EPCORE DLBCL-3: Fixed-Duration Epcoritamab Monotherapy in Older (≥75 y), Anthracycline-Ineligible Patients With Previously Untreated Large B-Cell Lymphoma (LBCL)

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Background

- For newly diagnosed patients with DLBCL, chemotherapy-containing regimens, including R-CHOP and R-mini-CHOP, are considered standards of care[1]
  - However, ~10% of newly diagnosed patients may not be suitable candidates for standard chemotherapy (R-CHOP and R-mini-CHOP) due to advanced age and/or underlying comorbidities[2,3]
  - Older patients with comorbidities have limited treatment options and worse outcomes, including lower ORR and shorter PFS and OS[4,5]
- Epcoritamab is a subcutaneously administered CD3xCD20 bispecific antibody that has demonstrated deep and durable responses across lines of therapy and lymphoma types and may provide a chemotherapy-free treatment option[6-10]

Objective: To present efficacy and safety results from the EPCORE® DLBCL-3 phase 2 trial of fixed-duration epcoritamab monotherapy in older (≥75 y) patients with newly diagnosed LBCL and comorbidities

1. Sehn LH, Salles G. *N Engl J Med*. 2021;384:842-58. **2.** Hershman DL, et al. *J Clin Oncol*. 2008;26:3159-65. **3.** Moccia AA, et al. *Blood Adv*. 2021;5:1483-9. **4.** Lugtenburg PJ, Mutsaers PGNJ. *Blood*. 2023;141:2566-75. **5.** Morrison VA, et al. *Ann Oncol*. 2015;26:1058-68. **6.** Thieblemont C, et al. *Leukemia*. 2024;38:2653-62. **7.** Linton KM, et al. *Lancet Haematol*. 2024;11:e593-e605. **8.** Vermaat JSP, et al. ASH 2023. Abstract 4457. **9.** Brody JD, et al. ASCO 2024. Abstract 7037. **10.** Falchi L, et al. ASH 2024. Abstract 581.

Study Design: EPCORE® DLBCL-3

A phase 2, open-label trial evaluating the efficacy and safety of fixed-duration epcoritamab in older patients with newly diagnosed LBCL and comorbidities

Key inclusion criteria

- Newly diagnosed CD20+ LBCL
  - DLBCL, NOS
  - T-cell/histiocyte-rich DLBCL
  - Double-hit or triple-hit DLBCL
  - FL grade 3B
- ICE score ≥8[a]
- ECOG PS 0–2
- Ineligible for anthracycline-based therapy/cytotoxic chemotherapy due to:
  - Age ≥80 y, or
  - Age ≥75 y with a comorbid condition[b]
- Measurable disease by CT or MRI

Data cutoff: September 21, 2024
Median follow-up: 9.5 mo (range, 0.4–17.7+)

1:1 RANDOMIZATION

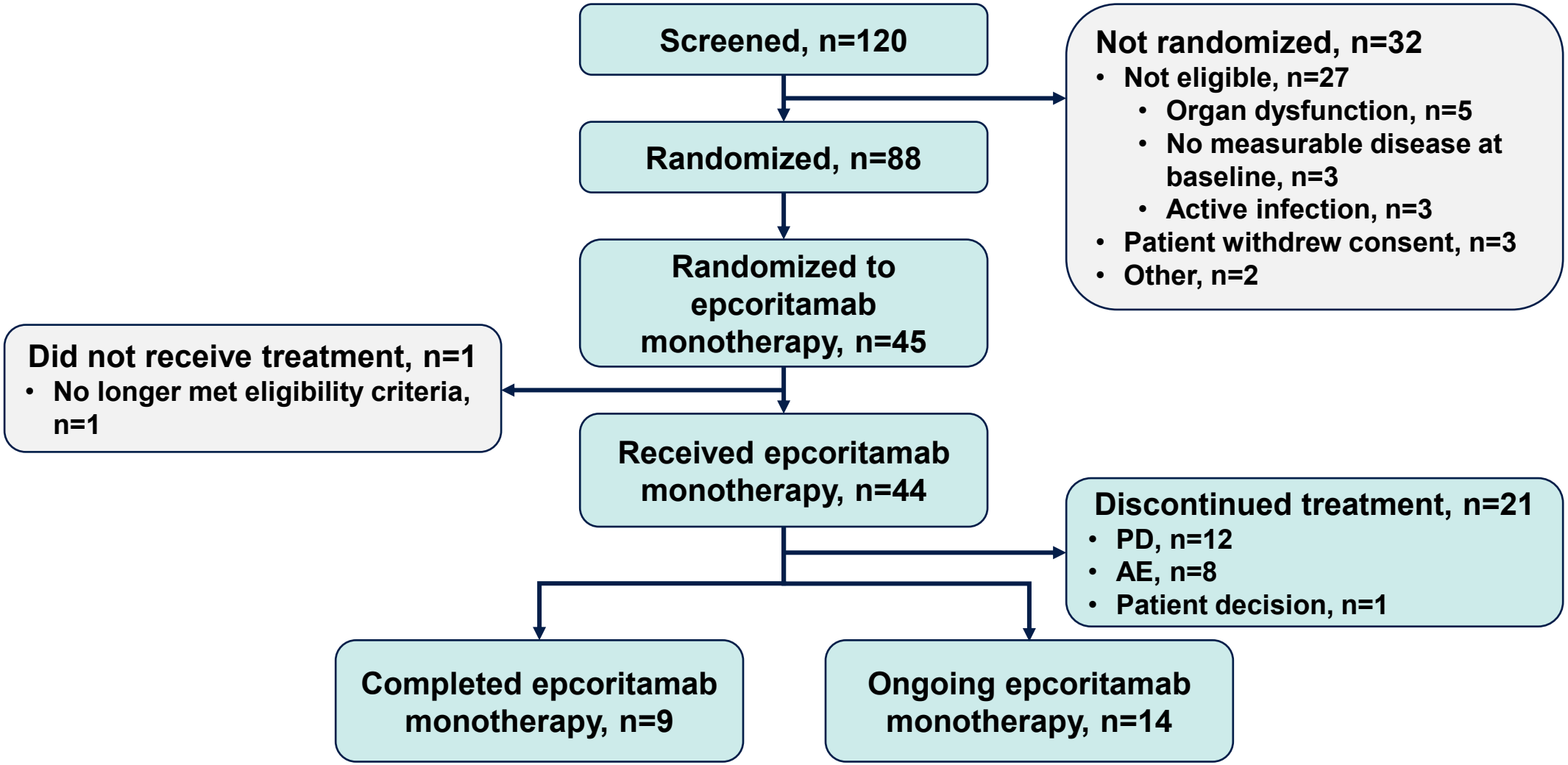
Agent	C1–3	C4–12
Epcoritamab SC 48 mg[c]	QW	Q4W

