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Clinical outcomes according to baseline comorbidities and age in patients with relapsed/refractory (R/R) follicular lymphoma (FL) treated with the bispecific antibody (bsAb) odronextamab in the Phase 2 ELM-2 study

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Background and objectives

- There is no widely accepted FL frailty index, and outcomes data by baseline comorbidities in patients treated with bsAbs are lacking
- Odronextamab, an off-the-shelf CD20×CD3 bsAb, demonstrated compelling efficacy and a generally manageable safety profile in heavily pretreated patients with R/R FL in the Phase 2 ELM-2 study (NCT03888105; data cut-off date: October 20, 2023):[1]
  - ORR: 80%; CR rate: 73%
  - Rate of Grade ≥3 TEAEs: 86%
  - Rate of treatment discontinuation due to TEAEs: 16%
- This *post-hoc* analysis of patients with R/R FL from the ELM-2 study aimed to assess outcomes by frailty according to a modified version of the Charlson Comorbidity Index (mCCI)[2] that excluded age. Outcomes by age group were assessed separately

Key takeaways

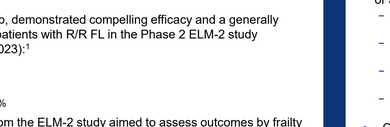
- Odronextamab showed efficacy and maintained generally manageable safety regardless of mCCI score or age in patients with R/R FL
  - DOR was similar in fit versus frail subgroups until ~18 months (the median in the frail subgroup), with responses sustained for longer in the fit subgroup thereafter, but did not show a clear trend by age
  - PFS and OS were similar in fit and frail subgroups until ~20 and ~18 months, respectively, exceeding the median durations of odronextamab treatment exposure, while trends by age were not distinct
  - Infections were reported in ~90% of patients who were frail or aged 70–79 years. Less than half of these were considered treatment related
  - CRS was mostly Grade 1 or 2 (Grade ≥3, n=5), with a lower incidence in fit vs frail subgroups (55.3% vs 64.3%) but no clear trend by age
- Overall, these results support the use of odronextamab as a potential treatment option in patients with heavily pretreated R/R FL and highlight the potential utility of the mCCI as a frailty index in this population

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

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



Measures taken to facilitate diverse, inclusive enrollment:[1]
- Diverse trial sites
- Translated consent forms
- Extended screening windows
- Broad eligibility criteria

Primary endpoint
- ORR§ by ICR

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

Subgroup analysis
Patients were assessed by baseline mCCI score and age:
- **Fit**: mCCI 0/1
- **Frail**: mCCI ≥2
- **Age <50 yrs**
- **Age 50–59 yrs**
- **Age 60–69 yrs**
- **Age 70–79 yrs**

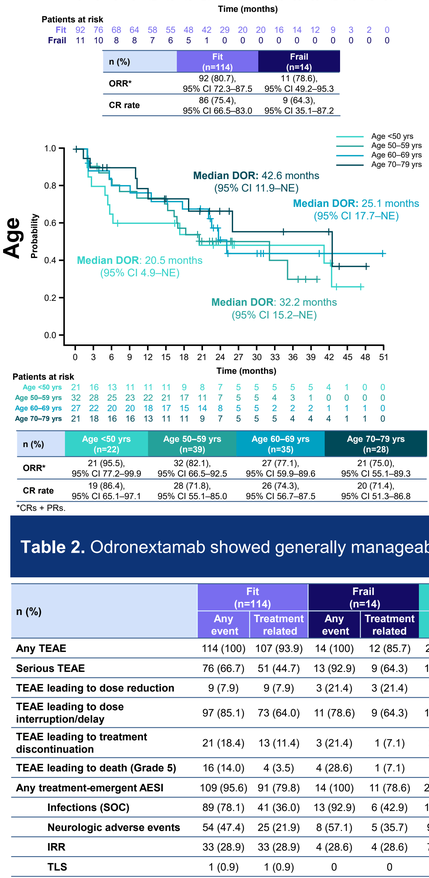
Anti-infection prophylaxis, including IVIg supplementation and antivirals, was recommended, and PJP prophylaxis was mandated

*Per WHO 2017 classification;[3] †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 the Cycle 1 step-up regimen included dexamethasone, diphenhydramine, and acetaminophen; §According to Lugano criteria.[4]

Table 1. Baseline characteristics depict a heavily pretreated, highly refractory patient population

Patient and disease characteristics		Fit (n=114)	Frail (n=14)	Age <50 yrs (n=22)	Age 50–59 yrs (n=39)	Age 60–69 yrs (n=35)	Age 70–79 yrs (n=28)
Median age (range), yrs		61.0 (22–84)	64.5 (37–84)	41.5 (22–49)	56.0 (50–59)	64.0 (60–69)	73.0 (70–79)
Male, %		54.4	42.9	50.0	61.5	48.6	46.4
Race, %	White / Asian / other / unknown / NR	62.3 / 24.6 / 0.9 / 1.8 / 10.5	57.1 / 42.9 / 0 / 0 / 0	45.5 / 45.5 / 4.5 / 0 / 4.5	64.1 / 23.1 / 0 / 0 / 12.8	60.0 / 25.7 / 0 / 2.9 / 11.4	71.4 / 21.4 / 0 / 3.6 / 3.6
Ethnicity, %	Not Hispanic or Latino / Hispanic or Latino / NR	82.5 / 3.5 / 14.0	100 / 0 / 0	86.4 / 4.5 / 9.1	84.6 / 0 / 15.4	80.0 / 2.9 / 17.1	89.3 / 7.1 / 3.6
ECOG PS, %	0 / 1 / 2	53.5 / 45.6 / 0.9	28.6 / 71.4 / 0	50.0 / 50.0 / 0	64.1 / 35.9 / 0	48.6 / 51.4 / 0	39.3 / 57.1 / 3.6
Ann Arbor stage III/IV, %		86.0	78.6	100	79.5	91.4	75.0
FLIPI risk score, %	0–1 / 2 / 3–5	15.8 / 25.4 / 58.8	21.4 / 28.6 / 50.0	18.2 / 31.8 / 50.0	30.8 / 38.5 / 30.8	2.9 / 11.4 / 85.7	14.3 / 21.4 / 64.3
Bulky disease, %		14.9	7.1	18.2	12.8	17.1	10.7
Median number of prior lines of therapy (range)		3.0 (2–13)	2.5 (2–6)	2.0 (2–5)	2.0 (2–7)	3.0 (2–13)	2.5 (2–8)
Prior PI3K inhibitor, %		14.0	14.3	9.1	15.4	11.4	17.9
Prior R², %		14.0	7.1	9.1	15.4	20.0	3.6
Prior ASCT, %		30.7	28.6	31.8	41.0	34.3	14.3
Primary refractory, %		46.5	42.9	63.6	53.8	40.0	32.1
Refractory to last line of therapy, %		71.9	71.4	90.9	66.7	62.9	75.0
Refractory to anti-CD20 antibody, %		76.3	57.1	86.4	87.2	62.9	60.7
Double refractory to an alkylator and an anti-CD20 antibody, %		42.1	35.7	40.9	51.3	31.4	35.7
POD24, %		50.9	35.7	63.6	51.3	48.6	35.7
Median duration of treatment exposure (range), weeks		42.8 (0.4–238.6)	46.1 (2.0–111.4)	48.5 (13.0–213.3)	53.0 (2.0–142.9)	42.0 (2.1–152.0)	38.0 (0.4–238.6)

Figure 2. DOR was numerically longer in fit versus frail subgroups, but there was no clear trend by age

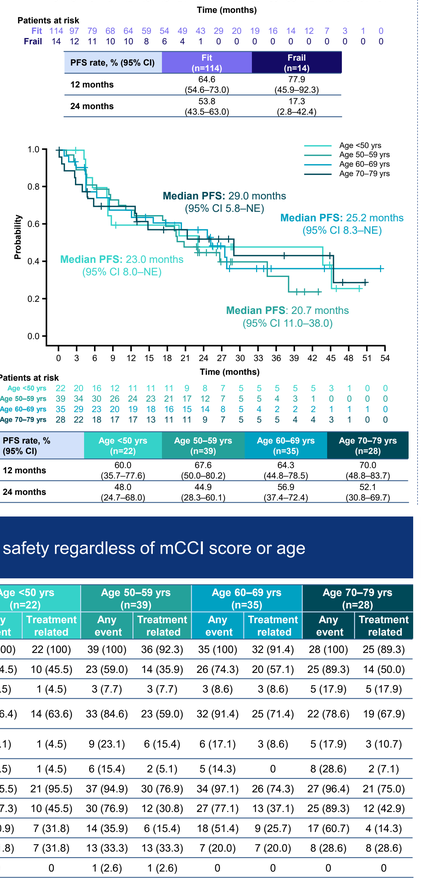


n (%)	Fit (n=114)	Frail (n=14)
ORR*	92 (80.7), 95% CI 72.3–87.5	11 (78.6), 95% CI 49.2–95.3
CR rate	86 (75.4), 95% CI 66.5–83.0	9 (64.3), 95% CI 35.1–87.2

n (%)	Age <50 yrs (n=22)	Age 50–59 yrs (n=39)	Age 60–69 yrs (n=35)	Age 70–79 yrs (n=28)
ORR*	21 (95.5), 95% CI 77.2–99.9	32 (82.1), 95% CI 66.5–92.5	27 (77.1), 95% CI 59.9–89.6	21 (75.0), 95% CI 55.1–89.3
CR rate	19 (86.4), 95% CI 65.1–97.1	28 (71.8), 95% CI 55.1–85.0	26 (74.3), 95% CI 56.7–87.5	20 (71.4), 95% CI 51.3–86.8

*CRs + PRs.

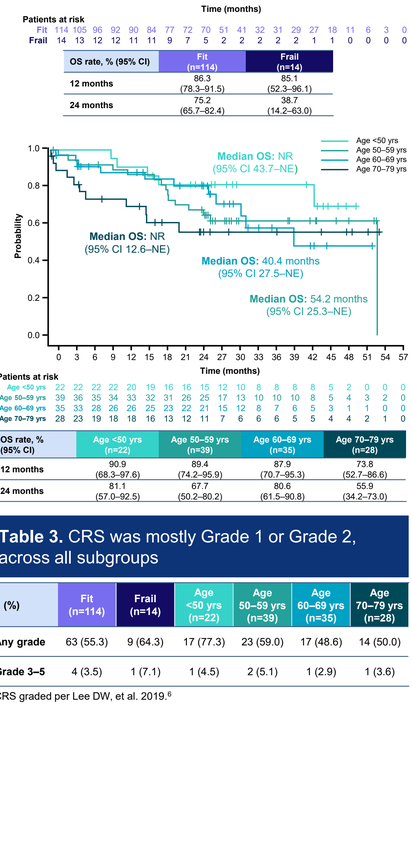
Figure 3. PFS was similar in fit and frail subgroups until ~20 months, exceeding the median durations of treatment exposure, while the trend by age was unclear



PFS rate, % (95% CI)	Fit (n=114)	Frail (n=14)
12 months	64.6 (54.6–73.0)	77.9 (45.9–92.3)
24 months	53.8 (43.5–63.0)	17.3 (2.8–42.4)

PFS rate, % (95% CI)	Age <50 yrs (n=22)	Age 50–59 yrs (n=39)	Age 60–69 yrs (n=35)	Age 70–79 yrs (n=28)
12 months	60.0 (35.7–77.6)	67.6 (50.0–80.2)	64.3 (44.8–78.5)	70.0 (48.8–83.7)
24 months	48.0 (24.7–68.0)	44.9 (28.3–60.1)	56.9 (37.4–72.4)	52.1 (30.8–69.7)

Figure 4. OS was similar in fit and frail subgroups until ~18 months, exceeding the median durations of treatment exposure, and showed no clear trend by age



OS rate, % (95% CI)	Fit (n=114)	Frail (n=14)
12 months	86.3 (78.3–91.5)	85.1 (52.3–96.1)
24 months	75.2 (65.7–82.4)	38.7 (14.2–63.0)

OS rate, % (95% CI)	Age <50 yrs (n=22)	Age 50–59 yrs (n=39)	Age 60–69 yrs (n=35)	Age 70–79 yrs (n=28)
12 months	90.9 (68.3–97.6)	89.4 (74.2–95.9)	87.9 (70.7–95.3)	73.8 (52.7–86.6)
24 months	81.1 (57.0–92.5)	67.7 (50.2–80.2)	80.6 (61.5–90.8)	55.9 (34.2–73.0)

Table 2. Odronextamab showed generally manageable safety regardless of mCCI score or age

n (%)	Fit (n=114)		Frail (n=14)		Age <50 yrs (n=22)		Age 50–59 yrs (n=39)		Age 60–69 yrs (n=35)		Age 70–79 yrs (n=28)	
	Any event	Treatment related	Any event	Treatment related	Any event	Treatment related	Any event	Treatment related	Any event	Treatment related	Any event	Treatment related
Any TEAE	114 (100)	107 (93.9)	14 (100)	12 (85.7)	22 (100)	22 (100)	39 (100)	36 (92.3)	35 (100)	32 (91.4)	28 (100)	25 (89.3)
Serious TEAE	76 (66.7)	51 (44.7)	13 (92.9)	9 (64.3)	12 (54.5)	10 (45.5)	23 (59.0)	14 (35.9)	26 (74.3)	20 (57.1)	25 (89.3)	14 (50.0)
TEAE leading to dose reduction	9 (7.9)	9 (7.9)	3 (21.4)	3 (21.4)	1 (4.5)	1 (4.5)	3 (7.7)	3 (7.7)	3 (8.6)	3 (8.6)	5 (17.9)	5 (17.9)
TEAE leading to dose interruption/delay	97 (85.1)	73 (64.0)	11 (78.6)	9 (64.3)	19 (86.4)	14 (63.6)	33 (84.6)	23 (59.0)	32 (91.4)	25 (71.4)	22 (78.6)	19 (67.9)
TEAE leading to treatment discontinuation	21 (18.4)	13 (11.4)	3 (21.4)	1 (7.1)	2 (9.1)	1 (4.5)	9 (23.1)	6 (15.4)	6 (17.1)	3 (8.6)	5 (17.9)	3 (10.7)
TEAE leading to death (Grade 5)	16 (14.0)	4 (3.5)	4 (28.6)	1 (7.1)	1 (4.5)	1 (4.5)	6 (15.4)	2 (5.1)	5 (14.3)	0	8 (28.6)	2 (7.1)
Any treatment-emergent AESI	109 (95.6)	91 (79.8)	14 (100)	11 (78.6)	21 (95.5)	21 (95.5)	37 (94.9)	30 (76.9)	34 (97.1)	26 (74.3)	27 (96.4)	21 (75.0)
Infections (SOC)	89 (78.1)	41 (36.0)	13 (92.9)	6 (42.9)	17 (77.3)	10 (45.5)	30 (76.9)	12 (30.8)	27 (77.1)	13 (37.1)	25 (89.3)	12 (42.9)
Neurologic adverse events	54 (47.4)	25 (21.9)	8 (57.1)	5 (35.7)	9 (40.9)	7 (31.8)	14 (35.9)	6 (15.4)	18 (51.4)	9 (25.7)	17 (60.7)	4 (14.3)
IRR	33 (28.9)	33 (28.9)	4 (28.6)	4 (28.6)	7 (31.8)	7 (31.8)	13 (33.3)	13 (33.3)	7 (20.0)	7 (20.0)	8 (28.6)	8 (28.6)
TLS	1 (0.9)	1 (0.9)	0	0	0	0	1 (2.6)	1 (2.6)	0	0	0	0

Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0,[5] except CRS, which was graded per Lee DW, et al. 2019.[6]

Table 3. CRS was mostly Grade 1 or Grade 2, across all subgroups

n (%)	Fit (n=114)	Frail (n=14)	Age <50 yrs (n=22)	Age 50–59 yrs (n=39)	Age 60–69 yrs (n=35)	Age 70–79 yrs (n=28)
Any grade	63 (55.3)	9 (64.3)	17 (77.3)	23 (59.0)	17 (48.6)	14 (50.0)
Grade 3–5	4 (3.5)	1 (7.1)	1 (4.5)	2 (5.1)	1 (2.9)	1 (3.6)

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

Abbreviations

AESI, adverse event of special interest; ASCT, autologous stem cell transplantation; B-NHL, B-cell non-Hodgkin lymphoma; CD, cluster of differentiation; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; D, Day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ICR, independent central review; IRR, infusion-related reaction; IV, intravenous; IVIg, intravenous immunoglobulin; mCCI, modified Charlson Comorbidity Index; 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; QXW, every X weeks; R², lenalidomide + rituximab; R/R, relapsed/refractory; SOC, system organ class; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; WHO, World Health Organization; yrs, years.

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