Cellular Therapy in Lymphoma: Where are we now?

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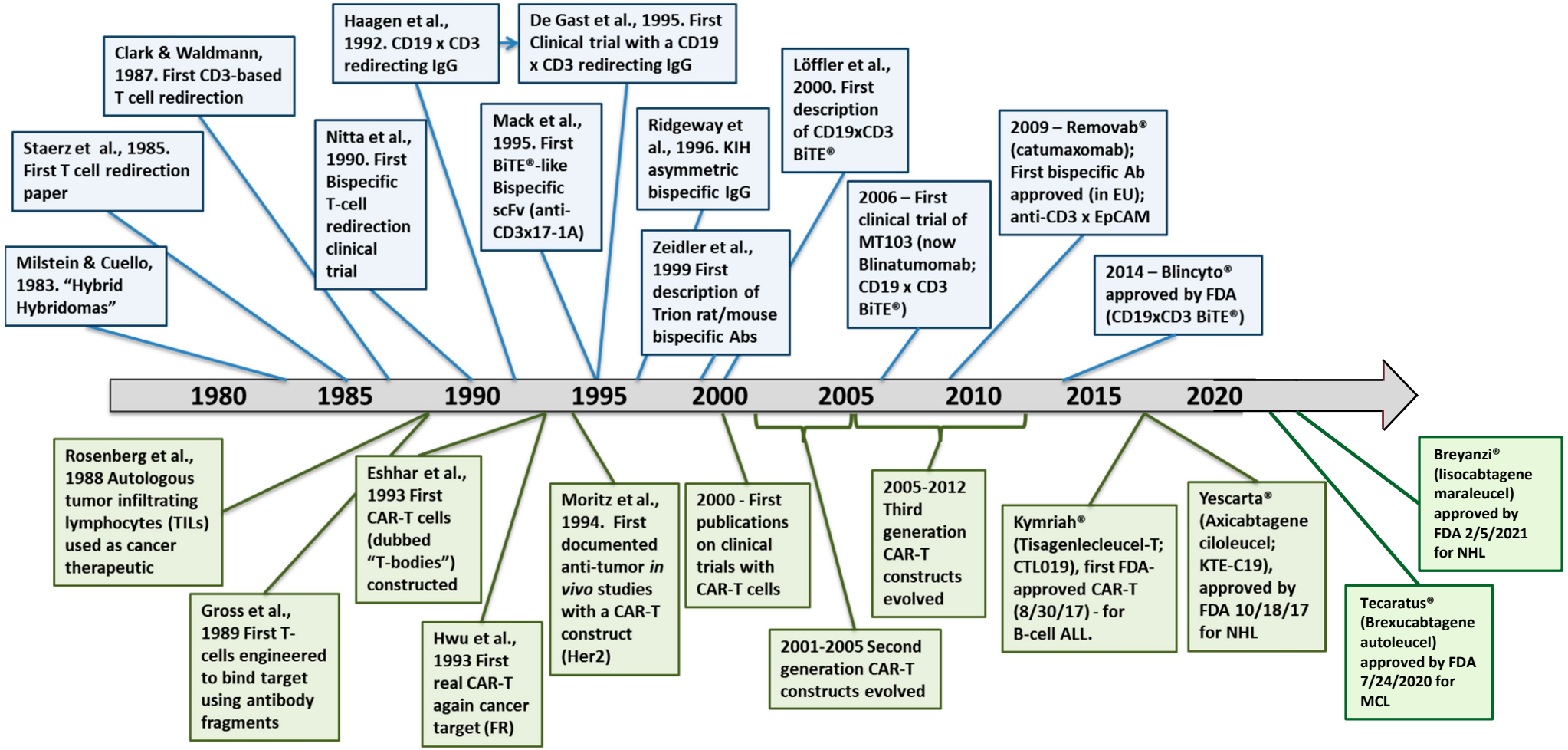
Disclosures

- Peter Riedell has served as a consultant and/or advisory board member for AbbVie, Bayer, BeiGene, BMS, Janssen, Karyopharm, Kite/Gilead, Novartis, Nurix, and Takeda. He has served as a speaker for Kite Pharma and has received honoraria from Novartis. Research support from BMS, Calibr, CRISPR Therapeutics, Fate Therapeutics, Kite Pharma, MorphoSys, Novartis, Tessa Therapeutics, and Xencor.

- I will discuss drugs and indications currently under investigation and/or that have not been approved by regulatory authorities.

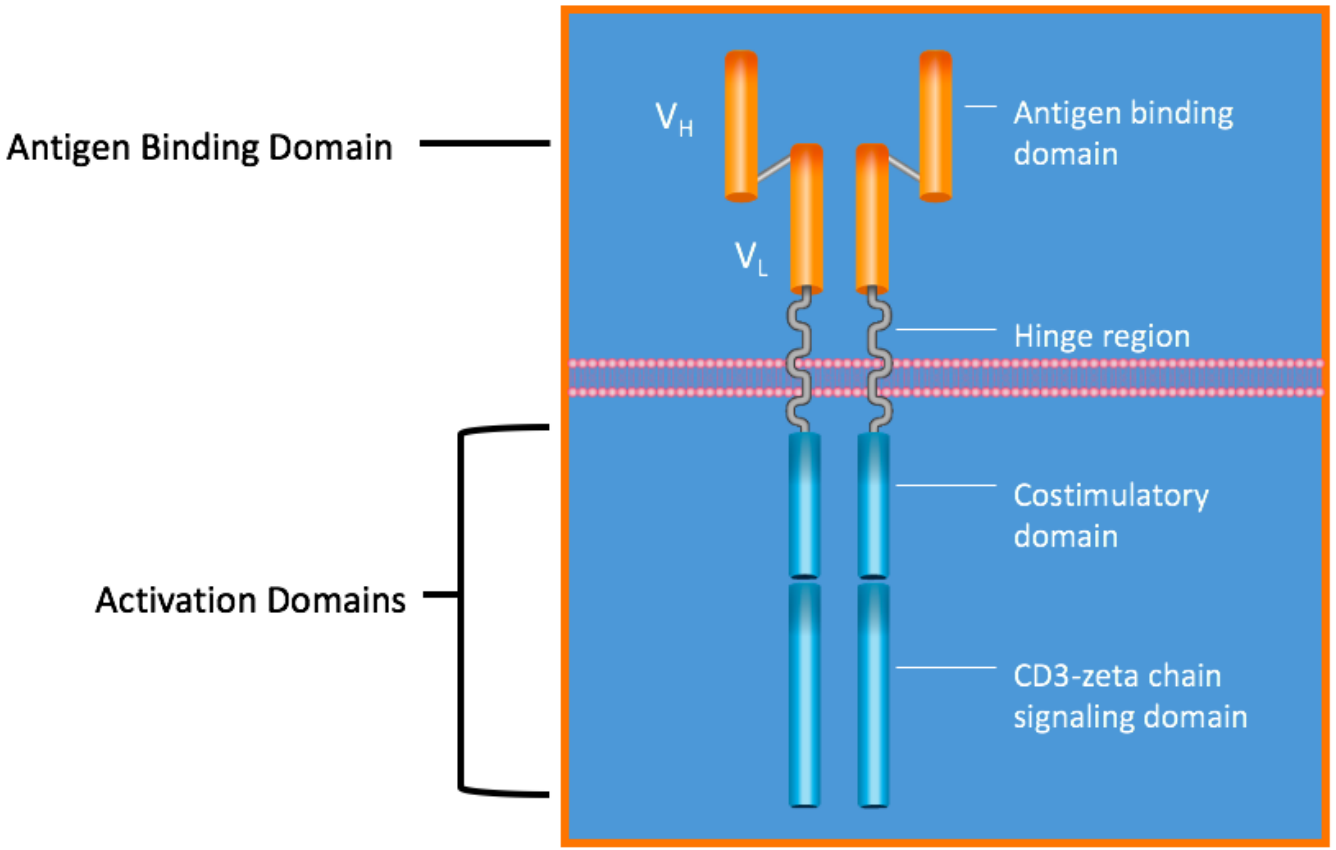
Development Timeline of Cellular Therapy



Adapted from Strohl WR, et al. *Antibodies*. 2019;8:41.

CAR T-cell Therapy

Anatomy of a Chimeric Antigen Receptor (CAR)



scFv
Single-chain variable fragment (scFv) allows direct activation of T cell by cancer cell antigens

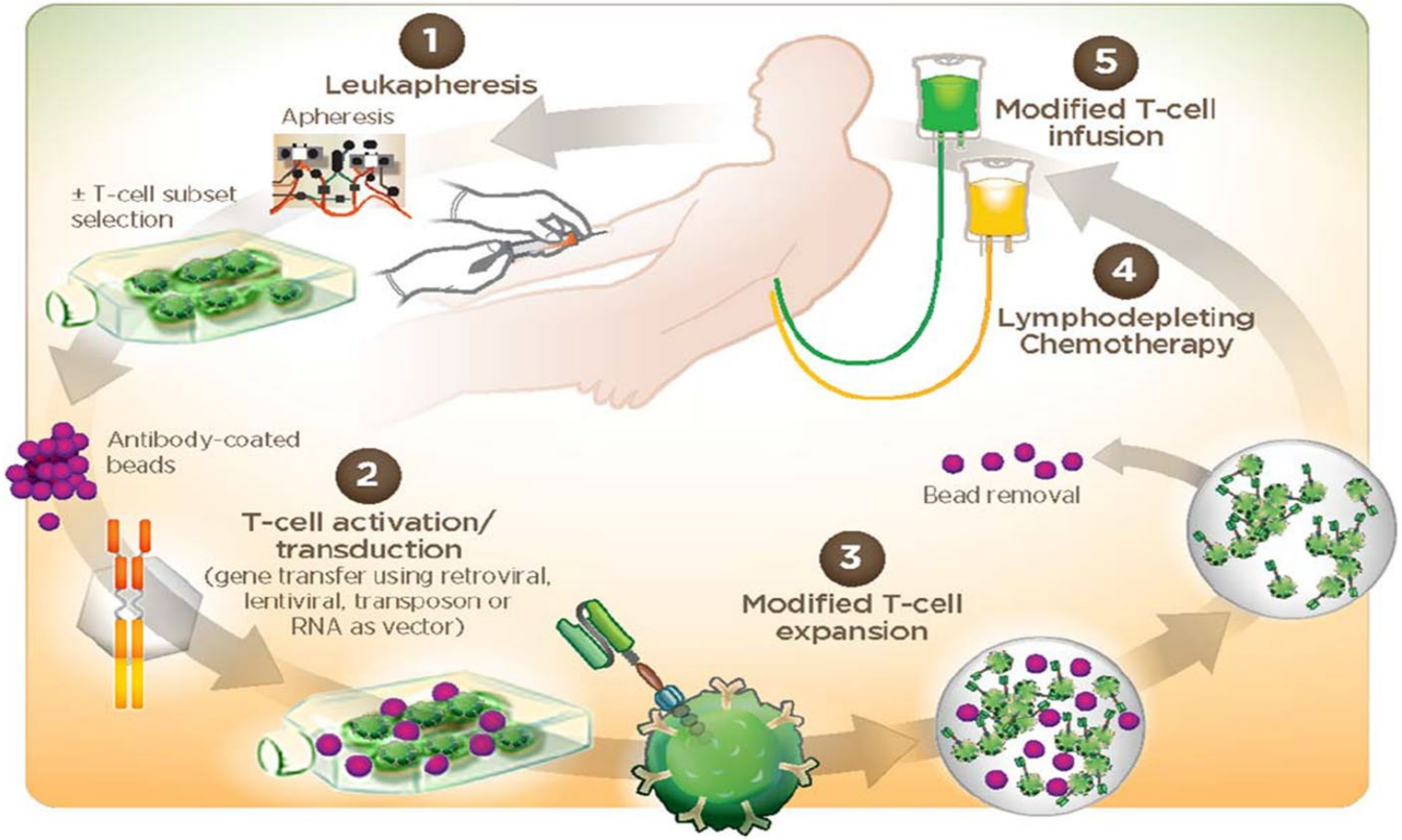
Hinge region
Allows optimal antigen binding

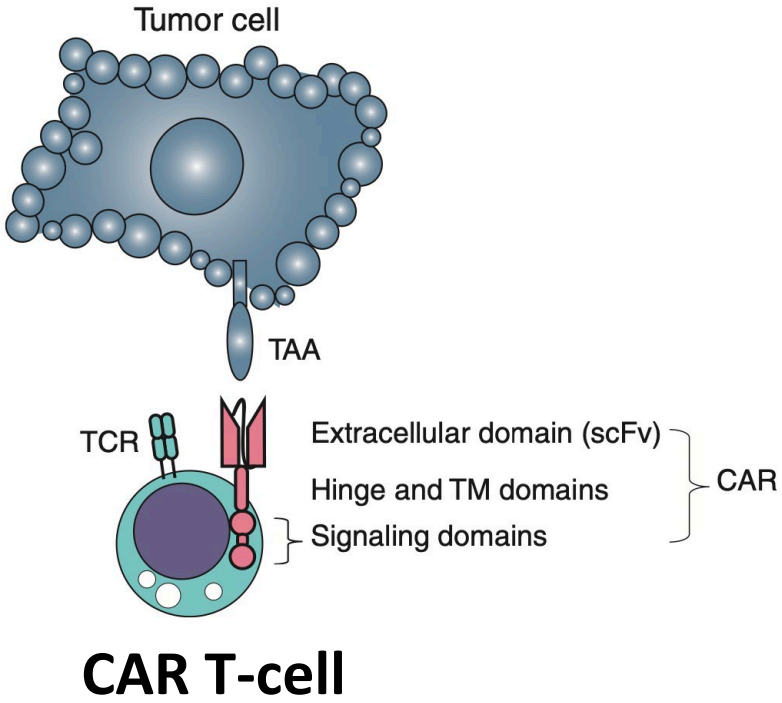
Costimulatory Domain: CD28 or 4-1BB
Enhances CAR T cell proliferation, cytotoxicity and persistence

Signaling Domain: CD3-zeta chain
Proliferation & activation of CAR T cells
CAR T cell-mediated killing of tumor cells

Adapted from Park JH, et al. *Discov Med.* 2010;9:277-88.

CAR T-cell Clinical Process

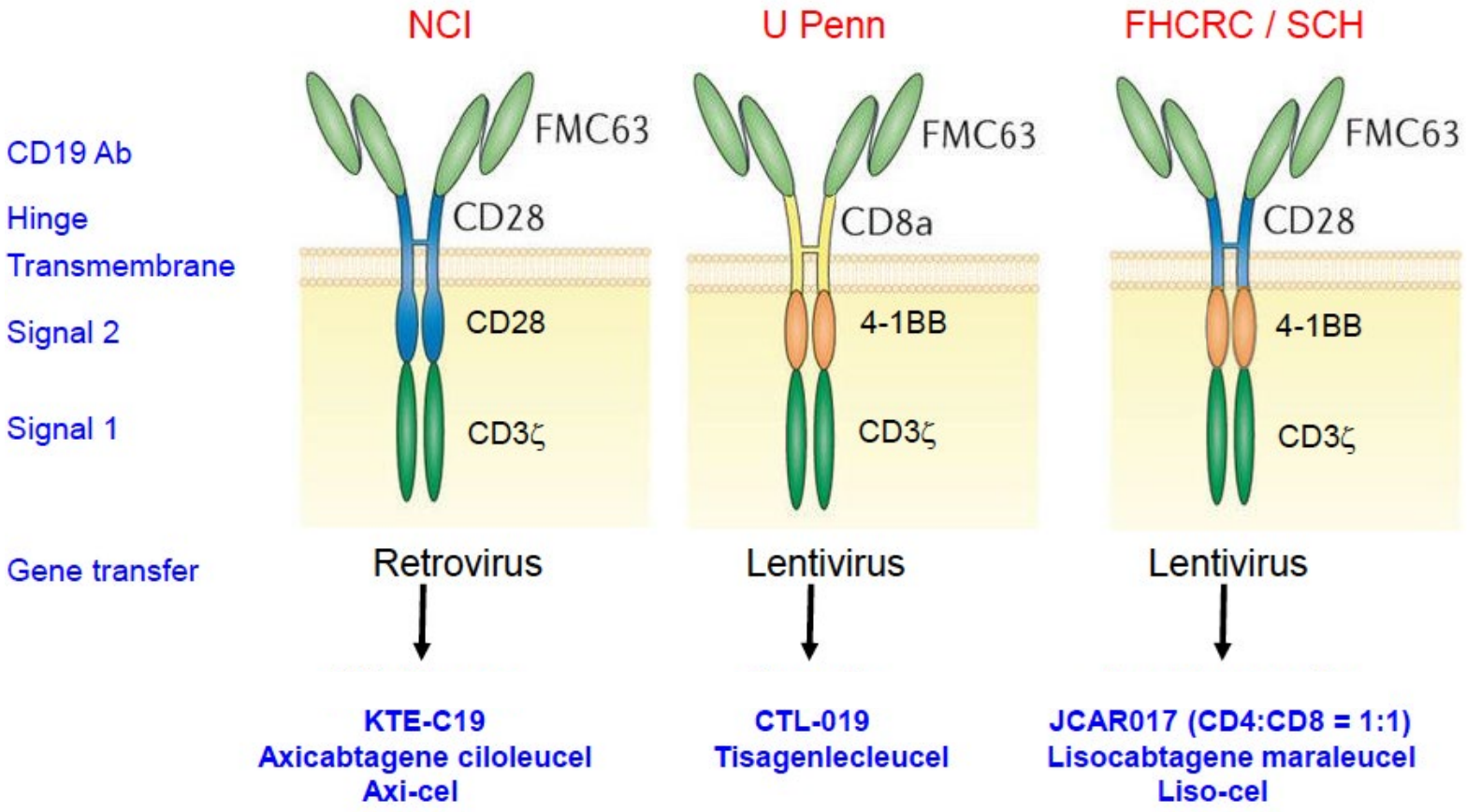




CAR T-cell

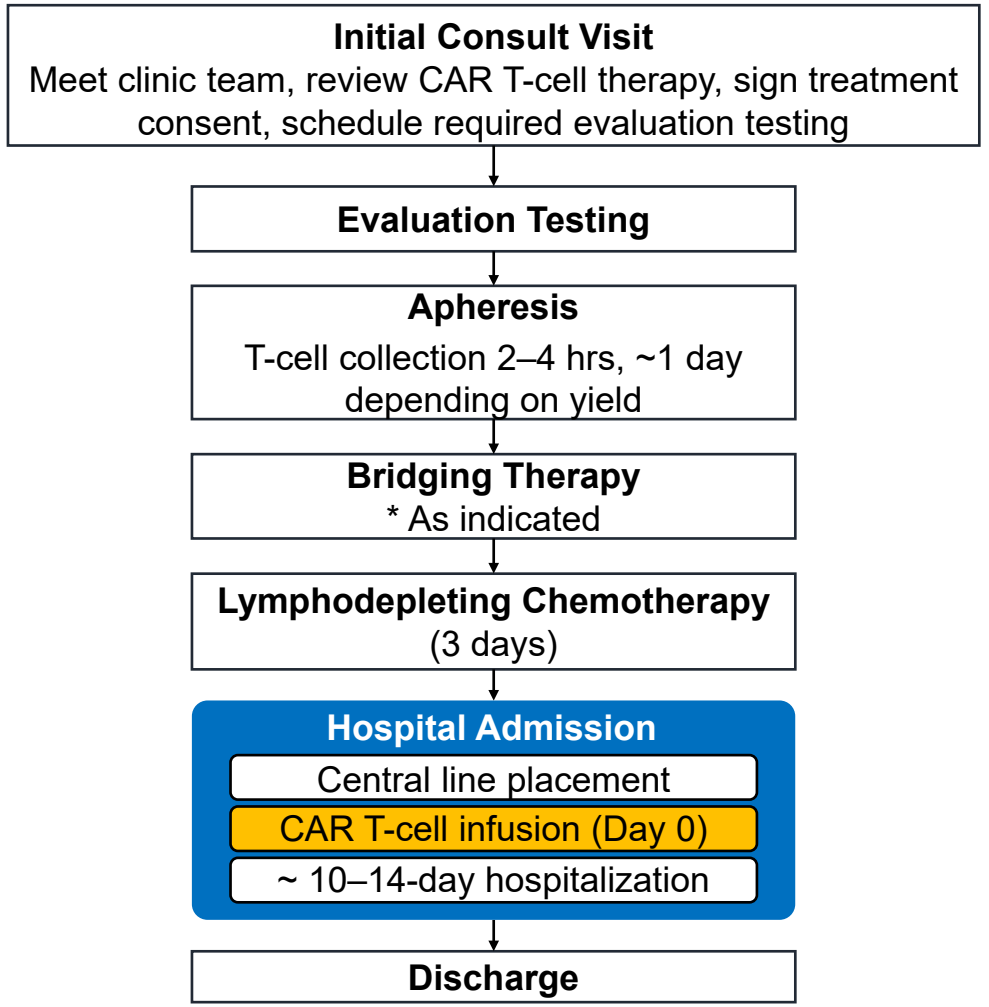
Frey, et al. *Am J Hem*. 2016.
Slaney CY, *Cancer Discov*. 2018;8:924

CD19 Directed CAR T-cell Products



Adapted from van der Steegan et al. *Nat Rev Drug Discov*, 2015.

CAR T-cell Workflow



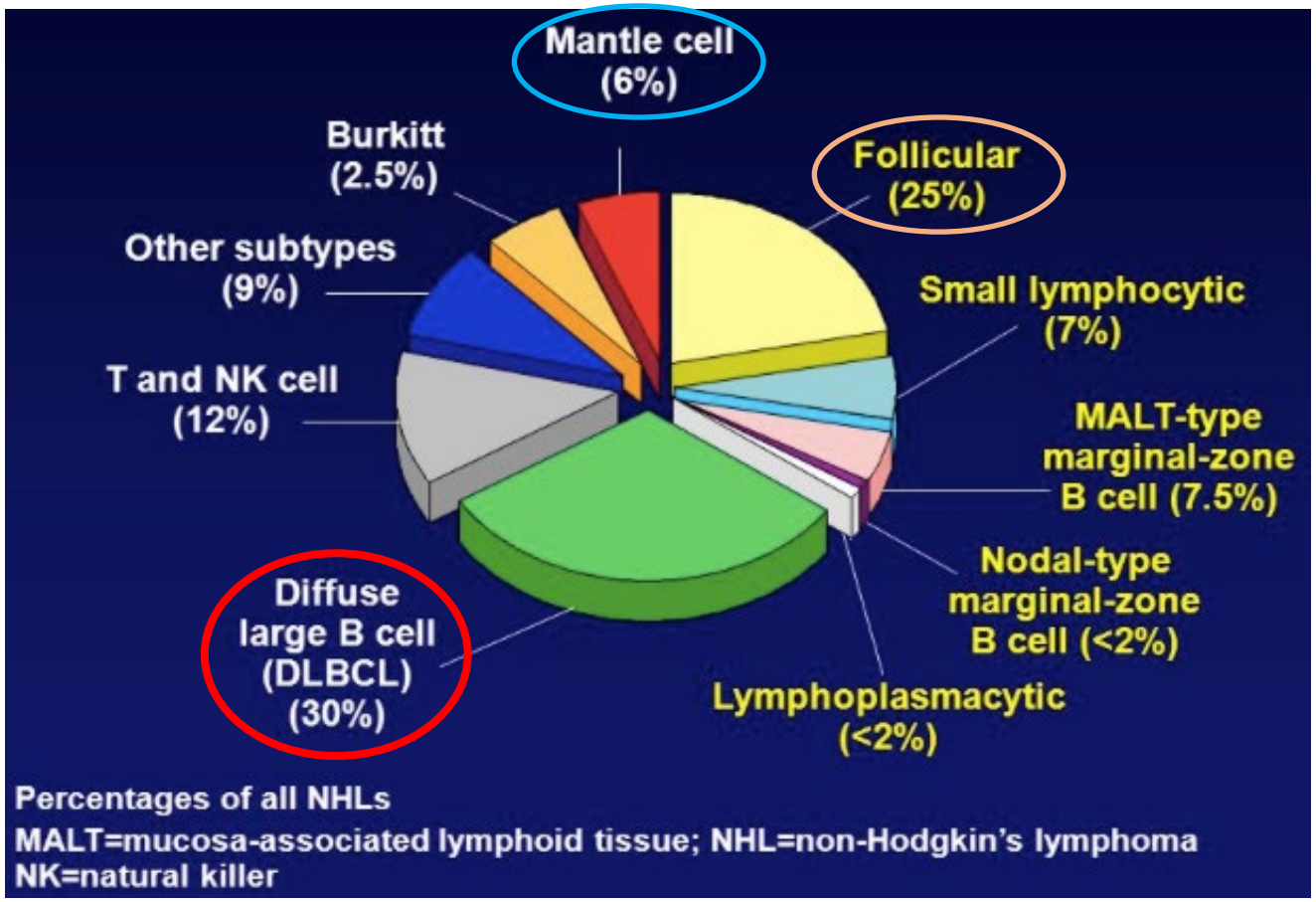
2–4 Weeks*

~17–28 Days

Takes ~4–8 weeks from initial consult to starting LD chemotherapy

* Maybe extended due to insurance approval

There are nearly 100 types of lymphoma



Goals of therapy vary by histology and expected clinical behavior:

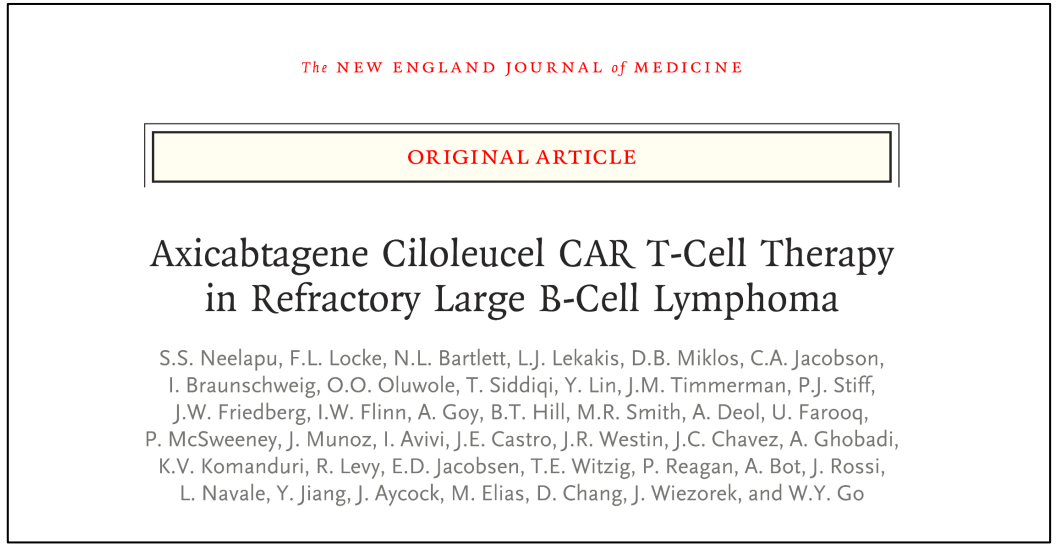
- ❑ **Curative intent**
- ❑ **Palliative intent**

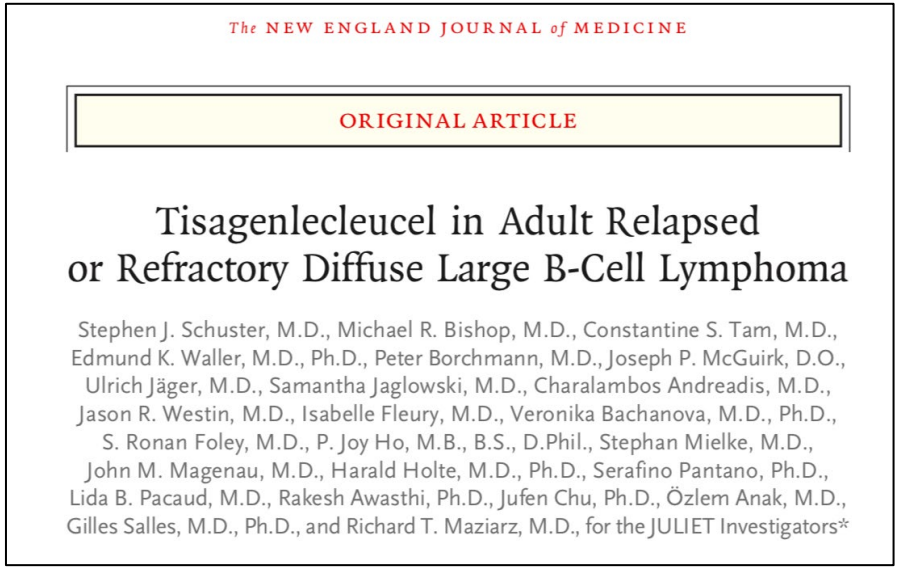
Swerdlow S, et al. *Blood*. 2016;127
Lichtman MA Williams Hematology. 7th ed. New York. McGraw Hill; 2006,1408.

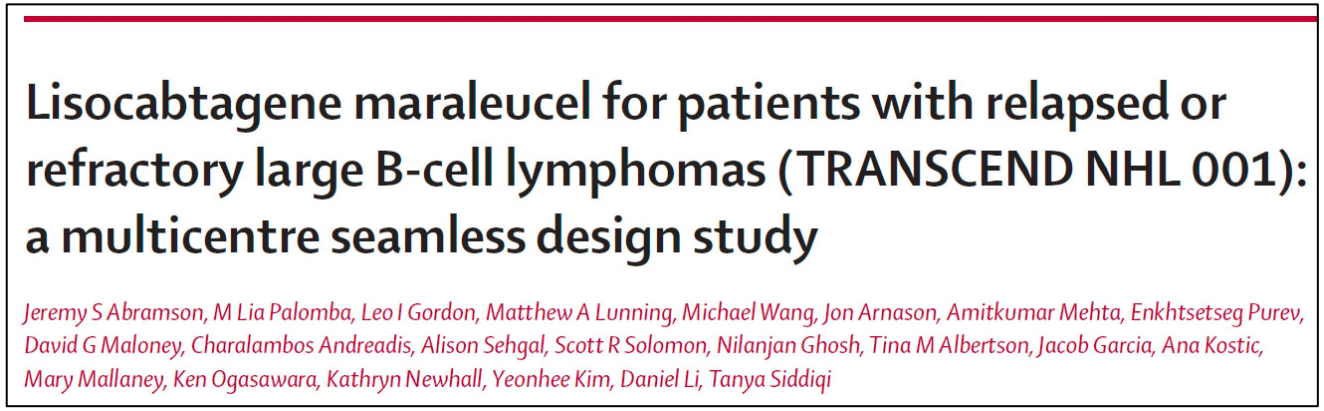
Approved CAR T-cell Therapy in Lymphoma

- Axicabtagene ciloleucel (axi-cel)
  - **Aggressive large B-cell lymphoma**
    - 2nd line for primary refractory or early relapse (≤12 months)—*4/1/22*
    - 3rd line and beyond—*10/18/17*
  - **Follicular lymphoma**
    - 3rd line and beyond—*3/5/21*
- Tisagenlecleucel (tisa-cel)
  - **Aggressive large B-cell lymphoma**
    - 3rd line and beyond—*5/1/18*
- Lisocabtagene maraleucel (liso-cel)
  - **Aggressive large B-cell lymphoma**
    - 3rd line and beyond—*2/5/21*
- Brexucabtagene autoleucel (brexu-cel)
  - **Mantle cell lymphoma**
    - 2nd line and beyond—*7/24/20*

CAR T-cell Therapy in R/R DLBCL—3rd Line







Neelapu SS, et al. *N Engl J Med*. 2017;377:2531.
Schuster SJ, et al. *N Engl J Med*. 2019;380:45.
Abramson JS, et al. *Lancet*. 2019;396:839.

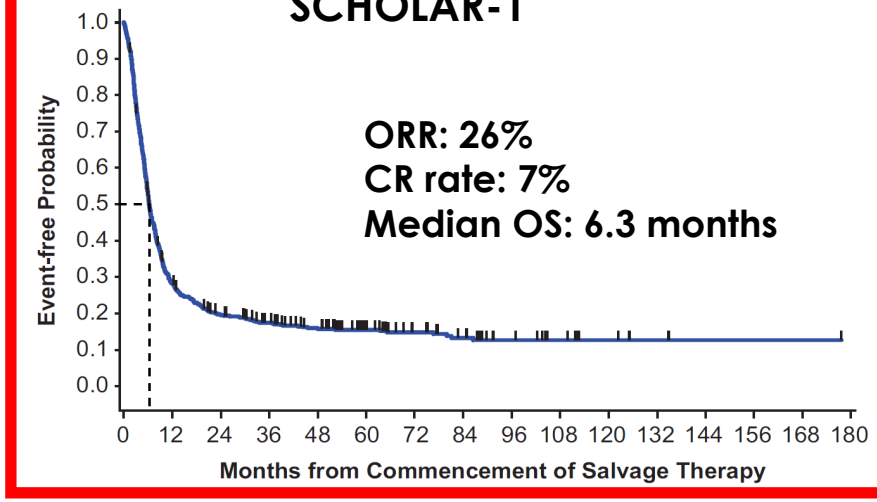
CAR T-cell Therapy in R/R DLBCL—3rd Line

Characteristic	ZUMA-1	JULIET	TRANSCEND
Cellular therapy	Axi-cel	Tisa-cel	Liso-cel
Co-stimulatory domain	CD28	4-1BB	4-1BB
Number (enrolled/treated)	119/108	165/111	342/268
Median age (range), yr	58 (23-76)	56 (22-76)	63 (18-86)
Prior autoSCT	21%	49%	33%
Bridging therapy	0%	92%	59%
Median turnaround time, d	17	54	24
Best response (ORR/CR) rate	83%/58%	52%/40%	73%/53%
1-yr PFS (of infused patients)	44%	35%	44%
1-yr OS (of infused patients)	59%	49%	58%

Neelapu SS, et al. *N Engl J Med*. 2017;377:2531.
Schuster SJ, et al. *N Engl J Med*. 2019;380:45.
Abramson JS, et al. *Lancet*. 2019;396:839.

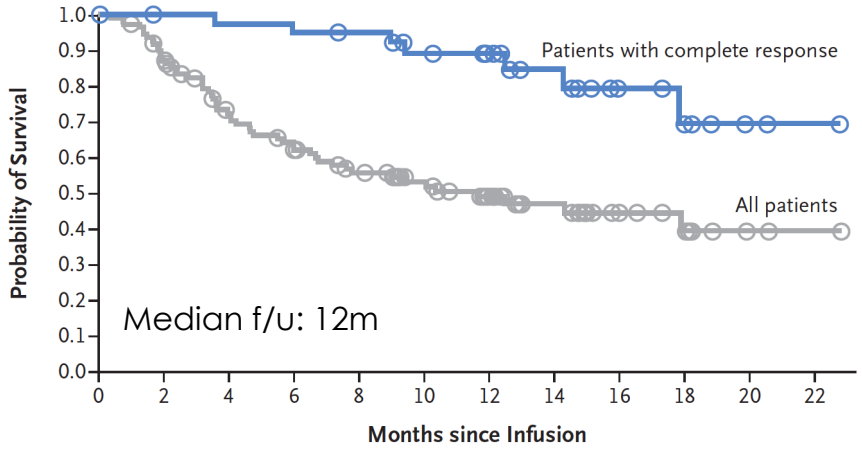
CAR T-cell Therapy in R/R DLBCL—3rd Line

SCHOLAR-1



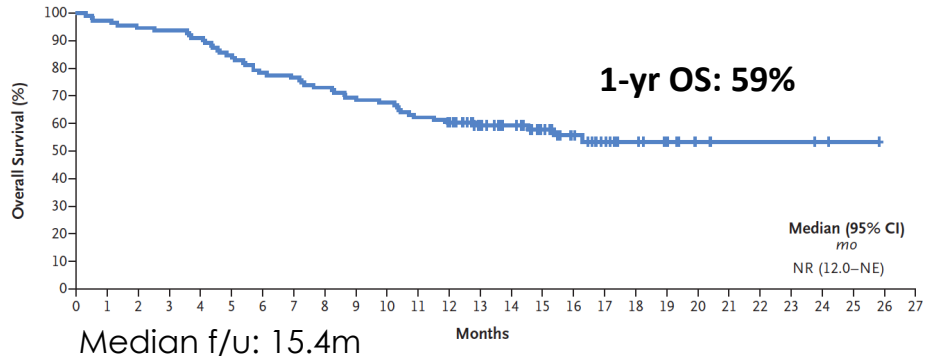
ORR: 26%
CR rate: 7%
Median OS: 6.3 months

JULIET



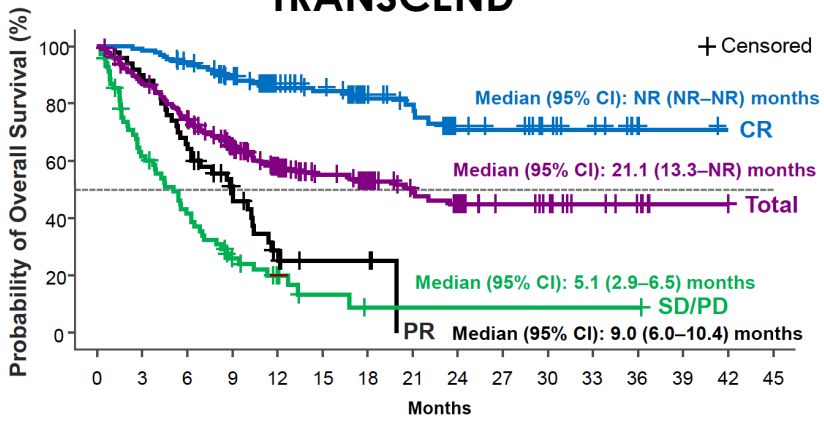
1-yr OS: 49%

ZUMA-1



1-yr OS: 59%

TRANSCEND

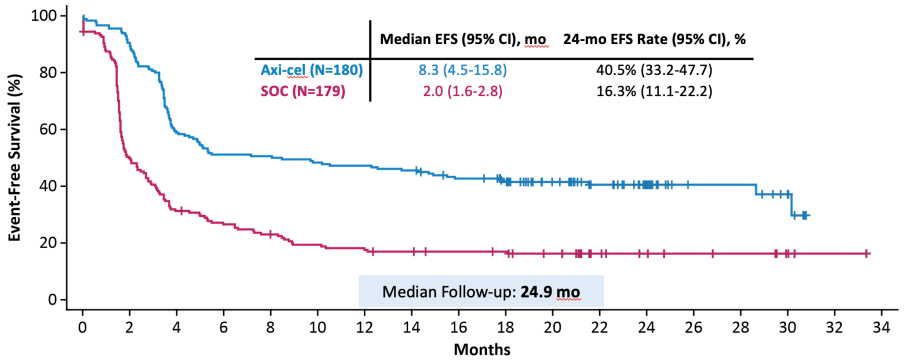


1-yr OS: 58%

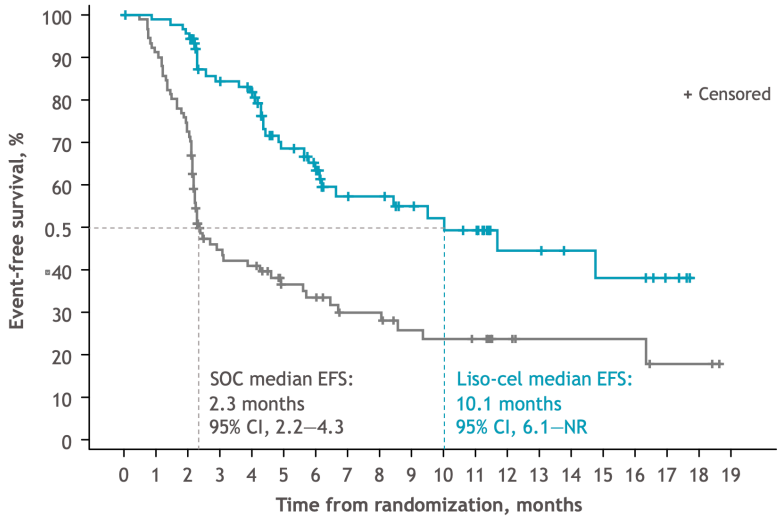
Neelapu SS, et al. *N Engl J Med*. 2017;377:2531.
Schuster SJ, et al. *N Engl J Med*. 2019;380:45.
Abramson JS, et al. *Lancet*. 2019;396:839.

CAR T-cell Therapy in R/R DLBCL—2nd Line

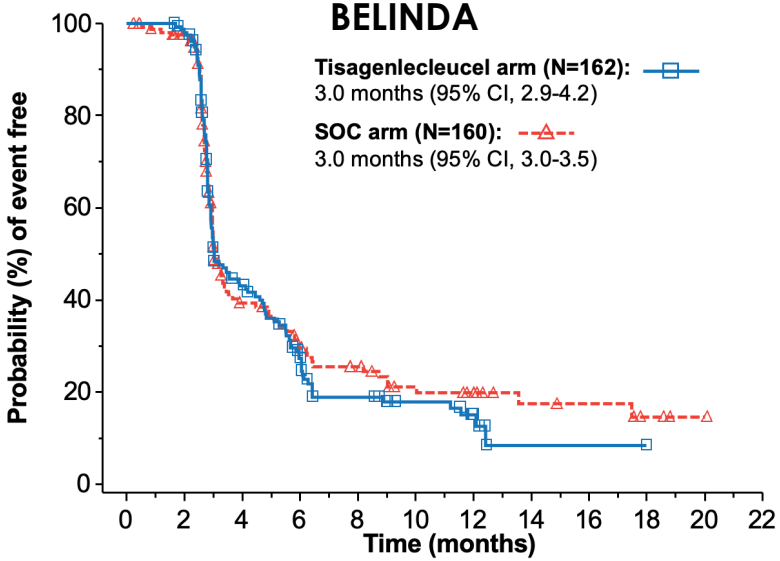
ZUMA-7



TRANSFORM



BELINDA



	Trial	Median EFS, m		CR rate		2-yr OS		Median f/u, m
		CAR-T	SOC	CAR-T	SOC	CAR-T	SOC	
-	BELINDA	3	3	28%	28%	Not reached		10
+	ZUMA-7	8.3	2	65%	32%	61%	52%	24.9
+	TRANSFORM	10.1	2.3	66%	39%	Not reached		6.2

Locke FL, et al. *N Engl J Med*. 2021; Dec 11.
Kamdar M, et al. *Blood*. 2021;138(suppl 1):91.
Bishop MR, et al. *N Engl J Med*. 2021;Dec 14.

