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 Tisagenlecleucel (new therapeutic indication: follicular lymphoma, pretreated patients)

of 1 December 2022

Contents

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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient tisagenlecleucel (Kymriah) was listed for the first time on 15 September 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 29 April 2022, Novartis Pharma GmbH received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

Kymriah for the treatment of relapsed or refractory follicular lymphoma after two or more lines of systemic 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.

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 and probability of the additional benefit are assessed on the basis of the approval studies by the G-BA.

On 25 May 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient tisagenlecleucel with the new therapeutic indication of relapsed or refractory follicular lymphoma after two or more lines of systemic therapy in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 1 September 2022 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 G22-23) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering 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 tisagenlecleucel.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Tisagenlecleucel (Kymriah) in accordance with the product information

Kymriah is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 1 December 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

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

Justification:

For the benefit assessment, the results of the pivotal, single-arm, multicentre phase II ELARA study were presented in the dossier. Furthermore, the pharmaceutical company presented an indirect comparison without a bridge comparator between the ELARA study and the RECORD-FL study to derive the additional benefit.

ELARA study

The ELARA study has been running since 2018 and is being conducted in 32 study sites across USA, Europe, Japan and Australia. Recruitment has been completed. The last tisagenlecleucel infusion was administered in May 2020. The pharmaceutical company states November 2025 as the expected end of the study.

A total of 98 patients were enrolled in the study. 89.8% of patients had grade 1 or 2 follicular lymphoma and 10.2% of patients had grade 3a follicular lymphoma at the time of enrolment in the study. However, grade 3b patients were not enrolled in the study. Patients had to be at least refractory to second or subsequent line of systemic therapy; have relapsed during or within 6 months of anti-CD-20 antibody therapy; or have shown relapse after autologous stem cell transplant.

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

The majority of patients had stage IV (59.2%) or stage III (26.5%) at the start of the study. On average, the patients had missed 3.9 previous lines of therapy. 36.7% had previously received an autologous stem cell transplant. 57.1% of the enrolled patients had an ECOG status of 0 and 39.8% of them 1. None of the patients had B symptomatology at the time of enrolment in the study. The LDH level was pathologically increased in 58.2%. A bulky disease was shown by 63.6% of the patients.

The study is divided into the following phases. A screening phase took place beforehand, during which leukapheresis was performed (n = 119). Only patients from whom a leukapheresis product was obtained were enrolled in the study (enrolled set = intention-to-treat population; n = 98). During the pretreatment phase, in which the CAR-T product was produced, 44.8% of the patients received bridge therapy. After lymphocyte depletion, the patients using CAR-T infusion (n = 97) entered the treatment and follow-up phase. This is followed by a long-term safety follow-up phase of 15 years, which is carried out according to a separate study protocol.

The median time from screening / enrolment in the study to tisagenlecleucel infusion is 46 days.

The primary endpoint of the study is the complete remission rate according to the IRC (Independent Review Committee).

In the dossier, the pharmaceutical company presented results of the data cut-off from 3 August 2021. With the written statement procedure, the pharmaceutical company submitted analyses on the data cut-off from 29.03.2022. This is a data cut-off that follows the study protocol requirements of regular updating. As this is only a short time after the data cut-off presented in the dossier and therefore no additional knowledge gain can be expected from it, the data cut-off from 3 August 2021 is used for the benefit assessment.

Indirect comparison to the ReCORD-FL study

The ReCORD-FL study is a retrospective cohort study whose data were collected in 9 study sites. A total of 187 subjects with refractory or relapsed grade 1, 2 or 3a follicular lymphoma were enrolled in the study. The possible treatment regimens for enrolment in the study were bendamustine + rituximab, rituximab, R-CHOP (rituximab + cyclophosphamide + hydroxydaunorubicin + vincristine + predniso(lo)ne), RICE (rituximab + ifosfamide + cytarabine + etoposide), cyclophosphamide + fludarabine + rituximab and idelalisib.

An indirect comparison between the ELARA and ReCORD-FL studies was conducted by the pharmaceutical company without a bridge comparator. In addition to results based on a propensity score weighted Cox proportional hazards model, the pharmaceutical company also presents the results of a non-weighted Cox proportional hazards model.

For the propensity score weighted Cox proportional hazards model, the pharmaceutical company conducted a systematic literature review and expert interviews to identify prognostic factors and confounders. Factors identified in the systematic literature review were FLIPI-SCORE, age, haemoglobin level, lymph node regions, Ann Arbor stage, LDH level, bone marrow involvement, lesion size, serum B2 microglobulin level, performance status, FL grade, number of prior therapies, refractoriness to last treatment and chemoresistance status. Of the experts interviewed by the pharmaceutical company, FLIPI score, chemoresistance status, refractoriness to the last treatment, presence of B symptoms and histological transformation were rated as very relevant. Age, LDH level, serum B2 microglobulin level,

number of prior therapies, performance status and, in addition to the factors identified in the literature review, positive PET scan at the end of induction therapy and POD24 (disease progression within 24 months of the first line of therapy) were considered relevant.

Finally, covariates included in the propensity score analysis were age at the start of treatment, region, sex, prior autologous stem cell transplant, number of prior lines of systemic therapy, disease stage at initial FL diagnosis, number of months between initial FL diagnosis and the start of treatment, number of lymph nodes involved at the start of treatment and double refractoriness.

With regard to the procedure described, it should be noted that the systematic literature review was not designed to record prognostic factors and that there are uncertainties and deviations from the pre-specified procedure with regard to the ranking by experts. Overall, it is uncertain whether all relevant prognostic factors and confounders could be identified based on the systematic literature review and the expert interviews.

Furthermore, in the following selection of covariates to be considered in the propensity score analysis, strong emphasis was placed on availability and less on relevance. Factors whose relevance was rated as low by experts (sex, region, stage of the disease at initial diagnosis, number of affected lymph nodes at the start of treatment) were included, whereas factors considered (very) relevant were not taken into account (FLIPI score, chemoresistance status, presence of B symptoms, age, LDH level, serum B2 microglobulin level, performance status and positive PET scan after the end of induction therapy).

There are differences between the ELARA and ReCORD-FL studies with regard to the inclusion and exclusion criteria, which is why there are uncertainties in the comparability of the study populations. Uncertainty exists in particular with regard to the extent of the patients' need for therapy. None of the patients enrolled in the ELARA study had B symptomatology at the start of the study. In the written statement procedure, clinical experts pointed out that for some of the patients, B symptomatology is decisive for an indication for therapy. Even if it is generally assumed that all patients enrolled in the ELARA study were in need of therapy, there are discrepancies with the reality of care, in which the presence of B symptomatology represents an indication for therapy. In contrast, in the ReCORD-FL study, it is assumed that the assessment was made analogously to the reality of care.

Furthermore, it should be taken into account that the survey period of the ReCORD-FL study began as early as 1998. It can be assumed that the care of patients has evolved over the years (e.g., with regard to the assessment of the need for therapy).

Overall, there are relevant uncertainties in the comparability of the two study populations.

Due to the limitations regarding the confounders, structural equality cannot be established in the propensity score analyses, which is why the results of the Cox proportional hazards model weighted by propensity score are not taken into account.

The results of the non-weighted Cox proportional hazards model do not indicate any effects on an order of magnitude, where it can be assumed with sufficient certainty that the observed differences are not due to systematic risk of bias alone.

Overall, the presented indirect comparison between the ELARA and ReCORD-FL studies is considered unsuitable for deriving reliable statements on the extent of additional benefit.

Mortality

Overall survival

The overall survival was defined in the ELARA study as the time from tisagenlecleucel infusion until death from any cause. In addition, evaluations for overall survival since the time of enrolment in the study (enrolled set) were submitted by the pharmaceutical company. However, only patients for whom a leukapheresis product could be successfully produced were enrolled in the study. Leukapheresis is already part of the overall therapeutic concept. For a valid overall survey, the subjects who underwent leukapheresis without successfully producing a product should therefore also have been considered.

10.2% of the patients in the enrolled set (n = 98) had died by the time of the data cut-off (median observation period 19.5 months). The Kaplan-Meyer estimator in month 18 is 93.2%.

Due to the single-arm study design, a comparative assessment of the mortality data is not possible.

Morbidity

Complete remission rate

The primary endpoint of the ELARA study is the complete remission rate, which is determined by an Independent Review Committee (IRC). In addition, the assessment of the complete remission rate by medical investigators was presented as a sensitivity analysis. The endpoint is operationalised as the percentage of patients who achieved a complete remission (CR) in the time from tisagenlecleucel infusion up to disease progression or start of a new therapy.

The assessment was conducted using the Lugano criteria based on imaging methods (PET-CT or CT).

68.3% of the patients from the enrolled set had complete remission as assessed by IRC at the data cut-off presented.

Health status (EQ-5D VAS)

General health status was assessed in the ELARA study using the visual analogue scale of the European Quality of Life 5 Dimensions.

