IQWiG Reports – Commission No. A22-81

Trastuzumab deruxtecan (breast cancer, after ≥ 2 prior therapies) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Trastuzumab-Deruxtecan (Mammakarzinom, nach ≥ 2 Vortherapien) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 October 2022). 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
Trastuzumab deruxtecan (breast cancer, after ≥ 2 prior therapies) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
29 July 2022

Internal Commission No.
A22-81

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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

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

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Keywords: Trastuzumab, Breast Neoplasms, Benefit Assessment

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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
PFS	progression-free survival
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug trastuzumab deruxtecan. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 July 2022.

Research question

The aim of the present report is the assessment of the added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice as appropriate comparator therapy (ACT) in adults with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have previously received 2 or more HER2-targeted therapies.

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

Table 2: Research question of the benefit assessment of trastuzumab deruxtecan

Therapeutic indication	**ACT**[a]
Adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies	Treatment of physician's choice[b]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the following treatment options are considered equally suitable comparators in the context of treatment of physician's choice: lapatinib in combination with capecitabine, trastuzumab in combination with lapatinib (only for patients with hormone receptor-negative breast cancer) and trastuzumab in combination with capecitabine.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The company generally followed the specification of the G-BA by designating treatment of physician's choice as the ACT. In addition to the options that are considered suitable comparators according to the G-BA, the company also took into account trastuzumab emtansine (only for patients who have not yet received trastuzumab emtansine in their pretreatment) and the combination of tucatinib, trastuzumab and capecitabine as further options. The present assessment is conducted in comparison with the ACT specified by the G-BA. Only the drug combinations specified by the G-BA as suitable comparators are taken into account.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Direct comparison

From its information retrieval, the company identified the randomized controlled trial (RCT) DESTINY-Breast02 conducted by the company for the direct comparison of trastuzumab deruxtecan against treatment of physician's choice. In agreement with the company, the completeness check did not identify any other RCT of direct comparison apart from the DESTINY-Breast02 study.

According to the information provided by the company in Module 4 B of the dossier, no analyses of the DESTINY-Breast02 study were available at the time of dossier submission. The first data cut-off of the study took place on 30 June 2022, so that, according to the company, the data could not be used for the present benefit dossier. However, the company pointed out in Module 4 B of the dossier that data from the DESTINY-Breast02 study would be available soon.

Further investigations

The company did not include any studies for a direct comparison. It therefore carried out an information retrieval for further investigations, and identified, in addition to one uncontrolled study on the intervention side, 8 studies on the comparator side, from which it used individual arms in each case.

Evidence provided by the company

For its assessment, the company conducted a descriptive comparison of the results of the uncontrolled DESTINY-Breast01 study on trastuzumab deruxtecan against the results of individual arms from the studies on the ACT for the outcomes of overall survival and progression-free survival (PFS). In addition to the descriptive comparison of the results for these outcomes, the company's assessment also took into account the results for other outcomes under treatment with trastuzumab deruxtecan from the DESTINY-Breast01 study. For these outcomes, the company did not present an evaluation of results from the studies on the ACT in Module 4 B of the dossier.

For the outcomes of overall survival and PFS, in addition to the descriptive comparison of results from the DESTINY-Breast01 study and the results of individual arms from the studies on the ACT, the company also presented matching-adjusted indirect comparison (MAIC) analyses to compare these results. According to the company, it used these analyses to support its assessment of the added benefit.

The assessment of the company was thus largely based on the consideration of single-arm data on treatment with trastuzumab deruxtecan from the DESTINY-Breast01 study and the purely descriptive comparison of these data with the data from individual arms of studies on the ACT for selected outcomes.

Assessment of the evidence presented by the company

The analyses presented by the company are unsuitable for the benefit assessment of trastuzumab deruxtecan in comparison with the ACT.

The consideration of single-arm data on treatment with trastuzumab deruxtecan from the DESTINY-Breast01 study allows no comparison with the ACT and is therefore not suitable for the derivation of an added benefit. The purely descriptive comparison of the data from the DESTINY-Breast01 study with the data from individual arms of studies on the ACT for selected outcomes is also not suitable for the derivation of an added benefit.

In addition, the supportive MAIC analyses presented by the company to compare the results of the DESTINY-Breast01 study with the results of individual arms from the studies on the ACT are also not usable for the benefit assessment.

MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment. In case of non-randomized comparisons without a common comparator, meaningful approaches towards confounder adjustment are usually only those that – unlike the MAIC analysis – involve the use of individual patient data. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data. Hence, the results presented by the company on the basis of MAIC analyses are unsuitable for assessing the added benefit of trastuzumab deruxtecan. Furthermore, the company's approach of carrying out the MAIC analyses only for individual outcomes is not appropriate.

Irrespective of the company's approach, in the present scenario of indirect comparison without a common comparator, there are no effects for which it can be ruled out with sufficient certainty that they are based solely on systematic bias due to confounders.

Irrespective of these deficiencies, it is not possible to adequately check on the basis of the available information whether the studies on the comparator side correspond to the present research question at all. Due to insufficient information on pretreatment, it remains unclear in particular whether the entire study population is in the treatment situation of the present therapeutic indication or whether only a subpopulation of the studies fulfils this requirement.

Results on added benefit

No suitable data for the assessment of added benefit in comparison with the ACT are available for assessing trastuzumab deruxtecan in adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies. This results in no hint of an added benefit of trastuzumab 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]

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

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

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies	Treatment of physician's choice[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the following treatment options are considered equally suitable comparators in the context of treatment of physician's choice: lapatinib in combination with capecitabine, trastuzumab in combination with lapatinib (only for patients with hormone receptor-negative breast cancer) and trastuzumab in combination with capecitabine.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report is the assessment of the added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice as ACT in adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies.

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

Table 4: Research question of the benefit assessment of trastuzumab deruxtecan

Therapeutic indication	**ACT**[a]
Adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies	Treatment of physician's choice[b]
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the following treatment options are considered equally suitable comparators in the context of treatment of physician's choice: lapatinib in combination with capecitabine, trastuzumab in combination with lapatinib (only for patients with hormone receptor-negative breast cancer) and trastuzumab in combination with capecitabine. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company generally followed the specification of the G-BA by designating treatment of physician's choice as the ACT. In addition to the options that are considered suitable comparators according to the G-BA, the company also took into account trastuzumab emtansine (only for patients who have not yet received trastuzumab emtansine in their pretreatment) and the combination of tucatinib, trastuzumab and capecitabine as further options. The present assessment is conducted in comparison with the ACT specified by the G-BA. Only the drug combinations specified by the G-BA as suitable comparators are taken into account.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on trastuzumab deruxtecan (status: 8 June 2022)
- bibliographical literature search on trastuzumab deruxtecan (last search on 27 April 2022)
- search in trial registries/trial results databases for studies on trastuzumab deruxtecan (last search on 23 May 2022)
- search on the G-BA website for trastuzumab deruxtecan (last search on 7 June 2022)
- bibliographical literature search on the ACT (last search on 27 April 2022)
- search in trial registries/trial results databases for studies on the ACT (last search on 20 May 2022)
- search on the G-BA website for the ACT (last search on 7 June 2022)

To check the completeness of the study pool:

- search in trial registries for studies on trastuzumab deruxtecan (last search on 9 August 2022); for search strategies, see I Appendix A of the full dossier assessment

Direct comparison

From its information retrieval, the company identified the RCT DESTINY-Breast02 [3,4] conducted by the company for the direct comparison of trastuzumab deruxtecan against treatment of physician's choice. In agreement with the company, the completeness check did not identify any other RCT of direct comparison apart from the DESTINY-Breast02 study.

According to the information provided by the company in Module 4 B of the dossier, no analyses of the DESTINY-Breast02 study were available at the time of dossier submission. The first data cut-off of the study took place on 30 June 2022, so that, according to the company, the data could not be used for the present benefit dossier. However, the company pointed out in Module 4 B of the dossier that data from the DESTINY-Breast02 study would be available soon.

The DESTINY-Breast02 study is an ongoing, open-label, multicentre RCT comparing trastuzumab deruxtecan with treatment of physician's choice. Available options for the treatment of physician's choice in the study are lapatinib in combination with capecitabine or trastuzumab in combination with capecitabine. The decision for one of these combinations had to be made before randomization. The study included adult patients with unresectable or metastatic HER2-positive breast cancer and prior trastuzumab emtansine treatment. According to the inclusion criteria, patients had to have documented radiographic progression of disease during or after the last pretreatment or within 6 months after completion of adjuvant therapy.

In addition, previous capecitabine treatment was not allowed. Based on the information on the study design and the inclusion and exclusion criteria available in the dossier, the DESTINY-Breast02 study is assessed as potentially relevant to the research question of the present benefit assessment. However, without further information on the included patients, for example regarding pretreatment, it is not possible to assess whether the entire study population is relevant for the benefit assessment or only a subpopulation that is in the relevant treatment situation according to the present research question.

Further investigations

The company did not include any studies for a direct comparison. It therefore carried out an information retrieval for further investigations, and identified, in addition to one uncontrolled study on the intervention side, 8 studies on the comparator side, from which it used individual arms in each case. A check of the completeness of the study pool was omitted because the data presented by the company are generally unsuitable for drawing conclusions on the added benefit of trastuzumab deruxtecan for patients in the present therapeutic indication. This is explained below.

Evidence provided by the company

Study with trastuzumab deruxtecan: DESTINY-Breast01

On the intervention side, the company identified the uncontrolled DESTINY-Breast01 study [5]. This study is an ongoing, 2-part study investigating treatment with trastuzumab deruxtecan in adult patients with unresectable or metastatic HER2-positive breast cancer whose disease is resistant or refractory to treatment with trastuzumab emtansine. The study consists of 2 parts. In the randomized first part of the study, different dosages of trastuzumab deruxtecan were compared. In the non-randomized second part, all patients are treated with 5.4 mg/kg body weight trastuzumab deruxtecan, which corresponds to the dosage according to the Summary of Product Characteristics (SPC) [6]. In the dossier, the company presented results from the DESTINY-Breast01 study on patients who were treated with this dosage in the course of the study.

Studies with the appropriate comparator therapy

On the ACT side, the company identified a total of 8 studies, including 4 RCTs (EGF100151 [7], NALA [8], EGF104900 [9], HER2CLIMB [10]), and 4 single-arm studies (Bian 2014 [11], Cetin 2014 [12], Kroep 2010 [13], TRASTYVERE [14]). These studies investigated the different drug combinations specified as suitable comparators by the G-BA. Each of the studies included different patient populations, which, due to different inclusion criteria regarding pretreatment, differed especially with regard to the treatment situations of the included patients.

An overview with details on the included patient populations and the drug combinations used in the studies can be found in Table 6 in I Appendix B of the full dossier assessment.

Analyses presented by the company

For its assessment, the company conducted a descriptive comparison of the results of the DESTINY-Breast01 study on trastuzumab deruxtecan against the results of individual arms from the studies on the ACT for the outcomes of overall survival and PFS. In addition to the descriptive comparison of the results for these outcomes, the company's assessment also took into account the results for tumour response and adverse events under treatment with trastuzumab deruxtecan from the DESTINY-Breast01 study. For these outcomes, the company did not present an evaluation of results from the studies on the ACT in Module 4 B of the dossier.

For the outcomes of overall survival and PFS, in addition to the descriptive comparison of results from the DESTINY-Breast01 study and the results of individual arms from the studies on the ACT, the company also presented MAIC analyses to compare these results. The MAIC analyses for trastuzumab deruxtecan were based on results from individual patient data. For the studies on the ACT options, however, data for the outcomes of overall survival and PFS were generated according to the method of Guyot 2012 [15] from the Kaplan-Meier curves in the publications of the individual studies. If several studies on an ACT option were available, the company additionally conducted meta-analyses based on the MAIC analyses. According to the company, it used the results of the MAIC analyses and of the meta-analyses to support its assessment of the added benefit.

The assessment of the company was thus largely based on the consideration of single-arm data on treatment with trastuzumab deruxtecan from the DESTINY-Breast01 study and the purely descriptive comparison of these data with the data from individual arms of studies on the ACT for selected outcomes.

Assessment of the evidence presented by the company

The analyses presented by the company are unsuitable for the benefit assessment of trastuzumab deruxtecan in comparison with the ACT. This is explained below.

The consideration of single-arm data on treatment with trastuzumab deruxtecan from the DESTINY-Breast01 study allows no comparison with the ACT and is therefore not suitable for the derivation of an added benefit. The purely descriptive comparison of the data from the DESTINY-Breast01 study with the data from individual arms of studies on the ACT for selected outcomes is also not suitable for the derivation of an added benefit.

Comparisons of individual arms of different studies are not suitable for the benefit assessment

The supportive MAIC analyses presented by the company to compare the results of the DESTINY-Breast01 study with the results of individual arms from the studies on the ACT are also not usable for the benefit assessment.

MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment [1]. In case of non-randomized comparisons without a common comparator, meaningful approaches towards confounder adjustment are usually only those that – unlike the MAIC analysis – involve the use of individual patient data [16]. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data. Hence, the results presented by the company on the basis of MAIC analyses are unsuitable for assessing the added benefit of trastuzumab deruxtecan. Furthermore, the company's approach of carrying out the MAIC analyses only for individual outcomes is not appropriate.

Irrespective of the company's approach, in the present scenario of indirect comparison without a common comparator, there are no effects for which it can be ruled out with sufficient certainty that they are based solely on systematic bias due to confounders.

Irrespective of the deficiencies described above, it is not possible to adequately check on the basis of the available information whether the studies on the comparator side correspond to the present research question at all. For the majority of the studies on the ACT options taken into account by the company, it remains unclear whether the entire study population is in the treatment situation of the present therapeutic indication or whether only a subpopulation of the studies fulfils this requirement. In particular, the company did not provide any information on the pretreatment of the included patients with HER2-targeted therapies in Module 4 B of the dossier. For this reason, it is not possible to assess for the majority of the studies whether the respective study population corresponds to the population in the present therapeutic indication. The company did not address this issue in the dossier, but nevertheless used the results of the entire study populations for all studies it considered on the ACT side for its comparative analyses. This approach is not appropriate. From each the studies, only the subpopulation that is in the relevant treatment situation of the present research question should be taken into account.

Furthermore, it is already evident on the basis of the available information for some of the studies on the comparator side that the ACT was not implemented for part of the study population. For example, a high proportion of hormone receptor-positive patients were included in the studies on the therapy option of trastuzumab in combination with lapatinib (EGF104900 study: 49.0%, TRASTYVERE study: 63.5%). However, the G-BA specified this therapy option as suitable comparator only for hormone receptor-negative patients. This means that the ACT was not implemented for a large proportion of patients in the studies EGF104900 and TRASTYVERE.

I 4 Results on added benefit

No suitable data for the assessment of added benefit in comparison with the ACT are available for assessing trastuzumab deruxtecan in adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies. This results in no hint of an added benefit of trastuzumab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of trastuzumab deruxtecan in comparison with the ACT is summarized in Table 5.

Table 5: Trastuzumab deruxtecan – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies	Treatment of physician's choice[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the following treatment options are considered equally suitable comparators in the context of treatment of physician's choice: lapatinib in combination with capecitabine, trastuzumab in combination with lapatinib (only for patients with hormone receptor-negative breast cancer) and trastuzumab in combination with capecitabine.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable, at least considerable added benefit in comparison with the treatment options in the context of treatment of physician's choice specified by the G-BA.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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