CAR T-cell approval in 2nd line R/R DLBCL

FDA approves axicabtagene ciloleucel for second-line treatment of large B-cell lymphoma

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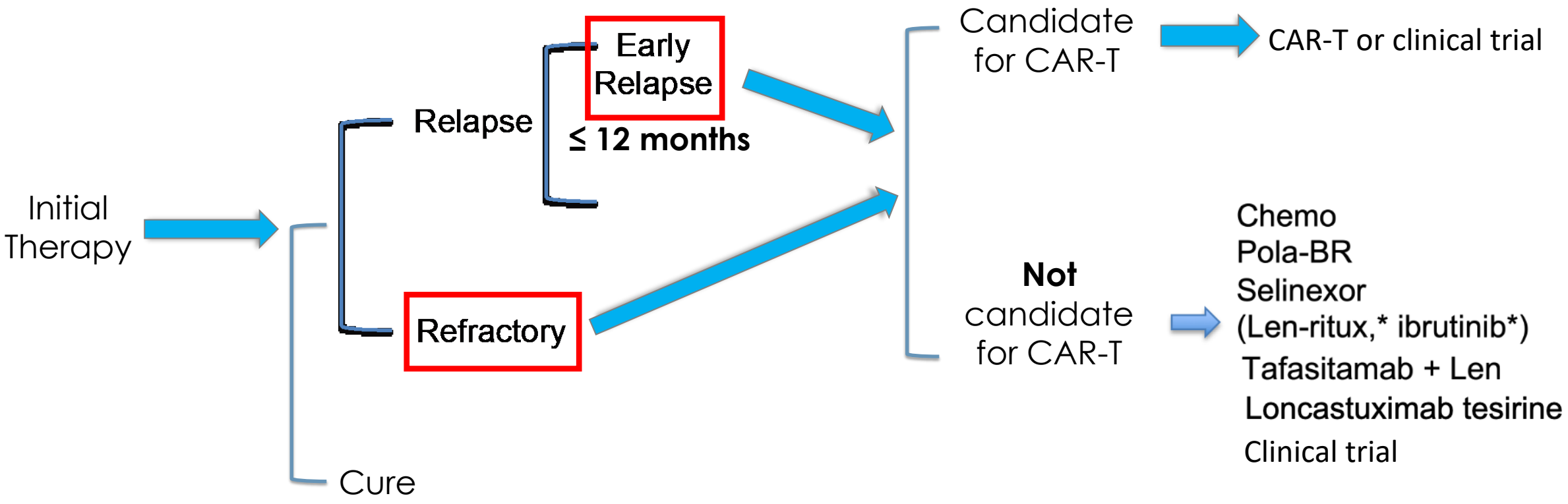
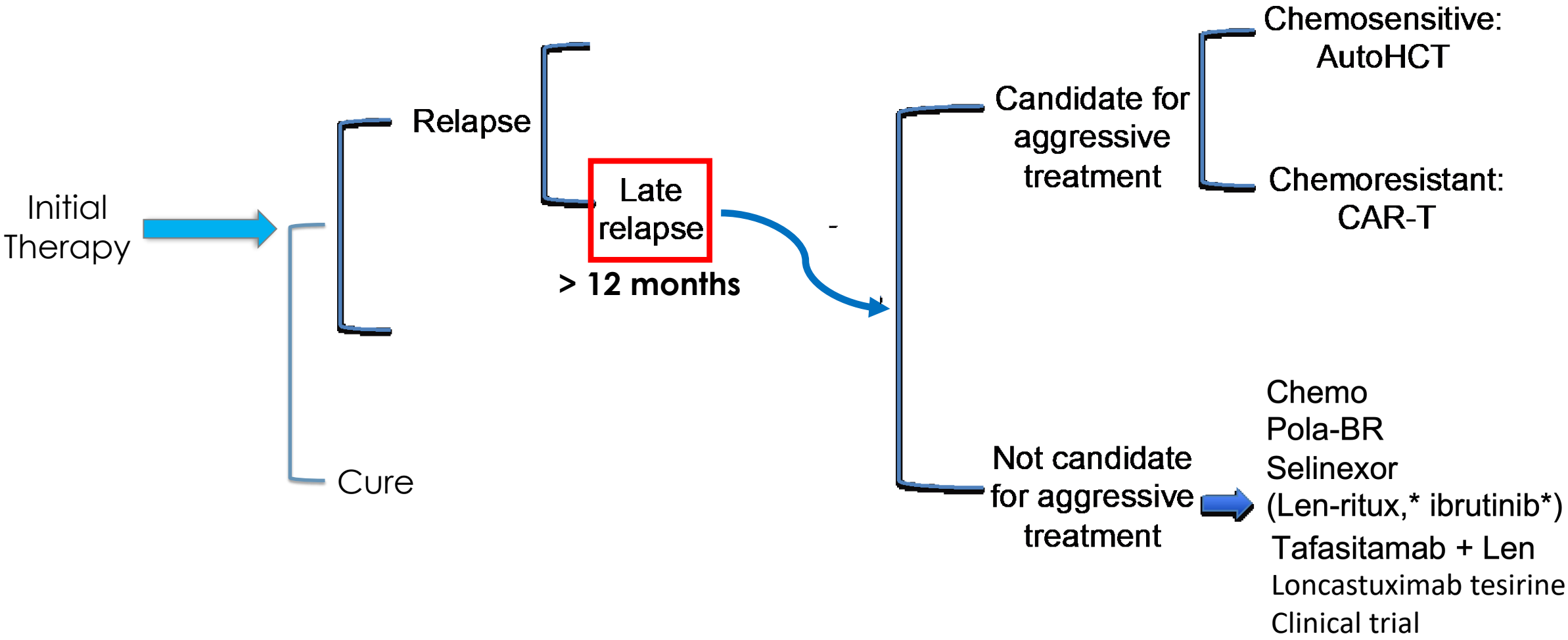
On April 1, 2022, the Food and Drug Administration approved axicabtagene ciloleucel (Yescarta, Kite Pharma, Inc.) for adult patients with large B-cell lymphoma (LBCL) that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy. It is not indicated for the treatment of patients with primary central nervous system lymphoma.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-second-line-treatment-large-b-cell-lymphoma

Treatment Algorithm for DLBCL in 2022



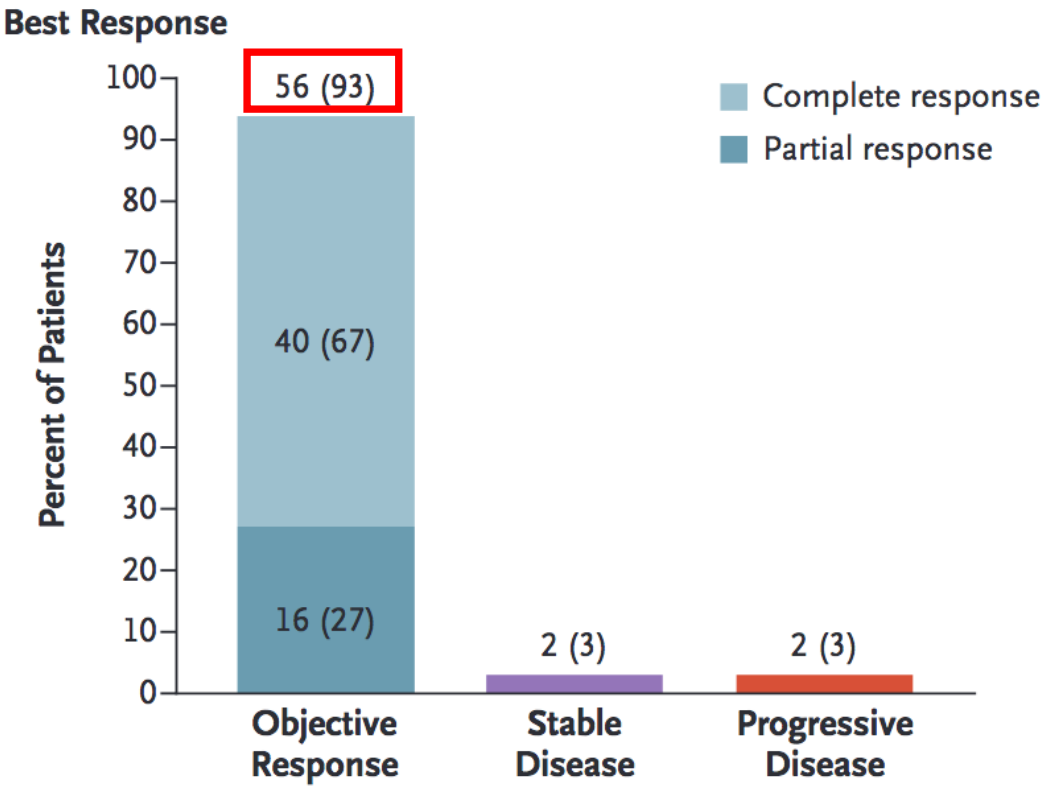
Treatment Algorithm for DLBCL in 2022



CAR-T in MCL: ZUMA-2 Study of Brexucabtagene autoleucel (brexu-cel) in R/R MCL

Table 1. Baseline Characteristics of All 68 Treated Patients.*

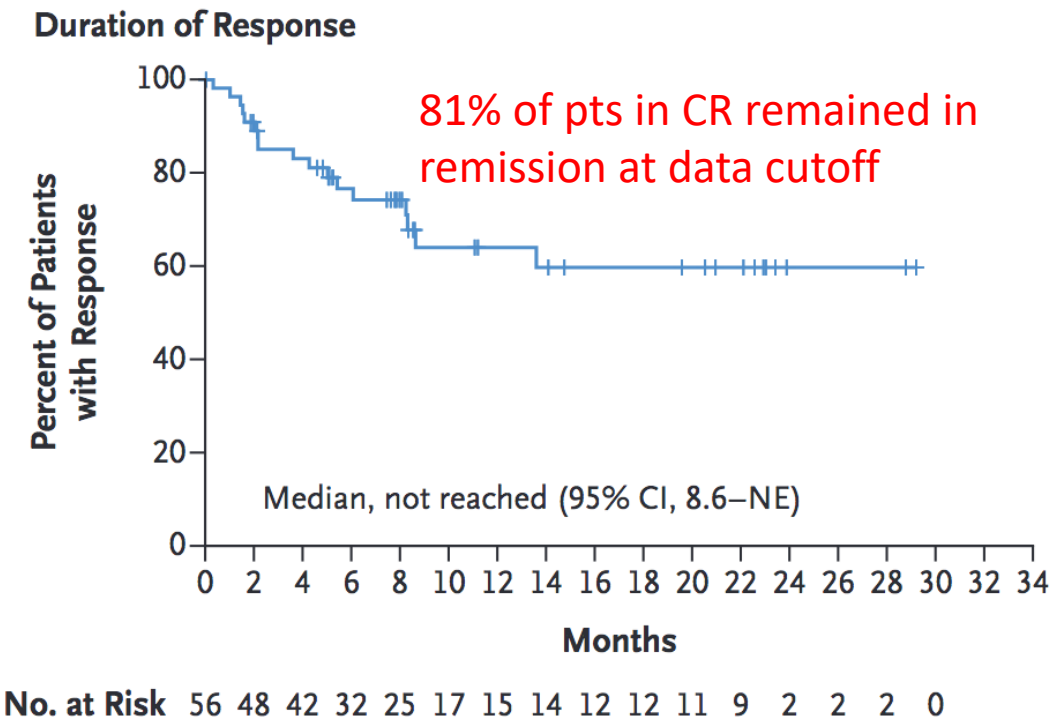
Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)

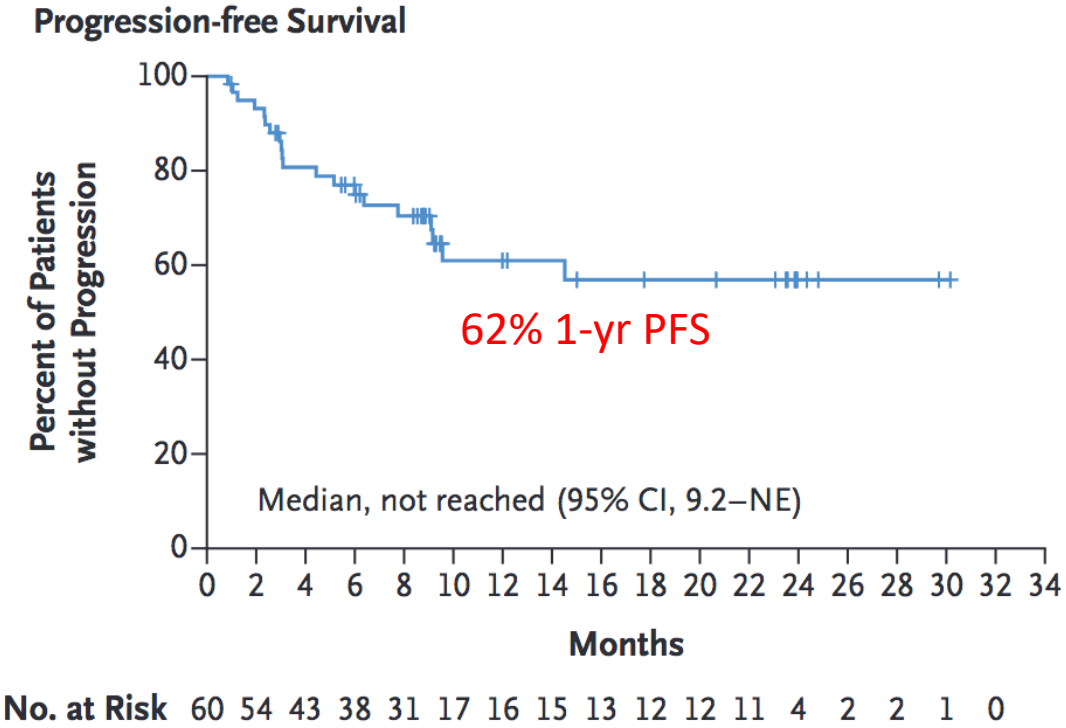


Wang M, et al. *N Engl J Med.* 2020;382:1331

CAR-T in MCL: ZUMA-2 Study of Brexucabtagene autoleucel (brexu-cel) in R/R MCL

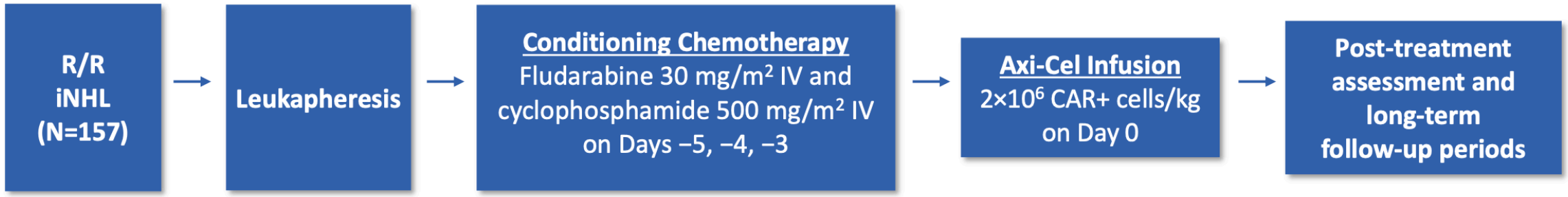
- Median follow-up: 12.3m





Wang M, et al. *N Engl J Med.* 2020;382:1331

CAR-T in Indolent NHL: ZUMA-5 Study of Axi-cel



Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)[a]
- ≥2 Prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary Endpoint

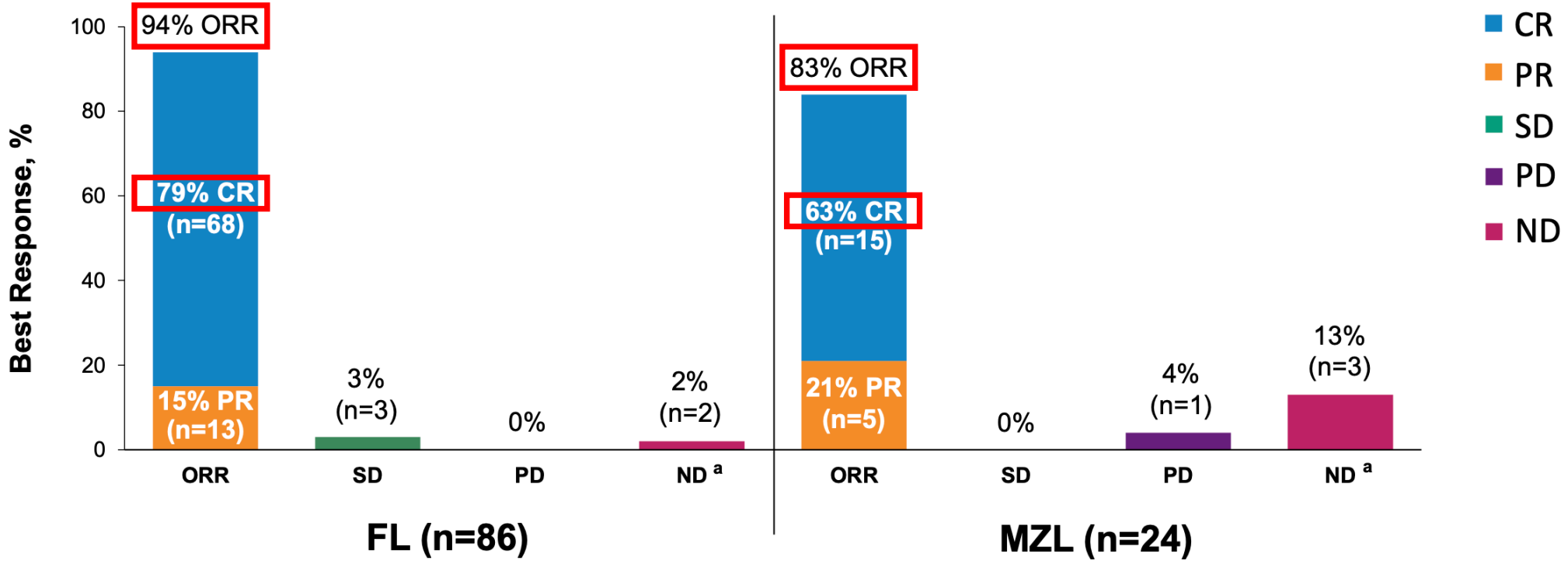
- ORR (IRRC assessed per the Lugano classification[1])

Key Secondary Endpoints

- CR rate (IRRC assessed)
- Investigator-assessed ORR[a]
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

Neelapu et al, #93 ASH 2021

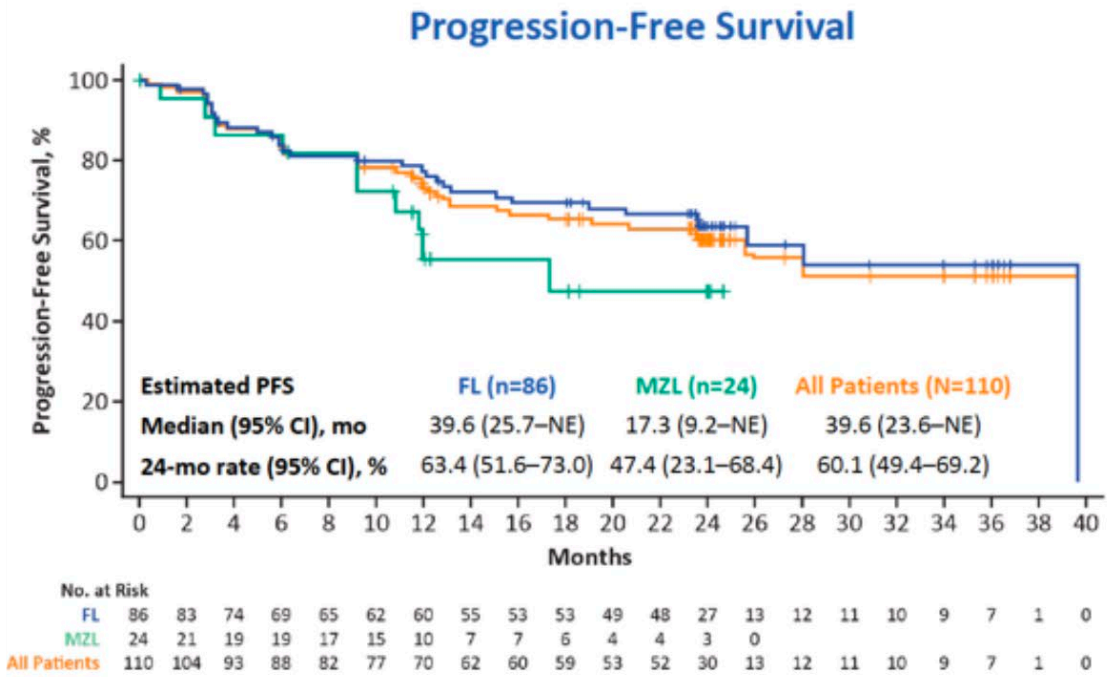
CAR-T in Indolent NHL: ZUMA-5 Study of Axi-cel

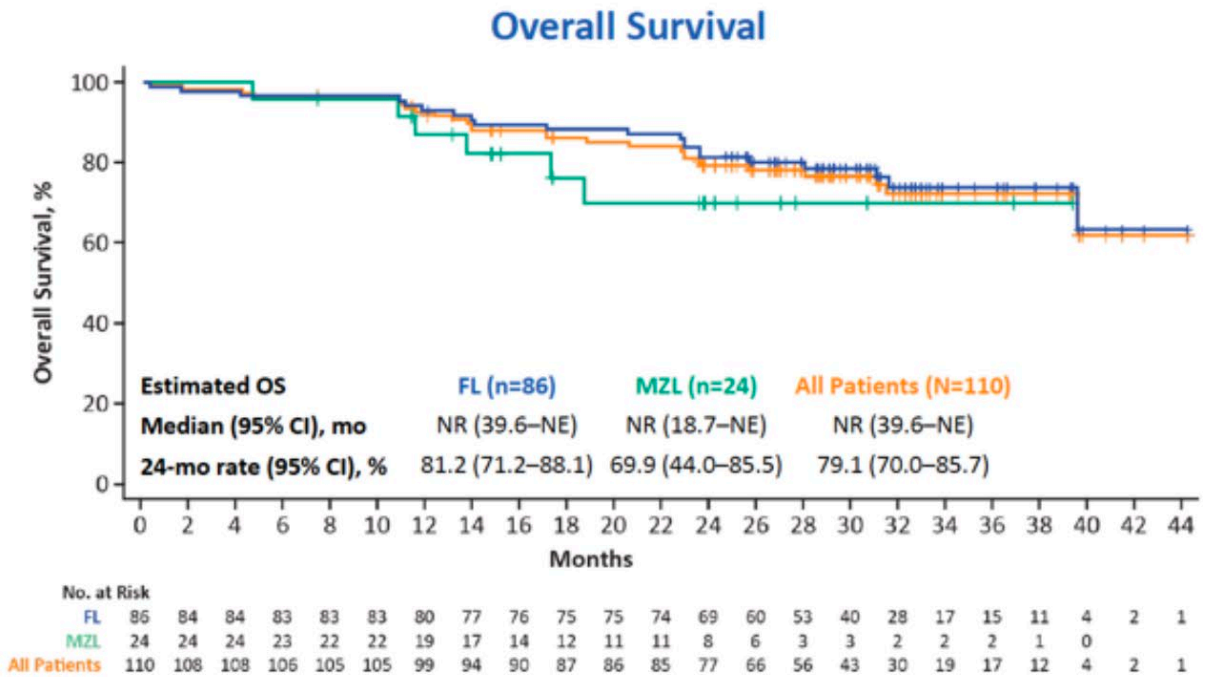


- In iNHL, efficacy evaluable population: ORR 92% (CR 75%)

Neelapu et al, #93 ASH 2021

CAR-T in Indolent NHL: ZUMA-5 Study of Axi-cel

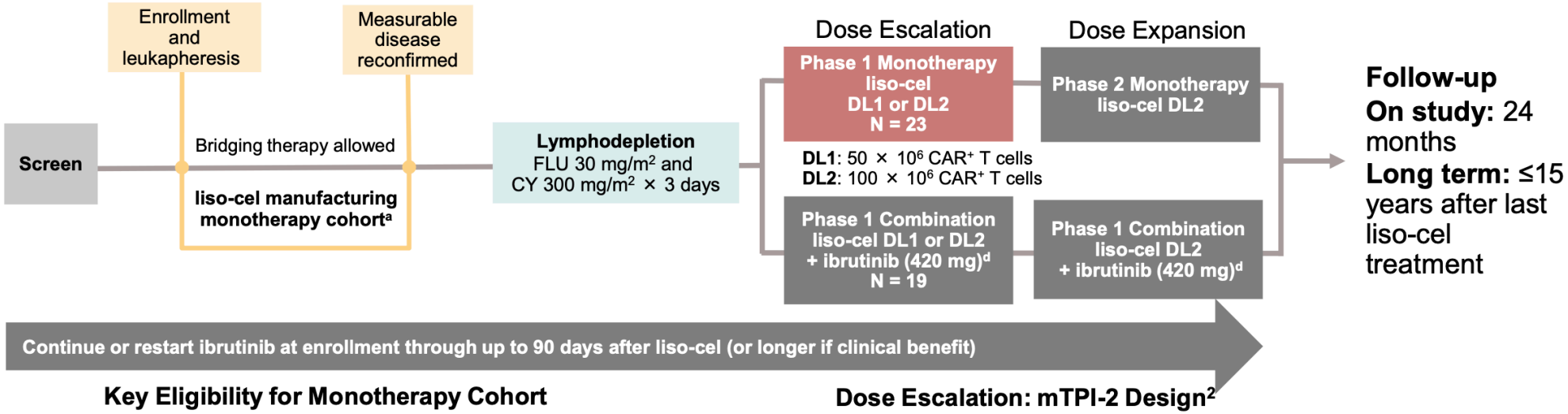




- Median OS not reached in FL or MZL
- Among patients with FL, 3 deaths occurred after Month 24; no PD observed after Month 24

Neelapu et al, #93 ASH 2021

CAR-T in CLL/SLL: TRANSCEND CLL 004 Phase 1/2 Study with liso-cel



Key Eligibility for Monotherapy Cohort

- R/R CLL/SLL
- Ineligible for BTKi or prior BTKi failure[b]
- High-risk disease[c]: ≥2 prior therapies failed
- Standard-risk disease: ≥3 prior therapies failed
- ECOG PS of 0—1

Dose Escalation: mTPI-2 Design[2]

28-day dose-limiting toxicity period

Primary objectives

- Safety
- Determine recommended dose

Exploratory objectives

- Antitumor activity (iwCLL 2018)[3]
  - Testing for MRD[e]
- Cellular kinetic profile (qPCR)

Siddiqi et al, #546 ASH 2020

CAR-T in CLL/SLL: TRANSCEND CLL 004 Phase 1/2 Study with liso-cel

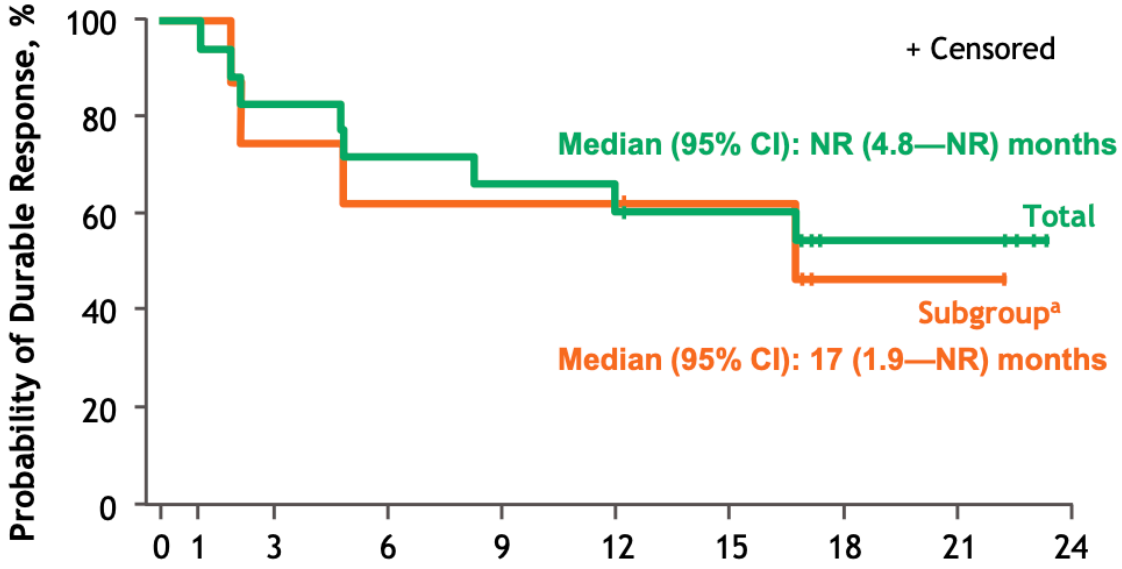
Characteristic	Monotherapy Cohort (N = 23)	BTKi Progression/Venetoclax Failure Subgroup[c] (n = 11)
Median age, y (range)	66 (50–80)	68 (59–76)
Male, n (%)	11 (48)	6 (55)
Median time since diagnosis, mo (range)	87.5 (30–209)	106 (30–209)
Bulky disease ≥5 cm, n (%)[a]	8 (35)	4 (36)
Median SPD, cm^2 (range)	25 (2–197)	41 (2—197)
Median BALL risk score[1] (range)	2 (0–3)	2 (0–3)
Median LDH, U/L (range)	235 (1–1956)	240 (1–1956)
Stage, n (%)		
Rai stage III/IV	15 (65)	7 (64)
Binet stage C	16 (70)	8 (73)
High-risk feature (any), n (%)	19 (83)	10 (91)
Del(17p)	8 (35)	4 (36)
TP53 mutated	14 (61)	8 (73)
Complex karyotype[b]	11 (48)	5 (45)
Median no. of lines of prior therapy (range)	4 (2–11)	5 (4–10)
Ibrutinib progression, n (%)	17 (74)	11 (100)
Ibrutinib intolerant, n (%)	6 (26)	0
Received bridging therapy, n (%)	17 (74)	8 (73)

