Odronextamab (Ordspono®) as monotherapy for the treatment of relapsed or refractory follicular lymphoma (r/r FL) or diffuse large B-cell lymphoma (r/r DLBCL)

General information [1]

Drug description

The active substance of Ordspono® is odronextamab, an antineoplastic agent. Odronextamab is a bispecific antibody that binds to CD20-expressing B cells and CD3 expressed on T cells. Simultaneously engaging both induces T-cell activation and the generation of a polyclonal cytotoxic T-cell response, which results in the lysis of the targeted cells, including malignant B cells.

Indication

- ❖ Ordspono® as monotherapy is indicated for the treatment of adult patients with r/r FL after two or more lines of systemic therapy.
- ❖ Ordspono® as monotherapy is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy.

Incidence

Follicular lymphoma [2]

- ❖ FL is the most common indolent non-Hodgkin lymphoma in Western Europe and in the U.S.; in Asia, its incidence is very rare.
- ❖ In Europe, FL accounts for 20–35% of newly diagnosed non-Hodgkin lymphomas.

DLBCL [3]

- ❖ The incidence of DLBCL is approximately 7 cases per 100,000 inhabitants per year. The disease is more common in Caucasians than in Africans or Asians, and men are more frequently affected than women. The frequency of diagnosis increases with age.

Current treatment [2, 3]

The Onkopedia treatment recommendations for the treatment of FL and DCBC are displayed in Figure 1 and Figure 2 of the Appendix.

Regulatory status

EMA [1]	FDA
Approval status for this indication: On 27 June 2024, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Ordspono®. The full indication is: ❖ Ordspono® as monotherapy is indicated for the treatment of adult patients with r/r FL after two or more lines of systemic therapy. ❖ Ordspono® as monotherapy is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy. Ordspono® will be available as a concentrate (2 mg, 80 mg and 320 mg) for solution for infusion. **Other indications**: none ✓ **Orphan status**	**Approval status for this indication**: not approved In September 2023, the FDA accepted for Priority Review the Biologics License Application (BLA) for odronextamab to treat adult patients with r/r FL or r/r DLBCL, who have progressed after at least two prior systemic therapies [4]. In March 2024, the FDA has issued Complete Response Letters (CRLs) for the BLA for odronextamab in r/r FL and in r/r DLBCL, each after two or more lines of systemic therapy. The only approvability issue is related to the enrollment status of the confirmatory trials. The CRLs – one for r/r FL and one for r/r DLBCL – did not identify any approvability issues with the odronextamab clinical efficacy or safety, trial design, labelling or manufacturing [5]. **Other indications**: none

Manufacturer

Ordspono® is manufactured by Regeneron.

Costs

Currently, there is no cost information available.

Warnings and precautions

Currently, no EMA EPAR is available.

Study characteristics [6-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
ELM-2 NCT03888105	**DLBCL:** 127 (efficacy-evaluable)/ 141 /safety-evaluable) **FL:** 131	Odronextamab IV was administered weekly in 21-day cycles during Cycles 1-4[1]	-	ORR by ICR	**DLBCL**: 26.6 months **FL:** 22.4 months	**ongoing**[2], global, multicentre, phase 2 study	-	Regeneron	ELM-2 (abstract data) [6, 7]

Inclusion criteria

- For the FL grade 1-3a cohort only: Central histopathologic confirmation of the FL Grade 1 to 3a diagnosis must be obtained before study enrolment. Patients with FL grade 3b are ineligible for this cohort but may be included in the "other B-NHL" cohort. FL subtyping is based on the WHO classification (Swerdlow, 2017).
- Disease-specific cohorts that have relapsed after or are refractory to at least 2 prior lines of systemic therapy as defined in the protocol.
- DLBCL cohort: Patients with DLBCL that has relapsed after or is refractory to at least 2 prior lines of systemic therapy as defined in the protocol.
- MCL after BTK inhibitor therapy cohort: New enrolment is paused until further notice.
- MZL cohort: Patients with MZL that have relapsed or are refractory to at least 2 prior lines of systemic therapy.
- Other B-NHL cohort: Patients with B-NHL other than FL grade 1-3a, DLBCL, MCL, or MZL that has relapsed after or is refractory to at least 2 prior lines of systemic therapy as defined in the protocol. New enrolment stopped for patients with Burkitt lymphoma and Burkitt-like lymphoma.
- Patients should in the judgment of the investigator require systemic therapy for lymphoma at the time of study enrolment.

Exclusion criteria

- Primary CNS lymphoma or known involvement by non-primary CNS NHL.
- Treatment with any systemic anti-lymphoma therapy within 5 half-lives or within 28 days prior to the first administration of the study drug, whichever is shorter.
- History of allogeneic stem cell transplantation
- Prior treatment with any CAR-T therapy.
- Continuous systemic corticosteroid treatment with more than 10 mg per day of prednisone or anti-inflammatory equivalent within 72 hours of the start of the study drug.
- History of neurodegenerative condition or CNS movement disorder. Patients with a history of seizure within 12 months prior to study enrolment are excluded.
- Another malignancy except B-NHL in the past 5 years, with the exception of non-melanoma skin cancer that has undergone potentially curative therapy or in situ cervical carcinoma, or any other tumour that has been deemed to be effectively treated with definitive local control and with curative intent.
- Uncontrolled infection with HIV, hepatitis B or hepatitis C infection; CMV infection as noted by detectable levels on a blood PCR assay as defined in the protocol or other uncontrolled infections.

Patient characteristics at baseline, abstract data

Safety-evaluable DLBCL population (n=141)

- Median age: 66 years (range 24-88)
- Male sex: 60% male, 80%
- Ann Arbor stage III-IV: 80%
- IPI score ≥3: 56%
- Median prior lines of therapy: 2 (range 2-8). 17% of
- Patients who had transformed the disease from indolent lymphoma: 17%
- Richter's transformation: 5%
- Double-hit and triple-hit: 12% and 6%. In total, 57% of
- Primary refractory: 57%
- Double refractory to an anti-CD20 antibody and an alkylator in any line of therapy: 66%

FL cohort (n=131)

- Median age: 61 years (range 22–84)
- Male sex: 53%
- Median prior lines of therapy: 3 (range 2–13)
- Refractory to last therapy: 71%

[1] Odronextamab was administered with steroid prophylaxis and step-up doses of 0.7/4/20 mg during cycle 1, followed by 160 mg on Days 1, 8, and 15 of cycles 2-4. After cycle 4, odronextamab maintenance treatment continued at 320 mg every 2 weeks until disease progression or unacceptable toxicity.

[2] The ELM-2 trial is currently ongoing; estimated study completion date is 02/2028.

❖ Measurable disease on cross sectional imaging as defined in the protocol documented by diagnostic imaging (CT or MRI. ❖ ECOG PS 0 or 1. ❖ Adequate bone marrow, hepatic, and renal function as defined in the protocol.	❖ Known hypersensitivity to both allopurinol and rasburicase. ❖ Prior treatment with an anti-CD20 x anti-CD3 bispecific therapy.	❖ Progression of disease within 2 years: 48%

Efficacy, abstract data	Safety, abstract data
<u>Efficacy-evaluable DLBCL population (n=127), data cutoff 31 January 2023</u> **ORR** confirmed by ICR: 52% **CR rate** confirmed by ICR: 31% **Median DoR**: 10.2 months (95% CI: 5.0-NE) **Median duration of CR:** 17.9 months (95% CI: 9.2-NE) **Probability of maintaining CR for 24 months**: 48%. **<u>Prespecified analysis of the FL cohort (n=131), data cutoff 15 September 2022</u>** **ORR by ICR**: 82% **CR by ICR**: 75% **Median duration of response and a median duration of CR**: 20.5 months **Median PFS**: 20.2 months (95% CI, 14.8–NE) **Median OS**: not reached (95% CI NE–NE)	**<u>Safety-evaluable DLBCL population (n=141), data cutoff 31 January 2023</u>** TRAEs leading to odronextamab **interruption/delay**: 53% TRAEs leading to odronextamab **discontinuation:** 10% **CRS[3]:** 55% **Anaemia**: 43% **Pyrexia**: 42% **Infections grade ≥3**: 37% **Infections grade 5**: 11% **COVID-19 infections**: 16 % (grade 5 in 4%) **<u>Prespecified analysis of the FL cohort (n=131), data cutoff 15 September 2022</u>** **TEAEs considered treatment-related:** 90% **TRAEs grade 5**: n=3[4] **TRAEs leading to discontinuation**: n=10 **CRS[5]:** 56% **Neutropenia**: 40% **Pyrexia:** 31%

Patient-reported outcomes [9], abstract data
❖ Patient-reported outcomes were collected at baseline, weeks 2–4, 10, then Q8W in year 1, and Q12W in year 2. ❖ Post-hoc POD24[6] subgroup analyses were performed on 6 EORTC QLQ-C30 scales, the EQ-5D-3L VAS, and FACT-Lym LymS. ❖ Estimated mean change from baseline (CFB) was analysed using mixed models for repeated measures through week 42 (≥10 patients at the last assessment). ❖ Published meaningful CFB thresholds were used to define deterioration/improvement in responder analyses. ❖ By 31 January 2023, 140 patients with r/r FL had received odronextamab. Patients with POD24 (n=70) were younger than patients without POD24 (n=70; median age 57.5 vs 62.0 years), had fewer prior treatment lines (median 2 vs. 3), and a higher proportion double refractory to anti-CD20 Ab + alkylator (53% vs. 29%). ❖ PRO questionnaire completion ranged from 52–95% through week 42 across groups. ❖ Descriptive analyses suggest baseline patient-reported outcome scores were similar by POD24 status, showing good HRQoL/functioning and low symptom burden, and were generally maintained through week 42 with minimal between-group differences (overlapping 95% CIs for LS mean CFB). ❖ In both groups, more patients reported patient-reported outcome maintenance or improvement vs. deterioration across visits, except for fatigue at week 10 in patients without POD24.

[3] With the optimized 0.7/4/20 mg step-up regimen (n=74), 98% of CRS events were grade 1/2, and only one grade 3 CRS (confounded by pancreatitis) was reported. CRS events resolved with supportive measures; 26% of pts received tocilizumab for CRS management with the optimized regimen.
[4] Pneumonia, progressive multifocal leukoencephalopathy, systemic mycosis (n = 1 each).
[5] With the 0.7/4/20 step-up regimen (n = 63), grade 3 CRS was observed in 1 pt (no grade 4 or 5 CRS; all CRS events resolved).
[6] POD24=disease progression within 2 years of frontline chemoimmunotherapy.

- In patients with heavily pretreated r/r FL, odronextamab treatment maintained HRQoL, functioning, and symptoms irrespective of POD24 status.

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS could not be applied (currently, only abstract data is available).											

Risk of bias - study level (case series) [11]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
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10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
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Overall risk of bias: The risk of bias could not be assessed (currently, only abstract data is available)

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date
NCT03888105 / ELM-2	Please see above.	02/2028
NCT06149286 / OLYMPIA-5	A phase 3, open-label, randomised study to compare the efficacy and safety of odronextamab in combination with lenalidomide vs. rituximab in combination with lenalidomide therapy in r/r participants with FL and marginal zone lymphoma.	10/2029

Available assessments

- No assessments were identified via NICE, CDA-AMC, ICER, G-BA and NIHR.

Other aspects and conclusions

- In June 2024, the **CHMP adopted a positive opinion**, recommending the granting of a conditional marketing authorisation for Ordspono® as monotherapy for the treatment of adult patients with r/r FL after two or more lines of systemic therapy and as monotherapy is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy. These indications have not been **approved** by the **FDA**.
- **ELM-2** (NCT03888105) is an **ongoing**, open-label, phase 2 study assessing odronextamab in patients with r/r B-cell NHL.
- The **primary endpoint is ORR** by ICR. ORR among patients of the efficacy-evaluable DLBCL population was 52%; ORR in a prespecified analysis of the FL cohort was 82%. Of note, currently only **abstract** data is available.
- Evaluation of **patient-reported outcomes** showed that odronextamab treatment **maintained** HRQoL, functioning, and symptoms irrespective of POD24 status in patients with heavily pretreated r/r FL (only abstract data available).
- Due to the lack of data, the ESMO-MCBS is currently not applicable, and the risk of bias is not evaluable.
- One phase 3 trial, comparing the efficacy and safety of odronextmab combined with lenalidomide vs. rituximab in combination with lenalidomide therapy in patients with r/r FL and marginal zone lymphoma, was identified.
- To date, the efficacy and safety of odronextamab in pretreated patients with r/r FL and r/r DBCL **cannot be assessed sufficiently**. Final analysis (full text) data is required urgently.

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Abbreviations: AE=adverse event, AJ=adjustment, BLA= Biologics License Application, BTK=Bruton tyrosine kinase, C=comparator, CAR-T=chimeric antigen receptor, T-cell CDA-AMC=Canada's Drug Agency, CFB=change from baseline, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CMV= cytomegalovirus, CNS=central nervous system, COVID-19=coronavirus disease 2019, CRLs=Complete Response Letters, CT=computed tomography, DLBCL=diffuse large B-cell lymphoma, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EPAR=European public assessment report, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-LYM=Functional Assessment of Cancer Therapy–Lymphoma, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FL=follicular lymphoma, G-BA=Gemeinsamer Bundesausschuss, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, ICR=independent review committee, Int.=intention, MCL=mantle cell lymphoma, MG=median gain, MRI=magnetic resonance imaging, MZL=marginal zone lymphoma, n=number of patients, NE=not estimable, NICE=National Institute for Health Care Excellence, NHL=Non-Hodgkin Lymphoma, ORR=objective response rate, OS=overall survival, PCR=polymerase chain reaction, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, POD24=disease progression within 2 years of frontline chemoimmunotherapy, QoL=quality of life, r/r=relapsed/refractory, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse events, TRAE=treatment-related adverse events, VAS=visual analogue scale, WHO=World Health Organization

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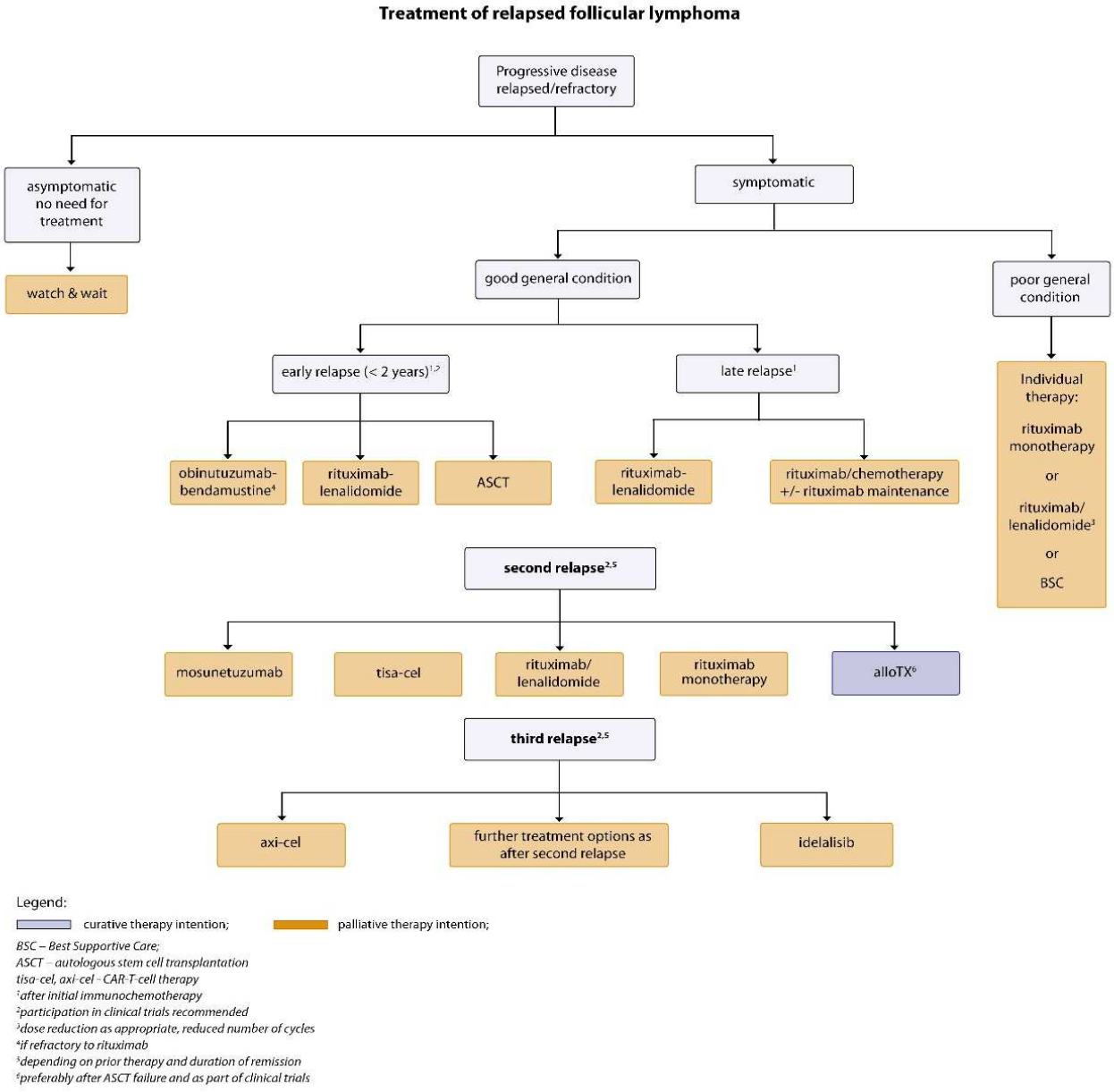
Appendix – Figure 1:



Appendix – Figure 2: