Trastuzumab deruxtecan (gastric or gastroesophageal junction adenocarcinoma)

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

EXTRACT

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[1] Translation of Sections I 1 to I 7 of the dossier assessment *Trastuzumab-Deruxtecan (Adenokarzinom des Magens oder des gastroösophagealen Übergangs) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, Germany

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.

IQWiG employees involved in the dossier assessment

- Philip Böhler
- Nadia Abu Rajab
- Lars Beckmann
- Merlin Bittlinger
- Tobias Effertz
- Katrin Nink
- Annika Orland
- Regine Potthast

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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
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GEJ	gastroesophageal junction
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
ISH	in situ hybridization
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)

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 3 February 2023.

Research question

The aim of the present report is to assess the added benefit of trastuzumab deruxtecan compared with the appropriate comparator therapy (ACT) in adults with advanced human epidermal growth factor receptor 2 (HER2) positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received prior trastuzumab-based therapy.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

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

Research question	Therapeutic indication	ACT[a]
1	Adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received 1 prior trastuzumab-based regimen in first-line therapy[b]	Treatment of physician's choice[c]
2	Adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received at least 2 prior regimens, including trastuzumab[b]	Trifluridine/tipiracil

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the planned therapeutic indication presumably includes patients in an inoperable, locally advanced or metastatic stage of the disease.
c. According to the G-BA, guidelines recommend systemic therapy in the present treatment situation. Based on their approval status, options for this purpose are the drug ramucirumab or the drug combination ramucirumab plus paclitaxel. The drugs irinotecan, docetaxel, and paclitaxel (monotherapy) have not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indications and those recommended in guidelines. According to the G-BA, the following treatment options are deemed suitable comparators for treatment of physician's choice: irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel. According to the G-BA, added benefit can be assessed versus 1 of the above treatment options within the framework of a single-comparator study.

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

In this benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- research question 1: patients in second-line therapy

- research question 2: patients in third-line and higher lines of therapy

In its dossier, the company refers to 2 separate consultations from 2021, where the G-BA specified an ACT for the patient population with trastuzumab-based prior therapy (see research question 1) and another for the patient population with at least 2 prior therapies, including anti-HER2 therapy (see research question 2). The respective ACTs correspond to those specified by the G-BA for the 2 research questions of the present assessment after dossier submission (February 2023).

For research question 1 (patients in second-line therapy), the ACT defined by the company is treatment of physician's choice, including irinotecan, docetaxel, paclitaxel as well as ramucirumab in combination with paclitaxel. This corresponds to the G-BA's specification for this research question.

For research question 2 (patients in third line or later lines of therapy), the company defined the ACT as treatment of physician's choice, including irinotecan, docetaxel, paclitaxel, ramucirumab in combination with paclitaxel as well as trifluridine/tipiracil. This departs from the specification by the G-BA, which included only trifluridine/tipiracil as the ACT for this research question. The company's departure from the ACT specified by the G-BA is not appropriate. This is explained below.

Company's rationale for departing from the ACT specified by the G-BA for research question 2

From the company's point of view, the ACT for the therapeutic indication of research question 2 is treatment of physician's choice, which includes as treatment options not only trifluridine/tipiracil but also irinotecan, docetaxel, paclitaxel, or ramucirumab in combination with paclitaxel. To justify its position, the company argues that no targeted HER2-specific standard therapy currently exists for the treatment of HER2-positive gastric and GEJ adenocarcinoma in second-line and later lines of treatment. The company concludes that non-HER2-targeted therapies must be resorted to (irinotecan, docetaxel, paclitaxel as well as ramucirumab in combination with paclitaxel and, for third-line and later lines of therapy, additionally trifluridine/tipiracil). The company deems treatment options which were not used in the patient's 2 or more prior therapies to be of value in the subsequent line of therapy. The company bases this view on various studies, particularly on the use of irinotecan in third-line or later therapies, the opinion of professional societies regarding the specification of the ACT, and a market research analysis from the year 2022.

Company's reasoning unsuitable for justifying the deviation

The information submitted by the company does not allow deducing that irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel can be deemed ACTs alongside trifluridine/tipiracil in the present research question 2. Regarding the studies cited

by the company for irinotecan, the criteria according to which the company chose its sources are also unclear. In line with the recommendations given in the opinion of the professional societies, current guidelines recommend trifluridine/tipiracil as a priority treatment option, while other drugs such as irinotecan or taxanes are mentioned as lower-priority options. Overall, the company's arguments are unsuitable for justifying a departure from the ACT specified by the G-BA.

This assessment was conducted for both research questions separately, each in comparison with the ACT specified by the G-BA. This departs from the approach used by the company, which derived added benefit compared to the ACTs specified by the company and did so for the entire target population, without drawing separate conclusions for the respective subpopulations under research questions 1 and 2.

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

Study pool

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of trastuzumab deruxtecan in comparison with the ACT.

In departure from this, the company used the results of the randomized controlled trial (RCT DESTINY-Gastric01 for comparing trastuzumab deruxtecan versus treatment of physician's choice as well as the results of the single-arm DESTINY-Gastric02 study for its assessment.

Both studies presented by the company are unsuitable for drawing conclusions on the added benefit of trastuzumab deruxtecan compared to the ACT for the patients of research questions 1 and/or 2. This is explained below for each research question.

In general, it must be noted that the company draws conclusions on added benefit for the entire target population on the basis of both studies. The company does not distinguish between research questions 1 and 2.

Research question 1: patients in second-line therapy

DESTINY-Gastric01 and DESTINY-Gastric02 studies presented by the company

The DESTINY-Gastric01 study is a multicentre, randomized, open-label, active control phase II study comparing trastuzumab deruxtecan with treatment of physician's choice, selecting from irinotecan or paclitaxel. It included patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had received at least 2 prior treatment regimens including trastuzumab.

The DESTINY-Gastric02 study is a phase II, multicentre, non-controlled, open-label trial of trastuzumab deruxtecan in patients with unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma who had disease progression during or after first-line trastuzumab-based therapy. A total of 79 patients were enrolled in the study. The study's primary outcome was overall response. Further outcomes include outcomes on mortality, health-related quality of life, and adverse events.

Studies presented by the company unsuitable for assessing added benefit

The DESTINY-Gastric01 study enrols patients who have already received at least 2 previous treatment regimens including trastuzumab and thus does not include any patients relevant for research question 1 (patients in second-line therapy).

The DESTINY-Gastric02 study, which the company used as supplementary information to derive added benefit, is a single-arm study which does not allow a comparison with the ACT specified by the G-BA.

Both studies are therefore unsuitable for drawing conclusions on the added benefit of trastuzumab deruxtecan compared to the ACT for patients in second-line therapy.

Results on added benefit

No suitable data are available to assess the added benefit of trastuzumab deruxtecan compared with treatment of physician's choice in adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received 1 prior trastuzumab-based regimen in first-line therapy. This results in no hint of added benefit of trastuzumab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: patients in third-line and higher lines of therapy

DESTINY-Gastric01 and DESTINY-Gastric02 studies presented by the company

For this research question, the company likewise used the results of the DESTINY-Gastric01 RCT comparing trastuzumab deruxtecan versus treatment of physician's choice as well as the results of the single-arm DESTINY-Gastric02 study.

The results of DESTINY-Gastric01 are unsuitable for the present benefit assessment because the study failed to implement the ACT specified by the G-BA (see section below).

The DESTINY-Gastric02 study, which the company used as supplementary information to derive added benefit is a single-arm study and therefore does not allow a comparison with the ACT specified by the G-BA.

Failure to implement the ACT

The DESTINY-Gastric01 study presented by the company is unsuitable for assessing the added benefit of trastuzumab deruxtecan in comparison with the ACT. This is because rather than the study implementing the ACT specified by the G-BA, trifluridine/tipiracil, comparator arm participants received treatment of physician's choice, selecting from irinotecan or paclitaxel.

The company nevertheless used the DESTINY-Gastric01 study to derive added benefit for trastuzumab deruxtecan. From the company's point of view, the ACT for the therapeutic indication of research question 2 is treatment of physician's choice, which includes the options of trifluridine/tipiracil as well as irinotecan, docetaxel, paclitaxel, or ramucirumab in combination with paclitaxel.

However, the company does not provide any information to justify its deviation from the ACT specified by the G-BA. The ACT specified by the G-BA was not implemented in the DESTINY-Gastric01 study. Therefore, this study is unsuitable for deriving added benefit of trastuzumab deruxtecan versus trifluridine/tipiracil for research question 2.

Results on added benefit

No suitable data are available to assess the added benefit of trastuzumab deruxtecan compared with trifluridine/tipiracil in adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have already received at least 2 prior treatment regimens including trastuzumab. This results in no hint of an added benefit of trastuzumab deruxtecan in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

Overall conclusion on added benefit

Table 3 summarizes the result of the assessment of added benefit of trastuzumab deruxtecan in comparison with the respective ACT.

Table 3: Research questions of the benefit assessment of trastuzumab deruxtecan

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit[b]
1	Adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received 1 prior trastuzumab-based regimen in first-line therapy[c]	Treatment of physician's choice[d]	Added benefit not proven
2	Adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received at least 2 prior regimens, including trastuzumab[c]	Trifluridine/tipiracil	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. 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].
c. According to the G-BA, the planned therapeutic indication presumably includes patients in an inoperable, locally advanced or metastatic stage of the disease.
d. According to the G-BA, guidelines recommend systemic therapy in the present treatment situation. Based on their approval status, options for this purpose are the drug ramucirumab or the drug combination ramucirumab plus paclitaxel. The drugs irinotecan, docetaxel, and paclitaxel (monotherapy) have not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indications and those recommended in guidelines. According to the G-BA, the following treatment options are deemed suitable comparators for treatment of physician's choice: irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel. According to the G-BA, added benefit can be assessed versus 1 of the above treatment options within the framework of a single-comparator study.

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of trastuzumab deruxtecan compared with the ACT in adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received prior trastuzumab-based therapy.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

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

Research question	Therapeutic indication	ACT[a]
1	Adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received 1 prior trastuzumab-based regimen in first-line therapy[b]	Treatment of physician's choice[c]
2	Adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received at least 2 prior regimens, including trastuzumab[b]	Trifluridine/tipiracil

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the planned therapeutic indication presumably includes patients in an inoperable, locally advanced or metastatic stage of the disease.
c. According to the G-BA, guidelines recommend systemic therapy in the present treatment situation. Based on their approval status, options for this purpose are the drug ramucirumab or the drug combination ramucirumab plus paclitaxel. The drugs irinotecan, docetaxel, and paclitaxel (monotherapy) have not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. According to the G-BA, the following treatment options are deemed suitable comparators for treatment of physician's choice: irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel. According to the G-BA, added benefit can be assessed versus 1 of the above treatment options within the framework of a single-comparator study.

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

In this benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- research question 1: patients in second-line therapy
- research question 2: patients in third-line and higher lines of therapy

In its dossier, the company refers to 2 separate consultations from 2021 [3,4], in which the G-BA specified an ACT for the patient population with trastuzumab-based prior therapy (research question 1) and another for the patient population with at least 2 prior therapies including anti-HER2 therapy (research question 2). The respective ACTs correspond to those specified by the G-BA for the 2 questions of the present assessment after dossier submission (February 2023 [5]) (see Table 4). In the present assessment, added benefit is evaluated in comparison with the ACT presented in Table 4.

For research question 1 (patients in second-line therapy), the ACT defined by the company is treatment of physician's choice, including irinotecan, docetaxel, paclitaxel as well as ramucirumab in combination with paclitaxel. This corresponds to the G-BA's specification for this research question.

For research question 2 (patients in third line or later lines of therapy), the company defined the ACT of treatment of physician's choice, including irinotecan, docetaxel, paclitaxel, ramucirumab in combination with paclitaxel as well as trifluridine/tipiracil. This departs from the specification by the G-BA, which included only trifluridine/tipiracil as the ACT for this research question. The company's departure from the ACTs specified by the G-BA is not appropriate. This is explained below.

Company's rationale for departing from the ACT specified by the G-BA for research question 2

From the company's point of view, the ACT for the therapeutic indication of research question 2 is treatment of physician's choice, which includes as treatment options not only trifluridine/tipiracil but also irinotecan, docetaxel, paclitaxel, or ramucirumab in combination with paclitaxel. To justify its position, the company argues that no targeted HER2-specific standard therapy currently exists for the treatment of HER2-positive gastric and GEJ adenocarcinoma in second-line and later lines of treatment. The company concludes that non-HER2-targeted therapies must be resorted to (irinotecan, docetaxel, paclitaxel as well as ramucirumab in combination with paclitaxel and, for third-line and later lines of therapy, additionally trifluridine/tipiracil). The company deems treatment options which were not used in the patient's 2 or more prior therapies to be of value in the subsequent line of therapy. In the company's view, this conclusion can be derived from the Shitara 2018 study [6] comparing trifluridine/tipiracil in combination with best supportive care (BSC) versus placebo in combination with BSC, where few patients reportedly exhibited remission and received ramucirumab-containing therapies, among others, after the administration of trifluridine/tipiracil. Citing several studies [7-11], the company deems evidence for use in third-line and later lines of therapy to be available not only for trifluridine/tipiracil, but also particularly for irinotecan.

