Refractory status — no. (%)		
Lenalidomide	208 (100.0)	211 (100.0)
Bortezomib	55 (26.4)	48 (22.7)
Carfilzomib	51 (24.5)	45 (21.3)
Any anti-CD38 antibody	50 (24.0)	46 (21.8)
Daratumumab	48 (23.1)	45 (21.3)
Ixazomib	15 (7.2)	17 (8.1)
Pomalidomide	8 (3.8)	9 (4.3)
Triple-class‖	30 (14.4)	33 (15.6)
Penta-drug**	2 (1.0)	1 (0.5)

ORIGINAL ARTICLE

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

J. San-Miguel, B. Dhakal, K. Yong, A. Spencer, S. Anguille, M.-V. Mateos, C. Fernández de Larrea, J. Martínez-López, P. Moreau, C. Touzeau, X. Leleu, I. Avivi, M. Cavo, T. Ishida, S.J. Kim, W. Roeloffzen, N.W.C.J. van de Donk, D. Dytfeld, S. Sidana, L.J. Costa, A. Oriol, R. Popat, A.M. Khan, Y.C. Cohen, P.J. Ho, J. Griffin, N. Lendvai, C. Lonardi, A. Slaughter, J.M. Schecter, C.C. Jackson, K. Connors, K. Li, E. Zudaire, D. Chen, J. Gilbert, T. Yeh, S. Nagle, E. Florendo, L. Pacaud, N. Patel, S.J. Harrison, and H. Einsele



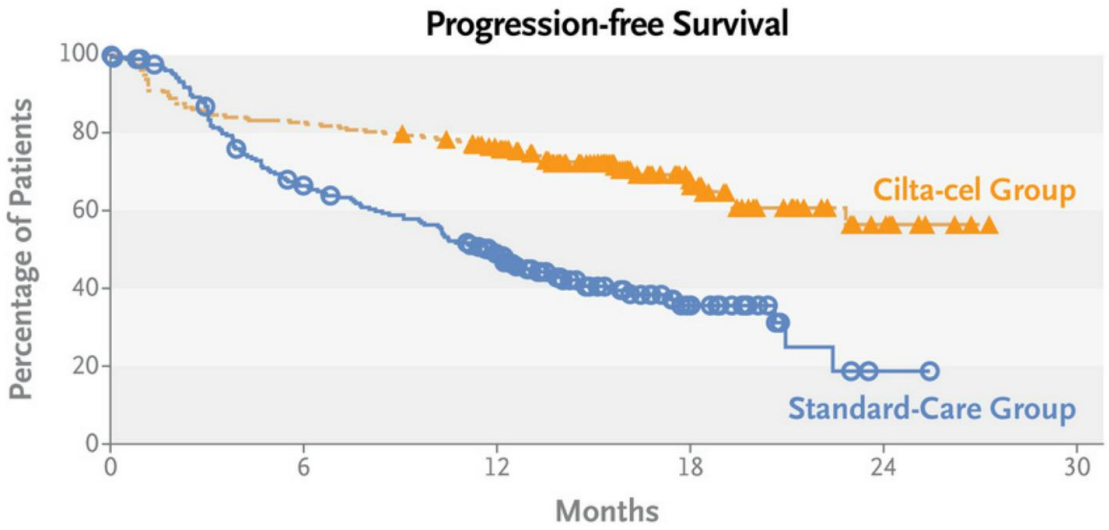


Table 3. Adverse Events (Safety Population).*

Adverse Event	Cilta-cel (N=208)		Standard Care (N=208)	
	All	Grade 3 or 4	All	Grade 3 or 4
Any adverse event — no. (%)	208 (100.0)	201 (96.6)	208 (100.0)	196 (94.2)
Hematologic event — no. (%)	197 (94.7)	196 (94.2)	185 (88.9)	179 (86.1)
Neutropenia	187 (89.9)	187 (89.9)	177 (85.1)	171 (82.2)
Thrombocytopenia	113 (54.3)	86 (41.3)	65 (31.2)	39 (18.8)
Anemia	113 (54.3)	74 (35.6)	54 (26.0)	30 (14.4)
Lymphopenia	46 (22.1)	43 (20.7)	29 (13.9)	25 (12.0)
Infection — no. (%)	129 (62.0)	56 (26.9)	148 (71.2)	51 (24.5)
Upper respiratory tract†	39 (18.8)	4 (1.9)	54 (26.0)	4 (1.9)
Covid-19‡	29 (13.9)	6 (2.9)	55 (26.4)	12 (5.8)
Lower respiratory tract or lung§	19 (9.1)	9 (4.3)	36 (17.3)	8 (3.8)
Other — no. (%)				
Nausea	101 (48.6)	0	38 (18.3)	2 (1.0)
Hypogammaglobulinemia	88 (42.3)	15 (7.2)	13 (6.2)	1 (0.5)
Diarrhea	70 (33.7)	8 (3.8)	56 (26.9)	5 (2.4)
Fatigue	60 (28.8)	4 (1.9)	68 (32.7)	2 (1.0)
Headache	55 (26.4)	0	27 (13.0)	0
Constipation	49 (23.6)	1 (0.5)	44 (21.2)	2 (1.0)
Hypokalemia	39 (18.8)	8 (3.8)	14 (6.7)	3 (1.4)
Asthenia	36 (17.3)	1 (0.5)	34 (16.3)	5 (2.4)
Peripheral edema	35 (16.8)	0	24 (11.5)	2 (1.0)
Decreased appetite	34 (16.3)	2 (1.0)	11 (5.3)	0
Peripheral sensory neuropathy	33 (15.9)	0	38 (18.3)	1 (0.5)
Back pain	33 (15.9)	2 (1.0)	39 (18.8)	2 (1.0)
Arthralgia	32 (15.4)	2 (1.0)	25 (12.0)	1 (0.5)
Pyrexia	32 (15.4)	0	32 (15.4)	2 (1.0)
Dyspnea	28 (13.5)	1 (0.5)	41 (19.7)	1 (0.5)
Insomnia	23 (11.1)	2 (1.0)	52 (25.0)	6 (2.9)
CAR-T–associated adverse event — no./total no.¶				
Cytokine release syndrome	134/176 (76.1)	2/176 (1.1)	—	—
Neurotoxicity‖	36/176 (20.5)	5/176 (2.8)	—	—
Immune effector cell–associated neurotoxicity syndrome and associated symptoms	8/176 (4.5)	1/176 (0.1)	—	—
Other	30/176 (17.0)	4/176 (2.3)	—	—
Movement or neurocognitive	1/176 (0.6)	0	—	—

KarMMa-3 vs CARTITUDE-4

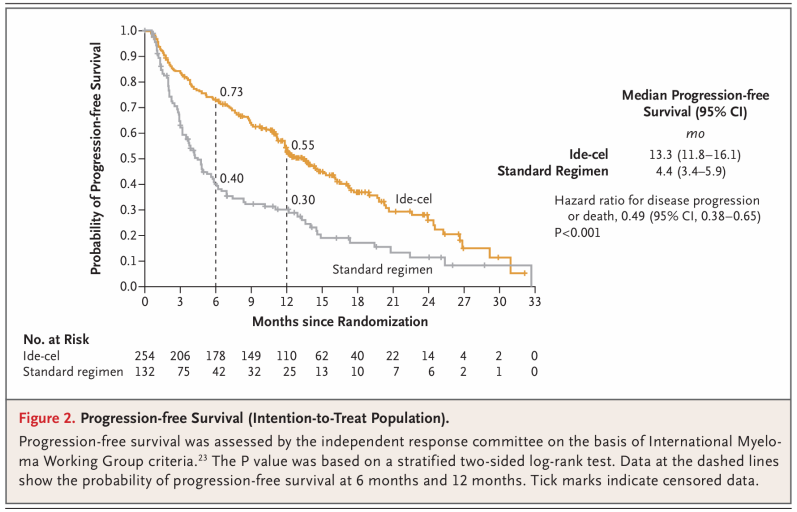
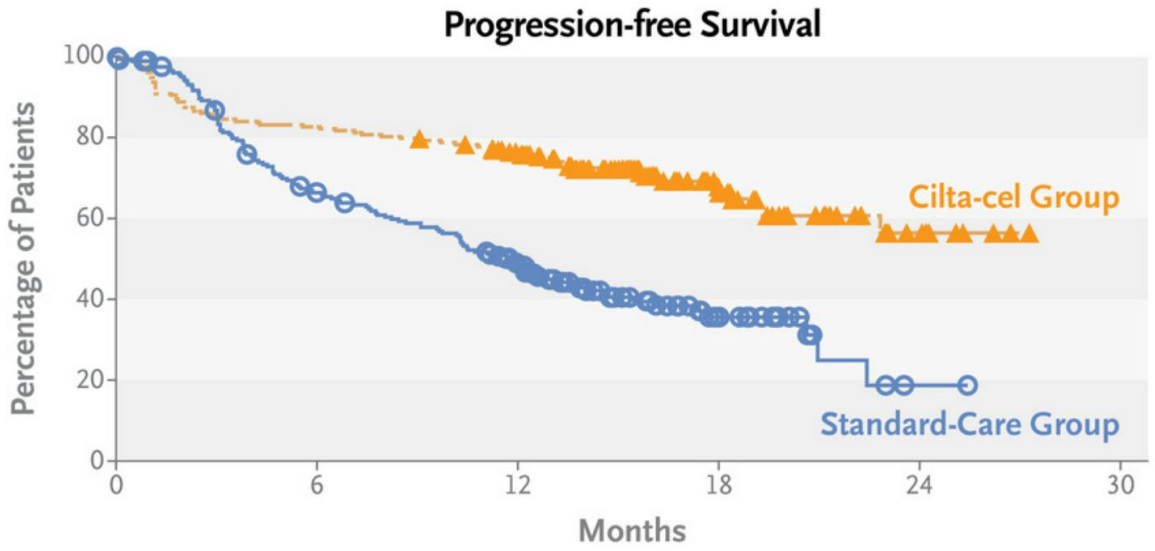


Figure 2. Progression-free Survival (Intention-to-Treat Population).
Progression-free survival was assessed by the independent response committee on the basis of International Myeloma Working Group criteria.[23] The P value was based on a stratified two-sided log-rank test. Data at the dashed lines show the probability of progression-free survival at 6 months and 12 months. Tick marks indicate censored data.

Higher percentage of triple class refractory(65% vs 25%)
OS?



OS-trend

At the second interim analysis, overall survival (OS) was significantly improved with cilta-cel vs SoC (HR, 0.55; *P*=0.0009).

Cilta-cel first line

Table 2. Ongoing phase 3 clinical trials of ide-cel and cilta-cel in earlier lines

	CARTITUDE-5	CARTITUDE-6
Setting	NDMM following VRd without planned ASCT	NDMM, transplant eligible, following DVRd
Product	Cilta-cel	Cilta-cel
Control arm	Rd maintenance	ASCT
Primary end point	PFS	PFS, sustained MRD-CR
Estimated enrollment	650	750
Study start date	June 2021	February 2022
Estimated primary completion date	June 2026	June 2026
NCT ID	NCT04923893	NCT05257083

DVRd, daratumumab, bortezomib, lenalidomide and dexamethasone; NDMM, newly diagnosed multiple myeloma; VRd, bortezomib, lenalidomide and dexamethasone.

Treatment landscape in MM[1]

1L treatment[1,2]

ASCT eligible	ASCT ineligible
Anti-CD38 mAb + PI + IMiD + DEX	DARA-LEN-DEX
ASCT	DARA-VMP
LEN	RVd

2L treatment[1,2]

Based on sensitivity/refractoriness to DARA and LEN

Anti-CD38 mAb + carfilzomib-DEX	Pomalidomide-bortezomib-DEX
Anti-CD38 mAb + pomalidomide-DEX	Selinexor-bortezomib-DEX
	Carfilzomib-DEX

3L treatment[1,2]

Anti-CD38 mAb + pomalidomide-DEX

Elotuzumab-pomalidomide-DEX

(Previous combinations, if elegible)

4L treatment[1,3-7]

BCMA-targeted therapy[3-6]		GPRC5D-targeted therapy[7]
CAR T cells	**BsAbs**	**BsAbs**
Ide-cel	Teclistamab	Talquetamab
Cilta-cel	Elranatamab	

1L, first line; 2L, second line; 3L, third line; 4L, fourth line; ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CD, cluster of differentiation; cilta-cel, ciltacabtagene autoleucel; DARA, daratumumab; DEX, dexamethasone; GPRC5D, G-protein coupled receptor 5D; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory drug; LEN, lenalidomide; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; RVd, lenalidomide, bortezomib and dexamethasone; VMP, bortezomib, melphalan and prednisone.

1. Mateos MV, personal communication; 2. Dimopoulos MA, et al. Ann Oncol. 2021;32:309-322; 3. Ide-cel SmPC 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/abecma-epar-product-information_en.pdf (accessed January 2024); 4. Cilta-cel SmPC 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/carvykti-epar-product-information_en.pdf (accessed January 2024); 5. Teclistamab SmPC 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/tecvayli-epar-product-information_en.pdf (accessed January 2024); 6. Elranatamab SmPC 2023. Available at: https://ec.europa.eu/health/documents/community-register/2023/20231207161098/anx_161098_en.pdf (accessed January 2024); 7. Talquetamab SmPC 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/talvey-epar-product-information_en.pdf (accessed January 2024).

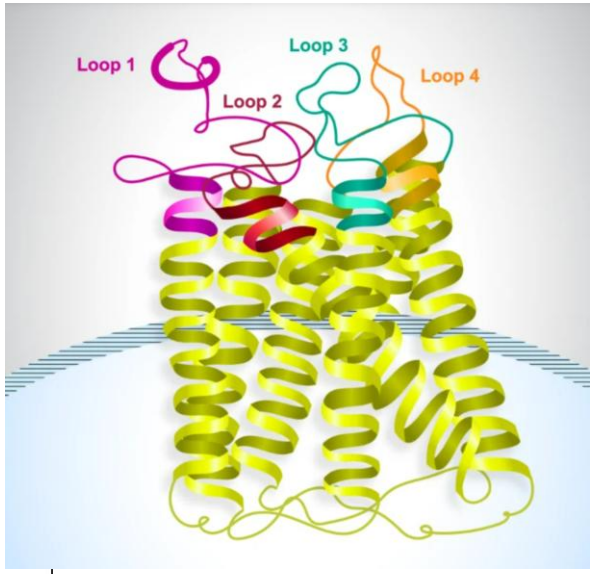
IBSAL

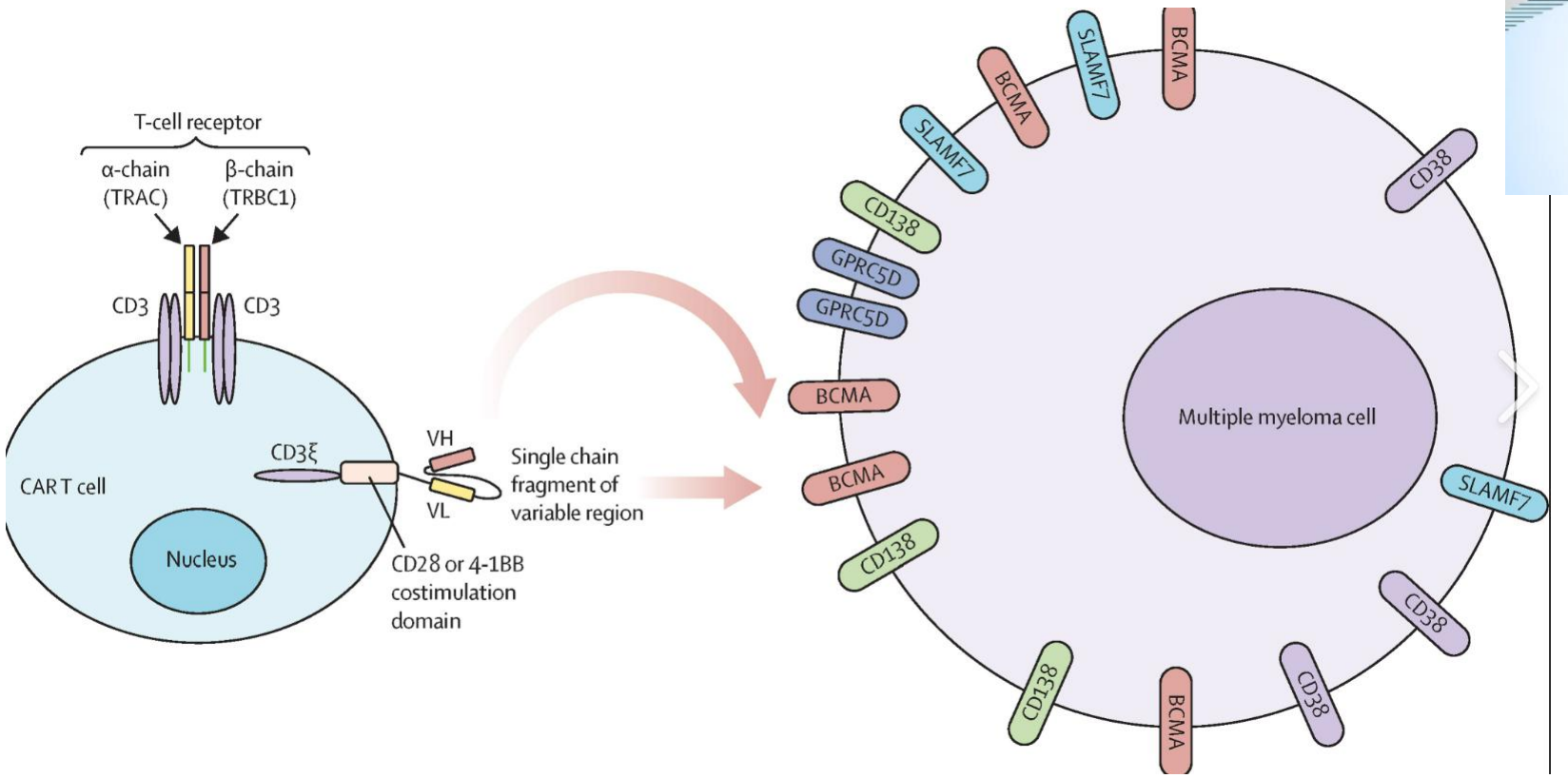
Role of maintanance

Key features suggesting the need for maintenance therapy:

- The absence of a clear plateau in PFS differs from what has been observed in DLBCL or B-ALL ??with currently approved CD-19-directed CAR-T cells.
- MM is a very heterogeneous disease with clonal heterogeneity and a highly deregulated marrow microenvironment.

Beyond BCMA

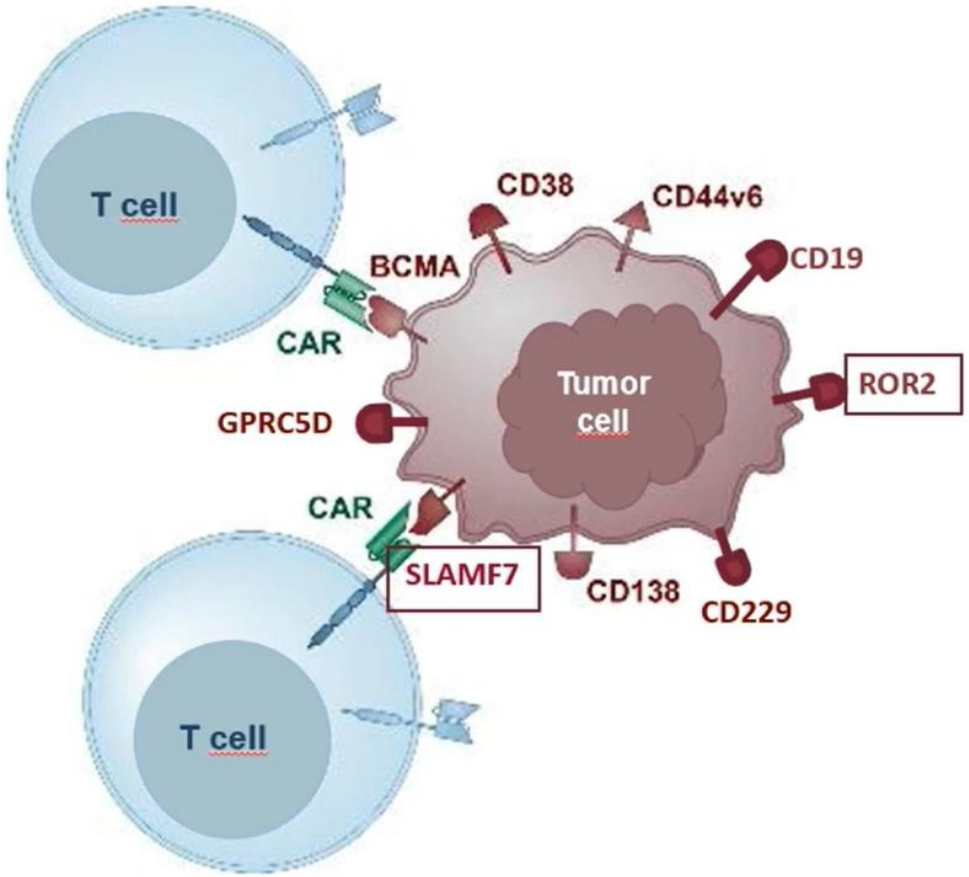




plasma cells and in epithelial structures of the skin and tongue

CAR T Cell Therapy in Multiple Myeloma: Beyond BCMA and GPRC5D

Uniklinikum Würzburg



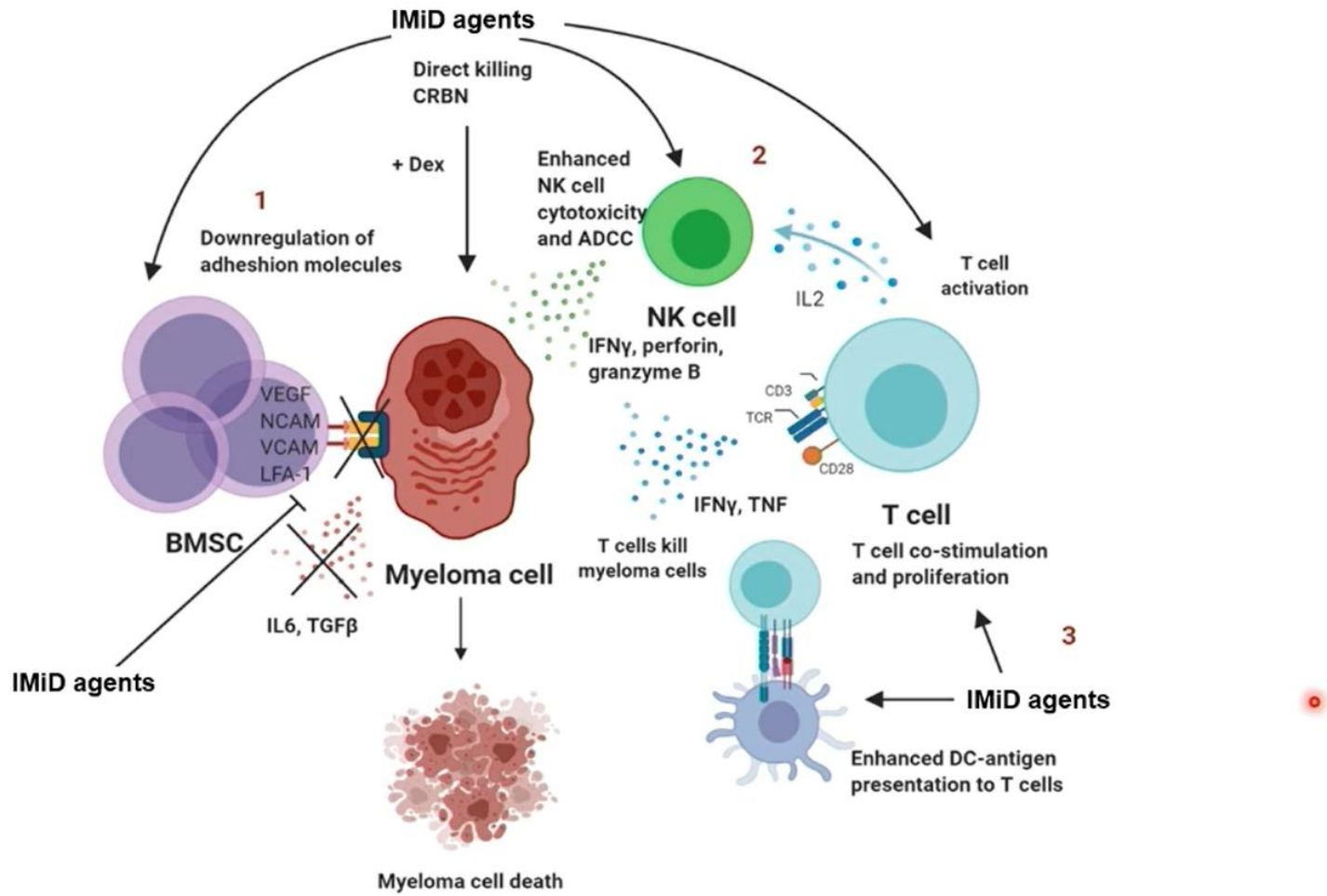
Danhof, S. et al., Safety and Feasibility of SLAMF7 CAR-T Cells in Multiple Myeloma
Thursday, February 15, 19:00h - BA1 Best Abstracts and Awards

Weber, J. et al., ROR2-CART Elicit Potent Anti-tumor Reactivity in MM and ccRCC
Thursday, February 15, 20:15h - PT2 Poster Tour 2

16:56

Modulation of the bone marrow microenvironment prior to immune therapy may be beneficial

Uniklinikum Würzburg



D'Souza C., et al., Front Immunol 2021;12:632399

Key points in MM

- BCMA-directed CAR-T cell therapy shows very encouraging results in triple-class refractory multiple myeloma populations, but there is not yet a survival plateau
- To maintain responses and prolong survival, different strategies are being investigated, such as **dual targeting** to prevent antigen loss, **manufacturing changes** to increase the proportion of long-lived T cells with a memory phenotype in the infused product, to **consolidate responses is combination with immunostimulatory drugs**, such as IMIDs or checkpoint inhibitors, to improve functional CAR-T cell persistence and avoid exhaustion.

Key points in MM

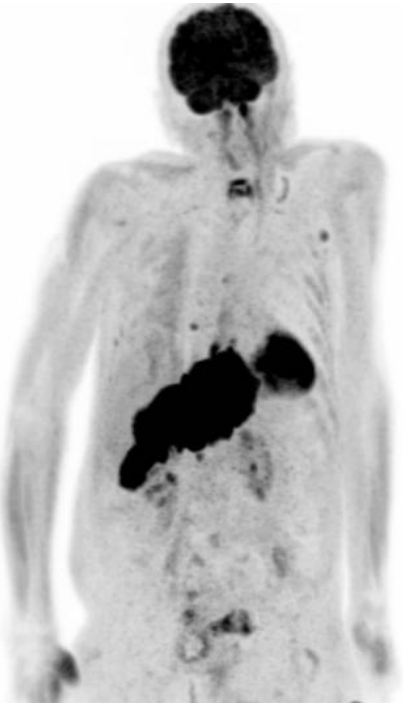
- Data are **not** yet available to elucidate what **optimal rescue therapies** should be proposed after CAR-T cell progression.
- Salvage treatments should include drugs with new mechanisms of action (Selinexor, CelMods) or targeting different antigens on the surface of plasma cells (i.e., GPRC5dD (talquetamab) or FcRH5 (cevostamab).

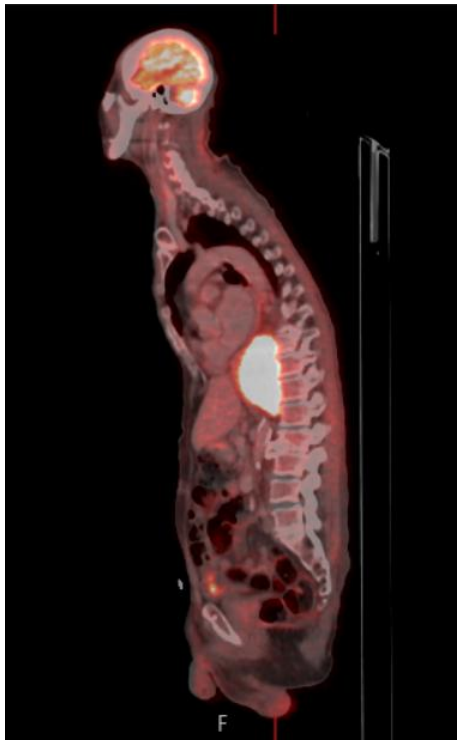
Case presentation

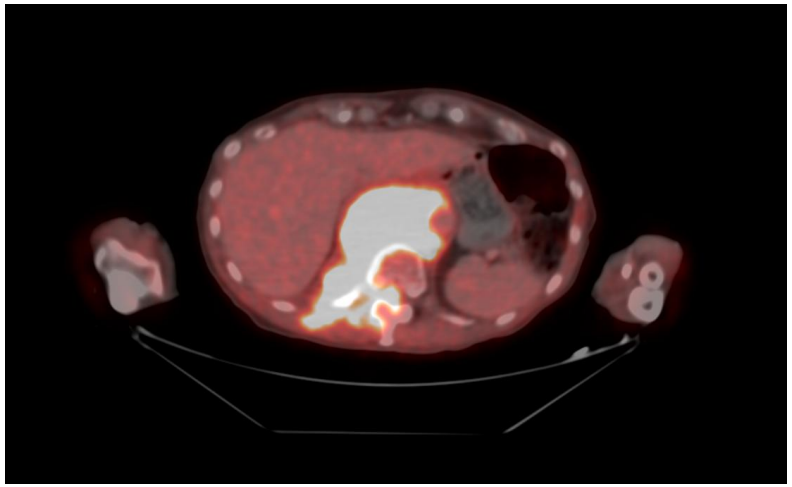
- Initial presentation (February 2024) – 79 y.o male presented with **spinal cord compression** (back pain, leg weakness, and urinary retention). Imaging revealed a substantial mass compressing the spinal cord from T11 to L5 vertebrae. LDH -315
- Past medical history – hypertension, **atrial fibrillation** (treated with apixaban, s/p 2 ablations), **ischemic heart disease**.
- Pathology report: Cores of **mantle cell lymphoma**, positive for CD19, CD20, PAX5, bcl1, SOX11, CD5, bcl2. A subset of cells are positive for bcl6, MUM1. **Ki67 is 70-80%**. C-myc positive in 5% of cells. Negative for CD10, CD30, TDT, CD23.

Case presentation

- PET-CT (FDG) –
  - High FDG uptake in a 9*14*14.5 cm mass spanning the **posterior mediastinum, retro-caval and retroperitoneal regions.**
  - The mass **engulfs the descending aorta**, **erodes the T10-L1 vertebrae**, and **compresses the spinal canal** these levels.
  - Additional uptakes in the left axilla and right internal mammary and supra-diaphragmatic lymph nodes.
- **In short – stage 4B mantle cell lymphoma with a high proliferation index and spinal cord compression on presentation. MIPI score = 8 (high risk). TP53 unmutated (FISH).**

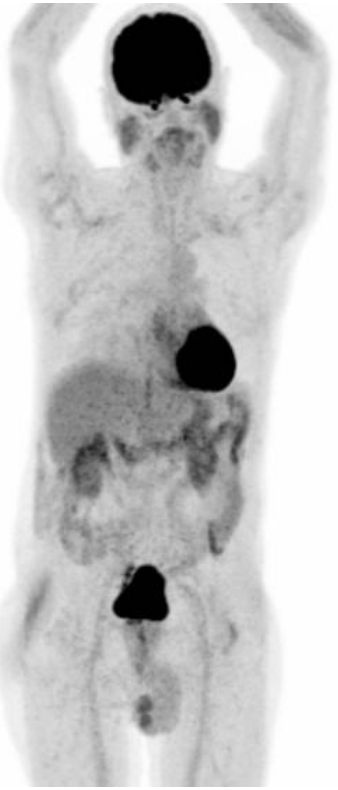


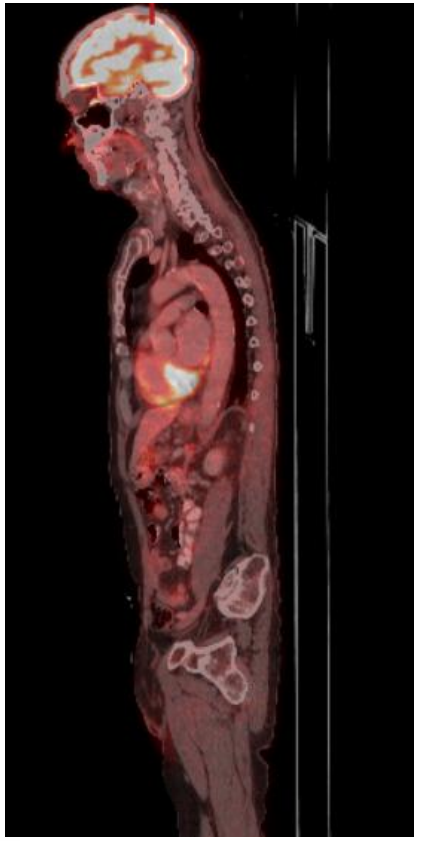


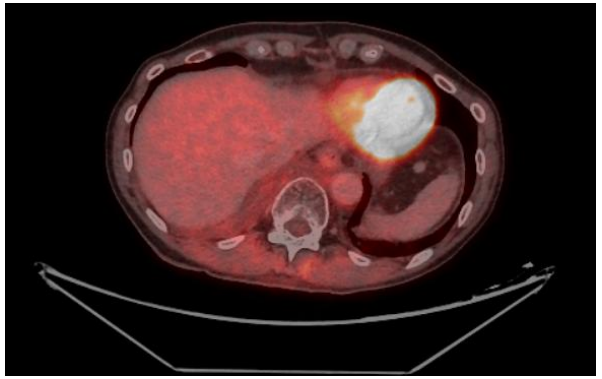


Initial management

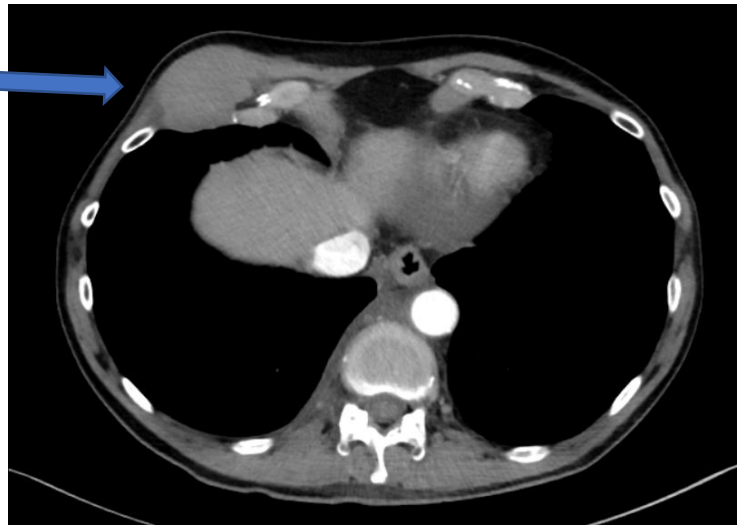
- The patient was **emergently treated with high-dose dexamethasone and radiotherapy** to the T9-L2 vertebral levels (30 cGy total).
  - **Remarkable improvement with treatment** – the patient could walk again and was weaned off a urinary catheter.
- 1st line treatment (initiated on 5/3/24) - **Rituximab + bendamustine** (70 mg/m^2)
  - Interim PET-CT after 3 cycles (21/5/24) – **complete metabolic response**.
  - Completed 6th cycle (26/7/24), PET-CT (2/9/24) – maintained CMR.



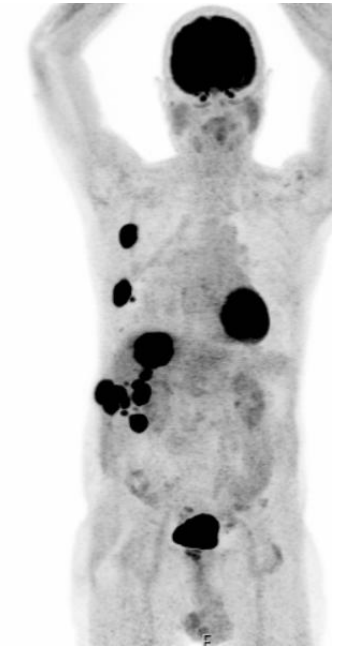


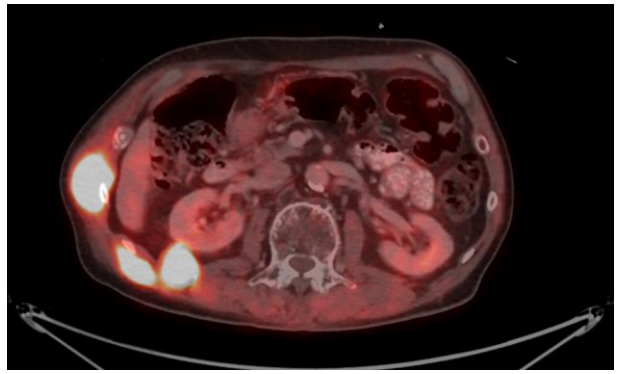


Subsequent disease course



- Relapse (29/10/24) –appearance of a 7 cm lesion palpable on the right ribs. **Biopsy confirmed MCL relapse.**
  - PET-CT (20/11/24) - several new masses in the thoracic wall and abdomen.
- 2nd line treatment (initiated on 25/11/24) - **acalabrutinib 100mg once daily**.
  - No clear clinical improvement with treatment. **Dose increased to 100mg twice daily (17/12/24)**
  - **Last follow-up (31/12/24) – only a minor improvement.**
- **3rd line treatment needed**

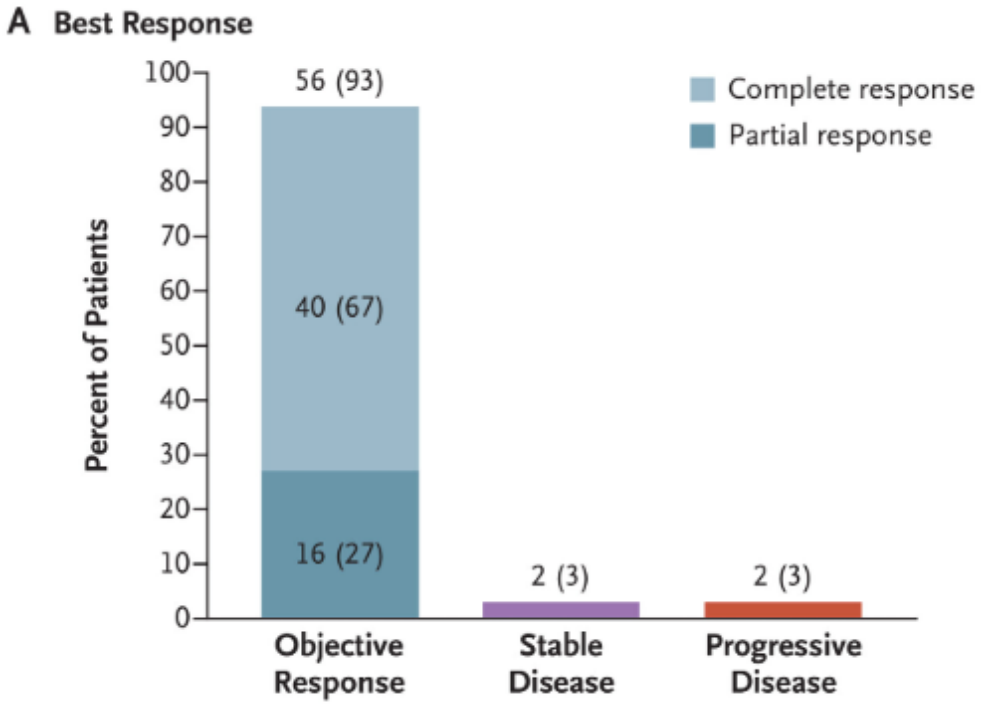




Treatment options for R/R MCL

- **Other chemo-immunotherapy combinations (e.g. RCHOP, RBAC, GemOX)**
- **Autologous stem cell transplant** - not applicable in a 79 y.o man (ECOG PS=0)
- **CD19 CAR-T cell therapy**
  - Brexucabtagene autoleucel (Tecartus®)
  - Lisocabtagene maraleucel (Breyanzi®)
  - **Non-covalent BTK inhibitors (e.g. pirtobrutinib)**
- **Clinical trial**

CAR-T cells



- The anti-CD19 brexu-cel was approved in July 2020 for R/R MCL.
- The ZUMA-2 trial [1]:
  - Median age 65 (range 35-79)
  - **All patients had received prior BTKi** (85% ibrutinib)
  - Responses: ORR – 93%, CR – 67%. 1-year PFS – 61%.
  - **Non-negligible toxicity**:
    - Grade≥3 adverse events – 99% of patients.
    - 32% had grade≥3 infections
    - **CRS – 91% of patients, grade ≥3 in 15% of patients**
    - **Neurologic events (not specified as ICANS) – 63%, grade ≥3 in 31% of patients**
- 3-year f/u of ZUMA-2 [2] – median DOR – 28.2 months, median PFS – 25.8 months, median OS – 46.6 months. Late AEs were rare (3%).
- The results from the ZUMA-18 (an ongoing open-label, expanded-access study) are consistent with the above [3]

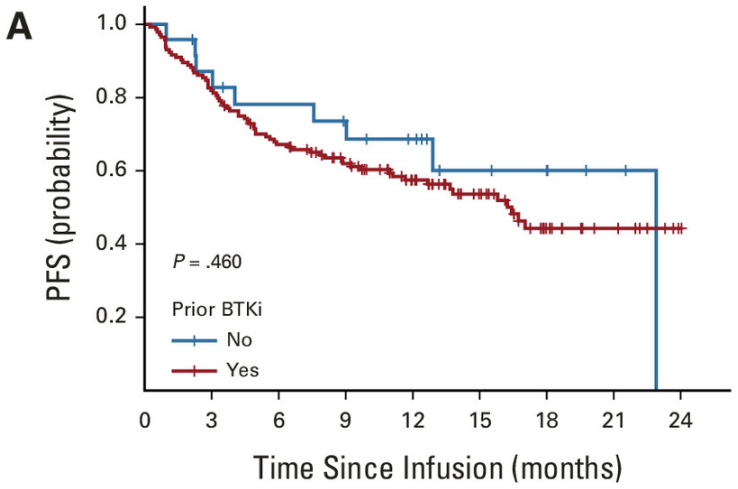
[1] Wang M et al, NEJM 2020

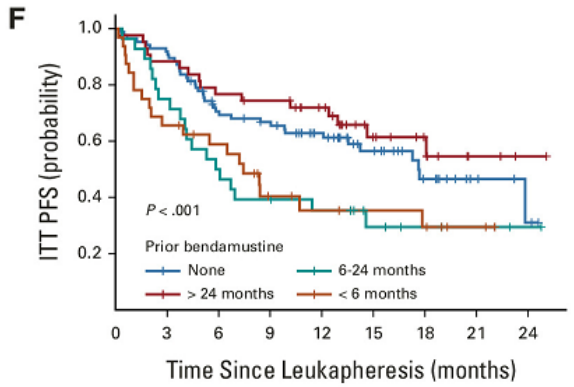
[2] Wang M et al, JCO 2023

[3] Goy A et al, 2023 ASH abstract

CAR-T cells

- In a “real-world” study on 189 patients, results were encouraging [1]
  - Median age 67 (range 34-89)
  - ORR – 90%, CR – 82%. 1-year PFS – 69%
  - Of note – **79% would not have met ZUMA-2 eligibility criteria** (mostly d/t comorbidities, disease status and prior lines of therapy).
  - **Grade ≥ 3 CRS – 8%; Grade ≥ 3 neurotoxicity - 32%**
  - **Patients with recent bendamustine exposure (<24 months before leukapheresis) had shorter PFS and OS on UV analysis.**

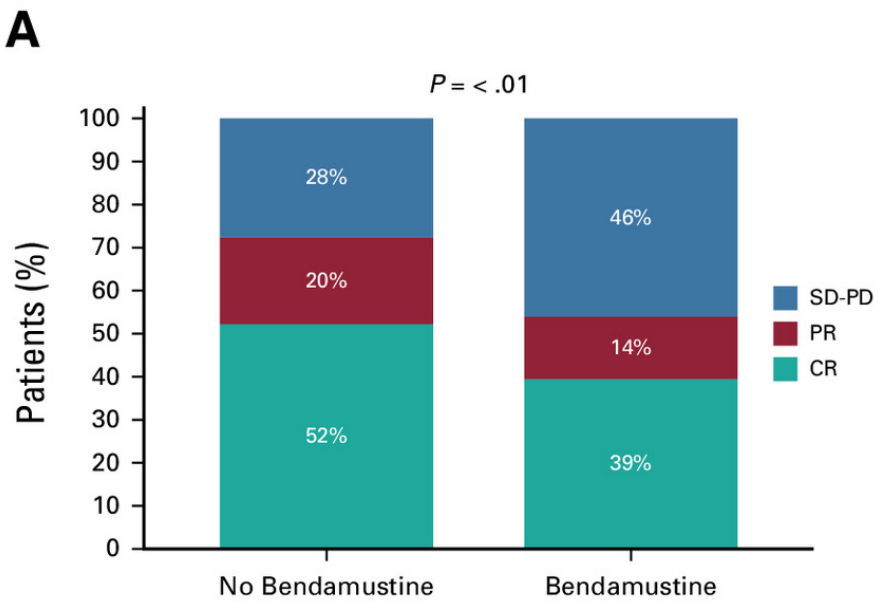




[1] Wang Y et al, JCO 2023

The bendamustine complexity

- Several studies have reported **concerns in patients who received prior bendamustine**:
  - MCL patients treated with bendamustine exhibited **lymphocyte recovery only at 9-12 months post-treatment**. [1]
  - DLBCL patients exposed to bendamustine < 9 months before leukapheresis for CD19 CAR T-cells had **inferior ORR, PFS, and OS**. [2]



[1] Donzelli L et al, Ann Hematol 2024

[2] Iacoboni G et al, JCO 2024

Discussion

1. At this time, should this patient be considered for brexu-cel?
2. If available, is pirtobrutinib the best choice at this time?

Case continue

1. Pirtobrutinib initiated for 3 months- refractory
2. Apharesis for brexu-cel and administration of CAR-T cells.
3. During hospitalization- CRS grade 2 and ICANS grade 3