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 Pembrolizumab (new therapeutic indication: melanoma, adjuvant therapy)

of 19 September 2019

At its session on 19 September 2019, 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 following information shall be added after No. 4 to the information on the benefit assessment of pembrolizumab in accordance with the resolution of 20 June 2019:

Pembrolizumab

Resolution of: 19 September 2019
Entry into force on: 19 September 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 12 December 2018):

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection (see Section 5.1).

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adjuvant treatment of adult patients with Stage III melanoma and lymph node involvement who have undergone complete resection

Appropriate comparator therapy:

Monitoring wait-and-see approach

Extent and probability of the additional benefit of pembrolizumab compared with a monitoring wait-and-see approach:

Indication for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Adjuvant treatment of adult patients with Stage III melanoma and lymph node involvement who have undergone complete resection

KEYNOTE-054 study: Pembrolizumab **vs** placebo

Mortality

Endpoint	**Pembrolizumab**		**Placebo**[a]		Pembrolizumab vs placebo
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[b]
Overall survival					
At the time of the 1st and 2nd data cut-off, no evaluation was planned.[c]					

[1] Data from the dossier evaluation of the IQWiG (A19-29) unless otherwise indicated.

Morbidity

Endpoint	Pembrolizumab		Placebo		Pembrolizumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value Absolute difference (AD)[b]
Relapses[d,e] (2nd data cut-off 2 May 2018)					
	514	158 (30.7)	505	246 (48.7)	0.63 [0.54; 0.74][f] < 0.001[g] AD: −18.0%
Local/regional relapse	514	59 (11.5)	505	83 (16.4)	-[h]
Remote metastases	514	88 (17.1)	505	138 (27.3)	-[h]
Local/regional relapse and remote metastases[i]	514	9 (1.8)	505	24 (4.8)	-[h]
Death	514	2 (0.4)	505	1 (0.2)	-[h]
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[b]
Relapse-free survival	514	n.a. *158 (30.7)*	505	21.7 [17.1; n.c.] *246 (48.7)*	0.56 [0.44; 0.72][j] < 0.001[j,k] AD: n.c.
Symptomology - EORTC QLQ-C30 symptom scales					
	No usable data[l]				
Symptomology - EQ-5D VAS					
	No usable data[l]				

Health-related quality of life

EORTC QLQ-C30 functional scales and global health status scale
No usable data[l]

Side effects (1st data cut-off: 2 November 2017)

Endpoint	Pembrolizumab		Placebo		Pembrolizumab vs placebo
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[b]
Adverse events (AEs, presented additionally)					
	509	0.7 [0.7; 0.8] *475 (93.3)*	502	0.8 [0.7; 0.9] *453 (90.2)*	-
Serious adverse events (SAEs)					
	509	n.a. *128 (25.1)*	502	n.a. *82 (16.3)*	1.56 [1.18; 2.06][m] 0.002[k,m] AD: n.c.
Adverse events (CTCAE grade ≥ 3)					
	509	n.a. [14.0; n.c.] *158 (31.0)*	502	n.a. *96 (19.1)*	1.66 [1.29; 2.14][m] < 0.001[k,m] AD: n.c.
Discontinuation because of AEs					
	509	n.a. *70 (13.8)*	502	n.a. *18 (3.6)*	3.78 [2.25; 6.34][m] < 0.001[k,m] AD: n.c.
Specific AEs					
Immune-mediated AEs					
	509	n.a. [13.9; n.c.] *173 (34.0)*	502	n.a. *38 (7.6)*	5.15 [3.63; 7.32][m] < 0.001[k,m] AD: n.c.
Serious immune-mediated AEs					
	509	n.a. *42 (8.3)*	502	n.a. *3 (0.6)*	14.00 [4.34; 45.15][m] < 0.001[k,m] AD: n.c.

Immune-mediated AEs (CTCAE grade ≥ 3)					
	509	n.a. *36 (7.1)*	502	n.a. *3 (0.6)*	11.74 [3.62; 38.12][m] < 0.001[k,m] AD: n.c.
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][f] p value[g] Absolute difference (AD)[b]
Other specific AEs					
Infections and infestations (SOC, AE)	509	225 (44.2)	502	167 (33.3)	1.33 [1.13; 1.56] < 0.001 AD: + 10.9%
Skin and subcutaneous tissue disorders (SOC, AE)	509	272 (53.4)	502	198 (39.4)	1.35 [1.18; 1.55] < 0.001 AD: + 14.0 %
Xerostomia (PT, AE)	509	30 (5.9)	502	10 (2.0)	2.96 [1.46; 5.99] 0.001 AD: + 3.9%
Dyspepsia (PT, AE)	509	19 (3.7)	502	6 (1.2)	3.12 [1.26; 7.76] 0.010 AD: + 2.5%
Reduced appetite (PT, AE)	509	36 (7.1)	502	13 (2.6)	2.73 [1.47; 5.09] < 0.001 AD: + 4.5%
Pain of the muscular and skeletal system (PT, AE)	509	23 (4.5)	502	8 (1.6)	2.84 [1.28; 6.28] 0.007 AD: + 2.9%
Dyspnoea (PT, AE)	509	46 (9.0)	502	25 (5.0)	1.81 [1.13; 2.91] 0.012 AD: + 4.0%
General disorders and administration site conditions (SOC, SAE)	509	11 (2.2)	502	0 (0)	22.68 [1.34; 383.91] < 0.001 AD: + 2.2%
Gastrointestinal disorders	509	26 (5.1)	502	10 (2.0)	2.56 [1.25; 5.26]

(SOC, AE (CTCAE grade ≥ 3)					0.008 AD: + 3.1%
Respiratory, thoracic, and mediastinal disorders (SOC, AE [CTCAE grade ≥ 3])	509	10 (2.0)	502	2 (0.4)	4.93 [1.09; 22.39] 0.022 AD: + 1.6%

[a] Adequate approximation to the appropriate comparator therapy monitoring wait-and-see approach
[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[c] The KEYNOTE-054 study is still ongoing. In accordance with the study protocol, no interim analysis is foreseen for the overall survival endpoint. A final analysis is to be made after a total of 380 death events. At the time of the 1st data cut-off (2 October 2017), 25 patients in the pembrolizumab arm and 35 patients in the placebo arm had died.
[d] Proportion of patients with local/regional relapse, remote metastasis, or death of any cause, whichever occurred first (see Section 2.7.4.3.2); the individual components are shown in the lines below.
[e] At the time of the first data cut-off of 2 October 2017, 135 patients (26.8%) in the pembrolizumab arm and 216 patients (42.8%) in the placebo arm had a relapse: RR [95% CI]; p value: 0.61 [0.51; 0.73]; < 0.001.
[f] Calculation of the IQWiG
[g] Calculation of the IQWiG, unconditional exact test (CSZ method according to Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555–574.)
[h] No calculation of effect estimates. The events shown do not fully represent the endpoint. Only the events that come into play during the formation of the combined endpoint are shown.
[i] Patients had a local/regional relapse and remote metastases at the same time (diagnosis period within 30 days).
[j] Effect estimate HR and 95% confidence interval from Cox proportional hazard model with treatment as covariates stratified by disease stage (IIIA [metastases > 1 mm], IIIB, IIIC [1–3 positive lymph nodes], IIIC [≥ 4 positive lymph nodes]) at the time of randomisation.
[k] Wald p value
[l] There are no usable evaluations available; see Section 2.7.4.3.2 of the IQWiG dossier evaluation for reasons.
[m] From Cox proportional hazard model with treatment as covariates

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; EQ-5D: European Quality of Life-5 Dimensions; HR = hazard ratio; 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; PT = preferred term; SOC = system organ class; RR = relative risk; VAS = visual analogue scale; vs = versus

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

Adjuvant treatment of adult patients with Stage III melanoma and lymph node involvement who have undergone complete resection

approx. 2670–3400 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 Keytruda® (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 5 August 2019):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in skin and venereal diseases, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with melanomas.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on pembrolizumab:

- Training and information material for doctors/medical professionals
- Training and information material for the patient

4. Treatment costs

Annual treatment costs:

Adjuvant treatment of adult patients with Stage III melanoma and lymph node involvement who have undergone complete resection

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab	€ 103,757.46
Appropriate comparator therapy:	
Monitoring wait-and-see approach	not quantifiable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2019)

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17	€ 1,207

II. Entry into force

1. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 19 September 2019.

2. The period of validity of the resolution is limited to 1 April 2024.

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

Berlin, 19 September 2019

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

Prof Hecken