Sacituzumab govitecan (breast cancer)

Addendum to Project A23-86 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CDK	cyclin-dependent kinase
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

1 Background

On 12 January 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Project A23-86 (Sacituzumab govitecan – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the data and analyses submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2] as well as in the follow-up to the oral hearing, taking into account the information provided in the dossier [3]:

- assessment of the documents for the EVER-132-002 study
- assessment of the documents for the meta-analysis of the studies EVER-132-002 and TROPiCS-02

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

A subpopulation of the TROPiCS-02 study that had been assigned to treatment with capecitabine, eribulin or vinorelbine before randomization, and which was presented by the company with the dossier [3] was used for the benefit assessment of sacituzumab govitecan in adult patients with unresectable or metastatic hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who have received endocrine-based therapy, and at least 2 additional systemic therapies in the advanced setting. As part of dossier assessment A23-86 [1], the potentially relevant EVER-132-002 study was additionally identified by checking the completeness of the study pool. As no results were yet available for the EVER-132-002 study at the time of dossier preparation, the relevance of this study for the benefit assessment could not be conclusively assessed.

In the commenting procedure and after the oral hearing, the company presented analyses for 2 subpopulations of the EVER-132-002 study. One of these subpopulations is relevant for the benefit assessment (see Section 2.1 for a description of the study and the subpopulations presented as well as the reasons for its relevance). Accordingly, the assessment in the present addendum is based on the studies EVER-132-002 and TROPiCS-02 (see Table 1).

Table 1: Study pool – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication (yes/no [citation])
EVER-132-002	No	Yes	No	Yes [4]	Yes [5]	No
IMMU-132-09 (TROPICS-02[d])	Yes	Yes	No	Yes [6,7]	Yes [8,9]	Yes [10,11]

a. Capecitabine or eribulin or gemcitabine or vinorelbine.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. The tables below refer to this study by this acronym.

CSR: clinical study report; RCT: randomized controlled trial

The present addendum is structured as follows: Section 2.1 describes the EVER-132-002 study and its subpopulation relevant for the assessment. Detailed characteristics of the TROPiCS-02 study including the relevant subpopulation can be found in dossier assessment A23-86 [1]. An assessment of the suitability of the studies EVER-132-002 and TROPiCS-02 for a meta-analysis and information on subsequently submitted data for the TROPiCS-02 study can be found in

Section 2.2, followed by the presentation of the results and the derivation of the overall conclusion on added benefit based on both studies in Sections 2.3 and 2.4.

2.1 Characteristics of the EVER-132-002 study

Table 2 and Table 3 describe the EVER-132-002 study.

Table 2: Characteristics of the study included – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
EVER-132-002	RCT, open-label, parallel-group	Adult patients with pathologically confirmed breast cancer: ▪ metastatic ▪ hormone receptor positive[c] ▪ HER2-negative[d] ▪ who have received ≥ 1 endocrine-based therapy, ≥ 1 taxane, and 2–4 chemotherapies in the metastatic stage[e] ▪ ECOG PS 0 or 1	Sacituzumab govitecan (N = 166) Treatment of physician's choice[a] (N = 165) ▪ capecitabine (N = 11) ▪ eribulin (N = 131) ▪ gemcitabine (N = 10) ▪ vinorelbine (N = 13) Relevant subpopulation thereof[f]: sacituzumab govitecan (n = 160) treatment of physician's choice[a] (n = 155)	Screening: up to 28 days Treatment: until disease progression[g], unacceptable toxicity, withdrawal of consent, treatment discontinuation due to investigator's decision, or end of study Observation[h]: outcome-specific, at most until death, lost to follow-up, or end of study	41 centres in China, South Korea, and Taiwan 11/2020–ongoing Data cut-off: 30 April 2023[i]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. In the EVER-132-002 study, the treatment options were capecitabine, eribulin, gemcitabine, and vinorelbine (each as monotherapy). The ACT options suitable for the benefit assessment are capecitabine, eribulin, and vinorelbine.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
c. At least 1% oestrogen and/or progesterone receptor-positive tumour cell nuclei.
d. Defined as IHC ≤ 2+ or FISH negative.
e. (Neo)Adjuvant chemotherapy was counted as one of the prior chemotherapy regimens if unresectable, locally advanced, or metastatic disease had developed within 12 months.
f. The subpopulation comprises patients for whom treatment with capecitabine, eribulin, or vinorelbine was specified prior to randomization in case of allocation to the control arm. Patients for whom gemcitabine treatment was assigned prior to randomization are disregarded below.
g. Radiologically determined disease progression according to RECIST criteria, version 1.1.
h. Outcome-specific information is provided in Table 4.
i. Primary (final) analysis for the outcome of PFS (planned to be implemented after approximately 250 events)

Table 2: Characteristics of the study included – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
ACT: appropriate comparator therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours						

Table 3: Characteristics of the intervention – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study	Intervention	Comparison
EVER-132-002	Sacituzumab govitecan 10 mg/kg BW[b] IV on Day 1 and Day 8 of a 21-day cycle	Treatment of physician's choice; one of the following chemotherapies was determined per patient prior to randomization: ▪ Capecitabine: 1000–1250 mg/m² BSA orally twice daily on Days 1–14 of a 21-day cycle[c] ▪ Eribulin: 1.4 mg/m² BSA, IV, on Day 1 and Day 8 of a 21-week cycle[c] ▪ Vinorelbine: 25 mg/m² BSA IV once weekly[c]
	Dose adjustments 2 dose adjustments (first dose reduction by 25%, second dose reduction by 50%[d]) and dose delay (for a maximum of 21 days) allowed due to side effects	**Dose adjustments** Dose adjustments in accordance with local approvals of the respective drug
	Prior treatment ▪ at least 2 and no more than 4 prior systemic chemotherapy regimens in metastatic stage[e] ▪ at least one taxane-containing chemotherapy ▪ at least one endocrine-based therapy **Disallowed prior and concomitant treatment** ▪ Topoisomerase-1 inhibitor before screening ▪ Chemotherapy, radiotherapy, or small-molecule targeted therapy within 2 weeks prior to Cycle 1, Day 1, biologics within 4 weeks prior to Cycle 1, Day 1, and any antineoplastic therapy during the study[f] ▪ High-dose systemic corticosteroids within 2 weeks prior to Cycle 1, Day 1, and during the study ▪ Blood transfusions or haematopoietic growth factors within 2 weeks prior to Cycle 1, Day 1 **Allowed concomitant treatment** ▪ Premedication before the infusion[g] ▫ Antipyretics, H1 and H2 blockers to prevent infusion-related reactions ▫ Corticosteroids (50 mg hydrocortisone or equivalent [oral or IV]) for infusion-related reactions following infusion ▫ Preventive anti-emetic treatment with 2 drugs (with 5-hydroxytryptamine receptor antagonist [ondansetron or palonosetron or other drug according to local standards] and dexamethasone [10 mg orally or IV]), and if required, with neurokinin-1 receptor antagonist ▫ Olanzapine for the treatment of persistent or anticipatory nausea ▪ Any further palliative and/or supportive therapy (e.g. with analgesics, antidiarrhoeal drugs, blood transfusions, granulocyte colony-stimulating factors [at the discretion of the investigator for the treatment of AEs])	

Table 3: Characteristics of the intervention – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study	Intervention	Comparison
a. Capecitabine or eribulin or vinorelbine. b. The dose is calculated based on body weight on Day 1 of each 21-day cycle (more frequently if the patient's body weight has changed by > 10% since the prior application). c. Treatment with capecitabine, eribulin, and vinorelbine should be carried out in accordance with the local approvals of the respective drugs. d. No dose increase was allowed after a dose reduction. e. This includes (neo)adjuvant chemotherapy if unresectable, locally advanced, or metastatic disease has developed within 12 months. f. Except for study medication and palliative radiotherapy of a symptomatic, solitary non-target lesion or whole-brain radiotherapy (not indicated by tumour progression). g. In the intervention arm, preventive treatment was to be administered to avoid infusion-related reactions, and preventive anti-emetic treatment was recommended. In the control arm, treatment of nausea and vomiting was to be in accordance with local guidelines. AE: adverse event; BSA: body surface area; BW: body weight; IV: intravenous; RCT: randomized controlled trial		

The EVER-132-002 study is an ongoing, open-label randomized controlled trial (RCT) comparing sacituzumab govitecan versus treatment of physician's choice, selecting from capecitabine, eribulin, gemcitabine, and vinorelbine. The study included adult patients with metastatic hormone receptor-positive, HER2-negative breast cancer who had already received at least one endocrine-based therapy and at least one taxane-containing therapy as well as 2 to 4 chemotherapy regimens in the metastatic stage. (Neo)adjuvant chemotherapy was counted as one of the prior chemotherapy regimens if patients developed unresectable, locally advanced, or metastatic disease within 12 months. At baseline, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

A total of 331 included patients were randomly allocated in a 1:1 ratio to either treatment with sacituzumab govitecan (N = 166) or treatment of physician's choice (N = 165). For all patients, the investigator decided before randomization which of the available treatment options (capecitabine, eribulin, gemcitabine, vinorelbine) the patient should be treated with in case of allocation to the control arm. The subsequent randomization was stratified according to the number of prior chemotherapy regimens in the metastatic stage (2 versus 3 or 4), visceral metastases (yes versus no), and prior cyclin-dependent kinase (CDK)4/6 inhibitor therapy in the metastatic stage (yes versus no).

Gemcitabine is not an ACT option. In its comment, the company presented a relevant subpopulation of the EVER-132-002 study. The subpopulation comprises 160 versus 155 patients for whom capecitabine, eribulin, or vinorelbine was specified prior to randomization as the drug to be received in the case of allocation to the control arm (see section below on the relevant subpopulation).

Analogous to the dosage and type of application of the drugs used in the TROPiCS-02 study, treatment with sacituzumab govitecan and eribulin in the EVER-132-002 study was carried out in compliance with the specifications of the corresponding Summary of Product Characteristics (SPC) [12,13], the use of capecitabine and vinorelbine was largely in compliance with the specifications of the respective SPC [14,15] (for explanation, see dossier assessment A23-86 [1]).

The study medication was to be administered until disease progression, unacceptable toxicity, withdrawal of informed consent, discontinuation of therapy due to the investigator's decision, or until the end of the study.

Combining the available treatment options during the treatment phase was not allowed in the control arm of the EVER-132-002 study. There is no evidence suggesting that there were any restrictions regarding the choice of antineoplastic subsequent therapies after discontinuation of the study medication.

The study's primary outcome is progression-free survival (PFS). Patient-relevant secondary outcomes are overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Relevant subpopulation of the EVER-132-002 study

For the EVER-132-002 study, the company presented analyses for 2 subpopulations:

- Subpopulation a: Patients assigned to treatment with capecitabine, eribulin or vinorelbine before randomization
- Subpopulation b: Patients who were assigned to treatment with capecitabine, eribulin or vinorelbine before randomization, and who had been pretreated with CDK4/6 inhibitors

Gemcitabine is neither part of the ACT specified by the G-BA nor approved as a monotherapy in this therapeutic indication [16,17]. The company therefore formed a subpopulation of the EVER-132-002 study which, in the intervention and control arms, includes only patients for whom capecitabine, eribulin, or vinorelbine had been specified as the treatment option prior to randomization. Patients who had been assigned treatment with gemcitabine prior to randomization were excluded by the company (subpopulation a). This approach used by the company is appropriate. Subpopulation b, which the company considered to be the relevant subpopulation for the benefit assessment in its written comments, was formed both by excluding patients who had been assigned treatment with gemcitabine before randomization and by excluding those patients who had not been pretreated with (at least) one CDK4/6 inhibitor. With regard to a pooled analysis of the studies EVER-132-002 and TROPiCS-02, the company justified this by stating that previous therapy with (at least) one CDK4/6 inhibitor was an inclusion criterion of the TROPiCS-02 study and that previous therapy with CDK4/6

inhibitors in combination with endocrine therapy corresponded to the German healthcare context. The company's reasoning is not appropriate. According to the approval, patients without prior therapy with (at least) one CDK4/6 inhibitor (corresponds to subpopulation a) are also covered by the present therapeutic indication [12]. In subpopulation a, there was essentially no relevant effect modification in patient-relevant outcomes due to the characteristic of prior therapy with CDK4/6 inhibitors in the metastatic stage (see Appendix A). Since subpopulation a also represents a notably larger sample, this subpopulation is used for the benefit assessment.

Implementation of the ACT

Prior anthracycline treatment

As already explained in dossier assessment A23-86 [1], in compliance with the corresponding SPCs, the treatment options relevant for the benefit assessment (capecitabine, eribulin, vinorelbine) were only be used in the respective control arms of the studies if

- taxane and anthracycline therapy had failed or further anthracycline treatment was not indicated (capecitabine [14])
- the prior therapy contained an anthracycline and a taxane, unless this treatment was unsuitable for the patient (eribulin [13])
- therapy with taxanes and anthracyclines had failed or was not suitable (vinorelbine [15])

Since prior treatment with (at least) one taxane was an inclusion criterion for the EVER-132-002 study, all patients had presumably already received (at least) one taxane-containing chemotherapy. Analogous to the TROPiCS-02 study, prior treatment with anthracyclines was not mandatory for study inclusion. The data presented by the company show that some of the patients in the control arm of the relevant subpopulation (EVER-132-002: 16%; TROPiCS-02: 21%) had not been pretreated with (at least) one anthracycline. The proportion of patients for whom treatment with anthracyclines was not indicated or not suitable is unknown. For those patients for whom treatment with anthracyclines would have been indicated, treatment with the study medication in the control arm would not have been in compliance with the approval. Since the proportions of patients who had not received prior therapy with anthracyclines are low overall, this has no consequences for the benefit assessment.

Combination therapy

As described in dossier assessment A23-86 [1], according to guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth [18-20]. Analogous to the procedure in the TROPiCS-02 study, according to the information in the study protocol of the EVER-132-002

study, no combination therapy as part of the treatment of physician's choice selecting from the treatment options of capecitabine, eribulin, gemcitabine and vinorelbine was permitted in the control arm. The company's comments did not provide any information on the proportion of patients for whom combination therapy would have been preferable to monotherapy.

Overall, the treatment in the control arm of the relevant subpopulation is regarded as a sufficient implementation of the ACT specified by the G-BA.

Planned duration of follow-up observation

Table 4 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 4: Planned duration of follow-up observation – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
EVER-132-002	
Mortality	
Overall survival	Until death, lost to follow-up, or end of study
Morbidity	
Symptoms (EORTC QLQ-C30)	Up to 7 days after the last dose of the study medication
Health status (EQ-5D VAS)	Up to 7 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	Up to 7 days after the last dose of the study medication
Side effects	
AEs/SAEs/severe AEs[b]	Until 30 days after the last dose of the study medication
PRO-CTCAE	Up to 7 days after the last dose of the study medication

a. Capecitabine or eribulin or vinorelbine.

b. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; 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 are systematically shortened in the EVER-132-002 study because these outcomes were recorded only for the period of treatment with the study drug (plus 7 days or 30 days). However, in order to be able to draw a reliable conclusion about the entire study period or

about the time until patient death, it would be necessary for these outcomes – such as overall survival – to be recorded over the entire period.

Characteristics of the relevant subpopulation

Table 5 shows the characteristics of the patients in the relevant subpopulation of the EVER-132-002 study.

Table 5: Characteristics of the study population and of study/treatment discontinuation – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Characteristic Category	Sacituzumab govitecan N = 160	Treatment of physician's choice[a] N = 155
EVER-132-002		
Age [years], mean (SD)	52 (9)	52 (10)
Sex [F/M], %	100/0	99/1
Region, n (%)		
China	113 (71)	111 (72)
South Korea	30 (19)	32 (21)
Taiwan	17 (11)	12 (8)
Family origin, n (%)		
Asian	160 (100)	155 (100)
ECOG PS, n (%)		
0	31 (19)	37 (24)
1	129 (81)	118 (76)
BRCA1/2 mutation status, n (%)[b]	ND	ND
Time between detection of metastasis and randomization [months]		
Mean (SD)	45.7 (32.0)	40.8 (28.3)
Median [min; max]	39.5 [4.1; 156.2]	35.7 [0.8; 171.0]
Visceral metastases, n (%)		
Yes	140 (88)	139 (90)
No	20 (13)	16 (10)
Information on prior therapies		
Number of prior systemic therapies, mean (SD)	6.0 (1.7)	5.9 (1.8)
Number of prior chemotherapy regimens, mean (SD)	3.4 (1.0)	3.3 (0.9)
CDK4/6 inhibitor therapy in the metastatic stage, n (%)	79 (49)	73 (47)
Endocrine-based therapy, n (%)[c]	ND	ND
Anthracyclines, n (%)	134 (84)	131 (85)
Taxanes, n (%)[c]	ND	ND
(Neo)Adjuvant chemotherapy, n (%)	114 (71)	112 (72)
Early recurrence after (neo)adjuvant chemotherapy, n (%)[d]		
Yes	18 (16[e])	13 (12[e])
No	95 (83)[e]	98 (88)[e]
Missing	1 (< 1[e])	1 (< 1[e])
Number of chemotherapy regimens in the metastatic stage, n (%)[f]		
2	88 (55)	88 (57)
3 or 4	72 (45)	67 (43)

Table 5: Characteristics of the study population and of study/treatment discontinuation – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Characteristic Category	Sacituzumab govitecan N = 160	Treatment of physician's choice[a] N = 155
Treatment discontinuation, n (%)[g]	150 (94)	144 (93)
Study discontinuation, n (%)[h]	68 (43)	90 (58)

a. Capecitabine or eribulin or vinorelbine.
b. No information is available for the relevant subpopulation of the EVER-132-002 study. In the total population, the BRCA1/2 mutation status was unknown for the majority of patients in both study arms (95% in each case).
c. One inclusion criterion of the EVER-132-002 study was prior treatment with at least one taxane and at least one endocrine-based therapy.
d. Defined as evidence of metastatic disease within 12 months of completion of (neo)adjuvant chemotherapy.
e. Institute's calculation.
f. (Neo)Adjuvant chemotherapy was counted as one of the prior chemotherapy regimens if unresectable, locally advanced, or metastatic disease develops within 12 months.
g. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression (80% vs. 76%), withdrawal of consent (8% vs. 8%), and AEs (4% vs. 3%).
h. Common reasons for study discontinuation in the intervention arm versus the control arm were death (40% vs. 55%), withdrawal of consent (2% vs. 2%).

AE: adverse event; BRCA: breast cancer susceptibility gene; CDK: cyclin-dependent kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely comparable between the study arms. The patients were on average 52 years old, almost exclusively female (2 men in the control arm) and the majority came from China (approximately 71%). About 78% of the patients had an ECOG PS of 1 at baseline. On average, patients in both study arms each had received 6 prior systemic therapies before study start, including 3.4 chemotherapy regimens (irrespective of stage). About half were pretreated with (at least) one CDK4/6 inhibitor in the metastatic stage. The proportion of patients treated with 3 to 4 prior chemotherapy regimens in the metastatic stage was about 44%.

In both study arms, over 90% of patients discontinued treatment with the study medication. The most common reason was disease progression (80% versus 76%). The proportion of patients with study discontinuation was notably higher in the control arm at 58% than in the intervention arm (43%). A large proportion of the study discontinuations in both study arms was due to deaths.

Information on the course of the study

Table 6 shows the patients' mean/median treatment durations and the mean/median observation periods for individual outcomes.

Table 6: Information on the course of the study – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study **Duration of the study phase** **Outcome category**	**Sacituzumab govitecan** **N = 160**	**Treatment of physician's choice[a]** **N = 155**
EVER-132-002		
Treatment duration [months][b]		
Median [min; max]	5.1 [0.0; 24.9]	3.5 [0.0; 28.1]
Mean (SD)	6.4 (5.2)	4.3 (4.2)
Observation period [months]		
Overall survival[c]		
Median [Q1; Q3]	14.3 [8.6; 19.5]	12.8 [7.0; 17.7]
Mean (SD)	14.2 (6.4)	12.7 (6.5)
Symptoms (EORTC QLQ-C30)[d]		
Median [min; max]	–[e]	–[e]
Mean (SD)	–[e]	–[e]
Health status (EQ-5D VAS)[d]		
Median [min; max]	5.6 [0.8; 23.3]	4.2 [0.3; 26.5]
Mean (SD)	6.9 (5.0)	4.8 (4.0)
Health-related quality of life (EORTC QLQ-C30)[d]		
Median [min; max]	–[e]	–[e]
Mean (SD)	–[e]	–[e]
AEs/SAEs/severe AEs[b, f]		
Median [min; max]	5.7 [3.4; 10.4]	4.5 [2.2; 6.5]
Mean (SD)	7.3 (5.1)	5.2 (4.1)
PRO-CTCAE		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

Table 6: Information on the course of the study – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study **Duration of the study phase** **Outcome category**	**Sacituzumab govitecan** **N = 160**	**Treatment of physician's choice[a]** **N = 155**
a. Capecitabine or eribulin or vinorelbine. b. Data refer to the safety population, which includes all patients who received (at least) one dose of the study medication (159 vs. 156 patients). c. The observation period is defined as the time from randomization to death or to the last contact. d. Data refer to all patients with a baseline value and (at least) one post-baseline value (155 vs. 149 patients). e. The observation periods of a median of 2.9 months in the intervention arm and 2.3 months in the control arm for the outcomes of symptoms (EORTC QLQ-C30) and health-related quality of life (EORTC QLQ-C30), which were provided by the company in the subsequent submission to the written comments, are not plausible, as the observation period was linked to the end of treatment in each case and it can therefore be assumed that they roughly correspond to the respective treatment duration plus 7 days. f. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of randomized patients; ND: no data; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale		

The median treatment duration of patients in the relevant subpopulation of the EVER-132-002 study was longer in the intervention arm than in the control arm (5.1 versus 3.5 months) as of the data cut-off date of 30 April 2023.

The median observation period for overall survival is 14.3 months in the intervention arm and 12.8 months in the control arm. For the outcome of health status (EQ-5D visual analogue scale [VAS]) and for the outcomes on side effects, whose observation period was linked to the end of treatment (see Table 4), slightly longer observation periods were seen in the intervention arm than in the control arm due to the previously described differences in treatment duration between the 2 study arms. The information on median observation periods for the outcomes on symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) at 2.9 months and health-related quality of life (EORTC QLQ-C30) at 2.3 months provided in the company's subsequent submission are not plausible because the observation period was linked to the end of treatment in each case and it can therefore be assumed that they roughly correspond to the corresponding treatment duration plus 7 days. This assumption is further supported by the response rates; in the intervention arm, values for fewer than half of the patients were only available at Week 25 (about Month 5.8), and in the control arm at Week 19 (about Month 4.4).

Information on subsequent therapies

Table 7 shows the subsequent therapies patients received after discontinuing the study medication as of the data cut-off from 30 April 2024.

Table 7: Information on subsequent antineoplastic therapies (≥ 2% of patients in at least one study arm) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Subsequent therapy[b]	Patients with subsequent therapy, n (%)	
	Sacituzumab govitecan N = 159	Treatment of physician's choice[a] N = 156
EVER-132-002		
Data cut-off: 30 April 2023		
Total	124 (78.0)	123 (78.8)
Abemaciclib	27 (17.0)	37 (23.7)
Fulvestrant	26 (16.4)	31 (19.9)
Cisplatin	17 (10.7)	23 (14.7)
Exemestane	18 (11.3)	17 (10.9)
Bevacizumab	19 (11.9)	15 (9.6)
Capecitabine	16 (10.1)	18 (11.5)
Eribulin	26 (16.4)	6 (3.8)
Vinorelbine tartrate	11 (6.9)	21 (13.5)
Eribulin mesylate	27 (17.0)	4 (2.6)
Gemcitabine hydrochloride	12 (7.5)	19 (12.2)
Gemcitabine	14 (8.8)	15 (9.6)
Nab-paclitaxel	11 (6.9)	14 (9.0)
Cyclophosphamide	12 (7.5)	12 (7.7)
Utidelone	12 (7.5)	9 (5.8)
Carboplatin	12 (7.5)	7 (4.5)
Letrozole	7 (4.4)	11 (7.1)
Vinorelbine	8 (5.0)	10 (6.4)
Paclitaxel	6 (3.8)	11 (7.1)
Catequentinib hydrochloride	7 (4.4)	9 (5.8)
Everolimus	5 (3.1)	10 (6.4)
Doxorubicin	3 (1.9)	10 (6.4)
Fluorouracil	6 (3.8)	7 (4.5)
Disitamab vedotin	6 (3.8)	6 (3.8)
Methotrexate	6 (3.8)	6 (3.8)
Dalpiciclib isethionate	7 (4.4)	2 (1.3)
Goserelin acetate	5 (3.1)	4 (2.6)
Catequentinib	6 (3.8)	2 (1.3)

Table 7: Information on subsequent antineoplastic therapies (≥ 2% of patients in at least one study arm) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Subsequent therapy[b]	Patients with subsequent therapy, n (%)	
	Sacituzumab govitecan N = 159	Treatment of physician's choice[a] N = 156
Palbociclib	3 (1.9)	5 (3.2)
Docetaxel	3 (1.9)	4 (2.6)
Leuprorelin acetate	3 (1.9)	4 (2.6)
Camrelizumab	4 (2.5)	1 (0.6)
Chidamide	4 (2.5)	0 (0)
Doxorubicin hydrochloride, PEG liposomal	4 (2.5)	0 (0)

a. Capecitabine or eribulin or gemcitabine or vinorelbine.
b. Assignment according to WHO Drug Dictionary, Version March 2023.

n: number of patients with subsequent therapy; N: number of analysed patients; nab: albumin-bound nanoparticles; PEG: polyethylene glycol; RCT: randomized controlled trial; WHO: World Health Organization

The proportion of patients in the relevant subpopulation of the EVER-132-002 study with (at least) one subsequent antineoplastic therapy was comparable between the 2 study arms (78% versus 79%). Of these, subsequent therapy with bevacizumab was used in 19 (12%) patients in the intervention arm and 15 (10%) patients in the control arm. According to guidelines, however, the administration of bevacizumab in combination with chemotherapy in metastatic breast cancer is only recommended in first-line therapy [19,21]. Since the difference in the proportions of patients with subsequent bevacizumab therapy between the study arms was small, it can be assumed that the treatment in the study that was not in compliance with the guideline had no distorting influence on the study results.

Risk of bias across outcomes (study level)

Table 8 shows the risk of bias across outcomes (risk of bias at study level).

Table 8: Risk of bias across outcomes (study level) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
EVER-132-002	Yes	Yes	No	No	Yes	Yes	Low

a. Capecitabine or eribulin or vinorelbine.

RCT: randomized controlled trial

The risk of bias across outcomes for the EVER-132-002 study is rated as low.

Limitations resulting from the open-label study design are described in Section 2.3.2 of the present addendum under outcome-specific risk of bias.

2.2 Meta-analysis of the studies EVER-132-002 and TROPiCS-02 presented by the company

The results of an individual patient data (IPD) meta-analysis based on the relevant subpopulations of the studies EVER-132-002 and TROPiCS-02 (population without patients who were assigned to gemcitabine treatment before randomization) are available for the benefit assessment in the context of the present addendum. The 2 studies EVER-132-002 and TROPiCS-02 have an identical design. There is a difference with regard to one inclusion criterion; prior therapy with (at least) one CDK4/6 inhibitor was only required in the TROPiCS-02 study before study entry. While the TROPiCS-02 study was conducted in centres in North America and Europe, the EVER-132-002 study included only patients of Asian family origin. All other patient characteristics are sufficiently similar. The subpopulation of the EVER-132-002 study was on average 4 years younger than the subpopulation of the TROPiCS-02 study; at approximately 78%, the proportion with ECOG PS 1 was about 24 percentage points higher; and the mean time between the detection of metastasis and randomization was shorter (43 months versus 53 months). Since the IPD meta-analyses subsequently submitted by the company for the outcomes on mortality, morbidity and side effects showed no effect modification by the characteristic of study, a statistical analysis as meta-analysis is considered appropriate and used for the benefit assessment.

Data cut-offs

The analysis was carried out for all outcomes included in the assessment for the following data cut-offs:

- Study TROPiCS-02: 1 December 2022
- Study EVER-132-002: 30 April 2023

As explained in dossier assessment A23-86 [1], the dossier contained only analyses for the data cut-off of 1 July 2022 for the outcomes on morbidity, health-related quality of life and side effects based on the relevant subpopulation of the TROPiCS-02 study. Although results of time-to-event analyses for the data cut-off of 1 December 2022 for the TROPiCS-02 study were included in the IPD meta-analysis, the company did not present these separately in the commenting procedure or in the supplementary submission to the comments. For outcomes with identical event rates at both data cut-offs, results from dossier assessment A23-86 [1] could be used for the TROPiCS-02 study. For different event rates, no information at the individual study level is provided in the results table for the data cut-off of 1 December 2022 (see Table 13).

Data on the TROPiCS-02 study subsequently submitted by the company

For the relevant subpopulation of the TROPiCS-02 study, both information on the duration of treatment for the data cut-off of 1 December 2022 (see Table 9) and information on subsequent therapies used after discontinuation of the study medication for the data cut-off of 1 July 2022 (see Table 10) were subsequently submitted in the commenting procedure.

Table 9: Information on treatment duration – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (TROPiCS-02 study)

Study **Duration of the study phase** **Outcome category**	**Sacituzumab govitecan** **N = 201**	**Treatment of physician's choice[a]** **N = 194**
TROPiCS-02		
Data cut-off: 1 December 2022		
Treatment duration [months][b]		
Median [min; max]	4.0 [0.0; 35.4]	2.6 [0.0; 22.2]
Mean (SD)	5.8 (6.0)	3.8 (3.8)

a. Capecitabine or eribulin or vinorelbine.
b. Data refer to the safety population, which includes all patients who received (at least) one dose of the study medication (201 vs. 194 patients).

max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

At the 1 December 2022 data cut-off date, the median treatment duration in the intervention arm was 4.0 months, about 1.5 times longer than in the control arm at 2.6 months. Based on the data subsequently submitted by the company, there is therefore no change in comparison with dossier assessment A23-86 [1].

Table 10: Information on subsequent antineoplastic therapies (≥ 2% of patients in at least one study arm) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (TROPiCS-02 study) (multipage table)

Study **Subsequent therapy[b]**	**Patients with subsequent therapy, n (%)**	
	Sacituzumab govitecan **N = 201**	**Treatment of physician's choice[a]** **N = 194**
TROPiCS-02		
Data cut-off: 1 July 2022		
Total	143 (71.1)	118 (60.8)
Eribulin	66 (32.8)	18 (9.3)
Gemcitabine	32 (15.9)	33 (17.0)
Carboplatin	27 (13.4)	32 (16.5)
Cyclophosphamide	26 (12.9)	32 (16.5)
Vinorelbine	24 (11.9)	13 (6.7)
Paclitaxel	15 (7.5)	20 (10.3)
Capecitabine	21 (10.4)	13 (6.7)
Fulvestrant	17 (8.5)	14 (7.2)
Vinorelbine tartrate	7 (3.5)	22 (11.3)
Doxorubicin	14 (7.0)	13 (6.7)
Fluorouracil	12 (6.0)	14 (7.2)
Doxorubicin hydrochloride, PEG liposomal	12 (6.0)	13 (6.7)
Everolimus	9 (4.5)	15 (7.7)
Doxorubicin, liposome-encapsulated	8 (4.0)	11 (5.7)
Epirubicin	5 (2.5)	13 (6.7)
Alpelisib	10 (5.0)	7 (3.6)
Exemestane	6 (3.0)	11 (5.7)
Methotrexate	6 (3.0)	9 (4.6)
Sacituzumab govitecan	1 (0.5)	13 (6.7)
Trastuzumab deruxtecan	4 (2.0)	10 (5.2)
Pembrolizumab	7 (3.5)	6 (3.1)
Abemaciclib	6 (3.0)	6 (3.1)
Etoposide	4 (2.0)	8 (4.1)
Docetaxel	5 (2.5)	6 (3.1)
Eribulin mesylate	7 (3.5)	2 (1.0)
Gemcitabine hydrochloride	2 (1.0)	7 (3.6)

Table 10: Information on subsequent antineoplastic therapies (≥ 2% of patients in at least one study arm) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (TROPiCS-02 study) (multipage table)

Study Subsequent therapy[b]	Patients with subsequent therapy, n (%)	
	Sacituzumab govitecan N = 201	Treatment of physician's choice[a] N = 194
Nab-paclitaxel	6 (3.0)	3 (1.5)
Letrozole	4 (2.0)	4 (2.1)
Vincristine	5 (2.5)	1 (0.5)
Ixabepilone	1 (0.5)	4 (2.1)
Mitomycin	1 (0.5)	4 (2.1)
Radiotherapy	5 (2.5)	0 (0)
Trastuzumab	0 (0)	4 (2.1)

a. Capecitabine or eribulin or gemcitabine or vinorelbine.
b. Assignment according to WHO Drug Dictionary, Version March 2023.

n: number of patients with subsequent therapy; N: number of analysed patients; nab: albumin-bound nanoparticles; PEG: polyethylene glycol; RCT: randomized controlled trial; WHO: World Health Organization

The company did not submit any information on the subsequent therapies used in the relevant subpopulation of the TROPiCS-02 study as of the data cut-off of 1 December 2022; the information provided on the data cut-off of 1 July 2022 has not changed the assessment from dossier assessment A23-86 [1].

2.3 Results on added benefit

2.3.1 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, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - Serious adverse events (SAEs)

- Severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
- Discontinuation due to AEs
- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
- Hand-foot syndrome (Preferred Term [PT], AEs)
- Gastrointestinal toxicity (System Organ Class [SOC] gastrointestinal disorders, severe AEs)
- Neutropenia (PT compilation of the company, severe AEs)
- Other specific AEs, if any

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

Table 11 shows the outcomes for which data were available in the studies included.

Table 11: Matrix of outcomes – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a]

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	PRO-CTCAE	Hand-foot syndrome[c]	Gastrointestinal toxicity[d]	Neutropenia[e]	Further specific AEs[b]
EVER-132-002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	No[g]
TROPiCS-02	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	Yes[g]

a. Capecitabine or eribulin or vinorelbine.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as palmar-plantar erythrodysaesthesia syndrome (PT, AEs).
d. Operationalized as gastrointestinal disorders (SOC, severe AEs).
e. Operationalized as a compilation predefined by the company of the PTs of neutropenia, neutrophil count decreased, and febrile neutropenia (each severe AEs).
f. No suitable data available; for the reasoning, see dossier assessment A23-86 [1] and Section 2.3.1 of the present addendum.
g. Data on common AEs, SAEs and severe AEs (operationalized as CTCAE grade ≥ 3) are available for the TROPiCS-02 study (see dossier assessment A23-86 [1]); the company did not submit any suitable data for the EVER-132-002 study; a specific AE selection based on results pooled in a meta-analysis is therefore not possible (see Section 2.3.1)

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

Notes on outcomes

Side effects

AEs, SAEs, and severe AEs

In both the EVER-132-002 study and the TROPiCS-02 study, it was planned not to record as AEs events that were clearly attributable to the progression of the underlying disease. For the overall rates of AEs, SAEs and severe AEs, the company's Module 4 A had presented analyses for the TROPiCS-02 study excluding disease-related events in addition to analyses considering all AEs (see dossier assessment A23-86 [1]). For the EVER-132-002 study, the company did not

provide any information on whether the overall AE rates had been analysed without disease-related events in each case. In the total population of the EVER-132-002 study, only 2 or 3 patients had (at least) one event in the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps) (each with CTCAE grade ≤ 2). It can therefore be assumed that there is no important difference in the overall rates of AEs (irrespective of severity), including or excluding disease-related events.

For the EVER-132-002 study, the company presented no data on common AEs, SAEs and severe AEs for subpopulation a. Since the proportion of the subpopulation of the total population of the EVER-132-002 study is 95% and the overall rates of AEs, SAEs and severe AEs in the individual study arms differ only slightly between the subpopulation and the total population, the total population would in principle be suitable for a selection of specific AEs. However, the clinical study report of the EVER-132-002 study provided only a descriptive presentation of the events (SOC/PT) that occurred in the total population (see Appendix D); a selection of specific AEs based on frequencies and differences between the study arms is not suitable due to the different treatment durations and thus observation periods in the study arms (see Table 4). The company also did not present IPD meta-analyses (time-to-event analyses) based on the relevant subpopulations of the studies EVER-132-002 and TROPiCS-02 for common AEs, SAEs and severe AEs. Thus, no suitable data for a selection of specific AEs based on results pooled in a meta-analysis are available in the context of the present addendum. The effects of the lack of suitable data are taken into account in the overall conclusion (see Section 2.4.2).

PRO-CTCAE

In the EVER-132-002 study, side effects were also recorded in accordance with the study protocol using the PRO-CTCAE instrument [22-24], which represents a valuable addition to the usual recording and analysis of AEs. In the commenting procedure, no data were presented for the outcome of PRO-CTCAE for the EVER-132-002 study. In accordance with the procedure in the TROPiCS-02 study (see dossier assessment A23-86 [1]), 9 symptomatic AEs from the PRO-CTCAE were recorded in the EVER-132-002 study according to protocol:

- Decreased appetite
- Nausea
- Vomiting
- Constipation
- Diarrhoea
- Abdominal pain
- Shortness of breath

- Hair loss
- Fatigue

Analogous to the TROPiCS-02 study, neither a detailed justification for the selection of the 9 symptomatic AEs from the PRO-CTCAE system nor a suitable analysis is available in the documents of the EVER-132-002 study (for an explanation, see dossier assessment A23-86 [1]). Overall, no suitable data for this outcome are therefore available for the present assessment.

2.3.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a]

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[b]	Discontinuation due to AEs	PRO-CTCAE	Hand-foot syndrome[c]	Gastrointestinal toxicity[d]	Neutropenia[e]	Further specific AEs[b]
EVER-132-002	L	L	H[f, g]	H[f, g]	H[f, g]	H[g]	H[g]	H[h]	–[i]	H[f, g]	H[g]	H[g]	–[j]
TROPiCS-02	L	L	H[f, g, k]	H[f, g, k]	H[f, g, k]	H[g]	H[g]	H[h]	–[i]	H[f, g]	H[g]	H[g]	–[j]

a. Capecitabine or eribulin or vinorelbine.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as palmar-plantar erythrodysaesthesia syndrome (PT, AEs).
d. Operationalized as gastrointestinal disorders (SOC, severe AEs).
e. Operationalized as a compilation predefined by the company of the PTs of neutropenia, neutrophil count decreased, and febrile neutropenia (each severe AEs).
f. Lack of blinding in subjective recording of outcomes.
g. Incomplete observations for potentially informative reasons with different lengths of follow-up observation.
h. Lack of blinding in the presence of subjective decision on treatment discontinuation.
i. No suitable data available; for the reasoning, see dossier assessment A23-86 [1] and Section 2.3.1 of the present addendum.
j. Data on common AEs, SAEs and severe AEs (operationalized as CTCAE grade ≥ 3) are available for the TROPiCS-02 study (see dossier assessment A23-86 [1]); the company did not submit any suitable data for the EVER-132-002 study; a specific AE selection based on results pooled in a meta-analysis is therefore not possible (see Section 2.3.1)
k. High proportion of patients excluded from the analysis (> 10%).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

In dossier assessment A23-86 [1], the risk of bias of the results of all outcomes of the TROPiCS-02 study , with the exception of the outcome of overall survival, was rated as high. No suitable data were available for the outcome of PRO-CTCAE.

