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Long-term follow-up of the Phase 2 ELM-2 study: Efficacy and survival outcomes with odronextamab in relapsed/refractory follicular lymphoma

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Background and objectives

- There is an unmet need for therapies that can induce durable responses and extend survival in patients with R/R FL
  - Response rates worsen and durations of response decline with successive lines of therapy in patients with R/R FL[1]
- Odronextamab, an off-the-shelf CD20×CD3 bispecific antibody, demonstrated compelling efficacy and a generally manageable safety profile in heavily pretreated patients with R/R FL in the primary analysis of the Phase 2 ELM-2 study (NCT03888105; median efficacy follow-up: 20.1 months):[2]
  - ORR: 80%; CR rate: 73%
  - Median PFS: 20.7 months; median OS: not reached
  - Rate of serious TEAEs: 68%
  - Most common Grade 3/4 TEAEs: neutropenia (32%), anemia (12%), and neutrophil count decreased (12%)
- Long-term survival outcome data in patients with R/R FL receiving bispecific antibodies are limited
- Here, we present updated efficacy and safety data for odronextamab in patients with R/R FL from the ELM-2 study after >2 yrs of follow-up

Key takeaways

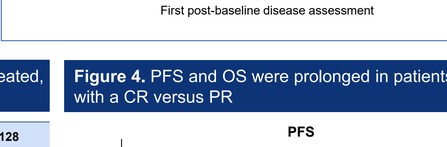
- With long-term follow-up, odronextamab treatment demonstrated deep and durable responses in heavily pretreated patients with R/R FL from the ELM-2 study
  - ORR: 80%; CR rate: 74% (92% of responders); median DOCR: 32.2 months
  - ORR and CR rate were consistent across most high-risk subgroups
  - Median PFS: 23.0 months; median OS: >4 yrs
  - PFS was longer in patients with undetectable ctDNA at Week 12 than in those with detectable ctDNA
- The safety profile of odronextamab was generally manageable
  - With 0.7/4/20 mg step-up (n=60), CRS was mostly Grade 1 (45%) or Grade 2 (10%) (Grade 3 in one patient)
  - Grade 2 ICANS reported in one patient; no new ICANS events since the previous data cutoff (October 2023)[2]
  - Any-grade infections reported in 80% of patients (COVID-19 in 37%); infection rates similar to those observed at the previous data cutoff[2]
- Overall, these compelling results suggest that high CR rates with durability may lead to prolonged survival in heavily pretreated patients with R/R FL, with no new safety concerns, supporting odronextamab treatment as a potential off-the-shelf treatment option
- Phase 3 randomized trials in FL are ongoing in earlier lines of therapy, with fixed treatment duration in an outpatient setting[10–12]
  - OLYMPIA-1 (NCT06091254), OLYMPIA-2 (NCT06097364), and OLYMPIA-5 (NCT06149286)

Figure 1. Patients with R/R FL from ELM-2 were analyzed for efficacy and safety

ELM-2: Phase 2, open-label, multicohort, multicenter study of odronextamab monotherapy in patients with R/R B-NHL (NCT03888105)

Key eligibility criteria
- Age ≥18 yrs
- FL Grade 1–3a*
- ECOG PS 0 or 1
- Refractory to or relapsed after ≥2 prior lines of systemic therapy including an anti-CD20 antibody and an alkylating agent

Odronextamab IV administration†



Primary endpoint
- ORR¶ by ICR

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

Exploratory endpoints
- MRD and other biomarkers

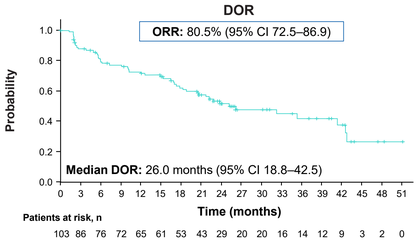
*Per WHO 2017 classification;[3] †Anti-infection prophylaxis including IVIg supplementation and antivirals was recommended, and PJP prophylaxis was mandated; ‡Each cycle = 21 days; §The study initiated with a Cycle 1 step-up regimen of 1/20 mg. This was modified to 0.7/4/20 mg to further mitigate the risk of CRS. Premedication administered during Cycle 1 step-up included dexamethasone, diphenhydramine, and acetaminophen; ¶According to Lugano criteria;[4] **Adverse events graded per NCI Common Terminology Criteria for Adverse Events v5.0,[5] except CRS, which was graded per Lee DW, et al. 2019.[6]

Table 1. Baseline characteristics: Heavily pretreated, highly refractory population

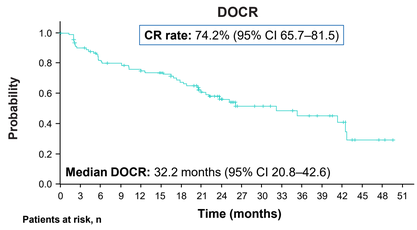
Patient and disease characteristics		N=128
Median age (range), yrs		61.0 (22–84)
Age, yrs, %	<65 / ≥65 to <75 / ≥75	61.7 / 28.9 / 9.4
Male, %		53.1
Race, %	White / Asian / other / unknown / NR	61.7 / 26.6 / 0.8 / 1.6 / 9.4
Ethnicity, %	Not Hispanic or Latino / Hispanic or Latino / NR	84.4 / 3.1 / 12.5
ECOG PS, %	0 / 1 / 2	50.8 / 48.4 / 0.8
Ann Arbor Stage III–IV, %		85.2
FLIPI risk score, %	0–1 / 2 / 3–5	16.4 / 25.8 / 57.8
Bulky disease, %		14.1
Median number of prior lines of therapy (range)		3 (2–13)
Prior PI3K inhibitor, %		14.1
Prior R², %		13.3
Prior ASCT, %		30.5
Primary refractory, %		46.1
Refractory to last line of therapy, %		71.9
Refractory to anti-CD20 Ab, %		74.2
Double refractory to an alkylator and anti-CD20 Ab, %		41.4
POD24, %		49.2

- Median duration of treatment exposure was 42.9 weeks (range 0.4–238.6) at data cutoff (**Suppl. Table 1**)

Figure 2. Responses were durable



24-month DOR rate: 52.0% (95% CI 40.9–62.0)
36-month DOR rate: 42.1% (95% CI 29.6–54.1)

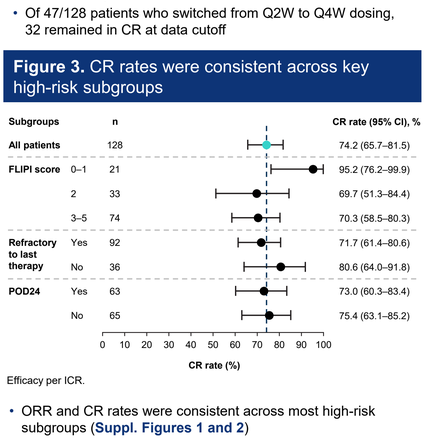


24-month DOCR rate: 56.3% (95% CI 44.6–66.4)
36-month DOCR rate: 45.6% (95% CI 32.2–58.1)

Efficacy per ICR.

- Median follow-up duration: 28.3 months (95% CI 25.5–32.8)
- 92.2% of responders had a CR
- Of 47/128 patients who switched from Q2W to Q4W dosing, 32 remained in CR at data cutoff

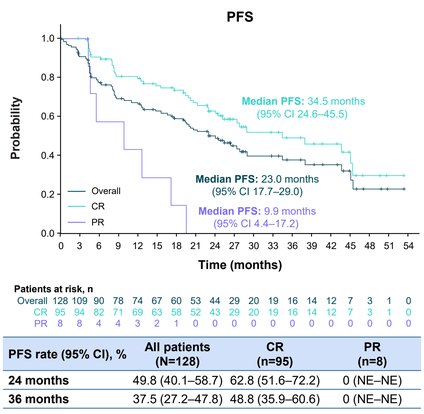
Figure 3. CR rates were consistent across key high-risk subgroups



Efficacy per ICR.

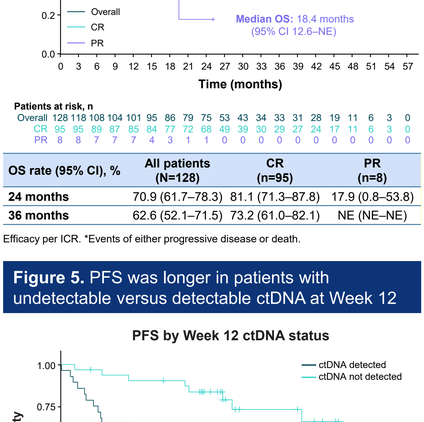
- ORR and CR rates were consistent across most high-risk subgroups (**Suppl. Figures 1 and 2**)

Figure 4. PFS and OS were prolonged in patients with a CR versus PR



PFS rate (95% CI), %	All patients (N=128)	CR (n=95)	PR (n=8)
24 months	49.8 (40.1–58.7)	62.8 (51.6–72.2)	0 (NE–NE)
36 months	37.5 (27.2–47.8)	48.8 (35.9–60.6)	0 (NE–NE)

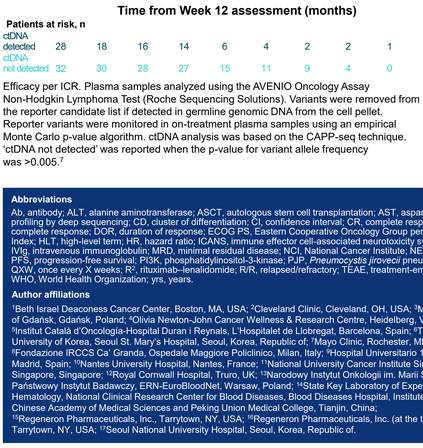
- Median PFS in patients who were event-free* at:
  - 1 year (n=74): 43.7 months (95% CI 27.8–NE)
  - 2 yrs (n=44): 45.5 months (95% CI 38.0–NE)



OS rate (95% CI), %	All patients (N=128)	CR (n=95)	PR (n=8)
24 months	70.9 (61.7–78.3)	81.1 (71.3–87.8)	17.9 (0.8–53.8)
36 months	62.6 (52.1–71.5)	73.2 (61.0–82.1)	NE (NE–NE)

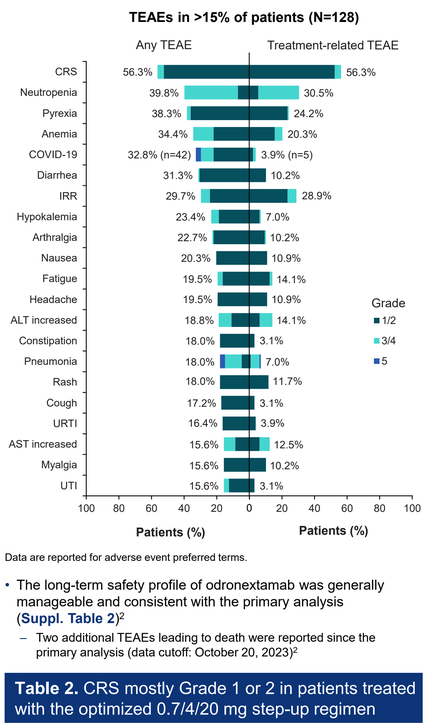
Efficacy per ICR. *Events of either progressive disease or death.

Figure 5. PFS was longer in patients with undetectable versus detectable ctDNA at Week 12



Efficacy per ICR. Plasma samples analyzed using the AVENIO Oncology Assay Non-Hodgkin Lymphoma Test (Roche Sequencing Solutions). Variants were removed from the reporter candidate list if detected in germline genomic DNA from the cell pellet. Reporter variants were monitored in on-treatment plasma samples using an empirical Monte Carlo p-value algorithm. ctDNA analysis was based on the CAPP-seq technique. 'ctDNA not detected' was reported when the p-value for variant allele frequency was >0.005.[7]

Figure 6. Most common TEAEs were CRS, neutropenia, and pyrexia



Data are reported for adverse event preferred terms.

- The long-term safety profile of odronextamab was generally manageable and consistent with the primary analysis (**Suppl. Table 2**)[2]
  - Two additional TEAEs leading to death were reported since the primary analysis (data cutoff: October 20, 2023)[2]

Table 2. CRS mostly Grade 1 or 2 in patients treated with the optimized 0.7/4/20 mg step-up regimen

CRS*		0.7/4/20 mg (n=60)
Any grade, n (%)		34 (56.7)
Grade 1 / 2		27 (45.0) / 6 (10.0)
Grade 3 / ≥4		1 (1.7) / 0
Median time to CRS onset (range), hours		19.7 (0.7–159.0)
Median CRS duration (range), hours		7.7 (0.6–184.0)
CRS management, n (%)	Systemic steroids / tocilizumab / both	20 (33.3) / 10 (16.7) / 9 (15.0)

*CRS graded per Lee DW, et al. 2019.[6]

- ICANS was reported in one patient (Grade 2)

Table 3. Infections were reported in most patients, expected given the heavily pretreated population and B-cell depletion seen with odronextamab[2,8,9]

Infections, n (%)	N=128	
	Patients with any infection	Patients with COVID-19 infection*
Any grade	102 (79.7)	47 (36.7)
Grade 1	7 (5.5)	9 (7.0)
Grade 2	39 (30.5)	16 (12.5)
Grade 3	36 (28.1)	14 (10.9)
Grade 4	4 (3.1)	0
Grade 5	16 (12.5)†	8 (6.3)

*Incidence of COVID-19 equates to incidence of coronavirus infection (HLT), as all preferred-term infection events reported under this HLT were COVID-19–related; †Non–COVID-19 fatal infections: pneumonia (n=3), *Escherichia* sepsis, progressive multifocal leukoencephalopathy, pseudomonal pneumonia, sepsis, and systemic mycosis (n=1 each), and pneumonia plus sepsis in one patient. The patient with fatal systemic mycosis also had Grade 5 COVID-19 pneumonia.

- Serious infections or infestations reported in 60 patients (46.9%)
- ELM-2 was performed during the height of the COVID-19 pandemic[2]

Abbreviations
Ab, antibody; ALT, alanine aminotransferase; ASCT, autologous stem cell transplantation; AST, aspartate aminotransferase; B-NHL, B-cell non-Hodgkin lymphoma; CAPP-seq, cancer personalized profiling by deep sequencing; CD, cluster of differentiation; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; ctDNA, circulating tumor DNA; D, Day; DOCR, duration of complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HLT, high-level term; HR, hazard ratio; ICANS, immune effector cell-associated neurotoxicity syndrome; ICR, independent central review; IRR, infusion-related reaction; IV, intravenous; IVIg, intravenous immunoglobulin; MRD, minimal residual disease; NCI, National Cancer Institute; NE, not evaluable; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol-3-kinase; PJP, *Pneumocystis jirovecii* pneumonia; POD24, progression of disease within 2 years of frontline therapy; PR, partial response; Q2W, once every X weeks; R², rituximab–lenalidomide; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection; WHO, World Health Organization; yrs, years.

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