Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on a Finding in the Procedure of Routine Practice Data Collection and Evaluations according to Section 35a, paragraph 3b SGB V: Autologous Anti-CD19-transduced CD3+ Cells (relapsed or refractory mantle cell lymphoma) - Study protocol and statistical analysis plan submission

of 16 March 2023

At its session on 16 February 2023, the Federal Joint Committee (G-BA) decided the following in the procedure for routine practice data collection and evaluations according to Section 35a, paragraph 3b SGB V for the active ingredient autologous anti-CD19-transduced CD3+ cells (hereinafter referred to as brexucabtagene autoleucel; relapsed or refractory mantle cell lymphoma):

I. It is stated that the requirements for routine practice data collection and evaluations are insufficiently implemented in the study protocol and statistical analysis plan prepared by the pharmaceutical company and submitted to the G-BA for review. The following adjustments deemed necessary shall be made to the study protocol (version 1.0; 21 December 2022) and the statistical analysis plan (version 1.0; 21 December 2022):

a) Question according to PICO: Patient population; inclusion criteria

The study protocol must specify in detail how the requirement "Information on the operationalisation of the criteria for the suitability of treatment with brexucabtagene autoleucel" is implemented within the inclusion criteria. It is not appropriate to assign patients to the comparator group who, according to the decision of the tumour board, are ineligible for therapy with brexucabtagene autoleucel due to disease-related characteristics. Specific exclusion criteria for therapy with brexucabtagene autoleucel in the implementation of the above requirement shall be stated. This includes at least a contraindication to cyclophosphamide and fludarabine due to the mandatory lymphodepletion prior to therapy with brexucabtagene autoleucel.

b) Question according to PICO: Outcome; patient-reported endpoints (PRO)

In the study protocol, a consistent procedure must be defined with regard to the transmission of the results of the PRO endpoints collected in each case to the treating

study sites in terms of whether information is regularly not provided or is provided in full for both groups.

c) Question according to PICO: Outcome; adverse events (AEs) leading to hospitalisation or prolonging existing hospitalisation or leading to death

The study protocol shall specify a joint evaluation of adverse events (AEs) leading to death and AEs leading to hospitalisation or prolonging an existing hospitalisation.

d) Question according to PICO: Outcome; specific AE with CTCAE grade ≥ 3

For the specific adverse events mentioned in the study protocol, in addition to the information on the respective severity grade, the respective criterion mentioned in the CTCAE classification for a CTCAE grade 3 or higher or the general criterion "significant impairment of the activity of daily living" must be collected and these events must be evaluated separately accordingly.

e) Data source: Confounders

Confounders must be identified through a systematic literature review and supplemented by expert interviews. The procedure for confounder selection carried out by the pharmaceutical company is not considered appropriate by the G-BA. The section on the identification and definition of confounders in the study protocol therefore needs to be revised, taking into account the aspects outlined in the justification.

In the specific case at hand, the G-BA considers it possible to implement the requirements of the G-BA by defining the following factors as relevant confounders for the present routine practice data collection, taking into account the benefit assessment conducted in accordance with Section 35a SGB V on brexucabtagene autoleucel in the present indication, the consultation conducted on the preparation of the study protocol and statistical analysis plan (SAP) for the present routine practice data collection and the confounders already named in the study protocol:

- Age
- Sex
- ECOG status
- Comorbidity
- Stage of the disease
- Extranodal disease
- Infestation of the bone marrow
- Lactate dehydrogenase (LDH)
- Leukocyte count
- Morphology
- B symptoms
- Mantle Cell Lymphoma International Prognostic Index (MIPI)

- Number of previous lines of therapy
- Previous autologous stem cell transplantation
- Duration of previous Bruton tyrosine kinase (BTK) inhibitor treatment
- Response to previous BTK inhibitor treatment
- Ki-67
- TP53 mutation

f) Data source: Exact definition or operationalisation of exposure (type and duration of medicinal therapy and other concomitant therapies), clinical events and confounders

A unique list of variables of the process data for the routine practice data collection is to be completed. In addition, the list of variables for the baseline data has to be finalised.

g) Data source: Use of exact dates for the patient, the disease, important examinations and treatments/ interventions

It must be clarified which specific information or investigations are subsumed under the term "assessments". For information not related to patient history, exact dates are required. In the context of the revision of the study documents, the pharmaceutical company must check whether there is a need for further adaptation of this quality criterion.

h) Data source: Strategies to avoid selection bias in patient inclusion to achieve representativeness

The recruitment measures for the treatment groups specified in the study protocol are to be aligned to avoid selection effects. In this context, measures must be defined for both treatment groups that will lead to active recruitment at both national and international level.

i) Study design: Recruitment of the study population

The involvement of countries or study sites outside Germany must be clarified before the start of data collection and described in the study protocol.

j) Study design or data analysis: Information on the adaptation of the routine practice data collection

Information must be added to the study protocol and SAP in order to implement the requirement to review the sample size estimate in the first interim analysis on the basis of the mortality endpoint and a shifted hypothesis boundary. In addition, information on discontinuation criteria due to futility must be added to the study protocol and SAP.

It must also be specified in the study documents that any changes to the implementation of the routine practice data collection and its evaluation must be coordinated with the G-BA. This applies in particular to any change in the sample size estimate, the possible discontinuation of the routine practice data collection as well as

to the Data Review Meeting (DRM) before database lock described in the study documents.

k) Evaluation of the data: shifted hypothesis boundary

In the study protocol and SAP, it is to be specified, taking into account the non-randomised study design, that a shifted hypothesis boundary of 0.2 to 0.5 is used for the evaluation and interpretation of the results data, depending on the quality of the data collection and evaluation.

l) Data evaluation: Propensity score method

The following aspects of the propensity score procedure should be added to the SAP:

- Criteria for when visual examination of the propensity score histograms results in sufficient overlap and when it does not.
- A decision algorithm to adjust the propensity score analysis in the absence of overlap and balance after applying the first method. In this context, it is necessary to specify which alternative method is to be chosen under which conditions.
- What is the consequence if no propensity score method can be found with which a sufficient overlap and balance of the groups to be compared can be achieved.
- Statements on the necessity for a detailed description of the patient population resulting from the application of the respective propensity score method, including the need for a comparison of this patient population with the original target population of the routine practice data collection.

m) Data evaluation: Dealing with missing values

The stipulation that a confounder with more than 30% missing data is not to be taken into account in the adjustment is not appropriate and should be deleted from the SAP. Instead, the pharmaceutical company must describe in the SAP the effects of missing data on confounders and how the loss of information will be dealt with in the context of the evaluation. Furthermore, it is necessary to describe under which conditions the attempt to adjust for confounders still makes sense at all.

The planned replacement of the month potentially leads to significant distortions and is not appropriate. This provision should therefore be deleted. Instead, the pharmaceutical company shall add what efforts are being made to minimise the rate of missing values in the date specification.

In addition, the SAP shall define reasonable replacement strategies for missing data on endpoints and describe appropriate measures to minimise the percentage of missing values on endpoints.

n) Data evaluation: EORTC QLQ-C30 or EORTC QLQ-NHL-HG29

For the evaluation of the EORTC questionnaires, only a response threshold of 10 points is to be considered in relation to the responder analysis. The evaluation for the response criterion 15 points should therefore be deleted from the SAP.

In order to avoid inconsistencies, the pharmaceutical company must check whether the need for changes in the study protocol described here leads to corresponding subsequent changes in the SAP and vice versa.

II. The revised study protocol and the revised SAP are to be submitted to the G-BA by 13 April 2023.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 March 2023.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 16 March 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken