Tisagenlecleucel (reassessment after the deadline: B-cell acute lymphoblastic leukaemia (ALL), relapsed/ refractory, 0 ≤ 25 years)

Resolution of: 15 February 2024 valid until: unlimited
Entry into force on: 15 February 2024
Federal Gazette, BAnz AT 28 03 2024 B6

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 and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

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>Children, adolescents and young adults up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse</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]

Children, adolescents and young adults up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

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		

- **ELIANA study:** single-arm, multicentre, phase II study, data cut-off from 17 November 2022
- **ENSIGN study:** single-arm, multicentre, phase II study, data cut-off from 24 May 2019
- **B2001X study:** single-arm, multicentre, phase IIIb study, data cut-off from 13 October 2020
- **Long-term follow-up study (LTFU A2205B):** All patients who have received CAR-T therapy under a treatment protocol of the pharmaceutical company as part of a clinical trial or a managed access programme (in this case, patients from the ELIANA, ENSIGN and B2001X studies), data cut-off from 3 May 2022

[1] Data from the dossier assessment of the G-BA (published on 1. Dezember 2023), and from the amendment to the dossier assessment from 26 January 2024, unless otherwise indicated.

Mortality

Endpoint	ELIANA (+ LTFU)		ENSIGN (+ LTFU)		B2001X (+ LTFU)[b]	
	N	Median survival time in months[a] [95% CI] *Patients with event n (%)*	N	Median survival time in months[a] [95% CI] *Patients with event n (%)*	N	Median survival time in months[a] [95% CI] *Patients with event n (%)*
Overall survival						
	98	47.6 [19.4; n.r.] 50 (51)	75	28.5 [10.2; n.r.] 41 (54.7)	74	54.7 [38.8; n.r.] 28 (37.8)
		Kaplan-Meier estimator [95% CI]		Kaplan-Meier estimator [95% CI]		Kaplan-Meier estimator [95% CI]
At study month 6	98	77.2 [67.5; 84.4]	75	78.7 [67.1; 86.5]	74	87.5 [77.3; 93.3]
At study month 12	98	69.9 [59.6; 78.0]	75	59.9 [47.4; 70.3]	74	78.5 [66.9; 86.5]
At study month 24	98	58.0 [47.4; 67.2]	75	55.8 [43.4; 66.5]	74	68.7 [56.0; 78.4]
At study month 36	98	52.3 [41.7; 61.8]	75	43.5 [31.5; 54.8]	74	63.8 [50.9; 74.2]
At study month 48	98	48.8 [38.2; 58.5]	75	40.2 [28.5; 51.6]	74	-
At study month 60	98	46.3 [35.8; 56.1]	75	40.2 [28.5; 51.6]	74	-

Morbidity

Endpoint	ELIANA		ENSIGN		B2001X	
	N	Remission rate [95% CI][c] *Patients with event n*	N	Remission rate [95% CI][c] *Patients with event n*	N	Remission rate [95% CI][c] *Patients with event n*
Response (CR/CRi; presented additionally)[d]						
Total	98	68.4 [58.2; 77.4] 67 (68.4)	75	60.0 [48.0; 71.1] 45 (60.0)	74	77.0 [65.8; 86] 57 (77.0)
CR	98	- 55 (56.1)	75	- 38 (50.7)	74	- 39 (52.7)
CRi	98	- 12 (12.2)	75	- 7 (9.3)	74	- 18 (24.3)

Endpoint	ELIANA		ENSIGN		B2001X	
	N	Remission rate [95% CI][c)] *Patients with event n*	N	Remission rate [95% CI][c)] *Patients with event n*	N	Remission rate [95% CI][c)] *Patients with event n*
MRD remission (presented additionally)[e)]						
	98	67.3 [57.1; 76.5] 66 (67.3)	75	57.3 [54.3; 78.4] 43 (57.3)	74	40.5 [29.3; 52.6] 30 (40.5)
	ELIANA (+ LTFU)		**ENSIGN (+ LTFU)**		**B2001X (+ LTFU)**	
	N	Median time in months[a)] [95% CI] *Patients with event n (%)*	N	Median time in months[a)] [95% CI] *Patients with event n (%)*	N	Median time in months[a)] [95% CI] *Patients with event n (%)*
Recurrence-free survival[f)]						
	80	46.8 [17.8; n.r.] 26 (38.8)	64	n.r. [14.8; n.r.] 16 (35.6)	69	51.4 [24.0; n.r.] 23 (40.4)
EQ-5D VAS[g)]						
No usable data available						

Health-related quality of life

PedsQL[g)]
No usable data available

Side effects

Endpoint	Chemotherapy Lymphocyte depletion		Tisagenlecleucel infusion until study week 8		Study week 9 to study month 12	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Total adverse events (presented additionally)						
ELIANA	78	62 (79.5)	80	79 (98.8)	75	69 (92.0)
ENSIGN	61	51 (83.6)	64	63 (98.4)	56	46 (82.1)
B2001X	63	45 (71.4)	69	69 (100)	60	48 (80.0)
Serious adverse events (SAE)						
ELIANA	78	8 (10.3)	80	54 (67.5)	75	23 (30.7)

Endpoint	Chemotherapy Lymphocyte depletion		Tisagenlecleucel infusion until study week 8		Study week 9 to study month 12	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
ENSIGN	61	9 (14.8)	64	46 (71.9)	56	21 (37.5)
B2001X	63	10 (15.9)	69	39 (56.5)	60	19 (31.7)
Severe adverse events (CTCAE grade 3/4)[h)]						
ELIANA	78	30 (38.4)	80	67 (83.8)	75	36 (48.0)
ENSIGN	61	38 (62.3)	64	54 (84.4)	56	26 (46.4)
B2001X	63	27 (42.8)	69	50 (72.5)	60	27 (45.0)
Therapy discontinuation due to adverse events						
ELIANA	78	1 (1.2)[i)]	80	n.r.	75	n.r.
ENSIGN	61	0	64	n.r.	56	n.r.
B2001X	63	0	69	n.r.	60	n.r.
Severe adverse events according to MedDRA (incidence ≥ 5% at SOC level)						
Blood and lymphatic system disorders						
ELIANA	78	11 (14.1)	80	39 (48.8)	75	10 (13.3)
ENSIGN	61	18 (29.5)	64	38 (59.4)	56	7 (12.5)
B2001X	63	11 (17.5)	69	22 (31.8)	60	7 (11.7)
Cardiac disorders						
ELIANA	78	-	80	8 (10.0)	75	-
ENSIGN	61	-	64	-	56	-
B2001X	63	-	69	-	60	-
Gastrointestinal disorders						
ELIANA	78	-	80	14 (17.6)	75	-
ENSIGN	61	-	64	11 (17.2)	56	4 (7.1)
B2001X	63	-	69	5 (7.2)	60	-
General disorders and administration site conditions						
ELIANA	78	-	80	11 (13.8)	75	-
ENSIGN	61	-	64	10 (15.7)	56	-
B2001X	63	-	69	8 (11.5)	60	-
Hepatobiliary disorders						
ELIANA	78	-	80	6 (7.6)	75	-
ENSIGN	61	-	64	-	56	-

Endpoint	Chemotherapy Lymphocyte depletion		Tisagenlecleucel infusion until study week 8		Study week 9 to study month 12	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
B2001X	63	-	69	-	60	-
Immune system disorders						
ELIANA	78	-	80	43 (53.8)	75	4 (5.3)
ENSIGN	61	-	64	22 (34.4)	56	-
B2001X	63	-	69	23 (33.3)	60	-
Infections and infestations						
ELIANA	78	5 (6.4)	80	19 (23.8)	75	20 (26.7)
ENSIGN	61	4 (6.5)	64	7 (10.9)	56	12 (21.5)
B2001X	63	5 (7.9)	69	11 (15.9)	60	14 (23.4)
Investigations						
ELIANA	78	18 (23.0)	80	45 (56.3)	75	16 (21.4)
ENSIGN	61	26 (42.6)	64	44 (68.7)	56	12 (21.4)
B2001X	63	14 (22.2)	69	25 (36.2)	60	10 (16.6)
Metabolism and nutrition disorders						
ELIANA	78	4 (5.1)	80	29 (36.3)	75	7 (9.3)
ENSIGN	61	8 (13.1)	64	24 (37.5)	56	4 (7.1)
B2001X	63	-	69	11 (15.9)	60	-
Musculoskeletal and connective tissue disorders						
ELIANA	78	-	80	5 (6.3)	75	-
ENSIGN	61	-	64	-	56	-
B2001X	63	-	69	-	60	-
Nervous system disorders						
ELIANA	78	-	80	10 (12.5)	75	-
ENSIGN	61	-	64	5 (7.9)	56	-
B2001X	63	-	69	7 (10.1)	60	-
Psychiatric disorders						
ELIANA	78	-	80	6 (7.5)	75	-
ENSIGN	61	-	64	-	56	-
B2001X	63	-	69	-	60	-

Endpoint	Chemotherapy Lymphocyte depletion		Tisagenlecleucel infusion until study week 8		Study week 9 to study month 12	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Renal and urinary disorders						
ELIANA	78	-	80	9 (11.3)	75	-
ENSIGN	61	-	64	7 (10.9)	56	-
B2001X	63	-	69	-	60	-
Respiratory, thoracic and mediastinal disorders						
ELIANA	78	-	80	23 (28.8)	75	6 (8.0)
ENSIGN	61	4 (6.6)	64	12 (18.8)	56	3 (5.4)
B2001X	63	-	69	6 (8.6)	60	-
Vascular disorders						
ELIANA	78	-	80	17 (21.3)	75	5 (6.7)
ENSIGN	61	4 (6.6)	64	16 (25.0)	56	-
B2001X	63	-	69	7 (10.1)	60	-
SAEs according to MedDRA (incidence ≥ 5% at SOC level)						
Blood and lymphatic system disorders						
ELIANA	78	-	80	16 (20.0)	75	4 (5.3)
ENSIGN	61	7 (11.5)	64	23 (35.9)	56	5 (8.9)
B2001X	63	-	69	-	60	-
Cardiac disorders						
ELIANA	78	-	80	5 (6.3)	75	-
ENSIGN	61	-	64	-	56	-
B2001X	63	-	69	-	60	-
Gastrointestinal disorders						
ELIANA	78	-	80	5 (6.3)	75	5 (6.7)
ENSIGN	61	-	64	5 (7.8)	56	-
B2001X	63	-	69	-	60	-
General disorders and administration site conditions						
ELIANA	78	-	80	5 (6.3)	75	-
ENSIGN	61	-	64	4 (6.3)	56	5 (8.9)
B2001X	63	5 (7.9)	69	7 (10.1)	60	6 (10.0)

Endpoint	Chemotherapy Lymphocyte depletion		Tisagenlecleucel infusion until study week 8		Study week 9 to study month 12	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Immune system disorders[j)]						
ELIANA	78	-	80	50 (62.5)	75	-
ENSIGN	61	-	64	41 (64.1)	56	-
B2001X	63	-	69	28 (40.6)	60	-
Infections and infestations						
ELIANA	78	-	80	11 (13.8)	75	16 (21.3)
ENSIGN	61	-	64	9 (14.1)	56	12 (21.4)
B2001X	63	4 (6.3)	69	-	60	13 (21.7)
Metabolism and nutrition disorders						
ELIANA	78	-	80	4 (5.0)	75	-
ENSIGN	61	-	64	3 (4.7)	56	-
B2001X	63	-	69	-	60	-
Musculoskeletal and connective tissue disorders						
ELIANA	78	-	80	-	75	-
ENSIGN	61	-	64	-	56	3 (5.4)
B2001X	63	-	69	-	60	-
Nervous system disorders						
ELIANA	78	-	80	5 (6.3)	75	-
ENSIGN	61	-	64	9 (14.1)	56	-
B2001X	63	-	69	-	60	-
Renal and urinary disorders						
ELIANA	78	-	80	5 (6.3)	75	-
ENSIGN	61	-	64	4 (6.3)	56	-
B2001X	63	-	69	-	60	-
Respiratory, thoracic and mediastinal disorders						
ELIANA	78	-	80	10 (12.5)	75	6 (8.0)
ENSIGN	61	-	64	8 (12.5)	56	-
B2001X	63	-	69	-	60	-
Vascular diseases						
ELIANA	78	-	80	8 (10.0)	75	-

Endpoint	Chemotherapy Lymphocyte depletion		Tisagenlecleucel infusion until study week 8		Study week 9 to study month 12	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
ENSIGN	61	-	64	8 (12.5)	56	-
B2001X	63	-	69	-	60	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
B2001X	63	-	69	-	60	3 (5.0)

Endpoint	Tisagenlecleucel infusion until study week 8		Study week 9 to study month 12		Study month 12 to study month 60		From study month 60 (LTFU)	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
AEs of special interest								
Cytokine release syndrome								
ELIANA	80	61 (76.3)	75	0 (0)	50	1 (2.0)	30	0 (0)
ENSIGN	64	50 (78.1)	56	0 (0)	32	0 (0)	14	0 (0)
B2001X	69	46 (66.7)	60	1 (1.7)	40	0 (0)	40	0 (0)
Haematopoietic cytopenias								
ELIANA	80	53 (66.3)	75	26 (34.7)	50	7 (14.0)	30	0 (0)
ENSIGN	64	27 (42.2)	56	0 (0)	32	0 (0)	14	0 (0)
B2001X	69	0 (0)	60	0 (0)	40	0 (0)	40	0 (0)
Infections								
ELIANA	80	35 (43.8)	75	40 (53.3)	50	23 (46.0)	30	3 (10)
ENSIGN	64	26 (40.6)	56	33 (58.9)	32	11 (34.4)	14	2 (14.3)
B2001X	69	26 (37.7)	60	35 (58.3)	40	8 (16.0)	40	9 (22.5)
Prolonged B-cell depletion or agammaglobulinaemia								
ELIANA	80	37 (46.3)	75	15 (20.0)	50	4 (8.0)	30	0 (0)
ENSIGN	64	27 (42.2)	56	8 (14.3)	32	1 (3.1)	14	2 (14.3)
B2001X	69	21 (30.4)	60	7 (11.7)	40	3 (6.0)	40	0 (0)
Serious neurologic events								
ELIANA	80	31 (38.8)	75	5 (6.7)	50	2 (4.0)	30	0 (0)
ENSIGN	64	19 (29.7)	56	2 (3.6)	32	2 (6.3)	14	0 (0)

Endpoint	Tisagenlecleucel infusion until study week 8		Study week 9 to study month 12		Study month 12 to study month 60		From study month 60 (LTFU)	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
B2001X	69	17 (24.6)	60	2 (3.3)	40	2 (4.0)	40	0 (0)
Tumour lysis syndrome								
ELIANA	80	4 (5.0)	75	1 (1.3)	50	0 (0)	30	0 (0)
ENSIGN	64	1 (1.6)	56	1 (1.8)	32	0 (0)	14	0 (0)
B2001X	69	1 (1.4)	60	0 (0)	40	0 (0)	40	0 (0)
Recurrence or exacerbation of an autoimmune disease								
ELIANA	80	35 (43.8)	75	15 (20.0)	50	5 (10.0)	30	0 (0)
ENSIGN	64	1 (1.6)	56	3 (5.4)	32	1 (3.1)	14	0 (0)
B2001X	-							
Exacerbation of the graft-versus-host response								
ELIANA	80	0 (0)	75	2 (2.7)	50	2 (4.0)	30	0 (0)
ENSIGN	64	1 (1.6)	56	3 (5.4)	32	0 (0)	14	0 (0)
B2001X	-							
Secondary malignancies								
ELIANA	80	0 (0)	75	1 (1.3)	50	0 (0)	30	0 (0)
ENSIGN	64	0 (0)	56	2 (3.6)	32	1 (3.1)	14	0 (0)
B2001X	-							
Cerebral oedema								
ELIANA	80	0 (0)	75	0 (0)	50	0 (0)	30	0 (0)
ENSIGN	64	1 (1.6)	56	0 (0)	32	0 (0)	14	0 (0)
B2001X	-							

a. Percentiles with 95% CI were calculated using PROC LIFETEST according to the method of Brookmeyer and Crowley (1982).
b. Since the primary follow-up phase of the B2001X study is 12 months post infusion, the data cut-off from 13 October 2020 was not presented. Only the LTFU data cut-off from 3 May 2022 is shown.
c. Data according to the exact Clopper-Pearson method.
d. Primary endpoint of the ELIANA and ENSIGN studies; assessment by the Independent Review Committee (IRC)
e. The MRD remission was estimated by IRC. The reference value is all patients who achieved a CR/CRi within 6 months according to the IRC.
f. The response was estimated by IRC. According to the study report, all recurrences that were categorised as an event were confirmed by the IRC. The reference value is all patients who achieved a CR/CRi within 6 months according to the IRC. Evaluations with censoring at the time of allogeneic stem cell transplantation and taking into account the data of the long-term follow-up study A2205B. The reliability of data of the effect estimator for the B2001X study is limited due to the small number of subjects with a correspondingly long observation period at the time the median was reached.

g. Return rate < 70%
h. The pharmaceutical company presents adverse events for CTCAE grades 3 and 4 separately. The joint presentation of CTCAE grades 3/4 is based on own calculation.
i. Enrolled set
j. PT Cytokine release syndrome

Abbreviations used:
AD = absolute difference; CR = complete remission; CRi = complete remission with incomplete haematologic recovery; 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; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; n.r. = not relevant; MRD = minimal residual disease; vs = versus

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

Children, adolescents and young adults up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

approx. 40 – 90 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) at the following publicly accessible link (last access: 5 January 2024):

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 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 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).

4. Treatment costs

Annual treatment costs:

Children, adolescents and young adults up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tisagenlecleucel	€ 239,000
Additionally required SHI services	*€ 505.87 - € 966.97*

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
Medicinal product to be assessed					
Tisagenlecleucel: Lymphocyte depletion					
Cyclophosphamide	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	2	2.0	€ 200
Fludarabine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	4	4.0	€ 400

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:

Children, adolescents and young adults up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

- 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.