Input from manufacturer on the 2nd draft assessment "POLATUZUMAB VEDOTIN IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB FOR THE TREATMENT OF RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WHO ARE NOT CANDIDATES FOR HEMATOPOIETIC STEM CELL TRANSPLANT"

Project ID: PTJA06

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Comments on the 2nd draft rapid assessment on polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large b-cell lymphoma (dlbcl) who are not candidates for hematopoietic stem cell transplant

The objective of this reviewer form is to standardise the process of the factual accuracy check of the rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment on polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large b-cell lymphoma (dlbcl) who are not candidates for hematopoietic stem cell transplant was open to review by the manufacturer [Roche] between **02/02/2020 and 06/02/2020**.

Comments received from:

Marketing Authorisation Holder
Roche

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments on the 2nd draft rapid assessment on polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large b-cell lymphoma (dlbcl) who are not candidates for hematopoietic stem cell transplant

Comments from Marketing Authorisation Holder [Roche]

Page	Line	Comment	Character of comment[i]	Reply from author
General		For the final version, the consistency issues summarized below should be checked and adapted throughout the full REA report: ● Correct "DLBCL" to "R/R DLBCL" across the document where appropriate, including the Tables ● Ensure consistency of Table titles when referring to "overall DLBCL population" versus "Arm C and D - study GO29365"; for example see Table 12 and Table 13. The MAH suggests not to include "Arm C and Arm D" in the Table titles but to instead include this within the Tables, and keep Table titles as "R/R DLBCL, Randomized Phase II", where appropriate. ● Throughout the majority of the report there are only a few references to the Tables within the text. In order to help the reader of this report, the MAH suggests to refer to the relevant Tables in the text. ● Replace "IRC-confirmed" by "IRC-assessed", where applicable in the text, Tables, and Table titles, for consistency. ● Ensure consistency by adding "IRC-assessed" either in Table titles or in directly in the Tables, (where applicable) Ensure consistency with respect to numbers following the decimal point in the text and all Tables (e.g. Table 9 – there are 2 numbers following the decimal point; Table 15 there is one number following the decimal point).	2	Based on MAH comments, the authoring team modified the following formal issues: • Use of R/R DLBCL instead of DLBCL • Replace IRC confirmed by IRC assessed (including in tables) This comment is not related to a factual mistake.
General		For accuracy, please replace "overall DLBCL population" with "overall **R/R** DLBCL population" throughout the report.	2	Modification accepted by the authoring team. This comment is not related to a factual mistake.
General		Throughout the report, "polatuzumab" is used. The MAH suggests to replace this with "polatuzumab vedotin" as this is the correct name of the active substance as described in Table 5 (Page 22) of the REA report.	2	This comment is not related to a factual mistake. It is clearly stated in the report that Polatuzumab vedotin is named polatuzumab in this report

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General		The scope defined by the EUnetHTA Assessment Team in the project plan for this Joint Relative Effectiveness Assessment (REA) was based on three PICOs: ● PICO 1a: Patients after failure of first-line therapy; ● PICO 1b: Patients after failure of two or more therapies; ● Overall R/R DLBCL patient population MAH Response: The MAH provided an explanation for their position on their scope for this Joint REA on Page 23 and Page 24 of the REA submission dossier. Stem cell transplant ineligibility represents the major therapeutic challenge. Regardless of treatment line, patients with R/R DLBCL who are ineligible for stem cell transplant (SCT) treatment are treated without curative intent. There are only a few therapeutic options for patients with R/R DLBCL who are ineligible for SCT due to age, comorbidities or lack of response to salvage treatment or have relapsed after SCT. Furthermore, there are no universally-established therapies or regulatory-approved treatments in this setting. Therefore, the goal for these patients is to achieve a prolonged response and to ultimately extend survival. Due to the heterogeneity of the patient population with overlapping disease characteristics and limited treatment options, patients with first-line and later-line relapse, are described as a patient segment with a uniformly high unmet need due to little chance at prolonged control of disease with a dismal survival outcome. Furthermore, there is no clear consensus in clinical guidelines, such as those put forth by the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) with regards to management by treatment-line for R/R DLBCL patients who are ineligible for SCT. The unmet need for these patients is reflected in the ESMO guidelines that recommend non-curative platinum- and/or gemcitabine- based regimens and enrolment into clinical trials investigating novel drugs due to the absence of effective therapies. Thus, our position and the focus of this assessment is that R/R DLBCL patients who are ineligible for SCT should be treated as one single population.	1	This comment is outside of the scope of the factual accuracy check. Rationale of these positions can be found in the report and/or project plan.
General		As mentioned above and discussed during the scoping face-to-face meeting with the EUnetHTA Assessment Team and Coordination Team in April 2019, the MAH's position is that R/R DLBCL patients who are ineligible for SCT should be treated as one single population. This is in alignment with the scope of the EMA and the label that received conditional marketing authorization on 21 January 2020. Therefore, in the REA submission dossier the MAH provided efficacy and safety data for this overall R/R DLBCL population. In addition, as already explained by the MAH in their responses to the information requests from the EUnetHTA Assessment Team received on 9 July 2019, the EMA requested efficacy data by prior line of therapy during the filing process and, for transparency reasons these same efficacy data were also provided to the EUnetHTA	1	This comment is outside of the scope of the factual accuracy check. Rationale of these positions can be found in the report and/or project plan.

Page	Line	Comment	Character of comment[i]	Reply from author
		Assessment Team either in the main body of the REA submission dossier and/or in the appendices of the REA submission dossier. It should be noted that safety data by prior line of therapy was neither requested nor provided to the EMA and hence not provided to the EUnetHTA Assessment Team.		
General		The MAH provided efficacy data by prior line of therapy (where available) either in the main body of the REA submission dossier and/or in the appendices of the REA submission dossier. These are the same data provided to the EMA during the filing process. Where data are not available, the IQWiG has provided their own calculations. However, there are instances where the IQWiG have provided calculations but have not stated this in the footnote (e.g. Table 3, risk difference [RD] for IRC-assessed complete response). As a result, the MAH is of the opinion that more clarity is needed with regards to the Tables provided in the REA report as they can be confusing to the reader. Furthermore, the MAH would like it to be noted that for them to be able to conduct a thorough fact check of calculations made by IQWIG in under 4 working days is neither realistic or feasible. The MAH would like the authors of the report to ensure that all data, whether provided by the MAH or calculated by the IQWiG or taken from the EPAR are clearly captured and with the appropriate footnotes.	1	This comment is not related to a factual mistake. Consistency of footnotes marking own calculations (summary vs. main results part) was ensured in the medical editing step that was conducted in parallel to the fact check
General		The data for the relative risk included in the report have been calculated by the IQWiG. In addition to the justification provided on Page 80 of the REA submission dossier, the MAH provided the same justification in their responses to the information requests from the EUnetHTA Assessment Team received on 9 July 2019. For reference, this justification is provided again below: “The methods used for analyzing and reporting safety endpoints for the GO29365 was pre-specified in the protocol (see Section 6.5, GO29365 Protocol provided in Appendix 1) and were based on the recommendations from the Extension of the CONSORT Statement (Ioannidis et al. 2004) and the International Conference of Harmonization (ICH) E9 (Statistical Principles for Clinical Trials). Typically, the safety and tolerability implication are best addressed using descriptive statistical methods because most trials lack the power to test harm-related hypotheses or have no explicit pre-specified harm-related hypotheses. Additionally, conducting statistical tests over multiple safety outcomes such as AEs causes the multiple testing issue which inflates the Type I error.”	2	This comment is outside of the scope of the factual accuracy check.
General		The following is stated numerous times throughout the REA report: ● “The risk of bias at study level was rated as high, because study GO29365 was open-label and not free from potential sources of bias beyond randomisation, allocation concealment or selective outcome reporting.”	2	This comment is outside of the scope of the factual accuracy check.

Page	Line	Comment	Character of comment[i]	Reply from author
		MAH Response: The MAH acknowledges that an open-label study carries a risk of bias but the risk was mitigated by the randomized clinical trial design.		Rationale of these positions can be found in the report and/or project plan.
General		The following is stated numerous times throughout the report: ● "The risk of bias at outcome level was also rated as high for all available outcomes." ● "The result has a high risk of bias." MAH Response: The risk of bias at the outcome level, for complete response (CR) and progression-free survival (PFS), was mitigated by: ● The assessment by an Independent Review Committee(IRC) As acknowledged by the authors in the REA report, "Even though GO29365 is an open label", the risk of bias for overall survival (OS) is "considered low, as the determination of death is considered sufficiently certain."	2	This comment is outside of the scope of the factual accuracy check. Rationale of these positions can be found in the report and/or project plan.
General		The following is stated numerous times throughout the report: ● "For the second data cut-off, only results for overall survival were available." MAH Response: For the second clinical cut-off date (CCOD; 11 October 2018), the following data, in addition to OS, were provided to the EUnetHTA Assessment Team in the REA submission dossier: ● Updated PFS as assessed by the Investigator (PFS-INV) in the overall R/R DLBCL patient population (See Pages 115-117 of the REA submission dossier). ● Updated PFS-INV by prior line of therapy, relevant for PICO 1a (submitted as an appendix to the REA submission dossier) Updated safety data from the GO29365 study (CCOD: 11 October 2018) was provided in Section 4.6.3 of the REA submission dossier. Additionally, the Biologics License Application (BLA) 90-day Safety Update Report, which was submitted to the United States Food & Drug Administration (FDA) and provides cumulative safety data from the pivotal GO29365 study was also provided to the EUnetHTA Assessment Team in Appendix 15 of the REA submission dossier.	1	The authors decided to include in the assessment PFS assessed by IRC as the relevant outcome operationalisation for the assessement. Data on IRC confirmed PFS was not available for the second clinical cut-off date. For safety, results of the randomised study phase are only available for the treatment arm BR (Arm D). For polatuzumab + BR, results are only

Page	Line	Comment	Character of comment[i]	Reply from author
				available by combining the Phase Ib safety run-in arm and the Phase II randomised Arm C (combined N = 45). A comparative assessment of Arms C and D is therefore not possible (see footnote d in table 14)
Page 1	Lines 17 & 18	Please include the full approved label wording on the front cover of the REA report so that it is aligned with the European Summary of Product Characteristics (SmPC). Proposed Amendment: Polatuzumab vedotin 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.	2	This comment is outside of the scope of the factual accuracy check.
Page 3	Further Contributors Table	Instead of referring to “Roche”, please use “Roche Registration GmbH”	2	Based on MAH comments, the authoring team modified this sentence
Page 10	Line 7	The report states: “Polatuzumab vedotin-piiq” Proposed Amendment: “Polatuzumab vedotin” The “-piiq’ is an FDA suffix, outside of the United States the product is known only as “polatuzumab vedotin”. Therefore, please remove “-piiq”.	3	The authoring team modified this sentence in the medical editing step that was conducted in parallel to the fact check
Page 10	Line 7	The following is stated in the report: “(POLIVY, named polatuzumab in this report)…” Proposed Amendment: “Polatuzumab vedotin” This is the correct name of the active substance as described in Table 5 (Page 22) of the REA report.	2	This comment is outside of the scope of the factual accuracy check. It is clearly stated in the report that Polatuzumab vedotin is named

Page	Line	Comment	Character of comment[i]	Reply from author
				polatuzumab in this report
Page 13	Lines 7 & 8	The following is stated in the report: "For the second data cut-off, only results for overall survival were available and no addendum to the clinical study report was submitted." <u>MAH Response:</u> This statement is not correct. For the second clinical cut-off date (CCOD; 11 October 2018), the following data, in addition to OS, were provided tot he EUnetHTA Assessment Team in the REA submission dossier: ● Updated PFS as assessed by the Investigator in the overall R/R DLBCL patient population (See Pages 115-117 of the REA submission dossier) ● Updated PFS as assessed by the Investigator by prior line of therapy, relevant for PICO 1a (submitted as an appendix to the REA submission dossier) Updated safety data from the GO29365 study (CCOD: 11 October 2018) was provided in Section 4.6.3 of the REA submission dossier. Additionally, the BLA 90-day Safety Update Report, which was submitted to the United States FDA and provides cumulative safety data from the pivotal GO29365 study was also provided to the EUnetHTA Assessment Team in Appendix 15 of the REA submission dossier.	1	See comment and answer above (page 6)
Page 19	Line 9	The report states: "…GP29365.." <u>Proposed Amendment:</u> The study number has been captured incorrectly. Please replace with "GO29365".	2	The authoring team modified the study number in the medical editing step that was conducted in parallel to the fact check
Page 16	Table 3	The data on the risk difference (RD) for complete response (CR) do not correspond with the data provided by the MAH in Appendix 9 of the REA submission dossier. Therefore, footnote 'e' should be clarified and it stated clearly who made this calculation.	2	There is no factual error. There is no data for Risk difference (RD) for complete response (CR) in Appendix 9. RD was calculated by IQWiG. Consistency of footnotes marking own calculations

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				(summary vs. main results part) was ensured in the medical editing step that was conducted in parallel to the fact check
Page 18	Table 4	The data provided in Table 4 of the REA report was not provided by the MAH. Assuming that the data provided are based on IQWiG calculations, this should be clearly stated either in the Table title, or footnote 'a' should be applied to all numbers within the Table.	2	Data in table 4 was calculated based on data provided by the MAH: OS: App 7 (p. 4 and p.7) and Forest Plot in dossier p. 98 PFS: Forest Plot (IRC) in dossier (p. 100) and App 8 (p. 4 and p.7) Complete response: App 9 (p.5 and p.6) Own calculations are marked by footnotes.
Page 20	Line 32 & 33	The following is stated in the report: "The populations in the two study arms are imbalanced, notably regarding the reason for SCT ineligibility or prognostic factors of the disease, which might favour the polatuzumab + BR arm." <u>Proposed Amendment:</u> In alignment with the EPAR (Page 124), the MAH suggests to add the following text: "All transplant ineligible subgroups of patients derived clinical benefit from Pola+BR independently of the reasons for their ineligibility. Based on subgroups analysis on primary endpoint, PFS and OS the effect remains stable across subgroups, independently of baseline imbalances between arms in the RR TNE [transplant non-eligible] DLBCL patients	2	This comment is outside of the scope of the factual accuracy check. Rationale of these positions can be found in the report and/or project plan.

Page	Line	Comment	Character of comment[i]	Reply from author
		supporting the internal consistency of the study."		
Page 20	Line 37 & 39	The following is stated in the report: "The randomised stage of the study GO29365 was performed using the liquid formulation of polatuzumab, which is not intended for marketing. It should be noted that evidence regarding the marketed formulation only relies on a single-arm cohort that included 42 patients." <u>Proposed Amendment:</u> The MAH suggests to include the following text from the EPAR: "The applicant provided preliminary analyses from the single-arm cohort, Arm G, of the GO29365 study with R/R DLBCL patients receiving the lyophilized formulation of polatuzumab vedotin (140 mg/vial) in combination with BR". "The PK analysis supports the comparability of both liquid and lyophilised formulations." (EPAR Page 125) "A similar profile was observed in the safety population of Arm G in study GO29365, with 140 lyo DP Pola+BR." (EPAR Page 129)	2	This comment is outside of the scope of the factual accuracy check. Rationale of these positions can be found in the report and/or project plan.
Page 20	Line 40	The report states: "Additional results from a second non-randomised arm of study GO29365 (Arm H) are expected in 2022." <u>Proposed Amendment:</u> The primary analysis of Arm H (n=64) as well as the pooled analysis of Arm G (n=42) and Arm H (n=64) is a specific obligation for the conditional marketing authorization and will be submitted to the EMA in Q3 2020.	2	Based on MAH comments, the authoring team modified this sentence.The authors want to highlight that according to the submission dossier, the data from Arm H were expected in 2022 and therefore this comment is not related to a factual mistake.
Page 22	Line 9	The report states: "Polatuzumab vedotin-piiq"	3	The authoring team modified this wording in the medical editing step

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		Proposed Amendment: "Polatuzumab vedotin" The "-piiq' is an FDA suffix, outside of the United States the product is known only as "polatuzumab vedotin". Therefore, please remove "-piiq".		that was conducted in parallel to the fact check
Page 22	Table 5	The report states: "Polatuzumab vedotin-piiq" Proposed Amendment: "Polatuzumab vedotin" The "-piiq' is an FDA suffix, outside of the United States the product is known only as "polatuzumab vedotin". Therefore, please remove "-piiq".	3	The authoring team modified this wording in the medical editing step that was conducted in parallel to the fact check
Page 22	Table 5	In Table 5 of the report under 'Monitoring Required", it is stated that "Healthcare professionals are asked to report any suspected adverse reactions." Proposed Amendment: "Healthcare professionals are asked to report any adverse events."	2	This comment is not endorsed. In the SmPC the exact labeling is "adverse reactions".
Page 29	Lines 28-30	The report states that "the list of excluded studies was missing." and that "there is a link to a document within the systematic literature review (Appendix 4 in Appendix 17), but it is not possible to open the individual documents." MAH Response: The MAH would like to highlight that the list of excluded studies was available as an appendix to the systematic literature review at the time of submission and during the assessment. However, during the completeness check the MAH was not notified that this appendix was not accessible.	2	This comment is outside of the scope of the factual accuracy check. In the fomal completeness request we pointed out regarding Template Section "Section 5.1 Identification and selection of relevant studies": „*Section is missing in the submission. Please provide this section according to the template".* .

Page	Line	Comment	Character of comment[i]	Reply from author
Page 30	Table 9	The MAH would like it to be made clear what available documentation were provided as part of their REA submission. These were as follows: 1. Interim Clinical Study Report (Report number 1078954; June 2019) (reference 11 in the REA report) 2. Supplemental Results Report - Arm G (March 2019) (reference 13 in the REA report) 3. United States FDA BLA 90-day Safety Update Report (March 2019) (reference 13 in the REA report) Study Registry Entries (references 14 and 15 in the REA report)	2	There is no factual mistake. The Supplemental report for Arm G is dated june 2019
Page 31	Line 10	The report states: “4.4 Study G029365” Proposed Amendment: The study number has been captured incorrectly. Please replace with “G**O**29365”.	2	The authoring team modified the study name in the medical editing step that was conducted in parallel to the fact check
Page 31	Line 12	The report states: “Table 11: Description of study G029365” Proposed Amendment: The study number has been captured incorrectly. Please replace with “G**O**29365”.	2	The authoring team modified the study name in the medical editing step that was conducted in parallel to the fact check
Page 31	Table 11	In Table 11 under the main characteristics of the study design the following is stated in the text for Arms A to D “…indication approved by the CHMP.” Proposed Amendment: This is not accurate. The indication was approved by the European Commission. The MAH suggests the following text “indication approved by the European Commission”	2	Based on MAH comments, the authoring team modified this sentence.
Page 31	Table 11	In Table 11 under the main characteristics of the study design the following is stated in the text for Arms E and F “…indication approved by the CHMP.” Proposed Amendment: This is not accurate. The indication was approved by the European Commission. The MAH suggests the following text “indication approved by the European Commission”	2	Based on MAH comments, the authoring team modified this sentence.
Page 32	Table 11	In Table 11 under the main characteristics of the study design the following is stated in the text for Arms G and H “…indication approved by the CHMP.”	2	Based on MAH comments, the authoring

Page	Line	Comment	Character of comment[i]	Reply from author
		Proposed Amendment: This is not accurate. The indication was approved by the European Commission. The MAH suggests the following text "indication approved by the European Commission"		team modified this sentence.
Page 32	Table 11, row 4	In Table 11 under main characteristics of the study design it is stated "However, only results from Arm G are currently available; results from Arm H are expected in Q1 2022." Proposed Amendment: The primary analysis of Arm H (n=64) as well as the pooled analysis of Arm G (n=42) and Arm H (n=64) is a specific obligation for the conditional marketing authorization and will be submitted to the EMA in Q3 2020.	2	Based on MAH comments, the authoring team modified this sentence. The authors want to highlight that according to the submission dossier, the additional data from Arm H were expected in 2022 and therefore this comment is not related to a factual mistake.
Page 32	Table 11, row 5	In Table 11 under the conduct of study it is stated that the date for the last patient included in the single-arm cohort (Arm G) was "not available" Proposed Amendment: The last patient was included in the single-arm cohort (Arm G) on 8 July 2019.	2	This comment cannot be taken into account without an official document. This information could not be find in any of the submitted documents.
Page 36	Lines 7 & 8	The following is stated in the report: ● Line 7: "Second data cut-off (11 October 2018): updated efficacy and safety." ● Line 8: "For the second data cut-off, only results for overall survival were available." MAH Response: For the second clinical cut-off date (CCOD; 11 October 2018), the following data, in addition to OS, were provided to the EUnetHTA Assessment Team in the REA submission dossier: ● Updated PFS as assessed by the Investigator (PFS-INV) in the overall R/R DLBCL patient population (See Pages 115-117 of the REA submission dossier). Updated safety data from the GO29365 study (CCOD: 11 October 2018) was provided in Section 4.6.3 of the	1	See above (page 6)

Page	Line	Comment	Character of comment[i]	Reply from author
		REA submission dossier. Additionally, the Biologics License Application (BLA) 90-day Safety Update Report, which was submitted to the United States Food & Drug Administration (FDA) and provides cumulative safety data from the pivotal GO29365 study was also provided to the EUnetHTA Assessment Team in Appendix 15 of the REA submission dossier.		
Page 37	Line 11 & 12	The report states the following: "Patients in each treatment arm had received a median of two prior lines of anti-lymphoma chemotherapy (up to a maximum of seven)". Proposed Amendment: "Patients in each treatment arm had received a median of two prior lines of anti-lymphoma chemotherapy (up to a maximum of seven in the Pola + BR arm and up to a maximum of 5 in the BR arm)".	2	This comment is outside of the scope of the factual accuracy check.
Page 40	Line 7	The following is stated in the report: "For the first data cut-off, data were available for overall survival, adverse events, PFS and complete response; for the second data cut-off, only for overall survival." MAH Response: For the second clinical cut-off date (CCOD; 11 October 2018), the following data, in addition to OS, were provided to the EUnetHTA Assessment Team in the REA submission dossier: ● Updated PFS as assessed by the Investigator (PFS-INV) in the overall R/R DLBCL patient population (See Pages 115-117 of the REA submission dossier). Updated safety data from the GO29365 study (CCOD: 11 October 2018) was provided in Section 4.6.3 of the REA submission dossier. Additionally, the Biologics License Application (BLA) 90-day Safety Update Report, which was submitted to the United States Food & Drug Administration (FDA) and provides cumulative safety data from the pivotal GO29365 study was also provided to the EUnetHTA Assessment Team in Appendix 15 of the REA submission dossier.	1	See above (page 6)
Page 44	Table 16	Table 16 of the report states that for SAEs the risk of bias is low and that for Severe AEs (CTCAE Grade 3-4) the risk of bias is high. The MAH believes this to be contradictory since if the bias is low for SAEs the same would be expected for Grade 3-4 AEs.	2	This comment is outside of the scope of the factual accuracy check. Rationale of these positions can be found in the report and/or project plan.
Page 47	Line 4	The report states the following: "The median PFS time was 9.5 months (95% CI: 6.2, 13.9 months) in the polatuzumab + BR group versus 3.7	2	Based on MAH comments, the authoring

Page	Line	Comment	Character of comment[i]	Reply from author
		months (95% CI: 2.1, **5.4** months) in the BR group…" The upper confidence interval for the median PFS in the BR arm is incorrect. The number in the text does not match that in Table 19 (see Table 23 of the REA submission dossier or Table 25 of the CSR). Proposed Amendment: "The median PFS time was 9.5 months (95% CI: 6.2, 13.9 months) in the polatuzumab + BR group versus 3.7 months (95% CI: 2.1, **4.5** months) in the BR group…"		team modified this sentence.
Page 49	Line 5	The report states: "Safety analyses were performed in a modified intention-to-treat (mITT) population…" Proposed Amendment: As described on Page 78 of the REA submission dossier "Safety analyses were based on the safety evaluable population which included all treated patients (i.e. patients who received any amount of study medication) according to actual treatment received".	2	Based on MAH comments, the authoring team modified this sentence. .
Page 50	Line 9	The report states: "Results from Arm G (formulation of polatuzumab intended for marketing) were extracted…." Proposed Amendment: "Preliminary results from Arm G…"	2	This comment is outside of the scope of the factual accuracy check.
Page 53	Lines 6-8	The report states: "It should be noted that while polatuzumab in combination with BR was compared to axicel using the mITT population, the comparison with tisagenlecleucel was performed using the ITT population." MAH Response: The MAH would like to highlight that both CAR-T comparisons were performed using the ITT populations. For the comparison with axicel, aggregated data from the 81 patients comprising the DLBCL ITT in ZUMA-1 trial were used (See Page 207 of the REA submission dossier).	2	Based on MAH comments, the authoring team modified this sentence.
Page 58	Lines 2 & 3	The following is stated in the report: "For the first data cut-off, data were available for overall survival, adverse events, PFS and complete response; for the second data cut-off, only for overall survival." MAH Response: For the second clinical cut-off date (CCOD; 11 October 2018), the following data, in addition to OS, were provided to the EUnetHTA Assessment Team in the REA submission dossier:	1	See above (page 6)

Page	Line	Comment	Character of comment[i]	Reply from author
		Updated PFS-INV by prior line of therapy, relevant for PICO 1a (submitted as an appendix to the REA submission dossier)		
Page 64	Lines 10 & 11	The report states: “Patients in each treatment arm had received a median of two prior lines of anti-lymphoma chemotherapy (up to a maximum of seven)”. Proposed Amendment: “Patients in each treatment arm had received a median of two prior lines of anti-lymphoma chemotherapy (up to a maximum of seven in the Pola + BR arm and up to a maximum of 5 in the BR arm)”.	2	This comment is outside of the scope of the factual accuracy check. See above.
Page 66	Table 29	In Table 29, the Time from last anti-lymphoma therapy [days], median [min; max] for the BR arm is included as “79**,**5” Proposed Amendment: 79**.**5	3	The authoring team modified this wording in the medical editing step that was conducted in parallel to the fact check
Page 70	Table 32	The data provided in Table 32 was not provided by the MAH. Assuming that the data provided is based on IQWiG calculation, this should be clearly stated either in the Table title, or footnote ‘a’ should be applied to all numbers within the Table.	2	See comment above regarding table 4
Page 72	Table 33	The data provided in Table 33 was not provided by the MAH. Assuming that the data provided is based on IQWiG calculation, this should be clearly stated either in the Table title, or footnote ‘a’ should be applied to all numbers within the Table.	2	See comment above regarding table 4
Page 73	Table 34	The data provided in Table 34 was not provided by the MAH. Assuming that the data provided is based on IQWiG calculation, this should be clearly stated either in the Table title, or footnote ‘a’ should be applied to all numbers within the Table.	2	See comment above regarding table 4
Page 75	Line 7	The report states: “GP29365” Proposed Amendment: The study number has been captured incorrectly. Please replace with “G**O**29365”.	3	The authoring team modified this wording in the medical editing step that was conducted in parallel to the fact check
Page 76	Lines 28 & 29	The following is stated in the report: “The populations in the two study arms are imbalanced, notably regarding the reason for SCT ineligibility or prognostic factors of the disease, which might favour the polatuzumab + BR arm.” Proposed Amendment:	2	This comment is outside of the scope of the factual accuracy check.

Page	Line	Comment	Character of comment[i]	Reply from author
		In alignment with the EPAR (Page 124), the MAH suggests to add the following text: "All transplant ineligible subgroups of patients derived clinical benefit from Pola+BR independently of the reasons for their ineligibility. Based on subgroups analysis on primary endpoint, PFS and OS the effect remains stable across subgroups, independently of baseline imbalances between arms in the RR TNE [transplant non-eligible] DLBCL patients supporting the internal consistency of the study."		
76	Lines 33-35	The following is stated in the report: "The randomised stage of the study GO29365 was performed using the liquid formulation of polatuzumab, which is not intended for marketing. It should be noted that evidence regarding the marketed formulation only relies on a single-arm cohort that included 42 patients." <u>Proposed Amendment:</u> The MAH suggests to include the following text from the EPAR: "The applicant provided preliminary analyses from the single-arm cohort, Arm G, of the GO29365 study with R/R DLBCL patients receiving the lyophilized formulation of polatuzumab vedotin (140 mg/vial) in combination with BR". "The PK analysis supports the comparability of both liquid and lyophilised formulations." (EPAR Page 125) "A similar profile was observed in the safety population of Arm G in study GO29365, with 140 lyo DP pola +BR." (EPAR Page 129)	2	This comment is outside of the scope of the factual accuracy check. Rationale of these positions can be found in the report and/or project plan.
76	Line 35 & 36	The report states: "Additional results from a second non-randomised arm of study GO29365 (Arm H) are expected in 2022." <u>Proposed Amendment:</u> The primary analysis of Arm H (n=64) as well as the pooled analysis of Arm G (n=42) and Arm H (n=64) is a specific obligation for the conditional marketing authorization and will be submitted to the EMA in Q3 2020.	2	Based on MAH comments, the authoring team modified this sentence The authors want to highlight that according to the submission dossier, the data from Arm H were expected in 2022 and therefore this

Page	Line	Comment	Character of comment[i]	Reply from author
				comment is not related to a factual mistake.
Page 77	Lines 34 & 35	Reference number 12: Hoffmann-La Roche. Supplemental results report for study GO29365: arm G 90-day safety update (CCOD: 15 March 2019) [unpublished]. 2019. <u>Proposed amendment:</u> Hoffmann-La Roche. Supplemental results report for study GO29365: arm G (CCOD: 15 March 2019) [unpublished]. 2019.	2	Based on MAH comments, the authoring team modified this sentence
Page 77	Line 36 & 37	Reference number 13: Hoffmann-La Roche. 90-day safety update: polatuzumab vedotin (CCOD: 19 March 2019) [unpublished]. 2019. <u>MAH Response:</u> The CCOD is not correct. The date of 19 March 2019 corresponds to the date of the report. The updated cumulative safety data presented for the pivotal GO29365 study in the US BLA 90-day safety update was based on a CCOD of 11 October 2018.	2	Based on MAH comments, the authoring team modified this sentence
Page 84	Table 36	In Table 36, the percentatge of Investigations in the BR arm is included as **2,6** <u>Proposed Amendment:</u> Please replace with **2.6**	3	The authoring team modified this format in the medical editing step that was conducted in parallel to the fact check
Page 85	Table 37	In Table 37, the percentage of total number of AE (CTCAE Grade ≥3 in the Pola+BR arm is included as **84,6** and similarly, the percentage in the BR arm is included as **74,4** <u>Proposed Amendment:</u> Please replace with **84.6** and **74.4**, respectively	3	The authoring team modified this fromat in the medical editing step that was conducted in parallel to the fact check
Page 87	Table 38	In Table 38, the percentage of neutropenia in the Pola + BR arm is included as **7,7** <u>Proposed Amendment:</u> Please replace with **7.7**	3	The authoring team modified this fromat in the medical editing step that was conducted in parallel to the fact check
Page 89	Table 40	In Table 40, the percentage of neutropenia in the Pola + BR arm is included as **7,7**	3	The authoring team modified this fromat in

Page	Line	Comment	Character of comment[i]	Reply from author
		Proposed Amendment: Please replace with **7.7**		the medical editing step that was conducted in parallel to the fact check
Page 95	Line 14	The report states the following: "☒ no: It is clear from the information that no blinded assessment took place." MAH Comment: Blinded IRC-assessment took place for the endpoints for PFS and CR rate.	2	Based on MAH comments the authoring team modified this sentence.

[i] Character of comment
- 'major'=1
- minor'= 2

'linguistic'=3