Gemeinsamer Bundesausschuss

Justification

on the Resolution of the Federal Joint Committee (G-BA) on the 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

Contents

1. Legal basis

According to Section 35a, paragraph 3b, sentence 1 SGB V, the Federal Joint Committee (G-BA) can demand the pharmaceutical company to submit routine practice data collections and evaluations for the purpose of the benefit assessment within a reasonable period of time for the following medicinal products:

1. in the case of medicinal products authorised to be placed on the market in accordance with the procedure laid down in Article 14, paragraph 8 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4, 7.1.2019, p. 24), or for which a marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No. 726/2004; and
2. for medicinal products approved for the treatment of rare diseases under Regulation No. 141/2000.

2. Key points of the resolution

At its session on 21 July 2022, the G-BA decided on the requirement of routine data collection and evaluations for the active ingredient autologous anti-CD19-transduced CD3+ cells (hereinafter referred to as brexucabtagene autoleucel) in accordance with Section 35a, paragraph 3b, sentence 1 SGB V.

In order to check whether the G-BA's requirements for routine practice data collection and evaluations have been implemented, the pharmaceutical company submitted drafts for a study protocol and a statistical analysis plan (SAP) to the G-BA in due time in a letter dated 21 December 2022. The documents were reviewed by the G-BA with the involvement of the Institute for Quality and Efficiency in Health Care (IQWiG).

On the basis of this review, the G-BA came to the conclusion that the requirements for routine practice data collection and evaluations in the study protocol and SAP prepared by the pharmaceutical company and submitted to the G-BA for review were insufficiently implemented.

The present declaratory resolution and the associated justification establish and justify the necessary need for adaptation of the study protocol (version 1.0; 21 December 2022) and SAP (version 1.0; 21 December 2022).

2.1 Necessary adjustments to study protocol and statistical analysis plan

On the necessary adjustments in detail:

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

In the present version of the study protocol, it remains unclear how specifically the positivity of the enrolled patient population between intervention and comparator is ensured. In accordance with the inclusion criteria listed, the pharmaceutical company proposes that the principal investigator answers a question about the patient's suitability in principle for brexucabtagene autoleucel as well as for the patient-individual therapy at the time of the treatment decision. However, the pharmaceutical company points out in the study protocol that it is currently unclear whether such a query could be implemented by the EMCL registry. Prior to the start of data collection, the implementation of this essential inclusion criterion must be established and appropriate. Specific exclusion criteria for therapy with brexucabtagene autoleucel should be included as part of this implementation. This includes at least a contraindication to cyclophosphamide and fludarabine due to the mandatory lymphodepletion prior to therapy with brexucabtagene autoleucel. In this context, it is also pointed out that the assumption of positivity for patients who, according to the decision of the tumour board, are ineligible for therapy with brexucabtagene autoleucel due to disease-related characteristics, cannot be regarded as fulfilled.

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

For individual oncological entities, it has been shown that medical care that uses PRO information in the course of treatment is superior to care without such information. In order to avoid possible difficulties in data interpretation at a later stage, a consistent procedure in this regard should be defined in the study protocol for both study arms.

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

To ensure sufficient approximation of the serious adverse event (SAE) endpoint, a joint evaluation of AE leading to hospitalisation or prolonging an existing hospitalisation and AE leading to death shall be defined in the study protocol.

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

In contrast to the general definition of SAEs, severe AEs are characterised by the fact that they also include events that significantly impair the activity of daily living but do not lead to hospitalisation. In the ZUMA-2 study, the rate of severe AEs for specific AEs was significantly higher than the rate of SAEs for specific AEs. Considering the effort and relevance for the present routine practice data collection, instead of a complete assessment of severe AEs only for the specific AEs 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" is to be surveyed and these events are to be evaluated separately accordingly.

e) Data source: Confounders

Confounders must be identified through a systematic literature review and supplemented by expert interviews. The systematic research conducted by the pharmaceutical company is in principle suitable for finding systematic reviews and guidelines as a basis for identifying confounders, including the associated statistical evidence. However, suitable primary studies with sufficient statistical evidence are not included to a sufficient extent in the secondary literature identified by the pharmaceutical company, nor is the information necessary for the assessment of the confounders reported to a sufficient extent. The resulting cursory manual search by the pharmaceutical company is not appropriate, as this does not represent a systematic procedure. Instead, it would have made sense to conduct a search for primary studies with STOPP criteria according to the procedure in Pufulete et al. (2022)[1] . The lack of preparation of the statistical evidence cannot be replaced by the subsequent expert survey either, since the statistical evidence must be taken into account in the latter. Irrespective of this, it would in principle be desirable to (additionally) involve experts in the context of the expert survey who are not directly involved in the administrative work on the primary data sources for the routine practice data collection.

Although the list of potential confounders resulting from the pharmaceutical company's approach is extensive, the lack of preparation of the associated statistical evidence is inappropriate. Therefore, in principle, a revision of the systematic research for the identification of confounders is needed. Irrespective of this, the procedure of classifying the individual confounders in the study protocol is not appropriate.

In the specific case at hand, the G-BA considers it possible to implement the requirements of the G-BA by defining the factors listed in the resolution as relevant confounders for the 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. If necessary, the pharmaceutical company may define further factors as relevant confounders (e.g. p53 overexpression), taking into account an appropriate methodological approach for the identification and definition of confounders.

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

The degree of fulfilment of this quality criterion is described as "project-specific" in the study protocol, although the specific meaning of this classification remains unclear. In the

[1] Pufulete M, Mahadevan K, Johnson TW et al. Confounders and co-interventions identified in non-randomised studies of interventions. J Clin Epidemiol 2022; 148: 115-123.

study protocol, a summary list of variables is only available for the baseline data, but not for the process data (e.g. endpoints). This is to be completed for the routine practice data collection. In addition, the operationalisation of the PRO assessment at baseline is missing from the list of variables for the baseline data. The list of variables for the baseline data is to be finalised accordingly.

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

The degree of fulfilment of this quality criterion is described as "limited" in the study protocol. It is not completely clear which specific data or studies are subsumed under the term "assessments". This must be clarified. For the so-called "assessments", exact dates are missing according to the study protocol. Unless this restriction refers only to patient history information, the approach would be inappropriate. Overall, the relevance of the limited fulfilment of the present quality criterion cannot be conclusively assessed against the background of the missing list of variables of the process data. Accordingly, the pharmaceutical company must check within the scope of the revision of the study documents whether there is a need for further adaptation of the present quality criterion.

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

The degree of fulfilment of this quality criterion is classified as "N/A" in the study protocol, since according to the pharmaceutical company all patients who fulfil the inclusion criteria can be documented in the EMCL registry. This is considered inappropriate by the G-BA to fulfil the present quality criterion. From the explanations in the study protocol, it is clear that, on the one hand, recruitment measures are being used that relate solely to study sites that provide therapy with brexucabtagene autoleucel. In order to standardise the recruitment measures between the group treated with brexucabtagene autoleucel and the comparator group, the measures described should also be extended to study sites that are not qualified for the use of CAR-T cells. On the other hand, selection effects may arise if the registry operator is actively informed by the pharmaceutical company exclusively about a request for brexucabtagene autoleucel by a treating site. This is a biased recruitment measure and may lead to differences in data quality between treatment groups.

In conclusion, the recruitment measures for the treatment groups specified in the study protocol should be aligned to avoid selection effects. The pharmaceutical company shall describe measures for both treatment groups that lead to active recruitment (for example, also a query in the treatment sites on the use of therapy options of the specified comparator). If individual measures cannot be implemented for both treatment groups, these specific measures are then not to be implemented for both treatment groups. Furthermore, it should be noted that recruitment measures are applied at both national and international levels.

i) Study design: Recruitment of the study population

From the study protocol submitted, it appears that the process to involve other European study sites has not yet been completed. The EMCL register is a Europe-oriented registry. For the recruitment of the comparator group, the involvement of further European study sites is important. Therefore, the G-BA considers it necessary that the involvement of the Member States or study sites outside Germany is clarified prior to the start of data collection and described accordingly in the study protocol.

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

The submitted study documents lack information on a review of the sample size estimate in the context of the first interim analysis as well as on the discontinuation criteria due to futility. These are to be supplemented taking into account the described requirements of the G-BA in the demand resolution of 21 July 2022.

The study protocol and SAP describe that a Data Review Meeting (DRM) be conducted prior to database lock. On the one hand, this is intended to resolve existing inconsistencies; on the other, the decisions in the DRM can supplement or even overwrite the methods described in the SAP. The G-BA does not consider it appropriate if changes are made to the prespecified information in the study protocol and SAP without consultation with the G-BA. The routine practice data collection is to be carried out on the basis of the study documents agreed with the G-BA. Subsequent changes that are not agreed with the G-BA jeopardise the objective and usability of the data collection. Therefore, it must be added to the study documents that any changes to the routine practice data collection and its evaluation must be coordinated with the G-BA.

k) Evaluation of the data: shifted hypothesis boundary

The hypothesis boundary of 0.85 set by the pharmaceutical company is outside the range of 0.2 to 0.5 (depending on the quality of data collection and evaluation) required for a proper interpretation of the data.

The effect to be assumed between brexucabtagene autoleucel and the comparator is composed of the true difference between the two treatment options and the risk of bias due to the non-randomised study design. Due to unknown confounders, a statement on the benefit or harm of an intervention can only be derived from a certain effect magnitude. The specific threshold results from the quality of the data. In the study protocol, the pharmaceutical company justifies the weakening of the shifted hypothesis boundary to 0.85 exclusively on the basis of the expected true effect magnitude without taking potential risk of bias into account. The interpretation of the data is not necessarily prejudiced by the definition of a shifted hypothesis boundary outside the range of 0.2 to 0.5 for the sample size planning, but ultimately results from the final quality of the data collection and evaluation. However, it is mandatory for the evaluation of the data obtained that a shifted hypothesis boundary of 0.2 to 0.5 is taken into account depending on the quality of the data collection and evaluation. In this context, the G-BA points out

that it is generally not considered useful to define a differently shifted hypothesis boundary for sample size planning and subsequent evaluation.

In addition, the significance of the data collected in the context of the routine practice data collection is determined by the quality of the data in the specific case, for example, by the knowledge of relevant confounders. Therefore, a section should be added to the study protocol and SAP that addresses the interpretation of the results of the data, taking into account the non-randomised study design and using an appropriate shifted hypothesis boundary (in the range between 0.2 and 0.5).

l) Data evaluation: Propensity score (PS) procedure

The pharmaceutical company plans an optimum PS matching in the ratio 2:1 without reserve with a calliper distance of 0.25 of the pooled standard deviation of the logit of the PS.

For the assessment of overlap, there is only information on the visual examination of the PS histograms, but no information on the criteria for assessing whether there is sufficient or insufficient overlap. These are to be supplemented.

The pharmaceutical company defines a value of the standardised mean difference (SMD) of < 0.25 for sufficient balance in the study documents. This represents the weakest criterion for sufficient balance. The actual SMD achieved must be taken into account accordingly when interpreting the results on the basis of a shifted hypothesis boundary.

There is a lack of further information on which methods should be used if sufficient overlap and balance with the initially defined method cannot be achieved, and under which conditions which alternative methods should be chosen. The decision algorithm for adjusting the PS procedure in the absence of overlap and balance is to be completed in the SAP. Furthermore, it must be added what consequence will be drawn if no PS procedure can be found that leads to sufficient overlap and balance. As a rule, the question should be reconsidered in these cases. The consequences of a resulting naive comparison without adjustment for the interpretation of results must be addressed in the SAP.

After successful application of a PS procedure, it should be carefully checked whether the patient population resulting from the PS procedure corresponds to the original target population of the routine practice data collection to a sufficient extent. If this is not the case, the sub-population of the original target population to which the analyses resulting from the PS procedure refer shall be described. In PS matching in particular, patients who meet the inclusion criteria are excluded as expected during the analysis. Therefore, the necessity of a detailed description of the patient population resulting from the application of the respective PS procedure, including the necessity of a comparison of this patient population with the original target population of the routine practice data collection in the SAP must be compulsorily added.

m) Data evaluation: Dealing with missing values

While measures to avoid missing data are described in detail in the study protocol, only basic information is provided in the SAP.

The pharmaceutical company plans to replace missing confounder data by means of multiple imputation if there are less than 30% missing values. In contrast, the pharmaceutical company does not plan to consider confounders with more than 30% missing values in the adjustment. This is inappropriate as a relevant confounder does not lose its significance because there is insufficient data on it in the data set. This stipulation in the SAP should therefore be deleted. Instead, the pharmaceutical company has to supplement how the loss of information in the case of missing values for confounders is dealt with in the context of the evaluation, as well as under which conditions an adjustment for confounders is still meaningful at all. To ensure the usability of the data from the routine practice data collection, special efforts must be made to avoid missing data on confounders.

A sensible replacement strategy for missing months does not exist. The planned replacement of the month potentially leads to significant risk of bias. Therefore, the replacement strategy of the month set in the SAP is to be deleted. Instead, the efforts taken to avoid missing values for dates should be added.

If necessary, the G-BA recommends defining a possible substitution of the month within the framework of sensitivity analyses including different replacement strategies in the study protocol or statistical analysis plan.

