Nuove strategie terapeutiche anti-CD19 nel paziente ricaduto/refrattario DLBCL

Le alternative terapeutiche attuali

Enrico Derenzini

Divisione di Oncoematologia
Istituto Europeo di Oncologia

Dipartimento di Scienze della Salute
Universita' di Milano

MONDO LINFOMI:
UN'INCREDIBILE DINAMICITÀ

13 SETTEMBRE 2023
Starhotels E.c.Ho.

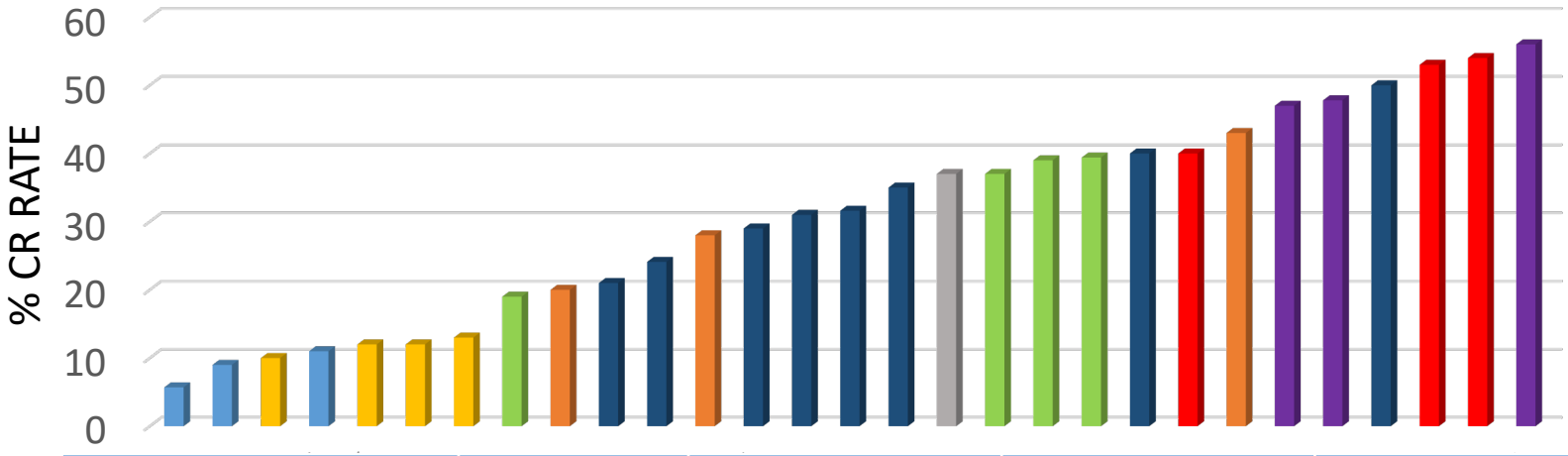
Milano

DICHIARAZIONE

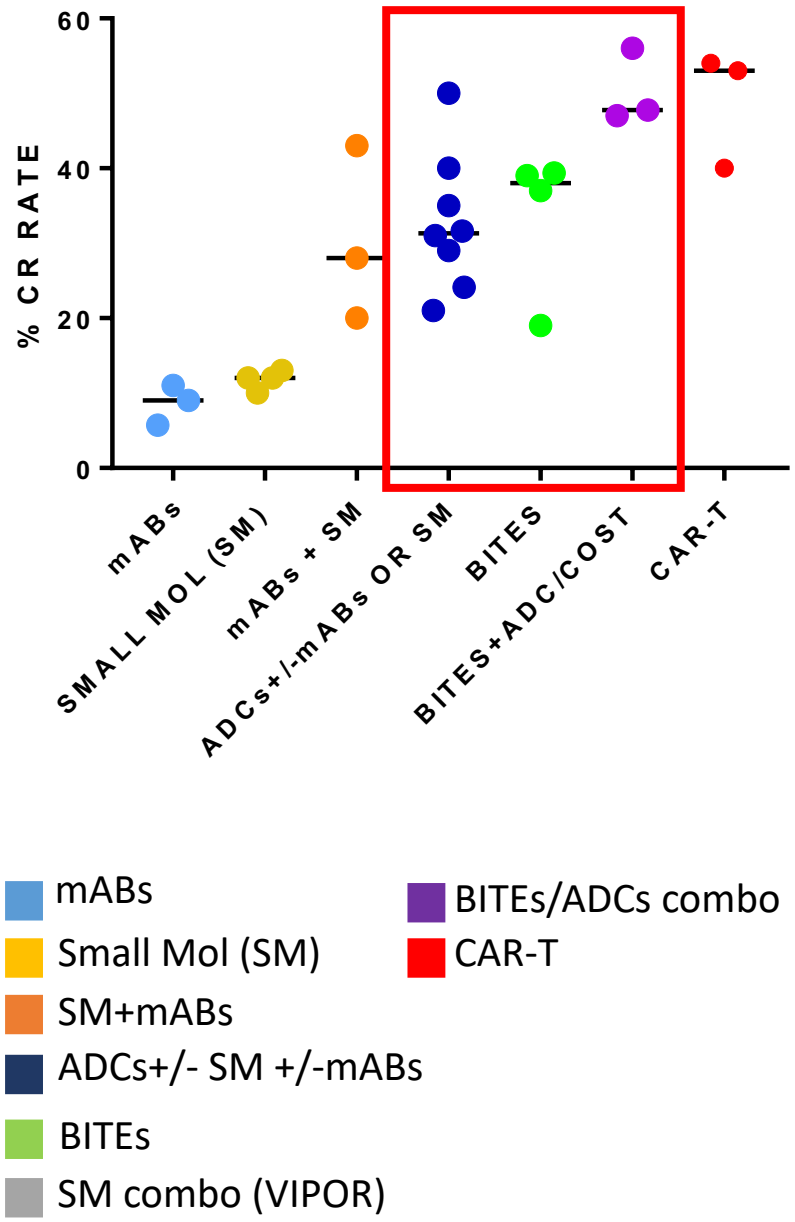
Relatore: Enrico Derenzini

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Roche, Astra Zeneca)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(ADC-Therapeutics, Takeda)**
- Partecipazione ad Advisory Board **(Roche, Astra-Zeneca, Takeda, Beigene, Gilead, Abbvie)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

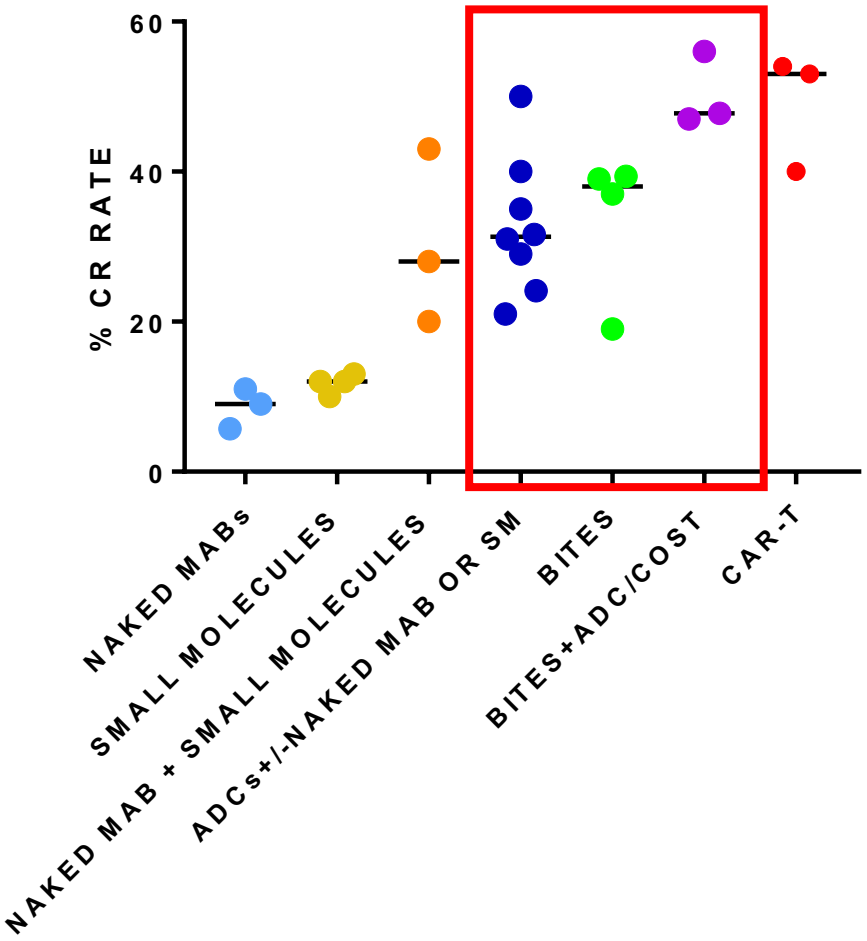


AGENT/REGIMEN	TARGET	TYPE	LINE OF THERAPY	FIRST LINE
AXICEL	CD19	CAR-T	>1 (R/R <12m), >2	YES (INVEST.)
LISOCEL	CD19	CAR-T	>1 (R/R <12m), >2	-
TISACEL	CD19	CAR-T	>2	-
TAFA-LEN	CD19	MAB	>1	YES (INVEST.)
LONCASTUXIMAB	CD19	ADC	>2	YES (INVEST.)
POLATUZUMAB-(B)R	CD79b	ADC	>1	YES APPROVED
GLOFITAMAB	CD20XCD3	BITE	>2	YES (INVEST.)
EPCORITAMAB	CD20XCD3	BITE	>2	YES (INVEST.)
ODRONEXTAMAB	CD20xCD3	BITE	-	YES (INSEST.)



NON CD19-ADCs (+MABs)

- POLATUZUMAB VEDOTIN
- NARATUXIMAB EMTANSINE
- BRENTUXIMAB VEDOTIN



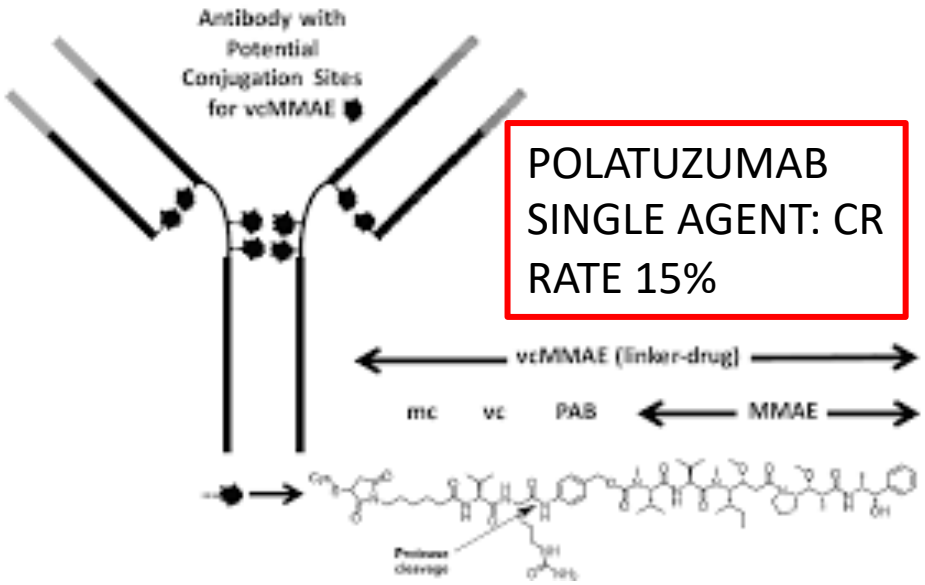
CD20xCD3 BITES

- GLOFITAMAB
- EPCORITAMAB
- ODRONEXTAMAB
- PLAMOTAMAB

COMBINATIONS

- ADCs + ADCs
- BITEs + ADCs
- BITEs + COST. MOLECULES

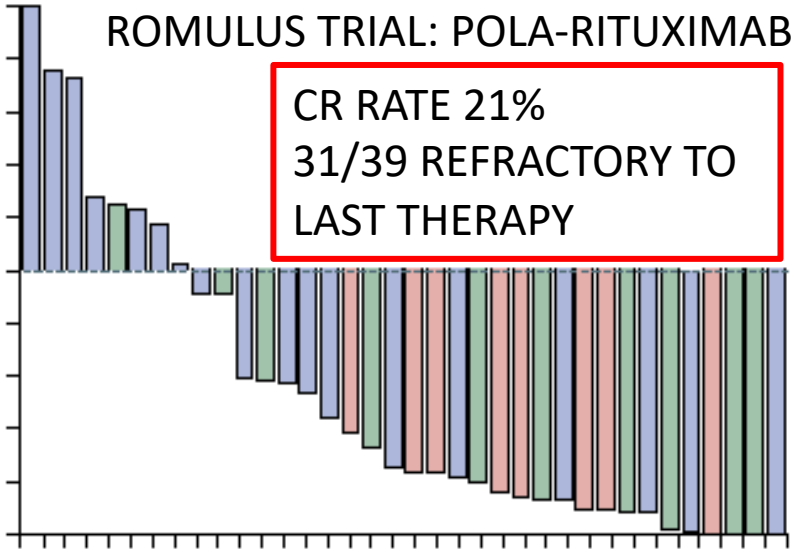
CD79b ADC Polatuzumab Vedotin



POLATUZUMAB SINGLE AGENT: CR RATE 15%

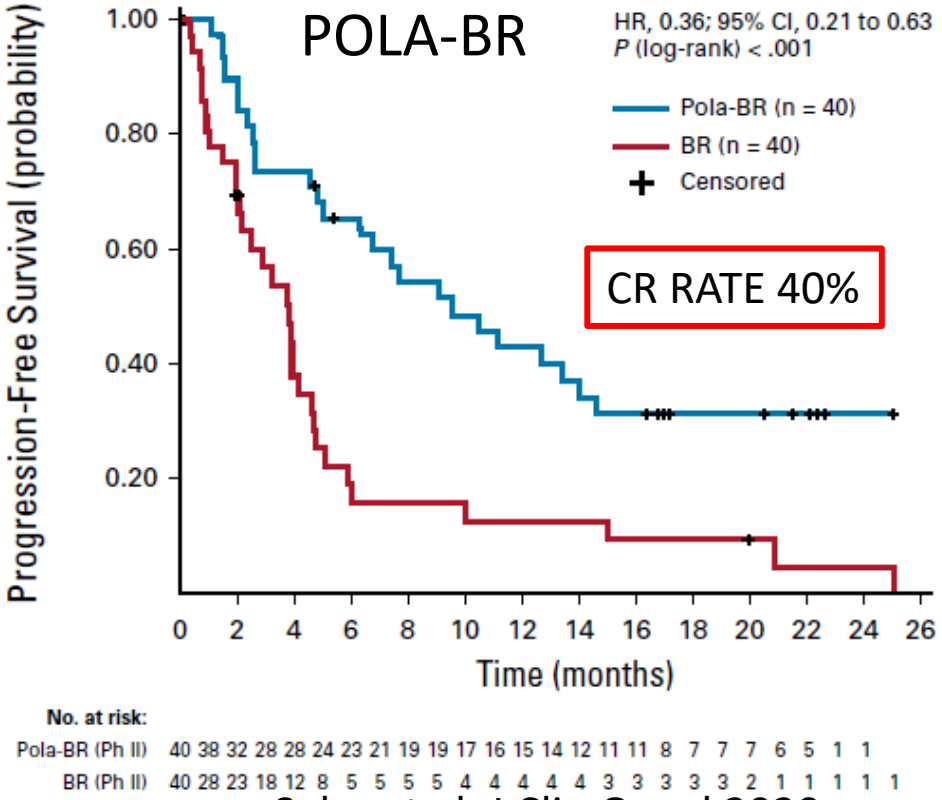
Palanca-Wessels et al. Lancet Oncology 2015

ROMULUS TRIAL: POLA-RITUXIMAB



CR RATE 21%
31/39 REFRACTORY TO LAST THERAPY

Morschhauser et al. Lancet Haematology 2019

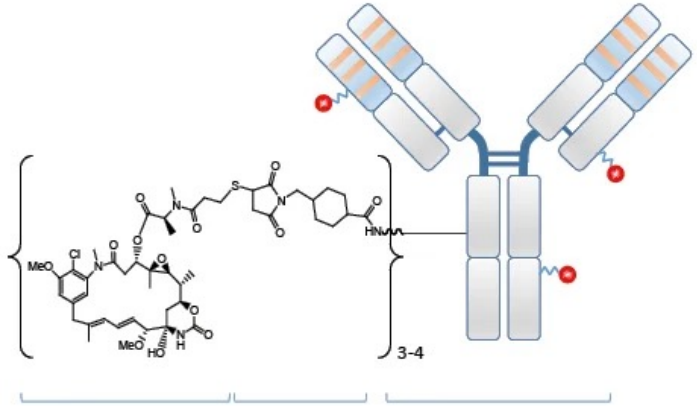


CR RATE 40%

Sehn et al. J Clin Oncol 2020

PHASE 2- RANDOMIZED TRIAL
80 PTS ENROLLED: POLA-BR=40; BR=40
75% REFRACTORY TO LAST THERAPY IN POLA-BR ARM

CD37 ADC Naratuximab Emtansine



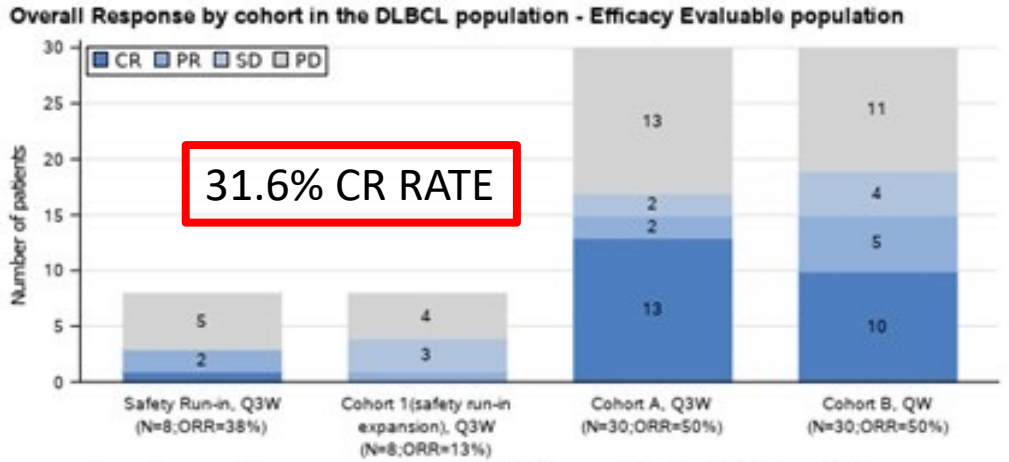
Part 1		Part 2
Safety run-in	**Run-in expansion**	
R/R NHL: •DLBCL: N=9 •Other NHL: N=8 •Q3W	Cohort 1: •R/R DLBCL: N=8 •Q3W Cohort 2: •Other R/R NHL: N=12 •Q3W	Cohort A: •DLBCL: N=33 •Q3W Cohort B: •DLBCL: N=30 •QW

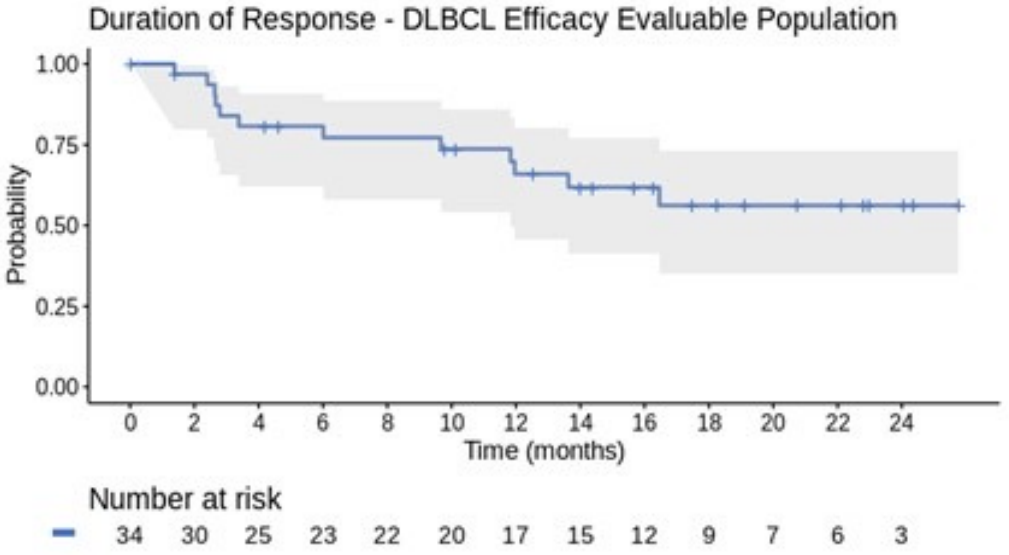
DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin's lymphoma; QW: 21-day cycles, nara on day 1, 0.4 mg/kg, and on days 8 and 15, 0.2 mg/kg, followed by rituximab 375 mg/m² on day 1; Q3W: 21-day cycles, nara on day 1, 0.7 mg/kg, followed by rituximab 375 mg/m²; R/R: relapsed/refractory

PHASE 2 NARA-RITUXIMAB COMBO

100 PTS ENROLLED
80 DLBCL

12.5% PRIMARY REFRACTORY





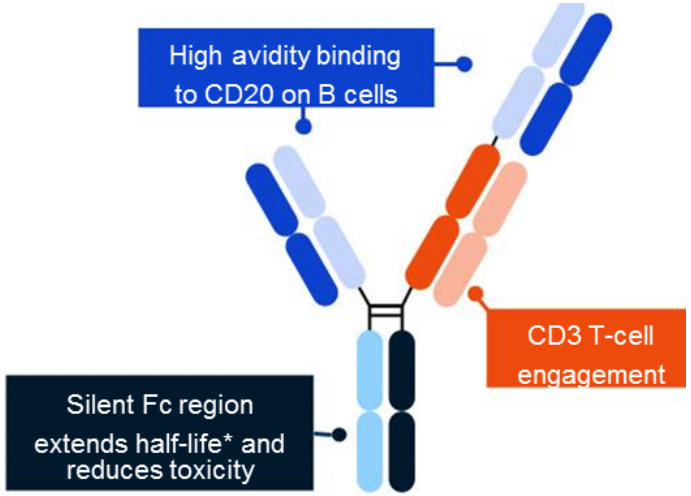
Levy et al, ASH 2021

CD20 x CD3

Dickinson M et al, ICML 2023

Dickinson MJ et al, N Eng J Med 2022

GLOFITAMAB



Pivotal Phase II study in patients with R/R LBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, trFL, or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - Anti-CD20 antibody
  - Anthracycline

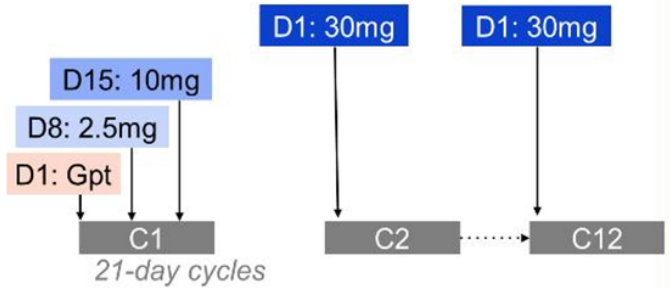
Glofitamab IV administration

Fixed-duration treatment

- Maximum 12 cycles

CRS* mitigation:

- Obinutuzumab pre-treatment (1 x 1000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



Endpoints

- **Primary**: CR rate (as best response) by IRC†
- **Key secondary**: ORR‡, DoR, DoCR‡, PFS, OS

Landmark analyses

- PFS and OS post-hoc analysis were performed by response (landmark at C3, or EOT)

n (%)	N=155
Median no. of prior lines of therapy, n (range)	3 (2–7)
2 prior lines	61 (39)
≥3 prior lines	94 (61)

PRIOR CAR-T 34%
PRIMARY REFRACTORY 59%

CRS 64%
MOSTLY G1-2
DURING 1° CYCLE

ICANS 8%

INFECTIONS 40%
NO GLOFIT RELATED G5 EVENTS

CD20 x CD3

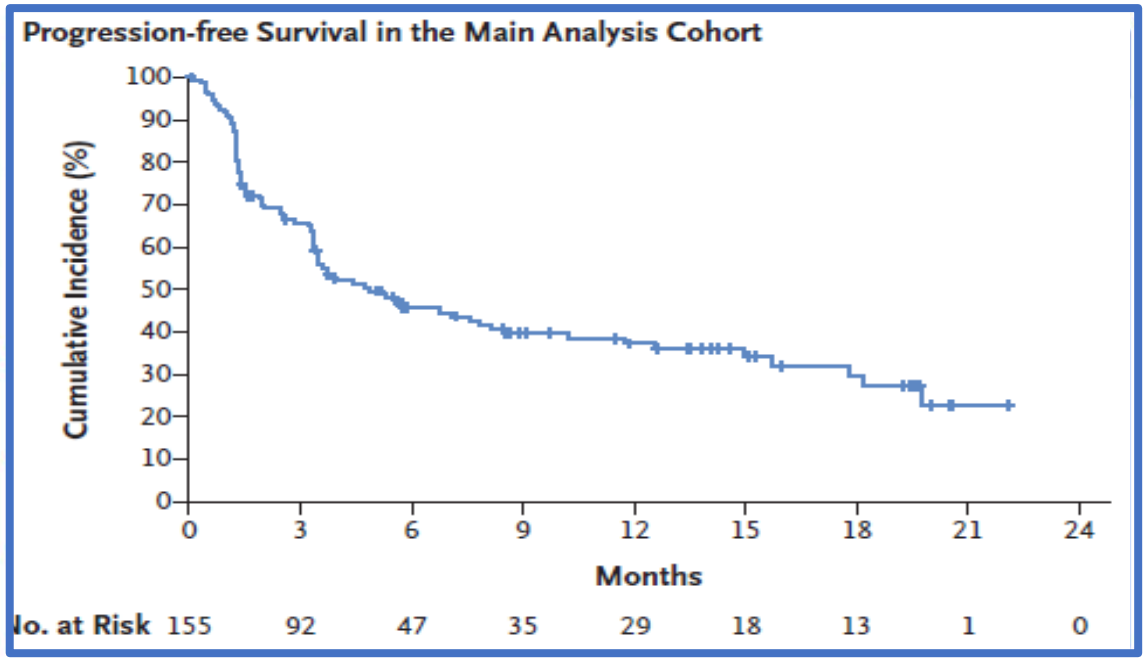
Dickinson M et al, ICML 2023

Dickinson MJ et al, N Eng J Med 2022

GLOFITAMAB

ORR 52%
CR RATE 40%

	IRC (N=155)*
CR rate†, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median CR follow-up, months (range)	18.2 (0–33)
18 months DoCR, n (%) [95% CI]	67.0 (53.3–80.8)
Ongoing CRs, n/N (%)	42/62 (68)
Median DoCR, months (95% CI)	26.9 (18.4–NR)



- The median time on study was 21.2 months (range: 0–34)

An estimated 67% of patients with a CR at any time remained in remission at 18 months

*Intent-to-treat population. †Best overall response. CI, confidence interval; NR, not reached.

CD20 x CD3

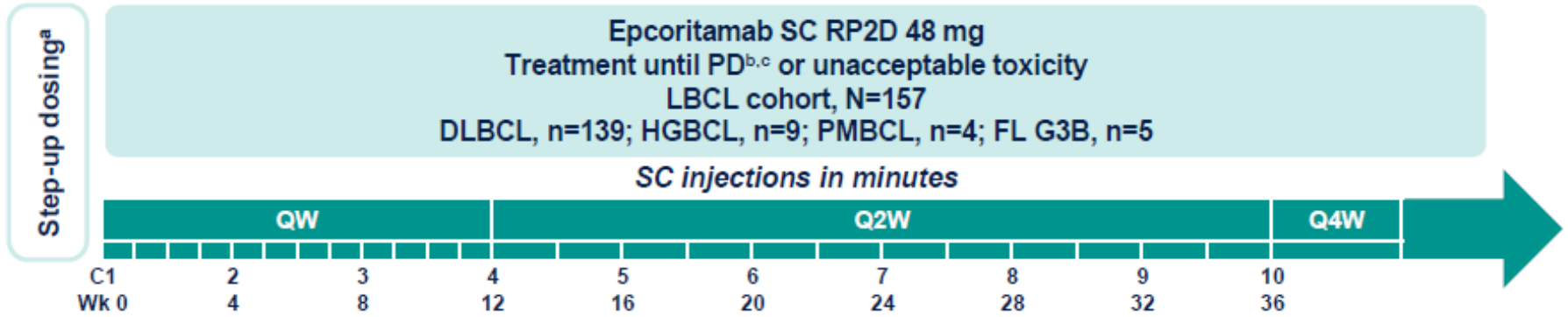
EPCORE NHL-1 TRIAL, JURCZAK ET AL. EHA 2023

Thieblemont et al JCO 2022

Epcoritamab (DuoBody®)-CD3×CD20)

CD3-binding arm

CD20-binding arm



- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

ophylaxis were used to mitigate CRS. [b]Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo 36.

Prior Treatments	DLBCL, n=139	LBCL, N=157
Median time from initial diagnosis to first dose, mo	19	19
Median time from end of last therapy to first dose, mo	2.4	2.4
Median prior lines of therapy (range)	3 (2–11)	3 (2–11)

PRIOR CAR-T 39%

PRIMARY REFRACTORY 61%

CRS 49%
MOSTLY G1-2
DURING 1° CYCLE (d15)

ICANS 6.4%

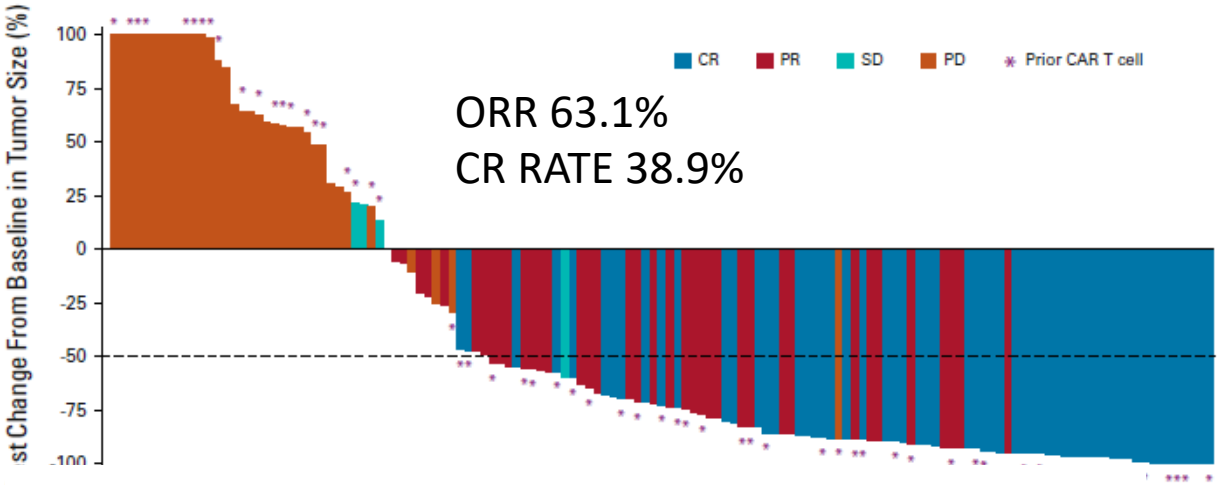
INFECTIONS 45%, G3-4 15%.

1 FATAL ICANS IN A PT WITH SEVERAL CONFOUNDING FACTORS

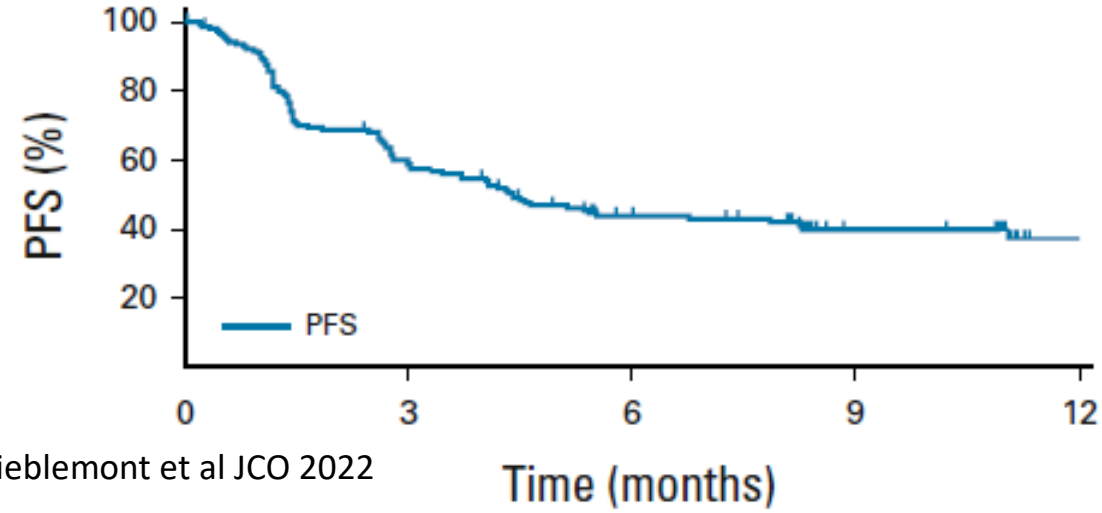
CD20 x CD3

Epcoritamab (DuoBody®)-CD3×CD20)

EPCORE NHL-1 TRIAL, JURCZAK ET AL. EHA 2023

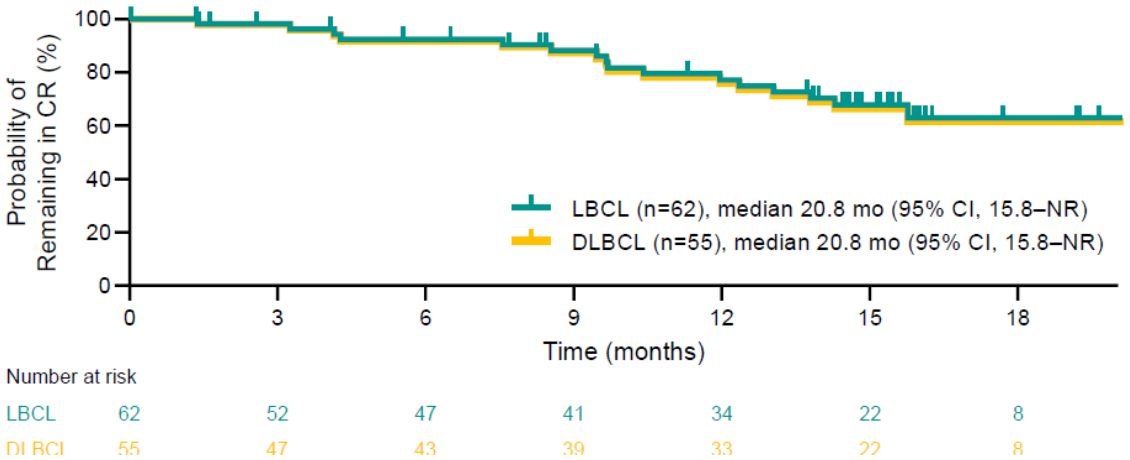


ORR 63.1%
CR RATE 38.9%

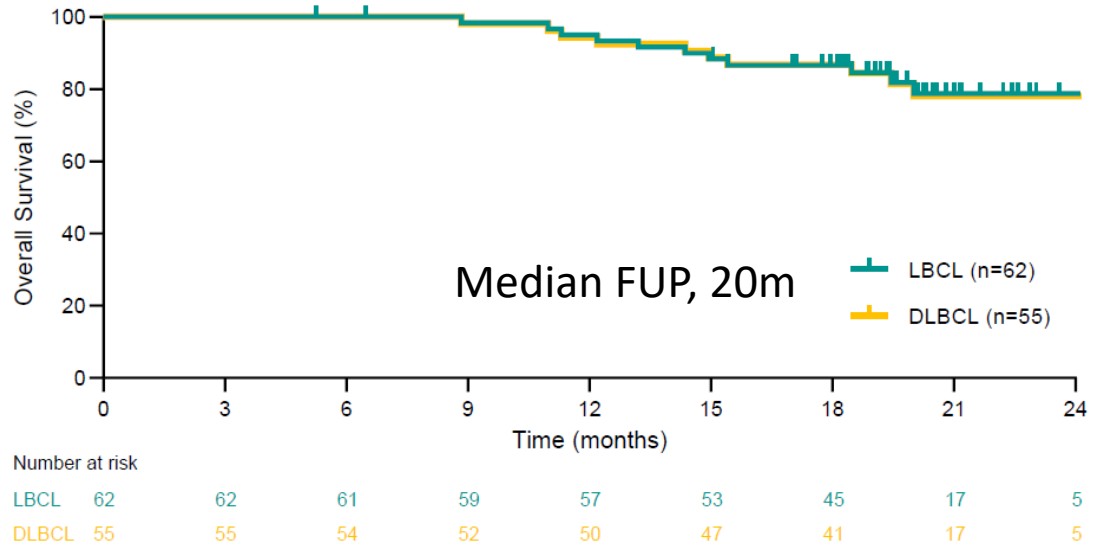


Thieblemont et al JCO 2022

Durable Complete Responses



Overall Survival Among Complete Responders



CD20 x CD3

ODRONEXTAMAB

N=145 pts

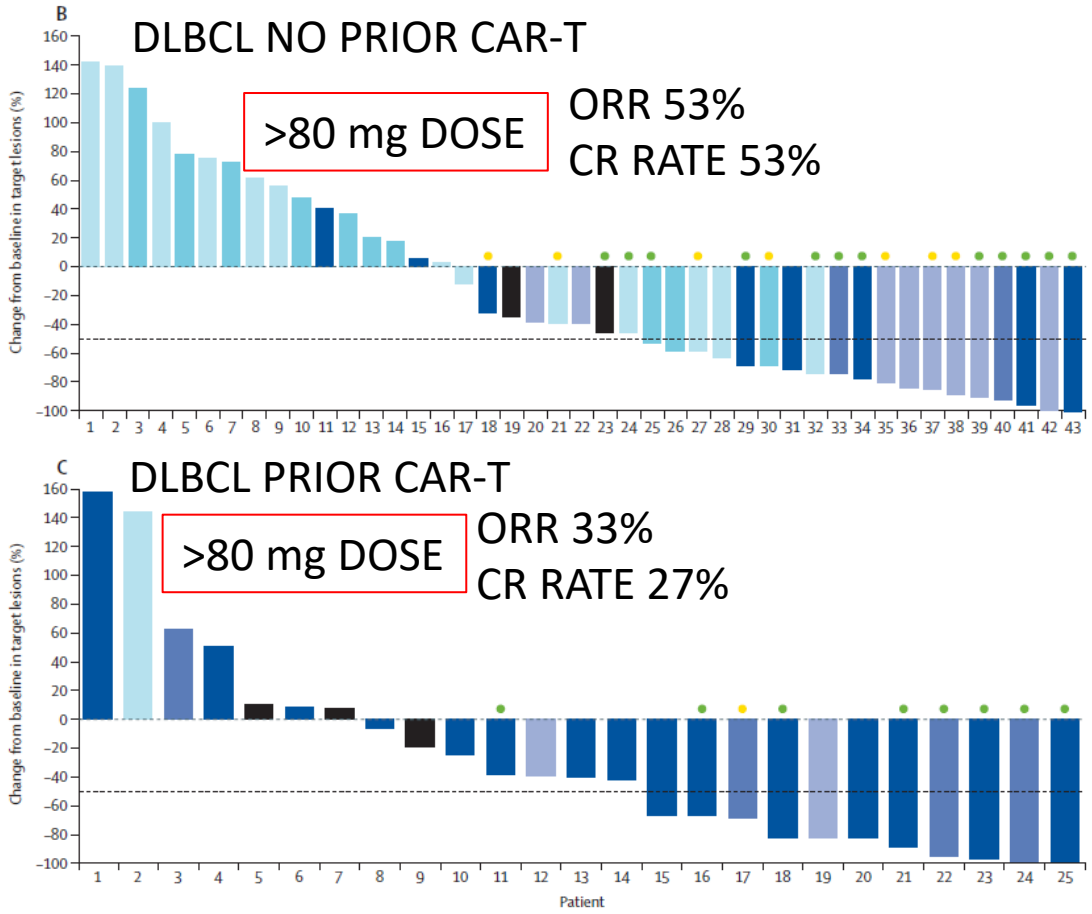
Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial

Rajat Bannerji, Jon E Arnason, Ranjana H Advani, Jennifer R Brown, John N Allan, Stephen M Ansell, Jeffrey A Barnes, Susan M O'Brien, Julio C Chávez, Johannes Duell, Andreas Rosenwald, Jennifer L Crombie, Melanie Ufkin, Jingjin Li, Min Zhu, Srikanth R Ambati, Aafia Chaudhry, Israel Lowy, Max S Topp

	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Pyrexia	105 (72%)	2 (1%)	0	0
Cytokine release syndrome	79 (54%)	9 (6%)	1 (1%)	0

CR RATE 24% ACROSS ALL DOSE LEVELS

49% INFECTIONS, 23% ≥ G3

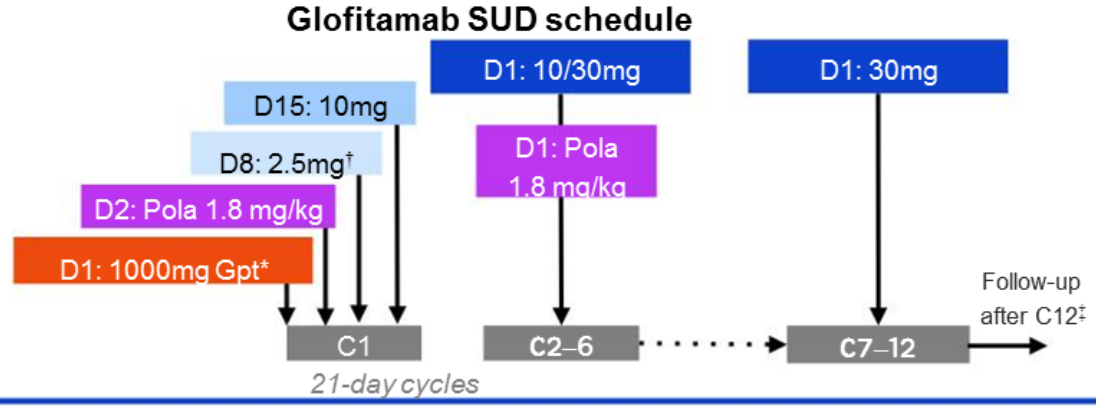


Bannerji et al Lancet Haem 2022

Hutchings et al. ICML 2023

BITEs + ADCs
Polatuzumab Vedotin
Glofitamab

Glofit-Pola administration in R/R DLBCL



Key inclusion criteria

- R/R DLBCL
- Aged ≥**18** years
- ECOG PS 0–2
- ≥**1** **prior** therapy

Endpoints

- **Primary:** RP2D (identified as 30mg from Part I of the study)
- **Secondary:** safety, efficacy, pharmacokinetics
- **Exploratory:** biomarker evaluation

Treatment period

- **Fixed treatment duration**: maximum 12 cycles of glofitamab plus six cycles of Pola (21-day cycles)
- As of January 25, 2023 (CCOD), 111 patients had received ≥**1** **dose of study drug**
- **Median follow-up: 13 months (range: 11.8–16.6)**

*Patients received obinutuzumab 1000mg on D1 of the first 21-day cycle to mitigate risk of CRS; †Mandatory 24-hour hospitalization for first glofitamab infusion;
‡Patients with CR, PR or SD were followed until disease progression, those with PD had an end of study visit then were followed for survival.

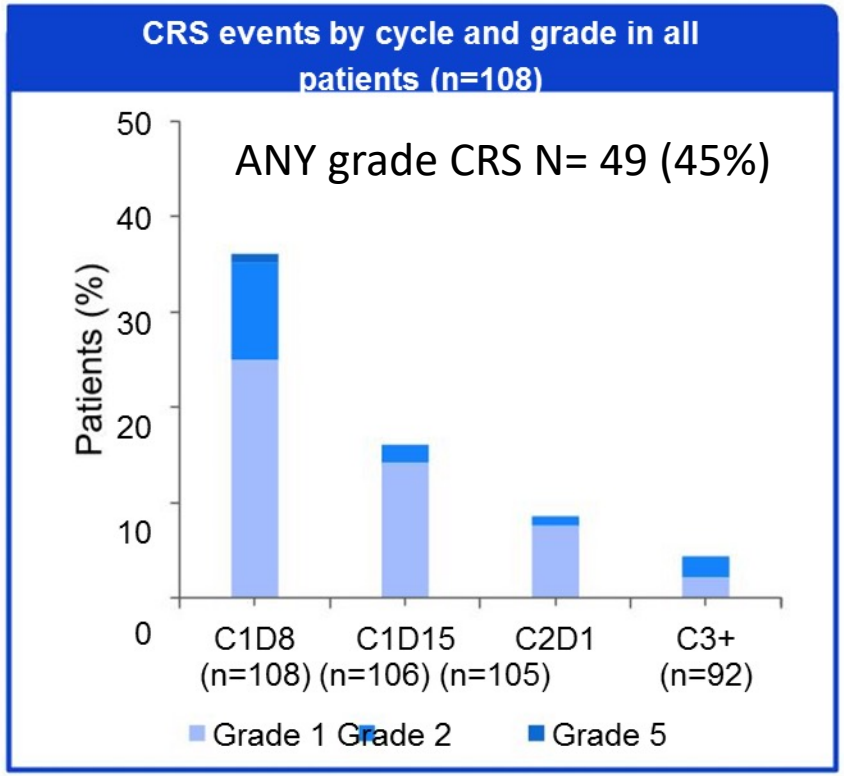
C, cycle; CCOD, clinical cut-off date; CR, complete response; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Glofit, glofitamab; Gpt, obinutuzumab pretreatment; PD, progressive disease; Pola, polatuzumab vedotin; PR, partial response; RP2D, recommended Phase 2 dose; SD, stable disease; SUD, step-up dosing.

Hutchings et al. ICML 2023

BITEs + ADCs
Polatuzumab
Vedotin
Glofitamab

N=111
56 DLBCL
26 trFL
27 HGBCL
2 PMBCL

n (%) unless stated	N=111
Ann Arbor stage	
I/II	25 (22.5)
III/IV	86 (77.5)
Bulky disease	
>6cm	46 (41.4)
>10cm	15 (13.5)
Median prior lines of therapy (range)	2 (1–7)
Number of prior lines of therapy	
1	43 (38.7)
≥2	68 (61.3)
Prior CAR T-cell therapy	27 (24.3)
Refractory to primary therapy	67 (60.4)
Refractory to last prior therapy	79 (71.2)

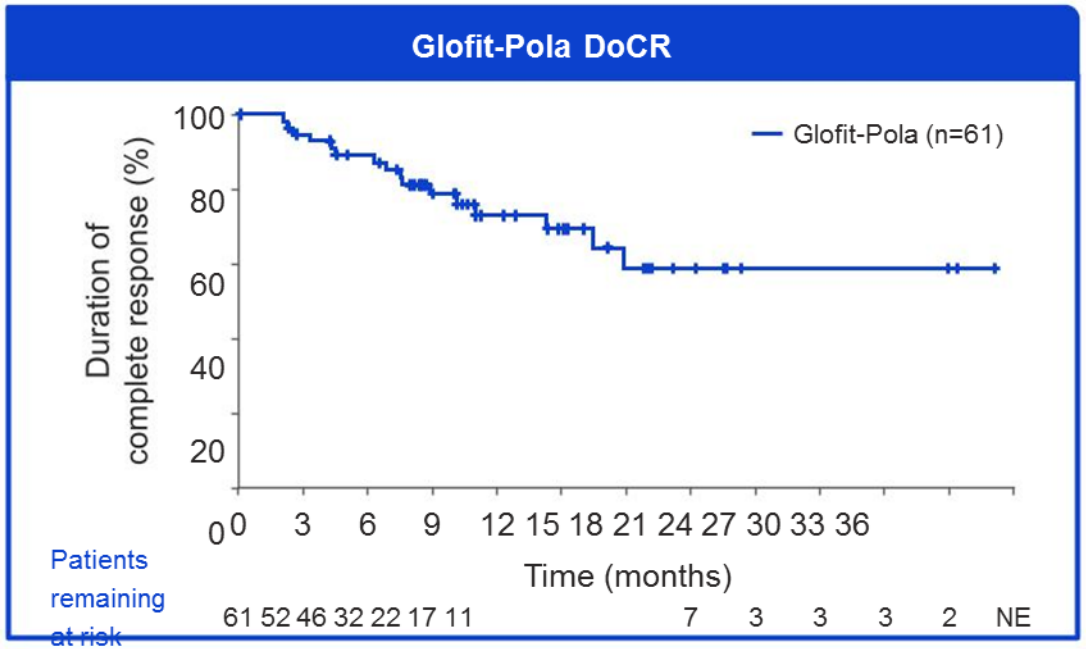


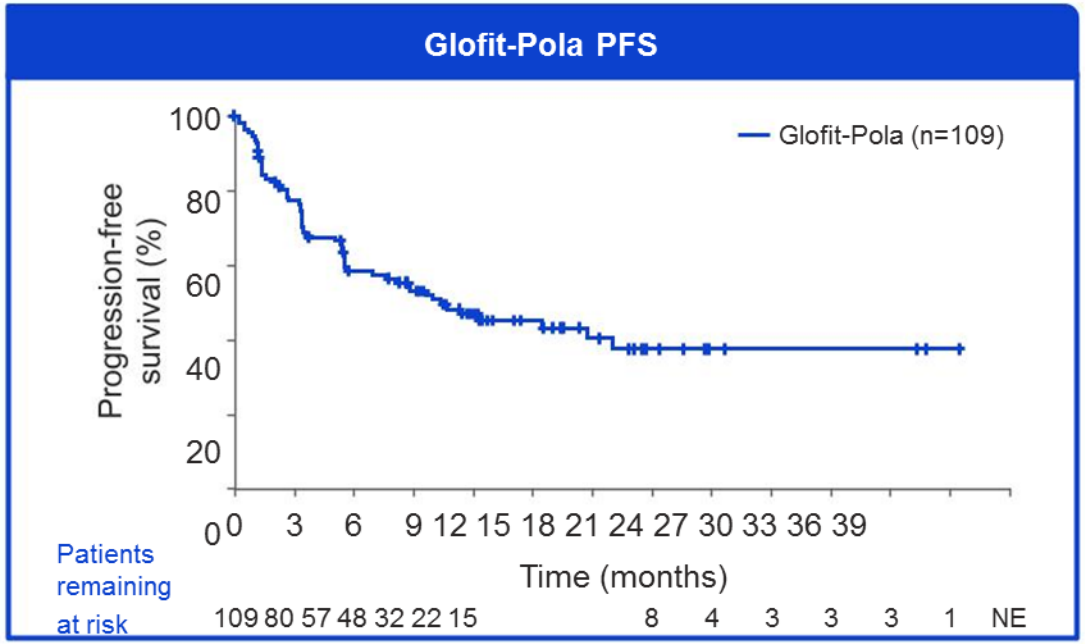
ICANS ≥ G3 N= 3 (2.7%)

INFECTIONS G ≥ G3 N= 30 (27%)
COVID-19 RELATED N=20

BITEs + ADCs
Polatuzumab Vedotin
Glofitamab

n (%)	All patients (n=109)*	*de novo* DLBCL (n=56)	HGBCL† (n=25)	trFL (n=26)	PMBCL (n=2)
Objective response	**85 (78.0)**	**48 (85.7)**	**15 (60.0)**	20 (76.9)	2 (100)
Complete response	**61 (56.0)**	**34 (60.7)**	**11 (44.0)**	14 (53.8)	2 (100)





Hutchings et al. ICML 2023

ADCs COMBOS
BITEs + ADCs

CD19-ADCs + NON CD19-ADCs

- Loncastuximab + Polatuzumab

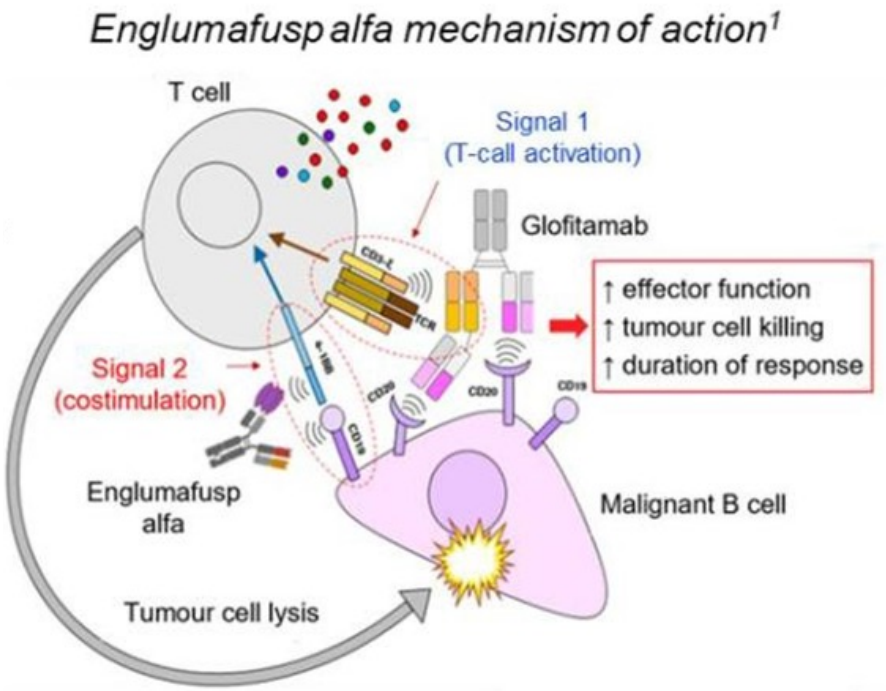
CD19-ADCs + CD20XCD3 BITES

- Loncastuximab + Glofitamab
- Loncastuximab + Mosunetuzumab

LOTIS-7 TRIAL

Dickinson et al. ICML 2023

BITEs + COST.
BITEs
Englumafusp
Glofitamab



ENGLUMAFUSP
CD19 x 4-1BB

BP41072 study overview

Open-label Phase 1 study investigating escalating englumafusp alfa dose levels in combination with glofitamab in patients with R/R B-cell NHL

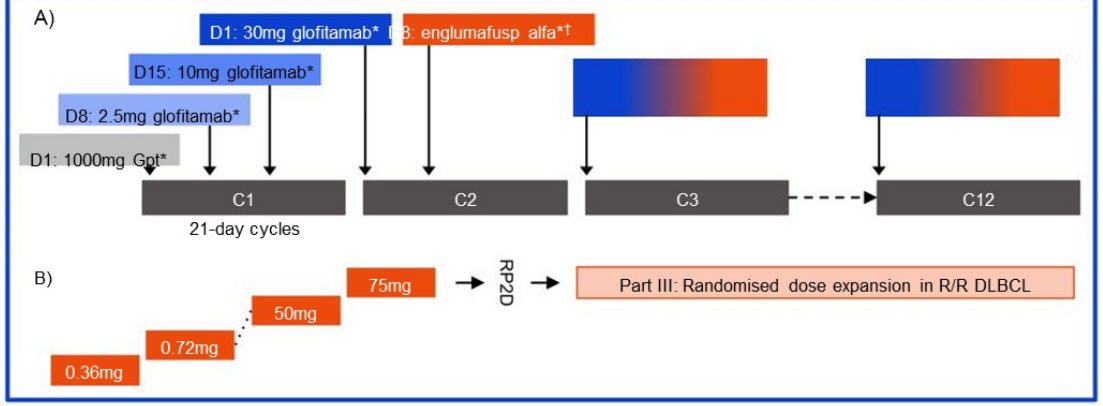
Patients

- Age ≥18 years
- R/R B-cell NHL
- ≥1 measurable lesion
- ≥2 prior therapies
- Adequate haematologic and liver function
- ECOG PS ≤1

Primary objectives

- Safety
- Tolerability
- PK
- RP2D

Treatment schedule (A) and dose escalation (B)



Englumafusp alfa is initiated after glofitamab step dosing on C2D8 and is co-administered with glofitamab on the same day from C3 onwards

*IV administration; †escalating dose levels; C, Cycle; D, Day; DLBCL, diffuse large B-cell lymphoma; Gpt, obinutuzumab pre-treatment
IV, intravenous; NHL, non-Hodgkin lymphoma; PK, pharmacokinetics; PS, performance status; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory

Dickinson et al. ICML 2023

BITEs + COST.
BITEs
Englumafusp
Glofitamab

AGGRESSIVE B-CELL LYMPHOMA N=86
61 DLBCL
19 trFL
4 trOTHER
2 G3B FL

N=113
CRS 51.3%
COVID-19 25.7%

N (%) unless stated	aNHL (N=86)
Median number of prior lines of therapy, N (range) ≥2 prior lines	3 (1–8) 73 (84.9%)
Prior anti-CD20 antibody	85 (98.8%)†
Prior CAR T-cell	33 (38.4%)
Prior ASCT	8 (9.3%)
Refractory to any prior therapy	71 (82.6%)

	N response evaluable	CRR	BORR
aNHL			
≥1 dose of any study treatment	86	37 (43.0%)	54 (62.8%)
≥1 dose of englumafusp alfa	78	37 (47.4%)	53 (67.9%)
iNHL			
≥1 dose of any study treatment	26	17 (65.4%)	23 (88.5%)
≥1 dose of englumafusp alfa	25	17 (68.0%)	23 (92.0%)

- Median number of cycles received: 7 aNHL; 12 iNHL

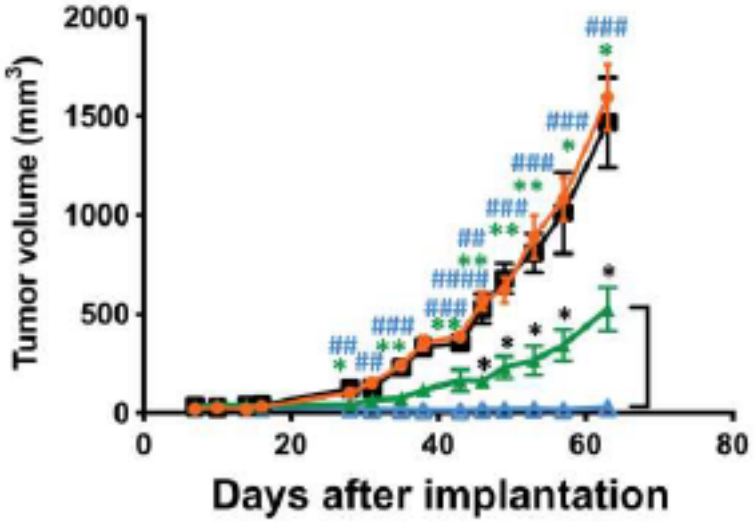
78/86 aNHL and 25/27 iNHL patients received at least one dose of englumafusp alfa (0.36–75mg)

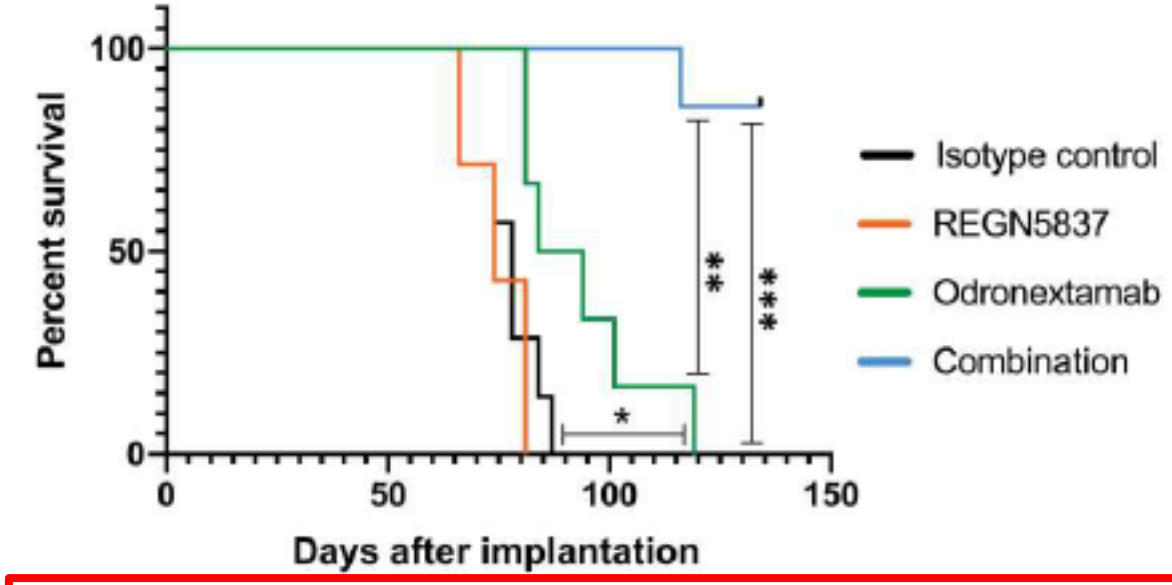
BITEs + COST.
BITEs
REGN5837
Odronextamab

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER IMMUNOTHERAPY

CD22-targeted CD28 bispecific antibody enhances antitumor efficacy of odronextamab in refractory diffuse large B cell lymphoma models





Abstract CT129: Trial in progress: ATHENA-1 - a phase 1, open-label, first-in-human study to assess safety and tolerability of REGN5837 in combination with odronextamab in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphomas

Wei C et al. Sci Trans Med 2022

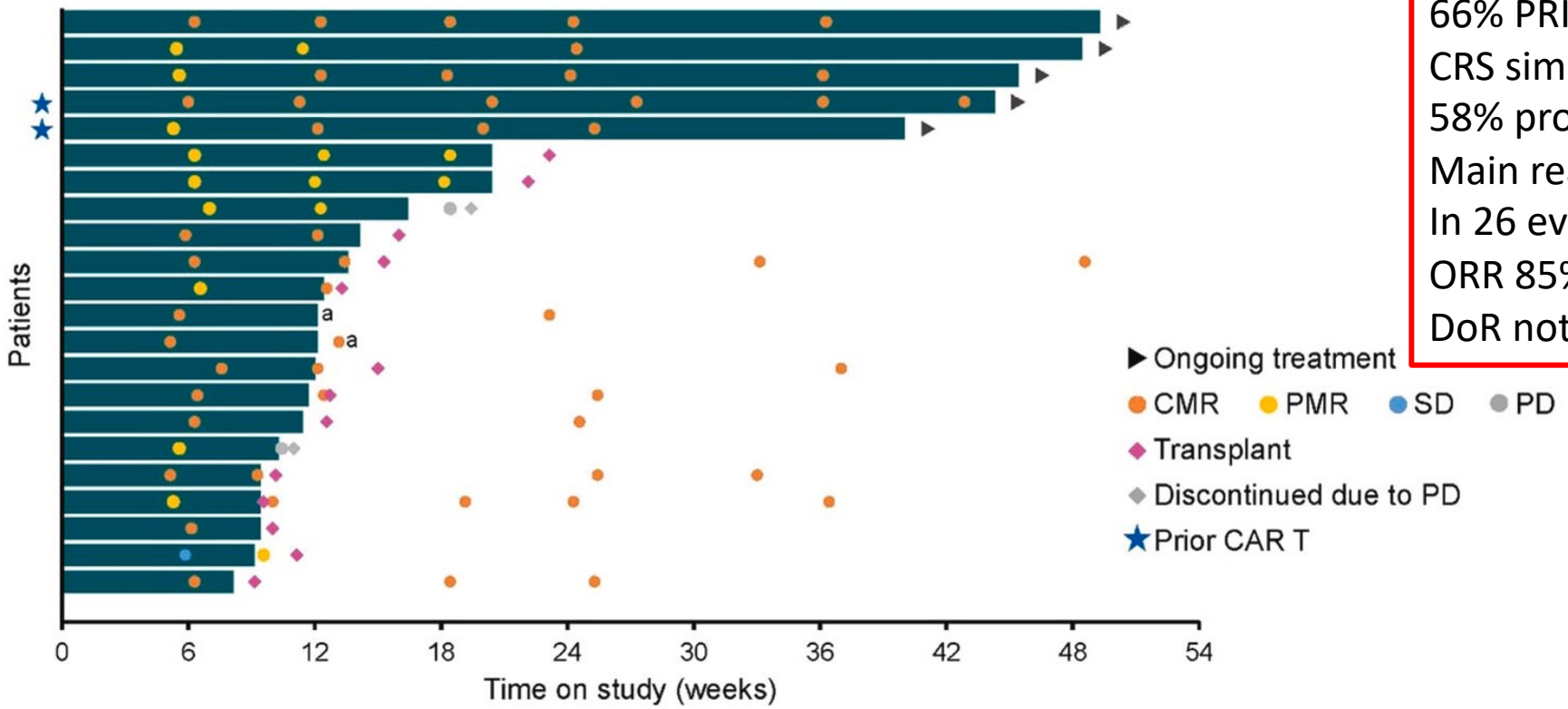
Baird J et al. AACR 2023

Subcutaneous Epcoritamab + R-Dhax/C in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Eligible for Autologous Stem Cell Transplant: Updated Phase 1/2 Results

BITEs + Chemo-R
Epcoritamab
R-DHAX

N=29
72% 2L
66% PRIMARY REFRACTORY
CRS similar to Epco single agent
58% proceeded to ASCT (CR 80%)
Main reason of no ASCT: pt choice
In 26 evaluable pts:
ORR 85%, CR RATE 65%
DoR not reached in pts not undergoing ASCT

Figure. Response profile with epcoritamab + R-DHAX/C in EPCORE NHL-2 arm 4.

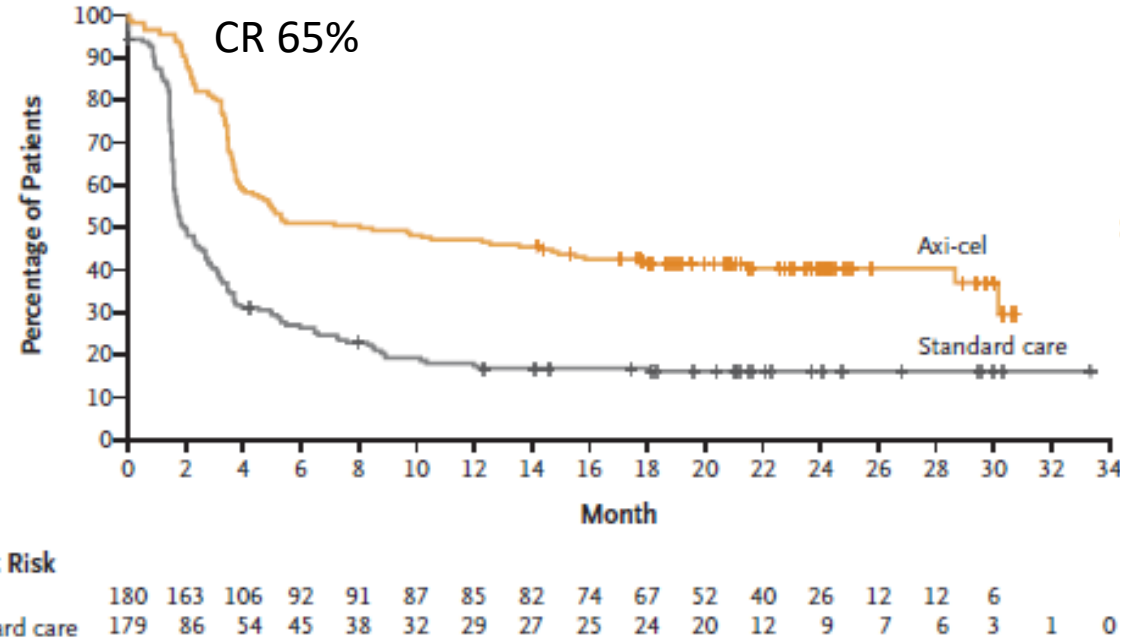


Data cutoff: June 10, 2022. Per protocol, patients continued to receive scans if they discontinued treatment for reasons other than PD.
CAR T, chimeric antigen receptor T-cell therapy; CMR, complete metabolic response; PD, progressive disease; PMR, partial metabolic response; R-DHAX/C, rituximab, dexamethasone, cytarabine, and oxaliplatin or carboplatin; SD, stable disease.
[a]Two additional patients received transplant.

Abrisqueta P et al. ASH 2022

ORIGINAL ARTICLE

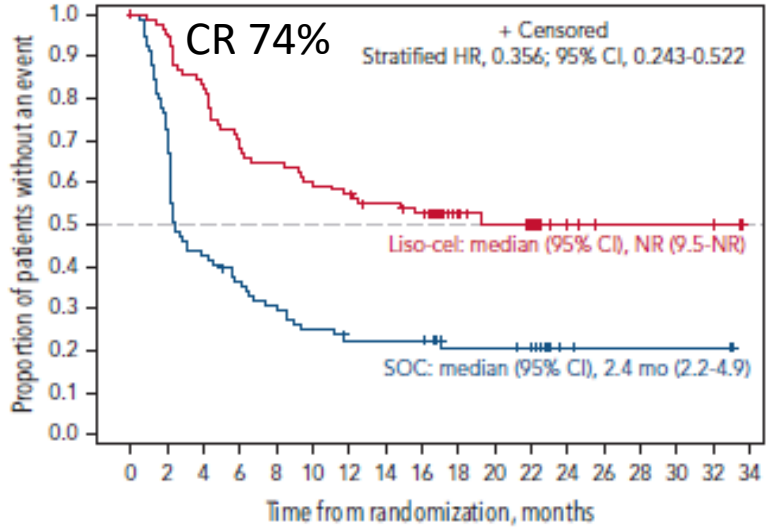
Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma



No. at Risk																	
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

CLINICAL TRIALS AND OBSERVATIONS

Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study



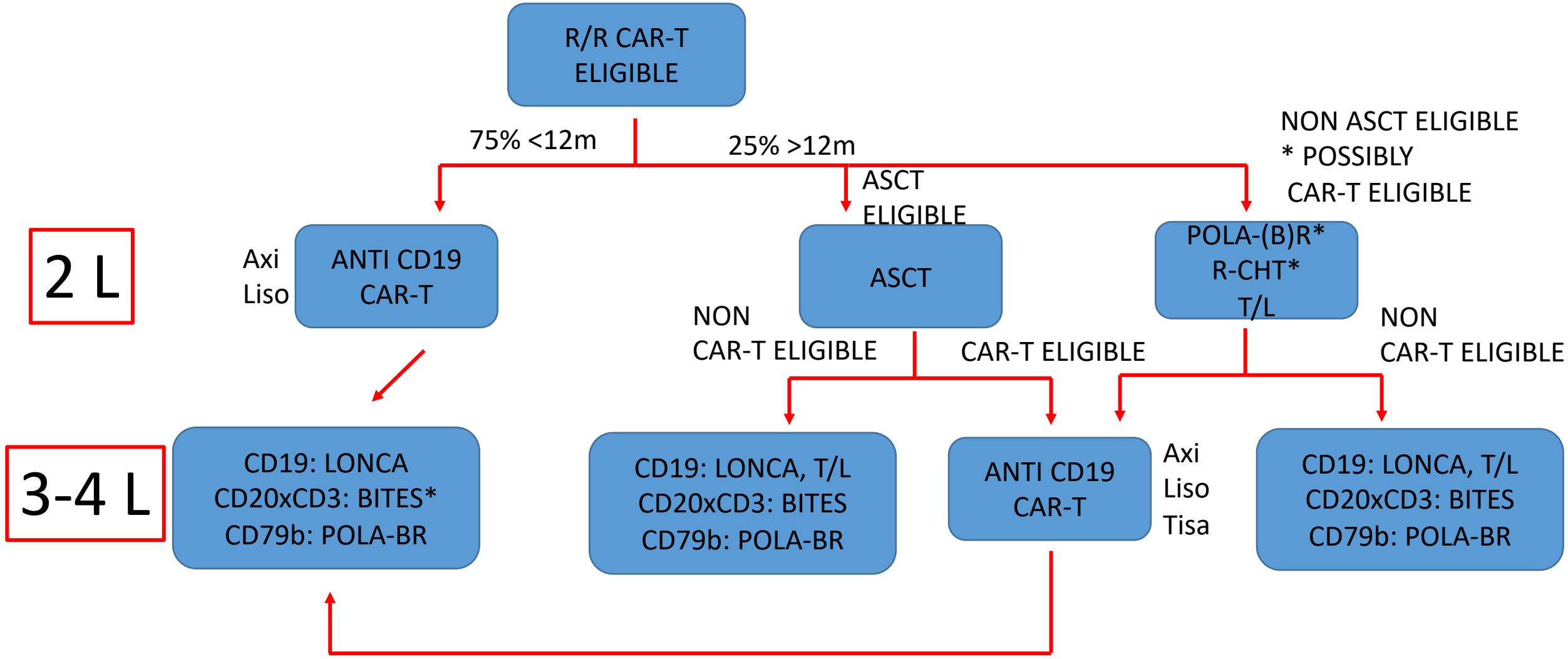
No. at risk																	
SOC	92	66	39	32	27	22	19	19	19	12	12	10	3	2	2	2	2	0
Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	3	0

INCREASED FRACTION OF PTS TREATED EARLY WITH ANTI CD19 DIRECTED THERAPY

SIGNIFICANT FRACTION OF PTS IS NOT CAR-T ELIGIBLE

Locke FL et al. N Eng J Med 2022

Abramson JS et al. Blood 2023

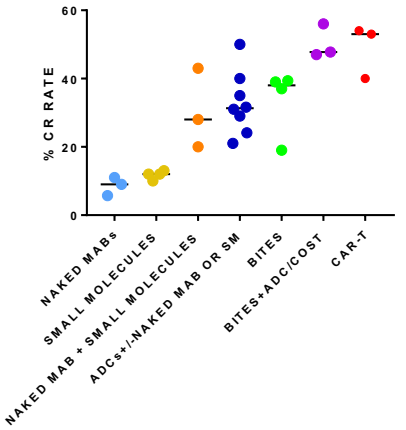

R/R CAR-T
ELIGIBLE
75% <12m
25% >12m
ASCT
ELIGIBLE
NON ASCT ELIGIBLE
* POSSIBLY
CAR-T ELIGIBLE
2 L
Axi
Liso
ANTI CD19
CAR-T
ASCT
POLA-(B)R*
R-CHT*
T/L
NON
CAR-T ELIGIBLE
CAR-T ELIGIBLE
NON
CAR-T ELIGIBLE
3-4 L
CD19: LONCA
CD20xCD3: BITES*
CD79b: POLA-BR
CD19: LONCA, T/L
CD20xCD3: BITES
CD79b: POLA-BR
ANTI CD19
CAR-T
Axi
Liso
Tisa
CD19: LONCA, T/L
CD20xCD3: BITES
CD79b: POLA-BR

CONCLUSIONS

1- SEVERAL NEW TREATMENT OPTIONS AVAILABLE

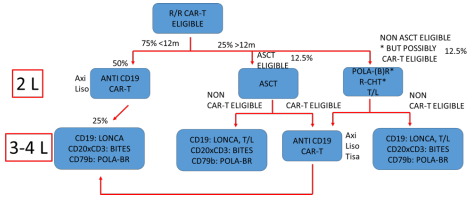
2- R/R DLBCL TREATMENT ALGORITHM IS GETTING MORE COMPLEX

3- BITES and ADCs BASED COMBO VERY PROMISING (POSSIBLY 2° LINE?)



4- CD19 CAR-T CELL THERAPY AVAILABLE IN 2° AND 3° LINE

5- CD19 DIRECTED THERAPY POSSIBLY AVAILABLE IN FIRST LINE IN THE NEXT FUTURE



6- POSSIBLY 5-6 DIFFERENT TYPES OF FIRST-LINE THERAPIES IN THE NEXT YEARS

7- DIFFERENT SPECIFIC SEQUENCING STRATEGIES DEPENDING ON THE FIRST LINE REGIMEN RECEIVED

8- BIOMARKERS TO PREDICT TREATMENT EFFICACY URGENTLY NEEDED

1-R-CHOP + ADCs
2-R-CHOP + BTKi
3-R-CHOP + BITES
4-R-CHOP + T/L
5- CAR-T in HR
6-ANTI CD19 ADCs OR CD20xCD3 BITE
CHEMOFREE ELDERLY