Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V – Tisagenlecleucel (diffuse large B-cell lymphoma)

From 7 March 2019

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 for the treatment of a rare condition (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, the additional medical benefit is deemed to be proven through the grant of market authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparative therapy need not 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 evaluation of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, Nos. 2 and 3 SGB V in conjunction with the 5th Chapter Sections 5 et seq. of the Rules of Procedure of the Federal Joint Committee (G-BA) (VerfO) has not been carried out. Only the extent of the additional benefit must be demonstrated.

However, the restricted benefit assessments for orphan drugs as linked by law to marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical manufacturer must, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5 Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparative therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO. In this report, the pharmaceutical manufacturer must also provide evidence of the additional benefit in relation to the appropriate comparative 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; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen). On the basis of the statutory requirement in Section 35a paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its meeting on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparative therapy as the basis for the legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is assessed exclusively on the basis of the approval studies.

Accordingly, at its meeting on 15 March 2012, the Federal Joint Committee amended the mandate given to IQWiG by 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 in such a way that, in the case of orphan drugs, IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparative therapy when the sales volume of the drug concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). 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 shall decide 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 relevant date for the first placing on the market of the active ingredient Tisagenlecleucel in accordance with Chapter 5, Section 8, paragraph 1, point 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is the 15 September 2018. The pharmaceutical manufacturer has submitted the final dossier to the Federal Joint Committee 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, number 1 VerfO on 14 September 2018.

Tisagenlecleucel for the treatment of diffuse large B-cell lymphoma is authorised as a medicinal product for the treatment of a rare condition 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 deemed to be proven through the grant of market authorisation. The extent of the additional benefit is 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 manufacturer in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 17 December 2018 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also held.

The G-BA made its resolution on the basis of the dossier of the pharmaceutical manufacturer, the dossier evaluation carried out by the G-BA, the assessment of treatment cost and patient numbers (IQWiG G18-11) prepared by IQWiG, and the statements submitted in the written and oral hearing procedure.

In order to determine the extent of the additional benefit, the Federal Joint Committee has evaluated the studies relevant for approval 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 IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of Tisagenlecleucel .

In the light of the above, and taking into account the statements received and the oral hearing, the Federal Joint Committee has arrived at the following assessment:

[1] General methods, Version 5.0 from 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Tisagenlecleucel (Kymriah®) in accordance with specialist information

Kymriah® is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

2.1.2 Extent of the additional benefit of tisagenlecleucel

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

The G-BA classifies the extent of the additional benefit of tisagenlecleucel to be assumed solely from a legal point of view according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V on the basis of the criteria in Section 5 paragraph 7 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable taking into account the severity of the disease and the therapeutic objective in the treatment of the disease.

Grounds:

To determine the extent of the additional benefit of tisagenlecleucel in adult patients with relapsed or refractory (R/R) diffuse large cell B-cell lymphoma (DLBCL) after two or more lines of systemic therapy the following sources were available: the results of the single-arm pivotal phase II trial JULIET, the supportive case series by Schuster *et al.* from 2017[2], and indirect comparisons with historical controls.

Series of cases of Schuster *et al.* (2017)

In the series of cases of Schuster *et al.* (2017) the efficacy and safety of tisagenlecleucel in 23 patients with DLBCL was investigated. In this series of cases relevant information regarding the study methodology (e.g. definition of the endpoints) and the study characteristics (e.g. course of the study, protocol breaches) is absent. It is also unclear what the percentage of patients with detectable disease after primary therapy was. These patients are not covered by tisagenlecleucel's approved therapeutic indication. Due to these uncertainties, the series of cases of Schuster *et al.* of 2017 is not used for the benefit assessment.

The JULIET study

The JULIET study is a single-arm, multicentre phase II study to determine the safety and efficacy of tisagenlecleucel in adult patients with r/r DLBCL.

The JULIET study contains two patient cohorts. In the main cohort patients were included who received tisagenlecleucel from the American production site, whereas cohort A consisted of patients for whom tisagenlecleucel was manufactured in the European production site. Since the present study on tisagenlecleucel is an open-label and non-randomised phase II study, in principle, a high potential for distortion for all endpoints must be assumed

The study is being conducted at 27 study centres in America, Australia, Asia and Europe. Tisagenlecleucel was administered in a one-off intravenous infusion. Repeated administration

[2] Schuster et al. (NCT02030834): „Phase IIa study of redirected autologous T cells engineered to contain ANTI-CD19 attached to TCRζ and 4-1BB signalling domains in patients with chemotherapy relapsed or refractory CD19+ Lymphomas"

of tisagenlecleucel was not envisaged in the study. Patients were monitored after receiving tisagenlecleucel infusion during primary, secondary or survival follow-up.

The pharmaceutical manufacturer has submitted a total of four data cut-offs from the JULIET study (8 March 2017, 6 September 2017, 8 December 2017, 21 May 2018). With the exception of the primary analysis of 8 March 2017, these were not explicitly scheduled in the protocol. According to information provided by the pharmaceutical manufacturer, the 6 September and 8 December 2017 data cut-offs took place by arrangement with the European Medicines Agency, while the 21 May 2018 data cut-off was scheduled to meet the Japanese marketing authorisation procedure. Enrolment of patients in the JULIET study and administration of outstanding infusions to patients who had already been enrolled was only completed by the date of the last data cut-off on 21 May 2018. In its dossier, the pharmaceutical manufacturer describes the three more recent data cut-offs as additional analyses. However, for these data samples, important information on the course and execution of the JULIET study is missing. Thus, the additional analyses presented were not sufficient to provide a comprehensive overview of the course of the study and the flow of patients to the respective data cut-off. In addition, data on the administered concomitant medication (e.g. bridge chemotherapy, chemotherapy for lymphocyte depletion), data on follow-up for adverse events, and an overview of the protocol breaches and protocol changes are missing for each data cut-off point.

In its written statement, the pharmaceutical manufacturer submits the patient flow before the administration of Tisagenlecleucel for all data cut-offs. However, this still does not include information on protocol amendments and protocol violations, on the course of the study after tisagenlecleucel administration, on concomitant medications administered, on the median observation duration of the various follow-up phases of the study and on the median observation duration of the follow-up for adverse events for the data cut-offs of 6 September 2017, 8 December 2017 and 21 May 2018.

