Gemeinsamer Bundesausschuss

Tisagenlecleucel (reassessment after the deadline (diffuse large B-cell lymphoma, (DLBCL)))

Resolution of: 15 February 2024
Entry into force on: 15 February 2024
Federal Gazette, BAnz 27 03 2024 B2

Valid until: unlimited

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

Therapeutic indication of the resolution (resolution of 15 February 2024):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Tisagenlecleucel is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy</u>

Extent of the additional benefit and significance of the evidence of tisagenlecleucel:

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

Study results according to endpoints:[1]

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

JULIET study: single-arm, multicentre, phase II study, data cut-off from 22.12.2022

LTFU: long-term follow-up study, data cut-off from 03.05.2022

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

Mortality

Endpoint	JULIET study with addition of LTFU	
	N	**Median survival time in months [95% CI][a]** ***Patients with event n (%)***
Overall survival		
ITT population	167	8.2 [5.8; 11.7] *108 (64.7)*
Kaplan-Meier estimator [95% CI][b]		
at study month 3	167	79.0 [71.6; 84.6]
at study month 6	167	56.8 [48.4; 64.4]
at study month 9	167	46.2 [37.9; 54.0]
at study month 12	167	41.0 [32.9; 48.9]
at study month 24	167	33.3 [25.6; 41.2]

[1] Data from the dossier assessment of the G-BA (published on 1. Dezember 2023), unless otherwise indicated.

Endpoint	JULIET study with addition of LTFU	
	N	Median survival time in months [95% CI][a] *Patients with event n (%)*
at study month 36	167	29.4 [22.1; 37.2]
at study month 48	167	27.9 [20.7; 35.6]
at study month 60	167	25.5 [18.5; 33.1]

Morbidity

Endpoint	JULIET study	
	N	Median time in months [95% CI] *Patients with event n (%)*
Progression-free survival (PFS)[c] - presented additionally		
	167	4.8 [3.7; 5.3] *102 (61.1)*
Best overall response rate (ORR) - presented additionally		
		according to the assessment by IRC / according to the assessment by the investigators[d]
Response rate (CR + PR)	167	36.5 [29.2; 44.3] / 32.9 [n.d.]
CR	167	*45 (26.9)* / *39 (23.4)*
PR	167	*16 (9.6)* / *16 (9.6)*

Quality of life[e]

Endpoint	JULIET study	
	N	Patients with event n (%)
FACT-Lym		
No usable data available		
SF-36		
No usable data available		

Side effects

Endpoint	**Chemotherapy Lymphocyte depletion** **N = 109**	**Tisagenlecleucel infusion until study week 8** **N = 115[f]**	**Study week 9 to study month 12** **N = 100[f]**
	Patients with event n (%)	*Patients with event n (%)*	*Patients with event n (%)*
Total adverse events (presented additionally)	*90 (82.6)*	*115 (100)*	*71 (71)*
Serious adverse events (SAE)	*8 (7.3)*	*56 (48.7)*	*30 (30)*
Adverse events CTCAE grade ≥ 3	*50 (45.9)*	*98 (85.2)*	*51 (51)*
Adverse events, which led to the discontinuation of the study medication	*1 (0.9)*	*-[g]*	*-[g]*
SAEs with incidence ≥ 5% according to MedDRA system organ class[h]			
Blood and lymphatic system disorders[i]	-	*12 (10.4)*	-
General disorders and administration site conditions	-	*9 (7.8)*	*6 (6.0)*
Immune system disorders	-	*31 (27.0)*	-
Infections and infestations[i]	-	*7 (6.1)*	*13 (13.0)*
Nervous system disorders[i]	-	*7 (6.1)*	-
Renal and urinary disorders	-	-	-
Respiratory, thoracic and mediastinal disorders	-	*8 (7.0)*	-

Endpoint	JULIET study					
	Chemotherapy lymphocyte depletion **N = 109**		**Tisagenlecleucel infusion until study week 8** **N = 115[f]**		**Study week 9 to study month 12** **N = 100[f]**	
	Patients with event n (%)		*Patients with event n (%)*		*Patients with event n (%)*	
	Total	Grade 3/4[j]	Total	Grade 3/4[j]	Total	Grade 3/4[j]
AEs according to MedDRA system organ class[h] (incidence ≥ 10% and AE CTCAE grade 3/4 with incidence ≥ 5%)						
Blood and lymphatic system disorders	*32 (29.4)*	*24 (22.0)*	*72 (62.6)*	*62 (53.9)*	*21 (21.0)*	*18 (18.0)*
Cardiac disorders	-	-	*24 (20.9)*	*8 (7.0)*	-	-
Gastrointestinal disorders	*38 (34.9)*	-	*65 (56.5)*	*10 (8.7)*	*31 (31.0)*	*6 (6.0)*
General disorders and administration site conditions	*27 (24.8)*	-	*76 (66.1)*	*12 (10.4)*	*24 (24.0)*	*5 (5.0)*
Immune system disorders	-	-	*68 (59.1)*	*28 (24.4)*	-	-
Infections and infestations[i]	*15 (13.8)*	-	*43 (37.4)*	*22 (19.1)*	*41 (41.0)*	*18 (18.0)*
Investigations	*40 (36.7)*	*32 (29.4)*	*75 (65.2)*	*61 (53.0)*	*34 (34.0)*	*22 (22.0)*
Metabolism and nutrition disorders	*16 (14.7)*	*7 (6.4)*	*52 (45.2)*	*29 (25.2)*	*15 (15.0)*	*7 (7.0)*
Musculoskeletal and connective tissue disorders	-	-	*34 (29.6)*	-	*23 (23.0)*	-
Nervous system disorders	-	-	*46 (40.0)*	*12 (10.4)*	*16 (16.0)*	*5 (5.0)*
Psychiatric disorders	-	-	*29 (25.2)*	*8 (7.0)*	-	-
Renal and urinary disorders	-	-	*18 (15.7)*	*7 (6.1)*	-	-
Respiratory, thoracic and mediastinal disorders	*12 (11.0)*	-	*39 (33.9)*	*13 (11.3)*	*18 (18.0)*	-
Skin and subcutaneous tissue disorders	-	-	*32 (27.8)*	-	*12 (12.0)*	-
Vascular diseases	-	-	*33 (28.7)*	*10 (8.7)*	-	-

Endpoint	JULIET study								LTFU	
	Chemotherapy lymphocyte depletion N = 109		**Tisagenlecleucel infusion until study week 8 N = 115[f]**		**Study week 9 to study month 12 N = 100[f]**		**From study month 13 N = 47[f]**		**N = 20[l]**	
	Patients with event n (%)		*Patients with event n (%)*		*Patients with event n (%)*		*Patients with event n (%)*		*Patients with event n (%)*	
	Total	Grade 3/4[j]	Total	Grade 3/4[j]	Total	Grade 3/4[j]	Total	Grade 3/4[j]	Total	Grade 3/4[j]
AEs of special interest										
Important identified risks										
Cytokine release syndrome	*0[c]*	*0[c]*	*66 (57.4)*	*26 (22.6)*	*0[c]*	*0[c]*	*0[c]*	*0[c]*	*n.d.*	*n.d.*
Tumour lysis syndrome	*0[c]*	*0[c]*	*2 (1.7)*	*2 (1.7)*	*0[c]*	*0[c]*	*0[c]*	*0[c]*	*n.d.*	*n.d.*
Infections	*15 (13.8)*	*3 (2.8)*	*43 (37.4)*	*22 (19.1)*	*41 (41.0)*	*18 (18.0)*	*22 (46.8)*	*10 (21.3)*	*3 (15.0)*	*1 (5.0)*
Haematological disorders including cytopenias[k]	*48 (44.0)*	*44 (40.4)*	*88 (76.5)*	*85 (73.9)*	*32 (32.0)*	*29 (29.0)*	*11 (23.4)*	*8 (17.0)*	*n.d.*	*n.d.*
Prolonged B-cell depletion or agammaglobulin-aemia	*0[4)]*	*0[4)]*	*7 (6.1)*	*4 (3.5)*	*13 (13.0)*	*4 (4.0)*	*3 (6.4)*	*0*	*2 (10.0)*	*1 (5.0)*
Serious neurologic events	*3 (2.8)*	*1 (0.9)*	*23 (20.0)*	*13 (11.3)*	*5 (5.0)*	*3 (3.0)*	*1 (2.1)*	*1 (2.1)*	*n.d.*	*n.d.*
Important potential risks[l]										
Cerebral oedema	*0[c]*	*0[c]*	*1 (0.9)*	*0*	*0[c]*	*0[c]*	*0[c]*	*0[c]*	*n.d.*	*n.d.*
Recurrence or exacerbation of an autoimmune disease	2 (1.8)	1 (0.9)	17 (14.8)	10 (8.7)	8 (8)	2 (2)	5 (10.6)	0	n.d.	n.d.
Secondary malignancies	1 (0.9)	1 (0.9)	1 (0.9)	-	4 (4)	3 (3)	8 (17)	6 (12.8)	n.d.	n.d.

a. The median survival time in the ITT population comprises the time from enrolment in the study to death or censoring.
b. The estimators for 72, 78 and 84 months are not reported as the number of subjects at risk (ITT: N = 7 at 72 months, N = 1 at 78 months) is too low.
c. Information from the dossier of the pharmaceutical company

Endpoint	JULIET study								LTFU	
	Chemotherapy lymphocyte depletion **N = 109**		**Tisagenlecleucel infusion until study week 8** **N = 115[f]**		**Study week 9 to study month 12** **N = 100[f]**		**From study month 13** **N = 47[f]**		**N = 20[l]**	
	Patients with event n (%)		*Patients with event n (%)*		*Patients with event n (%)*		*Patients with event n (%)*		*Patients with event n (%)*	
	Total	Grade 3/4[j]	Total	Grade 3/4[j]	Total	Grade 3/4[j]	Total	Grade 3/4[j]	Total	Grade 3/4[j]

d. Response data according to investigators were only available for the FAS population. As for the ITT population, it is assumed that subjects who withdrew from the study without infusion showed no response. The share by percentage was calculated based on this assumption.
e. The return rates for all post-baseline values are < 70% in relation to the population with infusion (does not correspond to the ITT). The pharmaceutical company does not provide any information on the reasons for the low return rate. The data are therefore not used for the benefit assessment.
f. Data related to the FAS population: n = 115 in the period from infusion to study week 8, n = 100 in the period from study week 9 to study month 12. Subjects who had a progression in the first year after infusion entered the secondary follow-up phase, in which no complete collection of AEs took place.
g. Therapy discontinuation due to AEs after the infusion is not possible as tisagenlecleucel is administered as a single dose.
h. If a study participant had several events in a particular system organ class, this was counted as a single event in the system organ class.
i. This is an AESI or a SOC that contains AESI.
j. The pharmaceutical company presents AEs for CTCAE grades 3 and 4 separately. The joint presentation of AEs of CTCAE grade 3/4 was based on own calculations based on information provided by the pharmaceutical company.
k. The pharmaceutical company states that the heading "haematological disorders including cytopenias" from the important potential risks is identical to the previously used heading from the potential risks "haematological disorders (incl. aplastic anaemia and bone marrow failure)".
l. Important potential risks "emergence of replication-competent lentiviruses", "deterioration of the graft-versus-host reaction", "transmission of infectious agents", "decrease in cell viability" were not reported for the JULIET study. It is unclear whether they were not collected or whether no events occurred. No important potential risks were reported for the LTFU.

Abbreviations used:
AD = absolute difference; CR = complete remission; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; IRC = Independent Review Committee; CI = confidence interval; KM = Kaplan-Meier; LTFU = long-term follow-up study; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; vs = versus

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

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

approx. 530 – 1,200 patients[2]

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Kymriah (active ingredient: tisagenlecleucel) at the following publicly accessible link (last access: 16 November 2023):

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

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

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

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

[2] It refers to the relevant patient population that is eligible for CAR-T cell therapy or stem cell transplantation.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tisagenlecleucel[3,4]	€ 239,000.00
Additionally required SHI services:	€ 412.45

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 January 2024)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Lymphocyte depletion					
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3.0	€ 300
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3.0	€ 300

[3] It concerns only the cost of the medicinal product Kymriah.
[4] Since leukapheresis is part of the manufacture of the medicinal product in accordance with Section 4, paragraph 14 Medicinal Products Act,
no further costs are incurred in this regard for the medicinal product to be assessed.

5. Designation of 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 the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.