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EMADOC-1700519818-708261 Corr.[1]
Committee for Orphan Medicinal Products

# Orphan Maintenance Assessment Report

Minjuvi (tafasitamab)
Treatment of diffuse large B-cell lymphoma
EU/3/14/1424
Sponsor: Incyte Biosciences Distribution B.V.

**Note**

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

[1] Corrigendum (20 December 2021) to the OMAR EMADOC-1700519818-708261: the section on significant benefit has been updated

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# 1. Product and administrative information

| **Product** | |
|---|---|
| Designated active substance(s) | Humanised Fc engineered monoclonal antibody against CD19 |
| Other name(s) | - |
| International Non-Proprietary Name | Tafasitamab |
| Tradename | Minjuvi |
| Orphan condition | Treatment of diffuse large B-cell lymphoma |
| Sponsor's details: | Incyte Biosciences Distribution B.V.<br>Paasheuvelweg 25<br>1105 BP Amsterdam<br>Noord-Holland<br>Netherlands |
| **Orphan medicinal product designation procedural history** | |
| Sponsor/applicant | MorphoSys AG |
| COMP opinion | 11 December 2014 |
| EC decision | 15 January 2015 |
| EC registration number | EU/3/14/1424 |
| **Post-designation procedural history** | |
| Transfer of sponsorship | Transfer from MorphoSys AG to Incyte Biosciences Distribution B.V – EC decision of 3 July 2020 |
| **Marketing authorisation procedural history** | |
| Rapporteur / Co-rapporteur | S. B. Sarac / A. Moreau |
| Applicant | Incyte Biosciences Distribution B.V. |
| Application submission | 30 April 2020 |
| Procedure start | 21 May 2020 |
| Procedure number | EMA/H/C/0005436 |
| Invented name | Minjuvi |
| Proposed therapeutic indication | 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).<br><br>Further information on Minjuvi can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/minjuvi |
| CHMP opinion | 24 June 2021 |
| **COMP review of orphan medicinal product designation procedural history** | |
| COMP rapporteurs | Elisabeth Johanne Rook / Karri Penttila |
| Sponsor's report submission | 27 January 2021 |
| COMP discussion and adoption of list of questions | 15-17 June 2021 |
| Oral explanation | 13 July 2021 |
| COMP opinion | 15 July 2021 |

# 2. Grounds for the COMP opinion

**Orphan medicinal product designation**

The COMP opinion that was the basis for the initial orphan medicinal product in 2015 designation was based on the following grounds:

"The sponsor MorphoSys AG submitted on 25 September 2014 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing humanised Fc engineered monoclonal antibody against CD19 for treatment of diffuse large B-cell lymphoma (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

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

- the intention to treat the condition with the medicinal product containing humanised Fc engineered monoclonal antibody against CD19 was considered justified based on preliminary clinical data showing reduced tumour size in treated patients affected by the condition;
- 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 in patients not responding to treatment;
- the condition was estimated to be affecting approximately 2.5 in 10,000 persons in the European Union, at the time the application was made.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised Fc engineered monoclonal antibody against CD19 may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition who had relapsed or did not respond to previous treatments. These patients showed clinically relevant responses when treated with the product. The Committee considered that this constitutes a clinically relevant advantage.

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

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing humanised Fc engineered monoclonal antibody against CD19 as an orphan medicinal product for the orphan indication: treatment of diffuse large B-cell lymphoma."

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

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

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

**Condition**

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL) in adults, accounting for 30% to 40% of all cases globally (Chaganti et al,2016) and for approximately 31% of all NHLs in Europe (Martelli et al,2013). DLBCL usually affects adults, especially around 60 to 70 years, but also rarely occurs in adolescents and children. Hereditary and acquired immunodeficiencies, occupational exposures, and pharmacological immunosuppression in the setting of transplantation or treatment of autoimmune diseases have been identified as factors thought to potentially confer increased risk of developing DLBCL.

The sponsor identified that there were significant changes to the condition since the orphan drug designation was initially granted in 2014. The revision of the World Health Organization classification of lymphoid neoplasms in 2016 (Swerdlow et al, 2016) has led to a major change in the pathological category of DLBCL, due to the presence of rearrangements of transcription factors MYC and BCL2 and/or BCL6. Based on a better understanding of these genetic alterations in large B-cell lymphomas, the updated WHO classification has established a new category of high-grade B-cell lymphoma (HGBL), with rearrangements of MYC and BCL2 and/or BCL6, so-called "double-hit" lymphomas (DHL) or "triple-hit" lymphomas (THL). The sponsor claims that between 7% and 10% of former DLBCL cases harbour MYC and BCL2 and/or BCL6 rearrangements (DHL, THL) and are therefore not considered as DLBCL any longer, i.e. they are excluded from the condition. Despite these changes in sub-classifications, the condition DLBCL is still a suitable orphan condition.

The approved therapeutic indication "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)" 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 been confirmed by the positive benefit/risk assessment of the CHMP, please see EPAR.

**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, the sponsor argued that DLBCL remains a chronically debilitating and life-threatening disease with a median survival of less than one year if left untreated. In Europe, the 5-year overall survival is estimated between 50% and 60% (Le Guyader-Peydou et al, 2017, Sant et al, 2014, Székely et al, 2014, Issa et al, 2015) underscoring the life-threatening nature of the disease. While around 50% of newly diagnosed patients can be cured with first-line therapy a combination

treatment of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) / R-CHOP + etoposide (CHOEP) chemotherapy, prognosis remains particularly poor in those patients refractory to first-line treatment (about 10-15%), with overall survival (OS) less than 1 year. Poor outcomes are also observed among patients who are ineligible for stem cell transplantation (median OS: 6 to 11 months) or have refractory disease after any line of treatment (median OS: 6.1 to 7.1 months) (Arcari et al 2016; Crump et al 2017; Czuczman et al 2017).

The 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.

**Number of people affected or at risk**

As the sponsor has not identified any sources where the prevalence is given for DLBCL specifically they have estimated the prevalence based on:

- identification of incidence of NHL,
- percentage of DLBCL from NHL,
- mean duration of DLBCL and
- validation of the results.

The percentage of DLBCL varies in the literature with the most recent ESMO guideline indicating between 30% and 58% of the NHL series. While most publications report about 30% of all NHL cases being DLBCL, Smith et al, 2015 report 47.8% of NHL constituting DLBCL based on data from the Hematologic Malignancy Research Network (HMRN) in the UK from 2004 to 2012. To be on the conservative side the sponsor uses this figure for the estimate. It was recognised that the figure is on the higher side of reported percentages and is rather conservative. With regards to the prevalence, the sponsor was asked to further discuss and justify the most suitable proportion of DLBCL in relation to NHL and disease duration. In this context it should also be noted that data from the UK should no longer be taken into account for the prevalence calculations.

The most recent registries cited are the Spanish, German and Slovenian, in which the percentage of DLBCL range from 28.4-39.7% respectively, although none of these registries is very large. However, even if the highest of these figures were used it would still be below 40%.

The data on incidence for NHL was taken from ECIS 2020 and was concluded to be 0.92 per 10,000 for DLBCL in the EU. GLOBOCAN-2018 and RARECARENet gives lower figures, while the crude incidence from NORDCAN is approximately 0.89 per 10,000. The incidence reported from literature is also below the estimate based on NHL incidence from ECIS.

The sponsor has not found any indication that the incidence is increasing in the last 20 years, rather a stabilisation occurred, and therefore the assumptions made are considered justified.

The sponsor proposed to use a 5-year duration of the condition for the purpose of the prevalence estimate. They justify this based on:

- >50% of patients will be cured after R-CHOP treatment.
- Although OS for DLBCL patients relapsing after first line treatment continued to improve during the 15 years following the introduction of rituximab, this improvement has been modest (Epperla et al, 2019).

- The recent approvals of polatuzumab vedotin or CAR T-cell therapies have not had a clinically relevant effect on overall survival (according to the clinical trial results, and since little or no post-approval data is available).
- Patients with complete remission are considered cured after 2 years of diagnosis (Maurer et al, 2014; Tilly et al, 2015; Crump et al, 2017), positively impacting the 5-year relative survival rate of the overall DLBCL population.

The sponsor originally proposed an estimated prevalence in the EU of **4.6 in 10,000** based on a 5-year duration and an incidence of 0.92 in 10,000.

Two sensitivity analysis were also performed:

In analysis No 1 the sponsor argues that patients cured should not be included in the estimate. As DLBCL is not a chronic disease, those persons that are cured because of a successful treatment no longer belong to the persons affected by DLBCL and thus no longer count for the prevalence calculation. Therefore, it is justified to not count these persons for a 10-year prevalence calculation but only the remaining 50% of the population relapsing after R-CHOP treatment. The respective 10-year prevalence, assuming an incidence of 0.46 per 10,000 (i.e. 50% of the overall incidence of DLBCL in EU-27), is 4.6 per 10,000.

In analysis No 2 the sponsor uses a lower figure for the percentage of DLBCL of 40% instead of 47.8%. This is based on the consistently reported lower figures but also on the deduction of high-grade B lymphoma with MYC and/or BCL6 rearrangements, which previously accounted for approximately 8% of DLBCL. The estimated prevalence would then be 3.9 in 10,000.

Although very sparse data on the actual prevalence of DLBCL in the EU is available, the proposed figure is supported by what the sponsor has identified.

Discussion by the sponsor in response to outstanding issues on the prevalence:

In written responses to a list of questions the sponsor argued that most of the publications report a percentage of 30%-40% of all NHL cases representing DLBCL. To more precisely estimate the percentage of DLBCL from NHL, the Sponsor used 11 recent sources from 8 European countries. These percentages varied between the 17.2 and 43.5%, resulting in a median about 35% of all NHL cases being DLBCL. This is in alignment with data reported from the United States with 30% of all NHL cases being DLBCL in 2018 (SEER, 2021). The sponsor proposes that, in order not to underestimate the prevalence, a proportion of 30-35% could be used.

With regards to the duration of the disease the sponsor added information from France, Belgium and Sweden and the percentage of patients surviving 5 years (Monnereau et al., 2021, Belgian Cancer Registry, 2020, Harrysson et al., 2021). An improvement in survival seems to have taken place from the 90s but this seems to have stagnated around 2010. This is also reported for the Integral Cancer Center Netherlands (IKNL) which described improved survival for all age categories from 1996 up to 2013, with a plateau observed since then.

Overall, 5-year survival rates in the EU range from 60-65%, with shorter survival in the elderly population. The survival rate is positively impacted by those 50% of patients who respond to first -line treatment with R-CHOP and are event-free 24 months after diagnosis, have excellent long-term outcomes, and can be considered to be cured. In contrast, the prognosis for patients with relapsed/refractory disease continues to be poor, despite the emergence of new therapies. In summary, the sponsor concludes that a mean disease duration of 5 years for DLBCL is considered justified.

During an oral presentation the sponsor summarised that DLBCL accounts for about 30% of all NHL. The disease duration was suggested to be 5 years for the purpose of the prevalence calculation considering that 50% of patients are actually cured within two years of onset. In the end a prevalence range of 2.9 - 4.6 in 10,000 was given, depending on the percentage used (30-47.5). With the uncertainties of both the duration of disease and the percentage of NHL the COMP accepted the outcome of the second sensitivity analysis where the sponsor used 40%, 5 year and concluded on a prevalence of 3.9 in 10,000. This was rounded up 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**

The sponsor lists all used and approved treatments for NHL or DLBCL in table 1.

**Table 1**

| Medicinal product(s) | Authorized indications | Marketing authorization status | Source |
|---|---|---|---|
| **Treatment of first line DLBCL (established therapies as per ESMO guidelines; Tilly et al, 2015)** | | | |
| Rituximab | CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy | Centralized | MabThera SmPC 2020 |
| Cyclophosphamide | Malignant diseases | National | Endoxana SmPC Ireland 2018 |
| Doxorubicin | NHL | National | Doxorubicin SmPC Ireland 2019 |
| Vincristine | Lymphoma | National | Vincristine SmPC Ireland 2020 |
| Prednisone/ Prednisolone | Malignant lymphoma | National | Prednisolone SmPC Ireland 2019 |
| Bleomycin | NHL | National | Bleomycin Accord SmPC Austria 2019 |
| Vindesine | Malignant lymphoma | National | Eldisin SmPC Austria 2018 |
| **Treatment of R/R DLBCL (established therapies as per ESMO guidelines; Tilly et al, 2015)** | | | |
| Cytarabine | NHL | National | Cytarabine SmPC Ireland 2018 |

| Medicinal product(s) | Authorized indications | Marketing authorization status | Source |
|---|---|---|---|
| Cisplatin | Various solid tumors | National | Cisplatin SmPC Ireland 2019 |
| Dexamethasone | NHL | National | Dexsol SmPC Ireland 2019 |
| Ifosfamide | Malignant diseases | National | Mitoxana SmPC Ireland 2019 |
| Carboplatin | Malignant diseases | National | Carboplatin SmPC Ireland 2019 |
| Etoposide | NHL | National | Etoposide SmPC Ireland 2019 |
| Gemcitabine | Solid tumors | National | Gemcitabine SmPC Ireland 2019 |
| Carmustine | NHL | National | Carmustine SmPC Ireland 2020 |
| Melphalan | Various solid tumors/multiple myeloma | National | Alkeran SmPC Ireland 2018 |
| Oxaliplatin | Various solid tumors | National | Oxaliplatin SmPC Ireland 2020 |
| Methotrexate | NHL | National | Methotrexate SmPC Ireland 2020 |
| **Treatment of R/R DLBCL (centrally authorized treatments)** | | | |
| Pixantrone | Multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL). | Centralized | Pixuvri SmPC 2012 |
| Axicabtagene ciloleucel | 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. | Centralized | Yescarta SmPC 2020 |
| Tisagenlecleucel | Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy | Centralized | Kymriah SmPC 2020 |

| Medicinal product(s) | Authorized indications | Marketing authorization status | Source |
|---|---|---|---|
| Polatuzumab vedotin | Relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for hematopoietic stem cell transplant in combination with bendamustine and rituximab. | Centralized | Polivy SmPC 2020 |
| **Further authorized therapies in NHL** | | | |
| Bendamustine | NHL | National | Bendamustine SmPC Ireland 2019 |
| Chlorambucil | NHL | National | Leukeran SmPC Ireland 2018 |
| Lomustine | NHL | National | Lomustine Medac SmPC Austria 2020 |
| Mitoxantrone | NHL | National | Leukeran SmPC Ireland 2018 |

The proposed therapeutic indication for Minjuvi is in **second line therapy for patients who are not eligible for ASCT**.

R-CHOP is standard of care in first line treatment, but not used after progression. For younger, high-risk patients, R-CHOEP is a valid option. Patients eligible for Minjuvi will have relapsed after R-CHOP and therefore the therapeutic indication is not the same.

The chemotherapeutic agent pixantrone (Pixuvri) is approved for use as monotherapy in adult patients with multiple relapsed or refractory aggressive NHL (Pixuvri Summary of Product Characteristics [SmPC] 2020), i.e. third-line or later. As Minjuvi can be used earlier than Pixuvri the therapeutic indications are not considered to be completely overlapping.

Two CAR T-cell therapies targeting CD19 (same target as Minjuvi) have been approved: axicabtagene ciloleucel/Yescarta® (August 2018); and tisagenlecleucel/Kymriah® (August 2018), respectively, for patients with R/R DLBCL who have failed at least two prior lines of systemic therapy. As for Pixuvri, the target patient population for the CAR T-cell therapies is later in the treatment armamentarium as compared to Minjuvi.

The only approved product with a completely overlapping therapeutic indication is the CD79b-targeting antibody-drug conjugate polatuzumab vedotin (Polivy), which in combination with bendamustine and rituximab (BR) (POLA-BR), was granted a conditional marketing authorization (CMA) by the European Commission for the treatment of adult R/R DLBCL patients who are not candidates for hematopoietic stem cell transplantation in January 2020. Polivy is therefore considered a satisfactory method for the target population for Minjuvi and should be considered for the discussion on significant benefit.

**Significant benefit**

The sponsor sought protocol assistance for the justification of significant benefit, in particular related to indirect comparisons, in June 2019 (EMEA/H/SA/3466/3/2019/PA/II). At the time, the COMP noted that it would be challenging to show a significant benefit.

The sponsor has done a matched adjusted indirect comparison (MAIC) vs the polatuzumab vedotin regimen, using data from the L-MIND study and GO29365 study, which are the pivotal registration studies for tafasitamab and polatuzumab vedotin, respectively. The L-MIND study was an uncontrolled single-arm study in 81 R/R DLBCL patients who were not eligible for ASCT, where tafasitamab was given add-on to lenalidomide for 12 monthly cycles. Thereafter, patients could continue with tafasitamab monotherapy until disease progression. GO29365 was a randomised open-label study, where 80 R/R DLBCL patients were randomized 1:1 to receive polatuzumab vedotin plus BR (bendamustine-rituximab) or BR alone for six 21-day cycles. A MAIC was considered feasible due to similar inclusion and exclusion criteria of the GO29365 study and the L-MIND study. However, according to the sponsor, the MAIC remains subject to uncertainty due to some prognostic factors/effect modifiers that were not reported at baseline. Overall, the patient population enrolled in the polatuzumab vedotin study GO29365 was similar to the L-MIND study (R/R DLBCL, ineligible for transplantation or experienced treatment failure with ASCT), although the GO29365 population was more heavily pre-treated and included more primary refractory patients. On the other hand, patients with transformed lymphomas and peripheral neuropathy > Grade 1 were eligible in the L-MIND study, in contrast to GO29365 (Sehn et al, 2020a). Eight patients with a DLBCL that transformed from a prior indolent lymphoma were enrolled in the L-MIND study.

Overall, no statistically significant difference in treatment effect could be established in the comparison of tafasitamab + LEN versus polatuzumab vedotin + BR. However, a numerical advantage in favor of tafasitamab + LEN was found for duration of response (DoR), OS and progression-free survival (PFS) for both analysed populations. The most favorable hazard ration (HR) was observed for the tafasitamab + LEN combination in terms of DoR with 0.39 [0.13, 1.12] and a p-value of 0.079 for the matched population. The duration of response is especially important for this patient population, which is ineligible for potentially curative treatment such as ASCT, and hence has short OS otherwise (Farooq et al, 2017). In view of the high chance of relapse in this population, the DoR advantage represented for tafasitamab + LEN compared with polatuzumab vedotin + BR in this analysis could be considered clinically relevant.

The **sponsor** claims a SB based on the following arguments:

1. Tafasitamab is associated with substantially longer durability of responses translating into longer overall survival, which is of high clinical relevance for patients, in view of their ineligibility for a potentially curative treatment option, such as ASCT.
2. Tafasitamab + LEN demonstrated clinical benefit in patients with a transformed lymphoma, which were excluded from the treatment with polatuzumab vedotin + BR.
3. Although not fatal, serious or leading to study withdrawal, peripheral neuropathy was very commonly reported for the polatuzumab vedotin + BR combination which is not the case for the tafasitamab + LEN combination. In addition, the tafasitamab + LEN combination is supposed to be used in a wider population, e.g. while polatuzumab vedotin is contraindicated in patients with active severe infection, this is not as strictly the case for tafasitamab + LEN.

The COMP considerate that in relation to the first claim:

- The combination regimes for both products might impact the effect. Polivy is administered together with rituximab and bendamustin for a duration of maximum 6 months. The effect of the chemotherapy part of the regimen might be the reason for the numerically better figures for ORR and CRR. Minjuvi on the other hand is given as a long-term treatment in combination with a product with limited information on the response in DLBCL. The fact that Minjuvi is given for a longer time might contribute to the numerically improved survival and DOR figures.
- The DOR of >50% at 2 years is considered to be relevant for the target population of patients who are at high risk of relapsing.

In relation to the second claim:

- It is recognised that patients with transformed lymphoma were not included in study GO29365; however, while there is evidence to say that de novo DLBCL patients have a better outcome with first line treatment (R-CHOP), this is less well established for second line treatment and might not necessarily mean that the patient population in L-MIND was more severe.

Finally, in relation to the third claim, the COMP considered that:

- It is challenging to compare the two products on their own as they are given in as part of the combination therapy.
- Treatment related all-grade thrombocytopenia and anemia were substantially lower with tafasitamab + LEN (anemia 23.5% vs 46.7%, thrombocytopenia 24.7% vs 46.7%, febrile neutropenia 7.4% vs 11.1 %), rates for neutropenia were comparable for tafasitamab + LEN and polatuzumab vedotin + BR (48.1% vs 46.7%). Among reported infections, pneumonia was more frequently considered related to treatment with polatuzumab vedotin (15.6%) vs tafasitamab (7.4%).

Given the limited experience with Minjuvi thus far, the claim of better safety cannot be concluded on at present stage.

The COMP agreed that the two studies have similar patient populations included, i.e. first relapse ineligible to ASCT, but the report from the sponsor did not provide much information apart from the results on five endpoints. A detailed description of the model that was used or the covariates that were considered would be needed for a complete assessment. It is not clear what has been done to derive the Naïve and MAIC-adjusted estimates. The estimates differ substantially (e.g. 0.90 vs. 0.69 for ORR or 0.57 vs. 0.79 for OS). This is neither explained nor discussed by the sponsor and. a reference could have been provided. Finally, an overview of the baseline characteristics is lacking in the submission, and it would have been essential to compare the two trials.

The COMP considered that more details on the MAIC and the indirect comparison to polatuzumab vedotin were needed for a final conclusion.

Discussion by the sponsor in response to outstanding issues on the Significant Benefit

The MAIC methodology follows the approach introduced by Signorovitch et al.2012, and the UK National Institute for Health and Care Excellence (NICE) guidelines.

In order to achieve the best compromise between increasing the number of covariates, while preserving an acceptable sample size, clinical experts advised the sponsor to prioritize matching for age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, International Prognostic Index (IPI) score, refractoriness of patients (primary refractoriness or refractoriness to prior lines of therapy), number of prior treatment lines, prior SCT, and cell type of origin of the disease.

However, these turned out to be too many variables and the model did not converge. In the final model, cell type of origin of the disease was not included in the adjustment due to the very high number of missing values reported in the L-MIND study for this variable. Primary refractoriness was also not included. The first MAIC analysis was conducted based on the primary analysis results of study L-MIND and is presented in the Orphan drug maintenance report of 19 March 2021. An updated analysis, which was performed on the updated efficacy data of October 2020, was provided in the answer to the LoQ. The outcome was in line with the first analysis:

- Relative estimates for DoR-IRC after matching showed a larger treatment effect of tafasitamab + lenalidomide over Pola + BR, acknowledging however, that the sample size was small.
- Single hazard ratios estimate for OS and PFS-IRC numerically favoured tafasitamab + lenalidomide over Pola + BR, although no statistically significant differences were found, and the upper 95% confidence intervals of the medians were not reached.
- A numerical advantage favouring Pola + BR over tafasitamab + lenalidomide was found on ORR and CRR, although no statistically significant differences were found.

Indirect comparisons before and after the MAIC are provided in the table below.

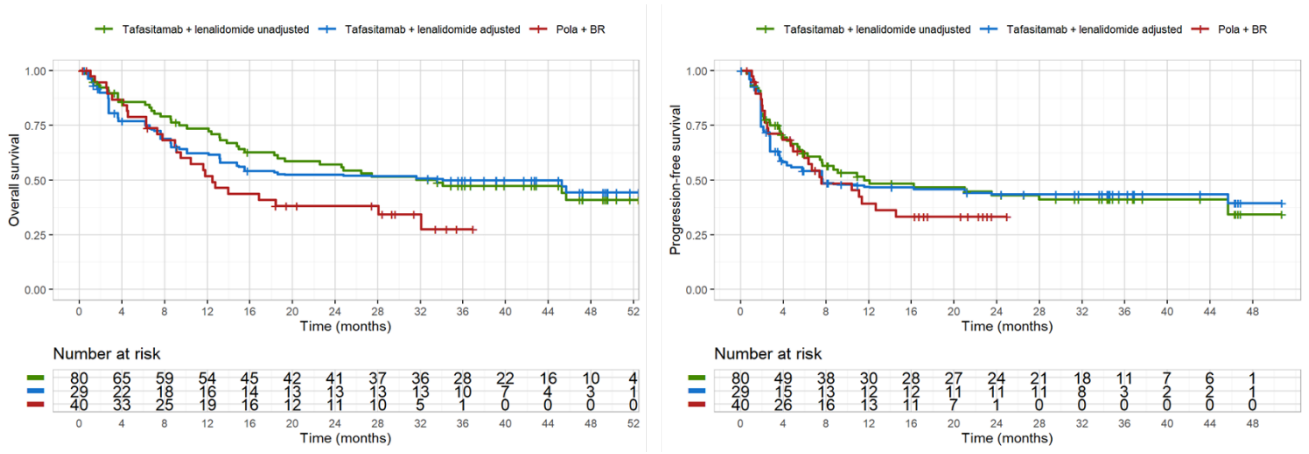
**Table 2:** Relative efficacy of tafasitamab + lenalidomide vs. Pola+BR

| | **Relative Efficacy of tafasitamab + lenalidomide vs. Pola + BR (95% CI) [p-value]** | |
|---|---|---|
| **Outcome** | **Unadjusted Comparison** | **Population-adjusted Comparison** |
| **OS** | HR: 0.59 (0.36, 0.97) [0.039]<br>(HR: 0.48 (0.27, 0.86) [0.013]<br>after 4 months of follow-up) | HR: 0.68 (0.35, 1.34) [0.268]<br>(HR: 0.41 (0.19, 0.90) [0.026]<br>after 4 months of follow-up) |
| **PFS-IRC** | HR: 0.79 (0.49, 1.30) [0.354]<br>(HR: 0.61 (0.30, 1.27) [0.186]<br>after 4 months of follow-up) | HR: 0.88 (0.45, 1.73) [0.719]<br>(HR: 0.39 (0.14, 1.06) [0.065]<br>after 4 months of follow-up) |
| **DoR-IRC** | HR: 0.49 (0.23, 1.04) [0.062] | HR: 0.34 (0.12, 0.98) [0.045] |
| **ORR-IRC** | OR: 0.81 (0.37, 1.80) [0.607] | OR: 0.68 (0.25, 1.86) [0.450] |
| **CRR-IRC** | OR: 0.67 (0.31, 1.46) [0.309] | OR: 0.74 (0.27, 2.07) [0.571] |

**Figure 1.** Pola + BR vs adjusted and unadjusted tafasitamab + lenalidomide KM curves

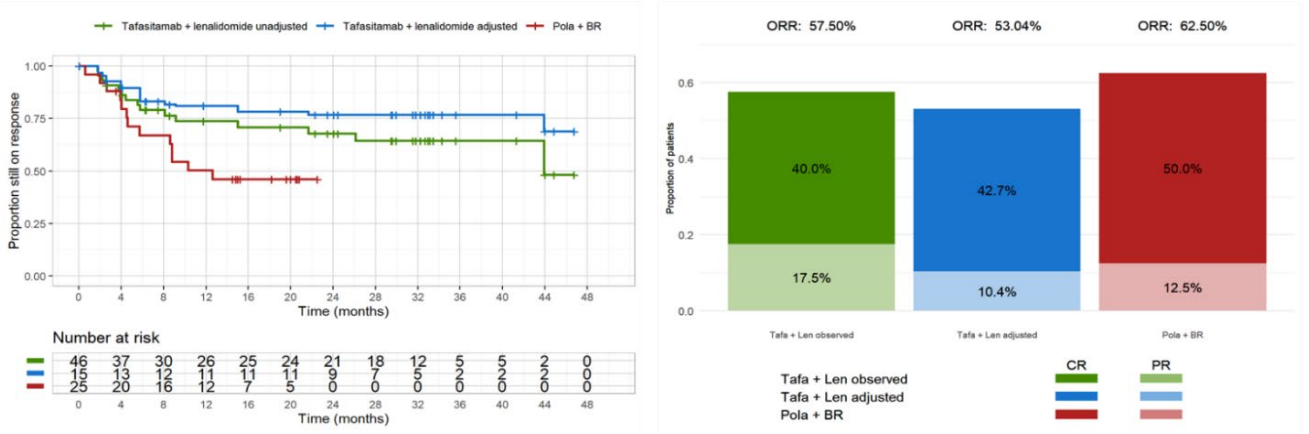
**- A**

| Observed and weighted KM estimates of OS for TAFA + LEN against reported OS estimates for POLA + BR | Observed and weighted KM estimates of PFS-IRC for TAFA + LEN against reported PFS-IRC estimates for POLA + BR |
|---|---|




**- B**

| Observed and weighted KM estimates of DOR-IRC for TAFA + LEN against reported DOR-IRC estimates for POLA + BR | Depth of IRC-responses of patients enrolled in the L-MIND study before and after the population matching and reported for POLA + BR |
|---|---|




To further validate the results of the MAIC analysis, the sponsor presented an additional comparative analysis with study RE-MIND2. This comparison was based on real world Pola + BR data collected from an observational trial and was done using a different methodological approach, using propensity score matching based on patient level data between the two therapies. The results are supportive of the MAIC outcome.

Despite the differences in treatment duration (6 months for polatuzumab and 12 months for tafasitamab + lenalidomide, followed by monotherapy), the sponsor considered it possible to compare the two treatments, in particular as the endpoints measured were the same and the duration of follow up was similar. They also emphasised the possibility to treat patients with tafasitamab (a single immunotherapeutic agent without chemotherapy) until progression, which was not evaluated for Pola+BR because of its toxicity.

The sponsor also claimed that the vast majority of prior precedents in oncology clearly rely on durable responses, establishing the importance of favourable effects on both endpoints, ORR and DoR. The significance of ORR is assessed by its magnitude and duration. Based on the MAIC analysis, after adjusting for the differences in key prognostic factors, the DoR of patients treated with tafasitamab + lenalidomide was longer than for the patients who were treated with polatuzumab vedotin + BR. There was a trend towards prolonged PFS and OS, but the presented single HR were not statistically significant.

During the oral explanation some further aspects of the MAIC were clarified. The specific model was selected by the sponsor as it had the highest sample size and all models with less than 16 patients were rejected. The consistency between the models was considered reassuring, with the obvious difference that the confidence interval became wider for the models with lower sample size. With the limitations recognised by the sponsor, the COMP accepted the results from the MAIC.

The possibility of reliably comparing the survival data from the pivotal studies was also discussed. The sponsor claimed that, for Polivy, most events had happened at month 20, after which the curve would stay the same at best. However, that was not the case for Minjuvi-treated patients. This was appreciated by the COMP, however, due to the single arm nature of L-MIND and the small datasets for both treatments (tafasitamab and polatuzumab vedotin), the survival data was not considered to be supportive for the significant benefit. DoR is not to be considered as a surrogate endpoint for clinically relevant and confirmatory endpoints like PFS and OS, and the sponsor concurred that there is no literature to support this. The uncontrolled study design of L-MIND did not allow for any conclusions to be drawn on whether the continuation of tafasitamab monotherapy had contributed to the prolonged DoR.

Furthermore, it was clarified that tafasitamab was well tolerated in the mono-therapy part of the study and that there were lower AEs than in the phase where tafasitamab was given in combination with lenalidomide as compared to Pola + BR.

The sponsor considered that the synergistic effect of lenalidomide and tafasitamab is the reason for why this product will work, as opposed to other products. Based on data from a few patients, the sponsor also confirmed that CD19 function is preserved after treatment with Minjuvi, which was considered important as it would allow for further treatment with CAR T-cell products.

In conclusion, the COMP acknowledged that there are limited treatment options for patients with DLBCL refractory to R-CHOP and considered that the considerable longer duration of response with Minjuvi over Polivy could be of clinical relevance and supportive of a significant benefit, in a target population with limited treatment options and poor prognosis.

# 4. COMP position adopted on 15 July 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of diffuse large B-cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening in patients not responding to first-line treatment;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Minjuvi may be of potential significant benefit to those affected by the orphan condition still holds. Patients who relapsed after or were refractory to first line treatment and were not eligible for autologous stem cell transplantation, achieved comparable response rates and a longer duration with Minjuvi as indirectly compared to the other approved product in this setting, Polivy. This was considered clinically relevant given a target population with limited treatment options and poor prognosis.

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 Minjuvi, Humanised Fc engineered monoclonal antibody against CD19, tafasitamab for treatment of diffuse large B-cell lymphoma (EU/3/14/1424) is not removed from the Community Register of Orphan Medicinal Products.