EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 August 2018
EMA/511556/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Yescarta (Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor)

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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Introductory comment:

The therapeutic indication refers to “the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy.” It is acknowledged that the therapeutic indication falls entirely within two of the granted orphan designations, “treatment of primary mediastinal large B-cell lymphoma”, and “treatment of diffuse large B-cell lymphoma”.

Yescarta for treatment of diffuse large B cell lymphoma EU/3/14/1393 (EMA/OD/171/14)

1. Product and administrative information

Product	
Active substance	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor
International Non-Proprietary Name	Axicabtagene ciloleucel
Orphan indication	Treatment of diffuse large B cell lymphoma
Pharmaceutical form	Suspension for injection
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	-
Sponsor's details:	Kite Pharma EU B.V Science Park 408 1098 XH Amsterdam The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Kite Pharma UK, Ltd
COMP opinion date	08 October 2015
EC decision date	11 November 2015
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 04 April 2017
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Jan Mueller-Berghaus, Claire Beuneu
Applicant	Kite Pharma EU B.V.
Application submission date	29 July 2017
Procedure start date	17 August 2017
Procedure number	EMA/H/C/004480
Invented name	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor
Therapeutic indication	YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Further information on Yescarta 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	K. Penttila/ I. Wang
Sponsor's report submission date	14 August 2017

COMP discussion and adoption of list of questions	19-21 June 2018
Oral explanation	17 July 2018
COMP opinion date	19 July 2018

1.1. Grounds for the COMP opinion at the designation stage

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor was considered justified based on preliminary clinical data showing 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.
- 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.

1.2. 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 refers to "the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL)" It is acknowledged that the therapeutic indication falls entirely within the granted orphan designation "treatment of 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, and referred to a study by Mounier and co-workers (Lancet Haematol. 2015 Nov;2(11):e481-91). In Europe, the 5-year overall survival is around 60% (Haematologica March 2017 102: 584-592).

The COMP acknowledged that the condition is chronically debilitating due to involvement of single or multiple nodal or extra nodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as 26% for the high risk patients. Although the overall cure rate of DLBCL is 60-70%, about 30-40% of patients relapse and 10% have refractory disease.

Number of people affected or at risk

For the number of people affected by the condition, an upwards-revised estimate for a point prevalence of 4.5 per 10,000 was proposed. This was calculated in three steps:

1. Crude incidence of all non-Hodgkin lymphomas as appearing in the European Cancer Information System (ECIS) portal, which is then:
2. Corrected by applying a 47.8% rate to account for DLBCL (as per Smith et al Br J Cancer. 2015 Apr 28;112(9):1575-84), and
3. Finally multiplied by 5 years which is assumed to be a measure for the duration of the condition. The latter duration appears to be based on a 46.3% 5-year survival rate (again per the Smith paper, Br J Cancer. 2015 Apr 28;112(9):1575-84).

The COMP acknowledged the estimate but also considered that the highest prevalence figure cited in the Smith paper was 4.55/10,000 (citing a 10-year partial prevalence in the range of 41.1–45.5) and an approximately 4.6 per 10.000 figure was considered for the purpose of maintenance.

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 1. 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

To address the issue of significant benefit in DLBCL, the applicant drew from the observations of the pivotal ZUMA-1 study and historical SCHOLAR-1 study, separated the observations pertaining specifically to DLBCL patients, discussed the received treatments and performed indirect comparisons of the results versus the existing products.

The pivotal study was KTE-C19-101 (ZUMA-1). ZUMA-1 enrolled subjects with refractory aggressive NHL (DLBCL, PMBCL, and Transformed follicular lymphoma) across multiple study centres. Phase 1 enrolled 7 subjects and identified a tolerable regimen for further study in Phase 2. Phase 2 comprises

of 3 cohorts: Cohorts 1 and cohort 2 have completed enrolment and Cohort 3 is currently enrolling subjects. Most subjects had stage III or IV disease and were refractory to second- or greater-line therapy; nearly half had International Prognostic Index (IPI) scores of 3 or 4. The outcomes for all enrolled patients can be summarised as follows (detailed results can be found in the Yescarta EPAR): the primary endpoint (superiority of ORR compared to a historic control ORR of 20%) was met in Phase 2 for Cohort 1 at the second interim analysis and subsequently in Cohorts 1 and 2 combined. Additionally, ORR among all 101 subjects treated in Phase 2 was 83% (95% CI: 74%, 90%), with a CR rate of 58%. The ORR among all 101 subjects based on central review was 72% (95% CI: 62%, 81%), with a CR rate of 51%, respectively. ORR in all 111 enrolled patients in Cohorts 1 and 2 was 77% (95% CI: 69%, 85%) with a CR rate of 55% per local investigator and 66% (95% CI: 56%, 75%) with a CR rate 47% per central reviewer. With regards to the controls used, SCHOLAR-1 was a patient pooled, retrospective analysis, which integrated data from 2 randomized Phase 3 studies (LYSARC-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational databases (MD Anderson Cancer Center and Mayo Clinic/University of Iowa Specialized Program of Research Excellence [SPORE]) of patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL), with refractory defined as progressive disease (PD) or stable disease (SD) < 6 months as best response to last line of chemotherapy (≥ 4 cycles of first-line or 2 cycles of later-line therapy) or relapse ≤ 12 months after autologous stem cell transplantation (ASCT).

Specifically for the demonstration of significant benefit in DLBCL, the sponsor presents data from ZUM-1 in patients with DLBCL and noted an ORR of 84% versus 26% in the control study. All subjects with DLBCL in SCHOLAR-1 received an anthracycline containing regimen and an anti-CD20 agent during first line therapy, while second line regimens consisted of platinum agents with an anti-CD20 agent and were predominantly comprised of ICE, DHAP, or GDP. In ZUMA-1, DLBCL patients were required to have received prior treatment with an anthracycline regimen and an anti-CD20, and the majority received a platinum-containing second line therapy. This comparison is depicted in the table below:

Table 2. Response rates and OS in Patients with DLBCL in ZUMA-1 (pivotal) and SCHOLAR-1 (control).

	ZUMA-1 (N= 93)	**SCHOLAR-1 (N=462)**
ORR (%) [95% CI]	84 (75, 91)	26 (22, 30)
CR (%)	57	9
Duration of Responsea, median (months) [95% CI]	8.1 (2.4, NR)	NA
Duration of Responsea, CR, median (months) [95% CI]	NR (11.1, NR)	NA
Overall Survival, median (months) [95% CI]	NR (11.5, NR)	6.6 (6.1, 7.6)
6 month OS (%) [95% CI]	79 (69, 86)	56 (51, 60)
12 month OS (%) [95% CI]	59 (49, 68)	28 (24, 32)
18 month OS (%) [95% CI]	50 (37, 61)	24 (20, 28)

[a] Minimum follow-up of 12 months with median follow up of 15.1 months.

It was also pointed out that the response rates in the pivotal trial compared favourably to pixantrone monotherapy (ORR of 40%) in heavily pretreated R/R aggressive non-Hodgkin lymphomas (Pettengel et al. Leukemia & Lymphoma, May 2012; 53(5): 836–841), and that there are no options specifically recommended after 2nd relapse in the ESMO guidelines.

Overall the COMP considered that 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 considered that this constitutes a clinically relevant advantage.

1.3. 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 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.

Yescarta for treatment of primary mediastinal large B-cell lymphoma EU/3/15/1553 (EMA/OD/078/15)

2. Product and administrative information

Product	
Active substance	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor
International Non-Proprietary Name	Axicabtagene ciloleucel
Orphan indication	Treatment of primary mediastinal large B-cell lymphoma
Pharmaceutical form	Suspension for intravenous injection
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	-
Sponsor's details:	Kite Pharma EU B.V Science Park 408 1098 XH Amsterdam The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Kite Pharma UK, Ltd
COMP opinion date	08 October 2015
EC decision date	11 November 2015
EC registration number	EU/3/15/1553
Post-designation procedural history	
Transfer of sponsorship	Transfer from Kite Pharma UK, Ltd to Kite Pharma EU B.V – EC decision of 04 April 2017
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Jan Mueller-Berghaus, Claire Beuneu
Applicant	Kite Pharma EU B.V.
Application submission date	29 July 2017
Procedure start date	17 August 2017
Procedure number	EMA/H/C/004480
Invented name	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor
Therapeutic indication	YESCARTA is indicated for the treatment of adult patients with primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. Further information on Yescarta can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/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	K. Penttila/ I. Wang

Sponsor's report submission date	14 August 2017
COMP discussion and adoption of list of questions	19-21 June 2018
Oral explanation	17 July 2018
COMP opinion date	19 July 2018

2.1. Grounds for the COMP opinion at the designation stage

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor was considered justified based on preliminary clinical data in patients affected by the condition who responded to treatment with the product as assessed by imaging;
- the condition is life-threatening due to relapses in 20-30% of patients who have poor prognosis and chronically debilitating in particular due to superior vena cava syndrome, night sweats, fever and weight loss;
- the condition was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made;.
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate radiological responses in relapsed/refractory patients with B-cell neoplasias, including primary mediastinal large B-cell lymphoma. The Committee considered that this constitutes a clinically relevant advantage.

2.2. 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

As regards any evolution of the underlying classification, the 2016 revision of the World Health Organization classification of lymphoid neoplasms (Swerdlow et al, Blood 2016 127:2375-2390) still includes the proposed condition in the list of mature B cell neoplasms.

PMBCL is regarded as unique B-cell lymphoma that is thought to arise from a putative thymic medulla B cell. It constitutes 2–4% of non-Hodgkin lymphomas and occurs most frequently in young females (Martelli 2014, Expert Review of Hematology, 8:2, 173-186). The tumour is often bulky, and symptoms are related to the mediastinal mass, frequently with superior vena cava syndrome. Spread to supraclavicular ad cervical nodes can occur, and absence of other node on marrow involvement is a prerequisite to exclude systemic DLBCL with secondary mediastinal involvement.

The therapeutic indication refers to “the treatment of adult patients with primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy.” It is acknowledged that the therapeutic indication falls entirely within the granted orphan designation“treatment of primary mediastinal 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 sponsor has not identified any change in the seriousness of the condition since the designation stage, and noted that patients with PMBCL vary in clinical presentation, prognosis, and response to current therapies. As with DLBCL, PMBCL is an aggressive lymphoma and if left untreated, results in survival of weeks to months (Cultrera and Dalia 2012). Patients with PMBCL often present with a bulky tumour in the anterior mediastinum that is rapidly progressive and gives rise to local compressive symptoms, including early dyspnoea, cough, dysphagia and compromising the airway or great vessels, producing a superior vena cava syndrome.

In line with the initial designation application, it was accepted that the condition is life-threatening due to relapses in 20-30% of patients who have poor prognosis and chronically debilitating in particular due to superior vena cava syndrome, night sweats, fever and weight loss.

Number of people affected or at risk

For the number of people affected by the condition, an estimate of approximately 0.45 per 10,000 was proposed based on the assumption that PMBCL accounts for up to 10% of DLBCL cases with reference to ESMO guidelines (Vitolo et al., Ann Oncol. 2016;27(suppl 5):v91-v1022016).

The DLBCL figure has been in turn estimated based on ECIS and HMRN data, as described in the corresponding section above (DLBCL). An approximately 0.5 per 10,000 estimate for PMBCL was consequently agreed.

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 designation stage, the COMP considered that products authorised for broader indications, including e.g. DLBCL or NHL indications, should be taken into consideration as existing authorised treatments.

As per the ESMO guidelines (Vitolo et al, Annals of Oncology, Volume 27, Issue suppl_5, 1 September 2016, Pages v91–v102), the combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) or with VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin)/MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin) (R-V/MACOP-B), dose-dense CHOP (R-CHOP14) or more intensive

regimens such as DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine cyclophosphamide, doxorubicin and rituximab) are the current standard treatments.

Consolidative mediastinal RT is recommended in responding patients treated with standard-dose chemoimmunotherapy (R-CHOP/R-V/MACOP-B). HDCT followed by ASCT is not recommended in patients who achieved complete remission, but in young patients who do not obtain an adequate response, an intensification therapy with HDCT/ASCT is recommended (Vitolo et al, Annals of Oncology, Volume 27, Issue suppl_5, 1 September 2016, Pages v91–v102).

In particular for relapsed/refractory PMBCLs, ESMO guidelines note that salvage treatment strategies of similar to nodal DLBCLs and include attempting reinduction with non-cross-resistant agents followed by consolidation with HDCT/ASCT in patients with chemosensitive disease.

Significant benefit

To address the issue of significant benefit in PMBCL, similarly to what was done for DLBCL, the applicant drew from the observations of the pivotal ZUMA-1 study and historical SCHOLAR-1 study, separated the observations pertaining specifically to PMBCL patients, discussed the received treatments and performed indirect comparisons of the results versus the existing products.

The sponsor clarified that all PMBCL subjects in SCHOLAR-1 received first line therapy containing an anthracycline and an anti-CD20 monoclonal antibody and received 2nd or later line therapy consisting of R-DHAP (6 subjects), R-GDP (2 subjects), R-GEMOX followed by R-DHAP (1 subject) and R-ICE followed by R-DHAP (1 subject). These regimens are consistent with the subjects with PMBCL enrolled into ZUMA-1 in the subjects with PMBCL treated in ZUMA-1 Phase 2, 6 out of 8 subjects (75%) responded, all of whom were complete responders, and median overall survival for these subjects has not been reached. Across all outcome measures, data are generally consistent with outcomes of ZUMA-1 subjects with DLBCL. This compares to a response rate of 20% in the 10 PMBCL subjects in SCHOLAR-1 (none of whom achieved complete response). Median overall survival was 7.7 months for PMBCL subjects in SCHOLAR-1. The following table describes the responses for PMBCL.

Table 3. Responses in PMBCL patients

	ZUMA-1 (N= 8)	**SCHOLAR-1 (N=10)**
ORR (%) [95% CI]	75 (35, 97)	20 (3, 56)
CR (%)	75	0
Duration of Response, median (months) [95% CI]	NR (11.1, NR)	NA
Duration of Response, CR, median (months) [95% CI]	NR (11.1, NR)	NA
Overall Survival, median (months) [95% CI]	NR (4.9, NR)	7.7 (4.3, NR)
6 month OS (%) [95% CI]	88 (39, 98)	60 (25, 83)
12 month OS (%) [95% CI]	75 (32, 93)	48 (16, 75)
18 month OS (%) [95% CI]	75 (32, 93)	48 (16, 75)

During the oral explanation further indirect comparisons between the above results were discussed. It was also pointed out that the response rates in the pivotal trial compared favourably to pixantrone monotherapy (ORR of 40%) in heavily pretreated R/R aggressive non-Hodgkin lymphomas (Pettengel et al. Leukemia & Lymphoma, May 2012; 53(5): 836–841), and that there are no options specifically recommended after 2nd relapse in the ESMO guidelines, similarly to what was discussed for DLBCL (see corresponding section above).

Overall the committee considered that the sponsor has provided clinical data showing responses in patients with relapsed or refractory PMBCL, which compare favourably to responses with existing treatments in historical controls. The COMP considers that this constitutes a clinically relevant advantage.

2.3. 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 primary mediastinal large b-cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to relapses in 20-30% of patients who have poor prognosis and chronically debilitating in particular due to superior vena cava syndrome, night sweats, fever and weight loss;
- 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 primary mediastinal 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/3/15/1553 for Treatment of primary mediastinal large B-cell lymphoma is not removed from the Community Register of Orphan Medicinal Products.