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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Yescarta (axicabtagene ciloleucel, autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor)
Treatment of follicular lymphoma
EU/3/15/1579

Sponsor: Kite Pharma EU B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor
Other name(s)	Yescarta, Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor, Yescarta.
International Non-Proprietary Name	Axicabtagene ciloleucel
Tradename	Yescarta
Orphan condition	Treatment of follicular lymphoma
Sponsor's details:	Kite Pharma EU B.V. Tufsteen 1 2132 NT Hoofddorp Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Kite Pharma UK, Ltd
COMP opinion	08 October 2015
EC decision	11 November 2015
EC registration number	EU/3/15/1579
Post-designation procedural history	
Transfer of sponsorship	Transfer from Kite Pharma UK, Ltd, to Kite Pharma EU B.V. – EC decision of 03 April 2017
Type II variation procedural history	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus/ Claire Beuneu
Applicant	Kite Pharma EU B.V.
Application submission	23 July 2021
Procedure start	14 August 2021
Procedure number	EMA/H/C/004480/II/0042
Invented name	Yescarta
Approved therapeutic indication	Treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy Further information on Yescarta can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/Yescarta
CHMP opinion	22 April 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland/ Bozenna Dembowska-Baginska
Sponsor's report submission	20 August 2021
COMP discussion and adoption of list of questions	15-17 February 2022

Oral explanation cancelled	10 May 2022
COMP opinion	12 May 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2015 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor was considered justified based on preliminary clinical data showing a response in relapsed/refractory patients;
- 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 2.8 in 10,000 persons in the European Union, at the time the application was made.
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that remission was recorded in relapsed and refractory patients. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of type II variation

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., 2016).

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 of the disease 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., 2016; 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 "*Treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after 3 or more lines of systemic therapy"* 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 CAT/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 2015. 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 performed a review of epidemiological data to calculate the prevalence of FL in Europe. Published data from national, regional and global population-based cancer registries and other relevant sources including the Association of Nordic Cancer Registries (ANCR; Denmark, Sweden, Finland, Norway, and Iceland; 2018 data), CancerMPact (Europe5: Germany, Italy, Spain, France, and the UK; 2021 data), Global Burden of Disease (GBD; EU28; 2019 data), HMRN (Yorkshire region in the UK; 2007-2016 data), and International Agency for Research on Cancer (IARC; EU28 as defined by WHO; 2020 data) were searched. In addition, a search on PubMed and Google Scholar for peer-reviewed articles reporting frequency measures for FL during the period 2007-2020 was conducted, but no information on direct prevalence estimates for FL was obtained from the published reports found.

The sponsor has provided a prevalence estimate based on a literature search and assumptions regarding 5 year and 10 to 20-year survival. They do not appear to have consulted ECIS.

The sponsor noted that the median survival rate of FL ranges between 10-20 years, with a 5-year survival of 80-90% (Buske et al., 2012; Federico et al., 2009; Provencio et al., 2017). In addition, FL has been reported to represent 20% of all NHL cases (Casulo 2015a et al., Luminari et al., 2019, Maurer et al., 2014).

Table 1 highlights the crude prevalence rates the sponsor submitted.

Table 1. Crude prevalence rates for FL in Europe

	Data source	Country/Region	Period	Reported prevalence rate of FL /10,000 persons
1-year prevalence	ANCR, 2018	Nordic countries	2018	-
	GBD, 2019	Europe	2019	-
	GBD, 2019	UK	2019	-
	HMRN, 2019	UK	2007-2016	0.40
	IARC, 2020	UK	2020	-
	IARC, 2020	Europe	2020	-
5-year prevalence	ANCR, 2018	Nordic countries	2018	-
	CancerMpact, 2020	Europe5	2020	1.51
	CancerMpact, 2020	UK	2020	1.58
	GBD, 2019	Europe	2019	-
	HMRN, 2019	UK	2007-2016	1.52
	IARC, 2020	Europe	2020	-

10-year prevalence	ANCR, 2018	Nordic countries	2018	-
	CancerMpact, 2020	Europe5	2020	2.52
	CancerMpact, 2020	UK	2020	2.60
	HMRN, 2019	UK	2007-2016	2.48

FL, Follicular Lymphoma; NHL, non-Hodgkin's Lymphoma; ANCR, Association of Nordic Cancer Registries; Nordic countries include Denmark, Sweden, Finland, Norway and Iceland; Europe5 countries include France, Germany, Italy, Spain and the United Kingdom; UK, United Kingdom; GBD, Global Burden of Disease; HMRN, Haematological Malignancy Research Network, IARC, International Agency for Research on Cancer.

A literature search regarding the incidence across a range of European countries is presented below.

Table 2. Publications reporting incidence rates of FL in Europe, sorted by period

Study reference European Country(ies)	**Period**	**Codes used for classification**	**Condition description**	**Incidence rate per 10,000**
Sant et al., 2010	2000-2002	ICD-O-3 9690 9691 9695 9698	 FL, NOS FL, grade 2 FL, grade 1 FL, grade 3	0.22 (0.21–0.22)
Mitchell et al., 2012 EU 5	2000-2002	UK: ICD-O-3 codes 9690, 9691, 9695, 9698	FL	UK: 0.22 Republic of Ireland: 0.31 Germany: 0.24
Shirley et al., 2013 UK	Jan 2001 – Dec 2007	ICD-O-3 969	FL	0.09
Smith et al., 2011 UK	Sept 2004 – Aug 2009	ICD-O-3	FL	UK: 0.31 (0.28-0.33)
Smith et al., 2015 UK	Sep 2004 – Aug 2012, with follow up to Mar 2014.	Not specified	FL	0.28 (0.27-0.33)

FL, Follicular Lymphoma; ICD, Classification of Disease; UK, United Kingdom; sorted by period

The sponsor argued that the epidemiology of FL has not been well characterised. There are only a few peer-reviewed published articles on the epidemiology of FL in Europe and there is limited information provided in the epidemiological data sources. Most population-based studies and epidemiological data sources estimate haematological malignancies at broader categories (such as Hodgkin versus non-Hodgkin lymphoma). For example, data sources such as ANCR, GBD, and IARC registries do not provide direct FL estimates. It has been noted that due to the paucity of epidemiological literature on FL, it is unclear whether the distribution of NHL prevalence by age and sex is similar in FL.

Based on the review of the epidemiological data sources found and the above-mentioned assumptions, the sponsor concluded that the highest 1-year, 5-year and 10-year prevalence of FL reported in Europe was 2.09, 2.02 and 3.63 per 10,000 persons, respectively {ANCR 2018, GBD 2019, HMRN 2019, IARC 2020}. In view of the most recent prevalence figures accepted for this condition, it appeared that the assumptions regarding the incidence and survival for the prevalence estimate are underestimated.

The sponsor provided a revised prevalence estimate for FL upon request. According to ECIS, the 2020 age standardized incidence of NHL in EU27 was 1.83 per 10,000 persons (a). Kanas and colleagues established NHL subtype distribution from peer-reviewed literature and showed that the weighted average (weighted by study population size) for the FL proportion across EU was 16.3% (Kanas et al., 2022a) (b). The incidence of FL was estimated using the formula: Incidence of NHL (a) x Proportion of NHL presented as FL (b). The estimated incidence of FL based on this was 0.298 per 10,000 persons.

The sponsor then indicated that a search of epidemiological data sources was conducted to estimate the overall median duration of the disease, based on reported median overall survival (OS), which ranged from 11 years to 16.3 years (Mozas et al., 2020; Provencio et al., 2017). For this estimation, the sponsor limited the sources to studies published using real-world data only, randomized control trials and USA only specific estimates were excluded.

A maximum median OS was then used by the sponsor to estimate the complete prevalence for FL (16.3 years). The updated prevalence was calculated using the standard formula Prevalence (P) = Incidence of FL (I) x Median OS (D) = 0.298 x 16.3 = 4.85 per 10,000 persons in the EU. The final proposed estimate of 4.85 in 10,000 people was accepted by the COMP and rounded off to 4.9 in 10,000 people in the European community.

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 2020). 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), 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.

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 identify two types of FL patient populations that are offered two different treatment algorithms depending on their tumour burden.

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.

This indication extension of Yescarta is intended to include treatment of adult patients with r/r FL after three or more lines of systemic therapy. An overview of medicinal products authorised in the EU for the treatment of relapsed FL and whether they are considered satisfactory methods of treatment relevant for a discussion on the significant benefit of axicabtagene ciloleucel (hereinafter referred to as axi-cel; Yescarta) in FL is presented in the table below.

Table 3. 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 axi-cel
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 axi-cel
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 axi-cel
Levact (bendamustine)	Indolent NHL as monotherapy in patients who have progressed during or within 6 months following	1st MA approval in Germany in 2005	Non satisfactory as only indicated for patients with rituximab-refractory FL

Product name (INN)	Indication	Approval Date	Satisfactory method
	treatment with rituximab or a rituximab containing regimen		
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
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	Non satisfactory as only indicated for patients with r/r 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

* Patients with histological grade 3b FL were excluded from the pivotal study for the indication extension of Yescarta to FL (Procedure No. EMEA/H/C/004480/II/0042). Since grade 3b FL biologically is more closely related to DLBCL than to the other forms of FL, these patients are often treated as an aggressive lymphoma such as DLBCL, for which Yescarta is already indicated. The CAT/CHMP therefore concluded during the assessment of the type II variation that the product should be intended for FL without any grade-relevant restrictions, since an extrapolation of the positive benefit/risk balance of Yescarta observed in the studied FL grade 1-3a and DLBCL populations to patients with FL grade 3b can be considered acceptable. The label of Yescarta is thus for all grades of FL.

Significant benefit

The sponsor did not seek protocol assistance for the justification of significant benefit.

The sponsor argued that axi-cel represents a significant benefit based on the improved efficacy observed in the pivotal study ZUMA-5 for the indication extension compared to therapies approved in the EU for the treatment of adult patients with r/r FL in the fourth- and later lines setting. A post hoc analysis using supportive datasets from SCHOLAR-5 was presented to provide further context to the clinical outcomes in ZUMA-5.

The primary data supporting the efficacy and safety of axi-cel in the extension of indication to include treatment of adult patients with relapsed or refractory (r/r) FL were obtained from the ongoing, open-label, multicentre, single-arm phase 2 study ZUMA-5. The study is designed to evaluate the efficacy and safety of axi-cel in adults with r/r indolent NHL (iNHL), including FL. Eligible FL patients (≥18 years) had r/r FL grade 1-3a after at least two prior lines of therapy, which must have included an anti-CD20 therapy combined with an alkylating agent. Patients with histological grade 3b FL were excluded from the study. Axi-cel was administered as a single IV infusion with a target dose of $2x10^6$ anti-CD19 CAR+ T-cells/kg ($1.0\text{-}2.4\times10^6$ anti-CD19 CAR+ T-cells/kg). For patients weighing greater than 100 kg, a maximum flat dose of $2x10^8$ anti-CD19 CAR+ T-cells was administered.

Data were reported from an extended 24-month follow-up analysis with a data cut-off (DCO) date of 31-mar-2021. The primary endpoint of ZUMA-5 is objective response rate (ORR), defined as the proportion of patients who achieved a complete response (CR) and partial response (PR) as assessed by central review per Lugano 2014 classification response criteria (Cheson, J Clin Oncol. 2014; 32(27): 3059-68). Secondary efficacy endpoints included ORR and CR per central assessment for patients who had at least three lines of prior therapy, duration of response (DOR) and progression-free survival (PFS) both per central and investigator assessments, and OS.

Among the 75 patients with FL who received 3 or more prior lines of therapy in the FAS excluding centrally confirmed non-FL, the median age was 60.0 years (range: 34-79) and 31% (23/75) were 65 years of age or older. Most of the patients were white (93%; 70/75) and males (63%; 47/75). The majority had stage III or IV disease (87%; 65/75) (at initial diagnosis) and refractory disease (77%; 58/75). More than half of the patients (57%; 43/75) had high tumour bulk as defined by GELF criteria. The FLIPI score was also high in 45% (34/75) of the patients and around half of patients (51%; 38/75) had a history of disease progression within 24 months of initiating their first chemoimmunotherapy (POD24). The patients had a median of 4 prior lines of therapy (range: 3-10), where 33% (25/75) had received 4 prior lines and 27% (20/75) had received 5 or more prior lines of therapy. All patients had received a prior anti-CD20 therapy and an alkylated agent, and 24% (18/75) were considered double refractory (refractory to the first 2 lines of therapy). In addition, 29% (22/75) had previously received an ASCT, 40% (30/75) had previously received a PI3K inhibitor, and 37% (28/75) had previously been treated with lenalidomide.

The baseline data submitted showed that patients recruited included those who were relapsed or refractory to 5 lines or more of therapy where PI3K inhibitors such as Zydelig and Copiktra, or anti-CD20 therapy such as MabThera, Gazyvaro and Zevalin, or anthracyclins such as Pixruvi as well as Revlimid (lenalidomide) had been used.

At the DCO for the extended 24-month follow-up analysis, the primary endpoint ORR was 91% (68/75; 95% CI: 82, 96) in FL patients who had received 3 or more prior lines of therapy (FAS, leukapheresed patients). The observed benefit of axi-cel in terms of ORR was supported by the secondary endpoints. The CR rate was 77% (58/75; 95% CI: 66, 86) in the subset of patients corresponding to the proposed therapeutic indication. The Kaplan-Meier median estimates for DOR was 38.6 months (95% CI: 24.7, not estimable [NE]) and 40.2 months (95% CI: 26.6, NE) for PFS. The median OS was not reached at the last DCO.

Contextualization of the clinical outcomes reported from ZUMA-5 was performed with an adjusted, indirect treatment comparison to an external control arm, based on the international observational, retrospective, cohort study SCHOLAR-5. The SCHOLAR-5 cohort comprised of 82 patients who were identified from 3 sub-cohorts. Among these patients, 58 patients were identified in the real-world setting (Sub-cohort A and Sub-cohort B), and 24 patients were identified from a clinical study called DELTA (Gopal et al., 2014; Sub-cohort C). All 82 patients had a histologically confirmed diagnosis of r/r FL (grade 1, grade 2, or grade 3a) and ≥3 prior lines of therapy. The SCHOLAR-5 cohort was balanced for patient characteristics in ZUMA-5 through propensity scoring on pre-specified prognostic factors using standardized mortality ratio weighting. Clinical outcomes were compared between an effective sample of 59 patients from SCHOLAR-5 and 60 patients in ZUMA-5 who had three or more prior lines of therapy. The ORR was higher in ZUMA-5 than SCHOLAR-5 (95.0% versus 40.3%), for an odds ratio of 28.13 (95% CI: 7.37-107.30). Overall, the comparative analyses between the RWD from SCHOLAR-5 and ZUMA-5 suggested an improvement in ORR in r/r FL patients treated with axi-cel after 3 or more lines of systemic therapy. It should be noted that SCHOLAR-5 is a post hoc analysis, and these data can therefore only be considered as supportive.

Additional clinical data was provided upon request to further support the claim for significant benefit of Yescarta over existing methods of treatment for the target FL population. Descriptive comparisons to the currently authorised anti-CD20 containing regimens MabThera (rituximab), Revlimid (lenalidomide) plus rituximab, and Gazyvaro (obinutuzumab) plus bendamustine, the radioimmunotherapy Zevalin (ibritumomab), and the PI3K inhibitors Zydelig (idelalisib) and Copiktra (duvelisib) were provided. A summary of the authorised therapies in the EU with potential overlap with the indication extension for axi-cel and their efficacy outcomes in r/r FL after at least three prior therapies is given below. Of these products, only Zevalin is considered a satisfactory method of treatment for the target FL population for Yescarta (axi-cel) and the comparative discussion for this product is therefore presented below.

Table 1. Authorised medicinal products in the EU and available fourth line FL data

Medicinal product	Landmark/ pivotal studies	ORR, %	CR, %	mDOR, m	mPFS, m
Zevalin (90Y ibritumomab tiuxetan)	-				
	{Witzig 2002a}	74	15	6.4	6.8
Gazyvaro (obinutuzumab) plus bendamustine	{Sehn 2016} {Cheson 2018}	79	17	NE	26.8
Copiktra (duvelisib)	{Flinn 2019a}	42.2	1.2	10	9.5
Zydelig (idelalisib)[a]	{Gopal 2014}	56	17	11.8	11
Yescarta (axi-cel)		91	77	38.6	40.2

NR: Not reported, AE: adverse events, ORR: overall response rate, CRR: CR rate, DOR: duration of response, PFS: progression free survival. [a] Based on the overall study population.

Descriptive comparison to the radioimmunotherapy Zevalin (ibritumomab)

The sponsor noted that ibritumomab is currently approved for the treatment of adult patients with rituximab-relapsed or refractory CD20+ follicular B-cell NHL (Zevalin SmPC). The main evidence of efficacy with ibritumomab is based on 2 clinical studies enrolling 197 patients. The pivotal single-arm phase 2 study 106-06 enrolled 54 patients with relapsed FL who were refractory to rituximab and the phase 3 randomized comparative study 106-04 compared ibritumomab (n=73, 55 with FL) versus rituximab (n=70). Study 106-04 was conducted in 143 rituximab-naïve patients with r/r low-grade or follicular NHL, or transformed B-cell NHL (Witzig et al., 2002a; Witzig et al, 2002b).

In study 106-06, treatment with ibritumomab resulted in an ORR and CR rate of 74% (95% CI: 60, 85) and 15% (95% CI: 7, 27), respectively. 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. In study 106-04, the ORR and CR rate was significantly higher in patients treated with ibritumomab compared to rituximab with 80% versus 56%, and 30% versus 16%, respectively. Of note, all patients in this study were rituximab naïve which would challenge applicability of the efficacy outcomes in the contemporary era where almost all r/r FL patients have received prior treatment with rituximab. The duration of CR and TTP, 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). The median PFS was 11.2 and 10.1 months for patients in the ibritumomab and rituximab arms, respectively (Zevalin SmPC). By contrast, ZUMA-5 demonstrated an ORR of 91%, with a CR rate of 77%, and the median PFS was 40.2 months.

The sponsor concluded that the efficacy outcomes observed in ZUMA-5 demonstrated a substantial benefit of axi-cel in r/r FL patients after ≥3 prior lines of therapy, a disease setting which currently lacks any optimal authorised treatments.

The data obtained from the pivotal phase 2 study 106-06 is considered the most relevant evidence to contextualize the benefit of Yescarta over Zevalin. The sponsor did not provide any comparison of baseline characteristics for the study populations from the two pivotal studies ZUMA-5 and 106-06 but noted that ZUMA-5 encompassed a more heavily pre-treated patient population, enriched for high-risk features such as POD24 and refractory disease. The reported efficacy outcomes from the two clinical studies indicated that patients with r/r FL treated with axi-cel in ZUMA-5 achieved a more durable and higher ORR and CR rate compared to patients treated with ibritumomab in the pivotal study 106-06. Specifically, the CR rate of axi-cel in ZUMA-5 was >5 times higher than that reported for ibritumomab in study 106-06 (77% vs. 15%). The ORR was also higher (91% vs. 74%) and the reported DOR more durable for axi-cel than ibritumomab (median 6.4 months for ibritumomab and 38.6 months for axi-cel at the DCO for an extended 24-month follow-up analysis) in patients with r/r FL who had received three or more prior lines of therapy.

The indirect comparison of efficacy data from the two pivotal single-arm studies ZUMA-5 and 106-06 provide adequate evidence to support the claim for SB of axi-cel based on better efficacy in terms of higher, deeper, and more durable responses compared to ibritumomab in r/r FL patients in the fourth- and later lines setting.

The COMP agreed to recommend maintaining the orphan designation.

4. COMP position adopted on 12 May 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 4.9 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 Yescarta may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical study data which demonstrated improved and sustained response rates after treatment with Yescarta as compared to Zevalin in adult patients with relapsed or refractory follicular lymphoma after three or more 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 Yescarta, autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor, axicabtagene ciloleucel for treatment of follicular lymphoma (EU/3/15/1579) is not removed from the Community Register of Orphan Medicinal Products.