Agent	C1–3	C4–12
Epcoritamab SC 48 mg[c]	QW	Q4W
Lenalidomide PO 10–20 mg	QD D1–21	QD D1–21

- **Primary endpoint:** CR rate per Lugano criteria[1]
- **Key secondary endpoints:** ORR, TTR, DOR, DOCR, PFS, OS, MRD negativity,[d] and safety

ClinicalTrials.gov: NCT05660967. 28-d cycles. Tumor response was evaluated by PET-CT obtained at 6, 12, 24, 36, and 48 wk, and every 24 wk thereafter. [a]ICE score per the Immune Effector Cell–Associated Encephalopathy assessment tool (score ranges from 0 [patient unarousable] to 10 [patient unimpaired]).[2] [b]Comorbid conditions: impaired cardiac function; moderate to severe valvular heart disease; previous cardiotoxic cancer treatment; elevated baseline troponin and/or elevated baseline BNP or NT-proBNP; and pulmonary, hepatic, renal, or other comorbidities that made the patient ineligible for cytotoxic drug treatment. [c]Two step-up doses of epcoritamab (0.16 mg and 0.8 mg) administered before the first full dose. [d]MRD negativity was assessed by ctDNA using the AVENIO assay. **1.** Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-68. **2.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

Patient Disposition



Baseline Demographics and Disease Characteristics

Characteristic	N=45
Median age, y (range)	81 (77–95)
≥75 to <80 y, n (%)	8 (18)
≥80 to <85 y, n (%)	20 (44)
≥85 y, n (%)	17 (38)
Male sex at birth, n (%)	18 (40)
Race,[a] n (%)	
White	32 (71)
Asian	8 (18)
LBCL classification at baseline, n (%)	
DLBCL[b]	42 (93)
De novo, n/n (%)	40/42 (95)
Transformed from FL, n/n (%)	2/42 (5)
T-cell/histiocyte-rich LBCL	1 (2)
HGBL[b]	3 (7)
FL grade 3B	2 (4)
Cell of origin,[c] n (%)	
Germinal center B cell	22 (49)
Non–germinal center B cell or activated B cell	13 (29)
Unknown	7 (16)

Characteristic	N=45
ECOG PS, n (%)	
0–1	34 (76)
2	11 (24)
Ann Arbor stage, n (%)	
II	15 (33)
III	5 (11)
IV	25 (56)
IPI score, n (%)	
1–2	19 (42)
3–5	26 (58)
Renal function by CrCl, n (%)	
≥60 mL/min	12 (27)
30 to <60 mL/min	31 (69)
15 to <30 mL/min	2 (4)
Bulky disease per investigator,[d] n (%)	
<7 cm	31 (69)
7–10 cm	8 (18)
>10 cm	5 (11)
Median time from initial diagnosis to first dose, mo (range)	1.3 (0.2–45.7)

[a]Race was not reported or missing for 5 patients. Ethnicity data were not collected. [b]Three patients had double-hit lymphoma per central laboratory. [c]Cell of origin was not evaluated for 3 patients. [d]Bulky disease assessment was missing for 1 patient.

Cardiovascular Comorbidities and Risk Factors

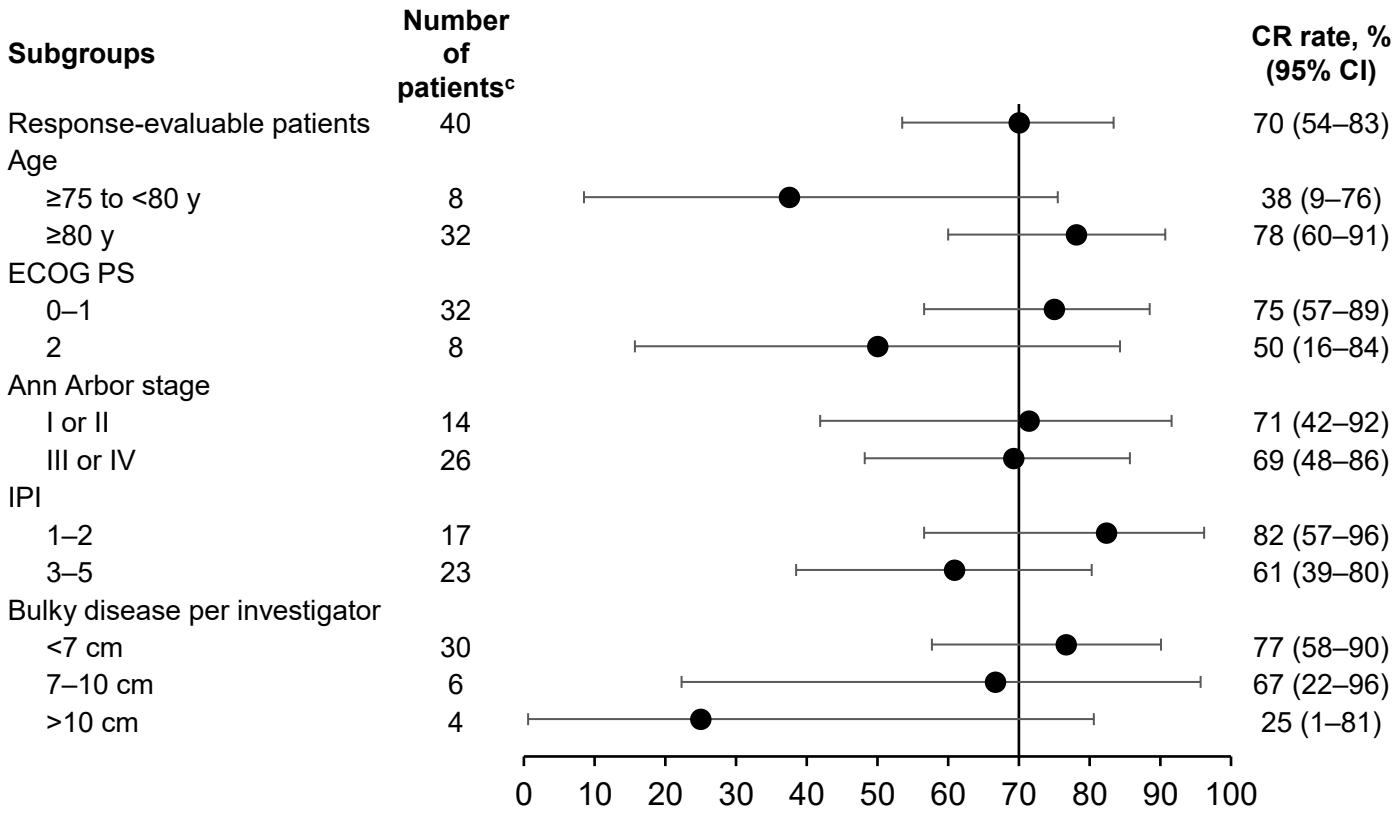
n (%)	N=45
Hypertension	35 (78)
Elevated cardiac enzymes[a]	32 (71)
Atrial fibrillation	7 (16)
Coronary artery disease/prior myocardial infarction	7 (16)
Moderate to severe valvular heart disease	6 (13)
Diabetes mellitus	5 (11)
Previous cardiotoxic therapy	3 (7)
Thrombosis	3 (7)
Cerebral small vessel ischemic disease	3 (7)
Reduced LVEF (<50%)	2 (4)
Carotid artery stenosis	2 (4)
Arteriosclerosis	2 (4)

- 87% had cardiac and/or cardiovascular disorders
- 40% had other comorbidities that made the patient ineligible for cytotoxic drug treatment

[a]Baseline troponin and/or BNP or NT-proBNP elevated above the upper limit of normal for local laboratory reference range.

High CR and MRD-Negativity Rates Were Observed

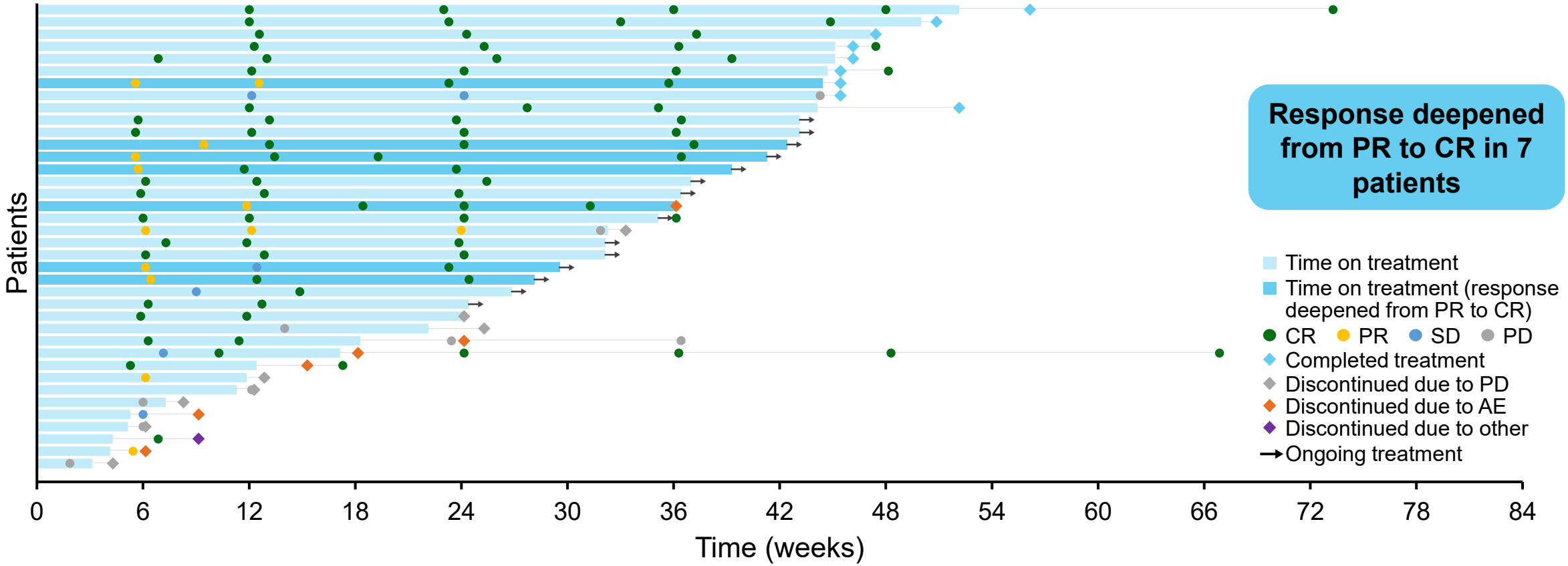
Best Response,[a] n (%)	Full Analysis Set[b] N=45	Response Evaluable[c] n=40
ORR	31 (69)	31 (78)
CR	28 (62)	28 (70)
PR	3 (7)	3 (8)
SD	2 (4)	2 (5)
PD	5 (11)	5 (13)
NA	7 (16)	2 (5)



- 15 responders (14 with CR, 1 with PR) were evaluated for MRD; the MRD-negativity rate[d] at C3D1 was 93% (14/15)

[a]Responses are based on investigator assessment and Lugano criteria. [b]Based on the full analysis set, defined as all randomized patients. [c]Based on response-evaluable population, defined as patients who received ≥1 dose of epcoritamab, had measurable disease at baseline, and had ≥1 postbaseline disease evaluation or died within 60 d of first trial treatment. [d]Data cutoff for MRD analysis: April 2024. NA, not assessed.

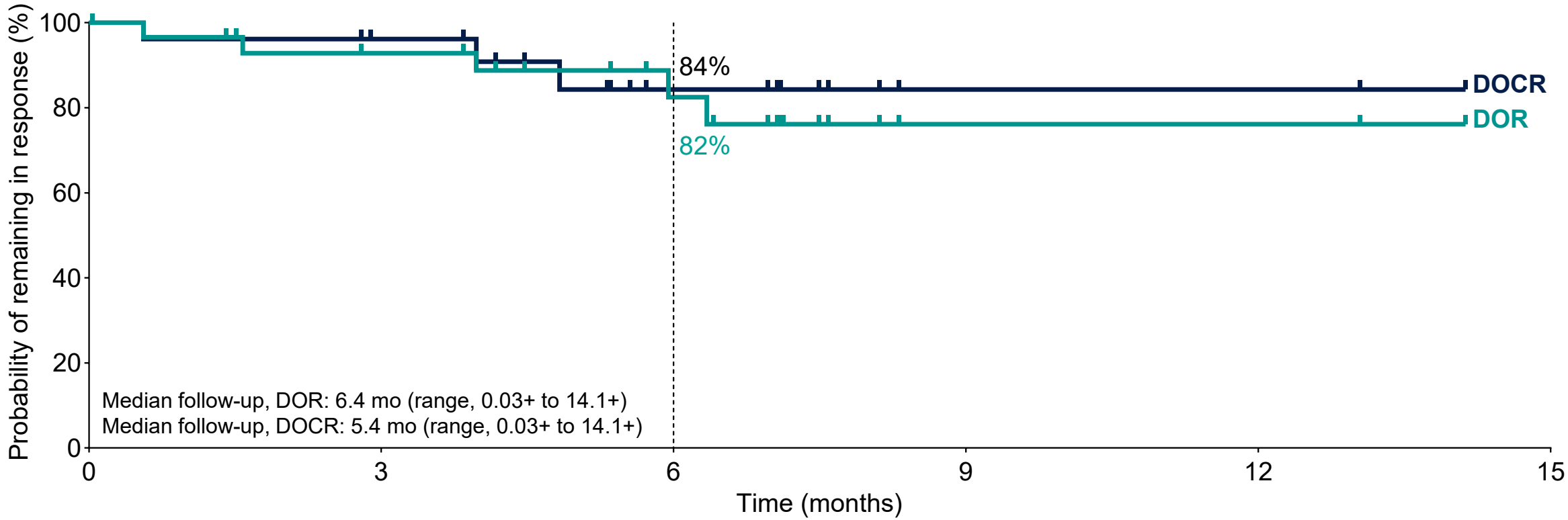
Most Responses Occurred Early



- Median epcoritamab cycles initiated: 7 (range, 1–12); median duration of treatment: 6.6 mo (range, 0.03–12.0)
- Median time to response: 1.5 mo (range, 1.2–3.4); median time to CR: 2.5 mo (range, 1.2–5.4)
- Of the 9 patients who completed treatment, 8 remained in CR at the data cutoff

Patients in the full analysis set (defined as all randomized patients) excluding patients who had no assessment (n=7).

Responses Were Deep and Durable



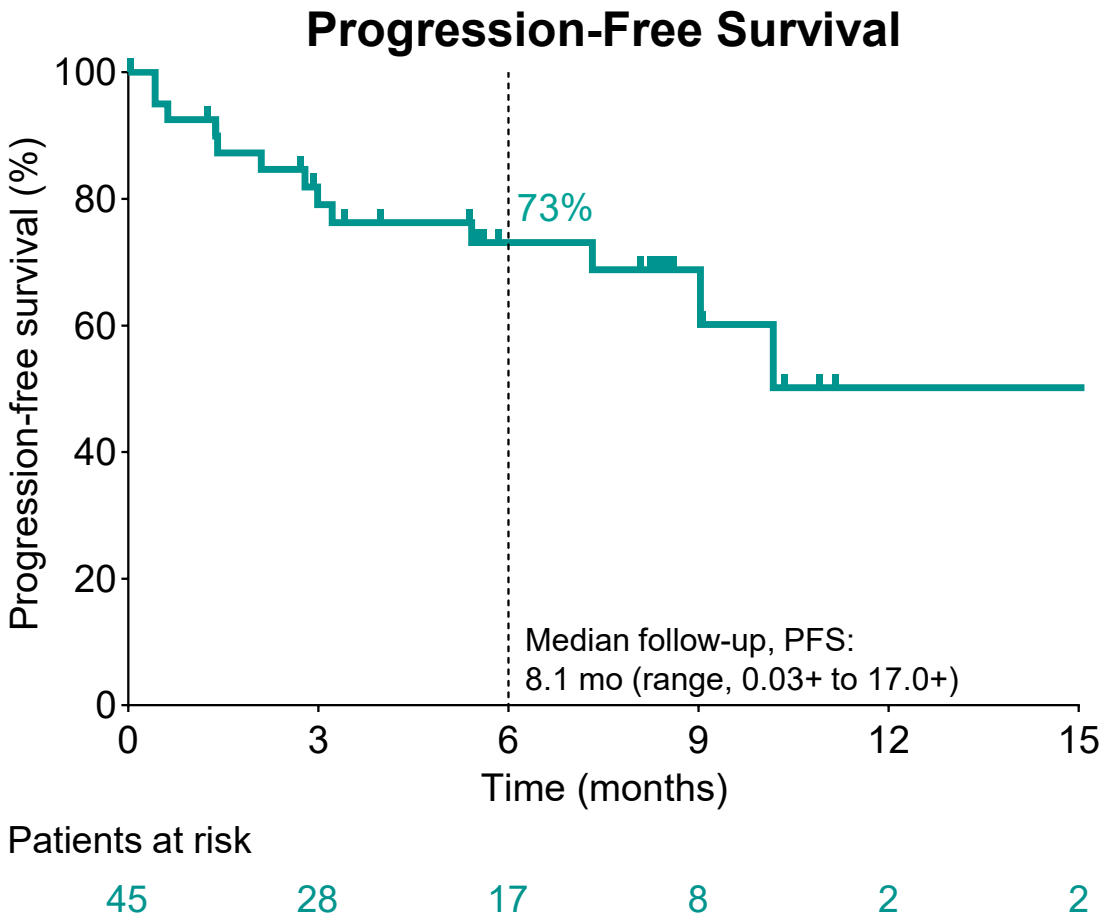
Patients at risk

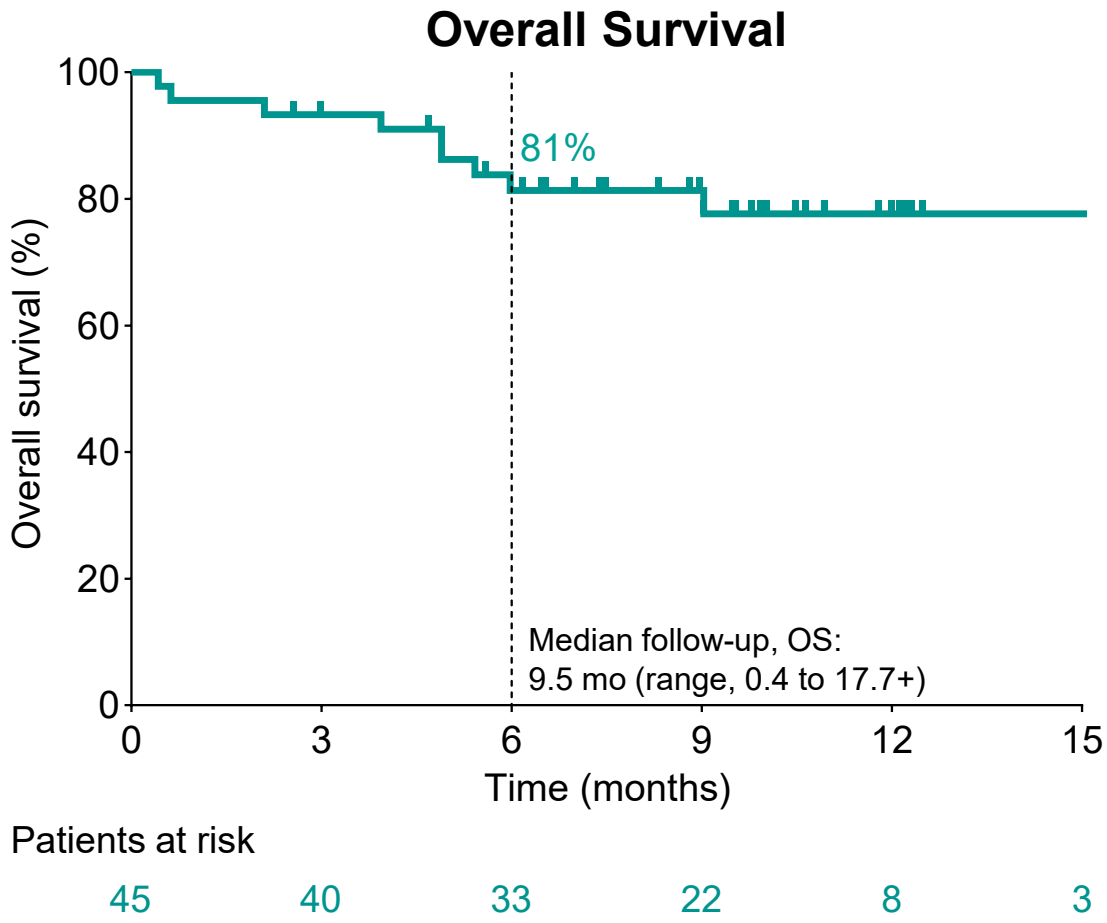
31	24	13	2	2	0
28	19	9	2	2	0

- At data cutoff, 84% of all responses (26/31) and 89% of complete responses (25/28) were ongoing

Median study follow-up: 9.5 mo (range, 0.4–17.7+).

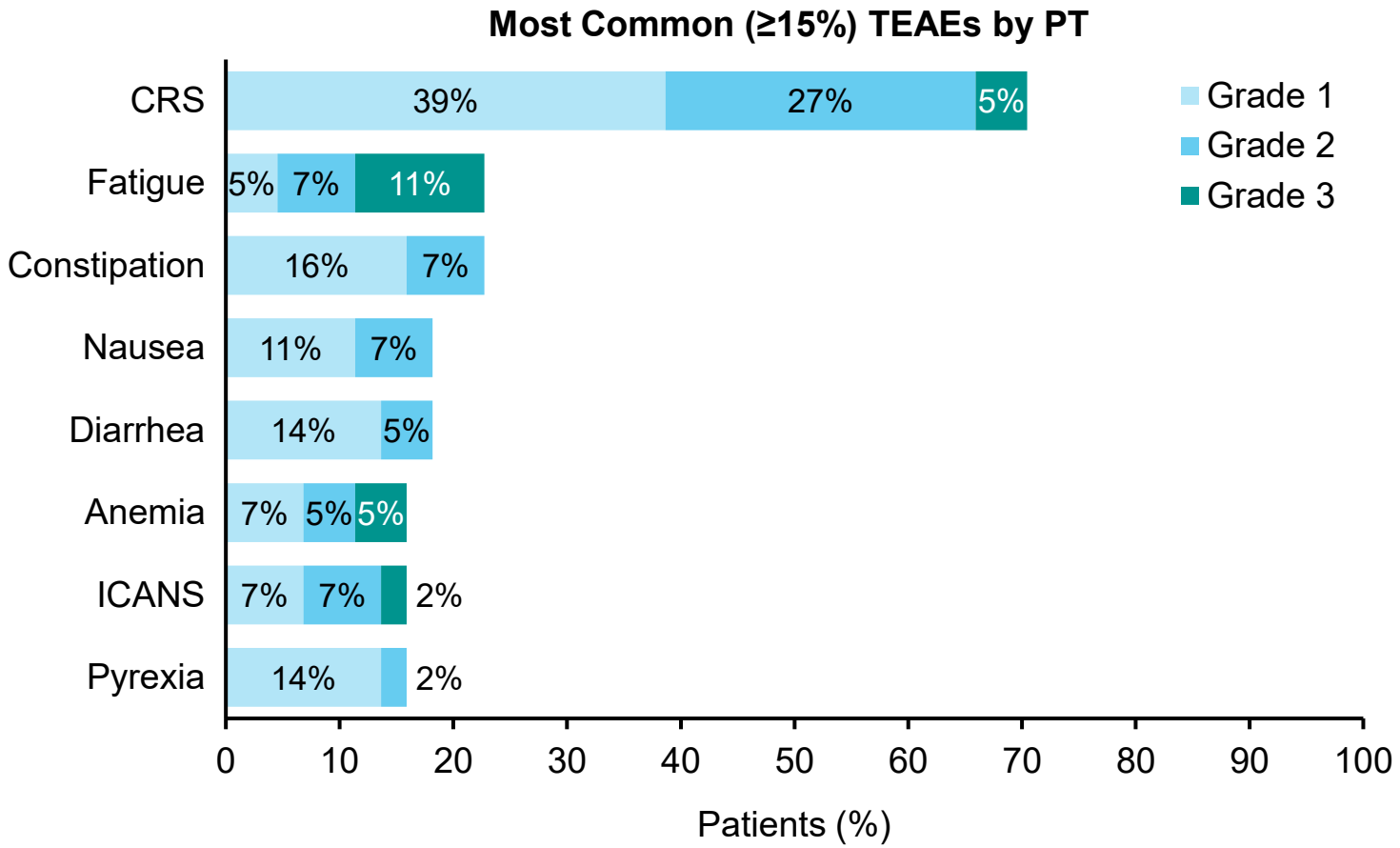
Favorable Long-Term Survival Observed





Median study follow-up: 9.5 mo (range, 0.4–17.7+).

Epcoritamab Was Generally Well Tolerated

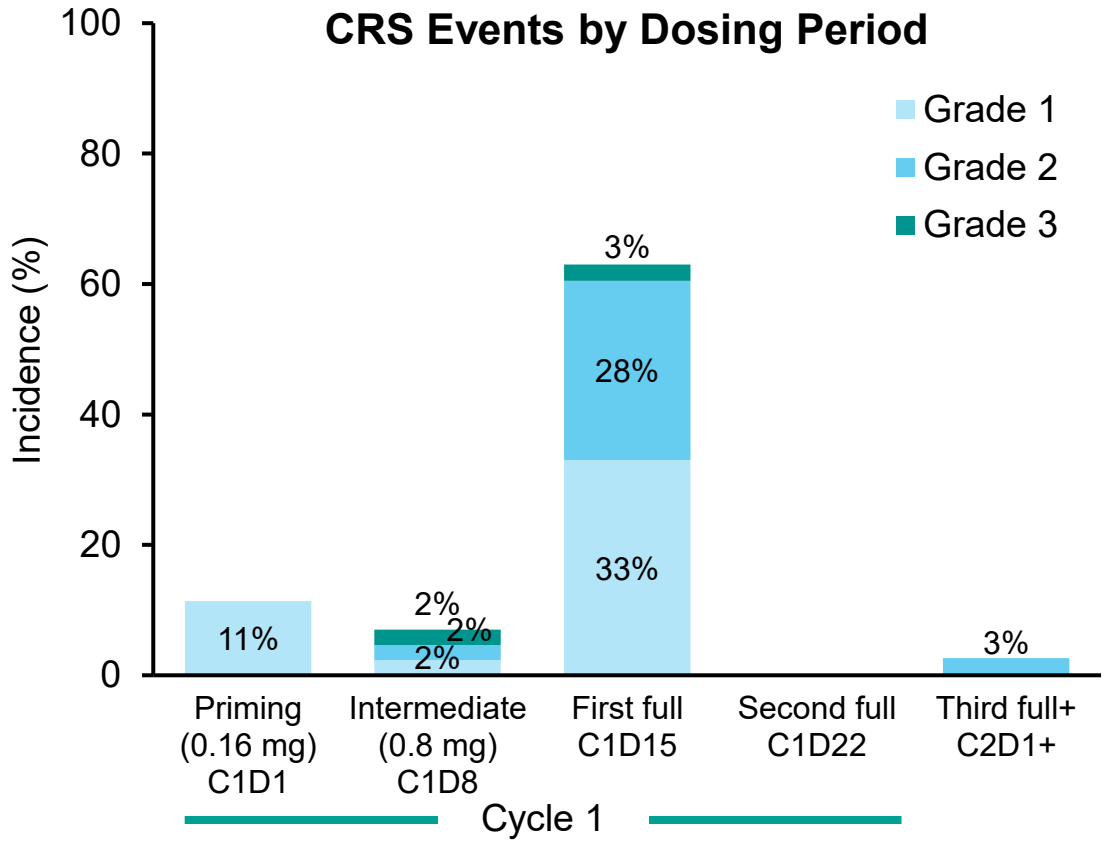


- 8 patients (18%) experienced a serious infection; 4 (9%) had serious COVID-19
- Neutropenia was reported for 4 patients (9%),[a] with no cases of febrile neutropenia
- 8 patients (18%) experienced TEAEs that led to epcoritamab discontinuation[b]
- 5 patients had fatal TEAEs (COVID-19 [n=2], CMV reactivation, TLS, tumor hemorrhage)

Data are from the safety analysis set, defined as patients who received ≥1 dose of epcoritamab. [a]Neutropenia: grade 3, n=1; grade 4, n=3. [b]Treatment-related AEs leading to discontinuation: anemia and neutropenia, ataxia, ICANS, respiratory failure, and tumor lysis syndrome; AEs not considered related to treatment leading to discontinuation: COVID-19 pneumonia, fatigue, and neuroendocrine tumor of the lung.

CRS Was Manageable and Mostly Low Grade, and Timing Was Predictable

	n=44
CRS,[a] n (%)	31 (71)
Grade 1	17 (39)
Grade 2	12 (27)
Grade 3	2 (5)
Median time to onset from first full dose, h (range)	15 (9–26)
Treated with tocilizumab, n (%)	14 (32)
Treated with corticosteroids, n (%)	10 (23)
CRS resolution,[b] n/n (%)	30/31 (97)
Median time to resolution, d (range)	2 (1–5)
Leading to treatment discontinuation, n (%)	0



- 97% of CRS events occurred in cycle 1

Data are from the safety analysis set, defined as patients who received ≥1 dose of epcoritamab. Corticosteroid prophylaxis (prednisolone or dexamethasone) was used in C1 to mitigate CRS; standard hydration was recommended. [a]Lee et al 2019 criteria.[1] [b]One patient died with ongoing (unresolved) CRS.

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

ICANS Events Were Manageable, and All Resolved

- ICANS was reported in 7 patients (16%)
- 4 patients had concurrent CRS or capillary leak syndrome
- Median time to ICANS onset was 28 d (range, 17–38)
- All ICANS events resolved; median time to ICANS resolution was 2 d (range, 1–22)
- ICANS led to treatment delay in 5 patients (11%) and treatment discontinuation in 1 patient (2%)

Baseline Characteristics		ICANS Details		ICE Score[a]		Ongoing Events at Time of ICANS
Age, y	Select Comorbidities/ Risk Factors	Grade	Predominant Manifestation	Baseline	Worst ICE[b]	
79	Carotid artery stenosis, acute renal failure, sleep apnea	3	Confusional state	10	0	CRS
92	Ischemic stroke, confusion	2	Depressed consciousness	8	8	Viral pneumonia
89	COPD, dyspnea	2	Disorientation	8	9	Intracranial hemorrhage, wound infection, tumor hemorrhage
		2	Disorientation, somnolence	8	8	
83		2	Delirium	8	5	CRS
89	Restless legs syndrome, insomnia, peripheral motor and sensory neuropathy	1	Cognitive disorder	10	7	Capillary leak syndrome, CMV infection
86	Prior CVA, hyponatremia, peripheral neuropathy, anxiety	1	Disorientation	9	8	Influenza
80	Residual ischemic cerebral lesions	1	Delirium	10	9	CRS

[a]ICE score per the Immune Effector Cell–Associated Encephalopathy assessment tool (score ranges from 0 [patient unarousable] to 10 [patient unimpaired]).[1] [b]Worst ICE score reported since most recent epcoritamab dose and prior to ICANS resolution.

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

Conclusions

- Fixed-duration, subcutaneous epcoritamab monotherapy led to high response rates and a manageable safety profile in older patients with newly diagnosed LBCL and comorbidities, a population with significant unmet need and poor outcomes
  - ORR: 78%; CR rate: 70%; 89% of complete responses were ongoing
- Early and deep responses were observed
  - Median time to response was 1.5 mo
  - 93% of MRD-evaluable responders were MRD negative at C3D1
- Safety was consistent with prior reports of epcoritamab monotherapy
  - CRS was manageable and timing was predictable; ICANS was mostly low grade and occurred in patients with other ongoing complications, and all events resolved

Please scan the QR code for a copy of this presentation and a plain-language summary of these data.

Epcoritamab monotherapy is a promising chemotherapy-free treatment option for older patients with newly diagnosed LBCL who have comorbidities and are not candidates for standard chemotherapy

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- These results were previously presented in part at the American Society of Hematology Annual Meeting; December 7–10, 2024; San Diego, CA, USA

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