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 Lisocabtagene maraleucel (Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma and follicular lymphoma grade 3B, after ≥ 2 prior therapies)

of 6 April 2023

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was 1 September 2022 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA for the first placing on the (German) market of the active ingredient lisocabtagene maraleucel. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 23 August 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier.

The benefit assessment was published on 16 January 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of lisocabtagene maraleucel compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment 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 evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of lisocabtagene maraleucel.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Lisocabtagene maraleucel (Breyanzi) according to the product information

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 06.04.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy

Appropriate comparator therapy for lisocabtagene maraleucel:

Patient-individual therapy with selection of:

- CEOP (cyclophosphamide, etoposide, vincristine, prednisone),
- dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone),
- MINE (mesna, ifosfamide, mitoxantrone, etoposide),
- polatuzumab vedotin + bendamustine + rituximab (only for subjects with DLBCL who are ineligible for haematopoietic stem cell transplant),

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

- tafasitamab + lenalidomide (only for subjects with DLBCL who are ineligible for autologous stem cell transplant),
- pixantrone monotherapy,
- rituximab monotherapy (only for subjects with FL3B),
- tisagenlecleucel (only for subjects with DLBCL and FL3B),
- axicabtagene ciloleucel (only for subjects with DLBCL and PMBCL),
- radiation,
- stem cell transplant (autologous or allogeneic),
- or best supportive care;

taking into account the lymphoma subentity, biology of the disease, prior therapy, the course of the disease and the general condition

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In terms of authorisation status, the following active ingredients are available for the treatment of relapsed or refractory DLBCL, PMBCL and FL3B: bleomycin, carmustine, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, loncastuximab tesirine, melphalan, methotrexate, methylprednisolone, mitoxantrone, pixantrone, polatuzumab vedotin, prednisolone, prednisone, tafasitamab, trofosfamide, vinblastine, vincristine, vindesine, rituximab, axicabtagene ciloleucel and tisagenlecleucel.

Some of the medicinal products listed have a marketing authorisation for the superordinate therapeutic indication "non-Hodgkin lymphoma". The marketing

authorisations are partly linked to (specified) concomitant active ingredients or do not fully cover the present therapeutic indication.

on 2. In principle, autologous or allogeneic stem cell transplantation can be considered as a non-medicinal treatment for relapsed or refractory DLBCL, PMBCL and FL3B. In addition, radiotherapy can be administered, for example, to treat localised residual manifestations of the lymphoma after completion of chemotherapy.

on 3. For this therapeutic indication, there are the following resolutions or guidelines of the G-BA for medicinal applications or non-medicinal treatments:

- Axicabtagene ciloleucel – resolution of 3 November 2022
- Tafasitamab – resolution of 3 March 2022
- Tisagenlecleucel – resolution of 17 September 2020
- Polatuzumab vedotin – resolution of 20 August 2020
- Pixantrone – resolution of 16 May 2013

Guideline for Hospital Treatment Methods (last revised 16 January 2020: Allogeneic stem cell transplantation for aggressive B-cell non-Hodgkin lymphoma):

- Section 4 Excluded methods: Allogeneic stem cell transplantation in adult patients with aggressive B-non-Hodgkin lymphoma who have not yet been treated with autologous stem cell transplantation (exceptions: a) patients who have a very high risk of recurrence and who achieve a response at least in the sense of stable disease after salvage therapy; b) patients in whom sufficient stem cell harvesting for autologous stem cell transplantation was not possible and who achieve a response at least in the sense of stable disease after salvage therapy).
- Annex I: Methods required for hospital care: Allogeneic stem cell transplantation in adult patients with aggressive B-non-Hodgkin lymphoma who relapse after autologous stem cell transplantation and achieve a response at least in the sense of stable disease after salvage therapy.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

In the limited evidence available, various treatment options are mentioned for the treatment of the patient population covered by the therapeutic indication. In this regard, the present patient population generally refers to patients with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy and is not limited in terms of patient eligibility or ineligibility for an intensive therapeutic approach. Therefore, the G-BA considers it appropriate to consider both treatment options with a potentially curative therapeutic approach and treatment options that are used as part of a palliative therapy concept when determining the appropriate comparator therapy for the present patient population.

Based on the available guidelines and the written statement of the scientific-medical societies, no standard can be defined for the heterogeneous patient population at hand. The therapy is selected taking into account individual factors such as the lymphoma subentity, biology of the disease, prior therapy, the course of the disease and the general condition.

For patients who can be treated intensively, the guidelines mainly mention CAR-T cell therapies and stem cell transplant.

For the CAR-T cell therapies axicabtagene ciloleucel (resolution of 3 November 2022) and tisagenlecleucel (resolution of 17 September 2020), a non-quantifiable additional benefit was determined in each case within the framework of an orphan drug assessment. The period of validity of the resolution on tisagenlecleucel is limited to 1 September 2023.

The present therapeutic indication also includes patients who cannot be treated with intensive therapy due to the course of their disease or their general condition. For these patients, different treatment options are listed in the guidelines.

The antibody-drug conjugate polatuzumab vedotin is approved in combination with bendamustine and rituximab (Pola-BR) for the treatment of adults with relapsed or refractory diffuse DLBCL if they are ineligible for haematopoietic stem cell transplantation. By resolution of 20 August 2020, a non-quantifiable additional benefit was identified for polatuzumab vedotin as a medicinal product for the treatment of rare diseases (orphan drug) compared to bendamustine in combination with rituximab.

The CD19-specific antibody tafasitamab is approved in combination with lenalidomide for the treatment of patients with relapsed or refractory DLBCL for who are ineligible for autologous stem cell transplantation. By resolution of 3 March 2022, a hint for a non-quantifiable additional benefit was identified for tafasitamab within the scope of an orphan drug assessment because the scientific data does not allow quantification.

The active ingredient pixantrone has explicit marketing authorisation for the treatment setting of multiple relapsed or refractory aggressive non-Hodgkin B-cell lymphoma (NHL). By resolution of the G-BA of 16 May 2013, it was determined that an additional

benefit of pixantrone compared to the appropriate comparator therapy is not proven. Pixantrone is mentioned in the written statement of the DGHO as a therapeutic alternative to the treatment of multiple relapsed, aggressive B-cell lymphomas.

Rituximab is approved as monotherapy for the treatment of adults with stage III-IV follicular lymphoma.

The guidelines discuss various combinations of rituximab and chemotherapies (doxorubicin + methylprednisolone + cytarabine + cisplatin; bendamustine, cyclophosphamide + etoposide + prednisone + procarbazine; CEOP; dose-adjusted EPOCH, dexamethasone + cisplatin + cytarabine; dexamethasone + cytarabine + oxaliplatin; dose-intensified cyclophosphamide + etoposide + cisplatin; etoposide + methylprednisolone + cytarabine + cisplatin; gemcitabine + oxaliplatin; gemcitabine + dexamethasone + cisplatin or carboplatin; gemcitabine + vinorelbine, ifosfamide + carboplatin + etoposide; methotrexate + etoposide + cisplatin; MINE; prednisolone + etoposide + procarbazine + cyclophosphamide).

However, individual components of the combination chemotherapies recommended in the guidelines are not explicitly approved for the present treatment setting: Cisplatin, carboplatin, gemcitabine, oxaliplatin, procarbazine and vinorelbine. In addition, the active ingredients bendamustine, chlorambucil and lenalidomide are not approved for the present indication.

Furthermore, various targeted substances for specific subgroups of the present patient population (e.g. brentuximab vedotin for the treatment of patients with CD30+ DLBCL; ibrutinib for the treatment of patients with non-GCB DLBCL) are listed in guidelines, which, however, do not have the marketing authorisation for the present indication.

In addition, autologous or allogeneic stem cell transplantation is recommended in these guidelines for eligible subjects.

Guidelines cite selinexor as a treatment option for select patients, including those with progressive disease following stem cell transplantation or CAR T-cell therapy. However, selinexor is not approved for the present indication.

In addition, for patients in the present therapeutic indication, which includes both patients who are candidates for a potentially curative therapeutic approach and patients who have a palliative therapeutic approach, the implementation of best supportive care can also represent a therapeutic alternative within the framework of a patient-individual treatment decision. Best supportive care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

A discrepancy is identified between medicinal products approved in the indication and those used in healthcare/ recommended by the guidelines.

In the present case, the above-mentioned medicinal products recommended in the guidelines or used in healthcare, which do not have a marketing authorisation for the present indication or not an explicit one, cannot be considered as appropriate comparator therapy in the narrower sense within the meaning of Section 2, paragraph 1, sentence 3, Section 12 SGB V, and should therefore, according to the statements of the BSG (judgement of 22.02.2023, file ref.: B 3 KR 14/21 R), not be used as a comparator therapy for the benefit assessment.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

Change of the appropriate comparator therapy

Originally, in addition to the treatment options listed above, the following comparators were also considered suitable comparators in the context of patient-individual therapy, taking into account the evidence and the medical treatment situation:

- *ASHAP (doxorubicin, methylprednisolone, cytarabine, cisplatin),*
- *bendamustine,*
- *CEPP (cyclophosphamide, etoposide, prednisone, procarbazine),*
- *DHAP (dexamethasone, cisplatin, cytarabine),*
- *DHAX (dexamethasone, cytarabine, oxaliplatin),*
- *DICEP (dose-intensified cyclophosphamide, etoposide, cisplatin),*
- *ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin),*
- *GemOx (gemcitabine, oxaliplatin),*
- *GDP (gemcitabine, dexamethasone, cisplatin or carboplatin),*
- *gemcitabine + vinorelbine,*
- *ICE (Ifosfamide, carboplatin, etoposide),*
- *lenalidomide (only for patients with non-GCB DLBCL),*
- *MEP (methotrexate, etoposide, cisplatin),*
- *PEP-C (prednisolone, etoposide, procarbazine, cyclophosphamide),*

  each with or without rituximab;

- *brentuximab vedotin monotherapy (only for patients with CD30+ DLBCL),*
- *chlorambucil monotherapy,*
- *etoposide monotherapy,*
- *gemcitabine + rituximab,*
- *ibrutinib monotherapy (only for patients with non-GCB DLBCL).*

By the present resolution, these treatment options that are not approved in the present therapeutic indication are removed from the selection of patient-individual treatment options.

The change in the appropriate comparator therapy is necessary due to the judgement passed by the Federal Social Court on 22.02.2023, file ref.: D 3 KR 14/21 R, as it considers the designation of medicinal products in off-label use as an appropriate comparator therapy to be fundamentally inadmissible if this does not comply with the requirements of appropriateness in the narrower sense within the meaning of Section 2, paragraph 1, sentence 3, Section 12 SGB V.

This change in the appropriate comparator therapy means that the evaluations presented for the comparators used in the NDS-NHL-001 study only partially correspond to the presently determined appropriate comparator therapy. Therefore, the resolution is limited in time. The time limit enables the pharmaceutical company to submit suitable evaluations that correspond to the appropriate comparator therapy determined by the present resolution.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

For the benefit assessment of lisocabtagene maraleucel, the pharmaceutical company submitted data from the single-arm TRANSCEND-NHL-001 and TRANSCEND WORLD studies, which investigate the safety and efficacy of lisocabtagene maraleucel in patients with refractory or relapsed non-Hodgkin lymphoma.

In addition, the pharmaceutical company presents indirect comparisons without a bridge comparator with data from individual arms of the retrospective NDS-NHL-001 study as well as from the single-arm ZUMA-1 and JULIET studies.

<u>Studies on lisocabtagene maraleucel</u>

TRANSCEND-NHL-001

The TRANSCEND-NHL-001 *study* is a single-arm, phase I/II cohort study to investigate lisocabtagene maraleucel in patients with mantle cell lymphoma and DLBCL. Only the DLBCL cohort in which a total of 345 patients were enrolled is considered for the present benefit assessment.

The ongoing study has been conducted at 14 study sites in the USA since January 2016.

The TRANSCEND-NHL-001 study enrolled adults with DLBCL, PMBCL or FL3B who had relapsed or refractory disease either after at least 2 prior therapies, including an anthracycline and rituximab (or another CD20 active ingredient), or after an autologous stem cell transplantation.

The study treatment included leukapheresis for peripheral blood mononuclear cell collection, which occurred within 2 weeks of enrolment in the study. According to the study design, the subsequent infusion with lisocabtagene maraleucel should take place within 4 weeks after leukapheresis; in fact, the median time between leukapheresis and infusion was 37 days. Within this time, patients could receive bridge therapy. Prior to administration of the lisocabtagene maraleucel infusion, patients received a premedication of paracetamol and diphenhydramine.

Primary endpoints of the TRANSCEND-NHL-001 study were overall response rate (ORR), probability of dose-limiting toxicity and adverse events (AEs). Secondary endpoints included overall survival, morbidity and health-related quality of life. The follow-up period was 24 months after lisocabtagene- maraleucel infusion.

For the TRANSCEND-NHL-001 study, the primary data cut-off of 12 April 2019, the data cut-off of 12 August 2019 relevant to the marketing authorisation, and the data cut-offs of 19 June 2020 and 4 January 2021 submitted in the marketing authorisation procedure are available. In the dossier, the pharmaceutical company presents results on the data cut-offs of 12 August 2019 and 4 January 2021. For the indirect comparisons, it also draws in part on evaluations based on earlier data cut-offs.

TRANSCEND WORLD

The TRANSCEND WORLD study is a single-arm, phase II study of lisocabatgen maraleucel in adults with aggressive B-cell non-Hodgkin lymphoma, comprising a total of 7 cohorts. For the benefit assessment, the pharmaceutical company presents the results of cohorts 1 (N = 44) and cohort 3 (N = 14) relevant for the present therapeutic indication, in which patients with relapsed or refractory DLBCL (de novo or transformed FL), highly malignant B-cell lymphoma (HGBL) or FL3B, which were not further specified, were enrolled.

The ongoing TRANSCEND WORLD study started in June 2018 has been conducted at 18 study sites in Europe and two study sites in Japan.

The study treatment was similar to that of the TRANSCEND-NHL-001 study, with minor deviation. In contrast to the TRANSCEND-NHL-001 study, the time between leukapheresis and lisocabtagene maraleucel infusion, which should have been about 5 weeks according to the study design, was actually 42 days on median.

The primary endpoint of the study was ORR; secondary endpoints included overall survival, morbidity, health-related quality of life and AEs. The follow-up duration of the TRANSCEND WORLD study was also 24 months.

For the benefit assessment, the pharmaceutical company submitted evaluations for the endpoints of overall survival, tumour response, progression-free survival (PFS) and AEs for the intention-to-treat (ITT) population of cohorts 1 and 3 as of the 3rd data cut-off of 19 June 2020 and as of the 4th data cut-off of 4 January 2021. For further endpoints of the categories morbidity and health-related quality of life, only evaluations of the treated population were presented.

According to the information provided by the pharmaceutical company, an interim analysis dated 22.02.2019, the data cut-off of 13.09.2019 relevant to the marketing authorisation, the

primary analysis dated 19.06.2020 and a data cut-off of 04.01.2021, which was subsequently submitted in the course of the marketing authorisation procedure, are available for the TRANSCEND WORLD study. For the benefit assessment, the pharmaceutical company submitted evaluations of the data cut-offs of 19.06.2020 and 04.01.2021 in the dossier.

Studies on the appropriate comparator therapy

NDS-NHL-001 study

The NDS-NHL-001 study is a retrospective study conducted by the pharmaceutical company for the treatment of patients with aggressive B-cell NHL with relapsed or refractory disease after at least two prior lines of therapy.

Patients with histologically confirmed DLBCL NOS, HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL or FL3B were enrolled in the NDS-NHL-001 study. In addition, patients had to have relapsed or refractory disease after at least 2 prior therapies, including treatment with an anthracycline and rituximab (or another anti-CD20 active ingredient). Patients who received their initial diagnosis since 2003 were enrolled in the NDS-NHL-001 study.

Data sources were clinical study sites (2 study sites with N = 250 in North America and 9 study sites with N = 399 in Europe) and research databases. In addition, data from electronic patient records collected from the COTA (N = 392) and Flatiron (N = 277) databases and the Guardian Research Network (N = 133) on patients whose treatment took place in the US healthcare context were considered. A total of 1,451 patients were enrolled in the initial cohort of the NDS-NHL-001 study. A matched qualifying comparator cohort (aQCC cohort) was selected from this patient pool.

The patients included in the aQCC cohort mainly received immuno-chemotherapies. In contrast, newer treatment options, such as antibody-drug conjugates or CAR-T cell therapies were hardly used or not used at all.

For the endpoints collected (overall survival, PFS and various treatment response endpoints), patients were observed in the study from the start of the corresponding line of therapy (index date) until month 24.

For the present benefit assessment, the pharmaceutical company submits results for the aQCC cohort (N = 182) for the endpoint of overall survival as of the data cut-off of 20.12.2019.

ZUMA-1 study

The ZUMA-1 study is a single-arm, phase I/II study to investigate the efficacy and safety of axicabtagene ciloleucel in patients with refractory DLBCL, PMBCL or transformed FL.

The ZUMA-1 study has been ongoing since 2015 at 24 study sites in USA and Israel.

Patients were enrolled after ≥ 1 line of chemotherapy, including an anti-CD20 antibody and an anthracycline, whose disease was refractory to the last chemotherapy, who relapsed within the last 12 months after an autologous stem cell transplantation, or who were refractory to or did not respond to the last salvage therapy after an autologous stem cell transplantation.

Phase II of the ZUMA-1 study included a total of 6 cohorts, of which only pivotal cohorts 1 and 2 were treated according to the product information of axicabtagene ciloleucel. Therefore, only cohorts 1 and 2 are relevant for the indirect comparison between the ZUMA-1 study and the TRANSCEND-NHL-001 and TRANSCEND WORLD studies on lisocabtagene maraleucel.

In the ZUMA-1 study, according to the study design, screening examinations were to take place within 28 days prior to enrolment in the study and leukapheresis within 5 days after eligibility was determined. The enrolment in the study took place at the same time as the leukapheresis. The median time between leukapheresis and axicabtagene ciloleucel infusion was 23 days. Bridge therapy in the period between leukapheresis and CAR-T cell infusion was not allowed in cohorts 1 and 2 of the ZUMA-1 study. Premedication with paracetamol and diphenhydramine prior to axicabtagene ciloleucel infusion was also not provided for all patients in the ZUMA-1 study.

The primary endpoint of the study was overall response rate (ORR), secondary endpoints included overall survival, PFS and AEs. After axicabtagene ciloleucel infusion, patients enrolled in the ZUMA-1 study were followed up for up to 15 years.

For the present benefit assessment, the pharmaceutical company considered aggregated data from cohorts 1 and 2 of phase 2 at the data cut-off of 11 August 2018, which were submitted as part of the benefit assessment procedure of axicabtagene ciloleucel (resolution of 3 November 2022). For the analyses of the endpoints of overall survival and ORR, all patients included in cohorts 1 and 2 were considered (N = 111); for the comparison of AEs, all patients from these cohorts who were treated with axicabtagene ciloleucel were considered (N = 101).

JULIET study

The JULIET study is a single-arm, phase II study investigating tisagenlecleucel in adults with relapsed or refractory DLBCL.

The JULIET study was conducted from 2015 to 2022 at 27 study sites in North America, Europe, Australia and Japan.

Patients after ≥ 2 lines of chemotherapy, including rituximab and anthracycline, who did not respond to, were unsuitable for, or did not consent to autologous stem cell transplantation were enrolled. A total of 167 patients were enrolled in the main cohort (US, N = 147) and in cohort A (EU, N = 20), of whom 115 patients received tisagenlecleucel infusion.

In the JULIET study, screening should take place within 4-8 weeks before the planned infusion. Leukapheresis should either be done as part of the screening or a leukapheresis product already collected prior to screening could be used. Enrolment in the JULIET study occurred with the production site's acceptance and confirmation of the suitability of the leukapheresis product. The information in the benefit assessment procedure for tisagenlecleucel (resolution of 17 September 2020) shows that the median time between screening and infusion or study withdrawal was 112 days. Bridge therapy was allowed in the JULIET study.

For the present benefit assessment, the pharmaceutical company takes into account aggregated data of the data cut-off of 01.07.2019 of the JULIET study, which were submitted within the scope of the benefit assessment procedure of tisagenlecleucel (resolution of 17 September 2020). For the analyses of the endpoints of overall survival and ORR, all enrolled

patients (N = 167) were considered; for the comparison of AEs, all patients treated with tisagenlecleucel (N = 115) were considered.

On the indirect comparisons presented

For the benefit assessment of lisocabtagene maraleucel, the pharmaceutical company presents indirect comparisons without a bridge comparator between lisocabtagene maraleucel and conventional treatment options (TRANSCEND-NHL-001 / TRANSCEND WORLD vs NDS-NHL-001), between lisocabtagene maraleucel and axicabtagene ciloleucel (TRANSCEND-NHL-001 / TRANSCEND WORLD vs ZUMA-1) and lisocabtagene maraleucel and tisagenlecleucel (TRANSCEND-NHL-001 / TRANSCEND WORLD vs JULIET).

TRANSCEND studies vs NDS-NHL-001

Regarding the indirect comparison between lisocabtagene maraleucel and conventional chemotherapies, relevant information on patient characteristics of the aQCC cohort of the NDS-NHL-001 study was not provided by the pharmaceutical company in the dossier. For example, no information on Eastern Cooperative Oncology Group Performance Status (ECOG-PS) is available for 41% of patients in the aQCC cohort, no information on International Prognostic Index (IPI) score is available for 96%, and no information on Ann Arbor disease stage is available for 29%. Therefore, neither the suitability of the patients in the aQCC cohort for CAR-T cell therapy nor their suitability for other treatment options such as high-dose chemotherapy with autologous stem cell transplantation can be assessed. It is therefore questionable to what extent there was sufficient comparability between the patient population of the NDS-NHL-001 study and the TRANSCEND studies.

Consequently, it is unclear to what extent the best possible patient-individual therapy was adequately implemented for the patients in the aQCC cohort.

Furthermore, the percentage of patients with an autologous stem cell transplantation differs significantly between the aQCC cohort of the NDS-NHL-001 study and the study population of the TRANSCEND studies. This suggests different medical treatment situations between the TRANSCEND studies, which were conducted from 2016 and 2018 respectively, and the NDS-NHL-001 study, which enrolled patients with first diagnosis since 2003.

Furthermore, apart from results on the endpoint of overall survival from the NDS-NHL-001 study, no results are available on other patient-relevant endpoints, in particular on adverse events.

The submitted indirect comparison of the TRANSCEND-NHL-001 and TRANSCEND WORLD studies with the NDS-NHL-001 study is not used for the benefit assessment, in particular due to the relevant differences between the patient populations, as well as due to the lack of information on relevant patient characteristics.

TRANSCEND studies vs ZUMA-1

The ZUMA-1 study only enrolled patients who did not show a better response than stable disease to the last chemotherapy or who had a relapse after autologous stem cell transplantation. In deviation from this, the TRANSCEND studies also allowed the inclusion of

patients with relapse after the last chemotherapy whose disease had responded to the last chemotherapy.

In addition, the patients in the ZUMA-1 study were more often in advanced disease stages III and IV according to Ann Arbor (about 85%) than the patients in the TRANSCEND-NHL-001 study (about 69%) or in the TRANSCEND WORLD study (about 55%) and were also more often in a later line of therapy (≥ 4) than in the studies on the intervention side.

In addition to these relevant differences between the patient populations, the ZUMA-1 study shows clear differences compared to the TRANSCEND studies with regard to the study design: While no bridge therapy between leukapheresis and CAR T-cell infusion was allowed in the ZUMA-1 study, 64% of patients in the TRANSCEND-NHL-001 study and 83% of patients in the TRANSCEND- WORLD study received bridge therapy.

Due to these relevant differences between the study designs, the requirements for conducting a matching-adjusted indirect comparison are not met.

Overall, due to the lack of comparability of the patient populations and relevant differences in the study design, the submitted indirect comparison between lisocabtagene maraleucel and axicabtagene ciloleucel is not used for the benefit assessment.

TRANSCEND studies vs JULIET

There are clear differences between the TRANSCEND studies and the JULIET study in the pretreatment phases prior to infusion of the CAR-T cell preparation, which call into question the comparability of the patients on the intervention and comparison side for the evaluations presented. While the median time between leukapheresis and CAR-T cell infusion in the JULIET study was 112 days, patients in the lisocabtagene maraleucel studies waited 37 days (TRANSCEND-NHL-001) and 42 days (TRANSCEND WORLD) for the CAR-T cell infusion. Patients were enrolled in the JULIET study also at a relevant time interval after leukapheresis, while patients in the TRANSCEND studies were enrolled immediately after leukapheresis.

Due to these relevant differences between the study designs, the requirements for conducting a matching-adjusted indirect comparison are not met.

Overall, the submitted indirect comparison between lisocabtagene maraleucel and tisagenlecleucel is not used for the benefit assessment, in particular due to the lack of comparability of the study design of the TRANSCEND studies and the JULIET study.

<u>Conclusion</u>

The indirect comparisons presented are subject to considerable uncertainties. Overall, this is due to the lack of comparability of the respective patient populations, as well as relevant differences in the study design of the studies on CAR-T cell therapies. Therefore, the indirect comparisons of the TRANSCEND-NHL-001 and TRANSCEND WORLD studies with the NDS-NHL-001, ZUMA-1 and JULIET studies submitted by the pharmaceutical company are unsuitable for the assessment of the additional benefit of lisocabtagene maraleucel.

Overall assessment

Results from the single-arm TRANSCEND-NHL-001 and TRANSCEND WORLD studies are available for the assessment of the additional benefit of lisocabtagene maraleucel in adults with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy.

The results of the single-arm TRANSCEND-NHL-001 and TRANSCEND WORLD studies presented are unsuitable for assessment of the additional benefit as they do not allow a comparison with the appropriate comparator therapy.

Furthermore, the pharmaceutical company presented indirect comparisons with the retrospective NDS-NHL-001 study as well as with the single-arm ZUMA-1 and JULIET studies.

Due to a lack of comparability of the respective patient populations, as well as relevant differences between the study designs of the studies on CAR-T cell therapies, the indirect comparisons presented are fraught with considerable uncertainties and are unsuitable for the benefit assessment of lisocabtagene maraleucel.

Overall, the data presented are therefore not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of lisocabtagene maraleucel in adults with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy is not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of lisocabtagene maraleucel 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 the below-mentioned objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

Due to the present change in the appropriate comparator therapy, the G-BA considers it appropriate to limit the resolution on the additional benefit of lisocabtragen maraleucel. The limitation enables the pharmaceutical company to submit suitable evaluations, which correspond to the appropriate comparator therapy determined by the present resolution, in a new dossier in a timely manner. For this purpose, a limitation of the resolution to 6 months is considered to be appropriate.

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 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product with the active ingredient lisocabtagene maraleucel 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 lisocabtagene maraleucel (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-

BA may determine that an additional benefit is considered as being not proven. The possibility that a benefit assessment for the medicinal product with the active ingredient lisocabtagene maraleucel 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.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Breyanzi" with the active ingredient "lisocabtagene maraleucel".

Lisocabtagene maraleucel is approved for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

A patient-individual therapy was determined as the appropriate comparator therapy, taking into account the lymphoma subentity, biology of the disease, prior therapy, the course of the disease and the general condition.

To demonstrate the additional benefit of lisocabtagene maraleucel compared to the appropriate comparator therapy, the pharmaceutical company presents indirect comparisons between the TRANSCEND-NHL-001 and TRANSCEND WORLD studies versus the NDS-NHL-001, ZUMA-1 and JULIET studies. Overall, the submitted indirect comparisons are considered unsuitable for the benefit assessment due to the lack of comparability between the included patient populations and the study designs.

An additional benefit of lisocabtagene maraleucel in adults with relapsed or refractory diffuse DLBCL, PMBCL and FL3B after two or more lines of systemic therapy, is therefore not proven.

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

approx. 1,420 - 1,980 patients

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 assessment of the IQWiG (mandate A22-90). The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainties.

The estimates of the pharmaceutical company are based on sample sizes of new cases in the diagnosis years 2012 - 2017 of the Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute, on the basis of which average annual rates of increase were determined and the sample sizes for 2021 were estimated. It is assumed that 30 - 40% of patients suffer a relapse or a progression after first-line therapy. In the following, the further course of therapy for patients who are suitable for high-dose therapy and autologous stem cell transplantation and those who are ineligible for this are shown separately.

Uncertainties arise from the fact that in deriving the patient numbers from the second line of therapy onwards, the same course and the same percentage values are assumed for the

PMBCL and FL3B subentities as for DLBCL. Furthermore, no restriction to adults is made when determining the number of patients. In addition, the pharmaceutical company only considers patients with relapsed and refractory disease after second-line therapy in its derivation. Patients in later lines of therapy are not considered, which may lead to an underestimation of the target population.

Further uncertainties arise from the fact that a treatment rate of 100% is assumed in both first-line and second-line therapy. This can lead to an overestimation, as it can be assumed that with each line of therapy the percentage of patients who cannot be given any further therapy increases.

Furthermore, the pharmaceutical company assumes a percentage value of 42.2% of patients who are eligible for high-dose therapy and autologous stem cell transplantation. Regarding this share, different values are discussed in the literature, resulting in further uncertainties.

Compared to the resolutions on the benefit assessment of tisagenlecleucel (resolution of 17 September 2020) and axicabtagene ciloleucel (resolution of 3 November 2022), there is a significantly higher number of patients in the target population. This is due in particular to a higher incidence estimate based on the case numbers of the ZfKD, to a higher upper limit of the percentage value of patients whose disease has relapsed or is refractory after first-line therapy, and to different percentage values with regard to the course of therapy in second-line therapy.

Despite the uncertainties described, the pharmaceutical company's approach is assessed as plausible overall. The benefit assessment is based on the patient numbers stated in the pharmaceutical company’s dossier.

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 Breyanzi (active ingredient: lisocabtagene maraleucel) at the following publicly accessible link (last access: 22 February 2023):

https://www.ema.europa.eu/en/documents/product-information/breyanzi-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 lisocabtagene maraleucel 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 1 dose 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 lisocabtagene maraleucel and to carry the patient emergency card at all times.

Lisocabtagene maraleucel must be used in a qualified treatment facility. The quality assurance measures according to the ATMP Quality Assurance Guideline apply to the application of lisocabtagene maraleucel in the therapeutic indication of large B-cell lymphoma as well as follicular lymphoma (FL). Annex I CAR-T cells in B-cell neoplasms of the ATMP Quality Assurance Guideline provides further details.

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: 15 March 2023).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The active ingredients lisocabtagene maraleucel, axicabtagene ciloleucel and tisagenlecleucel are listed in the LAUER-TAXE®, but are only dispensed to appropriately qualified inpatient treatment facilities. Accordingly, the active ingredients are not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculations are based on the purchase prices of the clinic pack, in deviation from the LAUER-TAXE® data usually taken into account.

Lisocabtagene maraleucel, axicabtagene ciloleucel and tisagenlecleucel are administered as a single intravenous infusion according to the indications in the product information.

Lisocabtagene maraleucel, axicabtagene ciloleucel and tisagenlecleucel concern autologous T cells that have been genetically modified *ex vivo* with a retroviral 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 for the active ingredients mentioned above.

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				
Lisocabtagene maraleucel				
Lisocabtagene maraleucel	Single dose	1	1	1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Cyclophosphamide + etoposide + vincristine + prednisone (CEOP)[2]				
Cyclophosphamide	1 x every 21 days	17.4	1	17.4
Etoposide	Day 1 to 3 of a 21-day cycle	17.4	3	52.2
Vincristine	1 x every 21 days	17.4	1	17.4
Prednisone	Day 1 to 5 of a 21-day cycle	17.4	5	87.0
Etoposide + vincristine + doxorubicin + cyclophosphamide + prednisone (dose-adjusted EPOCH)[3]				
Etoposide	Day 1 - 4 of a 21-day cycle	17.4	4	69.6
Vincristine	Day 1 - 4 of a 21-day cycle	17.4	4	69.6
Doxorubicin	Day 1 - 4 of a 21-day cycle	17.4	4	69.6
Cyclophosphamide	Day 5 of a 21-day cycle	17.4	1	17.4
Prednisone	2 x daily on day 1 to 5 of a 21-day cycle	17.4	5	87.0
Mesna + ifosfamide + mitoxantrone + etoposide (MINE)[4]				
Mesna	Day 1 to 3 of a 21 or 28-day cycle	13.0 - 17.4	3	39.0 - 52.2
Ifosfamide	Day 1 to 3 of a 21 or 28-day cycle	13.0 - 17.4	3	39.0 - 52.2
Mitoxantrone	Day 1 of a 21 or 28-day cycle	13.0 - 17.4	1	13.0 - 17.4
Etoposide	Day 1 to 3 of a 21 or 28-day cycle	13.0 - 17.4	3	39.0 - 52.2

[2] Advani RH et al. A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) alternating with pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from T-cell consortium trial. British Journal of Haematology 2016; 172: 535-544.

[3] Wilson WH et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002 April;8 (99): 2685-2693.

[4] Rodriguez MA et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphomas. Ann Oncol. 1995 Jul;6(6):609-11

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Polatuzumab vedotin + bendamustine + rituximab				
Polatuzumab vedotin	1 x per 21-day cycle	6.0	1	6.0
Bendamustine	2 x per 21-day cycle	6.0	2	12.0
Rituximab	1 x per 21-day cycle	6.0	1	6.0
Tafasitamab + lenalidomide				
Tafasitamab	Cycle 1: Day 1, 4, 8, 15 and 22. Cycle 2 and 3: Day 1, 8, 15 and 22. Cycle 4 up to progress: Day 1 and 15. Cycle duration: 28 days	13.0	Cycle 1: 5 Cycle 2 and 3: 4 from cycle 4 onwards: 2	33.0
Lenalidomide	Day 1 to 21 of a 28-day cycle	12.0	21	252.0
Pixantrone monotherapy				
Pixantrone	Day 1, 8, 15 of a 28-day cycle	1.0 - 6.0	3	3.0 - 18.0
Rituximab monotherapy				
Rituximab	1 x every 7 days	4.0	1	4.0
Axicabtagene ciloleucel				
Axicabtagene ciloleucel	Single dose	1	1	1
Tisagenlecleucel				
Tisagenlecleucel	Single dose	1	1	1
Radiation				
Radiotherapy	Different from patient to patient			
Best supportive care				
Best supportive care[5]	Different from patient to patient			

[5] In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.

Consumption:

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).[6]

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

The consumption of vials and infusion bags is presented for the medicinal product to be assessed, lisocabtagene maraleucel, and the appropriate comparator therapy, tisagenlecleucel, according to the indications in the product information. These are administered to the patient in a single infusion depending on the number of cells per vial or infusion bag. The annual treatment costs of lisocabtagene maraleucel and tisagenlecleucel are independent of the specific number of vials or 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					
Lisocabtagene maraleucel					
Lisocabtagene maraleucel	100 x 10^6 viable CAR+ T cells	100 × 10^6 viable CAR+ T cells	1 or more vial(s)	1	1 or more vial(s)
Appropriate comparator therapy					
Cyclophosphamide + etoposide + vincristine + prednisone (CEOP)[2]					
Cyclophosphamide	750 mg/m² = 1,425 mg	1,425 mg	1 x 1,000 mg + 1 x 500 mg	17.4	17.4 x 1,000 mg + 17.4 x 500 mg
Etoposide	100 mg/m² = 190 mg	190 mg	1 x 200 mg	52.2	52.2 x 200 mg
Vincristine	2 mg	2 mg	1 x 2 mg	17.4	17.4 x 2 mg
Prednisone	100 mg/m² = 190 mg	190 mg	10 x 20 mg	87.0	870 x 20 mg
Etoposide + vincristine + doxorubicin + cyclophosphamide + prednisone (dose-adjusted EPOCH)[3]					
Etoposide	50 mg/m² = 95 mg	95 mg	1 x 100 mg	69.6	69.6 x 100 mg
Vincristine	0.4 mg/m²	0.76 mg	1 x 1 mg	69.6	69.6 x 1 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	= 0.76 mg				
Doxorubicin	10 mg/m² = 19 mg	19 mg	2 x 10 mg	69.6	139.2 x 10 mg
Cyclophos-phamide	750 mg/m² = 1,425 mg	1,425 mg	1 x 1,000 mg + 1 x 500 mg	17.4	17.4 x 1,000 mg + 17.4 x 500 mg
Prednisone	60 mg/m² = 114 mg	*2* x 114 mg	12 x 20 mg	87.0	1,044 x 20 mg
Mesna + ifosfamide + mitoxantrone + etoposide (MINE)[4]					
Mesna - IV	1.33 g/m² = 2.53 g	2.53 g	7 x 400 mg	39.0 - 52.2	273.0 x 1,000 mg - 365.4 x 1,000 mg
Mesna - PO	500 mg 4h after IV Administration	500 mg	0.5 x 600 mg + 0.5 x 400 mg	39.0 - 52.2	19.5 x 600 mg - 26.1 x 600 mg + 19.5 x 400 mg - 26.1 x 400 mg
Ifosfamide	1.33 g/m² = 2.53 g	2.53 g	1 x 2,000 mg + 1 x 1,000 mg	39.0 - 52.2	39.0 x 2,000 mg - 52.2 x 2,000 mg + 39.0 x 1,000 mg - 52.2 x 1,000 mg
Mitoxantrone	8 mg/m² = 15.2 mg	15.2 mg	1 x 20 mg	13.0 - 17.4	13.0 x 20 mg - 17.4 x 20 mg
Etoposide	65 mg/m² = 123.5 mg	123.5 mg	1 x 100 mg + 1 x 50 mg	39.0 - 52.2	39.0 x 100 mg - 52.2 x 100 mg + 39.0 x 50 mg - 52.2 x 50 mg
Polatuzumab vedotin + bendamustine + rituximab					
Polatuzumab vedotin	1.8 mg/kg = 138.6 mg	138.6 mg	1 x 140 mg	6.0	6.0 x 140 mg
Bendamustine	90 mg/m² = 171 mg	171 mg	7 x 25 mg	12.0	84.0 x 100 mg
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	6.0	6.0 x 500 mg + 18.0 x 100 mg
Tafasitamab + lenalidomide					
Tafasitamab	12 mg/kg = 924 mg	924 mg	5 x 200 mg	33.0	165 x 200 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	252.0	252.0 x 25 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Pixantrone monotherapy					
Pixantrone	50 mg/m² = 95 mg	95 mg	4 x 29 mg	3.0 - 18.0	12.0 x 29 mg - 72.0 x 29 mg
Rituximab monotherapy					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	4.0	4.0 x 500 mg + 12.0 x 100 mg
Axicabtagene ciloleucel					
Axicabtagene ciloleucel	2 x 10^6 viable CAR+ T cells/kg	1.54 x 10^8 viable CAR+ T cells	1 single infusion bag	1	1 single infusion bag
Tisagenlecleucel					
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 bag(s)	1	1 or more infusion bag(s)
Radiation					
Radiotherapy	Different from patient to patient				
Best supportive care					
Best supportive care	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

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				
Lisocabtagene maraleucel	1 or more vial(s)	€ 345,000	€ 0[7]	€ 345,000
Appropriate comparator therapy				
Axicabtagene ciloleucel	1 single infusion bag	€ 282,000	€ 0[7]	€ 282,000
Tisagenlecleucel	1 or more infusion bag(s)	€ 265,000.00	€ 0[7]	€ 265,000.00

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Appropriate comparator therapy					
Bendamustine 25 mg	5 PIC	€ 374.78	€ 2.00	€ 17.25	€ 355.53
Cyclophosphamide 500 mg	6 PSI	€ 84.41	€ 2.00	€ 9.25	€ 73.16
Cyclophosphamide 1,000 mg	6 PSI	€ 127.41	€ 2.00	€ 11.02	€ 114.39
Doxorubicin 10 mg	1 INF	€ 40.28	€ 2.00	€ 2.29	€ 35.99
Etoposide 50 mg	1 CIS	€ 28.69	€ 2.00	€ 1.65	€ 25.04
Etoposide 100 mg	1 CIS	€ 46.52	€ 2.00	€ 1.67	€ 42.85
Etoposide 100 mg	10 CIS	€ 403.85	€ 2.00	€ 18.63	€ 383.22
Etoposide 200 mg	1 CIS	€ 81.86	€ 2.00	€ 3.35	€ 76.51
Ifosfamide 1 g	1 INF	€ 49.84	€ 2.00	€ 1.83	€ 46.01
Ifosfamide 2 g	1 INF	€ 80.21	€ 2.00	€ 3.27	€ 74.94
Lenalidomide 25 mg	21 HC	€ 64.12	€ 2.00	€ 2.51	€ 59.61
Mesna 400 mg	10 SFI	€ 32.23	€ 2.00	€ 0.99	€ 29.24
Mesna 400 mg	20 FCT	€ 108.54	€ 2.00	€ 9.23	€ 97.31
Mesna 600 mg	20 FCT	€ 146.72	€ 2.00	€ 12.85	€ 131.87
Mitoxantrone 20 mg	1 CIS	€ 235.54	€ 2.00	€ 10.64	€ 222.90
Pixantrone 29 mg	1 PIC	€ 485.40	€ 2.00	€ 18.75	€ 464.65
Polatuzumab vedotin 140 mg	1 PIC	€ 11,906.03	€ 2.00	€ 483.33	€ 11,420.70

[7] The medicinal product is exempt from VAT at the applied LAUER-TAXE® last revised.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Prednisone 20 mg	100 TAB	€ 29.25	€ 2.00	€ 1.42	€ 25.83
Rituximab 100 mg	2 CIS	€ 748.07	€ 2.00	€ 69.93	€ 676.14
Rituximab 500 mg	2 CIS	€ 3,639.48	€ 2.00	€ 350.68	€ 3,286.80
Tafasitamab 200 g	1 PCI	€ 654.44	€ 2.00	€ 61.05	€ 591.39
Vincristine 1 mg	1 VIA	€ 24.72	€ 2.00	€ 1.34	€ 21.38
Vincristine 2 mg	1 SFI	€ 37.63	€ 2.00	€ 1.25	€ 34.38
Abbreviations: VIA = vial, FCT = film-coated tablets, HC = hard capsules, CIS = concentrate for the preparation of an infusion solution, SFI = solution for injection, INF = infusion solution, PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate, PCI = powder for a concentrate for the preparation of a solution for infusion, TAB = tablets,					

LAUER-TAXE® last revised: 15 March 2023

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.

Lymphocyte depletion

Lisocabtagene maraleucel, axicabtagene ciloleucel and tisagenlecleucel are autologous cell products 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 Medicinal Products Act, no further costs are incurred in this respect for the medicinal product to be assessed and the mentioned active ingredients of the appropriate comparator therapy.

According to the product information of lisocabtagene maraleucel, axicabtagene ciloleucel and tisagenlecleucel, the administration of lymphocyte-depleting chemotherapy is recommended prior to the administration of the CAR-T cells. For this, a regimen of fludarabine and cyclophosphamide should be administered intravenously on three days before infusion.

To reduce potential acute infusion reactions, patients must be pretreated with paracetamol and diphenhydramine or another H1 antihistamine approximately 30 to 60 minutes prior to infusion of lisocabtagene maraleucel. For axicabtagene ciloleucel and tisagenlecleucel, this premedication alone is recommended. For this reason, costs of premedication are only shown for lisocabtagene maraleucel.

Screening for infections with hepatitis B, hepatitis C and HIV

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with lisocabtagene maraleucel. This examination is not required for all comparators in the context of patient-individual therapy. Since there is a regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis B, hepatitis C and HIV, the costs of additionally required SHI services are presented in the resolution.

Premedication for prevention

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129, paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

In the context of premedication, additionally required SHI services are incurred that usually differ between the medicinal product to be assessed and rituximab as an appropriate comparator therapy and are consequently taken into account as additionally required SHI services in the resolution.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed:							
Lisocabtagene maraleucel							
Lymphocyte depletion							
Cyclophosphamide (300 mg/m², IV)	10 PSI each 200 mg	€ 62.76	€ 2.00	€ 4.89	€ 55.87	3	€ 55.87
Fludarabine (30 mg/m², IV)	1 CII each 50 mg	€ 118.50	€ 2.00	€ 5.09	€ 111.41	3	€ 668.46
Premedication							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	1	€ 15.86
Paracetamol	incalculable						
HBV, HCV and HIV screening							
Hepatitis-B HBV-antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1	€ 9.80
HIV HIV-1 and HIV-2 antibody status	-	-	-	-	€ 4.45	1	€ 4.45

(GOP: 32575)							
Appropriate comparator therapy:							
Polatuzumab vedotin in combination with rituximab							
Premedication							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	6	€ 47.58
Paracetamol[8] (500 mg - 1,000 mg, PO)	10 TAB each 500 mg - 10 TAB each 1,000 mg	€ 2.96 - € 3.32	€ 0.15 - € 0.17	€ 0.13 - € 0.14	€ 2.68 - € 3.01	6	€ 2.68 - € 3.01
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1	€ 5.50
Hepatitis-B HBV-antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1	€ 5.90
Rituximab monotherapy							
Premedication							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	5	€ 23.67	€ 2.00	€ 5.81	4	€ 31.72
Paracetamol[8] (500 mg - 1,000 mg, PO)	10 TAB each 500 mg - 10 TAB each 1,000 mg	€ 2.96 - € 3.32	€ 0.15 - € 0.17	€ 0.13 - € 0.14	€ 2.68 - € 3.01	4	€ 2.68 - € 3.01
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1	€ 5.50
Hepatitis B antibody status (GOP number	-	-	-	-	€ 5.90	1	€ 5.90

[8] Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

32614)							
Axicabtagene ciloleucel							
Lymphocyte depletion							
Cyclophosphamide (500 mg/m^2, IV)	6 PSI each 500 mg	€ 84.41	€ 2.00	€ 9.25	€ 73.16	3	€ 73.16
Fludarabine (30 mg/m^2, IV)	1 CII each 50 mg	€ 118.50	€ 2.00	€ 5.09	€ 111.41	3	€ 668.46
HBV, HCV and HIV screening							
Hepatitis-B HBV-antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1	€ 4.45
Tisagenlecleucel							
Lymphocyte depletion							
Cyclophosphamide (250 mg/m^2, IV)	1 PSI each 500 mg	€ 23.47	€ 2.00	€ 1.54	€ 19.93	3	€ 59.79
Fludarabine (25 mg/m^2, IV)	1 CII each 50 mg	€ 118.50	€ 2.00	€ 5.09	€ 111.41	3	€ 334.23
HBV, HCV and HIV screening							
Hepatitis-B HBV-antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1	€ 4.45
Abbreviations: SFI = solution for injection, CII = concentrate for injection or infusion solution, PSI = powder for solution for injection, TAB = tablets							

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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 ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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

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

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

At its session on 10 March 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 24 November 2020.

On 23 August 2022, the pharmaceutical company submitted a dossier for the benefit assessment of lisocabtagene maraleucel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 23 August 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient lisocabtagene maraleucel.

After it was determined that IQWiG's benefit assessment of 1 December 2022 was unsuitable for drafting a resolution in accordance with Section 35a, paragraph 3 SGB V, IQWiG was commissioned to conduct a supplement to the benefit assessment prepared to date, taking into account the newly submitted information. The benefit assessment procedure of lisocabtagene maraleucel according to Section 35a, paragraph 2 SGB V was provisionally suspended for a period of six weeks and four days by resolution of the G-BA on 1 December 2022.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 16 January 2023. The deadline for submitting written statements was 6 February 2023.

The oral hearing was held on 20 February 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 28 March 2023, and the proposed resolution was approved.

At its session on 6 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 March 2020	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	6 September 2022	New implementation of the appropriate comparator therapy
Working group Section 35a	14 February 2023	Information on written statements received; preparation of the oral hearing
Subcommittee on	20 February 2023	Conduct of the oral hearing

Medicinal Products		
Working group Section 35a	28 February 2023 14 March 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee on Medicinal Products	28 March 2023	Concluding discussion of the draft resolution
Plenum	6 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 April 2023

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

Prof. Hecken