IQWiG Reports – Commission No. A16-77

# Trifluridine/tipiracil (colorectal cancer) –

## Addendum to Commission A16-54[1]

## Addendum

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| BSC | best supportive care |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| 5-FU | 5-fluorouracil |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HR | hazard ratio |
| IPD | individual patient data |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| KRAS | Kirsten rat sarcoma viral oncogene homologue |
| PH | proportional hazard |
| SAE | serious adverse event |
| SPC | Summary of Product Characteristics |

## 1 Background

On 22 December 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for commission A16-54 (Trifluridine/tipiracil – Benefit assessment according to §35a Social Code Book V [1]).

With its written comments [2] and after the oral hearing, the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information [3], which went beyond the information provided in the dossier on trifluridine/tipiracil [4], to prove the added benefit. This was the following information:

- results on adverse events (AEs) with and without progression (serious adverse events [SAEs] and severe AEs with Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3, discontinuation due to AEs)
- subgroup analyses for the outcomes "overall survival", "SAEs" and "severe AEs" (CTCAE grade ≥ 3) according to the characteristics "number of prior regimens" and "Kirsten rat sarcoma viral oncogene homologue (KRAS) mutation status"
- information on pretreatment and subsequent treatment of the patients

The G-BA commissioned IQWiG to assess this information.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

# 2 Assessment

## 2.1 Results in side effects without progression

With its original dossier, the company had presented time-adjusted analyses for the overall rates of AEs, which it used to assess side effects. These analyses also included events that, in the opinion of the investigators, were due to clinical progression of the underlying disease. With its written comments, the company presented analyses of AEs without events that are due to disease progression. These analyses only comprised effect estimates with the corresponding 95% confidence interval. Information on the median time to event, event rates (with the exception of discontinuations due to AEs) and Kaplan-Meier curves was not presented. The data on the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3) were therefore incomplete. The supplemented analyses on the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3) subsequently submitted by the company after the oral hearing therefore additionally contained the median time to event. These analyses of SAEs and severe AEs (CTCAE grade ≥ 3) without progression subsequently submitted were also incomplete because they contained neither frequencies of events nor corresponding Kaplan-Meier curves. The results on SAEs and severe AEs (CTCAE grade ≥ 3) therefore concurred with those of the dossier assessment. Hence the results on the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3) already presented in dossier assessment A16-54 were used for the derivation of an added benefit. The data presented in the company's comments were used for the outcome "discontinuation due to AEs".

The data presented by the company are shown in Table 1.

Table 1: Side effects without progression – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

| Study<br>Outcome category<br>Outcome | Trifluridine/tipiracil + BSC<br>N | Trifluridine/tipiracil + BSC<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Placebo + BSC<br>N | Placebo + BSC<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Trifluridine/tipiracil + BSC vs. placebo + BSC<br>HR [95% CI]; p-value |
|---|---|---|---|---|---|
| **RECOURSE** | | | | | |
| **Side effects** | | | | | |
| SAEs | 533 | NA [8.7; NA]<br>ND[a] | 265 | 5.4 [5.1; NA]<br>ND[a] | 0.67 [0.51; 0.89];<br>0.005 |
| Severe AEs (CTCAE grade ≥ 3) | 533 | 1.6 [1.4; 1.9]<br>ND[a] | 265 | 2.5 [2.1; 3.8]<br>ND[a] | 1.45 [1.18; 1.77];<br>< 0.001 |
| Discontinuation due to AEs | 533 | NA [ND]<br>19 (3.6) | 265 | NA [ND]<br>4 (1.5) | 1.22 [0.40; 3.75];<br>0.723 |

a: The company describes that no information on event rates is available and explains: "However, the rates of events for which the investigator determined a relation with clinical progression (trifluridine/tipiracil + BSC: 6.7%; placebo + BSC: 11.7%) can be found in the CSR (see also IQWiG benefit assessment page 38). This rate therefore represents the maximum value of events excluded for the analysis subsequently submitted."

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

## 2.2 Subgroup analyses

After the oral hearing, the company presented subgroup analyses according to the characteristic "number of prior regimens" alone and in combination with the characteristic "KRAS mutation status" for the outcomes "overall survival", "SAEs" and "severe AEs" (CTCAE grade ≥ 3). In the dossier, the company had presented subgroup analyses according to the characteristic "number of prior regimens", but for overall survival only for the first data cut-off. The analyses now provided by the company only contained the subgroup-specific hazard ratios (HRs) and no interaction tests, however.

The company justified the fact that it did not present interaction tests for the subgroup analysis according to the characteristic "number of prior regimens" with the explanation that the survival time curves crossed after about 10 months in the subgroup of patients with 2 prior regimens, which violated the assumption of proportional hazards (PHs) (see Figure 5 in Appendix A). This rationale was not followed.

Since the curves do not differ notably before or after the crossing, the data do not necessarily contradict the PH assumption. Under the null hypothesis that the hazards in both treatment arms are equal, the crossing of the curves may be due to chance, i.e. the hazard ratio randomly

fluctuates around 1 over the observation period. The result (HR 1.12 [0.74; 1.69]) does not result in rejection of the null hypothesis. There are statistical tests to check the PH assumption, which the company, having recognized the problem, could have used.

The company provided no reasons for the lack of interaction tests for the subgroup analyses for both characteristics, KRAS mutation status and number of prior regimens. However, it noted that, from the company's point of view, no valid conclusions on the treatment effect can be derived due to the low patient numbers. This rationale was also not followed. The certainty of results of analyses can be restricted in concrete situations. The corresponding analyses have to be available for this assessment, however.

The company's analyses were supplemented with the Institute's calculations of interaction tests based on aggregate data.

### 2.2.1 Overall survival

**Subgroup analyses by number of prior regimens and KRAS mutation status**

In dossier assessment A16-54, the outcome "overall survival" was considered separately by KRAS mutation status because, based on the subgroup analyses presented by the company, there was an indication of an effect modification by the characteristic "KRAS mutation status". In its comments on the dossier assessment, the company presented a prespecified individual patient data (IPD) analysis for the first data cut-off. This analysis showed no important interaction regarding the KRAS mutation status (comments by the company, page 12, Table 3 [2]). Subgroup analyses by number of prior regimens (2, 3, ≥ 4) and KRAS mutation status (wild type, mutant) confirmed this result (see Figure 1 in Appendix A). In these analyses, the KRAS mutation status within the subgroups was investigated by number of prior regimens.

No signs of heterogeneity regarding the KRAS mutation status were shown within the subgroups by number of prior regimens ($p > 0.20$ in all 3 subgroups).

Due to the IPD analyses conducted by the company and the interaction tests, hereinafter the KRAS mutation status is not considered separately. Instead, the effect modification by the number of prior regimens alone is considered.

**Subgroup analysis by number of prior regimens**

The subgroup analysis by number of prior regimens showed important heterogeneity ($p = 0.022$, $I^2 = 73.7\%$; see Figure 2 in Appendix A). Pooling the subgroups is therefore inadequate. A statistically significant difference in favour of trifluridine/tipiracil + best supportive care (BSC) was only shown in the subgroup of patients with ≥ 4 prior regimens.

A further analysis considered the subgroups with 3 and ≥ 4 prior regimens jointly because the effect estimates in these subgroups pointed in the same direction (see Figure 3 in Appendix A). The available data showed no heterogeneity ($p = 0.336$, $I^2 = 0\%$) so that both

subgroups can be pooled. The interaction test between the groups with 2 prior regimens versus the groups with ≥ 3 prior regimens showed an effect modification by the characteristic ($p = 0.010$, $I^2 = 85.0\%$) so that pooling the subgroups is inadequate (see Figure 4 in Appendix A).

The final results of the subgroup analyses by the characteristic "number of prior regimens" for the outcome "overall survival" (second data cut-off from 8 October 2014) are presented in Table 2. Kaplan-Meier curves, if available, and figures on the interaction tests are available in Appendix A.

Table 2: Subgroups (mortality) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

| **Study**<br>**Outcome** | **Trifluridine/tipiracil + BSC** | | **Placebo + BSC** | | **Trifluridine/tipiracil + BSC vs. placebo + BSC** | |
|---|---|---|---|---|---|---|
| **Characteristic**<br>**Subgroup** | **N** | **Median survival time in months [95% CI]**<br>**Patients with event n (%)** | **N** | **Median survival time in months [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]** | **p-value** |
| **RECOURSE** | | | | | | |
| **Overall survival** | | | | | | |
| Number of prior regimens[a] | | | | | | |
| 2 | 95 | 6.2 [4.7; 7.3]<br>88 (92.6) | 45 | 4.8 [3.7; 7.2]<br>39 (86.7) | 1.12 [0.74; 1.69] | 0.595 |
| ≥ 3 | 439 | NC<br>375 (85.4%) | 221 | NC<br>210 (95.0%) | 0.62 [0.52; 0.74][b] | < 0.001[b] |
| *3* | *119* | *6.7 [5.9; 7.5]*<br>*107 (89.9)* | *54* | *5.1 [3.5; 6.7]*<br>*51 (94.4)* | *0.72 [0.51; 1.03]* | *0.072* |
| *≥ 4* | *320* | *7.8 [6.9; 9.2]*<br>*268 (83.8)* | *167* | *5.5 [4.5; 6.2]*<br>*159 (95.2)* | *0.59 [0.48; 0.72]* | *< 0.001* |
| Total | Heterogeneity: | | $Q = 6.67$; $df = 1$; $p = 0.010$, $I^2 = 85.0\%$ | | | |

a: Adjuvant, neoadjuvant and for the metastatic disease.
b: Meta-analysis with random effects, Institute's calculations.
c: p-value from Q-test for heterogeneity, referring to the subgroups with 2 versus 3 or more prior regimens.
BSC: best supportive care; CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Since there was proof of an effect modification for the characteristic "number of prior regimens" ($p < 0.05$), the 2 subgroups, 2 versus 3 and more prior regimens, were considered separately. According to the findings, there was no statistically significant difference between the treatment arms for patients with 2 prior regimens. Hence there was no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC; an added benefit is therefore not proven for these patients. A statistically significant advantage of trifluridine/ tipiracil + BSC in comparison with placebo + BSC was shown for the subgroup of patients

with ≥ 3 prior regimens. Due to the reduced informative value of the results of the RECOURSE study (described in dossier assessment A16-54 [1]), at most hints of an added benefit can be derived. This results in a hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC for patients with ≥ 3 prior regimens.

This deviates from the assessment of the company, which had calculated no interaction tests for the subgroups and derived no separate conclusions for the subgroups by prior therapy.

### 2.2.2 Side effects

The company presented subgroup analyses by prior therapy and/or KRAS mutation status for the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3), but not for the outcome "discontinuation due to AEs". It is not clear from the company's documents whether the analyses subsequently submitted, as in the dossier, also included results that, in the opinion of the investigators, were due to clinical progression of the underlying disease. In addition, the company presented neither frequencies of events nor the corresponding Kaplan-Meier curves. The company did not address the lack of the frequencies of events; it justified the lack of the Kaplan-Meier curves with the short period of time for the subsequent submission of the data. This justification is not comprehensible.

The subgroup analyses conducted by the company for the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3) are therefore not interpretable.

## 2.3 Pretreatment/subsequent treatment of the patients

Table 3 shows information on the pretreatment of the patients in the RECOURSE study for the total population and by KRAS mutation status. Table 4 shows information on the treatment after discontinuation of the study medication for the total population and by number of prior regimens.

Table 3: Anti-tumour treatment before randomization in the RECOURSE study for the total population by KRAS mutation status – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

| **Study Characteristics Population Category** | **Trifluridine/ tipiracil + BSC** | **Placebo + BSC** |
|---|---|---|
| **RECOURSE** | | |
| **Radiotherapy, n (%)** | | |
| Total population | N[a] = 534 | N[a] = 266 |
| Yes | 139 (26.0) | 65 (24.4) |
| Palliative | 67 (12.5) | 37 (13.9) |
| Curative | 84 (15.7) | 33 (12.4) |
| KRAS wild type[b] | N[a] = 262 | N[a] = 131 |
| Yes | 79 (30.2) | 33 (25.2) |
| Palliative | 40 (15.3) | 19 (14.5) |
| Curative | 47 (17.9) | 16 (12.2) |
| KRAS mutation[b] | N[a] = 272 | N[a] = 135 |
| Yes | 60 (22.1) | 32 (23.7) |
| Palliative | 27 (9.9) | 18 (13.3) |
| Curative | 37 (13.6) | 17 (12.6) |
| **Treatment situation of the prior systemic anti-tumour treatment, n (%)** | | |
| Total population | N[a] = 534 | N[a] = 266 |
| Metastatic | 534 (100.0) | 266 (100.0) |
| **Number of prior systemic treatments[c], n (%)** | | |
| Total population | N[a] = 534 | N[a] = 266 |
| 1 | 0 | 0 |
| 2 | 95 (17.8) | 45 (16.9) |
| 3 | 119 (22.3) | 54 (20.3) |
| ≥ 4 | 320 (59.9) | 167 (62.8) |
| KRAS wild type[b] | N[a] = 262 | N[a] = 131 |
| 1 | 0 | 0 |
| 2 | 25 (9.5) | 8 (6.1) |
| 3 | 51 (19.5) | 22 (16.8) |
| ≥ 4 | 186 (71.0) | 101 (77.1) |
| KRAS mutation[b] | N[a] = 272 | N[a] = 135 |
| 1 | 0 | 0 |
| 2 | 70 (25.7) | 37 (27.4) |
| 3 | 68 (25.0) | 32 (23.7) |
| ≥ 4 | 134 (49.3) | 66 (48.9) |

(continued)

Table 3: Anti-tumour treatment before randomization in the RECOURSE study for the total population by KRAS mutation status – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (continued)

| **Study Characteristics Population Category** | **Trifluridine/ tipiracil + BSC** | **Placebo + BSC** |
|---|---|---|
| **RECOURSE** | | |
| **Number of prior systemic treatments in the metastatic stage, n (%)** | | |
| Total population | N[a] = 534 | N[a] = 266 |
| 1 | 15 (2.8) | 9 (3.4) |
| 2 | 123 (23.0) | 59 (22.2) |
| 3 | 154 (28.8) | 68 (25.6) |
| ≥ 4 | 242 (45.3) | 130 (48.9) |
| KRAS wild type[b] | N[a] = 262 | N[a] = 131 |
| 1 | 0 | 0 |
| 2 | 39 (14.9) | 16 (12.2) |
| 3 | 70 (26.7) | 33 (25.2) |
| ≥ 4 | 153 (58.4) | 82 (62.6) |
| KRAS mutation[b] | N[a] = 272 | N[a] = 135 |
| 1 | 15 (5.5) | 9 (6.7) |
| 2 | 84 (30.9) | 43 (31.9) |
| 3 | 84 (30.9) | 35 (25.9) |
| ≥ 4 | 89 (32.7) | 48 (35.6) |

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Data based on IVRS.
c: Including neoadjuvant and adjuvant treatments and treatments in the metastatic stage.
BSC: best supportive care; IVRS: interactive voice response system; KRAS: Kirsten rat sarcoma viral oncogene homologue; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Depending on treatment and mutation status, between 20% and 30% of the patients had received radiotherapy; this proportion was slightly higher in patients with KRAS wild type than in patients with KRAS mutation. About half of the radiotherapies were palliative.

About half of the patients in the total population and in the subgroups by KRAS mutation status had received more than 4 systemic treatments before the start of the study. In the subgroup of patients with KRAS wild type, the proportion of patients with ≥ 4 prior regimens was higher than in patients with KRAS mutation (over 70% versus about 49%). Patients with KRAS wild type had received more regimens overall and for the treatment of the metastatic disease than patients with KRAS mutation.

All patients in the RECOURSE study except one patient in each treatment group had received treatment with 5-fluorouracil (5-FU) or capecitabine. The proportion of patients who had received an unapproved drug was below 20% in both treatment arms (trifluridine/tipiracil + BSC: 82 patients [15.4%]; placebo + BSC: 35 patients [13.2%]). The proportion of patients who had received unapproved drugs was lower in patients from Western (non-Asian) countries (trifluridine/tipiracil + BSC: 5 patients [1.4%]; placebo + BSC: 3 patients [1.7%]). The data are presented in Appendix 2 of the data subsequently submitted by the company [3].

Table 4: Anti-tumour treatment after discontinuation of the study medication in the RECOURSE study by number of pretreatments – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

| **Study Characteristics**<br>**Population**<br>**Category** | **Trifluridine/ tipiracil + BSC** | **Placebo + BSC** |
|---|---|---|
| **RECOURSE** | | |
| **Radiotherapy, n (%)** | | |
| Total population | 0 (0.0) | 0 (0.0) |
| **Systemic regimens after discontinuation of the study medication, n (%)** | | |
| Total population | N[a] = 534 | N[a] = 266 |
| Any number of regimens after discontinuation of the study medication | 222 (41.6) | 113 (42.5) |
| 1 regimen | 170 (31.8) | 88 (33.1) |
| 2 regimens | 41 (7.7) | 22 (8.3) |
| ≥ 3 regimens | 11 (2.1) | 3 (1.1) |
| 2 prior systemic regimens | N[a] = 95 | N[a] = 45 |
| Any number of regimens after discontinuation of the study medication | 39 (41.1) | 22 (48.9) |
| 1 regimen | 28 (29.5) | 15 (33.3) |
| 2 regimens | 10 (10.5) | 7 (15.6) |
| ≥ 3 regimens | 1 (1.1) | 0 (0.0) |
| 3 prior systemic regimens | N[a] = 119 | N[a] = 54 |
| Any number of regimens after discontinuation of the study medication | 51 (42.9) | 19 (35.2) |
| 1 regimen | 39 (32.8) | 12 (22.2) |
| 2 regimens | 10 (8.4) | 5 (9.3) |
| ≥ 3 regimens | 2 (1.7) | 2 (3.7) |
| ≥ 4 prior systemic regimens | N[a] = 320 | N[a] = 167 |
| Any number of regimens after discontinuation of the study medication | 132 (41.3) | 72 (43.1) |
| 1 regimen | 103 (32.2) | 61 (36.5) |
| 2 regimens | 21 (6.6) | 10 (6.0) |
| ≥ 3 regimens | 8 (2.5) | 1 (0.6) |

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

BSC: best supportive care; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

As already described in the dossier assessment, more than 40% of the patients in the total population received further treatments after discontinuation of the study medication. Overall, the number of regimens the patients received after discontinuation of the study medication

was comparable in the subgroups by number of pretreatments. The majority of the patients received one further treatment. The patients did not receive radiotherapy after discontinuation of the study medication in the observation period.

It not only remains unclear from the data whether the patients had exhausted all treatment options before the study, but also whether some of the therapies used in the subsequent treatment could have been used during the study as BSC.

## 2.4 Summary on the population of the RECOURSE study

The analyses subsequently submitted by the company and the calculations conducted by the Institute show that the median overall survival in both treatment arms in the RECOURSE study increased slightly with the number of prior regimens. This increase was slightly higher under treatment with trifluridine/tipiracil + BSC than under placebo + BSC. Since the number of regimens after discontinuation of the study medication did not differ notably in the subgroups by number of prior regimens, it is unclear whether this effect was due to the subsequent treatment of the patients. One further reason could be a selection of patients with potentially higher overall survival despite more intense prior therapy. Under consideration of the effect modification by the number of prior regimens, there is a hint of an added benefit for patients with $\geq 3$ prior therapies. An added benefit is not proven for patients with 2 prior regimens, however.

It is not clear from the data subsequently submitted by the company whether the patients in the study had been treated with all available treatments before the start of the study or whether they were unsuitable for further treatments as specified in the Summary of Product Characteristics (SPC) for the use of trifluridine/tipiracil [5]. This information cannot be inferred from the inclusion criteria of the RECOURSE study, either. Irrespective of the number of prior therapies, all patients were in good general condition at the start of the study (inclusion criterion Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1).

## 2.5 Extent and probability of added benefit

### 2.5.1 Derivation of extent and probability of added benefit at outcome level

Hereinafter, the derivation of extent and probability of the added benefit is presented at outcome level under consideration of the present addendum and dossier assessment A16-54. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

Table 5 shows the results of the RECOURSE study relevant for the derivation of the added benefit.

Table 5: Extent of added benefit at outcome level: trifluridine/tipiracil + BSC vs. placebo + BSC

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trifluridine/tipiracil + BSC versus placebo + BSC**<br>**Median time to event**<br>**HR [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Mortality** | | |
| Overall survival<br>Number of prior regimens | | |
| 2 | 6.2 vs. 4.8 months<br>1.12 [0.74; 1.69]<br>p = 0.595 | Added benefit not proven |
| ≥ 3 | NC<br>0.62 [0.52; 0.74]<br>p < 0.001<br>probability: "hint" | Outcome category: mortality<br>$CI_u < 0.85$<br>added benefit, extent: "major" |
| **Morbidity** | | |
| No patient-relevant outcomes of this category recorded | | |
| **Health-related quality of life** | | |
| Not investigated in the study included | | |
| **Side effects** | | |
| SAEs (clinical progression and side effects) | NA vs. 5.4 months<br>0.70 [0.53; 0.91]<br>p = 0.008<br>probability: "hint" | Outcome category: serious/severe symptoms and side effects<br>$0.90 \leq CI_u < 1.00$<br>added benefit, extent: "minor" |
| Severe AEs (CTCAE grade ≥ 3)[c] | 1.6 vs. 2.5 months<br>1.44 [1.18; 1.77]<br>0.69 [0.56; 0.85][d]<br>p < 0.001<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>greater harm, extent: "non-quantifiable", at least "considerable"[e] |
| Discontinuation due to AEs | NA vs. NA<br>1.22 [0.40; 3.75];<br>p = 0.723 | Greater/lesser harm not proven |

(continued)

Table 5: Extent of added benefit at outcome level: trifluridine/tipiracil + BSC vs. placebo + BSC (continued)

| |
|---|
| a: Probability provided if statistically significant differences are present.<br>b: Estimations of effect size are made depending on the outcome category with different limits based on the $CI_u$.<br>c: Only analyses that also included events caused by clinical progression are available.<br>d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.<br>e: The extent is potentially underestimated due to events caused by progression (see Section 2.7.2.4.3 of dossier assessment A16-54).<br>AE: adverse event; BSC: best supportive care; CI: confidence interval; $CI_u$: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NA: not achieved; NB: not calculable; SAE: serious adverse event; vs.: versus |

The documents subsequently submitted resulted in the following changes in comparison with dossier assessment A16-54:

- The total population is considered separately by number of prior regimens:
  - The added benefit for the outcome "overall survival" is not proven for patients with 2 prior regimens.
  - For patients with ≥ 3 prior regimens, there is a hint of a major added benefit for the outcome "overall survival".

### 2.5.2 Overall conclusion on added benefit

Table 6 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 6: Positive and negative effects from the assessment of trifluridine/tipiracil + BSC compared with placebo + BSC

| **Positive effects** | **Negative effects** |
|---|---|
| Mortality<br>▪ overall survival<br>▫ number of prior regimens: ≥ 3<br>hint of an added benefit – extent: "major"<br><br>Serious/severe symptoms and side effects<br>▪ SAEs (clinical progression and side effects): hint of an added benefit – extent: "minor" | Serious/severe side effects<br>▪ severe AEs CTCAE grade ≥ 3: hint of greater harm – extent: "non-quantifiable", at least "considerable"[a] |
| Health-related quality of life was not investigated in the study included | |
| a: The extent is potentially underestimated due to events caused by progression that were included in the analysis.<br>AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event; vs.: versus | |

In the overall assessment, there are positive and negative effects of equal certainty of results ("hint"). Since the results for the outcome "overall survival" showed a relevant effect modification by the number of prior regimens, the overall conclusion on the added benefit was derived separately for patients with 2 prior regimens and with ≥ 3 prior regimens.

**Patients with 2 prior regimens**

The added benefit in the category "mortality" is not proven for patients with 2 prior regimens. On the positive side, there is an added benefit with the extent "minor" in the category "serious/severe symptoms and side effects" (SAEs [clinical progression and side effects]). On the negative side in the category "serious/severe side effects", this is accompanied by greater harm (severe AEs with CTCAE grade ≥ 3) with the extent "non-quantifiable", at least "considerable".

Overall, the advantage in SAEs (clinical progression and side effects) is called into question by the greater harm in severe AEs with CTCAE grade ≥ 3.

In summary, the added benefit of trifluridine/tipiracil in comparison with the appropriate comparator therapy (ACT) for patients with 2 prior regimens is not proven.

**Patients with ≥ 3 prior regimens**

For patients with ≥ 3 prior regimens, on the positive side, there is an added benefit with the extent "major" in the category "mortality". As in patients with 2 prior regimens, there is additionally an added benefit with the extent "minor" in the category "serious/severe symptoms and side effects" (SAEs [clinical progression and side effects]). On the negative side in the category "serious/severe side effects", this is accompanied by greater harm (severe AEs with CTCAE grade ≥ 3) with the extent "non-quantifiable", at least "considerable".

Overall, in patients with ≥ 3 prior regimens, the major mortality advantage and the minor advantage in SAEs (clinical progression and side effects) is limited by the greater harm, which is at least "considerable", in severe AEs with CTCAE grade ≥ 3.

In summary, there is a hint of a minor added benefit of trifluridine/tipiracil in comparison with the ACT for patients with ≥ 3 prior regimens, as was the case in the dossier assessment.

The result of the assessment of the added benefit of trifluridine/tipiracil in comparison with the ACT is summarized in Table 7.

Table 7: Trifluridine/tipiracil – extent and probability of added benefit

| **Therapeutic indication** | **ACT**[a] | **Subgroup** | **Extent and probability of added benefit** |
|---|---|---|---|
| Adult patients with MCRC who have been previously treated with, or are not considered candidates for, available therapies. These therapies include fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. | Best supportive care[b] | 2 prior regimens | Added benefit not proven |
| | | ≥ 3 prior regimens | Hint of minor added benefit |

a: Presentation of the ACT specified by the G-BA.
b: Best supportive care means the best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.
ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

## 3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Trifluridin/Tipiracil (Kolorektalkarzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-54 [online]. 11.11.2016 [Accessed: 23.12.2016]. (IQWiG-Berichte; Volume 461). URL: https://www.iqwig.de/download/A16-54_Trifluridin-Tipiracil_Nutzenbewertung-35a-SGB-V.pdf.

2. Servier Deutschland. Stellungnahme zum IQWiG-Bericht Nr. 461: Trifluridin/Tipiracil (Kolorektalkarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-54. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/258/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

3. Servier Deutschland. Randomised, double-blind, phase 3 study of TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer refractory to standard chemotherapies: study TPU-TAS-102-301; Zusatzanalysen [unpublished]. 2016.

4. Servier Deutschland. Trifluridin/Tipiracil (Lonsurf): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom, die bereits mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind; diese Therapien beinhalten Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierte Chemotherapien, Anti-VEGF- und Anti-EGFR-Substanzen; Modul 4 A; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 10.08.2016 [Accessed: 12.07.2017]. URL: https://www.g-ba.de/downloads/92-975-1668/2016-08-10_Modul4A_Trifluridin-Tipiracil.pdf.

5. Servier Deutschland. Lonsurf: Fachinformation [online]. 04.2016. URL: http://www.fachinfo.de/.

6. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

## Appendix A – Figures on subgroup analyses

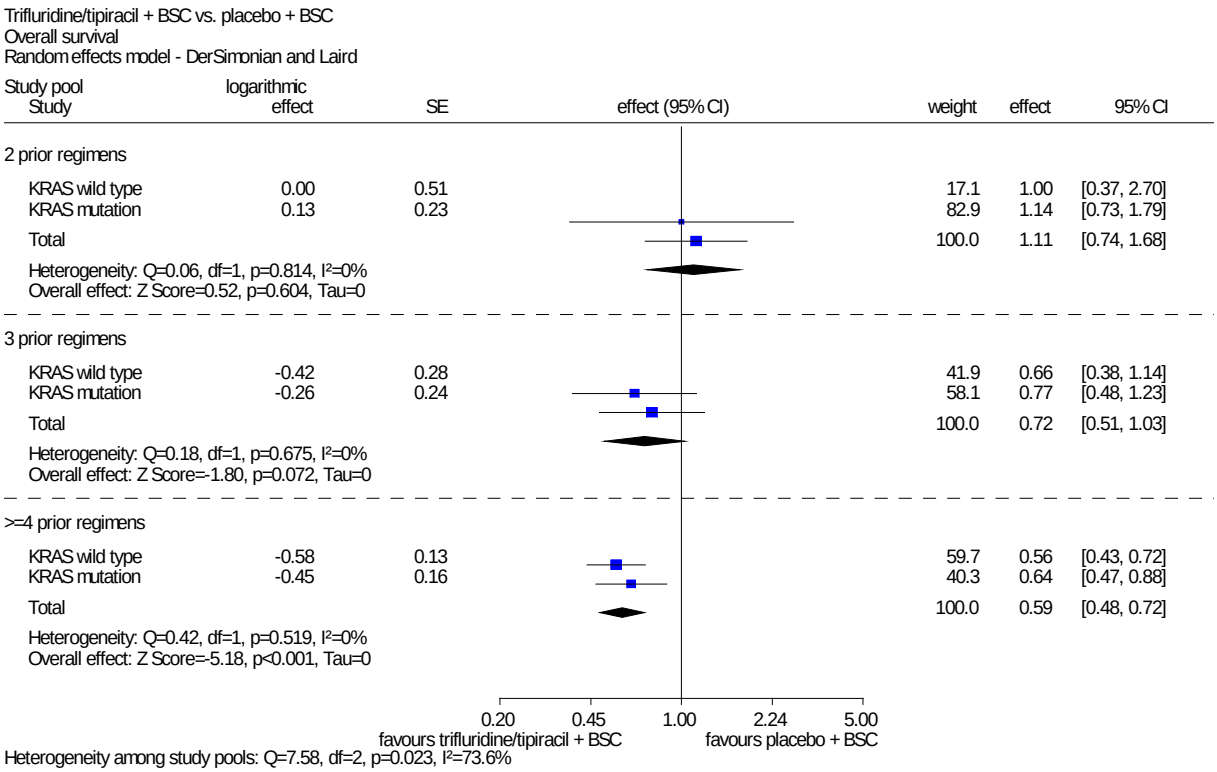


Figure 1: Interaction tests for KRAS mutation status within the subgroups by number of prior regimens for the outcome "overall survival" in RECOURSE (second data cut-off from 8 October 2014)

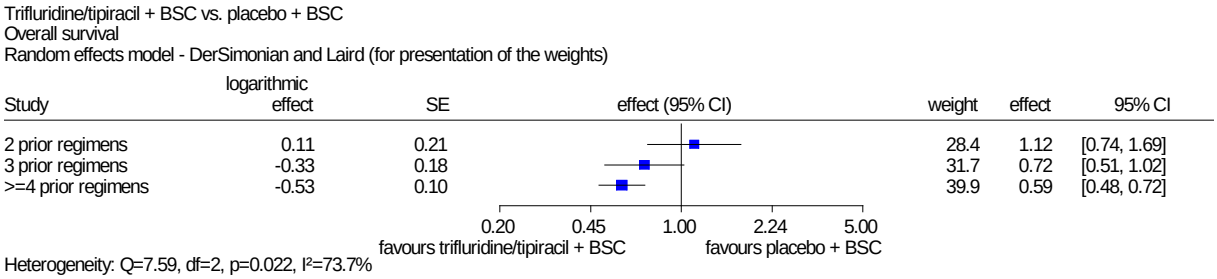


Figure 2: Interaction test for number of prior regimens for the outcome "overall survival" in RECOURSE (second data cut-off from 8 October 2014)

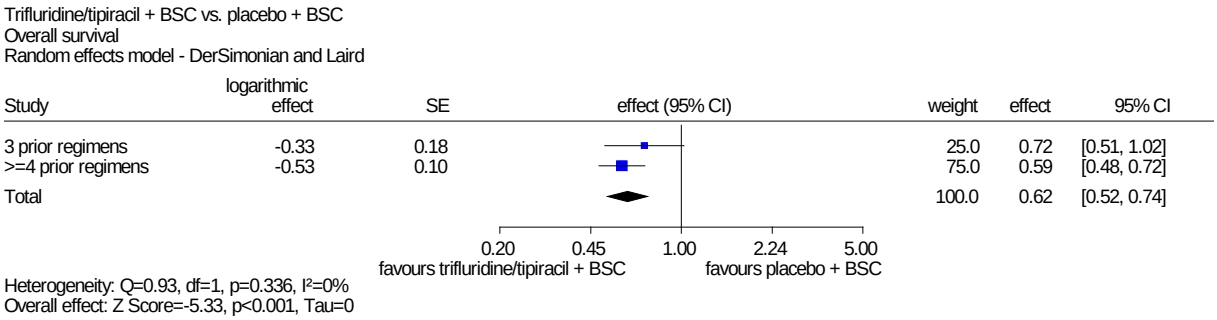


Figure 3: Interaction test for number of prior regimens (3 vs. ≥ 4) for the outcome "overall survival" in RECOURSE (second data cut-off from 8 October 2014)

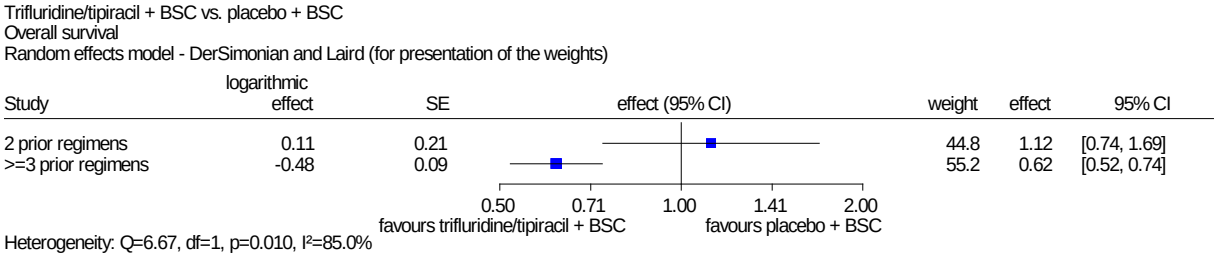


Figure 4: Interaction test for number of prior regimens (2 vs. ≥ 3) for the outcome "overall survival" in RECOURSE (second data cut-off from 8 October 2014)

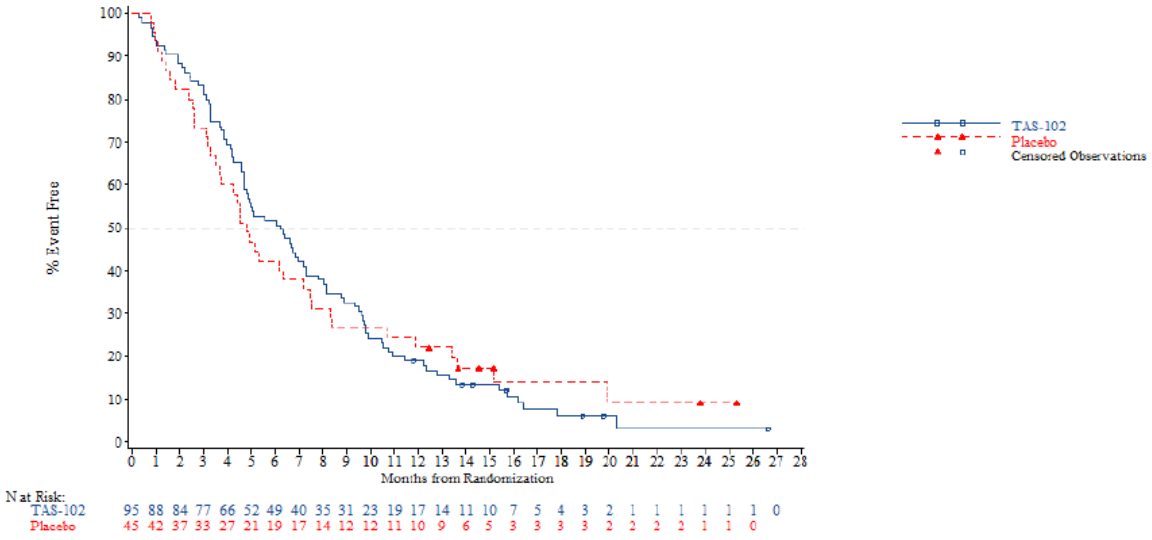


Figure 5: Kaplan-Meier plot for overall survival in RECOURSE (second data cut-off from 8 October 2014), subgroup of patients with 2 prior regimens

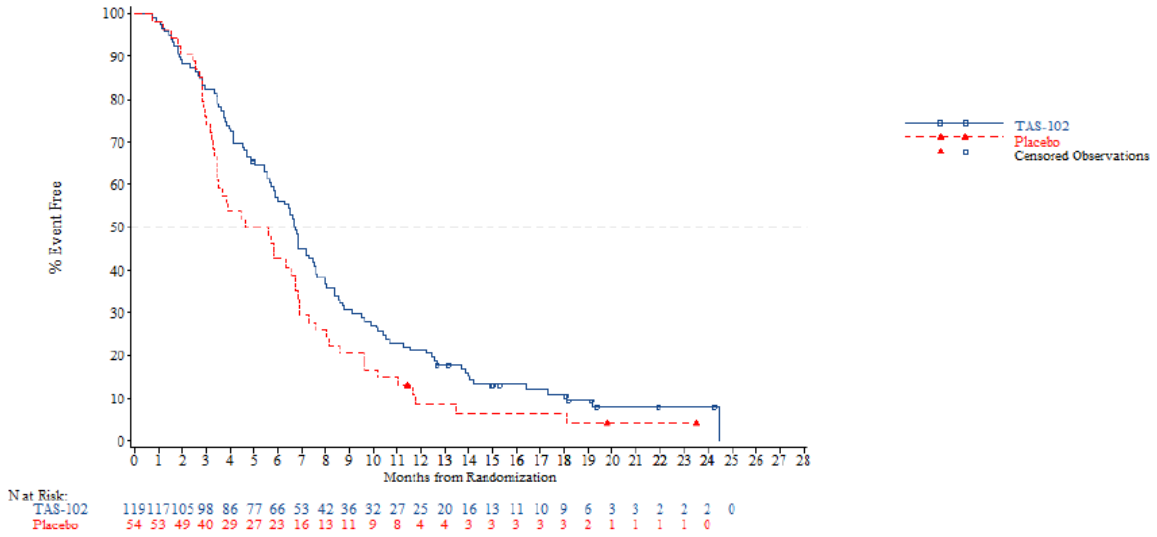


Figure 6: Kaplan-Meier plot for overall survival in RECOURSE (second data cut-off from 8 October 2014), subgroup of patients with 3 prior regimens

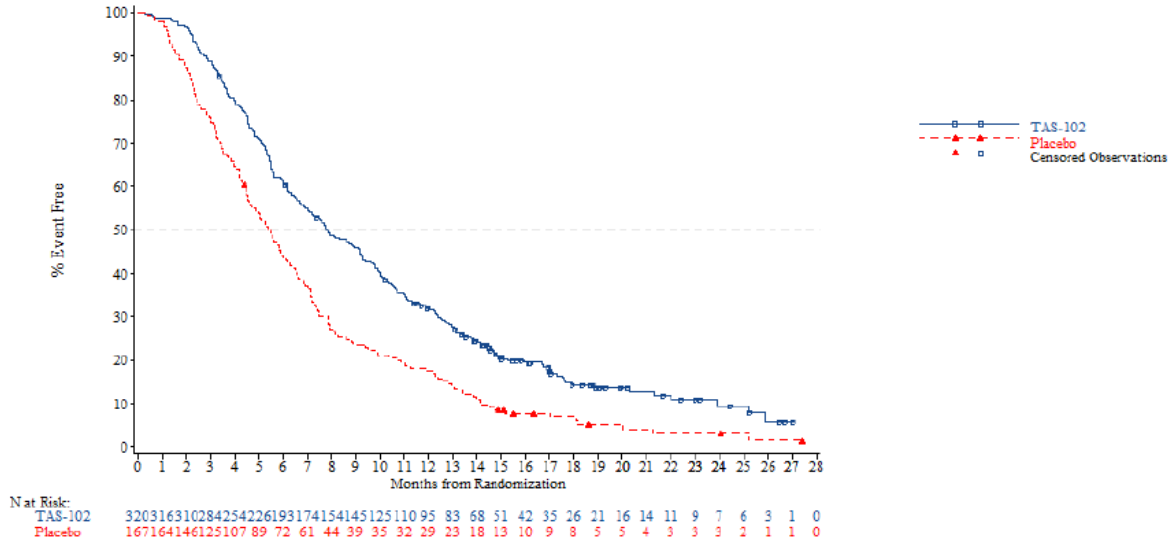


Figure 7: Kaplan-Meier plot for overall survival in RECOURSE (second data cut-off from 8 October 2014), subgroup of patients with ≥ 4 prior regimens