For the EVER-132-002 study, the risk of bias for the outcome of overall survival is rated as low. For the outcomes on morbidity (symptoms [EORTC QLQ-C30] and health status [EQ-5D VAS]) and on health-related quality of life (EORTC QLQ-C30), the risk of bias of the results is rated as high in each case due to incomplete observation for potentially informative reasons and lack of blinding in the presence of subjective outcome recording. For the results of the outcomes of SAEs, severe AEs, and non-serious/non-severe side effects, the risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons with different lengths of follow-up observation in the study arms. For the results of non-serious/non-severe side effects, the risk of bias is additionally increased due to lack of blinding in the presence of subjective outcome recording. The risk of bias for the outcome of discontinuation due to AEs is rated as high because of lack of blinding in the presence of subjective decision on treatment discontinuation. Since no suitable data are available for the outcome of PRO-CTCAE and for specific AEs (see Section 2.3.1), the risk of bias is not assessed.

2.3.3 Results

Table 13 summarizes the results on the comparison of sacituzumab govitecan versus treatment of physician's choice in adult patients with unresectable or metastatic hormone receptor-positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies for advanced disease. Where necessary, calculations conducted by the Institute supplement the data from the dossier and the data subsequently submitted by the company in the commenting procedure and after the oral hearing.

Forest plots of the meta-analyses conducted by the Institute can be found in Appendix A. For the EVER-132-002 study, Kaplan-Meier curves on time-to-event analyses are presented in Appendix C. The Kaplan-Meier curve for the outcome of health status (EQ-5D VAS) was not presented by the company. Tables on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in Appendix D. For the TROPiCS-02 study, the Kaplan-Meier curves and the tables on common AEs, SAEs, severe AEs, and discontinuations due to AEs were already presented in dossier assessment A23-86 [1].

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category Outcome Study	Sacituzumab govitecan		Treatment of physician's choice[a]		Sacituzumab govitecan vs. treatment of physician's choice[a]
	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
Mortality					
Overall survival					
TROPiCS-02	205	14.4 [12.8; 16.0] 165 (80.5)	213	11.2 [10.1; 12.8] 176 (82.6)	0.85 [0.69; 1.05]; 0.136[b]
EVER-132-002	160	21.1 [18.0; NC] 64 (40.0)	155	15.3 [13.2; 18.4] 85 (54.8)	0.64 [0.46; 0.88]; 0.006[c]
Total	365	16.2 [14.7; 19.1] 229 (62.7)	368	12.8 [11.6; 14.9] 261 (70.9)	0.77 [0.64; 0.92]; < 0.001[d]
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration)[e]					
Fatigue					
TROPiCS-02	172	2.1 [1.6; 2.8] 121 (70.3)	162	1.3 [1.0; 1.8] 124 (76.5)	0.67 [0.52; 0.87]; 0.002[b]
EVER-132-002	155	1.9 [1.5; 3.0] 99 (63.9)	147	1.7 [1.5; 2.6] 101 (68.7)	0.87 [0.65; 1.15]; 0.300[c]
Total	327	2.0 [1.6; 2.8] 220 (67.3)	309	1.5 [1.4; 1.9] 225 (72.8)	0.75 [0.63; 0.91]; 0.002[d]
Nausea and vomiting					
TROPiCS-02	173	2.4 [1.6; 3.9] 106 (61.3)	165	4.6 [2.9; 9.5] 77 (46.7)	1.26 [0.93; 1.69]; 0.127[b]
EVER-132-002	154	2.0 [1.5; 2.8] 110 (71.4)	149	5.5 [2.8; NC] 68 (45.6)	1.63 [1.20; 2.23]; 0.002[c]
Total	327	2.1 [1.7; 2.8] 216 (66.1)	314	5.5 [3.5; 7.2] 145 (46.2)	1.44 [1.17; 1.78]; 0.002[d]

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category Outcome Study	Sacituzumab govitecan		Treatment of physician's choice[a]		Sacituzumab govitecan vs. treatment of physician's choice[a]
	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
Pain					
TROPiCS-02	169	3.8 [2.8; 6.1] 95 (56.2)	159	3.2 [2.2; 4.3] 90 (56.6)	0.83 [0.62; 1.12]; 0.212[b]
EVER-132-002	154	5.6 [3.3; 7.7] 79 (51.3)	145	2.9 [2.3; 4.1] 88 (60.7)	0.67 [0.49; 0.92]; 0.010[c]
Total	323	4.8 [3.5; 6.1] 174 (53.1)	304	3.0 [2.7; 3.9] 178 (58.8)	0.75 [0.61; 0.93]; 0.020[d]
Dyspnoea					
TROPiCS-02	170	ND[f] 80 (47.1)	161	3.9 [2.4; 7.5] 84 (52.2)	ND[f]
EVER-132-002	152	23.3 [6.1; NC] 59 (38.8)	148	5.6 [3.9; 11.2] 66 (44.6)	0.71 [0.50; 1.02]; 0.060[c]
Total	322	7.2 [5.8; 18.2] 139 (43.2)	309	4.5 [3.1; 6.9] 150 (48.5)	0.67 [0.53; 0.85]; < 0.001[d]
Insomnia					
TROPiCS-02	160	8.7 [6.0; 18.9] 68 (42.5)	150	3.6 [2.3; NC] 69 (46.0)	0.67 [0.48; 0.95]; 0.021[b]
EVER-132-002	150	7.4 [4.2; 11.0] 69 (46.0)	144	5.6 [4.3; NC] 59 (41.0)	1.00 [0.70; 1.42]; 1.000[c]
Total	310	7.7 [5.9; 12.5] 137 (44.2)	294	5.3 [3.6; 8.3] 128 (43.5)	0.81 [0.64; 1.03]; 0.200[d]
Appetite loss					
TROPiCS-02	167	3.3 [1.7; 5.9] 97 (58.1)	156	3.7 [2.3; 5.4] 78 (50.0)	1.08 [0.79; 1.46]; 0.633[b]
EVER-132-002	151	2.9 [2.0; 4.2] 95 (62.9)	148	4.2 [2.7; NC] 71 (48.0)	1.17 [0.86; 1.60]; 0.300[c]
Total	318	3.0 [2.2; 4.2] 192 (60.4)	304	4.1 [2.8; 5.4] 149 (49.0)	1.12 [0.90; 1.39]; 0.600[d]

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category Outcome Study	Sacituzumab govitecan		Treatment of physician's choice[a]		Sacituzumab govitecan vs. treatment of physician's choice[a]
	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
Constipation					
TROPiCS-02	170	5.4 [3.2; 9.1] 83 (48.8)	158	4.8 [3.2; 8.2] 70 (44.3)	1.01 [0.73; 1.40]; 0.942[b]
EVER-132-002	153	7.0 [4.2; NC] 64 (41.8)	146	8.5 [4.4; NC] 51 (34.9)	1.08 [0.73; 1.58]; 0.700[c]
Total	323	7.0 [4.2; 11.2] 147 (45.5)	304	5.7 [4.2; NC] 121 (39.8)	1.04 [0.82; 1.33]; 0.100[d]
Diarrhoea					
TROPiCS-02	172	2.0 [1.6; 3.4] 104 (60.5)	164	8.2 [5.8; NC] 55 (33.5)	2.41 [1.72; 3.37]; < 0.001[b]
EVER-132-002	154	2.9 [1.9; 4.8] 95 (61.7)	149	9.6 [5.8; NC] 45 (30.2)	2.23 [1.55; 3.20]; < 0.001[c]
Total	326	2.5 [1.8; 3.6] 199 (61.0)	313	9.6 [5.9; NA] 100 (31.9)	2.29 [1.79; 2.92]; < 0.001[d]
Health status (EQ-5D VAS, time to first deterioration)[g]					
TROPiCS-02	168	11.8 [6.9; NC] 63 (37.5)	162	7.0 [4.6; 12.7] 64 (39.5)	0.72 [0.51; 1.03]; 0.073[b]
EVER-132-002	155	ND 49 (31.6)	149	ND 54 (36.2)	0.68 [0.46; 1.01]; 0.050[h]
Total	323	12.3 [8.5; NC] 112 (34.7)	311	6.9 [5.3; 12.7] 118 (37.9)	0.71 [0.54; 0.92]; 0.010[d]
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[i]					
Global health status					
TROPiCS-02	173	4.9 [3.0; 6.7] 95 (54.9)	164	2.6 [2.0; 3.5] 103 (62.8)	0.66 [0.50; 0.88]; 0.004[b]
EVER-132-002	154	3.8 [2.8; 4.7] 89 (57.8)	147	2.8 [2.1; 4.1] 86 (58.5)	0.87 [0.64; 1.18]; 0.400[c]
Total	327	4.1 [3.2; 5.0] 184 (56.3)	311	2.8 [2.2; 3.5] 189 (60.8)	0.76 [0.62; 0.93]; 0.020[d]

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category Outcome Study	Sacituzumab govitecan		Treatment of physician's choice[a]		Sacituzumab govitecan vs. treatment of physician's choice[a]
	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
Physical functioning					
TROPiCS-02	174	5.6 [3.1; 8.3] 88 (50.6)	164	3.4 [2.2; 4.6] 87 (53.0)	0.72 [0.53; 0.97]; 0.029[b]
EVER-132-002	154	4.5 [2.9; 9.9] 79 (51.3)	149	2.8 [2.1; 4.2] 91 (61.1)	0.64 [0.47; 0.88]; 0.005[c]
Total	328	5.6 [3.5; 8.4] 167 (50.9)	313	3.0 [2.6; 3.9] 178 (56.9)	0.68 [0.55; 0.84]; 0.001[d]
Role functioning					
TROPiCS-02	171	2.8 [1.7; 4.3] 111 (64.9)	159	2.2 [1.5; 2.9] 102 (64.2)	0.77 [0.58; 1.01]; 0.055[b]
EVER-132-002	152	4.1 [2.8; 6.9] 83 (54.6)	149	2.7 [1.7; 3.5] 94 (63.1)	0.73 [0.54; 0.99]; 0.040[c]
Total	323	3.0 [2.6; 4.4] 194 (60.1)	308	2.5 [1.8; 2.8] 196 (63.6)	0.76 [0.62; 0.93]; 0.005[d]
Emotional functioning					
TROPiCS-02	169	ND[j] 62 (36.7)	164	4.5 [3.4; 9.5] 75 (45.7)	ND[j]
EVER-132-002	154	9.9 [4.1; NC] 61 (39.6)	149	5.3 [6.1; NC] 64 (43.0)	0.75 [0.52; 1.08]; 0.100[c]
Total	323	11.1 [7.2; NC] 123 (38.1)	313	4.7 [4.2; 7.2] 139 (44.4)	0.69 [0.54; 0.89]; 0.010[d]
Cognitive functioning					
TROPiCS-02	174	5.2 [3.0; 11.1] 86 (49.4)	164	ND[k] 68 (41.5)	ND[k]
EVER-132-002	155	3.8 [2.8; 4.7] 88 (56.8)	148	2.7 [1.7; 2.9] 95 (64.2)	0.63 [0.47; 0.85]; 0.002[c]
Total	329	4.0 [3.2; 5.6] 174 (52.9)	312	3.2 [2.8; 4.2] 163 (52.2)	0.80 [0.64; 0.99]; < 0.001[d]

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category Outcome Study	Sacituzumab govitecan		Treatment of physician's choice[a]		Sacituzumab govitecan vs. treatment of physician's choice[a]
	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
Social functioning					
TROPiCS-02	170	2.4 [1.7; 4.3] 101 (59.4)	157	3.5 [2.6; 4.3] 88 (56.1)	0.99 [0.74; 1.33]; 0.958[b]
EVER-132-002	152	4.2 [2.9; 7.2] 87 (57.2)	146	3.0 [2.1; 4.4] 82 (56.2)	0.78 [0.57; 1.06]; 0.100[c]
Total	322	3.5 [2.7; 4.3] 188 (58.4)	303	3.1 [2.7; 4.2] 170 (56.1)	0.90 [0.73; 1.11]; 0.400[d]
Side effects					
AEs (supplementary information)					
TROPiCS-02	201	0.1 [0.1; 0.1] 201 (100.0)	194	0.2 [0.1; 0.2] 185 (95.4)	–
EVER-132-002	160	ND 160 (100.0)	155	ND 155 (100.0)	–
SAEs					
TROPiCS-02	201	NA [17.9; NC] 55 (27.4)	194	NA 34 (17.5)	1.42 [0.93; 2.19]; 0.107[b]
EVER-132-002	160	NA [12.8; NC][l] 36 (22.5)	155	NA[l] 31 (20.0)	0.95 [0.59; 1.55]; 0.846[c, l]
Total	361	NA [17.9; NC] 91 (25.2)	349	NA 65 (18.6)	1.20 [0.87; 1.66]; 0.400[d]
Severe AEs[m]					
TROPiCS-02	201	0.8 [0.7; 1.0] 151 (75.1)	194	2.4 [1.1; 3.7] 110 (56.7)	1.49 [1.17; 1.91]; 0.002[b]
EVER-132-002	160	0.7 [0.5; 0.8][l] 131 (81.9)	155	0.7 [0.5; 1.2][l] 109 (70.3)	1.08 [0.83; 1.39]; 0.565[c, l]
Total	361	0.7 [0.6; 0.9] 282 (78.1)	349	1.2 [0.8; 2.0] 219 (62.8)	1.29 [1.08; 1.53]; < 0.001[d]

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category Outcome Study	Sacituzumab govitecan		Treatment of physician's choice[a]		Sacituzumab govitecan vs. treatment of physician's choice[a]
	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
Discontinuation due to AEs					
TROPiCS-02	201	NA 14 (7.0)	194	NA 6 (3.1)	1.70 [0.64; 4.53]; 0.282[b]
EVER-132-002	160	NA[l] 5 (3.1)	155	NA[l] 5 (3.2)	0.78 [0.22; 2.77]; 0.703[c, l]
Total	361	NA 19 (5.3)	349	NA 11 (3.2)	1.26 [0.60; 2.68]; 0.300[d]
PRO-CTCAE					
TROPiCS-02				No suitable data[n]	
EVER-132-002				No suitable data[n]	
Hand-foot syndrome[o]					
TROPiCS-02	201	NA 4 (2.0)	194	NA 14 (7.2)	0.19 [0.05; 0.65]; 0.003[b]
EVER-132-002	159	NA 2 (1.3)	156	NA 4 (2.6)	0.45 [0.08; 2.49]; 0.350[c]
Total					0.25 [0.09; 0.69]; 0.008[p]
Gastrointestinal toxicity[q]					
TROPiCS-02	201	NA 31 (15.4)	194	NA 11 (5.7)	2.63 [1.32; 5.24]; 0.004[b]
EVER-132-002	159	NA 19 (11.9)	156	NA 5 (3.2)	3.25 [1.20; 8.82]; 0.015[c]
Total					2.81 [1.60; 4.96]; < 0.001[p]
Neutropenia[r]					
TROPiCS-02	201	1.6 [1.0; 4.6] 111 (55.2)	194	9.6 [4.3; NC] 77 (39.7)	1.55 [1.15; 2.08]; 0.003[b]
EVER-132-002	159	0.9 [0.7; 1.1] 112 (70.4)	156	1.1 [0.6; 1.9] 99 (63.5)	1.05 [0.80; 1.38]; 0.722[c]
Total					1.26 [1.03; 1.54]; 0.025[p]

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category Outcome Study	Sacituzumab govitecan		Treatment of physician's choice[a]		Sacituzumab govitecan vs. treatment of physician's choice[a]
	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
Other specific AEs					
TROPiCS-02				No suitable data[s]	
EVER-132-002				No suitable data[s]	

a. Capecitabine or eribulin or vinorelbine.
b. Effect and CI from stratified Cox regression model, p-value from stratified log-rank test; stratified according to the number of prior chemotherapy regimens in the metastatic stage (2 vs. 3 or 4), visceral metastases (yes vs. no), and endocrine-based therapy in the metastatic stage for ≥ 6 months (yes vs. no).
c. Effect and CI from stratified Cox regression model, p-value from stratified log-rank test; stratified according to the number of prior chemotherapy regimens in the metastatic stage (2 vs. 3 or 4), visceral metastases (yes vs. no), and prior CDK4/6 inhibitor therapy in the metastatic stage (yes vs. no).
d. IPD meta-analysis: Effect and CI from stratified Cox regression model, p-value from stratified log-rank test; stratified according to the number of prior chemotherapy regimens in the metastatic stage (2 vs. 3 or 4), visceral metastases (yes vs. no), treatment and study are included in the model as covariates.
e. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. Between the data cut-off of 1 July 2022 and the data cut-off of 1 December 2022, an event occurred in 2 further patients. No effect estimate [95% CI] is available for the data cut-off of 1 December 2022. At the data cut-off of 1 July 2022, the hazard ratio was 0.66 (95% CI: [0.48; 0.90]).
g. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
h. Effect and CI from unstratified Cox regression; p-value from unstratified log-rank test.
j. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
j. Between the data cut-off of 1 July 2022 and the data cut-off of 1 December 2022, an event occurred in one further patient. No effect estimate [95% CI] is available for the data cut-off of 1 December 2022. At the data cut-off of 1 July 2022, the hazard ratio was 0.65 (95% CI: [0.46; 0.91]).
k. Between the data cut-off of 1 July 2022 and the data cut-off of 1 December 2022, an event occurred in one further patient. No effect estimate [95% CI] is available for the data cut-off of 1 December 2022. At the data cut-off of 1 July 2022, the hazard ratio was 1.02 (95% CI: [0.74; 1.41]).
l. Data refer to the safety population, which includes all patients who received (at least) one dose of the study medication (159 vs. 156 patients).
m. Operationalized as CTCAE grade ≥ 3.
n. No suitable data available; for the reasoning, see dossier assessment A23-86 [1] and Section 2.3.1 of the present addendum.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category Outcome Study	Sacituzumab govitecan		Treatment of physician's choice[a]		Sacituzumab govitecan vs. treatment of physician's choice[a]
	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
o. Operationalized as palmar-plantar erythrodysaesthesia syndrome (PT, AEs). p. Meta-analysis: fixed-effect model, inverse variance method. q. Operationalized as gastrointestinal disorders (SOC, severe AEs). r. Operationalized as a compilation predefined by the company of the PTs of neutropenia, neutrophil count decreased, and febrile neutropenia (each severe AEs). s. No suitable data available; a specific AE selection based on results pooled in a meta-analysis is not possible (for reasoning, see Section 2.3.1). AE: adverse event; CDK: cyclin-dependent kinase; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale					

On the basis of the meta-analysis, at most proof can be derived for the outcome of overall survival and, due to the high risk of bias of the results in each case, at most indications, e.g. of added benefit, can be derived for the outcomes in the categories of morbidity, health-related quality of life, and side effects.

Mortality

Overall survival

In the meta-analysis, a statistically significant difference in favour of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of overall survival. There is proof of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice.

Morbidity

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the EORTC QLQ-C30 instrument.

Dyspnoea

In the meta-analysis, a statistically significant difference in favour of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of dyspnoea. There is an indication of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice.

Nausea and vomiting, and diarrhoea

In the meta-analysis, a statistically significant difference to the disadvantage of sacituzumab govitecan in comparison with treatment of physician's choice was shown for both of the outcomes of nausea and vomiting, and diarrhoea. There is an indication of lesser benefit of sacituzumab govitecan in comparison with treatment of physician's choice.

Fatigue and pain

In the meta-analysis, a statistically significant difference in favour of sacituzumab govitecan in comparison with treatment of physician's choice was shown for both of the outcomes of fatigue and pain. However, the extent of the effect for these outcomes in the category of non-serious/non-severe symptoms/late complications is no more than minor. There is no hint of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice for any of them; an added benefit is therefore not proven.

Insomnia, appetite loss, and constipation

The meta-analysis did not show a statistically significant difference between treatment groups for any of the outcomes of insomnia, appetite loss, or constipation. There is no hint of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice for any of them; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

In the meta-analysis, a statistically significant difference in favour of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of health status, recorded with the EQ-5D VAS. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms/late complications is no more than minor. There is no hint of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life outcomes were recorded using the EORTC QLQ-C30 instrument.

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

In the meta-analysis, a statistically significant difference in favour of sacituzumab govitecan in comparison with treatment of physician's choice was shown for each of the outcomes of global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning. In each case, there is an indication of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice.

Social functioning

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of social functioning. There is no hint of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Side effects

Severe AEs

In the meta-analysis, a statistically significant difference to the disadvantage of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of severe AEs. There is an indication of greater harm of sacituzumab govitecan in comparison with treatment of physician's choice.

SAEs and discontinuation due to AEs

The meta-analysis showed no statistically significant difference between treatment groups for the outcomes of SAEs and discontinuation due to AEs. There is no hint of greater or lesser harm from sacituzumab govitecan in comparison with treatment of physician's choice for either of them; greater or lesser harm is therefore not proven.

PRO-CTCAE

No suitable data are available for the outcome of PRO-CTCAE. There is no hint of greater or lesser harm from sacituzumab govitecan in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Specific AEs

Hand-foot syndrome (AEs)

In the meta-analysis, a statistically significant difference in favour of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of hand-foot syndrome (AEs). There is an indication of lesser harm from sacituzumab govitecan in comparison with treatment of physician's choice.

Gastrointestinal toxicity (severe AEs) and neutropenia (severe AEs)

In the meta-analysis, a statistically significant difference to the disadvantage of sacituzumab govitecan in comparison with treatment of physician's choice was shown for both of the outcomes of gastrointestinal toxicity and neutropenia (each severe AEs). In each case, there is an indication of greater harm from sacituzumab govitecan in comparison with treatment of physician's choice.

2.3.4 Subgroups and other effect modifiers

Analogue to dossier assessment A23-86 [1], the following subgroup characteristics are considered:

- age (< 65 years/≥ 65 years)
- visceral metastases (yes/no)

The characteristic of sex is disregarded as the relevant subpopulations of the 2 studies EVER-132-002 and TROPiCS-02 comprised a total of only 7 men.

The company did not present any subgroup analyses for the analyses based on the IPD meta-analysis of the 2 subpopulations of the respective studies relevant for the benefit assessment that were subsequently submitted in the commenting procedure and following the oral hearing.

2.4 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* [25].

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.

2.4.1 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 2.3 (see Table 14).

Determination of the outcome category for the morbidity outcomes

For the following outcomes in the morbidity category, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Therefore, the categorization for these outcomes is justified accordingly.

Symptoms

Fatigue, nausea and vomiting, pain, dyspnoea, and diarrhoea (EORTC QLQ-C30)

For the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, and diarrhoea, insufficient information is available to classify the severity category as serious/severe. These outcomes are therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Health status (EQ-5D VAS)

For the outcome of health status, insufficient information is available to classify the severity category as serious/severe. This outcome is therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 14: Extent of added benefit at outcome level: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category **Outcome**	**Sacituzumab govitecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Outcomes observed over the entire study duration		
Mortality		
Overall survival	14.4–21.1 vs. 11.2–15.3[d] HR: 0.77 [0.64; 0.92] p < 0.001 Probability: "proof"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ Added benefit, extent: "considerable"
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	1.9–2.1 vs. 1.3–1.7[d] HR: 0.75 [0.63; 0.91] p = 0.002	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
Nausea and vomiting	2.0–2.4 vs. 4.6–5.5[d] HR: 1.44 [1.17; 1.78] HR: 0.69 [0.56; 0.85][f] p = 0.002 Probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Lesser benefit, extent: "minor"
Pain	3.8–5.6 vs. 2.9–3.2[d] HR: 0.75 [0.61; 0.93] p = 0.020	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
Dyspnoea	ND–23.3 vs. 3.9–5.6[d] HR: 0.67 [0.53; 0.85] p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Insomnia	7.4–8.7 vs. 3.6–5.6[d] HR: 0.81 [0.64; 1.03] p = 0.200	Lesser/added benefit not proven
Appetite loss	2.9–3.3 vs. 3.7–4.2[d] HR: 1.12 [0.90; 1.39] p = 0.600	Lesser/added benefit not proven

Table 14: Extent of added benefit at outcome level: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category **Outcome**	**Sacituzumab govitecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Constipation	5.4–7.0 vs. 4.8–8.5[d] HR: 1.04 [0.82; 1.33] p = 0.100	Lesser/added benefit not proven
Diarrhoea	2.0–2.9 vs. 8.2–9.6[d] HR: 2.29 [1.79; 2.92] HR: 0.44 [0.34; 0.56][f] p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser benefit; extent: "considerable"
Health status (EQ-5D VAS – time to first deterioration)	11.8–ND vs. ND–7.0[d] HR: 0.71 [0.54; 0.92] p = 0.010	Outcome category: non-serious/non-severe symptoms/late complications 0.90 ≤ CI_u < 1.00 Lesser/added benefit not proven[e]
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration		
Global health status	3.8–4.9 vs. 2.6–2.8[d] HR: 0.76 [0.62; 0.93] p = 0.020 Probability: "indication"	Outcome category: health-related quality of life 0.90 ≤ CI_u < 1.00 Added benefit, extent: "minor"
Physical functioning	4.5–5.6 vs. 2.8–3.4[d] HR: 0.68 [0.55; 0.84] p = 0.001 Probability: "indication"	Outcome category: health-related quality of life 0.75 ≤ CI_u < 0.90 Added benefit, extent: "considerable"
Role functioning	2.8–4.1 vs. 2.2–2.7[d] HR: 0.76 [0.62; 0.93] p = 0.005 Probability: "indication"	Outcome category: health-related quality of life 0.90 ≤ CI_u < 1.00 Added benefit, extent: "minor"
Emotional functioning	ND–9.9 vs. 4.5–5.3[d] HR: 0.69 [0.54; 0.89] p = 0.010 Probability: "indication"	Outcome category: health-related quality of life 0.75 ≤ CI_u < 0.90 Added benefit, extent: "considerable"
Cognitive functioning	3.8–5.2 vs. 2.7–ND[d] HR: 0.80 [0.64; 0.99] p < 0.001 Probability: "indication"	Outcome category: health-related quality of life 0.90 ≤ CI_u < 1.00 Added benefit, extent: "minor"

Table 14: Extent of added benefit at outcome level: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category **Outcome**	**Sacituzumab govitecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Social functioning	2.4–4.2 vs. 3.0–3.5[d] HR: 0.90 [0.73; 1.11] p = 0.400	Lesser/added benefit not proven
Side effects		
SAEs	NA vs. NA[d] HR: 1.20 [0.87; 1.66] p = 0.400	Greater/Lesser harm not proven
Severe AEs	0.7–0.8 vs. 0.7–2.4[d] HR: 1.29 [1.08; 1.53] HR: 0.78 [0.65; 0.93][f] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Discontinuation due to AEs	NA vs. NA[d] HR: 1.26 [0.60; 2.68] p = 0.300	Greater/lesser harm not proven
PRO-CTCAE	No suitable data[g]	Greater/lesser harm not proven
Hand-foot syndrome (AEs)	NA vs. NA[d] HR: 0.25 [0.09; 0.69] p = 0.008 Probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: "considerable"
Gastrointestinal toxicity (severe AEs)	NA vs. NA[d] HR: 2.81 [1.60; 4.96] HR: 0.36 [0.20; 0.63][f] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Neutropenia (severe AEs)	0.9–1.6 vs. 1.1–9.6[d] HR: 1.26 [1.03; 1.54] HR: 0.79 [0.65; 0.97][f] p = 0.025 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Other specific AEs	No suitable data[h]	Greater/lesser harm not proven

Table 14: Extent of added benefit at outcome level: sacituzumab govitecan vs. treatment of physician's choice[a] (multipage table)

Outcome category **Outcome**	**Sacituzumab govitecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
a. Capecitabine or eribulin or vinorelbine. b. Probability provided if a statistically significant and relevant effect is present. c. Estimates of the effect size are made with different limits depending on the outcome category using the upper limit of the confidence interval (CI_u). d. Minimum and maximum medians of time to event per treatment arm in the included studies. e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. g. No suitable data available; for the reasoning, see dossier assessment A23-86 [1] and Section 2.3.1 of the present addendum. h. No suitable data available; a specific AE selection based on results pooled in a meta-analysis is not possible (for the reasoning, see Section 2.3.1). AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; ND: no data; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale		

2.4.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Positive and negatives effects from the assessment of sacituzumab govitecan in comparison with treatment of physician's choice[a]

Positive effects	**Negative effects**
Outcomes observed over the entire study duration	
Mortality ▪ Overall survival: proof of added benefit – extent "considerable"	–
Outcomes with shortened observation period	
Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-C30): ▪ Dyspnoea: indication of added benefit – extent: "minor"	Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-C30): ▪ Nausea and vomiting: indication of lesser benefit – extent: "minor" ▪ Diarrhoea: indication of lesser benefit – extent: "considerable"
Health-related quality of life EORTC QLQ-C30: ▪ Global health status: indication of added benefit – extent: "minor" ▪ Physical functioning: indication of added benefit – extent: "considerable" ▪ Role functioning: indication of added benefit – extent: "minor" ▪ Emotional functioning: indication of added benefit – extent: "considerable" ▪ Cognitive functioning: indication of added benefit – extent: "minor"	–
–	Serious/severe side effects ▪ Severe AEs: indication of greater harm – extent: "minor", including ▫ gastrointestinal toxicity (severe AEs): indication of greater harm – extent: "major" ▫ neutropenia (severe AEs): indication of greater harm – extent: "minor"
Non-serious/non-severe side effects ▪ Hand-foot syndrome (AEs): indication of lesser harm – extent: "considerable"	–
No suitable data are available for the outcome of PRO-CTCAE and further specific AEs.	
a. Capecitabine or eribulin or vinorelbine. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire Core 30	

Overall, there are both several positive and several negative effects for sacituzumab govitecan compared with treatment of physician's choice. The effects only refer to the entire

observation period for overall survival, but to the shortened period (until the end of treatment [plus 7 or 30 days]) for the outcomes on morbidity, health-related quality of life and side effects. On the side of positive effects, there is proof of considerable added benefit for the outcome of overall survival. For health-related quality of life, there are exclusively positive effects in several outcomes with the extents “minor” or “considerable”, each with the probability of an indication. In the categories of symptoms/late complications and side effects (in each case non-serious/non-severe), there is one positive effect each with the extent “minor” or “considerable”. These are offset by negative effects in the categories of non-serious/non-severe symptoms/late complications and severe/serious side effects with the extent “minor” to “major”. No suitable data are available for the PRO-CTCAE and further specific AEs. In the present data situation, however, the results of these outcomes are not assumed to call into question the positive effects in the outcome of overall survival or the health-related quality of life outcomes.

In summary, for adult patients with unresectable or metastatic hormone receptor-positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies for advanced disease, there is proof of considerable added benefit of sacituzumab govitecan compared with treatment of physician’s choice.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion drawn in dossier assessment A23-86 on the added benefit of sacituzumab govitecan: For adult patients with unresectable or metastatic hormone receptor-positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies for advanced disease, there is proof of considerable added benefit of sacituzumab govitecan compared with treatment of physician’s choice.

Table 16 below shows the result of the benefit assessment of sacituzumab govitecan, taking into account dossier assessment A23-86 and the present addendum.

Table 16: Sacituzumab govitecan – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**[b]
Adult patients[c] with unresectable or metastatic hormone receptor-positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the advanced setting[d]	▪ Capecitabine or ▪ eribulin or ▪ vinorelbine or ▪ an anthracycline-containing or taxane-containing regimen (only for patients who have not yet received an anthracycline-containing and taxane-containing regimen or who are eligible for renewed anthracycline-containing or taxane-containing treatment)[e]	**Proof of considerable added benefit**[f]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Changes in comparison with dossier assessment A23-86 are printed in **bold**.
c. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men are predominantly based on the recommendations for the treatment of women. Within the framework of the benefit assessment, separate consideration of men can be useful.
d. When specifying the ACT, the G-BA assumed that
- (neo)adjuvant chemotherapy is counted as one of the prior chemotherapy regimens if unresectable, locally advanced, or metastatic disease develops within 12 months.
- as part of prior therapy, patients typically received anthracycline-containing and/or taxane-containing chemotherapy.
- in the present therapeutic indication, (secondary) resection or radiotherapy with curative intent is not indicated.
- patients with genomic BRCA1/2 mutation are not candidates for BRCA-specific therapy at the time of therapy with sacituzumab govitecan.

e. According to guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth.
f. The studies EVER-132-002 and TROPiCS-02 included only patients with an ECOG PS of 0 or 1. In addition, the subpopulations relevant for the benefit assessment comprise only 7 male patients. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 and to male patients.

ACT: appropriate comparator therapy; BRCA: breast cancer susceptibility gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor-2

The G-BA decides on the added benefit.

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Appendix A Presentation of subgroup results of the EVER-132-002 study (in the subgroups with/without prior CDK4/6 inhibitor therapy [subpopulation a])

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Outcome Characteristic Subgroup	Sacituzumab govitecan N	Sacituzumab govitecan Median time to event in months [95% CI] Patients with event n (%)	Treatment of physician's choice[a] N	Treatment of physician's choice[a] Median time to event in months [95% CI] Patients with event n (%)	Sacituzumab govitecan vs. treatment of physician's choice[a] HR [95% CI][b]	Sacituzumab govitecan vs. treatment of physician's choice[a] p-value[b]
EVER-132-002						
Mortality						
Overall survival						
Prior CDK4/6 inhibitor therapy						
Yes	79	21.1 [14.7; NC] 28 (35.4)	72	13.2 [10.7; 17.3] 43 (59.7)	0.50 [0.31; 0.81]	0.004
No	ND	ND	ND	ND	0.74 [0.48; 1.16]	0.189
Total					Interaction:	0.181[c]
Morbidity						
Symptoms (EORTC QLQ-C30 – time to first deterioration)[d]						
Fatigue						
Prior CDK4/6 inhibitor therapy						
Yes	75	1.9 [1.5; 4.3] 47 (62.7)	69	1.9 [1.5; 4.2] 45 (65.2)	0.85 [0.57; 1.29]	0.454
No	ND	ND	ND	ND	0.84 [0.58; 1.23]	0.367
Total					Interaction:	0.965[c]
Nausea and vomiting						
Prior CDK4/6 inhibitor therapy						
Yes	74	1.9 [1.5; 2.8] 54 (73.0)	70	2.8 [1.5; 5.6] 36 (51.4)	1.24 [0.81; 1.90]	0.315
No	ND	ND	ND	ND	2.19 [1.41; 3.40]	< 0.001
Total					Interaction:	0.076[c]

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Outcome Characteristic Subgroup	Sacituzumab govitecan N	Sacituzumab govitecan Median time to event in months [95% CI] Patients with event n (%)	Treatment of physician's choice[a] N	Treatment of physician's choice[a] Median time to event in months [95% CI] Patients with event n (%)	Sacituzumab govitecan vs. treatment of physician's choice[a] HR [95% CI][b]	Sacituzumab govitecan vs. treatment of physician's choice[a] p-value[b]
Pain						
Prior CDK4/6 inhibitor therapy						
Yes	74	6.1 [3.0; NC] 34 (45.9)	67	2.3 [1.5; 3.4] 43 (64.2)	0.42 [0.27; 0.67]	< 0.001
No	ND	ND	ND	ND	0.96 [0.63; 1.44]	0.828
Total					Interaction:	0.008[c]
Dyspnoea						
Prior CDK4/6 inhibitor therapy						
Yes	73	23.3 [6.5; NC] 26 (35.6)	69	5.6 [2.9; NC] 26 (37.7)	0.68 [0.39; 1.18]	0.170
No	ND	ND	ND	ND	0.74 [0.47; 1.17]	0.201
Total					Interaction:	0.854[c]
Insomnia						
Prior CDK4/6 inhibitor therapy						
Yes	74	8.2 [3.0; NC] 33 (44.6)	67	5.6 [3.9; NC] 23 (34.3)	1.03 [0.60; 1.76]	0.925
No	ND	ND	ND	ND	1.00 [0.63; 1.59]	0.999
Total					Interaction:	0.860[c]
Appetite loss						
Prior CDK4/6 inhibitor therapy						
Yes	72	4.1 [2.8; 8.2] 41 (56.9)	69	2.9 [1.7; 5.6] 34 (49.3)	0.84 [0.53; 1.33]	0.447
No	ND	ND	ND	ND	1.69 [1.11; 2.58]	0.014
Total					Interaction:	0.027[c]
Constipation						
Prior CDK4/6 inhibitor therapy						
Yes	75	NA [3.3; NC] 31 (41.3)	68	6.0 [3.1; NC] 22 (32.4)	1.09 [0.63; 1.88]	0.768
No	ND	ND	ND	ND	1.08 [0.65; 1.77]	0.777
Total					Interaction:	0.998[c]

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Outcome Characteristic Subgroup	Sacituzumab govitecan N	Sacituzumab govitecan Median time to event in months [95% CI] Patients with event n (%)	Treatment of physician's choice[a] N	Treatment of physician's choice[a] Median time to event in months [95% CI] Patients with event n (%)	Sacituzumab govitecan vs. treatment of physician's choice[a] HR [95% CI][b]	Sacituzumab govitecan vs. treatment of physician's choice[a] p-value[b]
Diarrhoea						
Prior CDK4/6 inhibitor therapy						
Yes	75	2.2 [1.6; 4.8] 50 (66.7)	70	5.9 [4.1; NC] 21 (30.0)	2.09 [1.25; 3.49]	0.005
No	ND	ND	ND	ND	2.21 [1.35; 3.63]	0.002
Total					Interaction:	0.868[c]
Health status (EQ-5D VAS – time to first deterioration)[e]						
Prior CDK4/6 inhibitor therapy						
Yes	75	12.3 [8.5; NC] 23 (30.7)	70	6.3 [4.6; 9.9] 27 (38.6)	0.49 [0.27; 0.86]	0.013
No	ND	ND	ND	ND	0.87 [0.51; 1.49]	0.611
Total					Interaction:	0.202[c]
Health-related quality of life						
EORTC QLQ-C30 – time to first deterioration[f]						
Global health status						
Prior CDK4/6 inhibitor therapy						
Yes	75	4.1 [3.0; 5.6] 40 (53.3)	68	2.1 [1.7; 4.1] 39 (57.3)	0.69 [0.44; 1.08]	0.101
No	ND	ND	ND	ND	1.06 [0.71; 1.59]	0.760
Total					Interaction:	0.136[c]
Physical functioning						
Prior CDK4/6 inhibitor therapy						
Yes	74	5.9 [2.9; NC] 36 (48.6)	70	3.9 [2.1; 4.4] 37 (52.9)	0.66 [0.41; 1.05]	0.081
No	ND	ND	ND	ND	0.65 [0.43; 0.97]	0.036
Total					Interaction:	0.838[c]

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Outcome Characteristic Subgroup	Sacituzumab govitecan N	Sacituzumab govitecan Median time to event in months [95% CI] Patients with event n (%)	Treatment of physician's choice[a] N	Treatment of physician's choice[a] Median time to event in months [95% CI] Patients with event n (%)	Sacituzumab govitecan vs. treatment of physician's choice[a] HR [95% CI][b]	Sacituzumab govitecan vs. treatment of physician's choice[a] p-value[b]
Role functioning						
Prior CDK4/6 inhibitor therapy						
Yes	74	3.6 [2.2; 5.8] 42 (56.8)	70	1.9 [1.5; 4.1] 44 (62.9)	0.75 [0.49; 1.15]	0.186
No	ND	ND	ND	ND	0.68 [0.45; 1.04]	0.076
Total					Interaction:	0.797[c]
Emotional functioning						
Prior CDK4/6 inhibitor therapy						
Yes	75	NA [5.7; NC] 27 (36.0)	70	4.2 [2.7; 6.0] 32 (45.7)	0.56 [0.33; 0.94]	0.027
No	ND	ND	ND	ND	1.00 [0.62; 1.62]	0.995
Total					Interaction:	0.104[c]
Cognitive functioning						
Prior CDK4/6 inhibitor therapy						
Yes	75	4.0 [2.8; 7.0] 40 (53.3)	70	2.6 [1.5; 3.8] 41 (58.6)	0.59 [0.38; 0.92]	0.019
No	ND	ND	ND	ND	0.69 [0.47; 1.02]	0.062
Total					Interaction:	0.716[c]
Social functioning						
Prior CDK4/6 inhibitor therapy						
Yes	72	3.9 [2.8; 8.4] 43 (59.7)	68	3.0 [1.6; 4.4] 35 (51.5)	0.74 [0.46; 1.17]	0.192
No	ND	ND	ND	ND	0.87 [0.58; 1.31]	0.511
Total					Interaction:	0.733[c]
Side effects						
AEs (supplementary information)						
Prior CDK4/6 inhibitor therapy						
Yes	ND	ND	ND	ND	–	–
No	ND	ND	ND	ND	–	–

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Outcome Characteristic Subgroup	Sacituzumab govitecan N	Sacituzumab govitecan Median time to event in months [95% CI] Patients with event n (%)	Treatment of physician's choice[a] N	Treatment of physician's choice[a] Median time to event in months [95% CI] Patients with event n (%)	Sacituzumab govitecan vs. treatment of physician's choice[a] HR [95% CI][b]	Sacituzumab govitecan vs. treatment of physician's choice[a] p-value[b]
SAEs						
Prior CDK4/6 inhibitor therapy						
Yes	79	NA [12.8; NC] 13 (16.5)	72	NA [9.2; NC] 17 (23.6)	0.54 [0.26; 1.13]	0.100
No	ND	ND	ND	ND	1.52 [0.78; 2.96]	0.219
Total					Interaction:	0.028[c]
Severe AEs[g]						
Prior CDK4/6 inhibitor therapy						
Yes	79	0.7 [0.6; 1.0] 63 (79.7)	72	1.1 [0.5; 2.0] 49 (68.1)	1.03 [0.71; 1.51]	0.863
No	ND	ND	ND	ND	1.15 [0.81; 1.63]	0.422
Total					Interaction:	0.741[c]
Discontinuation due to AEs						
Prior CDK4/6 inhibitor therapy						
Yes	79	NA 1 (1.3)	72	NA 2 (2.8)	0.36 [0.03; 3.97]	0.402
No	ND	ND	ND	ND	1.09 [0.24; 4.91]	0.909
Total					Interaction:	0.298[c]
Hand-foot syndrome[h]						
Prior CDK4/6 inhibitor therapy						
Yes	79	NA 1 (1.3)	72	NA 2 (2.8)	0.45 [0.04; 4.92]	0.499
No	ND	ND	ND	ND	ND	ND
Total					Interaction:	ND
Gastrointestinal toxicity[i]						
Prior CDK4/6 inhibitor therapy						
Yes	79	NA 7 (8.9)	72	NA 3 (4.2)	1.61 [0.40; 6.51]	0.500
No	ND	ND	ND	ND	ND	ND
Total					Interaction:	ND

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a] (EVER-132-002 study) (multipage table)

Study Outcome Characteristic Subgroup	Sacituzumab govitecan N	Sacituzumab govitecan Median time to event in months [95% CI] Patients with event n (%)	Treatment of physician's choice[a] N	Treatment of physician's choice[a] Median time to event in months [95% CI] Patients with event n (%)	Sacituzumab govitecan vs. treatment of physician's choice[a] HR [95% CI][b]	Sacituzumab govitecan vs. treatment of physician's choice[a] p-value[b]
Neutropenia[j]						
Prior CDK4/6 inhibitor therapy						
Yes	79	0.9 [0.7; 1.6] 54 (68.4)	72	1.2 [0.5; 3.3] 43 (59.7)	1.03 [0.69; 1.54]	0.886
No	ND	ND	ND	ND	1.06 [0.74; 1.54]	0.741
Total					Interaction:	0.897[c]

a. Capecitabine or eribulin or vinorelbine.
b. Effect, CI and p-value from unstratified Cox model.
c. Interaction term from Cox model with treatment, subgroup, and interaction between treatment and subgroup as covariates.
d. A score increase by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
e. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
f. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
g. Operationalized as CTCAE grade ≥ 3.
h. Operationalized as palmar-plantar erythrodysaesthesia syndrome (PT, AEs).
i. Operationalized as gastrointestinal disorders (SOC, severe AEs).
j. Operationalized as a compilation predefined by the company of the PTs of neutropenia, neutrophil count decreased, and febrile neutropenia (each severe AEs).

AE: adverse event; CDK: cyclin-dependent kinase; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; 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; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Appendix B Forest plots for the outcomes of hand-foot syndrome (AEs), gastrointestinal toxicity (severe AEs), and neutropenia (severe AEs) (Institute's calculations)

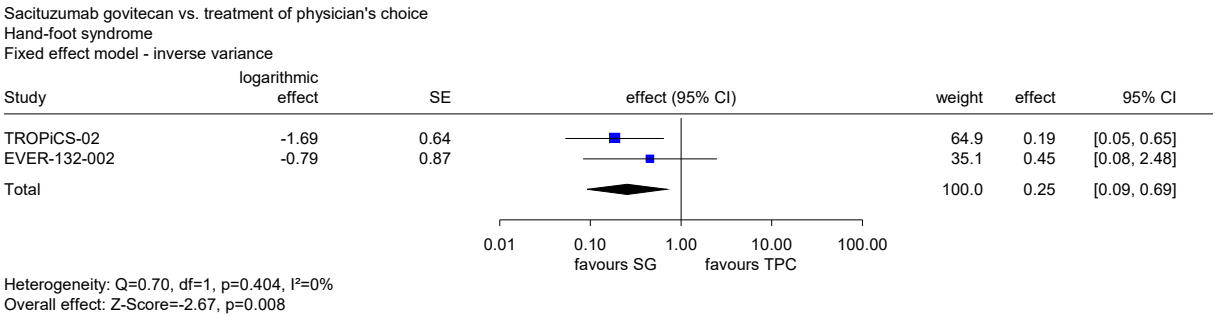

Figure 1: Meta-analysis for the outcome of hand-foot syndrome (AEs), studies EVER-132-002 and TROPiCS-02 (subpopulation of each study)

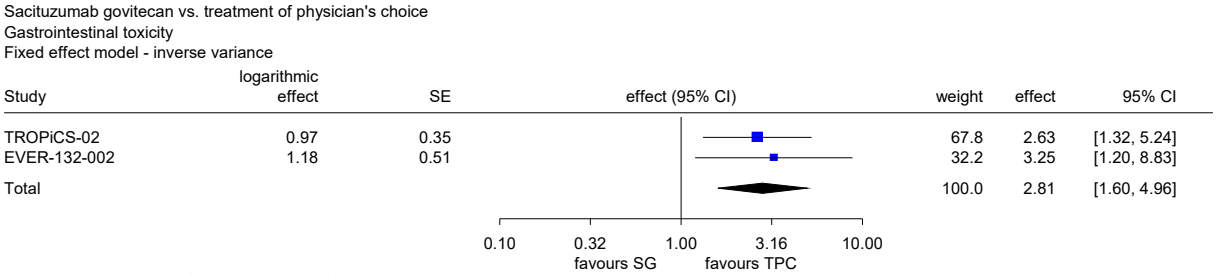

Figure 2: Meta-analysis for the outcome of gastrointestinal toxicity (severe AEs), studies EVER-132-002 and TROPiCS-02 (subpopulation of each study)

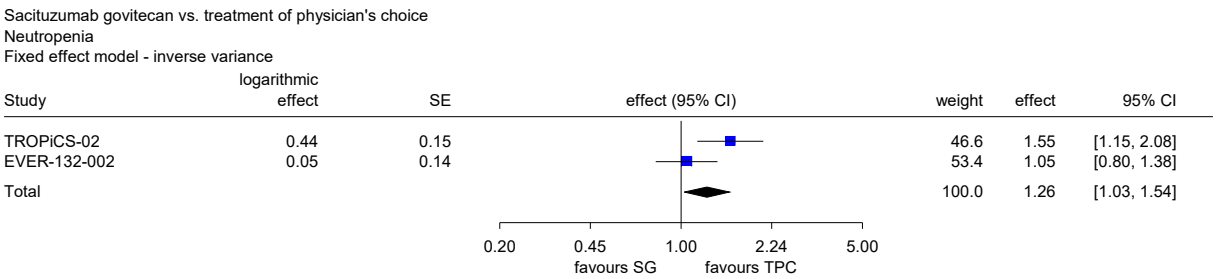

Figure 3: Meta-analysis for the outcome of neutropenia (severe AEs), studies EVER-132-002 and TROPiCS-02 (subpopulation of each study)

Appendix C Graphic display of the time-to-event analyses of the EVER-132-002 study presented in the addendum (Kaplan-Meier curves)

C.1 Mortality

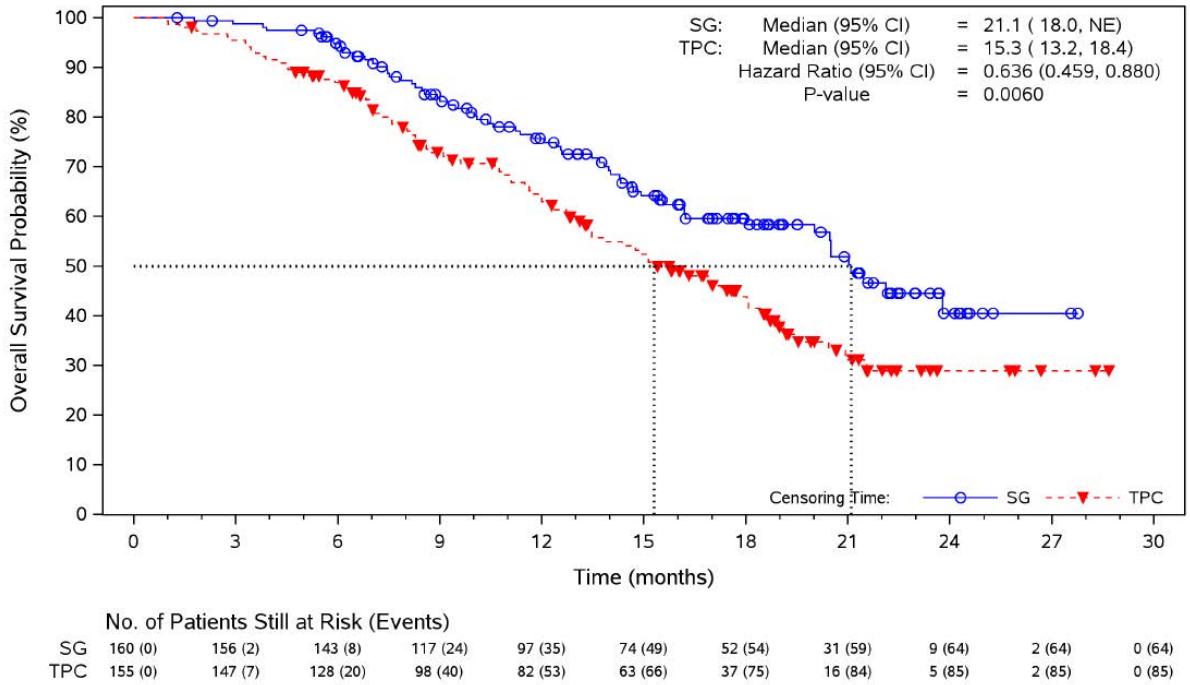

Figure 4: Kaplan-Meier curves for the outcome of overall survival, EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

C.2 Morbidity

C.2.1 Symptoms (EORTC QLQ-C30)

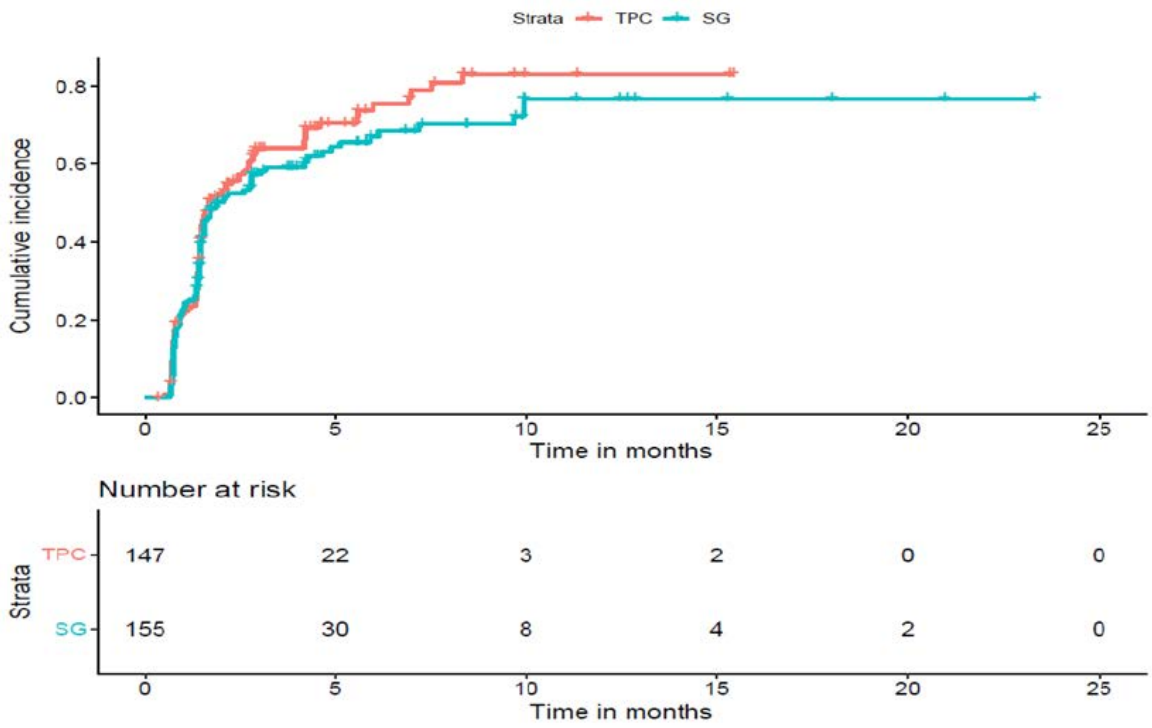

Figure 5: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

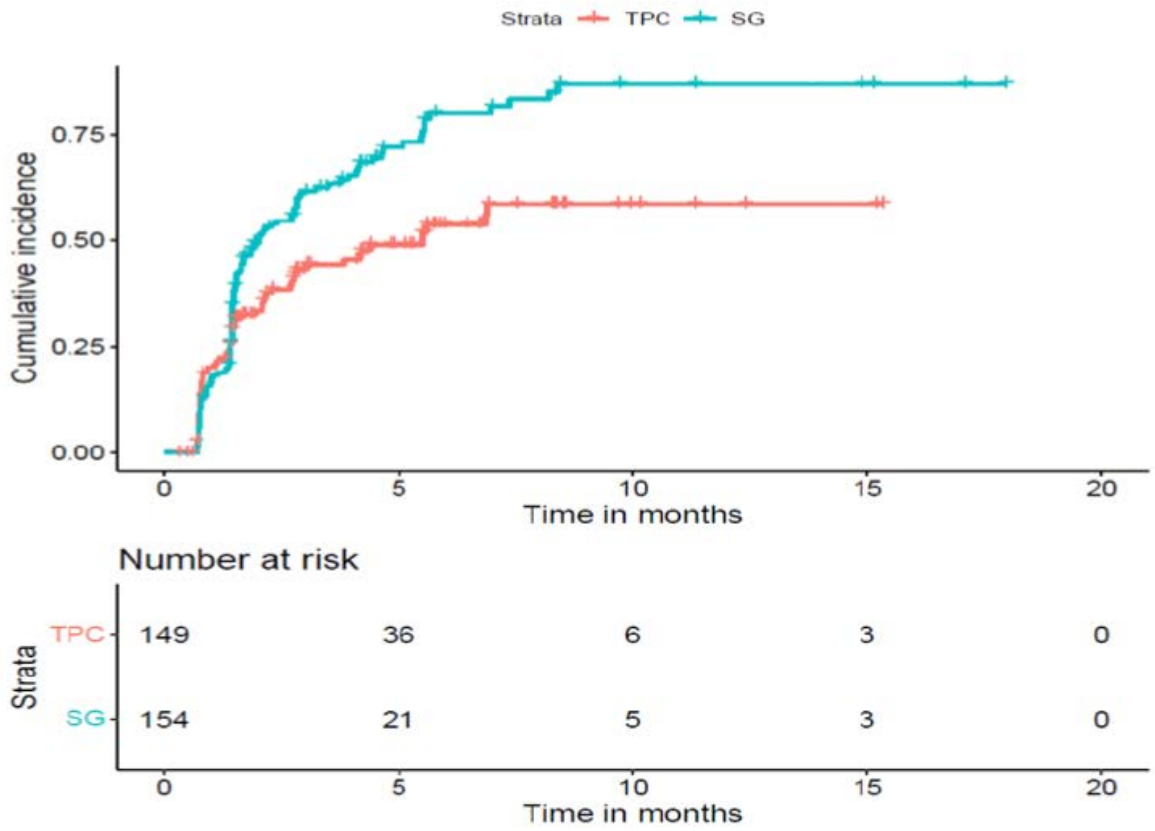

Figure 6: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

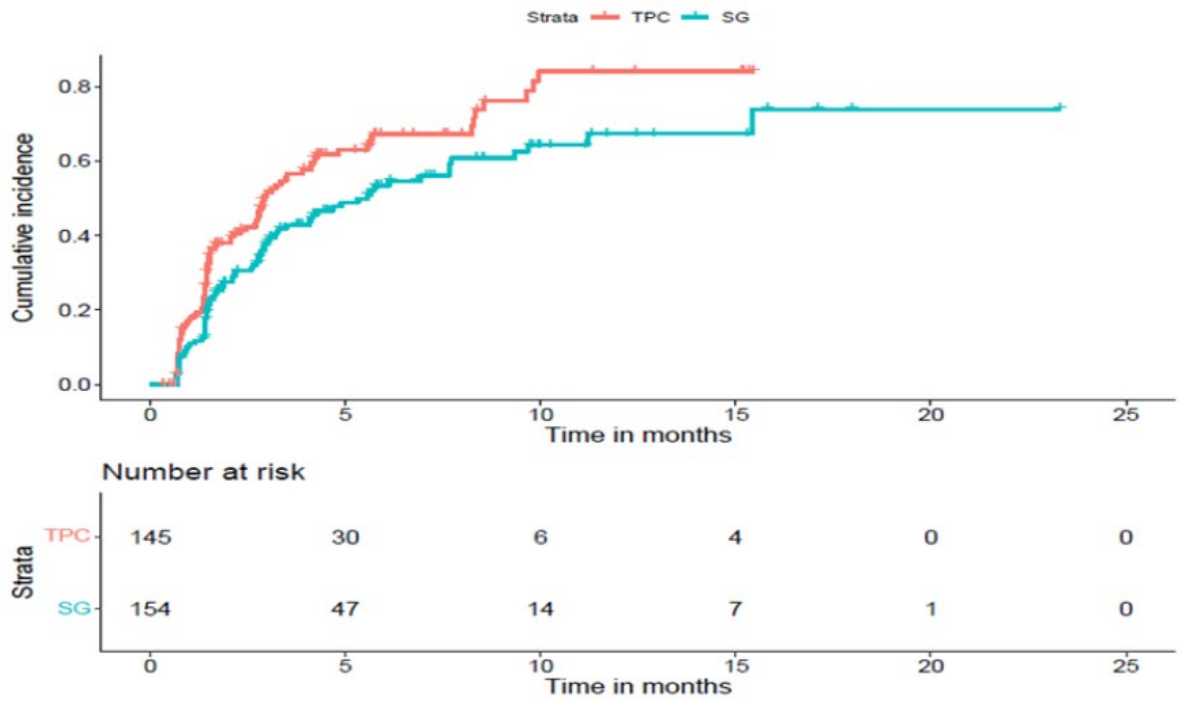

Figure 7: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

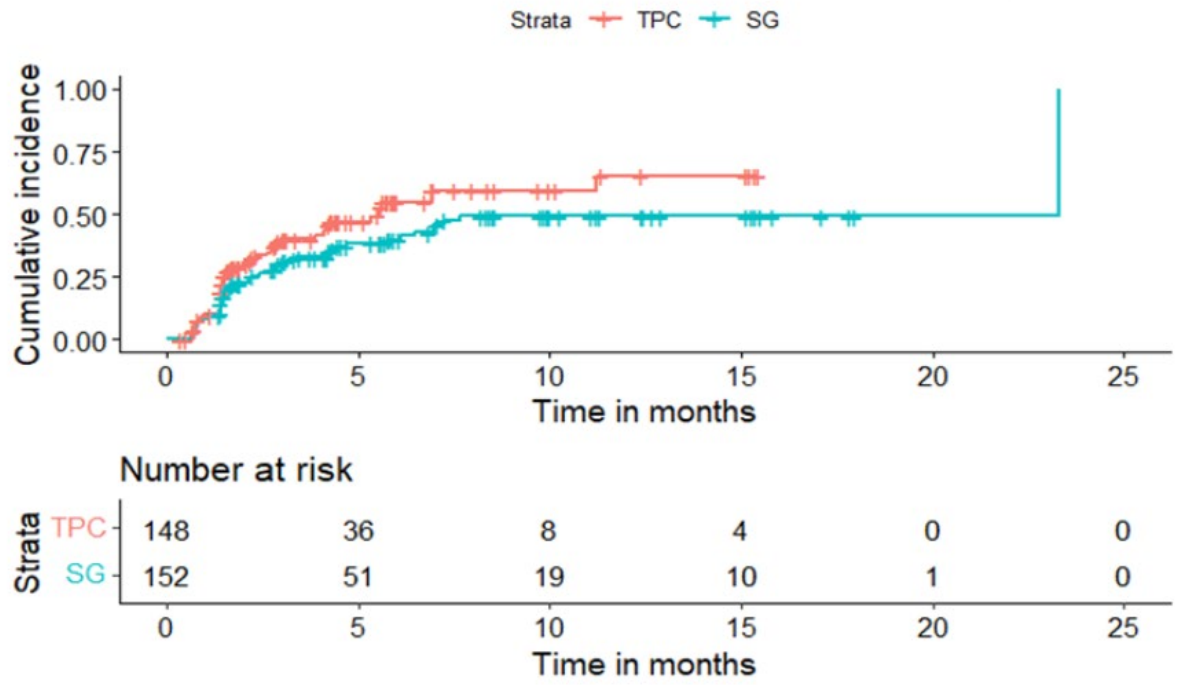

Figure 8: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

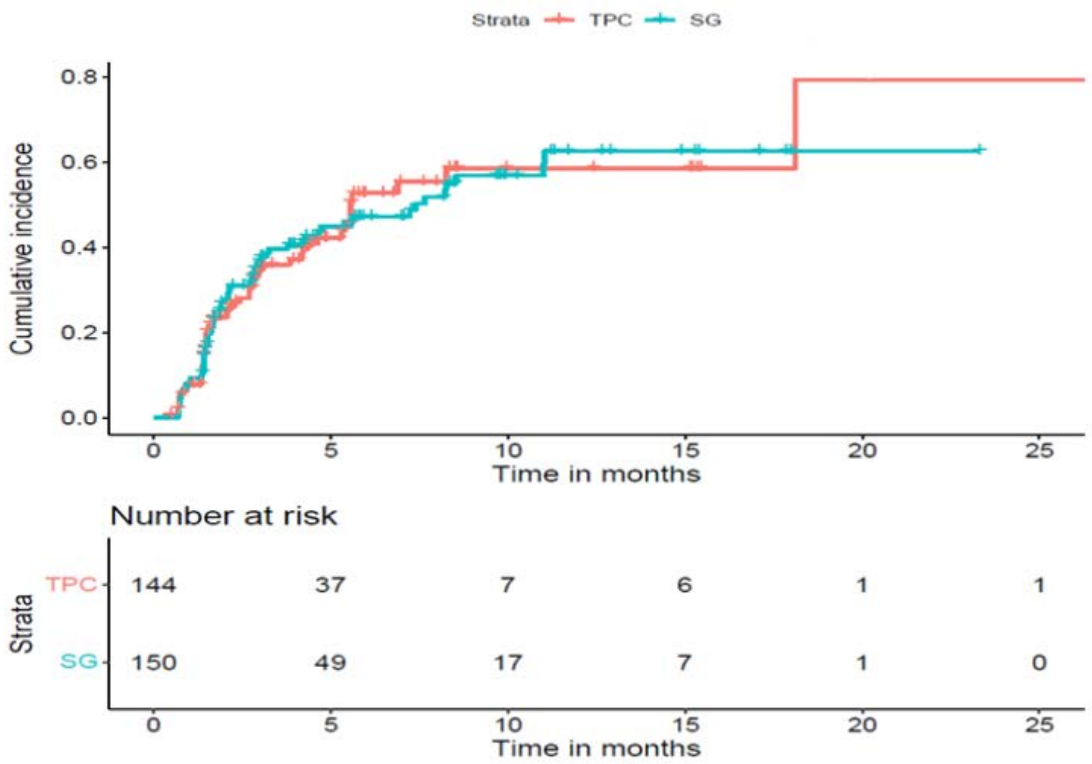

Figure 9: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

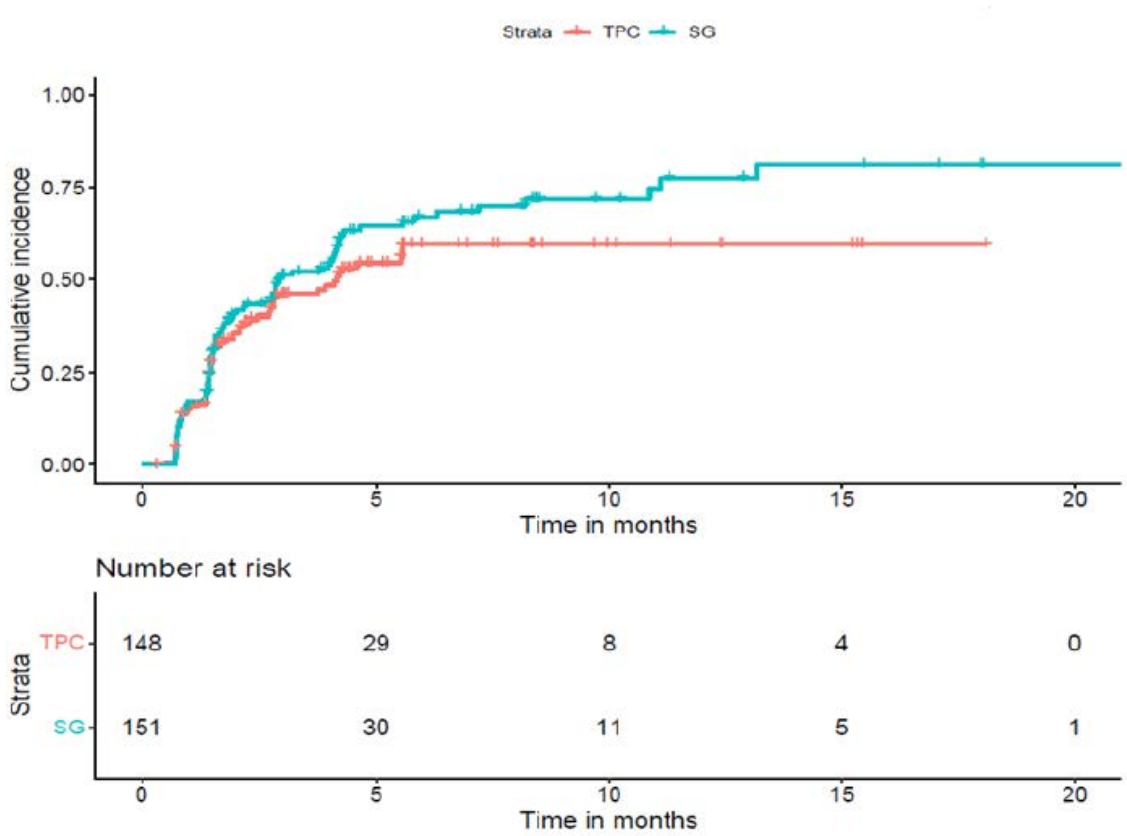

Figure 10: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

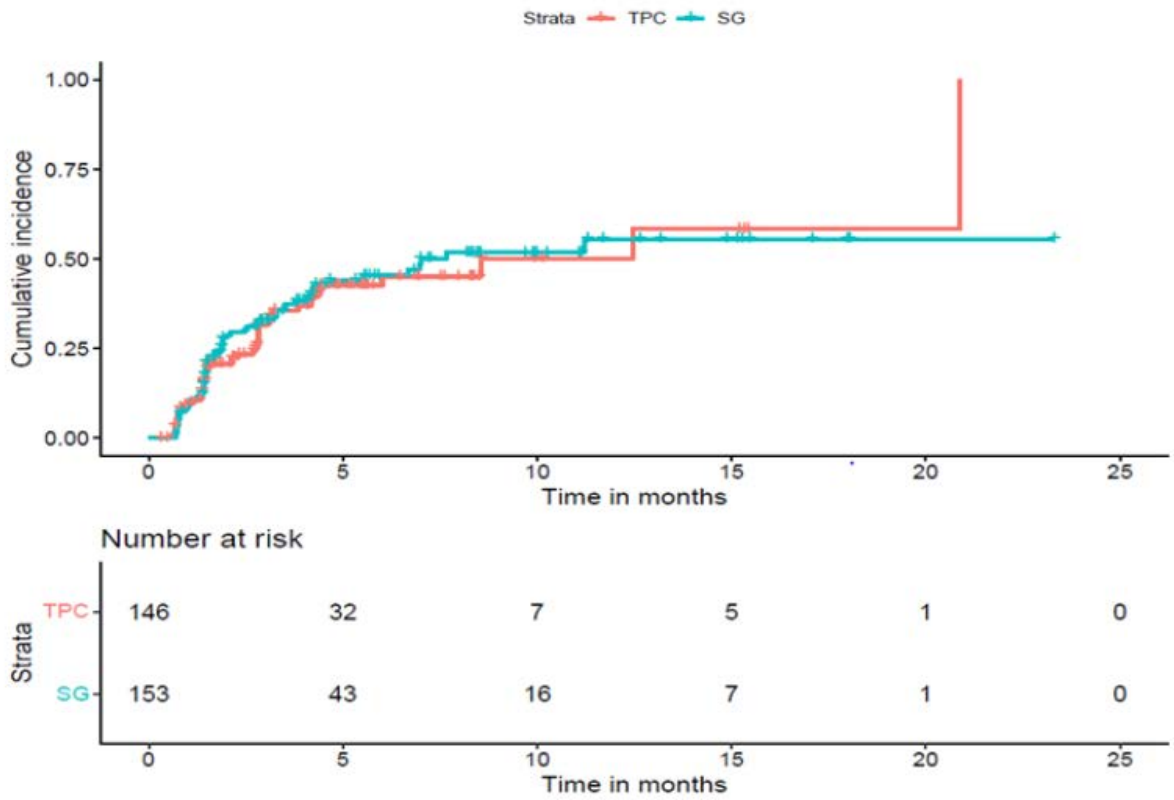

Figure 11: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

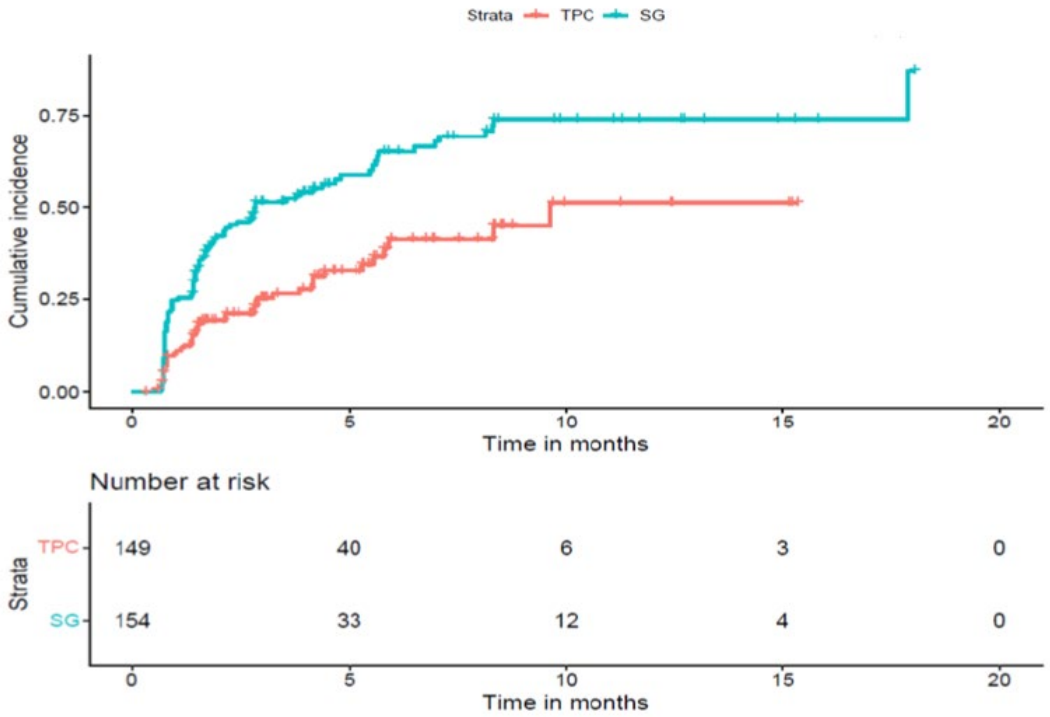

Figure 12: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

C.3 Health-related quality of life

C.3.1 EORTC QLQ-C30

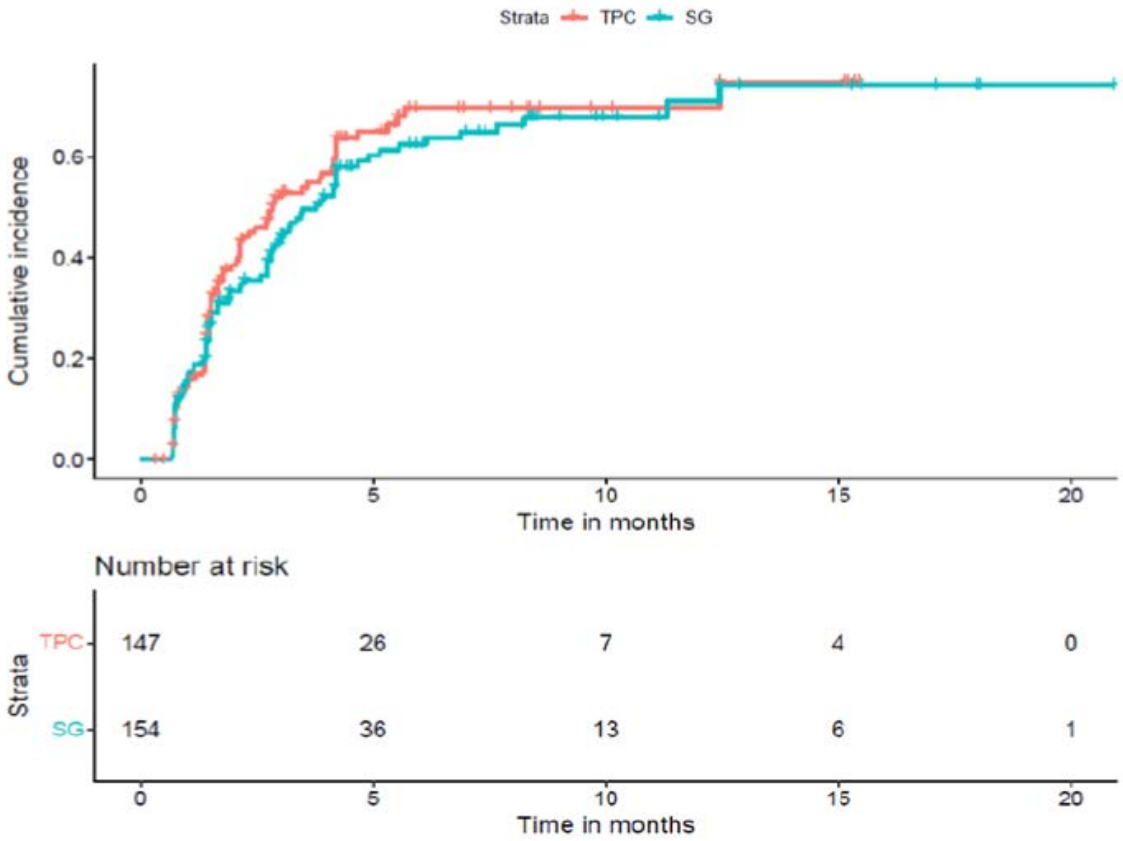

Figure 13: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

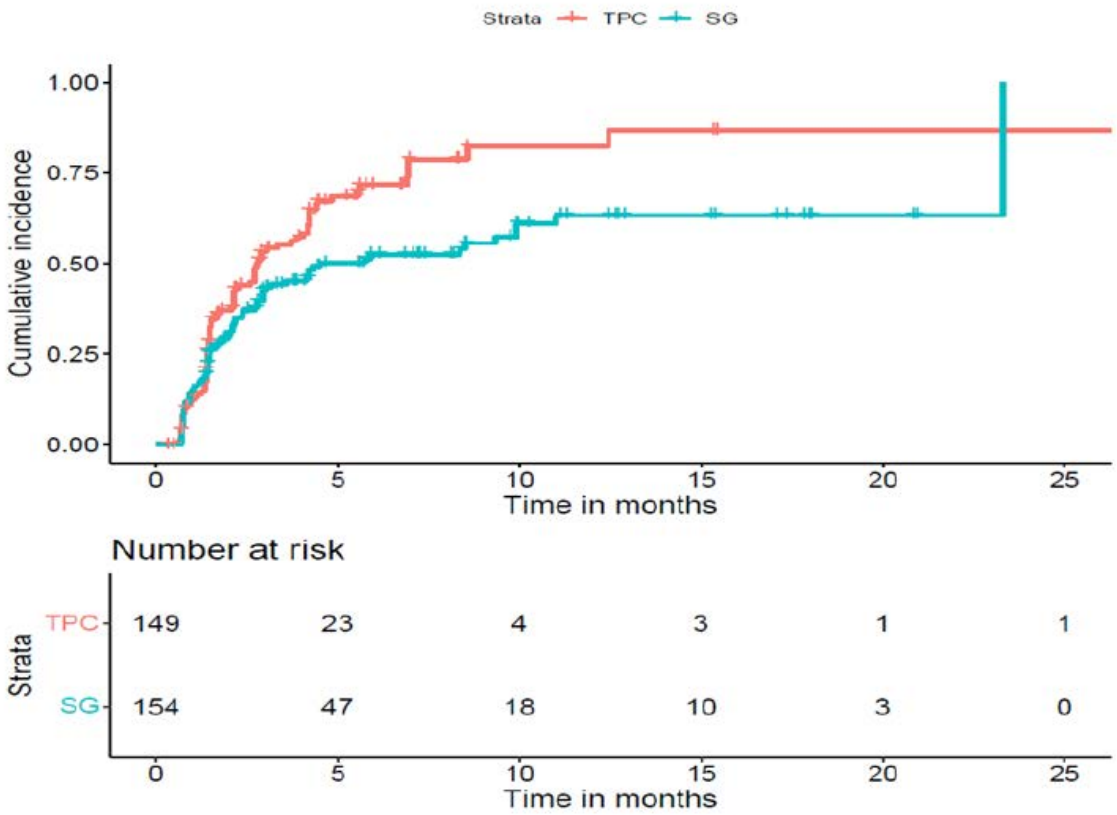

Figure 14: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

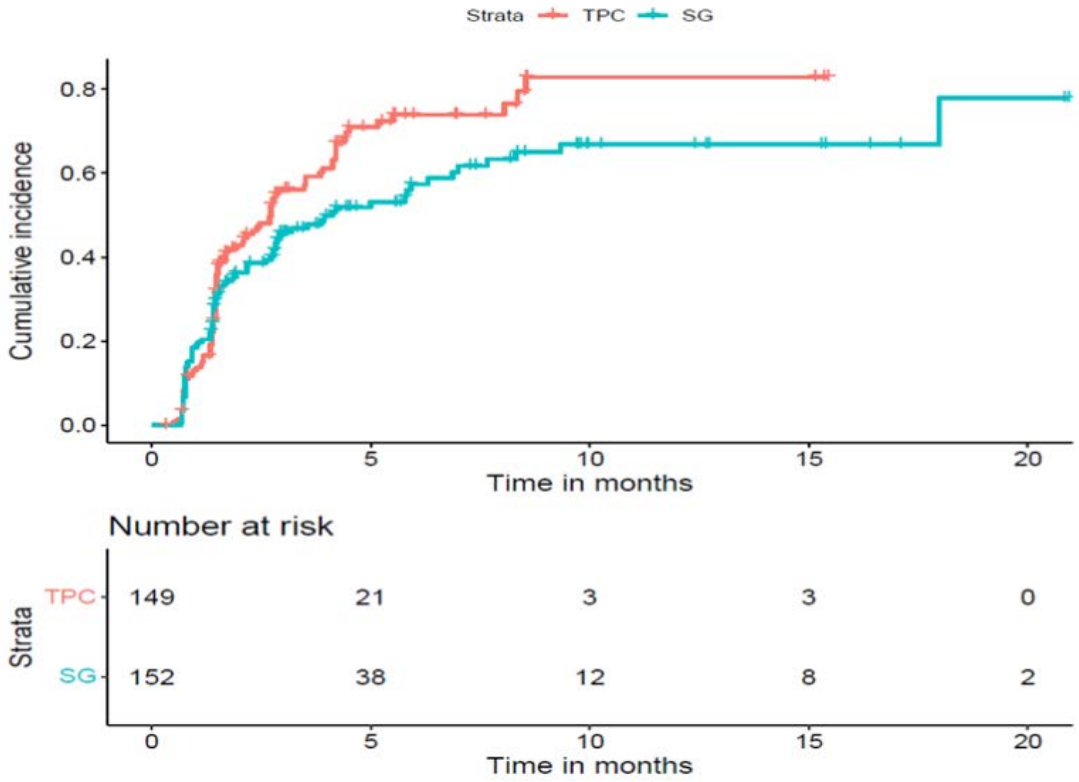

Figure 15: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

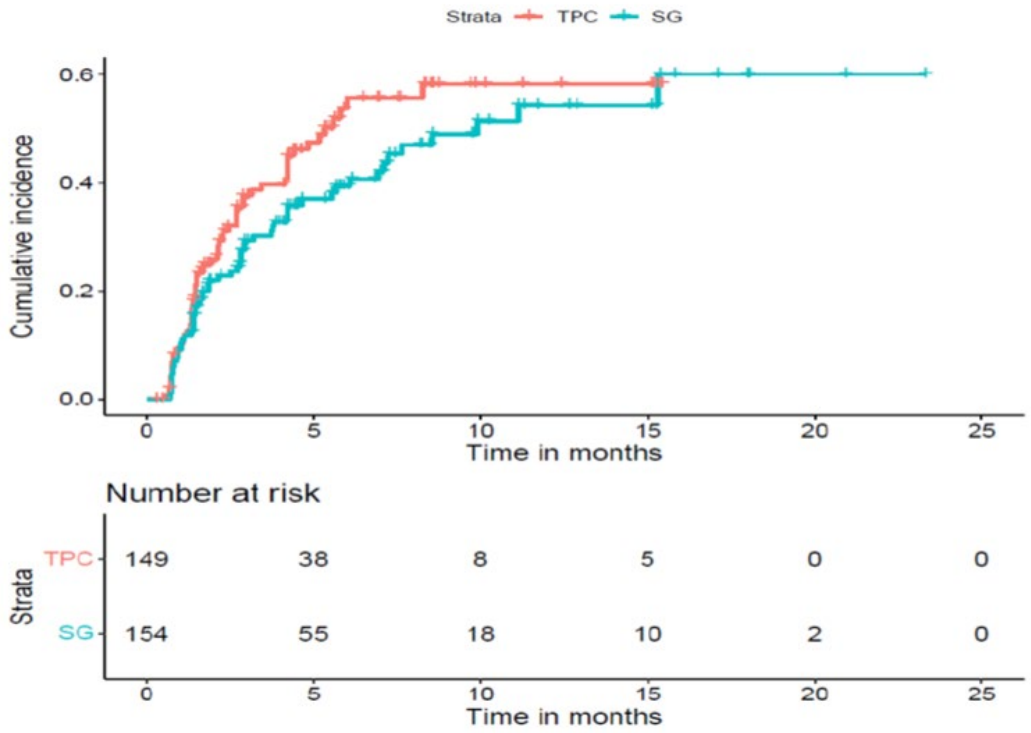

Figure 16: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

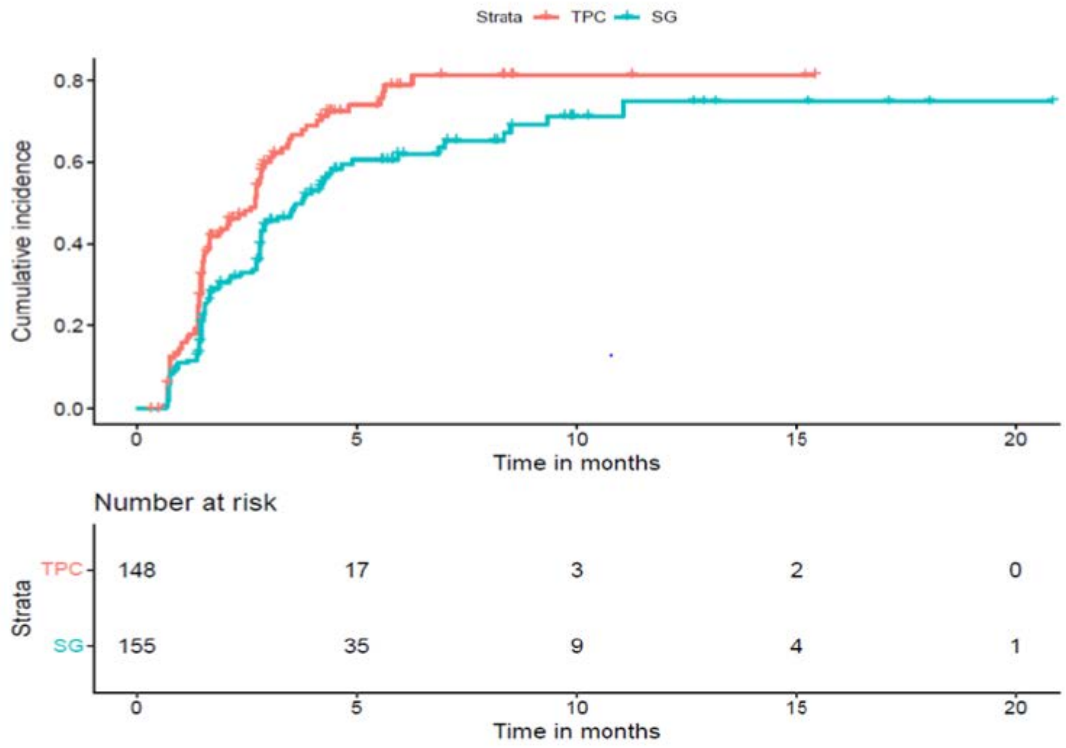

Figure 17: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

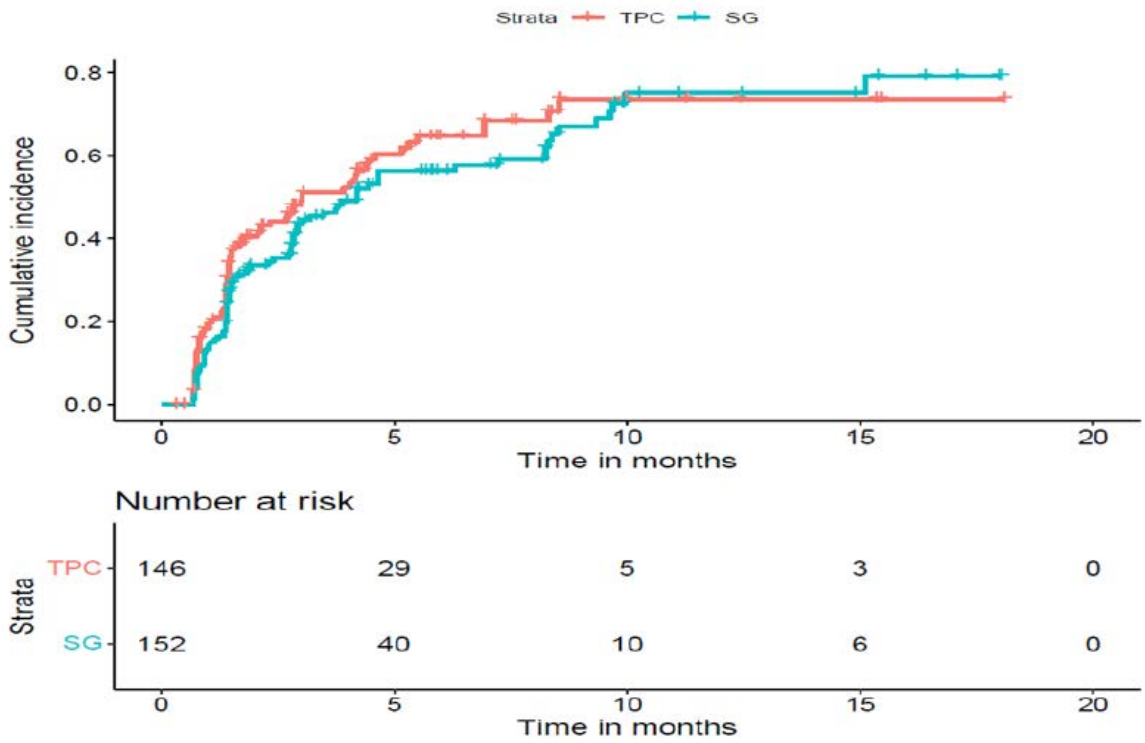

Figure 18: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30 – time to first deterioration), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

C.4 Side effects

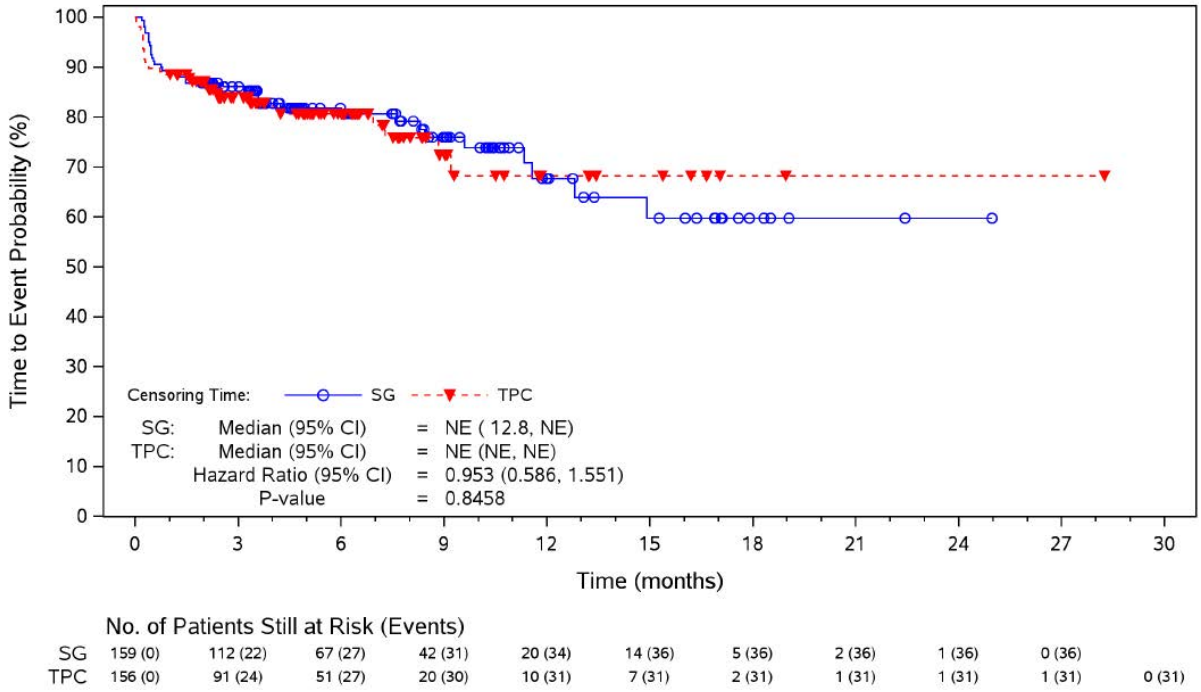

Figure 19: Kaplan-Meier curves for the outcome of SAEs, EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

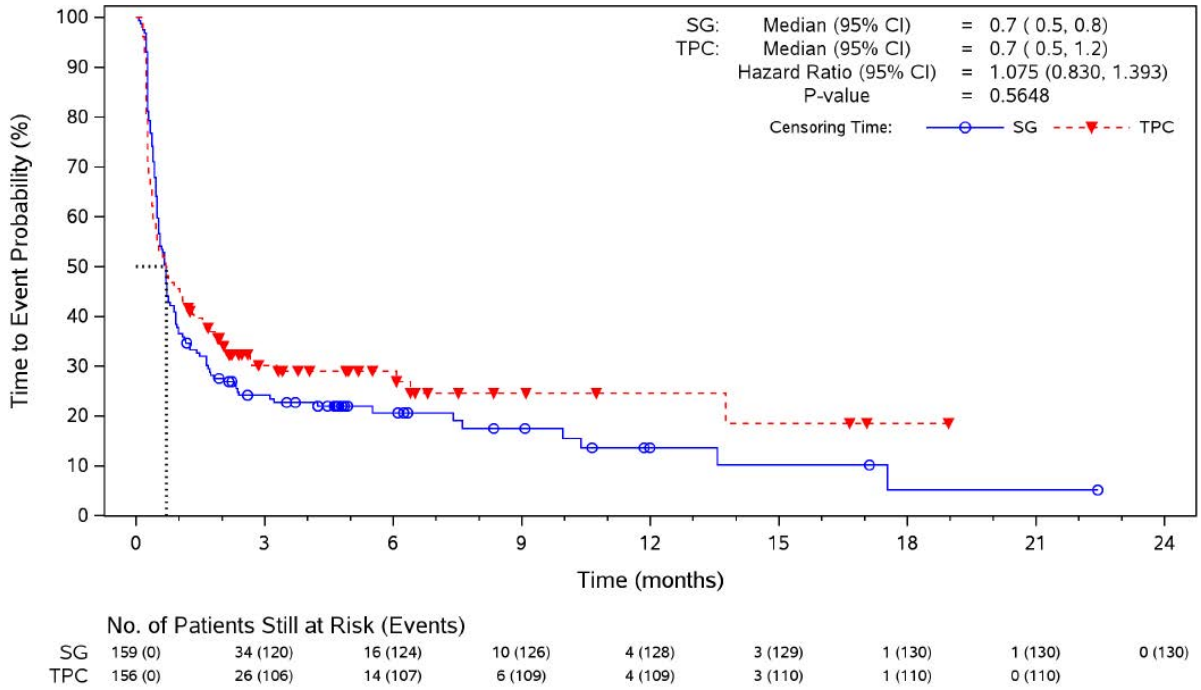

Figure 20: Kaplan-Meier curves for the outcome of severe AEs (CTCAE grade ≥ 3), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

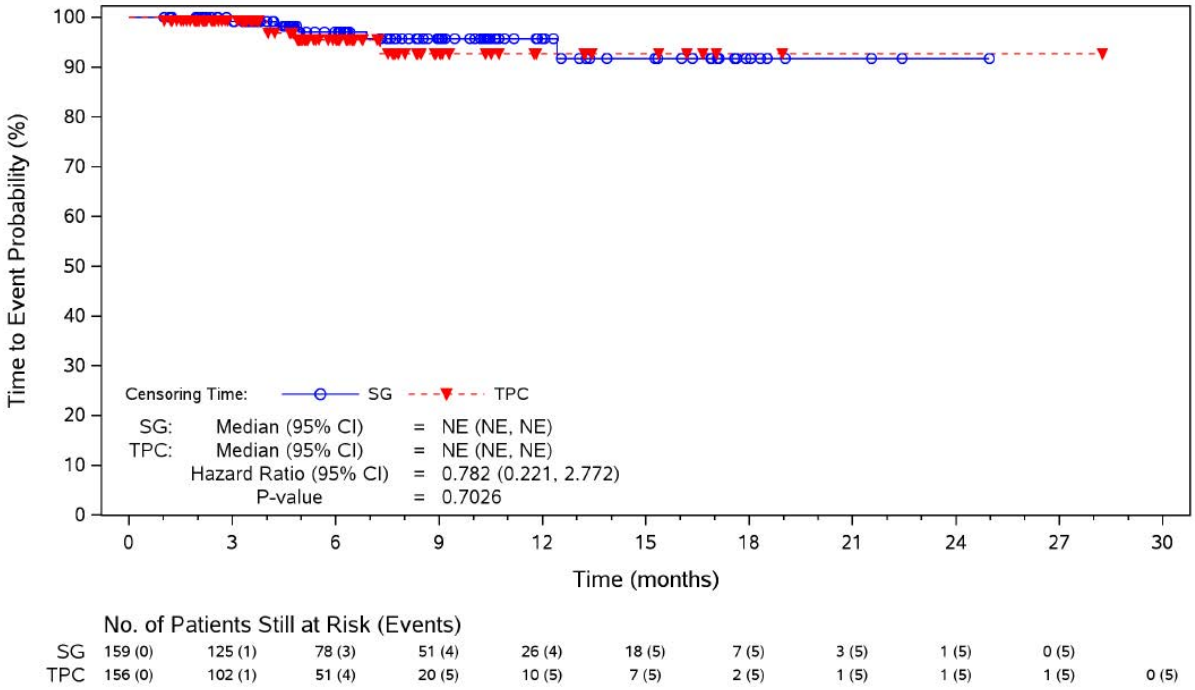

Figure 21: Kaplan-Meier curves for the outcome of discontinuation due to AEs, EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

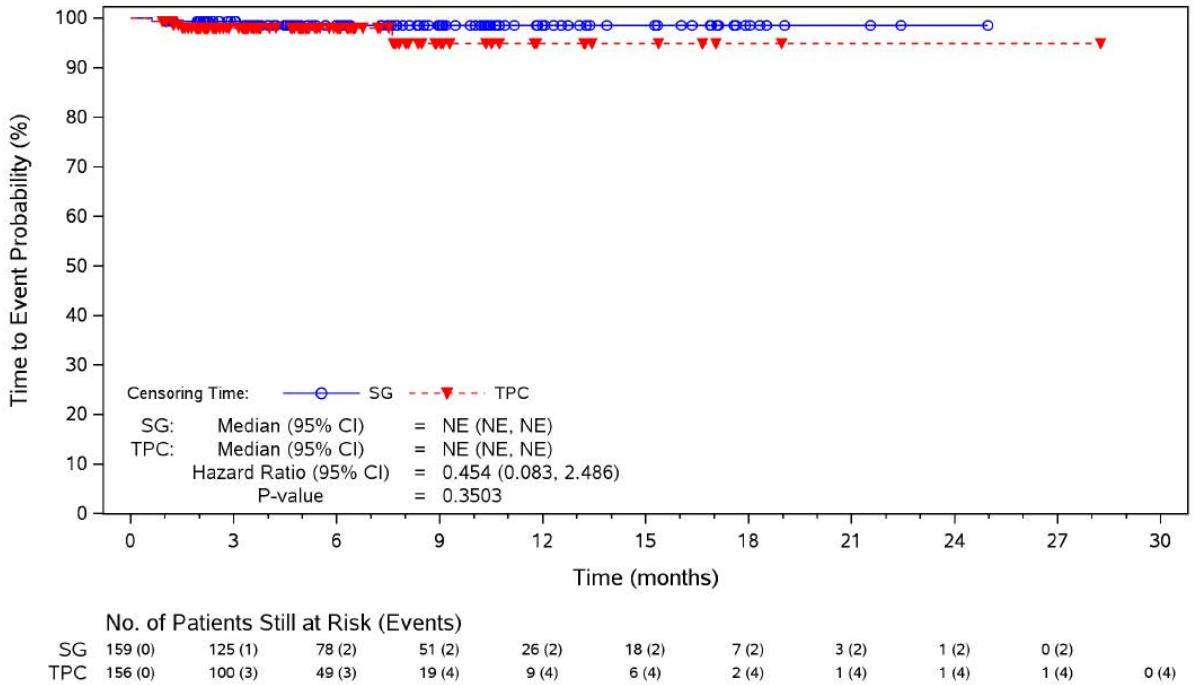

Figure 22: Kaplan-Meier curves for the outcome of hand-foot syndrome (PT, AEs), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

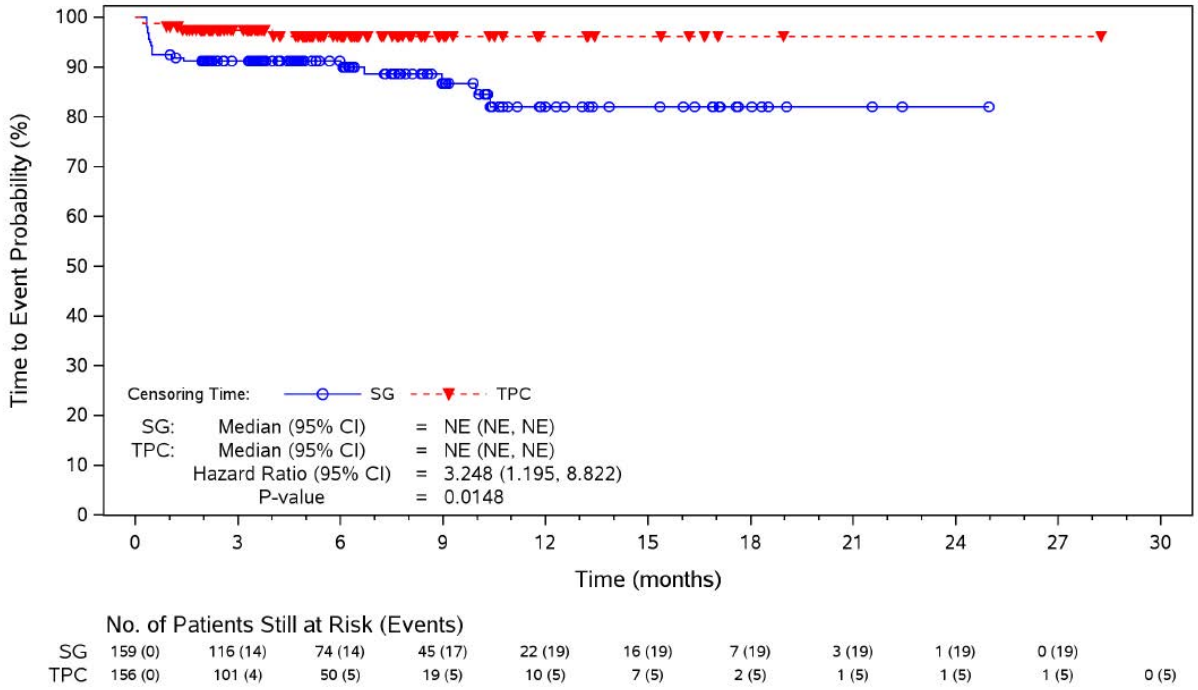

Figure 23: Kaplan-Meier curves for the outcome of gastrointestinal toxicity (SOC gastrointestinal disorders, severe AEs), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

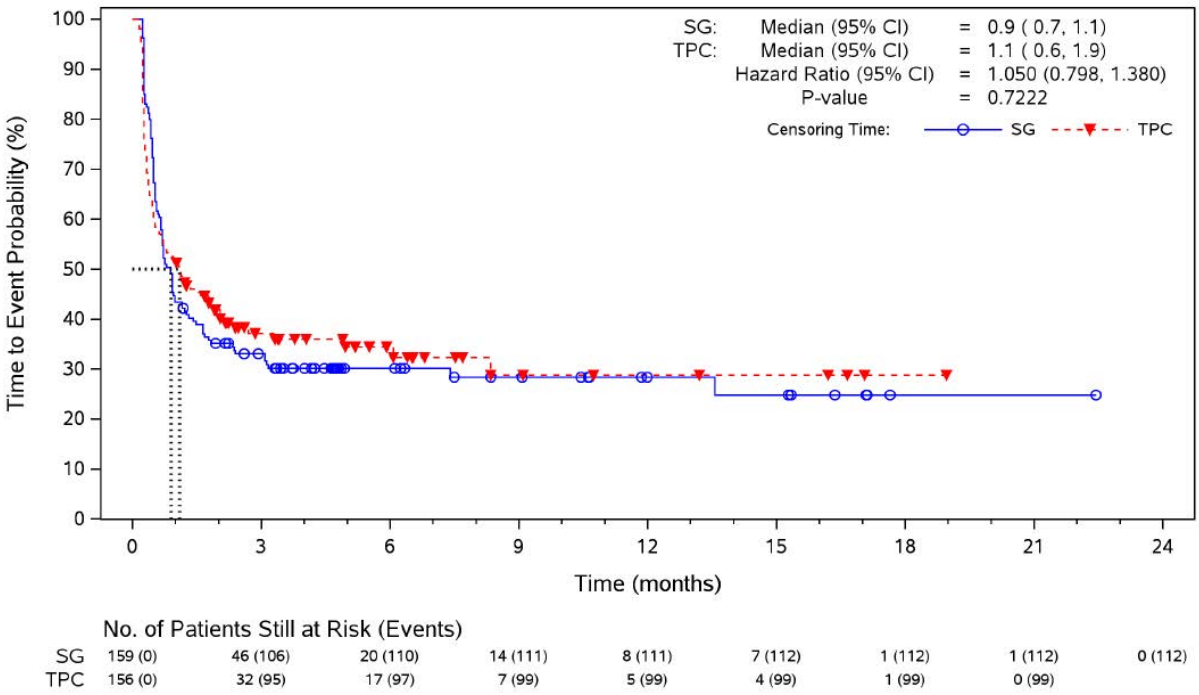

Figure 24: Kaplan-Meier curves for the outcome of neutropenia (PT compilation of the company, severe AEs), EVER-132-002 study (subpopulation a), data cut-off: 30 April 2023

Appendix D Results on side effects in the EVER-132-002 study

Table 18: Common AEs[a] – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[b], EVER-132-002 study (total population) (multipage table)

Study	Patients with event n (%)	
SOC[c] PT[c]	Sacituzumab govitecan N = 165	Treatment of physician's choice[b] N = 164
EVER-132-002		
Overall AE rate	165 (100.0)	164 (100.0)
Blood and lymphatic system disorders	158 (95.8)	143 (87.2)
Neutropenia	145 (87.9)	128 (78.0)
Leukopenia	113 (68.5)	104 (63.4)
Anaemia	117 (70.9)	91 (55.5)
Thrombocytopenia	33 (20.0)	58 (35.4)
Lymphopenia	31 (18.8)	27 (16.5)
Cardiac disorders	20 (12.1)	13 (7.9)
Gastrointestinal disorders	133 (80.6)	104 (63.4)
Nausea	95 (57.6)	52 (31.7)
Diarrhoea	84 (50.9)	22 (13.4)
Constipation	59 (35.8)	40 (24.4)
Vomiting	60 (36.4)	27 (16.5)
Abdominal pain	36 (21.8)	17 (10.4)
Abdominal pain upper	17 (10.3)	11 (6.7)
Stomatitis	13 (7.9)	12 (7.3)
Mouth ulceration	11 (6.7)	9 (5.5)
Dyspepsia	10 (6.1)	9 (5.5)
Abdominal distension	11 (6.7)	7 (4.3)
General disorders and administration site conditions	101 (61.2)	87 (53.0)
Fatigue	57 (34.5)	29 (17.7)
Pyrexia	21 (12.7)	28 (17.1)
Malaise	28 (17.0)	12 (7.3)
Asthenia	18 (10.9)	21 (12.8)
Infections and infestations	70 (42.4)	55 (33.5)
Upper respiratory tract infection	28 (17.0)	15 (9.1)
COVID-19	16 (9.7)	15 (9.1)
Urinary tract infection	19 (11.5)	9 (5.5)
Injury, poisoning and procedural complications	6 (3.6)	10 (6.1)

Table 18: Common AEs[a] – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[b], EVER-132-002 study (total population) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Sacituzumab govitecan** **N = 165**	**Treatment of physician's choice[b]** **N = 164**
Investigations	112 (67.9)	112 (68.3)
Alanine aminotransferase increased	61 (37.0)	53 (32.3)
Aspartate aminotransferase increased	54 (32.7)	58 (35.4)
Blood alkaline phosphatase increased	31 (18.8)	43 (26.2)
Gamma-glutamyltransferase increased	28 (17.0)	41 (25.0)
Blood lactate dehydrogenase increased	25 (15.2)	29 (17.7)
Weight decreased	17 (10.3)	15 (9.1)
Blood bilirubin increased	17 (10.3)	14 (8.5)
Blood creatinine increased	11 (6.7)	5 (3.0)
Reticulocyte count increased	10 (6.1)	4 (2.4)
Alpha hydroxybutyrate dehydrogenase increased	3 (1.8)	10 (6.1)
Reticulocyte count decreased	10 (6.1)	1 (0.6)
Metabolism and nutrition disorders	120 (72.7)	110 (67.1)
Decreased appetite	68 (41.2)	50 (30.5)
Hypoalbuminaemia	39 (23.6)	32 (19.5)
Hypokalaemia	40 (24.2)	28 (17.1)
Hyperglycaemia	31 (18.8)	35 (21.3)
Hyponatraemia	25 (15.2)	23 (14.0)
Hypocalcaemia	31 (18.8)	13 (7.9)
Hyperuricaemia	15 (9.1)	21 (12.8)
Hypertriglyceridaemia	10 (6.1)	13 (7.9)
Musculoskeletal and connective tissue disorders	45 (27.3)	50 (30.5)
Back pain	14 (8.5)	20 (12.2)
Pain in extremity	12 (7.3)	14 (8.5)
Myalgia	5 (3.0)	11 (6.7)
Nervous system disorders	53 (32.1)	53 (32.3)
Headache	17 (10.3)	13 (7.9)
Hypoaesthesia	12 (7.3)	17 (10.4)
Dizziness	17 (10.3)	11 (6.7)
Peripheral sensory neuropathy	5 (3.0)	12 (7.3)
Psychiatric disorders	29 (17.6)	35 (21.3)
Insomnia	25 (15.2)	23 (14.0)

Table 18: Common AEs[a] – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[b], EVER-132-002 study (total population) (multipage table)

Study	Patients with event n (%)	
SOC[c] PT[c]	**Sacituzumab govitecan N = 165**	**Treatment of physician's choice[b] N = 164**
Renal and urinary disorders	20 (12.1)	12 (7.3)
Proteinuria	10 (6.1)	5 (3.0)
Respiratory, thoracic and mediastinal disorders	46 (27.9)	42 (25.6)
Cough	21 (12.7)	17 (10.4)
Dyspnoea	11 (6.7)	11 (6.7)
Productive cough	10 (6.1)	5 (3.0)
Skin and subcutaneous tissue disorders	113 (68.5)	78 (47.6)
Alopecia	103 (62.4)	66 (40.2)
Pruritus	10 (6.1)	9 (5.5)
Rash	16 (9.7)	3 (1.8)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Capecitabine or eribulin or gemcitabine or vinorelbine.
c. MedDRA version 26.0; SOC and PT notation taken without adaptation from the clinical study report.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 19: Common SAEs[a] – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[b], EVER-132-002 study (total population)

Study	Patients with event n (%)	
SOC[c] PT[c]	**Sacituzumab govitecan N = 165**	**Treatment of physician's choice[b] N = 164**
EVER-132-002		
Overall SAE rate	38 (23.0)	32 (19.5)
Blood and lymphatic system disorders	16 (9.7)	12 (7.3)
Gastrointestinal disorders	10 (6.1)	6 (3.7)
Infections and infestations	12 (7.3)	5 (3.0)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. Capecitabine or eribulin or gemcitabine or vinorelbine.
c. MedDRA version 26.0; SOC and PT notation taken without adaptation from the clinical study report.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class

Table 20: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[b], EVER-132-002 study (total population)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Sacituzumab govitecan N = 165**	**Treatment of physician's choice[b] N = 164**
EVER-132-002		
Overall rate of severe AEs (CTCAE grade ≥ 3)	135 (81.8)	114 (69.5)
Blood and lymphatic system disorders	125 (75.8)	106 (64.6)
Neutropenia	114 (69.1)	101 (61.6)
Leukopenia	69 (41.8)	60 (36.6)
Anaemia	30 (18.2)	10 (6.1)
Febrile neutropenia	9 (5.5)	7 (4.3)
Lymphopenia	10 (6.1)	4 (2.4)
Gastrointestinal disorders	19 (11.5)	5 (3.0)
Diarrhoea	11 (6.7)	0 (0)
General disorders and administration site conditions	16 (9.7)	6 (3.7)
Fatigue	12 (7.3)	3 (1.8)
Infections and infestations	12 (7.3)	5 (3.0)
Investigations	6 (3.6)	15 (9.1)
Gamma-glutamyltransferase increased	1 (0.6)	10 (6.1)
Metabolism and nutrition disorders	22 (13.3)	7 (4.3)
Hypokalaemia	16 (9.7)	5 (3.0)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. Capecitabine or eribulin or gemcitabine or vinorelbine.
c. MedDRA version 26.0; SOC and PT notation taken without adaptation from the clinical study report.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 21: Discontinuation due to AEs – RCT, direct comparison: sacituzumab govitecan vs. treatment of physician's choice[a], EVER-132-002 study (subpopulation a)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Sacituzumab govitecan** **N = 159**	**Treatment of physician's choice[a]** **N = 156**
EVER-132-002		
Overall rate of discontinuations due to AEs	5 (3.1)	5 (3.2)
Blood and lymphatic system disorders	1 (0.6)	0 (0)
Anaemia	1 (0.6)	0 (0)
General disorders and administration site conditions	2 (1.3)	1 (0.6)
Fatigue	2 (1.3)	1 (0.6)
Infections and infestations	1 (0.6)	1 (0.6)
Pneumonia	0 (0)	1 (0.6)
Septic shock	1 (0.6)	0 (0)
Musculoskeletal and connective tissue disorders	0 (0)	1 (0.6)
Muscular weakness	0 (0)	1 (0.6)
Nervous system disorders	0 (0)	1 (0.6)
Peripheral sensory neuropathy	0 (0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	1 (0.6)
Asphyxia	0 (0)	1 (0.6)
Interstitial lung disease	1 (0.6)	0 (0)

a. Capecitabine or eribulin or vinorelbine.
b. MedDRA version 26.0; SOC and PT notation taken without adaptation from the data subsequently submitted.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class