Odronextamab in Patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Results from a Prespecified Analysis of the Phase 2 Study ELM-2

Won Seog Kim[1], Tae Min Kim[2], Seok-Goo Cho[3], Isidro Jarque[4], Elżbieta Iskierka[5], Michelle Poon[6], H. Miles Prince[7], Sung Yong Oh[8], Francesca Lim[9], Cecilia Carpio[10], Tran-Der Tan[11], Sabarish Ayyappan[12], Antonio Gutierrez[13], Jingjin Li[14], Melanie Ufkin[14], Min Zhu[14], Aafia Chaudhry[14], Hesham Mohamed[14], Srikanth Ambati[14], Jan Walewski[15], on behalf of ELM-2 Investigators

[1]Samsung Medical Center, Center for Hematologic Malignancy, Seoul, South Korea; [2]Seoul National University Hospital, Seoul, South Korea; [3]The Catholic University of Korea, Seoul St. Mary's Hospital Hematology, Seoul, South Korea; [4]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [5]Copernicus Memorial Hospital, Department of Hematology, Medical University of Łódź, Łódź, Poland; [6]Hematology Oncology National University Hospital, Singapore; [7]Epworth Healthcare and University of Melbourne, East Melbourne, Australia; [8]Dong-A University Hospital, Busan, South Korea; [9]Singapore General Hospital, Singapore; [10]Department of Hematology, Vall d'Hebron Institute of Oncology (VHIO), University Hospital Vall d'Hebron, Autonomous University of Barcelona (UAB), Barcelona, Spain; [11]Hematology and Medical Oncology Koo Foundation Sun Yat Sen Cancer Center, Taipei City, Taiwan; [12]University of Iowa Hospital and Clinics, Iowa City, IA, USA; [13]Hospital Universitari Son Espases, IdISBa Palma, Spain; [14]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [15]Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie Państwowy Instytut Badawczy, Warszawa, Poland

ClinicalTrials.gov ID: NCT03888105

This study was funded by Regeneron Pharmaceuticals, Inc.

Medical writing support was provided by Lewis Cawkwell of Apollo, OPEN Health Communications, and funded by Regeneron Pharmaceuticals, Inc.

Presented at the Korean Society of Hematology International Conference & 64th Annual Meeting, March 30–April 1, 2023, Seoul, Korea.
Previously presented at ASH 2022 Annual Conference, December 10–13, 2022 (Kim WS, et al. oral presentation #444).

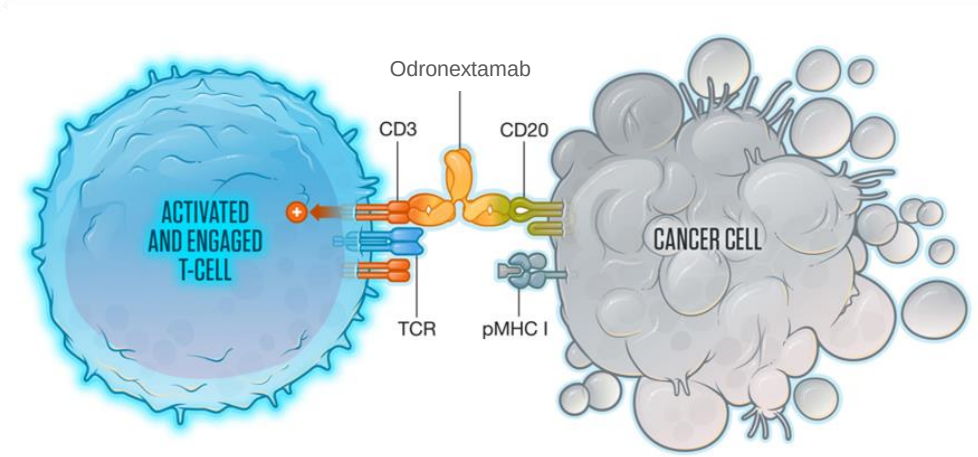
Disclosures of NAME SURNAME

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Beigene	x						
Sanofi	x						
Boryong	x						
Roche	x						
Kyowa-Kirin	x						
Donga	x						
Celltrion			x				

Background

- Despite advances in care, patients with R/R DLBCL have very poor outcomes[1,2]
  - Significant unmet need for off-the-shelf therapies that can provide rapid antitumor control and improve long term outcomes, especially in patients who cannot access, are ineligible for, or are refractory to CAR T therapy[2]
- Odronextamab, a CD20xCD3 bispecific antibody, was investigated in the Phase 1 trial (ELM-1, NCT02290951)[3]
  - Encouraging efficacy and manageable safety observed in heavily pre-treated subjects with R/R DLBCL
    - No prior CAR T: 53% ORR, 53% CR, mDOR not reached
    - Post-CAR T: 33% ORR, 27% CR, mDOR not reached
  - Dose expansion in R/R DLBCL patients post-CAR T is ongoing
- Here we report the first interim results of the pivotal Phase 2 trial ELM-2 in patients with R/R DLBCL (NCT03888105)

Odronextamab
Hinge-stabilized CD20×CD3 bispecific antibody

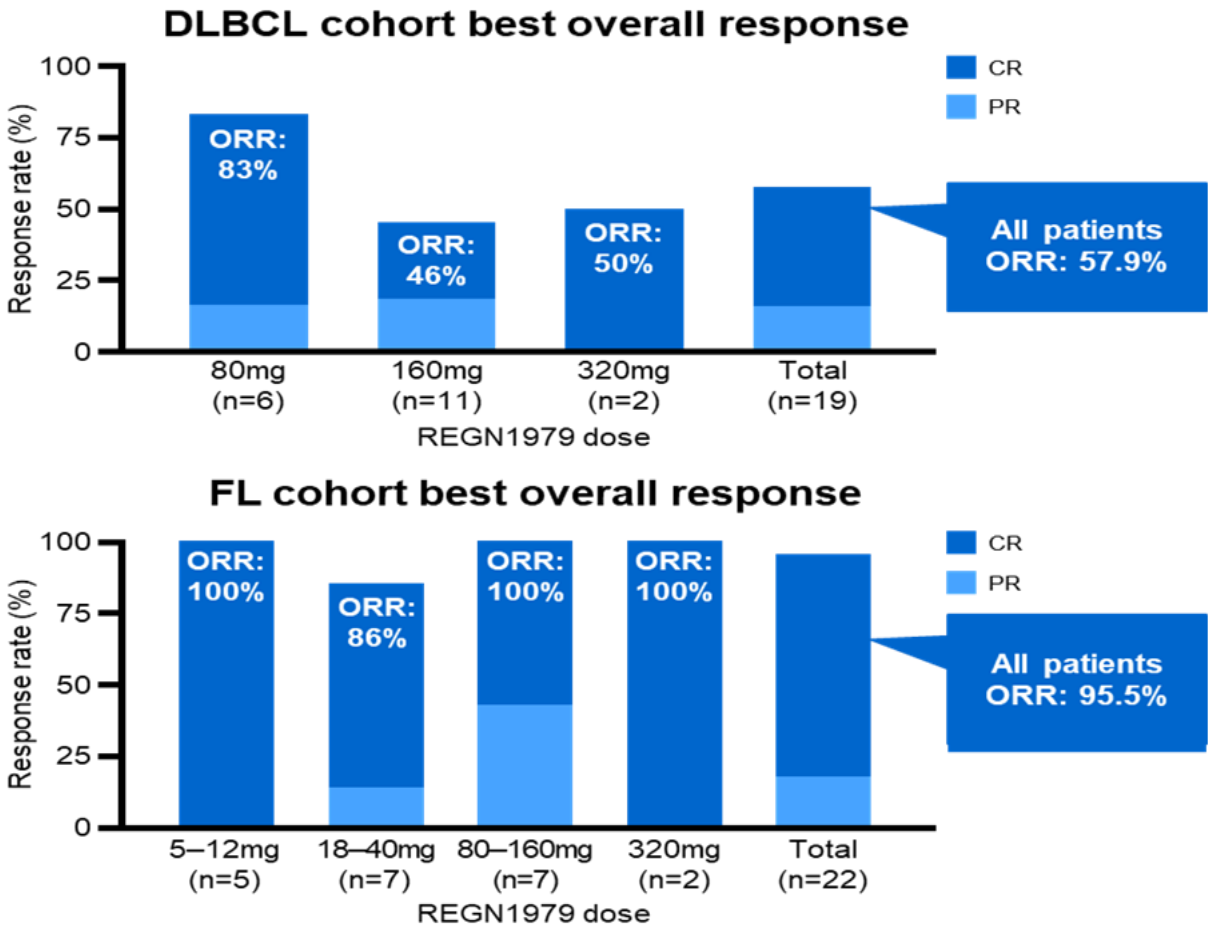


Binds CD20 on malignant B-cells and CD3 on T cells, to elicit T-cell-mediated cytotoxicity

CAR T, chimeric antigen receptor T cell; CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; mDOR, median duration of response; ORR, objective response rate; pMHC I, peptide major histocompatibility complex type I; R/R, relapsed/refractory; TCR, T-cell receptor.

1. Crump M, et al. *Blood*. 2017;130(16):1800–1808. 2. Chow VA, et al. *Am J Hematol*. 2019;94(8):e209–e213. 3. Bannerji R, et al. *Lancet Haematol.* 2022;9(5):e327–e339.

Odronextamab : ELM-1

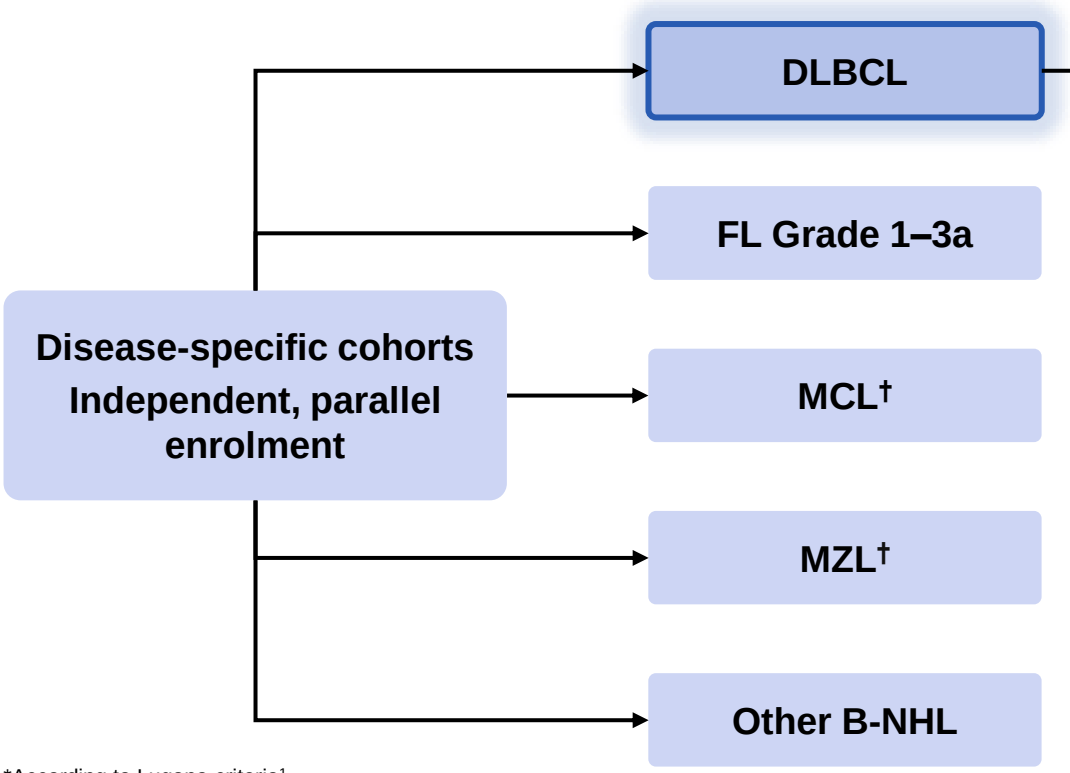


Grade 3/4 AEs, %	N=110
Anaemia	21.8%
Hypophosphataemia	19.1%
Neutropenia	19.1%
Lymphopenia	19.1%
Thrombocytopenia	13.6%
CRS	6.4%

Bannerji R, et al. ASH 2019; abstr #762

ELM-2 study design – DLBCL cohort

- Phase 2, open-label, multi-cohort, multicenter study of odronextamab monotherapy for patients with R/R B-NHL (NCT03888105)
  - R/R FL cohort results presented at ASH 2022: oral presentation #949



Key eligibility criteria

- DLBCL per WHO 2016 classification
- ECOG PS 0 or 1
- Refractory to or relapsed after ≥2 prior lines of therapy, including an anti-CD20 antibody and an alkylator

Primary endpoint

- ORR* by ICR

Key secondary endpoints

- ORR* by local investigator
- CR, DOR, PFS, and OS
- Safety and tolerability

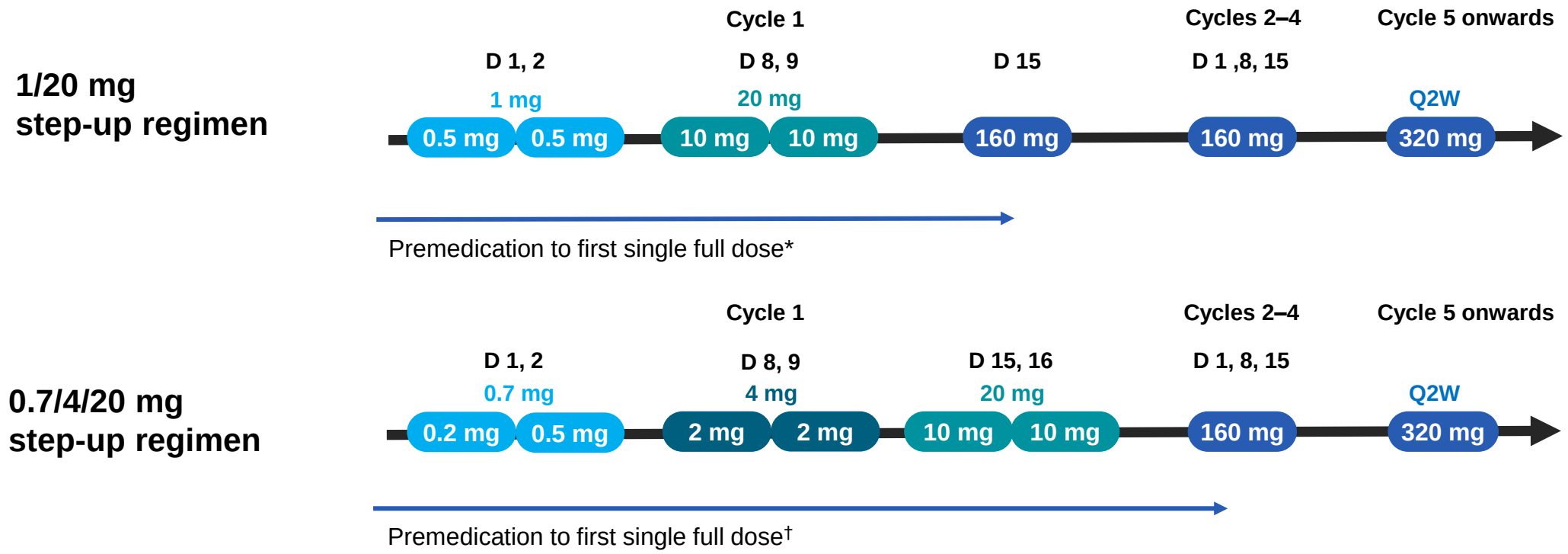
Odronextamab administration:

- IV, 21-day cycles
- Cycle 1 Step-up
- Cycles 2-4 160mg Days 1, 8,15
- Cycle 5 onwards 320mg Q2W
- Treatment until disease progression

*According to Lugano criteria[1]
†New enrolment is currently paused.
B-NHL, B-cell non-Hodgkin's lymphoma; 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; Q2W, every 2 weeks; R/R, relapsed/refractory; WHO, World Health Organization.
1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059–3068.

Cycle 1 step-up regimen optimized to mitigate the risk for cytokine release syndrome

- The study initiated with a Cycle 1 step up regimen of 1/20 mg
- This was modified to 0.7/4/20 mg during Cycle 1 to further mitigate the risk of CRS



Updated guidelines for tocilizumab and steroids introduced with 0.7/4/20 mg regimen.
*20 mg IV dexamethasone 1 to 3 hours prior to each split or initial single infusion. †10 mg dexamethasone orally 12 to 24 hours prior to the first split infusion. On each day of split or single infusion: dexamethasone 20 mg IV 1 to 3 hours before infusion; diphenhydramine 25 mg IV or orally and acetaminophen 650 mg orally 30 to 60 minutes before infusion.
CRS, cytokine release syndrome; D, day; IV, intravenous; Q2W, every 2 weeks.

Baseline characteristics

- Heavily pretreated, highly refractory patient population

Patient and disease characteristics		N=140
Median age, years (range)		66 (24–88)
Male		59.3%
ECOG performance status	0 / 1	32.1% / 67.9%
Ann Arbor stage	III–IV	80%
IPI	0–1 / 2	15.0% / 27.9%
	3 / 4–5	31.4% / 25.0%
Cell of origin	GCB / non-GCB	33.6% / 45.7%
DLBCL subtype	transformed	22.1%
DLBCL double or triple hit	double-hit / triple-hit	13.6% / 5.7%
Bulky disease (investigator assessment)		22.9%
Median no. of prior lines, n (range)		2 (2–8)
Prior ASCT		15.7%
Primary refractory		57.1%
Refractory to any prior line of therapy		90.7%
Refractory to last line of therapy		86.4%
Refractory to anti-CD20 antibody in any line		78.6%
Double refractory to alkylator/anti-CD20 Ab in any line		65.7%

Data cut-off date: Sep 15, 2022.
Ab, antibody; ASCT, autologous stem cell transplantation; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group, GCB, germinal centre B-cell; IPI, International Prognosis Index.

Patient disposition

	N=140
Cycle 1 step-up regimen (1/20 mg) / (0/7/4/20 mg)	47.9% / 52.1%
Median duration of exposure, weeks (range)	14.9 (0.9–118.9)
Median number of doses received, no. (range)	15 (1–52)
Median number of cycles completed, no. (range)	5 (0–57)
Completed Cycle 1	128 (91.4%)
≥4 cycles completed	82 (58.6%)
Treatment ongoing	34 (24.3%)
Treatment discontinued Disease progression Adverse event Death Patient or physician decision / withdrawal of consent	75.7% 41.4% 9.3% 12.9% 12.1%

Data cut-off date: Sep 15, 2022.

Odronextamab efficacy: Objective response rate

Best overall response	Independent central review N=130*	Investigator evaluation N=130*
Objective response rate (ORR)†	**49.2%** [95% CI 40.4%–58.1%]	**50.0%** [95% CI 41.1%–58.9%]
Complete response	**30.8%**	**36.2%**
Partial response	18.5%	13.8%
Stable disease	3.8%	3.1%
Progressive disease	22.3%	21.5%

Week 12 response assessment by independent central review	1/20 step-up regimen N=67	0.7/4/20 step-up regimen N=63
ORR	46.3% [95% CI: 34.0–58.9%]	42.9% [95% CI: 30.5–56.0%]
Complete response	26.9%	20.6%

- 63% of responders achieved a complete response
- Consistent efficacy observed at Week 12 regardless of Cycle 1 step-up regimen

- Median opportunity of follow-up: 21.3 months (range 2.6–29.8)

Data cut-off date: Sep 15, 2022.
*Efficacy evaluable (with an opportunity for assessment at 12 weeks); †ORR = complete responses + partial responses.
CI, confidence interval; ORR, objective response rate.

Odronextamab Efficacy: DLBCL patients with prior CAR T

- Consistent efficacy (objective and complete responses) observed in post-CAR-T patients enrolled in Phase 1 dose expansion cohort

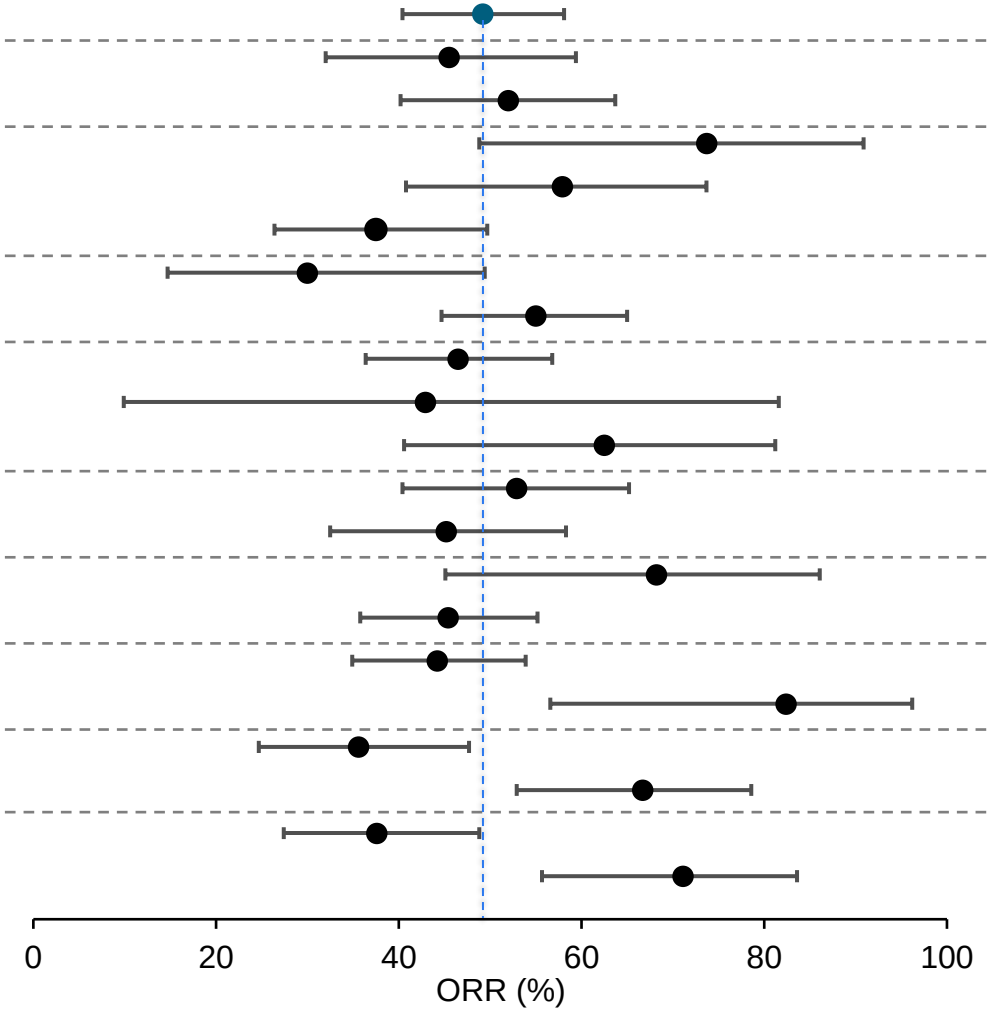
Best overall response	Independent central review N=31	Investigator evaluation N=31
Objective response rate (ORR)	**48.4%** [95% CI 30.2%–66.9%]	38.7% [95% CI 21.8%–57.8%]
Complete response	**32.3%**	32.3%
Partial response	16.1%	6.5%
Stable disease	6.5%	3.2%
Progressive disease	9.7%	29.0%
Duration of response, median (months)	Not reached [95% CI 2.3–NE]	Not reached [95% CI 2.3–NE]
Duration of complete response, median (months)	Not reached [95% CI 2.3–NE]	Not reached [95% CI 2.3–NE]

- Median opportunity of follow-up: 24.3 months (range 2.7–38.5)

Data cut-off date from ELM-1: Aug 11, 2022.
CAR T, chimeric antigen receptor T cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; NE, not evaluable; ORR, objective response rate.

Odronextamab efficacy: Consistent efficacy in high risk subgroups

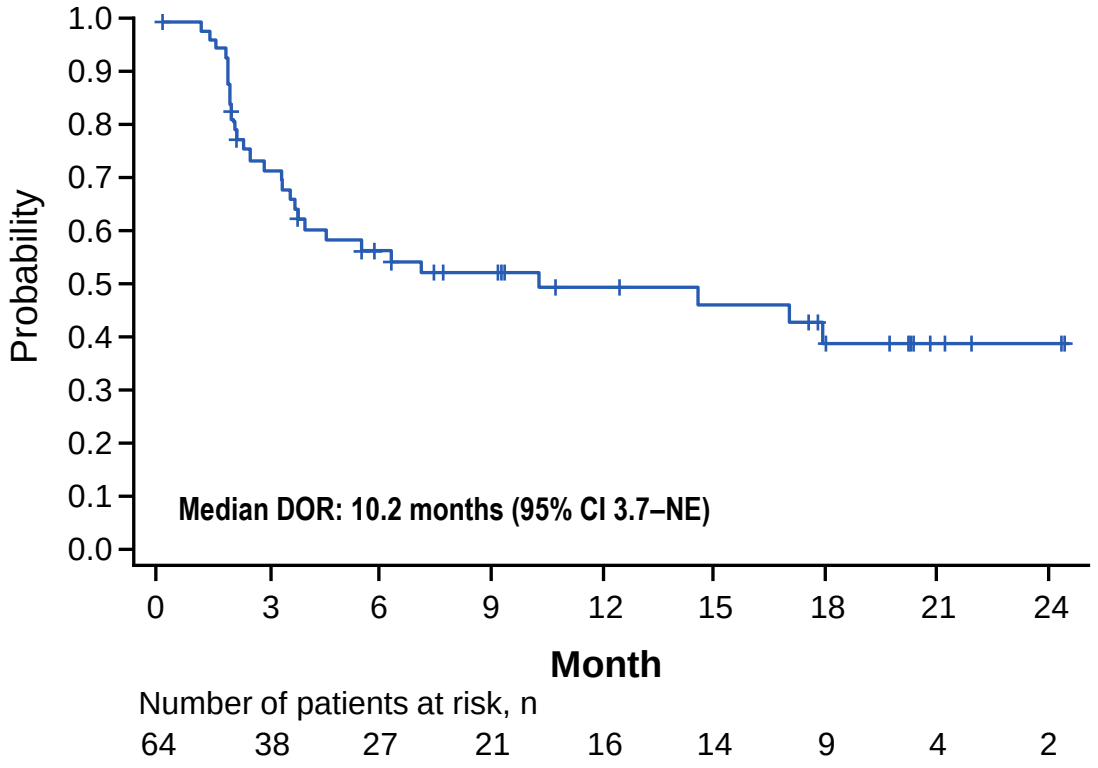
Subgroup		N	ORR (95% CI)
All patients		130	49.2 (40.4–58.1)
Age	<65	55	45.5 (32.0–59.4)
	≥65	75	52.0 (40.2–63.7)
IPI	0–1	19	73.7 (48.8–90.9)
	2	38	57.9 (40.8–73.7)
	3–5	72	37.5 (26.4–49.7)
Bulky disease	Yes	30	30.0 (14.7–49.4)
	No	100	55.0 (44.7–65.0)
Subtype	De novo	99	46.5 (36.4–56.8)
	Transformed, Richter	7	42.9 (9.9–81.6)
	Transformed, non-Richter	24	62.5 (40.6–81.2)
Prior lines	2	68	52.9 (40.4–65.2)
	>2	62	45.2 (32.5–58.3)
Prior ASCT	Yes	22	68.2 (45.1–86.1)
	No	108	45.4 (35.8–55.2)
Refractory to last line	Yes	113	44.2 (34.9–53.9)
	No	17	82.4 (56.6–96.2)
Primary refractory	Yes	73	35.6 (24.7–47.7)
	No	57	66.7 (52.9–78.6)
Double refractory	Yes	85	37.6 (27.4–48.8)
	No	45	71.1 (55.7–83.6)



Data cut-off date: Sep 15, 2022.
Responses as per independent central review.
ASCT, autologous stem cell transplant; CI, confidence interval; IPI, International Prognosis Index; ORR, objective response rate.

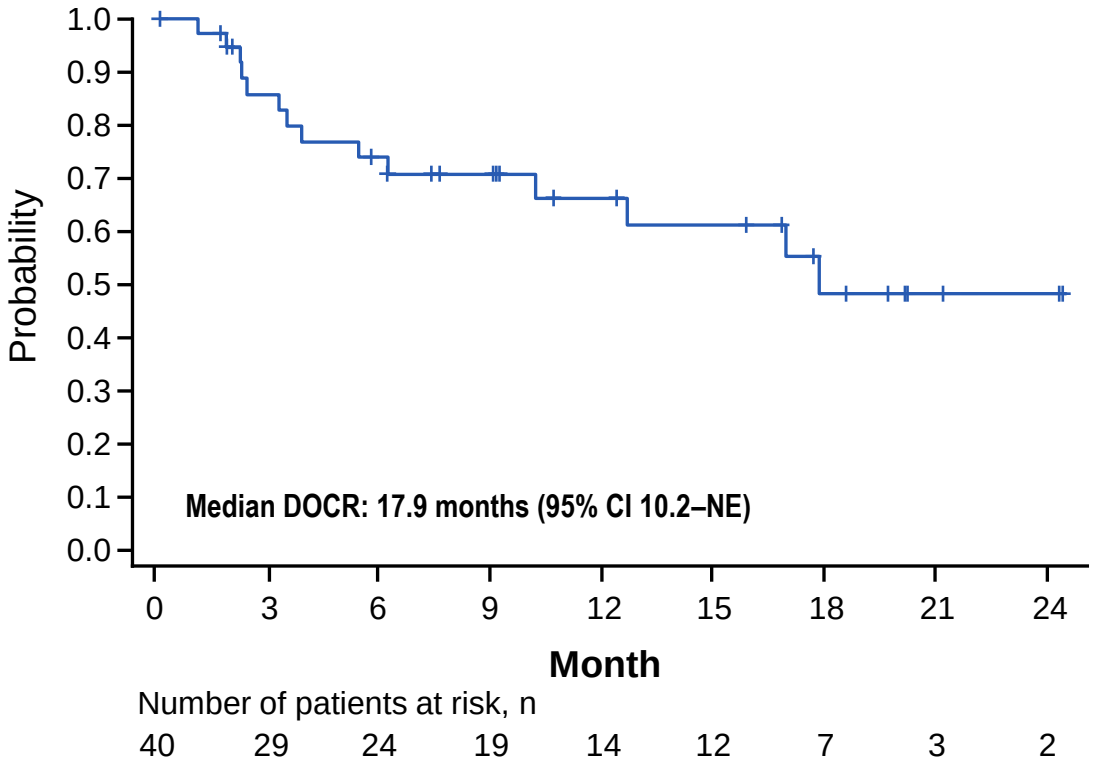
Odronextamab efficacy: Responses appear durable

Duration of response – Independent central review



- 12-month DOR: 49.4% (95% CI: 35.0–62.2)
- 18-month DOR: 38.9% (95% CI: 23.9–53.6)

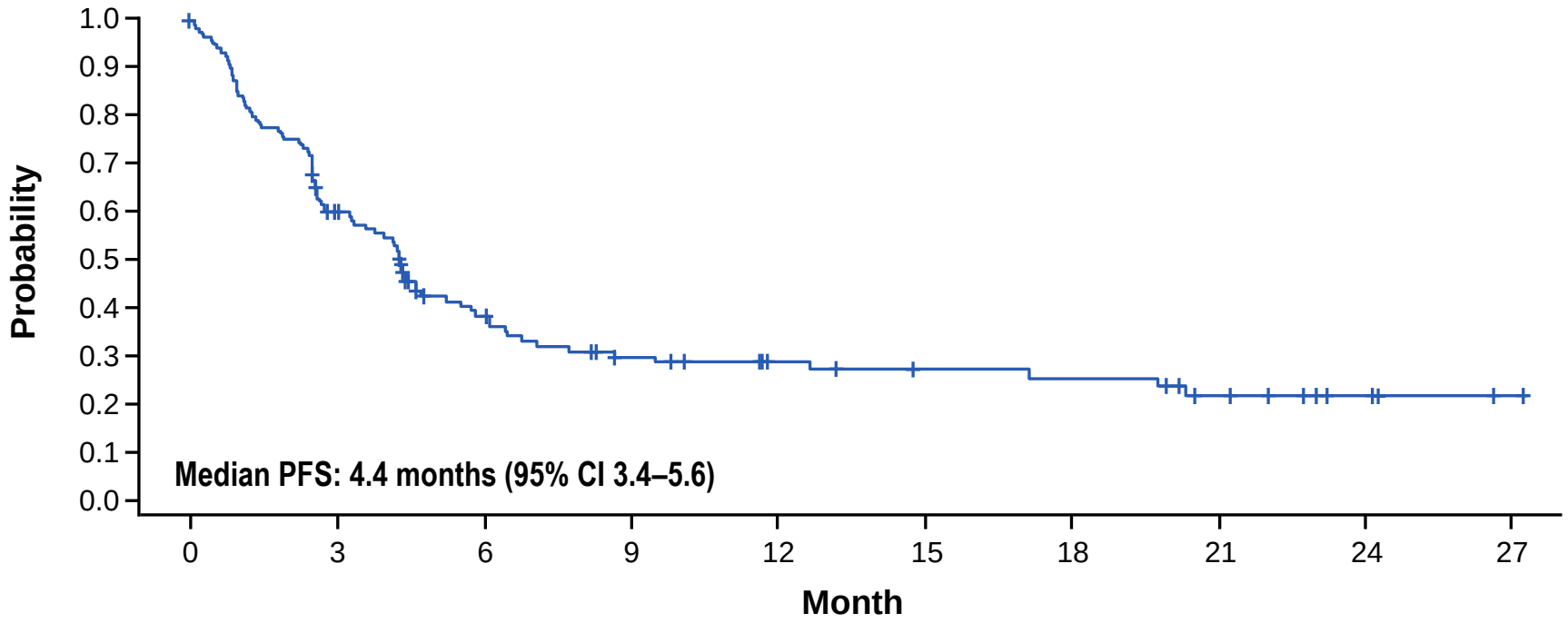
Duration of complete response – Independent central review



- 12-month DOCR: 66.4% (95% CI: 47.1–80.1)
- 18-month DOCR: 48.3% (95% CI: 26.1–67.4)

Data cut-off date: Sep 15, 2022.
CI, confidence interval; DOCR, duration of complete response; DOR, duration of response; NE, not evaluable.

Progression-free survival



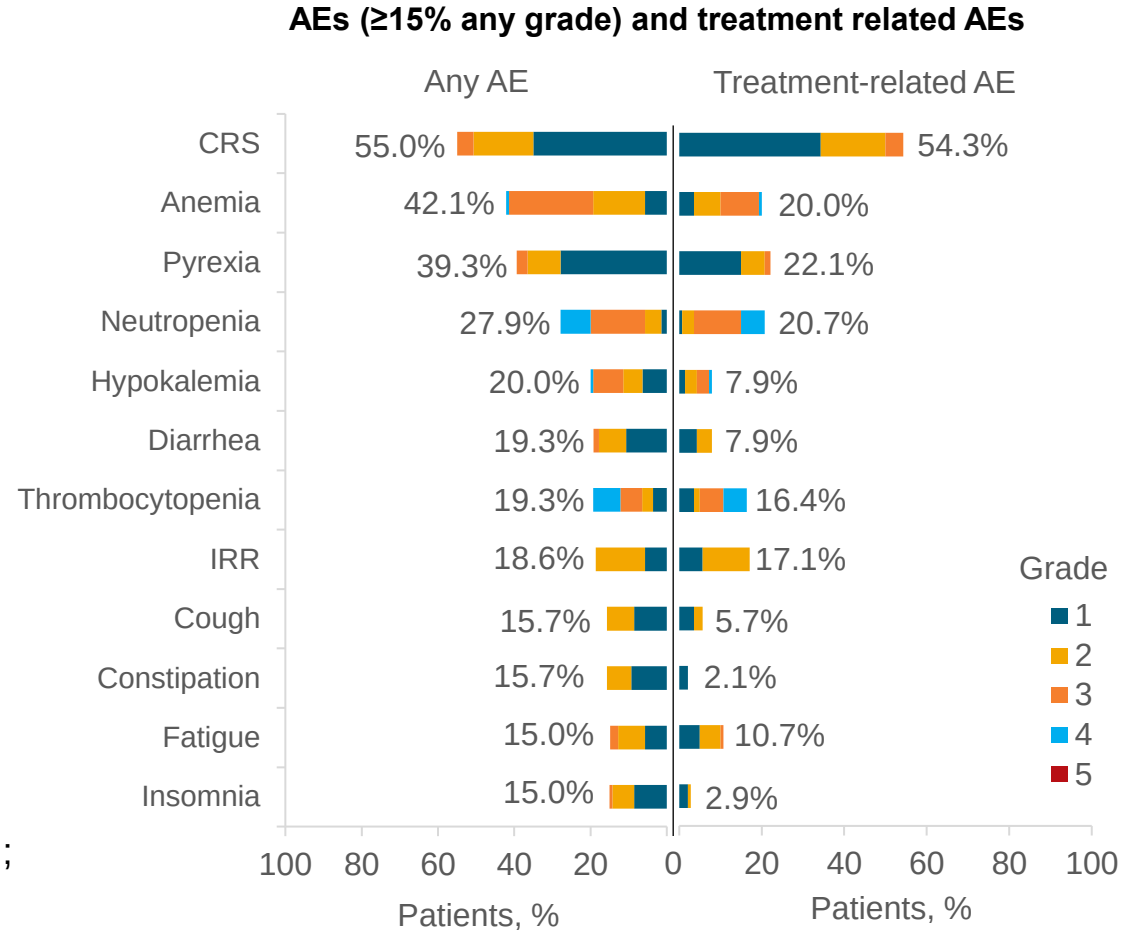
Number of patients at risk, n	130	70	38	26	19	16	15	10	4	1

- 12-month PFS rate: 29.3% (95% CI: 20.9–38.2)
- 18-month PFS rate: 26.0% (95% CI: 17.6–35.2)

Data cut-off date: Sep 15, 2022.
CI, confidence interval; NE, not evaluable; PFS, progression-free survival.

Odronextamab safety profile

Treatment-emergent adverse events, n (%)	Patients N=140 Any event	Treatment-related
Any TEAE	139 (99.3%)	123 (87.9%)
Grade ≥3 TEAE	110 (78.6%)	74 (52.9%)
Serious AE	85 (60.7%)	64 (45.7%)
Grade 5 TEAE Related to COVID-19 Other grade 5 events	20 (14.3%) 5 (3.6%) 15 (10.7%)	5 (3.6%) 1 (0.7%) 4 (2.9%)
TEAE leading to treatment discontinuation	14 (10.0%)	11 (7.9%)



- Grade 5 TRAEs: pneumonia (n=3), COVID-19 (n=1) and pseudomonal sepsis (n=1)
- TRAEs leading to treatment discontinuation: encephalopathy (n=2); aphasia; CRS; sclerosing cholangitis; SVT; CMV reactivation (n=1 each); cough and pneumonia (n=1); PJP pneumonia and neutrophil count decreased (n=1); pancreatitis, tachycardia, septic shock and CRS (n=1); interstitial pneumonia and fungal pneumonia (n=1);

Data cut-off date: Sep 15, 2022.
AEs per NCI-CTCAE v5.0. CRS per Lee 2019 criteria.
adverse event; CMV, cytomegalovirus; CRS, cytokine release syndrome; IRR, infusion related reaction; PJP, pneumocystis jirovecii pneumonia; SVT, supraventricular tachycardia; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Adverse events: Cytokine release syndrome

n, (%)	1/20 regimen N=67	0.7/4/20 regimen N=73
CRS any Grade	38 (56.7%)	39 (53.4%)
Grade 1	21 (31.3%)	28 (38.4%)
Grade 2	12 (17.9%)	10 (13.7%)
Grade 3	5 (7.5%)	1 (1.4%)
Grade 4	0	0
Grade 5	0	0
Received corticosteroids	13 (19.4%)	15 (20.5%)
Received tocilizumab	10 (14.9%)	19 (26.0%)
Received vasopressors	5 (7.5%)	1 (1.4%)

- 0.7/4/20 mg step-up regimen reduced the incidence of grade 2 and grade 3 CRS
- Approximately half of R/R DLBCL patients had CRS, mostly grade 1
- Only 1 case of grade 3 CRS with 0.7/4/20 mg step-up regimen (in the setting of acute pancreatitis at week 6) and no grade 4 or higher CRS events
- All CRS events resolved within a median time to resolution of 2 days (range 1–133)
- No patients required mechanical ventilation or ICU admission for the management of CRS

Data cut-off date: Sep 15, 2022.
CRS per Lee 2019.
CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ICU, intensive care unit; R/R relapsed/refractory.

Other adverse events of interest

n (%)	1/20 regimen (N=67)	0.7/4/20 regimen (N=73)	All patients (N=140)
ICANS, any grade	3 (4.5%)	1 (1.4%)	4 (2.9%)
Grade ≥3	1 (1.5%)*	0	1 (0.7%)
Infusion related reaction, any grade	16 (23.9%)	8 (11.0%)	24 (17.1%)
Grade ≥3	0	0	0
Infection, any grade	40 (59.7%)	43 (58.9%)	83 (59.3%)
Grades 1–2	13 (19.4%)	24 (32.9%)	37 (26.4%)
Grades 3–4	21 (31.3%)	12 (16.4%)	33 (23.6%)
Grade 5	6 (9.0%)	7 (9.6%)	13 (9.3%)
Tumor lysis syndrome, any grade	1 (1.5%)	0	1 (0.7%)
Grade ≥3	1 (1.5%)		1 (0.7%)

Data cut-off date: Sep 15, 2022.
*Grade 3 ICANS event = encephalopathy.
ICANS, immune effector cell-associated neurotoxicity syndrome.

Conclusions

- Odronextamab is an off-the-shelf investigational CD20xCD3 bispecific antibody
- First results from pivotal Phase 2 trial of odronextamab demonstrate clinically important antitumor activity in heavily pretreated, R/R DLBCL
  - ORR 49.2%; CR 30.8%
  - Reponses were deep and durable, mDOCR 17.9 months
- Consistent efficacy prior to and post-CAR T
- Odronextamab generally has a manageable safety profile with the optimized step-up regimen
  - CRS was mostly grade 1 and occurred mainly with Cycle 1 step-up
  - No cases of TLS and no grade 3 or higher ICANS or IRR reported
- Phase 3 randomized controlled studies will be initiating in earlier lines of therapy

CAR T, chimeric antigen receptor T cell; CD, cluster of differentiation; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IRR, infusion related reaction; mDOCR, median duration of complete response; TLS, tumor lysis syndrome; ORR, objective response rate; R/R, relapsed/refractory.

Acknowledgments

The authors would like to thank the patients, their families, the ELM-2 study team, all other investigators, and all investigational site members involved in this study, especially during the challenging times of the coronavirus pandemic

Scan the QR code to download the presentation slides