EUnetHTA Joint Action 3 2016-2020

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***

Project description and planning

IQWIG, Germany

HAS, France

Template Version 2, December 2018

Version Log

Version number	Date	Modification	Reason for the modification
V0.1	27/02/2019	First draft of the project plan	
V0.2	03/04/2019	Second draft of the project plan	Incorporated feedback from dedicated reviewers
V0.3	11/07/2019	Thrid draft of the project plan	Incorporated change in wording of the proposed indication EU (was revised to state “relapsed/refractory” instead of “previously treated”)
V1.0	22/11/2019	Final version of the project plan	Final, after positive CHMP opinion released, including updated timelines
V2.0	12/02/2020	Modification of the final version of the Project Plan	Updated title to align with EC approved indication

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List of abbreviations

AE	Adverse event
B-symptoms	Systemic symptoms (Fever, night sweats, weight loss)
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DHAP+/- R	DH – Dexamethasone A – Cytarabine (also known as Ara C) P – Cisplatin R – Rituximab
DLBCL	Diffuse large B-cell Lymphoma
DOICU	Declaration of Interest and Confidentiality Undertaking
DR	Dedicated Reviewer
EPAR	European Public Assessment Report
EUnetHTA	European Network for Health Technology Assessment
F2F	Face to Face meeting
PM	Project Management
(p)MAH	(prospective) Marketing Authorisation Holder
ICE +/- R	I – Ifosfamide C – Carboplatin E – Etoposide (also known as Vepesid, Etopophos or Eposin) R – Rituximab
SAE	Serious adverse events
SOC	System Organ Class

1 Introduction

On 21/12/2018, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of polatuzumab vedotin (Roche) agreed that EUnetHTA will perform a joint relative effectiveness assessment of 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. Once finalised this assessment is made publicly available and can be used by European HTA bodies for their national processes supporting reimbursement and pricing decisions.

2 Research question and scope

The aim of this project is to compare the clinical effectiveness and safety of polatuzumab vedotin in the target patient populations with relevant comparators. The target patient populations and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope below.

The following table provides the scope identified for the assessment of polatuzumab vedotin.

Table 2-1: Assessment scope: relevant PICOs identified for the planned assessment

Description	Assessment scope
PICO 1a	
Population	Adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for hematopoietic stem cell transplant – after failure of first line therapy.
Intervention	Polatuzumab vedotin in combination with bendamustine and rituximab (in the approved application).
Comparison	Antineoplastic therapy according to physician's choice (regimens with regulatory approval or a recommendation in evidence-based clinical guidelines, respectively) under consideration of the previous therapy and patients characteristics. Treatment regimens can include: Platinum-and/or gemcitabine based regimens (like GemOx) Platinum based regimens (like ICE or DHAP +/- R) without conditioning chemotherapy for transplant (if necessary with reduced dosage) Rituximab – bendamustine combination (specifically in elderly patients or patients with comorbidities) It is assumed that patients after first-line immunotherapy are treated generally with curative intent. Therefore, palliative care or Best Supportive Care is not considered appropriate as a comparator.
Outcomes[1]	Critical outcomes: ▪ Mortality ▪ Health-related quality of life ▪ Adverse events (AE, SAE, AE according to CTCAE, AE resulting in withdrawal (overall and by SOCs and PT, respectively)) ▪ Symptoms (e.g. like B-symptoms or fatigue) Other outcomes: ▪ Progression free survival (PFS) ▪ Complete Response ▪ Number of patients with polatuzumab antibodies

PICO 1b	
Population	Adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for hematopoietic stem cell transplant – after failure of two or more therapies
Intervention	Polatuzumab vedotin in combination with bendamustine and rituximab (in the approved application)
Comparison	Therapy according to physician's choice (regimens with regulatory approval or a recommendation in evidence-based clinical guidelines, respectively) under consideration of the previous therapy and patients characteristics. After failure of two or more therapies the comparator can include: ▪ axicabtagene ciloleucel ▪ tisagenlecleucel ▪ pixantrone ▪ Rituximab – bendamustine combination (specifically in elderly patients or patients with comorbidities) ▪ Best supportive care (BSC) refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve quality of life
Outcomes[1]	<u>Critical outcomes:</u> ▪ Mortality ▪ Health-related quality of life ▪ Adverse events (AE, SAE, AE according to CTCAE, AE resulting in withdrawal (overall and by SOCs and PT, respectively)) ▪ Symptoms (e.g. like B-symptoms or fatigue) <u>Other outcomes:</u> ▪ Progression free survival (PFS) ▪ Complete Response ▪ Number of patients with polatuzumab antibodies

[1] The outcomes listed include all outcomes deemed relevant by any of the PICO survey respondents. This does not mean that all outcomes were considered relevant by all respondents.

In addition, the assessment will consider the comparison of polatuzumab vedotin in combination with bendamustine and rituximab versus the rituximab and bendamustine combination in adult patients with relapsed/refractory DLBCL who are not candidates for hematopoietic stem cell transplant.

3 Methods

The EUnetHTA Guidelines, available at https://www.eunethta.eu/methodology-guidelines/, will be consulted throughout the assessment process.

3.1 Inclusion criteria

During the assessment the inclusion criteria applied by the pMAH will be checked to evaluate if they capture the PICOs defined for the assessment.

3.2 Information retrieval

The assessment will be based on a submission dossier submitted by the pMAH. To allow for a meaningful assessment, the submission dossier has to be complete with regard to the available evidence relevant for the research question(s). This requires the systematic identification of all published and unpublished studies relevant to the assessment according to the research question and scope defined in Section 2 [7]. The assessment will investigate whether these requirements are met and thus whether the evidence base for the assessment is complete.

The cut-off date for the pMAH's list of sponsored studies and the searches should be a maximum of three months before submission (of the submission dossier). This cut-off date will also be relevant for the assessment. There will be no updates of searches beyond this cut-off by the authors of the assessment.

During the assessment, the evidence base with regard to the drug under assessment provided by the pMAH will be reviewed. Search strategies will be checked for appropriateness and the results of information retrieval included in the pMAH's submission dossier will be checked for completeness against a search in study registries and against the studies included in the regulatory assessment report. If there are major flaws in the search conducted by the manufacturer, further supplementary searches, as appropriate, will be conducted to check for possible incompleteness of the study pool. The search date, complete search strategies and the results of these searches will be reported in the assessment.

If the evidence provided in the submission dossier is incomplete it will not be supplemented by own searches and analyses by the authors of the assessment. The incompleteness and its consequences for the conclusions of the report will be described in the assessment report.

3.3 Data analysis and synthesis

The assessment will be based on the data and analyses included in the submission dossier prepared by the pMAH. During the assessment, the completeness of data and analyses in the submission dossier will be verified. Furthermore, the methods for data analysis and synthesis applied by the pMAH will be checked against the requirements of the submission dossier and applicable EUnetHTA Guidelines and assessed with regard to scientific validity. The results of this assessment and the results of the included studies, as appropriate, will be presented in the assessment report according to the research questions defined in Section 2.

3.3.1 Data extraction

Information used for the assessment of benefits and harms will be extracted from the submission dossier and verified against the Clinical Study Reports (CSR) or other original documentation provided in the submission dossier.

3.3.2 Assessment of risk of bias

The assessment of risk of bias should follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials [8] and non-randomised studies on interventions [9]. The risk of bias of the results of each included study should be described separately for each patient-relevant outcome. For this purpose, risk of bias should be assessed at the study level as well as at the outcome level.

If the outcome-specific risk of bias is classified as high for an outcome, this should not lead to exclusion of the corresponding data. Rather, the risk-of-bias classification should inform the discussion on heterogeneous study results and the determination of certainty of results.

During the assessment, the methods and outcome of the risk-of-bias assessment presented in the submission dossier will be evaluated. Risk-of-bias will be assessed by the authors only for outcomes (and studies) that are included based on the research question(s) (PICO). The result of the risk-of-bias assessment will be presented in the assessment report.

3.3.3 Description of design and results of individual studies

During the assessment, the information in the submission dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalization) and study results will be evaluated. The results of this evaluation will be presented, used for identification of relevant analyses and considered for the conclusions of the assessment report.

3.3.4 Synthesis of study results

Meta-analyses

If several studies are available for the same PICO, they should be quantitatively pooled in a meta-analysis if they are sufficiently comparable from a clinical (e.g. patient groups) and methodological (e.g. study design) point of view [10].

During the assessment, the methods applied for the meta-analyses presented in the submission dossier, and, if applicable, the justification for deviations from the procedures described above will be evaluated. The meta-analyses relevant for the research questions (see Section 2) will be presented in the assessment report.

Sensitivity analyses

To evaluate the robustness of results, sensitivity analyses with regard to methodological factors presented in the submission dossier and the corresponding methods applied will be evaluated. These methodological factors arise from decisions made within the framework of the retrieval and assessment of information, for example, the specification of cut-offs for the time point of data collection or the choice of effect measure. The sensitivity analysis should in particular consider the classification of the risk of bias of study results. The result of the sensitivity analysis can affect the assessment of the certainty of results.

Subgroup analyses and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the submission dossier and the corresponding methods applied will be evaluated. The evaluation also includes the justification for the choice of cut-offs if quantitative characteristics were categorized. If potential effect modifiers are identified, the conclusions inferred from the effects observed in the complete patient group can possibly be formulated more precisely.

Indirect comparisons

If indirect comparisons are included in the submission dossier, the methods applied, and if applicable, the justification in the event of deviations from the required approaches will be evaluated [10]. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the assessment report.

4 Project organisation

4.1 Participants

Table 4-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Institute for quality and efficiency in health care [IQWiG]	Author	Germany	Author will draft the report, all important milestones will be discussed in advance with the co-author
2.	Haute Autorité Sante [HAS]	Co-Author	France	Co-author will review and comment on all parts of the report Fact check
3.	Institute for quality and efficiency in health care [IQWiG], Haute Autorité Sante [HAS]	Information specialist	Germany, France	Review of information retrieval, conduct of searches required for checking completeness of information retrieval in submission dossier; reporting information retrieval check in the assessment report
4.	Institute for quality and efficiency in health care [IQWiG], Haute Autorité Sante [HAS]	Statistical specialist	Germany, France	Expert review of statistical analyses presented in submission dossier, statistical support for authors
5.	Finnish Medicines Agency [FIMEA]	Dedicated Reviewer	Finland	
6.	State Institute for Drug Control [SUKL]	Dedicated Reviewer	Czech Republic	
7.	Dental and Pharmaceutical Benefits Agency [TLV]	Dedicated Reviewer	Sweden	
8.	National Authority of Medicines and Health Products [INFARMED]	Dedicated Reviewer	Portugal	
9.	Gemeinsamer Bundesausschuss [G-BA]	Observer	Germany	

Contributors				
10.	MD PhD Fazila Asmar	External expert	Denmark	Questionaire and in addition (if applicable) answer specific question during the assessment.
11.	Patient organisations (for details see Assessemnt report)	Patient organisations		Complete the EUnetHTA open call in order to inform the scope of the assessment
12.	Institute for quality and efficiency in health care [IQWIG]	Medical Editor	Germany	Responsible for the medical editing of the report
13.	Nederland [ZIN]	Project Manager	Netherlands	Coordination between involved parties throughout the assessment period

4.2 Project stakeholders

Table 4-2: Project stakeholders

Organisation	**Role in the project**
Hoffmann-La Roche	Manufacturer [MAH]; Completing the submission dossier; Fact check of the draft assessment report.

4.3 Milestones and deliverables

Table 4-3: Milestones and deliverables

Milestones/Deliverables	Start date	End date
Project duration	**21-12-2018**	**13-02-2020**
Expression of interest of manufacturer	21-12-2018	
Scoping phase	**01-02-2019**	**14-11-2019**
Scoping and development of draft Project Plan incl. preliminary PICOs from Member States	01-02-2019	27-02-2019
PICO survey – request relevant PICO from Member States	01-02-2019	15-02-2019
Open call for patient input	13-02-2019	05-04-2019
Review of draft Project Plan by DR	27-02-2019	11-03-2019
Development of second draft Project Plan & answers to DR comments	12-03-2019	20-03-2019
Receive scoping F2F meeting documents from pMAH	11-03-2019	
Pre-scoping e-meeting with the assessment team	28-03-2019	
Scoping F2F meeting with manufacturer	12-04-2019	
(pre-)Assessment phase	**27-06-2019**	**13-11-2019**
Receive Submission Dossier from pMAH	27-06-2019	
Check for formal completeness of submission dossier	27-06-2019	08-07-2019
Receive missing items and comments on the requests from the formal completeness check from pMAH	15-07-2019	
CHMP opinion	14-11-2019	
Publication final Project Plan by PM	22-11-2019	
Grace period to update Submission Dossier by pMAH (based on CHMP opinion)	14-11-2019	15-11-2019
Assessment phase	**14-11-2019**	**13-02-2020**
Writing first draft rapid assessment	14-11-2019	14-01-2020
Review by DR(s)	15-01-2020	24-01-2020
Consensus e-meeting with author, co-author and DR	*TBD*	
Writing second draft rapid assessment	25-01-2020	01-02-2020
Medical editing of second draft rapid assessment	02-02-2020	06-02-2020
Fact Check by pMAH (parallel with medical editing)	02-02-2020	06-02-2020
Final version of rapid assessment + response Fact Check	07-02-2020	11-02-2020
Expected EPAR	07-02-2020	
Final editing and publication final assessment report by PM	12-02-2020	13-02-2020

4.4 Conflict of interest management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Authors, co-authors and dedicated reviewers who declare a conflict of interest will be excluded from parts of or the whole work on this specific topic. However, they may still be included in other assessments.

For external experts and patients, conflict of interest declarations are collected with regard to the topic. External experts or patients who declare conflict of interest will be excluded from parts of or the whole work on this specific topic. However, they may still be included in other assessments.

5 References

1. European Network For Health Technology Assessment (EuNetHTA). Comparators & Comparisons: Criteria for the choice of the most appropriate comparator(s) [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/Criteria_WP7-SG3-GL-choice_of_comparator_amend2015.pdf.

2. European Network For Health Technology Assessment (EuNetHTA). Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/02/WP7-SG3-GL-clin_endpoints_amend2015.pdf.

3. European Network For Health Technology Assessment (EuNetHTA). Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/surrogate_endpoints.pdf.

4. European Network For Health Technology Assessment (EuNetHTA). Endpoints used for Relative Effectiveness Assessment: Composite endpoints [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/composite_endpoints.pdf.

5. European Network For Health Technology Assessment (EuNetHTA). Endpoints used for Relative Effectiveness Assessment: Health related quality of life and utility measures [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/Endpoints-used-for-Relative-Effectiveness-Assessment-Health-related-quality-of-life-and-utility-measures_Amended-JA1-Guideline_Final-Nov-2015.pdf.

6. European Network For Health Technology Assessment (EuNetHTA). Endpoints used in Relative Effectiveness Assessment: Safety [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/WP7-SG3-GL-safety_amend2015.pdf.

7. European Network For Health Technology Assessment (EuNetHTA). Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness [online]. December 2017 [Access : 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/Guideline_Information_Retrieval_V1-2_2017.pdf.

8. European Network For Health Technology Assessment (EuNetHTA). Levels of Evidence - Internal validity of randomised controlled trials [online]. November 2015 [Access : 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf.

9. European Network For Health Technology Assessment (EuNetHTA). Internal validity of non-randomised studies (NRS) on interventions [online]. July 2015 [Access : 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-non-randomised-studies-NRS-on-interventions_Guideline_Final-Jul-2015.pdf.

10. European Network For Health Technology Assessment (EuNetHTA). Comparators & Comparisons: Direct and indirect comparisons [online]. November 2015 [Access: 14.03.2018]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/Direct_comparators_comparisons.pdf.