Trifluridine/tipiracil (colorectal cancer; combination with bevacizumab)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mCRC	metastatic colorectal cancer
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire Core 30
RAS	rat sarcoma viral oncogene homologue
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug trifluridine/tipiracil. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 August 2023.

Research question

The aim of this report is to assess the added benefit of trifluridine/tipiracil in combination with bevacizumab (hereinafter trifluridine/tipiracil + bevacizumab) compared with trifluridine/tipiracil as the appropriate comparator therapy (ACT) in adult patients with metastatic colorectal cancer (mCRC) who have already received 2 prior cancer therapies. These therapies include fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents, and anti-epidermal growth factor receptor (EGFR) agents.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of trifluridine/tipiracil + bevacizumab

Therapeutic indication	**ACT**[a]
Combination therapy with bevacizumab for the treatment of adults with mCRC[b] who have received 2 prior anticancer treatment regimens. These therapies include fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.	Trifluridine/Tipiracil[c]
a. Presented is the ACT specified by the G-BA. b. As per G-BA, patients are presumed to not be therapeutically indicated for treatment with curative intent and to exhibit primary or secondary resectability. c. As per the G-BA, patients are presumed to be indicated to receive antineoplastic therapy for the approved therapies; consequently, best supportive care was not considered as an ACT. ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; mCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor	

The company followed the specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit.

Study pool and study design

The study pool for the present assessment consists of the SUNLIGHT study. This is an open-label randomized study comparing trifluridine/tipiracil in combination with bevacizumab versus trifluridine/tipiracil monotherapy. It enrolled patients with histologically confirmed inoperable adenocarcinoma of the colon or rectum with known rat sarcoma viral oncogene homologue (RAS) mutation status.

The enrolled patients had to have received prior treatment with ≤ 2 chemotherapy regimens for advanced colorectal cancer and have exhibited progression or intolerance after the last chemotherapy regimen. The prior therapies had to include fluoropyrimidine-based, oxaliplatin-based, irinotecan-based chemotherapy, anti-VEGF and/or anti-EGFR substances in the presence of RAS wild type. Additionally, only patients with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1 were included.

A total of 492 patients were randomly allocated in a 1:1 ratio to treatment with either trifluridine/tipiracil in combination with bevacizumab (N = 246) or with trifluridine/tipiracil monotherapy (N = 246).

Treatment with trifluridine/tipiracil in the form of monotherapy and in combination with bevacizumab was carried out in accordance with the marketing authorization.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were those measuring morbidity, health-related quality of life, and adverse events (AEs).

Two data cutoffs were implemented for the SUNLIGHT study: A data cutoff for the clinical data (except overall survival) was implemented on 5 July 2022. For overall survival, a data cutoff was planned to be implemented after 331 deaths and was carried out on 19 July 2022. According to the company, the results presented in Module 4 A on all relevant outcomes are based on the 19 July 2022 data cutoff.

Risk of bias

The risk of bias across outcomes is rated as low for the SUNLIGHT study.

For the results on the outcome of overall survival, the risk of bias is deemed low.

For the patient-reported outcomes of symptoms (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 [QLQ-C30]), health status (European Quality of Life Questionnaire – 5 Dimensions [EQ-5D] visual analogue scale [VAS]), and health-related quality of life (EORTC-QLQ-C30), the open-label study design is associated with a high risk of bias of the results. Additionally, observations are incomplete for potentially

informative reasons due to the observation duration being linked to the treatment duration as well as a potential association between outcome and reason for treatment discontinuation.

No suitable data are available for the outcomes of the categories of side effects (see section below). The risk of bias is therefore not assessed for the results of these outcomes.

Results

Mortality

Overall survival

A statistically significant difference in favour of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil was shown for the outcome of overall survival. This results in an indication of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Morbidity

Symptoms (EORTC QLQ-C30)

Fatigue, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea

No statistically significant differences between the treatment groups were shown for each of the outcomes of fatigue, dyspnoea, insomnia, loss of appetite, constipation, or diarrhoea. In each case, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

Nausea and vomiting

For the outcome of nausea and vomiting, there was an effect modification by the characteristic of sex. For women, there was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

For men, however, a statistically significant difference between treatment groups in favour of trifluridine/tipiracil + bevacizumab was shown. This results in a hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Pain

There was an effect modification by the characteristic of sex for the outcome of pain. For women, there was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

For men, however, a statistically significant difference between treatment groups was shown in favour of trifluridine/tipiracil + bevacizumab. This difference was no more than marginal, however. This results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There was an effect modification by the characteristic of sex for the outcome of health status. For women, there was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

For men, however, a statistically significant difference between treatment groups was shown in favour of trifluridine/tipiracil + bevacizumab. This results in a hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Health-related quality of life

EORTC QLQ-C30

Global health status, role functioning, emotional functioning, cognitive functioning, and social functioning

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, role functioning, emotional functioning, cognitive functioning, and social functioning. In each case, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

Physical functioning

A statistically significant difference between the treatment groups in favour of trifluridine/tipiracil + bevacizumab was shown for the outcome of physical functioning. This results in a hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Side effects

AEs, severe AEs, discontinuation due to AEs, and specific AEs (myelosuppression, gastrointestinal toxicity, bleeding)

Due to unclear information on the collection of AEs (duration of follow-up and potential inconsistency between the information in Module 4 A and the study documents with regard to the consideration of disease-related events in the overall AE rates), the data presented by the company are not suitable for the present benefit assessment. In each case, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven for any of them.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the presented results, the probability and extent of added benefit of the drug trifluridine/tipiracil + bevacizumab in comparison with the ACT are assessed as follows:

Overall, adults with mCRC who have already received 2 prior cancer therapies exhibited exclusively favourable effects of trifluridine/tipiracil + bevacizumab compared to trifluridine/tipiracil. There was an indication of major added benefit for overall survival. In the health-related quality of life category, there is a hint of minor added benefit for physical functioning. Furthermore, for men, there is a hint of minor added benefit for the outcome of nausea and vomiting and a hint of considerable added benefit for the outcome of health status. The results on outcomes in the side effects category are not suitable for the present benefit assessment due to unclear information on the survey (duration of follow-up and potential inconsistency between the information in Module 4 A and the study documents with regard to the consideration of disease-related events in the overall AE rates). In light of the considerable extent of the added benefit for the outcome of overall survival, the results on side effects would be unlikely to completely call this effect into question. However, it is not possible to quantify the added benefit due to the lack of suitability of the available data on AEs. In the present situation, it is nevertheless assumed that the extent of the added benefit is at least considerable.

In summary, for adult patients with mCRC who have already received 2 prior cancer therapies, there is an indication of a non-quantifiable, at least considerable added benefit of trifluridine/tipiracil + bevacizumab compared with the ACT of trifluridine/tipiracil.

Table 3 shows a summary of probability and extent of the added benefit of trifluridine/tipiracil + bevacizumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Trifluridine/tipiracil + bevacizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Combination therapy with bevacizumab for the treatment of adults with mCRC[b] who have received 2 prior anticancer treatment regimens. These therapies include fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.	Trifluridine/Tipiracil[c]	Indication of non-quantifiable added benefit[d,e]

a. Presented is the ACT specified by the G-BA.
b. As per G-BA, patients are presumed to not be therapeutically indicated for treatment with curative intent and to exhibit primary or secondary resectability.
c. As per the G-BA, patients are presumed to be indicated to receive antineoplastic therapy for the approved therapies; consequently, best supportive care was not considered as an ACT.
d. The SUNLIGHT study included only patients with an ECOG-PS of 0 or 1. Furthermore, the SUNLIGHT study was limited to patients with adenocarcinoma. It remains unclear whether the observed effects can be transferred to patients with ECOG-PS ≥ 2 or with other tumour types.
e. In the present situation, it is assumed that the extent of the added benefit is at least considerable.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; mCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of trifluridine/tipiracil in combination with bevacizumab (hereinafter trifluridine/tipiracil + bevacizumab) compared with trifluridine/tipiracil as the ACT in adult patients with mCRC who have already received 2 prior cancer therapies. These therapies include fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of trifluridine/tipiracil + bevacizumab

Therapeutic indication	**ACT[a]**
Combination therapy with bevacizumab for the treatment of adults with mCRC[b] who have received 2 prior anticancer treatment regimens. These therapies include fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.	Trifluridine/Tipiracil[c]
a. Presented is the ACT specified by the G-BA. b. As per G-BA, patients are presumed to not be therapeutically indicated for treatment with curative intent and to exhibit primary or secondary resectability. c. As per the G-BA, patients are presumed to be indicated to receive antineoplastic therapy for the approved therapies; consequently, best supportive care was not considered as an ACT. ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; mCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor	

The company followed the specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on trifluridine/tipiracil (status: 22 June 2023)
- bibliographical literature search on trifluridine/tipiracil (last search on 26 June 2023)
- search in trial registries / trial results databases for studies on trifluridine/tipiracil (last search on 26 June 2023)
- search on the G-BA website for trifluridine/tipiracil (last search on 26 June 2023)

To check the completeness of the study pool:

- search in trial registries for studies on trifluridine/tipiracil (last search on 22 August 2023); for search strategies, see I Appendix A of the full dossier assessment

The check of the study pool identified the study CL3-95005-007 (SUNLIGHT), which was used by the company and included in the benefit assessment, as well as the IIT-95005-006-DNK study [3].

IIT-95005-006-DNK study

The IIT-95005-006-DNK study is an investigator-initiated study which, according to Module 4 A, was supported by the company. The company identified the IIT-95005-006-DNK study but excluded it from the study pool. It justified this by declaring that the inclusion criterion "population" was not met. The company has not stated any specific reason.

The inclusion criteria of the IIT-95005-006-DNK study largely correspond to those of the SUNLIGHT study, which the company included for the benefit assessment. The IIT-95005-006-DNK study enrolled adults with mCRC who had failed or were intolerant to prior therapy with fluoropyrimidine-based, irinotecan-based, oxaliplatin-based chemotherapy, cetuximab, or panitumumab (only in the presence of RAS wild type). Patients were randomly allocated to treatment with either trifluridine/tipiracil in combination with bevacizumab (N = 46) or with trifluridine/tipiracil monotherapy (N = 47). According to the inclusion criteria of the IIT-95005-006-DNK study, there were no restrictions with regard to the number of prior therapies in the metastatic stage.

From the IIT-95005-006-DNK study, at minimum the results of participants who received 2 prior cancer therapies in the metastatic stage of colorectal cancer are potentially relevant for the present benefit assessment. No information is available on how many of the included patients had received 2 prior cancer therapies in the metastatic stage. However, even when

taking into account the total population (93 patients), the study is less than one-fifth as large (< 20%) as the study population of the SUNLIGHT study (N = 492). The influence on the results of the present benefit assessment is therefore presumably low.

The company excluded the study IIT-95005-006-DNK in its entirety. It should be noted that, according to the dossier's Module 5, the company has access to the study protocol and the study report (on the total population), but no further data or documents on the study have not been made available to the company. According to this information, it is not possible for the company to separately present the results of a potentially relevant subpopulation of this study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Study CL3-95005-007 (SUNLIGHT)[c]	Yes	Yes	No	Yes [4]	Yes [5,6]	Yes [7,8]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SUNLIGHT	RCT, open-label, parallel-group	Adult patients with CRC (ECOG-PS ≤ 1) with ≤ 2 prior chemotherapy regimens[b] for the treatment of advanced CRC with ▪ tumour progression after the last treatment or ▪ intolerance to the last treatment	Trifluridine/tipiracil + bevacizumab (N = 246) Trifluridine/tipiracil (N = 246)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, protocol violation, withdrawal of informed consent, treatment discontinuation at the investigator's decision, pregnancy, or end of study Observation[c]: outcome-specific, at most until death or end of study[d]	99 centres in Austria, Belgium, Brazil, Denmark, France, Germany, Hungary, Italy, Poland, Russia, Spain, Ukraine, United States 11/2020 through 09/2023 Data cutoff on 5 July 2022: ▪ clinical data other than overall survival Data cutoff on 19 July 2022: ▪ overall survival	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. The prior therapies had to include fluoropyrimidine-based, oxaliplatin-based, irinotecan-based chemotherapy, anti-VEGF and/or anti-EGFR substances in the presence of RAS wild type colorectal cancer.
c. Outcome-specific information is provided in Table 8.
d. The end of the study is planned to occur 19 months after the first dose of study medication of the last randomized patient and is defined as the date of the last follow-up examination of the last patient or the date of the last contact attempt if the patient has been declared lost to follow-up.

AE: adverse event; CRC: colorectal cancer; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; N: number of randomized patients; RAS: rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

Table 7: Characteristics of the intervention – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil

Study	Intervention	Comparison
SUNLIGHT	35 mg trifluridine / 14.33 mg per m^2 BSA orally, twice daily, on Days 1–5 and 8–12 of each 28-day cycle + 5 mg/kg bevacizumab i.v. on Days 1 and 15 of each 28-day cycle	35 mg trifluridine / 14.33 mg per m^2 BSA orally, twice daily, on Days 1–5 and 8–12 of each 28-day cycle
	Dose adjustment Dose reduction/interruption according to the Summary of Product Characteristics **Prior treatment** ▪ ≤ 2 prior chemotherapy regimens for the treatment of mCRC with the following drugs: ▫ fluoropyrimidine, irinotecan, oxaliplatin, a monoclonal anti-VEGF antibody and/or a monoclonal anti-EGFR antibody (in case of RAS wild type) ▪ adjuvant/neoadjuvant chemotherapy was allowed to be counted as a regimen in mCRC if patients had relapsed during chemotherapy or within 6 months of the end of chemotherapy **Prohibited prior and concomitant treatment** ▪ Investigational drugs or other anticancer therapy for the treatment of mCRC within 4 weeks prior to randomization and during the study ▪ Systemic immunosuppressants (except steroids for prophylaxis or in a permanent low dose [equivalent to 20 mg prednisone/day]) or short-term administration of steroids in a higher daily dose than permitted for acute care by the protocol ▪ Radiotherapy within 4 weeks before randomization[a]	

a. Short-term therapy for symptom relief before randomization and palliative radiotherapy during the study were permitted.

BSA: body surface area; EGFR: epidermal growth factor receptor; i.v.: intravenous; mCRC: metastatic colorectal carcinoma; RAS: rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

Study design

The SUNLIGHT study is an open-label randomized study comparing trifluridine/tipiracil in combination with bevacizumab versus trifluridine/tipiracil monotherapy. The study enrolled patients with histologically confirmed inoperable adenocarcinoma of the colon or rectum with known RAS mutation status.

The enrolled patients had to have received prior treatment with ≤ 2 chemotherapy regimens for advanced colorectal cancer and have exhibited progression or intolerance after the last chemotherapy regimen. The prior therapies had to include fluoropyrimidine-based, oxaliplatin-based, irinotecan-based chemotherapy, anti-VEGF and/or anti-EGFR substances in the presence of RAS wild type. Adjuvant and neoadjuvant chemotherapies were allowed to be counted as a regimen if patients had relapsed within 6 months after the adjuvant/neoadjuvant chemotherapy. Table 9 presents the prior treatments of the study population.

Patients were to have an Eastern Cooperative Oncology Group Performance Status [ECOG-PS] ≤ 1 at the start of the study; consequently, no conclusions can be drawn from the SUNLIGHT study about patients with an ECOG-PS ≥ 2.

A total of 492 patients were randomly allocated in a 1:1 ratio to treatment with either trifluridine/tipiracil in combination with bevacizumab (N = 246) or with trifluridine/tipiracil monotherapy (N = 246). Stratification factors were RAS mutation status (wild type versus mutation), time since diagnosis of the first metastasis (< 18 months versus ≥ 18 months), and geographical region (North America versus European Union versus rest of the world).

Treatment with trifluridine/tipiracil in the form of monotherapy and in combination with bevacizumab was carried out in accordance with the marketing authorization [9,10].

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were those measuring morbidity, health-related quality of life, and AEs.

Data cutoffs

The SUNLIGHT study was planned to analyse 331 death events. The study report contains results for the clinical data (except overall survival) as of 5 July 2022 and for overall survival as of 19 July 2022.

In Module 4 A, the company states that 19 July 2022 is the relevant data cutoff for the benefit assessment and presents results on this data cutoff for all outcomes of the study. For the clinical outcomes (except overall survival), the study report contains analyses only for 5 July 2022. It is unclear whether the company conducted additional analyses on the clinical outcomes (except overall survival) as of 19 July 2022 specifically for the benefit assessment. This remains without consequence for the present benefit assessment.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil

Study **Outcome category** **Outcome**	**Planned follow-up observation**
SUNLIGHT	
Mortality	
Overall survival	Until death, discontinuation of study participation, or end of study
Morbidity	
Health status (EQ-5D VAS) Symptoms (EORTC QLQ-C30)	Up to 4 weeks after discontinuation of treatment and before administration of a subsequent therapy or up to the time of the primary analysis
Health-related quality of life (EORTC QLQ-C30)	Up to 4 weeks after discontinuation of treatment and before administration of a subsequent therapy or up to the time of the primary analysis
Side effects	
All outcomes in the side effects category	Until 30 days after treatment discontinuation[a]
a. SAEs which were related to the medication (study medication, non-study medication, experimental medication) could be followed up until the end of the study. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

The observation periods for the outcomes of morbidity, health-related quality of life, and side effects were systematically shortened because they were logged only for the time period of treatment with the study medication (plus 4 weeks for the outcomes of morbidity and health-related quality of life or 30 days for side effects). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study Characteristic **Category**	**Trifluridine/tipiracil + bevacizumab** **N[a] = 246**	**Trifluridine/tipiracil** **N[a] = 246**
SUNLIGHT		
Age [years], mean (SD)	61 (11)	62 (11)
Sex [f/m], %	50/50	46/54
Geographical region, n (%)		
North America	8 (3)	8 (3)
European Union	158 (64)	157 (64)
Rest of the world	80 (33)	81 (33)
Primary diagnosis (adenocarcinoma), n (%)		
Colon	180 (73)	181 (74)
Rectum	66 (27)	65 (26)
Number of organs with metastases, n (%)		
1–2	152 (62)	141 (57)
≥ 3	94 (38)	105 (43)
Metastasis location, n (%)		
Liver	194 (79)	188 (76)
Lung	157 (64)	154 (63)
Lymph nodes	95 (39)	101 (41)
Peritoneum	60 (24)	60 (24)
Soft tissue	9 (4)	9 (4)
Bones	22 (9)	30 (12)
Brain	2 (< 1)	0 (0)
Skin	0 (0)	1 (< 1)
Other	31 (13)	38 (15)
ECOG-PS, n (%)		
0	119 (48)	106 (43)
1	127 (52)	139 (57)
2	0 (0)	1 (< 1)
RAS status, n (%)		
Mutated[b]	174 (71)	173 (70)
Wild type[b]	71 (29)	71 (29)
Not assessable[b]	1 (< 1)	2 (< 1)
Creatinine clearance (mL/min), n (%)		
< 60 mL/min[c]	30 (12)	28 (11)
≥ 60 mL/min[c]	215 (88)	218 (89)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study Characteristic **Category**	**Trifluridine/tipiracil + bevacizumab** **N[a] = 246**	**Trifluridine/tipiracil** **N[a] = 246**
Number of prior drug treatments for metastatic disease[d] n (%)		
1	11 (4)	15 (6)
2	229 (93)	224 (91)
≥ 3	6 (2)	7 (3)
Prior therapies for metastatic disease[d]		
Fluoropyrimidine	246 (100)	246 (100)
Irinotecan	246 (100)	245 (100)
Oxaliplatin	241 (98)	243 (99)
Anti-VEGF monoclonal antibodies	178 (72)	176 (72)
Anti-EGFR monoclonal antibodies	67 (27[e])	66 (27[e])
Treatment discontinuation, n (%)[f]	214 (87)	242 (98)
Study discontinuation, n (%)[g]	145 (59)	169 (69)

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line.
b. The RAS test was conducted on all patients in both treatment arms.
c. Percentages are based on n = 245 patients in the trifluridine/tipiracil + bevacizumab arm and n = 246 patients in the trifluridine/tipiracil arm.
d. Prior drug treatment which was carried out in a palliative setting or in an adjuvant/neoadjuvant setting and in which progression occurred during or within 6 months of the end of drug treatment.
e. Institute's calculation.
f. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression (78% vs. 89%) and AE (7% vs. 7%).
g. The most common reason for study discontinuation in the intervention arm vs. the control arm was death (58% vs. 67%).

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; EGFR: epidermal growth factor receptor; f: female; m: male; n: number of patients in the category; N: number of randomized patients; RAS: rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; SD: standard deviation; VEGF: vascular endothelial growth factor

The patient characteristics are comparable between the 2 treatment arms. The average participant age was around 62 years, about half of patients were female, and around 29% had a RAS wild type of mCRC.

It should be noted that the therapeutic indication to be assessed comprises only patients with 2 prior therapies in the metastatic stage. No such restriction was applied in the SUNLIGHT study, but approximately 92% had received 2 prior drug therapies in the metastatic stage. This deviation therefore has no consequence for the present benefit assessment.

Furthermore, as per approval, treatment with trifluridine/tipiracil + bevacizumab is an option for all mCRC tumour types [10]. However, the SUNLIGHT study enrolled only patients with adenocarcinoma, which accounts for the majority of colorectal cancers in clinical practice, at over 95% [11]. Data on patients with other tumour types are not available for the present benefit assessment.

Treatment duration and observation period

Table 10 shows the mean/median participant treatment duration and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil

Study **Duration of the study phase** **Outcome category**	**Trifluridine/tipiracil + bevacizumab** **N = 246**	**Trifluridine/tipiracil** **N = 246**
SUNLIGHT		
Treatment duration [months]		
Median [Q1; Q3]	5.0 [2.1; 8.9]	2.1 [1.8; 4.4]
Mean (SD)	6.1 (4.3)	3.4 (2.5)
Observation duration [months]		
Overall survival[a]		
Median [min; max]	14.2 [0.1; 18.9]	13.6 [0.6; 19.1]
Mean (SD)	ND	ND
Morbidity		
Health status (EQ-5D VAS)		
Median [min; max]	4.8 [0.0; 17.6]	2.2 [0.0; 14.3]
Mean (SD)	5.8 (4.3)	3.2 (2.6)
Symptoms (EORTC QLQ-C30)		
Median [min; max]	4.8 [0.0; 17.6]	2.2 [0.0; 14.3]
Mean (SD)	5.8 (4.2)	3.3 (2.6)
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	4.8 [0.0; 17.6]	2.2 [0.0; 14.3]
Mean (SD)	5.8 (4.2)	3.3 (2.6)
Side effects	-[b]	

a. Median observation period calculated according to the inverse Kaplan-Meier method.
b. According to Module 4 A, AEs are observed up to 30 days after discontinuation of treatment (see also Table 8 of this assessment). However, the follow-up times for AEs stated in Appendix 4-G of Module 4 A are substantially longer (8.7 vs. 6.8 months) (see also the body of text below).

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; max: maximum; min: minimum; N: number of patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration was markedly longer in the intervention arm at 5 months than in the control arm at 2.1 months.

The median observation period for overall survival was 14.2 months in the intervention arm and 13.6 months in the comparator arm. For the outcomes on morbidity, health-related quality of life, and AEs, the observation periods were linked to the end of treatment and were therefore significantly shorter in the comparator arm than in the intervention arm.

For the AEs, it should also be noted that the follow-up was planned to continue for up to 30 days after the end of treatment (see Table 8). Given a median treatment duration of 5.0 months in the intervention arm versus 2.1 months in the comparator arm, the median observation durations reported by the company in Module 4 A of 8.7 months in the intervention arm and 6.8 months in the comparator arm are not plausible.

Subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study **Main therapeutic group** **Pharmacological subgroup** **Therapeutic subgroup** **Drug**	**Patients with subsequent therapy n (%)[a]**	
	Trifluridine/tipiracil + bevacizumab **N = 246**	**Trifluridine/tipiracil** **N = 246**
SUNLIGHT		
Total	108 (43.9)	113 (45.9)
Antineoplastic drugs	101 (41.1)	107 (43.5)
Antimetabolites	69 (28.0)	67 (27.2)
Pyrimidine analogues	67 (27.2)	65 (26.4)
Fluorouracil	45 (18.3)	42 (17.1)
Capecitabine	20 (8.1)	28 (11.4)
Tipiracil hydrochloride, trifluridine	4 (1.6)	2 (0.8)
Folic acid analogues	2 (0.8)	3 (1.2)
Raltitrexed	2 (0.8)	3 (1.2)
Other antineoplastic agents	57 (23.2)	58 (23.6)
Oxaliplatin	37 (15.0)	40 (16.3)
Monoclonal antibodies	34 (13.8)	31 (12.6)
Bevacizumab	19 (7.7)	18 (7.3)
Cetuximab	7 (2.8)	5 (2.0)
Panitumumab	5 (2.0)	5 (2.0)
Trastuzumab	1 (0.4)	3 (1.2)
Other antineoplastic agents	2 (0.8)	6 (2.4)
Aflibercept	2 (0.8)	3 (1.2)
Protein kinase inhibitors	40 (16.3)	51 (20.7)
Regorafenib	36 (14.6)	47 (19.1)
VEGFR tyrosine kinase inhibitors	4 (1.6)	3 (1.2)
Fruquintinib	4 (1.6)	3 (1.2)
Herbal alkaloids and other natural remedies	38 (15.4)	26 (10.6)
TOP-1 inhibitors	38 (15.4)	26 (10.6)
Irinotecan	37 (15.0)	26 (10.6)
Cytotoxic antibiotics and related substances	0 (0)	6 (2.4)
Mitomycin	0 (0)	6 (2.4)
Anthracyclines and related substances	0 (0)	3 (1.2)
Epirubicin	0 (0)	3 (1.2)

Table 11: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study **Main therapeutic group** **Pharmacological subgroup** **Therapeutic subgroup** **Drug**	**Patients with subsequent therapy n (%)[a]**	
	Trifluridine/tipiracil + bevacizumab **N = 246**	**Trifluridine/tipiracil** **N = 246**
All other therapeutic agents	38 (15.4)	33 (13.4)
Folinic acid	21 (8.5)	17 (6.9)
Calcium folinate	15 (6.1)	12 (4.9)
Investigational preparations	10 (4.1)	14 (5.7)
New radiotherapy for the treatment of CRC	12 (4.9)	13 (5.3)

a. Percentages are based on the total population.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; TOP-1: topoisomerase-1; VEGFR: vascular endothelial growth factor receptor

The SUNLIGHT study implemented no restrictions regarding the administration of subsequent therapies. The proportion of the drugs used as subsequent therapy were largely balanced between the treatment arms. Overall, 43.9% of the patients in the intervention arm and 45.9% of the patients in the comparator arm received subsequent antineoplastic therapy. The most frequently used drugs were fluorouracil (18.3% versus 17.1%), oxaliplatin (15% versus 16.3%), regorafenib (14.6% versus 19.1%), and irinotecan (15% versus 10.6%). According to the guideline recommendation, the third-line or fourth-line therapy should be individualized for each patient and depends on the prior therapy, the treatment goal, the rapidly accelerated fibrosarcoma - isoform B (BRAF) as well as RAS status, and the microsatellite instability (MSI) status [11].

It remains unclear how many of the patients did not receive subsequent therapy despite being eligible for it. Overall, a total of 87% of patients in the intervention arm and 98% of patients in the comparator arm discontinued therapy (see Table 9), while only just under half of patients received subsequent therapy.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
SUNLIGHT	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the SUNLIGHT study is rated as low.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company argues that the SUNLIGHT study is the relevant study for the European marketing authorization and that the patients included therefore correspond to the marketing authorization valid in Europe or Germany.

It goes on to explain that, contrary to the marketing authorization, the study also included patients with only 1 prior therapy or with > 2 prior therapies. However, according to the company, no significant interactions were found in corresponding subgroup analyses (number of prior drug treatments for metastatic disease [1 versus ≥ 2]). The company notes that a total of approximately 89% of the patients included in the SUNLIGHT study met the criteria of the population defined by the marketing authorization. For the overall survival outcome, a sensitivity analysis based on the study population covered by the marketing authorization was also carried out. Thus, the company considers the transferability of the study results of the total population to the authorized patient population to be guaranteed overall.

The company further states that the treatment regimen and dosage in the studies corresponds to the European and German Summaries of Product Characteristics. At 48%, the proportion of women in the SUNLIGHT study reportedly largely corresponds to the proportion of women with colorectal cancer in Germany. At 62 years (trifluridine/tipiracil + bevacizumab) or 64 years (trifluridine/tipiracil), the median age of patients in the study is reportedly slightly lower than in Germany, where more than half of patients have a disease onset after the age of 70. However, the study included a total of 126 patients aged 70 and over. Since the subgroup analyses for age did not show any effect modification relevant to the conclusion for

any outcome, the company argues that the effect of trifluridine/tipiracil in combination with bevacizumab can be assumed to be independent of age.

Since most of the included patients are from the European Union, the company assumes good transferability to the German healthcare context. Subgroup analyses for the characteristic of geographical region reportedly likewise show no effect modification relevant to the conclusion.

The company further states that, according to the inclusion criteria of the SUNLIGHT study, only patients with ECOG-PS 0-1 were allowed to participate in the study. However, data from the compassionate use programme for trifluridine/tipiracil and the non-randomized comparative study TALLISUR [12] reportedly show that, in German healthcare practice, few patients with ECOG-PS ≥ 2 are treated beyond the second line. The company concludes that the proportion of patients with ECOG-PS ≥ 2 in this treatment situation is so low that the data from the SUNLIGHT study are transferable to the German healthcare context in terms of ECOG-PS.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded using the EORTC QLQ-C30
  - health status, surveyed using the EQ-5D VAS
- Health-related quality of life
  - surveyed with the EORTC QLQ-C30
- Side effects
  - serious adverse events (SAEs)
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - myelosuppression, operationalized as blood and lymphatic system disorders (System Organ Class [SOC], severe AEs)
  - gastrointestinal toxicity, operationalized as gastrointestinal disorders (SOC, severe AEs)
  - bleeding (Preferred Term [PT], severe AEs)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used other outcomes in the dossier (Module 4 A).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC-QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Myelosuppression[a,b]	Gastrointestinal toxicity[a,c]	Bleeding (PT, severe AEs)[a]	Other specific AEs
SUNLIGHT	Yes	Yes	Yes	Yes	No[d]	No[d]	No[d]	No[d]	No[d]	No[d]	No[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as blood and lymphatic system disorders (SOC, severe AEs).
c. Operationalized as gastrointestinal disorders (SOC, severe AEs).
d. No suitable data available; see body of text below for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Patient-reported outcomes on morbidity and health-related quality of life

For the EORTC QLQ-C30, the company's dossier presents the analyses of time to definitive deterioration by ≥ 10 points, which were predefined in the study protocol (scale range of 0-100). Definitive deterioration was defined as a deterioration by ≥ 10 points without an improvement above this threshold being observed in the further course of the study. In addition, the company presents analyses up to the first deterioration. Analyses of definitive deterioration are meaningful if the observation period is long enough to achieve a definitive deterioration and if the observation periods between the treatment arms are sufficiently similar. In the SUNLIGHT study, however, the observation periods differ markedly between treatment arms. Therefore, the analyses up to the first deterioration by ≥ 10 points are used for the present benefit assessment.

For the health status assessed using the EQ-5D VAS, the company presented non-prespecified analyses of the time to first deterioration by ≥ 15 points and supplementary analyses of the time to definitive deterioration by ≥ 15 points. Analogous to the analyses of the EORTC

QLQ-C30, the analyses for the EQ-5D VAS are also used until the first deterioration of ≥ 15 points.

Side effects

The AE data presented by the company are unsuitable for the present benefit assessment. This is explained below.

Assessing the side effects of trifluridine/tipiracil + bevacizumab requires analyses which disregard clearly disease-related events (e.g. progression). The disregarded events should be clearly defined for this purpose.

For the results of AEs in Module 4 A, the company describes that AEs which, in the investigator's opinion, were related to the progression of the underlying disease were disregarded in the analyses of the overall rates. The company has not provided any further information on the specific events which were disregarded in the overall rates.

For the results on AEs presented in the study report, the study documents provide no information indicating that events in connection with the progression of the underlying disease were disregarded in the presented results. Nevertheless, the results of the overall rates for SAEs and for discontinuation due to AEs are identical between Module 4 A and the study report.

Only for the outcome of severe AEs (CTCAE grade ≥ 3) do the results of the overall rates and the results at the SOC/PT level differ between Module 4 (Module 4 A) and the study report. As per study report, 178 (72.4%) serious AEs occurred in the intervention arm versus 171 (69.5%) in the comparator arm. In Module 4 A, in contrast, 154 (62.6%) versus 156 (63.4%) events were reported for the respective treatment arms. It is unclear (a) to what extent this difference is solely due to the exclusion of events in connection with the underlying disease or (b) what is the root cause of the differences between the data in the study report versus Module 4 A.

In addition, as described in Section I 3.2, there are uncertainties regarding the follow-up of AEs.

Overall, these aspects (potential inconsistency between the information in Module 4 A and the study documents with regard to the consideration of disease-related events in the overall AE rates and implausible duration of follow-up) lead to an unclear relevance of the SUNLIGHT study results on AEs and consequently to them being unusable for the benefit assessment.

Under the assumption that the results presented in Module 4 A can be used, the following outcomes in the side effects category would be relevant for the present benefit assessment:

- SAEs
- severe AEs (CTCAE Grade ≥ 3)
- discontinuation due to AEs
- myelosuppression, operationalized as blood and lymphatic system disorders (SOC, severe AEs).
- gastrointestinal toxicity, operationalized as gastrointestinal disorders (SOC, severe AEs)
- bleeding (PT, severe AEs)
- infections and infestations (SOC, SAEs)
- general disorders and administration site conditions (SOC, severe AEs)
- hypertension (PT, severe AEs)

Results on these outcomes are presented as supplementary information in Appendix B of the full dossier assessment. In the absence of further information on the consideration of disease-related events as well as on the survey period of the AEs included in the analysis, the relevance of these data remains unclear.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC-QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Myelosuppression[a,b]	Gastrointestinal toxicity[a,c]	Bleeding (PT, severe AEs)[a]	Further specific AEs[a]
SUNLIGHT	L	L	H[d]	H[d]	H[d]	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as blood and lymphatic system disorders (SOC, severe AEs).
c. Operationalized as gastrointestinal disorders (SOC, severe AEs).
d. Lack of blinding in the presence of subjective survey of outcomes and incomplete observations for potentially informative reasons at different follow-ups.
e. No usable data available; see Section I 4.1 for the reasoning.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

For the results on the outcome of overall survival, the risk of bias is deemed low.

For the patient-reported outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS), and health-related quality of life (EORTC QLQ-C30), the high risk of bias of the results is due to the open-label study design. Additionally, observations are incomplete for potentially informative reasons due to the observation duration being linked to the treatment duration as well as a potential association between outcome and reason for treatment discontinuation.

No suitable data are available for the outcomes of the categories of side effects (see Section I 4.1). The risk of bias is therefore not assessed for the results of these outcomes.

I 4.3 Results

Table 15 summarizes the results on the comparison of trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil in patients with mCRC. Where necessary, calculations conducted by the Institute are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix C of the full dossier assessment. Results on AEs, SAEs, severe AEs, and discontinuation due to AEs are presented as supplementary information in I Appendix B of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study Outcome category Outcome	Trifluridine/tipiracil + bevacizumab		Trifluridine/tipiracil		Trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil
	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 (%)	HR [95% CI]; p-value
SUNLIGHT					
Mortality					
Overall survival	246	10.8 [9.4; 11.8] 148 (60.2)	246	7.5 [6.3; 8.6] 183 (74.4)	0.61 [0.49; 0.77]; < 0.001[a]
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration)[b]					
Fatigue	246	3.3 [2.7; 4.5] 141 (57.3)	246	2.3 [1.9; 3.0] 145 (58.9)	0.79 [0.62; 1.01]; 0.060[a]
Nausea and vomiting	246	6.5 [4.7; NC] 109 (44.3)	246	6.9 [3.7; NC] 96 (39.0)	0.95 [0.72; 1.26]; 0.724[a]
Pain	246	4.6 [3.7; 6.0] 129 (52.4)	246	3.3 [2.8; 5.1] 123 (50.0)	0.87 [0.67; 1.12]; 0.285[a]
Dyspnoea	246	NR [9.0; NC] 79 (32.1)	246	9.7 [5.8; NC] 82 (33.3)	0.76 [0.55; 1.04]; 0.087[a]
Insomnia	246	10.6 [8.3; NC] 87 (35.4)	246	8.1 [6.9; NC] 82 (33.3)	0.88 [0.64; 1.20]; 0.408[a]
Appetite loss	246	4.7 [3.8; 7.5] 125 (50.8)	246	4.6 [3.7; 6.9] 105 (42.7)	0.97 [0.74; 1.27]; 0.828[a]
Constipation	246	NR [8.8; NC] 87 (35.4)	246	NR [10.6; NC] 68 (27.6)	1.13 [0.82; 1.56]; 0.459[a]
Diarrhoea	246	NR [6.5; NC] 91 (37.0)	246	NR [5.8; NC] 77 (31.3)	1.03 [0.75; 1.40]; 0.858[a]
Health status (EQ-5D VAS, time to deterioration[c])	246	NR [8.1; NC] 85 (34.6)	246	7.8 [4.5; NC] 87 (35.4)	0.70 [0.51; 0.95]; 0.023[a]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study Outcome category Outcome	Trifluridine/tipiracil + bevacizumab		Trifluridine/tipiracil		Trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil
	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 (%)	HR [95% CI]; p-value
Health-related quality of life					
EORTC-QLQ C30 – time to first deterioration[d]					
Global health status	246	5.6 [4.2; 9.5] 120 (48.8)	246	5.5 [3.7; 6.7] 109 (44.3)	0.84 [0.64; 1.10]; 0.201[a]
Physical functioning	246	6.9 [4.6; 11.3] 108 (43.9)	246	5.0 [3.3; 6.1] 115 (46.7)	0.73 [0.55; 0.95]; 0.020[a]
Role functioning	246	5.0 [3.8; 8.8] 123 (50.0)	246	4.4 [3.3; 6.5] 117 (47.6)	0.80 [0.62; 1.05]; 0.107[a]
Emotional functioning	246	NR [8.3; NC] 84 (34.1)	246	7.9 [6.9; NC] 83 (33.7)	0.83 [0.61; 1.14]; 0.252[a]
Cognitive functioning	246	8.1 [5.5; NC] 101 (41.1)	246	6.9 [4.7; NC] 87 (35.4)	0.94 [0.70; 1.26]; 0.675[a]
Social functioning	246	6.9 [4.8; 13.2] 107 (43.5)	246	5.8 [4.4; 9.7] 102 (41.5)	0.84 [0.63; 1.11]; 0.225[a]
Side effects					
AEs (supplementary information)	No suitable data available[f]				
SAEs	No suitable data available[f]				
Severe AEs[e]	No suitable data available[f]				
Discontinuation due to AEs	No suitable data available[f]				
Myelosuppression, operationalized as blood and lymphatic system disorders (SOC, severe AEs)[e]	No suitable data available[f]				
Gastrointestinal toxicity, operationalized as gastrointestinal disorders (SOC, severe AEs)[e]	No suitable data available[f]				
Bleeding (PT, severe AEs)[e]	No suitable data available[f]				
Other specific AEs	No suitable data available[f]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study Outcome category Outcome	Trifluridine/tipiracil + bevacizumab		Trifluridine/tipiracil		Trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil
	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 (%)	HR [95% CI]; p-value
a. Effect and CI: Cox proportional hazards model; p-value: log-rank test. Each stratified by RAS status (mutated versus wild type), the time since diagnosis of the first metastasis (< 18 months versus ≥ 18 months), and geographical region (North America versus European Union versus rest of the world). b. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). Patients are censored at the time point of death. c. The company's Module 4 A describes that the original scale values were transformed for the present analyses so that the lowest scale value 0 represents the best possible state of health and the highest scale value 100 represents the worst state of health. An increase of the transformed score on the VAS by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100). Patients are censored at the time point of death. d. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). Patients are censored at the time point of death. e. Operationalized as CTCAE grade ≥ 3. f. See Section I 4.1 of the present dossier assessment for the reasoning. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: Preferred Term; RAS: rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale				

The available information allows deriving no more than an indication, e.g. of an added benefit, for the outcome of overall survival. Therefore, at most hints, e.g. of an added benefit, can be derived for all other outcomes.

Mortality

Overall survival

A statistically significant difference in favour of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil was shown for the outcome of overall survival. This results in an indication of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Morbidity

Symptoms (EORTC QLQ-C30)

Fatigue, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea

No statistically significant differences between the treatment groups were shown for each of the outcomes of fatigue, dyspnoea, insomnia, loss of appetite, constipation, or diarrhoea. In each case, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

Nausea and vomiting

No statistically significant difference between treatment groups was found for the outcome of nausea and vomiting. However, an effect modification by the characteristic of sex was found. For women, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven. For men, however, this results in a hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil for the outcome of nausea and vomiting (see Section I 4.4).

Pain

No statistically significant difference between the treatment groups was shown for the outcome of pain. However, an effect modification by the characteristic of sex was found. For women, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven. For men, a statistically significant difference between treatment groups in favour of trifluridine/tipiracil + bevacizumab was shown when compared to trifluridine/tipiracil. This difference was no more than marginal, however (see Section I 4.4). For men, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

A statistically significant difference between the treatment groups in favour of trifluridine/tipiracil + bevacizumab was shown for the outcome of health status. However, an effect modification by the characteristic of sex was found. For women, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven. For men, in contrast, there is a hint of added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil for the outcome of health status (see Section I 4.4).

Health-related quality of life

EORTC QLQ-C30

Global health status, role functioning, emotional functioning, cognitive functioning, and social functioning

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, role functioning, emotional functioning, cognitive functioning, and social functioning. In each case, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

Physical functioning

A statistically significant difference between the treatment groups in favour of trifluridine/tipiracil + bevacizumab was shown for the outcome of physical functioning. This results in a hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Side effects

AEs, severe AEs, discontinuation due to AEs, and specific AEs (myelosuppression, gastrointestinal toxicity, bleeding)

No suitable data are available for outcomes in the side effects category. In each case, this results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven for any of them.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Presented are only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 summarizes the subgroup results on the comparison of trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil in patients with mCRC. Kaplan-Meier curves on the

presented time-to-event analyses can be found in I Appendix C.4 of the full dossier assessment.

Table 16: Subgroups (morbidity) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study Outcome Characteristic Subgroup	Trifluridine/tipiracil + bevacizumab N	Median time to event in months [95% CI] Patients with event n (%)	Trifluridine/tipiracil N	Median time to event in months [95% CI] Patients with event n (%)	Trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil HR [95% CI][a]	p-value[b]
SUNLIGHT						
Symptoms (EORTC QLQ-C30, nausea and vomiting – time to first deterioration[c])						
Sex						
Female	124	3.3 [2.3; 4.7] 71 (57.3)	112	NR [3.7; NC] 41 (36.6)	1.46 [0.99; 2.17]	0.056
Male	122	NR [8.8; NC] 38 (31.1)	134	6.9 [3.2; NC] 55 (41.0)	0.54 [0.35; 0.83]	0.004
Total					Interaction[d]:	< 0.001
Symptoms (EORTC QLQ-C30, pain – time to first deterioration[c])						
Sex						
Female	124	3.8 [2.4; 5.6] 69 (55.6)	112	4.6 [3.0; NC] 51 (45.5)	1.14 [0.79; 1.64]	0.499
Male	122	5.4 [4.2; 8.8] 60 (49.2)	134	3.0 [2.1; 4.5] 72 (53.7)	0.65 [0.46; 0.93]	0.016
Total					Interaction[d]:	0.048
Health status (EQ-5D VAS, time to first deterioration[e])						
Sex						
Female	124	7.2 [4.4; NC] 53 (42.7)	112	7.9 [4.7; NC] 37 (33.0)	1.04 [0.67; 1.59]	0.873
Male	122	NR [10.2; NC] 32 (26.2)	134	6.9 [4.4; NC] 50 (37.3)	0.47 [0.30; 0.73]	< 0.001
Total					Interaction[d]:	0.010

Table 16: Subgroups (morbidity) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Study Outcome Characteristic Subgroup	Trifluridine/tipiracil + bevacizumab		Trifluridine/tipiracil		Trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil	
	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 (%)	HR [95% CI][a]	p-value[b]

a. Effect and CI: unstratified Cox proportional hazards model.
b. p-value: unstratified log-rank test.
c. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). Patients are censored at the time point of death.
d. Interaction test from Cox proportional hazards regression model with treatment, subgroup, and interaction term between treatment and subgroup.
e. The company describes in Module 4 A that the original scale values were transformed for the present analyses so that the lowest scale value 0 represents the best possible state of health and the highest scale value 100 represents the worst state of health. An increase in the transformed score by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). Patients are censored at the time point of death.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; VAS: visual analogue scale

Morbidity

Symptoms (EORTC QLQ-C30)

Nausea and vomiting

For the outcome of nausea and vomiting, there was an effect modification by the characteristic of sex. For women, there was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

For men, however, a statistically significant difference between treatment groups was shown in favour of trifluridine/tipiracil + bevacizumab. This results in a hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Pain

There was an effect modification by the characteristic of sex for the outcome of pain. For women, there was no statistically significant difference between the treatment groups. This

results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

For men, however, a statistically significant difference between treatment groups was shown in favour of trifluridine/tipiracil + bevacizumab. This difference was no more than marginal, however. This results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There was an effect modification by the characteristic of sex for the outcome of health status. For women, there was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

For men, however, a statistically significant difference between treatment groups was shown in favour of trifluridine/tipiracil + bevacizumab. This results in a hint of an added benefit of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 17).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

Nausea and vomiting and pain (EORTC QLQ-C30), health status (EQ-5D VAS)

For the outcomes of nausea and vomiting as well as pain (EORTC QLQ-C30) and health status (EQ-5D VAS), insufficient information is available to classify the severity category as serious/severe. The outcomes of health status, nausea and vomiting as well as pain are therefore allocated to the outcome category of non-serious/non-severe symptoms / late complications.

Table 17: Extent of added benefit at outcome level: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes observed over the entire study duration		
Mortality		
Overall survival	10.8 vs. 7.5 HR = 0.61 [0.49; 0.77]; p < 0.001 Probability: indication	Outcome category: mortality $CI_u < 0.85$ Added benefit; extent: major
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	3.3 vs. 2.3 HR = 0.79 [0.62; 1.01]; p = 0.060	Lesser/Added benefit not proven
Nausea and vomiting Sex Female	3.3 vs. NR HR = 1.46 [0.99; 2.17]; p = 0.056	Lesser/Added benefit not proven
Male	NR vs. 6.9 HR = 0.54 [0.35; 0.83]; p < 0.004 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
Pain Sex Female	3.8 vs. 4.6 HR = 1.14 [0.79; 1.64]; p = 0.499	Lesser/Added benefit not proven
Male	5.4 vs. 3.0 HR = 0.65 [0.46; 0.93] p = 0.016 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/Added benefit not proven[c]
Dyspnoea	NR vs. 9.7 HR = 0.76 [0.55; 1.04]; p = 0.087	Lesser/Added benefit not proven
Insomnia	10.6 vs. 8.1 HR = 0.88 [0.64; 1.20]; p = 0.408	Lesser/Added benefit not proven

Table 17: Extent of added benefit at outcome level: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Appetite loss	4.7 vs. 4.6 HR = 0.97 [0.74; 1.27]; p = 0.828	Lesser/Added benefit not proven
Constipation	NR vs. NR HR = 1.13 [0.82; 1.56]; p = 0.459	Lesser/Added benefit not proven
Diarrhoea	NR vs. NR HR = 1.03 [0.75; 1.40]; p = 0.858	Lesser/Added benefit not proven
Health status (EQ-5D VAS, time to first deterioration)		
Sex		
Female	7.2 vs. 7.9 HR: 1.04 [0.67; 1.59]; p = 0.873	Lesser/Added benefit not proven
Male	NR vs. 6.9 HR: 0.47 [0.30; 0.73]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Health-related quality of life		
EORTC-QLQ C30 – time to first deterioration		
Global health status	5.6 vs. 5.5 HR = 0.84 [0.64; 1.10]; p = 0.201	Lesser/Added benefit not proven
Physical functioning	6.9 vs. 5.0 HR = 0.73 [0.55; 0.95]; p = 0.020 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Role functioning	5.0 vs. 4.4 HR = 0.80 [0.62; 1.05]; p = 0.107	Lesser/Added benefit not proven
Emotional functioning	NR vs. 7.9 HR = 0.83 [0.61; 1.14]; p = 0.252	Lesser/Added benefit not proven
Cognitive functioning	8.1 vs. 6.9 HR = 0.94 [0.70; 1.26]; p = 0.675	Lesser/Added benefit not proven

Table 17: Extent of added benefit at outcome level: trifluridine/tipiracil + bevacizumab versus trifluridine/tipiracil (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Social functioning	6.9 vs. 5.8 HR = 0.84 [0.63; 1.11]; p = 0.225	Lesser/Added benefit not proven
Side effects		
SAEs	No suitable data available	Greater/Lesser harm not proven
Severe AEs	No suitable data available	Greater/Lesser harm not proven
Discontinuation due to AEs	No suitable data available	Greater/Lesser harm not proven
Myelosuppression (severe AEs)	No suitable data available	Greater/Lesser harm not proven
Gastrointestinal toxicity (severe AEs)	No suitable data available	Greater/Lesser harm not proven
Bleeding (severe AEs)	No suitable data available	Greater/Lesser harm not proven

a. Probability provided there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; SAE: serious adverse; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil

Favourable effects	**Unfavourable effects**
Outcomes observed over the entire study duration	
Mortality ▪ Overall survival: indication of added benefit – extent: major	–
Outcomes with shortened observation period	
Non-serious/non-severe symptoms / late complications ▪ Nausea and vomiting: Sex (men): hint of an added benefit – extent: minor ▪ Health status: Sex (men): hint of an added benefit – extent: considerable	–
Health-related quality of life ▪ Physical functioning: hint of an added benefit – extent: minor	–
No suitable data are available for outcomes of the category of side effects.	

Overall, adults with mCRC who have already received 2 prior cancer therapies exhibited exclusively favourable effects of trifluridine/tipiracil + bevacizumab compared to trifluridine/tipiracil. There was an indication of major added benefit for overall survival. In the health-related quality of life category, there is a hint of minor added benefit for physical functioning. Furthermore, for men, there is a hint of minor added benefit for the outcome of nausea and vomiting and a hint of considerable added benefit for the outcome of health status. The results on outcomes in the side effects category are not suitable for the present benefit assessment due to unclear information on the survey (duration of follow-up and potential inconsistency between the information in Module 4 A and the study documents with regard to the consideration of disease-related events in the overall AE rates). In light of the considerable extent of the added benefit for the outcome of overall survival, the results on side effects would be unlikely to completely call this effect into question. However, it is not possible to quantify the added benefit due to the lack of suitability of the available data on AEs. In the present situation, it is nevertheless assumed that the extent of the added benefit is at least considerable.

In summary, for adult patients with mCRC who have already received 2 prior cancer therapies, there is an indication of a non-quantifiable, at least considerable added benefit of trifluridine/tipiracil + bevacizumab compared with the ACT of trifluridine/tipiracil.

Table 19 summarizes the result of the assessment of added benefit of trifluridine/tipiracil + bevacizumab in comparison with the ACT.

Table 19: Trifluridine/tipiracil + bevacizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Combination therapy with bevacizumab for the treatment of adults with mCRC[b] who have received 2 prior anticancer treatment regimens. These therapies include fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.	Trifluridine/tipiracil[c]	Indication of non-quantifiable added benefit[d,e]

a. Presented is the ACT specified by the G-BA.
b. As per G-BA, patients are presumed to not be therapeutically indicated for treatment with curative intent and to exhibit primary or secondary resectability.
c. As per the G-BA, patients are presumed to be indicated to receive antineoplastic therapy for the approved therapies; consequently, best supportive care was not considered as an ACT.
d. The SUNLIGHT study included only patients with an ECOG-PS of 0 or 1. Furthermore, the SUNLIGHT study was limited to patients with adenocarcinoma. It remains unclear whether the observed effects can be transferred to patients with ECOG-PS ≥ 2 or with other tumour types.
e. In the present situation, it is assumed that the extent of the added benefit is at least considerable.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; mCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor

The assessment described above deviates from that by the company, which derived an indication of added benefit of at least considerable extent.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-85.html.