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 (Reassessment after the Deadline: Metastatic Colorectal Cancer)

of 1 October 2020

At its session on 1 October 2020 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 will be amended as follows:

1. The information on trifluridine/tipiracil as amended by the resolution of 2 February 2017 (Federal Gazette, BAnz AT 13 March 2017 B3) last amended on 5 July 2018 (Federal Gazette, BAnz AT 2 August 2018 B3) is hereby repealed.

2. 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 April 2020:

Trifluridine/Tipiracil

Resolution of: 1 October 2020
Entry into force on: 1 October 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 25 April 2016):

Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

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

Adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

Appropriate comparator therapy:

Best supportive care

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

Hint for a minor additional benefit.

Study results according to endpoints:[1]

RECOURSE study (RCT): Trifluridine/tipiracil **vs** best supportive care

TERRA study (RCT): Trifluridine/tipiracil **vs** best supportive care (relevant sub-population: patients who have been pre-treated in accordance with the marketing authorisation after European marketing authorisation (mITT))

[1] Data from the dossier assessment of the IQWiG (A20-35) and the addendum (A20-72) unless otherwise indicated.

Endpoint **Study**	**Trifluridine/tipiracil + BSC**		**BSC**		**Trifluridine/tipiracil +BSC vs BSC**
	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)[s]
Mortality					
Overall survival (OS)					
RECOURSE[a]	534	7.2 [6.6; 7.8] 463 (86.7)	266	5.2 [4.6; 5.9] 249 (93.6)	0.69 [0.59; 0.81] < 0.001[b] AD: 2.0 months
TERRA[c]	61	8.0 [6.3; 9.2] 53 (86.9)	33	4.4 [3.2; 7.2] 29 (87.9)	0.69 [0.43; 1.10] 0.118[d]
Total					0.70 [0.60; 0.81] < 0.001[e]
Morbidity					
Progression-free survival (PFS)[t]					
RECOURSE	534	2.0 [1.9; 2.1] 496 (92.9)	266	1.7 [1.7; 1.8] 254 (95.5)	0.49 [0.42; 0.58] < 0.001 AD: 0.3 months
TERRA	61	2.2 [1.9; 3.5] 58 (95.1)	33	1.8 [1.7; 1.9] 27 (81.8)	0.46 [0.28; 0.75] 0.002 AD: 0.4 months
Total					0.48 [0.41; 0.56] < 0.001
Health-related quality of life					
No usable data					

(Continuation)

Endpoint With/without progression or manifestation of specific AEs Study	**Trifluridine/tipiracil**		**BSC**		**Trifluridine/tipiracil +BSC vs BSC**
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value
Side effects					
Adverse events in total					
With progression of the underlying disease					
RECOURSE[a]	533	0.2 [0.2; 0.3] 524 (98.3)	265	0.4 [0.3; 0.4] 249 (94.0)	–
TERRA[f]	61	0.4 [0.3; 0.4] 61 (100)	33	0.4 [0.2; 0.9] 29 (87.9)	–
Without progression of the underlying disease[g]					
RECOURSE[a]	553	0.3 [0.2; 0.3] 520 (97.6)	265	0.4 [0.4; 0.4] 244 (92.1)	–
Serious adverse events (SAE)					
With progression of the underlying disease					
RECOURSE[a]	533	11.6 [8.7; n.a.] 162 (30.4)	265	5.4 [5.1; n.a.] 89 (33.6)	0.72 [0.55; 0.94]; 0.014[b]
TERRA[f]	61	n.a. [n.a.; n.a.] 15 (24.6)	33	n.a. [n.a.; n.a.] 12 (36.4)	0.53 [0.25; 1.14]; 0.098[d]
Total					0.69 [0.54; 0.89]; 0.004[e]
Without progression of the underlying disease[g]					
RECOURSE[a]	553	n.a. [n.a.; n.a.] 118 (22.1)	265	n.a. [n.a.; n.a.] 45 (17.0)	1.02 [0.72; 1.45]; 0.904[b]
Severe adverse events (CTCAE grade ≥ 3)					
With progression of the underlying disease					
RECOURSE[a]	533	1.5 [1.3; 1.8] 372 (69.8)	265	2.5 [2.0; 3.3] 138 (52.1)	1.44 [1.18; 1.77] < 0.001[b]
TERRA[f]	61	2.3 [1.9; 6.1] 34 (55.7)	33	1.4 [0.5; n.a.] 18 (54.5)	0.75 [0.42; 1.35]; 0.342[d]
Total					1.36 [1.12; 1.64]; 0.002[e]
Without progression of the underlying disease[g]					
RECOURSE[a]	533	1.8 [1.6; 2.0] 343 (64.4)	265	3.8 [2.8; 18.6] 110 (41.5)	1.74 [1.40; 2.17]; < 0.001[b]

Endpoint With/without progression or manifestation of specific AEs Study	Trifluridine/tipiracil		BSC		Trifluridine/tipiracil + BSC vs BSC
	N	Median in months [95% CI] *Patients with event* *n (%)*	**N**	Median in months [95% CI] *Patients with event* *n (%)*	HR [95% CI] p value
Side effects(continued)					
Therapy discontinuation because of adverse events					
With progression of the underlying disease					
RECOURSE[a]	533	n.a. [n.a.; n.a.] 57 (10.7)	265	n.a. [n.a.; n.a.] 36 (13.6)	0.63 [0.41; 0.96]; 0.030[b]
TERRA[f]	61	n.a. [n.a.; n.a.] 5 (8.2)	33	n.a. [n.a.; n.a.] 7 (21.2)	0.36 [0.12; 1.15]; 0.072[d]
Total					0.59 [0.39; 0.87]; 0.009[e]
Without progression of the underlying disease[g]					
RECOURSE[a]	533	n.a. [n.a.; n.a.] 16 (3.0)	265	n.a. [n.a.; n.a.] 4 (1.5)	1.64 [0.54; 4.98]; 0.376[b]
Specific adverse events					
Gastrointestinal toxicity, operationalised as gastrointestinal disorders (SOC, AE)[h]					
RECOURSE[a]	533	0.5 [0.4; 0.5] 414[k] (77.7)	265	1.5 [1.1; 1.9] 162[k] (61.1)	1.62 [1.34; 1.95][i]; < 0.001[j]
TERRA[f]	61	1.0 [0.4; 1.3] 43 (70.5)	33	1.8 [1.5; 5.1] 20 (60.6)	1.49 [0.85; 2.59][i]; 0.159[j]
Total					1.56 [1.31; 1.86]; < 0.001[e]
Diarrhoea (PT, AE)[h, l]					
RECOURSE[a]	533	10.3 [7.7; 18.2] 173 (32.5)	265	n.a. [n.a.; n.a.] 33 (12.5)	2.58 [1.78; 3.76][i]; < 0.001[j]
TERRA[f]	61	n.a. [n.a.; n.a.] 9 (14.8)	33	5.1 [5.1; n.a.] 3 (9.1)	1.42 [0.38; 5.31][i]; 0.598[j]
Total					2.50 [1.75; 3.59]; < 0.001[e]
Nausea (PT, AE)[h, l]					
RECOURSE[a]	533	3.4 [2.2; 13.5] 261 (49.0)	265	17.7 [n.a.; n.a.] 64 (24.2)	2.38 [1.81; 3.14][i]; < 0.001[j]
TERRA[f]	61	5.3 [1.3; n.a.] 28 (45.9)	33	n.a. [n.a.; n.a.] 5 (15.2)	3.47 [1.34; 9.00][i]; 0.006[j]

Endpoint With/without progression or manifestation of specific AEs Study	Trifluridine/tipiracil		BSC		Trifluridine/tipiracil + BSC vs BSC
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value
Side effects(continued)					
Nausea (PT, AE)[h, l]					
Total					2.41 [1.85; 3.14]; < 0.001[e]
Vomiting (PT, AE)[h]					
RECOURSE[a]	533	n.a. [n.a.; n.a.] 151 (28.3)	265	17.7 [n.a.; n.a.] 39 (14.7)	1.93 [1.35; 2.77][i]; < 0.001[j]
TERRA[f]	61	n.a. [n.a.; n.a.] 15 (24.6)	33	n.a. [n.a.; n.a.] 6 (18.2)	1.26 [0.48; 3.29][i]; 0.633[j]
Total					1.78 [1.28; 2.49]; < 0.001[e]
Myelosuppression, operationalised as blood and lymphatic system disorders (SOC, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	6.9 [4.7; 9.7] 193 (36.2)	265	n.a. [n.a.; n.a.] 11 (4.2)	8.77 [4.77; 16.13][i]; < 0.001[j]
TERRA[f]	61	n.a. [n.a.; n.a.] 17 (27.9)	33	n.a. [n.a.; n.a.] 5 (15.2)	1.57 [0.57; 4.30][i]; 0.377[j]
Total					5.57 [3.30; 9.38]; < 0.001[e]
Anaemia (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	17.9 [15.8; n.a.] 92 (17.3)	265	n.a. [n.a.; n.a.] 7 (2.6)	5.49 [2.53; 11.89][i]; < 0.001[j]
TERRA[f]	61	n.a. [n.a.; n.a.] 7 (11.5)	33	n.a. [n.a.; n.a.] 5 (15.2)	0.70 [0.22; 2.22][i]; 0.546[j]
Total					2.97 [1.56; 5.65]; 0.004[e]
Febrile neutropoenia (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	n.a. [n.a.; n.a.] 21 (3.9)	265	n.a. [n.a.; n.a.] 0 (0.0)	RR: 21.42 [1.30; 352.23] 0.001[m]
TERRA[f]	61	no data available	33	no data available	no data available
Leukopenia (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	n.a. [n.a.; n.a.] 15 (2.8)	265	n.a. [n.a.; n.a.] 0 (0.0)	RR: 15.44 [0.93; 257.08] 0.006[m]

Endpoint With/without progression or manifestation of specific AEs Study	Trifluridine/tipiracil		BSC		Trifluridine/tipiracil + BSC vs BSC
	N	Median in months [95% CI] *Patients with event n (%)*	**N**	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value
Side effects(continued)					
Leukopenia (PT, CTCAE grade ≥ 3)[h]					
TERRA[f]	61	no data available	33	no data available	no data available
Neutropoenia (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	n.a. [n.a.; n.a.] 110 (20.6)	265	n.a. [n.a.; n.a.] 0 (0.0)	RR: 110.09 [6.87; 1764] < 0.001
TERRA[f]	61	n.a. [n.a.; n.a.] 10 (16.4)	33	n.a. [n.a.; n.a.] 0 (0.0)	RR: 11.52 [0.70; 190.52] 0.0878
Total					RR: 61.61 [8.53; 445] < 0.001[n]
Psychiatric disorders (SOC, AE)[h]					
RECOURSE[a]	533	n.a. [n.a.; n.a.] 51 (9.6)	265	n.a. [n.a.; n.a.] 42 (15.8)	0.48 [0.32; 0.73][i]; < 0.001[j]
TERRA[f]	61	no data available	33	no data available	no data available
Hypertension (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	n.a. [n.a.; n.a.] 8 (1.5)	265	n.a. [n.a.; n.a.] 10 (3.8)	0.33 [0.13; 0.86][i]; 0.017[j]
TERRA[f]	61	no data available	33	no data available	no data available

a. Data cut-off of 8 October 2014
b. Log rank test, stratified by KRAS status, time since diagnosis of the first metastasis, and region
c. Data cut-off of 16 February 2016
d. Log rank test, stratified by KRAS status and country
e. Model with fixed effect based on individual patient data, stratified by KRAS status
f. Data cut-off of 23 December 2015
g. AEs that, in the opinion of the investigator, were associated with the progression of the underlying disease were not included in the evaluations of the overall rates shown here
h. With progression of the underlying disease
i. Effect and CI: Cox Proportional Hazards Model, adjusted by region, ECOG-PS at the start of study, and prior ramucirumab treatment
j. Log rank test, adjusted by region, ECOG-PS at the start of study, and prior ramucirumab treatment
k. Contradictory information on frequencies. Other frequencies are mentioned elsewhere in Module 4 A (trifluridine/tipiracil + BCS: n = 413 vs placebo + BCS: n = 161).
l. SOC and PT spelling taken over from MedDRA without adaptation
m. Own calculation, exact unconditional test (CSZ method according to [33])
n. Own calculation, model with fixed effect (method according to Mantel-Haenszel). In both studies, the correction factor 0.5 was added to each cell frequency of the four-field table.
s. Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

t. Results from Dossier Module 4A dated 30 March 2020

Abbreviations used:
AD = absolute difference; BCS: best supportive Care; CTCAE = Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group- Performance Status; HR = hazard ratio; CI = confidence interval; KRAS: Kirsten Rat Sarcoma viral oncogene homologue; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; vs = versus; PT: preferred term; RCT: randomised controlled study; RR: relative risk; SOC: system organ class; AE: adverse event

Summary of results for relevant clinical endpoints

Endpoint category	**Direction of effect/ Risk of bias**	**Summary**
Mortality	↑	Advantage in overall survival
Morbidity	∅	There are no suitable data for the benefit assessment.
Health-related quality of life	∅	There are no suitable data for the benefit assessment.
Side effects	↔	There are advantages and disadvantages in terms of side effects.

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

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

approx. 6,900 to 12,200 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: trifluridine/tipiracil) at the following publicly accessible link (last access: 7 May 2020):

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

Treatment with trifluridine/tipiracil should 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 metastatic colorectal cancer.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Trifluridine/tipiracil	€ 42,876.08
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 September 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 1 October 2020.

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

Berlin, 1 October 2020

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

Prof. Hecken