Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Tabelecleucel (Epstein-Barr virus positive post-transplantation lymphoproliferative disease)

of 5 October 2023

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit

assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient tabelecleucel on 15 April 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 13 April 2023.

Tabelecleucel for the treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Tabelecleucel concerns a somatic cell therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 17 July 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G28-08) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7,

sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tabelecleucel.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Tabelecleucel (Ebvallo) in accordance with the product information

Ebvallo is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

Therapeutic indication of the resolution (resolution of 5 October 2023):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Patients 2 years of age and older with Epstein-Barr virus positive post-transplant lymphomas (EBV+ PTLD) who have received at least one prior antineoplastic therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

In summary, the additional benefit of tabelecleucel is assessed as follows:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

For the assessment of the extent of additional benefit of tabelecleucel in the therapeutic indication of relapsed or refractory Epstein-Barr virus positive post-transplantation lymphoproliferative disease (EBV+ PTLD) after at least one pretreatment, data from the single-arm, open-label pivotal phase III study ALLELE and the open-label, single-arm expanded access study EBV-CTL-201 were submitted in particular by the pharmaceutical company. In addition, the pharmaceutical company has submitted an indirect comparison without a bridge comparator, which is based on data from the chart review ATA129-RS002 and the pivotal study ALLELE.

ALLELE study

The ALLELE study is a multicentre, open-label, single-arm phase III study that has been ongoing since December 2017 to investigate the efficacy and safety of tabelecleucel in children aged 2 years and older and adults with EBV+ PTLD after at least one prior treatment. The study is being conducted in 24 study sites in Australia, France, Great Britain and the USA.

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

43 patients with EBV+ PTLD were enrolled to date. Patients aged 16 years or older had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3, children under 16 years had a Lansky score ≥ 20. Of these 43 patients in total, 29 had received a solid organ transplantation (SOT) in the past, of which 13 were pretreated with rituximab and 16 with rituximab plus chemotherapy, and 14 had received hematopoietic cell transplantation (HCT).

Based on a partial HLA match as well as appropriate HLA restriction between donor and recipient, the tabelecleucel cell products for each diseased subject were selected from a database of available tabelecleucel cell product batches and administered at a dose of 2×10^6 cells/kg per application in multiple 35-day cycles on days 1, 8 and 15 in up to 2 (SOT cohort) or 4 (HCT cohort) different HLA restrictions.

The primary endpoint of the ALLELE study was the overall response rate (ORR) in the SOT or HCT cohort. Secondary endpoints included duration of response (DOR), overall survival, progression-free survival (PFS), rates of graft loss/ rejection episodes as well as time to response and time to best response.

Monitoring for response after end of treatment or discontinuation thereof will be done every 3 months for the first 24 months after day 1 of the 1st cycle and then every 6 months for 5 years after day 1 of the 1st cycle to determine survival status.

Two pre-specified interim analyses, the data cut-off for the submission of the marketing authorisation application and a data cut-off required by the regulatory authority EMA are currently available. For the benefit assessment, the most recent data cut-off from 05.11.2021 required by the EMA was taken into account.

EBV-CTL-201 study

The EBV-CTL-201 study is a multicentre, open-label, single-arm expanded access study for the treatment of subjects with EBV-associated viraemia or malignomas. In addition to other EBV-associated diseases, this study also includes 26 patients with EBV+ PTLD, 12 of whom received SOT (5 of whom were pretreated with rituximab and 7 of whom received rituximab plus chemotherapy) and 14 of whom received HCT. This study was conducted at 15 study sites in the USA between July 2016 and September 2020.

The enrolled patients aged at least 17 years had an ECOG status ≤ 4, children and adolescents aged up to 16 years had a Lansky Score ≥ 20.

Based on a partial HLA match as well as appropriate HLA restriction between donor and recipient, tabelecleucel cell products for the respective diseased subject were selected from a database of available tabelecleucel cell product batches and administered at a dose of 2×10^6 cells/kg per application (+ 0%/- 20% variability, depending on cell availability) in multiple 35-day cycles on days 1, 8 and 15 until maximum response, unacceptable toxicity or failure of tabelecleucel occurs in up to 4 different HLA restrictions.