After the oral hearing, the pharmaceutical manufacturer submitted further data on the 21 May 2018 cut-off (protocol amendments, protocol breaches, median follow-up period for adverse events). Regarding the patient flow after tisagenlecleucel infusion, the pharmaceutical manufacturer only provided information on the number of patients who withdrew during follow-up and the reasons for the withdrawal. The documents do not reveal whether the data relates to the overall follow-up or a particular follow-up phase (e.g. primary, secondary). Consequently, it remains unclear what follow-up phase the patients were in on the data cut-off date, how many patients withdrew during the respective follow-up phase and what the individual reasons for discontinuation were. In addition, specific data is still missing on administered concomitant medications, on the median period between screening and tisagenlecleucel infusion or, respectively, between study inclusion and tisagenlecleucel infusion, on the median follow-up period from the time of tisagenlecleucel infusion and on the median period of the various follow-up phases. Regarding the primary data cut-off of 8 March 2017, no further documents were subsequently submitted by the pharmaceutical entrepreneur after the oral hearing.

Since the course and conduct of the JULIET study at the date of the data cut-offs on 6 September 2017, 8 December 2017 and 21 May 2018 could not be comprehensively traced, these data cut-offs were considered unusable with respect to the benefit assessment.

There is a study report available for the data cut-off of 8 March 2017. Data is missing on the median period of the secondary follow-up phase and the survival follow-up as well as the median follow-up period for adverse events. In addition, this data is subject to high levels of uncertainty due to the ongoing recruitment of patients into the JULIET study and the very short median follow-up period of only 3.71 months.

At the time of the primary data cut-off of 8 March 2017, 147 patients had been included in the study (ITT population (enrolled set)). The median period between inclusion in the study and infusion of tisagenlecleucel was 54 days. Of the total patients enrolled, 43 had ceased participating in the study before receiving tisagenlecleucel. This corresponds to around 30 % of the study population. The primary causes for abandoning the study were death or the advice of the doctor. For 5 patients included in the study, the infusion was still outstanding on the data cut-off date. Thus, 99 patients were treated with tisagenlecleucel. All patients who received a tisagenlecleucel infusion are referred to in the JULIET study as the "Full Analysis Set" (FAS) or Safety Set and are referred to in the following document as the "FAS population".

After inclusion in the study, there was a pre-infusion phase for several weeks, in which the patients could receive one or several bridge chemotherapy(s) in order to stabilise their disease until generation and infusion of tisagenlecleucel. Approximately 90% of the FAS population followed this pattern. There is no information available on treatment with bridge chemotherapy in the ITT population. The most frequently administered drugs were rituximab, gemcitabine, dexamethasone, etoposide, cytarabine, cisplatin and cyclophosphamide. This was followed by the lymphocyte depletion phase, in which a lymphocyte-depleting chemotherapy was administered to the patient 2–14 days prior to the infusion of tisagenlecleucel. Of the ITT population, 95 patients received chemotherapy for lymphocyte depletion. 73 patients received fludarabine and cyclophosphamide, and 19 patients received bendamustine. For three patients, no information was available on the active substances administered.

At the data cut-off of 8 March 2017, 40 patients in the FAS population were in the primary follow-up phase and 59 patients had discontinued this. Out of the 59 patients who had left the primary follow-up phase, 36 entered into the secondary follow-up phase. The main reasons for the failure to complete the primary follow-up were death (n = 10) and disease progression (n = 45). In the further course of the study, 12 patients left the secondary follow-up phase, mainly due to deaths (n = 10). At the time of the primary data cut-off, there were seven patients in the survival follow-up and two patients in the CTL019A2205B study for the long-term follow-up. For seven patients of the FAS population, it is unclear what follow-up phase the patients were in or whether they left the JULIET study without a further follow-up. Data on the median observation period of the individual follow-up phases is not available.

Antineoplastic therapies after the tisagenlecleucel infusion mostly included monoclonal antibodies in 22.2 % of the patients (including nivolumab and rituximab) as well as various cytostatic drugs. The percentage of patients undergoing stem cell transplantation (SCT) after tisagenlecleucel infusion is included in the study report in the Patient Data Listings, but these were not available. In the latest publication on the JULIET study of Schuster *et al.*[3], which relates to the data cut-off of 8 December 2017, six patients are referred to, who, due to an insufficient response to tisagenlecleucel, received a haematopoietic SCT (5 patients with allogeneic SCT and 1 patient with autologous, followed by an allogeneic SCT).

Treatment with tisagenlecleucel is inherently associated with the process of leukapheresis, waiting time until the product is available, and the frequently associated administration of bridge chemotherapy as well as lymphocyte-depleting chemotherapy. The influence of these components on the treatment of patients with tisagenlecleucel in the clinical care context can only be adequately addressed by assessing the ITT population. The consideration of the ITT population also takes into account the fact that for some of the highly pre-treated and often rapidly progressive patients, a potentially more rapidly available alternative treatment option

[3] Schuster S.J. *et al.* Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019.

was not available due to the waiting time for tisagenlecleucel. The problems of the relatively long period between study inclusion and tisagenlecleucel infusion had also been discussed as part of the European marketing authorisation procedure, against the background of the state of health of the patients under discussion. The production time in the JULIET study was between 30 and 357 days (median 54 days). Due to this long production time and the associated high proportion of patients who left the JULIET study already prior to the infusion (30 % of the study population), it is likely that any consideration of the study results based on the infused patients (FAS population) will be subject to a distorting selection effect. As a result, the patient characteristics of the FAS population differ from those of the ITT population. The FAS population tends to be younger, has a better performance status and fewer patients with >5 previous therapies. There were 10 % more FAS patients than ITT patients with an IPI of < 2 points.

In addition to the high level of uncertainty regarding the utility of the 8 March 2017 data cut-off point due to incomplete recruitment and the very short median follow-up time, the pharmaceutical manufacturer's dossier contains no analysis of overall survival time for the ITT population for this data cut-off point. For the 8 December 2017 data cut-off point, overall survival data for the ITT population are available in the EPAR[4], but this data cut-off point cannot be used for the benefit assessment due to the uncertainties described above. The pharmaceutical manufacturer in its written statement has also submitted analyses on the overall survival of the ITT population at the 21 May 2018 data cut-off. However, this opinion lacks information on the reasons for censoring and frequency of censoring, and the number of deaths cannot be reconstructed on the basis of the subsequent documentation on the patient flow after tisagenlecleucel infusion. Following the oral hearing, the pharmaceutical manufacturer referred to the study report on the primary data cut-off of 8 March 2017 and to the publication by Schuster *et al.* regarding the reasons for censoring. However, the publication by Schuster *et al.* refers to the data cut-off of 8 December 2017. Thus, no information is available for the ITT population on the frequency of the reasons for censoring for the 21 May 2018 data cut-off. Survival time analyses for the ITT population based on the only data cut-off of 8 March 2017 that can be used for the benefit assessment have not been provided by the pharmaceutical manufacturer.

One criticism is that the pharmaceutical manufacturer did not provide all the information deemed necessary for the most recent data cut-off, even though the benefit assessment published on 17 December 2018 and the oral hearing on 29 January 2019 drew attention to the deficits of the data prepared by the pharmaceutical manufacturer. In summary, due to the lack of data, it is not possible to draw any reliable conclusions on the extent of the additional benefits.

Historical comparisons

The pharmaceutical manufacturer has submitted indirect historical comparisons for the efficacy endpoints of the JULIET study. The data on the historical comparative populations submitted in the dossier stems from the two SCHOLAR-1 and CORAL studies. In addition, the statement of the pharmaceutical manufacturer is based on an indirect historical comparison with patient data from the study by Eyre *et al.*

[4] European Public Assessment Report - Kymriah (19 September 2018)

The SCHOLAR-1 study

The SCHOLAR-1 study is an international, retrospective study, which includes patient data from a total of four studies.

The data of the "MD Anderson Cancer Center (MDACC)" study and the study of the "Specialized Program of Research Excellence (SPORE)" of the Mayo Clinic and University of Iowa (MC/IA) were obtained from observation studies. Patients with r/r DLBCL and TFL after two preceding therapy lines were included in the MDACC study. The preceding therapy lines had to include a chemotherapy containing rituximab and a platinum-based salvage chemotherapy. In the MC/IA study, patients with newly diagnosed lymphoma were included and their treatment or, respectively, disease status was documented prospectively.

In addition, the SCHOLAR-1 study includes data from the follow-up phase of two randomised, controlled phase III studies. In the LY.12 study of the National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG), patients with a relapse after a chemotherapy containing an anthracycline were included. The study medication consisted of two different salvage chemotherapy regimens. The phase III CORAL study (Collaborative Trial in Relapsed Aggressive Lymphoma) of the French Lymphoma Academic Research Organization (LYSARC) includes patients with a primary relapsed DLBCL after a chemotherapy containing an anthracycline. The study medication in this study also consisted of two different salvage chemotherapy regimens with the aim of subsequently performing a consolidating autologous SCT. After the SCT the participants were further randomised for follow-up observation or maintenance therapy with rituximab.

Consistent with the criteria used by the pharmaceutical manufacturer to select the historical comparison population, patients of the SCHOLAR-1 study with primary refractory DLBCL were also taken into account (approximately 28% of the study population). This patient population lies outside of the approved therapeutic indication for tisagenlecleucel. In the SCHOLAR-1 study, although the subgroups were analysed with regards to the "number of prior therapies", no baseline characteristics are available for the specific patient population of patients having received at least 2 prior therapies. The pharmaceutical manufacturer, in its written statement, addresses the subsequent submission of the historical comparison to the SCHOLAR-1 study excluding primary relapsed patients, but still does not go on to submit patient characteristics for the historical comparison population selected by this approach. Therefore, it remains unclear whether the patient population of the SCHOLAR-1 study without taking into account the patients with primary refracted DLBCL is sufficiently comparable with the patient characteristics of the JULIET study. The population of the SCHOLAR-1 study taken as whole can be regarded as being significantly different from the patient characteristics of the JULIET study, for example in terms of ECOG performance status, IPI points and number of previous lines of therapy.

The CORAL study

The phase III CORAL study constitutes one of four studies from which the patient data flows into the SCHOLAR-1 study described above. The CORAL study includes patients with a primary relapsed DLBCL, who, in the second therapy line, received a salvage chemotherapy (R-ICE[5] or R-DHAP[6]) during the study, with the goal of conducting a subsequent autologous SCT. Of the 481 patients included, 255 were able to undergo an autologous SCT. These patients were randomised again and received either a maintenance treatment with rituximab

[5] Rituximab in combination with ifosfamide, carboplatin and etoposide
[6] Rituximab in combination with dexamethasone, high-dose cytarabine and cisplatin

or were only observed. The study was conducted between July 2003 and June 2008 in study centres in America, Australia and Europe.

In the pharmaceutical manufacturer's submitted historical comparison on the one hand the patients were considered from the CORAL study who suffered from a relapse after undergoing autologous SCT (n = 71) and consequently required third line therapy. On the other hand, patients who have not received autologous SCT during the study and for whom data were available concerning third-line therapy (n = 203) were referred to. A protocol amendment to the CORAL study, which was published separately, defined retrospectively how the data for third-line chemotherapy were collected. The methodology and timing of the retrospective data collection cannot be reconstructed based on the information available. The data was published only in the years 2016[7] and 2017[8]. Consequently, eight or, respectively, nine years had elapsed between the end of the study and the data collection. It is unclear how much time had elapsed between the occurrence of the events and their documentation, what efforts were made in order to achieve data completeness and how censoring was conducted. This raises uncertainties regarding data validity. There are also relevant differences between the JULIET and CORAL studies with respect to their patient characteristics (e.g. prior therapy, risk factors according to IPI) and the duration of follow-up (3.71 months vs. 32.8 months).

Notwithstanding the questionable comparability and data validity of the CORAL study, methodological shortcomings also exist. The two studies have different definitions of the overall survival endpoint. While in the CORAL study survival time is considered to start as early as the time of failure of salvage chemotherapy or the time of relapse, in the JULIET study definition it is considered to start at the time of infusion of tisagenlecleucel for the FAS population or at the time of inclusion in the study for the ITT population. Hence, the logical conclusion of the JULIET study's definition of overall survival is that its patients enjoy a period in which death cannot occur. In its statement, the pharmaceutical manufacturer states that the median time between patient relapse and inclusion in the JULIET study is around 2.3 months. This results in a significant distortion of the indirect comparison, since in this period around 20 % of the study population of the CORAL study had already died.

Against the background of the above-mentioned deficits in the data of the JULIET study, its comparability with the CORAL study cited as an indirect comparison cannot currently be assessed with sufficient certainty.

Study of Eyre et al.

In its written statement, the pharmaceutical manufacturer additionally refers to the study of Eyre *et al.* of 2016[9] as an indirect historical comparison. This study was a retrospective, multi-centre study conducted in Great Britain, which included 92 patients, who received pixantrone in the third or later therapy line to treat r/r DLBCL. For this historical patient population, the comparability of the patient characteristics is missing or unclear. The median age of patients in the study by Eyre *et al.* is approximately ten years older than that of the patients in the JULIET study, and the percentage of patients with an unfavourable IPI score of ≥ is higher. The comparability of patient populations with respect to prognostically relevant mutations and the molecular subtype cannot be assessed in the absence of more information.

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7 Van den Neste *et al.* Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016; 51 (1):51-57.

8 Van den Neste *et al.* Outcome of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplant: an analysis of patients included in the CORAL study. Bone Marrow Transplant 2017; 52 (2):216-221.

9 Eyre *et al.* Results of a multicentre UK-wide retrospective study evaluating the efficiency of pixantrone in relapsed, refractory diffuse large B-cell lymphoma. Br J Haematol. 2016 June;173(6):896-904.

Conclusion regarding the submitted historical comparisons

Overall, the submitted indirect comparisons reveal that there are not only, as described, uncertainties relating to the historical control populations, but also considerable uncertainties, on the other hand, regarding the patient population treated with tisagenlecleucel, due to the deficient data available from the JULIET study. It is, therefore, not possible to draw sufficiently valid conclusions on the extent of the additional benefit of tisagenlecleucel based on the submitted indirect historical comparisons.

Overall assessment

The GB-A has been provided with results on mortality, morbidity, quality of life and side effects from the pivotal single-arm Phase II study JULIET in order to evaluate the extent of the additional benefit of tisagenlecleucel to treat relapsed or refractory diffuse large B-cell lymphoma.

The submitted literature on the JULIET study is deficient. There is a lack of elementary information on the conduct of the study and on the course of the study for the current data cut-offs, making these data cut-offs unusable for the benefit assessment. The data from the primary data cut-off of 8 March 2017 available to assess benefit are highly unreliable owing to incomplete recruitment of patients and the very short median follow-up period. In addition, there are no overall survival analyses for this data cut-off that take into account the ITT population. Treatment with tisagenlecleucel is inherently associated with the process of leukapheresis, waiting for the product to generated, frequent associated administration of bridging chemotherapy and lymphocyte-depleting chemotherapy. The effect that these factors might have on patients in a clinical setting on the success of tisagenlecleucel therapy can only be adequately addressed by assessing the ITT population. In summary, due to the lack of data, it is not possible to draw any reliable conclusions on the extent of the additional benefits.

The pharmaceutical manufacturer has made indirect comparisons with various historical studies to demonstrate the extent of the added value of tisagenlecleucel.

Due to the deficit data available from the JULIET study and further uncertainties regarding comparability with the studies cited as indirect comparisons, no sufficiently valid conclusions on the extent of the additional benefit of tisagenlecleucel can be drawn at present based on the indirect historical comparisons presented.

As a result, the G-BA classifies the extent of additional benefit of tisagenlecleucel as unquantifiable solely from a legal point of view based on the criteria in Section 5 paragraph 7 AM-NutzenV taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. In accordance with Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V, an additional benefit exists but is not quantifiable because the scientific data basis does not permit this.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of tisagenlecleucel has 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 this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

On the basis of the data available from the pivotal single-arm phase II JULIET study, no reliable conclusions can be drawn regarding the extent of the additional benefit of tisagenlecleucel.

The present limitation is intended to enable a more meaningful data situation to be included in the benefit assessment also with regard to potentially further findings, in particular on patient-relevant endpoints in treatment with tisagenlecleucel.

Conditions of the time limit

For the renewed benefit assessment, a data cut-off of the JULIET study is to be carried out on 1 July 2019, and a separate report on the results of the study for this data cut-off is to be submitted. This report is intended to fully map the data available on the data cut-off for all patient-relevant endpoints, patient characteristics, patient flow, and study outcome for both the FAS and ITT populations.

In addition, it should be examined and explained to what extent evidence beyond the study that justifies the marketing authorisation is available for the reassessment of the additional benefit (e.g. also from observational studies), which could contribute to a relevant further gain of knowledge for the benefit assessment.

With regard to an indirect comparison, it should be examined and explained to what extent any data and information that may have developed in the meantime can be used for an indirect comparison, taking into account the criticisms of the indirect comparison presented in the current assessment.

For this purpose, the Federal Joint Committee considers a limitation of the resolution until 15 March 2020 to be appropriate.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1 paragraph 2, number 7 VerfO, the procedure for the benefit assessment of tisagenlecleucel begins again when the deadline has expired. For this purpose, the pharmaceutical manufacturer must submit a dossier to the Federal Joint Committee at the latest on the day of expiry of the deadline 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).

The possibility that a benefit assessment for tisagenlecleucel can be carried out at an earlier point in time for other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 – 6 VerfO) remains unaffected by this.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the medicinal product Kymriah® with the new active ingredient tisagenlecleucel. Tisagenlecleucel has been granted market authorisation as an orphan drug. The current assessment relates to the therapeutic indication claim: "Kymriah is indicated for the treatment of adult patients with relapsed or refractory diffuse large cell B-cell lymphoma (DLBCL) after two or more lines of systemic therapy".

The pharmaceutical manufacturer has submitted the study results of the single-arm phase II JULIET study, the series of supportive cases of Schuster *et al.* (2017) as well as unadjusted indirect comparisons to various historical control studies.

The series of cases of Schuster *et al.* has not been employed for the benefit assessment, since, among other things, relevant information on the study methodology and study characteristics is missing.

The data from the pivotal single-arm JULIET study is deficient. For the more up-to-date data cut-offs, there is a lack of necessary information on the course and conduct of the study, rendering it unsuitable for the benefit assessment. The data presented for the benefit

assessment from the 8 March 2017 data cut-off are associated with a high level of uncertainty due to the very short median follow-up time and the incomplete recruitment of patients. In addition, no overall survival analyses for the ITT population are available for this data cut-off point. Treatment with tisagenlecleucel is inherently associated with the process of leukapheresis, waiting time until the product is available, and the frequently associated administration of bridge chemotherapy as well as lymphocyte-depleting chemotherapy. The influence of these components on the treatment of patients with tisagenlecleucel in the clinical care context can only be adequately addressed by assessing the ITT population. In summary, due to the lack of data, it is not possible to draw any reliable conclusions on the extent of the additional benefits.

Due to the deficit data available from the JULIET study and further uncertainties regarding comparability with the studies cited as indirect comparisons, no sufficiently valid conclusions on the extent of the additional benefit of tisagenlecleucel can be drawn at present based on the indirect historical comparisons presented.

Overall, solely from a legal point of view, the additional benefit is deemed to be non-quantifiable.

The resolution will expire on 15 March 2020.

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

The number of suitable patients is equivalent to the target population insured under statutory health insurance (SHI) funds.

The G-BA bases its resolution on the patient numbers presented in the dossier by the pharmaceutical manufacturer.

The sources cited by the pharmaceutical manufacturer to determine the upper and lower limits of the number of newly diagnosed patients with DLBCL include patients with other forms of diffuse B-cell lymphoma. In addition, it is uncertain whether the ascertained incidence rate could be extrapolated to model the German health-care environment, as only one of the sources cited includes cases from a German register.

The pharmaceutical manufacturer uses the guidelines of the European Society for Medical Oncology (ESMO) to evaluate whether patients have relapsed or become refractory in first-line therapy. However, the information in these guidelines only pertains to relapses. The percentage rate in the source is not specified as referring to first-line therapy. In addition, the guideline does not specify the methodology for determining the stated figure of 30 % and the associated observation period.

When determining the percentage of patients unsuitable for autologous SCT, the pharmaceutical manufacturer also includes very elderly patients (over 80 years of age), who, however, are not included in the target population for tisagenlecleucel.

When determining whether a patient unsuited for transplantation has relapsed and requires second-line chemotherapy, the pharmaceutical manufacturer derives a percentage value from a paper by El Gnaoui *et al.*, but this value does not solely relate to second-line chemotherapy. In addition, it is uncertain to what extent the patient population of this study corresponds to the German healthcare context, as this only included patients with CD20-positive DLBCL and 35% of the patients were pre-treated with biological and/or experimental therapies. In addition, the number of patients was low (n = 33) and the median observation period was limited to 28 months. Due to the short observation time, it can be assumed that the percentage share was

underestimated, as the possibility cannot be ruled out that other patients would have gone on to relapse after a longer observation period.

In another calculation, the pharmaceutical manufacturer employs the CORAL study to determine the percentage of patients who have become refractory to second-line therapy. The calculation is performed by inverting the number of patients who went into remission on second-line therapy. In doing so, the manufacturer uses the figure for both CR and PR patients. This approach is inadequate, as the number of deaths is ignored. The manufacturer relates the figure of 37 % arrived at in this way to both patients who are suited for autologous SCT and patients who would not be considered suitable. It is uncertain whether this percentage can be employed in relation to both patient populations. The pharmaceutical manufacturer still ignores patients who relapsed or became refractory on a later line of therapy, which tends to underestimate the value.

When attempting to determine the percentage of patients who despite going into remission did not receive autologous SCT during second-line therapy and to determine the percentage of patients who suffered a relapse after autologous SCT, the pharmaceutical manufacturer makes various assumptions concerning patient percentages that are neither comprehensible nor justifiable.

In summary, the patient figures arrived at by the manufacturer are associated with uncertainties and tend to be underestimates.

2.3 Requirements for quality-assured application

A. Regulatory requirements for marketing authorisation

The requirements of the specialist information and the Risk Management Plan (RMP) under the terms of the marketing authorisation must be taken into account. The European Medicines Agency (EMA) provides the contents of the specialist information as well as the conditions or restrictions for the safe and effective use of Kymriah® (active ingredient: Tisagenlecleucel) agreed upon in the context of the market authorisation under the following link (last access: 30 January 2019):

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

According to the requirements of the European Medicines Agency (EMA) regarding additional measures to minimise risk, the pharmaceutical manufacturer must provide training material and a patient emergency card. The training material for all healthcare professionals who are to prescribe, deliver, and administer tisagenlecleucel contains instructions for the identification, treatment, and monitoring of cytokine-release syndrome and neurological side effects. It also includes instructions on the thawing of cells, the availability of four doses of tocilizumab at the site of treatment, the provision of relevant information to patients, and the full and adequate reporting of adverse events.

The patient training programme is designed to educate patients about the risks of cytokine release syndrome and serious neurological side effects as well as the need to report symptoms immediately to the attending physician, stay near the treatment facility for at least four weeks after tisagenlecleucel infusion, and carry their patient emergency card with them at all times.

B. Further requirements for the quality-assured use of tisagenlecleucel in qualified treatment facilities

Against the background of the highly malignant and advanced disease of the patients considered here, the immunosuppressive measures necessary for the administration of tisagenlecleucel as well as the possible very severe CAR-T cell-specific side effects such as CRS[10] and CRES[11], treatment with tisagenlecleucel represents a highly specialised and complex medical service.

The medicinal product must be used at a qualified treatment facility in accordance with the instructions in the summary of product characteristics. Therapy should be started and supervised under the guidance and supervision of healthcare professionals with experience in the treatment of haematological malignancies who are trained in the use of tisagenlecleucel and the management of patients treated with this medicinal product.

An optimal structure and process quality of the treatment facility is required for an optimal benefit-risk assessment for the respective patient and for guaranteeing patient safety by fast and appropriate care, among other things in the event of the occurrence of CAR-T cell-specific side effects such as CRS[10] and CRES[11]. The infrastructure of the treatment facility must also ensure adequate handling of the final cell product because incorrect handling can relevantly limit the viability of the CAR-T cells and thus the probability of therapeutic success.

Against this background, in order to ensure a reliable and quality-assured supply of the medicinal product, in particular from the point of view of ensuring sufficient patient safety, it is appropriate but also necessary to establish more detailed requirements for the quality-assured use of the medicinal product, in particular with regard to the adequate qualification of a treatment facility.

Taking into account the consistent recommendations of the expert organisations and persons of medical science and practice in the context of the benefit assessment, the Federal Joint Committee assumes that a quality-assured supply of the medicinal product tisagenlecleucel can take place in accordance with the following requirements for quality-assured use. Tisagenlecleucel may only be used at a qualified treatment facility, which must meet at least the following criteria.

1. Requirements for the qualification of the treatment facilities

1.1 Extensive experience in the treatment of the respective underlying malignant disease

1.1.1 Documented by the treatment of ≥ 50 cases of large cell B-cell lymphoma in adults (C83.3 or C85.1 after ICD-10-GM-2018) within the last three years, and participating in studies of the German Lymphoma Alliance (GLA) or a comparable study group.

Grounds:

The establishment of a minimum quantity in the form of numbers of cases as evidence of sufficient experience to supply the medicinal product is appropriate and justified. The authority to determine minimum quantities is based on Section 35a

[10] Cytokine-release syndrome
[11] CAR-T-related encephalopathy syndrome

paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V. Accordingly, the G-BA should also specify requirements for quality-assured use with the medicinal products with the resolution on the benefit assessment. From the general authority, it can be concluded that from the outset, the legislator did not want to limit the scope of the G-BA to a final catalogue of measures for quality-assured administration. Because the determination of minimum quantities in Section 35a paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V is not explicitly mentioned as a measure for quality-assured use of medicinal products, it cannot be concluded that it is not covered by the authority. This corresponds to the fact that, according to the case law of the BSG, suitable requirements for minimum quantities (e.g. in the form of minimum patient numbers) can generally also be considered as a quality assurance measure. There is no doubt that minimum quantities can in principle be an instrument of quality assurance (BSG, judgement of 29 November 2017 – B 6 KA 32/16 R, cited by juris, marginal 37 et seq.). Based on the fundamental suitability and social-law recognition of minimum quantities as an instrument of quality assurance, it cannot be concluded from the special regulations on minimum quantities laid down in SGB V as a prerequisite for the provision of certain services by hospitals that minimum quantities in all other areas would be completely excluded as an instrument of quality assurance (cf. BSG, judgement of 29 November 2017 – B 6 KA 32/16 R, cited by juris, marginal 37 et seq.). In the light of this consideration, the regulations in Section 35a paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V give the G-BA a sufficiently wide scope for the definition of requirements for the quality-assured use of medicinal products, which also includes the determination of minimum quantities.

R/r DLBCL is a rare disease, which affects fewer than 1000 patients yearly in Germany. The treatment of r/r DLBCL is a highly specialised and complex service, which requires a special level of practice and experience. For a medically adequate indication, an individual assessment of the available therapy alternatives is necessary because of the lack of comparative study data. Sufficient therapeutic experience in the treatment of DLBCL is therefore essential in order to adequately assess the benefit-risk ratio for the use of tisagenlecleucel in multiple pre-treated patients compared with other possible therapy alternatives. Study data for the relationship between treatment volume and mortality specifically for the indication r/r DLBCL are not available. However, for the disease acute myeloid leukaemia (AML), which has a similar complexity with regard to its disease characteristics and the course of therapy, there was a correlation between the amount of treatment and mortality[12]. From these points of view, there is a reasonable probability that a minimum number of cases will lead to considerable quality advantages with respect to the highly specialised and complex medical services available here.

Treatment cases are documented in accordance with the regulations adopted by the G-BA in the field of quality assurance. The application of the regulations adopted by the G-BA in the field of quality assurance remains unaffected in accordance with Item 3 of the requirements for quality-assured administration.

[12] Giri et al. Impact of hospital volume on outcomes of patients undergoing chemotherapy for acute myeloid leukaemia: a matched cohort study. Blood 2015 125:3359–3360

1.2 Extensive experience in cell therapy

1.2.1 As documented by > 120 allogeneic first transplantations reported to the German Registry for Stem Cell Transplantation / European Bone Marrow Transplantation Registry (DRST/EBMTR) within the last three reviewed years.

Grounds:

The use of tisagenlecleucel represents a highly complex treatment approach because of, among other things, the immunosuppressive measures required in most cases and the possible serious side effects. Because of the novelty of the therapy approach, a connection between treatment quantity and treatment quality for tisagenlecleucel and CAR-T cells cannot currently be demonstrated in studies. Therefore, in the present case, the closest therapy concept of allogeneic stem cell transplantation, which has been established for the present indication and treatment situation, is used. As with CAR-T cells, allogeneic stem cell transplantation requires the administration of high-intensity conditioning chemotherapy, which strongly compromises the patient's immune system. Dealing with severely immunosuppressed patients, including early diagnosis and the treatment of serious infections, is therefore decisive for the rate of serious or fatal complications for both therapeutic approaches. In addition, CAR-T cells as well as allogeneic stem cell transplantation are based on the immunogenic properties of human cells that trigger an immune response. Thus, both therapy approaches can lead to severe immune-mediated complications, which affect multiple organs. In the worst-case scenario, these can lead to death. For the lowest possible mortality and morbidity resulting from acute therapy complications, the rapid and qualified early detection of complications and appropriate intervention are essential. In treatment facilities with sufficient experience in allogeneic stem cell transplantation, it is ensured that personal experience with such complications exists, that the interface to intensive care medicine is adequately defined, that workflows are standardised, and that haemato-oncological expertise also flows into the field of intensive care medicine. There is also the handling of long-term complications and the aftercare of patients. While chronic graft-versus-host-disease is a well-known long-term complication for allogeneic stem cell transplantation, possible long-term sequelae from treatment with tisagenlecleucel are largely unexplained. Potential long-term complications listed by the European Medicines Agency include sustained immunodeficiency or B-cell depletion, secondary tumours, and autoimmune diseases. In treatment facilities with sufficient experience in allogeneic stem cell transplantation or with outpatient specialists cooperating with these treatment facilities, structured aftercare is generally implemented in order to identify long-term consequential damage. For allogeneic stem cell transplantation, study data provide evidence of a causal relationship between treatment volume and mortality as well as the success of therapy (freedom from leukaemia, absence of relapse)[13,14]. Because the common characteristics described between CAR-T cells and allogeneic stem cell transplantation largely determine the quality and risks of the medical service,

[13] Giebel et al. The impact of centre experience on results of reduced intensity: allogeneic haematopoietic SCT for AML. An analysis from the Acute Leukaemia Working Party of the EBMT. Bone Marrow Transplant. 2013 Feb;48(2):238-42.

[14] Loberiza et al. Transplant center characteristics and clinical outcomes after haematopoietic stem cell transplantation: what do we know. Bone Marrow Transplantation volume 31, pages 417–421 (2003)

considerable quality advantages can also be expected for the CAR-T cells through the defined minimum quantities for the performance or detection of allogeneic stem cell transplantation. The present minimum quantities, which were calculated over three years, allow for the compensation of random fluctuations from personnel or organisational aspects. They also prevent a treatment facility from reaching a short-term threshold resulting from a medically unjustified increase in quantities.

Documentation is provided by the reporting of >120 allogeneic first transplantations to the German Registry for Stem Cell Transplantation/European Bone Marrow Transplantation Registry (DRST/EBMTR) within the last three years evaluated. In this respect, it is a special regulation that finally defines the documentation requirements in relation to other regulations of the G-BA (cf Item 3 of the Requirements for Quality Assured Application).

1.3 Personnel and technical requirements

1.3.1 The medical director and deputy director responsible for treating adults with tisagenlecleucel must be specialists in internal medicine, haematology, and oncology. The medically responsible management or its deputy must have at least two years' professional experience in a treatment centre in which allogeneic stem cell transplantations are carried out in accordance with the criteria set out in Points 1.1 and 1.2 below. If the activity is conducted on a part-time basis, allogeneic stem cell transplantations performed on the ward may be allocated proportionately to full-time work.

1.3.2 Requirements for the qualifications of the nursing service

1.3.2.1 The management and their representation on the ward for the care of patients treated with tisagenlecleucel are nurses with oncological specialisation or have worked full-time for at least 36 months in a ward with a haematological-oncological specialisation and have participated in the in-house training for the treatment of patients with tisagenlecleucel. If the activity is conducted on a part-time basis, the corresponding working hours may be allocated proportionately to full-time work.

1.3.2.2 Each shift is led by nurses who have worked full-time for at least 12 months in a haematological-oncological ward, have experience in the intensive chemotherapy of leukaemia/lymphoma patients, and have participated in in-house training for the treatment of patients with tisagenlecleucel. If the activity is

conducted on a part-time basis, the corresponding working hours may be allocated proportionately to full-time work.

1.3.3 Sufficient training and documented experience of the medical staff involved (doctors, nurses) in the treatment with cytotoxic and immunosuppressive substances as well as cryopreserved cells must be demonstrated.

2. Infrastructure and organisational requirements

2.1 Establishment of a tumour board:

2.1.1 The indication for treatment with tisagenlecleucel in adults must be presented at an interdisciplinary tumour conference in which at least physicians with the following qualifications participate:

- Internal medicine, haematology and oncology
- Radiation therapy
- Pathology
- Diagnostic radiology

2.1.2 The date, participants and outcome of discussions at the tumour conference must be documented in writing.

2.2 The responsible pharmacy must be integrated into the treatment facility by binding regulations for the timely fulfilment of statutory requirements.

2.3 The rooms for the treatment of patients with tisagenlecleucel are located in the vicinity of the intensive care unit. The treatment facility must have the necessary equipment to perform at all times endoscopy, including bronchoscopy, invasive ventilation, and renal replacement therapy. Specific SOPs[15] deal with complications of CAR-T cell therapy, including the use and sufficient availability of tocilizumab on site at all times in accordance with the specialist information. There is also a binding and regulated definition of the rapid and unhindered admission of intensive care patients to the intensive care unit.

2.4 There are SOPs[15] for clinical, instrumental, and laboratory chemical monitoring for the early detection of CRS[16] and CRES[17] as well as for the procedure for transferring the patient to the intensive care unit (e.g. decision-making authority, persons involved).

2.5 Medical care in accordance with specialist standards (internal medicine, haematology, and oncology) must be available without interruption for the inpatient care of patients treated with tisagenlecleucel; at least one on-call service must be provided outside working hours.

2.6 When transferring to the intensive care unit, it must be ensured that a visit is carried out daily by a specialist in internal medicine, haematology and oncology. This physician

[15] Standard Operating Procedure
[16] Cytokine release syndrome
[17] CAR-T-related encephalopathy syndrome

must also have personal experience in the treatment with CAR T cells. The treatment concept on the intensive care unit must be discussed with this physician.

2.7 In addition, the following specialist disciplines must be available at all times; the necessary examinations and treatments should be possible without the need for patient transport (in alphabetical order):

- Ophthalmology
- Gastroenterology (endoscopy of the gastrointestinal tract)
- Vascular surgery
- Otorhinolaryngology
- Cardiology
- Laboratory medicine
- Microbiology (availability within 24 hours is sufficient)
- Nephrology (dialysis)
- Neurosurgery
- Neurology (with proof of participation in the in-house training programme)
- Pneumology (bronchoscopy)
- Psychiatry
- Radiology (with CT and MRI)
- Thoracic surgery
- Urology

Outside working hours, at least one on-call standby service must be provided. On-call duty means that a specialist of the treatment facility with the corresponding qualification certificates is available to the patient at any time (24 hours a day, seven days a week) within a maximum of 30 minutes.

2.8 Accommodation in specific rooms for patients in Risk groups 2 or 3 according to the guidelines of the Robert Koch Institute[18] is generally not required. However, it must be ensured that such accommodation is possible at all times.

2.9 Outpatient after-care

2.9.1 Medical care in accordance with specialist standards (internal medicine, haematology, and oncology) must be available at all times for outpatient follow-up of patients treated with tisagenlecleucel.

2.9.2 The spatial environment must enable the outpatient care of immunosuppressed patients.

2.9.3 The spatial environment must make it possible to examine and treat patients with contagious infections separately. A suitable infrastructure for infusion treatment and the transfusion of blood products must be available.

2.10 Further quality assurance measures

The treatment facility participates in inter-institutional quality assurance and knowledge-generating care measures (registries, quality circles, and analysis of quality

[18] Recommendation of the Commission for Hospital Hygiene and Infection Prevention at the Robert Koch Institute (RKI). Hygiene requirements for the medical care of immunosuppressed patients. Bundesgesundheitsblatt [Federal Health Gazette] 2010 53:357–388.

indicators) offered nationally or internationally by professional organisations, the pharmaceutical industry, and regulatory authorities.

2.11 Documentation

The documentation is part of the conditions imposed by the European Medicines Agency on pharmaceutical companies. The treatment facility must maintain the personnel and structural requirements for the connection to the planned register modules for CAR-T cells in the German Register for Stem Cell Transplantation (DRST), in the Paediatric Register for Stem Cell Transplantation (PRST), or in the Register of the European Society for Blood and Marrow Transplantation (EBMT) as well as for timely documentation. The following in particular should be documented:

- Prior therapies
- Adverse drug effects
- Type and duration of response
- Follow-up therapies
- Overall survival

3. The findings according to Items 1 and 2 regulate minimum requirements for the quality-assured use of tisagenlecleucel. The validity of other provisions of the G-BA remains unaffected provided that these do not conflict with the minimum requirements.

2.4 Treatment costs

The treatment costs are based on the information in the specialist information, the pharmaceutical manufacturer's information on the selling price from Module 3 of the dossier, and its written statement. Although tisagenlecleucel is listed in Lauer-Taxe® (the recognized price source for all drugs in Germany), it is only sold to qualified inpatient treatment facilities. The active ingredient is therefore not subject to the pharmaceutical price regulation and there are no discounts according to Section 130 or Section 130a SGB V. The calculation is based on the selling price of the pharmaceutical manufacturer. This differs from the information usually taken into account in the Lauer-Taxe.

As specified in the summary of product characteristics, tisagenlecleucel is administered as a single intravenous infusion.

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

Usage and consumption:

In the following, the consumption of infusion bags is presented according to the specifications in the specialist information. These are administered to the patient in a single infusion depending on the number of cells in each infusion bag. The annual treatment costs of tisagenlecleucel are independent of the actual number of infusion bags used.

Designation of the therapy	Dosage	Dose / patient / treatment days	Consumption according to potency/ treatment day	Treatment days / patient/ year	Annual average consumption according to potency
Medicinal product to be assessed					
Tisagenlecleucel					
	$0.6 – 6.0 \times 10^8$ CAR-positive viable T cells	$0.6 – 6.0 \times 10^8$ CAR-positive viable T cells	1–3 infusion bags	1	1–3 infusion bags

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (Selling price of the manufacturer) [19]	Value added tax	Cost
Medicinal product to be assessed				
Tisagenlecleucel				
	1–3 infusion bags (0.6 to 6.0 x 10^8 CAR-positive viable T cells)	€ 320,000	€ 0 [20]	€ 320,000

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 costs for the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed in accordance with the specialist 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 usual expenditure in the course of the treatment are not shown.

Tisagenlecleucel is an autologous cell product produced from the patient's own T cells. Leukapheresis is therefore regularly necessary to obtain the cell material. Because leukapheresis is part of the manufacture of the medicinal product under Section 4 paragraph 14 AMG, no further costs are incurred in this respect for the medicinal product to be assessed.

According to the specialist information of tisagenlecleucel, before the administration of the CAR-T cells, the administration of lymphocyte-depleting chemotherapy is recommended provided that the number of white blood cells is not under ≤ 1,000 cells/µl one week before the infusion. The recommended regimen is fludarabine (25 mg/m2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m2 intravenous daily for 3 days).

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 used as a basis. This results in a range based on the average body surface area of children under 1 year of 0.36 m^2 (average body height: 0.67 m; average body weight: 7.6 kg) and the average body surface area of young adult patients under 25 years of 1.90 m^2

[19] Manufacturer's information on the selling price from module 3 of the dossier.

[20] According to the comments made by the pharmaceutical manufacturer in the statement based on information from the Central Tax Office in Nuremberg in accordance with Section 89 paragraph 2 German Tax Code to the pharmaceutical manufacturer, the supply of tisagenlecleucel (Kymriah®) in accordance with to Art. 132 paragraph 1 lit. d) of the European Value Added Tax Directive or in accordance with Section 4 paragraph 17 lit a) of the Value Added Tax (VAT) Act is qualified as exempt from VAT.

(average body height: 1.75 m; average body weight: 74.7 kg; calculation according to Du Bois 1916)**Fehler! Textmarke nicht definiert.**.

Type of service	Cost per package	Cost after deduction of statutory discounts[21,22]	Cost per service	Treatment days per year	Cost per patient / year
Medicinal product to be assessed					
Tisagenlecleucel					
Lymphocyte depletion					
Fludarabine (25 mg/m^2, i.v.)	€ 118.20 1 x 50 mg	€ 111.34 (€ 1.77, € 5.09)	€ 111.34	3	€ 334.02
Cyclophosphamide (250 mg/m^2, i.v.)	€ 22.80 1 x 500 mg	€ 19.53 (€ 1.77, € 1.50)	€ 19.53	3	€ 58.59

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15. February 2019

Other SHI services:

The special agreement contractual unit costs of retail pharmacist services [Hilfstaxe"] (contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from finished medicinal products in oncology in the Hilfstaxe according to Section 129 paragraph 5c sentences 2 - 5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Appendix 3 to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"].

3. Bureaucratic costs

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

21 Sales discount pursuant to section 130 SGB V
22 Sales discount pursuant to section 130a SGB V

4. Procedural sequence

On 14 September 2018, the pharmaceutical manufacturer submitted a dossier on the benefit assessment of Tisagenlecleucel to the G-BA in due time and in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure.

The benefit assessment of the G-BA was published on 17 December 2018 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 7 January 2019. The oral hearing was held on 29 January 2019.

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

The evaluation of the written statements received and the oral hearing were discussed at the meeting of the subcommittee on 26 February 2019, and the proposed resolution was approved.

At its meeting on 7 March 2019, the plenary adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject under deliberation
Subcommittee Medicinal product	11 December 2018	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	15 January 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	29 January 2019	Conduct of the oral hearing
Working group Section 35a	5 February 2019 19 February 2019	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal product	26 February 2019	Concluding discussion of the proposed resolution
Plenum	7 March 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 7 March 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof. Hecken