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 Trifluridine/Tipiracil (New Therapeutic Indication: Metastatic Gastric Carcinoma, Pretreated Patients)

of 2 April 2020

On 2 April 2020, the Federal Joint Committee (G-BA) resolved by written statement 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 trifluridine/tipiracil in accordance with the resolution of 2 February 2017, last amended on 5 July 2018:

Trifluridine/tipiracil

Resolution of: 2 April 2020
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 3 September 2019):

Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease (see section 5.1).

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

Adult patients with metastatic gastric cancer, including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease

Appropriate comparator therapy:

Best supportive care

Extent and probability of the additional benefit of trifluridine/tipiracil compared with best supportive care:

Indication of a minor additional benefit

Study results according to endpoints[1]:

TAS-102-302 (TAGS) study

Trifluridine/tipiracil + best supportive care vs placebo + best supportive care

Study design: randomised, double-blind, Phase III

Data cut-off: 31 March 2018 (unless otherwise indicated)

Mortality

Endpoint	**Trifluridine/tipiracil + best supportive care**		**Placebo + best supportive care**		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 (%)*	Hazard ratio[a] [95% CI] p value[b] Absolute difference (AD)[c]
Overall survival[d]					
	337	5.7 [4.8; 6.2] *244 (72.4)*	170	3.6 [3.1; 4.1] *140 (82.4)*	0.69 [0.56; 0.855] < 0.001 AD: 2.1 months

Morbidity

Progression-free survival (PFS)[e]					
	337	2.0 [1.9; 2.3] *287 (85.2)*	170	1.8 [1.7; 1.9] *156 (91.8)*	0.5723 [0.4674; 0.7008] < 0.0001 AD: 0.2 months
Symptomatology					
EORTC QLQ-C30 symptom scales and EORTC QLQ-STO22					
No usable data					

Health-related quality of life

EORTC QLQ-C30 functional scales
No usable data

(Continuation)

[1] Data from the dossier evaluation of the IQWiG (A19-85) unless otherwise indicated.

Side effects[f]

Endpoint	Trifluridine/tipiracil + best supportive care		Placebo + best supportive care		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 (%)*	Hazard ratio[a] [95% CI] p value[b] Absolute difference (AD)[c]
Total adverse events (presented additionally)					
	335	0.5 [0.4; 0.5] *326 (97.3)*	168	0.5 [0.3; 0.5] *157 (93.5)*	-
Serious adverse events (SAE)					
	335	4.9 [4.0; 10.7] *143 (42.7)*	168	n.a. [2.5; n.c.] *70 (41.7)*	0.81 [0.61; 1.08] 0.152
Effect modification by the characteristic region					
EU member states	179	4.6 [3.8; 10.7] *79 (44.1)*	96	2.5 [1.4; n.c.] *49 (51.0)*	0.60 [0.42; 0.87] 0.007[g] AD: 2.1 months
Rest of the world	156	5.4 [3.9; 12.1] *64 (41.0)*	72	n.a. *21 (29.2)*	1.26 [0.77; 2.07] 0.352[g]
				Interaction:	p = 0.022[h]
Severe adverse events (CTCAE grade ≥ 3)					
	335	1.5 [1.3; 1.8] *267 (79.7)*	168	1.8 [1.4; 3.1] *97 (57.7)*	1.40 [1.11; 1.77] 0.004 AD: 0.3 months

(Continuation)

Effect modification by the characteristic region					
EU member states	179	1.5 [1.2; 1.9] *143 (79.9)*	96	1.4 [1.0; 2.3] *62 (64.6)*	1.12 [0.83; 1.52] 0.453[g]
Rest of the world	156	1.6 [1.3; 1.9] *124 (79.5)*	72	3.6 [1.6; n.c.] *35 (48.6)*	1.99 [1.36; 2.90] < 0.001[g] AD: 2.0 months
				Interaction:	p = 0.020[h]
Therapy discontinuation because of adverse events					
	335	n.a. [11.3; n.c.] *43 (12.8)*	168	n.a. *28 (16.7)*	0.58 [0.36; 0.94] 0.026 AD: n.c.
Specific adverse events					
Anaemia (PT, severe AE [CTCAE grade ≥ 3])	335	n.a. [9.9; n.c.] *63 (18.8)*	168	n.a. *13 (7.7)*	1.83 [1.00; 3.35] 0.046 AD: n.c.
Neutropenia (PT, severe AE [CTCAE grade ≥ 3])	335	n.a. [8.6; n.c.] *78 (23.3)*	168	n.a. *0 (0)*	n.c. < 0.001 AD: n.c.
Leukopenia (PT, severe AE [CTCAE grade ≥ 3])	335	n.a. *23 (6.9)*	168	n.a. *0 (0)*	n.c. 0.002 AD: n.c.
Gastrointestinal disorders (SOC severe AE [CTCAE grade ≥ 3])	335	n.a. [12.1; n.c.] *70 (20.9)*	168	n.a. *48 (28.6)*	0.61 [0.42; 0.89] 0.009 AD: n.c.
Skin and subcutaneous tissue disorders (SOC, AE)	335	12.5 [12.5; n.c.] *46 (13.7)*	168	n.a. *8 (4.8)*	2.57 [1.21; 5.46] 0.011 AD: n.c.

(Continuation)

General disorders and administration site conditions (SOC, severe AE [CTCAE grade ≥ 3])	335	n.a. *59 (17.6)*	168	9.1 [9.1; n.c.] *36 (21.4)*	0.64 [0.42; 0.98] 0.037 AD: n.c.

a Hazard ratio, confidence interval (CI): Cox Proportional Hazards Model
b p value: Log-rank test; stratified by region [Japan vs rest of the world], the ECOG-PS (0 vs 1), and a pretreatment with ramucirumab (yes vs no)
c Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.
d Data cut-off: 27 March 2018; 253 (75.1%) patients in the intervention arm vs 142 (83.5%) in the placebo arm had died on the data cut-off of 30 April 2018. Median overall survival was 5.6 [4.7; 6.1] months in the intervention arm vs 3.6 [3.1; 4.1] in the placebo arm; HR [95% CI]: 0.71 [0.57; 0.87]; p = 0.001.
e Information from the dossier of the pharmaceutical company
f Details with recording of events that can be assigned to the progress of the underlying disease.
g Testing for treatment effect in the sub-groups: Log-rank test (stratified by region [Japan vs rest of the world], the ECOG-PS [0 vs 1], and a pretreatment with ramucirumab [yes vs no])
h Interaction testing: Cox Proportional Hazards Model (unstratified) with corresponding interaction term

Abbreviations used:

AD: Absolute difference; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Stomach 22; CI: confidence interval; n: number of patients with (at least one) event; N: number of patients evaluated; n.c: not calculable; n.a.: not achieved; PT: preferred term; SOC: system organ class; AE: adverse event; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	n.a.	not assessable
Health-related quality of life	n.a.	not assessable
Side effects	↔	Advantage in the endpoint therapy discontinuation because of AE; disadvantage in the endpoint severe AE (CTCAE grade ≥ 3)

Explanations:
↑: positive statistically significant and relevant effect with low/unclear reliability of data
↓: negative statistically significant and relevant effect with low/unclear reliability of data
↑↑: positive statistically significant and relevant effect with high reliability of data
↓↓: negative statistically significant and relevant 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

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

approx. 590 to 1030 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 Lonsurf® (active ingredient combination: trifluridine/tipiracil) at the following publicly accessible link (last access: 18 March 2020):

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

Treatment with trifluridine/tipiracil should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and gastroenterology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with gastric cancer.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed	
Trifluridine/ tipiracil	€ 43,985.80
Best supportive care	different for each individual patient
Appropriate comparator therapy	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 2 April 2020.

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

Berlin, 2 April 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken