Expanding Horizons for immunotherapy in Onco-Hematology

New Drugs in NHLs
Bispecific Antibodies

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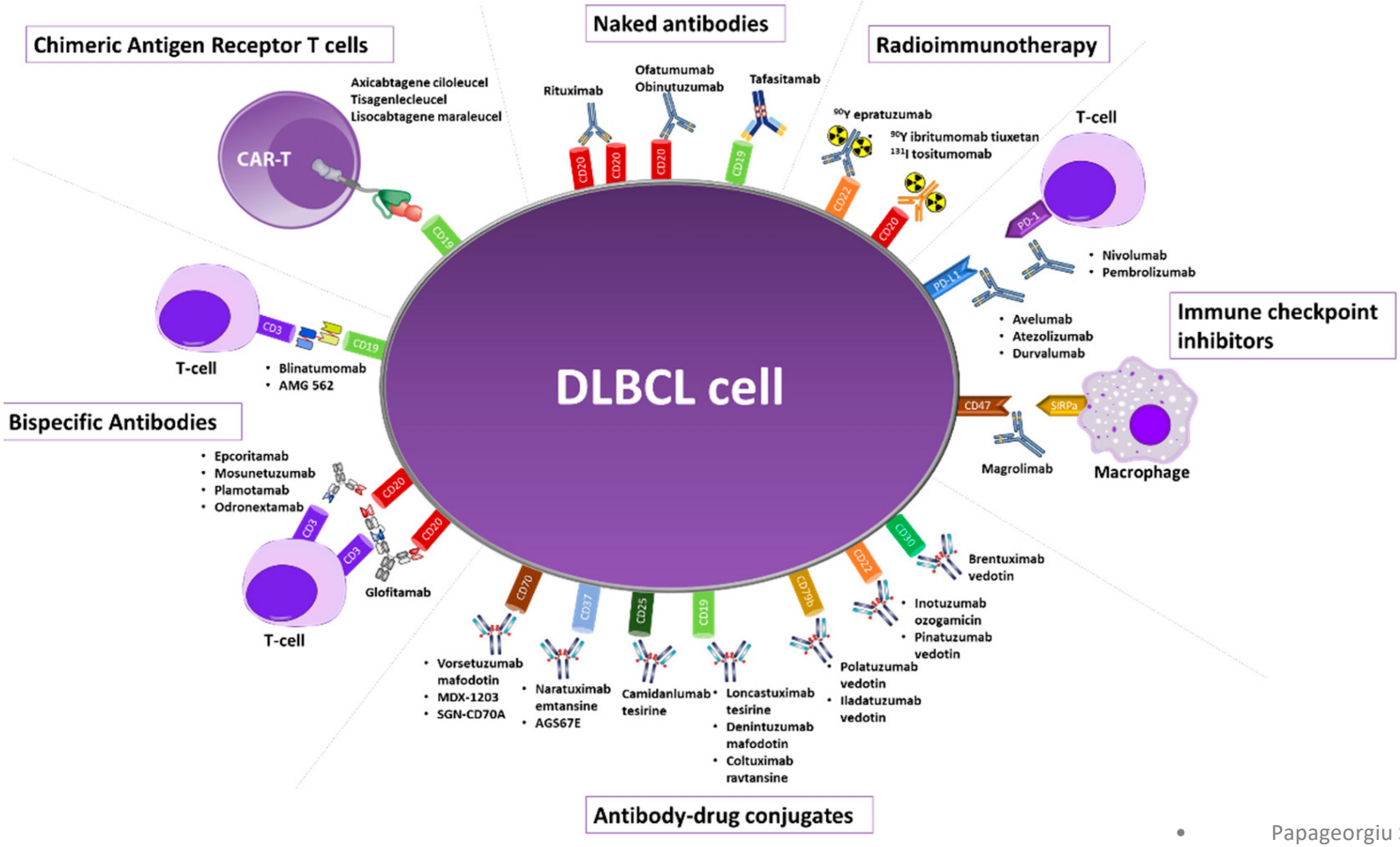
Disclosures

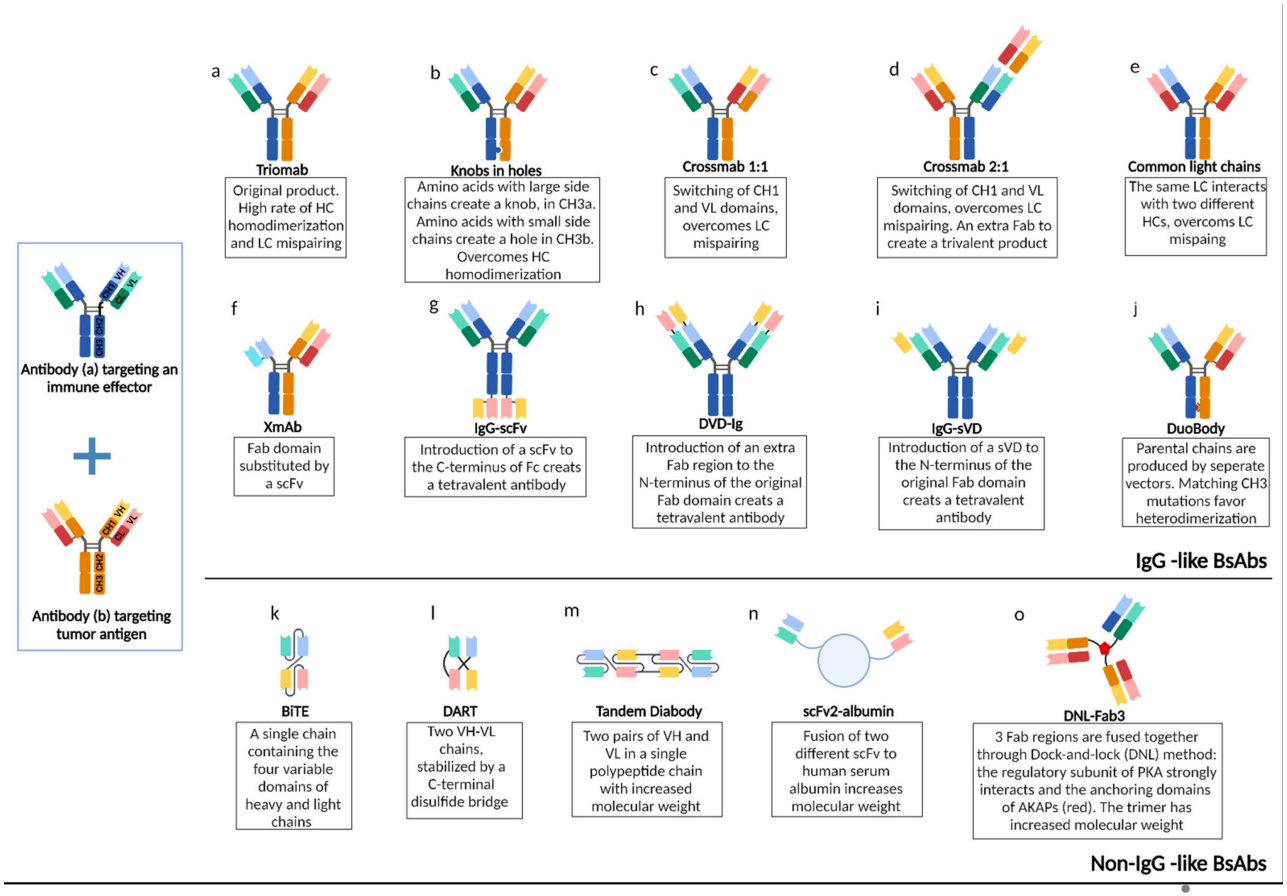
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X		
Bayer					X	X	
Constellation						X	
Genmab						X	
Gilead					X	X	
Incyte					X	X	
Janssen					X	X	
Morphosys	X					X	
Novartis					X		
Regeneron						X	

Monoclonal antibodies investigated in DLBCL



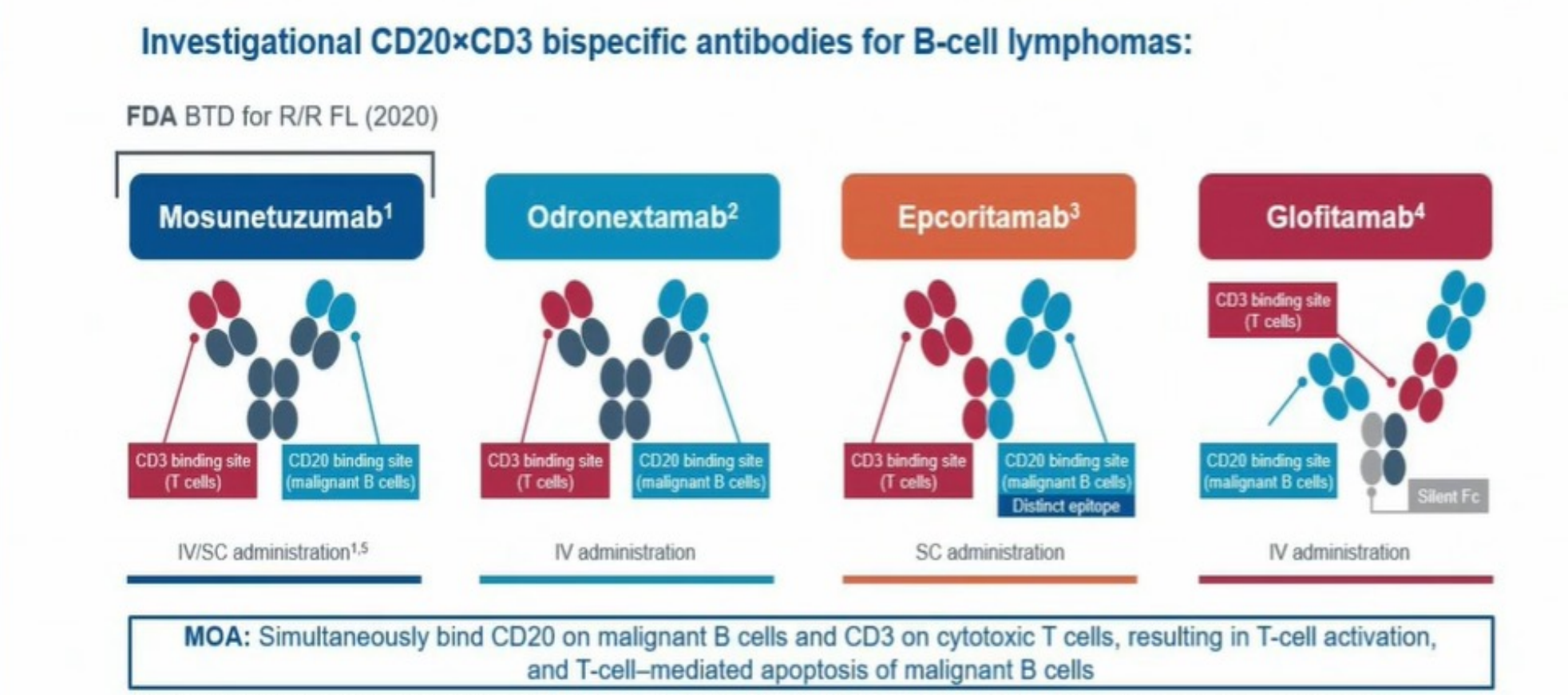
- Papageorgiu SG et al Cancers 2022

Structures of bispecific antibodies

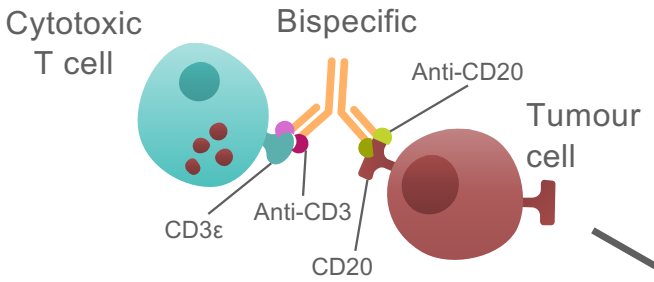


Papageorgiu SG et al Cancers 2022

Emerging therapies: Bispecific Antibodies



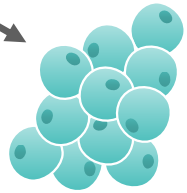
Mode of action of anti-CD20/CD3 bispecific antibodies



1. Local secretion of chemokines leading to the recruitment of T cells from the periphery

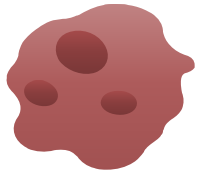
Anti-CD20/CD3 bispecifics redirect endogenous non-specific T cells to engage and eliminate malignant B cells in NHL[1–3]

2. T cells undergo proliferation and expansion at the tumour site



3. T-cell activation occurs via downstream signalling events leading to the secretion of cytotoxic granules

5. Apoptosis

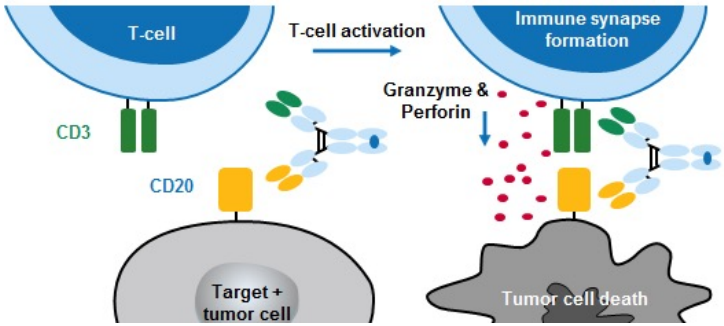


4. Potent lysis of tumour cells

6. T cell–mediated tumour killing

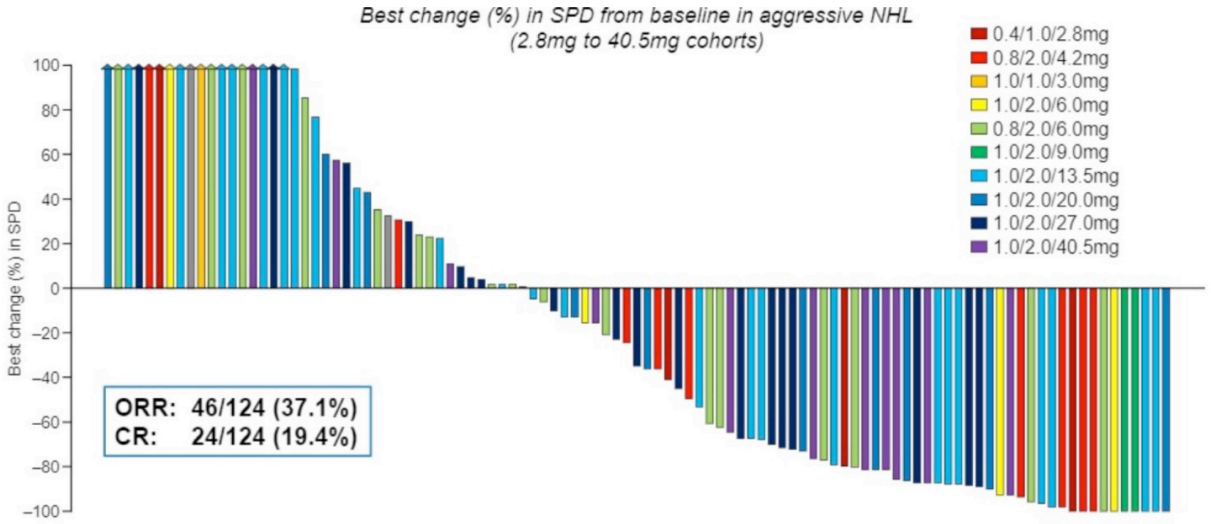
1. Sun LL, et al. Sci Transl Med 2015;7:287ra70; 2. Dieckmann NM, et al. J Cell Science 2016;129:2:2881–6
3. Bacac M, et al. Clin Cancer Res 2018;24:4785–97
Adapted from Aldoss I, et al. Leukemia 2017;31:777–87

GO29781: Mosunetuzumab in R/R NHL Results



	Patients
Efficacy-evaluable iNHL, n (%)	**67**
ORR	**42 (63)**
CR	**29 (43)**
Efficacy-evaluable aNHL, n (%)	**124**
ORR	**46 (37)**
CR	**24 (19)**
Efficacy-evaluable prior CAR T, n	**18**
ORR	**7 (39)**
CR	**4 (22)**

- Increased efficacy of aNHL patients was observed with higher exposure, as measured by CD20 receptor occupancy
- 4 patients were retreated with monsunetuzumab, 3 of whom achieved responses, with 1 CR



	Safety N=270	Prior CAR T
CRS (Lee et al, 2014)	29%	27%
Grade 1/2	28%	23%
Grade 3	1%	3%
NT	44%	43%
Grade 1/2	40%	33%
Grade 3	4%	10%
Potential ICANS	1%	0%

Schuster S et al, ASH 2019.

Mosunetuzumab Monotherapy for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II

		N=90
Median number of prior lines, n (range)		3 (2–10)
Prior systemic therapy	Anti-CD20 therapy	90 (100%)
	Alkylator therapy	90 (100%)
	PI3K inhibitor	17 (18.9%)
	IMiD	13 (14.4%)
	CAR-T	3 (3.3%)
Prior ASCT		19 (21.1%)
Refractory to last prior therapy		62 (68.9%)
Refractory to any prior aCD20 therapy		71 (78.9%)
Refractory to any prior aCD20 therapy and alkylator therapy (double refractory)		48 (53.3%)
POD24		47 (52.2%)

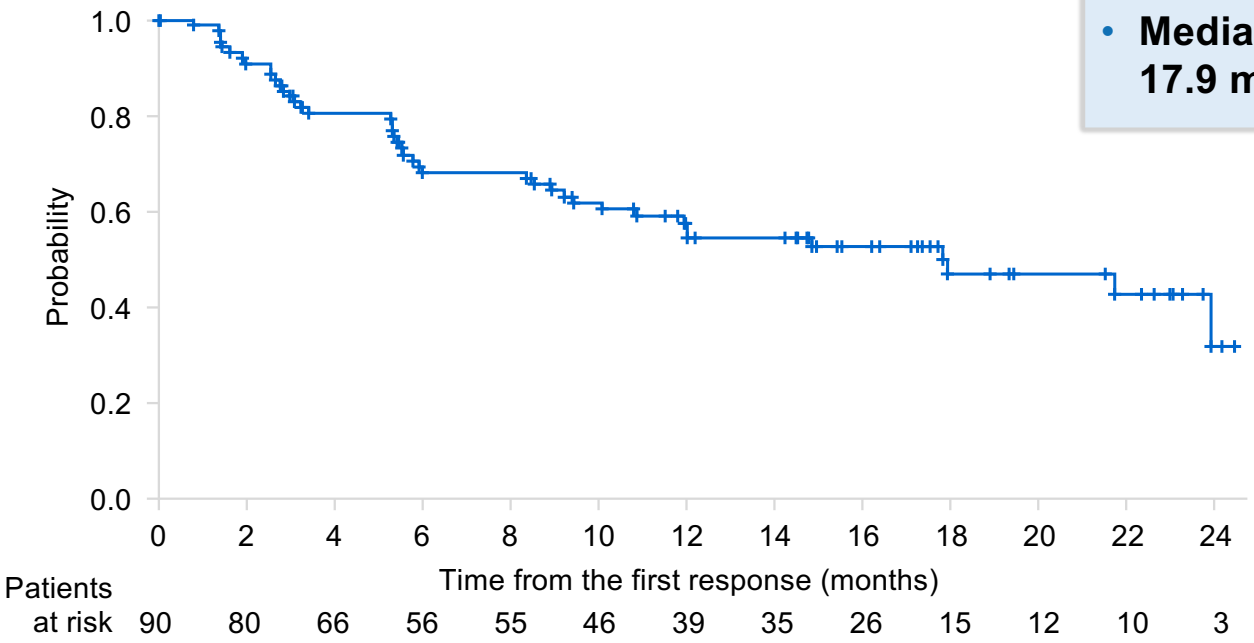
Efficacy endpoint [1]	IRF N (%) [95% CI]	Investigator N (%) [95% CI]	Concordance IRF vs investigator
CR	**54 (60%)** [49%, 70%]	54 (60%) [49%, 70%]	93%
ORR	**72 (80%)** [70%, 88%]	70 (78%) [68%, 86%]	96%

*exact binomial test with two-sided alpha level of 5%; CI, confidence interval

- Budde LE et al Ash 2021.

Progression-free survival

Progression-free survival (N=90)

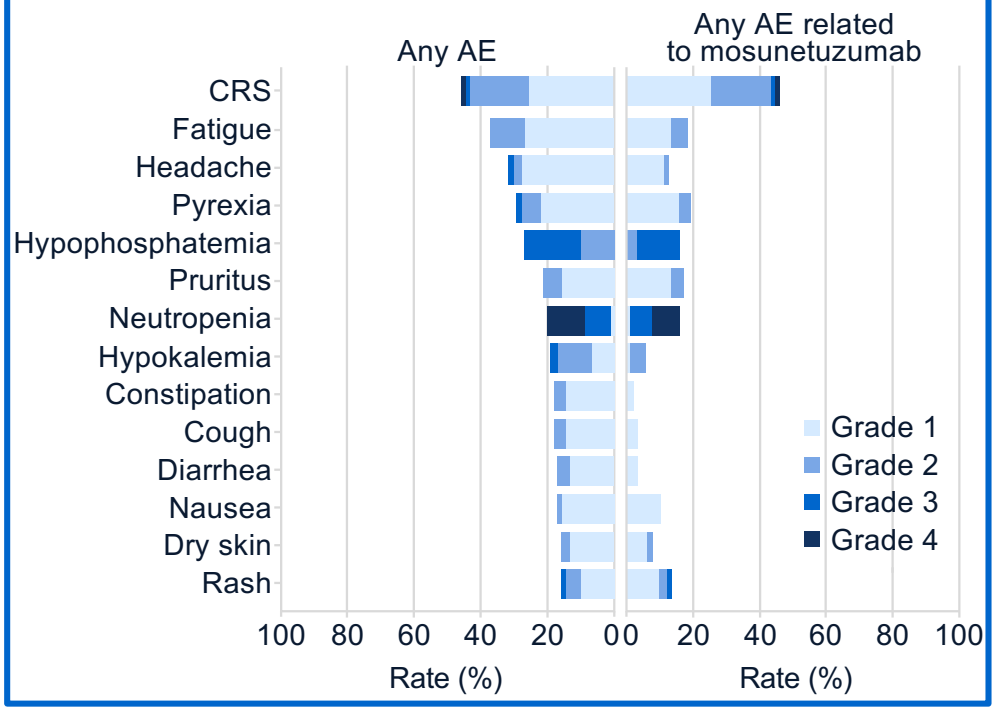


- **Median PFS: 17.9 months (95% CI: 10.1, NE)**

Safety of Mosunetuzumab

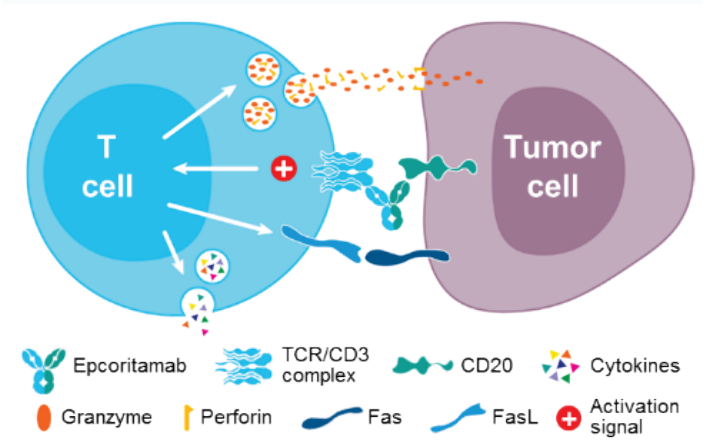
N (%)	N=90
AE	90 (100%)
Mosunetuzumab related*	83 (92.2%)
Grade 3–4 AE	63 (70.0%)
Mosunetuzumab related*	46 (51.1%)
Serious AE	42 (46.7%)
Mosunetuzumab related*	30 (33.3%)
Grade 5 (fatal) AE	2 (2.2%)†
Mosunetuzumab related*	0
AE leading to discontinuation of treatment	4 (4.4%)‡
Mosunetuzumab related*	2 (2.2%)‡

AEs (≥15%) by Gr and relationship with mosunetuzumab

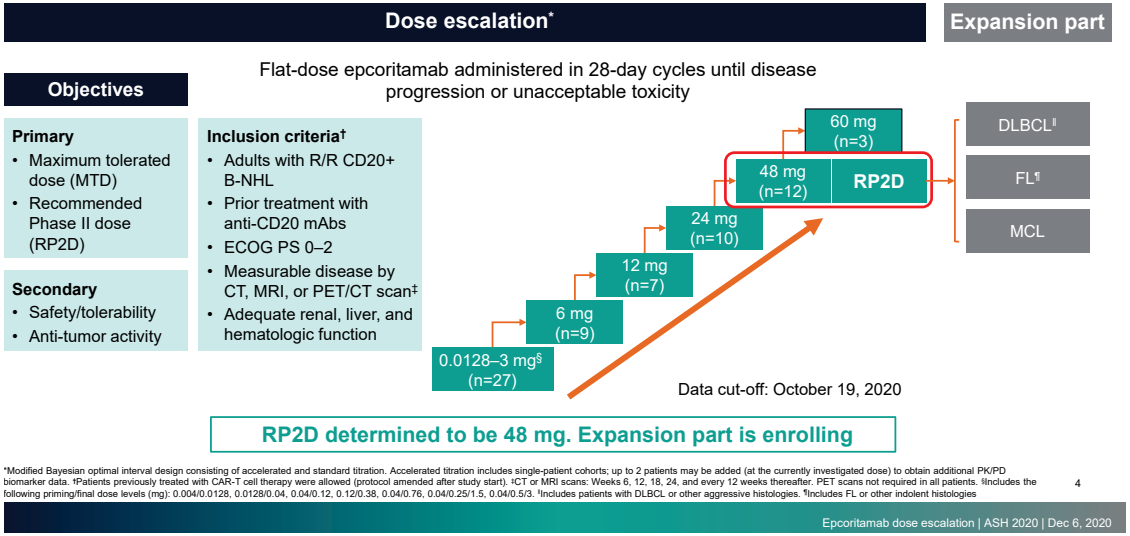


*AE considered related to treatment by the investigator; †mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (1 patient each); ‡mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each); AE, adverse event; Gr, Grade ;

Escalating dose of subcutaneous epcoritamab in R/R B-cell NHL: high rate of complete response and favorable safety profile



- **Induces T-cell activation** by binding to CD3 on T cells and CD20 on malignant B cells
- **Promotes immunological synapse** between bound cells, resulting in apoptosis of B cells
- **Binds to a distinct epitope on CD20**, different from the epitopes of rituximab and obinutuzumab
- **Retains activity** in the presence of CD20 mAbs



Engelberts PJ et al, EBioMedicine 2020, 52:102625, Hutchings M et al, Lancet 2021.

Escalating dose of subcutaneous epcoritamab in R/R B-cell NHL: high rate of complete response and favorable safety profile

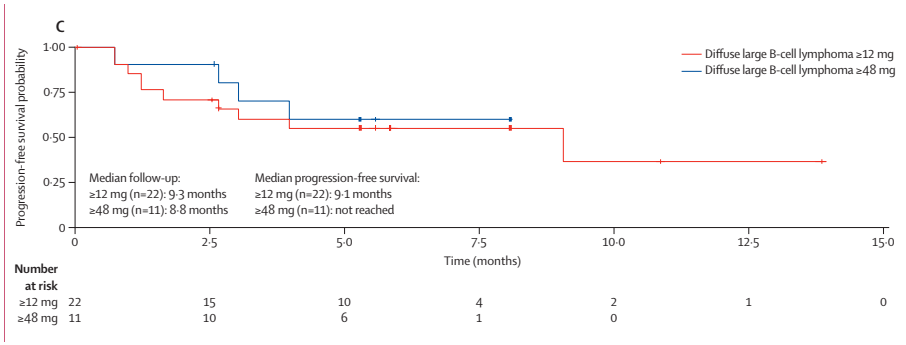
Adverse events of special interest	All histologies (N=68)
CRS, n (%)	40 (59)
Grade 1	20 (29)
Grade 2	20 (29)
Symptoms of CRS ≥10%, n (%)	
Pyrexia	40 (59)
Hypotension	16 (24)
Hypoxia	12 (18)
Tachycardia	10 (15)
Chills	7 (10)

- Most CRS events occurred in cycle 1
- No CRS event with second full dose at RP2D
- Median time (range) to resolution was 2 (1.0–9.0) days
- Risk of CRS was mitigated by route of administration, step-up dosing, and pretreatment with corticosteroids

Response by histology

Response*	DLBCL (n=46)		FL (n=12)		MCL‡
	12–60 mg (n=23)	48–60 mg† (n=12)	0.76–48 mg (n=11)	12–48 mg (n=5)	0.76–48 mg (n=4)
Evaluable patients, n	22§	11§	10‖	5	4**
ORR, n (%)¶	15 (68)	10 (91)	9 (90)††	4 (80)	2 (50)
CR	10 (46)	6 (55)	5 (50)	3 (60)	1 (25)
PR	5 (23)	4 (36)	4 (40)	1 (20)	1 (25)
Stable disease, n (%)	1 (5)	0	0	0	1 (25)
Progressive disease, n (%)	5 (23)	0	1 (10)	1 (20)	0

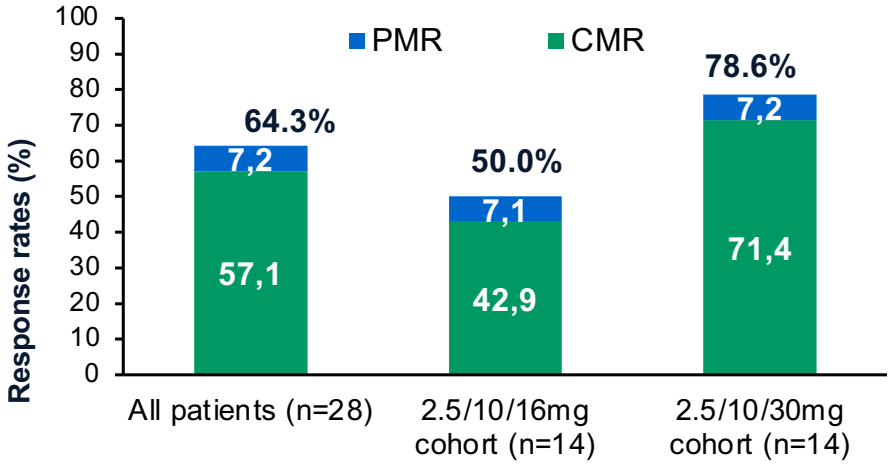
*Response assessments were based on Lugano 2014 response criteria by investigator assessment (modified response-evaluable population). †Includes 3 patients who received 60-mg dose before RP2D was determined. ‡1 patient had blastoid/pleomorphic MCL; 1 had unknown histology. §Excludes 1 patient who discontinued before first assessment due to COVID-19. ‖Excludes 1 patient who discontinued before first assessment due to post cardiac (CABG) surgery. ¶Response rates are based on number of evaluable patients (defined as patients with at least 1 post-baseline disease assessment or who died without a post-baseline disease assessment). **Includes 1 patient who died before assessment. ††6/10 patients had response evaluation by PET scans (not mandatory until recent protocol amendment)



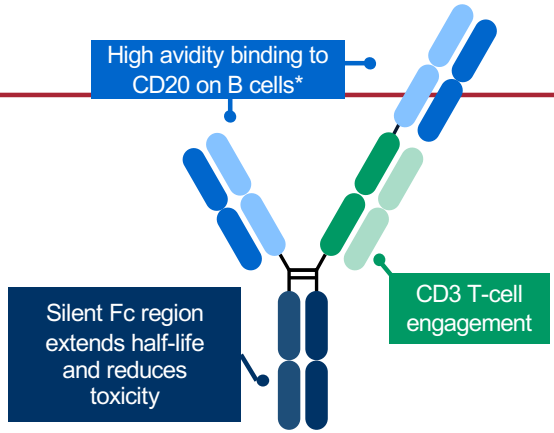
Hutchings M et al, Lancet 2021.

Glofitamab in R/R B-cell lymphoma patients. CRS 67%, Grade 3-4 6%

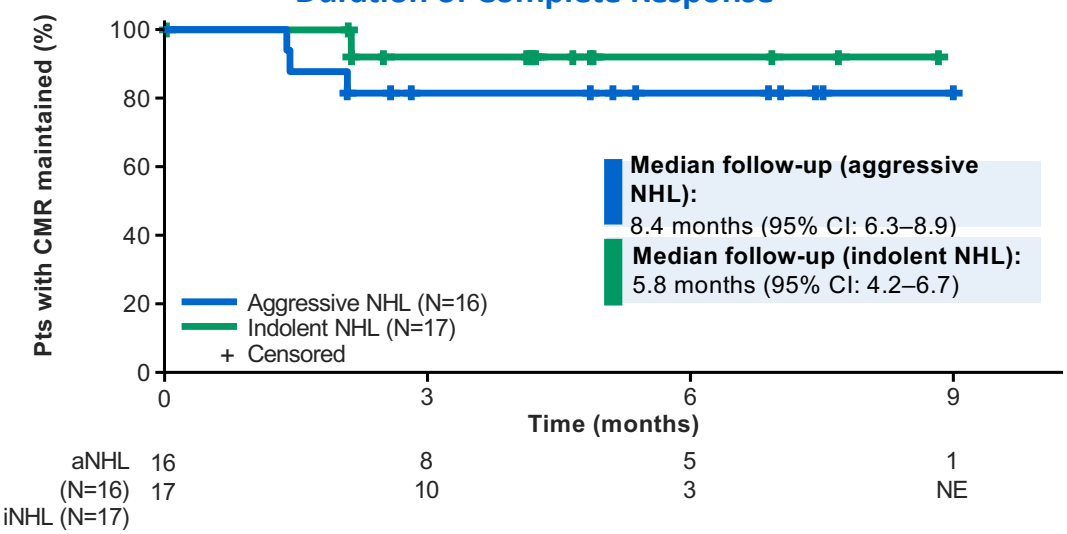
Response rate: Aggressive NHL



For aggressive NHL, a trend of improved response was observed at the RP2D (2.5/10/30mg; N=14), with a **CMR rate of 71.4%**



Duration of Complete Response

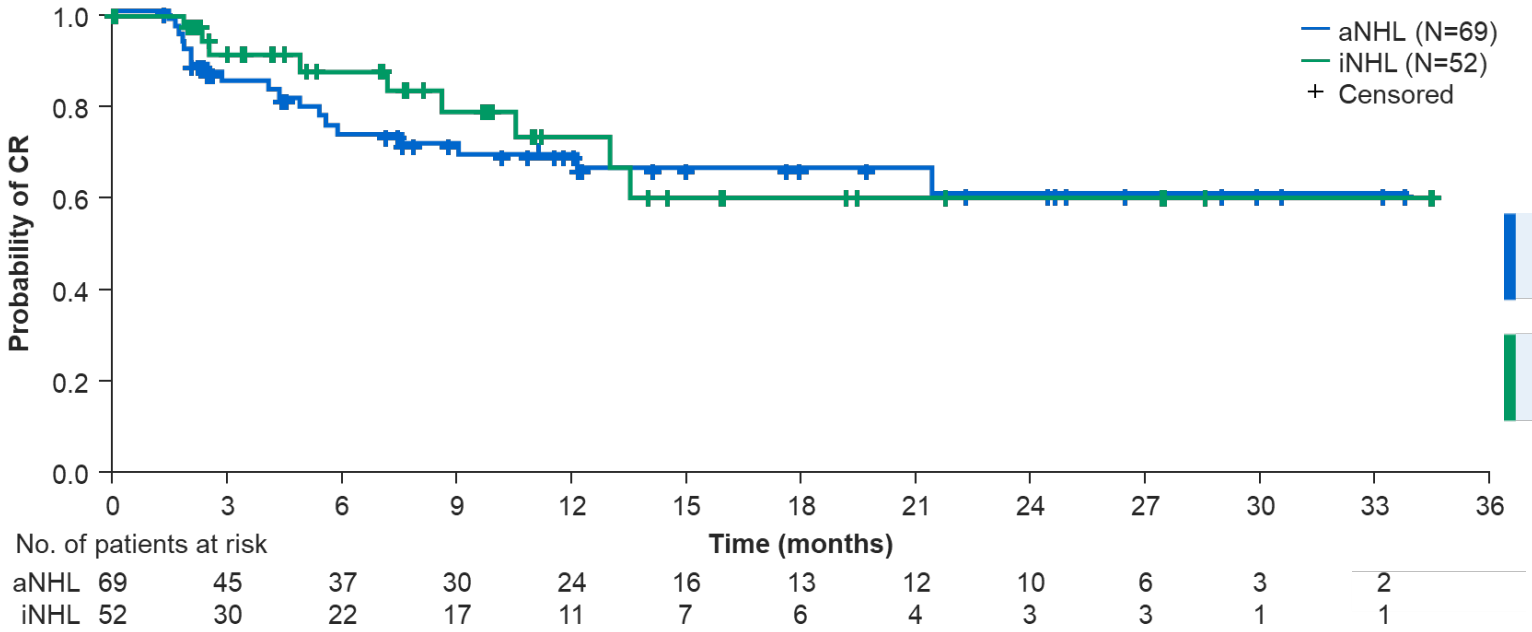


- The median duration of response for complete responders have not been reached
- **Aggressive NHL**: 13/16 CMRs are ongoing, 8 CMRs lasting >3 months; 5 CMRs lasting >6 months
- **Indolent NHL**: 16/17 CMRs are ongoing, 10 CMRs lasting >3 months; 3 CMRs lasting >6 months

Hutchings M et al, JCO 2021, Carlo-Stella, ICML-16.

Expanded phase 2 study with Glofitamab in R/R aNHL (183) and iNHL (75). ORR aNHL 53.7% and iNHL 81.3%; CR aNHL 39.4% and iNHL 69.3%. Duration of response

- Median follow-up of patients who achieved CR exceeded 12 months for patients with aNHL and median follow-up of CR was 5.3 months for iNHL
- Responses were durable beyond the end of treatment (approximately month 9):
  - **aNHL:** after a median CR follow-up of 12 months, 50/69 (72.5%) patients had an ongoing CR
  - **iNHL:** after a median CR follow-up of 5.3 months, 43/52 (82.7%) patients had an ongoing CR



Median CR follow-up (aNHL): 12.0 months (range: 0–34 months)

Median CR follow-up (iNHL): 5.3 months (range: 0–34months)

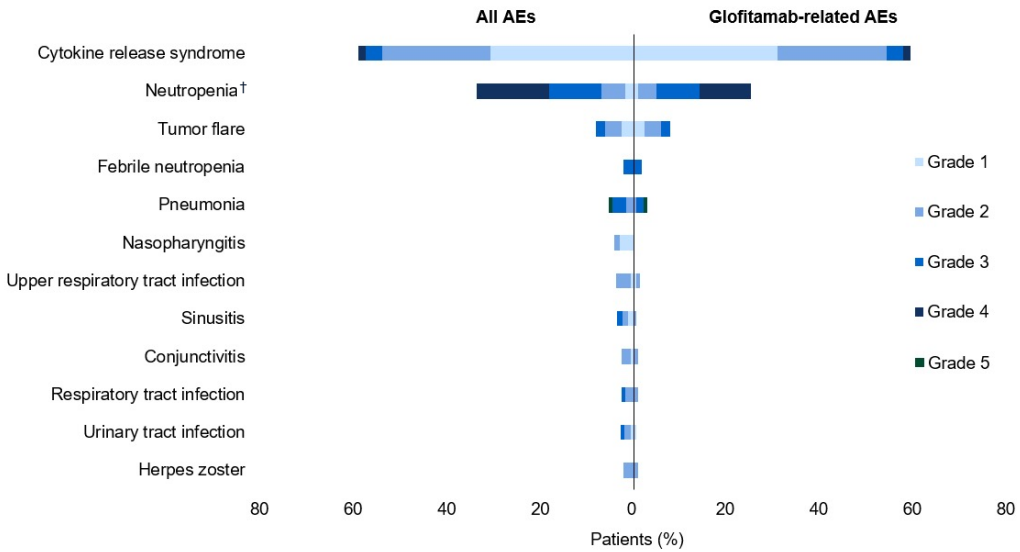
Dickinson M et al ASH 2021

Safety: CRS, pyrexia and neutropenia most common AEs

- Commonly reported AEs were CRS (58.9%), pyrexia (31.4%)* and neutropenia (34.1%)†
  - CRS events were mostly mild and mainly confined to cycles 1 and 2
  - Glofitamab related NAEs potentially consistent with ICANS occurred in 4 patients – all were non-serious and resolved at clinical cut-off

AE, n (%)	All patients (N=258)
Total AEs (occurring in ≥1 pt)	246 (95.3)
Serious AEs	149 (57.8)
Treatment related	123 (47.7)
Death (grade 5) AEs	7 (2.7)
Grade 3–4 AEs	139 (53.9)
Treatment related	89 (34.5)
AEs leading to treatment	
Discontinuation	6 (2.3)‡

Other AEs of interest



*Pyrexia events were separate from CRS. †Includes neutrophil count decreased. ‡Treatment-related AEs that led to discontinuation were: Cytomegalovirus chorioretinitis (Gr 3); colitis (Gr 4); hypovolemic shock (Gr 5); neutropenia (Gr 4); pneumonia (Gr 5); tumor flare (Gr3)
AE, adverse event; CRS, cytokine release syndrome; Gr, grade; ICANS, immune effector cell-associated neurotoxicity syndrome

CD20xCD3 bispecific antibodies + SoC

Rational combinations of targeted therapies

Mosunetuzumab/glofitamab (+obi) + lenalidomide
Phase 1, R/R FL
NCT04246086 (est. completion Aug 2022)

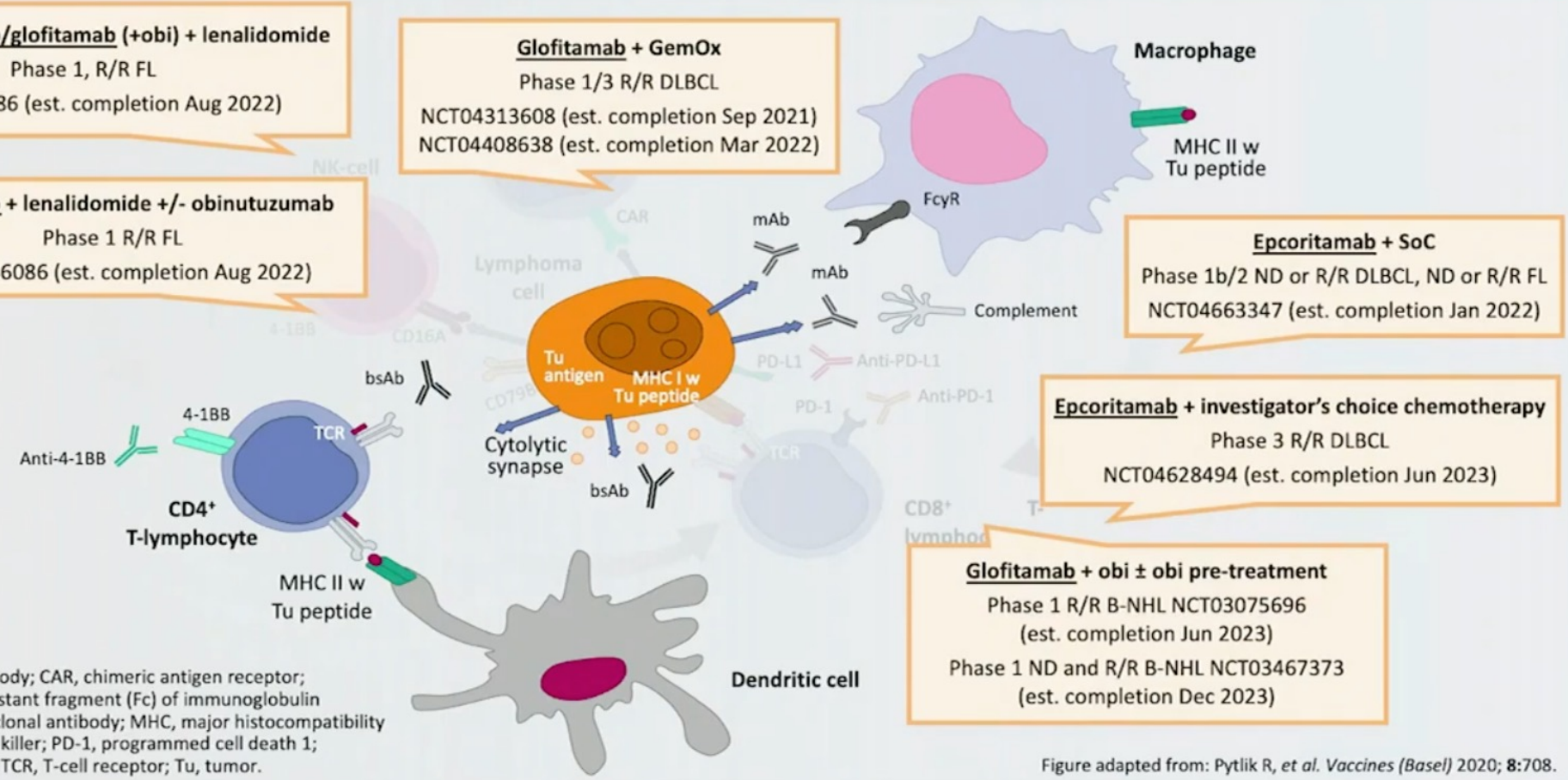
Glofitamab + lenalidomide +/- obinutuzumab
Phase 1 R/R FL
NCT04246086 (est. completion Aug 2022)

Glofitamab + GemOx
Phase 1/3 R/R DLBCL
NCT04313608 (est. completion Sep 2021)
NCT04408638 (est. completion Mar 2022)

Epcoritamab + SoC
Phase 1b/2 ND or R/R DLBCL, ND or R/R FL
NCT04663347 (est. completion Jan 2022)

Epcoritamab + investigator's choice chemotherapy
Phase 3 R/R DLBCL
NCT04628494 (est. completion Jun 2023)

Glofitamab + obi ± obi pre-treatment
Phase 1 R/R B-NHL NCT03075696
(est. completion Jun 2023)
Phase 1 ND and R/R B-NHL NCT03467373
(est. completion Dec 2023)



bsAb, bispecific antibody; CAR, chimeric antigen receptor; FcR, receptor for constant fragment (Fc) of immunoglobulin gamma; mAb, monoclonal antibody; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death 1; PD-L1, PD-1 ligand 1; TCR, T-cell receptor; Tu, tumor.

Figure adapted from: Pytlik R, *et al. Vaccines (Basel)* 2020; **8**:708.

By courtesy of Salles G, ICML 2021

Study Design: EPCORE NHL-2 Arm 2

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 R² 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 level 1: Epcoritamab 24 mg	Dose level 2: Epcoritamab 48 mg	Cohort 2a: Epcoritamab 48 mg	Cohort 2b: Epcoritamab 48 mg
QW C1–3, Q2W C4–9, Q4W C10+ **+ R²** C1–12	QW C1–3, Q2W C4–9, Q4W C10+ **+ R²** C1–12	QW C1–3, Q2W C4–9, Q4W C10+ **+ R²** C1–12	QW C1–2, Q4W C3–26 **+ R²** 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]	

Data cutoff: September 16, 2021

C, cycle; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; GELF, Groupe d'Etude des Lymphomes Folliculaires; IV, intravenous; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria.

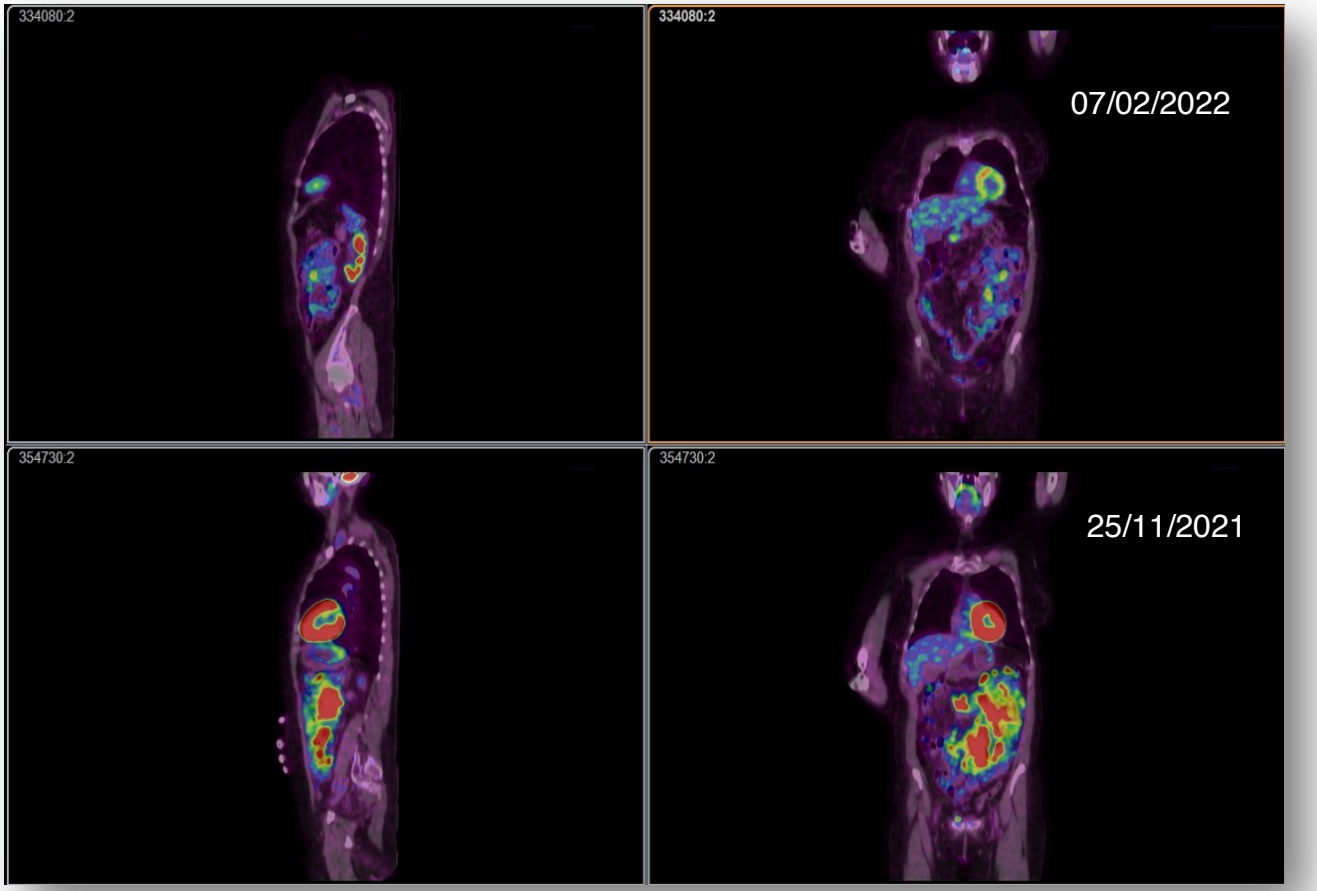
[a]Patients received SC epcoritamab with step-up dosing (ie, priming and intermediate doses before first full dose) and corticosteroid prophylaxis as previously described[2] to mitigate CRS. Epcoritamab was administered in 28-d cycles as shown. Rituximab regimen: 375 mg/m² IV QW in C1 and Q4W in C2–5; lenalidomide regimen: 20 mg QD (oral administration) for 21 d in C1–12. [b]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. Lugano criteria and LYRIC were used to assess response. AEs were graded by CTCAE, v5.0; CRS was evaluated by Lee et al[3] criteria. ClinicalTrials.gov Identifier: NCT04663347.

1. Brice P, et al. *J Clin Oncol*. 1997;15:1110-7. 2. Hutchings M, et al. *Lancet*. 2021;398:1157-69. 3. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38

Epcoritamab + Lenalidomide in FL at Third relapse
Candiolo Cancer Institute experience

- May 2015 FL stage IV, FLIPI High Risk: R-CHOP x 6 (Foll12)
- January 2017 relapse low tumor burden: Rituximab single agent + Rituximab maintenance
- April 2020 second relapse high tumor burden, bulky abdominal mass: R-bendamustine + HDC + ASCT (January 2021)
- Ten months later (November 2022) The patient came at outpatient clinic visit with a left inguinal lymph node enlargement
- PET November 2021: pathological uptake at bulky abdominal mass, mesenteric, iliac with bowel infiltration (SUV max 14) and modest uptake at the spleen
- CT scan maximum diameter 6 cm
- Left inguinal lymphnode biopsy: confirmed follicular lymphoma G1-G2, CD20+
- Bone marrow biopsy: no bone marrow infiltration

Epcoritamab + Lenalidomide in FL at Third relapse: baseline and assessement after two courses of R2+Epcoritamab



Best Overall Response

Response, n (%)[a]	Total n=21
Overall response	21 (100)
Complete Metabolic Response	17 (81)
Partial Metabolic Response	4 (19)
Stable disease	0
Progressive disease	0

Data cutoff: September 16, 2021. [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[1] Criteria

	Total N=29
CRS, n (%)	14 (48)
Grade 1	8 (28)
Grade 2	4 (14)
Grade 3	2 (7)
CRS onset at study day ≥15, n/n (%)[a]	9/14 (64)

Data cutoff: September 16, 2021. [a]Percent based on number of patients with CRS. The first full dose was administered on C1D15.

Linton KM et al ASH 2021

Glofitamab in Combination with Polatuzumab Vedotin: Phase Ib/II in 59 pts with R/R Diffuse Large B-Cell Lymphoma (DLBCL)

- Glofit + Pola arm: study design in R/R DLBCL

Key inclusion criteria (DLBCL arm)

- Age ≥18 years
- R/R DLBCL (including trFL and HGBCL)
- ECOG performance status 0–2

Objectives

Primary:

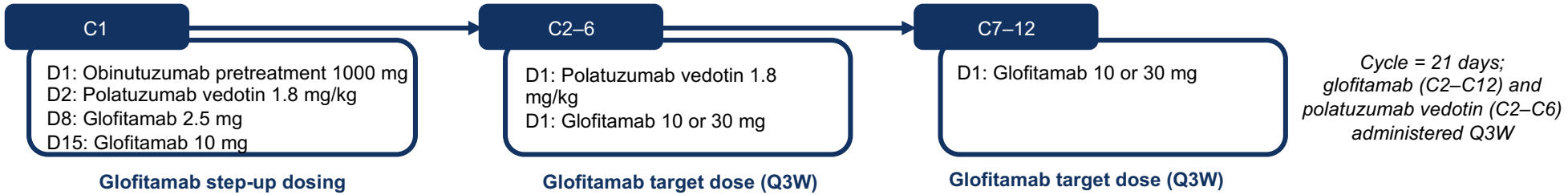
- DLTs
- Determine MTD and/or RP2D for Glofit + Pola (including obinutuzumab pretreatment)

Secondary:

- Safety and tolerability
- Efficacy (CR rate and BORR per Lugano 2014[1])

Glofit + Pola administration in R/R DLBCL

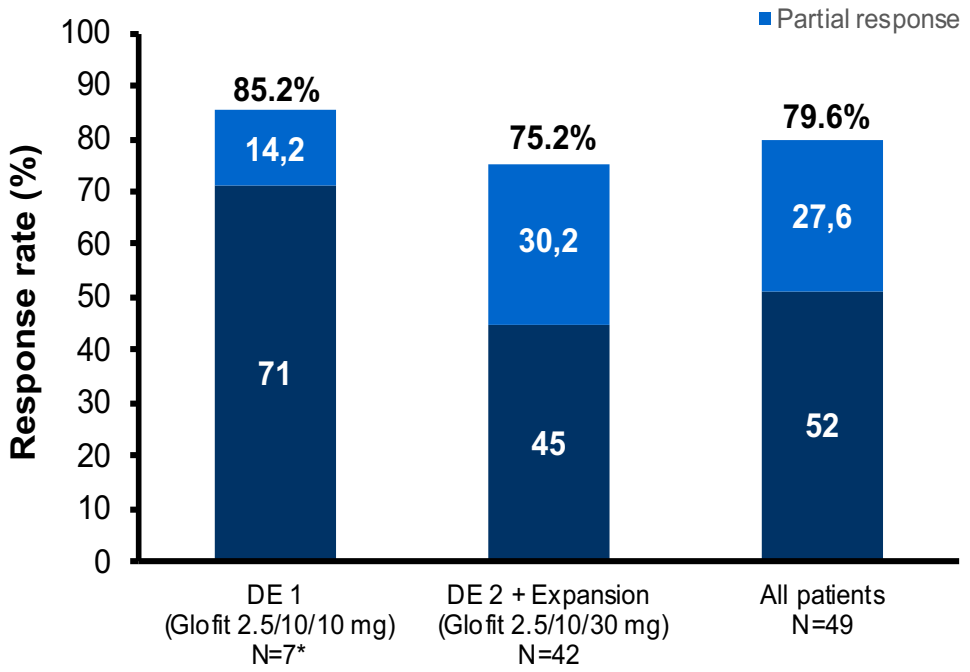
- Target enrollment ~90 patients
- CRS mitigation: obinutuzumab IV 1000 mg 7 days prior to glofitamab administration (step-up dosing)
- Efficacy assessments with PET-CT C3D1, C6D1 C8D15, EOT and Q3M



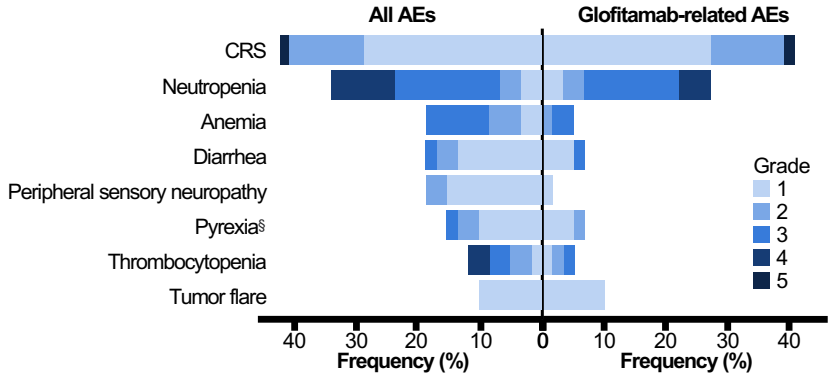
Hutchings M et al. Abs#525, ASH 2021.

Glofitamab in Combination with Polatuzumab Vedotin: response rate and adverse events

Response rate by Glofit + Pola dosing cohort



AEs with an incidence of ≥10% in all patients (N=59)



- Two fatal AEs (COVID-19 pneumonia*; Grade 5 CRS†)
- Study treatment was discontinued in 4 patients due to AEs‡:
  - Grade 4 thrombocytopenia; Grade 3 worsening of pre-existing renal impairment; Grade 5 CRS (Grade 3 CRS and TLS with clinical deterioration); Grade 4 jejunal perforation

Hutchings M et al. Abs#525, ASH 2021.

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
  - "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

Dose level 1:
Epcoritamab 24 mg
QW C1–4,
Q3W C5–6,
Q4W C7+
+ R-CHOP
C1–6

n=4 enrolled

Dose level 2:
Epcoritamab 48 mg
QW C1–4,
Q3W C5–6,
Q4W C7+
+ R-CHOP
C1–6

n=7 enrolled

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

Expansion

Epcoritamab 48 mg
QW C1–4, Q3W C5–6, Q4W C7+
+ R-CHOP
C1–6

n=13 enrolled
n≈20 planned

Primary objective: Antitumor activity[d]

Data cutoff: September 16, 2021

C, cycle; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBCL, high-grade B-cell lymphoma; IV, intravenous; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; NOS, not otherwise specified.
[a]Patients received SC epcoritamab with step-up dosing (ie, priming and intermediate doses before first full dose) and corticosteroid prophylaxis as previously described[1] to mitigate CRS. R-CHOP regimen in C1–6, 21 d each: rituximab 375 mg/m^2 IV Q3W; cyclophosphamide 750 mg/m^2 IV Q3W; doxorubicin 50 mg/m^2 IV Q3W; vincristine 1.4 mg/m^2 IV (with a recommended maximum of 2 mg) Q3W; and prednisone 100 mg/d IV or orally on days 1–5. Subsequent cycles of epcoritamab were 28 d. [b]De novo or histologically transformed from FL or nodal marginal zone lymphoma; based on World Health Organization 2016 classification.[2] [c]Classified as HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations. [d]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. Lugano criteria and LYRIC were used to assess response.
AEs were graded by CTCAE, v5.0; CRS was evaluated by Lee et al[9] criteria. ClinicalTrials.gov Identifier: NCT04663347.
1. Hutchings M, et al. *Lancet*. 2021;398:1157-69. **2.** Swerdlow SH, et al. *Blood*. 2016;127:2375-90.

Best Overall Response and CRS Graded by Lee et al Criteria

Response, n (%)[a]	Total n=11
Overall response	11 (100)
CMR	8 (73)
PMR	3 (27)
Stable disease	0
Progressive disease	0

Data cutoff: September 16, 2021. [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.

	Total N=24
CRS, n (%)	9 (38)
Grade 1	4 (17)
Grade 2	4 (17)
Grade 3	1 (4)
CRS onset at study day ≥15, n/n (%)[a]	7/9 (78)
Median time to resolution, d (range)[b]	2 (1–5)

Data cutoff: September 16, 2021. [a]Percent based on number of patients with CRS. The first full dose was administered on C1D15. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS; range is defined by shortest and longest CRS duration.

Conclusions

- Many patients with R/R B-cell lymphomas are not eligible to or relapsed after ASCT and/or CART and the prognosis is dismal
- Bispecific antibodies are a new type of immunotherapy allowing a direct cytotoxic effect of T-cell against B lymphoma cells.
- Bispecific antibodies are effective as single agents both in DLBCL and FL with manageable side effects
- Bispecific antibodies have the possibility to be combined with chemotherapeutic agents or other monoclonal antibodies or immunomodulating agents. They might represent an easy accessible, off-the shelf and most promising agents in the treatment of R/R DLBCL and FL and ready for an earlier use in the course of treatment.