Gemeinsamer Bundesausschuss

Tisagenlecleucel

Resolution from: 7 March 2019 Valid until: 15 March 2020
Entry into force on: 7 March 2019
BAnz AT 02.04.2019 B2

Resolution from: 1 August 2019
Entry into force on: 1 August 2019
BAnz AT 27.08.2019 B8

Therapeutic indication (according to the marketing authorisation of 23 August 2018):

Kymriah is indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

1. Extent of the additional benefit of the medicinal product

Tisagenlecleucel has been approved as a medicinal product for the treatment of orphan diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Pursuant to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medicinal benefit is considered to be already proven through the grant of market authorisation.

According to Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure, the Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups experiencing a therapeutically significant additional benefit. This additional benefit is quantified using the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure.

Children, adolescents, and young adult patients up to 25 years of age with refractory or relapsed (relapse after transplantation or second or later relapse) acute lymphoblastic B-cell leukaemia (ALL)

Extent of additional benefit of tisagenlecleucel:

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.

Study results according to endpoints:[1]

Children, adolescents, and young adult patients up to 25 years of age with refractory or relapsed (relapse after transplantation or second or later relapse) acute lymphoblastic B-cell leukaemia (ALL)

ELIANA study: single-arm, multi-centre Phase II study
(Data cut-off 25 April 2017)

ENSIGN study: single-arm, multi-centre Phase II study
(Data cut-off 1 February 2016)

Mortality

Endpoint	**ELIANA**		**ENSIGN**	
	N	Median survival time in months[a)] [95%-CI][c)] *Patients with event n (%)*	N	Median survival time in months[b)] [95%-CI][c)] *Patients with event n (%)*
Overall survival (OS)				
ITT population	92	No data available 33 *(35.9)*[d)]	35	No data available 14–16 *(40.0 to 45.7)*[e)]
FAS population	75	19.1 [15.2; n. c.] 19 *(25.3)*	29	n. a. [6.9; n. c.] 10 *(34.5)*

Morbidity

Endpoint	**ELIANA**		**ENSIGN**	
	N	Response rate in %[f)] [95%-CI][h)i)] *Patients with event n (%)*	N	Response rate in %[g)] [98.95%-CI][h)j)] *Patients with event n (%)*
Response (CR/CRi) – ITT population				
Total	92	No data available	35	No data available
CR	92	No data available	35	No data available
CRi	92	No data available	35	No data available

[1] Data from the dossier evaluation of the G-BA (published on 17 December 2018) unless otherwise indicated.

Morbidity

Endpoint	**ELIANA**		**ENSIGN**	
	N	Response rate in %[f)] [95%-CI][h)i)] *Patients with event n (%)*	N	Response rate in %[g)] [98.95%-CI][h)j)] *Patients with event n (%)*
Response (CR/CRi) – FAS population				
Total	75	81.3 [70.7; 89.4] *61 (81.3)*	29	69.0 [43.6; 88.1] *20 (69.0)*
CR	75	- *45 (60.0)*	29	- *18 (62.1)*
CRi	75	- *16 (21.3)*	29	- *2 (6.9)*
Endpoint	**ELIANA**		**ENSIGN**	
	N	Median in months[k)] [95%-CI][c)] *Patients with event n (%)*	N	Median in months[l)] [95%-CI][c)] *Patients with event n (%)*
Relapse -free survival				
FAS population	61[m)]	n. a. [8.6; n. c.] *17 (27.9)[o)]*	20[n)]	n. a. [5.4; n. c.] *8 (40.0)[o)]*
Endpoint	**ELIANA**		**ENSIGN**	
	N	Percentage of patients with MRD-negative status [95%-CI][h)] *(%)*	N	Percentage of patients with MRD-negative status [95%-CI][h)] *(%)*
MRD-negative status[p)]				
FAS population	75	61 [70.7; 89.4] *(81.3)*	29	18 [42.3; 79.3] *(62.1)*
Endpoint	**ELIANA**		**ENSIGN**	
	N	Median in months [95%-CI] *Patients with event n (%)*	N	Median in months [95%-CI] *Patients with event n (%)*
EQ-5D VAS				
No usable data[q)]				

Quality of life

Endpoint	ELIANA		ENSIGN	
	N	Median in months [95%-CI] *Patients with event n (%)*	N	Median in months [95%-CI] *Patients with event n (%)*
PedsQL				
No usable data[q)]				

Side effects

Endpoint[r)]	Chemotherapy lymphocyte depletion		Tisagenlecleucel infusion up to Study week 8		Study week 9 to Study week 12	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
AE (total)						
ELIANA	73	58 *(79.5)*	75	74 *(98.7)*	70	65 *(92.9)*
ENSIGN	28	23 *(82.1)*	29	28 *(96.6)*	21	19 *(90.5)*
Severe AE (CTCAE grade 3/4)						
ELIANA	73	30 *(41.1)*	75	62 *(82.7)*	70	31 *(44.3)*
ENSIGN	28	13 *(46.4)*	29	24 *(82.8)*	21	10 *(47.6)*
Serious AE (SAE)						
ELIANA	73	8 *(11.0)*	75	51 *(68.0)*	70	22 *(31.4)*
ENSIGN	28	4 *(14.3)*	29	23 *(79.3)*	21	7 *(33.3)*
Severe AE (CTCAE grade 3/4) with incidence ≥ 5% at SOC level						
Blood and lymphatic system disorders						
ELIANA	73	11 *(15.1)*	75	37 *(49.3)*	70	4 *(5.7)*
ENSIGN	28	8 *(28.6)*	29	20 *(69.0)*	21	-
Cardiac disorders						
ELIANA	73	-	75	8 *(10.7)*	70	-
ENSIGN	28	-	29	3 *(10.3)*	21	-
Gastrointestinal disorders						
ELIANA	73	-	75	14 *(18.7)*	70	-
ENSIGN	28	-	29	7 *(24.1)*	21	2 *(9.5)*
General disorders and administration site conditions						
ELIANA	73	-	75	11 *(14.7)*	70	-
ENSIGN	28	-	29	5 *(17.2)*	21	-

Endpoint[r)]	**Chemotherapy lymphocyte depletion**		**Tisagenlecleucel infusion up to Study week 8**		**Study week 9 to Study week 12**	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Hepatobiliary disorders						
ELIANA	73	-	75	4 *(5.3)*	70	-
ENSIGN	28	-	29	2 *(6.9)*	21	-
Immune system disorders						
ELIANA	73	-	75	35 *(50.7)*	70	-
ENSIGN	28	-	29	12 *(41.4)*	21	-
Infections and infestations						
ELIANA	73	5 *(6.8)*	75	18 *(24.0)*	70	19 *(27.1)*
ENSIGN	28	3 *(10.7)*	29	3 *(10.3)*	21	5 *(23.8)*
Investigations						
ELIANA	73	18 *(24.7)*	75	41 *(54.7)*	70	14 *(20.0)*
ENSIGN	28	8 *(28.6)*	29	18 *(62.1)*	21	6 *(28.6)*
Metabolism and nutrition disorders						
ELIANA	73	4 *(5.5)*	75	28 *(37.3)*	70	5 *(7.1)*
ENSIGN	28	6 *(21.4)*	29	14 *(48.3)*	21	2 *(9.5)*
Musculoskeletal and connective tissue disorders						
ELIANA	73	-	75	5 *(6.7)*	70	-
Nervous system disorders						
ELIANA	73	-	75	10 *(1*3.3)	70	-
Psychiatric disorders						
ELIANA	73	-	75	6 *(8.0)*	70	-
Renal and urinary disorders						
ELIANA	73	-	75	8 *(10.7)*	70	-
ENSIGN	28	-	29	5 *(17.2)*	21	-
Respiratory, thoracic and mediastinal disorders						
ELIANA	73	-	75	21 *(28.0)*	70	6 *(8.6)*
ENSIGN	28	3 *(10.7)*	29	9 *(31.0)*	21	-
Vascular disorders						
ELIANA	73	-	75	17 *(22.7)*	70	-
ENSIGN	28	3 *(10.7)*	29	9 *(31.0)*	21	-

Endpoint[r)]	**Chemotherapy lymphocyte depletion**		**Tisagenlecleucel infusion up to Study week 8**		**Study week 9 to Study week 12**	
SOC ***PT***	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Serious AE (SAE) with incidence ≥ 5%						
Blood and lymphatic system disorders (SOC)						
ELIANA	73	-	75	17 *(22.7)*	70	-
ENSIGN	28	3 *(10.7)*	29	11 *(37.9)*	21	-
Febrile neutropenia (PT)						
ELIANA	73	-	75	13 *(17.3)*	70	-
ENSIGN	28	3 *(10.7)*	29	10 *(34.5)*	21	-
Cardiac disorders(SOC)						
ELIANA	73	-	75	5 *(6.7)*	70	-
Gastrointestinal disorders (SOC)						
ELIANA	73	-	75	5 *(6.7)*	70	-
ENSIGN	28	-	29	2 *(6.9)*	21	-
General disorders and administration site conditions (SOC)						
ELIANA	73	-	75	5 *(6.7)*	70	5 *(7.1)*
ENSIGN	28	-	29	2 *(6.9)*	21	-
Pyrexia (PT)						
ELIANA	73	-	75	-	70	4 *(5.7)*
ENSIGN	28	-	29	2 *(6.9)*	21	-
Immune system disorders (SOC)						
Cytokine-release syndrome (PT)						
ELIANA	73	-	75	47 *(62.7)*	70	-
ENSIGN	28	-	29	20 *(69.0)*	21	-
Infections and infestations (SOC)						
ELIANA	73	-	75	10 *(13.3)*	70	15 *(21.4)*
ENSIGN	28	3 *(10.7)*	29	5 *(17.2)*	21	5 *(23.8)*
Clostridium difficile colitis (PT)						
ENSIGN	28	-	29	2 *(6.9)*	21	-
Metabolism and nutrition disorders (SOC)						
ELIANA	73	-	75	4 *(4.5)*	70	-

Endpoint[r)]	**Chemotherapy lymphocyte depletion**		**Tisagenlecleucel infusion up to Study week 8**		**Study week 9 to Study week 12**	
SOC ***PT***	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Nervous system disorders (SOC)						
ELIANA	73	-	75	5 *(6.7)*	70	-
ENSIGN	28	-	29	5 *(17.2)*	21	-
Seizure (PT)						
ENSIGN	28	-	29	2 *(6.9)*	21	-
Renal and urinary disorders (SOC)						
ELIANA	73	-	75	5 *(6.7)*	70	-
ENSIGN	28	-	29	2 *(6.9)*	21	-
Acute kidney injury (PT)						
ELIANA	73	-	75	4 *(5.3)*	70	-
Respiratory, thoracic and mediastinal disorders (SOC)						
ELIANA	73	-	75	10 *(13.3)*	70	6 *(8.6)*
ENSIGN	28	-	29	4 *(13.8)*	21	-
Hypoxia (PT)						
ENSIGN	28	-	29	2 *(6.9)*	21	-
Vascular disorders (SOC)						
Hypotension (PT)						
ELIANA	73	-	75	8 *(10.7)*	70	-
ENSIGN	28	-	29	4 *(13.8)*	21	-

Endpoint[r)]	**Tisagenlecleucel infusion up to Study week 8**		**Study week 9 to Study week 12**	
	N	Patients with event n (%)	N	Patients with event n (%)
AE of special interest (Group Term)				
Cytokine-release syndrome				
ELIANA	75	58 *(77.3)*	70	No data available
ENSIGN	29	26 *(89.7)*	21	No data available
Febrile neutropenia				
ELIANA	75	26 *(34.7)*	70	3 *(4.3)*
ENSIGN	29	10 *(34.5)*	21	No data available

Endpoint[r)]	Tisagenlecleucel infusion up to Study week 8		Study week 9 to Study week 12	
	N	Patients with event n (%)	N	Patients with event n (%)
AE of special interest (Group Term)				
Haematopoietic cytopenia persisting on day 28				
ELIANA	75	28 *(37.3)*	70	-[s)]
ENSIGN	29	9 *(31.0)*	21	-[s)]
Infections				
ELIANA	75	32 *(42.7)*	70	35 *(50.0)*
ENSIGN	29	14 *(48.3)*	21	No data available
Transient neurological event				
ELIANA	75	30 *(40.0)*	70	4 *(5.7)*
ENSIGN	29	9 *(31.0)*	21	No data available
Tumour lysis syndrome				
ELIANA	75	3 *(4.0)*	70	1 *(1.4)*
ENSIGN	29	0 *(0.0)*	21	No data available

a) The median observation period of the FAS population is 10.48 months. There is no data available for the ITT population.
b) The median observation period of the FAS population is 7.29 months. There is no data available for the ITT population.
c) PROC LIFETEST according to the method of Brookmeyer and Crowley (1982).
d) Deaths for patients who did not receive infusion with tisagenlecleucel were reported as part of safety: A total of 14 of the 17 patients who did not receive tisagenlecleucel died. Mortality data calculated from number of deaths before infusion (N = 14) and number of deaths in the FAS population (N = 19).
e) It is not possible to give an exact figure for deaths in the ITT population because of the lack of information on deaths in the context of safety. Calculation based on the number of deaths in the FAS (n = 10) and the data on deaths in the course of the study (n = 4 deaths) within the patients who did not receive infusion with tisagenlecleucel and the difference between the ITT and FAS populations (n = 6).
f) Response within 3 months after tisagenlecleucel infusion
g) Response within 6 months after tisagenlecleucel infusion
h) Exact method according to Clopper-Pearson
i) In accordance with SAP specifications, the significance level should be determined according to the O'Brien-Fleming alpha-spending approach of LanDeMet. It is unclear whether the significance level was adjusted.
j) The significance level was determined according to the O'Brien-Fleming alpha-spending approach of LanDeMet. However, this was not pre-specified in the SAP of the ENSIGN study (B2205J), which was valid for the data cut-off under consideration.
k) The median observation period is 7.49 months. According to the study report, all recurrences that were considered events were confirmed by the IRC.
l) The median observation period is 6.41 months. According to the study report of the ENSIGN study, all events were relapses. In no patient did death occur before recurrence.
m) All patients who had a response (CR/CRi) within 3 months.
n) All patients who had a response (CR/CRi) within 6 months.
o) Information on the amount of censored patients and the reasons for the censoring were not available in the documents submitted by the pharmaceutical manufacturer.
p) The MRD status was determined in patients who showed a response (CR/CRi) after infusion with tisagenlecleucel (ELIANA: n = 61; ENSIGN: n = 20). If there was a response on day 28, the MRD status on day 28 was determined. If no response was present at this time (CR/CRi), the MRD status was determined at the time of the response, recommended for Study month 3 or 6.
q) It is not possible to determine the return rates in the ITT population at baselines or for individual surveys during follow-up. It is therefore unclear whether the return rates are ≥ 70 %. The data can therefore not be used for the benefit assessment.
r) In the ENSIGN study, the AE was measured according to MedDRA Version 19.0 and in the ELIANA study, according to MedDRA Version 20.0. The severity classification was performed according to CTCAE version 4.03 with the exception of the cytokine-release syndrome, which was classified according to PGS-CRS (Penn

Grading Scale for Cytokine Release Syndrome). According to the present definition, only the recurrence or deterioration of existing adverse events was recorded. Therefore, AE that have occurred up to Study week 8 may persist after Study week 8. Information on the follow-up period of the AE is not available.

s) AE was defined as haematopoietic cytopenia persisting on study day 28 after tisagenlecleucel administration. The endpoint is thus reported only in the follow-up phase within the first 8 weeks after treatment.

CR = complete remission; CRi = complete remission with incomplete haematological recovery; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D VAS = European Quality of Life-5 Dimensions visual analogue scale; FAS = full analysis set (all patients who received a tisagenlecleucel infusion); IRC = Independent Review Committee; ITT = intention-to-treat (all patients included in the ELIANA or ENSIGN study); CI = confidence interval; MRD = minimal residual disease; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PedsQL = Paediatric Quality of Life Inventory; PT = Preferred Term; SAP = Statistical Analysis Plan; SOC = System Organ Class; SAE = Severe Adverse Event; AE= Adverse Event

2. Number of patients or demarcation of patient groups eligible for treatment

Children, adolescents, and young adult patients up to 25 years of age with refractory or relapsed (relapse after transplantation or second or later relapse) acute lymphocytic B-cell leukaemia (ALL)

Approx. 50 – 65 patients

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 program 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

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 facility

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

1.1.1 In adults, documented by the treatment of > 20 cases with this diagnosis (C91.0 according to ICD-10-GM-2018) in the treatment facility within three years and participation in studies of the German Multi-centre Study Group for Adult Acute Lymphoblastic Leukaemia (GMALL) or a comparable multi-centre study group.

1.1.2 For children and adolescents up to 18 years of age: Fulfilment of the requirements of the Directive on Paediatric Oncology of the Federal Joint Committee (Gemeinsamer Bundesausschusses; G-BA).

1.2 Extensive experience in cell therapy

1.2.1 In adults, documented by reporting > 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.

1.2.2 For children and adolescents up to 18 years of age, documented by evidence of allogeneic transplantations in this age group by reporting to DRST/EBMTR within the last three years evaluated.

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 can be credited pro rata in relation to full-time work.

1.3.2 For the treatment of children and adolescents up to the age of 18, the management responsible for the treatment with tisagenlecleucel and their deputies must be medical specialists for paediatrics and adolescent medicine with a main focus on paediatric haematology and oncology.

1.3.3 Requirements for the qualification of the caregiver service:

1.3.3.1 The management and their representation on the ward for the care of patients treated with tisagenlecleucel are caregiver or paediatric caregiver 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.

1.3.3.2 Each shift is led by caregiver or paediatric caregiver 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.

1.3.4 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 For children and adolescents up to 18 years of age, specialists in paediatrics and adolescent medicine with a main focus on paediatric haematology and oncology will take part in the tumour conference instead of internal specialists.

2.1.3 The date, participants, and results of the consultation 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[2] 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[2] for clinical, instrumental, and laboratory chemical monitoring for the early detection of CRS[3] and CRES[4] 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 or paediatric and juvenile medicine with a focus on paediatric 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 or, in the case of patients up to the age of 18, by a specialist in paediatric and juvenile medicine specialising in paediatric haematology and oncology in the intensive care unit. This physician must have personal experience in treatment with CAR-T cells. The treatment concept for 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)

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2 Standard Operating Procedure
3 Cytokine release syndrome
4 CAR-T-related encephalopathy syndrome

- Vascular surgery
- Otolaryngology
- Cardiology
- Laboratory medicine
- Microbiology (availability within 24 hours 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.

2.8 Accommodation in specific rooms for patients in Risk groups 2 or 3 according to the guidelines of the Robert Koch Institute[5] is generally not required. However, it must be ensured that such accommodation is possible at all times.

2.9 Outpatient aftercare

2.9.1 Medical care in accordance with specialist standards (internal medicine, haematology, and oncology or paediatric and juvenile medicine with a focus on paediatric 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 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

[5] 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.

Society for Blood and Marrow Transplantation (EBMT) as well as for timely documentation. The following in particular should be documented:

- Prior treatments
- 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.

4. Treatment costs

Annual treatment costs:

Children, adolescents, and young adult patients up to 25 years of age with refractory or relapsed (relapse after transplantation or second or later relapse) acute lymphoblastic B-cell leukaemia (ALL)

Designation of the therapy	Annual therapy costs/patient
Tisagenlecleucel[6,7,8]	€ 320,000.00[9]
Additional SHI services required:	
Lymphocyte depletion	€ 484.42 – 944.62

Pharmaceutical Retail Price (Lauer-Taxe®) as last revised: 15. February 2019

Other SHI benefits:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Lymphocyte depletion					
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€81	4	4	€324
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€81	2	2	€162

6 Information provided by the pharmaceutical manufacturer on its selling price from Module 3 of the dossier.
7 This relates exclusively to the cost of the medicinal product Kymriah®.
8 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 evaluated.
9 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.