CAR-T, bi-specifics and drugs in the pipeline

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ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

University of Southampton

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Celgene, a Bristol Myers Squibb Company	Research funding, advisory board, honorarium, travel to scientific conferences
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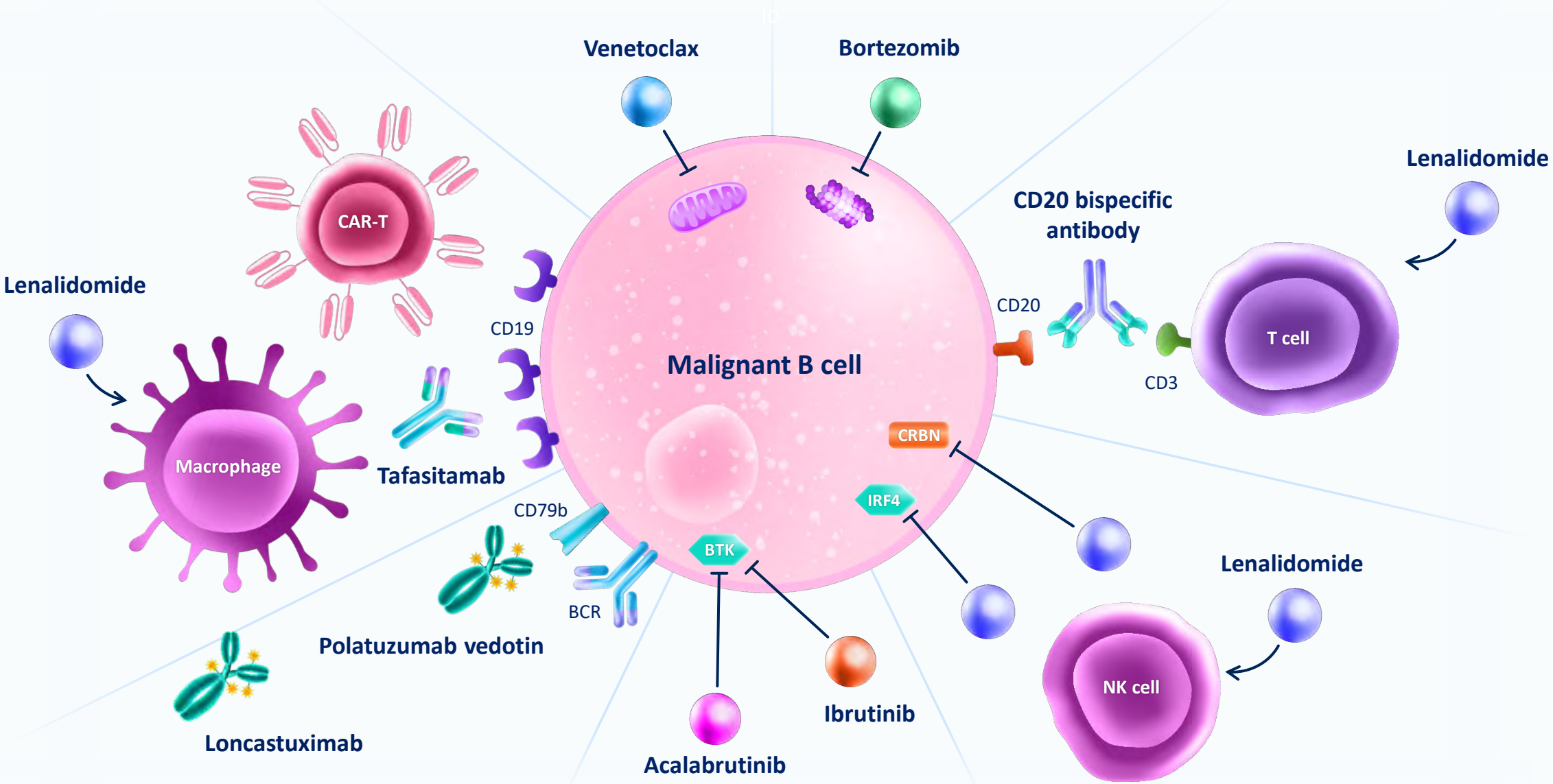
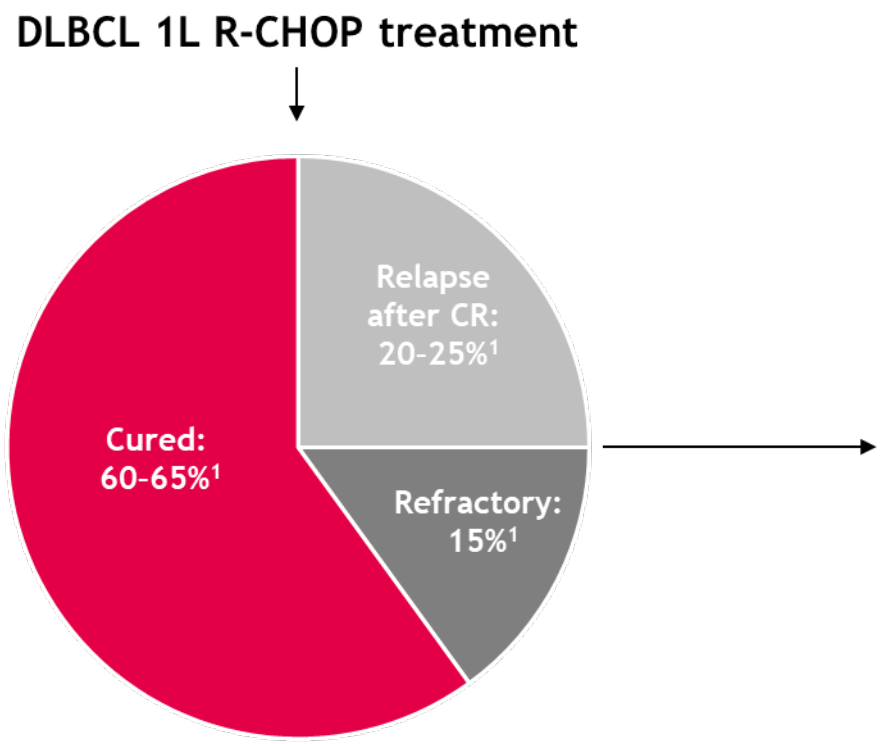
Abbvie	Advisory Boards, honorarium
Genmab	Advisory Boards
Janssen	Honorarium, research support
MSD	Research support
Acerta Pharma/AstraZeneca	Research support, honorarium
Prelude	Advisory Board
Incyte	Advisory board
Sobi	Advisory Board

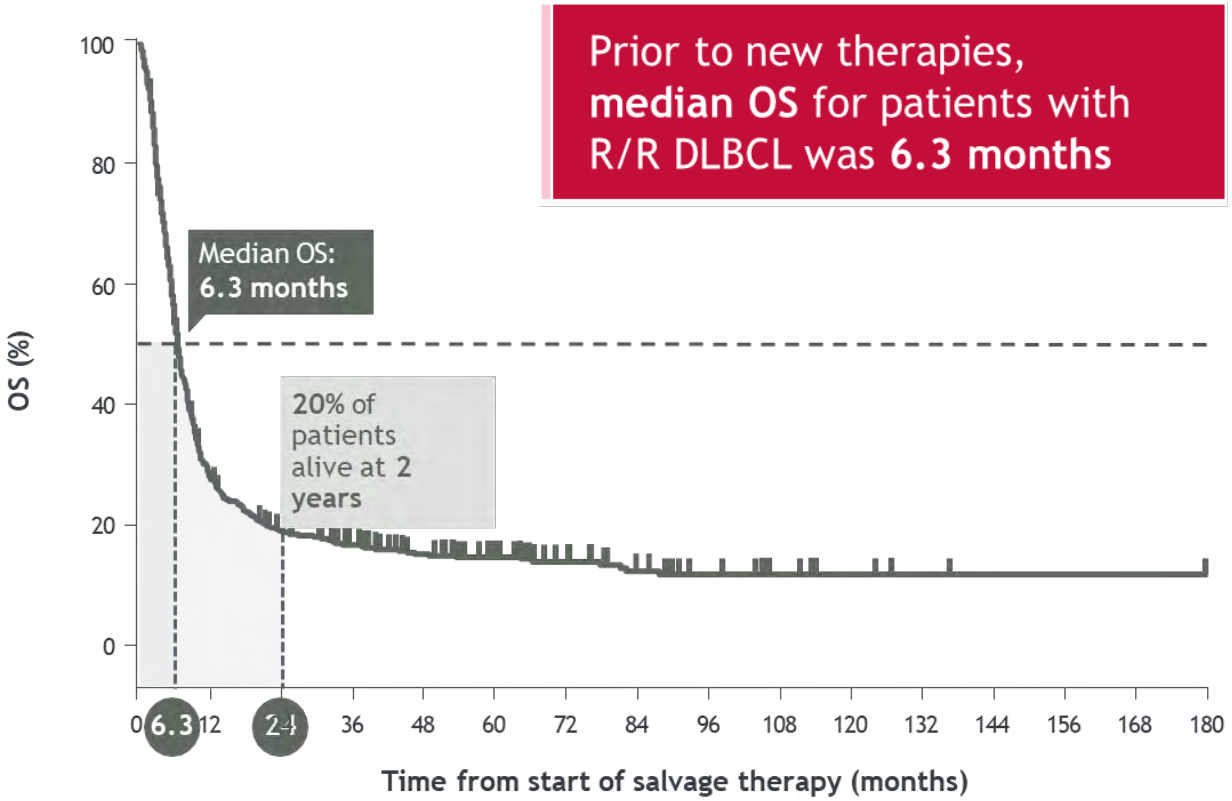
New therapeutic targets



Diffuse large B-cell lymphoma

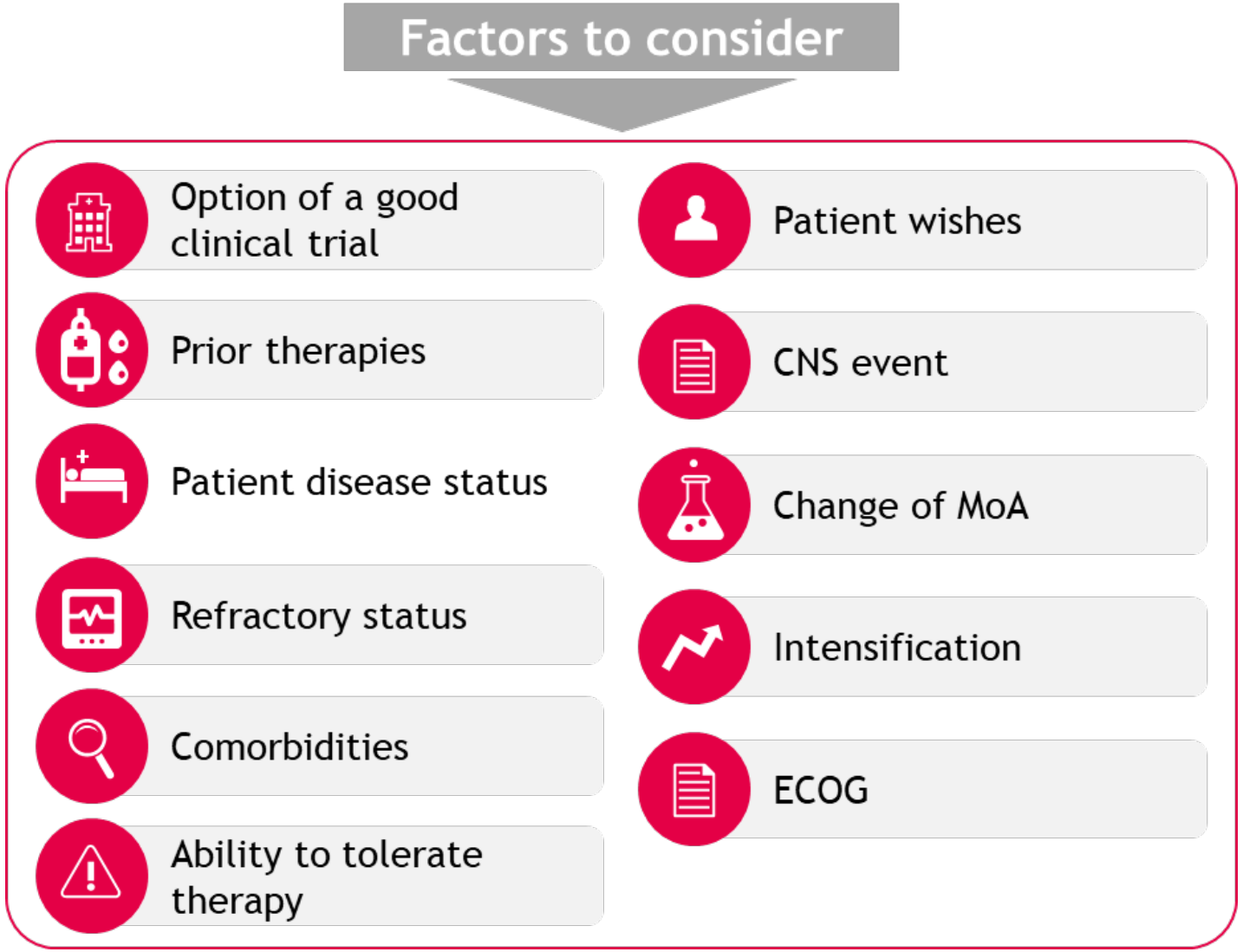
Outcomes are poor for patients who are refractory to or relapse following 1L therapy



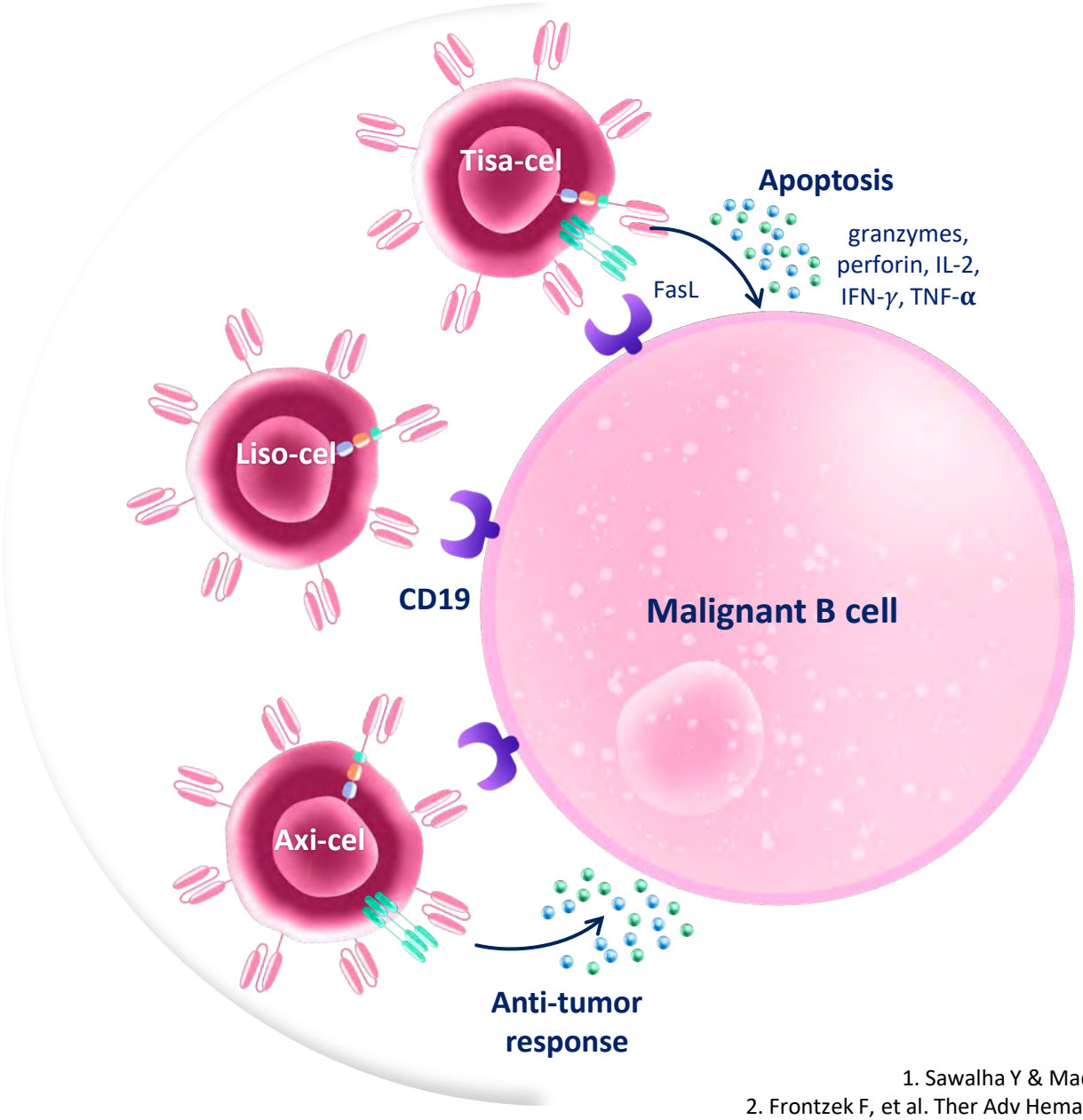


1L, first line; 2L, second line; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone

New therapies: More considerations

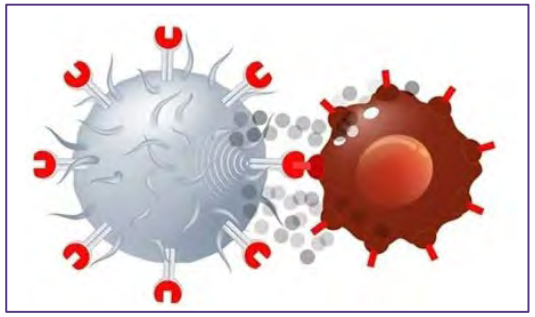


CAR-Ts target CD19 in DLBCL

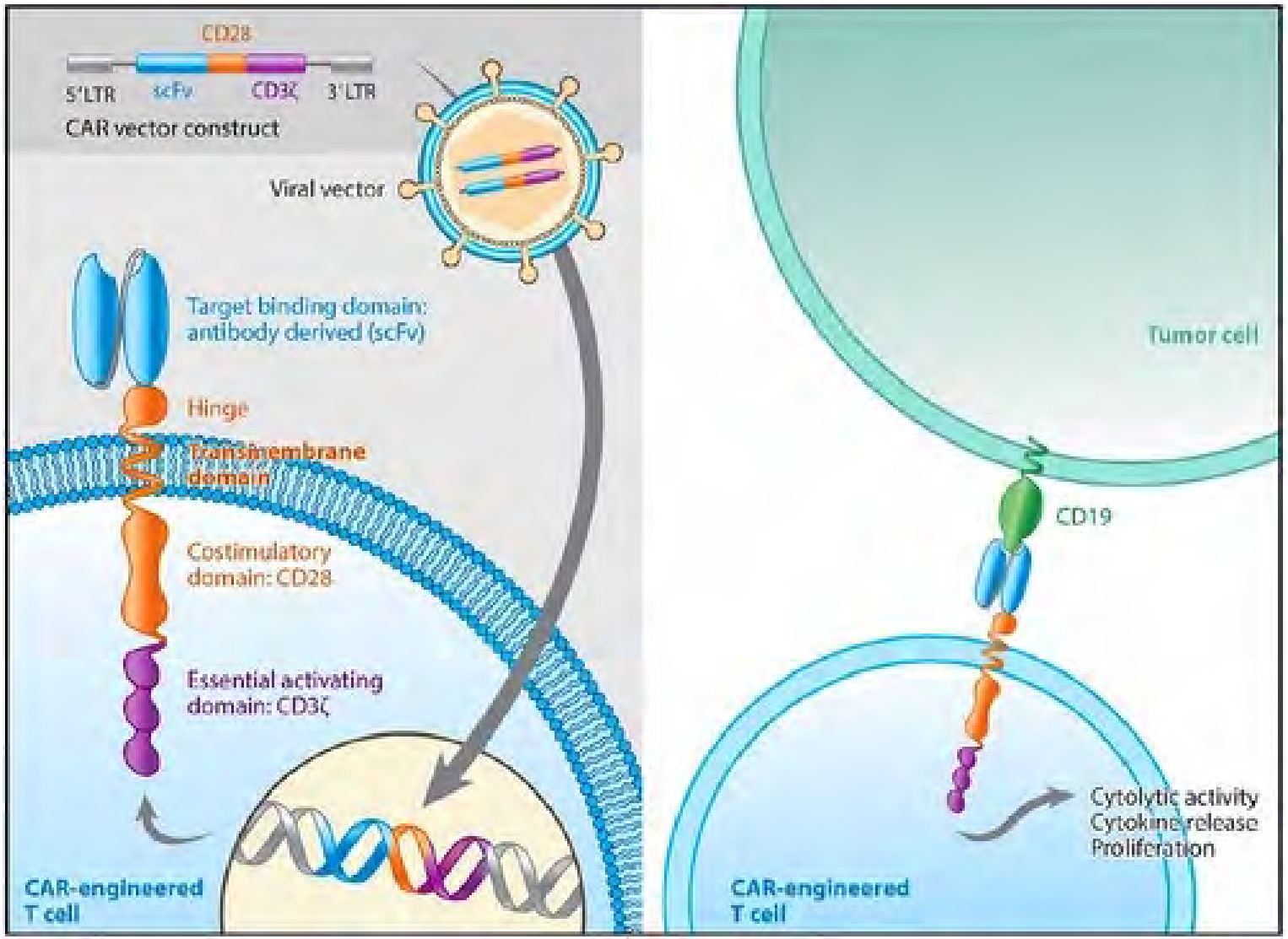


1. Sawalha Y & Maddocks K. BMJ 2022; 377:e063439;
2. Frontzek F, et al. Ther Adv Hematol. 2022;13:20406207221103321;
3. Khurana A & Lin Y. Curr Treat Options Oncol. 2022;23:171–187;
4. Meng J, et al. Front Oncol 2021;11:698607.

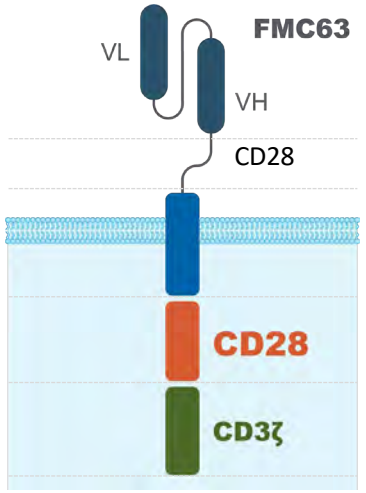
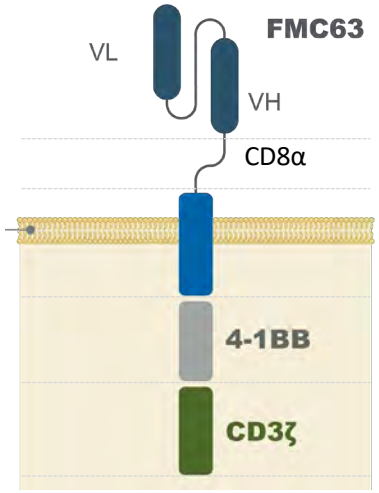
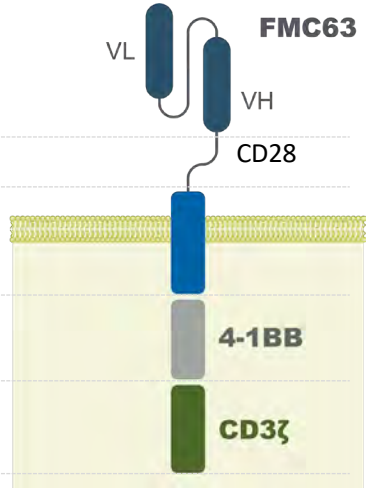
Approved CD19-directed CAR T cells in DLBCL*



McKenzie S. CAR-T cell toxicity and safety profiles. https://www.news-medical.net/health/CAR-T-Cell-Toxicity-and-Safety-Profiles.aspx. 2019.



CAR T-cell therapy for of R/R DLBCL?

	Axicabtagene ciloleucel (ZUMA-1)[1] Kite, a Gilead Company	Tisagenlecleucel (JULIET)[2] Novartis	Lisocabtagene maraleucel (TRANSCEND-NHL-001)[3] BMS
	Also licensed for the treatment of R/R PMBCL	**Also licensed for the treatment of R/R ALL in patients ≤25 years old**	**Not currently licensed in Europe**
Anti-CD19 scFv			
Hinge			
Transmembrane			
Costimulatory domain			
Essential activation domain			
Gene transfer vector	 Gammaretrovirus	 Lentivirus	 Lentivirus
Dose ratio	–	–	CD4/CD8 1:1

Axicabtagene ciloleucel has a **CD28** costimulatory domain compared with 4-1BB for other CAR T-cell products

ALL: acute lymphoblastic leukaemia; PMBCL: primary mediastinal B-cell lymphoma

Adapted from van der Stegen SJ, *et al*. *Nat Rev Drug Discov* 2015; 14:499–509. Scarfò I & Maus M. *J Immunother Cancer* 2017; 5:28.

1. Axicabtagene ciloleucel CHMP assessment report (Jun 2018; available at www.ema.europa.eu).
2. Tisagenlecleucel CHMP assessment report (Jun 2018; available at www.ema.europa.eu). 3. Abramson JS, *et al*. *Lancet* 2020; 396:839–852 (incl. suppl.)

Autologous CAR T: *Reprogramming immune cells to generate a living drug*

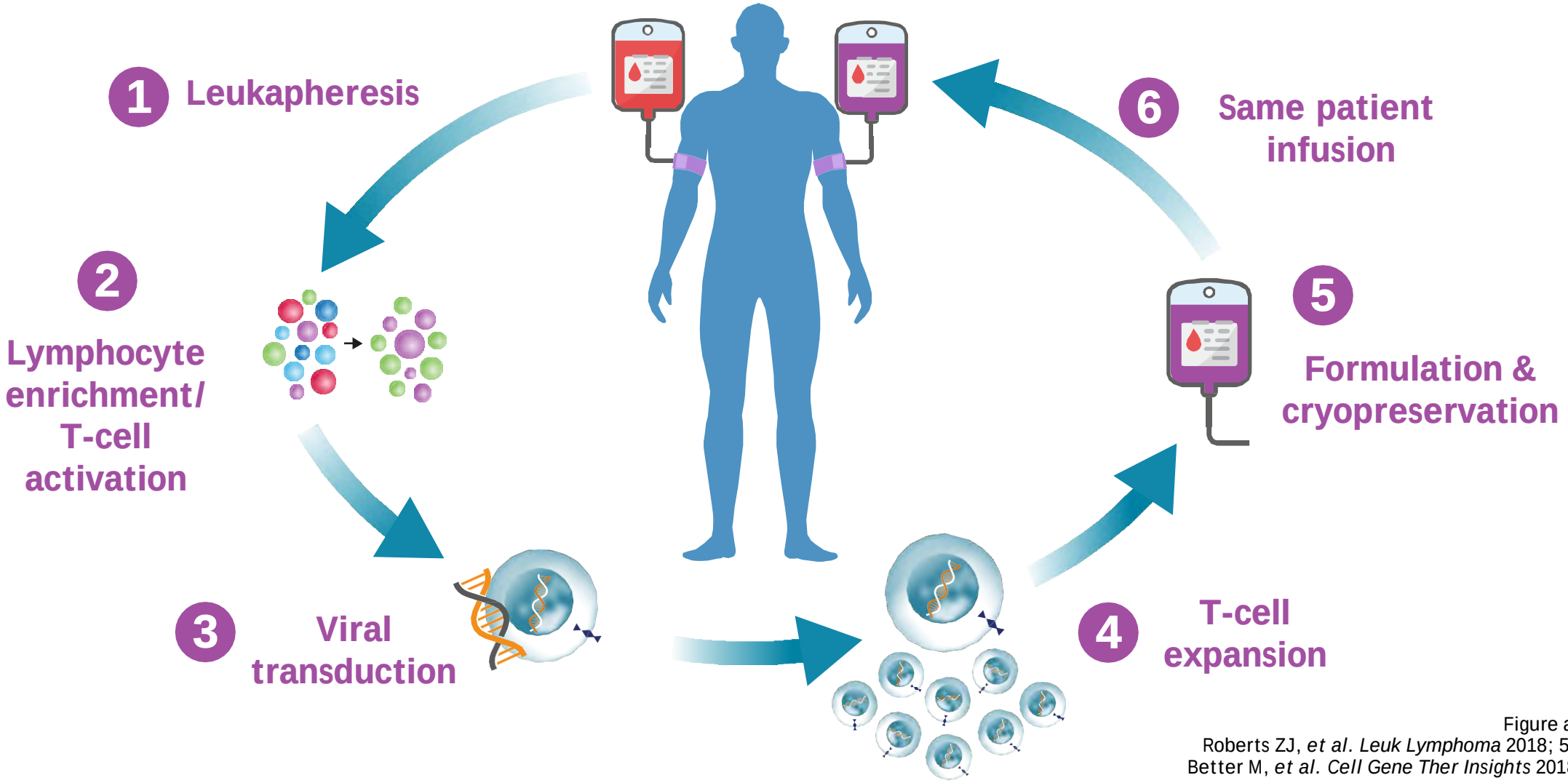
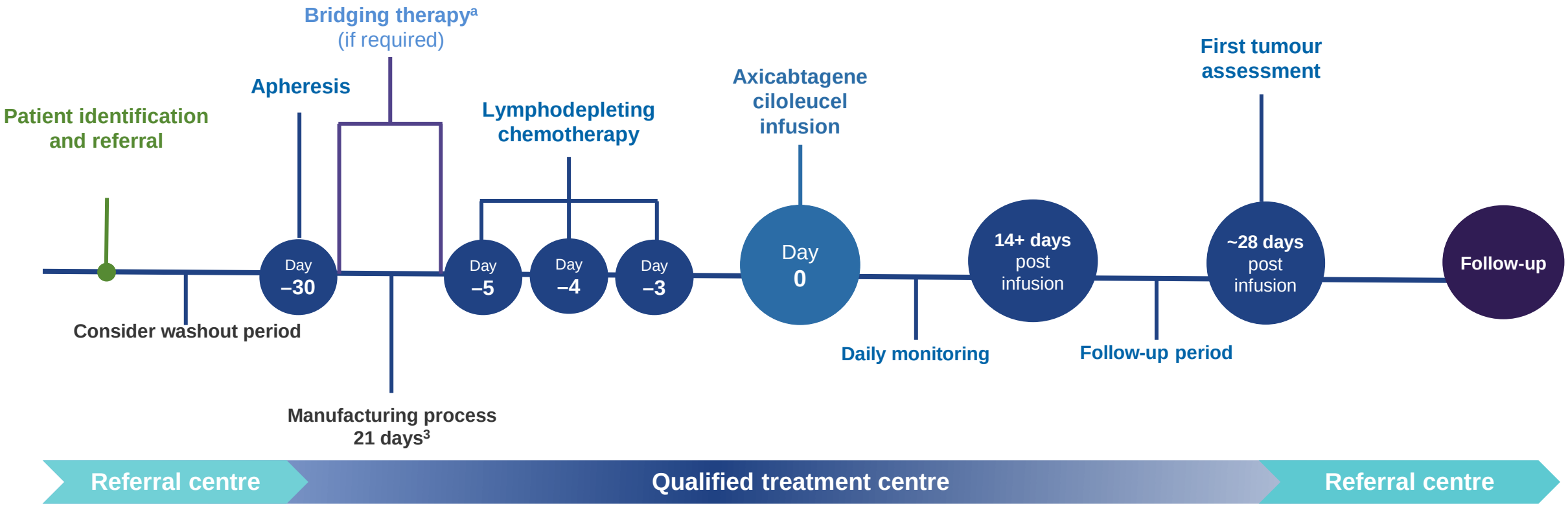


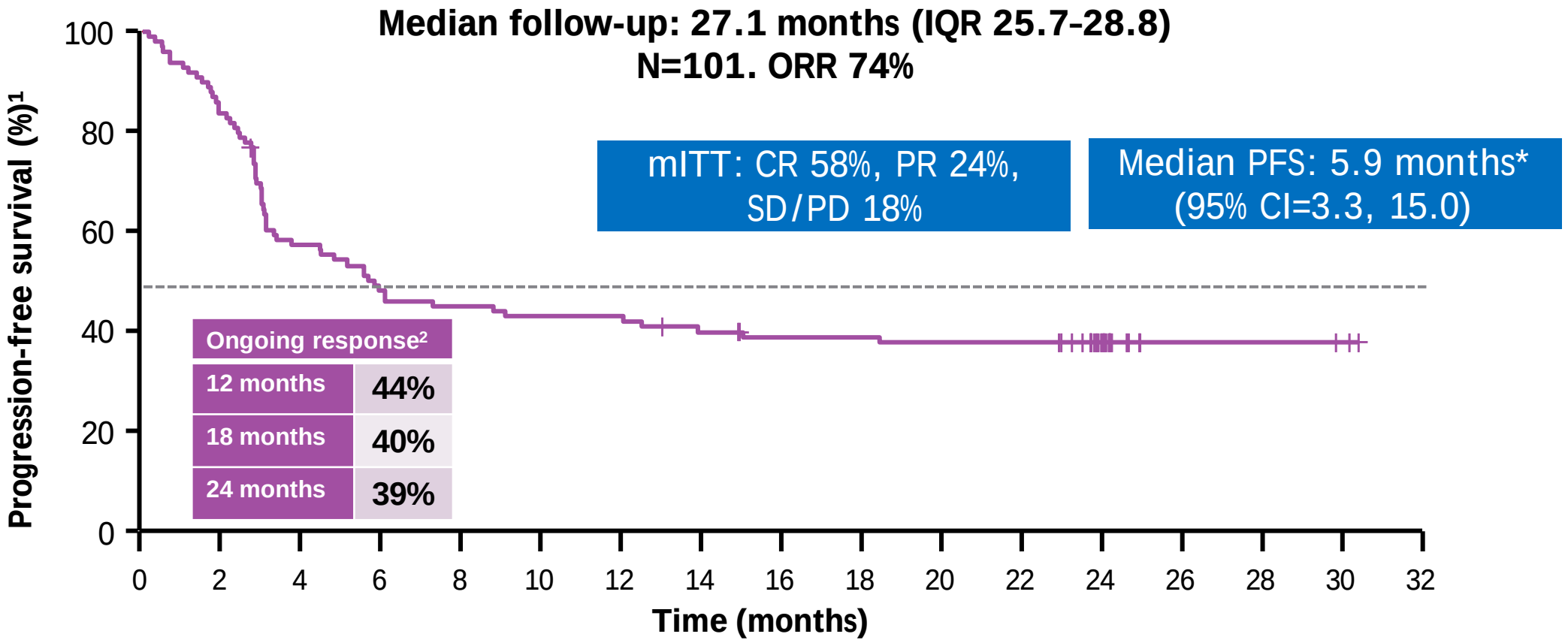
Figure adapted from
Roberts ZJ, *et al*. *Leuk Lymphoma* 2018; 59:1785–1796.
Better M, *et al*. *Cell Gene Ther Insights* 2018; 4:173–186.

Ask for the therapy that is ***one and done***



[a] Bridging therapy was not permitted in ZUMA-1
CAR: chimeric antigen receptor
Adapted from 1. Axicabtagene ciloleucel SmPC (Jul 2021; available at www.ema.europa.eu).
2. Axicabtagene ciloleucel European Public Assessment Report (Jun 2018; available at: www.ema.europa.eu).
3. Gilead Sciences Europe Ltd. Data on file: Yescarta turnaround time TCF04. 2022.

ZUMA-1: Durable responses shown with longest follow-up of any registrational study of CAR T therapy in lymphoma patients



AN ESTIMATED 72% OF PATIENTS WERE PROGRESSION-FREE AT 24 MONTHS AMONG THOSE WITH A CR AT 3 MONTHS, AND AN ESTIMATED 75% AMONG THOSE WITH A PR AT 3 MONTHS[1]
MEDIAN DURATION OF RESPONSE FOR COMPLETE RESPONDERS WAS NOT REACHED[1]

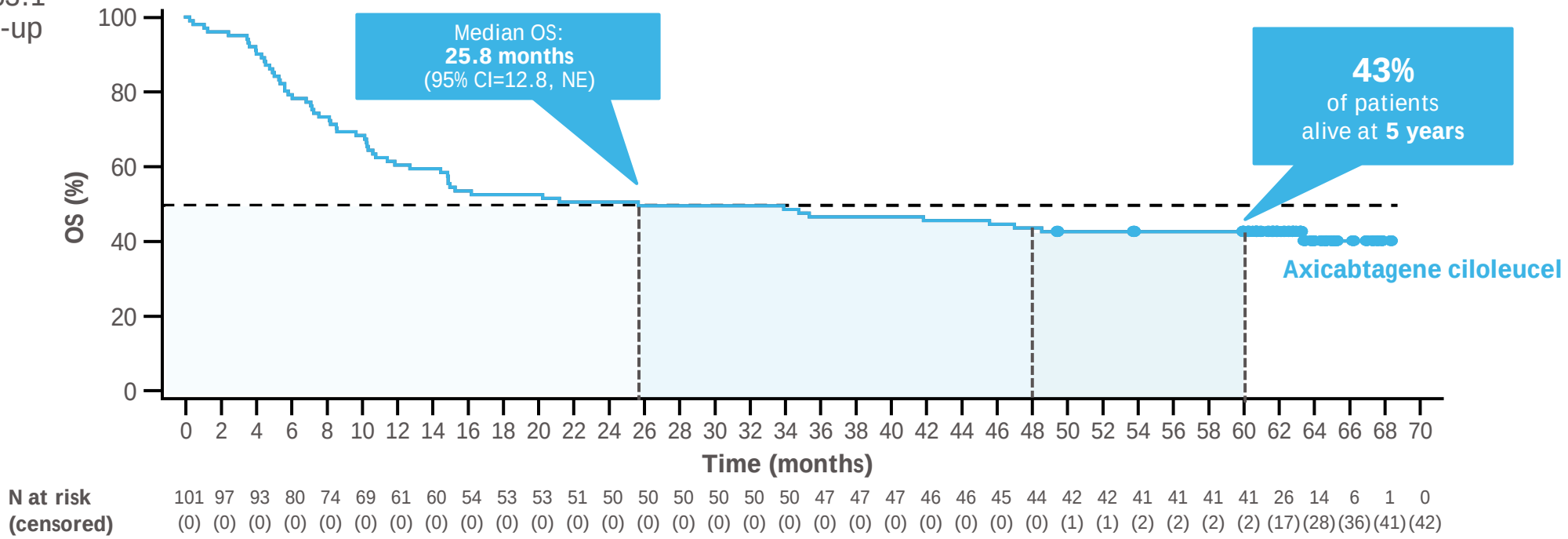
CI: confidence interval; IQR: interquartile range

1. Locke FL, *et al. Lancet Oncol* 2019; 20:31–42 (incl. suppl.).
2. Neelapu SS, *et al.* ASH 2018 (Abstract 2967; poster).

With long-term follow-up, how has axicabtagene ciloleucel: 43% of patients alive at 5 years

ZUMA-1:

OS at median 63.1 months' follow-up (N=101)[1]

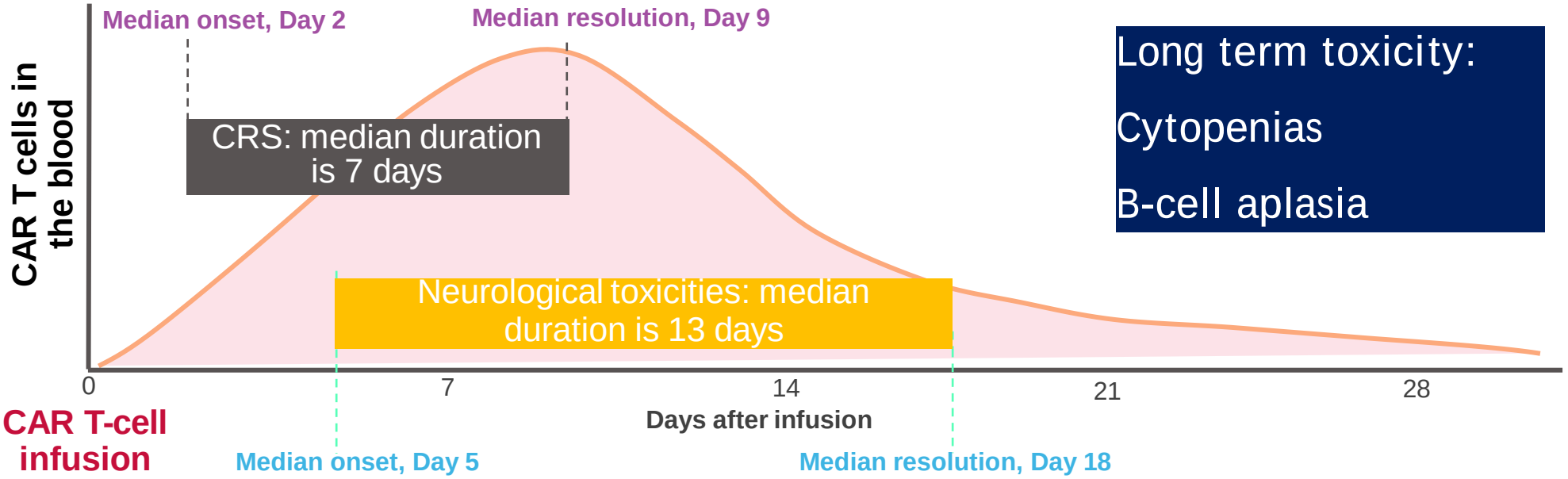


1. Jacobson C, *et al*. ASH 2021 (Abstract 1764; poster).

Clinical trials have established the timing and duration of acute adverse events

- Toxicity (broadening populations)
- Delivery logistics
- Economics

CRS coincides with maximal T-cell expansion[1]
CRS may occur within minutes but more typically within days[1,2]



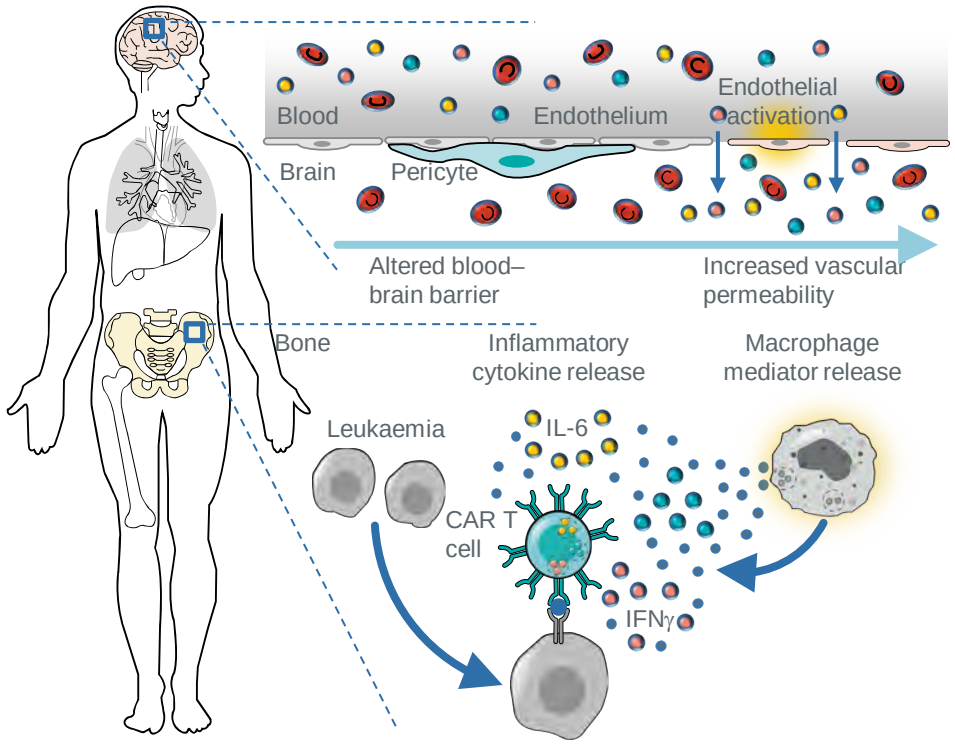
Long term toxicity:
Cytopenias
B-cell aplasia

Neurological toxicities are generally reversible in most patients; rare cases of long-term symptoms[1]

CRS: cytokine release syndrome

1. Lee DW, *et al*. *Blood* 2014;124:188–195. 2. Axicabtagene ciloleucel SmPC (Jan 2019; available at www.ema.europa.eu).

CAR T therapy is associated with a safety profile that requires informed management

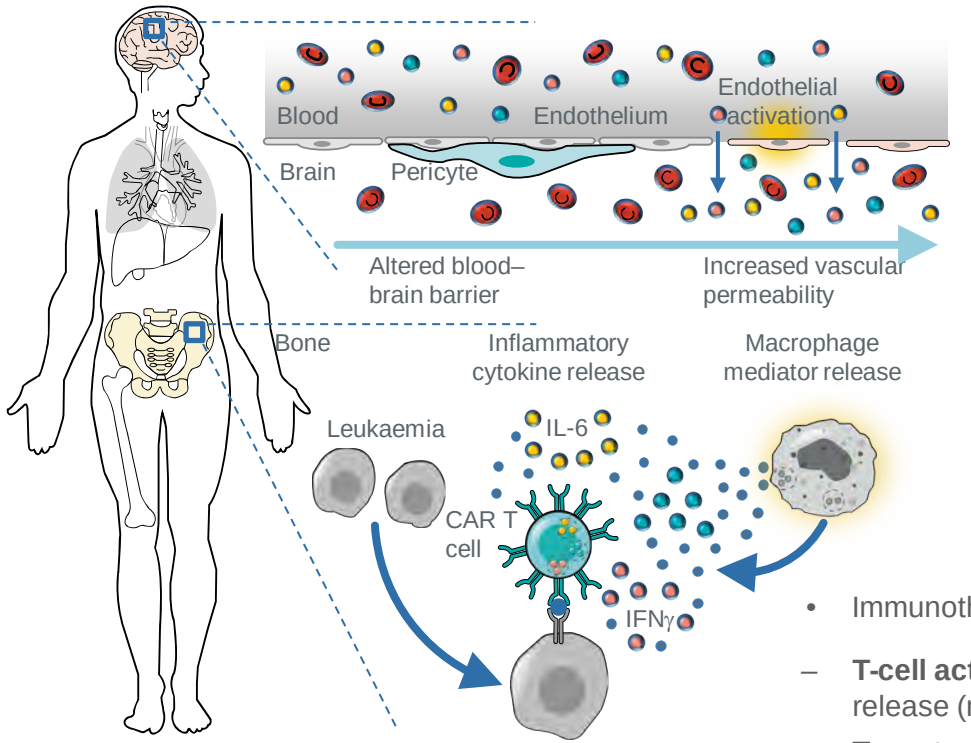


1. Cytokine release syndrome
2. Neurological events

IFN: interferon

Figure adapted from June CH, *et al*. *Science* 2018; 359:1361–1365.

CAR T therapy is associated with a safety profile that requires informed management



1. Cytokine release syndrome

- Pyrexia
- Hypotension
- Arrhythmia
- Capillary leak syndrome
- Coagulopathy
- HLH/MAS

2. Neurological events

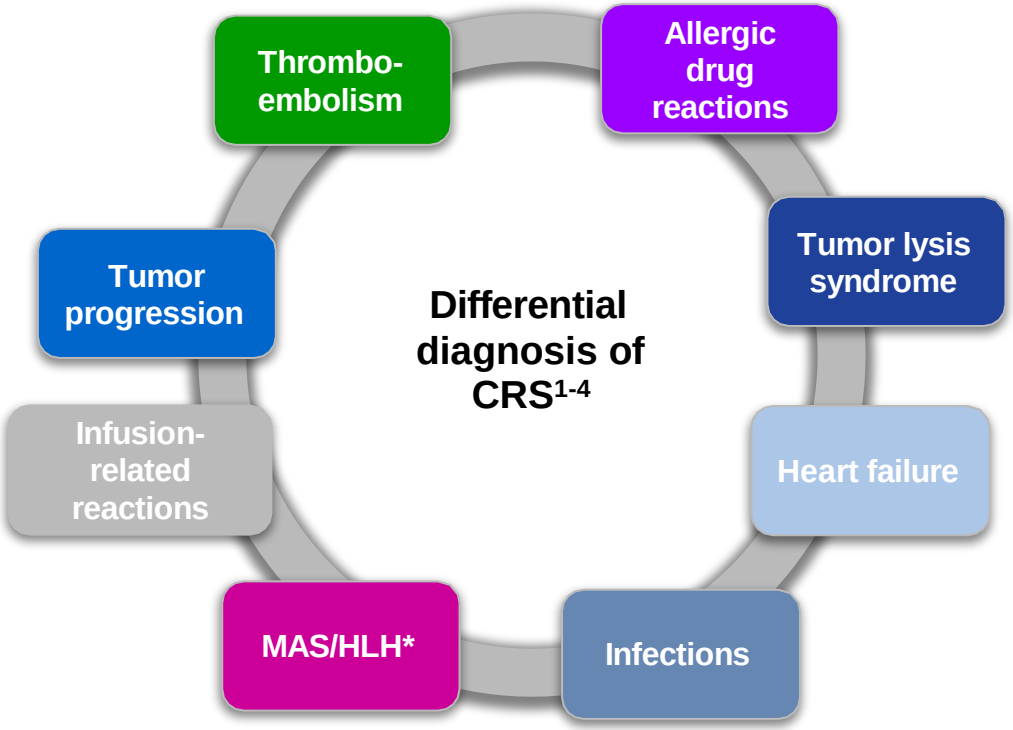
- Immunotherapy triggers CRS via[1]
  - **T-cell activation** with subsequent cytokine release (mainly IL-6, IFN-γ and TNF-α)
  - **Target cell lysis** with subsequent cytokine release
- These cytokines trigger a chain reaction that involves the activation of innate immune cells, such as macrophages and endothelial cells, which results in the release of additional cytokines
- Activated endothelial cells release stored Ang2 and VWF, while macrophages trigger the production of NO, which promotes vasodilation and hypotension
- Additional and uncontrolled immune cell recruitment and activation then occurs, resulting in the release of further cytokines

HLH/MAS: haemophagocytic lymphohistiocytosis/macrophage activation syndrome

Figure adapted from June CH, *et al. Science* 2018; 359:1361–1365. Axicabtagene ciloleucel SmPC (Jun 2020; available at www.ema.europa.eu).

Differential diagnosis of CRS can be challenging

- As patients with CRS present with a wide range of signs and symptoms, accurate diagnosis can be challenging[1]
- Neurologic AEs, such as headaches, confusion, dysphasia and ataxia, can occur alongside CRS in the context of T-cell targeted immunotherapy[2,3]



- Recognizing whether symptoms are related to CRS or another condition is key to optimal management

*Familial or secondary MAS/HLH

1. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56; 2. Chavez JC, et al. Hematol Oncol Stem Cell Ther 2020;13:1–6
3. Brudno N, and Kochenderfer JN. Blood 2016;127:3321–30; 4. Doessegger L & Banholzer ML. Clin Transl Immunol 2015;4:e39

Management interventions determine the grade of CRS

(ASTCT criteria; Lee et al. 2019)[1]

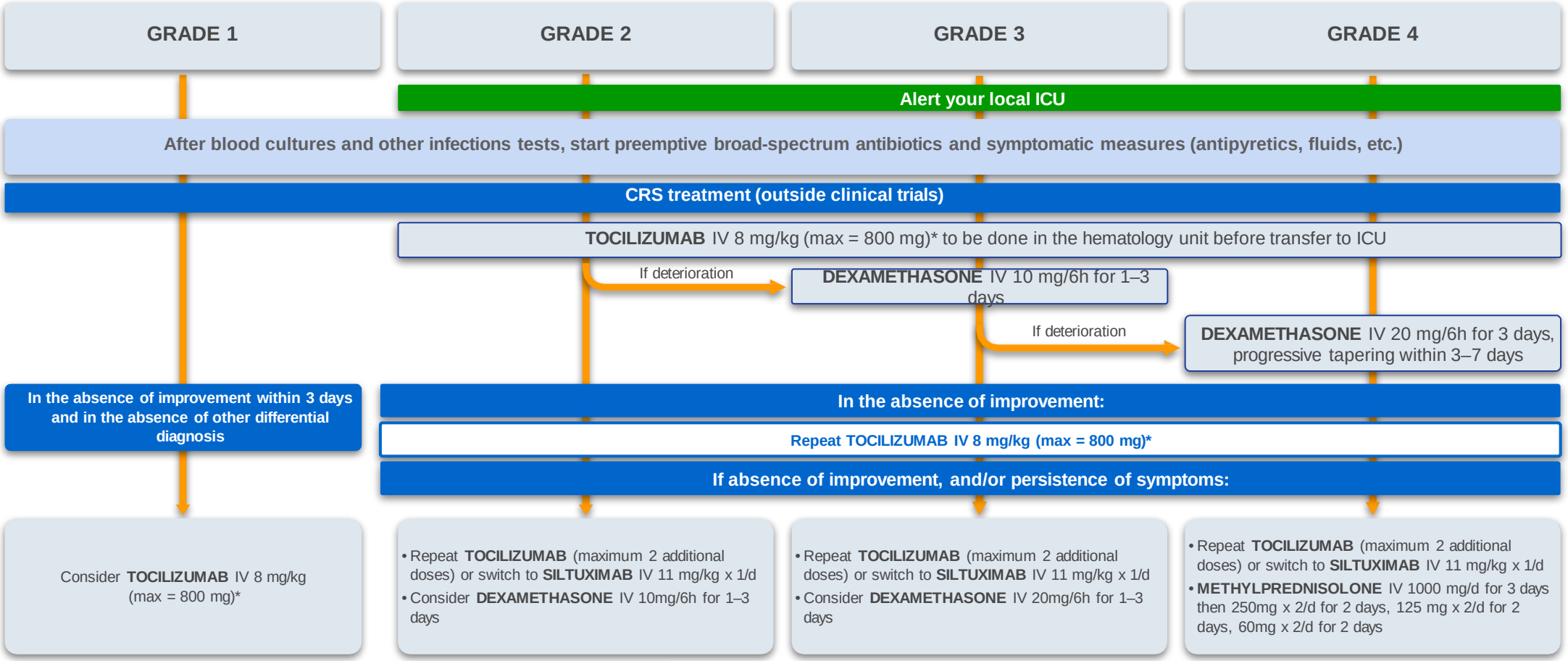
CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
			With	
Hypotension	None	Does not require a vasopressor	Requires a vasopressor with or without vasopressin	Requires multiple vasopressors (excluding vasopressin)
			And/or†	
Hypoxia	None	Requires low-flow cannula‡ or blow-by	Requires high-flow nasal cannula,‡ facemask, nonrebreather mask, or Venturi mask	Requires positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Note: differences versus Lee et al. 2014[2] criteria include the removal of single (low dose) vasopressor for hypotension from the Grade 2 criteria, and the removal of organ toxicity from the criteria

*Defined as temperature ≥38°C not attributable to any other cause. In patients who receive antipyretic or anticytokine therapy, fever is no longer required to grade subsequent CRS severity and CRS grading is driven by hypotension and/or hypoxia.
†CRS grade is determined by the most severe event; hypoxia or hypotension not attributable to any other cause.
‡Low -flow nasal cannula is defined as oxygen delivered at ≤6L/minute; high-flow is defined as oxygen delivered at >6L/minute.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38
2. Lee DW, et al. Blood 2014;124:188–95

Treatment algorithms can guide management of CRS



*In children less than 30 kg, **TOCILIZUMAB** is given at the dose of 12 mg/kg.

Yakoub-Agha I, et al. Haematologica 2020;105:297–316

Note: consult the SmPC for any drug-specific recommendations

CRS does no correlate with outcome

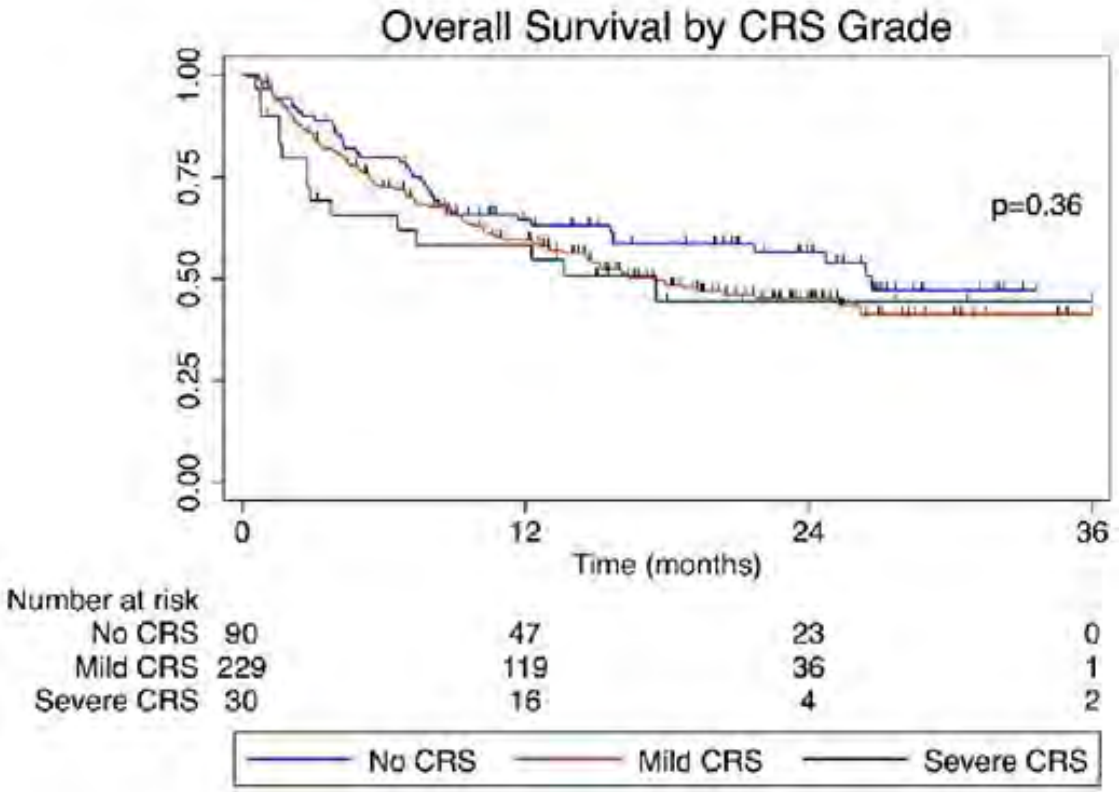
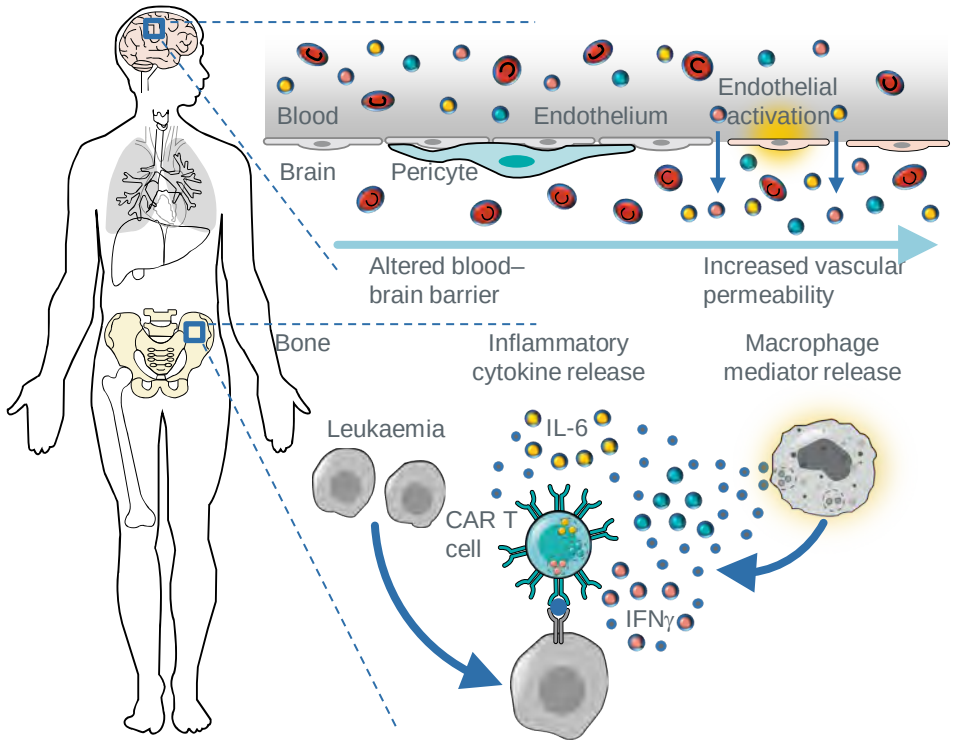


Table 1. Multivariate Cox Regression Analysis

Effect	P-value	HR	95% CI
OS			
Developed CRS	0.549	0.87	0.54-1.39
Peak ferritin>5000	<0.001	2.38	1.50-3.76
LDH>ULN	<0.001	2.34	1.55-3.53
Stage 3-4	0.336	1.24	0.80-1.93
Bulky disease	0.005	1.81	1.20-2.75
Refractory to most recent chemo vs. Primary refractory	0.552	0.89	0.59-1.32
Relapsed vs. Primary refractory	0.173	0.72	0.44-1.16
Received steroids	0.775	1.06	0.73-1.53
Bridging therapy	0.3	1.23	0.83-1.84
Effect	**P-value**	**HR**	**95% CI**
PFS			
Developed CRS	0.239	0.79	0.53-1.17
Peak ferritin>5000	<0.001	2.61	1.71-3.98
LDH>ULN	<0.001	2.11	1.49-2.98
Stage 3-4	0.333	1.21	0.82-1.80
Bulky disease	0.219	1.27	0.87-1.87
Refractory to most recent chemo vs. Primary refractory	0.427	0.86	0.60-1.24
Relapsed vs. Primary refractory	0.085	0.7	0.47-1.05
Received steroids	0.74	0.73	0.52-1.03
Bridging therapy	0.011	1.58	1.11-2.24

Bhasker et al. 2022

CAR T therapy is associated with a safety profile that requires informed management



1. Cytokine release syndrome

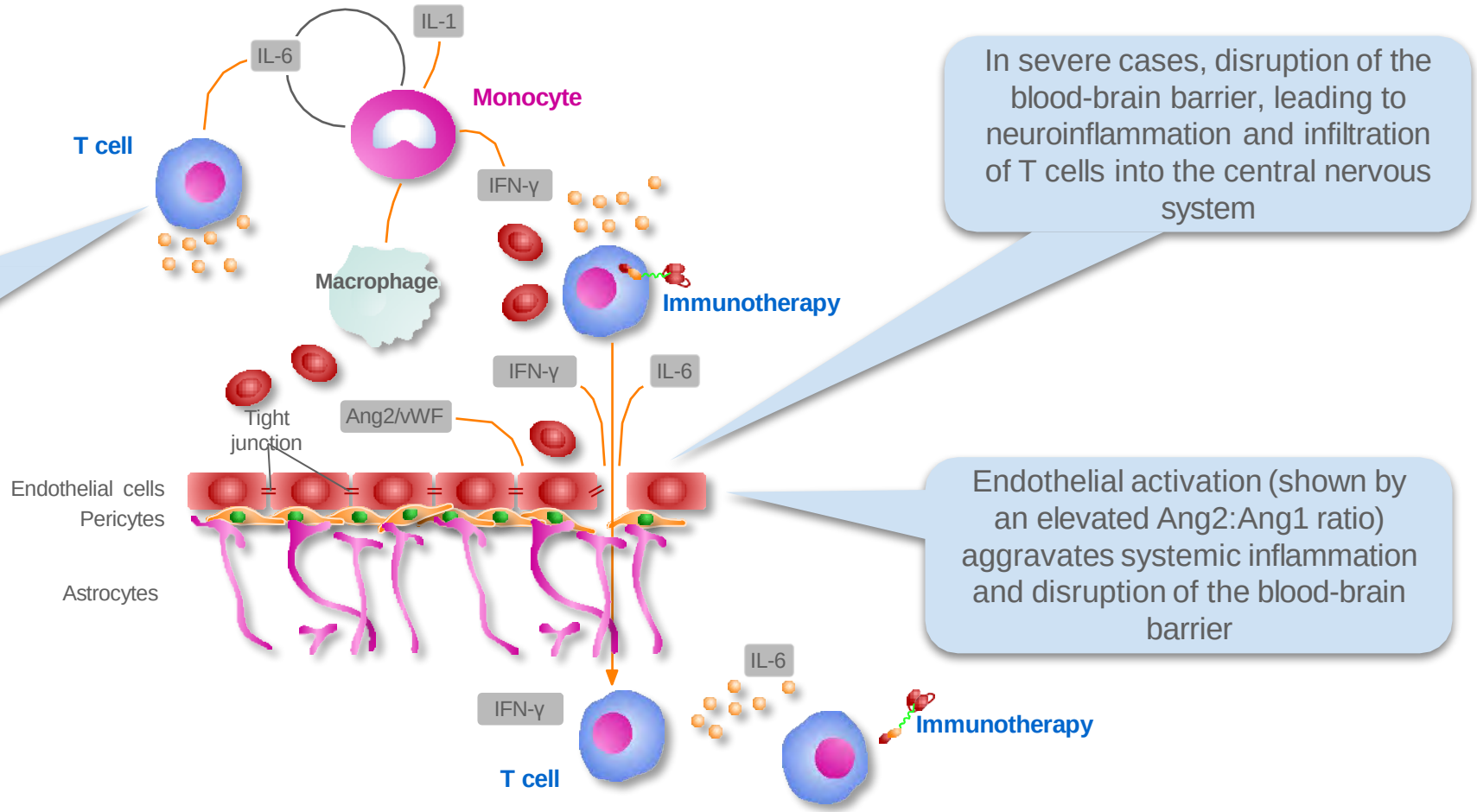
2. Neurological events

- Headache
- Confusion
- Hallucinations
- Delirium
- Aphasia
- Paresis
- Seizures
- Cerebral oedema
- Intracranial haemorrhage

IFN: interferon

Figure adapted from June CH, *et al. Science* 2018; 359:1361–1365. Brudno JN & Kochenderfer JN. *Blood* 2016; 127:3321–3330.

Immunotherapy is believed to trigger ICANS via different mechanisms



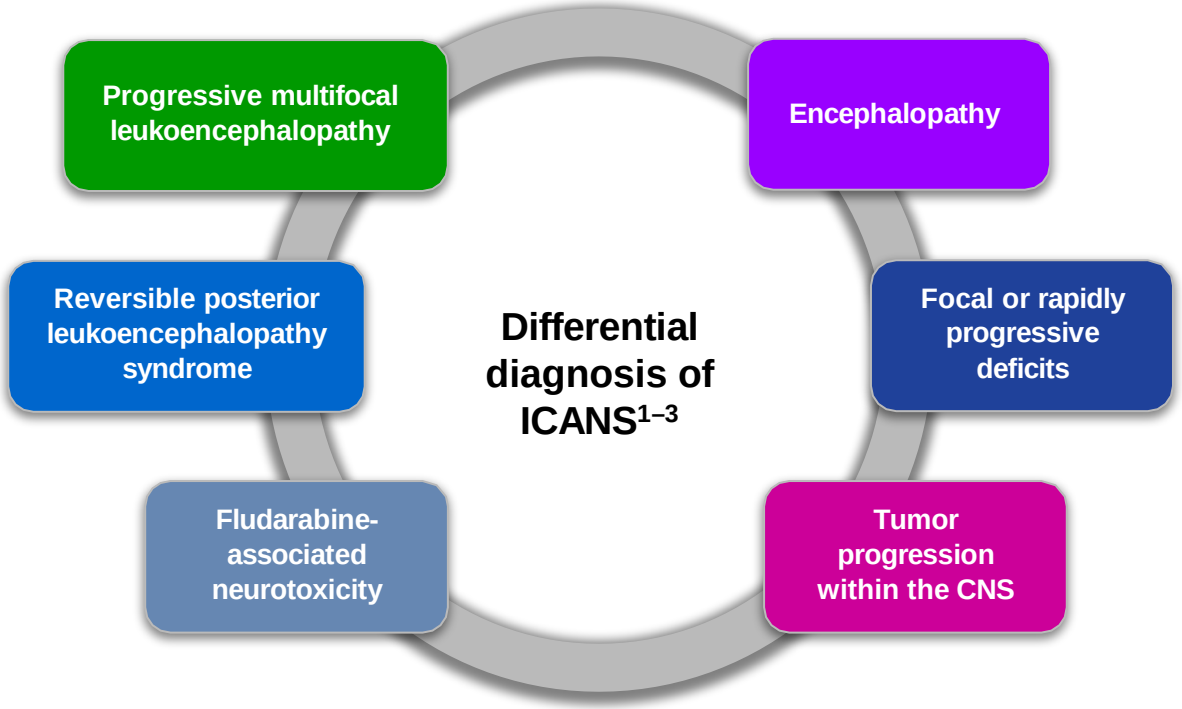
IL-1-triggered activation of monocytes, which in turn produces IL-6 and other cytokines, resulting in systemic inflammation via activation of T cells and macrophages

In severe cases, disruption of the blood-brain barrier, leading to neuroinflammation and infiltration of T cells into the central nervous system

Endothelial activation (shown by an elevated Ang2:Ang1 ratio) aggravates systemic inflammation and disruption of the blood-brain barrier

Borrega JG, et al. HemaSphere 2019;3:e191

Diagnosis of ICANS



1. Lowe KL, et al. Gene Ther 2018;25:176
2. Anderson RC, et al. Front Neurol 2020; 11:463
3. Neil EC, et al. Blood Adv 2017;1:2041

ICANS severity is graded using ASTCT criteria (Lee et al. 2019)

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7–9	3–6	0–2	0 (patient is unrousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unrousable and requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or inconclusive seizures on EEG that resolve without intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizure without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP / cerebral oedema	N/A	N/A	Focal/local oedema on neuroimaging§	Diffuse cerebral oedema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve IV palsy; or papilloedema; or Cushing's triad

*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia or grade 4 ICANS if unrousable

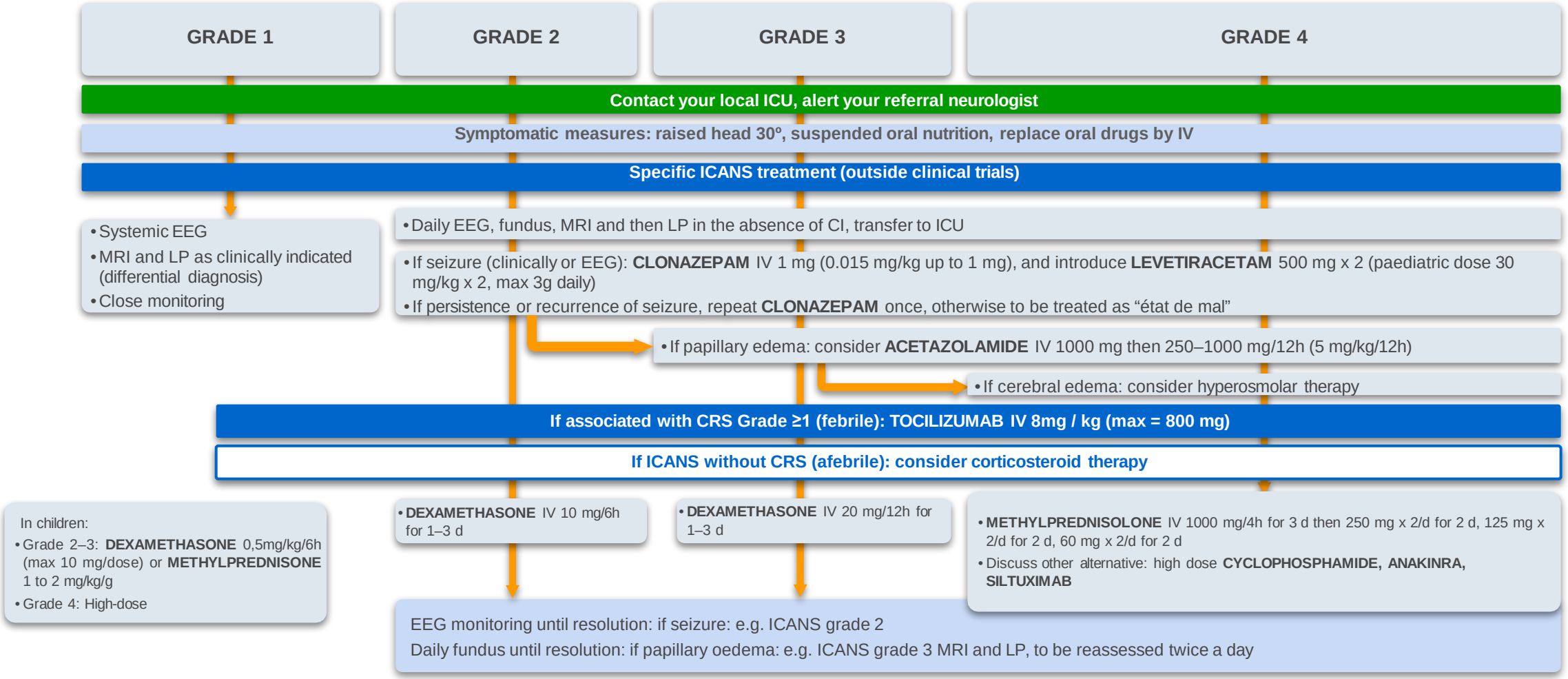
†Depressed level of consciousness should be attributable to no other cause

‡Tremor associated with immune effector cell therapies may be graded according to CTCAE v5.0 but are excluded from ICANS grading

§ICH with or without associated oedema may be graded according to CTCAE v5.0 but is excluded from ICANS grading

Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38

Treatment algorithms can guide management of ICANS



Note: consult the SmPC for any drug-specific recommendations

Yakoub-Agha I, et al. Haematologica 2020;105:297–316

Toxicity of axicabtagene ciloleucel in r/r DLBCL

	Axicabtagene ciloleucel
Construct	Anti-CD19-**CD28**-CD3z
Patients, n	101
Any CRS, %	93
Median time to onset, days	2
Grade ≥ 3 CRS, %[a]	13
Any neurological toxicity, %	64
Grade ≥ 3 neurological toxicity, %	28
Tocilizumab, %	43
Steroid use, %	27

[a] CRS toxicity grading scales differ across studies. Axicabtagene ciloleucel used Lee criteria.

CRS, cytokine release syndrome.

Locke FL, et al. Lancet Oncol. 2019;20:31-42. Neelapu SS, et al. N Engl J Med. 2017;377:2531-44.

JULIET: response, PFS, and OS of patients with r/r DLBCL receiving tisagenlecleucel

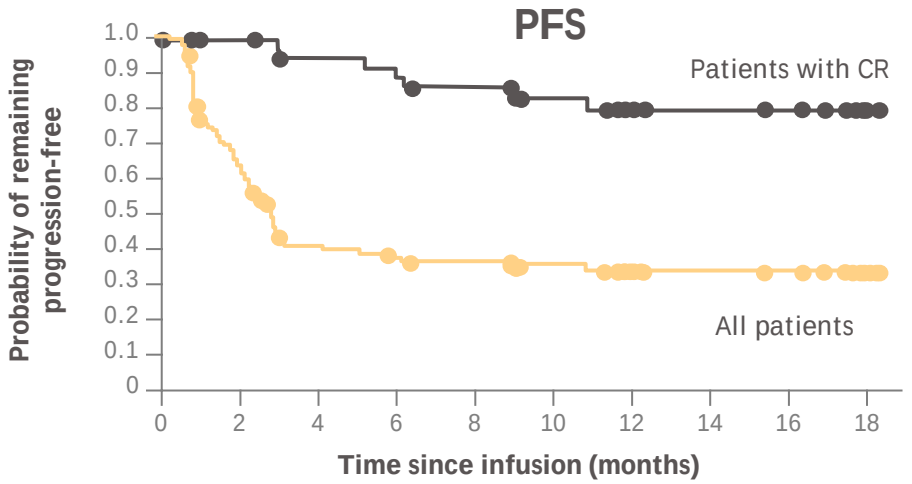
Characteristics	Patients (N = 111)
Median age, years (range)	56 (22–76)
Double-/triple-hit lymphoma, %	27
Number of prior lines of therapy, %	
2	44
3	31
4–6	21
Refractory to last therapy, %	55
Prior ASCT, %	49

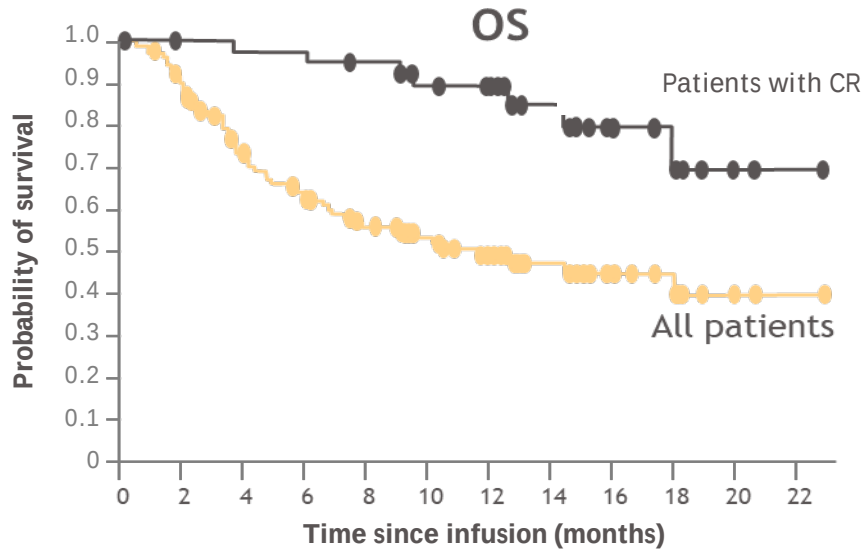
Investigator-assessed response[a]	Patients (n = 93)
ORR, n (%)	48 (52)
CR, n (%)	37 (40)
Median DOR, months	NE

[a] Included all patients who received tisagenlecleucel infusion ≥ 3 months before data cut-off.

NE, not evaluable

Schuster SJ, et al. N Engl J Med. 2019;380:45–56.





Toxicity of tisagenlecleucel in r/r DLBCL

	Tisagenlecleucel
Construct	Anti-CD19-**41BB**-CD3z
Patients, n	111
Any CRS, %	58
Median time to onset, days	3
Grade ≥ 3 CRS, %[a]	22
Any neurological toxicity, %	21
Grade ≥ 3 neurological toxicity, %	12
Tocilizumab, %	14
Steroid use, %	10

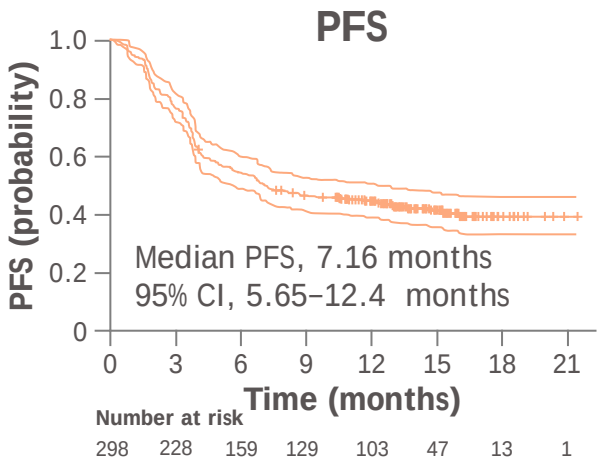
[a] CRS toxicity grading scales differ across studies. Tisagenlecleucel used Penn criteria.

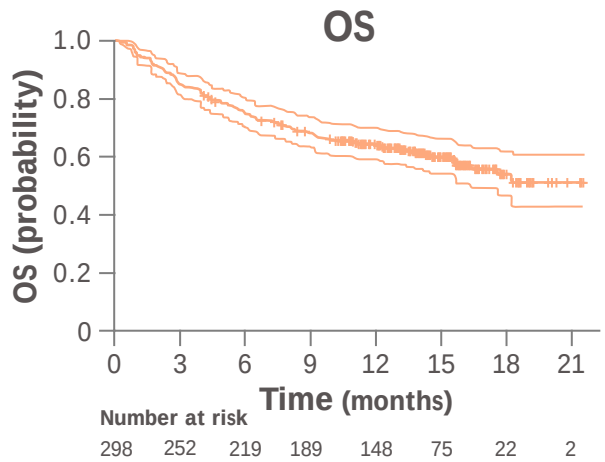
Schuster SJ, et al. N Engl J Med. 2019;380:45-56.

US Lymphoma CAR-T Consortium: real-world analysis of axicabtagene ciloleucel in r/r large B-cell lymphoma

Characteristics	Patients (N = 298)
Age, years, median	
Median (range)	60 (21–83)
≥ 60	154 (51.7)
Disease type	
DLBCL	203 (68.1)
PMBCL	19 (6.4)
TFL	76 (25.5)
LDH > ULN at leukapheresis	157 (60.6)
LDH > ULN at conditioning chemotherapy	155 (59.4)
Bulky disease (≥ 10 cm)	68 (22.7)
Prior therapies	
≥ 3 prior lines of therapy	222 (74.5)
Median no. of prior lines of therapy (range)	3 (2–11)
History of primary refractory disease	101 (33.9)

Outcomes	
ORR, %	82
CR, %	64
DOR, median, months % (95% CI)	NR (6.2–NR)
PFS at 12 months, % (95% CI)	45 (39–51)
OS at 12 months, % (95% CI)	68 (63–74)
Grade ≥ 3 CRS, %	7
Grade ≥ 3 NE, %	31

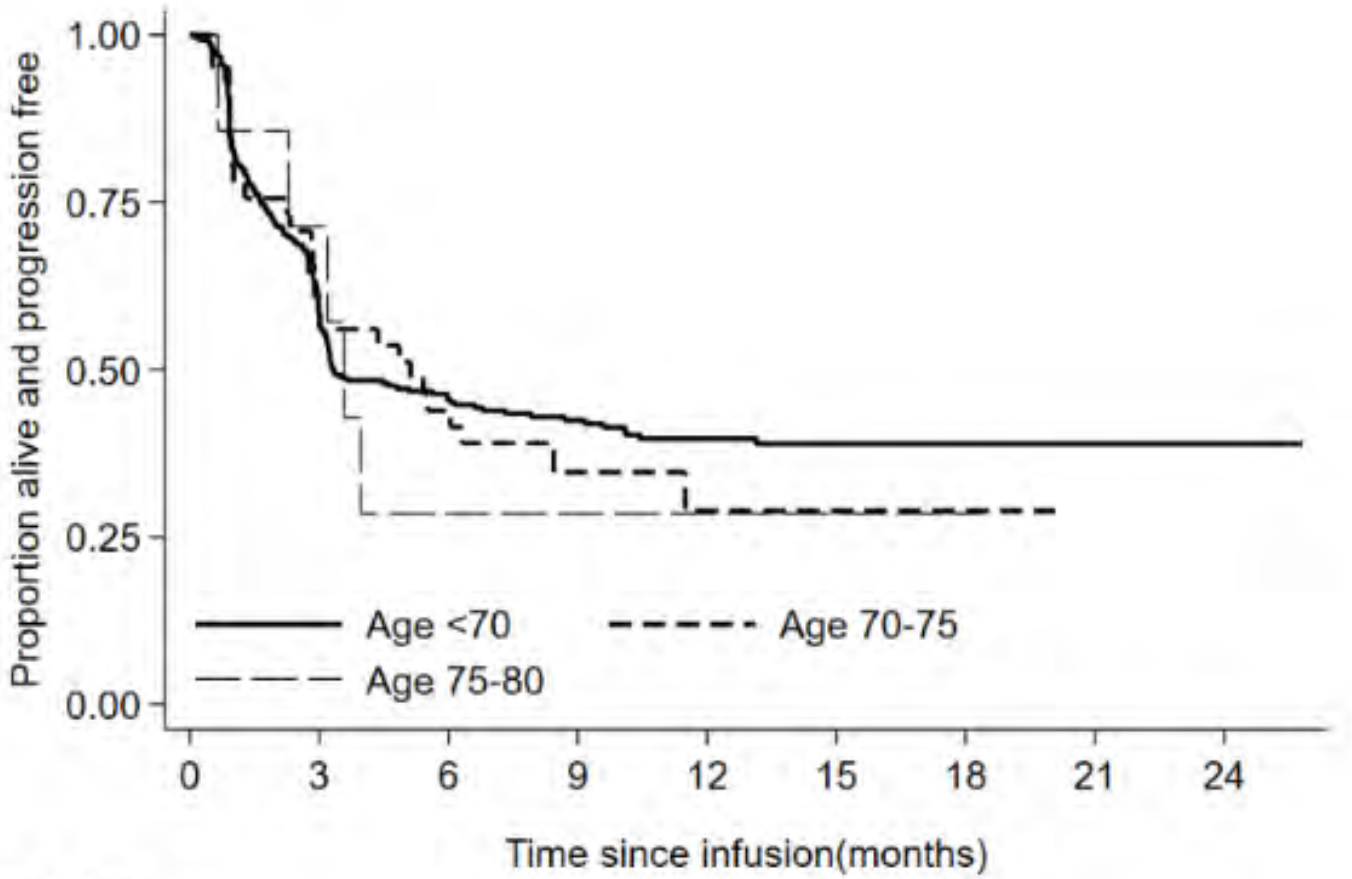




LDH, lactate dehydrogenase; NE, neurological event; No., number.
TFL, transformed follicular lymphoma; ULN, upper limit of normal.

Nastoupil LJ, et al. J Clin Oncol. 2020;38:3119-28.

Older patients: PFS by age group

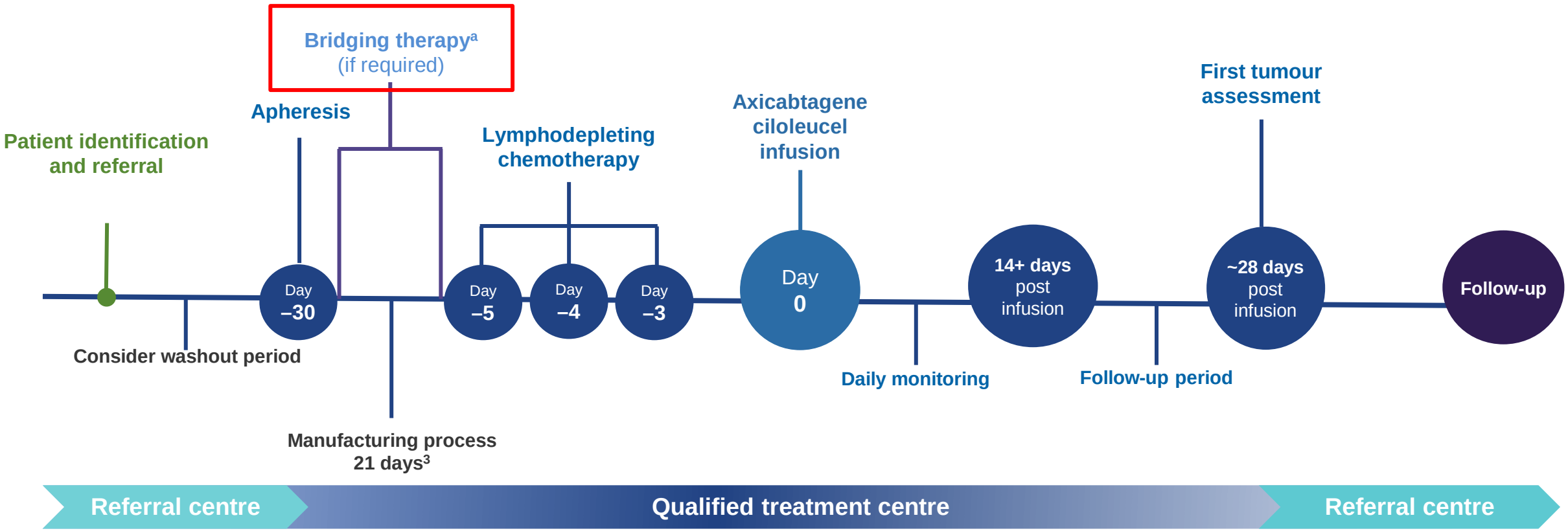


Number at risk

Age <70	252	147	112	82	59	41	31	14	4
Age 70-75	41	24	18	8	3	2	2	0	0
Age 75-80	7	5	2	1	1	1	1	0	0

Kuhnl et al. BJH 2023

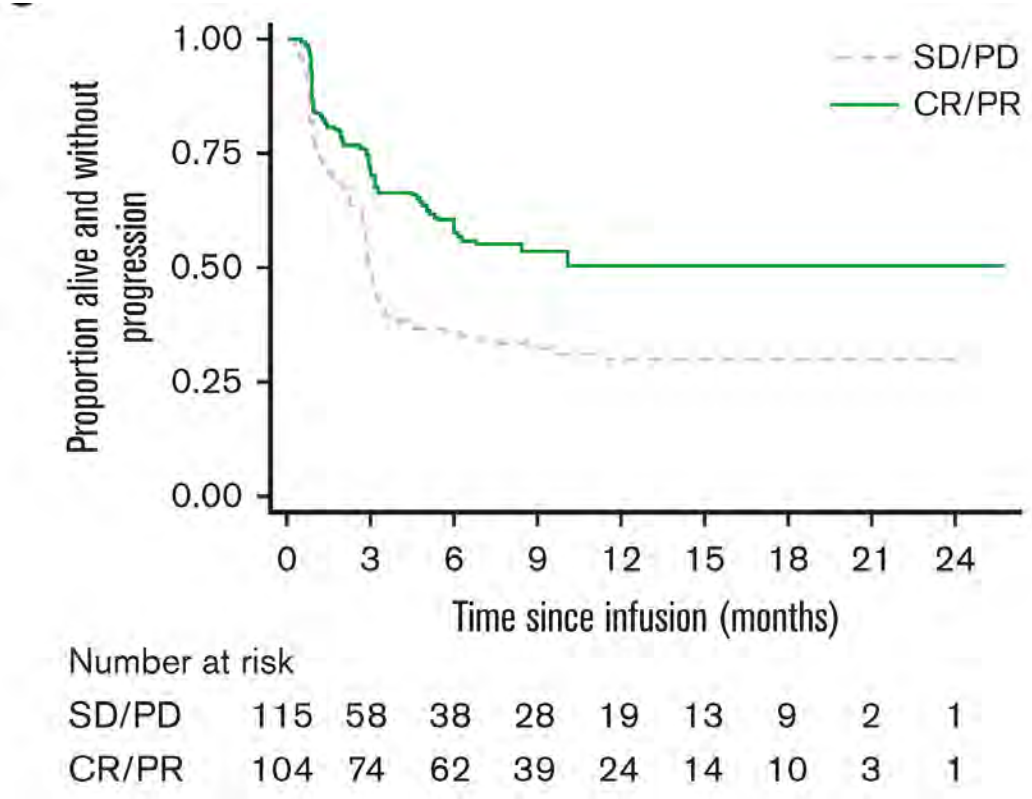
Bridging therapy



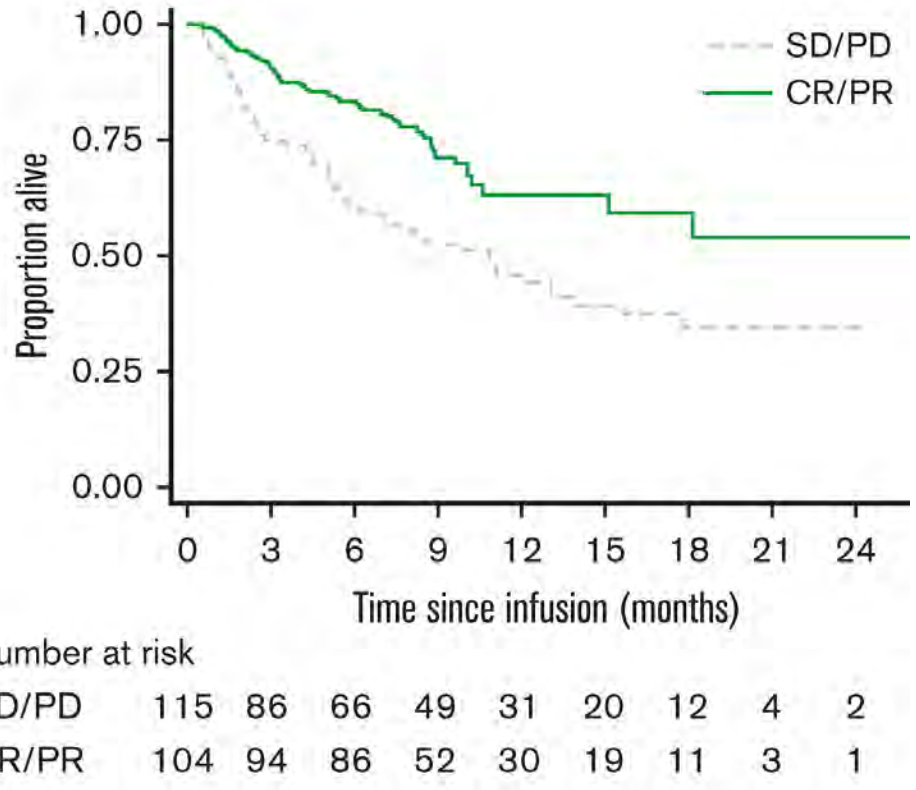
[a] Bridging therapy was not permitted in ZUMA-1
CAR: chimeric antigen receptor
Adapted from 1. Axicabtagene ciloleucel SmPC (Jul 2021; available at www.ema.europa.eu).
2. Axicabtagene ciloleucel European Public Assessment Report (Jun 2018; available at: www.ema.europa.eu).
3. Gilead Sciences Europe Ltd. Data on file: Yescarta turnaround time TCF04. 2022.

Impact of effective bridging strategies: 42% reduction in risk of progression/death

PFS



OS

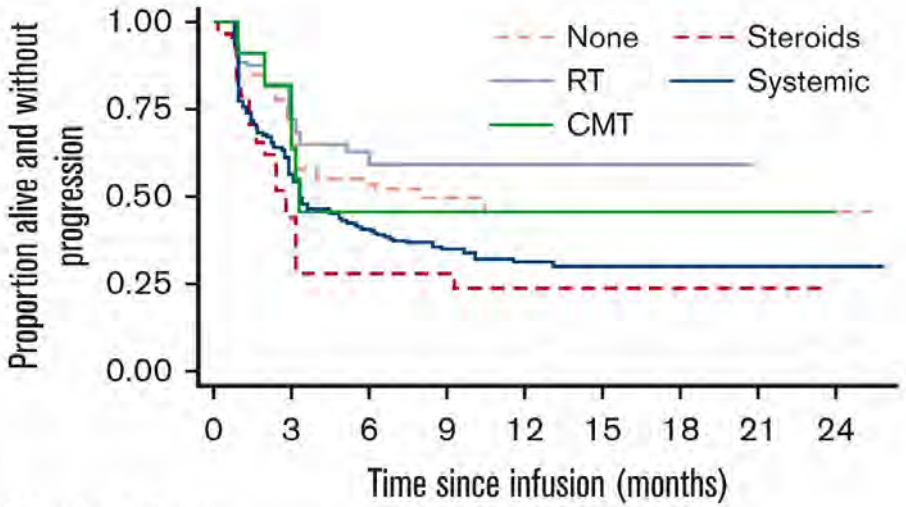


Multivariate analysis likelihood of response to bridging: Response to last line therapy, the absence of bulky disease, and the use of polatuzumab-containing chemotherapy regimens

Roddie et al. BJH 2023

Impact of mode of bridging therapy

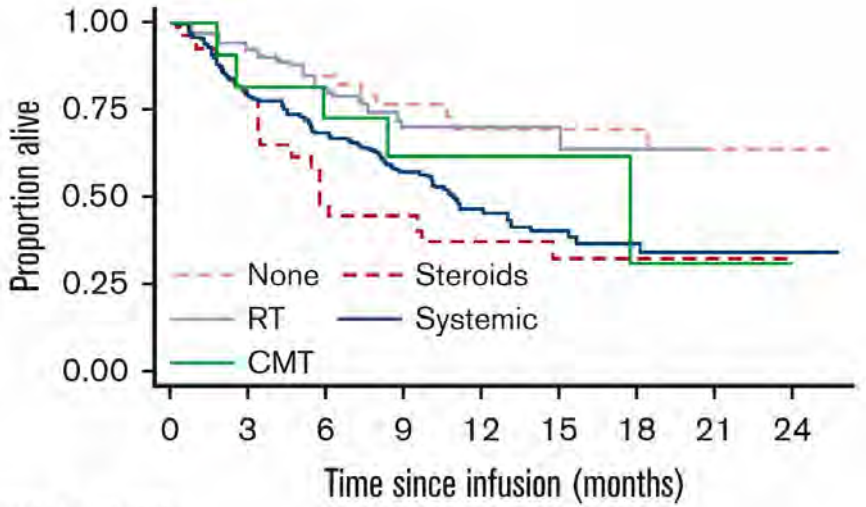
PFS



Number at risk

None	40	26	21	14	12	10	9	4	2
Steroids	29	13	8	7	6	6	6	5	0
RT	54	39	33	26	14	10	8	0	0
Systemic	166	90	65	40	27	15	10	4	1
CMT	11	8	5	4	4	3	1	1	1

OS



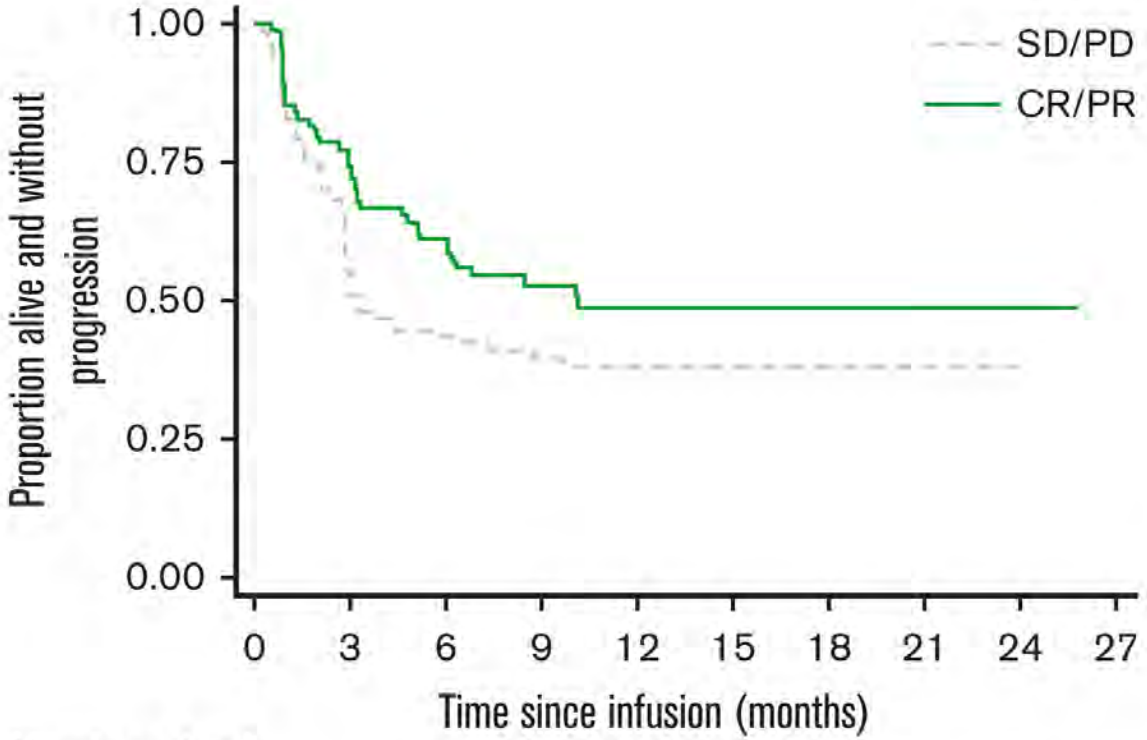
Number at risk

None	40	37	34	23	18	15	13	5	3
Steroids	29	23	14	12	10	7	7	6	0
RT	54	50	42	30	17	13	8	0	0
Systemic	166	132	111	71	42	24	14	6	2
CMT	11	9	8	6	5	4	1	1	1

Roddie et al. BJH 2023

Impact of response to bridging on Axi-cel vs Tisa-cel outcomes

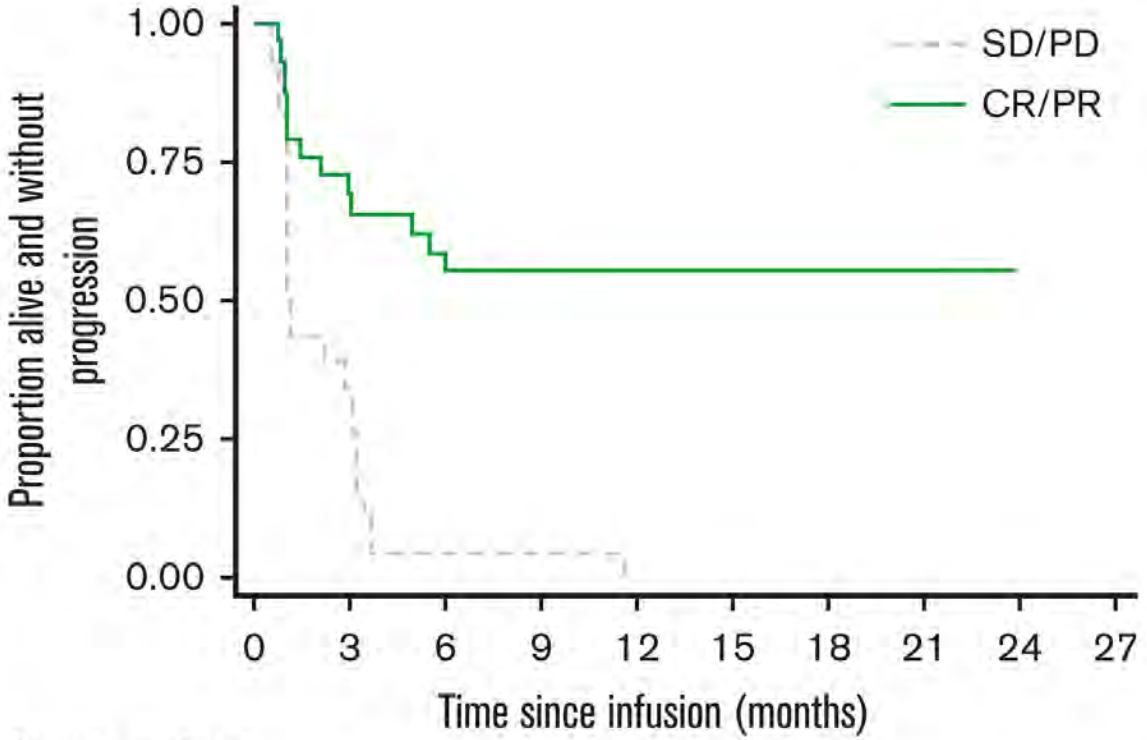
Axi-cel



Number at risk

SD/PD	92	51	37	27	19	13	9	2	1	0
CR/PR	75	55	46	29	17	9	6	2	1	0

Tisa-cel

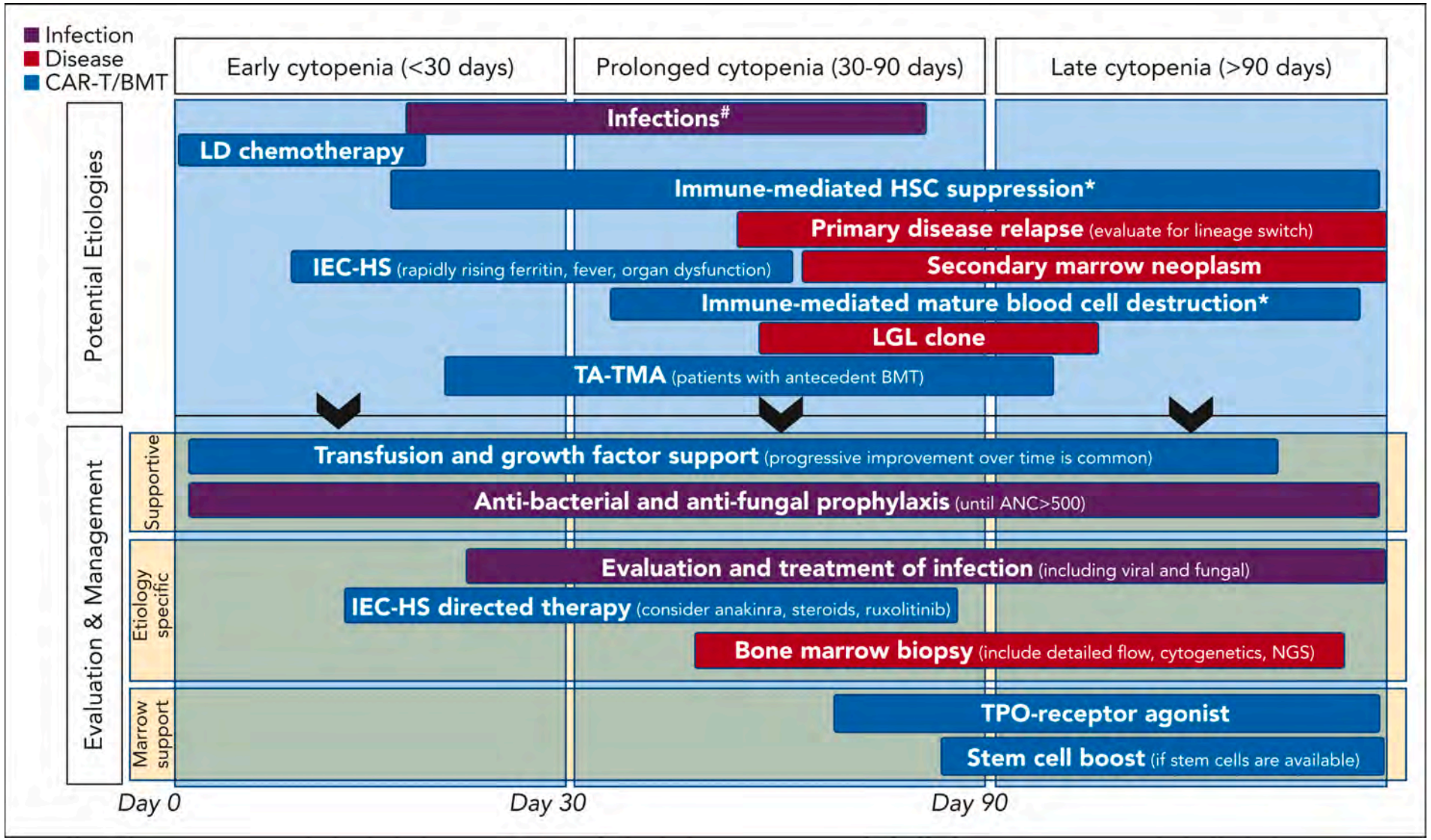


Number at risk

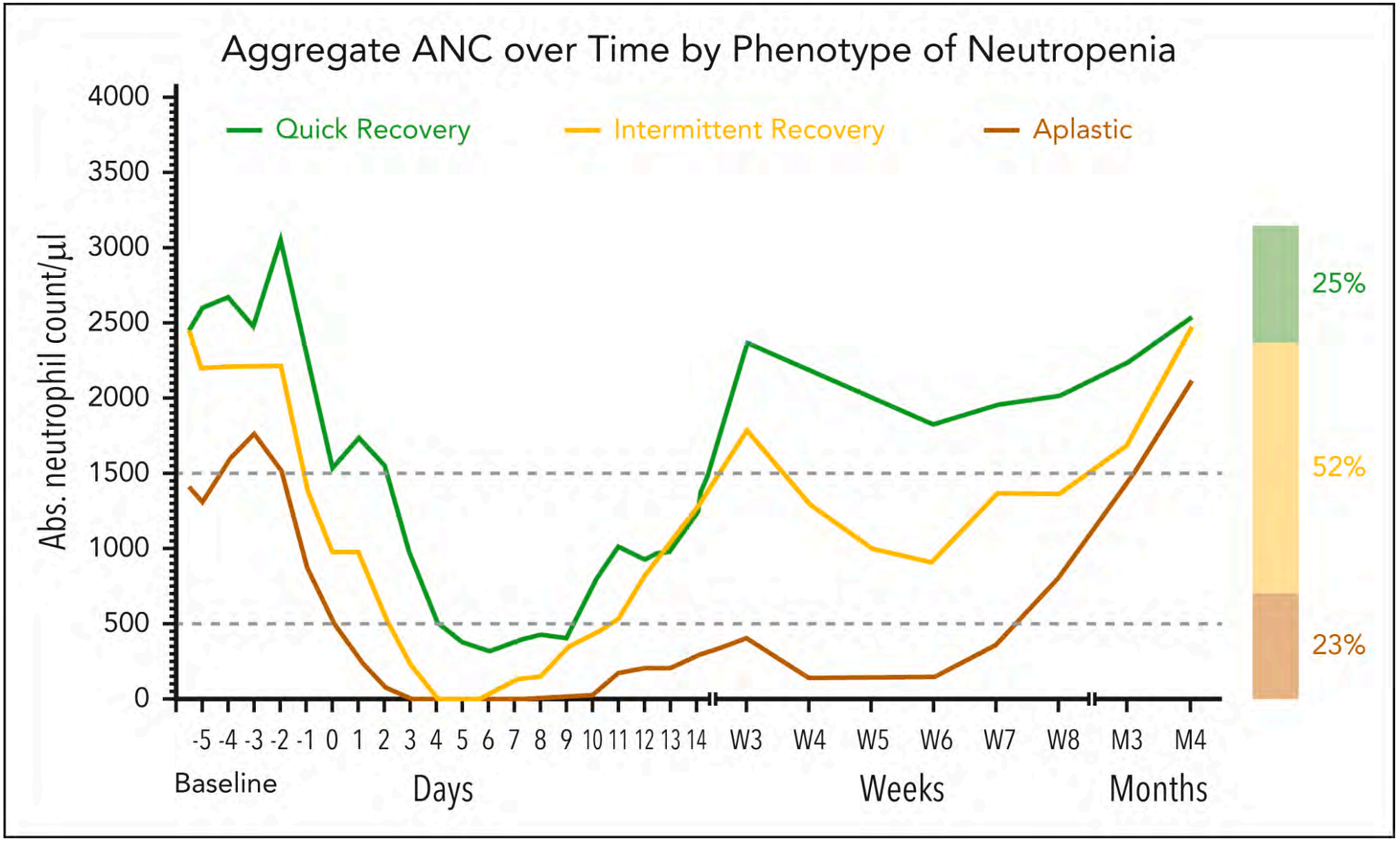
SD/PD	23	7	1	1	0	0	0	0	0	0
CR/PR	29	19	16	10	7	5	4	1	0	0

Roddie et al. BJH 2023

Cytopenias after CAR T-cell therapy: Common and result in morbidity and reduced QoL

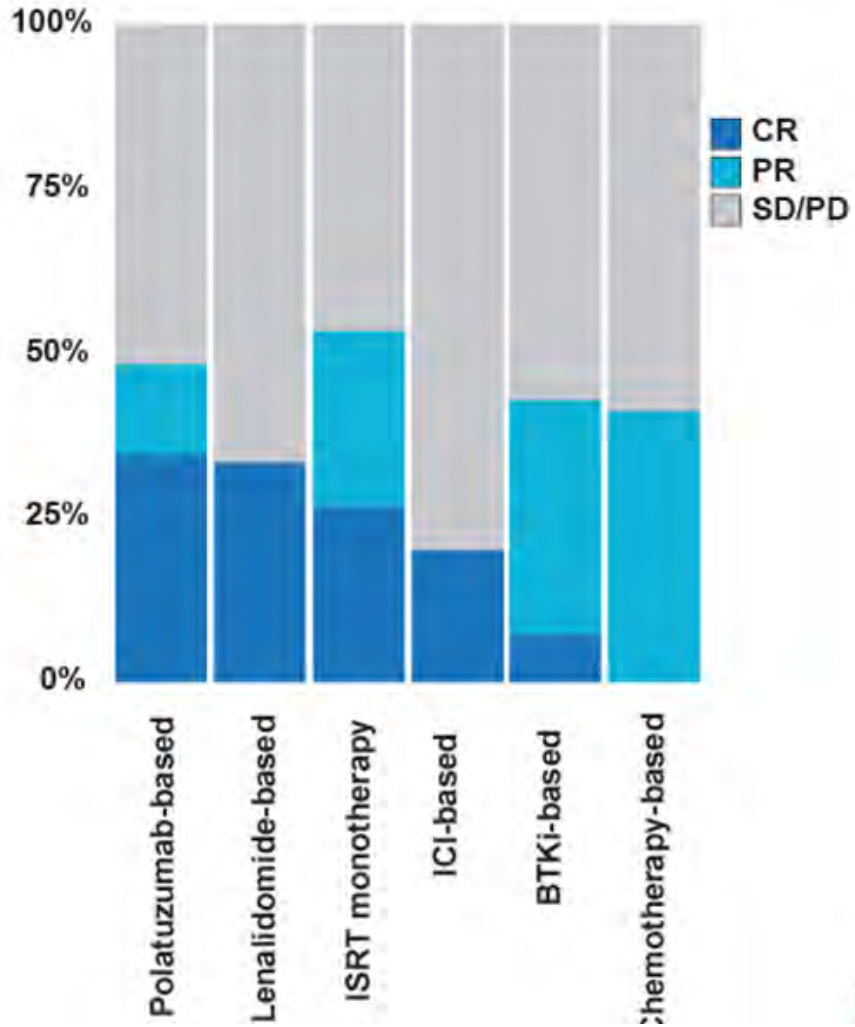


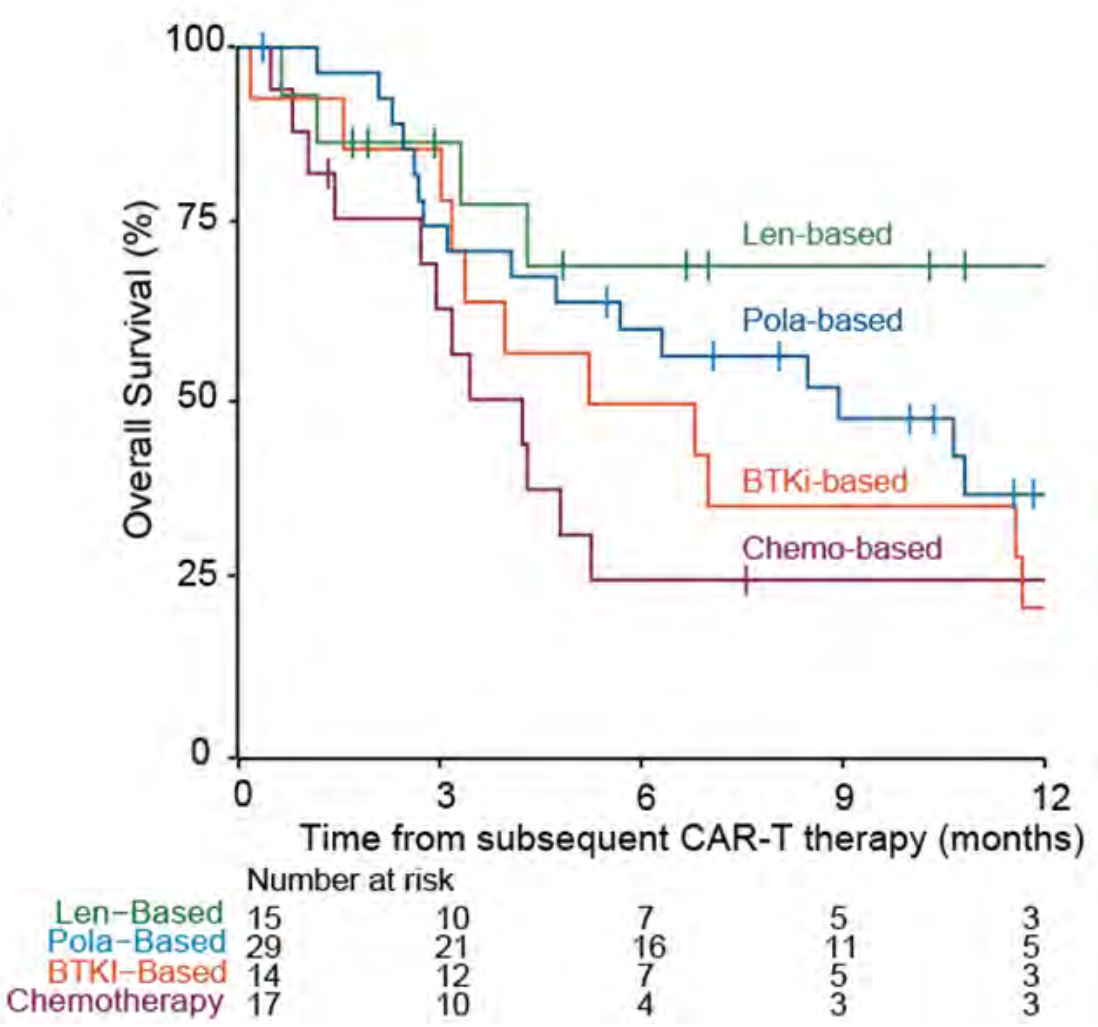
Tania Jain,Timothy S. Olson,Frederick L. Locke, How I treat cytopenias after CAR T-cell therapy, Blood, 2023



Tania Jain,Timothy S. Olson,Frederick L. Locke, How I treat cytopenias after CAR T-cell therapy, Blood, 2023.

Delivering therapy post CAR-T is challenging



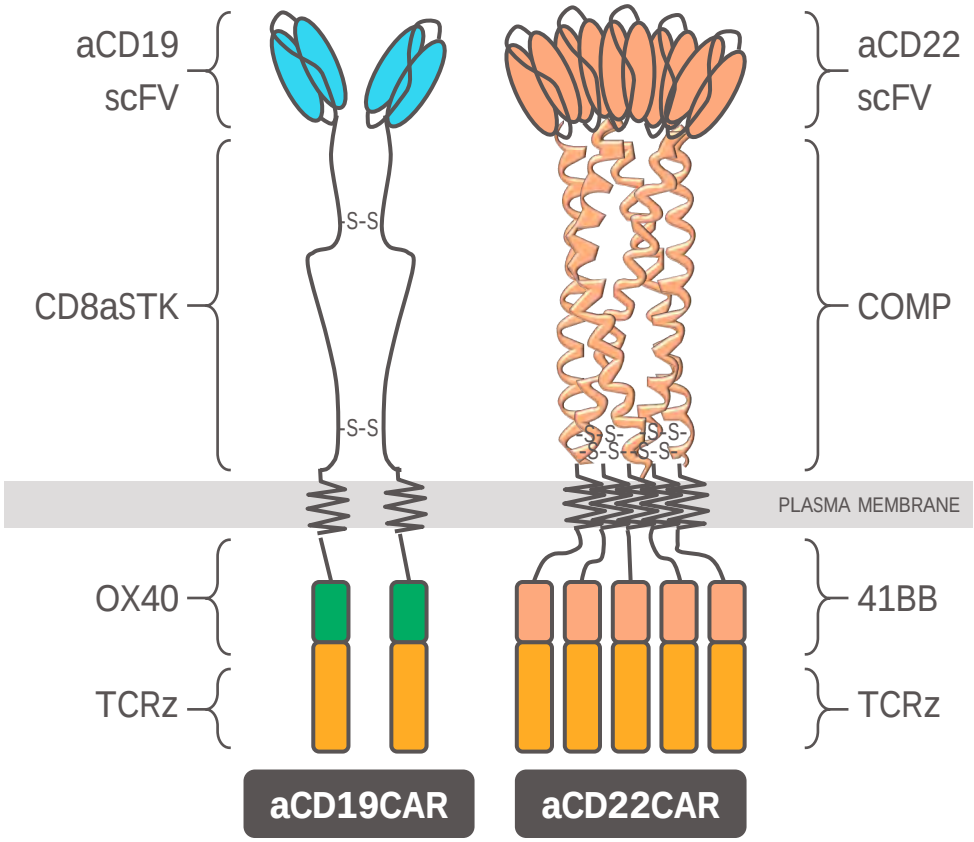


Tomas et al. Leukemia 2023

AUTO3: CD19 and CD22 targeting bicistronic CAR T cell therapy

- Gamma retroviral-based vector with RD114 pseudotype

- Dual antigen targeting
- Two independent CARs delivered in single retroviral vector
- Humanized binders
- CD22 CAR with novel pentameric spacer
- OX40/41BB costimulatory domains designed to improve persistence
- Independently target CD19 and CD22

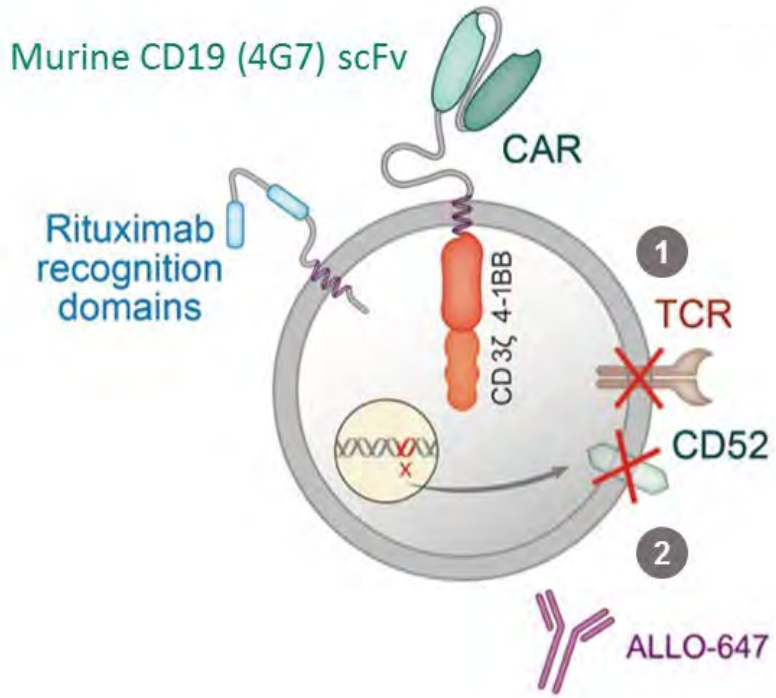


AUTO3 is not approved by any regulatory agency.

Osborne W, et al. Presented at EHA 2020;abstract S240.

Allogeneic CAR T cell therapy for r/r NHL

1. TALEN-mediated TRAC KO eliminates TCRα expression to minimize risk of GvHD



2. TALEN-mediated CD52 KO allows selective lymphodepletion with ALLO-647

Allogeneic CAR T cell therapy may provide the benefits of autologous CAR T cell therapy while addressing challenges:

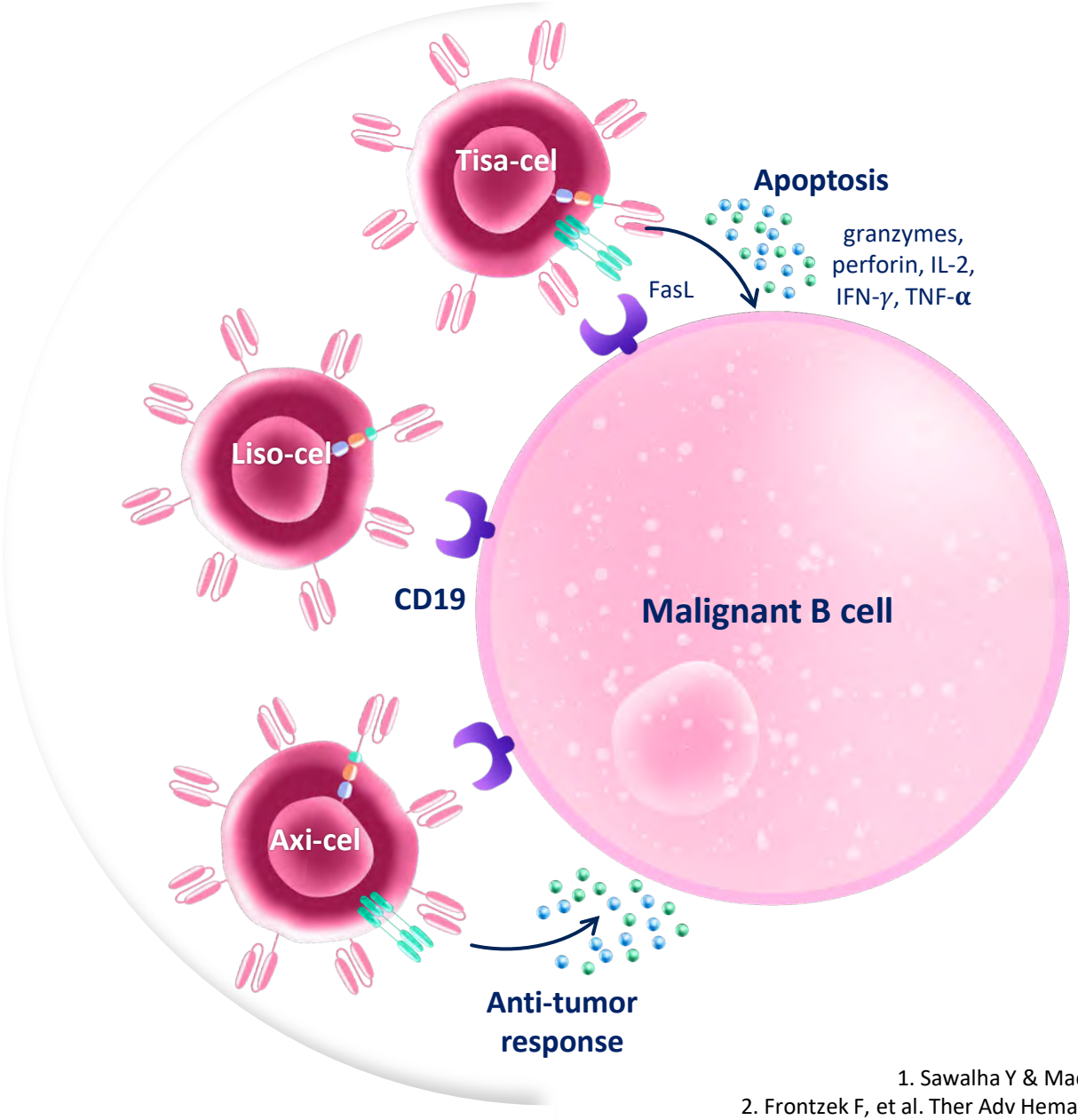
- Access
  - Potential to treat all eligible patients
  - Convenience of repeat dosing
  - No need for complex logistics
- Speed/reliability
  - "Off-the-shelf" treatment
  - Less product variability, made from healthy T-cells

ALLO-501 and ALLO-647 are not approved by any regulatory agency.

ALLO, allogeneic; GvHD, graft-versus-host disease; KO, knock out; TALEN, transcription activator-like effector nuclease; TRAC, T-cell receptor alpha chain.

Davies A. Personal communication. Neelapu SS, et al. Presented at ASCO 2020:abstract 8002.

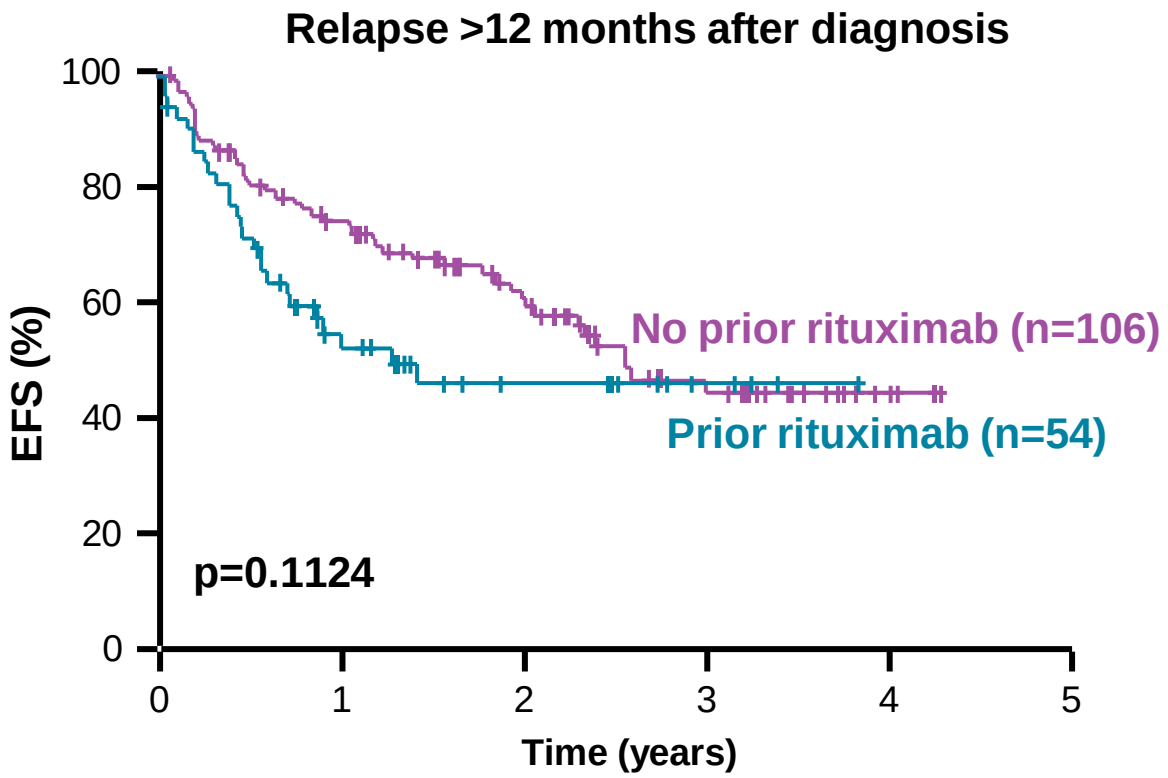
Moving CAR-T earlier in disease course

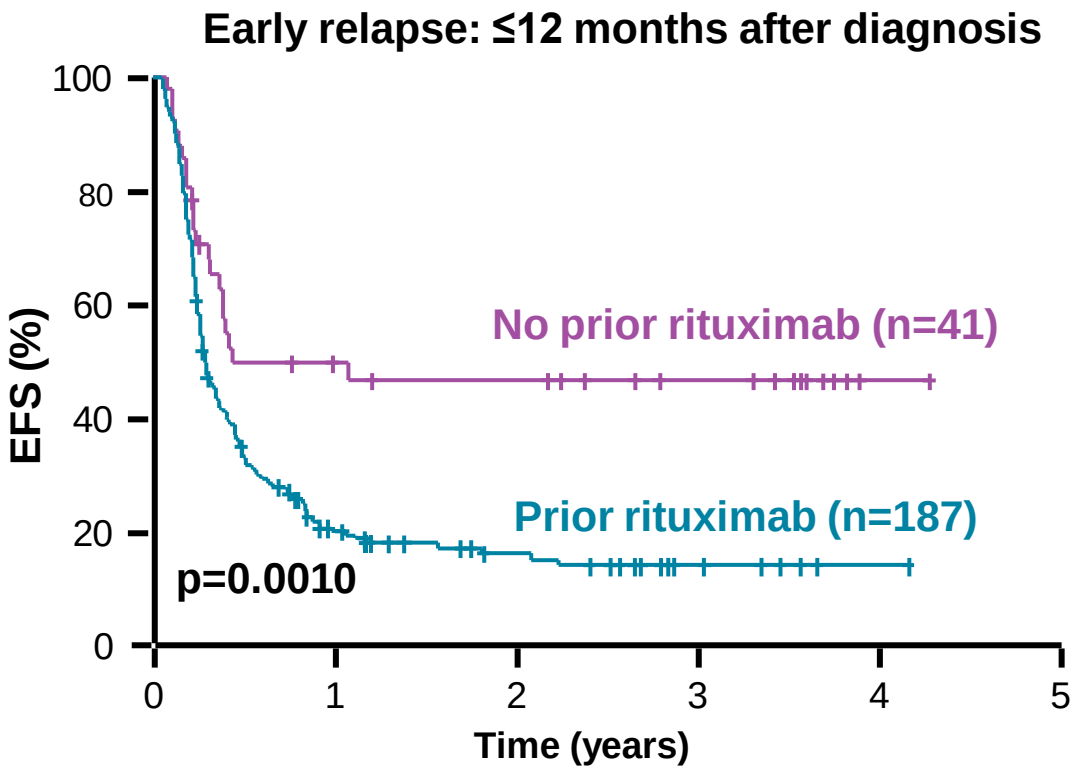


1. Sawalha Y & Maddocks K. BMJ 2022; 377:e063439;
2. Frontzek F, et al. Ther Adv Hematol. 2022;13:20406207221103321;
3. Khurana A & Lin Y. Curr Treat Options Oncol. 2022;23:171–187;
4. Meng J, et al. Front Oncol 2021;11:698607.

CORAL study: Standard regimens do not overcome poor prognosis of early relapse

CORAL: Randomised study of R-ICE vs. R-DHAP in patients with R/R DLBCL after 1L R-CHOP (N=396)





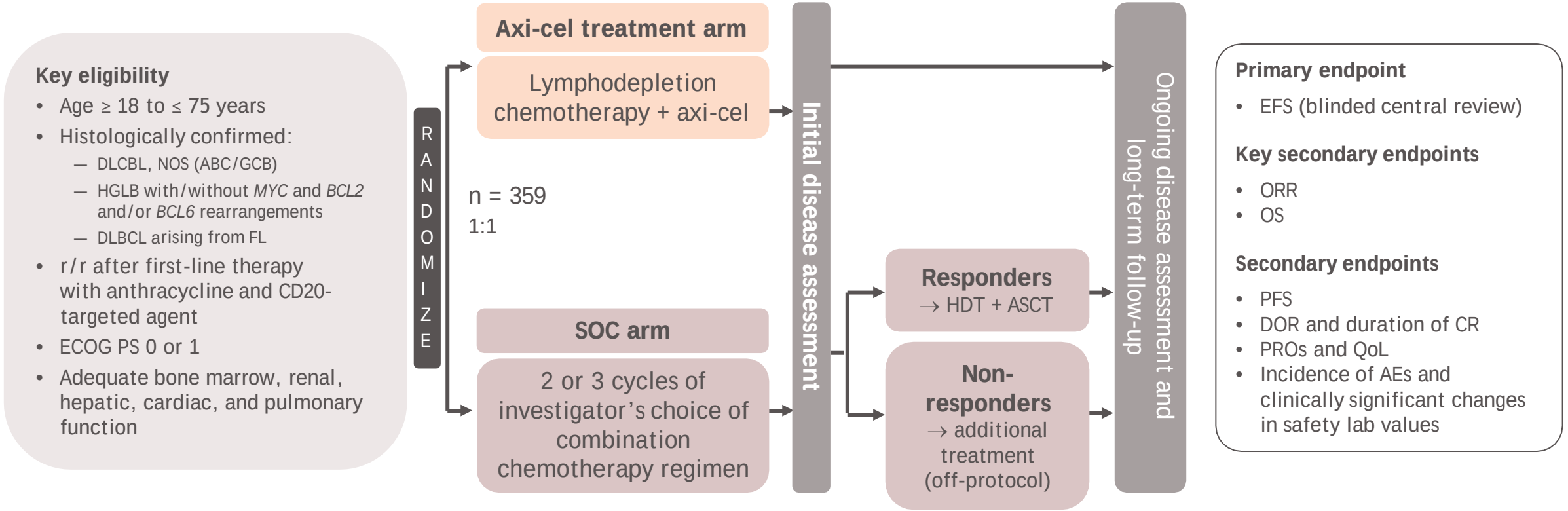
EARLY RELAPSE AND PRIOR RITUXIMAB TREATMENT DEFINED A POPULATION WITH A POOR RESPONSE RATE TO STANDARD SALVAGE TREATMENT

CORAL: Collaborative Trial in Relapsed Aggressive Lymphoma

Gisselbrecht C, *et al. J Clin Oncol* 2010; 28:4184–4190.

Progression to the second line of therapy?

ZUMA-7, a randomized, open label, phase 3 trial of second-line axicabtagene ciloleucel versus standard of care in adult patients with r/r DLBCL

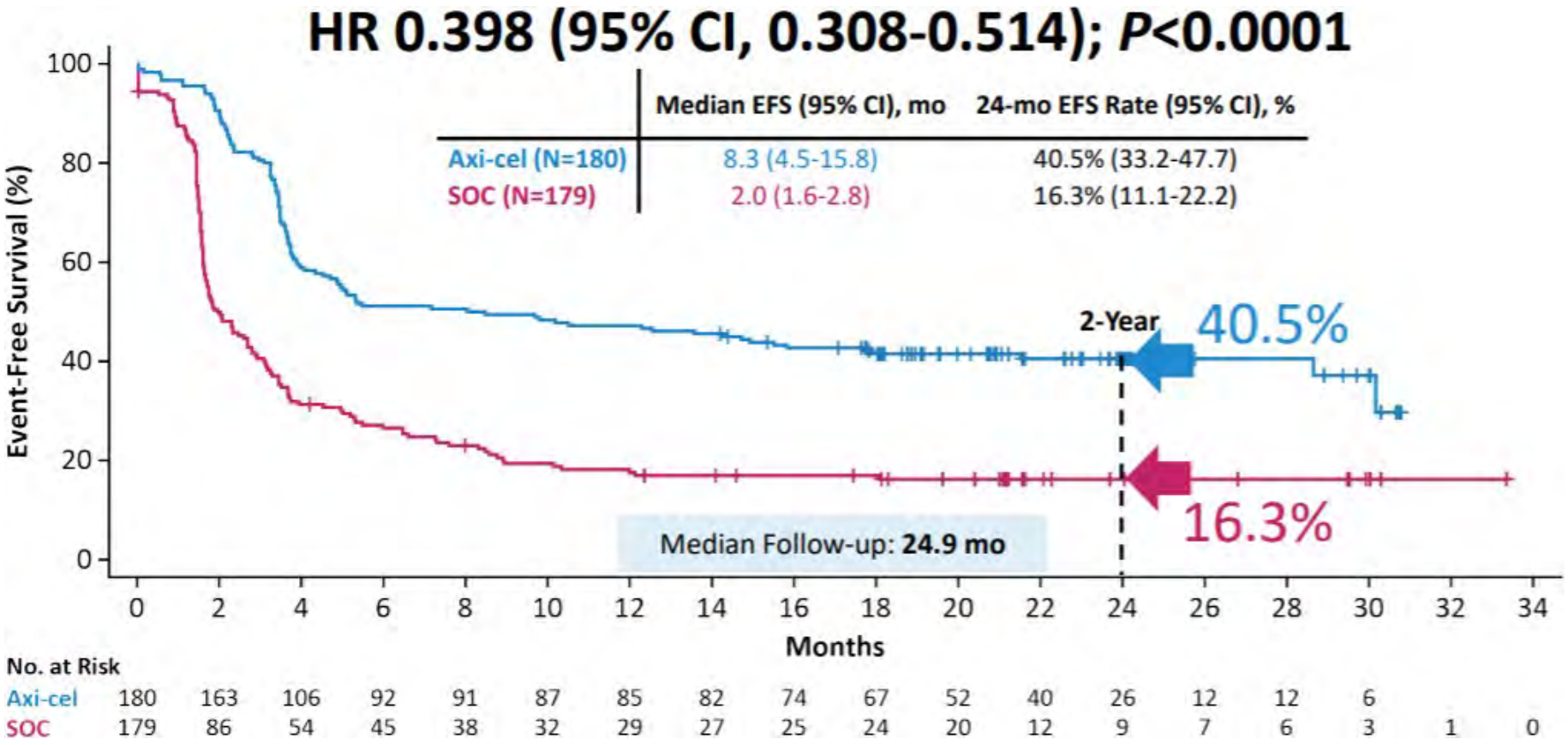


Axi-cel, axicabtagene ciloleucel; HDT, high-dose therapy; NOS, not otherwise specified; PRO, patient-reported outcome; QoL, quality of life; SOC, standard of care.

NCT03391466. Available from: https://clinicaltrials.gov/ct2/show/NCT03391466. Accessed October 2020.

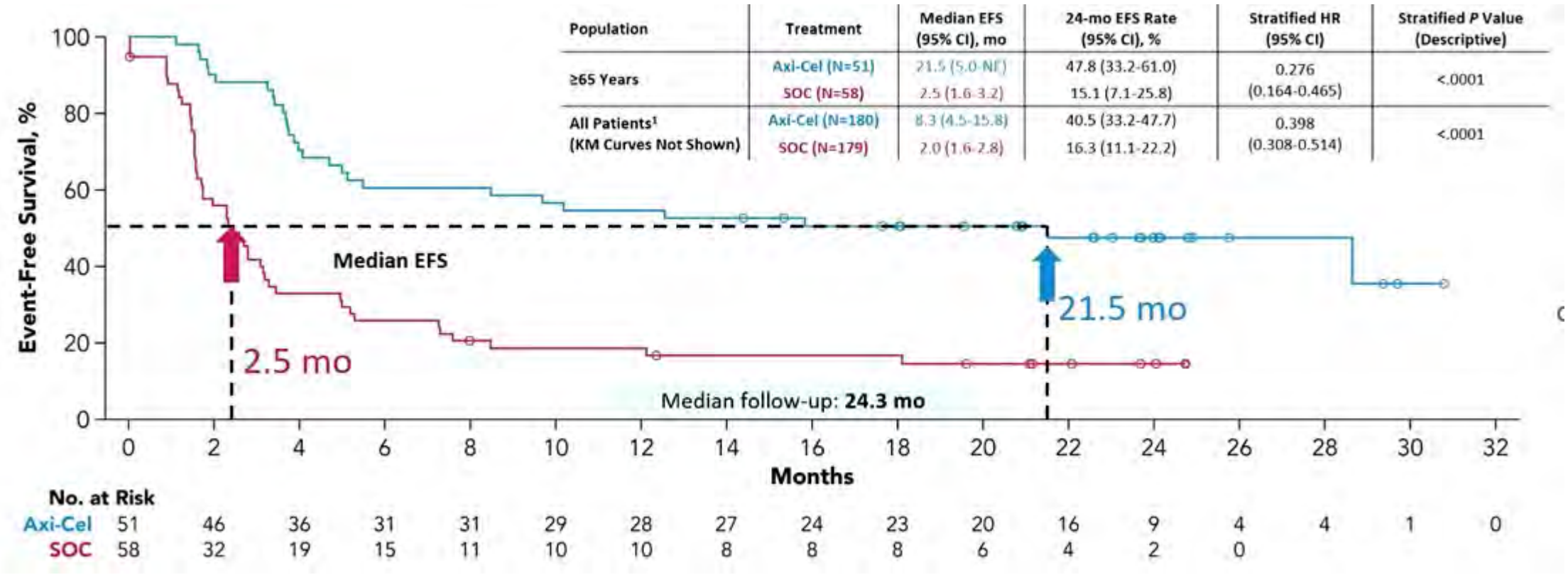
TRANSFORM (l**isocabtagene maraleucel**) and BELINDA (tisagenlecleucel)

Zuma-7 Primary endpoint: Event-Free Survival



Locke et al ASH 2021

This is an option in the elderly (eldest 81)



Population	Treatment	Median EFS (95% CI), mo	24-mo EFS Rate (95% CI), %	Stratified HR (95% CI)	Stratified *P* Value (Descriptive)
≥65 Years	Axi-Cel (N=51)	21.5 (5.0-NE)	47.8 (33.2-61.0)	0.276 (0.164-0.465)	<.0001
	SOC (N=58)	2.5 (1.6-3.2)	15.1 (7.1-25.8)		
All Patients[1] (KM Curves Not Shown)	Axi-Cel (N=180)	8.3 (4.5-15.8)	40.5 (33.2-47.7)	0.398 (0.308-0.514)	<.0001
	SOC (N=179)	2.0 (1.6-2.8)	16.3 (11.1-22.2)		

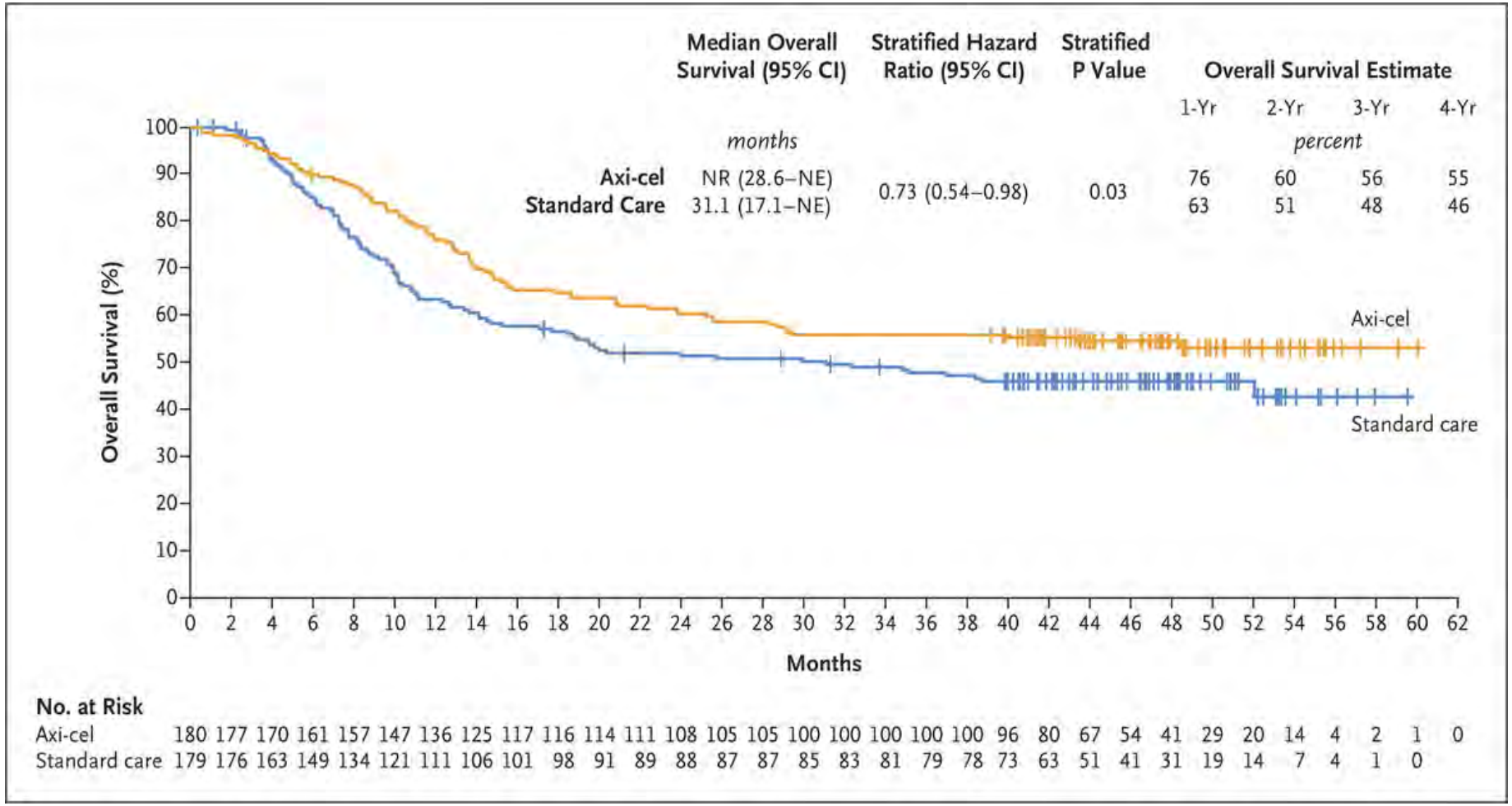
At a median follow-up of 24.3 months, medial EFS was 21.5m [95% CI, 5.0-NE] with axi-cel vs 2.5m [95% CI, 1.6-3.2] with SOC in patients aged ≥ 65 years

IRC, independent review committee; EFS, event-free survival; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; KM, Kaplan meier; CI, confidence interval; mo, months; SOC, standard of care; NE, not evaluable

Adapted from Sureda A et al. EHA 2022, Oral Presentation S211

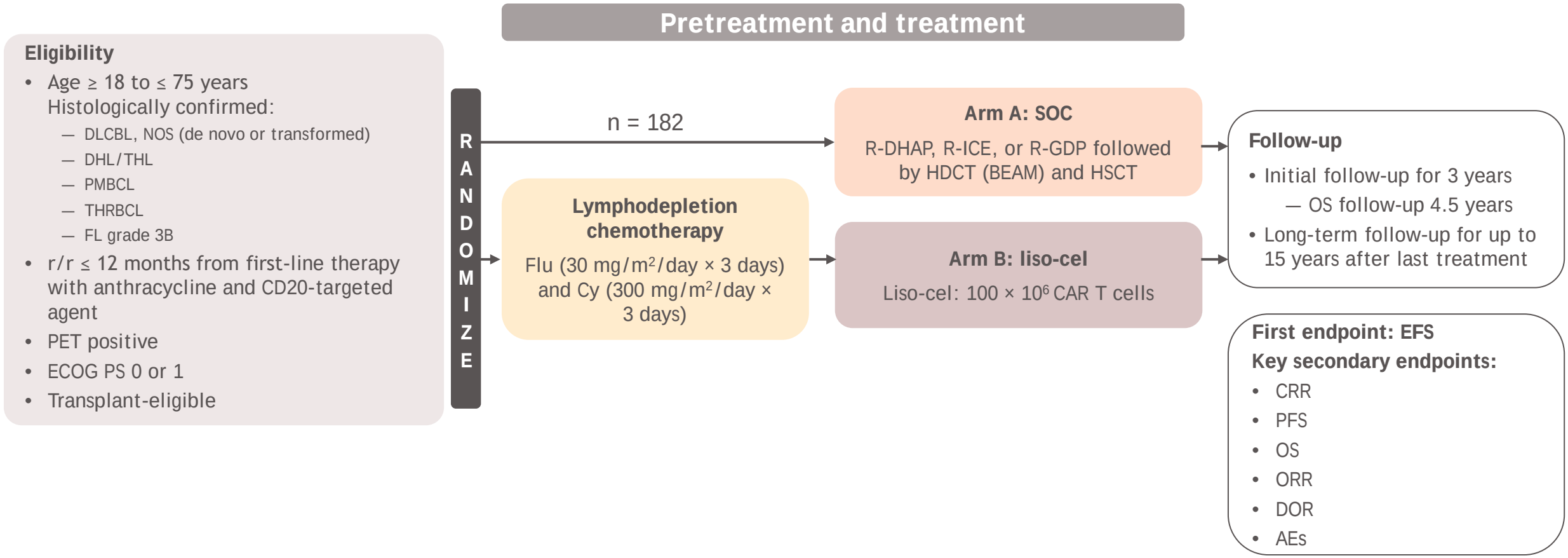
1. Locke FL, et al. *N Engl J Med.* 2022;386:640-654

Overall Survival advantage.



JR Westin et al. N Engl J Med 2023;389:148-157.

TRANSFORM: lisocabtagene maraleucel compared to standard of care second-line therapy in r/r aggressive B-cell NHL

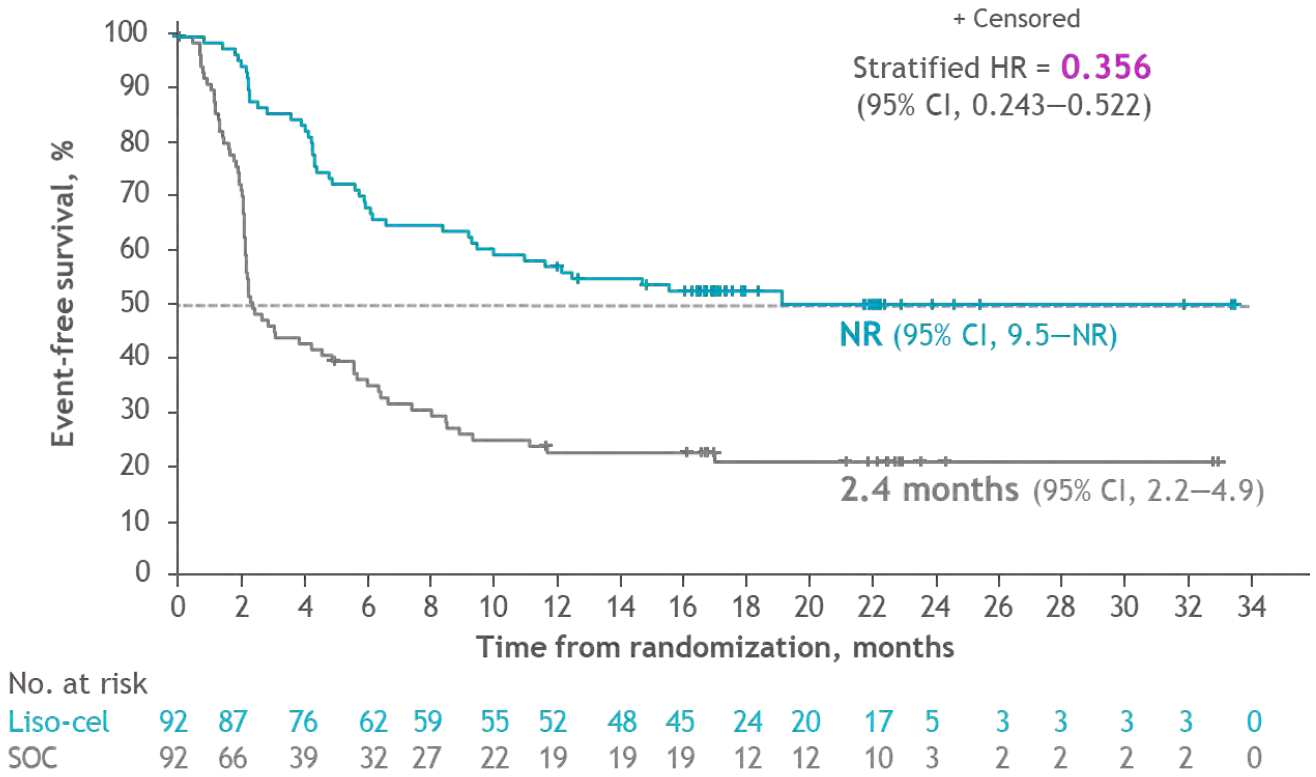


Lisocabtagene maraleucel is not approved by any regulatory agency.

BEAM, carmustine, etoposide, cytarabine, melphalan; CR, complete response; HRQoL, health-related quality of life; HDCT, high-dose chemotherapy; ORR, overall response rate; PFS-2, progression after the next line of therapy.

NCT03575351. Available from: https://clinicaltrials.gov/ct2/show/NCT03575351. Accessed October 2020.

TRANSFORM: EFS per IRC (ITT set; primary endpoint)



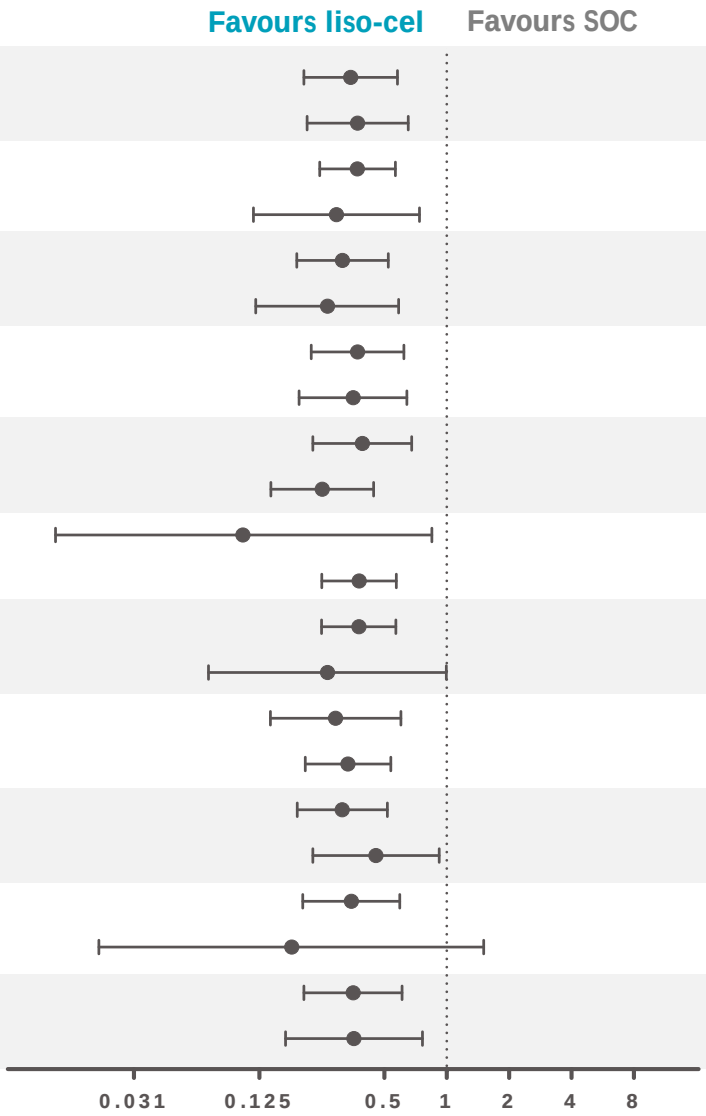
18-month EFS rate	
Liso-cel	SOC
52.6%	20.8%
(95% CI, 42.3–62.9)	(95% CI, 12.2–29.5)

Median follow-up: 17.5 months

EFS was defined as the time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomisation, or start of a new antineoplastic therapy due to efficacy concerns, whichever occurred first. This endpoint was not statistically retested for the primary analysis.
EFS, event free survival; IRC, independent review committee; ITT, intent-to-treat; NR, not reached.

Abramson JA et al, Oral 655, ASH 2022

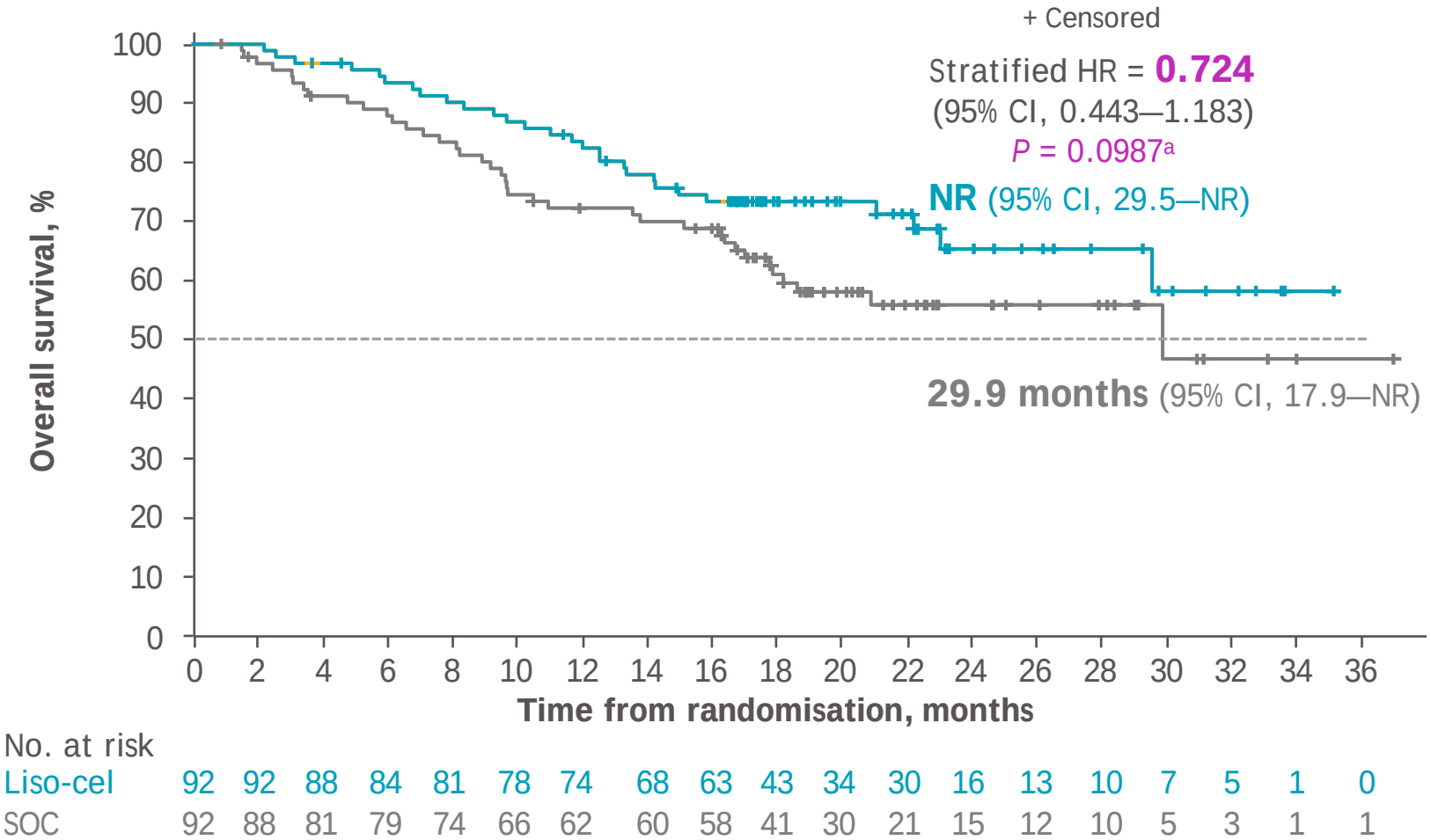
TRANSFORM: EFS per IRC by subgroup (ITT set)



	Liso-cel, n/N	SOC, n/N	Stratified HR (95% CI)
sAAIPI: 0 or 1	23/56	39/55	0.34 (0.21–0.58)
sAAIPI: 2 or 3	21/36	32/37	0.37 (0.21–0.65)
Prior response status: refractory	37/67	57/70	0.37 (0.24–0.57)
Prior response status: relapse to last prior therapy	7/25	14/22	0.29 (0.12–0.74)
Age group, years: < 65	23/56	51/67	0.31 (0.19–0.52)
Age group, years: ≥ 65 to < 75	21/36	18/23	0.27 (0.12–0.59)
Sex: male	23/44	47/61	0.37 (0.22–0.62)
Sex: female	21/48	24/31	0.35 (0.19–0.64)
ECOG PS (at screening): 0	20/48	40/57	0.39 (0.23–0.68)
ECOG PS (at screening): 1	24/44	31/35	0.25 (0.14–0.44)
SPD: > 50 cm^2	3/10	9/10	0.10 (0.01–0.85)
SPD: ≤ 50 cm^2	38/77	59/76	0.38 (0.25–0.57)
Lactate dehydrogenase: < 500 unit/L	38/79	60/81	0.38 (0.25–0.57)
Lactate dehydrogenase: ≥ 500 unit/L	5/10	11/11	0.27 (0.07–1.00)
Prior CT response status: chemorefractory (PD, SD)	18/26	17/18	0.29 (0.14–0.60)
Prior CT response status: chemosensitive (PR, CR)	26/66	54/74	0.33 (0.21–0.54)
NHL type: DLBCL	25/60	46/58	0.31 (0.19–0.52)
NHL type: HGBCL	18/22	18/21	0.46 (0.23–0.92)
DLBCL subtype: DLBCL NOS de novo	23/53	39/50	0.35 (0.20–0.59)
DLBCL subtype: DLBCL transformed from indolent NHL	2/7	7/8	0.18 (0.02–1.51)
DLBCL subtype based on cell of origin: GCB	27/45	32/40	0.35 (0.21–0.61)
DLBCL subtype based on cell of origin: ABC, non-GCB	10/21	26/29	0.36 (0.17–0.76)

CT, chemotherapy; SD, stable disease; SPD, sum of the product of perpendicular diameters.

Survival is evolving:TRANSFORM overall survival (ITT set)



18-month OS rate	
Liso-cel	**SOC**
73.1%	**60.6%**
(95% CI, 63.9—82.3)	(95% CI, 50.2—71.1)

Median follow-up: 17.5 months

- Patients in SOC arm who crossed over to receive liso-cel continue to be followed for OS in the SOC arm

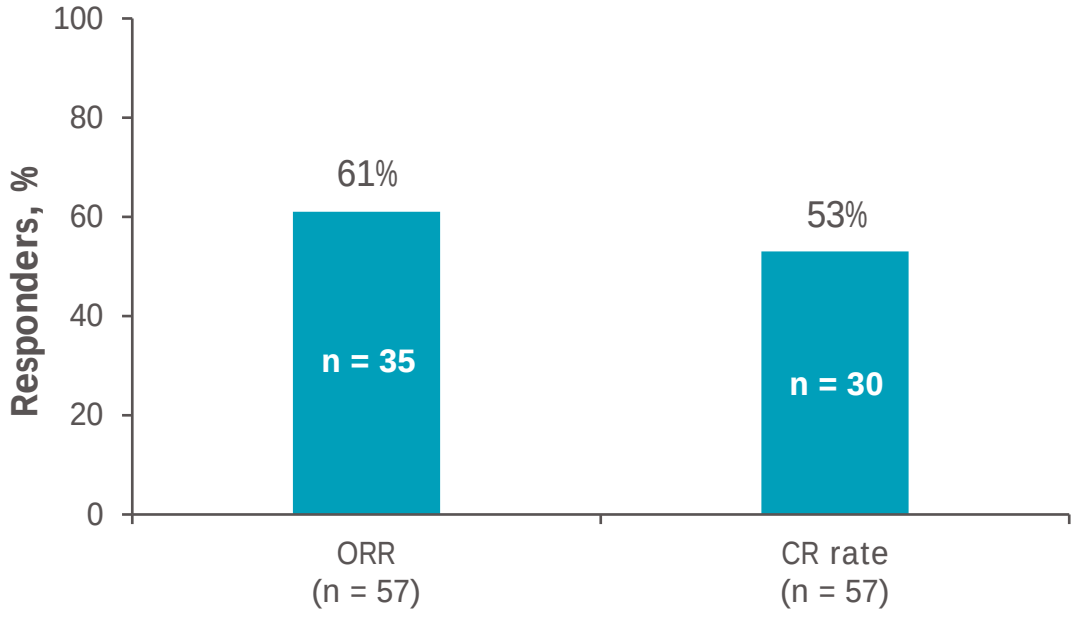
[a]One-sided *P* value significance threshold to reject the null hypothesis was ≤ 0.021.
OS was defined as the time from randomization to death from any cause. ITT, Intent-to treat; liso-cel, lisocabtagene maraleucel; NR, not reached

Abramson JA et al, Oral 655, ASH 2022

TRANSFORM: efficacy outcomes in the crossover subgroup

Of 92 patients in the SOC group, 61 (66%) were approved for crossover to receive liso-cel

- 58 received CAR$^+$ T cells (57 received liso-cel, 1 received nonconforming product)
- Median time from crossover approval to liso-cel infusion was 15 days (range, 8–95)

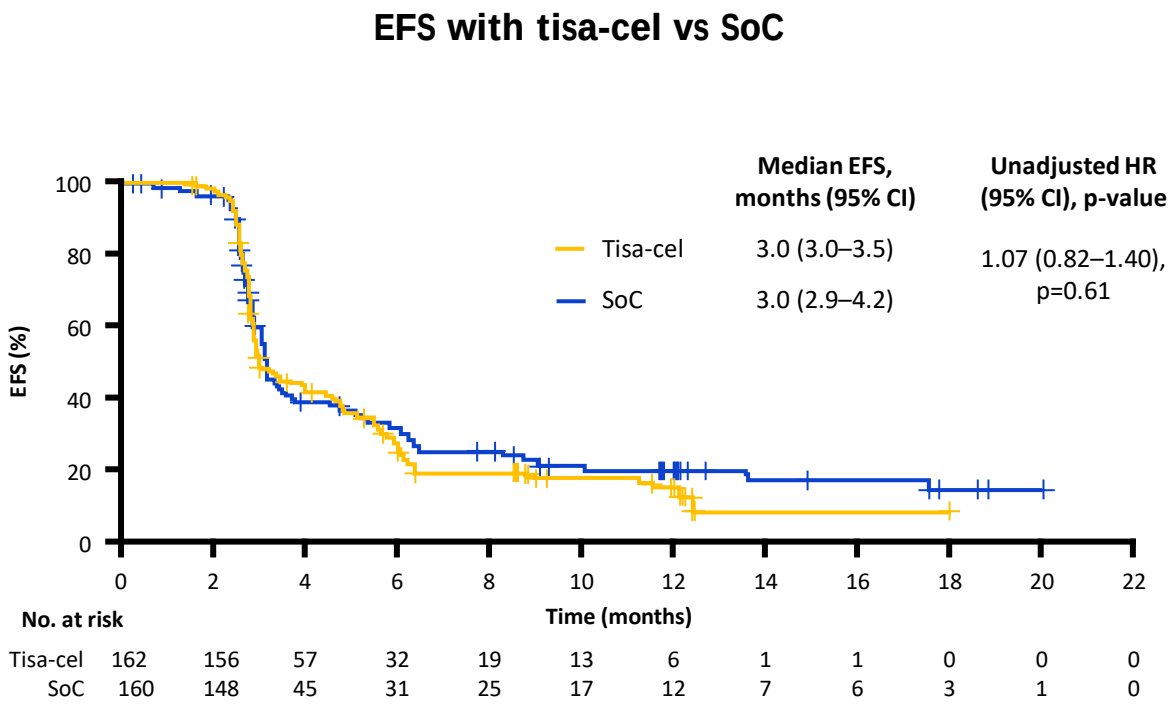


	Crossover subgroup (n = 57)[a]
Median (range) follow-up, months[b]	12.0 (1.4–28.1)
Median (95% CI) EFS, months[c]	5.9 (3.1–15.1)
Median (95% CI) PFS, months[c]	5.9 (3.2–26.5)
Median (95% CI) OS, months[c]	15.8 (11.8–NR)

All endpoints were evaluated from the time of liso-cel infusion.

[a]Three patients approved for crossover who did not receive liso-cel and 1 patient who received nonconforming product were not included in the efficacy analyses; [b]Calculated for the 58 patients randomised to the SOC group who were approved for crossover and received CAR$^+$ T cells; [c]Median estimates of time to event were Kaplan-Meier product-limit estimates.

BELINDA: Tisa-cel failed to show improved efficacy vs SoC in 2L R/R aggressive B-cell lymphoma



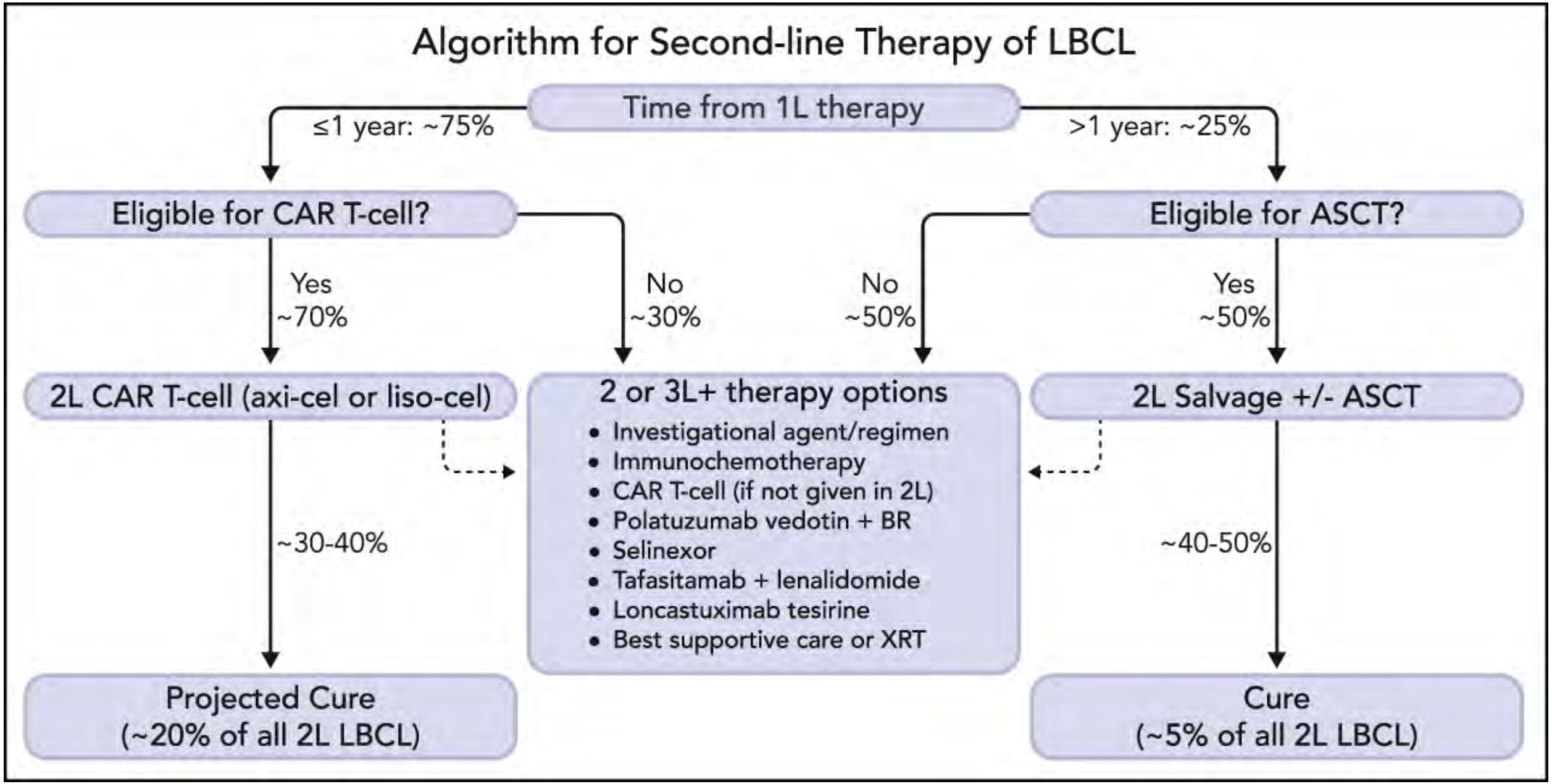
Response rates

- **At week 6**, 38.3% of patients receiving tisa-cel and 53.8% of those receiving SoC had a response
- **From week 12**, a response occurred in 46.3% of patients receiving tisa-cel and 42.5% receiving SoC

Safety, n (%)	Tisa-cel (n=162)	SoC (n=160)
Grade ≥3 AEs	136 (84.0)	144 (90.0)
Treatment-related Grade ≥3 AEs	121 (74.7)	137 (85.6)
Grade ≥3 CRS*	8 (5.2)	NA
Grade ≥3 neurologic events*	3 (1.9)	NA
Fatal AEs	10 (6.2)	13 (8.1)

*A total of 155 patients from the tisa-cel arm were evaluable for CRS and neurologic events.

Bishop MR, et al. N Engl J Med 2022;386:629–39.



Westin and Sehn 2022

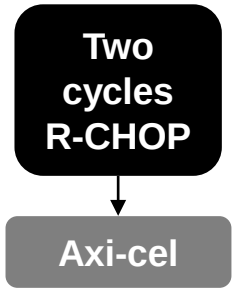
CAR-T however remain significantly challenging: Further options needed

- Manufacturing challenges/disease kinetics
- Tolerability
- Geographical constraints
- Social and economic challenges. Equity of access
- High rate of treatment failure.

ZUMA-12: Phase II study of axi-cel as first-line therapy for high-risk DLBCL

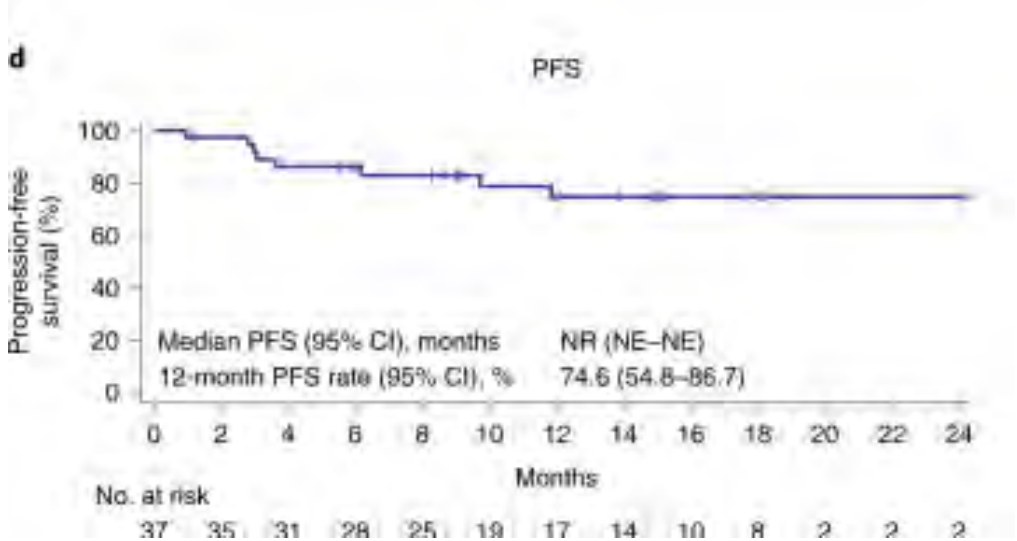
1L high-risk LBCL (N=40):

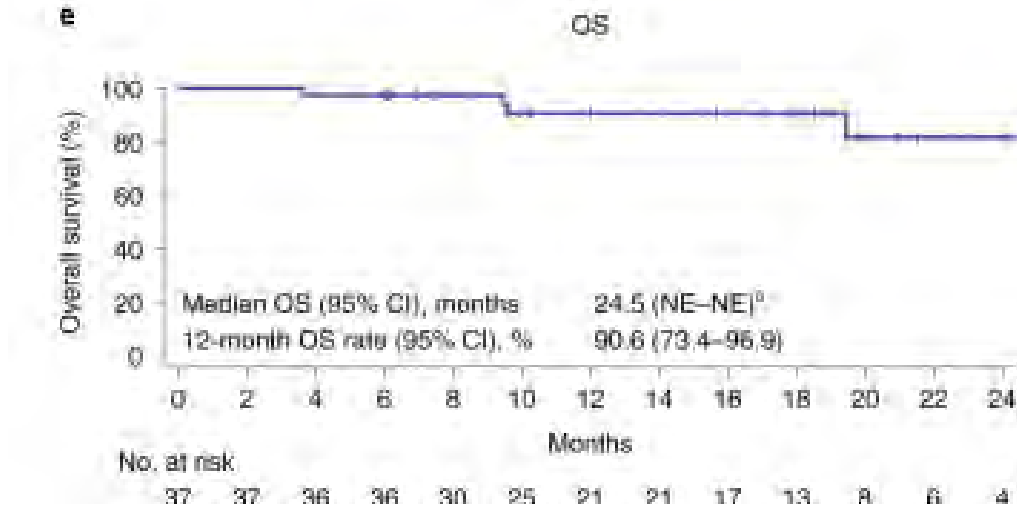
1. Double-/triple-hit lymphoma with IPI score ≥3
2. Positive interim PET* after 2 cycles of anti-CD20 mAb + anthracycline-containing regimen (dynamic risk assessment)



89% ORR
78% CR

CRS ≥3 in 3 cases
Neurology AE ≥ 3 in 8

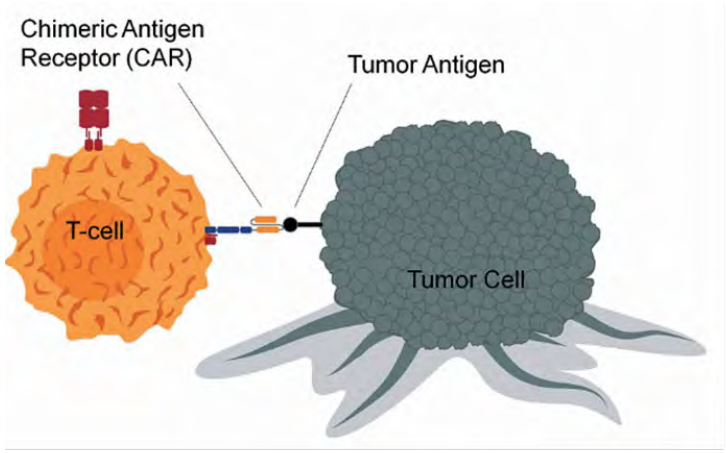




Neelapu et al., Nature Med 2022; 28(4): 735-742

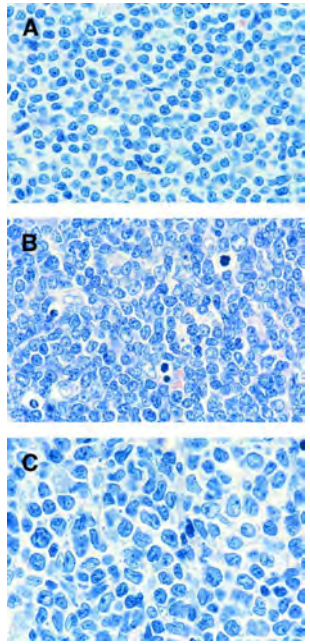
Zuma 23 IPI 4-5

CAR-T in mantle cell lymphoma



Mantle cell lymphoma (MCL)

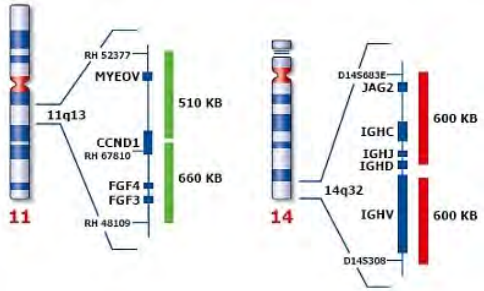
- Mature B-cell NHL[1]
- Classified as an indolent lymphoma, but often aggressive behaviour[1]
- 3–6% of adult NHL presentations in US/Europe[2–4]
- Male predominance (3:1)[5]
- Median age at presentation: 65 years[5]
- Incidence increasing (1—2/100,000)[5,6]
- Diagnosis from biopsy, preferably LN, or BM for rare leukaemic form[5]

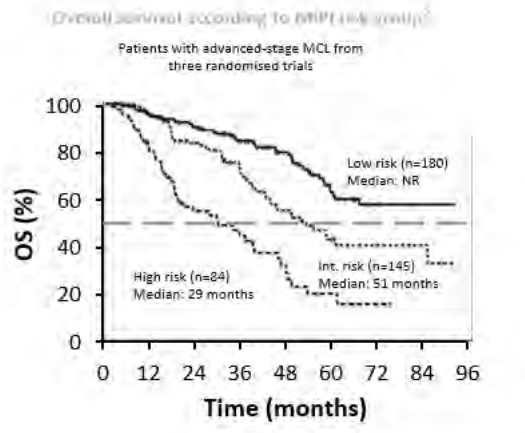


CD5 positive, small to medium size[5]

Morphological variants[5]:
- Blastoid
- Pleomorphic
- Small-cell
- Marginal zone-like

>95% have *CCND1* translocation t(11;14)[7]

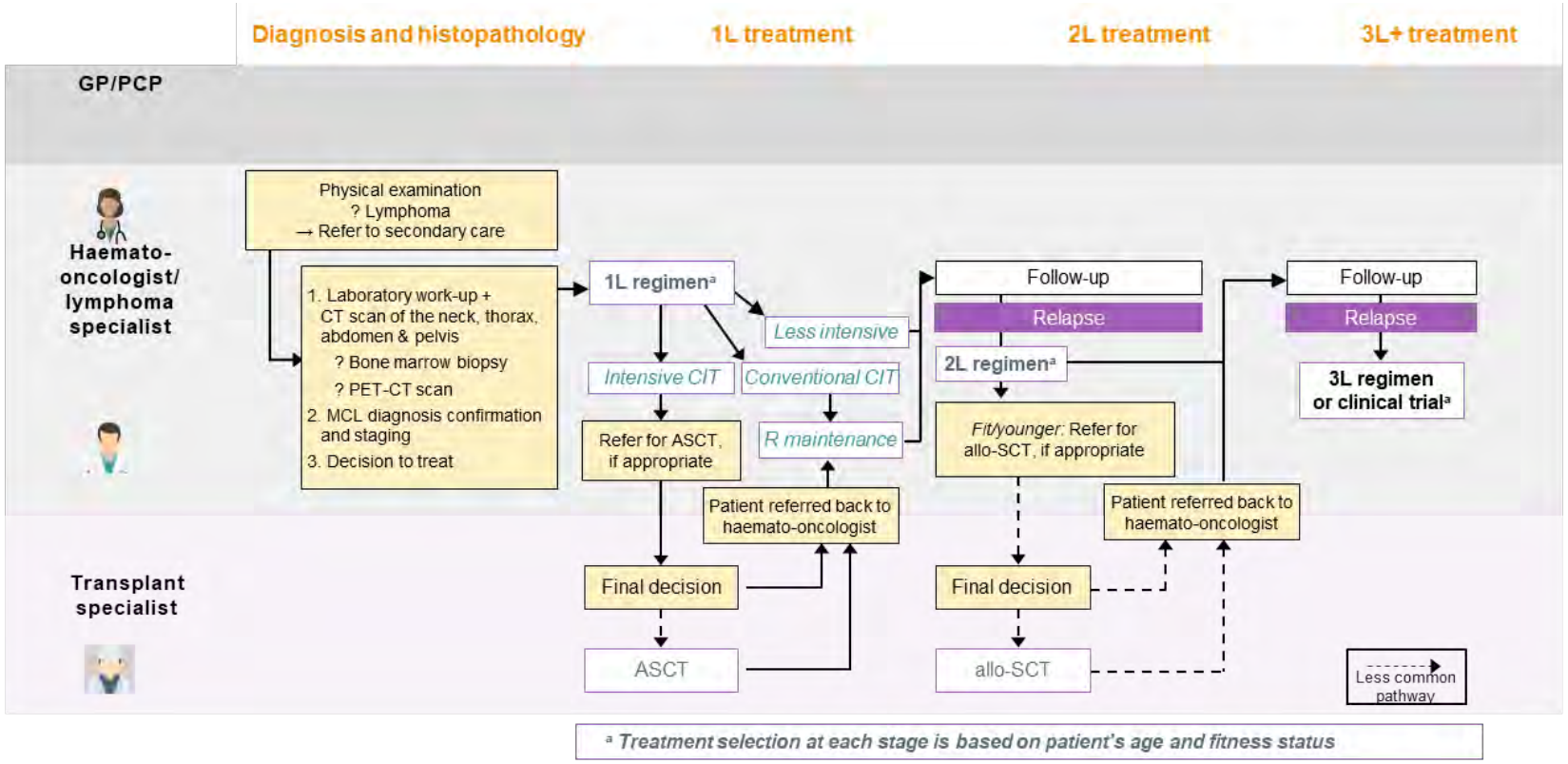




BM: bone marrow; LN: lymph node; NHL: non-Hodgkin's lymphoma; CD: clusters of differentiation

1. Swerdlow S, *et al. Blood* 2016; 127:2375–2390. 2. Al Hamadani M, *et al. Am J Hematol* 2015; 90:790–795. 3. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997; 89:3909–3918.
4. Zhou Y, *et al. Cancer* 2008; 113:791–798. 5. Dreyling M, *et al. Ann Oncol* 2017; 28(suppl. 4):iv62–iv71. 6. Fu S, *et al. Oncotarget* 2017; 8:112516–112529.
7. Medeiros LJ & Carr J. *Arch Pathol Lab Med* 1999; 123:1189–1207. Image from https://www.intergenetics.eu/en/exam/translocation-t1114-detected-by-fish/

Patient journey: Diagnosis and treatment of MCL

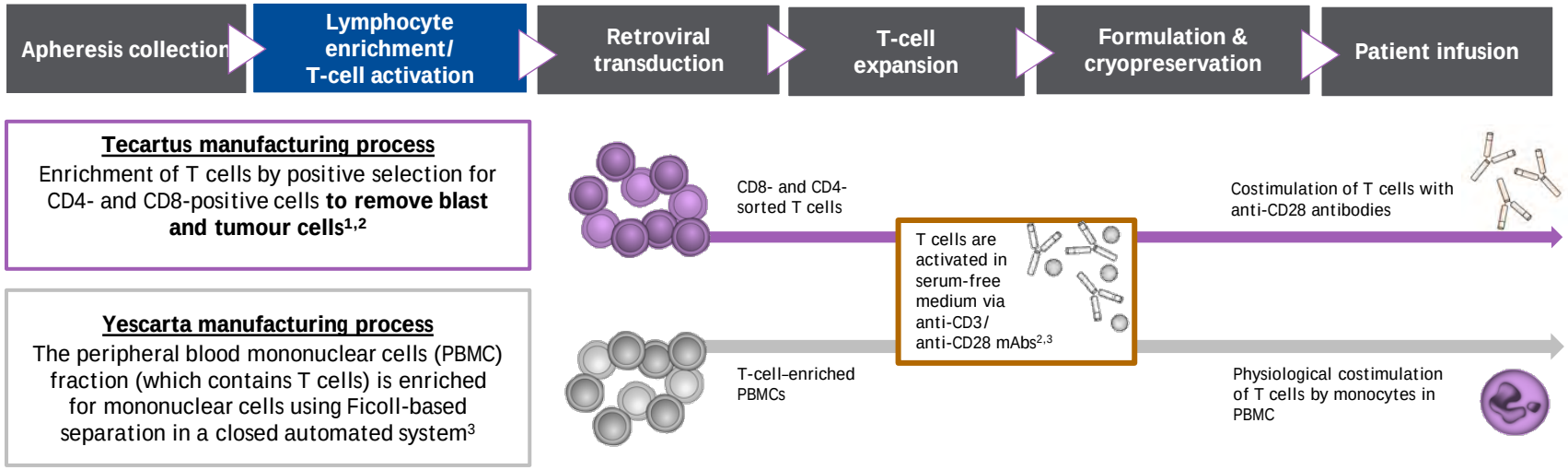


1L: first line; 2L: second line; 3L: third line; allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; CIT: chemoimmunotherapy; CT: computed tomography;
GP: general practitioner; PCP: primary care practitioner; PET: positron emission tomography; R: rituximab
Based on Dreyling M, *et al. Ann Oncol* 2017; 28(suppl. 4):iv62-iv71.

Considered an incurable disease and although outcomes have improved, long-term treatment options remain poor

Poor clinical outcomes in the majority of patients with primary or secondary ibrutinib resistance

Manufacturing process for brexucabtagene is different to that of axicabtagene



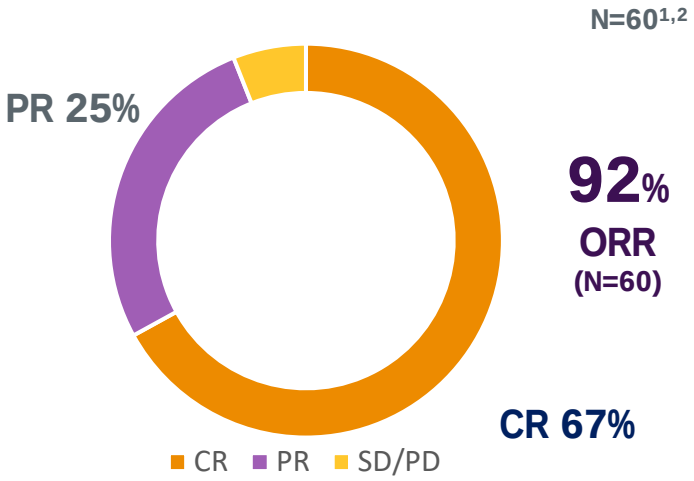
Tecartus manufacturing process reduces the likelihood of circulating CD19-expressing tumour cells in leukapheresis material[4]

IL: interleukin; PBMC: peripheral blood mononuclear cell

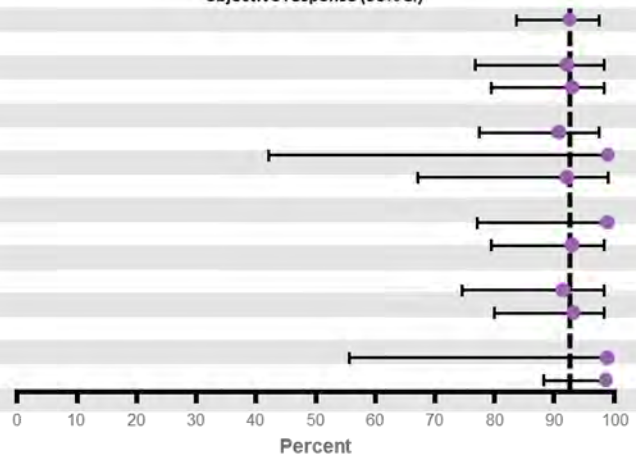
1. Sabatino M, *et al*. ASH 2016 (Abstract 1227; oral). 2. Data on file. XLP Manufacturing Process. Gilead Sciences Europe Ltd. 2020.

3. Better M, *et al*. *Cell Gene Ther Insights* 2018; 4:173–186. 4. Wang M, *et al*. *N Engl J Med* 2020; 382:1331–1342.

ZUMA-2: Response rates (n=60)



Subgroup[1]	No. of patients	No. of patients with response	Percent of patients with objective response (95% CI)
All patients	60	56	93 (84, 98)
Age			
<65 years	28	26	93 (76, 99)
≥65 years	32	30	94 (79, 99)
Morphological characteristic of MCL			
Classical MCL	35	32	91 (77, 98)
Pleomorphic MCL	4	4	100 (40, 100)
Blastoid MCL	14	13	93 (66, 100)
Ki-67 proliferation index			
<50%	14	14	100 (77, 100)
≥50%	32	30	94 (79, 99)
Simplified MIPI risk assessment			
Low risk	25	23	92 (74, 99)
Intermediate or high risk	33	31	94 (80, 99)
TP53 mutation detected			
Yes	6	6	100 (54, 100)
No	30	30	100 (88, 100)



Median time to initial response: **1.0 month**
(95% CI=0.8, 3.1)

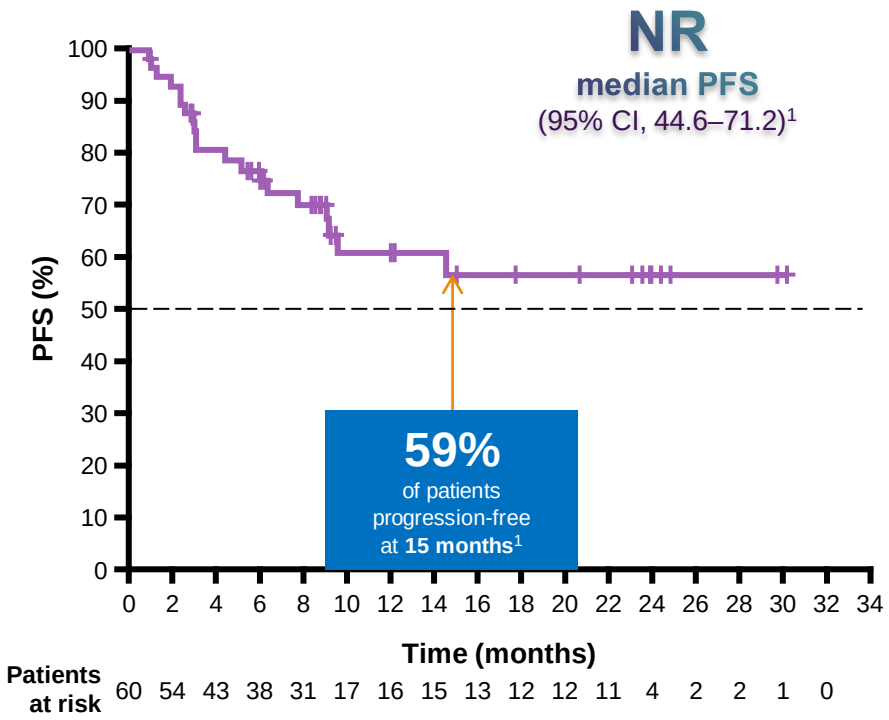
Primary efficacy analysis (n=60) according to the protocol was conducted on the first 60 treated patients followed up for a minimum of 7 months

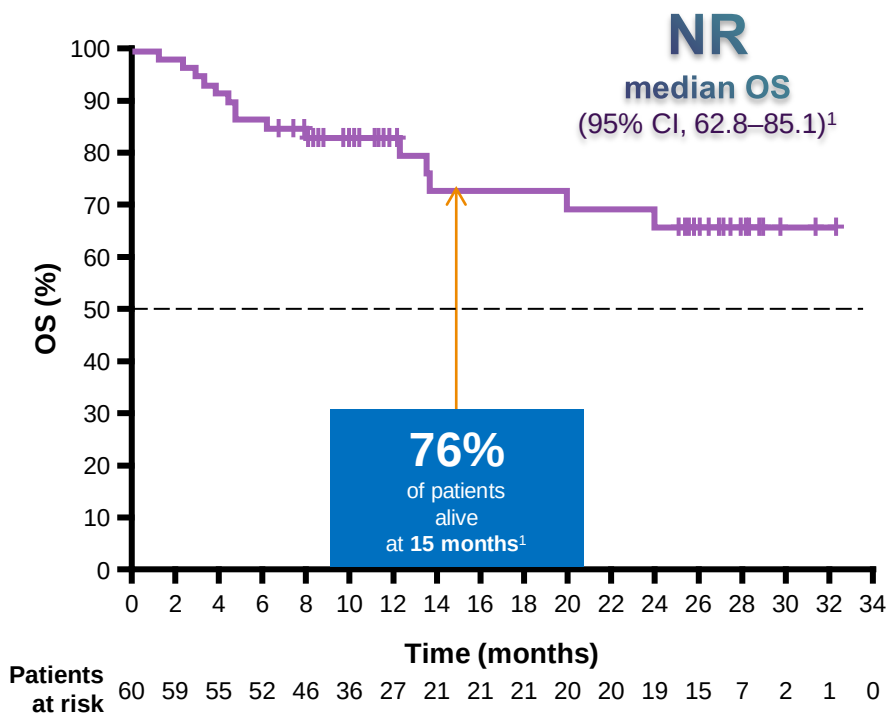
ORR by IRRC Assessment Was 92% (95% CI, 82–97) with a CR Rate of 67% (95% CI, 53–78)[1,2]

Due to rounding, percentages do not add up to 93%
CI: confidence interval; CR: complete response; PR: partial response; SD: stable disease

1. Wang M, *et al.* ASH 2019 (Abstract 754; oral). 2. Wang M, *et al. N Engl J Med* 2020; 382:1331–1342. 3 Wang M *et al* ASH 2020 (Abstract1120, poster)

ZUMA-2: Median PFS and OS were not reached after 17.5 months median follow-up in evaluable patients (n=60)[1,2]

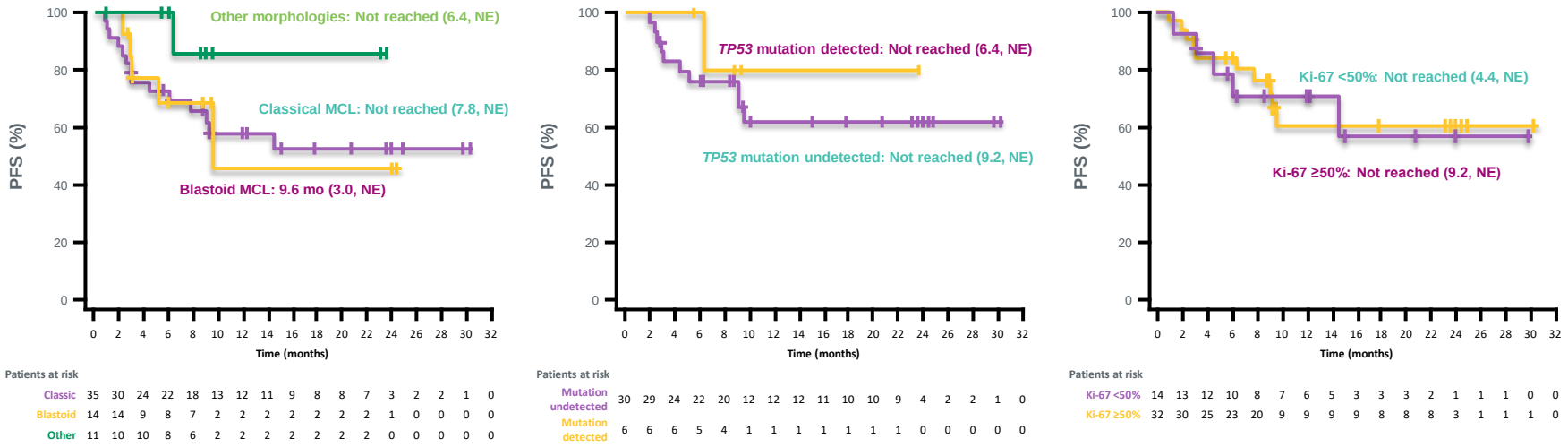




NE: not estimable: NR: not reached

1. Wang M *et al* ASH 2020 (Abstract1120, poster) 2. Wang M, et al. N Engl J Med 2020; 382:1331–1342

ZUMA-2: Progression-free survival in high-risk subgroups



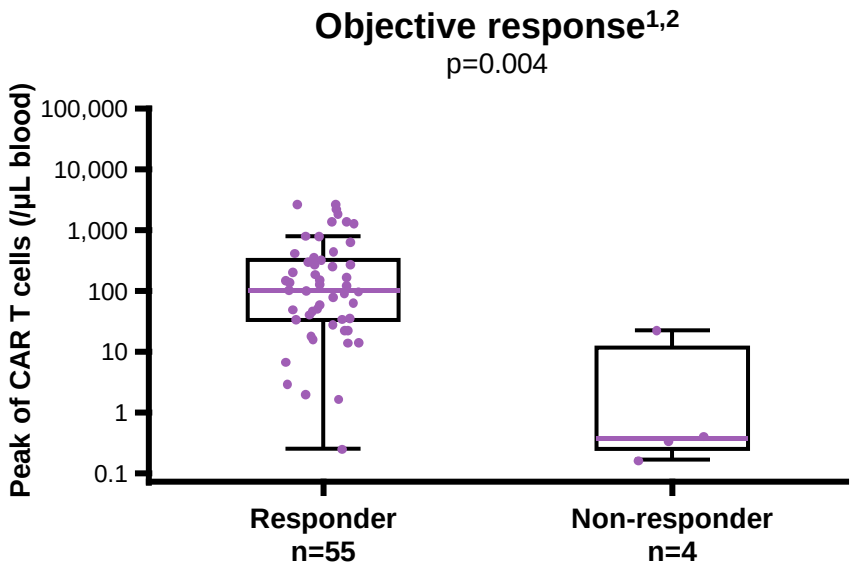
Blastoid morphology

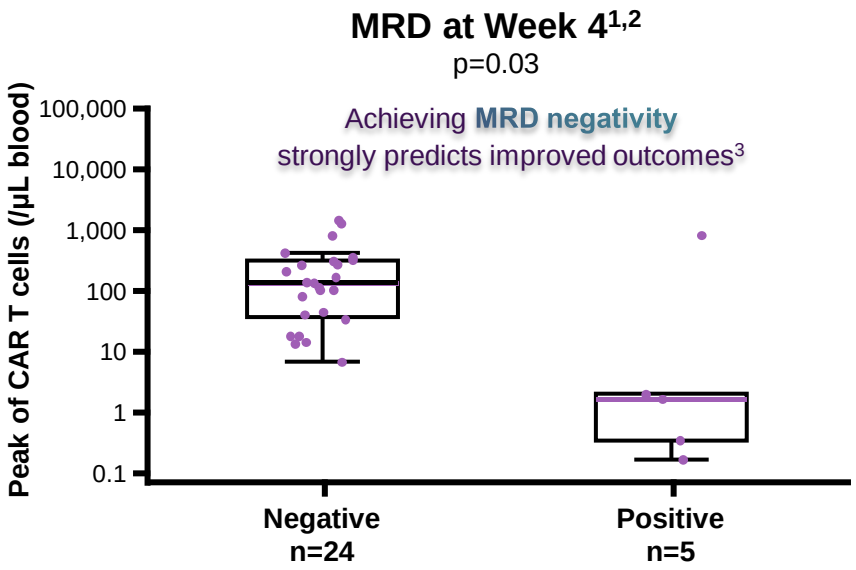
TP53 mutation

Ki-67 ≥50%

Wang M, *et al. N Engl J Med* 2020; 382:1331–1342 (incl. suppl.).

ZUMA-2: Robust expansion of anti-CD19 CAR T cells in blood was associated with objective response and MRD negativity[a]





Median time to peak anti-CD19 CAR T-cell levels after infusion is **15 days** (range, 8–31)

Impact of bendamustine on T-cell expansion

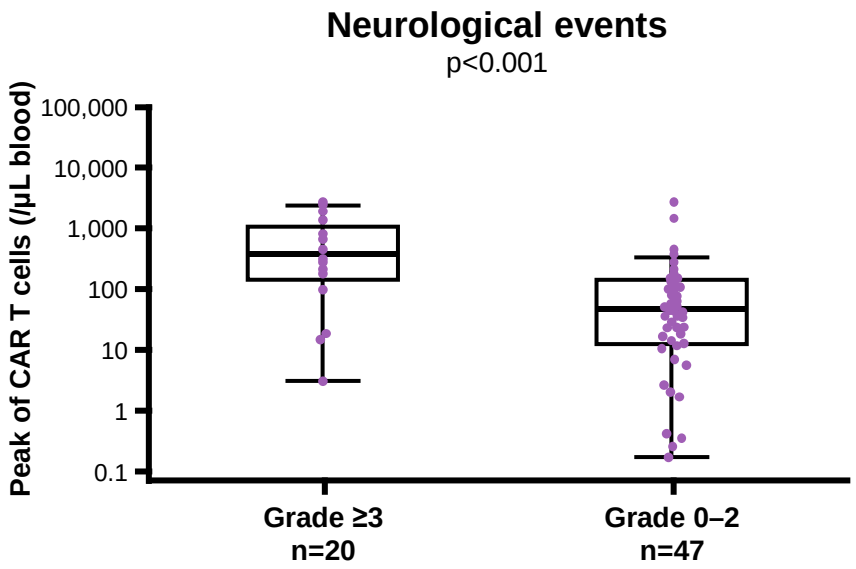
p-values were calculated using the Wilcoxon rank-sum test and were not adjusted for multiplicity

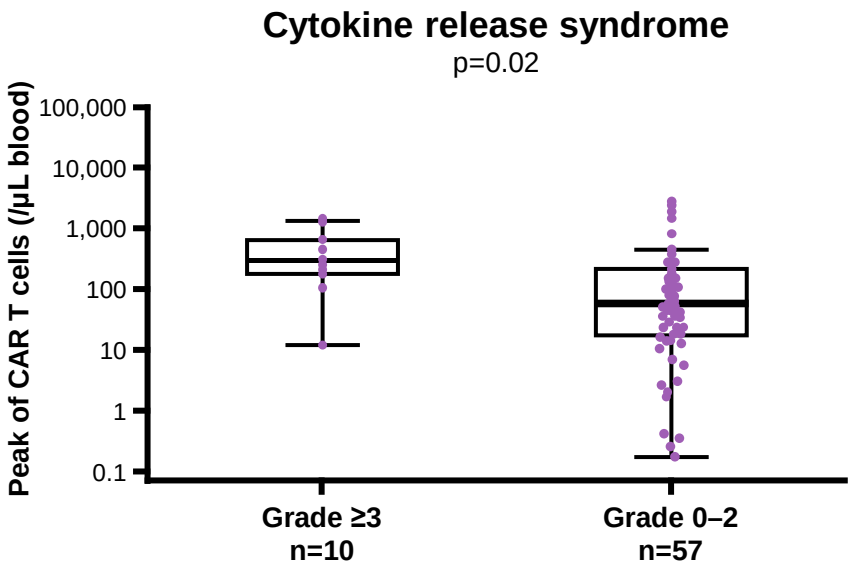
[a] High-sensitivity molecular MRD assessment by NGS

MRD: minimal residual disease; NGS: next-generation sequencing

1. Wang M, *et al.* ASH 2019 (Abstract 754; oral). 2. Wang M, *et al. N Engl J Med* 2020; 382:1331–1342 (incl. suppl.).
3. Pott C, *et al. Blood* 2006; 107:2271–2278.

ZUMA-2: Patients with the most robust expansion were at a higher risk of experiencing Grade ≥3 vs. ≤2 adverse events

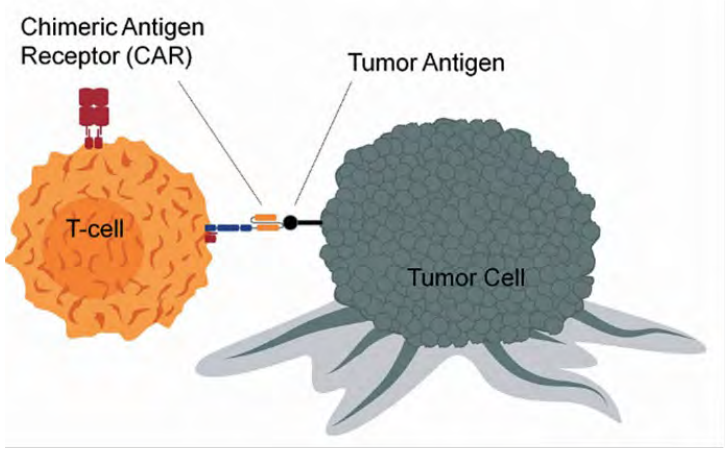




p-values were calculated using the Wilcoxon rank-sum test and were not adjusted for multiplicity

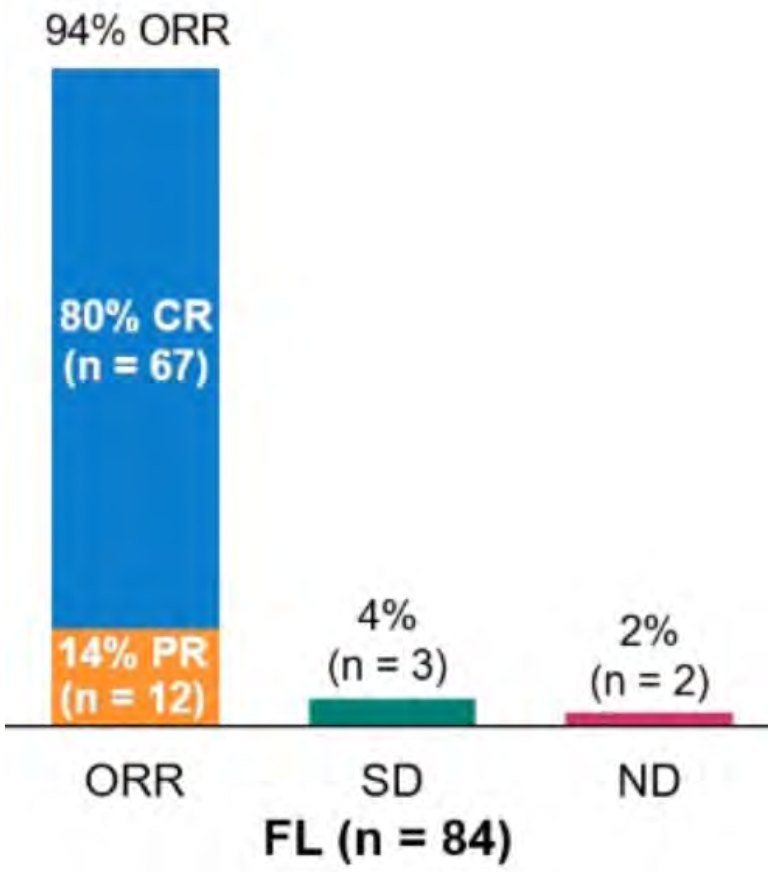
Wang M, *et al*. ASH 2019 (Abstract 754; oral). Wang M, *et al. N Engl J Med* 2020; 382:1331–1342 (incl. suppl.).

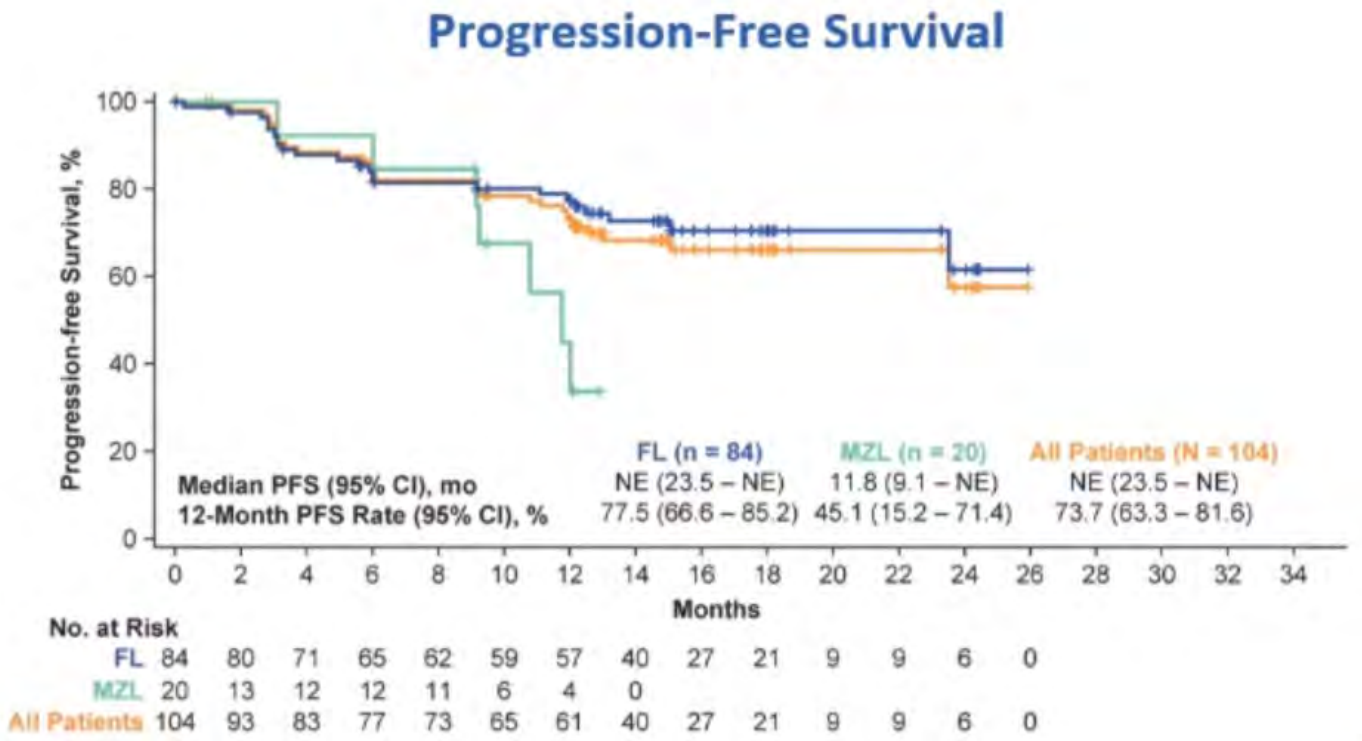
CAR-T in follicular lymphoma



Zuma 5: Primary analysis

≥2 line of therapy including anti CD20 and alkyator





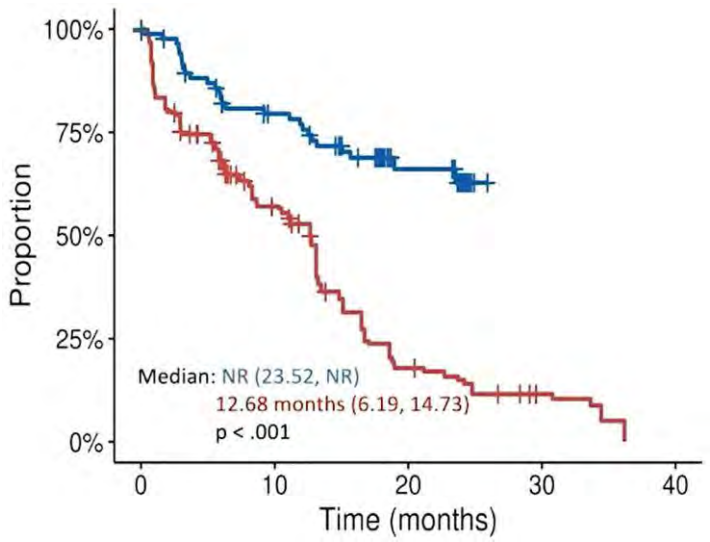
Benefit observed in POD24 patients

Jacobson et al ASH 2020

ZUMA-5 / SCHOLAR-5 comparisons

Among patients who failed ≥2 prior lines of therapy (LoT)		SCHOLAR-5	ZUMA-5	Odds Ratio (95% CI)	p-value
Overall response rate	Yes	42 (49.9%)	81 (94.2%)	16.24 (5.63, 46.85)	<0.0001
	No	43 (50.1%)	5 (5.8%)		
Complete response	Yes	25 (29.9%)*	68 (79.1%) **	8.86 (4.3, 18.25)	<0.0001
	No	60 (70.1%)	18 (20.9%)		

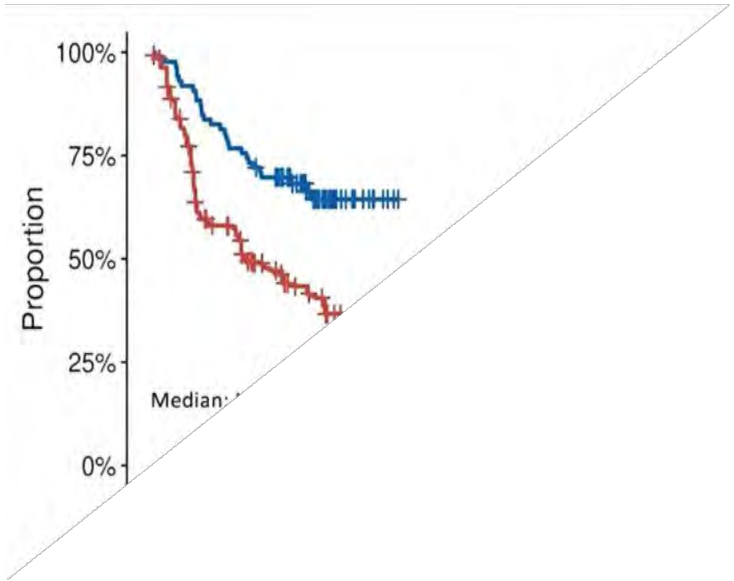
Progression Free Survival



HR: 0.30 (0.12 – 0.48)

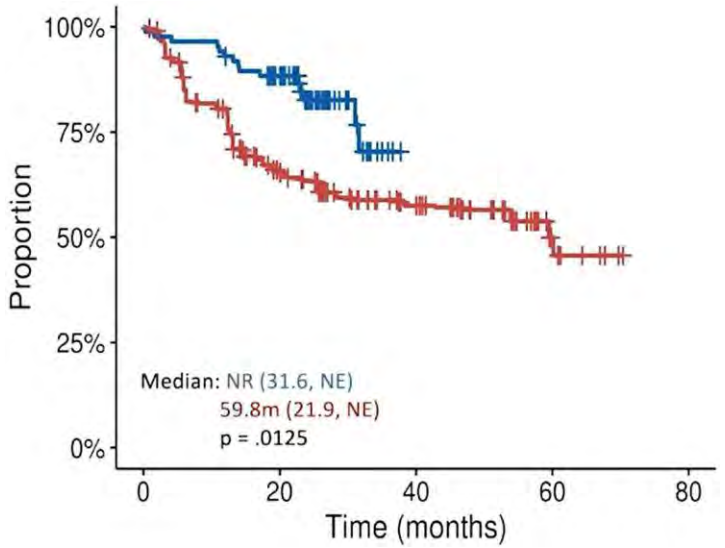
Survival

Time to Next Treatment



HR: 0.42 (0.16 – 0.58)

Overall



HR: 0.42 (0.21 – 0.63)

Ghione P, et al. EHA 2021

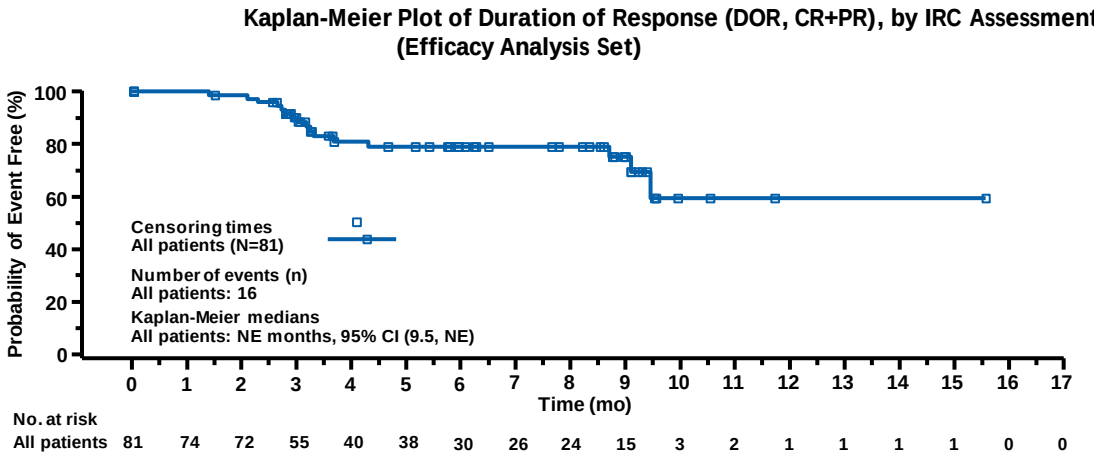
ELARA Trial

Response

Best Overall Response Rate

Response Rate, %	Patients Evaluable for Efficacy[b] (n=94)
CR	66.0[b]
PR	20.2
ORR (CR+PR)	86.2

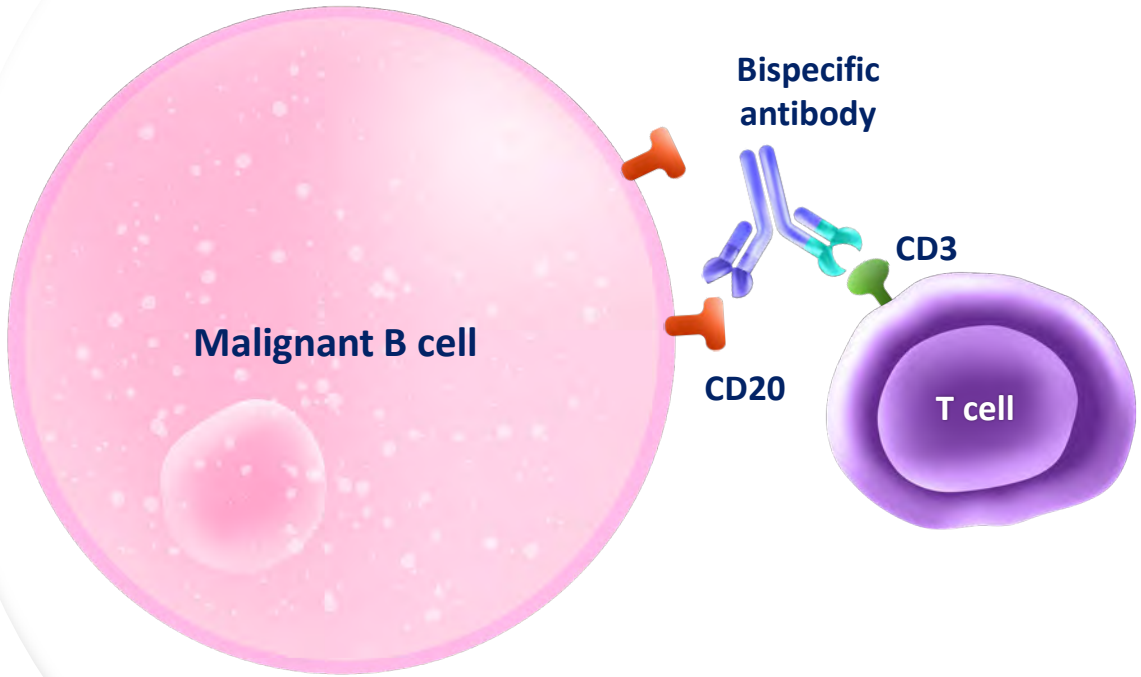
Duration of Response



- Median follow-up for efficacy (n=94): 11 (4.3-19.7) months
- Probability for a responding patient to remain in response ≥6 months was 79% (95% CI, 66-87)
- 12 of 31 PRs (38.7%) converted to CRs; all but 1 occurred between Month 3 and Month 6
- Median time to next antilymphoma treatment was not reached

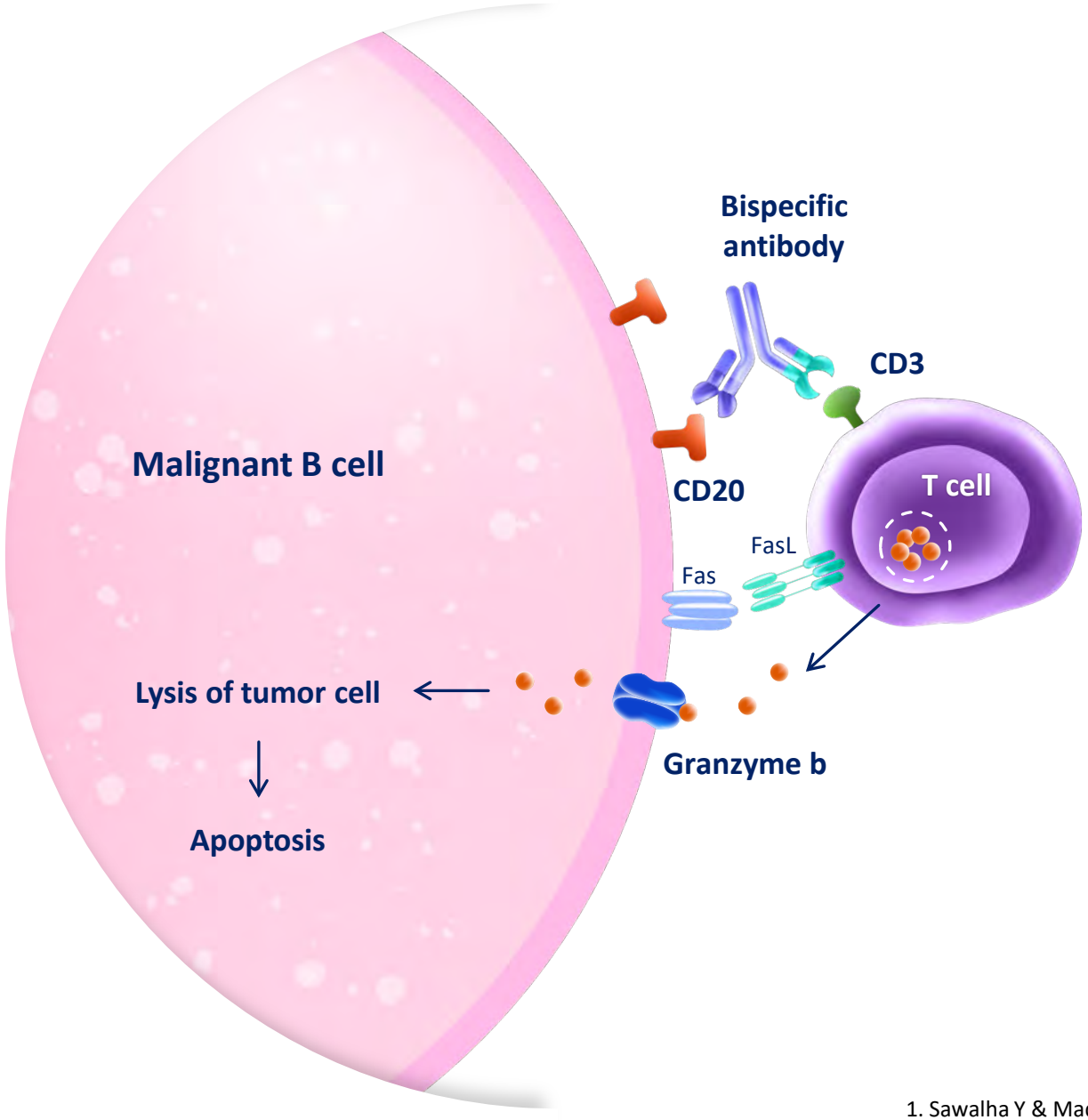
Schuster S, et al. EHA 2021

Bispecific antibodies



1. Sawalha Y & Maddocks K. BMJ 2022; 377:e063439;
2. Frontzek F, et al. Ther Adv Hematol. 2022;13:20406207221103321;
3. Tian Z, et al. J Hematol Oncol 2021;14:75.

Bispecific antibodies



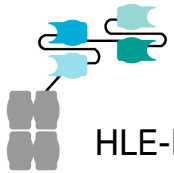
1. Sawalha Y & Maddocks K. BMJ 2022; 377:e063439;
2. Frontzek F, et al. Ther Adv Hematol. 2022;13:20406207221103321;
3. Tian Z, et al. J Hematol Oncol 2021;14:75.

Bispecific Antibodies (bsAbs)

- bsAbs are single molecules that target multiple antigens
- There are many different formats of bsAbs, including the select examples below
- Characteristics such as size, stability, binding affinity, and PK/PD properties impact their clinical efficacy and safety
- BsAbs with Fc component have extended plasma half-life vs Fab-only constructs

Single-chain variable fragment (scFv)


BiTE


HLE-BiTE

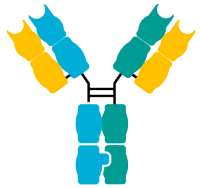

DART

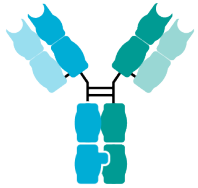

DART Fc

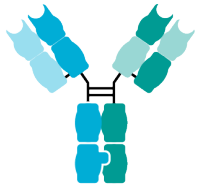

TandAb

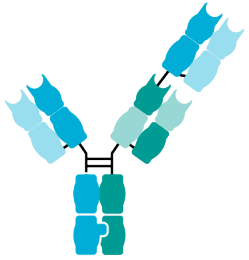

TriKE

IgG-based, heterodimeric

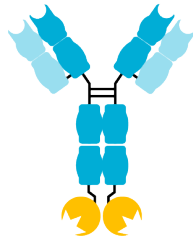

Common light chain

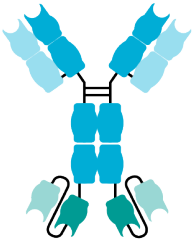

DuoBody

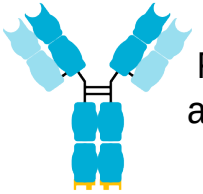

1+1 CrossMAb


2+1 CrossMAb

IgG-based, homodimeric

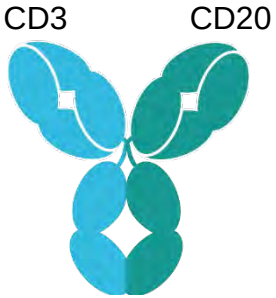

IgG-anticalin fusion protein


Grabody, IgG-scFv

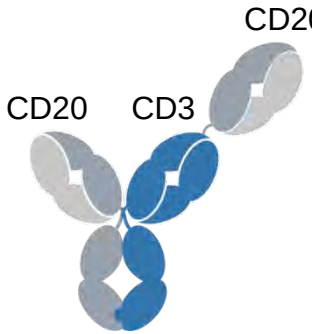

Fc region with antigen binding (Fcab), mAb^2

BiTE, bispecitic T-cell engager; DART, dual affinity retargeting; HLE, half-life extended; PK/PD, pharmacokinetic/pharmacodynamic; TandAb, Tandem Diabody; TriKE, trispecific killer engager.
You G, et al. *Vaccines*. 2021;9:724.

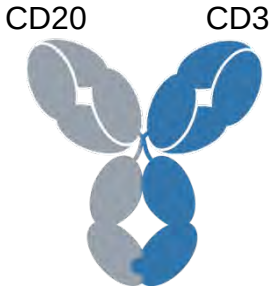
CD20xCD3 bispecific antibodies of various formats are in early clinical development for NHL[1-3]



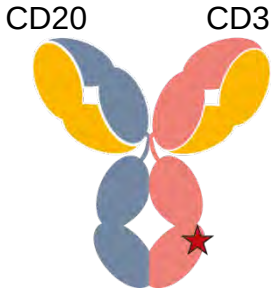
Epcoritamab
DuoBody-CD3×CD20
IgG1



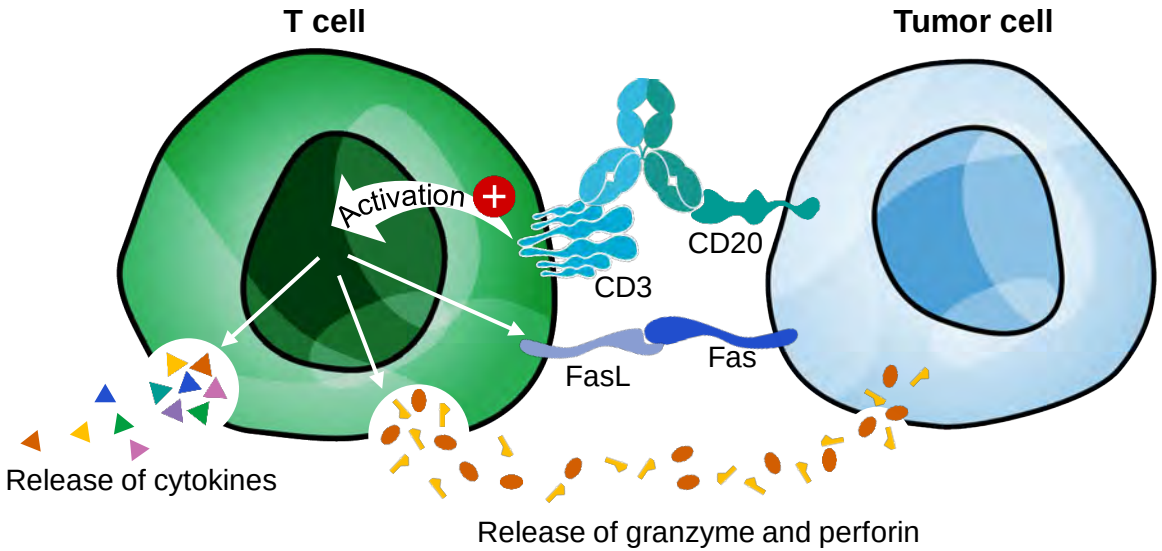
Glofitamab
2+1 CrossMab
IgG1



Mosunetuzumab
Knob-in-hole
IgG1



Odronextamab
VELOCI-Bi
IgG4



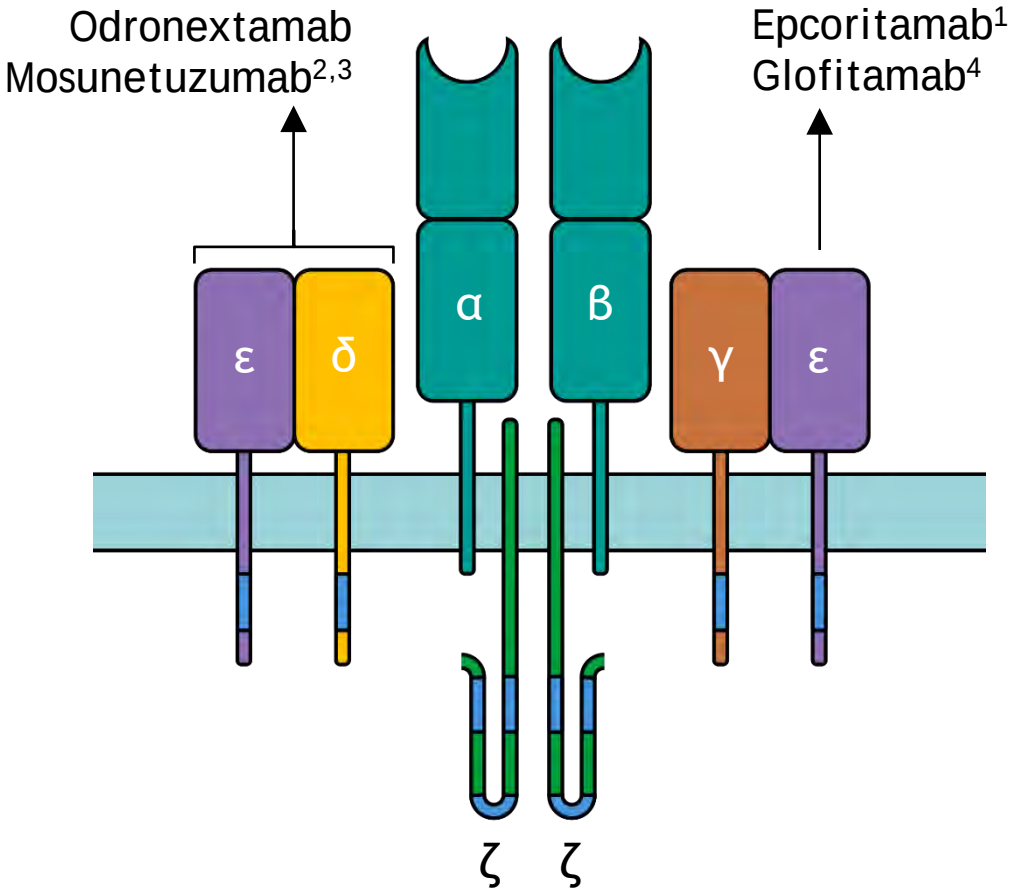
- CD3 ×CD20 bsAbs bring together T cells and CD20+ tumor cells to induce T cell-mediated killing of the tumor cell[2]
- Able to induce effector T cell binding without requiring MHC-mediated antigen presentation[2]

B-NHL, B-cell non-Hodgkin lymphoma; bsAb, bispecific antibody; MHC, major histocompatibility complex; TCR, T-cell receptor.

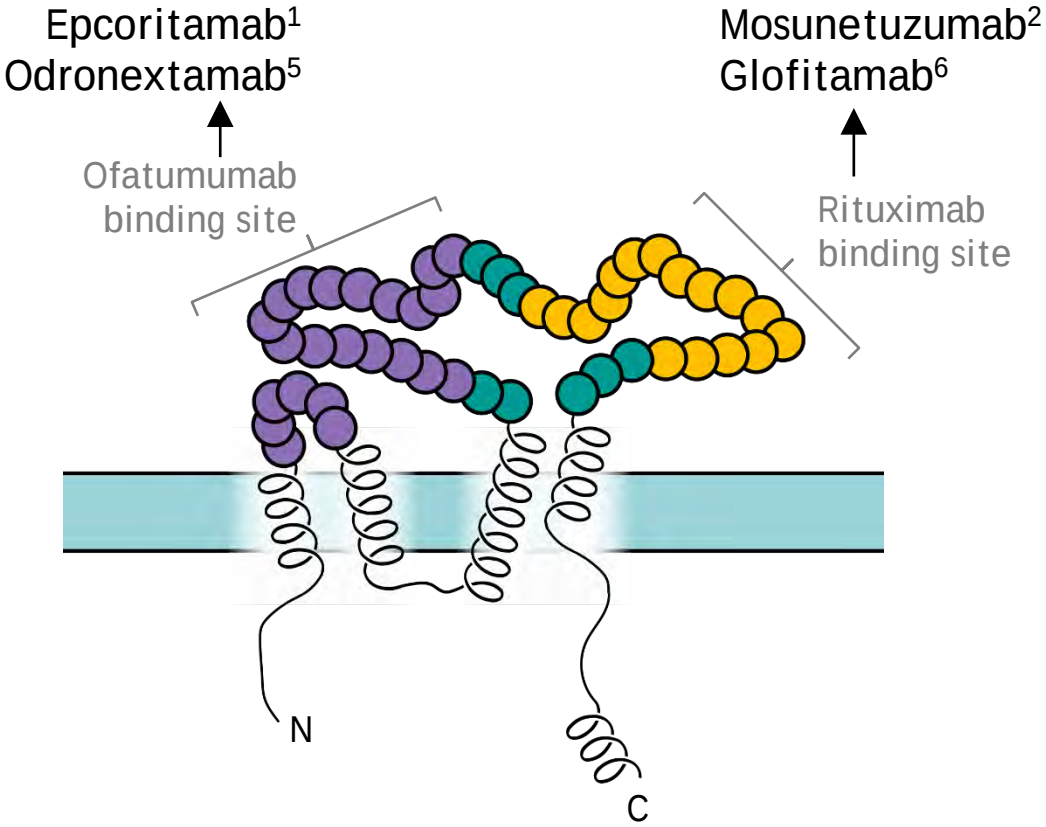
1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625. 2. Schuster SJ. *Hematological Oncology*. 2021;39(S1):113–116. 3. You G, et al. *Vaccines*. 2021;9:724.

Binding Sites of Select CD3×CD20 bsAbs

TCR (CD3) Complex



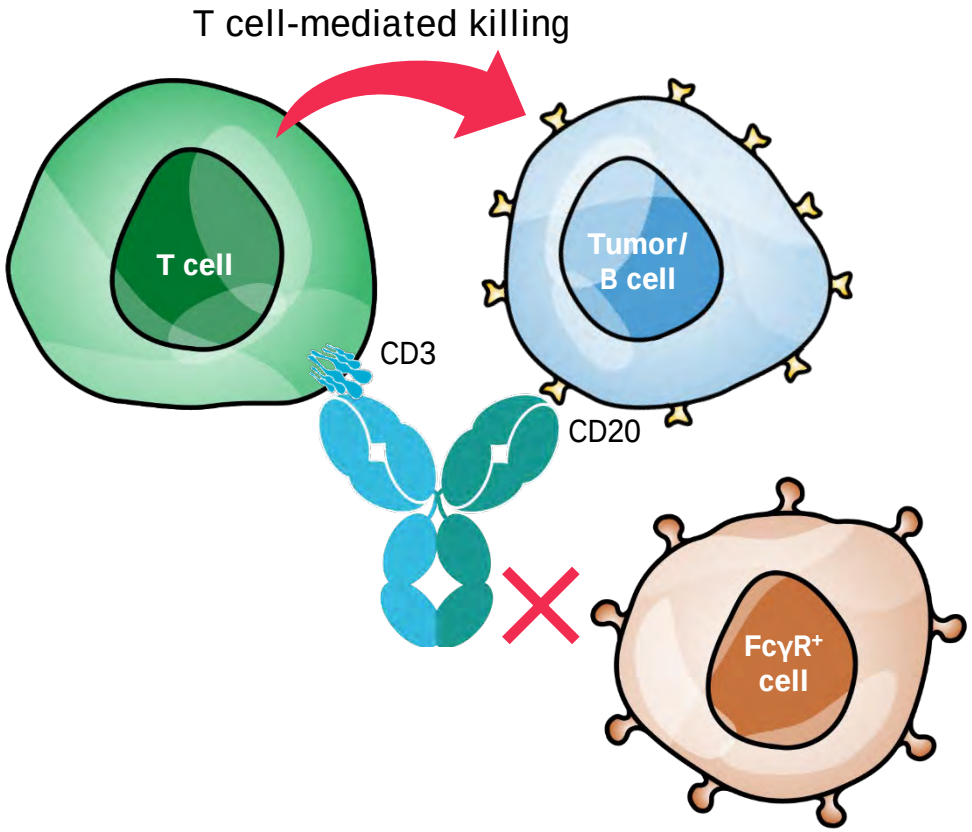
CD20



bsAb, bispecific antibody; TCR, T-cell receptor.

1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625. 2. Sun LL, et al. *Sci Transl Med*. 2015;7(287):287ra70. 3. Arnett KL, et al. *PNAS*. 2004;101:16268-16273. 4. Bacac M, et al. *Clin Cancer Res.* 2018;24:4785-4797.
5. Smith EJ, inventor; Regeneron Pharmaceuticals, Inc., assignee. US Patent No. 11,072,656 B2. July 27, 2021. 6. Kaplon H, et al. *MAbs*. 2022;14:e2014296.

Mechanism of Action



T cell-mediated killing of CD20-expressing cells

- Dependent on simultaneous binding of CD3 and CD20
- Independent of the specificity of the T-cell receptor
- Immunological synapse formed between T and B cells
- Killing through perforin/granzyme B-induced apoptosis

Has an effector function-silenced Fc Region that ensures target-specific T-cell activation

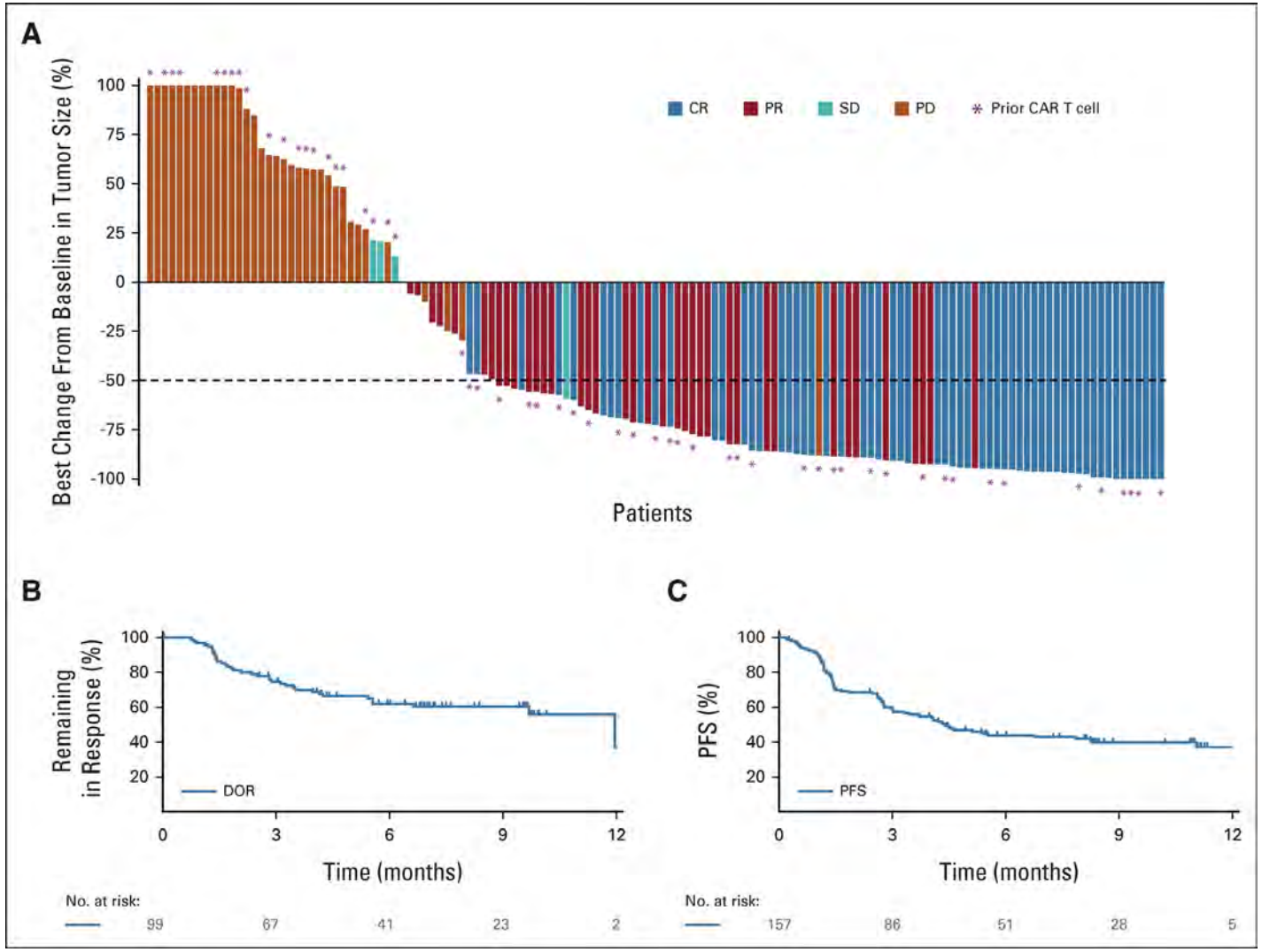
Point mutations are introduced that ensure:

- no Fcγ receptor binding (no ADCC or ADCP induction)
- no C1q binding (no CDC induction)
- normal FcRn binding (long plasma half-life like a native IgG1 antibody)

ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; FcRn, neonatal Fc receptor; FcγR, Fc gamma receptor.
Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625.

Epcoritamab: responses in relapsed/refractory DLBCL

- 157 patients ≥2 lines of therapy
- 61 prior CAR-T therapy
- 0.16 →0.8 →48mg SC
- Overall response rate 63% (55.0 to 70.6)
- CR 39% (31.2 to 46.9).
- Median duration of response 12.0 months
- 50% CRS, 2.5% grade 3



Thieblemont C et al., J Clin Oncol 2022

155 patients ≥ 2 lines of therapy

52 prior CAR-T therapy

Obinutuzumab pre-dose

Glofitamab 2.5 →10 → 30 mg IV

Up to 12 doses (median 5 given)

39% CR rate 52% ORR (35% among CAR-T group)

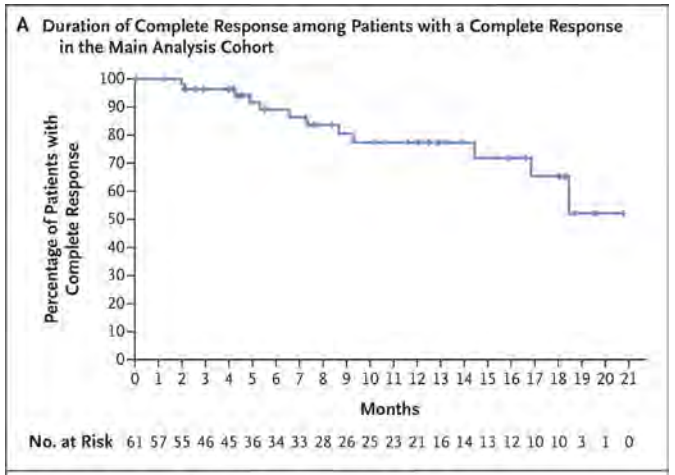
CRS in 63%, ≥grade 3 in 4%

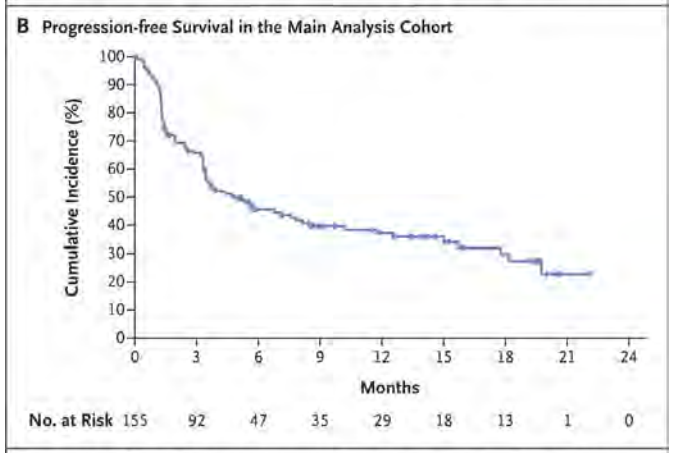
Median follow-up: 12.6 months (range, 0.1 to 22.1)

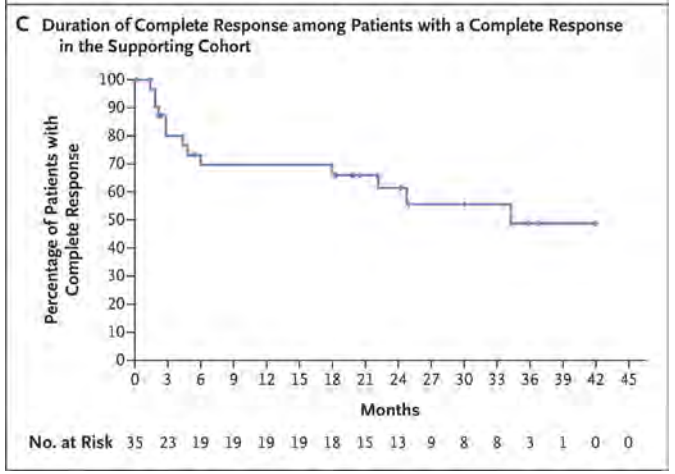
6-month progression-free survival was 46% (95% CI, 37 to 54)

12-month progression-free survival was 37% (95% CI, 28 to 46).

12-month OS 50% (95% CI, 41 to 58)

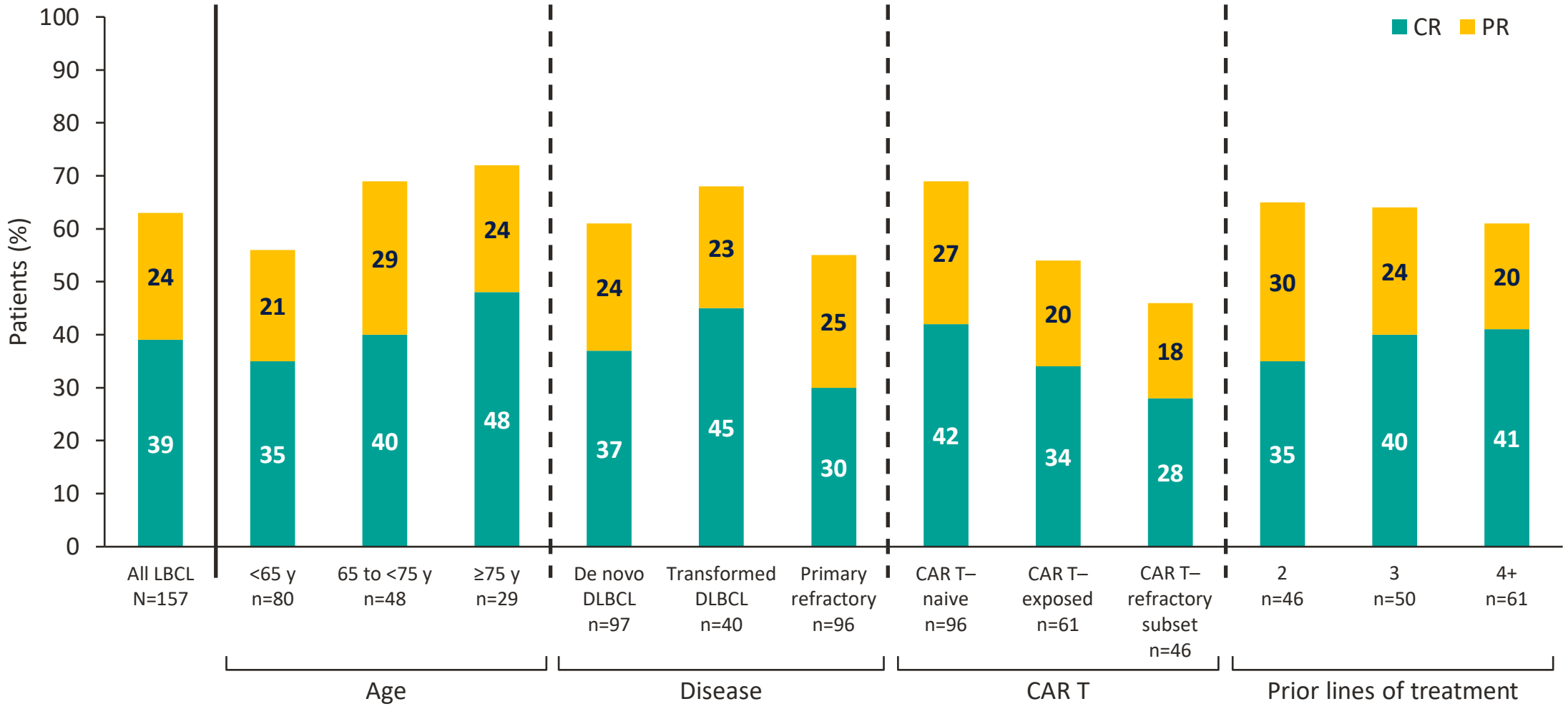






GDickinson *et al*. NEJM 2022

Subgroup Data (Response Rates)[1]



Based on IRC assessment and Lugano criteria. CAR-T, chimeric antigen receptor therapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; IRC, independent review committee; LBCL, large B-cell lymphoma; PR, partial response.

1. Thieblemont C et al. 2022. Presented at EHA Congress 2022.

Delivery

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	29	21	22	23	24	25	26	27	28	29	30
Epcoritamab																														
Glofitamab																														

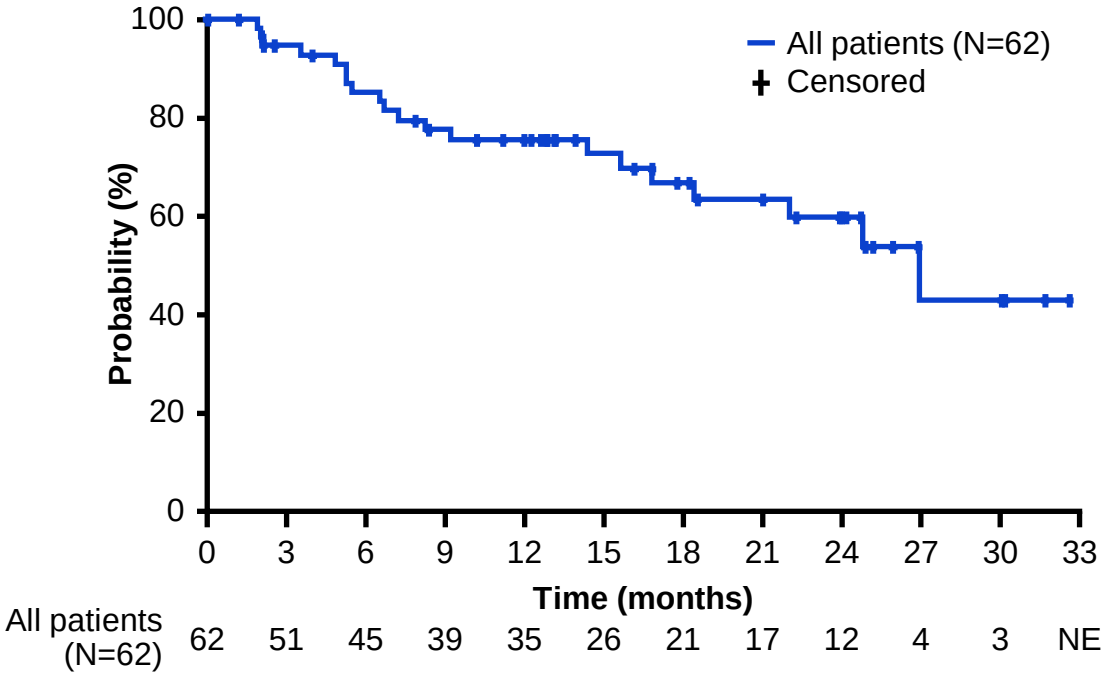
Week	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Epcoritamab																														
Glofitamab																															

Week	61	62	63	64	65	66	67	68	68	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
Epcoritamab																														
Glofitamab																														

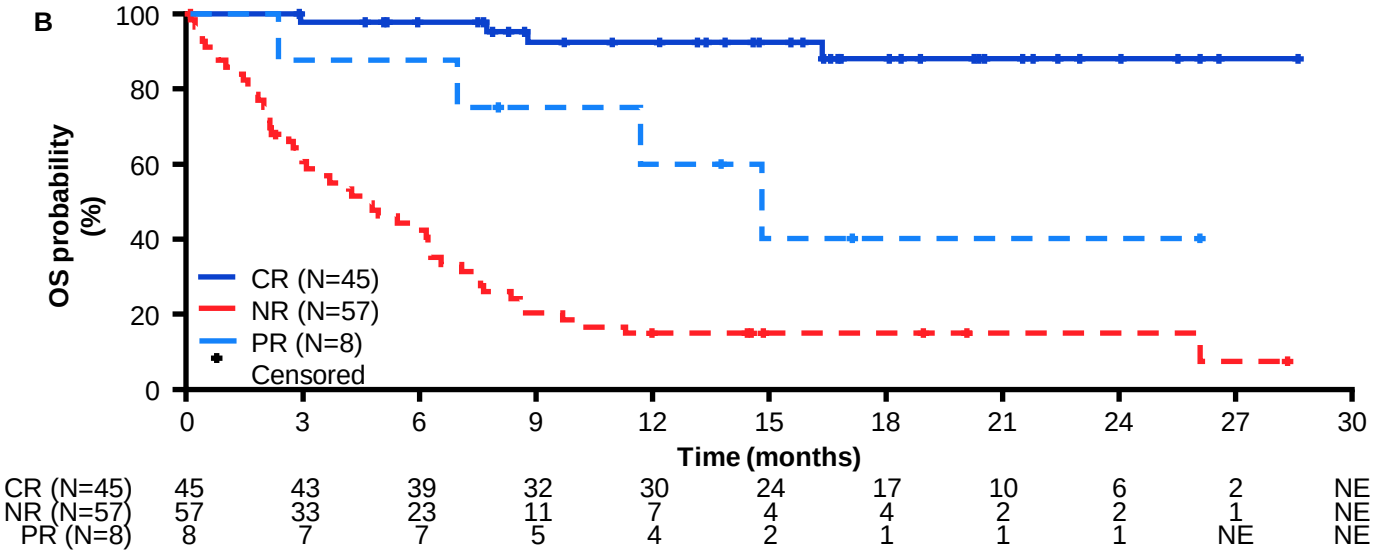
Thieblemont et al. JCO 2022 Dickinson *et al*. NEJM 2022

Glofitamab monotherapy continues to demonstrate early/rapid durable response rates in heavily pretreated patients with R/R DLBCL

Duration of complete response by IRC[1]



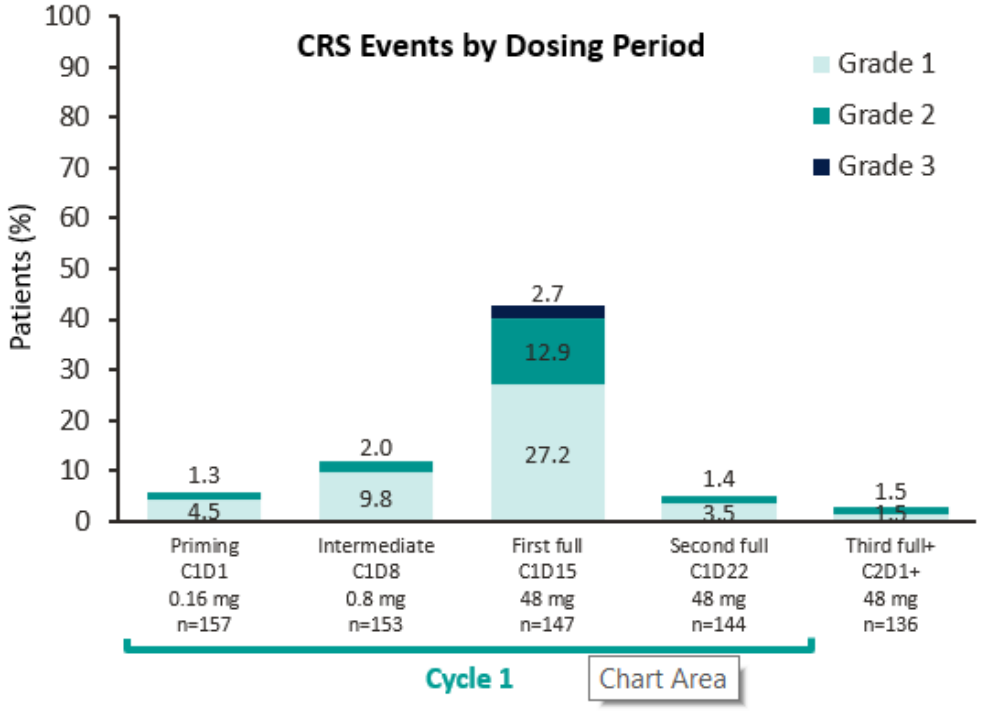
OS landmark analysis by response at EOT



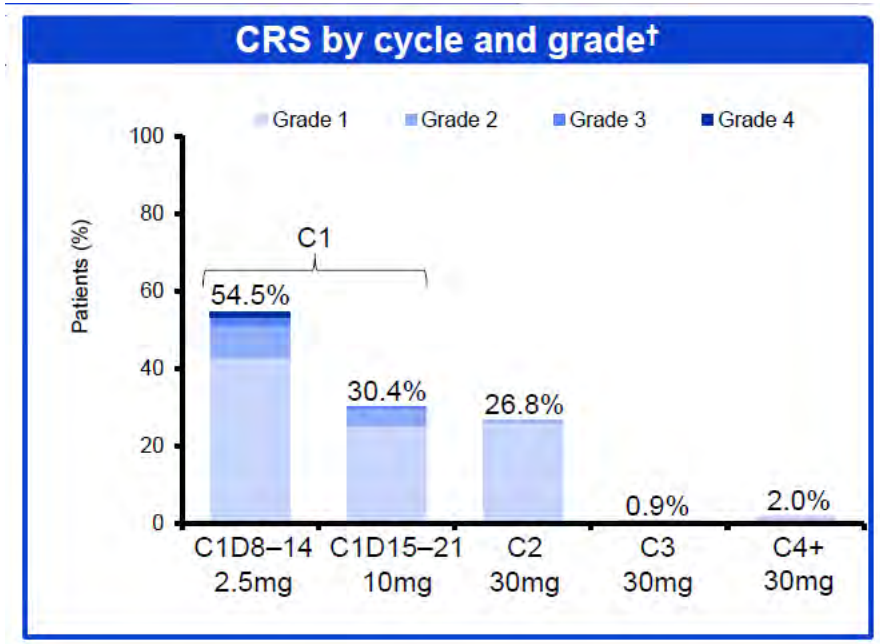
1. Falchi, et al. Presented at ASCO 2023;
2. Dickinson MJ et al. N Engl J Med 2022;387:2220–31.

Despite step-up dosing, CRS still occurs in 50% of patients receiving bispecifcs:

Are we ready to deal with this?



Thieblemont et al. EHA 2022 and JCO 2022



Dickinson et al. EHA 2022 and NEJM 2022

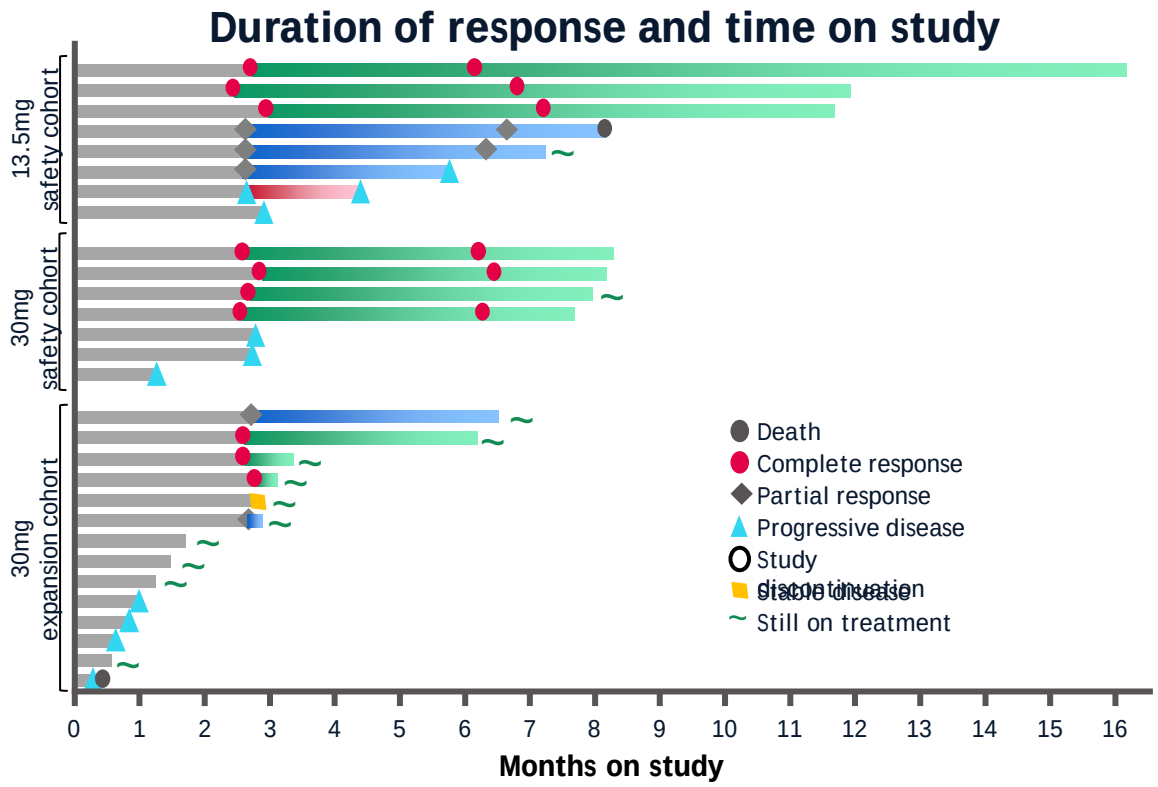
First line chemo-free: Mosunetuzumab monotherapy in elderly/unfit patients

Summary of AEs, n (%)	1L DLBCL (N=29)
Any AE	25 (86)
Treatment related	17 (59)
Serious AE	8 (28)
Treatment related	4 (14)
Grade 3-4 AE	9 (31)
Treatment related†	4 (14)
Grade 5 (fatal) AE	0
AE leading to treatment discontinuation	0
CRS[2] (any grade)	6 (21)
Grade ≥3	0

Most CRS events resolved within 1 day

Response (%)*	All efficacy evaluable patients (n=22)
Best overall response	63.5
Complete response (primary endpoint: PET-CT by INV using Lugano 2014)	45.5
Partial response	18.0

Early durable complete responses were observed



GO40554 (NCT03677154)
*Data presented are from the secondary efficacy population (patients enrolled in the study for ≥3 months); 17 patients have been enrolled in the study for ≥6 months and reached the primary response assessment with ORR=8 (47%); CR=6 (35%); PR=2 (12%); SD=1 (6%), PD=6 (35%), 2 not done/not evaluable.

1. Olszewski A, et al. ASH 2020. Oral 401.
2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-38.

Bispecific combinations

- Not convincing evidence to suggest that bispecifics will add chemotherapy
- Chemotherapy is lymphodepleting (remember the C in R-CHOP) and does not make sense

7523

First-line treatment (Tx) with subcutaneous (SC) epcoritamab (epco) + R-CHOP in patients (pts) with high-risk diffuse large B-cell lymphoma (DLBCL): phase 1/2 data update

Lorenzo Falchi, MD,[1*] Fritz Offner, MD, PhD,[2] David Belada, MD, PhD,[3] Joshua Brody, MD,[4] Kim M. Linton, MBChB, PhD,[5] Yasmin Karimi, MD,[6] Raul Cordoba, MD, PhD,[7] Sylvia Snauwaert, MD, PhD,[8] Ageel Abbas, MS,[5] Liwei Wang, PhD,[9] Jun Wu, MD, MS,[10] Brian Elliott, MD,[5] Michael Roost Clausen, MD, PhD[11]

Study Design: EPCORE NHL-2 Arm 1

Arm 1 of EPCORE NHL-2, a phase 1b/2, open-label, multicenter trial, is evaluating the safety and antitumor activity of SC epcoritamab + standard R-CHOP for 6 cycles of 21 days, followed by epcoritamab monotherapy for a total of 1 year, in adults with previously untreated DLBCL with high-risk features[a]

Key inclusion criteria
- Newly diagnosed CD20[+] DLBCL[b]
  - DLBCL, NOS
  - T-cell/histiocyte–rich DLBCL
  - "Double-" or "triple-hit" DLBCL[c]
  - FL grade 3B
- IPI score ≥3
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Dose escalation, n=10 → Expansion, n=23

Step-up dosing: Epcoritamab (SC) 24 mg (n=4) or 48 mg (n=6) QW C1–4, Q3W C5–6, Q4W C7+ + R-CHOP C1–6

Step-up dosing: Epcoritamab (SC) 48 mg QW C1–4, Q3W C5–6, Q4W C7+ + R-CHOP C1–6

Data cutoff: March 25, 2022
Median follow-up: 6.9 mo

Primary objectives: DLT/safety and tolerability
Key secondary objective: Antitumor activity[d]

Primary objective: Antitumor activity[d]
Treatment up to 1 year

Best Overall Responses

Response, n (%)[a]	Total n=31
Overall response	31 (100)
CMR	24 (77)
PMR	7 (23)
Stable disease	0
Progressive disease	0

Data cutoff: March 25, 2022. [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first dose.

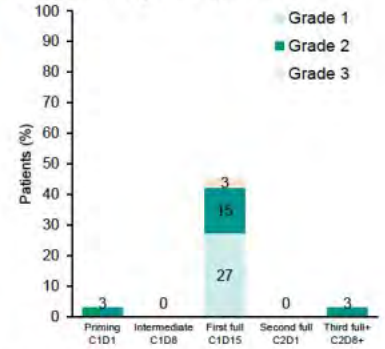
CRS Graded by Lee et al[9] 2019 Criteria

	Total N=33
CRS, n (%)	17 (52)
Grade 1	9 (27)
Grade 2	7 (21)
Grade 3	1 (3)
CRS resolution, n (%)	17 (100)
Median time to resolution, d (range)[a]	2 (1–11)
CRS leading to treatment discontinuation, n (%)	0
Tocilizumab use, n (%)	5 (15)

Data cutoff: March 25, 2022. [a]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS; range is defined by shortest and longest CRS duration.

- CRS was mostly low grade; all cases resolved

CRS Events by Dosing Period



Data cutoff: March 25, 2022. Priming dose: n=33; intermediate dose: n=33; first full dose: n=33; second full dose: n=32; third full dose and later: n=32.

- CRS occurrence was predictable; most cases occurred following the first full dose with a median time to onset of 2 days (range, 1–4)

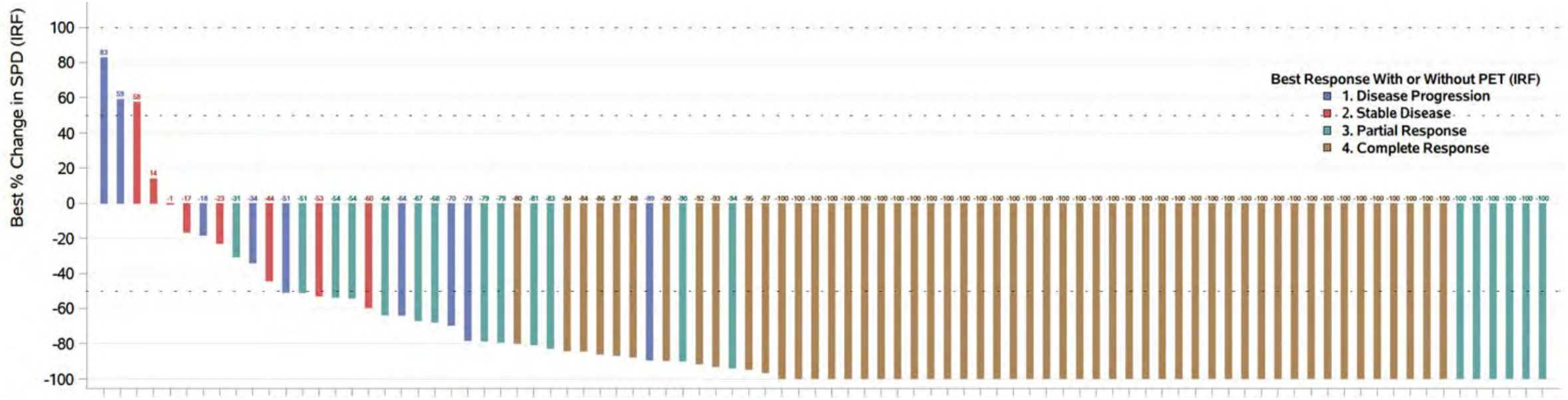
Mosuntezumab:Best overall response: 3L+ FL

B11 exp 3L+ FL (n = 90)	IRF n (%) [95% CI]	INV n (%) [95% CI]	Concordance[1] IRF vs. INV
CR rate	52 (58%) [47%, 68%]	51 (57%) [46%, 67%]	94% (84/89)
ORR	71 (79%) [69%, 87%]	70 (78%) [68%, 86%]	97% (86/89)

Efficacy in high-risk FL subgroups	Double refractory (n = 48)	POD24[2] (n = 47)
CR rate	48% [33%, 63%]	55% [40%, 70%]
ORR	69% [54%, 81%]	83% [69%, 92%]

[1]Concordance excluded one patient without any post-screening response assessments
[2]PD within 24 months from start of first systemic therapy

FL mosuntezumab: Best change in SPD by IRF



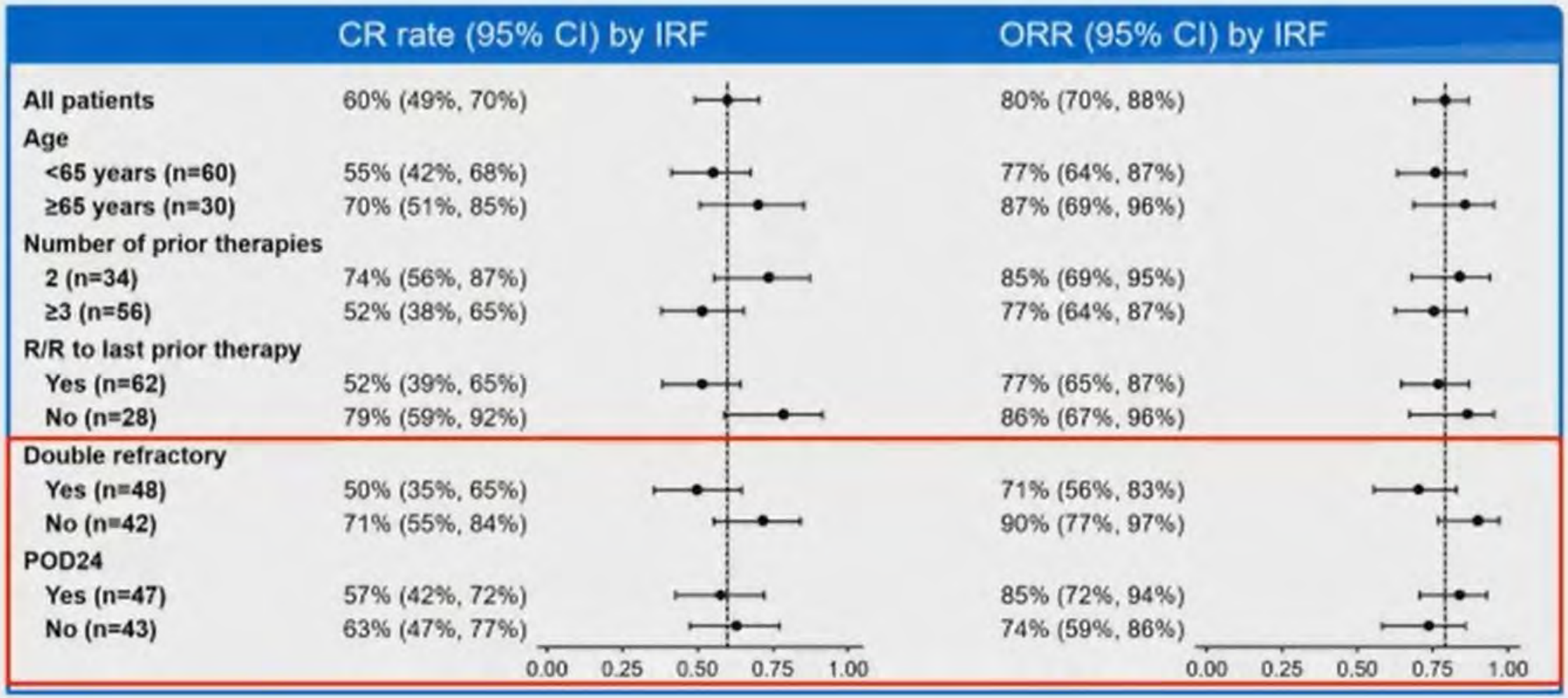
Note: Two out of the 90 patients in the B11 FL cohort did not have post-baseline SPD data and were excluded from the plot.

- PET/CT with diagnostic CT is required at screening and on-treatment timepoints; CT with or without PET is allowed at post-treatment follow-up
- Best CR rate with PET by IRF: 60% (49-70)

SPD, sum of the products diameters; IRF, independent-review facility

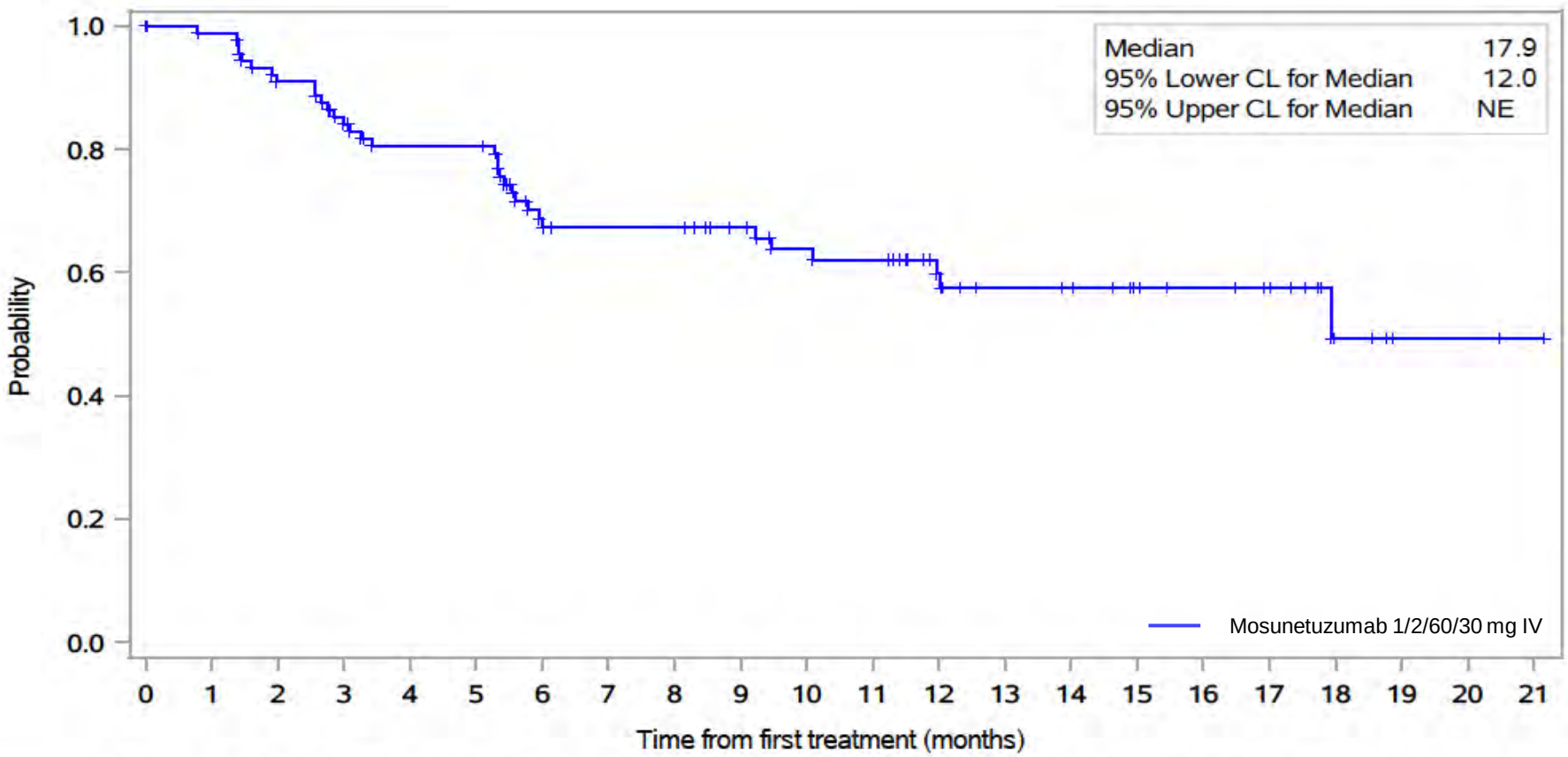
Budde et al. ASH 2021

Comparable response rates in high-risk subgroups



Budde et al. ASH 2021

PFS by IRF: 3L+ FL



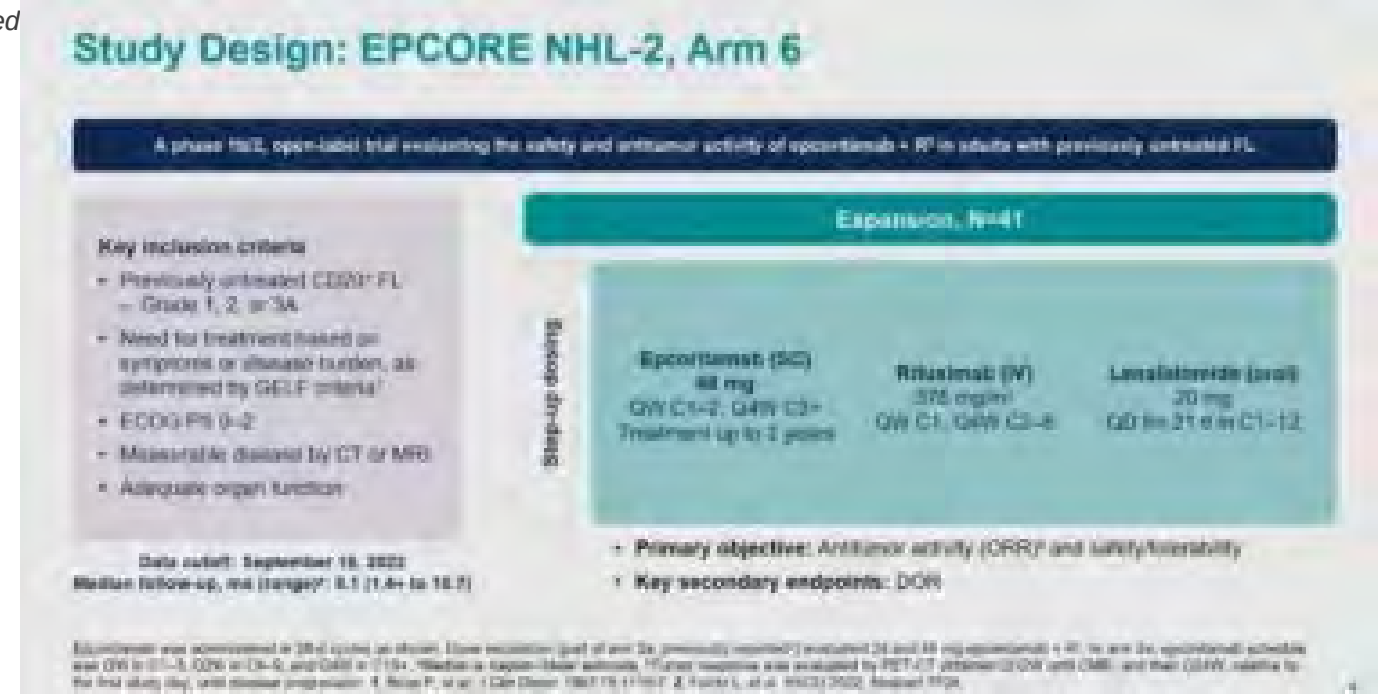
Patients Remaining at Risk	90	87	80	73	66	66	48	46	46	41	36	35	26	21	20	16	14	12	5	2	2	1
Patients Censored	0	2	2	3	7	7	16	17	17	22	25	25	33	37	38	42	44	46	52	55	55	56
Patients with an Event	0	1	8	14	17	17	26	27	27	27	29	30	31	32	32	32	32	32	33	33	33	33

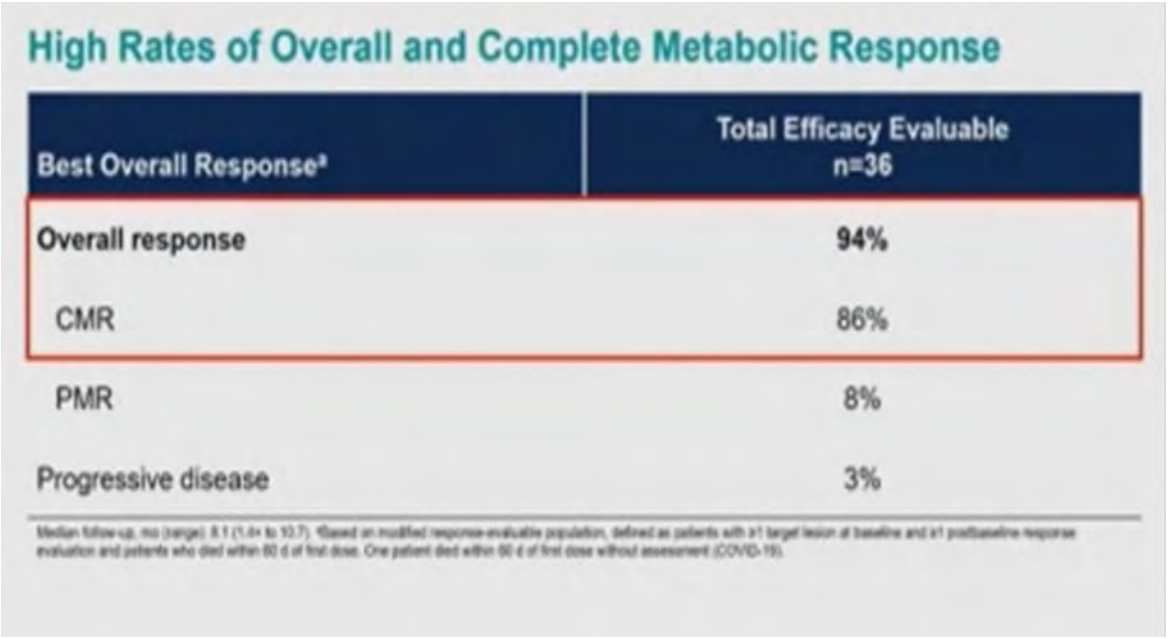
IRF, independent-review facility; PFS, progression free survival

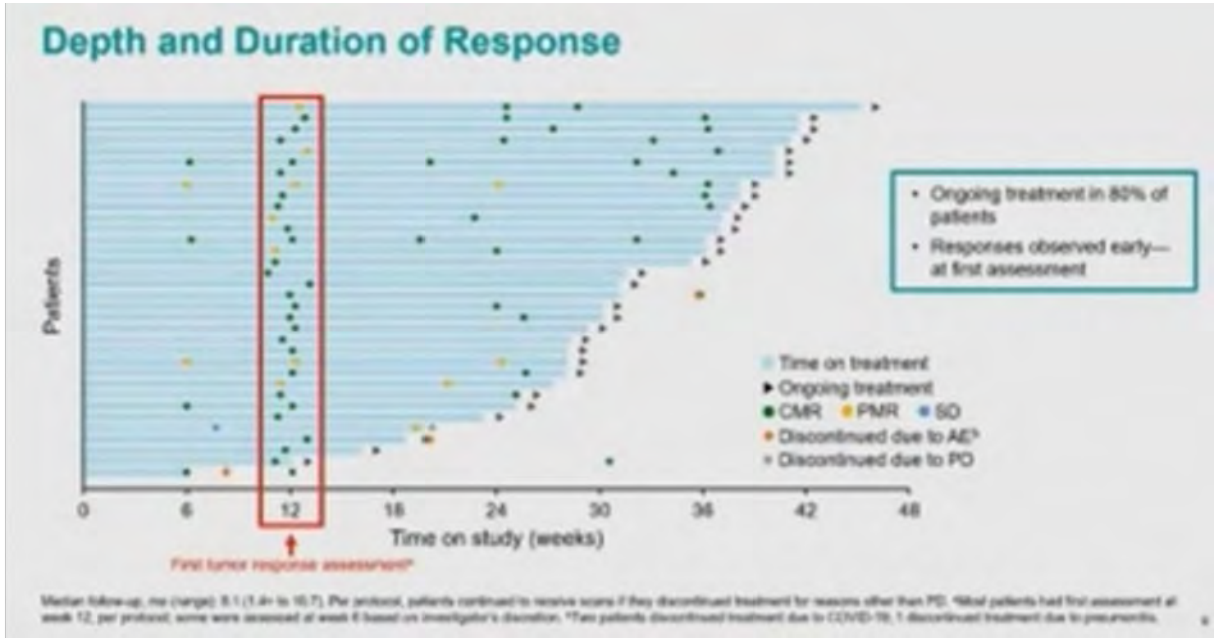
Subcutaneous Epcoritamab in Combination with Rituximab + Lenalidomide (R2) for First-Line Treatment of Follicular Lymphoma: Initial Results from Phase 1/2 Trial

Lorenzo Falchi ASH 2022

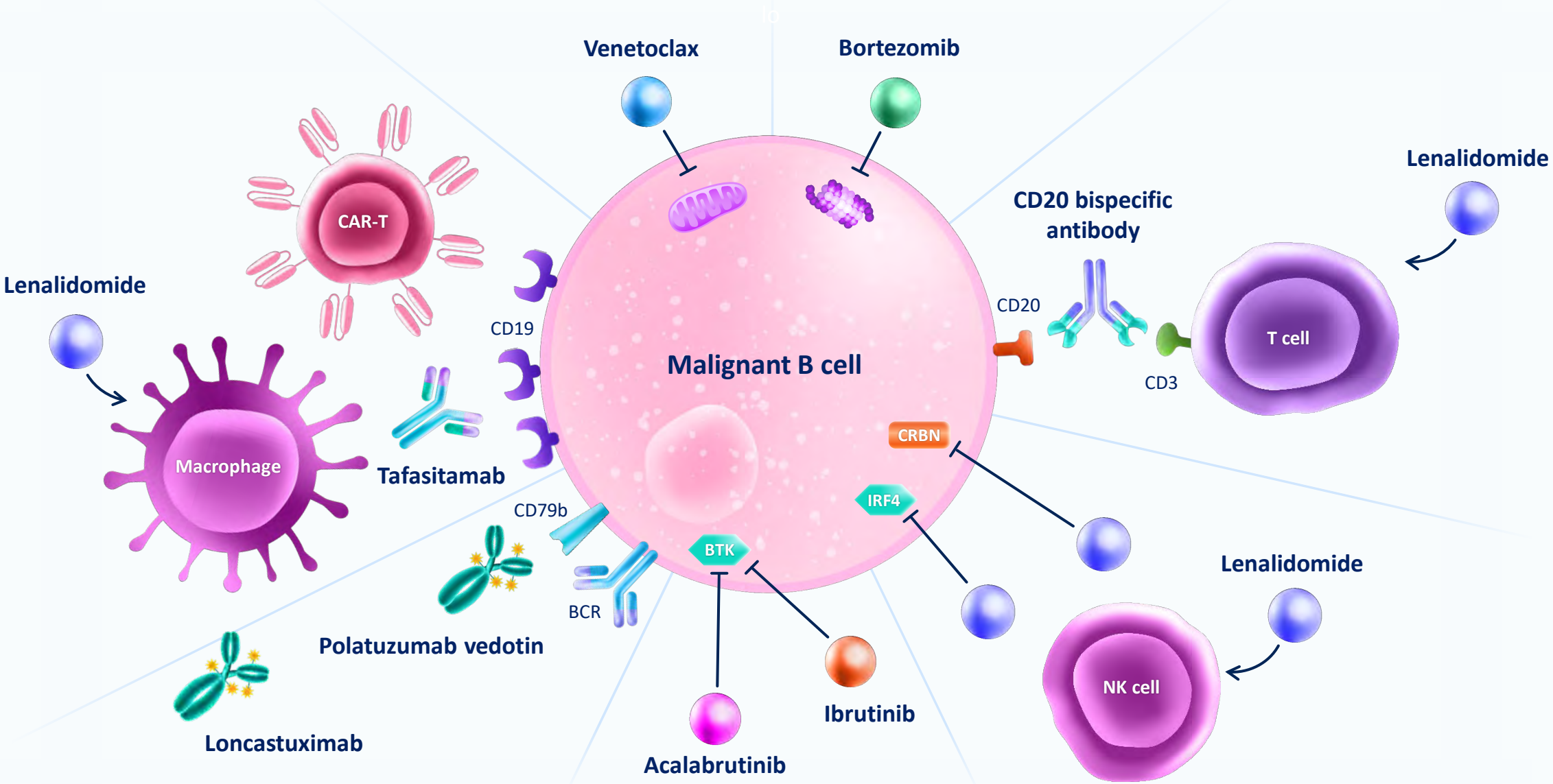
- Median age was 57 y (range, 39-78)
- Median time from initial diagnosis to first dose of epcoritamab was 12 wk (range, 2-352)
- The majority (85%) had grade 2 or 3A FL
- 39% and 51% had stage III and IV disease





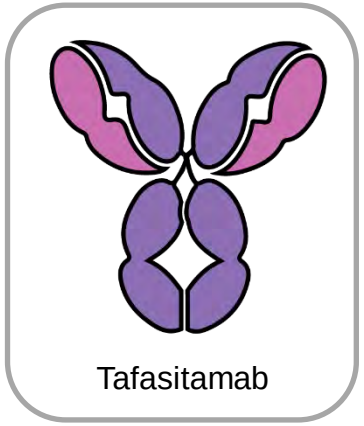


Therapeutic targets in DLBCL

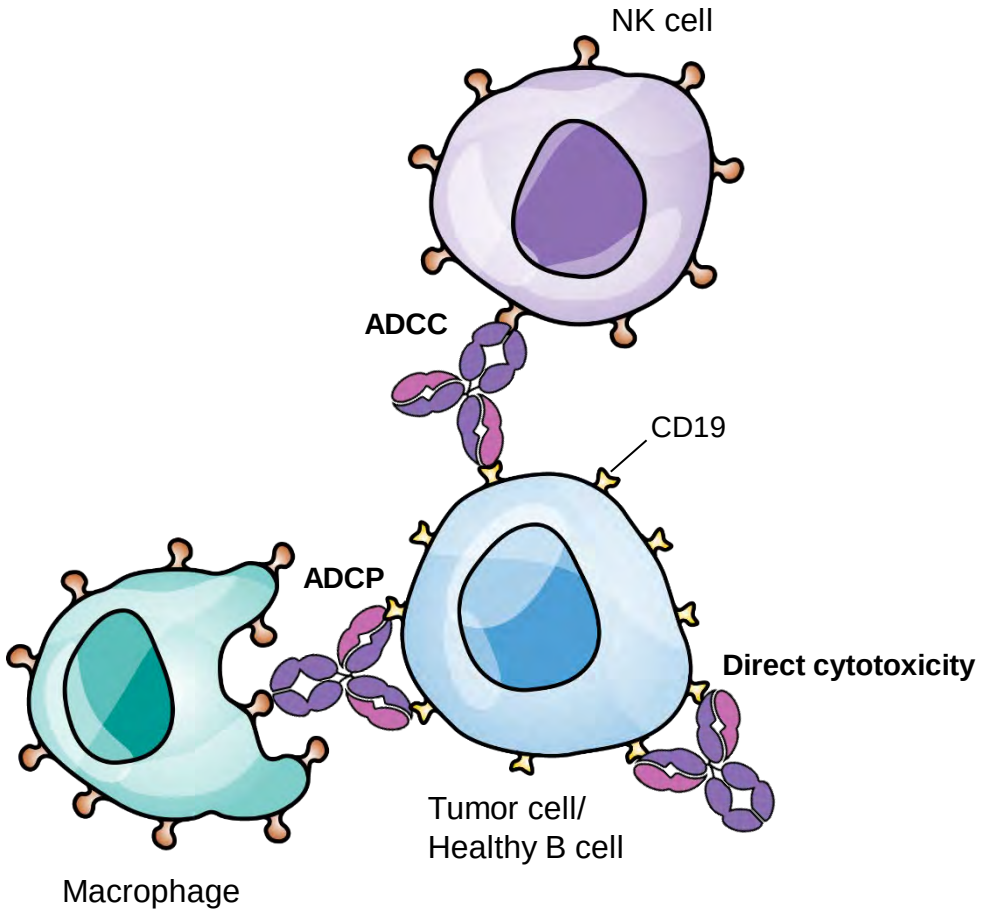


Tafasitamab

- Tafasitamab is an Fc-enhanced monoclonal antibody that targets the CD19 antigen expressed on the surface of B lymphocytes[1]
- Upon binding to CD19, tafasitamab mediates B-cell lysis through[1]:
  - Engagement of immune effector cells such as natural killer cells and phagocytes
  - Direct induction of cell death (apoptosis)
- The Fc modification results in enhanced ADCC and ADCP[1,2]
- In vitro, tafasitamab + lenalidomide increased ADCC activity compared with either agent alone[2]



Mechanism of Action[2]



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MOA, mechanism of action.

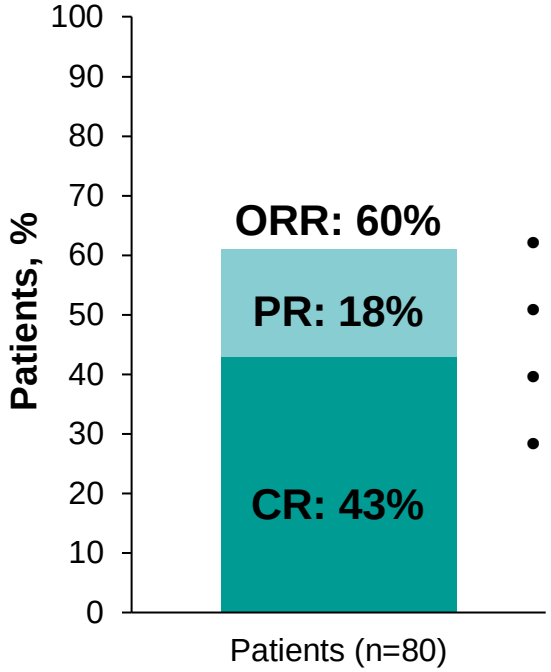
1. Salles G, et al. *Lancet Oncol.* 2020;21:978-988. 2. Monjuvi (Tafasitamab) Package Insert. Boston, MA: MorphoSys. June 2021.

L-MIND Phase 2 Trial
Tafasitamab + Lenalidomide in R/R DLBCL

Eligibility
- Aged ≥18 years
- R/R DLBCL
- 1-3 prior regimens including anti-CD20
- Not primary refractory
- Ineligible for HDCT-ASCT

Tafa 12 mg/kg IV
C1: D1, 4, 8, 15, 22
C2-3: D1, 8, 15, 22
C4+: D1, 15 until progression
+ **Len** PO 25 mg D1-21 for up to 12 cycles
28-day cycles

- Prior CD19-directed therapy (eg, CAR T) not permitted



- Median DOR: 21.7 mo
- 12-month DOR: 72%
- Median PFS: 12.1 mo
- Median OS: NR

Most Common TEAEs (>20% Any Grade or >5% Grade ≥3)

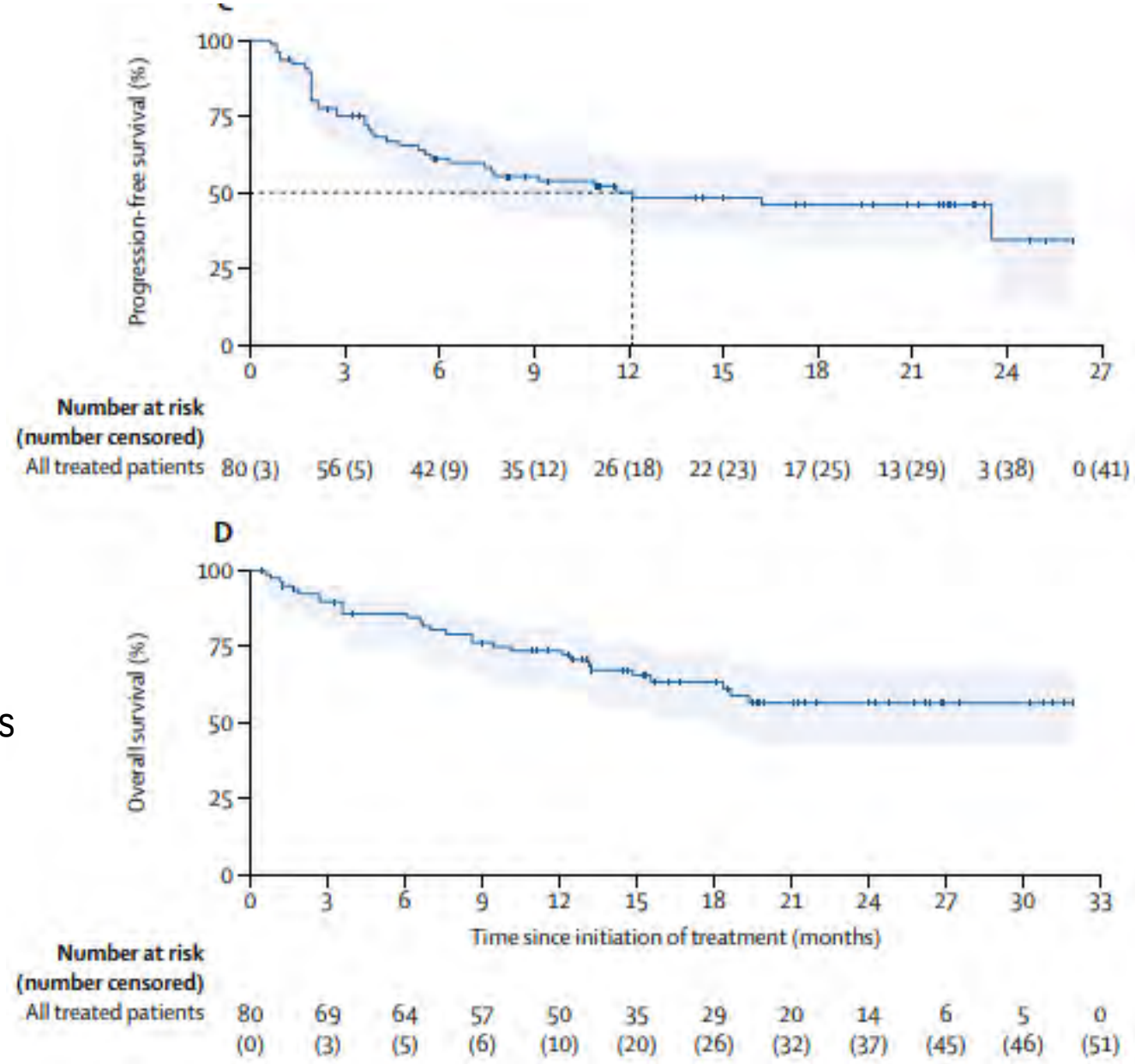
Patients, %	Patients (N=81)	
	Grade 1-2	Grade 3-4
Neutropenia	1	48
Rash[a]	27	9
Anemia	27	7
Diarrhea	32	1
Thrombocytopenia	14	17
Asthenia	21	2
Cough	21	1
Peripheral edema	22	0
Pyrexia	20	1
Hypokalemia	12	6
Leukopenia	6	9
Febrile neutropenia	0	12
Pneumonia	1	6

Median follow-up 13.2 months.
[a]Defined by customized Medical Dictionary for Regulatory Activities query.
ASCT, autologous stem cell transplant; C, cycle; CAR T, chimeric antigen receptor T cell; CR, complete response; DOR, duration of response; DLBCL, diffuse large B-cell lymphoma; HDCT, high-dose chemotherapy; IV, intravenous; Len, lenalidomide; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, oral; PR, partial response; R/R, relapsed/refractory; Tafa, Tafasitamab; TEAE, treatment-emergent adverse event.
Salles G, et al. *Lancet Oncol*. 2020;21:978-988.

Durable benefit seen

Median PFS: 12·1 months (95% CI 5·7 to not reached)

Median OS: median overall survival was not reached (95% CI 18·3 to not reached)



Salles G, et al. Lancet Oncol. 2020;21:978-988

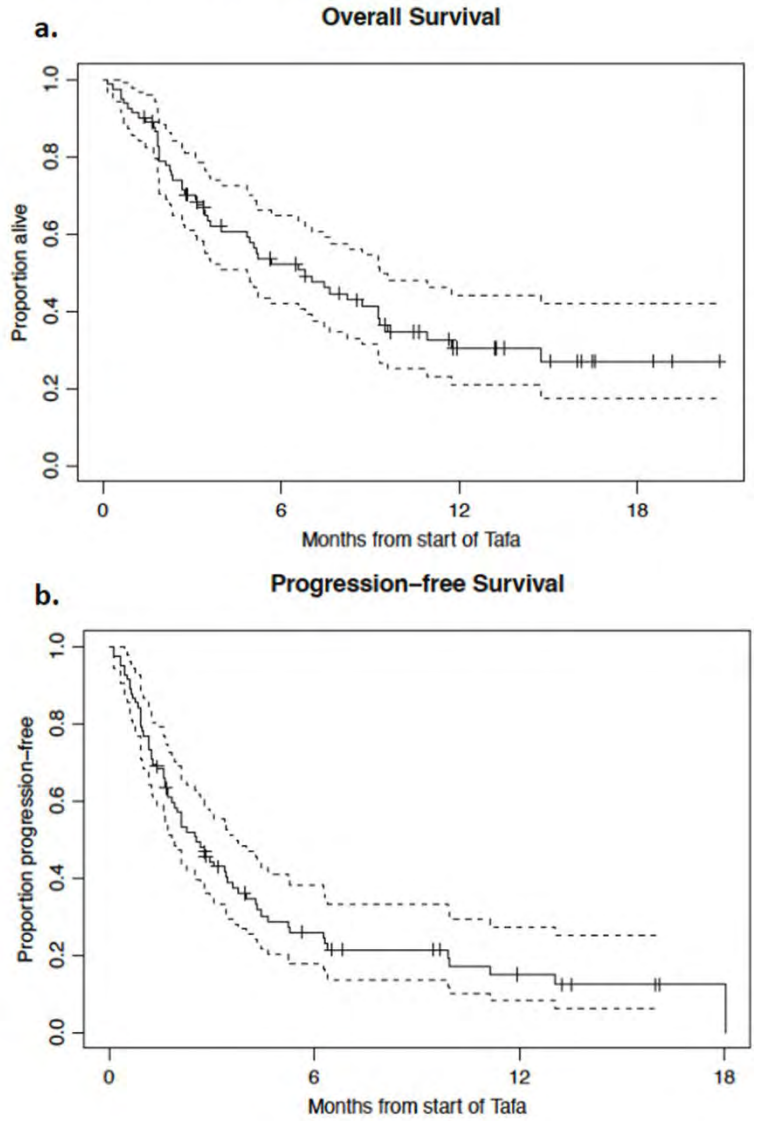
Real World data

Table 1. Patient characteristics from the real-world retrospective study (right) and the L-MIND clinical trial (left) for comparison.

Characteristic	L-MIND	Real World
Number of patients	80	82
Female sex	37 (46)	45 (55)
Age (yrs), median (range)	72 (41-86)	77 (44-92)
Race		
White, all ethnicity	72 (89)	76 (93)
White, Hispanic	Unknown	7 (9)
Asian	2 (2)	5 (6)
Other/Unknown	1 (1)	1 (1)
LBCL Subtype		
DLBCL, NOS	71 (89)	45 (55)
Transformed DBLCL	7 (9)	27 (33)
HGBCL with double/triple-hit translocation	2 (2)	8 (10)
Other*	0 (0)	2 (2)
Cell of Origin		
GCB	38 (47)	46 (57)
non-GCB/ABC	21 (26)	35 (43)
Unknown	22 (27)	1 (1)
Risk (IPI)		
0-2	40 (49)	17 (21)
3-5	41 (51)	65 (79)
Ann Arbor Stage		
I-II	20 (25)	6 (7)
III-IV	61 (75)	76 (93)
Prior lines of therapy		
Median (range)	2 (1-4)	2 (0-11)
1	40 (49)	15 (18)
2	35 (43)	24 (29)
3	5 (6)	17 (21)
4	1 (1)	5 (6)
≥5	0 (0)	18 (22)
Primary Refractory	15 (18)	38 (46)
Refractory to last therapy	36 (44)	57 (70)
Prior SCT	9 (11)	12 (15)
Prior CAR T	0	17 (21)
L-MIND eligible	-	7 (9)

Values are represented as number (%) unless otherwise stated.
*Other histologies: T-cell/Histiocyte-rich B cell lymphoma, primary mediastinal B-cell lymphoma
Abbreviations: LBCL, large B cell lymphoma; DLBCL, diffuse large B cell lymphoma; HGBCL, high-grade B cell lymphoma; IPI, international prognostic index; SCT, stem cell transplantation; CAR T, chimeric antigen receptor T cell therapy

Figure 1. Kaplan-Meier curves of overall survival (a) and progression-free survival (b) with 95% confidence intervals (dotted lines) for all patients receiving TL off clinical trial.

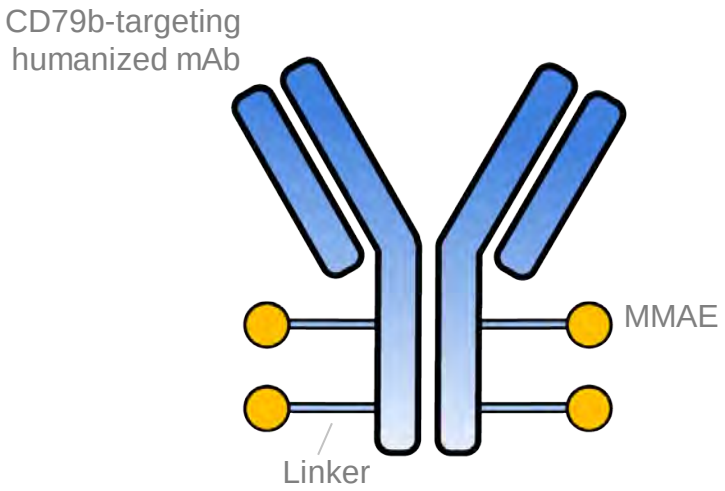


Qualls et al. 2022

ADCs:
Polatuzumab Vedotin and Loncastuximab Teserine

Polatuzumab Vedotin

- Polatuzumab vedotin is an ADC targeting CD79b, a B-cell receptor component expressed in a majority of malignant lymphomas[1]
- The payload is the anti-mitotic cytotoxic agent MMAE, which is attached via a cleavable linker[1]
  - MMAE binds to microtubules and kills dividing cells by inhibiting division and inducing apoptosis



ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E; PBD, pyrrolobenzodiazepine.

1. Deeks ED. *Drugs*. 2019;79:1467-1475. 2. Lee A. *Drugs*. 2021;81:1229-1233. 3. Zynlonta® (loncastuximab teserine) Package Insert. ADC Therapeutics SA; 2021.

GO29365 Phase 1/2 Trial
Polatuzumab Vedotin + BR in R/R DLBCL

Eligibility
- Aged ≥18 years
- R/R DLBCL
- ≥1 prior line of therapy
- ECOG PS 0-2
- Transplant ineligible/failed

Randomized cohorts

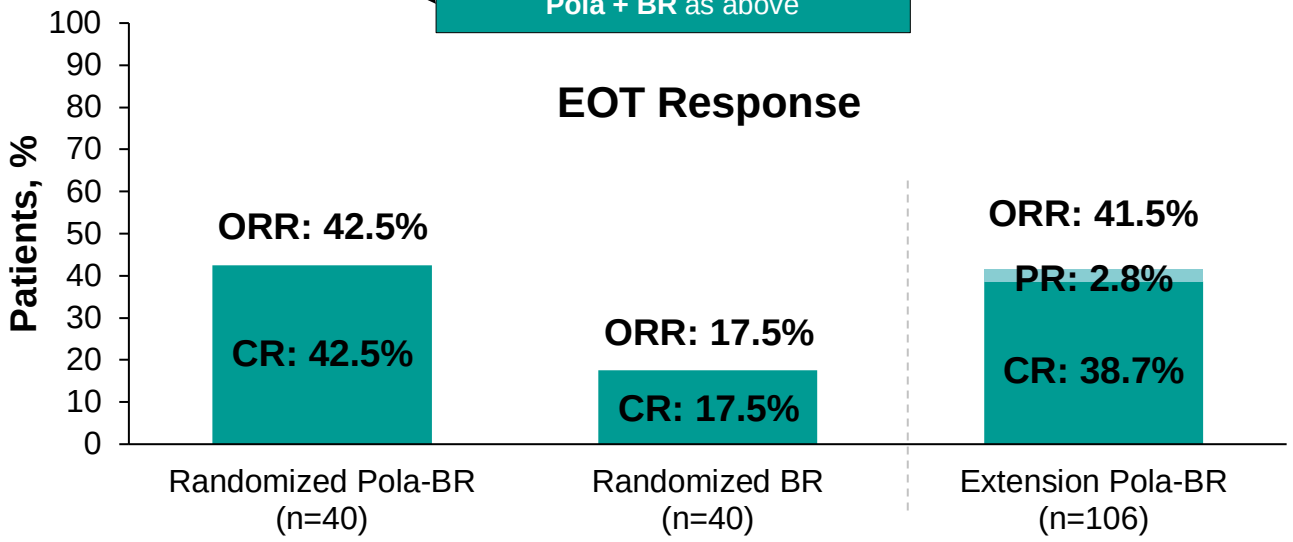
Pola + BR (21-day cycles)
Pola 1.8 mg/kg IV C1D2, C2-6D1
B 90 mg/m^2 IV C1D2-3, C2-6D1-2
R 375 mg/m^2 IV C1-6D1

BR (21-day cycles)
B 90 mg/m^2 IV C1D2-3, C2-6D1-2
R 375 mg/m^2 IV C1-6D1

Extension cohort

Pola + BR as above

- 1 patient in the extension cohort received prior CAR T



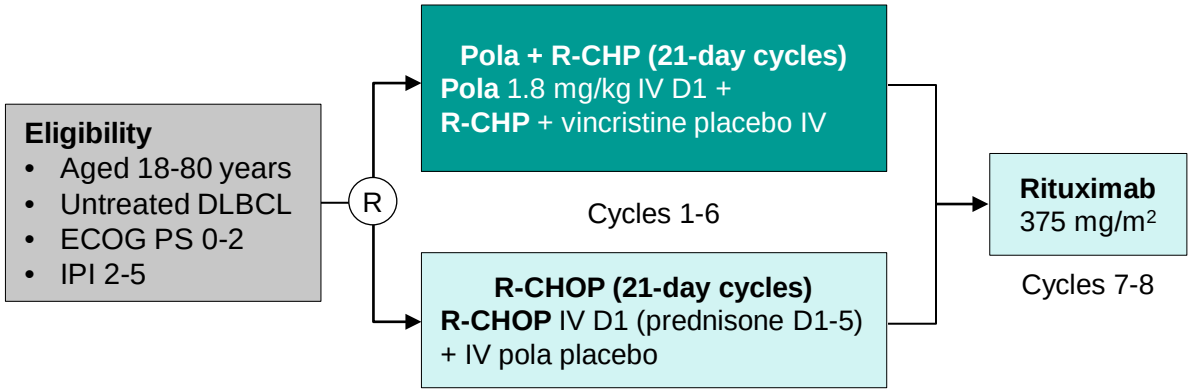
	Randomized Pola-BR (n=40)	Randomized BR (n=40)	Extension Pola-BR (n=106)
Median DOR:	10.9 mo	10.6 mo	9.5 mo
Median PFS:	9.2 mo	3.7 mo	6.6 mo
Median OS:	12.4 mo	4.7 mo	12.5 mo

Most Common AEs (≥20% Any Grade or ≥10% Grade 3-4)

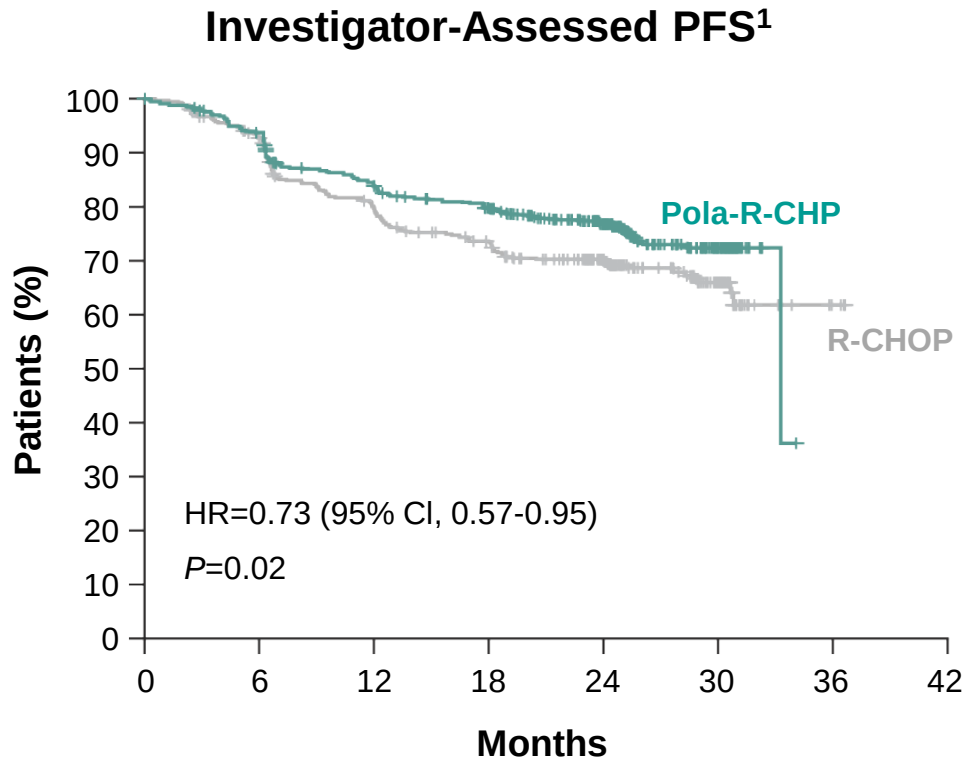
Patients, %	Pooled Pola + BR (N=151)	
	Grade 1-2	Grade 3-4
Infections/infestations	27.2	21.9
Neutropenia	4.6	32.5
Thrombocytopenia	11.9	20.5
Anemia	19.9	12.6
Diarrhea	31.8	4.0
Nausea	32.4	0.7
Pyrexia	27.8	1.3
Fatigue	24.5	2.0
Decreased appetite	23.2	2.6
Peripheral neuropathy	29.1	2.0

Median follow-up: 48.9 mo for randomized pola + BR, 48.3 mo for BR, and 15.2 mo for extension.
AE, adverse event; B, bendamustine; C, cycle; CAR T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Pola, polatuzumab vedotin; PR, partial response; PS, performance status; R, rituximab; R/R, relapsed/refractory.
Sehn LH, et al. *Blood Adv*. 2022;6:533-543.

POLARIX Phase 3 Trial
Polatuzumab Vedotin + R-CHP in 1L DLBCL



- Pola-R-CHP improved PFS vs R-CHOP for 1L DLBCL[1]
  - OS did not differ significantly between treatment arms (HR=0.94 [95% CI, 0.65–1.37]); *P*=0.75
- There were no unexpected safety findings[1]
- Based on these results, Pola-R-CHP was approved in the EU and FDA for adult patients with previously untreated DLBCL[2]
- Funding approval in a range of territories



No. at risk:

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

Median follow-up: 28.2 months.

1L, first-line; CHMP, Committee for Medicinal Products for Human Use; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; HR, hazard ratio; IPI international prognostic index; IV, intravenous; OS, overall survival; PFS, progression-free survival; Pola, polatuzumab vedotin; PS, performance status; R-CH(O)P, rituximab, cyclophosphamide, doxorubicin, (vincristine), and prednisone; US FDA, United States Food and Drug Administration.

1. Tilly H, et al. *N Engl J Med*. 2022;386:351-363. 2. Roche's Polivy combination approved by European Commission for people with previously untreated diffuse large B-cell lymphoma [press release]. May 25, 2022. https://www.roche.com/media/releases/med-cor-2022-05-25b.

ADCs: Polatuzumab Vedotin and Loncastuximab Teserine

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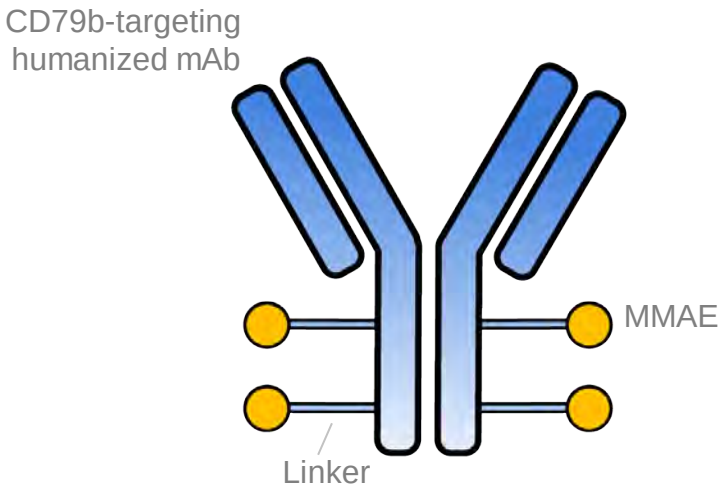
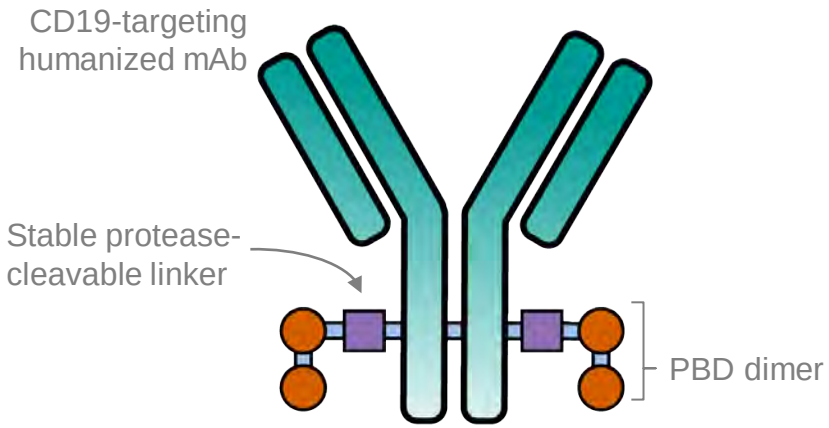
- The payload is the anti-mitotic cytotoxic agent MMAE, which is attached via a cleavable linker[1]
  - MMAE binds to microtubules and kills dividing cells by inhibiting division and inducing apoptosis



Loncastuximab Teserine

- Loncastuximab tesirine is an ADC targeting CD19, which is expressed exclusively on the surface of B cells[2,3]
- The payload is a small molecule PBD dimer and alkylating agent[3]
  - The PBD dimer binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, inducing tumor cell death



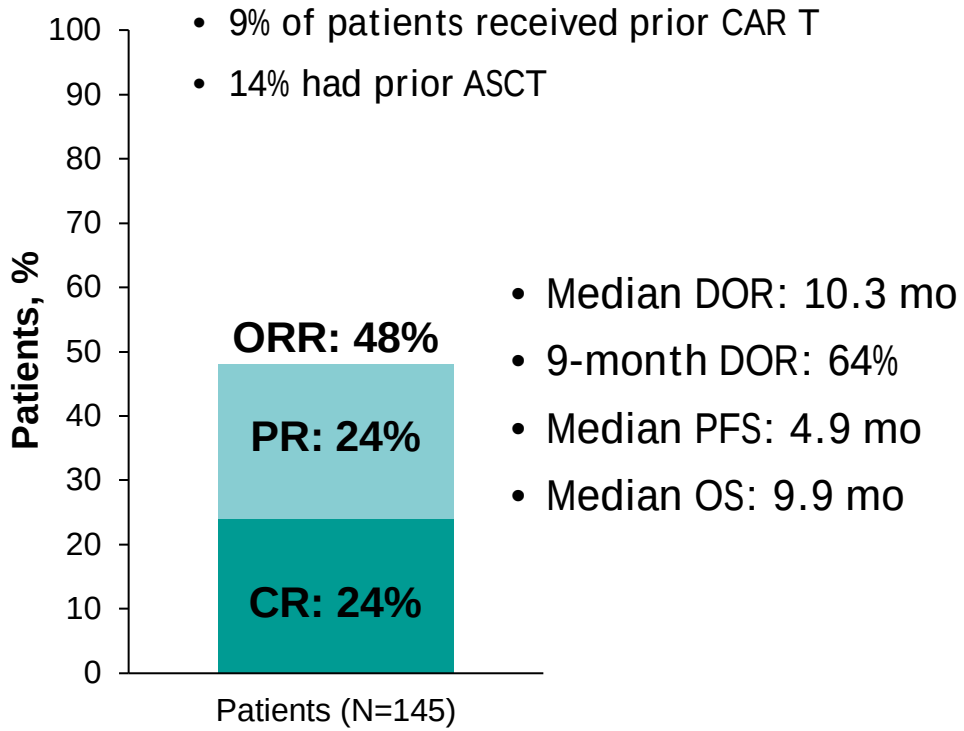
ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E; PBD, pyrrolobenzodiazepine.

1. Deeks ED. *Drugs*. 2019;79:1467-1475. 2. Lee A. *Drugs*. 2021;81:1229-1233. 3. Zynlonta® (loncastuximab teserine) Package Insert. ADC Therapeutics SA; 2021.

LOTIS-2 Phase 2 Trial
Loncastuximab Teserine in 3L+ DLBCL

Eligibility
- Aged ≥18 years
- R/R DLBCL
- ≥2 prior regimens
- Prior CAR T permitted (persistent CD19 expression required)

Lonca IV as 30-min infusion
In 21-d cycles
C1-2: 150 µg/kg Q3W
C3+: 75 µg/kg Q3W for up to 1 year or PD/unacceptable toxicity



Most Common TEAEs (≥20% Any Grade or ≥5% Grade ≥3)

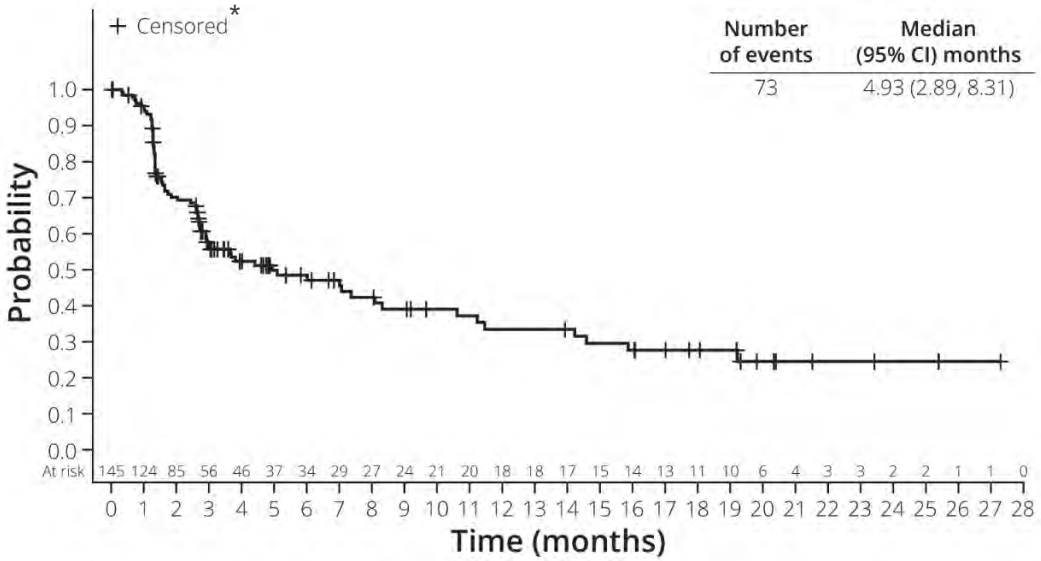
Patients, %	Patients (N=145)	
	Grade 1-2	Grade 3-4
Neutropenia	14	26
GGT increased	24	16
Thrombocytopenia	15	18
Anemia	16	10
Fatigue	26	1
Nausea	23	0
Cough	21	1
Peripheral edema	19	1
Blood alkaline phosphatase increased	19	1
Hypophosphatemia	10	6
Leukopenia	6	9
Lymphopenia	2	6

Median treatment duration was 45 days.
3L, third-line; ASCT, autologous stem cell transplant; C, cycle; CAR T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; GGT, gamma-glutamyl transferase; Lonca, loncastuximab teserine; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
Caimi P, et al. *Lancet Oncol.* 2021;22:790-800.

OS and PFS

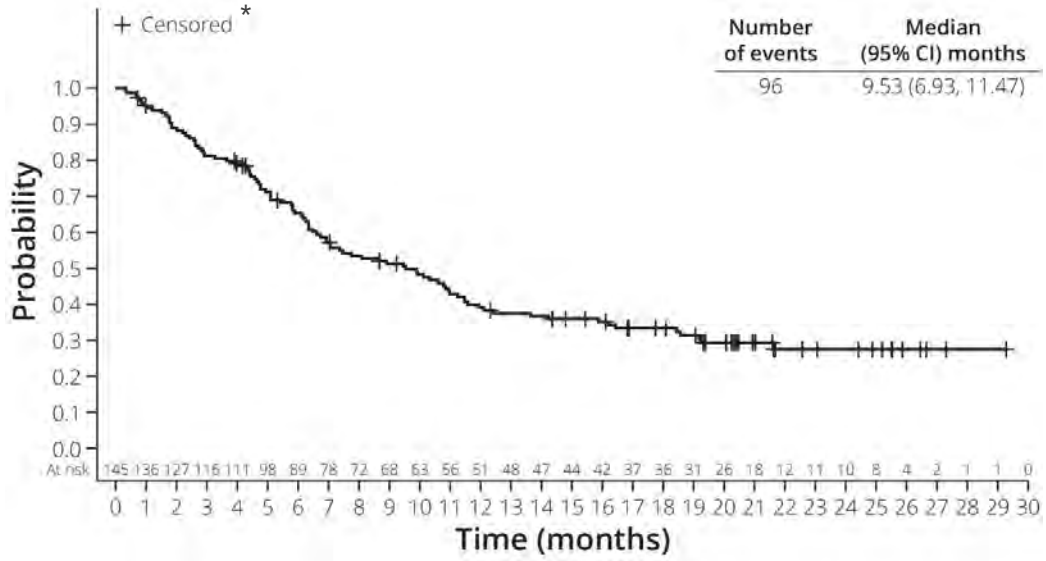
Follow-up analysis

PFS (all-treated population) (N=145)



mPFS was 4.9 months

OS (all-treated population) (N=145)

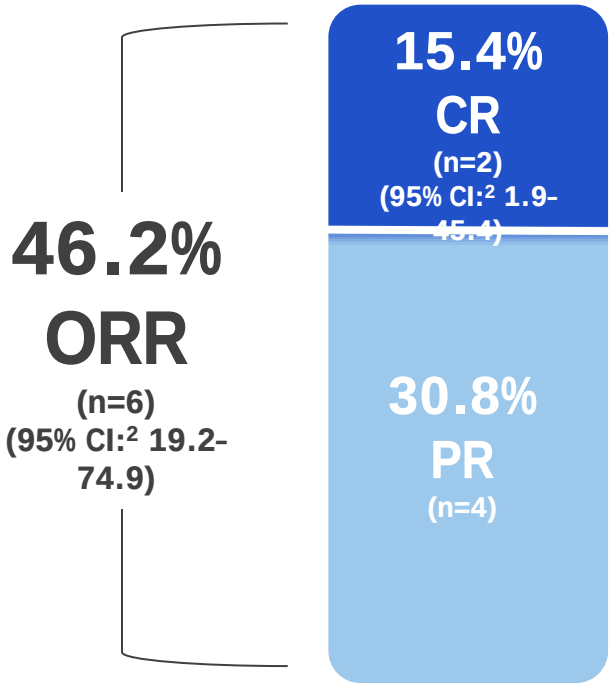


mOS was 9.5 months

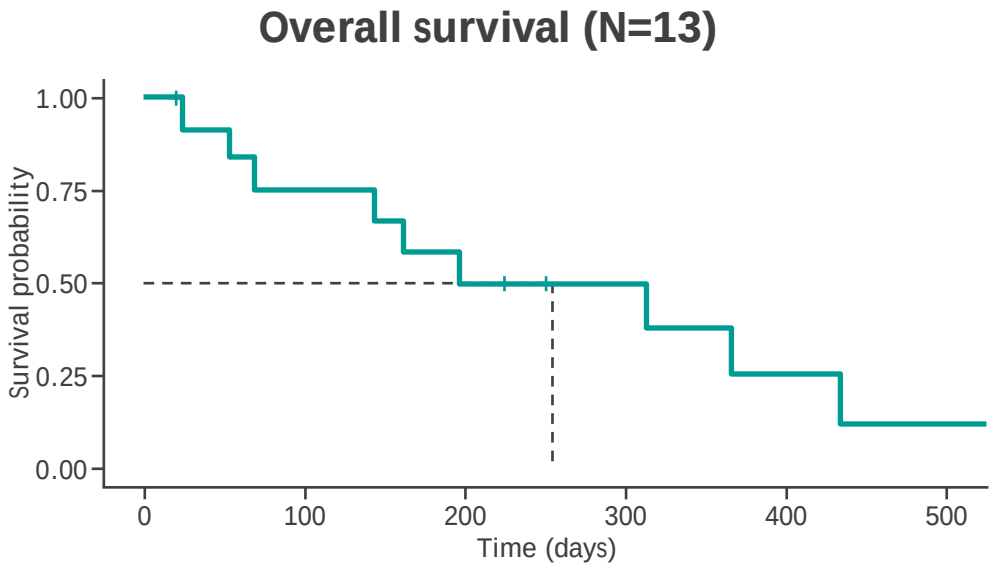
Data cut-off: March 1, 2021.
Patients with events after start of subsequent anticancer therapy or procedure, or progression free and alive at data cut-off, or who had unknown status were censored at last valid tumour assessment on or before start of subsequent anticancer therapy or procedure or data cut-off.[2]
CI, confidence interval; m, median; OS, overall survival; PFS, progression-free survival.
1. Zinzani et al. ICML 2021 **2.** Caimi et al. *Lancet Oncol* 2021.

Efficacy in patients who previously received CAR-T[1]

After a median follow-up of 8 months, 13 patients received a median of 2 cycles of Lonca (range 1-9)



Median DOR: 8 months
(95% CI: 103 days–NR)



Median OS after Lonca: **8.2 months**
(95% CI: 144d–NR)

CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; DOR, duration of response; Lonca, loncastuximab tesirine; NR, not reached; ORR, overall response rate; PR, partial response.

1. Caimi et al. *Clin Lymphoma Myeloma Leuk* 2022 **2.** Data on file.

Thoughts

- Our treatment paradigms are changing. More options for patients
- Better understanding of the ‘best fit’ for patients.
- Will build confidence in sequencing with increased data.
- Wil need to identify better biomarkers for response and understand mechanisms of resistance.
- Challenges for regulators and funders.
- Challenges for delivery teams/out of hours