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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Kymriah (tisagenlecleucel)
Treatment of follicular lymphoma
EU/3/21/2464
Sponsor: Novartis Europharm Limited

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	Tisagenlecleucel
Other name	Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19
International Non-Proprietary Name	Tisagenlecleucel
Tradename	Kymriah
Orphan condition	Treatment of follicular lymphoma
Sponsor's details:	Novartis Europharm Limited Vista Building Elmpark Merrion Road Dublin 4 D04 A9N6 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited
COMP opinion	24 June 2021
EC decision	19 July 2021
EC registration number	EU/3/21/2464
Type II variation procedural history	
Rapporteur / Co-rapporteur	Rune Kjeken / Dariusz Sladowski
Applicant	Novartis Europharm Limited
Application submission	31 August 2021
Procedure start	18 September 2021
Procedure number	EMA/H/C/004090/II/0044
Invented name	Kymriah
Proposed therapeutic indication	Treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy Further information on Kymriah can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/kymriah
CHMP opinion	24 March 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Frauke Naumann-Winter
Sponsor's report submission	27 September 2021
COMP discussion and adoption of list of questions	15-17 March 2022
Oral explanation cancelled	12 April 2022
COMP opinion	13 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 tisagenlecleucel was considered justified based on preliminary clinical data showing that a high proportion of relapsed/refractory patients achieve durable complete responses;
- 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 4.9 in 10,000 persons in the European Union, at the time the application was made;
- 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 tisagenlecleucel will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate sustained complete responses in a high proportion of heavily pre-treated relapsed/refractory patients who have failed several approved therapies. 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) is an indolent B-cell lymphoproliferative disorder of transformed follicular center B cells consisting of a mixture of centrocytes (small to medium-sized cleaved cells) and centroblasts (large non-cleaved 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.

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.

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. Only around 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. Most patients therefore have widespread disease at diagnosis, including peripheral and central (abdominal and thoracic) lymphadenopathy and splenomegaly. The bone marrow is involved in 40-70% of the cases (Swerdlow et al., 2017; Freedman, 2020).

The approved therapeutic indication "*Kymriah is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two 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 (B/R) 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 many 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).

No changes have occurred in the chronically debilitating and life-threatening nature of the condition since the orphan designation. FL remains life-threatening and chronically debilitating, mainly due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation into aggressive lymphoma.

Number of people affected or at risk

The sponsor has not provided an updated prevalence estimate indicating that the prevalence hasn't changed since the orphan designation in 2021 and referred to the epidemiology report used then.

In the epidemiology report, the sponsor discussed thoroughly both the limitations and strengths of the different methods used for the prevalence estimates which were presented. The prevalence of FL

ranged from 2.40 (10-year prevalence; Globocan 2020) to 4.92 (20-year partial prevalence; ECIS 2020) per 10,000 for the limited-duration prevalence estimates, while the complete prevalence (ECIS 2020; UK HMRN) was estimated to be 4.56 per 10,000 people.

The sponsor stated in the epidemiological report that FL accounts for about 11-19% of all prevalent NHL cases in the 4 largest EU member states plus UK (EU4 [France, Germany, Italy, and Spain] and UK) and 20-25% in the US (Dulac et al., 2013). The sponsor further concluded that the maximum proportion of incident FL cases among all incident NHL cases in the European Community is approximately 20%. This proportion was obtained from the upper range of proportions of incident cases reported in the published literature, where the proportion of FL among all NHL ranged from 16.3% in Italy (Luminari et al., 2007) to 21.9% in Sweden and France (Ekberg et al., 2020; Le Guyader-Peyrou et al., 2016). This proportion of FL within all NHL cases was then used for the indirect estimate of the complete prevalence. The assumption proposed by the sponsor on a FL proportion of 20% among all NHL cases in the European Community could be considered acceptable based on current knowledge of the COMP.

They also discussed the observed variability of median survival time reported for FL in population-based studies conducted in various European countries and regions. The sponsor acknowledged that the OS of patients with FL has improved over the last 25 years and suggested that the improvement may be a result of the sequential application of effective therapies, including rituximab, and better supportive care (Anderson et al., 1998; Karmali et al., 2018; Salles, 2007; Tan et al., 2013). The reported median OS in the literature studied ranged from around 6 years to 13 years (Dandoit et al., 2015; Krol et al., 2003). In another study conducted in selected Spanish hospitals, the median OS for FL was approximately 19 years (Provencio et al., 2017). The latter source, which reported survival of FL patients in a Spanish population, reflects survival of FL from a more recent period from 1980-2013 and is considered more contemporary than some of the other sources found. However, the patient population included in this study had only FL grades 1-3a since patients with grade 3b were excluded. In addition, these patients appeared to be rather young with a mean age at diagnosis of 58 years. Consequently, the median OS of 19.25 years reported in this study could be considered to represent the upper range of the survival for FL patients in the European population.

The sponsor did not consider any of the proposed prevalence estimates to be more accurate than the others for the current prevalence of FL in Europe. Instead, the sponsor highlighted that the different nature of the supplementary information used for the calculations, despite use of the same starting information, may contribute to the differences in the estimates presented, contrary to what would be expected if the prevalence estimates were calculated using information from only one source and by use of identical methods. This argument was supported.

Although both the complete and the 20-year prevalence estimates presented for FL are close to the established orphan designation threshold, the estimates are still below the upper limit of 5 cases per 10,000 people. Hence, based on the data provided, the COMP accepted that the condition currently is not affecting more than 5 in 10,000 people in the European Community.

The COMP concluded that the upper conservative estimate of approximately 4.9 per 10,000 people in the European community remains acceptable.

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

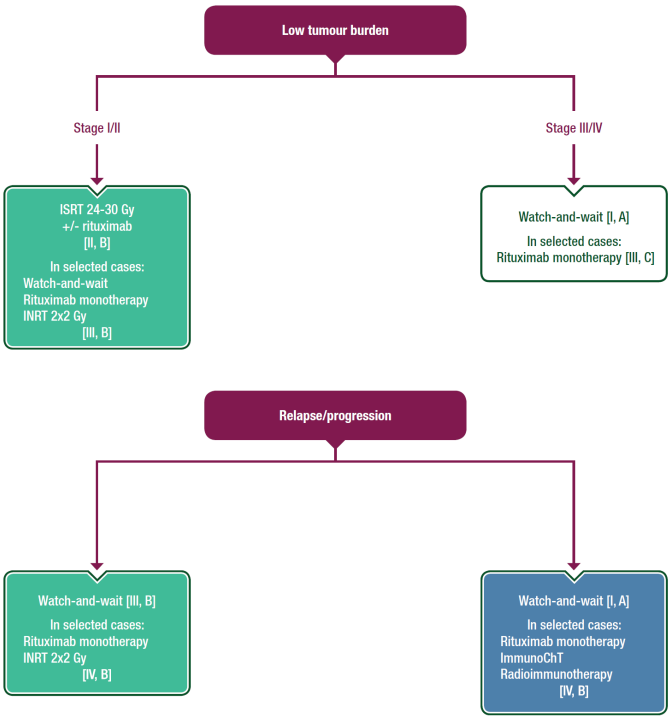
Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor provided a list of medicinal products approved in the EU for the treatment of patients with relapsed FL and their approved therapeutic indications. 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), obinutuzumab (Gazyvaro), lenalidomide (Revlimid), idelalisib (Zydelig), duvelisib (Copiktra), yttrium-90 [90Y]-radiolabelled ibritumomab tiuxetan (Zevalin), 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.

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 relapsed or refractory (r/r) FL patients depends on the patient's health, age, stage of disease and the duration of response to prior therapy. The most recent ESMO guidelines for newly diagnosed and relapsed FL describe the current standard of care (SOC) 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 clinical treatment guideline identifies two types of FL populations that are offered two different treatment algorithms depending on their tumour burden, being either low (Figure 1) or high (Figure 3).

Figure 1. Treatment algorithm for FL patients with low tumour burden



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

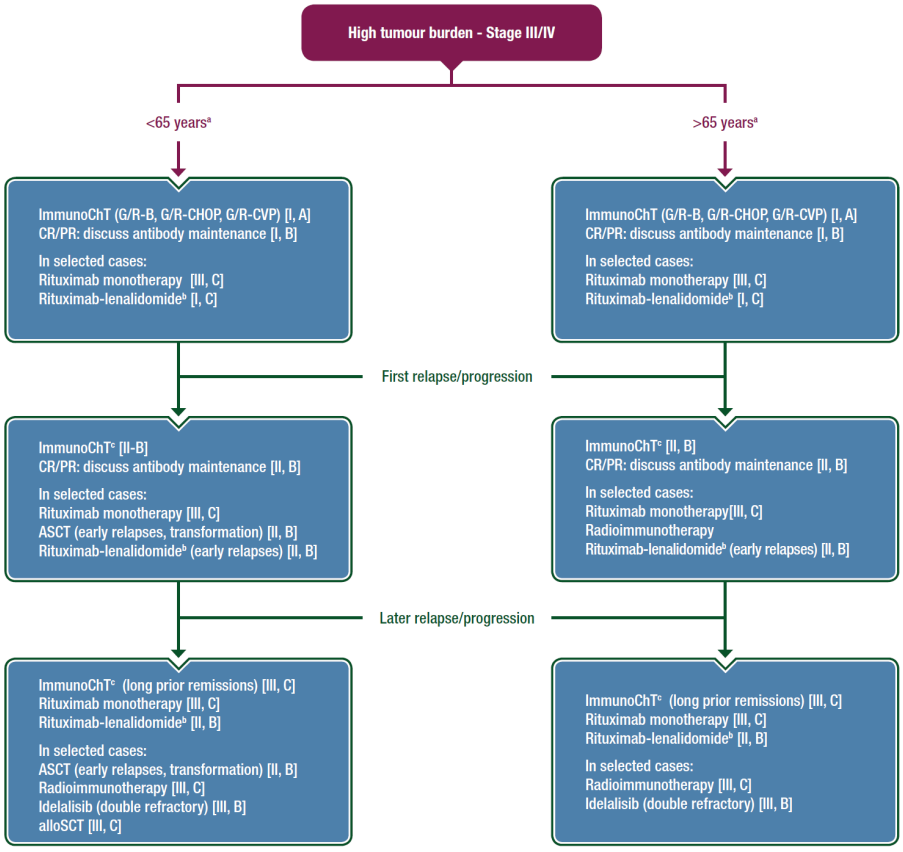
Figure 2.

Table 5. High tumour burden criteria in FL [modified from Groupe d'Etude des Lymphomes Folliculaires (GELF)[59] and British National Lymphoma Investigation (BNLI)][60]

Parameter	High tumour burden criteria
LNs	Bulk (>7 cm) or 3 LNs in distinct areas >3 cm
Spleen	Symptomatic splenic enlargement
(Potential) complication	Organ compression by tumour, pleural or peritoneal effusion
Serum markers	Elevated LDH or elevated B2M
Blood count	Leukaemic phase (>5 × 10^9/l) Cytopaenia (neutrophils <1 × 10^9/l, platelets <100 × 10^9/l)
Clinical presentation	B symptoms (see Table 2)

B2M, b2-microglobulin; LDH, lactate dehydrogenase; LN, lymph node.

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 disease lacks curative options, and although treatments are available, most patients eventually relapse or become refractory to their treatment.

This indication extension of Kymriah is intended to include treatment of adult patients with r/r FL after two or more lines of systemic therapy. An overview of medicinal products authorised for the 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 tisagenlecleucel (hereinafter referred to as tisa-cel) in FL is presented in the table below.

Table 1. 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	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 Kymriah to FL (Procedure No. EMEA/H/C/004090/II/0044). 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 Kymriah 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 B/R balance of Kymriah observed in the studied FL grade 1-3a and DLBCL populations to patients with FL grade 3b can be considered acceptable. The label of Kymriah is thus for all grades of FL.

Significant benefit

The sponsor is targeting a patient population for which treatment options exist but for which they consider that their product will be of significant benefit. Thesponsor did not seek protocol assistance to agree on the approach for the justification of significant benefit.

The primary data supporting the efficacy of tisa-cel in the proposed extension of indication to include treatment of adult patients with r/r FL are obtained from an ongoing (but not recruiting), open-label, multicentre, single-arm, phase 2 study CTL019E2202 (ELARA; hereafter referred to as study E2202). The study is designed to evaluate the efficacy and safety of tisa-cel in adults with r/r FL. Eligible patients (≥18 years) had r/r FL grade 1-3a after at least 2 prior lines of therapy, including an anti-CD20-directed therapy and an alkylating agent, or had failed prior ASCT. Patients with histological

grade 3b FL were excluded from the study. Tisa-cel was administered as a single IV infusion with a recommended dose range of 0.6-6.0×10^8 anti-CD19 chimeric antigen receptor (CAR)+ T-cells.
The primary endpoint of study E2202 is complete response rate (CRR) as assessed by central review per Lugano 2014 classification response criteria (Cheson, J Clin Oncol. 2014; 32(27): 3059-68). The analysis of the primary endpoint was conducted based on the efficacy analysis set (EAS), which contained all patients who have received tisa-cel and had measurable disease at baseline per IRC. Secondary efficacy endpoints included overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS) per independent review committee (IRC), overall survival (OS), and patient reported outcomes (PROs). Data were reported from an extended follow-up analysis with a data cut-off (DCO) date of 03-aug-2021.

The sponsor argued that data from the pivotal study (N=98/97 for the ITT/mITT) demonstrated a remarkably higher CRR and ORR with tisa-cel compared to non-CAR-T cell therapies currently indicated for treatment of r/r FL patients in the third- or later line setting. The sponsor provided real-world data (RWD) from the ReCORD and Flatiron databases to contextualise the clinical outcomes in study E2202.

The efficacy of a single tisa-cel infusion was observed with a CRR of 69.1% (95% CI: 58.9, 78.1) in the infused patients with FL grade 1-3a compared to a reported CRR value within the range of 1-38% for existing methods of treatment for the target patient population. The median DOR was not reached in study E2202 at the last DCO, supporting a sustained response in the treated FL patients. The estimated probability of remaining in response for 9 months was 87.0% (95% CI: 75.6, 93.3) for patients who achieved a best response of CR and 76.2% (95% CI: 64.9, 84.3) for all responding patients. The sponsor thinks that this compares favourably to the 18-30% they report from currently approved therapies specifically indicated in the third- or later line setting. Moreover, subgroup analyses showed that the CRRs to tisa-cel in various demographic and prognostic subgroups were consistent with that observed in the overall study population, including groups of high-risk FL patients such as those who experienced disease progression within 24 months from the start of front-line systemic therapy (36/61; 59.0% [95% CI: 45.7, 71.4]), those who were double-refractory to 2 lines of therapies (43/65; 66.2% [53.4, 77.4]), and patients with a high FLIPI score (36/57; 63.2% [95% CI: 49.3, 75.6]). The CRR values ranged from 40.0% to 87.9% in all subgroups analysed.

Two indirect comparisons using individual patients-level data from ReCORD (N=143/99) and Flatiron (N=98/88) were conducted to provide comparative, contextual evidence to the clinical efficacy of tisa-cel reported from study E2202 based on the current SOC. The data collection period in Flatiron and for a subgroup analysis of the ReCORD data was from 2014-2020 to match with the introduction of the new Lugano response criteria as well as the EU approval of Zydelig (idelalisib). The results from the indirect comparisons of the effectiveness as reported in the two RWD sources on patients with r/r FL compared to the efficacy as reported in study E2202 is presented in the table below.

Figure 4.

	Chart review N=143*	Electronic Health records N=98**
Difference in CR[1], 95% CI	31.8 (18.1, 45.3)	51.4 (21.2, 68.8)
(E2202 vs External Control)	(69.1 vs 37.3)	(69.1 vs 17.7)
Difference in ORR[1], 95% CI	22.0 (9.4, 34.5)	27.4 (-3, 65)
(E2202 vs External Control)	(85.6 vs 63.6)	(85.6 vs 58.1)
OS HR[2], 95% CI	0.20 (0.02, 0.38)	0.41 (0.11,1.47)
Time to new therapy or death HR[2], 95% CI	0.31 (0.14, 0.49)	0.34 (0.15, 0.78)
PFS HR[2] considering new anti-cancer therapy as event, 95% CI	0.60 (0.34, 0.86)	0.45 (0.27, 0.83)

** Sample size after weighting (i.e., sum of weights) was 99.*

*** Sample size after weighting (i.e., sum of weights) was 88. .CR and ORR are based on N=72 patients for whom the response assessment was available*

[1] Difference in % from values obtained for Study E2202 population and the medical records review populations.

[2] Hazard ratio calculated by Cox proportional hazard model for indirect comparison between the Study E2202 population and the medical records review populations.

The interpretation of the RWD was complicated by the fact that it was not possible to fully emulate the inclusion criteria in the pivotal study E2202. The patient populations were therefore similar but not identical. Important prognostic values were lacking and could not be adjusted for in the analyses. Response assessments were also lacking in the RWD sets, necessitating changes to the endpoint definition (ReCORD), or further exclusion of patient that otherwise would qualify (Flatiron). This results in considerable uncertainty when used to contextualise the efficacy data. However, although the validity of the endpoint assessment for response in the retrospective analysis of electronic health records could not be verified, the observed large difference to tisagenlecleucel was reassuring. The RWE presented therefore suggested a clinically meaningful benefit for patients with r/r FL treated with tisa-cel juxtaposed to existing SOC regimens used in the third- and later lines setting.

The sponsor concluded that the data from study E2202 and the supportive data sets were sufficient to demonstrate a significant benefit of tisa-cel based on improved efficacy over currently available non-CAR-T cell therapies for the treatment of adult patients with r/r FL after two or more lines of therapy. It is agreed that the data provided indicate an improvement in CRR and ORR in patients treated with tisa-cel compared to the reported outcomes for all the SOC regimens investigated in the two RWD sets for the treatment of r/r FL in the third- and later lines setting.

Indirect comparison to Zevalin

Zevalin (ibritumomab tiuxetan) is a murine anti-CD20 monoclonal antibody (mAb) that is conjugated to the radioisotope yttrium-90. Data from clinical trials and RWD were submitted by the sponsor to contextualize the claim for significant benefit based on improved efficacy of Kymriah over Zevalin in the third- and later lines setting for the target FL population. The sponsor emphasised that only data in the EU approved indication for the treatment of patients with r/r FL, including patients with rituximab-refractory FL were considered relevant for contextualizing the benefit of Kymriah over Zevalin.

Six clinical trials (106-01 to 106-06) and a pooled analysis based on four clinical trials of Zevalin were identified as potentially useful clinical evidence (Zevalin Scientific discussion 2006; Emmanouilides et al., 2009). Information on the six trials and pooled analysis with Zevalin are summarized in Table 2.

Table 2. Summary of Zevalin clinical trial evidence

Study	Description	Population	CRR/ORR	Rational for study inclusion for efficacy assessment
106 – 01	Phase 1 single dose escalation trial	n=17 enrolled, refractory to standard treatment (12 with SL or FL, 4 intermediate grade NHL, and 1 NHL of undefined type)*	14 patients who received Zevalin: CRR 28%, ORR 64%	No (single dose, small sample size, no results for FL subgroup)
106 – 02	Phase 1 multiple dose escalation trial	Only 1 patient enrolled	NA	No (study terminated with 1 enrolled patient)
106 – 03	Phase 1/2 dose-finding trial	n=51, r/r B-cell lymphoma (3 with SL, 33 with FL, 15 with other types of NHL)	For low-grade lymphoma: CRR 26%, ORR 82%	No (multiple dose levels, no information on prior rituximab exposure, results of FL subgroup not available)
106 – 04	Phase 3 randomized trial versus. rituximab	n=73 in Zevalin arm, r/r low-grade or follicular or transformed NHL (55 FL, 9 transformed, 9 others) n=70 in rituximab arm	Zevalin arm: CRR 30%, ORR 80%	No (rituximab naive, median no. of prior regimens 2 [1-6])
106 – 05	Phase 2 trial in patients with mild thrombocyto penia	n=30, r/r FL and with mild thrombocytopenia (25 FL, 5 others) A reduced dose (0.3 mCi /kg)	CR 37%, ORR 83%	No (median no. of prior regimens 2 [1-9], no information on prior rituximab exposure, results of FL subgroup not available, reduced Zevalin dose)
106 – 06	Phase 2 trial in patients with rituximab-refractory NHL	n=57 r/r FL-type who were refractory to rituximab* (54 FL, 3 others)	For FL: CRR 15%, ORR 74%	Yes (rituximab-refractory, median no. of prior regimens 4 [1-9], results of FL subgroup available)

Pooled analysis of 106-03, 04, 05, 06	See above	n=211, 108 pts with FL and received at least 2 lines of prior treatment	For FL: CRR 28%, ORR 80%	No (some of the 108 patients had no exposure of rituximab or were not refractory to rituximab). Patients with rituximab-refractory disease were from study 106-06 which was included in the comparison already.

*: 375 mg/m^2 once weekly for 4 weeks, and either did not respond or had a relapse of within 6 months.

The rational for selecting the relevant available clinical data from Zevalin relative to Kymriah from study E2202 for assessing efficacy was based on the following key criteria:

- Third- and later lines FL (number of prior regimens to be similar to study E2202). In study E2202, the median number of previous regimens is 4 (range: 2-13).
- Previous exposure to anti-CD20 mAb and most of the studied patients needed to be refractory to anti-CD20 mAb. In study E2202, 100% of the patients had prior exposure to anti-CD20 mAb and 87% of the patients were refractory to anti-CD20 mAb.

After the assessment of patient population and data availability from the six Zevalin trials and the pooled analysis, study 106-06 (Witzig et al., 2002a) was deemed the most relevant trial to contextualize the benefit between Kymriah to Zevalin. The validity of this cross-trial comparison is considered highly uncertain in view of the large differences in SOC and response criteria between the two study periods.

The baseline characteristics of the two clinical studies E2202 and 106-06 are provided in Table 3. In general, the study populations from these two studies are similar though the patients in study E2202 were likely with poorer diagnosis based on FLIPI score, bulky disease, and extra-nodal disease sites.

Table 3. Summary of baseline characteristics of the two studies E2202 and 106-06

Baseline characteristics	**Study E2202[1]** n=98	**Study 106-06[2]** n=57
Age, yrs, median (range)	57 (29-73)	54 (34-73)
Disease stage at study entry, III-IV, n (%)	84 (86)	51 (90)
Bone marrow involvement, n (%)	37 (38)	18 (32)
Bulky disease at baseline, n (%)	62 (63)	25 (44)
FLIPI high (≥3) at study entry, n (%)	59 (60)	11 (19)
Median no. of previous therapies (range)	4 (2-13)	4 (1-9)
Two or more extra-nodal disease sites	30 (31)	10 (18)
ECOG performance status (0-1)	95 (97)	54 (95)

The efficacy outcomes of these two studies E2202 and 106-06 are shown in Table 3. The primary efficacy endpoint of study E2202 is CRR. Based on the results reported from study E2202 at a median follow up of 21 months (DCO: 03-aug-2021), the CRR of Kymriah was substantially higher (> 4 times higher) than that reported for Zevalin in study 106-06 and the lower bound of the 95% CI for CRR of

tisa-cel (58%) was more than two times higher than the upper bound of the 95% CI for Zevalin (27%). The lower bound of the 95% CI for ORR of tisa-cel (77%) was also higher than the ORR of Zevalin (74%). In addition, the response associated with Kymriah was more durable than Zevalin as measured by DOR (median 6.4 months for Zevalin and not reached for tisa-cel after 12 months of minimum follow-up for all patients). Higher and more durable responses were also noted in improved PFS estimates with tisa-cel (median 6.8 months for Zevalin and 30.7 months for tisa-cel).

Table 3 Summary of efficacy outcomes of the two studies E2202 and 106-06

	E2202[1] n=98	**106-06[2]** n=54
Complete response rate (CRR) (%) (95% CI)	68 (58, 77)	15 (7, 27)
ORR (%) (95% CI)	86 (77, 92)	74 (60, 85)
Duration of response (DOR) Median (months) (95% CI) % event free probability at 9 months (95% CI)	 Not reached (20.9, NE) 76 (65, 84)	 6.4 (not reported) Not reported
Progression free survival (PFS) Median (months) (95% CI) % event free probability at 12 months (95% CI)	 30.7 (18.8, NE) 72 (61, 80)	 6.8 (not reported) Not reported

Real-world evidence

The RWE of Zevalin in the third- and later lines setting for the target FL population was limited. This may reflect the limited use of Zevalin in this patient population. Two RWD data sources were consulted, specifically Record-FL (Europe) and Flatiron (US). The results are summarized below:

Data from Record-FL

A total of 12 patients out of 187 patients in ReCORD (sites in mainly EU) had been identified as having received Zevalin either as single agent or in combination with other medicinal products in the third- or later lines of therapy. Of them, 5 patients received Zevalin in monotherapy: 3 in the 3rd line (with 1 CR and 2 partial responses [PRs] achieved as best overall response), 1 patient in the 4th line (with progressive disease [PD]), and 1 patient in 5th line treatment (with PR).

Data from Flatiron

A total of 2 patients out of 98 patients in Flatiron (all US patients) were identified, both receiving Zevalin as 3rd line therapy. Both patients were PDs.

Real-world data in literature

The literature of RWD for Zevalin in the third- and later lines FL patients who had rituximab-refractory disease is limited. For example:

- Jurczak and colleagues (2007) reported real-world experience of Zevalin in 12 r/r FL patients (>2 lines of treatment with prior rituximab exposure) from three Poland centers.
- Tsukamoto and colleagues (2018) reported real-world experience of Zevalin in 8 r/r FL patients (>2 lines of treatment) from Gunma University Hospital. No information on prior rituximab exposure was reported.

- Leahy and Turner (2011) reported a single-institution experience of Zevalin in Australia. Out of 142 patients, 66% (94/142) with FL, 46% (65/142) with 2 or more prior therapies, and 56% (80/142) with prior rituximab exposure (no information on rituximab-refractory status). However, no data of baseline characteristics and efficacy outcome were reported for the target FL population (r/r FL in 3rd line or more with rituximab exposure). Study reported worse outcomes for later line patients (4th line versus earlier line: CR+CRu 33% vs. 45-55%) and patients with rituximab exposure (with exposure versus no exposure: CR+CRu 38% vs. 67%).

As the sample sizes were small and information on baseline characteristics were limited in these RWD studies, the results were considered unlikely to provide meaningful information to contextualize the effectiveness of Kymriah over Zevalin.

The sponsor concluded that the overall clinical evidence available strongly supports significant benefit based on improved efficacy of Kymriah over Zevalin in the third- and later lines setting for the target r/r FL population. The COMP concluded that they could recommend the maintenance of the orphan designation.

4. COMP position adopted on 13 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 4.9 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 Kymriah may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data which demonstrated compelling complete response rates of Kymriah compared to Zevalin in patients with relapsed and refractory follicular lymphoma in the third- and later lines setting who had previously been treated with anti-CD20-directed 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 Kymriah, tisagenlecleucel for treatment of Follicular lymphoma (EU/3/21/2464) is not removed from the Community Register of Orphan Medicinal Products.