The primary endpoint of the EBV-CTL-201 study was overall response rate (ORR), with additional endpoints including duration of response (DOR), overall survival and progression-free survival (PFS). A follow-up examination was carried out 30 days after the last dose. In addition, after the last dose, further quarterly follow-ups were conducted until 24 months after the start of the 1st treatment cycle.

The results of a post-hoc evaluation from 05.11.2021 are available and will be considered for the benefit assessment.

About the evaluation population

The ALLELE and EBV-CTL-201 studies enrolled patients with solid organ transplantation (SOT) and stem cell transplantation (HCT). The SOT cohort is further divided into patients after rituximab and chemotherapy (SOT-R-Chemo cohort) and patients after rituximab monotherapy (SOT-R cohort) depending on the previous therapy. Previous therapy with rituximab and chemotherapy was concurrent or sequential.

Only patients who have received chemotherapy pretreatment are included in the approved therapeutic indication according to the product information, unless they are eligible for chemotherapy. According to the statements of the clinical experts in the oral hearing, there may be numerous reasons against chemotherapy treatment due to the heterogeneous and vulnerable patient population.

However, the lack of eligibility for chemotherapy treatment in the SOT-R cohort was documented in neither the ALLELE nor the EBV-CTL-201 study. It is therefore not possible to retrospectively assess whether chemotherapy was medically indicated for the patients. For this reason, the benefit assessment does not consider the SOT-R cohort in these two studies.

Indirect comparison between ATA129-RS002 and ALLELE

In the dossier for the benefit assessment, the pharmaceutical company additionally presents an indirect comparison without a bridge comparator between data from the chart review ATA-120-RS002 and the pivotal study ALLELE.

ATA129-RS002 is a multicentre, multinational, retrospective, non-interventional, observational study to determine the overall response and overall survival of standard subsequent therapy after relapse or progression of disease due to treatment with rituximab monotherapy or rituximab and chemotherapy (concurrent or sequential) in subjects with EBV+ PTLD after allogeneic HCT or SOT. Data collection took place at 29 treatment centres in Europe and North America between October 2018 and January 2021.

For the comparative analyses with the pivotal ALLELE study, all subjects from ATA129-RS002 who had failed SOT on rituximab and chemotherapy (N = 48) and HCT on rituximab monotherapy (N = 36) and who had received further systemic therapy after failure were then included. These 84 patients in the external control arm were compared with 30 patients (HCT after rituximab monotherapy N = 14; SOT after rituximab and chemotherapy N = 16) from the ALLELE study (data cut-off: 05.11.2021) in a pooled analysis of the HCT and SOT cohorts.

Due to the lack of information regarding the selection of the study sites in the ATA129-RS002 study, there is neither a rationale for this selection nor for the identification of the patients in the control group. A selection bias can therefore not be ruled out. It also remains unclear why patients from other studies, such as the EBV-CTL-201 study, could not have been included.

In addition to the primarily planned naive comparison, two different propensity score (PS)-based weighting strategies (IPTW and SMWR) were also used to improve the balance of potential confounders between treatment arms.

In order to achieve the necessary structural equality between the treatment groups, especially against the background of the very heterogeneous patient population in the present therapeutic indication, the consideration of all relevant confounders as adjustment variables is an essential prerequisite for carrying out an indirect comparison without a bridge comparator.

According to the study report, a literature search was conducted to identify prognostic factors with an influence on overall survival. Further details are not reported. It remains unclear

whether the literature search is subject to a systematic and methodologically adequate approach for this purpose. In addition, it should be noted that the identified confounders differ from the confounders actually considered. Furthermore, a relevant percentage of patients in the ATA129-RS002 study have missing values for some confounders or no baseline data are available.

Assessment:

Overall, there are considerable uncertainties due to the insufficiently described procedure for confounder identification and selection as well as missing values. On the basis of the available information, it cannot be assumed that the structures are identical.

Depending on the model and the time of evaluation, the hazard ratio is about 0.40 with a relatively wide confidence interval. Moreover, since the ALLELE study is an ongoing study with many early censoring steps, there are further uncertainties.

In view of the limitations, the results of the indirect comparison presented indicate neither for the naive nor for the PS-based analyses any effects of a magnitude at which it can be assumed with sufficient certainty that the effects do not result exclusively from systematic risk of bias.

In view of the aforementioned reasons, the submitted indirect comparison between the ALLELE and ATA129-RS002 studies is assessed overall to the effect that it does not form a sufficient data basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit. The presented indirect comparison without bridge comparator is therefore not used for the present benefit assessment.

On the results of the ALLELE study:

Mortality

The overall survival was defined in both studies as the time from start of treatment until death from any cause.

In the ALLELE study, 7 patients died in the SOT-R cohort (44%) and 4 patients died in the HCT cohort (29%). In the SOT cohort, a relevant percentage of the population was already censored before month 6. In the HCT cohort, a good half of the censoring steps occurred between month 12 and month 18. The median Kaplan-Meier estimator at month 12 was 64.3% in the SOT-R-chemo cohort and 70.1% in the HCT cohort.

In the EBV-CTL-201 study, patients died in SOT-R cohort 1 (17%) and HCT cohort 5 (36%). In the SOT cohort, of the 6 subjects, 1 was censored early due to withdrawal of consent. Based on the Kaplan-Meier curves, a relevant part of the censoring steps in the HCT cohort occurred prematurely, before reaching month 24, and partly before month 6. In the absence of censoring reasons, it is unclear why these subjects were censored prematurely. The median Kaplan-Meier estimate in the HCT cohort at month 12 was 61.5% and in the SOT-R-chemo cohort at both month 12 and month 24 was 83.3%. Due to the partly short median follow-up period and missing information on censoring reasons, the data on overall survival are subject to increased uncertainty.

Median survival was not reached in either study.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Morbidity

Overall response

In the ALLELE study, response is assessed according to the Lugano classification with LYRIC expansion (*Lymphoma Response to Immunmodulatory Therapy Criteria*). In this process, the locally performed imaging examinations (PET/CT and MRI) are sent to the central "*radiology vendor*" and evaluated blinded with regard to response, while the assessments of the principal investigator are used as the basis for clinical decisions. An additional independent radiological assessment as well as an independent assessment of oncologic response (IORA) was planned a priori.

In the EBV-CTL-201 study, response was assessed according to the Lugano classification for EBV-associated lymphoma and was based on investigator grading. After protocol amendment in May 2018, the Lugano criteria were updated to include the LYRIC modification. In this study, an additional post-hoc assessment was performed by an IORA based on the clinical data and central radiological examinations available in the study database.

In both studies, overall response was operationalised as follows:

- "Overall response" is defined as the percentage of subjects with complete remission (CR) or partial remission (PR) after administration of tabelecleucel in up to 2 (ALLELE study) or 4 (CTL-201 study) different HLA restrictions. Subjects without a response or valid disease assessment are considered non-responders in the EBV-CTL-201 study.

In the ALLELE study, 9 (56%; central assessment) and 7 (44%; investigator assessment) patients in the SOT cohort achieved a CR or PR, respectively. In the HCT cohort, 7 (50%) patients achieved a CR or PR after both central and investigator assessment.

In the EBV-CTL-201 study, 5 (83%; SOT-R cohort) and 7 (50%; HCT cohort) patients achieved a CR or PR after both central and investigator assessment.

In both studies, however, the assessment of the overall response is not symptom-related, but mainly based on imaging methods within the framework of the Lugano classification and in the ALLELE study regularly with the LYRIC extension. For this reason, this endpoint is classified as not patient-relevant.

The overall response rate is presented additionally as a primary endpoint of the study.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Graft loss/ rejection reaction

The ALLELE study evaluated the rate of graft loss and the rate of patients with organ rejection in the SOT cohort, where loss is defined as removal of the allograft, resumption of renal replacement therapy (kidney), use of a ventricular assist device (heart), the need for mechanical ventilation or extracorporeal membrane oxygenation (lung), re-transplantation (any organ) or inclusion on a transplant list. The rejection episodes are defined according to the corresponding criteria for the respective organ transplant and both the frequency and the percentage of SOT patients with rejection status (no rejection, existing rejection including grade or organ loss) were reported by organ.

In the EBV-CTL-201 study, the rate of graft loss is defined as the percentage of subjects in the SOT cohort for whom graft loss is reported in the eCRF for organ allograft status during the study. The frequency and percentage of patients with organ rejection (existing rejection or organ loss) are reported by organ and worst grade for each organ.

In the present operationalisation, this endpoint is considered patient-relevant.

For the ALLELE study, information on organ transplant status after baseline is available for 11 (69%) patients. A grade 3 rejection occurred in a patient with a kidney transplant that was already present at the time of screening. In addition, a grade 1 rejection reaction has been described in a patient with a heart transplant. No graft losses occurred after the start of treatment.

Neither rejection reactions nor graft losses occurred in the EBV-CTL-201 study.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Health status (EQ-5D VAS)

Health status was assessed in both the ALLELE and EBV-CTL-201 studies using the EQ-5D visual analogue scale (VAS) on day 1 of each cycle, on day 15 of the 1st cycle, at safety follow-up and every 6 months thereafter in follow-up.

However, the return rate was below 70% in both studies during the course of the study. The data on the EQ-5D-VAS are thus classified as being unusable.

Notwithstanding this, no statement can be made on the extent of additional benefit based on these results due to the absence of comparator data.

Quality of life

Health-related quality of life was assessed in both the ALLELE and EBV-CTL-201 studies using the *lymphoma-specific Functional Assessment of Cancer Therapy - Lymphoma* (FACT-Lym) questionnaire on day 1 of each cycle, day 15 of the 1st cycle, at safety follow-up and every 6 months thereafter in follow-up.

However, the return rate was below 70% in both studies during the course of the study. The data on the FACT-Lym are thus classified as being unusable.

Notwithstanding this, no statement can be made on the extent of additional benefit based on these results due to the absence of comparator data.

Side effects

In both studies, AEs were collected in full until 30 days after the last dose of tabelecleucel or until the initiation of non-protocol subsequent therapy directed against EBV+PTLD. Subsequently, AEs were recorded that were assessed by the investigators as possibly related to the test preparation.

In the dossier for the benefit assessment, the pharmaceutical company does not present any evaluations excluding AEs that are due to the underlying disease. In the ALLELE study, disease progression and associated complications, such as "pneumonia", were also classified as AEs. For the EBV-CTL-201 study, the recording of AEs attributable to the progression of the underlying disease is also not explicitly excluded. Considering the collection of AEs and the available results, it can be assumed that AEs that can be attributed to the symptomatology of the underlying disease are included in the results on AEs to the relevant extent.

Within the framework of the written statement procedure, safety analyses excluding the *preferred term* "disease progression" were submitted by the pharmaceutical company.

Compared to the benefit assessment, this results in only minor changes for any AEs, the severe and serious AEs.

Almost all patients experienced at least one AE during the course of the respective study.

Severe AEs occurred in 63% to 86% and serious AEs in 50% to 83% of patients, depending on the study and cohort. Most frequently, with up to 50% each, "gastrointestinal disorders" and "infections and infestations" were observed.

There were no relevant differences between the SOT-R-chemo and HCT cohorts.

Only in the ALLELE study did 1 (7%) therapy discontinuation occur due to AEs.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Overall assessment

For the benefit assessment, data on mortality, morbidity, health-related quality of life and side effects from the label-enabling, single-arm ALLELE study and the expanded access EBV-CTL-201 study are available.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Furthermore, the pharmaceutical company presents an indirect comparison without bridge comparator between the ALLELE study and the retrospective, non-interventional observational study ATA129-RS002.

Structural equality of the study populations cannot be assumed especially due to considerable uncertainties regarding the identification and selection of confounders as well as missing values for some confounders.

Neither the effect estimator of the naive nor those of the PS-weighted indirect comparisons indicate effects of a magnitude where it can be assumed with sufficient certainty that the observed difference is not due to systematic risk of bias alone.

Overall, the submitted indirect comparison is assessed to the effect that it does not form a sufficient data basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit.

In summary, the extent of the available results is classified as non-quantifiable because the scientific data basis does not permit quantification.

Significance of the evidence

The benefit assessment is based on the data from the single-arm phase III study ALLELE and the single-arm expanded access study EBV-CTL-201, which do not allow a comparative assessment. Overall, the submitted indirect comparison is assessed to the effect that it does not form a sufficient data basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit.

Thus, a comparative assessment is not possible overall, which is why the reliability of data is rated in the hint category.

In the overall assessment, the result is a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Ebvallo with the active ingredient tabelecleucel.

Tabelecleucel has been approved as an orphan drug in exceptional circumstances for the treatment of paediatric patients aged 2 years and older and adults with Epstein-Barr virus positive post-transplantation lymphoma (EBV+ PTLD) who have received at least one prior antineoplastic therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

For the benefit assessment, data from the single-arm phase III study ALLELE, the single-arm expanded access study EBV-CTL-201 as well as an indirect comparison without bridge comparator between the ALLELE study and the retrospective, non-interventional observational study ATA129-RS002 are available.

The pharmaceutical company submitted data on mortality, morbidity, quality of life and side effects for the ALLELE and EBV-CTL-201 studies. The data collected on the patient-reported endpoints in the morbidity and quality of life categories are not usable. Notwithstanding this, no statement can be made on the extent of additional benefit based on these results due to the absence of comparator data.

For the indirect comparison without a bridge comparator, there are considerable uncertainties, especially with regard to the identification and selection of confounders and thus also with regard to the structural equality of the study populations. In addition, the effect estimators of the indirect comparison are not in an order of magnitude where it can be assumed with sufficient certainty that observed differences are not based solely on systematic risk of bias, so that the indirect comparison presented cannot be used for the benefit assessment.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The pharmaceutical company's approach is methodologically largely comprehensible, but mathematically only partially comprehensible.

Against the background that the percentage values are partly based on estimates, the incidence data of post-transplantation lymphoma after SOT only refer to certain organs and there are uncertainties about the reason why the pharmaceutical company transfers the percentage values of adults to the total sum of children, adolescents and adults, the determined patient numbers are subject to uncertainties in the overall analysis.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Ebvallo (active ingredient: tabelecleucel) at the following publicly accessible link (last access: 26 September 2023):

https://www.ema.europa.eu/en/documents/product-information/ebvallo-epar-product-information_en.pdf

For the use of the ATMP tabelecleucel in the present therapeutic indication, measures for quality-assured application were defined by resolution of 17 August 2023 "First version of Annex III – Tabelecleucel in EBV-positive post-transplant lymphomas". As soon as corresponding regulations according to the ATMP Quality Assurance Guideline come into force, they must also be observed.

Treatment with tabelecleucel should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with EBV-positive post-transplantation lymphoma.

This medicinal product was approved under "exceptional circumstances". This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2023).

The product information does not specify a maximum number of cycles. However, according to the treatment algorithm, treatment with tabelecleucel can be given for 2-8 cycles depending on the response. The annual treatment costs are thus presented as a range.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tabelecleucel	35-day cycle 1 x on day 1, 8, 15	2-8 cycles	3	6-24

Consumption:

According to the product information, the total number of vials in each pack (between 1 and 6 vials) corresponds to the dosage requirement for each patient, depending on the patient's body weight.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tabelecleucel	2×10^6/kg	2×10^6/kg	1 pack	6-24	6-24 packs

Costs:

Costs of the medicinal product:

The active ingredient tabelecleucel is listed on LAUER-TAXE®, but is only dispensed to appropriately qualified inpatient treatment facilities. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. According to LAUER-TAXE®, tabelecleucel is subject to the full value added tax rate of 19%. The calculation is based on the purchase price of the clinic pack plus 19 % value-added tax, in deviation from the LAUER-TAXE® data usually taken into account. Tabelecleucel is a somatic cell product produced from allogenic T cells.

Designation of the therapy	Packaging size	Costs (sales price of the pharmaceutical company)	Value-added tax	Costs of the medicinal product
Medicinal product to be assessed				
Tabelecleucel	1-6 vials	€ 75,000.00	€ 14,250.00	€ 89,250.00

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

Other SHI benefits: not applicable

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is authorised exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called indetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in

combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGBV.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Patients 2 years of age and older with Epstein-Barr virus positive post-transplant lymphomas (EBV+ PTLD) who have received at least one prior antineoplastic therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 13 April 2023, the pharmaceutical company submitted a dossier for the benefit assessment of tabelecleucel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 17 July 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 7 August 2023.

The oral hearing was held on 28 July 2023.

An amendment to the benefit assessment with a supplementary assessment was submitted on 12 September 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 26 September 2023, and the proposed resolution was approved.

At its session on 5 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 June 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	23 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	28 August 2023	Conduct of the oral hearing
Working group Section 35a	6 September 2023 20 September 2023	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	26 September 2023	Concluding discussion of the draft resolution
Plenum	5 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 5 October 2023

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

Prof. Hecken