Datopotamab deruxtecan (breast cancer)

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

EXTRACT

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Medical and scientific advice

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the patient organization 'Frauenselbsthilfe Krebs Bundesverband e. V.' for participating in the written exchange and for their support. The respondent and the 'Frauenselbsthilfe Krebs Bundesverband e. V.' were not involved in the actual preparation of the 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
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie (Gynaecological Oncology Group)
BICR	blinded independent central review
CDK	cyclin-dependent kinase
CSR	clinical study report
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
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IL	Item Library
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
PFS	progression-free survival
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PRO	patient-reported outcome
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

Abbreviation	Meaning
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 datopotamab deruxtecan. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 28 May 2025.

Research question

The aim of this report is the assessment of the added benefit of datopotamab deruxtecan in comparison with the appropriate comparator therapy (ACT) in patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of datopotamab deruxtecan

Research question	Therapeutic indication	ACT[a]
Adults with unresectable or metastatic HR-positive, HER2-negative[b] breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting[c, d]		
1	HER2-0 breast cancer, one line of chemotherapy in the advanced setting	▪ capecitabine or ▪ eribulin or ▪ vinorelbine or ▪ an anthracycline- or taxane-containing therapy (only for patients who have not yet received anthracycline- and/or taxane-containing therapy or for whom renewed anthracycline- or taxane-containing therapy is an option)
2	HER2-low breast cancer, one line of chemotherapy in the advanced setting	▪ trastuzumab deruxtecan
3	HER2-0 or HER2-low breast cancer, at least 2 lines of chemotherapy in the advanced setting	▪ sacituzumab govitecan or ▪ trastuzumab deruxtecan (only for patients with HER2-low tumour status)

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, all patients in the therapeutic indication are classified as HER2-negative. This includes patients with HER2-0 breast cancer (IHC 0) and with HER2-low breast cancer (IHC 1+ or IHC 2+ / ISH-). These designations are used in this benefit assessment to distinguish between the different research questions.
c. According to the G-BA it is assumed that, as part of prior therapy, patients typically received taxane- and/or anthracycline-containing chemotherapy.
d. 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.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; ISH: in situ hybridization

The company followed the G-BA's ACT.

In the designation of the subpopulations for research questions 1 to 3, the company referred to the consultation with the G-BA on 28 March 2024 in Module 4 A. The company's description in Module 4 A deviated from the research questions listed in Table 2 and contained the specification that patients in the respective subpopulation had progressive disease under endocrine therapy and that endocrine therapy was no longer appropriate. According to the current guideline recommendations of the German Gynaecological Oncology Group (AGO) and the European Society for Medical Oncology (ESMO), endocrine therapy is not a

recommended treatment for patients in this therapeutic indication. Hence this deviation had no consequences for the benefit assessment.

The assessment was 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 to derive the added benefit. This concurred with the company's inclusion criteria.

Research question 1: HER2-0 breast cancer, one line of chemotherapy in the advanced setting

Study pool and study design

The TROPION-Breast01 study was included in the benefit assessment.

The TROPION-Breast01 study is an ongoing, open-label RCT comparing datopotamab deruxtecan versus treatment of physician's choice selecting from capecitabine, eribulin, gemcitabine and vinorelbine. The study included adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer whose disease had progressed on endocrine therapy and for whom endocrine therapy was not an option. In addition, patients had to be pretreated with 1 or 2 lines of systemic chemotherapy in the advanced setting and had to be in good general health, concurring with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

A total of 732 patients were included and randomly assigned in a 1:1 ratio to either treatment with datopotamab deruxtecan (N = 365) or treatment of physician's choice, selecting from capecitabine, eribulin, gemcitabine and vinorelbine (N = 367). The decision as to which of the 4 available treatment options the patient should receive in the event of allocation to the control arm had to be made prior to randomization. The drug gemcitabine was not part of the ACT. The subpopulation treated with gemcitabine was not considered in the benefit assessment.

Treatment with datopotamab deruxtecan and eribulin in the TROPION-Breast01 study was in compliance with the recommendations in the respective summaries of product characteristics (SmPCs). Treatment with capecitabine and vinorelbine deviated in some respects from the information provided in the SmPCs. However, these deviations were not assumed to have a relevant influence on the result of the benefit assessment.

Treatment was to continue until disease progression, unacceptable toxicity, or treatment discontinuation at the patient's or investigator's decision. Further treatment with the study treatment could be continued beyond progression of the disease at the discretion of the investigator. Switching between the study arms was not allowed.

The primary outcomes of the TROPION-Breast01 study were progression-free survival (PFS) as assessed in a blinded independent central review (BICR), and overall survival. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

The results of the current 3rd data cut from 24 July 2024 were used for this benefit assessment.

Relevant subpopulation of TROPION-Breast01

In the TROPION-Breast01 study, the drugs capecitabine, eribulin, vinorelbine and gemcitabine were available as part of the treatment of physician's choice. Gemcitabine was not part of the ACT specified by the G-BA. In its dossier, the company therefore presented analyses of a TROPION-Breast01 subpopulation that in both the intervention and control arms only included patients for whom capecitabine, eribulin or vinorelbine had been selected as a treatment option for possible treatment in the control arm prior to randomization. Furthermore, the subpopulation presented by the company according to research question 1 exclusively comprised patients with HER2-0 breast cancer who had received one line of chemotherapy in the advanced setting.

This benefit assessment used the subpopulation formed by the company as the relevant population. It consisted of a total of 118 patients, of whom 63 were included in the intervention arm and 55 in the control arm. This corresponded to a proportion of 17.3% and 15.0% of patients in the total population, respectively.

Prior therapy with anthracyclines and/or taxanes

According to the applicable SmPCs, the treatment options relevant to the dossier assessment (capecitabine, eribulin, vinorelbine) in the control arm of the TROPION-Breast01 study should only be used if prior therapy with anthracyclines and taxanes had already been given or these treatments were unsuitable for the patients.

The subgroup analyses presented in Module 4 showed that in the control arm, only 55% of patients in the relevant subpopulation had already been treated with both an anthracycline and a taxane. The remaining patients either had been previously treated with anthracycline or taxane alone (in particular, 40% in the control arm had not received any anthracyclines to date) or had not received any prior treatment with drugs from these groups (16% in the control arm). However, it was unclear whether these data referred to prior therapies throughout the entire course of treatment, including possible neoadjuvant or adjuvant therapy, or exclusively to the unresectable or metastatic setting. For an assessment of whether patients had received appropriate prior therapy and on-label treatment in the control arm of the TROPION-Breast01 study, information on the entire course of treatment would be necessary. Furthermore ,the proportion of patients for whom anthracyclines or taxanes were

not suitable, for example because of a contraindication, was unknown. However, it could not be ruled out overall that treatment with an anthracycline and/or a taxane would have been indicated for a relevant proportion of patients in the TROPION-Breast01 study. Treatment with capecitabine, eribulin or vinorelbine would therefore not have been appropriate in these cases. As a result of this uncertainty, the certainty of conclusions for the TROPION-Breast01 study was limited.

Information on the course of the study

No information on treatment and observation period was available for the relevant subpopulation in the TROPION-Breast01 study. However, information on the duration of treatment and observation is necessary for interpreting study results in a benefit assessment. This is also reflected by the dossier templates. The lack of information on the duration of treatment and observation was taken into account when selecting the appropriate effect measure to determine the extent of the added benefit for the outcomes in the side effects category.

Subsequent therapies

The company's dossier did not contain any information on the subsequent therapies received by patients in the relevant subpopulation. It was therefore impossible to assess whether the subsequent therapy was appropriate in both study arms. The lack of information on subsequent therapies was taken into account when assessing the outcome-specific risk of bias for the outcome overall survival.

Notes on the outcomes in the side effects category

Due to a lack of information on observation and treatment durations for the relevant subpopulation, it was not possible to assess which effect measure (hazard ratio or relative risk) was appropriate in the given situation. The comparison of the hazard ratio analyses and the Institute's calculation of the relative risk showed differences in the extent of the added benefit for some AE outcomes. Therefore, both effect measures were taken into account in the determination of the added benefit for AE outcomes for which the relative risk showed an extent of the added benefit that differed from the hazard ratio, but it was not possible to quantify the extent of the added benefit in these cases.

Risk of bias

For the TROPION-Breast01 study, the risk of bias across outcomes was rated as low.

For the results on the outcome of overall survival, the risk of bias was assessed as high due to the lack of information on the subsequent therapies used.

The risk of bias for the outcomes in the side effects category was also assessed as high. For the higher-level operationalizations of serious and severe AEs, as well as for the Preferred

Term (PT) neutropenia, this was due to a shortened observation for potentially informative reasons, as almost all patients discontinued treatment prematurely and observation was discontinued 28 days later. In the outcome of interstitial lung disease (ILD) and pneumonitis, the lack of blinding in subjective recording of outcomes led to a high risk of bias. Both reasons applied to the remaining non-serious/non-severe AEs.

The risk of bias for the outcome of discontinuation due to AEs is rated as high because of lack of blinding with subjective decision on treatment discontinuation. The certainty of results was additionally limited by the fact that treatment might also be discontinued for reasons other than AEs. These reasons represented a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion of 'discontinuation' is no longer applicable to them. It was impossible to estimate how many AEs this affected.

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Results

Mortality

Overall survival

No statistically significant difference between the study arms was shown for the outcome of overall survival. There is no hint of an added benefit of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30 and PGIS) and health status (EQ-5D VAS)

No suitable data were available for the outcomes symptoms, recorded using the EORTC QLQ-C30 and PGIS, and health status, recorded using the EQ-5D VAS. There is therefore no hint of an added benefit of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data were available for the outcome of health-related quality of life, recorded using EORTC QLQ-C30, either. There is therefore no hint of an added benefit of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, there is no statistically significant difference between the study arms. There is no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference in favour of datopotamab deruxtecan in comparison with chemotherapy of physician's choice was shown for the outcome of severe AEs. There is a hint of lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice. There were differences in the extent of added benefit depending on whether the hazard ratio or the relative risk was considered. This was taken into account when determining the extent (see Section *Probability and extent of added benefit, patient groups with therapeutically important added benefit*).

Discontinuation due to AEs

There was no statistically significant difference between the study arms for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

PRO-CTCAE

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

ILD and pneumonitis (AEs), hand-foot syndrome (AEs)

For the outcomes ILD and pneumonitis (AEs) as well as hand-foot syndrome (AEs), there was no statistically significant difference between the study arms. In each case, there is no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

Keratitis

No suitable data were available for the outcome keratitis. There is therefore no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

Other specific AEs

Nausea (AEs), stomatitis (AEs)

A statistically significant difference to the disadvantage of datopotamab deruxtecan in comparison with chemotherapy of physician's choice was shown for each of the outcomes nausea (AEs) and stomatitis (AEs). In each case, there is a hint of greater harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice.

Decreased appetite (AEs)

A statistically significant difference in favour of datopotamab deruxtecan in comparison with chemotherapy of physician's choice was shown for the outcome decreased appetite. There were differences in the extent of added benefit depending on whether the hazard ratio or the relative risk was considered. Since it was not possible to reliably assess which effect measure was appropriate without information on observation periods and treatment durations, the results of both effect measures were taken into account. The extent of the effect was no more than marginal when considering the relative risk, but considerable when considering the hazard ratio. In the given situation, it was therefore not possible to clearly determine whether there was lesser harm for the outcome decreased appetite. There is therefore no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

Neutropenia (severe AEs)

A statistically significant difference in favour of datopotamab deruxtecan in comparison with chemotherapy of physician's choice was shown for the outcome neutropenia (severe AEs). There is a hint of lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice. There were differences in the extent of added benefit depending on whether the hazard ratio or the relative risk was considered. This was taken into account when determining the extent (see Section *Probability and extent of added benefit, patient groups with therapeutically important added benefit*).

Research question 2: HER2-low breast cancer, one line of chemotherapy in the advanced setting

Results

Concurring with the company, the review of the information retrieval did not identify any relevant studies. There were therefore no suitable data.

Results on added benefit

No data were available for the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HR-positive, HER2-low breast cancer who have received endocrine therapy and one line of chemotherapy in the

advanced setting. There is no hint of an added benefit of datopotamab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

Research question 3: HER2-0 or HER2-low breast cancer, at least 2 lines of chemotherapy in the advanced setting

Results

Concurring with the company, the review of the information retrieval did not identify any relevant studies. There were therefore no suitable data.

Results on added benefit

No data were available for the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HR-positive, HER2-0 or HER2-low breast cancer who have received endocrine therapy and at least 2 lines of chemotherapy in the advanced setting. There is no hint of an added benefit of datopotamab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

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

Research question 1: HER2-0 breast cancer, one line of chemotherapy in the advanced setting

Based on the results presented, the probability and extent of the added benefit of the drug datopotamab deruxtecan in comparison with the ACT are assessed as follows:

For research question 1 of this benefit assessment, there are positive and negative effects of datopotamab deruxtecan in comparison with chemotherapy of physician's choice in the relevant subpopulation.

In terms of positive effects, there is a hint of lesser harm in the overall rate of severe AEs and the specific AE of severe neutropenia included therein in the category of serious/severe side effects. Due to the lack of information on observation periods and treatment durations in the relevant subpopulation and discrepant results when considering the hazard ratio and the relative risk, the extent is non-quantifiable, but at least considerable, for the overall rate of severe AEs. In terms of negative effects, there is a hint of greater harm of considerable extent

[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].

for each of the PTs nausea and stomatitis in the category of non-serious/non-severe side effects. The results refer to the shortened period up to 28 days after discontinuation of the study treatment for the AEs mentioned.

No conclusion could be drawn regarding the morbidity and health-related quality of life of patients from research question 1, as no suitable data were available for these outcome categories. In addition, there was some uncertainty regarding the result for the outcome of overall survival due to a lack of information on subsequent therapies. Another uncertainty was due to the prior therapy of patients with anthracyclines and/or taxanes.

Given the available data situation with the uncertainties described, for example in terms of overall survival, the shortened observation period for which the AE outcomes with statistically significant effects provided conclusions, and in particular the lack of suitable data on patient-reported outcomes, it was ultimately not possible to weigh up the various positive and negative effects of the adverse events with sufficient certainty. In the given data situation, the advantage in the overall rate of severe AEs was insufficient to derive an added benefit.

In summary, there is therefore no hint of an added benefit of datopotamab deruxtecan in comparison with the ACT for adults with unresectable or metastatic HR-positive, HER2-0 breast cancer who have received endocrine therapy and one line of chemotherapy in the advanced setting; an added benefit is therefore not proven.

The assessment described above differs from that of the company, which derived an indication of considerable added benefit.

Research question 2: HER2-low breast cancer, one line of chemotherapy in the advanced setting

Since the company did not present any data for the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HR-positive, HER2-low breast cancer who have received endocrine therapy and one line of chemotherapy in the advanced setting, an added benefit is not proven.

Research question 3: HER2-0 or HER2-low breast cancer, at least 2 lines of chemotherapy in the advanced setting

Since the company did not present any data for the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HR-positive, HER2-0 or HER2-low breast cancer who have received endocrine therapy and at least 2 lines of chemotherapy in the advanced setting, an added benefit is not proven.

Table 3 shows a summary of probability and extent of the added benefit of datopotamab deruxtecan.

Table 3: Datopotamab deruxtecan – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	
Adults with unresectable or metastatic HR-positive, HER2-negative[b] breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting[c, d]			
1	HER2-0 breast cancer, one line of chemotherapy in the advanced setting	▪ capecitabine or ▪ eribulin or ▪ vinorelbine or ▪ an anthracycline- or taxane-containing therapy (only for patients who have not yet received anthracycline- and/or taxane-containing therapy or for whom renewed anthracycline- or taxane-containing therapy is an option)	Added benefit not proven
2	HER2-low breast cancer, one line of chemotherapy in the advanced setting	▪ trastuzumab deruxtecan	Added benefit not proven
3	HER2-0 or HER2-low breast cancer, at least 2 lines of chemotherapy in the advanced setting	▪ sacituzumab govitecan or ▪ trastuzumab deruxtecan (only for patients with HER2-low tumour status)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, all patients in the therapeutic indication are classified as HER2-negative. This includes patients with HER2-0 breast cancer (IHC 0) and with HER2-low breast cancer (IHC 1+ or IHC 2+ / ISH-). These designations are used in this benefit assessment to distinguish between the different research questions.
c. According to the G-BA it is assumed that, as part of prior therapy, patients typically received taxane- and/or anthracycline-containing chemotherapy.
d. 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. Only one man was included in each of the intervention and control arms of the TROPION-Breast01 study. It therefore remains unclear whether the observed effects can be transferred to men.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; ISH: in situ hybridization

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 the assessment of the added benefit of datopotamab deruxtecan in comparison with the appropriate comparator therapy (ACT) in patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of datopotamab deruxtecan

Research question	Therapeutic indication	ACT[a]
Adults with unresectable or metastatic HR-positive, HER2-negative[b] breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting[c, d]		
1	HER2-0 breast cancer, one line of chemotherapy in the advanced setting	▪ capecitabine or ▪ eribulin or ▪ vinorelbine or ▪ an anthracycline- or taxane-containing therapy (only for patients who have not yet received anthracycline- and/or taxane-containing therapy or for whom renewed anthracycline- or taxane-containing therapy is an option)
2	HER2-low breast cancer, one line of chemotherapy in the advanced setting	▪ trastuzumab deruxtecan
3	HER2-0 or HER2-low breast cancer, at least 2 lines of chemotherapy in the advanced setting	▪ sacituzumab govitecan or ▪ trastuzumab deruxtecan (only for patients with HER2-low tumour status)

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, all patients in the therapeutic indication are classified as HER2-negative. This includes patients with HER2-0 breast cancer (IHC 0) and with HER2-low breast cancer (IHC 1+ or IHC 2+ / ISH-) [3,4]. These designations are used in this benefit assessment to distinguish between the different research questions.
c. According to the G-BA it is assumed that, as part of prior therapy, patients typically received taxane- and/or anthracycline-containing chemotherapy.
d. 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.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; ISH: in situ hybridization

The company followed the G-BA's ACT.

In the designation of the subpopulations for research questions 1 to 3, the company referred to the consultation with the G-BA on 28 March 2024 in Module 4 A [5]. The company's description in Module 4 A deviated from the research questions listed in Table 4 and contained the specification that patients in the respective subpopulation had progressive disease under endocrine therapy and that endocrine therapy was no longer appropriate. According to the current guideline recommendations of AGO and ESMO, endocrine therapy is not a recommended treatment for patients in this therapeutic indication [6,7]. Hence this deviation had no consequences for the benefit assessment.

The assessment was 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 to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Research question 1: HER2-0 breast cancer, one line of chemotherapy in the advanced setting

I 3.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on datopotamab deruxtecan (status: 18 April 2025)
- Bibliographical literature search on datopotamab deruxtecan (last search on 27 March 2025)
- Search of trial registries/trial results databases for studies on datopotamab deruxtecan (last search on 27 March 2025)
- Search on the G-BA website for datopotamab deruxtecan (last search on 27 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on datopotamab deruxtecan (last search on 10 June 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: datopotamab deruxtecan vs. ACT

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
D9268C00001 (TROPION-Breast01[c])	Yes	Yes	No	Yes [8]	Yes [9-11]	Yes [12]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

ACT: appropriate comparator therapy; CSR: clinical study report; RCT: randomized controlled trial

The study pool for the benefit assessment concurred with that of the company. To answer the research question, the company used analyses of a subpopulation of the study, which is described in more detail in Section I 3.1.2.

I 3.1.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy 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]
TROPION-Breast01	RCT, open-label, parallel	Adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer[c] ▪ whose disease has progressed on endocrine therapy and for whom endocrine therapy is not an option ▪ treated with 1 or 2 prior lines of systemic chemotherapy in the advanced setting and with progression on the most recent line of chemotherapy ▪ ECOG PS 0 or 1	datopotamab deruxtecan (N = 365) Chemotherapy of physician's choice[a] (N = 367) ▪ capecitabine (N = 76) ▪ eribulin (N = 220) ▪ gemcitabine (N = 33) ▪ vinorelbine (N = 38) Relevant subpopulation thereof[d]: datopotamab deruxtecan (n = 63) Chemotherapy of physician's choice[a] (n = 55) ▪ capecitabine (n = 9) ▪ eribulin (n = 41) ▪ vinorelbine (n = 5)	Screening: up to 28 days Treatment until disease progression[e, f], unacceptable toxicity, treatment discontinuation at the patient's or investigator's decision Observation[g]: outcome-specific, at most until death, withdrawal of consent, or study end	166 centres in Argentina, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Italy, Japan, Netherlands, Poland, Russia, South Africa, South Korea, Spain, Taiwan, United Kingdom, United States 10/2021–ongoing Data cut-offs: ▪ 17 July 2023[h] ▪ 29 April 2024[i] ▪ 24 July 2024[j]	Primary: ▪ PFS (BICR) ▪ Overall survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy 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. The decision as to which of the available treatment options the patient should receive in the event of allocation to the control arm had to be made prior to randomization. b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. c. Based on local laboratory results according to ASCO/CAP guidelines; HR-positive defined as either ER- and/or PgR-positive (ER or PgR ≥ 1%). d. The subpopulation consists of patients with HER2-0 breast cancer (IHC 0) for whom capecitabine, eribulin or vinorelbine was determined prior to randomization as the drug to be administered in case of allocation to the control arm. Patients who were assigned gemcitabine are not considered further below. e. As per RECIST 1.1 in the assessment of the investigator. f. Further treatment with the study medication may be continued beyond progression of the disease at the discretion of the investigator. Switching between the study arms is not allowed. g. Outcome-specific information is provided in Table 8. h. Prespecified final analysis for the PFS outcome and first interim analysis for the overall survival outcome after approximately 419 PFS events according to BICR. i. Prespecified 2nd interim analysis for the overall survival outcome after approximately 355 deaths. j. Prespecified final analysis for the overall survival outcome after approximately 444 deaths. AE: adverse event; ASCO: American Society of Clinical Oncology; BICR: blinded independent central review; CAP: College of American Pathologists; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; PgR: progesterone receptor; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours					

Table 7: Characteristics of the intervention – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study	Intervention	Comparison
TROPION-Breast01	datopotamab deruxtecan 6 mg/kg IV on Day 1 of the cycle Duration of cycle: 21 days	capecitabine: 1000 mg/m² or 1250 mg/m² orally twice daily on Days 1–14 of the cycle[b] eribulin: 1.4 mg/m² IV[c] on Day 1 and Day 8 of the cycle[d] vinorelbine: 25 mg/m² IV on Day 1 and Day 8 of the cycle Duration of cycle: 21 days each
	Dose modification: ▪ datopotamab deruxtecan: ▫ Dose interruptions (for reasons other than toxicity) permitted for ≤ 84 days ▫ Up to 2 dose reductions permitted: - 1st dose reduction: 4 mg/kg IV - 2nd dose reduction: 3 mg/kg IV ▫ Subsequent dose re-escalation not permitted	
	Prior treatment ▪ an endocrine therapy[e] and, in the unresectable/metastatic setting 1–2 lines of chemotherapy[f] **Prohibited prior and concomitant treatment** ▪ Chemotherapeutic agents for the targeted inhibition of topoisomerase I prior to randomization ▪ TROP2-targeted therapy prior to randomization ▪ Treatment with the same chemotherapy of investigator's choice prior to randomization ▪ Radiation therapy including palliative radiation to chest within 4 weeks (palliative radiation therapy to other areas within 2 weeks) prior to randomization and during the study[g] ▪ Anticancer therapy including hormonal therapy within 3 weeks (for small molecule targeted agents within 2 weeks or 5 half-lives, whichever is longer)[h] prior to randomization and during the study[i] ▪ Immunotherapy within 2 weeks or 5 half-lives (whichever is longer) prior to randomization ▪ Other investigational products or investigational medical devices within 4 weeks prior to the start of the study treatment and during the study ▪ Major surgical procedure within 3 weeks prior to randomization ▪ Chronic use of systemic (IV or oral) corticosteroids or other immunosuppressive medications during the study, except for managing AEs ▪ Chloroquine/hydroxychloroquine within 14 days prior to randomization and during the study	

Table 7: Characteristics of the intervention – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study	Intervention	Comparison
	Concomitant treatment Required premedication**:** ▪ Antihistamines and paracetamol, with or without glucocorticoids, before each dose of datopotamab deruxtecan Recommended: ▪ Prophylaxis with an antiemetic agent before and after administration of datopotamab deruxtecan ▪ Prophylaxis and treatment of stomatitis / oral mucositis with steroid-containing mouthwash in the intervention arm ▪ Daily use of moisturizing eye drops	

a. capecitabine or eribulin or vinorelbine.
b. Choice of dose as per local standard; dose reduction by 25% in participants with moderate renal impairment (creatinine clearance 30–49 mL/min).
c. The dosage information refers to eribulin mesylate.
d. A lower dose of 1.1 mg/m^2 is recommended for participants with moderate renal impairment (renal impairment 30-49 mL/min) or mild hepatic impairment (Child-Pugh A).
e. < 5% of the total population did not receive prior endocrine therapy. No data are available for the relevant subpopulation.
f. If a chemotherapy was changed within 28 days to another drug in the same class, the first treatment was not counted as a line.
g. Palliative radiation therapy to areas other than the chest was permitted during the study.
h. Antibody-based anticancer therapy (with the exception of RANKL inhibitors) was not allowed within 4 weeks prior to randomization.
i. With the exception of bisphosphonates and denosumab for the treatment of bone metastases.
j. If a treatment is necessary, the study intervention must be interrupted and a washout period of at least 14 days is required before restarting study intervention.

AE: adverse event; IV: intravenous; RANKL: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; TROP-2: trophoblast cell surface antigen 2

I 3.1.2.1 Study design

The TROPION-Breast01 study is an ongoing, open-label RCT comparing datopotamab deruxtecan versus treatment of physician's choice selecting from capecitabine, eribulin, gemcitabine and vinorelbine. The study included adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer whose disease had progressed on endocrine therapy and for whom endocrine therapy was not an option. In addition, patients had to be pretreated with 1 or 2 lines of systemic chemotherapy in the advanced setting and had to be in good general health, concurring with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

A total of 732 patients were included in the global cohort and randomly assigned in a 1:1 ratio to either treatment with datopotamab deruxtecan (N = 365) or treatment of physician's choice, selecting from capecitabine, eribulin, gemcitabine and vinorelbine (N = 367). The

decision as to which of the 4 available treatment options the patient should receive in the event of allocation to the control arm had to be made prior to randomization. Randomization was stratified according to the number of previous lines of chemotherapy (1 versus 2), prior use of cyclin-dependent kinase (CDK)4/6 inhibitor (yes versus no) and geographic region (United States, Canada and Europe versus rest of the world).

According to the study protocol, the randomization of patients in mainland China was to continue beyond the completion of recruitment to the global cohort described above if this was required for regulatory purposes. According to the study design, these additionally randomized patients from mainland China were not included in the primary analysis population of the study. The Chinese cohort, consisting of all patients randomized in mainland China as part of the study, was to be analysed separately. The company did not present any results for the Chinese cohort, nor did it provide any information on whether this cohort was actually recruited.

Treatment with datopotamab deruxtecan and eribulin in the TROPION-Breast01 study was in compliance with the recommendations in the respective SmPCs [13,14]. Treatment with capecitabine and vinorelbine deviated in some respects from the information provided in the SmPCs [15,16]. These deviations are described in Section I 3.1.2.3. As described in Section I 3.1.2.2, the drug gemcitabine was not part of the ACT. The subpopulation treated with gemcitabine was not considered in the benefit assessment.

Treatment was to continue until disease progression, unacceptable toxicity, or treatment discontinuation at the patient’s or investigator’s decision. Further treatment with the study treatment could be continued beyond progression of the disease at the discretion of the investigator. Switching between the study arms was not allowed.

The primary outcomes of the TROPION-Breast01 study were progression-free survival (PFS) as assessed in a blinded independent central review (BICR), and overall survival. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

I 3.1.2.2 Relevant subpopulation of TROPION-Breast01

In the TROPION-Breast01 study, the drugs capecitabine, eribulin, vinorelbine and gemcitabine were available as part of the treatment of physician’s choice. Gemcitabine was not part of the ACT specified by the G-BA (see Table 4). In its dossier, the company therefore presented analyses of a TROPION-Breast01 subpopulation that in both the intervention and control arms only included patients for whom capecitabine, eribulin or vinorelbine had been selected as a treatment option for possible treatment in the control arm prior to randomization. Furthermore, the subpopulation presented by the company according to research question 1

exclusively comprised patients with HER2-0 breast cancer who had received one line of chemotherapy in the advanced setting.

This benefit assessment used the subpopulation formed by the company as the relevant population. It consisted of a total of 118 patients, of whom 63 were included in the intervention arm and 55 in the control arm. This corresponded to a proportion of 17.3% and 15.0% of patients in the total population, respectively.

I 3.1.2.3 Uncertainties in the implementation of the ACT

Dosage of capecitabine

The study protocol of TROPION-Breast01 specified a capecitabine dosage of 1000 mg/m² or 1250 mg/m² twice daily on Days 1 to 14 of a 21-day cycle. However, only the higher dosage of 1250 mg/m² is specified in the SmPC for capecitabine [15]. The dose range of 1000 mg/m² to 1250 mg/m² is found in the National Comprehensive Cancer Network (NCCN) guideline for the treatment of patients with unresectable or metastatic breast cancer [17]. Furthermore, the justification for the G-BA's resolution on the benefit assessment procedure for trastuzumab deruxtecan indicates that, according to comments from clinical experts, the use of capecitabine in lower doses concurs with the therapeutic standard in clinical practice [18]. The lower dosage used in the TROPION-Breast01 study was therefore not assumed to have a relevant influence on this benefit assessment.

Dosage of vinorelbine

Vinorelbine was administered at a dosage of 25 mg/m² on Days 1 and 8 of a 21-day cycle, according to the study protocol. This did not concur with the information provided in the SmPC (25 mg/m² to 30 mg/m² once weekly) or with the recommendations of the S3 Guideline on Early Detection, Diagnostics, Therapy and Follow-up of Breast Cancer, which specifies a dosage of 30 mg/m² on Days 1 and 8 of a 21-day cycle [16,19]. However, the dosage was consistent with the NCCN guideline recommendations [17]. In the control arm, approximately 9% of patients in the relevant subpopulation were treated with vinorelbine. Overall, this deviation was not assumed to have a relevant influence on the result of the benefit assessment.

Prior therapy with anthracyclines and/or taxanes

According to the applicable SmPCs, the treatment options relevant to the dossier assessment (capecitabine, eribulin, vinorelbine) in the control arm of the TROPION-Breast01 study should only be used if

- taxane and anthracycline therapy have failed or further anthracycline treatment is not indicated (capecitabine [15]);
- prior therapy included an anthracycline and a taxane unless patients were not suitable for these treatments (eribulin [14]);

- treatment with anthracycline- and taxane-containing chemotherapy has failed or is not suitable (vinorelbine [16]).

In addition, the G-BA stated that an anthracycline or taxane-containing regimen is an ACT only for patients who have not previously received an anthracycline and/or taxane-containing regimen or who are eligible for renewed anthracycline or taxane-containing treatment. Prior treatment with anthracyclines or taxanes was not mandatory for inclusion in the TROPION-Breast01 study. The subgroup analyses presented in Module 4 showed that in the control arm, only 55% of patients in the relevant subpopulation had already been treated with both an anthracycline and a taxane (see Table 9). The remaining patients either had been previously treated with anthracycline or taxane alone (in particular, 40% in the control arm had not received any anthracyclines to date) or had not received any prior treatment with drugs from these groups (16% in the control arm) (see Table 9). However, it was unclear whether these data referred to prior therapies throughout the entire course of treatment, including possible neoadjuvant or adjuvant therapy, or exclusively to the unresectable or metastatic setting. For an assessment of whether patients had received appropriate prior therapy and on-label treatment in the control arm of the TROPION-Breast01 study, information on the entire course of treatment would be necessary. Furthermore ,the proportion of patients for whom anthracyclines or taxanes were not suitable, for example because of a contraindication, was unknown. However, it could not be ruled out overall that treatment with an anthracycline and/or a taxane would have been indicated for a relevant proportion of patients in the TROPION-Breast01 study. According to the respective SmPCs, treatment with capecitabine, eribulin or vinorelbine would therefore not have been appropriate in these cases [14-16]. As a result of this uncertainty, the certainty of conclusions for the TROPION-Breast01 study was limited (see Section I 3.2.2).

I 3.1.2.4 Data cut-offs

The study is ongoing. Three data cuts are already available:

- 1st data cut-off (17 July 2023):
  prespecified final analysis of the PFS outcome and 1st interim analysis for the overall survival outcome after approximately 419 progression events according to BICR in the total population
- 2nd data cut-off (29 April 2024):
  prespecified 2nd interim analysis for the overall survival outcome after approximately 355 deaths in the total population
- 3rd data cut-off (24 July 2024):
  prespecified final analysis for the overall survival outcome after approximately 444 deaths in the total population

In Module 4 A, the company presented results from the 3rd data cut to derive the added benefit for all outcomes, with the exception of the PFS outcome. The PFS assessment according to BICR was only performed up to the 1st data cut-off. The results of the current 3rd data cut from 24 July 2024 were used for this benefit assessment.

I 3.1.2.5 Planned duration of follow-up

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

Table 8: Planned duration of follow-up – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a]

Study Outcome category Outcome	Planned follow-up
TROPION-Breast01	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, PGIS)	Up to 18 weeks after disease progression[b]
Health status (EQ-5D VAS)	Up to 18 weeks after disease progression[b]
Health-related quality of life (EORTC QLQ-C30)	Up to 18 weeks after disease progression[b]
Side effects	
AEs / SAEs / severe AEs[c]	Up to 28 days after the last dose of the study medication[d]
PRO-CTCAE	Until the end of the study treatment

a. capecitabine or eribulin or vinorelbine.
b. Data from Module 5; the data from Module 4 are partially discrepant.
c. Operationalized as CTCAE grade ≥ 3.
d. Recording of the outcome ILD/pneumonitis was to be continued beyond this point in time.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; ILD: interstitial lung disease; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for patient-reported outcomes (PROs) in the categories of morbidity and health-related quality of life were systematically shortened. They were observed for up to 18 weeks after disease progression. Thus, although the planned observation periods did not cover the entire study period, it was positive to note that they were at least recorded beyond the progression of the disease.

The observation periods for the outcomes of the category of side effects were also systematically shortened because they were recorded only for the period of treatment with

the study medication (adverse events [AEs], serious adverse events [SAEs], and severe AEs: plus 28 days). In contrast, the recording of the outcome ILD/pneumonitis was to be continued beyond this point in time.

However, drawing a reliable conclusion on the total study period or the time to patient death would require recording all outcomes listed for the total period, as was done for overall survival and the outcome ILD/pneumonitis.

I 3.1.2.6 Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study **Characteristic** **Category**	**datopotamab deruxtecan** **N = 63**	**Chemotherapy of physician's choice[a]** **N = 55**
TROPION-Breast01		
Age [years], mean (SD)	52 (11)	57 (11)
Sex [F/M], %	98/2	98/2
Family origin, n (%)		
Caucasian	31 (49)	24 (44)
Asian	21 (33)	21 (38)
Black or African American	1 (2)	0 (0)
Other	0 (0)	2 (4)
Not specified	10 (16)	8 (15)
ECOG PS, n (%)		
0	35 (56)	33 (60)
1	26 (41)	21 (38)
2	2 (3)	1 (2)
Disease classification, n (%)		
Locally advanced / unresectable	2 (3)	0 (0)
Metastatic	61 (97)	55 (100)
Visceral metastases, n (%)		
Yes	60 (95)	54 (98)
No	3 (5)	1 (2)
Time between last disease progression and randomization [days], median [min; max]	28.0 [2; 150]	33.0 [2; 136]
Disease duration: time between first diagnosis and randomization [years], median [min; max]	5.0 [0; 24]	5.4 [0; 23]

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study Characteristic Category	datopotamab deruxtecan N = 63	Chemotherapy of physician's choice[a] N = 55
Previous use of CDK4/6 inhibitors, n (%)		
Yes	52 (83)	45 (82)
No	11 (18)	10 (18)
Previous use of anthracyclines and taxanes, n (%)[b]		
Anthracyclines only	1 (2[c])	3 (5[c])
Taxanes only	19 (30[c])	13 (24[c])
Both anthracyclines and taxanes	32 (51[c])	30 (55[c])
Neither anthracyclines nor taxanes	11 (17[c])	9 (16[c])
Treatment discontinuation, n (%)[d]	62 (98)	54 (98)
Study discontinuation, n (%)[e]	ND[f]	ND[f]

a. capecitabine or eribulin or vinorelbine.
b. These data are inferred from the subgroup analyses presented in Appendix 4 G to Module 4 A. It is unclear to which stages of treatment the information refers.
c. Institute's calculation.
d. The most common reason for treatment discontinuation in the intervention arm vs. the control arm was disease progression (84% vs. 75%). The data also include patients who died during treatment with the study medication (intervention arm: 0% vs. control arm: 2%).
e. The reason for study discontinuation in the intervention vs. control arm was: withdrawal of consent (3% vs. 0%). The data additionally include patients who died during the course of the study (intervention arm: 70% vs. control arm: 65%).
f. Calculations conducted by the Institute taking into account the number of deaths and censorings (with the exception of the censoring reason 'still under follow-up') result in the following values: intervention arm: 73%, control arm: 65%.

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 in the relevant subpopulation; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in the TROPION-Breast01 subpopulation relevant for the benefit assessment were largely balanced between the study arms. The patients in the intervention arm were slightly younger than those in the control arm (52 years versus 57 years). The majority of patients were female (98%) and had Caucasian or Asian family origins (82%). The majority had an ECOG PS of 0 (56% versus 60%) and were in the metastatic stage of the disease (97% versus 100%).

Approximately 98% of patients in both study arms discontinued the study treatment, primarily due to disease progression. Information on the proportion of patients who discontinued the study was not available in Module 4 A. The calculation conducted by the Institute showed that

the proportion between the study arms was largely balanced, with the majority of study discontinuations documented as being due to deaths.

I 3.1.2.7 Information on the course of the study

Table 10 shows the treatment duration of the patients and the observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a]

Study **Duration of the study phase** **Outcome category/outcome**	**datopotamab deruxtecan** **N = 63**	**Treatment of physician's choice[a]** **N = 55**
TROPION-Breast01		
Treatment duration [months]		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Observation period [months]		
Overall survival		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Symptoms (EORTC QLQ-C30, PGIS)		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Health status (EQ-5D VAS)		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30)		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Side effects (AEs, SAEs, PRO-CTCAE)		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND

a. capecitabine or eribulin or vinorelbine.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; N: number of patients in the relevant subpopulation; ND: no data; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

No information on treatment and observation period was available for the relevant subpopulation in the TROPION-Breast01 study. However, information on the duration of

treatment and observation is necessary for interpreting study results in a benefit assessment. This is also reflected by the dossier templates.

Module 5 of the dossier contained information on the duration of treatment and observation for the total population. However, as the relevant subpopulation accounted for only 17.3% (intervention arm) and 15.0% (control arm) of the total population, it was not possible to derive any assessments for the subpopulation from these data.

The lack of information on the duration of treatment and observation was taken into account when selecting the appropriate effect measure to determine the extent of the added benefit for the outcomes in the side effects category (see Section I 3.2.1).

I 3.1.2.8 Subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a]

Study **Drug class** **Drug**	**Patients with subsequent therapy, n (%)**	
	datopotamab deruxtecan **N = 63**	**Treatment of physician's choice[a]** **N = 55**
TROPION-Breast01		
Total, n (%)	59 (93.7)	53 (96.4)
Drug class	ND	ND
Drug	ND	ND
a. capecitabine or eribulin or vinorelbine. n: number of patients from the relevant subpopulation with subsequent therapy; N: number of analysed patients; ND: no data; RCT: randomized controlled trial		

In the TROPION-Breast01 study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. According to information provided by the company, subsequent therapies were selected by the investigator taking into account the guideline recommendations. In both the intervention arm and the control arm, the majority of patients in the relevant subpopulation received subsequent therapy (93.7% versus 96.4%), but the dossier did not provide any information on which therapies were used. Module 5 only contained information on subsequent therapies for patients in the total population. However, the relevant subpopulation only accounted for approximately 17.3% (intervention arm) and 15.0% (control arm) of the total population; it was therefore not possible to derive an adequate assessment of the subsequent therapies in the relevant subpopulation.

The results of the overall survival outcome are largely influenced by the subsequent antineoplastic therapies used after disease progression. The use of appropriate subsequent therapies is therefore of great importance for assessing the results of overall survival and also for all other outcomes observed beyond progression. For the relevant subpopulation, it was not possible to assess whether the patients in both study arms received appropriate subsequent therapies due to the lack of information on the subsequent therapies used.

In addition, the data on subsequent therapies in the total population indicated that the use of subsequent therapies may not have been optimal in all patients in the relevant subpopulation:

The current guidelines from AGO and ESMO recommend treatment with an antibody-drug conjugate or chemotherapy, depending on previous therapies [6,7]. There was some uncertainty regarding the use of sacituzumab govitecan in the TROPION-Breast01 study. For adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the advanced setting, the G-BA determined an indication of considerable added benefit for sacituzumab govitecan versus chemotherapy as the ACT [20]. For the corresponding patient population from research question 3 of this benefit assessment (at least 2 lines of chemotherapy in the advanced setting), the G-BA specified sacituzumab govitecan as the ACT for patients with HER2-0 breast cancer. Overall, sacituzumab govitecan was presumed to be a relevant option among the available subsequent therapy options for patients from research question 1. However, in TROPION-Breast01, only 4.1% and 7.1% of the total population in the intervention and control arms, respectively, received sacituzumab govitecan as subsequent therapy. It was unclear whether and how many patients in the relevant subpopulation received sacituzumab govitecan after their disease progressed.

Furthermore, in the total population of TROPION-Breast01, a relevant proportion of patients in both study arms were treated with endocrine therapy or CDK inhibitors. These treatments did not concur with the guideline recommendations. In addition, the study only included patients for whom endocrine therapy was not an option.

The lack of information on subsequent therapies and the aspects described above were taken into account in the assessment of the outcome-specific risk of bias for the outcome overall survival (see Section I 3.2.2).

I 3.1.2.9 Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
TROPION-Breast01	Yes	Yes	No	No	Yes	Yes	Low

a. capecitabine or eribulin or vinorelbine.

RCT: randomized controlled trial

For the TROPION-Breast01 study, the risk of bias across outcomes was rated as low.

Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

I 3.1.2.10 Transferability of the study results to the German health care context

The company considered the results of the TROPION-Breast01 study to be transferable to the German health care context. According to the company, the relevant subpopulation concurred with the demographic and disease-specific characteristics of the target population in Germany, and sex distribution and average age of patients was also comparable to the German patient population. It added that a high proportion of patients in both study arms came from Europe or countries with a comparable health care context, and that transferability to the German health care context could be assumed also with regard to prior therapies and treatments in the control arm.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity

- Symptoms
  - recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
  - recorded using the Patient Global Impression of Severity (PGIS)
- Health status
  - recorded using the EQ-5D visual analogue scale (VAS)

- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
  - ILD and pneumonitis (Standardized Medical Dictionary for Regulatory Activities Query [SMQ] interstitial lung disease [narrow] and other relevant PTs, adjudicated by an independent adjudication committee, AEs)
  - Keratitis
  - Hand-foot syndrome (PT, AEs)
  - Other specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a]

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30, PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEsb	PRO-CTCAE	ILD and pneumonitis[d] (AEs)	Keratitis	Hand-foot syndrome[e] (PT, AEs)	Other specific AEs[c, f]
TROPION-Breast01	Yes	No[g]	No[g]	No[g]	Yes	Yes	Yes	No[g]	Yes	No[g]	Yes	Yes

a. capecitabine or eribulin or vinorelbine.
b. According to the study protocol, progression-related events were not recorded as AEs.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Operationalized via the SMQ interstitial lung disease (narrow) and other PTs, adjudicated by an independent adjudication committee; see the next section.
e. Operationalized via the PT palmar-plantar erythrodysaesthesia syndrome.
f. The following events (coded according to MedDRA) are considered: nausea (PT, AEs), stomatitis (PT, AEs), decreased appetite (PT, AEs) and neutropenia (PT, severe AEs).
g. No suitable data available; see the following text section for reasons.

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; PGIS: Patient Global Impression of Severity; 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; SMQ: Standardized MedDRA Query; VAS: visual analogue scale

Notes on the included outcomes

Patient-reported outcomes in the categories of symptoms, health status and health-related quality of life

For the PROs in the categories of symptoms, health status and health-related quality of life, Module 4 A contained responder analyses for the time to first deterioration. Furthermore, Appendix 4 G to Module 4 A contained analyses of mean differences from a mixed-effects model with repeated measures (MMRM), in which the change from baseline was modelled.

The company presented the EORTC QLQ-C30 for the recording of symptoms and health-related quality of life, and the EQ-5D VAS for health status. In addition, it presented analyses of the PGIS for symptoms and of the Patient Global Impression of Change (PGIC) for health status, which assessed the severity of cancer-related symptoms (PGIS) and changes in health status from baseline (PGIC). However, due to its similarity in content to the EQ-5D VAS and

the relatively short planned duration of follow-up of only 12 weeks after the start of study treatment, the PGIC is not presented in the benefit assessment.

For the recording of symptoms, the company additionally provided 2 item lists (EORTC Item Library [IL]116 and EORTC IL117) based on the EORTC Item Library [21]. The validity of these item lists was not verified within the benefit assessment, as the results presented by the company for all PROs could not be used for the assessment. This is justified below:

The response rates of the PROs presented by the company in Module 4 A showed that a relevant proportion of patients in the subpopulation were already excluded from the analyses at the baseline survey. At baseline, there were the following proportions of analysed questionnaires in the intervention versus control arm: EORTC QLQ-C30: 71.4% versus 65.5%; EQ-5D VAS: 66.7% versus 54.5%; PGIS: 66.7% versus 56.4%. It was unclear why the questionnaires from the other patients were missing. The response rates for these questionnaires continued to decline over the course of the study. For example, by Week 15, the response rate for the EORTC QLQ-C30 was already below 60% in the intervention arm and 40% in the control arm. Overall, the results of the PROs were not suitable for use in the benefit assessment due to the high proportion of missing values.

Side effects

AEs, SAEs, and severe AEs

When considering side effects, the primary factor is how many patients experienced an event. The relative risk is the appropriate effect measure for these analyses. In time-to-event analyses using the hazard ratio as an effect measure, however, effects may arise solely due to the earlier or later occurrence of the event, even if the number of people affected does not differ. For these reasons, relative risk is preferable to hazard ratio as an effect measure. However, there are situations with different observation periods between the study arms in which the relative risk is not suitable, and instead time-to-event analyses are the appropriate method of analysis [1].

In Module 4 A, the company only presented time-to-event analyses without providing any further justification. Furthermore, as already described, no data on observation periods and treatment durations were available for the relevant subpopulation (see Table 10). It was therefore impossible to assess whether the relative risk would also be a suitable effect measure in the given situation, which, for the reasons described above, would be preferable where there are comparable observation periods. Based on an initial estimate of the observation period using the available information on the time to disease progression, it was at least conceivable that the observation periods between the study arms were sufficiently similar and that the relative risk therefore represented the relevant effect measure. However, further information on the actual observation periods in the subpopulation would be required

for a final decision. In addition, it would be necessary for the company to submit corresponding analyses of the effect measure of relative risk (RR) for sufficiently comparable observation periods. A comparison of the analyses of the hazard ratio and the Institute's calculations of the relative risk revealed differences in the extent of the added benefit for some AE outcomes, for example for the overall rate of severe AEs (see Table 15 and Table 16). Due to the uncertainties described above, both effect measures were taken into account for AE outcomes for which the relative risk showed an extent of the added benefit that differed from the hazard ratio, but it was not possible to quantify the extent of the added benefit in these cases (see Section I 3.2.3 and Table 16).

Furthermore, no information was available on the effect estimation of the time-to-event analyses for AE outcomes with 0 events in one study arm. One way to obtain point and interval estimates for time-to-event analyses in such situations is to use the Firth correction to the Cox model [22-25] in combination with profile likelihood methods for the 95% confidence intervals.

PRO-CTCAE

In TROPION-Breast01, side effects were also recorded with the PRO-CTCAE instrument. Overall, this instrument is a valuable addition to the usual recording and analysis of AEs. It comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection of individual patient-reported symptomatic AEs should be prespecified in the study protocol and comprehensible, e.g. ensuring the recording of all important potential AEs of the drugs used in the intervention and control arms.

The suitability of the item selection and operationalization presented was not reviewed, as the analyses submitted by the company could not be used due to insufficient questionnaire response rates. The information on PRO-CTCAE provided by the company showed that, similar to the PROs in the categories of symptoms, health status and health-related quality of life, a relevant proportion of patients were not included in the analyses. Even at the recording at baseline, the proportion of completed questionnaires in the intervention and control arms was only around 70% and 58% respectively. Furthermore, the results for PRO-CTCAE in Appendix 4 G to Module 4 A were presented in a descriptive manner only. The results for the PRO-CTCAE outcome were therefore not used for this assessment.

ILD and pneumonitis

In Module 4 A, the company presented results for the outcomes ILD and pneumonitis. According to the clinical study report (CSR), the outcome was operationalized via the SMQ interstitial lung disease (narrow) and other PTs. All events that occurred were adjudicated by an independent adjudication committee. However, it was unclear which other PTs besides

SMQ were included in the operationalization. However, the results from the total population of TROPION-Breast01 showed that all events that occurred (PT interstitial lung disease, PT pneumonitis and PT radiation pneumonitis) are included in the SMQ interstitial lung disease (narrow). As this SMQ was assessed as a suitable operationalization for the outcome ILD and pneumonitis, the data presented by the company on this outcome were used for the benefit assessment.

Keratitis

To represent the outcome keratitis, a complete, summarized presentation of all relevant events, including the PTs keratitis, punctate keratitis and ulcerative keratitis, is appropriate. Such operationalization was also described by the European Medicines Agency (EMA) as part of the risk management plan for datopotamab deruxtecan [26]. The SmPC for datopotamab deruxtecan also includes the PTs keratitis, punctate keratitis and ulcerative keratitis to represent the side effect keratitis [13]. However, for the relevant subpopulation, the dossier only contained results for the PT punctate keratitis (9 patients with events in the intervention arm versus 3 in the control arm). It was unknown whether the PTs keratitis and ulcerative keratitis occurred in the relevant subpopulation, as Appendix 4 G to Module 4 A only presented AEs with a frequency of at least 10% (serious and severe AEs: at least 5%) in at least one study arm at System Organ Class (SOC) and PT level. In summary, the company's dossier contained no suitable data for the outcome keratitis.

Testing for effects with increased significance level

In its dossier, the company described that consideration of the relevant subpopulation was accompanied by a loss of power and that the probability of showing an effect that actually existed on the basis of the subpopulation was reduced. It explained that, according to a working paper by IQWiG on methods for the applicability of study results to subpopulations [27], in this case it could be checked separately for each outcome whether certain statistical requirements for testing effects at the increased significance level of 15% were met in the relevant subpopulation. The company therefore examined these criteria for all outcomes in Module 4 A and took this into account in the derivation of the added benefit.

Irrespective of the statistical requirements, in order to conduct a test of the treatment effect at an increased significance level, above all clinical/content requirements must be met. One prerequisite is to demonstrate that, from a clinical/content perspective, the results of the population not relevant to the benefit assessment (non-target population) are sufficiently transferable to the subpopulation relevant to the benefit assessment (target population). However, the company did not provide any information indicating that the target population was comparable to the non-target population in terms of content. Rather, the following aspects called into question the transferability: The target population comprised exclusively patients who had received one line of chemotherapy in the advanced setting. In contrast,

approximately 45% of the non-target population had already received 2 lines of chemotherapy. The company itself described in the study protocol that the results of the primary outcomes, PFS and overall survival, were expected to differ depending on whether a patient had received 1 or 2 lines of prior chemotherapy, and therefore chose stratification by lines of chemotherapy (1 versus 2) for the TROPION-Breast01 study. Furthermore, unlike the target population, at least 49% of the non-target population were patients with HER2-low breast cancer.

Overall, the target population and the non-target population were not assumed to be sufficiently similar. Deviating from the company, the results of the relevant subpopulation were therefore used without testing with an increased significance level. However, this had no impact on the result of the benefit assessment, as testing with an increased significance level did not reveal any differences in the extent of the added benefit for the outcomes used (see Section I 3.2.1).

I 3.2.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a]

Study	Study level	Outcomes											
		Overall survival	Symptoms (EORTC QLQ-C30, PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEsb	PRO-CTCAE	ILD and pneumonitis[d] (AEs)	Keratitis	Hand-foot syndrome[e] (PT, AEs)	Other specific AEs[c, f]
TROPION-Breast01	L	H[g]	–[h]	–[h]	–[h]	H[i]	H[i]	H[j]	–[h]	H[j]	–[h]	H[i, j]	H[i, j]

a. capecitabine or eribulin or vinorelbine.
b. According to the study protocol, progression-related events were not recorded as AEs.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Operationalized via the SMQ interstitial lung disease (narrow) and other PTs, adjudicated by an independent adjudication committee; see Section I 3.2.1.
e. Operationalized via the PT palmar-plantar erythrodysaesthesia syndrome.
f. The following events (coded according to MedDRA) are considered: nausea (PT, AEs), stomatitis (PT, AEs), decreased appetite (PT, AEs) and neutropenia (PT, severe AEs).
g. Lack of information on subsequent therapies in the relevant subpopulation.
h. No suitable data available; for reasoning, see Section I 3.2.1 of this benefit assessment.
i. Shortened observation for potentially informative reasons.
j. Lack of blinding in subjective recording of outcomes or decision to discontinue; applies to the following PTs for the other specific AEs: nausea, stomatitis, decreased appetite.

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; PGIS: Patient Global Impression of Severity; 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; SMQ: Standardized MedDRA Query; VAS: visual analogue scale

For the results on the outcome of overall survival, the risk of bias was assessed as high due to the lack of information on the subsequent therapies used (see Section I 3.1.2.8).

The risk of bias of the results on the outcomes in the side effects category was also assessed as high. For the higher-level operationalizations of serious and severe AEs, as well as for the PT neutropenia, this was due to a shortened observation for potentially informative reasons, as almost all patients discontinued treatment prematurely – 84% versus 75% of all patients in the relevant subpopulation solely due to progression, for example – and observation was discontinued 28 days later (see Section I 3.1.2.5). In the results for the outcomes ILD and

pneumonitis, the lack of blinding in subjective recording of outcomes led to a high risk of bias. Both reasons applied to the remaining non-serious/non-severe AEs.

The risk of bias in the results for the outcome of discontinuation due to AEs was assessed as high because of lack of blinding in subjective decisions regarding treatment discontinuation. The certainty of results was additionally limited by the fact that treatment might also be discontinued for reasons other than AEs. These reasons represented a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion of 'discontinuation' is no longer applicable to them. It was impossible to estimate how many AEs this affected.

Assessment of the certainty of conclusions

Regardless of the aspects described for the risk of bias, the certainty of conclusions of the study results was limited due to the uncertainty regarding the prior therapy of patients with anthracyclines and taxanes described in Section I 3.1.2.3.

I 3.2.3 Results

Table 15 summarizes the results of the comparison of datopotamab deruxtecan versus chemotherapy of physician's choice in adult patients with unresectable or metastatic HR-positive, HER2-0 breast cancer who have received endocrine therapy and one line of chemotherapy in the advanced setting. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on time-to-event analyses of the included outcomes are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study Outcome category Outcome	datopotamab deruxtecan		Chemotherapy of physician's choice[a]		datopotamab deruxtecan vs. chemotherapy 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]
TROPION-Breast01					
Mortality					
Overall survival	63	17.5 [15.2; 20.2] 44 (69.8)	55	14.1 [11.1; 23.0] 36 (65.5)	1.05 [0.67; 1.64]; 0.837
Morbidity					
Symptoms (EORTC QLQ-C30, PGIS)				No suitable data[c]	
Health status (EQ-5D VAS)				No suitable data[c]	
Health-related quality of life					
EORTC QLQ-C30				No suitable data[c]	
Side effects					
AEs (supplementary information)	63	0.2 [0.1; 0.3] 61 (96.8)	55	0.3 [0.2; 0.5] 53 (96.4)	–
SAEs	63	NA 7 (11.1)	55	NA [12.2; NC] 9 (16.4)	0.51 [0.19; 1.37]; 0.173
Severe AEs[d]	63	NA [7.6; NC] 17 (27.0)	55	2.8 [0.9; 11.7] 31 (56.4)	0.35 [0.19; 0.64]; < 0.001[e]
Discontinuation due to AEs	63	NA 2 (3.2)	55	NA [12.2; NC] 4 (7.3)	0.25 [0.04; 1.39]; 0.089
PRO-CTCAE				No suitable data[c]	
ILD and pneumonitis[f] (AEs)	63	NA 2 (3.2)	55	NA 0 (0.0)	NC; 0.292
Keratitis				No suitable data[c]	
Hand-foot syndrome[g] (PT, AEs)	63	NA 2 (3.2)	55	NA 6 (10.9)	0.28 [0.06; 1.38]; 0.095
Nausea (PT, AEs)	63	4.9 [0.8; NC] 32 (50.8)	55	NA 11 (20.0)	2.82 [1.41; 5.64]; 0.002
Stomatitis (PT, AEs)	63	4.5 [2.1; NC] 30 (47.6)	55	NA 9 (16.4)	3.50 [1.66; 7.39]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study Outcome category Outcome	datopotamab deruxtecan		Chemotherapy of physician's choice[a]		datopotamab deruxtecan vs. chemotherapy 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]
Decreased appetite (PT, AEs)	63	NA 6 (9.5)	55	NA 13 (23.6)	0.27 [0.10; 0.77]; 0.009[h]
Neutropenia (PT, severe AEs[d])	63	NA 0 (0.0)	55	NA 10 (18.2)	NC; < 0.001[i]

a. capecitabine or eribulin or vinorelbine.
b. HR and CI from Cox proportional hazards model; p-value from log-rank test. Each stratified according to number of previous lines of chemotherapy (1 vs. 2), geographic region (United States, Canada and Europe vs. rest of the world) and prior use of CDK4/6 inhibitor (yes vs. no).
c. See Section I 3.2.1 for reasoning.
d. Operationalized as CTCAE grade ≥ 3.
e. Differences in the extent of the results when considering the HR and the Institute's calculations of the RR (RR: 0.48 [0.30; 0.76]; p = 0.001); see Table 16.
f. Operationalized via the SMQ interstitial lung disease (narrow) and other relevant PTs, adjudicated by an independent adjudication committee; see Section I 3.2.1.
g. Operationalized via the PT palmar-plantar erythrodysaesthesia syndrome.
h. Differences in the extent of the results when considering the HR and the Institute's calculations of the RR (RR: 0.40 [0.16; 0.99]; p = 0.043); see Table 16.
i. Comparison between HR (not feasible) and Institute's calculations of the RR (RR: 0.04 [0.002; 0.70]; p < 0.001); see Table 16.

AE: adverse event; CDK: cyclin-dependent kinase; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ILD: interstitial lung disease; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PGIS: Patient Global Impression of Severity; 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; RR: relative risk; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; SAE: serious adverse event; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, could be determined for all outcomes (for reasoning, see Section I 3.2.2).

Mortality

Overall survival

No statistically significant difference between the study arms was shown for the outcome of overall survival. There is no hint of an added benefit of datopotamab deruxtecan in

comparison with chemotherapy of physician's choice; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30 and PGIS) and health status (EQ-5D VAS)

No suitable data were available for the outcomes symptoms, recorded using the EORTC QLQ-C30 and PGIS, and health status, recorded using the EQ-5D VAS. There is therefore no hint of an added benefit of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data were available for the outcome of health-related quality of life, recorded using EORTC QLQ-C30, either. There is therefore no hint of an added benefit of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, there is no statistically significant difference between the study arms. There is no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference in favour of datopotamab deruxtecan in comparison with chemotherapy of physician's choice was shown for the outcome of severe AEs. There is a hint of lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice. There were differences in the extent of added benefit depending on whether the hazard ratio or the relative risk was considered. This is explained in Table 16 in the corresponding footnote.

Discontinuation due to AEs

There was no statistically significant difference between the study arms for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

PRO-CTCAE

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

ILD and pneumonitis (AEs), hand-foot syndrome (AEs)

For the outcomes ILD and pneumonitis (AEs) as well as hand-foot syndrome (AEs), there was no statistically significant difference between the study arms. In each case, there is no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

Keratitis

No suitable data were available for the outcome keratitis. There is therefore no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

Other specific AEs

Nausea (AEs), stomatitis (AEs)

A statistically significant difference to the disadvantage of datopotamab deruxtecan in comparison with chemotherapy of physician's choice was shown for each of the outcomes nausea (AEs) and stomatitis (AEs). In each case, there is a hint of greater harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice.

Decreased appetite (AEs)

A statistically significant difference in favour of datopotamab deruxtecan in comparison with chemotherapy of physician's choice was shown for the outcome decreased appetite. There were differences in the extent of added benefit depending on whether the hazard ratio or the relative risk was considered. Since it was not possible to reliably assess which effect measure was appropriate without information on observation period and treatment duration, the results of both effect measures were taken into account. The extent of the effect was no more than marginal when considering the relative risk, but considerable when considering the hazard ratio (see Table 16). In the given situation, it was therefore not possible to clearly determine whether there was lesser harm for the outcome decreased appetite. There is therefore no hint of greater or lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice; greater or lesser harm is therefore not proven.

Neutropenia (severe AEs)

A statistically significant difference in favour of datopotamab deruxtecan in comparison with chemotherapy of physician's choice was shown for the outcome neutropenia (severe AEs). There is a hint of lesser harm of datopotamab deruxtecan in comparison with chemotherapy

of physician's choice. There were differences in the extent of added benefit depending on whether the hazard ratio or the relative risk was considered. This is explained in Table 16 in the corresponding footnote.

I 3.2.4 Subgroups and other effect modifiers

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

- Age (< 65 years versus ≥ 65 years)
- Brain metastases (yes versus no)

The characteristic of sex was disregarded because there were only 2 male patients in the relevant subpopulation.

The subgroup characteristics mentioned were defined a priori in the TROPION-Breast01 study for the outcomes of overall survival and PFS (BICR) based on the total population.

Interaction tests are performed when 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.

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

Applying the methods described above, no effect modifications relevant to the benefit assessment were shown for the characteristics of age and brain metastases.

I 3.3 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 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 3 (see Table 16).

Table 16: Extent of added benefit at outcome level: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category **Outcome**	**datopotamab deruxtecan vs. chemotherapy of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	17.5 vs. 14.1 months HR: 1.05 [0.67; 1.64] p = 0.837	Lesser benefit not proven / added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, PGIS)	No suitable data[d]	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS)	No suitable data[d]	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data[d]	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 0.51 [0.19; 1.37]; p = 0.173	Greater/lesser harm not proven
Severe AEs	NA vs. 2.8 HR: 0.35 [0.19; 0.64]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: non-quantifiable, but at least considerable[e]
Discontinuation due to AEs	NA vs. NA HR: 0.25 [0.04; 1.39]; p = 0.089	Greater/lesser harm not proven
PRO-CTCAE	No suitable data[d]	Greater/lesser harm not proven
ILD and pneumonitis (AEs)	NA vs. NA HR: NC; p = 0.292	Greater/lesser harm not proven
Keratitis	No suitable data[d]	Greater/lesser harm not proven
Hand-foot syndrome (AEs)	NA vs. NA HR: 0.28 [0.06; 1.38]; p = 0.095	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category **Outcome**	**datopotamab deruxtecan vs. chemotherapy of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Nausea (AEs)	4.9 vs. NA HR: 2.82 [1.41; 5.64]; HR: 0.35 [0.18; 0.71][f]; p = 0.002 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Stomatitis (AEs)	4.5 vs. NA HR: 3.50 [1.66; 7.39]; HR: 0.29 [0.14; 0.60][f]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Decreased appetite (AEs)	NA vs. NA HR: 0.27 [0.10; 0.77]; p = 0.009 Probability: hint	Outcome category: non-serious/non-severe side effects Greater/lesser harm not proven[g]
Neutropenia (severe AEs)	NA vs. NA HR: NC; p < 0.001 Probability: hint	Outcome category: serious/severe side effects Lesser harm, extent: non-quantifiable[h]

a. capecitabine or eribulin or vinorelbine.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
d. See Section I 3.2.1 for reasoning.
e. Extent when considering HR: major; extent when considering RR: considerable (0.48 [0.30; 0.76]; p = 0.001).
f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
g. Extent when considering the HR: considerable; extent when considering the RR: no more than marginal (0.40 [0.16; 0.99]; p = 0.043); due to this discrepancy, it is unclear whether there is greater or lesser harm.
h. Extent when considering the HR: non-quantifiable (HR cannot be calculated); extent when considering the RR: major (0.04 [0.002; 0.70]; p < 0.001, risk ≥ 5%).

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ILD: interstitial lung disease; NA: not achieved; NC: not calculable; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

I 3.3.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of datopotamab deruxtecan in comparison with the ACT

Positive effects	**Negative effects**
Outcomes with shortened observation period	
Serious/severe side effects ▪ Severe AEs: hint of lesser harm – extent: non-quantifiable, but at least considerable, including ▫ Neutropenia: hint of lesser harm – extent: non-quantifiable	–
–	Non-serious/non-severe side effects ▪ Nausea: hint of greater harm – extent: considerable ▪ Stomatitis: hint of greater harm – extent: considerable
No suitable data are available for the outcomes of morbidity and health-related quality of life, or for the outcomes PRO-CTCAE and keratitis in the side effects category.	
ACT: appropriate comparator therapy; AE: adverse event; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events	

For research question 1 of this benefit assessment, there are positive and negative effects of datopotamab deruxtecan in comparison with chemotherapy of physician's choice in the relevant subpopulation.

In terms of positive effects, there is a hint of lesser harm in the overall rate of severe AEs and the specific AE of severe neutropenia included therein in the category of serious/severe side effects. Due to the lack of information on observation periods and treatment durations in the relevant subpopulation and discrepant results when considering the hazard ratio and the relative risk, the extent is non-quantifiable, but at least considerable, for the overall rate of severe AEs. In terms of negative effects, there is a hint of greater harm of considerable extent for each of the PTs nausea and stomatitis in the category of non-serious/non-severe side effects. The results refer to the shortened period up to 28 days after discontinuation of the study treatment for the AEs mentioned.

No conclusion could be drawn regarding the morbidity and health-related quality of life of patients from research question 1, as no suitable data were available for these outcome categories. In addition, there was some uncertainty regarding the result for the outcome of overall survival due to a lack of information on subsequent therapies. Another uncertainty was due to the prior therapy of patients with anthracyclines and/or taxanes (see Section I 3.2.2).

Given the available data situation with the uncertainties described, for example in terms of overall survival, the shortened observation period for which the AE outcomes with statistically significant effects provided conclusions, and in particular the lack of suitable data on patient-reported outcomes, it was ultimately not possible to weigh up the various positive and negative effects of the adverse events with sufficient certainty. In the given data situation, the advantage in the overall rate of severe AEs was insufficient to derive an added benefit.

In summary, there is therefore no hint of an added benefit of datopotamab deruxtecan in comparison with the ACT for adults with unresectable or metastatic HR-positive, HER2-0 breast cancer who have received endocrine therapy and one line of chemotherapy in the advanced setting; an added benefit is therefore not proven.

The assessment described above differs from that of the company, which derived an indication of considerable added benefit.

I 4 Research question 2: HER2-low breast cancer, one line of chemotherapy in the advanced setting

I 4.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on datopotamab deruxtecan (status: 18 April 2025)
- Bibliographical literature search on datopotamab deruxtecan (last search on 27 March 2025)
- Search of trial registries/trial results databases for studies on datopotamab deruxtecan (last search on 27 March 2025)
- Search on the G-BA website for datopotamab deruxtecan (last search on 27 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on datopotamab deruxtecan (last search on 10 June 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, this review did not identify any relevant studies.

I 4.2 Results on added benefit

No data were available for the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HR-positive, HER2-low breast cancer who have received endocrine therapy and one line of chemotherapy in the advanced setting. There is no hint of an added benefit of datopotamab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

Since the company did not present any data for the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HR-positive, HER2-low breast cancer who have received endocrine therapy and one line of chemotherapy in the advanced setting, an added benefit is not proven.

The assessment described above concurs with that by the company.

I 5 Research question 3: HER2-0 or HER2-low breast cancer, at least 2 lines of chemotherapy in the advanced setting

I 5.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on datopotamab deruxtecan (status: 18 April 2025)
- Bibliographical literature search on datopotamab deruxtecan (last search on 27 March 2025)
- Search of trial registries/trial results databases for studies on datopotamab deruxtecan (last search on 27 March 2025)
- Search on the G-BA website for datopotamab deruxtecan (last search on 27 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on datopotamab deruxtecan (last search on 10 June 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, this review did not identify any relevant studies.

I 5.2 Results on added benefit

No data were available for the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HR-positive, HER2-0 or HER2-low breast cancer who have received endocrine therapy and at least 2 lines of chemotherapy in the advanced setting. There is no hint of an added benefit of datopotamab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

I 5.3 Probability and extent of added benefit

Since the company did not present any data for the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HR-positive, HER2-0 or HER2-low breast cancer who have received endocrine therapy and at least 2 lines of chemotherapy in the advanced setting, an added benefit is not proven.

The assessment described above concurs with that by the company.

I 6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of datopotamab deruxtecan in comparison with the ACT is summarized in Table 18.

Table 18: Datopotamab deruxtecan – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	
Adults with unresectable or metastatic HR-positive, HER2-negative[b] breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting[c, d]			
1	HER2-0 breast cancer, one line of chemotherapy in the advanced setting	▪ capecitabine or ▪ eribulin or ▪ vinorelbine or ▪ an anthracycline- or taxane-containing therapy (only for patients who have not yet received anthracycline- and/or taxane-containing therapy or for whom renewed anthracycline- or taxane-containing therapy is an option)	Added benefit not proven
2	HER2-low breast cancer, one line of chemotherapy in the advanced setting	▪ trastuzumab deruxtecan	Added benefit not proven
3	HER2-0 or HER2-low breast cancer, at least 2 lines of chemotherapy in the advanced setting	▪ sacituzumab govitecan or ▪ trastuzumab deruxtecan (only for patients with HER2-low tumour status)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, all patients in the therapeutic indication are classified as HER2-negative. This includes patients with HER2-0 breast cancer (IHC 0) and with HER2-low breast cancer (IHC 1+ or IHC 2+ / ISH-) [3,4]. These designations are used in this benefit assessment to distinguish between the different research questions.
c. According to the G-BA it is assumed that, as part of prior therapy, patients typically received taxane- and/or anthracycline-containing chemotherapy.
d. 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. Only one man was included in each of the intervention and control arms of the TROPION-Breast01 study. It therefore remains unclear whether the observed effects can be transferred to men.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; ISH: in situ hybridization

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 7 References for English extract

Please see full dossier assessment for full reference list.

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