The first EQ-5D VAS survey took place with the screening visit. Subsequently, the EQ-5D VAS was only assessed in patients who had received an infusion with tisagenlecleucel (enrolled set). However, the leukapheresis, the waiting time until the product is produced and the lymphodepleting chemotherapy are also components of the treatment with tisagenlecleucel, which is why the treatment as a whole can only be assessed by considering all patients from the start of leukapheresis. Accordingly, a restriction to the enrolled set is considered critical. The time interval chosen until the second survey is also considered to be restrictive. This did not take place until three months after tisagenlecleucel infusion, which may not reflect direct and any short-term effects associated with administration.

The return rate of the data presented in the dossier is already below 70% in month 3. This is also not remedied by the information subsequently submitted in the written statement procedure.

The available data on health status collected by EQ-5D VAS are therefore not considered usable.

Notwithstanding this, due to the single-arm study design, a comparative assessment of the data on morbidity is not possible.

Quality of life

FACT-Lym

Disease-specific quality of life was assessed using the validated Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) questionnaire.

With regard to the survey on the basis of the enrolled set, the time interval between the first and second survey as well as the return rates, reference is made to the corresponding explanations on the EQ-5D VAS.

The available data on quality of life recorded via FACT-Lym are therefore not considered usable.

SF-36

Furthermore, quality of life was assessed using the validated generic Short Form (SF)-36 questionnaire.

With regard to the survey on the basis of the enrolled set, the time interval between the first and second survey as well as the return rates, reference is made to the corresponding explanations on the EQ-5D VAS.

The available data on quality of life recorded by means of the SF-36 are therefore not considered usable.

Notwithstanding this, due to the single-arm study design, a comparative assessment of the data on quality of life is not possible.

Side effects

The report on adverse events (AEs) is divided into several time periods within which a different survey was conducted.

Data on AEs with reference to leukapheresis were not presented in the SAP, contrary to the pre-specification.

In the period from the time of enrolment in the study to lymphodepleting chemotherapy (LDC) and in the subsequent period until tisagenlecleucel infusion, only AEs ≥ grade 3, infections, clinically relevant laboratory parameters and AEs related to a study procedure were reported. An assessment of AEs before LDC was not obligatory for the study sites.

The focus of AE reporting was in the phase after tisagenlecleucel infusion. Any AEs were recorded in the periods up to week 8 and after week 8 to 1 year after infusion. It should be noted that, according to the operationalisation, only newly occurring or deteriorating AEs were recorded in the study.

From 1 year after infusion, only specific AEs were recorded.

AEs of special interest (AESI) were only defined with EU Risk Management Plan v3.0 due to limited data in this regard.

Almost all patients experienced an AE during the course of the study, with a focus on the 8 weeks after tisagenlecleucel infusion, as expected.

During this period, 71.1% of the patients experienced an AE of severity grade ≥ 3 (according to CTCAE or for cytokine release syndrome according to Lee et al. 2014) and 27.8% experienced a serious adverse event (SAE).

Subsequently, up to 1 year after infusion, 44.8% of patients suffered an AE of severity grade ≥ 3 and 20.8% an SAE.

Among the AESIs, haematological disorders including cytopenias (in 75.3% of patients at 8 weeks post-infusion) and cytokine release syndrome (in 48.5% of patients at 8 weeks post-infusion) occurred most frequently in all phases following infusion.

Tisagenlecleucel is administered as a single dose. Data on AEs leading to therapy discontinuation were therefore not presented.

Due to the single-arm study design, a comparative assessment of the data on side effects is not possible.

Overall assessment/ conclusion

Data from the pivotal, single-arm, multicentre phase II ELARA study are available for the benefit assessment. Furthermore, the pharmaceutical company presented an indirect comparison between the ELARA study and the retrospective ReCORD study without a bridge comparator.

For the propensity score weighted indirect comparison, there are considerable uncertainties regarding the comparability of the study populations.

Due to limitations in identifying confounders and effect modifiers, the results based on the propensity score weighted Cox proportional hazards model are not included.

The results of the non-weighted Cox proportional hazards model do not indicate any effects on an order of magnitude, where it can be assumed with sufficient certainty that the observed differences are not due to systematic risk of bias alone, so that these are also not taken into account.

The pharmaceutical company submitted data on mortality, morbidity, quality of life and side effects for the ELARA study. The data collected on the patient-reported endpoints in the morbidity and quality of life categories are not usable. Notwithstanding this, due to the single-arm study design, a comparative assessment in all endpoint categories is not possible.

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

Significance of the evidence

The benefit assessment is based on data from the single-arm phase II ELARA study. There is no adequate comparison.

Since only single-arm data are available and a comparative assessment is not possible, the reliability of data is assessed with a hint.

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

2.1.3 Limitation and period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of tisagenlecleucel finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a paragraph 1 SGB V.

The pharmaceutical company was commissioned by the US Food and Drug Administration (FDA) to conduct a randomised phase 3 study in adults with relapsed or refractory follicular lymphoma as part of the accelerated marketing authorisation for the present therapeutic indication. Patients are to be randomised to treatment with tisagenlecleucel or to standard therapy according to *investigator's choice*. According to the FDA, progression-free survival as the primary endpoint and overall survival and objective response rate as secondary endpoints are to be considered. The planned end of the study is mentioned in the provisions as 31 March 2028.

Since clinical data concerning the overall survival are expected to be relevant for the assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of tisagenlecleucel. The limitation enables the expected results from the FDA-specified study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

For this purpose, the G-BA considers a limitation for the resolution until 1 September 2028 to be appropriate.

Conditions of the limitation:

For the new benefit assessment after expiry of the deadline, the FDA-specified study results on overall survival as well as on all other patient-relevant endpoints used for the proof of an additional benefit are to be presented in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of the medicinal product tisagenlecleucel recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of tisagenlecleucel (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO). If the assessment is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product tisagenlecleucel can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient tisagenlecleucel.

Tisagenlecleucel has a marketing authorisation as an orphan drug. This assessment relates to the therapeutic indication "Kymriah is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy".

For the assessment of the additional benefit, the pharmaceutical company submitted data from the single-arm phase II ELARA study. In addition, the pharmaceutical company presented an indirect comparison without a bridge comparator between the ELARA study and the ReCORD-FL study.

For the propensity score weighted indirect comparison, there are considerable uncertainties regarding the comparability of the study populations.

Due to limitations in identifying confounders and effect modifiers, the results based on the propensity score weighted Cox proportional hazards model are not included.

The results of the non-weighted Cox proportional hazards model do not indicate any effects on an order of magnitude, where it can be assumed with sufficient certainty that the observed differences are not due to systematic risk of bias alone, so that these are also not taken into account.

Due to the single-arm study design of the ELARA study, no comparative assessment is possible for the endpoints on mortality and side effects. The data collected on the patient-reported endpoints in the morbidity and quality of life categories are not usable.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified for tisagenlecleucel since the scientific data does not allow quantification.

The validity of the resolution is limited to 1 September 2028.

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 resolution is based on the information from the dossier of the pharmaceutical company. The pharmaceutical company first derives the percentage of patients based on the InGef database and then extrapolates this to the SHI population. Overall, the derivation is fraught with uncertainties. On the one hand, it is unclear whether all relevant ICD-10-GM codes have been taken into account. Furthermore, there may be uncertainty and a tendency to underestimate the identification of the percentage of patients who have ≥ 2 prior therapies and require treatment anew. For this purpose, the pharmaceutical company examined the patients who received a specific therapy in 2020 and had received at least two lines of systemic therapy in the previous 6 years. This neglected patients who had already received at least one therapy before this period. This step is also fraught with uncertainties in the selection and search for therapies that are considered specific. Furthermore, there are uncertainties in the extrapolation to the SHI population.

Despite the uncertainties described, the number of patients presented appears to be more adequate than the number presented in the proceedings on duvelisib (resolution of 21 July 2022). Therefore, in the present procedure, the number presented in the dossier of the pharmaceutical company is taken as a basis.

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 Kymriah (active ingredient: tisagenlecleucel) at the following publicly accessible link (last access: 28 July 2022):

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient emergency card. Training material for all healthcare professionals who will prescribe, dispense, and administer tisagenlecleucel includes instructions for identifying, treating, and monitoring cytokine release syndrome and neurological side effects. It also includes instructions on the cell thawing process, availability of tocilizumab at the point of treatment, provision of relevant information to patients, and full and appropriate reporting of side effects.

The patient training programme should explain the risks of cytokine release syndrome and serious neurologic side effects, the need to report symptoms immediately to the treating physician, to remain close to the treatment facility for at least 4 weeks after infusion of tisagenlecleucel, and to carry the patient emergency card at all times.

Tisagenlecleucel must be used in a qualified treatment centre. For the infusion of tisagenlecleucel in the present therapeutic indication, the quality assurance measures for the use of CAR-T cells in B-cell neoplasms apply (ATMP Quality Assurance Guideline, Annex 1).

Patients with grade 3b follicular lymphoma were not investigated in the ELARA study. Grade 3b follicular lymphoma is treated in accordance with the generally accepted state of medical knowledge, analogous to diffuse large B-cell lymphoma (DLBCL). Tisagenlecleucel has a separate marketing authorisation for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 01 October 2022).

Although tisagenlecleucel is listed on LAUER-TAXE®, it is only dispensed to appropriate qualified inpatient treatment facilities. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 30 or Section 130a SGB V apply. The calculation is based on the sales price of the pharmaceutical company, in deviation from the usually taken into account data of the LAUER-TAXE®.

Tisagenlecleucel is administered as a single intravenous infusion according to the information provided in the product information.

Tisagenlecleucel concerns autologous T cells that have been genetically modified ex vivo with a lentiviral vector encoding a chimeric antigen receptor (CAR) directed against CD19. Accordingly, the concentration of viable CAR-positive T cells may vary between patient-specific batches. One or more infusion bags contain a total of 1.2 x 10^6 to 6 x 10^8 viable CAR+ T cells.

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				
Tisagenlecleucel	Single dose	1	1	1

Consumption:

In the following, the consumption of infusion bags is shown according to the information in the product information. These are administered to the patient in a single infusion depending on the number of cells per infusion bag. The annual treatment costs of tisagenlecleucel are independent of the specific number of infusion bags used.

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					
Tisagenlecleucel	0.6 to 6 x 10^8 viable CAR+ T cells	0.6 to 6 x 10^8 viable CAR+ T cells	1 or more infusion sachets	1	1 or more infusion sachets

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (sales price of the pharmaceutical company)	Value-added tax	Costs
Medicinal product to be assessed				
Tisagenlecleucel				
	1 or more infusion sachets (0.6 to 6 x 10^8 viable CAR+ T cells)	€ 265,000.00	€ 0	€ 265,000.00

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.

Tisagenlecleucel is an autologous cell product produced from the patient's own T cells. Therefore, a leukapheresis is usually necessary to obtain the cell material. Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14, of the Medicinal Products Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.

Prior to the administration of CAR-T cells, the administration of lymphodepleting chemotherapy is recommended, according to the tisagenlecleucel product information, provided that the white blood cell count is not below ≤ 1,000 cells/µl one week prior to the infusion. To this end, a regimen comprising fludarabine (daily 25 mg/m^2 intravenously for 3 days) and cyclophosphamide (daily 250 mg/m^2 intravenously for 3 days) should preferably be administered. For dosages depending on body weight or body surface, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied (average body height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[2].

To reduce potential acute infusion reactions, it is recommended that patients be given paracetamol and diphenhydramine or another H1 antihistamine approximately 30-60 minutes prior to infusion of Kymriah. The product information of Kymriah does not give any specific dosage recommendations, which is why these costs are reported as unquantifiable.

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Type of service	Cost per pack	Costs after deduction of statutory rebates[3,4]	Costs per service	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed					
Tisagenlecleucel					
Lymphocyte depletion					
Fludarabine (25 mg/m² = 47.5 mg IV, 3-day cycle)	€ 118.50 1 x 50 mg	€ 111.64 (€ 1.77, € 5.09)	€ 111.64	3	€ 334.92
Cyclophosphamide (250 mg/m² = 475 mg IV, 3-day cycle)	€ 23.47 1 x 500 mg	€ 20.16 (€ 1.77, € 1.54)	€ 20.16	3	€ 60.48
Premedication					
Paracetamol	Incalculable				
Diphenhydramine	Incalculable				

LAUER-TAXE® last revised: 1 November 2022

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active

[3] Rebate according to Section 130 SGB V
[4] Rebate according to Section 130a SGB V

ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with tisagenlecleucel

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 25 May 2022, the pharmaceutical company submitted a dossier for the benefit assessment of tisagenlecleucel to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

The benefit assessment of the G-BA was published on 1 September 2022 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 written statements was 22 September 2022.

The oral hearing was held on 10 October 2022.

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 22 November 2022, and the proposed resolution was approved.

At its session on 1 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 August 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	4 October 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 October 2022	Conduct of the oral hearing
Working group Section 35a	18 October 2022 1 November 2022 15 November 2022	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	22 November 2022	Concluding discussion of the draft resolution
Plenum	1 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 December 2022

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

Prof. Hecken