Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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:

Tucatinib (breast cancer, HER2-positive, at least 2 prior therapies, combination with trastuzumab and capecitabine)

of 2 September 2021

At its session on 2 September 2021, 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 on DD. 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 Tucatinib as follows:

Tucatinib

Resolution of: 02.09.2021
Entry into force on: 02.09.2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 11 February 2021):

TUKYSA is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.

Therapeutic indication of the resolution (resolution of 2 September 2021):

see therapeutic indication according to marketing authorisation.

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

Adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens

Appropriate comparator therapy for tucatinib in combination with trastuzumab and capecitabine:

- Therapy according to doctor's instructions

Extent and likelihood of additional benefit of Tucatinib in combination with trastuzumab and capecitabine compared with treatment according to doctor's instructions:

A hint of a considerable additional benefit

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Adult patients with HER2-positive, locally advanced or metastatic breast cancer who have received at least two prior HER2-targeted treatment regimens:

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↔	No relevant difference for the benefit assessment
Health-related quality of life	∅	There are no data.
Side effects	↔	No difference relevant for the benefit assessment in detail disadvantage in diarrhoea and advantage in dyspnoea
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		

HER2CLIMB study: Tucatinib + trastuzumab + capecitabine **vs** trastuzumab + capecitabine

Study design: ongoing, double-blind phase 2 RCT

Mortality

Endpoint	Tucatinib + trastuzumab + capecitabine		Trastuzumab + capecitabine		Intervention vs control
	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 (%)*	Effect estimator [95 % CII] [b] p-value Absolute difference (AD)[a]
Overall survival (data cut-off: 04 September 2019)					
	410	21.9 [18.3; 31.0] 130 (31.7)	202	17.4 [13.6; 19.9] 85 (42.1)	0.66 [0.50; 0.88] 0.005 AD: +4.5 months

[1] Data from the dossier assessment of the IQWiG (A21-26) and from the addendum (A21-102), unless otherwise indicated.

Morbidity

Endpoint	Tucatinib + trastuzumab + capecitabine		Trastuzumab + capecitabine		Intervention vs control
	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 (%)*	Effect estimator [95 % CII] [b] p-value Absolute difference (AD)[a]
Progression-free survival (PFS) (data cut-off: 04.09.2019)[g]					
	410	8.1 [7.6; 9.6] 198 (48.3)	202	5.5 [4.3; 6.9] 112 (55.4)	0.535 [0.420; 0.682] <0.0001 AD: +2.6 months
Health status (EQ-5D VAS) (data cut-off: 04 September 2019)					
≥ 7 points	217	n.a. [7.6; n.c.] 73 (33.6)	112	5.8 [4.3; n.c.] 42 (37.5)	0.81 [0.55; 1.18] 0.261
≥ 10 points	217	n.a. [7.7; n.c.] 71 (32.7)	112	6.7 [4.3; n.c.] 40 (35.7)	0.82 [0.56; 1.21] 0.313

Health-related quality of life

No data on health-related quality of life were assessed in the HER2CLIMB study.

Side effects (data cut-off: 04 September 2019)

Endpoint	Tucatinib + trastuzumab + capecitabine		Trastuzumab + capecitabine		Intervention vs control
	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 (%)*	Effect estimator [95 % CII] [b] p-value Absolute difference (AD)[a]
Total adverse events (presented additionally)[c]					
	404	0.13 [0.13; 0.16][d] 401 (99.3)	197	0.26 [0.20; 0.33][d] 191 (97.0)	-
Endpoint	**Tucatinib + trastuzumab + capecitabine**		**Trastuzumab + capecitabine**		Intervention vs control

	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 (%)*	Effect estimator [95 % CII] [b] p-value Absolute difference (AD)[a]
Serious adverse events (SAE) [c]					
	404	30.94 [21.39; n.c.][d] 104 (25.7)	197	n.a. [11.04; n.c.][d] 53 (26.9)	0.81 [0.58; 1.14] 0.232
Severe adverse events (CTCAE grade 3 or 4)[c]					
	404	4.80 [3.55; 7.98][d] 223 (55.2)	197	9.03 [4.14; 10.45][d] 96 (48.7)	1.10 [0.87; 1.41] 0.427
Therapy discontinuation due to adverse events[e]					
	404	n.a. 45 (11.1)	197	18.20 [16.26; n.c.][d]	0.95 [0.55; 1.64] 0.846
Specific adverse events					
Gastrointestinal disorders (SOC, AEs)	404	0.23 [0.20; 0.26] 382 (94.6)	197	0.49 [0.43; 0.72] 162 (82.2)	1.91 [1.57; 2.31] < 0.001 AD: -0.26 months
Diarrhoea (PT, AEs)	404	0.49 [0.43; 0.53] 327 (80.9)	197	3.48 [2.14; 6.01] 105 (53.3)	2.39 [1.92; 2.99] <0.001 AD: -2.99 months
Alanine aminotransferase elevated (PT, severe AEs)	404	n.a. 22 (5.4)	197	n.a. 1 (0.5)	10.62 [1.43; 78.79] 0.021[f]
Aspartate aminotransferase elevated (PT, severe AEs)	404	n.a. 18 (4.5)	197	n.a. 1 (0.5)	8.81 [1.18; 65.94] 0.034[f]
Dyspnoea (PT, severe AEs)	404	n.a. 7 (1.7)	197	n.a. 10 (5.1)	0.31 [0.12; 0.83] 0.019[f]

[a] Absolute difference (AD) is given only in the case of a statistically significant difference; own calculation
[b] HR and CI: Cox-Proportional-Hazards-Model; p-value: log-rank test; each stratified by brain metastases at start of study (yes vs no), ECOG-PS (0 vs 1), and region (North America vs rest of the world)
[c] AEs excluding events attributed to progression of the underlying disease according to the pharmaceutical company (not including PTs "cancer pain", "tumour pain", "malignant pleural effusion" and "tumour thrombosis" from SOC "Neoplasms benign, malignant and unspecified [incl cysts and polyps]").
[d] Calculation by IQWiG
[e] Discontinuation ≥ 1 active ingredient component
[f] without stratification factors
[n] Information from the dossier of the pharmaceutical company

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; 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; pU = pharmaceutical company; RCT = randomised controlled trial; SOC = system organ class; vs = versus

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

approx. 1,350 to 1,640 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 Tukysa (active ingredient: tucatinib) at the following publicly accessible link (last access: 2 June 2021):
https://www.ema.europa.eu/documents/product-information/tukysa-epar-product-information_de.pdf

Treatment with tucatinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, obstetrics and gynaecology, and specialists participating in the Oncology Agreement are experienced in the treatment of adults with breast cancer.

4. Treatment costs

Annual treatment costs:

Adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	

Designation of the therapy	Annual treatment costs/patient
Tucatinib	€ 131,492.99
Capecitabine	€ 2,374.25
Trastuzumab	€ 36,433.48
Total:	€ 170,300.72
Appropriate comparator therapy:	
Therapy according to doctor's instructions[a]	
Lapatinib in combination with capecitabine	
Lapatinib	€ 40,974.38
Capecitabine	€ 2,374.25
Total:	€ 43,348.63
Lapatinib in combination with trastuzumab (only for patients with hormone-receptor negative breast cancer)	
Lapatinib	€ 32,779.50
Trastuzumab	€ 39,598.26
Total:	€ 72,377.76
[a] Only costs for lapatinib in combination with capecitabine and lapatinib in combination with trastuzumab are shown. In addition, trastuzumab in combination with cepacitabine represents a suitable comparator for the present benefit assessment in the context of therapy according to the doctor's instructions. However, this medicinal product therapy is not authorised for the present therapeutic indication, and therefore no costs are presented for these medicinal products.	

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 August 2021)

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Trastuzumab (in combination	Surcharge for the preparation of	€ 71	1	17.4	€ 1,235.40

with tucatinib and capecitabine)	a parenteral solution containing monoclonal antibodies				
Trastuzumab (in combination with lapatinib)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	52.1	€ 3,699.10

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 2 September 2021.

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

Berlin, 2 September 2021

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

Prof. Hecken