EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 August 2018
EMA/581378/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Kymriah (tisagenlecleucel)

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

Introductory comment

The therapeutic indications:

- “Paediatric and young adult patients up to 25 years of age with B cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post transplant or in second or later relapse”
- “Adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy”

fall within the scope of the two designated orphan conditions “B-lymphoblastic leukaemia/lymphoma” and “diffuse large B-cell lymphoma”.

1. Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 for treatment of B-lymphoblastic leukaemia/lymphoma EU/3/14/1266 (EMA/OD/187/13)

1.1. Product and administrative information

Product	
Active substance	Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19
International Non-Proprietary Name	Tisagenlecleucel
Orphan indication	Treatment of B-lymphoblastic leukaemia/lymphoma
Pharmaceutical form	Dispersion for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	other antineoplastic agents (Not yet assigned)
Sponsor's details:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited, United Kingdom
COMP opinion date	12 March 2014
EC decision date	29 April 2014
EC registration number	EU/3/14/1266
Post-designation procedural history	
Transfer of sponsorship	Transfer from Novartis Europharm Limited, United Kingdom, to Novartis Europharm Limited, Ireland – EC decision of 16 May 2018
Marketing authorisation	
Rapporteur / co-Rapporteur	R. Kjeken, C. Niederlaender
Applicant	Novartis Europharm Limited
Application submission date	2 November 2017
Procedure start date	23 November 2017
Procedure number	EMA/H/C/004090
Invented name	Kymriah
Therapeutic indication	Kymriah is indicated for the treatment of: Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. Further information on Kymriah can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports

CHMP opinion date	28 June 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	F. Naumann-Winter/ K. Penttila
Sponsor's report submission date	31 October 2017
COMP discussion	17-19 April 2018
COMP opinion date	19 July 2018

1.2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2014 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 was considered justified based on preliminary clinical data in patients;
- the condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukemic forms being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the tumour cells of the bloodstream, the bone marrow and/or the lymph nodes and other lymphatic organs, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage;
- the condition was estimated to be affecting approximately less than 1 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 lentiviral vector containing a chimeric antigen receptor directed against CD19 may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product was efficacious in patients who relapsed or were refractory to previous treatment in the condition. The Committee considered that this constitutes a clinically relevant advantage.

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

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

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

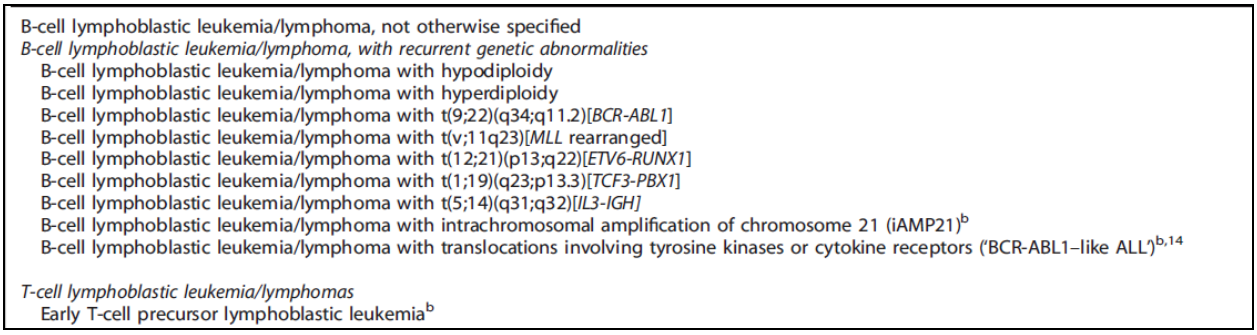
Condition

B-lymphoblastic leukaemia/lymphoma is a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood and extramedullary sites. While 80% of the condition occurs in children, it represents a devastating disease when it occurs in adults. The pathogenesis of B-lymphoblastic leukaemia/lymphoma involves the abnormal proliferation and differentiation of a clonal population of lymphoid cells. The hallmark of B-lymphoblastic leukaemia/lymphoma is chromosomal

abnormalities and genetic alterations involved in differentiation and proliferation of lymphoid precursor cells. (Blood Cancer Journal (2017) 7, e5770)

The WHO classification of B-lymphoblastic leukaemia/lymphoma is summarised below.

Figure 1.



Most of the clinical manifestations of B-lymphoblastic leukaemia/lymphoma reflect the accumulation of malignant, poorly differentiated lymphoid cells within the bone marrow, peripheral blood, and, extramedullary sites.

Diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood.

The therapeutic indication "*Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse"* falls within the scope of the orphan designation "*B-lymphoblastic leukaemia/lymphoma*".

Intention to diagnose, prevent or treat

Further to the CHMP opinion the intention to treat the orphan condition was considered justified. Please see EPAR - scientific discussion.

Chronically debilitating and / or life-threatening nature

The applicant has not identified any change in the seriousness of the condition. B-lymphoblastic leukaemia/lymphoma is a heterogeneous disease with outcomes dependent on patient age, mutational status and co-morbid conditions.

Regardless of prognostic factors, the likelihood of initial remission is ≥ 95% in children and 70 to 90% in adults. About 75% of children and 30 to 40% of adults have continuous disease-free survival for 5 years and appear cured. Patients with B-lymphoblastic leukaemia/lymphoma refractory to induction or re-induction chemotherapy have poor prognosis if they do not undergo haematopoietic stem cell transplantation (HSCT). With induction therapy, some patients achieve complete remission but the majority of patients relapse. The long-term event-free survival is only 30-35%.

Number of people affected or at risk

The sponsor has provided an extensive and comprehensive prevalence report for B-lymphoblastic leukaemia/lymphoma in Europe. They have access several national registries as well as RARECARENet. From this they offer total point prevalence and a partial 15-year prevalence for B-lymphoblastic leukaemia/lymphoma which is summarised below:

- In the RARECARENet database (http://app.rarecarenet.eu/)., the 15-year observed prevalence for B-lymphoblastic leukaemia/lymphoma (including Burkitt lymphoma, estimated to represent 5% of B-lymphoblastic leukaemia/lymphoma cases in this data source) was 1.18 per 10,000 persons (95% confidence interval 1.16-1.20) in the EU-28, Iceland, Liechtenstein, and Norway.
- The complete prevalence estimate for B-lymphoblastic leukaemia/lymphoma patients diagnosed in the EU-28, Iceland, Liechtenstein, and Norway at any time and alive on 01 January 2008 was 4.27 per 10,000 for the EU-28 and Liechtenstein, 2.46 per 10,000 for Iceland, and 2.38 per 10,000 for Norway.

Both proposed values are below the 5 in 10,000 threshold. The COMP decided to designate 1.2 per 10,000 in line with the RARECARENet 15-year prevalence figure.

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

At the time of designation in 2013 there were several products authorised in Europe for the condition: cyclophosphamide monohydrate, cytarabine, asparaginase, daunorubicin hydrochloride, doxorubicin hydrochloride, mercaptopurine, methotrexate, vincristine sulphate, clofarabine, dasatinib, imatinib, nelarabine, ponatinib.

Since then the sponsor has noted that several products have been authorised namely: inotuzumab ozogamicin, blinatumomab and 6-mercaptopurine monohydrate.

A specific European Guideline for the treatment and management of the condition has also been published by ESMO (Annals of Oncology 27 (Supplement 5):v69-v82, 2016). A paediatric guideline for the condition does not appear to exist although there are well written reviews of how to manage paediatric patients with the condition such as Pediatr Clin North Am. 2015 February ; 62(1): 61–73.

According to the current ESMO guidelines for ALL (*Annals of Oncology 27 (Supplement 5): v69–v82, 2016)* the treatment schedule can be summarised in the following manner:

- Newly diagnosed ALL: A pre-phase therapy with corticosteroids alone, or in combination with another drug (e.g. vincristine, cyclophosphamide), is often given together with allopurinol and hydration Remission induction therapy and consolidation treatment: Most regimens are centred on vincristine, corticosteroids, and anthracycline (daunorubicin, doxorubicin, rubidazone, idarubicin), with or without cyclophosphamide or cytarabine. L-Asparaginase is the only ALL-specific drug that depletes the asparagine levels.
- Maintenance therapy: Maintenance therapy usually consists of daily 6-mercaptopurine and weekly methotrexate. In some treatment regimens, repeated cycles of vincristine, dexamethasone or other drugs in monthly or longer intervals are given.
- Targeted therapy:
- The bispecific antibody blinatumomab combines single chain antibodies to CD19 and CD3, and thereby T cells lyse the CD19-bearing B cells. It is effective in patients with positive MRD or refractory/relapsed ALL. Stem-cell transplantation.

- Relapsed or refractory ALL: There is no universally accepted treatment protocol. For B-Cell Precursor ALL, blinatumuab and inotuzumab is indicated.
- Chemotherapy for relapsed ALL. The most commonly used regimens in Europe are fludarabine- and anthracycline-containing regimens, for example, FLAG-Ida (fludarabine, high-dose ara-C, granulocyte colony-stimulating factor and idarubicin).

Significant benefit

Three new products have been authorised since the sponsor's initial orphan designation. These are mercaptopurine, blinatumomab and inotuzumab ozogamicin. Only mercaptopurine is indicated for use in children. The other two are indicated for use in adults only.

Their respective indications are:

- Mercaptopurine: Xaluprine is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.
- Blinatumomab: BLINCYTO is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).
- Inotuzumab ozogamicin:" BESPONSA is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22- positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI)."

Kymriah has obtained the following indication: *"Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse"*

According to the ESMO Guidelines from 2016: "Relapsed ALL in adults is still a major clinical challenge. There is no universally accepted treatment protocol and a lack of evidence based on randomised, controlled trials. However, there is consensus on the general approach to managing these patients."

It is noted in paediatric patients that: *Despite significant advances in treatment, approximately 15% to 20% of patients with ALL will suffer relapsed disease, the most common cause of treatment failure. With intensive therapy that may include HSCT, overall survival from relapsed ALL is approximately 40%.* (*Pediatr Clin North Am. 2015 February ; 62(1): 61–73.)*

The sponsor claims that they will offer a clinically relevant advantage in paediatric and young adult patients who are refractory, in relapse post-transplant or in second or later relapse. To support this claim the sponsor has supported data from their main study CTL019B2202 (ELIANA).

The target patient population was aged 3 to 25 years and were: *primary refractory, chemo-refractory, relapsed after allogeneic SCT, or were otherwise ineligible for allogeneic SCT.* The average number of prior chemotherapy regimens was 3.4. With a median number of previous lines of treatment of 3, at least half of the patients were in their 3rd or 4th relapse. Median age at initial diagnosis was 7.5 years. Patients infused were between the ages of 3 and 23 years with 41.3% <10 years of age, 41.3% ≥ 10 to <18 years and 17.3% ≥ 18 years. These are patients for whom there is limited or no treatment and where there is currently an unmet need. The primary efficacy endpoint was overall response rate (ORR) during the 3 months following tisagenlecleucel administration per modified NCCN Guidelines for response in ALL as measured by IRC. The ORR is defined as the proportion of patients with a best overall disease response of complete response (CR) or CRi, where the best overall disease response is defined as the best disease response recorded from tisagenlecleucel infusion until the start of new anticancer therapy.

Secondary efficacy endpoints included duration of remission (DOR), relapse free survival (RFS), event-free survival (EFS) and overall survival (OS).

The results of obtained from this study showed the following for primary endpoint:

Table 1.

Interim efficacy analysis = 50 first patients who receive tisagnelecleucel infusion				
		n (%)	All patients N=50 95% CI	p-value
Best overall response (BOR)	CR CRi NR or unknown ORR: (CR+CRi)	34 (68.0) 7 (14.0) 9 (18.0) 41 (82.0)	(68.6, 91.4)	<0.0001 [1]
Full analysis set: 25-Apr-2017 cutoff				
		n (%)	All patients N=75 95% CI	p-value
Best overall response (BOR)	CR CRi No response Unknown (UNK) ORR: (CR+CRi)	45 (60.0) 16 (21.3) 6 (8.0) 8 (10.7) 61 (81.3)	(70.7,89.4)	<0.0001 [2]

[1] Indicates statistical significance (one-sided) at the 0.0057 level so that the null hypothesis that ORR ≤ 0.2 is rejected.
[2] No formal significance testing was conducted. Nominal p-value is presented.

Results of the B2202 study demonstrated that a single infusion with tisagenlecleucel shows a high increase of ORR in aggressive relapsed or refractory B-lymphoblastic leukaemia/lymphoma.

The table below helps to contextualise the effect size of Kymriah compared to treatments used in B-lymphoblastic leukaemia/lymphoma. Although the patient populations are not the same, as the Kymriah patients are chemoresistant and the patients in the other studies were chemosensitive, the overall survival of 19.1 months should be noted.

Table 2. Efficacy of available treatments for paediatric and young adult r/r ALL patients

	Clofarabine mono[1]	Clofarabine+ etoposide+ cyclo[2]	Clofarabine+ etoposide+ cyclo[3]	Blinatumomab[4]	CTL019 B2202[5]
Patients, N	61	25	17	70	75
≥3 prior regimens	62%	28%	NA	7%	60%
ORR (CR+CRi)	20%	44%	76%	39%	81.3%
Median OS	**3.0 months**	**2.5 months**	**9.0 months**	**7.5 months**	**19.1 months**
12 months OS	20%	30%	33%	40%	76.4%
Early mortality (within 30 days)	25%	20%	NA	7%	3%

1 Jeha 2006 2 Hijiya et al 2011 3 Locatelli et al 2009 4 von Stackelberg et al 2016
5 Full analysis set (FAS), all patients who received an infusion of tisagenlecleuce

The data submitted by the sponsor shows that Kymriah offers a clinically relevant advantage primarily in paediatric patients and young adult patients up to 25 years of age, who have already received 3 previous lines of therapy, who are refractory, in relapse post-transplant, or in second or later relapse. The COMP noted that there are no alternative treatments for this advanced stage of the disease in these patients. The significant benefit of Kymriah is therefore based on the clinical relevant advantage in this patient population and treatment setting.

1.4. COMP position adopted on 19 July 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of B-lymphoblastic leukaemia/lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be 1.2 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 depending on the response to treatment, with acute leukaemic forms being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the tumour cells of the bloodstream, the bone marrow and/or the lymph nodes and other lymphatic organs, resulting in the lack of normal blood cells, bone marrow failure, and specific organ damage;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Kymriah is of significant benefit in paediatric and young adult patients with B-lymphoblastic leukaemia/lymphoma who presented with primary refractory or chemo-refractory disease or relapsed after allogeneic SCT still holds. The sponsor has provided clinical data which shows improved outcomes compared to published data when their product was used as salvage in these patients who otherwise have a poor prognosis. The COMP was of the opinion 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 Kymriah, autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19, tisagenlecleucel, EU/3/14/1266 for treatment of B-lymphoblastic leukaemia/lymphoma is not removed from the Community Register of Orphan Medicinal Products.

2. Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 for treatment of diffuse large B-cell lymphoma EU/3/16/1745 (EMA/OD/087/16)

2.1. Product and administrative information

Product	
Active substance	Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19
International Non-Proprietary Name	Tisagenlecleucel
Orphan indication	Treatment of diffuse large B-cell lymphoma
Pharmaceutical form	Dispersion for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	other antineoplastic agents (Not yet assigned)
Sponsor's details:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited, United Kingdom
COMP opinion date	8 September 2016
EC decision date	14 October 2016
EC registration number	EU/3/16/1745
Post-designation procedural history	
Transfer of sponsorship	Transfer from Novartis Europharm Limited, United Kingdom, to Novartis Europharm Limited, Ireland – EC decision of 18 May 2018
Marketing authorisation	
Rapporteur / co-Rapporteur	R. Kjeken, C. Niederlaender
Applicant	Novartis Europharm Limited
Application submission date	2 November 2017
Procedure start date	23 November 2017
Procedure number	EMA/H/C/004090
Invented name	Kymriah

Therapeutic indication	Kymriah is indicated for the treatment of: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) 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/Find medicine/Human medicines/European public assessment reports
CHMP opinion date	28 June 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	F. Naumann-Winter/ K. Penttila
Sponsor's report submission date	31 October 2017
COMP discussion	17-19 April 2018
COMP discussion and adoption of list of questions	22-24 May 2018
Cancellation of oral explanation	17 July 2018
COMP opinion date	19 July 2018

2.2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 was considered justified based on preclinical data and preliminary clinical data showing antitumor activity of the proposed product;
- 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 less than 4.5 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 lentiviral vector containing a chimeric antigen receptor directed against CD19 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses in patients affected by the condition relapsing from previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

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

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

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

Condition

Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphoma (NHL), accounting for 30% to 40% of all newly diagnosed cases. It has an unknown aetiology. A family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors of DLBCL. (Annals of Oncology 26 (Supplement 5): v116–v125, 2015)

DLBCL occurs in adult patients, with a median age in the seventh decade, but the age range is broad, and it may also occur in children. Clinical presentation and prognosis are variable, depending mainly of the extranodal site when they arise. These malignancies present in localised manner in approximately 20% of patients. Disseminated extranodal disease is less frequent, and one third of patients have systemic symptoms (Critical Reviews in Oncology/Hematology 87 (2013) 146–171).

The 2016 revision of the World Health Organization classification of lymphoid neoplasms (Swerdlow et al, Blood 2016 127:2375-2390) makes additions to the DLBCL entity. In particular, DLBCL-NOS (with two further subtypes added compared to the previous 2008 version, Germinal center B-cell type, and activated B-cell type), Primary DLBCL of the CNS, Primary cutaneous DLBCL, EBV+DLBCL NOS (new modification), HHV8+DLBCL NOS (new addition), DLBCL associated with chronic inflammation, T-cell histiocytic rich large B cell lymphoma are all listed in the new classification. The therapeutic indication "*Adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy"* falls within the scope of the orphan designation "*diffuse large B-cell lymphoma*".

Intention to diagnose, prevent or treat

Further to the CHMP opinion the intention to treat the orphan condition was considered justified. Please see EPAR - scientific discussion.

Chronically debilitating and/or life-threatening nature

The applicant has not identified any change in the seriousness of the condition. In Europe, the 5-year overall survival is around 60% (Haematologica March 2017 102: 584-592). The COMP was of the opinion that the sponsor has provided sufficient evidence that the condition is life-threatening. The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow. Although the overall cure rate of DLBCL is 60-70%, about 30-40% of patients relapse and 10% have refractory disease. Refractory/relapsed DLBCL is a major cause of morbidity and mortality, with an expected mortality in <6 months. Mortality is also higher when the age or comorbidities limit tolerability of chemotherapy.

Number of people affected or at risk

The estimated age-standardised (to the European population) incidence rate reported by the sponsor was 6.60 (6.60–6.70) per 100,000 person-years.

The sponsor provided 5-year and 10-yearr survival rates from 17 different publications many of which are after 2010. The data presented range from the 1980s to as recent as 2014. From this compilation of publications the sponsor proposes an overall 5-year survival of ~45% and a 10-year survival between 20-37%. Recent publications report current estimates for 5-year survival in Europe of 60%. The survival rates proposed appear to be an under-estimate and this could be down to the mix of older publications with the newer ones. The literature reports that the introduction of rituximab has improved survival in these patients significantly, which the sponsor has not discussed (Pathology, (January 2018) 50(1),pp74-87;Ann Haemtol (2015)94:803-812). Data from several national and international registries were also presented. For example Globocan data from 2012 and the Rarecare report from 2014 are discussed. Each offers observations as to what the current partial prevalences of the condition could be in Europe. There is no discussion of point prevalence nor the complexities of the different subgroups and survival associated with them.

It was noted that the data from some of the national registries were more current than that derived from scientific publications submitted. From these national registries the sponsor reports for example a 10-year partial prevalence based on the Haematological Malignancy Research Network HMRN database in York UK of 4.63 per 10,000 [estimated from data on patients diagnosed from 2004 through 2014 (HMRN, 2015)]. A 15-year prevalence is reported from the AIRTUM group in Italy with 4.14 per 10,000 population (Italian cancer figures-Report 2015)

Both the UK and Italian data bases offer more recent insight than Rarecare, Globocan and other sources used. The COMP accepted the partial prevalence estimates from these national sources with the highest prevalence of 4.6 in 10,000 as reported by the HMRN database..

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

Several medicinal products are authorised for broader indications such as Non-Hodgkin lymphomas, and the COMP has previously considered them satisfactory in the treatment of DLBCL and should be considered for the purpose of significant benefit. These include cyclophosphamide, doxorubicine, bendamustine, bleomycin, vincristine, vindesine, etoposide, iphosphamide, chlorabucil, lomustine, prednisone, and prednisolone. Previously the COMP has also considered rituximab, docetaxel, mitoxantrone, methotrexate, epirubicin, dexamethasone, cytarabine, and pixantrone.

ESMO guidelines exist for the treatment of diffuse large B-cell lymphoma (Tilly et al. Ann Oncol (2015) 26 (suppl 5): v116-v125). Specifically for the relapsed refractory settings, which is the focus of this orphan maintenance procedure the following recommendations stand:

- In patients aged <65–70 years with good performance status and no major organ dysfunction, salvage regimens with rituximab and chemotherapy followed, in responsive patients, by HDC and ASCT, are recommended. Salvage regimens such as R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone) or R-ICE (rituximab, ifosfamide, carboplatin, etoposide) appear to have similar outcomes. R-GDP (rituximab, cisplatin, gemcitabine, dexamethasone) is also recommended in the

ESMO guidelines. BEAM (carmustine, etoposide, cytarabine and melphalan) is the most commonly used high-dose regimen.

- Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens as R-GEMOX (rituximab, gemcitabine, oxaliplatin). Pixantrone, is also discussed in these guidelines as an option in heavily pre-treated patients.

Table 3. R/R recommendations from Tilly et al. Ann Oncol (2015) 26 S5.

First relapse/progress	
Eligible for transplant	Not eligible for transplant
Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE, R-GDP) as salvage treatment For chemosensitive patients: R-HDCT with ASCT as remission consolidation Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor-risk factors at relapse	Platinum- and/or gemcitabine-based regimens Clinical trials with novel drugs
>2 relapse/progress	
Eligible for transplant	Not eligible for transplant
Allogeneic transplantation Clinical trials with novel drugs	Clinical trials with novel drugs Palliative care

Significant benefit

The sponsor has submitted data from study CTL019C2201 (JULIET) designed to support efficacy and safety of Kymriah in adult patients with r/r DLBCL. This is a single arm, open-label, multicentre Phase 2 study. Patient population was defined as adult patients ≥ 18 years with r/r DLBCL after ≥ 2 lines of chemotherapy and not eligible for SCT. The ESMO guidelines do not indicate that there is any recommended chemotherapy for these patients.

The COMP initially considered that the data from the Juliet study could be inconclusive regarding the clinically relevant advantage the product in this target patient population as the patients had previously received many different treatment regimens, which makes it difficult to identify a homogenous group of patients that could benefit. A significant benefit on the grounds of a major contribution to patient care was not supported by the Quality of Life data that was submitted.

In response to the COMP's concerns the sponsor further provided indirect historical comparisons to three studies namely SCHOLAR-1, PIX301 and CORAL. SCHOLAR-1 was an international, multicohort retrospective non-Hodgkin lymphoma research study, evaluating responses and OS rates in patients with refractory NHL, including DLBCL, transformed follicular lymphoma (TFL) and primary mediastinal B cell lymphoma (PMBCL).

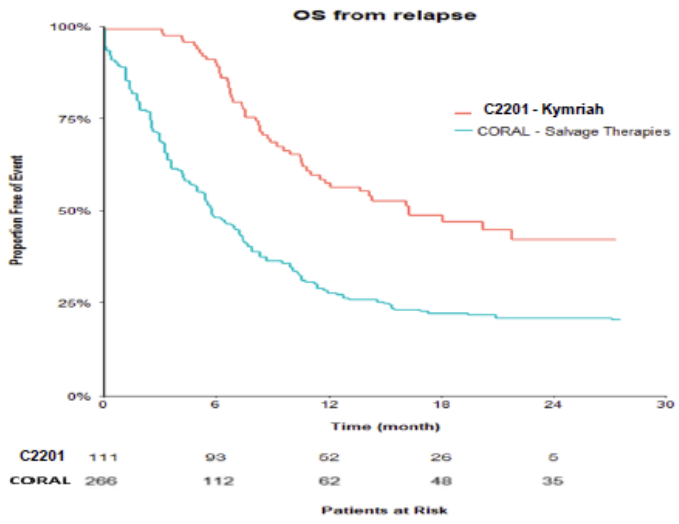
SCHOLAR-1 pooled data from the observational follow-up of 2 phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center (MDACC) and University of Iowa/Mayo Clinic (IA/MC) Lymphoma Specialized Program of Research Excellence). Only the published aggregated data for SCHOLAR-1 was submitted (Crump et al 2017).

The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study was a collaborative effort by 12 countries worldwide. Patients with refractory or relapsed CD20 DLBCL were randomly assigned to one of the following two widely used regimens that included rituximab: rituximab, ifosfamide, carboplatin, and etoposide (R-ICE)13 or rituximab, dexamethasone, high-dose cytarabine, and cisplatin(R-DHAP) (Gisselbrecht C et al 2010). CORAL consisted of pooled data from two extension studies in DLBCL patients, who relapsed after ASCT (n=75) and patients, who failed to proceed to per-protocol ASCT (n=203). ORR was 40.3% with CR 28.4%. Median OS from last relapse was 5.8 months (95% CI: 4.7, 7.2).

PIX301 was a randomised trial of pixantrone versus chemotherapy in patients with relapsed, aggressive non-Hodgkin's lymphoma. Patients with prior rituximab treatment use, who received pixantrone as third or fourth line treatment, were included. ORR was 30% with CR 20%.

Out of the three comparisons the indirect comparison between the Juliet (2201) and Coral offered the most relevant guidance on the clinically relevant advantage of using Kymriah in the treatment of advanced relapsed/refractory diffuse large B-cell lymphoma patients over the authorised counterparts. The sponsor conducted matching-adjusted indirect comparisons (MAICs) and used individual level data from C2201 to match baseline summary statistics reported from CORAL extensions. It was observed that the complete response rate observed in the Juliet study (40.6%) was in the range of what has been observed with other treatment modalities (28.4%, CORAL studies). However, the duration of response when compared to the CORAL study was considered remarkable, with more than 60% of responders still responding after a median follow-up of 19 months in patients treated with Kymriah. Overall, based on the response rate and duration of response, and given the available treatment options, the clinical benefit was considered established despite of the limitations of time-dependent endpoints in single arm trials.

Figure 2.



CORAL curve was truncated at the maximum follow-up for C2201

The COMP considered these findings represent a clinically relevant advantage in the treatment of a diffuse large B-cell lymphoma patient population thereby supporting the basis of significant benefit.

2.4. COMP position adopted on 19 July 2018

The COMP concluded that:

- 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 in 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 Kymriah may be of potential significant benefit to patients who have refractory diffuse large B-cell Lymphoma for whom there are very limited treatment options. The sponsor has provided clinical data which would support improved outcomes when their product was used as a third line treatment in these patients. In contrast with other treatment options with a potential for long-term improvement (HSCT), the treatment with the proposed product does not require the patients to obtain a response to chemotherapy. The COMP was of the opinion 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 Kymriah, autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19, tisagenlecleucel, EU/3/16/1745 for treatment of diffuse large B-cell lymphoma is not removed from the Community Register of Orphan Medicinal Products.