Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Tabelecleucel (Epstein-Barr virus positive post-transplantation lymphoproliferative disease)

of 5 October 2023

At its session on 5 October 2023, the Federal Joint Committee (G-BA) resolved to amend the 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Tabelecleucel as follows:

Tabelecleucel

Resolution of: 5 October 2023
Entry into force on: 5 October 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 16 December 2022):

Ebvallo is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

Therapeutic indication of the resolution (resolution of 5 October 2023):

See therapeutic indication according to marketing authorisation.

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

Tabelecleucel 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).

Patients 2 years of age and older with Epstein-Barr virus positive post-transplant lymphomas (EBV+ PTLD) who have received at least one prior antineoplastic therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

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

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

Study results according to endpoints:[1]

Patients 2 years of age and older with Epstein-Barr virus positive post-transplant lymphomas (EBV+ PTLD) who have received at least one prior antineoplastic therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

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		

ALLELE study

- Single-arm phase III study
- Results of the data cut-off from 05.11.2021
- Patients with EBV+ PTLD undergoing solid organ transplantation (SOT) after rituximab plus chemotherapy (SOT-R-chemo cohort) or stem cell transplantation (HCT) after rituximab (HCT cohort)

Mortality

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	Median survival time in months [95% CI][a] *Patients with event n (%)*	N	Median survival time in months [95% CI][a] *Patients with event n (%)*
Overall survival	16	16.4 [3.5; n.r.] *7 (44)*	14	n.r. [5.7; n.r.] *4 (29)*
Overall survival rate		*Kaplan-Meier estimator [95% CI]*		*Kaplan-Meier estimator [95% CI]*
at month 12		64.3 [33.8; 83.5]		70.1 [38.5; 87.6]

[1] Data from the dossier assessment of the G-BA (published on 17. Juli 2023), and from the amendment to the dossier assessment from 12 September 2023, unless otherwise indicated.

Morbidity

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)* [95% CI][b]	N	*Patients with event n (%)* [95% CI][b]
Overall response (ORR) assessed by central assessment (IORA) (presented additionally)[c]				
Best response Subjects with CR Subjects with PR Subjects with SD Subjects with PD not evaluable[d]	16	 5 (31) 4 (25) 0 4 (25) 3 (19)	14	 6 (43) 1 (7) 3 (21) 2 (14) 2 (14)
ORR (CR or PR)	16	9 (56) [30; 80]	14	7 (50) [23; 77]
Overall response (ORR) assessed by the investigators (presented additionally)[c]				
Best response Subjects with CR Subjects with PR Subjects with SD Subjects with PD not evaluable[d]	16	 4 (25) 3 (19) 2 (13) 4 (25) 3 (19)		 6 (43) 1 (7) 2 (14) 4 (29) 1 (7)
ORR (CR or PR)	16	7 (44) [20; 70]		7 (50) [23; 77]

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Graft loss	11	0	14	n.e.[e]
Rejection reaction	11	2 (18)	14	n.e.[e]
EQ-5D VAS	There are no usable data.			

Health-related quality of life

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*
FACT-Lym	There are no usable data.			

Side effects

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Total adverse events (presented additionally)	16	15 (94)	14	14 (100)
Serious adverse events (SAE)	16	8 (50)	14	7 (50)
Severe adverse events (CTCAE grade 3 or 4)	16	10 (63)	14	8 (57)
Therapy discontinuation due to adverse events	16	0	14	1 (7)

MedDRA system organ class[2] Preferred terms	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Severe adverse events according to MedDRA				
Pneumonia	16	-	14	2 (14)
Sepsis	16	-	14	3 (21)
Neutropenia	16	3 (19)	14	4 (29)
Leukopenia	16	-	14	1 (7)
Loss of appetite	16	-	14	1 (7)
Hypoxia	16	-	14	1 (7)
SAEs according to MedDRA				
General disorders and administration site conditions	16	**1 (6)**	14	**1 (7)**
Gastrointestinal disorders	16	**2 (13)**	14	**-**
Infections and infestations	16	**5 (31)**	14	**6 (43)**
Pneumonia	16	-	14	2 (14)
Sepsis	16	-	14	3 (21)

a. For subjects who have survived the relevant data cut-off, the survival time at the last known point of survival time is censored. 95% CI of KM analysis using log-log transformation.
b. 95% CI calculated using the exact binomial method.

[2] AE with incidence ≥ 10% related to the total evaluation of the ALLELE and EBV-CTL-201 studies

MedDRA system organ class[2] Preferred terms	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*

c. Primary endpoint of the ALLELE
d. Includes not evaluable, missing values and indeterminate response in subjects who are still in the study at the time of the data cut-off.
e. Graft loss and rejection reactions are only reported for the SOT cohort
f. Events of the high level term "rejection reaction" or "graft".
g. Results on bone marrow or organ rejection have already been presented for morbidity.

Abbreviations used:
CR = complete remission; CTCAE = Common Terminology Criteria for Adverse Events; HCT = = haematopoietic cell transplant; IORA = Independent Oncologic Response Adjudication; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.e. = not evaluable; n.c. = not calculable; n.r. = not reached; PD = disease progression; PR = partial remission; R-Chemo = rituximab plus chemotherapy; SD = stable disease; SOT = solid organ transplantation; vs = versus

EBV-CTL-201 study

- Single-arm phase expanded access study
- Results of the post-hoc analysis of 05.11.2021
- Patients with EBV+ PTLD undergoing solid organ transplantation (SOT) after rituximab plus chemotherapy (SOT-R-chemo cohort) or stem cell transplantation (HCT) after rituximab

Mortality

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	Median survival time in months [95% CI][a] *Patients with event n (%)*	N	Median survival time in months [95% CI][a] *Patients with event n (%)*
Overall survival	6	n.r. [2.6; n.r.] *1 (17)*	14	n.r. [1.5; n.r.] *5 (36)*
Overall survival rate		*Kaplan-Meier estimator [95% CI]*		*Kaplan-Meier estimator [95% CI]*
at month 12	6	83.3 [27.3; 97.5]	14	61.5 [30.8; 81.8]
at month 24	6	83.3 [27.3; 97.5]	14	n.r.

Morbidity

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)* [95% CI][b]	N	*Patients with event n (%)* [95% CI][b]
Overall response (ORR) assessed by central assessment (IORA) (presented additionally)[c]				
Best response Subjects with CR Subjects with PR Subjects with SD Subjects with PD not evaluable[d]	6	 2 (33) 3 (50) 0 1 (17) 0	14	 1 (7) 6 (43) 2 (14) 1 (7) 4 (29)
ORR (CR or PR)	6	5 (83) [36; 100]	14	7 (50) [23; 77]
Overall response (ORR) assessed by the investigators (presented additionally)[c]				
Best response Subjects with CR Subjects with PR Subjects with SD Subjects with PD not evaluable[d]	6	 3 (50) 2 (33) 0 1 (17) 0		 4 (29) 3 (21) 2 (14) 4 (29) 1 (7)
ORR (CR or PR)	6	5 (83) [36; 100]		7 (50) [23; 77]

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Graft loss	6	0	14	n.e.[e]
Rejection reaction	6	0	14	n.e.[e]
EQ-5D VAS	There are no usable data.			

Health-related quality of life

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*
FACT-Lym	There are no usable data.			

Side effects

Endpoint	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Total adverse events (presented additionally)	6	6 (100)		14 (100)
Serious adverse events (SAE)	6	5 (83)	14	8 (57)
Severe adverse events (CTCAE grade 3 or 4)	6	5 (83)	14	12 (86)
Therapy discontinuation due to adverse events	6	0	14	0

MedDRA system organ class[2] Preferred terms	Tabelecleucel			
	SOT-R-chemo cohort		HCT cohort	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Severe adverse events according to MedDRA				
Pneumonia	6	2 (33)	14	2 (14)
Neutropenia	6	-	14	1 (7)
Leukopenia	6	-	14	2 (14)
Loss of appetite	6	-	14	2 (14)
Hypoxia	6	-	14	3 (21)
SAEs according to MedDRA				
General disorders and administration site conditions	6	**1 (17)**	14	**2 (14)**
Gastrointestinal disorders	6	**3 (50)**	14	**-**
Infections and infestations	6	**3 (50)**	14	**5 (36)**
Pneumonia	6	2 (33)	14	1 (7)

a. For subjects who have survived the relevant data cut-off, the survival time at the last known point of survival time is censored. 95% CI of KM analysis using log-log transformation.
b. 95% CI calculated using the exact binomial method.
c. Primary endpoint of the EBV-CTL-201
d. Includes not evaluable, missing values and indeterminate response in subjects who are still in the study at the time of the data cut-off.
e. Graft loss and rejection reactions are only reported for the SOT cohort

Abbreviations used:
CR = complete remission; CTCAE = Common Terminology Criteria for Adverse Events; HCT = = haematopoietic cell transplant; IORA = Independent Oncologic Response Adjudication; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.e. = not evaluable; n.r. = not reported; n.r. = not reached; PD = disease progression; PR = partial remission; R-Chemo = rituximab plus chemotherapy; SD = stable disease; SOT = solid organ transplantation; vs = versus

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

Patients 2 years of age and older with Epstein-Barr virus positive post-transplant lymphomas (EBV+ PTLD) who have received at least one prior antineoplastic therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

approx. 7-30 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 Ebvallo (active ingredient: tabelecleucel) at the following publicly accessible link (last access: 26 September 2023):

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

For the use of the ATMP tabelecleucel in the present therapeutic indication, measures for quality-assured application were defined by resolution of 17 August 2023 "First version of Annex III – Tabelecleucel in EBV-positive post-transplant lymphomas". As soon as corresponding regulations according to the ATMP Quality Assurance Guideline come into force, they must also be observed.

Treatment with tabelecleucel should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with EBV-positive post-transplantation lymphoma.

This medicinal product was approved under “exceptional circumstances”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

4. Treatment costs

Annual treatment costs:

Patients 2 years of age and older with Epstein-Barr virus positive post-transplant lymphomas (EBV+ PTLD) who have received at least one prior antineoplastic therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tabelecleucel	€ 535,500 - € 2,142,000

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2023

Costs for additionally required SHI services: not applicable

5. Designations 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 medicinal product Tabelecleucel to be assessed

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:

Patients 2 years of age and older with Epstein-Barr virus positive post-transplant lymphomas (EBV+ PTLD) who have received at least one prior antineoplastic therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

– No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 5 October 2023.

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

Berlin, 5 October 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken