Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Tisagenlecleucel (Reassessment after Expiry: Diffuse Large B-cell Lymphoma)

of 17 September 2020

At its session on 17 September 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the information on the benefit assessment of the active ingredient tisagenlecleucel (diffuse large B-cell lymphoma) in the version of the resolution of 7 March 2019 (Federal Gazette BAnz AT 2 April 2019 B3) is adopted as follows:

“Tisagenlecleucel

Resolution of: 17 September 2020
Entry into force on: 17 September 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Approved 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 and significance of the evidence

Tisagenlecleucel is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (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).

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 and significance of the evidence for tisagenlecleucel:

Hint for a non-quantifiable additional benefit because the scientific data does not permit quantification

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 1 July 2019, ITT population)

[1] Data from the dossier assessment by the G-BA (published on 1 July 2020) unless otherwise indicated.

Mortality

Endpoint	JULIET	
	N	Median survival time in months [95% CI] *Patients with event n (%)*
Overall survival		
	167	8.2 [5.8; 11.7] *99 (59.3)*
		Kaplan-Meier estimator [95% CI]
Study month 3	167	79.0 [71.6; 84.6]
Study month 6	167	56.8 [48.4; 64.4]
Study month 9	167	46.2 [37.9; 54.0]
Study month 12	167	41.0 [32.9; 48.9]
Study month 18	167	36.3 [28.4; 44.2]
Study month 24	167	33.0 [25.2; 40.9]
Study month 30	167	32.1 [24.4; 40.0]

Morbidity

Endpoint	JULIET	
	N	Median time in months [95% CI] *Patients with event n (%)*
Progression-free survival[a]		
	167	4.8 [3.7; 5.3] *97 (58.1)*
Endpoint	**JULIET**	
	N	Response rate in % [95% CI] *Patients with event n (%)*
Best overall response (ORR)		
Assessment by IRC		
Best response (CR/PR)	167	35.9 [28.7; 43.7] *60 (35.9)*
CR	167	-

		44 (26.3)
PR	167	- *16 (9.6)*
Assessment by medical testing staff[b]		
Best response (CR/PR)	167	no data available *55 (32.9)*
CR	167	- *39 (23.4)*
PR	167	- *16 (9.6)*

Quality of life

Endpoint	JULIET
FACT-Lym	
No usable data[c]	
SF-36	
No usable data[c]	

Side effects

Endpoint	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 (overall)						
	109	90 (82.6)	115	115 (100)	100	71 (71.0)
Severe AE (CTCAE Grade 3/4)[d]						
	109	50 (45.9)	115	98 (85.2)	100	50 (50.0)
Serious AE (SAE)						
	109	8 (7.3)	115	56 (48.7)	100	30 (30.0)
Therapy discontinuation because of adverse events						
	109	1 (0.9)	115	n.r.[e]	100	n.r.[e]
Severe AE (CTCAE grade 3/4) with incidence ≥ 5% at the SOC level[d]						
Blood and lymphatic system disorders						
	109	24 (22.0)	115	62 (53.9)	100	18 (18.0)

Cardiac disorders						
	109	-	115	8 (7.0)	100	-
Gastrointestinal disorders						
	109	-	115	10 (8.7)	100	6 (6.0)
General disorders and administration site conditions						
	109	-	115	12 (10.4)	100	5 (5.0)
Immune system disorders						
	109	-	115	28 (24.4)	100	-
Infections and infestations						
	109	-	115	22 (19.1)	100	18 (18.0)
Investigations						
	109	32 (29.4)	115	61 (53.1)	100	22 (22.0)
Metabolism and nutrition disorders						
	109	7 (6.4)	115	29 (25.2)	100	7 (7.0)
Nervous system disorders						
	109	-	115	12 (10.4)	100	5 (5.0)
Psychiatric disorders						
	109	-	115	8 *(7.0)*	100	-
Renal and urinary disorders						
	109	-	115	7 *(6.1)*	100	-
Respiratory, thoracic, and mediastinal disorders						
	109	-	115	13 (11.3)	100	-
Vascular disorders						
	109	-	115	10 (8.7)	100	-

Endpoint	**Chemotherapy lymphocyte depletion**		**Tisagenlecleucel infusion up to Study week 8**		**Study week 9 to Study week 12**	
SOC[f] ***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)						
	109	-	115	12 (10.4)	100	-
Febrile neutropoenia (PT)						
	109	-	115	7 (6.1)	100	-

General disorders and administration site conditions (SOC)						
	109	-	115	9 (7.8)	100	6 (6.0)
Immune system disorders (SOC)						
Cytokine release syndrome (PT)						
	109	-	115	31 (27.0)	100	-
Infections and infestations (SOC)						
	109	-	115	7 (6.1)	100	13 (13.0)
Nervous system disorders (SOC)						
	109	-	115	7 (6.1)	100	-
Renal and urinary disorders (SOC)						
	109	-	115	-	100	-
Respiratory, thoracic, and mediastinal disorders						
	109	-	115	8 (7.0)	100	-

Endpoint[h)]	**Tisagenlecleucel infusion up to Study week 8**		**Study week 9 to Study week 12[h]**	
	N	Patients with event n *(%)*	N	Patients with event n *(%)*
AE of special interest (Group Term)[g]				
Cytokine release syndrome				
	115	66 (57.4)	100	0
Tumour lysis syndrome				
	115	2 (1.7)	100	no data available
Infections				
	115	43 (37.4)	100	40 (40.0)
Haematopoietic cytopoenia persisting on Day 28[i]				
	115	52 (45.2)	100	-
Prolonged B-cell depletion or agammaglobulinemia				
	115	7 (6.1)	100	12 (12.0)
Serious neurological event				
	115	23 (20.0)	100	5 (5.0)

[a] Information from the dossier of the pharmaceutical company
[b] Response data from medical examiners were only available only for the FAS population. As for the ITT population, it is assumed that people who dropped out of the study without an infusion showed no response. The percentage share was calculated under this assumption.
[c] The return rate to the questionnaires was < 70%.
[d] The pharmaceutical company presents AE for CTCAE grades 3 and 4 separately. The common presentation of the CTCAE grade 3/4 is done by own calculation. The graduation of the CRS was based on the PGS-CRS.
[e] A therapy discontinuation because of AE is not possible because tisagenlecleucel is administered in a single dose.
[f] In the case of several events involving a study participant in a particular SOC, this was counted as a single event in the SOC.

[g] People with AE are counted only once per unit category. AE of special interest were collected only from infusion with tisagenlecleucel.
[h]According to the protocol, the evaluation was planned only for the period until Week 8.
[h] In accordance with operationalisation, cytopoenia persisting on Day 28 cannot occur from Study week 9 to Study month 12.

CR = Complete Remission; CTCAE = Common Terminology Criteria for Adverse Events; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; IRC = Independent Review Committee; 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 = serious adverse event; AE= adverse event

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	not assessable
Morbidity	n.a.	not assessable
Health-related quality of life	n.a.	not assessable
Side effects	n.a.	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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

2. Number of patients 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. 450–720 patients

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) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 14 August 2020):

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

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as 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 tocilizumab at the place of treatment, the provision of relevant information to patients, and the full and adequate reporting of side effects.

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

The resolution of 17 September 2020 on quality assurance measures for the application of CAR-T cells in B-cell neoplasia provides further details.

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 treatment costs/patient
Tisagenlecleucel[2,3]	€ 275,000.00
Additionally required SHI services:	
Lymphocyte depletion	€ 382.29

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 September 2020

[2] This relates exclusively to the costs of the medicinal product Kymriah®.

[3] Because leukapheresis is part of the manufacture of the medicinal product under Section 4, paragraph 14 AMG, no further costs are incurred in this respect for the medicinal product to be assessed.

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs per unit	Number per cycle	Number per patient per year	Costs 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

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II. Entry into force

1. **The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 17 September 2020.**
2. **The period of validity of the resolution is limited to 1 September 2023.**

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de .

Berlin, 17 September 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken