3 June 2022
EMA/OD/0000082933
EMADOC-1700519818-823423
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Lunsumio (mosunetuzumab)
Treatment of follicular lymphoma
EU/3/21/2517
Sponsor: Roche Registration GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Product and administrative information

Product	
Designated active substance	Mosunetuzumab
Other name(s)	Mosunetuzumab Roche Registration GmbH
International Non-Proprietary Name	Mosunetuzumab
Tradename	Lunsumio
Orphan condition	Treatment of follicular lymphoma
Sponsor's details:	Roche Registration GmbH Emil-Barell-Straße 1 Grenzach 79639 Grenzach-Wyhlen Baden-Württemberg Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Roche Registration GmbH
COMP opinion	7 October 2021
EC decision	12 November 2021
EC registration number	EU/3/21/2517
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Aaron Sosa Mejia / Karin Janssen van Doorn
Applicant	Roche Registration GmbH
Application submission	10 September 2021
Procedure start	28 October 2021
Procedure number	EMA/H/C/005680
Invented name	Lunsumio
Proposed therapeutic indication	Lunsumio as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies. Further information on Lunsumio can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/lunsumio
CHMP opinion	22 April 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttilä / Maria Elisabeth Kalland
Sponsor's report submission	18 February 2022
COMP discussion	15-17 March 2022
Oral explanation	Not applicable
COMP opinion (adoption via written procedure)	29 April 2022

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2021 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing mosunetuzumab was considered justified based on preliminary clinical data which showed that heavily pre-treated patients with relapsed/refractory follicular lymphoma achieved partial or complete responses which were durable;
- the condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma;
- the condition was estimated to be affecting approximately 4.8 in 10,000 persons in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mosunetuzumab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate sustained partial and complete responses in a high proportion of heavily pre-treated relapsed/refractory patients with follicular lymphoma who have failed several lines of approved therapies. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Follicular lymphoma (FL) represents the second most common subtype of non-Hodgkin's lymphoma (NHL). It is an indolent B-cell lymphoproliferative disorder of transformed germinal center B-cells consisting of a mixture of centrocytes (small to medium-sized cleaved follicular center cells) and centroblasts (large non-cleaved follicular center cells), mixed with non-malignant cells such as T-cells, follicular dendritic cells, and macrophages (Smith et al., 2013; Xerri et al., 2016). The WHO classification has adopted a grading from 1-3, where grade 3 has been subdivided into grade 3a, in which centrocytes are present, and grade 3b, in which there are sheets of centroblasts (Ott et al., 2002). The clinical aggressiveness of FL increases with increasing numbers of centroblasts, and subsequently grades. FL grade 1-3a comprises the most prevalent indolent (low-grade) lymphoma subtype of NHL. FL grade 3b is categorized with other FLs but is at an intermediate stage of large cell transformation and is typically treated as an aggressive (high-grade) lymphoma (Dreyling et al., 2021; Swerdlow et al., 2017).

The aetiology of FL is still poorly understood. It has been suggested that age, gender, and ethnicity may affect a person's likelihood of developing FL. The incidence increases with age; although in principle FL may occur at any age, it is extremely rare in children and adolescents. The median age at diagnosis of FL is around 60-65 years. Although onset can be gradual at the time of initial diagnosis, advanced FL is typically incurable, and the response rates are lower with shorter durations of response with successive lines of therapy.

FL involves lymph nodes, but also spleen, bone marrow, peripheral blood and Waldeyer ring. Involvement of non-haematopoietic extra-nodal sites, such as the gastrointestinal (GI) tract or soft tissue are uncommon but may occur in a setting of widespread nodal disease. FL may occasionally be primary in extra-nodal sites, including skin, GI tract, particularly the duodenum, ocular adnexa, breast, and testis.

Patients with FL generally present with asymptomatic lymphadenopathy, with waxing and waning symptoms present for years. Most patients therefore have widespread disease at diagnosis, including peripheral and central (abdominal and thoracic) lymphadenopathy and splenomegaly. Approximately 10% of the patients have localized disease at diagnosis and less than 20% present with B symptoms (fever, night sweats and weight loss) and elevated serum lactate dehydrogenase (LDH) levels. The bone marrow is involved in 40-70% of the cases (Swerdlow et al., 2017; Freedman, 2020). As an intrinsic disease characteristic, FL typically evolve over time to an aggressive subtype, in 15% of cases. Disease relapse is usually rapid, where remissions become a serious challenge despite multiple interventions. Eventually, patients succumb to the refractory, high-grade disease transformation and the complications driven by treatments.

The approved therapeutic indication "*Lunsumio as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies"* falls within the scope of the designated orphan condition "treatment of follicular lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Patients with advanced stage FL disease may experience B symptoms and suffer from unexplained fatigue/asthenia, local effects of lymphadenopathy such as abdominal pain, chest pain, cough or dyspnoea, or symptoms of bone marrow failure leading to cytopenia. Other symptoms depend on the location of the lymphoma (e.g., GI bleeding due to GI lymphomas, superior vena cava syndrome due to vein compression, renal failure due to ureter compression, and rarely spinal cord compression). Particularly patients with relapsed disease may have reduced quality of life.

Although the life expectancy has improved due to recent therapeutic advances, FL patients frequently relapse and become progressively more refractory to subsequent lines of therapy. Advanced-stage FL is considered incurable with conventional chemotherapy, although patients often have good responses to treatment and might live for several years. The survival outcome worsens significantly as the patients progress through multiple lines of therapy and most patients eventually die of progressive lymphoma and its complications (Link et al., 2019). Furthermore, histologic transformation to high-grade NHLs that are clinically more aggressive with a poor outcome is relatively common in patients with FL, occurring at a rate of approximately 2-3% per year (Kridel et al., 2016; Freedman, 2018).

The sponsor has not identified any changes in the severe nature of the condition since the orphan designation in 2021. FL remains life-threatening and chronically debilitating, mainly due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation to aggressive lymphoma.

Number of people affected or at risk

The sponsor conducted an extensive review of cancer registry data from the 27 EU member states (EU27) for the estimation of the prevalence of FL. Two different approaches were applied. For one of the methods, prevalence data were directly extracted from the following population-based cancer registries: the Integraal Kankercentrum Nederland (IKNL), Slovenian Cancer Registry, the Italian Association of Cancer Registries (AIRTUM), the Spanish Cancer Registries Network (REDECAN), Belgium Cancer Registry, HMRN (Yorkshire region in the UK), and the Surveillance, Epidemiology, and End Results (SEER) program in US (representing 28% of the US population). For the other method, the prevalence of NHL reported by the two population-based cancer registries NORDCAN (Nordic countries: Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, and Sweden) and the national German cancer registry Robert Koch Institute were used for indirect estimation. In the latter approach, the ratio of the crude incidence of FL to NHL was applied to the NHL prevalence. The NHL crude incidence estimates were obtained directly from the European Cancer Information System (ECIS).

Two methodologies have been used in the direct approach based on data abstracted from available national cancer registries in the EU27 (i.e., IKNL, Slovenian Cancer Registry, and AIRTUM). Data from the HMRN and US SEER registry were only used to help indicate the potential direction the prevalence was going in for FL. The indirect methodology was conducted in a two-step process using data abstracted from cancer registry sources. Firstly, data were obtained on NHL prevalence, NHL incidence, and FL incidence, then the incidence rate ratio of FL to NHL was applied, multiplied by NHL prevalence.

Table 1. Updated FL prevalence (per 10,000) based on estimates extracted from population-based cancer registry sources in the EU27, UK and USA

Cancer Registry	Country	Year (latest)	Population	Prevalence Period Capture			
				5 years	10 years	20 years	Complete/ lifetime
NORDCAN (FL/NHL incd = 17.58%)[a,b]	Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, Sweden	2019	27,036,000	1.30	2.16	3.43	-
NORDCAN (FL/NHL incd = 18.3%)[a,b]	As above	2019	As above	1.35	2.25	3.57	-
NORDCAN (FL/NHL incd = 20%)[a,b]	As above	2019	As above	1.48	2.46	3.9	-
IKNL[c]	The Netherlands	2020	17,440,000	1.34	2.33	3.48	-
Slovania Cancer Registry[d]	Slovania	2018	2,074,000	1.82	3.17	-	5.06
AIRTUM[e]	Italy	2020	60,731,000	-	-	-	4.89
Robert Kock Institut[f]	Germany	2017	82,349,000	1.34	2.19	-	-
REDECAN[g]	Spain	2020	46,445,000	1.41	-	-	4.54
Belgium Cancer Registry[h]	Belgium	2018	11,430,000	1.54	2.70	-	-
HMRN	United Kingdom	2016	65,610,000	1.52	2.48	-	-
SEER[i]	USA	2018	326,800,000	1.54	2.70	4.14	4.49
	EU 27 estimate[j]	**2021**		**1.39**	**2.32**	**3.74**	**4.74**

FL = follicular lymphoma; incd = incidence; NHL = non-Hodgkin's lymphoma; USA = United States of America.
Note: Items highlighted in grey indicate estimates that are not from the EU27 countries.
[a] Based on pooled cancer registry data from seven Nordic countries: Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, Sweden for 2019.
[b] Based on applying E.U. population-based weighted average incidence ratio of FL to NHL to NORDCAN NHL prevalence estimates. All NHL incidence estimates in the

ratios are from ECIS 2020. 17.58% (Table row 2) FL/NHL ratio is based on FL incidence from the 17+ England PBRs, which is 0.348 per 10,000. The 18.3% (Table row 3) is the FL/NHL ratio that excludes cancer registry incidence data before 2015; incidence from the remaining 14 PBRs is 0.330 per 10,000. The 20% (Table row 4) is the FL/NHL ratio recommended by the COMP, when applied to the EU27 NHL incidence gives an FL incidence of 0.392 per 10,000.

[c] Based on extracting total counted prevalence cases for 2020 for the duration of interest (5 yr = 2309, 10 yr = 4034, 20 yr = 6018), divided by the 2020 population in The Netherlands.

[d] Based on extracting total counted prevalence cases for 2018 for the duration of interest (5 yr = 378, 10 yr = 658, lifetime = 1051), divided by the 2018 population in Slovenia.

[e] Based on the number of FL cases reported (n=29,597) divided by the 2020 population.

[f] Based on applying German 2017 FL to NHL ratio (17%) to the total NHL reported prevalence cases in 2017.

[g] Based on applying Spanish 2015 FL to NHL ratio (21.5%) to the total NHL reported prevalence cases in 2020 at 5 yrs (n=31,052) and lifetime (n=100,058).

[h] Based on extracting total counted prevalence cases for 2018 for the duration of interest (5 yr = 1762, 10 yr =3086), divided by the 2020 population in Belgium.

[i] SEER registry calculates complete prevalence using 26 year period up to year 2018.

[j] EU27 population-based weighted estimate for countries with reported prevalence estimates. Weights are based on population size and countries in the EU27 that report prevalence for the period of capture.

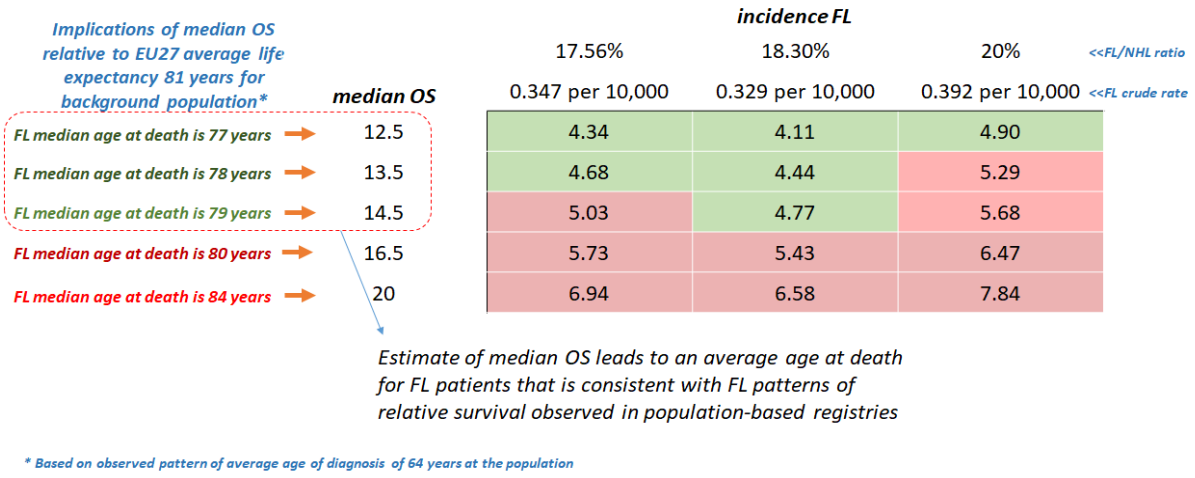
Regarding the direct estimate for the prevalence, the sponsor noted they combined the directly reported complete prevalence for Slovenia (5.06 per 10,000), Italy (4.89), Spain (4.54), and the approximations used for the Nordic countries, the Netherlands and Germany (4.49) (based on the US data to establish trends). The sponsor arrived at a complete prevalence for these countries as 4.74 per 10,000 people.

A second prevalence estimate based on an indirect methodology was also discussed to supplement the direct estimates for the prevalence as noted above. The sponsor used a population-based incidence of 0.329 per 10,000 for FL in this method, which represented a FL to NHL incidence ratio of 18.3%. This estimate was calculated based on data sources from cancer registries published after 2015. The sponsor proposed two indirect calculations and challenged the use of a median OS of 20 years. It was highlighted that hospital-based cancer registries are biased, especially when attempting to extrapolate to the broader population (dos Santos Silva 1999). As for the specific case of FL, hospital-based registries (relative to population-based cancer registries) overestimated survival by 5-10 years (Batlevi et al., 2020; Janikova et al., 2018; Mozas et al., 2020; Provencio et al., 2017) when compared with population-based registries from the European sources and lower median ages at diagnosis were reported (57-58 years versus 64-65 years). Data from population-based cancer registries was therefore considered more appropriate than data obtained from hospital-based cancer registries when attempting to estimate the total number of people affected by the disease at a population level.

The sponsor acknowledged that survival of FL patients is improving and provided a population-based median OS estimate range of 12.5 to 14.8 years. When the median OS of 12.5 years was applied to the average age of FL diagnosis of 64 years (at the population level), the average age at death equated to 77 years. Similarly, if a median OS of 14.8 years was applied, an average age at death of 79 years was approached. This correlated with the age range seen in recent publications reported from Denmark, Sweden, and Spain.

Following these assumptions, a sensitivity analysis of indirect prevalence estimates of FL was explored using various ranges of median OS and incidence rates. as summarized in the diagram below:

Figure 1.



* 17.56% based on a FL to NHL incidence ratio for 17 EU countries and England (0.347/ 1.978 per 10,000).
**18.3% based on an estimate excluding patients diagnosed before 2015 (0.329 / 1.801 per 10,000).
*** 20% is based on a ratio previously recommended by the COMP and applied to the EU27 members states rate of (0.2 x 1.96 per 10,000 = 0.392 per 10,000).

The sponsor then proposed that the conservative estimate of 4.77 (which could be rounded up to 4.8) in 10,000 people can be taken as the estimate for the prevalence using the indirect method.

In conclusion, the sponsor arrived at a complete prevalence estimate of 4.74 (or 4.7) per 10,000 people for the EU27 population by using directly reported estimates (which also included an upper range of 4.8) and a range which included 4.8 in 10,000 people in the indirectly reported prevalence estimates.

The sponsor rechecked each of the EU27 cancer registries used for the estimation of the FL prevalence which was accepted for the orphan designation in 2021 with updated information and did not find any major change. The COMP agreed that the estimate of approximately 4.8 per 10,000 persons in the European community remains accurate at this stage.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor described the treatment methods available to patients with FL based on European and American treatment guidelines (Dreyling et al., 2021; NCCN 2021). Several therapies are authorised both centrally and nationally in the EU for treatment of adult patients with FL, NHL, and lymphomas. These medicines include rituximab (MabThera), yttrium-90 [90Y]-radiolabelled ibritumomab tiuxetan (Zevalin), idelalisib (Zydelig), duvelisib (Copiktra), obinutuzumab (Gazyvaro), lenalidomide (Revlimid), pixantrone (Pixuvri), bendamustine, chlorambucil, cyclophosphamide, doxorubicin, mitoxantrone, etoposide, interferon-alpha-2a/b, prednisolone, and vincristine. Other treatment options also exist, such as radiotherapy and autologous stem cell transplantation (ASCT) or allogenic SCT.

The clinical course of FL is characterized by recurrences requiring multiple lines of treatment until eventually patients run out of treatment options and develop fatal disease resistant to any available treatment.

Patients with newly diagnosed FL are generally treated with an anti-CD20 antibody in monotherapy, rituximab (R) or obinutuzumab (G), or an anti-CD20-containing regimen (e.g., G/R-B, G/R-CHOP, and G/R-CVP) Available treatment options for r/r FL patients depends on the patient's health, age, stage of disease, comorbidities, tumour burden, and the type and duration of response to prior therapy. The most recent European Society for Medical Oncology (ESMO) guidelines for newly diagnosed and relapsed FL describe the current standard of care for these patients (Dreyling, Ann Oncol. 2021; 32(3): 298-308). According to the guidelines, therapy should be initiated only upon the development of symptoms. The guidelines identifies two types of FL patient populations that are offered two different treatment algorithms depending on their tumour burden, being either low (Figure 1) or high (Figure 2).

Figure 2. Treatment algorithm for FL patients with low tumour burden.

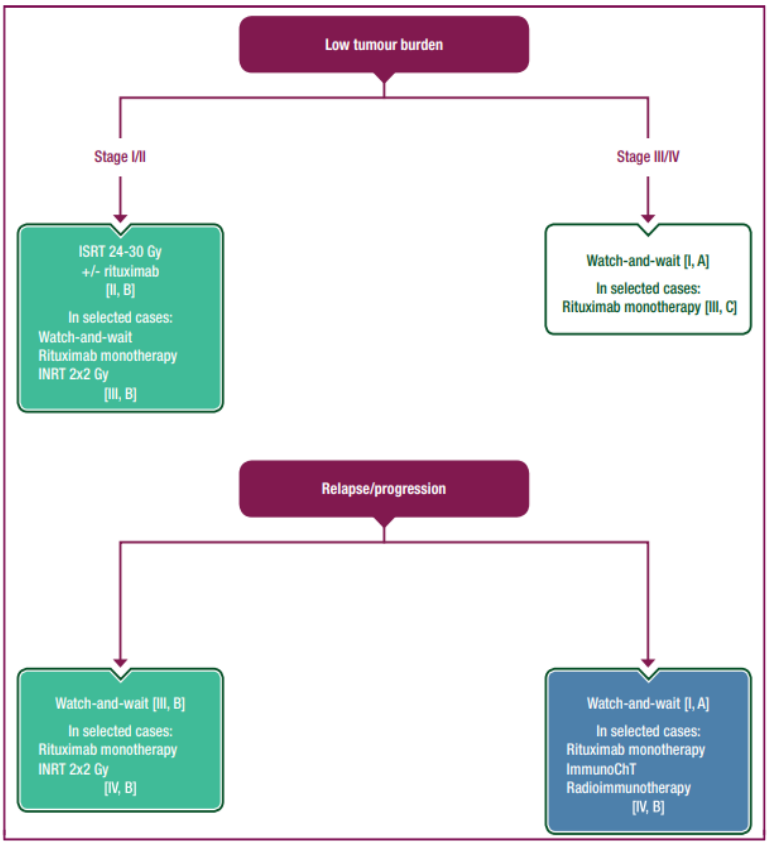
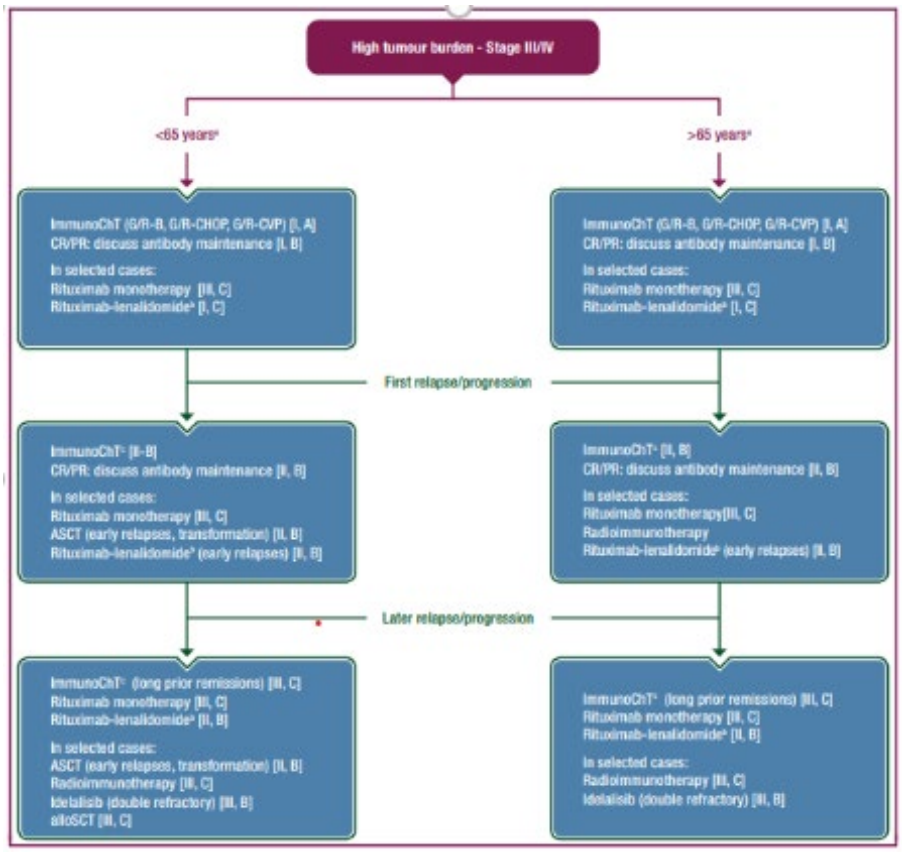


Figure 2. **Consensus-driven recommendations—low tumour burden FL.**
ChT, chemotherapy; FL, follicular lymphoma; INRT, involved-node radiotherapy; ISRT, involved-site radiotherapy.

ChT, chemotherapy; FL, follicular lymphoma; INRT, involved-node radiotherapy; ISRT, involved-site radiotherapy

Figure 3. Treatment algorithm for FL patients with high tumour burden



alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ChT, chemotherapy; CR, complete response; CVP, cyclophosphamide, vincristine, prednisolone; FL, follicular lymphoma; G, obinutuzumab; PR, partial response; R, rituximab. a Biological age (years). b Off-label. c Preferred in rituximab-refractory cases.

The sponsor's product mosunetuzumab is intended to treat adults with r/r FL who have received at least two prior lines of systemic therapy. An overview of medicinal products authorised for treatment of relapsed FL in the EU and whether they are considered satisfactory methods of treatment relevant for a discussion on the significant benefit of mosunetuzumab in FL is presented in the table below.

Table 2. Medicinal products authorised for the treatment of relapsed FL in the EU

Product name (INN)	**Indication**	**Approval Date**	**Satisfactory method**
MabThera (rituximab)	MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. MabThera maintenance therapy is indicated for the treatment of FL patients responding to induction therapy.	08-Jun-1998 25-Oct-2010	Non satisfactory in view that rituximab is indicated for an earlier line of treatment compared to tisagenlecleucel.
IntronA (interferon alfa-2b)	Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.	09-Mar-2000	Non satisfactory in view of a different patient population being eligible for treatment with tisagenlecleucel
Zevalin ([^{90}Y]-ibritumomab tiuxetan	[^{90}Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).	16-Jan-2004	Satisfactory as there is a complete overlap with the approved FL indication for tisagenlecleucel
Levact (bendamustine)	Indolent NHL as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen	1st MA approval in Germany in 2005	Non satisfactory as only indicated for patients with rituximab-refractory FL
Zydelig (idelalisib)	Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment	18-Sep-2014	Non satisfactory as only indicated for patients with double-refractory FL

Product name (INN)	Indication	Approval Date	Satisfactory method
Gazyvaro (obinutuzumab)	Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.	13-Jun-2016	Non satisfactory as only indicated for patients with rituximab-refractory FL
Revlimid (lenalidomid)	Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a)	18-Dec-2019	Satisfactory as it covers previously treated patients with FL grade 1-3a
Copiktra (duvelisib)	Copiktra monotherapy is indicated for the treatment of adult patients with Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies	19-May-2021	Non satisfactory as only indicated for patients with double-refractory FL
Pixuvri (pixantrone)	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiple relapsed or refractory aggressive non-Hodgkin B-cell lymphomas. The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy	10-May-2012	Non satisfactory as only indicated for patients with r/r aggressive NHL such as DLBCL and only FL grade 3b and is not approved in fifth and later lines

Significant benefit

The sponsor did not seek protocol assistance from EMA for the justification of significant benefit. However, prior to the granting of the orphan designation, the sponsor received scientific advice on the mosunetuzumab clinical development plan in FL (Procedure No. EMEA/H/SA/4405/1/2020/III, EMEA/H/SA/4405/1/FU/1/2020/III).

The sponsor argued that mosunetuzumab, which is a novel bispecific anti-CD20/CD3 antibody, has demonstrated to be of significant benefit with a clinically relevant advantage in terms of higher and durable observed complete responses (CRs) compared to those reported for existing methods of treatment for the target patient population. It was further emphasised that the improved efficacy has been demonstrated over the recommended treatment options for later relapse/progression in patients with low tumour burden (immunochemotherapy, rituximab monotherapy, radioimmunotherapy) and high tumour burden (immunochemotherapy, radioimmunotherapy, rituximab monotherapy, rituximab combined with lenalidomide, PI3K inhibitor) in both younger (<65 years) and older adults (>65 years).

According to the sponsor, the clinical data from the pivotal study, with a clinical cut-off date of 15 March 2021, showed that mosunetuzumab had similar efficacy and safety in the two age groups of r/r FL patients <65 years old and ≥65 years old. The primary data supporting the efficacy and safety of mosunetuzumab in FL in the CMA application were obtained from the ongoing, open-label, multicentre, dose-escalation and dose-expansion phase 1/2 study GO29781 (n=90) conducted in patients with r/r hematologic malignancies expected to express CD20, including B-cell NHL and chronic lymphocytic leukaemia (CLL). Eligible patients in the expansion cohorts with FL had histologically documented grade 1-3a after ≥2 prior lines of systemic therapy and must have received prior treatment with an anti-CD20-directed therapy and an alkylating agent. The median age of the enrolled patients treated with mosunetuzumab at the recommended phase two dose (RP2D) in the expansion cohort was 60 years (range: 29-90) and 31.1% were >65 years. Mosunetuzumab demonstrated a high response rate and CR rate in both age groups analysed. The ORR was 77% versus 83% in patients <65 years compared to those ≥65 years, and the CR rate was 52% versus 70%, respectively. In the broader patient population who received mosunetuzumab with the IV Cycle 1 step-up dosing regimen (Group B; N=410), the median age was 63 (range: 19-96), and 40.5% were >65 years. The safety profile of mosunetuzumab IV monotherapy in Group B was generally similar between patients aged 18-65 years (N=244) and those aged >65 years (N=166), supporting the use of mosunetuzumab in both age groups.

Mosunetuzumab had consistent response rates in high-risk patient subgroups with r/r FL, including those with double-refractory disease (n=48; ORR: 69%, CR: 48%), those who progressed within 24 months of initial first-line systemic therapy (POD24 [n=47]; ORR: 83%, CR: 55%), and patients who were refractory to PI3K inhibitors (n=12; ORR: 75%, CR: 50%). In the pivotal B11 r/r FL expansion cohort, the median number of prior lines of anti-lymphoma therapies was 3 (range: 2-10), and a high proportion had disease that was refractory to the last prior therapy (69%; 62/90), with approximately half of the patients double-refractory to a prior anti-CD20 and alkylator therapy (53%; 48/90). Around half of the patients had also POD24 (52%; 47/90), a prognostic factor being predictive of poor OS (Casulo et al., 2017; Seymour et al., 2019). Efficacy subgroup analyses revealed high and consistent CR rate and ORR in all analysed subgroups defined by various demographic- and baseline disease characteristics, including with regards to prior therapies and refractory status, supporting the use of mosunetuzumab in the broad r/r FL population after two prior systemic therapies.

In the heavily pre-treated r/r FL population in study GO29781 that has exhausted several available treatment options, mosunetuzumab induced a high CR rate of 57.8% (95% CI: 46.9, 68.1), with an

ORR of 78.9% (95% CI: 69.0, 86.8), which compares favourably with other approved therapies. CR induced by mosunetuzumab was demonstrated to be sustained. In patients who achieved a CR as the best response, it was estimated that 80.1% (95% CI: 67.4, 92.7) maintained their response at 12 months after the first response.

The sponsor has provided table overviews of indirect comparisons to currently authorised medicinal products such as the PI3K inhibitors Zydelig (idelalisib) and Copiktra (duvelisib), the anti-CD20 containing regimens MabThera (rituximab) plus Revlimid (lenalidomide), and Gazyvaro (obinutuzumab) plus bendamustine, and bendamustine in monotherapy. The data for these therapies were selected to support the claim for significant benefit as they were granted full approval in the EU for treatment of adult patients with r/r FL after at least two prior systemic therapies (see the tables below). Of these medicinal products, only the combination treatment with Revlimid plus rituximab is considered a satisfactory method of treatment for the target FL population for mosunetuzumab. In addition, Zevalin is another treatment method considered relevant for a discussion on the significant benefit of Lunsumio in r/r FL patients after two or more lines of systemic therapy. A descriptive comparison to Zevalin was also provided.

Table 3. Comparison of Key Efficacy and Safety of Mosunetuzumab and Available Therapies Granted Full Approval in the EU to Treat Patients with R/R FL Specifically After ≥2 or 3 Prior Systemic Therapies

Therapy (efficacy-evaluable patients)	**Idelalisib (N=72)**	**Duvelisib[b] (N=73)**	**Mosunetuzumab (n=90)**
Study	DELTA	DYNAMO	GO29781
Population	³2 prior therapies, refractory to rituximab and alkylator	³2 prior therapies refractory to rituximab and to either chemotherapy or radioimmuno-therapy	³2 prior therapies
Median Prior Treatments (range)	4 (2-12)	3 (1-18)	3 (2-10)
Rituximab-Refractory	100%	98%	79% (to prior anti-CD20)
Tumor assessment[f]: Imaging Response Criteria	CT/MRI IHP 2007[g]	CT/MRI, PET IHP 2007[g]	CT/MRI, PET IHP 2007[g]
ORR (95% CI)	56% (43, 67)	40% (31, 54)	79% (69, 87)
CR	17%	0%	58% (47, 68)

Therapy (efficacy-evaluable patients)	Idelalisib (N=72)	Duvelisib[b] (N=73)	Mosunetuzumab (n=90)
Median DOR, months	11.8	10.0[i]	NE (65% at 12 mo)
Median duration of follow-up, months	8.1	NR	10.7 (DOR follow-up)
Treatment discontinuation due to AE	20%	35%	4%
Important Safety and Tolerability Issues	hepato-toxicity, severe diarrhea, colitis, pneumonitis, intestinal perforation, severe cutaneous reactions, anaphylaxis, neutropenia, embryo-fetal toxicity	infections, diarrhea or colitis, cutaneous reactions, pneumonitis, hepatotoxicity, neutropenia, embryo-fetal toxicity. This medicinal product is subject to additional monitoring	Proposed Special Warnings and Precautions for Use: cytokine release syndrome, serious infections, tumor flare, tumor lysis syndrome

AE = adverse event; CI = confidence interval; CR = complete response; CT = computed tomography; EZH2 = enhancer of zeste homolog 2; DOR = duration of response; IHP =International Harmonization Project; MRI = magnetic resonance imaging; NE =not evaluable; NR =not reported; ORR = overall response rate; PET = positron emission tomography; WT = wild-type.

[b] Flinn et al. 2019.

[f] Response rates and DOR shown are based on assessments by an independent review committee (IRC).

[g] Cheson et al. 2007.

[i] Due to early censoring, the estimated DOR may not be reliable.

Sources: Zydelig EU SmPC; Copiktra EU SmPC; Aliqopa USPI; Ukoniq USPI; Tazverik USPI; Yescarta USPI

The rituximab-lenalidomide regimen was investigated in two phase 3 studies (the AUGMENT study and the ongoing MAGNIFY study) which enrolled earlier line, less heavily pre-treated, and less refractory patients, making the patient populations and efficacy results in these studies less comparable to those reported for mosunetuzumab in study GO29781. Between these two phase 3 studies, the MAGNIFY study allowed enrolment of rituximab-refractory patients (47%) while AUGMENT excluded rituximab-refractory patients. The sponsor therefore considered the study results from MAGNIFY to be a better comparator for study GO29781, which enrolled 79% of patients who were refractory to prior anti-CD20-directed therapy. In MAGNIFY, the ORR was 54% and the CR rate was 14% for the rituximab-lenalidomide regimen in the subpopulation of patients with r/r FL who had received at least 2 prior therapies. The median duration of response (DOR) was 5.1 months (95% CI: 2.3, 8.5). The sponsor noted that the efficacy of mosunetuzumab compares favourably to that reported for this regimen with higher response rates and longer DOR in a more refractory patient population, which is supported.

Table 4. Key Efficacy and Safety for Available Therapies Granted Full Approval in the EU to Treat Patients with R/R FL (Subanalysis of Patients ≥2 Prior Therapies)

Therapy	**Rituximab+ Lenalidomide**	**Rituximab+ Lenalidomide**	**Bendamustine+ Obinutuzumab**	**Bendamustine**
Study	MAGNIFY (NCT01996865)	AUGMENT (NCT01938001)	GADOLIN (NCT01059630)	
Efficacy-evaluable patients	115	67	79	94
Prior Therapy, Median (range)	3 (2-10)	3 (2-12)	2 (2-10)	
Rituximab-Refractory	47%	0	100%	
ORR (95% CI)	57% (48, 66)	81% (69, 89)	75% (63, 84)	79% (69, 86)
CR	13%	34%	20%	20%
Median DOR, months (95% CI)	5.1 (2.3, 8.5)	NR (19.6, –)	NR (19.5, –)	13 (8.9, 16.8)
Important Safety and Tolerability Issues	<u>Rituximab:</u> infusion reactions, TLS, mucocutaneous reactions, PML infections, cardiac arrhythmias and angina, bowel obstruction and perforation, cytopenias, hepatitis B reactivation, immunization <u>Lenalidomide:</u> embryo-fetal toxicity, hematologic toxicity, venous and arterial thromboembolism cardiac, secondary primary malignancies, hepatotoxicity, cutaneous reactions, TLS, tumor flare, impaired stem cell mobilization, hypersensitivity Note: This medicinal product is subject to additional monitoring.		<u>Obinutuzumab:</u> Hepatitis B reactivation, PML infusion reactions, hypersensitivity reactions including serum sickness, TLS, infections, neutropenia, thrombocytopenia, immunization <u>Bendamustine:</u> Myelosuppression, infections, infusion reactions and anaphylaxis, TLS, skin reactions, other malignancies, use in pregnancy	

CR = complete response; DOR = duration of response; NR = not reached; ORR = overall response rate; PML = progressive multifocal leukoencephalopathy; TLS = tumor lysis syndrome.
Source: Adapted from Table 6 of Multidisciplinary Review and Evaluation NDA 213176 UKONIQ™ (Umbralisib) (U.S.).

<u>Descriptive comparison to the radioimmunotherapy Zevalin (ibritumomab)</u>

Ibritumomab is authorised in the EU for the treatment of adult patients with rituximab-relapsed or refractory CD20+ follicular B-cell NHL (Zevalin SmPC) and may represent an effective treatment approach in elderly patients with comorbidities not appropriate for chemotherapy.

In the pivotal single-arm phase 2 study 106-06 conducted in 54 patients with relapsed FL who were refractory to rituximab, an ORR of 74% (95% CI: 60, 85) and a CR rate of 15% (95% CI: 7, 27) were observed in response to treatment with ibritumomab. A median DOR of 6.4 months and a median time to progression (TTP) of 6.8 months was shown (Zevalin SmPC; Witzig et al., 2007). The FL patients in this study had received a median of 4 (range: 1-9) prior regimens. Another phase 3 randomized study compared ibritumomab (n=73, 55 with FL) versus rituximab (n=70) in rituximab-naïve patients with

r/r low-grade or follicular NHL or transformed B-cell NHL. The ORR was significantly higher for patients treated with ibritumomab (80% versus 56%, p=0.002). The duration of CR and time to progression, however, were not significantly different between the two treatment arms, not in the overall patient population, nor in the FL subgroup (Gordon et al., 2004).

Because of bone marrow depletion, haematological toxicity has been very commonly observed with ibritumomab and is dose-limiting. Due to this risk, ibritumomab is contraindicated in patients with >25% of the bone marrow infiltrated by lymphoma cells, or prior external beam radiation affecting more than 25% of active bone marrow, or decreased platelet counts or neutrophil counts, or those who had prior bone marrow transplant or stem cell support. The use of ibritumomab is also associated with an increased risk of secondary malignancies, including acute myeloid leukaemia and myelodysplastic syndrome (Zevalin SmPC).

The sponsor concluded that the sustained CR rate and ORR combined with an acceptable safety profile as observed in the patient population from the pivotal B11 expansion cohort in study GO29781 support a favourable benefit-risk profile for mosunetuzumab in r/r FL patients after ≥2 prior therapies and demonstrate a clinically meaningful advantage over currently available therapies in the EU.

It is agreed that the data provided indicate improved and sustained responses in patients treated with mosunetuzumab compared to authorised therapies for r/r FL in the third- and later lines setting, including the satisfactory methods of treatment lenalidomide in combination with rituximab, and ibritumomab. The CRR observed for mosunetuzumab in GO29781 was almost 4 times higher than those reported in the pivotal study 106-06 for ibritumomab and in the MAGNIFY study for rituximab and lenalidomide (58% vs. 15% and 14%, respectively). The ORR for mosunetuzumab was comparable to that reported for ibritumomab (79% vs. 74%), but higher than for the rituximab-lenalidomide regimen (79% vs. 54%). The DOR observed for mosunetuzumab was also more durable than those reported for both ibritumomab and the rituximab-lenalidomide regimen (not reached for mosunetuzumab after a median follow-up of 10.7 months, median 6.4 months for ibritumomab, and median 5.1 months for rituximab plus lenalidomide) in patients with r/r FL. In addition, the patients enrolled in the MAGNIFY study appeared to have a better prognosis than those enrolled in study GO29781.

In summary, the indirect comparisons of clinical efficacy data presented provide adequate evidence to support the claim for significant benefit of mosunetuzumab based on improved efficacy in terms of higher and more durable responses as compared to treatment with lenalidomide (Revlimid) plus rituximab and Zevalin in patients with r/r FL who have received at least two prior lines of systemic therapy.

4. COMP position adopted on 29 April 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of follicular lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 4.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation to aggressive lymphoma;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Lunsumio may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided clinical data that demonstrated improved and sustained response rates after treatment with Lunsumio as compared to treatment with Revlimid plus rituximab and Zevalin in patients with relapsed and refractory follicular lymphoma who have received at least two prior lines of systemic therapy.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Lunsumio, mosunetuzumab for treatment of follicular lymphoma (EU/3/21/2517) is not removed from the Community Register of Orphan Medicinal Products.