4 April 2022
EMADOC-1700519818-808606
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Breyanzi

Sponsor: Bristol-Myers Squibb Pharma EEIG

Note

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

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1. Introductory comment

The marketing authorisation of Breyanzi was associated with three orphan designations in the following conditions:

- Treatment of diffuse large B-cell lymphoma EU/3/17/1890
- Treatment of follicular lymphoma EU/3/18/2018
- Treatment of primary mediastinal large-B-cell lymphoma EU/3/18/2099

The three orphan maintenance assessments are covered in this one document. Of note, the sponsor of the designations withdrew all three orphan designations for Breyanzi prior to COMP final opinion.

2. Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor (lisocabtagene maraleucel)

EU/3/17/1890

2.1. Product and administrative information

Product	
Designated active substance(s)	Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor
Other name(s)	-
International Non-Proprietary Name	Lisocabtagene maraleucel
Tradename	Breyanzi
Orphan condition	Treatment of diffuse large B-cell lymphoma
Sponsor's details:	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 D15 T867 Dublin 15 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Celgene Europe B.V. - The Netherlands
COMP opinion	15 June 2017
EC decision	17 July 2017
EC registration number	EU/3/17/1890
Post-designation procedural history	
Transfer of sponsorship	Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 12 February 2019 Transfer from Celgene Europe B.V. to Bristol-Myers Squibb Pharma EEIG – EC decision of 21 January 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Concetta Quintarelli/ Claire Beuneu
Applicant	Bristol-Myers Squibb Pharma EEIG
Application submission	29 June 2020
Procedure start	16 July 2020
Procedure number	EMA/H/C/004731
Invented name	Breyanzi

Proposed therapeutic indication	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after two or more lines of systemic therapy. Further information on Breyanzi can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi
CHMP opinion	27 January 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
Sponsor's report submission	27 July 2020
COMP discussion and adoption of list of questions	18-20 January 2022
Oral explanation	15 February 2022
Sponsor's removal request	16 February 2022

2.2 Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 17 July 2017 designation was based on the following grounds:

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 CD4+ and CD8+ T cells expressing a CD19-specific CAR was considered justified based on clinical data showing that complete responses (CRs) may be achieved in patients with disease relapsed and refractory to the second line treatment;
- 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;
- the condition was estimated to be affecting approximately 4.3 in 10,000 persons in the EU, 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 CD4+ and CD8+ T cells expressing a CD19-specific CAR will be of significant benefit to those affected by the condition. The Sponsor has provided clinical data that demonstrate that patients who are relapsed and refractory to the second line (2L) treatment achieved either partial or complete responses. The overall response rate compared favourably at 3 months of treatment to that of the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

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

The sponsor is proposing that diffuse large B-cell lymphoma continues to be an orphan condition. Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin's lymphoma (NHL) accounting for about 35% of NHL and 80% of aggressive lymphomas.

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. Histologic transformation of FL to DLBCL (TFL) occurs in approximately 15% of patients and is generally associated with a poor clinical outcome.

Most cases of DLBCL appear to result at least in part from the stepwise development of gene changes such as mutations, altered expressions, amplifications (i.e. increases in the number of copies of specific genes), and translocations from normal sites to other chromosomal sites. These changes often result in gains or losses in the production or function of the product of these genes and thereby the activity of cell signalling pathways that regulate the maturation, proliferation, survival, spread, evasion of the immune system, and other malignant behaviours of the cells in which they occur. While scores of genes have been reported to be altered in DLBCL many of these may not contribute to DLBCL. Changes in the following genes occur frequently in, and are suspected of contributing to, this disease's development and/or progression.

Microscopic examinations of involved tissues reveal large neoplastic cells that are typically classified as B-cells based on their expression of B-cell marker proteins (e.g. CD20, CD19, CD22, CD79, PAX5, BOB1, OCT2, an immunoglobulin [usually IgM but occasionally IgG or IgA)], CD30, and in ~20–25% of cases PD-L1 or PD-L2 (PD-L1 and PD-L2 are transmembrane proteins that normally function to suppress attack by the immune system). These cells arrange in a diffuse pattern, efface the tissues' architecture, and resemble Centroblast cells (80% of cases), Immunoblast cells (8–10% of cases), or anaplastic cells (9% of cases; anaplastic cells have bizarre nuclei and other features that may mimic the Reed–Sternberg cells of Hodgkin disease or the neoplastic cells of anaplastic large cell lymphoma). Rarely, these neoplastic cells are characterized as having signet ring or spindle shaped nuclei, prominent cytoplasmic granules, multiple microvillus projections, or, when viewed by electron microscopy, tight junctions with other cells. These neoplastic tissue infiltrates are often accompanied by small non-malignant T-cell lymphocytes and histiocytes that have a reactive morphology

The proposed therapeutic indication "Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy. " 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 CHMP.

Chronically debilitating and/or life-threatening nature

At the time of initial designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening.

At the time of this review DLBCL was presented to the COMP to remain chronically debilitating and life-threatening disease with a median survival of less than one year if left untreated. Approximately 60% of patients may be cured with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), the current standard of care. The clinical course can be 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.

The COMP concluded that the condition remains chronically debilitating and life-threatening.

Number of people affected or at risk

The sponsor has provided a prevalence estimate based on the European Cancer Information System (ECIS). ECIS is the reference source for European cancer estimates. This data source reports cancer incidence and mortality data for the 27 member states of the EU only. The ECIS definition of NHL includes ICD-10 (2010 version) codes C82-86, C88.4, and C96 (ECIS, 2020). According to ECIS, the number of incident cases of NHL in EU27 was 86,321 persons.

Based on recent publications and using the same definition of NHL as ECIS, or one as close as possible, the proportion of DLBCL in European countries was:

- 33.6% in Girona (Spain) in 1996-2015 (Solans, 2019)
- 35.5% in Sweden in 2000-2016 (Ekberg, 2020)
- 34.6% in France in 2010-2013 (Laurent, 2017)
- 38.8% in the Netherlands, estimate for 2020 (Netherlands Cancer Registry)
- 39.5% in the UK in 2010-2016 (Haematological Malignancy Research Network)

For this range (34% to 40%), the corresponding incident cases of DLBCL in 2020 would be between 29,349 (86,321 × 0.34) and 34,528 (86,321 × 0.40). The population estimate for EU in 2020 from Eurostat is 447,671,046 (Eurostat Population Statistics, 2021). Therefore, the incidence rate for the DLBCL population ranges from 0.66 per 10,000 (29,349 / 447,671,046) to 0.77 per 10,000 (34,528 / 447,671,046). Note that all calculations in this section, aimed at evaluating the prevalences, have been rounded at the end of the process.

The sponsor notes that DLBCL is readily curable with first-line immunochemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) in 50 to 70% of patients (Crump, 2017; Coiffier, 2016). Based on real-world data, there is also a proportion of 8% to 14% of patients who do not start treatment with curative intent and have a median OS of less than 3 months (Arboe, 2019; Harrysson, 2021). According to literature, the proportion of R/R DLBCL is approximately 24% to 44% of the entire DLBCL population (Harrysson, 2021; Ermann, 2020; Sarkozy, 2018; Rovira, 2015). For R/R DLBCL patients, the prognosis is dismal. The reported median overall survival after second-line treatment from the time of relapse is less than 1 year (Farooq, 2017; Crump, 2017; Filliatre-Clement, 2018; Ayers, 2020). In conclusion, at least half of the DLBCL patients are cured 5

years after diagnosis, and the remainder of the patients have survived for a mean duration well below 5 years. The Sponsor concludes it is reasonable to consider the maximum mean duration of the disease to be 5 years.

The sponsor notes that there is scarce recent evidence of increasing trends in incidence of DLBCL in Europe. Only some data for Western Europe were found. In Sweden, the incidence of DLBCL increased by 2.2% annually between 2000 and 2016 (Ekberg, 2020). Whereas, in France, incidence rates for DLBCL increased annually by 1.2% in men and decreased by 3.3% in women from 2005-2012 (Le Guyader-Peyrou, 2016).

Published sources for the estimates of the prevalence of DLBCL

In Belgium, the number of 5-year and 10-year prevalent cases alive in 2018 was reported from the Belgian Cancer Registry (2021): namely, 2674 five-year cases (2014-2018) and 4495 ten-year cases (2009-2018). Using the 2018 Belgian population (11,427,054) (Eurostats, 2021), the corresponding 5-year and 10-year prevalence per 10,000 in 2018 is 2.34 and 3.9, respectively.

In conclusion, the 5-year prevalence, which is considered the most appropriate to ascertain the prevalence of patients living with the disease, ranges from 2.34 per 10,000 persons (from the Belgian Cancer Registry) to 3.85 per 10,000 persons (from our calculation based on ECIS data), which is below the threshold of orphan disease of 5 per 10,000.

With the uncertainties of both the duration of disease and the percentage of NHL the COMP accepted the prevalence estimate rounded off to 4 in 10,000.

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

There are authorised products in the EU for the treatment of DLBCL:

- Rituximab (Mabthera) is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.
- Pixantrone (Pixuvri) is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL). Some chemotherapy agents are approved nationally in several EU countries under different trade names for the treatment of certain cancer types.
- Axicabtagene ciloleucel (Yescarta) 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.
- Tisagenlecleucel (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.
- Polatuzumab vedotin (Polivy) in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant."

- Tafasitamab MINJUVI is indicated in combination with lenalidomide followed by MINJUVI monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).

Several medicinal products are authorised and used for the treatment of Non-Hodgkin lymphomas. These include cyclophosphamide, doxorubicine, bendamustine, bleomycin, vincristine, vindesine, etoposide, iphosphamide, chlorabucil, lomustine, prednisone, and prednisolone, docetaxel, mitoxantrone, methotrexate, epirubicin, dexamethasone, cytarabine.

There is an ESMO treatment guideline on DLBCL (Tillly et al, Ann Oncol (2015) 26 (suppl 5): v116-v125) outlining the best standard of care of patients affected by the condition. The treatment guidelines are not updated to reflect currently authorised treatment options, i.e. tisagenlecleucel and axicabtagene ciloleucel or polatuzumab vedotin.

Recently ESMO has provided additional recommendations regarding DLBCL within the context of the Covid 19 pandemic. They recommend that both clinical practice including CAR-T treatment (when indicated) as well as clinical trials should continue with special attention to prophylaxis of infections.

Significant benefit

The sponsor is proposing that significant benefit is based on a clinically relevant advantage. Two different maintenance reports were submitted one in July 2020 and a revised follow-up report in November 2021. Assessment involved both reports for the sake of completeness.

Protocol Assistance was sought by the Sponsor on the proposed clinical development plan of JCAR017 in DLBCL, PMBCL, and FL in support of significant benefit over existing therapies.

A summary of the advice received from the COMP and how this was considered is provided below.

For the demonstration of significant benefit based on improved efficacy through indirect comparisons, the COMP recommended to provide indirect comparisons of adequate methodology and encouraged the Sponsor to explore the possibility to use data from real world evidence (RWE) from patients that are treated with the currently authorised products to support significant benefit.

With the indication targeted by the sponsor, the following products listed below are approved in 3L+ DLBCL:

- Yescarta
- Kymriah
- Minjuvi
- Polivy
- Pixuvri
- Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP chemotherapy)
- Salvage therapies

Indirect comparisons of efficacy and safety between JCAR017 and the approved products in 3L+ DLBCL were discussed to support the significant benefit of JCAR017 over currently authorised treatments.

Polivy's and Minjuvi's therapeutic indications may be regarded as broader compared to Breyanzi in view that they may include patients who only failed one prior line of treatment.

The difficulty of providing indirect and unbiased comparisons versus the outcomes of studies with the authorised CAR-T cell products is acknowledged in view of the general challenges when performing indirect comparisons of results from single-arm trials. In addition, differences of the population characteristics and study designs are noted vis-à-vis the pivotal studies on Kymriah and Yescarta (enrolled conditions, proportion and type of bridging therapy; proportion of enrolled patients undergoing leukaphereses and being treated; time of follow-up).

The recommendation in the Protocol assistance was to use RWE but the sponsor states that only limited RWE data were available from patients treated with authorised CAR-T therapies. Thus, for significant benefit comparison with Yescarta and Kymriah, the SmPCs and EPAR data have been utilised instead.

Yescarta:

In their submission the sponsor makes claims of improved safety with "at least comparable efficacy" and a major contribution to patient care.

In their support of comparable efficacy, the sponsor provides an indirect comparison to the ZUMA-1 study (Yescarta pivotal study) where bridging therapy between leukapheresis and lymphodepleting chemotherapy was not permitted. In the Breyanzi 017001 study, 59% of the included patients received bridging therapy before infusion of CAR-T cells.

This leads the sponsor to compare results from Yescarta study ZUMA-1 (DLBCL subset only; 12-month follow-up results as described in OMAR) with a patient subset from Breyanzi study 017001 (patients without prior bridging therapy, to approximate the ZUMA-1 population).

	Breyanzi (DLBCL subset without bridging therapy before liso-infusion from study 01700)	Yescarta (DLBCL subset from ZUMA-1 study)
ORR (BOR)	80.4% [71.1, 87.8]	84% [75, 91]
CR (BOR)	63.9% [53.5%, 73.4%]	57%
mDOR (months)	15.0 [5.0, NR]	8.1 [2.4, NR]
mOS (months)	48.5 [22.0, NR]	NR [11.5, NR]

The sponsor did not present results in the full DLBCL population from study 017001 (including patients who receive bridging therapy following leukapheresis) in Table submitted. However, these results were presented in the Table for the comparison against Kymriah.

It was noted that when the ZUMA-1 DLBCL data are compared to the full DLBCL dataset from study 017001 (including patients with bridging therapy), Breyanzi results are slightly worse in terms of ORR (72% vs. 84%) and CR rate (52.3% vs. 57%), and OS rates (cave: different follow-up time), and slightly better for mDoR (11.1m vs. 8.1m).

The sponsor has also submitted some retrospective RWD analyses (Jain 2019, Nastoupil 2018, Jacobson 2018), which suggest that patients who received bridging therapy prior to Yescarta treatment had worse outcomes (ORR, CR, PFS, OS) compared to those who did not.

The RWE study performed by the sponsor included only 7 Yescarta-treated patients (4 evaluable for efficacy: 1x CR, 3x PD) and is thus considered not appropriate for a meaningful comparison.

To support the claim of comparable efficacy results for Breyanzi to Yescarta, the sponsor further provided results from a matching-adjusted indirect treatment comparison (MAIC). This was performed based on the 017001 subset without prior bridging therapy and the ZUMA-1 population, including two sensitivity analyses. A report describing the methodology for the MAIC was not submitted in the context of the orphan maintenance assessment..

To support improved safety as the basis for significant benefit the sponsor excluded the subset of 017001 patients who received a bridging therapy in order to provide a more valid comparison to Yescarta. As highlighted by the sponsor, the presented ZUMA-1 safety data set for Yescarta includes DLBCL as well as PMBCL patients, whereas the 017001 data set for Breyanzi included only DLBCL patients. This leads to the following observations as presented by the sponsor:

	Breyanzi (DLBCL subset without bridging therapy before liso-infusion from study 01700)	Yescarta (DLBCL + PMBCL from ZUMA-1 study)
Grade ≥3 TEAEs	69.3%	98.1%
Serious TEAEs	33.7%	52%
CRS (all grade)	30.7%	93%
CRS (Grade ≥3)	1%	11%
Grade ≥3 infections	9.9%	26%

They also report adverse events for which at least a 20% difference between Breyanzi and Yescarta was detected (in favour of Breyanzi). These included: pyrexia, hypotension, tachycardia, encephalopathy, febrile neutropenia, chills, hypoxia, and nausea.

The sponsor puts forward the observation that for the total dataset of 017001 (including PMBCL and FL3B patients and patients who received prior bridging therapy), higher percentages of adverse events are reported, which were still lower than those reported for Yescarta.

A report describing the methodology for the MAIC was not submitted in the context of the orphan maintenance assessment.

Major contribution of patient care (MCPC) was claimed by a comparison regarding quality of life (QoL) assessment in the pivotal study. In this comparison the sponsor discusses the clinically meaningful improvements in QoL of Breyanzi-treated patients based on two validated questionnaires. In Yescarta ZUMA-1 study, only n=34 patients were assessed for QoL, but with a different questionnaire. These, patient also showed an improvement of QoL. However, these findings are insufficient to assume a MCPC over Yescarta.

The COMP noted that regarding their claim of improved safety for DLBCL versus Yescarta, the relevance of the quantitative difference of the adverse events should be further discussed in view of the high risk of selective reporting of safety outcomes noted and the general challenges when performing an indirect comparison based on results from single-arm trials. The methods used for the MAIC should be further clarified.

Kymriah:

Regarding significant benefit to Kymriah, the sponsor has claimed significant benefit due to a clinically relevant advantage which is based on improved efficacy and at least comparable safety. The sponsor also presents arguments in support of claiming a major contribution to patient care.

The submitted descriptive efficacy comparison of Breyanzi to Kymriah was noted to be hampered due to differences in the proportion of patients with prior bridging therapy (59% in Breyanzi trial, 90% in Kymriah trial). Unlike for the comparison of Breyanzi vs. Yescarta (discussed above), the sponsor does not limit the analysis to the subpopulation of 017001 patients who received bridging therapy. The sponsor is asked to explain the reasons for this.

According to table 11 of the most current maintenance report, Breyanzi shows a better efficacy than Kymriah in terms of ORR, CR, and mOS in the 017001 study among DLBCL patients. Of note, there is an approximate 20% difference with respect to bridging therapy before CAR-T-cell infusion between the JULIET and the 017001 trial.

Table 11: Efficacy Results From JULIET and Study 017001 in 3L+ DLBCL

Product	**Kymriah**	**JCAR017**
Study	**JULIET**[a]	**017001**[b]
Population	DLBCL[c]	DLBCL[d]
Analysis population	Efficacy analysis set[e]	Efficacy Evaluable[f]
Sample size (N)	99	239
Median follow-up (months)	NA (24-month data update)	23.1 for DOR
ORR (IRC), % (95% CI)	53.5 (43.2, 63.6)	72.0 (65.8, 77.6)
CR rate (IRC), % (95% CI)	40.4	52.3 (45.8, 58.8)
DOR, median (months) (95% CI)	NR[g] (10.0 to NE)	11.1[g] (6.0, 21.1)
OS, median (months) (95% CI)	10.3 (6.6, 21.1)[h]	21.1 (11.6, 35.2)[i]
6-month OS, % (95% CI)	62[j,k]	73.8 (67.7, 78.9)
12-month OS, % (95% CI)	47.9[j,l]	56.6 (50.0, 62.6)

3L+ = third-line or later; CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EMA = European Medicines Agency; HGL = high-grade lymphoma; IRC = Independent Review Committee; NA = not available; NE = not estimable; NR = not reached; ORR = objective response rate; OS = overall survival; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent lymphoma other than follicular lymphoma.

[a] Source: Kymriah SmPC, 2020 and Kymriah EPAR, 2018

[b] Source: D180 017001 Tables 14.2.1.1.5.1, 14.2.2.6.10.1, and 14.2.5.3.1.1

[c] Includes 3L+ DLBCL NOS, tFL, and HGL

[d] Includes 3L+ DLBCL NOS, tFL, tiNHL, and HGL

[e] All patients who received CAR T-cell infusion and least 3 months prior to data cutoff date

[f] All patients in the DLBCL Treated Set who had PET-positive disease present before JCAR017 administration based on IRC assessment and had baseline PET/CT assessment repeated after anticancer therapy for disease control (excludes patients who received JCAR017 manufactured using the original manufacturing process)

[g] EMA censoring rule was used for Study 017001; censoring rule used for JULIET study not confirmed.

[h] OS was defined as time from date of Kymriah infusion to the date of death due to any cause (N = 115).

[i] OS was defined as time from the date of the first JCAR017 infusion to the date of death due to any reason.

[j] Source: 08 December 2017 updated data cutoff in Kymriah EPAR (2018).

[k] Sample size for 6-month OS was 111

[l] Sample size for 12-month OS was 115

Data cutoff date for Study 017001: 04 Jan 2021.

In their submission, the sponsor highlights the outcomes of the high-grade lymphoma (HGL) patients who were included in both trials (Breyanzi ORR 76% (25/33), Kymriah ORR 42% (5/12)). They also emphasised that patients with adverse prognostic features were excluded from JULIET trial (CNS secondary lymphoma, renal impairment, ECOG 2), resulting in a population with a more favourable prognosis compared to Breyanzi. They do not, however, describe how many of the analysed patients received bridging therapy making this comparison likely to be biased as well.

Finally, a matching-adjusted indirect comparison (MAIC) was performed. The MAIC confirmed improved efficacy of Breyanzi compared to Kymriah for ORR, CR, OS. A report describing the methodology for the MAIC was not submitted in the context of the orphan maintenance assessment.

The comparison of safety data between Study 017001 and JULIET demonstrates overall comparable safety of JCAR017 to Kymriah. This is supported by a detailed indirect comparison of data from Study 017001 to published data from JULIET (without adjustment), as well as an MAIC of the two studies. The sponsor indicates that they believe this comparison supports comparable safety between Breyanzi and Kymriah.

Major contribution to patient care is based on a comparison of QoL in 017001 study (Breyanzi) versus the JULIET study (Kymriah). Both showed improvements in QoL, however, different questionnaires were used and data are not comparable. The claim of MCPC over Kymriah in terms of QoL is therefore not adequately substantiated.

In conclusion, the sponsor claims improved efficacy of Breyanzi versus Kymriah. The methods for indirect comparison, are not presented with sufficient details. The analysis was performed only for the full patient dataset, even though the proportion of patients who received prior bridging therapy differs significantly (which was considered a relevant aspect in the SB discussion over Yescarta). The COMP therefore invites the sponsor to compare only the patient subsets who received prior bridging therapy, in a similar manner to that described in the significant benefit discussion versus Yescarta. The methods used for the MAIC should be further clarified.

Pixuvri:

The sponsor claimed a significant benefit of Breyanzi based on improved efficacy over pixantrone.

The patient populations were similar with respect to the type of lymphoma in the Breyanzi 017001 study (n=239) and the Pixuvri study PIX301 (n=70 randomised to treatment arm). However, it is noted that the presented analysis sets favour Breyanzi since data on Pixuvri includes all patients randomised to Pixuvri (which would be most comparable to all patients enrolled in the JCAR017 trial), whereas data for Breyanzi are only presented in the efficacy evaluable analysis set. This results in the following comparison as presented by the sponsor:

Table 15: Key Efficacy Results From PIX301 and Study 017001 in 3L+ DLBCL

Product	**Pixuvri**	**JCAR017**
Study	**PIX301**[a]	**017001**[b]
Population	DLBCL + FL3B (1 subject)	DLBCL
Analysis Set	Patients randomized to Pixuvri	Efficacy evaluable[c]
Sample size (N)	70	239
Median follow-up (months)	NA[d]	23.1 (for DOR)
ORR (IRC), % (95% CI)	37.1[e] (25.9, 49.5)	72.0 (65.8, 77.6)
CR (IRC), % (95% CI)	20.0[f] (11.4, 31.3)	52.3 (45.8, 58.8)
DOR, median (months) (95% CI)	7.0[g] (3.8, 11.6)	11.1[h] (6.0, 21.1)
OS, median (months) (95% CI)	10.2[i] (6.4, 15.7)	21.1[j] (11.6, 35.2)

3L+ = third-line or later; CI = confidence interval; CR = complete response; CRu = unconfirmed complete response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; FL3B = follicular lymphoma Grade 3B; IRC = Independent Review Committee; NA = not applicable; ORR = objective response rate; OS = overall survival; PET = positron emission tomography.

[a] Source: Pixuvri SmPC, 2020

[b] Source: D180 017001 Tables 14.2.1.1.5.1, 14.2.2.6.10.1, and 14.2.5.3.1.1

[c] All patients in the DLBCL Treated Set who had PET-positive disease present before JCAR017 administration based on IRC assessment and had baseline PET/CT assessment repeated after anticancer therapy for disease control (excludes patients who received JCAR017 manufactured using the original manufacturing process)

[d] Study included an 18-month follow-up period

[e] At end of treatment in Pixuvri EPAR, 2012

[f] CR/CRu rate (end of study) in Pixuvri EPAR, 2012. 8/70 (11.4%) CR and 6 (8.6%) unconfirmed CR/CRu reported in Pixuvri SmPC, 2020

[g] Median for CR/CRu/PR at end of study in Pixuvri EPAR, 2012

[h] EMA censoring rule was used.

[i] Median at the end of study in Pixuvri EPAR, 2012

[j] OS was defined as time from the date of the first JCAR017 infusion to the date of death due to any reason.

Data cutoff date for Study 017001: 04 Jan 2021.

The COMP noted that data on Pixuvri patients from the RWE study NDS-NHL-001 were not included. The COMP however, concluded that significant benefit through an indirect comparison to Pixuvri can be accepted as the treatment effect differences appear large enough for a descriptive cross-trial comparison.

Rituximab and other salvage therapies:

The final comparisons made by the sponsor were to rituximab and other salvage therapies:

R-CHOP is authorised for the treatment of first-line patients. Rituximab in combination with other chemotherapy regimens (ICE, DHAP, GDP) is also recommended in R/R DLBCL (ESMO guideline 2015).

The COMP noted that the inclusion criterion for Breyanzi study 017001 was prior treatment with an anthracycline regimen and anti-CD20, the majority received a platinum-containing second-line therapy. The responses in a population R/R to these treatments was therefore considered sufficient to demonstrate significant benefit.

The sponsor also submitted an efficacy comparison to SCHOLAR-1. This was accepted as a valid external control for significant benefit submission in the Yescarta orphan maintenance procedure. SCHOLAR-1 is a large, retrospective study with results pooled from RCTs and additional clinical databases, which also encompasses R/R DLBCL.

The data on salvage therapy/R-CHOP treated patients from the RWE study NDS-NHL-001 were shown and although outcomes were better than those described in the SCHOLAR-1 study, Breyanzi still seems clearly superior in terms of ORR, CR rate, DOR, and mOS.

In conclusion, the COMP considered that the basis for significant benefit had not been adequately addressed and the sponsor was invited to elaborate further on several methodological issues and inconsistencies noted in the assessment.

2.4 COMP list of issues

Significant Benefit

The justification for significant benefit over authorised CAR-T cell products requires further discussion.

The sponsor is asked to provide the results of the pivotal studies for Breyanzi and the authorised CAR-T-cell products in a structured way and to aim at optimal comparability of analyses juxtaposed with respect to definitions of population and follow up time. If available, outcomes should be reported according to disease subtype and the same/similar timepoints (12 mo/24 mo).

The reasoning for the matching with respect to bridging therapy are understood and further justification for not performing such analyses in the comparison to Kymriah with respect to efficacy should be provided.

In order to justify comparable or improved efficacy the sponsor is asked to provide a table with listings of the following analyses of all CAR-T products (per pivotal study):

a) enrolled patients

b) treated patients (i.e. having received an infusion of CAR-T-cells)

c) long-term experience with authorised products.

With respect to the claim of an improved safety for DLBCL, the sponsor is asked to provide more detail on the methods used for the MAIC (e.g. clear description of adjustments made per comparison beyond bridging chemotherapy). The relevance of the quantitative difference of the adverse events should be discussed in view of the high risk of selection bias.

3. Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor (lisocabtagene maraleucel)

EU/3/18/2018

3.1 Product and administrative information

Product	
Designated active substance(s)	Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor
Other name(s)	Lisocabtagene maraleucel
International Non-Proprietary Name	Lisocabtagene maraleucel
Tradename	Breyanzi
Orphan condition	Treatment of follicular lymphoma
Sponsor's details:	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 D15 T867 Dublin 15 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Celgene Europe B.V. - The Netherlands
COMP opinion	18 October 2018
EC decision	19 November 2018
EC registration number	EU/3/18/2018
Post-designation procedural history	
Transfer of sponsorship	Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 12 February 2019 Transfer from Celgene Europe B.V. to Bristol-Myers Squibb Pharma EEIG – EC decision of 21 January 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Concetta Quintarelli/ Claire Beuneu
Applicant	Bristol-Myers Squibb Pharma EEIG
Application submission	29 June 2020
Procedure start	16 July 2020
Procedure number	EMA/H/C/004731
Invented name	Breyanzi

Proposed therapeutic indication	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after two or more lines of systemic therapy. Further information on Breyanzi can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi
CHMP opinion	27 January 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
EMA scientific officer	Segundo Mariz
Expert	-
Sponsor's report submission	27 July 2020
COMP discussion and adoption of list of questions	18-20 January 2022
Oral explanation	15 February 2022
Sponsor's removal request	16 February 2022

3.2 Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 25 May 2018. The designation was based on the following grounds:

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 CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor was considered justified based on preliminary clinical observations in relapsed or refractory (R/R) patients who responded to treatment with the proposed product;
- the condition is life-threatening and chronically debilitating due to due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma;
- the condition was estimated to be affecting approximately 3.8 in 10,000 persons in the EU, 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 exist in the EU, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD4+ and CD8+ T cells expressing a CD19-specific CAR will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in R/R patients who had durable responses. The Committee considered that this constitutes a clinically relevant advantage.

3.3 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

Follicular lymphoma (FL) is an indolent B cell lymphoproliferative disorder of transformed follicular center B cells consisting of a mixture of centrocytes (small to medium-sized cells) and centroblasts (large cells), mixed with non-malignant cells such as T cells, follicular dendritic cells and macrophages.

Almost all FLs carry breaks at 18q21, with > 85% of them having a translocation involving chromosomes 14 and 18 (t[14;18][q32;q21]). The t(14;18) translocation ultimately results in the juxtaposition of the apoptosis regulating gene B-cell lymphoma (BCL) 2 on chromosome 18 with the IGH transcriptional enhancer of immunoglobulin heavy-chain locus on chromosome 14. This leads to the constitutive overexpression of BCL-2, which blocks apoptosis and gives the cells a survival advantage.

The aetiology of follicular lymphoma is still poorly understood. It has been suggested that age, gender and ethnicity may affect a person's likelihood of developing follicular lymphoma. The incidence increases with age; although in principle follicular lymphoma may occur at any age, it is extremely rare in children.

Follicular lymphoma involves lymph nodes, but also spleen, bone marrow, peripheral blood and Waldeyer ring. Involvement of non-haematopoietic extranodal sites, such as the gastrointestinal tract or soft tissue may occur in a setting of widespread nodal disease. Follicular lymphoma may occasionally be primary in extranodal sites, including skin, gastrointestinal tract, particularly the duodenum, ocular adnexa, breast and testis.

Most patients have widespread disease at diagnosis, including peripheral and central (abdominal and thoracic) lymphadenopathy and splenomegaly. The bone marrow is involved in 40-70% of cases. As an intrinsic disease characteristic, FL typically evolve over time to an aggressive subtype, in 15% of cases. Disease relapse is usually rapid, where remissions become a serious challenge despite multiple interventions. Eventually, patients succumb to the refractory, high-grade disease transformation and the complications driven by treatments.

The approved therapeutic indication "Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy." falls within the scope of the designated orphan condition "Treatment of follicular lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

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

Number of people affected or at risk

The sponsor has provided a current prevalence estimate which is based on the ECIS database. They report that the proportion of FL cases in NHL was searched from recent European population-based studies. Based on cancer registries, or a nationwide lymphoma registry, the proportion of incident FL cases (time period) was:

- 16.23% (2000-2014) in Poland (Szumera-Ciećkiewicz, 2020)
- 20.23% (1996-2015) Girona, Spain (Solans, 2019)
- 14.76% (1997-2003) in Italy (Luminari, 2007)
- 17.15% (2000-2016) in Sweden (Ekberg, 2020)

The proportion of FL based on the French Lymphopath Network, which captured 70% of the lymphoma cases diagnosed in 2010 to 2013 in France (Laurent, 2017), was 17.08% (5208 FL/ 30,496 NHL). Another report from France was identified that provided incidence of FL; however, it was not possible to determine a denominator similar to the ECIS definition of NHL for the FL proportion calculation (Le Guyader-Peyrou, 2019).

Based on the calculation presented by the Sponsor below, the estimated incidence rate of FL in EU27 is 0.326 per 10,000 population (assuming a proportion of FL of 16.8% within NHL). Details of the calculation are presented below.

The proportions of FL derived from Poland, Spain, Italy, Sweden, and France were extrapolated to vicinity countries. The geographical division of Europe in 4 geographic areas defined by ECIS was used (Randi, 2018) – namely:

- Central and Eastern Europe (C&E)
- Northern Europe (N)
- Southern Europe (S)
- Western Europe (W)

The EU27 countries corresponding to each region are displayed on Table 1.

As shown in Table 1, the proportion from Poland was extrapolated to Central and Eastern Europe, the proportion from Sweden was extrapolated to Northern Europe, the proportion of Spain was extrapolated to Portugal and that of Italy to Croatia, Cyprus, Greece, Malta, and Slovenia, and the proportion from France was extrapolated to Western Europe.

Table 1: Number of Incident Cases of NHL and Estimated Cases of FL in the EU27

Country	Incident cases of NHL (ECIS), N	Region	Proportion of FL	Estimated FL cases, N
Austria	1374	W	0.1708	235
Belgium	2833	W	0.1708	484
Bulgaria	647	C&E	0.1623	105
Croatia	577	S	0.1476	85
Cyprus	182	S	0.1476	27
Czechia	1860	C&E	0.1623	302
Denmark	1458	N	0.1715	250
Estonia	237	N	0.1715	41
Finland	1342	N	0.1715	230
France	14446	W	0.1708	2467
Germany	18549	W	0.1708	3168
Greece	1554	S	0.1476	229
Hungary	1581	C&E	0.1623	257
Ireland	905	N	0.1715	155
Italy	14032	S	0.1476	2071
Latvia	258	N	0.1715	44
Lithuania	485	N	0.1715	83
Luxembourg	103	W	0.1708	18
Malta	96	S	0.1476	14
Netherlands	4105	W	0.1708	701
Poland	4351	C&E	0.1623	706
Portugal	2098	S	0.2023	424
Romania	1909	C&E	0.1623	310
Slovakia	701	C&E	0.1623	114
Slovenia	617	S	0.1476	91
Spain	8202	S	0.2023	1659
Sweden	1819	N	0.1715	312
Total EU27	**86321**	**All**	**—**	**14582**

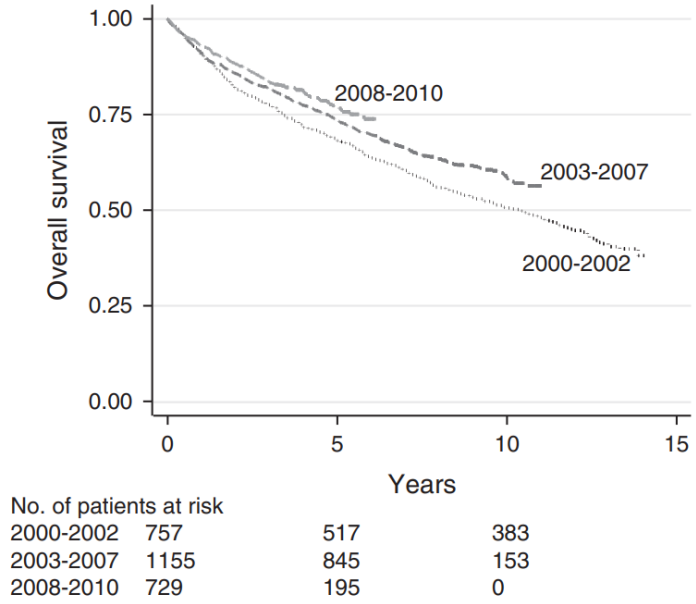
C&E = Central and Eastern Europe; FL = follicular lymphoma; ECIS = European Cancer Information System; N = Northern Europe; NHL = non-Hodgkin lymphoma; S = Southern Europe; W = Western Europe.

Survival

It has been noted that there is substantial evidence that survival has considerably increased in FL over the past 3 decades (Mozas, 2020; Dinnessen, 2021; Junlén, 2015). This increase is partly due to the uptake of rituximab in the 2000s. Although incidence of FL has stabilized in some European countries, prevalence is likely to increase as survival increases (Ekberg, 2020).

The sponsor has used 2 studies which they consider the most appropriate to use in the prevalence calculation, as they are population-based studies in 'all FL' populations diagnosed after 2000 (Junlén, 2015; Smith, 2015). In the study of the Swedish Lymphoma Registry (Junlén, 2015), the 5-year OS was 74% (95% CI: 71–76%) in those diagnosed with any grade FL in 2003-2007, and 77% (95% CI: 73–80%) in those diagnosed in 2008-2010 (Figure 1).

Figure 1: Overall Survival of FL in Sweden. Kaplan–Meier graphs by Calendar Period of Diagnosis



Source: Junlén, 2015

The sponsor indicates that one may speculate based on this figure that the OS for those diagnosed in 2003-2007 is just under 15 years and for those diagnosed in 2008-2010 may reach around 15 years. It is also reasonable to believe that after the advent of rituximab, which considerably increased survival between 2000 and 2010, no other major advances in therapy have occurred, so it is likely that survival has stabilized in the past decade.

Therefore, an OS of 15 years is the most relevant estimate to use in the prevalence calculation.

Based on the presented data originated from unselected populations of FL patients in countries with high-quality healthcare and using the formula [prevalence= incidence × duration of disease], one can speculate that the maximum median OS may currently be 15 years in the EU, which would yield a maximum complete prevalence of (0.326 × 15) = 4.89 per 10,000.

The COMP accepted the final prevalence estimate of 4.89 in 10,000, rounded off to 4.9 in 10.000.

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

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

Existing methods

The sponsor described the treatment methods available to patients with FL based on European and American treatment guidelines (Dreyling et al. 2021; NCCN 2020). Several therapies are authorised both centrally and nationally in the EU for treatment of adult patients with FL, NHL, and lymphomas. These medicines include rituximab (MabThera), yttrium-90 [90Y]-radiolabelled ibritumomab tiuxetan (Zevalin), idelalisib (Zydelig), duvelisib (Copiktra), obinutuzumab (Gazyvaro), lenalidomide (Revlimid), bendamustine, chlorambucil, cyclophosphamide, doxorubicin, mitoxantrone, etopophos, interferon-alpha-2a/b, prednisolone, and vincristine. Other treatment options also exist, such as radiotherapy and autologous stem cell transplantation (ASCT) or allogenic SCT.

The clinical course of follicular lymphoma is characterized by recurrences requiring multiple lines of treatment until eventually patients run out of treatment options and develop fatal disease resistant to any available treatment.

Patients with newly diagnosed FL are generally treated with an anti-CD20 antibody in monotherapy, rituximab (R) or obinutuzumab (G), or an anti-CD20-containing regimen (e.g., G/R-B, G/R-CHOP, and G/R-CVP). Available treatment options for r/r FL patients depends on the patient's health, age, stage of disease, comorbidities, tumour burden, and the type and duration of response to prior therapy. The most recent European Society of Medical oncology (ESMO) guidelines for newly diagnosed and relapsed FL describe the current standard of care for these patients (Dreyling, Ann Oncol. 2021; 32(3): 298-308). According to the guidelines, therapy should be initiated only upon the development of symptoms. The guideline identifies two types of FL patient populations that are offered two different treatment algorithms depending on their tumour burden, being either low (Figure 1) or high (Figure 2).

Figure 2. Treatment algorithm for FL patients with low tumour burden

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

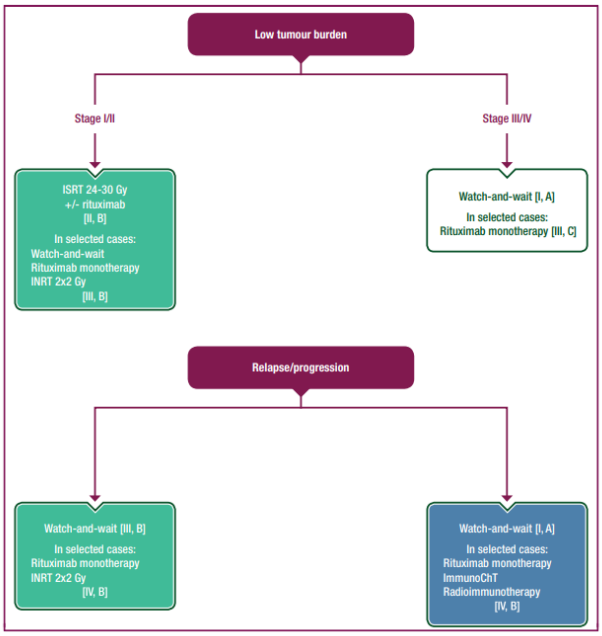


Figure 2. **Consensus-driven recommendations—low tumour burden FL.**
ChT, chemotherapy; FL, follicular lymphoma; INRT, involved-node radiotherapy; ISRT, involved-site radiotherapy.

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

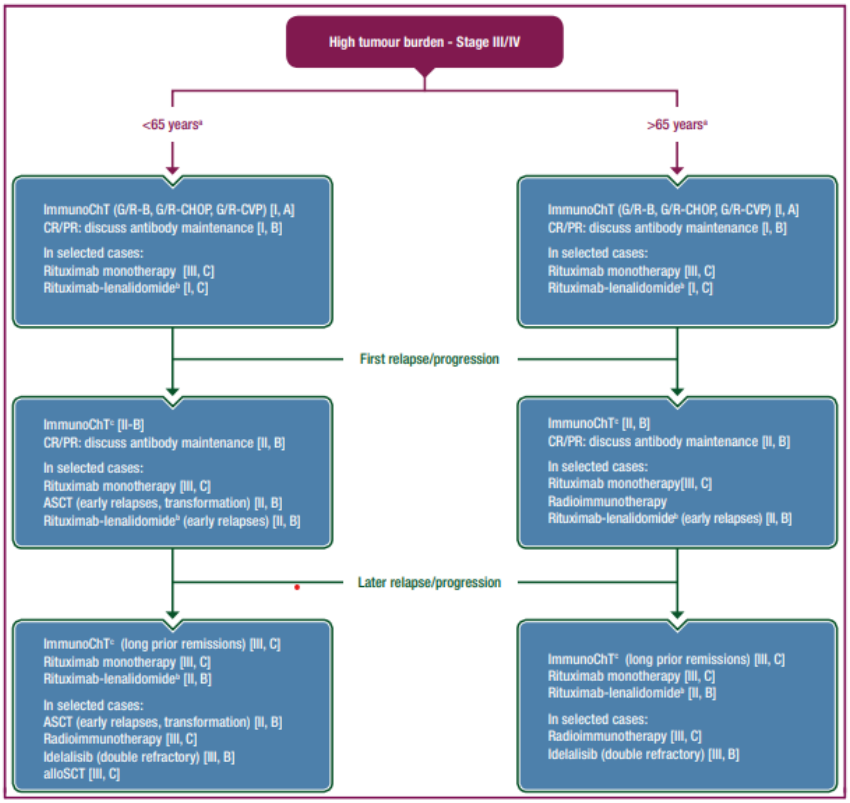


Figure 3. **Consensus-driven recommendations—high tumour burden FL.**
alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ChT, chemotherapy; CR, complete response; CVP, cyclophosphamide, vincristine, prednisolone; FL, follicular lymphoma; G, obinutuzumab; PR, partial response; R, rituximab.
[a] Biological age (years).
[b] Off-label.
[c] Preferred in rituximab-refractory cases.

First-line treatment

Induction. In the majority of patients with advanced stage III and IV disease, no curative therapy is yet established. Because the natural course of the disease is characterised by spontaneous regressions in 10%-20% of cases and varies significantly from case to case, therapy should be initiated only upon the development of symptoms, including B symptoms (unexplained fever >38C, drenching night sweats or loss of >10% body weight within 6 months), hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression [I, A]. In three randomised trials conducted before the rituximab era, early initiation of therapy in asymptomatic patients did not result in any improvement in disease-specific survival or overall survival (OS) [I, D].In a more recent study, early initiation of rituximab resulted in improved PFS (82% versus 36% at 3 years, P < 0.0001), but no survival benefit has been demonstrated to date,19 and the benefit of rituximab maintenance in this setting appears doubtful. Thus, the currently recommended therapeutic approach is based on clinical risk factors, symptoms and patient perspective. Four prospective first-line trials, two salvage trials and a systematic meta-analysis confirmed an improved overall response rate, PFS and OS if rituximab was added to ChT [I, A]. If complete remission and long PFS are the therapeutic goals, rituximab in combination with ChT such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or bendamustine should be used [I, B]. Cyclophosphamide, vincristine and prednisone (CVP) is inferior to these two regimens in terms of PFS but similar in OS. If there is evidence (histological grade 3B or clinical signs of transformation) of more aggressive lymphoma, an anthracycline-based regimen (rituximab-CHOP) should be applied. Extended anti-infectious prophylaxis should be considered, especially after bendamustine-containing induction therapy, as long-term CD4-positive T lymphocytopaenia has been observed [IV, B]. Awareness of a potential adverse impact on future cellular immunotherapeutic options, such as chimeric antigen receptor T-cell (CAR-T) treatment (see below), is important. In a large randomised trial, the anti-CD20 antibody obinutuzumab (immunochemotherapy and maintenance for 2 years) resulted in significantly prolonged PFS in comparison with rituximab and, therefore, is considered as an additional, potentially more efficacious option, although no OS benefit was observed [I, B]. In another international phase III trial, lenalidomideerituximab appeared to have a similar efficacy as immunochemotherapy [I, C]. Similarly, lenalidomide + rituximab achieve a longer PFS in comparison to rituximab monotherapy. Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab remain alternatives for patients with a low-risk profile or when conventional ChT is contraindicated [III, C].

Consolidation/maintenance. Rituximab maintenance every 2 months for 2 years improves PFS after various induction regimens (median PFS 10.5 years versus 4.1, P < 0.0001), but there is no impact on OS [I, B] whereas a shorter maintenance period results in inferior benefit. Radioimmunotherapy consolidation also prolongs PFS after ChT, but its benefit seems to be inferior in comparison to rituximab maintenance for 2 years [II, B]. However, a recent study showed an improved PFS but no difference in OS and an increased cumulative risk of myeloid malignancies after iodine-131 (131I)etositumomab radioimmunotherapy consolidation in comparison to rituximab in combination with ChT. Myeloablative consolidation followed by autologous stem-cell transplantation (ASCT) prolongs PFS after ChT, but its benefit after a rituximab-containing induction is minor and no OS advantage has been observed. Therefore, such an approach is not recommended in first-line therapy of responding patients [I, D]

This indication extension of Yescarta targets the adult patient population of FL relapsed and refractory after at least three prior lines of systemic therapy. The authorised treatment options in this setting include rituximab and obinutuzumab either in monotherapy or combined with chemotherapy for patients who did not receive them previously, idelalisib, duvelisib, lenalidomide plus rituximab, and

ibritumomab tiuxetan. Table 1 below show the currently authorized treatments in the EU and their therapeutic indications.

Medicinal products authorised for the treatment of relapsed FL (I)

Approved Products	**Active substance**	**Indication**	**Approval Date**
MabThera	rituximab	MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. MabThera maintenance therapy is indicated for the treatment of FL patients responding to induction therapy.	08Jun1998 25Oct2010
IntronA	interferon alfa-2b	Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.	09Mar2000
Zevalin	Y90 ibritumomab tiuxetan	[90Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).	16Jan2004
Levact	bendamustine	Indolent NHL as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen	1st MA approval in Germany in 2005
Zydelig	idelalisib	Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment	18Sep2014

Approved Products	Active substance	Indication	Approval Date
Gazyvaro	obinutuzumab	Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.	13Jun2016
Revlimid	lenalidomid	revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a)	
Copiktra	duvelisib	Copiktra monotherapy is indicated for the treatment of adult patients with Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies	February 2021
Pixuvri	pixantrone dimaleate	Pixantrone is indicated as monotherapy for the treatment of adult patients with multiple relapsed or refractory aggressive non-Hodgkin B-cell lymphomas. The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.	May 2012

The COMP noted that FL Grade 1-3a comprises the most prevalent indolent (low-grade) lymphoma subtype of NHL. FL grade 3b is categorised with other FLs but is at an intermediate stage of large cell transformation and is typically treated as an aggressive (high-grade lymphoma.

Significant benefit

The sponsor is proposing that their product can be used to target relapsed/refractory patients who failed two lines of prior therapy. They are seeking the following indication: *Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B),* after two or more lines of systemic therapy*".* The CHMP has also requested that the follicular lymphoma subtype identified by the FL3B should be included into the therapeutic indication so this may need to be considered for the assessment of a clinically relevant advantage to support significant benefit.

Currently the following products have overlapping indications with the one proposed by the sponsor.

- Zydelig (idelalisib) *is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment*
- Copiktra (duvelisib) *monotherapy is indicated for the treatment of adult patients with Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies*
- MabThera (rituximab) *monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy*
- *Zevalin [90Y]-radiolabelled ibritumomab tiuxetan is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).*

- *Pixantrone is indicated as monotherapy for the treatment of adult patients with multiple relapsed or refractory aggressive non-Hodgkin B-cell lymphomas. The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy*

The sponsor identifies pixantrone (authorised for multiply R/R, aggressive NHL) as the only product applicable for significant benefit assessment. For all other authorised products with later line therapeutic indications (ibritumomab, rituximab, obinutuzumab, idelalisib and duvelisib), the registrational studies were conducted in indolent FL and/or do not cover the 3L+ FL3B indication. Therefore, the sponsor states that a comparison of data is thus not possible. Furthermore, as treatment with anti-CD20 was an inclusion criterion for study 017001, responses in this population can be regarded as sufficient to establish SB over rituximab. However, as the therapeutic indications do not rule out FL3B patients they still have to be considered for the purpose of significant benefit.

With regards to the comparison to pixantrone only very little data on FL3B patients are available from the registrational trials (n=1 for Pixuvri, n=8 for Breyanzi) and the SB comparison is based on data on the larger study populations (mainly DLBCL for both products).

ORR: 72.8% [66.9, 78.1] vs. 37.1% [25.9, 49.5]

CR rate: 52.9% [46.6, 59.2] vs. 20% [11.4, 31.3]

mDOR: 16.8m [8.1, NR] vs. 7.0m [3.8, 11.6]

mOS: 27.3m [16.2, 45.6] vs. 10.2m [6.4, 15.7]

Additionally, the sponsor emphasises the favourable responses and DOR of the 8 patients with FL3B .

No data on Pixuvri-treated patients from the RWE study NDS-NHL-001 are provided.

The COMP discussed the proposed indirect comparison and concluded that significant benefit to Pixuvri had been established. Based on the same reasoning with regards to a descriptive comparison of high efficacy in a largely different patient population the significant benefit over Zevalin can also be accepted. During further discussions it was noted that the COMP was at variance with the assumptions the sponsor has made for copanlisib and idelalisib considering that an indirect comparison should also have been provided in view that the therapeutic indications of the other more recently approved products do not mention the subtype of FL.

3.4 COMP list of issues

Significant Benefit

The sponsor is asked to justify significant benefit over all treatments authorised for follicular lymphoma in greater than second line therapy including copanlisib and idelalisib.

4. Lisocabtagene maraleucel

EU/3/18/2099

4.1 Product and administrative information

Product	
Designated active substance(s)	Lisocabtagene maraleucel
Other name(s)	Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor
International Non-Proprietary Name	Lisocabtagene maraleucel
Tradename	Breyanzi
Orphan condition	Treatment of primary mediastinal large-B-cell lymphoma
Sponsor's details:	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 D15 T867 Dublin 15 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Celgene Europe B.V. - The Netherlands
COMP opinion	18 October 2018
EC decision	19 November 2018
EC registration number	EU/3/18/2099
Post-designation procedural history	
Transfer of sponsorship	Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 12 February 2019 Transfer from Celgene Europe B.V. to Bristol-Myers Squibb Pharma EEIG – EC decision of 21 January 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Concetta Quintarelli/ Claire Beuneu
Applicant	Bristol-Myers Squibb Pharma EEIG
Application submission	29 June 2020
Procedure start	16 July 2020
Procedure number	EMA/H/C/004731
Invented name	Breyanzi

Proposed therapeutic indication	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after two or more lines of systemic therapy. Further information on Breyanzi can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi
CHMP opinion	27 January 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
EMA scientific officer	Segundo Mariz
Expert	-
Sponsor's report submission	27 July 2020
COMP discussion and adoption of list of questions	18-20 January 2022
Oral explanation	15 February 2022
Sponsor's removal request	16 February 2022

4.2 Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2018 was based on the following grounds:

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 lisocabtagene maraleucel was considered justified based on clinical observations in relapsed/refractory patients who responded to treatment with the proposed product;
- 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 0.5 in 10,000 persons in the EU, 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 exist in the EU, the sponsor has provided sufficient justification for the assumption that the medicinal product containing lisocabtagene maraleucel will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in heavily pretreated relapsed or refractory (R/R) patients, who responded to treatment with the proposed product. Moreover, the rates of cytokine release syndrome (CRS) in the treated patients were reported to be lower in comparison to the currently authorised chimeric antigen receptor (CAR) T-cell product. The Committee considered that this constitutes a clinically relevant advantage.

4.3 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

Primary mediastinal B-cell lymphoma (PMBCL) is a relatively rare lymphoma subtype affecting mainly young adults. Its molecular signature and clinical features resemble classical Hodgkin lymphoma. Gene expression profile studies showed that it shares common features with classical Hodgkin lymphoma. Primary mediastinal large B-cell lymphoma (PMBCL) represents ~10% of all DLBCLs and it is more commonly seen in women in their third to fourth decades of life.

PMBCL arises in the thymus from a so-called thymic B-cell originating either from a germinal center or a nongerminal center but with an expression of an activation induced cytidine deaminase (AID) gene. Cells are heterogenous, medium-sized to large-sized, with a pale, abundant cytoplasm. Their nuclei also show a degree of heterogeneity. They could be oval, irregular, pleomorphic like Reed-Sternberg cells or multilobated like in DLBCL. Characteristic feature of PMBCL is sclerosis dividing tumour tissue into compartments. Collagen bands are fine and not as broad as in cHL nodular sclerosis (NS) types. (Curr Hematol Malig Rep (2014) 9:273–283)

PMBCL typically presents as a large, fast-growing tumour with invasion usually limited to the anterior-upper mediastinum although it tends to infiltrate adjacent thoracic structures like the chest wall, pleura, lungs, pericardium, and heart causing pleural/pericardial effusion in approximately 30–50 % of cases. The disease is mainly locally advanced. Eighty percent of patients have clinical stage I and II and 75 % of them have bulky disease with a tumour mass exceeding 10 cm. Enlarged lymph nodes localized outside the mediastinum are rarely found. Bone marrow infiltration is seen in few cases.

The World Health Organization has classified PMBCL as a unique entity on the basis of its unique clinical and immunophenotypic presentation and molecular features. (Zhou et al. Blood Cancer Journal (2020) 10:49)

The COMP continues to designate this condition.

The proposed therapeutic indication "*Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma Grade 3B (FL3B) after* two or more lines of systemic therapy*"* falls within the scope of the designated orphan condition "Treatment of primary mediastinal large-B-cell lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

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. It can be 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.

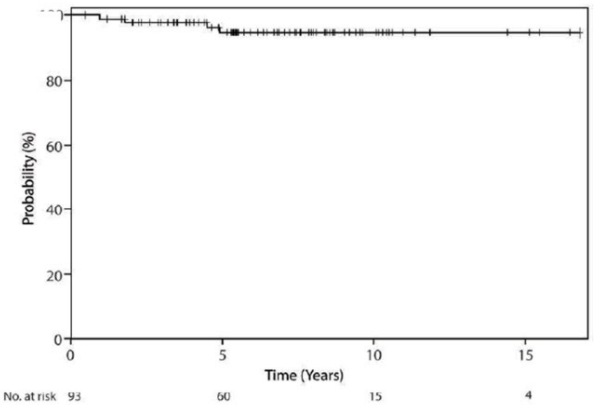
Number of people affected or at risk

The sponsor has consulted the European Cancer Information System (ECIS). According to the most recent data release, the number of NHL incident cases in the EU-27 was 86,321 in 2020 (ECIS, 2020). They indicate that the reported proportion of PMBCL cases in NHL is 2% to 4% (Dabrowska-Iwanicka, 2014).

A conservative approach was applied using 4% as the proportion of PMBCL and would indicate that the number of PMBCL cases in the EU-27 is 3,453. Using recently published Eurostat data, the population in the EU-27 was 447,671,046 in January 2020 (Eurostat Population Statistics, 2021), so the estimated annual incidence rate per 10,000 population is 0.077 (3453 / 447,671,046).

The sponsor notes that median duration of survival varies among patient groups, particularly with age of disease onset. The only estimate of mean survival duration was found in one study based on 28 patients (Al Shemmari, 2014). Other literature reported 5-year survival (both OS and PFS) ranging from 50% to 100% with most around 70% to 90% (Dabrowska-Iwanicka, 2014; Al Shemmari, 2014). With such high 5-year survival estimates, the median survival for PMBCL may be indeterminate due to censoring. One published review on PMBCL included data from various regimens for PMBCL which included survival estimates. In one trial, the investigators reported a 10.9-year OS of 66% and PFS of 50% (Dabrowska-Iwanicka, 2014). This is the closest estimate to the median survival that could be found in the literature; therefore, for the calculation of the point prevalence, 10.9 years was used as the average duration. There have not been any recent publications reporting median survival for PMBCL. PMBCL is currently considered a highly curable disease (Fakhri, 2021; Shah, 2018) and the favored initial treatment with dose-adjusted EPOCH-R without radiotherapy, results in over 90% of the patients cured at 5 years (Figure 1)

Kaplan–Meier Estimates of Overall Survival of Patients following Treatment with DA-EPOCH-R



CI = confidence interval; DA-EPOCH-R = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab. Overall survival 94.7% (95% CI, 86.3-98.0) at 8 years for the total cohort. Source: Melani, 2018

Despite excellent responses to first-line therapy, outcomes of RR PMBCL remain dismal (Ahmed, 2021).

In view of the high cure rates, taking 10.9 years as the average duration is a very conservative approach that overestimates the true duration of disease, which is likely not above 5 years. However, even if the hypothetical median survival were 5 times longer than 10.9 years, the prevalence would still be well below the threshold for orphan condition of 5 per 10,000 people. Using the guidance calculation method of Prevalence = Incidence × Disease duration, the updated 2020 prevalence for PMBCL is 0.84 per 10,000 (0.077 x 10.9) in the EU27 which is below the threshold for orphan condition of 5 per 10,000 people (EMA, 2019)

The COMP accepted the proposed prevalence calculation of 0.8 in 10,000.

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

Yescarta has received a centralised marketing authorisation for "for 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". In addition to that, 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

The sponsor is proposing that their product will offer a clinically relevant advantage in patients who are relapsed or refractory after 2 previous lines of therapy.

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

With the indication targeted by the Sponsor, the following products as listed in their submission are approved in 3L+ PMBCL:

- Yescarta
- Pixuvri
- Salvage therapies

The only product which has a similar indication is Yescarta:

Yescarta is indicated for 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.

As there is a full overlap of the therapeutic indications an assessment of significant benefit is required.

Protocol Assistance was sought by the Sponsor on the proposed clinical development plan of JCAR017 in DLBCL, PMBCL, and FL in support of significant benefit over existing therapies

The COMP suggested that: For the demonstration of significant benefit based on improved efficacy through indirect comparisons, the COMP recommended to provide indirect comparisons of adequate methodology and encouraged the Sponsor to explore the possibility to use data from real world evidence (RWE) from patients that are treated with the currently authorized products to support significant benefit.

The sponsor has submitted indirect comparisons of efficacy and safety between JCAR017 and the approved products in 3L+ previously treated PMBCL.

Yescarta:

The sponsor claims a clinically relevant advantage based on safety versus Yescarta and that their product is at least comparable in efficacy.

Improved safety:

The sponsor performs a safety comparison of the total populations (including DLBCL (and FL) patients) of Yescarta ZUMA-1 trial (n=109, 24 month follow-up analysis) and Breyanzi 017001 study (n=270).

Grade ≥3 TEAEs: 78.9% vs. 98.1%

Serious TEAEs: 45.2% vs. 51.9%

All grade CRS: 41.9% vs. 92.6%

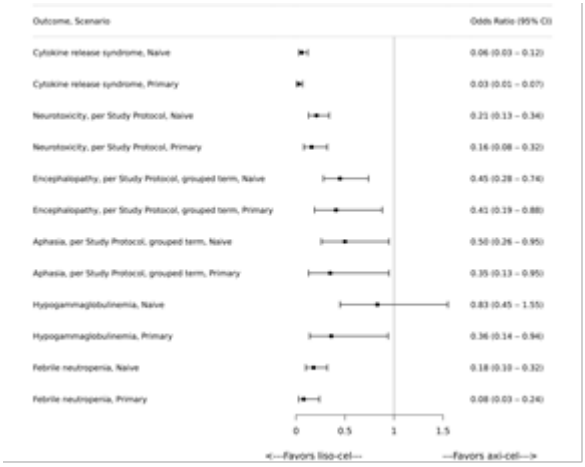
Grade ≥3 infections: 12.2% vs. 25.9%

Grade ≥3 neurological toxicities: 10.0% vs 32.4%

ICU admissions: 7.0% vs. 16%

Further adverse events for which at least 20% difference between Breyanzi and Yescarta could be detected (in favour of Breyanzi), include: pyrexia, hypotension, tachycardia, encephalopathy, febrile neutropenia, chills, hypoxia, and nausea.

In addition, a matching-adjusted indirect treatment comparison (MAIC) was performed based on study 017001 (Breyanzi pivotal study) and ZUMA-1 (Yescarta pivotal study), which demonstrated significantly lower odds of a broad number of AEs.



In the ZUMA-1 study (Yescarta), bridging therapy was not permitted between leukapheresis and infusion . In contrast, in the Breyanzi 017001 study,
59% of the patients included did receive prior bridging therapy.

Thus, the sponsor compares results from Yescarta study ZUMA-1 (**n=8** PMBCL, 12-month follow-up results as described in the OMAR)
with a patient subset from Breyanzi study 017001 (**n=6** PMBCL patients without prior bridging therap y, to approximate the ZUMA-1 population).

ORR: 83% (5/6) vs. 75% (6/8)

CR: 67% (4/6) vs. 75% (6/8)

mDoR: NR vs. NR

1y-OS: 83% (5/6) vs. 75% (6/8)

Efficacy data of the whole study populations (including DLBCL) is not mentioned, however, in the maintenance report for DLBCL, efficacy data for the whole populations are shown and can be regarded as comparable.

Finally, a matching-adjusted indirect treatment analysis (MAIC) was performed based on the 017001 subset without prior bridging therapy and the ZUMA-1 population, including two sensitivity analyses which included the patients with bridging therapy. The analysis yielded comparable efficacy results for Breyanzi and Yescarta.

The COMP could conclude the following regarding significant benefit over Yescarta:

The significant benefit claim over Yescarta was discussed during the plenary. At the time of orphan designation, significant benefit over Yescarta was accepted based on improved safety. It was also supported by non-clinical data showing the possibility of B-cell ablation in view of the inclusion of a truncated EGFR into the viral vector. However, the COMP noted that no clinical data was submitted to demonstrate the clinical utility of this difference. While this would be in line with what is expected for such a rare clinical situation at the time of initial registration, the clinically relevant advantage versus Yescarta based on safety using so few patients affected by PMLBC would not be acceptable to the COMP without additional support from a similar setting (in this case R/R DLBCL).

The COMP considered that significant benefit based on a clinically relevant safety advantage had not been shown and that the sponsor should be invited to elaborate further on this point.

Pixuvri:

In their comparison to Pixuvri the sponsor makes claim of improved efficacy. Pixuvri (pixantrone), an anthraquinone-based inhibitor of topoisomerase II, which was approved by the EMA in the broad indication of R/R aggressive B-
NHL: *"Pixantrone is indicated as monotherapy for the treatment of adult patients with multiple relapse d or refractory aggressive non-Hodgkin B-cell lymphomas.*
The benefit of pixantrone treatment has not been established in patients when used as fifth line or gre ater chemotherapy in patients who are refractory to last therapy."

The COMP noted that PMBCL patients were not included in the Pixuvri registration study and that the sponsor assumes that results in PMBCL patients would be similar to those reported in the whol e study population (mainly DLBCL patients).
Thus, the whole Pixuvri study population (n=70) is compared to the subset of PMBCL patients included in Breyanzi study 017001 (n=14).

ORR: 78.6% [49.2, 95.3] vs. 37.1% [25.9, 49.5]

CR: 50.0% [23.0, 77.0] vs. 20.0% [11.4, 31.3]

mDOR: NR [4.4, NR] vs. 7.0m [3.8, 11.6]

mOS: NR [12.1, NR] vs. 10.2m [6.4, 15.7]

Data from Pixuvri patients in the RWE study NDS-NHL-001 are not mentioned. No data regarding the efficacy of Pixuvri in PMBCL were presented. The COMP however, considered that the large difference in efficacy between Breyanzi vs. Pixuvri in the DLBCL dataset could be regarded as sufficient to establish significant benefit based on a clinically relevant advantage for the PMBCL indication.

Rituximab and other salvage therapies

R-CHOP is authorised for the treatment of first-line patients. Rituximab in combination with other chemotherapy regimens (ICE, DHAP, GDP) is also recommended in R/R PMBCL (ESMO guideline 2016).

The inclusion criterion for the Breyanzi study 017001, was prior treatment with an anthracyclin regimen and anti-CD20 with the majority received a platinum-containing second-line therapy. The responses reported in a population who were relapsed or refractory to these treatments was considered sufficient to demonstrate SB.

In addition, the sponsor performed and presented an efficacy comparison to SCHOLAR-1 and to the RWE study NDS-NHL-001. This approach was accepted as a valid external control for SB in the Yescarta orphan maintenance procedure. SCHOLAR-1 is a large, retrospective study with results pooled from RCTs and databases, which also encompasses R/R PMBCL (n=10). In NDS-NHL-001, n=17 PMBCL patients were included

Breyanzi compares favourably to salvage therapies as described above:

ORR: 78.6% (11/14) vs. 20% (2/10) vs. 41.6% (7/17)

CR: 67% (4/6) vs. 0% (0/10) vs. 23.5% (4/17)

mOS: NR (12.1, NR) vs. 7.7m (4.3, NR) vs. 6.1m (4.0, NR)

The COMP considered that significant benefit to Rituximab + salvage therapies as proposed by the sponsor could be accepted.

During the the plenary discussion, the COMP considered that the sponsor had adequately addressed significant benefit criteria over Pixuvru and salvage therapies. They, however, were of the opinion that while equivalent efficacy to Yescarta had been established, a clinically relevant advantage regarding safety had not been shown that would support their significant benefit claim. The sponsor was therefore invited to further elaborate on what this significant benefit based on safety could be versus Yescarta.

4.4 COMP list of issues

Significant benefit

The sponsor is invited to further elaborate on the indirect comparison regarding better safety to Yescarta.

In view of the low number of patients included with PMBCL, significant benefit for PMBCL needs to be supported by an agreement on the justification of significant benefit for DLBCL.