Trifluridine/tipiracil (colorectal cancer; combination with bevacizumab)

Addendum to Project A23-85 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
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
RCT	randomized controlled trial
SAE	serious adverse events
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 9 January 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-85 (Trifluridine/tipiracil – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the new analyses of side effects presented by the pharmaceutical company (hereinafter referred to as the “company”) in the commenting procedure [2], taking into account the information provided in the dossier [3].

In addition, the present addendum corrects the incorrect information on the median observation period of side effects from benefit assessment A23-85.

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

2 Assessment

The randomized controlled trial (RCT) SUNLIGHT was used for the benefit assessment of trifluridine/tipiracil + bevacizumab. A detailed description of the study can be found in dossier assessment A23-85 [1].

As described in dossier assessment A23-85, the data presented by the company in the dossier [3] were not taken into account in benefit assessment A23-85 due to unclear information on the recording of adverse events (AEs). The unclear information related to the duration of follow-up observation of AEs and potential inconsistencies 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 accordance with the commission, the analyses of side effects subsequently submitted by the company in the commenting procedure are assessed below.

2.1 Information on the duration of the follow-up observation of side effects

In Module 4 A, the company stated median treatment durations of 5.0 versus 2.1 months in the intervention arm versus the comparator arm, and a follow-up observation of up to 30 days after the end of treatment with median observation periods of 8.7 versus 6.3 months (dossier assessment A23-85 incorrectly stated 8.7 vs. 6.8 months, which is corrected by the present assessment) [3]. The median observation periods mentioned did not appear plausible.

In its comments, the company described that the observation periods for AEs presented in the dossier took into account all safety assessment parameters defined in the study protocol (including clinical laboratory tests, concomitant treatments, vital signs) over the entire study period, including the follow-up.

With its comments, the company presented new calculations, showing the observation period of AEs for the treatment phase defined in the study protocol. In the company's view, the calculation of the observation periods is aligned with the events included in the event time analyses. The newly calculated median observation periods for AEs were 5.4 months in the intervention arm versus 2.5 months in the comparator arm. The data presented by the company seem plausible.

2.2 Consideration of disease-related events in the AE analyses

Contrary to the information on their operationalization, the analyses of AEs presented in Module 4 A also included AEs that were associated with the progression of the underlying disease. As part of the commenting procedure, the company presented overall AE rates, excluding AEs that, in the investigator's opinion, were associated with the progression of the underlying disease.

Assessing the side effects of trifluridine/tipiracil + bevacizumab requires analyses that disregard clearly disease-related events (e.g. progression). For such analyses, the study protocol ideally specifies in advance which events are to be considered disease-related events. This was not the case in the SUNLIGHT study. In this study, the investigator assessed individually for each AE whether the event was associated with the progression. Particularly in view of the open-label study design of the SUNLIGHT study and the therefore unblinded investigator assessment, this procedure leads to potentially biased results. Furthermore, also when looking at the overall AE rates without events that the investigator considered to be associated with the progression of the underlying disease, it is noticeable that in the present add-on situation in the intervention arm, where the patients received bevacizumab in addition to treatment with trifluridine/tipiracil, for example, fewer serious AEs (SAEs) occurred than in the comparator arm, where the patients received trifluridine/tipiracil without additional administration of bevacizumab (see Table 5 in Appendix A). It can be assumed that disease-related events are still included to a relevant extent in the overall AE rates without events that, in the investigator's opinion, were associated with the progression of the underlying disease.

In the present data situation, the results on the overall rates of AEs, in which those events are taken into account that were assessed as disease-related events by the investigator, are therefore used for the benefit assessment. These can be interpreted as a mixture of progression of the underlying disease/symptoms and side effects. As supplementary information, Appendix A presents the overall AE rates, excluding AEs that, in the investigator's opinion, were associated with the progression of the underlying disease. The choice of operationalization of the overall AE rates has no impact on the overall conclusion on added benefit.

2.2.1 Included outcomes in the side effects category

For the present addendum, the following outcomes in the side effects category are used for the benefit assessment:

- 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)
- Haemorrhage (Preferred Term [PT], severe AEs)
- Infections and infestations (SOC, SAEs)

- General disorders and administration site conditions (SOC, severe AEs)
- Hypertension (PT, severe AEs)

2.2.2 Risk of bias

For the outcomes of SAEs, severe AEs and specific AEs, the risk of bias of the results is rated as high due to potentially informative censoring in the presence of large differences in the observation periods between the intervention arm and the comparator arm (see Section 2.1). For the outcome of discontinuation due to AEs, the risk of bias of the results is rated as high due to the open-label study design.

2.2.3 Results

The results on the outcomes of the side effects category are presented in Table 1. Kaplan-Meier curves on the presented event time analyses can be found in Appendix B. Results on common AEs can be found in dossier assessment A23-85 [1].

Table 1: Results (side effects) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab vs. 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					
Side effects[a]					
AEs	246	0.5 [0.3; 0.5] 241 (98.0)	246	0.5 [0.4; 0.5] 241 (98.0)	–
SAEs	246	NA [12.9; NC] 61 (24.8)	246	8.7 [5.8; NC] 77 (31.3)	0.51 [0.36; 0.72]; < 0.001[b]
Severe AEs[c]	246	3.0 [2.6; 4.1] 154 (62.6)	246	2.1 [1.9; 2.8] 156 (63.4)	0.74 [0.59; 0.93]; 0.010[b]
Discontinuation due to AEs	246	NA 36 (14.6)	246	NA [11.7; NC] 31 (12.6)	0.75 [0.46; 1.24]; 0.268[b]
Myelosuppression, operationalized as blood and lymphatic system disorders (SOC, severe AEs)[c]	246	9.2 [5.9; NC] 97 (39.4)	246	4.2 [3.3; NC] 89 (36.2)	0.87 [0.65; 1.17]; 0.357[b]
Anaemia (PT, severe AEs)[c]	246	NA 2 (0.8)	246	NA 12 (4.9)	0.10 [0.02; 0.49]; < 0.001[b]
Neutropenia (PT, severe AEs)[c]	246	9.2 [5.9; NC] 95 (38.6)	246	NA [4.2; NC] 72 (29.3)	1.09 [0.80; 1.49]; 0.584[b]
Gastrointestinal toxicity, operationalized as gastrointestinal disorders (SOC, severe AEs)[c]	246	NA 22 (8.9)	246	NA 23 (9.3)	0.71 [0.39; 1.29]; 0.258[b]
Haemorrhage (PT, severe AEs)[c]				ND	
Infections and infestations (SOC, SAEs)	246	NA 18 (7.3)	246	NA 20 (8.1)	0.48 [0.24; 0.93]; 0.028[b]
General disorders and administration site conditions (SOC, severe AEs)[c]	246	NA 9 (3.7)	246	NA [10.09; NC] 20 (8.1)	0.30 [0.13; 0.69]; 0.003[b]
Hypertension (PT, severe AEs)[c]	246	NA 13 (5.3)	246	NA 3 (1.2)	3.59 [1.01; 12.74]; 0.035[c]

a. Progression events included.
b. Effect and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
c. Operationalized as CTCAE grade ≥ 3.

Table 1: Results (side effects) – RCT, direct comparison: trifluridine/tipiracil + bevacizumab vs. 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
AE: adverse event; CI: confidence interval; 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; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class					

On the basis of the available information, at most hints, e.g. of greater harm, can be determined for all outcomes in the side effects category.

Side effects

SAEs and severe AEs

A statistically significant difference in favour of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil was shown for the outcomes of SAEs and severe AEs. In each case, there is a hint of lesser harm from trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; greater or lesser harm is therefore not proven.

Specific AEs

Myelosuppression

In the present data situation, the outcome of myelosuppression was operationalized as severe AEs of the SOC blood and lymphatic system disorders, considering the PTs anaemia and neutropenia as common manifestations of myelosuppression.

No statistically significant difference between treatment groups was shown at the level of the SOC blood and lymphatic system disorders or the PT neutropenia. In each case, there is no

hint of greater or lesser harm from trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; greater or lesser harm is therefore not proven.

A statistically significant difference in favour of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil was shown for the PT anaemia. There is a hint of lesser harm from trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Gastrointestinal toxicity

In the present data situation, the outcome of gastrointestinal toxicity was operationalized as severe AEs of the SOC gastrointestinal disorders.

No statistically significant difference between treatment groups was shown for the SOC gastrointestinal disorders (severe AEs). There is no hint of greater or lesser harm from trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; greater or lesser harm is therefore not proven.

Haemorrhages (severe AEs)

No suitable data are available for the outcome of haemorrhages (severe AEs). There is no hint of greater or lesser harm from trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil; greater or lesser harm is therefore not proven.

Infections and infestations (SAEs) and general disorders and administration site conditions (severe AEs)

A statistically significant difference in favour of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil was shown for each of the outcomes of infections and infestations (SAEs) and general disorders and administration site conditions (severe AEs). In each case, there is a hint of lesser harm from trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

Hypertension (severe AEs)

A statistically significant difference to the disadvantage of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil was shown for the outcome of hypertension (severe AEs). There is a hint of greater harm from trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil.

2.2.4 Subgroups and effect modifiers

The following subgroup characteristics are relevant for the benefit assessment of trifluridine/tipiracil in patients with metastatic colorectal cancer (MCRC):

- 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 one 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.

Using the methods described, no relevant effect modification by the subgroup characteristics of age or sex at baseline was identified for the used outcomes of specific AEs.

2.2.5 Probability and extent of added benefit

2.2.5.1 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 2.2.3 and the results of benefit assessment A23-85 [1] (see Table 2).

Table 2: Extent of added benefit at outcome level: trifluridine/tipiracil + bevacizumab vs. 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. NA HR = 1.46 [0.99; 2.17]; p = 0.056	Lesser/added benefit not proven
Male	NA 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	NA 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 2: Extent of added benefit at outcome level: trifluridine/tipiracil + bevacizumab vs. 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	NA vs. NA HR = 1.13 [0.82; 1.56]; p = 0.459	Lesser/added benefit not proven
Diarrhoea	NA vs. NA 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	NA 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 ≤ 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	NA 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 2: Extent of added benefit at outcome level: trifluridine/tipiracil + bevacizumab vs. 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	NA vs. 8.7 HR = 0.51 [0.36; 0.72]; p < 0.001 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: “major”
Severe AEs	3.0 vs. 2.1 HR = 0.74 [0.59; 0.93]; p = 0.010 Probability: “hint”	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Lesser harm, extent: “minor”
Discontinuation due to AEs	NA vs. NA HR = 0.75 [0.46; 1.24]; p = 0.268	Greater/lesser harm not proven
Myelosuppression (severe AEs)	9.2 vs. 4.2 HR = 0.87 [0.65; 1.17]; p = 0.357	Greater/lesser harm not proven
Anaemia (severe AEs)	NA vs. NA HR = 0.10 [0.02; 0.49]; p < 0.001 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk < 5% Lesser harm, extent: “considerable”
Neutropenia (severe AEs)	9.2 vs. NA HR = 1.09 [0.80; 1.49]; p = 0.584	Greater/lesser harm not proven
Gastrointestinal toxicity (severe AEs)	NA vs. NA HR = 0.71 [0.39; 1.29]; p = 0.258	Greater/lesser harm not proven
Haemorrhage (severe AEs)	ND	Greater/lesser harm not proven
Infections and infestations (SAEs)	NA vs. NA HR = 0.48 [0.24; 0.93]; p = 0.028 Probability: “hint”	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Lesser harm, extent: “minor”

Table 2: Extent of added benefit at outcome level: trifluridine/tipiracil + bevacizumab vs. 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]
General disorders and administration site conditions (severe AEs)	NA vs. NA HR = 0.30 [0.13; 0.69]; p = 0.003 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Lesser harm, extent: "major"
Hypertension (severe AEs)	NA vs. NA HR = 3.59 [1.01; 12.74]; HR: 0.28 [0.08; 0.99][d] p = 0.035 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"

a. Probability provided if 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.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; NA: not achieved; ND: no data; SAE: serious adverse; VAS: visual analogue scale

2.2.5.2 Overall conclusion on added benefit

Table 3 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of trifluridine/tipiracil + bevacizumab in comparison with trifluridine/tipiracil

Positive effects	**Negative 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”	–
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: “major” ▪ Severe AEs: hint of lesser harm – extent: “minor” ▪ Anaemia: hint of lesser harm – extent: "considerable" ▪ Infections and infestations: hint of lesser harm – extent “minor” ▪ General disorders and administration site conditions: hint of lesser harm – extent: “major”	Serious/severe side effects ▪ Hypertension: hint of greater harm – extent: “minor”
AE: adverse event; SAE: serious adverse event	

In comparison with dossier assessment A23-85, results for the side effects category are now used for the benefit assessment.

In addition to the advantages already described in dossier assessment A23-85 in the categories of mortality, morbidity and health-related quality of life, the following additional positive effects of trifluridine/tipiracil + bevacizumab compared with trifluridine/tipiracil and an effect to the disadvantage of trifluridine/tipiracil + bevacizumab were found in the side effects category.

There are hints of lesser harm from trifluridine/tipiracil + bevacizumab compared with trifluridine/tipiracil for each of the outcomes of SAEs and severe AEs and for the specific AEs of anaemia (severe AEs), infections and infestations (SAEs), and general disorders and administration site conditions (severe AEs). In contrast, there is a hint of a greater harm from trifluridine/tipiracil + bevacizumab compared with trifluridine/tipiracil for the outcome of hypertension (severe AEs).

In summary, for adult patients with MCRC who have received 2 prior anticancer treatment regimens, there is an indication of major added benefit of trifluridine/tipiracil + bevacizumab compared with the appropriate comparator therapy trifluridine/tipiracil.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of trifluridine/tipiracil + bevacizumab from dossier assessment A23-85.

Table 4 below shows the result of the benefit assessment of trifluridine/tipiracil + bevacizumab, taking into account dossier assessment A23-85 and the present addendum.

Table 4: 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 including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents	Trifluridine/tipiracil[c]	Indication of major added benefit

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 in the therapeutic indication are presumed to be indicated to receive antineoplastic therapy; 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.

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.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Trifluridin/Tipiracil (Kolorektalkarzinom; Kombination mit Bevacizumab); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 17.11.2023]. URL: https://dx.doi.org/10.60584/A23-85.

2. Servier Deutschland. Stellungnahme zum IQWiG-Bericht Nr. 1673: Trifluridin/Tipiracil (Kolorektalkarzinom; Kombination mit Bevacizumab) - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/985/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Servier Deutschland. Trifluridin/Tipiracil (Lonsurf); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 06.12.2023]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/985/.

Appendix A Overall AE rates excluding events that, in the investigator's opinion, were associated with the progression of the underlying disease, presented as supplementary presentation

Table 5: Results (side effects) presented as supplementary information – RCT, direct comparison: trifluridine/tipiracil + bevacizumab vs. trifluridine/tipiracil

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					
Side effects					
SAEs[a]	246	NA 45 (18.3)	246	11.1 [8.8; NA] 50 (20.3)	0.59 [0.39; 0.89]; 0.012[b]
Severe AEs[a, c]	246	3.7 [2.8; 4.8] 144 (58.5)	246	2.8 [2.1; 3.3] 133 (54.1)	0.83 [0.65; 1.05]; 0.125[b]
Discontinuation due to AEs[a]	246	NA 22 (8.9)	246	NA 7 (2.8)	2.09 [0.87; 4.99]; 0.091[b]

a. AEs considered by the investigator to be associated with the progression of the underlying disease were not taken into account.
b. Effect and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; 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; RCT: randomized controlled trial; SAE: serious adverse event

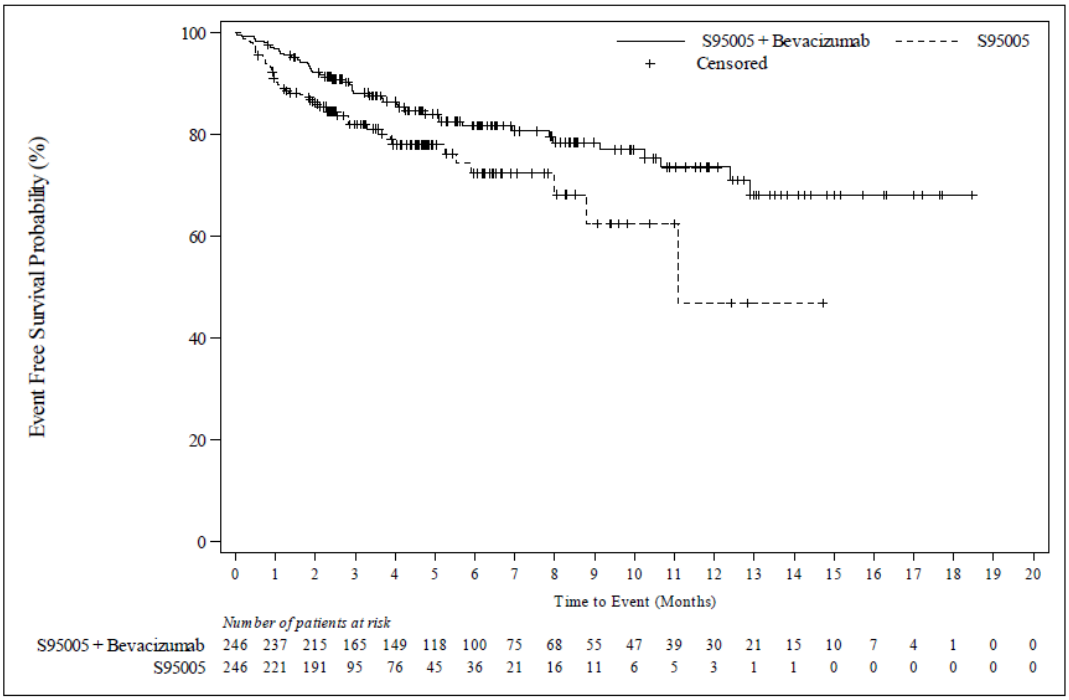

Figure 1: Kaplan-Meier curve for the outcome of SAEs excluding events that, in the investigator's opinion, were associated with the progression of the underlying disease

The Kaplan-Meier curve for the outcome of severe AEs excluding events that, in the investigator's opinion, were associated with the progression of the underlying disease is not available.

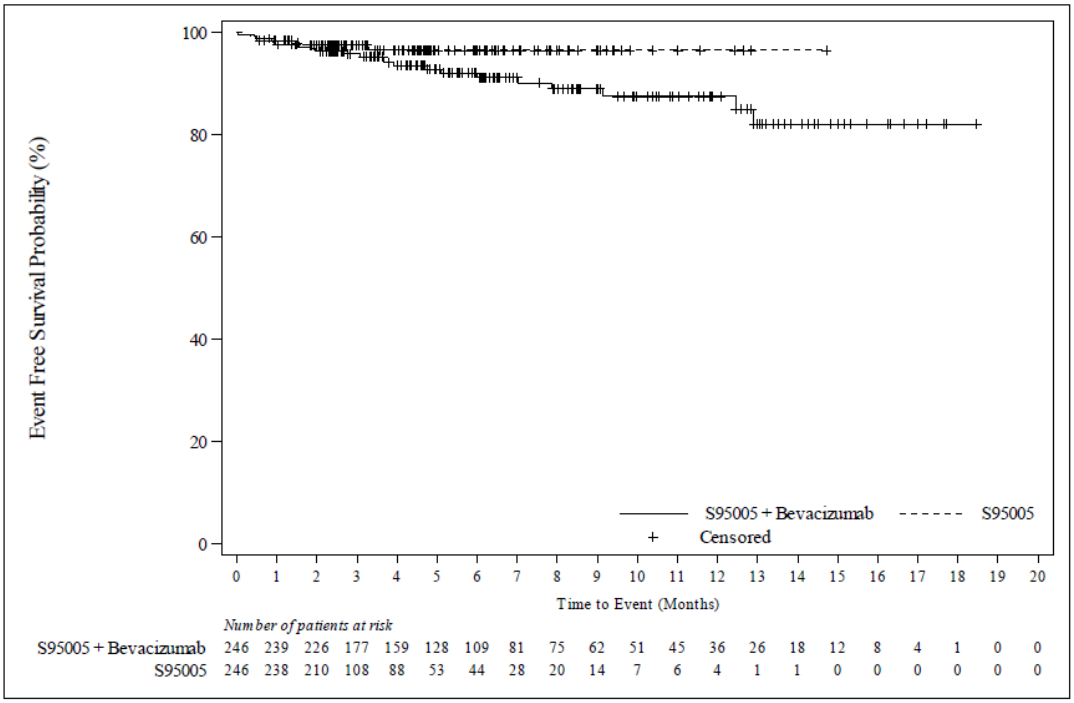

Figure 2: Kaplan-Meier curve for the outcome of discontinuation due to AEs excluding events that, in the investigator's opinion, were associated with the progression of the underlying disease

Appendix B Kaplan-Meier curves

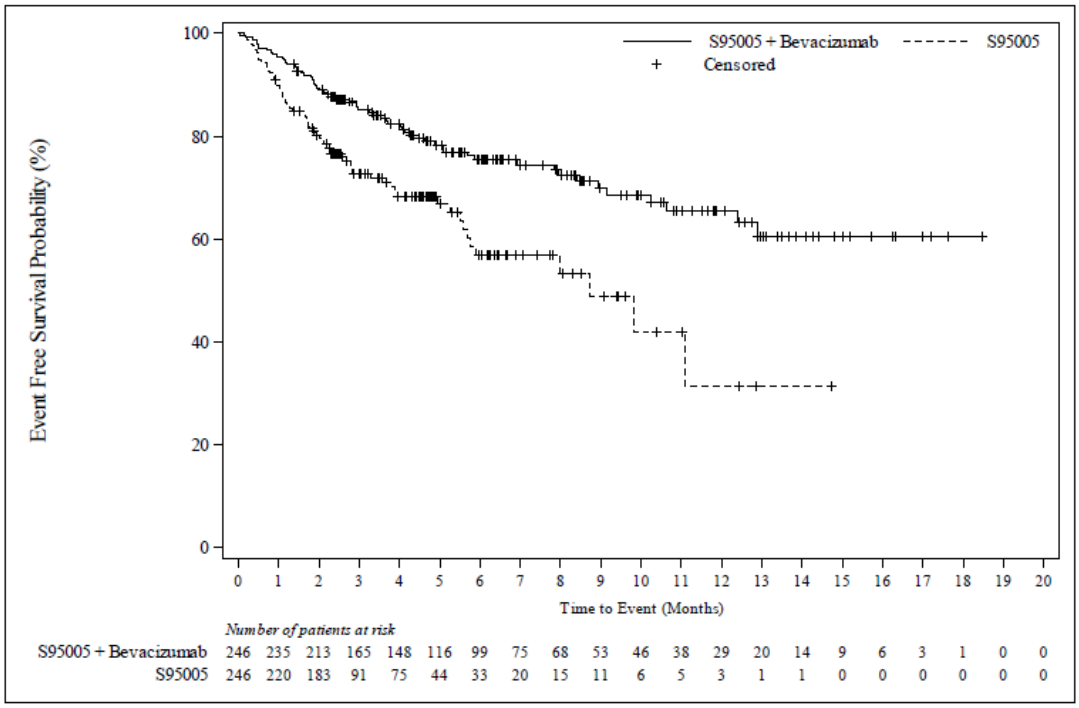

Figure 3: Kaplan-Meier curve for the outcome of SAEs

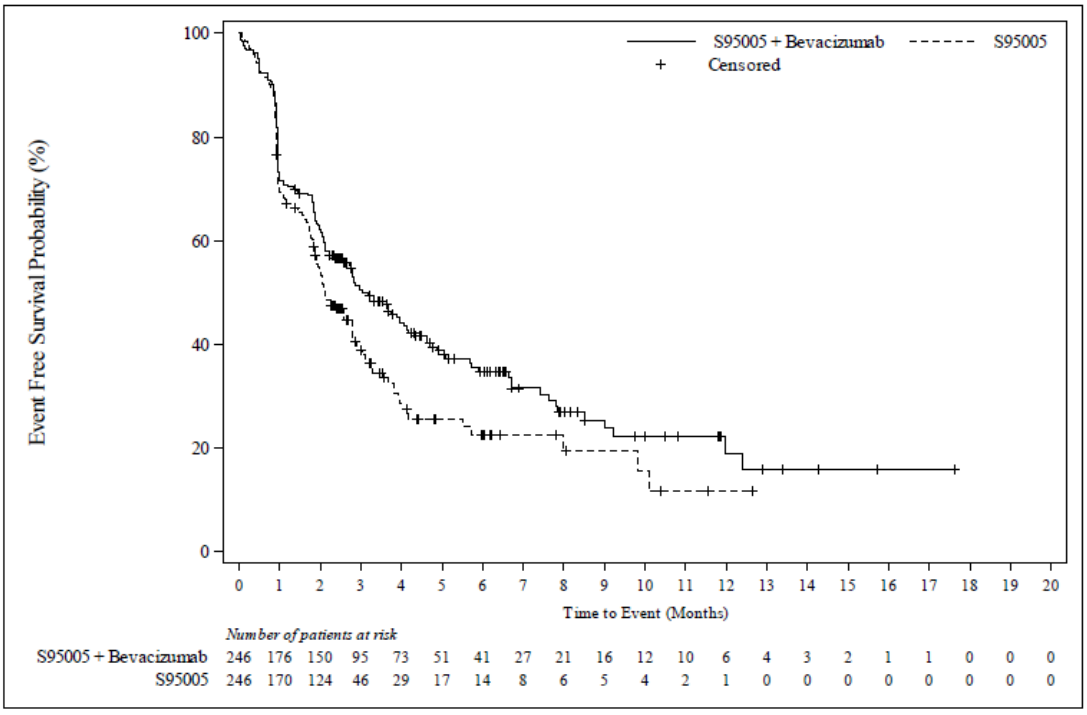

Figure 4: Kaplan-Meier curve for the outcome of severe AEs

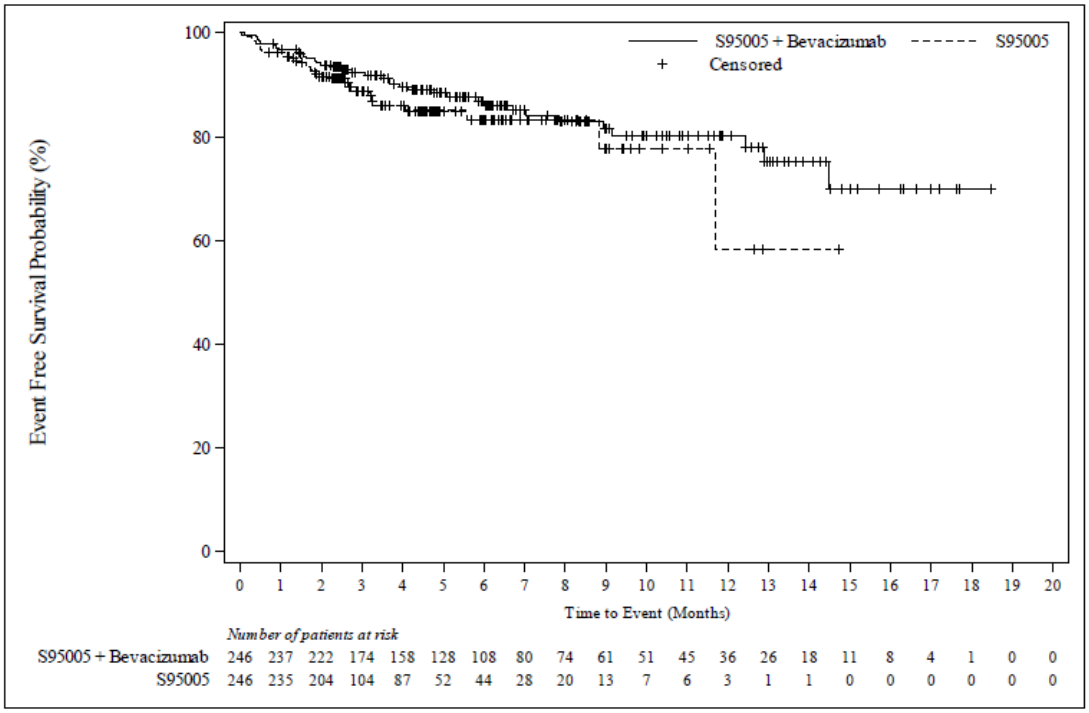

Figure 5: Kaplan-Meier curve for the outcome of discontinuation due to AEs

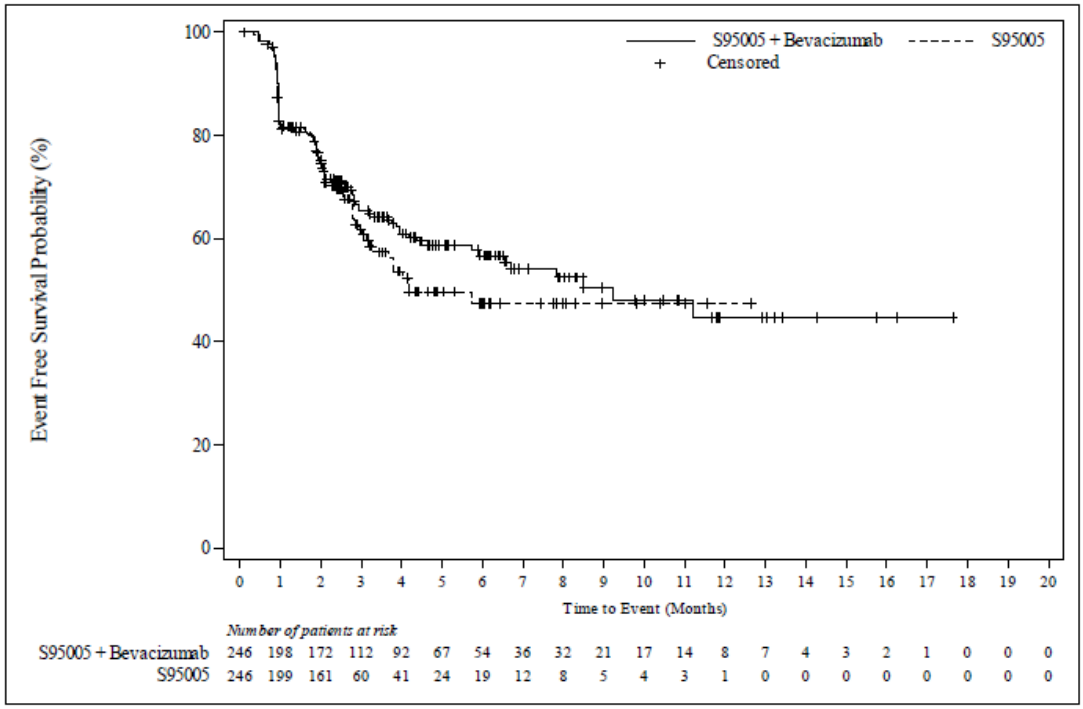

Figure 6: Kaplan-Meier curve for the outcome of blood and lymphatic system disorders (SOC, severe AEs)

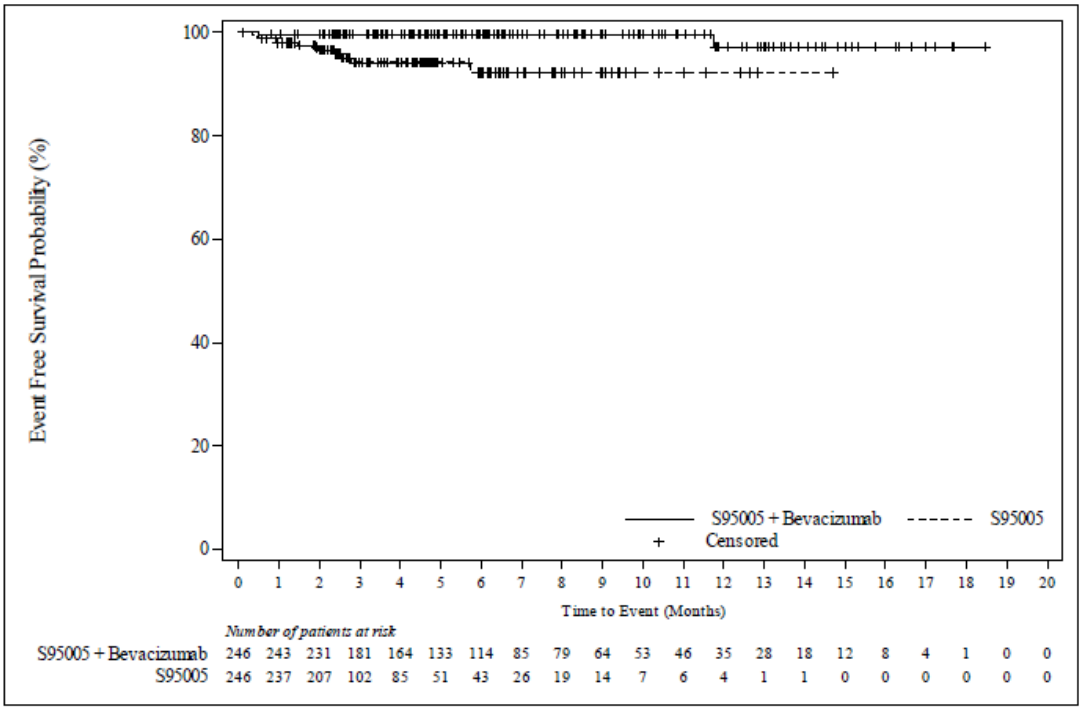

Figure 7: Kaplan-Meier curve for the outcome of anaemia (PT, severe AEs)

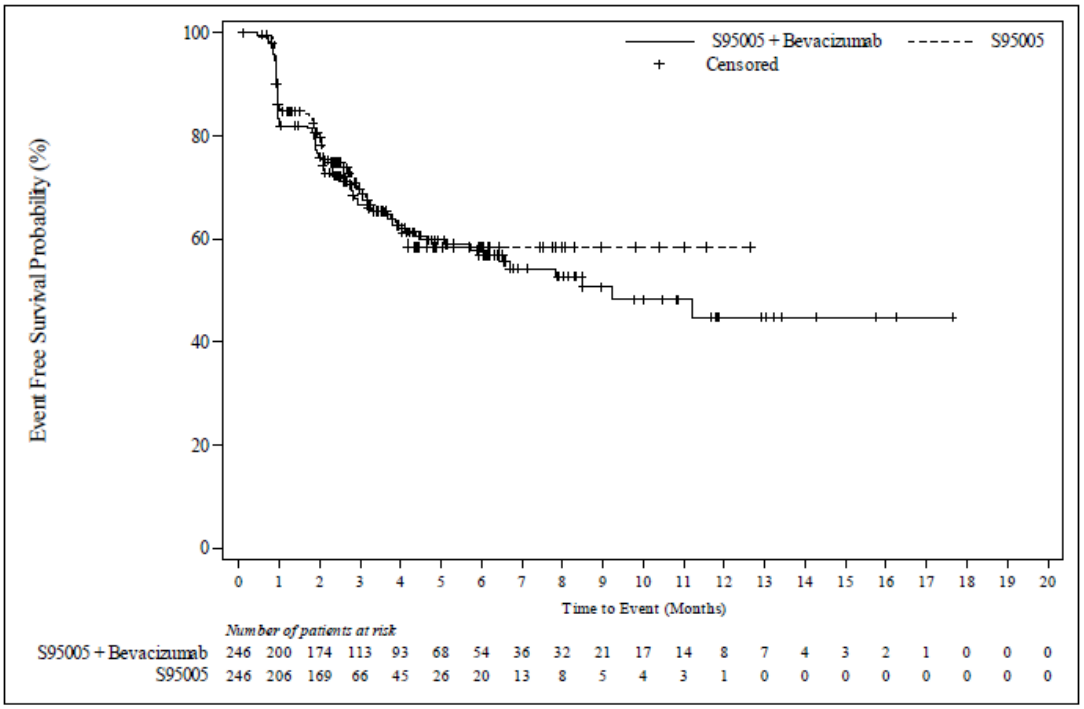

Figure 8: Kaplan-Meier curve for the outcome of neutropenia (PT, severe AEs)

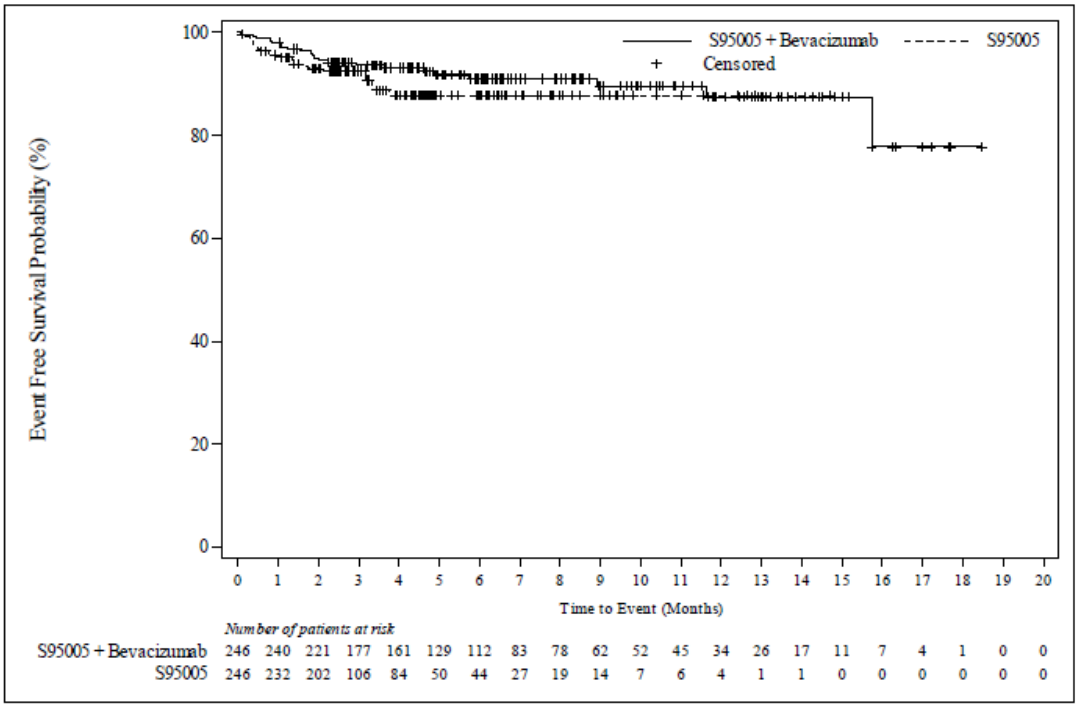

Figure 9: Kaplan-Meier curve for the outcome of gastrointestinal disorders (SOC, severe AEs)

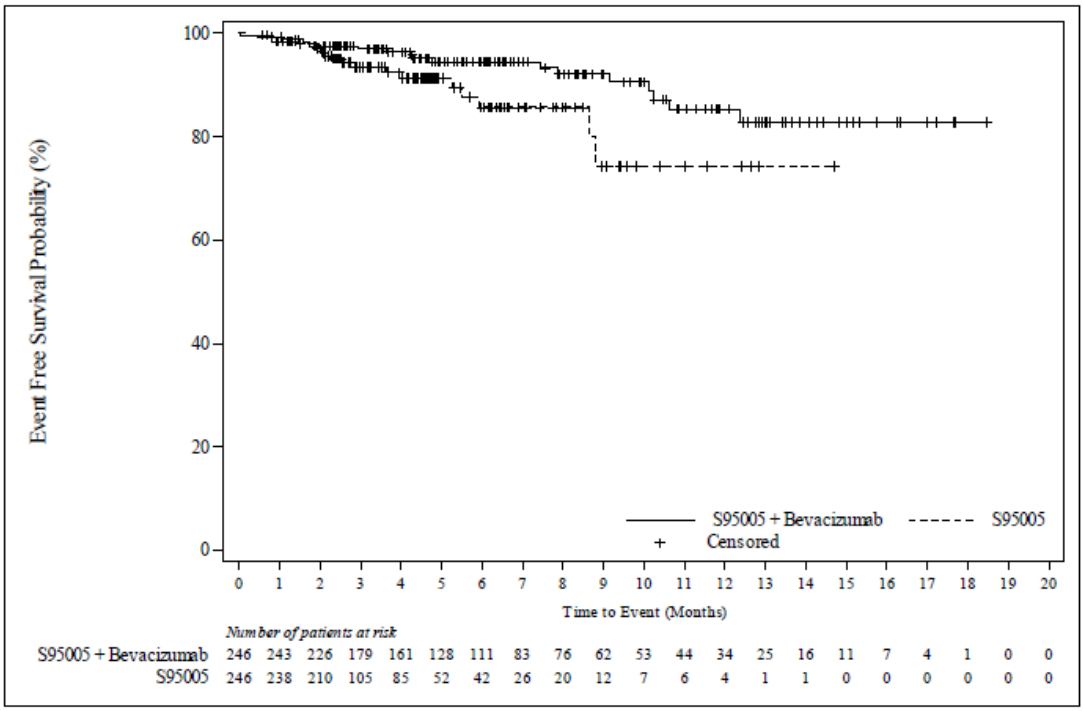

Figure 10: Kaplan-Meier curve for the outcome of infections and infestations (SOC, SAEs)

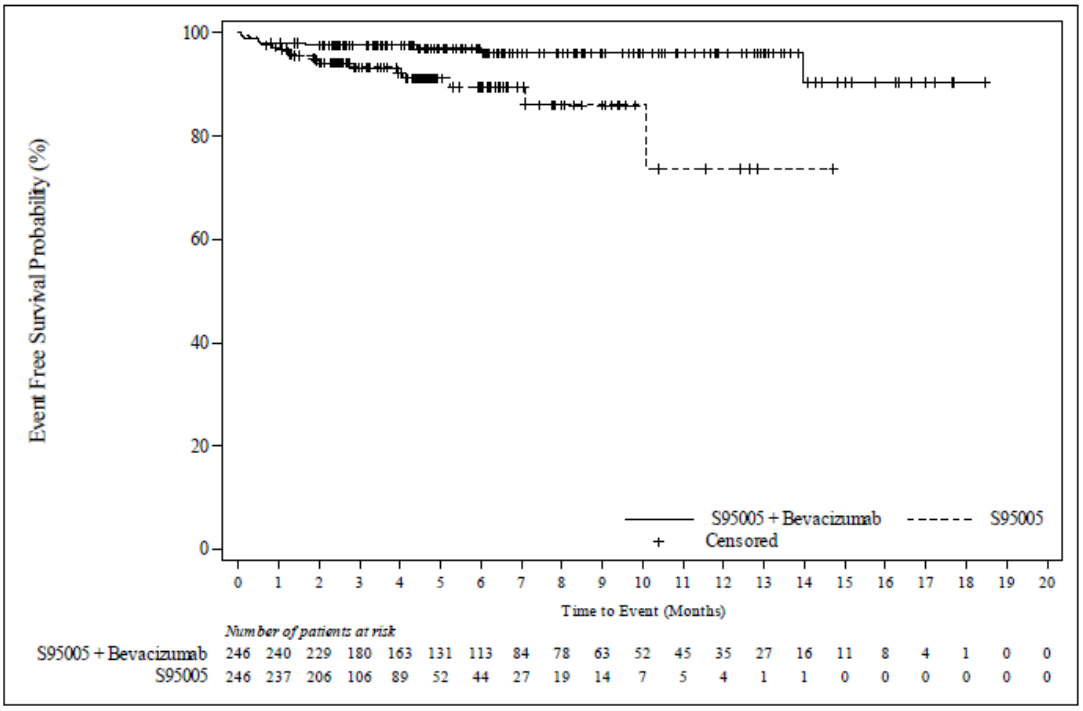

Figure 11: Kaplan-Meier curve for the outcome of general disorders and administration site conditions (SOC, severe AEs)

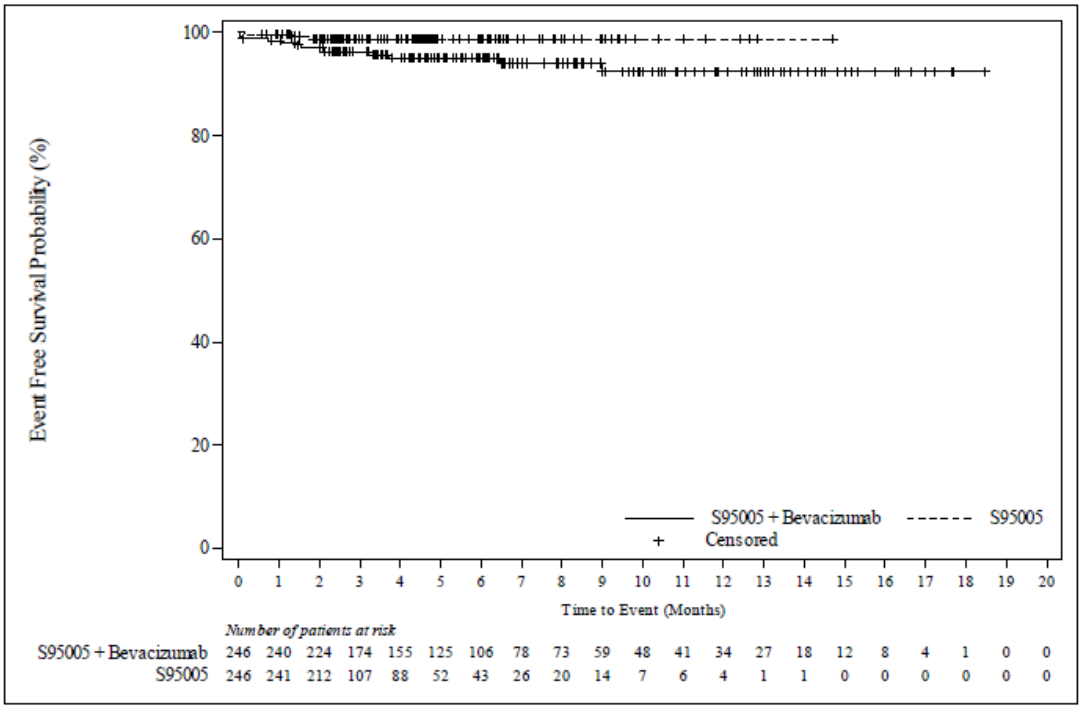

Figure 12: Kaplan-Meier curve for the outcome of hypertension (PT, severe AEs)