The company also refers to the opinion of professional societies on the specification of the ACT [5,12]. This opinion recommends individualized treatment of physician's choice, taking into account trifluridine/tipiracil, with the treatment decision depending on comorbidities, general health, and patient wishes. Furthermore, the company cites a market research analysis [13] in which the prescribing behaviour of 60 physicians from various oncology specialties in different regions of Germany was recorded in the period March 2022 to May 2022. From this analysis, the company deduces that, in German routine care, trifluridine/tipiracil is not the only treatment option for patients in third-line or later lines of

therapy for metastatic HER2-positive gastric carcinoma, but that the predominant treatments currently are ramucirumab in combination with paclitaxel and irinotecan as well as irinotecan monotherapy or irinotecan in combination with fluorouracil.

Company's reasoning unsuitable for justifying the deviation

On the basis of the information provided by the company, it is impossible to deduce that alongside trifluridine/tipiracil, irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel are ACT options in the present research question 2. Furthermore, the criteria the company used to select its sources are unclear regarding the studies it cited for irinotecan [7-11]. Consistent with the recommendations issued in the opinion of the professional societies, current guidelines recommend trifluridine/tipiracil as a priority treatment option, while other drugs such as irinotecan or taxanes are mentioned as secondary [14,15]. According to the Onkopedia guideline, for instance, trifluridine/tipiracil should be used if oral therapy is feasible. Only if the patient prefers intravenous therapy may the administration of irinotecan or a taxane be taken into account, unless these drugs have been used in a previous line of therapy [15]. However, the information provided in the company's dossier fails to demonstrate that trifluridine/tipiracil treatment is not an option for patients in the DESTINY-Gastric01 study submitted by the company (see Section I 5.2). Overall, the company's arguments are unsuitable for justifying a departure from the ACT specified by the G-BA.

This assessment was conducted for both research questions separately, each in comparison with the ACT specified by the G-BA. This departs from the approach used by the company, which derived added benefit compared to the ACTs specified by the company and did so for the entire target population, without drawing separate conclusions for the respective subpopulations under research questions 1 and 2.

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: 28 November 2022)
- bibliographical literature search on trastuzumab deruxtecan (last search on 3 January 2023)
- search in trial registries / trial results databases for studies on trastuzumab deruxtecan (last search on 20 January 2023)
- search on the G-BA website for trastuzumab deruxtecan (last search on 20 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on trastuzumab deruxtecan (last search on 15 February 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any relevant studies for assessing the added benefit of trastuzumab deruxtecan in comparison with the ACT.

In contrast, the company identified the RCT DESTINY-Gastric01 [16-21] comparing trastuzumab deruxtecan versus treatment of physician's choice and included the study in its study pool.

The DESTINY-Gastric01 study is not relevant for research question 1 because it enrolled only patients with at least 2 prior therapies. The study is also not relevant for research question 2 because it failed to implement the ACT defined for research question 2. For a detailed explanation, please refer to Chapters I 4 (research question 1) and I 5 (research question 2).

In addition, the company identified the single-arm study DESTINY-Gastric02 (DS8201-A-U205) [22-24] as another investigation, which it used for supplementary information to derive added benefit.

Due to its single-arm design, the DESTINY-Gastric02 study does not allow a comparison with the ACT for either research question 1 or research question 2 (see Chapters I 4 and I 5). Since no relevant other investigations were therefore available, the check for completeness of the study pool of further investigations was foregone.

It must be noted that the company draws conclusions on added benefit for the entire target population on the basis of both studies. The company does not distinguish between research questions 1 and 2.

I 4 Research question 1: patients in second-line therapy

I 4.1 Evidence provided by the company

DESTINY-Gastric01 study

The DESTINY-Gastric01 study is a multicentre, randomized, open-label, active control phase II study comparing trastuzumab deruxtecan with treatment of physician's choice, selecting from irinotecan or paclitaxel. It included patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had received at least 2 prior treatment regimens including trastuzumab. The study is described in detail in Section I 5.2.

DESTINY-Gastric02 study

The DESTINY-Gastric02 study is a phase II, multicentre, non-controlled, open-label trial of trastuzumab deruxtecan in patients with unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma who had disease progression during or after first-line trastuzumab-based therapy. A total of 79 patients were enrolled in the study. The study's primary outcome was overall response. Further outcomes include outcomes on mortality, health-related quality of life, and adverse events.

Approach of the company

The company uses the RCT DESTINY-Gastric01 and additionally the single-arm study DESTINY-Gastric02 to assess the added benefit of trastuzumab deruxtecan and presents results of both studies in the dossier. Across all research questions, it derives an indication of considerable added benefit of trastuzumab deruxtecan.

Studies presented by the company unsuitable for assessing added benefit

The company's approach is not appropriate. The DESTINY-Gastric01 study includes patients who have already received at least 2 prior treatment regimens including trastuzumab and thus does not offer a patient population relevant for research question 1 (patients in second-line therapy).

The DESTINY-Gastric02 study, which the company used as supplementary information to derive added benefit, is a single-arm study which does not allow a comparison with the ACT specified by the G-BA.

In departure from the company's assessment, both studies are therefore unsuitable for drawing conclusions on the added benefit of trastuzumab deruxtecan compared to the ACT for patients in second-line therapy.

I 4.2 Results on added benefit

No suitable data are available to assess the added benefit of trastuzumab deruxtecan compared with treatment of physician's choice in adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received 1 prior trastuzumab-based regimen in first-line therapy. This results in no hint of added benefit of trastuzumab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

I 5 Research question 2: patients in third-line and higher lines of therapy

I 5.1 Evidence provided by the company

DESTINY-Gastric01 study

The company used the multicentre, randomized, open-label, active control phase II study DESTINY-Gastric01 comparing trastuzumab deruxtecan versus treatment of physician's choice, selecting from irinotecan or paclitaxel to assess added benefit [16-21]. The DESTINY-Gastric01 study is unsuitable for assessing the added benefit of trastuzumab deruxtecan compared to the ACT because rather than implementing the ACT of trifluridine/tipiracil as specified by the G-BA, comparator arm patients received treatment of physician's choice, using irinotecan or paclitaxel. This is described in detail in Section I 5.2.

DESTINY-Gastric02 study

In addition, the company uses the single-arm study DESTINY-Gastric02 (DS8201-A-U205) [22-24] as a further investigation for assessing added benefit. However, as stated in Section I 4.1, this study is unsuitable for assessing the added benefit of trastuzumab deruxtecan because it is a single-arm study, therefore not allowing a comparison with the ACT specified by the G-BA. This study is therefore not described in more detail below.

I 5.2 Study characteristics of the DESTINY-Gastric01 study

Table 5 describes the study DESTINY-Gastric01 used by the company to assess added benefit.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: trastuzumab deruxtecan versus treatment of physician's choice

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DESTINY-Gastric01	RCT, open-label, parallel	Adults (≥ 20 years) with HER2-positive[b], locally advanced or metastatic gastric or GEJ adenocarcinoma and disease progression during or after 2 or more prior therapies[c]	Trastuzumab deruxtecan (N = 126)[d] Treatment of physician's choice, selecting from irinotecan or paclitaxel (N = 62)[d]	Screening: 28 days Treatment: until disease progression, unacceptable toxicity, medical decision, withdrawal of consent, pregnancy, end of study, loss to follow-up, or death Observation: outcome-specific, at most until death or final data cutoff	66 study sites in Japan and South Korea 11/2017–12/2020 Data cutoffs: ▪ 8/11/2019[e] ▪ 3/06/2020[f]	Primary: overall response rate (ORR) by independent central review Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes comprise information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 A.
b. HER2 status was determined by IHC and, where appropriate, ISH (FISH or DISH). Tumours with IHC 3+ or with IHC 2+ and ISH+ were deemed HER2-positive.
c. Prior treatment regimens had to include a fluoropyrimidine and a platinum derivative. In addition, disease progression had to have occurred under prior trastuzumab administration. Based on the information provided in the company's dossier, all included patients had already received at least 2 therapies in advanced disease.
d. The data refer to the randomized (primary) cohort, the results of which were presented by the company and used to derive added benefit. The company did not use the study's 2 other, non-randomized (exploratory) cohorts.
e. Primary data cutoff for overall response rate (ORR) and interim analysis of overall survival, planned to occur after assessment of tumour status in all patients in the randomized cohort approx. 24 weeks after randomization.
f. Final data cutoff for overall survival, planned to be conducted after approximately 133 events in the randomized cohort.

AE: adverse event; DISH: dual in situ hybridization; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; N: number of randomized patients; RCT: randomized controlled trial

The DESTINY-Gastric01 study is a completed, multicentre, randomized, open-label, active control phase II study comparing trastuzumab-deruxtecan versus treatment of physician's choice, selecting from irinotecan or paclitaxel, in adults 20 years of age and older with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma whose disease had progressed during or after at least 2 prior treatment regimens including a fluoropyrimidine and a platinum derivative as well as on trastuzumab-based therapy. Disease progression had to have occurred during or after the most recent prior therapy. Based on the information provided in the company's dossier, all included patients had already received at least 2 therapies in advanced disease. Progression within 6 months after prior (neo-)adjuvant therapy was deemed rapid progression and thus equivalent to progression in advanced stage. The study documents do not provide differentiated information on the number of patients with rapid progression. At enrolment, patients had to have Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1.

A total of 188 patients were allocated in a 2:1 ratio to treatment with trastuzumab deruxtecan (N = 126) or treatment of physician's choice, selecting from irinotecan or paclitaxel (N = 62). Randomization was stratified by geographic region (Japan or South Korea), ECOG-PS (0 or 1), and HER2 status (immunohistochemistry [IHC] 3+ or IHC 2+/ in situ hybridization [ISH] +).

In both study arms, treatment was to continue until disease progression, unacceptable toxicity, medical decision, withdrawal of consent, pregnancy, end of study, loss to follow-up, or death.

After discontinuation of the study medication, patients were allowed to start subsequent therapy. However, the company's dossier does not provide any information on whether and, if so, which follow-up therapies were used. The study documents fail to clarify whether participants were allowed to switch treatment from the comparator intervention to the experimental intervention.

The primary outcome was ORR. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life, and adverse events.

Lack of implementation of the ACT

The DESTINY-Gastric01 study presented by the company is unsuitable for assessing the added benefit of trastuzumab deruxtecan in comparison with the ACT. The reason for this is that the ACT specified by the G-BA (trifluridine/tipiracil) was not implemented. Instead, the patients in the comparator arm received a treatment based on the physician's discretion using irinotecan or paclitaxel.

This deviates from the approach used by the company, which relied on the DESTINY-Gastric01 study to derive added benefit for trastuzumab deruxtecan. From the company's point of view,

the ACT for the therapeutic indication of research question 2 is treatment of physician's choice, which includes the options of trifluridine/tipiracil as well as irinotecan, docetaxel, paclitaxel, or ramucirumab in combination with paclitaxel.

However, the company does not provide any information to justify its deviation from the ACT specified by the G-BA (see Chapter I 2).

Overall, the DESTINY-Gastric01 study submitted by the company does not allow comparing trastuzumab deruxtecan versus the ACT specified by the G-BA for patients under research question 2, trifluridine/tipiracil.

I 5.3 Results on added benefit

No suitable data are available to assess the added benefit of trastuzumab deruxtecan compared with trifluridine/tipiracil in adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have already received at least 2 prior treatment regimens including trastuzumab. This results in no hint of an added benefit of trastuzumab deruxtecan in comparison with trifluridine/tipiracil; an added benefit is therefore not proven.

I 6 Overall conclusion on added benefit

Table 6 summarizes the result of the assessment of added benefit of trastuzumab deruxtecan in comparison with the respective ACT.

Table 6: Research questions of the benefit assessment of trastuzumab deruxtecan

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received 1 prior trastuzumab-based regimen in first-line therapy[b]	Treatment of physician's choice[c]	Added benefit not proven
2	Adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received at least 2 prior regimens, including trastuzumab[b]	Trifluridine/tipiracil	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the planned therapeutic indication presumably includes patients in an inoperable, locally advanced or metastatic stage of the disease.
c. According to the G-BA, guidelines recommend systemic therapy in the present treatment situation. Based on their approval status, options for this purpose are the drug ramucirumab or the drug combination ramucirumab plus paclitaxel. The drugs irinotecan, docetaxel, and paclitaxel (monotherapy) have not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. According to the G-BA, the following treatment options are deemed suitable comparators for treatment of physician's choice: irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel. According to the G-BA, added benefit can be assessed versus 1 of the above treatment options within the framework of a single-comparator study.

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

The above assessment differs from the assessment by the company, which derived an indication of considerable added benefit for trastuzumab deruxtecan overall for adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based treatment regimen, without regard to the 2 separate research questions.

The G-BA decides on the added benefit.

I 7 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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