14 October 2022
EMADOC-1700519818-943901
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Yescarta (axicabtagene ciloleucel)
Treatment of diffuse large B-cell lymphoma
EU/3/14/1393

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)	--
International Non-Proprietary Name	Axicabtagene ciloleucel
Tradename	Yescarta
Orphan condition	Treatment of diffuse large B-cell 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	13 November 2014
EC decision	16 December 2014
EC registration number	EU/3/14/1393
Post-designation procedural history	
Transfer of sponsorship	Transfer from Kite Pharma UK, Ltd to Kite Pharma EU B.V. EC decision of 3 April 2017
Type II variation procedural history	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus/ Claire Beuneu
Applicant	Kite Pharma EU B.V.
Application submission	5 November 2021
Procedure start	27 November 2021
Procedure number	EMA/H/C/004480/II/0046
Invented name	Yescarta
Proposed therapeutic indication	Treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy. Further information on Yescarta can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Yescarta
CHMP opinion	15 September 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland/ Bozenna Dembowska-Baginska
Sponsor's report submission	6 December 2021

COMP discussion and adoption of list of questions	15-17 February 2022 12-14 July 2022 6-8 September 2022
COMP opinion (adoption via written procedure)	22 September 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 designation in 2014 was based on the following grounds:

The sponsor Kite Pharma UK, Ltd submitted on 20 August 2014 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor for treatment of diffuse large B cell lymphoma (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- 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 anti-cancer activity in patients with refractory disease;
- the condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as approximately one in four patients for the high risk group;
- the condition was estimated to be affecting approximately 2.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, 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 showing a favourable response in patients with progressive disease who are refractory to previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor as an orphan medicinal product for the orphan indication: treatment of diffuse large B cell lymphoma.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2018 was based on the following grounds:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of diffuse large B-cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening with 5-year survival rates reported as low as approximately 25% for high risk patients;
- although satisfactory methods of 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 data showing responses in patients with relapsed or refractory diffuse large B-cell lymphoma, which compare favourably to responses with existing treatments in historical controls. The COMP considers that this constitutes a clinically relevant advantage.

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, EU/3/14/1393 for treatment of diffuse large B cell lymphoma is not removed from the Community Register of Orphan Medicinal Products.

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

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma (NHL) in adults. It comprises a group of aggressive lymphoid malignancies that accounts for around 30% to 40% of all NHL cases globally (Chaganti et al., 2016). Patients with DLBCL often present with single or multiple rapidly enlarging symptomatic masses, with up to 40% occurring at extra-nodal sites (Martelli et al., 2013). The disease usually affects adults, especially around 60 to 70 years, but also rarely occurs in adolescents and children. Hereditary and acquired immunodeficiencies, occupational exposures, and pharmacological immunosuppression in the setting of transplantation or treatment of autoimmune diseases have been identified as factors thought to potentially confer increased risk of developing DLBCL.

DLBCL often arises de novo, but it can also represent a malignant progression or transformation of a less aggressive lymphoma (e.g., follicular lymphoma [FL], chronic lymphocytic leukaemia [CLL], small lymphocytic lymphoma and mucosa associated lymphoid tissue lymphoma; Martelli et al., 2013). The most frequently dysregulated genes include BCL6 (rearrangement in 35%−40%; mutation in 5′ noncoding region in 70%), BCL2 (translocation 15%, amplification 24%), and cMYC (5%−15%; Skinnider et al. 1999).

In recognition of the unique clinical and pathological features of DLBCL subtypes and associated therapeutic implications, the World Health Organization (WHO) made several changes to the classification of lymphoid neoplasms in 2016. The different entities previously categorized as DLBCL subtypes were separated from DLBCL, NOS. Cell of origin subtypes (GCB and ABC) were formally recognized for DLBCL, NOS, whereas double- and triple-hit lymphomas were included in a new category of large B-cell lymphoma (LBCL) called high-grade B-cell lymphoma (HGBL), which is distinct from DLBCL (Sehn et al., 2021; Swerdlow et al., 2016). According to the 2016 WHO classification, HGBL comprises 2 subcategories: (1) HGBL with MYC, BCL2, and/or BCL6 translocations, which includes LBCL with MYC, BCL2, and/or BCL6 rearrangements, also known as "double- or triple-hit" lymphomas, and excludes follicular lymphoma or lymphoblastic lymphoma; and 2) HGBL NOS, which includes LBCL that are cytologically "high-grade" and would previously be characterized as B-cell lymphoma unclassifiable, and lack genetic features of double- or triple-hit lymphomas (Swerdlow et al., 2016). Consequently, the aggressive B-cell NHL subset LBCL now includes both DLBCL (including DLBCL NOS and other DLBCL subgroups) and HGBL subtypes, in addition to primary mediastinal large B-cell lymphoma (PMBCL). DLBCL accounts for >80% of all cases of LBCL and HGBL accounts for up to 13% of the LBCL cases.

The approved extension of the therapeutic indication "*Yescarta is indicated for the treatment of adult patients with diffuse large B cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy*" falls within the scope of the designated orphan condition "Treatment of diffuse large B-cell 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

In Europe, the 5-year overall survival (OS) is estimated to be between 50% and 60% (Le Guyader-Peydou et al., 2017; Sant et al., 2014; Székely et al., 2014; Issa et al., 2015) underscoring the life-threatening nature of the disease. While around 50% of newly diagnosed patients can be cured with the standard first-line immuno-chemotherapy R-CHOP/CHOEP, prognosis remains particularly poor in those patients being refractory to first-line treatment (about 10-15%), with an OS of less than 1 year. In addition, patients with double-hit lymphoma or MYC and BCL-2 protein double-expressor lymphomas are associated with poorer response to standard immuno-chemotherapy with a median OS of less than 12 months (Petrich et al., 2014; Tumati et al., 2018). Poor outcomes are also observed among patients who are ineligible for stem cell transplantation (SCT) (median OS: 6 to 11 months) or have refractory disease after any line of treatment (median OS: 6.1 to 7.1 months) (Arcari et al., 2016; Crump et al., 2017; Czuczman et al., 2017).

The sponsor has not identified any changes in the seriousness of the proposed condition since the orphan designation (OD) in 2014 and the maintenance of the OD criteria at the time of marketing authorisation in 2018. The COMP has previously acknowledged that the clinical course of DLBCL (including HGBL) can be chronically debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia, and life-threatening in patients not responding to treatment. The severe nature of the orphan condition earlier accepted by the COMP remains acceptable for this procedure.

Number of people affected or at risk

The sponsor has conducted a literature search as well as accessing registry data to establish the prevalence of DLBCL (including HGBL) in Europe: i) European cancer registries such as International Agency for Research on Cancer (IARC; EU28 as defined by WHO; 2020 data), National Institute for Cancer Epidemiology and Registration (NICER; 2019 data), Association of Nordic Cancer Registries (ANCR: Denmark, Sweden, Finland, Norway, and Iceland; 2018 data), and Haematological Malignancy Research Network (HMRN: Yorkshire region in the UK; 2004-2016 data), ii) online data platforms: Global Burden of Disease (GBD; EU28; 2019 data), and iii) databases: Medline and Google Scholar. Apart from for HMRN, all other sources reported the prevalence of NHL. The DLBCL prevalence was therefore indirectly calculated using the reported NHL prevalence. The sources used are summarized in the table below:

Table 1. List of sources and reported NHL prevalence rate estimates, sorted by reporting year

Source, Region	Year	Prevalence rates, per 10,000 persons	
		1 year	5 year
Publications			
Colonna et al, France	2002, Female	NR	2.9
	2002, Male	NR	3.8
Mitchell et al, Italy	2006, Female	NR	6.4
	2006, Male	NR	7.6
	2006, All	NR	6.9
Online Epidemiological data sources			
HMRN, United Kingdom	2017, Age and Sex standardised	1.8*	6.7*
ANCR, Nordic countries	2018, Female	1.5	6.6
	2018, Male	1.9	8.1
NICER, Switzerland	2019, Crude	1.7	6.7
GBD, Europe	2019, Crude	6.9	NR
	2019, Age and Sex standardised	4.1	NR
IARC, Europe	2020, Crude	1.3	5.2

HMRN, Haematological Malignancy Research Network; ANCR, Association of Nordic Cancer Registries; NICER, National Institute for Cancer Epidemiology and Registration; NR, Not reported; GBD, Global Burden of Disease; IARC, International Agency for Research on Cancer; std, standardized.
*Age and/sex standardized estimates

The sponsor proposed a DLBCL prevalence estimate that was indirectly calculated using the highest reported proportion of DLBCL (including HGBL) among NHL cases in Europe of 47.8% based on 2004 to 2012 data from HMRN in the UK (Smith et al., 2015) and the highest reported 5(1)-year NHL prevalence (6.9 per 10,000) in Europe derived from GBD 2019 data. The assumptions produce a final calculation for the prevalence estimate of 3.3 per 10,000 persons in the European Union (EU). The sponsor emphasised that the proposed calculation of the prevalence included patients with HGBL. The sponsor did not consult available data from the European Cancer Information System (ECIS) database.

In a recent submission, the COMP noted that if the population-based weighted incidence of DLBCL to the ECIS estimate of crude NHL incidence (1.94 per 10,000) for the 27 EU countries (EU27) is applied, the estimated proportion of DLBCL among the overall NHL population is 35.6%. The COMP also noted that the OS for DLBCL is expected to be higher than 5 years and that a 5-year partial prevalence therefore is considered insufficient. Recent estimates that have been considered generally have taken the assumption that 10 years survival data should be used indicating that the prevalence is higher than the estimate of 3.3 in 10,000 as currently presented.

The sponsor was requested to provide a more current estimate based on relevant and comprehensive data sources in Europe, including ECIS, a DLBCL percentage within all NHL cases more in line with the COMP's current understanding of approximately 35% and a 10-year disease duration.

In the revised prevalence estimate the sponsor has used data sources as recommended by the COMP, including ECIS incidence data for 2020, and applied both direct and indirect approaches to estimate the current DLBCL prevalence in the Europe community.

Direct method

A review of published literature and relevant online databases was conducted to search for 5-year or higher prevalence estimates for DLBCL from studies published during 01-Jan-2012 through 06-Jun-2022. Only studies examining individuals residing in the EU countries were considered.

The reported DLBCL prevalence estimates ranged from 2.13 to 2.84 per 10,000 for a 5-year partial prevalence and 4.21 to 4.62 per 10,000 persons for a 10-year partial prevalence.

Table 2. Sources of data for direct prevalence estimates of DLBCL

Source	**Country or Region**	**Study Years**	**5-year Prevalence Estimate (per 10,000)**	**10-year prevalence Estimate (per 10,000)**	**15-year prevalence Estimate (per 10,000)**
Smith, 2015 {Smith 2015}	UK	2004-2014	2.59	4.33	not reported
Ekberg, 2020 {Ekberg 2020}	Sweden	2000-2016	2.84	4.62	not reported
The Haematological Malignancy Research Network (HMRN) [1] [a]	UK	2006-2016	2.62	4.22	not reported
RARECARENet Information Network on Rare Cancers [2] [b]	EU	1993-2007	not reported	not reported	2.78
NORDCAN [3] [c]	EU (Nordic region)	2020	2.56	4.29	not reported
Robert Koch Instituted [4] [d]	Germany	2018	2.54	4.21	not reported
REDECAN [5] [e]	Spain	2020	2.13	not reported	not reported

a Estimate based on sum of prevalences of Diffuse large B-cell lymphoma (DLBCL), Not otherwise specified (NOS); Tcell/histiocyte-rich large B-cell lymphoma; Primary diffuse large B-cell lymphoma of the central nervous system; Primary cutaneous DLBCL, leg type; Primary mediastinal large B-cell lymphoma; Plasmablastic lymphoma; age and sexstandardized.
b Estimate for diffuse B-lymphoma; complete prevalence.
c Pooled data from Nordic cancer registry (containing information from Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, Sweden). Kite applied an EU weighted average ratio of DLBCL to NHL (34.2%) to the prevalence proportion for the year 2020 {Kanas 2022}.

[1] The Haematological Malignancy Research Network. From: https://hmrn.org/statistics/prevalence. Accessed on 06 June 2022.
[2] RARECARENet Information Network on Rare Cancers. From: http://www.rarecarenet.eu/rarecarenet/. Accessed on 06 June2022.
[3] NORDCAN Association of Nordic Cancer Registries. From https://nordcan.iarc.fr/en. Accessed on 15 July 2022.
[4] Zentrum Fur Krebsregisterdaten, Robert Koch Institute, From https://www.krebsdaten.de/Krebs/EN/Home/homepage_node.html. Accessed on 15 July 2022.
[5] REDECAN, Spanish Network of Cancer Registries. From https://redecan.org/en. Accessed on 15 July 2022.

d Based on applying German DLBCL to NHL ratio (32.4%) {Kanas 2022} to the total NHL reported prevalence cases in 2018 for each period, divided by the 2018 population in Germany.
e Based on applying Spanish DLBCL to NHL ratio (32.5%) {Kanas 2022} to the total NHL reported prevalence cases in 2020 at 5 years (n=31,052), divided by the 2020 population in Spain.

The publication by Smith and colleagues used an older set of data (2004-2014) from the HMRN (Smith et al., 2015) than the most current estimates that are available (2006-2016). Results of 5- and 10-year DLBCL prevalence were nearly identical across the data sets. The cancer prevalence estimates provided include all those who have ever been diagnosed with DLBCL, regardless of whether they have been cured or not. Most national registries report prevalence on NHL, and the sponsor used the recent publication by Kanas and colleagues on the DLBCL to NHL ratio to derive the prevalence (Kanas et al., 2022).

Indirect method

The sponsor indicated that previously published studies examining the prevalence of DLBCL are limited, however, prevalence could be retrieved from a NHL estimate. Hence, to supplement the direct estimates, the sponsor has derived DLBCL prevalence by using a recently published incidence estimate in combination with disease duration.

Using data from the ECIS, the 2020 crude incidence of NHL in the EU27 was 1.94 per 10,000 persons. The sponsor emphasised that the reported percentage of NHL cases that are DLBCL varies in the literature. According to Dotlic and colleagues, DLBCL frequency in NHL was more common in South-eastern Europe (39%) than in Western Europe (28.3%) (Dotlic et al., 2015). While most of the publications found report that around 30% of all NHL cases in Europe are DLBCL (Perry et al., 2016; Thandra et al., 2021), Smith and colleagues reported that DLBCL constitutes 47.8% of all NHL cases (Smith et al., 2015). A recently published article by Kanas and colleagues estimated the distribution of NHL subtypes using data from the peer-reviewed literature and reported that the weighted average for DLBCL across the EU was 34.2% (out of total NHL cases) (Kanas et al., 2022). Given the percentage of DLBCL among all NHL cases reported in the literature varied, the sponsor calculated a range of DLBCL incidence estimates based on the lowest (28.3%) and highest (47.8%) reported values. The estimated incidence of DLBCL thus ranged from 0.549 (1.94 x 28.3%) to 0.927 (1.94 x 47.8%) per 10,000 persons in the EU.

Concerning the estimate for the disease duration, the sponsor proposed to use a conservative 5-year duration of the condition for the calculation of the prevalence estimate based on certain assumptions. It was noted that more than 50% of DLBCL patients with complete remission after first-line SOC treatment with R-CHOP will be considered cured 2 years after diagnosis (Habermann et al., 2006; Jakobsen et al., 2017; Maurer et al., 2014; Pfreundschuh et al., 2011) and that these patients should not be included in the disease duration calculation after this point. The remaining patients will either be refractory to first-line treatment or have a relapse after initial response. According to published real-world studies that were reviewed, the 5-year OS for patients with r/r DLBCL is less than 50% (Rovira et al., 2015; Abu Sabaa et al., 2021; Vardhana et al., 2017). Among patients with relapse, the majority will manifest within 2 years of diagnosis (79%) (Harrysson et al., 2021). Recent approvals of polatuzumab vedotin (Polivy) or CAR-T cell therapies have not been reported to have had a clinically relevant effect on OS (Sermer et al., 2020, Tilly et al., 2022). Based on the above-mentioned, the sponsor concluded that the maximum duration of DLBCL is 5 years.

Using the standard formula P=I*D, both the low and high estimates for the DLBCL incidence, and a conservative 5-year duration of the condition for the calculation, the updated prevalence of DLBCL was estimated to span between 2.8 (0.549 x 5 years) and 4.6 (0.927 x 5 years) per 10,000 persons in the EU. No sensitivity analysis was conducted as requested because the sponsor used the highest reported

DLBCL to NHL ratio found in the literature for the estimate and a conservative duration of the disease, and therefore considered the upper bound as an overestimate.

Based on the review of the epidemiological data sources found, the sponsor concluded on a revised 5-year prevalence estimate for DLBCL of **4.6 per 10,000** persons in the EU. The proposed estimate was based on a disease duration of maximum 5 years for the whole DLBCL population, which is considered rather low, and the highest reported proportion of DLBCL among NHL cases in Europe of 47.8% (Smith et al., 2015). The COMP has recently accepted a 10-year disease duration for DLBCL and agreed that a 10-year partial prevalence is appropriate to use in the prevalence estimate to reflect the impact of improved survival of DLBCL patients in recent years. Furthermore, the proportion of DLBCL among all NHL cases reported by Smith and colleagues, which was used for the revised estimate, seemed to be rather high as most of the publications found reported that DLBCL constitutes around 30-35% of all NHL cases in Europe.

The revised estimate is slightly higher than those accepted in recent designations for DLBCL seen recently where it has been concluded that the condition is affecting around 4-4.3 per 10,000 people in the European community. In one of the latest orphan maintenance procedures seen where an average 10-year prevalence estimate for DLBCL was provided, a prevalence of **4.3 per 10,000** persons in the EU was concluded based on more current publications and updated registries (EMA/OD/0000074173). The latter estimate is in line with the 10-year prevalence reported by NORDCAN and was therefore considered for this maintenance procedure as well based on current knowledge of the COMP.

The COMP concluded that a prevalence of **4.3 in 10,000** persons in the community was within the range proposed by the sponsor and agreed to recommend maintaining the orphan designation.

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 referred to the latest European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up of DLBCL, which describe some of the treatment strategies available to these patients in Europe and outlined the current standard of care (SOC) in the first- and second-line setting based on European and American treatment guidelines as summarised below (Tilly et al., 2015; NCCN 2021). The sponsor has also provided an extensive list of existing treatment regimens used for DLBCL and focused on the approved therapies for DLBCL, including the more recently approved products that have been authorised in the EU after 2015 and are therefore not included in the current ESMO guidelines.

The standard-of-care therapy for DLBCL involves multi-agent chemotherapy with complimentary mechanisms of action combined with immunotherapy. Up to 6-8 cycles of R-CHOP (the anti-CD20-directed monoclonal antibody rituximab + CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisolone]) which is administered every 21 days (CHOP-21) or CHOP-like chemotherapy are considered to be the SOC for patients with previously untreated DLBCL. Roughly 20-40% of the patients ultimately relapse to R-CHOP, and approximately 10-15% are refractory to R-CHOP as first-line therapy (i.e., have primary refractory disease) (Chaganti et al., 2016; Green et al., 2012). The CD79b targeted antibody-drug conjugate polatuzumab vedotin was also recently granted a new indication in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for

the treatment of adult patients with previously untreated DLBCL (Polivy; MA extension: 24/05/2022, Procedure No. EMEA/H/C/004870/II/0012).

Medicinal products and standard of care used as second-line therapy

Yescarta (axicabtagene ciloleucel; hereinafter referred to as axi-cel) was approved in the EU (Procedure No. EMEA/H/C/004480) on 23-aug-2018 and is authorised for the treatment of adult patients with relapsed or refractory (r/r) DLBCL who have received two or more lines of systemic therapy. This indication extension of Yescarta is intended to include treatment of adult patients with DLBCL and HGBL in the second line setting who are refractory to or have relapsed early after first line chemoimmunotherapy. An overview of SOC treatments and medicinal products authorised within the EU for r/r DLBCL and NHL (Table 1), and whether they are considered relevant for a discussion on the significant benefit of axi-cel (Yescarta) in second-line r/r DLBCL and HGBL is presented below.

In patients progressing or relapsing after first-line treatment, the ultimate treatment goal is autologous SCT (ASCT) for those who are eligible. This is a potentially curative treatment, significantly improving the disease-free survival and OS. However, ASCT requires high doses of chemotherapy, and is therefore not an option for vulnerable elderly patients or patients with co-morbidities. Only 50% of relapsed patients can proceed to ASCT, mostly due to insufficient response to salvage chemotherapy or stem cell collection failure (Gisselbrecht et al., 2010; Kondo et al., 2016; Van Den Neste et al., 2016), and it cannot therefore be considered a satisfactory method for the entire patient population for which Yescarta is intended to treat in second line.

According to the ESMO guidelines, recommendations for patients who are not eligible for transplant in first relapse mainly include platinum- and/or gemcitabine-based regimens or recruitment to clinical trials with novel drugs. None of the medicinal products recommended by the ESMO guidelines is specifically approved as a second-line treatment for patients with DLBCL (including HGBL), but rather for broader indications such as for the treatment of NHL and malignant lymphomas. These medicines include bendamustine, bleomycin, carmustine, chlorambucil, cyclophosphamide, doxorubicine, etoposide, iphosphamide, lomustine, melphalan, methotrexate, mitoxantrone, vincristine, vindesine, dexamethasone, prednisolone, and methylprednisolone. Since the approved therapeutic indications for these products are very broad, they completely overlap with the indication extension of Yescarta and therefore are considered satisfactory methods of treatment relevant for a discussion on the significant benefit of axi-cel in r/r DLBCL and HGBL.

Table 3. Approved products for the treatment of adults with DLBCL and HGBL within the Community

EU Centralised number; MA	Product name (INN)	Approved therapeutic indication	Significant benefit discussion needed
EMEA/H/C/000165; 02/06/1998	MabThera (rituximab)	MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.	No, it is only approved in combination with CHOP, which is the prevailing standard of care in first line treatment, and for which patients eligible for Yescarta must have failed as first-line chemoimmunotherapy
EMEA/H/C/002055; 10/05/2012	Pixuvri (pixantrone dimaleate)	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply r/r aggressive NHL. 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.	No, covers only patient with r/r NHL in later lines
EMEA/H/C/004090; 23/08/2018	Kymriah (tisagenlecleucel)	Kymriah is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy.	No, covers only patient with r/r DLBCL in later lines
EMEA/H/C/004731; 04/04/2022	Breyanzi (lisocabtagene maraleucel)	Breyanzi is indicated for the treatment of adult patients with r/r DLBCL, primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.	No, covers only patient with r/r DLBCL in later lines
EMEA/H/C/004870; 16/01/2020	Polivy (polatuzumab vedotin)	Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with r/r DLBCL who are not candidates for haematopoietic SCT.	No, covers only r/r DLBCL patient who are ineligible to HSCT
EMEA/H/C/005436; CMA 26/08/2021	Minjuvi (tafasitamab)	Minjuvi is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with r/r DLBCL who are not eligible for ASCT.	No, covers only r/r DLBCL patient who are ineligible to ASCT

MA: marketing authorisation; CMA: conditional MA; SCT: stem cell transplant; ASCT: autologous SCT

Significant benefit

The sponsor argued that axi-cel represents an important new therapeutic option for the treatment of adult patients with r/r DLBCL and HGBL based on the magnitude of improvements in event-free

survival (EFS), progression-free survival (PFS), and objective response rate (ORR) observed in the pivotal study ZUMA-7, which is anticipated to provide a significant benefit compared to currently available treatments for the target patient population in the second line setting.

The primary data supporting the efficacy and safety of axi-cel in the concerned extension of indication are obtained from an ongoing, randomized, open label, multicenter phase 3 study called ZUMA-7 (also known as KTE-C19-107). The study is designed to evaluate the efficacy and safety of axi-cel versus standard of care therapy (SOCT) in subjects with r/r LBCL, including DLBCL and HGBL disease subtypes. Subjects with r/r LBCL whose tumours progressed after first line rituximab and anthracycline based chemotherapy were randomized in a 1:1 ratio to receive axi-cel (N=180) or SOCT (N=179; i.e., salvage chemotherapy followed by high dose chemotherapy [HDCT] and ASCT). Randomization was stratified by response to first line therapy (primary refractory, relapse ≤ 6 months of first line therapy, or relapse > 6 and ≤ 12 months of first line therapy) and second-line age adjusted International Prognostic Index (sAAIPI) (0 to 1, or 2 to 3), as assessed at the time of screening. Subjects randomized to the axi-cel arm of the study underwent leukapheresis, optional steroid bridging therapy, and lymphodepleting chemotherapy, followed by a single IV infusion of axi-cel at a recommended target dose of 2×10^6 anti-CD19 CAR-T cells/kg. For patients weighing greater than 100 kg, a maximum flat dose of 2×10^8 anti-CD19 CAR-T cells was administered. For subjects randomized to the SOCT arm, treatment consisted of a protocol-defined, platinum-based salvage chemotherapy regimen as selected by the treating investigator. Subjects who responded to salvage chemotherapy and were deemed eligible for transplant proceeded to HDCT and ASCT, whereas subjects not responding to salvage chemotherapy could receive additional treatment off protocol.

As of the data cut off (DCO) date of 18-mar-2021 for the primary analysis of ZUMA-7, 170 subjects were treated with axi-cel and 168 subjects had received at least 1 dose of salvage chemotherapy in the SOCT arm. It is noted that most patients in the SOCT arm of ZUMA-7 received rituximab in combination with ifosfamide, carboplatin, and etoposide (R-ICE; 84 of 168 patients [50%]), followed by rituximab plus gemcitabine, dexamethasone, and cisplatin/carboplatin (R-GDP; 42 of 168 patients [25%]), rituximab combined with either cisplatin, dexamethasone, and high-dose cytarabine, or dexamethasone, cytarabine, and oxaliplatin (R-DHAP/ R-DHAX; 37 of 168 patients [22%]), and rituximab plus etoposide, methylprednisolone, cytarabine and cisplatin (R-ESHAP; 5 of 168 patients [3%]). These platinum- and/or gemcitabine-based regimens are commonly used in the second line setting and considered as satisfactory methods since at least one or two of the products used as part of these regimens are approved for the treatment of the target patient population for the concerned indication extension of Yescarta.

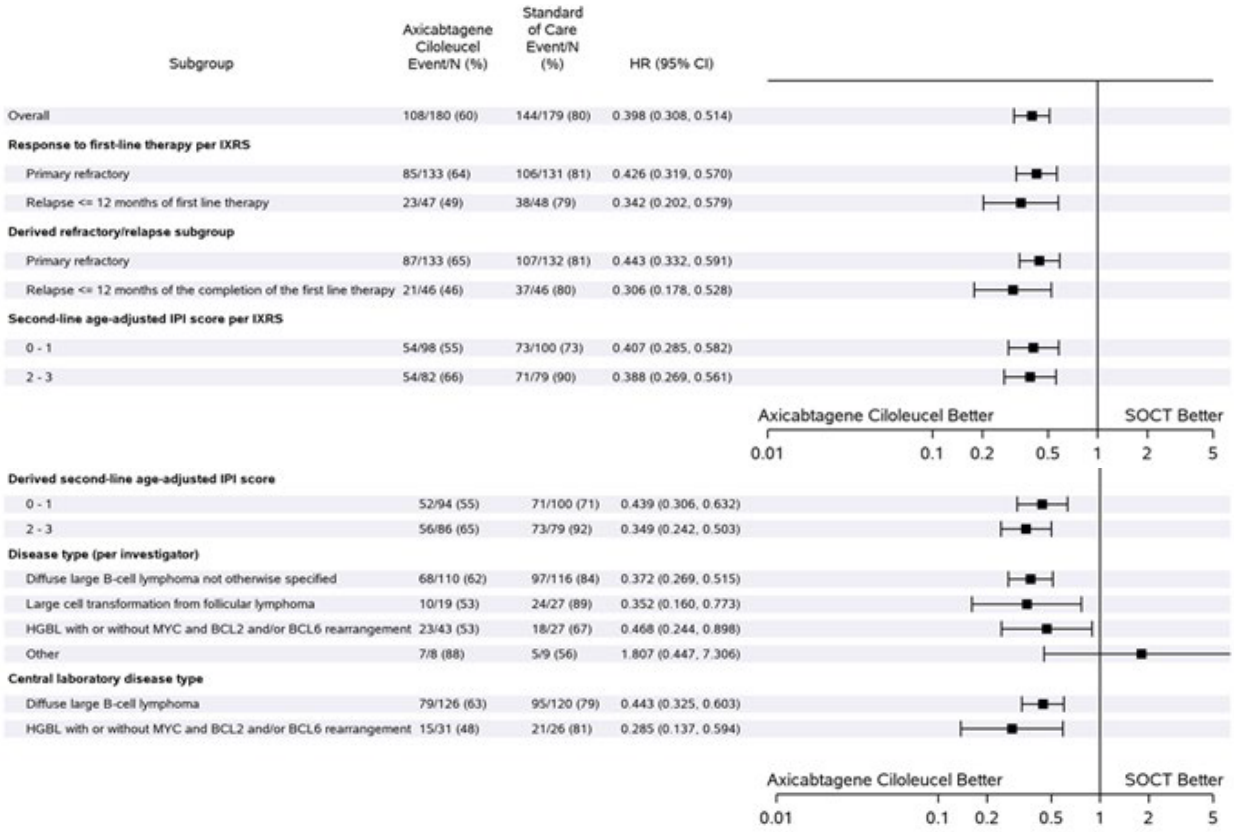
The primary objective of ZUMA-7 is to determine whether axi-cel is superior to SOCT, as measured by EFS determined by blinded central assessment. The primary endpoint of EFS is defined as the time from randomization to the earliest date of disease progression per Lugano 2014 Classification response criteria (Cheson et al., 2014) as determined by blinded central assessment, commencement of new lymphoma therapy, or death from any cause. EFS is an established time-to-event endpoint and is correlated with OS in DLBCL (Maurer et al., 2014).

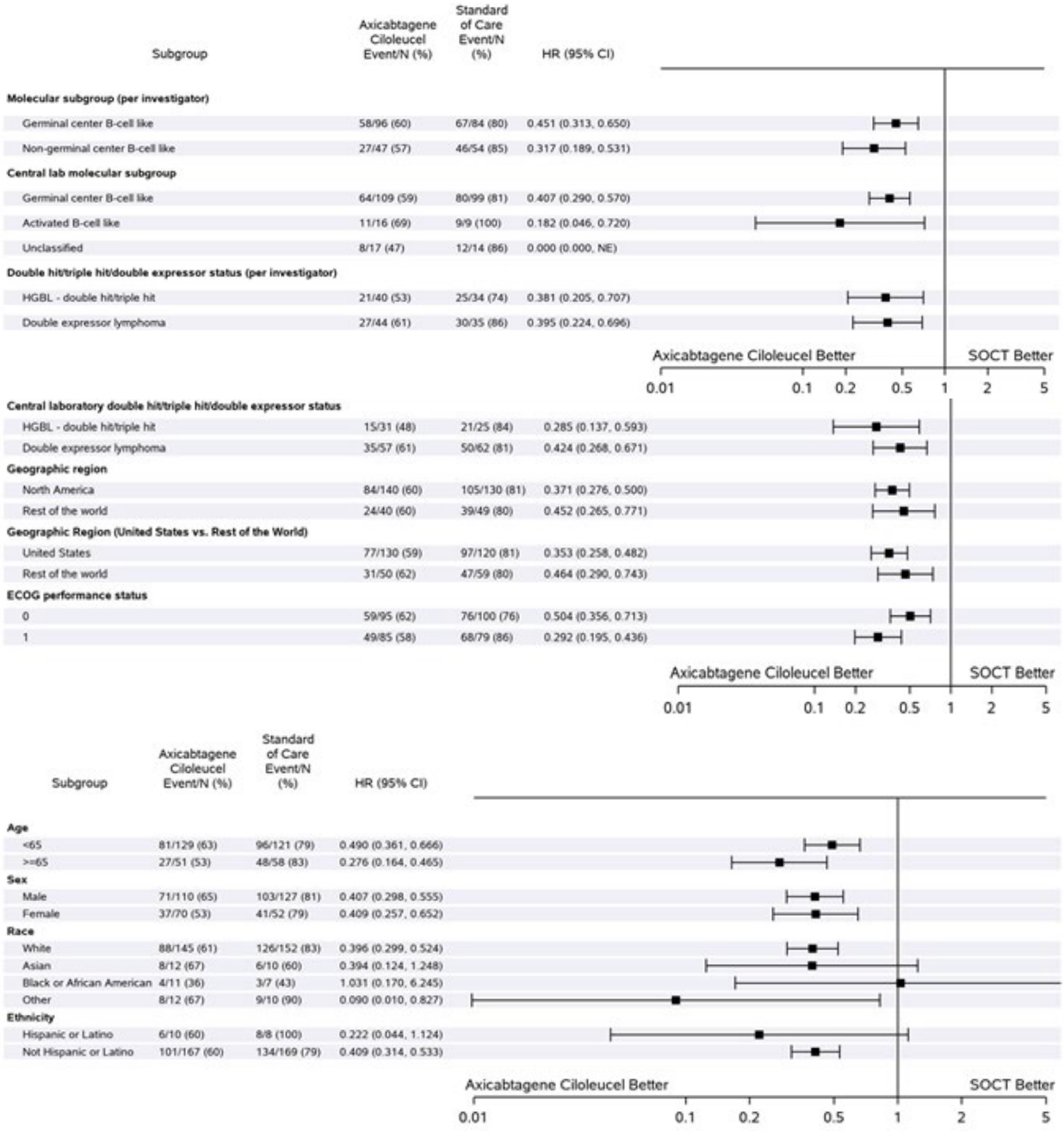
Overall, baseline characteristics were generally comparable between the two treatment arms. As categorized by the investigator, the most common disease type for subjects in both the axi-cel and SOCT arms were DLBCL, NOS (110 of 180 subjects [61%] and 116 of 179 subjects [65%], respectively), HGBL with or without MYC and BCL2 and/or BCL6 rearrangement (43 of 180 subjects [24%] and 27 of 179 subjects [15%], respectively), and large cell transformation from FL (19 of 180 subjects [11%] and 27 of 179 subjects [15%], respectively). Forty-four subjects (24%) in the axi-cel

arm and 35 subjects (20%) in the SOCT arm had double-expressor lymphoma as reported by the investigator.

The data from the primary analysis of ZUMA-7 (DCO: 18-mar-2021) demonstrated that for adult subjects with r/r LBCL, including subjects with DLBCL and HGBL subtypes, the risk of an EFS event was significantly reduced with axi-cel treatment compared with SOCT (stratified HR: 0.398 [95% CI: 0.308, 0.514]; stratified log-rank p < 0.0001). The EFS rate at 2 years was 2.5 times higher in the axi-cel arm compared with the SOCT arm, with a 6.3-month (i.e., 4.15-fold) improvement in median EFS time. EFS results showed HRs favouring axi-cel over SOCT across most subgroups, including subjects with HGBL or double-expressor lymphoma, primary refractory or early relapsed disease, high or low sAAIPI score, and all age groups including patients ≥ 65 years of age (Figure 1). Trends for subgroup analyses of EFS per randomization stratification factors (response to first-line therapy and sAAIPI and high-risk groups (HGBL) and age were similar to those observed for EFS per central assessment of response.

Figure 1. Forest Plot of EFS by Subgroups per Central Assessment (FAS)





Data Cutoff Date = 18MAR2021.
Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus, ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HGBL, high-grade B-cell lymphoma; HR, hazard ratio; IxRS, interactive voice/web response system; NE, not estimable; SOCT, standard of care therapy.
Notes: EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy (including stem cell transplant in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and/or second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via IxRS. Stratified Cox regression models are used to provide the estimated HR and 2-sided 95% CIs for axicabtagene ciloleucel relative to SOCT. The Breslow method is used to handle the ties for the Cox regression models. Disease type of "Other" includes T cell/histiocyte rich large B cell lymphoma, EBV + DLBCL, primary cutaneous DLBCL (leg type), and other types. HGBL – double hit is defined as presence of MYC and either BCL2 or BCL6 rearrangements; HGBL - triple hit is defined as presence of BCL2, BCL6, and MYC rearrangements; double-expressor lymphoma is defined as overexpression of MYC and BCL2 proteins not related to underlying chromosomal rearrangements. In subgroup for central lab molecular as unclassified, the number of subjects and/or number of events are sparse across stratification factors between the treatment arms and resulted in estimated HR < 0.00001.
Source: Figure 14.2.1.2.2.

The observed benefit of axi-cel in terms of the primary endpoint EFS was supported by the secondary endpoints. A statistically significant improvement in ORR was demonstrated with ORR rates of 83% in the axi-cel arm and 50% in the SOCT arm. Given that objective response is a prerequisite to reach HDCT and subsequent ASCT, the ORR translates into at least 50% of patients in the SOCT arm not being able to reach definitive therapy. The complete response (CR) rate was 2-fold higher in the axi-cel arm compared with the SOCT arm (65% versus 32%). The ZUMA-7 interim OS results suggested a trend favouring axi-cel (median OS had not been reached) over SOCT (median OS of 35.1 months). The median OS observed in the SOCT arm should be considered in the context of subsequent therapies. Although there was no planned crossover between treatment arms, 56% of patients in the SOCT arm received subsequent cellular immunotherapy after SOCT (i.e., treatment switching rate). Sensitivity analyses of OS that were pre-specified to account for the treatment switching rate were consistent with the OS results in the FAS and supported the positive trend of the OS benefit shown with axi-cel over SOCT.

The clinical data derived from ZUMA-7 demonstrate the capacity of axi-cel to prolong EFS and support the basis of significant benefit based on a clinically relevant advantage in terms of improved efficacy versus SOC for adult patients with DLBCL and HGBL in the second line setting who are refractory to or have relapsed early after first line chemoimmunotherapy.

4. COMP position adopted on 22 September 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 diffuse large B-cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia, and life-threatening in patients not responding to treatment;
- 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 an improvement in event free survival after treatment with Yescarta as compared to standard of care treatment in adult patients with relapsed or refractory diffuse large B-cell lymphoma including high-grade B-cell lymphoma in the second line setting.

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 diffuse large B-cell lymphoma (EU/3/14/1393) is not removed from the Community Register of Orphan Medicinal Products.