Gemeinsamer Bundesausschuss

Tisagenlecleucel

Resolution of: 7. March 2019 Valid Until: 15 March 2020
Entry into force on 7. March 2019
Federal Gazette, BAnz AT 02 04 2019 B3

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

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

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.

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Extent of the 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]:

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

JULIET study: single-arm, multi-centre phase II study
(Data cut-off date 8 March 2017)

Mortality

Endpoint	**JULIET**	
	N	Median survival period in months[a)] [95 % CI][b)] *Patients with event n (%)*
Overall survival (OS)		
ITT population	147	No data available *58 (39.4)[c)]*
FAS population	99	n. a. [6.5; n. c.] *29 (29.3)*

Morbidity

Endpoint	**JULIET**	
	N	Median time in months [95 % CI][b)] *Patients with event n (%)*
Progression-free survival (PFS)[d)]		
ITT population	147	No data available
FAS population	99	2.9 [2.2; 6.2] *47 (47.5)*

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

Morbidity

Endpoint	JULIET	
	N	Response rate in % [95 % CI][e)] *Patients with event n (%)*
Overall Response Rate (ORR) - patients from the main cohort of the Efficacy Analysis Sets (EAS) and patients of the main cohort who were included but not infused[f)]		
ORR	125	34.4 [26.1; 43.4] *43 (34.4)*
CR	125	- *32 (25.6)*
PR	125	- *11 (8.8)*
Overall Response Rate (ORR) - patients from the main cohort of the Efficacy Analysis Sets (EAS)		
ORR	81	53.1 [41.7; 64.3] *43 (53.1)*
CR	81	- *32 (39.5)*
PR	81	- *11 (13.6)*

Quality of life

Endpoint	JULIET	
	N	MV (SD) *Patients with event n (%)*
FACT-Lym		
No usable data[g)]		
SF-36		
No usable data[g)]		

Side effects

Endpoint[h)]	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)						
	95	76 *(80.0)*	99	98 *(99.0)*	78	53 *(67.9)*
Severe AE (CTCAE grade 3/4)						
	95	41 *(43.2)*	99	82 *(82.8)*	78	30 *(38.5)*
Serious AE (SAE)						
	95	7 *(7.4)*	99	50 *(50.5)*	78	18 *(23.1)*
Severe AE (CTCAE grade 3/4) with incidence ≥ 5% at the SOC level						
Blood and lymphatic system disorders						
	95	21 *(22.1)*	99	51 *(51.5)*	78	11 *(14.1)*
Cardiac disorders						
	95	-	99	6 *(6.1)*	78	-
Gastrointestinal disorders						
	95	-	99	9 *(9.1)*	78	-
General disorders and administration site conditions						
	95	-	99	11 *(11.1)*	78	-
Immune system disorders						
	95	-	99	24 *(24.2)*	78	-
Infections and infestations						
	95	-	99	20 *(20.2)*	78	10 *(12.8)*
Investigations						
	95	22 *(23.2)*	99	50 *(50.5)*	78	11 *(14.1)*
Metabolism and nutrition disorders						
	95	6 *(6.3)*	99	24 *(24.2)*	78	-
Nervous system disorders						
	95	-	99	11 *(11.1)*	78	-
Psychiatric disorders						
	95	-	99	8 *(8.1)*	78	-
Renal and urinary disorders						
	95	-	99	6 *(6.1)*	78	-
Respiratory, thoracic and mediastinal disorders						
	95	-	99	11 *(11.1)*	78	-

Endpoint[h)]	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 *(%)*
Vascular disorders						
	95	-	99	9 *(9.1)*	78	-

Endpoint[h)]	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 the lymphatic system disorders (SOC)						
	95	-	99	11 *(11.1)*	78	-
Febrile neutropenia (PT)						
	95	-	99	7 *(7.*1)	78	-
General disorders and administration site conditions (SOC)						
	95	-	99	8 *(8.1)*	78	4 *(5.1)*
Immune system disorders (SOC)						
Cytokine-release syndrome (PT)						
	95	-	99	29 *(29.3)*	78	-
Infections and infestations (SOC)						
	95	-	99	6 *(6.1)*	78	8 *(10.3)*
Nervous system disorders (SOC)						
	95	-	99	5 *(5.1)*	78	-
Renal and urinary disorders (SOC)						
	95	-	99	5 *(5.1)*	78	-
Respiratory, thoracic and mediastinal disorders						
	95	-	99	5 *(5.1)*	78	-

Endpoint[h)]	Tisagenlecleucel infusion up to study week 8		Study week 9 to Study week 12[i)]	
	N	Patients with event n *(%)*	N	Patients with event n *(%)*
AEs of special interest (group term)				
Cytokine-release syndrome				
	99	57 *(57.6)*	78	0 *(0.0)*
Febrile neutropenia				
	99	13 *(13.1)*	78	No data available
Haematopoietic cytopenia persisting on day 28				
	99	36 *(36.4)*	78	-[j)]
Infections				
	99	34 *(34.3)*	78	26 *(33.3)*
Neurological events				
	99	21 *(21.2)*	78	3 *(3.8)*
Tumour lysis syndrome				
	99	1 *(1.0)*	78	No data available
Decrease in cardiac ejection fraction				
	99	No data available	78	No data available
Hepatic events				
	99	No data available	78	No data available

a) The median observation period of the FAS population is 3.58 months. No data is available for the ITT population.
b) PROC LIFETEST according to the method of Brookmeyer and Crowley (1982).
c) Deaths for patients who did not receive a tisagenlecleucel infusion were reported in the interests of patient safety: Overall, 29 of the 43 patients who did not receive tisagenlecleucel died. Data on the mortality calculated from the number of deaths prior to infusion (N = 29) and number of deaths in the FAS population (N = 29).
d) Data from the pharmaceutical manufacturer's dossier and from the study report on the JULIET study. The median observation period is 2.14 months. At the cut-off date for data collection of 8 March 2017 no patient in the FAS population had a stem cell transplantation after infusion and prior to the progression event.
e) Exact method according to Clopper-Pearson
f) The efficacy analysis set (EAS) includes all patients who received the infusion with tisagenlecleucel and for whom at least 3 months (90 days) had passed between the infusion and the data cut-off date. The number of patients of N = 125 in this analysis is not comprehensible. This should be composed of the 81 patients of the main cohort of the EAS and a maximum of 43 patients who left prior to the infusion. This would result in N = 124. No data was provided for the ITT population. The analysis used best corresponds to the ITT principle.
g) Due to the low return rates (< 70 %) the data is not usable.
h) The AE data was collected in accordance with MedDRA version 20.0. The degree of severity was classified according to CTCAE Version 4.03 with the exception of cytokine-release syndrome, which was classified according to PGS-CRS (Penn Grading Scale for Cytokine Release Syndrome). According to the currently employed definition, only the recurrence or deterioration of existing adverse events was recorded. Therefore, AEs that had occurred by study week 8 were likely to persist after study week 8. No data is available for the AE follow-up period.
i) The protocol only schedules evaluation until week 8. The study report includes data on cytokine-release syndrome, infections and neurological events from study week 9 to study month 12.
j) The 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; CTCAE = Common Terminology Criteria for Adverse Events; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; FAS = Full Analysis Set (all patients who have received a tisagenlecleucel infusion); IRC = Independent Review Committee; ITT = Intention-to-treat (all patients who were included in the JULIET study); No data available. = not applicable; CI = Confidence Interval; N = Number of patients evaluated; n = Number of patients with (at least one) event; n. c. = not calculable; n. a. = not achieved; PR = Partial Remission; PT = Preferred Term; SF-36 = Short-Form 36; SOC = System Organ Class; SAE = Severe Adverse Event; AE= Adverse Event

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

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

Approx. 440–700 patients

3. Requirements to ensure quality of administration

A. Regulatory requirements for marketing authorisation

The requirements of the specialist information and the Risk Management Plans (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 facilities

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

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

1.2 Extensive experience in cell therapy

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

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 Requirements for the qualifications of the nursing service:

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

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

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

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

2. Infrastructure and organisational requirements

2.1 Establishment of a tumour board:

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

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

2.1.2 The date, participants and 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 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 SOPs2 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) must be available without interruption for the inpatient care of patients treated with tisagenlecleucel; at least one on-call service must be provided outside working hours.

2.6 When transferring to the intensive care unit, it must be ensured that a visit is carried out daily by a specialist in internal medicine, haematology and oncology. This physician must have personal experience in the treatment with CAR T cells. The treatment concept on the intensive care unit must be discussed with this physician.

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

- Ophthalmology
- Gastroenterology (endoscopy of the gastrointestinal tract)

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

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

Outside working hours, at least one on-call standby service must be provided.

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) 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

[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.

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

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

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

4. Treatment costs

Annual treatment costs:

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

Designation of the therapy	Annual therapy costs/patient
Tisagenlecleucel[6,7,8]	€ 320,000.00[9]
Additional SHI services required	
Lymphocyte depletion	€ 392.61

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

Other services covered by SHI funds:

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	3	3	€ 243
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	3	€ 243

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.