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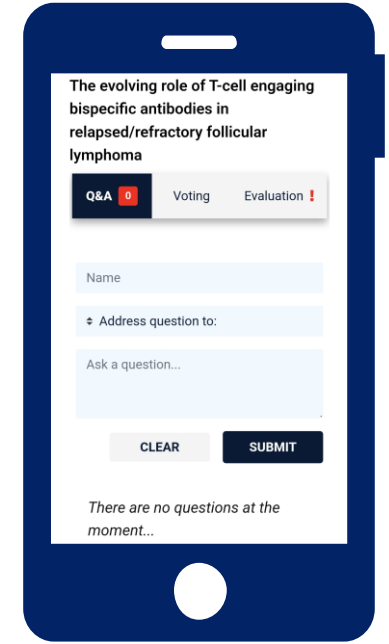

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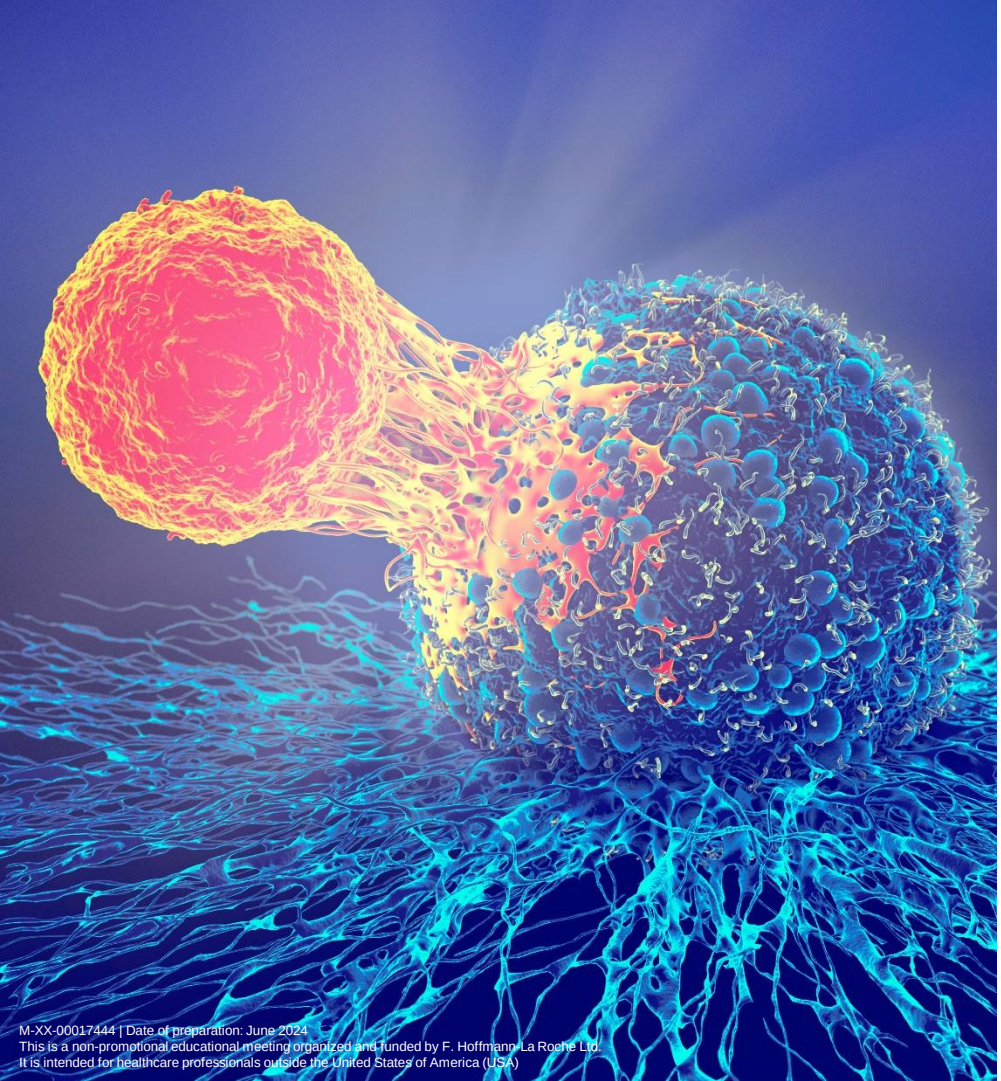

The evolving role of T-cell engaging bispecific antibodies in relapsed/refractory follicular lymphoma

28th Congress of the European Hematology Association (EHA)

Roche-sponsored satellite symposium

M-XX-00017444 | Date of preparation: June 2024

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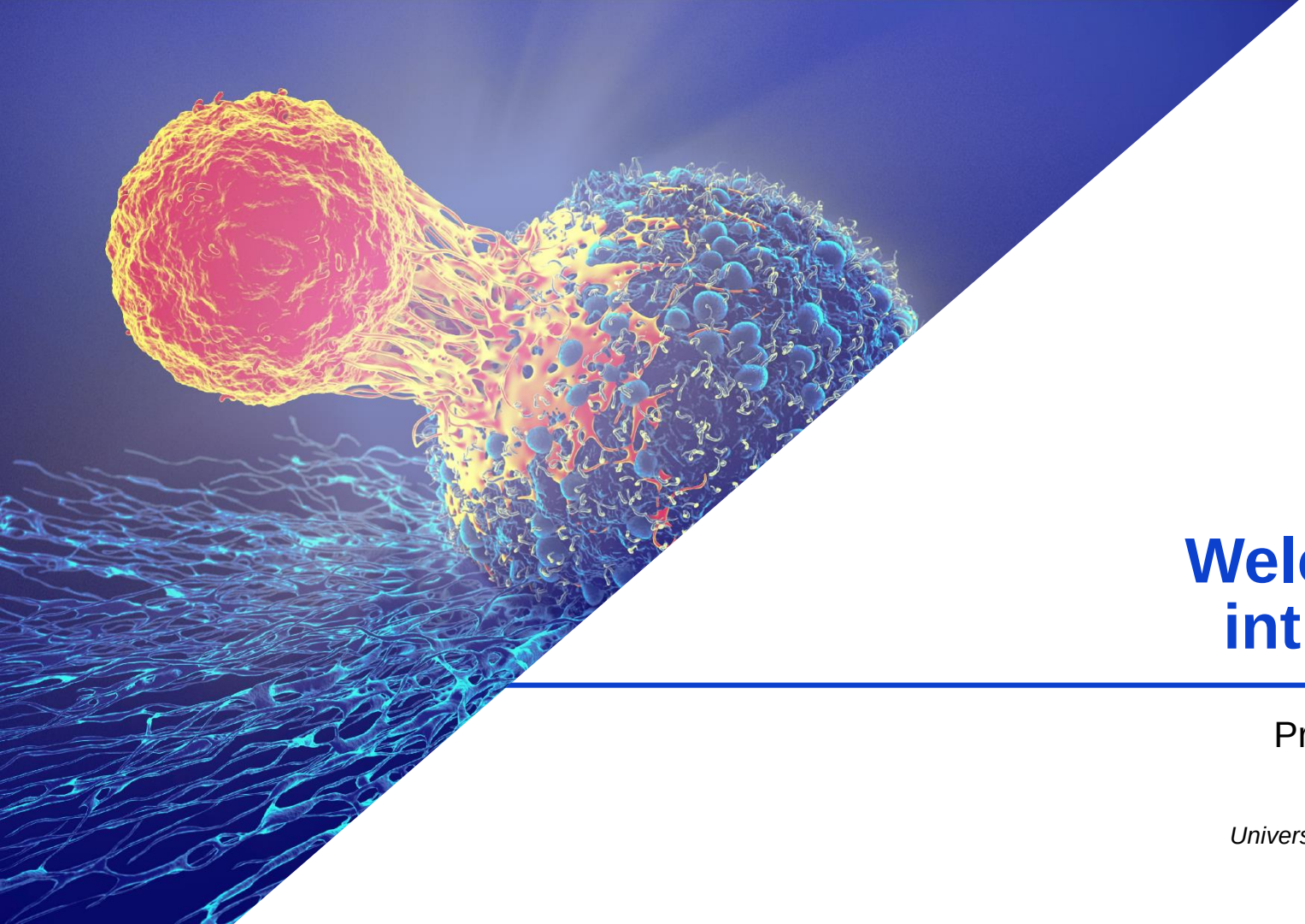

Welcome and introduction

Prof. Marco Ladetto

Università del Piemonte Orientale, Alessandria, Italy

Disclosures

- **Consultancy, advisory boards, scientific meetings, institutional research support and contracts:** AbbVie, ADC Therapeutics, Amgen, AstraZeneca, BeiGene, Celgene/BMS, Eli Lilly, Ellipses Eusapharma, F. Hoffmann-La Roche Ltd, Gentili, Gilead/Kite, GSK, Incyte, Jazz, J&J, Novartis, Regeneron, Sobi
- **PI/strategic investigator:** ADC Therapeutics, BeiGene, BMS/Celgene, F. Hoffmann-La Roche Ltd, J&J

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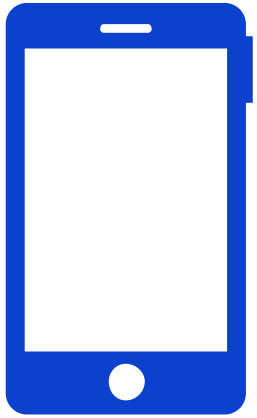

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Agenda and faculty

Welcome and introduction

Prof. Marco Ladetto, Chair

Università del Piemonte Orientale, Alessandria, Italy

Recent progress in the treatment of relapsed/refractory follicular lymphoma

Prof. Elizabeth Budde

City of Hope National Medical Center, Duarte, CA, USA

How can we maximize the potential of bispecific antibodies in relapsed/refractory follicular lymphoma?

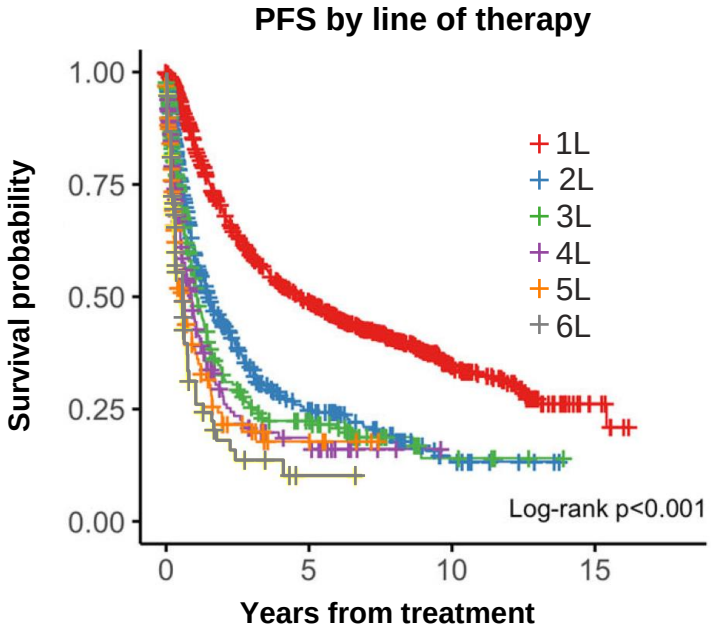
Prof. Sascha Dietrich

UKD Universitätsklinikum, Düsseldorf, Germany

Panel discussion

FL is often characterized by decreasing PFS with subsequent lines of therapy

Survival among patients with FL by line of therapy

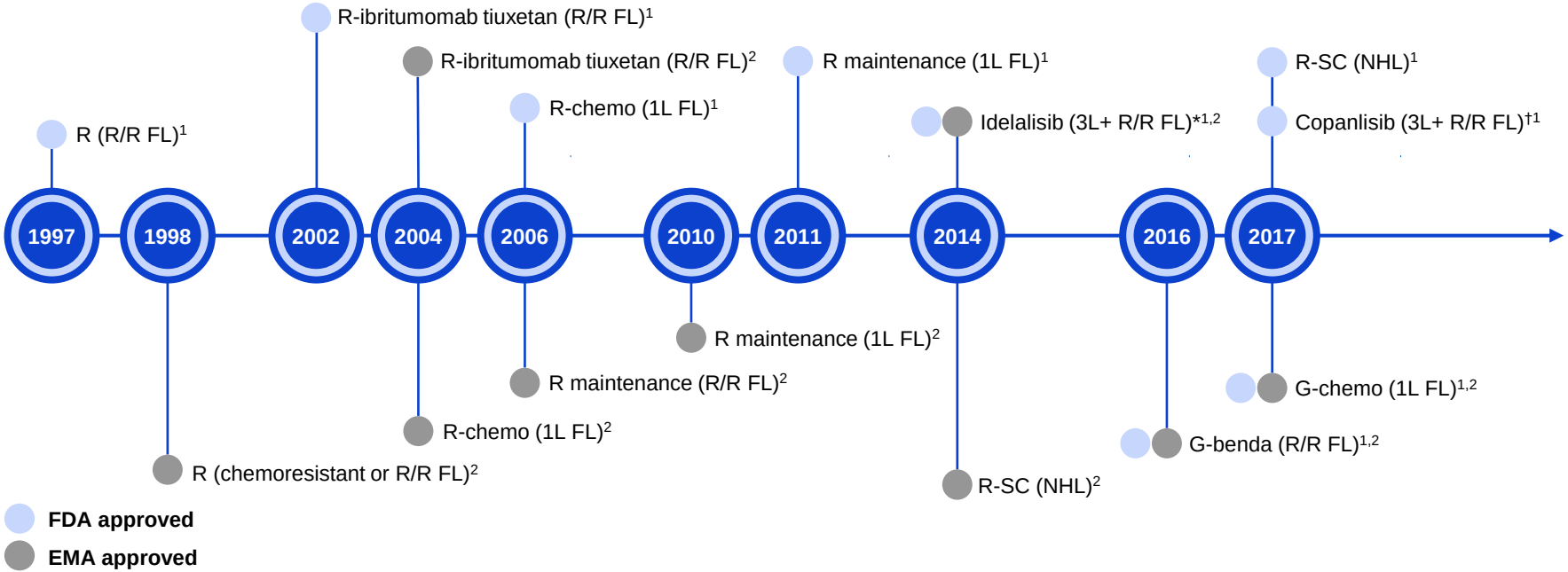


Line of therapy	n	Median PFS (95% CI), years	Median OS (95% CI), years
1L	922	4.73 (3.93–5.71)	NR (NR–NR)
2L	457	1.51 (1.22–1.92)	11.67 (9.67–NR)
3L	299	1.07 (0.93–1.39)	8.75 (6.84–NR)
4L	198	0.90 (0.59–1.10)	5.34 (3.51–NR)
5L	128	0.55 (0.33–0.92)	3.13 (2.22–6.13)
6L	81	0.48 (0.28–0.71)	1.93 (1.25–5.52)

CI, confidence interval; FL, follicular lymphoma; L, line; OS, overall survival; PFS, progression-free survival.

Batlevi CL, et al. Blood Cancer J 2020;10:74.

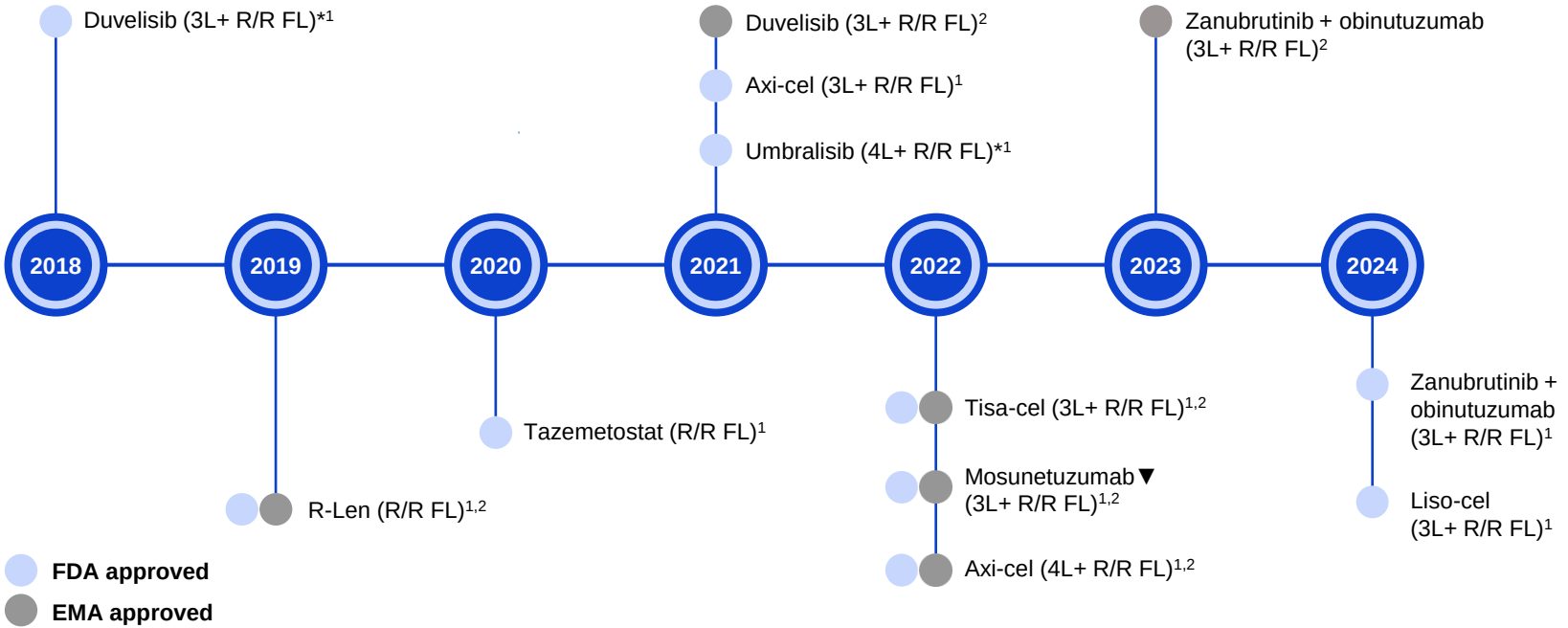
Treatment options in R/R FL: historical perspective



*FDA approval withdrawn in 2022.[3] †FDA approval withdrawn in March 2024.[4]
Benda, bendamustine; EMA, European Medicines Agency; FDA, Food and Drug Administration; G, obinutuzumab; NHL, non-Hodgkin lymphoma; R, rituximab; SC, subcutaneous.

1. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/;
2. EU SmPC. Available from: www.ema.europa.eu/en/medicines;
3. FDA Federal Register. Available from: https://www.federalregister.gov/documents/2022/05/26/2022-11277/gilead-sciences-inc-withdrawal-of-approval-of-indications-for-relapsed-follicular-lymphoma-and;
4. FDA Federal Register. Available from: https://www.federalregister.gov/documents/2024/03/18/2024-05619/bayer-healthcare-pharmaceuticals-inc-withdrawal-of-approval-of-new-drug-application-for-aliqopa.

Treatment options in R/R FL: historical perspective (cont'd)



▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.Healthcare professionals are asked to report any suspected adverse reactions.
*FDA approval withdrawn in 2022.[3]
Axi-cel, axicabtagene ciloleucel; Len, lenalidomide; liso-cel, lisocabtagene maraleucel; tisa-cel, tisagenlecleucel.

1. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/;
2. EU SmPC. Available from: www.ema.europa.eu/en/medicines;
3. FDA Federal Register. Available from: https://www.federalregister.gov/documents/2022/04/13/2022-07931/secura-bio-inc-withdrawal-of-approval-of-relapsed-or-refractory-follicular-lymphoma-indication-for.

ESMO treatment guidelines for FL

ESMO guidelines for diagnosis, treatment and follow-up of newly diagnosed and R/R FL

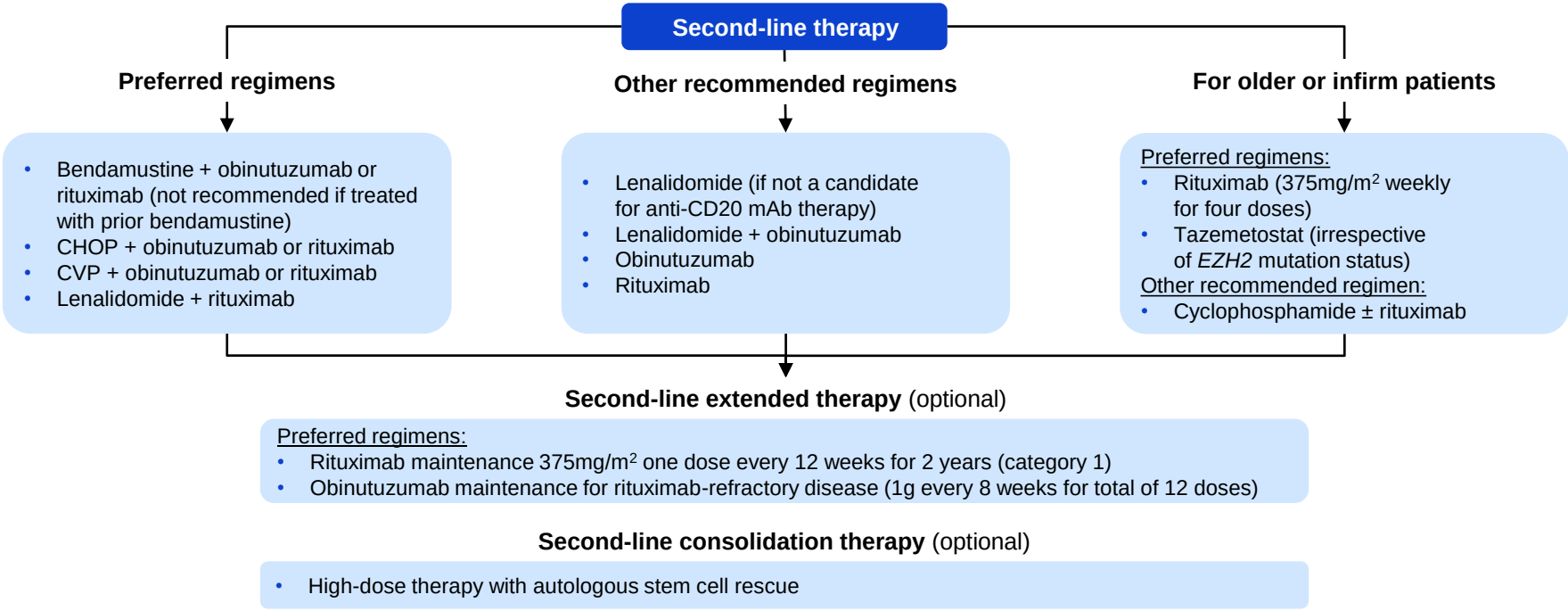
High tumor burden (stage III/IV)

	First relapse/progression	Later relapse/progression
	• Immunochemotherapy (G/R-benda, G/R-CHOP, G/R-CVP) – **CR/PR:** discuss antibody maintenance • In select cases: – R monotherapy – R-Len	• **Immunochemotherapy** – **CR/PR:** discuss antibody maintenance • **In select cases:** – R monotherapy – ASCT (patients aged <65 years with early relapses or transformation) – Radioimmunotherapy (patients aged >65 years) – R-Len (early relapses)	• **Immunochemotherapy (long prior remissions)** • **R monotherapy** • **R-Len** • **In select cases:** – ASCT (patients aged <65 years with early relapses or transformation) – Radioimmunotherapy – Idelalisib (double-refractory) – alloSCT (patients aged <65 years)

alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CR, complete response; CVP, cyclophosphamide, vincristine and prednisone; ESMO, European Society for Medical Oncology; PR, partial response.

Dreyling M, et al. Ann Oncol 2021;32:298–308.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for 2L FL



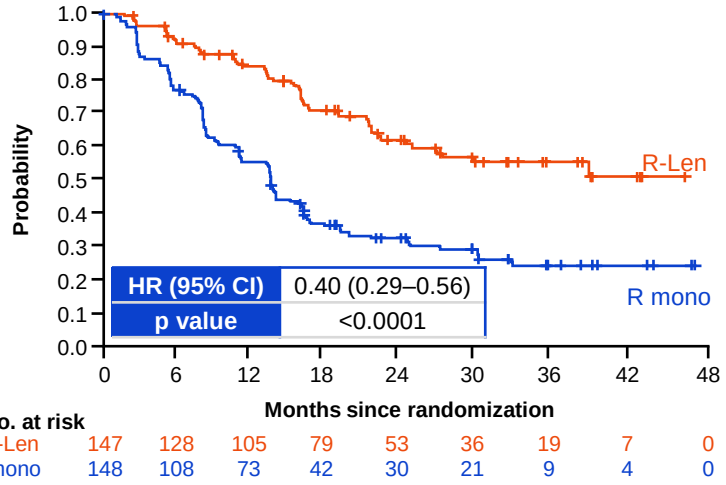
mAb, monoclonal antibody.

R-Len is an effective treatment option for R/R FL

Phase III AUGMENT study of R-Len versus R mono in R/R iNHL

Baseline characteristic (FL population), %[1,2]	R-Len n=147	R mono n=148
ECOG PS 0	67	71
FLIPI high risk	37	31
POD24	38	39
Refractory to last therapy	18	17
Prior therapies ≥3*	29	24

PFS (FL population)[2]



R-Len is superior versus R mono, but most patients will relapse

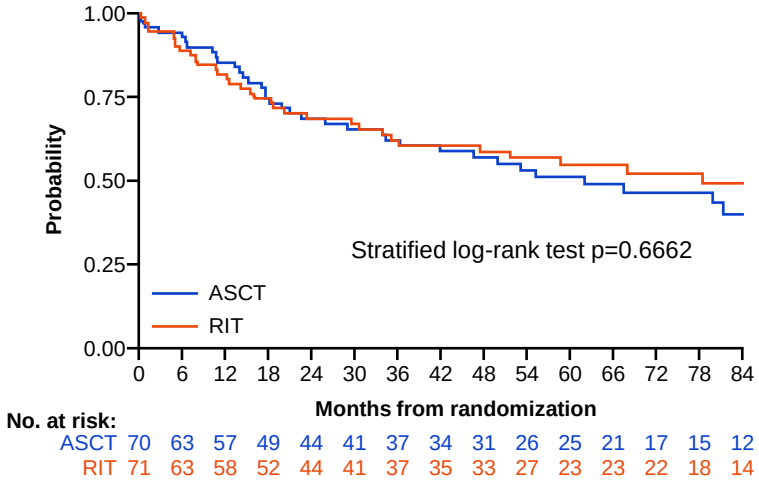
*R-Len, n=145 and R mono, n=146.
ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; iNHL, indolent non-Hodgkin lymphoma; POD24, progression of disease within 24 months; mono, monotherapy.

1. Leonard JP, et al. J Clin Oncol 2019;37:1188–99;
2. Leonard JP, et al. ICML 2019; Oral presentation (abstract #069).

Consolidation therapy remains a possible treatment option for R/R FL

Phase III FIL FLAZ-12 study of consolidation therapy with anti-CD20 radioimmunotherapy versus ASCT in R/R FL

PFS



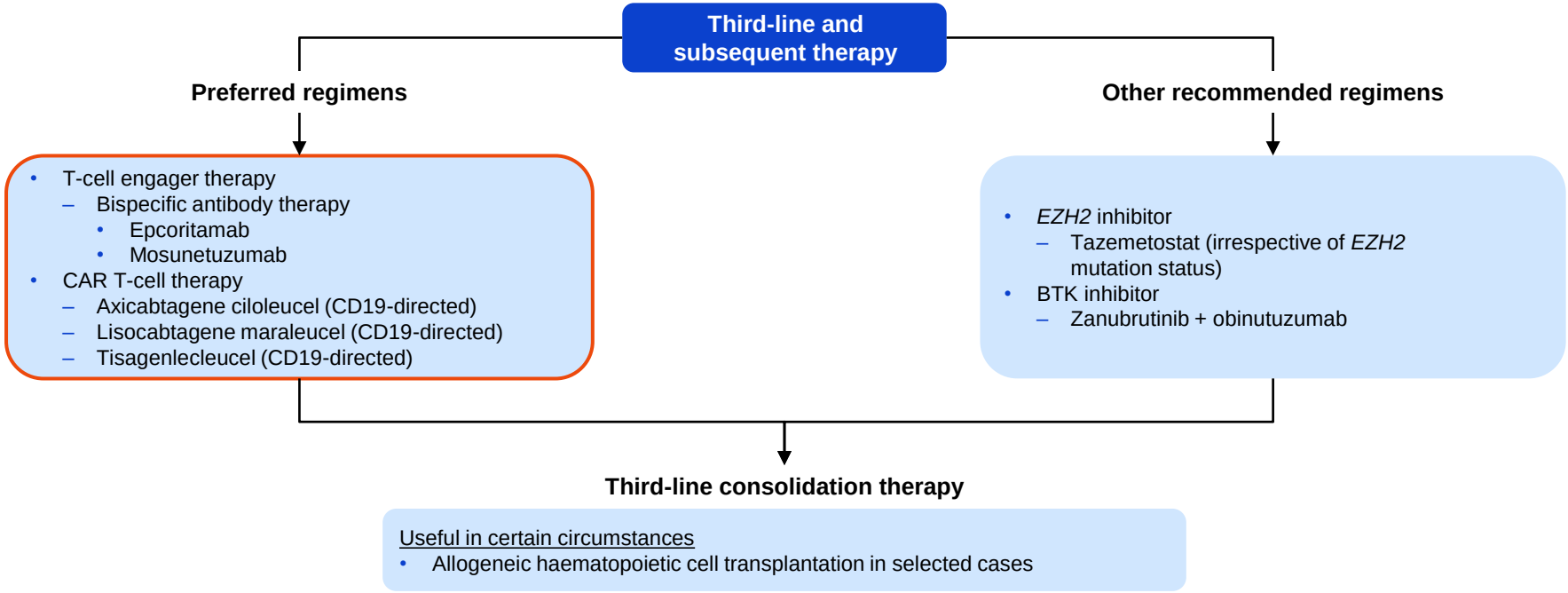
Efficacy	RIT n=71	ASCT n=70
Median PFS, months	78	62
3-year PFS rate, %	62	62
6-year PFS rate, %	52	46

ASCT had a continuous pattern of relapse and was not superior to non-intensified radioimmunotherapy

RIT, radioimmunotherapy.

Ladetto M, et al. Ann Oncol 2024;35:118–29.

NCCN Guidelines® for 3L+ FL



BTK, Bruton's tyrosine kinase;
CAR, chimeric antigen receptor.

Desirable characteristics for new R/R FL therapies

Efficacy

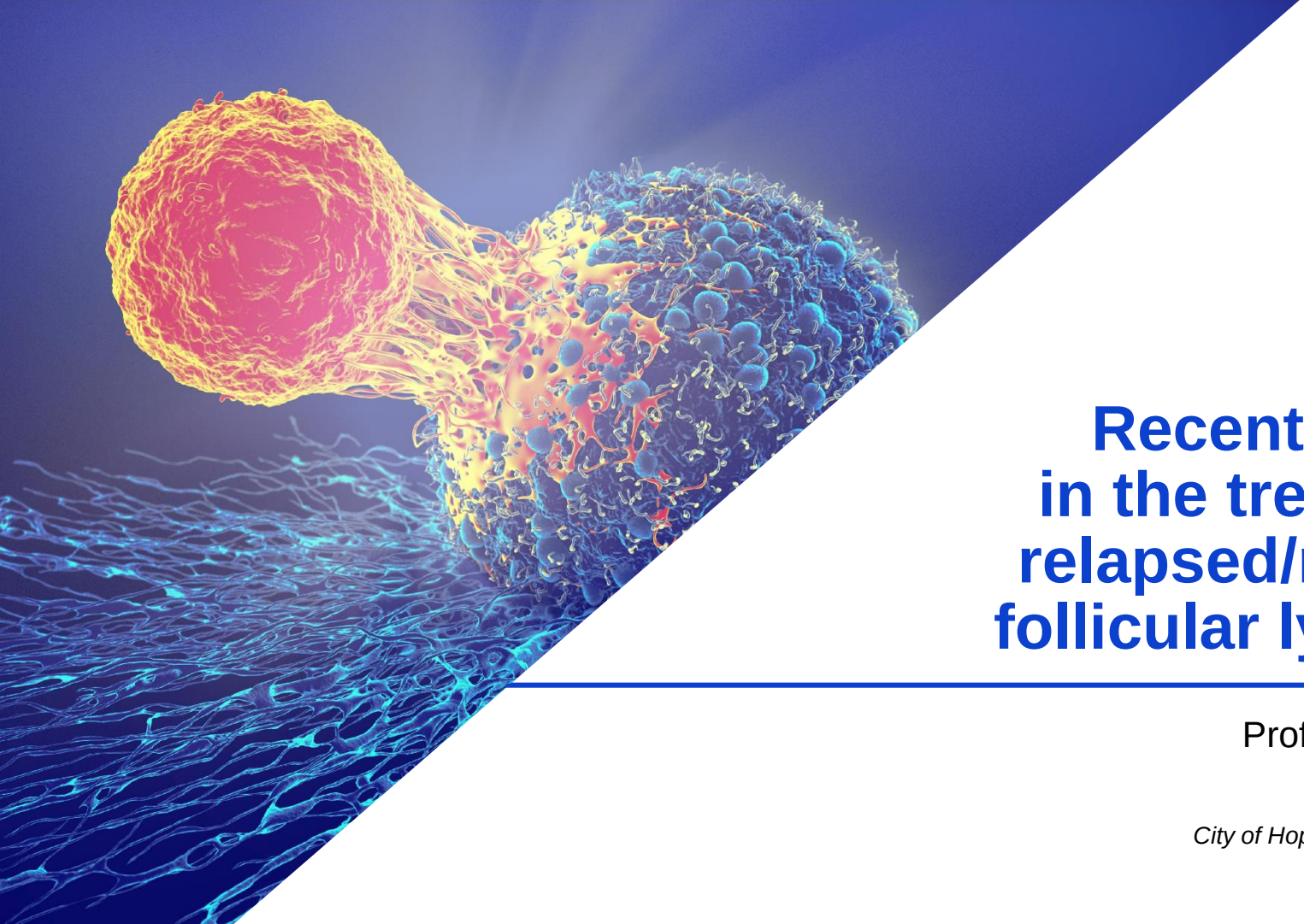
- Improved durability of responses
- Higher survival rates

Safety

- Manageable long-term and short-term safety profiles

Patient convenience

- Off-the-shelf availability
- Widely available
- SC formulation
- Convenient, fixed-duration, treatment schedule



Recent progress in the treatment of relapsed/refractory follicular lymphoma

Prof. Elizabeth Budde

City of Hope National Medical Center, Duarte, CA, USA

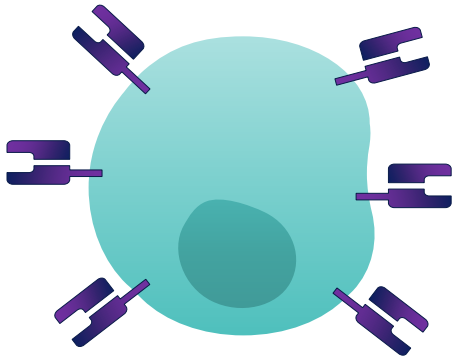
Disclosures

- **Research funding:** Amgen, AstraZeneca, Merck Inc, Mustang Bio
- **Consultancy/honoraria:** BeiGene, Genentech Inc, Gilead, F. Hoffmann-La Roche Ltd, Novartis

T-cell engaging therapies

Two main classes of T-cell engaging therapies[1]

CAR T-cell therapies	Bispecific antibodies



Mosunetuzumab▼, a bispecific antibody currently used for R/R FL, targets CD20 on malignant B cells and CD3 on T cells[2–4]

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

1. Batlevi CL, et al. Nat Rev Clin Oncol 2016;13:25–40; 2. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/; 3. EU SmPC. Available from: www.ema.europa.eu/en/medicines; 4. Sun LL, et al. Sci Transl Med 2015;7:287ra70.

Bispecific antibodies in 3L+ R/R FL

Therapy	Structure	Formulation	Key Phase II study	Treatment schedule	Status
Mosunetuzumab	Full-length, humanized IgG1 CD20:CD3 1:1[1]	IV or SC[2,3]	GO29781 (median follow-up: >36 months)[2,4,5]	**Fixed duration:** Q3W* for up to 17 cycles[2,4]	First-in-class bispecific antibody **approved in 3L+ R/R FL** by the EMA and FDA[6,7]
Epcoritamab†	Full-length, human IgG1 CD20:CD3 1:1[8]	SC[9]	EPCORE NHL-1 (median follow-up: 17.4 months)[10,11‡]	QW, C1–3; Q2W for six cycles (C4–9); Q4W* **until progression**[11]	FDA priority review[12]
Odronextamab†	Hinge-stabilized, fully human IgG4 CD20:CD3 1:1[13,14]	IV or SC[14]	ELM-2 (median follow-up: 20.1 months)[15,16]	QW, for four cycles;* Q2W **until progression**[16§]	In development phase

*Following step-up dosing; †Investigational drug/indication, not authorized; ‡Median follow-up for the pivotal cohort. The median follow-up for the C1 optimization cohort was 6.7 months; §Or Q4W if CR was durable for 9 months.
C, cycle; IgG1, immunoglobulin G1; IV, intravenous; QW, once weekly; Q2/3/4W, once every 2/3/4 weeks.

1.Sun LL, et al. Sci Transl Med 2015;7:287ra70; 2. Budde LE, et al. Lancet Oncol 2022;23:1055–65;
3. Bartlett NL, et al. ASH 2021; Poster presentation (abstract #P3573); 4. NCT02500407. Available at: https://clinicaltrials.gov;
5. Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603); 6. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/;
7. EU SmPC. Available from: www.ema.europa.eu/en/medicines; 8. Engelberts PJ, et al. eBioMed 2020;52:102625;
9. Hutchings M, et al. Lancet 2021;398:1157–69; 10. NCT03625037. Available at: https://clinicaltrials.gov;
11. Vose JM, et al. ASCO 2024; Oral presentation (abstract #7015); 12. AbbVie news release 2024. Available from: https://news.abbvie.com/;
13. Smith EJ, et al. Sci Rep 2015;5:17943; 14. Bannerji R, et al. Lancet Haematol 2022;S2352–3026;
15. NCT03888105. Available at: https://clinicaltrials.gov; 16. Taszner M, et al. EHA 2024 (abstract #S232).

Phase II GO29781 study of mosunetuzumab in R/R FL

Key inclusion criteria[1]

- FL (Grade 1–3a)
- ECOG PS 0 or 1
- ≥2 prior regimens, including an anti-CD20 antibody and an alkylator

Endpoints[1]

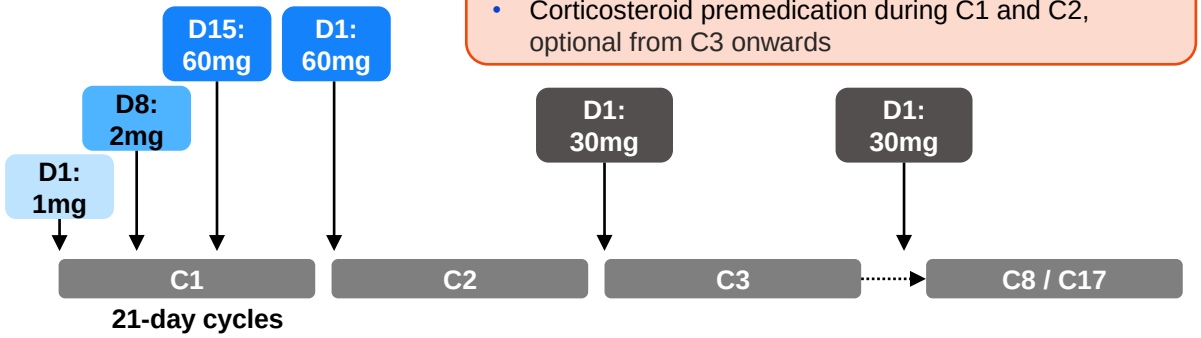
- Primary: CR (best response) rate by independent review*
- Secondary: ORR, DOR, PFS, safety and tolerability

Mosunetuzumab administration[1]

- Q3W intravenous administration
- **Fixed-duration treatment**
  - Eight cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**
- Retreatment permitted at relapse for patients who achieved a CR

CRS mitigation

- Step-up dosing during C1
- Corticosteroid premedication during C1 and C2, optional from C3 onwards

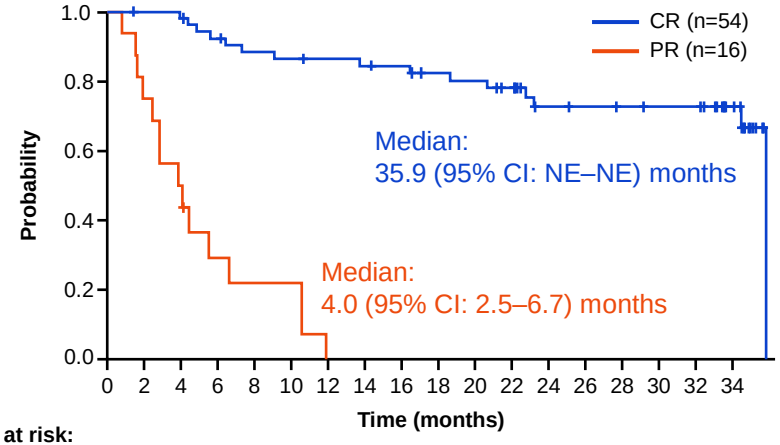


*Assessed by CT and PET-CT using Cheson 2007 criteria and versus 14% historical control CR rate.[2,3]
CRS, cytokine release syndrome; CT, computed tomography; D, day; DOR, duration of response; ORR, overall response rate; PET-CT, positron emission tomography-computed tomography; SD, stable disease.

1. Budde EL, et al. Lancet Oncol 2022;23:1055–65;
2. Cheson BD, et al. J Clin Oncol 2007;25:579–86;
3. Dreyling M, et al. J Clin Oncol 2017;35:3898–905.

GO29781: mosunetuzumab efficacy

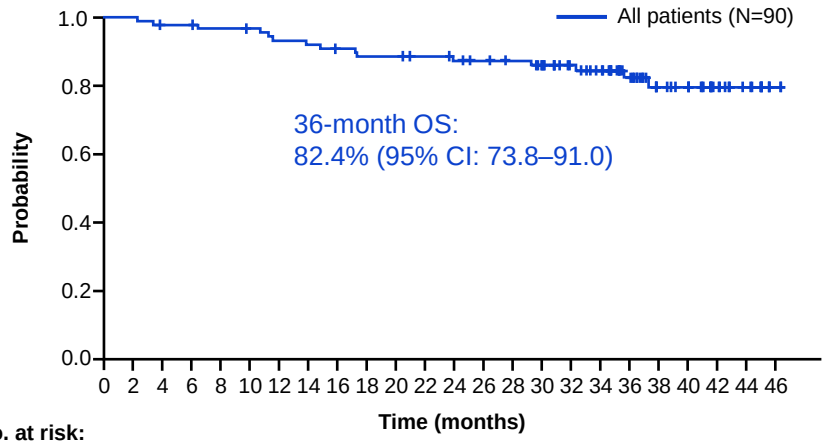
DOR for CR versus PR



No. at risk:

CR	54	53	52	48	45	44	43	42	41	38	37	34	26	25	24	23	23	15
PR	16	12	8	4	3	3	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Overall survival



No. at risk:

90 89 87 86 85 84 81 80 78 76 76 74 72 70 68 62 56 51 39 26 21 14 8 1

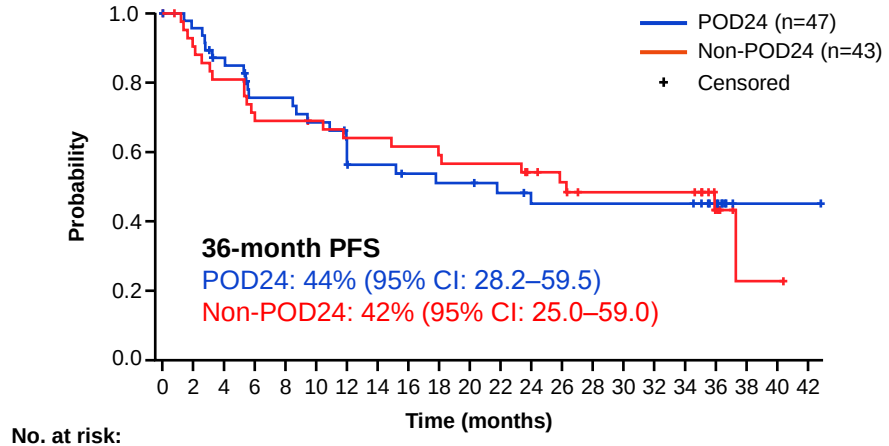
After extended follow-up of over 3 years, mosunetuzumab achieved extensive remissions and high OS

NE, not estimable.

Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603).

GO29781: mosunetuzumab efficacy – POD24 status

PFS in non-POD24 versus POD24



Efficacy endpoints*	Overall population (N=90)	POD24 status	
		Non-POD24 (n=43)	POD24 (n=47)
ORR, n (%) [95% CI]	70 (78) [67.8–85.9]	32 (74) [58.8–86.5]	38 (81) [66.7–90.9]
CR rate, n (%) [95% CI]	54 (60) [49.1–70.2]	26 (61) [44.4–75.0]	28 (60) [44.3–73.6]
Median DOCR, months [95% CI]	NR [33.0–NE]	NR [31.5–NE]	NR [18.7–NE]
30-month DOCR, % [95% CI]	71 [58.2–84.0]	75 [56.5–92.6]	67 [48.8–86.1]

After extended follow-up of over 3 years, mosunetuzumab achieved durable remissions regardless of POD24 status

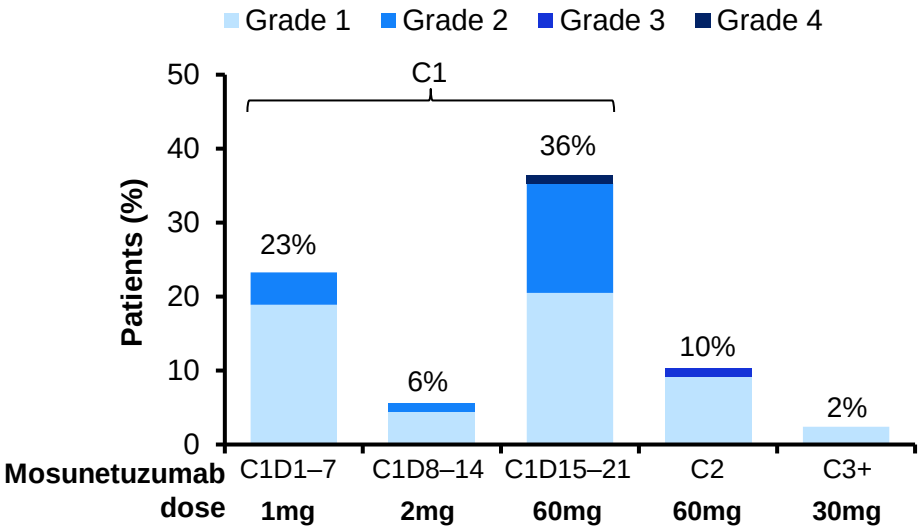
*By investigator assessment.
DOCR, duration of complete response; NR, not reached.

Assouline S, et al. EHA 2024; Oral presentation (abstract #S233).

GO29781: mosunetuzumab safety

CRS by ASTCT criteria[1,2]	N=90
CRS (any grade), n (%) Grade 1 Grade 2 Grade 3 Grade 4	40 (44) 23 (26) 15 (17) 1 (1) 1 (1)
Median time to CRS onset, hours (range) C1D1 C1D15	 5 (1–24) 27 (0–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n (%)	10 (11)*
Tocilizumab for CRS management, n (%)	7 (8)*
Events resolved, (%)	100

CRS by cycle and grade[1]



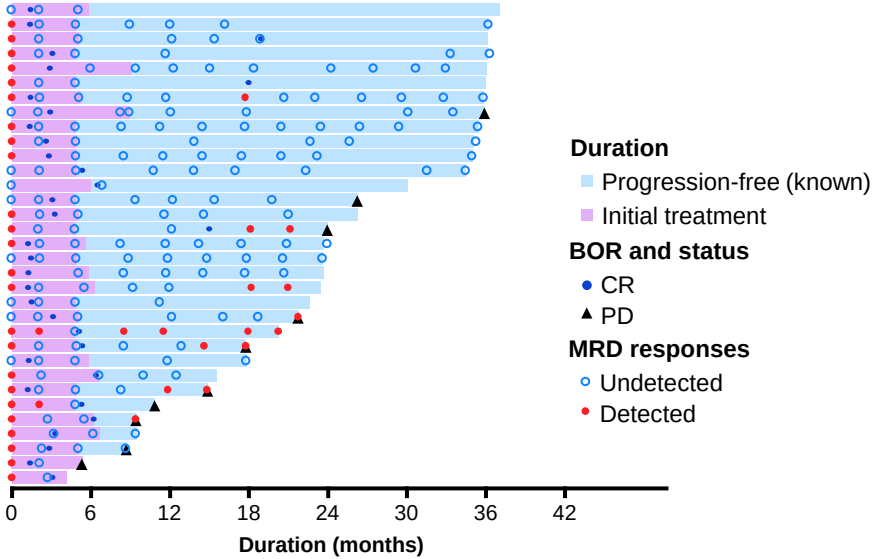
CRS was manageable; events were predominantly low-grade and occurred during C1

*Four patients received both corticosteroids and tocilizumab for CRS management.
ASTCT, American Society for Transplantation and Cellular Therapy.

1. Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603);
2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

GO29781: MRD kinetics with fixed-duration mosunetuzumab treatment

Swimlane plot of patients with a CR evaluable for MRD analysis (n=33)



uMRD was achieved with fixed-duration dosing:

- uMRD occurred by C4 in most patients who achieved a CR
- All evaluable patients with a CR had uMRD at the end of treatment
- MRD kinetics were consistent with observed durable responses

BOR	C4 uMRD/tested	C8 uMRD/tested
CR	**93%** (28/30)	**100%** (28/28)

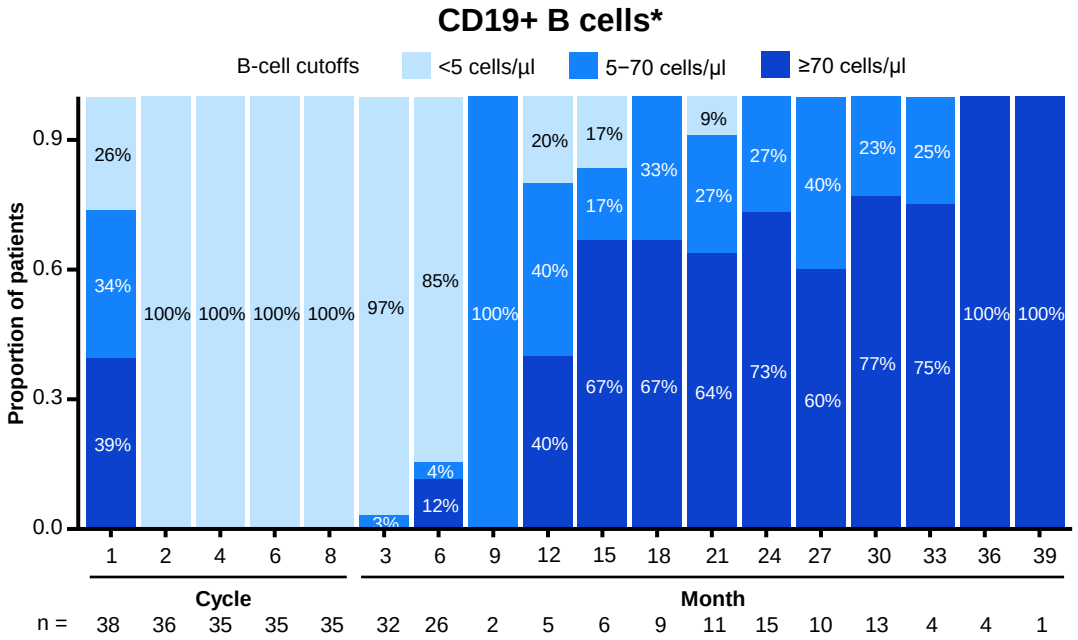
73% (24/33) samples had detectable MRD prior to dosing
Detection threshold 1e-6

Durable deep responses are achieved with fixed-duration treatment

Exploratory analysis using ClonoSeq in patient PBMC collected longitudinally during and post mosunetuzumab treatment.
BOR, best overall response; MRD, minimal residual disease; PBMC, peripheral blood mononuclear cells; uMRD, undetectable MRD.

Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603).

B-cell recovery after fixed-duration mosunetuzumab treatment



- B-cell depletion occurred rapidly before the initiation of C2 dosing in all patients (n=74)
- Time-to-event analysis was performed to assess B-cell recovery in patients with end-of-treatment (C8) and follow-up samples (n=38)

B-cell recovery was observed after completion of fixed-duration treatment

*CD19+ B-cells were monitored by flow cytometry at C1, C2, C4, C6, and C8, and every 3 months during follow-up or until progression or next lymphoma treatment. The lower limit of quantitation was 5 cells/µl and the lower limit of normal was 70 cells/µl. Depletion was analyzed in all patients with a pre-dose and at least one on-treatment sample. †In patients with end-of-treatment (C8) and follow-up samples.

Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603).

Phase I/II EPCORE NHL-1 study of epcoritamab in R/R FL

Study design[1]

First C1 OPT–Focused Data Disclosure From EPCORE® NHL-1

Key inclusion criteria

- R/R CD20+ FL grade 1–3A
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 regimen with an anti-CD20 mAb
- Prior treatment with an alkylating agent or lenalidomide
- FDG-avid disease by PET/CT
- Prior CAR T allowed

Pivotal[a]

CRS prophylaxis with prednisolone

C1D1 SUD 1: 0.16 mg

C1D8 SUD 2: 0.8 mg

C1D15 First full dose: 48 mg

Hospitalization required for 24 h following the first full dose

Primary objective: ORR by independent review committee

Data cutoff: April 21, 2023

Median follow-up: 17.4 mo

C1 optimization[a]

CRS prophylaxis with dexamethasone and recommendations for adequate hydration

C1D1 SUD 1: 0.16 mg

C1D8 SUD 2: 0.8 mg

C1D15 SUD 3: 3 mg

C1D22 First full dose: 48 mg

Hospitalization not mandated

Primary objective: Assess incidence and severity of CRS

Data cutoff: January 8, 2024

Median follow-up: 5.7 mo

Phase 1/2 trial. C, cycle; CAR T, chimeric antigen receptor T-cell therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; MRD, minimum residual disease; OPT, optimization; ORR, overall response rate; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SUD, step-up dose. [a]Patients received subcutaneous epcoritamab QW C1–3, Q2W C4–9, and Q4W C≥10 until progressive disease (≥2 measurable [by CT/MRI] and FDG PET–positive lesions) or unacceptable toxicity. 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 thereafter. MRD was assessed in peripheral blood using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. ClinicalTrials.gov: NCT03625037; EudraCT: 2017-001748-36.

CRS mitigation[1,2]

- Step-up dosing during C1
- Prophylaxis before the first four epcoritamab injections in C1 and as needed during C2: corticosteroids (prednisolone 100mg or equivalent), antipyretics, antihistamines

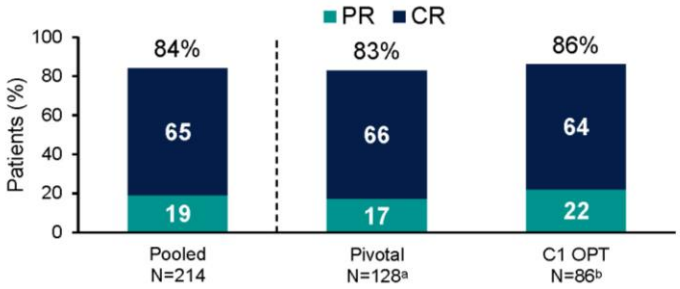
Investigational drug/indication, not authorized.

FDG, fluorodeoxyglucose; mo, months; PET/CT, positron emission tomography or computed tomography, SUD, step-up dose.

1. Vose JM, et al. ASCO 2024; Oral presentation (abstract #7015);
2. Hutchings M, et al. Lancet 2021;398:1157–69.

EPCORE NHL-1: epcoritamab efficacy

High Rates of Complete Response and MRD Negativity



MRD-Negativity Rate	n (%)
Pooled (n=135)	89 (66)
Pivotal (n=91)	61 (67)
C1 OPT (n=44)	28 (64)

Based on MRD-evaluable population per clonoSEQ® PBMC assay with 10^{-6} cutoff.

- At 6 mo in C1 OPT, an estimated 86% of patients with CR remained in CR
- No impact on time to response in C1 OPT
  - Median time to response was 1.4 mo in both cohorts[c]
  - Median time to complete response was 1.5 mo in both cohorts[d]

CR was complete metabolic response (ie, PET negativity). CR, complete response; PBMC, peripheral blood mononuclear cell; PR, partial response. [a]Three patients (2%) were not evaluable. [b]Five patients (6%) were not evaluable. [c]Range: 1.2–4.4 in C1 OPT, 1.0–3.0 in pivotal. [d]Range: 1.2–4.7 in C1 OPT, 1.2–11.1 in pivotal.

High response rates were observed

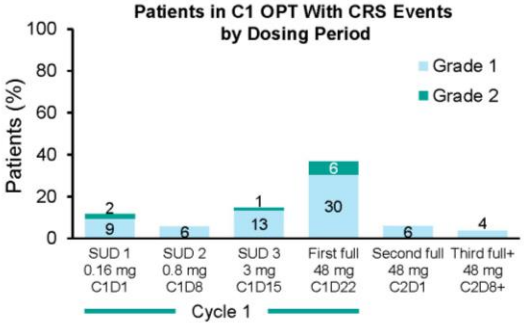
Investigational drug/indication, not authorized.
OPT, optimization.

Vose JM, et al. ASCO 2024; Oral presentation (abstract #7015).

EPCORE NHL-1: epcoritamab safety

C1 OPT Substantially Reduced Incidence and Severity of CRS and ICANS

	Pivotal N=128	C1 OPT N=86
CRS,[a] n (%)	85 (66)	42 (49)
Grade 1	51 (40)	34 (40)
Grade 2	32 (25)	8 (9)
Grade 3	2 (2)	0
Treated with tocilizumab, n (%)	31 (24)	10 (12)
Leading to epcoritamab discontinuation, n (%)	**0**	**0**
CRS resolution, n/n (%)	**85/85 (100)**	**42/42 (100)**
Median time to resolution, d (range)	2 (1–54)	2 (1–14)
ICANS, n (%)	8 (6)[b]	0



- In C1 OPT, with no mandatory hospitalization, 54% of patients who received the first full dose (44/82) had outpatient monitoring for CRS
  - Regardless of hospitalization status at the first full dose, 77% of patients with CRS following the first full dose (23/30) had CRS onset in the outpatient setting; all were able to identify CRS signs/symptoms in a timely manner and receive adequate treatment
- In both cohorts, most CRS occurred after the first full dose and was confined to C1; median time to CRS onset after the first full dose was 2.5 days in C1 OPT

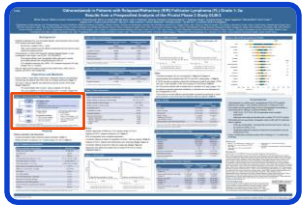
[a]Graded by Lee et al 2019 criteria.[1] [b]All grade 1–2; none leading to discontinuation. **1.** Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-38.

CRS was mostly low grade

Investigational drug/indication, not authorized.
ICANS, immune effector cell-associated neurotoxicity syndrome.

Vose JM, et al. ASCO 2024; Oral presentation (abstract #7015).

Phase I/II ELM-2 study of odronextamab in R/R FL



Study design[1]

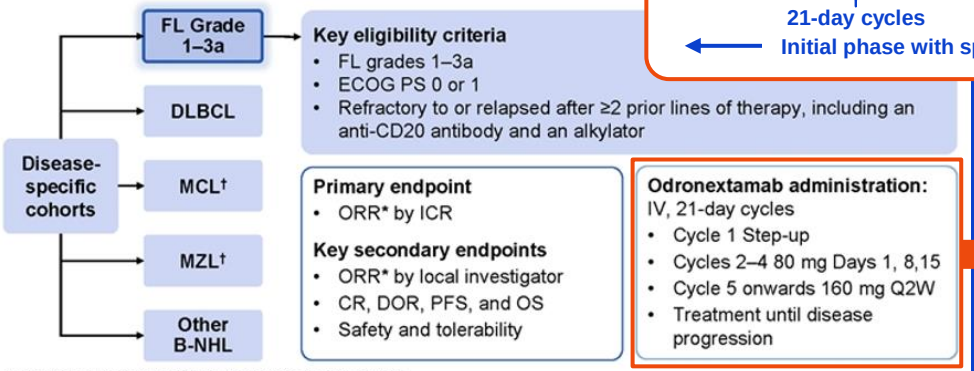
Odronextamab treatment schedule[2]

Cycle 1						Cycles 2–4			Cycle 5 onwards		
Week 1		Week 2		Week 3		Week 1	Week 2	Week 3	Week 1	Week 2	Week 3
D1	D2	D8	D9	D15	D16	D1	D8	D15	D1		D15
0.7mg		4mg		20mg		80mg	80mg	80mg	160mg		160mg
0.2mg	0.5mg	2mg	2mg	10mg	10mg						

21-day cycles

Initial phase with split dosing and step-up design → ← Maintenance phase →

Figure 1. ELM-2 study design – FL cohort



*According to Lugano criteria;[3] †New enrolment is currently paused.
CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; FL, follicular lymphoma; ICR, independent central review; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; Q2W, every 2 weeks.

CRS mitigation[1–3]

- Step-up dosing during C1
- Steroid prophylaxis: four days per week during C1*

Investigational drug/indication, not authorized.
*Prior to first and second split infusion and on each day of split infusion of odronextamab.
B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma;
ICR, independent central review; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

1. Taszner M, et al. EHA 2023; Poster presentation (abstract #P1083);
2. Taszner M, et al. EHA 2024; Oral presentation (abstract #S232);
3. Bannerji R, et al. Lancet Haematol 2022;S2352–3026.

ELM-2: odronextamab efficacy and safety

Abstract: S232

Title: PRIMARY ANALYSIS OF THE PHASE 2 ELM-2 STUDY: ODRONEXTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

Abstract Type: Oral Presentation

Session Title: Follicular and mantle cell lymphoma - Role of bispecifics

Background:

Relapsed/refractory follicular lymphoma (R/R FL) is an incurable disease, and outcomes worsen with successive relapses. There remains a high unmet need for therapies that improve tumor control and extend survival after relapse. Odronextamab, an off-the-shelf CD20×CD3 bispecific antibody, demonstrated compelling efficacy, generally manageable safety, and maintenance of patient-reported overall quality of life scores from baseline in an interim analysis of the ELM-2 study (NCT03888105) in heavily pretreated patients with R/R FL (Villasboas JC et al. ASH 2023). Here, for the first time, we present the primary analysis of R/R FL in ELM-2.[1]

Aims:

To report the efficacy and safety of continued odronextamab treatment in heavily pretreated patients with R/R FL from the ELM-2 study.

Methods:

Intravenous odronextamab was administered in 21-day cycles (C) until disease progression or unacceptable toxicity. Steroid prophylaxis and step-up dosing (0.7/4/20 mg) were used in C1 to mitigate the risk of cytokine release syndrome (CRS), followed by 80 mg on Days (D) 1, 8, and 15 of C2–4. Maintenance dosing continued at 160 mg every 2 weeks, or every 4 weeks if complete response (CR) was durable for 9 months (mo). The primary endpoint was objective response rate (ORR) per Lugano criteria by independent central review (BICR). Secondary endpoints included CR rate, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). The primary analysis was performed when 128 patients had ≥52 weeks' follow-up. All patients provided informed consent.

Results:

At data cutoff (October 20, 2023), 128 patients with FL Grade (Gr) 1–3a were evaluable for efficacy and safety: median age 61 years (range 22–84); Follicular Lymphoma International Prognostic Index (FLIPI) risk score 3–5 57.8%, progression of disease within 2 years of frontline chemoimmunotherapy (POD24) 49.2%; median 3 prior lines of therapy (range 2–13); 71.9% refractory to last treatment; 74.2% refractory to an anti-CD20 antibody. The median number of treatment cycles was 19.4 (range 0.1–95.9); 95.3% and 85.2% of patients completed C1 and C4, respectively.

Median efficacy follow-up was 20.1 mo. ORR was 80.5% and CR rate was 73.4% confirmed by BICR. Responses were durable (median DOR 22.6 mo; median duration of CR 25.1 mo). Median PFS was 20.7 mo, and 24-mo PFS was 46.1%. Median OS was not reached, and 24-mo OS was 70.1%.

The odronextamab safety profile was generally manageable and consistent with previous reports. Treatment-emergent adverse events (AEs) occurred in all patients (Gr ≥3 85.9%). 15.6% had AEs leading to treatment discontinuation. With 0.7/4/20 mg step-up (n=60), CRS events were mostly low grade (Gr 1 45.0%; Gr 2 10.0%; Gr 3 in one patient), occurred mostly in C1, and resolved in a median of 2 days; immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in one patient (Gr 2). Infection rates were consistent with those expected in heavily pretreated, immunosuppressed patients (Leonard JP et al. *JCO* 2019; Hayre J et al. *BBMT* 2020), occurring in 79.7% (102/128) of patients (Gr 4/5 14.0%; COVID-19 36.7% [Gr 5 6.3%]).

Summary/Conclusion:

Odronextamab demonstrated deep and durable responses in heavily pretreated patients with R/R FL; 91% of responders achieved CR, correlating with favorable PFS and OS at 24 mo. Odronextamab had a generally manageable safety profile with a low incidence of Gr 3 CRS and any-grade ICANS. Odronextamab could offer an important off-the-shelf treatment option for patients with heavily pretreated R/R FL.

Keywords: Bispecific, Non-Hodgkin's lymphoma, Follicular lymphoma, Phase II

Efficacy endpoints	N=128
ORR, %	80.5
CR, %	73.4
Median DOR, months	22.6
Median DOCR, months	25.1

CRS summary	0.7/4/20mg step-up n=60
Grade 1, %	45.0
Grade 2, %	10.0
Grade 3, %	1.7
Median time to resolution, days	2

Responses were durable; CRS was mostly Grade 1/2

Investigational drug/indication, not authorized.

Taszner M, et al. EHA 2024 (abstract #S232).

Summary

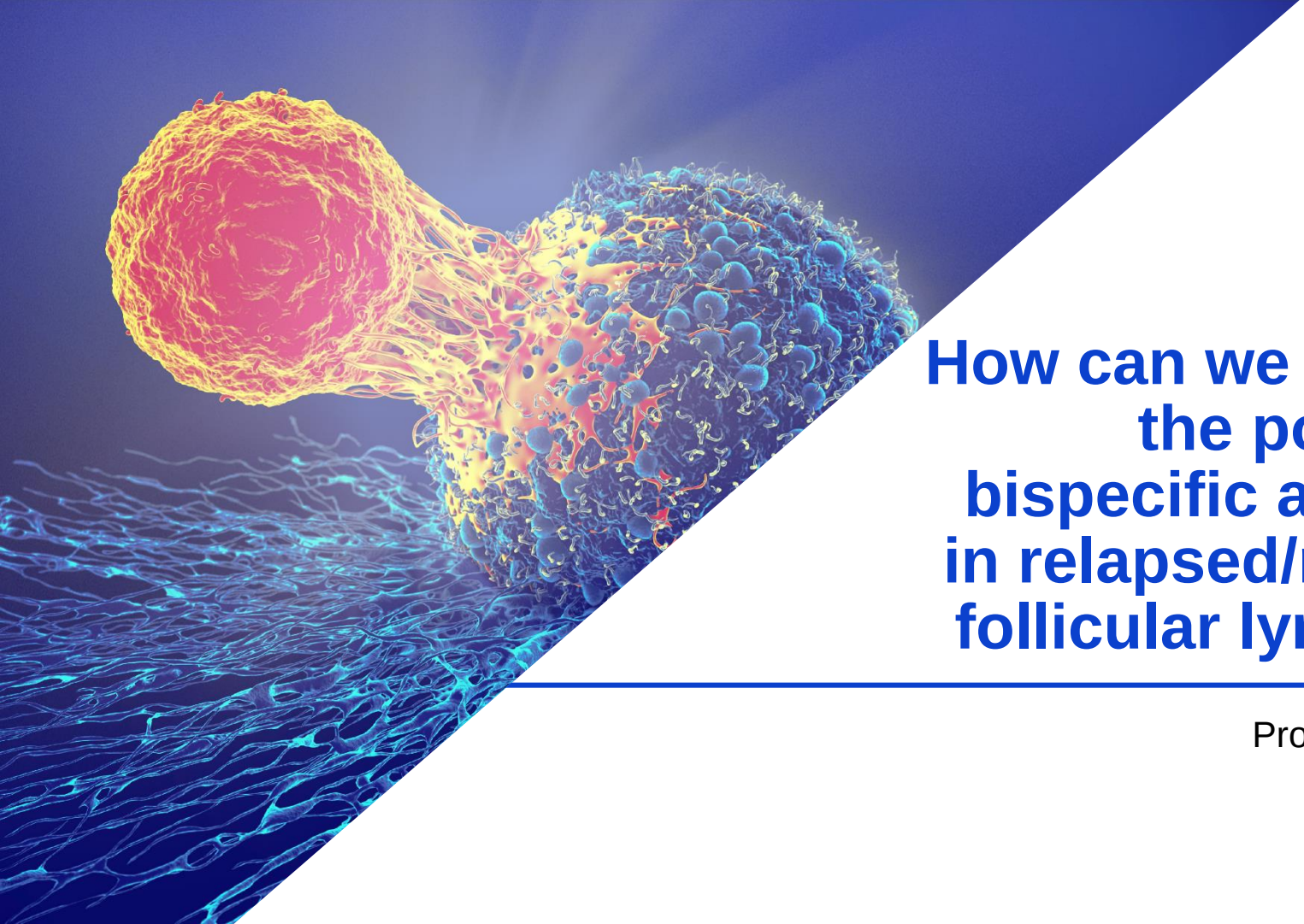
Bispecific antibodies are a promising off-the-shelf treatment option for patients with R/R FL

- High CR rates have been observed[1–3]
- Observed safety profiles are manageable[1,2,4]

Mosunetuzumab is the first fixed-duration bispecific antibody approved by the EMA and FDA for the treatment of patients with R/R FL after ≥2 prior therapies[5,6]

- High CR rates were observed and remain durable with over 3 years of follow-up[4]
- Suitable for outpatient administration

1. Linton KM, et al. ASH 2023; Poster presentation (abstract #1655); 2. Taszner M, et al. EHA 2023; Poster presentation (abstract #P1083);
3. Assouline S, et al. EHA 2024; Oral presentation (abstract #S233); 4. Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603);
5. EU SmPC. Available from: www.ema.europa.eu/en/medicines; 6. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/.



How can we maximize the potential of bispecific antibodies in relapsed/refractory follicular lymphoma?

Prof. Sascha Dietrich

UKD Universitätsklinikum, Düsseldorf, Germany

Disclosures

- **Consultancy:** F. Hoffmann-La Roche Ltd, Gilead/Kite Pharma

Building on the benefits of monotherapy

Monotherapy with bispecific antibodies[1–4]

- High response rates
- Manageable safety profiles

Can we further optimize the efficacy and safety of these therapies?

Potential benefits of combination therapy

Increased efficacy through synergistic/additive effects[5,6]

Targeting multiple pathways minimizes drug resistance[5,6]

1. Linton KM, et al. ASH 2023; Poster presentation (abstract #1655); 2. Taszner M, et al. EHA 2023; Poster presentation (abstract #P1083);
3. Budde LE, et al. Lancet Oncol 2022;23:1055–65; 4. Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603);
5. Mokhtari RB, et al. Oncotarget 2017;8:38022–43; 6. Sun Y, et al. Acta Pharma Sin B 2023;13:3583–97.

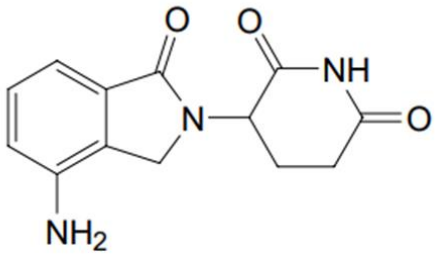
Rationale for combinations with lenalidomide

Lenalidomide has **additive/synergistic activity** with anti-CD20 antibodies in preclinical lymphoma models and in patients with R/R FL[1,2]

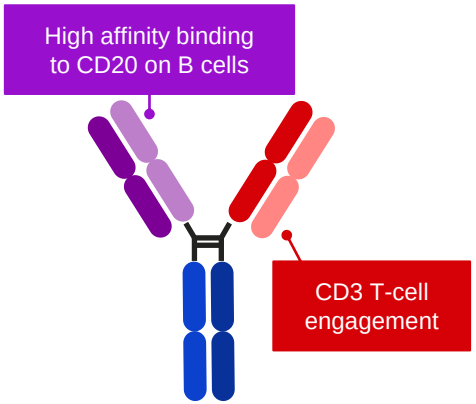
Lenalidomide is a potent **immunomodulatory** agent:[1]

- Activates CD28 and enhances T-cell responses[3]
- Leads to **cytokine production**[1]
- Has direct **anti-proliferative activity** against lymphoma cells[1]

Lenalidomide: oral immune modulator[1,4]



Mosunetuzumab▼: CD20xCD3 bispecific antibody[5]



▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

1. Gribben JG, et al. J Clin Oncol 2015;33:2803–11; 2. Morschhauser F, et al. Blood 2021;138(S1):129; 3. Kotla V, et al. J Hematol Oncol 2009;2:36; 4. Reddy LM, et al. E-J Chem 2011;9:1165–74; 5. Sun LL, et al. Sci Transl Med 2015;7:287ra70.

Bispecific antibody combination therapy in R/R FL

Therapy	Trial (Phase)	Regimen	Patients (R/R FL cohorts)	Treatment duration and administration	Primary endpoint
Mosunetuzumab	**CO41942** (Phase Ib/II)[1,2]	Mosun-Len	187	**Mosun** (IV/SC) 12 cycles: C1 SUD; C2–12 Q4W **Len** (oral) 11 cycles: C2–12	Safety
	CELESTIMO (Phase III)[3,4]	Mosun-Len versus R-Len*	~400†	**Mosun** (IV) 12 cycles: C1 SUD; C2–12 Q4W **Len** (oral) 11 cycles: C2–12	PFS (by IRC)
Epcoritamab	**EPCORE NHL-2** (Phase I/II)[5,6]	Epcoritamab + R-Len	111	**Epcoritamab** (SC) 12 cycles: C1–3 QW (SUD); C4–9 Q2W; C10–12 Q4W OR C1–2 QW; C3 onwards Q4W for up to 2 years **R** (IV) plus **Len** (oral) 12 cycles	Safety
	EPCORE FL-1 (Phase III)[7,8]	Epcoritamab + R-Len versus R-Len‡	~520†	**Epcoritamab** (SC) 12 cycles: C1 SUD; C2–3 QW; C4–12 Q4W **R** (IV) 5 cycles plus **Len** (oral) 12 cycles	PFS (by IRC)
Odronextamab	**OLYMPIA-5** (Phase III)[9,10]	Odronextamab-Len versus R-Len‡	~352†	**Odronextamab** (IV) 12 cycles: C1 SUD; C2–3 QW; C4–6 Q2W; C7–12 Q4W **Len** (oral) 12 cycles	PFS (by IRC)

Investigational drug/indications, not authorized.
*R-Len: R (IV) 6 cycles plus Len (oral) 12 cycles. †Planned enrolment.
‡R-Len: R (IV) 5 cycles plus Len (oral) 12 cycles.
IRC, Independent Review Committee; Mosun, mosunetuzumab.

1. Morschhauser F, et al. ASH 2021; Oral presentation (abstract #129); 2. NCT04246086. Available at: https://clinicaltrials.gov; 3. Nastoupil L, et al. ASCO 2022; Poster presentation (abstract #TPS7588); 4. NCT04712097. Available at: https://clinicaltrials.gov; 5. Merryman R, et al. ASCO 2023; Oral presentation (abstract #7506); 6. NCT04663347. Available at: https://clinicaltrials.gov; 7. Falchi L, et al. ASH 2023; Oral presentation (abstract #3053); 8. NCT05409066. Available at: https://clinicaltrials.gov; 9. Vitolo U, et al. ASCO 2024 (abstract #TPS7094); 10. NCT06149286. Available at: https://clinicaltrials.gov.

Phase Ib CO41942 trial of Mosun-Len in R/R FL

Study overview

Key inclusion criteria

- CD20+ FL Grade 1–3a
- R/R to ≥1 prior chemo-immunotherapy regimen including an aCD20 antibody; prior lenalidomide allowed
- ECOG PS 0–2

Objectives

- Primary: safety and tolerability of M-Len
- Other: efficacy (response, durability of response) and pharmacokinetics

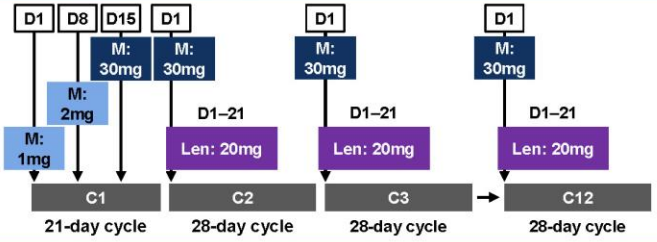
M-Len administration

Mosunetuzumab

- IV administration for 12 cycles (C1: Q3W; C2–12: Q4W)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Lenalidomide

- Oral administration for 11 cycles (C2–12)

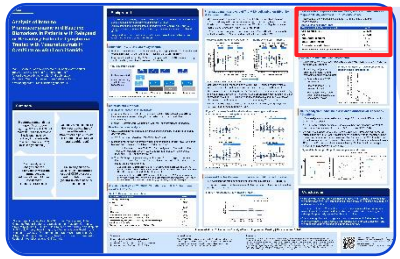


C, Cycle; CRS, cytokine release syndrome; D, Day; IV, intravenous; Q3W, once every 3 weeks; Q4W, once every 4 weeks

Investigational drug/indication, not authorized.
M, mosunetuzumab.

Morschhauser F, et al. ASH 2021; Oral presentation (abstract #129).

Mosun-Len in R/R FL: efficacy



Best objective response rate was 89.7%, with complete metabolic response (CMR) observed in 21 patients (72.4%).

- Five cases of early progressive disease (PD) (≤6 cycles of treatment) were observed.

Table 2. Best response rates.

Efficacy endpoint, n (%), unless specified	N=29
Objective response rate	26 (89.7)
CMR	21 (72.4)
Partial metabolic response	5 (17.2)
Non-metabolic response	1 (3.4)
Progressive metabolic disease	2 (6.9)
Median duration of follow-up, months (range)	10.9 (3–19)

Investigational drug/indication, not authorized.

Bishton M, et al. ASH 2022; Poster presentation (abstract #P1544).

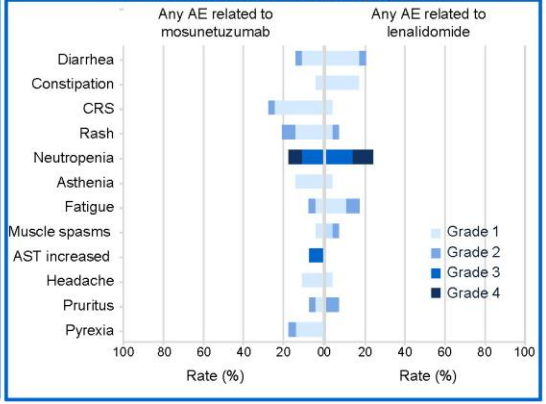
Mosun-Len in R/R FL: AE summary

Adverse event summary

- Median duration of follow-up: 5.4 months (range: 3–12)

	N=29
AE Related to mosunetuzumab / lenalidomide	29 (100%) 27 (93.1%) / 23 (79.3%)
Grade 3–4 AE Related to mosunetuzumab / lenalidomide	13 (44.8%) 1 (3.4%) / 1 (3.4%)
Serious AE Related to mosunetuzumab / lenalidomide	9 (31.0%) 6 (20.7%) / 1 (3.4%)
Grade 5 (fatal) AE	0
AE leading to mosunetuzumab / lenalidomide discontinuation	0 / 1 (3.4%)
AE leading to mosunetuzumab dose delay	6 (20.7%)
AE leading to lenalidomide dose reduction	2 (6.9%)
AE leading to lenalidomide temporary dose interruption	6 (20.7%)
AE leading to lenalidomide dose reduction AND temporary dose interruption	4 (13.7%)

AEs with ≥15% incidence overall and corresponding rates of treatment-related events by Grade



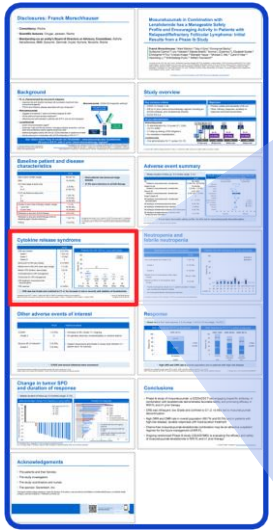
- **M-Len had a favorable safety profile. No AEs led to mosunetuzumab discontinuation.**

AE, adverse event; AST, aspartate aminotransferase

Investigational drug/indication, not authorized.
AST, aspartate aminotransferase.

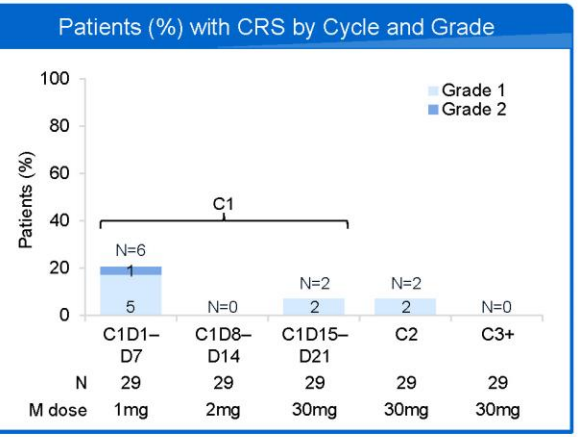
Morschhauser F, et al. ASH 2021; Oral presentation (abstract #129).

Mosun-Len in R/R FL: CRS



Cytokine release syndrome

	N=29
CRS (any Grade)*	8 (27.6%)
Grade 1	7 (24.1%)
Grade 2	1 (3.4%)†
Grade ≥3	0
Serious AE of CRS (any Grade)	4 (13.8%)‡
Median time to first CRS onset, days (range)	1 (1–28)
Median CRS duration, days (range)	3 (2–5)
Corticosteroids for CRS management	0
Tocilizumab for CRS management	0
CRS leading to mosunetuzumab discontinuation	0
CRS resolved	8 (100%)



- **CRS was low Grade and confined to C1–2. No increase in rate or severity with addition of lenalidomide.**

*assessed using ASTCT criteria[1]; †patient with WBC of 108k/uL at treatment initiation and circulating FL; patient had fever and hypoxia that required 2L nasal cannula oxygen; ‡Grade 1: 3 patients (10.3%); Grade 2: 1 patient (3.4%)

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

Investigational drug/indication, not authorized.

Morschhauser F, et al. ASH 2021; Oral presentation (abstract #129).

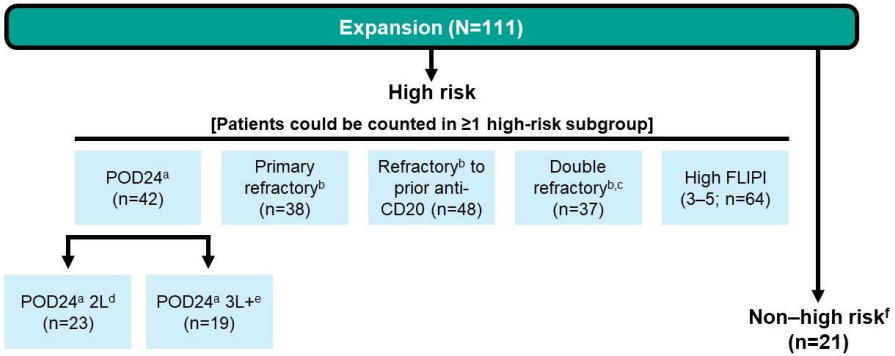
Phase I/II EPCORE NHL-2 study of epcor-R^2 in R/R FL

Study Design and Patient Disposition

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

Data cutoff: January 31, 2023
Median follow-up: 11.4 mo
Primary objectives: Safety and antitumor activity[g]



First pooled analysis of arms 2a and 2b for epcoritamab SC + R^2 in R/R FL patients

[a]POD24: Progression within 2 y of initiating first-line treatment that included chemoimmunotherapy. [b]Refractory: No response or relapse within 6 mo after therapy. [c]Double refractory: Refractory to both anti-CD20 and an alkylating agent. [d]Patients received epcoritamab SC in second line. [e]Patients received epcoritamab SC in third line or beyond. [f]Non–high risk: Patients who do not meet criteria for any of the predefined high-risk factors (eg, POD24, primary refractory, refractory to prior anti-CD20, double refractory, and high FLIPI). [g]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. **1.** Brice P, et al. *J Clin Oncol*. 1997;15:1110-7.

Investigational drug/indication, not authorized.
Epcor, epcoritamab; GELF, Group d'Etude des Lymphomes Folliculaires; MRI, magnetic resonance imaging; R^2, rituximab plus lenalidomide.

Merryman R, et al. ASCO 2023; Oral presentation (abstract #7506).

EPCORE NHL-2: efficacy

Antitumor Activity with Epcoritamab SC + R^2

Response[a]	Efficacy Evaluable for Epcoritamab SC + R^2 n=104
Overall response	**98%**
CMR	87%
PMR	12%
Stable disease	1%
Progressive disease	1%

Data cutoff: January 31, 2023. Median follow-up: 11.4 mo (range, 2.1–22.1). [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.

High ORR and CMR rate observed with epcoritamab SC + R^2

Investigational drug/indication, not authorized.

Merryman R, et al. ASCO 2023; Oral presentation (abstract #7506).

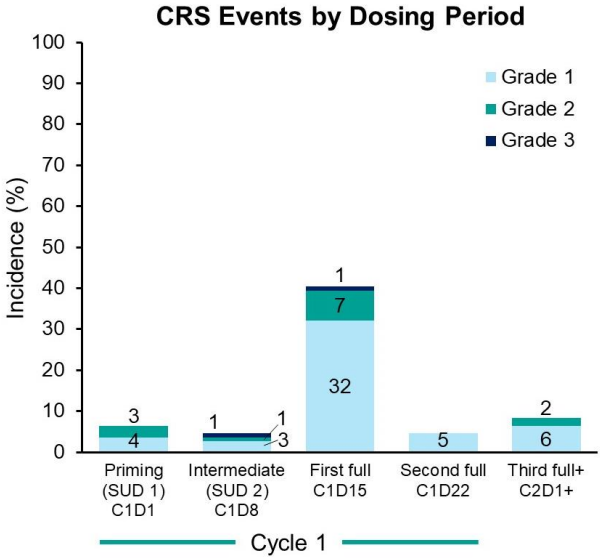
EPCORE NHL-2: CRS

CRS Summary

	Total N=111
CRS, n (%)[a]	53 (48)
Grade 1	38 (34)
Grade 2	13 (12)
Grade 3	2 (2)
Median time to onset after first full dose, d (range)	2 (1–9)
CRS resolution, n (%)	53 (100)
Median time to resolution, d (range)[b]	3 (1–23)
Treated with tocilizumab, n (%)	14 (13)
Leading to epcoritamab SC discontinuation, n (%)	**0**

[a]Graded by Lee et al 2019 criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS.

- CRS occurrence was predictable
- Majority of CRS events were low grade
- All CRS events resolved



SUD 1, first step-up dose; SUD 2, second step-up dose.

Investigational drug/indication, not authorized.

Merryman R, et al. ASCO 2023; Oral presentation (abstract #7506).

Current FL treatment landscape

First line[1,2]

- Chemoimmunotherapy*
- Anti-CD20 -/+ lenalidomide

Second line[1]

- Chemoimmunotherapy*
- Anti-CD20 -/+ lenalidomide
- ASCT
- Radioimmunotherapy
- EZH2 inhibitor (tazemetostat)

Third and later lines[1–3]

- Chemoimmunotherapy*
- Anti-CD20 -/+ lenalidomide
- ASCT
- Radioimmunotherapy
- PI3K inhibitor (duvelisib†)
- alloSCT
- CAR T-cell therapy
- Mosunetuzumab
- Zanubrutinib + obinutuzumab

*High tumor burden (stage III/IV). †Duvelisib was withdrawn from the US market for FL in 2022 but remains in the EU market.
PI3K, phosphoinositide 3-kinase.

1. Dreyling M, et al. Ann Oncol 2021;32:298–308;
2. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/;
3. EU SmPC. Available from: www.ema.europa.eu/en/medicines.

Current FL treatment landscape

First line[1,2]

- Chemoimmunotherapy*
- Anti-CD20 -/+ lenalidomide

Long term

- Bispecific antibody combination therapy

Second line[1]

- Chemoimmunotherapy*
- Anti-CD20 -/+ lenalidomide
- ASCT
- Radioimmunotherapy
- EZH2 inhibitor (tazemetostat)

Intermediate term

- Bispecific antibody combination therapy
- CAR T-cell therapy (specific subpopulations)

Third and later lines[1–3]

- Chemoimmunotherapy*
- Anti-CD20 -/+ lenalidomide
- ASCT
- Radioimmunotherapy
- PI3K inhibitor (duvelisib†)
- alloSCT
- CAR T-cell therapy
- Mosunetuzumab
- Zanubrutinib + obinutuzumab

Near term

- Other bispecific antibodies
- Other CAR T-cell therapies

Changes are predicted based on ongoing studies

*High tumor burden (stage III/IV). †Duvelisib was withdrawn from the US market for FL in 2022 but remains in the EU market.

1. Dreyling M, et al. Ann Oncol 2021;32:298–308;
2. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/;
3. EU SmPC. Available from: www.ema.europa.eu/en/medicines.

Factors influencing treatment selection

- Treatment access due to approval and reimbursement
- Dosing regimens, including duration of treatment
- Ability to administer in the outpatient setting
- Formulation
- Tolerability of treatments, including long-term toxicity

Summary

The treatment landscape for FL is evolving

Studies of bispecific antibodies as combination therapies are ongoing in all lines of treatment[1–9]

Bispecific antibodies in combination with lenalidomide have shown promising activity in patients with R/R FL[10,11]

Optimal sequencing of T-cell engaging therapies remains a current and future challenge

1. Olszewski AJ, et al. ASCO 2023; abstract #TPS7588; 2. NCT04792502. Available at: https://clinicaltrials.gov;
3. NCT05169658. Available at: https://clinicaltrials.gov; 4. Nastoupil L, et al. ASCO 2022; abstract #TPS7588; 5. NCT04712097. Available at: https://clinicaltrials.gov;
6. NCT05783609. Available at: https://clinicaltrials.gov; 7. Falchi L, et al. ASH 2023; abstract #3053; 8. NCT05409066. Available at: https://clinicaltrials.gov;
9. Leslie LA, et al. ASCO 2024; abstract #7014; 10. Morschhauser F, et al. ASH 2021; abstract #129; 11. Merryman R, et al. ASCO 2023; abstract #7506.

Panel discussion

Marco Ladetto, Elizabeth Budde
and Sascha Dietrich

Panel discussion

To submit questions:

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