Datopotamab deruxtecan (breast cancer)

Addendum to Project A25-69 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

Project: A25-130 Version: 1.0 Status: 31 Oct 2025 DOI: 10.60584/A25-130_en

[1] Translation of the addendum *Datopotamab deruxtecan (Mammakarzinom) – Addendum zum Projekt A25-69 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Datopotamab deruxtecan (breast cancer) – Addendum to Project A25-69

Commissioning agency

Federal Joint Committee

Commission awarded on

7 October 2025

Internal Project No.

A25-130

https://doi.org/10.60584/A25-130_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Datopotamab deruxtecan (breast cancer); Addendum to Project A25-69 (dossier assessment) [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-130_en.

Keywords

Datopotamab deruxtecan, Breast Neoplasms, Benefit Assessment, NCT05104866

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie (Gynaecological Oncology Group)
CDK	cyclin-dependent kinase
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

1 Background

On 7 October 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-69 (Datopotamab deruxtecan – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the following supplementary information on the TROPION-Breast01 study [2] submitted by the pharmaceutical company (hereinafter referred to as 'the company') in the commenting procedure, taking into account the information provided in the dossier [3]:

- Prior therapy with anthracyclines and/or taxanes
- Data on treatment duration and observation period
- Subsequent antineoplastic therapies

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

2 Assessment

In dossier assessment A25-69 [1], analyses of a subpopulation of the TROPION-Breast01 study were used to assess the added benefit of datopotamab deruxtecan in comparison with the appropriate comparator therapy (ACT) in adults with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-0 breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting (research question 1 of the dossier assessment). TROPION-Breast01 is an open-label randomized controlled trial (RCT) comparing datopotamab deruxtecan versus treatment of physician's choice selecting from capecitabine, eribulin, gemcitabine and vinorelbine. A detailed description of TROPION-Breast01 can be found in benefit assessment A25-69 [1].

As described in assessment A25-69, the company dossier contained no information on treatment duration and observation period, or on subsequent antineoplastic therapies, for the relevant subpopulation. Furthermore, it was noted that it was unclear at what stage of the treatment course prior therapy with anthracyclines and/or taxanes was administered, and for which patients such treatment was contraindicated or unsuitable for other reasons.

As part of the commenting procedure, the company provided the missing data on treatment and observation period and subsequent therapies for the relevant subpopulation of TROPION-Breast01, as well as additional information on prior treatment with anthracyclines and/or taxanes [2]. These data are presented and assessed below.

2.1 Prior therapy with anthracyclines and/or taxanes

It was described in the dossier assessment that it was unclear which stage of treatment the information on prior therapy with anthracyclines and/or taxanes in Module 4 referred to: to the entire course of treatment, or exclusively to the unresectable or metastatic setting. In its comments, the company provided additional data for the relevant subpopulation and clarified that all stages of treatment were included. In both the intervention arm and the control arm of TROPION-Breast01, the majority of patients received anthracyclines and/or taxanes as adjuvant therapies (61.9% versus 63.6%, based on patients in the relevant subpopulation). 20.6% versus 23.6% of patients in the relevant subpopulation received these treatments during the neoadjuvant treatment phase. The company did not provide data split by drug class (taxanes/anthracyclines) or on the extent to which these substances were used in the advanced setting.

As described in dossier assessment A25-69, the treatment options available for the relevant subpopulation in the control arm of the TROPION-Breast01 study (capecitabine or eribulin or vinorelbine) should only be used if prior therapy with anthracyclines and taxanes has already been given or these treatments are unsuitable for the patients, according to the applicable summaries of product characteristics (SmPCs) [4-6]. The guideline of the Gynaecological

Oncology Group (AGO) also refers to the marketing authorization of the respective drugs with regard to prior treatment [7]. The company's dossier 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 reasons why the remaining patients did not receive anthracyclines and/or taxanes – such as unsuitability or patient request – remained unknown after the company's comments. As already described in dossier assessment A25-69, it could therefore not be ruled out that treatment with an anthracycline and/or a taxane instead of the study medication of the control arm (capecitabine or eribulin or vinorelbine) would have been an option for a relevant proportion of patients in the TROPION-Breast01 study. This uncertainty continued to limit the certainty of conclusions from the study results (see Section 2.4.1).

2.2 Data on treatment duration and observation period

Table 1 shows the data submitted by the company as part of the commenting procedure regarding the treatment duration for patients in the relevant subpopulation and the observation period for individual outcomes.

Table 1: 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[b] = 63**	**Treatment of physician's choice[a]** **N[b] = 55**
TROPION-Breast01		
Treatment duration [months]		
Median [min; max]	6.3 [1.4; 20.9]	3.7 [0.2; 22.1]
Mean (SD)	8.0 (5.5)	5.1 (5.0)
Observation period [months]		
Overall survival[c]		
Median [min; max]	17.4 [3; 32]	14.1 [1; 28]
Mean (SD)	16.2 (6.8)	15.4 (7.8)
EORTC QLQ-C30[d]		
Median [min; max]	7.8 [0; 22]	4.1 [0; 18]
Mean (SD)	7.9 (5.1)	5.4 (4.5)
PGI-S[d]		
Median [min; max]	8.0 [1; 22]	4.2 [0; 18]
Mean (SD)	8.0 (5.0)	5.4 (4.6)
EQ-5D VAS[d]		
Median [min; max]	8.0 [1; 22]	4.2 [0; 18]
Mean (SD)	8.0 (5.0)	5.3 (4.5)
Side effects[e]		
Median [min; max]	6.3 [1; 21]	4.1 [1; 22]
Mean (SD)	8.0 (5.5)	5.4 (5.0)

a. Capecitabine or eribulin or vinorelbine.
b. Number of patients in the relevant subpopulation; values that are based on other patient numbers are marked in the corresponding line.
c. Information on how the observation period was calculated is not available.
d. The data are based on the following patient numbers in the intervention arm versus the control arm: EORTC QLQ-C30: 53 vs. 45; PGI-S: 52 vs. 44; EQ-5D VAS: 52 vs. 44.
e. It is assumed that the PRO-CTCAE and ILD/pneumonitis outcomes are not included in the data, as the planned follow-up periods for these outcomes differ from those for the other side effect outcomes.

EORTC: European Organisation for Research and Treatment of Cancer; ILD: interstitial lung disease; max: maximum; min: minimum; N: number of patients in the relevant subpopulation; 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; VAS: visual analogue scale

The median treatment duration of patients in the relevant subpopulation was notably longer in the intervention arm of the TROPION-Breast01 study than in the control arm (6.3 months versus 3.7 months).

It was also shown that the median observation periods for the outcomes in the categories of morbidity, health-related quality of life and side effects, which were systematically shortened, were notably shorter than those for the overall survival outcome. Furthermore, the median observation periods of the individual outcomes were longer in the intervention arm than in the control arm.

The subsequently submitted information on the duration of treatment and observation was taken into account when selecting the appropriate effect measure to determine the added benefit for the outcomes in the side effects category. This showed that the observation periods of side effects varied between the study arms (see Table 1). The hazard ratio was therefore the appropriate effect measure in this situation and was taken into account in this assessment when evaluating the added benefit (see Sections 2.4.2 and 2.5.1).

2.3 Subsequent therapies

Table 2 shows the information submitted by the company as part of the commenting procedure regarding the subsequent antineoplastic therapies received by patients in the relevant subpopulation.

Table 2: Information on subsequent antineoplastic therapies – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study Drug class Drug	Patients with subsequent therapy, n (%)	
	datopotamab deruxtecan N = 63	Treatment of physician's choice[a] N = 55
TROPION-Breast01		
Total	50 (79.4)	48 (87.3)
Anthracyclines and related substances	14 (22.2)	14 (25.5)
Doxorubicin	7 (11.1)	6 (10.9)
Epirubicin	2 (3.2)	1 (1.8)
Epirubicin hydrochloride	1 (1.6)	1 (1.8)
Liposomal doxorubicin	0	3 (5.5)
Liposomal doxorubicin hydrochloride	0	1 (1.8)
Mitoxantrone	1 (1.6)	1 (1.8)
Pegylated liposomal doxorubicin	1 (1.6)	1 (1.8)
Pegylated liposomal doxorubicin hydrochloride	2 (3.2)	0
Anti-oestrogens	7 (11.1)	4 (7.3)
Elacestrant	2 (3.2)	1 (1.8)
Fulvestrant	6 (9.5)	4 (7.3)
Toremifene citrate	2 (3.2)	0

Table 2: Information on subsequent antineoplastic therapies – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study	**Patients with subsequent therapy, n (%)**	
Drug class **Drug**	**datopotamab deruxtecan** **N = 63**	**Treatment of physician's choice[a]** **N = 55**
Antineoplastic agents	2 (3.2)	0
Investigational antineoplastic drugs	2 (3.2)	0
Aromatase inhibitors	8 (12.7)	10 (18.2)
Anastrozole	0	1 (1.8)
Exemestane	4 (6.3)	6 (10.9)
Letrozole	4 (6.3)	4 (7.3)
Combinations of antineoplastic agents	1 (1.6)	0
Cyclophosphamide; doxorubicin	1 (1.6)	0
CDK inhibitors	8 (12.7)	7 (12.7)
Abemaciclib	2 (3.2)	1 (1.8)
Dalpiciclib	0	2 (3.6)
Palbociclib	2 (3.2)	2 (3.6)
Pf07104091	1 (1.6)	0
Ribociclib	3 (4.8)	2 (3.6)
Detoxification agents for treatment with cytostatics	1 (1.6)	0
Gimeracil	1 (1.6)	0
Oteracil potassium	1 (1.6)	0
Folic acid analogues	1 (1.6)	1 (1.8)
Methotrexate	0	1 (1.8)
Methotrexate sodium	1 (1.6)	0
HER2 inhibitors	4 (6.3)	11 (20.0)
Pertuzumab	0	1 (1.8)
Trastuzumab	0	1 (1.8)
Trastuzumab deruxtecan	4 (6.3)	7 (12.7)
Trastuzumab deruxtecan Nxki	0	3 (5.5)
mTOR kinase inhibitors	4 (6.3)	5 (9.1)
Everolimus	3 (4.8)	5 (9.1)
Sirolimus	1 (1.6)	0
Nitrogen mustard analogues	8 (12.7)	8 (14.5)
Cyclophosphamide	7 (11.1)	8 (14.5)
Cyclophosphamide; Panax ginseng total ginsenoside extract	1 (1.6)	0

Table 2: Information on subsequent antineoplastic therapies – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study	**Patients with subsequent therapy, n (%)**	
Drug class **Drug**	**datopotamab deruxtecan** **N = 63**	**Treatment of physician's choice[a]** **N = 55**
Other antineoplastic agents	17 (27.0)	9 (16.4)
eribulin	14 (22.2)	5 (9.1)
Eribulin mesilate	3 (4.80)	2 (3.6)
Other antineoplastic agents	0	1 (1.8)
Zotatifin	1 (1.6)	1 (1.8)
Other cytotoxic antibiotics	1 (1.6)	1 (1.8)
Mitomycin	1 (1.6)	1 (1.8)
Other drugs affecting bone structure and mineralization	1 (1.6)	0
Denosumab	1 (1.6)	0
Other monoclonal antibodies and antibody drug conjugates	4 (6.3)	8 (14.5)
AZD 8205	0	2 (3.6)
Py 314	1 (1.6)	0
Sacituzumab govitecan	3 (4.8)	4 (7.3)
Sacituzumab govitecan Hziy	0	2 (3.6)
PD-1/PD-L1 inhibitors	2 (3.2)	1 (1.8)
Camrelizumab	1 (1.6)	0
Pembrolizumab	1 (1.6)	1 (1.8)
PI3K inhibitors	2 (3.2)	0
Alpelisib	2 (3.2)	0
Platinum compounds	11 (17.5)	7 (12.7)
Carboplatin	7 (11.1)	5 (9.1)
Cisplatin	4 (6.3)	2 (3.6)
PARP inhibitors	2 (3.2)	0
Olaparib	2 (3.2)	0
Progestogens	0	1 (1.8)
Megestrol	0	1 (1.8)
Pyrimidine analogues	22 (34.9)	14 (25.5)
Capecitabine	13 (20.6)	7 (12.7)
Gemcitabine	9 (14.3)	6 (10.9)
Gemcitabine hydrochloride	1 (1.6)	0
Gimeracil; oteracil potassium; tegafur	1 (1.6)	2 (3.6)
Tegafur	1 (1.6)	0

Table 2: Information on subsequent antineoplastic therapies – RCT, direct comparison: datopotamab deruxtecan vs. chemotherapy of physician's choice[a] (multipage table)

Study	**Patients with subsequent therapy, n (%)**	
Drug class **Drug**	**datopotamab deruxtecan** **N = 63**	**Treatment of physician's choice[a]** **N = 55**
Taxanes	12 (19.0)	11 (20.0)
Docetaxel	0	1 (1.8)
Paclitaxel	9 (14.3)	9 (16.4)
Paclitaxel, albumin-bound nanoparticles	3 (4.8)	2 (3.6)
VEGFR tyrosine kinase inhibitors	1 (1.6)	0
Rivoceranib	1 (1.6)	0
VEGF/VEGFR inhibitors	1 (1.6)	0
Bevacizumab	1 (1.6)	0
Vinca alkaloids and analogues	2 (3.2)	6 (10.9)
Vinorelbine	2 (3.2)	4 (7.3)
Vinorelbine tartrate	0	2 (3.6)

a. Capecitabine or eribulin or vinorelbine.

CDK: cyclin-dependent kinase; HER2: human epidermal growth factor receptor 2; mTOR: mammalian target of rapamycin; n: number of patients with subsequent therapy; N: number of patients in the relevant subpopulation; PARP: poly(adenosine diphosphate-ribose) polymerase; PD-1: programmed cell death 1; PD-L1: programmed death-ligand 1; PI3K: phosphatidylinositol-3-kinase; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

As described in dossier assessment A25-69, subsequent antineoplastic therapies were permitted without restriction in both study arms of the TROPION-Breast01 study, and, according to the company, were selected by the investigator in accordance with the guidelines.

As Module 4 did not contain any data on subsequent therapies in the relevant subpopulation, the proportion of patients receiving subsequent therapy (more than 90%) presented in dossier assessment A25-69 was based on the data for the outcome 'time to first subsequent therapy'. This outcome also included deaths. In the commenting procedure, the company submitted suitable data showing that the majority of patients in both the intervention and control arm received subsequent therapy (79.4% vs. 87.3%). The proportion in relation to patients with disease progression was unclear, as the information on disease progression in the company's dossier related solely to the first data cut, which was not used for the assessment. However, the proportions of patients with subsequent therapy shown here appeared plausible. In both study arms, the most common subsequent therapies were chemotherapies; endocrine therapies, cyclin-dependent kinase (CDK) inhibitors and antibody-drug conjugates were also used.

The current guidelines from AGO and the European Society for Medical Oncology (ESMO) recommend treatment with an antibody-drug conjugate or chemotherapy, depending on previous therapies [8,9]. As described in dossier assessment A25-69, the G-BA determined an indication of considerable added benefit for sacituzumab govitecan versus chemotherapy as the ACT 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 [10]. For patients in the therapeutic indication in question, it was therefore assumed that, if sacituzumab govitecan is suitable, it represents an appropriate option for follow-up therapy that is superior to chemotherapy. However, in the relevant subpopulation, only 4.8% of patients in the intervention arm and 10.9% in the control arm received sacituzumab govitecan as subsequent therapy.

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

In this late line of treatment, it is assumed that the choice of subsequent therapy is influenced by factors such as comorbidities, prior treatments and side effects. In such a situation, it is difficult to assess which follow-up therapy is most suitable for each individual patient. Nevertheless, given the uncertainties described above, it was assumed that a relevant proportion of patients received subsequent therapy that was potentially suboptimal. This led to a reduced certainty of conclusions for the overall survival outcome, which was substantially influenced by the subsequent therapies administered following disease progression (see Section 2.4.1).

2.4 Results on added benefit

2.4.1 Risk of bias

Compared with dossier assessment A25-69, the assessment remained unchanged for both the cross-outcome and the outcome-specific risk of bias in the TROPION-Breast01 study, with the exception of the overall survival outcome. As the company provided additional information on subsequent therapies for patients in the relevant subpopulation during the commenting procedure, the outcome-specific risk of bias for the overall survival outcome was rated as low; however, the certainty of conclusions for this outcome was nevertheless limited due to deficiencies in the use of subsequent therapies in both study arms (see below).

Assessment of the certainty of conclusions

Regardless of the assessment of the risk of bias, the certainty of conclusions for the study results remained limited due to the ambiguities regarding prior treatment with anthracyclines

and/or taxanes (see Section 2.1). For the overall survival outcome, the uncertainties regarding the subsequent therapies described in Section 2.3 also contributed to the limited certainty.

2.4.2 Results

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 were presented and described in dossier assessment A25-69 [1]. Based on the available information, as per assessment A25-69 still at most hints, e.g. of an added benefit, could be determined for all outcomes (for reasoning, see Section 2.4.1).

Due to the lack of information on treatment duration and observation period, A25-69 considered both the results on the relative risk and the results on the hazard ratio in the extent of the added benefit for the outcome 'decreased appetite' (adverse events [AEs]), and no greater or lesser harm was determined for this outcome. The information subsequently provided by the company in the commenting procedure showed that the hazard ratio was the appropriate effect measure in this scenario (see Section 2.2). An analysis of the hazard ratio showed a statistically significant difference in favour of datopotamab deruxtecan compared with chemotherapy of physician's choice for this outcome (see dossier assessment A25-69 [1]). Thus, in deviation from dossier assessment A25-69, there is a hint of lesser harm of datopotamab deruxtecan in comparison with chemotherapy of physician's choice for the outcome decreased appetite (AEs). Furthermore, given the clarification of the appropriate effect measure in the current data scenario, it was now also possible to clearly quantify the extent of the outcome severe AEs (see Section 2.5.1).

2.5 Probability and extent of added benefit

2.5.1 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 dossier assessment A25-69 and in Section 2.4.2 (see Table 3).

Table 3: 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: major
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 3: 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][e]; 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][e]; 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 CI_u < 0.80 Lesser harm, extent: considerable
Neutropenia (severe AEs)	NA vs. NA HR: 0.04 [0.00; 0.28][f]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: major

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 are made with different limits based on the upper limit of confidence interval (CI_u).
d. For justification see dossier assessment A25-69 [1].
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. Calculation using the Firth correction (subsequently submitted by the company as part of the commenting procedure)

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; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 4 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 4: 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: major, including ▫ Neutropenia: hint of lesser harm – extent: major	–
Non-serious/non-severe side effects ▪ Decreased appetite: hint of lesser harm – extent: considerable	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	

Overall, both positive and negative effects of datopotamab deruxtecan in comparison with chemotherapy of physician's choice were shown for the relevant subpopulation of the TROPION-Breast01 study.

On the positive side, there is a hint of lesser harm of a major extent in the category of serious/severe side effects, in particular for the overall rate of severe AEs. In addition, there are both positive and negative effects in individual specific AEs on gastrointestinal events, which fall into the category of non-serious/non-severe side effects. All these results refer exclusively to the shortened period up to 28 days after discontinuation or termination of study treatment.

Some of the uncertainties addressed in dossier assessment A25-69 could be resolved based on the data subsequently submitted by the company in the commenting procedure, in particular regarding treatment duration and observation period as well as subsequent therapies for patients in the relevant subpopulation. However, uncertainties remained regarding the prior therapy with anthracyclines and/or taxanes (see Section 2.1). Furthermore, as described in dossier assessment A25-69, no conclusions could be drawn regarding morbidity and health-related quality of life of patients in the relevant subpopulation, as no suitable data were available for these outcome categories. In addition, the certainty of conclusions regarding the overall survival outcome remained limited.

In the given situation, weighing up the positive and negative effects was only possible to a limited extent due to the uncertainties described and the shortened observation periods for all outcomes included in the overall conclusion on the added benefit. However, since the advantages of major extent in the category of serious/severe side effects clearly outweigh the

disadvantages of considerable extent in the category of non-serious/non-severe side effects, the advantage of datopotamab in comparison with the ACT was not entirely called into question.

In summary, there is therefore a hint of a non-quantifiable 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.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure altered the conclusion on the added benefit of datopotamab deruxtecan from dossier assessment A25-69 for research question 1: There is a hint of a non-quantifiable 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.

For research question 2 and 3, there was no change in comparison with dossier assessment A25-69.

Table 5 below shows the result of the benefit assessment of datopotamab deruxtecan, taking into account dossier assessment A25-69 and this addendum.

Table 5: 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)	Hint of a non-quantifiable added benefit [e]
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-) [11,12]. 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.
e. The TrOPION-Breast01 study included patients with an ECOG PS of 0 or 1. (In the relevant subpopulation, 2 patients in the intervention arm vs. 1 patient in the control arm had an ECOG PS of 2.) It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; ISH: in situ hybridization

The G-BA decides on the added benefit.

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