Regarding missing data for the endpoints, it is only described that missing data will not be replaced because it is routine data without mandatory follow-up. This procedure is considered inappropriate by the G-BA as it can lead to loss of information and relevant risk of bias of the results. Accordingly, sensible replacement strategies for endpoints in the SAP are to be added. Furthermore, appropriate measures shall be described to minimise the percentage of missing values for endpoints.

Any additional measures other than those defined so far required to avoid missing values for the individual addressed aspects shall be defined accordingly in the study documents.

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

For the benefit assessment, only a responder analysis with a response threshold of 10 points is relevant in relation to the EORTC questionnaires.

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.

In addition to the mandatory adaptations, the G-BA makes the following recommendations for further adaptations of the study protocol and the SAP:

o) Question according to PICO: EORTC-QLQ-C30

The "Financial difficulties" scale does not represent a symptom in the true sense of the word and is generally not used in the benefit assessment. Therefore, it is not necessary to assess this scale as part of the routine practice data collection.

p) Question according to PICO: other AE endpoints

In the context of the benefit assessment, no consideration is given to AEs in which, in the assessment of the principal investigator, the respective AE is attributable to the treatment. Therefore, the collection and evaluation of such an AE endpoint can be dispensed with in the context of the routine practice data collection.

q) Data source: Completeness of the data

In the study protocol, the pharmaceutical company renders the completeness of the data collection relative in several places. In the study protocol, this is mainly related to the data collection, which takes place outside the brexucabtagene autoleucel implementing study sites.

In this regard, it should be noted that the restriction of the authority to supply care for brexucabtagene autoleucel in the present indication was decided on 21 July 2022. As made clear in the justification for the corresponding resolution, the authorised care providers must work towards the most complete data transfer possible. Furthermore, it is the responsibility of the pharmaceutical company to take appropriate measures to implement valid routine practice data collection as well as the evaluation of the collected data and to enable a corresponding quantification of the additional benefit within the framework of the renewed benefit assessment.

Therefore, the G-BA recommends revising the corresponding statements in the study protocol. Where appropriate, the pharmaceutical company should define and describe further measures necessary to ensure the completeness and quality of the data collection both in the brexucabtagene autoleucel performing study sites and outside the brexucabtagene autoleucel performing study sites.

r) Data source: Ensuring scientific independence and transparency

To ensure scientific independence and transparency, it is recommended deleting the requirement that all abstracts, posters and publications must be approved by the pharmaceutical company.

s) Data evaluation: Evaluation of the PRO endpoints

Currently, the pharmaceutical company plans to evaluate the time to first deterioration of PRO endpoints. With relevantly different durations of observation between the treatment arms, the time until the first change is the only responder evaluation that can be meaningfully interpreted for the benefit assessment. However, according to the study protocol, no early end of observation is planned in the context of the routine practice data collection. The pharmaceutical company could therefore also consider defining an additional operationalisation that also takes into account the follow-up data collections

after the first deterioration, for example in the form of a deterioration confirmed once or twice.

As sensitivity analyses, comparisons of the mean change from baseline are provided for each survey time point. The G-BA also recommends defining responder analyses with a response threshold of 10 points for each survey time point within the scope of the sensitivity analyses.

2.2 Deadline for submission of the revised study protocol and statistical analysis plan

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

When submitting the revised version of the SAP and the study protocol, the pharmaceutical company must ensure that the changes made can be completely and clearly understood. For this purpose, a version of the documents must usually be submitted in which the changes have been marked in detail, as well as a current version of the documents without marking the changes. Amendments that do not result from the need for adjustment set out in this resolution and the justification shall be justified separately.

3. Process sequence

In order to check whether the requirements of the G-BA for routine data collection and evaluations for the active ingredient brexucabtagene autoleucel have been implemented as specified in the resolution of 21 July 2022, the pharmaceutical company submitted drafts of a study protocol and an SAP to the G-BA. The documents were reviewed by the G-BA with the involvement of IQWiG.

The issue was discussed in the working group WG RPDC and in the Subcommittee on Medicinal Products.

At its session on 16 March 2023, the plenum decided on the outcome of the review regarding the submitted study protocol (version 1.0; 21 December 2022) and the statistical analysis plan (version 1.0; 21 December 2022).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	13 February 2023 2 March 2023	Consultation on the study protocol and statistical analysis plan (SAP)
Subcommittee Medicinal products	7 March 2023	Consultation on the outcome of the review of the study protocol and SAP
Plenum	16 March 2023	Resolution on the outcome of the review of the study protocol and SAP

Berlin, 16 March 2023

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

Prof. Hecken