Siddiqi et al, #546 ASH 2020

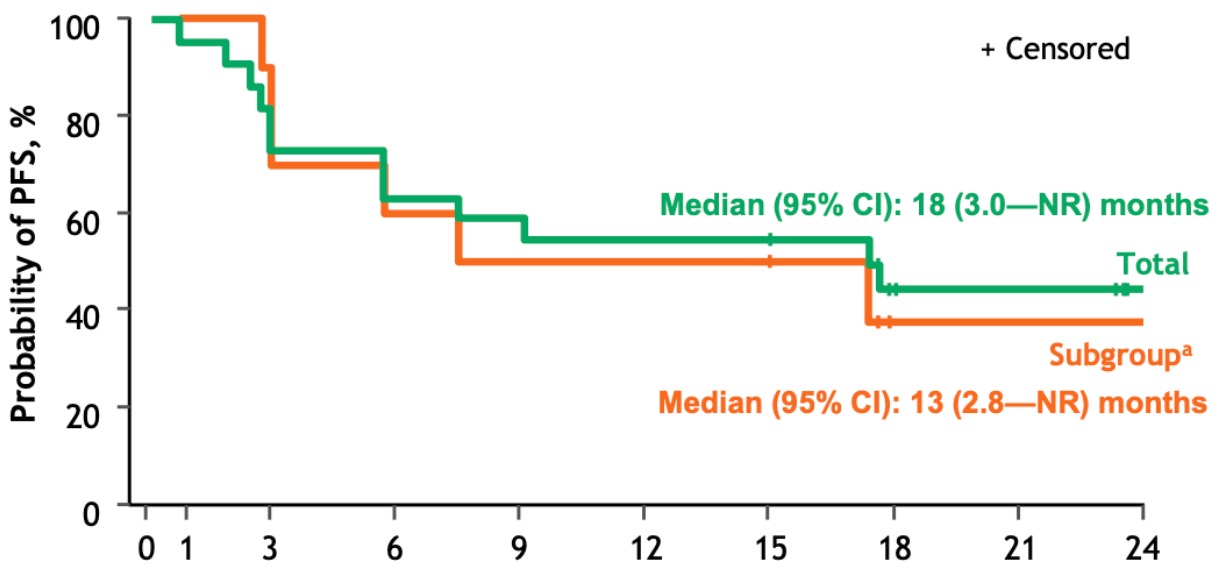
CAR-T in CLL/SLL: TRANSCEND CLL 004 Phase 1/2 Study with liso-cel

- ORR: 82% (CR/CRi 46%)
- 27% had a deepening of response
- At 12m, 50% were in response, only 2 pts progressed beyond 12m

Duration of Response



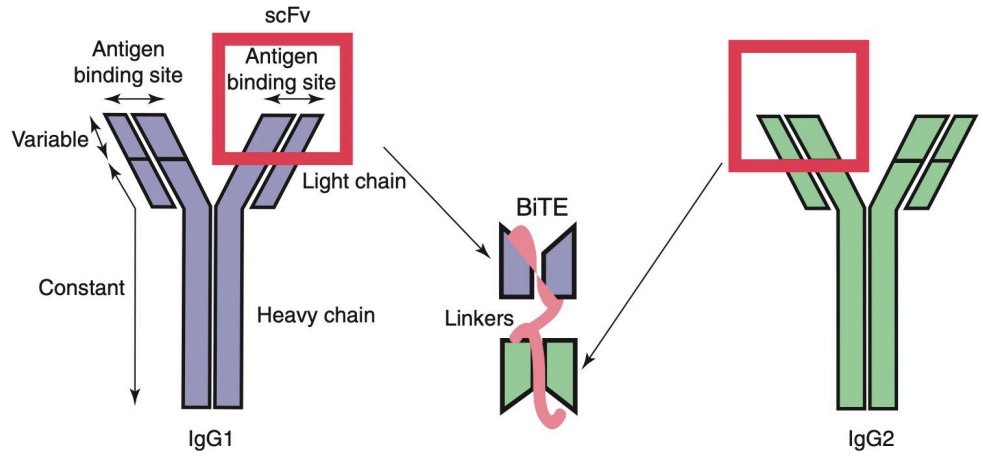
Progression-Free Survival

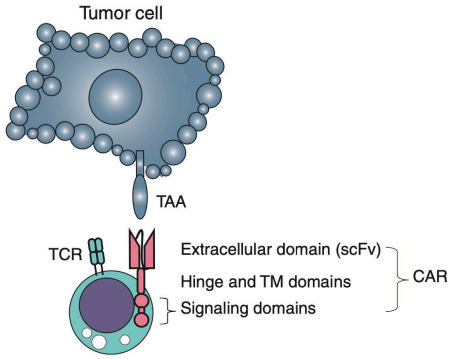


Siddiqi et al, #546 ASH 2020

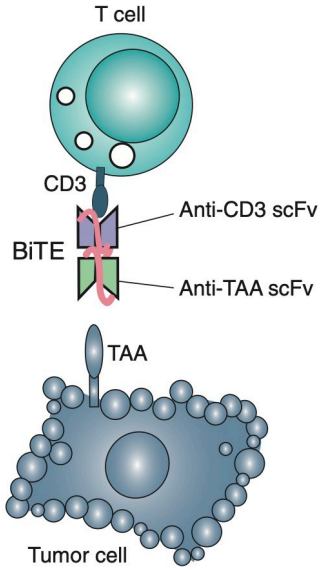
Bispecific Antibody Therapy

Bispecific Antibodies





CAR T-cell



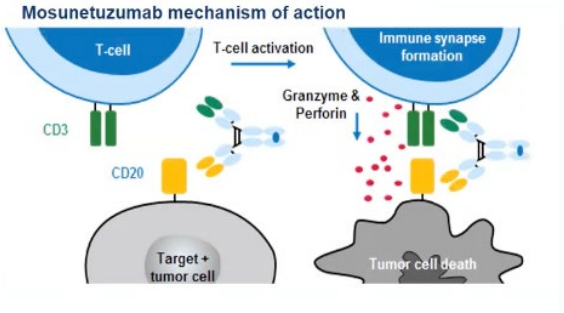
Bispecific Antibody Therapy

- Engineered antibodies to prolong half-life
- Targets CD3 (on T-cells) and CD20 (on B-cells)
- Induces T-cell mediated cytotoxic activity against CD20 expressing B-cells

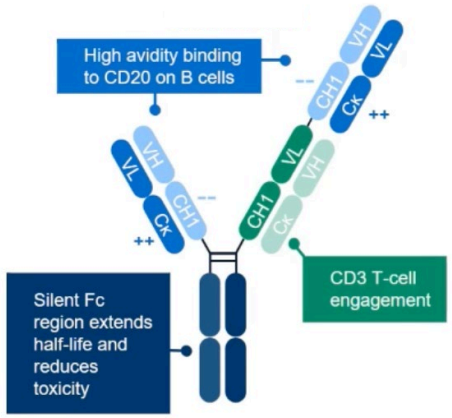
Slaney CY, *Cancer Discov.* 2018;8:924

CD3/CD20 Bispecific Antibodies in B-NHL

Mosunetuzumab

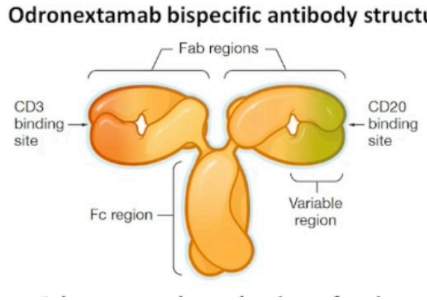


Glofitamab



Epcoritamab

Odronextamab

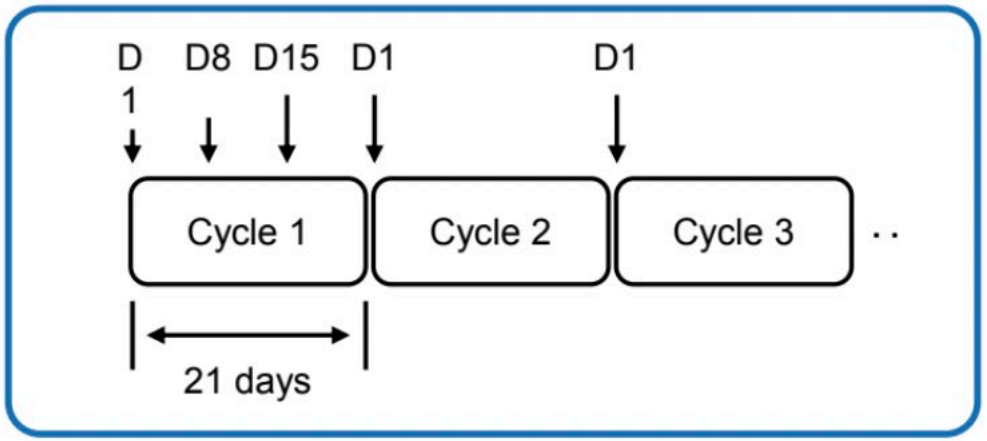


Plamotamab

- ”Off the shelf” therapy
- Route of administration: IV or SC
- Being explored in various subtypes of B-NHL

Mosunetuzumab in R/R B-NHL

Administration Schedule



- IV outpatient administration
- Cycle 1 step-up dosing followed by fixed dosing
- Key inclusion:
  - R/R B-NHL after ≥1 prior regimen
  - ECOG 0-1
  - No viable therapeutic options

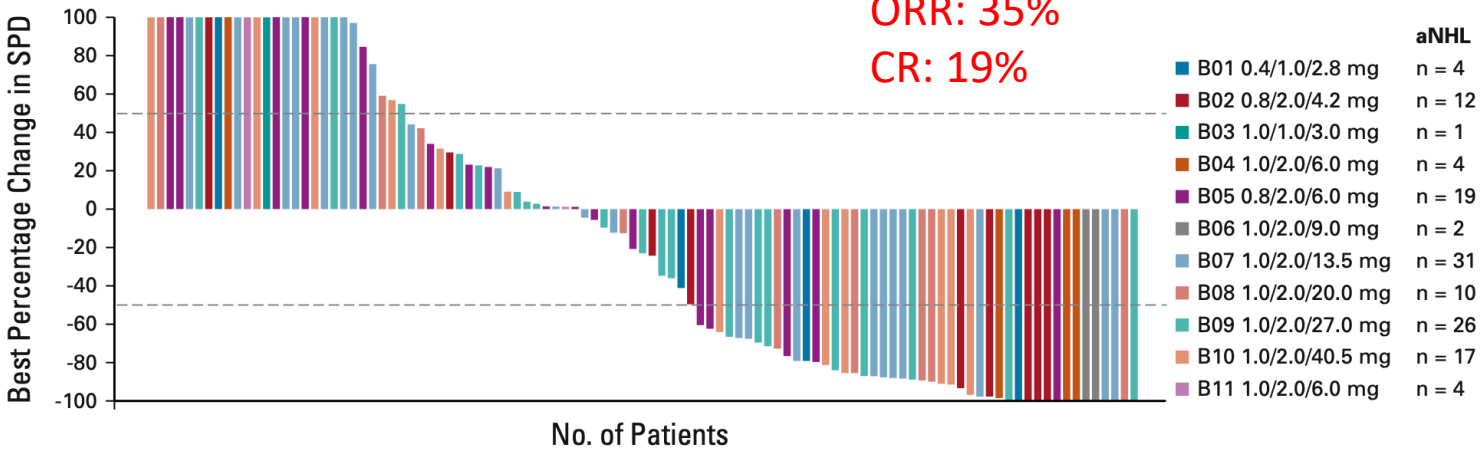
- Initial treatment= 8 cycles; if CR then d/c
  - If PR/SD then continue up to 17 cycles

Characteristic	Aggressive NHL[a] (n = 129)	Indolent NHL[b] (n = 68)
Age, years		
Median	63.0	60.5
Range	19-91	27-85
Prior systemic therapies, No.		
Median	3	3
Range	1-14	1-11
Prior CAR-T therapy, No. (%)	15 (11.6)	4 (5.9)
Prior autologous stem-cell transplant, No. (%)	44 (34.1)	12 (17.6)
Refractory to last therapy, No. (%)[d]	106 (82.2)	43 (63.2)
Refractory to prior anti-CD20 therapy, No. (%)[d]	100 (77.5)	51 (75.0)

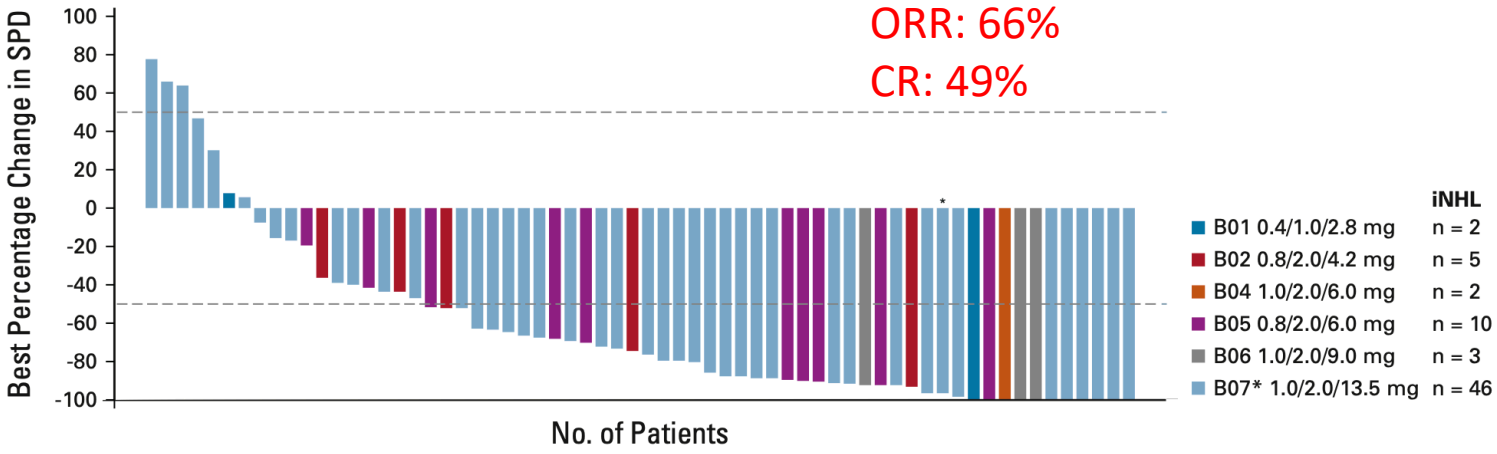
Budd LE, *J Clin Oncol.* 2022;40:481

Mosunetuzumab in R/R B-NHL

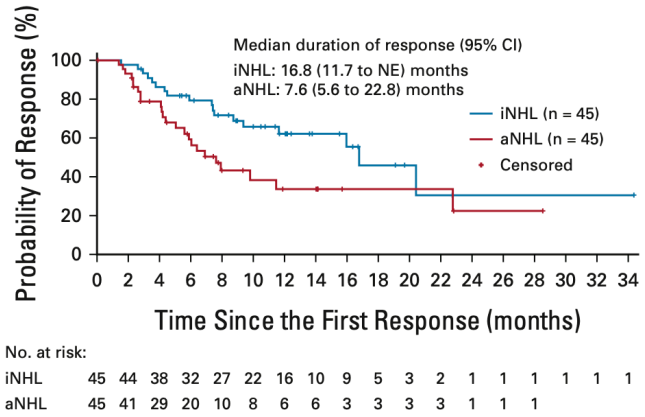
Aggressive B-NHL



Indolent B-NHL



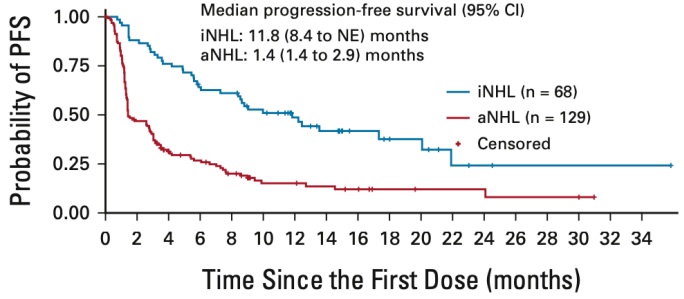
Duration of Response



No. at risk:

iNHL	45	44	38	32	27	22	16	10	9	5	3	2	1	1	1	1	1
aNHL	45	41	29	20	10	8	6	6	3	3	3	3	1	1	1		

Progression-Free Survival

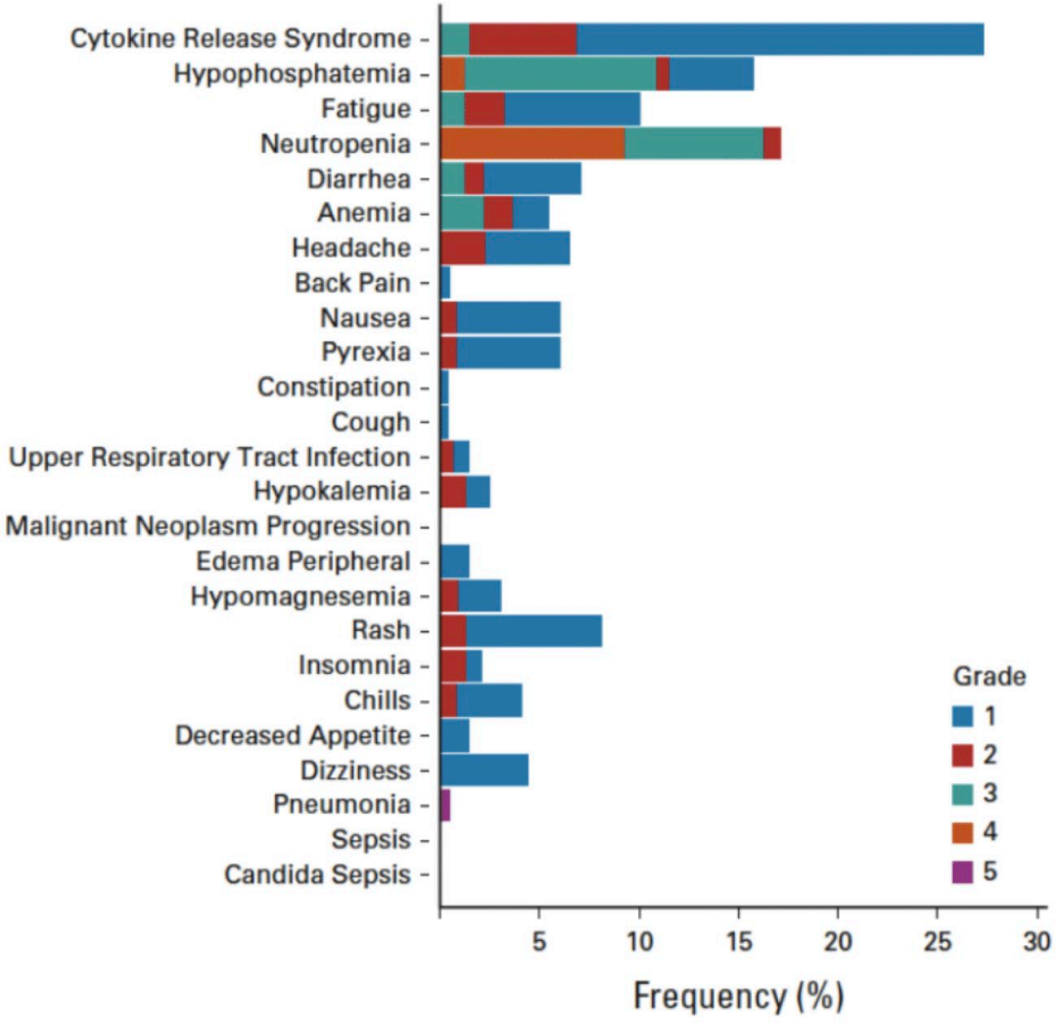


No. at risk:

iNHL	68	59	51	42	40	29	22	17	10	8	7	3	2	1	1	1	1
aNHL	129	58	35	29	20	11	11	9	7	4	3	3	3	2	2	2	0

Budd LE, *J Clin Oncol.* 2022;40:481

Mosunetuzumab in R/R B-NHL



- CRS:
  - All Grade: 27%
  - Grade 1: 21%
  - Grade 2: 6%
  - **Grade 3: 1%**
- Tocilizumab used in 3 patients

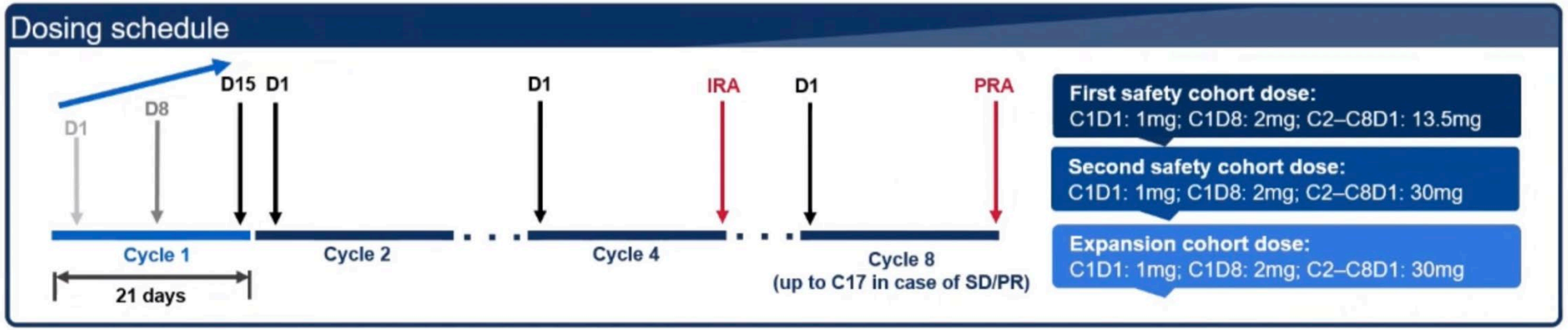
- Neurologic toxicity:
  - Headache: 18%
  - Insomnia: 11%
  - Dizziness: 10%
  - **Grade 3: 1%**

Budd LE, *J Clin Oncol*. 2022;40:481

Single-Agent Mosunetuzumab a Chemotherapy-Free Regimen for Elderly/Unfit Patients with Previously Untreated DLBCL

- Key Inclusion Criteria
  - Treatment naïve DLBCL or HGBL
  - Age ≥ 80 yrs or 60-79 yrs w/ impairment in ≥1 of the following:
    - ADL
    - Instrumental ADL
    - Inability to tolerate full dose chemoimmunotherapy
- Study Design
  - Optional pre-phase prednisone +/- vincristine
  - Response assessment: at cycle 4, cycle 8, every 6 months

- Primary Objectives
  - PET/CT CR rate
  - Safety/tolerability
  - PK
- N=29
  - 2 dosing cohorts
  - 22 efficacy evaluable

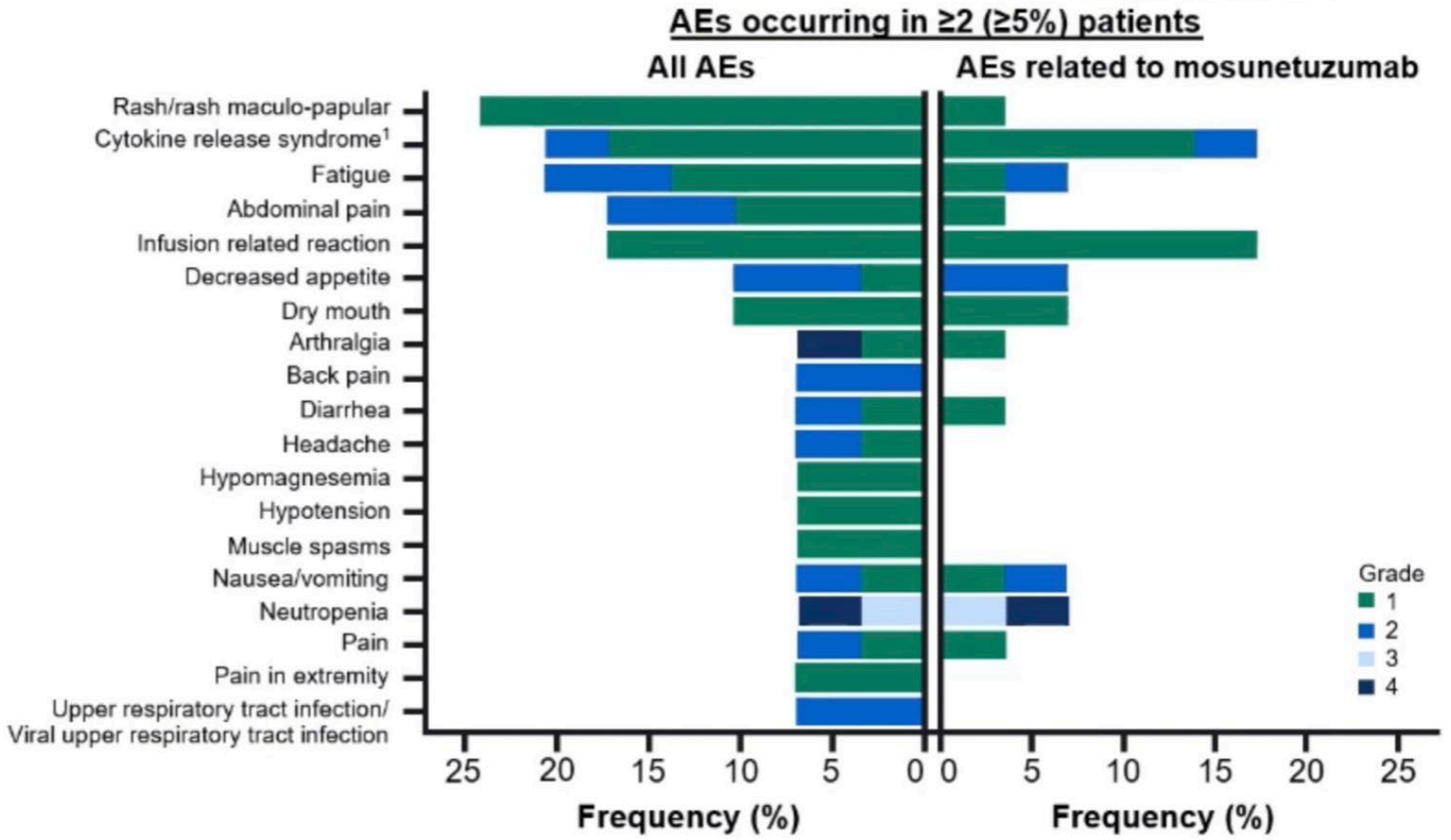


Olszewski et al #401 ASH 2020

Single-Agent Mosunetuzumab a Chemotherapy-Free Regimen for Elderly/Unfit Patients with Previously Untreated DLBCL

Summary of AEs, n (%)	1L DLBCL (N=29)
Any AE Treatment related	25 (86) 17 (59)
Serious AE Treatment related*	8 (28) 4 (14)
Grade 3–4 AE Treatment related†	9 (31) 4 (14)
Grade 5 (fatal) AE	0
AE leading to treatment discontinuation	0

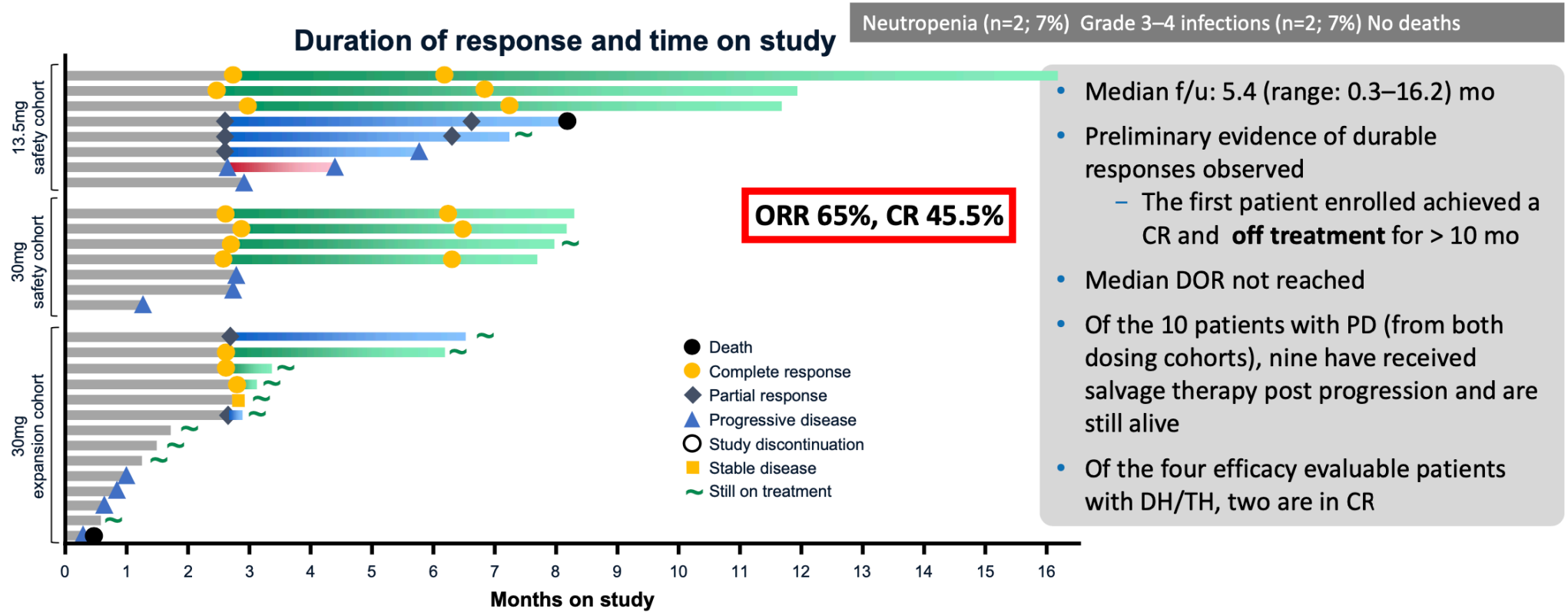
Low rates of neutropenia (n=2; 7%) and Grade 3–4 infections (n=2; 7%) were observed



- Manageable safety profile in elderly/unfit patients
  - No G3-4 CRS

Olszewski et al #401 ASH 2020

Early durable CRs with mosunetuzumab in elderly/unfit 1L DLBCL



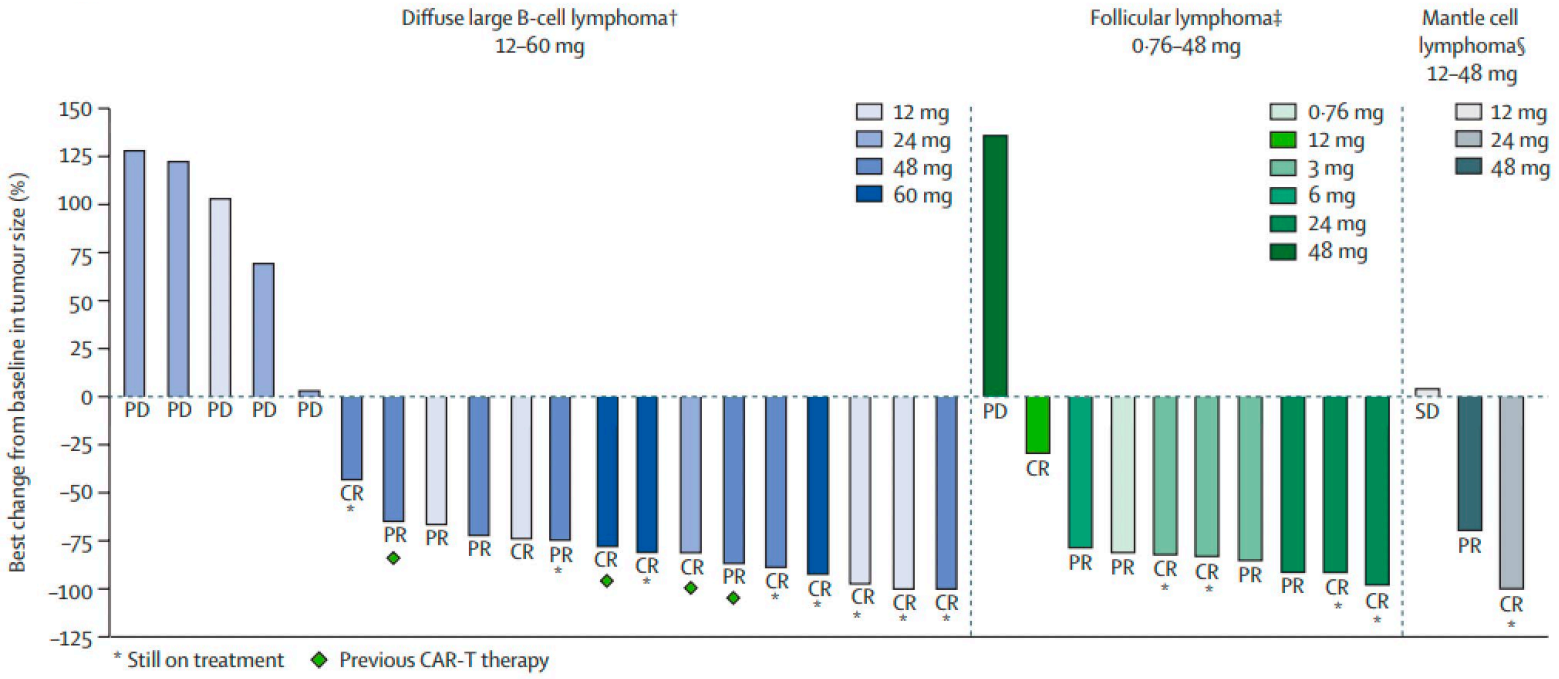
Neutropenia (n=2; 7%) Grade 3–4 infections (n=2; 7%) No deaths

- Median f/u: 5.4 (range: 0.3–16.2) mo
- Preliminary evidence of durable responses observed
  - The first patient enrolled achieved a CR and **off treatment** for > 10 mo
- Median DOR not reached
- Of the 10 patients with PD (from both dosing cohorts), nine have received salvage therapy post progression and are still alive
- Of the four efficacy evaluable patients with DH/TH, two are in CR

- No PD in patients achieving CR

Olszewski et al #401 ASH 2020

Epcoritamab in R/R B-NHL



	Grade 1–2	Grade 3	Grade 4
Pyrexia*	43 (63%)	4 (6%)	0
Cytokine release syndrome	40 (59%)	0	0
Injection site reaction	32 (47%)	0	0
Fatigue	26 (38%)	4 (6%)	0
Diarrhoea	18 (26%)	0	0
Hypotension*	17 (25%)	4 (6%)	0
Dyspnoea	16 (24%)	0	1 (1%)
Tachycardia*	14 (21%)	0	0
Anaemia	7 (10%)	9 (13%)	0

*Most pyrexia, hypotension, and tachycardia events were associated with cytokine release syndrome.

Table 2: **Treatment-emergent adverse events that occurred in at least 20% of the full analysis population (n=68)**

- Subcutaneous step-up administration
- DLBCL ORR: 68% (CR 45%)
- FL ORR: 90% (CR 50%)

Hutchings M, *Lancet*. 2021;398:1157

Epcoritamab + Lenalidomide and Rituximab (R^2) in R/R FL

Arm 2 of EPCORE NHL-2, a phase 1b/2, open-label, multicenter trial, is evaluating the safety and antitumor activity of SC epcoritamab + standard R^2 for 12 cycles of 28 days, followed by epcoritamab monotherapy for a total of 2 years, in adults with R/R FL[a]

Key inclusion criteria

- R/R $CD20^+$ FL
  - Grade 1, 2, or 3A
  - Stage II–IV
- Need for treatment based on symptoms or disease burden, as determined by GELF criteria[1]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Dose escalation → **Expansion**

Dose escalation		Expansion	
Dose level 1: Epcoritamab 24 mg QW C1–3, Q2W C4–9, Q4W C10+ **+ R^2** C1–12	**Dose level 2: Epcoritamab 48 mg** QW C1–3, Q2W C4–9, Q4W C10+ **+ R^2** C1–12	**Cohort 2a: Epcoritamab 48 mg** QW C1–3, Q2W C4–9, Q4W C10+ **+ R^2** C1–12	**Cohort 2b: Epcoritamab 48 mg** QW C1–2, Q4W C3–26 **+ R^2** C1–12
n=3 enrolled	n=3 enrolled	n=23 enrolled	n≈80 planned
Primary objectives: DLT/Safety and tolerability **Key secondary objective:** Antitumor activity[b]		**Primary objective:** Antitumor activity[b]	

Linton KM, et al #3535 ASH 2021

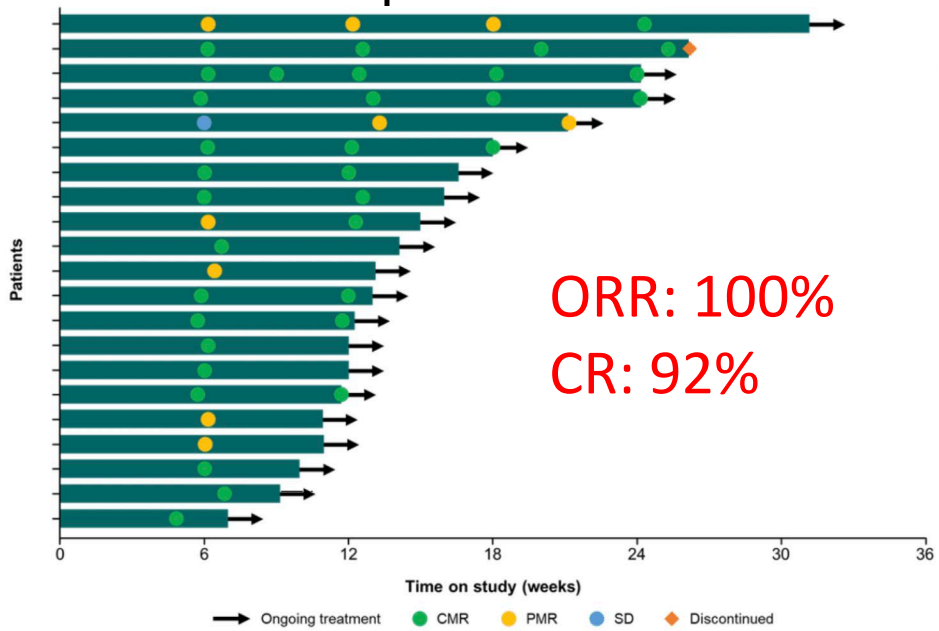
Epcoritamab + R^2 in R/R FL

Treatment-Related Adverse Events

TEAE ≥15%, n (%)	Total N=29			
	Grade 1–2	Grade 3	Grade 4	Any grade
CRS	12 (41)	2 (7)	0	14 (48)
Injection-site reaction[a]	12 (41)	0	0	12 (41)
All infections[b]	9 (31)	2 (7)	0	11 (38)
Constipation	8 (28)	0	0	8 (28)
Cough	8 (28)	0	0	8 (28)
Fatigue	6 (21)	1 (3)	0	7 (24)
Nausea	7 (24)	0	0	7 (24)
Muscle spasms	6 (21)	0	0	6 (21)
Neutropenia[c]	1 (3)	4 (14)	1 (3)	6 (21)
Tremor	5 (17)	0	0	5 (17)

Data cutoff: September 16, 2021. [a]Combined term includes injection-site reaction, erythema, pain, and rash. [b]Includes all events under the System Organ Class of infections and infestations; cellulitis, conjunctivitis, device-related infection, infection, mucosal infection, nasopharyngitis, neuroborreliosis, oral fungal infection, oral herpes, pneumonia, rhinovirus infection, sinusitis, staphylococcal infection, tinea pedis, and urinary tract infection (each n=1 [3%]). Three grade 3 infections were observed in a total of 2 patients overall: cellulitis, neuroborreliosis, and pneumonia. [c]Combined term includes neutropenia and neutrophil count decreased; 1 patient (3%) had febrile neutropenia.

Response Profile



ORR: 100%

CR: 92%

- No DLTs reported for epcoritamab
- No ICANS or clinical TLS

- 95% of responders remained in response

Linton KM, et al #3535 ASH 2021

Bispecific Antibody combinations in B-NHL

- Immunomodulatory drugs
  - Lenalidomide
- Targeted agents
  - BTKi
- Antibody-drug conjugates
  - Polatuzumab Vedotin
- Standard chemoimmunotherapy
  - Front-line: Bispecific + R-CHOP
  - Salvage therapy: Platinum-based salvage therapy

CAR T-cell Therapy vs. Bispecific Antibodies

	CAR T-cell Therapy	BiTE Therapy
Lead Time	~4-8 weeks	Immediate use
Access	Specialized/Academic centers	Scalable. Maybe more conducive for treatment in community setting
Need for ongoing treatment	No	Yes
Treatment setting	Typically inpatient	Potentially inpatient for initial dose/cycle(s)
Lymphodepleting chemotherapy	Yes	No
CRS	++++	++
ICANS	+++	+
Cytopenias	+++	++
Less fit patients	Challenging	More feasible
Clinical Experience	+++	+

Adapted from Patel A, et al. *Br J Haemat.* 2021;195:689

Conclusions

The future is bright!

CAR T-cell therapy

- Emerged as a SOC in B-NHL
  - *DLBCL*: 2nd line primary refractory/early relapse (≤12m), and in 3rd line
  - *FL*: 3rd line
  - *MCL*: 2nd line
- Longer term follow-up and more clinical experience
- Drive to expand treatment landscape of CD19-directed CAR T-cell therapy in B-NHL

Bispecific antibody therapy

- CD20/CD3 bispecific antibody therapy is highly active in B-NHL
  - Impressive ORRs and CR rates, but longer f/u needed
  - Efficacy approaching results seen w/ CAR T
  - Favorable safety profile
    - Lower incidence/severity of CRS/ICANS vs CAR T

Unanswered Questions

1) How to approach patient selection for CAR-T vs bispecifics?
2) How do we best administer bispecific therapies?
   - IV vs SQ?
   - Optimal step-up dosing?
   - Combinations?
3) What duration of bispecific therapy is needed?
4) How do you sequence these therapies?
5) What are the mechanisms of relapse/resistance?