Sacituzumab govitecan (breast cancer)

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

EXTRACT

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
CDK	cyclin-dependent kinase
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
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 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

I 1 Executive summary of the benefit assessment

Background

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

Research question

The aim of this report is to assess the added benefit of sacituzumab govitecan compared with the appropriate comparator therapy (ACT) in 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 for advanced disease.

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

Table 2: Research question of the benefit assessment of sacituzumab govitecan

Therapeutic indication	**ACT**[a]
Adult patients[b] 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[c]	▪ **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)[d]

a. Presented is the 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. 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.
c. 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.

According to guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor-2

The company selected capecitabine, eribulin, and vinorelbine from the ACT options specified by the G-BA. In addition to the therapy options presented in Table 2, it also cited trastuzumab deruxtecan as an option for adult patients with HER2-low breast cancer. Because the company included no study with trastuzumab deruxtecan as a comparator, the company identifying this drug as an alternative therapy option is of no consequence for the present benefit assessment. The benefit assessment was conducted in comparison with the ACT specified by the G-BA.

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

Study pool and study design

The TROPiCS-02 study was used for the benefit assessment of sacituzumab govitecan. This is an ongoing, open-label RCT which compares 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 1 endocrine-based therapy, at least 1 therapy with cyclin-dependent kinase (CDK)4/6 inhibitors, and at least 1 taxane-containing therapy as well as 2 to 4 chemotherapy regimens in the metastatic stage. In this context, (neo)adjuvant chemotherapy was counted as 1 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.

Overall, 543 patients were included in the study and randomly allocated in a 1:1 ratio to either treatment with sacituzumab govitecan (N = 272) or treatment of physician's choice (N = 271). In each case, a decision had to be made before randomization as to which of the available treatment options the patient was to be treated with in the event of allocation to the control arm. Gemcitabine is not an ACT option. For the benefit assessment, therefore, the subpopulation of 205 versus 213 patients for whom capecitabine, eribulin, or vinorelbine was selected as the drug to be administered in case of allocation to the control arm is relevant.

In the TROPiCS-02 study, treatment with sacituzumab govitecan and eribulin was in line with the respective Summaries of Product Characteristics (SPCs). Capecitabine and vinorelbine treatment was largely in line with the respective SPCs.

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 study end.

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 TROPiCS-02 study

The G-BA specified as the ACT 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). In the TROPiCS-02 study, the following monotherapies were available under treatment of physician's choice: capecitabine, eribulin, vinorelbine, and gemcitabine. Gemcitabine is not an ACT option specified by the G-BA and is approved as a monotherapy for patients in this therapeutic indication. With the dossier, the company therefore presents analyses on a subpopulation of the TROPiCS-02 study

which, in the intervention and control arms, includes only patients for whom capecitabine, eribulin, or vinorelbine had been specified as the corresponding treatment option prior to randomization. The company's procedure for forming the subpopulation is appropriate; the subpopulation formed by the company is used for the benefit assessment.

Data cutoffs

In the dossier, the company presents results for 2 data cutoffs (1 July 2022: analyses for all outcomes; 1 December 2022: analysis exclusively for the outcome of overall survival). For the present benefit assessment, the 1 December 2022 data cutoff is the primary one for the outcome of overall survival; the 1 July 2022 data cutoff is used for all other outcomes.

Risk of bias

The risk of bias across outcomes is rated as low for the TROPiCS-02 study.

For the outcome of overall survival, the risk of bias of the results is rated as low. For the results of the outcomes of symptoms, health status, and health-related quality of life, the risk of bias is classified as high due to (a) the high proportion of patients excluded from the analysis, (b) incomplete observation for potentially informative reasons, and (c) a lack of blinding in the presence of subjective recording of outcomes. For the outcomes of serious adverse events (SAEs) and severe adverse events (AEs), the risk of bias of the results is deemed high due to incomplete observations for potentially informative reasons with different lengths of follow-up in the study arms. For non-serious/non-severe AEs, the risk of bias of results 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 was rated as high because of lack of blinding in the presence of subjective decision on treatment discontinuation.

No suitable data are available for the outcome of Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), rendering an assessment of the risk of bias unnecessary.

Results

Mortality

Overall survival

At both data cutoffs, the analyses showed no statistically significant difference between the treatment groups for the outcome of overall survival. This results in 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.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30])

Fatigue

A statistically significant difference in favour of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of fatigue. This results in a hint of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice.

Diarrhoea

A statistically significant difference to the disadvantage of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of diarrhoea. This results in a hint of lesser benefit of sacituzumab govitecan in comparison with treatment of physician's choice.

Dyspnoea and insomnia

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 dyspnoea and insomnia. 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. This results in 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.

Nausea and vomiting, pain, loss of appetite, and constipation

No statistically significant differences between the treatment groups were shown for any of the outcomes of nausea and vomiting, pain, loss of appetite, or constipation. This results in 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 (European Quality of Life 5 Dimensions [EQ-5D] visual analogue scale [VAS])

No statistically significant difference between the treatment groups was shown for the outcome of health status, surveyed via the EQ-5D VAS. This results in 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

Global health status, physical functioning, and emotional functioning

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, and emotional functioning. This results in a hint of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice for each of them.

Role functioning, cognitive functioning, and social functioning

No statistically significant difference between the treatment groups was shown for the outcomes of role functioning, cognitive functioning, or social functioning. This results in 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.

Side effects

Severe AEs

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. This results in a hint of greater harm from sacituzumab govitecan in comparison with treatment of physician's choice.

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. This results in no hint of added benefit of 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. This results in 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), diseases of the nervous system (severe AEs), and diseases of the respiratory tract, chest and mediastinum (severe AEs)

For the outcomes of hand-foot syndrome (AEs), diseases of the nervous system (severe AEs), and diseases of the respiratory tract, chest and mediastinum (severe AEs), there was a statistically significant difference in favour of sacituzumab govitecan compared to treatment of physician's choice. This results in a hint of lesser harm from sacituzumab govitecan in comparison with treatment of physician's choice for each of them.

Gastrointestinal toxicity (serious AEs), neutropenia (serious AEs), and skin and subcutaneous tissue disorders (AEs)

For each of the outcomes of gastrointestinal toxicity (serious AEs), neutropoenia (severe AEs), and diseases of the skin and subcutaneous tissue (AEs), there was a statistically significant

difference to the disadvantage of sacituzumab govitecan compared to treatment of physician's choice. This results in a hint of greater harm from sacituzumab govitecan in comparison with treatment of physician's choice for each of them.

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

On the basis of the presented results, the probability and extent of added benefit of the drug sacituzumab govitecan in comparison with the ACT are assessed as follows:

Overall, there were both favourable and unfavourable effects for sacituzumab govitecan compared to treatment of physician's choice, but only for the shortened observation period. The outcome categories of non-serious/non-severe symptoms / late complications and (non-)serious/(non-)severe side effects each result in favourable and unfavourable effects of varying severity with the probability of a hint. In the outcome category of health-related quality of life, only favourable effects of minor or considerable extent were found. In the outcome category of health-related quality of life, the unfavourable effects do not completely jeopardize the favourable effects.

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 a hint of minor added benefit of sacituzumab govitecan compared with treatment of physician's choice.

Table 3 shows a summary of the probability and extent of added benefit of sacituzumab govitecan.

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

Table 3: Sacituzumab govitecan – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
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 in the advanced setting[c]	▪ **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)[d]	Hint of minor added benefit[e]

a. Presented is the 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. 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.
c. 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.

d. According to guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth.
e. The TROPiCS-02 study included only patients with an ECOG-PS of 0 or 1. In addition, the subpopulation relevant for the dossier assessment comprises only 5 male patients. It remains unclear whether the observed effects can be transferred to patients with ECOGPS ≥ 2 and to male patients.

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

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

I 2 Research question

The aim of this report is to assess the added benefit of sacituzumab govitecan compared with the ACT 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.

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

Table 4: Research question of the benefit assessment of sacituzumab govitecan

Therapeutic indication	**ACT**[a]
Adult patients[b] 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[c]	▪ **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)[d]

a. Presented is the 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. 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.
c. 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.

d. According to guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor-2

The company selected capecitabine, eribulin, and vinorelbine from the ACT options specified by the G-BA. In addition to the therapy options presented in Table 4, it also cited trastuzumab deruxtecan as an option for adult patients with HER2-low breast cancer. The company justifies its addition by the fact that the G-BA determined the medical benefit of trastuzumab deruxtecan in adults with HER2-low breast cancer in a benefit assessment procedure [3] and

the drug is included in current guidelines and the German guideline by the Breast Commission of the German Society of Gynaecological Oncology (AGO) from 2023 as a treatment option for patients with metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic stage [4-7]. The company's designation of trastuzumab deruxtecan as an alternative treatment option is of no consequence for the present benefit assessment because the company did not include a study employing this drug as a comparator. The benefit assessment is conducted in comparison with the ACT specified by the G-BA.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on sacituzumab govitecan (status: 3 July 2023)
- bibliographical literature search on sacituzumab govitecan (last search on 3 July 2023)
- search in trial registries / trial results databases for studies on sacituzumab govitecan (last search on 3 July 2023)
- search on the G-BA website for sacituzumab govitecan (last search on 3 July 2023)

To check the completeness of the study pool:

- search in trial registries for studies on sacituzumab govitecan (last search on 24 August 2023); for search strategies, see I Appendix A of the full dossier assessment

This check identified the potentially relevant study EVER-132-002 (NCT04639986) [8] in addition to the TROPiCS-02 study presented by the company. The company-sponsored RCT investigates sacituzumab govitecan in comparison to treatment of physician's choice in adult patients with metastatic hormone receptor-positive, HER2-negative breast cancer who have already received at least 1 taxane, at least 1 endocrine-based therapy, and 2 to 4 systemic chemotherapy regimens in the metastatic stage. The company includes this RCT in its study list for sacituzumab govitecan and presents both the study protocol and the statistical analysis plan with the dossier. The 2 studies EVER-132-002 and TROPiCS-02 follow almost identical study protocols, but no results are yet available for the EVER-132-002 study – which was conducted with 331 patients in centres in China, South Korea, and Taiwan, according to the registry entry at ClinicalTrials.gov. The first results are expected in March 2024. The relevance of this study cannot yet be assessed.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: sacituzumab govitecan versus 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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication (yes/no [citation])
IMMU-132-09 (TROPICS-02[d])	Yes	Yes	No	Yes [9,10]	Yes [11,12]	Yes [13,14]

a. Capecitabine or eribulin 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.

RCT: randomized controlled trial

The study pool for the benefit assessment concurs with that by the company.

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
TROPiCS-02	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 CDK4/6 inhibitor, ≥ 1 taxane, and 2–4 chemotherapies in the metastatic stage[e] ▪ ECOG-PS 0 or 1	Sacituzumab govitecan (N = 272) Treatment of physician's choice[a] (N = 271) ▪ Capecitabine (N = 22[f]) ▪ Eribuline(N = 130) ▪ Gemcitabine (N = 56[f]) ▪ Vinorelbin (N = 63[f]) Relevant subpopulation thereof[g]: Sacituzumab govitecan (n = 205) Treatment of physician's choice[a, h] (n = 213[i])	Screening: up to 28 days Treatment: until disease progression[j], unacceptable toxicity, withdrawal of consent, treatment discontinuation due to investigator's decision, or end of study Observation[k]: outcome-specific, maximum until death, withdrawal of consent, or end of study	91 centres in Belgium, Canada, France, Germany, Italy, Netherlands, Spain, United Kingdom, United States 05/2019–ongoing Data cutoffs: ▪ 03/01/2022[l] ▪ 01/07/2022[m] ▪ 01/12/2022[n]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]

a. In the TROPiCS-02 study, the treatment options were capecitabine, eribulin, gemcitabine, and vinorelbine (each as monotherapy). The ACT options suitable for the dossier 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 ISH 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. Information from the study report; the information on patient numbers per drug differs slightly between Module 4 A and Appendix 4-G of the dossier versus the study report (only concerning a few patients).
g. The subpopulation comprises patients for whom capecitabine, eribulin, or vinorelbine was specified prior to randomization as the drug to be received in case of allocation to the control arm. Patients for whom gemcitabine was assigned are disregarded below.
h. Information on the number of patients treated with capecitabine or vinorelbine in the control arm differs slightly between Module 4 A and Annex 4-G of the dossier (only concerns a few patients).
i. Information from Module 4 A; according to the information in the study report, the population relevant for the dossier assessment comprises 215 patients in the control arm.
j. Continuation of treatment with the study medication was allowed after the first detection of disease progression as per RECIST criteria, version 1.1, if the patient was deemed to benefit from it by the investigator. If the disease progressed and/or clinical benefit was lost, treatment was to be discontinued.
k. Outcome-specific information is provided in Table 8.
l. Final analysis for the outcome of PFS and first interim analysis for the outcome of overall survival (planned to be implemented after approximately 272 deaths).
m. Second interim analysis for the outcome of overall survival (planned to be implemented after approximately 350 deaths).
n. Additional data cutoff for the outcomes of PFS and overall survival which was submitted to the EMA to confirm previous results and for which the company submitted data for the outcome of overall survival in the dossier.

AE: adverse event; CDK: cyclin-dependent kinase; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; HER2: human epidermal growth factor receptor-2; IHC: immunohistochemistry; ISH: in situ hybridization; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study	Intervention	Comparison
TROPiCS-02	Sacituzumab govitecan 10 mg/kg BW[b] i.v. on Day 1 and Day 8 of a 21-day cycle	Treatment of physician's choice; 1 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] ▪ Eribuline: 1.23 mg/m² BSA (in European centres) or 1.4 mg/m² BSA (in North American centres) i.v. on Day 1 and Day 8 of a 21-day cycle[c] ▪ Vinorelbine: 25 mg/m² BSA i.v. 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[e]) allowed due to side effects	**Dose adjustments** Dose adjustments in accordance with local marketing authorizations for the respective medicinal products or local standards
	Prior treatment ▪ At least 2 and no more than 4 prior systemic chemotherapy regimens in metastatic stage[f] ▪ At least 1 taxane-containing chemotherapy ▪ At least 1 endocrine-based therapy ▪ At least 1 CDK4/6 inhibitor therapy **Disallowed prior and concomitant treatment** ▪ Topoisomerase-1 inhibitor before screening ▪ Chemotherapy, radiotherapy, or small-molecule targeted therapy within 2 weeks prior to randomization, biologics within 4 weeks prior to randomization, and any antineoplastic therapy during the study[g] ▪ High-dose systemic corticosteroids within 2 weeks prior to randomization and during the study ▪ Blood transfusions or haematopoietic growth factors within 2 weeks prior to screening	
	Allowed concomitant treatment ▪ Premedication before the infusion[h] ▫ antipyretics, H1 and H2 blockers to prevent infusion-related reactions ▫ corticosteroids (50 mg hydrocortisone or equivalent [oral or intravenous]) for infusion-related reactions following infusion ▫ preventive antiemetic treatment with 2 drugs or in case of persistent nausea and vomiting with 3 drugs (with 5-hydroytryptamine receptor antagonist [e.g. ondansetron or palonosetron], neurokinin-1 receptor antagonist [fosaprepitant or aprepitant], and dexamethasone [10 mg orally or i.v.]) ▫ 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 [in case of severe neutropenia], or dietary measures)	

Table 7: Characteristics of the intervention – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study	Intervention	Comparison
a. Capecitabine or eribulin or vinorelbine. b. The dose is calculated based on body weight on Day 1 of a 21-day cycle (additionally on Day 8 of a 21-day cycle if the patient's body weight has changed by > 10% since the prior application). At a change in body weight by ≤ 10%, dose adjustments were possible according to local guidelines. c. Treatment with capecitabine, eribulin, and vinorelbine should be carried out in accordance with the local marketing authorizations of the respective drugs or the NCCN guidelines. d. No dose increase was allowed after a dose reduction. e. If the dose administration was delayed by > 21 days due to side effects, treatment was discontinued. f. This includes (neo)adjuvant chemotherapy if unresectable, locally advanced, or metastatic disease has developed within 12 months. g. Except for study medication and palliative radiotherapy of a symptomatic, solitary non-target lesion or whole-brain radiotherapy (not indicated by tumour progression). h. In the intervention arm, preventive treatment was to be administered to avoid infusion-related reactions, and preventive antiemetic treatment was recommended. In the control arm, treatment to prevent infusion-related reactions and to prevent chemotherapy-induced nausea and vomiting was allowed at the investigator's discretion. BSA: body surface area; BW: body weight; CDK: cyclin-dependent kinase; i.v.: intravenous; NCCN: National Comprehensive Cancer Network; RCT: randomized controlled trial		

The TROPiCS-02 study is an ongoing, open-label 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 1 endocrine-based therapy, at least 1 therapy with cyclin-dependent kinase (CDK)4/6 inhibitors, and at least 1 taxane-containing therapy as well as 2 to 4 chemotherapy regimens in the metastatic stage. In this context, (neo)adjuvant chemotherapy was counted as 1 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.

The 543 included patients were randomly allocated in a 1:1 ratio to either treatment with sacituzumab govitecan (N = 272) or treatment of physician’s choice (N = 271). In each case, a decision had to be made before randomization as to which of the available treatment options the patient was to receive in the event of allocation to the control arm. 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 endocrine-based therapy in the metastatic stage for at least 6 months (yes versus no).

Gemcitabine is not an ACT option. For the benefit assessment, the company has presented a relevant subpopulation of the TROPiCS-02 study. The subpopulation comprises 205 versus 213 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).

In the TROPiCS-02 study, treatment with sacituzumab govitecan and eribulin complied with the respective SPC [15,16]. For patients receiving these drugs, the SPCs recommend administering or considering treatment to prevent chemotherapy-induced nausea and vomiting before each infusion. However, based on the information presented in the company's dossier, it remains unclear which proportion of patients in the relevant subpopulation treated with sacituzumab govitecan or eribulin did not receive regular treatment for the prevention of chemotherapy-induced nausea and vomiting in the course of the study. Given the available data, however, it is safe to assume that no disadvantage to the control arm which would influence the study results can be attributed to a potential lack of antiemetic prophylaxis before the administration of eribulin.

Treatment with capecitabine and vinorelbine was largely carried out in accordance with the specifications of the respective SPC [17,18]. For capecitabine, however, a specified dosage of 1000 to 1250 mg/m² body surface area (BSA) provided the option, for some patients, of using a lower starting dose than recommended by the SPC (1250 mg/m^2 BSA) [17]. The dose range of 1000 to 1250 mg/m² BSA can be found in the National Comprehensive Cancer Network (NCCN) guideline for the treatment of patients with locally advanced, unresectable, or metastatic breast cancer [7]. In addition, the supporting reasons for the G-BA's decision on the benefit assessment procedure for trastuzumab deruxtecan suggest that the use of capecitabine at the lower dosage reflects the therapeutic standard in clinical practice in the opinions of clinical experts [19].

Vinorelbine was administered at a dose of 25 mg/m² BSA in the TROPiCS-02 study [7]. According to the SPC, vinorelbine is usually used in this therapeutic indication at a dose of 25 to 30 mg/m² BSA [18]. The vinorelbine dosage used in the study therefore corresponds to the lowest dosage which is still compliant with the marketing authorization.

Overall, it is assumed that the lower doses of capecitabine and vinorelbine which were potentially used in monotherapy in the TROPiCS-02 study have no relevant effects on the present benefit assessment.

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. Patients were allowed to continue treatment after the first detection of disease progression according to version 1.1 of the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, provided the investigator deemed them to benefit from continued treatment. Data on the proportion of such patients are not available. However, if

the disease progressed and/or clinical benefit was lost in the further course, treatment with the study medication had to be discontinued.

Switching between the available treatment options during the treatment phase was not allowed in the control arm of the TROPiCS-02 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 TROPiCS-02 study

The G-BA specified the ACT to be 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). In the TROPiCS-02 study, the following monotherapies were available under treatment of physician's choice: capecitabine, eribulin, vinorelbine, and gemcitabine. Approximately 21% of patients in the control arm of the TROPiCS-02 study received gemcitabine monotherapy. Gemcitabine is (a) not an ACT option as specified by the G-BA and is (b) not approved as a monotherapy for patients in this therapeutic indication [20]. For the benefit assessment, the company's dossier therefore presents analyses on a subpopulation of the TROPiCS-02 study which, in the intervention and control arm, includes only patients for whom capecitabine, eribulin, or vinorelbine had been specified as the corresponding treatment option prior to randomization. The company's approach of forming the subpopulation is appropriate. For this reason, the subpopulation formed by the company is used for the present benefit assessment.

Implementation of the ACT

Prior anthracycline treatment

According to the corresponding SPCs, the treatment options relevant for the dossier assessment (capecitabine, eribulin, vinorelbine) in the TROPiCS-02 control arm are to be used only if

- therapy with taxanes and anthracyclines has failed or further anthracycline treatment is not therapeutically indicated (capecitabine [17]).
- the prior therapy contained an anthracycline and a taxane, unless this treatment was unsuitable for the patient (eribulin [16]).
- therapy with taxanes and anthracyclines has failed or is not suitable (vinorelbine [18]).

Prior treatment with (at least) 1 taxane was an inclusion criterion for the TROPiCS study-02. Therefore, all patients had presumably already received (at least) 1 taxane-containing chemotherapy. However, prior treatment with anthracyclines was not mandatory for study inclusion. Based on the information presented by the company in the dossier, it remains unclear to what extent patients in the control arm of the relevant subpopulation received prior treatment with (at least) 1 anthracycline and how high the proportion of those for whom this therapy was not suitable may be. The information on the total population of the TROPiCS-02 study shows that the majority (around 80%) of patients in the control arm had received prior treatment with (at least) 1 anthracycline. Since the proportion of those patients in the overall population who had not received prior therapy with anthracyclines or for whom this therapy was unsuitable is relatively low, this described uncertainty has no consequences for the present benefit assessment.

Combination therapy

As per guideline recommendations, combination therapy is to be considered for patients with high remission pressure in case of severe symptoms and rapid tumour growth [7,21,22]. According to the study protocol, treatment of physician's choice in the TROPiCS-02 study generally does not allow combination therapy selecting from the treatment options of capecitabine, eribulin, gemcitabine and vinorelbine. Although the company explains in Module 4 A of the dossier that combination therapy may be considered in individual cases for patients in the present therapeutic indication, it does not state how high the proportion of patients in the TROPiCS-02 study might have been for whom combination therapy would have been preferable to monotherapy in the course of the study.

Summary on the ACT

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. The subpopulation of the TROPiCS-02 study formed by the company is used as the relevant population in the present benefit assessment.

Data cutoffs

The company presents results on 2 data cutoffs in Module 4 A of the dossier:

- 1 July 2022 (planned 2nd interim analysis for the outcome of overall survival): analyses for all outcomes
- 1 December 2022 (additional data cutoff for the outcomes of PFS and overall survival, which was submitted to the European Medicines Agency [EMA] to confirm previous results): analysis only for the outcome of overall survival

For all outcomes of the categories of morbidity, health-related quality of life, and side effects, the dossier therefore contains only analyses for the data cutoff of 1 July 2022 for the relevant subpopulation. Since the analyses of those outcomes presented in the company's dossier only cover the treatment period (plus 30 days) (see Table 8) and only a few patients in the intervention and control arms were still being treated with the study medication at the 1 July 2022 data cutoff (7 versus 2 patients), the 1 December 2022 data cutoff would be unlikely to have produced different results at a follow-up until 30 days after the end of treatment. For the benefit assessment, the 1 December 2022 data cutoff is the primary one for the outcome of overall survival; for all other outcomes, the 1 July 2022 data cutoff is used.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
TROPiCS-02	
Mortality	
Overall survival	Until death, withdrawal of consent, or end of study
Morbidity	
Symptoms (EORTC QLQ-C30)	Until 30 days after the last dose of the study medication[b]
Health status (EQ-5D VAS)	Until 30 days after the last dose of the study medication[b]
Health-related quality of life (EORTC QLQ-C30)	Until 30 days after the last dose of the study medication[b]
Side effects	
AEs / SAEs / severe AEs[c]	Until 30 days after the last dose of the study medication
PRO-CTCAE	Until 30 days after the last dose of the study medication[b]

a. Capecitabine or eribulin or vinorelbine.
b. Before protocol amendment 4 dated 13 March 2020 until disease progression under subsequent therapy; analyses in Module 4 A of the dossier include a follow-up observation of 30 days after the last dose of study medication.
c. 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 TROPiCS-02 study surveyed only overall survival to the end of the study. The observation times for the outcomes of AEs, SAEs, and serious AEs are systematically shortened because

the TROPiCS-02 study recorded them only for the period of treatment with the study medication (plus 30 days). Prior to protocol amendment 4 of 13 March 2020, outcomes in the morbidity and health-related quality of life categories as well as the outcome of PRO-CTCAE were to be recorded beyond 30 days after the end of treatment (every 60 days until disease progression under subsequent therapy). The collection of patient-reported outcomes over a longer follow-up observation period is generally preferable. The company's dossier does not provide the reasoning for protocol amendment 4 specifying that these outcomes were to be recorded only until the end of treatment (plus 30 days). For the present benefit assessment, the company has presented analyses for these outcomes which covered the period up to the end of treatment (plus 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 study period.

Characteristics of the relevant subpopulation

Table 9 shows the patient characteristics of the included study's relevant subpopulation.

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study Characteristic Category	Sacituzumab govitecan N = 205	Treatment of physician's choice[a] N = 213
TROPiCS-02		
Age [years], mean (SD)	56 (11)	55 (10)
Sex [f/m], %	99/1	99/1
Region, n (%)		
North America	80 (39)	83 (39)
Europe	125 (61)	130 (61)
Ancestry, n (%)		
White	143 (70)	143 (67)
Black or African American	7 (3)	8 (4)
Asian	7 (3)	5 (2)
Other	0 (0)	5 (2)[b]
Missing[c]	48 (23)	52 (24)
ECOG-PS, n (%)		
0	90 (44)	99 (47)
1	115 (56)	114 (54)
BRCA1/2 mutation status, n (%)		
Negative	83 (41)	90 (42)
Positive	19 (9)	6 (3)
Missing	103 (50)	117 (55)
Time between detection of metastasis and randomization [months]		
Mean (SD)	53.7 (33.9)	52.3 (32.3)
Median [min; max]	46.0 [6.7; 216.2]	46.6 [3.0; 248.8]
Visceral metastases, n (%)		
Yes	196 (96)	205 (96)
No	9 (4)	8 (4)
Information on prior therapies		
Number of prior systemic therapies, mean (SD)	7.0 (2.3)	7.0 (2.2)
Number of prior chemotherapy regimens, mean (SD)	3.5 (1.1)	3.6 (1.1)
CDK4/6 inhibitor therapy, n (%)[d]	205 (100)	213 (100)
Endocrine-based therapy, n (%)[d]	ND	ND
Anthracyclines, n (%)	ND	ND
Taxanes, n (%)[d]	ND	ND

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study Characteristic Category	Sacituzumab govitecan N = 205	Treatment of physician's choice[a] N = 213
(Neo)Adjuvant chemotherapy, n (%)	125 (61)	145 (68)
Early recurrence after (neo)adjuvant chemotherapy, n (%)[e]		
Yes	13 (10[b])	17 (12[b])
No	105 (84[b])	124 (86[b])
Missing	7 (6[b])	4 (3[b])
Number of chemotherapy regimens in the metastatic stage, n (%)[f, g]		
2	96 (47)	102 (48)
3 or 4	109 (53)	111 (52)
Treatment discontinuation at the 01/07/2022 data cutoff, n (%)[h]	194 (95)	192 (90)
Study dropout by the 01/07/2022 data cutoff, n (%)[i]	151 (74)	166 (78)
Treatment discontinuation by the 01/12/2022 data cutoff, n (%)[j]	196 (96)	193 (91)
Study discontinuation by the 01/12/2022 data cutoff, n (%)[k]	169 (82)	185 (87)

a. Capecitabine or eribulin or vinorelbine.
b. Institute's calculation.
c. Not surveyed based on local guidelines.
d. One inclusion criterion of the TROPiCS-02 study was prior treatment with at least 1 taxane, at least 1 CDK4/6 inhibitor, and at least 1 endocrine-based therapy.
e. Defined as evidence of metastatic disease within 12 months of completion of (neo)adjuvant chemotherapy.
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. As per inclusion criteria of the TROPiCS-02 study, all patients were allowed to have received a maximum of 4 chemotherapy regimens in the metastatic stage. Deviating from this, Appendix 4-G to Module 4 A shows that the study included 3 versus 0 patients with 5 lines of therapy and 1 versus 0 patients with 6 lines of therapy, each in the metastatic stage.
h. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression (79% versus 75%), withdrawal of consent (4% versus 7%), and AEs (7% versus 3%).
i. Common reasons for study discontinuation in the intervention arm versus the control arm were death (66% versus 56%) and withdrawal of consent (4% versus 16%).
j. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression (80% versus 76%), withdrawal of consent (4% versus 7%), and AEs (7% versus 3%).
k. Common reasons for study discontinuation in the intervention arm versus the control arm were death (75% versus 65%), withdrawal of consent (4% versus 16%).

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 demographic and clinical characteristics of the patients who are part of the TROPiCS-02 subpopulation relevant for the dossier assessment are comparable between the 2 study arms. The patients' average age was 56 years, the majority were female (99%), and most of them

came from Europe (61%). More than half of the patients (55%) had an ECOG-PS of 1 at baseline. On average, patients in the intervention and control arms each received 7 prior systemic therapies, including around 4 chemotherapy regimens (regardless of stage). In the metastatic stage, the proportion of patients treated with 3 to 4 prior chemotherapy regimens is around 53%.

At the 1 July 2022 data cutoff, 95% of patients in the intervention arm and 90% in the control arm had already discontinued treatment with the study medication. The most common reason for this was disease progression. At this data cutoff, 74% of patients in the intervention arm and 78% of those in the control arm discontinued the study prematurely, with the TROPiCS-02 study also counting deaths, which accounted for the majority of discontinuations, as study discontinuation. At the 1 December 2022 data cutoff, the respective proportion of patients who discontinued the study was 82% and 87%.

Information on the course of the study

Table 10 shows patients' median and mean treatment durations and the median and mean observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study **Duration of the study phase** **Outcome category**	**Sacituzumab govitecan** **N = 205**	**Treatment of physician's choice[a]** **N = 213**
TROPiCS-02		
Data cutoff: 1 December 2022		
Treatment duration [months]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	13.9 [8.9; 20.9]	10.8 [5.7; 20.7]
Mean (SD)	15.2 (8.8)	13.4 (9.0)
Data cutoff: 01/07/2022		
Treatment duration[c] [months]		
Median [min; max]	4.0 [0.0; 30.4]	2.6 [0.0; 22.2] Capecitabine: 4.5 [0.2; 12.9] Eribulin: 3.4 [0.0; 22.2] Vinorelbine: 1.2 [0.0; 8.1]
Mean (SD)	5.6 (5.6)	3.8 (3.7) Capecitabine: 4.8 (4.1) Eribulin: 4.3 (4.0) Vinorelbine: 1.9 (1.8)
Observation duration [months]		
Overall survival		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Symptoms (EORTC QLQ-C30)		
Median [Q1; Q3]	5.4 [2.6; 8.3]	3.7 [1.8; 6.5]
Mean (SD)	6.8 (5.7)	4.7 (3.8)
Health status (EQ-5D VAS)		
Median [Q1; Q3]	5.0 [2.6; 8.2]	3.9 [1.8; 6.7]
Mean (SD)	6.6 (5.6)	4.8 (3.8)
Health-related quality of life (EORTC QLQ-C30)		
Median [Q1; Q3]	5.4 [2.6; 8.3]	3.7 [1.8; 6.5]
Mean (SD)	6.8 (5.7)	4.7 (3.8)
AEs / SAEs / severe AEs[d]		
Median [Q1; Q3]	5.0 [2.2; 8.2]	3.5 [1.9; 6.2]
Mean (SD)	6.5 (5.5)	4.6 (3.7)

Table 10: Information on the course of the study – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study Duration of the study phase Outcome category	Sacituzumab govitecan N = 205	Treatment of physician's choice[a] N = 213
PRO-CTCAE		
Median [Q1; Q3]	5.0 [2.1; 8.1]	3.1 [1.4; 5.9]
Mean (SD)	6.4 (5.6)	4.2 (3.8)

a. Capecitabine or eribulin or vinorelbine.
b. The observation period is defined as the time from randomization to death or to the last contact.
c. Data refer to the safety population, which includes all patients who received (at least) 1 dose of the study medication (201 versus 194 patients).
d. 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; VAS: visual analogue scale

For the 1 December 2022 data cutoff, the company did not provide any information on the duration of treatment for the relevant subpopulation of the TROPiCS-02 study. At the 1 July 2022 data cutoff date, the median treatment duration in the intervention arm was 4.0 months, around 1.5 times longer than in the control arm at 2.6 months.

The median observation period for overall survival at the 1 December 2022 data cutoff was 13.9 months in the intervention arm and 10.8 months in the control arm. Information on the observation period for the 1 July 2022 data cutoff is missing in the dossier for this outcome. For all outcomes of the categories of morbidity, health-related quality of life, and side effects, whose observation duration is linked to the end of treatment in each case (see Table 8), the difference in the treatment duration between the intervention and control arms as described above also results in different observation durations for the 1 July 2022 data cutoff.

Information on subsequent therapies

In the dossier, the company does not provide any information on the subsequent therapies used for the relevant subpopulation. The information on the use of subsequent therapies in patients in the overall population of the TROPiCS-02 study (including, e.g. eribulin, gemcitabine, and carboplatin) appears, however, to be generally plausible for this therapeutic indication (see I Appendix B of the full dossier assessment).

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (on the study level) – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
TROPiCS-02	Yes	Yes	No	No	Yes	Yes	Low

a. Capecitabine or eribulin or vinorelbine.

RCT: randomized controlled trial

The risk of bias across outcomes is rated as low for the TROPiCS-02 study.

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

Transferability of the study results to the German health care context

The company argues that the demographic characteristics of the TROPiCS-02 subpopulation relevant for the assessment reflect those of the target population in the German healthcare context. It reasons that the TROPiCS-02 participants' median age of 56 years in the intervention arm and 55 years in the control arm is comparable to the median age of 59.1 years for participants with hormone receptor-positive, HER2-negative breast cancer in a cohort study of the Munich Tumour Registry [23]. It adds that the small number of 5 male participants of the TROPiCS-02 study in the therapeutic indication accurately reflects routine care, as men are rarely affected by breast cancer (approximately 1% of all new cases). In addition, the company explains that the majority of study participants is from Europe, participants are primarily of Caucasian ancestry, and the treatment in the control arm of the subpopulation relevant for the assessment was carried out according to routine practice in the German healthcare system.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded using the EORTC QLQ-C30
  - health status, surveyed using the EQ-5D VAS
- Health-related quality of life
  - surveyed with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - 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 taken by the company, which used other outcomes in the dossier (Module 4 A).

Table 12 shows the outcomes for which data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: sacituzumab govitecan versus 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]	Other specific AEs[b,f]
TROPiCS-02	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[g]	Yes	Yes	Yes	Yes

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 combination predefined by the company of the PTs of neutropenia, neutrophil count decreased, and febrile neutropenia (each severe AEs).
f. The following events are considered (coded according to MedDRA): diseases of the skin and subcutaneous tissue (SOC, AEs), diseases of the nervous system (SOC, severe AEs), and diseases of the respiratory tract, chest and mediastinum (SOC, severe AEs).
g. No suitable data available; for reasoning, see Section I 4.1 of this dossier assessment.

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

Analyses of outcomes in the categories of morbidity, health-related quality of life, and side effects

Response criterion for the scales of the EORTC QLQ-C30

In its dossier, the company presented responder analyses for patient-reported outcomes on morbidity and health-related quality of life, assessed using the EORTC QLQ-C30, for the time until the first deterioration by ≥ 10 points (scale range 0 to 100 in each case). These are used for the benefit assessment.

Side effects

AEs, SAEs, and severe AEs

For the overall rates of AEs, SAEs, and severe AEs, the company presents in Module 4 A not only analyses including all AEs but also analyses excluding disease-related events. As disease-related events, it has defined the following PTs from the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps): malignant pleural effusion, cancer pain, skin metastases, tumour pain. In this context, the company named any PTs which occurred in the total population of the TROPiCS-02 study in the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps). In addition, as per study protocol, events which were clearly attributable to the progression of the underlying disease were not to be recorded as AEs. Overall, the total rates excluding disease-related events in the relevant subpopulation do not differ from those including disease-related events.

PRO-CTCAE

In the TROPiCS-02 study, adverse events were also recorded in accordance with the study protocol using the PRO-CTCAE instrument [24-26], which represents a valuable addition to the usual recording and analysis of AEs. The PRO-CTCAE system comprises 78 symptomatic AEs of the CTCAE system, from which the AEs relevant to the study situation are to be selected. The selection of the individual patient-reported symptomatic AEs was to be prespecified and plausible in the study protocol, e.g. to ensure the recording of all important potential AEs of the drugs used in the intervention and control arms. For a detailed description of the PRO-CTCAE instrument, see the corresponding explanations in dossier assessment A20-87 [27].

In the TROPiCS-02 study, the following 9 symptomatic AEs from the PRO-CTCAE were recorded:

- decreased appetite
- nausea
- vomiting
- constipation
- diarrhoea
- abdominal pain
- shortness of breath
- hair loss
- fatigue

The documents submitted by the company do not provide detailed reasoning supporting the selection of the 9 symptomatic AEs used from the PRO-CTCAE system. In the study protocol, the company merely states that AEs which were selected reflect the respective safety profile of the drugs used in the TROPiCS-02 study. Based on this information, it cannot be determined whether the company implemented the approaches described in dossier assessment A20-87 for a selection according to Tolstrup [28] or Taarnhøj [29].

Irrespective of this, the descriptive analyses presented for the individual AEs are unsuitable for assessing the added benefit of sacituzumab govitecan in comparison with the ACT. For the assessment of the outcome, analyses are required which adequately take into account the different observation durations.

I 4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sacituzumab govitecan versus 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]	Other specific AEs[b,f]
TROPiCS-02	L	L	H[g, h, i]	H[g, h, i]	H[g, h, i]	H[i]	H[i]	H[j]	–[k]	H[h, i]	H[i]	H[i]	H[i, l]

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 combination predefined by the company of the PTs of neutropenia, neutrophil count decreased, and febrile neutropenia (each severe AEs).
f. The following events are considered (coded according to MedDRA): diseases of the skin and subcutaneous tissue (SOC, AEs), diseases of the nervous system (SOC, severe AEs), and diseases of the respiratory tract, chest and mediastinum (SOC, severe AEs).
g. High proportion of patients excluded from the analysis (> 10%).
h. Lack of blinding in the presence of subjective recording of outcomes.
i. Incomplete observations for potentially informative reasons with different lengths of follow-up observation.
j. Lack of blinding in the presence of subjective decision on treatment discontinuation.
k. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
l. Lack of blinding in the presence of subjective recording of outcomes (in the case of non-serious / non-severe AEs)

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

The risk of bias of the results for the outcome of overall survival is rated as low. For the results of the outcomes of symptoms, health status, and health-related quality of life, the risk of bias is classified as high due to (a) the high proportion of patients excluded from the analysis (each about 19%), (b) incomplete observation for potentially informative reasons, and (c) lack of blinding in the presence of subjective recording of outcomes. For the outcomes of SAEs and severe AEs, 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 non-serious/non-severe AEs, the risk of bias of results is additionally increased due to lack of blinding in the presence of subjective recording of outcomes. The risk of bias for the

outcome of discontinuation due to AEs was rated as high because of lack of blinding in the presence of subjective decision on treatment discontinuation.

No suitable data are available for the outcome of PRO-CTCAE (see Section I 4.1), rendering an assessment of the risk of bias unnecessary.

I 4.3 Results

Table 14 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.

The Kaplan-Meier curves for the time-to-event analyses of the included outcomes are shown in I Appendix B of the full dossier assessment, and the tables for common AEs, in I Appendix D of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	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[b]
TROPiCS-02					
Mortality					
Overall survival					
Data cutoff: 01/12/2022	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
Data cutoff: 01/07/2022	205	14.1 [12.8; 15.5] 145 (70.7)	213	11.3 [10.1; 12.9] 153 (71.8)	0.86 [0.69; 1.09]; 0.206
Morbidity (data cutoff: 01/07/2022)					
Symptoms (EORTC QLQ-C30 – time to first deterioration)[c]					
Fatigue	174	2.1 [1.6; 2.8] 121 (70.3)	165	1.3 [1.0; 1.8] 124 (76.5)	0.67 [0.52; 0.87]; 0.002
Nausea and vomiting	174	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
Pain	174	3.8 [2.8; 6.1] 95 (56.2)	165	3.2 [2.2; 4.3] 90 (56.6)	0.83 [0.62; 1.12]; 0.212
Dyspnoea	174	6.7 [4.6; 9.5] 78 (45.9)	165	3.9 [2.4; 7.5] 84 (52.2)	0.66 [0.48; 0.90]; 0.009
Insomnia	174	8.7 [6.0; 18.9] 68 (42.5)	165	3.6 [2.3; NC] 69 (46.0)	0.67 [0.48; 0.95]; 0.021
Appetite loss	174	3.3 [1.7; 5.9] 97 (58.1)	165	3.7 [2.3; 5.4] 78 (50.0)	1.08 [0.79; 1.46]; 0.633
Constipation	174	5.4 [3.2; 9.1] 83 (48.8)	165	4.8 [3.2; 8.2] 70 (44.3)	1.01 [0.73; 1.40]; 0.942
Diarrhoea	174	2.0 [1.6; 3.4] 104 (60.5)	165	8.2 [5.8; NC] 55 (33.5)	2.41 [1.72; 3.37]; < 0.001
Health status (EQ-5D VAS – time to first deterioration)[d]	175	11.8 [6.9; NC] 63 (37.5)	164	7.0 [4.6; 12.7] 64 (39.5)	0.72 [0.51; 1.03]; 0.073

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	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[b]
Health-related quality of life (data cut-off: 01/07/2022)					
EORTC QLQ-C30 – time to first deterioration[e]					
Global health status	174	4.9 [3.0; 6.7] 95 (54.9)	165	2.6 [2.0; 3.5] 103 (62.8)	0.66 [0.50; 0.88]; 0.004
Physical functioning	174	5.6 [3.1; 8.3] 88 (50.6)	165	3.4 [2.2; 4.6] 87 (53.0)	0.72 [0.53; 0.97]; 0.029
Role functioning	174	2.8 [1.7; 4.3] 111 (64.9)	165	2.2 [1.5; 2.9] 102 (64.2)	0.77 [0.58; 1.01]; 0.055
Emotional functioning	174	NR [6.5; NC] 61 (36.1)	165	4.5 [3.4; 9.5] 75 (45.7)	0.65 [0.46; 0.91]; 0.012
Cognitive functioning	174	5.2 [3.0; 11.1] 86 (49.4)	165	5.4 [3.3; NC] 67 (40.9)	1.02 [0.74; 1.41]; 0.906
Social functioning	174	2.4 [1.7; 4.3] 101 (59.4)	165	3.5 [2.6; 4.3] 88 (56.1)	0.99 [0.74; 1.33]; 0.958
Side effects (data cutoff: 01/07/2022)					
AEs (supplementary information)	201	0.1 [0.1; 0.1] 201 (100.0)	194	0.2 [0.1; 0.2] 185 (95.4)	–
SAEs	201	NR [17.9; NC] 55 (27.4)	194	NR 34 (17.5)	1.42 [0.93; 2.19]; 0.107
Severe AEs[f]	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
Discontinuation due to AEs	201	NR 14 (7.0)	194	NR 6 (3.1)	1.70 [0.64; 4.53]; 0.282
PRO-CTCAE				No suitable data[g]	
Hand-foot syndrome[h]	201	NR 4 (2.0)	194	NR 14 (7.2)	0.19 [0.05; 0.65]; 0.003
Gastrointestinal toxicity[i]	201	NR 31 (15.4)	194	NR 11 (5.7)	2.63 [1.32; 5.24]; 0.004
Neutropenia[j]	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
Skin and subcutaneous tissue disorders (SOC, AEs)	201	1.0 [0.7; 2.3] 120 (59.7)	194	5.7 [3.5; NC] 79 (40.7)	1.81 [1.36; 2.41]; < 0.001

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan versus treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	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[b]
Diseases of the nervous system (SOC, severe AEs[f])	201	29.7 [NC; NC] 7 (3.5)	194	NR 14 (7.2)	0.32 [0.12; 0.84]; 0.015
Diseases of the respiratory tract, chest and mediastinum (SOC, severe AEs[f])	201	NR 11 (5.5)	194	NR 17 (8.8)	0.46 [0.21; 1.02]; 0.049

a. Capecitabine or eribulin or vinorelbine.
b. 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. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
d. A score decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
f. Operationalized as CTCAE grade ≥ 3.
g. The results of the outcome PRO-CTCAE were presented only descriptively in the dossier (see Section I 4.1 of this dossier assessment).
h. Operationalized as palmar-plantar erythrodysaesthesia syndrome (PT, AEs).
i. Operationalized as gastrointestinal disorders (SOC, severe AEs).
j. Operationalized as a combination predefined by the company of the PTs of neutropenia, neutrophil count decreased, and febrile neutropenia (each severe AEs).

AE: adverse event; 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 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; 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; SAE: serious adverse event; SOC: System Organ Class; RCT: randomized controlled trial; VAS: visual analogue scale

On the basis of the available information, at most an indication can be derived for the outcome of overall survival and, due to the high risk of bias, at most hints, e.g. of added benefit, can be derived for all outcomes in the categories of morbidity, health-related quality of life, and side effects.

Mortality

Overall survival

At both data cutoffs, the analyses showed no statistically significant difference between the treatment groups for the outcome of overall survival. This results in 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.

Morbidity

Symptoms (EORTC QLQ-C30)

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

Fatigue

A statistically significant difference in favour of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of fatigue. This results in a hint of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice.

Diarrhoea

A statistically significant difference to the disadvantage of sacituzumab govitecan in comparison with treatment of physician's choice was shown for the outcome of diarrhoea. This results in a hint of lesser benefit of sacituzumab govitecan in comparison with treatment of physician's choice.

Dyspnoea and insomnia

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 dyspnoea and insomnia. 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. This results in 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.

Nausea and vomiting, pain, loss of appetite, and constipation

No statistically significant differences between the treatment groups were shown for any of the outcomes of nausea and vomiting, pain, loss of appetite, or constipation. This results in 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)

No statistically significant difference between treatment groups was shown for the outcome of health status recorded with the EQ-5D VAS. This results in 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, and emotional functioning

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, and emotional functioning. This results in a hint of added benefit of sacituzumab govitecan in comparison with treatment of physician's choice for each of them.

Role functioning, cognitive functioning, and social functioning

No statistically significant difference between the treatment groups was shown for the outcomes of role functioning, cognitive functioning, or social functioning. This results in 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.

Side effects

Severe AEs

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. This results in a hint of greater harm from sacituzumab govitecan in comparison with treatment of physician's choice.

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. This results in no hint of added benefit of 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. This results in 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), diseases of the nervous system (severe AEs), and diseases of the respiratory tract, chest and mediastinum (severe AEs)

For the outcomes of hand-foot syndrome (AEs), diseases of the nervous system (severe AEs), and diseases of the respiratory tract, chest and mediastinum (severe AEs), there was a statistically significant difference in favour of sacituzumab govitecan compared to treatment of physician's choice. This results in a hint of lesser harm from sacituzumab govitecan in comparison with treatment of physician’s choice for each of them.

Gastrointestinal toxicity (serious AEs), neutropenia (serious AEs), and skin and subcutaneous tissue disorders (AEs)

For each of the outcomes of gastrointestinal toxicity (serious AEs), neutropoenia (severe AEs), and diseases of the skin and subcutaneous tissue (AEs), there was a statistically significant difference to the disadvantage of sacituzumab govitecan compared to treatment of physician’s choice. This results in a hint of greater harm from sacituzumab govitecan in comparison with treatment of physician’s choice for each of them.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

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

Sex is disregarded because the relevant subpopulation comprises only 5 men.

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

Presented are only results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

Using the methods described above, the subgroup results presented with the dossier do not show any effect modifications.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 15).

Determination of the outcome category for symptom outcomes

For the following outcomes on symptoms, it is not clear from the company's dossier whether these are serious/severe or non-serious/non-severe. Therefore, the categorization for these outcomes is justified accordingly.

Symptoms

Fatigue, dyspnoea, insomnia, and diarrhoea (EORTC QLQ-C30)

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

Table 15: Extent of added benefit at outcome level: sacituzumab govitecan versus 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		
Data cutoff: 01/12/2022	14.4 vs. 11.2 HR: 0.85 [0.69; 1.05] p = 0.136	Lesser/Added benefit not proven
Data cutoff: 01/07/2022	14.1 vs. 11.3 HR: 0.86 [0.69; 1.09] p = 0.206	Lesser/Added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	2.1 vs. 1.3 HR: 0.67 [0.52; 0.87] p = 0.002 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.90$ Added benefit; extent: minor
Nausea and vomiting	2.4 vs. 4.6 HR: 1.26 [0.93; 1.69] p = 0.127	Lesser/Added benefit not proven
Pain	3.8 vs. 3.2 HR: 0.83 [0.62; 1.12] p = 0.212	Lesser/Added benefit not proven
Dyspnoea	6.7 vs. 3.9 HR: 0.66 [0.48; 0.903] p = 0.009	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/Added benefit not proven[d]
Insomnia	8.7 vs. 3.6 HR: 0.67 [0.48; 0.95] p = 0.021	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u \leq 1.00$ Lesser/Added benefit not proven[d]
Appetite loss	3.3 vs. 3.7 HR: 1.08 [0.79; 1.46] p = 0.633	Lesser/Added benefit not proven

Table 15: Extent of added benefit at outcome level: sacituzumab govitecan versus 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 vs. 4.8 HR: 1.01 [0.73; 1.40] p = 0.942	Lesser/Added benefit not proven
Diarrhoea	2.0 vs. 8.2 HR: 2.41 [1.72; 3.37] HR: 0.41 [0.30; 0.58][e] p < 0.001 Probability: hint	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 vs. 7.0 HR: 0.72 [0.51; 1.03] p = 0.073	Lesser/Added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration		
Global health status	4.9 vs. 2.6 HR: 0.66 [0.50; 0.88] p = 0.004 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.90$ Added benefit; extent: considerable
Physical functioning	5.6 vs. 3.4 HR: 0.72 [0.53; 0.97] p = 0.029 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Role functioning	2.8 vs. 2.2 HR: 0.77 [0.58; 1.01] p = 0.055	Lesser/Added benefit not proven
Emotional functioning	NR vs. 4.5 HR: 0.65 [0.46; 0.91] p = 0.012 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Cognitive functioning	5.2 vs. 5.4 HR: 1.02 [0.74; 1.41] p = 0.906	Lesser/Added benefit not proven
Social functioning	2.4 vs. 3.5 HR: 0.99 [0.74; 1.33] p = 0.958	Lesser/Added benefit not proven

Table 15: Extent of added benefit at outcome level: sacituzumab govitecan versus 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]**
Side effects		
SAEs	NR vs. NR HR: 1.42 [0.93; 2.19] p = 0.107	Greater/Lesser harm not proven
Severe AEs	0.8 vs. 2.4 HR: 1.49 [1.17; 1.91] HR: 0.67 [0.52; 0.85][e] p = 0.002 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Discontinuation due to AEs	NR vs. NR HR: 1.70 [0.64; 4.53] p = 0.282	Greater/lesser harm not proven
PRO-CTCAE	No suitable data[f]	Greater/Lesser harm not proven
Hand-foot syndrome (AEs)	NR vs. NR HR: 0.19 [0.05; 0.65] p = 0.003 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Gastrointestinal toxicity (severe AEs)	NR vs. NR HR: 2.63 [1.32; 5.24] HR: 0.38 [0.19; 0.76][e] p = 0.004 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Neutropenia (severe AEs)	1.6 vs. 9.6 HR: 1.55 [1.15; 2.08] HR: 0.65 [0.48; 0.87][e] p = 0.003 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Skin and subcutaneous tissue disorders (AEs)	1.0 vs. 5.7 HR: 1.81 [1.36; 2.41] HR: 0.55 [0.41; 0.74][e] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Nervous system disorders (severe AEs)	29.7 vs. NR HR: 0.32 [0.12; 0.84] p = 0.015 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable

Table 15: Extent of added benefit at outcome level: sacituzumab govitecan versus 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]**
Respiratory, thoracic and mediastinal disorders (severe AEs)	NR vs. NR HR: 0.46 [0.21; 1.02] p = 0.049 Probability: hint	Outcome category: serious/severe side effects Lesser harm; extent: minor[g]

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. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. For justification see Section I 4.1 of this dossier assessment.
g. Discrepancy between CI and p-value; the extent is rated as minor.

AE: adverse event; CI: confidence interval; CIu: 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; NR: not reached; 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

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 16: Favourable and unfavourable effects from the assessment of sacituzumab govitecan in comparison to treatment of physician's choice[a]

Favourable effects	Unfavourable effects
Outcomes observed over the entire study duration	
–	–
Outcomes with shortened observation period	
Non-serious/non-severe symptoms / late complications Symptoms (EORTC QLQ-C30): ▪ Fatigue: hint of an added benefit – extent: minor	Non-serious/non-severe symptoms / late complications Symptoms (EORTC QLQ-C30): ▪ Diarrhoea: hint of lesser benefit – extent: considerable
Health-related quality of life EORTC QLQ-C30: ▪ Global health status: hint of added benefit – extent: considerable ▪ Physical functioning: hint of added benefit – extent: minor ▪ Emotional functioning: hint of added benefit – extent: minor	–
Serious/severe side effects ▪ Diseases of the nervous system (severe AEs): hint of lesser harm – extent: considerable ▪ Diseases of the respiratory tract, chest and mediastinum (severe AEs): hint of lesser harm – extent: minor	Serious/severe side effects ▪ Severe AEs: hint of greater harm – extent: considerable, including ▫ gastrointestinal toxicity (severe AEs): hint of greater harm – extent: considerable ▫ neutropenia (severe AEs): hint of greater harm – extent: considerable
Non-serious/non-severe side effects ▪ Hand-foot syndrome (AEs): hint of lesser harm – extent: considerable	Non-serious/non-severe side effects ▪ Diseases of the skin and subcutaneous tissue (AEs): hint of greater harm – extent: considerable
No suitable data are available for the outcome of PRO-CTCAE.	
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 were both favourable and unfavourable effects for sacituzumab govitecan compared to treatment of physician's choice, but only for the shortened observation period. The outcome categories of non-serious/non-severe symptoms / late complications and (non-) serious/(non-)severe side effects each result in favourable and unfavourable effects of varying severity with the probability of a hint. In the outcome category of health-related quality of life, only favourable effects of minor or considerable extent were found. In the outcome category of health-related quality of life, the unfavourable effects do not completely jeopardize the favourable effects.

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 a hint of minor added benefit of sacituzumab govitecan compared with treatment of physician's choice.

Table 17 summarizes the result of the assessment of added benefit of sacituzumab govitecan in comparison with the ACT.

Table 17: Sacituzumab govitecan – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
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 in the advanced setting[c]	▪ **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)[d]	Hint of minor added benefit[e]

a. Presented is the 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. 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.
c. 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.

d. According to guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth.
e. The TROPiCS-02 study included only patients with an ECOG-PS of 0 or 1. In addition, the subpopulation relevant for the dossier assessment comprises only 5 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 associated gene; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor-2

The assessment described above deviates from that by the company, which derived a hint of considerable added benefit.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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