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 Trastuzumab deruxtecan (new therapeutic indication: breast cancer, HER2+, after 1 prior therapy)

of 2 February 2023

At its session on 2 February 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. **In Annex XII, the following information is added after no. 4 to the information on the benefit assessment of Trastuzumab deruxtecan according to the resolution of 2 February 2023 on the therapeutic indication "unresectable or metastatic HER2-positive breast cancer, after two or more prior anti-HER2-based regimens":**

Trastuzumab deruxtecan

Resolution of: 2 February 2023
Entry into force on: 2 February 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 11 July 2022):

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

Therapeutic indication of the resolution (resolution of 2 February 2023):

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one prior anti-HER2-based regimen.

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

Adults with HER2-positive unresectable or metastatic breast cancer previously treated with one anti-HER2 based therapy

Appropriate comparator therapy:

- Trastuzumab emtansine

Extent and probability of the additional benefit of trastuzumab deruxtecan compared to trastuzumab emtansine:

Indication of non-quantifiable additional benefit

Study results according to endpoints:[1]

[1] Data from the dossier assessment of the IQWiG (A22-80) and from the addendum (A22-126), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	↔	Advantages for symptoms in the arm region, disadvantages for nausea and vomiting, appetite loss and diarrhoea. Overall, no relevant difference.
Health-related quality of life	↔	Advantages in role functioning and cognitive functioning, disadvantages in body image. Overall, no relevant difference.
Side effects	↑	Advantages in the endpoints SAE and severe AEs (CTCAE grade 3 or 4)

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.c.: not calculable

DESTINY-Breast03 study: Trastuzumab deruxtecan **vs** trastuzumab emtansine
Study design: open-label, randomised, controlled
Data cut-off from 25 July 2022

Mortality

Endpoint	Trastuzumab deruxtecan		Trastuzumab emtansine		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio[a] [95% CI] p value Absolute difference (AD)[b]
Overall survival					
	261	n.a. [40,5: n.c.] *72 (27.6)*	263	n.a. [34.0; n.c.] *97 (36.9)*	0.64 [0.47; 0.87] 0.004
Effect modification by the characteristic age					
< 65 years	212	n.a. [40.5; n.c.] *55 (25.9)*	206	37.7 [30.7; n.c.] *81 (39.3)*	0.54 [0.39; 0.77] <0.001
≥ 65 years	49	n.a. [26.3; n.c.] *17 (34.7)*	57	n.a. *16 (28.1)*	1.29 [0.65; 2.56] 0.463
				Interaction:	0.026

Morbidity

Progression-free survival (PFS)[c]					
	261	28.8 [22.4; 37.9] *117 (44.8)*	263	6.8 [5.6; 8.2] *171 (62.4)*	0.33 [0.26; 0.43]; < 0.000001 AD = 22 months
Symptomatology (EORTC QLQ-C30; time to first deterioration)					
Fatigue	261	5.6 [3.0; 9.9] *162 (62.1)*	263	3.6 [2.8; 5.5] *157 (59.7)*	0.83 [0.67; 1.04]; 0.103
Nausea and vomiting	261	2.8 [1.6; 3.0] *196 (75.1)*	263	9.7 [8.3; 13.9] *118 (44.9)*	1.99 [1.58; 2.51]; < 0.001 AD = 6.9 months
Pain	261	8.5 [5.6; 14.5] *153 (58.6)*	263	6.9 [5.3; 9.8] *138 (52.5)*	0.88 [0.70; 1.12]; 0.297
Dyspnoea	261	23.3 [16.6; n.c.] *116 (44.4)*	263	15.2 [11.7; 31.8] *103 (39.2)*	0.85 [0.65; 1.12]; 0.237
Insomnia	261	19.4 [10.7; n.c.] *129 (49.4)*	263	12.7 [7.2; n.c.] *115 (43.7)*	0.89 [0.69; 1.15]; 0.367
Appetite loss	261	4.2 [2.9; 5.6] *166 (63.6)*	263	10.3 [6.6; 20.5] *119 (45.2)*	1.41 [1.11; 1.79]; 0.006 AD = 6.1 months
Constipation	261	5.6 [4.2; 8.3] *160 (61.3)*	263	8.5 [5.7; 12.9] *125 (47.5)*	1.24 [0.98; 1.57]; 0.077
Diarrhoea	261	27.6 [17.1; n.c.] *116 (44.4)*	*263*	n.a. [22.4; n.c.] *67 (25.5)*	1.69 [1.24; 2.29]; < 0.001
Symptomatology (EORTC QLQ-BR23; time to first deterioration)					
Side effects of systemic therapy	261	5.7 [4.3; 11.0] *153 (58.6)*	263	11.7 [8.3; 17.0] *115 (43.7)*	1.23 [0.96; 1.58]; 0.094
Chest symptoms	261	n.a. [36.8; n.c.] *67 (25.7)*	263	30.9 [27.9; n.c.] *58 (22.1)*	0.84 [0.59; 1.20]; 0.340
Arm symptoms	261	10.3 [7.7; 16.7] *147 (56.3)*	263	5.6 [4.2; 9.0] *139 (52.9)*	0.78 [0.62; 0.99]; 0.037 AD = 4.7 months
Burden due to hair loss	No usable data available[d]				
Health status (EQ-5D VAS – Time to first deterioration)					
	261	31.5 [21.7; n.c.] *103 (39.5)*	263	15.2 [12.0; n.c.] *96 (36.5)*	0.79 [0.59; 1.05]; 0.105

Health-related quality of life

EORTC QLQ-C30 – Time to first deterioration					
Global health status	261	6.9 [4.4; 10.4] *157 (60.2)*	263	7.2 [5.7; 10.3] *137 (52.1)*	1.00 [0.80; 1.27]; 0.993

Physical functioning	261	22.0 [14.5; 31.5] *122 (46.7)*	263	17.2 [8.3; n.c.] *105 (39.9)*	0.91 [0.70; 1.19]; 0.487
Role functioning	261	11.6 [6.2; 21.7] *144 (55.2)*	263	6.3 [4.7; 8.9] *142 (54.0)*	0.75 [0.59; 0.96]; 0.019 AD = 5.3 months
Emotional functioning	261	18.5 [13.0; 24.9] *127 (48.7)*	263	11.1 [8.4; 15.2] *112 (42.6)*	0.78 [0.60; 1.02]; 0.064
Cognitive functioning	261	10.3 [8.6; 14.8] *152 (58.2)*	263	8.3 [4.8; 10.3] *136 (51.7)*	0.78 [0.62; 1.00]; 0.045 AD = 2 months
Social functioning	261	7.3 [5.6; 11.8] *156 (59.8)*	263	8.4 [5.8; 11.7] *132 (50.2)*	0.99 [0.78; 1.25]; 0.893
EORTC QLQ-BR23 – Time to first deterioration					
Body image	261	16.6 [10.7; 32.2] *127 (48.7)*	263	31.2 [13.6; n.c.] *83 (31.6)*	1.34 [1.01; 1.78]; 0.040 AD = 14.6 months
Sexual activity	261	n.a. *62 (23.8)*	263	n.a. *57 (21.7)*	0.93 [0.65; 1.34]; 0.717
Sex pleasure	No usable data available[d]				
Future prospects	261	32.5 [28.6; n.c.] *97 (37.2)*	263	n.a. [21.2; n.c.] *74 (28.1)*	1.02 [0.75; 1.38]; 0.917

Side effects

Endpoint	**Trastuzumab deruxtecan**		**Trastuzumab emtansine**		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio[e] [95% CI] p value Absolute difference (AD)[b]
Total adverse events (presented additionally) [e]					
	257	0.1; [n.c.] *256 (99.6)*	261	0.2 [0.1; 0.2] *249 (95.4)*	–
Serious adverse events (SAE) [e]					
	257	n.a. *65 (25.3)*	261	27.4 [22.7; n.c.] *58 (22.2)*	0.65 [0.45; 0.95]; 0.024
Severe adverse events (CTCAE grade 3 or 4) [e]					
	257	11.0 [7.0; 16.6] *145 (56.4)*	261	8.0 [4.2; 13.1] *135 (51.7)*	0.77 [0.61; 0.98]; 0.040 AD = 3 months

Therapy discontinuations due to adverse events [e]					
	257	n.a. [38.2; n.c.] *55 (21.4)*	261	n.a. *24 (9.2)*	1.19 [0.73; 1.94]; 0.493
Specific adverse events					
Cardiac disorders (SOC, severe AEs)	257	n.d. *0 (0)*	261	n.d. *0 (0)*	–
Thrombocytopenia (PT, severe AEs)	257	n.a. *20 (7.8)*	261	n.a. *52 (19.9)*	0.32 [0.19; 0.54]; < 0.001
Gastrointestinal disorders (SOC, AEs)	257	0.1 [0.1; 0.1] *239 (93.0)*	261	2.8 [1.4; 6.5] *152 (58.2)*	2.87 [2.33; 3.54]; < 0.001 AD = 2.7 months
Skin and subcutaneous tissue disorders (SOC, AEs)	257	6.0 [2.9; 14.3] *155 (60.3)*	261	15.1 [12.5; n.c.] *77 (29.5)*	2.07 [1.57; 2.72]; < 0.001 AD = 9.1 months
Nosebleeds (PT, AEs)	257	n.a. *35 (13.6)*	261	n.a. [21.8; n.c.] *46 (17.6)*	0.42 [0.26; 0.66]; < 0.001
Pyrexia (PT, AEs)	257	n.a. *39 (15.2)*	261	n.a. [28.4; n.c.] *42 (16.1)*	0.46 [0.29; 0.74]; < 0.001
Malaise (PT, AEs)	257	n.a. *30 (11.7)*	261	n.a. *9 (3.4)*	2.99 [1.41; 6.34]; 0.003
General disorders and administration site conditions (SOC, severe AEs)	257	n.a. *31 (12.1)*	261	n.a. *5 (1.9)*	4.23 [1.63; 11.03]; 0.001
Neutropenia (PT, severe AEs)	257	n.a. *41 (16.0)*	261	n.a. *8 (3.1)*	3.90 [1.82; 8.39]; < 0.001
Leukopenia (PT, severe AEs)	257	n.a. *16 (6.2)*	261	n.a. *2 (0.8)*	5.48 [1.25; 24.02]; 0.011
Alanine aminotransferase increased (PT, severe AEs)	257	n.a. *4 (1.6)*	261	n.a. *12 (4.6)*	0.31 [0.10; 0.96]; 0.031
Aspartate aminotransferase increased (PT, severe AEs)	257	n.a. *2 (0.8)*	261	n.a. *14 (5.4)*	0.12 [0.03; 0.55] 0.001
Fatigue (PT, severe AEs)	257	n.a. *15 (5.8)*	261	n.a. *2 (0.8)*	5.28 [1.19; 23.48]; 0.015
Nausea (PT, severe AEs)	257	n.a. *18 (7.0)*	261	n.a. *1 (0.4)*	17.02 [2.27; 127.73]; < 0.001

[a] Hazard ratio calculated using a stratified Cox proportional hazards regression model and the 95 % CI using the Wald test. Two-sided p-value based on a stratified log-rank test. Stratification factors were hormone-receptor status, prior treatment with pertuzumab and history of visceral disease

[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation

[c] Information from the dossier of the pharmaceutical company; PFS according to BICR

[d] Unclear proportion of patients with missing values at the start of the study and during the course of the study, until 1st. data collection time point drastically decreasing percentage in the evaluation

[e] The pharmaceutical company submits evaluations including progression of the underlying disease for endpoints of the category side effects

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; n.d. = no data available; 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; QLQ-BR23 = Quality of Life Questionaire – Breast Cancer 23; QLQ-C30 = Quality of Life Questionnaire – Core 30; SOC = system organ class; AE = adverse event; VAS = visual analogue scale; vs = versus

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

approx. 3,370 – 3,750 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 Enhertu (active ingredient: trastuzumab deruxtecan) at the following publicly accessible link (last access: 17 November 2022):

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

Treatment with trastuzumab deruxtecan should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with breast cancer, as well as specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Trastuzumab deruxtecan	€ 151,314.58
Appropriate comparator therapy:	
Trastuzumab emtansine	€ 78,742.48

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

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Trastuzumab deruxtecan	Surcharge for production of parenteral solutions	€ 100	1	17.4	€ 1,740
Trastuzumab emtansine	Surcharge for production of parenteral solutions	€ 100	1	17.4	€ 1,740

5. 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 Trastuzumab deruxtecan

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with trastuzumab deruxtecan for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who have received one prior anti-HER2-based regimen:

Adults with HER2-positive unresectable or metastatic breast cancer previously treated with one anti-HER2 based therapy

- 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 2 February 2023.

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

Berlin, 2 February 2023

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

Prof. Hecken