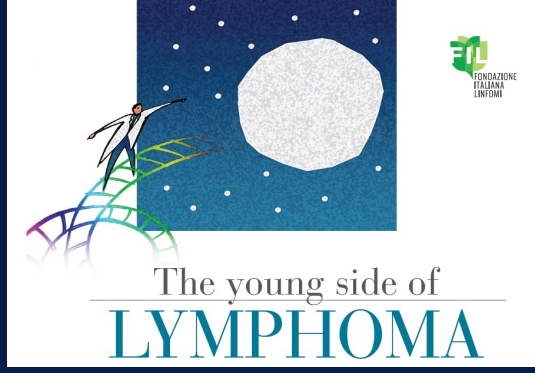


DLBCL TALK: efficacia e gestione di epcoritamab nella pratica clinica italiana nei pazienti recidivati refrattari

Dott. ssa Vittoria Tarantino
AOOR Villa Sofia Cervello
Palermo

CODICE VEEVA: IT-TDLBCL-250059 Relazione effettuata su incarico di AbbVie. Il contenuto della presentazione è stato creato in maniera indipendente ed autonoma

Uomo di 59 anni

Anamnesi patologica remota

Ipertensione arteriosa

FA cronica in NAO

Presentazione clinica

- Comparsa di linfoadenopatie sopra e sottodiaframmatiche (bulky lc 8 cm)
- ECOG 0
- Sintomi B (sudorazioni notturne)

Maggio 2023

Diagnosi

Biopsia di linfonodo Ic: linfoma follicolare G3a

Stadiazione

TC: linfonodi sopra e sottodiaframmatici con bulky Ic e mediastinico di 8,5 cm
PET: SUV max > 20
BOM: non infiltrazione
Esami di lab: Hb e LDH nei limiti

Linfoma Follicolare G3a, stadio IIIB, FLIPI 2

I linea

I linea: GCHOP21X 6

RP (TC , PET DS4)
Avvia mantenimento (Dicemb 2023- Aprile 2024)

…in corso di mantenimento…

Diagnosi

Biopsia di linfonodo lc DLBCL GCB cmyc 30%

Stadiazione

TC : > ln lc sovraclaveare 3,4 cm vs 1,57cm
PET: SUV max 20,5 in sede sovraclaveare
Esami di lab: LDH nei limiti

II linea

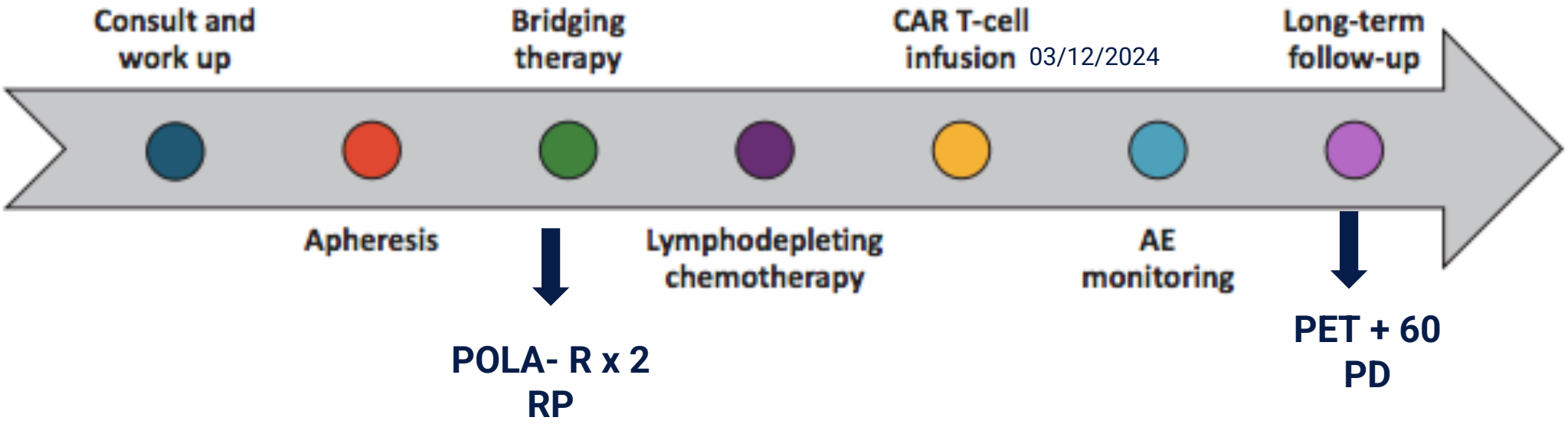
II Linea: R DHAOX + ASCT

PET 2: DS 5 (incremento dell'estensione in sede sovraclaveare)

Paziente POD24 con trasformazione in DLBCL GB

Terza Linea: CART

3L+ DLBCL



Febbraio 2025

Diagnosi

Agobiopsia di linfonodo addominale DLBCL GCB CD20+, Cd19+

Stadiazione

TC : linfonodi mediastinici (dt max 3 cm),addominali (dt max 5 cm)
PET: SUV max 17 in sede addominale

IV linea

Epcoritamab sc

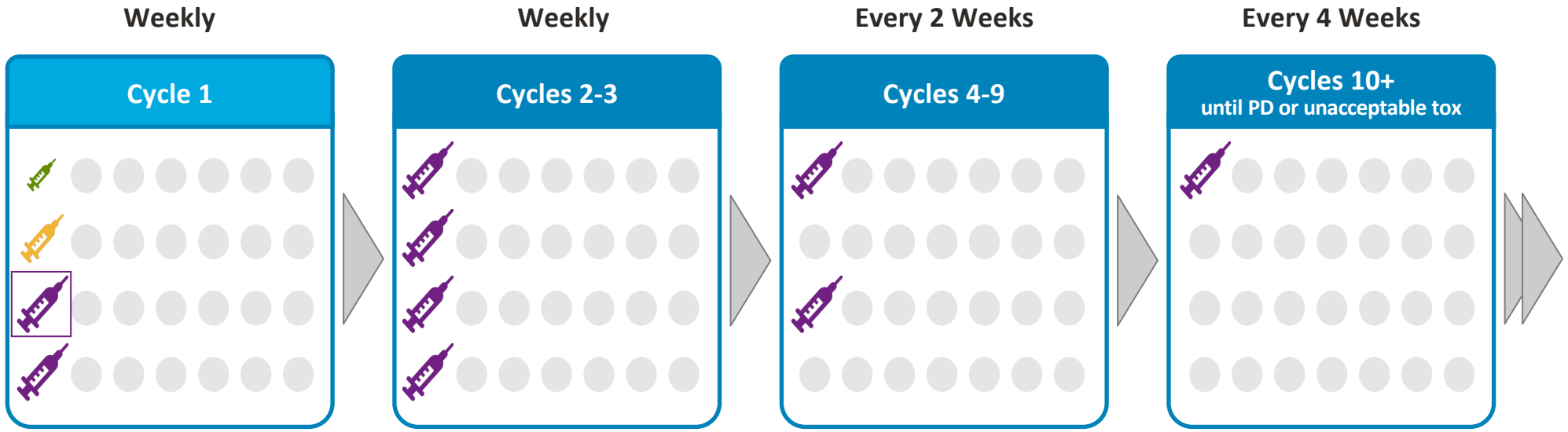
EPCORITAMAB DOSING GUIDE

3L+ DLBCL

Administer subcutaneous epcoritamab according to the following schedule in 28-day cycles

Dosing:

- Step-up dose 1 = 0.16 mg (Priming)
- Step-up dose 2 = 0.8 mg (Intermediate)
- First full dose = 48 mg
- 48 mg



Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS and/or ICANS.

Pre-medication

Prednisolone (D1-4)
100 mg IV or PO

OR **Dexamethasone (D1-4)**
15 mg IV or PO

Diphenhydramine (D1)
50 mg IV or PO

Paracetamol (D1)
650 to 1000 mg PO

Rivalutazione PET dopo IV cicli: RC

Allotrapianto

Novel agents in R/R LBCL

Single US centre retrospective experience in R/R LBCL patients treated with novel agents (Jan 2019 – Mar 2024)

Treatment	N (%)	Treatment	ORR (%)	CRR (%)	Median EFS*	1-year EFS*
Pola (alone or with R±B)	91 (69)	40% bridging/holding tx	**46**	**22**	4.2 months (n=55)	24% (n=55)
Lonca	45 (34)	89% definitive tx	**44**	**22**	2.7 months (n=40)	6% (n=40)
Tafa/Len	39 (30)	95% definitive tx	**30**	**14**	2.5 months (n=37)	14% (n=37)
BsAb†	35 (27)	100% definitive tx	**55**	**27**	4.0 months (n=35)	28% (n=35)

132 patients identified

- Median age was 66 years (range 24–86)
- 60% of patients had DLBCL, 16% HGBCL, and 18% transformed indolent
- 78% had primary refractory or early relapse disease post first-line treatment
- 61% had prior CAR-T
- Median no. of prior LoT was 5 (range 2–17)

Novel agent pre-CAR-T (n=30)

Novel agents post-CAR-T (n=62)

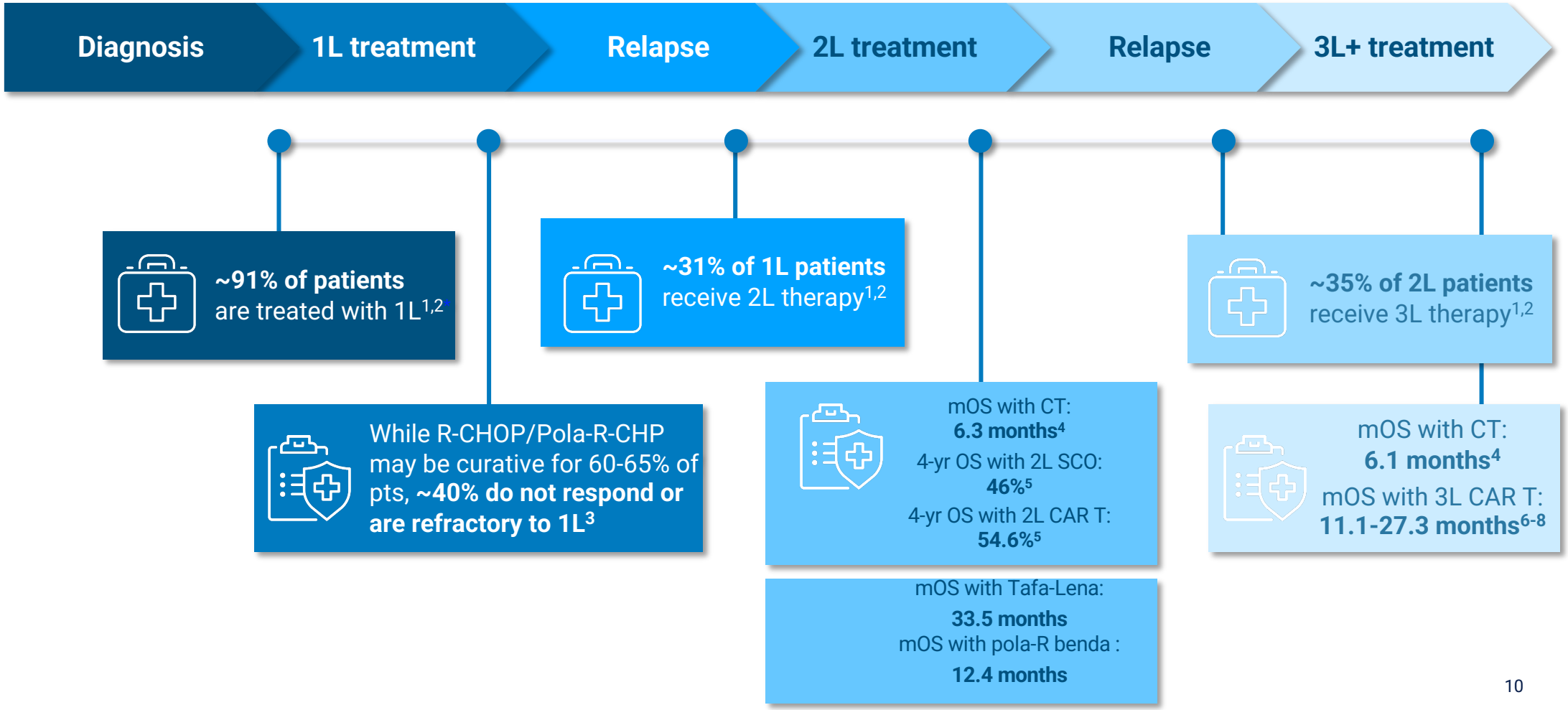
Patients who did not receive CAR-T (n=52)

- The most used novel agent in the post-CAR-T and no-CAR-T setting was Pola (40%), followed by Lonca (23%)
- For the first novel agent after CAR-T:
  - Best ORR 54%, CR 31% (missing n=1)
  - Median EFS 3.1 months, 1-year EFS 17%

Study shows poor outcomes with currently-approved novel agents in post-CAR-T and CAR-T-ineligible patients.

Godbole et al. ASH 2024; Poster #4460.

Is DLBCL a curable disease?



1. Kanas G, et al. Leuk Lymphoma. 2022;63(1):54-63. 2. Johnston, et al. AMCP Nexus. 2022. 3. Sehn LH, et al. J Clin Oncol. 2020;38(2):155-165. 4. Crump M, et al. Blood. 2017;130(16):1800-1808.
5. Westin J, et al. N Engl J Med 2023; 389:148-157. 6. Neelapu S, et al. Blood (2023) 141 (19): 2307–2315. 7. Abramson J, et al. Blood. 2024 Feb 1;143(5):404-416. 8. Schuster SJ, et

The therapeutic choice for R/R DLBCL patients is increasingly complex and many factors can be involved

Disease factors

- Biology of the disease (DH/TH lymphoma)
- Clinical presentation
- Refractoriness

Patient factors

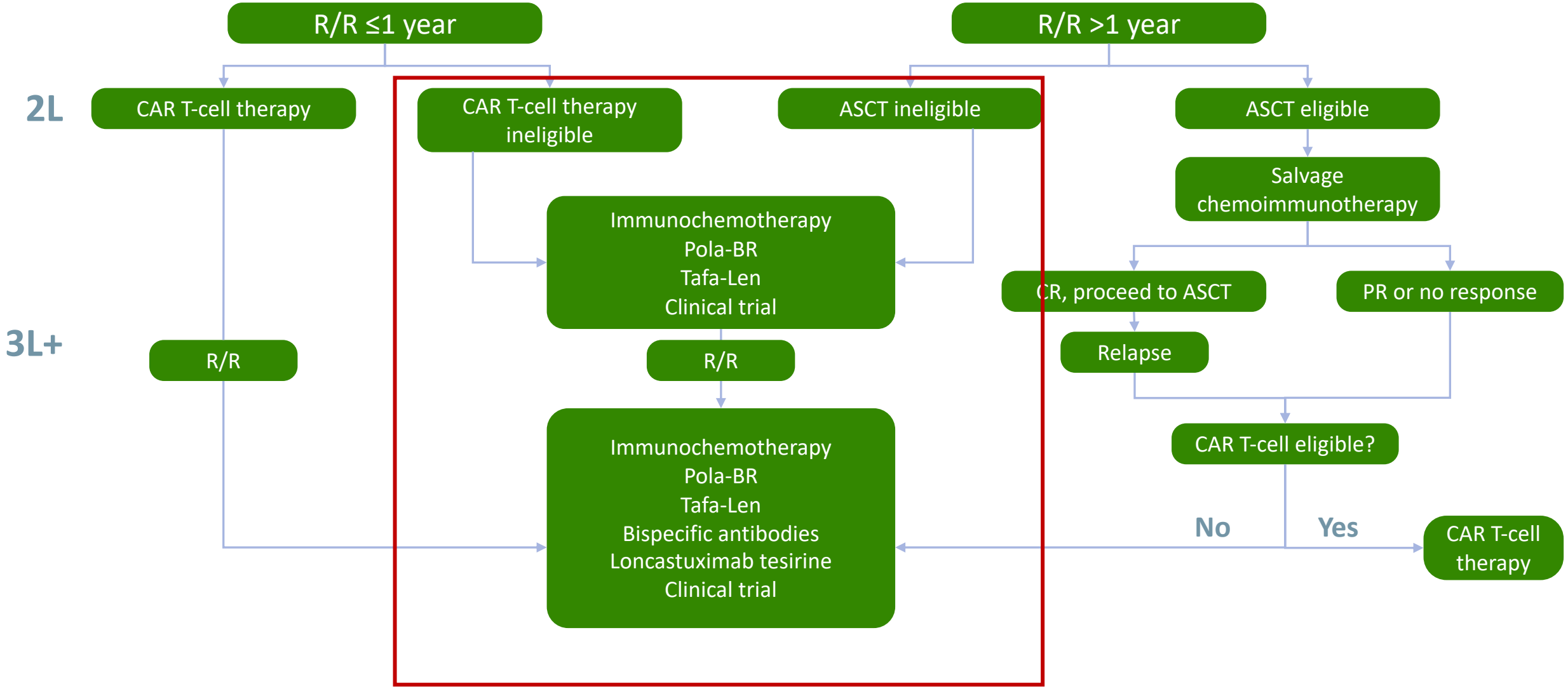
- Age
- Fitness/comorbidities
- Family/social support
- Patient preference

Treatment considerations

- Treatment history and sequencing
- Efficacy and tolerability
- Schedule of administration
- Cumulative toxicity
- Processing and logistics
- Availability and reimbursement

How do we navigate R/R DLBCL treatment?

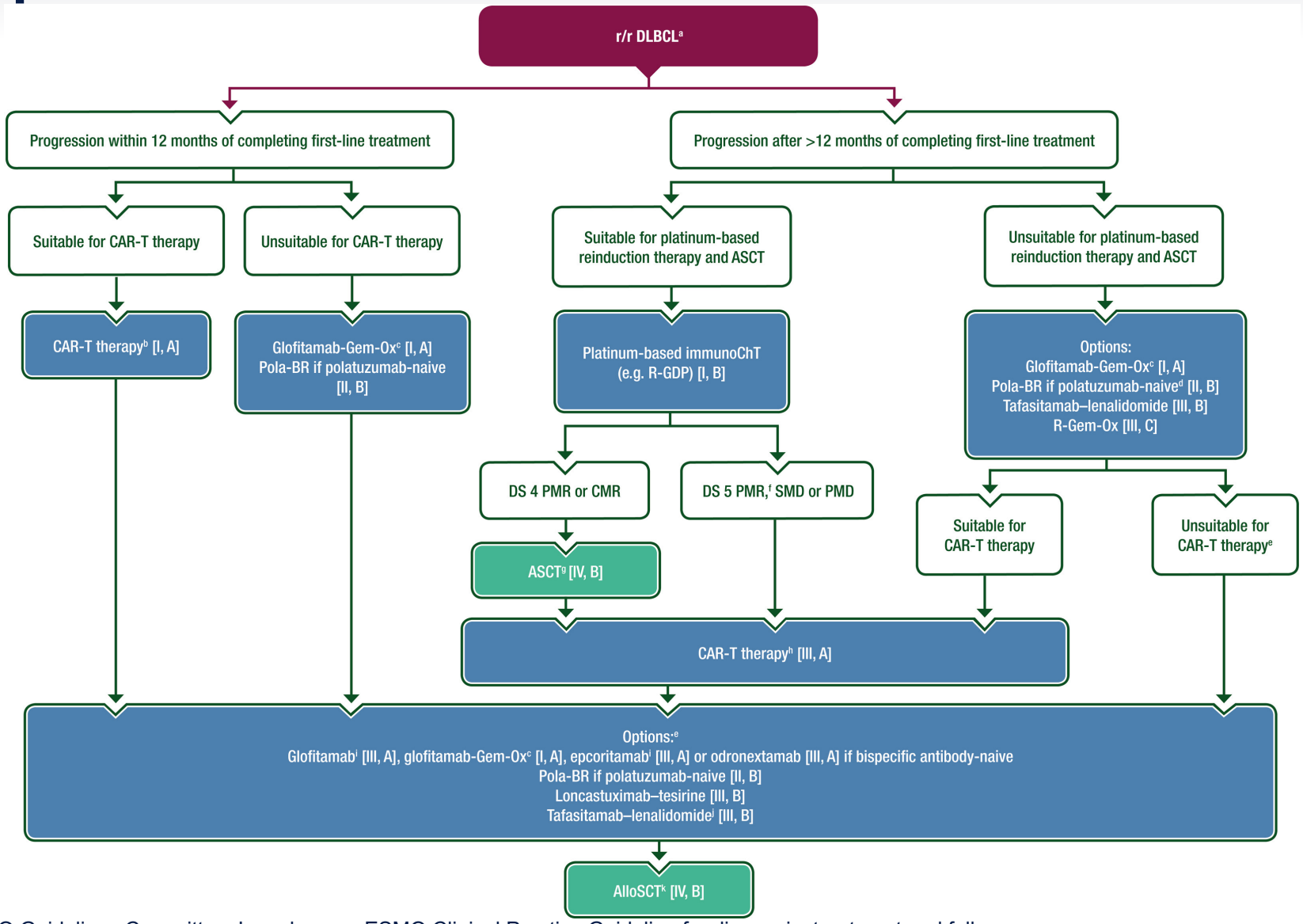
Novel 2L treatment options are available, but not all patients are eligible and only a small proportion are ultimately cured



Adapted from Gonzalez Barca. *J Clin Med* 2023

ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

3L+ DLBCL



Eyre TA, et al. on behalf of the ESMO Guidelines Committee. Lymphomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
Annals of Oncology (2025), doi: https://doi.org/10.1016/ j.annonc.2025.07.014.

Deciding Between Available Bispecific Antibodies and Other 3L+ Treatments for R/R DLBCL

How do bispecific antibodies compare to other therapies?

“Off the shelf” option (availability): means we can give right away whereas therapies like CAR T-cells require adequate cell collection, manufacturing time, etc

Safety profiles:

- Lower toxicity risks/safer: including for patients not good candidate for CAR T-cell therapy
- Shorter hospitalization times
- Different targets (CD20 vs CD19) which means that CAR T-cell does not preclude bispecific antibody and vice versa

What are the advantages for bispecific antibodies over chemotherapy?

Improved efficacy, potentially better safety and/or improved QoL

Deciding Between Available Bispecific Antibodies and Other 3L+ Treatments for R/R DLBCL

Reduced dosing frequency

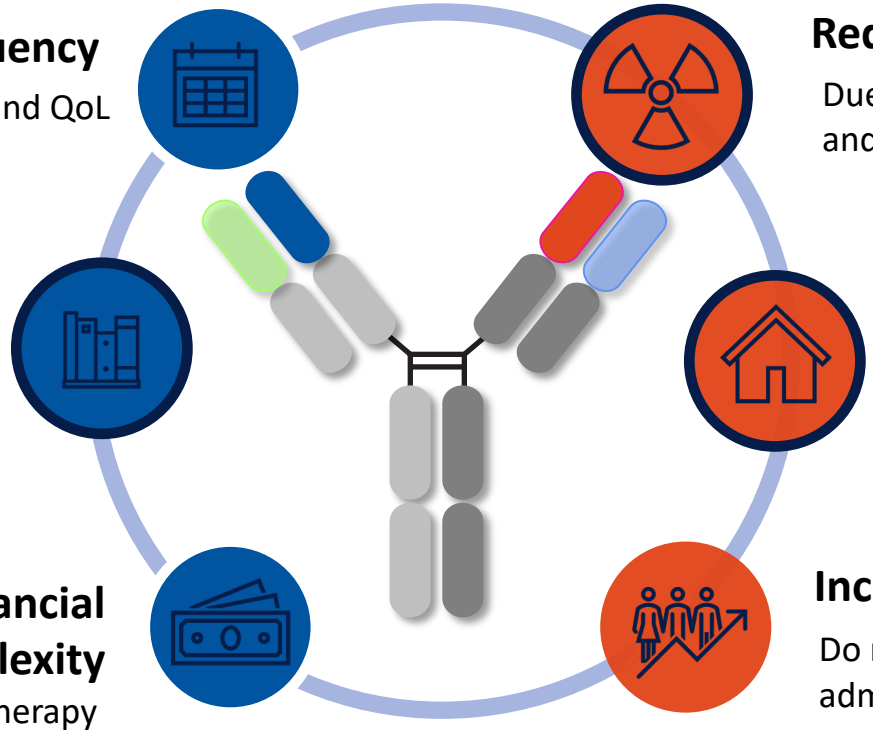
Patient convenience and QoL

Available off the shelf

Easier to initiate therapy compared with CAR T-cell therapy

Decreased financial complexity

Compared with CAR T-cell therapy



Reduced risk of adverse events

Due to construct, step-up dosing, and mitigation strategies

Outpatient administration

Patient convenience and QoL

Increased access

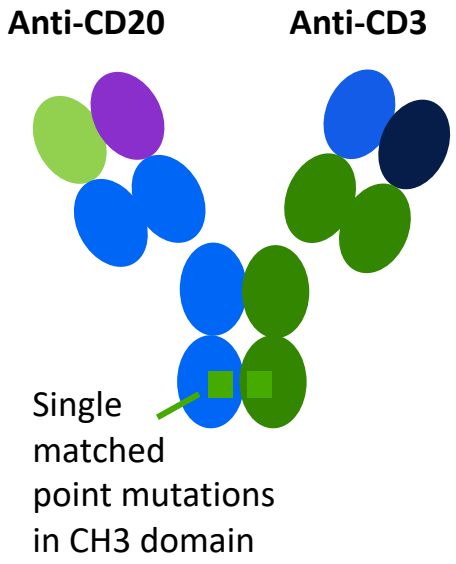
Do not need to be a certified center to administer; no driving restrictions; may not need a caregiver

Cassanello. Oncoimmunology. 2024;13:2321648.

Focus on : CD20/CD3 Bispecific Antibodies in B-Cell Lymphomas

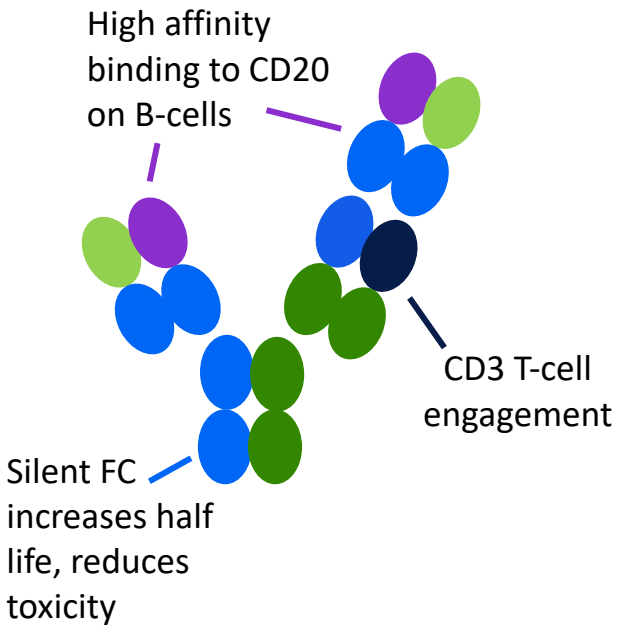
3L+ DLBCL

Humanized mouse IgG1-based mAb



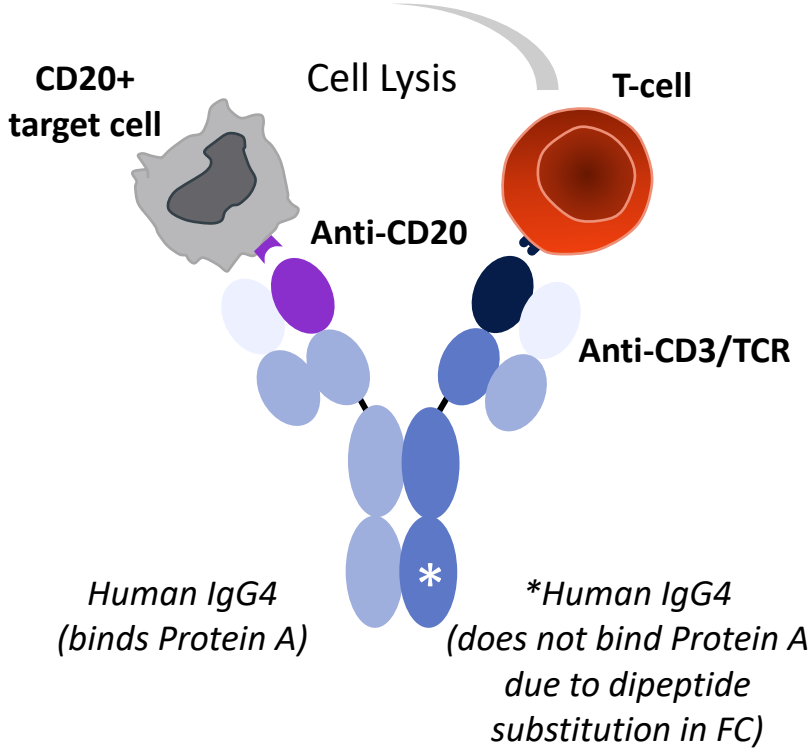
Epcoritamab (SC)

3L+ R/R DLBCL



Glofitamab (IV)

3L+ R/R DLBCL



Odronextamab (IV)

Approval Status: Priority Review for 3L+ R/R FL and DLBCL

Castaneda-Puglianni. Drugs Context. 2021;10:2021. Bannerji. ASH 2020. Abstr 42. Budde. ASH 2018. Abstr 399. Hutchings. Lancet. 2021;398:1157. Engelberts. eBioMedicine. 2020;52:102625. Hutchings. JCO. 2021;39:1959. Epcoritamab PI. Glofitamab PI.

EPCORE NHL-1 study design

3L+ DLBCL

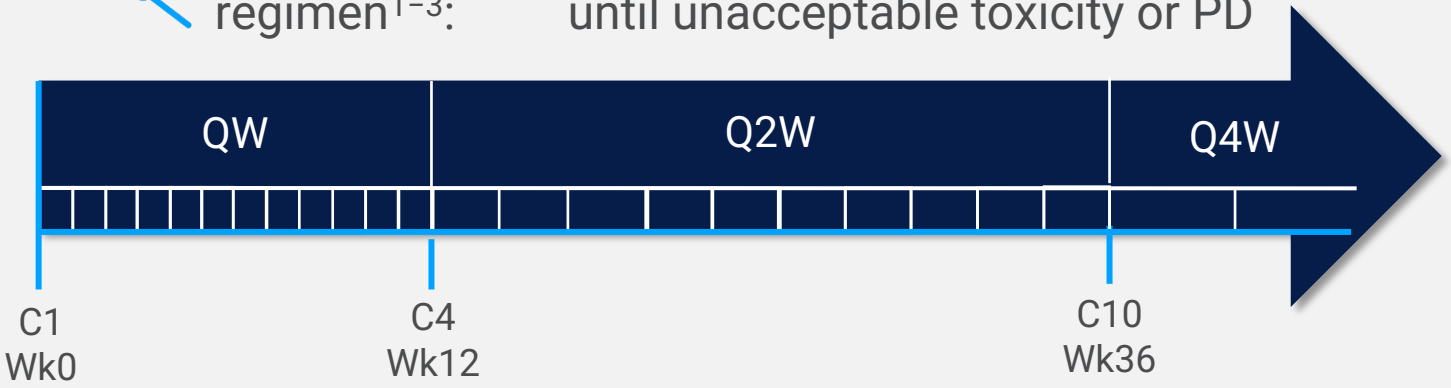
Phase 2 of the ongoing multicenter, open-label, phase 1/2 clinical trial (NCT03625037)[1–3]

Patients with
R/R CD20+ DLBCL

- ≥ 18 years of age
- ECOG PS 0–2
- ≥ 2 prior LOT[a]

Treatment regimen[1–3]:

SC **epcoritamab** RP2D 48 mg until unacceptable toxicity or PD



KEY ENDPOINTS[1]

EFFICACY
- **ORR[f] (primary endpoint)**
- **DOR**
- **PFS**
- **OS**

SAFETY
- **CRS**
- **ICANS**

[a] Including an anti-CD20 mAb. [b] SUD 1: priming, 0.16 mg; SUD 2: intermediate, 0.8 mg. Corticosteroid prophylaxis was used in C1 to mitigate CRS. [c] Inpatient 24-hour monitoring was required at first full dose in the extension part of the study to ensure patient safety and better characterize CRS. [d] C1 optimization recommendations: dexamethasone 15 mg premedication[g]; administer 500 mL of isotonic IV fluids on the day of each dose prior to administration; hospitalization not required but patients must remain close to the treatment facility for 24 hours after the first full dose; other recommendations include 2–3 L of fluid intake during the 24 hours prior to and following each dose, holding antihypertensive medications for 24 hours prior to each dose, and self-monitoring of temperature 3 times daily for 4 days following each dose.

1. Thieblemont C, et al. *Leukemia* 2024 Sep 25:1-0. 2. Thieblemont C, et al. Poster at the European Hematology Association Annual Congress; June 13–16, 2024; Madrid, Spain. Poster P1151. 3. Thieblemont C, et al. Poster at the American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2024; Chicago, IL, US. Poster 7039.

Baseline characteristics

3L+ DLBCL

Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
<65 y, n (%)	80 (51.0)
65 to <75 y, n (%)	48 (30.6)
≥75 y, n (%)	29 (18.5)
ECOG PS[a], n (%)	
0	74 (47.1)
1	78 (49.7)
2	5 (3.2)
Disease Characteristics[b]	**LBCL, N=157**
Disease type, n (%)	
DLBCL[c]	139 (88.5)
De novo	97/139 (69.8)
Transformed	40/139 (28.8)
DLBCL with DH/TH by central FISH[d]	13/99 (13.1)
HGBCL	9 (5.7)
PMBCL	4 (2.5)
FL G3B	5 (3.2)

Prior Treatments	LBCL, N=157
Median time from initial diagnosis to first dose[e], y	1.6 (0.0–28.4)
Median time from end of last therapy to first dose, mo	2.4 (0.0–153.0)
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (70.7)
Primary refractory[f] disease, n (%)	96 (61.1)
Refractory[f] to last systemic therapy, n (%)	130 (82.8)
Refractory[f] to ≥2 consecutive lines of therapy, n (%)	119 (75.8)
Prior ASCT, n (%)	31 (19.7)
Prior CAR T therapy, n (%)	61 (38.9)
Refractory[f] to CAR T therapy	46/61 (75.4)

As of January 31, 2022, 51 patients (32%) were receiving epcoritamab treatment at a median follow-up of 10.7 months

Thieblemont C, et al. J Clin Oncol. 2023;41:2238-47.

Responses Rate and Duration of Response

3L+ DLBCL

63.1%

Overall Response Rate

95% CI: 55.0–70.6

40.1%

Complete Response Rate

95% CI: 32.4–48.2

11 patients converted from PR to CR after wk 36 as later as wk 96

20.8 months

Median Duration of Response

95% CI: 13–32.5

1.4 months

Median Time to Response

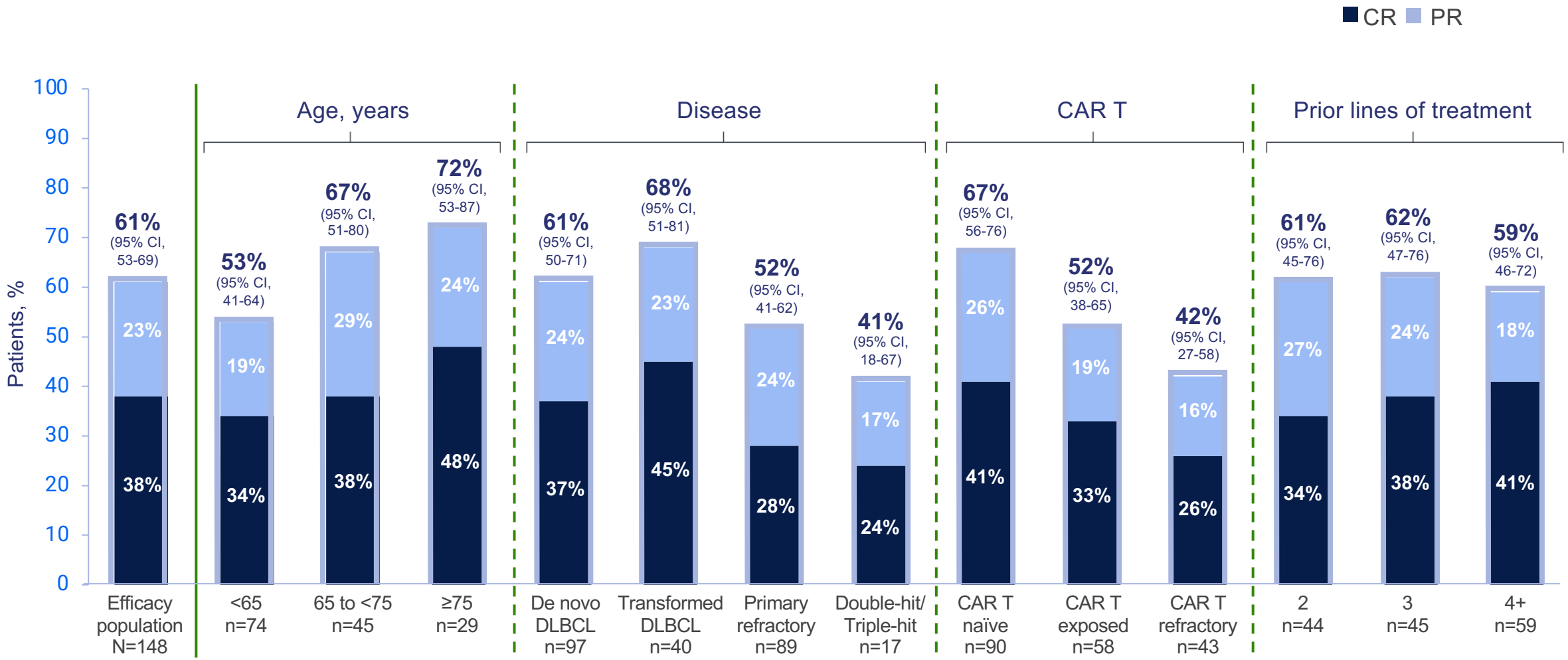
95% CI: 1–8.4

Median follow-up time: 37.1 months (95% CI: 0.3–45)

Thieblemont C et al, Leukemia, 2024 doi: 10.1038/s41375-024-02410-8
Vose JM et al. ASH 2024; Dec 2024; P4480, San Diego, Virtual

Response Rates Observed Across all Subgroups

3L+ DLBCL



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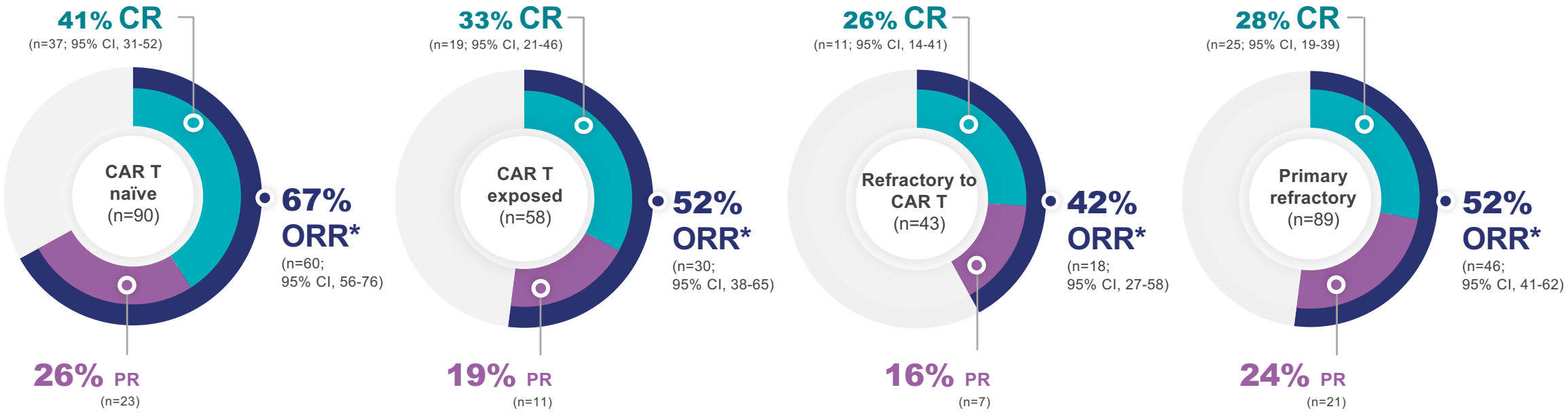
1, Thieblemont C, et al. J Clin Oncol. 2022. doi: 10.1200/JCO.22.01725.

Response Rate according CART exposure

3L+ DLBCL

ORR CR PR



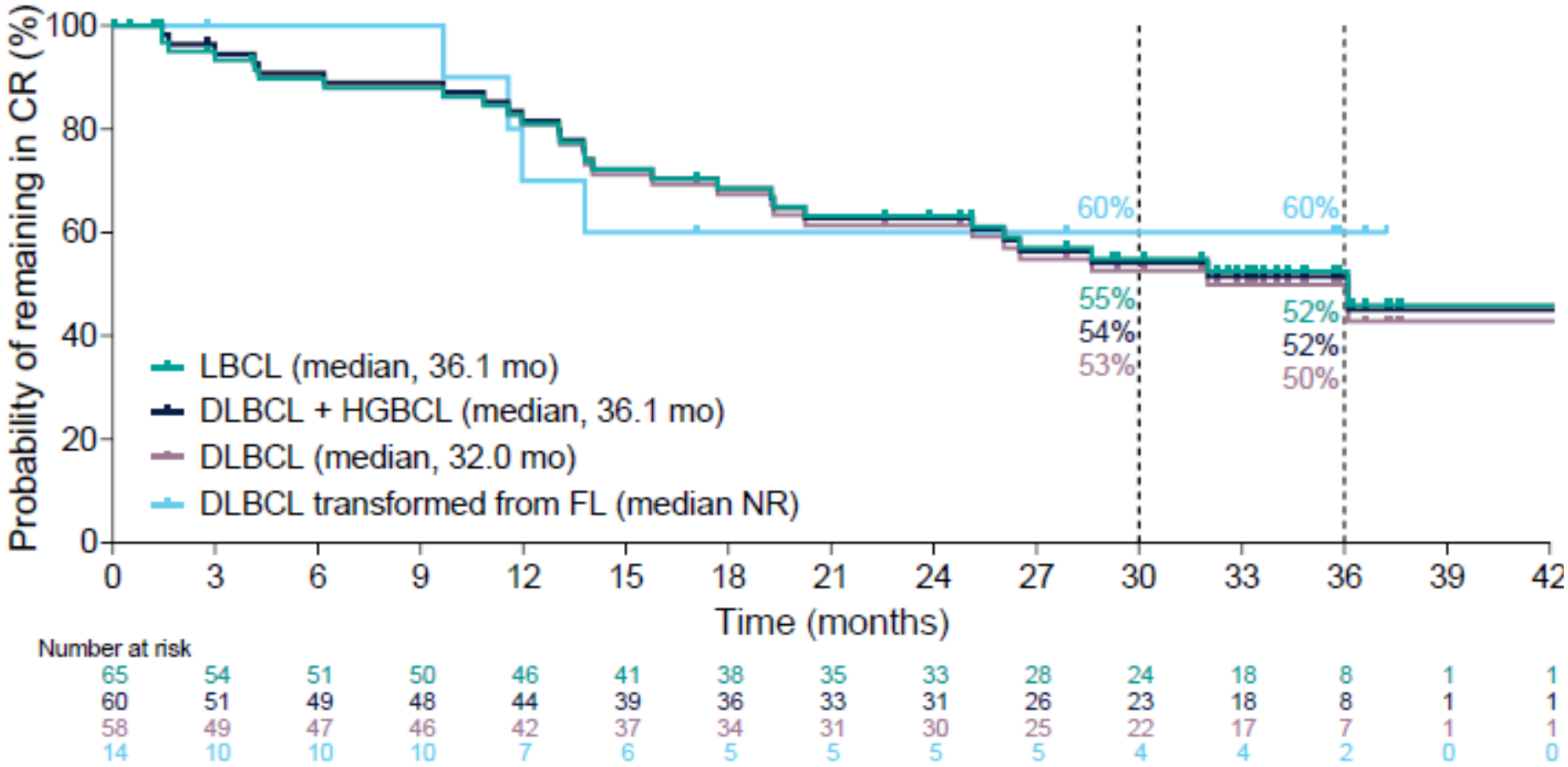
*ORR was determined by Lugano criteria (2014) as assessed by an IRC.

Thieblemont C, et al. J Clin Oncol. 2022. doi: 10.1200/JCO.22.01725.

Long-Term Efficacy Outcomes

Deep and Durable Responses by Disease Subtype

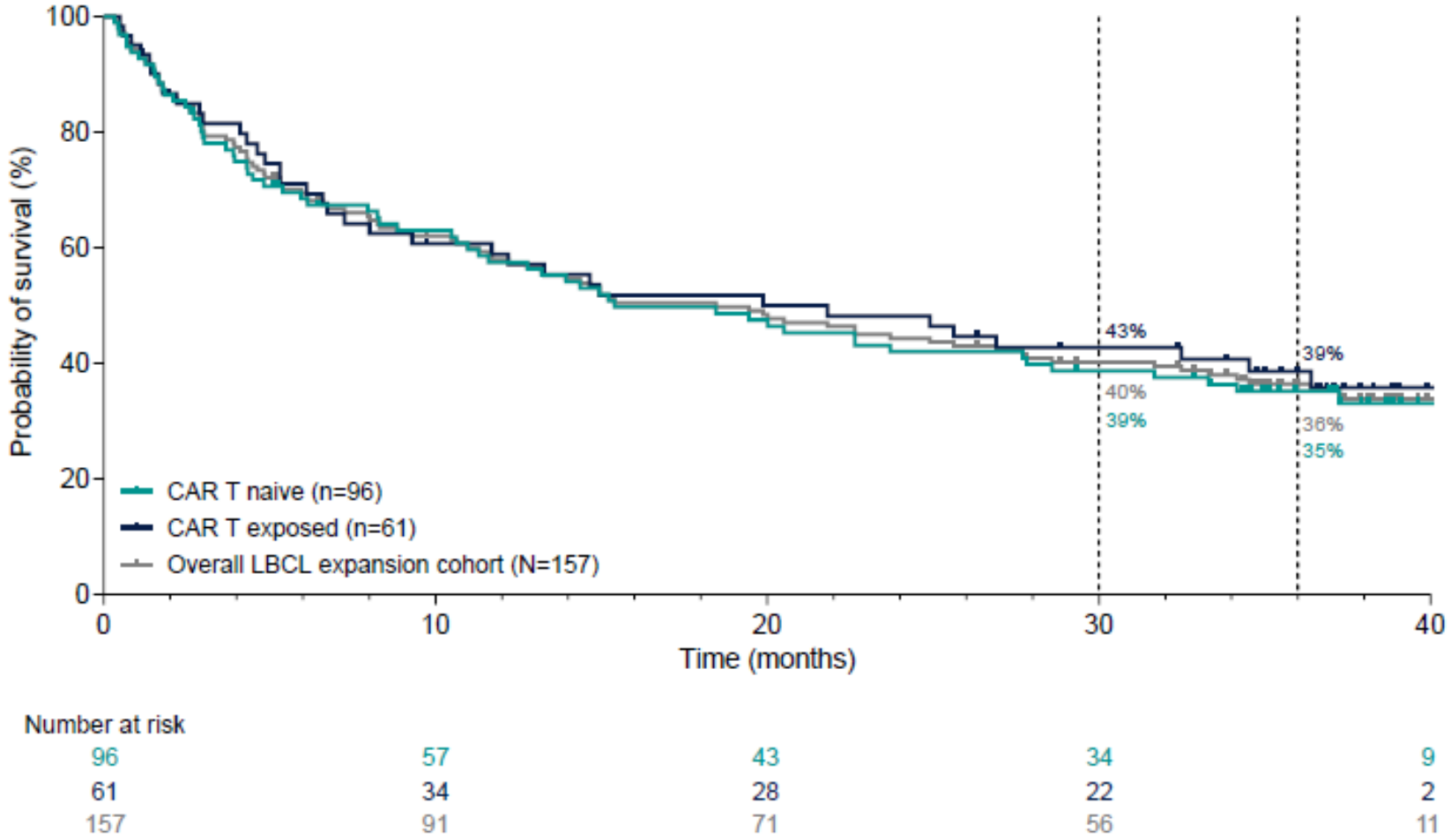
3L+ DLBCL



Overall Median DOCR 36.1 months (20.2 – NR)

Long Term Efficacy
Overall Survival in CAR-T naive and Exposed patients

3L+ DLBCL

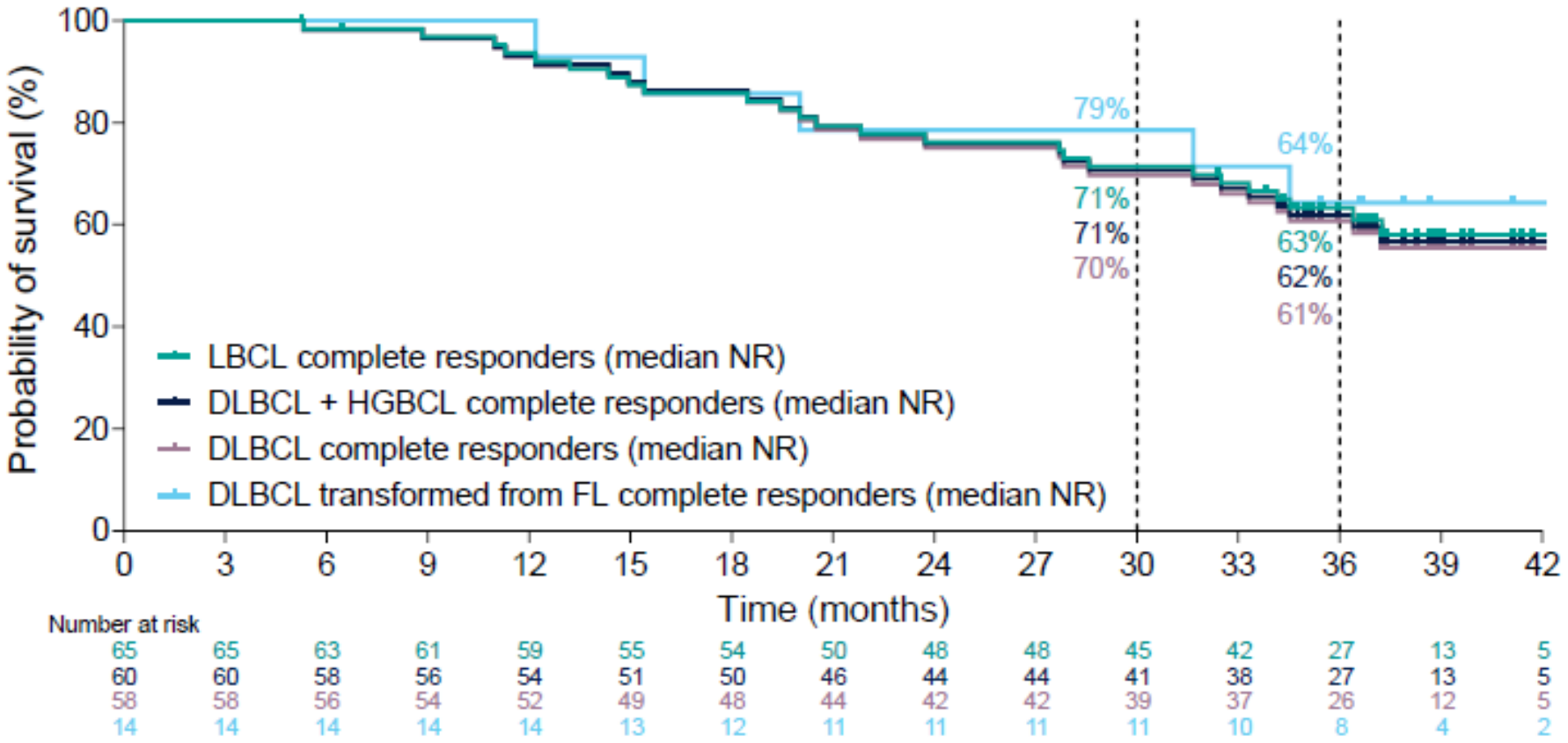


Median OS in DLBCL 19.4 mos[2]

1. Karimi YH et al. ASH 2024; Dec 2024; P1737, San Diego, Virtual
2. Thieblemont C, et al. *Leukemia* 2024 Sep 25:1-0.

Long term PFS and OS Benefits with CR

3L+ DLBCL



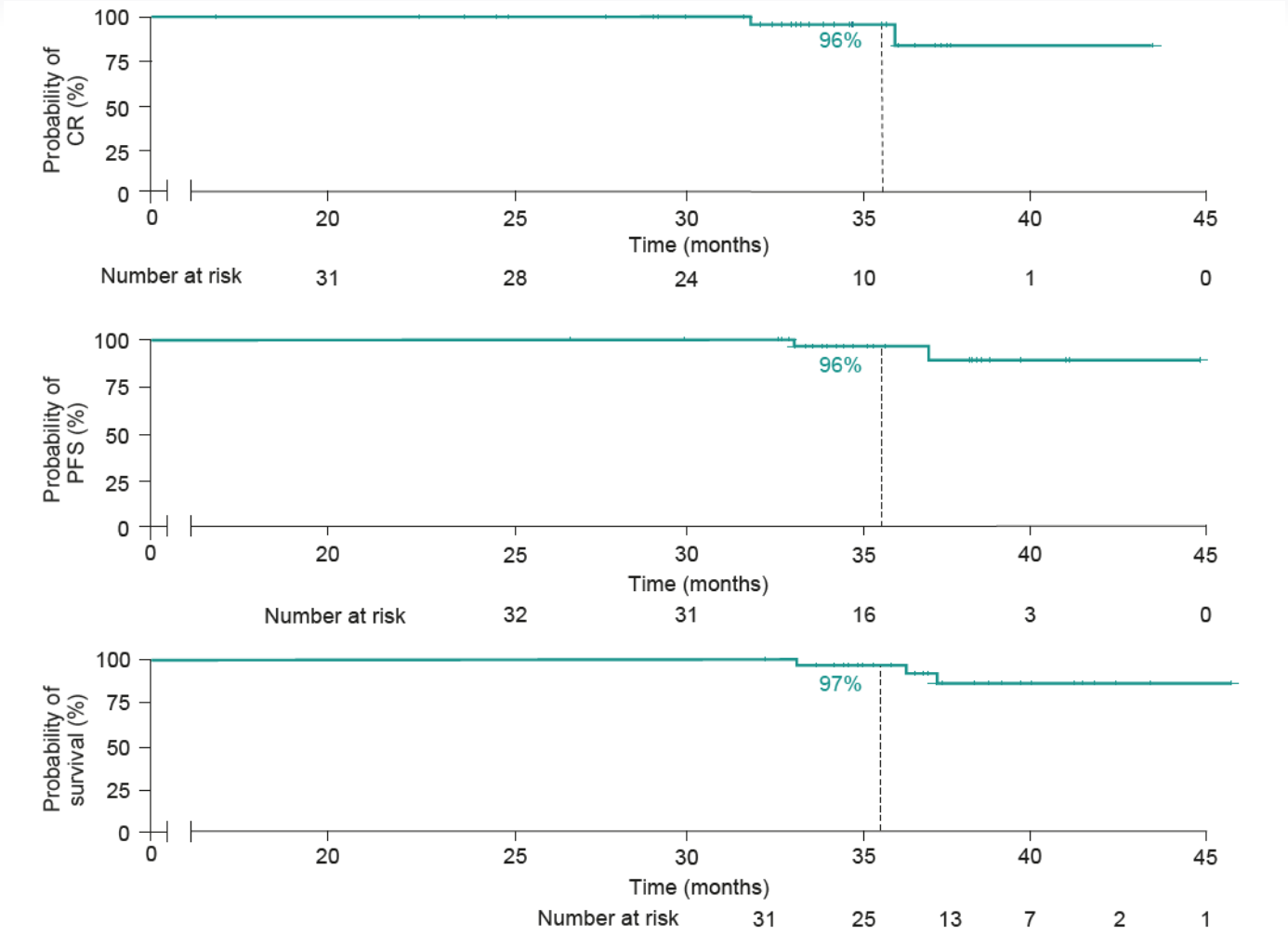
6 out of 10 patients in CR were still alive at 36 months

- Among complete responders (n=65), median PFS was 37.3 mo (95% CI, 26-NR)

Vose JM et al. ASH 2024; Dec 2024; P4480, San Diego, Virtual

Long-Term Efficacy Outcomes in pts with CR after 2 ys

3L+ DLBCL



Median DOCR was not reached; an estimated 96% of patients remained in CR at 3 years, and the **longest ongoing CR was >43 months** Median PFS and median OS were not reached: An estimated 96% and 97% of patients remained progression free and alive, respectively, at 3 years

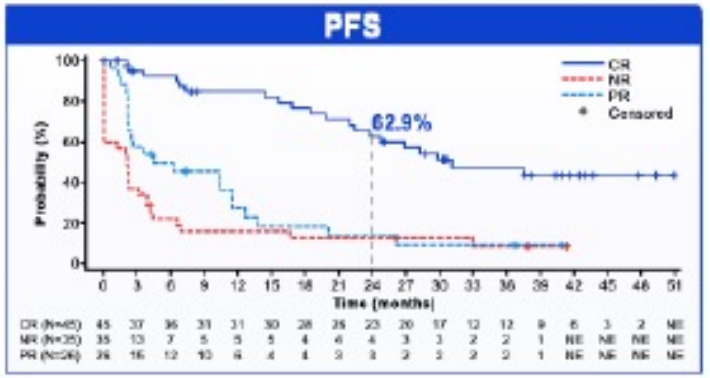
Chen Y. C. et al, Poster 320, EHA 2025

Landmark analysis

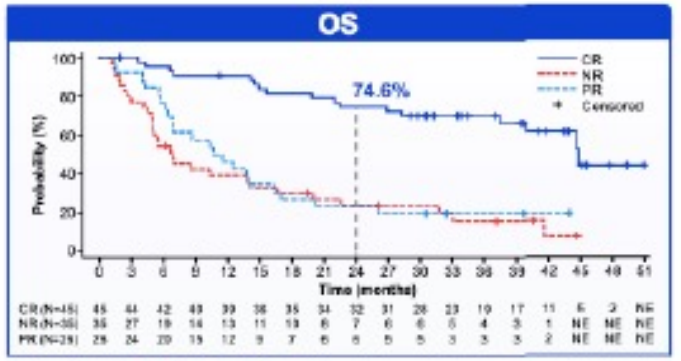
CR at C3 is an early predictor of long-term outcomes

GLOFITAMAB

by response at C3



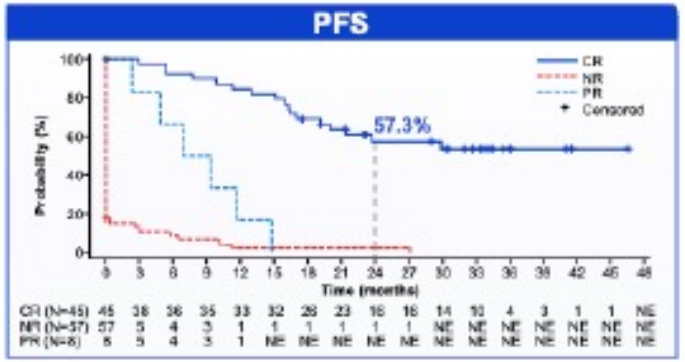
Landmark PFS from C3 in patients with CR at C3*	N=45
Median PFS, months (95% CI)	31.1 (23.8–NE)
24-month PFS rate, % (95% CI)	62.9 (47.5–78.4)



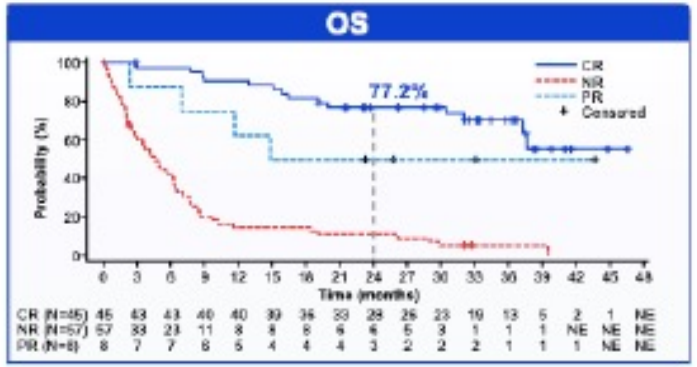
Landmark OS from C3 in patients with CR at C3*	N=45
Median OS, months (95% CI)	44.8 (40.0–NE)
24-month OS rate, % (95% CI)	74.6 (61.6–87.6)

Most patients with a CR at C3 remained progression-free and alive after 24 months

by response at EOT



Landmark PFS from EOT in patients with CR at EOT*	N=45
Median PFS, months (95% CI)	NE (20.0–NE)
24-month PFS rate, % (95% CI)	57.3 (41.2–73.4)



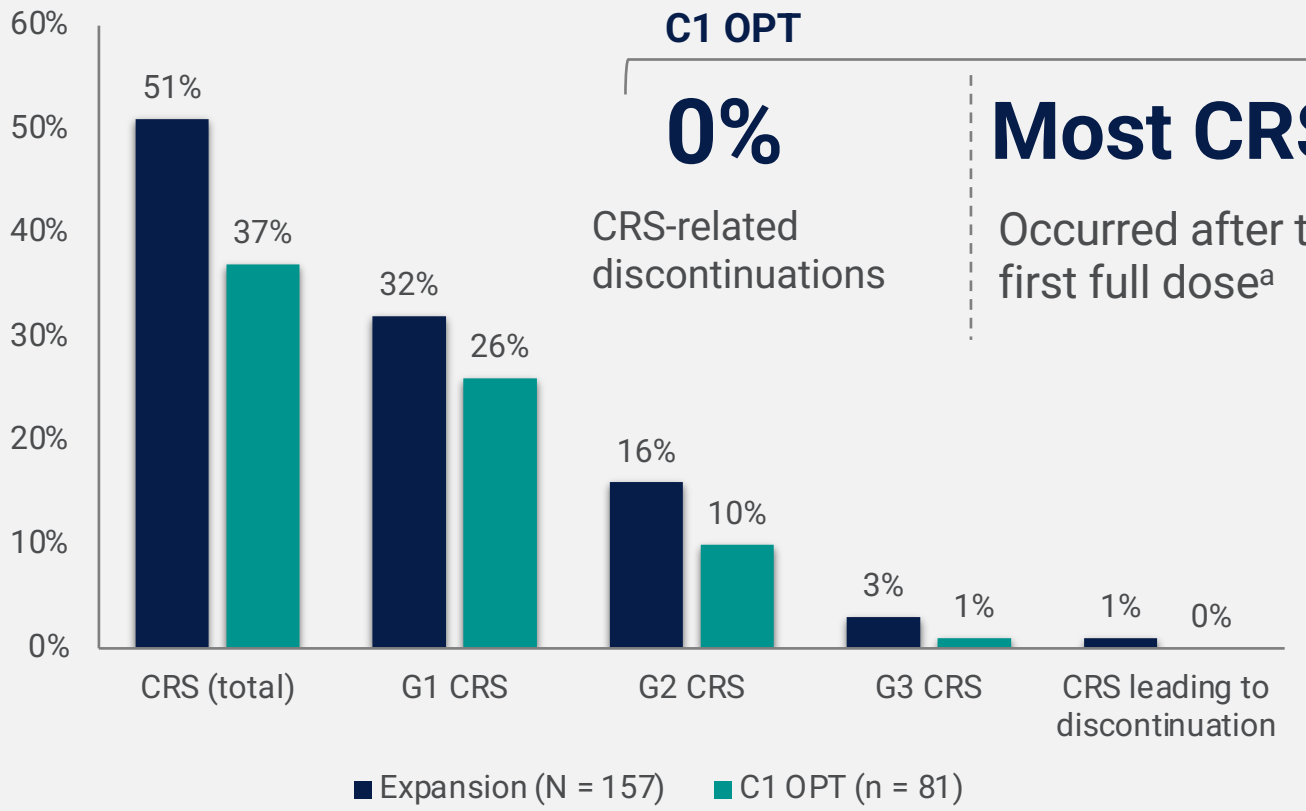
Landmark OS from EOT in patients with CR at EOT*	N=45
Median OS, months (95% CI)	NE (37.2–NE)
24-month OS rate, % (95% CI)	77.2 (64.8–89.6)

Most patients with a CR at EOT remained progression-free and alive at 24 months after EOT

Dickinson M. et al., ASH 2024 oral presentation

Overview of CRS Events

Cycle 1 Optimization Led to Decreased Rates and Severity of CRS



C1 OPT

0%
CRS-related discontinuations

Most CRS
Occurred after the first full dose[a]

100%
Events resolved

2 days
Median time to CRS resolution

Simple prophylaxis with dexamethasone and hydration in C1 reduced CRS rates and severity

[a] Among the C1 OPT patients (n = 78) who received the first full dose, treatment prior to first full dose included: dexamethasone (86%); IV fluid (81%); IV fluid and dexamethasone (69%); other corticosteroids (14%).
C, cycle; OPT, optimization cohort; CRS, cytokine release syndrome; D, day; G, grade; IV, intravenous(ly); LBCL, large B-cell lymphoma.

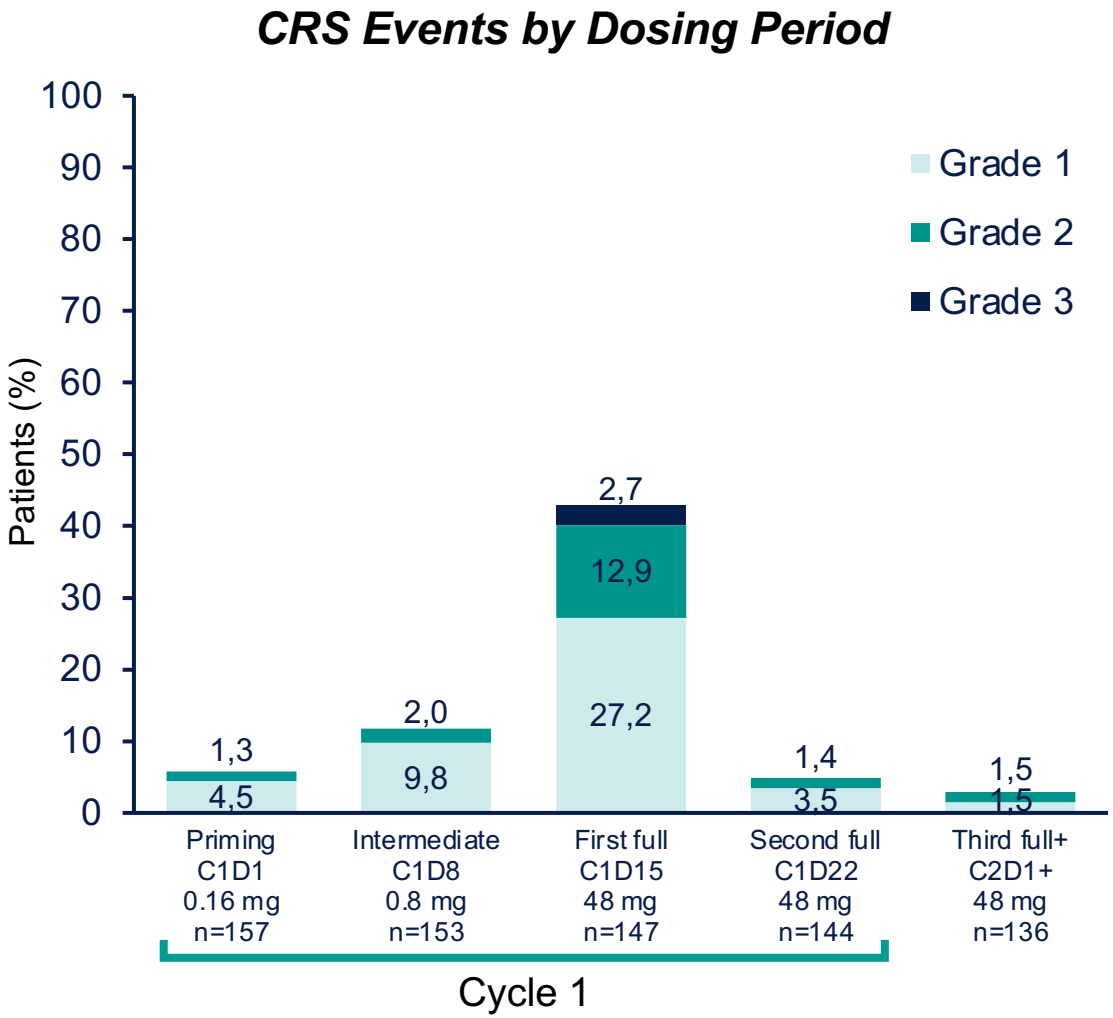
1. Thieblemont C, et al. Poster at the European Hematology Association Annual Congress; June 13–16, 2024; Madrid, Spain. Poster P1151.
2. Thieblemont C, et al. Poster at the American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2024; Chicago, IL, US. Poster 7039.

SC Administration and Step-up Dosing May Mitigate CRS

	LBCL N=157
CRS events, n (%)[a]	78 (49.7)
Grade 1	**50 (31.8)**
Grade 2	24 (15.3)
Grade 3	4 (2.5)
Median time to onset from first full dose, d	**0.8 (20 h)**
CRS resolution, n (%)	77 (98.7)
Median time to resolution from first full dose, d	**2 (48 h)**
Treated with tocilizumab, n (%)	22 (14.0)
Treated with corticosteroids, n (%)	16 (10.2)
Leading to treatment discontinuation, n (%)	**1 (0.6)**

[a]Graded by Lee et al. 2019 criteria.

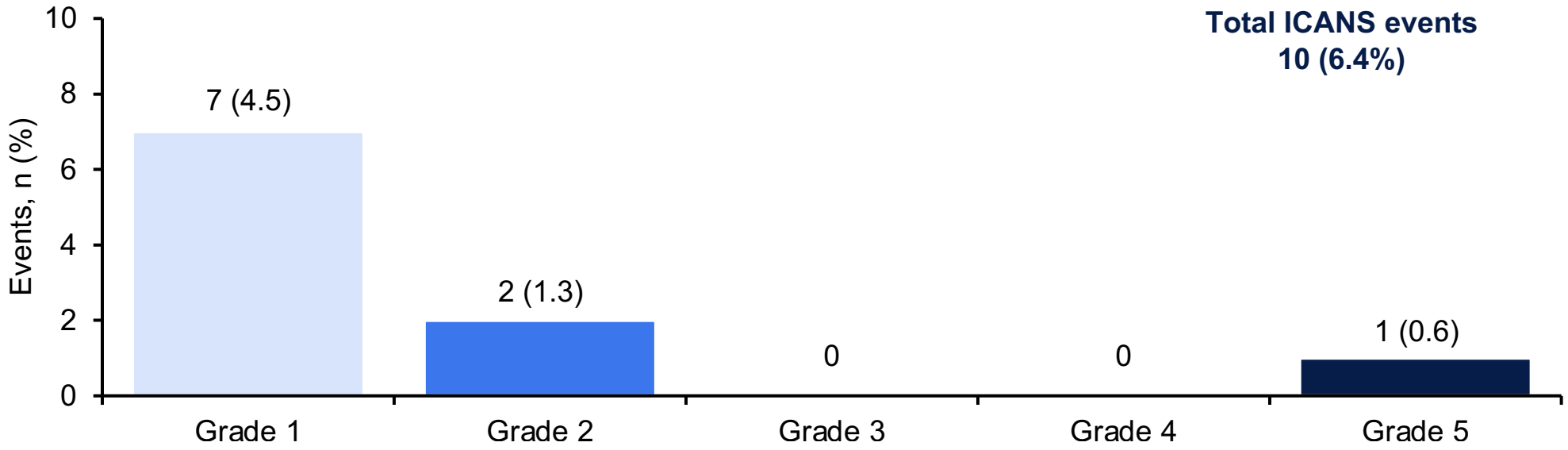
CRS was primarily low grade and predictable: most events occurred following the first full dose



Thieblemont C, et al. J Clin Oncol. 2022. doi: 10.1200/JCO.22.01725.

ICANS Incidence

Incidence of ICANS[b] (LBCL; N=157)[1]



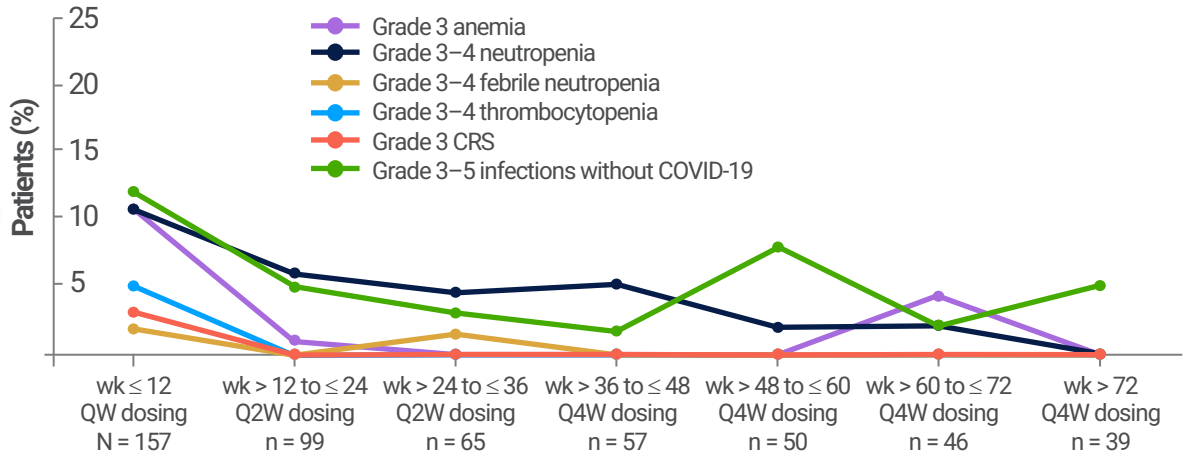
As of the May 3, 2024, data cutoff, incidence and severity of ICANS remained unchanged from prior reports.[2]

. Data on File at Genmab, Plainsboro, NJ. GCT3013-01 Expansion Part - Patients in aNHL Cohort. 2. Vose JM, et al. Presented at the American Society of Hematology Annual Meeting; December 7–10, 2024; San Diego, CA. Poster 4480.

Infection rates

3L+ DLBCL

Median follow-up 20.0 months



Median follow-up 25.1 months

Infections (Grade 3–4 in ≥ 2% patients)	Any grade No. (%)	Grade ≥ 3 No. (%)
COVID-19	30 (19.1)	13 (8.3)
Pneumonia	13 (8.3)	5 (3.2)
Sepsis	5 (3.2)	5 (3.2)
COVID-19 pneumonia	9 (5.7)	4 (2.5)

Median follow-up 30.6 months

29% Had Grade ≥ 3 serious infections

10% Discontinued treatment due to infections

11% Had fatal TEAEs

12 Had Grade 5 infections[a]

2 of 3 Treatment-related Grade 5 AEs were infections[b]

6% Had ICANS[c]

[a] Nine were COVID-19. [b] COVID-19 pneumonia and bacterial pneumonia. [c] All events were Grade 1–2, except for 1 Grade 5 event.

1. Thieblemont C, et al. *Leukemia* 2024 Sep 25:1-0.
2. Thieblemont C, et al. Poster at the European Hematology Association Annual Congress; June 13–16, 2024; Madrid, Spain. Poster P1151. 3. Thieblemont C, et al. Poster at the American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2024; Chicago, IL, US. Poster 7039.
4. Thieblemont C, et al. *J Clin Oncol* 2023;41:2238–47.

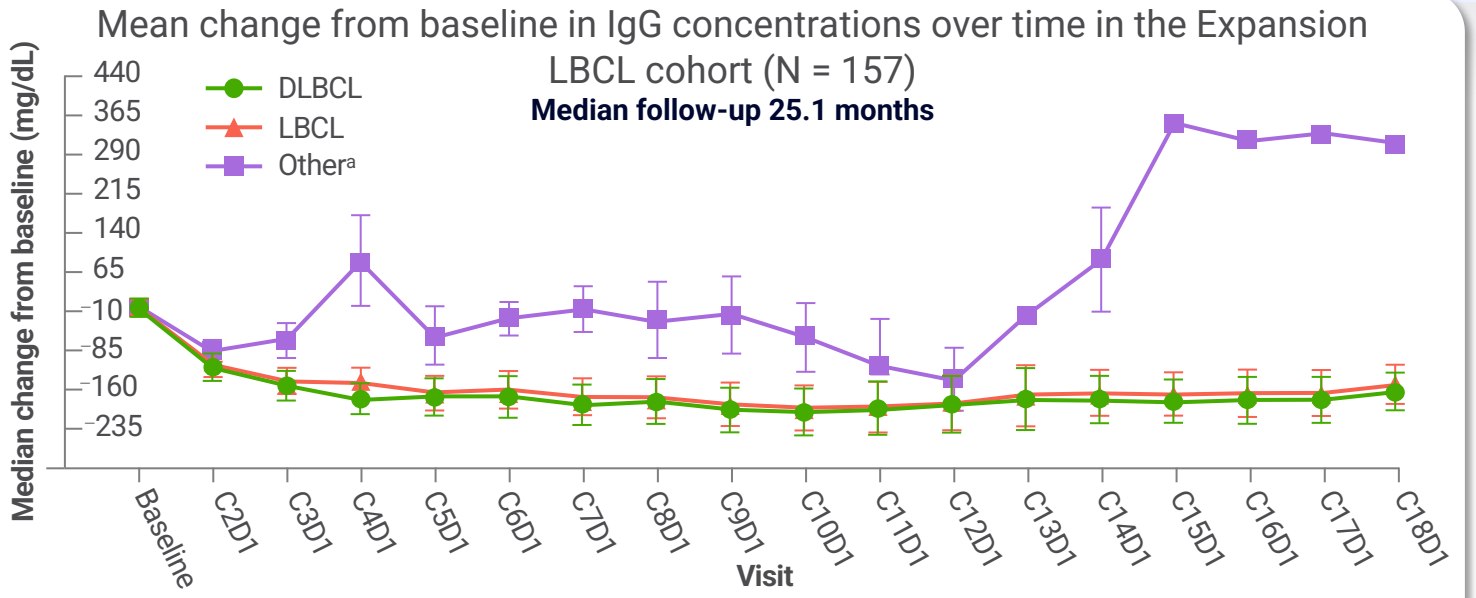
IgG levels and infection rates[1,2]

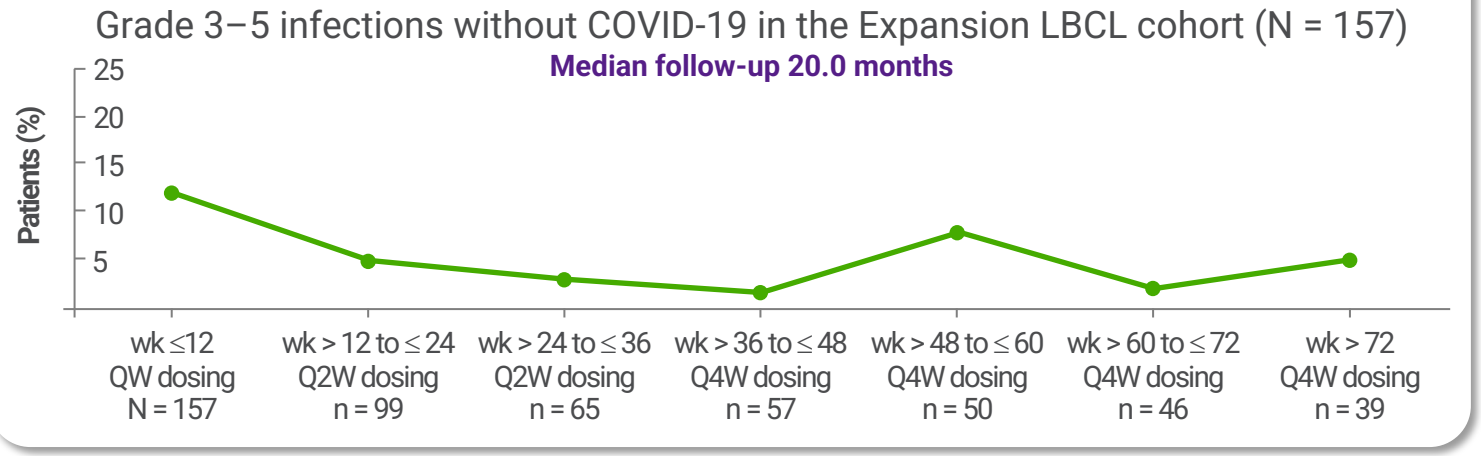
3L+ DLBCL

IgG levels remained stable after an initial drop

Non-COVID infection rates were manageable

The percentage of patients with Grade 3 or 4 infections (excluding COVID-19) was higher during the first 12 weeks (10.8%) than during subsequent time periods (1.9–6.7% per analysis period)





1. Thieblemont C, et al. *Leukemia* 2024 Sep 25:1-0.
2. Thieblemont C, et al. *J Clin Oncol* 2023;41:2238–47.

Conclusions

- ✓ In less than 5 years the treatment landscape of DLBCL has dramatically changed with a significant improving in OS
- ✓ We are progressively going towards a chemo –free approach in DLBCL
- ✓ Despite a rapidly growing knowledge on the results of the new approaches, little is still known about the best association and sequencing
- ✓ In a short time we will have more possible treatment's choice for the first line of DLBCL but not compared them with each other and some options now available in second and third line will move in first line of therapy
- ✓ It is advisable in the therapeutic algorithm to try to replicate clinical studies to obtain the best results